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Highly Efficient and Reusable Supported Pd Catalysts for Suzuki–Miyaura Reactions of Aryl Chlorides[†]

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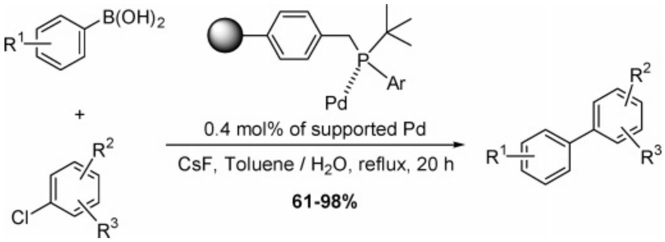
ABSTRACT



Syntheses of air- and moisture-stable heterogeneous (*tert*-butylarylphosphino)polystyrene-supported Pd catalysts and their use for versatile Suzuki–Miyaura reactions of aryl chlorides and arylboronic acids under non-anhydrous conditions are reported. The catalysts are easily recovered by filtration. They can be used many times (more than seven) without showing any loss of activity, and the amount of Pd leached is extremely low (<0.1%).

The Suzuki−Miyaura Pd-catalyzed cross-coupling reaction of aryl halides with arylboronic acids is a fundamental transformation in modern organic synthesis and offers a powerful way for the construction of aryl−aryl bonds under mild reaction conditions.[1] The resulting biaryls are often key building blocks for the preparation of more elaborated molecules which find widespread applications in the fields of medicinal chemistry,[2] molecular recognition,[3] liquid crystals,[4] and metal ligands for catalysis.[5] In addition, their synthesis is frequently performed on an industrial scale.[6]

The Suzuki−Miyaura reaction is usually performed by reacting aryl bromides or iodides with arylboronic acids in the presence of a homogeneous (soluble) Pd catalyst.[7] From an industrial point of view, aryl chlorides are much more advantageous due to their low price and to their large availability.[8] However, their major drawback is their relative inertness. The development of highly active homogeneous Pd catalysts for Suzuki−Miyaura reactions involving aryl chlorides arose, therefore, considerable interest. Significant success has been achieved in this field by the groups of Buchwald,[9] Fu,[10] Beller,[11] Herrmann,[12] Nolan,[13] and others.[14]

[†] This paper is dedicated to the memory of Prof. Charles Mioskowski, who passed away on June 2, 2007.

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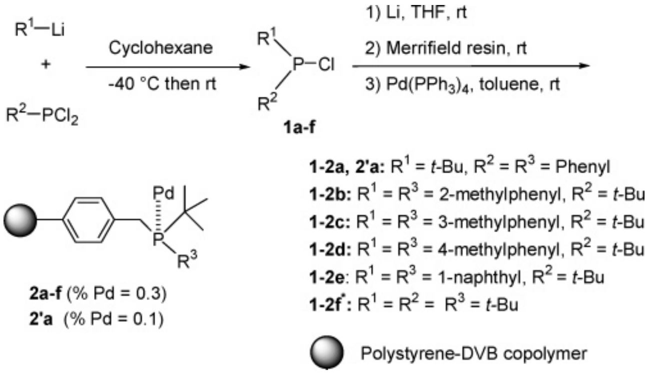
The major disadvantages of these Pd catalysts lie in the difficulty to avoid the presence of small amounts of metal in the reaction product and the impossibility to recover the expensive catalysts for reuse. Because homogeneous Pd catalysts have found widespread use in synthesis, the development of heterogeneous alternatives where the metal is grafted on inorganic or organic supports has attracted great attention in the past years.[15] Despite the fact that numerous heterogeneous Pd catalysts have been described for Suzuki−Miyaura reactions involving aryl bromides or iodides,[16] only few such Pd catalysts have been reported to date for cross-couplings with aryl chlorides.[17,18] Moreover, compared to their homogeneous analogues, heterogeneous Pd catalysts often suffer from a lower efficiency, which sometimes happens to decrease[18c] or even disappear after use.[18d] In 2000, Miyaura and Inada have reported Suzuki−Miyaura reactions of electron-deficient aryl chlorides or chloropyridines with 4-methylphenylboronic acid in the presence of relatively high amounts of (diphenylphosphino)polystyrene-supported Pd (3 mol %).[18a] Later, Buchwald and Parrish have described a five-step preparation of polymer-supported dialkylphosphinobiphenyls which have been used as Pd ligands[18b] for Suzuki−Miyaura couplings of aryl bromides or chlorides under anhydrous conditions, but the reactions involving aryl chlorides require a large excess of arylboronic acids (3 equiv) and up to 1 mol % of Pd to afford the biaryls in high yields. The group of Bedford has reported that polystyrene-supported palladacycles performed Suzuki−Miyaura couplings involving aryl chlorides, but these heterogeneous catalysts cannot be reused.[18d] Finally, Sinou and his group have developed a polymer-supported (dicyclohexylphosphino)biphenyl ligand for the Pd-catalyzed coupling of electron-deficient aryl chlorides and phenylboronic or 4-methylphenylboronic acid, but only one coupling of a deactivated (i.e., electron-rich) aryl chloride has been described, moreover affording a very low yield.[18c] The development of reusable Pd catalysts of general application for Suzuki−Miyaura reactions using aryl chlorides is therefore highly desirable. Herein, we describe short syntheses of (aryl-*tert*-butylphosphino)polystyrene-supported Pd catalysts and their use for Suzuki−Miyaura couplings of aryl chlorides.[19]

