Suzuki–Miyaura Cross-Coupling of Aryl Chlorides in Water Using Ligandless Palladium on Activated Carbon

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Abstract: Aqueous reaction conditions that activate various aryl chlorides in Suzuki–Miyaura cross-coupling have been developed. These environment friendly conditions utilize ligandless Pd/C (Pd concentrations 0.2–2 mol%) that allow easy separation of the catalyst at the end of the reaction.

Key words: aryl chlorides, water, palladium, cross-coupling, biaryls

Activation of aryl chlorides in the Suzuki–Miyaura cross-coupling reactions[1] is of great interest as these can serve as cheap and readily available starting materials in the synthesis of fine chemicals and pharmaceuticals. Unfortunately, they are much more difficult to activate than aryl iodides and aryl bromides. Effort has been invested in developing catalysts and ligands[2] that can activate the less reactive aryl chlorides. Some drawbacks are the availability of the palladium complexes and the stability of some of the ligands. Furthermore, these ligands and catalysts can be difficult to separate from the end product. Protocols that use ligandless palladium in aryl chloride activation have been demonstrated. Pd/C,[3] minerals containing palladium,[4] and $Pd(OAc)_2$[5] have been reported effective although organic solvents and long reaction times were needed. In 1997 Badone et al.[6] showed that aryl bromides coupled readily in water using $Pd(OAc)_2$ and tetrabutylammonium bromide (TBAB) as additive but did not report any aryl chloride activation. Bumagin and Bykov[7] showed that $PdCl_2$ could catalyze the reaction of sodium tetraphenyl borate and aryl chlorides in water. Arcadi and coworkers[8] published a few examples of aryl chloride activation using Pd/C in water with surfactants and recently it was reported[9] that some aryl chlorides could be coupled using homogeneous $Pd(OAc)_2$ in molten TBAB in the presence of water. In both cases long reaction times (17–24 h) were needed. We wish to report a general procedure for aryl chloride activation, including ones containing sensitive functional groups, in water under ambient atmosphere using ligandless palladium on activated carbon. This general procedure generates the corresponding biaryls in good to excellent yield.

We chose to investigate the applicability of a heterogeneous Pd/C catalyst in the Suzuki–Miyaura reaction of aryl chlorides without addition of ligands. This would lead to a cleaner reaction and also offer simple removal of the palladium after the reaction as it was previously reported[10] that palladium leaches from the carbon support during the reaction and then reprecipitates on the charcoal at the end of the reaction.

In our initial experiments we focused on a Pd/C catalyst possessing high Pd dispersion, high degree of unreduced Pd [Pd(II)] and a high water content >50%. Tetrabutylammonium bromide (TBAB) was added to the reaction since tetrabutylammonium salts have been reported[11] to heighten the efficiency by stabilizing palladium nanoparticles. Applying this catalyst using low palladium concentration (0.2 mol%) and addition of 0.5 equivalents TBAB in the reaction of 4-chloroacetophenone and phenylboronic acid gave diverse results proving that the choice of reaction condition is of major importance.

NMP–water mixture (Table 1, entry 1a), which in several cases with heterogeneous catalysts has been the condition of choice,[3] showed moderate conversion and selectivity. Dioxane and dioxane–water worked very sluggishly, as did methanol and acetone–water (entries 1b, 1c, 1e, 1h, 1i). DMF–water (entries 1f and 1g) proved to facilitate the oxidative addition but the selectivity was low and led to a 50:50 mixture of the biaryl product and dehalogenated starting material. Turning to water without organic co-solvent (entries 1d, 1j–1m) the reaction went smoothly with full conversion in only 1.5 hours with very high selectivity (>99%, entry 1k). Lowering the reaction temperature to 80 °C for two hours resulted in almost full conversion (87%, entry 1l) but at room temperature no reaction was observed. The amount of TBAB was tested and 0.5 equivalents were found to be optimal and in the absence of TBAB poor conversion was observed (entry 1n). Using these very active and selective reaction conditions, scope and limitations of the reaction were investigated.

