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Silver-Catalyzed Decarboxylative Alkylfluorination of Alkenes

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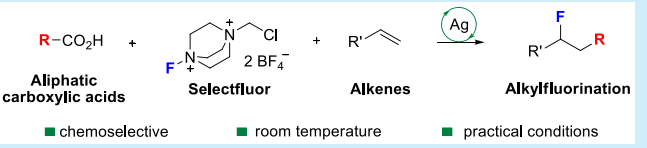
Supporting Information

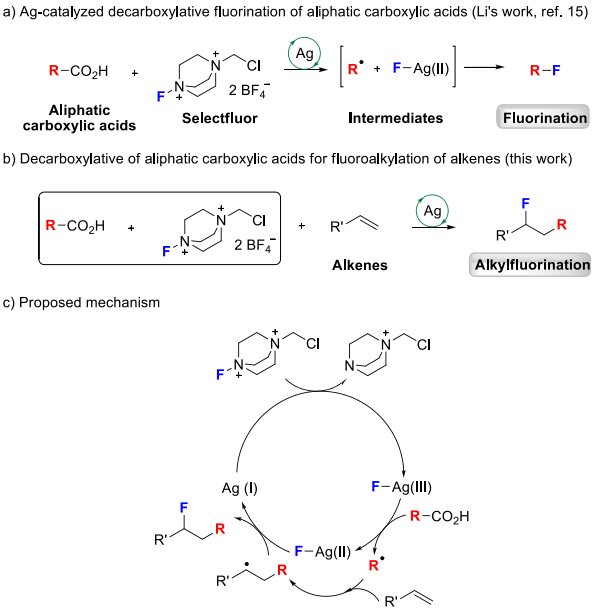
ABSTRACT: A decarboxylation of alkyl carboxylic acids for alkylfluorination of alkene was developed, with the catalysis of silver(I) and Selectfluor as both the oxidant and fluorine source. This reaction is highly chemoselective, producing the decarboxylative alkylfluorination products rather than the competitive fluorination of aliphatic carboxylic acids. This practical transformation proceeds efficiently in aqueous media at room temperature and exhibits a large range of functional-group tolerance in various primary and secondary aliphatic carboxylates and alkenes.



The fluorine substituent has been increasingly applied in pharmaceuticals and agrochemicals as well as in materials science due to its ability to regulate the pK_a of molecules, alter the acidity and alkalinity of nearby groups, increase the lipophilicity of molecules, and provide metabolic stability and bioavailability.[1] Therefore, the development of efficient approaches to synthesize fluorinated molecules has become a hot topic in organic synthesis.[2] Among the methods to introduce fluorine atoms into a molecule, the difunctionalization of alkenes with fluorinating reagents is a powerful synthetic tool, as it is able to not only install a fluorine atom but also introduce other useful groups into the molecules in an atom-economical fashion.[3,4] As a consequence, a number of fluorination reactions of alkenes via difunctionalization have been successfully developed, including oxyfluorination,[5] aminofluorination,[6] phosphonofluorination,[7] sulfofluorination,[8] difluorination,[9] hydrofluorination,[10] carbofluorination,[11] and others.[12] Despite the significance of these reactions, much undiscovered progress remains to be explored in this area. To the best of our knowledge, it is difficult to synthesize fluorinated compounds via decarboxylative difunctionalization of alkenes.[13]

Aliphatic carboxylic acids have often been used as alkyl synthons in various types of coupling reactions in recent years, not only because of their low cost and availability but also because they are relatively stable and it is easy for them to generate alkyl radicals.[14] Such decarboxylation reactions are usually achieved by the catalysis of transition metals, including silver,[15,16] copper,[17] manganese,[18] and photocatalysis,[19] among others.[20] In particular, Li and co-workers innovatively developed a silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acids that uses Selectfluor as the fluorine source (Scheme 1a).[15] Elegant mechanistic investigations of this reaction have revealed the alkyl radical and Ag(II)−F intermediates are involved in the catalytic cycle. On the basis of the serendipitous discovery, we hypothesized that a combination of radical acceptors, such as alkenes, might lead the alkyl radical intermediates to attack the unsaturated double bonds of alkenes, followed by the abstraction of the fluorine atom in the Ag(II)−F to produce alkylfluorination products

Scheme 1. Ag-Catalyzed Decarboxylation of Aliphatic Carboxylic Acids for the Synthesis of Organic Fluorides



