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Lewis Acid-Catalyzed Rearrangement of Fluoroalkylated Propargylic Alcohols: An Alternative Approach to β-Fluoroalkyl-α,β-enones

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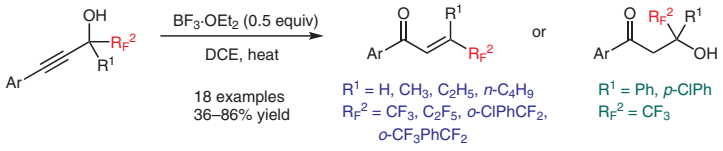

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Abstract A practical Lewis acid-catalyzed Meyer–Schuster rearrangement of fluoroalkylated propargylic alcohols, leading to a series of β-fluoroalkyl-α,β-enones, is developed. The methodology reported herein features moderate to high yields and high stereoselectivity in the synthesis of β-alkyl-β-fluoroalkyl-α,β-enones.

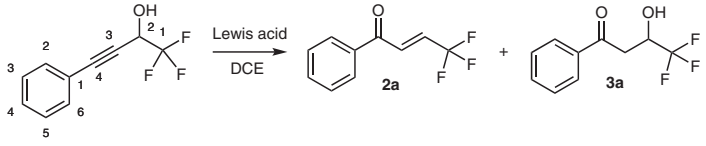
Key words Lewis acids, Meyer–Schuster rearrangement, β-trifluoromethyl-α,β-enones, metal triflates, fluorinated compounds

Fluorine and fluorinated groups are common functionalities in the field of organic and medicinal chemistry. Introduction of these structural motifs to an organic molecule significantly alters its physical and biological properties such as solubility, polarity, lipophilicity, and metabolic stability.[1] Compared with the parent compounds, fluorinated counterparts are often more suitable for practical uses in materials science, agrochemistry, and pharmaceutical industries. β-Trifluoromethyl-α,β-enones are versatile building blocks in a variety of synthetic transformations such as asymmetric Diels–Alder reactions,[2] Nazarov reactions,[3] enantioselective conjugate alkynylations,[4] phosphine-catalyzed [3+2] cycloadditions,[5] and other reactions.[6] The preparation of β-trifluoromethyl-α,β-enones has been achieved by the aldol condensation of trifluoroacetaldehyde hemiacetal or hydrate with ketone followed by an acid-mediated dehydration process.[7] Other methods describing the preparation of β-trifluoromethyl-α,β-enones include the base-promoted isomerization of 4,4,4-trifluorinated propargylic alcohols,[8] the gold-catalyzed rearrangement of CF_3-substituted propargylic carboxylates,[9] the ruthenium-catalyzed isomerization of β-trifluoromethylated secondary allylic alcohols,[10] and the Mitsunobu reagent-induced redox isomerization of CF_3-containing propargylic alcohols.[11] Meyer–Schuster rearrangement of secondary and tertiary propargylic alcohols is a straightforward method for the preparation of α,β-unsaturated carbonyl compounds.[12] The high atom economy, the easily accessible starting materials, and the high substrate tolerance are features of this method. However, synthesis of β-trifluoromethyl-α,β-enones directly from the Meyer–Schuster rearrangement of trifluoromethylated propargylic alcohols is rare. Recently, our group reported a new Lewis acid-catalyzed defluorinative cycloaddition/aromatization cascade reaction,[13] in which the difluorophenylmethylated propargylic alcohols were prone to cyclizing with nitriles but did not rearrange to α,β-enone products. Activated benzylic C–F bonds were found to be necessary for the cascade reaction. During our ongoing efforts toward an efficient methodology for preparing fluorinated compounds, we became curious as to whether the similar Lewis acid-catalyzed conditions, with minor modifications to the fluoroalkylated propargylic alcohols and solvents, could cause the rearrangement to α,β-enones. Herein, we report the Lewis acid-catalyzed rearrangement of fluoroalkylated propargylic alcohols for the synthesis of β-fluoroalkyl-α,β-enones and β-hydroxy-β-trifluoroalylated ketones.

