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Editor's choice paper

Investigation of activity, stability, and degradation mechanism of surface-supported Pd-PEPPSI complexes for Suzuki-Miyaura coupling

Angela N. Marquard, Laura E. Slaymaker, Robert J. Hamers, Randall H. Goldsmith*

Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison, WI 53706, United States

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ABSTRACT

Secure surface-molecule linkages are critical to designing recyclable surface-supported molecular catalysts. A series of N-heterocyclic carbene (NHC)-functionalized Pd-PEPPSI complexes are tethered using different linker chemistries to polymer and silica supports and examined for their reactivity in Suzuki-Miyaura cross-coupling reactions. Attachment chemistries investigated include tetrazine-norbornene cycloaddition click chemistry onto a polystyrene bead, incorporation via ring-opening metathesis polymerization (ROMP) into a poly(norbornene) polymer, and immobilization onto silica gel via silyl ether linkage. Palladium black formation suggests that the catalysts become detached from the support, and soluble palladium particles are the catalytically active species. These results help probe the manner in which the pyridine ligand of the PEPPSI complex helps to stabilize the catalysts and ultimately, how the catalysts fail. Further, we highlight the interplay between catalyst stability, recyclability, and reliable surface linkages.

1. Introduction

Homogeneous palladium catalysts are widely applied in organic synthesis, particularly in carbon–carbon coupling reactions [1–3] including Negishi [4], Heck [5], Sonogashira [6], Kumada-Tamau-Corriu [7], and Suzuki-Miyaura [8] reactions. However, homogeneous catalysts have considerable disadvantages including difficulty in separating the catalysts from reaction products, and the inability to recycle the catalyst, leading to the loss of expensive metals and ligands.

Many of the difficulties associated with these homogeneous cross-coupling catalysts can be overcome by anchoring the catalyst to a solid support [9] and new catalytic activity can be added [10]. Palladium can be attached to a large variety of supports such as carbon [11,12], metal oxides [13], zeolites [14], and others [15–17]. The most common supports used to immobilize molecular catalysts are silica [18] and polymers [19], where ligands are typically covalently bound to the support. Supported catalysts can often be removed from the reaction by simple filtration or centrifugation allowing for convenient recyclability [20,21]. Polymer-supported catalysts can be attached to insoluble, cross-linked polymer resins [22] or soluble polymers [23] where the solubility can be tuned by modifying the polymer backbone to make either organo- or water-soluble catalysts [24]. It is more difficult to remove soluble polymer catalysts from reaction mixtures, but is achievable via precipitation. Silica-supported catalysts have the advantages of excellent stability and wide availability of silica. In particular, convenient attachment of organic functionality to the silica surface is readily achieved through use of a silyl ether linker [25]. However, though silica and insoluble polymer-supported catalysts are easy to purify [26], characterization of the supported catalyst species is challenging because traditional solution-phase spectroscopy techniques cannot be applied, though solid-state techniques can provide some chemical insight [27–30].

The most common strategy for immobilizing catalysts onto both silica and polymers is to first covalently functionalize the surface with ligands followed by complexation with palladium salts [31,32]. In this method, the metal complex is formed *after* attachment to the surface, making chemical characterization of the surface species very difficult. This lack of definitive characterization is a problem when confidence about the chemical identity of the species attached to the surface is critical.

Despite the advantages of heterogeneous catalysts, many of these materials are composed of a mixture of surface species that are difficult to characterize, and the structure of their active sites is not well-understood [33]. Because of this difficulty, surface-supported catalysts with well-characterized organometallic centers are desirable. A suitable well-defined supported catalyst

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* Corresponding author.
E-mail address: rhg@chem.wisc.edu (R.H. Goldsmith).

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will have only one species attached to the surface (single site), and be easily characterized by spectroscopy techniques prior to surface attachment. Ideally, the active catalyst species will have a similar structure to the fully-characterized precatalyst, removing ambiguity about the structure of the active site.

Accordingly, the Pd-PEPPSI (pyridine-enhanced precatalyst preparation stabilization and initiation) catalyst system developed by Organ and coworkers [34] is an attractive catalytic system to study catalyst immobilization techniques. These catalysts have the advantage that the precatalyst is structurally very similar to the active catalyst [34] making it a fitting candidate for a surface-supported molecular catalyst. The organometallic species can be fully characterized before surface attachment ensuring a single supported species. These advantages have combined to make surface-supported Pd-PEPPSI catalysts excellent model systems for exploring mechanisms of initiation at the single-molecule level [35,36]. Pd-PEPPSI complexes are of great interest due to their air and moisture stability, ease of preparation, and use in Suzuki-Miyaura [34,37], Negishi [37–39], Kumada-Tamau-Corriu [34,40], and Buchwald-Hartwig [41] reactions making them very versatile cross-coupling catalysts. The Pd^{II} precatalyst has one N-heterocyclic carbene (NHC) ligand, two anionic chloride ligands, and a pyridine "throw away" ligand (Fig. 1). The pyridine ligand aids in the preparation and stabilization of the precatalyst and readily dissociates upon catalyst activation [37]. Organ and coworkers have proposed that the active catalyst species is a monoligated Pd^0-NHC species, and that the dissociated pyridine ligand may return and stabilize intermediate palladium species throughout the catalytic cycle [37]. Recently, a Pd-PEPPSI precatalyst attached to a silica support via an azide-alkyne cycloaddition reaction was reported and the catalyst's competence for Negishi couplings was explored [39].

