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Suzuki cross-coupling reactions over Pd(II)-hydrotalcite catalysts in water

Manuel Mora, César Jiménez-Sanchidrián, José Rafael Ruiz *

Departamento de Química Orgánica, Universidad de Córdoba, Campus de Rabanales, Edificio Marie Curie,
Carretera Nacional IV-A, km 396, 14014 Córdoba, Spain

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Abstract

We studied the Suzuki cross-coupling reaction between bromobenzene and phenylboronic acid at room temperature in aqueous media containing K_2CO_3 as the base and solids consisting of Pd(II) supported on an Mg/Al hydrotalcite as catalysts. Based on the results, a surfactant facilitating the dissolution of phenylboronic acid in water is required for the reaction to develop at room temperature. Sodium dodecylsulphate proved the most effective surfactant among those tested for this purpose, which included anionic, cationic and neutral compounds. The conversion and selectivity results were excellent and on a par with previously reported values. However, ICP-MS measurements of palladium content before and after the reaction revealed that some metal in the catalyst was dissolved, so the catalytic process was not completely heterogeneous; rather, the reaction involves substantial homogeneous catalysis.

Keywords: Suzuki cross-coupling; Palladium; Hydrotalcite; Water; Surfactant

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1. Introduction

The Suzuki cross-coupling reaction, which involves the formation of biphenyl by coupling of an aryl halide or triflate to a phenylboronic acid in the presence of a palladium catalyst (see Scheme 1), constitutes one of the most widely used methods for the formation of carbon–carbon bonds in organic synthesis [1–5]. In most cases, the reaction is conducted with homogeneous catalysts, which are effective even with inactivated substrates [6] and provide excellent turnover values; also, the reaction medium is most often an organic solvent. However, removing residual palladium and its ligands from the reaction medium is usually a labour-intensive process [7], which has restricted the industrial use of these catalysts; also, the organic solvents employed can be the source of environmental problems. In addition, the high cost of palladium ligands and the difficulty of removing the catalyst from the reaction mass for reuse have further restricted the use of homogeneous catalysts on a large scale. The previous problems can in principle be minimized by using heterogeneous catalysts, which are usually more inexpensive, readily obtained and easily removed from the reaction medium (*e.g.* by filtration) than are homogeneous catalysts. However, few heterogeneous catalysts can compete in activity with homogeneous catalysts for the Suzuki cross-coupling reaction; specially effective among the former are palladium ligands supported on, or bound to, inorganic solids [8–12], Pd(0) and Pd(II) salts deposited on various supports [13–16]. Although the Suzuki cross-coupling reaction has scarcely been conducted with heterogeneous Pd catalysts and water as solvent, an increasing number of applications have been reported in recent years [17–20].

Based on its generally accepted mechanism (Scheme 2) [1], the Suzuki reaction requires the presence of a base to develop to an adequate extent. In previous work, we reported the synthesis of catalysts consisting of palladium ligands and salts [12,16,21], and their use in the cross coupling of arylbenzenes with phenylboronic acid in the presence of various bases. The results showed K_2CO_3 to be the most effective base and toluene the best solvent: no leaching was observed at a reaction temperature of 55 °C. In this work, we conducted the reaction under more environmentally benign conditions; to such an end, we used the same

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* Corresponding author. Tel.: +34 957 21 86 38; fax: +34 957 21 20 66.
E-mail address: qo1ruarj@uco.es (J.R. Ruiz).

