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Pd-Catalyzed Cross-Coupling of Baylis–Hillman Acetate Adducts with Bis(pinacolato)diboron: An Efficient Route to Functionalized Allyl Borates

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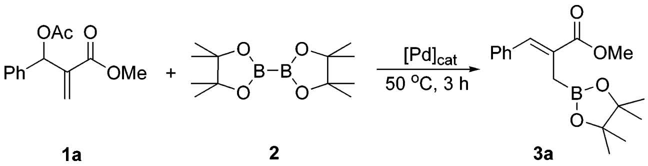
Abstract: The cross-coupling of Baylis–Hillman acetate adducts and bis(pinacolato)diboron proceeds readily in high yields in the presence of palladium catalyst to produce 3-substituted-2-alkoxycarbonyl allylboronates. These allylboronates can be transformed to stable allyl trifluoroborate salts by addition of excess aqueous KHF_2. Both the allylboronate and allyltrifluoroborate derivatives react with aldehydes to afford functionalized homoallylic alcohols stereoselectively.

Allylmetal reagents of boron, silicon, and tin have found widespread use in organic synthesis.[1] The addition of allylmetal reagents to carbonyl compounds has proven to be enormously successful for the synthesis of homoallylic alcohols and is widely used in organic synthesis. Among allylmetal reagents, allylboron compounds are very useful because of the high yield and excellent stereocontrol they provide in reactions with carbonyl compounds via a six-membered, cyclic chair transition state characterized by internal activation of the aldehyde by the boron.[2] Brown,[3] Hoffman,[4] and Roush[5] investigated this transformation in detail. However, availability of functionalized allylboron reagents remains limited. In addition to traditional methods,[5a,6] the prerequisite allylboronates can be prepared via transition metal mediated processes,[7] cross-metathesis reactions of olefins and allylboronates,[8] and a three-component assembly of allenes, acyl chlorides, and bis(pinacolato)diboron.[9] Recently, Kennedy and Hall reported the preparation of 2-alkoxycarbonylallylboronates by carbocupration of alkynoate esters.[10] These results encouraged us to investigate the preparation of substituted 2-alkoxycarbonyl allylboron reagents from Baylis–Hillman adducts.

The Baylis–Hillman reaction has great synthetic utility as it converts simple starting materials into densely functionalized products[11] that are useful in a variety of synthetic transformations. In a continuation of our study of reactions involving organoboron reagents,[12] we investigated the cross-coupling reaction of bis(pinacolato)diboron, **2**, with acetates of Baylis–Hillman adducts **1** in the presence of palladium to form highly functionalized allyl boronates and the corresponding trifluoroborates. The preparation of allylboronate **3a** using the Baylis–Hillman adduct methyl 3-acetoxy-3-phenyl-2-methylenepropanoate, **1a**, and bis(pinacolato)diboron in the presence of different palladium catalysts was first investigated (Table 1).[13] Among the catalysts used, $Pd(OAc)_2$ and $Pd_2(dba)_3$ worked well without additional ligand requirements. The reactions were most efficient in THF and toluene. The highest yields were obtained utilizing $Pd_2(dba)_3$, but the allylboronate products readily decomposed during

TABLE 1. Optimizing Reaction Conditions for the Preparation of Allylboronate 3a from Baylis–Hillman adduct 1a



solvent	catalyst[a]	ligand[b]	yield (GC–MS)
THF	$Pd(OAc)_2$	PPh_3	36
THF	$Pd(OAc)_2$	dppf	48
THF	$Pd(OAc)_2$		92
THF	$PdCl_2(PPh_3)_2$		0
THF	$PdCl_2(dppf)$		0
THF	$Pd_2(dba)_3$[c]		95
ether	$Pd(OAc)_2$		82
toluene	$Pd(OAc)_2$		96
Toluene	$Pd_2(dba)_3$[c]		96

[a] 5 mol % catalyst was used unless otherwise mentioned. [b] 10 mol % ligand was used. [c] 3 mol % catalyst was used.

