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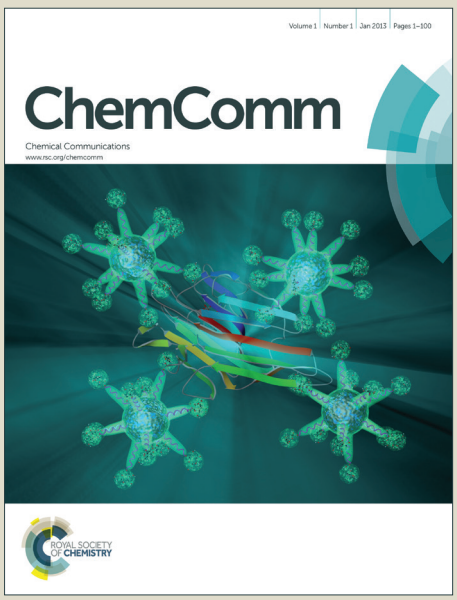

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A rapid and selective synthesis of α,α-fluorohalo esters via fluorohalogenative or difluorinative hydration of ynol ethers

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A Selectfluor-mediated fluorohalogenative or difluorinative hydration of ynol ethers is described, giving various α,α-fluorohalo esters including α,α-bromofluoro, α,α-chlorofluoro, α,α-fluoroiodo, and α,α-difluoro derivatives in a highly selective manner under very mild reaction conditions. The resultant products can be applied to the facile synthesis of α-monofluoro-α-amino acids. This reaction represents a new advance in the trifunctionalization of alkynes.

Due to the unique physical, chemical, and biological properties, fluorinated compounds have attracted increasing attention in the areas of biomedicine, agriculture, and material science.[1] In this respect, α,α-fluorohalo carbonyl compounds, such as α,α-bromofluoro and α,α-chlorofluoro ones, have found wide applications including the enantiomeric analysis of chiral alcohols,[2] biological isosteres of *gem*-difluoromethylene motifs,[3] and valuable starting materials or intermediates for the synthesis of molecules with a fluorinated tertiary or quaternary carbon center.[4] Surprisingly, few methods exist regarding the synthesis of these scaffolds.[5] The traditional method usually relies on the iterative α-halogenation of carbonyl moieties (Scheme 1).[5a-5d] Although the one-pot procedure can be realized in the case of activated methylene compounds like β-ketoesters, the transformation of non-activated methylenes often involves stepwise process, as exemplified by an effective construction of α,α-chlorofluoro ketones and aldehydes by Shibatomi and Yamamoto.[5b] In contrast, the invention of a straightforward as well as general method for the preparation of α,α-fluorohalo esters from readily accessible starting materials is much more challenging and remains to be explored.

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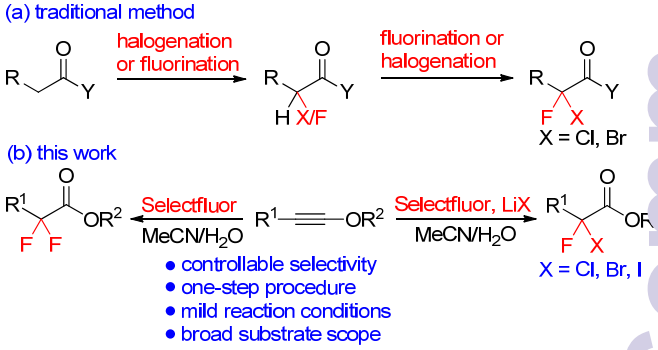
As part of our continuing interest on ynol ethers,[6,7] we describ here a novel, expedient, and highly selective method for th generation of α,α-fluorohalo esters, including α,α-bromofluor α,α-chlorofluoro, and α,α-fluoroiodo derivatives, via a unprecedented Selectfluor[8]-mediated fluorohalogenative hydration of ynol ethers featuring the use of environmentally friendly lithiu halides (LiX) as halogen sources. In this reaction, three different functional groups, namely F, X (X = Cl, Br, or I), and OH groups, ac to the C-C triple bonds of ynol ethers in a fully regiocontrolled manner, which constitutes one of the rare examples on th trifunctionalization of alkynes.[9] Meanwhile, in the absence of LiX, a difluorinative hydration of ynol ethers has also been realized, givi α,α-difluoro esters in moderate to excellent yields under very mild reaction conditions, which represents a new advance in th difluorination of monocarbonyl compounds.[10]

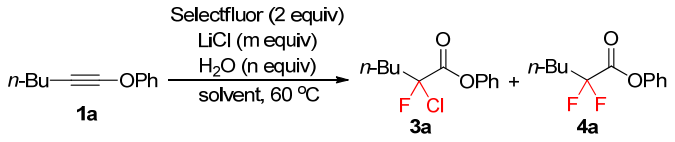


Scheme 1 Synthesis of α,α-fluorohalo carbonyl compounds.

