

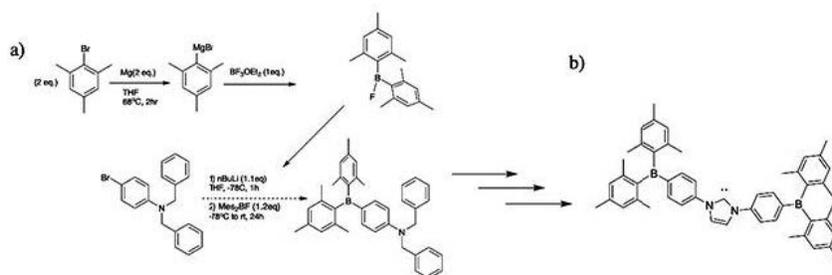
# Summer Scholar Report

## Grignard vs. Mother Nature

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### Synthetic Plan

The proposed plan for the Summer of 2019 was originally a synthetic route to produce my desired N-Heterocyclic carbene (NHC) (**Figure 1**), a project that I had already been working on for about 5 months, inconsistently, by the time summer started. During the spring semester, I was able to form the N,N-dibenzyl-4-bromoaniline (**Figure 1**) species with ease during the first week spent researching under my scholarship. The next step required the generation of bismesityl-boronfluoride ( $\text{Mes}_2\text{BF}$ ) using a Grignard reaction.



**Figure 1.** a) Grignard Reaction steps to make dimesityl-boronfluoride ( $\text{Mes}_2\text{BF}$ ) to then be reacted with N,N-dibenzyl-4-bromoaniline to yield N,N-dibenzyl-4-(dimesityl)borylaniline. First 2 reaction steps form  $\text{Mes}_2\text{BF}$  through the Grignard reaction, with 2-bromomesitylene as starting material. Last 2 steps expected to form the desired product (N,N-dibenzyl-4-(dimesityl)borylaniline) in project's synthetic route. b) Desired NHC product, from originally proposed synthetic route, for the Summer Undergraduate Research Scholarship 2019.

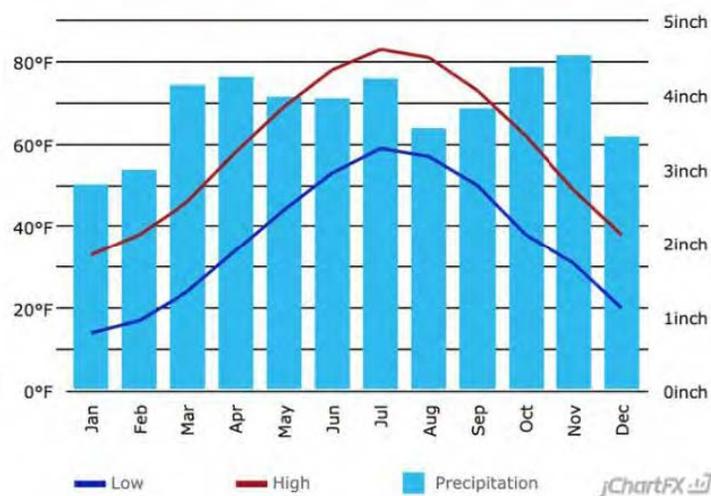
Victor Grignard shared The Nobel Prize in Chemistry with Paul Sabatier in 1912 for the discovery of the Grignard Reagent, one of the most widely used organic chemistry methods for the formation of carbon-carbon bonds.<sup>4</sup> The simplicity of the Grignard reaction is probably the main reason behind its widespread popularity over the past 100+ years. However, as chemists, we know that nothing is ever quite as simple as mixing two starting materials together.

Upon being taught how to perform this reaction by my coworkers, following a literature procedure,<sup>2</sup> it seemed doable, but it slowly became clear that no amount of expertise in making  $\text{Mes}_2\text{BF}$  would make up for one single factor: the humidity. I underwent a total of 13 attempts to make bismesityl-boronfluoride ( $\text{Mes}_2\text{BF}$ ) using the Grignard reaction, to

couple mesityl bromide with trifluoroboron etherate (**Figure 1**). Mes<sub>2</sub>BF was a very crucial part of my proposed synthesis for this Norris-Richards fellowship project, as it was one of two key starting materials for my planned synthetic route to a new N-heterocyclic carbene (NHC) ligand. Sadly, not a single one of my attempts furnished the desired product, which led to a halt in my forward progress, until sometime in the last 2 weeks of my 10-week research stint. This meant that I was only able to complete the first step of my synthetic route, something I had been able to make, in good yield the previous semester!

I understood that what was holding me back from successfully generating Mes<sub>2</sub>BF was the fact that it was summertime. If you didn't already know, summer in New Hampshire typically consists of sweltering hot and humid days. Oftentimes, a very good dose of warm summer rain helps keeps the humidity around. Lucky for us, this weather pattern usually lasts until the end of August.

Below I have included a climograph (**Figure 2**) plotting the average rainfall and temperature recorded each month in Durham, NH. It is clear that the peak rainfall did indeed occur during the 3 months I was employed at the University of New Hampshire. If you don't understand what I am trying to get at here, it became abundantly clear to me that Grignard reactions will not work when it is humid outside and that this particular project may have been better suited for a winter research fellowship or, alternatively, carried out somewhere New Mexico, rather than New Hampshire! I don't know how Floridians ever use Grignard reactions for anything!



