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Facile conversion of CF_3-containing propargylic alcohol derivatives via the corresponding allenes

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ABSTRACT

Empirical information on the acidity of the propargylic proton from our previous work allowed us to develop novel synthetic transformations of readily available terminally trifluoromethylated propargylic alcohols **1** into the corresponding allenyl tosylates **3a**, 1-tosyloxy- or 1-acyloxy-4,4,4-trifluorobutan-2-ones **4**, and 2-(2,2,2-trifluoroethyl)prop-2-en-1-ones **5**, which was enabled by such common bases as NaOH and tertiary amines for affecting ready abstraction of this proton.

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1. Introduction

Organofluorine compounds have attracted considerable interest in the field of medicines and functional materials due to their unique effects, which are not usually attained by any other groups nor elements.[1] Our research group has recently paid attention for clarification of synthetic utility of propargylic alcohols **1** with a trifluoromethyl (CF_3) group at the terminal position of the triple bond.[2] This type of compounds was first prepared from 3,3,3-trifluoropropyne,[3] while its gaseous nature and high cost might prevent further expansion of this method in the organic chemistry field. We originally devised convenient construction of **1** from the commercially available oily materials such as 2-bromo-[2a] and 1-chloro-3,3,3-trifluoropropene.[4] Due to more facile availability and handling, these propargylic alcohols **1** have been employed thus far in such a variety of procedures as [2+2+2] cycloadditions with other alkynes,[5] 1,3-dipolar cycloadditions with azides,[6] allene formation,[7,8] Pd-catalyzed cyclocarbonation for butenolide synthesis,[9] and elaboration to biologically interesting sugars[2a,10] and amino acids.[11] All of these transformations basically employed the carbon–carbon triple bond or the corresponding double bond after partial reduction as the key functional groups. During our study for further development of the novel utilization method of **1**, we wondered the lability of its propargylic proton: if this proton is acidic enough, its abstraction would open totally different routes to a variety of materials previously unable to be accessed by way of the isomeric allenes as the important synthetic intermediates. On the basis of our previous reports[2,13] on the redox type isomerization of **1** into the corresponding α,β-unsaturated ketones, it is quite reasonable to consider that deprotonation was actually and easily occurred at this position, and utilization and modification of this information allowed us to find out an intriguing conversion of propargylic tosylates **2a** into the corresponding allenyl tosylates **3a**.[12] Moreover, this **2a** or the related propargylic esters were smoothly transformed into the 1-substituted 1-tosyloxy- or 1-acyloxy-4,4,4-trifluorobutan-2-ones **4** via the intramolecular attack of carbonyl oxygen in hydroxy protective groups to the central carbon atom of the intermediary allenes **3**. Alkanesulfonyl moieties like ethanesulfonyl (R′=CH_3, R″=H) were proved to be a special case, which led to the formation of 2-(2,2,2-trifluoroethyl) prop-2-en-1-ones (*E*)-**5** by the intramolecular attack of carbanion α to the sulfur atom in these instances to the same position of **3**. These three processes are quite unique and intriguing because of hitherto unknown types of reactions initiated from abstraction of the propargylic proton.[13] In this article, we would like to report full detail of these reactions of **1** as common substrates (Scheme 1).

2. Results and discussion

2.1. Base-mediated transformation of propargylic tosylates with a CF_3 group to the corresponding allenyl tosylates

Toluenesulfonates **2a** employed in this study as key substrates were synthesized from alcohols **1**[2a] by the condensation with

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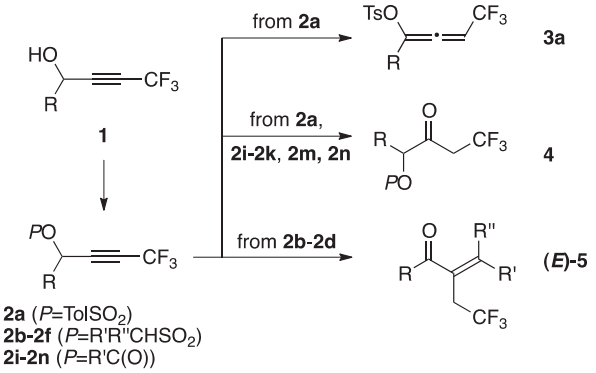
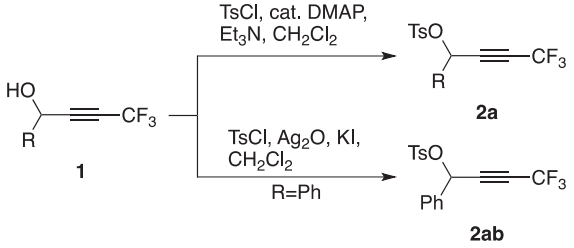


Scheme 1. Various transformation of protected propargylic alcohols **2**.

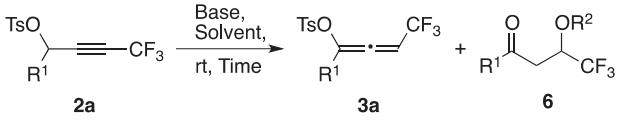
p-toluenesulfonyl chloride (TsCl) mediated by Et_3N and a catalytic amount of 4-(dimethylamino)pyridine. However, **2ab**[14] was the exception, which was obtained from **1b** (R=Ph) and TsCl in the presence of Ag_2O and KI, and the resultant **2ab** should be used without purification due to its relative instability (Scheme 2).[15] For the base-mediated conversion to the corresponding allenyl tosylates **3a**, various bases and solvents were screened using **2aa** (R=$PhCH_2CH_2$–) as the representative substrate (Table 1). As expected, this isomerization was found to proceed by the action of DBU in MeOH, which was more effective than CH_3CN, but the former solvent furnished a small amount of β-methoxyketone **6aa** as a byproduct (entries 2 and 3). Higher nucleophilicity of a base seemed to prefer the formation of this byproduct, giving a larger amount of **6aa** by use of NaOMe (entry 3), and this tendency became more intense under the NaOEt/EtOH system to produce 89% yield of **6ba** (entry 4). Formation of **6aa** would be interpreted as the initial attack to the electronically positive sulfur atom in **3aa** by these stronger alkoxide bases, which would further participate for the conjugate addition to the resultant α,β-unsaturated ketone. This mechanism was supported by the independent reaction of this ketone with NaOEt in EtOH at room temperature for 3 h, actually affording **6ba** in excellent 92% yield. Change of a base to weaker K_2CO_3 succeeded in suppression of such removal of a tosyl group with retaining this isomerization ability, and the yield of **3aa** increased to 92% along with **6ba** forming in only 8% (entry 7). Steric bulkiness of the solvent had a crucial role in this process, and methanol preferentially afforded the byproduct, β-methoxyketone **6aa**, in 42% yield along with the desired **3aa** in 56% yield (entry 3), while bulkier *i*-PrOH almost did not promote the reaction (entry 8). Although it required longer time by using 1.1 equiv of NaOH (entry 9), we have eventually found out NaOH (3 equiv) as a base and a THF/H_2O mixed solvent in a ratio of 2:1 as the best conditions, and after 5 h at room temperature, the desired product **3aa** was isolated almost in a quantitative fashion[16] (entry 10).

