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# Suzuki−Miyaura Cross-Coupling of Potassium Trifluoroboratohomoenolates

**Gary A. Molander* and Daniel E. Petrillo**

*Roy and Diana A. Vagelos Laboratories, Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104-6323*

*gmolandr@sas.upenn.edu*

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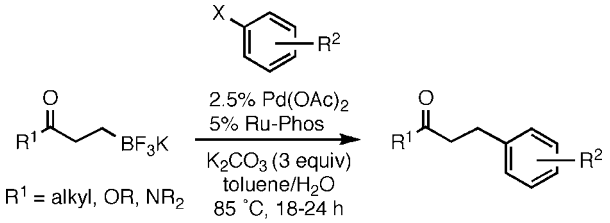
## ABSTRACT



**Ketone-, ester-, and amide-containing potassium trifluoroboratohomoenolates were prepared in good to excellent yields from the corresponding unsaturated carbonyl compounds. They were shown to be effective coupling partners in the Suzuki-Miyaura reaction with a variety of electrophiles including electron-rich and electron-poor aryl bromides and -chlorides.**

Homoenolates[1] or their equivalents are important synthetic reagents, and when employed as nucleophiles in synthetic schemes they exhibit "umpolung" reactivity.[2] Previous methods to generate homoenolates have relied most heavily on the Lewis acid-mediated cleavage of 1-alkoxy-1-siloxycyclopropanes, generating the air- and moisture-sensitive titanium[3] and zinc[4] homoenolates. These useful organometallic compounds have been shown to participate in aldol-type reactions,[3a] copper-mediated conjugate additions,[4] and palladium-catalyzed cross-coupling reactions.[4]

One limitation of commonly used homoenolates is that primarily $\beta$-metallo esters have been employed; the corresponding $\beta$-metallo ketones often react irreversibly to form metallocyclopropanoxides.[5] The limited examples of carbon−carbon bond-forming reactions involving ketone homoenolates include the palladium-catalyzed cross-coupling of zinc homoenolates with acid chlorides[6] and the coupling of in situ generated palladium homoenolates with aryl triflates.[7] Although $\beta$-stannyl ketones have been prepared,[8] to the best of our knowledge there are no examples of their use in a Migita−Stille cross-coupling.

Organoboron reagents are versatile synthetic reagents that participate in many selective carbon−carbon bond-forming reactions.[9] They are known for their functional group tolerance and exhibit minimal toxicity. Potassium organotrifluoroborates have recently been shown to exhibit increased chemical and physical stability compared to other organometallic species.[10] In some cases, they have demonstrated enhanced reactivity compared to other organoborons.[11]

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(1) Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, **1991**; Vol. 2p 441.

(2) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239.

(3) (a) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1977**, *99*, 7360. (b) Nakamura, E. Kuwajima, I. *J. Am. Chem. Soc.* **1983**, *105*, 652.

(4) Nakamura, E.; Aoki, S.; Sekiya, K.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1987**, *109*, 8056.

(5) Shiner, C. S.; Berks, A. H.; Fisher, A. M. *J. Am. Chem. Soc.* **1988**, *110*, 957.

(6) Tamaru, Y.; Ochia, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1157.

(7) (a) Aoki, S.; Fujimura, T.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1988**, *110*, 3296. (b) Fujimura, T.; Aoki, S.; Nakamura, E. *J. Org. Chem.* **1991**, *56*, 2809.

(8) (a) Burley, J. W.; Hutton, R. E.; Oakes, V. *J. Chem. Soc., Chem. Commun.* **1976**, 803. (b) Nakahira, H,; Ryu, I.; Ogawa, A.; Kambe, N.; Sonoda, N. *Organometallics* **1990**, *9*, 277.

(9) Zaidlewicz, M.; Brown, H. C. *Organic Syntheses via Boranes*; Aldrich Chemical Co.: Milwaukee, 2002.

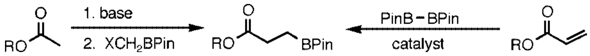
(10) For reviews of organotrifluoroborates, see: (a) Darses, S.; Genet, J.-P. *Chem. Rev.* **2008**, *108*, 288. (b) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (c) Stefani, H. A.; Cellia, R.; Vieira, A. *Tetrahedron* **2007**, *63*, 3623. (d) Molander, G. A.; Figueroa, R. *Aldrichim. Acta* **2005**, *38*, 49.

(11) Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827.

