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Biaryl Formation Using the Suzuki Protocol: Considerations of Base, Halide, and Protecting Group.

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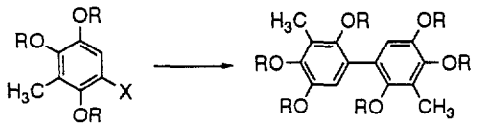
Abstract. The generation of aryl anions prior to quenching with a trialkyl borate has been shown to be sensitive to the composition of the aryl substrate. Aryl iodides containing remote benzyl ether substituents undergo *trans*-metallation with *sec*-BuLi to cleanly give the desired aryl anions whereas the corresponding bromides afford appreciable quantities of dianionic intermediates. The aryl boronic acids derived from alkylation of these anions subsequently undergo a palladium mediated coupling with aryl halides to provide good yields of the desired biaryls.

In the course of our studies on the formation of polycyclic quinoidal systems, we desired to effect the dimerization of aryl halides of type **1** (Fig. 1). Copper and nickel catalyzed methods[1] failed in our hands, and the palladium-mediated couplings of magnesium or lithium anions[2] afforded biaryls in poor yield (10-18%). The Suzuki coupling of aryl boronic acids with aryl halides, however, provided biaryls in synthetically useful quantities.[3] The intermediate boronic acids were formed from the corresponding aryl halide via a standard metal-halogen exchange reaction followed by addition of a trialkylborate and hydrolysis. We have discovered a competitive deprotonation process during the formation of highly oxygenated aryl lithiums and now report these findings along with the results of the subsequent coupling reactions. The sensitivity of these reactions to the alkyl lithium reagent used, the identity of the starting halide and the choice of ether protecting groups is also discussed.



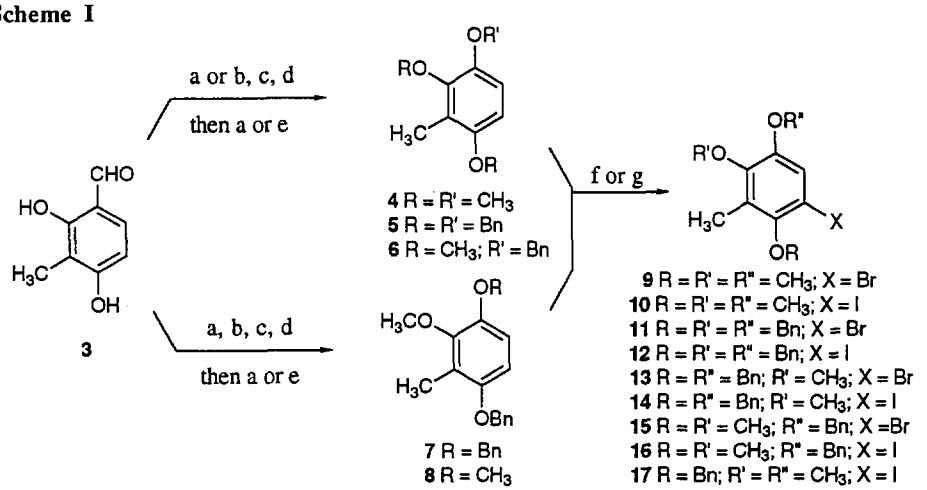
1 **2**

Figure 1

The substrates for our investigations were prepared from 2-methyl resorcinol by the process outlined in Scheme I. A Gatterman reaction ($Zn(CN)_2/HCl$)[4] provided aldehyde **3** which, after a standard transformation sequence, afforded the symmetrically protected toluene derivatives

4 and **5**.[5] With careful monitoring of the alkylation process, the *mono*-benzylated product could be obtained and further processed to the differentiated derivatives **6**, **7**, and **8**. Halogenation of these derivatives was affected with the appropriate *N*-halosuccinimide in THF with a catalytic amount of H_2SO_4[6] or with Br_2 in THF for **13** and **15**.[7]

Scheme I



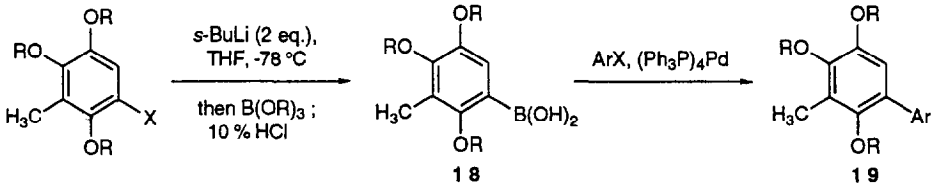
Reagents: a) BnCl, K_2CO_3, Bu_4NI, Acetone, Δ; b) $(H_3CO_2)_2SO_2$, K_2CO_3, Acetone, Δ; c) *m*-CPBA, CH_2Cl_2; d) $NaOCH_3$, CH_3OH, Δ; e) $(H_3CO)_2SO_2$, NaH, THF, 0 °C; f) NIS or NBS, H_2SO_4 (cat.), THF; g) Br_2, THF.

Metal-halogen exchange of aryl halide **9** conducted with *s*-BuLi (2.2 equivalents, THF, -78 °C) afforded a dark orange solution of the aryl lithium anion which provided the aryl boronic acid in moderate yield (41%) upon addition of tri-*O*-methyl borate and hydrolysis.[8] Better results were obtained using tri-*O*-isopropyl borate followed by hydrolysis with 10% HCl (Table I). These conditions provided consistent yields of the boronic acids as stable, easily handled solids after chromatography; the use of *n*-BuLi provided boronic acids in lower isolated yields while *t*-BuLi was ineffective for this transformation. Aryl iodides or bromides worked equally well, and the reaction was insensitive to the identity of the ether at C6. Substrates which contained a benzyl ether at C3 however, provided anomalous results (runs c, e and g). Aryl iodide **12** afforded the desired boronic acid while the corresponding bromide **11** provided a 2.5:1 mixture of products; the major was the expected boronic acid **18c** while the other was **23c**, a boronic acid *that had undergone alkylation at the C3 benzyl ether*![9] A deprotonation and alkylation process had occurred at the more reactive benzylic position prior to the addition of the borate such that two boronic acid products were formed.

