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An Efficient Palladium N-Heterocyclic Carbene Catalyst Allowing the Suzuki–Miyaura Cross-Coupling of Aryl Chlorides and Arylboronic Acids at Room Temperature in Aqueous Solution

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Abstract: The application of a highly active Pd-NHC catalyst for the Suzuki–Miyaura cross-coupling of a broad variety of electronically activated and deactivated aryl chlorides with different arylboronic acids in excellent yields is described. This catalyst can be handled under aerobic conditions, is active with low catalyst loadings at room temperature and in an aqueous reaction medium and allows the application of cheap potassium carbonate as the base.

Keywords: aqueous conditions; homogeneous catalysis; N-heterocyclic carbenes; palladium; Suzuki–Miyaura coupling

The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction[1] is one of the most powerful methods for synthesizing biaryl motifs that are present in the structure of several biologically active compounds and in advanced materials.[2] Due to economic reasons low cost and readily available but poorly reactive aryl chlorides are desirable as substrates for this coupling reaction. Consequently significant efforts have been devoted during the last decade to develop more reactive catalysts allowing the conversion of challenging aryl chlorides.[3] A plethora of novel catalyst structures and ligand modifications have been examined for this purpose,[4] among them, bulky and electron-rich phosphines,[5] N-heterocyclic carbenes,[6] and palladacycles.[7] Due to their unique steric and electronic properties and their specific coordination chemistry N-heterocyclic carbenes have in particular turned out to provide highly reactive palladium based C−C coupling catalysts. They stabilize and activate metal centers in the key catalytic steps of catalytic reactions thus disfavoring palladium black formation throughout the course of the transformation. Their strong σ-donor character facilitates the oxidative addition of unreactive aryl halogenides and the bulkiness of certain substituents at the nitrogen atoms next to the carbene center enhances the reductive elimination of the product.

Especially the groups of Glorius,[8] Beller,[9] Herrmann,[10] Nolan,[11] and Organ[12] have achieved significant improvements in Suzuki–Miyaura reactions. However most of these protocols suffer from high catalyst loading, hazardous solvents, and harsh conditions. Performing cross-coupling reactions in water as the (co-)solvent should offer additional benefit in terms of designing safer processes. This approach also facilitates the separation of the non-polar biaryl products possessing low solubility in water.

In 2012 Köhler et al. reinvestigated the known accelerating effect of water on Suzuki–Miyaura reactions in detail by comparing hydrophilic and hydrophobic pre-catalysts and ruling out the role of the base and of Bu_4N^+ salts often applied as phase-transfer catalysts.[13] They came to the conclusion that, in aqueous systems, containing an immiscible aryl halide as an additional organic phase, the palladium(II) pre-catalyst will be reduced to Pd(0) in the aqueous phase by boronate, generated from the boronic acid and the base. However, the subsequent oxidative addition will take place in the organic phase requiring a phase transfer of the reduced palladium species. For the following transmetallation, the boronate has to be transferred into the organic phase, which becomes accelerated by the presence of Bu_4N^+.

Recently, we established a route for the synthesis of 4-(4-nitrophenyl)-1,3-bis-(2,4,6-trimethylphenyl)-4,5-dihydro-3*H*-imidazolium chloride being a suitable precursor for NHC ligands functionalized in the periphery and found that its palladium complex **1** (Scheme 1) shows fairly high catalytic activity in the Suzuki–Miyaura cross-coupling of aryl bromides and phenylboronic acids.[14] Structurally the palladium(II) NHC complex **1** is closely related to so-called PEPPSI catalysts mainly established by Organ et al., a class of catalysts exhibiting high activities in a series of different coupling reactions.[10,15] In the present contribution we show that this catalyst is also highly active towards a broad variety of aryl chlorides.

