

Highlights of the Career of Robert G. Bergman

Vy M. Dong
MacMillan Group Meeting
May 17, 2002

Career Sketch of Robert G. Bergman

1963 B.S. Carleton College

1966 Ph.D. in Chemistry from University of Wisconsin, advisor: Jerome A. Berson

1966-67 Postdoctoral Fellow at Columbia University with Ronald Breslow

1968 to 1977 Professor, California Institute of Technology

1977 to present Professor, University of California, Berkeley



Trained as an organic chemist

Ventured into organometallic chemistry (1970's)

Synthesis and chemistry of several types of organotransition metal complexes and the understanding of their mechanisms

Selected Topics for Discussion from the Career of Bergman

I. Bergman Cyclization

- a. Significance in chemistry and biology

II. Activation of C-H Bonds

- a. Stoichiometric Reactions: Highlights on study of mechanism, kinetics and selectivity

III. Chemo- and enantioselective reactions of metal heteroatom bonds with organic molecules

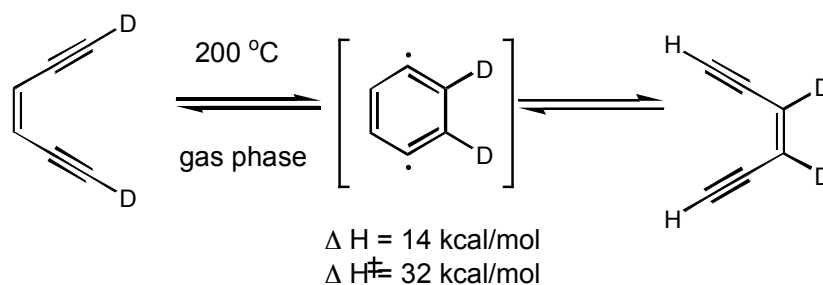
- a. Zirconocene Imido Complexes with Allenes: Study of selectivity and mechanism

I. The Bergman Cyclization

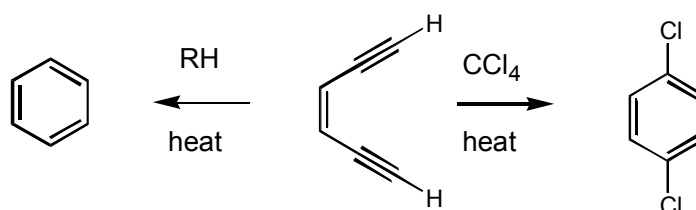
Bergman Cyclization

In the pursuit of physical organic chemistry and theoretically interesting molecules

Radical 1,4 dehydrobenzene: important molecule in field of reactive intermediates and aromaticity