Inspired by a precedent report from our group, the syntheses of catalysts **2a**−**f** and **2′a** were performed (Scheme 1).[16f] Elemental analysis proved that more than 99% of the amount of Pd used was grafted on the resin and that comparable P/Pd ratios were obtained for **2a**−**f** (for further details see Supporting Information). Finally, catalysts **2a** and **2′a** were successfully prepared on a 20 g scale. They are air- and moisture-stable and can therefore be easily stored and handled.

Scheme 1. Preparation of Catalysts **2a**−**f** and **2′a**



* **1f** is commercially available.

The reactivity of catalysts **2a**−**f** and **2′a** for Suzuki−Miyaura reactions was then evaluated using 4-chloroacetophenone and phenylboronic acid as model substrates (Table 1). This coupling was initially performed using catalyst **2′a** (% Pd = 0.1) and Na_2CO_3 as a base in a 5:1:1 mixture of toluene/EtOH/H_2O at reflux.[16f] The biaryl **3a** was obtained quantitatively in the presence of only 0.05 mol % of supported Pd. However, the second use of catalyst **2′a** afforded only a <40% yield of **3a**. It should be noted that because the loss of Pd during the first use of the catalyst was only 1% of the initial amount the deactivation of the catalyst is not linked with a loss of precious metal. Similar observations were made with catalyst **2a** (% Pd = 0.3). Therefore, the reaction conditions had to be optimized to allow reuse of the catalyst, and it turned out that hydroxylic solvents should be avoided because the catalyst lost its efficiency when refluxed in toluene/EtOH/H_2O. Upon optimization using catalyst **2a**, we found that CsF as a base in

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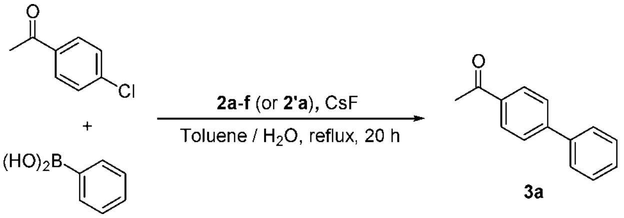
Table 1. Suzuki−Miyaura Reaction between 4-Chloroacetophenone and Phenylboronic Acid Using Catalysts **2a**−**f** and **2′a**



entry	catalyst[a]	Pd (mol %)	calculated yield (%)[b]
1	**2a**	0.4	84
2	**2b**	0.4	29
3	**2c**	0.4	74
4	**2d**	0.4	83
5	**2e**	0.4	31
6	**2f**	0.4	36
7	**2′a**	0.4	100[c]
8	**2′a**	0.05	45
9	Pd Encat TPP30	0.4	no reaction[d]
10	Pd EnCat NP30	0.4	no reaction[d]

[a] Reactions performed with 1.0 equiv of 4-chloroacetophenone, 1.4 equiv of phenylboronic acid, and 1.5 equiv of CsF in toluene/H_2O. [b] Yields were calculated by ^1H NMR of the crude reaction mixtures. [c] When the reaction was performed with 1.0 equiv of 4-chloroacetophenone, 1.1 equiv of phenylboronic acid and 1.5 equiv of CsF, a 84% yield was obtained. [d] The starting materials were recovered unchanged.

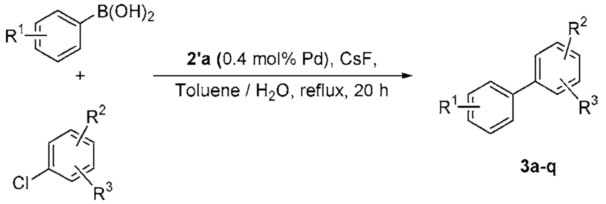
Table 2. Recycling Test of Catalyst **2′a**

run[a]	1	2	3	4	5	6	7
calculated yields[b]	100	95	100	98	100	98	98

[a] According to Table 1, entry 7. [b] Yields were calculated by ^1H NMR of the crude reaction mixtures.

