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Efficient synthetic method of β-fluorocinnamate by arylboronic acids and ethyl 3,3,3-trifluoropropionate under palladium-catalyzed conditions

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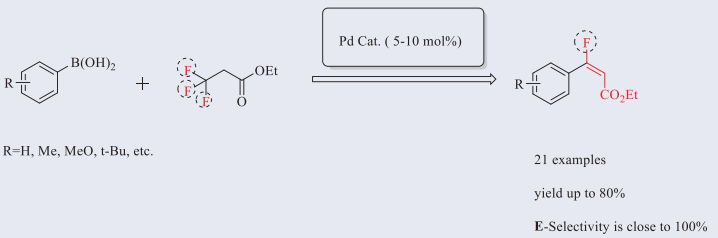
ABSTRACT

A convenient and efficient method for synthesizing β-fluorocinnamate and derivatives is reported. Palladium (II) catalysis was employed in β-F elimination and coupling reaction of phenylboronic acid and ethyl 3,3,3-trifluoropropionate with a high yield and E-selectivity. The reaction was conducted under mild conditions and could be widely adapted to boronic acid substrates.

GRAPHICAL ABSTRACT



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KEYWORDS
Ethyl 333-trifluoropropionate; β-fluorocinnamate; one-step synthesis; palladium catalysis; phenylboronic acid

Introduction

Monofluoroolefin compounds are highly important in medicinal and peptide chemistry research[1–4] owing to the fact that the selective introduction of fluorine atoms can significantly change the pharmacological properties of organic drug molecules.[5–8] As one of the most important monofluorinated compounds, fluorocinnamates have attracted much attention because cinnamate compounds are widely used in daily life, including in perfumes and cosmetics,[9] research has shown that β-fluorocinnamate can slightly improve the body's resistance to drug-induced allergies.[10] Moreover, the fluorocinnamic acid structure has superior chemical versatility and potential for further conversion to fluorinated compounds with considerable application prospects.[9–13] Therefore, the synthesis of β-fluorocinnamate is very valuable and provides an important tool for synthetic and medicinal chemistry.

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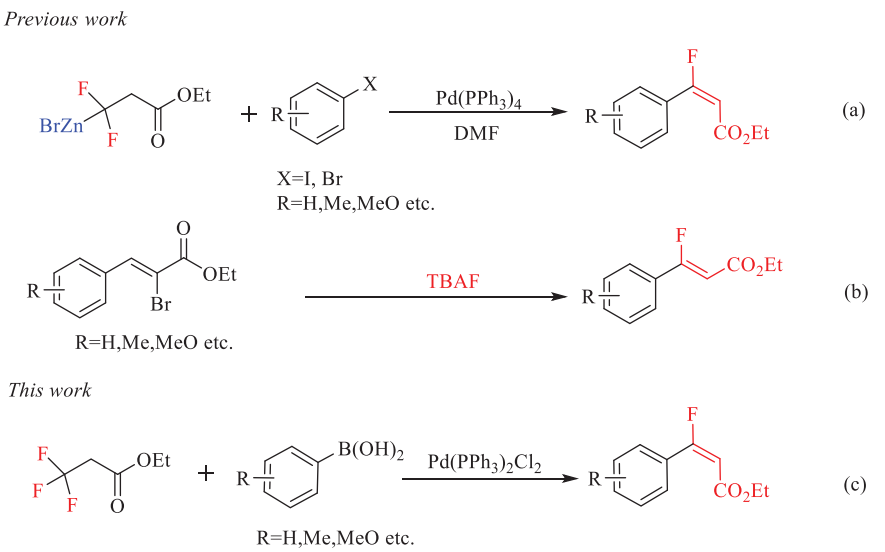


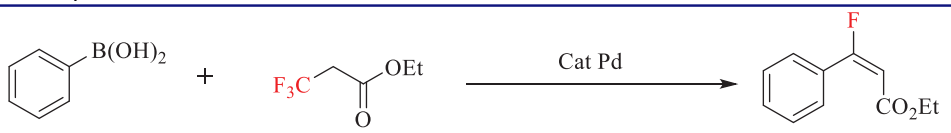
Scheme 1. (a–c) Reported method for fluorocinnamates and method presented herein.

