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Graphical Abstract

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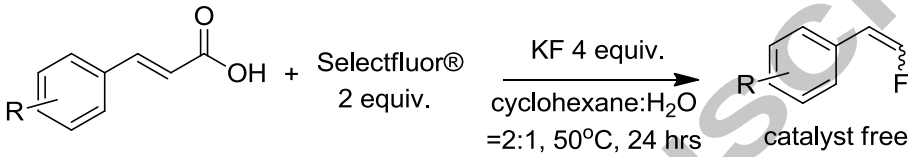

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Transition Metal Free Decarboxylative Fluorination of Cinnamic Acids with Selectfluor®

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ABSTRACT

Herein we report a transition metal free decarboxylative fluorination of cinnamic acids with selectfluor®. A range of functionalized cinnamic acid derivatives reacted with 2 equivalents of selectfluor® and 4 equivalent of base in hydrophobic solvent and water to afford β-fluorostyrene with good yield and Z-stereoselectivity. Kinetic study was conducted.

Fluorine-containing structures have become common sense in drug candidate development.[1] The special nature of fluorine atom equipped the medicines with a variety of properties, including enhanced binding interactions, metabolic stability, changes in physical properties and selective relativities.[2] Advances in fluorine chemistry have provided synthetic chemists with various carbon-fluorine bond synthesis methods.[3] Among them, creation of C(sp^2)–F bonds attracted much attention.[4] Elegant examples included bromo/triflate-fluorine exchange,[5] fluorination of aryl trifluoroborates[6] and deoxofluorination of phenol.[7] However, employment of the other common C(sp^2) functionalities, such as widely available carboxylic acid, are still missing. The early fluorodecarboxylation of carboxylic acid employed toxic F_2 or XeF_2 with low yields.[8] Recently, several examples of aliphatic acid decarboxylative fluorination were reported (scheme 1). Li group reported silver-catalyzed decarboxylative fluorination of aliphatic carboxylic acids in aqueous solution.[9] Sammis group reported both alkyl fluorination of peresters with *N*-fluorobis(benzenesulfonyl)imide (NSFI) and catalytic photoredox decarboxylative fluorination of aryloxyacetic acid.[10] McMillan group developed a general method for the photoredox catalyzed decarboxylative fluorination of aliphatic carboxylic acids.[11] Despite those progresses, the fluorination of C(sp^2) carboxylic acid remains virtually unexplored and is still challenging. Herein, we wish to report a transition metal free decarboxylative fluorination of α,β-unsaturated carboxylic acids with commercial available, stable selectfluor®.

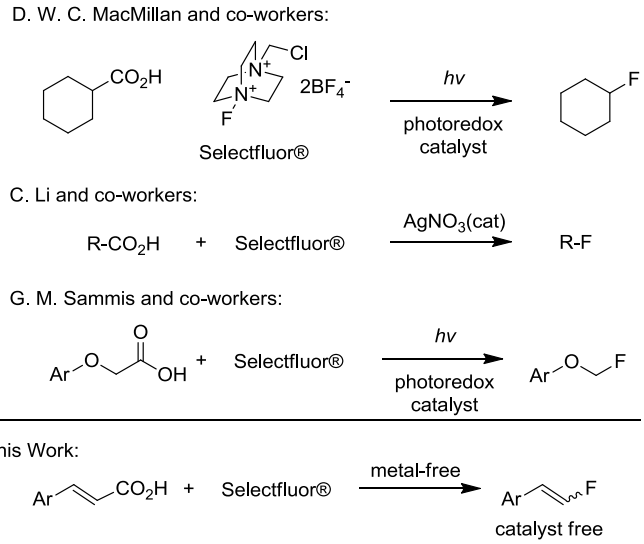

Figure 1. Recent advances in decarboxylative fluorination

Our study started with cinnamic acid (**1a**), selectfluor® (2 equiv.) and potassium fluoride (4 equiv.) in aqueous solution of acetonitrile at room temperature (Table 1). This condition afforded about 7% NMR yield with prevailed *Z*-isomer stereoselectivity of 3.7:1 (entry 1).[12] Further solvent test revealed that hydrophobic solvents, such as toluene and cyclohexane, resulted in higher yields and selectivities than hydrophilic solvents, such as acetonitrile and dioxane (entries 2 to 5). Neither pure water nor pure cyclohexane afforded any fluorinated

