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β-FLUOROENOL TRIFLATES: SYNTHESIS AND SOME PALLADIUM CATALYZED REACTIONS

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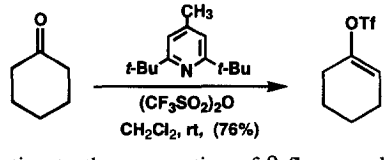
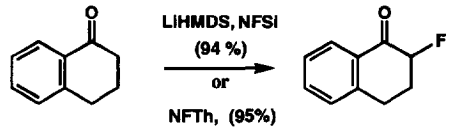
Abstract: β-Fluroenol triflates **2** have been prepared from the corresponding α-fluoro ketones **1** using Stang's procedure. Some palladium catalyzed reactions of **2a** are also reported. Copyright © 1996 Elsevier Science Ltd

Fluoroorganic compounds have found wide utility in the agrochemicals and pharmaceutical industries.[2] It is believed that fluorine considerably alters the physicochemical properties of organic compounds thus modifying the activity of biologically important compounds.[3] In an unrelated research, we became interested in preparing β–fluoro alkenylstannanes. We envisioned preparing the target stannanes from the corresponding triflates by a palladium catalyzed cross coupling reaction with hexamethylditin.[4] However, β-fluoroenol triflate have never been reported in the literature. Several attempts to prepare this class of compounds were not successful. In particular, attempts to trap enolates derived from α-fluoro ketones with various triflating agents such as N-phenyl triflamide, 2-[N,N-bis(trifluoromethylsulphonyl)amino]-5-chloropyridine (*Comins' reagent*) resulted in decomposition.[5]

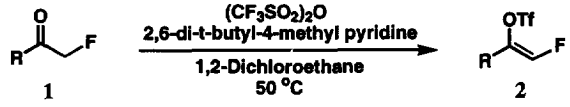
Almost fifteen years ago Stang reported[6] a very useful and versatile method for the preparation of enol triflates from the corresponding carbonyl compounds. It may be noted that this reaction does not proceed through the enolates, rather it is thought to proceed through an oxonium ion intermediate.[6]



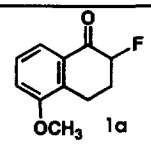
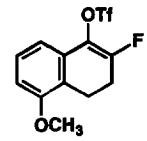
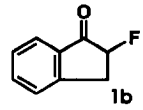
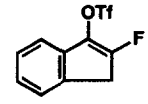
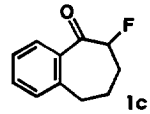
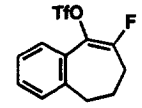
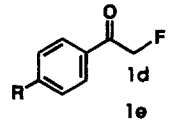
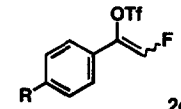
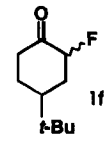
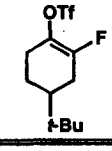
We thus chose to apply this reaction to the preparation of β-fluoroenol triflates from the corresponding α-fluoro ketones. Fluorination α- to carbonyl compounds using electrophillic fluorinating agents[7] such as NFSi, NFTh, and NFPy has been well documented.[8] Very recently Stavber and Zupan have reported[8c] an efficient synthesis of α-fluoro ketone using Accufluoro^{TM}-NFTh.[7] We prepared α-fluoro ketones for this study according to the literature procedures.[8]



Here we wish to report the first synthesis of β-fluoroenol triflates using Stang's procedure. In our hands, the reaction of 2-fluoro-5-methoxytetralone (**1a**) with 2,6-di-*t*-butyl-4-methylpyridine and triflic anhydride in 1,2-dichloroethane at 50 °C gave the fluoroenol triflate **2a**[9] in 89% yield (entry 1, Table 1). Some of our other results are shown in Table 1.



1 2

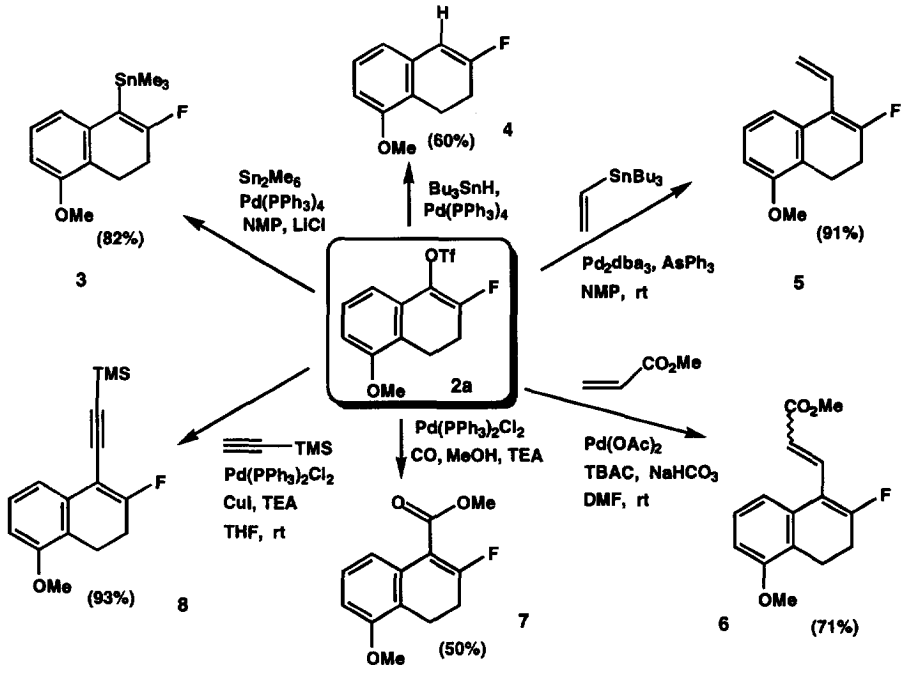
Entry	Fluoro Ketone[a]	β-Fluoroenol Triflate	Yield[b]
1	 1a	 2a	89%
2	 1b	 2b	71%
3	 1c	 2c	92%
4	 1d	 2d R = CH_3	72%[c]
5	1e	2e R = CF_3	76%[c]
6	 1f	 2f	40%