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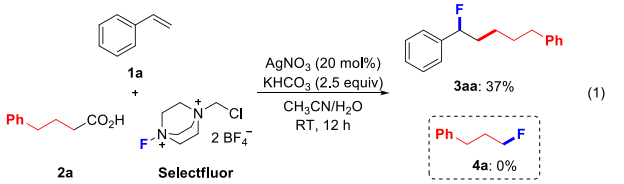
(Scheme 1b). As depicted in Scheme 1c, aliphatic carboxylic acids could be oxidized by the proposed Ag(III)−F intermediate to give Ag(II)−F and an alkyl radical with one carbon atom removed. The addition of an electrophilic alkyl radical to olefin to form the corresponding nucleophilic carbon-centered radical, followed by the transfer of the fluorine atom from Ag(II)−F to the adduct radical, generates the alkylfluorination product and regenerates the Ag(I) catalyst for the next catalytic circle. However, we are mindful of the chemoselectivity issue for this process to become successful: the catalytic reaction should suppress the competitive undesired decarboxylative fluorination. The interaction of alkyl radicals with alkenes should be much faster than that with Ag(II)−F intermediates, leading to the formation of alkylfluorination products rather than fluorination byproducts.

Driven by the above hypothesis, we set out to explore this possibility by evaluating the reaction of styrene (**1a**) with 4-phenylbutanoic acid (**2a**) and Selectfluor under a silver-catalyzed reaction system at room temperature [eq 1]. We

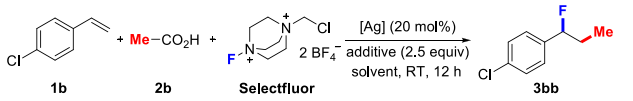


(1)

were delighted to observe the expected decarboxylative alkylfluoroation product **3aa** in 37% yield, while the unexpected decarboxylative alkylfluorination product **4a**, as well as the possible hydrogenation and hydroxylation by-product, were not detected on the basis of the NMR and GC-MS analyses. This positive outcome suggested the feasibility of our proposed assumption. Herein, we wish to report the decarboxylative alkyl carboxylic acids for alkylfluorination of unsaturated double bonds in aqueous solution with the Selectfluor reagents as oxidants and fluorine sources, which was achieved under the silver-catalyzed conditions. The reaction conditions are mild, operate simply, and can be achieved directly at room temperature.

Consequently, to explore the general reactivity of this transformation, acetic acid (**2b**) (a challenging primary alkyl carboxylic acid due to its low reactivity) was selected as the model substrate for decarboxylative fluoromethylation of 1-chloro-4-vinylbenzene (**1b**). Intriguingly, the target product **3bb** was obtained in 15% yield under Ag-catalyzed conditions (Table 1, entry 1). Encouraged by this outcome, we examined different silver salts and found that $AgNO_3$ showed slightly higher reactivity compared with other Ag(I) salts (Table 1, entries 2−3). Among the different solvents tested, the mixed solvents 1,4-dioxane/H_2O (v/v = 1/1) demonstrated superior results compared to other solvents (Table 1, entries 4−6), leading to the formation of the alkylfluorination product **3bb** in 47% yield (Table 1, entry 7). The reactions in pure organic solvents such as CH_3CN, CH_2Cl_2, acetone, DMF, or 1,4-dioxane failed to give any desired product (Table 1, entry 8), indicating the essential role of water. Then, the introduction of other additives was evaluated, and $KHCO_3$ was found to be the most effective (Table 1, entries 9−13). To our delight, the yield was improved to 69% when KOAc was employed as the addictive (Table 1, entry 14). Then, KOAc was used instead of acetic acid (**2b**) as the methyl source for the decarboxylative fluoromethylation, further improving the yield to 76% (Table 1, entry 15). In contrast, no product formed when the fluorine source was switched to NFSI (Table 1, entry 16), and no reaction occurred in the absence of silver catalyst (Table 1, entry 17).

