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Mesyloxy-Group Migration as the Stereoselective Preparation Method of Various Functionalized Olefins and Its Reaction Mechanism

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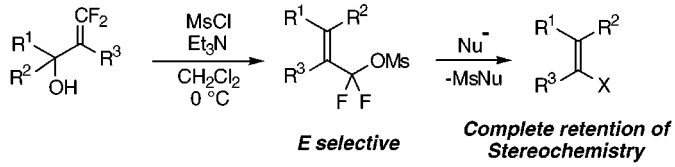
ABSTRACT



X: CH_2OH ($Nu^-=H^-$), C(O)F ($Nu^-=F^-$), CO_2R ($Nu^-=RO^-$), $C(O)NR_2$ ($Nu^-=R_2N^-$)

It was demonstrated that mesylation of appropriate γ,γ-difluorinated allylic alcohols under usual conditions furnished the corresponding α,α-difluorinated allylic mesylates, possibly by way of 1,3-mesyloxy-group migration after formation of the expected "normal" intermediates, γ,γ-difluorinated allylic mesylates. This rearrangement was conveniently applied to the construction of trisubstituted allylic alcohols, α,β-unsaturated esters, amides, or ketones in good to excellent chemical yields with exclusive *E* selectivities.

Recent investigation has demonstrated the versatility of difluorinated olefins as potent reactive substrates,[1] and among them, one of the most extensively studied substrates would be terminally difluorinated enols.[2,3] For example, O-alkylated derivatives[2] are usually prepared in a facile fashion by the *n*-BuLi-mediated deprotonation of O-protected 2,2,2-trifluoroethanols, while diverse methods have been developed thus far for the formation of the corresponding enol silyl ethers or ketene silyl acetals.[3] On the other hand, preparation of difluoroolefins without any heteroatoms attached to the C=C framework was performed mainly on the basis of the well-accepted Wittig protocol[3c,4] or employment of F_2C=CR−metal species.[5]

Recently, our attention has been focused on the construction of fluorine-containing chiral aldol structures by way of appropriately protected glucose-based *exo*-difluoromethylenated materials.[6] During our work on this subject, we have noticed the unexpected production of the totally defluorinated allylic alcohol **4** in 78% total yield just by the addition of **1** to a CH_2Cl_2 solution containing mesyl chloride and triethylamine, followed by the $NaBH_4$ reduction (Scheme 1). This process would be elucidated as the consequence of the quick

(1) Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619.

(2) (a) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 9201. (b) Lee, J.; Tsukazaki, M.; Snieckus, V. *Tetrahedron Lett.* **1993**, *34*, 415. (c) Kodama, Y.; Yamane, H.; Okumura, M.; Shiro, M.; Taguchi, T. *Tetrahedron* **1995**, *51*, 12217.

(3) (a) Yamana, M.; Ishihara, T.; Ando, T. *Tetrahedron Lett.* **1983**, *24*, 507. (b) Jin, F.-Q.; Xu, Y.-Y.; Huang, W.-Y. *J. Chem. Soc., Perkin Trans. 1* **1993**, 795. (c) Houlton, J. S.; Motherwell, W. B.; Ross, B. C.; Tozer, M. J.; Williams, D. J.; Slawin, A. M. Z. *Tetrahedron* **1993**, *49*, 8087. (d) Brigaud, T.; Doussot, P.; Portella, C. *J. Chem. Soc., Chem. Commun.* **1994**, 2117. (e) Shi, G.-Q.; Cai, W.-L. *Synlett* **1996**, 371. (f) Schoth, R.-M.; Lork, E.; Seifert, F. U.; Breuer, E.; Röschenthaler, G.-V. *Chem. Ber.* **1997**, *130*, 279. (g) Iseki, K.; Kuroki, Y.; Asada, D.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron* **1997**, *53*, 10271. (h) Uneyama, K.; Maeda, K.; Kato, T.; Katagiri, T. *Tetrahedron Lett.* **1998**, *39*, 3741.

