

**DISTINGUISHING BETWEEN SURFACE & SOLUTION
CATALYSIS FOR PALLADIUM CATALYZED C-C COUPLING
REACTIONS: USE OF SELECTIVE POISONS**

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John Michael Richardson

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**DISTINGUISHING BETWEEN SURFACE & SOLUTION
CATALYSIS FOR PALLADIUM CATALYZED C-C COUPLING
REACTIONS: USE OF SELECTIVE POISONS**

Approved by:

Dr. Christopher W. Jones, Advisor
School of Chemical & Biomolecular
Engineering
Georgia Institute of Technology

Dr. Rachel Chen
School of Chemical & Biomolecular
Engineering
Georgia Institute of Technology

Dr. Pradeep K. Agrawal
School of Chemical & Biomolecular
Engineering
Georgia Institute of Technology

Dr. Marcus Weck
Department of Chemistry
New York University

Dr. E. Kent Barefield
School of Chemistry and Biochemistry
Georgia Institute of Technology

Date Approved: January 09, 2008 □

Wisdom is supreme; therefore get wisdom. Though it cost all you have, get understanding
-Proverbs 4:7

The most exciting phrase to hear in science, the one that heralds new discoveries, is not Eureka! (I found it!) but rather, "hmm.... that's funny...."
-Isaac Asimov

One's first step in wisdom is to question everything - and one's last is to come to terms with everything.
-George C. Lichtenberg

We learn wisdom from failure much more than from success. We often discover what will do, by finding out what will not do; and probably he who never made a mistake never made a discovery.
-Samuel Smiles

The important thing in science is not so much to obtain new facts as to discover new ways of thinking about them.
-Sir William Bragg

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NOMENCLATURE

BET	Brunauer-Emmett-Teller: a method of determining surface area
BJH	Barrett-Joyner-Halenda: a method of determining pore size
DCM	dichloromethane
DGDE	diethylene glycol dibutyl ether
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
EO-PO-EO	poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide)
GC	gas chromatography
h	hour(s)
HMDS	hexamethyldisilazane
HPLC	high performance liquid chromatography
IPA	isopropanol
M	metal
m	minute(s)
MDA	methyl(dicyclohexyl)amine
NEt ₃	triethylamine
Ni/C	nickel on carbon
PB-PPh ₃	polymer bound triphenylphosphine
Pd/C	palladium on carbon
Ph	phenyl
ppm	parts per million

PVPy	poly(4-vinylpyridine)
R	alkyl or aryl group
SBA	type of mesoporous silica with hexagonal arrangement of pores
SCS	order of atoms bonding to palladium in a tridentate organometallic pincer ligand
STA	simultaneous thermal analysis
TGA	thermogravimetric analysis
THF	tetrahydrofuran
TMOS	tetramethyl orthosilicate
TOF	turn over frequency (moles product per moles catalyst per time)
TON	turn over number (moles product per moles catalyst)
X	halogen (F, Cl, Br, or I)

SUMMARY

The goal of this work was to assess the nature of the active species for a number of immobilized metal ions utilized as catalysts for C-C couplings. The anchored metal catalysts primarily studied in this work include: (i) tethered organometallic Pd(II) pincer complexes, (ii) a Pd(II) complex encapsulated inside a polymer matrix, (iii) mercapto-modified mesoporous silica metalated with Pd(II), and (iv) amino-functionalized mesoporous silicas metalated with Ni(II). These metalated materials were used to promote Heck, Suzuki, or Kumada reactions. In all cases it was determined that the active species was not from a heterogeneous catalyst. Rather, all catalysis was observed to occur via leaching of active metal from the support. This conclusion is supported by a variety of experiments designed at elucidating where catalysis is occurring, with a focus on the use of metal scavengers as selective poisons of homogeneous metal. Traditional methods used to distinguish homogeneous from heterogeneous catalysis can lead to ambiguous results. At the very best they can only demonstrate that some leaching occurs, but they cannot rule out the possibility of some heterogeneous catalysis. The selective poisoning strategy is demonstrated as an elegant and definitive method for distinguishing homogeneous from heterogeneous catalysis. The results are contrasted against the current understanding of this field of research. Subtleties of methods used for distinguishing homogeneous from heterogeneous catalysis are presented and discussed. Three materials are presented as selective poisons, and their strengths and weaknesses are addressed. Thiol-functionalized silica was found as the best selective poisoning material studied for Heck and Suzuki reactions in this work.

This work is instrumental in helping build the growing consensus that all immobilized Pd catalysts for Heck and Suzuki reactions, in conventional organic media, operate via leaching of metal. The method of selective poisoning is rigorously presented as an elegant and straightforward test for determining heterogeneous from homogeneous catalysis. We recommend selective poisoning as a standard method for homogeneous/heterogeneous testing protocols. Some potential areas of research are presented that focus on understanding and expanding the selective poisoning strategy. Also, some suggested direction is discussed regarding development of catalytic systems for potential reuse and recovery of catalysts for C-C couplings.

PREFACE

The majority of this dissertation was either (i) written for intent to publish or (ii) written and accepted for publication in scientific journals. Modifications to sections previously accepted for publication were made, where necessary, to format the material in a consistent manner throughout this dissertation. Chapter 1 provides some general background information for concepts and data discussed in Chapters 2-5, which include more detailed introductory material and present the experimental findings and interpretations of this work.

CHAPTER 1

INTRODUCTION

1.1 General

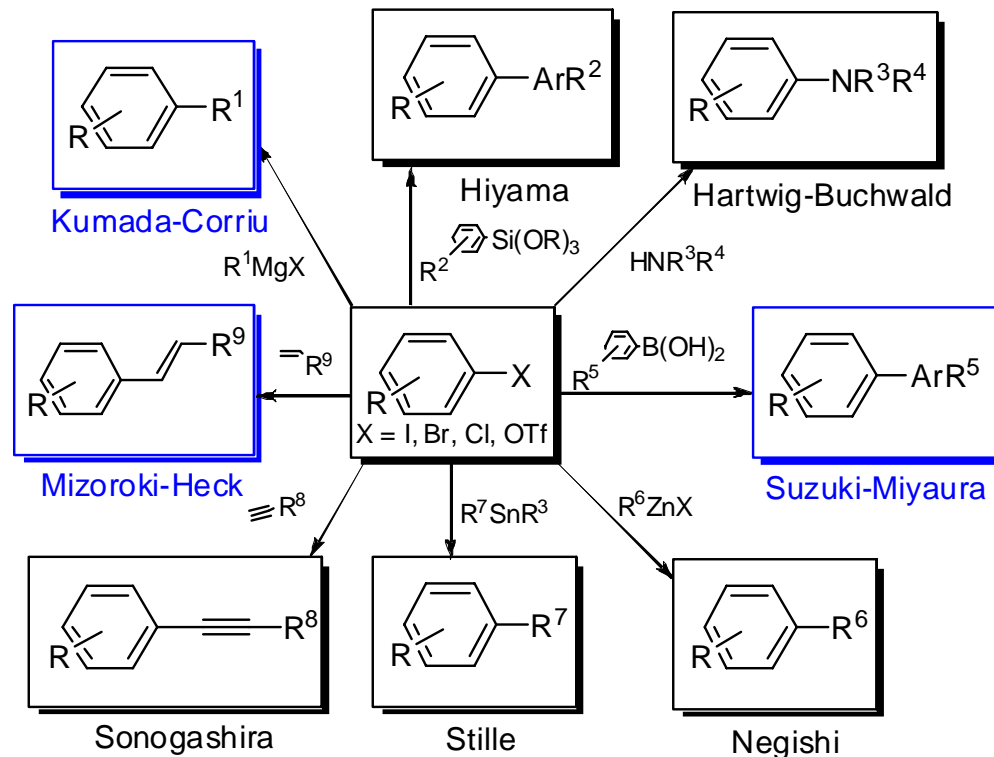
Transition metal-catalyzed C-C bond forming reactions are indispensable for both every day organic synthesis and for the formation of fine chemical and pharmaceutical compounds.^[1-3] The current literature on this topic is vast, as many different transition metals have been utilized for a wide range of substrates and reaction conditions. Chapters 2-5 each include their own introductory sections, which highlight and discuss the key concepts and past works that pertain to each chapter's content. Therefore, this introductory chapter focuses on a short background on transition metal-catalyzed C-C reactions, the key components of the reactions used in this work, why this work was undertaken, and the goals of this work. For the sake of brevity and simplicity this chapter is not an exhaustive review of the literature. More comprehensive and detailed information regarding transition metal-catalyzed C-C bond forming reactions and the specific C-C reactions studied in this work can be found in a number of publications and references therein.^[1-14]

1.2. C-C bond formations

The ground breaking paper that set the stage for investigating C-C couplings catalyzed by transition metals is the 1941 work by Kharasch et al. who reported the combined use of NiCl₂ and bromobenzene to promote the formation of biphenyl from

phenylmagnesium bromide.^[15] The 1970's saw a rapid increase in research in transition metal-catalyzed C-C couplings and many of these reaction types are commonly referred by the names of the people who discovered them. For instance, perhaps the most studied and utilized C-C bond forming reaction is the so called Mizoroki-Heck reaction,¹ named after T. Mizoroki^[16] and R. Heck,^[17] who separately reported on how palladium can catalyze the reaction of an olefin with an aryl halide. Today, Pd is the most widely preferred metal for catalysis of a wide range of C-C cross coupling reactions. A selected representation is given in Scheme 1.1.

¹ This reaction is often also referred to in the literature as simply the Heck reaction.



Scheme 1.1 Selected examples of named reactions catalyzed by Pd. Each reaction starts in the center with an aryl-X compound and reacts with different substrates (next to arrows) to form the coupling products (in outer boxes). Reactions shown in blue are studied in this work.

Common objectives of many of the research efforts into C-C bond forming reactions catalyzed by transition metals focus on maximizing activity and/or selectivity. Altering the activity and selectivity is often done by tuning the ligands bound to the metal, which can alter the electronic structure of the metal or introduce sterics that can inhibit certain pathways while promoting others. Thus, understanding the steps in the catalytic cycle of the various C-C forming reactions is important for catalyst design. Schemes 1.2-A, 1.2-B, and 1.2-C are the generic reaction cycles of the three C-C coupling reactions studied in this work. Scheme 1.2-A is the textbook cycle for the Mizoroki-Heck reaction and serves as an example of the types of steps required for

catalysis and product formation.^[6] First the metal is assumed to be reduced from Pd(II) to Pd(0) *in situ*. In this electron rich state the Pd(0) inserts into the R-X bond of a reagent, forming R-Pd-X. This process is deemed oxidative addition as the R-X is added to the Pd(0) and raises the formal oxidation number to Pd(II). Next, the π electrons of an olefin bind to a coordination site on the Pd, which is followed by a 1,2-insertion into the R-Pd bond. This is the critical C-C bond forming step. A β -hydrogen, from the newly formed organic molecule, binds to the metal resulting in the formations of a hydride, Pd-H, and a new carbon-carbon double bond, which is weakly held to the Pd and dissociates away. This step is called β -hydride elimination, and is the step by which the product of the Heck reaction is removed from the metal center. In the last step, regeneration of Pd(0) proceeds via reductive elimination of the Pd(II)(HX), releasing H-X, which is typically scavenged by an added base. These steps of oxidative addition, olefin insertion, β -hydride elimination, and reductive elimination are the key steps in the Heck reaction. The details of how each can occur are sometimes debatable and can depend on a variety of factors.^[14] Proposed alternative cycles, which include the formation of anionic Pd species, are gaining acceptance as the mechanisms by which the majority of moderate and high temperature Heck reactions occur.^[14, 18, 19]

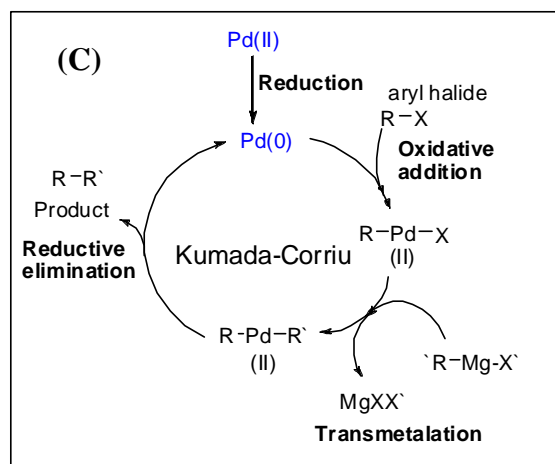
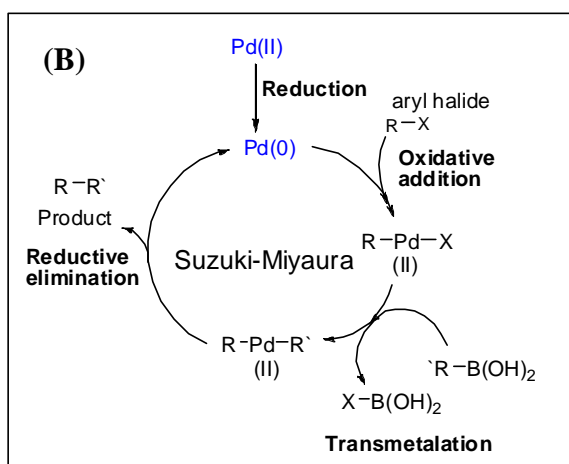
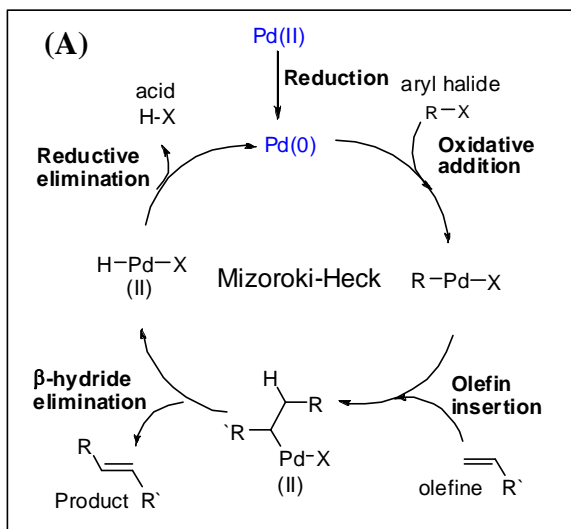
Many of the other catalyzed C-C bond forming reactions contain similar steps as the Mizoroki-Heck reaction, but do not have an olefin insertion step. Instead, a process known as transmetalation occurs in which a ligated molecule on the Pd is exchanged with

a different ligated molecule on another metal. For instance, in the Suzuki-Miyaura² reaction the X group on R-Pd-X is exchanged with the R' group attached to a boronic acid, R'-B(OH)₂, to form R-Pd-R' and B(OH)₂X (Scheme **1.2-B**).^[20] The product is formed by reductive elimination of R-R' to regenerate Pd(0). Scheme **1.2-C** is the Kumada-Corriu³ reaction, which also has a transmetalation step involving R-M-X (M = Pd or Ni) and a magnesium bearing Grignard reagent R'-Mg-X to form R-M-R' and MgX₂.^[21] Reductive elimination of R-R' yields the product and regenerates M(0). Kumada-Corriu reactions also differ from Heck and Suzuki in that the presence of a base is not required as there is not an acid byproduct. Also, the Kumada-Corriu reaction is one of the best known for coupling sp³ carbons as well as for coupling the typically difficult to react alkyl or aryl chlorides.

One should note that exceptions to the “textbook” mechanisms in Scheme **1.2** are given in the literature and these exceptions can depend on the initial source of Pd, whether or not ligands are used, choice of reagents, and reaction conditions.^[14] Thus, the mechanisms presented in Scheme **1.2** are presented for instructional purposes and not intended as absolute descriptions of all Mizoroki-Heck, Suzuki-Miyaura, and Kumada-Corriu catalyst mechanisms.

² This is often referred in the literature as simply the Suzuki reaction.

³ This is often referred in the literature as simply the Kumada reaction.



Scheme 1.2 General catalytic cycles of (A) the Mizoroki-Heck reaction, (B) the Suzuki-Miyaura reaction and (C) the Kumada-Corriu reaction.

1.3 Research motivation

1.3.1 Homogeneous vs. heterogeneous catalysis

Research into transition metal-catalyzed C-C bond formations can take many different avenues. These research interests *generally* include one or more of the following objectives and can have some degree of overlap:

- I. Develop more active catalysts
- II. Develop more selective catalysts
- III. Understand the steps of the catalytic mechanism
- IV. Explore catalysts effective for one reaction type for use in other reaction types
- V. Optimize reaction conditions to achieve maximum activity and selectivity for a given catalyst
- VI. Develop recoverable and reusable catalysts
- VII. Explore if, and to what extent, a novel, metal bearing material is catalytically active

A general understanding of homogeneous and heterogeneous catalysis is required to understand why this work was undertaken.

Historically, the use, study, and development of chemical catalysts have been divided into two distinct areas, homogeneous and heterogeneous catalysis⁴. Homogeneous catalysts are soluble species that are usually very active and selective, whose synthesis is guided by molecular design principles, but are often difficult to use in industry. They suffer from high costs associated with separating them from products and consequential difficulties in recycling. The inability to purify and reuse organometallic catalysts has environmental and health ramifications as these organometallic complexes are often toxic. For instance, Pd has no known biological function and current EPA guidelines mandate less than 5 ppm of Pd can reside in the product.^[22] An alternative to homogeneous catalysts are heterogeneous catalysts, which are insoluble, easy to recover catalysts whose construction is guided by material design principles. However, they are typically much less selective and active than homogeneous catalysts. This lower activity is typically attributed to a distribution of active sites on the surface and to mass transfer limitations of reagents and products. Also, it can be a daunting task to elucidate the location and the mode by which catalysis is occurring on a heterogeneous surface. Despite these negative attributes, heterogeneous catalysts make up the majority of those used in industry due to their lower cost and ease of separation. With regards to Pd, a

⁴ I am using a classical definition of the term homogeneous to define a catalyst that exists in the same phase as the reaction medium, which for C-C reactions is typically a liquid. Conversely, a heterogeneous catalyst exists as a separate phase (most often as a solid) from that of the reaction medium.

great deal of focus is in developing heterogeneous *or homogeneous*⁵ catalysts that both minimize cost and minimize product contamination.^[23]

Most catalysts studied for transitioned metal catalyzed C-C couplings are of a homogeneous nature. They can contain easily dissociated ligands that do not have η^2 donating groups (such catalysts are often termed “ligandless”), or contain ligand fragments which bind to the metal via two or more contiguous atoms. This latter class of ligands can affect the catalyst’s ability to perform various steps of the catalytic cycle by influencing the electronic and steric properties of the metal center.

Phosphine ligands are the basis for the “lion’s share” of homogeneous catalysts studied and employed for Mizoroki-Heck, Suzuki-Miyaura, and Kumada-Corriu reactions. This class of ligands is often chosen because the lone pair of electrons on the phosphines can readily bind to palladium. The electronic influence of this lone pair can be adjusted by altering the molecular structure of the groups bound to the phosphine. Also, by changing the structure of phosphine ligands, the steric environment of the metal can be influenced. Unfortunately, drawbacks of phosphines can include (i) sensitivity toward oxygen and moisture and (ii) toxicity exhibited towards humans. Thus, it is important, especially in the synthesis of pharmaceutical compounds, to remove the phosphines from the product stream, which can be an extremely difficult and costly task. Non-phosphine based ligands do exist and typically utilize nitrogen, oxygen, or sulfur

⁵ There is currently much interest in designing homogeneous catalysts that work at exceptionally low loadings, < 5 ppm. Thus the need for recovery would be eliminated, because such small amounts are required. The cost of the sacrificed catalyst would be insignificant and purification would be a non issue, since the trace amount of Pd in the product stream would be in accordance with government regulations.

donors to the metal. Today, many homogeneous Pd catalysts can achieve great selectivity and can achieve high turnover numbers, TON's, (moles product per mole catalyst) in the millions and indeed even a report in the billions has been published.^[14, 24, 25] However, despite the achievement of great selectivity and activity with homogeneous Pd catalysts, they are sometimes not employed in commercial applications. This lack of utilization is because they suffer from the common setbacks that many homogeneous catalysts face for any catalytic operation (*vide supra*). A potential strategy to overcome these setbacks is to immobilize organometallic catalysts with the hope that they retain their activities and selectivities, but are now recoverable and reusable.

The stability of an organometallic catalyst, whether homogeneous or heterogeneous, is a critical component for recovery and reuse. For immobilized organometallic complexes, the determination of whether the catalytically active site is free in solution or is from an immobilized complex is vitally important, but can be hard to elucidate especially in cases in which only a small amount of metal is required for catalysis. Often, only one or two tests are employed to “prove” heterogeneity. However, as will be discussed in the following sections, using only one or two strategies to test for heterogeneity can lead to incorrect conclusions.

This thesis work focuses on a suite of techniques used to determine homogeneous vs. heterogeneous catalysis with conclusions based on a collective analysis of the data from each test. Such tests include hot filtration,^[14, 26, 27] analysis of reagent yield after recovery and recycle,^[28] Hg(0) poisoning,^[14, 27, 29-34] use of metal scavengers,^[32-39] elemental analysis,^[35] and the so called three phase test.^[32-35, 40, 41] Each test gives part of the picture and when taken as a whole, can lead to strong determinations as to whether or

not leaching occurs. Table 1.1 outlines the advantages and limitations of each test, which are described in more detail in the ensuing sections 1.3.1.1 through 1.3.1.5.

Table 1.1 A comparison of the tests used in this thesis work for determining heterogeneous from homogeneous catalysis.

Technique	Indications	Advantages	Limitations
Hot filtration	Positive tests for soluble kinetically active species.	If observe reaction then strong proof for soluble species.	Inactive filtrate does not indicate heterogeneity as the leached species can be deposited or deactivated during filtration. Does not distinguish how much activity is from heterogeneous catalysis.
Recycle kinetics	Can show loss of initial catalyst activity due to loss of metal or from catalyst deactivation.	Provides strong insight into reusability of the catalyst.	Does not distinguish loss in activity due to metal leaching and/or catalyst poisoning.
Hg(0) poisoning	Positive test for soluble metal(0) catalytically active species.	Easy to perform. Strong quenching of metal (0).	Not expected to quench ligand bound metal or metal above zero oxidation state. Can also quench catalysis from metal (0) on solid surfaces.
Selective poisons	Distinguishes between heterogeneous and homogeneous catalysis.	Wide variety of metal scavengers available. Cannot penetrate pores of catalyst support. Should not quench catalysis from immobilized complexes	Uncertainty of poisoning strength. Needs control tests for each homogeneous catalyst to probe this. Poisoning ability may need optimization for each catalyst system.
Elemental analysis	Determine metal content before and after reaction of both solid and solution.	Best quantitative measure of amount of metal present before and after reaction.	If catalyst re-deposits during recovery, then EA will not show loss of metal even though leaching did occur. It is expensive.
3-phase	Determines if catalysis occurs from soluble species.	Elegant test of reaction from soluble species.	Must be able to immobilize a reagent. Separation from solid catalyst post reaction is difficult. Uncertainty of how immobilization of reagent affects its reactivity.

1.3.1.1 Hot filtration test

Hot filtration involves filtering off the solid catalyst during some point of the reaction at the reaction temperature (Fig. 1.1).^[42, 43] The filtrate is then allowed to continue to react. If substrate conversion is observed in the filtrate, then this is a positive test that a soluble catalytically active species is present (Fig. 1.1-A). What if the filtrate is inactive? Commonly this is interpreted as proof that leaching did not occur and heterogeneity of the catalyst is claimed. However, for palladium the leached metal may be pulled out of solution during the filtration process or it may be deactivated (Fig. 1.1-B). This is because the process of filtration itself can cause soluble metal species to either re-deposit on the catalyst surface and/or on the filter medium. Thus, for Pd catalyzed C-C couplings only the positive of the hot filtration test can be taken as conclusive evidence that leaching of active, soluble metal occurred during the reaction. A lack of filtrate activity suggests that leaching did not occur, but other tests are needed to support a conclusion of no leaching.

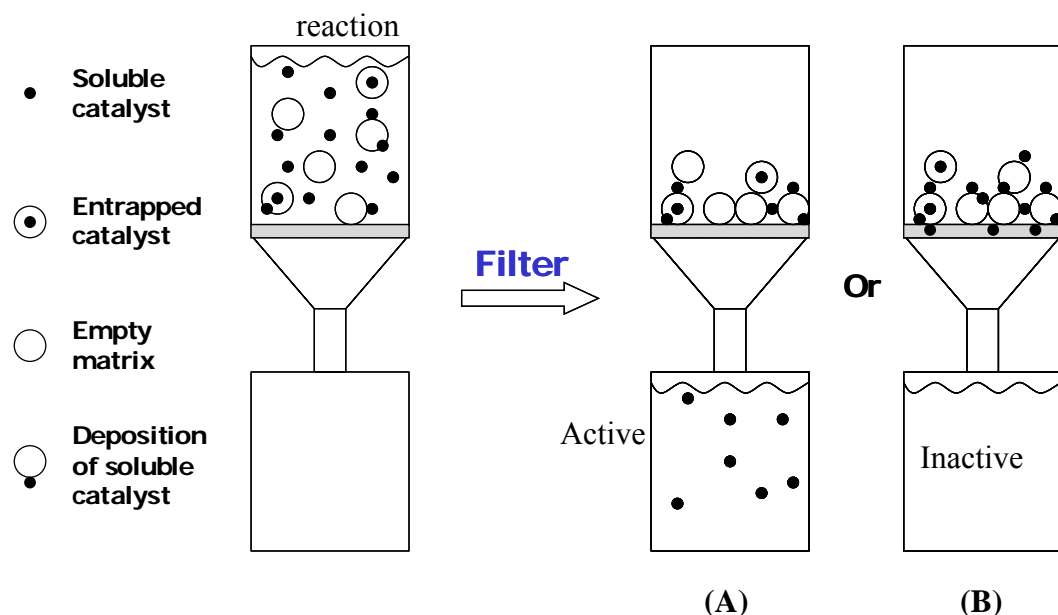


Figure 1.1 Cartoon depicting hot filtration test of an anchored catalyst, which before reaction, is encapsulated inside a matrix. The solids are filtered off during the reaction, and the filtrate is measured for continued activity. Part **(A)** is the scenario in which the catalyst leaches into solution, survives the hot filtration, enters the filtrate, and continues activity. Part **(B)** represents the scenario in which leaching did occur, but the catalyst redeposits or is deactivated during the filtration process resulting in an inactive filtrate.

1.3.1.2 Activity after recycle as test of catalyst heterogeneity

Proof of catalyst recyclability and *heterogeneity* is often given by recovery of catalyst, usually by filtration or centrifugation, and then reusing it in subsequent reactions without a drop in conversion. Conversion comparisons between each run are usually done using final yields reported at some period of time. If the yields are the same, or close, to the first run, the catalyst is said to have retained its activity and is reported as a recoverable and recyclable *heterogeneous* catalyst. While this test does demonstrate that some of the catalyst, or precatalyst, can be recovered and reused, it does not prove

heterogeneity. If only a small amount of metal is leached, then the solid may act as a reservoir of released catalytic species. Hence it can be reused multiple times without significant activity loss, but with the actual catalysis occurring in solution. By comparing final yields, *without studying reaction profiles*, a determination of catalyst activity can be misleading.^[14, 43] For instance, say in the first run the catalyst quickly reaches final yield in 3 hours but the data point is taken at 25 hours. If the second reaction occurs more slowly due to loss of metal, but reaches the same *final yield* at 7 hours, then the two reactions will appear to have the same activity if both are only measured at 25 hours. Analysis of the full reaction profile is therefore required to adequately compare the two and show whether catalytic activity has been (i) retained or (ii) reduced by either metal loss or catalyst poisoning (Figure 1.2).

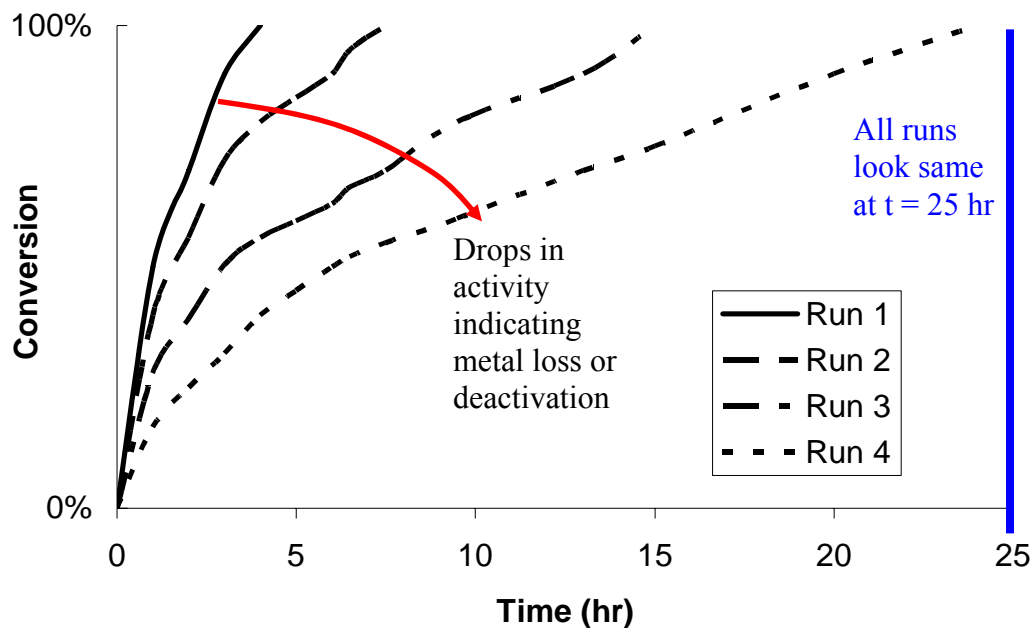


Figure 1.2 Fictitious example demonstrating how recycle data can be misinterpreted of a recycled, “heterogeneous” catalyst that is losing metal. If final yield taken at $t = 25$ h (blue line), then all runs would look the same at 100% conversion. This can be misinterpreted as having a completely recoverable and recyclable catalyst if comparisons are only made at 25 h. However, if kinetic profile of each run is measured, then a decrease in early age kinetics (red line) would be observed implying loss of metal or poisoning of catalyst sites.

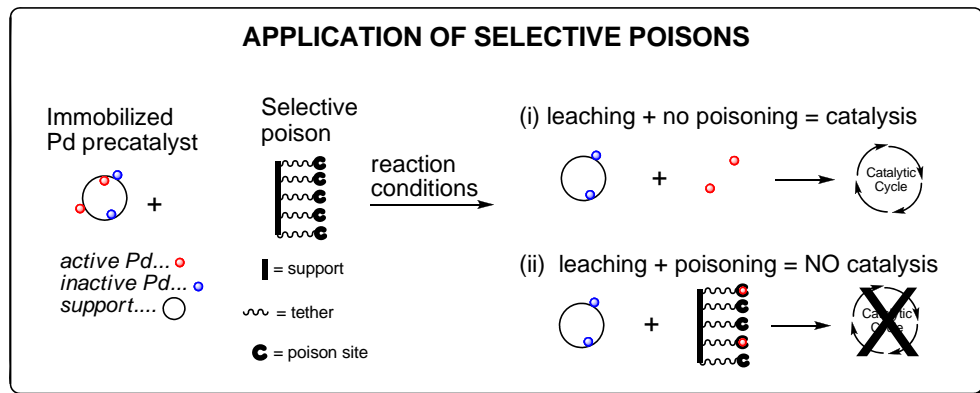
1.3.1.3 Mercury poisoning test

The formation of amalgams with $\text{Hg}(0)$ is known to occur for a variety of metals in their zero oxidation state. Thus, if the metal dissociates from its ligands, it can bind with mercury thereby killing its catalytic activity. Historically, a lack of quenching of catalysis by $\text{Hg}(0)$ addition has been interpreted as demonstrating heterogeneous

catalysis.^[29, 31] However, more recent literature suggests that these tests can only confirm homogeneous, but not heterogeneous catalysis.^[44, 45] The original works by Anton^[29] and Foley^[31] were performed with oxidized metals bound to protective ligands. Mercury is not expected to be able to quench metals bound to protective ligands or metals in a raised oxidation state.^[14, 32, 33] Thus, the Hg(0) is best interpreted as determining whether bare, M(0) (M = metal) is participating in the catalytic cycle.^[14]

1.3.1.4 Selective poisoning test

Use of insoluble metal scavengers, such as poly(vinylpyridine) and Quadrapure™ TU used in this thesis work, can be used to distinguish homogeneous from heterogeneous catalysis. Metal scavengers typically work by providing a large number of metal binding sites on a solid scaffold, such as an insoluble polymer or mesoporous silica. Traditional usage of metal scavengers is to purify reaction solutions by removing any dissolved metal from a solution after the reaction is complete. We propose that if an excess of metal scavenger is added before or during a reaction, it can selectively remove soluble, catalytically active species, thereby shutting down homogeneous catalysis (Scheme 1.3). This is envisioned to work best for metals not bound by ligands, because without ligand binding the maximum number of coordination sites are available to the poison. Also, the presence of ligands will affect the steric accessibility of the poison to the metal. Thus, a strong binding constant between poison site and metal would be needed to kill catalysis of stable, ligand bound metal complexes.



Scheme 1.3 Schematic describing how selective poisons are envisioned to poison catalysis from leached metal. In case (i) no poison is used and catalysis occurs via leached, active metal (red dots). In case (ii) the presence of the selective poisons grabs the active, leached metal from solution, thereby stopping catalysis from occurring.

However, consider a heterogeneous catalyst with a ligand tethered to the surface. If the ligand is immobilized on a surface or in a porous matrix it is very *unlikely* that the scavenger sites, also on an insoluble surface, will be able to interfere with the catalysis from metal bound to the anchored ligands. This should also hold true for any heterogeneous, active site. This assumption that the selective poison will not interfere with heterogeneous catalysis is the crux of how the selective poisoning test works. Serious problems arise in interpretation of selective poisoning results if the material used as the selective poison interferes in the catalysis in ways other than poisoning homogeneous metal. These concerns include;

- I. The insoluble poison must be stable and not leach poisons that could then access heterogeneous sites. Conversely, the poison sites must be readily accessible to the leached metal in solution.

- II. The selective poison must also not negatively interact with the reagents in solution or with the solvent itself.
- III. Addition of solid poisons should not severely alter the reaction medium, e.g., by creating a dense slurry or by severely altering the reaction viscosity, both of which could create mass transfer issues.

These concerns are best addressed by performing control tests in which the selective poison is used to quench catalysis by known, homogeneous catalysts before being applied to heterogeneous precatalysts. Once these concerns are met, then quenching by selective poisons will be taken as a positive test that catalysis is occurring via leached metal species. If a complete lack of activity is observed in the *presence* of selective poisons, then the activity observed in the *absence* of poison cannot be attributed to heterogeneous catalysis.

1.3.1.5 Elemental analysis of catalyst before and after reaction

Elemental analysis provides a measurement of the amount of metal present with respect to amounts of other atoms. This analysis can be performed both before and after a catalyst has been used. It can also be applied to reaction solutions to determine the amount of metal concentration in solution. Elemental analysis is commonly used to demonstrate a low level of leaching catalyst heterogeneity when both (i) the amount of metal in solution is low and (ii) the amount of metal in the recovered catalyst is very close to the same as the unused material. This interpretation is reasonable only if the

amount of leached metal is not enough to effect significant catalytic activity (e.g. for some Pd reactions only ppm amounts of metal are required). Also, if there is a possibility that the metal can redeposit onto the solid surface, then elemental analysis of the recovered catalyst material can only provide a lower bound of metal loss. The actual amount leached could be higher if the metal leaches under reaction conditions but redeposits at the end of the reaction. In this scenario, elemental analysis cannot be used as a reliable method to prove catalyst heterogeneity.

1.3.1.6 Three phase test

The three phase test involves the immobilization of a reagent onto an insoluble support (phase one), while the catalyst is immobilized onto another support (phase 2). The rest of the reagents are dissolved into solution (phase 3). If the catalyst remains bound to its support during reaction, it should not be able to catalyze the reaction of the immobilized reagent. Thus, any conversion of the immobilized reagent must be catalyzed by leached metal, provided there is minimal background reaction. This is perhaps one of the more elegant tests for soluble catalytic species. However, care must be taken not to over interpret the results as there are some important subtleties regarding the use of the 3-phase test. These subtleties include;

- I. The anchored reagent must be reactive under normal reaction conditions.

Therefore a control experiment must be performed in which a known, active

homogeneous catalyst is successfully used to promote reaction of the anchored reagent.

- II. Some amount of soluble reagent, similar in molecular structure to the anchored reagent, must be included to both (i) verify that activity is possible under the 3-phase conditions and (ii) to more closely mimic reaction conditions, as the presence of soluble reagent might be required for leaching of the metal under normal reaction conditions.^[41]
- III. The conversion of anchored reagent is best interpreted only as evidence that leaching is occurring. The absence of activity of the anchored reagent can *suggest* a heterogeneous pathway for the anchored catalyst. Even then, two further complications exist; (i) The presence of the heterogeneous catalyst can obscure the results if it serves as a metal deposition site once soluble reagent has been consumed. This removal of metal from solution can prohibit or slow reaction of the anchored reagent. (ii) Partial leaching may occur, which would provide a lower amount of catalyst to the anchored reagent. Thus, the anchored reagent may proceed at a much slower pace than anticipated, which could be misinterpreted as supporting a conclusion of little to no leached species.

To conclude that a lack of activity of surface bound aryl halide is a proof of heterogeneous catalysis, one must also address these concerns. The three phase test is better utilized as confirming the presence of leached catalysts, but *not* as a test to confirm heterogeneity.

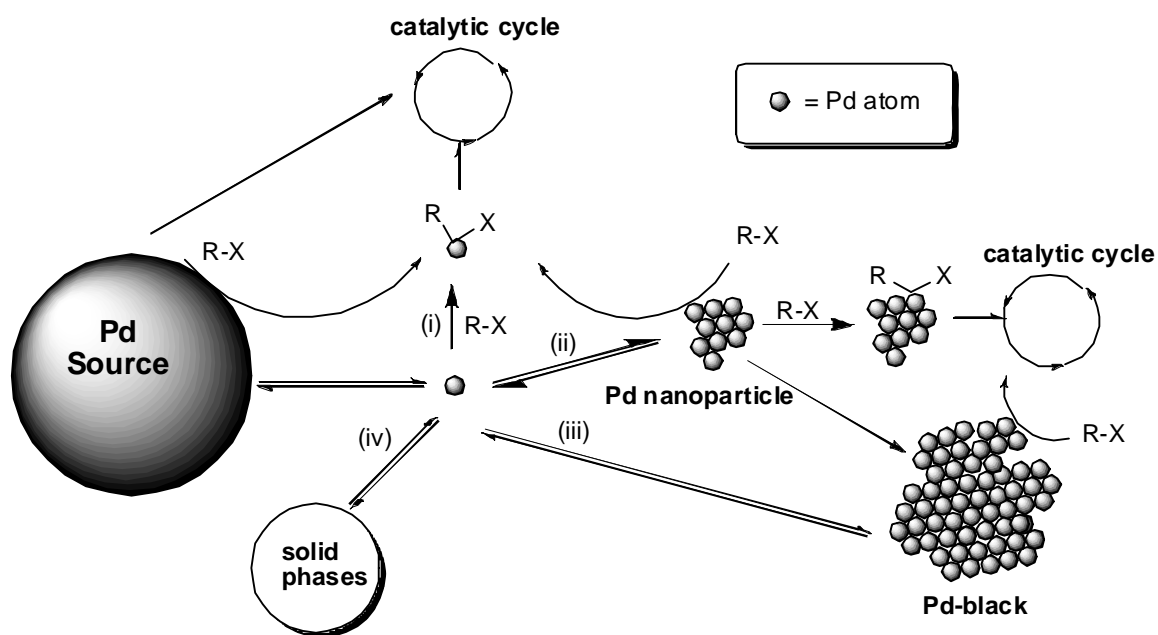
1.3.2 Summary of heterogeneity tests

Many researchers simply rely on one or two of the tests to “conclusively” demonstrate heterogeneous catalysis. The two most often used tests are hot filtration and comparison of final yields of recycle experiments. However, they can no longer be used alone to prove heterogeneity. More efforts are needed to demonstrate a more rigorous methodology using these tests, and understanding is needed of their subtleties when applied to C-C coupling reactions. This thesis work undertakes this effort with a particular focus on the use of selective poisons. For more information on distinguishing homogeneous from heterogeneous catalysis see the reviews by Jones^[14] and Finke.^[27] The next section discusses important nuances of Pd when it is used to catalyze C-C couplings.

1.3.2 Nuances of Pd chemistry for C-C couplings

A wide variety of Pd precatalysts have been used to catalyze C-C coupling reactions. This demonstrates the power of Pd for these types of reactions and provides many options when seeking a catalyst for a desired C-C coupling reaction. However, there are subtleties regarding the use of Pd that must be considered when studying the nature of the active catalyst. Pd can partition into a variety of forms, which can exist in equilibrium with each other. This partitioning can create problems when interpreting results from tests designed to probe heterogeneity (*vide infra*). Thus, when an experimenter observes a Pd species, is it the catalytic species, a dormant state of Pd, or a

deactivated form? What if the true catalytic species accounts for only a small fraction of the total metal in the reaction? Scheme 1.4 depicts the different forms that Pd can partition into when used for C-C couplings, and it highlights the complexity of studying catalytic Pd species. In this depiction all forms of palladium are shown to be possible for catalytic activity, whereas in reality only one or a few may be viable as active catalyst species, and some forms (especially on surfaces; see below) may not be catalytically active in any circumstance. More detailed discussions of Pd partitioning are found in the literature.^[14, 46, 47]



Scheme 1.4 Cartoon depicting the various forms that Pd is envisioned to take starting from a Pd source, which is depicted in this cartoon as a heterogeneous phase. Starting from the Pd source, catalysis can occur on the surface or Pd can leach into solution. Once the Pd atom is leached it (i) can undergo oxidative addition with R-X and enter the catalytic cycle, (ii) cluster to form small nanoparticles, (iii) cluster to form large aggregates of Pd-black, or (iv) can redeposit onto other solids (if present). Individual Pd atoms can be freed from nanoparticles or Pd-black by direct dissolution or by extraction by R-X. Also, catalysis could possibly occur on the nanoparticle or Pd-black surface.

