

Microwave-promoted Suzuki–Miyaura coupling of arylboronic acids with 1-bromo-2-naphthol, *o*-bromophenol, and *o*-chlorophenol

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Abstract—In this letter we report a simple and efficient way for the direct Suzuki–Miyaura cross-coupling of unprotected 2-hydroxyaryl bromides and of 2-chlorophenol with arylboronic acids using suitable phosphine/Pd(OAc)₂ catalysts systems with moist K₃PO₄/toluene or moist CsF/dioxane and microwave heating (20 min 105 °C to 3 h 100–120 °C) with an internal temperature control providing 2-hydroxybiaryls in yields up to 98%.

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The Suzuki–Miyaura cross-coupling of aryl halides and arylboronic acids has emerged as an extremely powerful and environmentally friendly tool and is today certainly the most widely used method in the synthesis of biaryls,^{1–3} which are a key element in a growing number of pharmaceuticals and natural products⁴ and highly efficient asymmetric catalysts with axial chiral ligands.⁵ The particular advantages of the Suzuki–Miyaura coupling are the wide tolerance of functional groups, the stability to water and oxygen and the nontoxic properties of organoboronic acids. Recent research revealed that in situ Pd-catalysts with highly basic and bulky phosphine or *N*-heterocyclic carbene ligands^{3,6} or bulky palladacycles⁷ in combination with suitable salts like K₃PO₄, Cs₂CO₃, KF, CsF or *n*Bu₄NBr allow the coupling of arylboronic acids even with bulky and deactivated aryl halides including chlorides under mild conditions. Since the reactivity of aryl halides is substantially lowered by hydroxylate donor groups formed in the presence of basic salts like phosphates or carbonates, usually protected phenol derivatives are employed to synthesize hydroxyl-biaryls. However, the direct use of hydroxyaryl halides would be desirable to simplify the synthesis not only of biaryl-based natural products but also simple hydroxybiaryls. 4-Iodophenol is known to

be sufficiently reactive to couple with various arylboronic acids even in the presence of Pd/C catalysts in aqueous K₂CO₃ in high yields, 2-iodophenol in a lower yield.⁸ 4-Bromophenol is much less suitable under these conditions, but catalysis with the highly efficient Pd₂(dba)₃/P(*t*-Bu)₃/KF catalyst system introduced by Fu et al. furnished 4-hydroxybiphenyl in an excellent yield.⁹ Coupling of the more bulky 2-bromophenol with phenylboronic acid in the presence of Pd(OAc)₂/(*m*-C₆H₄SO₃Na)₃P/*i*Pr₂NH (CH₃CN/H₂O 3:1) required extended heating (72 h) and a high catalyst load to afford 60% of 2-hydroxybiphenyl.¹⁰ Electron-releasing groups like 3-CHO or COOMe in the 2-bromophenol and use of Pd(PPh₃)₄/K₂CO₃ or K₃PO₄/DMF or DME–water reduced the reaction time with arylboronic acids or their pinacol esters to 16–49 h at 90–120 °C.¹¹ Two to four bromine or iodine atoms in the phenol allow rapid coupling with phenyl boronic acid in the microwave-assisted coupling, catalyzed by Pd(OAc)₂/KF–Al₂O₃.¹² The reaction of 1-bromo-2-naphthol with 4-methoxyphenylboronic acid in the presence of Pd(PPh₃)₄/Na₂CO₃/DME–EtOH–water is somewhat faster, as shown by the consumption of all reactants after 4 h reflux, but the yield of the coupling product was only 56%.¹³

Hydroxyfunctional aryl chlorides have been used to the best of our knowledge so far only in very few recent examples to obtain hydroxybiphenyls: (1) coupling of 2-chloro-6-methylphenol with phenyl- and 3-furylboronic

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acid, respectively, catalyzed by a not commercially available very bulky and basic phosphine stabilized palladacycle in the presence of KF/dioxane (110 °C overnight, yield 60% and 41%, respectively),¹⁴ (2) low yield (26%) coupling of a 2,3-dichlorophenol derivative with phenylboronic acid in the presence of Pd₂(dba)₂/cHex₃P/Cs₂CO₃ in toluene (1 h 80 °C),¹⁵ and (3) the coupling of the electron-deficient 5-chloro-3-hydroxypyridine with 3-pyridylboronic acid which gives much better yield (87%) even with the ‘classical’ Pd₂(dba)₃/PCy₃/K₃PO₄ (dioxane–water, 18 h, 100 °C).¹⁶

Continuing earlier investigations on 2-hydroxy-2'-phosphinobiaryl ligands¹⁷ with a changed synthesis strategy, we studied the Suzuki–Miyaura coupling of 1-bromo-2-naphthol and *o*-bromophenol with excessive phenyl- and 1-naphthylboronic acid choosing at first a ‘classical’ catalyst system Pd(OAc)₂/R₃P/K₃PO₄ (toluene) with R = Ph, *o*-Tol, Mes, *t*-Bu. Microwave heating was applied in most of the experiments, since this technique is reported to shorten the reaction times of Suzuki–Miyaura couplings, in particular in water or aqueous organic media.² The coupling experiments were usually carried out at 105 °C with heating for 20 min.¹⁸ Screening of the coupling of phenylboronic acid with 1-bromo-2-naphthol to **1** with various phosphine ligands, usually in a Pd/R₃P 1:2 molar ratio, showed an increased yield in the presence of the basic and bulky ligands *t*-Bu₃P and *o*-Tol₃P as compared to the use of neat Pd(OAc)₂/K₃PO₄ while Ph₃P lowered the yield, and, surprisingly, the more bulky Mes₃P in a 1:2 ratio deactivated the catalyst (Table 1, entries 1–5). To improve the efficiency of microwave heating, small amounts of water (0.5 mL) were added. Indeed, the yields of **1** increased in all experiments using stabilising phosphine additives by about 10% (except the deactivating trimesitylphosphine) while the yield decreased when neat Pd(OAc)₂/K₃PO₄ was used (Table 1, entries 7–11).

