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Article

Agarose-Alumina Composite Supported Palladium Catalyst for Suzuki Coupling Reactions

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The palladium catalyst supported on agarose-alumina composite and its utilization in the Suzuki reaction have been investigated. The agarose-alumina composite was prepared and modified with organofunctional groups by reacting with the coupling reagent 3-aminopropyltriethoxysilane (APTES) through Al–O–Si bonds. Palladium was efficiently loaded on the composite by the amino groups. The Suzuki coupling reaction can proceed successfully at room temperature under air. High yields of various aryl-aryl products have been obtained. Recycling studies have shown that the catalyst can be easily recovered and reused several times. The yields decreased from 95% to 85% in five cycles.

Keywords: palladium, composite, Suzuki coupling reaction, catalyst

Introduction

Transition-metal catalysts play an important role in current organic synthesis, especially palladium-catalyzed cross-coupling.[1-3] Palladium catalysts play a vital role in various coupling reactions, including Mizoroki-Heck reaction, Suzuki-Miyaura reaction, Stille reaction, Sonogashira reaction and Buchwald-Hartwig reaction.[4-8] They have been widely used in the pharmaceutical industry,[9] agrochemicals,[10] dyestuff and materials.[11-13] Moreover, Suzuki-Miyaura reaction has been widely employed in the construction of C–C bond, especially aryl-aryl bond formation.[14] Aryl-aryl bond can be very often found in natural products such as alkaloids as well as in numerous organic conductors or semiconductors as well as biologically active parts of pharmaceutical and agrochemical specialities.[15-18]

Palladium, as the commonly used catalyst in Suzuki reaction, has some advantages including easy operation, high conversion and yield.[19] However, traditional homogeneous palladium catalysts are expensive and cannot be reused or recycled, which might lead to high cost and difficult to industrialization in view of economic factor. Also, this kind of catalyst might result in palladium contamination particularly in pharmaceutical production, because trace amounts of Pd is difficult to remove. Significantly, supported palladium catalysts can efficiently and successfully solve these problems.[20-22] Many materials have been used as the carriers for supported palladium catalyst. Thereinto, natural polymers such as cellulose, chitosan, cyclodextrin and lignin have aroused wide research interests because of their merits of cheap, abundant and biodegradable.[23-26]

Agarose as a polysaccharide polymer material is frequently used in molecular biology for the separation of large molecules.[27] Moreover, it has been used as supporter to load catalyst because of its unlimited availability and biodegradability.[28,29] This polymer is relatively inert to treatment with commonly used solvents, because the hydroxyl groups, which are responsible for the majority of the reactions, are involved in inter and intra-molecular hydrogen bonding. The character of agarose can be changed by physical or chemical modification. The hydroxyl groups of agarose could be modified with the organofunctionalized alkoxysilane coupling reagents to form the C–O–Si bonds on the surface of agarose. However, the C–O–Si bonds in this functionalized agarose are unstable in aqueous solution.[30] Recently, numerous organic-inorganic hybrid catalysts have been designed and applied in various reactions.[31-33] Encouraged by these

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reports, we intended to design and prepare an organic-inorganic hybrid material based on agarose as the carrier to support palladium. Aluminum oxide was applied to the surface modification of agarose, which might make agarose more reactive with a good degree of adhesion. Al–OH groups on the surface of agarose-Al_2O_3 composite can be used to react with 3-aminopropyltriethoxysilane (APTES) resulting in stable Al–O–Si bonds with a high degree of organofunctionalization.

To the best of our knowledge,[34] agarose-Al_2O_3 composite based organic-inorganic hybrid palladium catalyst has not been reported. Herein, we demonstrated that this hybrid catalyst can successfully catalyze Suzuki reaction with high catalytic and reusability at room temperature.

Experimental

General methods

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker-300 MHz spectrometer. Chemical shifts are reported relative to tetramethylsilane (TMS); coupling constants are given in hertz. Melting points were measured on a WRS-2A meltingpoint apparatus and are uncorrected. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Yields refer to the isolated yields of the products after purification by silica-gel column chromatography (200-300 mesh). Commercial reagents were used as received. Analytical-grade solvents and commercially available reagents were used without further purification.

Catalyst preparation

Aluminium chloride hexahydrate (9 g) was dissolved in water (240 mL) and to this solution, agarose (9 g) was added and the mixture was stirred for 5 h. The mixture was filtered and the solid was exposed to ammonia gas, washed with water three times and dried under vacuum at room temperature to afford agarose-Al_2O_3 composite **1**.

