

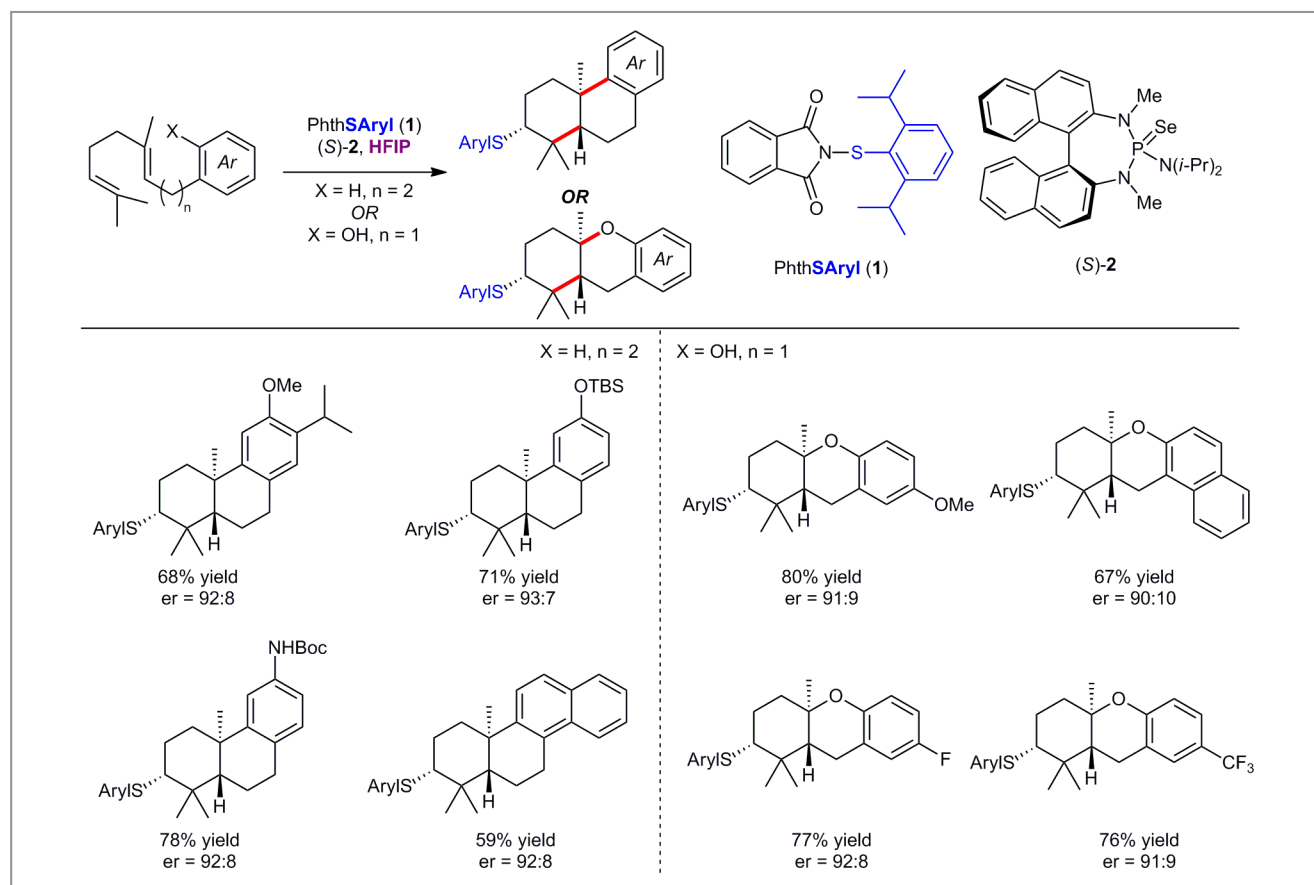
Enantioselective, Lewis Base Catalyzed Sulfenocyclization of Polyenes