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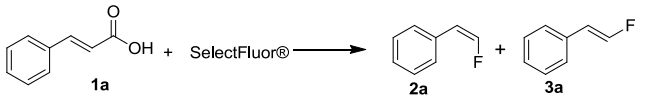
product. Upon heating to 50°C, the yield of this transformation was successfully improved to 79% albeit the selectivity decreased to 3.7:1 (entry 5). Various bases were screened (see supporting information table S2). Fluoride-containing bases such as sodium fluoride (NaF) and cesium fluoride (CsF) produced the similar or slightly higher yield than potassium fluoride (KF). We chose KF as our choice of base due to its cost and wide availability. Other weak base such sodium acetate (NaOAc) afforded comparable yield (76%, entry 8). This result excluded fluoride anion's participation in this reaction. The ratio of base to selectfluor® was optimized to be 2:1 (see supporting information table S1). Various transition metal catalyzed conditions for decarboxylative trifluoromethylations, such as silver nitrate and copper sulphate, were also tested and lower yields were observed.[13] The other electrophilic fluorination reagents, such as NSFI and *N*-fluoropyridium salts (NFPY), were also tested and afforded no yields.[14] This further proved selectfluor® as the only specialty for this transformation. Finally, simple mixture of potassium salt of cinnamic acid and selectfluor® afforded 23% yield with a little higher selectivity (entry 12).

Table 1. Optimization of reaction conditions[a]

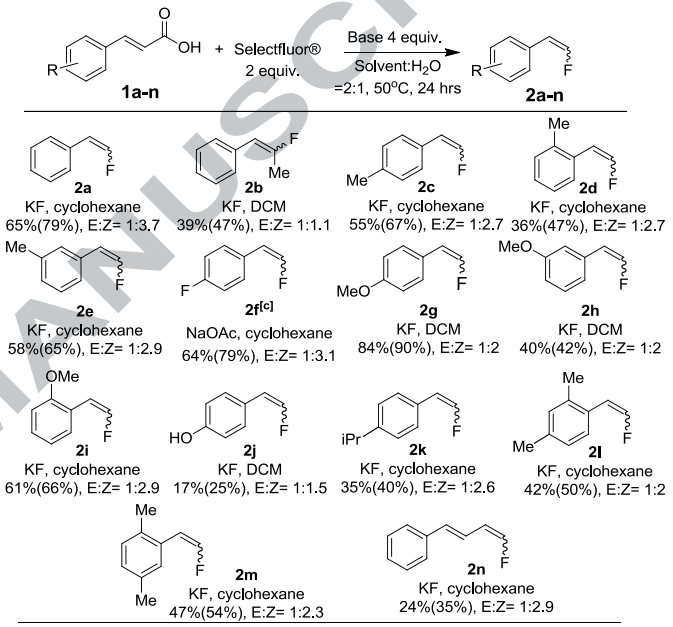


Entry[a]	Solvent	Base	Additive	Yield(%)[b] (**2a**:**3a**)
1	MeCN	KF	none	7 (3.7:1)
2	dioxnae	KF	none	9 (3.5:1)
3	toluene	KF	none	36 (5.6:1)
4	cyclohexane	KF	none	53 (5.3:1)
5	DCM	KF	none	42 (5.0:1)
6[c]	cyclohexane	KF	none	79 (3.7:1)
7[d]	cyclohexane	KF	none	52 (4.2:1)
8[c]	cyclohexane	NaOAc	none	76 (3.2:1)
9[c]	cyclohexane	KF	$CuSO_4$ (10%)	48 (3.6:1)
10[c]	cyclohexane	KF	$AgNO_3$ (10%)	15 (3.6:1)
11[c]	cyclohexane	KF	NSFI	0
12[c,e]	cyclohexane	none	none	23 (4.0:1)

[a] Reaction condition: **1a** 0.2 mmol, selectfluor® 0.4 mmol, base 0.8 mmol, H_2O:solvent= 1 mL: 2 mL, room temperature, 24 hrs.
[b] ^{19}F NMR yield based on 4-fluorotoluene as internal standard
[c] 50°C
[d] 70°C
[e] Potassium salt of cinnamic acid instead of **1a**