a) α-Fluoro ketones are prepared according to the procedure reported by Differding.[8b]

b) Isolated yields. c) 1:1 mixture of *E* and *Z* isomers.

In most cases the yields are quite high except entry 6. This is essentially a simple two step procedure for the conversion of commercially available ketones to the corresponding β-fluoroenol triflates via α-fluoro ketones.

Having a reliable procedure for the synthesis of β-fluoroenol triflates **2** in hand, we turned our attention to the application of **2** to the synthesis of fluoroorganic compounds. Some of the palladium catalyzed reactions of **2a** with various electrophiles are shown in Scheme 1.



Scheme 1. Palladium Catalyzed Reactions of **2a**.

The reaction of **2a** with hexamethylditin[4] gave β-fluoro alkenylstannane **3**.[10] Reduction[11] of **2a** with tributyltinhydride provided fluoroalkene **4**. Stille coupling under Farina conditions[12] gave fluorodiene **5**. Heck arylation under Jeffrey conditions[13] afforded δ-fluoro dienoate **6**. Carbonylation with carbon monoxide in methanol resulted β-fluoro enoate **7** and finally Sonogashira coupling[14] with trimethylsilylacetylene provided fluoroenyne **8**.[15] Notably, the reactions of **2a** with various electrophiles gave good to excellent yields. More importantly, **2a** reacts under considerably milder conditions than the corresponding parent triflates. In particular, Stille and Heck reactions of **2a** were carried out at room temperature, where as the parent triflate was unreactive at those conditions. Thus **2** appears to be a quite versatile intermediate for the synthesis of various fluoroorganic compounds.[16]

In summary, we have developed the first method for preparation of β-fluoroenol triflates using Stang's triflation procedure, and we believe that this methodology will become a useful tool in the synthesis of fluoro organic compounds.

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9. Compound **2a**, pale yellow oil: ^{1}H NMR (270 MHz, $CDCl_3$) 7.25 (t, J = 7.8 Hz, 1 H), 6.97 (d, J = 7.8 Hz, 1 H), 6.85 (d, J = 7.8 Hz, 1 H), 3.85 (s, 3 H), 3.07 (td, J = 8.6, 2.4 Hz, 2 H), 2.73 (td, J = 8.4, 4.1 Hz, 2 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) 155.6, 153.8 (d, $J_{C\text{-}F}$ = 312 Hz), 129.5, 127.9, 124.0, 119.8, 117.3 (q, $J_{C\text{-}F}$ = 339 Hz), 113.6 (q, $J_{C\text{-}F}$ = 6.7 Hz), 110.9, 55.5, 24.8, 19.9; HRMS calcd for $C_{12}H_{10}F_4O_4S$ 326.0236, found 326.0236.
10. Compound **3**, colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) 7.13 (t, J = 8.0 Hz, 1 H), 6.73 (d, J = 8.0 Hz, 1 H), 6.66 (d, J = 8.0 Hz, 1 H), 3.84 (s, 3 H), 2.99 (td, J = 8.3, 2.4 Hz, 2 H), 2.52 (m, 2 H), 0.35 (s, 9 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) 155.9, 146.1, 129.5, 127.1, 124.0, 118.5 (t, $J_{C\text{-}F}$ = 316 Hz), 117.8, 113.6, 111.5, 54.5 21.7, 18.9; HRMS calcd for (^{118}Sn) $C_{14}H_{19}FOSn$ 340.0436, found 340.0434; calcd for (^{120}Sn) 342.0441, found 342.0433.
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15. To a solution of **2a** (163.0 mg, 0.50 mmol) in THF:Et_3N (4:1, 5 mL) were added trimethylsilylacetylene (85 μL, 0.60 mmol), bis(triphenylphosphine)palladium(II) dichloride (17.5 mg, 0.03 mmol) and CuI (9.5 mg, 0.05 mmol) in the order given. The reaction mixture was stirred at rt for 30 min and then diluted with EtOAc, washed with 0.5N HCl, H_2O, brine, dried ($MgSO_4$) and solvent removed under reduced pressure to obtain a dark brown oil (130 mg, 100%). Purification by flash chromatography (10:1 hexane:EtOAc) afforded **8** (120 mg, 93%) as a light brown semisolid. ^{1}H NMR (270 MHz, $CDCl_3$) 7.20 (d, J = 8.5 Hz, 1 H), 7.18 (d, J = 7.2 Hz, 1 H), 6.77 (dd, J = 7.2, 2.0 Hz, 1 H), 3.83 (s, 3 H), 3.00 (td, J = 8.4, 2.7 Hz, 2 H), 2.61 (td, J = 8.6, 4.0 Hz, 2 H), 0.29 (s, 9 H); HRMS calcd for $C_{16}H_{19}FOSi$ 274.1189, found 274.1187.
16. All new compounds were characterized by NMR and mass spectroscopy.

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