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Suzuki–Miyaura reactions in PEG–water solutions using Pd/BaSO$_4$ as catalytic source

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Suzuki–Miyaura reactions between halobenzenes and other substituted (hetero)arenes and boronic acids were carried out in PEG–water solution using Pd/BaSO$_4$ as catalytic source in a ligand-free system. High to moderate yields were generally obtained. The catalytic system could be recycled up to six times, showing a slight decrease in activity after each cycle. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: Suzuki; biaryls; PEG-H$_2$O; Pd/BaSO$_4$

Introduction

Cross-coupling reactions represent an extremely versatile tool in organic synthesis.[1] The Suzuki cross-coupling reactions of arylboronic acids and aryl halides provide an effective synthetic route to biaryls.[2] The coupling reaction of arylboronic acid derivatives with aryl halides in the presence of Pd(PPh$_3$)$_4$ and base to afford biaryls was first reported in 1981.[3]

The search for new processes involves the use of heterogeneous catalysts.[4] In cross-coupling reactions, particularly in the Suzuki reaction, the use of common Pd/C[5] and several polymer- and silica-supported complexes[6] has been previously disclosed. Pb–Pd/CaCO$_3$ (Lindlar's catalyst) and Pd/BaSO$_4$ (Rosemund's catalyst), which are effective as catalysts in hydrogenation,[7] are rarely used in these reactions.

Our group has reported some previous studies on cross-coupling reactions.[8a–h] Our results using Pd/CaCO$_3$ showed the production of biaryls in high yields, the catalyst being reused seven times without any perceptible loss of activity.[8b] We have previously used Pd/BaSO$_4$ as a catalyst in the Stille reaction, which yielded biaryls with high yields and, in this case, the solution could be reused three times with good activity.[8h] Therefore, it is highly desirable to have a catalytic system that can be reused several times.[8i–k]

The use of Pd/CaCO$_3$[8a,e] and Pd/BaSO$_4$[8h] as catalytic sources in different C–C cross-coupling reactions deserves further investigation. These (and other) sources are expected to show different behaviors, mainly because these (and other) supported Pd nanoparticles have different basicity (acidicity), sizes and dispersions,[8l] among other properties.

Both Genêt's group[9] and Beller and Kühlein[10] carried out Heck reactions between several heterogeneous Pd(0/II) sources, including Pd/CaCO$_3$ and Pd/BaSO$_4$, showing that these catalysts can be used in C–C cross coupling reactions.

In addition to the use of heterogeneous catalyst sources, the replacement of expensive, toxic and flammable organic solvents by water or aqueous systems is highly desirable for reducing costs and for developing environmentally benign synthetic reactions that facilitate catalyst recycling.[11] Various previous examples of carbon-carbon bond formations using PEGs including Suzuki,[12] Sonogashira,[13] Heck[14] and Stille[15] reactions have been reported so far.

In the present work, our results concerning the use of Pd/BaSO$_4$ as catalyst in the Suzuki cross-coupling reaction, in PEG–water in a ligand-free aqueous system, are disclosed.

Results and Discussion

In our previous study of cross-coupling reaction, it was found that the Stille reaction using Pd/BaSO$_4$ in EtOH–water solution in the absence of ligands furnished biaryls with high yields.[8h] Therefore, continuing the search for new processes, it was decided to investigate this catalyst in different solvents, applying it to the Suzuki–Miyaura reaction using different reaction media. Our initial investigation started with the cross-coupling reaction of iodobenzene and phenylboronic acid as a model system (Scheme 1). The reaction was carried out in the presence of Pd/BaSO$_4$ as catalyst, in a ligand-free system, in different solvents at room temperature and at 80 °C for 24 h. Our results are summarized in Table 1.