Table 1. Screening of the Reaction Conditions[a]



entry	[Ag]	additive	solvent	yield[b] (%)
1	$AgNO_3$	$KHCO_3$	CH_3CN/H_2O	15
2	$AgOA_3$	$KHCO_3$	CH_3CN/H_2O	13
3	$AgBF_4$	$KHCO_3$	CH_3CN/H_2O	11
4	$AgNO_3$	$KHCO_3$	CH_3CN/H_2O	0
5	$AgNO_3$	$KHCO_3$	acetone/H_2O	27
6	$AgNO_3$	$KHCO_3$	DMF/H_2O	25
7	$AgNO_3$	$KHCO_3$	1,4-dioxane/H_2O	47
8	$AgNO_3$	$KHCO_3$	CH_3CN, CH_2Cl_2, acetone, DMF, 1,4-dioxane	0
9	$AgNO_3$	K_2CO_3	1,4-dioxane/H_2O	31
10	$AgNO_3$	*t*BuOK	1,4-dioxane/H_2O	23
11	$AgNO_3$	Cs_2CO_3	1,4-dioxane/H_2O	26
12	$AgNO_3$	DBU	1,4-dioxane/H_2O	30
13	$AgNO_3$	CsF	1,4-dioxane/H_2O	19
14	$AgNO_3$	KOAc	1,4-dioxane/H_2O	69
15[c]	$AgNO_3$	KOAc	1,4-dioxane/H_2O	76
16[d]	$AgNO_3$	KOAc	1,4-dioxane/H_2O	0
17	-	KOAc	1,4-dioxane/H_2O	0

[a]Reaction conditions: **1b** (0.2 mmol), **2b** (0.6 mmol), Selectfluor (0.6 mmol), $AgNO_3$ (0.04 mmol), additive (0.5 mmol), solvent (v/v = 1/1, 2 mL), at room temperature for 12 h. [b]Isolated yield. [c]With KOAc (0.6 mmol) in the absence of acetic acid (**2b**). [d]With NFSI instead of Selectfluor. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. NFSI = *N*-fluorobis(benzenesulfonyl)imide.

With the optimal conditions established, we investigated the scope and limitation of this decarboxylative alkylfluorination method with different aliphatic carboxylic acids (Scheme 2). Primary aliphatic carboxylic acids underwent efficient alkylfluorination, affording the corresponding products (**3aa**−**3ae**) in moderate to good yields. The transformation of secondary aliphatic carboxylic acids also proceeded smoothly, furnishing products **3af**−**3ah** in moderate yields. Unfortunately, the reactions with tertiary aliphatic carboxylic acids deliver the desired alkylfluorination product in trace amounts, with the decarboxylative fluorination as the main side reaction. Aromatic acids did not react under the standard reaction conditions, with the acids being fully recovered.

Next, the scope of the alkylfluorination reaction for alkenes was examined (Scheme 3). A range of styrenes containing an electron-donating or electron-withdrawing group underwent the alkylfluorination to give the corresponding desired products (**3cc**−**3jc**) ranging from 43% to 81% yield where various *para*-, *meta*-, or *ortho*-substitutents were well tolerated. A variety of functional groups including nitrile, fluoro, chloro, and bromo were compatible under these mild reaction conditions. The reaction of naphthyl ethylene exhibited moderate reactivity (**3kc**). The 1,1-disubstitued alkene was also a suitable substrate (**3lb**). Moreover, the nonstyrene olefins could also react smoothly to afford the desired alkylfluorination products (**3mb**, **3nc**) in moderate yields.