(4) (a) Hayashi, S.; Nakai, T.; Ishikawa, N.; Burton, D. J.; Naae, D. G.; Kesling, H. S. *Chem. Lett.* **1979**, 983. (b) Vinson, W. A.; Prickett, K. S.; Spahic, B.; de Montellano, P. R. O. *J. Org. Chem.* **1983**, *48*, 4661. (c) Serafinowski, P.; Barnes, C. L. *Tetrahedron* **1996**, *52*, 7929. (d) Burton, D. J.; Yang, Z.; Qiu, W. *Chem. Rev.* **1996**, *96*, 1641.

(5) (a) Tellier, F.; Sauvêtre, R. *J. Fluorine Chem.* **1996**, *76*, 79. (b) Ichikawa, J.; Kobayashi, M.; Noda, Y.; Yokota, N.; Amano, K.; Minami, T. *J. Org. Chem.* **1996**, *61*, 2763. (c) Fujiwara, M.; Ichikawa, J.; Okauchi, T.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 7261.

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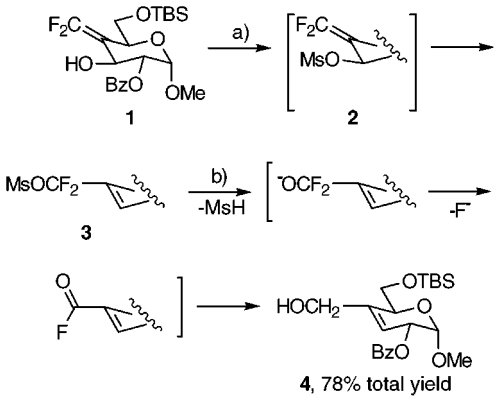
Scheme 1[a]



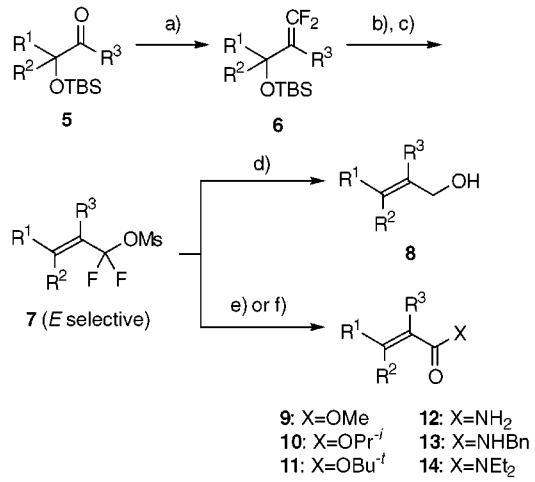
[a] Key: (a) MsCl, Et_3N/CH_2Cl_2, 0 °C → rt, 1 h; (b) $NaBH_4$/EtOH, rt, 1 h.

mesyloxy-group migration of the initially formed γ,γ-difluorinated allylic mesylate **2** to the corresponding α,α-difluorinated counterpart **3**, and nucleophilic hydride attack at the mesyl sulfur atom[7] might trigger the fluoride elimination to provide **4** by the exhaustive reduction of the resultant acid fluoride.

In this paper, we wish to report the extension of the above method to general acyclic materials which enabled us to synthesize not only allylic alcohols[8] but also variously substituted α,β-unsaturated carbonyl compounds from single intermediates in a highly stereoselective manner. Moreover, an ^{18}O tracer experiment was carried out to prove that this transposition was at least mainly caused by the [3,3]-sigmatropic rearrangement.

As depicted in Scheme 2 and Table 1, the starting α-siloxyketones **5b**−**f** and the corresponding aldehydes **5a**,**g**,**h** were prepared by way of the well-known cyanohydrin

Scheme 2[a]



[a] Key: (a) CF_2Br_2, HMPT/THF; (b) TBAF/THF; (c) MsCl, Et_3N/CH_2Cl_2; (d) $NaBH_4$/EtOH; (e) ROM/ROH; (f) MNR_2/THF (M: metal).