Our investigations began by the treatment of ynol ether **1a** with 2 equiv of Selectfluor, 2 equiv of LiCl, and 1 equiv of H_2O in MeCN at 60 °C. As a result, the α,α-chlorofluoro ester **3a** was obtained in 27% yield, together with the formation of 11% yield of the difluorinated adduct **4a** (Table 1, entry 1). Increasing the amounts of H_2O to 20 equiv appeared to be beneficial, providing **3a** in 75% yield (entries 2-4). On other hand, decreasing the amounts of LiCl to

1.2 equiv stood out to be the most suitable for the selective chlorofluorinative hydration, which delivered **3a** in 87% yield (entries 5 and 6). In contrast, no reaction ocurred when Selectfluor was replaced by either *N*-fluorobenzenesulphonimide (NSFI) or 1-fluoropyridinium tetrafluoroborate (entries 7 and 8). Furthermore, a variety of solvents such as dioxane, CH_2Cl_2, DMSO, and DMF were examined, and they were found to be much less effective than MeCN (entries 9-12).

Table 1. Screening of the reaction conditions[a]



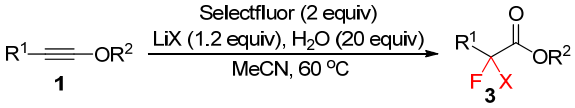
Entry	m	n	Solvent	Yield of **3a** (%)[b]	Yield of **4a** (%)[b]
1	2.0	1	MeCN	27	11
2	2.0	5	MeCN	48	11
3	2.0	20	MeCN	75	6
4	2.0	200	MeCN	63	trace
5	1.5	20	MeCN	82	7
6	1.2	20	MeCN	87	trace
7[c]	1.2	20	MeCN	trace	trace
8[d]	1.2	20	MeCN	trace	trace
9	1.2	20	dioxane	trace	trace
10	1.2	20	CH_2Cl_2	trace	trace
11	1.2	20	DMSO	20	trace
12	1.2	20	DMF	24	trace

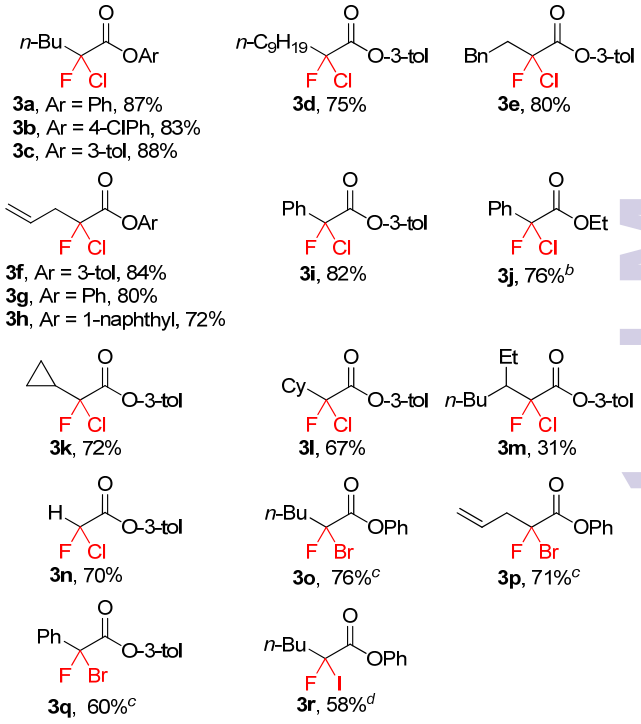
[a] Reaction conditions: **1a** (0.25 mmol), Selectfluor (2 equiv), LiCl (m equiv), H_2O (n equiv), solvent (4 mL), 60 °C, 5 h. [b] Isolated yield. [c] NFSI was used instead of Selectfluor. [d] 1-Fluoropyridinium tetrafluoroborate was used instead of Selectfluor. DMSO = Dimethylsulfoxide. DMF = *N*,*N*-Dimethylformamide.