J. Am. Chem. Soc. **2018**, *140*, 3569–3573

Polyene cyclization is one of the most general methods for constructing diverse polycyclic skeletons, such as those found in steroid and terpenoid natural products. The reaction, which finds its origins in the biosynthesis of polycyclic terpenes, is also attractive for synthetic chemistry, owing to its ability to form products with multiple rings and stereogenic centers in a non-stop process from simple, linear, achiral starting materials. Many methods for cyclization of polyenes have been developed that involve cationic, anionic, and radical intermediates. Despite the many advances that have been made in this area, catalytic, enantioselective polyene cyclizations are significantly less well developed. The existing catalytic processes share common drawbacks, including: (1) low func-

tional group compatibility because of the strongly acidic conditions needed, (2) incomplete cyclizations, which require further downstream steps, and (3) highly engineered substrates which deter post-cyclization modifications and limit the potential to access natural products. Thus, a high-yielding and operationally simple method for catalytic, enantioselective polyene cyclizations is still needed. Recently, the group of Professor Scott Denmark at the University of Illinois (USA) described a chiral thiiranium ion induced, polyene cyclization that proceeds in good yields with high enantioselectivities under mild conditions.

“As part of an ongoing research program to apply the concept of Lewis base activation of Lewis acids to the reactions



Scheme 1 Selected examples of enantioselective, Lewis base catalyzed polyene sulfenocyclization

of main group elements, we have focused on the activation of sulfur(II) electrophiles in recent years,” explained Professor Denmark. He continued: “Prior disclosures have demonstrated enantioselective, intramolecular oxy-, amino-, and carbosulfenylations of unactivated double bonds. To extend the utility of this concept, the application to polyene cyclization was undertaken.”

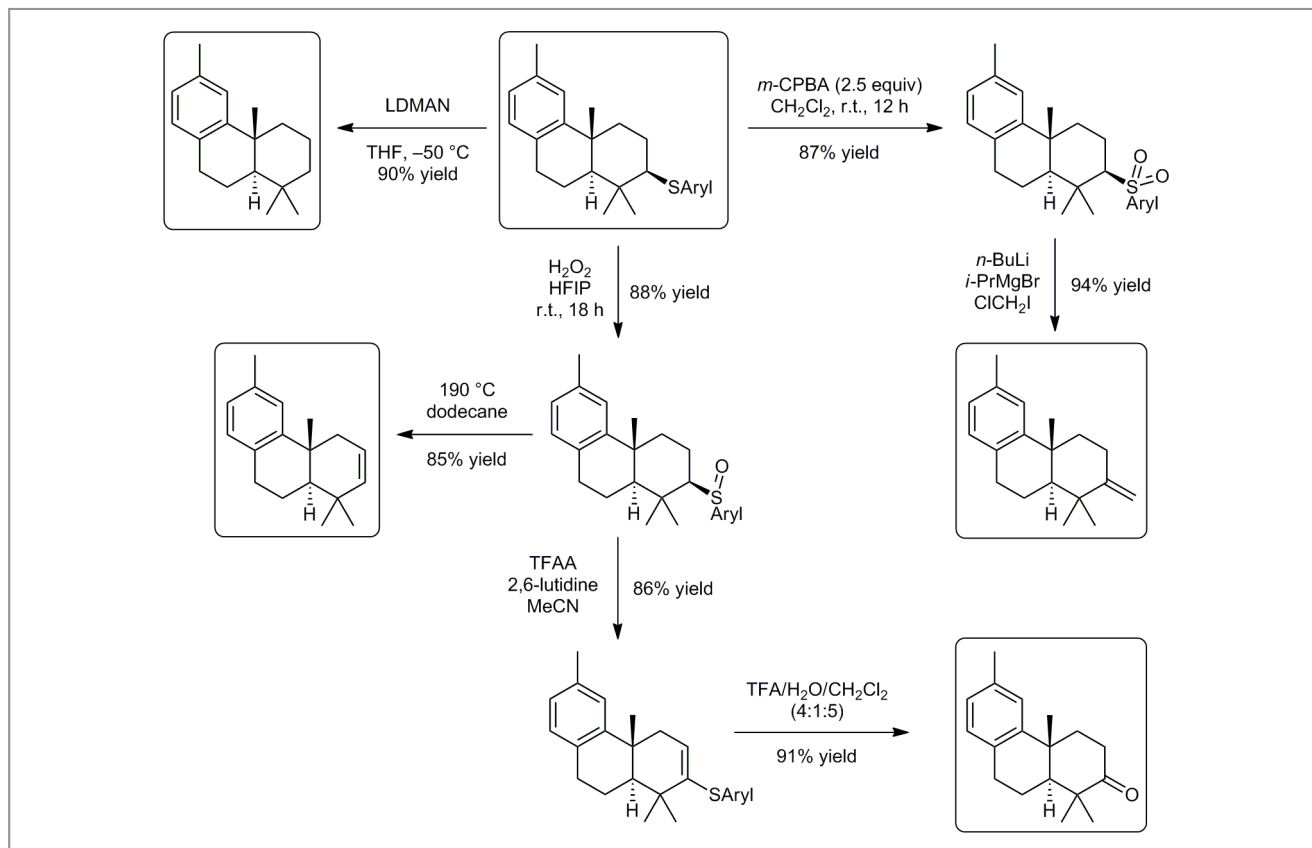
Professor Denmark revealed that initial attempts using established reaction conditions were uniformly unsuccessful owing to poor chemoselectivity. Inspired by the solvophobic effect, which assists protein folding *in vivo*, the researchers surveyed a variety of polar solvents to minimize the solvent-accessible surface area of the lipophilic polyene substrates. “We were delighted to find that hexafluoroisopropyl alcohol (HFIP) was an excellent solvent for the reaction, resulting in synthetically useful yields of the desired cyclization products,” said Professor Denmark. He speculated: “Presumably, the solvophobic effect favors a conformer of the substrate in which the distal olefin is more accessible than the internal olefin, thus improving chemoselectivity. Additionally,

