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Heterogeneous Suzuki reactions catalyzed by Pd(0)–Y zeolite

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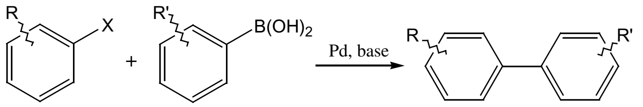
Abstract—The Pd(0)–Y zeolite showed high activity in the Suzuki cross-coupling reactions of aryl bromides without added ligands. The type of base and organic solvent were found to be critical for the efficiency of the reaction. The presence of water was essential within the reaction medium. The coupling reactions occurred on the external surface of the zeolite. The catalyst is reusable.

The Pd-catalyzed cross-coupling of aryl halides with aryl boronic acids, that is the Suzuki reaction, is recognized as being one of the most powerful and popular methods for the construction of unsymmetrical biaryls, which are widely used for the synthesis of valuable organic compounds such as pharmaceuticals and agrochemicals.[1] The particular merits of this reaction are that the reaction can be performed under mild conditions in aqueous solutions and that it tolerates a broad range of functional groups.



Many Pd complexes have been investigated in homogeneous systems in the Suzuki reaction of aryl halides. However, palladium reagents tend to be expensive and sometimes difficult to manipulate, recover, and reuse. One method to construct a recoverable and reusable catalyst is to immobilize the active palladium species on a solid material. Several types of solid materials have been used to support palladium species.

A few groups have used polymer-supported palladium compounds.[2] However, in some cases recovery, reuse or activity of the catalyst have not been satisfactory for deactivated bromoarenes. Pd/C was determined to be active in Suzuki reactions for iodoarenes in ethanol/water mixtures[3] and iodophenols in water,[4] yet led to low yields for bromoarenes. In a study by Heidenreich et al., a relatively high reaction temperature (120 °C) was required for effective coupling of bromo- and iodoarenes over Pd/C, the activity being markedly reduced by more than 50% when reused.[5] It was shown that Pd/C catalyzes the Suzuki cross-coupling reaction of activated chloroarenes with various arylboronic acids upon fine adjustment of the *N*,*N*-dimethylacetamide (DMA)/water ratio.[6] However, long reaction times were required (24 h) and reusability was not tested for the catalyst. Also, it was shown in a recent study, that Pd/C can be used as a recyclable catalyst in the Suzuki reactions of aryl halides in water and in the presence of surfactants.[7] In a study by Kabalka et al., while a Pd-doped alumina support was found to be activating for iodoarenes in Suzuki reactions, it had low activity for bromoarenes.[8]

One method of immobilization of Pd complexes is covalent anchoring of the complex onto a solid carrier. Researchers have found that a Pd–phosphine loaded MCM-41 zeolite and alumina catalyze the cross coupling of 4-iodoanisole with phenylboronic acid.[9] Tzschucke et al. used a silica surface to immobilize a perfluoro-tagged Pd complex for Suzuki reactions.[10] However, the catalyst showed poor activity for electron-rich bromoarenes. An oxime-carbapalladacycle complex covalently anchored onto silica was recently reported to be highly active for the Suzuki reaction of 4-chloroacetophenone and phenylboronic acid in water and to be reusable without decreased activity.[11] A silica supported palladacyle complex[12] and a Pd–dihydroimidazole complex[13] were shown to be active and reusable for Suzuki coupling reactions.

Keywords: Suzuki reaction; Coupling; Palladium; Zeolite; Heterogeneous catalysts; Aryl halides.

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In initial studies, we tested the Pd(II) exchanged NaY zeolite in Suzuki reactions of activated and unactivated bromobenzenes, and an activated chlorobenzene.[14] We found that the catalyst displayed high activity for bromobenzenes in an *N*,*N*-dimethylformamide (DMF)/water (1:1) mixture, almost quantitative coupling yields being obtained at room temperature (rt), and was moderately active for 4-chlorobenzotrifluoride at relatively higher temperatures. In a study by another group, $PdCl_2$ adsorbed zeolites were tested in Suzuki reactions.[15] Substantial palladium leaching was observed when a polar solvent system (alcohol/water mixture) was used, however, the use of toluene as a solvent eliminated the Pd leaching, but the reaction rate was remarkably slow even at higher reaction temperatures.

