Efficient and Convenient Route to (*Z*)-*α*,*β*-Unsaturated Difluoromethyl Ketones Based on the Reaction of 2,3,3-Trifluoro-1-tosyloxy-1-propenyllithium with Carbonyl Compounds

Kazumasa Funabiki,# Tetsuya Ohtsuki, Takashi Ishihara, and Hiroki Yamanaka
Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606

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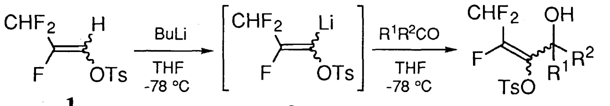
2,3,3-Trifluoro-1-tosyloxy-1-propenyllithium, generated from 2,3,3-trifluoro-1-propenyl *p*-toluenesulfonate with butyllithium, underwent coupling reaction with various carbonyl compounds to give good yields of 3,4,4-trifluoro-2-tosyloxy-2-butenyl alcohols, whose treatment with concentrated sulfuric acid at room temperature afforded the corresponding (*Z*)-α,β-unsaturated difluoromethyl ketones in good yields.

Fluorinated ketones have been gaining much attention due to their versatile utility as potential inhibitors of hydrolytic enzymes as well as key intermediates for preparing fluorine-containing bioactive compounds[1] and, therefore, methods are still required for the access to various types of fluorinated ketones and their derivatives. A number of reports have hitherto appeared dealing with the synthetic methods for such ketones including α,β-unsaturated fluoromethyl[2] or trifluoromethyl ketones,[3,4] and some of these methods may be applicable for difluoromethyl derivatives provided taking appropriate starting materials.

In our continuing studies to extend the synthetic utilizations of fluorinated enol tosylates,[5] we have now developed a facile and efficient method for the stereoselective synthesis of (*Z*)-α,β-unsaturated difluoromethyl ketones **4**, which is based upon the coupling reaction of fluorinated vinyllithium **2** with various carbonyl compounds followed by allylic hydrolysis with acid.[6]



1 **2** **3**

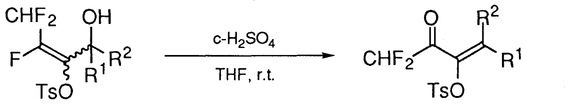
When enol tosylate **1** (Z:E = 84:16) was exposed to butyllithium (1.1 equiv.) in THF at -78 °C for 10 min, followed by treatment with benzaldehyde (1.5 equiv.) at the same temperature for 30 min, fluorinated allyl alcohol **3a**[7] (Z:E = 83:17) was obtained in 81% yield, as shown in Table 1 (Entry 1). Lithium diisopropylamide (LDA) was less efficient than butyllithium for the lithiation of **1** (Entry 2). Other aromatic and aliphatic aldehydes including α,β-unsaturated aldehydes participated well in the reaction with **2**[8] affording the corresponding alcohols **3** in moderate to good yields. The reactions with 2,2-dimethylpropanal or 3-pentanone also proceeded smoothly to give the products **3j** and **3k** in 49% or 63% yield, respectively (Entries 11 and 12). It should be noted that the *Z*- to *E*-isomer ratios of **3** are essentially the same as those of the starting enol tosylate **1**. This fact[9] not only suggests the configurational integrity of **2** during the reaction but also gives a support for the stereochemical assignment to the products **3**.