toluene containing only traces of H_2O (0.3%) gave **3a** in a 84% yield, in the presence of 0.4 mol % of supported Pd (entry 1). The catalyst was then reusable. No improvement was achieved by using catalysts **2b**−**f** (entries 2−6) which, moreover, are somewhat more difficult to prepare. Interestingly, the use of **2′a** (0.4 mol % of supported Pd) under these optimized reaction conditions resulted in a considerable increase of the yield (entry 7). Noteworthily, decreasing the amount of supported Pd (entry 8), the excess of phenylboronic acid, or the temperature afforded **3a** only in lower yields. The commercially available Pd EnCat TPP30 and Pd EnCat NP30 turned out to be totally inefficient (entries 9 and 10).[20] The possibilities of reuse of catalyst **2′a** were then ascertained (Table 2): the catalyst was used seven times without showing any loss of efficiency. Additionally, a hot filtration test was performed. For this purpose, after 20 min of reaction (Table 1, entry 7), **2′a** was filtered (yield of **3a** at that point: 73%), and the filtrate was heated at reflux for another 20 h after which the yield reached only 74%. The amount of Pd present in the filtrate obtained after hot filtration was less than 0.1% of the initial amount.[21] Finally, catalyst **2′a** was studied by transmission electronic microscopy which showed only very scarce Pd crystallites. Interestingly, many crystallites appeared in **2′a** very quickly during use: they were already present after 20 min of reaction. However, neither their size (up to ca. 15 nm) nor their abundance changed significantly thereafter, even after seven uses (see TEM images in Supporting Information). Identical results, within experimental error, were obtained for the Pd contents of the fresh catalyst and of the catalyst recovered after seven uses.

Table 3. Suzuki−Miyaura Reactions between Various Aryl Chlorides and Arylboronic Acids Using **2′a**



entry[a]	R¹	R²	R³	product	yield (%)[b]
1	H	4-Ac	H	**3a**	90
2	4-OMe	4-Ac	H	**3b**	93
3[c]	3-NH_2	4-Ac	H	**3c**	69
4	4-Me	4-Ac	H	**3d**	90
5	2-Me	4-Ac	H	**3e**	86
6[c]	3-NO_2	4-Ac	H	**3f**	78
7	H	3-Ac	H	**3g**	78
8	H	2-Ac	H	**3h**	90
9	H	4-NO_2	H	**3i**	86
10	H	H	H	**3j**	98
11	H	4-Me	H	**3k**	86
12	H	4-OMe	H	**3l**	72
13[d]	H	4-Cl	H	**3m**	66
14	H	3-Me	H	**3n**	79
15	H	2-Me	H	**3o**	82
16	H	2-Me	6-Me	**3p**	88
17	2-Me	2-Me	6-Me	**3q**	61

[a] Reactions performed with 1.0 equiv of aryl chloride, 1.4 equiv of arylboronic acid and 1.5 equiv of CsF in toluene/H_2O. [b] Isolated yields after flash chromatography of the crude reaction mixture on silica gel. [c] Reactions performed in the presence of EtOH (see Supporting Information). [d] Reaction performed with 1.0 equiv of 1,4-dichlorobenzene, 1.1 equiv of phenylboronic acid and 1.2 equiv of CsF in toluene/H_2O.

Various aryl chlorides and arylboronic acids were reacted in the presence of catalyst **2′a** (Table 3). The couplings of 4-chloroacetophenone with electron-deficient or electron-rich arylboronic acids afforded the expected biaryls in very good isolated yields (entries 1−6). Similar results were also obtained by cross-coupling phenylboronic acid with aryl

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chlorides bearing both electron-rich and electron-deficient substituents (entries 7−16). Noteworthily, 2-substituted, 2,6-disubstituted, and even 2,6,2′-trisubstituted biaryls could be prepared in good yields (entries 5, 8, and 15−17). 1,4-Dichlorobenzene reacted with 1.1 equiv of phenylboronic acid to give the monosubstituted biaryl **3m** in 66% yield (entry 13). However, in the presence of 2.8 equiv of phenylboronic acid and 3.1 equiv of CsF, *p*-terphenyl was obtained in 86% yield. Finally, **2′a** can be successfully used for cross-couplings involving heterocyclic aryl chlorides or heterocyclic arylboronic acids. The reaction between 3-thiopheneboronic acid and 4-chloroacetophenone gave the expected biaryl **3r** in 64% yield, whereas the cross-coupling of 2-chloropyridine and phenylboronic acid afforded 2-phenylpyridine (**3s**) in 88% isolated yield.

In summary, we have reported here the short synthesis of an air- and moisture-stable heterogeneous (*tert*-butylphenylphosphino)polystyrene-supported Pd catalyst and its application for the Suzuki−Miyaura coupling of aryl chlorides with arylboronic acids. These heterogeneous catalysts can easily be recovered by filtration and can be reused more than seven times with no loss of efficiency. Moreover, it is well-known that the presence of Pd in the reaction products is often a drawback of Pd-catalyzed reactions, especially in the pharmaceutical industry. Here, only less than 4 microequivalents of Pd are lost during the reaction; therefore, the crude product obtained contains only a negligible amount of Pd, which greatly simplifies its purification.

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Supporting Information Available: Full experimental details, copies of ^{1}H and ^{31}P NMR spectra of compounds **1a−e**, ^{1}H NMR spectra of biaryls **3a−s**, and TEM images of catalysts **2′a** are given. This material is available free of charge via the Internet at http://pubs.acs.org.

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