

Catalyst for rapid and selective alkene isomerization

Background

Alkenes are fundamental chemical feedstocks used on massive industrial scales. The alkene functional group is crucial to fine chemical synthesis, including multistep natural product synthesis. While the existing alkene isomerization catalysts selectively make and react with trans-alkenes from terminal alkenes, they struggle to kinetically control the positional as well as geometric E/Z isomerism. Catalysts that can exhibit regio- and/or stereoselectivity for substrates and control the formation and chemistry of alkenes will be useful for the making of pharmaceuticals or other high value compounds.

For natural oils containing more than one carbon-to-carbon double bond, the double bonds are generally separated by a methylene group, commonly referred to as being "methylene interrupted." This limits their capability for industrial applications, including polymerization (e.g., for use as coatings, adhesives, etc.). For these fats and oils to be used industrially, they need to polymerize rapidly, and for this to occur, it is advantageous to have the double bonds adjacent to one another or "conjugated", i.e., the methylene interrupt to be shifted or relocated. Also, conjugated isomers of certain compounds (such as linoleic acid, which has two methylene interrupted double bonds) may have beneficial effects on health.

The problem

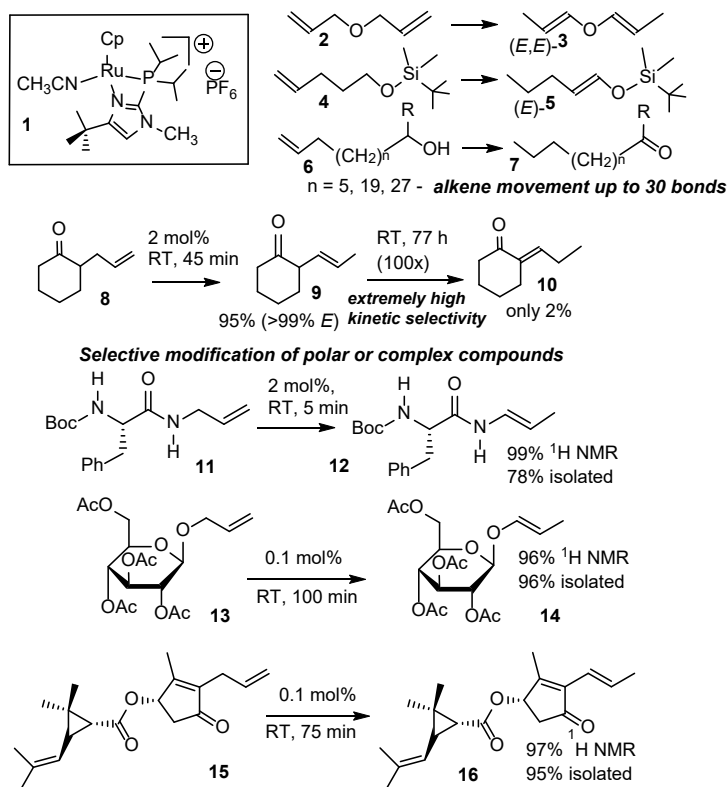
Although many transition metal complexes can catalyze alkene isomerization reactions, few have the ability to select for the position and geometry of the double bond formed in the product. For many alkene substrates, isomerization under thermodynamic control creates mixtures of products, the separation of which is difficult. The lack of selectivity has hindered the use of isomerization as a practical method for the synthesis of olefins.

SDSU Solution

Dr. Douglas Grotjahn has patented bifunctional alkene isomerization catalysts that can isomerize alkenes with unprecedentedly high selectivity for forming (*E*)-internal alkenes from terminal alkenes, and for acting on internal (*E*)-alkenes to make new isomers, such as conjugate natural oils and fats either in acid or ester forms. The flagship catalyst (**Scheme 1**) is the CpRu complex **Ru(acn)** [Ru^{II}(η⁵-C₅H₅) (κ²-PN) (CH₃CN)]⁺[PF₆]⁻; PN = (1-methyl-4-tertbutylimidazol-2-yl)-di-iso-propylphosphine], which stands out among transition metal complexes because of its high kinetic (*E*)-selectivity and fast reactions for isomerization of many olefins, particularly unhindered chains.

Scheme 1 shows the ability of **1** to move an alkene over 30 positions, as well as its superbly selective transformation of complex and / or polar alkene substrates. Free alcohols, amide NH groups, hindered alkenes, and even a tert-butyl thioether and carboxylic acid are all tolerated. Furthermore, incorporation of deuterium can be accomplished by adding D₂O during the isomerization process.

