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Silver-catalyzed decarboxylative acylfluorination of styrenes in aqueous media<sup>+</sup>

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A mild catalytic decarboxylative acylfluorination of styrenes with  $\alpha$ -oxocarboxylic acids and Selectfluor is reported. This operationally simple and efficient method provides a fundamentally novel approach toward the synthesis of  $\beta$ -fluorinated 3-aryl ketones with a wide range of substrate scope.

The development of C-F bond forming reactions is one of the most important research fields in organic chemistry because it provides an appealing way for the synthesis of valuable organofluorine compounds.<sup>1</sup> In this field, the catalytic site-specific construction of C(sp<sup>3</sup>)-F bonds is among the most challenging of the C-F bond forming reactions, and some efficient methods have been developed in the past few years.<sup>2</sup> One of the most common methods is the fluorination of unsaturated carbon-carbon bonds, such as oxyfluorination,  $3^{a-c}$  aminofluorination,  $3^{d-i}$  hydrofluorination,  $3^{j-l}$  carbofluorination,  $3^{m,n}$  phosphonofluorination  $3^{o}$  and azidofluorination<sup>3p</sup> of alkenes. Recently, another important progress has also been made in the formation of C(sp<sup>3</sup>)-F bonds based on the direct fluorination of unactivated sp<sup>3</sup> C-H bonds.<sup>4</sup> Although some great advances have been achieved in this field, exploitation of the new catalytic C(sp<sup>3</sup>)-F bond forming reaction still remains a significant challenge for synthetic chemists. Especially, a catalytic reaction capable of utilizing environmentally friendly and inexpensive substrates and proceeding under mild conditions is still highly desirable.<sup>2</sup>

In recent years, transition metal-catalyzed decarboxylative crosscoupling reactions have received much attention, owing to the prospects of the use of stable and readily available carboxylic acids and CO<sub>2</sub> as the sole waste product.<sup>5</sup> Very recently, several decarboxylative fluorination reactions of carboxylic acids and anhydrides to construct C(sp<sup>3</sup>)–F bonds have been developed.<sup>6</sup> However, there are no reports for the formation of C(sp<sup>3</sup>)–F bonds *via* an intermolecular tandem decarboxylative fluorination process.<sup>1</sup> Encouraged by our recent success in the oxidative coupling of  $\alpha$ -oxocarboxylic acids<sup>7</sup> and in the oxidative difunctionalization of activated alkenes,<sup>8</sup> we turned our attention to much more challenging oxidative difunctionalization of unactivated alkenes with  $\alpha$ -oxocarboxylic acids. Herein, we report a mild catalytic decarboxylative acylfluorination of styrenes into the corresponding benzylic fluorides. This novel method provides a complementary approach to synthesize  $\beta$ -fluorinated 3-aryl ketones,<sup>4d</sup> which have widespread applications in pharmaceuticals, fine chemicals and materials.<sup>9</sup>

Initially, we investigated the reaction of styrene (1a) and phenylglyoxylic acid (2a) with Selectfluor. Treatment of 1a, 2a and Selectfluor with 20 mol% AgNO<sub>3</sub> in EtOAc/H<sub>2</sub>O (1:1) at 50 °C for 12 h led to the desired 3-fluoro-1,3-diphenylpropanone (3a) in 23% yield (Table 1, entry 1). Among the homogeneous reaction solvents, such as CH<sub>3</sub>CN/H<sub>2</sub>O, DMF/H<sub>2</sub>O and acetone/H<sub>2</sub>O, acetone/H<sub>2</sub>O gave the best yield (entries 2–4). When the reaction was carried out

Table 1	Optimization	of the	reaction	conditions
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Ph	+ Ph OH	AgNO <sub>3</sub> (20 mol%) Selectfluor additive, solvent, rt	= 0 Ph
1a	2a		3a
Entry	Additive (equiv.)	Solvent	$\operatorname{Yield}^{b}(\%)$
1	_	EtOAc/H <sub>2</sub> O $(1:1)$	23 <sup>c</sup>
2	—	$CH_3CN/H_2O(1:1)$	$18^c$
3	—	$DMF/H_2O(1:1)$	$45^c$
4	—	Acetone/ $H_2O(1:1)$	$47^c$
5	—	Acetone/ $H_2O(1:1)$	57
6	$Na_2SO_4(1)$	Acetone/ $H_2O(1:1)$	68
7	$K_2SO_4(1)$	Acetone/ $H_2O(1:1)$	53
8	$(NH_4)_2 SO_4 (1)$	Acetone/ $H_2O(1:1)$	46
9	$BaSO_4(1)$	Acetone/ $H_2O(1:1)$	53
10	$MgSO_4(1)$	Acetone/ $H_2O(1:1)$	52
11	$CuSO_4(1)$	Acetone/H <sub>2</sub> O $(1:1)$	$n.r.^d$
12	$NaHCO_3(1)$	Acetone/H <sub>2</sub> O $(1:1)$	$40 (41)^e$

<sup>*a*</sup> Reaction conditions: AgNO<sub>3</sub> (20 mol%), **1a** (0.2 mmol, 1 equiv.), **2a** (0.3 mmol, 1.5 equiv.), Selectfluor (0.3 mmol, 1.5 equiv.), solvent (1 mL), rt, 12 h. <sup>*b*</sup> Yields of isolated products. <sup>*c*</sup> 50 °C. <sup>*d*</sup> n.r. = no reaction. <sup>*e*</sup> Yield of chalcone (**3a**') is given in parentheses.

