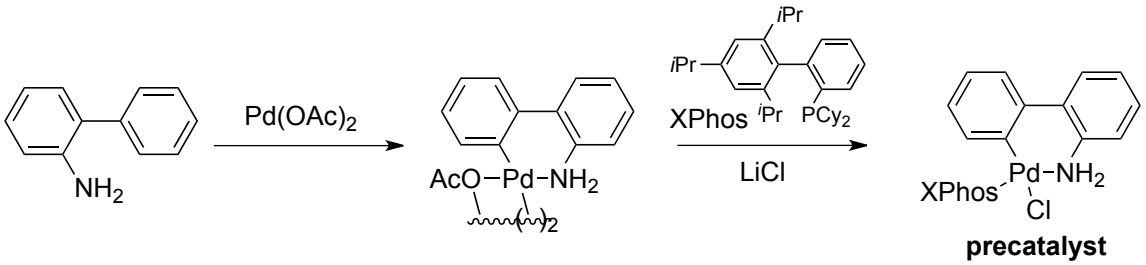
CHEM 135: EXPERIMENTAL SYNTHETIC CHEMISTRY
SPRING 2015

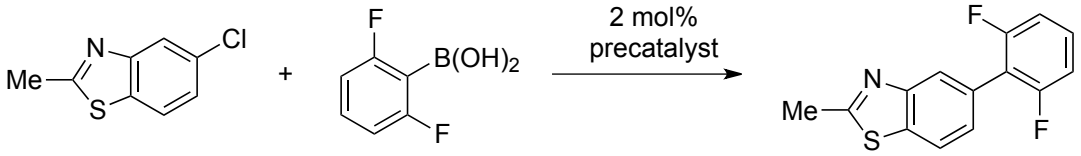
EXPERIMENT 2:
WEEKS 6 – 8
(3/3/2015 – 3/22/2015)

(1) SYNTHESIS OF A PALLADIUM PRECATALYST



J. Am. Chem. Soc. **2010**, *132*, 14073.

(2) PALLADIUM CATALYZED CROSS-COUPLING OF AN ARYL CHLORIDE WITH A BORONIC ACID



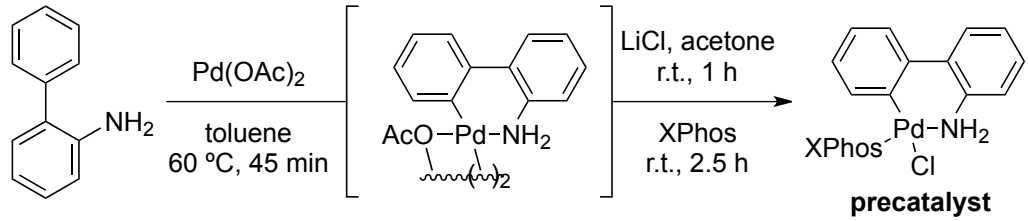
J. Am. Chem. Soc. **2010**, *132*, 14073.

NOTE: While working in the lab you are required to wear lab coats and safety glasses at all times! Furthermore, you will have to complete a short online safety quiz before starting lab work. The teaching staff will evaluate your answers and based on your result you will either receive permission to start your experiment or you will have to go back and consult the instructions again.

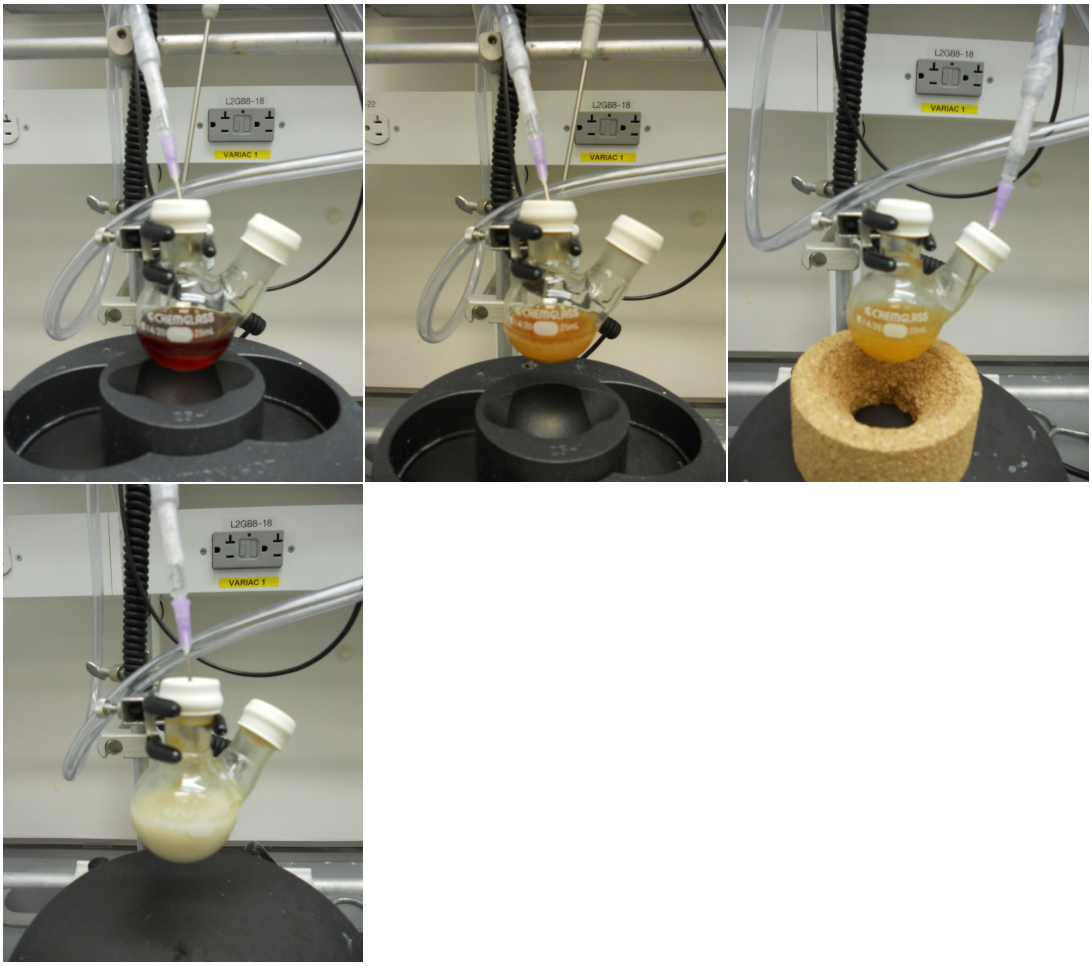
developed by Eugene E. Kwan and Andreas Roetheli

SYNTHESIS OF THE PALLADIUM PRECATALYST

Reaction Scheme



Possible Experimental Setup



Reaction mixture before heating. Reaction mixture after heating. After stirring with LiCl for 1 h. After stirring with XPhos for 2.5 h.

Procedure

Reaction: ca. 6 h

See a TF for instructions on making a cannula filter. It's OK if the solution isn't completely *homogeneous.*

A mixture of $Pd(OAc)_2$ (0.337 g, 1.50 mmol) and 2-amino-biphenyl (0.264 g, 1.56 mmol) in toluene (anhydrous, 9 mL) in a 25-mL, oven-dried, 2-necked round bottom flask was heated at 60 °C under nitrogen for 45 min, at which point the initial red color of the solution faded and a grey precipitate had formed. After the reaction cooled to room

temperature, the toluene was removed via a cannula filter. The remaining solid was washed with toluene (anhydrous 2 × 2 mL) and then suspended in acetone (reagent-grade, 9 mL); use the acetone to forcibly rinse any remaining solid off the cannula filter. After addition of anhydrous lithium chloride (0.191 g, 4.5 mmol), the resulting slurry was stirred at room temperature under nitrogen for 1 h to give a homogenous yellow solution. XPhos (0.677 g, 1.42 mmol) was then added. The mixture was stirred at room temperature for 2.5 h, at which point a significant amount of precipitate had formed.

Work-up:
ca. 45 min

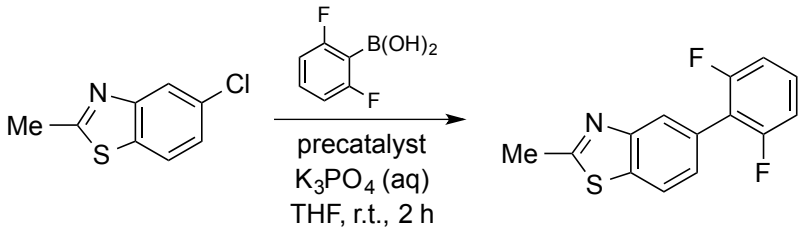
Removal of about 90% of the solvent under vacuum afforded an off-white to yellow slurry, to which was added methyl *tert*-butyl ether ("MTBE," 2 mL) and pentane (5 mL). The mixture was then placed in a -30 °C refrigerator for 1 h (can be left in the fridge overnight and isolated during a subsequent lab period). After that time, the product was collected by suction filtration, washed with water (3 × 5 mL), and dried under vacuum overnight. This procedure afforded the XPhos aminobiphenyl palladium chloride precatalyst as a beige or yellow solid (lit. mp. 202-210 °C).

