High Yields of Unsymmetrical Biaryls *via* Cross Coupling of Arylboronic Acids with Haloarenes using a Modified Suzuki–Beletskaya Procedure

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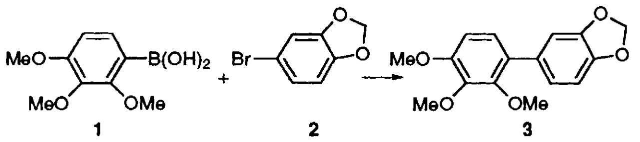
Unsymmetrical biaryls are obtained in high yields from cross coupling of arylboronic acids with haloarenes in the presence of a base using palladium acetate as a catalyst for reactions in aqueous ethanol at ambient temperature in the absence of oxygen.

Unsymmetrical biaryls are frequently prepared using the palladium-catalysed Suzuki coupling of arylboronic acids with haloarenes.[1] Reactions usually involve $Pd(PPh_3)_4$/aqueous Na_2CO_3/benzene at 80 °C[2] or $Pd(PPh_3)_4$/aqueous Na_2CO_3/DME at *ca.* 100 °C.[3] Suzuki has recently reported that shorter reaction times can be used and high yields of hindered biaryls obtained by replacing the Na_2CO_3 with a stronger base *e.g.* $Ba(OH)_2$.[4] In an extensive series of papers, Beletskaya and her coworkers have described the preparation of unsymmetrical biaryls in high yields by the $Pd(OAc)_2$[5] or $PdCl_2$[6] catalysed reactions of arylboronic acids with water-soluble haloarenes at 20 °C. Reactions involving water-insoluble reactants require more severe conditions and are heated at 100 °C.[7]

We required significant quantities of the antimitotic agent **3** but found that when coupling of the boronic acid **1** with arylbromide **2** was carried out using $Pd(PPh_3)_4$ as catalyst in benzene or DME significant incorporation of phenyl groups from the PPh_3 ligand occurred.[8] We now report that high yields of unsymmetrical biaryls can be obtained under very mild conditions when arylboronic acids are reacted with haloarenes and a base in aqueous ethanol using palladium acetate as a catalyst. The unsymmetrical biaryl **3** was isolated in yields of >80% when **1** was treated with a slight excess of **2** in the presence of 2 mol dm^{-3} aqueous Na_2CO_3 and $Pd(OAc)_2$ (5 mol%) in 95% aqueous ethanol at ambient temperature for 17 h. Comparable yields of **3** were obtained when the aqueous Na_2CO_3 was replaced by solid Na_2CO_3 or $Ba(OH)_2$. Use of $Ba(OH)_2$ led to complete conversion after 2 h in agreement with Suzuki's findings.[4] Similarly, a reaction of 4-fluoroboronic acid with iodobenzene gave a quantitative yield of 4-fluorobiphenyl under these conditions. However, reaction of 1-naphthylboronic acid with 4-methoxyiodobenzene was significantly slower using aqueous Na_2CO_3 as base and HPLC showed significant quantities of starting materials were present after 17 h reaction. A reaction using $Ba(OH)_2$ as base gave complete conversion (by HPLC) under the same conditions. Exclusion of oxygen from these reactions was found to be crucial. Incomplete deoxygenation led to the formation of significant quantities of protodeboronated material (1,2,3-trimethoxybenzene) and the symmetrical biphenyl (2,3,4,2′,3′,4′-hexamethoxybiphenyl). When a reaction of the boronic acid **1** with **2** was carried out using $Pd(PPh_3)_4$ in place of $Pd(OAc)_2$ in aqueous ethanol with $Ba(OH)_2$, complete conversion of the boronic acid had occurred after 5 h reaction. The unsymmetrical biphenyl **3** was isolated in 60% yield. The reaction was not optimised as $Pd(OAc)_2$ is so much easier to obtain and handle.



1 **2** **3**

Table 1 Cross coupling of arylboronic acids with haloarenes[a]

Arylboronic acid	Haloarene	Base	t/h	Biaryl yield[b] (%)
1	**2**	aq. Na_2CO_3 (2 mol dm^{-3})	17	82
1	**2**	Solid Na_2CO_3	17	80
1	**2**	Solid $Ba(OH)_2$	2	96
4-$FC_6H_4B(OH)_2$	PhI	aq. Na_2CO_3 (2 mol dm^{-3})	17	>95
1-Naphthyl$B(OH)_2$	4-$MeOC_6H_4I$	aq. Na_2CO_3 (2 mol dm^{-3})	17	50
1-Naphthyl$B(OH)_2$	4-$MeOC_6H_4I$	Solid $Ba(OH)_2$	17	60 (>95 HPLC)

[a] Reaction conditions: arylboronic acid (0.5 mmol), haloarene (0.55 mmol), base (0.75 mmol), $Pd(OAc)_2$ (0.021 mmol) in degassed 95% aqueous ethanol (6 ml) under N_2. [b] Yields of isolated products.

These results demonstrate that high yields of biaryls can be obtained from reactions in 95% aqueous ethanol at ambient temperature when palladium catalysts not involving phosphine ligands are used in these coupling reactions. The reactions are accompanied by rapid deposition of colloidal palladium. Although no details of the coupling mechanism under these conditions are known the formation of colloidal palladium may be related to the proposed involvement of colloidal metal in platinum-catalysed alkene hydrosilylation reactions.[9]

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