This base-mediated isomerization was carried out for a variety of substrates **2a** under the optimized conditions as described above.



Scheme 2. Preparation of CF_3-containing propargylic tosylates.

Table 1
Transformation of propargylic tosylates to the corresponding allenes



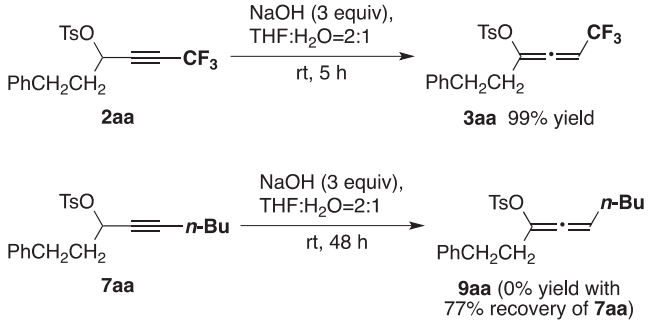
Entry	R^1	Base[a]	Solvent	Time (h)	Isolated yield (%)	
					3a	**6**
1	$PhCH_2CH_2$– (**a**)	DBU	MeCN	4.5	23[b]	0
2	$PhCH_2CH_2$– (**a**)	DBU	MeOH	3	46[b]	19[b,c] (**6aa**)
3	$PhCH_2CH_2$– (**a**)	NaOMe	MeOH	3	56[b]	42[b,c] (**6aa**)
4	$PhCH_2CH_2$– (**a**)	NaOEt	EtOH	3	1[b]	89[b] (**6ba**)
5	$PhCH_2CH_2$– (**a**)	AcONa	MeOH	3	0	0
6	$PhCH_2CH_2$– (**a**)	K_2CO_3	MeOH	3	15	69[b,c] (**6aa**)
7	$PhCH_2CH_2$– (**a**)	K_2CO_3	EtOH	2	92	8[b] (**6ba**)
8	$PhCH_2CH_2$– (**a**)	K_2CO_3	*i*-PrOH	3	6	0
9	$PhCH_2CH_2$– (**a**)	NaOH	THF/H_2O[e]	40	89	0
10	$PhCH_2CH_2$– (**a**)	NaOH[d]	THF/H_2O[e]	5	99	0
11	Ph– (**b**)	NaOH[d]	THF/H_2O[e]	1	—[f]	0
12	C_9H_{19}– (**c**)	NaOH[d]	THF/H_2O[e]	24	90	0
13	$BnO(CH_2)_2$– (**d**)	NaOH[d]	THF/H_2O[e]	24	80	0
14	*c*-Hex (**e**)	NaOH[d]	THF/H_2O[e]	48	99	0
15	Ph(MOMO)CH– (**f**)	NaOH[d]	THF/H_2O[e]	48	78	0
16	*t*-Bu– (**g**)	NaOH[d]	THF/H_2O[e]	48	97	0

[a] Base of 1.1 equiv was employed unless otherwise noted.
[b] Yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
[c] Compound **6aa**: R^2=Me, **6ba**: R^2=Et.
[d] Base of 3 equiv was used.
[e] A mixture of a solvent and H_2O in a ratio of 2:1 was used.
[f] A complex mixture was obtained.

In the case of **2ab**, the fact that only a complex mixture was formed would be elucidated by the presence of the 'too activated' hydrogen atom at the propargylic position by an additional phenyl group (entry 11). Other compounds were found to nicely follow this process to produce **3a** in high to excellent yields (entries 12 and 13) in spite of requirement of longer reaction times for **2a** with bulkier R^1 groups (entries 14–16).

For obtaining experimental proof on the electronic character of a CF_3 group, the non-fluorinated counterpart **7aa** was synthesized for comparison and subjected to the similar reaction conditions (Scheme 3). Although the propargylic tosylate **2aa** reacted smoothly to almost quantitatively afford the corresponding allenyl tosylate **3aa** as shown in Table 1, exchange of a CF_3 group to a *n*-Bu moiety totally suppressed this pathway and **7aa** was recovered in 77% yield even after prolonged reaction time. It is apparent that a CF_3 group plays an important role in stabilization of the deprotonated intermediate while an electron-releasing *n*-Bu moiety should work in an opposite manner. This discrepancy directly led to estimation of the lower acidity of the propargylic proton in **7aa**, which would be the major reason for the failure of this reaction.

During the course of optimization of this isomerization, we have also noticed that aqueous DMF affected in a different manner

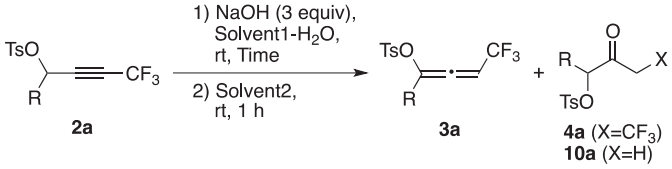


Scheme 3. Comparison of reactivity.

to form 1-substituted 4,4,4-trifluoro-1-tosyloxybutan-2-ones **4a** as the major products. Thus, although the case of entry 9 in Table 1 furnished the allenyl tosylate **3aa** selectively, simple exchange the solvent from THF to DMF completely altered the reaction course, and **4aa** was obtained in 44% yield without formation of **3aa** (entry 1 in Table 2). This intriguing observation allowed us to further investigate a variety of factors related to this formal hydration of **2a**. Other water-soluble solvents like EtOH, *i*-PrOH, and DMSO resulted in the unequivocal construction of **3aa**, and **4aa** was not produced at all (entries 2–4). Importance of DMF was recognized at this point, and addition of DMF was found to be more effective after completion of isomerization to the allene, which is apparent from the comparison between the result of entry 1 and the ones of entries 5 and 6. It is interesting to note that *N*,*N*′-dimethyl-propyleneurea (DMPU) and *N*,*N*-dimethylacetamide (DMA) with a similar structure to DMF did not exhibit such product preference, and **2aa** was selectively converted into the allenyl tosylate **3aa** with the negligible yield of **4aa** (entries 8 and 9). At this stage, we have determined the conditions in entry 6 as the best, and scope and limitation of substituents R in **2a** was checked. In the case of entries 10, 11, and 13, ketones **4a** were isolated in good yields along with a small amount of the totally difluorinated **10a**. Substrate **2ae** with a cyclohexyl moiety was found to be reluctant to the present conversion, requiring an increased amount of DMF for promotion of the reaction (under the standard conditions, reaction did not proceed at all) to afford **4ae** only in 26% yield. The sterically most demanding **2ag** among substrates tested furnished **3ag** in excellent yields in spite of such forcing conditions as a larger amount of DMF and heating to 90 °C (entry 15).