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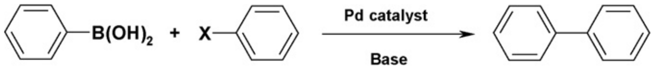
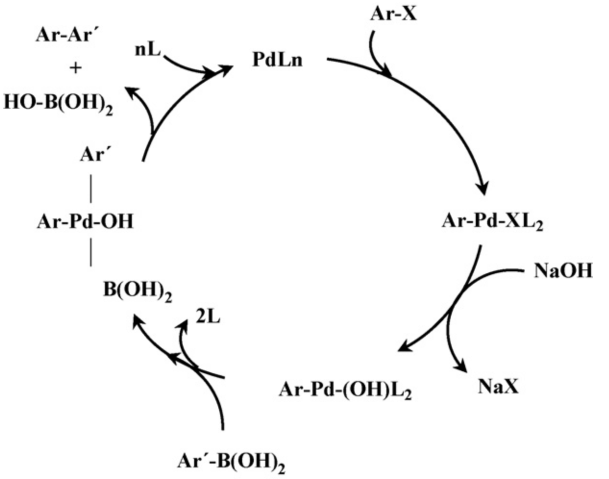


Scheme 1. General Suzuki cross-coupling reaction.



Scheme 2. Generally accepted mechanism for the Suzuki reaction in a homogeneous phase.

catalysts as in previous work, but room temperature and water rather than toluene as solvent.

Hydrotalcites have aroused much interest by virtue of their potential uses in various scientific fields such as organic synthesis [22–24]. The structure of these compounds is based on that of a natural mineral called hydrotalcite [25]. This is a magnesium–aluminium hydroxyl-carbonate of formula $Mg_6Al_2(OH)_{16}CO_3{\bullet}4H_2O$ structurally similar to brucite, $Mg(OH)_2$, except for the fact that some Mg^{2+} ions have been replaced with Al^{3+}, which results in the presence of layers bearing positive charge that is countered by carbonate ions in the interlayer spacing. Replacing the magnesium, aluminium or both cations with another metal, or the carbonate with another anion, allows a large family of compounds known as hydrotalcite-like compounds (HTs) or layered double hydroxides (LDHs) to be prepared.

2. Experimental

2.1. General procedure for the preparation of Mg/Al hydrotalcite

Hydrotalcite (HT) was prepared from solutions of $Mg(NO_3)_2{\bullet}6H_2O$ and $Al(NO_3)_3{\bullet}9H_2O$ in an Mg(II)/Al(III) ratio of 2, using a coprecipitation method described elsewhere [25]. In a typical synthetic run, a solution containing 0.2 mol of $Mg(NO_3)_2{\bullet}6H_2O$ and 0.1 mol of $Al(NO_3)_3{\bullet}9H_2O$ in 250 mL of de-ionized water was used. This solution was slowly dropped over 500 mL of an Na_2CO_3 solution at pH 10 at 60 °C under vigorous stirring, the pH being kept constant by adding appropriate volumes of a 1 M solution of NaOH during precipitation. The suspension thus obtained was kept at 80 °C for 24 h, after which the solid was filtered off and washed with 2 L of de-ionized water.

The resulting HT was ion-exchanged with carbonate to remove intercalated ions between layers. The procedure involved suspending the solid in a solution containing 0.345 g of Na_2CO_3 in 50 mL of bidistilled, de-ionized water per gram of HT at 100 °C for 2 h. Then, the solid was filtered off *in vacuo* and washed with 200 mL of bidistilled, de-ionized water. The HT thus obtained was subjected to a second ion-exchange operation under the same conditions. The final solid was characterized from its X-ray diffraction pattern, which exhibited the typical signals for hydrotalcite [26], and by elemental analysis, which provided the empirical formula $Mg_{0.70}Al_{0.35}(OH)_2(CO_3)_{0.225}{\bullet}0.72H_2O$.

2.2. General procedure for synthesizing the catalysts

The HT solid was used to support the $Pd(CH_3COO)_2Py_2$ complex by mixing appropriate amounts of palladium acetate, pyridine and HT at 80 °C for 1 h, after which the solid was filtered off and washed with 100 mL of toluene. The catalyst thus obtained was named HT-$Pd(AcO_2)Py_2$. The other catalysts were synthesized by impregnation, intercalation or precipitation as described elsewhere [26].

