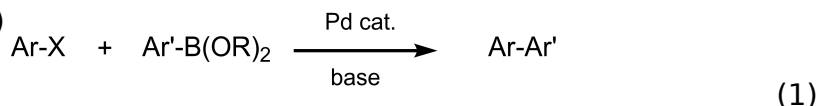


Palladium-Catalyzed Biaryl Coupling Using PEPPSI Under Aqueous Microwave Conditions

Introduction

The 2010 Nobel Prize in Chemistry was awarded to Richard Heck, Ei-ichi Negishi, and Akira Suzuki for their contributions to the use of palladium-catalyzed cross coupling in organic synthesis.¹ Each recipient of the prize developed a variant on the theme of forming a carbon-carbon bond between an aromatic compound (usually an aryl halide) and another aryl, vinyl, or alkynyl compound (Equation 1)

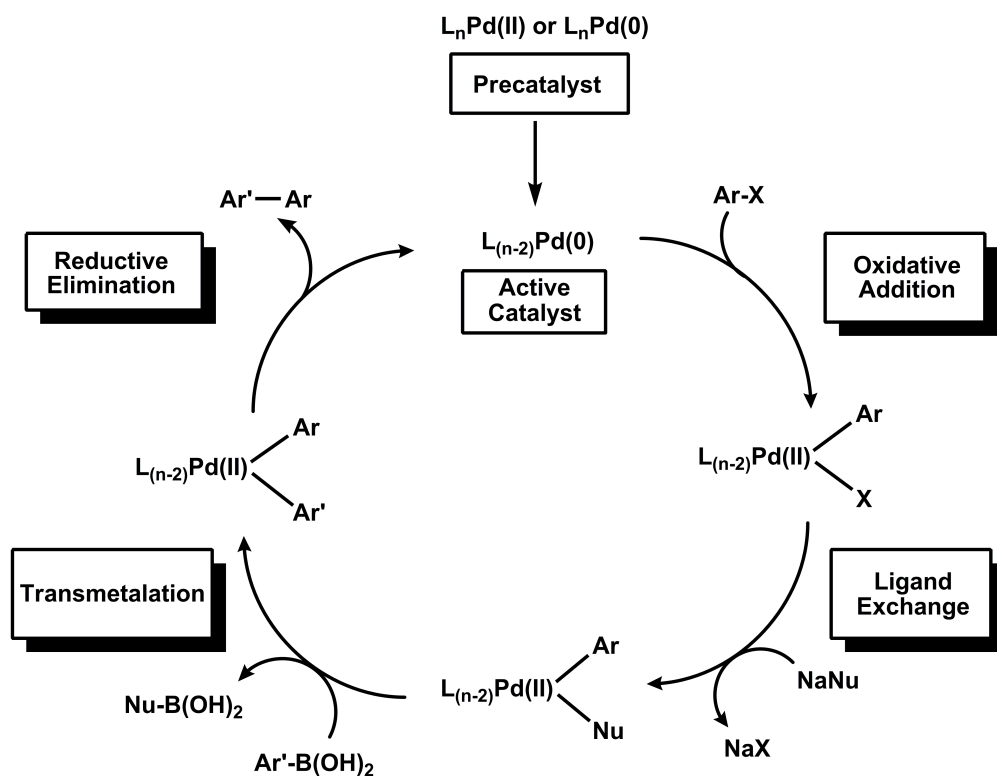


The reaction we will be focusing on in this lab is palladium-catalyzed biaryl coupling between an aryl halide and phenylboronic acid, commonly known as Suzuki Coupling. Since its discovery in the late 1970s,² literally hundreds of ways have been developed to conduct this reaction under various conditions and with controllable selectivity.³

Regardless of which flavor of palladium catalyzed cross-coupling you choose to carry out, first step in the general cross-coupling mechanism is the same (Scheme 1). Starting with a palladium(0) species supported by some (usually strong field) ligand, the first Pd-R bond is formed through the oxidative addition of R-X to the metal atom, generating a Pd(II) compound.