With the optimized reaction conditions in hand, we then explored the scope and limitations of this Selectfluor-mediated fluorohalogenative hydration of ynol ethers. As shown in Table 2, a wide range of α,α-chlorofluoro esters could be synthesized via this protocol. Specifically, the R^2 group of **1** had little impact on this reaction, as shown by the production of **3a**-**3c**. The reaction of ynol ether **1e** afforded α,α-chlorofluoro product **3e** in 80% yield. Remarkably, substrates **1f**-**1h**, possessing a terminal C-C double bond, underwent the transformation smoothly to form **3f**-**3h** in high yields, although alkenes usually exhibit higher reactivity than alkynes toward the electrophilic halogenation. We believe that the donation of electrons from the etheric oxygen atom to C-C triple bond of **1** may account for the reversed chemoselectivity.[7]

This reaction was well applicable to aryl ynol ethers such as **1i** and **1j**, leading to **3i** and **3j** in promising yields. The reaction of **1k**, with a cyclopropane substituent, provided α,α-chlorofluoro ester **3k** in 72% yield, indicating that the radical mechanism is less likely. Increasing the steric hindrance of R^1 group resulted in reduced yields, as demonstrated by the reaction of **1l** and **1m** (**3l** and **3m**). Pleasingly, terminal ynol ether **1n** was also an effective substrate for this reaction, giving rise to **3n** in a satisfactory yield. Besides α,α-chlorofluoro esters, α,α-bromofluoro and α,α-fluoroiodo analogues could also be assembled. Using LiBr instead of LiCl, the reaction of **1a** generated α,α-bromofluoro ester **3o** in 76% yield. Likewise, the selective formation of α,α-fluoroiodo ester **3r** was achieved with the use of LiI, albeit at an elevated reaction temperature (100 °C).

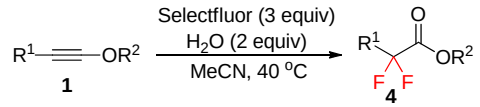
Table 2. Scope of fluorohalogenative hydration of ynol ethers[a]

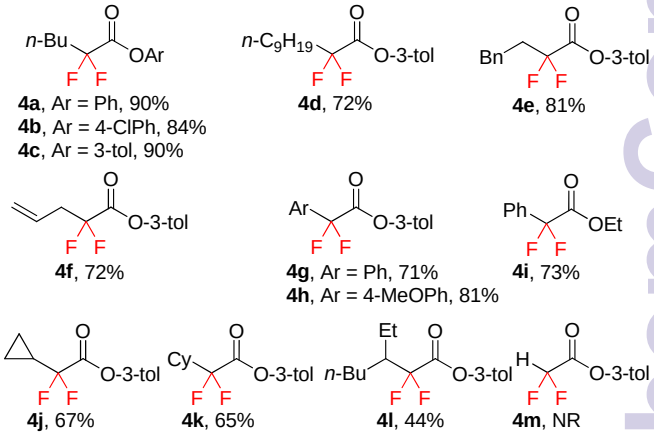




[a] Reaction conditions: **1** (0.25 mmol), Selectfluor (2 equiv), LiX (1.2 equiv), H_2O (20 equiv), MeCN (4 mL), 60 °C, 5 h; yields refer to the isolated yields. [b] A mixture of MeCN/DMAC (v/v = 3:1) was used instead of MeCN. [c] Run at 80 °C. [d] Run at 10 °C. DMAC = Dimethylacetamide.

Table 3. Scope of the difluorinative hydration of ynol ethers[a]

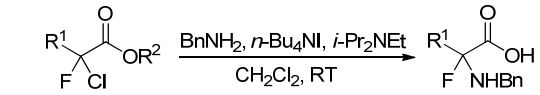




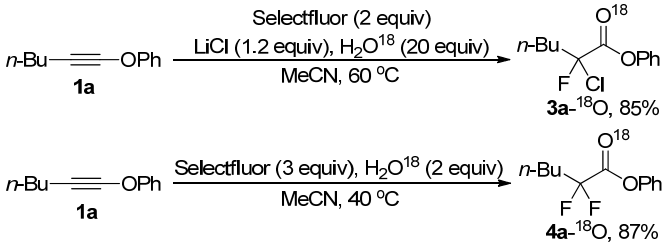
[a] Reaction conditions: **1** (0.25 mmol), Selectfluor (3 equiv), H_2O (2 equiv), MeCN (2 mL), 40 °C, 8 h; yields refer to isolated yields.

