

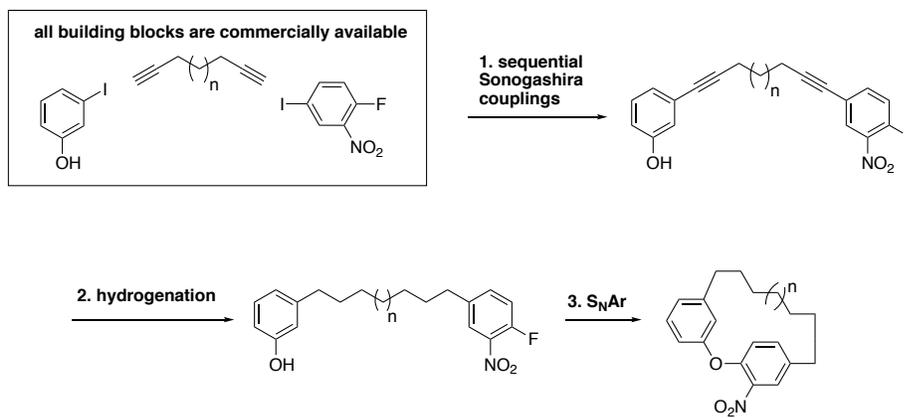
Research Progress

The goal of our work is to develop an iterative and scalable route to conformationally constrained diarylether cyclophanes. These show promise as a new scaffold for asymmetric ligands that would be of use in asymmetric hydroformylation

reactions to produce value added products from petroleum. Adapting known literature procedures in our first year, we completed the synthesis of two cyclophanes using an Ullmann coupling as the key step (Figure 1).

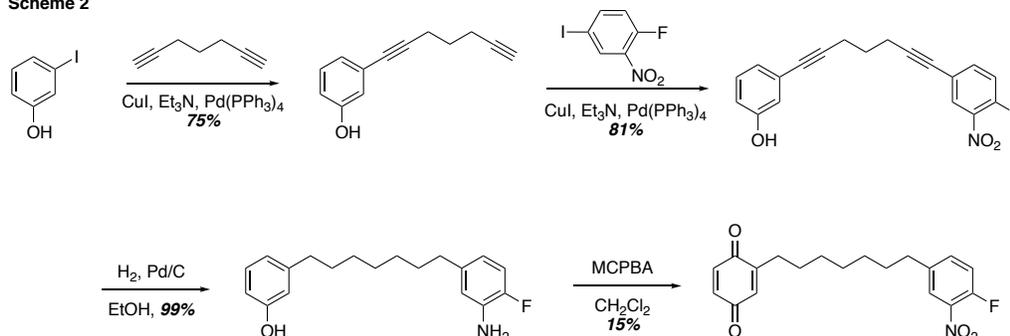
However, the low yields of the key step and the high step count rendered this approach unworkable for producing reasonable amounts of these key scaffolds. In the hands of a rotating cast of undergraduate researchers, this approach was not feasible.

Over the last year, our efforts have been focused on developing and optimizing a very short and potentially efficient route to these cyclophanes that utilizes a nucleophilic aromatic substitution as the key cyclophane forming step.

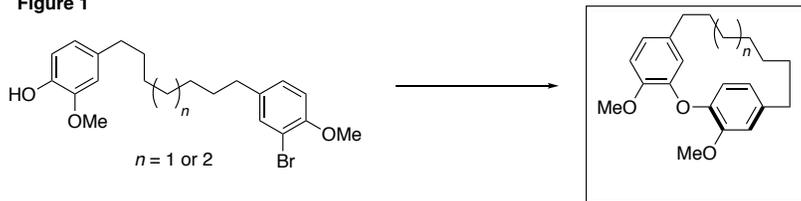
Scheme 1

reported in the literature. This plan would only require three stages and in eliminating protecting groups we hoped to significantly streamline the route to these important targets. Our plan is shown in Scheme 1. All of the necessary starting materials are commercially available and we could quickly build substrates by iterative Sonogashira couplings followed by catalytic hydrogenation. S_NAr would yield the necessary cyclophanes. Simply starting with a different terminal dialkyne would yield differing tether lengths in the cyclophanes.

