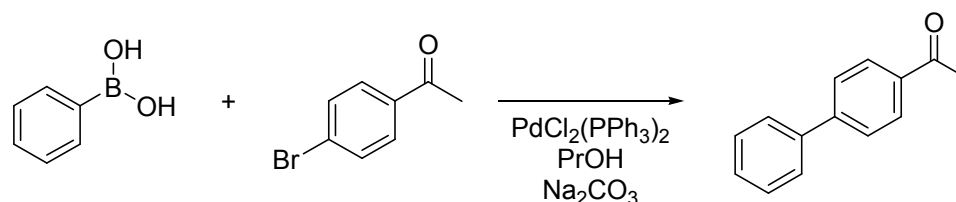


## Suzuki Cross-Coupling Reaction

### Overall Reaction



### Purpose

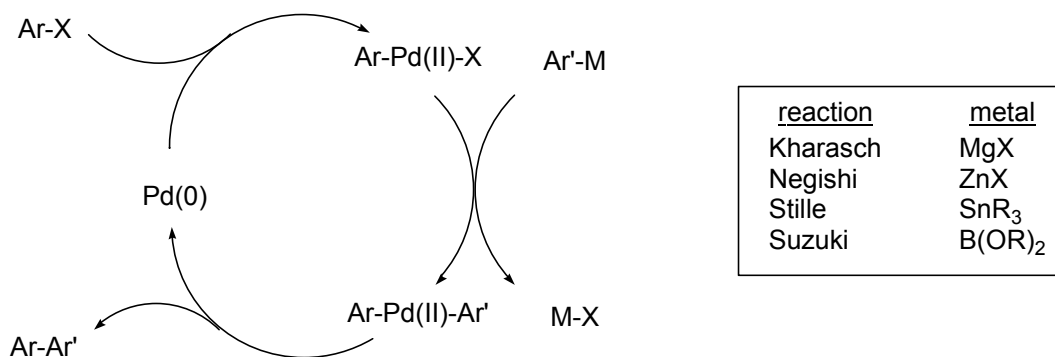
This experiment has the following goals:

- (1) perform a transition-metal catalyzed reaction
- (2) gain exposure to a standard carbon-carbon coupling process
- (3) perform a recrystallization.

### Background

Over the past 30 years, catalytic organometallic processes have revolutionized how organic chemists form carbon-carbon bonds. Some of the new reactions are very case-dependent and require exotic catalysts that are difficult to handle and/or expensive. Other new reactions show broad generality and are simple to perform. The latter reactions have become standards in the “toolkit” of organic chemists.

One example of a new standard is the palladium-catalyzed cross-coupling reaction. Many variations have been developed, including the Kharasch, Stille, Negishi, and Suzuki couplings. While each reaction is distinct, they all share a common catalytic cycle (Scheme 1). The catalyst,  $\text{Pd}(0)$ , oxidatively inserts into a carbon-halogen bond ( $\text{Ar-X}$ ). The  $\text{Ar-Pd-X}$  species then reacts with an aryl-metal ( $\text{Ar'-M}$ ) to form a diaryl palladium intermediate ( $\text{Ar-Pd-Ar'}$ ). This compound undergoes a reductive elimination to regenerate the  $\text{Pd}(0)$  catalyst and the biaryl product ( $\text{Ar-Ar'}$ ). Variations on this reaction involve changes in the identity of the metal. In our reaction, the Suzuki coupling, the metal is boron, and the aryl-metal is called a boronic acid. Boronic acids are easy to make, give products in high yields, and form benign waste products. All these factors combined have made the Suzuki coupling a popular reaction for making biaryl compounds.



Scheme 1. Pd-catalyzed coupling reactions

Biaryls are important intermediates in synthesis. They are common subunits in many molecules, so the synthesis of biaryls is an important field. Not many effective methods for directly linking

two aromatic rings were known before coupling chemistry was developed. Because coupling chemistry excels in this type of process, it has found very rapid acceptance and widespread use. Much chemistry is continuously being developed. The most valuable new chemistry evolves from research that is seeking to solve a problem or satisfy a need.

In all catalyzed reactions, a key aspect is the *loading* of the catalyst. In most reactions catalyzed by a transition metal, the catalyst is the most expensive reagent in the process. If the loading, or amount used, of the catalyst is low, then the reaction will cost considerably less to perform. Catalyst loadings are generally described in *mole percent* (mol%). In the 1970s, the benchmark for a catalyst was 10 mol%, meaning the reaction required 0.10 equivalents of the catalyst relative to the limiting stoichiometric reagent. At a loading of 10 mol%, the catalyst would need to *turnover* ten times to complete the reaction. The *turnover number* (TON) is important and indicates how robust the catalyst is in the reaction. Higher TONs (low loading values) are preferable to lower TONs (high loading). The benchmark for loading has steadily dropped over the years with 1-2 mol% (TON 50-100) being common in academic research. The catalyst in our reaction will be at approximately 1 mol%. In industrial processes, systems can be optimized to give TONs of 10,000 and higher.

**Experiment** (modified from Fairlamb *Org. Lett.* **2004**, *6*, 4435-4438)

Monday/Tuesday: Heat a sand bath to approximately 125°. In a 100 mL round-bottom flask, fully dissolve 4'-bromoacetophenone (5.0 mmol) and phenylboronic acid (5.5 mmol) in propanol (10 mL) with stirring. Once both reagents are in solution, add 2M aqueous Na<sub>2</sub>CO<sub>3</sub> (3.5 mL), water (2 mL), and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.05 mmol). [Be careful to keep the neck of the flask dry when adding the water so that catalyst will not stick to the ground glass surface.] Place the flask in the sand bath, add a condenser to the top of the flask, and allow the reaction to heat under reflux. After 30 min, check the reaction by TLC. If it is not complete, allow the reaction to heat for another 30 min. Remove the reaction from the sand bath but continue the stirring. [Keep the sand bath hot because it will be needed for the recrystallization.] Once the reaction has cooled to near room temperature, pour in water (50 mL). Filter the reaction in a Buchner funnel (5.5 cm paper) and use water to fully rinse the contents of the reaction flask into the funnel. Transfer the solid to a 125 mL flask and dissolve the solid into EtOAc (50 mL). Filter this solution through a plug of Celite in a sintered glass funnel (15 mL) into a 125 mL side-arm flask. Use a small amount of EtOAc to rinse the Celite plug. Transfer the filtrate to a 250 mL round-bottom flask

and concentrate. Scrape the solid out onto a piece of weighing paper, and place the solid into a 25 mL flask. Recrystallize the product from hot EtOH. Once the product has been cooled on ice for at least 5 min, filter the product with a Hirsch funnel. Wash the collected product with a minimal amount of ice-cold EtOH. Allow the solid to air dry.

Thursday: Determine the mass of the purified product. Obtain a satisfactory  $^1\text{H}$  NMR, GC-MS, and mp. (When including a mp in an experimental section, if the compound is known, you must cite the literature melting point for comparison.)