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at room temperature, the yield was increased to 57% (entry 5). To our delight, using 1 equiv. of Na<sub>2</sub>SO<sub>4</sub> as an additive improved the yield of **3a** to 68% (entry 6). Other sulfate additives proved to be less efficient (entries 7–10), and no coupling product was observed in the presence of CuSO<sub>4</sub> (entry 11). However, when NaHCO<sub>3</sub> was added, **3a** was isolated in 40% yield along with a considerable amount of chalcone **3a**' as a byproduct (41%, entry 12).<sup>10</sup>

To probe the scope and limitations of the reaction, we first investigated the reactions of **1a** and Selectfluor with different  $\alpha$ -oxocarboxylic acids (Table 2). As shown in Table 2, both electronrich and electron-poor *p*-substituents on the phenylglyoxylic acid gave the desired products in moderate to good yields (**3b**–**g**). Notably, the formation of  $\beta$ -fluorinated 3-aryl ketones **3** was also found to be compatible with synthetically valuable functional groups on the aryl moiety of the  $\alpha$ -oxocarboxylic acids (**3d**–**g**). To further explore the generality of this transformation, we carried out the reaction using 2-thienylglyoxylic acid and  $\beta$ -naphthyloxoacetic acid, and the desired products **3h** and **3i** were isolated in 39% and 52% yields, respectively. Unfortunately, only trace amounts of the desired products were observed when *o*-methyl phenylglyoxylic acid and  $\alpha$ -naphthyloxoacetic acid were used, probably due to steric hindrance.

We then extended this reaction to a wide variety of commercially available styrene derivatives 1 (Table 3). Styrene derivatives, bearing an electron-donating and -withdrawing group at either the 4-, 3- or 2-position of the aromatic ring, afforded the corresponding products **4a–f** in moderate to good yields. In the cases of **4d–f**, the low yields were obtained which were attributed to the low conversion of **1** and other unidentified byproducts were also detected. Gratifyingly,  $\alpha$ -methylstyrene derivatives **1g–j** having a methyl or halogen atom on the aromatic ring, gave the corresponding  $\beta$ -fluorinated 3-aryl ketones in moderate yields (**4g–j**). However, aliphatic terminal alkenes, such as **1k** and **1l** were not compatible with the reaction conditions.



Table 3 Scope of unactivated terminal alkenes



The Ag-catalyzed decarboxylation of  $\alpha$ -keto acids, leading to acyl radicals in the presence of persulfates, and coupling with other partners have previously been reported in the literature.<sup>11</sup> The reaction of 1a and 2a with Selectfluor could also be inhibited by addition of radical scavengers, such as TEMPO and BHT (eqn (1) and (2)), which implies that the reaction probably proceeded via a free radical process. Furthermore, the coupling of 1a and 2a was conducted with AgNO<sub>3</sub> (20 mol%), K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (2 equiv.) and KF (2 equiv.) in actone/H<sub>2</sub>O, no desired product 3a was detected (for details see the ESI<sup>+</sup>), suggesting that a new reaction pathway other than the one involving a common Ag(II)intermediate<sup>11</sup> might be involved. Based on these results, a plausible mechanism was proposed as shown in Scheme 1. Firstly, the oxidation of Ag(1) by Selectfluor generates an Ag(11)-F intermediate.<sup>3h,o,6b</sup> Secondly,  $\alpha$ -keto acids are converted into the corresponding nucleophilic acyl radicals in the presence of Ag(m),<sup>6b,11</sup> and then the acyl radical attacks the C=C double bond of styrenes 1 to afford the alkyl radical. Finally, the fluorine atom transfers from Ag(II)-F to the radical to give the fluoride products and regenerates the Ag(I) catalyst.





In summary, we have developed a novel Ag-catalyzed decarboxylative acylfluorination of styrenes for the synthesis of  $\beta$ -fluorinated 3-aryl ketones from  $\alpha$ -oxocarboxylic acids and Selectfluor under mild conditions. This method provides ready access to benzylic fluorides with high selectivities through tandem C–C and C–F bond formation in one step. Further investigations on the detailed mechanisms, and expanding the reaction scope to other types of alkenes, are in progress.

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