PRF# 59202-UNI1
Project Title: Tropone Iron Tricarbonyl as a Platform for the Synthesis of *aza*-Polycyclic Molecules
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In the past year, we have made steady progress with the research project funded by this grant. The preliminary results from our proposal concerning *aza*-Michael additions to tricarbonyl(tropone)iron formed the basis for the first publication of my independent career (this article was published shortly before the start of the grant period). In addition, a detailed account/demonstration of our experimental protocol was published in the *Journal of Visualized Experiments* this past summer. We have also developed a synthesis of a hitherto unknown azatricyclic skeleton by performing a Diels-Alder reaction with one of the *aza*-Michael adducts described in our initial publication. We plan on submitting this work for publication by the end of 2019. As we prepare these results for publication, we are concurrently pursuing the synthesis of several other bridged azapolycycles described in our proposal.

I. *Aza*-Michael Additions to Tricarbonyl(tropone)iron

To synthesize the requisite amine-functionalized tropone nucleus, we developed a solvent-free protocol for the *aza*-Michael addition of amines to tricarbonyl(tropone)iron (**1**). This reaction proved compatible with a wide variety of primary amines as well as unhindered secondary cyclic amines (see Table 1). On the other hand, we found that less nucleophilic amines (*i.e.* more sterically hindered amines and arylamines) could be added to the corresponding cationic tropone complex **3** (see Table 2 for representative substrate scope). To remove the iron tricarbonyl unit from the products, we found that the amine required protection with a Boc group prior to oxidative demetallation with cerium ammonium nitrate (CAN).

Table 1

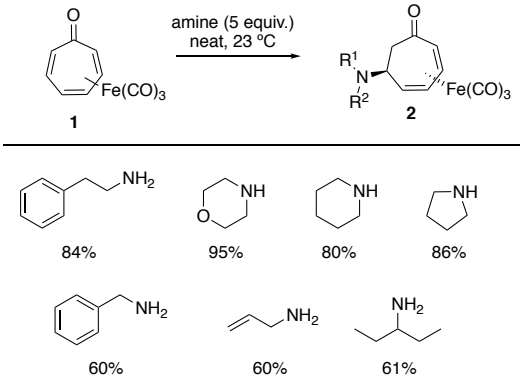
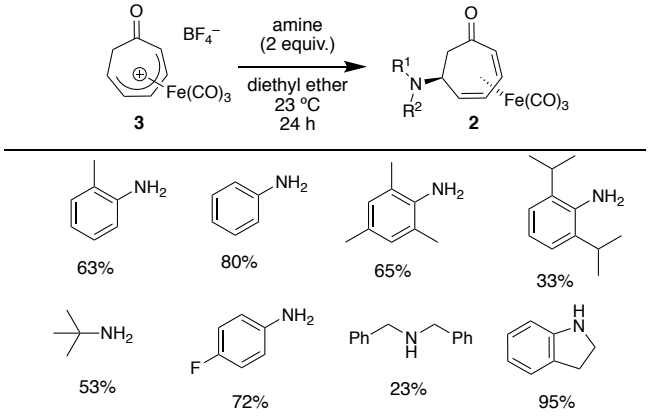