In this study we first showed that the Pd(0)–NaY zeolite, which is prepared by reduction of Pd(II) exchanged NaY,[16] is also highly active in Suzuki reactions of aryl bromides with arylboronic acids as had previously been known for the cross coupling of alkenyl halides with arylboronic acids,[17] Heck,[18] α-arylation of malonate,[19] and amination[20] reactions, and our results are reported herein. 4-Bromoanisole was used as a probe to investigate the scope of the Suzuki reaction using the catalyst.[21]

The presence of water appears to be essential in order to perform the reactions under mild conditions (Table 1). The conversion of 4-bromoanisole was negligible when DMF was the only solvent, even at 80 °C (entry 1). In neat water, no coupling took place at rt. The optimum ratio of the solvent mixture was determined to be 1:1 in the presence of Na_2CO_3 as the base at rt and for 1 h (entries 3–5). It is noteworthy that the reactions proceeded under very mild conditions.

Table 1. The effect of base and DMF/water ratio on the Pd(0)–NaY catalyzed Suzuki reaction of 4-bromoanisole with phenylboronic acid[a]

Entry	Base (mol equiv)	DMF/H_2O	Yield(%)[b]
1[c]	Na_2CO_3 (2)	1/0	2
2	Na_2CO_3 (2)	0/1	0
3	Na_2CO_3 (2)	1/1	95
4	Na_2CO_3 (2)	2/1	23
5	Na_2CO_3 (2)	1/2	64
6	Na_2CO_3 (1)	1/1	88
7	Na_2CO_3 (3)	1/1	100
8[d]	Na_2CO_3 (2)	1/1	98
9	Li_2CO_3 (2)	1/1	60
10	K_2CO_3 (2)	1/1	87
11	Rb_2CO_3 (2)	1/1	74
12	Cs_2CO_3 (2)	1/1	100
13	NaF (2)	1/1	33
14	$NaHCO_3$ (2)	1/1	26
15	NaOAc (2)	1/1	0
16	K_3PO_4 (2)	1/1	3
17	$N(C_2H_5)_3$ (2)	1/1	0
19	NaOH (2)	1/1	7

[a] Reaction conditions: 1.0 mmol of 4-bromoanisole, 1.2 mmol of phenylboronic acid, 0.025 mmol Pd, 10 mL of DMF/H_2O mixture, 1 h at room temperature under Ar.

[b] GC yield based on 4-bromoanisole.

[c] At 80 °C.

[d] Open to the atmosphere.

Various bases were examined for their effect on reaction efficiency. It is apparent that the efficiency does not follow basicity and that carbonate bases worked best. It seems that carbonate bases are more effective in activating the palladium catalyst (Table 1). The catalyst showed either no or very poor activity when no carbonate bases were used (entries 13–19). It was reported previously that sodium acetate and trialkylamine bases activate the coupling reactions over Pd-loaded zeolites when reactions were performed at higher temperatures (100–140 °C),[18–20] yet no detectable coupling products were observed in the presence of these bases in our study. This apparent difference may result mainly from the different mechanistic details of the reactions. When using a base/substrate molar ratio of 2, yields of 95% and 100% were obtained for Na_2CO_3 and Cs_2CO_3, respectively. A lower coupling product yield (88%) was obtained with a Na_2CO_3/substrate ratio of 1. Increasing the ratio to 3 afforded the coupled product quantitatively. Nevertheless, for economy, Na_2CO_3 was the best choice of base and a base/substrate ratio of 2 was used in all experiments.

A proposed mechanism for the Suzuki reaction suggests that the base is involved in the coordination sphere of the palladium and the formation of Ar–PdL_2–B from reversible oxidative addition, for example, Ar–PdL_2–X, is known to accelerate the subsequent transmetallation step.[1] It seems that carbonate accomplishes activation of the palladium better than other bases.

The fact that no homo-coupling products were detected is an important advantage. The reactions were routinely performed under an Ar atmosphere, however, it was an adventitious finding that the process was tolerant to the atmosphere (entry 8).

