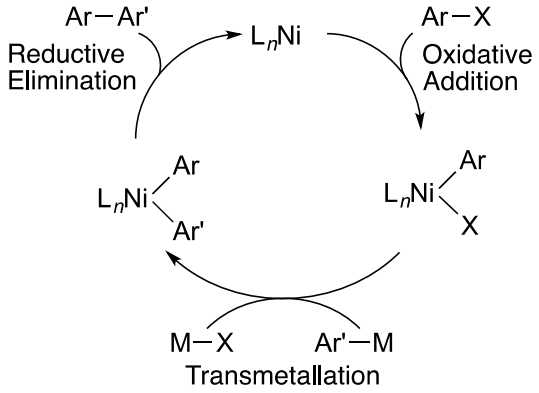
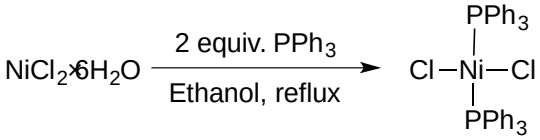
Nickel Catalyzed Suzuki-Miyaura Cross Coupling

Metal-catalyzed cross-coupling is a crucial method to construct carbon-carbon and carbon heteroatom bonds. It is a common organic transformation to connect molecules with sp^2 hybridized carbons. These reactions have been used heavily in the preparation of commodity chemicals, polymer synthesis, and drug discovery.

In this laboratory, you will prepare a bi-aryl compound using an arylbromide of your choice and phenylboronic acid. This reaction is known as a Suzuki-Miyaura coupling and the metal activates the two molecules to form the desired final compound with a new carbon-carbon bond. A simple scheme of the reaction mechanism is shown below where the metal catalysis pathway follows oxidative addition, transmetallation and reductive elimination. In this type of cycle the nickel catalyst reforms after formation of the biaryl compound which allows the cycle to repeat so only a small amount of the nickel catalyst is needed.



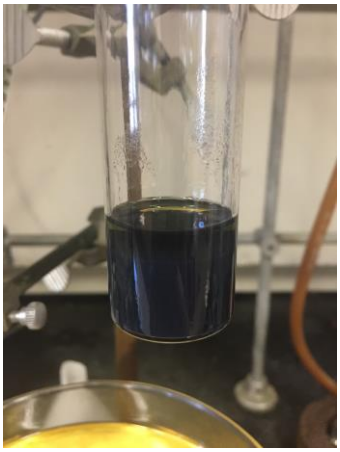
To begin, we need to synthesize the metal catalyst, which will be used in the cross-coupling. The desired metal precursor is $NiCl_{2(}PPh_3$) which can be prepared in a one step process from $NiCl_2 \cdot 6H_2O$.



Synthesis of $NiCl_2(PPh_3)_2$

Place 0.5 g of $NiCl_2 \cdot 6H_2O$ and 7 mL of ethanol into a 20 mL glass vial. Seal the vial and degas the solution with nitrogen for 15 minutes. Add 1.2 g of PPh_3 to the vial quickly and seal again. Stir the reaction mixture in an 80 °C hot water bath for an hour. Let the mixture cool to room temperature and then place in an ice-water bath for ten minutes.

Before

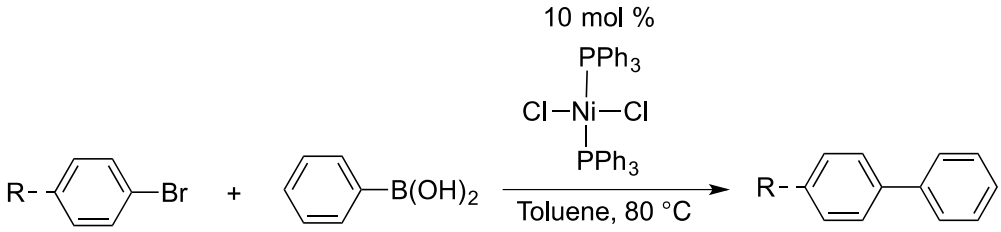


After

Collect the solids by vacuum filtration. Wash the solids on the filter with small portions of ethanol and ether. Dry the solids under vacuum for several minutes. Weigh the dried product and record your yield.

Dried product

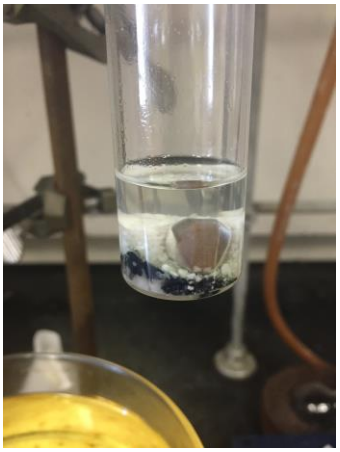
Use UV-Vis spectroscopy to characterize the catalyst. Add about 4 mg of catalyst to a 20 mL vial and fill with dichloromethane. Determine the λ_{max}. With the catalyst in hand, the Suzuki coupling reaction can be completed.



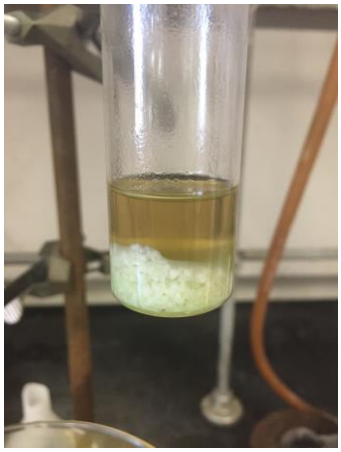
R = OCH_3, CO_2CH_3, CN,

Suzuki coupling reaction

Place 4 mmol of your chosen aryl halide, 0.5 g of phenylboronic acid, 0.13 g of $NiCl_2(PPh_3)_2$, and 1.7 g of crushed potassium phosphate into a 40 mL vial. Seal the vial and add 10 mL of degassed toluene with a syringe and a long needle. Degas the mixture for 15 minutes. Place the flask in an 80 °C hot water bath and let stir for an hour. Let mixture cool.



Before



After

Transfer reaction mixture to separatory funnel. Wash with 10 mL of water twice, removing the aqueous layer. Wash the organic layer with 5 mL of brine.

Purify the crude product by column chromatography as follows using silica gel and hexanes.

1. Plug the column with a small piece of cotton and add about ½ cm of sand over the cotton.
2. Weigh out 4.8 g of silica gel into an Erlenmeyer flask. Add about 15 mL of hexanes to the silica gel and mix to create slurry. Pour the slurry into the column with a funnel. Rinse the flask a few times with hexanes and add to the column.
3. If any silica gel is stuck to the sides of the column, drip hexanes down the sides with a pipet.
4. Drain the hexanes to the top of the silica gel (reserve the hexanes to use to elute the column).
5. Transfer crude product to the column using a pipet. Drain hexanes to the top of the silica gel. Rinse flask with couple mL of hexanes and add rinse to the column. Again drain to the top of the silica gel.
6. Add hexanes to the column and start collecting the eluent. Collect six 8 mL fractions. Add additional hexanes to the column as needed to maintain a few cm above the silica gel.

Check each fraction with TLC using a silica gel plate and hexanes. If product is still eluting in sixth fraction, collect additional fractions.

Combine fractions that show clean product into a pre-weighed round-bottom flask and remove hexanes by simple distillation. Weigh the product.

Analyze product by GC-MS, IR and ^{1}H NMR. To make the GC-MS sample, take about 1 mg of product and dissolve in 20 mL of ether. Transfer to a small GC-MS vial from stockroom and submit sample for analysis.