Table 1. Difluoromethylenation and Sulfonate Migration

					isolated yield (%)	
entry	**5**	R^1	R^2	R^3	**6**	**7**[a]
1	**a**	n-$C_6H_{13}^-$	H	H	83	*b*
2	**b**	CH_3^-	H	n-$C_5H_{11}^-$	83	88
3	**c**	n-$C_4H_9^-$	H	CH_3^-	73	81
4	**d**	n-$C_6H_{13}^-$	H	CH_3^-	96	86
5	**e**	CH_3^-	H	$Ph(CH_2)_2^-$	86	89
6	**f**	$PhCH(CH_3)^-$	H	CH_3^-	40	86
7	**g**[c]	Ph^-	CH_3^-	H	90	*b*
8	**h**[c]	n-$C_6H_{13}^-$	CH_3^-	H	80	*b*,*d*

[a] Only *E* isomers were detected unless otherwise noted. [b]Due to their inherent instability, the crude materials were employed for the next step without further purification. [c]A TMS group was attached instead of a TBS moiety. [d]*E*/*Z* = 73:27.

protocol in good to excellent yields (formation of cyanohydrins by the ZnI_2-catalyzed addition of TMSCN to $R^1C(O)R^2$, TBS protection of the OH group hydrolyzed upon workup,[9] followed by treatment with R^3MgX (**5b**−**f**) or DIBAL (**5a**,**g**,**h**), respectively). Substrates **5** were smoothly converted to the requisite *exo*-difluoromethylene compounds **6**[4b] which, after desilylation, were subjected to the mesylation conditions furnishing the corresponding mesyloxy-migrated α,α-difluorinated mesylates **7** as the sole products in an *E*-exclusive manner with good chemical yields. The substrate **5h** was the exception, giving rise to the formation of **7h** as the *E*,*Z* mixture (Table 1).

Addition of these intermediates **7** to an ethanol solution of $NaBH_4$ yielded, as expected, allylic alcohols **8** in excellent yields with complete retention of the original stereochemical integrity (Table 2, entries 4, 7, 9, 12, and 20). In the case of the substrates **7a** and **g**, since in situ generated EtONa by the reaction between $NaBH_4$ and EtOH was found to afford the corresponding ethyl ester as a byproduct, an ethereal solution of $LiAlH_4$ was alternatively employed for this reduction step.

After successful reduction, tetra-*n*-butylammonium fluoride (TBAF) was selected as the next nucleophile toward α,α-difluorinated mesylates **7**. This is based on our idea that, if fluoride ion works in a manner similar to hydride, **7** would furnish the corresponding acid fluoride with liberation of fluoride ion which might possibly constitute the catalytic

(6) (a) Yamazaki, T.; Hiraoka, S.; Kitazume, T. In *Asymmetric Fluoroorganic Chemistry: Synthesis, Applications, and Future Directions*; Ramachandran, P. V., Ed.; American Chemical Society: Washington, DC, 2000; p 142. (b) Hiraoka, S.; Yamazaki, T.; Kitazume, T. *Heterocycles* **1998**, *47*, 129. (c) Hiraoka, S.; Yamazaki, T.; Kitazume, T. *Chem. Commun.* **1997**, 1497. (d) Hiraoka, S.; Yamazaki, T.; Kitazume, T. *Synlett* **1997**, 669. (e) Yamazaki, T.; Hiraoka, S.; Kitazume, T. *Tetrahedron*: *Asymmetry* **1997**, *8*, 1157. For the intriguing cyclization of this compound in a 5-*endo*-*trig* manner, see: Yamazaki, T.; Hiraoka, S.; Sakamoto, J.; Kitazume, T. *J. Phys. Chem. A* **1999**, *103*, 6820.

(7) For other examples of nucleophilic S−O bond cleavage of sulfonates, see: (a) Baarschers, W. H. *Can. J. Chem.* **1976**, *54*, 3056. (b) Tsuda, Y.; Nishimura, M.; Ito, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1983.

(8) For other preparation methods of allylic alcohols, see: Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.: Pergamon Press: New York, 1991; Vol. 1, p 729.

(9) Because TMS ethers were not cleaved by the workup procedure, TBS protection was not required for **5g** and **h**.