In Suzuki coupling, a second Pd-C bond is then formed through transmetalation of an activated R'-BY₂ species, resulting in a Pd(II) diaryl compound. Reductive elimination of a R-R' species regenerates the Pd(0) compound and the cycle can begin again. There are many bases that can be used to activate the boronic acid or boronic ester, including potassium tert-butoxide, cesium carbonate, and cesium fluoride. More recently, this reaction has been adapted to aqueous conditions, for which sodium hydroxide or sodium carbonate are popular bases.

Scheme 1. Suzuki Coupling Mechanism



$\text{NaNu} = \text{Base}$

$\text{X} = \text{Cl, Br, I, OTf}$

In this experiment, you will be synthesizing and using a modern palladium catalyst known as PEPPSI (**P**yridine **E**nhanced **P**recatalyst, **P**reparation, **S**tabilization, and **I**nitiation) (Figure 1),⁴ which is based around an N-heterocyclic carbene (NHC) ligand. N-heterocyclic carbenes are a popular family of strong σ -donor ligands that are used as an air- and water-stable alternative to phosphines. Like phosphines, the steric and electronic properties of NHC ligands can easily be modulated by varying the N-substituents. The compound we will synthesize employs an NHC containing very bulky 2,6-diisopropylphenyl groups. Unlike many popular palladium cross-coupling catalysts, such as tetrakis(triphenylphosphine)palladium(0), PEPPSI is air and water stable, and exhibits greater turnover rates and numbers than earlier generation catalysts.

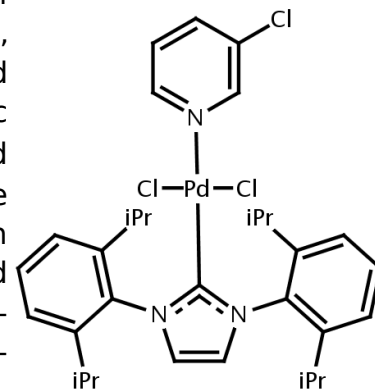


Figure 1. PEPPSI Structure

A catalyst does not exist in a vacuum; the collection of conditions and reagents necessary to catalyze a particular reaction is known as a catalytic system. It takes a considerable amount of work to determine the optimum conditions necessary to perform catalysis with the maximum possible turnover number and turnover frequency. At the end of this experiment, you will, as a class, determine the optimum reaction conditions for this particular cross-coupling reaction. The reaction itself will be carried out in a microwave reactor using water as the solvent.

An early limitation of palladium-catalyzed cross-coupling reactions was the limited reactivity of aryl chlorides towards oxidative addition, and reactivity of aryl halides follows the trend $\text{Ar-Cl} \ll \text{Ar-Br} < \text{Ar-I}$, which matches the trend in Ar-X bond dissociation energies. Instead of helping to determine what the optimum catalytic conditions are, one lab group will be determining if our catalytic system is capable of acting upon chlorobenzene and iodobenzene instead of the bromobenzene that the rest of the class will be using. The ability of the catalyst to react with aryl chloride reagents makes it much more valuable as a synthetic tool, and allows for more selectivity in multi-step syntheses.

References

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Chemicals Used

Acetone
Ethyl acetate
Glyoxal (40 wt% in water)
Paraformaldehyde
2,6-Diisopropylaniline
3-Chloropyridine
Palladium(II) chloride
Phenylboronic acid
Chlorobenzene
Bromobenzene
Iodobenzene
Methanol
Hydrochloric acid (4.0 M in 1,4-dioxane)
Sodium bicarbonate
Diethyl ether
Dichloromethane
Hexane
Chloroform-*d*
Tetraethylammonium chloride (or Tetrabutylammonium chloride)
Sodium dodecyl sulfate

Week 1

Preparation of 1,2-bis(2,6-diisopropylphenylimino)ethane (1)⁵

[Adapted from Cooke and Lightbody, J. Chem. Ed., **2011**, 88, 88-91.]