We have paid our attention to the possibility of DMF hydrolysis under the present aqueous basic conditions to furnish dimethylamine and sodium formate, and participation of either (or both) of them for the formation of **4a** from **3a**. Actually, hydrolytic decomposition of DMF was reported to proceed much faster than the case of DMA and DMPU.[17] On the basis of this fact, the isolated allenyl tosylate **3aa** was independently treated with some selected bases whose results were summarized in Table 3.

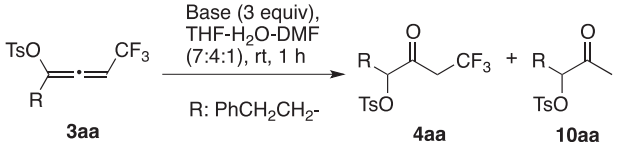
Table 2
Conversion of **2a** into the corresponding 1-substituted 4,4,4-trifluoro-1-tosyloxybutan-2-ones **4a**



Entry	R	Solvent 1[a]	Time (h)	Solvent 2[a]	Isolated yield (%)		
					3a	**4a**	**10a**
1[b]	$PhCH_2CH_2-$ (**a**)	DMF	1	—	0	44	—[c]
2[b]	$PhCH_2CH_2-$ (**a**)	EtOH	1	—	71[d]	0	0
3[b]	$PhCH_2CH_2-$ (**a**)	*i*-PrOH	1	—	83[d]	0	0
4[b]	$PhCH_2CH_2-$ (**a**)	DMSO	1	—	47[d]	0	0
5	$PhCH_2CH_2-$ (**a**)	MeCN	4	DMF	8[d]	57[d]	—[c]
6	$PhCH_2CH_2-$ (**a**)	THF	5	DMF	0	76	17
7[e]	$PhCH_2CH_2-$ (**a**)	THF	5	DMF	0	54[d]	—[c]
8	$PhCH_2CH_2-$ (**a**)	THF	5	DMPU	88[d]	0[d]	—[c]
9	$PhCH_2CH_2-$ (**a**)	THF	5	DMA	85[d]	3[d]	—[c]
10	n-$C_9H_{19}-$ (**c**)	THF	24	DMF	0	58	14
11	$BnO(CH_2)_2-$ (**d**)	THF	24	DMF	Trace	61	12
12[f]	*c*-Hex– (**e**)	THF	24	DMF	13	26	16
13	Ph(MOMO)CH– (**f**)	THF	24	DMF	0	41[d]	0
14	*t*-Bu– (**g**)	THF	48	DMF	86	0	0
15[f,g]	*t*-Bu– (**g**)	THF	48	DMF	75	0	0

[a] The ratio of solvent 1/H_2O/solvent 2 was 7:4:1 unless otherwise noted.
[b] The second step was omitted.
[c] Not determined.
[d] Determined by ^{19}F NMR by using $PhCF_3$ as the internal standard.
[e] LiOH was used instead of NaOH.
[f] The solvent system of THF/H_2O/DMF=2:1:1 was employed.
[g] The second step was heated to 90 °C.

Table 3
Effect of a base for the conversion of **3aa** into **4aa**



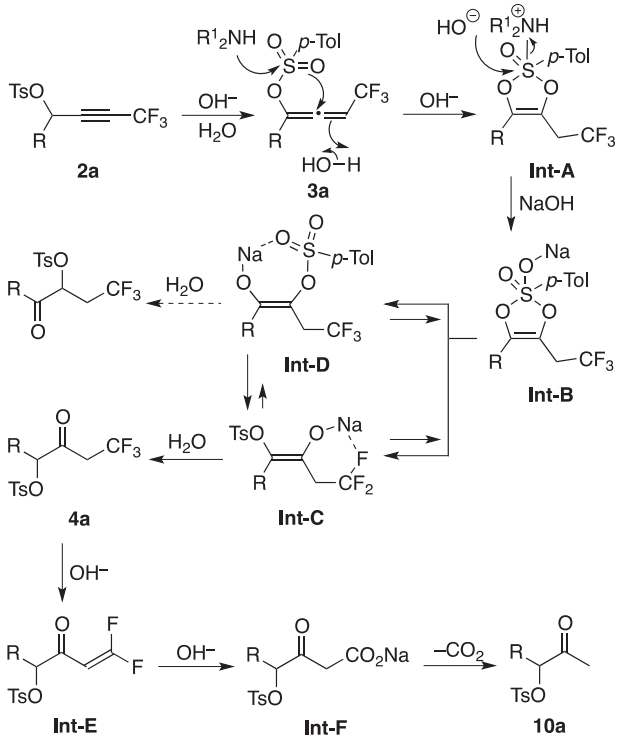
Entry	Base	Isolated yield (%)		Recovery (%)
		4aa	**10aa**	**3aa**
1	HCO_2Na	0	0	99
2	Me_2NH	48	15	28
3	Me_3N	0	0	99
4	$BuNH_2$	62	7	20
5	Pyrrolidine	44	30	22

Although sodium formate, one of the DMF hydrolysis products, did not work at all (entry 1), another component dimethylamine in fact converted **3aa** to **4aa** in 48% yield (entry 2). Primary and secondary amines like butylamine and pyrrolidine properly promoted this reaction (entries 4 and 5, respectively), while this was not the case for the representative tertiary amine, trimethylamine, only the starting **3aa** being quantitatively recovered (entry 3).

A possible mechanism for the present formal hydration is shown in Scheme 4. After facile base-mediated isomerization of propargylic tosylates **2a** to allenyl tosylates **3a**, attack of dimethylamine at the electropositive sulfonyl sulfur atom would facilitate the intramolecular cyclization by polarized sulfonate oxygen to the allene central carbon atom of **3a** to furnish **Int-A**. Elimination of this amine allowed the transformation to the cyclic sulfonates **Int-B**, which should be in an equilibrating relationship with **Int-C** and **Int-D**, the former of which was expected to be predominant due to the energetically favorable Na···F intramolecular chelation.[18] Final protonation of this intermediate **Int-C** would reasonably explain the base-mediated formation of 1-substituted 4,4,4-trifluoro-1-tosyloxybutan-2-ones **4a** from propargylic tosylates **2a**. Absence of the regioisomeric 4,4,4-trifluoro-2-tosyloxybutan-1-ones would be the good support of the energetic superiority of **Int-C** over **Int-D**. Consideration of the electron-withdrawing property of a CF_3 group close to an ester moiety[1,19] led us to speculation of the higher acidity of methylene protons between CF_3 and a carbonyl moiety in **4a**, and these protons would be readily eliminated under stronger basic conditions. Then, the following defluorination furnished the reactive **Int-E** with the highly electrophilic β-carbon not only by the α,β-unsaturated carbonyl framework but by this sp^2-hybridized carbon with two fluorine atoms giving rise to p-π repulsive interaction.[1] Successive sequence of addition of hydroxide and the following elimination of fluoride ions[20] affected total defluorination to furnish sodium salt of β-ketoacid **Int-F**, and this intermediate eventually followed facile decarboxylation to produce the byproduct **10a**.