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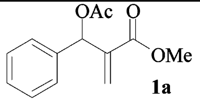
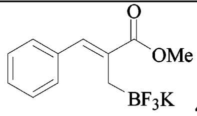
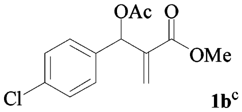
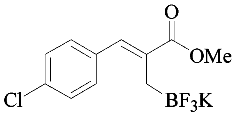
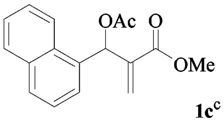
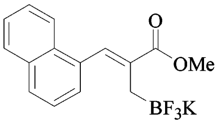
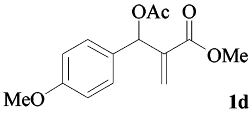
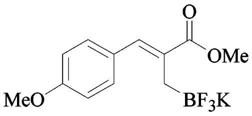
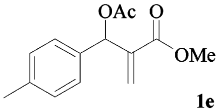
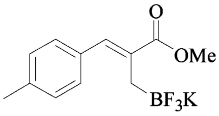
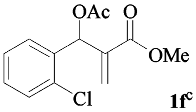
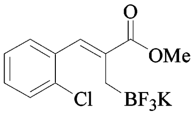
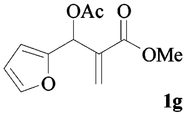
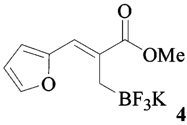
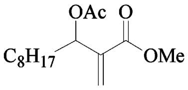
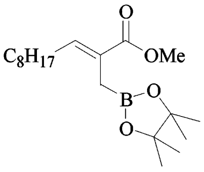
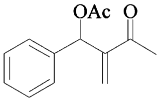
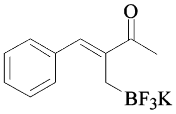
10.1021/jo0492618 CCC: $27.50

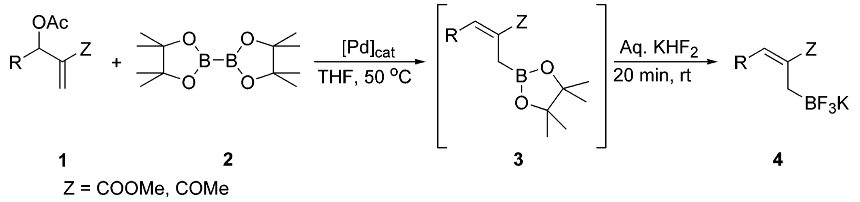
TABLE 2. Preparation of Substituted Allylboron Reagents from Baylis–Hillman Acetate Adducts (1)[a]

B-H acetate adduct	Product[b]	Yield
 **1a**	 **4a**	70
 **1b**[c]	 **4b**	57
 **1c**[c]	 **4c**	65
 **1d**	 **4d**	72
 **1e**	 **4e**	68
 **1f**[c]	 **4f**	56[d]
 **1g**	 **4g**	67
 **1h**	 **3h**	72[e,f]
 **1i**	 **4i**	62

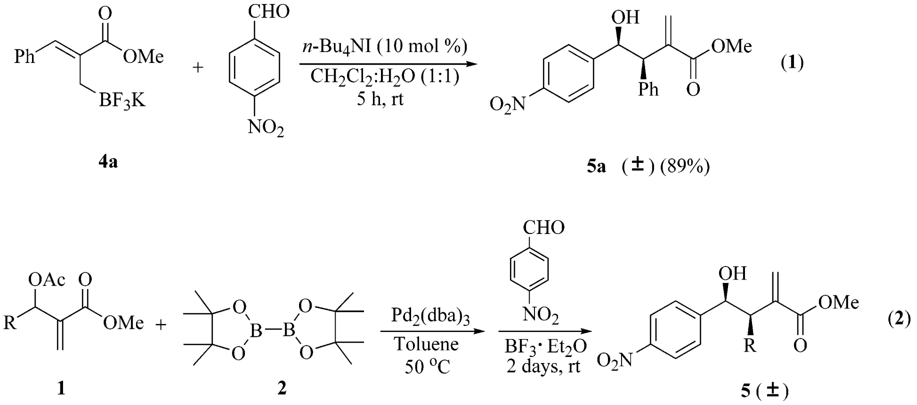
[a] The cross-coupling reaction was performed at 50 °C for 3 h using 5 mol % Pd(OAc)$_2$ in THF unless otherwise noted. [b] Structures confirmed using spectral (^{1}H, ^{13}C, ^{19}F) analyses. [c] 3 mol % Pd$_2$(dba)$_3$ used. [d] E:Z ratio is 97:3. [e] Reaction time was 6 h. [f] GC–MS yield.