The type of organic co-solvent was evaluated for those water miscible agents within the solvent mixture, using an organic solvent/water ratio of 1:1 (Table 2). Polar aprotic amides and their cyclic counterpart a lactam, *N*-methylpyrrolidone (NMP), were most efficacious for

Table 2. The effect of organic solvent in the organic solvent/water mixture (1:1) on the Pd(0)–NaY catalyzed Suzuki reaction of 4-bromoanisole with phenylboronic acid[a]

Entry	Solvent	Yield(%)[b]
20	DMA	96
21	NMP	76
22	THF	0
23	DMSO	0
24	Acetonitrile	0
25	Dioxane	13
26	Ethanol	7
27	Isopropyl alcohol	14
28	Acetone	30

[a] Reaction conditions are the same as those of entry 3 in Table 1.

[b] GC yield based on 4-bromoanisole.

Table 3. Pd(0)–NaY catalyzed Suzuki cross-coupling reaction of aryl halides and arylboronic acids[a]

Entry	Aryl halide	Arylboronic acid	Yield(%)[b]
29	3-$MeOC_6H_4Br$	$C_6H_5B(OH)_2$	97
30	2-$MeOC_6H_4Br$	$C_6H_5B(OH)_2$	85
31	C_6H_5Br	4-$MeC_6H_4B(OH)_2$	98
32	C_6H_5Br	4-$MeOC_6H_4B(OH)_2$	92
33	4-CNC_6H_4Br	$C_6H_5B(OH)_2$	100
34	4-$NO_2C_6H_4Br$	$C_6H_5B(OH)_2$	51
35	4-$MeCOC_6H_4Br$	$C_6H_5B(OH)_2$	71
36	4-$MeCOC_6H_4Cl$	$C_6H_5B(OH)_2$	26[c]

[a] Reaction conditions are the same as those of entry 3 in Table 1.

[b] GC yield based on aryl halide.

[c] At 100 °C, 25% acetophenone was also formed.

the reaction, implying that amides probably acted as ligands to beneficially activate the palladium species. DMA was comparable to DMF in reaction efficiency (entry 20). The use of NMP with water resulted in a lower coupled product yield (76%). This may be associated with the less polar nature of NMP. Product formation was nil in tetrahydrofuran (THF), dimethylsulfoxide (DMSO), and acetonitrile, and very low in dioxane, isopropyl alcohol, ethanol and acetone (entries 25–28).

The effect of varying the aryl halide and arylboronic acids was also tested (Table 3). 3-Bromoanisole underwent excellent coupling (97% yield). Sterically hindered 2-bromoanisole was well tolerated by the catalytic system and provided the corresponding coupled product in high yield (85%) under the established conditions. Nonactivated bromobenzene also revealed excellent reactivity towards the coupling reactions with 4-methyl- and 4-methoxyphenylboronic acids (entries 31, 32). Coupling product formation was quantitative with 4-bromobenzonitrile. Though it is an activated aryl bromide, 4-bromonitrobenzene afforded only a moderate yield of the corresponding coupled product (51%).

4-Chloroacetophenone was used as an electron-deficient probe for chloroarenes for the Suzuki coupling reaction. The conversion was complete, however, the yield was only 26% and was accompanied by the dechlorination product, acetophenone, in 25% yield at a reaction temperature of 100 °C. We also attempted a reaction with the activated chloroarene under the conditions of entry 36, but in the absence of boronic acid. The yield of 88% for the dechlorinated product verifies the oxidative activity of the catalyst for activated chloroarenes.

The catalyst was recovered by filtration and washed with both DCM and water, and subsequently reused under the conditions of entry 3. It was determined that the catalyst activity was reduced to 31% at rt, but the coupling product formation was quantitative at 50 °C during second use. However, regeneration of the catalyst by consecutive treatments with O_2 and H_2 was necessary to obtain high yields after the second use. The product yields were 93% and 94% after the third and fourth uses, respectively, at 50 °C and 1 h and reduced to 69% and 54% after the fifth and sixth uses, respectively.