2.2. Base-mediated conversion of CF_3-containing propargylic carboxylates

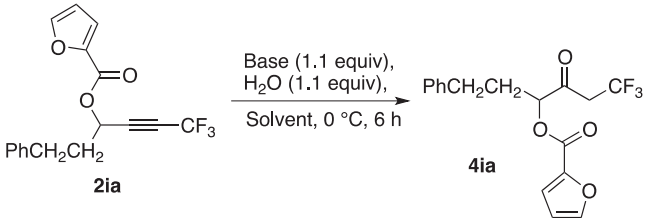
Having succeeded in the base-mediated transformation of propargylic tosylates **2a** to the corresponding allenyl tosylates **3a** and α-tosyloxy ketones **4a**, we next turned our attention to the



Scheme 4. Possible reaction mechanism.

similar type of process employing hydrolytically more labile propargylic esters. Investigation of the optimal reaction conditions for the model substrate **2ia** was undertaken with an appropriate amine base in an aprotic THF solvent because our preliminary experiment has already clarified that the simple acetate functionality was readily cleaved under isomerization conditions shown in Table 1 (3 equiv of NaOH in THF/H_2O=2:1, rt, 3 h furnished the hydrolyzed alcohol **1a** in 50% yield along with 48% recovery of the acetate). Tertiary amines and K_2CO_3 did not afford **4ia** at all with high to quantitative recovery of the starting material **2ia** (Table 4, entries 1–5). On the other hand, DBU and DBN with higher basicity specifically promoted the reaction nicely to afford the desired ketone **4ia** in excellent and moderate yields (entries 6 and 7, respectively). Solvent effect was briefly studied with DBU, and although Et_2O worked well, CH_2Cl_2 and EtOH were found to be irrelevant (entries 8–10). Consideration of the mechanism on the basis of the corresponding tosylates **2a** as depicted in Scheme 4 anticipated us that a catalytic amount of DBU should suffice, while reduction of this base to 20 mol % led to recovery of **2ia** in excellent yield without formation of the desired **4ia** (entry 11). Increase of the reaction temperature from 0 °C to rt resulted in decrease of the yield of **4ia** to some extent.

Table 4
Investigation of the reaction conditions for the conversion of **2ia** into **4ia**

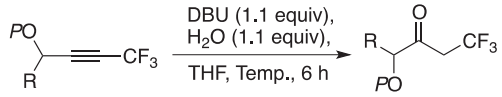


Entry	Base	Solvent	Yield[a] (%)	Recovery[a] (%)
1	Et_3N	THF	0	>99
2	Pyridine	THF	0	84
3	DMAP	THF	0	71
4	DABCO	THF	0	89
5	K_2CO_3	THF	0	>99
6	DBU	THF	87	<1
7	DBN	THF	44	<1
8	DBU	CH_2Cl_2	0	9
9	DBU	EtOH	0	60
10	DBU	Et_2O	60	0
11[b]	DBU	THF	0	83
12[c]	DBU	THF	52	0

[a] Yields were determined by ^{19}F NMR.
[b] The amount of DBU was reduced to 20 mol %.
[c] Reaction was carried out at room temperature.

At the next stage, the scope of propargylic esters was searched basically under the condition of entry 6 in Table 4. As shown in Table 5, not only esters **2ia**, **2ja**, and **2ka** (entries 1–3) but also the carbonate **2ma** and phosphate **2na** (entries 5 and 7) participated nicely for the present transformation to afford the corresponding ketones **4** in moderate to excellent yields, while the carbamate **2la**, tosylate **2aa**, and ether **2oa** (entries 4, 6, and 8) didn't work at all and, instead, decomposition of the substrates was observed. For the examination of the effect of substituents R at the propargylic position, **2jb** and **2jh** unfortunately failed to react properly, which would be as a consequence of the existence of an activated propargylic proton by the participation of an additional carbon–carbon double bond in R (entries 9 and 14). Steric crowding around the propargylic position of **2jg** might avoid the approach of a base to this site, allowing recovery of this substrate in 87% yield. This is in sharp contrast to the case of base-mediated isomerization with smaller NaOH in size where successful abstraction of the proton was realized (entry 14 in Table 2). On the other hand, the formal hydration of benzoates with saturated primary and secondary alkyl substituents as R was performed in moderate to high yields and the former appeared to proceed even at lower temperature (entries 10–12, and 15). Entries 16 and 17 demonstrated the examples of non-fluorinated substrates **7ja** and **8ja** with CO_2Et and *n*-Bu moieties instead of a CF_3 group, respectively. These substrates did not

Table 5
DBU-mediated transformation of **2** into **4**



2 **4**

Entry	R	P	Substrate	Temp (°C)	Product	Yield[a] (%)
1	$PhCH_2CH_2$–	2-Furyl–C(O)–	**2ia**	0	**4ia**	87
2	$PhCH_2CH_2$–	PhC(O)–	**2ja**	rt	**4ja**	85
3	$PhCH_2CH_2$–	4-O_2N–C_6H_4–C(O)–	**2ka**	rt	**4ka**	51
4	$PhCH_2CH_2$–	NH_2C(O)–	**2la**	0	**4la**	0
5	$PhCH_2CH_2$–	MeOC(O)–	**2ma**	rt	**4ma**	68
6	$PhCH_2CH_2$–	Ts–	**2aa**	rt	**4aa**	0
7	$PhCH_2CH_2$–	$(EtO)_2P$(O)–	**2na**	0	**4na**	53
8	$PhCH_2CH_2$–	MOM–	**2oa**	rt	**4oa**	0
9	Ph–	PhC(O)–	**2jb**	0	**4jb**	Trace
10	*n*-C_9H_{19}–	PhC(O)–	**2jc**	0	**4jd**	47
11	*c*-C_6H_{11}–	PhC(O)–	**2je**	rt	**4je**	77
12	PhCH(MOMO)–	PhC(O)–	**2jf**	rt	**4jf**	85[b]
13	*t*-Bu–	PhC(O)–	**2jg**	rt	**4jg**	Trace (87)
14	(*E*)-C_3H_7CH=CH–	PhC(O)–	**2jh**	rt	**4jh**	0
15	*n*-C_6H_{13}–	PhC(O)–	**2ji**	0	**4jc**	65
16[c]	$PhCH_2CH_2$–	PhC(O)–	**7ja**	rt	**11ja**	0 (9)
17[d]	$PhCH_2CH_2$–	PhC(O)–	**8ja**	rt	**12ja**	0 (88)

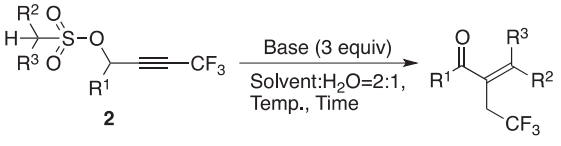
[a] Isolated yield and in the parenthesis was shown the recovery of the starting materials.
[b] Diastereomer mixture of 83:17 was obtained.
[c] A CF_3 group was substituted for a CO_2Et moiety.
[d] A CF_3 group was substituted for a *n*-Bu moiety.

undergo the present hydration at all: this result would be interpreted as the lower acidity of the propargylic proton by loosing an effective activation unit like a CF_3 group in the latter **8ja** case, and the former **7ja** seemed to experience hydrolysis at the terminal ethyl ester function. Thus, a characteristic property of a CF_3 group as a non-hydrolyzable strong electron-withdrawing moiety proved to effectively promote this process.

