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An Innovative "Green" Suzuki Coupling Reaction for the CRL-232 Lab

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Abstract & Introduction

A major objective of “Green Chemistry” is to provide a more modern chemical experience in the laboratory along with reducing the amount of waste generated and make the lab safer for our students. The latest effort is the continuance to update the chemical reactions in the CRL-232 Organic Chemistry Lab by employing a “water-based” Suzuki Coupling Reaction. The 2010 Nobel prize was awarded to Heck, Negishi, and Suzuki for the palladium-catalyzed cross coupling reaction. This reaction has gained wide acceptance in industry where it is used in large scale reactions to make drugs (naproxen, 5-HT1a Agonist), agricultural chemicals (Boscalid® fungicide, Prosulfuron® herbicide), and chemicals for electronics (Cyclotene® monomer). The reaction chosen is carried out in water in an open flask with the mild base sodium carbonate. Benzeneboronic acid is coupled to bromobenzoic acid isomers to give biphenylcarboxylic acids. The water-soluble palladium chelate catalyst undergoes 10,000 reaction cycles. Aspects of the reaction are used to teach green chemistry principles, catalysis, crystallization, isomer reactivity, and IR and NMR spectroscopic identification, and sustainability. A CRL-232 lab pilot run is planned for 2020 fall semester.

Goals & Objective

Provide the second semester organic chemistry lab with a green, modern carbon-carbon bond forming synthesis.

Background – Suzuki Coupling Reaction

Quite a few published studies describe Suzuki coupling reactions used in undergraduate lab classes. However, these do not meet the requirements of WCU for new experiments; Solid starting material, solid product, odorless compounds, no greater hazard than irritant, teach spectrographic compound identification, Green chemistry, high yield, 1,000 mg product scale. Hamilton describes the aqueous reaction of 4-bromobenzoic acid with benzeneboronic acid which comes close to meeting these requirements (Hamilton, et al., 2013). This reaction gives biphenyl-4-carboxylic acid as shown in Figure 1. The reaction is run in water and uses a water-soluble chelated palladium catalyst that is not air sensitive.

If you wish to discuss this poster, please email me at JW901213@wcupa.edu.