As summarized in Table 2 various aryl chlorides coupled nicely under these conditions (TOF 300 h^{-1}) although the different reactivity of the aryl chlorides is reflected in the reaction conditions. As higher conversions were observed on electron-rich chloroarenes using NaOH as the base experiments in Table 2 were performed with NaOH. All reactions were performed under ambient atmosphere, as biphenyl formation was minimal. Electron deficient aryl

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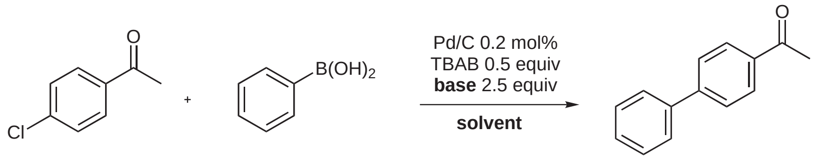
Table 1 Optimization of the Reaction Conditions in the Reaction of 4-Chloroacetophenone and Phenylboronic Acid



Entry[a]	Solvent	Base	Temp (°C)	Time (h)	Conversion (%)[b]	Yield (%)
1a	NMP–H_2O, 3:1	NaOH	140	4	72	54
1b	Dioxane	K_3PO_4	140	4	10	5
1c	Dioxane–H_2O, 3:1	K_3PO_4	140	4	8	5
1d	H_2O	K_2CO_3	100	4	100	>99
1e	H_2O–acetone, 1:1	K_2CO_3	100	4	8	5
1f	DMF–H_2O, 5:1	K_2CO_3	140	4	100	41
1g	DMF–H_2O, 5:1	KF	140	4	100	56
1h	MeOH	K_2CO_3	100	4	21	3
1i	MeOH	KF	100	4	3	1
1j	H_2O	K_2CO_3	100	2	100	>99
1k	H_2O	K_2CO_3	100	1.5	100	>99
1l	H_2O	K_2CO_3	80	2	87	86
1m	H_2O	K_2CO_3	r.t.	24	0	0
1n	H_2O	K_2CO_3	100	3	13	10[c]

[a] Reaction conditions: 2 mmol 4-chloroacetophenon, 2.2 mmol phenylboronic acid, 1 mmol TBAB in 4–6 mL solvent under argon, Pd/C (E105CA/W 5% Pd).

[b] Determined by GC analysis with diethyleneglycol dibutylether as internal standard.

[c] No TBAB added.

chlorides reacted nicely at low palladium concentrations (0.2–0.5 mol%), and only 1.1 equivalents of phenylboronic acid were needed to reach full conversion. Electron-rich chloroarenes required higher catalyst loading (2.0 mol%), 1.5 equivalents phenylboronic acid, higher temperature and longer reaction times (6 h).

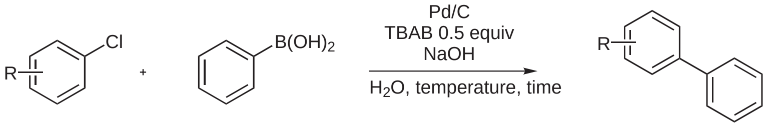
4-Chloroacetophenone and 4-chlorobenzonitrile showed the highest reactivity giving high yield (Table 2, entry 2a and 2b) at 100 °C with low catalyst loading. In the case with the benzonitriles and the methyl benzoates it was necessary to change the base due to substantial hydrolysis to the corresponding benzoic acid. K_2CO_3 and K_3PO_4 both led to benzoic acid formation but KF proved efficient to activate the phenylboronic acid[12] without causing severe hydrolysis of the ester or nitrile.