2.3. Novel transformation of CF_3-containing propargylic alkanesulfonates to α,β-unsaturated ketones in an (*E*)-specific manner

During examination of the formal hydration of various CF_3-containing propargylic sulfonates for clarification of the scope and limitation of this reaction, we unexpectedly discovered that the corresponding mesylate **2ca** afforded α,β-unsaturated ketones (*E*)-**5ba** in a stereospecific fashion (entry 9 in Table 6). Consideration of its utility allowed us to further search this interesting conversion using ethanesulfonate **2ba** as the model substrate (Table 6). THF and 1,4-dioxane were found to be acceptable solvents in the presence of NaOH at room temperature for 3 h (entries 1–4), and NaOH was the hydroxide bases of choice (entries 1 and 5–7). Further attempt for increase of the yield of the product (*E*)-**5ba**[21] to the acceptable level was noticed by simply raising the reaction temperature to 50 °C (entry 8). At the next stage, we have examined the effect of the sulfonate substituent (R^2R^3CH–). In the case of the methanesulfonate **2ca** (entry 9), although the reaction smoothly proceeded even at rt, sensitivity of the product **5ca** toward silica gel drastically reduced the isolated yield to 22% in spite of 63% before purification (determined by ^{19}F NMR). The bulkier sulfonate **2da** behaved in a different manner and the allenyl sulfonate **3ca** was obtained in 62% yield possibly as the result of steric congestion around the reacting carbanion, rendering its access to the allene central carbon atom difficult (entry 10). In the case of sulfonates **2ea** and **2fa**, only complex mixtures were formed presumably due to their higher reactivity (Cl α to the electron-attracting SO_3 group and the acidic hydrogen on the sulfur bound carbon atom; entries 11 and 12, respectively). Finally,

Table 6
Stereoselective formation of (*E*)-α,β-unsaturated ketones (*E*)-**5**



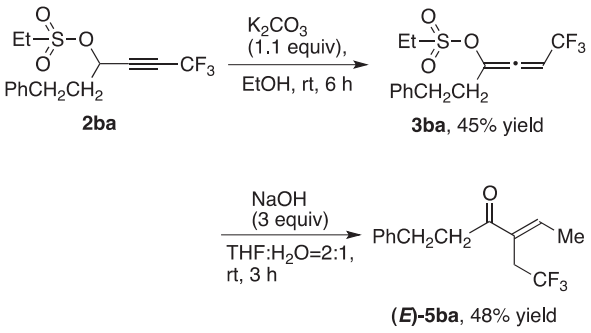
2 (***E***)**-5**

Entry	R^1	R^2	R^3	Sub[a]	Temp (°C)	Time (h)	Solvent	Base	Pro[b]	Isolated yield[c] (%)
1	$PhCH_2CH_2$–	CH_3–	H–	**2ba**	rt	3	THF	NaOH	**5ba**	(45)
2	$PhCH_2CH_2$–	CH_3–	H–	**2ba**	rt	3	CH_3CN	NaOH	**5ba**	(25)
3	$PhCH_2CH_2$–	CH_3–	H–	**2ba**	rt	3	1,4-Dioxane	NaOH	**5ba**	(44)
4	$PhCH_2CH_2$–	CH_3–	H–	**2ba**	rt	3	DMSO	NaOH	**5ba**	(4)
5	$PhCH_2CH_2$–	CH_3–	H–	**2ba**	rt	3	THF	LiOH	**5ba**	(37)
6	$PhCH_2CH_2$–	CH_3–	H–	**2ba**	rt	3	THF	KOH	**5ba**	(30)
7	$PhCH_2CH_2$–	CH_3–	H–	**2ba**	rt	3	THF	Me_4NOH	**5ba**	(31)
8	$PhCH_2CH_2$–	CH_3–	H–	**2ba**	50	3	THF	NaOH	**5ba**	75
9	$PhCH_2CH_2$–	H–	H–	**2ca**	rt	1	THF	NaOH	**5ca**	22 (63)
10	$PhCH_2CH_2$–	CH_3–	CH_3–	**2da**	50	3	THF	NaOH	**5da**	(6) [62][d]
11	$PhCH_2CH_2$–	CF_3–	H–	**2ea**	50	3	THF	NaOH	**5ea**	Trace
12	$PhCH_2CH_2$–	Cl–	H–	**2fa**	rt	3	THF	NaOH	**5fa**	Trace
13	*n*-C_9H_{19}–	CH_3–	H–	**2bc**	rt	24	THF	NaOH	**5bc**	56
14	$BnOCH_2CH_2$–	CH_3–	H–	**2bd**	rt	3	THF	NaOH	**5bd**	40
15	*c*-C_6H_{11}–	CH_3–	H–	**2be**	rt	24	THF	NaOH	**5be**	63
16	PhCH(OMOM)–	CH_3–	H–	**2bf**	rt	3	THF	NaOH	**5bf**	60
17	$PhCH_2CH_2$–	CH_3–	H–	**7ba**[e]	rt	3	THF	NaOH	—	0[f]

[a] Substrates.
[b] Products.
[c] Yields in parentheses were determined by ^{19}F NMR by using $PhCF_3$ as an internal standard.
[d] Isolated yield of 6,6,6-trifluoro-1-phenylhexa-3,4-dien-3-yl 1-methylethanesulfonate **3da**.
[e] A CF_3 group in **2ba** was substituted for a *n*-Bu moiety.
[f] Compound **7ba** was recovered in 97% yield.

some other ethanesulfonates **2b** with a variety of primary as well as secondary R^1 moieties were employed for clarification of the applicability of this intriguing novel transformation, and they worked in a similar fashion to furnish the desired products **5b** in good yields with unequivocal *E* stereospecificity (entries 13–16).