Scheme 1. Capabilities of 1 in selective isomerization



In a 2020 disclosure, using new time- and temperature-dependent kinetic studies based on NMR spectroscopic data with a new set of density functional theory (DFT) calculations of the butene isomerization mechanism, the team has identified the likeliest pathway from but-1-ene (**1**) to 2E, the isomer (*E*)-but-2-ene, and from **1** to (*Z*)-but-2-ene **2Z**. The initial catalyst–substrate complex Ru(**1**) discriminates against the pathway that would lead to the formation of **2Z**, suggesting a conformational justification for the strong (*E*)-selectivity.

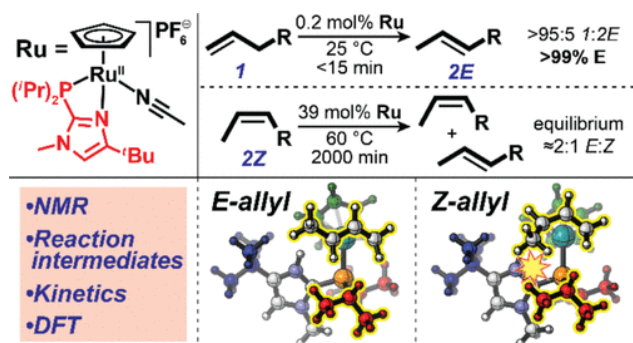


Figure 1. Structure of the alkene isomerization catalyst (**Ru(acn)**) and summary of its reactivity with terminal alkenes. R=aryl, allyl, OH, COOH, amide, S'-BU.

DFT calculations of the butene isomerization mechanism considered several pathways (**Figure 2**) among which the binding of the butene to the catalyst in an exo-orientation is predicted to be the initial step of the preferred pathway for forming but-2-ene, the *E* isomer favored over the *Z* by virtue of lower steric interactions while bound to the catalyst. Isomerization of **1** to **2E** using **Ru(acn)** was sufficiently fast in that data were obtained using only 0.2 mol % **Ru(acn)** and temperatures well below ambient ones, in the range of 253 to 283 K, using NMR spectroscopy (**Figure 3 A, B; Figure 4**).

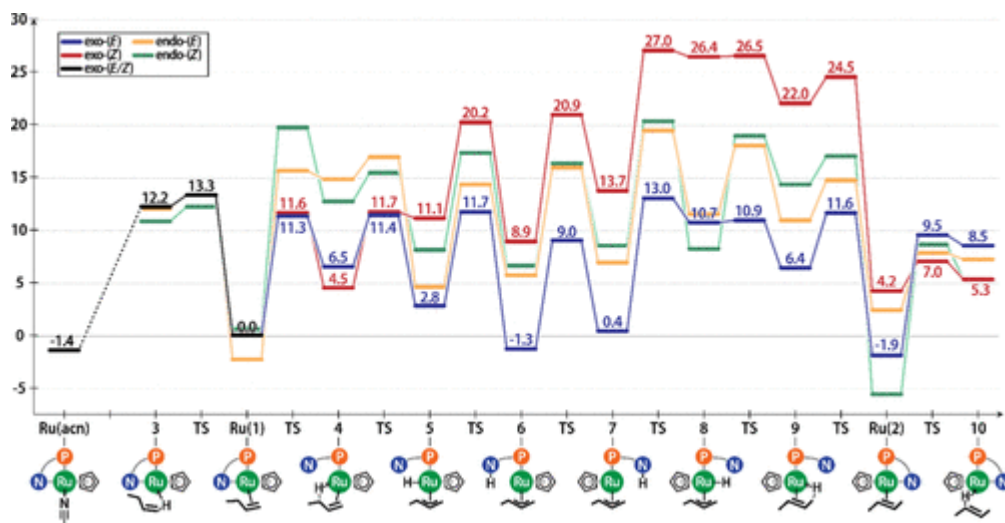


Figure 2. Four pathways that differ in relative stereochemistry between the prochiral alkene and prochiral metal fragment Ru. The lowest-energy pathway is exo-(E). Although individual forward reaction steps for the exo-(Z) pathway appear surmountable, the exo-(E) pathway is uniformly more favorable. Correspondingly, low barriers for the reverse reaction steps of the exo-(Z) pathway also contribute to strong kinetic bias toward the 1 → 2E over the 1 → 2Z reaction. Therefore, the computational model reproduces the experimentally observed (E)-selectivity.