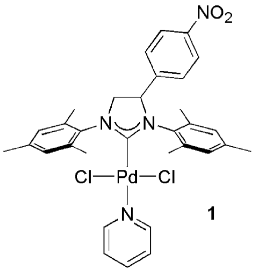
To optimize the outcome of the transformation, an extensive screening of the reaction conditions was carried out by investigating various parameters including catalyst concentration and the nature of the base and solvent. The starting point for this optimization was the use of chlorobenzene (1 mmol) and phenylboronic acid (1.1 mmol) as the substrates, Cs_2CO_3 (1.2 mmol) as base and 0.2 mol% of **1** for the evaluation of the solvent influence (Scheme 2). In all cases, the reactions were carried out room temperature for 6 h in open air, and the solvents were used without any further purification. The results are summarized in Table 1, entries 1–8.

The results prove that there is catalytic activity already at room temperature in all solvents being investigated. However, a clear trend related to solvent polarity can be figured out: solvents of low polarity lead to a decrease in performance while the use of alcohols, water and mixtures of these solvents results in excellent yields. This is a quite remarkable effect of water. It can however be explained by the higher solubility of the base in aqueous media that will lead to generation of the aryl-transferring boronate, which again is well-soluble in water according to the pK_a value of phenylboronic acid.[16] While the use of pure water provides lower yields than the use of pure alcohols, mixtures of in particular isopropyl alcohol with a high amount of water gives the best results. As ruled out by Köhler et al.,[11] biphasic mixtures of water and aryl halide intrinsically include phase-transfer reactions which are ruled out by the addition of a certain amount of an alcohol creating a one-phase system.

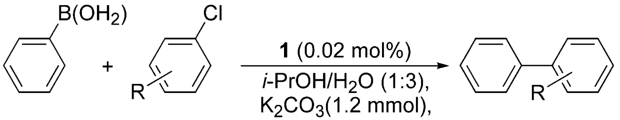
Table 1. Cross-coupling of chlorobenzene and phenylboronic acid catalyzed by **1** room temperature.[a]

Entry	Solvent	Base	Cat. Loading [mol%]	Yield [%]
1	1,4-dioxane	Cs_2CO_3	0.2	62
2	CH_2Cl_2	Cs_2CO_3	0.2	69
3	toluene	Cs_2CO_3	0.2	45
4	EtOH	Cs_2CO_3	0.2	70
5	*i*-PrOH	Cs_2CO_3	0.2	86
6	H_2O	Cs_2CO_3	0.2	75
7	*i*-PrOH/H_2O (1:2)	Cs_2CO_3	0.2	80
8	*i*-PrOH/H_2O (1:3)	Cs_2CO_3	0.2	90
9	*i*-PrOH/H_2O (1:3)	Na_2CO_3	0.2	93
10	*i*-PrOH/H_2O (1:3)	K_2CO_3	0.2	98
11	*i*-PrOH/H_2O (1:3)	K_2CO_3	0.1	98
12	*i*-PrOH/H_2O (1:3)	K_2CO_3	0.05	98
13	*i*-PrOH/H_2O (1:3)	K_2CO_3	0.02	98
14	*i*-PrOH/H_2O (1:3)	K_2CO_3	0.01	79

[a] *Reaction conditions:* 4 mL of solvent, PhCl (1 mmol), $PhB(OH)_2$ (1.1 mmol), base (1.2 mmol), 6 h, isolated yields.



Scheme 1. Chemical structure of the palladium NHC complex **1**.



Scheme 2. Suzuki–Miyaura cross-coupling of aryl chlorides and phenylboronic acid.

These results allowed investigation of cheap sodium and potassium carbonate as the base, both of which are only sparingly soluble in solvents other than water. As expected all alkaline metal carbonates give very good conversions, however, potassium carbonate showed an outstanding performance (Table 1, entries 8–10). The chance to avoid well soluble but expensive cesium carbonate is a clear advantage of the aqueous reaction medium employed here. To demonstrate the efficiency of catalyst **1**, the amount of the catalyst was reduced (Table 1, entries 10–14). The palladium loading could be decreased to 0.02 mol% and still the cross-coupling reaction afforded a 98% isolated yield of biphenyl. However, lowering the catalyst loading down to 0.01 mol% finally resulted in a decreased yield (79%) of the desired product. During the last years, a few reports were published wherein catalysts of comparable reactivity towards aryl chlorides were described working in protic solvents. In 2008 Cazin et al. showed that with $[Pd(\mu\text{-}Cl)Cl(IPr)]_2$ [IPr = bis(2,6-diisopropylphenyl)imidazol-2-ylidene] catalysts loadings as low as 0.1 mol% are possible.