To understand experiments designed to probe the nature of the active species, an appreciation is needed the various forms that Pd can partition into. This is especially true for interpreting experiments designed to distinguish heterogeneous from homogeneous catalysis (*vide supra*). As an example, consider the development of heterogeneous Pd catalysts for Mizoroki-Heck reactions. Much work has been done on developing heterogeneous palladium precatalysts for Mizoroki-Heck reactions. Such materials include P(II)-exchanged oxides or resins^[48-56], Pd(0) on standard supports such as activated carbon^[46, 57-60] or oxides.^[61, 62] Aggregates of Pd atoms, Pd-nanoparticles, have also been used as homogeneous or quasi-homogeneous catalysts^[63-67] and have also themselves been immobilized and used in Heck couplings.^[68-75] Even though a large number of research has been dedicated to developing and studying heterogeneous Pd precatalysts, the goal of developing a catalyst that is stable, recoverable, and reusable is still sought after. Why is this still a major area of research if there are so many claims of heterogeneous Pd catalysts for C-C couplings? There is growing evidence that for many of the “heterogeneous” Pd catalysts the majority of observed activity stems from leached metal.^[14, 46, 47, 49, 57-60, 76] In contrast there are still reports of immobilized Pd precatalysts that are surface active and do not leach metal.^[50, 51, 62] It is our opinion that many of the previously claims of heterogeneity stemmed from a lack of understanding (or possibly ignoring of) various forms that Pd can partition into. This resulted in misinterpretations of tests used to probe heterogeneity and incorrect conclusions regarding the nature of the active species. Thus, there is great interest in the ability to conclusively demonstrate that an immobilized Pd precatalyst is truly heterogeneously active for Heck reactions.

1.4 Goals of this work

Assessing the nature of the true catalyst in palladium catalyzed C-C is important for both academic and commercial reasons. Information as to the nature of the active species can aid in the design and development of practical catalysts for C-C reactions. Understanding the dynamic nature of Pd can aid in a researcher's ability to focus on the best methods by which to create highly active and selective catalysts while maintaining low costs and high product purity. The goals of this thesis fall into two categories; (1) Determine for a variety of anchored Pd and Ni precatalysts whether observed catalysis occurs via heterogeneously or homogeneously and (2) understand and develop better methods to distinguish heterogeneous from homogeneous catalysis for Heck, Suzuki, and Kumada reactions. A particular focus is placed on exploring the use of selective poisoning as a method to distinguish homogeneous from heterogeneous catalysis. It is hoped that by investigating the issue of heterogeneous from homogeneous catalysis for Pd catalyzed coupling reactions, the information and understanding garnered will help future investigators be able to more rigorously examine if immobilized Pd catalysts are truly heterogeneous or simply precatalysts of leached metal. Thus, the collective goal of achieving and *demonstrating* a truly recoverable and reusable Pd catalyst can be better realized.

1.5 References

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CHAPTER 2

INVESTIGATION OF HOMOGENEOUS AND ANCHORED SCS

PALLADIUM(II) PINCERS AS PRECATALYSTS FOR HECK

REACTIONS[†]

2.1 Introduction

The goal of this chapter was to investigate the nature of homogeneous and anchored SCS-Pd(II) pincers and entrapped PdCl₂(PPh₃)₂ as catalysts for coupling reactions of iodoarenes and acrylates. We desired to determine whether catalysis is caused by stable, intact SCS-Pd(II) pincers or by “naked” Pd species created by decomposition of the pincer precatalysts. Another goal was to determine if catalysis was undergoing a Pd(0)-Pd(II) or a Pd(II)-Pd(IV) cycle. For the anchored SCS-Pd(II) pincers, we sought to determine if catalysis occurred on the surface or due to leached, active species. As part of this latter objective, we were interested in evaluating and improving current methodologies, as well as possibly developing new strategies, for distinguishing homogeneous from heterogeneous catalysis.

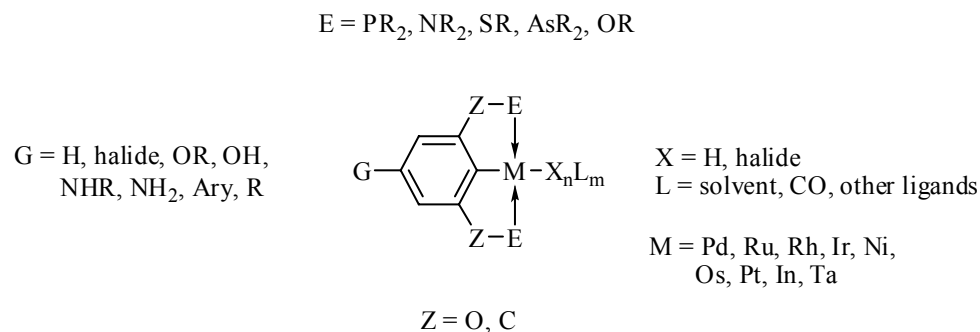
Palladium catalyzed couplings of aryl halides with olefins, known as Heck reactions, are one of the most important and most widely studied C-C coupling reactions.

[†] Portions of this work were previously published, K. Q. Yu, W. Sommer, J. M. Richardson, M. Weck, C. W. Jones, *Advanced Synthesis & Catalysis* **2005**, 347, 161.

A large number of both homogeneous and heterogeneous precatalysts have been studied. While homogeneous palladium precatalysts are often highly active and selective, they suffer from drawbacks that many homogeneous catalysts face such as the difficulty in recovering and reusing the catalyst and in purifying the product compounds from the expended catalyst. Therefore, heterogeneous catalysts are often preferred over homogeneous catalysts in large part due to the ability to recover and reuse the heterogeneous catalyst. Much work has been done on developing heterogeneous palladium precatalysts for Heck reactions. Such materials include P(II)-exchanged oxides or resins^[1-9], Pd(0) on established supports such as activated carbon^[10-14] or oxides.^[15, 16] Pd-nanoparticles have also been used as homogeneous or quasi-homogeneous catalysts^[17-21] and have also been immobilized and used in Heck couplings.^[22-29] The goal of developing a catalyst that is stable, recoverable, and reusable is still sought after despite the large amount of literature pertaining to heterogeneous Pd precatalysts. If previous reports claim heterogeneous catalysis, why is this goal still targeted? There is growing evidence that for many of the “heterogeneous” Pd catalysts the majority of observed activity stems from leached metal.^[2, 10-14, 30-32] In contrast, there are still reports of immobilized Pd precatalysts that are supposedly surface active and do not leach metal.^[3, 4, 16] Thus, conclusively demonstrating that an immobilized Pd catalyst can truly operate via a heterogeneous mechanism is of great interest.

One of the most well defined homogeneous transition metal complexes used for a wide variety of reactions, including Heck and Suzuki reactions, is the Pd(II) pincer (Scheme 2.1).^[29, 33-42] At the time of our investigations the pincer had been reported as extremely stable in organic solvents at elevated temperatures and could even perform

Heck catalysis in air. Bergbreiter et al. had successfully immobilized the SCS type Pd pincer on a polymer backbone and demonstrated that the system could promote the Heck coupling of iodoarenes and terminal olefins.^[43-48] Additionally, the polymer could be recycled with little or no decrease in final yield.^[43-48] In contrast, some SCS-Pd(II) pincers when exposed to Heck reaction conditions have been shown to decompose when an ether linkage was used to anchor the complex (*vide infra*).^[46, 49] Other immobilized Pd pincers use an amide-containing linkage and it has been reported that these “catalysts” can be used multiple times, implying that they are recyclable.^[43-48] In our laboratories Dr. Kunquan Yu was able to similarly replicate the synthesis of amide containing Pd pincers as well as to develop a method to immobilize them onto a silica support.^[50]



Scheme 2.1 Depiction of a generic pincer. In this work, G= NHR, Z = CH₂, E = SPh, M = Pd(II), and X = Cl, n = 1, and L is not used.

An intriguing aspect of the Pd(II) pincers is the mode by which they promote catalysis. Most Pd catalyzed Heck reactions are thought to undergo a Pd(0)-Pd(II) cycle as the formation of Pd(IV) complexes are difficult, with only a few, rare examples reported in the literature. Due to the covalent C-Pd bond, it is difficult to envision how the Pd(II) pincer could be reduced to Pd(0) while still remaining bound to the pincer

ligand. Previous postulations of Pd(II)-Pd(IV) cycles for Pd(II) pincers^[51-57] are largely given as a way to account for the observation of stable Pd(II) pincers found after they have been used for Heck catalysis. However, no confirmation of a Pd(II)-Pd(IV) mechanism for SCS-Pd(II) pincers has been demonstrated.^[31] We suggest the use of Hg(0) to evaluate if Pd(0) is involved in the catalytic cycle of Pd(II) pincers. Hg(0) has been known for quite some time to bind to metal surfaces resulting in a poisoning of catalytic activity for M(0) catalyzed reactions.^[58-60] It is not anticipated that Hg(0) will poison metal in higher oxidation states or metal bound by protective ligands as would be the case in complex the Pd(II) pincer. Thus, Hg(0) might be used to determine if a “naked” Pd(0) species is involved in the catalytic cycle, which would imply Pd(II) pincer decomposition.

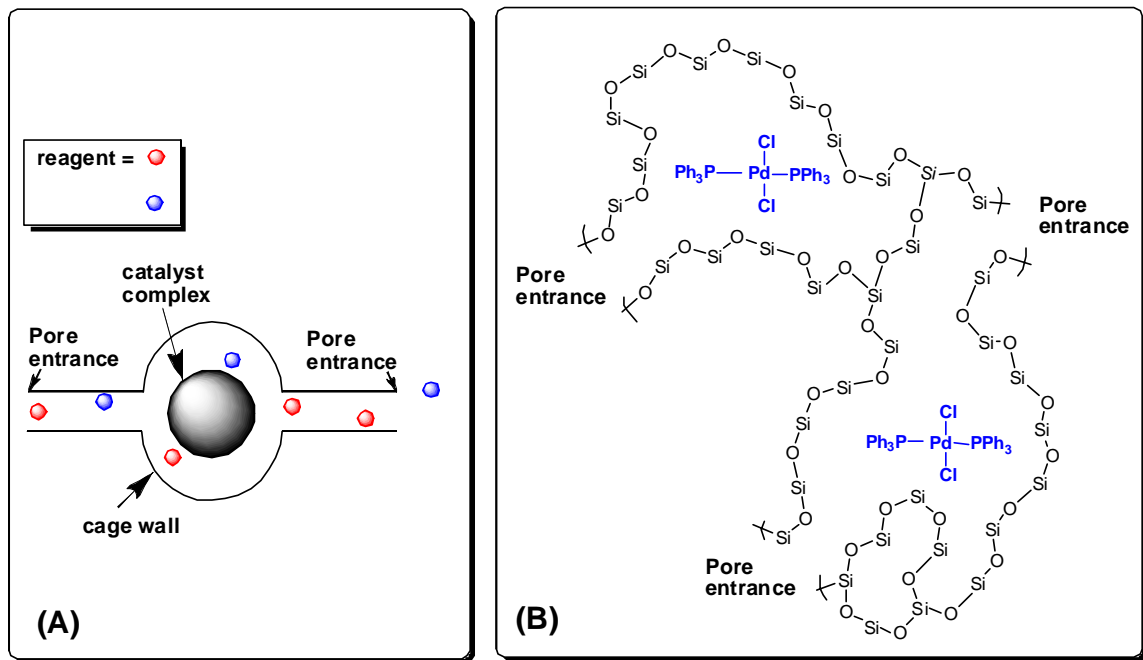
As discussed in Chapter 1, there are a variety of techniques available to distinguish heterogeneous from homogeneous catalysis. For Pd catalyzed coupling reactions there are subtleties for each of these tests that can cause misinterpretations of the data (for a discussion of these subtleties, see Chapter 1), leading to opposite conclusions of what is actually occurring. Thus, it is desired that better, more conclusive methodologies are developed to enable the elucidation of surface vs. solution catalysis. In a previous study of anchored Pd(II) pincers, Yu et al. demonstrated the use of cross-linked poly(vinylpyridine), PVPy, as an effective poison of soluble, catalytically active Pd species leached from O-SCS-Pd(II) pincers (*vide infra*).^[49] Also, in combination with the work presented in this chapter, Yu demonstrated that the basic pyridine sites of PVPy would not interfere with anchored sulfonic acids on mesoporous SBA-15 used to acid catalyze the dimerization of α -methlstyrene.^[61] This is evidence that the insoluble

PVPy cannot enter the pores of SBA-15 or interact with functional groups anchored therein. In this work, the SBA-15 support material for anchored SCS-Pd(II) pincers had smaller pores than that used in the acid study. Therefore, it is unlikely that the insoluble PVPy can interfere with immobilized SCS-Pd(II) pincers. Thus, the PVPy selective poisoning test was selected as a methodology to distinguish whether or not heterogeneous catalysis occurs for anchored SCS-Pd(II) pincers.

Prior to this work, Yu et al. had successfully applied many of the tests and concepts discussed above to a similar, silica anchored Pd pincer, O-SCS-Pd(II). The “O-SCS” is given to signify that this pincer contained an oxygen atom *para* to the C-Pd bond instead of a nitrogen atom used in this work.^[49] Yu studied the Heck reaction of iodobenzene and *n*-butyl acrylate using O-SCS-Pd(II). A loss in activity after recycle, filtrate activity of a hot filtration test, poisoning by PVPy, reaction of a three phase material, and poisoning by Hg(0) were all interpreted as being consistent with a mechanism by which O-SCS-Pd(II) decomposed to leach active Pd. This work by Yu et al. established the protocol for the work performed in this chapter, which focuses on whether or not changing from an oxygen atom to a nitrogen atom *para* to the Pd-C will result in a stable SCS-Pd(II) pincer.

Anchoring of organometallic complexes is not the only conceivable method by which to create a recoverable and reusable catalyst. Another interesting immobilization⁶ strategy is the encapsulation of organometallic complexes. This is a so called “ship in a bottle” strategy, in which the organometallic complex is engaged inside a pore. This pore is connected to the bulk solution via smaller pore channels that allow diffusion of reagent and product molecules, but are too small to allow the organometallic complex to escape (Scheme 2.2-A). While this strategy most likely introduces mass transport issues that can slow down the overall activity, it should allow for the recovery of the catalyst. The assumption, then, is that the organometallic complex does not decompose into a form small enough to escape the engaging matrix. An example is the work by Hamza et al., in which PdCl₂(PPh₃)₂ was entrapped in a sol-gel matrix (Scheme 2.2-B).^[62] This material was used as a catalyst for the Heck vinylation of aryl iodides. It was also described as “perfectly leach proof.” We were thus interested in (i) synthesizing the Pd sol-gel as described by Hamza et al., (ii) testing if these “perfectly leach proof” claims were true under our reaction conditions, and (ii) using a sol-gel strategy to engage an SCS-Pd(II) pincer. The reason for the latter is to explore recovery and reuse of intact pincer sites that may enter solution via degradation of the tether. If the tether of the SCS-Pd(II) pincer was decomposing under reaction conditions, then the freed, relatively large, pincer would still be recoverable due to its encapsulation in the sol-gel matrix.

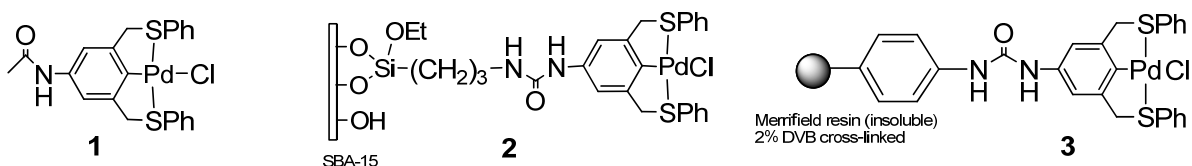
⁶ An argument could be made that entrapped homogeneous molecules are not strictly “immobilized” as they are free to move within the pore that they are engaged in. However, as their freedom of movement is severely restricted, provided they stay within the pore, then they are effectively immobilized from entering the bulk solution and are therefore recoverable. It is for this reason that the term “immobilized” is used.



Scheme 2.2 Cartoon (A) depicts and encapsulating strategy of an organometallic catalysts complex inside a pore that is connected to the outside via small pores. The small pores allow the diffusion of reagent and product molecules while disallowing diffusion of the catalyst complex. Cartoon (B) is a postulated representation of $\text{PdCl}_2(\text{PPh}_3)_2$ encapsulated inside a sol-gel matrix.

This work focused on studying homogeneous and anchored SCS-Pd(II) pincer catalysts having a nitrogen *para* to the Pd-C bond (Scheme 2.3). These materials were found to be precatalysts that were able to promote Heck reactions of iodoarenes and acrylates. The solid supported Pd pincers could be recovered and reused multiple times with no drop in final yields. However, upon closer inspection and with the use of additional testing, the activity was found to be promoted by leached Pd and not from an immobilized source. Furthermore it was determined that the active Pd undergoes a Pd(0)-P(II) cycle and no evidence was found to support activity from an intact SCS-Pd(II) pincer complex. This also rules out catalysis by a Pd(II)-Pd(IV) cycle as previously postulated to account for catalysis by an intact Pd pincer.^[51-57] Parallel

attempts to use a sol-gel encapsulation strategy to recover any intact SCS-Pd(II) pincers that could leach into solution from tether decomposition were proven unsuccessful, as the synthesized material was largely inactive. Additionally, it was determined that the activity from sol-gel materials containing encapsulated small molecule PdCl₂(PPh₃)₂ (synthesized in our laboratories) was due to Pd leaching from the sol-gel matrix.



Scheme 2.3: The three SCS-Pd(II) pincers used in this study. Complex **1** is a small molecule SCS-Pd(II) pincer with an amide group para to the Pd. Precatalyst **2** is an SCS-Pd(II) pincer anchored onto a mesoporous silica SBA-15 via a urea tether. Precatalyst **3** is an SCS-Pd(II) pincer anchored onto a cross-linked Merrifield resin via a urea tether.

2.2 Experimental

2.2.1 General

All chemicals were purchased from commercial sources unless otherwise noted. *N,N*-dimethylformamide, *n*-butyl acrylate, and triethylamine, were distilled over calcium hydride under an argon atmosphere. Poly(4-vinylpyridine) (2% cross-linked, Aldrich Co.) and 3-isocyanatopropyltriethoxysilane (Gelest, Inc.) were used as received. In reactions involving air- and moisture-sensitive compounds the experiments were carried out under dry nitrogen or argon atmospheres using an MBraun UniLab 2000 dry box (N₂ atmosphere) and/or standard Schlenk line techniques (Ar atmosphere). Gas

chromatographic (GC) analyses were performed on a Shimadzu GC 14-A gas chromatograph equipped with a flame-ionization detector and separation of organic compounds was achieved with an HP- 5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 mm). ¹H NMR (300 MHz) spectra were recorded on a Mercury VX instrument. A Bruker FRA-106 was used to collect FT-Raman spectra with at least 128 scans collected for each spectrum at resolutions between 2 – 4 cm⁻¹.

2.2.2 Synthesis and characterization of SCS-Pd(II) pincers 1, 2, and 3

SCS-Pd(II) pincers **1**, **2**, and **3** were synthesized and characterized by Yu.^[50]

2.2.3 Heck reactions using 1, 2, and 3

To an argon purged 3-neck flask, iodobenzene (1.37 mmole), *n*-butyl acrylate (2.74 mmole), and Pd catalyst (molar ratio of Pd to iodobenzene = 1:350) were mixed in 5 mL anhydrous DMF with ~ 150 mg of dodecane added as an internal standard. The mixture was brought to 120 °C via an oil bath and a solution of triethylamine, NEt₃, (2.06 mmole) dissolved in 0.5 mL of DMF was added to initiate the reaction. To monitor the reaction, ~0.1 mL aliquots were taken by syringe and diluted in room temperature THF or acetone to quench the reaction. In reactions using PVPy or Hg(0), the poisons were added to the reaction flask before the argon purge.

2.2.4 Hot filtration

Filtration of reaction solutions were performed using a swivel frit (medium sized frit) connected to an argon manifold on a Schlenk line. The reaction was allowed to progress for a certain amount of time and then filtered using the swivel frit into another 3-neck flask. The filtrate was magnetically stirred and monitored for activity.

2.2.5 Sol-gel synthesis

2.2.5.1 Entrapment of PdCl₂(PPh₃)₂ in sol-gel

A literature reported procedure as described by Hamza et al. was used to entrap PdCl₂(PPh₃)₂ inside a sol-gel matrix.^[62] A mixture of 5 mL TMOS and 4 mL HPLC grade water was mixed for 1 h at room temperature to hydrolyze the TMOS. A separate solution of 30 mg of PdCl₂(PPh₃)₂ was dissolved in 11 mL of THF. After the TMOS hydrolysis, the Pd/THF solution was added. Next, 50 μL of a 0.1 M tetrabutylammonium bromide solution was added to induce gelation. After aging for 16 h the solids were recovered and subjected to boiling toluene for 1 h, filtered, dried at < 7 mTorr for 12 h, sonicated in DCM, refluxed in DCM for 30 min, and finally dried at < 7 mTorr to remove residual solvent. The final solids were yellow tinted, and final solid masses typically ranged from 2.1 to 2.3 g.

2.2.5.2 Entrapment and tethering of SCS-Pd(II) pincer inside a sol-gel

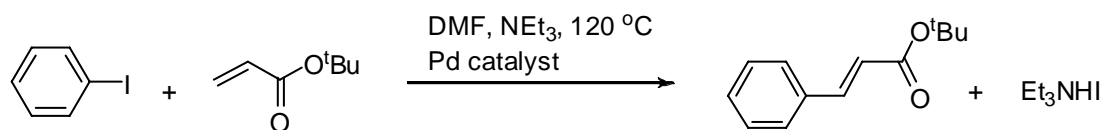
A total of 50 mg of the silane version of the SCS-Pd(II) pincer, [(MeO)₃Si(CH₂)₃(NH)(CO)(NH)(C₆H₄)(SPh)₂PdCl], was dissolved in 11 mL of dimethyl sulfoxide, DMSO, which was added to a solution of 5 mL TMOS and 4 mL water that had been previously stirred for 1 h to prehydrolyze the TMOS. The combined solutions were stirred for 2 h and 50 μL of gelation agent, tetrabutylammonium bromide, was added. The solution was stirred for 1 h, heated to 75 °C for 24 h, and finally heated to 95 °C for 36 h. The recovered solids were subjected to boiling toluene for 1 h, filtered, dried at < 7 mTorr for 12 h, sonicated in DCM, refluxed in DCM for 30 min, Soxhlet extracted with acetone for 24 h, and finally dried at < 7 mTorr to remove residual solvent. The final solids were orange tinted, which is consistent with the orange color of the SCS-Pd(II) pincer.

2.3 Results and discussion

2.3.1 Reaction activity and poisoning tests of SCS-Pd pincers

2.3.1.1 Application of poisoning tests to I

SCS-Pd(II) pincer **1** was used as the homogeneous precatalyst analog to anchored SCS-Pd(II) pincers **2** and **3** for a prototypical Heck coupling of iodobenzene and *n*-butyl acrylate (Scheme 2.3).



Scheme 2.3: Pd catalyzed Heck coupling of iodobenzene with *n*-butyl acrylate conducted at 120 °C using DMF as solvent, NEt₃ as base, and under an Ar atmosphere.

Complex **1**'s catalytic behavior under both normal Heck conditions and in the presence of poisons was evaluated (Fig. 2.1). In a Heck reaction of iodobenzene and *n*-butyl acrylate using NEt₃ as base, complete consumption (as determined by GC) of iodobenzene was observed within 15 minutes using a ratio of Pd:Iodobenzene of 1:350 as the catalyst loading. Having established **1**'s activity, tests were undertaken to probe its stability.

As discussed previously, cross-linked poly(4-vinyl pyridine), PVPy, when used in a large excess can poison catalysis by soluble Pd.^[49, 63] Before testing PVPy as a selective poison of SCS-Pd(II), the ability of molecular pyridine to poison catalysis by either binding to an intact Pd pincer or via over-coordinating soluble Pd atoms was probed (Fig. 2.1-B). The effect of soluble pyridine (300:1 pyridine to Pd) on the Heck catalysis of **1** was to moderately slow the rate of the reaction, but it still reached near complete conversion within 25 minutes. This demonstrates the possibility that pyridine sites can temporarily take up coordination sites on the Pd, which slows down access to reagents. However, the binding of pyridine to Pd is not permanent and is short lived. Would the same behavior be observed with anchored pyridines?

When the anchored pyridine sites of PVPy were added to the reaction with SCS-Pd pincer **1** at 300 equivalents of anchored pyridines to Pd, no activity was observed even up to 100 minutes (Figure 2.1-C). Why such a large difference in behavior between homogeneous and heterogeneous pyridine? The answer lies in the high local concentration of pyridine sites inside the PVPy matrix. In an analogous way that a spider web traps insects, once the Pd enters the PVPy matrix it has difficulty escaping, because even as it dissociates from one pyridine site, another pyridine site is nearby to recapture the Pd atom (Scheme 2.4). Thus, the PVPy acts as a pseudo chelating ligand, which can bind 1 to 4 coordination sites of the Pd at any given moment.

It was uncertain what form of Pd was being bound by the PVPy. Was the PVPy poisoning intact complex **1** or was it poisoning leached Pd metal? If **1** were to stay intact, then a traditional Heck reaction mechanism using a Pd(0)-Pd(II) cycle would be impossible and thus the hypothesized but experimentally unproven literature Pd(II)-Pd(IV) cycle could be plausible. Conversely, if the Pd were to be freed through decomposition of complex **1**, then it would be possible for a Pd(0)-Pd(II) cycle to operate. As discussed above, Hg(0) has been known for quite some time poison of catalytic activity for M(0) catalyzed reactions.^[58-60] To probe whether Hg(0) can interfere with known Pd(II) complexes, Pollino et al. investigated whether Hg(0) could disrupt the use of Pd(II) pincers are used as pyridine recognition sites for self assembly⁷.^[64] It was found that no disruption of the self assembly was observed when Hg(0) was

⁷ The use of Pd pincers as recognition units for self assembly is not of catalytic nature and thus a change in the oxidation state of the Pd is not expected.

added. This was taken as evidence that the Hg(0) was unable to interact strongly with the Pd(II) bound to the SCS ligand. In our laboratories when complex **1** was exposed to 300 equivalents of Hg(0) under Heck reaction conditions, complete cessation of activity was observed after 140 minutes (Figure 2.1-D). This is strong evidence that the catalysis observed using **1** involves a Pd(0) species and suggests that the activity is stemming from decomposition of **1**.

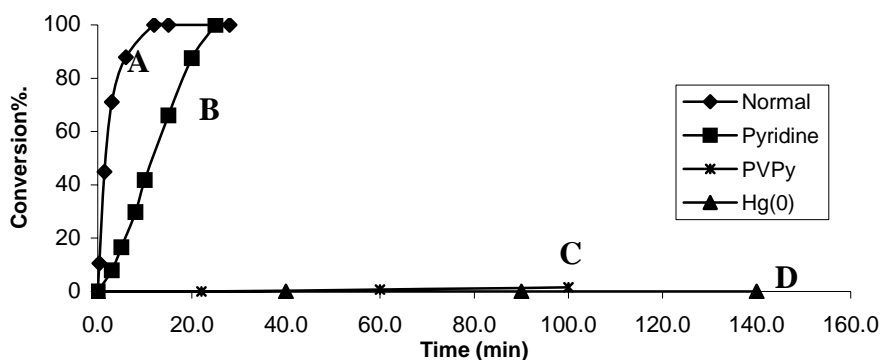
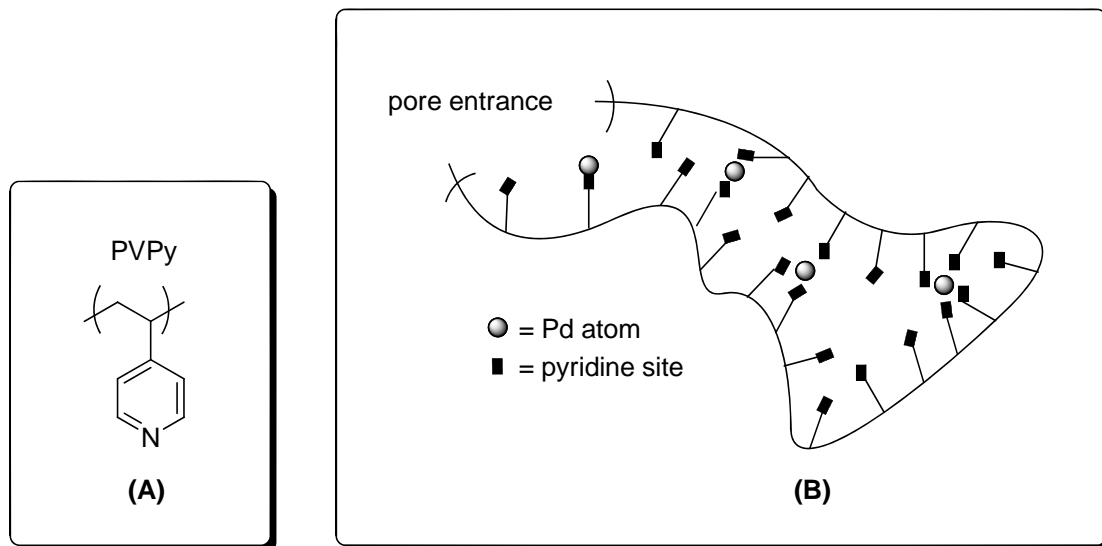


Figure 2.1 Conversion of iodobenzene in Heck couplings with *n*-butyl acrylate catalyzed by **1** using (A) no poison, (B) homogeneous pyridine at 300 equivalents pyridine to Pd, (C) PVPy at 300 equivalents pyridine sites to Pd, and (D) Hg(0) at 300 equivalents mercury to Pd.



Scheme 2.4 (A) Molecular structure of PVPy. (B) Cartoon depicting how the PVPy is envisioned to bind to Pd atoms once they enter the pore matrix of the PVPy. Pd atoms are represented by gray spheres and anchored pyridine sites are represented by black squares, which are tethered to the polymer backbone.

2.3.1.2 Application of poisoning tests to anchored Pd-Pincer

The above results strongly suggest that homogeneous complex **1** decomposes to liberate “naked” Pd species that act as the catalyst. Would the same behavior be observed for analogous Pd pincers tethered to an insoluble support? Materials **2** and **3** were synthesized and studied to answer this question.

Investigations into the activity and stability of anchored Pd pincer complexes **2** and **3** were performed under normal reaction conditions, with Hg(0) and with PVPy as poison (Table 2.1). Although slower than homogenous complex **1**, complex **2** was able to convert 93% of iodobenzene in less than 2 hours (Fig. 2.2-A). After the reaction, **2** was recovered, washed, and reused for a subsequent Heck reaction (Fig. 2.2-B). Again, a large conversion was observed, as 92% of iodobenzene was consumed in 2 h. However,

the initial rate was slower using recycled **2**. This reduction in activity is either a sign of catalyst deactivation or loss of catalyst complex and/or of metal. Elemental analysis of complex **2** after recovery from the second run showed that 6.3% of the Pd was lost from the support. This reduction in metal indicates that the drop in initial rate between the first use and the recycled use in Figure 2.2 is from leaching of Pd from the support.

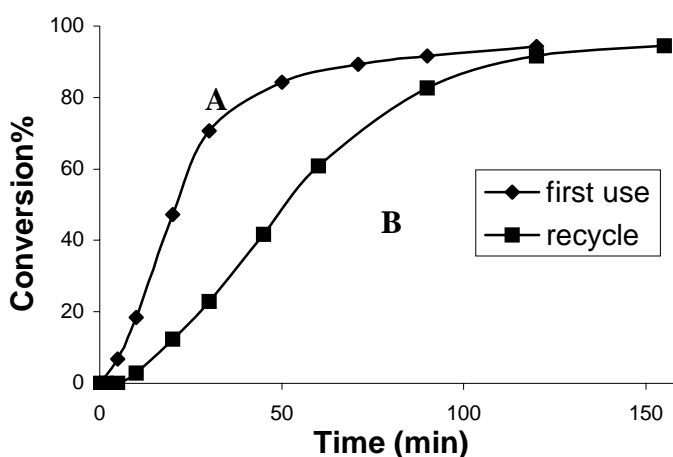


Figure 2.2 Conversion of iodobenzene in a Heck reaction with *n*-butyl acrylate using **2** as precatalyst. (A) is first use of **2** and (B) is a recycle experiment using recovered **2** from the first run.

A hot filtration experiment was conducted in which the solids were filtered off during a Heck reaction and the solid free filtrate was kept at reaction temperature. If the filtrate continues to react, this can be interpreted as strong evidence (provided there is little to know background reaction) that leaching of active metal from the precatalyst surface occurred. The reverse of this logic is that if the filtrate does not react, then the observed catalysis is from heterogeneous sites. This is how results from this test are commonly interpreted. However, in the case of Pd catalyzed coupling reactions, a lack of filtrate activity is not (on its own) strong evidence for heterogeneous catalysis, as the

solubilized metal can redeposit or become deactivated during the hot filtration process.^[31, 32, 65] This is further complicated by the observations that ppm levels of Pd have been shown to effect high levels of activity for the Heck reaction,^[66, 67] thus only a very small fraction of metal could be required for all observed activity when anchored Pd complexes are used as precatalysts. It is conceivable that the hot filtration test could disrupt the activity from such low levels of Pd in solution. After achieving 38% conversion of iodobenzene in a normal reaction using **2**, a hot filtration test was performed. Fresh reagents were added to the filtrate and the reaction continued at roughly half the reaction rate of a non filtered reaction demonstrating that some active Pd leaches from **2**. The reduced rate is due either to (i) some catalyst deactivation or (ii) removing activity associated with parallel heterogeneous catalysis when **2** is removed.

The results from both the recycle experiments and the hot filtration test are best interpreted as demonstrating that the catalysis is effected by leached, active metal but do not rule out the possibility of parallel catalysis from anchored Pd pincer sites that do not decompose. Solid PVPy should not affect catalysis stemming from truly heterogeneous sites, as the PVPy particles should not be able to enter the mesopores of **2**. Therefore if PVPy is added to a reaction catalyzed by **2**, then the catalytic pathway from leached metal should be shut down and only the heterogeneous pathway will continue. The extreme of zero catalysis with PVPy addition would strongly suggest that no catalysis can be attributed to the anchored Pd pincer complex. This is indeed the result obtained when 150 equivalents of PVPy to total Pd were added to a Heck reaction using **2** as the precatalyst. After 2.5 hours, less than 1% conversion of the iodobenzene was observed, indicating that no heterogeneous catalysis is occurring. Using excess Hg(0) with **2**

resulted in no activity as well, indicating a Pd(0)-Pd(II) mechanism, which suggests pincer decomposition and leaching of metal from the pincer sites.

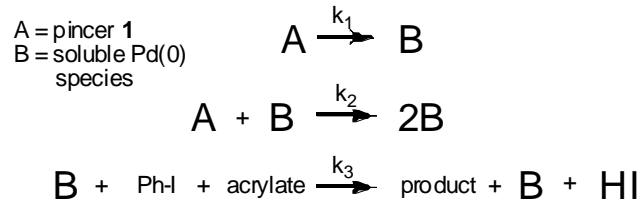
In considering the cause of leaching, we wondered if the nature of the support could promote pincer decomposition. The mesoporous silica SBA-15 support of **2** has residual silanol, Si-OH, groups that did not react during the silanation reaction when anchoring the SCS-Pd(II) pincer onto the solid. Although unlikely, we wondered if these silanol groups could aid in SCS-Pd(II) pincer decomposition. Kunquan Yu synthesized the insoluble SCS-Pd(II) Pd pincer Merrifield resin **3** as a material that would have an analogous anchored Pd pincer complex to **2**, but would be free of silanol groups or any other reactive functional groups that could interact with the Pd pincer site. The consumption of iodobenzene reached a final 88% conversion in 60 min in the Heck reaction of iodobenzene with *n*-butyl acrylate using precatalyst **3**. Both a PVPy test (150 equiv. of PVPy) and Hg(0) tests were performed on **3**. Less than 1% iodobenzene conversion was observed in the presence of PVPy after 3 h and no activity was observed when using Hg(0). Thus, **3** behaves catalytically similar to **2**, in that leached Pd is promoting catalysis. These results suggest it is unlikely that the silanol groups are causing decomposition of **2**. All results for activity and poisoning studies of **2** and **3** are summarized in Table 2.1.

Table 2.1 Summary of observations and implications of reactions using SCS-Pd(II) pincers **1**, **2**, and **3**.

Case	Precatalyst	Type of Test	Observations and Implications
i	1	Pyridine	High activity. Homogeneous pyridine cannot poison catalysis No activity. PVPy removes 1 and/or molecular Pd from solution and renders the catalytic species inactive.
ii	1	PVPY	
iii	1	Hg(0)	No activity. Catalysis is from Pd(0)-Pd(II) cycle. No activity. PVPy poisons active Pd metal, which must come from leaching
iv	2	PVPy	No activity. Catalysis is from Pd(0)-Pd(II) cycle implying pincer is decomposing.
v	2	Hg(0)	
vi	2	Hot Filtration	Activity in filtrate. Some active Pd is leached into solution. Activity is reduced. Catalyst is either deactivating or losing metal due to leaching.
vii	2	Recycle	No activity. PVPy poisons active Pd metal, which must come from leaching
viii	3	PVPy	No activity. Catalysis is from Pd(0)-Pd(II) cycle implying pincer is decomposing.
ix	3	Hg(0)	

2.3.1.2 Kinetic modeling of activity from Pd pincers

The sigmoidal kinetics observed in Figure 2.2 are potentially consistent with catalysis by Pd nanoparticles.^[58-60] Based on the work of Finke and others, catalysis by Pd nanoparticles formed *in situ* is expected to be rate limited by the formation of the Pd nanoparticles. A sequence of reactions as shown in Scheme 2.5 is expected to follow. First the Pd pincer sites on **1** (**A**) decompose to release soluble Pd(0) (**B**) in a pseudo-elementary step $\mathbf{A} \rightarrow \mathbf{B}$. This is followed by an autocatalytic surface growth pseudo-elementary step $\mathbf{A} + \mathbf{B} \rightarrow 2\mathbf{B}$ in which the metal species are added to a soluble nanoparticle. The final step is the pseudo-elementary step of the Heck reaction in which iodobenzene is combined with *n*-butyl acrylate and **B** to form product, plus acid, and **B**.



Scheme 2.5: Kinetic model of Heck coupling of iodobenzene with *n*-butyl acrylate catalyzed by *in situ* formed Pd(0) clusters from decomposition of Pd pincer **1**.

The change in concentration of iodobenzene in a Heck reaction using **1** was monitored and the kinetic model from Scheme 2.5 was applied to the data using a least-squares fit (Figure 2.3). A close match between the plots of the experimental data and the model data was found with rate constant $k_1 = 0.014 \text{ min}^{-1}$ and $k_2 = 216 \text{ M}^{-1}\text{min}^{-1}$. Such a close fit can be taken as suggestive evidence that observed catalysis from using **1** is from the formation of Pd nanoparticles. However, it should be noted that a good fit between model and experimental data does not *prove* a mechanism. It only says that the mechanism is plausible with the observed data. Indeed when the kinetic model in Scheme 2.5 is simplified by removing the pseudo-elementary autocatalytic step $\mathbf{A} + \mathbf{B} \rightarrow 2\mathbf{B}$, a similarly good fit of the data was found with k_1 six orders of magnitude smaller than k_2 . This would indicate that catalysis by molecular Pd(0) could also account for the observed behavior.

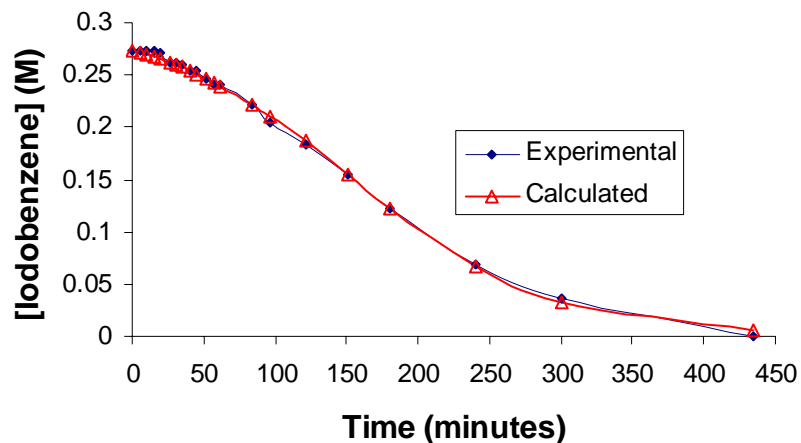


Figure 2.3 Concentration of iodobenzene with respect to time during a Heck reaction with *n*-butyl acrylate. Both experimental (blue line) and calculated (red line) data points are shown. Calculated data points are determined from using model shown in Scheme 2.5, which assumes an autocatalytic growth of Pd nanoparticles.