APTES (7.2 mL) was added to the solution of composite **1** (7.8 g) in absolute ethyl alcohol (100 mL) and stirred for 12 h at room temperature. The solid was filtered, washed with water and dried under vacuum to afford compound **2**.

In a small Schlenk tube, compound **2** (1.0 g) was mixed with $Pd(OAc)_2$ (100 mg, 0.44 mmol) in dry acetone (20 mL) and methanol (5 mL). The mixture was stirred at room temperature for 48 h. The solid was collected by filtration, washed with acetone, ultrapure water and acetone successively and dried under vacuum at room temperature for 12 h to afford 1.0 g of black-brown catalyst **3** (Pd@Al_2O_3-agarose).

General procedure for the Suzuki coupling reaction

Aryl halide (1.0 mmol), arylboronic acid (1.2 mmol), K_2CO_3 (2.0 mmol), Pd@Al_2O_3-agarose (100 mg) and EtOH (5 mL) were added to a Schlenk flask. The mixture was stirred at room temperature under air. Upon complete consumption of starting materials as determined by TLC analysis, the solid was filtered and washed with acetone (3 × 5 mL). The combined organic solvents were concentrated in vacuum to afford product which was purified by silica gel column chromatography (petroleum ether/EtOAc = 10:1).

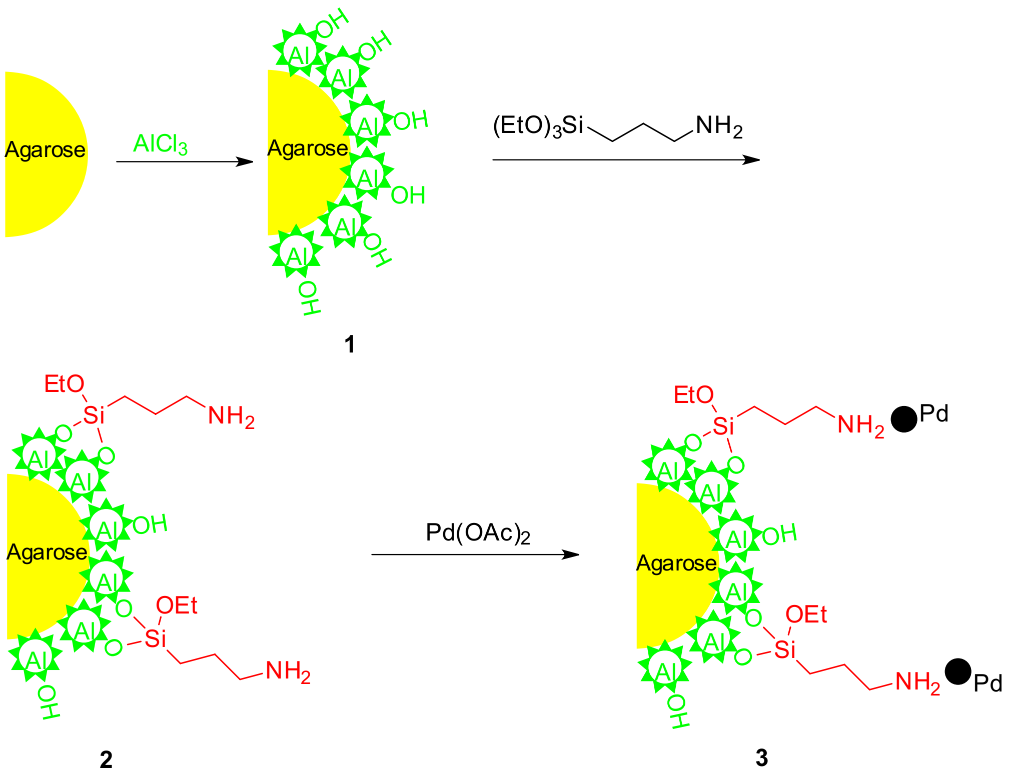
Results and Discussion

As described in Scheme 1, the hybrid catalyst **3** was obtained in three steps using agarose as starting material. Initially, agarose was modified with aluminium trichloride in ultrapure water to afford agarose-Al_2O_3 composite **1**. Then, organo-functionalized material **2** was obtained by Al–OH groups on the surface of agarose-Al_2O_3 composite reacting with APTES. According to the commonly used method of supported palladium catalyst,[24,35-38] composite **2** was employed to prepare the Pd@Al_2O_3-agarose catalyst **3**. The content of palladium in this catalyst was determined by inductively coupled plasma atomic emission spectroscopy (ICP-AES) was 0.18%, corresponding to 0.051 mmol g^{-1}.

