



Palladium-catalyzed Suzuki–Miyaura reaction of fluorinated vinyl chloride: a new approach for synthesis α and α,β -trifluoromethylstyrenes



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ABSTRACT

A mild and efficient palladium-catalyzed cross-coupling between fluorinated vinyl chloride and arylboronic acids is described. The use of ligand B successfully overcomes the strong electronic withdrawing of trifluoromethylated substrates and allows the efficient synthesis of a wide range of α and α,β -trifluoromethyl containing olefins. By using this method, the key intermediate for synthesis of Efavirenz can be obtained in a simple route. The efficient conversion of two freon molecules into useful α and α,β -trifluoromethyl containing olefins is a useful route in organic chemistry.

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1. Introduction

Trifluoromethylation of compounds such as pharmaceuticals, agricultural chemicals, and functional materials in most cases, significantly improves their performances.¹ α -Trifluoromethylstyrene derivatives have attracted considerable attention because they are industrially important compounds in the fields of medicinal, agricultural and material sciences.^{2,3} Conjugated aromatic systems with trifluoromethyl groups such as β -trifluoromethylstyrene derivatives have been found wide use in Organic Light Emitting Diodes (OLEDs) and other material chemistry.⁴ With regard to the metal-catalyzed coupling for synthesis of α and β -trifluoromethylstyrene derivatives, several research groups have reported methods for preparing of this kind of substrates.^{5,6} However, all of those methods use either toxic reagents or expensive substrates. On the other hand, less attention has been paid to the development of efficient and general methods for tri and tetra-substituted olefins.⁷ Especially for trifluoromethylation and fluorinated containing substrates.^{8,9} Therefore, it is of great interest to

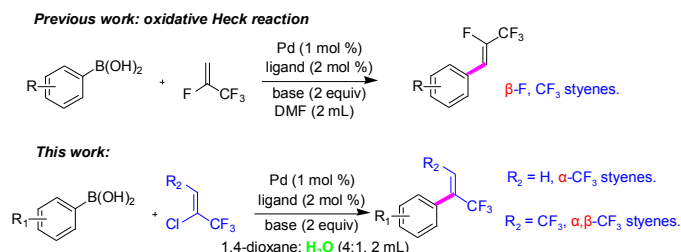
develop general and efficient strategies for synthesizing these compounds.

Suzuki–Miyaura reaction is a well-established and important cross-coupling reaction in organic synthesis. It is widely used to synthesize, poly-olefins, styrenes, and substituted biphenyls. Several reviews have been published describing advancements and the development of the Suzuki–Miyaura reaction.¹⁰ But, there is still a difficulty for Suzuki–Miyaura reaction in fluorinated aryl halide or halogenated hydrocarbon.

It is considered that freon molecules are involved in ozone layer destruction, tremendous stocks of freons have been accumulated during last century, which need to be utilized. Nowadays, how to convert them into fine chemical products is a challenging and urgent problem. 2-chloro-3,3,3-trifluoroprop-1-ene (HCFO-1233xf), is a commercially available compound with a boiling point of 27.7 °C at 760 mmHg, usually used as a refrigerant in automotive industry. If it is considered as a raw material for various useful chemicals, then opportunities exist for its use. Very few examples related to its chemical conversion were reported.¹¹ However, as we know, the coupling of HCFO-1233xf with aryl boronic acids has not been reported in any literature. As part of our systematic studies on transition-metal-catalyzed reactions for

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the efficient synthesis of fluorinated olefins (Scheme 1),¹² we report an efficient cross-coupling reaction for synthesis of trifluoromethylstyrenes by using trifluoromethylated vinyl chloride and arylboronic acids via palladium-catalyzed Suzuki–Miyaura reaction.



Scheme 1. Palladium-catalyzed for synthesis of α and α,β -trifluoromethylstyrenes.

2. Results and discussion

We initially chose 4-methoxyphenylboronic acid **1a** as a substrate for the screening of this coupling transformation. A solution of 4-methoxyphenylboronic acid **1a** and 2-chloro-3,3,3-trifluoroprop-1-ene **2** in 1,4-dioxane and water (4:1) was stirred using Pd(OAc)₂ (1 mol %) as a catalyst, PCy₃ (2 mol %) as a ligand and Na₂CO₃ as a base. Only 1-methoxy-4-(3,3,3-trifluoroprop-1-en-2-yl)benzene **3a** was formed in a low yield of 39% (Table 1,

Table 1
Optimization of palladium-catalyzed arylboronic acid coupling with 2-chloro-3,3,3-trifluoroprop-1-ene^a

Entry	Catalyst	Ligand	Base	Solvent ^b	Yield (%) ^c
1	Pd(OAc) ₂	PCy ₃	Na ₂ CO ₃	4:1	39
2	—	PCy ₃	Na ₂ CO ₃	4:1	0
3	Pd(OAc) ₂	—	Na ₂ CO ₃	4:1	0
4	PdCl ₂	PCy ₃	Na ₂ CO ₃	4:1	30
5	Pd(PPh ₃) ₂ Cl ₂	PCy ₃	Na ₂ CO ₃	4:1	45
6	Pd(PhCN) ₂ Cl ₂	PCy ₃	Na ₂ CO ₃	4:1	29
7	Pd(PPh ₃) ₂ Cl ₂	PPh ₃	Na ₂ CO ₃	4:1	2
8	Pd(PPh ₃) ₂ Cl ₂	DPPP	Na ₂ CO ₃	4:1	4
9	Pd(PPh ₃) ₂ Cl ₂	BINAP	Na ₂ CO ₃	4:1	12
10	Pd(PPh ₃) ₂ Cl ₂	A	Na ₂ CO ₃	4:1	13
11	Pd(PPh ₃) ₂ Cl ₂	B	Na ₂ CO ₃	4:1	65
12	Pd(PPh₃)₂Cl₂	B	NaHCO₃	4:1	97
13	Pd(PPh ₃) ₂ Cl ₂	B	Na ₂ HPO ₄	4:1	63
14	Pd(PPh ₃) ₂ Cl ₂	B	NEt ₃	4:1	71
15	Pd(PPh ₃) ₂ Cl ₂	B	K ₂ CO ₃	4:1	55
16	Pd(PPh ₃) ₂ Cl ₂	B	NaHCO ₃	H ₂ O	66
17	Pd(PPh ₃) ₂ Cl ₂	B	NaHCO ₃	1,4-Dioxane	58
18 ^d	Pd(PPh ₃) ₂ Cl ₂	B	NaHCO ₃	4:1	22

Bold entry signifies the best reaction condition.

