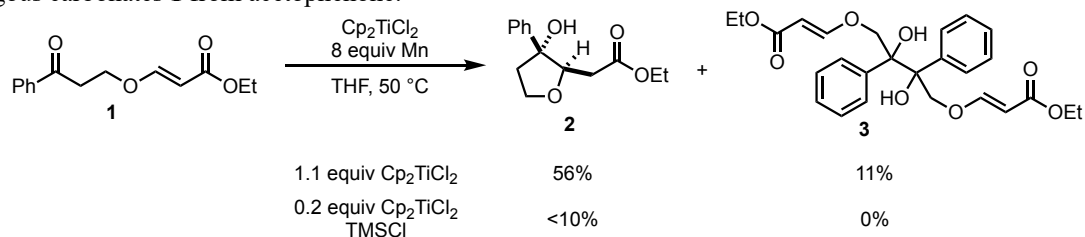


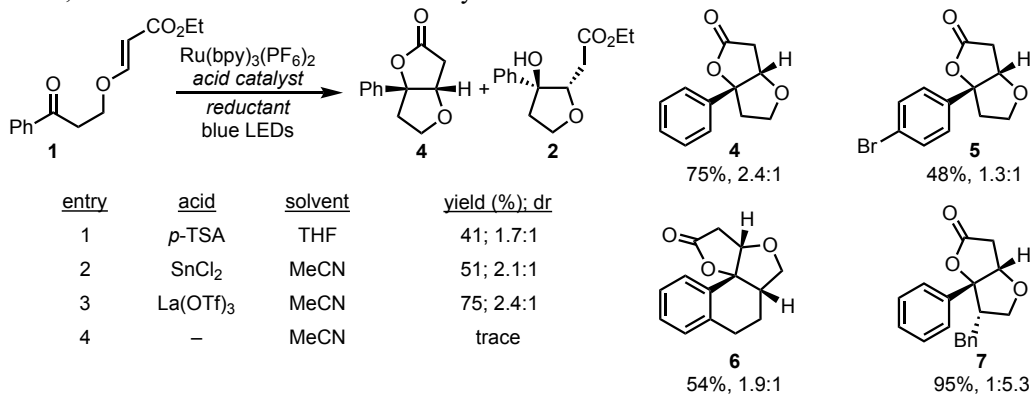
Catalytic methods, especially those involving transition metals, are a cornerstone of modern organic reaction development. The overarching goals of our research program are to facilitate a research program that engages undergraduate researchers in the stereoselective synthesis of carbon-carbon bonds using catalytic methods. Our early aims have been to utilize catalytically-generated ketyl radicals in stereoselective reactions. Nucleophilic ketyl radicals are a powerful intermediate for the umpolung reactivity of ketones in the formation of carbon-carbon bonds. Until recently, however, their strategic application has been limited by the necessary use of stoichiometric reducing metals such as samarium or tin. Our group has been interested in developing new catalytic methods to generate ketyl radicals in complex settings with a reduced chemical waste burden.

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. 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. We began by developing a high-yielding, six-step synthesis of vinylogous carbonates **1** from acetophenone.