Yields of more than 80 were obtained after 24 h at room temperature with EtOH as the solvent and alkoxides or NaOH as the base. The catalyst is almost unproductive in dioxane.[17] A similar catalyst bearing a weakly bound methylimidazole ligand giving yields of 85–99% with sterically not hindered substrates in a mixture of water and THF was published by Shao et al. in 2011.[18] Karimi et al. described in 2011 a soluble palladium-containing coordination polymer containing bifacial dicarbene ligands, which allows reduction of the catalyst loadings down to 0.05 mol% for activated aryl chlorides.[19] After 24–30 h yields of 75–95% could be obtained. Triazolylidene palladium complexes reported by Fukuzawa et al. gave yields up to 99% after 1 h in EtOH (KO-*t*-Bu) with catalyst loadings of 1 mo%.[20]

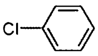
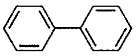
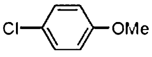
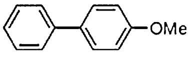
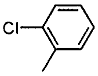
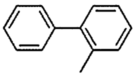
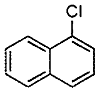
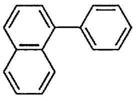
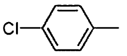
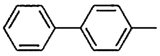
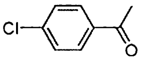
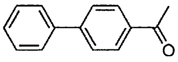
Given the high reactivity of the Pd-NHC catalyst, its utility in the cross-coupling of a series of different activated and non-activated chlorobenzenes with phenylboronic acid was examined under the conditions optimized above (Scheme 2 and Table 2).

Chlorobenzenes bearing electron-withdrawing as well as electron-donating substituents readily reacted with phenylboronic acid at room temperature in aqueous media (Table 2, entries 1–6). Often palladium-catalyzed Suzuki–Miyaura coupling reactions of aryl chlorides are inefficient as long as the substrate does not contain an electron-withdrawing substituent. Here this is not the case: catalyst **1** shows excellent activity independent from the nature of the substituent and the position it is attached to the benzene ring.

The high catalytic activity of **1** under the given reaction conditions encouraged us to explore Suzuki–Miyaura cross-couplings between further aryl chlorides and different aryl boronic acids such as 1-naphthylboronic and 2-thiopheneboronic acid. Both substrates undergo the coupling with excellent yields of the desired biaryl products (Table 3).

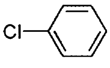
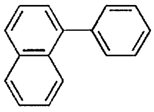
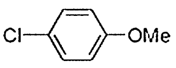
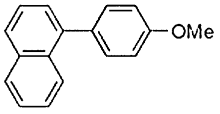
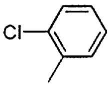
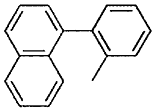
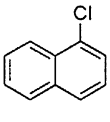
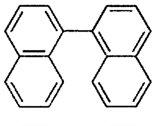
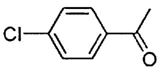
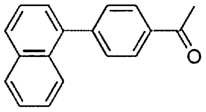
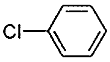
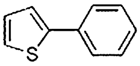
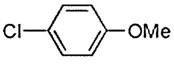
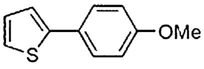
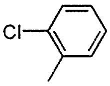
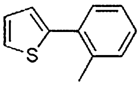
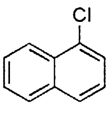
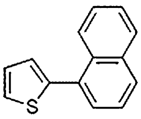
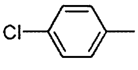
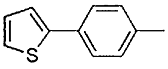
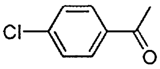
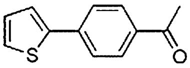
Thiophene-based materials play an important role as components in optoelectronic technologies includ-