The use of fluorine-containing intermediates has become an important trend in the synthesis of β-fluorocinnamate and other valuable fluorinated compounds in the last few decades.[14–17] For example, fluorinated organic zinc reagents ($ZnBrCF_2CH_2CO_2C_2H_5$)[18] were reported as fluorine sources for cross-coupling with halogenated aromatic hydrocarbons to obtain β-fluorocinnamate by Qing's group; however, the reaction requires the synthesis of ethyl 3-bromo-3-difluoropropionate via a two-step reaction, and the process is relatively complex (Scheme 1a). Tetrabutyl ammonium fluoride (TBAF)[19] has also been reported by Zhang et al. as a fluorine source to react with substituted ethyl α-bromocinamates to obtain β-fluorocinnamate (Scheme 1b). Jiang et al. found that AgF can be used as a fluorinating agent to participate in the high chemo- and region-selectivity fluorination of electron-deficient C≡C triple bonds to access β-fluorocinnamate.[20] In 2016, Patrick's team[21] reported that ethyl (Z)-3-fluoropentenoate could be a fluorine source to react with iodobenzene under palladium catalysis condition to obtain fluorocinnamate in medium yield, but the raw materials are expensive and difficult to obtain. Although great progress has been made in the synthesis of β-fluorocinnamate, the preparation of these fluorine sources often needs a multi-step reaction, resulting in a complicated and expensive process. Thus, the one-step synthesis of β-fluorocinnamate using cheap and convenient fluorine sources must be developed.

3,3,3-trifluoropropionic acid and its esters are important synthetic intermediates of bioactive compounds and functional materials[22–27] that have been commercialized. Since our department has successfully realized the pioneering work on Pd-catalyzed C–F activation of α-trifluoromethyl ketone and thus obtained a variety of α,β-unsaturated ketones.[28] We envisage using ethyl 3,3,3-trifluoropropionate as a fluorine source to approach β-fluorocinnamate.

Inspired by our continuous efforts in fluorine chemistry,[28,29] we report here a unique method of synthesizing β-fluorocinnamate in high yield and E-selectivity using ethyl 3,3,3-trifluoropropionate as the fluorine source. The reaction has the following

Table 1. Optimization of reaction conditions.



1a **2a** **3a**

Entry	Catalysis	Base (1:1)	Solvent	Temperature (°C)	Yield[b] (%)	Selectivity (E/Z)[c]
1	$PdCl_2$	K_3PO_4	CH_3CN	RT[a]	0	ND
2	$PdCl_2$(dppf)	K_3PO_4	CH_3CN	80	Trace	ND
3	$PdCl_2(MeCN)_2$	K_3PO_4	CH_3CN	80	<5	ND
4	$Pd(OAc)_2$	K_2CO_3	CH_3CN	80	11	>99:1
5	$Pd(PPh_3)_2Cl_2$	K_3PO_4	CH_3CN	80	43	>99:1
6	$Pd(PPh_3)_2Cl_2$	Na_2CO_3	CH_3CN	80	40	>99:1
7	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3	CH_3CN	80	46	>99:1
8	$Pd(PPh_3)_2Cl_2$	K_3PO_4+Na_2SiO_3	CH_3CN	80	62	>99:1
9	$Pd(PPh_3)_2Cl_2$	K_2CO_3+Na_2SiO_3	CH_3CN	80	75	>99:1
10	$Pd(PPh_3)_2Cl_2$	Ag_2CO_3+Na_2SiO_3	CH_3CN	80	64	>99:1
11	$Pd(PPh_3)_2Cl_2$	K_2CO_3+Na_2SiO_3	Toluene	80	52	>99:1
12	$Pd(PPh_3)_2Cl_2$	K_2CO_3+Na_2SiO_3	H_2O	80	<5	>99:1
13	$Pd(PPh_3)_2Cl_2$	K_2CO_3+Na_2SiO_3	THF	80	61	>99:1
14	$Pd(PPh_3)_2Cl_2$	K_2CO_3+Na_2SiO_3	CH_3CN	60	58	>99:1
15	$Pd(PPh_3)_2Cl_2$	K_2CO_3+Na_2SiO_3	CH_3CN	110	80	>99:1

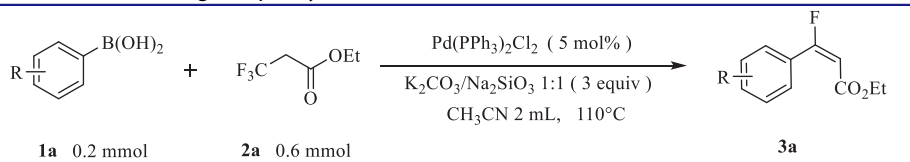
[a]RT: room temperature; [b]isolated yield shown in parentheses; [c]selectivity detected by ^1H NMR; ND: not detected.

advantages: (1) ethyl 3,3,3-trifluoropropionate is introduced as a new fluorine reagent to obtain β-fluorocinnamate, (2) fluorocinnamate is synthesized through a one-step reaction with simple reaction and mild conditions, and (3) stable and low-toxic arylboronic acid is used as a coupling reagent, providing a wide range of substrates for the reaction.

