adapted from Callum and Lowary, J. Chem. Educ. 2001, 78, pg 947

# Suzuki cross coupling reactions: synthesis of unsymmetrical biaryls in the organic laboratory

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## *Notes for the Student*

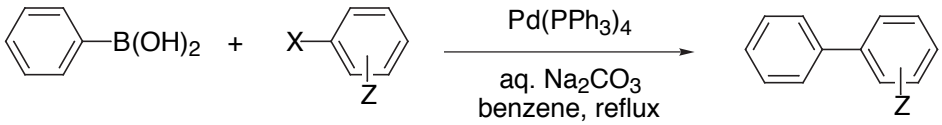
In the following document, notes preceded by "Ins" are notes for the instructor and can be found in the "Notes for the Instructor" document. Notes for the students are found at the end of this document.

***CAUTION!***

Aryl boronic acids and palladium acetate are irritants. Hydrochloric Acid is corrosive. Wear gloves and use caution in all steps of the laboratory experiment.

**Introduction**

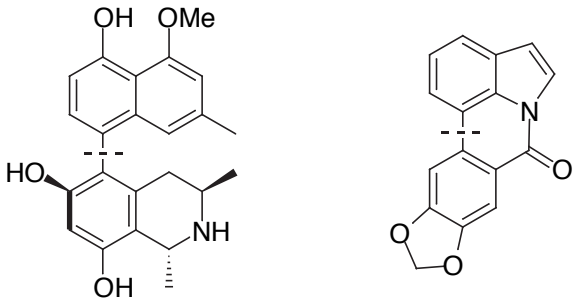
In 1981 Suzuki and coworkers developed an efficient methodology for the synthesis of $sp^2$-$sp^2$ carbon-carbon bonds between two aromatic rings (Scheme 1). The palladium (0) catalyzed coupling of aryl boronic acids with aryl halides (known as the Suzuki cross coupling reaction) represents one of the most efficient and simple methods for carbon-carbon bond




**Scheme 1**

formation in organic chemistry. The popularity of this and other palladium (0) catalyzed reactions has grown over the last twenty years and are now routine in the organic laboratory. The Suzuki reaction is by far the most versatile and useful synthetic reaction for the assembly of

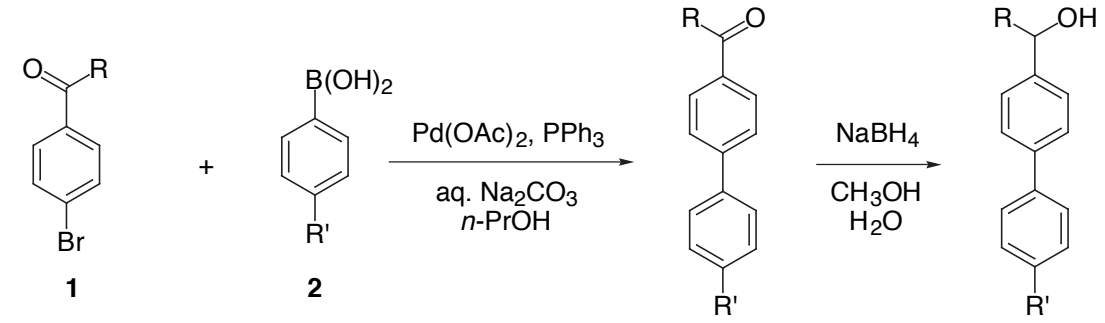
biaryl systems. Some of the molecules this reaction has been used to synthesize are Korupensamine A, an anti-malarial agent, and Hippadine, an alkaloid from *Crinum amaryllidacae* which shown biological activity (Scheme 2). Unlike the more familiar metal promoted organic reactions (*e.g.,* Grignard and organolithium reactions) the Suzuki cross coupling is catalytic in the metal and can be carried out in an aqueous environment. Furthermore, this reaction will tolerate a wide range of functional groups. For example, in this experiment you will synthesize a C–C bond in the presence of a carbonyl group in an aqueous environment. Such a reaction would be impossible with a Grignard reagent.




Korupensamine A Hippadine

**Scheme 2**

The molecule prepared in the experiment is a biaryl alcohol (**4**, Scheme 3). The goal of the experiment is two fold. The first goal is to perform the cross coupling reaction from two unknown coupling partners and isolate the product (**3**). Upon isolation of (**3**) the carbonyl group will be




**Scheme 3**

reduced with sodium borohydride to yield the biaryl alcohol (**4**) with an unknown substitution pattern. Both the intermediate (**3**) and final product (**4**) are solids. The second goal is to determine the structure of the product from its IR spectrum, NMR spectrum and melting point. In turn, you can determine the starting materials you were given. In the first period, you will perform the palladium catalyzed cross coupling reaction and corresponding work up to obtain a crude intermediate (**3**). In the second period, you will purify the intermediate (**3**) by recrystallization, reduce it with sodium borohydride and purify the resulting alcohol (**4**).