Table 2. Cross-coupling of chlorobenzenes and phenylboronic acid catalyzed by **1** at room temperature.[a]

Entry	Aryl chloride	Product	Yield [%]
1			98
2			96
3			93
4			98
5			98
6			98

[a] *Reaction conditions:* 4 mL of *i*-PrOH/H_2O (1:3), catalyst **1** (0.0002 mmol), ArCl (1 mmol), $PhB(OH)_2$ (1.1 mmol), K_2CO_3 (1.2 mmol), 6 h, isolated yields.

Table 3. Cross-coupling of aryl chlorides with 1-naphthylboronic and 2-thiopheneboronic acid catalyzed by **1** at room temperature.[a]

Entry	Aryl chloride	Product	Yield [%]
with 1-naphthylboronic acid			
1			98
2			96
3			91
4			94
5			98
with 2-thiopheneboronic acid			
6			98
7			95
8			90
9			91
10			90
11			94

[a] *Reaction conditions:* 4 mL of *i*-PrOH/H_2O (1:3), catalyst **1** (0.0002 mmol), ArCl (1 mmol), $ArB(OH)_2$ (1.1 mmol), K_2CO_3 (1.2 mmol), 6 h, isolated yields.

ing organic light emitting diodes (OLEDs), organic field effect transistors (OFETs) and organic solar cells (OSCs).[21] To the best of our knowledge, there are only a few catalysts that effectively couple thiopheneboronic acids with non-activated aryl chlorides.[22]

Finally we compared the catalytic performance of our system to data reported in the literature in terms of catalytic activity by calculating the turnover frequencies (TOFs, see the Supporting Information, Table S1). Taken into account that many of the Suzuki–Miyaura couplings with aryl chlorides were performed at elevated temperatures – usually 80–100 °C – it becomes clear that the performance of compound **1** is outstandingly high under the given reaction conditions. There are only a few reports on Suzuki–Miyaura couplings of aryl chlorides running in neat water or aqueous solutions performed at room temperature in the literature: M.-J. Jin et al. reported the use of an oxaminato palladium catalyst heterogenized on an inorganic support working at 50 °C.[23] Here the yields are comparable but the palladium loading is a factor of 50 higher although diffusion limitation caused by the porous support has to be taken into account.

In summary, we found excellent catalytic activities for the Suzuki–Miyaura cross-coupling of a broad variety of aryl chlorides and arylboronic acids using a palladium catalyst bearing a functionalized NHC ligand. The reactions were run under air in aqueous media at room temperature and require low loadings of the catalyst. These results represent a significant improvement in the field of the Suzuki–Miyaura cross-coupling. We are presently exploring the use of the nitrophenyl moiety at the NHC ligand for covalently grafting the catalyst onto an organic or inorganic support in order to investigate its performance and fate under heterogeneous conditions. The synthesis of the enantiomerically pure ligand is underway.

Experimental Section

The palladium catalyst **1** was synthesized as described in the literature.[11]

Catalytic Suzuki–Miyaura Cross-Couplings

In a typical run, a 50-mL round-bottom flask equipped with a magnetic stirring bar was charged with the aryl chloride (1 mmol), phenylboronic acid (1.1 mmol), and a mixture of isopropyl alcohol and water (1:3, 4 mL). After complete dissolution of the mixture, catalyst **1** (0.0002 mmol) and K_2CO_3 (1.2 mmol) were added. After the appropriate time, 5 mL of water were added to the reaction mixture. The organic layer was extracted with ethyl acetate, washed with 2 M aqueous NaOH and finally dried over sodium sulfate. The solvent was removed by evaporation and the residue was purified *via* flash chromatography on silica gel (hexane/EtOAc, 90/10). The yields were determined by a combination of weighing the product and ^{1}H NMR spectroscopy (see the Supporting Information) to examine the purity.

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