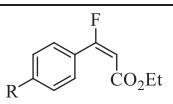
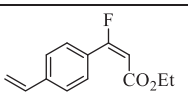
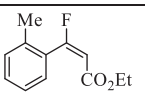
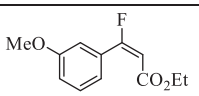
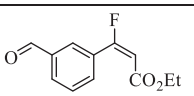
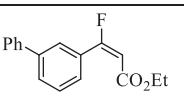
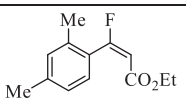
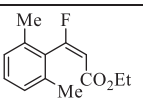
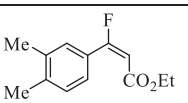
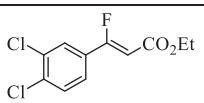
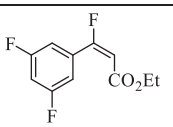
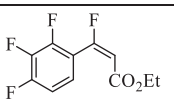
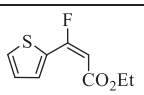
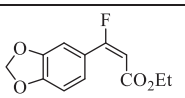
Results and discussion

The initial research was targeted to evaluate the performance of different palladium catalysts. Phenylboronic acid and ethyl 3,3,3-trifluoropropionate were used as model substrates (Table 1). No product was observed when $PdCl_2$ was used as a catalyst for the reaction (Table 1, entry 1). Upon adding the ligand, the reaction began to produce a trace of desired product. After comparison and screening, PPh_3 was found to be the most efficient ligand (Table 1, entries 2–5). Further research was performed to explore the effect of different bases on the reaction. A series of bases (K_3PO_4, Na_2CO_3, Ag_2CO_3) were studied to obtain the target product with CH_3CN as the solvent at 80 °C, the yield could be increased to 46% (Table 1, entries 6 and 7). It is worth mentioning that it was a pleasant surprise to find that the use of a mixed base significantly improves the yield. Indeed, the yield of **3a** increased to 75% when a mix of K_3CO_3/Na_2SiO_3 was used. The reaction yield can still reach 64% under the same ratio of Ag_2CO_3 and Na_2SiO_3 (Table 1, entries 8–10). The solvent of the reaction was then screened. When CH_3CN was changed to toluene, the yield dropped to 52%. Similarly, the conversion to THF indicated that the yield of the target product was also reduced, only 61% can be achieved; the experiment had also shown that water strongly inhibits the reaction (Table 1, entries 11–13). In addition, the temperature has an effect on the yield of

Table 2. Substrate range of phenylboronic acid.



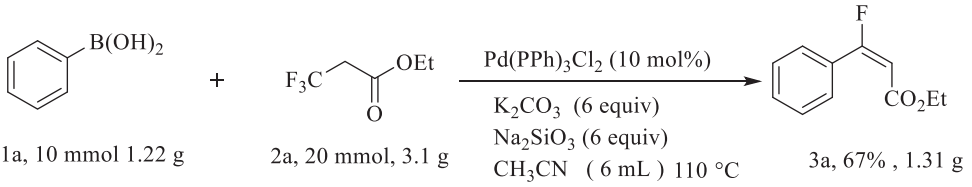
1a 0.2 mmol **2a** 0.6 mmol **3a**

 E-3a, R=H, 80% E-3e, R=F, 63% E-3b, R=Me, 74% E-3f, R=Cl, 60% E-3c, R=OMe, 70% E-3g, R=Br, 54% E-3d, R=t-Bu, 65% E-3h, R=CN, 42%	 E-3i, 57%	 E-3j, 77%
 E-3k, 74%	 E-3l, 61%	 E-3m, 59%
 E-3n, 80%	 E-3o, 72%	 E-3p, 84%
 Z-3q, 56%	 E-3r 66%	 E-3s, 35%
 E-3t, 71%	 3u, E/Z=9:1, 68%	

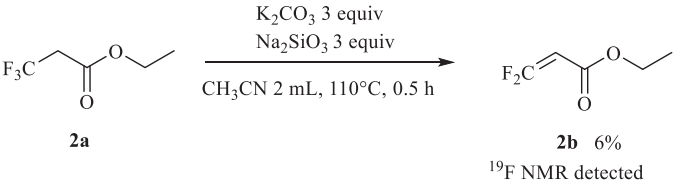
Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(PPh_3)_2Cl_2$ (5% mol), K_2CO_3/Na_2SiO_3 1:1 (3 equiv.), and CH_3CN (2 mL), at 110 °C, 12 h.

the reaction. The yield would decrease slightly when the temperature was lowered to 60 °C, but the reaction yield reached 80% at 110 °C (Table 1, entries 14 and 15). In addition, the structure of 3a detected was mainly E-configuration (E/Z = 99%).

