A Convenient Oxime-Carbapalladacycle-Catalyzed Suzuki Cross-Coupling of Aryl Chlorides in Water**

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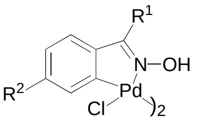
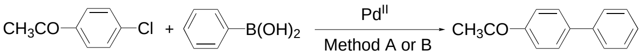
The importance of biaryl units[1] as components of many kinds of compounds, mainly pharmaceuticals, herbicides, and natural products, as well as in the field of engineering materials, such as conducting polymers, molecular wires, and liquid crystals, has attracted enormous interest from the chemistry community. Palladium- and nickel-catalyzed Suzuki–Miyaura cross-coupling[2] is the most important and efficient strategy for the construction of unsymmetrical biaryl compounds. This cross-coupling methodology allows the use of organic solvents and inorganic bases, tolerates many functional groups, is not affected by steric hindrance of the substrates, and is suitable for industrial processes.[3] From the industrial point of view, some important goals need to be realized for the development of this process: the functionalization of inexpensive and readily accessible aryl chlorides[4] and the use of water[5] as a safe and inexpensive solvent. Furthermore, to avoid an inert atmosphere, air-stable, efficient, and nontoxic catalysts are desired. The activation of both electron-deficient and electron-rich aryl chlorides has been achieved by palladium complexes in the presence of expensive and toxic phosphanes,[6] phosphites,[7] phosphane oxides,[8] palladium *N*-heterocyclic carbene complexes,[9] and palladium on carbon.[10] However, palladacycles[11] have only been used in the case of electron-deficient aryl chlorides.[12] Cross-coupling reactions with organoboranes are carried out in a mixture of an organic solvent and an aqueous inorganic base, generally under an inert atmosphere. In neat water, only sodium tetraphenylborate has been employed in the case of aryl chlorides, with $PdCl_2$ (3 mol%) as catalyst.[13] Herein we describe that oxime-derived palladacycles[14] are air- and water-stable catalysts that are suitable for cross-coupling different aryl and heteroaryl chlorides with boronic acids in neat water.



1a; $R^1 = CH_3$, $R^2 = H$
1b; $R^1 = CH_3$, $R^2 = OH$
1c; $R^1 = p\text{-}HOC_6H_4$, $R^2 = OH$

Different palladacycles and palladium salts were initially tested as possible candidates to study their catalytic activity on a model coupling reaction between phenylboronic acid and *p*-chloroacetophenone (Table 1). New oxime palladacycles **1b** and **1c** with hydroxy substituents on the aromatic ring were prepared by palladation with lithium tetrachloropalladate, as described for **1a**.[15] We have established the most efficient reaction conditions: palladium catalyst (0.01 mol%), K_2CO_3 base (2 equiv), and tetrabutylammonium bromide (TBAB, 0.5 equiv) in refluxing water (Method A). After 2 h, it was found that palladacycles **1** were very effective catalysts under these conditions, and gave high turnover numbers (TON; up to 7700) and turnover frequencies (TOF; up to 3850 h^{-1}) (Table 1, entries 1–3), whereas no reaction or very low conversions were obtained with Li_2PdCl_4 or $Pd(OAc)_2$, respectively (Table 1, entries 4 and 5). For room temperature coupling reactions it was necessary to use methanol/water (3:1), higher catalyst loading (1 mol% of palladium), KOH base (2 equiv), and TBAB (1 equiv) (Method B). Under these conditions after 18 h, up to 50% yield was observed with palladacycles **1**, whereas $Pd(OAc)_2$ gave less than 2% yield (Table 1, entries 6–9).

Table 1. Reaction conditions and catalyst studies on the Suzuki coupling of *p*-chloroacetophenone and phenylboronic acid.



