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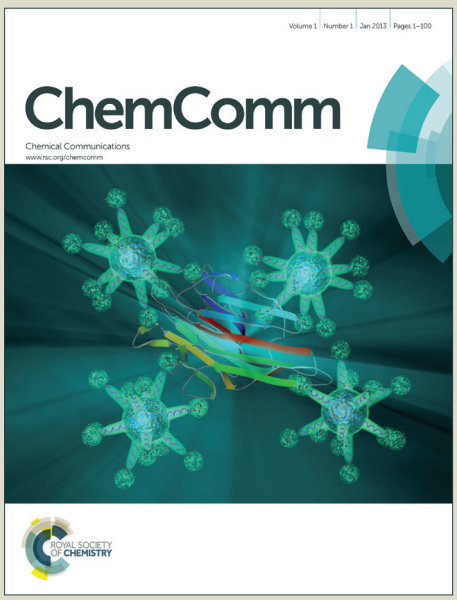

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ARTICLE TYPE

An Efficient Regioselective Hydrodifluoromethylation of Unactivated Alkenes with $TMSCF_2CO_2Et$ at Ambient Temperature

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A mild, versatile and efficient method for the regioselective hydrodifluoromethylation of unactivated alkenes has been developed. This Ag-mediated Csp^3-CF_2 bond forming reaction allows an easy access to a variety of vicinal α-difluoroacetate-containing alkanes.

Owing to the unique properties of the difluoromethylene group (CF_2), which can function as a bioisostere for mimicing the steric and electronic features of an oxygen atom or a carbonyl group, the incorporation of functionalized difluoromethylene groups in small molecules has a profound impact on the pharmaceutical, agrochemicals[1] It has been of great synthetic interest to develop efficient methods for the introduction of difluoromethylated group into diverse organic structures.

The transition-metal-mediated or catalyzed fluoroalkylation for the construction of Csp^2-CF_3 [2,3] or Csp^2-CF_2 [4-6] bonds have been intensively documented. The past three years has witnessed rapid advances in copper or palladium-catalyzed trifluoromethylation reactions for the construction of Csp^3-CF_3 bonds from alkenes.[7] Very recently, groups led by Qing, Buchwald, and Nicewicz developed Ag(I)-catalyzed, a visible-light-mediated, or metal-free hydrotrifluoromethylation of unactivated olefins in order to build Csp^3-CF_3 bonds.[8] These synthetic strategies provide a novel protocol for the construction of a vicinal Csp^3-CF_3 bond in a wider range of molecular context. In contrast to the significant achievements that have been made in the trifluoromethylation studies, the transition-metal-mediated hydrodifluoroalkylation to construct Csp^3-CF_2 bonds is still underdeveloped, because of the unstability of difluoroalkyl intermediates.

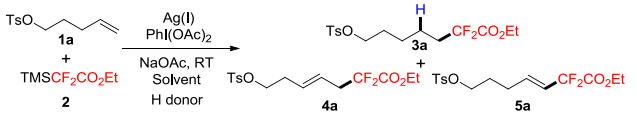
Among the reported functionalized difluoro moieties, the ethoxycarbonyldifluoromethyl (CF_2COOEt) moiety is extremely appealing due to the huge possibility of postfunctionalization.[9] For instance, Burton developed nickel catalytic reaction of alkenes with iododifluoroacetates to afford α-difluoroesters.[10a] Fuchigami described a photoinitated S-CF_2 bond cleavage in presence of olefins to provide regioselective addition products.[10b] Ryu demonstrated a reductive bromine atom-transfer reaction of alkenes with bromodifluoroacetate through photoirradiation to give hydroalkylation products of alkenes.[10c] Despite significant advances in the construction of Csp^3-CF_2COOEt, the difluoromethylation process still remains challenging, and only a handful of examples have been developed so far.[11]

Recently, the radical aromatic difluoromethylation through the copper-catalyzed cross-coupling reaction of aryl iodides with α-silyldifluoroacetates ($TMSCF_2COOEt$) described by Amii [12a] and a silver-mediated aromatic C-H difluoromethylation with α-silyldifluoroacetates reported by Brase,[12b] respectively, paved the way for the novel construction of Csp^2-CF_2COOEt in aromatic rings. It was reasonably envisioned that the novel construction of Csp^3-CF_2 could be considerably expanded if a difluoromethyl radical generated by the α-silyldifluoroacetates could undergo a hydrodifluoromethylation type addition on alkenes. Herein, we report the development of a net regioselective addition of H-CF_2COOEt onto unactivated alkenes. $TMSCF_2COOEt$ works as an efficient (ethoxycarbonyl) difluoromethylating reagent and Hanztsch ester as a useful hydrogen donor in this reductive intermolecular hydrodifluoromethylation. This operationally simple protocol can be readily applied to the introduction of a terminal CF_2COOEt group to a broad range of simple and complex alkenes under very mild reaction conditions. More interestingly, the incorporation of the terminal difluoroacetate group to alkenes in this reaction provides an easy access for further chemical modification of these fluorine-containing compounds, which overcomes the drawbacks of the recently reported trifluoromethylation on terminal alkenes.