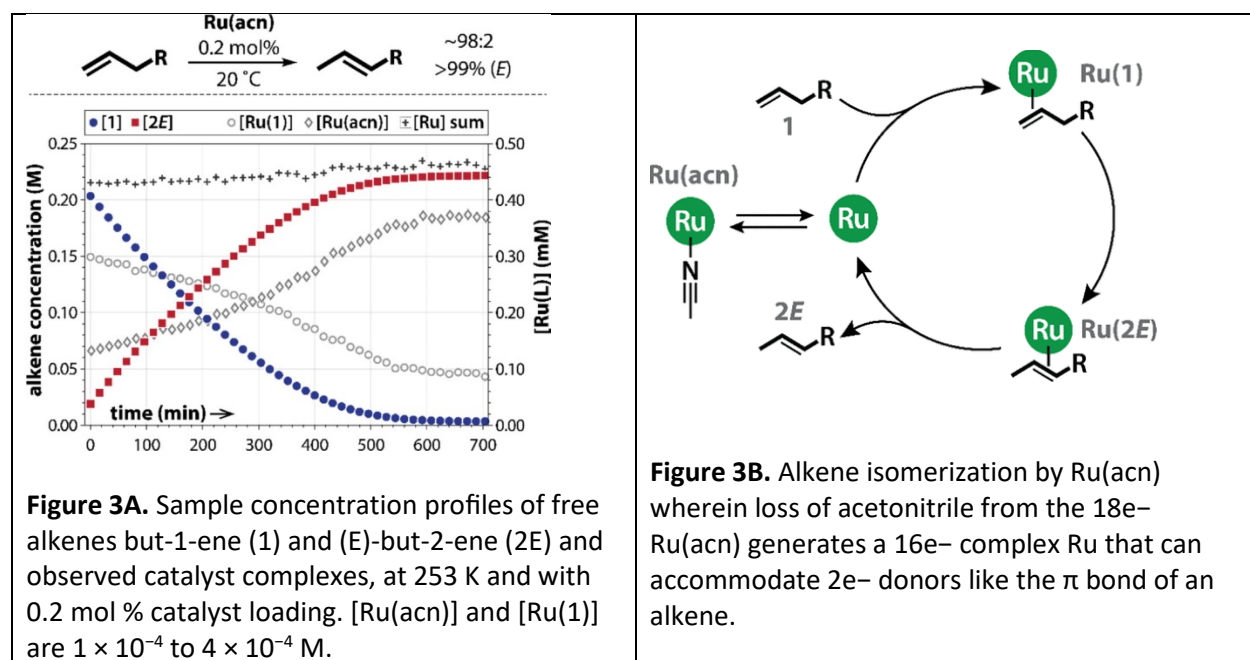


Figure 3A. Sample concentration profiles of free alkenes but-1-ene (1) and (E)-but-2-ene (2E) and observed catalyst complexes, at 253 K and with 0.2 mol % catalyst loading. [Ru(acn)] and [Ru(1)] are 1×10^{-4} to 4×10^{-4} M.

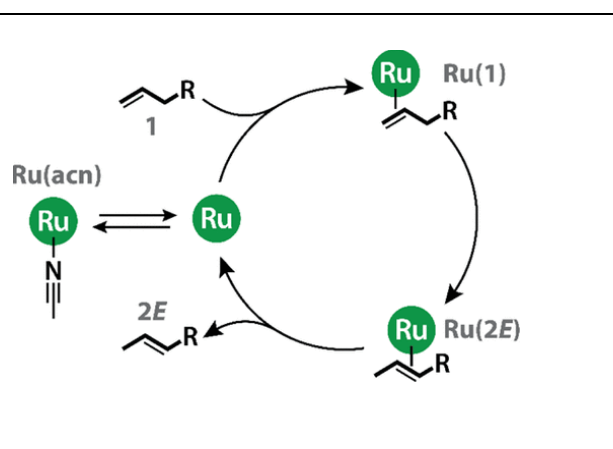


Figure 3B. Alkene isomerization by Ru(acn) wherein loss of acetonitrile from the 18e- Ru(acn) generates a 16e- complex Ru that can accommodate 2e- donors like the π bond of an alkene.

