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Homocoupling of alkyl-, alkenyl-, and arylboronic acids

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Abstract—Alkyl-, alkenyl-, and arylboronic acids undergo $Ag_2O/CrCl_2$ mediated homocoupling in moderate to good yields under mild conditions. The general utility of this methodology is illustrated by an intramolecular annulation between *sp* and sp^3 centers.

The Pd-catalyzed homocoupling[1] of aryl- and alkenylboronic acids has become a popular alternative to Cu and other transition metal mediated dimerizations typified by the Ullmann[2] and Pschorr reactions.[3] However, despite numerous improvements[4–7] in recent years to this version of the Suzuki protocol, some substrates give poor yields and/or afford mixtures of stereoisomers. Faced with such a situation, we re-investigated early reports[8,9] of aqueous $AgNO_3$ mediated boronic acid homocouplings and describe herein a $CrCl_2$ catalyzed version applicable to an extensive variety of alkyl-, alkenyl-, and arylboronic acids in organic solvents under mild conditions (Eq. (1)).

$$\text{R-B(OH)}_2 \xrightarrow[\substack{\text{CrCl}_2\text{ (cat)} \\ \text{THF}}]{\text{Ag}_2\text{O}} \text{R-R} \qquad (1)$$

To accommodate a wider range of substrates than possible using the previous aqueous media,[8,9] various metal salts [e.g. $NiCl_2$, CuBr, $Pb(OAc)_2$, Tl_2CO_3, MnO_2] in typical organic solvents were evaluated. Generally, silver salts were the most reliable, but yields of homocoupled adduct were generally poor unless the reaction was sustained by a catalytic amount of $CrCl_2$. Notably, the reaction was unsatisfactory using $CrCl_2$ alone, even in stoichiometric quantities, and in hydroxylic solvents. THF proved superior to DMSO, DMF, Et_2O, and toluene. Coupling failed completely using boronate esters. While the exact mechanism of the reaction remains obscure, we favor an initial de-boronylation via the corresponding silver salt, analogous to the de-carboxylation step in the Borodin–Hunsdiecker reaction,[10] resulting in a labile organo-silver or -chromium[11] intermediate that subsequently dimerizes.

Simple and functionalized aliphatic boronic acids (**1**, **3**, **5**, and **7**)[12] afforded moderate to good yields of dimer (**2**, **4**, **6**, and **8**, respectively) using Ag_2O with catalytic $CrCl_2$ in THF at 65°C overnight (Table 1). This contrasts with the normally sluggish reactivity of *n*-alkyl groups during Pd-catalyzed Suzuki homocouplings.[4] Despite its low yield, the conversion of α-methoxy boronic acid **9** to di-ether **10**, obtained as a mixture ($\sim$1:1) of *erythro*/*threo* isomers, merits attention; analogous transformations creating new bonds between carbons bearing heteroatoms are rare[13] and have obvious synthetic utility since two stereocenters are established simultaneously.

Reaction of vinyl boronic acid **11** under the standard conditions proceeded stereospecifically and furnished *E*,*E*-**12** as the sole product in excellent yield. A comparable coupling using $PdCl_2/Na_2CO_3$ gave a somewhat lower yield as a mixture of *Z*,*E*-stereoisomers.[4] Whereas earlier workers noted only protonolysis with aqueous $AgNO_3$,[9] we observed arylboronic acids readily homocoupled when subjected to our standard conditions. Electron withdrawing (**13** to **14**) or donating (**15** to **16**) substituents had comparatively little effect on the yield. Steric hindrance in some instances (**17** to **18**) seemed to improve coupling efficiency, possibly by retarding competing protonolysis which was the principle side reaction in most cases. Styryl (**19** to **20**) and *cis*-olefins (**21** to **22**), likewise, were compatible with the reaction conditions. The dimerizations of **23** and **25**

Keywords: dimerisation; annulation; chromium; boron; coupling reactions.

