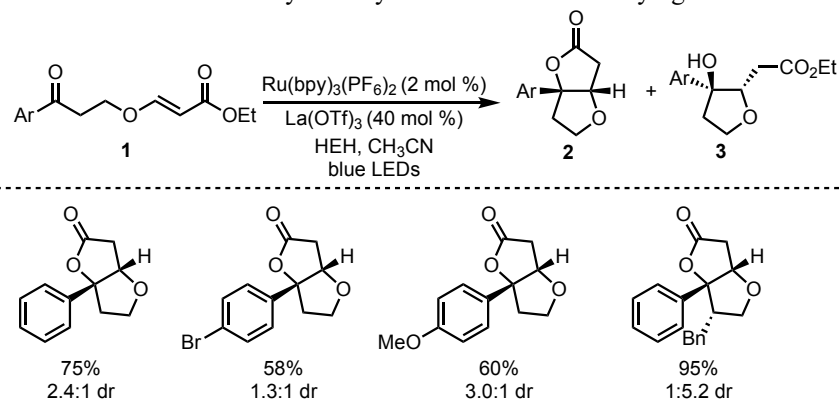


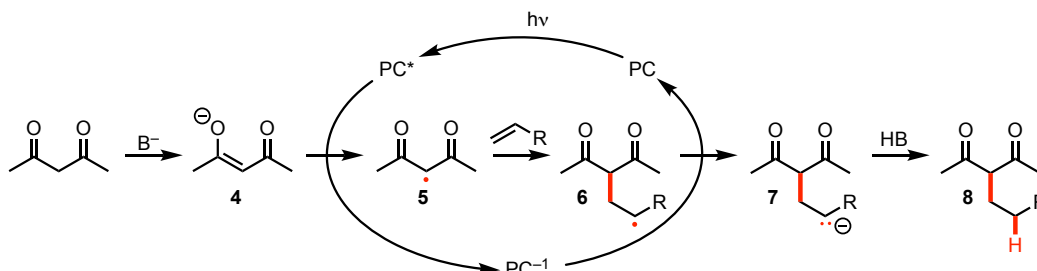
Catalytic methods, especially those involving transition metals, are a cornerstone of modern organic reaction development. Our overarching goal is to facilitate a research program that engages undergraduate researchers in the stereoselective synthesis of carbon-carbon bonds using catalytic methods. Our early aims were to utilize catalytically-generated ketyl radicals in stereoselective reactions. Our group was successful in developing a general application for the reactions of ketyl radicals that were generated by single-electron reduction from a photocatalyst. This work created an expertise in our group for photocatalytic umpolung reactivity that we have since expanded to include the generation of 1,3-dicarbonyl radicals.

We had initially become interested in the addition of ketyl radicals to pendant vinylogous carbonates in the synthesis of 2,6-dioxabicyclo[3.3.0]octan-3-ones. The 2,6-dioxabicyclo[3.3.0]octan-3-one structure is found in a variety of natural products and is considered to be the bioactive portion of these molecules. Such a reaction was unknown under catalytic conditions and was challenged by the potential sensitivity of the vinylogous carbonate group to both acidic and basic conditions. We had proposed to study this reaction using titanium(III) reagents that could be catalytically generated in the presence of strongly-reducing metals such as manganese or zinc. In the first year of this grant, we investigated Ti(III) reagents for this transformation and found that they were unsuitable because of their strong Lewis acidity. Only low yields were obtained with stoichiometric amounts of titanium, and our attempts to render these reactions catalytic failed. We then turned to photoredox catalysts for the generation of ketyl radicals. Contemporary studies by Knowles, Rueping, and Ngai had demonstrated the generation of ketyl radicals by the combined action of a photosensitizer and an acid co-catalyst. We discovered that this catalytic approach was indeed compatible with vinylogous carbonates, and that lanthanum triflate was the ideal co-catalyst (**Error! Reference source not found.**). Keto-vinylogous carbonates **1** were readily transformed to 2,3-disubstituted THF products **2** and **3** in good yields and modest diastereoselectivities. This avenue led to the discovery of a general procedure for the synthesis of 2,6-dioxabicyclo[3.3.0]octan-3-ones and our first PRF-supported publication in *Organic Letters*.

Scheme 1. Photoredox-catalyzed ketyl radical addition to vinylogous carbonates.