**Experimental – First Lab Period**

To a 100 mL three necked round bottomed flask equipped with a magnetic stir bar, condenser, and a nitrogen inlet balloon add the aryl halide (1.00 g, 5.02 mmol), the aryl boronic acid (0.692 g, 5.68 mmol), and *n*-propanol (10 mL). Stir the mixture for 15 min allowing complete dissolution of all solids. To the solution add palladium acetate (3.6 mg, 16.0 μmol), triphenylphosphine (12.8 mg, 48.8 μmol), 2M aqueous sodium carbonate (3.25 mL, 6.48 mmol), and deionized water (2.0 mL). Heat the solution at reflux under a nitrogen environment until complete (~ 1 h). The reaction progress can be monitored by TLC (4:1, hexanes:ethyl acetate) (Ins 2).

Cool the reaction to room temperature, add water (7 mL), and stir the mixture open to the air for 5 min (Stu 1, Ins 3). Dilute the reaction with ethyl acetate (10 mL) and transfer it to a separatory funnel. Separate the two layers and re-extract the aqueous layer with ethyl acetate (10 mL). Combine the organic extracts and wash them with a 5% sodium carbonate solution (2 x 10 mL) and brine (2 x 10 mL) sequentially (Stu 2, Ins 4). Transfer the organic phase to a 125 mL Erlenmeyer flask equipped with a magnetic stir bar and add activated charcoal (0.50 g) and sodium sulfate (1 g). Stir this mixture for 10 min.

Filter the solution through a 1 cm bed of Celite using a Buchner funnel into a 125 mL filter flask. After filtration, rinse the Celite with several portions of ethyl acetate. Concentrate the resulting pale yellow filtrate under reduced pressure to yield the biaryl product as a solid.

**Experimental – Second Lab Period**

Slurry the crude intermediate (**3**) in hexanes (5 mL) while warming to reflux. Add methanol (2 mL) to clarify the solution. Upon dissolution of the solid, remove the heat source and allow the solution to cool to induce crystal formation. Isolate the crystals by vacuum filtration and wash them with cold hexanes. Dry isolated crystals by suction filtration to afford the purified biphenyl adduct as a solid.

To a 50 mL Erlenmeyer flask equipped with a magnetic stir bar, add 20 mL of methanol and the biaryl adduct (**3**) (400 mg, 2.04 mmol). Stir the mixture at room temperature for 5 min (Stu 3, Ins 4). To the mixture, add dropwise over the course of 5 min a solution of sodium borohydride (0.09 g, 2.4 mmol) dissolved in 2 mL of water. Stir the reaction mixture at room temperature for 20 min and then pour it into a 50 mL beaker containing 10 mL of cold water and 1 mL of conc. HCl. Filter the mixture using vacuum filtration to yield the crude biaryl alcohol (Stu 4, Ins 5). Recrystallize the crude product from petroleum ether to yield the purified biaryl alcohol.

***Notes for Students***

Stu 1 Upon cooling the reaction , the mixture darkens and forms a thin black emulsion on top of the solution.

Stu 2 During the extractions in the work up, the thin black emulsion is taken with the organic layer each time until the final wash with brine when it is discarded.

Stu 3 The solids do not dissolve readily in the methanol until the addition of the sodium borohydride.

Stu 4 The crude solids should be thoroughly dried by suction filtration to remove any trace water prior to recrystallization.

*Approximate quantities of chemicals for 10 students**

***First Lab period***

| **Chemical** | **CAS Registry #** | **Amount** |
|---|---|---|
| Phenylboronic acid | [98-80-6] | 3 g |
| 4-Methylphenylboronic acid | [5720-05-8] | 3 g |
| 4-Methoxyphenylboronic acid | [5720-07-0] | 3 g |
| 4-Bromoacetophenone | [99-90-1] | 5 g |
| 4-Bromobenzaldehyde | [1122-91-4] | 5 g |
| *n*-Propanol | [71-23-8] | 100 mL |
| Triphenylphosphine | [603-35-0] | 0.150 g |
| Palladium(II) acetate | [3375-31-3] | 0.05 g |
| Sodium carbonate (2M aq.) | [497-19-8] | 35 mL |
| Activated charcoal | [64365-11-3] | 10 g |
| Silica | [112926-00-8] | 20 g |
| Sodium chloride (sat. aq.) | [7647-14-5] | 200 mL |
| Ethyl acetate | [141-78-6] | 200 mL |
| Sodium carbonate (5% aq) | [497-19-8] | 200 mL |
| Celite | [61790-53-2] | 25 g |
| Sodium sulfate | [7757-82-6] | 15 g |

***Second Lab Period***

| **Chemical** | **CAS Registry #** | **Amount** |
|---|---|---|
| Sodium borohydride | [16940-66-2] | 1.00 g |
| Methanol | [67-56-1] | 220 mL |
| Hydrochloric acid (conc.) | [7647-01-0] | 10 mL |
| Hexanes | [110-54-3] | 50 mL |

*Assuming equal distribution of unknowns.