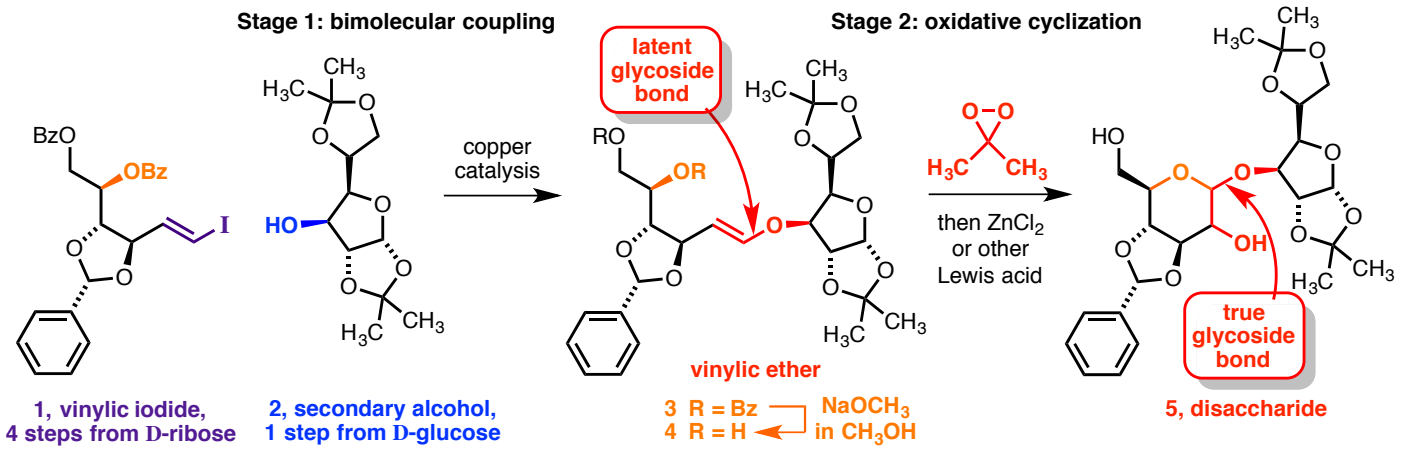
Overcoming Steric Challenges in Glycosylations: P. I. Frank E. McDonald, Professor of Chemistry

Advances in *glycobiology* require efficient methods for joining individual sugar components. However, the construction of *glycoside bonds* is notoriously difficult, as the desired bond-forming bimolecular coupling process between two sugars is complicated by unproductive collisions with other parts of the chemical structure, due to *steric hindrance*. This research project tests a hypothesis underlying a novel glycoside synthesis strategy: by decreasing the size of a reactive partner as the *sterically unhindered* vinylic iodide **1**, the glycoside bond synthesis will be more productive. The PERS grant will support preliminary experimentation leading to a future NIH grant application directed to the National Institute of General Medical Sciences (NIGMS).

Our proof-of-principle experiment will involve: **stage 1)** copper-catalyzed[1] bimolecular coupling of **vinylic iodide 1**[2] with the *hindered* **secondary alcohol of glucose derivative 2**, to form **vinylic ether 3** as a latent glycoside bond, followed by **deprotection of benzoate (Bz) esters**; and **stage 2) epoxidation**[3] of the vinylic ether of **4**, followed by Lewis acid-promoted *intramolecular addition* of alcohol to epoxide intermediate to form the **disaccharide 5**, containing a *sterically hindered* glycoside bond.



This unprecedented method may offer an easier alternative to the historically difficult bimolecular coupling stage. The successful execution of **stage 1** will diminish the subsequent challenge of constructing the *sterically hindered* **glycoside bond of disaccharide 5 from vinylic ether 4**, as **stage 2** will be *entropically neutral*, with one reactant molecule converted into one product molecule. We will address the positional selectivity of bond formation, *regioselectivity*, and the three-dimensional arrangement of atoms, *stereoselectivity*, by varying the stereochemistry of vinylic iodide **1** in **stage 1**, and the oxidative cyclization reagent in **stage 2**. Additional experiments will explore the scope of this method for other disaccharide structures. The overall impact of this project promises a more general synthetic method for glycoside bonds, affording a variety of substitution patterns and stereoisomers. Future experiments will apply this method to the synthesis of glycoside structures in bioactive oligosaccharides, including antibiotics and vaccines.

Budget: $10,000 total.

Supplies: $10,000 total: $5000 for chemical reagents, $2000 for solvents and purifications, $1500 for laboratory supplies, $1500 for instrument user fees.

Equipment: $0; existing equipment will be sufficient for this project.

Personnel expenses: $0; first-year graduate students and undergraduate students will work on this project.

Travel expenses: $0; travel not required for this project. Students will apply for other internal sources of travel funding, if warranted, to present results at a conference.

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[1] (a) "A Domino Copper-Catalyzed C-O Coupling-Claisen Rearrangement Process." Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978-4979. (b) "An Improved Cu-Based Catalyst System for Reactions of Alcohols with Aryl Halides." Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 284-286.

[2] The alkynyldiol precursor to compound **1** has been prepared by two independent routes. See: "1,5-α-D-Mannoseptanosides, Ring-Size Isomers That Are Impervious to α-Mannosidase-Catalyzed Hydrolysis." Boone, M. A.; McDonald, F. E.; Lichter, J.; Lutz, S.; Cao, R.; Hardcastle, K. I. *Org. Lett.* **2009**, *11*, 851-854.

[3] "Enol Ether Epoxides and Products Resulting from Their Reaction with Nucleophiles." Meyer, C.; Spiteller, G. *Liebigs Ann. Chem.* **1993**, 17-21.