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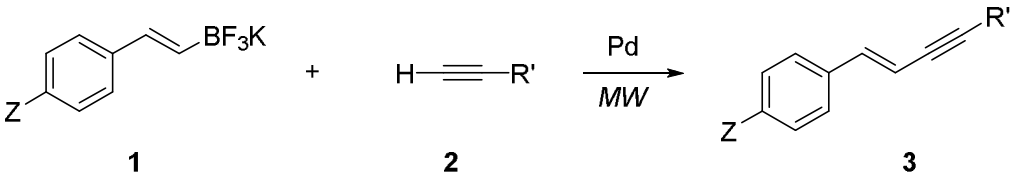
Effective catalytic effect of $PdCl_2(d^tbpf)$ in cross-coupling reaction of alkynes and potassium styryltrifluoroborates under microwave heating is developed.



1 **2** **3**

Microwave irradiated Pd-catalyzed C(sp)-H activation and cross-coupling with styryltrifluoroborates

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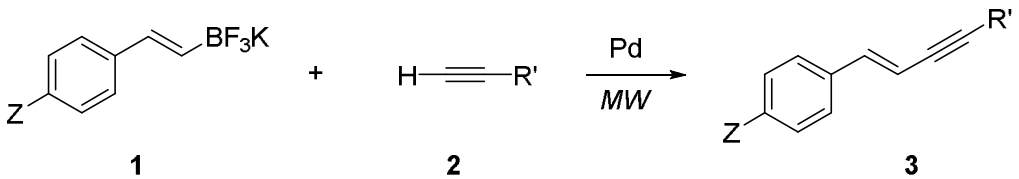
Abstract: Effective catalytic effect of $PdCl_2(d^tbpf)$ in the C-H activation of alkynes and its ability to overcome the limitations of styryltrifluoroborates in cross-coupling reactions by avoiding the effects of the C-X bond in starting materials is developed.

Keywords: C-H activation, styryltrifluoroborates, microwave, minute reaction

The fundamentals of cross-coupling chemistry for carbon-carbon bond formation reactions by potassium organotrifluoroborates have been well explained. Coupling partners, C-X (X= I, Br, Cl, OTf, ONf, OTs), are required to initiate the oxidative addition of Pd(0) to Pd(II) species of the catalytic cycle and furnish the product.[1] Direct activation of C-H bond will improve this valuable process by avoiding the presence of C-X in the starting material, an approach that is gaining attention in cross-coupling chemistry.[2] However, direct activation of C-H bond by a transition metal catalyst and cross-coupling with styryltrifluoroborates has not yet been fully explored. Developing new methods for conjugated enynes by the C-H activation of terminal alkynes and cross-coupling with potassium organotrifluoroborates is of particular interest because of the vital role they play in a wide range of industrial intermediates, pharmaceuticals, agro-chemicals, and molecular materials.[3] Also, microwave energy has been shown to offer significant benefits in organic synthesis, providing to be a valuable and reliable tool for organic chemists.[4] In this report, we describe the microwave irradiated palladium-catalyzed cross-coupling minute reaction of styryltrifluoroborates and C(sp)-H species (Scheme 1).

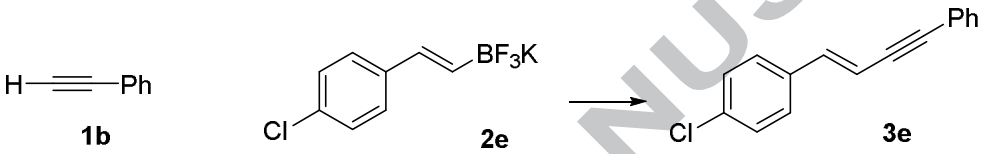
Scheme 1



1 **2** **3**

We selected phenyl acetylene (**1b**), as the C-H source because of it high reactivity in Sonogashira type coupling reactions[5] and ran the cross-coupling reaction of **1b** with potassium 4-chloro-(2-phenylvinyl) trifluoroborate (**2e**). Initially all attempts failed to yield the predicted cross-coupling product. Homocoupling of the phenyl acetylene was observed in GC-MS analysis. To find an effective catalyst system other palladium complexes and other active reagents choices were examined (Scheme 2). Recently, $PdCl_2(d^tbpf)$ complex has been successfully employed as a catalyst in various organic transformations involving potassium organotrifluoroborates.[6] The higher dihedral angle of P-Pd-P in $PdCl_2(d^tbpf)$ improves its effectiveness as a catalyst.[7] Of the many other available complexes, this Pd-complex demonstrates the foremost catalytic effect for the C-H activation of alkynes cross-coupled with styryltrifluoroborates. The results from this new process for the synthesis of conjugated enynes are summarized in Table 1.