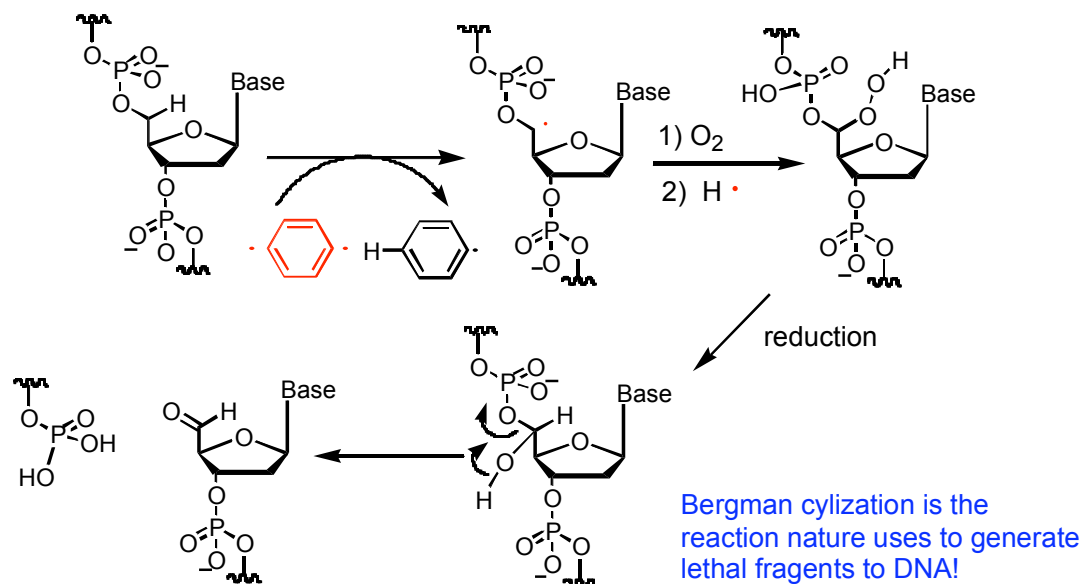


Evidence for the structure of the molecule

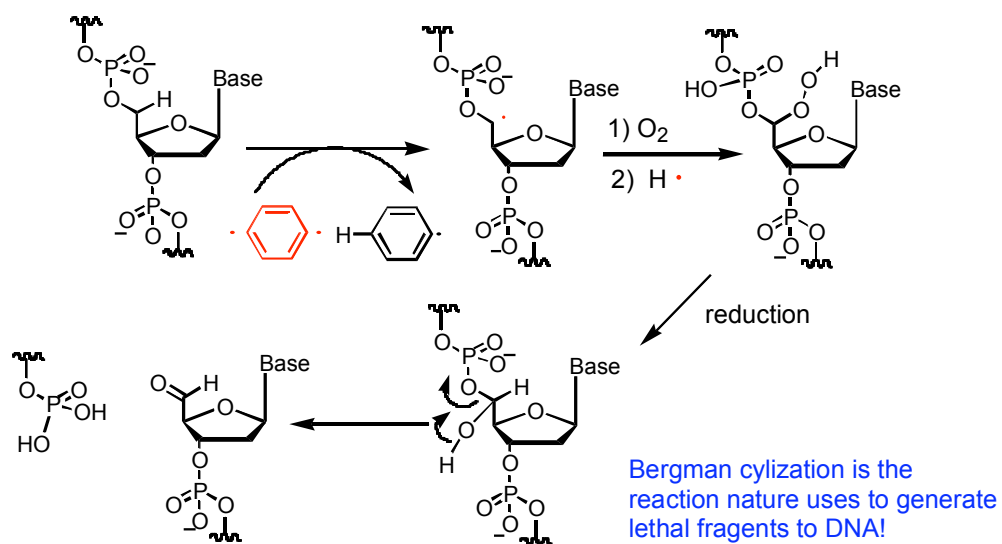


Bergman, R. G. *Acc. Chem. Res.* **1973**, 6, 25.

Bergman Cyclization and the Mechanism of DNA Damage



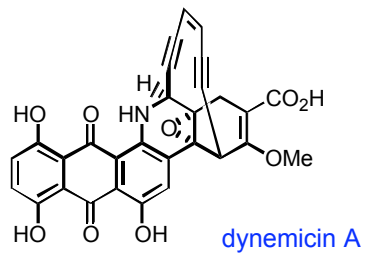
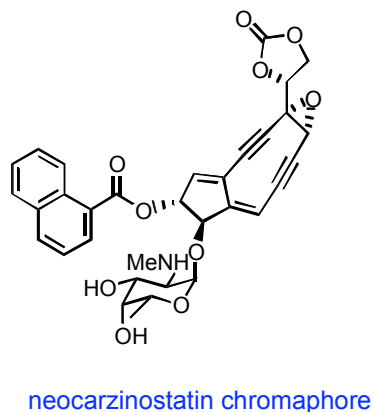
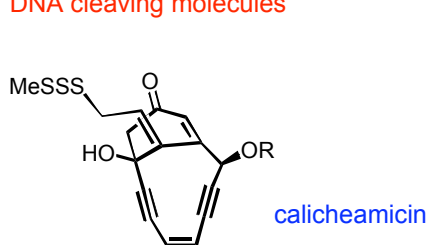
Bergman Cyclization and the Mechanism of DNA Damage



Nicolaou, K. C. *et al.* *ACIEE* **1991**, 30, 1387.