The fluoroalkylated propargylic alcohols **1a–s** used for the present study were prepared from the reduction or nucleophilic addition of the corresponding fluorinated alkyl alkynyl ketones.[14] Thus, 1,1,1-trifluoro-4-phenylbut-3-yn-2-ol **1a** was chosen as a model compound and dichloroethane was applied as the solvent to optimize the reaction conditions. AgOTf, $InCl_3$, $Sc(OTf)_3$, and $Cu(OTf)_2$ have been demonstrated to promote the Meyer–Schuster rearrangement in a catalytic manner.[15] Initial attempts to utilize these Lewis acids to promote the title reaction were made. Other rare-earth metal triflates[16] were also examined systematically. The results are compiled in Table 1. As shown in entries 1–3, the use of one equivalent of Lewis

acids such as AgOTf, $InCl_3$, and $Cu(OTf)_2$ did not promote the rearrangement even after 12 hours of stirring at 70 °C. The reaction in the presence of one equivalent of $Sc(OTf)_3$ under identical conditions (entry 4) afforded the desired β-trifluoromethyl-α,β-enone **2a**, but the yield was only 15%. Additionally, β-hydroxy-β-trifluoromethylated ketone **3a** that could result from the 1,4-addition of H_2O to **2a** was isolated as a side product with a yield of 13%. $Bi(OTf)_3$ and $Eu(OTf)_3$ displayed slightly inferior activities to that of $Sc(OTf)_3$, affording **2a** (15–10%) and **3a** (18–12%), respectively (entries 5 and 6). Endeavors to use $Yb(OTf)_3$, $Zn(OTf)_2$, and $In(OTf)_3$ were unsuccessful. In these cases, the starting material was recovered intact or decomposed (entries 7–9). It was previously reported that the use of an ionic liquid as the solvent medium significantly enhances the reaction rate and selectivity in metal triflate-catalyzed Friedel–Crafts reactions.[17] Inspired by this previous finding, we performed the rearrangement reaction by utilizing [bmim]BF_4 or [bmim]PF_6 as the solvent. As indicated in entries 10–13, although [bmim]PF_6 enhances the activity of both $Sc(OTf)_3$ and $Bi(OTf)_3$ for the rearrangement reaction, the formation of **3a** could still not be avoided. We then turned our attention to other Lewis acids. Further screening of the reaction using $BF_3{\cdot}OEt_2$[18] gave encouraging results. The use of 1.0 equivalent of $BF_3{\cdot}OEt_2$ afforded **2a** in good yield (76%, entry 14). The yield remained high upon decreasing the loading of $BF_3{\cdot}OEt_2$ from 1.0 to 0.8 and 0.5 equivalent (entries 15 and 16). The uses of lower catalyst loading (0.2 equivalents, entry 17) or of THF (entry 18) and 1,4-dioxane (entry 19) instead of dichloroethane were examined, but a reduction in the reaction yield was obtained in all of these cases. Therefore, the reaction conditions shown in entry 16 were considered to be optimal.[19]