2.3. Suzuki cross-coupling reaction

The Suzuki cross-coupling reaction was conducted in a two-mouth flask containing appropriate amounts of boronic acid, phenyl bromide and K_2CO_3 in addition to 5 mL of water, 0.02 mmol of Pd and 75 mg of surfactant, at room temperature. One of the flask mouths was fitted with a reflux condenser and the other was used for sampling at regular intervals. The reaction mass was stirred throughout the process. The resulting products were identified from their retention times by GC–MS analysis.

3. Results and discussion

3.1. Preliminary tests

One of the primary aims of modern chemical industry is the avoidance or reduction of the use of environmentally undesirable reactants. As noted in the Introduction, one way of reducing the environmental impact of industrial processes is by replacing polluting organic solvents with more benign alternatives or even water if at all possible. Massive energy consumption is one other serious problem with many industrial processes. In this work, we conducted the Suzuki reaction by using room temperature and water as solvent. The final working conditions were established by performing preliminary tests involving various solvents and temperatures. In previous work, we found 55 °C and toluene containing K_2CO_3 to be the optimum choice for the Suzuki cross-coupling reaction of phenylboronic acid not only with bromobenzene [12], but also with fluorobenzene [21], both of which occurred with no palladium leaching. The preliminary tests in this work were performed in different solvents at room temperature. Table 1 shows the conversion to biphenyl in the reaction between bromobenzene and phenylboronic acid

Table 1
Conversion results obtained in the Suzuki cross-coupling reaction of bromobenzene with phenylboronic acid in various solvents[a]

Entry	Solvent	T (°C)[b]	Conversion (%)[c]	t (h)[d]
1	DMF	R.T.	20	3
2	THF	R.T.	19	3
3	1-Butanol	R.T.	72	3
4	Ethanol	R.T.	82	3
5	Toluene	R.T.	0	3
6	Water	R.T.	0	3
7	DMF	55	29	3
8	THF	55	76	3
9	Toluene	55	100	0.25
10	Water	55	59	3

[a] Reaction conditions: solvent, 5 mL; BrPh, 1.98 mmol; $PhB(OH)_3$, 3 mmol; K_2CO_3, 3.96 mmol; Catalyst HT-$Pd(AcO)_2Py_2$, 0.04 mmol Pd.

[b] R.T., room temperature.

[c] Conversion to biphenyl.

[d] Reaction time.

under such conditions. Because phenylboronic acid is insoluble in water and toluene, the reactions in both media failed. The catalyst used consisted of the ligand $Pd(AcO)_2Py_2$ supported on a hydrotalcite, which was previously found to provide the best results among various heterogeneous Pd(II)-based catalysts in toluene [26]. Hydroxylated solvents (entries 3 and 4 in Table 1) provided excellent conversion results at room temperature. However, they also resulted in substantial dissolution of palladium and hence in heterogeneous catalysis. In order to improve the results, we raised the reaction temperature to 55 °C, where phenylboronic acid was completely dissolved in all solvents. However, neither water, DMF or THF improved the results obtained with toluene; in fact, although THF provided better results than at room temperature, the other solvents continued to perform poorly in the reaction. Neither ethanol nor butanol was tested at 55 °C since, if they caused substantial palladium leaching at room temperature, the effect would have been even stronger at the higher temperature.

3.2. *Influence of the surfactant*

As noted earlier, phenylboronic acid is insoluble in water at room temperature. The literature abounds with procedures for increasing the aqueous solubility of organic compounds. An additional problem arises from the low contact surface areas available when water is used as the solvent for an organic compound. Contact areas between aqueous and organic phases can be increased in various ways including the use of a surfactant. In fact, surfactants raise the solubility of organic reactants and expand the contact area between the organic and aqueous phase, thereby increasing the reaction rate. Thermodynamically, the addition of a surfactant to an aqueous solution is a spontaneous process, the two interacting in a way that depends on the surfactant structure and concentration [27]. We studied the effect of adding a surfactant to our reaction system. The most immediate outcome was that phenylboronic acid was dissolved at room temperature, which allowed the reaction to be conducted under milder conditions. We then examined the influence of the concentration of various surfactants on conversion. Based on the results, the conversion to biphenyl was fairly similar for amounts of surfactant over the range 75–300 mg; we therefore chose to use the smallest amount (75 mg) in subsequent tests.