The results obtained using Pd/BaSO4 as catalyst for 24 h show good to high yields, those obtained at 80 °C being generally better than those obtained at room temperature. Different solvents were tested for the Suzuki reaction between iodobenzene and phenylboronic acid using 5 mol% of Pd/BaSO$_4$. At room temperature, using ethanol as solvent, the reaction yielded 57% (entry 1), while water afforded biphenyl in poor yield (entry 2). As expected, the reaction using ethanol aqueous solution gave good yield (entry 3). PEGs that had been used in many cross-coupling reactions due to possible recycling[14b] were used. Therefore, PEG-300 afforded 55% yield at room temperature and 100% at 80 °C using 5.0 mol % Pd (entry 5). Decreasing loading to 2.0 and 1.0 mol% afforded good yields at 80 °C (entries 6 and 7 respectively), while practically no reaction was observed at room

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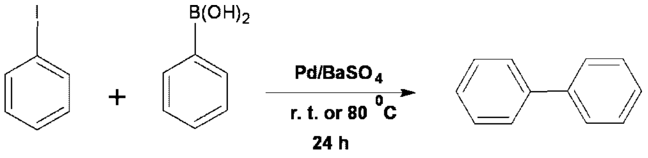
Table 1. Suzuki reaction using catalytic $Pd/BaSO_4$ system[a]

Entry	Solvent	mol% $Pd/BaSO_4$	Yield[b,c] (%)	TN[d] (r. t.)	Yield[d,e] (%)	TN (80 °C)
1	EtOH	5.0	57	11	85	17
2	H_2O	5.0	15	3	72	14
3	EtOH–H_2O 40%	5.0	75	15	99	20
4	EtOH–H_2O 40%	1.0	–	–	80	16
5	PEG 300	5.0	55	11	100	20
6	PEG 300	2.0	–	–	99	50
7	PEG 300	1.0	–	–	83	83
8	PEG 300–H_2O 40%	5.0	100	20	100	20
9	PEG 300–H_2O 40%	2.0	100	50	100	50
10	PEG 300–H_2O 40%	1.0	71	71	99	99
11	PEG 300–H_2O 40%	0.5	–	–	55	110

[a] 1.0 mmol iodobenzene, 1.0 mmol phenylboronic acid, 2.0 mmol K_2CO_3 and $Pd/BaSO_4$ in 20 ml (solvent) for 24 h.
[b] At room temperature.
[c] Measured by GC-MS.
[d] TN = no. mols products/no. mols catalyst.
[e] At 80 °C.



Scheme 1. Suzuki reaction between iodobenzene and phenylboronic acid using $Pd/BaSO_4$.

temperature. Water addition to PEG 300 had a dramatic effect when a reaction using PEG 300/H_2O solution in room temperature was carried out, affording 100% yield (entries 8 and 9) using 5.0 and 2.0 mol% at room temperature, while 1.0 mol% of catalyst afforded biphenyl with 71 and 99% at room temperature and at 80 °C, respectively (entry 10). Decreasing loading to 0.5 mol% furnished moderate yield at 80 °C (entry 11). Of course, calculated turnover numbers are not very good but are comparable to those generally obtained in these reactions.

To generalize the scope of our method, other aryl halides and boronic acids were tested using K_2CO_3 and 1 mol% $Pd/BaSO_4$ in PEG 300–H_2O solution under heating for 24 h. The results are described in Table 2.

Bromobenzene maintained a high yield (entry 1) but chlorobenzene, normally very unreactive, furnished a poor yield (entry 2). The coupling between *p*-iodonitrobenzene and phenylboronic acid using 1.0 mol% of $Pd/BaSO_4$ furnished 100% (entry 3). The reaction between the non-activated 4-iodoanisole and phenylboronic acid (entry 4) resulted in high yields. Use of *p*-bromoacetophenone furnished biaryl with high yield (entry 5). To go further, to verify the reactivity of heteroarenes, 2-bromopyridine furnished the heterocoupling product in good yield (entry 6). Other different boronic acids have been used, e.g. the reaction between iodobenzene and *p*-bromophenylboronic acid afforded 64% of the corresponding biaryl (entry 7). The coupling of iodobenzene and 2-thienylboronic acid, normally an unusual reaction, furnished the heteroarene product with 69% (entry 8). Finally, the unusual cross coupling reaction between benzyl bromide and phenylboronic acid yielded diphenylmethane in 55% yield (entry 9).[16,17] All compounds were characterized and analyzed by GC-MS, ^1H NMR and ^{13}C NMR.