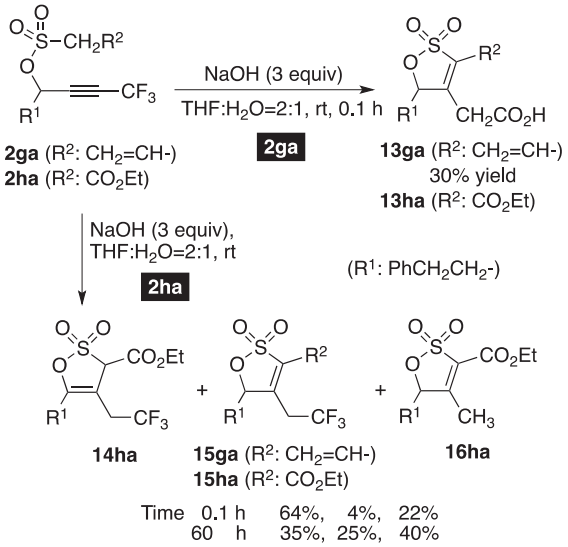
To gain mechanistic insight on the present process, we have performed two independent reactions. One was to employ the non-fluorinated substrate **7ba** (entry 17 in Table 6), and like the other instances, this substrate **7ba** was totally intact under the above standard reaction conditions and was recovered almost in quantitative yield. The other was to subject the separately prepared allenyl ethanesulfonate **3ba** to the same alkaline conditions (Scheme 5). Treatment of ethanesulfonate **2ba** with a weaker base like K_2CO_3 in EtOH at rt affected only the isomerization reaction



Scheme 5. Independent transformation of **2ba** into (*E*)-**5ba** via **3ba**.

suppressing the successive intramolecular attack to afford **3ba** in 45% yield which, after chromatographic purification, was introduced to a mixed solvent (THF/H_2O=2:1) containing 3 equiv of NaOH at rt for 3 h to in fact promote conversion into the desired product (*E*)-**5ba** in 48% isolated yield.

Sulfonates **2ga** and **2ha** with vinyl and ethoxycarbonyl groups as R^2, respectively, were found to behave in a different fashion and they offered a series of sultones **13** to **16** (Scheme 6). For example, the totally defluorinated carboxylic acid **13ga** was obtained in 30% yield as the major isolated product possibly by way of **15ga**. In the case of **2ha**, the reaction also proceeded in a quick manner within 0.1 h to furnish the isomeric mixture of sultones **14ha**, **15ha**, and **16ha**, and time-dependent transformation of **14ha** into the other two compounds was noticed.



Scheme 6. Sultone formation from **2ga** and **2ha**.

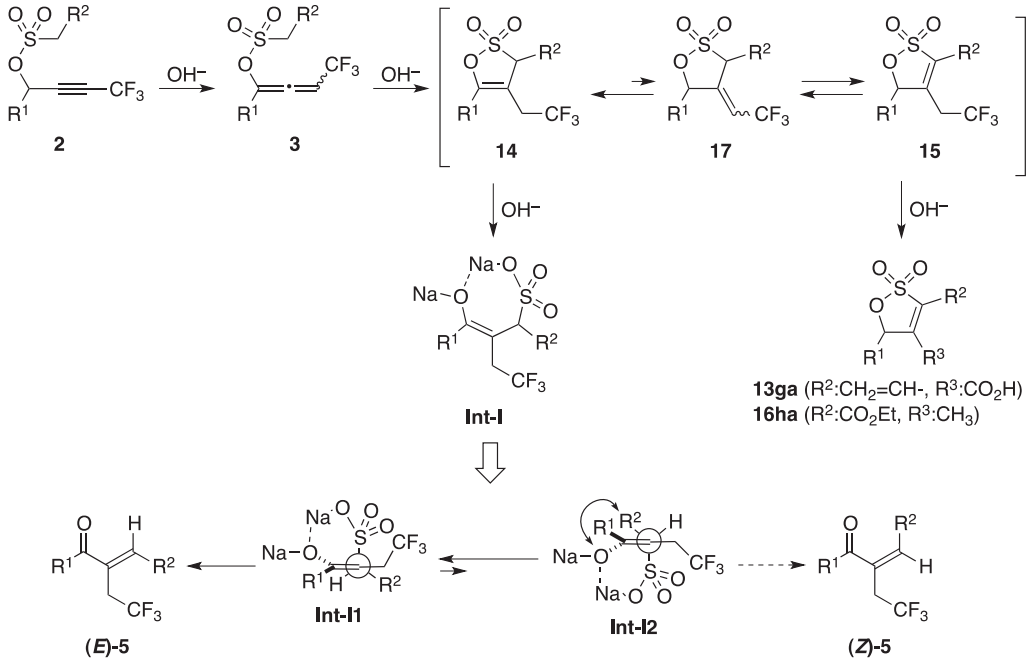
A possible mechanism for the above conversion of propargyl sulfonates **2** would be explained as shown in Scheme 7. With referring to the results in Scheme 5, **2** would experience the isomerization to the corresponding allenyl sulfonates **3** initiated by deprotonation of the acidic propargylic proton. Further action of NaOH to abstract the α proton to the sulfur atom furnished the anionic species, which would construct a new carbon–carbon bond comparison[22] of the model compounds **14bg** and **17bg** with R^1=R^2=CH_3 clarified the ca. 9 kcal/mol energetic preference of the former whose results led to semi-quantitative estimation that **14** would be the major intermediate at the cyclization.

The ready isomerization to the energetically more stable α,β-unsaturated carbonyl system by NaOH-mediated deprotonation–protonation sequence in an aqueous media was reasonably expected by the presence of the electron-withdrawing R^2 group in **14**. Moreover, such substituents R^2 also played an important role in increase of the acidity of the proton next to the CF_3 group in **15**, rendering the following dehydrofluorination and hydrolysis of the resultant terminally difluorinated vinyl moiety easier (see, similar decomposition of a CF_3 group in **4a** to **10a** in Scheme 4). This transformation should eventually produce **13** by losing all the fluorine atoms, and the stronger electron-withdrawing ester group allowed **13ha** to affect further decarboxylation to **16ha**. The possible route to the final product (*E*)-**5** would be by way of attack of hydroxide on the sulfur atom of **14** to open the sultone ring, and the produced ketone was successively converted to the enolate **Int-I** whose stereochemistry would be controlled by the favorably stabilizing intramolecular chelation (one possible structure was shown in Scheme 7). At the last stage, the sulfur-containing leaving group should occupy the position orthogonal to the C–C double bond, and because the steric repulsion between enolate oxygen and R^2 seemed to be the controlling factor, the less crowded **Int-I1** would be preferable to afford (*E*)-**5** with high selectivity.

