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Ag(I)-promoted Suzuki–Miyaura cross-couplings of *n*-alkylboronic acids

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Abstract—Ag(I) salts significantly enhance palladium-catalyzed Suzuki–Miyaura cross-couplings of *n*-alkylboronic acids with a wide variety of aryl and alkenyl halides/triflates. © 2001 Elsevier Science Ltd. All rights reserved.

The Suzuki–Miyaura cross-coupling reaction has emerged as one of the premier methods for the creation of carbon–carbon bonds under mild conditions.[1] Extensive exploration of reaction parameters and catalysts in recent years has significantly extended its scope.[2] While many types of organoboron compounds[3] are suitable donors, boronic acids are especially popular. The latter are readily prepared, thermally stable, tolerant of adventitious oxygen and water, and generate an innocuous by-product.[4] Aryl- and alkenylboronic acids typically afford good yields of cross-coupled adduct with a wide range of electrophiles, inter alia, chlorides, bromides, triflates,[5] sulfonium salts,[6] heteroaryl,[7] and sterically demanding aryl moieties.[8] In contrast, *n*-alkylboronic acids are often refractory, resulting in poor yields, even under forcing conditions.[9] To improve their reactivity, boronic acids are either (1) converted to potassium trifluoroborates;[10] (2) esterified and further elaborated into 'ate' complexes[11] or (3) complexed with highly toxic thallium salts.[12] However, we have observed Ag(I) salts[13] significantly enhance Suzuki–Miyaura cross-couplings of *n*-alkylboronic acids and we report herein the scope and limitations of this modification (Eq. (1)).

$$\mathrm{RCH_2\text{-}B(OH)_2} \xrightarrow[\mathrm{Pd(dppf)Cl_2} \atop \mathrm{Ag(I)^+,\ K_2CO_3}]{\textbf{E-X}} \mathrm{RCH_2\text{-}}\textbf{E} \qquad (1)$$

Some reaction parameters were briefly explored using commercial *n*-butylboronic acid[14] (**1**) and *cis*-alkenyl iodide **2**. The best yields of **3** were obtained with a combination of Ag_2O and Pd(dppf)Cl_2 in THF at 80°C (Table 1, entry 1).[15] The presence of additional base was also required for optimum performance; generally, powdered K_2CO_3 was preferable to aqueous KOH. As observed for **2**, cross-coupling of *cis*-alkenyl bromide **4** proceeded with complete retention of configuration giving rise to **3** (entry 2), but in somewhat diminished yield. Notably, even the sensitive homoallylic epoxide **5**[16] afforded a useful yield of adduct **6** (entry 3).[17] In contrast, dimerization predominated with *trans*-alkenyl iodide **7** and only a modest amount of silyl dec-5-enol **8** was produced (entry 4). Interestingly, aryl electrophiles were well behaved regardless of the presence of electron-rich or -deficient substituents. Aryl bromide **9** (entry 5), iodide **11** (entry 6), and triflate **12** (entry 7) furnished good yields of 4-(*n*-butyl)anisole (**10**). Similarly, ketone **14** and ester **16** were smoothly generated from bromides **13** (entry 8) and **15** (entry 9), respectively. Aryl and alkenyl chlorides, on the other hand, were poor substrates and afforded comparatively little adduct regardless of reaction conditions.[2a]

The transformation of terminal olefin **17** (entry 11), ester **19** (entry 12), and silane **21** (entries 13 and 14) into **18**, **20**, **22**, and **23**, respectively, demonstrated that a variety of functional groups are well tolerated on the boronic acid moiety. For the simplest case, i.e. methylboronic acid (**24**), cross-coupling with *cis*-alkenyl iodide **2** under the standard reaction conditions was sluggish and only a trace of **25** was isolated. However, efficiency was restored by the addition of *n*-PrOH to improve the solubility of **24** in the reaction medium (entry 15).

Keywords: Suzuki–Miyaura; alkylation; boron; coupling reactions; palladium.

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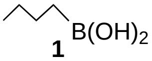
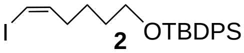
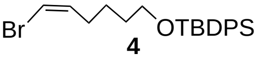
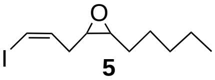
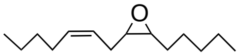
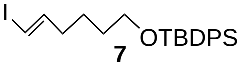
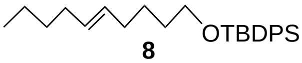
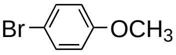
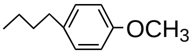
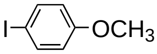
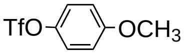
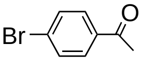
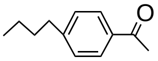
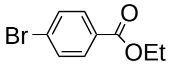
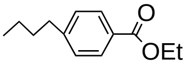
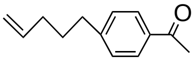
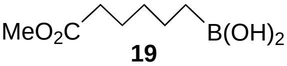
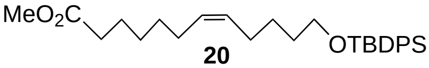
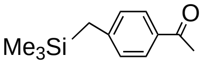
Table 1. Ag(I)-promoted Suzuki–Miyaura cross-couplings of *n*-alkylboronic acids

