

PRF# 59191-ND

Title: Intramolecular Nitrene-Mediated Modification of Simple Alcohols

PI: Florence J. Williams, Ph.D. University of Iowa (secondary affiliation: University of Alberta)

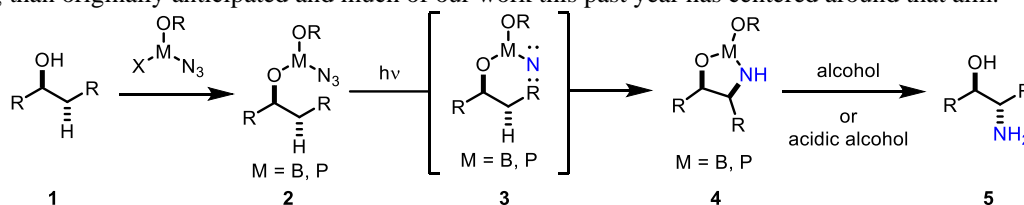
Summary of General Topics of Exploration

Research Aims of the Original Grant:

- 1) To use boron or phosphorous(III) as a tether to position a nitrene to perform a C–H insertion proximal to an alcohol and subsequently produce amino alcohol products
- 2) To perform the same procedure proximal to an alkenyl alcohol to provide aziridines

Foundational Information to Be Determined:

As outlined in the original grant, the use of boron is to be explored prior to phosphorous due to its synthetic ease of removal, non-toxic nature and minimal reactivity with azide precursors. The first goal was to provide a reliable route to the alkoxyborylazide intermediates (Scheme 1, 2, M=B) in order to test our hypothesis that the boron center would provide exceptional regioselectivity for the subsequent insertion. Developing such a route proved to be more challenging than originally anticipated and much of our work this past year has centered around that aim.

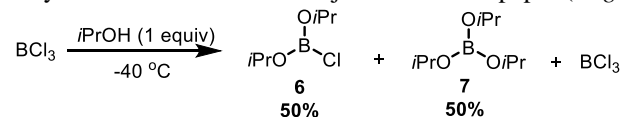


Scheme 1. Strategy for nitrene delivery for controlled C–H insertion.

Research Progress – Boron Chemistry Discoveries

Access to Dialkoxyboryl Chloride Intermediates:

Bettinger and coworkers had previously shown that dialkoxyboryl chlorides can be quantitatively transformed to the dialkoxyboryl azide by treatment with TMSN_3 .¹ As such, we identified early on that our goal was to produce dialkoxyboryl chlorides in a clean fashion. Early studies by Bren Jordan Atienza determined that beginning with alcohols and reacting directly with BCl_3 provided undesirable stoichiometric mixtures (Scheme 2). However, during the course of those investigations, Dr. Atienza determined that special mixtures of BBr_3 and BCl_3 lead to a reliable ether cleavage which occurred in a stepwise fashion and funneled to the dialkoxyboryl chloride, with alkyl bromide byproducts. As a side note of interest, this procedure also gave surprising levels of regioselectivity for unsymmetric alkyl ethers. This was the subject of our first paper (*Org. Lett.*, **2018**).



Scheme 2. Early work on alcohol displacement on BCl_3

In addition to the high regioselectivity of unsymmetric alkyl ether cleavage, the treatment of ethers with BBr_3 and BCl_3 mixtures further exhibited unusual chemoselectivity as well. The reaction targeted ether cleavage even in the presence of esters and alkenes, among other functional groups. Intrigued, we sought to

apply this boron trihalide mixture to a complex setting to challenge the chemoselectivity of the reaction.

We chose as our target lignocellulose. Lignocellulose is the most abundant biopolymer on the planet, composed of polysaccharides (cellulose/hemicellulose) and polyaromatics (lignin). It is the primary source of cellulose, which is used ubiquitously in industrial and biomedical applications, but the aromatic feedstocks which can be obtained from the lignin remain underutilized. The reason is that the process of removing cellulose modifies the lignin by adding additional C–C linkages which make it difficult or impossible to extract aromatic monomers of high commercial value. So, lignin remaining from the lignocellulose after the cellulose is extracted is typically just burned.

We imagined that our method would allow the gentle extraction of the lignin prior to cellulose extraction, and would test a general hypothesis in the field – that use of Lewis acids rather than Brønsted acids may prove to minimize undesirable C–C linkages. To our surprise, application of the BBr_3 and BCl_3 mixture led to a very mild cellulose extraction protocol, leaving behind the lignin. This was an extremely chemoselective process, as we saw no evidence of lignin extraction, even under repeated treatments. We published this discovery in a special edition *Tetrahedron* issue focused on boron-mediated chemistries (*Tetrahedron*, **2018**).