These discoveries increased the group's expertise in photoredox catalysis, and we began to investigate other types of umpolung radicals that could be generated by single-electron transfer. We were drawn to 1,3-dicarbonyls as a viable substrate because of the rich chemistry developed by Snider using manganese(III). These reactions, while powerful C–C bond constructing processes, are practically challenging because of the large amounts of transition metal byproducts that are generated. While recent work by Baran and Hilt have enabled some limited catalytic reactivity using electrochemistry, we proposed that the 1,3-dicarbonyl radical could be generated by the single-electron



Scheme 2. Proposed catalytic cycle for enolate oxidation

oxidation of enolate intermediates. We therefore initiated a program around a catalytic cycle for photoredox enolate oxidation (Scheme 2). In our proposal, the electron-rich enolate species **4** would be oxidized by a photoexcited transition metal complex to dicarbonyl radical **5**. Radical **5** could then undergo C–C bond formation with a nucleophilic alkene to form **6**, which would in turn be reduced by the catalyst to anion **7**. Product **8** would be formed without any stoichiometric byproducts after protonation of anion **7** by the initial 1,3-dicarbonyl substrate.

Initial studies have begun by examining the intramolecular hydroalkylation of β -ketoester styrene **9**. Substrates of this type are readily available in one step by allylation of the dianionic enolate of acylacetone derivatives. These substrates were chosen because resulting 5-exo-trig cyclization event would generate a highly stabilized benzylic radical. Reduction of this intermediate radical would provide cyclopentanone **10**. The resulting process is redox neutral, with oxidation of the β -ketoester counterbalanced by reduction of the alkene benzylic position. After extensive optimization, we found that $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$, which has a strong M^{-1}/M reduction potential, was capable of performing both the oxidation of enolate **4** and reduction of radical **6** without the need for additional additives. We were excited to find that the yields of this reaction are excellent: above 90% in most cases. Diastereoselectivities remain modest in these early studies, however. Both electron-poor and electron-rich styrenes are well tolerated, as well as α -substitution of the alkene. Lactones can also be generated by the same 5-exo-trig method. In our investigations so far, only functional groups that are sensitive to single-electron reduction or oxidation, such as nitro, are incompatible with this chemistry.

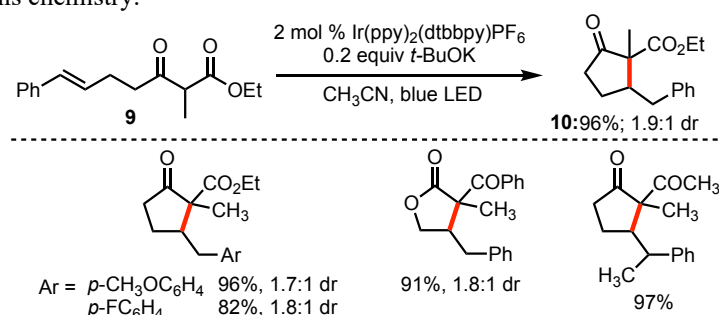


Figure 1. Photocatalyzed hydroalkylation and preliminary substrate investigations

We are continuing to investigate this exciting proof-of-concept reactivity. Our primary goal is to finalize the cyclization described in Figure 1. A full exploration of the scope of this reaction, as well as an understanding of the mechanism is underway. We are particularly interested in validating the mechanism proposed in Scheme 2 in order to understand how these intermediates could be applied to more complex systems. Furthermore, the discovery of photocatalytically-generated 1,3-dicarbonyl radicals lays the foundation for a broad research program in oxidative umpolung chemistry. Future studies will leverage our expertise in this area to intercept the 1,3-dicarbonyl radical to achieve other bond-forming reactions. For instance, cyclized radical intermediates could be intercepted by a number of well-studied chemistries such as single-electron oxidation, atom transfer, or radical chain reactions.

This grant has impacted every aspect of our research program. In the second year of this grant, we have been given the flexibility to investigate challenging and important chemistry that has become a foundational research program. The grant has allowed us to acquire the necessary specialized equipment and reagents to develop expertise in reaction development in photoredox catalysis. The research funded by the ACS-PRF has created a sustainable research trajectory in catalytic method development. Because we are located at a liberal arts college, the generous support of the ACS-PRF has further enhanced my ability to mentor a group of undergraduate researchers. This year, an additional five undergraduates have benefitted from the supply money provided by this grant, three students attended national conferences, and one student was supported by a summer research fellowship. This research experience has enabled these students to succeed; two graduates have gone on to graduate schools in chemistry, where the skills they learned at Oxy will be significantly useful in their pursuit of a PhD.