To ensure the quality of this hybrid catalyst, the characterization of composites **1** and **2** were analyzed firstly. We expected that the Al-OH on the surface of composite **1** had good adhesion and high affinity by the terminal silanol group of APTES. The content of aluminum was determined through ignition method under 600 °C for 8 h. The result found that the amount of residue alumina was 14.12 wt.%, suggesting the Al content in composite **1** was 1.34 mmol g^{-1}. Element analysis (EA) was applied to determine the content of organic groups and showed that nitrogen conten was 0.63% in composite **2**, which means that organic groups attached on **2** was 0.45 mmol g^{-1}.

The properties of the catalyst were crucial for its activity and application. Then our effort was focused on the characterization of Pd@Al_2O_3-agarose catalyst, including the powder X-ray diffraction (XRD), thermal stability and scanning electron microscopy (SEM) analysis.

Powder XRD patterns of the three composites (Figure S1, in the Supplementary Information (SI) section) showed the reflection due to the agarose phase. There is no



Scheme 1. Synthesis of Pd@Al_2O_3-agarose catalyst.

obvious reflections due to Pd in the XRD patterns, because the low content and high dispersion of Pd in the catalyst was far away from the dectection limit of the sensitivity of the detector used in this study.

Differential scanning calorimetry-thermal gravimetric analysis (DSC-TGA) spectrum of Pd@Al_2O_3-agarose catalyst is displayed in Figure 1. The results indicated that this catalyst was thermally stable up to 300 °C. The broad exothermic peak at 410 °C might be due to the decomposition of carbohydrates of agarose support. Weight loss around 5 wt.% from room temperature to 100 °C exhibited by TGA was caused by the loss of water in the catalyst. Moreover, the large weight loss (75 wt.%) from 250 °C to 600 °C was assigned to the oxidative decomposition of polymer carrier. The decomposition of this catalyst was completed when temperature was up to 600 °C and the main residue was mainly composed of Al_2O_3, SiO_2 and little palladium oxide.

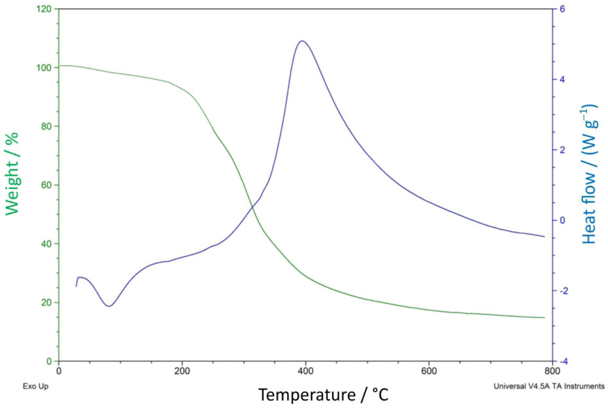


Figure 1. DSC-TGA spectrum of Pd@Al_2O_3-agarose catalyst.

The morphology of Pd@Al_2O_3-agarose catalyst (Figure 2a) was investigated by SEM analysis. Agglomerated morphology was observed with diameters in the range of several hundreds of nanometer up to a few micrometers. As displayed in the energy-dispersive X-ray spectroscopy (EDS) spectrum of catalyst **3** (Figure 2b), the hybrid catalyst **3** contained metallic elements aluminum and palladium, and non-metallic elements such as C, N, O and Si. These results indicated deposition of alumina on agarose, grafting of APTES on alumina and presence of palladium on the hybrid carrier.