Table 2
Conversion results obtained in the Suzuki cross-coupling reaction of bromobenzene with phenylboronic acid in the presence of various surfactants[a]

Entry	Surfactant	Conversion (%)[b]
1	Sodium dodecylsulphate	51
2	Sodim dodecylbenzenesulphonate	16
3	Sodim antraquinone 1,5-disulphonate	21
4	Sodium bis-2-(ethylhexyl)succinate	13
5	Cetyltrimethylammonium bromide	32
6	Tween-20[c]	21
7	Tween-40[d]	34
8	Tween-60[e]	11
9	Tergitol 15-S-9[f]	18
10	Tergitol 15-S-12[f]	24
11	Tergitol NP-35[f]	20
12	Triton N-101[f]	22
13	Octanoic acid	11
14	Palmitic acid	15
15	Lauric acid	14

[a] Reaction conditions: water, 5 mL; surfactant, 75 mg; PhBr, 0.99 mmol; $PhB(OH)_3$, 1.5 mmol; K_2CO_3, 1.98 mmol; 0.02 mmol Pd [HT-$Pd(AcO)_2Py_2$]; room temperature; reaction time, 3 min.

[b] Conversion to biphenyl.

[c] Polyoxyethylen sorbitan monolaurate.

[d] Polyoxyethylen sorbitan monopalmitate.

[e] Polyoxyethylen sorbitan monoestearate.

[f] Polyglycolethers.

One other variable to be considered was the nature of the surfactant (*i.e.* whether it was anionic, cationic or neutral). For example, Paetzold and Oehme performed the reaction of iodoanisole and phenylboronic acid in the presence of water-soluble palladium complexes with phosphine ligands and obtained near-quantitative yields in the presence of cationic and anionic surfactants at temperatures from room level to 78 °C [28]. Bhattacharya et al. used pure water and aqueous solutions of various surfactants in Suzuki cross-coupling reactions involving non-chelated palladium catalysts [29]; the actual catalysts for the process were nanometric colloids formed under the reaction conditions used. The surfactant employed, cetyltrimethylammonium bromide (CTAB), only acted as a phase transfer agent since the reaction was conducted at 100 °C, where phenylboronic acid is completely soluble. In this work, we used various anionic, cationic and neutral surfactants. As can be seen from Table 2, the results were excellent in most instances; thus, the conversion to biphenyl was generally in the range of 15–30% – and exceeded 50% with sodium dodecylsulphate (entry 1) – after only 3 min.

3.3. *Influence of the catalyst*

Once the addition of a surfactant was found to facilitate the reaction, we examined the effects of other heterogeneous catalysts which had previously been used in toluene at 55 °C [26] in order to find whether they continued to be less active

Table 3
Conversion results obtained in the Suzuki cross-coupling reaction of bromobenzene with phenylboronic acid in water containing sodium dodecylsulphate in the presence of various catalysts[a]

Entry	Catalyst	Conversion (%)[b]
1	HT-Pd(AcO)$_2$Py$_2$	52
2	HT-Pd(AcO)$_2$[c]	3
3	HT-PdCl$_2$[c]	20
4	HT-PdCl$_4$[c]	<1
5	HT-PdCl$_4$-INT[d]	13
6	HT-Pd[e]	<1
7	Pd(AcO)$_2$[f]	14
8	PdCl$_2$[f]	4
9	Na$_2$PdCl$_4$[f]	5

[a] Reaction conditions: water: 5 mL; sodium dodecylsulphate, 75 mg; PhBr, 0.99 mmol; PhB(OH)$_3$, 1.5 mmol; K$_2$CO$_3$, 1.98 mmol; catalyst, 0.02 mmol Pd; room temperature.

[b] Conversion to biphenyl.

[c] Supported catalyst (Ref. [26]).

[d] Catalyst containing PdCl$_4^{=}$ anions in the interlayer region of the hydrotalcite.