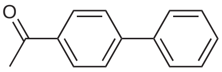
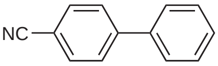
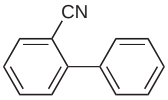
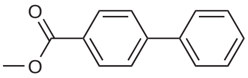
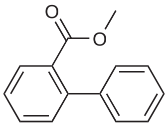
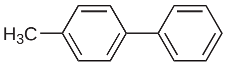
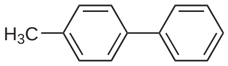
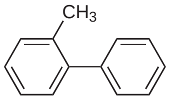
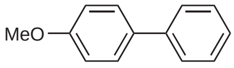
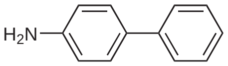
Using KF as base 4-chlorobenzonitrile and 2-chlorobenzonitrile gave excellent yields (98% and 89%, respectively, entry 2b and 2c). The methyl benzoates (entries 2d and 2e) could also be effectively coupled giving 87% and 63% yield, respectively. The lower yield from 2-chlorobenzoic acid methyl ester was due to incomplete conversion and hydrolysis during the reaction. Chlorobenzene could be satisfactory coupled with 4-tolylboronic acid using only 0.5 mol% palladium at 140 °C for 6 hours giving 73% yield (entry 2f). Coupling of deactivated 4-chlorotoluene and 4-chloroanisole produced high yields, 81% and 83%, respectively, and even the sterically demanding 2-chlorotoluene could be nicely converted although the product was contaminated with biphenyl.

4-Chloroaniline coupled nicely with only 2 mol% Pd at 140 °C but several attempts to isolate the product failed. Estimations based on ^1H NMR revealed a yield of ca. 66%.

In summary we have developed a procedure that facilitates efficient coupling of various aryl chlorides, including electron-rich and *ortho*-substituted derivatives, in water using ligandless supported palladium. This procedure is a very attractive way of accessing multifunctional biaryls as sensitive functional groups like ester and nitrile groups are tolerated. Comparisons of different palladium sources and the recycling of the catalysts are currently under survey in our laboratories.

Table 2 Suzuki Cross-Coupling of Aryl Chlorides in Water[1,3]



Entry[a]	R	Pd (%)	Temp (°C)	Time (h)	Ph-B(OH)$_2$ (equiv)	NaOH (equiv)	Product	Isolated yield (%)[b]
2a	4-COOH$_3$	0.2	100	2	1.1	2.5		99
2b	4-CN	0.5	100	3	1.1	2.5		98[c]
2c	2-CN	0.5	140	3	1.1	2.5		89[c]
2d	4-CO$_2$CH$_3$	0.5	140	3	1.1	2.5		87[c]
2e	2-CO$_2$CH$_3$	0.5	140	3	1.1	2.5		63[c,d]
2f	H	0.5	140	6	1.1	2.5		73[e]
2g	4-CH$_3$	2.0	140	6	1.5	5		81
2h	2-CH$_3$	2.0	140	6	1.5	5		74[f]
2i	4-OCH$_3$	2.0	140	6	1.5	5		83
2j	4-NH$_2$	2.0	140	6	1.5	5		66[g]

[a] Reaction conditions: 4 mmol arylhalide in H_2O (6mL) in a pressure tube under ambient atmosphere.

[b] Yield of chromatographically pure products.

[c] KF used as base.

[d] Product contaminated with 6% of 2-chlorobenzoic acid methyl ester.

[e] 4-Tolylboronic acid was used as nucleophile.

[f] Product contaminated with 5% of biphenyl.

[g] Determined by ^{1}H NMR.

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(13) **Representative Procedure.**
A pressure tube was charged with Pd/C (0.2 mol%; commercially available E105CA/W 5% Pd, product of Degussa AG, or self-prepared[14]), TBAB (2 mmol), NaOH (10 mmol), phenylboronic acid (4.4 mmol) and 4-chloroacetophenone (4 mmol). Then, H_2O (6 mL) was added and the flask was sealed with a Teflon screw cap and stirred at 100 °C for 2 h. After cooling to r.t., CH_2Cl_2 (15 mL) was added and the reaction was filtered through a plug of celite to remove the catalyst. The filter was flushed with CH_2Cl_2 (2×15 mL) and the combined organic phase was dried ($MgSO_4$), evaporated on Celite and purified by flash chromatography to yield 1-biphenyl-4-yl-ethanone (entry 2a, 776 mg, ca. 99%).

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