Scheme 2. Finding catalyst system for cross-coupling reactions of alkynes and styrylBF_3K.

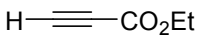
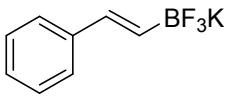
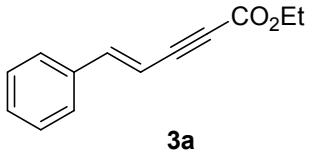
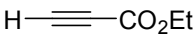
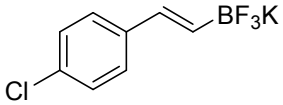
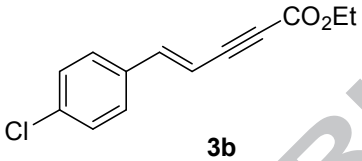
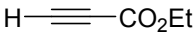
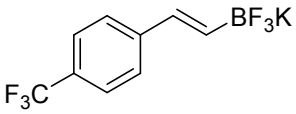
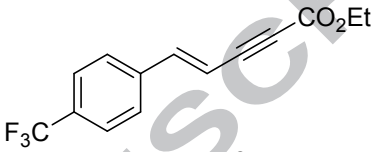
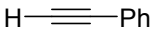
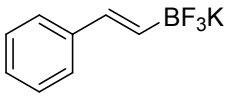
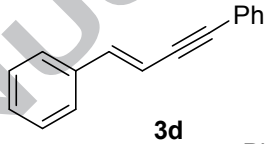
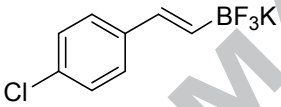
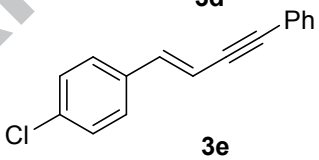
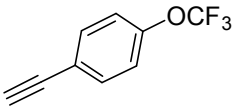
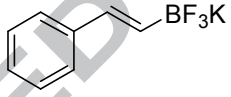
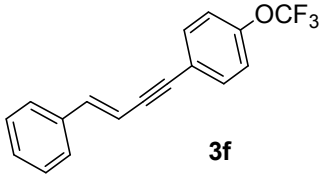
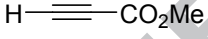
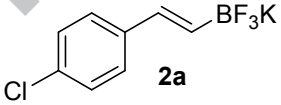
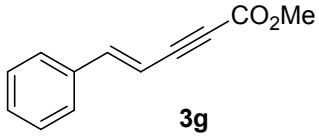
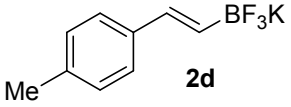
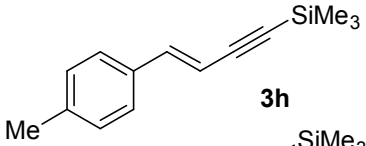
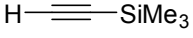
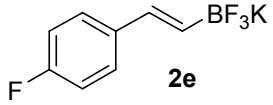
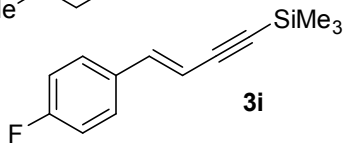
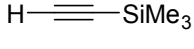
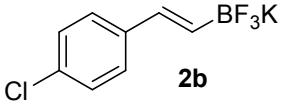
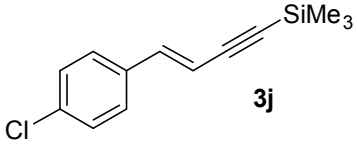


