

Cross Couplings with Emphasis on the Suzuki-Miyaura Coupling

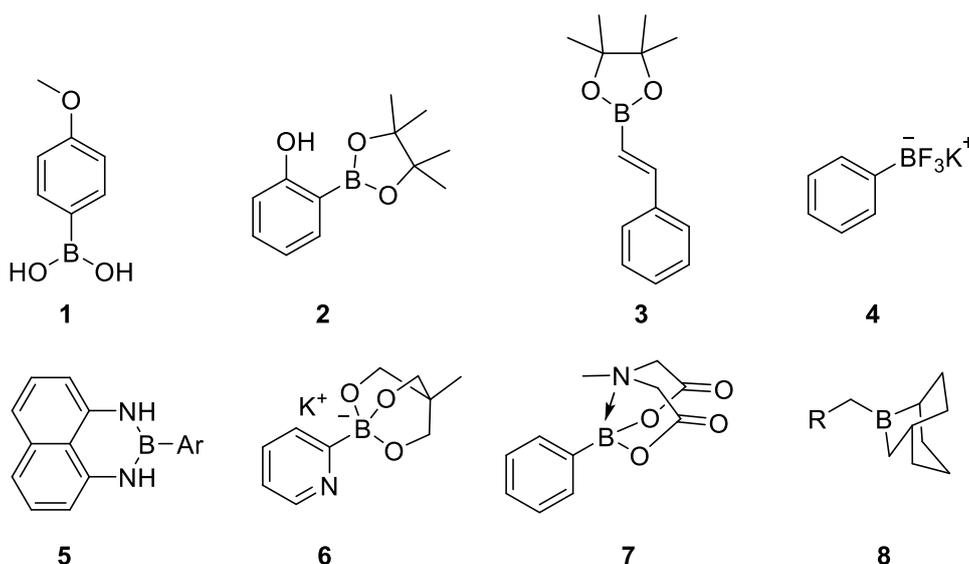
- 1) Provide general reaction equations for the following named reactions (i.e. $\text{Ar-X} + \text{Ar-B(OR)}_2$ or $\text{Ar-BR}_2 \rightarrow \text{Ar-Ar}$). Provide limitations of each reactant used in the coupling (i.e. if $\text{X} = \text{Cl, Br, I, OTf...etc.}$) as well as general reagents required to perform the cross coupling.

Provide catalytic cycles for the first 4 couplings.

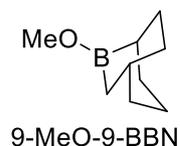
- 1) Suzuki-Miyaura Coupling
- 2) Sonogashira Coupling
- 3) Buchwald-Hartwig Coupling
- 4) Stille Coupling
- 5) Kumada Coupling
- 6) Negishi Coupling
- 7) Hiyama Coupling
- 8) Ullmann Coupling
- 9) Zirconium Coupling

This problem session will focus primarily on the Suzuki-Miyaura cross coupling reaction, looking at the phosphine ligands, palladium species, boron coupling partners and the role of base.

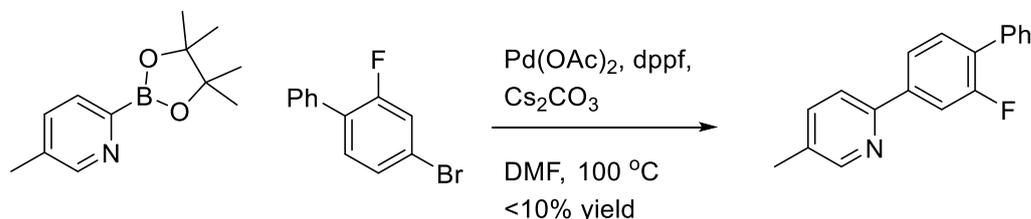
- 2) In the Suzuki-Miyaura cross coupling, the transmetalation pathway has received significant interest in elucidating the role of the base; what is the *boronate* pathway? what is the *oxo-palladium* pathway? What evidence has been provided for each pathway, focusing primarily on boronic acids? (See Denmark and Thomas, *Science*, **352**, 329-332 (2016)).
- 3) Give the general boron class names and provide possible preparations for the following boronic coupling partners. Also comment on their Lewis acidity and how prone they might be to protodeboronation. What is special about the stability of **5**.



- 4) Why is 9-BBN a boron of choice over disiamylborane, dicyclohexylborane, and diisopinocampheylborane?
 5) What are the advantages to using the reagent 9-MeO-9-BBN?
 6) Can the coupling become catalytic in 9-MeO-9-BBN? Explain.



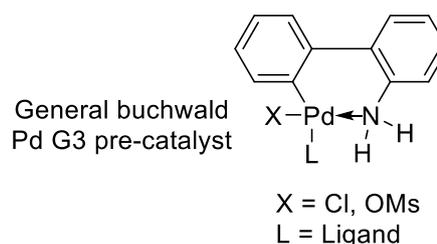
7)



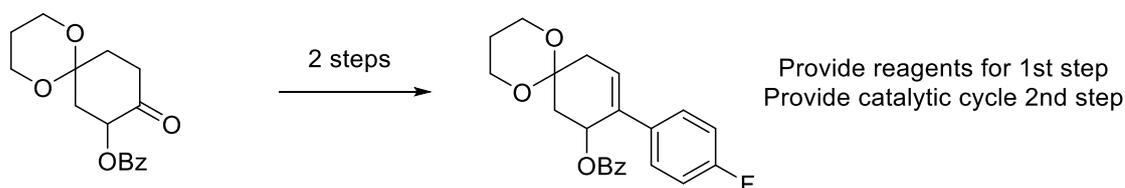
Why is the yield so low?
 What additive can be added to increase the yield?
 How does the additive work?

- 8) If adventitious oxygen enters a system where degassing of the solvent was not performed, homocoupling can occur. Provide a catalytic cycle for this process.
- 9) With reference to the ligand, what can you do to the ligand to increase the rate of oxidative addition to a palladium complex, allowing unactivated aryl chlorides to undergo Suzuki-Miyaura couplings under mild reaction conditions? (Phosphine ligands and NHC's) (See Carrow and Chen., Synlett, **28**, 280-288 (2017))
- 10) Tri(1-adamantyl)phosphine is said to not undergo C(sp³)-P bond scission or partake in cyclometallation when coordinated to a metal centre. With reference to a phosphine ligand on a metal centre; what is C(sp³)-P bond scission? Provide an example. What is cyclometallation and what can happen to the catalyst if it is irreversible? Provide an example. Why is an adamantyl group more stable to C(sp³)-P bond scission than a cyclohexyl group?

- 11) What is the general mode of activation of the Buchwald pre-catalysts? Provide a mechanism of its activation. Why is the formed palladium species considered more active than other palladium catalysts? The Pd G4 Buchwald palladium pre-catalysts consist of a methyl group in place of one hydrogen attached to the aniline, why was this modification made?



- 12) Give reason for your choice of cross coupling method in the 2nd step.



Extra question: Synthesize the SM