Laboratory Notes For Students

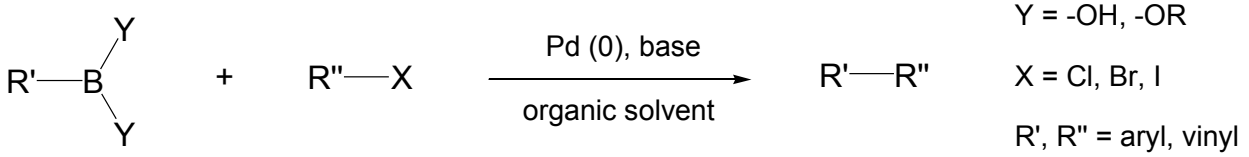
Estimated Length Of Experiment: 2 – 2.5 hours

Experimental Objectives

1. To synthesize 4-phenylphenol (4-hydroxybiphenyl) by a Suzuki reaction.
2. To characterize the reaction product by ^{1}H NMR, ^{13}C NMR and IR spectroscopy.
3. To appreciate the advantages of using water as the solvent for this (and other) organic reactions.
4. To consider this reaction in terms of atom economy.

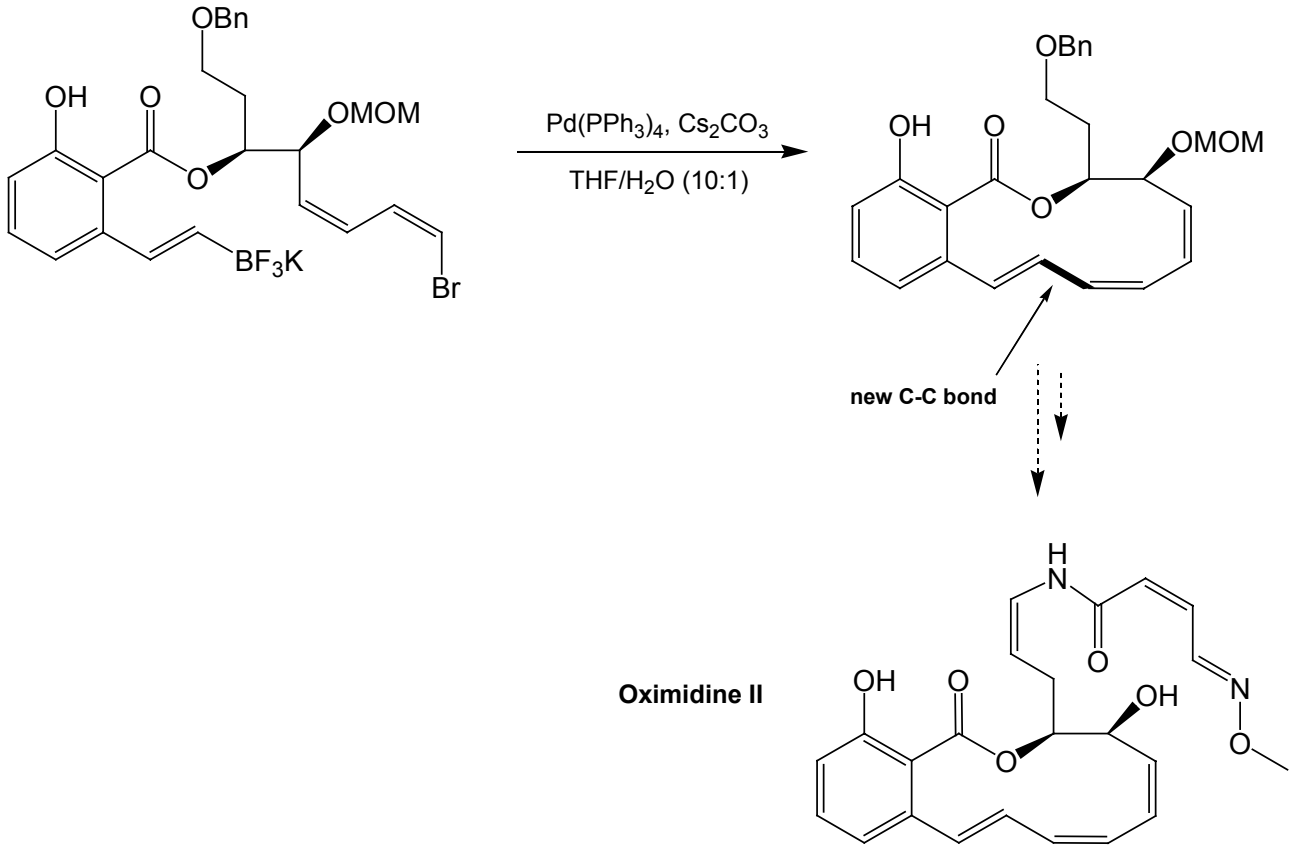
Background

The Suzuki reaction is a very popular, mild approach for synthesis of carbon-carbon sigma bonds. This strategy generally involves reaction of a boronic acid or ester with an aryl or vinyl halide under basic conditions in the presence of a palladium (0) catalyst (*1*) (below).