2.3.2 Use of sol-gels for entrapment and recovery of Pd precatalysts

During the course of studying anchored Pd pincers **2** and **3**, we wondered if the catalysis associated with leached metal was from (i) decomposition of the tether, which would liberate intact Pd pincers, or (ii) decomposition of the Pd pincer site, which would leach Pd atoms. In a previous work it was reported that entrapment of small molecule $\text{PdCl}_2(\text{PPh}_3)_2$ in a sol-gel matrix resulted in a “leach proof” catalyst.^[62] If this was indeed the case, then if the much larger Pd pincer is placed inside the sol-gel matrix should also not leach out. Furthermore, the sol-gel contains silanol sites that can be used to anchor organometallic complexes using silane condensation as was used to synthesize **2**. Thus, it was postulated that a Pd pincer could be both covalently tethered to the sol-gel support

and encapsulated at the same time. If the SCS-Pd(II) pincer tethers were to decompose during Heck reaction conditions, then *intact* Pd pincers should still remain inside the sol-gel due to physical entrapment.

With this in mind two research paths were pursued; (i) investigate the claims of “leach proof” catalysis by synthesizing and testing a sol-gel entrapped $\text{PdCl}_2(\text{PPh}_3)_2$ and (ii) synthesize and use of a Pd pincer sol-gel in which the Pd pincer is covalently tethered inside the sol-gel matrix.

2.3.2.1 $\text{PdCl}_2(\text{PPh}_3)_2$ entrapped in a sol-gel matrix

Following the procedure as described by Hamza et al., $\text{PdCl}_2(\text{PPh}_3)_2$ was entrapped in a sol-gel matrix.^[62] The final recovered solids are yellow in color, indicating the presence of the yellow $\text{PdCl}_2(\text{PPh}_3)_2$. Elemental analysis verified the presence of Pd and gave a 0.04 molar ratio of Pd:Si. The average pore size determined by N_2 adsorption⁸ was 40 Å, which is slightly higher than the 27 Å pore diameter previously reported.^[62] However, it is unclear if the 27 Å pore reported by Hamza et al. was actually measured on the Pd sol-gel or is an average number typically reported for the general synthesis of sol-gel materials. In this study the number is based on the N_2

⁸ It is not entirely clear how an “average” pore size should be interpreted for a material with a variable pore size distribution. It might be taken as a general guide to the extent of availability of sites within the pore network. However, as both the large encapsulated pores as well as the smaller connecting channels are part of the pore size distribution, the average pore size for a sol-gel gives more of a qualitative understanding of the order of magnitude of the porous matrix.

adsorption isotherm section using the BJH method. Hamza et al. did not report the method used for their pore size determination. Thus, there is some ambiguity in directly comparing pore sizes between those reported by Hamza et al. and those made in our laboratories. If the pore size differences are significantly different, then the results below may only apply to Pd sol-gel materials made in this work and not directly reflect on the materials made by Hamza et al.

A comparison of the activities of homogeneous and sol-gel entrapped $\text{PdCl}_2(\text{PPh}_3)_2$ was made using 0.2% Pd to iodobenzene in each run (Fig. 2.4 A and B). As expected, the homogeneous activity was significantly faster than the entrapped catalyst, which is most likely due to diffusion limitations of reactants and products into the sol-gel matrix *or* is quite possibly a reflection of the time required to leach Pd into solution if a leaching mechanism is also present. To test for leaching, a series of tests involving activity after recycle, hot filtration, PVPy poisoning, and Hg(0) was performed (Figure 2.4 C, D, E, and F). In the recycle tests a significant drop in activity upon recycle was observed. The first run reached 100% conversion (as determined by GC) of iodobenzene within 120 minutes, whereas only 40% conversion was observed in the recycle reaction after 200 minutes. Elemental analysis of the Pd sol-gel after the recycle experiment yielded a 0.23 molar ratio of Pd:Si, which is a 44% drop in Pd from the unused material. This indicates a substantial loss of metal due to leaching. No activity was observed in the presence of PVPy, which strongly suggests that the catalysis is occurring via leached metal and little to no catalysis is occurring within the sol-gel matrix (Figure 2.4-E). A lack of activity in the presence of Hg(0) also supports a Pd(0)-Pd(II)

catalytic cycle (Figure 2.4-F). This indicates that the $\text{PdCl}_2(\text{PPh}_3)_2$ did not remain intact. All of these observation point towards a significant amount of Pd leaching.

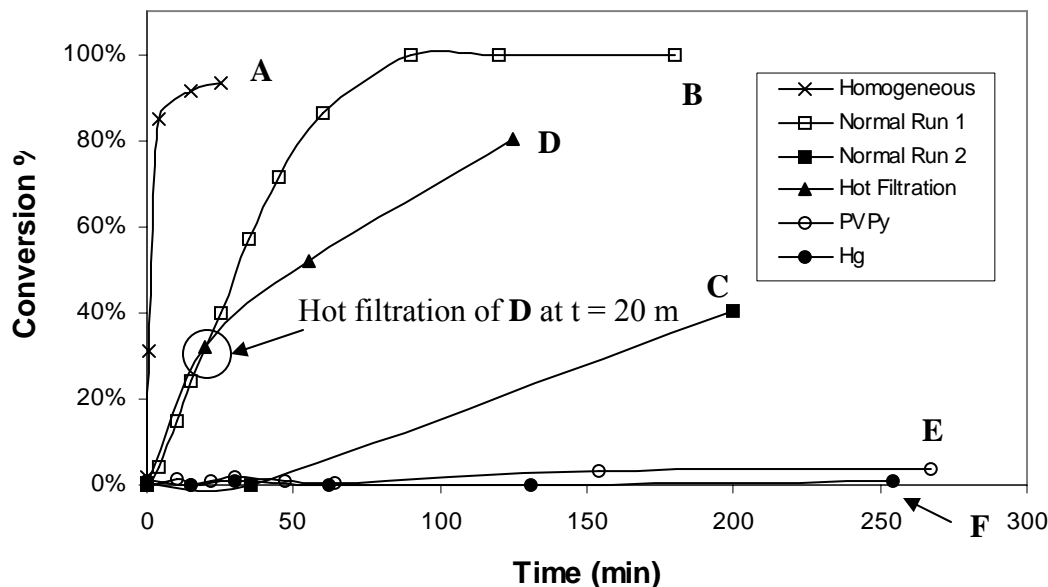
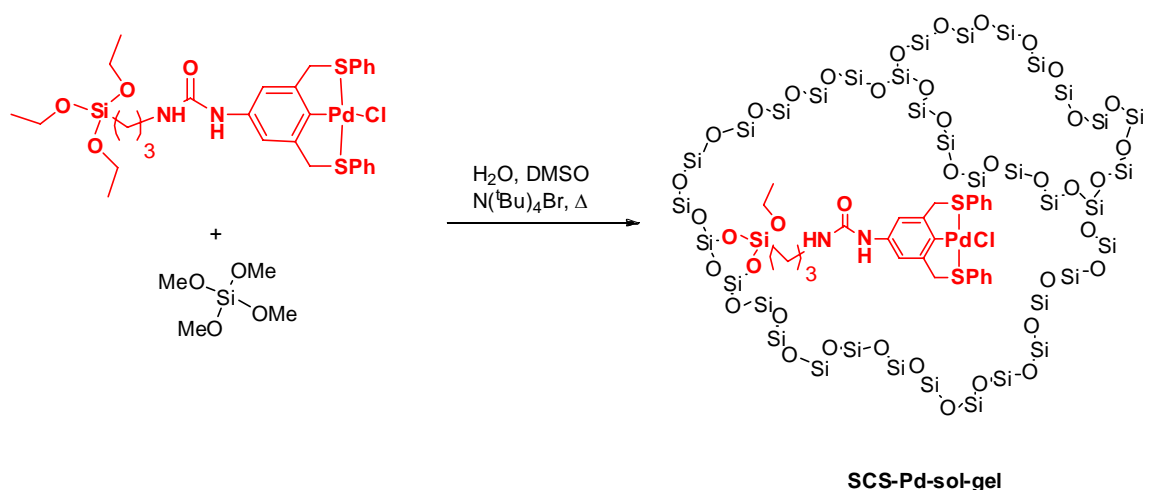


Figure 2.4 Conversions of Iodobenzene from Heck reactions using either (A) homogeneous $\text{PdCl}_2(\text{PPh}_3)_2$ or Pd sol-gel as precatalyst under a variety of conditions; (B) normal reaction, (C) run using recycled catalyst from B showing dramatic decrease in activity, (D) hot filtration experiment at $t = 20$ minutes, (E) poly(4-vinylpyridine), PVPy, poisoning showing little to no reaction, and (F) $\text{Hg}(0)$ poisoning showing virtually no reaction.

2.3.2.2 Pd pincer entrapped in a sol-gel matrix

We could find no previous reports of a Pd pincer covalently tethered and entrapped in a sol-gel matrix. Our initial attempt was to simply substitute the $\text{PdCl}_2(\text{PPh}_3)_2$ with the silane SCS-Pd(II) pincer used to make **2** (Scheme 2.6).



Scheme 2.6 Proposed method to make a covalently tethered and encapsulated Pd pincer inside a sol-gel matrix.

However, the silane SCS-Pd pincer was found to be insoluble in water and THF mixture. Thus, it could not be homogeneously dispersed during the sol-gel synthesis, which created significant doubt about whether or not the silane was co-condensing with the tetramethyl orthosilicate, TMOS. In order to dissolve the silane SCS-Pd(II) pincer, the sol-gel procedure was modified by dissolving 50 mg of SCS-Pd pincer in 11 mL of dimethyl sulfoxide, DMSO, which is more miscible in water than is THF. A solution of 5 mL TMOS and 4 mL water was stirred for 1 h to prehydrolyze the TMOS. After prehydrolysis, the pincer/DMSO solution was added to the solution of TMOS and water. The combined solutions were stirred for 2 h and 50 μ L of gelation agent was added, stirred for 1 h, heated to 75 $^{\circ}$ C for 24 h, and finally heated to 95 $^{\circ}$ C for 36 h. The recovered solids were worked up in a similar manner as the PdCl₂(PPh₃)₂ sol-gel materials with the exception that after refluxing in DCM a Soxhlet extraction with acetone was performed for 24 hours to remove any residual DMSO. The solids were

dried at 110 °C at < 7 mTorr for 24 hours before use. The final solid, SCS-Pd-sol-gel, had an orange color, which is consistent with the orange color of the SCS-Pd(II) pincer. TGA analysis of the sol-gel showed a 0.5% combustible mass loss of organic between 200 °C and 800 °C. Assuming that the Pd from the SCS-Pd pincer stays with the residual solids during the TGA test, then the molecular weight of combustible material is 529 mg/mmol. Thus the 0.5% mass loss from TGA gives an estimated loading of pincer of 0.009 mmol/g solids. Elemental analysis gave a 0.11 wt% Pd, which is a loading of 0.01 mmol Pd/g solids.

An amount of 100 mg of the SCS-Pd-sol-gel was used for a Heck reaction of 1.0 mmol iodobenzene with 1.2 mmol *n*-butyl acrylate (DMF, 110 °C, argon, and NEt₃ as base). After 425 minutes only 36% of the iodobenzene was converted. This activity was deemed unacceptably low. A second batch of SCS-Pd-sol-gel was made, but exhibited no Heck activity. To see if the Pd in this second batch was accessible to solution, the organics were burned off by calcination at 550 °C to free any Pd metal. The calcined solids were used in a Heck coupling. Again no activity was observed. This is surprising as the Pd should be available to solution and may indicate that the calcination process deactivated the Pd or caused the Pd to become inaccessible.

During the course of the study on the SCS-Pd-sol-gel, other findings in our laboratories (*vide supra*) and in the Weck laboratories here at Georgia Tech. suggested that the pincer decomposes under reaction conditions.^[68] The primary objective of the SCS-Pd pincer sol-gel study was to see if leaching from potential tether decomposition could be prevented by encapsulation. If the pincer itself is decomposing, then

encapsulation was not anticipated to be a viable method to recover the active Pd. Thus, further work on the SCS-Pd pincer sol-gel was stopped.

2.4 Distribution of work

The work in this chapter was part of a collaborative effort between that included a post doctoral researcher in our research group, Dr. Kunquan Yu. It has been reported collectively in this chapter. For the purposes of this thesis a distribution of how the work was performed is appropriate. Yu synthesized and characterized SCS-Pd(II) pincers **1**, **2**, and **3**. Both Yu and I performed the activity and poisoning studies of **1** and **2**. Yu performed the recycle and hot filtration experiments with **2**. I performed the PVPy and Hg(0) tests of **3**. The kinetic modeling and all sol-gel work was performed by me.

2.5 Conclusions

Both homogeneous SCS-Pd(II) pincers and anchored SCS-Pd(II) pincers with amide linkers effect Heck catalysis via decomposition of the pincer site. Thus the anchored SCS-Pd(II) pincers are not recyclable catalysts as the majority of catalysis is performed by leached, molecular Pd. The catalysis follows a Pd(0)-Pd(II) cycle and does not undergo a previously postulated Pd(II)-Pd(IV) cycle.^[51-57] Sol-gel encapsulation of small molecule PdCl₂(PPh₃)₂, although previously reported^[62] as “leach proof”, in our hands only effects catalysis via leaching of Pd. It is possible that differences in synthesis of the Pd sol-gel between us and Hamza et al. resulted in the observed Pd leaching. However, as the growing consensus is that catalysis from Pd(II) precatalysts forms molecular Pd(0) at some point in the catalytic cycle^[31, 32] it is unlikely that Pd atoms from

the entrapped PdCl₂(PPh₃)₂ solely remain within a sol-gel framework that is sufficiently porous to allow diffusion of reactants and products. Furthermore, it has been shown that at high temperatures phosphine ligand dissociation from Pd is more favored.^[31, 69, 70] Thus, it is unlikely that the PPh₃ ligands will stay bound to the Pd during the entire course of the reaction, which in effect makes the encapsulated Pd complex smaller and therefore more likely to diffuse out of the sol-gel.

2.6 References

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CHAPTER 3

INVESTIGATION OF POLYMER ENTRAPPED PALLADIUM(II) FOR HECK REACTIONS[†]

3.1 Introduction

In the previous chapter it was demonstrated that both (i) anchored SCS-Pd(II) pincers decompose under Heck reaction conditions and (ii) PdCl₂(PPh₃)₂ encapsulated in a sol-gel matrix acts as a reservoir for leached Pd metal. This latter finding made us wonder if the strategy of encapsulation would work for any Pd complex, especially if all Pd precatalysts simply decompose to release “naked” Pd atoms. In an encapsulating material that has small pores to allow reagent and product diffusion, the “naked” Pd atoms should also be able to diffuse out, which would defeat the main purpose using the encapsulating matrix. While working on the Pd sol-gel in Chapter 2, a commercially available polymer encapsulated palladium acetate became available. Made by Reaxa Ltd. and sold by Sigma-Aldrich, this material was claimed as a recoverable and reusable catalyst for a variety of coupling reactions. The goals of this chapter were to investigate if these claims were true as well as expand the method of selective poisoning from PVPy to another material that would serve better as a selective poison (less required material and stronger binding to Pd). The remainder of this chapter is the same as that previously

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published[†], but formatting changes have been performed to make this chapter consistent with the other chapters.

The ability to recycle and recover palladium catalysts for coupling reactions such as the Heck reaction is of great interest. Traditional heterogeneous precatalysts such as palladium on carbon (Pd/C)^[1-4] or palladium on oxides^[4-6] have been used effectively, although it has been conclusively shown in nearly all cases they operate by a release and capture mechanism, whereby soluble palladium that is the active catalyst is leached from the solid.^[4-8] After all the aryl halide is consumed, the soluble palladium can in some cases redeposit on the support. Despite numerous reports claiming palladium surface catalyzed Heck reactions, there is no conclusive proof in the literature to support them.^[8] Many other types of heterogeneous precatalysts have been prepared with a goal of achieving catalyst recovery and recycle, including Pd-loaded zeolites,^[4, 5, 9-11] silane-functionalized oxides,^[12-15] and immobilized Pd(II) complexes.^[16-24] In most cases where the authors carefully test for homogeneous vs. heterogeneous catalysis, the nature of the true active palladium species is clear,^[3-7, 8-10, 12, 13, 19-24] with it usually^[25] being leached, soluble palladium species, not supported palladium sites. However, in the vast majority of cases (primarily those not cited here), the identity of the true active species remains unclear, and routinely, only a few (often non-conclusive^[8]) control experiments are done to probe potential leaching of active or inactive palladium. Nonetheless, more often than not, new supported forms of palladium continue to be erroneously reported as recoverable, recyclable solid catalysts.

A variety of different control experiments have been applied to palladium-catalyzed coupling reactions to assess the nature of the true active species. Use of a

single test can lead to incorrect conclusions about the nature of the active species and therefore, numerous complimentary tests must be used together to gain an accurate picture of the catalysis.^[8, 26] Most often, a filtration or split test is used to analyze for palladium leaching from solid catalysts.^[27] In this case, the reaction is filtered, for example, midway through a reaction and the solid-free filtrate is monitored for reaction. This test alone, when positive (i.e. the filtrate is shown to have activity) is strong evidence that soluble species that were able to pass through the filter are active catalysts. However, a negative result from a filtration test, when conducted alone, is not sufficient proof that there are no leached active species when coupling reactions are probed. This is because of the possibility of the soluble species re-depositing on the support during the filtration, a behavior that has been observed by Lipshutz in related chemistries.^[28] Thus, while split tests or hot filtration tests are valuable tools in the chemist's arsenal for characterizing catalyst leaching, they should not be used as a sole test for heterogeneity in coupling chemistry.^[8, 26]

Elemental analysis (EA) of the filtered reaction solution by ICP-MS is another common technique to measure the amount of leached palladium, but it too is complicated by the same reasons as noted for hot filtration. Additionally, elemental analysis of the support before and after reaction is often used to quantify the amount of palladium lost, but the catalyst is often recovered via filtration and some or all of the previously soluble palladium can potentially redeposit back onto the solid during this process, thereby lowering the amount of lost palladium determined by EA. Furthermore, in many cases, the amount of leaching necessary to create soluble active species is so low,^[29, 30] the loss would not be detected by elemental analysis of the solid precatalyst before and after use

in a reaction. It should be noted that for practical application, the amount of leached palladium as determined by elemental analysis might be an extremely important parameter. However, for catalysis science, understanding of the location of the active site is critical and thus additional tests beyond EA are needed in fundamental investigations.

Similarly, recycling and reuse of a catalyst several times without loss in final *yield* is often given as proof that the catalyst is sufficiently recyclable.^[8, 31] However, it is often the case that reaction kinetics are not reported and although the final conversion might be the same for each reuse (given enough time), the catalyst activity is often significantly lower due to degradation or loss of metal. Average turnover frequencies (TOF's) can be useful for comparison, although as Beletskaya^[32] points out, these can be potentially misleading if induction periods of differing lengths exist for different samples or different runs.

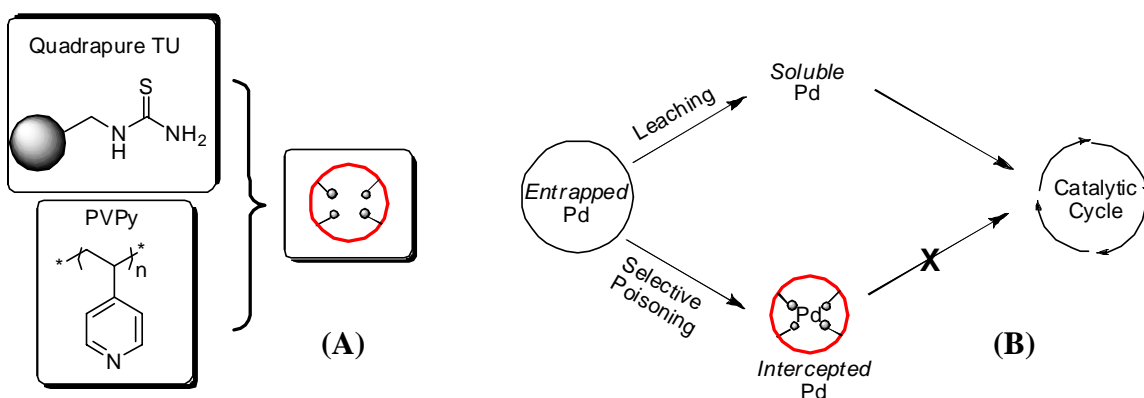
Poisoning of Pd(0) by elemental mercury is often used as a test for heterogeneous catalysis. If addition of Hg(0) to a reaction extinguishes activity, this is often viewed as a conclusive test for catalysis by metal surfaces, because this is the way the historic literature describes the test.^[33, 34] This is often the case *in the context of the original studies*. Indeed, the historic literature with the Hg(0) test focuses on hydrogenation reactions with metal complexes in elevated formal oxidation states bound by protective ligands. Certainly, these catalysts are not affected by Hg(0), as they are not M(0) species and they are protected by strong ligands. However, we hypothesize that “naked” molecular Pd(0) species that have been postulated to be the true active catalytic species in many cases^[35, 36] are an example of *homogeneous catalysts that should be affected by Hg(0)*, as a consequence of their lack of protecting strong ligands and their M(0) state.

This effect could be associated with interactions with molecular Pd(0) species, or more likely via amalgamation of the soluble palladium nanoparticles that are often present in equilibrium with active molecular palladium. Thus, we do not feel that, in the context of palladium catalyzed coupling chemistries, poisoning by Hg(0) can be taken as proof of catalysis by macroscopic or colloidal palladium particles.^[8]

The so called “three phase” test^[37-39] can be used to detect the presence of soluble catalytic palladium, whereby one of the reagents is anchored on a different solid from the catalyst and can only react if a soluble, catalytic palladium source is present (assuming negligible background reaction). This can be a powerful test, although it must be used carefully, as often one or several of the reagents are required to induce leaching of the palladium. Thus, if the immobilized reagent is the one required for leaching, one must be sure to add a soluble component as well,^[12] which can cloud the experimental results. For example, if an aryl halide is need for leaching of palladium (as is often but not always the case), soluble aryl halide must be added to the system.

It is noteworthy that all of the tests described above are capable of elucidating whether there is soluble catalysis, but none of them are capable of conclusively indicating if there is catalysis by immobilized catalytic species or a solid surface. Thus, in many contributions, authors have identified catalysis by soluble species but could not rule out some catalysis by supported sites. The Hg(0) test is capable of extinguishing catalysis by free Pd(0),^[8, 22-24, 26, 40, 41] although it is not believed that it can discriminate between heterogeneous, macroscopic palladium particles, soluble palladium nanoparticles, or homeopathic^[35, 36, 42, 43] palladium (vide supra).^[8] What is needed is a poison that is selective for leached, homogeneous species. Here we report on the use of insoluble,

cross-linked poly(4-vinylpyridine) (PVPy) and a thiourea functionalized polymer (Quadrapure™ TU) as selective traps for soluble catalytic palladium species (Scheme 3.1). These poisons are applied to the study of a relatively new catalyst system that has recently been reported as a recoverable, recyclable Pd catalyst for coupling reactions, Pd-EnCat, a poly(urea) entrapped Pd(OAc)₂ material.^[44-49]



Scheme 3.1 Selective poisons, Quadrapure™ TU and PVPy, used in this study (A) and an illustration of leaching of Pd from an entrapped matrix and then either entering the catalytic cycle or being intercepted by selective poisons (B).

3.2 Experimental

3.2.1 General

Pd-EnCat 40 (Aldrich) was purchased and used without further modification. *N,N*-dimethylformamide and *n*-butyl acrylate were dried by stirring with CaH₂ for 24 hours, distilled and stored at <4 °C until use. Isopropanol (< 50 ppm H₂O, ACROS) was

used as received and syringed under argon pressure. Elemental analyses were performed by Desert Analytics (Tucson, Arizona). All other reagents were used as received from commercial sources.

3.2.2 Heck reactions

In general iodobenzene was coupled with n-butyl acrylate in 5.0 ml of solvent at either 110 °C for DMF and toluene or 90 °C for isopropanol. Molar ratios of aryl halide, acrylate and base were 1.0:1.5:3.0, respectively, and all reactions were conducted under an argon atmosphere using standard Schlenk line techniques. Typically 60 mg of Pd-EnCat 40 or 85 mg of Pd-C were added to a 50ml 3-neck flask and a 5.0 ml solution of reagents (40:1 molar ratio of aryl halide to palladium) was added and the entire system was purged with argon. To initiate reaction the solution was immersed in a temperature controlled oil bath followed immediately by addition of a solution of base (0.5 ml of solvent) into the reaction mixture. Triethylamine was used as the base in reactions in which the solvent was DMF or toluene and tetra-n-butylammonium acetate was used as a base for reactions in isopropanol unless indicated otherwise. Time zero samples were taken just prior to base addition and conversions of iodobenzene or iodopyridine were monitored by gas chromatography and referenced to an internal standard, dodecane.^[24] A slightly different procedure was used for reactions involving iodopyridine. Reactions in which iodopyridine was used all reagents and base were stirred overnight at room temperature under argon to insure adequate dissolution of iodopyridine. Pd-EnCat 40

was then added under positive argon pressure and the solution was immediately immersed in a 90 °C oil bath to initiate reaction.

3.2.3 Poisoning studies

Poisons were either introduced prior to initiation of reactions by the addition of base or were added during the reaction sequence. Amounts of PVPy were adjusted to give 300 equivalencies of pyridine units to total palladium content. The reported palladium scavenging of Quadrapure™ TU is 0.19 mmole/g. Amounts of Quadrapure™ TU were adjusted such that double the amount required for complete scavenging all of the palladium introduced into the reaction. For example: when 60 mg (0.025 mmole of Pd) of Pd-EnCat 40 was used an amount of 250 mg of Quadrapure™ TU was added to quench the reaction. Enough Hg(0) was added to provide 300 equivalents of mercury to total palladium content and stirring was inspected to insure adequate break up of mercury.

3.2.4 Three phase test

Methacroloxypropyltrimethoxysilane was immobilized on hexagonal mesoporous silica SBA-15 with 100Å diameter pores by mixing 25 g of the silane with 4.5 g of SBA-15 in dry toluene under argon and refluxed for 24 hrs, at which point 0.4 ml of DI water was added. Reflux was continued for 4 hrs and reaction was allowed to cool and then

filtered and washed with approximately 750 ml of toluene and 500 ml of hexane. Filtered solids were then Soxhlet extracted for 72 hrs with dichloromethane. Solids were then dried under high vacuum for 16 hours. Loading of organic was determined by TGA (NETZSCH STA 409) and found to be 0.66 mmole/g. For synthesis of 100 Å SBA-15 refer to Galarneau et. al.^[66] 3-phase tests were then conducted using the acrylate functionalized silica by simply adding 500 mg of 3-phase material to a Heck reaction, similar as that described above, before the addition of base. N-butyl acrylate was excluded from all 3-phase tests.

3.2.5 Recycling and reuse of catalysts

Recovery of Pd-EnCat 40 was done by simple filtration under slight vacuum. Recovered solids were extensively washed with dichloromethane, THF and acetone, until GC analysis of the filtrate indicated no detectable amounts of reagents or products, followed by drying under high vacuum overnight. Recovered materials were stored in sealed sample vials until use.

3.2.6 Hot filtration

Hot filtration tests were conducted in which a reaction solution consisting of 163 mg of iodobenzene, 155 mg of n-butyl acrylate, 50 mg of Pd-EnCat 40, 136 mg of dodecane and 5.0 ml of solvent was preheated in an oil bath at the reaction temperature

for 25 minutes (90°C for IPA and 110°C for DMF). The hot solution was then quickly filtered under static vacuum in an inert atmosphere of argon by use of a swivel frit attached to a Schlenk line. Next, 131 mg of tri-n-propylamine, 1.2 equivalents to iodobenzene, was added to the catalyst-free filtrate to initiate the reaction, which was monitored by GC.

3.3 Results and discussion

3.3.1 Poly(4-vinylpyridine) as a poison

In our recent work on the nature of the active species using soluble and immobilized Pd(II) SCS and PCP pincer coupling catalysts, it was necessary to devise a poison that could selectively quench catalysis by soluble catalytic species while leaving immobilized sites within the pores of a silica support or on a polymer backbone unaffected.^[22-24] Recalling the use of bulky or polymeric amines as basic poisons for accessible acid sites (soluble sites or insoluble sites on the external surface of solids),^{[50,}^{51]} we surmised that such materials might work equally well for removing free Pd species from solution in coupling reactions. Indeed, it was found that the literature described that addition of a large excess of copolymers of PVPy effectively extinguished any activity associated with palladium nanoparticle precatalysts in the Heck reaction of styrene and 4-bromoacetophenone.^[52] In contrast, addition of molecular pyridine merely slowed the reaction rate. Thus, the poisoning effect of PVPy was ascribed to its ability to pull soluble Pd out of solution, binding it tightly in a multidentate manner. Another nice

example of an insoluble metal poison is polymer bound thiophenol, which was effectively used by Ley to show that palladium containing perovskites were actually sources of active, soluble palladium species.^[53]

In our work characterizing SCS and PCP Pd(II) complexes in Heck couplings, we utilized an array of tests to conclusively show that all catalysis in these systems was associated with leached Pd(0) species.^[22-24] Whereas it had been reported previously that palladacycles like the half pincer Herrmann-Beller complex decompose to give active Pd(0) species,^[20, 32, 54-58] it had never been possible to conclusively rule out small amounts of catalysis by Pd(II) or Pd(0) species that still retained the Pd-C palladacycle bond (operating in Pd(0)-Pd(II) or Pd(II)-Pd(IV) cycles).^[59] Similar results were obtained on phosphite PCP pincers at the same time we reported on decomposition in SCS pincers.^[41] Again, it was not possible to rule out small amounts of catalysis by intact metal-ligand complex in that work, although it was clear that the vast majority of catalysis was promoted by Pd(0) species (nanoparticles, it was suggested). In contrast, by immobilizing SCS and PCP pincer complexes onto insoluble porous silica supports and soluble poly(norbornenes), it was possible to conclusively show for the first time that there was effectively no catalysis by intact pincer species.^[22-24] Essentially complete poisoning of catalysis by Hg(0) and PVPy showed that only leached Pd(0) species were active. Generation of such species necessarily required breaking of the Pd-C palladacycle bond, and these supported systems were found to be simply another source of homeopathic palladium.^[35-36, 42-43]

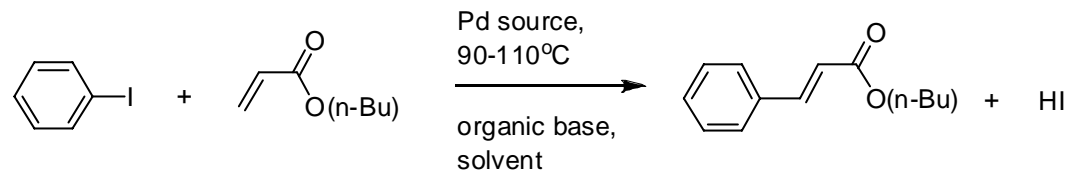
3.3.2 Entrapped Pd catalysts in coupling reactions

Palladium acetate entrapped in a poly-urea matrix is a commercially available series of catalysts sold as Pd-EnCat. It has been described as a recyclable, immobilized catalyst system that simplifies removal of Pd in C-C bond forming and reduction processes.^[44, 48, 60] As it has generally been accepted that solid precatalysts operate at high temperatures by releasing soluble palladium into solution, it was of interest to see if this precatalyst also behaved the same way. Thus, Pd-EnCat represented an interesting system for study using PVPy and Quadrapure™ TU as poisons. In particular, we focused on elucidating whether the catalysis occurs at palladium sites entrapped within the solid matrix, or whether, like other supported catalysts (Pd/C, Pd/SiO₂, etc.), these systems represented solids that released Pd into solution, where the catalysis could ultimately occur.

3.3.3 Catalytic studies

Palladium immobilized on carbon is widely known to be a source of soluble palladium for Heck couplings of iodoarenes.^[3, 6-8] We selected this as a model precatalyst to verify that PVPy and Quadrapure™ TU will quench catalysis from leached palladium species from solid sources under our reaction conditions. Figure 3.1 displays the results of the effect of PVPy and Quadrapure™ TU on the Heck coupling of iodobenzene with butyl acrylate in DMF (Scheme 3.2). Reactions were conducted at 110°C and activated by addition of triethylamine at an iodobenzene to catalyst ratio of 40:1. When 300

equivalents of PVPy *to total palladium content* were added after 15 minutes (50% conversion) the reaction slowed but did not immediately cease. When Quadrapure™ TU was used, complete loss of activity was observed. This is consistent with their use as efficient palladium scavengers. The amount of Quadrapure used was twice that required to bind all the added palladium based on the manufacturer's reported scavenging limit, 0.19 mmole Pd per gram polymer. In our previous studies, the PVPy was applied to systems where only a fraction of the total palladium content was leached into solution and thus 300 equivalencies *to total palladium content* was found to be sufficient for complete quenching. However, the fact that the Pd/C reaction is slowed upon addition of this much PVPy may suggest that the amount added was not sufficient to bind all the leached palladium. A subsequent reaction was performed in which the amount of PVPy added at 15 minutes was raised to 450 equivalents (Fig. 3.1). Complete cessation of activity was observed in this case, but not until several hours after addition of the PVPy. Thus, these initial studies confirmed that both PVPy and Quadrapure™ TU are effective poisons that can completely shut down reactivity using solid precatalysts that are known to operate by leaching of active, soluble species.



Scheme 3.2 General depiction of Heck coupling of iodobenzene with *n*-butyl acrylate. Listed conditions encompass those used in this study. Pd sources included Pd/C or Pd-EnCat 40 and solvents used were DMF, isopropanol, or toluene.

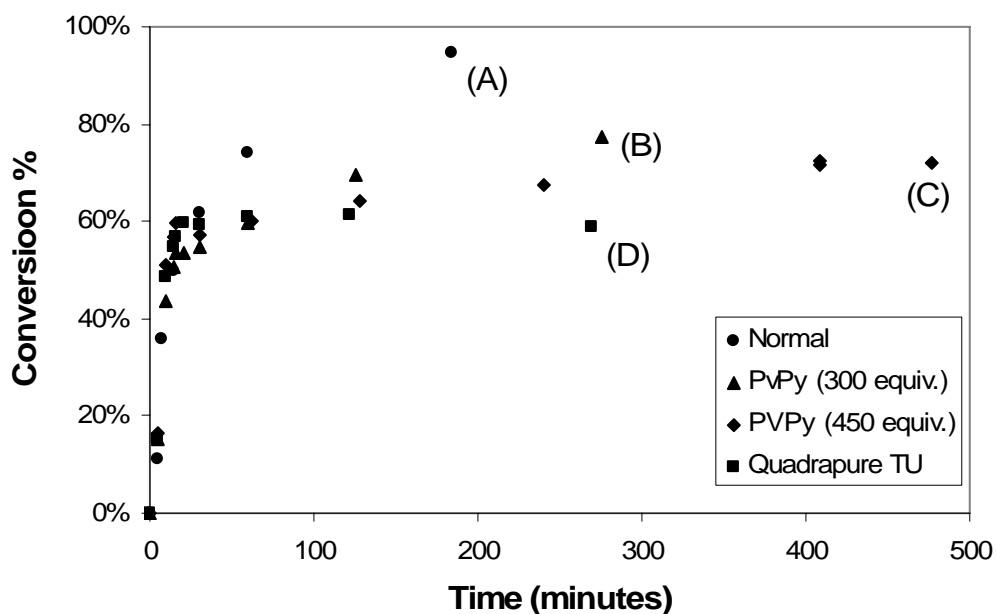


Figure 3.1 Conversion of iodobenzene as a function of time via Heck catalysis by Pd/C under normal conditions (A), with 300 equivalents of PVPy added at 15 minutes (B), with 450 equivalents of PVPy added at 15 minutes (C), and with Quadrapure™ TU added at 15 minutes (D). Reaction (A) reached full conversion by 750 minutes.

Next, we shifted our focus to Pd-EnCat 40 as a precatalyst for the Heck couplings. If leaching occurs with Pd-EnCat 40, it was expected to be less than that for the Pd/C and so the 300 equivalents of PVPy were kept constant across all reactions unless otherwise noted. Pd-EnCat 40 was purchased from Aldrich and used without further modification

in the Heck coupling of iodobenzene or iodopyridine and butyl acrylate in either isopropanol (IPA) at 90°C, toluene at 110°C, or DMF at 110°C. In all experiments with Pd-EnCat 40, a 40:1 ratio of aryl halide to palladium was used. Elemental analysis (Desert Analytics, Tucson Arizona) of the Pd-EnCat 40 showed a 4.8% atomic mass percent palladium corresponding to a palladium loading of 0.45 mmole per gram catalyst which is comparable to the 0.4 mmole per gram reported by the manufacturer. The makers of Pd-EnCat 40, Reaxa Ltd., report leaching tests of various solvents in which they stir the Pd-EnCat 40 at 80°C for two days, cool to room temp, and then filter off the catalyst, after which only ppm levels of palladium in the filtrate were measured.^[60] In the same report they also described the ability of various solvents to swell the polymer matrix of Pd-EnCat 40 at room temperature over two hours. These previous results indicated that among the three solvents selected for this study, DMF has the greatest percentage of polymer swelling and gives the most palladium in solution at 110% and 7 ppm, respectively. IPA and toluene have significantly less swelling at 5% and 0%, respectively, and both have < 1 ppm of palladium detected in solution. As the reported leaching tests were not performed under Heck reaction conditions it was difficult to determine, based on these results, how much palladium might leach during a Heck coupling. Also, it is possible that the amount of palladium in solution during the 80°C treatment was higher than that reported at the end, as the cooling step could cause palladium deposition on the Pd-EnCat 40 (via a release and recapture process akin to those observed with Pd/C) and/or formation of palladium black that is removed during the filtering process. In a separate report by Smith, it was suggested that when using Pd-EnCat 40 for Heck couplings in DMF at 200°C the catalyst acts as a slow reservoir of

soluble Pd(0) nanoparticles.^[61] Other reports described reactions performed in either IPA, supercritical carbon dioxide, or toluene as solvents.^[48, 49] When reacting in IPA, the palladium content of the crude reaction solution was the only measurement for detection of palladium leaching and a loss of 2.8% of the original palladium was reported. No other tests for leaching or tests to determine whether the reaction truly happens inside the polyurea matrix were performed, although it appears that this is a general hypothesis about how the Pd-EnCat catalyst line operates.^[60, 61]

Based on the previously mentioned results in the literature, DMF is the most likely reaction solvent to promote leaching of palladium from Pd-EnCat 40 as compared to toluene or IPA. A number of tests under varying reaction conditions were performed to verify this hypothesis. Figure 3.2 displays the results of the Heck coupling of iodobenzene and n-butyl acrylate in DMF. Two types of experiments were done, some with preheating of the catalyst and reaction solution (without base) for twenty-five minutes, followed by addition of base to initiate catalysis, and one where the catalyst and all reagents were added together and the reaction was initiated via immersion in an oil bath. Results from experiments with addition of PVPy, Quadrapure™ TU or Hg(0) at different points during the reaction are also shown. The preheated reaction progressed rapidly upon the addition of base, whereas the reaction proceeded slightly slower with a slight induction time without preheating the solution. In every case in which a known poison was used, the reaction was rapidly stopped after the addition of the poison, except for when Quadrapure™ TU was added at 3.5 minutes (10% conversion). This reaction continued until it ceased sometime between 7.5 and 10 minutes (30% conversion) and this was most likely due to a competition between the rate of reaction, which is quite fast under these conditions, and the rate of quenching by the Quadrapure™ TU. We hypothesize that once all of the leached palladium is finally bound the Quadrapure™ TU, the reaction no longer progresses. An argument could be made that in this case some

amount of reaction is still occurring inside the Pd-EnCat 40 matrix, but considering that the other reactions using PVPy essentially stop after addition of the poison, it is highly unlikely that this is occurring.

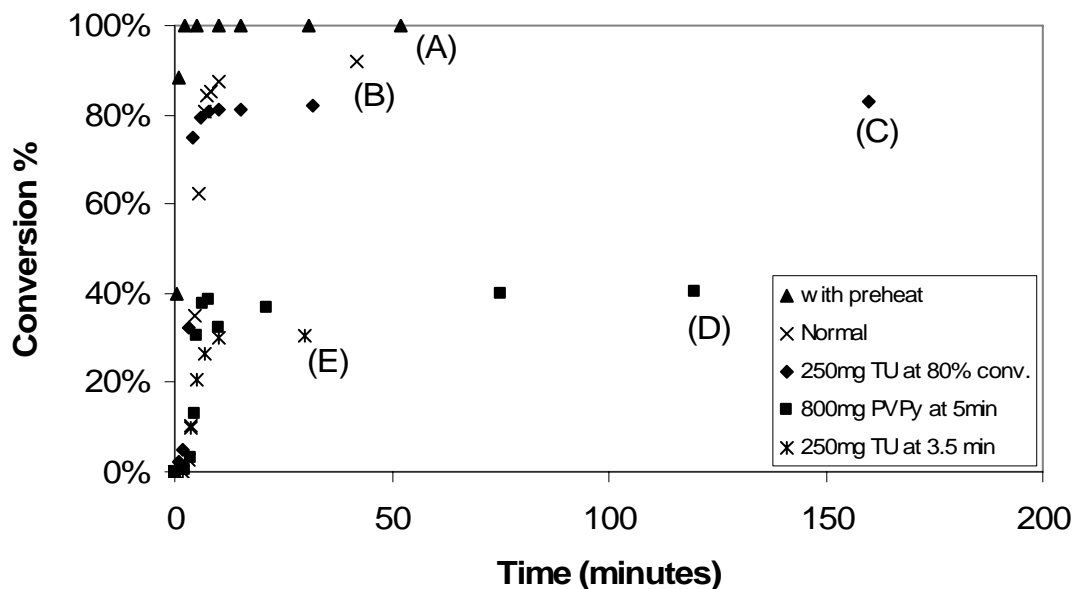


Figure 3.2 Conversion of iodobenzene as a function of time via Heck catalysis by Pd-EnCat 40 in DMF with preheat (A), under normal conditions (B), with Quadrapure™ TU added at 6 minutes (C), with 300 equivalents PVPy added at 5 min (D), and with Quadrapure™ TU added at 3.5 minutes (E).