It is a matter of debate whether the reactions are homogeneously or heterogeneously catalyzed in the presence of supported catalysts. Some conclusions can be drawn from the palladium level passed into the solvent during the course of reaction, because dissolved Pd may be the main active species that catalyzes the reaction.[5,18a,22] After the catalyst was filtered off through a membrane filter with 0.2 μm porosity and washed with DCM and water, at the end of the reactions we observed a Pd concentration of only <0.4 ppm (<0.3% loss based on the initial Pd quantity) in the filtrates, this being about one fifth of the amount that leached from Pd(II) loaded zeolite.[14] This observation coincides with previous findings that higher Pd leaching was observed from Pd(II) loaded zeolites than from Pd(0)–zeolites in Heck reactions.[18a] After 5 min, for a reaction performed under the conditions of entry 3, (at which stage the coupling product formation was found to be 44%) the product mixture was filtered and an AAS analysis of the filtrate revealed no detectable amount of Pd. Moreover, the reaction ceased when the solid catalyst was removed at this stage. These results may indicate that the reaction is truly heterogeneous.

We also performed probe reactions to verify whether the coupling process took place within the zeolite cages or not. As a probe reaction, the Suzuki reaction was carried out with 1-bromonaphthalene and phenylboronic acid. The product, 1-phenylnaphthalene, would not be detectable in the reaction solvent unless the zeolite matrix collapses, because the large size of 1-phenylnaphthalene would not allow it to pass through the zeolite apertures (~7 Å). Nevertheless, we found that 1-phenylnaphthalene formation was 95% after one hour of reaction at rt and the Pd concentration was 0.19 ppm in the solvent at the end of the reaction. This result verifies that this coupling reaction did not occur within the zeolite.

In another experiment we performed the Suzuki reaction of 4-bromoanisole with phenylboronic acid in the presence of PPh_3. Phosphines are commonly used as ligand additives in activating homogeneous Pd-catalyzed coupling reactions. If the coupling reactions were intrazeolite reactions, the presence of PPh_3 would not influence the course of the reaction at all, either in a positive or a negative manner, because PPh_3 in its most stable conformation has cross sections larger than the apertures of faujasite-type zeolites.[23] Nevertheless it was striking that the addition of PPh_3 in twofold molar equivalent with respect to Pd brought the coupling reaction to a halt. The presence of phosphine should have destroyed the activity of any exposed Pd species, but not those in the interior of the zeolite. Thus, these results presented us with precise evidence that the coupling reactions did not take place within the zeolite.

In summary, we have found that aryl bromides, in general, can be coupled with arylboronic acids in excellent yields using a Pd(0)-loaded NaY zeolite under mild conditions. However, the reactions occurred on the external surface of the catalyst. The catalyst can be reused subsequent to regeneration.

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16. *Catalyst preparation*: The preparation of Pd(II)–NaY zeolite has been described elsewhere.[14] Pd(0)–NaY was obtained by reduction under a flow of hydrogen (70 mL/min) and at a temperature of 200 °C for 30 min. The AAS analysis gave a Pd content of 1.0 ± 0.1 wt%. When the catalyst reduction was carried out at higher temperature (350 °C) as was applied in the preparation of the catalyst for the Heck reactions in previous studies (Refs. 18b–d,19,20) the Suzuki coupling yield was much lower. It was reported that higher reduction temperatures, typically >300 °C, reduces the Pd dispersion on NaY zeolite (see articles: Primet, M.; Taarit, Y. B. *J. Catal.* **1977**, *81*, 1317–1324; Sachtler, W. M. H.; Cavalcanti, F. A. P.; Zhang, Z. *Catal. Lett.* **1991**, *9*, 261–272).
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21. *Typical reaction procedure*: In a 50 mL flask equipped with a magnetic stirring bar were charged aryl halide (1 mmol), Na_2CO_3 (2 mmol), arylboronic acid (1.2 mmol) and Pd(0)–NaY (0.025 mmol Pd) in succession. The flask was attached to an argon line and the reaction was initiated by the addition of 10 mL DMF/water mixture (1:1). The mixture was vigorously stirred for 1 h at room temperature. The catalyst was filtered off and washed with dichloromethane and 0.6 mmol of hexadecane was added to the solution as an internal standard. The organic phase was separated from the aqueous phase and dried over Na_2SO_4. Products were analyzed by GC and GC/MS and isolated by column chromatography on silica gel using hexane and hexane/ethyl acetate mixture (9:1 v/v) as eluents, successively.
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