

# Determination of Solution Phase Heck Catalysis Leached from Immobilized Palladium on Propylthiol-Modified Mesoporous Silica

John M. Richardson and Christopher W. Jones\*

<sup>1</sup> Georgia Institute of Technology, School of Chemical & Biomolecular Engineering, Atlanta, GA 30332

\*cjones@chbe.gatech.edu

## Introduction

The use of palladium metal as a catalyst is ubiquitous in the development and manufacture of active pharmaceutical ingredients. Palladium is an expensive metal and its potential for negative biological effects are unknown. Therefore, the need to recover spent palladium is driven both by cost and by government regulations requiring residual palladium to be very low in product and waste streams. Thus, much research has been conducted to heterogenize active palladium, so that the catalyst can be removed via simple filtration and reused without significant loss of activity.

A large number of support materials and immobilization strategies have been employed. Examples include ionic palladium bound to charged surfaces, palladium entrapped in polymeric matrices, and organometallic palladium complexes covalently linked to silica materials or organic polymers. In most cases, these solid precatalysts are *assumed* to act as active, heterogeneous catalysts. Rarely are specific tests taken to elucidate the nature of the active species and in cases when tests are used, relatively ambiguous methods, such as hot filtration tests and comparisons of reaction yields upon catalyst recycle are most often employed. Despite these results there is a growing consensus that the majority of catalysis in Heck chemistry from immobilized pre-catalysts is actually from leached metal. This is usually determined after more rigorous testing has been employed [1-3]. Nonetheless, new heterogenized catalysts continue to be claimed every year.

Herein we present a rigorous re-examination on recently reported "heterogeneous" palladium pre-catalysts immobilized on alkylthiol-modified supports. Reinterpreting previous reports [4,5] we conclude that catalysis is solely from leached metal and that no evidence is found for catalysis by the immobilized palladium species. We also demonstrate how organically modified supports can be used as selective metal poisons, which can be used to test for presence of heterogeneous palladium catalysis [6].

## Experimental

3-mercaptopropyltrimethoxysilane was immobilized on mesoporous silica, SBA-15, via silane condensation. A portion of these materials was metalated by contacting with a solution of Pd(OAc)<sub>2</sub> in acetone; the extent of metalation was quantified by elemental analysis.

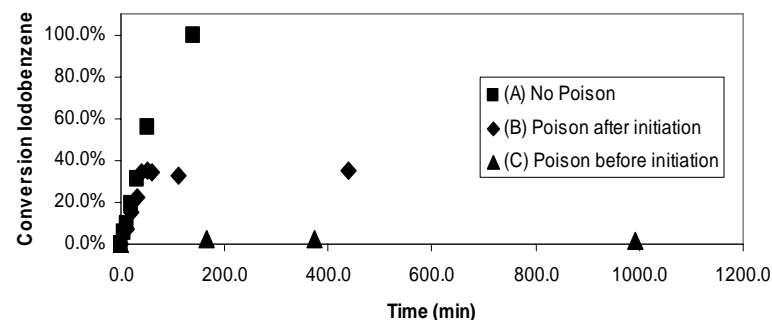
The metalated organically modified supports were used as pre-catalysts for carbon-carbon coupling reactions such as the Heck reaction. Typically, the reaction solution consisted of an aryl halide, such as iodobenzene or bromoacetophenone, n-butyl acrylate, a base, such as triethylamine or sodium acetate, and N,N-dimethylformamide as solvent. Reaction

temperatures ranged from 70°C to 120°C. Precatalyst amounts ranged from 0.05% to 1.0% palladium relative to aryl halide. Conversions were monitored via gas chromatography.

Determination of heterogeneous versus homogeneous catalysis included data from a range of tests, such as hot filtration, activity in presence of metal scavengers such as poly(4-vinylpyridine) and activity in presence of unmetalated propylthiol modified surfaces over a range of propylthiol to palladium ratios.

## Results and Discussion

Immobilized thiols metalated with palladium acetate are effective precatalysts for Heck reactions of both iodobenzene (Fig. 1) and bromoacetophenone. In the presence of PVPy no activity is observed, which is evidence against any heterogeneous catalysis since the cross-linked PVPy is insoluble in the reaction media. Unmetalated immobilized thiols are effective poisons of soluble Pd(OAc)<sub>2</sub> and also shut down activity from immobilized palladium precatalysts. This is strong evidence that all activity is from leached palladium metal and not surface catalysis from bound palladium. A variety of reaction conditions using both aryl iodides and activated aryl bromides were tested, and in all cases, the evidence supports the conclusion that activity is from leached palladium with no catalysis from immobilized palladium. This is consistent with the work of Davis [7].



**Figure 1.** Heck reaction of iodobenzene with n-butyl acrylate using metalated immobilized propylthiol as precatalyst (0.05% Pd to iodobenzene). (A) is without any poison. Poisoning capability of unmetalated immobilized thiol is demonstrated by (B) adding the poison 40 min after reaction has initiated and by (C) adding poison before the start of reaction.

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