Other tests were conducted in DMF to further probe whether or not leaching occurred. Reaction kinetics after one recycle were monitored and after a hot filtration test was performed in which the preheated solution was filtered while hot and base was immediately added to the filtrate to initiate reaction (Fig. 3.3). The decrease in reaction rate using recycled Pd-EnCat 40 indicates that some of the palladium was lost during reaction and/or was in some way deactivated. Reaction after hot filtration of the preheated solution indicates that some form of soluble palladium species was leached from the Pd-EnCat 40 and was active for Heck coupling. Elemental analysis of Pd-EnCat 40 after one reaction in DMF showed a decrease in atomic weight percent of palladium from

4.80% to 2.84%, a 41% loss of palladium. Given that some of the soluble palladium may have precipitated onto the polymer, this value should be viewed as a lower bound for leached palladium.

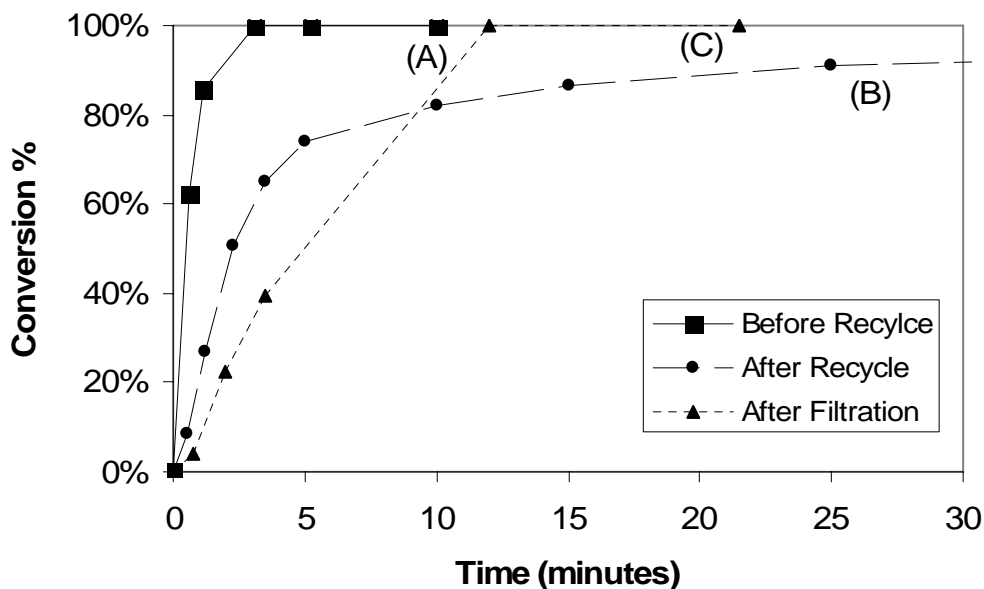
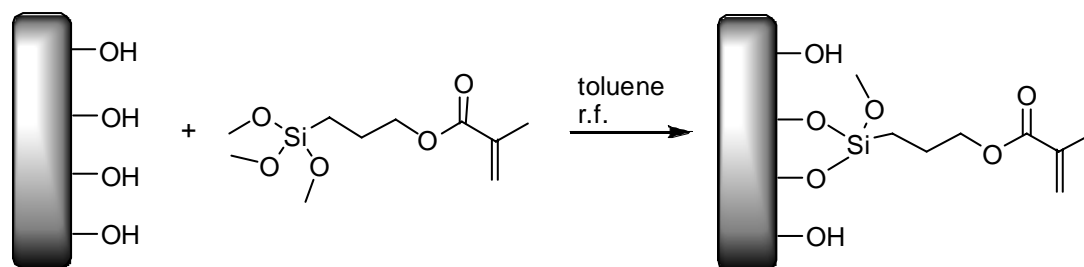


Figure 3.3 Conversion of iodobenzene as a function of time via Heck catalysis by Pd-EnCat 40 in DMF with preheated normal reaction (A), after recycle (B), and after hot filtration of the preheated solution (C).

A 3-phase test was conducted in which an acrylate, methacrolxypropyltrimethoxysilane, was immobilized on a porous silicate (Scheme 3.3). After 6.5 hours, 0.22 mmols of the iodobenzene was consumed, consistent with 73% of the initial 0.3 mmols of immobilized acrylate reacted. No presence of coupled product was detected in solution indicating negligible leaching of the acrylate from the silica. An attempt to identify solid-bound coupling product via FT-Raman analysis of the silica after reaction was inconclusive due to the low loading of organic on the silica and the difficulty in separating out the Pd-EnCat 40 from the silica particles after reaction.



Scheme 3.3 Immobilization of methacroloxypropyltrimethoxysilane on SBA-15 for use as 3-phase material in Heck catalysis.

Some additional observations of the Heck reactions in DMF also indicate the presence of soluble palladium. During the pre-heating of the solution (before activation by base) a significant color change of the solution was observed in DMF from clear to dark pinkish (also observed with Pd/C). Additionally, the Pd-EnCat 40 particles changed from reddish-orange to black. In contrast, no solution color change was observed in most reactions involving IPA, although the catalyst particles changed color as they did in DMF.^[62] The solution color changes attributed to Pd-EnCat 40 may be due to leaching of a significant amount entrapped palladium during the pre-heat in DMF.^[63] In the case of IPA, either not enough palladium is leached to cause a noticeable color change, the leached palladium is quickly deactivated by formation of palladium black or no palladium is leached during the preheat step. The blackish color change of the particles, which remains after the reaction and recovery of the particles, is consistent with formation of Pd(0). As this might be indicative of formation of palladium black on or inside the particles, a potential deactivation pathway, preheating the solution was only used for a limited number of reactions. After addition of either PVPy or Quadrapure™ TU to reactions in DMF using either Pd-EnCat 40 or Pd/C, the pinkish tinge disappeared, signifying removal of most if not all palladium from solution.

As noted previously, Heck couplings of various substrates with n-butyl acrylate in IPA were reported previously^[48] and leaching was reported to be more limited in this

solvent than in DMF.^[60] To this end, poisoning tests using Hg(0) and PVPy in IPA were performed on this system. Similar to the results reported above for reactions in DMF, the activity in IPA ceased after either Hg(0) or PVPy was added to the reaction (Fig. 3.4). Additional Heck couplings in IPA were performed with iodobenzene and n-butyl acrylate using two different bases, triethylamine or tri-n-propylamine. Addition of PVPy or QuadrapureTM TU to these reactions also resulted in a cessation of activity (Fig. 3.4). The results from these reactions performed in IPA indicate that all of the catalysis is performed via leached palladium. A hot filtration test (as was previously described for a pre-heated DMF solution), was performed with IPA as the solvent and iodobenzene as the aryl halide. Unlike in the case of DMF, where significant activity was observed in solution after addition of base, no reaction was observed in IPA. Since the filtration was of the pre-heated solution that was missing base, it is likely that the leaching only likely takes place after addition of base in this case, as leaching of Pd upon heating with pure IPA^[60] or with solvent and some reagents did not seem to occur. However, the reaction poisoning by QuadrapureTM TU or PVPy is interpreted as being consistent with all catalysis occurring via leached active palladium species.

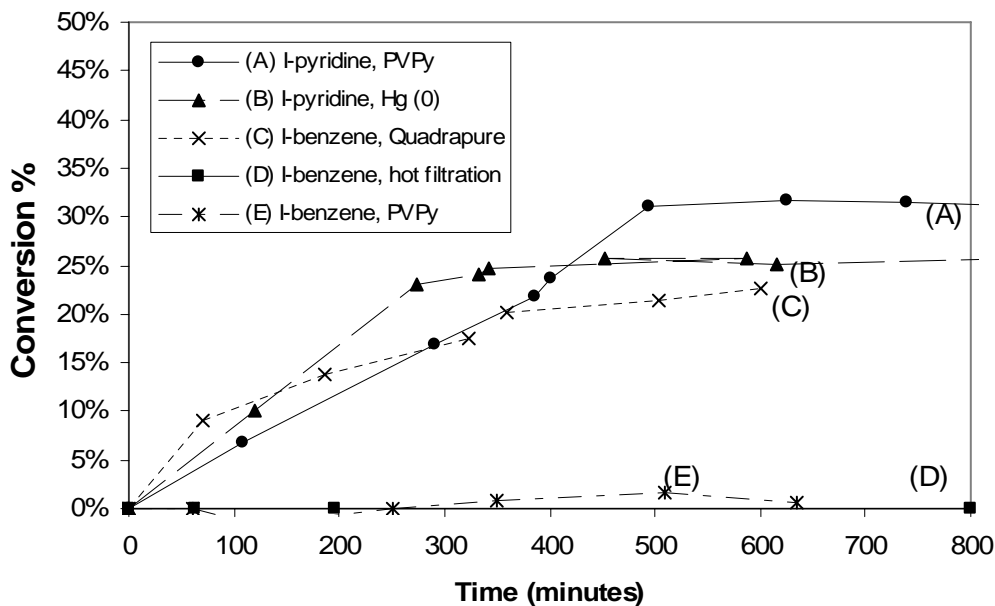


Figure 3.4 Conversion of iodopyridine as a function of time via Heck catalysis by Pd-EnCat 40 in isopropanol with 300 equivalents of PVPy added at 400 minutes (A), with 300 equivalents of Hg(0) added at 342 minutes (B). Conversion of iodobenzene as a function of time via Heck catalysis by Pd-EnCat 40 in isopropanol after adding Quadrapure™ TU at 350 minutes (C), after filtration of preheated solution (D), with 300 equivalents of PVPy added prior to start of reaction (E).

A series of reactions was also performed using toluene as a solvent. Reaction data with and without use of poisons are shown in Figure 3.5. Similar to when IPA was used, the reactions in toluene proceeded significantly slower than reactions performed under similar conditions in DMF. Observations regarding quenching by PVPy, Quadrapure™ TU, or Hg(0) are the same in toluene as was noted for DMF and thus the same conclusions apply, that all of the catalysis occurs via soluble palladium outside of the Pd-EnCat 40 matrix. This is further supported by a 3 phase test in which 0.12 mmols of iodobenzene was consumed in 6.5 hours when using the immobilized acrylate.

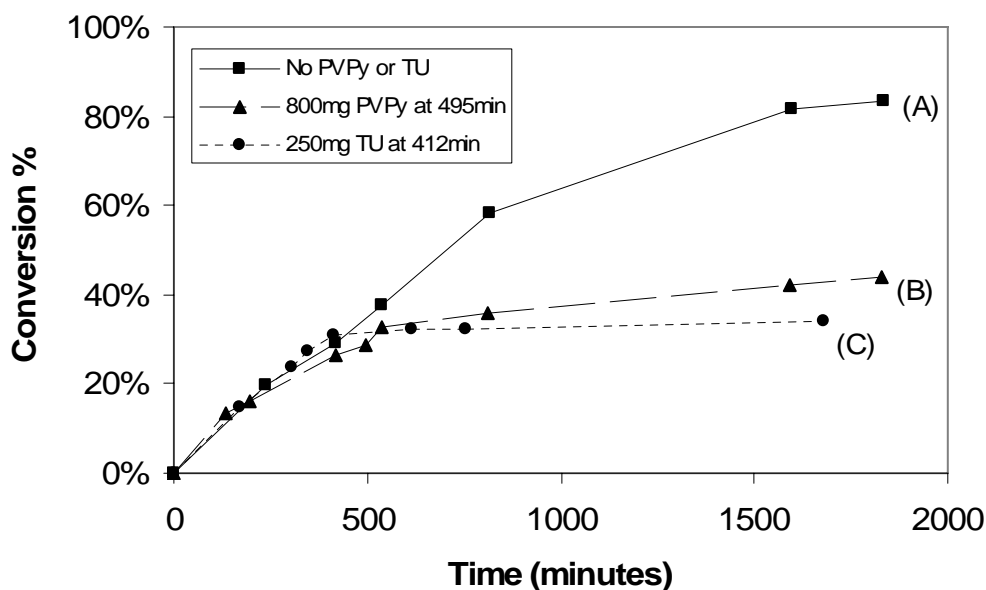


Figure 3.5 Conversion of iodobenzene as a function of time via Heck catalysis by Pd-EnCat 40 in toluene under normal conditions (A), with 300 equivalents of PVPy added at 400 minutes (B), and with Quadrapure™ TU added at 15 minutes (C).

Thus, in all solvents tested, Pd-EnCat 40 appears to be a reservoir for soluble, active palladium species that catalyze the reaction in solution under these conditions. Essentially no reaction appears to occur in the polymer matrix. These results are wholly consistent with those seen with more traditional palladium metal particle precatalysts such as Pd/C or Pd/Silica.^[3-10] Furthermore, it appears that the rate of reaction may correlate with the amount of palladium that is leached and stabilized in solution. Significant palladium leaching was observed when using DMF, which gave by far the highest rates. Use of IPA or toluene did appear to cut down on palladium leaching, making these potentially useful precatalysts as was previously reported,^[60] but these solvents severely reduced the reaction rate as well. Indeed, the averaged TOFs in IPA and toluene were 50 times lower than in DMF. These lower reaction rates may be a consequence of limited stabilization of leached palladium in IPA and toluene, or perhaps due to low levels of leaching in these solvents. It should also be noted that

substrate:catalyst ratio has a strong impact on the reaction rates and the relatively low substrate:catalyst ratio used here (40:1) may account for the markedly lower rates seen here in all solvents compared to previous reports.^[36]

The Pd-EnCat line has been reported to mediate a variety of different catalytic reactions while facilitating recovery of the palladium after reaction.^[44, 48, 60] While this report suggests that the activity associated with this precatalyst is completely derived from leached palladium species in the Heck reaction (and likely in other coupling reactions involving aryl halides as well), it does not necessarily imply that for all the other chemistries, the reaction cannot or does not occur within the polymer particles.

3.4 Conclusions

Under the reaction conditions studied, both cross linked poly(4-vinylpyridine) and QuadrapureTM TU are effective poisons of active soluble palladium species in Heck reactions. They have been successfully used for the detection of leached, active palladium from both Pd/C and from a poly(urea) encapsulated Pd(OAc)₂ during the catalysis. Results of this study also indicate that in the case of the polyurea encapsulated palladium, negligible reaction occurs inside the matrix as compared to that in solution from leached palladium when DMF, IPA, or toluene is used as the solvent. As noted in previous works,^[48, 49, 60, 61] careful choice of solvent allows Pd-EnCat 40 to be an effective *precatalyst* in Heck coupling reactions, as it limits the amount of soluble palladium that is generated, leading to reaction products potentially containing very little palladium. However, in doing so, the reaction rates are suppressed, as it appears that only leached palladium participates in the catalysis. It should be noted that after submission of this work, a careful, comprehensive study by Broadwater and McQuade

appeared that reached similar conclusions with regard to leaching of palladium from other Pd-EnCat catalysts under Heck and Suzuki conditions.^[64] Using 3-phase tests and TEM analysis they showed that leaching of catalytically active palladium was occurring, but they could not determine whether any catalysis was occurring inside the Pd-EnCat matrices. The absence of such activity was demonstrated here. We suggest that other metal scavengers could be similarly applied as selective poisons to other heterogeneous precatalysts for distinguishing whether or not leaching is occurring. However, it should be pointed out that a range of tests is needed to probe how much poison is required in each case, as catalysis can still occur if an insufficient amount of poison is added. Performing complimentary tests such as studying kinetics after recycle, hot filtration, and 3-phase analysis is advised as well.^[8] Ultimately, the reactivity of the Pd-EnCat 40 fits perfectly the trends described previously in the literature, with essentially all precatalysts (whether they be supported^[3-6], soluble^[32, 35, 42], or “entrapped”^[47,48]) giving active soluble ligand-free palladium when using high temperatures and aryl iodides as reagents^[8, 36, 65] in the Heck reaction.

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CHAPTER 4

INVESTIGATION OF ANCHORED PALLADIUM(II) ON SUPPORTED THIOLS FOR HECK AND SUZUKI REACTIONS[†]

4.1 Introduction

Chapters 2 and 3 presented findings on anchored Pd via tethered organometallic Pd complexes and findings on encapsulated small molecule Pd complexes. In all cases it was concluded that observed catalysis was from leached Pd and not from heterogeneous Pd. As part of these investigations, we also increased the understanding of using the selective poisoning test as way to distinguish heterogeneous from homogeneous catalysis. Up until this point only Heck reactions had been considered, and only polymer based materials had been used as selective poisons. The present chapter investigates Pd anchored on *previously tethered*, simple thiopropyl ligands as a precatalyst for both Heck and Suzuki reactions. Thus, the reaction scope of this thesis work is now expanded to include reactions between aryl halides and phenyl boronic acids. We also studied the use of the same thiopropyl modified silica as a selective poison for both Heck and Suzuki reactions, thereby expanding the class of selective poisons to include silica based materials. At first glance this may seem as paradoxical to the use of this thiol material as a support for catalytic Pd. Indeed, this strategy was chosen to answer some ambiguity in

[†] This work was previously published, J.M. Richardson and C.W. Jones, *Journal of Catalysis* **2007**, 251, 80.

the literature regarding whether or not supported thiols could be used as supports for heterogeneously active Pd (*vide infra*). The goals of this chapter are to investigate whether supported thiols can be used to (i) anchor catalytically active Pd for Heck and Suzuki reactions and (ii) used to selectively poison homogeneously active Pd for Heck and Suzuki reactions. If conditions (i) and (ii) were met, then we sought to understand why the same thiol modified silica could be catalytically active when metalated with Pd, but could also poison catalysis from homogeneous Pd. The remainder of this chapter is the same as our original publication, but formatting changes have been performed to make this chapter consistent with the other chapters.

Palladium catalyzed carbon-carbon coupling reactions, such as the Heck^[1] and Suzuki^[2] reactions represent an extremely important class of chemical transformations. A multitude of soluble and immobilized palladium precatalysts have been developed that are active and selective, but complications for commercial operations exist due to high metal cost and stringent requirements for removal of residual metal from exit streams. For example, palladium catalyzed reactions are often used by pharmaceutical companies in the synthesis of medicinal molecules and must meet government requirements of less than 5 ppm residual metal in product streams.^[3] These cost and purification pressures have spurred a large amount of research in two distinct areas; (i) development of highly active homogeneous catalysts which are active at ppm metal concentrations or (ii) immobilization of palladium such that it can be recovered and reused.^[4, 5]

The quest for a commercially viable, highly active, recoverable, and reusable palladium catalyst for Heck and Suzuki reactions is still ongoing despite the vast number of attempts and strategies employed to date. Despite the many claims of heterogeneous

catalysis by supported palladium, when more rigorous testing is undertaken, it is most often found that the true active species are from leached metal.^[5-17] In fact, in a thorough review of the literature, we have asserted that there is no direct evidence for a truly heterogeneous palladium Heck or Suzuki coupling catalyst based palladium nano or macroparticle catalyzed turnovers.^[5] However, many authors do not attempt to assess the nature of the truly catalytic species and instead appear to assume the form of palladium added to the reactor is the active catalyst. When authors do utilize various reaction tests to attempt to discern the location of the active species (i.e. leached palladium vs. solid phase palladium), results can be easily misinterpreted. This is because many of the tests historically employed to discern heterogeneous catalysis and recyclability, such as hot filtration and comparing final yield after recycle, give ambiguous results *for Pd(0) catalyzed coupling reactions*.^[5] This is due to three facts; (i) even trace amounts of soluble palladium metal can be very catalytically active^[11, 18-21], meaning only ppm of palladium need to leach to effect the catalysis, (ii) that multiple deactivation pathways exist for soluble palladium including re-deposition on supports, formation of palladium black, and over-coordination by strongly binding ligands, and (iii) due to leaching and deposition (especially once all the aryl halide is consumed) the palladium can be partitioned among different solid phases as well as in solution.^[22-24] The lifetime of active palladium species are therefore very sensitive to reaction conditions and to manipulations of the reaction solution both during and after catalysis. Commonly used heterogeneity tests must be carefully interpreted and supported by other methods. In previous studies we have introduced solid selective poisons to show that Pd(II) immobilized by pincer ligands^[12, 25, 26] and Pd(II) encapsulated in a polymeric matrix^[9]

are not heterogeneous catalysts, but are simply reservoirs of leached active palladium. In two recent reviews we suggested that immobilized thiols metalated with palladium warranted further investigation as a class of heterogeneous palladium precatalysts for C-C coupling reactions^[5, 27], as some authors have asserted that they leach active species while others claim they give truly heterogeneous catalysts (*vide infra*).

Thiol modified surfaces have been previously metalated with palladium and used for Heck and Suzuki reactions. Li and Jiang immobilized 3-mercaptopropyltriethoxysilane on a silica surface and then metalated with either palladium acetate or H_2PdCl_4 .^[28] These materials were then used in the Heck coupling of iodobenzene with various olefins. Tests for heterogeneity included recycling the catalyst three times and comparing final yields. Wang and Liu used polymers containing bidentate mercapto-hydroxyl ligands, which were metalated with palladium acetate, adsorbed onto silica, and used in Heck couplings.^[29] Leaching of palladium was detected and attributed to reduction of Pd(II) by the olefin followed by oxidative addition of the aryl halide. The palladium in the post reaction solution could be recovered by centrifuging away the precatalyst material and then adding non-metalated support material to scavenge the leached metal, which was successfully used in a subsequent Heck reaction. The authors also pointed out those materials with S:Pd ratios above 6 exhibited no catalytic activity.

Cai, Song, and Huang condensed 3-mercaptopropyltriethoxysilane with fumed silica and metalated with Pd(II) chloride, which was reduced to Pd(0).^[30] This material was used as a precatalyst for the Heck reaction of aryl iodides with styrene and acrylic acid. Heterogeneity was implicitly tested by studying the activity upon two successive

runs, which only decreased in activity by 3% each time. Later the same authors reported the synthesis of a similar material metalated with Pd(PPh₃)₄, which was used for a Sonogashira coupling with Cu(I) iodide as cocatalyst.^[31] Choudary et al. synthesized a bifunctional catalyst by tethering 3-mercaptopropyltrimethoxysilane to a silica gel surface and then partially reacted the thiols with a cinchona alkaloid.^[32] The material was metalated with Pd(II) chloride, which was assumed to only bind with the thiols, and the cinchona alkaloid was metalated in situ with OsSO₄. Heterogeneity tests of the catalyst were performed by testing activity of filtrates both from partially converted solutions and after addition of fresh reagents to completed reactions.

All of the above mentioned publications suggested that palladium can be bound to an immobilized thiol surface and then used as a precatalyst for Heck reactions. However, the two primary tests used to prove or suggest heterogeneity, hot filtration and final yield after recycle, may be ambiguous (*vide supra*) and are not conclusive.^[5] Up until the point of these publications (2002), the question had been unanswered as to whether catalysis from metalated, immobilized thiols is a result of leached or bound metal. To further complicate things, three more detailed, recent reports using similar precatalysts suggest different types of active species (two claim truly heterogeneous catalysis, while one claims all catalysis is from leached species), as noted below.

In 2004 Shimizu et al. reported a careful and detailed characterization of a mesoporous silica, FSM-16, grafted with 3-mercaptopropylsiloxanes and metalated with palladium acetate to form Pd-SH-FSM.^[33] This was the first work to confirm that the majority of Pd atoms are bound to two sulfur atoms and are in a Pd(II) oxidation state on these types of mercaptopropyl-modified silica supports. Pd-SH-FSM was used as a

precatalyst for both Heck and Suzuki reactions of activated bromides. The bulk of the reactions studied were Suzuki couplings, whereby the Pd-SH-FSM was reported as active, recoverable and recyclable. EXAFS data indicated that the majority of the palladium was still bound to thiols after the reaction and no detectable amount of palladium nanoparticles were observed in TEM. Only 0.05 % of the bound Pd was found in the filtrate after reaction, and truly heterogeneous catalysis was asserted. However, as palladium can redeposit once aryl halide is consumed^[22, 34, 35] and only traces of Pd are needed for high activity under some conditions, this is a lower bound on the amount that could have been in solution during the reaction. Under Heck conditions only 0.01% of Pd was reported to have leached, but in this case small nanoparticles (2-14 nm) were observed by TEM, the appearance of which is suggestive of palladium leaching followed by nanoparticle formation and redeposition onto the support. EXAFS and XANES data indicated that the majority of the Pd was similar to that of the fresh catalyst. Tests for heterogeneity included hot filtration, in which the authors used *10 times less* initial palladium (0.1%) than standard conditions (1.0%), after which no activity was observed. The Pd-SH-FSM catalyst was recycled up to five times without loss in productivity (based on final yield). However, careful comparison of the kinetics between the first and fifth run show a dramatic decrease in the initial rate of reaction after recycle. The combined data from this report were interpreted as supporting the hypothesis that the thiol-supported palladium was a heterogeneous catalyst.

Also in 2004, Crudden et al. studied mercaptopropyl-modified SBA-15, both co-condensed and post grafted with 3-mercaptopropyltrimethoxysilane, both of which were metalated with palladium acetate.^[36] The majority of the reactions tested involved

Suzuki couplings of either aryl bromides or aryl chlorides, but a smaller number of Heck couplings were also performed. It was found that only the co-condensed material exhibited effective catalytic behavior (S:Pd = 4:1) whereas the grafted material was inconsistent, with the majority of the prepared materials showing no activity. A significant achievement was the ability to catalyze the Suzuki reaction of chloroacetophenone (2 mol% catalyst, H₂O as solvent) with phenyl boronic acid, with the reaction proceeding to 93% (yield = 80%) at 80 °C and 99% (yield = 96%) at 90 °C. To test for heterogeneity for the Suzuki reaction, the activity of a small amount of soluble palladium acetate (0.5 ppm) was measured. Only 5% conversion of bromoacetophenone with phenylboronic acid was achieved as compared to 99% with Pd-SH-SBA-15. This was taken as evidence that the ppm levels of thiol-ligand-free palladium leached from the Pd-SH-SBA-15 could not have been the source of catalysis. A hot filtration test was also performed with only a small amount of conversion observed in the filtrate. Lastly, a three phase test^[37, 38] was performed in which an aryl bromide or aryl chloride was immobilized. Soluble aryl halide was added and conversions of both soluble and supported reagent were estimated. The majority of soluble reagent was consumed, however only small amounts of surface bound reagent were converted in some cases. Thus, in this case, the combined data also supported the conclusion that the vast majority of catalysis was from surface bound palladium. Later reports further strengthened the findings, describing these materials as “leach-proof catalysts.”^[39]

In contrast, another report suggested exactly the opposite – that all catalysis associated with thiol-supported palladium species was associated with leached, soluble species.^[40] In this 2005 contribution by Ji, Jain, and Davis, the Heck reaction of

iodobenzene with n-butyl acrylate in DMF with triethylamine as base were investigated using both Pd(II) and pre-reduced Pd(0) forms of the mercaptopropyl-silica supported precatalyst. The authors performed a variety of tests to determine whether catalysis was heterogeneous or from leached metal. In the presence of insoluble poly(4-vinylpyridine) (2% cross-linked) (PVPy) almost all catalytic activity was ceased. A series of hot filtration experiments were conducted, and in contrast to previous works, a significant amount of activity was observed for filtrates free of solid precatalysts. In the case of Pd-SH-SBA-15 after one hour the conversion of the filtrate (76%) was nearly the same as the regular reaction (80%). The authors found that iodobenzene was required for leaching of active palladium, which implies that oxidation of immobilized Pd(0) is a cause of leaching. This is consistent with previous observations that aryl iodides can pull Pd(0) into solution from Pd(0) nanoparticle surfaces.^[6, 11, 14, 41] Lastly, effluents from a continuous reaction system were found to be catalytically active confirming the presence of leached active metal. The final conclusion was that activity of Pd-SH-SBA-15 for the Heck reaction under these conditions is solely from leached palladium.

Shimizu, Crudden, and Davis each studied similar types of palladium immobilized catalysts using mercaptopropyl-modified silicas as supports but under markedly different conditions from each other (Table 4.1). Conclusions differed as to whether the catalysis was from supported or leached metal. In each case, the conclusions drawn by the authors appear reasonable based on the data presented. Unfortunately, a direct comparison of the results is difficult due to variations in reaction conditions from author to author. Shimizu and Crudden primarily looked at Suzuki reactions with activated bromides whereas Davis focused on Heck reactions of iodobenzene. The more

general question as to whether mercaptopropyl-modified materials can act as a supports for heterogeneous catalysis for both Heck and Suzuki reactions is still unanswered.

Table 4.1 Summary of results obtained using mercaptopropyl-modified silica materials as supports for Pd(OAc)₂ precatalysts in Heck and Suzuki couplings.

Author	Solvent		Halide		2 nd Reagent		Base		Catalysis	
	Heck	Suzuki	Heck	Suzuki	Heck	Suzuki	Heck	Suzuki	Heck	Suzuki
Shimizu Pd-SH-FSM-16 (S: Pd = 2.8)	NMP (403 K)	DMF (403 K)	4- bromoaceto phenone	4-bromoanisole 4-chlorobenzene 4-chloroacetophenone	ethyl acrylate	PhB(OH) ₂	KOAc	K ₂ CO ₃	surface	surface
Crudden Pd-SH-SBA-15 (S: Pd = 4)	DMF (393 K)	DMF H ₂ O DMF/H ₂ O (353 K, 363 K, 373 K)	4- bromoaceto phenone	4-bromotoluene 4-bromoanisole 4-bromobenzaldehyde	styrene	PhB(OH) ₂	NaOAc	K ₂ CO ₃	surface ^a	surface
Davis Pd-SH-SBA-15 (S: Pd = 1.6)	DMF (353 K, 373 K)	N/A	Ph-I	N/A	<i>n</i> -butyl acrylate	N/A	NEt ₃	N/A	leached	N/A

^a Surface catalysis is implied Heck reactions in ^[36] and more explicitly stated in ^[39] where catalysis is claimed as “leach-proof.”

To this end, here we report on the use of a mercaptopropyl-modified silica, SH-SBA-15, as a tethered ligand for palladium and introduce its use in unmetalated form as a selective poison of soluble, active palladium. Metalation with palladium acetate yields an immobilized palladium precatalyst, Pd-SH-SBA-15, which was used for Suzuki and Heck reactions under the same conditions reported by Shimizu^[33], Crudden^[36], and Davis^[40] both with and without SH-SBA-15 added as poison. In all cases in which bare SH-SBA-

15 was used as poison, no catalysis was observed. This is quite remarkable as SH-SBA-15 is the *exact same material* used as the catalyst support and should not affect the catalysis occurring from truly heterogeneous palladium species on separate but identical particles. Thus, our poisoning results strongly suggest that under all conditions tested here, catalysis is solely associated with leached palladium species. Poisoning by SH-SBA-15 also implies that the active soluble catalytic species is not from nanoparticle surfaces but rather from molecular or dimeric palladium, which is consistent with the work of de Vries^[20, 42, 43], Schmidt^[24], Rothenberg^[44] and Fiddy.^[45]

4.2 Experimental procedure

4.2.1 General

All organic materials were purchased from commercial sources. Palladium on carbon (10 wt%), QuadrapureTM TU (thiourea functionalized polystyrene, 3.3 mmole/g), and 3-mercaptopropyl-functionalized silica gel (1.2 mmole/g) were purchased from Sigma Aldrich and used without further treatment. *N,N*-dimethylformamide and butyl acrylate were dried with calcium hydride for 24 hours, distilled under an argon atmosphere and stored at 278 K until use. Acetone used for metalations was dried over sieves for 24 hr at room temperature, distilled under argon atmosphere, and stored in a N₂ dry box (Plas Labs, Lancaster, MI). Nitrogen physisorption was performed using a Micrometrics ASAP 2010 with pore size distributions determined using the BJH method applied to the adsorption isotherms. Surface areas from N₂ physisorption were determined using the

BET method. Hexagonal ordering of the mesopores was verified X-ray diffraction (PANalytical X'Pert PRO) using Cu K- α radiation. Loadings of organically modified supports were determined from simultaneous thermal analysis (NETZCH STA 409 PG Luxx) and verified by elemental analysis (Desert Analytics, Tucson, Arizona). Organically modified silica materials were stored in a N₂ dry box to prevent moisture adsorption. FT-Raman analyses were performed on a Bruker FRA-106 with 1028 scans collected for each sample with a 100 kW laser source. Gas chromatography was performed on a Shimadzu GC-17A equipped with a flame ionization detector and a HP-5 column. The column treatment program was the same as previously reported.^[12]

4.2.2 Synthesis of organically modified mesoporous silica

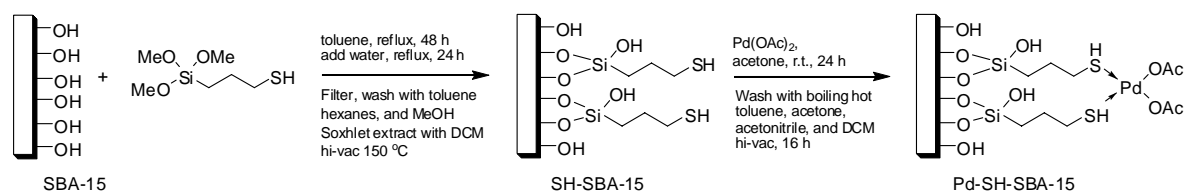
Large pore SBA-15 (110 Å) was synthesized by literature methods, utilizing the triblock poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (EO-PO-EO) nonionic surfactant as the structure-directing agent and 1,3,5-trimethylbenzene (TMB) as a swelling co-solvent.^[46] The as-prepared material was calcined using the following temperature program: (1) increasing the temperature (1.2 K/min) to 473 K, (2) heating at 473 K for 1h, (3) increasing the temperature (1.2 K/min) to 823 K, and (4) holding at 823 K for 6h. Prior to functionalization, the SBA-15 was dried under vacuum (5 mTorr) at 473 K for three hours and stored in a dry box (BET surface area = 780 m²/g, average pore diameter = 110 Å). Removal of all of the organic surfactant was confirmed by TGA analysis.

Organic modification of SBA-15 was achieved by mixing a toluene (120 mL) suspension of SBA-15 (4.1 g) and 3-mercaptopropyltrimethoxysilane (10 g) at reflux temperature for 48 hours under an argon atmosphere. Water (1.8 mL) was then added to promote the cross-linking and the mixture was heated at reflux for an additional 24 hours. The solids were then filtered and washed with copious amounts of toluene, hexanes, and methanol to remove un-reacted silanes. Recovered solids were Soxhlet extracted with dichloromethane at reflux temperature for 3 days. The resulting white solids were collected, kept under vacuum (5 mTorr) at room temperature overnight, dried at 423 K for 3 hours under vacuum (5 mTorr), and stored in a nitrogen glove box. FT-Raman analysis exhibited a strong peak at 2571 cm^{-1} , which is in the normal range found for S-H stretching. A loading of 7.5 wt% of sulfur (2.3 mmole S/ g solids) was found by elemental analysis. (BET surface area = $320\text{ m}^2/\text{g}$, average pore diameter = 80 \AA)

4.2.3 Metalation of organically modified SBA-15

Palladium acetate (450 mg, 2 mmole) was dissolved in 50 mL of dry acetone. This solution was added to SH-SBA-15 (1.1 g), resulting in an orange-brown colored suspension, which was stirred at room temperature for 24 hours (Scheme 4.1). The solids were filtered using a 150 mL fritted funnel (medium sized frit) and washed with 3 X 100 mL each of boiling acetone, toluene, acetonitrile and dichloromethane. Recovered solids were orange-brown in color. The solids were then exposed to high vacuum (5 mTorr) for 16 hours to remove any physisorbed solvent resulting in orange-brown solid particles. A loading of 11.06 wt% palladium (1.04 mmole Pd/ g solids) was determined by elemental

analysis based on the average of two EA tests for Pd (10.9 wt% and 11.21 wt%) giving a S:Pd ratio of 1.7. This material was used for the majority of the experiments. Two other partially metalated batches were made by mixing (i) 9 mg palladium acetate, 110 mg SH-SBA-15, in 5 mL acetone and (ii) 45 mg palladium acetate, 200 mg SH-SBA-15, and 25 mL acetone. Materials were washed using a scaled down filtration procedure (60 mL fritted funnel and 3 X 50 mL each of solvent). Final Pd loadings and S:Pd ratios were (4.1%, 5.7) and (8.4%, 2.6), respectively.



Scheme 4.1 Schematic of synthesis of mercaptopropyl modified mesoporous silica, SH-SBA-15, and further metalation with palladium acetate, Pd-SH-SBA-15.

4.2.4 Heck reactions

A variety of reaction conditions for Heck reactions were studied. For the majority of reactions the precatalyst Pd-SH-SBA-15 (1.2 mg, 1.25E-03 mmole Pd, 0.05 mol% Pd to aryl halide) was added to a 3-neck flask and connected to a condenser linked to a Schlenk line. The system was purged with argon and a solution of N,N dimethylformamide (5 mL), aryl halide (2.5 mmole), base (7.5 mmole) and diethylene glycol dibutyl ether (2.5 mmole, GC standard) was added. The mixture was magnetically stirred and pre-heated at reaction temperature for 25 min, at which time n-butyl acrylate

(3.75 mmole) was added to initiate reaction. Periodically 0.1 mL samples were withdrawn, dissolved in 1.5 mL acetone at room temperature, filtered through a small plug of silica gel loaded in a cotton plugged pipet, and analyzed by gas chromatography. In reactions in which homogeneous palladium acetate was used as the precatalyst, n-butyl acrylate was added prior to the pre-heat and the reaction was initiated by adding 0.1 mL of a 0.0125 M solution of palladium acetate in DMF. Exceptions to reaction conditions described above are noted where necessary.

4.2.5 Suzuki reactions of 4-bromoacetophenone or 4-chloroacetophenone

4.2.5.1 DMF as solvent

Aryl halide (1.0 mmole) and hexamethylbenzene (0.5 mmole, GC standard) were dissolved in 5 mL of DMF. The solution was added to a glass reactor with precatalyst (1.0% for bromoacetophenone and 2.0% for chloroacetophenone), K_2CO_3 (2.0 mmole), and phenyl boronic acid (1.5 mmole). The suspension was purged with argon, sealed, and immersed in an oil bath at 353 K and magnetically stirred for 6 or 8 hours. Reactions in DMF were analyzed by taking a 0.1 mL sample, which was dissolved in 1.5 mL acetone at room temperature, filtered through a small plug of silica gel loaded in a cotton plugged pipet, and analyzed by gas chromatography.

4.2.5.2 H₂O as solvent

Precatalyst (1.0% for bromoacetophenone and 2.0% for chloroacetophenone), K₂CO₃ (2.0 mmole), aryl halide (1.0 mmole), phenyl boronic acid (1.5 mmole), hexamethylbenzene (0.5 mmole, GC standard), and 5 mL of doubly distilled H₂O were added to a glass reactor and magnetically stirred at 353 K for 6 to 24 hours. In the original reporting of these conditions by Crudden, hexamethylbenzene is used as an internal standard.^[36] In this work hexamethylbenzene was again included in the reaction, but since the reaction is in water, we developed an alternate method to assess the conversion of aryl halide based on a GC calibration file made from known concentrations of aryl halide and 4-acetyl-biphenyl (product) with DGDE as standard. Reactions were extracted with 3 X 10 mL of dichloromethane. The DCM was then evaporated and a known amount of DGDE in 5 mL of acetone was added. A 0.1 mL solution was taken, dissolved in 1.5 mL of acetone, through a small plug of silica gel loaded in a cotton plugged pipet, and analyzed by GC. Final conversion was determined by comparing the ratio of aryl halide and DGDE to the calibration file.

4.2.6 Hot filtration

A Heck reaction solution was allowed to reach 20-30% conversion of iodobenzene and the solids were filtered off under static vacuum by means of a swivel frit^[47] connected to an empty reaction flask. The filtrate was kept at reaction temperature and conversion was monitored by GC.

4.2.7 Catalyst poisoning

In the majority of reactions the catalyst poison was added to the reaction flask prior to addition of reaction solution. Poly(4-vinylpyridine) was used in 350 equivalents of pyridine sites to total palladium unless otherwise noted. When Quadrapure™ TU, SH-SBA-15, or 3-mercaptopropyl-functionalized silica gel was used as a poison the molar ratio of poison to palladium was 35 to 1 unless stated differently. In reactions in which the poison was added after reaction initiation, a glass plug in the 3-neck flask was removed (briefly exposing reaction solution to air for approximately 3-5 seconds), the poison particles quickly added, and then the glass plug was re-inserted.