Table 2. Nucleophilic S−O Bond Cleavage of **7**

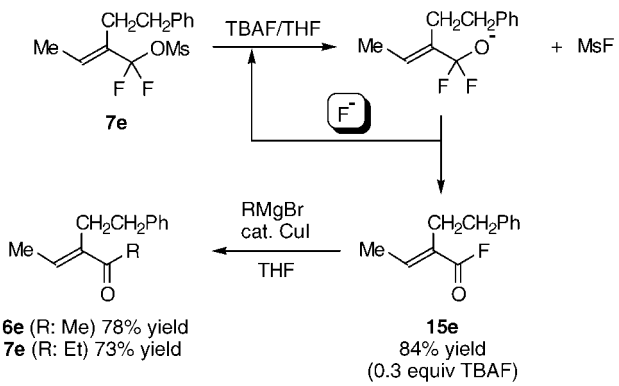
entry	7	Nu	product	X	yield (%)
1	**a**	$LiAlH_4$[a]	**8a**		74[b]
2		MeONa	**9a**	OMe	84[b]
3		BnHNLi	**13a**	NHBn	65
4	**b**	$NaBH_4$	**8b**		95
5		MeONa	**9b**	OMe	96
6		Et_2NLi	**14b**	NEt_2	85
7	**c**	$NaBH_4$	**8c**		86
8		MeONa	**9c**	OMe	91
9	**d**	$NaBH_4$	**8d**		96
10		MeONa	**9d**	OMe	90
11		Et_{2NLi}	**14d**	NEt_2	89
12	**e**	$NaBH_4$	**8e**		91
13		MeONa	**9e**	OMe	89
14		*i*-PrOLi	**10e**	$OPr\text{-}^i$	92
15		*t*-BuOK	**11e**	OBu^{-t}	88
16		H_{2NNa}	**12e**	NH_2	86
17		BnHNLi	**13e**	NHBn	92
18		Et_{2NLi}	**14e**	NEt_2	95
19		$n\text{-}Bu_{4NF}$	**15e**	F	84
20	**f**	$NaBH_4$	**8f**		89
21		MeONa	**9f**	OMe	96
22	**g**	$LiAlH_4$[a]	**8g**		50[b]
23		MeONa	**9g**	OMe	94[b]
24		BnHNLi	**13g**	NHBn	63[b]
25	**h**	MeONa	**9h**	OMe	87[b,c]

[a] In these cases, $LiAlH_4$ was employed because NaOMe by the reaction of $NaBH_4$ and MeOH reacted with **7**. [b]Total yield from **6**. [c]*E*/*Z* = 73:27.

cycle with accumulating the corresponding acid fluoride.[10] As shown in Scheme 3, this was actually the case and after purification by the conventional silica gel column chromatography, the acid fluoride **15e** was obtained in 84% yield by the action of 0.3 equiv of TBAF[11] to **7e**. ^{19}F NMR analysis of this crude reaction mixture enabled us to observe a peak at 223.3 ppm[12] (q, J = 3.8 Hz), reasonably attributable to the one of MsF. This was, in connection with the isolation of the acid fluoride **15e**, considered to be the direct support of nucleophiles actually attacking at the sulfonate sulfur atom.

We now turned our attention to construct α,*β*-unsaturated esters or amides from the same intermediates, α,α-difluorinated mesylates **7**. From the analogy of the instances already discussed above, it is anticipated that alkoxides or metal amides might possess the enough ability to attack the sulfonate sulfur atom and that the excess amount of reagents would react smoothly with the resultant acid fluoride. Various O- and N-nucleophiles were in fact proved to be efficiently applicable to the spontaneous elimination of the Ms group. It is interesting to note that, from the results of entries 13−15 and 16−18 in Table 2, the steric bulkiness of the nucleophilic reagents used did not seem to significantly influence the reaction course. The *E* stereochemistry at the olefinic part was unambiguously confirmed by comparing their spectroscopic data with the ones already reported or on the basis of NMR chemical shift information.[13,14]

Scheme 3



When organolithium or -magnesium reagents were utilized as nucleophilic species for the purpose of direct construction of ketones from the intermediates **7**, they only produced complex mixtures. However, preparation of ketones was realized by the reaction of the corresponding acid fluoride **15e** and Grignard reagents in the presence of a catalytic amount of CuI.