With the optimized reaction conditions in hand, the range of substrates was studied next (Table 2). A series of aryl boronic acids with different substituents on the benzene ring had good adaptability to this reaction. Substrates bearing electron-donating groups, such as methyl/methoxy/tert-butyl on the para position of the benzene ring, were



Scheme 2. Gram-scale experiment.

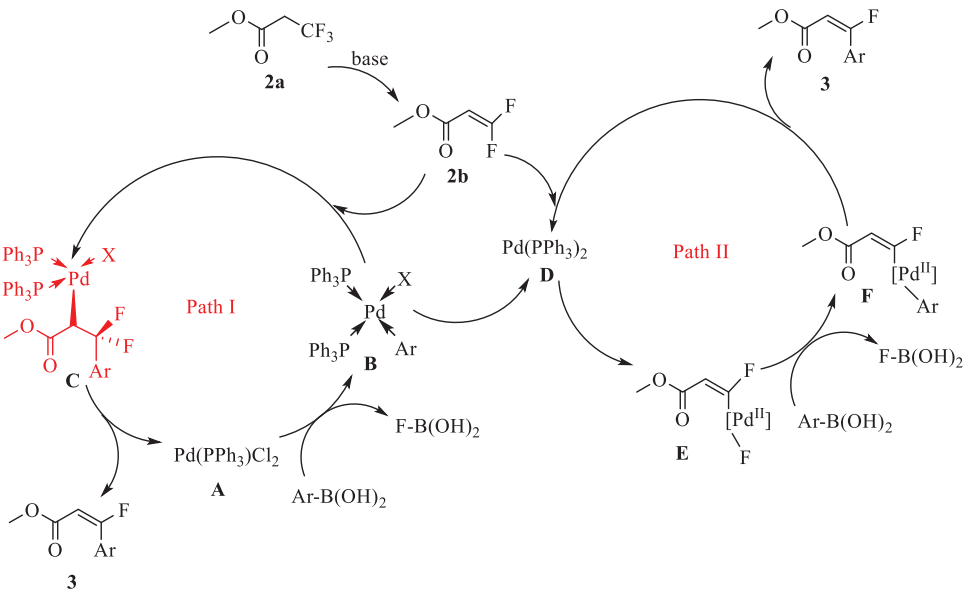


Scheme 3. Mechanism verification.

smoothly transformed into the corresponding E-configured fluorocinnamate ester **3b–d**. Halogen functional groups, that are sensitive to low-valence transition metals, can adapt to the reaction and afford **3e–g** in medium yields. Cyano groups that absorb electrons have less effect on the reaction and can obtain **3h** in moderate yields. 4-vinylphenylboronic acid has good adaptability to the reaction and provides 4-vinyl-β-fluorocinnamate **3i** in high yield. The ortho and meta substituents of the benzene ring were also well adapted to the reaction, and **3j–m** can be obtained in high yields. The poly-substituted phenylboronic acids, such as 2,4-dimethylphenylboronic, 2,6-dimethylphenylboronic and 3,4-dimethylphenylboronic acid, can be converted into **3n**, **3o**, and **3p** in high yields. 3,4-dichlorobenzeneboronic acid provides the corresponding fluorocinnamate **3q** in medium yield, it is worth mentioning that **3q** is the only Z-type fluorocinnamate among all substrates. The aryl boronic acid with benzene ring substituted by dihalogen only gives the corresponding 3,5-difluoro-β-fluorocinnamate **3r** in moderate yield. The obtention of **3 s** confirmed the suitability of tri-substituted phenylboronic acid for the reaction. Thiophene boronic acid can produce **3t** in high yields, which showed that the proposed reaction is also very suitable for heterocyclic boronic acid. Moreover, the phenylboronic acid substituted by 3,4-dimethyleneoxy can nicely adapt to the reaction, but a small amount of Z configuration was detected (E/Z 9:1). However, no desired product was obtained when a hydroxyl group was located on the benzene ring.

To prove the application prospect of the proposed fluorocinnamate synthesis method, a gram-scale experiment was performed, and product **3a** was obtained in 67% yield (Scheme 2).