Brønsted acid additives are no longer necessary because HFIP is sufficiently acidic to assist in formation of the catalytically active, cationic complex.”

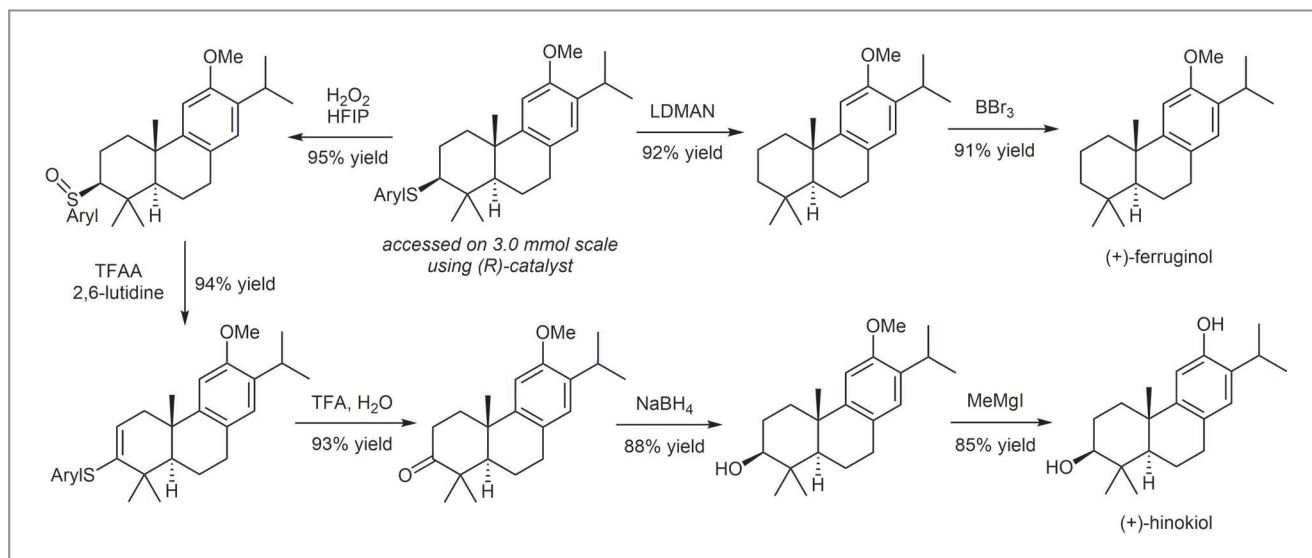
The final reaction conditions are extremely mild (Scheme 1), and the benefits include: (1) low catalyst loading (0.01 to 0.05 equiv), (2) high functional group tolerance, (3) rapid (<12 h) conversion at room temperature, (4) absence of harsh additives, and (5) no requirement for rigorous exclusion of air and water.