We initially examined the reaction of compound **1a** with $TMSCF_2COOEt$ in presence of $AgNO_3$ or $PhI(OAc)_2$ as an oxidant, respectively, and NaOAc as a base in DMF at ambient temperature (Table 1, and see Table S1, S2 in ESI for the screening of oxidants and bases). Unfortunately, this reaction did not work under this condition. Pleasingly, a mixture of hydro-difluoromethylated compound **3a** as the major product, with the deprotonated α-difluoromethylated side products of **4a** and **5a**, was afforded, when the combination of 1 equiv of $AgNO_3$ and 2.0 equiv of $PhI(OAc)_2$ as an co-oxidant, and 3.0 equiv of NaOAc as a base was applied (entry 2). Increasing the loading of $AgNO_3$ to 2.5 equiv provided the desired product **3a** with 47% yield (entry 3). In order to improve the efficiency of the hydrodifluoromethylation, a H-donor was used to suppress the difluoromethylated alkenes in this reaction. To our delight, the addition of Et_3SiH (1.0 equiv) and 1,4-cyclohexadiene (1.0 equiv) in this reaction remarkably increased the yield of the α-adduct product (entries 4, 5), while Hantzsch ester (1.0 equiv) provided the yield of the desired product up to 72% (entry 6). The use of solvents, such as MeOH, THF, DCE, DMPU, did not give acceptable results (entries 7-10). However, the reaction could proceed smoothly in polar solvents of CH_3CN, DMSO and NMP, while NMP proved to be the best (entries 11-13). Finally, a

variety of silver(I) salts were further evaluated (entries 14-19) and AgOTf was found to work more efficiently to afford the desired product in 86% yield (entry 20).

Table 1 Optimization of hydrodifluoromethylation of alkenes [a]