In the preliminary catalytic activity research, we chose the Suzuki coupling of phenylboronic acid and 1-bromo-4-methylbenzene as our model system. Several solvents and bases were used to screen the best reaction conditions. As indicated in Table 1, this coupling reaction proceeded successfully and smoothly in ethanol, 95% ethanol and water, employing Pd@Al_2O_3-agarose as the catalyst at room temperature (Table 1, entries 1-3). However, the yield in water was lower than ethanol. Trace coupling products were observed using acetonitrile, toluene or tetrahydrofuran (THF) as solvent, while this transformation cannot proceed

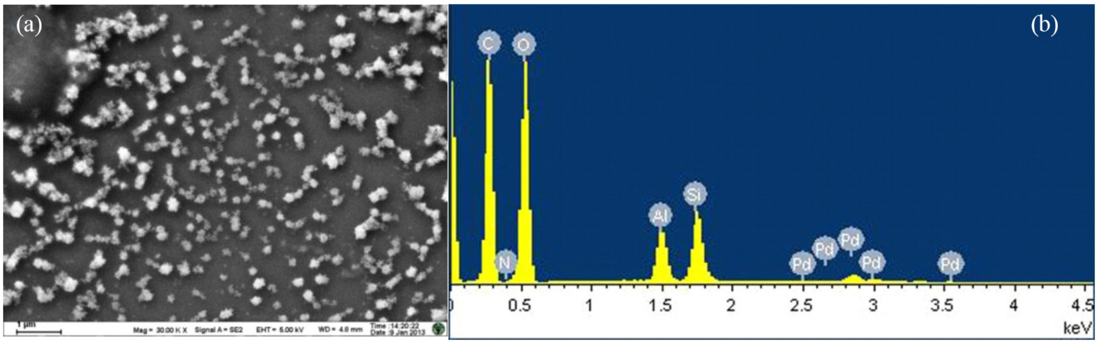
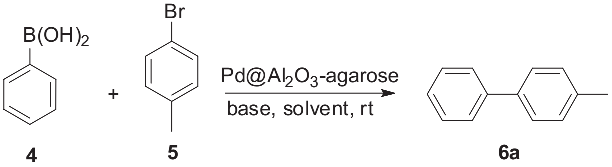


Figure 2. (a) SEM image of Pd@Al_2O_3-agarose catalyst prior to the coupling reaction. Scale bars: 1 μm. (b) EDS spectrum of Pd@Al_2O_3-agarose catalyst.

Table 1. Condition optimization of Suzuki-Miyaura cross coupling reaction of phenylboronic acid and 1-bromo-4-methylbenzene over Pd@Al_2O_3-agarose catalyst[a]



entry	Base	Solvent	Yield[b] / %
1	K_2CO_3	95% EtOH	92
2	K_2CO_3	EtOH	98
3	K_2CO_3	H_2O	88
4	K_2CO_3	CH_3CN	Trace
5	K_2CO_3	Toluene	Trace
6	K_2CO_3	THF	Trace
7	K_2CO_3	DMF	N.R.
8	K_2CO_3	Dioxane	N.R.
9	K_2CO_3	DME	N.R.
10	Cs_2CO_3	EtOH	45
11	Na_2CO_3	EtOH	84
12	K_3PO_4	EtOH	82
13	CH_3COOK	EtOH	65
14	*t*-BuOK	EtOH	94
15	KOH	EtOH	98
16	TEA	EtOH	Trace
17[c]	K_2CO_3	EtOH	85

[a]Unless otherwise stated, the reaction was carried out with phenylboronic acid (1.2 mmol) with 1-bromo-4-methylbenzene (1.0 mmol), base (2.0 mmol), Pd@Al_2O_3-agarose (100 mg), solvent (5 mL), rt; [b]isolated yield; [c]under nitrogen atmosphere.

in dimethylformamide (DMF), dioxane and dimethyl ether (DME) (Table 1, entries 4-9). Encouraged by these results, we screened several different bases for the coupling reaction catalyzed by the hybrid catalyst in ethanol. Modest yields of 4-methyl-1,1'-biphenyl were observed with Na_2CO_3 and K_3PO_4, which led to higher yields than Cs_2CO_3 and potassium acetate (Table 1, entries 10-13). However, organic base triethanolamine (TEA) was unsuitable for this transformation. Although excellent yields were detected with *t*-BuOK and KOH among the bases examined (Table 1, entries 14 and 15), K_2CO_3 was chosen as the optimum base for the Suzuki coupling reaction catalyzed by the Pd@Al_2O_3-agarose catalyst, considering the tolerance of substituents on aromatic ring. The influenece of oxygen has also been investigated by performing model reaction under nitrogen. It was observed that the yield decreased from 98% to 85%, indicating that this catalyst showed a remarkably high activity under air and this conversion was an aerobic Suzuki coupling reaction. The reason might be this catalyst could adsorb molecular oxygen on their surfaces in the presence of air.[39,40] As a result, the catalyst was more stable against aggregation and maintained high catalytic activity.