Table 2. Suzuki reaction between different aryl halides and boronic acids[a]

Entry	Aryl halide	Boronic acid	Yield (%)[b]
1	Bromobenzene	Phenylboronic acid	86
2	Chlorobenzene	Phenylboronic acid	12
3	*p*-Iodonitrobenzene	Phenylboronic acid	100
4	*p*-Iodoanisol	Phenylboronic acid	99
5	*p*-Bromoacetophenone	Phenylboronic acid	96
6	2-Bromopyridine	Phenylboronic acid	74
7	Iodobenzene	*p*-Bromophenylboronic acid	64
8	Iodobenzene	2-Thienylboronic acid	69
9	Benzyl bromide	Phenylboronic acid	55

[a] 1.0 mmol aryl halide, 1.0 mmol boronic acid, 2.0 mmol K_2CO_3 and 1 mol% $Pd/BaSO_4$ in 20 ml PEG 300–H_2O 40% for 24 h at 80 °C.
[b] Measured by GC-MS.

Table 3. Recycling of the Miayura–Suzuki reaction

Entry	Run	Recycle (%)[a,b]
1	1	99
2	2	98
3	3	95

[a] 1.0 mmol 4-nitroiodobenzene and 1.0 mmol phenylboronic acid at 80 °C for 24 h.
[b] Measured by GC-MS using an external standard.

Recycling the whole reaction media, the Suzuki reaction between *p*-iodonitrobenzene and phenylboronic acid, kept the reaction yield up to three cycles without any loss of activity (Table 3).

To generalize the recycling of the whole reaction media, 4-bromoacetophenone and phenylboronic acid were used, and it was demonstrated that the reaction yield was kept at least six times, showing a slight decrease in activity after each recycle (Table 4).

Table 4. Recycling of Suzuki reaction

Entry	Run	Recycle (%)[a,b]
1	1	95
2	2	91
3	3	85
4	4	81
5	5	79
6	6	67

[a] 1.0 mmol 4-bromo-acetophenone and 1.0 mmol phenylboronic acid at 80 °C for 24 h.
[b] Measured by GC-MS.

As previously published, the leached Pd(0/II) species to solution in very low concentrations are capable of catalyzing C–C cross-coupling in Stille reaction using $Pd/BaSO_4$[8h] and in Miyaura–Suzuki reaction using $Pd/CaCO_3$.[8a]

To generalize the protocol, in the present case, filtration of $Pd/BaSO_4$ and reuse of reaction medium in the present system in the reaction between 4-bromoacetophenone and phenylboronic acid furnished 74% of the cross-coupling product, indicating the presence of leached catalytic active Pd(0/II) species in the reaction medium.

Conclusions

In sumary, the $PEG–H_2O–Pd/BaSO_4$ system proved to be a suitable catalyst for Suzuki–Miyaura cross-coupling reactions. Substituted biaryls were obtained in good yields by this method. The catalytic system can be recycled up to six times, showing a continuous slight decrease in activity. Reuse of reaction medium after catalyst source removal indicated that the leached catalyst is able to yield 74% of the cross coupling product.

Experimental

General Procedure for Suzuki–Miyaura Reaction

In a 50 ml reaction flask containing iodobenzene (1 mmol; 0,11 ml) in 20 ml of PEG 300–H_2O 40%; phenylboronic acid (1.0 mmol; 0,120 g), $Pd/BaSO_4$ (0.01 mmol; 0,042 g) and K_2CO_3 (2 mmol; 0,280 g) were successively added. The reaction was then kept under stirring at 80 °C for 24 h. The reactional mixture was extracted with hexane or chloroform. The organic phase was washed with water and dried over anhydrous magnesium sulfate. The solution was filtered under celite®, the solvent was evaporated and crude product was analyzed by GC-MS, ^1H NMR and ^{13}C NMR.

