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Development of Cu-Catalyzed Oxidative Alkylboron Homocoupling

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1. Introduction

Carbon-carbon bonding is considered one of the most important chemical reaction classes in organic chemistry. The goal of this project is to perform a new carbon-carbon coupling reaction using copper to catalyze a radical boron reaction to form a sp^3-sp^3 C-C bond. Boron has been used in the past to form C-C bonds. What is novel about this research is the geometry of the two carbon atoms being joined. Two sp^2 carbon coupling from boron reagents has been achieved before² and one group was able to couple an sp^2 carbon and an sp^3 carbon.¹ This experiment seeks to oxidatively couple two sp^3 carbons to generate symmetrical alkyl products.

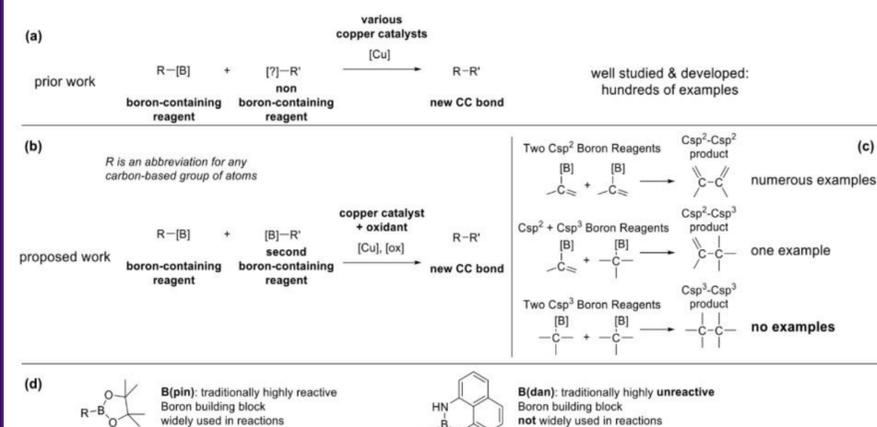


Figure 1. Context of proposed work

1. Ding, S.; et al. ACS Catalysis 2016, 6, 1329-1333

2. Li, J.; et al. Chem Commun 2020, 56, 6388-6391

2. Proposed Partial Mechanism and Rationale

Published research shows the formation of an sp^3-sp^3 C-C bond as a side reaction (below) using a boron-containing reagent and azaborine.³ This method of synthesis, however, is difficult to perform due to the lack of commercially available azaborines. The use of benzyl B(pin) as a substrate for the proposed reaction has previously been explored by this lab. Instead, benzyl B(dan) was used because we hypothesize that the B(dan) will do a better job of stabilizing the radical intermediate proposed in the reaction below than the B(pin). The stability of the radical intermediate is a critical factor in this reaction. Providing evidence for this hypothesis, the B(dan), which is typically much less reactive than B(pin) in cross coupling and many other B-based reactions, performs better for this reaction.⁴

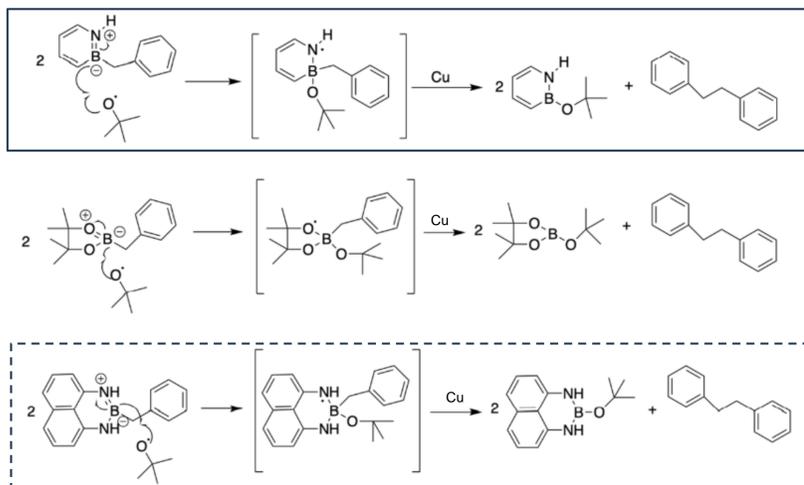


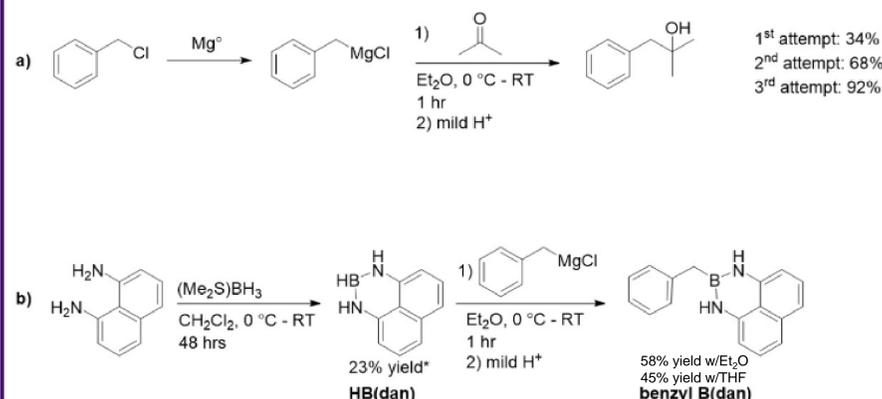
Figure 2. Proposed rationale for use of B(dan) group.

