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Simple and efficient protocol for catalyst recycling and product recovery in the Pd-catalyzed homogeneous Suzuki reaction

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Abstract—Poly(ethylene oxide) (PEO)/methanol can be used as solvent medium for the Pd-catalyzed Suzuki cross-coupling reaction under mild conditions. After the end of the reaction the product is extracted with heptane and the polar phase can be reused several times without any change in the activity. Pure biaryl products are obtained from the nonpolar phase in excellent isolated yields (>90%). The same catalyst-containing polar phase was used to coupling different aryl halides furnishing the biaryl products in good to high isolated yields.

The palladium-catalyzed Suzuki cross-coupling reaction is one of the most efficient methods for the construction of C_{aryl}–C_{aryl} bonds and has found widespread use in organic synthesis.[1] A plethora of palladium catalyst precursors promote the coupling of aryl halides with organoboron compounds.[2] One of the major drawbacks of homogeneous Suzuki cross-coupling reactions is the separation of the reaction product from the catalyst. The expensive palladium catalysts are difficult to recover and recycle. On the other hand, in order to obtain a pure biaryl product tedious and expensive workups are usually necessary. To overcome these problems, several heterogeneous Pd-catalyzed Suzuki coupling systems have been described in the last years, such as Pd/C,[3] polymer supported Pd-catalysts,[4] and the use of aqueous media,[5] and other systems.[6] However, in homogeneous catalysis, solvents play a critical role in rendering the reaction homogeneous and allowing more efficient molecular interactions and, in several cases, the heterogenization of the catalyst results in reduced activity. In this context, a homogenous coupling reaction that, at the end of the reaction, the catalyst can be easily separated from the product phase and recycled would be desirable. One example of this strategy was the use of ionic liquids as solvents for the Suzuki reaction.[7] The products are separated from the solvent by extraction with diethyl ether and the catalytic solution can be reused three times without loss of activity. However, the ionic solution needs to be washed with water and dried in vacuo before reuse. An alternative to the ionic liquids consists of using a mixture of organic solvents and poly(ethylene oxide) (PEO). In fact, ternary mixtures of PEO, heptane and one of the three organic solvents (MeOH, CH_2Cl_2 or $CHCl_3$) may be interchanged between homogeneous and biphasic regions by either composition or temperature alterations.[8] These characteristics have been used to achieve efficient separation and easy catalyst recycling in hydrogenation,[9] epoxidation[10] reactions by using PEO as polymer, and in cross-coupling reactions of aryl iodides (Heck and Suzuki reactions)[4b] by using tridentate SCS-Pd(II) catalyst bound to poly(N-isopropylacrylamide) or PEG. Otherwise, the application of poly(ethylene glycol) (PEG) as a reusable solvent has been described for the Heck reaction.[11] In this case, after the end of the first run, the reaction mixture was extracted with dry ether and the PEG and $Pd(OAc)_2$ were solidified and subjected to five recycles (yields: 88%, 82%, 80%, 74%, 73%, 70%). We wish to report here the application of PEO/MEOH as an efficient and reusable medium for Pd-catalyzed Suzuki reactions.

Initially, the coupling of 4-bromotoluene with phenylboronic acid was investigated. In order to test our system we chose a very simple catalyst system composed of $Pd(OAc)_2$ and PPh_3. Preliminary screening of solvent

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Keywords: Suzuki reaction; Palladium catalyst; Recycle; Poly(ethyleneoxide).

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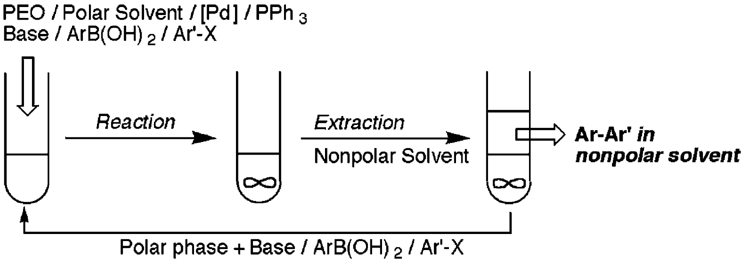
Table 1. Recycling experiments for the Pd-catalyzed Suzuki cross-coupling[a]



Run		Reaction 1	Reaction 2	Reaction 3	Reaction 4
	ArX	p-MeC_6H_4Br	p-MeC_6H_4Br	p-MeC_6H_4Br	p-MeC_6H_4I
	Solvent	PEO/MeOH	PEO/MeOH	MeOH	PEO/MeOH
	Catalyst	$Pd(OAc)_2/PPh_3$	$Pd(OAc)_2$	$Pd(OAc)_2/PPh_3$	$Pd(OAc)_2/PPh_3$
		Yield (%)[b]	Yield (%)[b]	Yield (%)[b]	Yield (%)
1		70	37	100	90
2		100	13	100	100 (91)
3		100	0	61	100 (81)
4		98		36	100 (92)
5		98		0	100 (98)
6		100 (93)			100 (93)
7		96			100 (95)
8		98			
9		93			
10		94			
11		97			
12		97			

[a] Reactions conditions: 0.25 mmol of aryl halide, 0.375 mmol of phenylboronic acid, 0.5 mmol of K_3PO_4, $Pd(OAc)_2$ (0.005 mmol), PPh_3 (0.015 mmol), MeOH (4 mL), PEO (1 g), 60 °C, 24 h for 4-bromotoluene and 3 h for 4-iodotoluene.