Entry	Catalyst (mol %)	Base (equiv)	Solvent 2.5 mL	Temperature	Time	Observations
1	$Pd(OAc)_2$ (5)	K_2CO_3 (3)	1,4-dioxane	120 °C	60 min	No reaction
2	$Pd(OAc)_2$ (5)	K_2CO_3 (2 and dppb	toluene	110 °C	30 min	homocoupling [a]
3	$PdCl_2$(dppf)DCM (2)	K_2CO_3 (3)	1,4-dioxane	140 °C	60 min	homocoupling [a]
4	$PdCl_2$(dppf)DCM (2)	K_2CO_3 (3) and dppb	toluene (4 mL)	100 °C	60 min	No reaction
5	$Pd_2dba_3.CHCl_3$	K_2CO_3 (3) and dppf	THF (2 mL)	100 °C	20 min	homocoupling [a]
6	$PdCl_2$(dppf)DCM (2)	Cs_2CO_3 (3)	1,4-dioxane	100 °C	60 min	complex
7	$PdCl_2(d^tbpf)$ (1.5)	K_2CO_3 (3)	Acetic acid (1 mL)	120 °C	20 min	No reaction
8	**$PdCl_2(d^tbpf)$ (1.5)**	**K_2CO_3 (3)**	**1,4 dioxane**	**120 °C**	**20 min**	**cross-coupling [b]**
9	$PdCl_2(d^tbpf)$ (1.5)	K_2CO_3 (3)	THF (2.5 mL)	140 °C	60 min	cross-coupling [b]

[a]Homocoupling of **1b** is major. [b]Cross-coupling product **3e** is major with trace homocoupling of **1b** . Equimolar amount of **1b** and **2e** are used. This study is based on GC-MS analysis. Reaction product was purified by preparative TLC (Hex/ethyl acetate =100/1) and yield was 70 % (Entry 8).

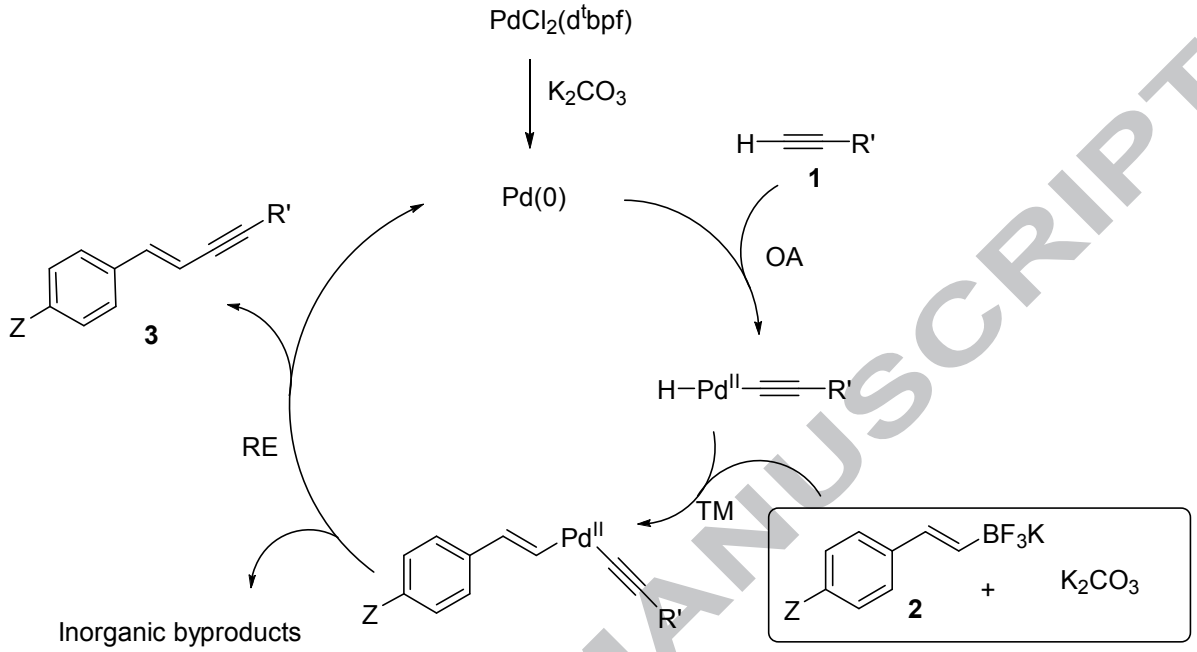
Many control experiments were run to optimize the reaction conditions and the best condition was one equivalent of styryltrifluoroborates and one equivalent of alkyne. The procedure of forming conjugated enyne **3e** from phenyl acetylene (**1b**) and 4-chloro-(2-phenylvinyl) trifluoroborate (**2e**) is a representative one. The reaction was completed in 0.5 mmol scale. After purging with argon a microwave reaction tube with stirrer bar was loaded with 135.5 mg (0.5 mmol, 90% pure) styryltrifluoroborate (**2e**), 207.0 mg (1.5 mmol) of potassium carbonate, and 4.0 mg (0.00625 mmol) of $PdCl_2(d^tbpf)$. The reaction tube was then capped and flushed with argon following which 0.056 mL (0.5 mmol) of phenyl acetylene (98 % pure) and 2.5 mL of 1,4-dioxane were added. The resulting reaction mixture was then irradiated at 140 ^{0}C for 20 min in a microwave (300 W). Crude reaction product was filtered through celite with dichloromethane as eluent. For purification the concentrated crude product was subjected to preparative TLC using hexane/ethyl acetate (100/1) as eluent and collected, yielding 84.0 mg (70%) pure product. Each entry of Table 1 was run at least 2 times. The cross-coupled conjugated enyne products are reactive molecules; therefore, chance of decomposition or oligomerization is high.[8] The crude product was subjected to silica gel chromatography for purification but unexpectedly, this shown less effective for separation as well as promoting decomposition. When we applied ethyl propiolate (**1a**), phenyl acetylene (**1b**), 4-trifluoromethoxyphenyl acetylene (**1c**), and methyl propiolate (**1d**) as C-H alkynes with styryltrifluoroborates, reactions ran for 20 min and furnished the corresponding cross-coupled conjugated enynes in good yields (Entries 1-7, Table 1). Homo-coupling minor products were also observed in GC-MS. In the case of trimethylsilyl acetylene (**1e**), reaction mixtures were microwaved for 60 min to optimize results. In all cases, *E*:Z mixtures (60:40 ratio) were obtained (Entries 8, 9, and 10, Table 1). Although our focus is to explore the reactivity of potassium styryltrifluoroborates, we verified arylvinylboronic acids as boron reagents with C-H alkynes for the same type of cross-coupling reactions.[9] When 1.0 mmol of 4-Chloro-(2-phenylvinyl) boronic acid (**2e**) was reacted with 0.5 mmol of ethyl propiolate (**1a**), phenyl acetylene (**1b**), and methyl propiolate (**1d**) under same reaction conditions, all exhibited the corresponding clean cross-coupling reaction products in GC-MS. Equimolar amounts of boronic acid and alkyne worked but the best result occurred when 2 equiv of boronic acid were loaded.