In this work, we explored a variety of covalent immobilization strategies for fully-characterized Pd-PEPPSI precatalysts, including attachment to insoluble polystyrene bead-, soluble poly(norbornene)- and silica supports. Multiple attachment chemistries are investigated to determine the most effective strategy for supporting Pd-PEPPSI catalysts and the activity of these immobilized catalysts are investigated in Suzuki-Miyaura coupling reactions (Scheme 1). We find evidence of significant catalyst decomposition suggesting that existing catalyst protective mechanisms are insufficient to stabilize the catalyst while surface-supported and further explore how the need for a robust surface linkage and a stable catalyst are interconnected.

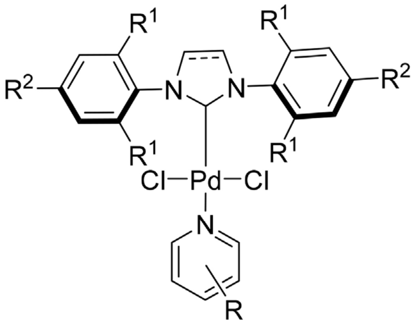


Fig. 1. General structure of a Pd-PEPPSI catalyst.

2. Results

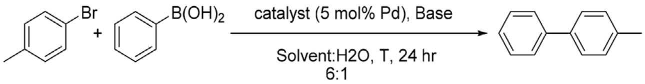
2.1. Click chemistry

A variety of high-yielding reactions with mild reaction conditions (often referred to as "click reactions") have been widely used as a method to add functionality to polymers [42,43] and biomolecules [44–46]. Because the mild conditions typical of click reactions are important to avoid interference with the fully-characterized precatalyst, click chemistry was investigated as a method to support a fully-formed Pd-PEPPSI precatalyst on a polystyrene polymer. The click reaction between norbornene and tetrazine was chosen due to the benign, metal-free conditions [47] which avoided the replacement of palladium with copper necessary for copper-catalyzed azide-alkyne cycloaddition click chemistry [39]. To this end, Pd-PEPPSI precatalyst **6a** was functionalized with a norbornene moiety (Scheme 2).

A Diels-Alder reaction between dicyclopentadiene and allyl bromide followed by treatment with magnesium gave a methyl norbornene Grignard reagent. A Grignard reaction with bisimine **1** followed by reduction yielded norbornene-functionalized diamine **2a** which was then reacted with HCl and triethylorthoformate to make norbornene-functionalized imidizolinium salt **4a**. The NHC salt was metallated with $Pd(OAc)_2$ to form palladium dimer **5a** then broken apart by 4-picoline to form norbornene-functionalized Pd-PEPPSI precatalyst **6a** which was fully characterized.

A carboxylic acid-functionalized tetrazine intermediate was synthesized according to literature procedure [47] and then coupled to amine-terminated telechelic polystyrene to form tetrazine-functionalized polymer **7a**. The success of the polystyrene functionalization was assessed by a two-dimensional HSQC NMR experiment where the spectrum of coupling product **7a** was compared to the spectrum of the amine-terminated polystyrene starting material. Six CH_2 groups could be distinguished from the polystyrene peaks corresponding to the six methylene groups in the linker between the polystyrene and tetrazine in the coupled product, and all of these peaks were shifted from the location of the peak corresponding to the proton alpha to the amine in the polymer starting material (see Fig. S2 in the Supplementary Data).

A click reaction between tetrazine-functionalized polymer **7a** and norbornene-functionalized PEPPSI precatalyst **6a** was carried out to form **8a** (Scheme 3) but the products were difficult to purify and characterize. Due to steric factors, the endo-product is the major isomer in the synthesis of the methyl norbornene Grignard reagent, and this stereochemistry carries throughout the synthesis to precatalyst **6a**. In the click reaction, the tetrazine molecule can approach from either the top or bottom of the norbornene ring leading to multiple product isomers as shown in Fig. 2. This diversity of products causes many overlapping peaks in the NMR spectrum, preventing definitive characterization of **8a.** Since it was challenging to purify and characterize soluble polystyrene precatalyst **8a**, the acid-functionalized tetrazine was attached in a similar coupling reaction to an amine-terminated insoluble, cross-linked polystyrene bead to form **7b** due to the ease of purification and potential recyclability of the polystyrene beads. The click reaction with **6a** was carried out to form catalyst-functionalized beads **8b** and the beads were tested for catalytic activity. The palladium loading was determined by ICP-AES to be 0.12 mmol Pd/g, indicating ~18% of amine sites on the amine-terminated polystyrene beads were functionalized with palladium.



Scheme 1. Suzuki coupling reaction.

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