4.3. Results

4.3.1 Aryl iodide conversions

4.3.1.1 Activity comparison between soluble and immobilized palladium acetate

A typical benchmark reaction for Heck couplings involves reacting aryl iodides with either styrene or an acrylate. Aryl iodides are more active than aryl bromides or aryl chlorides due to their rapid oxidative addition to Pd(0), forming a Pd(II) complex. Unless stabilizing ligands are present, Pd(0) can aggregate to form palladium black, a typically

inactive form of palladium that commonly precipitates out of solution. In the presence of excess oxidizing agents such as aryl iodides, deactivation by palladium black formation can be mitigated.^[14, 20, 41, 48] However, as the aryl iodide is consumed in the reaction, less of it is available to complex to Pd and the distribution of Pd can shift to favor Pd(0), leading to formation of palladium nanoparticles or palladium black. The overall catalytic activity represents a balance between completing turnovers in the Heck cycle and deactivation of the palladium associated with palladium black formation or other deactivated forms of palladium, such as over-coordinated palladium with strongly binding molecules or inactive palladium re-deposited on surfaces.

To compare the activity between soluble and immobilized palladium, Heck coupling reactions of iodobenzene with *n*-butyl acrylate were performed using two different palladium sources; homogeneous palladium acetate and immobilized palladium acetate on mercaptopropyl-modified mesoporous silica, Pd-SH-SBA-15 (Scheme 1). *N,N*-dimethylformamide, DMF, was used as the solvent and triethylamine was used as base. Comparisons in activity between soluble and immobilized palladium acetate are displayed in Figure 4.1. Reactions using soluble palladium acetate rapidly went to completion at 363 K and 343 K (Fig. 4.1, A and D). Increasing the amount of homogeneous palladium acetate is known to result in catalyst deactivation due to the higher concentrations of Pd(0) that rapidly cluster to form palladium black.^[20, 49] This self quenching was also observed under the reaction conditions studied in this report (Fig. 4.1, E). A 1.0% loading of palladium acetate was initially faster than the 0.05% loading, but after about 5 minutes the palladium began to self deactivate and the conversion

ultimately reached a lower value of 69% at 120 minutes compared to the 100% conversion at 40 minutes reached for the lower catalyst loading.

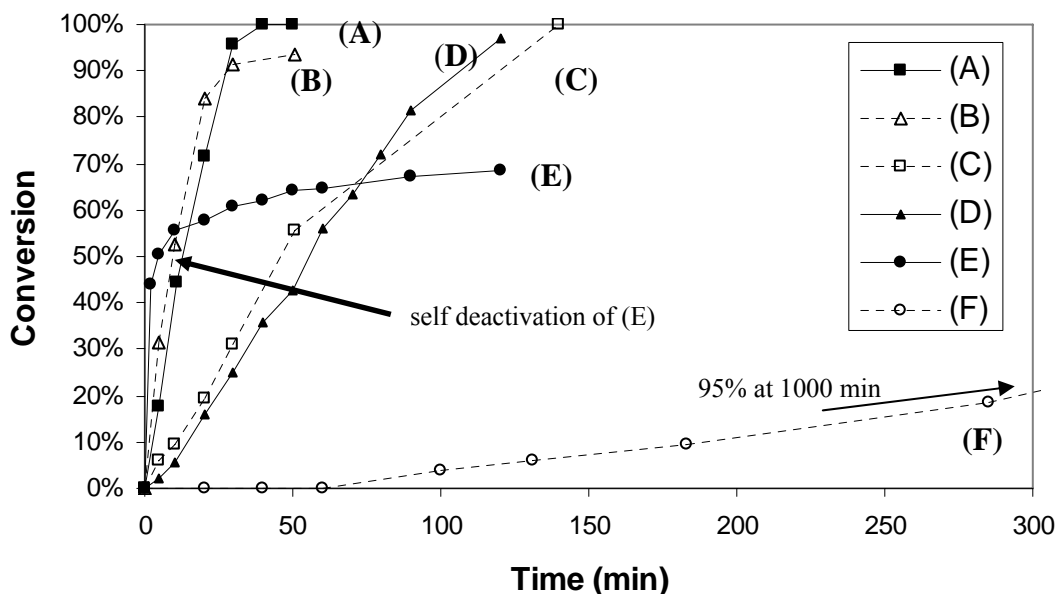


Figure 4.1 Activity comparisons of Heck coupling iodobenzene with *n*-butyl acrylate using; (A) 0.05% palladium acetate at 363K, (B) 0.5% Pd-SH-SBA-15 at 363 K, (C) 0.05% Pd-SH-SBA-15 at 363 K, (D) 0.05% palladium acetate at 343 K, (E) 1.0% palladium acetate at 363 K with start of self deactivation noted, and (F) 0.05% Pd-SH-SBA-15 at 343 K with final conversion at 1000 minutes.

Reactions with Pd-SH-SBA-15 were also active but displayed lower rates than reactions using homogeneous palladium acetate at the same temperature and palladium loading. The lowering of temperature from 363 K to 343 K significantly slowed the activity of Pd-SH-SBA-15 requiring a much longer time to both start, progress, and ultimately finish the reaction (Fig. 4.1, C and F). This dramatic decrease in activity could be either due to effects inhibiting reaction on the surface (if it were to occur there) or represent the temperature influence on leaching of immobilized palladium from supported thiols. Increasing the catalyst loading of Pd-SH-SBA-15 to 0.5% resulted in a

faster reaction rate (Fig. 4.1, B), which stands in contrast to the observed behavior of increasing homogeneous palladium acetate loadings.

The increased activity by raising the Pd-SH-SBA-15 loading could be explained by two possible scenarios; (i) Pd(0) formed during the Heck cycle cannot aggregate due to its binding to an immobilized organic surface and so increased activity is simply associated with more metal present or (ii) the amount of leached palladium from the surface is low and so the actual concentration of active catalytic species in solution is below levels that promote self-deactivation. In order to understand where the catalysis is occurring, tests are needed to confirm the presence of soluble palladium and determining to what extent, if any, catalysis is happening on the surface.

4.3.1.2 Hot filtration

A strong test to assess the presence of soluble active palladium is the hot filtration test, also known as the split test, in which solid precatalysts are filtered out of the reaction and the filtrate is monitored for continued activity.^[50] A lack of filtrate activity is traditionally interpreted as a proof of heterogeneous catalysis, but this interpretation cannot be applied palladium catalyzed reactions without support from other tests. Heck reactions can be catalyzed by extremely small amounts of palladium (0.00001% to 0.05%) and the self-deactivation at high loadings described above suggests very low loadings are ideal^[5, 20] Disruptions such as hot filtration could deactivate the small amount of active metal, which can lead to the incorrect conclusion that there are no active soluble catalytic species prior to the filtration.^[5, 51] In the present work, when Pd-SH-

SBA-15 (0.05%, 363 K) was hot filtered after 20% conversion the filtrate continued to react, which is evidence that some of the palladium is leaching from the surface and catalyzing the reaction (Fig. 4.2). In order to determine the amount of solution versus surface catalysis, a common method employed is to compare the rate of activity following hot filtration to that found under normal reaction conditions. However, as some of the active palladium can become deactivated during hot filtration, this method of comparison at best provides rough estimates. Other tests are needed in order to determine if any heterogeneous catalysis is indeed happening.

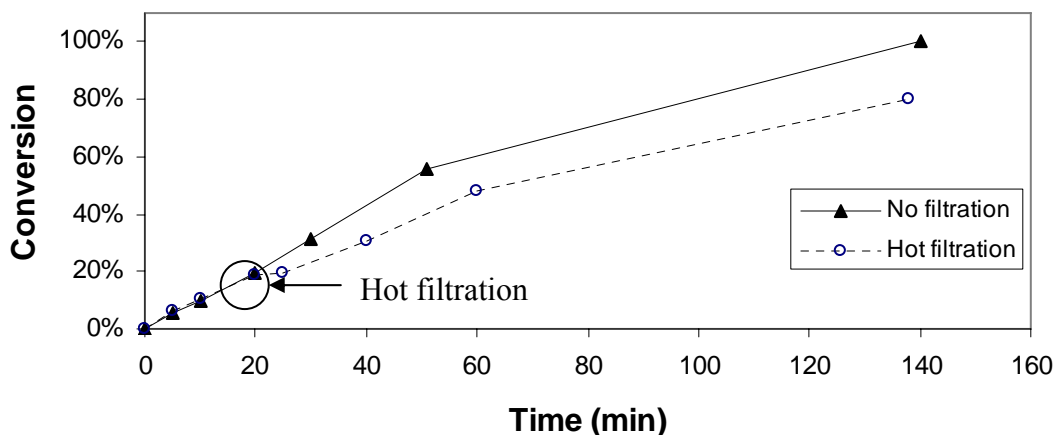


Figure 4.2 Application of hot filtration to the Pd-SH-SBA-15 catalyzed Heck coupling of iodobenzene with *n*-butyl acrylate at 363 K in 5 mL DMF with triethylamine as base. Hot filtration was applied at 20 minutes.

4.3.1.3 Tests of heterogeneous catalytic activity

In our work on assessing homogeneity/heterogeneity of catalysis associated with supported Pd precatalysts in coupling reactions we introduced the use of solid, insoluble

poisons for extinguishing solution phase catalysis.^[5,9,12,20-21] The insoluble metal scavenger poly(4-vinylpyridine), 2% crosslinked, was first used as a tool to determine if supported catalysis was or was not occurring for palladium pincer complexes immobilized on silica or organic polymers^[12, 25, 26], and later using Pd immobilized on amorphous silica^[40], and palladium acetate encapsulated in a poly(urea) matrix.^[9] When PVPy was used to poison Pd-SH-SBA-15, typically using 350 equivalents of pyridine sites to total palladium, no activity was observed. However, use of PVPy as a solid poison is not without its drawbacks. Due to the equilibrium on-off coordination of the palladium with the pyridine sites^[52] and the non-porous nature of the resin, a large excess of pyridine units are required to over coordinate the palladium (Fig. 4.3). This can sometimes introduce a large amount of solids to the solution and may result in some pore blocking of the SBA particles from agglomerated PVPy nanoparticles or partially solvated polymer. A further disadvantage is that polymer swelling might be needed for access to many of the pyridine sites; this is largely influenced by both choice of solvent and reaction temperature. For comparison to PVPy, 2-(4-pyridylethyl)triethoxysilane was grafted onto SBA-15, Pyr-SBA-15 (1.7 mmole pyridine/g solids and pyridine:Pd = 35:1), and substituted for PVPy as a poison of palladium acetate (Fig. 4.3). An induction time of 40 minutes was observed followed by significant activity, which is consistent with an on-off mechanism by which soluble palladium is first rapidly over coordinated by the immobilized pyridine sites and then eventually leaches back into solution. Under the same reaction conditions PVPy (pyridine:Pd = 35:1) exhibited almost no initial slowing of reaction and reached full conversion by 40 minutes. This comparison suggests the

importance of PVPy polymer swelling to make pyridine sites accessible for coordination to homogeneous palladium.

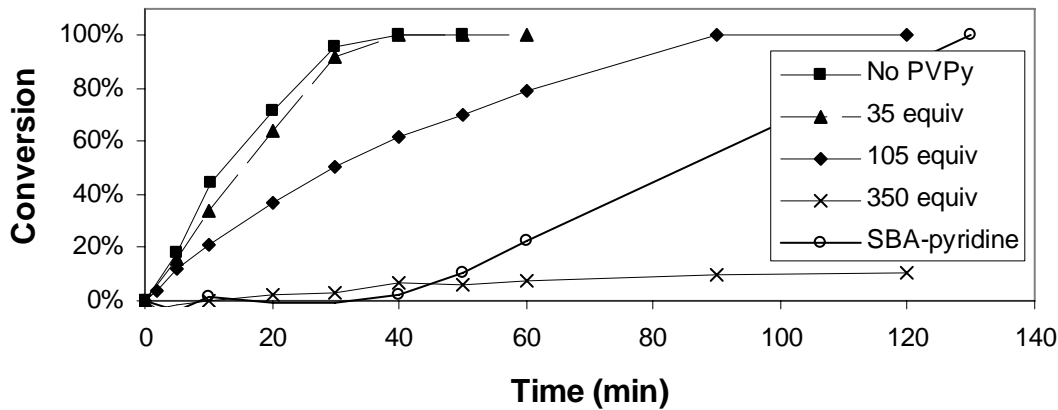


Figure 4.3 Plot of iodobenzene conversion showing the effect of increased equivalencies of PVPy for poisoning of homogeneous palladium acetate catalysis of the Heck coupling of iodobenzene with *n*-butyl acrylate. Poisoning by immobilized pyridine on SBA-15 (pyridine:Pd = 35:1) is also shown for comparison. Conditions are at 363 K under argon with DMF (5 mL) as the solvent and NEt_3 as the base.

For most immobilized Pd precatalysts, the amount of leached palladium is unknown, thus the amount of PVPy needed for poisoning becomes an optimization problem. As an example, 350 equivalents of PVPy did not completely stop catalysis when soluble palladium acetate (0.05%) was used, but did quench activity from Pd-SH-SBA-15. Comparing these results provides a qualitative estimate for the amount of palladium leached from Pd-SH-SBA-15 and indicates that not all Pd was removed from the surface when using the supported precatalyst. More importantly the quenching of activity by PVPy is strong evidence for catalysis solely by leached species, but due to its previously mentioned drawbacks, a more elegant selective poison is desired to provide supporting evidence.

Mercaptopropyl-modified surfaces, such as SH-SBA-15, have been used as effective palladium scavengers^[36, 53-55] as well as scavengers for other metals such as silver and mercury.^[56] SH-SBA-15 is a rigid mesoporous solid that does not swell under reaction conditions, a previously mentioned drawback of ligands immobilized on polymers such as PVPy. We thus hypothesized that *the same SH-SBA-15 material* used as a support for palladium acetate immobilization could also act as a selective poison of soluble palladium acetate if used in excess. Prior to its use as a selective poison the presence of S-H groups was verified by FT-Raman spectroscopy (Fig. 4.4). The presence of long range order and a hexagonal structure, as expected for SH-SBA-15, was verified by XRD (Fig. 5.5).

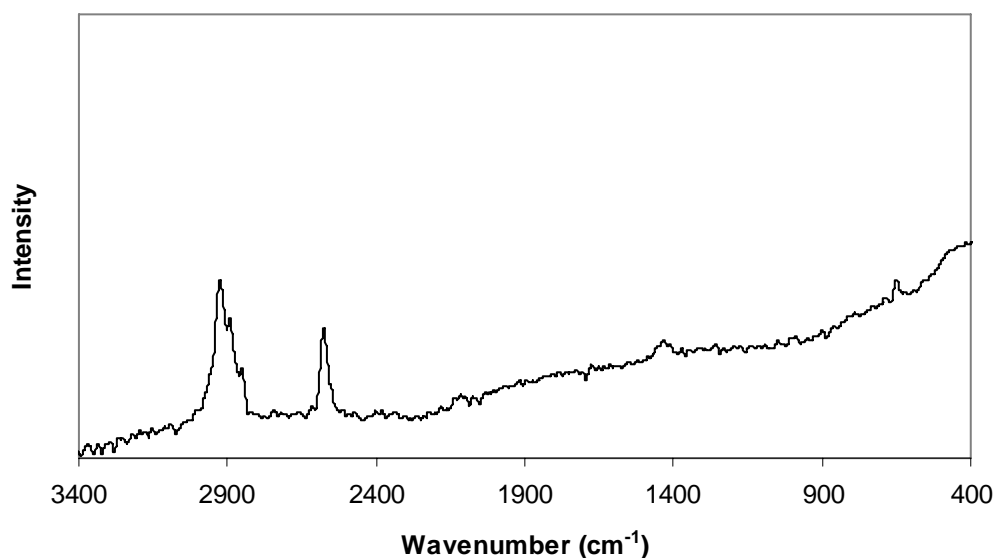


Figure 4.4 FT-Raman spectrum of SH-SBA-15. The peak at 2571 cm^{-1} is assigned to an S-H stretch.

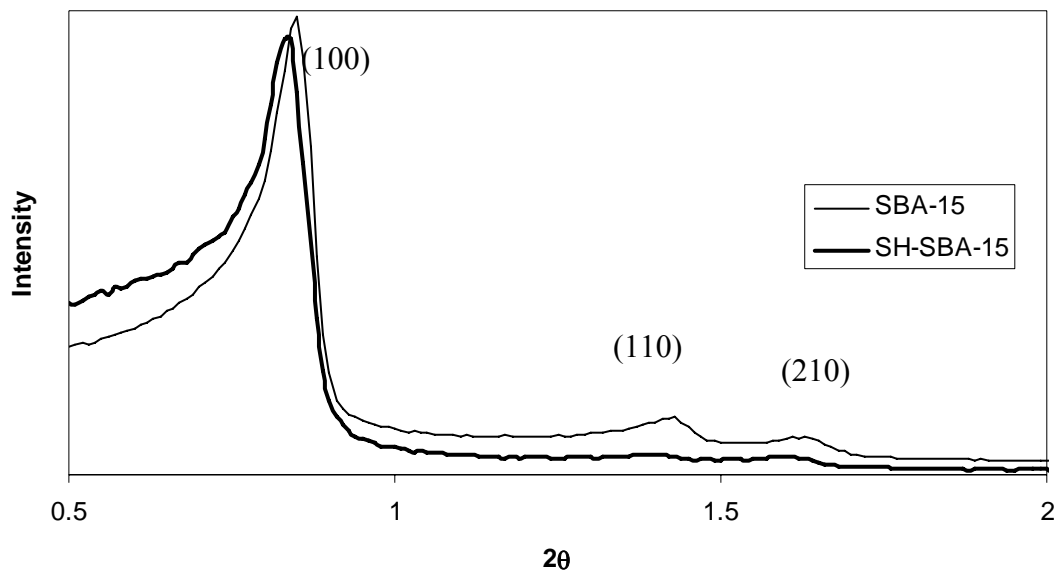


Figure 4.5 XRD patterns of SBA-15 before and after mercaptopropyl-functionalization. Retainment of long range ordering is demonstrated by a strong (100) peak.

Bare, palladium-free SH-SBA-15 was used to poison catalysis of the Heck coupling of iodobenzene with n-butyl acrylate using either homogeneous palladium acetate or Pd-SH-SBA-15 (Fig. 4.6). In all cases the presence of an excess of bare SH-SBA-15 to palladium of 35 to 1 resulted in complete cessation of activity. SH-SBA-15 was a more effective poison than PVPy and required less material, e.g. 20 mg of SH-SBA-15 versus 50 mg of PVPy, perhaps due to binding site accessibility. As shown in Fig. 4.3 above, 35 equivalents of PVPy had almost no poisoning effect whereas Pyr-SBA-15 stopped activity for 40 minutes and then activity was observed. In contrast SH-SBA-15 completely shut down activity even after 16 hours, demonstrating its superior performance as a poison and the ability of immobilized thiols to better retain palladium than immobilized pyridines. Also, as it is *the same material* as that used for the catalyst support, no poison-induced pore blocking occurs. To probe whether or not poisoning is

from the organic functionalization of SBA-15 and not from anything else inherent to the SBA-15, a control reaction was performed in which 50 mg of SBA-15 was substituted for SH-SBA-15 and tested as a poison. No difference in the kinetic profile was observed between reactions with SBA-15 and without, confirming that poisoning was caused by the mercaptopropyl modification of the surface and is not inherent to the SBA-15 material. A control experiment was conducted in which 1-propanethiol was mixed with Pd-SH-SBA-15 (4:1, propanethiol: Pd) under normal Heck reaction conditions. Kinetic activity was significantly slowed but did reach a maximum of 40% conversion after 20 h. A complementary reaction using SH-SBA-15 (4:1, SH-SBA-15: Pd) as the poison resulted in complete cessation of activity up to 33 h. These tests highlight the importance of the immobilization of the thiol groups for increasing poisoning capacity. This is most likely explained by a high local sulfur concentration effect of the bound thiols in which captured palladium is rapidly over coordinated by neighboring thiols before it can be released back into solution.

When SH-SBA-15 was mixed with Pd-SH-SBA-15 at either the beginning of the reaction or after the reaction has initiated, no additional conversion was observed (Fig. 4.6). This is strong evidence that all catalysis previously observed in this work with Pd-SH-SBA-15 was solely from leached palladium, which agrees with observations made by Davis.^[40] To determine the lower bound of required poison, the equivalency of SH-SBA-15 to Pd was lowered from 35 to 4 and no reaction of iodobenzene with n-butyl acrylate was observed up to 2000 minutes (0.05% catalyst, 363 K, DMF, NEt₃). Further lowering the equivalency to 1 resulted in a slow conversion to 58% after 700 minutes, which remained constant up to 1900 minutes. Thus, SH-SBA-15 is an effective poison of

leached palladium from Pd-SH-SBA-15 and can be effective in much lower amounts than PVPy

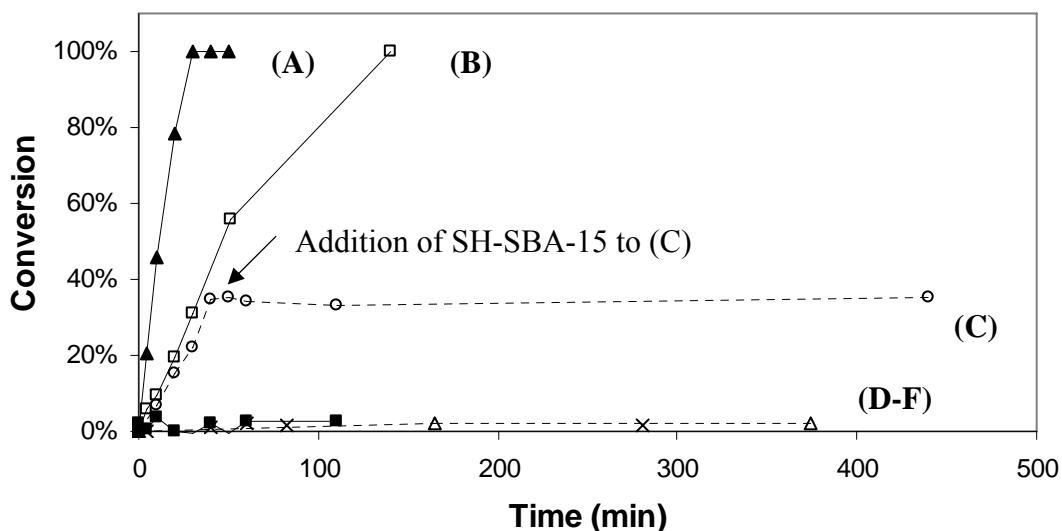


Figure 4.6 Plot of iodobenzene conversion with SH-SBA-15 used as a poison and either palladium acetate or Pd-SH-SBA-15 as catalyst: (A) control reaction at 363 K using SBA-15 instead of SH-SBA-15 as an ineffective poison of palladium acetate, (B) Pd-SH-SBA-15 activity without any poison, (C) cessation of Pd-SH-SBA-15 activity by adding SH-SBA-15 poison after 40 minutes of reaction, (D) cessation of Pd-SH-SBA-15 activity at 363 K by adding SH-SBA-15 at start of reaction, (E) cessation of Pd-SH-SBA-15 activity at 343 K by adding SH-SBA-15 at start of reaction, and (F) cessation of palladium acetate activity by adding SH-SBA-15 at start of reaction.

The ability of the SH-SBA-15 to effectively poison these precatalysts implies that the active catalyst species consists of only a small number of Pd atoms and not from the surface of Pd nanoparticles. Due to the rigid, cylindrical structure and large pore size of SH-SBA-15, it is difficult to envision the mercaptopropyl groups over-coordinating the entire surface of a Pd nanoparticle, whereas complexes of one to a few Pd atoms could be completely coordinated. Alternatively, it is also possible that the capture of free metal ions from solution by the SH-SBA-15 could prevent the aggregation of palladium to form

nanoparticles. In this scenario a demonstration of lack of nanoparticle surface catalysis would not be substantiated by the use of insoluble poisons. However, the rapid quenching of catalysis by addition of poison once activity has commenced (Fig. 4.6 curve C), presumably when nanoparticle formation could have already occurred, is suggested as evidence that if nanoparticles are formed, their surface is inactive as postulated above. Collectively, this evidence suggests Heck catalysis by molecular or dimeric palladium as postulated by de Vries^[5, 20, 42, 43] and Schmidt^[5, 24] and supported by Rothenberg^[44] and Fiddy.^[45] Further testing to conclusively demonstrate lack of activity of nanoparticle surfaces by use of insoluble poisons is outside the scope of this paper, but is suggested as a potentially interesting future work.

4.3.1.4 Probing mercaptopropyl ligand leaching

An alternative mechanism for poisoning of Pd-SH-SBA-15 by SH-SBA-15 is that the mercaptopropyl groups leach and poison surface bound palladium. In this case the poisoning experiments using SH-SBA-15 could not conclusively support a leaching mechanism of Pd-SH-SBA-15. However, if mercaptopropyl leaching was occurring for SH-SBA-15, then it would also be expected to occur for the mercaptopropyl groups used to immobilize palladium acetate on Pd-SH-SBA-15 unless the presence of palladium acetate somehow prevented this from happening. Mercaptopropyl leaching from SH-SBA-15 was explicitly probed by exposing 50 mg of SH-SBA-15 to reaction conditions for one hour and then hot filtering the solids. The filtrate was kept at 363 K and homogeneous palladium acetate (0.1 mL of a 0.0125M solution in DMF) was added.

Complete conversion was reached in < 30 minutes; therefore it is unlikely that significant leaching of thiols occurred under these conditions. An important assumption for this interpretation is that any leached thiols can survive the hot filtration process without redepositing on the surface (as leached palladium often does). Otherwise the observed activity of the filtrate could not confirm the absence of thiol leaching. Assuming nearly full coverage of the silica surface with silanes, small amounts of leached silane, if they were to exist, likely would not find bare silica surfaces to redeposit. Thus, we expect leached silane redeposition to be unimportant. To probe the retainment of the mercaptopropyl groups on the silica surface, the recovered solids from the hot filtration were rinsed with boiling hot toluene, dichloromethane, and acetone and exposed to high vacuum (5-6 mTorr) to remove any physisorbed organic material. Presence of residual S-H bonds was confirmed by FT-Raman analysis of both the untreated SH-SBA-15 and the SH-SBA-15 recovered from hot filtration. A strong FT-Raman peak at 2175 cm^{-1} was observed for both materials and assigned as an S-H stretch. The activity of the filtrate and FT-Raman analysis suggest that thiol leaching does not occur at a level that would allow poisoning of Pd-SH-SBA-15 if it were a heterogeneous catalyst. As noted in section 3.1.3., a large amount of leached thiol giving a S: Pd ratio in excess of 4:1 would be required to completely poison hypothesized surface-mediated catalysis.

4.3.2 Aryl bromide conversions

The previous results are strong evidence that Heck catalysis of aryl iodides from palladium immobilized on a mercaptopropyl surfaces is solely from leached palladium.

This is consistent with the accumulated literature on Heck coupling.^[5] However, when aryl bromides are substituted for aryl iodides, the effect on surface versus solution catalysis is less clear, especially when using thiol-supported precatalysts. Previous works suggested possible heterogeneous catalysis from palladium immobilized on mercaptopropyl modified surfaces for couplings between bromoacetophenone and either styrene^[36] or ethyl acrylate^[33] using inorganic bases instead of a soluble organic base. Conditions in which heterogeneous catalysis was suggested were replicated in this work, with the addition of using bare SH-SBA-15 as a selective poison (Table 4.2). Additional experiments were also conducted using the aryl bromide under the same conditions reported previously in this study for reactions involving iodobenzene (0.05% catalyst, DMF, NEt₃, butyl acrylate, 363 K). Without a poison present, Pd-SH-SBA-15 was an effective catalyst for the reactions listed in Table 4.2. Interestingly, in all cases in which SH-SBA-15 was added as a selective poison, little or no product formation was observed; confirming that activity observed for bromoacetophenone reactions was associated with leached palladium. Therefore substituting an aryl bromide for an aryl iodide or substituting an organic base with an inorganic base does not appear to promote heterogeneous catalysis in this case.

Table 4.2 Results of Heck coupling reactions of bromoacetophenone and various reagents^a

Entry	alkene	Base	Catalyst	Temp	SH-	Time	Conversion	Condition ^b
			mol%	(K)	SBA-15	(min)		
1 ^c	ethyl acrylate	KOAc	1.00%	403	NO	210	100%	3-neck
2 ^c	ethyl acrylate	KOAc	1.00%	403	YES	300	0%	3-neck
3	styrene	NaOAc	0.50%	393	NO	900	75%	Sealed
4	styrene	NaOAc	0.50%	393	YES	900	0%	Sealed
5	butyl acrylate	NaOAc	0.12%	393	NO	1350	87%	Sealed
6	butyl acrylate	NaOAc	0.12%	393	YES	1350	5%	Sealed
7	butyl acrylate	NaOAc	0.12%	393	NO	180	91%	3-neck
8	butyl acrylate	NaOAc	0.12%	393	YES	2000	0%	3-neck
9	butyl acrylate	NaOAc	0.05%	393	NO	165	93%	3-neck
10	butyl acrylate	NaOAc	0.05%	393	YES	1400	0%	3-neck
11	butyl acrylate	NEt ₃	0.05%	393	NO	1400	27%	3-neck
12	butyl acrylate	NEt ₃	0.05%	393	YES	1400	0%	3-neck

^a Reactions conditions used 1.0 mmole aryl halide, 1.5 mmole alkene, 2 mmole base, 1.0 mmole DGDE (internal standard for GC), and 5 mL of DMF under argon atmosphere unless otherwise noted.

^b Reactions using a 3-neck flask were under an atmosphere of argon using a Schlenk line and a mercury bubbler. Reactions under sealed conditions were inside a glass tube purged with argon and sealed with a Teflon-lined screw cap.

^c Amounts used were 3.0 mmole bromoacetophenone, 4.5 mmole ethyl acrylate, 4.5 mmole KOAc, 1.0 mmole benzonitrile (internal standard for GC), and 5 mL of N-Methyl-2-pyrrolidone, NMP.^[33]

4.3.3 Impact of the type of base

In comparing the activity under the variety of conditions it is of note that reactions using sodium acetate as the base went to a higher yield than comparable reactions using triethylamine (Table 4.2; entries 7, 9, & 11). To probe the effect of base on both leaching and activity, a variety of bases were used with iodobenzene and bromoacetophenone as the aryl halide and either palladium acetate or Pd-SH-SBA-15 as the catalyst (Table 4.3). The higher conversion of bromoacetophenone found when using sodium acetate instead of organic base was not observed for iodobenzene. Instead the opposite was true with higher conversions achieved when NEt_3 was used as the base than when NaOAc was employed. Using methyl(dicyclohexyl)amine, MDA, a base previously described as more active for couplings involving activated aryl bromides^[57], resulted in no activity with bromoacetophenone, but did exhibit significant activity for iodobenzene. Thus, the exact role of the base on activity is currently not clear with respect to leaching or stabilization of the leached catalytic species. In general the use of inorganic bases instead of organic bases promotes bromoacetophenone activity, but lowers iodobenzene activity. Changing the base does not promote heterogeneous catalysis, as all SH-SBA-15 poisoning experiments resulted in no activity (Table 4.2; entries 2,4,6,8,10, & 12 and Table 4.3; entry 3).

Table 4.3 Results for Heck couplings of aryl halide with butyl acrylate^a using various bases.

Entry	aryl halide	Base	Temp (K)	SH-SBA-	Time	Conversion
				15	(min)	
1	iodobenzene	NEt ₃	393	NO	30	100%
2	iodobenzene	NaOAc	393	NO	300	100%
3	iodobenzene	NaOAc	383	YES	1600	0%
4	iodobenzene	NaOAc	383	NO	285	95%
5	iodobenzene	NaOAc	363	NO	270, 960	31%, 48%
6 ^b	iodobenzene	NaOAc	363	NO	300, 1600	37%, 93%
7	iodobenzene	MDA	393	NO	30	97%
8	bromoacetophenone	MDA	393	NO	530	0%
9	bromoacetophenone	KOAc	393	NO	270	87%

^a Reaction conditions are 2.4 mmole aryl halide, 3.6 mmole butyl acrylate, 4.8 mmole base, 2.4 mmole DGDE (GC standard), and 5 mL DMF under argon atmosphere. Precatalyst is Pd-SH-SBA-15 (0.05%).

^b 0.00125 mmole of homogeneous palladium acetate was substituted for Pd-SH-SBA-15.

4.3.4 Reinterpretation of literature regarding activated bromide reactions: Part

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In this work all data strongly suggest that observed Heck catalysis is associated with leached palladium, which stands in contrast to interpretations based on previous compilations of data^[33, 36] (*vide supra*). A careful examination of these past works from a viewpoint of metal leaching as the primary mode of catalysis leads to some alternative

explanations for previously observed behavior. For the Heck reaction of 4-bromoacetophenone with ethyl acrylate, Shimizu observed 0.01% palladium leaching and the appearance of 2-14 nm-diameter palladium nanoparticles. The formation of nanoparticles is consistent with palladium leaching from the surface, aggregation during the reaction upon formation of Pd(0), and then re-deposition back onto the surface. A hot filtration test was performed on the Pd-SH-FSM precatalyst, but the conditions were with 10 times less catalyst than normal reaction conditions, 0.1% versus 1.0%. It is possible that a smaller total amount of palladium was leached, which was deactivated during the hot filtration test (*vide supra*). A lack of observed activity could occur as a result of deactivation of soluble active palladium species.^[51] The authors report conversions up to 95% within 2 h using a loading 0.0013 mol% of *immobilized palladium*, and after recycling for 5 times, the authors were able to again achieve around 95% conversion but this time in about 8 h. The lower rate of recycle is consistent with increased metal leaching or deactivation of the catalyst by leaching and redeposition. Overall, the data from Shimizu could be re-interpreted from a viewpoint of metal leaching as the primary or only catalytic mode. One of the major differences between the current study and the work by Shimizu is the use of SBA-15 as the silica support instead of FSM-16, but given the similar surface characteristics it is unlikely that this difference in support material would change whether or not the catalysis is occurring heterogeneously or homogeneously. The impact of the slight difference in the S:Pd ratios between Shimizu (2.8) and this study (1.7) is discussed in more detail later. To compare to Shimizu's conditions, select tests were also conducted with a material with a 2.6 S:Pd ratio in this work.

4.3.5 Aryl chloride conversions and Suzuki reactions

The ability to use aryl chlorides for Heck, Suzuki and other aryl couplings is of strong interest because these molecules are commonly cheaper than analogous iodides or bromides. However, the carbon-chlorine bond is stronger and harder to activate. Many homogeneous palladium complexes have been found to catalyze Heck and Suzuki reactions of aryl chlorides, but these usually require specific combinations of ligands, base and solvent.^[5, 58] Attempts to couple chloroacetophenone with n-butyl acrylate in the Heck reaction were met with no success using Pd-SH-SBA-15 at either 0.05% or 1.0% loadings (Table 4.4). However, a Suzuki reaction with chloroacetophenone and phenyl boronic acid (5 mL water, 2.0 mol% catalyst, K₂CO₃, 353 K) after 24 h resulted in 50 % conversion and Suzuki couplings of bromoacetophenone (1 mol% catalyst) went to completion in 5 h. Like the work described above on Heck reactions, no activity was observed with additional SH-SBA-15 present as a poison in any case. Thus, Pd-SH-SBA-15 is suggested to act as a source of leached palladium for Suzuki reactions of aryl chlorides and bromides under these conditions, just as it did for Heck reactions of aryl iodides and bromides.

Table 4.4 Results from Heck^a reactions of chloroacetophenone and Suzuki^b reactions of chloroacetophenone and bromoacetophenone [36]

Entry	aryl halide	Reaction	Catalyst Loading	Base	Temp (K)	SH-	Time (hr)	Conversion
						SBA-15		
1	chloroacetophenone	Heck	0.12%	NaOAc	393	NO	48	0%
2	chloroacetophenone	Heck	1.00%	NaOAc	393	NO	24	0%
3	chloroacetophenone	Suzuki	2.00%	K ₂ CO ₃	353	NO	24	50%
4	chloroacetophenone	Suzuki	2.00%	K ₂ CO ₃	353	YES	24	0%
5	bromoacetophenone	Suzuki	1.00%	K ₂ CO ₃	353	NO	8	100%
6	bromoacetophenone	Suzuki	1.00%	K ₂ CO ₃	353	YES	8	0%

^a Reactions conditions are 1.0 mmole chloroacetophenone, 1.5 mmole *n*-butyl acrylate, 2.0 mmole base, 1.0 mmole DGDE (internal standard), and 5 mL of DMF under argon atmosphere in a 3-neck flask.

^b Reaction conditions are 1.0 mmole aryl halide, 1.5 mmole phenyl boronic acid, 2.0 mmole base, 0.5 mmole hexamethylbenzene, and 5 mL H₂O under argon atmosphere in sealed reaction tube.

A series of selective poisoning experiments were conducted to both probe the effectiveness of other poisons for the Suzuki coupling of bromoacetophenone with phenyl boronic acid and to confirm the poisoning results of SH-SBA-15 (vide supra) (Table 4.5). Control reactions of homogeneous palladium acetate were compared to Pd-SH-SBA-15, and to palladium on carbon (Pd-C), which is a precatalyst known to operate by a leaching mechanism. Two solvents were utilized, DMF or H₂O, and Suzuki couplings were carried out under normal reaction conditions. In addition to SH-SBA-15,

two other poisons were tested, Quadrapure™ TU^[9] and 3-mercaptopropyl-functionalized silica gel (SH-SiO₂). Previously, Quadrapure™ TU was used as a poison in high temperature Heck reactions (90 °C and 110 °C) and extinguished all activity using carbon-supported precatalysts or supposedly “leach-proof” Pd-EnCat^[9]. Interestingly, for the majority of the tests with Quadrapure™ TU, some activity was observed for all three precatalysts, although this activity was significantly less than without the addition of Quadrapure™ TU. We attribute this to two primary phenomena. First, a small amount of activity was observed at room temperature before submersion into an 80 °C oil bath. Quadrapure™ TU is an organic polymer resin which requires swelling of the pore structure to increase access of poisoning sites to solubilized palladium. Therefore, observed activity could be due to soluble palladium catalysis before the polymer sufficiently swelled enough to allow Pd diffusion into the polymer matrix. Second, when water is used as the solvent, the bromoacetophenone melts, creating a separate organic liquid phase, which forms a small globule. The majority of Pd-SH-SBA-15 based particles were observed to preferentially collect inside the bromoacetophenone globule whereas the Quadrapure™ TU beads (average particle size ~ 500 microns) were suspended in the water or stuck to the outer surface of the organic phase. Under these conditions the diffusion of palladium from the Pd-SH-SBA to the Quadrapure™ TU may be further hampered, thereby allowing some catalysis to occur. Thus, under these conditions, application of Quadrapure™ TU as a poison is not ideal. Indeed, choosing the right solid poison to assess catalysis requires forethought and sometimes screening, and in some cases, marginal information may be obtained. For example, when using supported precatalysts that are soluble under reaction conditions (e.g. polymer-supported

precatalysts), solid phase poisons such as Quadrapure™ TU may prove to give ambiguous results.^[27, 59] However, in this work, with all tests using SH-SBA-15 or SH-SiO₂, no activity was observed, confirming the selective poisoning ability of tethered thiols and that observed catalysis without the presence of tethered poisons is associated with leached metal.

Table 4.5 Results from selective poisoning of different palladium precatalysts for Suzuki^a reactions of bromoacetophenone with phenylboronic acid

Precatalyst	Solvent	Time	Conversion with Poison			
			<i>none</i>	<i>SH-SBA-15</i>	<i>Quadrapure TU</i>	<i>SH-SiO₂</i>
Pd(OAc) ₂	DMF	6 h	100%	0%	0%, 20%	0%
	H ₂ O	6 h	100%	0%	20%	0%
Pd-SH-SBA-15	DMF	6 h	94%	0%	6%	0%
		8 h	100%	0%	---	---
	H ₂ O	6 h	80%	0%	30%	0%
Pd-C	DMF	6 h	48%	0%	0%	0%
	H ₂ O	6 h	76%	0%	---	---

^a Reaction conditions are 1.0 mmole bromoacetophenone, 1.5 mmole phenylboronic acid, 2.0 mmole K₂CO₃, 0.5 mmole internal standard (hexamethylbenzene for H₂O and DGDE for DMF), 1.0 % catalyst, and 5 mL solvent under argon atmosphere in sealed reaction tube. The molar ratio of poison to palladium was 35 for all poisons.

4.3.6 Reinterpretation of literature regarding activated bromide reactions Part 2

Crudden used a number of techniques to assess the heterogeneity of the Suzuki reactions catalyzed using mercaptopropyl-functionalized silica supported palladium precatalysts. One was a hot filtration test on a Suzuki coupling of bromoacetophenone with phenylboronic acid. When care was taken to charge the filtrate with fresh base and phenylboronic acid, an increase from 12% conversion to 17% conversion was observed in the filtrate. This was interpreted as evidence that some leached species were present, but that they were responsible for only a small amount of the catalysis occurring, with the majority attributable to heterogeneously catalysis. As noted above, the marginal increase in conversion after filtration could also be a reflection of the relatively small amount of solubilized palladium that survived the hot filtration process. A test using a trace amount of soluble catalyst (0.5 ppm of palladium acetate; 0.00023 mol% catalyst) resulted in less than 5% conversion with the conclusion that small amounts of solubilized palladium could not account for the observed activity for Pd-SH-SBA-15.^[36] The strongest evidence for heterogeneous catalysis came from the use of the 3-phase test in which soluble aryl bromides were reacted to a much greater extent than immobilized aryl bromides. Combining all these previous data, the conclusion that some heterogeneous catalysis was occurring appeared reasonable.