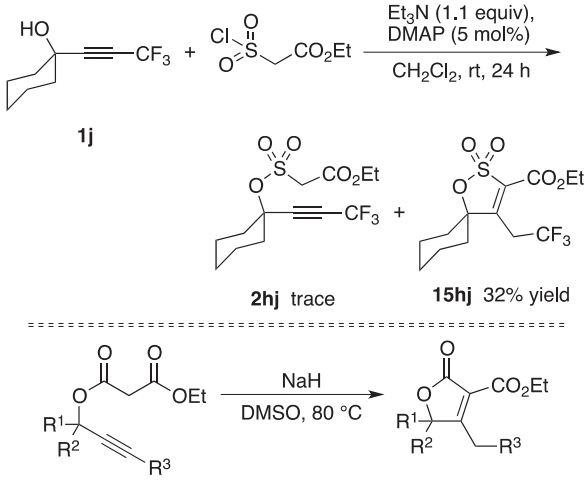
As shown in Scheme 5, this process was considered to be initiated from the formation of the allenyl sulfonates **3**, while we also obtained an interesting proof for this reaction proceeding via a direct attack of the carbanion to the triple bond carbon β to the CF_3 group. Thus, formation of the sulfonate **2hj** without propargylic hydrogen did not yield the desired material but the sultone **15hj** in 32% yield along with 55% recovery of the starting material **1j** (Scheme 8). This fact would be elucidated in a similar manner to the case of intramolecular lactone formation with the allene central carbon atom in an intramolecular manner to give the intermediates, **14** and/or **17**. Computational of ethyl propargyl malonates reported by Arcadi et al., which occurred in the presence of NaH in DMSO at 80 °C.[23] The ready room temperature reaction and applicability of a weaker base in our instance should be the reflection of the electrophilic activation of the carbon–carbon triple bond by the CF_3 group, which effectively lowered the LUMO energy level of the possible initial product **2hj**. At present, this 'direct' mechanism cannot be ruled out as the possible pathway.

3. Conclusion

In summary, we have demonstrated the successful NaOH-mediated transformation of propargylic tosylates with a CF_3 group **2** into the corresponding allenyl tosylates **3**. The same substrates **2** with other hydroxy protective groups realized formation of 4,4,4-trifluorobutan-2-ones **4** with a protected hydroxy moiety at the 1-position, or α,β-enones (*E*)-**5** with a 2,2,2-trifluoroethyl moiety at the α-position, both by way of the allenyl derivatives **3**. Characteristics of these novel reactions is the facile deprotonation of the activated propargylic proton by such commercially available



Scheme 7. Possible reaction mechanism.



Scheme 8. Direct formation of sultone **15hj**.

and low cost common bases as NaOH and DBU, and further application of these protocols is underway in this laboratory.

4. Experimental section

4.1. General

All reactions were carried out under an atmosphere of argon in dried glassware with magnetic stirring. Analytical thin-layer chromatography (TLC) was routinely used for monitoring reactions by generally using a mixture of hexane and AcOEt (v/v). Spherical neutral silica gel (63–210 μm) was employed for column chromatography. Anhydrous Et_2O, THF, and CH_2Cl_2 were purchased and were used without further purification. ^1H (300 MHz), ^{13}C (75 Hz), and ^{19}F (283 Hz) NMR spectra were recorded on a JEOL AL 300 spectrometer in $CDCl_3$ unless otherwise noted and chemical shifts were recorded in parts per million (ppm), downfield from internal tetramethylsilane (Me_4Si: δ 0.00, for ^1H and ^{13}C) or hexafluorobenzene (C_6F_6: δ −163.00 for ^{19}F). Data were tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sex, sextet; m, multiplet; br, broad peak), number of protons, coupling constants in hertz. Infrared (IR) spectra were obtained on a JASCO A-302 spectrometer and reported in wave numbers (cm^{-1}). Elemental analyses were performed by Perkin–Elmer SeriesII CHNS/O analyzer. Electrospray ionization mass spectrometry by Thermofisher Exactive was obtained using the negative and positive ionization modes.

4.2. Typical procedure for the preparation of propargyl sulfonates

To a solution of **1a** (2.28 g, 10.0 mmol), *p*-toluenesulfonyl chloride (2.09 g, 11.0 mmol), and 4-(*N*,*N*-dimethyl)pyridine (0.024 g,

0.20 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C triethylamine (1.67 mL, 12.0 mmol) and the resultant mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl aq (30 mL) and extracted with CH_2Cl_2 (3×70 mL). Concentration by rotary evaporator after dried over Na_2SO_4 furnished a crude material, which was purified by silica gel column chromatography (hexane/EtOAc=15:1) to give 3.59 g (9.39 mmol) of pure propargyl tosylate **2aa** in 94% yield.

In the case of preparation of **2ab**, after **1b** (1.00 g, 5.0 mmol), *p*-toluenesulfonyl chloride (1.14 g, 6.0 mmol), Ag_2O (1.39 g, 6.0 mmol), and KI (1.00 g, 6.0 mmol) in CH_2Cl_2 (15 mL) was refluxed for 4 h, the resultant mixture was filtered off and concentration furnished crude **2ab**, which was used without further purification.

*4.2.1. Compound **2aa**.*[24] Yield: 94%, R_f=0.46 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.08–2.28 (m, 2H), 2.45 (s, 3H), 2.71–2.84 (m, 2H), 2.71–2.84 (m, 2H), 7.13–7.36 (m, 7H), 7.80 (d, *J*=8.4 Hz, 2H).

4.3. Typical procedure for the preparation of propargyl esters

To a solution of **1a** (2.28 g, 10.0 mmol), 2-furyloyl chloride (1.08 g, 11.0 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (0.024 g, 0.20 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C triethylamine (1.67 mL, 12.0 mmol) and the resultant mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with saturated NH_4Cl aq (30 mL) and extracted with CH_2Cl_2 (3×70 mL). Concentration by rotary evaporator after dried over Na_2SO_4 furnished a crude material, which was purified by silica gel column chromatography (hexane/EtOAc=12:1) to give 3.19 g (9.90 mmol) of pure propargyl tosylate **2ia** in 99% yield.

*4.3.1. Compound **2ia**.* Yield: 99%, colorless oil, R_f=0.66 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.20–2.39 (m, 2H), 2.84 (t, *J*=7.5, 2H), 5.59–5.67 (m, 1H), 6.52 (dd, *J*=3.6, 1.8 Hz, 1H), 7.20–7.30 (m, 6H), 7.63 (dd, *J*=1.8, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=30.9, 35.2, 62.2 (q, *J*=1.3 Hz), 72.8 (q, *J*=53.1 Hz), 83.9 (q, *J*=6.6 Hz), 112.0, 113.8 (q, *J*=257.4 Hz), 119.2, 126.4, 128.6, 139.6, 143.4, 147.1, 156.9; ^{19}F NMR ($CDCl_3$, 283 MHz): δ=−51.97 (s); IR (neat): 700, 760, 885, 978, 1075, 1232, 1248, 1271, 1348, 1396, 1514, 1733, 2272, 3029, 3065 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{14}F_3O_3$ $[M+H]^+$ 323.0895; found 323.0867. Anal. Calcd for $C_{17}H_{13}O_3F_3$: C, 63.36; H, 4.07; Found: C, 63.48; H, 4.46.

4.4. Typical procedure for the preparation of allenyl tosylates (3a)

To a solution of **2aa** (0.153 g, 0.40 mmol) in THF (2.4 mL) was added an aqueous 1 M NaOH solution (1.2 mL) at rt and the mixture was stirred at that temperature for 5 h. The reaction mixture was quenched with 1 M HCl aq (3 mL) and extracted with EtOAc (3×15 mL). Concentration by rotary evaporator after dried over Na_2SO_4 furnished **3aa** in an almost pure conditions. If necessary, the residue was purified by short path column chromatography (hexane/EtOAc=8:1) to give pure allenyl tosylate **3aa** in quantitative yield (0.153 g, 0.40 mmol, quantitative yield).