Table 1 Optimization of the Reaction Conditions

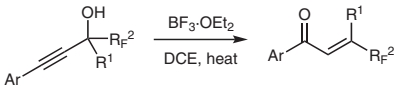


1,1,1-trifluoro-4-phenylbut-3-yn-2-ol

Entry	Lewis acid (equiv)	Temp (°C)	Time (h)	Yield (%)[a]	
				2a	**3a**
1	$InCl_3$ (1.0)	70	12	0	0
2	AgOTf (1.0)	70	12	0	0
3	$Cu(OTf)_2$ (1.0)	70	12	0	0
4	$Sc(OTf)_3$ (1.0)	70	12	15	13
5	$Eu(OTf)_3$ (1.0)	70	12	10	12
6	$Bi(OTf)_3$ (1.0)	70	12	15	18
7	$Yb(OTf)_3$ (1.0)	70	12	0	0
8	$Zn(OTf)_2$ (1.0)	70	12	0	0
9	$In(OTf)_3$ (1.0)	70	12	0	0
10	$Sc(OTf)_3$ (1.0)[b]	110	7	0	25
11	$Sc(OTf)_3$ (1.0)[c]	110	7	32	22
12	$Bi(OTf)_3$ (1.0)[b]	110	7	0	11
13	$Bi(OTf)_3$ (1.0)[c]	110	7	24	23
14	$BF_3{\cdot}OEt_2$ (1.0)	70	1.5	76	4
15	$BF_3{\cdot}OEt_2$ (0.8)	70	2	81	4
16	$BF_3{\cdot}OEt_2$ (0.5)	70	4	80	6
17	$BF_3{\cdot}OEt_2$ (0.2)	70	10	25	22
18	$BF_3{\cdot}OEt_2$ (0.5)[d]	70	3	46	22
19	$BF_3{\cdot}OEt_2$ (0.5)[e]	70	3	39	20

[a] Isolated yields after silica gel chromatography.
[b] [bmim]BF_4 was used as the solvent.
[c] [bmim]PF_6 was used as the solvent.
[d] THF was used as the solvent.
[e] 1,4-Dioxane was used as the solvent.

Table 2 $BF_3{\cdot}OEt_2$-Catalyzed Rearrangement of Fluoroalkylated Propargylic Alcohols



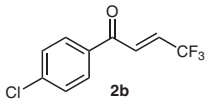
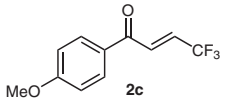
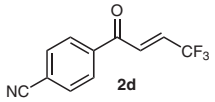
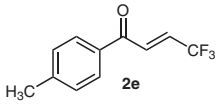
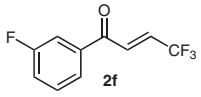
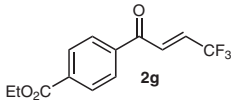
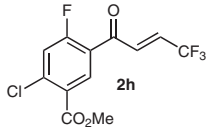
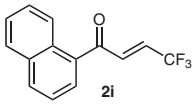
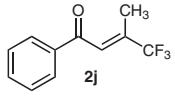
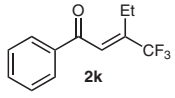
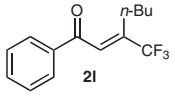
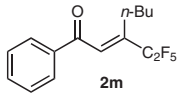
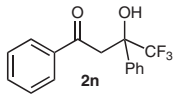
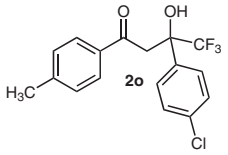
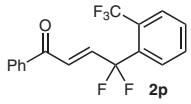
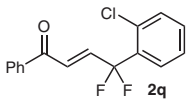
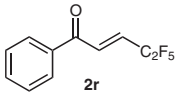
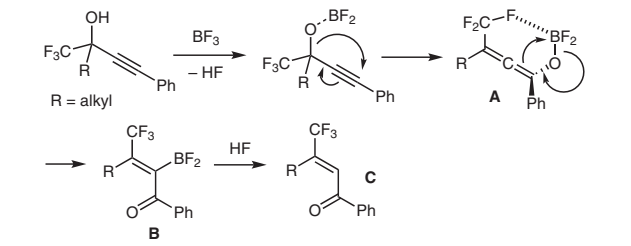
Entry	Product	Conditions	Yield (%)[a]
1	 **2b**	70 °C, 12 h	78
2	 **2c**	45 °C, 1 h	75
3	 **2d**	70 °C, 14 h	61
4	 **2e**	45 °C, 2 h	73
5	 **2f**	70 °C, 17 h	57
6	 **2g**	70 °C, 7 h	71
7	 **2h**	70 °C, 30 h	65
8	 **2i**	70 °C, 3 h	52
9	 **2j**	70 °C, 2 h	87
10	 **2k**	70 °C, 2 h	81
11	 **2l**	70 °C, 2 h	86
12	 **2m**	70 °C, 3 h	62

Table 2 (continued)

Entry	Product	Conditions	Yield (%)[a]
13	 **2n**	70 °C, 6 h	77
14	 **2o**	70 °C, 6 h	74
15	 **2p**	45 °C, 2 h	36
16	 **2q**	45 °C, 2 h	43
17	 **2r**	70 °C, 3 h	75

[a] Isolated yields after silica gel chromatography.