For the mechanistic clarification of this process, the ^{18}O isotope tracer experiment was planned at the next stage. Because of the relatively small isotope effect of oxygen,[15] only the naturally occurring quantity of ^{18}O (0.20%) should be found out in the product **21** as long as the pathway is concerted (route B). On the other hand, because of the S_N1 type mechanism,[16] the ^{18}O content of the same **21** via the alternative route A would depend on the nucleophilic ability of the cleaved $TMS^{18}OH$ and the solvent MeOH.

Following to the reported procedure (Scheme 4),[17] 1-phenylethanol with 29.6% of ^{18}O was utilized for the preparation of the ^{18}O-enriched difluorinated substrate **19** via acetophenone (^{18}O: 29.2%,[18] Table 3). As described in Table 3, 14.2% of ^{18}O was detected from the product **21** formed via the path A (73% yield) and this value could be recognized as the "standard S_N1 result" for the present substance. On the other hand, when **19** was subjected to our own protocol,

(10) (a) Funabiki, K.; Ohtsuki, T.; Ishihara, T. *Chem. Lett.* **1994**, 1075. (b) Funabiki, K.; Kurita, T.; Matsui, M.; Shibata, K. *Chem. Lett.* **1997**, 739.

(11) A smaller amount of fluoride ion source significantly affected the conversion of **7e** to **15e**: 0.1 equiv of TBAF yielded only 32% of **15e** with 56% recovery of **7e**.

(12) C_6F_6 was used as the internal standard.

(13) See, for example: (a) Mori, K.; Matsui, M. *Tetrahedron* **1970**, *26*, 2801. (b) Kinstle, T. H.; Mandanas, B. Y. *J. Chem. Soc., Chem. Commun.* **1968**, 1699. (c) Pascual, C.; Meier, J.; Simon, W. *Helv. Chim. Acta* **1966**, *49*, 164. (d) Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*; VCH: Weinheim, 1987.

(14) (a) Moppett, C. E.; Sutherland, L. K. *J. Chem. Soc. C* **1968**, 3040. (b) Jorgenson, M. J.; Leung, T. *J. Am. Chem. Soc.* **1968**, *90*, 3769.

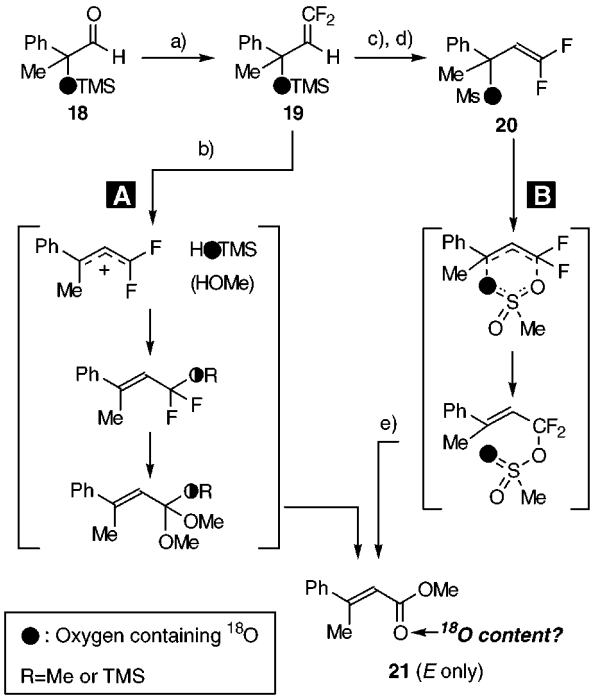
(15) At 25 °C, the reaction rate $^{16}O/^{18}O$ is reported to be at most 1.19. See: Collins, C. J.; Bowman, N. S. In *Isotope Effects in Chemical Reactions (ACS Monograph 167)*; Van Nostrand Reinhold Co.: New York, 1970; p 16.