*4.4.1. Compound **3aa**.* Yield: quant., colorless oil, R_f=0.70 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.45 (s, 3H), 2.56–2.63 (m, 2H), 2.70–2.76 (m, 2H), 5.66 (qt, *J*=5.7, 3.0 Hz, 1H), 7.09–7.35 (m, 7H), 7.75–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.3, 31.6, 33.2, 96.2 (q, *J*=39.1 Hz), 120.5 (q, *J*=271.6 Hz), 126.2, 128.1, 128.2, 128.3, 129.8, 130.3, 132.1, 139.3, 145.7, 199.3 (q, *J*=5.6 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz): δ=−63.38 (t, *J*=6.9 Hz); IR (neat): 650, 680, 700, 745, 819, 846, 865, 940, 1033, 1071, 1087, 1128, 1145, 1181, 1195, 1214, 1271, 1376, 1418, 1437, 1454, 1496, 1598, 1737, 2928, 3030 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{19}H_{18}F_3O_3S$ $[M+H]^+$ 383.0929; found 383.0950.

4.5. Typical procedure for the preparation of 4-tosyloxyketones

To a solution of **2aa** (0.33 g, 0.40 mmol) in THF (2.1 mL) was added an aqueous 1 M NaOH aq solution (1.2 mL) at rt. The mixture was stirred at that temperature for 4 h before addition of DMF (0.3 mL). After the resulting solution was stirred for additional 1 h, the reaction mixture was quenched with 1 M HCl aq (3 mL) and extracted with hexane/EtOAc (1:3, 3×15 mL). Concentration by rotary evaporator after dried over Na_2SO_4 furnished a crude mixture, which was purified by silica gel chromatography (hexane/EtOAc=7:1) to afford **4aa** in 73% yield (0.121 g, 0.30 mmol).

*4.5.1. Compound **4aa**.* Yield: 75%, colorless oil, R_f=0.43 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.91–2.10 (m, 2H), 2.39–2.49 (m, 1H), 2.47 (s, 3H), 2.58 (ddd, *J*=14.7, 9.3, 6.0 Hz, 1H), 3.40 (dq, *J*=18.0, 9.9 Hz, 1H), 3.50 (dq, *J*=18.0, 9.9 Hz, 1H), 4.65 (dd, *J*=7.8, 5.1 Hz, 1H), 6.96–6.98 (m, 2H), 7.17–7.25 (m, 3H), 7.38 (d, *J*=8.1 Hz, 2H), 7.79 (d, *J*=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=21.7, 30.4, 32.7, 41.7 (q, *J*=29.1 Hz), 82.8 (q, *J*=1.8 Hz), 123.4 (q, *J*=276.7 Hz), 126.5, 128.1, 128.3, 128.6, 130.2, 132.1, 139.2, 146.0, 197.2 (q, *J*=2.5 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz): δ=−63.66 (t, *J*=6.9 Hz); IR (neat): 667, 700, 750, 816, 834, 930, 982, 1017, 1051, 1109, 1177, 1192, 1275, 1374, 1410, 1455, 1496, 1598, 1742, 2931, 3030 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{19}H_{20}F_3O_4S$ $[M+H]^+$ 401.1034; found 401.1028.

4.6. Typical procedure for the preparation of α-acyloxyketones

To a solution of **2ia** (0.193 g, 0.60 mmol) in THF (5 mL) were added H_2O (11.9 μL, 0.60 mmol) and DBU (98.0 μL, 0.66 mmol) at 0 °C. After the resulting solution was stirred for 3 h at that temperature, the reaction mixture was quenched with a 1 M HCl aq solution (3 mL) and extracted with EtOAc (3×15 mL). Concentration by rotary evaporator after dried over Na_2SO_4 furnished a crude mixture, which was purified by silica gel chromatography (hexane/EtOAc, 12:1) to afford **4ia** (0.178 g, 0.522 mmol, 87%).

*4.6.1. Compound **4ia**.* Yield: 87%, pale yellow oil, R_f=0.46 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=2.23 (dt, *J*=7.8, 7.5 Hz, 2H), 2.71–2.85 (m, 2H), 3.28 (dq, *J*=17.1, 9.9 Hz, 1H), 3.40 (dq, *J*=17.1, 10.2 Hz, 1H), 5.14 (t, *J*=6.6 Hz, 1H), 6.58 (dd, *J*=3.6, 1.8 Hz, 1H), 7.16–7.32 (m, 6H), 7.66–7.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=30.9, 31.4, 41.9 (q, *J*=28.7 Hz), 77.6 (q, *J*=1.8 Hz), 112.1, 119.5, 123.4 (q, *J*=276.3 Hz), 126.3, 128.3, 128.5, 139.7, 143.1, 147.3, 157.6, 197.1 (q, *J*=1.9 Hz); ^{19}F NMR ($CDCl_3$, 283 MHz): δ=−63.52 (t, *J*=10.3 Hz); IR (neat): 644, 700, 1014, 1115, 1179, 1292, 1397, 1472, 1737, 2359, 2863, 2936, 3028, 3064, 3143 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{16}F_3O_4$ $[M+H]^+$ 341.1001; found 341.1018.

4.7. Typical procedure for transformation of propargylic ethanesulfonates to the corresponding α,β-unsaturated ketones 5

To a solution of **2ba** (0.128 g, 0.40 mmol) in THF (2.4 mL) was added a 1 M NaOH aq solution (1.2 mL) at rt. After the resulting solution was stirred for 3 h, the reaction mixture was quenched with a 1 M HCl aq solution (3 mL) and extracted with EtOAc (3×15 mL). Concentration by rotary evaporator after dried over Na_2SO_4 furnished a crude mixture that was purified by silica gel chromatography (hexane/EtOAc, 12:1) to afford **5ba** (0.0768 g, 75%).

4.7.1. Compound ***5ba***. Yield: 75%, colorless oil, R_f=0.49 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.94 (d, J=7.2 Hz, 3H), 2.91–3.04 (m, 4H), 3.26 (q, J=10.8 Hz, 2H), 7.03 (q, J=7.2 Hz, 1H), 7.17–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=15.4 (q, J=1.2 Hz), 29.0 (q, J=30.4 Hz), 30.4, 38.8, 125.9 (q, J=277.2 Hz), 126.1, 128.3, 128.4, 132.6 (q, J=2.6 Hz), 141.1, 143.6, 198.3; ^{19}F NMR ($CDCl_3$, 283 MHz): δ=−65.83 (t, J=9.0 Hz); IR (neat): 700, 751, 850, 1075, 1092, 1111, 1137, 1254, 1298, 1337, 1358, 1454, 1648, 1676 cm^{-1}; HRMS (FAB): m/z calcd for $C_{14}H_{15}F_3O$ $[M]^+$ 256.1075; found 256.1059.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/0.1016/j.tet.2012.05.131.

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