**Scheme 1.** Titanium-catalyzed cyclization reactions

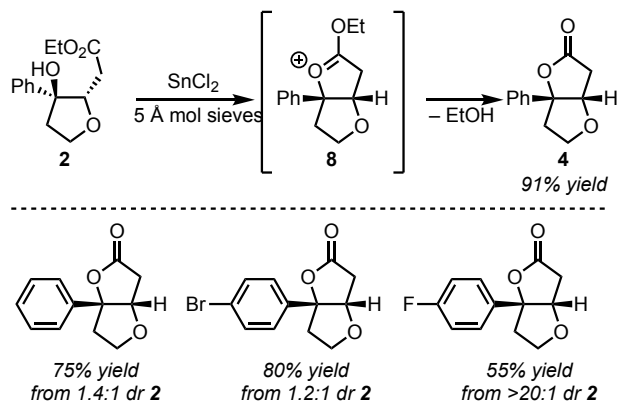
Our initial studies using titanocene reagents were promising (Scheme 1). We were able to cyclize substrate **1** to THF **2** in modest yield. Interestingly, this reaction was highly selective for a single diastereomer around the newly formed C–C bond. The majority of the mass balance was dimer **3**, which was the product of pinacol dimerization of ketone substrate **1**. Optimization of this reaction found that the titanium reagents were highly sensitive to adventitious oxygen, and special care had to be taken to remove and exclude oxygen from the reaction mixture. Unfortunately, no conditions attempted were sufficient to render this reaction catalytic. Titanium forms a very strong bond to oxygen, and all attempts to find additives that would efficiently release and turn over the titanium catalyst were ineffective. Furthermore, the vinylogous carbonate was not compatible with the highly acidic titanium salts, manganese salts, and TMSCl, leading to general decomposition of the starting material (**1**). Ultimately, this catalyst system was abandoned for this reaction; we intend to return to titanium catalysis for reactions with less sensitive substrates.



**Scheme 2.** Combined photoredox/Lewis acid-catalyzed reactions and representative scope

We began to investigate other methods for the generation of ketyl radicals that might be compatible with the labile vinylogous carbonate. Photoredox catalysis is a burgeoning field where visible light can be harvested to enable

challenging electron transfer reactions. 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 (Scheme 2). The diastereoselectivity of this process was only modest, ranging from 1.3 to 5:1 in favor of the cyclized dioxabicyclo[3.3.0]octanone (**4**). The substrate scope was fairly broad (**4**–**7**), with the best substrates including additional substitution on the THF ring (e.g., **7**). In general, these vinylogous carbonates (**1**) were more sluggish to react than other  $\alpha,\beta$ -unsaturated carbonyl electrophiles, yet the extended reaction times did not lead to significant decomposition of the starting material. This compatibility speaks to the mild nature of these dual catalytic conditions.



In order to address the modest diastereoselectivity of the ketyl cyclization reaction, an epimerization strategy was developed to convert minor diastereomer **2** to bicyclooctanone **4** (Scheme 3). While we had initially proposed an anionic  $\beta$ -elimination/addition cascade, Lewis acids proved to be the most effective for this transformation indicating that a cationic pathway through an intermediate such as **8** was more likely. Utilizing  $\text{SnCl}_2$  with 5 Å mol sieves enabled a highly efficient interconversion of **2** to **4** that was found to be general and also effective for the resolution of diastereomeric mixtures to stereochemically pure **4**. Overall, we were able to develop a mild, two-step, highly diastereoselective synthesis of 2,6-dioxabicyclo[3.3.0]octan-2-ones where the key ring-fusion carbon-carbon bond was generated using visible light photocatalysis.

Our work of the past year has generated significant results in the development of catalytic methods for the implementation of ketyl radicals in synthesis. The results reported above led to our first PRF-supported publication (*Org. Lett.* **2018**, *20*, 5727), and has formed the foundation for a robust research program. This publication included four undergraduate co-authors. Current efforts are focused on expanding this methodology to a wider substrate base. For example, we are studying the use of ketyls generated by photoredox catalysis in the intermolecular reductive annulation of ketones and  $\alpha,\beta$ -unsaturated esters in the synthesis of  $\gamma$ -lactones. We are also excited by the added potential that Lewis acids present for the use of ligands to modulate the reactivity of these ketyl intermediates. We are beginning to investigate the use of chiral ligands to control the stereoselectivity of ketyl radical additions, with the end goal of developing a general, enantioselective synthesis of substituted alcohols. We are also beginning to expand our expertise to other photoredox-generated umpolung reactions.

This grant has impacted every aspect of our research program. As a new independent researcher, it enabled me to learn about project design and development especially in the context of undergraduate research. Because we are located at a liberal arts college, the generous support of the ACS-PRF has enhanced my ability to mentor a group of undergraduate researchers. A total of nine undergraduates have benefitted from the supply money provided by this grant, and two students have so far been supported by a summer research fellowship. This research experience has enabled these students to succeed; one was selected as a Division of Organic Chemistry Summer Research Fellow, and 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.