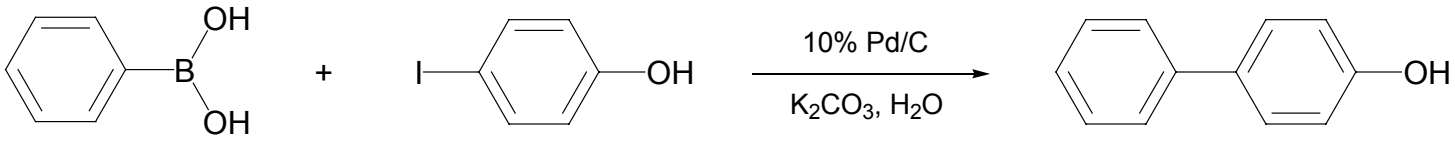
A Typical Suzuki Reaction

Many fundamental transformations involved in the synthesis of pharmaceutically significant compounds are achieved by Suzuki reactions (*2*). A recent example is during the preparation of Oximidine II, a substance that exhibits selective cytotoxicity for oncogene transformed cells (*3*). (An oncogene is a gene that causes the transformation of normal cells into cancerous tumor cells). The key step in the synthesis of Oximidine II is an intramolecular Suzuki reaction between a vinyl bromide and a potassium trifluoroborate salt (overleaf).

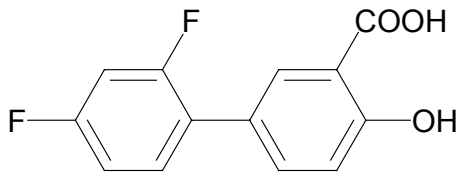


Synthesis Of Oximidine II, Incorporating A Suzuki Reaction (*3*)

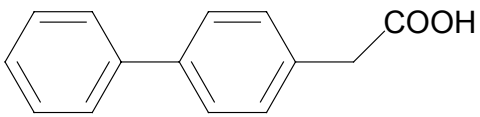
This example illustrates that Suzuki reactions are often undertaken in an organic solvent with water as a co-solvent. An inorganic base (such as sodium, potassium or cesium carbonate) is also commonly used. An educational example of this reaction type has been published (*4*). There is currently much active research in the area of "green chemistry" from a synthetic perspective, employing reaction conditions that are less deleterious to the environment than previous approaches. Most organometallic reactions (e.g. the Grignard and Gilman reactions) do not lend themselves to aqueous conditions but it is possible to use pure water as the solvent for certain processes. This is significant for reactions creating new carbon-carbon σ-bonds as these form the basis of organic synthesis (*5*). Today's reaction illustrates recent advances made in improving the "greenness" of an industrially important synthetic method. Phenylboronic acid is coupled with 4-iodophenol in the presence of 10% palladium on carbon and potassium carbonate (*6*). These conditions afford facile preparation of a biaryl product (4-phenylphenol) of the type currently marketed as non-steroidal anti-inflammatory drugs (NSAIDs). Two over-the-counter NSAIDs that you are likely familiar with are acetylsalicylic acid (aspirin) and ibuprofen.



Aqueous Suzuki Synthesis Of 4-Phenylphenol



Diflunisal



Felbinac

Two Biaryl Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Safety Notes

Wear eye protection, a laboratory coat and protective gloves during this experiment. Potassium carbonate is irritating to the eyes, respiratory system and skin. Phenylboronic acid and 4-iodophenol are skin irritants and harmful if inhaled. 10% Palladium on carbon is harmful if swallowed. Methanol is highly flammable and toxic if swallowed. Hydrochloric acid causes burns and is irritating to the respiratory system.