Our observation that addition of bare, unmetalated porous mercaptopropyl-modified support completely suppressed catalysis in both Heck and Suzuki reactions brings new data to be considered. These data can best be interpreted by hypotheses that leached, soluble palladium play a key role in the catalysis. Like all other ligand-metal

complexes, there exists an equilibrium between bound and free metal species in solution. Based on the results presented here, alkyl-thiol groups bind Pd more strongly than pyridyl groups and thus the mercaptopropyl-modified support is effective in significantly limiting the amount of soluble species that are in solution. One hypothesis explaining the combined data is that it is solely leached palladium species that are active for the observed coupling reactions. This is the most likely explanation of the data in our assessment, as it is consistent with the compiled information in the literature.^[5] An alternate hypothesis is that only traces of palladium at defect sites on the surface are active, and these species are more likely to leach than most of the other sites. Thus, addition of solid poison captures these species as they leach into solution, removing them from the solid precatalyst, rendering it inactive. In the context of the current catalyst system, one might envision palladium species bound to a single thiol as more likely to leach (and perhaps be active on the solid surface), whereas species bound by two or more thiol ligands are inactive and less likely to leach. This latter hypothesis seems less likely, as addition of a solid poison at a midpoint of a reaction should not result in instantaneous deactivation of active solid supported species. Instantaneous deactivation is most consistent with all the catalysis being associated with reactions promoted by soluble catalytic species (Fig. 4.6, C). The trend of increased deactivation with an increasing amount of excess surface thiol on partially metalated surfaces supports the notion that if enough bare, accessible thiol is present, then all palladium species can be over coordinated and they are therefore unavailable for leaching and catalysis.

Can the previous data of Crudden suggesting heterogeneous catalysis be rationalized in light of these new results? Both the filtration test and 3 phase test data

were used to suggest catalysis by solid-supported species. We suggest that a positive result for each test – observation of activity in the filtrate after filtration of a solid precatalyst and observation of conversion of solid-bound reactants in the three phase test - can be used as definitive evidence of some leaching of catalytic species when no background reaction exists. However, the negative of each test is, in our opinion, potentially ambiguous when applied to palladium catalyzed coupling reactions. As noted above and in previous works^[5, 9], the competing rates of palladium deactivation, redeposition and aggregation all can influence the clarity of these tests. For example, both the filtration and 3-phase tests gave results that suggested limited (but not zero) solution phase activity in past studies of Suzuki couplings of bromoacetophenone.^[36] In the 3-phase test using bromoacetophenone, the soluble bromoacetophenone was at 50% conversion whereas only 3% of the supported aryl bromide was converted after 5 hours. Increasing the reaction time to 13 h increased the soluble component yield to 97% and the immobilized yield to 7%. Combined with the observation that a trace amount of soluble catalyst (0.5 ppm of palladium acetate; 0.00023 mol% catalyst) resulted in less than 5% conversion of bromoacetophenone in a Suzuki coupling, it was suggested that small amounts of solubilized palladium could not account for the observed activity for Pd-SH-SBA-15. Furthermore, in a 3-phase test using soluble chloroacetophenone, after 24 h the yield of soluble aryl chloride was 80% and no conversion of the tethered chloride was observed. Thus, it was suggested that heterogeneous sites were responsible for the aryl chloride activity. However, this analysis based on the previous data needs to be re-examined in light of our new results. The previous analysis neglects the role that the immobilization of palladium plays in both protecting palladium from aggregation and

controlling how palladium is released into solution (at what rate, what temperature, etc.), making using the trace soluble Pd(OAc)₂ test difficult to compare to reactions using immobilized palladium. If the palladium leached from Pd-SH-SBA-15 is from oxidative addition of aryl halide, then the initial homogeneous source of Pd(II) into solution will be different from homogeneous palladium acetate, which is important with respect to reduction and deactivation pathways. Also, it is possible that the trace amount of homogeneous palladium acetate was deactivated during the heating of the reaction solution before catalysis could occur, whereas in an immobilized state the palladium might remain dormant until the temperature is high enough to promote both the controlled leaching and subsequent catalysis. In addition, this analysis neglects the role that tethering of a reactant in the three phase test plays on its reactivity.

The ability of aryl halides to stabilize solubilized palladium increases according to ease of oxidative addition (I > Br > Cl). With regards to the 3-phase test, the ease of oxidative addition and the availability of aryl bromide may play a crucial role in not only promoting leaching but also in preventing palladium deactivation and in inhibiting re-deposition. Also, the rate of reaction of supported aryl halide may be significantly slower than the homogeneous counterpart for steric reasons. As noted by Cruden, the aryl bromide conversion data show quite clearly that there is at least some active leached metal. The rise in yield of supported aryl halide with time could alternately be suggestive of a slow rate of reaction resulting from its immobilization on surface. Unfavorable competition for the small amount of homogeneous palladium between soluble and supported aryl halide could slow the reaction of the immobilized reagent until the majority of soluble boronic acid component is consumed by both Suzuki coupling and

self-coupling, but even then the palladium could be inaccessible due to Pd-Pd agglomeration or re-deposition. Therefore, while the 3-phase data clearly show the presence of leached, active palladium, they do not conclusively show, in our eyes, that the majority of catalysis is occurring on the surface. As demonstrated in this study, the ability of SH-SBA-15 to poison catalysis under similar conditions is strong evidence that the catalysis of the soluble component is more consistently interpreted, in light of the combined data of Shimizu, Crudden, Davis and the present work, as resulting from leached palladium.

4.3.7 Effect of S:Pd ratio on activity

One additional variable that warrants investigation is the role of the S:Pd ratio, as previous reports suggested this ratio to be important to the observed reactivity when using the solid precatalysts. In 1988 Wang and Liu reported their findings that macromolecular palladium chelates exhibited no activity in the Heck coupling of iodobenzene with ethyl acrylate when a S:Pd ratio of 6 or greater was employed.^[29] Reducing the ratio to 3:1 showed a moderate increase in activity and further reduction to 2:1 gave the highest yields. These findings highlight the importance of the S:Pd ratio on the catalyst activity and demonstrate that over coordination by sulfur can slow or quench catalysis. It is important to note that these ligands were first complexed to palladium before immobilization and thus do not give insight into how immobilized thiols coordinate to free palladium.

In 2005 Crudden synthesized two different mercaptopropyl-modified SBA-15 supports. The first was made by post grafting the mercaptopropyltrialkoxysilane with the preformed SBA-15. Out of 10 batches only 3 had any level of catalytic activity. Reasons for the lack of activity were not known at that time. The S:Pd ratio was not reported but based on the reported thiol loading and assuming all available palladium acetate was bound to the surface during the metalation, a ratio of 8.8 is calculated. A possible explanation for the lack of activity is that the large excess of available sulfur sites could conceivably bind leached palladium (or prevent leaching at all) and self-quenches the catalysis. Indeed when we reduced our palladium content of Pd-SH-SBA-15 from 11.06 wt% (S:Pd = 1.7) to 8.45 wt% (S:Pd = 2.6) and 4.6 wt% (S:Pd = 5.3) we observed a decrease in the Heck coupling of bromoacetophenone with butyl acrylate with each successive increase in the S:Pd ratio (Table 4.6). For the Heck coupling of iodobenzene, the increase in S:Pd ratio from 1.8 to 5.3 resulted in a small amount of Heck coupling of iodobenzene for one run (22% after 1300 min) and no activity for two replicates (standard conditions) (Table 4.6). This catalyst was also inactive for a Heck coupling of bromoacetophenone with *n*-butyl acrylate (standard conditions with data taken to 24 hr). Decreases in activity resulting from increases in the S:Pd ratio were also observed for Suzuki reactions of bromoacetophenone and phenylboronic acid. To probe the maximum capacity of SH-SBA-15 to quench catalysis by homogeneous palladium acetate, a reaction was performed in which palladium acetate was dosed into a reaction containing SH-SBA-15 (Fig. 4.7). Activity was not observed until the S:Pd ratio was lowered to 5.2, after which rapid conversion followed by a quenching of catalysis was observed. This

cessation is likely a reflection of the rate at which the partially metalated SH-SBA-15 is able to bind additional palladium against the rate of catalysis by the unbound palladium.

Table 4.6 Effect of S:Pd ratio on activity of Pd-SH-SBA-15 precatalysts^a.

S:Pd	Halide	Reaction	Solvent	Conversion	Time (min)
1.8	iodobenzene	Heck	DMF	100%	130
	bromoacetophenone	Heck	DMF	93%	165
	bromoacetophenone	Suzuki	DMF	100%	480
	bromoacetophenone	Suzuki	H ₂ O	80%	360
2.6 ^b	bromoacetophenone	Heck	DMF	14%	1130
	bromoacetophenone	Suzuki	DMF	42%	360
	bromoacetophenone	Suzuki	H ₂ O	31%	360
5.3	iodobenzene	Heck	DMF	0%, 0%, 22%	1300
	bromoacetophenone	Heck	DMF	0%	1440

^a Experiments conducted under normal Heck and Suzuki reaction conditions.

^b Addition of 35 equivalents of SH-SBA-15 poison resulted in no activity under similar Heck and Suzuki conditions when using a Pd-SH-SBA-15 precatalyst with a S:Pd ratio of 2.6

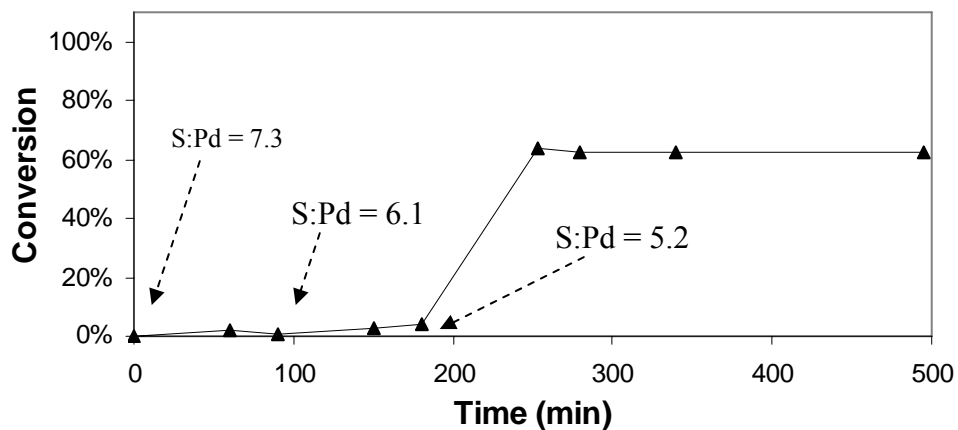


Figure 4.7 Plot of iodobenzene conversion (DMF, 90 °C, NEt₃) with SH-SBA-15 used as a poison with a 0.1 mL dose of a 0.063 mmols/mL solution of Pd(OAc)₂ in DMF added at time zero (S: Pd = 7.3) followed by additions of 0.02 mL added at 90 min (S: Pd = 6.1) and 180 min (S: Pd = 5.2).

4.3.8 Utility of Pd-SH-SBA-15 as a practical Heck and Suzuki precatalyst

Although these new data suggesting catalysis by leached species speak to nature of the true catalytic species, they do not address the functional utility of these precatalysts. The previous data on Suzuki couplings promoted by catalysts of this type strongly suggest that the amount of palladium in solution after reaction is quite small. Shimizu found that after reaction the palladium levels in solution for Pd-SH-FSM were 0.5 ppm for Suzuki reactions and 0.1 ppm for Heck reactions of activated bromides.^[33] Crudden reported that for Suzuki reactions using Pd-SH-SBA-15 the palladium leaching levels ranged from 0.003 ppm to 0.75 ppm depending on reaction conditions and that for Heck coupling of bromoacetophenone with styrene the palladium in solution was 0.27 ppm.^[36] However, the total amount of palladium leached was generally less than 0.2 ppm

at a S:Pd ratio of 2:1. Another recent publication also suggests that only traces of palladium remain in solution after reaction.^[60] These low levels of palladium leaching suggest that either the leached species are very active (i.e. if all conversions are catalyzed by the amount of palladium in solution after the reaction), or that a redeposition process is at play, whereby larger amounts of leached palladium are active during reaction, with some or most of the palladium redepositing on the SH-SBA-15 surface after reaction. After recovery this redeposited palladium may be available for further reaction as similarly found for other immobilized palladium precatalysts.^[16, 52, 61, 62] However, if the S:Pd ratio is above 2:1, then palladium capture and over coordination by excess surface thiols may result in a partial or complete deactivation of catalysts, as was observed for partially metalated SH-SBA-15 surfaces (vide supra). Either way, the amount of palladium in the products after reaction appear to be minute enough to make the precatalyst useful for producing nearly palladium-free Heck and Suzuki coupling products. A very recent report of thiol-supported palladium precatalysts also suggest only traces of palladium are found in solution after reaction.^[63] Although the nature of the true catalytic species was not addressed in this work, our results presented here strongly suggest this system also is simply a precatalyst that liberates soluble catalytic species in solution.

4.4 Conclusions

In summary, a mercaptopropyl-modified mesoporous silica, SH-SBA-15, was successfully synthesized and used as a solid support for immobilization of palladium acetate, Pd-SH-SBA-15. The metalated material was used as a catalyst for both Heck and Suzuki reactions under a range of conditions. Metal-free SH-SBA-15 was shown to be an effective poison of both homogeneous palladium acetate and Pd-SH-SBA-15 used as precatalysts for Heck and Suzuki reactions. Therefore, we assert Pd-SH-SBA-15 is simply a reservoir of leached palladium, which is in agreement with previous findings by Davis et al. with regards to Heck reactions using iodobenzene^[40] and suggests that previous interpretations of heterogeneous catalysis with these precatalysts in Heck and Suzuki couplings may need reinterpretation in light of the new data presented here.^[33, 36]

This work introduces SH-SBA-15 as a new selective poison for elucidating solution versus surface catalysis by palladium and demonstrates its use as a more effective and versatile poison than poly(4-vinylpyridine) and QuadrapureTM TU. Thus, selective poisons tethered onto silica substrates, such as SH-SBA-15 and SH-SiO₂, are a better class of materials for selective poisoning of palladium than are poisons tethered to insoluble organic polymers. The ability of insoluble, selective poisons to poison homogeneous palladium is dependent on the ratio of binding sites to soluble palladium. Therefore, control reactions in which known amounts of homogeneous palladium complexes are poisoned should be performed first to (i) verify poisoning ability and (ii) determine the proper amount of selective poison required to quench catalysis if all available immobilized Pd were to leach into solution. The 3-phase test can provide positive confirmation of catalysis from leached Pd, but lack of activity may not confirm

strictly heterogeneous catalysis. Quenching of palladium catalyzed reactions by SH-SBA-15 suggests that the active catalyst is comprised of at most a few atoms of palladium and not from catalysis on palladium nanoparticle surfaces.

4.5 References

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- [63] X. Jiang, J. Sclafani, K. Prasad, O. Repic, T.J. Blacklock, *Org. Process Res. Dev.* (2007) (in press). Note that the authors measured palladium solution content after passing the reaction solution through celite, washing with water, which was discarded, and drying the organic with MgSO₄. This procedure was most likely chosen to mimic procedures used in the pharmaceutical industry and thus gives a good representation of how much metal contamination would be found in the organic product stream. However, the employed workup procedures could have removed a significant amount of soluble metal from the reaction solution through deposition of palladium metal on celite and dissolution in the aqueous phase.

Thus palladium levels of the final workup are not reflective of palladium levels in the final reaction solution.

CHAPTER 5

INVESTIGATION OF HOMOGENEOUS AND ANCHORED Ni(II) COMPLEXES AS PRECATALYSTS FOR KUMADA REACTIONS

5.1 Introduction

In all previous chapters the focus was on Pd(II) precatalysts used for Heck or Suzuki reactions. In Chapter 2 we demonstrated that SCS-Pd(II) pincers decompose to leach active metal. In the next two chapters we demonstrated that both palladium acetate incarcerated in a poly(urea) matrix (Chapter 3) and immobilized on a mercaptopropyl modified surface (Chapter 4) are reservoirs for leached active metal for Heck^[1, 2] and Suzuki reactions.^[1] The work from these chapters are critical evidence for the growing consensus that the activity for immobilized palladium catalyzed coupling reactions is actually due to leached metal.^[1-5] We wondered if the same were true for other d¹⁰ transition metals and chose the nickel catalyzed Kumada-Corriu reactions as a relatively unexplored area for distinguishing homogeneous from heterogeneous catalysis. However, it was unknown to what extent the use of both nickel and Grignard reagents would have on the ability to discern the nature of the catalytic species and if the strategy of using selective poisons that works successfully for Pd catalyzed Heck and Suzuki couplings would work for Ni catalyzed Kumada-Corriu couplings. The first goal of this Chapter was to anchor Ni(II) onto tethered nitrogen bearing ligands and use these materials as precatalysts for Kumada-Corriu reactions. Keeping with the themes of the previous Chapters, we sought to distinguish whether observed catalysis was from either

heterogeneous or homogeneous nickel. Lastly, we were interested in exploring two tests, three phase and selective poisoning, never before used for Kumada-Corriu chemistry.

Metal-catalyzed carbon-carbon bond forming reactions are an indispensable tool for the synthesis of fine chemicals and pharmaceutical compounds. In 1941 Kharasch et al. reported the combined use of NiCl_2 and bromobenzene to promote the formation of biphenyl from phenylmagnesium bromide.^[6] It was not until the early 1970's that a variety of other transition metal catalyzed cross coupling reactions of practical use were discovered and set the stage for a tremendous amount of scientific investigation in this area. One of the very first cross coupling reactions discovered at this time was the nickel catalyzed reaction of sp^3 -hybridized and sp^2 -hybridized carbons with nucleophilic Grignard reagents, almost simultaneously reported by Kumada and Corriu and now such couplings are commonly referred to as Kumada-Corriu reactions.^[7, 8] Following these original works, the literature regarding Kumada-Corriu reactions is relatively sparse as compared to the vast amount of studies regarding other C-C coupling reactions such as the Heck and Suzuki reactions. This is most likely due to the difficulty in working with Grignard reagents, which typically have stability issues and low functional group tolerances. However the development of Kumada chemistries is of practical interest. Commercially desirable alkyl and aryl chlorides more readily undergo C-C couplings catalyzed by nickel under Kumada-Corriu conditions than under Heck and Suzuki conditions.^[9] Grignards are often used as building blocks for the formation of boronic acids, which are subsequently used in Suzuki coupling reactions and thus in these cases the direct use of Grignards would reduce the number of synthetic steps.^[10] Kumada-Corriu reactions have found practical use in the synthesis of commercially relevant

molecules, have been included in a number of patents^[11] and have been used at the plant level to synthesize fine chemicals.^[12] Of economic interest is the ability to perform Kumada-Corriu reactions at or near room temperature, thereby reducing energy costs.

The majority of nickel catalyzed Kumada-Corriu reactions of aryl halides with Grignard reagents have been performed with homogeneous catalysts. Examples include ligandless nickel^[13] and nickel complexed to phosphine ligands^[7, 8, 14-24], bis(pyridyl)-silane ligands^[25], phosphine sulfide ligands^[26], N,N,O-Chelating ligands^[27], allylic groups^[28], carbenes^[29] and imidazolium derived ligands.^[30, 31] Despite the high activities that can sometimes be achieved with homogeneous catalysts, the difficulties and high costs associated with recovery and reuse of homogeneous catalysts can hinder their commercial utilization. Thus, heterogeneous catalysts are often preferred in practical applications. An approach to such catalysts is to anchor organometallic complexes in the hope that they retain the desired catalytic properties of their homogeneous counterparts, but are also recoverable due to their attachment to an easily recovered solid.

There a small number of studies pertaining to immobilized metallic particles for potentially surface catalyzed Kumada-Corriu reactions. One of first such studies was a series of three papers by Lipshutz et al. in which nickel on carbon, Ni/C, was rigorously examined for both amination and Kumada-Corriu reactions under a range of reaction conditions.^[32-34] Verification of the presence of leached, active nickel was made by observing the promotion of amination activity and the decrease in Kumada activity in the presence of PPh₃ immobilized on a polymer, quantification of dissolved nickel in solution by ICP-AES, effects from added homogeneous PPh₃, and comparison of TON's between various metal loadings. It was also determined that leached nickel selectively partitions

into the porous carbon matrix. This selective partitioning resulted in near complete recovery of metal after recovery of the solid support material. These papers by Lipshutz et al. also stressed the danger of solely relying on ICP-AES and hot filtration experiments for determination of heterogeneous catalysis by immobilized transition metals. The topic of distinguishing homogeneous from heterogeneous catalysis will be addressed later in this work.

Styring and collaborators published a series of papers describing nickel anchored onto both polymer^[35-37] and silica materials^[38] via covalent grafting of a metal-salen coordination complex, that was employed in Kumada-Corriu reactions to form a variety of biaryls. In one study, the elemental analyses of the post reaction solutions showed sub-ppb levels of nickel, which was interpreted as conclusive proof for no nickel leaching.^[36] In a later study, 1% of the nickel was found in the post reaction solution, demonstrating that the majority of nickel could be recovered, but no claims as to the whether proceeded homogeneously or heterogeneously were made. It was noted that the catalyst could be recycled five times without significant loss in yield (no reaction kinetics were reported).^[37] Following this work, Phan et al. immobilized a nickel-salen on a silica surface and used this pre-catalyst in a micro-flow system to catalyze the Kumada-Corriu reaction of 4-bromoanisole with phenylmagnesium bromide.^[38] Again, only 1% nickel was found in post reaction solutions, indicating that the majority of nickel could be recovered. It is our assertion that the detection of low nickel levels in post-reaction solutions does not preclude a mechanism by which metal can leach, effect catalysis, and then redeposit after completion of reaction as has been observed for both nickel^[33, 39] and palladium in other studies.^[3, 40-47] Therefore, it is unclear as to what extent catalysis is

happening heterogeneously or homogenously for the nickel-salen materials, but it should be noted that these nickel salen materials demonstrate promise as recoverable nickel sources for Kumada-Corriu reactions that can be used with low levels of nickel bleed.

This chapter describes the anchoring of Ni(acac)₂ onto polymer bound (1% cross linked) ethylenediamine, *N*-(2-aminoethyl)-3-aminopropyl functionalized SBA-15, and onto an 2-(4-pyridylethyl) functionalized SBA-15. These materials are used as precatalysts for the Kumada reaction of 4-bromoanisole and phenylmagnesium chloride at room temperature. A series of tests are presented to demonstrate that leaching of active nickel does occur and is dependent of the presence of Grignard and not on the aryl halide, as is typically observed in palladium catalyzed coupling reactions. This work describes the first immobilized reagent for three phase testing of anchored nickel precatalysts. A nickel mediated aromatic transfer between aryl halide and Grignard is suggested to account for the observed byproducts and formation of increasing biphenyl with time.

5.2 Experimental

5.2.1 General

Reagents and solvent were purchased from commercial sources and used without further purification with the following exceptions. Dry tetrahydrofuran (THF) was passed through a packed bed solvent system containing copper oxide and alumina columns to remove water and then further dried with sodium metal under reflux and

distilled under an argon atmosphere. A commercially available 2 M solution of phenylmagnesium chloride in THF was stored in an MBraun UniLab 2000 dry box and 40 mL aliquots were transferred into a 50 mL Schlenk flask for use in experiments using standard Schlenk techniques. FT-Raman spectroscopy was performed on a Bruker FRA-106 with 1028 scans collected for each sample using a 100 kW laser source with a resolution set at 3 cm^{-1} . GC and GC-MS analyses were performed on a Shimadzu GCMS-QP2010S with a Shimadzu SHRX5 column for the flame ionization detector and a Shimadzu SHR5XLB column for the mass spectrometer detector. Simultaneous thermal analysis (Netzsch STA 409 PG Luxx) was used to determine the loadings of organically modified supports and atomic weight percents were verified by elemental analysis (Desert Analytics, Tucson, Arizona). Large pore (105 Å) SBA-15 was synthesized according to previous reported procedures.^[1]

5.2.2 Synthesis of *N*-(2-aminoethyl)-3-aminopropyl functionalized SBA-15

A suspension of 4.5 g of SBA-15 and 150 mL of dry toluene was made in a 250 mL round bottom flask. To this was added 9.0 g of *N*-(2-aminoethyl)-3-aminopropyltrimethoxysilane and the suspension was brought to reflux with vigorous magnetic stirring for 48 h. The solids were filtered with copious amounts of toluene and hexanes and then Soxhlet extracted with DCM for 36 h and dried at 105 °C under high vacuum for 16 h. STA analysis yielded 14.1 wt% of organics lost between 200 °C and 800 °C from which a loading of 1.8 mmol N/g solids was estimated. To cap silanol groups and hydroxyl groups the solids were added to 75 mL of dry toluene and 4 g of

capping agent 1,1,1-3,3,3-hexamethyldisilazane, HMDS, was added. The suspension was stirred at room temperature for 24 h and the solids were recovered by filtration and washed with toluene and hexanes. After Soxhlet extracting with DCM for 36 h the solids were dried at 80 °C for 16 h under high vacuum. Final STA analysis gave an organic loading of 16.3 wt% and elemental analysis gave a 1.9 mmoles N/g solids. Organic functionalization was also confirmed by FT-Raman spectroscopy (Fig. 5.1). Aliphatic $\nu(\text{C-H})$ stretching is observed at 2959 cm^{-1} and 2901 cm^{-1} wavenumbers.

5.2.3 Synthesis of 2-(4-pyridylethyl) functionalized SBA-15

A suspension of 4.5 g of SBA-15 and 150 mL of dry toluene was made in a 250 mL round bottom flask. To this was added 9.0 g of 2-(4-pyridylethyl)triethoxysilane and the suspension was brought to reflux with vigorous magnetic stirring for 48 h. To promote further silane cross-linking, 1.5 mL of doubly distilled H_2O was syringed into the suspension under positive argon flow and the suspension was kept at reflux for an additional 4 h. The solids were recovered by filtration and washed with copious amounts of toluene and hexanes and Soxhlet extracted with DCM for 36 h and dried at 80 °C under high vacuum for 16 h. STA analysis yielded 29.0 wt% of organics lost between 200 °C and 800 °C, corresponding to a loading of 2.7 mmoles N/g solids (assuming all methoxy groups of the silane reacted due to H_2O treatment). The solids were added to 75 mL of dry toluene and 4 g of 1,1,1-3,3,3-hexamethyldisilazane was added to cap any remaining O-H groups. The suspension was stirred at room temperature for 24 h and the

solids were recovered by filtration and washed with toluene and hexanes. After Soxhlet extracting with DCM for 3 d the solids were dried at 80 °C for 16 h under high vacuum. Final STA analysis yielded a 29.5 wt% loss. This 0.5 wt% increase from the noncapped material indicates few R-OH or Si-OH groups were available for capping.⁹ Elemental analysis gave a 2.8 mmol N/g solids. Organic functionalization was confirmed by FT-Raman spectroscopy. Strong aromatic $\nu(\text{C-H})$ stretching is observed at 3050 cm^{-1} and the aliphatic $\nu(\text{C-H})$ stretching is observed at 2896 cm^{-1} .

5.2.4 Metalation of *N*-(2-aminoethyl)-3-aminopropyl functionalized SBA-15

To 50 mL of THF was added 0.5 g of $\text{Ni}(\text{acac})_2$. After dissolution of the $\text{Ni}(\text{acac})_2$ 1.0 g of SBA-Diamine was added. The suspension was stirred at room temperature for 24 h, after which the solids were collected by filtration and washed with copious amounts of boiling hot methanol and boiling hot THF. The solids were then dried under high vacuum (< 7 mTorr) for 16 h at 65 °C. The final solid material has a faint blue color. Elemental analysis gave a 0.35 mmol Ni/g solids and a N:Ni ratio of 6.6 and a Ni:Si ratio of 0.03.

⁹ This assumes that the employed capping strategy could successfully cap R-OH and Si-OH groups of this material. The primary reason for capping was to eliminate potential interactions between Grignard reagents and the protons of the hydroxyl groups. If any hydroxyl groups were uncapped due to inaccessibility of the capping agent, then it is also unlikely they are inaccessible to Grignard reagents. Regardless, due to the small amounts of solids employed in relation to the amount of Grignard reagents used, any hydroxyl-Grignard interactions are assumed to be negligible.

5.2.5 Metalation of polymer bound (1% cross linked) ethylenediamine

To 50 mL of THF was added 0.5 g of Ni(acac)₂. After Ni(acac)₂ was observed to completely dissolve 1.0 g of PS-Diamine was added. The suspension was stirred at room temperature for 24h, after which the solids were collected by filtration and washed with copious amounts of boiling hot methanol and boiling hot THF. The solids were then dried under high vacuum (< 7 mTorr) for 16 h at 65 °C. The final solids were green in color. Elemental analysis gave a 0.65 mmoles Ni/g solids and a N:Ni ratio of 3.1.

5.2.6 Synthesis of 3-iodopropyl functionalized SBA-15

SBA-15, 2.0 g, was activated by heating at 200 °C for 2 h under high vacuum (< 7 mTorr) and placed inside an oxygen and moisture free glove box. The SBA-15 was added to 75 mL of dry toluene. An addition of 4.0 g of 3-iodopropyltrimethoxysilane was made and the resulting suspension was stirred at reflux for 48 h. The solids were filtered with copious amounts of toluene and hexanes and then Soxhlet extracted with dichloromethane for 36 h and dried at 75 °C under high vacuum for 16 h. The STA analysis yielded 27.8 wt% of organics lost between 200 °C and 800 °C. Assuming that most of the silane is bonded to two Si-OH groups on the surface, a loading of 1.4 mmoles I/g solids is estimated. Recovered solids were added to 75 mL of dry toluene and 4.0 g of 1,1,1-3,3,3-hexamethyldisilazane was added to cap any remaining O-H groups. The suspension was stirred at room temperature for 24 h and the solids were recovered by filtration and washed with toluene and hexanes. After Soxhlet extracting with DCM for

24 h the solids were dried at 75 °C for 16 h under high vacuum. STA analysis yielded 28.4 wt% of organics lost between 200 °C and 800 °C indicating few R-OH or Si-OH groups were available for capping. Elemental analysis yielded an iodine loading of 1.5 mmoles I/g solids. Aliphatic C-H stretching is observed at 2957 cm⁻¹ and 2893 cm⁻¹. The presence of C-I bonds was confirmed by observation of a strong peak in FT-Raman at 503 cm⁻¹.

5.2.7 Synthesis of SBA-Pyridine-Ni

Ni(acac)₂, 0.5 g, was dissolved in 50 mL of THF after which 1.0 g of SBA-pyridine was added. The solution was brought to reflux under argon for 24 h. The solids were filtered and washed with copious amounts of boiling hot methanol and boiling hot THF and subsequently dried at 65 °C under high vacuum for 16 h. The recovered particles had an aquamarine color. Elemental analysis gave a 0.26 mmoles Ni/g solids and a N:Ni ratio of 10.3 and a Si:Ni ratio of 40:1.

5.2.8 Kumada coupling

In experiments with anchored nickel precatalysts, the precatalyst was added to a 10 mL pear shaped flask, sealed with a red rubber septa, and purged with argon for 2 min. Separately 0.5 mmole of 4-bromoanisole and 100 µL of DGDE were added to 4.5 mL of dry THF. This solution was syringed into the flask. To alleviate the pressure during this step, the flask was connected to the argon manifold of a Schlenk line via a needle and red

rubber tubing. When homogeneous Ni(acac)₂ was used as the catalyst, 0.5 mL of a 0.005 M solution of Ni(acac)₂ in dry THF was syringed into the flask after the reagent solution was added. The flask was partially immersed in a glass beaker with water (to provide a heat sink for any heat generated from a subsequent addition of Grignard reagent) and the solution was stirred for 10 minutes at which time a time zero sample was taken. Next, 0.5 mL of a 2 M solution of phenylmagnesium chloride in THF was injected to initiate the reaction.

5.2.9 Reaction sampling

Samples for kinetic analysis were taken by syringing a 0.1 mL sample out of the solution. This sample was added to a solution of 1.5 mL DCM and 0.2 mL methanol. Approximately 0.2 mL of doubly distilled H₂O was added and the solution was mixed by syringing in and out of a pipet a minimum of 5 times. The solution was allowed to separate and the DCM fraction removed via pipet, dried with MgSO₄, and then passed through a cotton plugged pipet containing a small bed of celite and MgSO₄. This filtered solution was then analyzed by GC. Peak identification was performed by both using standards of commercially available compounds and by using a mass spectrometer. Calibration files of 4-bromoanisole, anisole, biphenyl, 4,4-dimethoxybiphenyl, 4-methoxybiphenyl, were created by adding known amounts of compounds to solutions of 5 mL THF. To each solution was added 100 μL of DGDE using a micropipet. Samples were taken and worked up in the same manner as that for reaction samples and the peak area ratios of each compound to DGDE were determined. For each compound a plot of

mmoles of compound to peak ratios was made from which linear trendlines were computed and used to quantify the amount of compounds in the reactions from the peak area ratios of the compound to internal standard.

5.2.10 Filtration experiments

Filtration of reaction solutions were performed at various times in the reaction profile using a swivel frit (medium frit) connected to an argon manifold on a Schlenk line. Reaction conditions were kept the same as for the normal reactions with the exception that a 15 mL 3-neck flask was used as the reaction vessel. The reaction was allowed to progress for a certain amount of time and then filtered using the swivel frit into another 3-neck flask. The filtrate was magnetically stirred and monitored for activity. Where indicated, the addition of either aryl halide or Grignard reagent was performed using a syringe.

5.2.11 Recycle experiments

To insure enough material for elemental analysis the reaction was adjusted from that of normal runs to bring the catalyst loading to 2 mol%. SBA-Dia-Ni (100 mg) was weighed into a 50 mL round bottom flask and sealed with a red rubber septum. The flask was purged with argon. A solution of 15.6 mL of dry THF, 1.73 mmole of 4-bromoanisole, and 340 μ L of DGDE was syringed into the flask under argon flow. The suspension was allowed to stir for 10 minutes at which point a time zero sample was

taken. A volume of 1.74 mL of a 2 M solution of phenylmagnesium chloride in THF was added to initiate the reaction. Samples were taken at 30, 120, and 240 m intervals. After 240 m the reaction solution was filtered and the solids were washed with methanol and diethyl ether to remove the magnesium salts and then with DCM and THF to remove any leftover organic materials. The solids were dried at 120 °C for 2 h, weighed, and then put exposed to <7 mTorr for 12 h. The mass before exposure to vacuum treatment was used as the amount of catalyst available for the next reaction and the amount of all reagents was adjusted according to the amount of recovered catalyst. As an example; 90 mg of catalyst was recovered after the first reaction and thus 1.56 mmoles of 4-bromoanisole, 318.6 mmole of DGDE, 1.6 mL of the 2 M phenylmagnesium chloride solution, and 14 mL of dry THF, were used in the next reaction. After 2 recycles the catalyst was sent for elemental analysis.

5.2.12 Three phase tests

SBA-Propyl-I, 125 mg, and the anchored catalyst were added to a 10 mL pear shaped flask, which was then purged with argon. 4-bromoanisole, 0.2 mmole, and 100 μ L of DGDE were dissolved in THF (4.5 mL when an anchored poison was used and 4.0 mL when homogeneous Ni(acac)₂ was used). This solution was syringed into the flask under argon flow. When homogeneous Ni(acac)₂ was used as the catalyst, 0.5 mL of a 0.005 M solution of Ni(acac)₂ was syringed into the flask. The final solution was allowed to stir for 10 minutes at which point a time zero sample was taken. A volume of 0.3 mL of a 2 M phenylmagnesium chloride solution in THF was syringed into the

solution to initiate reaction. The reaction was magnetically stirred for 6 h, a sample was taken, and the solids were filtered off and washed with MeOH and diethyl ether to remove the magnesium salts and DCM and THF to remove any residual organic molecules. The solids were subsequently dried at 120 °C in an oven and then analyzed by STA and FT-Raman.

5.3 Results and Discussion

5.3.1 Synthesis of PS-Dia-Ni and SBA-Dia-Ni

N-(2-aminoethyl)-3-aminopropyl functionalized SBA-15, SBA-Diamine, was synthesized by silane condensation of *N*-(2-aminoethyl)-3-aminopropyltrimethoxysilane onto the surface of SBA-15. The amount of tethered ligand was determined to be 1.8 mmole/g solids by STA analysis. The surface was capped with HMDS. FT-Raman confirmed the presence of aliphatic organic groups on the surface as seen by the strong C-H stretching at 2959 cm⁻¹ and 2901 cm⁻¹ wavenumbers (Fig. 5.1). Unfortunately N-H stretching was not observed, although this is often the case for FT-Raman spectra of tethered amines on silica surfaces. The presence of nitrogen was confirmed by elemental analysis and found to be 1.9 mmoles/g solids based, which is close to the estimated 1.8 mmoles/g solids based on STA analysis (*vide supra*). Thus, the tethering of the *N*-(2-aminoethyl)-3-aminopropyl group onto the SBA surface is deemed a success.

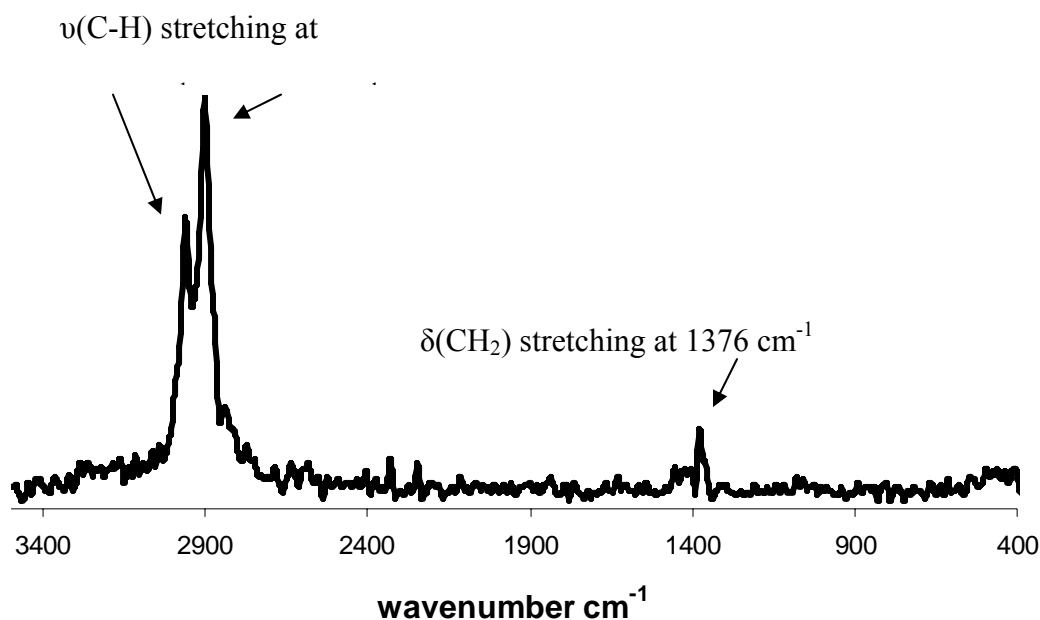
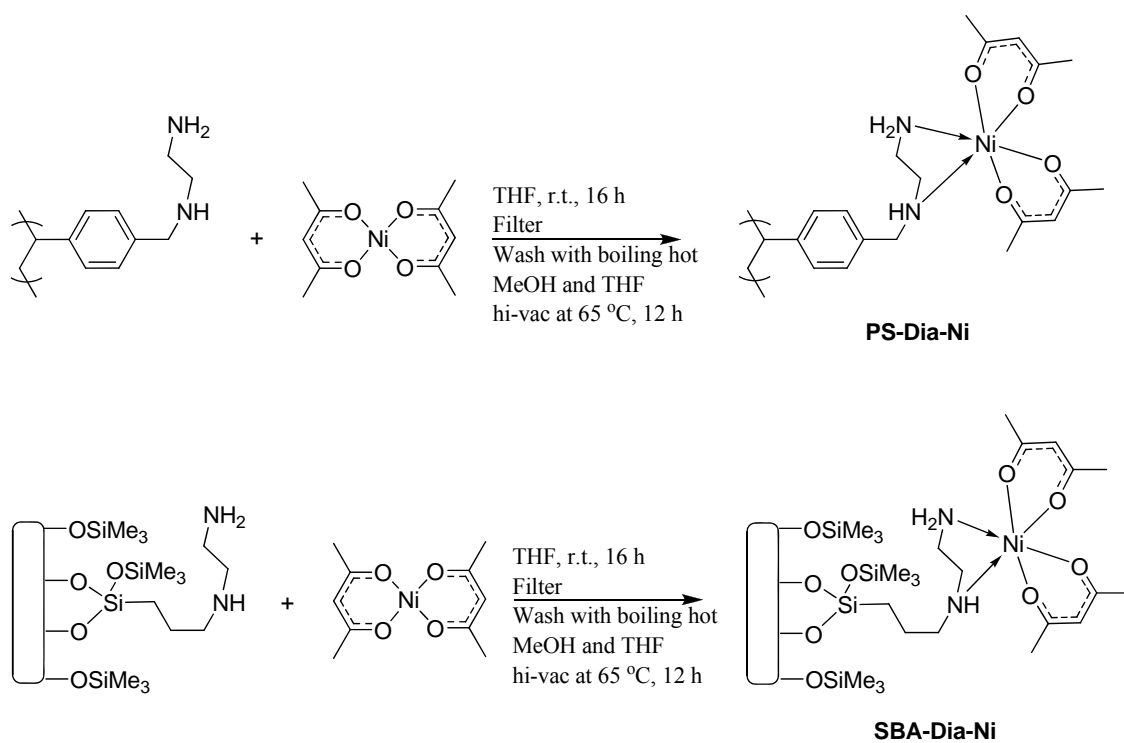


Figure 5.1 FT-Raman spectra of *N*-(2-aminoethyl)-3-aminopropyl functionalized SBA-15. Aliphatic $\nu(\text{C-H})$ stretching is observed at 2959 cm^{-1} and 2901 cm^{-1} wavenumbers.

