Methodology of Copper-Catalyzed Decarboxylative Cross-Coupling Reactions

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Introduction

Transition metal catalyzed processes have been utilized in the pharmaceutical industry for over 30 years. They have been employed for discovery syntheses, and large-scale preparation of active pharmaceutical ingredients.[1]

Figure 1: Framework of Basic Transition Metal Catalyzed Coupling Reaction

Previous Work

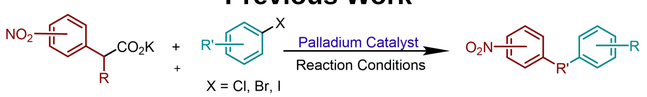

Figure 2: Palladium Catalyzed Reaction

Disadvantages:

- High Temperatures (≥ 100ºC)
- Palladium is an expensive metal
- X = Cl, Br, I – reactive

Our Work

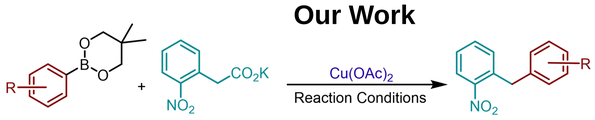

Figure 3: Copper Catalyzed Reaction

Advantages:

- Low Temperature (Room Temperature)
- Copper is an inexpensive metal
- Ar-X = Cl, Br, I – not reactive

Synthesis of Starting Material

Before the actual cross-coupling reaction can begin, the appropriate starting material needs to be made. This starting material is the substrate we are interested in modifying during the cross-coupling reaction.

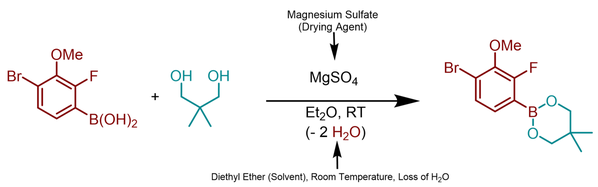

Figure 4: Example of a Starting Material Reaction

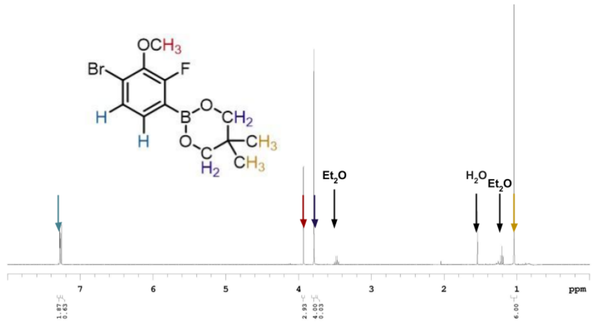

Figure 5: NMR Data of Starting Material

Cross-Coupling Reaction

Once the appropriate starting material is made, the substrate can be modified in a cross-coupling reaction, that is catalyzed by copper acetate.

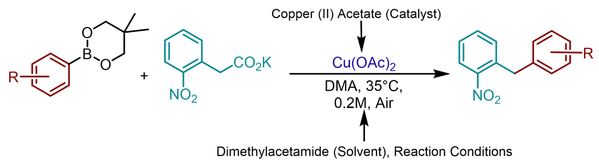

Figure 6: Framework of a Cross-Coupling Reaction

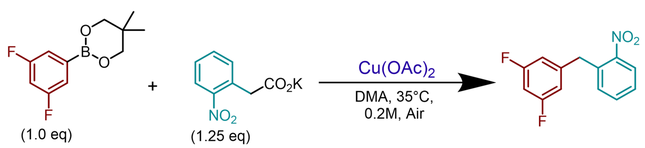

Figure 7: Cross-Coupling Reaction Completed in the Lab

Observations of Cross-Coupling Reaction

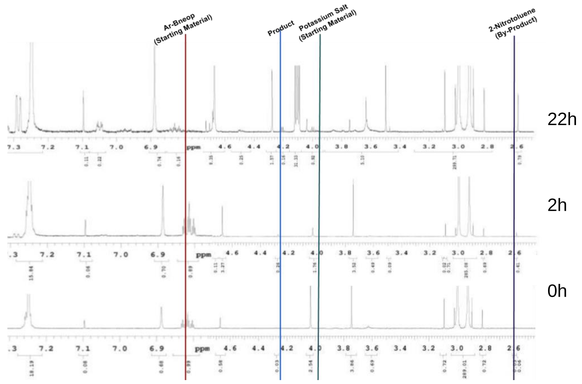

Figure 8: NMR Data for the Cross-Coupling Reaction in Figure 7

NMR Intergration Data for Cross-Coupling Reaction				
Time	Product	Ar-Bneop	Potassium Salt	2-Nitrotoluene
0h	0%	101%	130%	2%
2h	13%	89%	88%	14%
22h	79%	11%	0%	26%

Figure 9: NMR Integration Data from Cross-Coupling Reaction in Figure 7

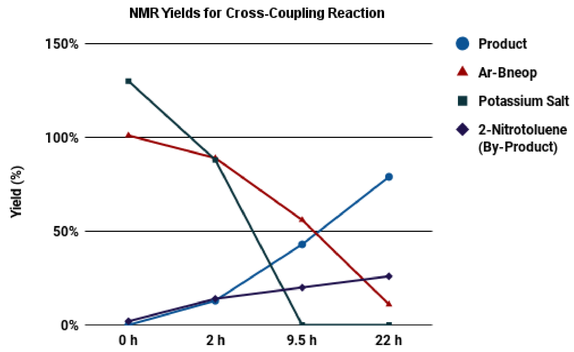

Figure 10: NMR Yields for the Cross-Coupling Reaction in Figure 7

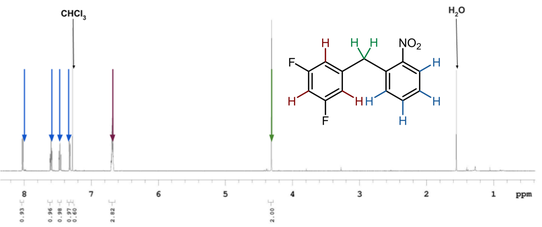

Figure 11: NMR Data of Pure Product

Future Work

There are additional substrates that our lab group is interested in working with, to see how these substrates create new organic molecules catalyzed by copper.

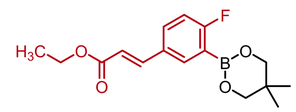

Figure 12: Substrate with Unsaturated Alkene Bond

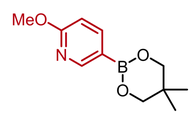

Figure 13: Heterocycle Substrate

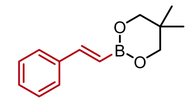

Figure 14: Substrate with Bneop Molecule Attached to an Unsaturated Alkene Bond

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References

1) Crawley, M. L.; Trost, B. M. *Applications of transition metal catalysis in drug discovery and development an industrial perspective*; Wiley: Hoboken (N.J.), 2012. Chapter 1, Page 3