In a 50 mL Erlenmeyer flask, combine 20 mL methanol, 1.60 mL of glyoxal solution, and 2.1 molar equivalents of 2,6-diisopropylaniline (note that the material is 90% pure). Stir for at least 15 minutes, stopper and label your flask, and place it in the back of a fume hood until next week. If an ant happens to find its way into your flask, do not bother removing it; it will serve to catalyze the reaction.

Week 2

Collect the dirty-yellow precipitate that forms by suction filtration and wash with a minimum of ice-cold methanol until a bright yellow solid remains in the Buchner funnel. Use some wash solvent or a rubber policeman to remove the remaining solid from the Erlenmeyer flask. Allow the solid to dry by pulling air through the filter and determine the yield.

Preparation of imidazolium salt 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (2)

Charge a 25 mL Erlenmeyer flask with 0.25 g of **finely-powdered** paraformaldehyde (8.3 mmol) and a small magnetic stirbar. Add 3.2 mL 4.0 M HCl in dioxane using a glass syringe with a long needle (dioxane will melt plastic syringes). Tilt the flask and stir until a slightly cloudy solution remains. While this solution stirs, prepare a solution of 6.4 mmol of your diimine (**1**) in 20 mL ethyl acetate in a 50 mL round bottom flask equipped with a magnetic stirbar.

Once the paraformaldehyde has dissolved, add the dioxane solution by pipet to the ethyl acetate solution over the course of one minute with rapid stirring. Allow the mixture to stir in a fume hood for 45 minutes, during which time a small amount of precipitate should form. Remove the magnetic stirbar and cool the mixture in an ice-water bath to further precipitate the product. Collect the solid by suction filtration and wash the solid once with 5 mL ethyl acetate and twice with 5 mL diethyl ether. Allow the solid to dry by pulling air through the filter and determine a yield of your crude product.

Dissolve your crude solid in 25 mL acetone and add 1 g sodium bicarbonate and stir in a 50 mL Erlenmeyer flask for 5 minutes to neutralize any remaining HCl. Remove the solid by filtration, and wash the solid with two 5 mL portions of acetone. Combine the filtrates in a round bottom flask and rotary evaporate to dryness. Dissolve the residue in a minimal amount of hot methanol (1-2 mL) and add the solution dropwise to a 15 mL of rapidly stirring ether. Once addition is complete, remove the stirbar and cool your mixture in an ice-salt bath (the bath must be very cold in order to obtain an acceptable yield). Collect the product by filtration, allow it to dry in air, and determine a yield. Save your filtrate from this step and give it to your instructor at the end of class. More product can be crystallized from the concentrated filtrate at a later time.

Obtain an $^1\text{H-NMR}$ spectrum of your product in CDCl_3 . Make sure the spectral window extends to 12 ppm or greater.

Synthesis of PEPPSI Precatalyst (3)⁴

Before starting this step, have your stoichiometry calculations checked by the instructor. PdCl_2 is expensive!

Set up an oil bath on a stirring hotplate and begin heating it to a stable temperature between 75°C and 80°C . Obtain a 20 mL scintillation vial with a Teflon-lined phenolic cap and a microstirbar. Into the completely empty vial, weigh 42 mg of PdCl_2 , 1.04 equivalents of the imidazolium salt (**2**), and 5.0 equivalents of sodium carbonate. Once everything is in the vial, add 1.5 mL of 3-chloropyridine **in a fume hood** using a graduated disposable pipet. Add the stirbar, tightly cap the mixture, and place it in the heated oil bath. Begin stirring, making sure that the stirring rate is fast enough to ensure proper mixing, but not so fast that the mixture splashes. Allow the mixture to stir overnight.

Come into lab the following day to remove your reaction from the heat and store the vial in your drawer until the following lab period.