Entry	Method[a]	Catalyst (mol% Pd)	*t* (h)	Yield (%)[b]	TON	TOF h^{-1}
1	A	**1a** (0.01)	2	69	6900	3450
2	A	**1b** (0.01)	2	77	7700	3850
3	A	**1c** (0.01)	2	69	6900	3450
4	A	Li_2PdCl_4(0.01)	2	–	–	–
5	A	$Pd(OAc)_2$(0.01)	2	5	500	250
6	B	**1a** (1)	18	43	43	2.4
7	B	**1b** (1)	18	50	50	2.8
8	B	**1c** (1)	18	42	42	2.3
9	B	$Pd(OAc)_2$(1)	18	1.5	1.5	0.008

[a] Method A: *p*-chloroacetophenone (2 mmol), $PhB(OH)_2$ (3 mmol), K_2CO_3 (4 mmol), TBAB (1 mmol), water (7 mL), 100 °C; Method B: *p*-chloroacetophenone (2 mmol), $PhB(OH)_2$ (3 mmol), KOH (4 mmol), TBAB (2 mmol), methanol/water (3:1, 8 mL), room temperature. [b] Determined by means of GC, based on the aryl chloride.

In both methods, the presence of TBAB[16, 17] was crucial to enhance the rate of the coupling, presumably because of the formation of $PhB(OH)_3^-Bu_4N^+$.[18] The catalyst **1b** was deactivated after the third cycle, when the coupling in water (Method A) was carried out in 1-h intervals (0.1 mol% catalyst): 99% (first and second cycle), 75% (third cycle), and 46% (fourth cycle).

The cross-coupling reactions with different aryl and heteroaromatic chlorides were studied with complex **1b** as catalyst (Table 2, Method A). For the synthesis of 4′-methylbiphenyl-2-carbonitrile, an intermediate in the preparation of angiotensin II receptor antagonists such as DuP753 and other antihypertensive drugs, 2-chlorobenzonitrile was coupled with *p*-tolylboronic acid (Table 2, entry 3).

For less reactive aryl chlorides, the catalyst loading and the amount of TBAB was increased to accelerate the reactions (Table 2, entries 4–9, 12, and 13). Biaryl/acetic acids have applications in the pharmaceutical industry as well as in materials science[21] and have been prepared recently by means of a Suzuki reaction on a multigram scale by using Pd/C (3 mol%) in refluxing isopropyl alcohol/water for four days.[22] Similar reaction conditions were employed for the synthesis of *p*-aryl mandelic acids.[23] We found that biphenylacetic acid and *p*-phenylmandelic acid could be prepared for

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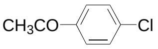
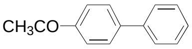
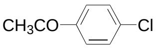
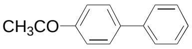
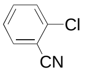
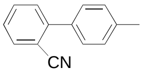
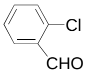
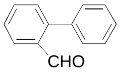
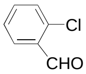
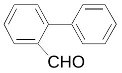
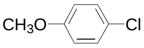
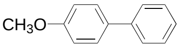
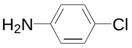
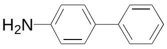
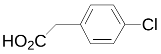
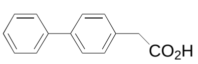
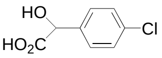
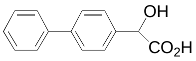
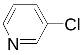
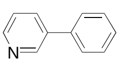
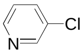
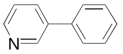
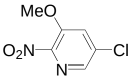
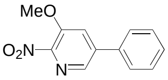
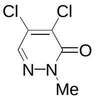
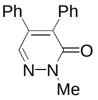
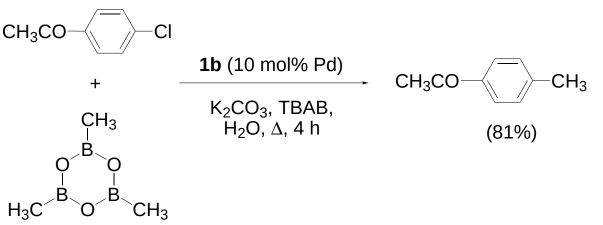
Table 2. Suzuki coupling of aryl chlorides and aryl boronic acids in water with **1b** as catalyst.