Surprisingly, the conversion was further improved by adding smaller amounts of water. Water was found unsuitable as solvent while moist K₃PO₄ with ca. 50 mg water/g K₃PO₄ (ca. 0.6 H₂O) proved to give excellent yields of **1** (87–92%) with 2.5 mol % Pd(OAc)₂/5 mol % *t*-Bu₃P or *o*-Tol₃P and yet 73% **1** with 0.25 mol % Pd(OAc)₂/0.5 mol % *o*-Tol₃P within 20 min at 105 °C. A strong excess of *o*-Tol₃P (5 mol %/0.25 mol % Pd) dropped the yield to about 50% (Table 1, entries 12–16). Heating in the classical way in a silicon oil bath required much longer time or higher temperature to reach a comparable yield using the same catalyst systems (entries 6 and 17). The separation of **1** from unconverted components and homocoupling products was performed by column chromatography on silica gel by an elution with *n*-hexane/methylene chloride (2:1).

The high yield of **1** in the above Suzuki–Miyaura cross-coupling with moist K₃PO₄ encouraged us to extend this protocol to the cross-coupling of both 1-bromo-2-naphthol with 1-naphthylboronic acid and of 2-bromophenol with phenyl- and 1-naphthylboronic acid. Tris(*o*-tolyl)phosphine was chosen as the ligand because of similar yields to *t*-Bu₃P in the above screenings but

Table 1. Suzuki–Miyaura cross-coupling of 1-bromo-2-naphthol with phenylboronic acid using various Pd catalysts and different amounts of moisture^a

Entry	Pd(OAc) ₂ (mol %)	R ₃ P (mol %)	Yield of 1 (%)
<i>Dry K₃PO₄</i>			
1	2.5	<i>t</i> -Bu ₃ P/5	65
2	2.5	<i>o</i> -Tol ₃ P/5	60
3	2.5	Ph ₃ P/5	19
4	2.5	Mes ₃ P/5	0
5	5.0	None	56
6 ^b	2.5	<i>o</i> -Tol ₃ P/5	61 ^b
<i>Dry K₃PO₄ and 0.5 mL of water</i>			
7	2.5	<i>t</i> -Bu ₃ P/5	75
8	2.5	<i>o</i> -Tol ₃ P/5	72
9	2.5	Ph ₃ P/5	29
10	2.5	Mes ₃ P/5	0
11	5	None	45
<i>Moist K₃PO₄^c</i>			
12	5	<i>t</i> -Bu ₃ P/10	87
13	2.5	<i>t</i> -Bu ₃ P/5	92
14	2.5	<i>o</i> -Tol ₃ P/5	90
15	0.25	<i>o</i> -Tol ₃ P/0.5	73
16	0.25	<i>o</i> -Tol ₃ P/5	50
17 ^d	2.5	<i>o</i> -Tol ₃ P/5	64 ^d

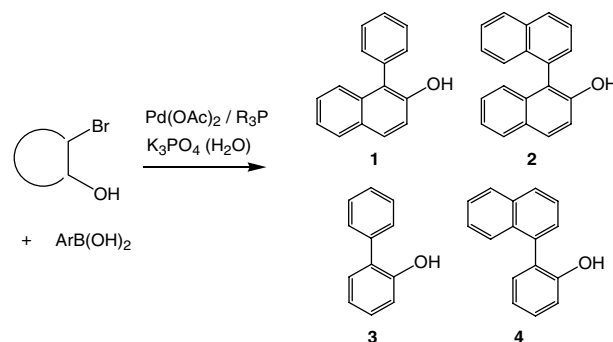
^a Reaction conditions: 1 equiv of hydroxyaryl bromide, 2 equiv of organoboronic acid, 2.5 mol % of Pd(OAc)₂, 5 mol % R₃P, 2 equiv of K₃PO₄, toluene (15 mL), microwave heating at 105 °C for 20 min, yield after separation by column chromatography on silica gel (average of each two experiments).

^b Heating in a silicon oil bath at 120 °C for 12 h, other conditions as in footnote a.

^c Water content 50 mg/g K₃PO₄.

^d Heating in a silicon oil bath at 140 °C for 30 min, other conditions as in footnote a.

much higher air stability. Naphthyl-naphthol **2** and naphthylphenol **4** were obtained in nearly quantitative yields while the cross-coupling to 2-hydroxydiphenyl **3** was less favourable under equal conditions (Scheme 1, Table 2, entries 1–4). The yield increases in the order **3** < **4** ≈ **1** < **2**. This effect is possibly due to the more extended π-delocalization of the negative charge in naphtholate compared to phenolate. By the usually strong response to steric hindrance of the Suzuki–Miyaura coupling it seems less likely that the naphthyl group favours the reductive elimination sterically. Tests with the biaryl ligand 2-dicyclohexylphosphino-1-(2-trimethylsilylphenyl)-pyrrole (**5**),¹⁹ a representative of a ligand



Scheme 1. Suzuki–Miyaura couplings with 2-hydroxyaryl bromides.

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