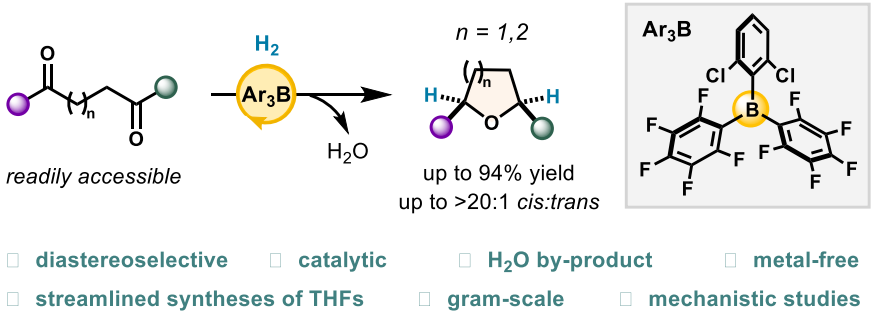
Diastereoselective Synthesis of *cis*-Substituted Cyclic Ethers via Borane-catalyzed Reductive Cyclization of Diketones

N. V. Shcherbakov[1], N. Potin[1], J. Mas-Roselló[1]*

[1]Laboratorium für Organische Chemie, D-CHAB, ETH Zürich,
Vladimir-Prelog-Weg 1-5/10, Zürich, 8093, Switzerland
nikolai.shcherbakov@org.chem.ethz.ch

Cyclic ethers, particularly α,α'-disubstituted tetrahydrofurans (THFs) and tetrahydropyrans (THPs), are prevalent motifs in natural products and pharmaceuticals.[1] However, efficient catalytic stereoselective methods for their synthesis are limited, often requiring precious transition-metal catalysts[2] or pre-functionalized substrates.[3] Herein, we report a direct metal-free catalytic approach to *cis*-2,5- and *cis*-2,6-disubstituted THFs and THPs via reductive cycloetherification of readily available 1,4- and 1,5-diketones.[4]



This transformation is enabled by a simple triarylborane catalyst and employs molecular hydrogen as the reductant, producing water as the sole byproduct. A broad range of products was obtained in high yields (up to 94%) and with high *cis*-selectivity (up to >20:1 dr). The method enabled streamlined access to medicinally relevant scaffolds and was scalable to gram quantities. Mechanistic studies support oxocarbenium ion reduction as the stereodetermining step, while DFT calculations suggest that weak, non-covalent interactions between the catalyst and substrate may contribute to the observed diastereoselectivity. This work introduces a tandem hydrogenation/cyclization strategy enabled uniquely by a standalone metal-free catalyst, offering a blueprint for sustainable hydrogenative syntheses of stereodefined heterocycles.

[1] Q. Lu, D. S. Harmalkar, Y. Choi, K. Lee, *Molecules*, **2019**, *24*, 3778–3799.
[2] J. Wysocki, N. Ortega, F. Glorius, *Angewandte Chemie International Edition*, **2014**, *53*, 8751–8755.
[3] F. de Nanteuil, E. Serrano, D. Perrotta, J. Waser, *Journal of the American Chemical Society*, **2014**, *136*, 6239–6242.
[4] N. V. Shcherbakov, N. Potin, J. Mas-Roselló, **2025**, DOI: 10.26434/chemrxiv-2025-sx0m4, under review.