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Microwave enhanced cross-coupling reactions involving alkenyl- and alkynyltrifluoroborates

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Abstract—Cross-coupling reactions of potassium alkenyltrifluoroborates and alkynyltrifluoroborates with aryl triflates in the presence of a palladium catalyst occur rapidly utilizing microwave irradiation. The coupled products are generated in good to excellent yields.

Palladium-catalyzed cross-coupling reactions are of great utility in organic chemistry.[1] Suzuki–Miyaura reactions are particularly useful since a wide variety of boron compounds are readily prepared or are commercially available. In addition, boron is relatively nontoxic, readily available, and has a low environmental load. The most common organoboron derivatives used in Suzuki reactions are boronic acids and boronic esters. There are several potential problems with these derivatives. For example, vinylboronic acids can be lost via polymerization side reactions. Furthermore, vinylboronic esters are not always selective in cross-coupling reactions, often yielding mixtures of Suzuki–Miyaura and Heck coupled products.[2] Recent studies have shown that potassium alkenyltrifluoroborates and alkynyltrifluoroborates offer solutions to problems that sometimes occur in organoboron coupling reactions.[3] The trifluoroborates are readily prepared by the addition of inexpensive KHF_2 to a variety of boronic acid derivatives. These materials are crystalline, air stable solids that are easy to manipulate yet remain quite reactive.

In recent years, microwave technology has gained importance in organic chemistry.[4] Microwave induced reactions are energy efficient and generally lead to enhanced product yields. As part of an ongoing project focused on microwave assisted Suzuki coupling reactions, we initiated a study of the behavior of alkenyltrifluoroborates and alkynyltrifluoroborates in Suzuki reactions using microwave irradiation.[5] We discovered that palladium-catalyzed coupling reactions of alkenyltrifluoroborates and alkynyltrifluoroborates with aryl triflates furnish the desired products within 15 min under aqueous conditions and in good yields (Scheme 1). Similar reactions require several hours under thermal conditions.[3g] In this Letter we outline the scope of the microwave assisted cross-coupling reactions of alkenyltrifluoroborates and alkynyltrifluoroborates with aryl triflates (Scheme 1).

Various palladium catalysts, solvents, and reaction conditions were examined using potassium (phenylethynyl)trifluroborate, **1**, and 4-cyanophenyl triflate, **2**, as model substrates (Scheme 1 and Table 1). A catalyst loading of 5 mol % $PdCl_2(dppf)CH_2Cl_2$, along with 3.0 equiv of Hunig's base (i-Pr_2NEt), in 2-propanol/water (2:1) at 100 °C was found to provide the coupled products in good to excellent yields (Table 1, entry 5). Reactions using $Pd_2dba_3{\cdot}CHCl_3$/dppf, $Pd_2dba_3/(o\text{-toyl})_3$, $Pd(OAc)_2$/dppf, and $Pd(OAc)_2$ resulted in lower yields than those using $PdCl_2(dppf)CH_2Cl_2$. In the absence of a palladium catalyst, no coupling product was observed. Reactions did not occur in pure water (Table 1, entry 4) whereas a mixture of THF–H_2O (2:1) gave moderate yield (67%). Hunig's base was found to be the most effective. Decreasing the reaction time to 10 min gave lower yields (Table 1, entry 6).

After optimization of the reaction conditions, we investigated the coupling of various alkynyltrifluoroborates with a number of triflates (Table 2). Triflates containing electron withdrawing groups successfully coupled with

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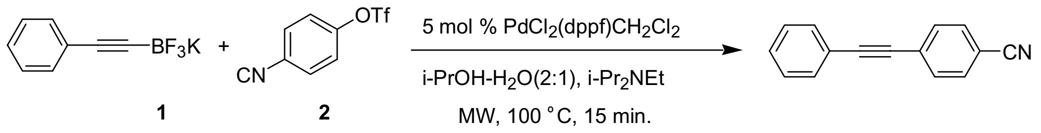


Scheme 1.

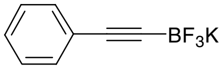
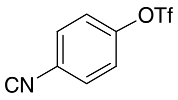
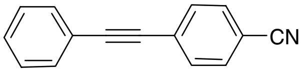
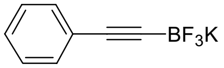
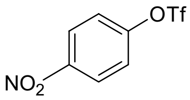
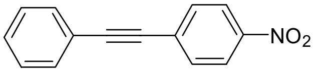
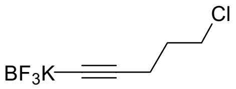
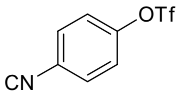
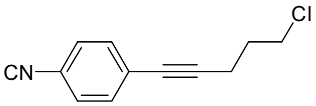
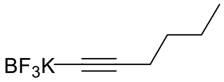
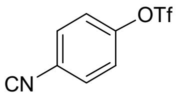
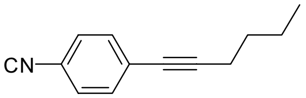
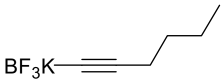
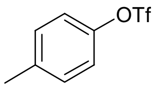
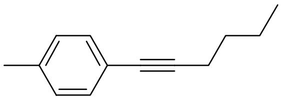
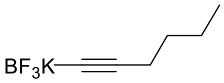
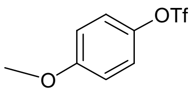
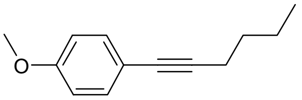
Table 1. Optimization of reaction conditions[a]

