ADVANCEMENTS IN Z-SELECTIVE OLEFIN CROSS-METATHESIS

Brenna Budaitis   April 6th, 2020

BACKGROUND

The stereoselective formation of C-C double bonds is an important transformation to access complex molecules. A key challenge, however, is accessing kinetic *Z*-olefin products with high efficiency and selectivity. Traditional methods rely on substrate-controlled Wittig, Stork-Zhao, and Horner-Wadsworth-Emmons reactions, in which high selectivities are limited due to use of unstable aldehydes under basic, cryogenic conditions. Lindlar hydrogenations of alkynes also provide *Z*-olefins, but alkyne preparations are limited, and controlled reductions and isomer purifications are challenging.[1]

Cross Metathesis (CM) reactions allows a means to rearrange the C-atoms of two olefins to generate two new olefins, utilizing readily accessible, inert alkenes. In contrast to prior methods, CM provides a route to access *Z*-selectivity via *catalyst-control*.[1] Challenges of this method, however, reside in (1) the preference in forming the thermodynamic E-alkene, and (2) the ability of multi-product formation due the reversibility of the mechanistic cycle.[1] The first *Z*-Selective Mo and Ru catalysts were

Figure 1. First Z-Selective CM Catalysts
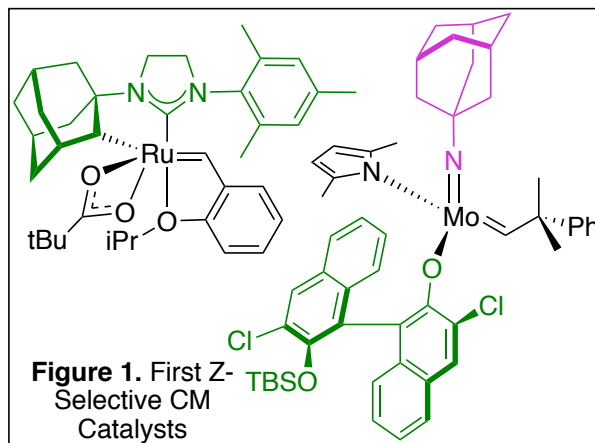
developed by the Hoveyda and Grubbs Groups respectively, in which ligand steric modification resulted in the preference of a cis-substituted metallacyclobutane intermediate followed by elimination to obtain the *Z*-alkene product.[1c] Current advancements show CM as an efficient method to improve *Z*-selectivities and to access previously inaccessible olefins.

EXPANDING Z-SELECTIVE FUNCTIONALITY.

The Grubbs Group exploited the chemoselective **Ru-cat. 1**[2] as a powerful platform to access

Scheme 1. Z-Selective Ru-Catalyzed CM of 3*E-1,3-dienes.*
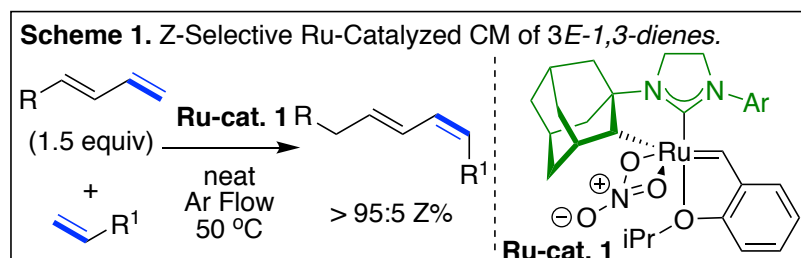
conjugated *E,Z*-dienes (>95% *Z*), demonstrating functional group tolerance proximal to the reactive site and the synthesis of insect pheromones. Modest diene excess further highlights the selectivity for CM over homodimerization. The minimal diene scope, however, limits the utility of the method toward complex natural product synthesis containing *E,Z*-diene motifs. The Hoveyda Group developed Ru-thiolate catalysts, expanding functional group tolerance in *Z*-selective CM. Using **Ru-cat 2.**, they report the first kinetically controlled CM to afford *Z*-trisubstituted allylic alcohols/ethers (>98:2