(16) Tellier, F.; Sauvêtre, R. *Tetrahedron Lett.* **1993**, *34*, 5433.

(17) Vinson, W. A.; Prickett, K. S.; Spahic, B.; Montellano, P. R. *J. Org. Chem.* **1983**, *48*, 4661.

(18) Calculation of the ^{18}O content was carried out with referring to the following report. Abe, M.; Inakazu, T.; Munakata, J.; Nojima, M. *J. Am. Chem. Soc.* **1999**, *121*, 6556.

Scheme 4 ^{18}O Tracer Experiment by Way of Two Independent Methods[a]



[a] Key: (a) CF_2Br_2, HMPT/THF; (b) cat. camphorsulfonic acid/MeOH; (c) TBAF/THF; (d) MsCl, Et_3N/CH_2Cl_2; (e) MeONa/MeOH.

the desired α,β-unsaturated ester **21**[19] was obtained in 95% yield. Mass spectroscopic analysis of this material demonstrated that only 1.3% of ^{18}O was contained in the product **21**, which strongly supported that the present mesyloxy migration reaction at least mainly followed by the concerted mechanism.

In conclusion, we described the novel migration of a mesyloxy group from γ,γ-difluoroallylic sulfonates to the corresponding α,α-difluorinated counterparts. Moreover, the present method realized, from single intermediates, the efficient synthesis of diverse allylic alcohols or α,β-unsaturated carbonyl compounds with various substitution patterns in good to excellent chemical yields as well as usually with very high *E*-stereoselectivities, just by the simple change of nucleophilic species.[20] Further investigations are in progress in our laboratory especially on the scope and limitation of this method for the syntheses of variously substituted olefins with appropriate functionalities.

Table 3. Mass Spectral Data for Natural and ^{18}O-Labeled Material[a]

	natural material			labeled material			^{18}O content[b]
compd	M	M + 1	M + 2	M	M + 1	M + 2	(%)
PhCH(OH)Me	100	8.87	0.57	100	14.83	43.14	29.57
PhC(O)Me	100	9.19	0.73	100	9.50	42.74	29.22
18[c]	100	16.92	4.76	100	19.25	45.64	26.80
21 (route A)	100	11.98	1.12	100	23.19	18.07	14.20
21 (route B)	100	11.98	1.12	100	12.89	2.43	1.27

[a] Measured by a Shimadzu Parvum QP-5000 (EI, 70 eV) spectrometer. [b] ^{18}O content = $[[(M+2)/(M+(M+2))]_{labeled} - [(M+2)/(M+(M+2))]_{natural}]100$. [c] Ready formyl elimination from **18** led us to detect not the M^+ but the $M^+ - 29$ peak, the latter of which was used for the calculation of ^{18}O content.

Supporting Information Available: Experimental procedure for the original migration (**1** to **4**) as well as the representative method for the formation of **6b**−**9b**, **14b**, **15e**, and **16e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) To a stirring THF solution of **19** (0.100 g, 0.370 mmol) was added 1.2 equiv of TBAF at 0 °C, and stirring was continued for 1 h. After removal of THF in vacuo, purification by short-path silica gel column chromatography afforded the difluoroallylic alcohol, which was subjected to the next mesylation condition (1.5 equiv of MsCl and Et_3N in CH_2Cl_2). After usual workup, the crude material was dissolved in MeOH where 4.0 equiv of NaOMe was added at 0 °C. Stirring at room temperature (0.5 h) and the usual workup and purification by silica gel column chromatography gave **21** (0.062 g, 0.352 mmol) in 95% yield.

(20) A similar type of reaction was reported (ref 16), while this method (1) requires H_2O or MeOH with strongly acidic 94% H_2SO_4 for the syntheses of the corresponding carboxylic acids or methyl esters, respectively, or (2) 3.5 equiv of metal amide for the conversion into amides, and (3) is limited only for the structure type $R^3 = H$ in Scheme 2 because of the structural feature of the starting material, $CF_2{=}CH_2$.