The anchoring of $\text{Ni}(\text{acac})_2$ onto (i) ethylenediamine, polymer-bound and (ii) SBA-Diamine was successfully achieved (Scheme 5.1). Each precatalyst is respectively abbreviated PS-Dia-Ni and SBA-Dia-Ni. PS-Dia-Ni has a green color while SBA-Dia-Ni has a light blue tint. The presence of nickel was verified for each precatalyst by elemental analysis. The homogeneous metalation of ethylenediamine with $\text{Ni}(\text{acac})_2$ has previously been characterized by X-ray diffraction, showing an octahedral structure determined around the nickel atom with *cis*-arrangements of the two amine atoms and of the oxygen pairs of the acac ligands.^[48-51] This structure is proposed, but not experimentally verified, for PS-Dia-Ni and SBA-Dia-Ni. Interestingly, when *N*-propylethylenediamine was added to a solution of THF and $\text{Ni}(\text{acac})_2$, the solution turned

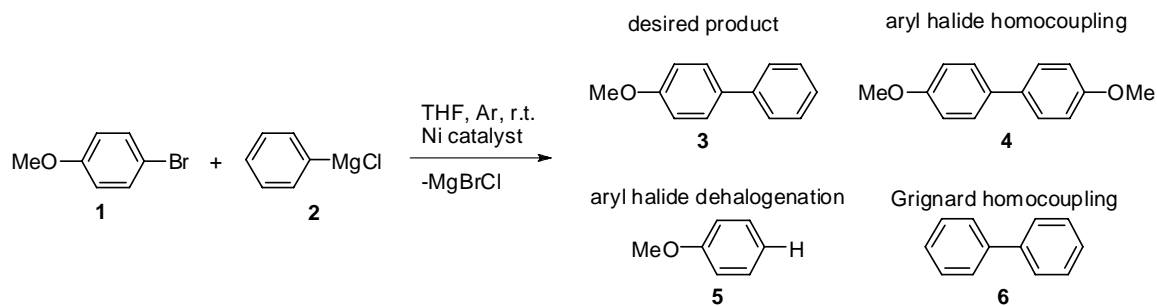
blue in color, which is consistent with the light blue color observed for SBA-Dia-Ni. The green color of the PS-Dia-Ni may be a result of either an influence of the π -electrons of the polymer backbone interacting with the nickel or evidence that some of the Ni(acac)₂ is simply entrapped in the polymer matrix, although the green color persisted after multiple washings with boiling solvents. Thus, it cannot be ruled out that some of the anchored nickel is not bound to the diamine ligand and is instead adsorbed inside the polymer matrix.



Scheme 5.1 Synthesis of anchored nickel precatalysts PS-Dia-Ni and SBA-Dia-Ni.

5.3.2 Activity of PS-Dia-Ni and SBA-Dia-Ni

The Kumada coupling of 4-bromoanisole with phenylmagnesium chloride (Scheme 5.2) was performed with PS-Dia-Ni, SBA-Dia-Ni, and homogeneous Ni(acac)₂ using a low precatalyst loading of 0.5% Ni (Fig. 5.2). All precatalysts exhibited good activity for the Kumada reaction with the activity increasing in order PS-Dia-Ni < SBA-Dia-Ni < Ni(acac)₂. The greater activity observed with SBA-Dia-Ni over that observed for PS-Dia-Ni is attributed to reduced accessibility of the nickel in the polymer matrix of the PS-Dia-Ni due to the possible need for polymer swelling. If the reaction proceeds by leached nickel then the need for polymer swelling could also reduce the amount of leached nickel into solution.



Scheme 5.2 The Kumada coupling of 4-bromoanisole (1) with phenylmagnesium chloride (2) to form desired product (3) and byproducts from aryl halide homocoupling (4), aryl halide dehalogenation (5), and Grignard homocoupling (6).

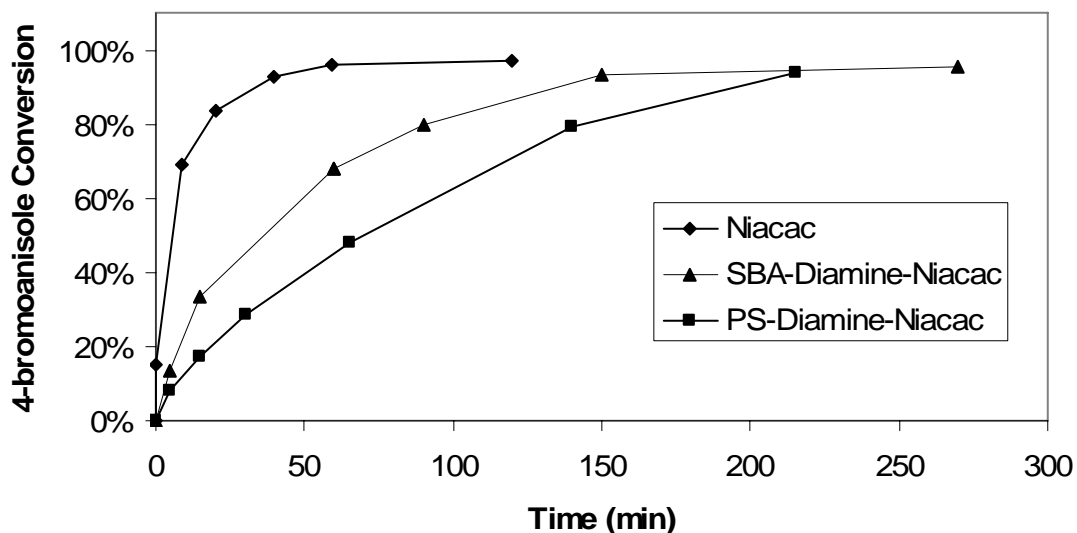


Figure 5.2 Conversion of 4-bromoanisole using either homogeneous Ni(acac)₂, SBA-Dia-Ni, or PS-Dia-Ni. Reactions were performed at room temperature under argon with 1 mmole of 4-bromoanisole, 2 mmole of phenylmagnesium chloride, 5 mL of THF, and 0.5% nickel catalyst.

For each precatalyst studied the desired biaryl 4-methoxybiphenyl, **3**, was formed along with a significant amount of side products, as was also found by previous investigators.^[31, 33, 52, 53] These side reactions include the homocoupling of aryl halide to form 4,4-dimethoxybiphenyl, **4**, the dehalogenation of aryl halide to form anisole, **5**, and the homocoupling of the Grignard reagent to form biphenyl, **6**. In a control experiment without nickel present, no Kumada product, aryl-aryl homocoupling, or dehalogenation was observed to occur. It should be noted in the control experiment that a small amount of biphenyl, 0.02 mmole, was observed at time zero and did not increase with time. A workup of a sample taken directly from a solution of 0.5 mL of the Grignard solution and THF also gave 0.02 mmole biphenyl. Therefore the observed biphenyl in this control experiment is an impurity of the fresh Grignard solution. All mass balances (vide infra) in which biphenyl was considered were adjusted by 0.02 mmole to account of this initial

impurity. Table 5.1 summarizes the final product and side product distributions found for reactions catalyzed by Ni(acac)₂, PS-Dia-Ni, and SBA-Dia-Ni.

Table 5.1 Final reaction distributions and mass balances of nickel catalyzed Kumada couplings of Ar-Br with Ph-Mg-Cl.

Catalyst	Reaction Distribution (mmole)					Mass Balance %	
	Ar-Br 1	Ar-Ph 3	Ar-Ar 4	Ar-H 5	Ph-Ph 6	Ph-Ph not included	Ph-Ph included
Ni(acac) ₂	0.02	0.24	0.06	0.06	0.16	90%	98%
	0.02	0.27	0.03	0.10	0.19	91%	102%
SBA-Dia-Ni	0.02	0.29	0.02	0.11	0.21	89%	103%
	0.01	0.27	0.04	0.09	0.17	88%	96%
PS-Dia-Ni	0.03	0.27	0.02	0.13	0.19	90%	99%

In performing a mass balance on the aryl halide, the sum of **1**, **2**, two times **3**, and **5** should equal 100%, as these products represent all of the typically suggested fates of the aryl halide. However, in this work, this is not the observed, as there is some unaccounted for disappearance of aryl halide. As noted in Table 5.1, the mass balances on aryl halide computed for these reactions are between 88% and 91%, and there is no observation of new peaks in the GC-MS. Also, the amount of biphenyl (**6**), which is usually assumed to arise solely from the reduction of the nickel,^[33] not only was more than two times the amount of nickel present, but also increased with conversion of the aryl halide (Fig. 5.3). Intrigued by this, we wondered if the increase in biphenyl that seems to follow product formation is a result of consumption of aryl halide and thus

might contribute to the missing aryl halide in the mass balance. First a postulated mechanism was needed to account for the biphenyl formation.

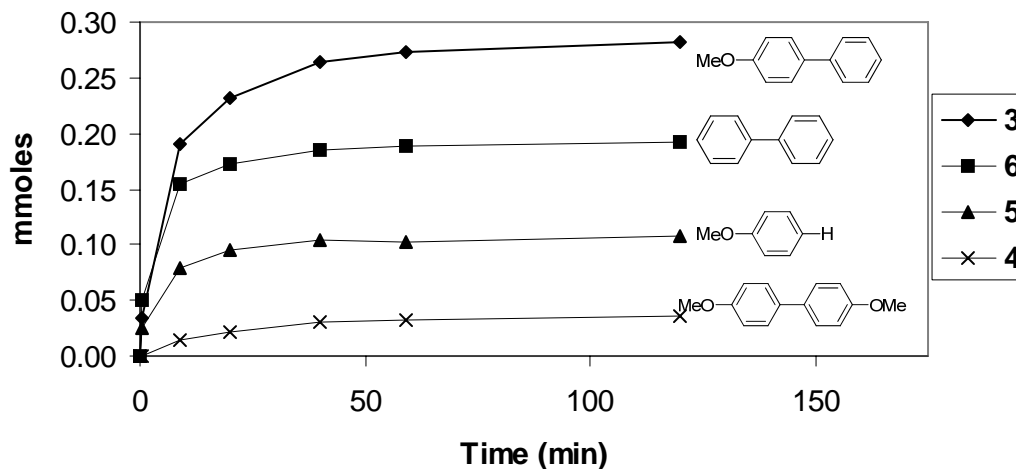


Figure 5.3 Comparison of the formation of product (3), biphenyl (6), and side products from dehalogenation (5) and aryl halide homocoupling (4) for homogeneous Ni(acac)₂ catalyzed reaction of 4-bromoanisole and phenylmagnesium chloride in Figure 5.2.

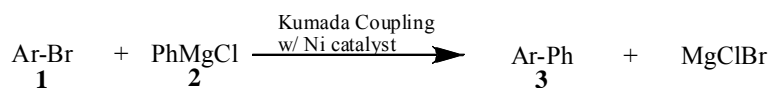
Phan et al. suggested the possibility that the magnesium transmetalates from the Grignard reagent into the C-Br bond of the aryl halide, thereby forming a new Grignard reagent and aryl halide *in situ*, but further studies to verify this were not performed^{10, [37]}. If bromobenzene is being formed from transfer of magnesium from phenylmagnesium chloride to 4-bromoanisole, then the Kumada coupling of bromobenzene with phenylmagnesium chloride could occur to form biphenyl (Scheme 5.3-A). In this work bromobenzene was not observed by GC or MS in the analysis of any of the reaction

¹⁰ The understanding of why homocoupling of the aryl halide occurs is important as this side reaction is an often encountered problem in the manufacturing of fine chemicals using Kumada-Corriu technology.^[7]

solutions, but it is possible that once formed it rapidly undergoes a Kumada coupling with the Grignard reagent¹¹ and so does not exist at a high enough concentration to be detected by GC or MS. Alternatively, the formation of bromobenzene may not occur if the halogen-magnesium exchange happens with the Ar-Ni-Br species forming Ph-Ni-Br and ArMgCl (Scheme **5.3-B**).

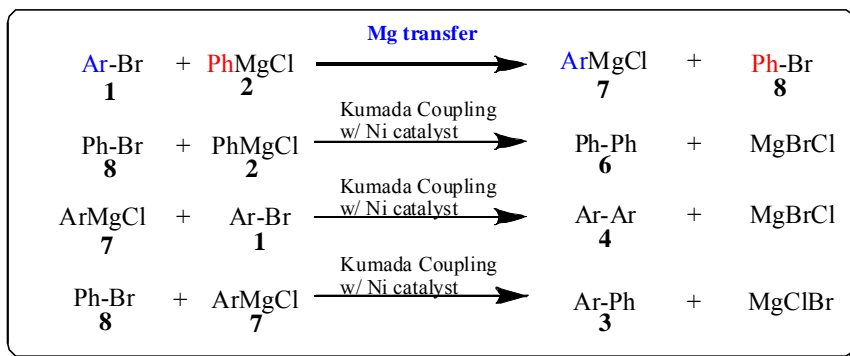
¹¹ Bromobenzene should be slightly more activated than 4-bromoanisole and react at a faster rate. The reason is that the -OMe group para to the bromide donates electron density to the aromatic ring thereby strengthening the Ar-Br bond.

Desired Product Formation

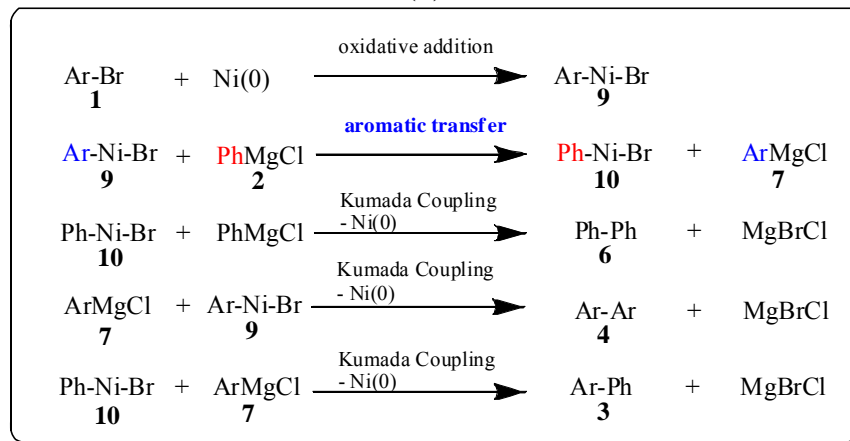


Side Product Formation

(A)



(B)



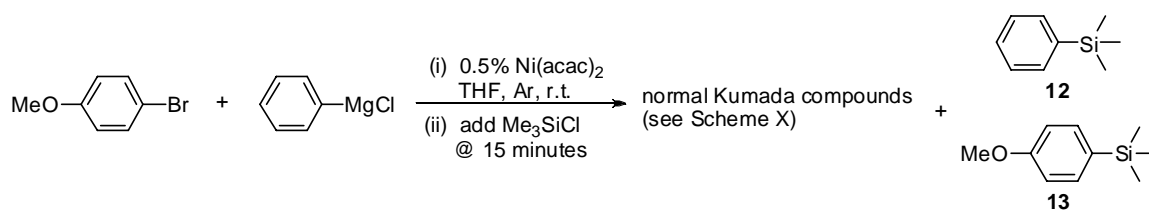
Scheme 5.3 Top reaction is of desired Kumada coupling of **1** and **2** to form product **3**. Scheme (A) is a possible path for Ni mediated Mg transfer between **1** and **2** to form new Grignard **7** and new aryl halide **8**. Subsequent reactions demonstrate how byproducts **6**, **4**, and **3** can be formed via currently accepted Kumada reaction pathways. Scheme (B) is a possible path for aromatic transfer after initial oxidative addition of **1** onto Ni(0) to form **9**, which then interacts with Grignard reagent **2** to exchange the aromatic groups forming **10** and **7**. Compound **10** can react with **2** to form byproduct **6**. The new Grignard **7** can undergo **2** reactions; (i) it can react with **1** to form homocoupling byproduct **4** or (ii) it can react with compound **10** to form desired Kumada product **3**. In both Schemes (A) and (B), the unreacted new Grignard reagent **7** will form Ar-H (**5**) upon workup.

Regardless of whether or not **8** forms, when the amount of biphenyl (minus the small amount from the fresh Grignard solution) is included in the mass balance, the total mass balances of 4-bromoanisole goes from 88-91% to ca. 100% (Table 5.1)¹² indicating that either Schemes **5.3-A** or **5.3-B** could account for observed byproduct formation. Control reactions in which **1** and **2** are mixed together without Ni exhibited no activity even after 24 h. Since no Ph-Br or Ph-Cl is detected by GC-MS (vide supra), the data is more consistent with Scheme **5.3-B**, however, as mentioned previously, the lack of detection of Ph-X (X = Br or Cl) could be a result of its rapid reaction/low concentration. In either Schemes **5.3-A** or **5.3-B**, a formation of Ar-Mg-Cl is predicted, thus we designed experiments to detect the possible formation of Ar-Mg-Cl (**7**).

Trimethylchlorosilane, TMS, was used as a selective reactant towards Grignard reagents. When 1 mmole of Ph-Mg-Cl in 5 mL of THF was exposed to 1 mL of TMS, Ph-SiMe₃, **12**, was exclusively formed (Scheme 5.4). No silanation was observed in control reactions of Ar-Br and Ar-H in the presence of 0.5% Ni(acac)₂ with TMS without Grignard present. To detect the presence of **7**, 1.0 mL of TMS was added after 15 m to a standard Ni(acac)₂ catalyzed reaction of Ar-Br with Ph-Mg-Cl (Fig. 5.4). Both the silanated products Ph-SiMe₃ and Ar-SiMe₃, **13**, stemming from reactions with Ph-Mg-Cl and Ar-Mg-X (X = Br or Cl) were detected by GC and confirmed by MS. Also, after

¹² When including the amount of biphenyl it should be noted that each mmole of biphenyl formed represents the formation of one mmole ArMgCl and therefore accounts for all subsequent reactions of ArMgCl, thus the amount of dehalogenated material (which is formed from the workup of unreacted ArMgCl) must be subtracted from the mass balance and the amount of Ar-Ar can only be counted once, since one half of it stems from the formation of ArMgCl.

addition of the silane the amount of anisole (Ar-H) dropped from 0.07 mmoles to 0.04 mmoles after which the amount of anisole stayed constant. Without TMS present the amount of anisole does not decrease (Fig. 5.4-5-A). Concurrently the amounts of silanated materials, as monitored by their peak area ratios to internal standard, rose after addition of TMS, but ceased rising at the same time the amount of Ar-H remained constant.



Scheme 5.4 Addition of TMS at $t = 15$ minutes to a normal Kumada reaction using 0.5% Ni(acac)₂. In addition to the normal Kumada products, two new compounds, Ph-SiMe₃, **12**, and Ar-SiMe₃, **13**, are observed by mass spec indicating the presence of Ar-Mg-Cl, **7**.

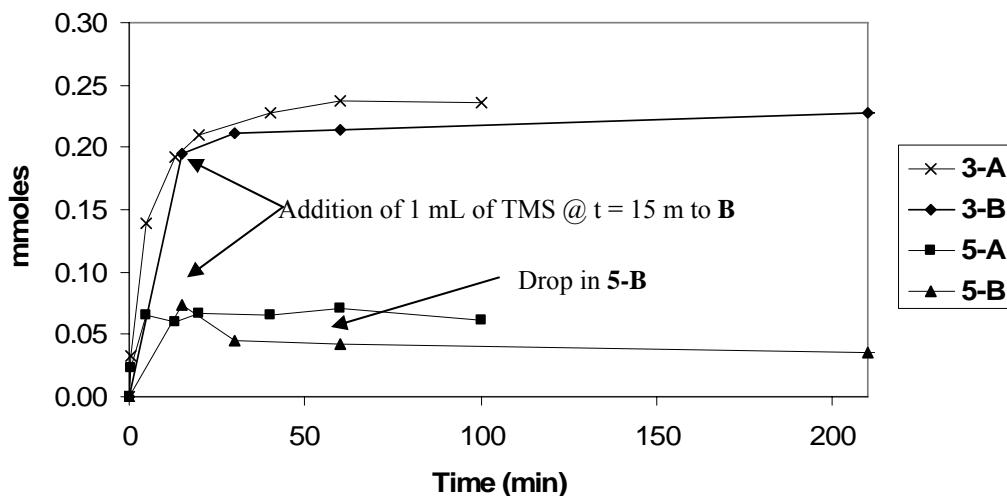


Figure 5.4 Kinetic profiles of formations of **3** and **5**. Plot (A) is without addition of TMS and (B) is addition of TMS at $t = 15$ min. Note the drop in **5** after addition of TMS to plot B.

A single electron transfer mechanism (SET) to form **4** as proposed by Lipshutz et al. cannot be ruled out with the data described above and could also be taking place concurrently.^[33] The SET mechanism occurs from interaction of the d-orbitals of the nickel atom with the pi* orbital of the phenyl group of the Grignard reagent. Thus if the amount of Grignard is lowered, then the amount of homocoupling **4** should decrease. However, when the phenylmagnesium chloride is reduced from 1.0 mmole to 0.5 mmole, after 2 hours the reaction reached 75% overall conversion of aryl halide with 22% forming **4** and only 13% to **5** (Table 5.2). Under normal conditions at approximately the same conversion of **1**, 9% forms **4** and 19% forms **5**. The decrease in Grignard loading resulting in a rise in homocoupling byproduct **4** with a concomitant drop in formation of dehalogenated byproduct **5** is more consistent with the proposed mechanism in Schemes **5.3-A** or **5.3-B** than with a SET mechanism. More aryl homocoupling byproduct **4** is formed because at a lower Grignard loading of **2**, there is less **2** to compete with Grignard **7** for reaction with aryl halide. Also, since more **7** is reacted in this situation with reduced **2**, the amount of dehalogenation byproduct **5** should be lower, as it stems from the aqueous workup of unreacted **7**. Conversely, if the amount of **2** is increased from normal conditions, then less **4** and more **5** should be formed. Indeed, this was observed when the amount of Grignard reagent **2** was doubled from 1.0 mmole to 2.0 mmole (Table 5.2). Under these conditions, the conversion of **1** associated with formation of **4** dropped to 3% whereas the percent of **5** rose to 27%. Taken together, both experiments in which the amount Grignard **2** was adjusted agree with the mechanisms proposed in Schemes **5.3-A** or **5.3-B**. Also, if the homocoupling of **2** is accounted for by this proposed mechanism, then it should be able to account for the

formation of **7** regardless of the amount of Grignard used. Thus, similar mass balance calculations made for normal reaction conditions (*vide supra*, Table 5.1), which consider the formation of **6**, should also be applicable to the reactions performed with different amounts of **2**. This is indeed the case as noted in Table 5.2 in which both mass balances on **1** for the case of (i) 0.5 mmole Grignard **2** result in 98% closure, whereas in the case of (ii) 2.0 mmole Grignard **2** the mass balance is 90% without considering **6** and 98% when **6** is included. These results are consistent with those in Table 5.1 and further support a mechanism by Schemes **5.3-A** or **5.3-B**.

Table 5.2 Distributions of product **3**, homocoupling **4**, and dehalogenation **5** from Kumada-Corriu conversion of **1** using different amounts of Grignard reagent **2**. Reaction conditions are 0.5 mmole **1**, 5 mL THF, 0.5% Ni(acac)₂, under Ar atmosphere at room temperature. Grignard reagent **2** was added to initiate each reaction.

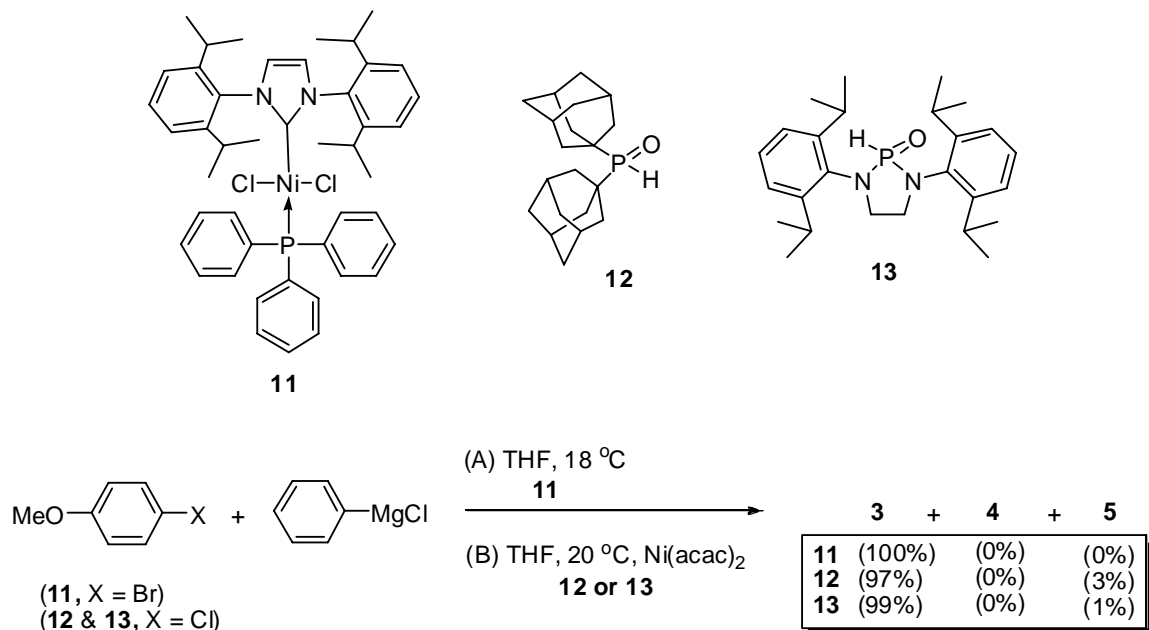
2 (mmole)	Conversion of 1 (%)			6 (mmoles)	Mass Balance %	
	3	4	5		6 not included	6 included
0.5	40%	22%	13%	0.11	98%	98%
1.0	42%	9%	19%	0.17	90%	101%
2.0	45%	3%	27%	0.19	90%	98%

Another possibility by which biphenyl could form is as a result of a shift in the Schlenk equilibrium, $R-Mg-X \leftrightarrow R_2Mg + X_2$, to form Ph_2Mg , which after workup would result in **6**. In a recent work, Ramnial et al. studied Kumada reactions in ionic liquids.^[54] A comparison was made between THF and phosphonium ionic liquids (PILs) as the reaction solvents. In a PIL with addition of *p*-benzoquinone, a SET step combined with a solvent induced shift in the Schlenk equilibrium to Ph_2Mg was used to explain the observed 80% biphenyl formation from phenylmagnesium bromide. In THF, no biphenyl

was formed under similar conditions because the THF was insufficiently polar to promote formation of Ph_2Mg . In the current work the amount of biphenyl increases in parallel with formation of product and increases solely in the presence of Ni. To test the unlikely result that product formation also incurs a shift in the Schlenk equilibrium to Ph_2Mg 0.5 mmole of **4** was mixed with 1.0 mmole of **2** in 5 mL of THF with 0.0025 mmole $\text{Ni}(\text{acac})_2$. After 5 hours, no additional **6** was formed. Thus, it is unlikely in this work that a shift to Ph_2Mg occurs in the Schlenk equilibrium due to the presence of THF or the formation of Kumada product **3**.

Our current interpretation of the data regarding the formation of side products **4**, **5**, and **6** is that the nickel is mediating an aromatic transfer between the oxidative product, **9** (formed from $\text{Ni}(0)$ and **1**), with the Grignard reagent **2** (Scheme **5.3-B**). However, a direct Mg transfer as shown in Scheme **5.3-A** cannot be ruled out, although no bromobenzene, **8**, was detected under any conditions. The nature of the transition state of the aromatic or magnesium transfer is not clear at this point and additional, more comprehensive mechanistic studies are needed to elucidate the mechanism by which this occurs. However, it should be noted that highest reported selectivities of Kumada products from anisole based aryl halides are with bulky ligands implying that the sterics of the ligand effect byproduct formation (Scheme 5.5). This is consistent with Schemes **5.3-A** and **5.3-B**. For instance, if the $\text{Ni}(\text{II})$ complex **9** is to exchange its aromatic groups directly with the Grignard reagent **2**, then there is likely a preferred, but yet unknown, geometric arrangement to allow this to transpire. However, if complex **9** is also bound to bulky ligands, then it is likely that the required geometric arrangement for aromatic

transfer is too sterically encumbered to occur, thus inhibiting formation of **7** and subsequently inhibiting byproducts **3** and **4**.



Scheme 5.5 Examples of bulky ligands **11**^[55], **12**, and **13**^[17] used to effect high selectivities of the conversion of MeO-Ph-X (X = Br or Cl) with Ph-Mg-Cl. The molar percentages of Kumada product **3**, dehalogenation **4**, and aryl halide homocoupling **5** are given for each ligand used.

5.3.3 Filtration experiments

Having established that the anchored nickel precatalysts generate active species for the Kumada coupling of 4-bromoanisole with phenylmagnesium chloride, it is of interest to determine whether the reaction is operating heterogeneously or

homogeneously. As previously mentioned, one of the most common methodologies for distinguishing heterogeneous from homogeneous reactions has been the use of hot filtration tests¹³ (also known as split tests).^[56-58] A very important subtlety about using this test is that only *continued activity* in the filtrate can be taken with confidence as evidence that leaching of active metal is occurring. A *lack of activity* of the filtrate cannot be taken as absolute proof that active metal did not solubilize prior to filtration, as the metal can be redeposit or deactivate during the filtration process.^[2, 3, 33, 39-47]

Following the completions of Kumada couplings catalyzed by PS-Dia-Ni and SBA-Dia-Ni, the solids were filtered off via a swivel frit and fresh aryl halide and Grignard were added to the filtrate. A conversion of 74% was observed for the freshly added 4-bromoanisole, **1**, in the filtrate after 100 min for PS-Dia-Ni, indicating the presence of leached active metal. A similar result was found for SBA-Dia-Ni, where 54% conversion was observed for added **1** in the filtrate after 90 min. To insure that these observations were not the result of catalyst decomposition post reaction, two tests were performed in which the solids were filtered off during the reaction cycle (Fig. 5.5). For both PS-Dia-Ni and SBA-Dia-Ni, the filtrates were active, although both proceeded more slowly than before filtration. This is likely a result of some Grignard deactivation, as the addition of Grignard resulted in increased activity of filtration tests (*vide infra*) in which conversion of **1** had ceased.

¹³ This test is typically call a “hot” filtration test as many catalyzed reactions are conducted above room temperature. In this study the reaction is at room temperature and the term “hot” is simply used to designate the type of test and not to imply the test is performed at elevated temperatures.

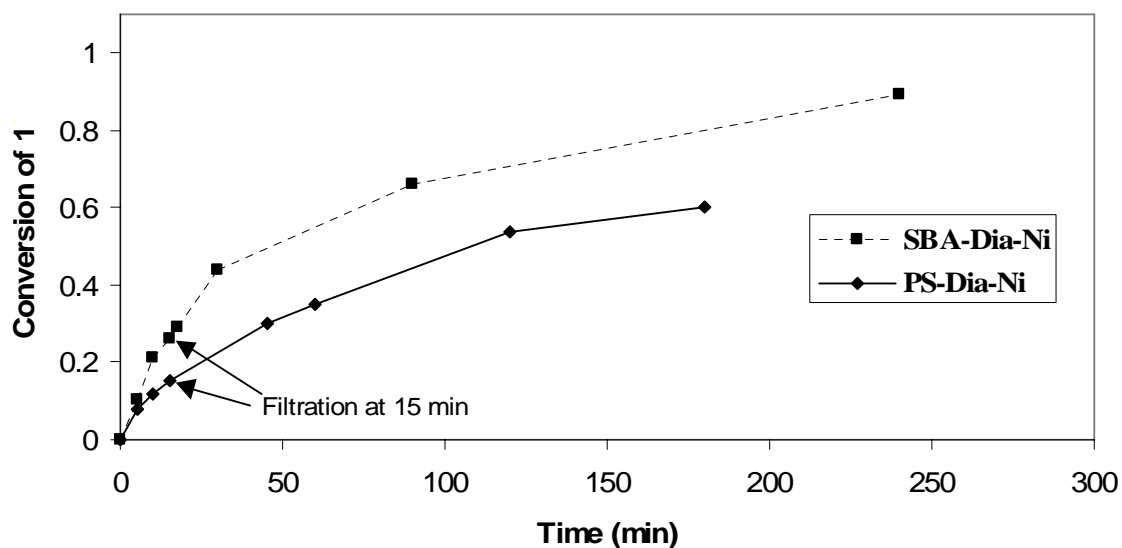


Figure 5.5 Hot filtration tests of SBA-Dia-Ni and PS-Dia-Ni showing conversion of 4-bromoanisole (**1**) before and after filtration. For both reactions the catalysts were filtered off at 15 min with a swivel frit and the filtrate activity was monitored.

The cause of Ni leaching was investigated by subjecting the precatalysts SBA-Dia-Ni to either (i) aryl halide and THF or (ii) Grignard and THF for two hours followed by filtration via a swivel frit and addition of the missing reagent (Fig. 5.6). In case (i) with aryl halide exposure, no activity was observed upon addition of Grignard to the filtrate indicating that exposure to solely aryl halide is not the cause of leaching. It has been previously demonstrated for palladium catalyzed Heck reactions that Pd is leached into solution from the oxidative addition to Pd(0) forming a soluble Pd(II) complex.^[59-67] It is possible that under Kumada reaction conditions, once Ni(0) is formed, the presence of aryl halide can then oxidatively add and pull Ni(II) into solution. In case (ii) when the SBA-Dia-Ni was exposed to Grignard without aryl halide, activity was observed upon addition of aryl halide to the filtrate, although it progressed at a slower rate than was observed for a normal reaction. This indicates that only the Grignard reagent is needed to

leach metal from the support. Based on the previous suggestion that a slower rate of the filtrate solution could be due to partial decomposition of the Grignard reagent during the filtration process, an additional 0.6 mmoles of Grignard was added after 250 minutes. After an additional 200 minutes (total reaction time = 450 minutes) the total conversion rose from 32% to 97%, indicating that some Grignard decomposition during the filtration process likely limits the conversion in the filtrate (Fig. 5.6-B). The reason why phenylmagnesium chloride induces nickel leaching is not completely understood, but might be due to two likely pathways. Reduction of the Ni increases the electron density on the Ni, which should make the N-Ni bond weaker due to electronic repulsions. Also the Grignard could deprotonate the amines bound to the nickel, which would result in a negative charge on the amine, but it is anticipated that this would lead to a stronger N-Ni(II) bond due to the increase in electron donating ability of the nitrogen anion to the electrophilic Ni(II).

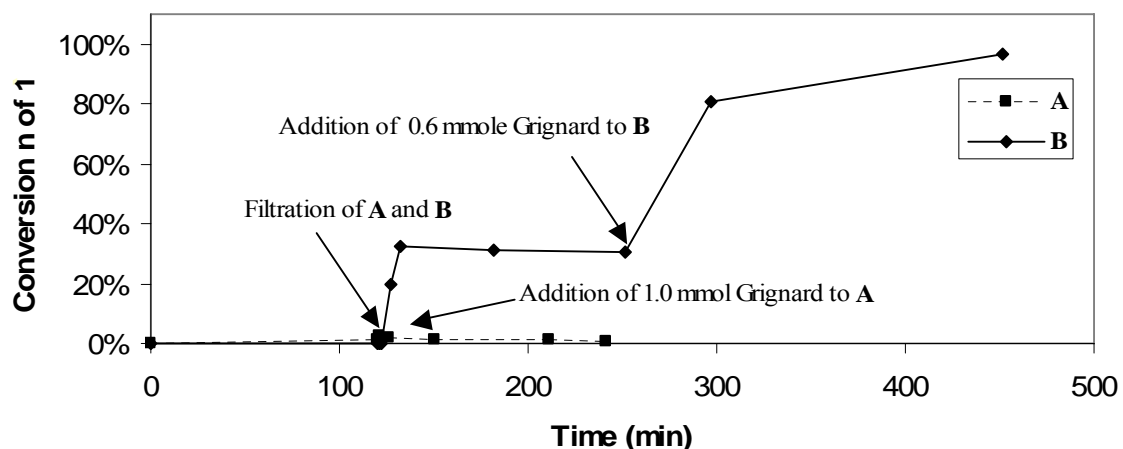


Figure 5.6 Leaching promotion tests of SBA-Dia-Ni with (A) 0.5 mmole **1** at time zero, filtration at 120 min followed by immediate addition of 1.0 mmole Grignard and (B) 1.0 mmole Grignard at time zero, filtration at 120 min with addition of 0.5 mmole **1**. An additional 0.6 mmole of Grignard to plot B was injected at 250 min. Reaction conditions are in THF, under argon, at room temperature.

If Grignard deprotonation of the amines is the cause of metal leaching, then Ni(II) anchored on pyridine ligands should not be effected in the same manner. Thus, 2-(4-pyridylethyl)triethoxysilane was anchored onto SBA-15. STA gave an estimated ligand loading of 2.8 mmole/g solids. FT-Raman confirmed the presence of organic loading with aromatic $\nu(\text{=C-H})$ stretching at 3050 cm^{-1} and aliphatic $\nu(\text{C-H})$ stretching is observed at 2896 cm^{-1} (Figure 5.7). Elemental analysis confirmed the presence of nitrogen with a loading of 2.9 mmoles N/g solids, which is similar to the estimated loading of 2.8 mmoles/g solids determined by STA analysis. Thus, the tethering of 2-(4-pyridylethyl)triethoxysilane onto SBA-15 was deemed a success..

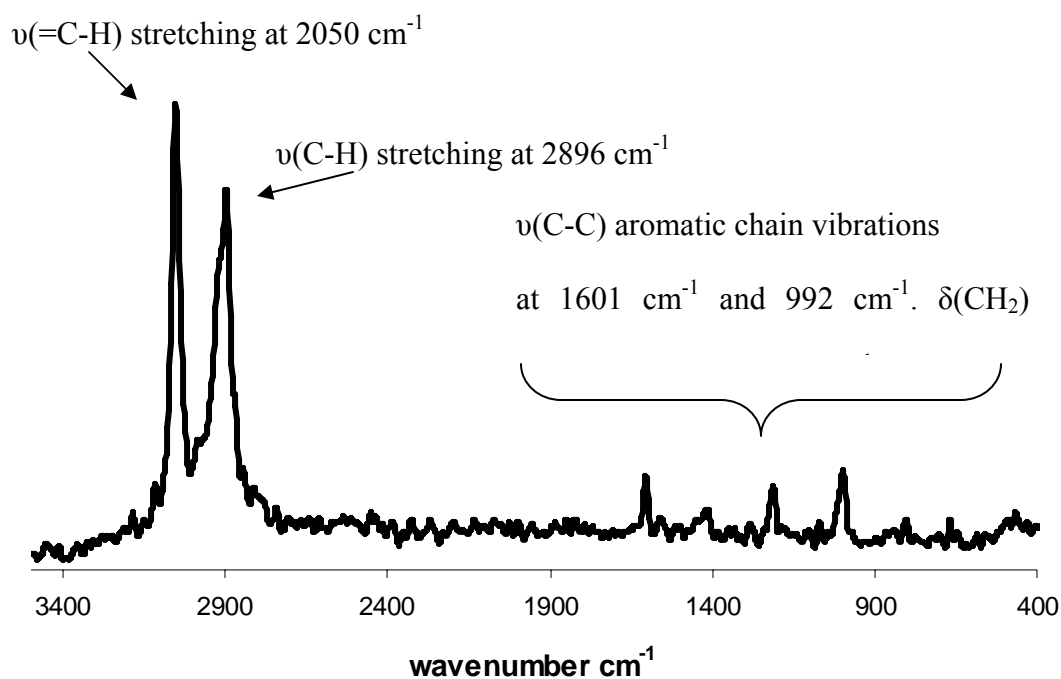


Figure 5.7 FT-Raman spectrum of 2-(4-pyridylethyl) functionalized SBA-15. Strong aromatic $\nu(=C-H)$ stretching is observed at 3050 cm^{-1} and the aliphatic $\nu(C-H)$ stretching is observed at 2896 cm^{-1} .

The 2-(4-pyridylethyl) functionalized SBA was metalated with $\text{Ni}(\text{acac})_2$ forming SBA-Pyridine-Ni (solids were light blue in color). This material was used in the Kumada coupling of 4-bromoanisole and phenylmagnesium chloride (Fig. 5.8). Leaching of Ni was also probed by using a split test and using reagent leaching tests (Fig. 5.8). The SBA-pyridine-Ni was active for this reaction as demonstrated by the conversion reaching $\sim 99\%$ after 420 minutes. However, this is a significantly longer time than was required using the other nickel precatalysts studied. In a filtration test after 30 minutes, the filtrate continued to react at near the same rate as a non-filtered reaction, confirming that active nickel is leached from the support. To explore the cause of leaching, the SBA-Pyridine-Ni was exposed to Grignard reagent without aryl halide for 120 minutes and then filtered. Addition of 4-bromoanisole to the filtrate resulted in activity, confirming that Grignard exposure can generate leached, active nickel. Similar

to that observed for SBA-Dia-Ni, exposure to aryl halide without Grignard did not induce leaching of active nickel from SBA-Pyridine-Ni. These results with SBA-Pyridine-Ni indicate that it is very likely reduction of Ni(II) to Ni(0) that promotes the leaching of nickel from the anchored nickel precatalysts.