Safety Remarks & Tips

- More toluene can be used in the initial wash if necessary.
- After the addition of LiCl, the solution may turn either green or yellow.
- Lithium chloride is a hygroscopic solid and should be weighed immediately prior to use.
- XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (MW = 476.72).
- Filtration step: try to shake well and pour the mixture into the funnel quickly; patience and a good spatula will be required to get all the solid out.
- NMR should be performed in $CDCl_3$.

PALLADIUM CATALYZED CROSS-COUPLING OF AN ARYL HALIDE AND A BORONIC ACID

Reaction Scheme



Procedure

Reaction:
ca. 3 h

Make 10 mL of 0.5 M aqueous K_3PO_4 solution before beginning

A 25 mL round bottom flask was equipped with a magnetic stir bar and charged with 5-chloro-2-methylbenzothiazole (184 mg, 1.0 mmol), boronic acid (237 mg, 1.5 mmol), and precatalyst (15.7 mg, 2 mol %). The flask was sealed with a rubber septum and evacuated and backfilled with nitrogen three times. THF (2 mL) was then added via syringe followed by 4 mL of 0.5 *M* aqueous K_3PO_4 solution. The reaction was stirred at room temperature for 2 h.

Work-up:
ca. 1 h

The reaction mixture was transferred into a 60 mL separatory funnel and diethyl ether (10 mL) and water (10 mL) were added. The layers were separated and the aqueous phase was extracted with diethyl ether (3 x 10 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*.

Purification:
ca. 4 h

The crude product was purified by flash chromatography (gradient elution: 2% to 25% EtOAc/hexanes) to afford 5-(2,6-difluorophenyl)-2-methylbenzothiazole as an off-white

to bright yellow-orange solid (lit. m.p. 122-125 °C).

Safety Remarks and Tips

• The reaction should be monitored by TLC (10% EtOAc/hexanes), but there is little separation between starting material and product, so it is advisable to let the reaction proceed to completion. Heating generally leads to increased proto-deboronation and is not advised

• NMR should be performed in $CDCl_3$.

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What to Hand In

Please hand in a typed report that contains:

(1) A copy of all lab notebook entries relevant to this experiment, including drawings of TLC plates and calculated R_f values.

(2) Experimental procedure for the synthesis of the palladium precatalyst in *JOC* format

(3) For the precatalyst: ^{1}H, ^{31}P NMR, and IR spectra and data in ACS format (no peak assignments necessary).

(4) Experimental procedure for cross-coupling reaction in *JOC* format

(5) For the cross-coupled product: ^{1}H, ^{13}C, ^{19}F NMR, and IR spectra and data in ACS format, with all peak assignments and *J*-values (including heteronuclear coupling) for all first-order multiplets; an ESI mass spectrum and data in ACS format; and a melting point.

(6) Answers to the following questions:

a. Based on a preliminary glance at the precatalyst structure, one may expect a single peak in the ^{31}P NMR spectrum. Suggest a reason why multiple peaks are actually observed. For full credit, you should illustrate the structures that give rise to these multiple peaks. (There are *at least* two reasonable answers here; any reasonable answer is acceptable.)

b. During pre-lab talks, you have seen a possible catalytic cycle for this Suzuki reaction. Based on this information, suggest a reason why the particular precatalyst we use is especially good for this reaction.

Grading Scheme

total: 18% of course grade

Laboratory component	*Written component*

- complete first attempt (+3)
- complete second attempt (+1)
- obtain >400 mg pre-catalyst (+2)
- obtain >700 mg pre-catalyst (+1)
- obtain >150 mg pure product (+1)
- obtain >200 mg pure product (+1)

- lab notebook entries (+2)
- experimental procedures (+2)
- characterization data (+3)
- responses to questions (+1)
- lab stewardship (+1)