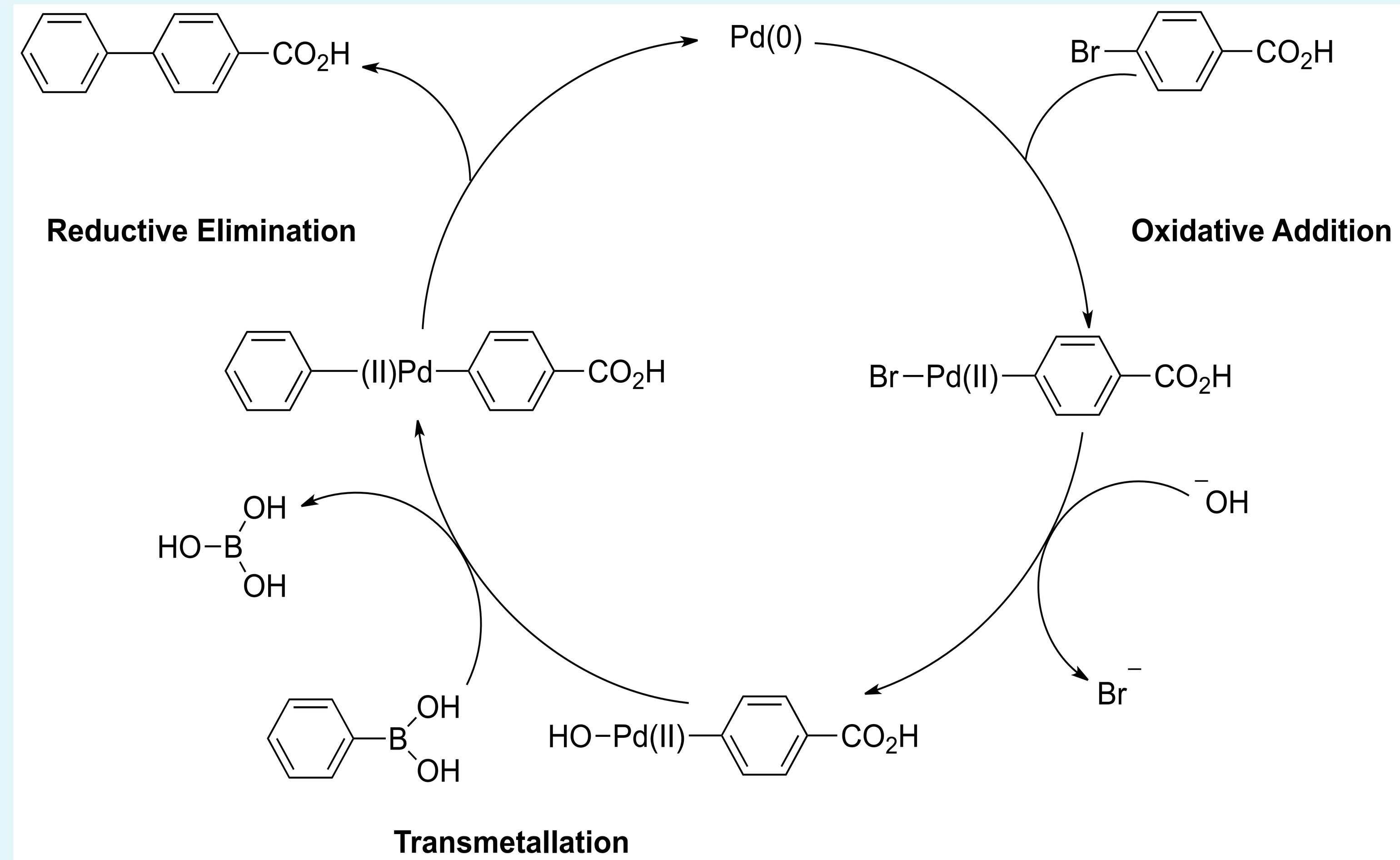

Figure 1. Palladium goes through about 10,000 reaction cycles during the 45-minute reaction time.

Results – Reaction Scope

The literature (Hamilton, et al., 2013) describes the reaction with 4-bromobenzoic acid with benzeneboronic acid. We have found that 3-bromobenzoic acid also reacts under these conditions to give the analogous biphenyl-3-carboxylic acid. The 2-bromobenzoic acid fails to react under these conditions and is recovered in high yield from the reaction mixture.

Methods & Results – Robustness testing

A 14-run Plackett-Burman screening design was executed to check the reaction robustness to student-controlled parameters. Levels tested were evaluated at +/- 5%: boronic acid, alkali, catalysis, solvent, 5 °C, 10 min reaction time, and the 3- and 4-bromobenzoic acid starting material. Yields ranged from 95 to 99 percent. As shown in figure 2, no factor had a significant effect on the yield, ($F<1.45$, $F_{crit}=2.57$).

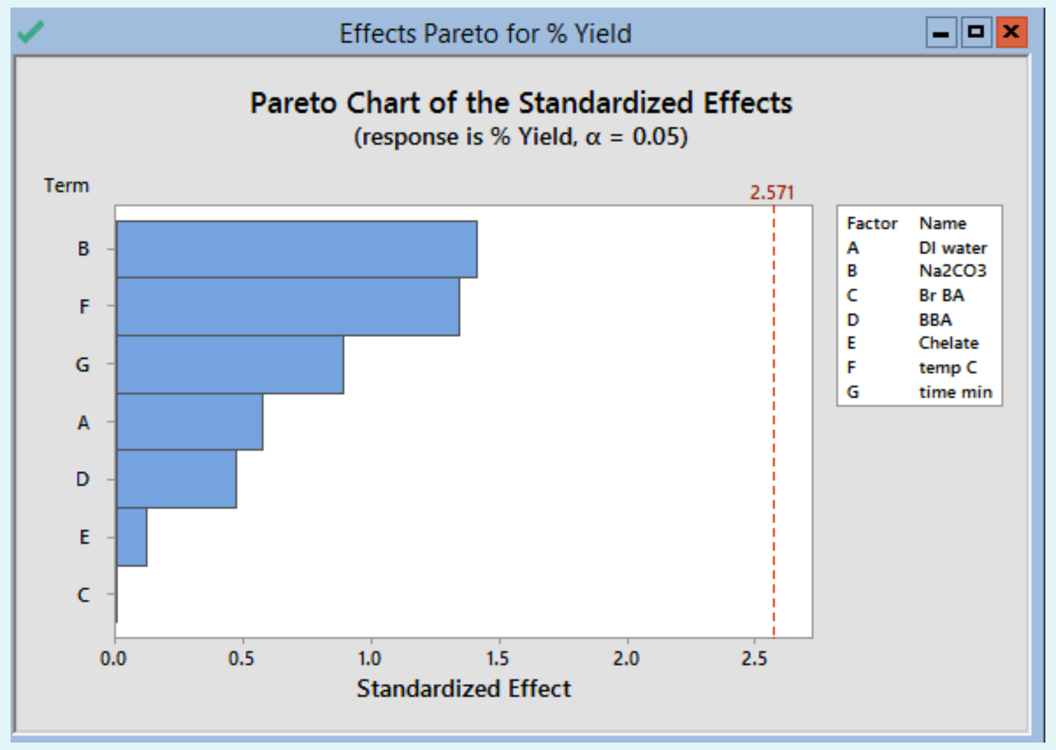

Figure 2. Pareto Chart showing factor effect F values were far short of the F=2.57 significance limit.