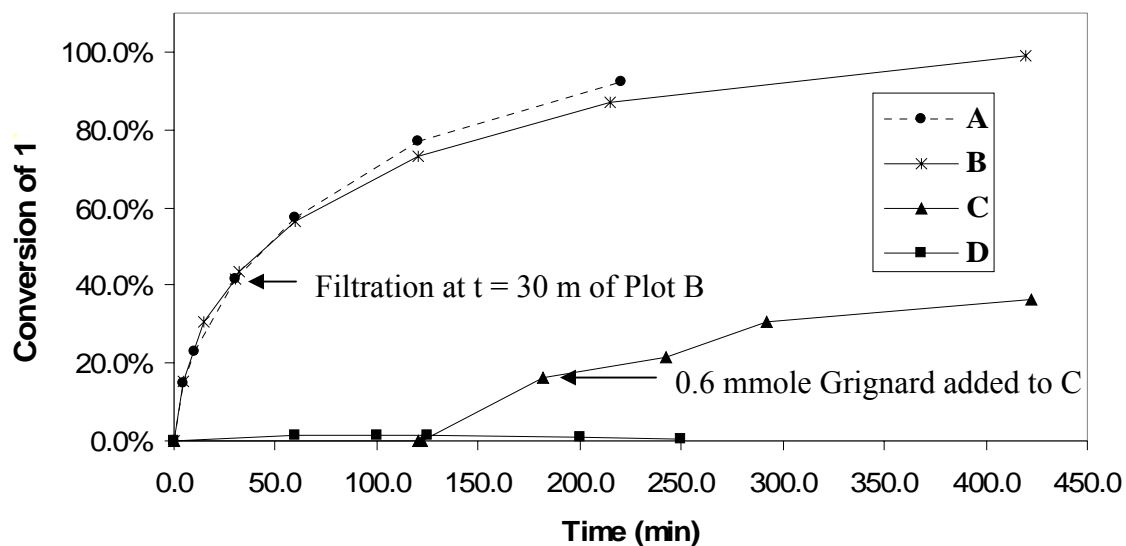


Figure 5.8 Plots of the conversion of 4-bromanisole (**1**) with phenylmagnesium chloride using SBA-Pyridine-Ni as catalyst both with and without filtration. Plot (**A**) is an activity test of SBA-Pyridine-Ni and plot (**B**) is a filtration test of SBA-Pyridine-Ni at $t = 30$ minutes. Reaction conditions are 0.5 mmole 4-bromoanisole (**1**), 1.0 mmole phenylmagnesium chloride, 5 mL THF, 100 μ L DGDE, and 1.0% SBA-Pyridine-Ni. Plot (**C**) demonstrates when SBA-Pyridine-Ni is exposed to Grignard reagent it will leach active Ni. In this test SBA-Pyridine-Ni was exposed to Grignard without **1** for 2 h, filtered, and then **1** was added to filtrate at 120 m. An additional 0.6 mmole Grignard was added at 180 m. Plot (**D**) demonstrates that aryl halide is not sufficient to leach active Ni on its own. In this test SBA-Pyridine-Ni was exposed to **1** without Grignard for 2 h, filtered, and then 1.0 mmole of Grignard was added to the filtrate at 120 m.

5.3.4 Three phase test

One of the more elegant methods for detection of active leached metal is the so called three phase test, where one of the reagents is anchored to a second solid phase (the first solid phase being the precatalyst). Thus the only mechanism by which the anchored reagent can react (provided no significant uncatalyzed background reaction) is by leaching of the metal (or less often the substrate) from the anchored catalyst. As with most any test, the three phase test has some subtleties that must be taken into account before conclusions can be drawn;

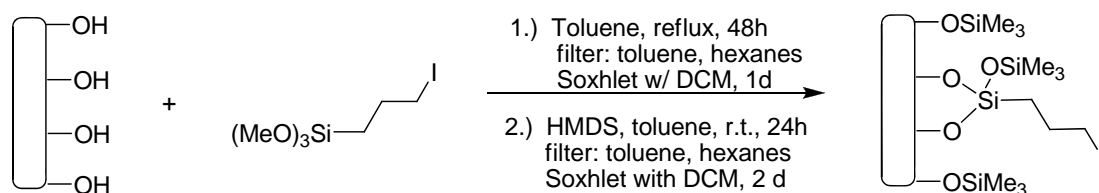
- 1) The immobilized reagent must be sufficiently active to allow for enough observable conversion under normal reaction conditions. Therefore a control experiment in which a known, active homogeneous catalyst is added must be performed.
- 2) Some amount of soluble reagent similar to (or the same as) the anchored reagent must be included to both verify that activity is possible under the 3-phase conditions and to mimic reaction conditions, as the presence of the soluble reagent might be required for leaching of the metal.^[59]
- 3) The conversion of anchored reagent is best interpreted as evidence that leaching is occurring. The absence of activity of the anchored reagent can *suggest* a heterogeneous pathway for the anchored catalyst only after it can be demonstrated that condition (1) above has been investigated. Even then, two further complications exist; (i) the presence of the heterogeneous catalyst can obscure the results if it serves as a deposition site once soluble reagent has been consumed, thereby scavenging active metal from solution and thus prohibiting reaction of the

anchored reagent. (ii) the concentration of leached metal may be significantly less than what is used by a researcher in proving reactivity of the anchored reagent in condition (1), thus when the “heterogeneous” catalyst is employed, the rate of reaction of the anchored reagent is greatly reduced because the concentration of soluble metal is lower than what was used in the homogeneous activity test.

A three phase test for Kumada reactions has not been previously performed¹⁴. In previous works we have synthesized three phase materials for the study of palladium catalyzed Heck reactions^[68, 69] and other authors^[70] have made similar materials bearing an aryl halide bond. However, the presences of carbonyl groups make these materials unsatisfactory for Kumada reactions due to propensity for nucleophilic attack of carbonyls by Grignard carbanionic alkyl groups. As such, the anchoring of a 3-iodopropyltrimethoxsilane onto a silica surface, SBA-propyl-I, using traditional silane chemistry was chosen to provide a highly reactive C-I bond while avoiding undesirable functional groups for Grignard reagents (Scheme 5.6). The amount of tethered alkyl halide was estimated by STA to be 1.4 mmoles/g solids. The presence of immobilized

¹⁴ Lipshutz et al.^[34] report a “three phase test” in which a phosphine ligand was immobilized, which constitutes a third solid phase. Calling this a three phase test is perfectly acceptable, however to avoid confusion when the term “three phase test” is used in this work it is only referring to anchoring of a reagent and not a ligand.

organic and C-I bonds was confirmed by FT-Raman spectroscopy¹⁵ (Fig. 5.9). Aliphatic $\nu(\text{C-H})$ stretching is observed at 2957 cm^{-1} and 2893 cm^{-1} . The peak at 503 cm^{-1} is assigned to C-I vibrations. Presence of iodine was also confirmed by elemental analysis, which gave loading of 1.5 mmoles I/g solids. This loading is consistent with the 1.4 mmoles/g solids estimated by STA analysis. SBA-15 was chosen as the silica material for anchoring the iodosilane as it has a large surface area for functionalization and should not interact with the supported catalyst or cause pore blocking since it is exactly the same silica material as that used for the nickel precatalysts.^[1]



Scheme 5.6 Synthesis of 3-iodopropyl functionalized SBA-15.

¹⁵ A large amount of fluorescence was observed in the FT-Raman of iodopropyl functionalized SBA-15. The reason for this is not clear at this time.

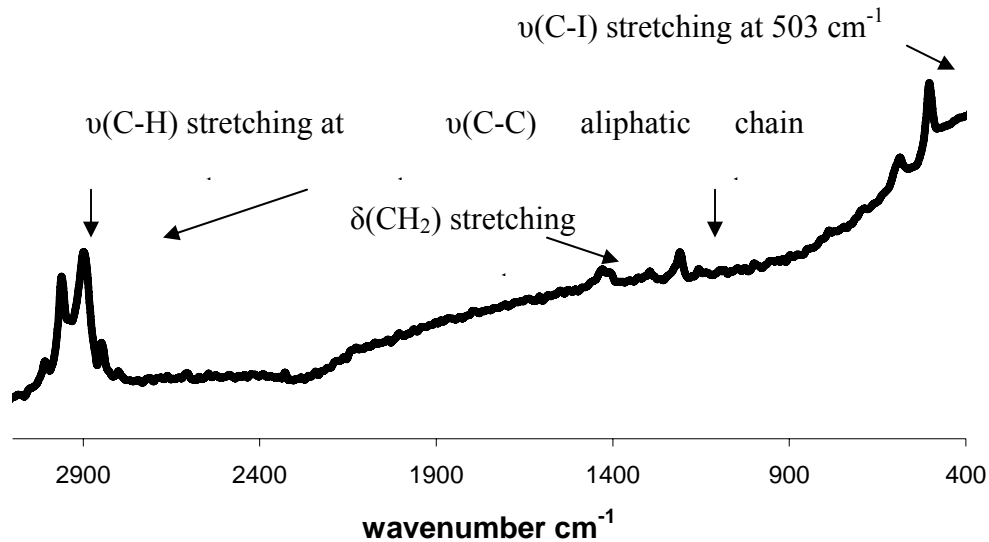


Figure 5.9 FT-Raman spectrum of 3-iodopropyl functionalized SBA-15. Aliphatic $\nu(\text{C-H})$ stretching is observed at 2958 cm^{-1} and 2890 cm^{-1} . The peak at 503 cm^{-1} is assigned as the C-I stretch.

A homogeneous control reaction of 0.5 mmole of 3-iodopropane and 1.0 mmole of phenylmagnesium chloride in the presence of 0.5% $\text{Ni}(\text{acac})_2$ resulted in complete conversion of the iodopropane within one minute. However, only a trace amount of the Kumada product propylbenzene was observed indicating that the majority of reaction occurred through dehalogenation of the iodopropane through Mg transfer. This is supported by the detection of a trace amount of iodobenzene and no detection of any other products (any propane resulting from formation of propylmagnesium iodide would have been lost to the gas phase during workup). The ultimate goal of the 3-phase test is the detection of active soluble nickel under Kumada conditions. As dehalogenation occurs concurrently with normal Kumada couplings, we suggest that the nickel catalyzed dehalogenation of anchored iodopropane can be used to detect leached, reactive nickel. Five 3-phase tests were performed using aryl halide, Grignard, and...

- 1) no catalyst
- 2) homogeneous Ni(acac)₂
- 3) SBA-Dia-Ni (0.00025 mmole Ni)
- 4) PS-Dia-Ni (0.00025 mmole Ni)
- 5) SBA-Dia-Ni (0.00025 mmole Ni) without aryl halide

After reaction the solids were recovered by filtration, rinsed with methanol, diethyl ether, THF, and DCM, and dried at 120 °C. The final dried solids were analyzed by TGA (Fig. 5.10) and elemental analysis. The TGA data clearly show that overall combustible mass loss due to anchored organic material is largely unaffected by the presence of either aryl halide or Grignard reagent when nickel is not present. However, in each case in which nickel is introduced, either by using homogeneous or anchored Ni(acac)₂, a dramatic decrease is observed in the amount of combustible organic mass. This is consistent with the iodopropyl surface substituting an iodine atom (MW = 126.9 mg/mmol) with either a phenyl group (C₆H₅, MW = 77 mg/mmol) or a hydrogen atom. Indeed with palladium catalyzed Kumada-Corriu reactions of alky iodides with Grignard reagents, the primary product was from dehalogenation and not from cross coupling.^[71]

Elemental analysis of the used three phase materials showed that in the control experiment without any nickel present the ratio of iodine to silicon dropped only 5% as compared to the fresh material. In the presence of nickel, the change in I:Si ratio was more substantial. When homogeneous Ni(acac)₂ was used, a 49% drop in the I:Si ratio was observed, and with SBA-Dia-Ni, the decrease was higher at 63%. This trend is

consistent with the larger decrease observed in combustible organic mass observed in Figure 5.10 between plots **A** and **D**.¹⁶ Thus, SBA-propyl-I can be used as a three phase material to detect the presence of leached nickel for Kumada reactions and confirms nickel leaching when used with PS-Dia-Ni and SBA-Dia-Ni.

¹⁶ Despite the use of MeOH to quench and dissolve any R-Mg-X species formed on the three phase material surface, it cannot be ruled out that some potentially incombustible Mg-I species is present on the three phase materials exposed to homogeneous Ni. Thus, this test, as described in this work, is for qualitative determination of leached Ni.

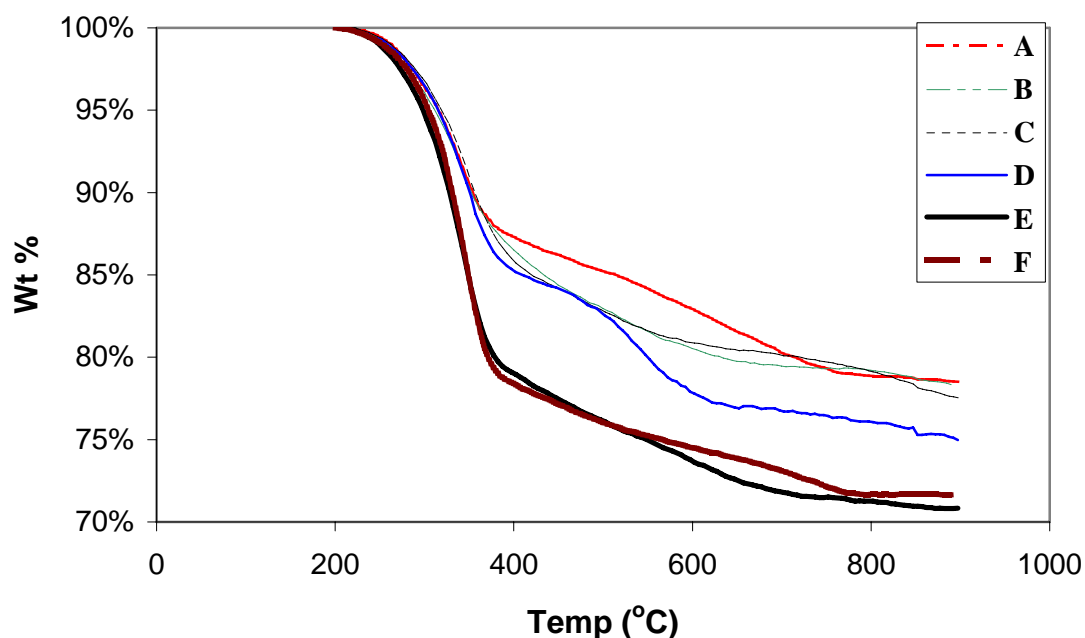


Figure 5.10 TGA wt% losses (normalized to mass at 200 °C) of various used three phase materials demonstrating presence of leached nickel. In each reaction 125 mg of three phase material, SBA-propyl-I, was exposed to (A) reaction conditions with 0.0025 mmole Ni from SBA-Dia-Ni, (B) same as A but without 4-bromoanisole, (C) reaction conditions with 0.0025 mmole Ni from PS-Dia-Ni, (D) reaction conditions with 0.0025 mmole Ni(acac)₂, (E) reaction conditions without nickel, and (F) no reaction conditions (unused material). Reaction conditions are 125 mg SBA-propyl-I, 0.2 mmole 4-bromoanisole, 0.6 mmole Ph-Mg-Cl, and 5 mL of THF. Each reaction was stirred under an argon atmosphere for 6 h before solids were recovered.

5.3.5 Catalyst recycling

For anchored palladium precatalysts, an ability to reuse the palladium by a release and recapture strategy has been demonstrated.^[40-42, 44-46] In such a system the palladium atoms are leached, catalyze the reaction, redeposit back onto the surface, and are recovered by filtration of the solids. Lipshutz et al. reported that nickel on charcoal leached from the surface to catalyzed Kumada couplings, but could be reused due to nickel's selective partitioning inside the charcoal pores and the propensity to redeposit

onto the charcoal surface.^[39] Could such a mechanism be at play with SBA-Dia-Ni? To probe this concept, a series of two recycles was performed with SBA-Dia-Ni. The amount of SBA-Dia-Ni was increased from that of the normal Kumada reaction to insure enough material for elemental analysis. The first reaction was performed using 100 mg of SBA-Dia-Ni (0.035 mmole Ni), 1.74 mmole aryl halide, 1.74 mL of 2 M phenylmagnesium chloride in THF, and 15.6 mL of dry THF. It is common in catalytic coupling literature to only report the final conversion after a given period of time. However, this can result in misleading conclusions if the total reaction time is sufficiently long to hide losses in early kinetic behavior resulting from metal loss or deactivation.^[2, 3, 56] With this in mind data points were taken at 30 min, 120 min, and 240 min to observe changes in the kinetic profile while minimizing catalyst loss from sampling. Due to unavoidable mechanical losses of 10 mg of catalyst for each recycle as determined by the mass of recovered solids, the reagent and solvent amounts were reduced by 90% and 80% respectively from the first run to insure the same ratio of reagent to nickel. After each recycle the initial rates were significantly reduced after 2 recycles (Fig. 5.11)¹⁷. Elemental analysis after the final recycle showed a reduction of the Ni:Si from 0.03 to 0.016, which is a 47% reduction in nickel content. Thus it is possible that release and capture of the Ni is occurring, but not at a level to sustain similar kinetics for each run. Also, the high amount of nickel lost indicates that metal recovery strategies such as the

¹⁷ Note that if *only final conversions* were compared at t = 240 m, each run would have appear to have same conversion, ca. 98%. Without evaluating the early age kinetics this might have erroneously implied retainment of catalyst activity.

use of metal scavengers would still be needed in order to purify products from nickel contamination.

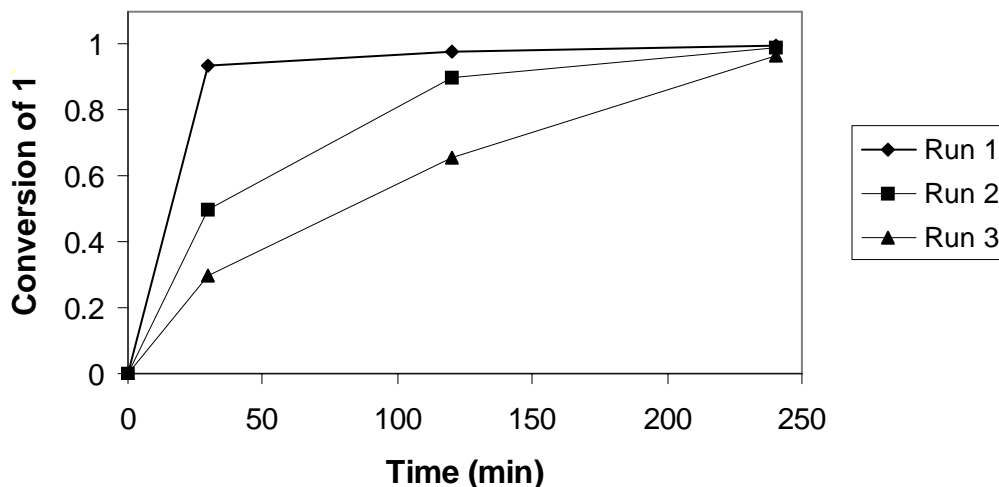


Figure 5.11 Recycle experiments using SBA-Dia-Ni showing a loss in initial rates due to metal loss. Concentrations were adjusted on each run to ensure the same concentration of reagent to catalyst. Reaction is Kumada coupling of **1** with **3** with catalyst loading at 2 mol% to **1**.

5.3.6 Selective poisoning

Previously we^[1, 2, 68, 69, 72] and others^[60, 73-76] have used selective poisons that target active, homogenous metal to determine whether or not heterogeneous catalysis is happening concurrently with homogeneous catalysis from leached metal. In the selection of an appropriate selective poison there are a few ideally desired attributes;

- 1) The selective poison should have no effect on the reagent activity or react directly with the reagents.

- 2) The selective poison should completely and rapidly quench soluble metal.
- 3) The selective poison should have no effect on any metal retained on the precatalyst surface.

Deviations from the ideal attributes listed above can only be tolerated if the deviations are understood and do not misconstrue the interpretations of the results. For instance, if the selective poison has a slight interaction with one of the reagents, then an additional amount of that reagent should be included such that the overall kinetics is not greatly effected.

A variety of selective poisoning materials were tried for the Kumada reaction catalyzed by homogeneous Ni(acac)₂. Previously we have used poly(4-vinylpyridine) to test the ability of anchored Pd precatalysts for Heck reactions.^[68, 69, 72] When 81 mg (300 equivalents pyridine to nickel) of PVPy was added to the Kumada coupling of 4-bromonanisole with phenylmagnesium chloride with 0.5% Ni(acac)₂ under otherwise normal conditions, the reaction reached 60% conversion of aryl halide within 30 minutes, but did not further react (all byproduct formation also ceased). A second reaction was run in which the amount of PVPy was increased to 200 mg. No product formation was observed. To test if the PVPy was poisoning nickel or interfering with one of the reagents, this reaction was filtered under argon and additional 0.5% of Ni(acac)₂ was added to the filtrate. However, no conversion was observed indicating that the PVPy was interfering with the catalysis presumably from interactions with the Grignard reagent. To test this, a third PVPy reaction was performed using 100 mg of PVPy. In this reaction total conversion after 240 minutes was 9% (with only small amounts of byproducts or

biphenyl formed). An additional 1 mmole of Grignard was added to this reaction at 240 minutes and after 50 more minutes the conversion rose to 72%. Thus, it is likely that the PVPy is predominantly interfering with the Grignard reagent and is not an adequate material for selective poisoning in this case. This also calls into question the use of pyridine based materials as ligands for Kumada reactions. It is reasonable to assume that when pyridine is used as a catalyst ligand, and assuming typical catalyst loadings < 1%, interactions between uncoordinated pyridine sites and Grignard are not noticed or do not affect the catalysis to an appreciable extent because the ratio of pyridine sites to Grignard is small. It is postulated that only under conditions with (i) a high pyridine to Grignard molar ratio, as is the case with the PVPy poisoning test above (pyridine:Grignard ~ 1.0), and (ii) use of anchored pyridine that pyridine-Grignard interactions become detrimental to Grignard reactivity due to Grignard adsorption onto the anchored pyridine sites.

QuadrapureTM Imidazol-1-yl propylaminobut-2-enoate ester (Quad IMDAZ), is an anchored imidazolium ligand on a cross linked polymer made by Reaxa Ltd. and is reported as a good scavenger of Ni(0) and Ni(II).^[77] When 167 mg of Quad IMDAZ (100 equivalents to Ni) was added in a similar fashion as for PVPy above, the conversion of aryl halide reached 75% in 240 minutes. Therefore, Quad IMDAZ was also rejected as an selective poison of homogenous nickel in these Kumada reactions.

In general, an adequate selective poison for homogeneous nickel for Kumada reactions was not found. For most materials tested either (i) the reaction progressed to a significant extent or (ii) the poison interacted with the Grignard reagent. In a related experiment Lipshutz et al. noted that when polymer-bound PPh₃ was added to a Kumada coupling using Ni/C as the catalyst only 42% conversion of aryl halide was observed as

compared to 100% without polymer-bound PPh₃ (PB-PPh₃).^[39] This was interpreted, in combination with results from other tests, as showing that there was little or no activity from heterogeneous nickel. In contrast to the Ni/C experiments, a reverse trend was noted when NiCl₂ was used as the catalyst. Without PB-PPh₃ the reaction progressed to 60% whereas with PB-PPh₃ it went to 70%. No explanation for this reverse trend was given. If the PB-PPh₃ is truly acting as a selective poison of soluble, active Ni, then the NiCl₂ reaction with PB-PPh₃ should have been lower. Also, in the case of amination reactions the PB-PPh₃ actually promoted activity although this could be a result of the different reaction conditions employed for the amination reactions. These results raise the possibility that the PB-PPh₃ was interfering with the Ni/C reaction in a different way than by simply poisoning soluble Ni, such as by blocking pores in the Ni/C or a potential interaction of Grignard¹⁸ with polymer-bound PPh₃ (this latter point was not discussed in the original paper). No further experiments with PB-PPh₃ with Ni catalysts in Kumada reactions were conducted¹⁹ and so conclusive interpretations about whether or not PB-PPh₃ acted as a selective poison in this previous work cannot be made. Thus, immobilized phosphines may exhibit potential as possible selective poisons of soluble, active Ni catalysts used for Kumada coupling reactions, but more experimentation is required to determine this.

¹⁸ The phosphine to Grignard molar ratio was 0.13 and the total amount of PB-PPh₃ solids added was 167 mg. Amount of solvent was 1.5 mL of THF. Under these conditions it is possible that a phosphine-Grignard and/or a solids-Grignard interaction was occurring.

¹⁹ This is most likely due to the fact that the use of PB-PPh₃ was not a central point to the author's original work as most of the PB-PPh₃ testing was used with amination reactions. [39] B. H. Lipshutz, S. Tasler, W. Chrisman, B. Spliethoff, B. Tesche, *Journal Of Organic Chemistry* **2003**, 68, 1177.

5.4 Conclusions

Ni(acac)₂ was immobilized onto (i) poly(styrene)ethylenediamine, (ii) ethylenediamine covalently tethered to a mesoporous silica, and (iii) ethylpyridine covalently tethered to a mesoporous silica. These materials were successfully used in the catalysis of a prototypical Kumada-Corriu reaction of 4-bromoanisole with phenylmagnesium chloride. Analysis of the formation of anisole, homocoupling of the aryl halide, increased formation of biphenyl with time, and formation of Ar-SiMe₃ after exposure to Me₃SiCl suggests that an exchange of the aromatics between the Grignard and the aryl halide is occurring. Activity of leached metal was determined by both room temperature filtration tests during and after the reaction. For the first time, an anchored alkyl halide (three phase test) was designed for Kumada-Corriu reactions and used to demonstrate that anchored nickel precatalysts leach active metal. Unlike anchored palladium catalysts in related coupling chemistries, it is not the presence of aryl halide that promotes leaching, but rather the presence of Grignard that pulls nickel into solution either by degradation of the ligand or a weakening of the ligand-metal bond by increasing electron density on the nickel through reduction to Ni(0). Anchored nickel could be recycled three times without significant loss in final yield, however decreases in early age activity and an 46% loss of nickel after the third run indicate that while a release and capture of the nickel is possible high conversions are not sufficiently sustainable over more than three runs unless reaction times are sufficiently increased. Attempts were made to design a selective poison for homogeneous nickel, but were proven unsuccessful due to interactions between the Grignard reagent with the poison or the inability of the

poison to remove nickel from the catalytic cycle. Therefore, determination of whether a surface catalyzed mechanism occurs concurrently with the leached metal is still yet to be determined. However, based on the observations of nickel leaching in this work and the collective literature on Pd leaching, it is unlikely that surface catalysis is occurring.

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CHAPTER 6

SUMMARY AND FUTURE WORK

5.1 Summary

The major objectives of this thesis work were to (i) investigate anchored Pd and Ni materials as heterogeneous precatalysts for C-C coupling reactions and (ii) investigate selective poisons as a strategy to distinguish heterogeneous from homogeneous catalysis.

The anchored Pd and Ni precatalysts included:

- I. Organometallic SCS-Pd(II) pincers tethered to silica and polymer supports
- II. Small molecule Pd complexes entrapped inside sol-gel and polymer matrices
- III. Thiol-functionalized mesoporous silica metalated with Pd
- IV. Anchored diamine, [R-NH-(CH₂)₂-NH₂], and pyridine ligands metalated with Ni

The Pd materials were used for the coupling of aryl halides with either terminal olefins (Heck reactions) or aryl boronic acids (Suzuki reaction). The Ni material was used for the coupling of aryl halides with aryl Grignard reagents (Kumada reaction). The collective evidence is best interpreted as concluding that the anchored Pd precatalysts are catalytically active via Pd leaching and not from heterogeneous sites. The form of leached palladium is suspected to be “naked” Pd atoms stabilized by coordination to reagents or by weak interactions with the solvent. This conclusion of metal leaching was supported by a battery of tests used to distinguish heterogeneous from homogeneous catalysis. These tests included:

- I. Hot filtration test
- II. Hg(0) drop test
- III. Evaluation of kinetic profiles of recycle experiments
- IV. Three phase test
- V. Elemental analysis
- VI. Selective poisoning tests

The subtleties and limitations of each test, when applied to Pd, are thoroughly discussed throughout this thesis work. Of particular focus in this thesis work has been the discovery and development of materials for the selective poisoning test. Three materials have been introduced as selective poisons of homogeneous, catalytically active Pd species. These materials are:

- I. Poly(4-vinylpyridine), PVPy; a cross-linked insoluble polymer with pyridine sites
- II. QuadrapureTM TU; a cross-linked insoluble polymer with thiourea sites
- III. Thiol-functionalized silica; a mesoporous silica with tethered thiopropyl ligands

It was found that PVPy can effectively quench catalysis of homogeneous Pd, but large excesses are required (300-750 equivalents to metal). QuadrapureTM TU was found to be a good selective poison of homogeneous Pd and can be used in lower amounts than PVPy (35 equivalents of QuadrapureTM TU was used in this thesis work). Both PVPy and QuadrapureTM TU are organic polymer materials, which are often chemically and

thermally less robust than mesoporous silicas, such as SBA-15. Thus, thiol-functionalized mesoporous silica was investigated and found to be a good material for selective poisoning of homogeneous Pd. Of the three selective poisoning materials studied, the thiol-functionalized poison exhibited the best overall poisoning ability as it could be used in low equivalents (< 7 equivalents) and in two phase aqueous/organic Suzuki coupling reactions. For homogeneous Ni(II) precatalysts used for Kumada reactions, a good selective poisoning material could not be found that could both poison homogeneous Ni and avoid interaction with the Grignard reagent.

Overall, it was concluded that all anchored metal materials studied in this work were reservoirs of homogeneous, catalytically active metal. The demonstration that thiol-functionalized materials metalated with Pd only act as reservoirs of active metal cleared previous ambiguity as to whether such materials could act as heterogeneous catalysts. This thesis work has added significant understanding and supporting evidence to the currently growing consensus that most, if not all, previously reported “heterogeneous” Pd catalysts have actually promoted reactions via leaching of active metal.^[1-4] Part of the reason for previous claims of heterogeneity is a lack of knowledge about (or an ignoring of) important subtleties of the traditional tests used to distinguish heterogeneous from homogeneous catalysis. In this work, we demonstrated that the selective poison test is the most definitive method for distinguishing heterogeneous from homogeneous catalysis for immobilized Pd materials. PVPy, Quadrapure™ TU, and thiol-functionalized silicas are introduced as effective selective poisons of homogeneous Pd. Of these three materials, the most robust and most applicable material is the thiol-functionalized silica. Given the effectiveness of selective poisoning, all future research in the area of heterogeneous Pd

catalysis for C-C couplings can no longer rely on ambiguous methods to support claims of heterogeneous catalysis. Future researchers can use the selective poisoning method to clearly distinguish between heterogeneous and homogeneous catalysis.

6.2 Suggestions for future work

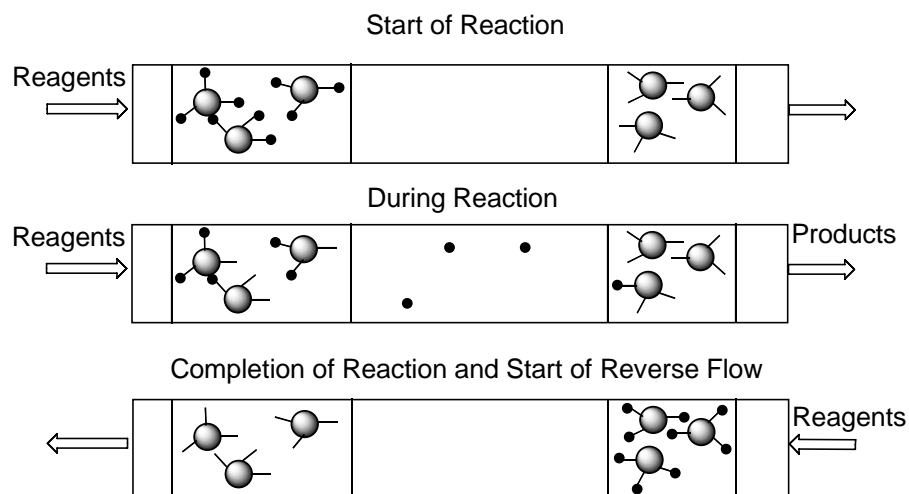
6.2.1 “Heterogeneous” Pd precatalysts

I agree with Farina that most of the literature of heterogeneous Pd precatalysts for C-C coupling reactions has largely been to investigate standard or novel Pd bearing materials for a catalytic application.^[2] As most any form of Pd will catalyze Heck reactions, especially those involving iodoarenes, this has resulted in a large number of publications. A smaller number of papers appear to have focused on creating a heterogeneous Pd catalyst *specifically* for C-C couplings. However, as mentioned previously, these materials are most likely precatalysts of leached metal. What then should be the focus of research in this area? To answer this question the true objective must first be clarified. Is the goal a creation of a heterogeneous catalyst whereby catalysis occurs on the surface? Or, is the objective achievement of a catalyst that is recoverable and reusable *regardless* of where catalysis actually occurs? Deciding this objective is important as several immobilized Pd materials have been shown to leach metal during the reaction, but then redeposit after completion or cooling of the reaction.^{[4-}

^{12]} Through this redeposition mechanism the Pd can be recovered, and therefore, potentially reused. Of course, if the redeposition results in an unsatisfactory degree of

deactivation, then the catalyst cannot be deemed completely reusable. The inability to reuse the catalyst in a consistent fashion will most likely kill its attractiveness for commercial applications.

While recovery of Pd has been demonstrated through redeposition, it is my opinion that a scientific understanding is lacking about how to control leaching and redeposition such that the Pd can be reused without a drop in activity. I propose that future research should explore the guiding principles of what controls Pd leaching and redeposition. Indeed, some work has been made in this area. It has been demonstrated that oxidative addition of aryl halide can both solubilize Pd and prevent its redeposition until most of the aryl halide has been consumed in the reaction.^[3, 13-21] Also, when a surface is covered with primarily Pd(II) atoms, the deposition of Pd(0) maybe less favored.^[3] Temperature can also play a critical role and, in general, the higher the temperature the more favored is Pd deposition onto surfaces.^[3, 4, 6] Much less is understood on how to scavenge the spent Pd in a form that is not deactivated. Perhaps “smart” ligands can be designed that allow some Pd leaching under reaction conditions, but at the end of the reaction, both scavenge the Pd and prevent Pd deactivation. Another promising route is the use of zeolites that diffuse out Pd, but mitigate Pd agglomerating on the surface by maintaining a high level of Pd dispersion within the zeolites framework.^[22] The task of controlled leaching and recovery is not trivial, but work towards understanding the principles affecting leaching and redeposition could lead to catalytic systems that act as a “boomerang” catalysts as depicted in Scheme 6.1. Perhaps using reverse flow adsorption as described in a recent work^[23] could facilitate this objective.



Scheme 6.1 Depiction of a “boomerang” catalyst in which the Pd atoms (black dots) are immobilized on a support at the start of a reaction. During the reaction the support acts as a reservoir of soluble, catalytically active Pd. At the end of the reaction, or at the product stream outlet, the leached Pd atoms are redeposited onto a bare support. This newly metalated supported is then used as the Pd reservoir for a subsequent reaction.

6.2.2 Selective poisoning

A large part of this work focused on identifying and studying materials that can act as selective poisons of catalytically active Pd metal. In my opinion, this selective poisoning test is underutilized as a method to distinguish heterogeneous from homogeneous catalysis for Pd catalyzed C-C couplings. This thesis work has provided the foundation for demonstrating the effectiveness of the selective poisoning methodology. To expand the scope from that studied in this work and increase awareness of selective poisoning, more scientific understanding is needed of how selective poisons work and what their limitations are for a range of metals and scavengers. For example, in

the course of this thesis, anchored thiol (*vide supra*), diamine, triamine, and thiocyanato ligands were found to quench catalysis whereas anchored primary amines, secondary amines, and thioesters did not quench Pd catalysis (Figure 6.1). An increase in understanding and awareness of selective poisons can be achieved in a number of conceivable ways;

- I. Explore the scope of selective poisons for other catalytically active metals. A good place to start is to use the best available scavengers of the metal of interest.
- II. Explore the influence of reaction conditions (e.g. temperature, additives, type of reactor) on the ability of selective poisons to quench homogeneous activity.
- III. Develop guiding principles by investigating electronic and structure relationships between selective poisons and metals of interest. Is a strong binding constant more important than the ability to take up multiple coordination sites?

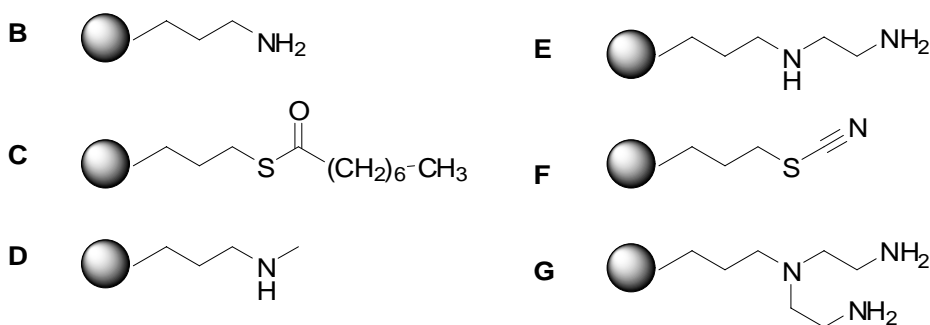
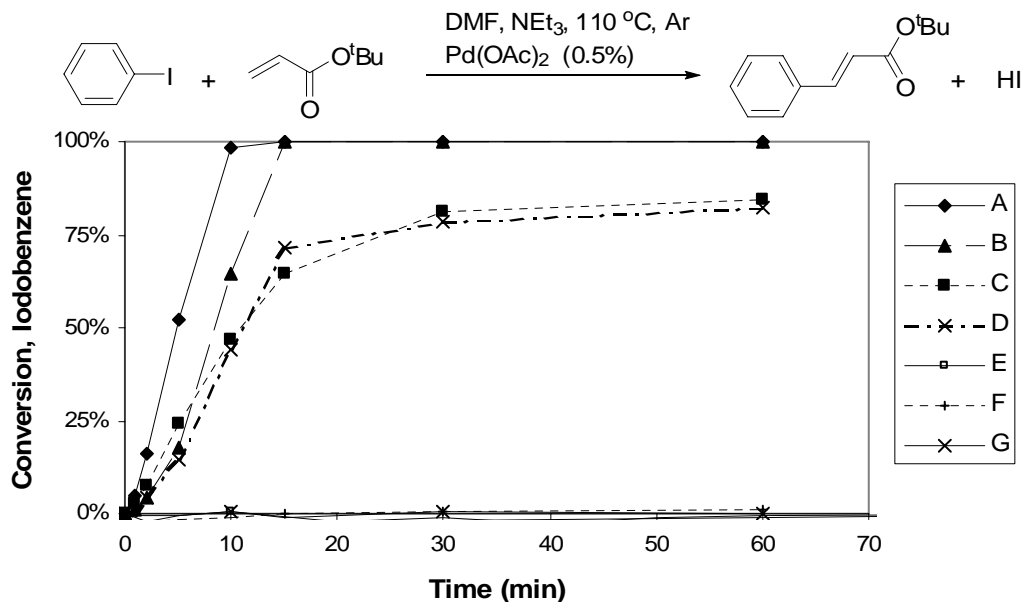


Figure 6.1 Selective poisoning screening of a variety of organically modified SBA-15 for the Heck reaction of iodobenzene and *n*-butyl acrylate with 0.5% Pd(OAc)₂. Plot (A) is without any poison, (B) is with anchored primary amine, (C) is with anchored thioesters, (D) is with anchored secondary amine, (E) is with anchored diamine, (F) with anchored thiocyanato, and (G) with anchored triamine. All poisons were introduced at the beginning of the reaction and were used at 35 equivalents of ligand to Pd.

6.3 Perspective

It is my opinion that more and more researchers are beginning to accept that previously claimed “heterogeneous” Pd catalysts are actually precatalysts of leached metal for C-C bond forming reactions. However, since most all forms of Pd can exhibit high activity for such reactions, novel, Pd bearing materials will continue to be touted as

“heterogeneous” and/or “leach proof.” It is also likely that “proof” for such claims will continue to be given by simple filtration tests and/or by comparing final yields (without observing kinetic profiles) after long reaction times. Both of these tests can no longer be used *as the sole methods* to prove heterogeneous catalysis. It is my hope that more researchers will (i) consider the current knowledge regarding the subtleties of distinguishing homogeneous from heterogeneous catalysis for Pd catalyzed C-C couplings and (ii) apply more rigorous testing, such as selective poisoning, before claiming heterogeneous catalysis. Until this becomes standard practice, I suggest great caution in accepting any claims of heterogeneous Pd catalysis of C-C cross-couplings unless very rigorous testing has been employed. The methodology of selective poisoning must be one of the critical tests performed to prove heterogeneous catalysis for metal catalyzed C-C couplings.

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VITA

JOHN M. RICHARDSON

John M. Richardson was born on May 06, 1978 in Nashville, TN. He attended public school in Celina, TN until end of 7th grade and then moved to Cookeville, TN where he finished his public education by graduating from Cookeville High School in 1996. He then obtained both a B.S. and M.S. in chemical engineering at Tennessee Technological University. In between his junior and senior years of college, John worked at the National Institute of Standards and Technology for 15 months as a guest researcher. He entered the Ph.D. program in chemical engineering at the Georgia Institute of Technology in the Fall of 2003 and finished the program in January of 2008. He has been married to Tave J. Richardson since May of 1999 and currently has one daughter, Alana J. Richardson. Upon completion of his dissertation, John will work for CRI/Criterion Inc., which is the global catalyst division of the Shell Group.