Subsequently, we explored the Selectfluor-mediated difluorinative hydration of ynol ethers. After some trials, the optimal reaction conditions for exclusive production of **4a** consisted of 3 equiv of Selectfluor and 2 equiv of H_2O in MeCN at 40 °C for 8 h. We were delighted to find that this protocol is quite general and a wide selection of ynol ethers underwent this reaction smoothly to form α,α-difluoro esters **4** in moderate to excellent yields. For instance, ynol ether **1c** was efficiently converted into **4c** in an excellent yield. Similarly, the terminal alkene was intact under the reaction conditions (**4f**). In the case of sterically demanding substrates **1k**-**1m**, relatively lower yields were observed (**4j**-**4l**). To our surprise, terminal ynol ether **1n** was not amenable to this difluorinative hydration reaction. The detailed reason is unclear at current stage.

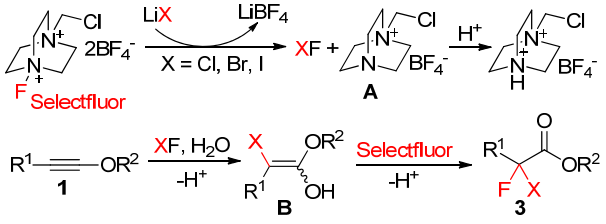
The synthetic utility of this reaction was then investigated. By treating **3e** with benzylamine in the presence of ethyldiisopropylamine and tetrabutylammonium iodide in CH_2Cl_2 at room temperature for 10 h, α-monofluorinated-α-amino acid **5a** was generated in 81% yield (Scheme 2). Compound **5b** was also synthesized from α,α-chlorofluoro ester **3g** without erosion of the yield. As such, we have developed an operationally simple and highly efficient method for the synthesis of fluorinated α-amino acids, an important class of building blocks in medicinal and biochemistry.[11]



Scheme 2 Synthetic usefulness of this protocol.



Scheme 3 Preliminary studies on the reaction mechanism.



Scheme 4 A possible mechanism.

To gain some insights into the reaction mechanism, the chlorofluorinative hydration of **1a** was conducted in the presence of H_2O^{18}, leading to the formation of **3a**-^{18}O as the sole product in 85% yield (Scheme 3). Similarly, **4a**-^{18}O was obtained by replacing H_2O with H_2O^{18} under the difluorinative hydration conditions. These results indicated that H_2O participated in this reaction and the carbonyl oxygen atom of **3** or **4** originated from H_2O. Therefore, a possible mechanism for the Selectfluor-mediated fluorohalogenative hydration of ynol ethers is proposed in Scheme 4. Initially, an active halogenation reagent XF is generated via the oxidation of LiX by Selectfluor in MeCN.[12] Then, in the presence of H_2O, a halohydration of **1** takes place to afford an intermediate **B** followed by electrophilic fluorination with Selectfluor as the fluorinating reagent to produce α,α-fluorohalo esters with the concurrent release of a proton. It should be noted that, in this reaction, the roles of Selectfluor are multifold: (1) an oxidant for the oxidation of LiX to give XF; (2) a good electrophilic fluorinating reagent; (3) a precursor for the formation of monocation salt which may suppress the unfavorable hydrolysis of ynol ethers via neutralizing the proton generated in situ.

In summary, we have demonstrated a mild, concise, and highly selective method for the preparation of α,α-fluorohalo esters, including α,α-bromofluoro, α,α-chlorofluoro, α,α-fluoroiodo, and α,α-difluoro derivatives, via a Selectfluor-mediated fluorohalogenative or difluorinative hydration of ynol ethers. It represents a significant advance in the selective trifunctionalization of C-C triple bonds. Furthermore, the resulting products can be utilized for the elaboration of fluorinated α-amino acids, which may be valuable for organic and medicinal chemistry. Further investigations on the synthetic application of this method are currently underway.

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