Fig 3. Bipheny-4-carboxylic acid, 40X, polarized light, ¼ wavelength filter, birefringent needles

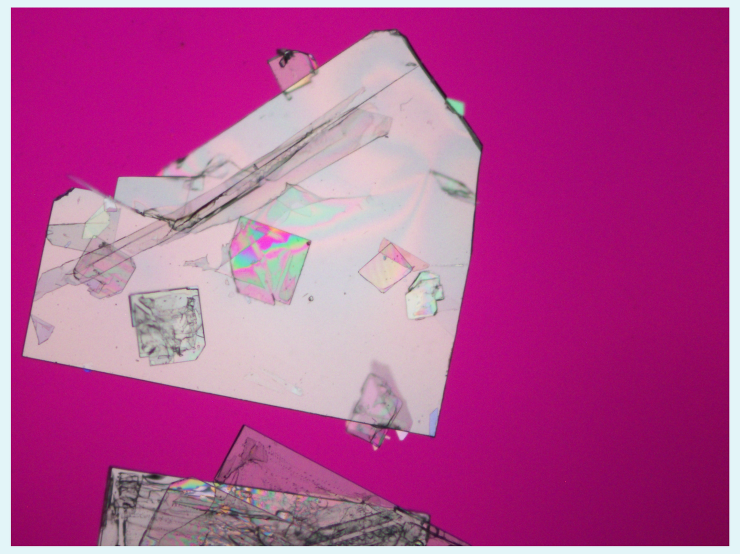

Fig 4. Biphenyl-3-carboxylic acid, 40X, polarized light, ¼ wavelength filter, birefringent platelets

The products can be identified based on crystal shape (figures 3&4), NMR (Figure 5), and melting point (225, 167, and 148 °C for unreacted 2-bromobenzoic acid).

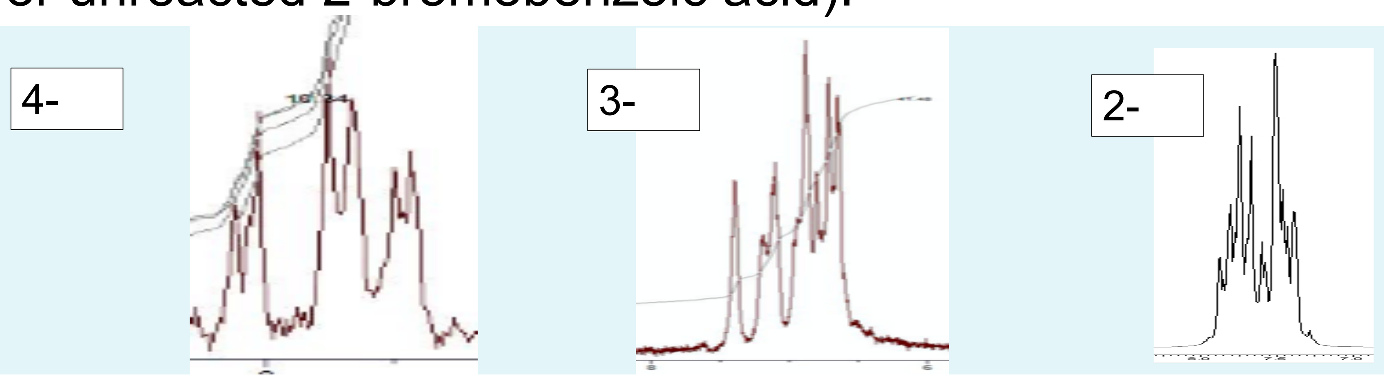

Figure 5. NMR of the aromatic region of 4-, and 3-biphenylcarboxylic acid and unreacted 2-bromobenzoic acid.

Discussion & Conclusions

Unlike what is described in the literature, the palladium acetate does not fully dissolve despite greatly extended reaction time and temperature. Communication with the author Chalker revealed that lot-to-lot differences have been seen. We will use dilution to a set visible absorption for consistent results.

Future Studies

When lab work is again permitted, the melting points for the products in the screen design reactions will be analyzed. A pilot class experiment had been planned for fall of 2020. This may need to be postponed to Spring 2021.

Acknowledgements and References

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Chalker, J. M.; Wood, C. S. C.; Davis, B. G. A Convenient Catalyst for Aqueous and Protein Suzuki-Miyaura Cross-Coupling. 2009, J. Am. Chem. Soc. 131, 16346-16347.
Hamilton AE, Buxton AM, Peeples CJ, and Chalker JM, 2013, J. Chem. Educ., 90, 1509−1513.
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Additional references available on request.