Journal of Molecular Catalysis A: Chemical 366 (2013) 186–194

Contents lists available at SciVerse ScienceDirect

Journal of Molecular Catalysis A: Chemical

journal homepage: www.elsevier.com/locate/molcata

Suzuki–Miyaura coupling under air in water promoted by polymer supported palladium nanoparticles

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ARTICLE INFO

Article history:
Received 24 July 2012
Received in revised form
13 September 2012
Accepted 24 September 2012
Available online 29 September 2012

Keywords:
Suzuki–Miyaura coupling
Palladium supported nanoparticles
Green solvent
Recyclable catalyst

ABSTRACT

Suzuki couplings of aryl bromides were efficiently performed by a polymer supported palladium catalyst under air in water at 100 °C without additives. In the case of activated aryl chlorides the reactions proceeded smoothly in the presence of a suitable phase transfer agent. The catalyst was active and recyclable for at least five times. Atomic absorption analyses revealed that the metal content in the polymeric support did not significantly decrease with the cycles while inductively coupled plasma analyses revealed that the palladium amount both in the mother liquors and in the organic products after reactions was lower than 500 ppb. The activity of the mother liquors has been investigated in detail. A transmission electron microscopy study of the supported catalyst before, during and after duty is also described.

1. Introduction

Suzuki–Miyaura reactions between organoboronic acid and aryl halides [1] play an important role in organic synthesis and find wide application in laboratory and industries. Usually, this cross-coupling reaction is catalyzed by soluble phosphane palladium complexes in organic solvents but such a protocol suffers from the difficulty in recovering and reusing the expensive homogeneous catalysts. To overcome this drawback, much work has been devoted to the development of reusable Pd heterogeneous catalysts [2–19]. In this regard, recyclable nanocatalysts [20–28] experienced great prosperity in the past decade, because they combine high surface area with excellent accessibility of the reactants to the active sites.

Another drawback of the classic Suzuki–Miyaura process is the organic solvents disposal, which is the major problem of pharmaceutical industries. With the aim to propose more sustainable protocols, much effort has been devoted in trying to substitute expensive, flammable and toxic organic solvents with water [14,27,29–34]. In fact, the use of water as reaction medium has several benefits, since it is cheap, non-toxic, non-flammable and allows an easy recovery of the products due to the insolubility in water of the majority of the Suzuki–Miyaura products.

We have recently prepared a supported palladium(II) complex (in the following *Pd-pol*) by co-polymerization of $Pd(AAEMA)_2$ [$AAEMA^-$ = deprotonated form of 2-(acetoacetoxy)ethyl methacrylate] with suitable methacrylic co-monomers and cross-linkers [35,36], which was found very active in palladium promoted reactions such as hydrogenations, Heck and Stille reactions, as well as asymmetric allylic alkylations [37–41]. Moreover, using *Pd-pol* as promoter for the reductive amination of aldehydes, we observed that the overall Pd(II) onto the insoluble support was reduced *in situ* to Pd(0) under H_2 atmosphere, forming supported Pd nanoparticles of average size of about 5 nm, exhibiting high catalytic efficiency and good recyclability [42].

Since Pd nanoparticles are known to facilitate the Suzuki reaction and given that the supported Pd(II), which incidentally swells well in water, could expectedly be reduced to Pd nanoparticles by the excess of aryl boronic acid, we started a study to evaluate the catalytic activity of *Pd-pol* for the Suzuki–Miyaura reaction of phenyl boronic acid with aryl bromides and chlorides under air in water. In fact, despite of the large number of reports concerning the use of polymer supported catalysts for promoting the Suzuki reaction in water, there are still margins of improvement. First of all the supported catalysts are generally less active (Pd mol% $\geq$ 0.1) than their homogeneous counterparts [12,14,16,43] (with homogeneous catalysts sometimes homeopathic concentration of palladium are sufficient [9,44]). In some cases supported catalysts suffer of considerable metal leaching and very often they

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http://dx.doi.org/10.1016/j.molcata.2012.09.022

are not able to promote the coupling of the aryl chlorides (more evaluable from an industrial point of view) [12,14,16]. Moreover, most of the polymer supported catalysts are not active in neat water (maybe for the swelling proprieties of the polymeric matrix), needing for promoting the reaction, even with aryl bromides and iodides, the presence of a conventional organic co-solvent [21,23,29,45,46] and/or the addition of a phase transfer agent [29], both disadvantageous from the environmental point of view. For example, a very active polymer supported Pd catalyst such as the one reported by Uozumi et al. (TON of up to 3,570,000) works in water only in the presence of tetrabutylammonium fluoride [28]. It is noteworthy that even supported palladium catalysts based on new polymeric materials such as covalent organic frameworks (COFs) promote the Suzuki reaction in not environmentally friendly conditions (p-xylene as the solvent, $T = 150\,^{\circ}C$, 0.5–1 Pd mol% with aryl iodides and bromides) [47].

Since it is known that the properties of the polymeric support playing a crucial role in catalysis [48] are: the swelling capability (*Pd-pol* swells in water), the porosity (*Pd-pol* is macroporous) and the mild reticular structure (*Pd-pol* is not too much cross-linked), we deemed it worthwhile to test *Pd-pol* as a supported catalyst for the Suzuki reaction in neat water. We found that *Pd-pol* was active and recyclable: (*i*) with aryl bromides as substrates without any additive or co-solvent, even using a Pd/substrate molar ratio of 1/10,000; (*ii*) with aryl chlorides, in the presence of a phase transfer agent. Moreover, although the catalytic cycle is promoted by Pd active species leached out from the insoluble support (which may re-deposit onto it at the end of reaction), the corresponding catalytic efficiencies are remarkable since the amounts of the leached Pd species are at ppb levels at any stage of the reaction.

