Pergamon

Tetrahedron Letters 40 (1999) 5813–5816

TETRAHEDRON
LETTERS

An Easily Prepared, Air and Moisture Stable, Resin-bound Palladium Catalyst for Suzuki Cross-Coupling Reactions

Tony Y. Zhang* and Matthew J. Allen

Chemical Process Research and Development
Lilly Research Laboratories
A Division of Eli Lilly and Company
Lilly Corporate Center, Indianapolis, IN 46285-4813

Received 3 June 1999; accepted 4 June 1999

Abstract: An air and moisture stable polymer supported palladium catalyst easily prepared from a commercial available thiourea resin Deloxan®THP was found to enable Suzuki cross-coupling reactions to be carried out in high yields and convenient manner. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: catalysis, catalyst, cross-coupling, palladium, Suzuki reactions, polymer support, thiourea, resin.

Palladium catalyzed carbon-carbon bond reactions are gaining prominence in organic synthesis for their remarkable chemo-, regio-, and stereoselectivities, mild reaction conditions, and high efficiency.[1] A great majority of these reactions proceed through various catalytic cycles involving Pd(0) and Pd (II) species. Ready interconversion of these two oxidation states enables the completion of the catalytic cycle, thus avoiding the use of stoichimetric amount of this rather expensive metal. For these and other reasons, palladium catalyzed reactions have been increasingly used in fine chemical and pharmaceutical manufacturing. When it comes to the formation of a carbon bond to a sp^2 hybridized carbon, one of the most useful processes is the Suzuki coupling of oragnoborates with aryl or alkenyl halides or triflates,[2] owing to its high efficiency and compatibility with a wide variety of functional groups.

Several challenges, however, remain for chemical practitioners to grapple with when performing a palladium catalyzed process at scale. First, the relatively high price of palladium complexes, albeit in catalytic amounts, contributes significantly to the overall cost of production. Spent palladium is usually recovered and sent to its manufacturer for salvage, and new catalyst needs to be purchased for each batch of reaction. Secondly, residual palladium in the product may have adverse impact on downstream chemistry and final product purity. Additionally, removal of ligands and byproducts derived from them may complicate workup and product isolation. To address these concerns, several solid supported palladium catalysts have been developed over the last two decades with varying degrees of success. Most of these resin-bound ligand systems, however, are based upon phosphine ligands attached to 1-2% cross-linked polystyrene,[3] a system which requires several demanding synthetic transformations and expensive reagents to prepare. In most cases additional free ligands such as PPh_3 have to be added to stabilize the polymer-phosphine-Pd complexes. Addition of soluble ligands, however, increases the chance for the metal to leach out of the system through disproportionation between the polymer-bound and free phosphines. More critically, poor swelling properties of polystyrene in protic solvents such as water or alcohol greatly limited their application in these environmentally benign media, which incidentally prove to be ideal solvents for Suzuki reactions.[2] An easily prepared, air and moisture stable, and recyclable solid catalyst system is highly desirable in both laboratory and production settings.

PII: S0040-4039(99)01147-8

Jang[4] and others[5] have recently demonstrated that polystyrene-bound phosphines prepared from the Merrifield resin could serve as ligands for Suzuki coupling. It intrigued us to see if a non-swelling, cross-linked resin would serve the same purpose. Toward this end, a commercially available resin-bound thiourea, Deloxan® THP II (1)[6] appeared very appealing. Whilst thiourea complexes of palladium are known, to the best of our knowledge, their application as a catalyst other than hydrogenation and carbonylations[7] has not been reported. The Deloxan resin has a highly cross-linked macroporous polysiloxane backbone, swells very little in most solvents including water, and its primary use has been serving as scavenger for removing residual heavy metal from processing stream. Similar resins have been used as a carrier for palladium-catalyzed hydrogenation reactions.[8]