Entry	Boronic Acid	Electrophile	Adduct	Yield (%)
1	 **1**	 **2**	 **3**	90
2	**1**	 **4**	**3**	78
3	**1**	 **5**	 **6**	84
4	**1**	 **7**	 **8**	38
5	**1**	 **9**	 **10**	80
6	**1**	 **11**	**10**	80
7	**1**	 **12**	**10**	92
8	**1**	 **13**	 **14**	84
9	**1**	 **15**	 **16**	82
11	 **17**	**15**	 **18**	77
12	 **19**	**2**	 **20**	90
13	 **21**	**2**	 **22**	63
14	**21**	**14**	 **23**	80
15	Me−B(OH)$_2$[a] **24**	**2**	 **25**	80

[a] *n*-PrOH (10 equiv) added.

In summary, we describe a practical, high yield modification of the Suzuki–Miyaura cross-coupling reaction utilizing unactivated, primary alkyl groups under mild conditions.

General procedure: A suspension of boronic acid (0.27 mmol, 1.1 equiv.), organic electrophile (1.0 equiv.), Pd(dppf)Cl$_2$ (0.1 equiv.), powdered K$_2$CO$_3$ (3 equiv.), and Ag$_2$O (2.5 equiv.) in THF (5 mL) was stirred under argon at 80°C in a sealed tube. After 6–10 h, the mixture was cooled to room temperature, quenched with 30% H$_2$O$_2$/10% aq. NaOH, and extracted thrice with Et$_2$O. The combined ethereal extracts were concentrated in vacuo and the residue was purified via SiO$_2$ chromatography (see Table 1).

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15. For example: $Pd(Ph_3P)_4$, $Pd(Cy_3P)_4$, $(dba)_3Pd_2/(t\text{-}Bu_3)P$, $Ni(dppe)Cl_2$, $Pt(Ph_3P)_4$ were inferior. In some instances, toluene as solvent gave comparable yields to those in THF, but dioxane and DMF were less satisfactory.
16. See *Tetrahedron Lett.* **2001**, *42*, 7211–7212 for the application of this methodology to the synthesis of bioactive eicosanoid metabolites.
17. Spectral data for **5**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.40 (dt, J=1.5, 7.0 Hz, 1H), 6.31 (apparent q, J=7.0 Hz, 1H), 3.01–3.07 (m, 1H), 2.91–2.98 (m, 1H), 2.39 (td, J=6.7, 1.5 Hz, 2H), 1.28–1.64 (m, 8H), 0.91 (t, J=7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 84.9, 57.1, 54.8, 33.9, 31.7, 27.8, 26.3, 22.6, 14.1. Adduct **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.50–5.58 (m, 1H), 5.38–5.48 (m, 1H), 2.90–2.98 (m, 2H), 2.34–2.45 (m, 1H), 2.15–2.26 (m, 1H), 2.07 (apparent q, J=6.4 Hz, 2H), 1.24–1.58 (m, 12H), 0.92 (m, 6H). (1*R*,2*R*,3*S*,5*R*)-(−)-Pinanediol ester of **17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76–5.89 (m, 1H), 4.90–5.05 (m, 2H), 4.25 (dd, J=2.0, 8.8 Hz, 1H), 2.29–2.39 (m, 1H), 2.18–2.26 (m, 1H), 2.02–2.12 (m, 3H), 1.80–1.96 (m, 2H), 1.52 (quintet, J=8.0 Hz, 2H), 1.39 (s, 3H), 1.29 (s, 3H), 1.12 (d, J=10.8 Hz, 1H), 0.81–0.88 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 114.6, 85.5, 77.7, 51.4, 39.7, 38.2, 36.5, 35.7, 28.8, 27.2, 26.6, 24.1, 23.7. (1*R*,2*R*,3*S*,5*R*)-(−)-Pinanediol ester of **21**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.25 (dd, J=2.4, 8.8 Hz, 1H), 2.30–2.39 (m, 1H), 2.18–2.26 (m, 1H), 2.05 (apparent t, J=5.2 Hz, 2H), 1.88–1.95 (m, 1H), 1.80–1.87 (m, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.17 (d, J=10.8 Hz, 1H), 0.85 (s, 3H), 0.13 (s, 2H), 0.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.3, 77.6, 51.5, 39.8, 38.3, 35.9, 29.0, 27.3, 26.7, 24.2, 0.61. Adduct **23**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (dt, J=1.8, 7.5 Hz, 1H), 7.56–7.60 (m, 1H), 7.29 (apparent t, J=7.8 Hz, 1H), 7.16–7.22 (m, 1H), 2.57 (s, 3H), 2.14 (s, 2H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 141.4, 137.2, 132.9, 128.5, 127.7, 124.4, 27.2, 26.9, −1.78.