CAUTION – PERFORM ALL SYNTHETIC AND PURIFICATION OPERATIONS IN A FUMEHOOD

Experimental Procedure

A table of the reactant/solvent physical properties is detailed below:

Compound	GMW	Amount Added	mmol	mp (°C)	bp (°C)	d (g/mL)
phenylboronic acid	121.93	122 mg	1.00	216-219		
4-iodophenol	220.01	220 mg	1.00	92-94		
potassium carbonate	138.21	415 mg	3.00	891		
10% palladium on carbon	106.42	3 mg				
2 M HCl	36.46					
methanol	32.04			-98	64	0.791

1. **IN A FUMEHOOD**, place the following in a 50-mL round-bottomed flask: phenylboronic acid (122 mg); potassium carbonate (415 mg); 4-iodophenol (220 mg); and water (10.0 mL – automatic delivery pipette). Add a magnetic stir bar.

2. Add water (~ 1 mL) to the supplied vial containing 10% palladium on carbon (3 mg) to create a suspension. Transfer the suspension to the reaction mixture.

3. Heat the mixture **vigorously** under reflux (water condenser) for 30 minutes, using a sand bath as the heat source and **maintaining rapid stirring**. Some solid may precipitate.

4. Remove the flask from the sand bath and allow cooling to room temperature.

5. Add aqueous HCl (2 M) to the filtrate until acidic to litmus paper. Collect the crude solid (still containing catalyst) by vacuum filtration (Hirsch funnel) and wash with water (10 mL).

6. Dissolve the collected solid in ~ 10 mL methanol (25-mL Erlenmeyer flask) and remove the Pd/C by gravity filtration (collect the filtrate in a 50-mL Erlenmeyer flask).

7. Add ~ 10 mL distilled water to the crude product dissolved in methanol, causing solid to precipitate. Heat until the entire product has gone into solution (adding 1 – 2 mL portions of methanol if necessary). Once complete dissolution has occurred, allow the solution to cool slowly to room temperature and then cool in an ice-bath.

8. Collect the recrystallized product by vacuum filtration (Hirsch funnel) and dry very thoroughly (can be left until the following laboratory period). Remove the solid from the funnel, weigh and calculate the percentage yield. Take appropriate physical measurements (mp, IR, ^{1}H, ^{13}C NMR spectra) to ascertain the purity of your compound, comparing with literature data where possible.

SUBMIT A SAMPLE OF YOUR SYNTHESIZED PRODUCT WITH YOUR REPORT

Clean-Up

Dispose of all waste into the appropriately marked containers in the fumehoods. Dismantle and clean all glassware with soap and water.

Laboratory Report

Your report should contain the following aspects:

1. Discussion of the Suzuki reaction performed, including

   (i) a detailed catalytic cycle illustrating formation of 4-phenylphenol. Points to include:

a) oxidative addition
b) transmetallation
c) reductive elimination and regeneration of Pd (0)
d) a rationale for the quantity of base used

(ii) the calculated percent yield, with reference to similar experiments (*6*)

(iii) calculation of the atom economy of the reaction (*7*). How might the atom economy be improved by changing the structure of one of the starting materials? Can you predict any drawbacks to doing this?

2. Discussion of spectral data obtained, including

(i) an IR spectrum analysis (in terms of product absorbances and similarities/differences from the IR spectra of 4-iodophenol and phenylboronic acid)

(ii) an interpretation of the ^{1}H NMR of 4-phenylphenol (with respect to chemical shifts and spin-spin splitting patterns).

3. An outline of the benefits of performing the Suzuki reaction under aqueous conditions (compare and contrast this reaction with the approach in reference (*4*), and original reports of the Suzuki reaction). Why is it important to develop reactions that use water as the solvent?

Useful References

1. Miyaura, N.; Suzuki, A. *Chem. Rev*., **1995**, *95*, 2457-2483.

2. Franzén, R.; Xu, Y. *Can. J. Chem*., **2005**, *83*, 266-272.

3. Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.*, **2004**, *126*, 10313-10318.

4. Callam, C. S.; Lowary, T. L. *J. Chem. Educ*., **2001**, *78*, 947-948.

5. Li, C-J. *Chem. Rev.*, **2005**, *105*, 3095-3165.

6. (a) Sakurai, H.; Tsukuda, T.; Hirao, T. *J. Org. Chem.*, **2002**, *67*, 2721-2722.

(b) Kuznetsov, A. G.; Korolev, D. N.; Bumagin, N. A. *Russ. Chem. Bull., Int. Ed.*, **2003**, *52*, 1882-1883.

7. Trost, B. M. *Science*, **1991**, *254*, 1471-1477.