

Exploring the Potential of an Acid-Initiated Vinylogous Aldol Reaction to form All-Carbon Quaternary Stereocenters (7/2017 - 8/2018)

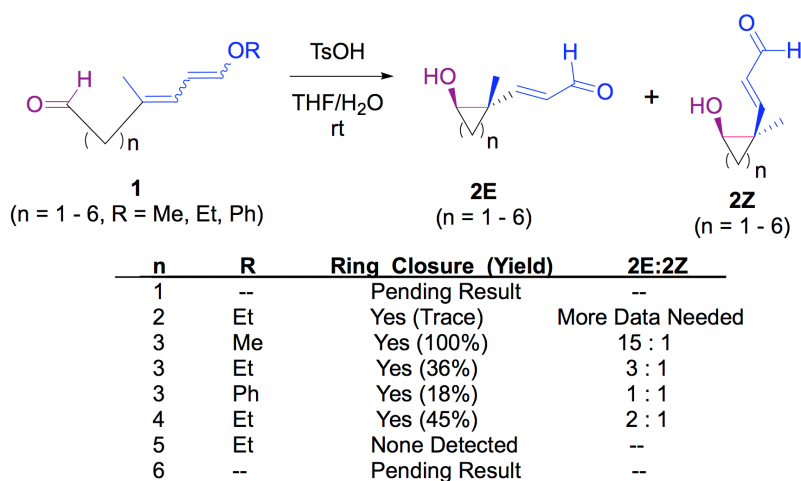
P.I. John Hofferberth PhD

Project Impacts:

The exploration of this intramolecular vinylogous aldol reaction (IVAR) is now the exclusive focus of my research laboratory and has important impacts on the many students who are engaged and my own scholarly work. Over the past year, seven undergraduate research students have taken on aspects of the project and four of them remained on campus over the summer to continue their work. Of the students on the project, one will be graduating in this fall and is applying for industrial chemistry positions and the two other seniors in the lab are applying to chemistry graduate programs. The junior members of the lab are thriving and rapidly developing their research skills in preparation for advanced study. Additionally, aspects of this project were piloted in fall 2018 as a course-based undergraduate research experience (CURE) in our *Organic Chemistry Laboratory II* course. In that way 35 additional students benefited. This CURE has now been expanded and the use of this IVAR to stereoselectively form all-carbon quaternary stereocenters (ACQSs) is now the focus of this 13-week intermediate lab course. To say the least, the impact and the number of students involved in this project has dramatically expanded over the last year.

Progress on the technical aims:

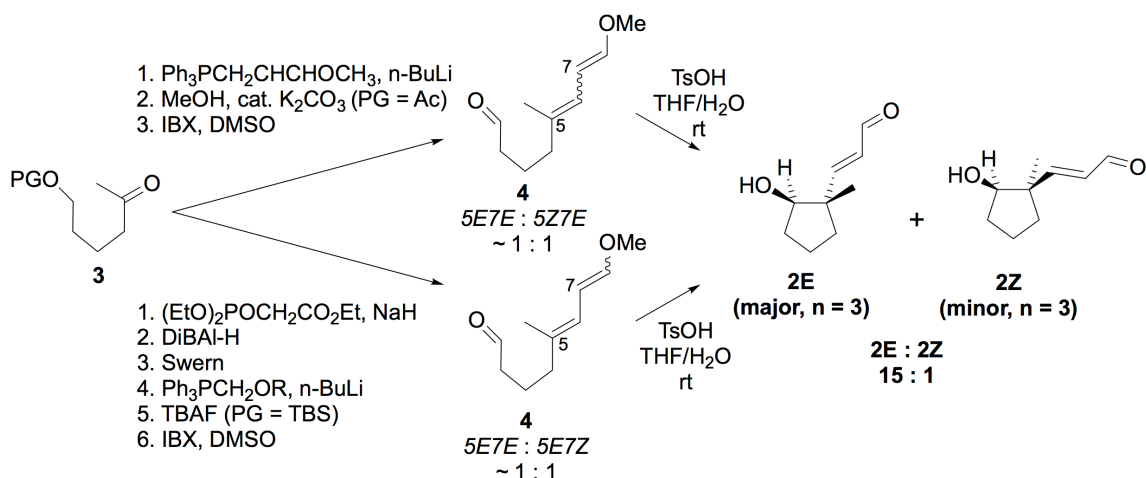
The overall goal of the project is to better understand the potential of the IVAR that occurs in substrates containing an aldehyde tethered to an alkyl or aryl dienol ether to generate ACQSs. We seek to learn about the impact of varying the alkyl or aryl group on the dienol ether (R in Scheme 1) and the length and nature of the tether on the yield and stereoselectivity of the process. Our study of substrates **1** revealed that methylene tethers varying from 2-4 carbons in length are capable of the IVAR. Importantly, the performance of the substrate containing a methyl dienol ether (n = 3, R = Me) was exceptional in both the yield (100%) and stereoselectivity (d.r. 15:1) of the process. As reported last year, there is a paucity of convenient methods to prepare methyl dienol ethers known to the literature and much of our effort over the past year involved exploring and developing methods to prepare them.