[e] Catalyst containing Pd(II) in hydrotalcite lattice.

[f] Homogeneous processes.

than the above-described palladium–pyridine complex under these conditions. Table 3 shows the conversion results obtained after 3 min. As before, the chelated catalyst was the most effective—even more so than salt-based homogeneous catalysts (entries 7–9).

Finally, we checked for potential homocoupling in phenylboronic acid by performing a test in the absence of bromobenzene and another three with the three-bromotoluene isomers. As can be seen from Table 4, the homocoupling pathway produced a certain amount of biphenyl that was greater with the three-bromotoluene isomers than with the parent compound. This may have been the result of a decreased reaction rate with the methyl-substituted substrates relative to bromobenzene.

3.4. *Study of leaching*

The phase where the catalytic process occurred was identified via a hot filtration test in one of the reactions. This test involves stopping the reaction after a preset conversion level is reached, filtering the reaction mass in order to remove the solid catalyst and then allowing the reaction to proceed in its absence. The results obtained under these conditions revealed that the filtrate was catalytically active and the reaction continued to develop in the absence of Pd-HT catalyst. This indicates not only that heterogeneous catalysis is present, but also that some soluble palladium species with catalytic activity even after filtering exists in the reaction medium.

Table 4
Homocoupling in the Suzuki cross-coupling reaction in water containing sodium dodecylsulphate[a]

Entry	Arylbromide	Conversion to cross-coupling product (%)	Conversion to homocoupling product (%)
1[b]	–	–	4
2[c]	2-Bromotoluene	5	12
3	3-Bromotoluene	3	4
4	4-Bromotoluene	16	19

[a] Reaction conditions: water, 5 mL; sodium dodecylsulphate, 75 mg; CH$_3$BrPh, 0.99 mmol; PhB(OH)$_3$, 1.5 mmol; K$_2$CO$_3$, 1.98 mmol; HT-Pd(AcO)$_2$Py$_2$, 0.02 mmol Pd; room temperature.

[b] Reaction in absence of bromotoluene.

[c] Conversion values at reaction time of 30 min.

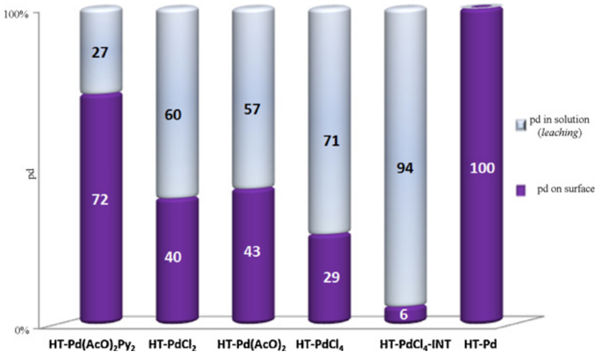


Fig. 1. Palladium leached in the Suzuki cross-coupling reaction studied with different catalysts.

All catalysts were subjected to a leaching test after one reaction cycle. Except for the catalyst containing Pd as a constituent of the hydrotalcite crystal lattice, all solids lost some palladium (see Fig. 1). For example, the catalyst exhibiting the highest catalytic activity, HT-Pd(AcO)$_2$Py$_2$, lost 27% of its initial Pd content. Also, it lost another 54% upon use in a second reaction cycle.

4. Conclusions

A solid consisting of a Pd(II) chelate with pyridine and acetate, Pd(AcO)$_2$Py$_2$, supported on an Mg/Al hydrotalcite is an active catalyst in the Suzuki cross-coupling reaction between bromobenzene and phenylboronic acid under environmentally benign conditions including ambient temperature and the use of water as solvent. However, a surfactant is required to facilitate dissolution of the acid in the reaction medium. These conditions result in Pd(II) leaching from the catalyst. None of the other catalysts studied improved the results obtained with the previous one; also, all except solid HT-Pd, where palladium was a constituent of the hydrotalcite crystal lattice, exhibited substantial losses of metal. Finally, sodium dodecylsulphate proved the most suitable surfactant for the reaction.

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