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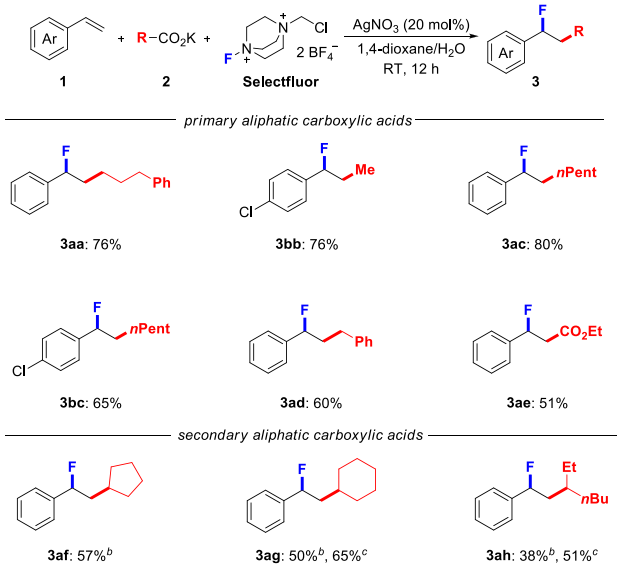
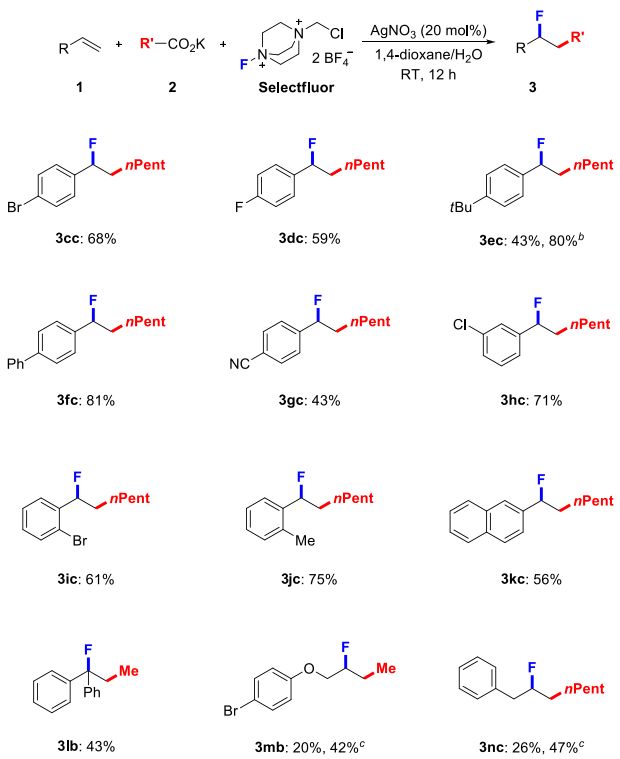
Scheme 2. Decarboxylation of Aliphatic Carboxylic Acids for Alkylfluorination[a]



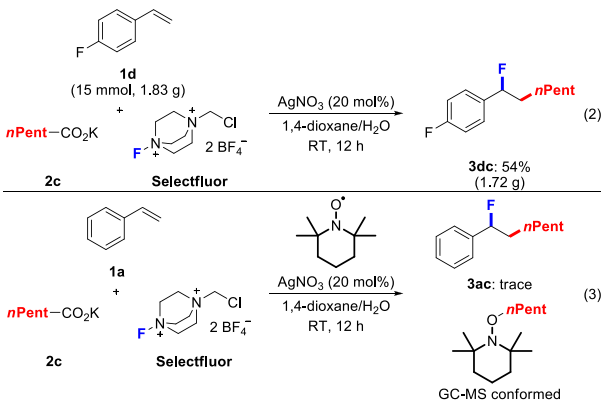
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), Selectfluor (0.6 mmol), $AgNO_3$ (0.04 mmol), 1,4-dioxane/H_2O (v/v = 1/1, 2 mL), at room temperature for 12 h. Isolated yield. [b]CH_3CN/H_2O (v/v = 1/1) as the solvent for 24 h. [c]Alkyl acids as the starting materials with $KHCO_3$ (0.5 mmol) as the additive in CH_3CN/H_2O (v/v = 1/1) solvent for 24 h.

Scheme 3. Decarboxylative Alkylfluorination of Alkenes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), Selectfluor (0.6 mmol), $AgNO_3$ (0.04 mmol), 1,4-dioxane/H_2O (v/v = 1/1, 2 mL), at room temperature for 12 h. Isolated yield. [b]CH_3CN/H_2O (v/v = 1/1) as the solvent for 24 h. [c]$KHCO_3$ (0.2 mmol) was added and in CH_3CN/H_2O (v/v = 1/1) solvent for 24 h.

A gram-scale reaction of 4-fluoro-styrene (**3d**) and potassium hexanoate (**2c**) was then performed [eq 2].



Delightfully, the yield was similar to that in the small-scale reaction. The above relative reactivities of carboxylic acids and the literature[15,16] suggested that the reaction proceeds via a radical mechanism. When 1 equiv of TEMPO (2,2,6,6-tetramethyl-1-oxylpiperidine), the radical trapper, was added in the reaction, the desired alkylfluorination product was reduced in a trace amount, with the adduct of the alkyl radical with TEMPO detected by GC-MS [eq 3], further indicating the single electron transfer pathway as shown in Scheme 1c.

To conclude, the decarboxylative alkylfluorination of unsaturated C=C double bonds has been successfully developed, which was achieved under the silver-catalyzed conditions in aqueous media at room temperature, with the Selectfluor reagent as both the oxidant and fluorine source. Thus, the reactions of a number of primary and secondary alkyl carboxylic acids afforded the corresponding alkylfluorination compounds with good chemoselectivity in an operationally simple and mild approach. This transformation provides a practical method for the synthesis of fluorinated molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03381.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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