PRF # 59102-UR1
New Methods for Nitrene Generation and Transfer in the Selective Aziridination of Alkenes
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Project Overview

Carbon-nitrogen (C-N) bonds are ubiquitous in a wide-ranging assortment of natural and unnatural small molecules, many of which have great utility in applied fields of research. Thus, we have proposed to cultivate and optimize fundamental synthetic protocols mediating C-N bond construction, which could be vital to the field of organic synthesis. More specifically, our current research is focused on the development of new synthetic methods, targeting the generation and use of reactive nitrene intermediates. Nitrene insertions into carbon-carbon double bonds (forming aziridines) or onto C-H bonds (affecting direct amination), are, perhaps, two of the most atom-economical approaches to the preparation of C-N bonds (**Figure 1**).

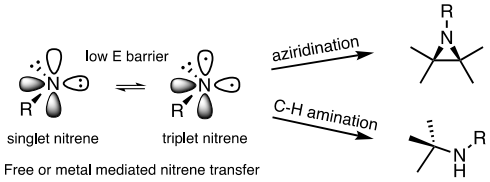


Figure 1.

To date, we have embarked upon work related to the first two Specific Aims of our original proposal narrative: (1) to evaluate the generation and reactivity of nitrenes derived from carbamate starting materials through (a) in situ, stoichiometric chemical oxidation and (b) visible light photocatalysis, and (2) to investigate the selectivity of both inter- and intramolecular metal-nitrene addition to C=C bonds while studying the scope of reactivity for aziridination, providing greater insight into the mechanism and selectivity of nitrene insertion. *A summary of the current progress of this work, for the funding period of September 2018 through August 2019, is summarized below.*

Progress of Research and Summary of Experimental Results

Our lab has undertaken a two-pronged approach in studying the generation and reactivity of nitrenes as they arise from either (1) pre- or (2) non-oxidized carbamates. Shown in **Figure 2**, the stabilized azide is an example of a well-studied nitrene precursor which easily reacts via thermal of photochemical activation. [1] The carbamate, however is a more attractive precursor due to its relative stability, ease of formation, and, based on literature precedent, capacity for C-N bond formation via in situ oxidation. [2]

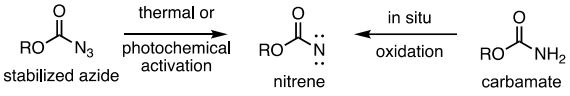
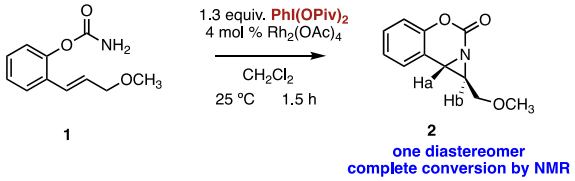


Figure 2.

A. Based on promising preliminary results from the time of our proposal submission, we have continued to design and synthesize substrates to test the feasibility of nitrene generation from carbamate ester precursors and subsequent intramolecular aziridination. For example, novel carbamate **1** was prepared in seven synthetic steps, from salicylaldehyde, to produce a diastereomeric mixture of cis/trans alkene isomers. Substrate **1** was then screened for optimal aziridination conditions based on the du Bois protocol designed for in situ sulfamate ester oxidation/nitrene generation. [3] During optimization, we found that the traditional du Bois protocol, using up to 4 equivalents of the hypervalent iodide oxidant, $PhI(OAc)_2$, was not satisfactory and a screening of other hypervalent iodide oxidants revealed that $PhI(OPiv)_2$ was much more effective at only 1.3 equivalents, Scheme **1**, presumably due to the attenuated nucleophilicity of the pivalate ligand, slowing any undesired side reactions with the substrate, nitrene, or metal catalyst. It should also be noted that, we were able to cleanly isolate the trans alkene diastereomer (**1**), which confirmed retention of stereochemistry during nitrene insertion to form **2**, indicating a concerted mechanism.



Scheme 1.

Recognizing that our initial test substrate (**1**) was designed to avoid completing C-H amination (no allylic or benzylic C-H bonds), we turned our attention to the system shown in **Figure 3**. This carbamate precursor (**6**, Table 1) was easily prepared from cis-3-hexenol in just one synthetic step. We efficiently screened following conditions for favorable aziridine formation over C-H amination: solvent, temperature, heating method, and hypervalent iodide catalyst. A snapshot of this screening is provided in **Table 1**. In all cases, less 0-10% of the C-H amination product **4** was observed in the crude ^1H NMR and that product was never effectively isolated. Overall, it is clear that the nature of the hypervalent iodide plays an integral role in nitrene formation and transfer in C-N bond formation. Contrary to reports where this reaction is proposed to proceed in the absence of the metal catalysts, we found

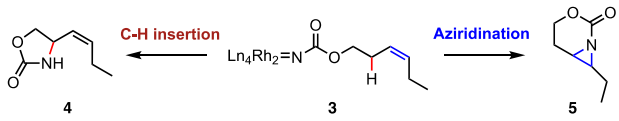
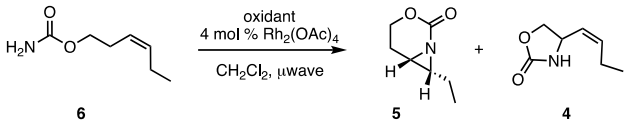


Figure 3

that repeating our optimized conditions (Entry 6, Table 1) with no catalyst produced no product of any kind, confirming the role of the dirhodium metal in aziridination.