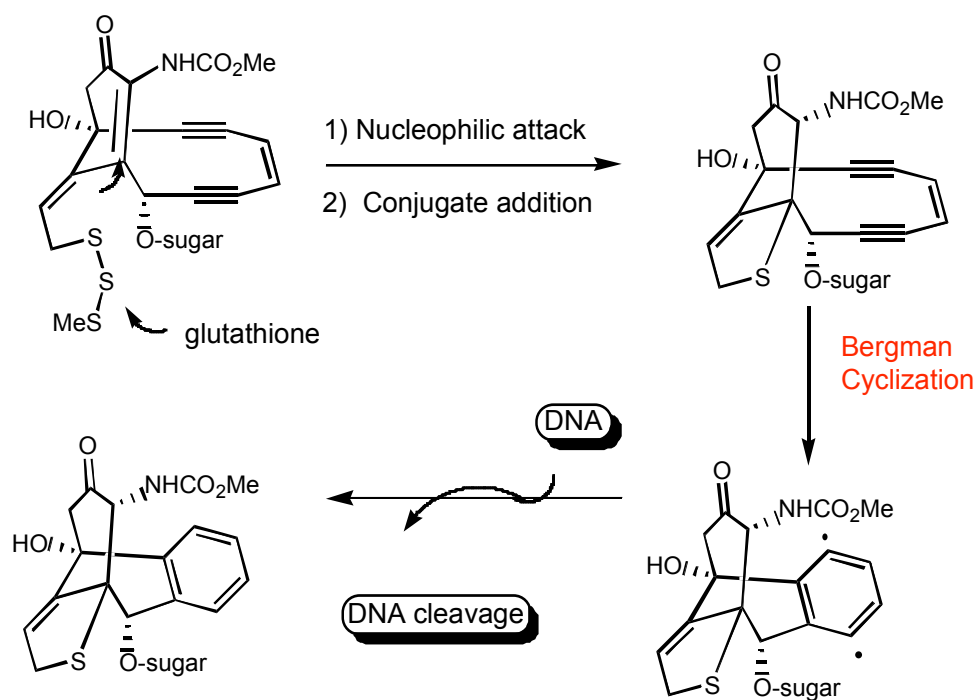
Structures of the Eneidyne Anticancer Antibiotics

DNA cleaving molecules



1980's: Attracted much attention due to their unique molecular structure and fascinating mode of action

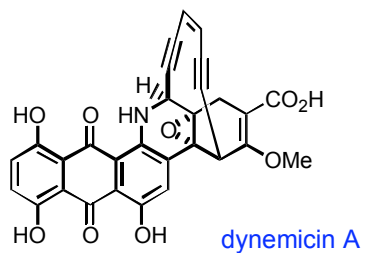
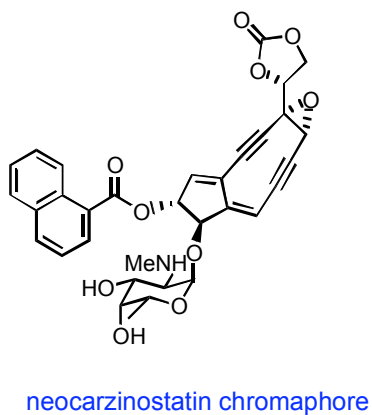
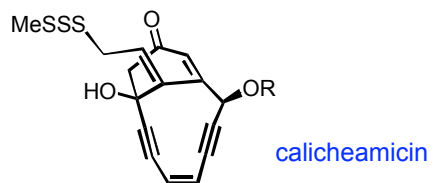
Calicheamicin's Mode of Action



II. The Activation of C-H Bonds of Hydrocarbons

Structures of the Eneidyne Anticancer Antibiotics

DNA cleaving molecules



1980's: Attracted much attention due to their unique molecular structure and fascinating mode of action