Table 1. Reaction of **2** with carbonyl compounds

Entry	Z:E^a	Carbonyl compd		Yield^b/%	Z:E^a
	of **1**	R^1	R^2	of **3**	of **3**
1	84:16	Ph	H	**3a** 81	83:17
2	84:16	Ph	H	**3a** 51^c	83:17
3	85:15	p-MeC$_6$H$_4$	H	**3b** 76	84:16
4	81:19	p-MeOC$_6$H$_4$	H	**3c** 68	81:19
5	85:15	p-ClC$_6$H$_4$	H	**3d** 84	87:13
6	81:19	1-naphthyl	H	**3e** 69	79:21
7	79:21	2-thienyl	H	**3f** 69	81:19
8	83:17	(*E*)-PhCH=CH	H	**3g** 55	82:18
9	81:19	(*E*)-MeCH=CH	H	**3h** 56	80:20
10	81:19	CH$_3$(CH$_2$)$_2$	H	**3i** 76	80:20
11	83:17	(CH$_3$)$_3$C	H	**3j** 49	86:14
12	86:14	Et	Et	**3k** 63	85:15

^{a}Determined by ^{19}F NMR. ^{b}Isolated yields. ^{c}LDA (1.1 equiv.) was used.

The alcohols **3** were subjected to allylic hydrolysis in the following manner. Thus, to a THF solution of **3** was added an excess amount of conc. H$_2$SO$_4$ (10 equiv.) at such a rate that the temperature should not rise above 0 °C. After stirring at room temperature for 30 min, the mixture was poured into crushed ice-water and extracted with ether. The extracts were washed with aqueous NaHCO$_3$ and brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel with benzene to give (*Z*)-α,β-unsaturated difluoromethyl ketone **4**[7,10] exclusively. The hydrolysis did not complete with a slight excess (3-5 equiv.) of H$_2$SO$_4$ and the use of trifluoroacetic acid in place of H$_2$SO$_4$ was ineffective. The results of these reactions are summarized in Table 2.

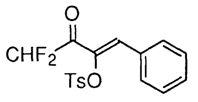
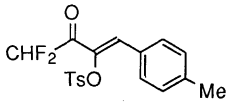
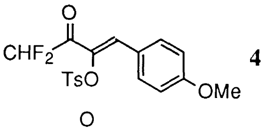
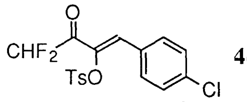
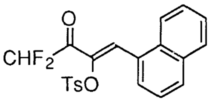
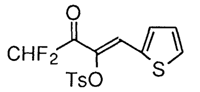
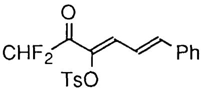
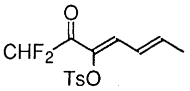
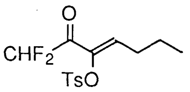
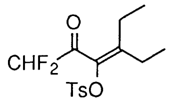


3 **4**

The allylic alcohols **3a-g**, derived from aromatic aldehydes, were easily hydrolyzed to give the corresponding (*Z*)-α,β-unsaturated difluoromethyl ketones **4** in excellent yields (Entries 1-7). The hydrolysis of **3h** derived from crotonaldehyde gave rise to a dehydrated product, 6,7,7-trifluoro-5-tosyloxy-1,3,5-heptatriene (**5**)[7] in 20% yield, in addition to the desired ketone **4h** (49%) (Entry 8). Likewise, the reaction of **3i** from butanal provided the ketone **4i** and 1,1,2-trifluoro-3-tosyloxy-2,4-heptadiene (**6**)[7] in 47% and 24% yields, respectively, though needed to be carried out in the presence of water (5 equiv.) without THF (Entry 9). The alcohol **3k** from 3-pentanone did not undergo the hydrolysis successfully under the similar conditions; as the major product was obtained 1,1,2-trifluoro-4-ethyl-3-tosyloxy-2,4-hexadiene (**7**)[7] in 62% yield and the difluoromethyl ketone **4k** was given only in 24% yield (Entry 10).