In order to elucidate the efficiency of this catalyst, several amounts of Pd@Al_2O_3-agarose were examined in ethanol. As shown in Table 2, it is clear that 0.5 mol% catalyst shows exceedingly high catalytic efficiency compared to 0.25 mol%. There was no significant improvement in the yield at a mole rate of 1.0 mol%, even increasing reaction temperature. Hence, the required catalyst to Pd@Al_2O_3-agarose is 0.5 mol%, beyond which no appreciable effect on the yield has been observed.

With the optimized condition in hand, the substrate scope of this coupling reaction was investigated, and the results are displayed in Table 3. A variety of aryl halides were efficiently coupled with phenylboronic acid to give corresponding biphenyl products (Table 3, entries 1-11). Both electron-donating and electron-withdrawing groups provided excellent yields, such as the coupling of methoxyl- and nitro-substituted bromobenzenes with phenylboronic acid. Compared with the *ortho*-substituents, the *para*-substituted aryl bromides exhibited more reasonable reactivity. Moreover, the optimized protocol was employed to various aryl boronic acids (Table 3, entries 12-15). When *para*-position of phenylboronic acid was substituted by methoxyl or trifluoromethoxyl group, the yields of corresponding products increased slightly. While the acetyl

Table 2. Amounts of catalyst optimization for the Suzuki-Miyaura cross coupling reaction[a]

entry	Amount of catalyst / mol%	time / h	Yield[b] / %
1	0.25	2	73
2	0.25	5	79
3	0.5	2	95
4	1.0	1	95
5[c]	1.0	1	95

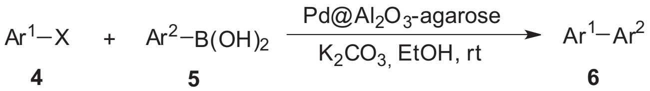
[a]Unless otherwise stated, the reaction was carried out with phenylboronic acid (1.2 mmol) with bromobenzene (1.0 mmol), base (2.0 mmol), Pd@Al_2O_3-agarose, EtOH (5 mL), rt; [b]isolated yield; [c]under reflux.

substituent decreased the yield obviously. The coupling ability of aryl chlorides and aryl iodides have also been evaluated under the optimized conditions. Due to their oxidative addition,[41] the aryl chlorides showed lower reactivity in cross-coupling reactions than aryl bromides and aryl iodides (Table 3, entries 16-18).

The reusability of the catalyst was examined in the case of the model reaction. The catalyst was readily reused after the treatment with acetone in the recycle experiments and the reuse experiments were repeated until lower yield was observed.

Table 4 presented the recycling results of Pd@Al_2O_3-agarose catalyst. It is seen that the catalyst

Table 3. The Suzuki-Miyaura cross coupling reaction of various aryl halides and phenylboronic acid over Pd@Al_2O_3-agarose catalyst[a]