In practice, virtually all of these steps proceeded in high yield. The two iterative Sonogashira couplings proceeded in 75% and 81% respectively (Scheme 2). At this point, only selective alkyne hydrogenation and cyclization remain

Scheme 2

our major challenges. Standard catalytic hydrogenation protocols with a variety of palladium or platinum catalysts and hydrogen gas invariably lead to exhaustive

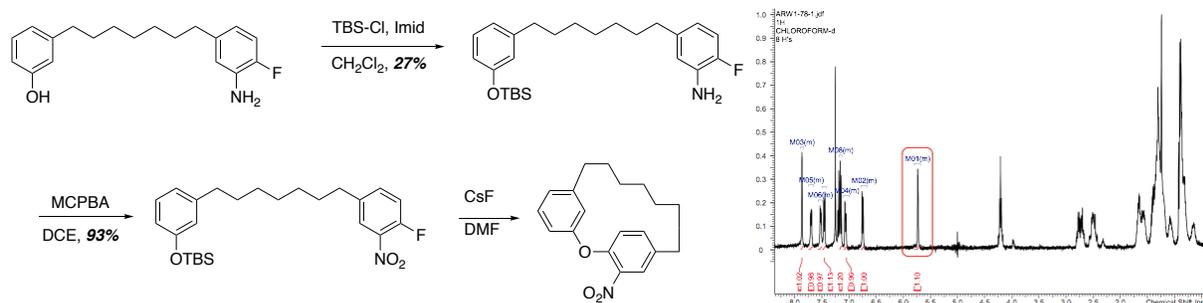
Figure 1

- Completed the synthesis of two cyclophanes
- Eight carbon tether is first ever reported
- Characterized each by 1H -NMR

hydrogenation of the alkynes as well as the nitro group. Unfortunately, this is not an adequate substrate for the S_NAr cyclization. Attempts to oxidize the aniline back to a nitro group failed to discriminate between the phenol and aniline groups and the major product isolated was the nitro-quinone shown. This result led us to explore the possibility of phenol protection before oxidation of the nitro group.

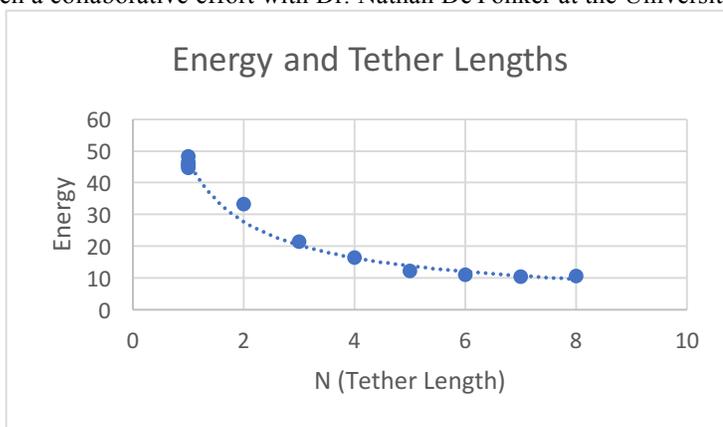
We have found that protection of the phenol leads to selective oxidation of the aniline to the nitro moiety. However, silylation of the phenol is problematic, likely due to competitive silylation of the aniline. Gratifyingly, simultaneous silyl ether deprotection and S_NAr cyclization led to the synthesis of milligram amounts of the nitro cyclophane as confirmed by the upfield shift of one of the aromatic hydrogens in the 1H -NMR spectrum.

Scheme 3



In the last year, we have also undertaken a collaborative effort with Dr. Nathan DeYonker at the University of Memphis to computationally determine the relationship between conformational mobility and tether length. These calculations suggest that room temperature racemization should occur around an 11-carbon ether ($n=5$ on the graph below). These results have informed our synthetic plan, now limiting the number of potential substrates we are targeting (7-12 carbon tether). A joint publication is planned when the syntheses and analysis is complete.

In the last year, we have developed an efficient method to append two different aromatic rings to a variable length tether. The only hurdle that remains is reduction of the



alkyne groups in the presence of the nitro group. Literature reports suggest that Wilkinson's catalyst can accomplish this selectivity, but initial experiments in our lab do not bear this out. In the future, we plan to attempt cyclization before hydrogenation, but we expect the product to be highly strained which might preclude efficient cyclization in these cases. We also plan to execute partial hydrogenation of the alkynes to *Z*-alkenes with Lindlar's catalyst, which we hope will prevent nitro-reduction and preorganize the substrate to a reactive cyclization conformation. Another obvious experiment is to explore other phenolic protecting groups aside from silyl ethers to prevent phenolic oxidation as a side reaction. While increasing the step count, we could also introduce the protecting group earlier in the synthetic sequence avoiding the competitive silylation/protection of the aniline in the middle of the synthesis.

Impact on Students

Over the past two years of the grant, twelve students have worked on the project of whom five are now enrolled in PhD programs in Chemistry. These students are currently enrolled in top Chemistry Ph.D. programs including Colorado State University, Texas A&M, University of Oregon, and Duke University. Participating in a long-term research project, especially full-time during the summer months, is an excellent way to prepare students for the rigors of graduate study. Faculty at Texas A&M have expressed that they are impressed with the quality of applicants graduating from Fort Lewis College. This is no doubt a reflection of the extent to which these students have been involved in long-term, meaningful research projects. In addition, six students presented a poster on this work during the annual Undergraduate Research Symposium here at FLC.