silica gel chromatography.[8] To solve this problem, we converted the boronate products, **3**, to the corresponding trifluoroborate derivatives, **4** (Scheme 1). Trifluoroborates are air- and moisture-stable but chemically reactive.[14,15]

SCHEME 1



SCHEME 2



R	Yield
Ph [**5a**]	81%
C_8H_{17} [**5h**]	59%

The reaction procedure is straightforward. The Baylis–Hillman acetate adduct **1** is allowed to react with bis(pinacolato)diboron in the presence of 5 mol % Pd(OAc)$_2$ or 3 mol % Pd$_2$(dba)$_3$ in THF at 50 °C for 3 h. This produces 2-alkoxycarbonyl-3-substituted allylboronate pinacol ester **3**, which is then treated with excess aqueous KHF$_2$ and stirred at room temperature for 20 min to obtain the (*E*)-2-alkoxy-3-substituted allyltrifluoroborate potassium salt **4**. The stereochemistry of the allylboronate was determined to be *E*, using ^{1}H and ^{13}C spectroscopy as well as protonolysis.[16] The results are consistent with earlier studies.[14c,17] It is important to note that allyl trifluoroborate salts are air- and water-stable solids and can be stored at room temperature, whereas allylboronates are unstable to moisture.

Several types of Baylis–Hillman acetate adducts readily participate in the reaction. As shown in Table 2, Baylis–Hillman acetate adducts derived from methyl acrylate (**1a**–**h**) and methyl vinyl ketone **1i** were transformed into the corresponding (*E*)-allylborates.

Allyl trifluoroborate salt **4**, prepared using the present method, reacts with *p*-nitrobenzaldehyde in the presence of tetrabutylammonium iodide to give the corresponding homoallylic alcohols in high yield with excellent diastereoselectivity (eq 1, Scheme 2).[15c] We also studied allylboration reactions without isolating the boron intermediates (eq 2).[18] For example, addition of *p*-nitrobenzaldehyde to the crude cross-coupling reaction mixture readily furnished the corresponding homoallylic alcohols in the presence of 30 mol % BF$_3$·Et$_2$O at room temperature.[19]

In conclusion, we have shown that Baylis–Hillman acetate adducts couple with bis(pinacolato)diboron to give 3-substituted-2-alkoxycarbonyl allylboronates **3**, which can be transformed into air- and water-stable allyltrifluoroborate salts **4** by addition of aqueous KHF$_2$. Alternatively, they can be utilized directly in allylboration reactions with carbonyl compounds to obtain highly functionalized homoallylic alcohols **5**. It is noteworthy that the reaction is *E*-stereoselective and is applicable to Baylis–Hillman acetate adducts derived from aryl, heteroaryl, and aliphilic aldehydes.

Acknowledgment. We thank the Robert H. Cole foundation for support of this research.

Supporting Information Available: Experimental procedures and spectroscopic data for compounds, **4a**–**g**, **4i**, **5a**, and **5h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Reaction of Baylis–Hillman adduct **1a** with bis(pinacolato)-diboron in the presence of Pd(OAc)$_2$ in THF gave allylboronate **3a** in 92% yield (GC–MS); however, when the reaction mixture was exposed to air, formation of (*E*)-2-methyl cinnamic acid methyl ester from **3a** was observed.

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(18) In both cases (Scheme 2, eqs 1 and 2) the diastereoselectivity was found to be >98% by ^{1}H NMR analysis.

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