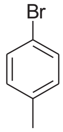
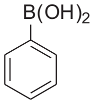
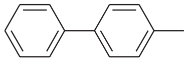
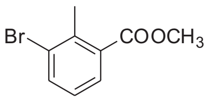
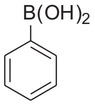
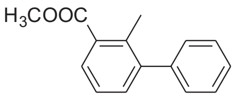
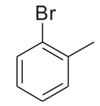
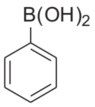
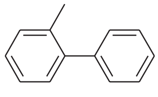
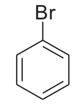
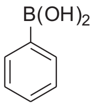
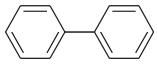
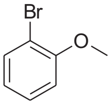
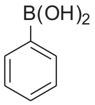
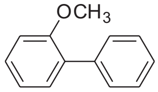
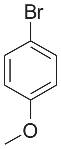
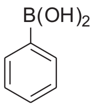
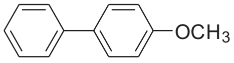
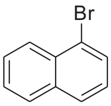
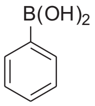
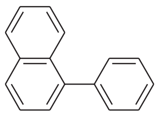
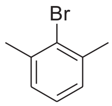
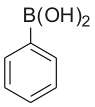
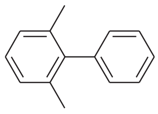
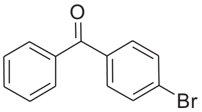
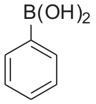
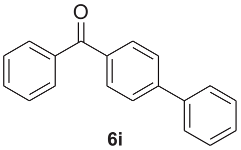
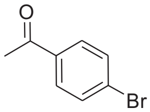
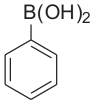
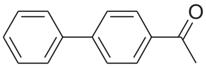
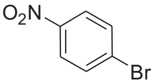
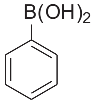
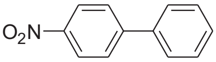
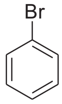
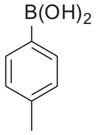
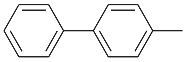
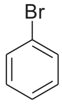
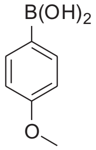
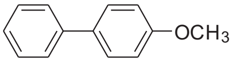
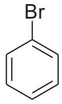
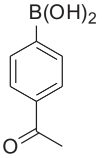
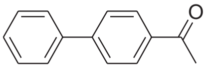
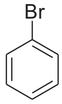
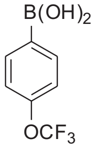
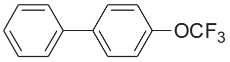
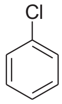
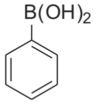
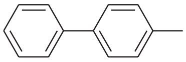
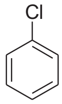
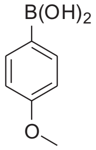
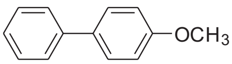
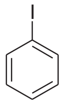
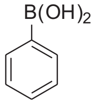
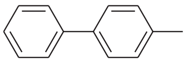
entry	Ar^1–X	Ar^2–B(OH)$_2$	Product	time / h	Yield[b] / %
1			 **6a**	2	98
2			 **6b**	2	96
3			 **6c**	2	97
4			 **6d**	2	95
5			 **6e**	2.5	94
6			 **6f**	2	97
7			 **6g**	2.5	92
8			 **6h**	4	90

Table 3. The Suzuki-Miyaura cross coupling reaction of various aryl halides and phenylboronic acid over Pd@Al_2O_3-agarose catalyst[a] (cont.)

entry	Ar^1–X	Ar^2–$B(OH)_2$	Product	time / h	Yield[b] / %
9			 **6i**	3	92
10			 **6j**	2.5	93
11			 **6k**	2	95
12			 **6a**	2	95
13			 **6f**	2	98
14			 **6j**	4	87
15			 **6l**	2	96
16			 **6a**	5	73
17			 **6f**	5	78
18			 **6a**	1	97

[a]Unless otherwise stated, the reaction was carried out with boronic acid (1.2 mmol) with aryl halides (1.0 mmol), K_2CO_3 (2.0 mmol), Pd@Al_2O_3-agarose (100 mg), EtOH (5 mL), rt; [b]isolated yield.

recycling showed a decrease of the total yield in every run. The reason might be slight palladium leaching after the reuse. Our results demonstrated that the catalyst **3** was an efficient and recyclable catalyst system for the Suzuki reaction under air.

Conclusions

In conclusion, the agarose-alumina composite supporting palladium has been designed and prepared as an efficient catalyst for Suzuki coupling reaction at room temperature

Table 4. Recyclability of the Pd@Al_2O_3-agarose catalyst in Suzuki-Miyaura cross coupling reaction[a]

entry	Cycle	time / h	Yield[b] / %
1	1	2	95
2	2	2	91
3	3	2.5	90
4	4	3	87
5	5	4	85

[a]Unless otherwise stated, the reaction was carried out with phenylboronic acid (1.2 mmol) with bromobenzene (1.0 mmol), K_2CO_3 (2.0 mmol), Pd@Al_2O_3-agarose (100 mg), EtOH (5 mL), rt; [b]isolated yield.

under air. The reactions of a variety of differently substituted aryl bromides and aryl boronic acids can proceed smoothly in good to excellent yields. Moreover, the catalysts can be easily recovered and reused several times. Additional investigations will focus on the extension of this catalytic system.

Supplementary Information

Supplementary data (NMR data and spectra of compounds) are available free of charge at http://jbcs.sbq.org.br as PDF file.

Acknowledgements

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