High Yields of Symmetrical Biaryls from Palladium Catalysed Homocoupling of Arylboronic Acids under Mild Conditions

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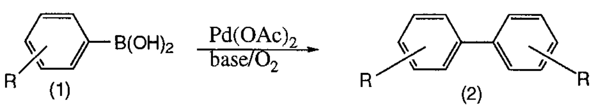
Abstract: Symmetrical biaryls can be obtained under very mild conditions in good yield by palladium catalysed coupling of arylboronic acids in aqueous ethanol (95%) containing sodium carbonate at ambient temperature and in the presence of oxygen.

The preparation of unsymmetrical biaryls by palladium catalysed coupling of arylboronic acids and aryl halides has been the centre of much recent attention and good yields of biaryls have been obtained under very mild reaction conditions.[1] In contrast, very few preparations of symmetrical biaryls from arylboronic acids have been reported.[2] Other methods of symmetrical biaryl formation frequently involve severe reaction conditions or sensitive catalysts[3] although high yields have been reported, e.g. in a nickel catalysed homocoupling of a bromoarene.[4] Suzuki[2] reported the preparation of biphenyl from phenylboronic acid in anhydrous conditions using $Pd(OAc)_2$ with PPh_3 as catalyst and $Cu(OAc)_2$ under N_2. However it is known that the phenyl group from PPh_3 can couple with arylboronic acids[5] to give an unsymmetrical biaryl which in this case would be indistinguishable from the reaction product. For other substituted boronic acids this would result in unwanted byproducts. We have previously reported a preparation of unsymmetrical biaryls using a phosphine free system which overcomes this problem.[6] The reactions of arylboronic acids with aryl halides were carried out under purified N_2 in an aqueous ethanol solution containing palladium acetate (5%) and a base, usually barium hydroxide, at ambient temperature and gave good yields of heterobiaryls. Traces of oxygen led to formation of small amounts of symmetrical biaryls from arylboronic acids. Others have found that rigorous exclusion of air using freeze thaw cycles is necessary to prevent homocoupling.[7] These observations suggested to us a basis for a synthesis of symmetrical biaryls.

We now report that good yields of symmetrical biaryls are obtained when solutions of arylboronic acids in aqueous ethanol (95%) containing palladium acetate (5%) and a base, preferably sodium carbonate, are stirred at ambient temperature with exposure to air (Scheme).



Scheme

In contrast to Suzuki,[2] we have found that anhydrous conditions, exclusion of air and the addition of $Cu(OAc)_2$ and PPh_3 ligands are not required. It should be noted however that the presence of air led to improved yields of dienes in palladium catalysed homo-coupling of alkenylboronates.[2] In addition our reactions are carried out under much milder conditions. Results for a selection of arylboronic acids are summarised in Table 1. Very good conversions were observed for the parent phenylboronic acid (**1a**), and for boronic acids substituted with both electron donating (**1b**) and electron withdrawing (**1c**) groups.

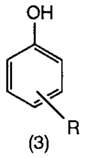
An alternative preparation of these symmetrical biaryls could involve coupling of an arylboronic acid with an identically substituted aryl halide using previously established conditions[1,6] which involve rigorous exclusion of air. Another advantage of using the methodology described in this paper is that separation of the product biaryl from any unreacted boronic acid is much more facile than separation from any unreacted aryl halide. A recent publication[8] describes a high yielding conversion of aryl halides into arylboronic acids. This methodology should help increase the availability and reduce the price of arylboronic acids.

Table 1. Product ratios from reactions of arylboronic acids#

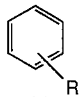
Reactant	Ratios of Products*		
Ar =	(2)	(3)	(4)
a. Ph†	79	8	-
b. 4-$MeOC_6H_4$†	83	6	1
c. 4-FC_6H_4†	84	10	4
d. 1-naphthyl	76	-	24
e. 2,3,4-(tri-MeO)C_6H_2	58	-	42

Reactions of arylboronic acids (0.47 mmol) in aqueous ethanol (95%, 6 ml) with palladium acetate (5 mg) and sodium carbonate (0.3 ml of 2 M solution, 0.6 mmol) for 72 h at ambient temperature with stirring and exposure to air.
* Relative percentage amounts determined using calibrated HPLC data.
† Reactant (1) (13, 10 and 2% respectively) was detected.

Some minor products (**3**) and (**4**) were also formed. Protodeboronation became a significant problem with the arylboronic acid (**1e**). Attempts to decrease the reaction time by carrying out reactions at 80°C for 17 h gave significant yields of phenols (**3**) and protodeboronated products (**4**).



(3)



(4)

The results shown in Table 2 indicate that the presence of base usually shows a marked enhancement of symmetrical biaryl formation. Reactions carried out in the absence of base were slower for (**1b**) and (**1c**), and for (**1e**) significant protodeboronation occurred. In contrast to the unsymmetrical coupling reactions where barium hydroxide was the preferred base,[1b,6] it was found that sodium carbonate was more effective than either thallium carbonate or barium hydroxide.