3. Baggett, A. W.; Liu, S. Y. J. Am. Chem. Soc. 2017, 139, 15229-15264

4. Baggett, A. W.; Liu, S. Y.; Baggett, M. J. Am. Chem. Soc. 2007, 129, 756-759

3. Synthesis

First, we purified benzyl chloride and ran test Grignard reactions since we planned to use a Grignard reaction to synthesize benzyl-B(dan).⁶ Next, we synthesized HB(dan). Boron is oxygen sensitive, so the reaction was conducted in an air-free environment under nitrogen. The oxygen stability of the reagent is greatly increased once the diamionaphthalene (dan) is attached. The synthesized HB(dan) was then purified by sublimation, which was used to synthesize benzyl-B(dan) via a Grignard reaction. The benzyl-B(dan) was purified by column chromatography



5. Inada, N.; Sugimoto, M. J. Organomet. Chem. 2009, 684, 1713-1717

6. Li, J.; Sakai, M.; Yamano, S.; Yashida, H. Chem. Commun. 2020, 56, 6388-6391

4. Condition Screening

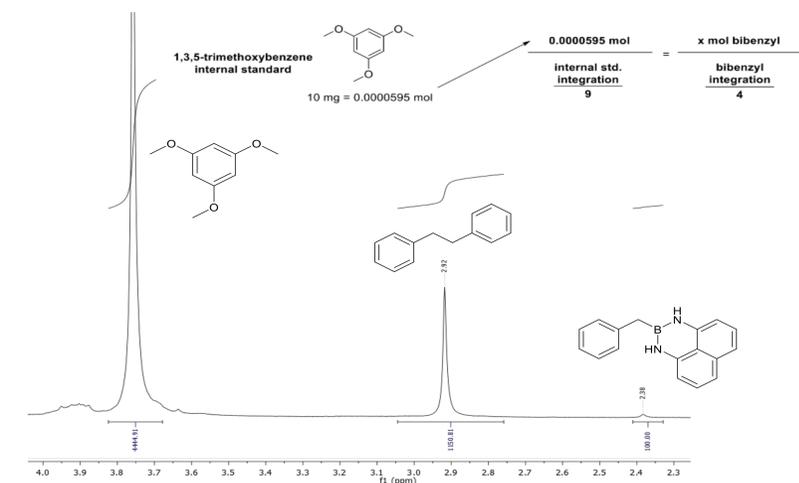
For this experiment, the reaction was heated for one hour at 100 °C (upper table). Previously, the reaction was performed by Katie Russell with the same conditions (lower table). Test reactions were conducted in which various reactants were removed to ascertain whether they are necessary to the reaction. All reactions were conducted under nitrogen.

Table 1: Condition Screening Reactions with improved procedure (1,2) and past screening conditions (3-7)

#	Change from Standard Conditions	Results	Notes
1	None (Average of 3)	97.4% conversion of starting material; 24% yield bibenzyl	Standard conditions
2	No CuBr (Average of 2)	8.75% conversion of starting material; 3.1% yield bibenzyl	Absence of copper catalyst; suppressed reaction
3	None	62% conversion of starting material; 22% yield bibenzyl	Standard conditions
4	No CuBr	5% conversion of starting material; 4% yield bibenzyl	Absence of copper catalyst; suppressed reaction
5	No DTBP	18% conversion of starting material; 2% yield bibenzyl	Absence of oxidative reactant; suppressed reaction
6	No pyridine	5% conversion of starting material; 5% yield bibenzyl	Absence of ligand for copper catalyst; suppressed reaction
7	B(pin) instead of B(dan)	3% conversion of starting material; 3% yield bibenzyl	Reinforces discussion of B(pin) radical instability

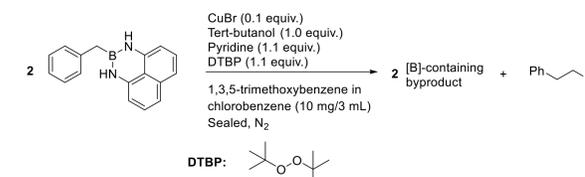
5. Analysis Techniques

To achieve the numbers in the table from section 4, an internal NMR standard was used. By including 10 mg of 1,3,5-trimethoxybenzene in each reaction, % conversion of starting material and % yield of bibenzyl could be calculated using ¹H NMR integrations of appropriate peaks.



6. Future Directions

One next step will be to run more screening reactions in order to optimize the conditions under which the benzyl-B(dan) will react. Additionally, experiments to discern key features of the mechanism will be performed. For example, BHT (butylated hydroxytoluene) will be added to the optimized reaction to see if a radical inhibitor can significantly suppress the reaction.



Another route would be to couple the following molecule to reinforce the selective reactivity of B(dan) over B(pin):



Once the conditions for synthesis were optimized, the next goal would be to expand the substrate scope of the reaction using this method. The first step would be to prove that this method works for other carbon groups attached to the B(dan). Then, we can test other boron substrates to determine which is the most effective in this kind of C-C coupling.

7. Acknowledgments and Funding

- Linfield Student-Faculty Collaborative Research Grant
- Katie Russell (Linfield '23) performed experiments shown in lower table in section 4
- Niko Loening + Lewis & Clark chemistry dept. for facilitating access to high-field ¹H and ¹¹B NMR
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