

Summer 2011 Research Proposal

Joseph Ramirez

Mentor: Professor Kenneth Brown, Department of Chemistry

A Comparison of Cross-Coupling Reactions Involving an Aryl Group and an R Group

The focus of this research project is to attach an R group (in this case, a long hydrocarbon chain) to an aryl group through cross-coupling reactions¹. In collaboration with Dr. Kenneth Brown of the Department of Chemistry and his previous and continuing research on hydride transfer in organic synthesis, I plan to find a procedure to synthesize and isolate these target compounds (Figure 1). In addition, Dr. Steve Bachofer's research on surfactant chemistry ties in closely with my research proposal because it focuses on the synthesis of surfactants. When the target compound is synthesized in good yield, this synthesized surfactant will be introduced into cells and analyzed. In order to proceed to this area of study, the surfactant has to be synthesized first.

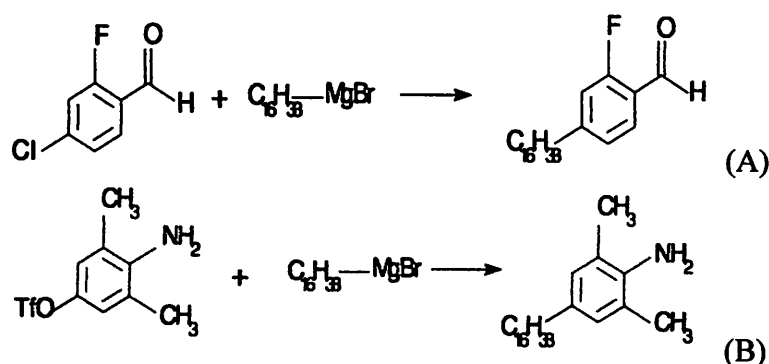
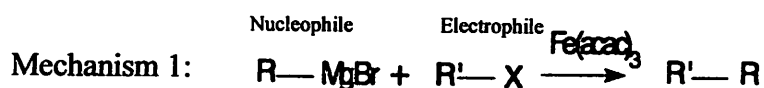


Figure 1. General synthesis of target compounds 2-fluoro, 4-hexadecane benzaldehyde (A) for Dr. Brown's research and 4-hexadecane-2,6-dimethylaniline (B) for Dr. Bachofer's research.

With the collaboration of Dr. Brown, my proposal suggests a way to synthesize these two compounds through the use of coupling reactions. Generally, coupling reactions involve a reaction between one molecule containing a halide and another molecule with an organometallic (in this case, the Grignard reagent MgBr). The goal is to combine these molecules to form a new carbon-carbon bond thus joining them together. The Grignard reagent acts as a nucleophile (an electron rich molecule) and attacks the electron deficient electrophile, displacing the halide, which serves as an excellent leaving group. This results in both compounds connecting together (Mechanism 1).



Simple reactions can be made to form the Grignard reagents in both the long alkyl chain and the aryl group.

The first reaction is adapted from Fürstner^{1,2}, involving the attachment of a Grignard reagent to an alkyl group and cross coupling this compound with the prepared aryl chloride. (Figure 3).

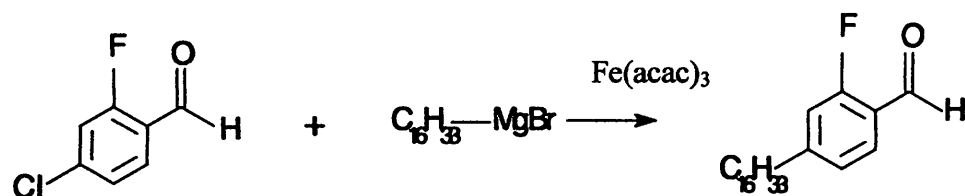


Figure 3. Iron-catalyzed cross coupling reaction involving an alkyl Grignard reagent with an aryl triflate (Füstner method).

A second type of coupling reaction, the Cahiez Method², is implemented in case the Füstner method does not work. It is very similar to the first reaction because it involves a cross-coupling reaction, but the location of the halide and Grignard reagent are switched. In this reaction, the Grignard reagent is formed on the aryl group and a bromide group is attached to the alkyl group (Figure 4).