Oxygen is essential for effective homocoupling reactions as when oxygen was rigorously excluded from reactions of (**1b**) and (**1c**) the yields of the biaryls decreased from 83% to 29%, and 79% to 8% respectively (see Table 3). Addition of copper(II) acetate to a reaction of (**1b**) in air resulted in an enhanced yield of biaryl, and a more selective synthesis. With (**1c**) the effect of copper(II) acetate was similar when carried out under N_2 or in air, though the former was cleaner. In contrast, the reaction of the electron rich boronic acid (**1e**) in air with copper(II) acetate resulted in a significant decrease of the desired product (**2e**), and greatly enhanced arene (**4e**) formation.

Table 2. Effect of base on homocoupling reactions[#]

Reactant	Base*	Ratios of Products†			
Ar =		(1)	(2)	(3)	(4)
b. 4-MeOC$_6$H$_4$	-	28	68	1	3
b. 4-MeOC$_6$H$_4$	Na$_2$CO$_3$	10	83	6	1
b. 4-MeOC$_6$H$_4$	Tl$_2$CO$_3$	58	38	3	1
b. 4-MeOC$_6$H$_4$	Ba(OH)$_2$	6	73	20	1
c. 4-FC$_6$H$_4$	-	84	11	-	5
c. 4-FC$_6$H$_4$	Na$_2$CO$_3$	2	84	10	4
c. 4-FC$_6$H$_4$	Tl$_2$CO$_3$	69	13	2	16
c. 4-FC$_6$H$_4$	Ba(OH)$_2$	9	49	16	26
d. 1-naphthyl	Na$_2$CO$_3$	-	76	-	24
d. 1-naphthyl	Tl$_2$CO$_3$	48	38	3	11
d. 1-naphthyl	Ba(OH)$_2$	15	29	46	10
e. 2,3,4-(tri-MeO)C$_6$H$_2$	-	-	21	-	79
e. 2,3,4-(tri-MeO)C$_6$H$_2$	Na$_2$CO$_3$	-	58	-	42
e. 2,3,4-(tri-MeO)C$_6$H$_2$	Tl$_2$CO$_3$	5	6	-	89
e. 2,3,4-(tri-MeO)C$_6$H$_2$	Ba(OH)$_2$	-	8	1	91

[#] Reactions of arylboronic acids (0.47 mmol) in aqueous ethanol (95%, 6 ml) with palladium acetate (5 mg) for 72 h at ambient temperature in air.

[*] Sodium carbonate solution (0.3 ml of 2 M solution, 0.6 mmol) was used whereas solid thallium carbonate (0.35 g, 0.75 mmol) and barium hydroxide (0.24 g, 0.75 mmol) were used.

[†] Relative percentage amounts determined using calibrated HPLC data.

Thus, copper(II) acetate as an oxidant additional to or instead of air does not have an uniform effect.

The products described in the Tables were analysed by HPLC so as not to lose volatile material, in particular the protodeboronated products (4). Preparative scale reactions (*ca.* 1 g) for 24 h were carried out with (**1a**), (**1b**) and (**1c**) and gave pure samples of the biaryls (**2a**), (**2b**) and (**2c**) in 60, 62, and 74% yields respectively.

In conclusion we have developed a simple, mild, high yielding procedure for the synthesis of symmetrical biaryls from arylboronic acids. The reaction utilises a minimum of reagents, is general in scope and avoids the need for anaerobic or anhydrous reaction conditions. A paper dealing predominantly with mechanistic aspects of these palladium-catalysed homocoupling reactions has recently appeared.[9]

Table 3. Effect of oxidants on homocoupling reaction

Reactant	Conditions#	Ratios of Products*			
Ar =		(1)	(2)	(3)	(4)
b. 4-MeOC$_6$H$_4$	N$_2$	69	29	2	<1
b. 4-MeOC$_6$H$_4$	O$_2$	10	83	6	1
b. 4-MeOC$_6$H$_4$	O$_2$/Cu(OAc)$_2$	<1	99	<1	<1
c. 4-FC$_6$H$_4$	N$_2$	86	8	-	6
c. 4-FC$_6$H$_4$	O$_2$	12	79	8	<1
c. 4-FC$_6$H$_4$	N$_2$/Cu(OAc)$_2$	15	82	<1	2
c. 4-FC$_6$H$_4$	O$_2$/Cu(OAc)$_2$	20	71	7	2
e. 2,3,4-(tri-MeO)-C$_6$H$_2$	O$_2$/Cu(OAc)$_2$	-	29	-	71

[#] Reactions of arylboronic acids (0.47 mmol) in aqueous ethanol (95%, 6 ml) with palladium acetate (5 mg), copper acetate monohydrate (0.094 g, 0.47 mmol) and sodium carbonate (0.3 ml of 2M solution, 0.6 mmol) for 17 h at ambient temperature. Deoxygenated solvents were used for reactions carried out under N$_2$.

[*] Relative percentage amounts determined using calibrated HPLC data.

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