II. The Activation of C-H Bonds of Hydrocarbons

Selective Transformations of C-H Bonds of Alkanes

a "holy grail" in synthetic organic chemistry

Importance

most ubiquitous chemical linkage in nature
fundamental understanding of chemical reactivity
abundant and inexpensive

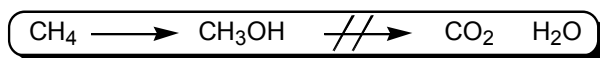
Challenges

lack of reactivity: C-H bond energy: 90-100 kcal/mol

C-H bond acidity: pKa = 45-60

free radical reaction, super acids (George Olah, Nobel prize)

lack of selectivity: ability to selectively attack one type of C-H bond over another
ability to convert the alkane into a functionalized product without having the product undergo an even faster reaction than the alkane



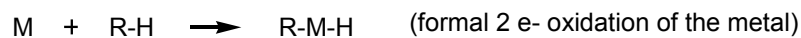
Intriguing Potential Solution

use of transition metal chemistry

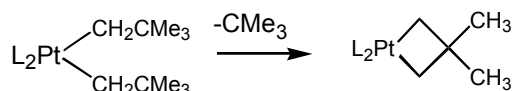
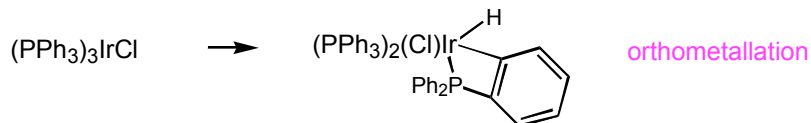
Arndtsen, B.A.; Bergman, R.G.; Mobley, T.A.; Peterson, T.H. *Acc. Chem. Res.* **1995**, 28, 154

Background on C-H Activation

Goal: A soluble complex capable of intermolecular oxidative addition



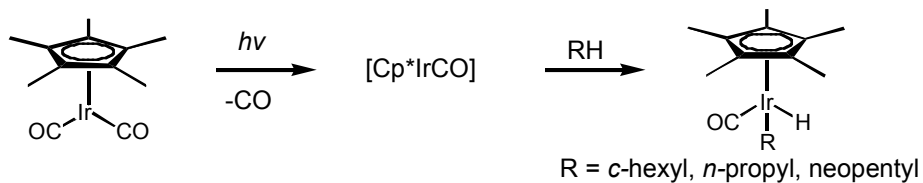
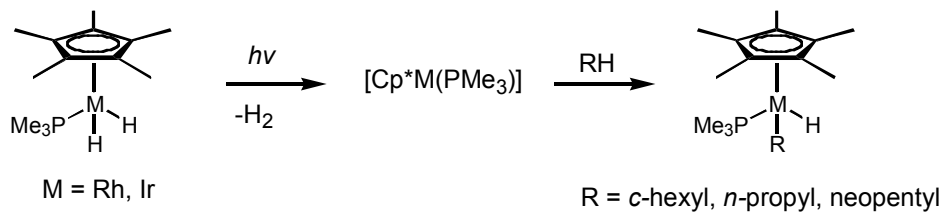
Many examples of intramolecular C-H oxidative addition were known for over a decade:



Bergman, R.G. *Science* **1984**, 223, 902

First Examples of Hydrocarbon Activation

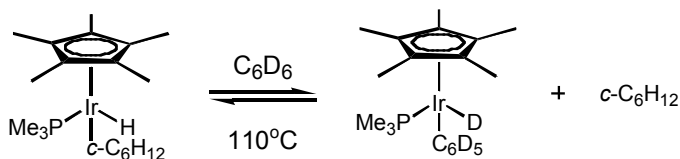
early 1980's by Bergman



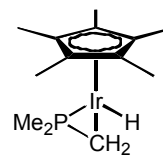
The 16-electron Cp*ML fragments believed to be responsible for hydrocarbon oxidative addition were not directly observable.