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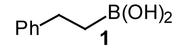
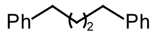
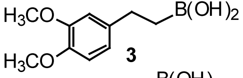
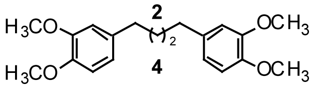
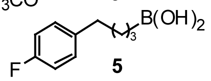
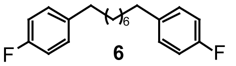
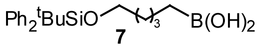
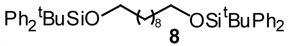
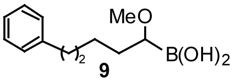
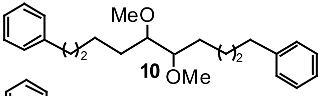
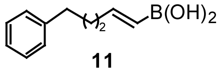
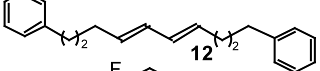
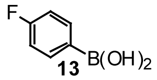
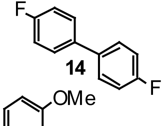
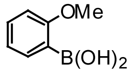
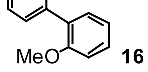
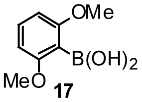
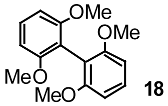
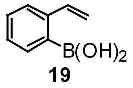
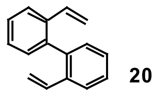
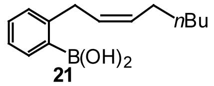
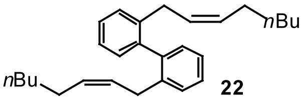
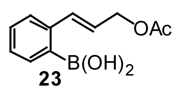
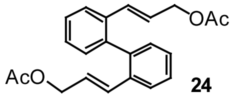
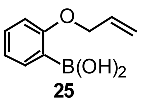
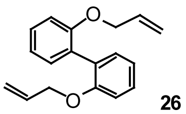
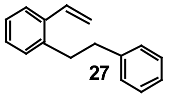
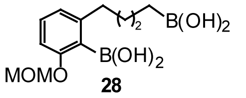
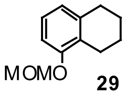
Table 1. Homocoupling of boronic acids

Entry	Boronic Acid	Adduct	Yield (%)
1	 1	 2	78
2	 3	 4	72
3	 5	 6	65
4	 7	 8	68
5	 9	 10	23
6	 11	 12	95
7	 13	 14	62
8	 15	 16	68
9	 17	 18	75
10	 19	 20	83
11	 21	 22	88
12	 23	 24	73
13	 25	 26	85
14	19 + 1	 27 + 2 (1:1.1)	81
15	 28	 29	85

generating **24** and **26**, respectively, in good yield deserve particular attention. Due to competing π-allyl complex formation, these homocouplings failed completely under the usual Pd-catalyzed conditions.[1] Interestingly, reaction of an equimolar amount of **1** and **19** led to an ~1:1.1 mixture of cross-coupled adduct **27** (sp^2–sp^3 union) and homocoupled **2** (sp^3–sp^3 union); little, if any, biphenyl **20** (sp^2–sp^2 union) was isolated, presumably reflecting its kinetically slower rate due to steric hindrance. The potential utility of the latter mixed coupling was illustrated in the intramolecular cyclization that yielded **29** from **28**.

In conclusion, we report an operationally simple, highly efficient homocoupling of a wide range of boronic acids. In contrast with dimerizations mediated by Pd-catalysts, this methodology is useful for the stereospecific homocoupling of olefinic boronic acids and is compatible with allylic acetates and ethers.

General procedure: Freshly prepared Ag_2O (3 mmol) and $CrCl_2$ (5 mol%) were added to a well stirred solution of boronic acid (1 mmol) in anhydrous THF (4 mL) under an argon atmosphere, then heated at 65°C. After 10–12 h, the mixture was cooled to room temperature, filtered, diluted with an equal volume of Et$_2$O, washed with H$_2$O (10 mL), brine (10 mL), dried and concentrated in vacuo. Purification of the residue via SiO$_2$ chromatography provided the adducts in the indicated yields (Table 1).