**Figure 2.** Climograph showing the average rainfall, and average temperature each month of the calendar year in Durham, NH.5

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Finally, my patience paid off and (with the generous help from one of my lab colleagues) I successfully obtained my intermediate  $\text{Mes}_2\text{BF}$  material and I was able to push one step further into the synthetic route towards my target NHC ligand. Even though I was not able to isolate the desired product from the second step, trying and learning a new reaction was a much-needed change, which, in itself felt like a reward.

## **Reflections**

Many would agree that most of the actual learning a young research chemist experiences — especially during one's first summer working at an academic institution — comes from these very types of trials and failures. I believe most chemists, especially the more experienced, would find this type of thing exciting; like a detective figuring out a cold case. For a young chemist, still unsure of what she wants out of life, I can assure you this was not the easiest or more enjoyable part of the 'chemistry game' to accept. It's a steep learning curve and one that doesn't get the attention it deserves!

This is not an essay on why synthetic chemistry is sometimes painstakingly difficult, or about how 99% of the time you will fail; it is simply a reflection that I hope highlights the beauty of repeatedly trying, and failing, getting up and trying again as you work towards a goal. In striving to create your synthetic target (it is what you are being paid to do every day as a student after all), but more than that, it is okay to fail, because each trial, and each error is a learning experience. In what other profession is this experimentation possible? Everyone's chemistry career is a different story of success, perhaps (as mine was) rooted in initial failure(s). What do you think keeps chemists coming to work every morning? I think perseverance and the joy of knowing that today might be the day you get it right, keeps us going. This past summer, I am proud to have learned the basis of

what many Eastern religions would call, ‘embracing your suffering’. What I mean by this is; as chemists, we are all encouraged to become best friends with our worst enemy, our failed reactions.

I know that even without completing my synthetic target, in fact not even getting a third of the way there, I still was able to walk away from this summer research experience with valuable knowledge gained and a unflappable perseverance that will allow me to always push further, in whatever career I choose.

Despite my synthetic struggles, I would like to express my gratitude in receiving this award. To have had the opportunity to continue working with my professor, along with the graduate and undergraduate students in the lab all summer, was not only a major learning opportunity in my experience as an undergraduate chemistry major and new researcher, but also provided me with valuable insight into the challenges of research, that has helped shape my future career goals.

## Experimental

Grignard reactions were performed under a nitrogen atmosphere, and all glassware was oven-dried prior to use. DMF and THF were obtained from solvent purification system, and THF was stored over 4Å molecular sieves. Pentane was dried over calcium hydride. Hexanes and ethyl acetate were used as obtained. All NMR spectra were gathered either on a Varian Mercury 400 MHz or Bruker 500 MHz spectrometer.

**N,N-dibenzyl-4-bromoaniline:** The following procedure was adapted from the literature.<sup>1</sup> 4-bromoaniline (2 g, 11 mmol, 1 eq.), DMF (10 mL), K<sub>2</sub>CO<sub>3</sub> (4.29 g, 31.0 mmol, 3 eq.), and benzyl bromide (3 mL, 25 mmol, 2.2 eq) were added to a 50 mL round bottom flask, and heated to reflux at 120<sup>o</sup> C for 30 h. Upon cooling to room temperature, a precipitate formed. Additional DMF was added until this precipitate redissolved. The excess K<sub>2</sub>CO<sub>3</sub> was removed by vacuum filtration. The product was extracted with 1:1 hexanes/ethyl acetate (130 mL), and washed with saturated LiCl (30 mL), water and brine. The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated by rotary evaporation, yielding a yellow oil (2.77 g). The crude product was then recrystallized in boiling EtOH (95%, 150 mL), and cooled slowly to room temperature, then to -20<sup>o</sup> C. Upon cooling the product formed as a white precipitate, which was isolated by gravity filtration (1.56 g, 4.7 mmol, 39% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.33 (dd, J = 8.2, 6.6 Hz, 4H), 7.28 (s, 2H), 7.24 – 7.18 (m, 6H), 6.62 – 6.56 (m, 2H), 4.63 (s, 4H).

**Dimesityl-boronfluoride:** Magnesium turnings (1.057 g, 30.77 mmol) were added to 3-neck round bottom flask. THF (45 mL) was cannula transferred into the flask and heated

to 50<sup>o</sup> C prior to slow addition of bromomesitylene (5 mL). The contents of the flask were then heated to reflux, until an opaque, charcoal-colored suspension was observed. BF<sub>3</sub>-OEt<sub>2</sub> (2 mL, 16.57 mmol, 48% solution in hexanes) was added to a separate 200ml Schlenk flask and cooled to -78<sup>o</sup> C. The Grignard suspension was then added dropwise to the BF<sub>3</sub>-OEt<sub>2</sub>. Halfway through addition, the contents were allowed to warm to room temperature. After complete addition of Grignard, THF was removed by dynamic vacuum on a Schlenk line, and pentane (15 mL) was added via cannula. Mg salts were removed by filtration through Celite, and pentane was removed *in vacuo*, yielding a yellow solid. The crude product was recrystallized from pentane (30 mL) at -78<sup>o</sup> C. Pentane was removed in vacuo, yielding a light-yellow solid (1.63 g, 6.1 mmol, 75% yield). <sup>11</sup>B{<sup>1</sup>H} NMR (160 MHz, CDCl<sub>3</sub>): δ 53.29 ppm. <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>): δ -14.43 ppm. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 6.81 (d, J = 10.0 Hz, 4H), 2.31 – 2.23 (m, 23H).

## References

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