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# Palladium-Catalyzed Cross-Coupling of Acetates of Baylis–Hillman Adducts and Potassium Organotrifluoroborates

**George W. Kabalka,* Bollu Venkataiah, and Gang Dong**

*Departments of Chemistry and Radiology, The University of Tennessee,*
*Knoxville, Tennessee 37996-1600*

*kabalka@utk.edu*

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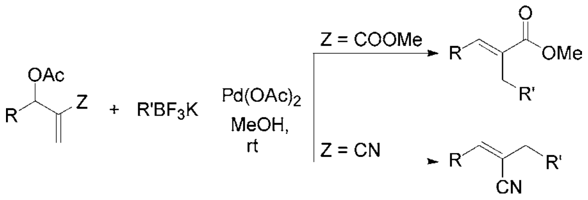
## ABSTRACT



**The cross-coupling of potassium organotrifluoroborates and acetates of Baylis–Hillman adducts proceeds readily in moderate to excellent yield in the presence of Pd(OAc)$_2$. The reaction tolerates hindered trifluoroborate salts, and the process is stereoselective.**

The palladium catalyzed cross-coupling of organoboron compounds and organic electrophiles to form carbon−carbon bonds is an important synthetic reaction.[1] The availability of the prerequisite reagents and the mild reaction conditions all contribute to the versatility of the reaction. Significantly, the reaction is unaffected by water, and a broad range of functional groups are tolerated. The cross-coupling is both regio- and stereoselective.

Palladium catalysts have been used in a wide variety of synthetically useful reactions involving stabilized carbon nucleophiles.[2] However, few studies have been reported in which boron reagents are used as nucleophiles in allylic coupling reactions.[3] Hayashi and co-workers described the reaction of phenylboronic acid with allyl acetates in water using a resin-supported palladium catalyst;[4] later, Balme extended the reaction utilizing various Pd catalytic systems and solvents.[5] These results encouraged us to study the reaction of organoborates with Baylis−Hillman acetates.

The Baylis−Hillman reaction provides molecules possessing hydroxyl, alkene, and electron-withdrawing groups in close proximity, which makes it valuable in a number of stereoselective processes.[6] In a continuation of our study of reactions involving organoboron reagents in nonconventional solvents,[7] we studied the cross-coupling reaction of potassium organotrifluoroborates with acetates of Baylis−Hillman adducts in the presence of Pd catalysts using methanol as the solvent.

We first examined the reaction of *p*-tolylboronic acid with a Baylis−Hillman acetate adduct; however, no reaction occurred. Potassium acetate was then added as a base, but the acetate behaved as a nucleophile and the S$_N$2′ substitution product formed instead of desired product.[8] We then carried out a reaction using cesium fluoride as the base since it has

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* To whom correspondence should be addressed.

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**Scheme 1**

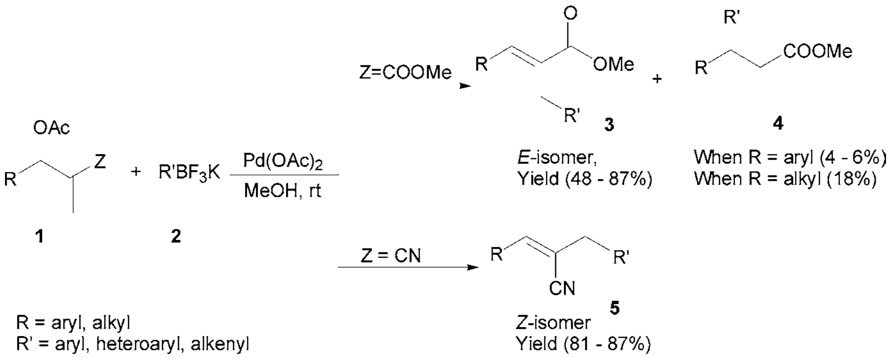
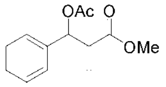
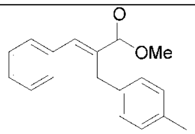
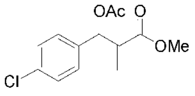
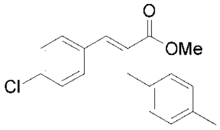
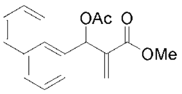
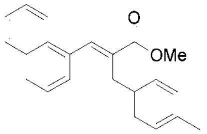
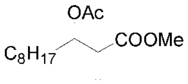
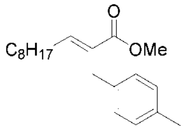
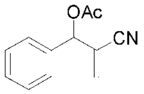
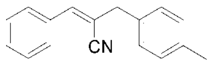
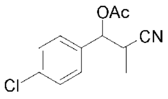
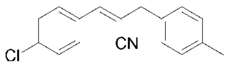
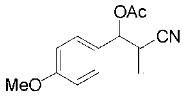
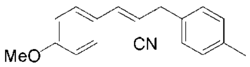
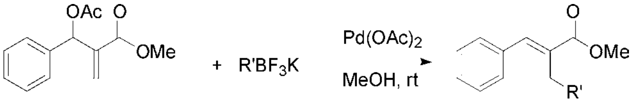


**Table 1.** Reaction of Potassium *p*-Tolyltrifluoroborate with Baylis−Hillman Adduct Acetates[a]

| entry | B-H acetate adduct | product[b] | yield (%)[c] |
|---|---|---|---|
| 1 |  |  | 87 |
| 2 |  |  | 83 |
| 3 |  |  | 84 |
| 4 |  |  | 48 |
| 5 |  |  | 84 |
| 6 |  |  | 87 |
| 7 |  |  | 81 |

[a] All reactions were carried out in the presence of 3 mol % Pd(OAc)$_2$ at room temperature for 3 h. [b] All products exhibited satisfactory spectral ($^1$H, $^{13}$C NMR) and analytical properties. [c] Isolated yields.