These results suggested that the rate of halide elimination from *s*-butyl iodide was considerably faster than from the bromide such that deprotonation of **20** to form the dianion **21** was competitive with the elimination process ($k_{elim} \approx k_{deprot}$) (Scheme II). The alkyl iodide from

12 was rapidly destroyed by the second equivalent of *s*-butyl lithium while, in the case of **11**, elimination was slower and deprotonation of the acidic benzylic position could occur at a comparable rate. The *s*-butyl bromide from the exchange was being partitioned between elimination and alkylation; no diboronic acid products were isolated. This was a general phenomenon as C3 benzyl ether substrates **13** and **15** provided a 3:2 and 1:1 ratio of boronic acid products, respectively, under the standard alkylating conditions.

Table I



18 **19**

Run	Substrate	**18** (%)	ArX	**19** (%)
a	**9**	72	**9**	66
b	**10**	63	**10**	67
c	**11**	57* (79%)	**11**	83
d	**12**	76	**12**	80
e	**13**	42* (56%)	-	-
f	**14**	91	**17**	93
g	**15**	35* (60%)	-	-
h	**16**	89	-	-

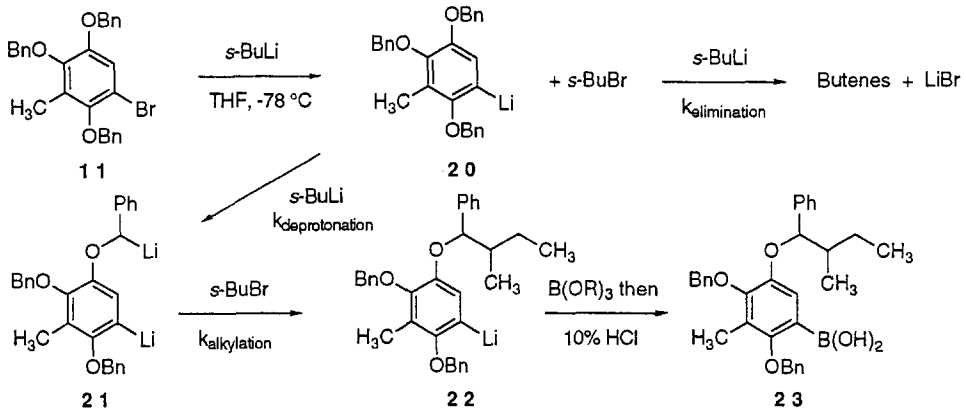
* -The boronic acid product was isolated as a mixture of **18** and **23**, the product derived from dianion formation. The total conversion is listed in parentheses.

Our initial attempts at the formation of the biaryl linkage utilized the one-pot procedure of Keay[10] however, very little (<20%) of the coupled material could be isolated. It was postulated that small amounts of phenolic by-products in the formation of the boronic acids could be interfering with the palladium catalyst; chromatographically pure boronic acids were smoothly converted into the desired compounds. While the standard alkaline conditions (2.0 M Na_2CO_3) afforded **18a** in modest yield (41%), the fluoride assisted procedure provided superior results and showed excellent reproducibility.[11]

In summary, highly oxygenated aryl boronic acids are accessible but the correct choice of aryl halide, lithium base, ether protecting group, and borate electrophile is essential. Simple substitutions can lead to anomalous results that are derived from dianionic intermediates, behavior

that can be eliminated by the use of aryl iodide precursors. A two step Suzuki protocol using a purified boronic acid intermediate provides excellent yields of the corresponding biaryls. Application of this methodology to the synthesis of quinoidal natural products is currently underway and will be reported in due course.

Scheme II



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5) All new compounds exhibited appropriate ^{1}H NMR, ^{13}C NMR, IR, and Elemental Analyses except for the boronic acids (**18**) which were converted into coupled materials and fully characterized.

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9) **18c**: ^{1}H NMR ($CDCl_3$) δ 7.48-7.30 (m, 16H), 6.01 (s, 2H), 5.15 (s, 2H), 5.06 (s, 2H), 4.77 (s, 2H), 2.20 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.6, 150.2, 148.8, 137.5, 137.0, 136.0, 128.9, 128.3, 128.0, 127.9, 126.6, 125.5, 117.4, 77.1, 74.5, 71.0, 10.2. **23c** (major diastereomer): ^{1}H NMR ($CDCl_3$) δ 7.65-7.35 (m, 16H), 6.02 (s, 2H), 5.29 (AB quartet, J_{AB} = 10.9 Hz, Δν = 10.6 Hz, 2H), 5.21 (d, J = 6.6 Hz, 1H), 4.83 (s, 2H), 2.30 (s, 3H), 2.29-2.12 (m, 1H), 1.95-1.89 (m, 1H), 1.47-1.37 (m, 1H), 1.07 (t, J = 7.4 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 157.0, 150.1, 148.2, 140.1, 137.8, 136.1, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 127.4, 127.1, 126.8, 125.2, 118.1, 84.2, 74.5, 41.4, 25.2, 15.2, 11.5, 10.2.

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