2. Experimental

2.1. General considerations

Tap water was de-ionized by ionic exchange resins (Millipore) before use. All other chemicals were purchased from commercial sources and used as received. *Pd-pol* was synthesized according to literature procedure [42]. Palladium content in *Pd-pol* was assessed after sample mineralization by atomic absorption spectrometry using a Perkin–Elmer 3110 instrument. The experimental error on the palladium percentage was ±0.3. Palladium amount in the mother liquors and in the organic products was assessed after sample mineralization by inductively coupled plasma-optical emission spectroscopy (ICP-OES, Thermo ICAP 6000) analyses. For the corresponding calibration curve the limit of detection was *ca.* 50 ppb. All Pd analyses on the mother liquors, organic products and the used *Pd-pol* were performed by carrying out the reactions on 5.0 mmol scale.

Mineralization of the different matrices prior to Pd analyses was carried by microwave irradiation with an ETHOS E-TOUCH Milestone applicator, after addition of 12 mL HCl/HNO_3 (3:1,v/v) solution to each weighted sample. In the case of the mother liquor analyses, 5.0 mL of sample was used. In the case of the organic products, the diethyl ether solutions coming from extraction were evaporated under vacuum and the solid residue was added of *aqua regia* and submitted to microwave irradiation.

Microwave irradiation up to 1000 W was used, the temperature being ramped from rt to 220 °C in 10 min and the sample being held at this temperature for 10 min. After cooling to room temperature the mother liquor and the organic products digested samples were diluted to 50 mL, while the digested *Pd-pol* was diluted to 1000 mL before submitting to metal analyses.

GC–MS data (EI, 70 eV) were acquired on a HP 7890 instrument using a HP-5MS cross-linked 5% PH ME siloxane (30.0 m × 0.25 mm × 0.25 μm) capillary column coupled with a mass spectrometer HP 5973. The products were identified by comparison of their GC–MS features with those of authentic samples or by their NMR ^{1}H and $^{13}C\{^{1}H\}$ spectra. Reactions were monitored by TLC carried out on 0.25 mm silica gel coated glass plates using UV light as visualizing agent or by GC–MS.

The microstructure of the polymeric matrix embedded Pd nanoparticles was determined by TEM observations at acceleration voltage of 200 kV (Model JEM 2010, Jeol, Akishima Tokyo, Japan), equipped with X-ray energy dispersive spectroscopy (EDS). The samples were prepared by dispersing the powders in distilled water using an ultrasonic stirrer and then placing a drop of suspension on a copper grid covered with a transparent polymer film, followed by drying and carbon coating. The particle size distributions were obtained by TEM image analysis using the ImageJ software (freeware software: http://rsb.info.nih.gov/ij/). Each morphology observation was accompanied by EDS confirmation for the presence of Pd.

2.2. Catalytic runs

The following procedure was adopted for the standard reaction catalyzed by *Pd-pol* (0.1 mol% Pd). A two necked round flask was charged in air with a magnetic stir bar, *Pd-pol* (2.2 wt% Pd), the aryl halide (1.0 mmol), phenyl boronic acid (1.5 mmol), K_2CO_3 (2.0 mmol), H_2O (4.0 mL) and the system was refluxed at 100 °C under vigorous magnetic stirring. In the case of aryl chlorides, K_2CO_3 was replaced by KOH (2.0 mmol) and tetrabutylammonium bromide (TBAB, 1.0 mmol) was added. The time to reach reaction completion, reported in Table 2, was ascertained in the following way: after 2 h reaction at 100 °C, the mixture was cooled down to room temperature, diethyl ether (10 mL) was added to the suspension and 0.1 mL of the organic phase was taken by means of a syringe and analyzed by GC–MS after purification on a microcolumn filled with silica gel. If the GC–MS control showed no residual aryl halide in solution, a new reaction was carried out in the same conditions but for a shorter time. If the GC–MS control showed residual aryl halide in solution, a new reaction was carried out in the same conditions but for a longer time until two subsequent reactions gave the same result in terms of product yield. This allowed us to ascertain the minimum time needed to reach reaction completion. The cross-coupling products were isolated by extracting the organic compounds from the water mixture with diethyl ether (10 mL), washing the water phase with 2× 10 mL diethyl ether and treating with brine (3× 10 mL) the collected organic layers. The obtained organic phase was dried over Na_2SO_4 and then the solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography using petroleum ether (b.p. 40–60 °C)–dichloromethane as eluent.

2.3. Catalyst recycling

2.3.1. "One-pot" reuse

A two necked round flask was charged in air with a magnetic stir bar, *Pd-pol* (0.1 mol% Pd), the aryl halide (1.0 mmol), phenyl boronic acid (1.5 mmol), K_2CO_3 (2.0 mmol), H_2O (4.0 mL) and the system was put in a thermostated bath at 100 °C under vigorous stirring and reflux. After the indicated time, the mixture was cooled down to room temperature. The minimum time needed to reach reaction completion was ascertained as described in Section 2.2. At reaction completion, the mixture comprised of water phase, supported catalyst and 10 mL diethyl ether (used for the monitoring) was put under vacuum (rotavapor) until the organic solvent was evaporated. Then, fresh aryl halide (1.0 mmol), phenyl boronic acid (1.5 mmol) and K_2CO_3 (2.0 mmol) was added to the water mixture (containing the catalyst and the products of the precedent run). The