



Synthesis of N-Aryl Substituted Amine using Palladium Catalyzed Cross-Coupling and t-butyl Amine

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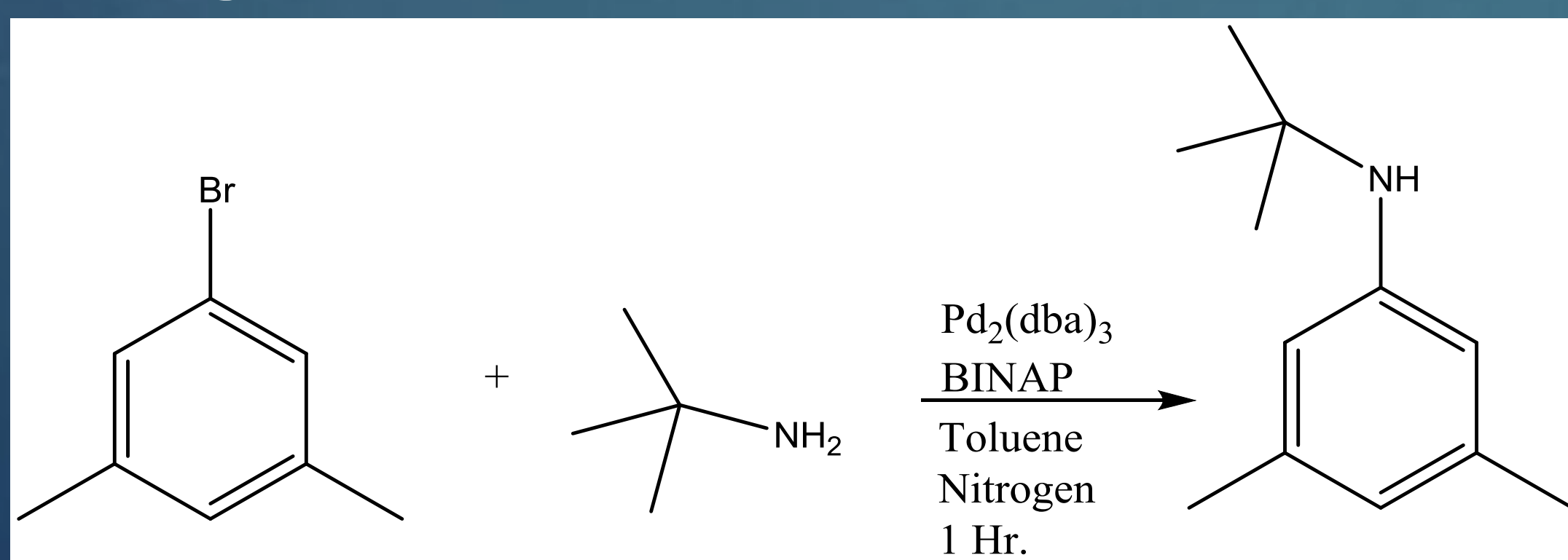
Introduction

Coupling reactions are a widely accepted, powerful, and a go-to strategy to form carbon-carbon and carbon-hetero bonds. They require hydrocarbon fragments to couple using a metal catalyst, one of the most popular being palladium. Historically, multiple palladium-cross-coupling reactions have been discovered and widespread, depending on the desired product or necessary conditions. A few examples of these cross coupling reactions are the Suzuki-Miyaura, Stille, Negishi, and Kumada, to name a few¹.

Palladium-catalyzed reactions were then advanced to the formation of carbon-nitrogen bonds, also known as palladium-catalyzed aminations. The importance of the carbon-nitrogen bond in pharmaceuticals cannot be stressed and the ease of palladium-catalyzed cross-coupling reactions opened a pathway in which these bonds could be easily synthesized. Despite early difficulties in deriving a proper reaction scheme, it was eventually completed when the use of bulky and electron rich phosphine ligands were employed. The electron donation allowed for easy reductive elimination and having such a large size, the palladium only had a single ligand attached, activating the palladium for catalysis. This information lead to one of the most famous palladium-catalyzed cross-coupling reactions, Buchwald-Hartwig reactions².

Experimental

Using a dry, 50mL two necked round bottom flask and stir-bar, a thermocouple controlled oil bath was be set up at 100°C. The glassware was then set up under nitrogen with a water condenser. 3,5-dimethyl-1-bromobenzene (5mmol, 0.9253g), t-butyl amine (5.25mmol, 0.5517mL), sodium t-butoxide (7mmol, 0.6727g), Pd₂(dba)₃ (.1mmol, 0.091572g), BINAP (.3mmol, 0.1868g), and dry toluene (10mL) was added to the flask prior to being heated to 100°C. The flask was then sealed using a glass stopper in the second neck and stirred in the oil bath for 1 hour. It is preferential to keep the reagents as dry as possible and avoid long periods of exposure to oxygen. The only time reagents were exposed to air was during the weighing process; they were immediately added to the nitrogen environment flask.