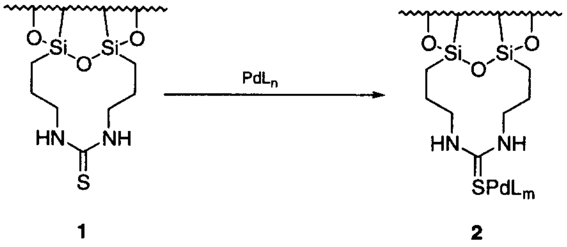


Figure 1

The resin-bound catalyst was prepared simply by treating the wet Deloxan® resin with a solution of $Pd(OAc)_2$ in methanol (Figure 1).[9] It was thoroughly washed with water and methanol to ensure removal of unbound metal. The treated resin can be used as such or dried in a vacuum oven at 50 °C to remove water. Using aryl bromide **3** and arylboronic acid **4** as cross-coupling partners, the Suzuki coupling reaction was carried out using resin equivalent to 2-3 mol % Pd in a mixture of water and isopropanol (Figure 2). We were delighted to find that the reactions proceeded in a rate and yield similar to that carried out using conventional homogeneous catalysts, such as $Pd(PPh_3)_4$. The catalyst appears very active toward aryl iodides and aryl bromides activated by electron withdrawing groups such as carbonyl or cyano functionalities (Table I).[10] The reaction was very slow when unactivated aryl bromides were used (entry 1). Upon completion of the reaction, the catalyst resin could be simply filtered and residual palladium content in the crude product was found to be well below 3 ppm.[11]

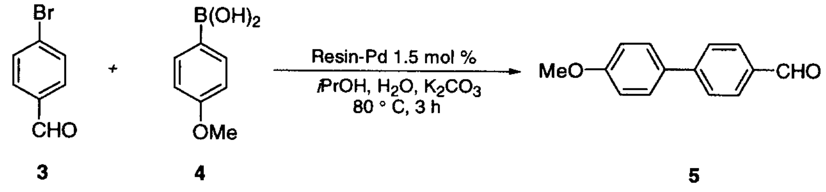
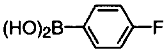
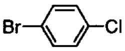
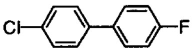
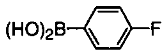
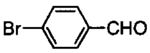
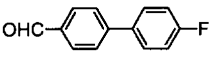
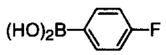
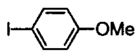
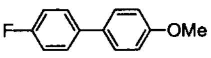
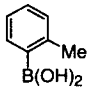
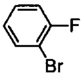
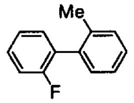
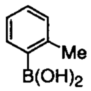
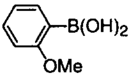
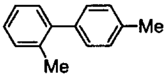
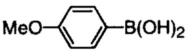
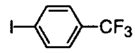
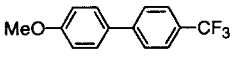
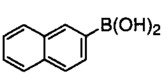
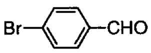
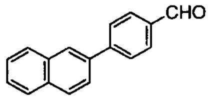
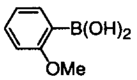
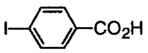
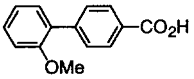
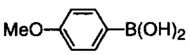
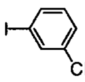
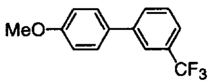
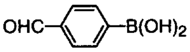
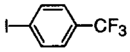
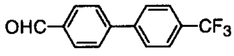


Figure 2

The resin could be recycled. However its activity appeared to deteriorate after 2-3 cycles as indicated by the increased reaction time needed.[12] We are currently investigating the possibility of improving effective catalyst life via chemically modifying the resin to ameliorate this problem. Unlike $Pd(PPh_3)_4$, this Deloxan supported catalyst proved to be very stable to air, moisture and prolonged storage at ambient temperature. Recycling of the catalyst involves a simple filtration and a solvent wash. The recovered catalyst can be used for the next cycle without regeneration.

Table I. Cross-Coupling of Aryl Halides and Arylboronic Acids Catalyzed by Thioureaesin-Bound Palladium

Entry	ArB(OH)2	Ar'X	Ar-Ar'	Yield[a]
1				27%
2				97%
3				99%
4				78%
5				58%
6				89%
7				73%
8				79%
9				71%
10[b]				89%

a. Isolated yield
b. Reaction carried out using recovered catalyst

In summary, we have found a practical and useful polymer supported catalyst for Suzuki reactions with the following noteworthy features: convenient preparation from a commercially available polymer; stability towards air, moisture, and prolonged storage;[13] and ability to be recycled. Additionally, utilization of this catalyst reduces the cost associated with Pd/ligands purchase and residual Pd removal. Studies toward applications of this catalyst to other Pd-catalyzed reactions and different transition metal systems are in progress.

