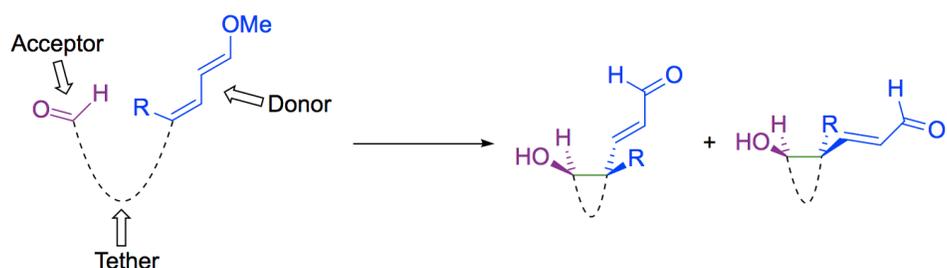


Exploring the Potential of an Acid-Initiated Vinylogous Aldol Reaction to form All-Carbon Quaternary Stereocenters

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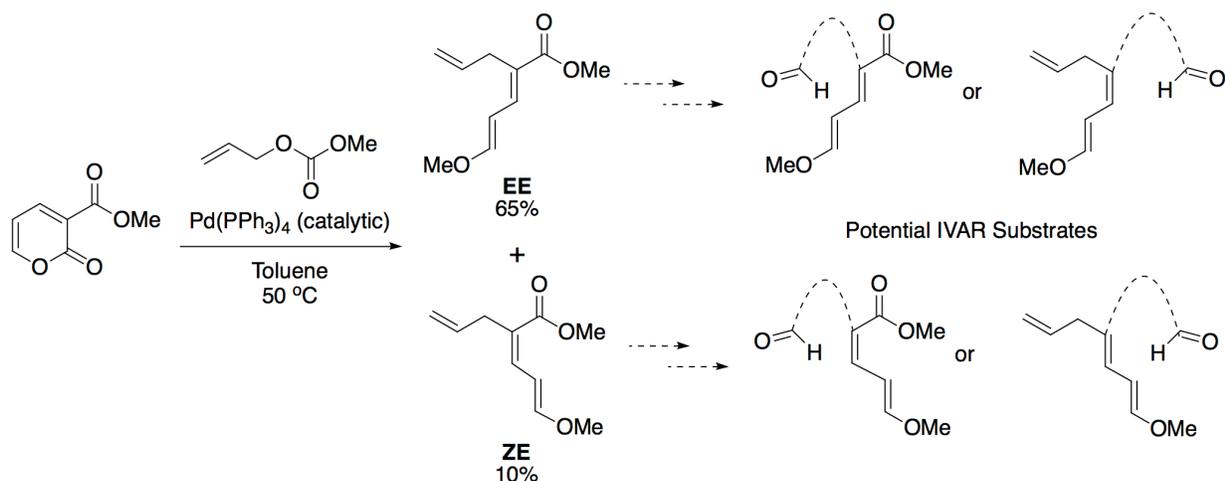
Project Aims:

The stereoselective preparation of all-carbon quaternary stereocenters (ACQSs) is an important challenge for the synthetic chemistry community. This project aims to explore the potential of an intramolecular vinylogous aldol reaction (IVAR) between an aldehyde (acceptor) tethered to an alkyl dienol ether (donor) to generate cyclic products containing an ACQS (Scheme 1).



Scheme 1 – Generic example of a IVAR to generate cyclic products with an ACQS (R = alkyl).

As reported in previous reports, we have demonstrated that this reaction takes place with hydrocarbon tethers with 3 or 4 methylene groups and when R is methyl. Established examples of the reaction vary in stereoselectivity and we now seek to understand the factors govern the stereochemical outcome. To date we have used VAR substrates that are mixtures of stereoisomers at the dienol ether. While we have observed diastereoconvergence when some of these mixtures undergo the IVAR, we recognize the need to work with stereoisomerically pure substrates in order to get a firm understanding of the course of the reaction. To that end, we identified the double-decarboxylative addition to pyrones reported by Maji and Tunge (*Org. Lett.* **2015**, *17*, 4766-4769) as a means to access stereochemically pure methyl dienol ether intermediates with the potential to be transformed into substrates for the IVAR (Scheme 2). Work over the past year has focused on developing this potential entry to IVAR substrates.