Professor Denmark explained: “Both homogeranylarenes and *ortho*-geranylphenols are viable substrates, delivering the cyclization products in high yields with high diastereo- and enantioselectivities. Additionally, the resulting thioether moiety in the cyclized products can be easily transformed into useful carbon and oxygen functionality (Scheme 2).”

To further demonstrate the utility of the sulfenocyclization reaction and subsequent sulfide derivatizations, two short total syntheses of (+)-ferruginol and (+)-hinokiol were easily accomplished (Scheme 3).



Scheme 2 Further derivatizations of a thioether product



Scheme 3 Total syntheses of (+)-ferruginol and (+)-hinokiol

Professor Denmark concluded: “Currently, the mechanism of the reaction is under study as is the extension of substrate scope to trienes and tetraenes, as well as the investigation of other terminating groups beyond arenes and phenols.”

Matthew Farnick

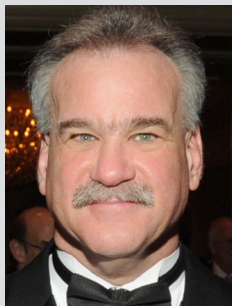
About the authors

Zhonglin Tao was born in China in 1989. He obtained his BS and PhD degrees from the University of Science and Technology of China (P. R. of China). In the last year of his undergraduate studies, he joined Professor Liu-Zhu Gong's laboratories to begin his studies in asymmetric catalysis. He completed his PhD in the same group focusing on palladium-catalyzed allylation reactions. Thereafter, he joined Professor Scott Denmark's laboratories at the University of Illinois (USA) as a postdoctoral research associate focusing on Lewis base catalyzed reactions.

Kevin A. Robb is a native of Missouri (USA). He received his BS in chemistry from Truman State University (USA) in 2013. The same year, he enrolled in graduate studies at the University of Illinois at Urbana-Champaign (USA), where he joined the research group of Professor Scott Denmark. He is currently a fifth-year PhD student.

Kuo Zhao was an undergraduate researcher in the Denmark laboratories from 2014 to 2017, and he received his BS in chemistry from the University of Illinois at Urbana-Champaign (USA) in 2017. He is currently a first-year graduate student at Princeton University in the group of Professor Rob Knowles.

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Prof. S. E. Denmark

Scott E. Denmark was born in Lynbrook, New York (USA) in 1953. He obtained an S.B. degree from MIT (USA) in 1975 (working with Richard H. Holm and Daniel S. Kemp) and his D. Sc. Tech. (under the direction of Albert Eschenmoser) from the ETH Zürich (Switzerland) in 1980. That same year, he began his career at the University of Illinois at Urbana-Champaign (USA) where since 1991 he has been the Reynold C. Fuson

Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry, and the origin of stereocontrol in fundamental

carbon–carbon bond-forming processes. Professor Denmark is currently the Editor-in-Chief of *Organic Reactions* and edited Volume 85 of *Organic Syntheses*. He served for six years as an Associate Editor of *Organic Letters* and for nine years as Editor of *Topics in Stereochemistry*. He is a Fellow of the Royal Society of Chemistry, the American Chemical Society and the American Academy of Arts and Sciences.