Acknowledgment

The authors wish to thank the administrators of the Lilly Summer Intern Program and CR&D management for support; and Dr. Charles Barnett for helpful discussions.

References:

1. Heck, R. F. *Palladium Reagents in Organic Synthesis*, Academic Press: **1985**, London.
2. Miyaura, N.; Suzuki. A. *Chem. Rev.* **1995**, *95*, 2457. For improved procedures for the preparation of biaryls via Suzuki reactions, see: (a) Huff, B. E.; Koenig, T. M.; Mitchell, D.; Staszak, M. A. *Org. Syn.* **1998**, *75*, 53; (b) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *Org. Syn.* **1998**, *75*, 61.
3. (a) Bruner, H.; Bailar, J. C. Jr. *Inorg. Chem.* **1973**, *12*, 1465. (b) Kaneda, K.; Kurosaki, H. Terasawa, M. Imanaka, T. Teranishi, S. *J. Org. Chem.* **1981**, *46*, 2356.
4. Jang, S-B. *Tetrahedron Lett.* **1997**, 38, 1793.
5. Fenger, I.; Le Drian, C. *Tetrahedron Lett.* **1998**, *39*, 4287.
6. Deloxan THP® II was purchased from Degussa A.-G.
7. (a) Gabriele, B.; Giuseppe, S.; Costa, M.; Chiusoli, G. P. *J. Organometallic Chem.* **1995**, *503*, 21. (b) De Munno, G.; Gabriele, B.; Salerno, G. *Inorg. Chim. Acta.* **1995**, *234*, 181.
8. Panster, P.; Wieland, S. Eur. Pat. Appl. EP 507132 A2 921007. CA:*119*:140357.
9. Procedure for the preparation of the resin-bound catalyst: A clear solution of 0.3 g of $Pd(OAc)_2$ in 300 mL of methanol was stirred with 30 g (75%wet) of Deloxan THP II resin for 1 h at room temperature. The resin was filtered, washed with methanol (100 mL x 5) and dried in vacuuo at 50°C for 16 h to give 7.8 g of a brown solid which was determined to contain 2.5 wt % of palladium.[11]
10. A representative procedure is as follows: *4-(naphthalen-2-yl)benzaldehyde* (Table, entry 7): To a flask containing 20 mL of isopropanol and 3 mL of water was added potassium carbonate (0.6 g, 4.34 mmol), the catalyst resin (0.30 g), 4-bromobenzaldehyde (0.37 g, 2.0 mmol), and 2-naphthaleneboronic acid (0.34 g, 2.0 mmol). The resulting mixture was purged with nitrogen for 10 min, stirred at reflux under positive nitrogen pressure for 4 h, and filtered. The filter cake was washed alternately with ethyl acetate (10 mL) and water (5 mL) three times. The washings were combined with the filtered reaction mixture. The organic layer was dried over magnesium sulfate, concentrated under reduced pressure, recrystalized from ethyl acetate (2 mL) and heptane (1 mL), and dried at 50°C oven under reduced pressure overnight to give 0.34 g of the title compound as a yellow solid (73% yield): ^{1}H NMR (300 MHz): δ 7.249-8.106 (m, 11 H), 10.079 (s, 1 H); IR (KBr, cm^{-1}) 3046.4, 1698, 1600, 1563, 1576, 1217, 1194, 1173, 829, 813, 747; Anal. Calcd for $C_{17}H_{12}O$: C, 87.91; H, 5.21. Found: C, 87.22; H, 5.48.
11. Palladium content was determined by Graphite Furnace Atomic Absorption method (GFAA).
12. After three cycles, Pd content of the catalyst dropped by 33%, most probably through leaching into aqueous phase upon workup.
13. No noticeable loss of activity was observed after storing the fresh catalyst at room temperature under normal atmosphere for 4 months.