Scheme 1: Exploring the impact of tether length and influence of enol ether substituent (R) on the IVAR

We have explored a number of potential routes to prepare substrates containing methyl dienol ethers and three have yielded the desired functional group. The first two of these methods (Scheme 2) rely on Wittig reactions to install the diene functionality. Of these two methods, neither generates isomerically pure IVAR substrates nor are they efficient enough to prepare quantities of the IVAR substrates for significant further study. However, the performance of the IVAR substrates (**4**) prepared by these two different methods is important and motivates our continued interest. When the methyl dienol ether is installed in one step from methyl ketone **3** the product mixture is composed of a nearly equal proportion of the *5E7E* and the *5Z7E* isomers (top route in Scheme 2). When instead the methyl dienol ether is installed by two sequential Wittig reactions

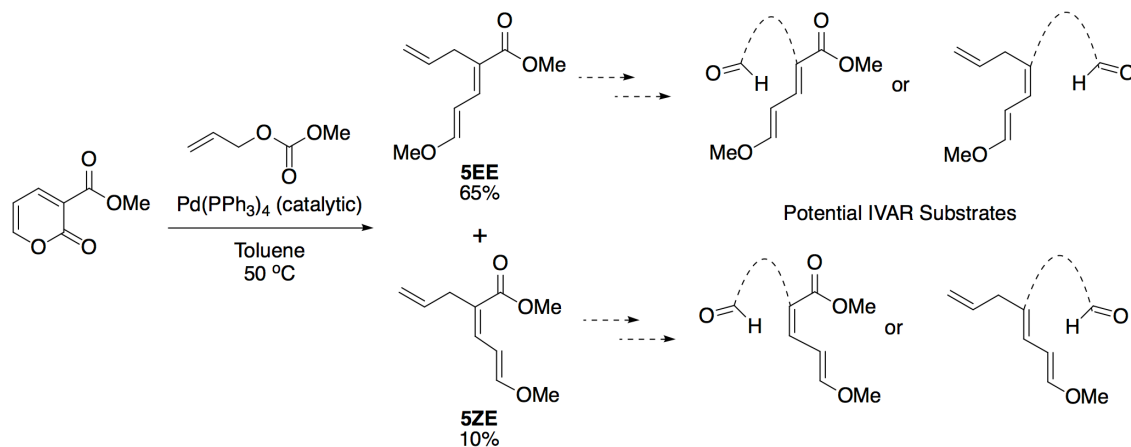
(bottom route Scheme 2) the product mixture contains a nearly equal proportion of the *5E7E* and the *5E7Z* isomers. These mixtures are inseparable by standard preparative chromatography and they were carried forward as mixtures to prepare the corresponding IVAR substrates **4**.



Scheme 2: Diastereoconvergence observed during the IVAR with methyl dienol ether substrates

When these mixtures of isomers of **4** are separately exposed to toluenesulfonic acid in wet THF they both cleanly generate diastereomeric aldol adducts **2E** ($n = 3$) and **2Z** ($n = 3$) in a 15 : 1 ratio, respectively. This diastereoconvergence was unexpected and prompts questions about the nature of stereocontrol and the details of the mechanism. Empirical study of this phenomenon would benefit from isomerically pure IVAR substrates and generation of such substrates is our current focus.

The third method we have explored to prepare a synthon containing a methyl dienol ether was described by Tunge (*Org. Lett.* **2015**, *17*, 4766-4769, Scheme 3). In this interesting palladium catalyzed double decarboxylation, readily separable adducts **5EE** and **5ZE** are prepared in high purity on 5-gram scale. So robust is this process that we have adapted the original protocol to use the simple glassware available in our teaching laboratories and it is being carried out as the first step in our CURE for second semester organic chemistry students. Students in my research laboratory and in the CURE class are now engaged in devising and executing synthetic routes to convert the pendant allyl group or the resident methyl ester into a tethered aldehyde to generate isomerically pure substrates for the IVAR. We have made some progress toward that end and our findings will be included in the sequel to this report.



Scheme 3 - Convenient preparation of isomerically pure methyl dienol ethers **5** reported by Maji and Tunge (*Org. Lett.* **2015**, *17*, 4766-4769, DOI: 10.1021/acs.orglett.5b02308) and their conversion to isomerically pure IVAR substrates