Entry	Base	Conditions	Catalysts	Solvent	Yields[b] (%)
1	$CsCO_3$	MW—15 min	$Pd(OAc)_2$	THF–water	45
2	$CsCO_3$	MW—15 min	$Pd_2dba_3{\cdot}CHCl_3$	*i*-PrOH–water	50
3	Hunig's base	MW—15 min	$PdCl_2(dppf)CH_2Cl_2$	THF–water	67
4	Hunig's base	MW—15 min	$PdCl_2(dppf)CH_2Cl_2$	Water	0
5	Hunig's base	MW—15 min	$PdCl_2(dppf)CH_2Cl_2$	*i*-PrOH–water	91
6	Hunig's base	MW—10 min	$PdCl_2(dppf)CH_2Cl_2$	*i*-PrOH–water	80
7	K_2CO_3	MW—15 min	$Pd_2dba_3{\cdot}CHCl_3$	*i*-PrOH–water	60

[a] All reactions were carried out at 100 °C.

[b] All yields are of pure products isolated by silica gel chromatography.

Table 2. Coupling reactions of alkynyltrifluoroborates[a]

Entry	R_1BF_3K	R_2-TOf	R_1–R_2	Yield[b] (%)
1				91
2				96
3				94
4				90
5				79
6				65

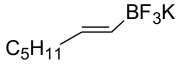
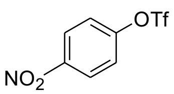
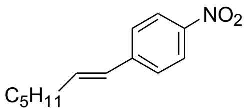
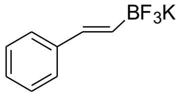
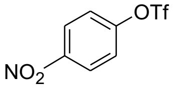
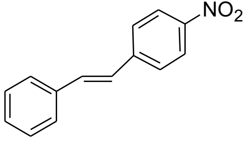
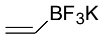
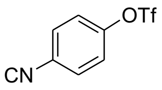
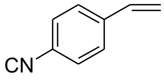
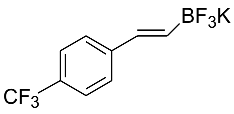
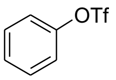
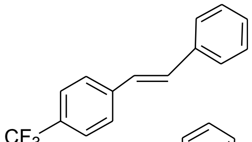
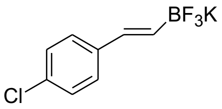
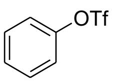
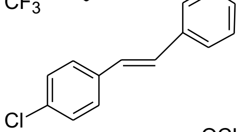
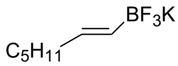
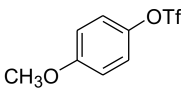
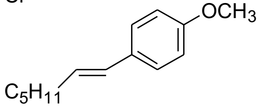
[a] All reactions were run in *i*-PrOH–H_2O (2:1) at 100 °C for 15 min.

[b] All yields are of pure products isolated by silica gel chromatography.

alkynyltrifluoroborates in good yields (Table 2, entries 1–4). Triflates containing electron donating groups gave moderately lower yields (Table 2, entries 5 and 6). Alkenyltrifluoroborates also readily participated in the reaction (Table 3), highest yields were obtained when electron withdrawing groups were present in the triflates (Table 3, entries 1–3). Electron withdrawing groups in the alkenyltrifluoroborates also enhanced the yields (Table 3, entry 4). All alkenyltrifluoroborates provided cross-coupled products in good yields (Table 3, entry 1–6).

Reactions are rapid and simple to perform. In a typical experiment, the organotrifluoroborate (0.55 mmol) and palladium catalyst (5 mol %) are placed in an argon flushed Pyrex tube. The aryl triflate (0.50 mmol) is then added along with di-isopropyl ethyl amine (1.5 mmol) and 5 ml of isopropanol/water (2:1). The Pyrex tube is

Table 3. Coupling reactions of alkenyltrifluoroborates[a]

Entry	R_1BF_3K	R_2-OTf	R_1–R_2	Yields[b] (%)
1				82
2				92
3				90
4				90
5				75
6				61

[a] All reactions were run in *i*-PrOH–H_2O (2:1) at 100 °C for 15 min.

[b] All yields are of pure products isolated by silica gel chromatography.

then capped with a rubber septum, placed in a CEM microwave unit, and allowed to react at 100 °C for 15 min. The product is isolated by adding water (15 ml) and ether (15 ml), the ether layer separated, the solvent removed under reduced pressure, and the product isolated by column chromatography.

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