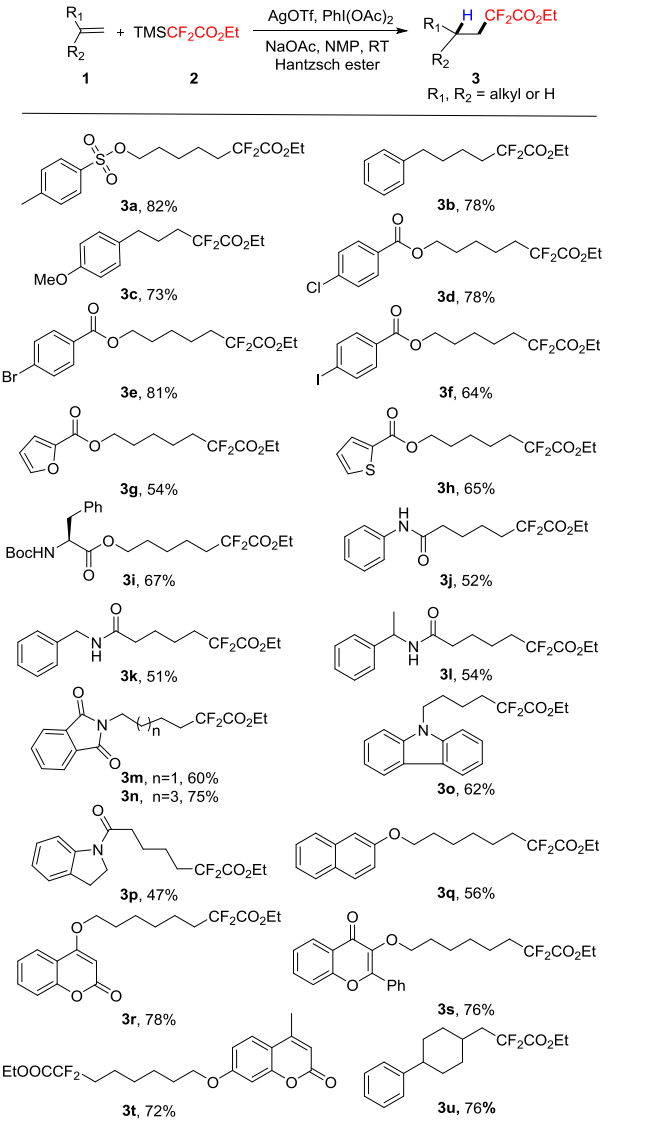


Entry	Ag salts	H Donor	$PhI(OAc)_2$	Solvent	Yield (%) [b]		
					3a	**4a**	**5a**
1	20% $AgNO_3$	/	2 eq.	DMF	1	--	1
2	100% $AgNO_3$	/	2 eq.	DMF	25	--	1
3	250% $AgNO_3$	/	2 eq.	DMF	47	3	2
4	250% $AgNO_3$	I	2 eq.	DMF	67	7	trace
5	250% $AgNO_3$	II	2 eq.	DMF	56	3	1
6	250% $AgNO_3$	III	2 eq.	DMF	72	8	2
7	250% $AgNO_3$	III	2 eq.	THF	3	--	--
8	250% $AgNO_3$	III	2 eq.	DMPU	11	--	3
9	250% $AgNO_3$	III	2 eq.	CH_3OH	--	--	--
10	250% $AgNO_3$	III	2 eq.	DCE	--	--	--
11	250% $AgNO_3$	III	2 eq.	CH_3CN	54	4	2
12	250% $AgNO_3$	III	2 eq.	DMSO	70	5	3
13	250% $AgNO_3$	III	2 eq.	NMP	79	8	5
14	250% AgOAc	III	2 eq.	NMP	34	6	3
15	250% Ag_2CO_3	III	2 eq.	NMP	--	--	--
16	250% Ag_2O	III	2 eq.	NMP	3	--	trace
17	250% AgF	III	2 eq.	NMP	12	--	trace
18	250% $AgBF_4$	III	2 eq.	NMP	68	8	4
19	250% $AgSbF_6$	III	2 eq.	NMP	80	3	1
20	250% AgOTf	III	2 eq.	NMP	86	7	3
21	250% AgOTf	III	2 eq.	NMP	--	--	--
22	0% AgOTf	III	2 eq.	NMP	--	--	--

[a] Reaction condition: **1a** (0.3 mmol), **2** (1.5 mmol, 5 eq.), NaOAc (0.9 mmol), 12h, N_2 atmosphere; [b] Determined by ^{19}F NMR spectroscopy; H donor (0.3 mmol): I = triethylsilane, II =1,4-cyclohexadiene, III = Hantzsch ester.

With the optimized protocol in hand, we examined the range of unactivated terminal monosubstituted alkenes that are capable of undergoing silver(I)-mediated hydrodifluoromethylation with $TMSCF_2COOEt$ (Table 2). The reactions afford highly regioselective products with the formation of hydrodifluoromethylation on the unactivated alkene in good to high yields. In all of the reactions, the hydrodifluoromethylated compounds **3** (i.e. **3a**-**3u**) are found to constitute the major product, whereas compound **4** and **5** are afforded as the side products with very low yields. In addition, the mild reaction condition in hydrodifluoromethylation on alkenes is found to allow high tolerance on a wide range of substrates and functional groups, including ester, sulfonic ester, ether, amide, imide, (hetero) arene, ketone, protected amine. Moreover, arene rings containing chloro, bromo or iodo substituents, which are prominent leaving groups in a variety of transition-metal catalyzed cross-coupling reactions, are compatible with the reaction in good yields within the range of 64-81% (**3d**, **3e**, **3f**). Terminal alkenes derived from coumarin **1r**, 3-hydroxyflavone **1s** and 4-methyl-umbelliferone **1t**, which contains two unequivalent alkenyl groups, showed excellent chemoselectivity to afford the hydrodifluoromethylation on the vicinal alkenyl group. To expand the scope of the method, disubstituted alkene was tested under the same reaction conditions. 1,1-disubstituted alkene **1u** was smoothly converted to the desired product **3u** in 76% yield.

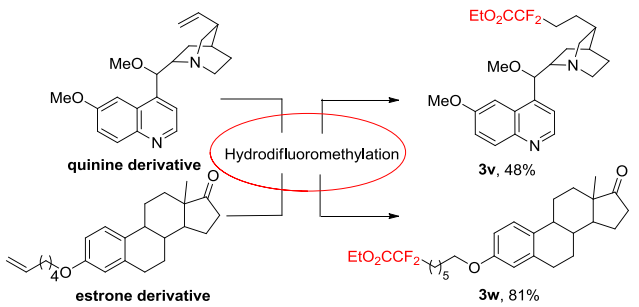
Table 2 Scope of regioselective hydrodifluoromethylation of terminal alkenes [a]



[a] Isolated yields.

Late-stage modification of drug candidates is valuable for structure-activity relationship studies, since the complex target molecules are more challenging to obtain. The protocol in this work offers the possibility of late-stage functionalization of biologically active compounds that contain an alkenyl group (Scheme 1). For example, quinine derivative, which has been used as an effective antimalarial drug, was smoothly converted to its difluoromethylated product **3v** (48% yield). Also, estrone derivative was transferred to the desired product **3w** (81% yield). It should be pointed out is that the versatile functionalization of the terminal ester in the above synthesized biologically active compounds could be readily realized, making it possible for the incorporation of another pharmacophore into one molecule. Thus, novel identical or non-identical twin drugs linked by the unusual difluoromethylene group are anticipated to show two different pharmacological activities stemming from the individual pharmacophores (dual action).[13] In addition, enhanced potent or

selective pharmacological effects could also be expected.