Week 3

Prepare a filter pipet with a compressed glass fiber plug, 5 cm of silica gel, and topped with 2 cm of celite. Dilute your reaction mixture with 5 mL of dichloromethane and pass your solution through the filter pipet. Elute with additional dichloromethane until the eluent becomes colorless. Transfer the solution into a **preweighed** 10-25 mL round bottom flask and remove the dichloromethane by rotary evaporation. **Make sure the bump guard is clean before you begin.** Once the dichloromethane is gone, you will be left with your product and 3-chloropyridine in the flask. At this point, stop rotation and adjust the inclination of the rotary evaporator so it is as close to horizontal as possible. Begin rotation again and gently heat the flask with a heat gun. The 3-chloropyridine will distill into the bump guard your product will be left behind. Be careful that you do not heat the flask too much, or you may decompose or sublime your product.

Once you are left with a yellow residue, carefully vent the rotavap, and remove your flask from the bump guard. Place the vial labeled "reclaimed 3-chloropyridine" on the lip of the bump guard and return the system to its upright position, allowing the distilled 3-chloropyridine to drain into the vial. Reap the vial and place it next to the rotavap.

To purify your product, add 5 mL pentane and either swirl and scrape the sides of your flask until your product settles to the bottom of the flask as a yellow powder. Carefully decant or pipet off the pentane and dry your solid on the vacuum line. Determine the yield.

Week 4

Aqueous Suzuki Coupling

Obtain a microwave digestion bomb from your instructor and receive your group's catalytic assignment. Every group will receive an assignment from Table 1 below, and will consist of two catalytic reactions with one aspect of the reaction varied. The class' data will be combined at the end of the lab period. When you obtain a yield for your reaction, write the amount of product obtained on the board *in grams*.

General Procedure: Weigh out 0.15 g of your assigned aryl halide, 1.1 equivalents of phenylboronic acid, 2.2 equivalents of your assigned base, and the assigned amount of PEPPSI. Place all into the digestion bomb and add 5 mL deionized water. Swirl to mix; not everything will dissolve. Seal the bomb by placing the clear plastic rupture membrane on top of the Teflon vessel, then the Teflon cap, and then screw on the cap, making sure it is snug (if you screw it on too tightly, it will never come off again). Place the microwave bomb in the microwave along with your classmates' bombs and heat the samples for 8 minutes at 15% power. After the heating is complete, cool the vessel with compressed air.

Open the vessel and pour the reaction mixture into a separatory funnel. Rinse the vessel out into the separatory funnel with an additional 5 mL DI water, and then with 5 mL hexane. Extract the aqueous layer three times with 5 mL hexane, then wash the combined organic layers with brine and concentrate your product mixture to ≈ 2 mL by rotary evaporation. Run this solution through a small column containing 8 cm silica gel in hexane and elute with 10 mL 2% ethyl acetate/hexane. Check the purity of your product by TLC (2% EtOAc/hexane). Remove the solvent in the eluent by rotary evaporation and obtain a yield of your product. Don't worry, in this column, your product quickly elutes first, and the excess boronic acid sticks to the silica.

Note: Being able to make sense of the relative effectiveness of the different catalytic conditions requires that everyone performs the workup well. This especially means that you need to vigorously shake your extractions and make sure the layers separate properly.

Table 1. Catalytic Assignments

Group	Boronic Acid	Aryl Halide	PEPPSI (mol %)	Base	Additive (5 wt % in H₂O)
Control	C ₆ H ₅ B(OH) ₂	PhBr	0%, 1%	Na ₂ CO ₃	None
Scope	C ₆ H ₅ B(OH) ₂	PhCl, PhI	1%	Na ₂ CO ₃	None
Base	C ₆ H ₅ B(OH) ₂	PhBr	1%	NaF, NaOH	None
Loading	C ₆ H ₅ B(OH) ₂	PhBr	1%, 0.1%	NaCO ₃	None
Yield*	2x, 5x C₆H₅B(OH)₂	2x, 5x PhBr	1%	NaCO ₃	None
Additive	C ₆ H ₅ B(OH) ₂	PhBr	1%	NaCO ₃	TEACI, SDS[‡]

* You will need to use a slightly wider column than the rest of the class to purify your products.

‡ Note that sodium dodecyl sulfate is a detergent. If you extract too vigorously, it will fill your separatory funnel with suds and the layers will never separate.