Scheme 1. Reaction scheme used for the Buchwald-Hartwig Palladium Cross-Coupling reaction

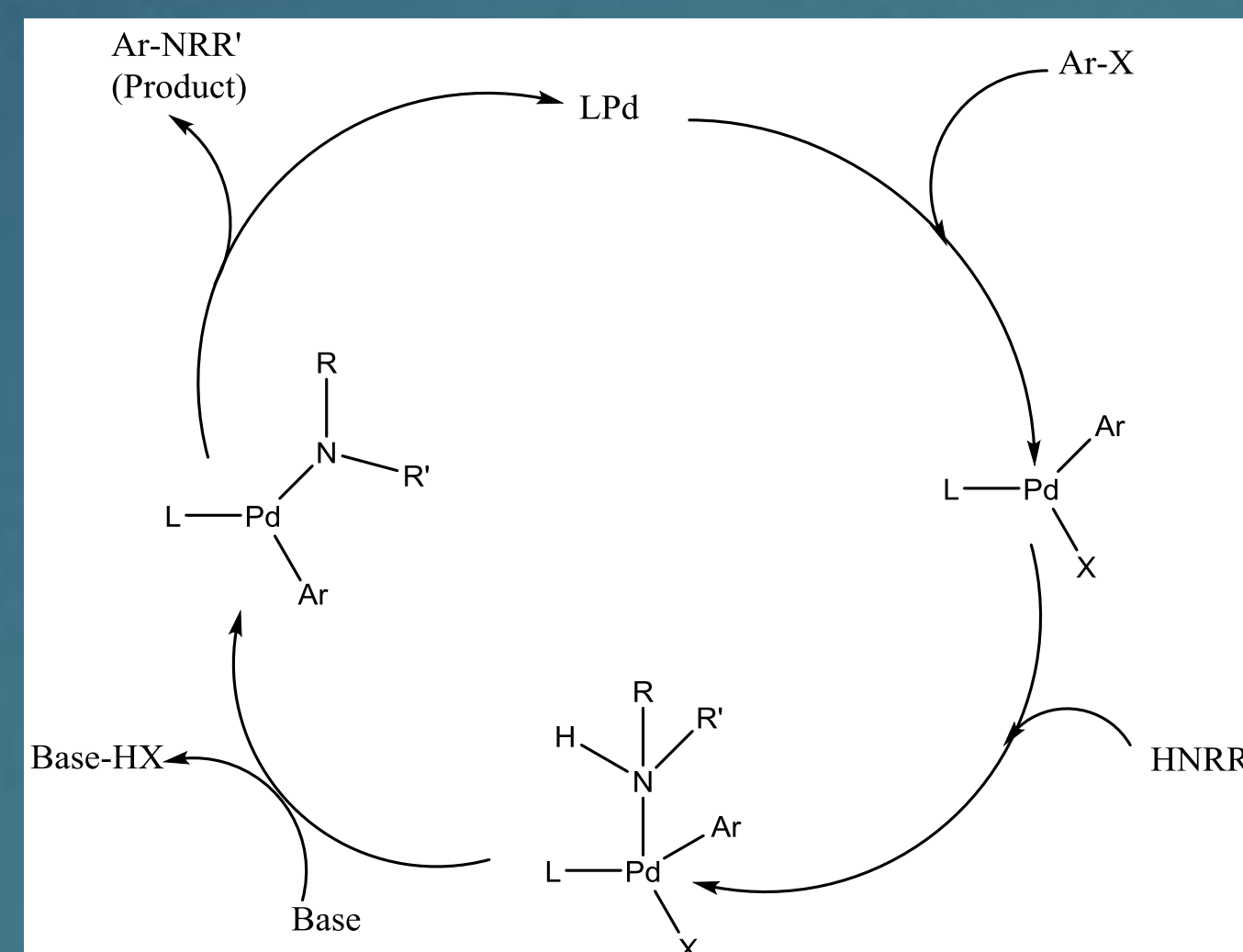


Figure 1. Palladium cross-coupling cycle mechanism with generic terms

Results and Discussion

Product was produced in trace yield, however, this may be due to a number of factors that affected the outcome of the experiment. First, the incorrect product may have been isolated as very little clear liquid was found, which was the projected product. Another alternative problem was that the product may have decomposed after being synthesized. TLC after a column was run and the desired fraction was isolated, however, the following day, running another TLC with the same mobile-phase lead to streaking and multiple fractions yet again on the plate. Many of the peaks at 6-7ppm are also in ranges of peaks of solvent, toluene, as well as starting materials. However, some product does seem present.