Z:E), exploiting the first example of carboxylic acid tolerance.[3] The constraint of using a methyl group demonstrates the difficulty of accessing tri-substitution in CM due to metallacyclobutane steric restrictions, and the necessity for allylic

Scheme 2. Synthesis of *Z*-Trisubstituted Allylic Alcohols/Ethers
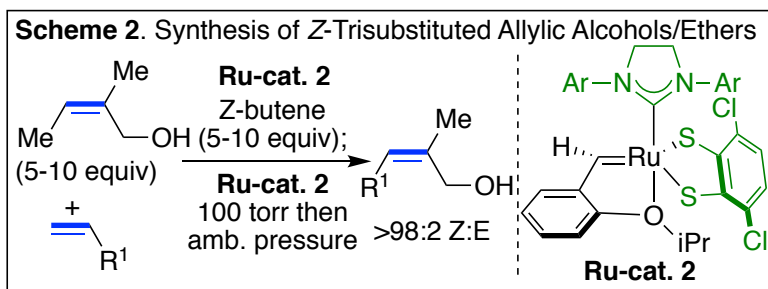
alcohols/esters toward reactivity underlines the need for catalyst development to expand reaction profile.

ACCESSING *Z*-SELECTIVE OLEFIN BUILDING BLOCKS.

Alkenyl halides are building blocks for key transformations, such as cross coupling reactions in which the selectivity is controlled by the starting *E/Z* alkenyl-halide. The Hoveyda Group utilize high-oxidation state **Mo-cat. 1** toward the preparation of Z-alkenyl halides (Br, Cl, F; up to >98:2 *Z:E*) using CM.[4] This method's utility was demonstrated toward complex molecule synthesis via cross coupling reactions and highlights the accessibility of *Z*-alkenyl-fluorides at late stage diversification, which is limited using prior methods. The

Figure 2. Mo-cat 1.
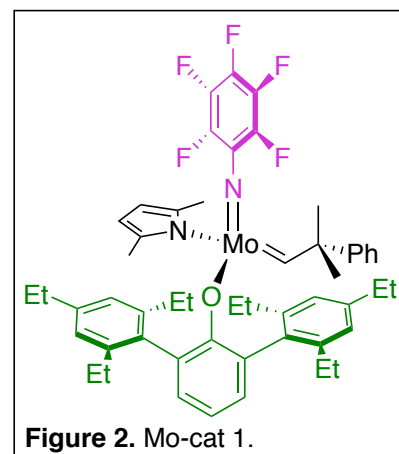
Hoveyda group further expanded Mo-catalysis toward the CM construction of *Z*-alkenyl nitriles (up to >98:2 *Z:E*), using equimolar amounts of each olefin.[5] This method accesses styrene substrates and showcases the tolerance of carboxylic acids via an in-situ protection. Trisubstituted *Z*-alkenyl nitriles show limited scope and selectivities, resulting in the synthesis of the *E*-alkenyl nitriles first, followed by a Heck reaction to access trisubstituted *Z*-alkenyl nitriles for complex molecule examples.

FUTURE DIRECTIONS

Z-selective CM is a newly developing field, providing as a complementary approach to access high selectivities, now via catalyst control. Further catalyst design to increase functional group tolerance proximal to the reactive site, and to address steric restrictions in expanding *Z*-trisubstituted alkene profiles and accessing *Z*-tetrasubstituted olefins, would be a significant advancement for future CM studies.

REFERENCES.

1. (a) Gottumukkala, A.L. et al. *ChemCatChem* **2012**, *4*, 462. (b) Hoveyda, A. et al. *Nature* **2007,** *450*, 243. (c) Shahane, S. et al. *ChemCatChem* **2013,** *5*, 3436.
2. Luo, S.X. et al. *J. Am. Chem. Soc.* **2016**, *138*(42), 14039.
3. Xu, C. et al. *J. Am. Chem. Soc.* **2017**, *139*(44), 15640.
4. Koh, M.J. et al. *Nature* **2016**, *531*, 459.
5. Mu, Y. et al. *Nat. Chem.* **2019**, *11*, 478.