Table 1. Cross-coupling reactions of alkynes and styryltrifluoroborates. [a]

Entry	Alkynes 1	StyrylBF$_3$K 2	Cross-coupled Enynes 3	Yield %
1	 **1a**	 **2a**	 **3a**	84
2	 **1a**	 **2b**	 **3b**	82
3	 **1a**	 **2c**	 **3c**	69
4	 **1b**	 **2a**	 **3d**	67
5	 **1b**	 **2b**	 **3e**	70
6	 **1c**	 **2a**	 **3f**	83
7	 **1d**	 **2a**	 **3g**	70
8	 **1e**	 **2d**	 **3h**	75[b]
9	 **1e**	 **2e**	 **3i**	82[b]
10	 **1e**	 **2b**	 **3j**	72[b]

[a]All reactions were repeated at least 2 times, Reaction scale (0.5 mmol), $PdCl_2(d^tbpf)$[1.25 mol %], Reaction time 20 min except Entries 8,9,10 (1 h). Yields (Isolated by Prep TLC technique). [b] ***E*** **:** ***Z*** *ratio* (*60:40*)

Scheme 3



This new result further demonstrates the effective catalytic effect of $PdCl_2(d^tbpf)$ in the C-H activation of alkynes and its ability to overcome the limitations of styryltrifluoroborates in cross-coupling reactions by avoiding the effects of the C-X bond in starting materials. In our consideration, $PdCl_2(d^tbpf)$ catalyst may convert to Pd(0) by potassium carbonate and acting as active catalyst by forming Pd^{II} species after oxidative addition, which then undergoes transmetallation followed by reductive elimination, and thereby forming the desired cross-coupling product. The probable catalytic cycle is shown in Scheme 3.

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