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12. Spectral data for new compounds, **5**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.77–0.85 (m, 2H), 1.34–1.48 (m, 2H), 1.50–1.72 (m, 2H), 2.55–2.65 (m, 2H), 4.80–4.91 (bs, 2H), 6.91–7.02 (m, 2H), 7.07–7.18 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 17.1, 28.2, 34.4, 36.8, 115.3, 130.2, 134.8, 160.2. **6**: ^{1}H NMR δ 1.73–2.01 (s, 12H), 2.55 (t, 4H, J=7.6 Hz), 6.91–6.98 (m, 4H), 7.09–7.14 (m, 4H); ^{13}C NMR δ 30.0, 30.3, 32.3, 36.2, 114.9, 129.5, 134.5, 160.2. **9** pinacol ester: ^{1}H NMR δ 1.24 (d, 12H, J=3.3 Hz), 1.25–1.48 (m, 2H), 1.60–1.83 (m, 4H), 2.58–2.65 (m, 2H), 3.16 (t, 1H, J=8.1 Hz), 3.32 (s, 3H), 7.14–7.27 (m, 5H); ^{13}C NMR δ 21.5, 23.6, 25.8, 32.9, 35.6, 55.1, 73.0, 88.8, 125.5, 127.7, 127.9, 135.5. **10** (mixture of erythro/threo-stereoisomers: ^{1}H NMR δ 1.31–1.68 (m, 12H), 2.61 (t, 4H, J=7.6 Hz), 3.08–3.13 (m, 2H), 3.30 (s, 3H), 3.31 (s, 3H), 7.18–7.39 (m, 10H); ^{13}C NMR δ 23.5, 23.8, 24.4, 28.6, 30.4, 31.5, 32.9, 54.4, 55.0, 79.0, 82.2, 125.3, 127.9, 130.2, 135.2. **12**: ^{1}H NMR δ 1.71 (apparent quintet, J=7.3 Hz), 2.10 (apparent quintet, 4H, J=7.3 Hz), 2.62 (t, 4H, J=7.8 Hz), 5.54–5.64 (m, 2H), 5.98–6.08 (m, 2H), 7.18–7.22 (m, 6H), 7.25–7.30 (m, 4H); ^{13}C NMR δ 29.9, 35.4, 36.2, 125.4, 127.6, 128.3, 128.5, 133.2, 138.3. **22**: ^{1}H NMR δ 0.85–0.92 (m, 6H), 1.21–1.45 (m, 12H), 2.05–2.20 (m, 4H), 3.40 (d, 4H, J=6.1 Hz), 5.52–5.56 (m, 4H), 7.18–7.32 (m, 8H); ^{13}C NMR δ 14.9, 22.7, 26.7, 30.2, 32.4, 34.1, 125.9, 126.6, 129.2, 129.5, 130.0, 134.6, 138.8, 139.1. **23**: ^{1}H NMR (300 MHz): δ 2.09 (s, 3H), 4.73 (d, 2H, J=6.3 Hz), 4.76–4.85 (bs, 2H), 6.05–6.15 (m, 1H), 7.10 (d, 1H, J=16.6 Hz), 7.25–7.31 (m, 1H), 7.37–7.44 (m, 4H), 7.69 (d, 1H, J=7.0 Hz); ^{13}C NMR δ 18.0, 70.6, 123.2, 125.6, 126.8, 127.3, 127.7, 128.4, 128.5, 136.6, 174.6. **24**: ^{1}H NMR δ 2.01 (s, 6H), 4.54 (d, 2H, J=6.1 Hz), 6.13–6.20 (m, 2H), 6.28 (d, 2H, J=15.8 Hz), 7.14 (d, 2H, J=7.3 Hz), 7.29–7.38 (m, 4H), 7.62 (d, 2H, J=7.6 Hz); ^{13}C NMR δ 18.4, 71.7, 175.1, 125.8, 126.1, 126.6, 126.7, 127.2, 127.7, 132.6, 136.2. **27**: ^{1}H NMR δ 2.84–2.88 (m, 2H), 2.95–3.01 (m, 2H), 5.31 (dd, J=9.7, 1.2 Hz, 1H), 6.66 (dd, J=15.8, 1.5 Hz, 1H); 6.97–7.04 (m, 1H), 7.15–7.28 (m, 8H), 7.49–7.51 (m, 1H); ^{13}C NMR δ 35.8, 36.9, 114.8, 126.0, 126.1, 127.3, 127.7, 128.5, 129.7, 133.6, 136.6, 136.8, 141.3.
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