10.1021/ol800357c CCC: $40.75

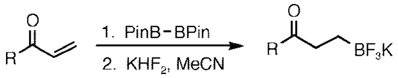
Boron homoenolates can be prepared by a number of methods, including alkylation of a halomethyl boronate species[12] as well as the 1,4-addition of diboron species to unsaturated ketones and esters (Scheme 1).[13] Although these species can be utilized in a number of synthetic applications,[14] their use in the Suzuki-Miyaura cross-coupling[15] is limited to a single example.[16]

**Scheme 1.** Preparation of Boron Homoenolates



As part of a research program in functionalized organoboron reagents[10b,d] we prepared several potassium trifluoroboratohomoenolates via the conjugate addition of bis(pinacolato)diboron to unsaturated carbonyl compounds according to the conditions of Yun and co-workers.[13c] Conversion to the potassium organotrifluoroborate salt was accomplished using $KHF_2$ (Table 1). The trifluoroboratohomoenolates thus prepared were all nonhygroscopic, free-flowing powders or crystalline solids that were indefinitely stable to the atmosphere.

**Table 1.** Preparation of Trifluoroboratohomoenolates[a]



| entry | starting material | product | % isolated yield |
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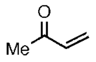
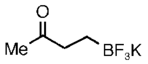
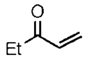
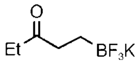
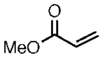
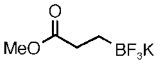
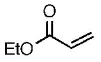
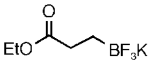
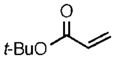
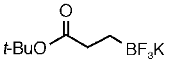
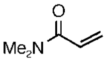
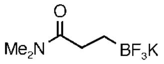
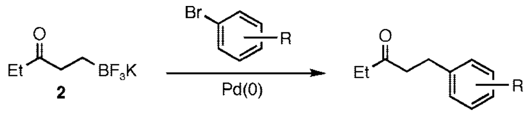
| 1 |  | <br>**1** | 80 |
| 2 |  | <br>**2** | 68 |
| 3 |  | <br>**3** | 74 |
| 4 |  | <br>**4** | 65 |
| 5 |  | <br>**5** | 90 |
| 6 |  | <br>**6** | 46 |

[a] Conditions: (1) 3% CuCl, 3% DPEPhos, 9% NaO*t*-Bu, THF/MeOH, 3 h; (2) $KHF_2$, MeCN, 0 °C, 3 h.

**Table 2.** Cross-Coupling of Electron-Poor Bromides[a]



| entry | ArBr | product | % isolated yield |
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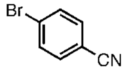
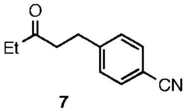
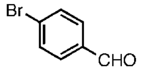
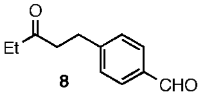
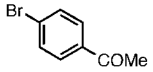
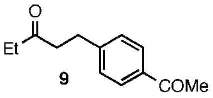
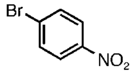
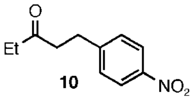
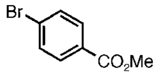
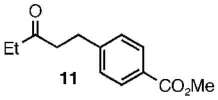
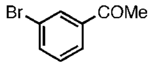
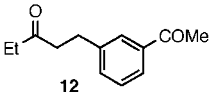
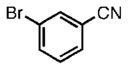
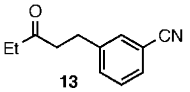
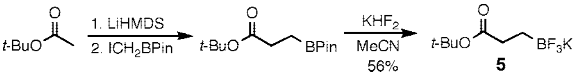
| 1 |  | <br>**7** | 88 |
| 2 |  | <br>**8** | 78 |
| 3 |  | <br>**9** | 83 |
| 4 |  | <br>**10** | 93 |
| 5 |  | <br>**11** | 89 |
| 6 |  | <br>**12** | 87 |
| 7 |  | <br>**13** | 87 |

[a] Conditions: 2.5% $Pd(OAc)_2$, 5% RuPhos, $K_2CO_3$ (3 equiv), toluene/water, 85 °C, 18 h.

The *tert*-butyl ester substituted trifluoroborate **5** was also prepared via alkylation of the lithium enolate of *tert*-butyl acetate with iodomethylpinacol boronate.[12a] The resulting pinacolboronate was converted to the potassium trifluoroborate through treatment with $KHF_2$ to give **5** in moderate yield (eq 1).