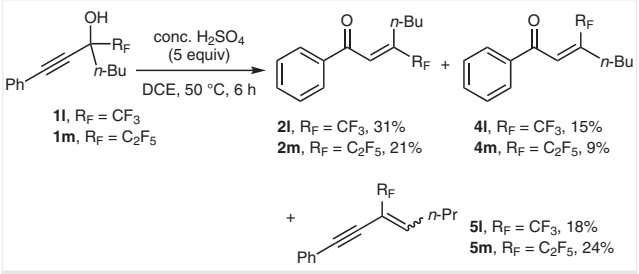
The generality of this $BF_3{\cdot}OEt_2$-catalyzed rearrangement was next examined by using a series of fluoroalkylated propargylic alcohols. As illustrated in Table 2, the reaction of secondary alcohols bearing either electron-withdrawing (–F, –Cl, –CN, and $–CO_2Et$) or electron-donating functional groups ($–CH_3$ and $–OCH_3$) on the phenyl ring proceeded to give the thermodynamically more stable (*E*)-products **2b–g** in moderate to good yields (57–78%, entries 1–6). Notably, an electron-donating group on the phenyl ring accelerated the present reaction, whereas an electron-withdrawing group slowed the reaction down. The electronic effects were validated again by the reaction of a more electron-deficient substrate **1h**. In this case (entry 7), a prolonged reaction time was required to attain full conversion of the starting material. The reaction with use of a substrate bearing a sterically demanding 1-naphthyl group yielded **2i** in 52% yield (entry 8). For trifluoromethylated tertiary alcohols with an alkyl group at the tetrasubstituted carbon center, the reaction provided the desired products **2j–l** in high yield (81–87%, entries 9–11) and stereoselectivity. Excellent stereoselectivity was also observed in the formation of β-pentafluoroethyl-α,β-enone **2m** (entry 12). We speculated that the stereocontrol could stem from an intramolecular interaction between boron and the fluorinated alkyl group in the boron allenolate intermediate **A**, facilitating the allenol–enone tautomerism to form (*E*)-intermediate **B**, followed by protonation to provide the final (*E*)-product **C** exclusively (Scheme 1).[21]



Scheme 1 Proposed mechanism for the exclusive formation of (*E*)-product **C**

However, in the cases of a tertiary alcohol substituted with a phenyl (entry 13) or 4-chlorophenyl group (entry 14) at the tetrasubstituted carbon center, the corresponding β-hydroxy ketones **2n** and **2o** were produced instead of the expected enone products. Other structurally diverse substrates, such as diflurophenylmethylated and pentafluoroalkylated alcohols (entries 15–17), were subjected to the BF_3·OEt_2-catalyzed reaction conditions and furnished the corresponding α,β-enones **2p–r** in moderate to good yields (36–75%). The inferior yields for **2p** and **2q** could be ascribed to the instability of the benzylic fluoride moiety under the BF_3·OEt_2-catalyzed conditions. Otherwise, the reaction was limited to aryl-substituted propargylic alcohols and failure was observed in the case of alcohol **1s** that has an *n*-butyl group at the acetylenic position.[22]

To confirm that the stereoselectivity of our method is superior to conventional methods,[23] we performed the rearrangement of **1l–m** by using an access amount of concentrated H_2SO_4. As shown in Scheme 2, the reactions provide the *E*/*Z*-isomer and a significant amount of dehydration product **5**.



Scheme 2 Sulfuric acid-induced rearrangement reaction of **1l** and **1m**

In conclusion, we have developed a new and practical procedure for the synthesis of β-fluoroalkyl-α,β-enones[24] by using the BF_3·OEt_2-catalyzed Meyer–Schuster reaction. The protocol is highly stereoselective for the conversion of trifluoroalkylated tertiary allylic alcohols into (*E*)-β-alkyl-β-fluoroalkyl-α,β-enones. We envision that the methods disclosed herein will find practical applications in the synthesis of structurally complex β-fluoroalkyl enones that are of importance in synthetic chemistry.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611694.

