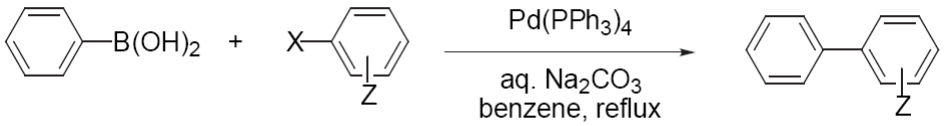
Suzuki Cross Coupling Reactions: Synthesis of Unsymmetrical Biaryls

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.

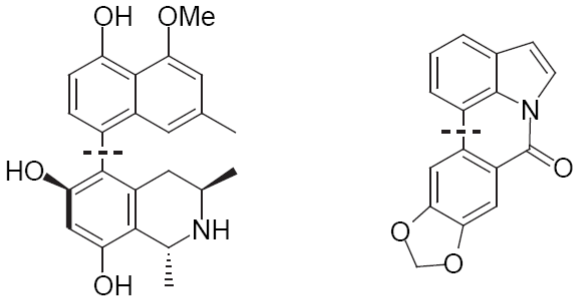
Introduction

In 1981 Suzuki and coworkers developed an efficient method for the synthesis of sp^2-sp^2 carbon-carbon bonds between two aromatic rings (Scheme 1).



Scheme 1

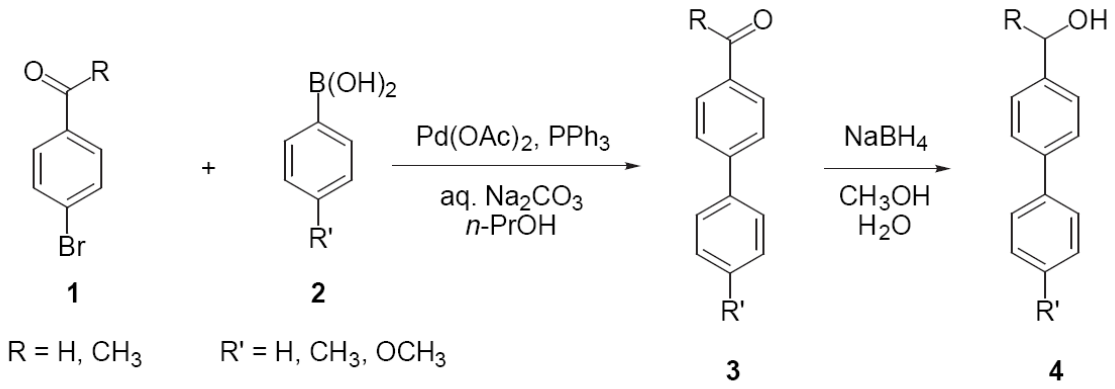
The palladium(0) catalyzed coupling of an aryl boronic acid with an aryl halide is now known as the Suzuki cross coupling reaction. This reaction is one of the most efficient and simple methods for carbon-carbon bond formation in organic chemistry. Its popularity has grown over the last twenty years and such reactions 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 shows biological activity (Scheme 2).



Korupensamine A Hippadine

Scheme 2

Unlike the more familiar organometallic 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 tolerates 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.



Scheme 3

The molecule prepared in this two-week experiment is a biaryl alcohol (**4**, Scheme 3). The main goal of the experiment is two-fold. The first goal is to perform the cross coupling reaction from an unknown aryl bromide (1) and an unknown aryl boronic acid (**2**) and isolate the product (**3**). Upon isolation of (**3**), the carbonyl group will be reduced with sodium borohydride to yield the biaryl alcohol (**4**). Both the intermediate (**3**) and final product (**4**) are solids. The second goal is to determine the structure of product **4** from its NMR spectrum. In turn, you can determine the structures of the starting materials you were given.

In the Week 9 lab, you will perform the palladium catalyzed cross coupling reaction and corresponding work up to obtain a crude intermediate (**3**). In the Week 12 lab, you will purify the intermediate (**3**) by recrystallization, reduce it with sodium borohydride, and purify the resulting alcohol (**4**).

Procedure

Assemble the reflux condenser with septum and a clamped nitrogen inlet balloon. To a 100 mL round bottomed flask equipped with a magnetic stir bar, add the aryl halide (1.00 g), the aryl boronic acid (0.692 g), and *n*-propanol (10 mL). To the solution add palladium acetate (3.6 mg), triphenylphosphine (12.8 mg), and 5.25 mL of 1.2 M aqueous sodium carbonate. Stir while purging with N_2 for 30 seconds. To the RBF, add a condenser, 19/22 septum, and a nitrogen inlet balloon. Stir the mixture for 15 min allowing complete dissolution of all solids. Heat the solution at reflux under a nitrogen environment until complete (~ 1 h). Run a TLC (4:1, hexanes:ethyl acetate) of the reaction mixture at the conclusion of the reflux to determine whether any unreacted starting material is still present.

Cool the reaction to room temperature, add water (7 mL), and stir the mixture open to the air for 5 min. Upon cooling the reaction, the mixture darkens and forms a thin black emulsion on top of the solution. 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. 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. 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 Büchner 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 crude biaryl carbonyl product as a solid.

The crude biaryl carbonyl compound (**3**) is recrystallized using a mixture of hexanes and methanol. Slurry the crude **3** in hexanes (5 mL) while warming to boiling. Add hot methanol 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 the isolated crystals by suction filtration to afford the purified biaryl carbonyl compound as a solid.

To a 50 mL Erlenmeyer flask equipped with a magnetic stir bar, add 20 mL of methanol and 400 mg of the biaryl adduct (**3**). Stir the mixture at room temperature for 5 min. The solids do not dissolve readily in the methanol until the addition of the sodium borohydride. To the mixture, add dropwise over the course of 5 min a solution of sodium borohydride (0.09 g) 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. The crude solids should be thoroughly dried by suction filtration to remove any trace water prior to recrystallization. Recrystallize the crude product from hexanes to yield the purified biaryl alcohol.

Prepare an NMR sample of the final product using acetone-d_6 as the solvent. Obtain a melting point of the final product.