We are currently following up on this by looking at the hydrogenation of the remaining lignin-enriched solids after boron trihalide treatment. Recent results have shown that the hydrogenation of the material goes to near quantitative completion under standard lignin hydrogenation protocols, which is strong evidence of minimal C–C bond formation prior to the hydrogenation. In fact, over-hydrogenation of the material is the key challenge currently.

Early Experiments with Borylazides:

Having developed a route to dialkoxyboryl chlorides (using the aforementioned ether cleavage), we are now able to ask our original fundamental questions. Can we obtain improved chemo- and regioselectivity for nitrene C–H insertion using boron as a delivery and stabilization agent? Nam Truong has performed our first experiments in this area and discovered that *indeed, we can*.

Our initial observations provided only two products: 1) the desired amino alcohol; and 2) the alcohol resulting only from ether cleavage. The current challenge is that we are only obtaining amino alcohol in 5-15% yield (theoretical yield is 50% due to only one alkoxy group on the boron center being modified). The exciting part of these observations is that we see *nothing except the desired amination*. Normally, nitrenes are promiscuously reactive and show poor chemoselectivity. In other words, typically you get many products and byproducts. That we only see two is already very exciting.

Our next work is to dig deep into the mechanism of the nitrene reactivity. We know that the azide precursor is completely consumed using ^{11}B NMR experiments. Two alternative pathways for the resultant nitrene would be reaction with solvent (CDCl_3), or reaction with another nitrene or azide equivalent (dimerization). Both behaviors are well documented in the literature. The dimer product would itself be interesting, as a molecule like that has never been made and would have unique reactivity.

Once we know what is limiting the reactivity of the nitrene with the alkoxide ligand, we can tune the reaction parameters (solvent choice, temperature, concentration, etc) to maximize conversion to the desired aminoalcohol and achieve Aim 1 of this grant. For year 2 I have hired a post-doctoral fellow, Dr. Benjamin Hale to pursue and advance this investigation. Subsequent to that, he will expand to the phosphorous(III) investigations.

Impacts of Research Program on Students and PI

Impact on the Career of my Students:

This grant has been instrumental in supporting many of my students and allowing me to invite undergraduates to participate in our research program. Of particular note, Mr. Nam Truong performed the majority of his Masters studies on this project. This money allowed him to switch from an early project that was not well suited to his interests to the current project where he flourished in developing his research confidence and became a leader in establishing the behavior of boron Lewis acids in the presence of ethers, as well as advancing some early nitrene reaction studies. Liyifang Yang and Luca Maiorana were both able to participate in my lab solely due to funds from this grant. Mr. Maiorana completed his BSc. and is currently a researcher in the Gibbs lab at University of Alberta; and Ms. Yang continues her undergraduate studies. Further, Mr. Zain Kazmi lead the applications of the Lewis acid treatment to lignocellulose. He is working on finishing the hydrogenation studies of the remaining solids from the reaction, which will be his second graduate publication. He is also collaborating with the Stryker lab at University of Alberta, who also have interests in lignin degradation, as a direct result of this grant. Without such funds, none of the lignocellulose investigations would have been pursued. While this exploration was not an original aim, its pursuit has proven fruitful and constitutes a discovery of significant interest to the materials and sustainability fields.

Impact on my Research Career:

I cannot understate how significant this support has been to my career. Due to personnel challenges, my research program did not gain any real momentum until the end of my third year when my start-up funds were to end. Had I not been able to obtain this PRF grant, my minimal funds would have forced me to reject interested students and run a very small group with high TA loads. We would have had to work on “safer” projects in the hopes that small successes would support future grant proposals. However, the PRF specifically allowed me to pursue my original ideas in their original form, and we are now able to look at the fundamentally challenging and interesting questions that so often lead to unexpected and impactful discoveries. I am so thankful to the ACS PRF Fund for making this possible and giving my research program that boost to continue forward.

This project, and spinoff areas of investigation, is going to be the foundation of my tenure package in a few years. The behaviors that we are observing for boron-mediated processes, not to mention the early results with our nitrene chemistry, are very unique. Even in the field of boron chemistry these investigations distinguish me and my research program. As such, having the financial support to ask the bold questions is vital and so very appreciated. Moreover, these early successes in boron research will strengthen future grant applications, such as a future NSF Career application in the summer of 2020. Success in that grant cycle will be directly connected to the advancements in this project that the PRF fund allowed for.

1. Filthaus, M.; Schwertmann, L.; Neuhaus, P.; Seidel, R. W.; Opperl, I. M.; Bettinger, H. F., C–H Bond Amination by Photochemically Generated Transient Borylnitrenes at Room Temperature: A Combined Experimental and Theoretical Investigation of the Insertion Mechanism and Influence of Substituents. *Organometallics* **2012**, *31* (10), 3894-3903.