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(18) For BF_3·OEt_2-mediated *syn*-selective Meyer–Schuster reaction, see: Puri, S.; Babu, M. H.; Reddy, M. S. *Org. Biomol. Chem.* **2016**, *14*, 7001.

(19) **General Procedure for the Synthesis of Compounds 2a–r**

The general procedure is illustrated immediately below with compound **2a** as a specific example.

A stirred solution of compound **1a** (100 mg, 0.50 mmol) and BF_3·OEt_2 (36 mg, 0.25 mmol) in dichloroethane (2 mL) was heated at 70 °C under nitrogen for 4 h. Then, water (2 mL) and saturated Na_2CO_3 solution (1 mL) were added to quench the reaction at 0 °C. The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were washed with brine, dried with $MgSO_4$, filtered, and concentrated to give the crude residue, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:19) to afford compound **2a** (80 mg, 80% yield) as a yellow oil and compound **3a** (5 mg, 4% yield) as colorless oil.

(*E*)-4,4,4-Trifluoro-1-phenylbut-2-en-1-one (2a)

The spectroscopic data were in good agreement with the literature data.[12b]

Colorless oil; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, *J* = 8.5 Hz, 2 H), 7.69–7.65 (m, 1 H), 7.58–7.54 (m, 3 H), 6.85 (dq, *J* = 15.5, 6.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 188.0, 136.1, 134.1, 131.0, 130.3 (q, *J* = 35.0 Hz), 129.0, 128.3, 122.5 (q, *J* = 268.7 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz): δ –65.1; HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_8F_3O$: 201.0527; found: 201.0525.

4,4,4-Trifluoro-3-hydroxy-1-phenylbutan-1-one (3a)

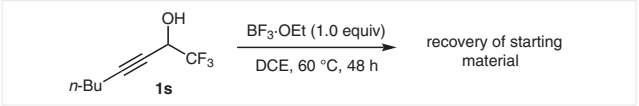
The spectroscopic data were in good agreement with the literature data.[20]

White solid; mp = 76.0–77.0 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95–7.93 (m, 2 H), 7.62–7.58 (m, 1 H), 7.49–7.46 (m, 2 H), 4.69–4.65 (m, 1 H), 3.56–3.55 (m, 1 H), 3.39–3.26 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 197.5, 136.0, 134.1, 128.8, 128.4, 124.7 (q, *J* = 277.0 Hz), 67.0 (q, *J* = 32.5 Hz), 38.2; ^{19}F NMR ($CDCl_3$, 470 MHz): δ –79.2.

(20) Xiong, H. Y.; Yang, Z. Y.; Chen, Z.; Zeng, J. L.; Nie, J.; Ma, J. A. *Chem. Eur. J.* **2014**, *20*, 8325.

(21) A similar mechanism in *syn*-selective Meyer–Schuster rearrangement, mediated by BF_3·OEt_2, was reported. See reference 18.

(22) As shown below, the BF_3·OEt_2-catalyzed reaction of **1s** did not proceed and only the starting substrate was recovered.



Scheme 3

(23) For Brønsted acid-promoted Meyer–Schuster reactions, see (a) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429. (b) Crich, D.; Natarajan, S.; Crich, J. Z. *Tetrahedron* **1997**, *53*, 7139. (c) Park, J.; Yun, J.; Kim, J.; Jang, D.-J.; Park, C. H. *Synth. Commun.* **2014**, *44*, 1924.

(24) All of the synthetic β-fluoroalkyl-α,β-enones were characterized according to their ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and mass spectra. The stereochemistry of (*E*)-β-alkyl-β-fluoroalkyl-α,β-enones was unequivocally determined by comparing their NMR spectra to those of structurally identical or similar compounds.