**Table 2.** Reaction of Different Potassium Organotrifluoroborates with Baylis−Hillman Adduct Methyl 3-Phenyl-3-acetoxy-2-methylene



| entry | R′ | time (h) | isolated yield (%) |
|---|---|---|---|
| 1 | phenyl | 3 | 86 |
| 2 | *p*-methoxyphenyl | 8 | 76 |
| 3 | 3-thiofuryl | 3 | 61 |
| 4 | 2-methylphenyl | 5 | 76 |
| 5 | 2,6-dimethylphenyl | 12 | 53 |
| 6 | 2,6-difluorophenyl | 48 | 68 |

been shown to be effective in Suzuki coupling reactions.[3f,9] The desired reaction occurred, but a significant quantity of the homo-coupling product formed.

We then utilized potassium organotrifluoroborate salts, which are more nucleophilic than the corresponding boronic acids. They are also air and moisture stable and can be synthesized readily from corresponding boronic acids by the addition of KHF$_2$.[10] Recent studies indicate that trifluoroborate salts have many advantages when compared to boronic acids.[10c,11] Reactions of Baylis−Hillman acetate adducts (**1**) with potassium organotrifluoroborates (**2**) take place in the presence of 3 mol % Pd(OAc)$_2$ in methanol at room temperature in good yields. 3-Acetoxy-2-methylenealkanoates react with a variety of potassium organotrifluoroborates to provide (*E*)-2-substituted 2-alkenoates (**3**) as the major products. Regioisomer **4** was also observed (Scheme 1).[12] However, **3** and **4** are readily separated by column chromatography.

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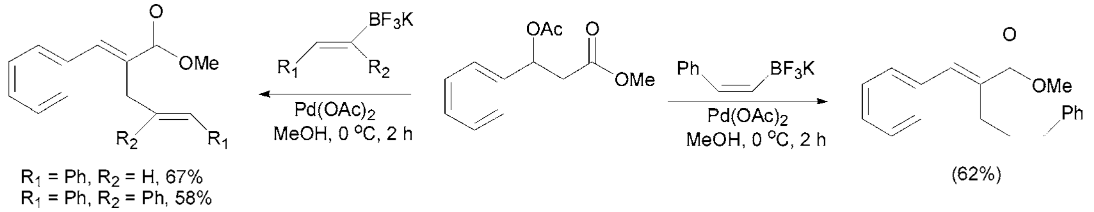
**Scheme 2**



The reaction of 3-acetoxy-2-methylenealkanenitriles provides (*Z*)-2-substituted alk-2-enenitriles (**5**). In this case, the formation of regioisomers was not observed (Scheme 1, Table 1). The formation of esters and nitriles is consistent with earlier studies.[6,13]

The stereochemistry of the products was established by comparing NMR values of olefinic and methylene protons with literature values.[14] In all cases, the stereoselectivity was found to be >98:2, as determined by $^1$H NMR analysis.

Several types of potassium trifluoroborates participate in this reaction (Table 2). These include aryl, heteroaryl, and even sterically hindered trifluoroborate salts. Alkenyltrifluoroborates can also be utilized (Scheme 2). It is noteworthy that (*E*)- and (*Z*)-alkenyl trifluoroborates couple with Baylis–Hillman acetates stereospecifically.[15,16]

In conclusion, we have developed a Pd-catalyzed coupling of potassium organotrifluoroborates with Baylis–Hillman acetate adducts. The protocol is applicable to aryl, heteroaryl, and alkenyltrifluoroborate salts. The reaction of vinylborates is stereospecific. No additional base or ligand is required, and the reaction takes place at room temperature in a straightforward fashion.[17]

**Acknowledgment.** We thank the Department of Energy and The Robert H. Cole Foundation for their support.

**Supporting Information Available:** $^1$H and $^{13}$C spectral and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) Isomer **4** was isolated in 18% yield for the aliphatic Baylis–Hillman reagent (Table 1, entry 4).

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(15) Similar selectivity was observed in the Suzuki cross-coupling of potassium alkenyltrifluoroborates: Molander, G. A.; Bernardi, C. R. *J. Org. Chem.* **2002**, *67*, 8424.

(16) It is interesting to note that trifluoroborate reagents have been shown to be ineffective in Suzuki coupling reactions with certain catalyst systems. See: Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

(17) **General Procedure.** The acetate of Baylis–Hillman adduct **1** (1 mmol) and 3 mol % $Pd(OAc)_2$ is added to a solution of potassium organotrifluoroborate salt **2** (1 mmol) in methanol (5 mL) at 0 °C under a nitrogen atmosphere. The reaction mixture is allowed to stir at room temperature until completion (TLC monitoring). The mixture is then diluted with diethyl ether (10 mL) and filtered to remove solids. The solvent is removed under reduced pressure and the product purified by chromatography (silica gel) to afford analytically pure product.