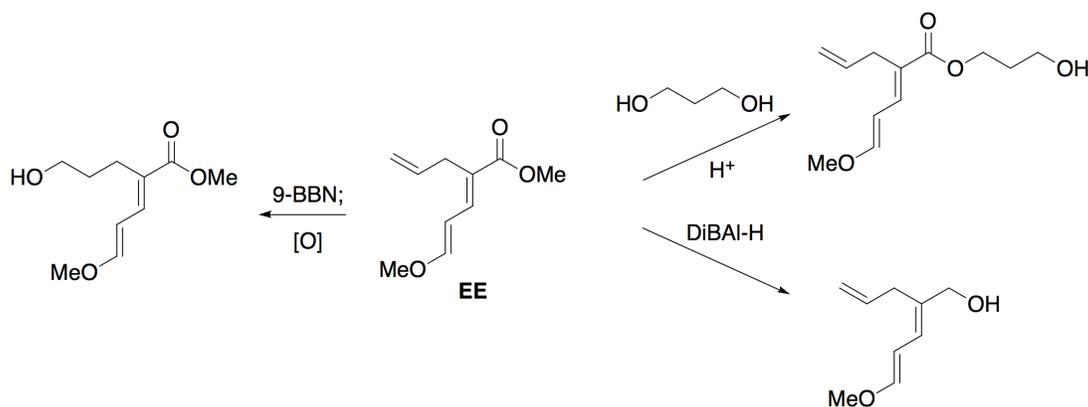


Scheme 2 – Proposed application of double-decarboxylative addition to a pyrone to access IVAR substrates.

Project Impacts and progress on the technical aims:

In addition to being a primary research focus of the P.I., undergraduate students have been richly engaged in the work in two different settings: (1) as a course-based research experience (CURE) in *Organic Chemistry Laboratory II* and (2) in faculty mentored independent research students in the laboratory of the P.I.. In the CURE laboratory, small teams of students (2 or 3 per team) were challenged to repeat the work of Maji and Tunge (Scheme 2) to produce the *EE* and *ZE* methyl dienol ether containing intermediates, separate them by careful column chromatography, and attempt a synthetic approach of their own design to convert the intermediates into an IVAR substrate (*ie.* a molecule with an aldehyde tethered to the dienol ether). This open-ended project is an authentic research experience without a known endpoint or expected result. Such experiences are defining features of CURE labs and they have profound pedagogical benefits. This project, over the past 3 years, has proven to be an excellent CURE and more than 60 undergraduates have benefitted from the experience in that setting.

Seven students worked in the research laboratory of P.I. throughout the past academic year with the same goal in mind: devising routes to convert the *EE* and *ZE* methyl dienol ethers in Scheme 2 into stereochemically pure IVAR substrates. The outcome of these student efforts are three promising approaches (Scheme 3)



Scheme 3 – Three promising entries to converting *EE* into a IVAR substrate.

Briefly, the relative electron richness and steric accessibility of the pendant allyl functional group was sufficient to allow regioselective hydroboration oxidation and thus introduce functional handle that will be elaborated into a tethered aldehyde. Transesterification of the methyl ester with propylene glycol provided a pendant alcohol, that after oxidation will be poised for the title IVAR. Finally, regioselective reduction of the methyl ester with DiBAL-H provided the corresponding allylic alcohol which is also a valuable functional handle for appending a tethered aldehyde. The elaboration of these intermediates (and closely related variants) into IVAR substrates is ongoing.

Six of the seven undergraduate research students who have been carrying the project forward in the research laboratory, presented their work at the American Chemical Society National Meeting and Exposition in Orlando, Florida (April 2019). This project and the support from the ACS Petroleum Research Fund to carry out the research and present it continues to have a substantial formative impact on the many students involved and has enriched the scholarship of the P.I. over the past three years. We are grateful for the support and will continue this project into the future.