(1)

We utilized trifluoroboratohomoenolate **2** in conjunction with *p*-bromobenzonitrile to determine optimal conditions

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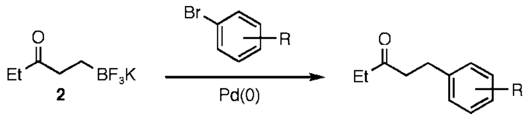
(12) (a) Whiting, A. *Tetrahedron Lett.* **1991**, *32*, 1503. (b) Matteson, D. S.; Majundar, D. *J. Am. Chem. Soc.* **1980**, *102*, 7590. (c) Matteson, D. S.; Cheng, T.-C. *J. Org. Chem.* **1968**, *33*, 3055.

(13) (a) Lawson, Y. G.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R. *Chem. Commun.* **1997**, 2051. (b) Takahashi, K.; Ishiyama, T.; Miyaura, N. *Chem. Lett.* **2000**, 982. (c) Mun, S.; Lee, J.-E.; Yun, J. *Org. Lett.* **2006**, *8*, 4887.

(14) (a) Curtis, A. D. M.; Whiting, A. *Tetrahedron Lett.* **1991**, *32*, 1507. (b) Mears, R. J.; Whiting, A. *Tetrahedron* **1993**, *49*, 177. (c) Curtis, A. D. M.; Whiting, A. *Tetrahedron* **1993**, *49*, 187. (d) Mears, R. J.; Sailes, H. E.; Watts, J. P.; Whiting, A. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 3250.

(15) (a) Suzuki, A.; Brown, H. C. *Organic Syntheses via Boranes: Volume 3 Suzuki Coupling*: Aldrich Chemical Co.: Milwaukee, 2003. (b) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

**Table 3.** Cross-Coupling of Electron-Rich Aryl Bromides[a]



| entry | ArBr | product | % isolated yield |
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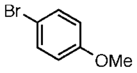
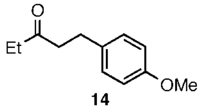
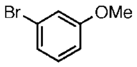
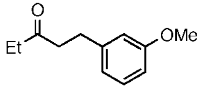
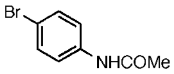
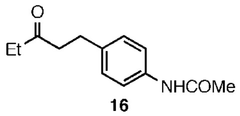
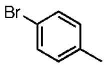
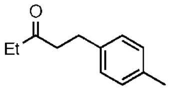
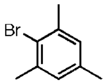
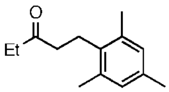
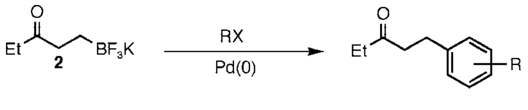
| 1 |  |  **14** | 86 |
| 2 |  |  **15** | 87 |
| 3 |  |  **16** | 78 |
| 4 |  |  **17** | 75 |
| 5 |  |  **18** | 76 |

[a] Conditions: 2.5% Pd(OAc)$_2$, 5% RuPhos, K$_2$CO$_3$ (3 equiv), toluene/water, 85 °C, 24 h.

**Table 4.** Cross-Coupling of Other Electrophiles[a]



| entry | RX | product | % isolated yield |
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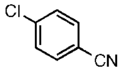
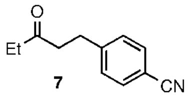
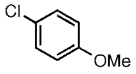
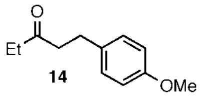
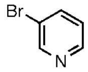
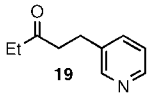
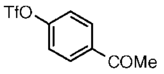
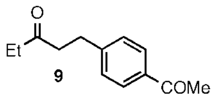
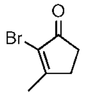
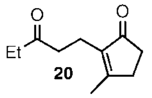
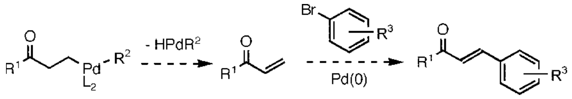
| 1 |  |  **7** | 85 |
| 2 |  |  **14** | 77 |
| 3 |  |  **19** | 73 |
| 4 |  |  **9** | 80 |
| 5 |  |  **20** | 78 |