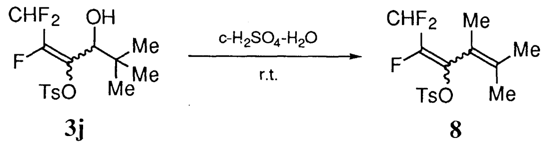
Interestingly, the alcohol **3j** prepared from 2,2-dimethyl-

Table 2. Synthesis of α,β-unsaturated difluoromethyl ketones **4**

Entry	**3** ($Z:E$)[b]	Difluoromethyl ketone **4**		Yield[a]/% ($Z:E$)[b]
1	**3a** (83 : 17)		**4a**	82 (>97 : <3)
2	**3b** (84 : 16)		**4b**	90 (>97 : <3)
3	**3c** (81 : 19)		**4c**	89 (97 : 3)
4	**3d** (87 : 13)		**4d**	87 (>97 : <3)
5	**3e** (79 : 21)		**4e**	81 (>97 : <3)
6	**3f** (81 : 19)		**4f**	89 (>97 : <3)
7	**3g** (82 : 18)		**4g**	94 (>97 : <3)
8	**3h** (80 : 20)		**4h**	49[c] (>97 : <3)
9[d]	**3i** (80 : 20)		**4i**	47[e] (>97 : <3)
10[d]	**3k** (85 : 15)		**4k**	24[f]

[a]Isolated yields. [b]Determined by ^{19}F NMR. [c]Fluorinated triene **5** was obtained in 20% yield. [d]Performed in the presence of 5 equiv. of water without THF. [e]Fluorinated diene **6** was formed in 24% yield. [f]Fluorinated diene **7** was obtained in 62% yield.

propanal was found, on treatment with conc. H_2SO_4 and water at ambient temperature for 30 min, to produce the Wagner-Meerwein rearrangement[11] product, 1,1,2-trifluoro-3-tosyloxy-4,5-dimethyl-2,4-hexadiene (**8**)[7] in 72% yield, no corresponding α,β-unsaturated ketone being formed.



3j **8**

In short, the present reactions described herein can serve as a new convenient and effective route to (Z)-α,β-unsaturated difluoromethyl ketones, which are difficult to obtain by other methods.

References and Notes

- \# Present address: Department of Chemistry, Faculty of Engineering, Gifu University, 1-1 Yanagido, Gifu 501-11.

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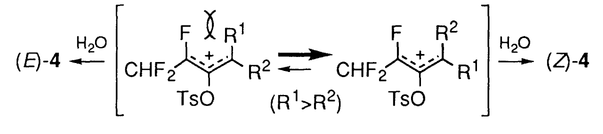
6 K. Tanaka, T. Nakai, and N. Ishikawa, *Tetrahedron Lett.*, **1978**, 4809.

7 All products gave satisfactory spectral and analytical data.

8 Fluorinated vinyllithium **2** reacted smoothly with other electrophiles, such as Me_3SiCl, Bu_3SnCl, and MeOTf, to give the corresponding enol tosylates[7] in 79%, 68%, and 79% yields, respectively.

9 The deuterolysis of **2** with ethanol-*d* gave quantitatively $CHF_2CF{=}C(D)OTs$ ($J(F\text{-}D)_{trans} = 2.2$ Hz, $J(F\text{-}D)_{cis} = 0$ Hz), whose isomer ratio was entirely identical with that of the starting enol tosylate **1**.

10 The typical spectral data for **4a**: IR (KBr) 1688 (C=O), 1618 (C=C) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.32 (s, 3H), 6.39 (dt, $J = 7.5$, 53.4 Hz, 1H), 7.12 and 7.69 (AB q, $J = 8.1$ Hz, 4H), 7.29 (m, 5H), 7.32 (s, 1H); ^{19}F NMR ($CDCl_3$, TFA) δ -45.8 (d, $J = 53.4$ Hz, 2F); HRMS Found: *m/z* 352.0581. Calcd for $C_{17}H_{14}F_2O_4S$: M, 352.0581. The stereochemistry of **4** was tentatively presumed in view of the relative stability of allylic cation intermediates in the hydrolysis, as shown below. See: B. M. Trost and J. L. Stanton, *J. Am. Chem. Soc.*, **97**, 4018 (1975); K. Tanaka, T. Nakai, and N. Ishikawa, *Chem. Lett.*, **1977**, 1379.



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