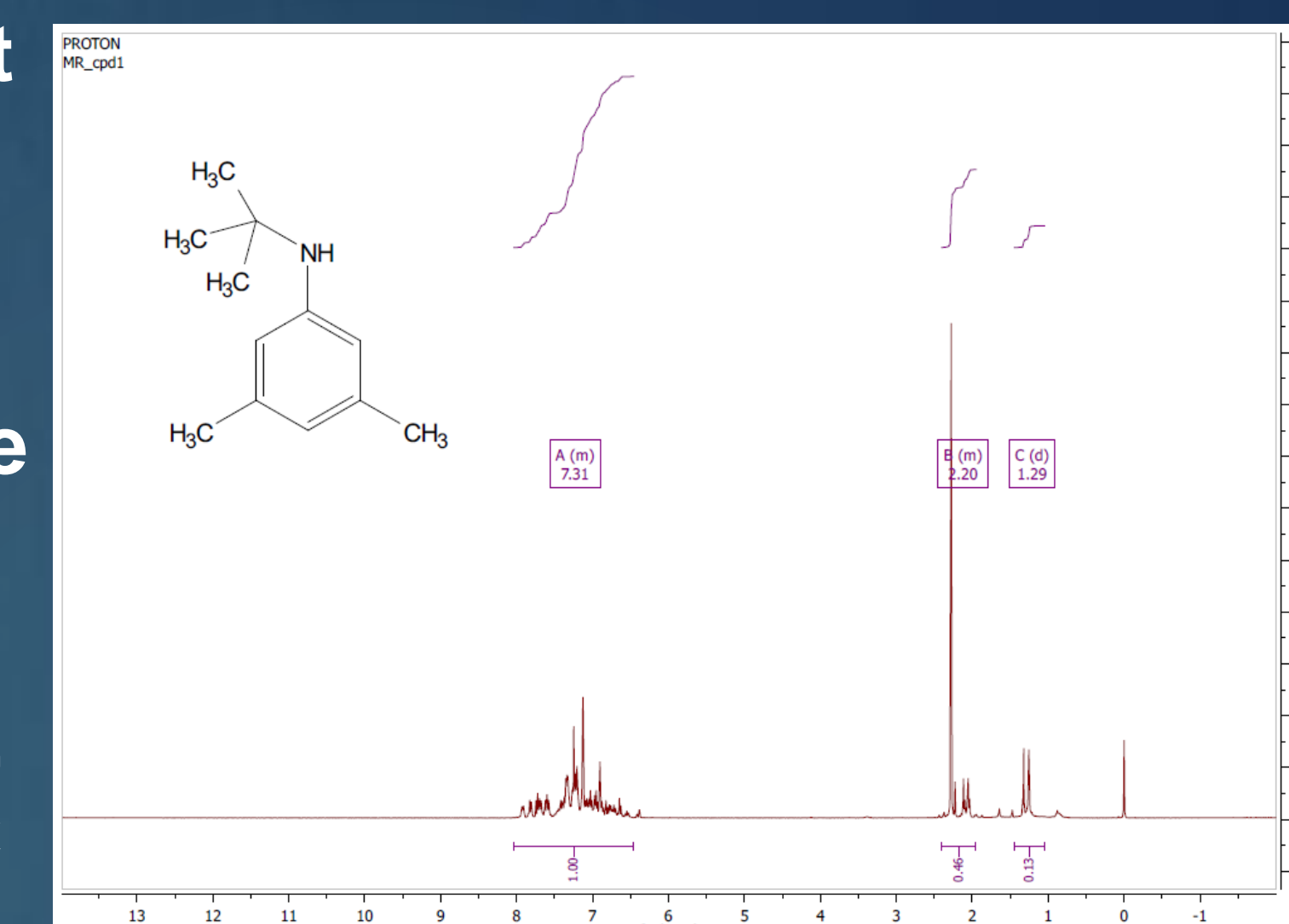


Figure 1. ¹H NMR of purified product. Remnants of starting material is very apparent as well as decomposition of product.

Future Work

Although this marks the end of the inorganic special projects, there could have been much more work done with this experiment. Investigating the reaction further and repeating it to purify the proper product would be beneficial to the outcome. In addition characterizing the product not only by NMR, but other techniques, such as infrared spectroscopy, would allow for a better characterization of the product.

Conclusions

Overall, the execution of the experiment had a few flaws, but there were remnants of desired product in the NMR. The experiment would require future work in order to gain viable results that would completely demonstrate the palladium cross-coupling reaction.

Acknowledgments

I'd like to thank Lea Nyiranshuti, Luke Fulton, and Roy Planalp for overseeing and supervising the reactions as well as offering their well of experience and knowledge.

We thank the Department of Chemistry, UNH, for funding.

References

1. Fischer Scientific. (2010). *Palladium-Catalyzed Coupling Chemistry*. Acros Organics. Houston, TX, US.
2. Buchwald, S. Surry, S. *Dialkylbiaryl phosphines in Pd-catalyzed amination: a user's guide*. Royal Society of Chemistry. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA.