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Suzuki–Miyaura cross-coupling reaction catalyzed by Pd/MgLa mixed oxide

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A new, reusable Pd/MgLa mixed oxide catalyst has been applied successfully in the Suzuki–Miyaura carbon–carbon cross-coupling reaction of aryl halides as well as benzylic bromide with boronic acids in ethanol. The catalyst is air stable, can be stored and handled under an ambient atmosphere and after the reaction it can be recovered by simple filtration and reused without significant loss of activity.

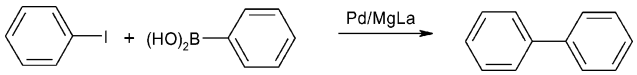
The palladium catalyzed cross-coupling of aryl halides or triflates with organoboronic acids in the presence of a base, known as the Suzuki–Miyaura reaction,[1] is one of the most versatile procedures for the synthesis of unsymmetrical biaryls. The popularity of this method is continuously increasing, since the organoboranes used in the reaction are air- and moisture-stable with relatively low toxicity, and the reaction can be carried out under mild reaction conditions and tolerates a wide range of functional groups. The biaryls are an important class of compounds in the synthesis of biologically active substances, such as pharmaceuticals[2] and herbicides.[3] Moreover they are also applied as chiral ligands for catalysis[4] and in material science, *e.g.* as liquid crystals.[5]

The reaction is traditionally performed in organic solvents using homogeneous Pd catalysts with phosphine-based ligands, in the presence of a base.[1] The removal of the residual palladium and ligands from the reaction mixture is difficult and the phosphorus ligands are often water- and air-sensitive. However, the use of heterogeneous catalysis simplifies the separation of the catalyst (simple filtration). In addition the catalyst can be reused, thus reducing the process costs and decreasing the contamination of the products with residual metal. From these economical and environmental points of view, the search for an efficient heterogeneous, insoluble metal catalyst is important and challenging. Therefore, over the past few years, progress in the development of catalysts for cross-coupling reactions has been significant. Numerous supported Pd catalysts have been reported in the literature for the Suzuki–Miyaura reaction *e.g.* Pd/C,[6] Pd(0)–Y zeolite,[7] Pd(II)–NaY zeolite,[8] Pd–sepiolite,[9] Pd/LDH,[10] and polymer supported Pd catalysts.[11] On the other hand, there has also been known the immobilization of Pd complexes on a solid support, such as Pd–phosphine on MCM-41 zeolite,[12] oxime–carbapalladacycle,[13] palladacycle,[14] or Pd–dihydroimidazole[15] complexes on silica.

Recently we used a new, air and moisture stable Pd/MgLa mixed oxide catalyst in the Heck reaction.[16] The reactions can be performed with only 1.5 mol% of Pd catalyst. The catalyst is air stable, can be stored and handled in air, and after the reaction it can be recovered by simple filtration and reused without significant loss of activity.

In this paper, we have explored the activity of this catalyst toward the Suzuki cross-coupling reaction. The Pd/MgLa catalyst was prepared according to the procedures reported previously.[16]

In order to determine the optimum reaction conditions, the reaction of iodobenzene with phenylboronic acid was studied first in the presence of different solvent sand bases and Pd^0/MgLa (1.5 mol% of Pd) (Scheme 1).



Scheme 1

The data in Table 1 show the effect of various parameters on the efficiency of the Suzuki reaction. Reactions were carried out using K_2CO_3 and Et_3N as bases and i-propanol–H_2O, ethanol–H_2O or ethanol as solvents. When we used K_2CO_3 and i-propanol–H_2O at 80 °C, a 99% yield of biphenyl was obtained, after just 1 h. An organic base such as Et_3N gave no product (entry 3). Changing the solvent from i-propanol to ethanol, the yield of the desired product did not change. No product was observed when the reaction was performed at room temperature, so heating is necessary for the reaction (entry 5). Finally, a smaller amount of catalyst (0.7 mol%) led to a moderately lower yield (91%, entry 7). From an economic aspect, we chose ethanol as the solvent for further reactions. Based on these experiments, the best reaction conditions were as follows: 1.5 mol% Pd/MgLa catalyst, 3 mol% K_2CO_3 as a base in ethanol at 78 °C.

To generalize the results obtained with the model reaction, other experiments were carried out using other aryl halides and boronic acids as substrates (Scheme 2).

Table 1 Effect of the reaction parameters on the Suzuki cross-coupling reaction[a]

Entry	Base	Solvent	Reaction temperature/°C	Reaction time/h	Yield[b] (%)
1	K_2CO_3	i-Propanol–H_2O (5 : 1)	80	5	99
2	K_2CO_3	i-Propanol–H_2O (5 : 1)	80	1	99
3	Et_3N	i-Propanol–H_2O (5 : 1)	80	1	—
4	K_2CO_3	Ethanol–H_2O (5 : 1)	78	1	99
5	K_2CO_3	Ethanol–H_2O (5 : 1)	25	1	—
6	K_2CO_3	Ethanol	78	1	99 (95)[d]
7[c]	K_2CO_3	Ethanol	78	1	91

[a] 1 mmol iodobenzene, 1.5 mmol phenylboronic acid, 3 mmol base, 1.5 mol% Pd. [b] Isolated yield. [c] Using 0.7 mol% of Pd. [d] With reused Pd/MgLa.

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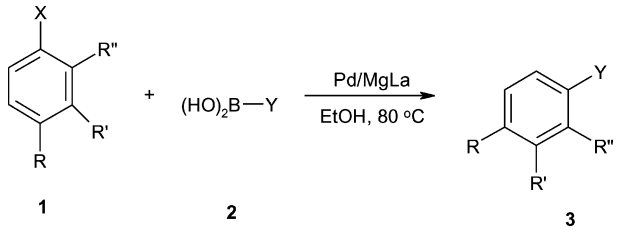
Table 2 Pd/MgLa catalyzed Suzuki cross-coupling reaction of various aryl halides with boronic acids[a]

Entry	Y	X	R	R′	R″	Reaction time/h	Yield[b] (%)
1	Bu	I	H	H	H	2	37
2	Ph	Br	H	H	H	1.5	97
3	Ph	Br	$COCH_3$	H	H	1.5	98
4	Ph	Br	H	H	$COCH_3$	1.5	97
5	Ph	Br	CH_3	H	H	1.5	83
6	Ph	Br	H	CH_3	OH	2	72
7	Ph	Br	H	H	CHO	1.5	88
						1	65
8	Ph	Cl	H	H	H	3	71
						6	71
9	Ph	Cl	$COCH_3$	H	H	2	96
10	Ph	Cl	H	H	$COCH_3$	2	97
11	Ph	Cl	CHO	H	H	2	83
12	Ph	Cl	H	H	CHO	2	83
13	Ph	Cl	H	H	CH_3	4	59

[a] 1 mmol aryl halide, 1.5 mmol boronic acid, 1.5 mol% Pd, 3 mmol K_2CO_3, 5 mL ethanol, 80 °C. [b] Isolated yield.



Scheme 2

The results are summarized in Table 2. As expected, the catalytic activity of our catalyst depends on the nature of the halide. The Suzuki reaction of bromobenzene with phenylboronic acid also furnished an excellent yield of biphenyl in 1.5 h (Table 2, entry 2). However, in the reaction of phenylboronic acid with chlorobenzene, only a 71% yield of biphenyl was obtained even after stirring the reaction mixture for longer (entry 8). Only a 37% yield of the coupling product was obtained in the reaction of butylboronic acid and iodobenzene, which was similar to the yield (29%) obtained with 5% Pd^0 on potassium fluoride/alumina reported by Kabalka *et al.*[17] (entry 1).

We examined the reaction with several substituted aryl bromides, chlorides and phenylboronic acid under the optimized reaction conditions. The use of aromatic halides with electron-withdrawing substituents, like CHO or $COCH_3$, led to the coupling products in excellent yields. Even the electron-rich *p*-bromotoluene, 3-methyl-2-bromo-phenol, or *o*-chlorotoluene reacted with phenylboronic acid, although the yields decreased to 83%, 72%, and 59%, respectively. The reaction is not sensitive to steric hindrance; bromo- and chlorobenzene derivatives having *ortho*-substituents also gave excellent yields, see *e.g.* *o*-bromobenzaldehyde (entry 7) or *o*-chloroacetophenone (entry 10).

There are relatively few reports in which a benzyl halide has been employed in the Suzuki–Miyaura reaction.[18] Maddaford and Keay coupled benzyl chloride under Suzuki conditions for the first time.[19a] Later, Chowdhury and Georghiou used $Pd(PPh_3)_4$ for the coupling of benzyl bromides and iodides in refluxing ethanol–DME–H_2O for 18 h under argon.[19b] We found that under our reaction conditions, in the reaction between phenylboronic acid and benzyl bromide we obtained the coupling product diphenylmethane in good yield, although a longer reaction time was required. Using a larger amount of Pd/MgLa catalyst (1.4 mol% of Pd) did not influence the yield (71%, Scheme 3).

During the examination of the Heck reaction, we found that under the reaction conditions, no increase in yield was observed when the catalyst was removed from the reaction mixture.[16] The possible leaching of palladium in the Suzuki–Miyaura reaction was tested analogously using the "hot filtration" test. Thus, the reaction of iodobenzene and phenylboronic acid was stopped after 30 min, the solid was filtered out from the hot solution (to avoid the precipitation of the possibly dissolved Pd from the solution onto the solid surface) and the reaction was continued with the filtrate and K_2CO_3. GC analysis of samples taken from this mixture showed that no progress in the reaction occurred even after a longer reaction time. The 73% yield obtained after 30 min did not increase even after 5 h. This means that no appreciable amount of Pd dissolved.

We have also investigated the reusability of the catalyst in the Suzuki reaction. After the first run, the catalyst was filtered off, washed with water to remove any chemicals, dried at room temperature and reused twice. Under the same reaction conditions, in the reaction of iodobenzene and phenylboronic acid the catalyst showed no significant loss of activity (99% and 95% for the first and second use, respectively, see Table 1, entry 6), which confirms its high stability.

In conclusion, we have shown that Pd/MgLa mixed oxide is an efficient catalyst in the Suzuki–Miyaura cross-coupling reaction of aryl bromides and chlorides with phenylboronic acid in good to excellent yields. Also, efficient cross-coupling could be effected with benzylic bromide. The use of our catalytic system has several advantages such as easy separation of catalyst, reusability, and the reaction does not require an inert atmosphere.†

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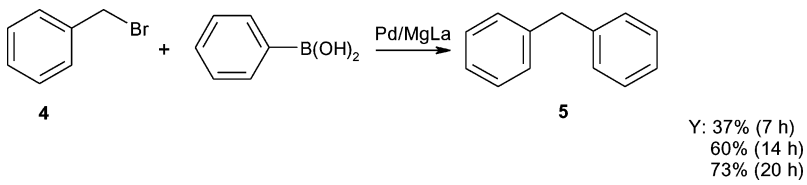

Scheme 3

Notes and references

† *Catalyst preparation:* MgLa mixed oxide was prepared according to a method described in the literature.[20] A solution containing Mg and La nitrates (0.386 mol and 0.129 mol in 0.5 L distilled water for an atomic ratio Mg/La = 3) was poured into a mixture of KOH (1 mol) and K_2CO_3 (0.26 mol) in 0.52 L of distilled water maintained at a constant pH 10. The solid was filtered, washed with distilled water, dried at 120 °C then calcined at 650 °C for 6 h. The material thus obtained should be stored under an inert atmosphere since storage in air induces carbonation of the surface. Chemical analysis of the solid gave the composition: La: 39.8%; K: 5.4%; H_2O: 37%. The Mg/La ratio in the solid is then 4.26, compared to 3 in the solution, therefore the precipitation of La is not complete at pH 10. The powder XRD pattern of the uncalcined Mg–La mixed oxide contains diffraction lines of a hydrated lanthanum carbonate as well as magnesium and lanthanum hydroxides. This triphasic solid probably consists of a layer of lanthanum oxide deposited on magnesia.

The MgLa mixed oxide thus obtained (1.5 g) was suspended in 150 mL of aqueous Na_2PdCl_4 (0.441 g, 1.5 mmol) solution and stirred at 25 °C for 12 h under a nitrogen atmosphere. The solid catalyst was filtered, washed thoroughly with 500 mL of water, and vacuum-dried to obtain brown Pd^{II}/MgLa mixed oxide (0.84 mmol of Pd/g, determined by ICP-OES). This substance (1 g) was reduced with hydrazine hydrate (1 g, 20 mmol) in ethanol (10 mL) for 3 h at room temperature, filtered, and washed with ethanol to give an air stable black powder of Pd^0/MgLa mixed oxide (0.73 mmol of Pd/g).

General procedure for the Suzuki reaction: in a typical reaction, Pd/MgLa (1.5 mol% Pd) was added to a mixture of aryl halide (1 mmol), boronic acid (1.5 mmol), and K_2CO_3 (0.41 g, 3 mmol) in ethanol (5 ml). The mixture was stirred at 80 °C until completion of the reaction (TLC) for 1 h to 6 h. Then the solvent was removed under reduced pressure and the product was extracted with hexane (10 mL). Removal of the solvent under vacuum furnished the desired coupling product. The residue, if necessary, was purified by column chromatography or recrystallized to give the corresponding biaryl. The known products were characterized by comparing the ^{1}H NMR, and melting point data with those reported in the literature. Selected data of biphenyl: white solid, mp: 67–68 °C (hexane) (lit. 70 °C[21]), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.27–7.58 (m, 10H). ^{13}C NMR (300 MHz, $CDCl_3$) δ (ppm): 127.1, 127.2, 128.6, 141.1.

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