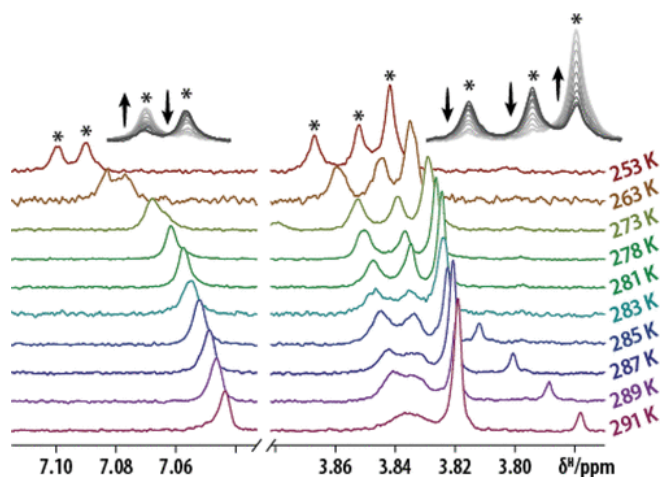


Figure 4. Evidence for alkene complexes in the time–concentration profiles of Ru(acn) and Ru(1). Peaks assigned to the sp³ N–CH₃ of Ru(1) and Ru(acn) complexes could be resolved and mimic changes in the concentrations of 1 and 2E, respectively, in the bulk solution. Black traces at top: Time-dependence of assigned Ru(acn) and Ru(1) NMR signals (*). Colored traces: Temperature dependence of N–CH₃ and ligand aromatic C–H signals (*) at early reaction times when the amount of 1 is maximal.

Advantages

Dr. Grotjahn and team have reported for the first time, a comprehensive experimental and theoretical study of butene isomerization by Ru(acn), as a model for isomerizations of other 1-alkenes to (*E*)-alk-2-enes. Their computational model shows that starting from 1 and Ru(acn), the initial catalyst–substrate complex Ru(1) discriminates against the pathway that would lead to the formation of 2Z, suggesting a conformational justification for the strong (*E*)-selectivity. There are several compositions and methods for harnessing the ability of a transition metal to migrate a double bond along a hydrocarbon chain. It is typically the group 8, 9 and 10 transition metals that are employed for this transformation, including a variety of ruthenium derivatives. **The advantages of Dr. Grotjahn’s catalysts include:**

- Combined action of the transition metal (ruthenium) and the bases or acids in the same molecule providing uniquely powerful and efficient capability for moving double bonds in organic molecules.
- Suitability for derivatives with more than one carbon-to-carbon double bond separated by, e.g., a methylene, ethylene or propylene or longer group
- Isomerization/conjugation of compounds either in acid or in ester form (e.g., as methyl esters), either exclusively or primarily to mixtures of the conjugated isomers
- Extremely specific conversion without affecting monounsaturated derivatives

Applications

- Products of manufacture, kits, and formulations, including liquid formulations and solid or semisolid (e.g., gel) supports and resins, e.g., ion exchange or any chromatography resin(s). Industrial polymerization applications such as coatings, adhesives - Generation of various oils with improved drying qualities and adhesives as bonding systems for wood and fiber products.
- Generation of conjugated linoleic acid (CLA) derivatives with anti-cancer properties, and as food additives
- Use of the fats and oils processed using the invention as feedstocks for other industrial products

Stage of Development

Catalyst engineering, characterization, and optimization completed

Intellectual Property

United States Patent US 8,501,032 B2 – “Catalysts for rapid and selective alkene isomerization and conjugation of double bonds in polyunsaturated fats and oils”

Key publications

- Cao TC, Cooksy AL, and Grotjahn DB, “Origins of High Kinetic (E)-Selectivity in Alkene Isomerization by a CpRu(PN) Catalyst: a Combined Experimental and Computational Approach,” *ACS Catal*, 2020, 10, 15250–15258 (<https://pubs.acs.org/doi/10.1021/acscatal.0c03497>)
- Paulson ER, Moore CE, Rheingold AL, Pullman DP, Sindewald RW, Cooksy AL and Grotjahn DB, “Dynamic π -Bonding of Imidazolyl Substituent in a Formally 16-electron Cp*Ru(κ^2 -P,N)+ Catalyst Allows Dramatic Rate Increases in (E)-Selective Monoisomerization of Alkenes,” *ACS Catal*, 2019, 9, 7217–7231.
- Grotjahn DB, Larsen, CR; Erdogan, G, “[Bifunctional Catalyst Control of Alkene Isomerization](#),” *Topics in Catalysis* 2014, 57, 1483-1489.

Contact information: Technology Transfer Office; San Diego State University Research Foundation

Douglas B. Grotjahn, Ph.D.
Principal Investigator and Professor
Organic, Organometallic, Bio-organometallic
Chemistry, Catalysis

Tommy Martindale
Director
(619) 594-0791
tmartindale@sdsu.edu