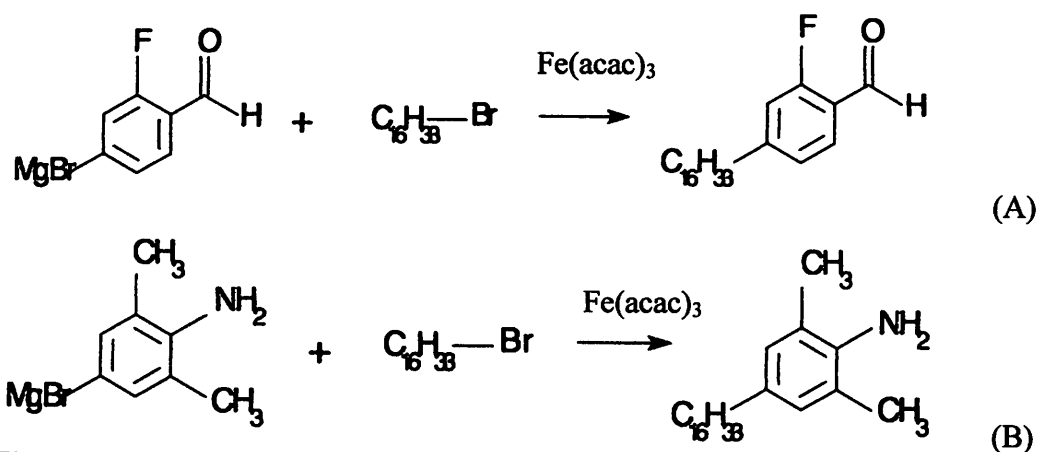


Figure 4. Iron-catalyzed cross coupling reaction involving an aryl Grignard reagent with an alkyl triflate (Cahiez Method) for Dr. Brown's research (A) and Dr. Bachofer's research (B).

Both of these reactions are iron-catalyzed cross-coupling reactions. The iron catalyst that is used for this project is $[\text{Fe}(\text{acac})_3]$ (acac: acetylacetonate) for a few reasons. First, an iron catalyst is relatively cheap in comparison to other metal catalysts, such as palladium and nickel. Furthermore, a high percent yield is obtained³. Lastly, using iron catalysts allow the use of easily observed and/or prepared reactants; these starting materials are readily available or easily purchased.

My first plan is to try and successfully complete the Füstner Method (Figure 3) and see if this reaction can undergo a cross-coupling reaction and if the target compound results in good yield. My second plan is to do the Cahiez Method (Figure 4) and to compare the reaction and the results to the Füstner Method to see if the percent recovery is better in one reaction or the other. It is not yet clear if both reactions will succeed or not due to the presence of different functional groups on the aryl ring. If these plans don't work out as expected, then a Palladium catalyst will be used as a back-up plan. After the reactions take place, the target compounds are purified and then isolated and ready to be analyzed through various sorts of instruments to positively identify the target compounds.

Overall, the goal of this research project is a cross-coupling reaction between a long hydrocarbon chain to an aryl group that already contains functional groups attached to it. Certain starting materials are needed in order to construct both the desired reactants in order for the coupling reaction to occur. Once the desired compounds are synthesized, isolated, and identified, further research is possible with Dr. Brown on hydride transfer and Dr. Bachofer on surfactant chemistry with these isolated compounds.

This research project will be conducted in chemistry research labs located in the third floor of Brousseau Hall. A majority of the lab equipment and instruments that will be needed in this project are already available at the research labs. In addition, some chemicals and reagents that are needed for the reaction are also available; however, some of the starting materials will have to be ordered through chemical manufacturers, such as Sigma-Aldrich and Matrix Scientific. Important lab techniques that I learned in taking two semesters of Organic Chemistry and one semester of Instrumental Analysis are also implemented in my research. Such methods include, but are not limited to, the following: reaction of Grignard reagents, purification of the target compound, and spectroscopic analysis via IR, ^1H NMR, GC-MS, and HPLC for the identification of the target compound. If the isolated compound is in good yield and purified, Dr. Brown's colleagues at California State University East Bay will run the compound through a high-field NMR for further analysis. I learned a myriad of techniques while taking organic chemistry and I want to further my education of organic chemistry by undertaking this wonderful research project.

References:

1. Fürstner, A., Leitner, A., Méndez, M., Krause, H. Iron Catalyzed Cross-Coupling Reactions. *J. Am. Chem. Soc.* **2002**, *124* (46), pp. 13856-13863.
2. Cahiez, G., Habiak, V., Duplais, C., Moyeux, A. Iron Catalyzed Alkylations of Aromatic Grignard Reagents. *Angew. Chem. Int. Ed.* **2007**, *46*, pp. 4364-4366.
3. Fürstner, A., Lietner, A., Seidel, G. 4-Nonylbenzoic Acid. *Organic Syntheses.* **2005** *81*, pp. 33-41.