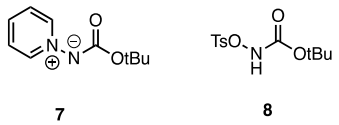


6 **5** **4**

Entry	*Oxidant*	*Equiv.*	*Solvent*	*Temp (°C)*	*Time (h)*	*Result*
1	$PhI(OAc)_2$	1.2	CH_2Cl_2	50	1	28% isolated yield
2	$PhI(OPiv)_2$	1.2	CH_2Cl_2	50	1	36% isolated yield
3	$PhI(OCOCF_3)_2$	1.2	CH_2Cl_2	50	1	No reaction
4	Iodosodilactone	1.2	CH_2Cl_2	50	1	No reaction
5	Koser's Reagent	1.2	CH_2Cl_2	50	1	No reaction
6	**$PhI(OPiv)_2$**	**3.0**	**CH_2Cl_2**	**50**	**2**	**47% isolated yield**

Table 1. Reaction conditions: substrate (0.75 mmol), $Rh_2(OAc)_4$ (4 mol%), solvent (10 mL)

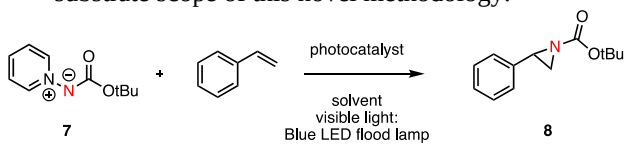
B. The transfer of nitrenes to alkenes is possibly the most direct and atom economical route for the synthesis of C-N bonds, and in an effort to bypass the use of super stoichiometric amounts of oxidant, we have also been investigating the use of non-azide, pre-oxidized nitrene precursors that we propose can be activated via visible-light photocatalysis. [4] To test photocatalytic activation and the feasibility of aziridination, we prepared multiple substrates, including the iminopyridinium ylide (**7**) and sulfonyl hydroxylamine (**8**) are shown here. In another extensive screening, we found success with ylide **7** in the intermolecular aziridination of styrene. Some examples our trials are provided in **Table 2**.



7 **8**

Figure 4

Entries 1 and 2 serve as controls, showing the requirement of a sensitizing photocatalyst and a light source. Entry 7 provides optimized conditions with a much shorter reaction time (compared to Entry 5 and others) when the amount of ylide is doubled. We are currently scaling up this reaction system in addition to testing the substrate scope of this novel methodology.



7 **8**

Entry	*Alkene (eq.)*	*Solvent*	*Light Source*	*Catalyst (loading)*	*Time (h)*	*Conversion*
1	2	$CDCl_3$	Blue LED FL	-	24	-
2	2	$CDCl_3$	-	$[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mol %)	24	-
3	2	$(CD_3)_2CO$	Blue LED FL	$[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ (1 mol %)	80	13 %
4	2	$(CD_3)_2CO$	Blue LED FL	$[Ir(dF(CF_3)(ppy)_2(dtbpy)]PF_6$ (1 mol %)	80	41 %
5	1	$CDCl_3$	Blue LED FL	$[Ir(ppy)_2(dtbbpy)]PF_6$ (5 mol %)	70	100 %
6	2	$CDCl_3$	Blue LED FL	$[Ir(ppy)_2(dtbbpy)]PF_6$ (5 mol %)	46	31 %
7	**0.5**	**$CDCl_3$**	**Blue LED FL**	**$[Ir(ppy)_2(dtbbpy)]PF_6$ (5 mol %)**	**20**	**100 %**

Table 2. Reactions were performed in NMR tubes. Percent conversion is a comparison to the limiting reagent in each case.

Impact Statement

Financial support from PRF during this grant period has enhanced my own research trajectory as well as the educational experience of the eight undergraduates I had the opportunity to mentor during the Bard Summer Research Institute (BSRI), four of whom spent significant time working on the project outlined above. With funds for dedicated research time, I have effectively produced promising preliminary results in a brand-new area of research for our lab: visible-light photocatalytic aziridination (Part B. above). I was also able to mentor a larger and more diverse group of students this summer, three women and two from traditionally underrepresented groups in STEM. All of these students, minus one graduated senior, are continuing projects in my research lab during this academic year where they learn about the challenges and rewards of research, how to work effectively as part of a research team, as leaders, as peer-mentors, and as owners of their own investigative work.

Funds from PRF also supported two undergraduate students to attend and present research posters at the ACS National Meeting in San Diego, CA in August. Attending this meeting was invaluable, not only as an opportunity for the students to showcase their work, but as a venue for learning about of new areas of research, and expanding their graduate school and career opportunities.

(1) Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.* **1965**, *87* (16), 3630–3637.
(2) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69* (19), 6377–6386.
(3) Guthikonda, K.; Wehn, P.; Caliando, B.; du Bois, J. *Tetrahedron* **2006**, *62*, 11331–11342.
(4) Miyazawa, K.; Koike, T.; Akita, M. *Tetrahedron* **2016**, *72* (48), 7813–7820.