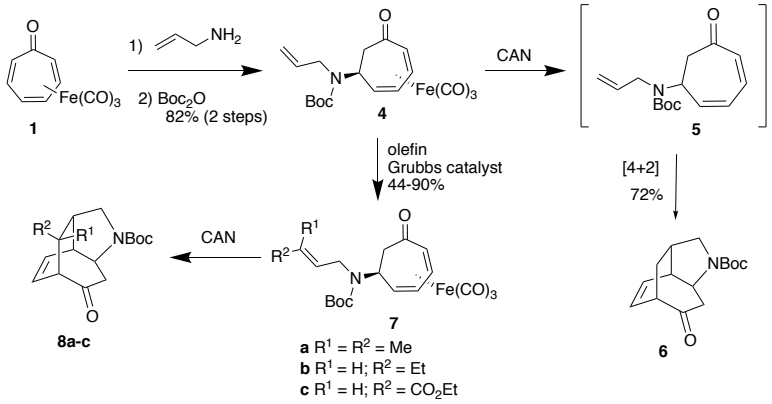
Table 2



II. Diels-Alder Approach to to the 2-azatricyclo[4.3.2.0^{4,9}] ring system

Using our *aza*-Michael reaction as a starting point, we have demonstrated an efficient synthesis of the novel 2-azatricyclo[4.3.2.0^{4,9}] ring system. This was accomplished via *aza*-Michael addition of allylamine to **1**. The crude initial adduct was protected as a Boc carbamate and then demetallated with CAN (Scheme 1). Notably, the intermediate demetallated triene (**5**) could not be isolated. Instead, the reaction cleanly and spontaneously delivered the desired azatricycle **6** in good yield (structure confirmed by X-ray crystallography). We have synthesized a number of diverse analogs of the azatricycle by installing various substituents on the dienophilic olefin of **4** via cross metathesis. This has allowed us to investigate reactivity trends regarding this intramolecular Diels-Alder reaction. Thus, we found that installing an electron-withdrawing group on the dienophile (**7c**) does not slow down the reaction (which we thought may occur given the possibility that we were observing an inverse electron-demand Diels-Alder reaction). In contrast, the cycloaddition proceeds more slowly when one or two alkyl groups are present on the dienophile (**7a, 7b**). Nevertheless, both of the corresponding cycloadducts (**8a**/**8b**) could be isolated in good yield by allowing the crude demetallation products to stand in solution at room temperature overnight (**7b**) or by heating a solution the crude products overnight (**7a**). In addition, we have found that increasing the length of the tether between the seven-membered ring and the dienophile by a single methylene unit prevents the intramolecular cycloaddition from occurring; all attempts to promote this cycloaddition have resulted in either no reaction or other side reactions.

Scheme 1

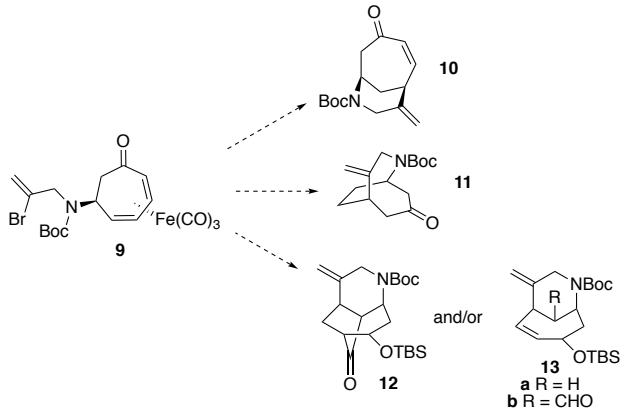


In addition to **8**, we have synthesized several other structural analogs from **6** and we are interested in screening these analogs against biological targets, especially those associated with the central nervous system. We have also identified related azapolycyclic skeletons found within some biologially active natural products and we are currently working towards extending this methodology to provide access to these ring systems.

III. Synthesis of Diverse Azapolycycles from a Single *Aza*-Michael Adduct

We have recently synthesized iron complex **9** with plans to develop a series of transformations to access multiple different complex polycycles from this single intermediate (**Scheme 2**). We anticipate being able to obtain polycycles **10** and **11** via demetallation of the complex followed by two variants of an intramolecular Heck reaction. We also hope to investigate the intramolecular addition of the vinyllithium obtained from **9** via lithium-halogen exchange to the diene *while the iron is still bound to it.* Additions of organolithium species to such iron diene complexes have only been sparsely reported in the literature. We anticipate that such a reaction could give rise to polycycles such as **12** or **13**.

Scheme 2



IV. Impact of Research on My Career and Students

This research project has been intellectually satisfying to pursue alongside my research students. The results that we have been able to obtain thus far and the corresponding publications have put me on a good path towards attaining tenure at Lafayette College. In addition, I look forward to establishing new collaborations as we begin to investigate the compounds we synthesize for potential bioactivity. My research students, most of whom have plans to attend graduate school, have gained valuable experience in conducting and communicating scientific research. In addition, five of the six students whom I have supervised in the past year have been co-authors on at least one publication. Those students who have attended the ACS National Meeting with me have gained critical exposure to many exciting areas of research within the broader discipline, which can often be difficult to achieve at a primarily undergraduate institution.