Further work was done mainly to study the reaction mechanism, Firstly, the fluorine source **2a** undergoes the first β-F elimination reaction in the presence of a base to generate a difluoroolefin intermediate **2b**,[30] we confirmed the existence of **2b** through experiment (Scheme 3). Intermediate **2b** may subsequently participate in two different pathways. In the first possible pathway (Scheme 4, Path I), aryl boronic acid transmetalated with Pd (II) to generate palladium-aryl species **B**.[31,32] Subsequently, **B** is inserted by the difluoroolefin intermediate **2b** to form an alkyl-palladium species **C**. Finally, the target product **3** is obtained by eliminating β-fluorine of **C**.[28] In the second possible pathway (Scheme 4,



Scheme 4. Proposed mechanism.

path II), the palladium-aryl species **B** undergoes transmetalation and reductive elimination to form Pd(0) complex **D**.[32,33] The Pd (0) complex **D** is then oxidatively inserted into the difluoroalkene structure to produce Pd(II)-olefin species **E**, Pd(0) is oxidized to Pd(II) in the process.[28] Transmetalation occurs from **E** to provide the key intermediate **F**. The target product **3** is obtained through a rapid reductive elimination of **F**,[28] and Pd (II) is reduced to Pd (0). The specific path is shown in Scheme 4.

Conclusion

A unique and efficient method has been developed for the synthesis of β-fluorocinnamate in high yields with excellent **E** selectivity. The use of ethyl 3,3,3-trifluoropropionate provides a convenient fluorine source for the synthesis of β-fluorocinnamate. The one-step synthesis of β-fluorocinnamate was realized through the β-F elimination of ethyl 3,3,3-propionate and coupling reaction with aryl boronic acids, which greatly reduces the reaction cost. Moreover, this method has wide applicability and can be adapted to most substrates with different substituents. Further research work will focus on the derivatization and functionalization of β-fluorocinnamate.

Experimental

^{1}H NMR (600 Hz) and ^{13}C NMR (150 Hz) were recorded in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard. Data for ^{1}H NMR are reported as follows: chemical shift (ppm, scale), multiplicity, coupling constants (Hz), and integral. Data for ^{13}C NMR are reported in terms of chemical shift (ppm, scale), multiplicity, and coupling constants (Hz). Data for ^{19}F NMR are reported in terms of chemical shift (ppm, scale),

multiplicity, and coupling constants (Hz). High-resolution mass spectra were obtained by ESI on a TOF mass analyzer. HRMS (EI) was determined on a PerkinElmer spectrometer.

General procedures for β-Fluorocinnamate (3a)

Phenylboronic acid 1a (0.2 mmol, 24.8 mg), $Pd(PPh_3)_2Cl_2$ (5 mol%, 7.1 mg), K_2CO_3 (3 equiv., 41.4 mg) and Na_2SiO_3 (3 equiv., 85.2 mg) were sequentially added to a dry Schlenk tube, then repeat the pumping and the vessel was degassed by three cycles of nitrogen and vacuum, followed by addition of 3,3,3-trifluoropropionate 2a (0.6 mmol, 93.6 mg) and CH_3CN (2 mL). The reaction mixture was stirred at 110 °C for 12 hours, chromatographic purification of the crude product on silica gel gave the desired product β-fluorocinnamate **3a** in 80% yield.

Spectral data for the selected compounds

Compound **3a**[18]: Following the general procedure, the product was purified by flash chromatography (PE/EA = 20:1) as a yellow oil (30.1 mg, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, J = 7.2 Hz, 2H), 7.46 (t, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 2H), 5.86 (d, J = 20.6 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H).^{13}C NMR (151 MHz, cdcl$_3$) δ 170.65, 168.89, 165.29, 131.21, 131.20, 129.01, 127.86, 101.70, 101.48, 77.00, 60.48, 14.04. ^{19}F NMR (564 MHz, $CDCl_3$) δ − 67.81. HRMS (ES) m/z calcd. for $C_{11}H_{11}FO_2$: 194.1493; found: 194.1495.

Compound **3e**[18]**:** Following the general procedure, the product was purified by flash chromatography (PE/EA = 20:1) as a yellow oil (26.7 mg, 63%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (dd, J = 8.5, 5.4 Hz, 2H), 7.10 (t, J = 8.5 Hz, 2H), 5.85 (d, J = 20.9 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.58, 167.83, 165.08, 163.42, 131.39, 125.96, 115.20, 115.03, 101.41, 77.20, 60.55, 14.07. ^{19}F NMR (564 MHz, $CDCl_3$) δ − 76.01, −107.53. HRMS (ES) m/z calcd. for $C_{11}H_{11}F_2O_2$: 212.0649; found: 212.0651

Full experimental details, ^{1}H, ^{13}C NMR and ^{19}F spectra. This material is found in the "Supplementary Content" section of this article's webpage.

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