Scheme 1. Hydroddifluoromethylation of biologically active compounds.

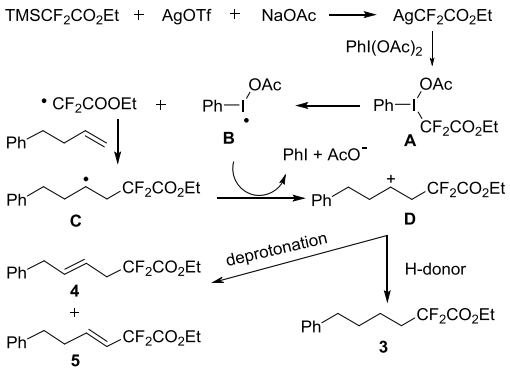
To figure out whether the in suit generated (ethoxycarbonyl)difluoromethyl radical species (·CF_2COOEt) would be involved in the reaction, we conducted the inhibition experiment of alkene **1b** with the addition of the known radical scavenger of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy, 1.0 equiv) under the standard reaction condition (see Supporting Information). The TEMPO-CF_2COOEt was afforded in 76% yield with greatly suppressed formation of the desired product **3b**. Furthermore, addition of the radical inhibitor hydroquinone or the ET scavenger 1,4-dinitrobenzene to the reaction mixture led to a significant decrease of the reaction efficiency. These results suggested that a CF_2COOEt radical species would act as an important role in the current reaction condition.

To obtain some information on the reaction pathway, we investigated the reaction of **1b** with AgOTf or $PhI(OAc)_2$ as oxidant, respectively, in presence of $Me_3SiCF_2CO_2Et$ and NaOAc (Table 1, entry 21, 22, and see ESI). The control experiments authenticated the importance of the combination of both of AgOTf and $PhI(OAc)_2$. The possible formation of CF_2COOEt radical species generated independently from oxidative AgOTf or $PhI(OAc)_2$, respectively, was ruled out.

In regard to the reaction mechanism through a probable radical process, we conducted the reaction by replacing the solvent of NMP with DMSO-d_6 in the absence of H-donor (see ESI). DMSO is known to have the ability to generate the methylsulfinic methyl radical $CH_3S(=O)CH_2$· via abstraction of a methyl hydrogen atom by an active radical, such as HO·, Cl·, R_{alkyl}·, etc.[14] To our surprise, we did not observe any incorporation of deuterium information in the hydrodifluoromethylation product.

Despite the successful capture of ·CF_2COOEt by TEMPO, the high selectivity for the formation of α-difluoroacetate alkane over that of the α-difluoroacetate alkenes in this reaction suggested that a possible hydrogen abstraction of an alkyl cation intermediate from the Hanztsch ester may be the major route involved in the reaction.

Thus, the collective mechanistic evidence, including the control experiments, suggested the critical roles of ·CF_2COOEt radical and subsequently formed alkyl cation in this reaction. Based on these results, we proposed a working hypothesis for the reaction mechanism, as illustrated in Scheme 2. A pathway of one-electron oxidation of the radical intermediate by oxidative hypervalent iodine was reasonable in the hydrodifluoromethylation process. Firstly, the ·CF_2COOEt radical intermediate is generated by the combination of Ag(I) and $PhI(OAc)_2$. Subsequent addition of the ·CF_2COOEt radical intermediate onto the C=C bond of the vicinal alkene affords the alkyl radical **C**. The alkyl radical **C** will be rapidly oxidized to an alkyl cation **D** by the oxidative hypervalent iodine centered radical **B**. The generated cation intermediate **D** undergoes an abstraction from the known H-donor, such Hantzsch ester, providing the main α-difluoromethylated alkane **3**. Deprotonation of the alkyl cation **D** gives the side products of α-difluoromethylated alkenes **4** and **5**.



Scheme 2. Proposed reaction mechanism.

In summary, we have described a mild and efficient procedure of silver-mediated hydrodifluoromethylation of diverse unactivated alkenes. This reaction affords a practical instance of hydro-(ethoxycarbonyl)difluoromethylation on the vicinal C=C bond to construct the Csp^3-CF_2 bond in molecules. The primary mechanistic investigations suggest that a CF_2COOEt radical species is involved, followed by a one-electron oxidation to afford an alkyl cation intermediate, in the current transformation. Ongoing studies in our group are focused on probing the mechanism and developing related Ag-catalyzed difluoroalkylation reactions.

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Notes and references

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