[b] GC yield (isolated yields are given in parentheses).

media and reaction conditions demonstrated that a mixture of MeOH/PEO was effective and that heating to 60 °C was sufficient.[12] Under these reaction conditions, the coupling of 4-bromotoluene was carried out in the presence of 2 mol% Pd catalyst and K_3PO_4 as base for 24 h furnishing 4-methylbiphenyl in 70% yield (Table 1, reaction 1, run 1). Then, the product was extracted under argon with *n*-heptane. The polar phase was reused in further runs by the addition of 4-bromotoluene, phenylboronic acid and K_3PO_4 in each run. For the first recycle the biphenyl product was obtained in quantitative yield, and eleven catalytic runs were performed without any significant loss of catalytic activity (Table 1, reaction 1, runs 2–12). The crude products of the first reaction were analyzed for Pd content by ICP-MS. For the first run a leaching of 5% of the palladium species from the polar phase was observed, but this leaching was lower for the following runs (>2%).

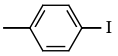
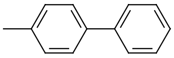
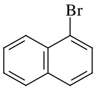
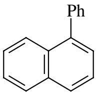
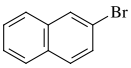
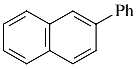
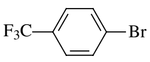
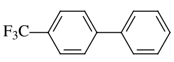
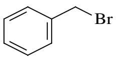
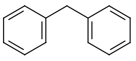
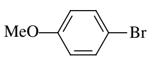
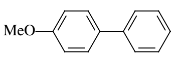
It is worth to note that ligandless $Pd(OAc)_2$ catalytic system efficiently promotes the coupling of aryl bromides with arylboronic acids using DMF as solvent.[13] However in the case of PEO/MeOH solvent media the presence of triphenylphosphine is necessary. In the absence of triphenylphosphine, only 37% yield was obtained in the first run and the reaction stopped in the third run (Table 1, reaction 2).

The coupling reaction was carried out using only methanol as solvent (Table 1, reaction 3). Despite the complete conversion in the first run, only four catalytic runs could be performed. These results indicate that the role of PEO is to increase the partitioning selectivity of the catalyst for the polar phase.

4-Iodotoluene was also efficiently coupled following this protocol (Table 1, reaction 4). As observed for the aryl bromide, incomplete conversion was observed in the first run. For the further runs complete conversion was achieved within 3 h. The workup procedure to isolate the biphenyl product is very simple. The apolar phase was washed with aqueous NaOH and brine and then dried over $MgSO_4$. After evaporation of the solvent 4-methylbiphenyl was obtained in 95% purity as judged by ^1H NMR and GC. The only side-reaction product observed was the biphenyl formed from the homocoupling of phenylboronic acid (2–5%).

In order to demonstrate the versatility of the catalyst recycling and product recovery in our protocol, the synthesis of different cross-coupled products using the same catalyst-containing polar phase was performed (Table 2). In the first run, 4-iodotoluene was coupled with phenylboronic acid to furnish 4-methylbiphenyl in 83% isolated yield (Table 2, run 1). Then, at the polar phase of this reaction, 1-bromonaphthalene, phenylboronic acid and K_3PO_4 were added and the coupling reaction afforded 1-phenylnaphthalene in 81% isolated yield (Table 2, run 2). Using this strategy we were able to obtain six different coupled products from the same catalyst solution.

Table 2. Recycling experiments for the Pd-catalyzed Suzuki cross-coupling changing the aryl halide in each recycle[a]

Run	Substrate	Product	Yield (%)[b]
1			92 (83)
2			100 (81)
3			100 (83)
4			88 (62)
5			75 (68)
6			100 (71)

[a] Reactions conditions: 0.25 mmol of aryl or benzyl halide, 0.375 mmol of phenylboronic acid, 0.5 mmol of K_3PO_4, MeOH (4 mL), PEO (1 g), 24 h.

[b] GC yield (isolated yields are given in parentheses).

In summary, we have developed a simple and efficient protocol for catalyst recycling and product recovery under homogenous Suzuki reaction conditions. At the end of the reaction the mixture is extracted with heptane and the polar phase can be reused several times without any significant loss of catalytic activity. Pure biaryl products are obtained from the nonpolar phase in excellent isolated yields (>90%). The same catalyst-containing polar phase can be reused in order to couple different aryl halides furnishing biaryl products in good to high isolated yields. This strategy has potential for combinatorial chemical investigations.

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12. In a typical experiment an oven-dried resealable Schlenk flask was evacuated and back filled with argon and charged with $Pd(OAc)_2$ (0.005 mmol), PPh_3 (0.015 mmol), K_3PO_4 (0.5 mmol), PEO 3350 (1 g) and phenylboronic acid (0.375 mmol). The flask was evacuated and back filled with

argon and then the aryl halide (0.25 mmol) and methanol (4 mL) were added. The reaction mixture was stirred at 60 °C for the desired time. The coupling product was extracted under argon with *n*-heptane (4 mL × 5–8 extractions depending on the biaryl product). The apolar phase was washed with aqueous NaOH (1 M, 5 mL) and brine (2 × 5 mL), and then dried over $MgSO_4$. The biaryl product was obtained in 95% purity as judged by ^1H NMR and GC. For the recycle reactions, the polar phase was transferred to a an oven dried resealable Schlenk flask under argon. Then, the aryl halide (0.25 mmol), phenylboronic acid (0.375 mmol) and K_3PO_4 (0.5 mmol) were added. The reaction mixture was stirred at 60 °C for the desired time and the product was isolated as described above.

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