Entry	ArCl	mol% Pd	TBAB(equiv)	*t*	Product	Yield (%)[a]
1		0.1	0.5	1 h		100 (98)
2		0.01	0.5	2.5 h		91
3	 [b]	0.1	0.5	2 d		69
4		1	1	2 h		27
5		1[c]	1	32 h		57
6		1	1	6 h		40
7		1	1	6 h		83
8		1	1	2.5 h		50
9		1	1	2.5 h		42[d]
10		1	0.5	3 h		92
11		0.1	0.5	3 h		60
12		1	1	4 h		76 (43)
13	 [e]	0.1	1	1 h		100 (92)

[a] Determined by means of GC, based on the aryl chloride; yields in parenthesis are those of purified products. [b] *p*-Methylphenylboronic acid was used. [c] Method B was used. [d] Determined by means of ^{1}H NMR spectroscopy. [e] $PhB(OH)_2$ (2 equiv) was used.

the first time from the corresponding chlorides instead of from the bromides in only 2.5 h in refluxing water (Table 2, entries 8 and 9). Heteroaryl chorides, such as chloropyridines (Table 2, entries 10–12) and 2-methyl-4,5-dichloro-3(2*H*)pyridazinone[24] (Table 2, entry 13) were transformed efficiently into the corresponding biaryl compounds. These reaction conditions for the large-scale synthesis of pyridazinones, which exhibit agrochemical and pharmaceutical activities, are more convenient than the previously described syntheses, which use $Pd(PPh_3)_4$ (3 mol%) in refluxing toluene under a N_2 atmosphere.[24]

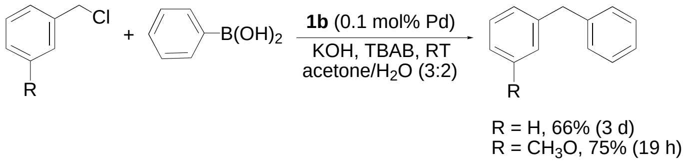
The cyclic anhydride trimethylboroxine (TMB) has been used recently for the $Pd(PPh_3)_4$-catalyzed (10 mol%) methylation of electron-deficient aryl chlorides in refluxing aqueous dioxane (10%) under nitrogen.[25] The use of TMB for the cross-coupling of 4-chloroacetophenone in refluxing water and with complex **1b** as catalyst (Method A) afforded 4-methylacetophenone in 81% yield after 4 h [Eq. (1)].



(1)

The Suzuki $Pd(PPh_3)_4$-catalyzed method has also been extended to the coupling of benzyl bromides and iodides with aryl boronic acids in refluxing EtOH/dimethoxyethane/water for 18 h under argon.[26] Oxime-derived palladacycle **1b** was an effective catalyst for the coupling of benzylic chlorides with phenylboronic acid. Benzyl chloride and 3-methoxybenzyl chloride reacted with phenylboronic acid at room temperature with low loading of catalyst (0.1 mol% Pd) to give diarylated methanes in 66 and 75% yield, respectively

[Eq. (2)]. The best conditions for this reaction were similar to those for Method B: KOH as base and acetone/water (3:2) as solvent. When the reaction was carried out in refluxing water, considerable amounts of alcohols were formed.



(2)

In summary, we have found that different types of Suzuki–Miyaura couplings can be carried out in water in the presence of TBAB with activated and deactivated aryl or heteroaromatic chlorides as well as benzylic chlorides by means of stable and easily available oxime-derived palladacycles. Degassing of the solvent or inert atmosphere were unnecessary and other factors, such as the cost and stability of the catalyst and the water medium make this green methodology more useful than others recently described. All these features are very appropriate for industrial environmentally friendly processes. The accessibility and structural versatility of these palladacycles render very promising catalysts and further studies in the applicability of these systems in other organic transformations are currently under investigation.

Experimental Procedure

A solution of aryl chloride (2 mmol), $PhB(OH)_2$ (0.37 g, 3 mmol), K_2CO_3 (0.55 g, 4 mmol), tetrabutylammonium bromide (0.64 g, 2 mmol), and compound **1b** (0.01 to 1 mol% Pd, see Tables 1 and 2) in water (7 mL) was heated at reflux. To measure the conversion of the reaction, a sample was taken from the cooled mixture and washed with H_2O and EtOAc. Subsequently the cooled reaction mixture was extracted with EtOAc, the organic phase was dried and evaporated under vacuum, and the crude product was purified by recrystallization or by chromatography on silica gel.

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