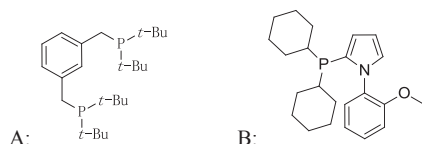
^a Reaction conditions: **1a** (1 mmol), **2** (18 mmol), catalyst (1 mol %), ligand (2 mol %), base (2 mmol), solvent (2.5 mL), 100 °C, 5 h.

^b 1,4-Dioxane: H₂O.

^c NMR yields were calculated by ¹⁹F NMR integration of products relative to the internal standard of ethyl *p*-fluoroacetophenone.

^d **2** (5 mmol) was added.

Structures of ligands:



entry 1). Control experiments revealed that the metal and ligand were both indispensable for the reaction (Table 1, entries 2 and 3). Next, the influence of palladium source was examined. It could be seen that Pd(PPh₃)₂Cl₂ was the best pre-catalyst for the reaction (Table 1, entries 4–6). When the ligand was switched from PCy₃ to **B**, a better yield was obtained (Table 1, entries 7–11). Thirdly, the influence of base was examined, and it was observed that NaHCO₃ was the best base for the reaction (Table 1, entries 12–15). Moreover, when the reaction solvent was changed to water, the target product **3a** was achieved in an acceptable yield of 66% (Table 1, entry 16). Suggesting that this strategy provided a useful route for synthesis of trifluoromethylated substituted olefins. However, when 1,4-dioxane used as solvent alone, the product **3a** can be obtained in yield of 58% (Table 1, entry 17). Finally, when the amount of **2** was decreased to 2 equiv, a poor yield of **3a** (22%) was obtained (Table 1, entry 18). In summary, the best reaction conditions for this coupling process were obtained using Pd(PPh₃)₂Cl₂ (1 mol %), B (2 mol %), NaHCO₃ (2 equiv) 1,4-dioxane and water (4:1, 2.5 mL) as the mixture solvent, at 100 °C for 5 h.

To explore the scope of the coupling reaction, various arylboronic acids were then examined for coupling with 2-chloro-3,3,3-trifluoroprop-1-ene **2** by using Pd(PPh₃)₂Cl₂/**B** as a catalyst and NaHCO₃ as a base. The results are summarized in Table 2. *Para*-substituted phenylboronic acids reacted smoothly with 2-chloro-3,3,3-trifluoroprop-1-ene **2** to afford excellent Yields (Table 2, **3a–3g**). In general, electron-rich substituted boronic acid demonstrated a higher reactivity than it is electron-withdrawing analogues. For instance, the yield of **3a** was significantly higher than that of **3e**. Substrates having *m*- or *o*-substituents also reacted with acceptable yields (Table 2, **3h–3n**). Disubstituted arylboronic acids were also tested, and good yields were obtained (Table 2, **3o–3q**). Furthermore, a carbazole-derived boronic acid could also be converted into the corresponding product in moderate yield (Table 2, **3r**).

Tri-substituted olefins are difficult to synthesize, in general, they were synthesized by two steps,¹³ especially for trifluoromethyl substituted styrenes.¹⁴ By using this method, we could obtain α,β -trifluoro substituted styrenes in one step directly when using (*Z*)-2-chloro-1,1,1,4,4,4-hexafluorobut-2-ene **3** as a coupling reagent.

A range of functional groups were tolerated in this transformation (Table 3). Comparing electron-rich and electron-withdrawing substituted phenylboronic acids, it was found that electron-rich substituted arylboronic acids were well suited for this process (Table 3, **4a–4c**). Moreover, di-substituted arylboronic acids could react smoothly with **3** catalyzed by palladium, and gave acceptable yields (Table 3, **4d–4e**).

Efavirenz is a potent non-nucleoside HIV reverse transcriptase inhibitor approved by the FDA for the treatment of AIDS.¹⁵ The trifluoroketone **6** is a key intermediate for the preparation of Efavirenz.¹⁶ Several research groups have reported synthesis methods for the trifluoroketone **5a**.¹⁷ However, all of those methods use either expensive materials or suffer from strict reaction conditions. By using this method, we could prepare the trifluorostyrene **5a** easily, and the styrene could convert into trifluoroketone **6** by using NaIO₄ and OsO₄, followed by hydrogenation (Scheme 2).¹⁸

A plausible mechanism of this Suzuki–Miyaura reaction is described in the perspective of the palladium catalyst (Scheme 3). The first step is the oxidative addition of palladium (**A**) to the halide (**2**) to form the organopalladium species (**B**). Reaction with base gives intermediate (**C**), which via transmetalation¹⁹ with the boron-ate complex (produced by reaction of the boronic acid with base) forms the organopalladium species (**D**). Reductive elimination of the desired product restores the original palladium catalyst²⁰ which completes the catalytic cycle. The use of ligand **B** possibly promotes the step of oxidative addition.

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