

Suzuki Cross-Coupling of Phenylboronic Acid and 5-Iodovanillin

The formation of bonds, especially carbon-carbon bonds, is certainly the single most important tool an organic chemist can use in constructing increasingly elaborate carbon frameworks, in order to synthesize complex organic compounds from simple molecules. The study and advancement of metal-catalyzed cross-coupling reactions have considerably increased the options available to synthetic organic chemists. These techniques permit the creation of much more complex molecular frameworks than have been developed in the past, and have found extensive application in total synthesis of natural products, herbicides, pharmaceuticals, conducting polymers, medical and process chemistry as well as biology and nanotechnology.

Prominent amid the cross-coupling processes is the palladium-catalyzed carbon-carbon bond formation reaction. Among the palladium-catalyzed reactions, the Suzuki-Miyaura cross-coupling reaction (also known as simply Suzuki cross-coupling) has become one of the most reliable and widely applied coupling reactions, playing a prominent role in total synthetic organic chemistry. Discovered by the Suzuki group in 1979, Suzuki-Miyaura coupling involves the palladium-mediated coupling of organic electrophiles, such as aryls or alkenyl halides and triflates, with organoboron compounds, such as phenyl boronic acids, in the presence of a base. The reaction begins with (1) an oxidative addition of organic halide to the Pd(0) species to form Pd(II); (2) followed by transmetalation of the X/R' (or a ligand substitution) and (3) *trans-cis* rearrangement and finally a reductive elimination to complete the cyclic process. The Suzuki reaction is particularly useful in constructing conjugated dienes and higher polyene systems of high stereoisomeric purity, as well as biaryl and related systems.

Traditionally, metal-catalyzed reactions such as the Suzuki cross-coupling reaction are performed in organic solvents such as tetrahydrofuran (THF) and ether, which are hazardous to safety and the environment. Products are also harder to isolate due to the ability of these solvents to readily dissolve both starting materials and end products. Recently, however, the benefits of potential recycling, simple recovery and low toxicity of environmentally friendly solvents in homogeneous-metal catalyzed reactions has become increasingly obvious, and therefore increasingly widely used.

Today, you will utilize a fundamental skill required of a chemist – bond formation – by attempting to synthesize 6-hydroxy-5-methoxy-1,1'-biphenyl-3-carbaldehyde *via* an aqueous phase Suzuki coupling reaction.

Procedure: Cross-Coupling of 5-iodovanillin and phenylboronic acid

Place 3 mL of water, 1 mL of 95% ethanol, a stir bar, and 1.0 millimole of 5-iodovanillin, 1.0 millimole (122 mg) of phenylboronic acid, ~0.5 g of the ion-exchange resin Amberlite IRA-400(OH), and 2 mg (0.01 mmol) of Pd(OAc)₂ into a 25mL round-bottomed flask. (Note: When adding the palladium (II) acetate, use a

clean small spatula, and add a minimal amount of the solid to the reaction. The reaction mixture should turn brown upon palladium addition.)

Seal the vessel with a septum with a needle opening, and place into a hot water bath at 60°C for 5 minutes.

After the mixture has been allowed to warm, add additional 95% ethanol dropwise up to 3mL or until almost all solute has dissolved. Allow the mixture to react, with vigorous stirring, for one to two hours, and then store it until the next lab period.

Recovering the product

Heat the reaction mixture to about 50°C. Perform a hot gravity filtration on the solution (while still warm) and allow the mixture to cool in an ice bath.

While cooling, add **cold** 10% HCl (aq) dropwise until you observe a precipitate, and continue adding the 10% hydrochloric acid solution until the mixture is appreciably acidic. Add 20 mL of water to the mixture.

In a separatory funnel, extract the aqueous layer with 3 x 10 mL of ethyl acetate, and combine the organic layers. Dry the organic extracts over MgSO₄ and remove the ethyl acetate by rotary evaporation to obtain the crude product. Allow the crude product to air dry for a few hours or overnight before obtaining NMR spectral data.

Potentially useful information

MW 5-iodovanillin:	278.05 g/mol
MW phenyl boronic acid:	121.93 g/mol
MW palladium (II) acetate:	224.50 g/mol

Study Questions

1. Write the general reaction for a Suzuki cross-coupling reaction.
2. Would this reaction be described as an addition, elimination, or substitution reaction? Please explain.

Suzuki Cross-Coupling of Phenylboronic Acid and 5-iodovanillin Lab Report

Draw a mechanism (use electron pushing) for the reaction performed in lab:

Draw the structure of the predicted product:

Physical Data: Report all required physical data below

M.P. Range (5-iodovanillin) : _____

Color (5-iodovanillin) : _____

M.P. Range (product) : _____

Color (product) : _____

Experimental Data:

Starting Materials

Compound	Amount
5-iodovanillin	grams
Phenylboronic acid	grams
Pd(OAc) ₂	grams
Amberlite IRA-400(OH)	grams
water	mL
ethanol	mL
Temperature	

Product

Amount (air dry) :	grams

Questions:

- 1) Why does the reaction require alkaline conditions?
- 2) Why did you need to acidify the solution after the reaction?
- 3) What is the purpose of hot gravity filtration?
- 4) What is the purpose of the resin in the reaction?

With this report, please provide the following:

- 1) NMR Spectrum of the product (if required by Professor)
- 2) Labeled (Name, Lab Day, Date, Reaction Performed) vial of product (if available)
- 3) Photocopy of lab notebook pages (must have procedure clearly written with observations) pertaining to this lab.