Biphenyl

^1H NMR ($CDCl_3$, 200 MHz) δ 7.56 (d, 4 H), 7.40 (dd, 4 H), 7.29 (d, 2 H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 140.8, 128.4, 126.9, 126.8. GC-MS: *m/z* 154, 77.

4-Nitrobiphenyl

^1H NMR ($CDCl_3$, 200 MHz) δ 8.30 (d, 2 H), 7.74 (d, 2 H), 7.64 (d 2 H), 7.52–7.44 (m, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 147.6, 147.1, 138.8, 129.2, 128.9, 127.8, 127.4, 124.1. GC-MS: *m/z* 199, 183, 169, 152.

4-Methoxybiphenyl

^1H NMR ($CDCl_3$, 200 MHz) δ 7.54 (t, 4 H), 7.42 (t, 2 H), 7.31 (t, 1 H), 7.21 (d, 2 H), 6.98 (d, 2 H), 3.86 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3. GC-MS: *m/z* 184, 169, 141, 115.

4-Phenylacetophenone

^1H NMR ($CDCl_3$, 200 MHz) δ 7.85 (d, 2 H), 7.63 (d, 2 H), 7.58 (d, 2 H), 7.40–7.37 (m, 3 H), 2.63 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 197.7, 145.7, 139.8, 135.9, 128.9, 128.1, 127.3, 26.2. GC-MS: *m/z* 196, 181, 153, 77.

2-Phenylthiophene

^1H NMR ($CDCl_3$, 200 MHz) δ 7.61 (m, 1 H), 7.37–7.16 (m, 3 H), 7.02 (m, 2 H), 6.99 (dd, 1 H), 6.81 (dd, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 148.5, 131.0, 129.7, 128.9, 127.9, 127.4, 125.9, 124.8. GC-MS: *m/z* 160, 82, 77.

2-Phenylpyridine

^1H NMR ($CDCl_3$, 200 MHz) δ 8.62 (d, 1 H), 7.98 (d, 2 H), 7.65 (d, 1 H), 7.64 (dd, 1 H), 7.44 (dd, 2 H), 7.38 (dd, 1 H), 7.14 (dd, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 157.3, 149.6, 139.3, 136.6, 128.9, 128.7, 126.8, 122.0, 120.3. GC-MS: *m/z* 155, 78, 77.

4-Bromobiphenyl

^1H NMR ($CDCl_3$, 200 MHz) δ 7.56–7.53 (m, 4 H), 7.40 (t, 2 H), 7.33 (t, 1 H), 7.27 (t, 2 H), 7.15 (t, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 141,3, 140.1, 131.9, 128.9, 128.7, 127.6, 127.0, 121.5. GC-MS: *m/z* 232, 151, 77.

Diphenylmethane

^1H NMR ($CDCl_3$, 200 MHz) δ 7.24 (m, 4 H), 7.15 (m, 6 H), 3.93 (s, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 141.0, 128.9, 128.4, 126.6, 41.9. GC-MS: *m/z* 168, 153, 91, 77.

General Procedure for Recycling Experiments to Suzuki–Miyaura Reaction

In a 50 ml reaction flask, 4-bromo-acetophenone (1.0 mmol; 0,200 g) and phenylboronic acid (1.0 mmol; 0,120 g) were successively added in the $PEG/H_2O–Pd/BaSO_4–K_2CO_3$ solution. The reaction was then kept under stirring at 80 °C for 24 h. The reaction mixture was extracted with chloroform. The organic phase was washed with water and dried over anhydrous magnesium sulfate. The solution was filtered under celite®, the solvent was evaporated and the crude product was analyzed by GC-MS.

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