Having the optimized conditions in hand, we investigated scope of decarboxylative fluorination of cinnamic acid derivatives with different combination of solvent and base (Table 2). A range of commercial available and functionalized α,β-unsaturated carboxylic acids **1a-n** underwent decarboxylative fluorination with selectfluor®. α-methyl cinnamic acid **1b** was converted to fluorinated product **2b** in 39% isolated yield with the rest of starting material recovered. Due to the volatility of the product and loss in the separation procedure, the isolated yield is lower than the NMR yield (47%). Moderate yields (36%-58%) were observed for the methyl-substituted aromatic ring derivatives **2c-e**. The reaction of 4-fluorocinnamic acid with KF at 50°C initially gave the expected product **2f** in 46% yield. Changing base to NaOAc, increasing selectfluor® to 4 equivalents and the temperature to 70°C effectively increased the yield to 79%. 4-Chloro- and bromo- substrates were also tested and did not afford more than 10% yield, likely due to their poor solubility in hydrophobic solvents. Different methoxy-substituted derivatives resulted in good yield in dichloromethane (**2g**-**2i**). On the other hand, the poor solubility of substrate **1j** and **1n** resulted in low yields under current condition. Cinnamic acids with electron withdrawing group on aromatic ring and heteroaromatic acrylic acids were also tested and no reaction was observed. At last, alkyl substituted cinnamic acids (**1k**-**1m**) proved to be effective substrates for this transformation with good yields and selectivities.

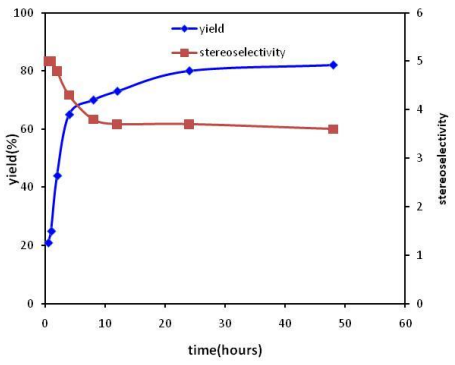
Table 2. Decarboxylative fluorination of unsaturated carboxylic acids [a,b]



[a] Reaction conditions: selectfluor® (2 equiv.), base (4 equiv.), **1** (1 equiv.) at 0.1 M in solvent, 50°C, 24 hrs.
[b] isolated yield, all yields are run on a 0.5 mmol scale at least twice, the number in parentheses refers to ^{19}F NMR yields on 0.1 mmol scale, E/Z selectivity measured by ^{1}H NMR
[c] 70°C, 2 more equivalent of selectfluor®

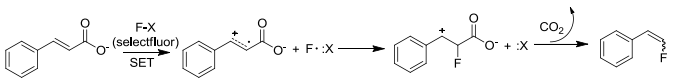
Kinetic study of cinnamic acid **1a** was conducted (Figure 2). The initial reaction was fast with 44% yield in 1 hour and 5:1 selectivity. The yield reached 65% after 4 hours. The slow-down and selectivity erosion have then been observed, *trans*- product formed faster than *cis*- product at this stage. Up to 48 hours, the reaction almost stopped and about 20% of the starting material left. The kinetic behaviour of **1a** revealed this transformation as high-ordered reaction with dependence on reactant concentration.

Figure 2. Kinetic study of **1a**



To gain some insight into the mechanism, radical scavenger TEMPO was added to the standard reaction condition, no product was observed. This result indicates that a free radical pathway might be involved in this transformation. A plausible mechanism based on single electron transfer (SET) radical pathway is depicted (Scheme 2). After deprotonation, cinnamic acid salt sequentially received an electron and fluorine from selectfluor® to form a cation intermediate.[16] Fast carbon dioxide elimination lead to the *Z*-isomer prevailed fluorostyrene.

Scheme 2. Plausible Mechanism



In conclusion, we have developed the C(sp^2) decarboxylative fluorination that employed selectfluor® as the fluorine source and potassium fluoride as base. The mild transition-metal-free experimental condition, *Z*-stereoselectivity, low cost of the fluorinating source and easy reactant recovery made it a practical method to synthesize β−fluorostyrene. Further work on employing this condition on aryl carboxylic acid is underway.

Acknowledgement

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

Highlights

- Transition metal catalyst free decarboxylative fluorination of C_{sp2} carboxylic acids
- Synthesis of β-fluorostyrene with primarily Z-selectivity
- Inexpensive, commercial available and safe fluorinating reagent selecfluor® was employed for this transformation