[a] Conditions: 2.5% Pd(OAc)$_2$, 5% RuPhos, K$_2$CO$_3$ (3 equiv), toluene/water, 85 °C, 18 −24 h.

for cross-coupling. Screening several common catalyst/ligand combinations, we found that the combination of 2.5 mol % Pd(OAc)$_2$/5 mol % RuPhos (2-dicyclohexylphosphino-2′,6′-diisopropoxy-l,l′-biphenyl) in the presence of three equivalents of K$_2$CO$_3$ in toluene/H$_2$O led to an 88% isolated yield of coupled product **7** after heating at 85 °C for 18 h (Table 2, entry 1). To the best of our knowledge, this is the first example of a cross-coupling reaction of a ketone homoenolate with an aryl halide.

Interestingly, there was little to no formation of the corresponding unsaturated products. These could result from $\beta$-hydride elimination of the presumed palladium(II) homoenolate intermediate to form an alkyl vinyl ketone, which could then undergo a Heck reaction. This elimination is a known reaction pathway for palladium homoenolates (eq 2).[17]



(2)

The conditions developed were shown to be general for a variety of electron-poor aryl bromides, providing the coupled products in good to excellent yield (Table 2). Many common functional groups were tolerated in the reaction mixture including an aldehyde, an ester, ketones, and nitriles. A nitro substituent, which is often reduced by alkyl organoboron compounds,[18] was also tolerated, giving the coupled product **10** in excellent yield.

Electrophiles containing an electron-donating group are often difficult coupling partners in the Suzuki−Miyaura reaction. Potassium trifluoroboratoketone **2** was shown to cross-couple to several electron-rich aryl bromides in good yield (Table 3). In addition, a sterically hindered aryl bromide (entry 5) also underwent the cross-coupling reaction effectively.

To demonstrate the scope of the cross-coupling reaction, other common electrophiles were investigated (Table 4). Both an electron-poor (entry 1) and an electron-rich (entry 2) aryl chloride were shown to take part in the cross-coupling reaction. A heteroaromatic bromide (entry 3) and an aryl triflate (entry 4) also gave a good yield of the cross-coupled products. Additionally, an alkenyl bromide (entry 5) participated in this reaction.

We then chose to examine the behavior of other potassium trifluoroboratohomoenolates. The ester homoenolate **5** derived from *tert*-butyl acrylate underwent cross-coupling to provide the product **21** in 70% yield (eq 3). Preliminary results indicate that the corresponding methyl and ethyl esters

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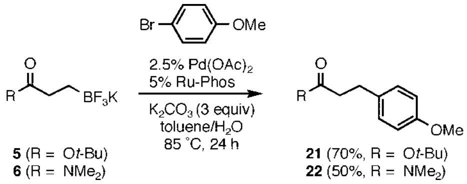
(16) Scherer, S.; Meudt, A.; Nerdinger, S., Lehnemann, B.; Jagusch, T.; Snieckus, V. Method for producing alkyl-substituted aromatic and heteroaromatic compounds by cross-coupling alkyl boronic acids with aryl- or heteroaryl halogenides or sulfonates under Pd catalysis in the presence of a ligand. Sep 21, 2006, WO 2006/097221.

(17) Ryu, I.; Matsumoto, K.; Ando, M.; Murai, S.; Sonoda, N. *Tetrahedron Lett.* **1980**, *21*, 4283.

(18) Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, *4*, 221.

are not effective partners in this process, perhaps owing to competitive ester hydrolysis during the course of the reaction. Pleasingly, the amide-containing homoenolate **6**, derived from dimethyl acrylamide, also participated in the Suzuki−Miyaura cross-coupling reaction under the general conditions to provide **22** in moderate yield. As is the case with ketone homoenolate coupling, this amide homoenolate cross-coupling is unprecedented, and its scope is currently being investigated.



(3)

In conclusion, we have prepared a variety of potassium trifluoroboratohomoenolates and shown that they are effective coupling partners in the Suzuki−Miyaura reaction. These novel coupling reagents are easily synthesized from the conjugate addition of bis(pinacolato)diboron to unsaturated carbonyl compounds, and they represent the most versatile metallohomoenolates for cross-coupling yet introduced. As examples, the methods developed allow the cross-coupling of ketone and amide homoenolates, both previously unrealized cross-coupling partners. Efforts toward the preparation of more complex potassium trifluoroboratohomoenolates and their use in other synthetically important reactions are currently underway.

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**Supporting Information Available:** Experimental procedures, compound characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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