Janowicz, A.H.; Bergman R.G., *JACS*, **1982**, *104*, 352.

Mechanistic Studies



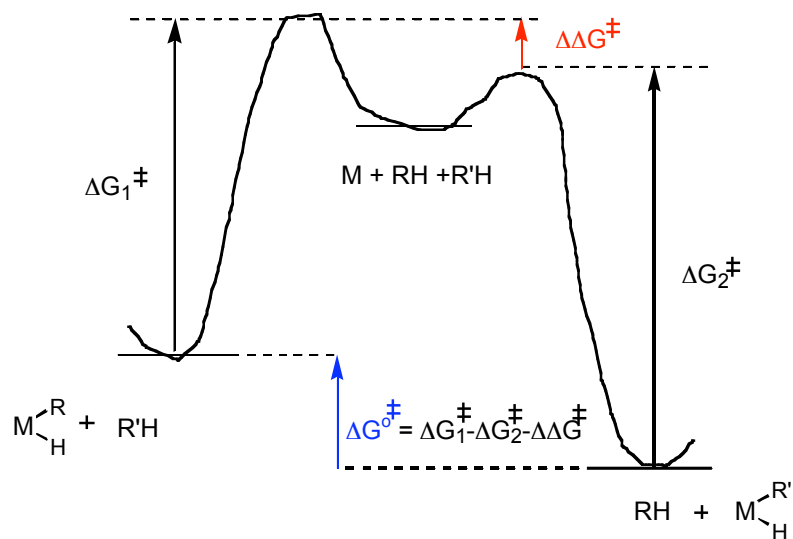
- thermally induced C-H activation
- first order in the loss of cyclohexane
- selective for intermolecular process



not observed

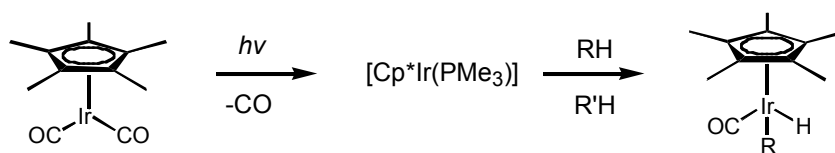
Selectivity in C-H Activation

Free Energy Diagram

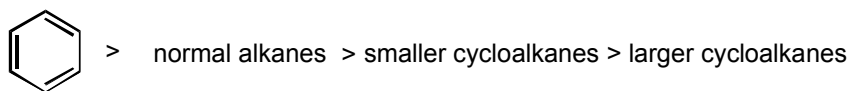


Kinetic Selectivity versus Thermodynamic selectivity

Relative Kinetic Selectivities For Different Types of C-H bonds



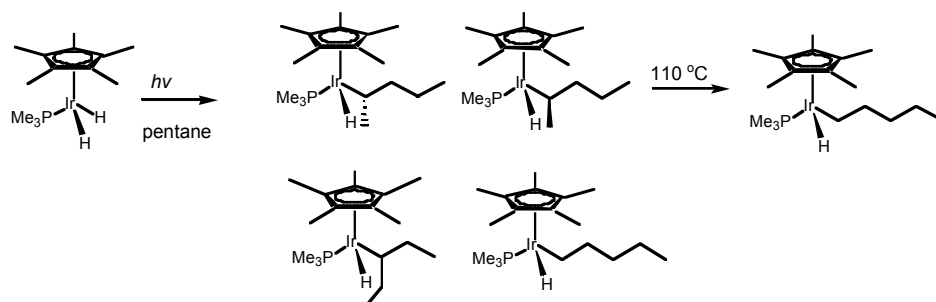
General trends observed:



This latter observation provided one of the strongest arguments against

primary C-H bonds > secondary C-H bonds > tertiary C-H bonds

Thermodynamic Selectivities Toward C-H Bond Activation



Strong preference for less hindered primary bonds over more hindered primary bonds and preference for primary over secondary bonds

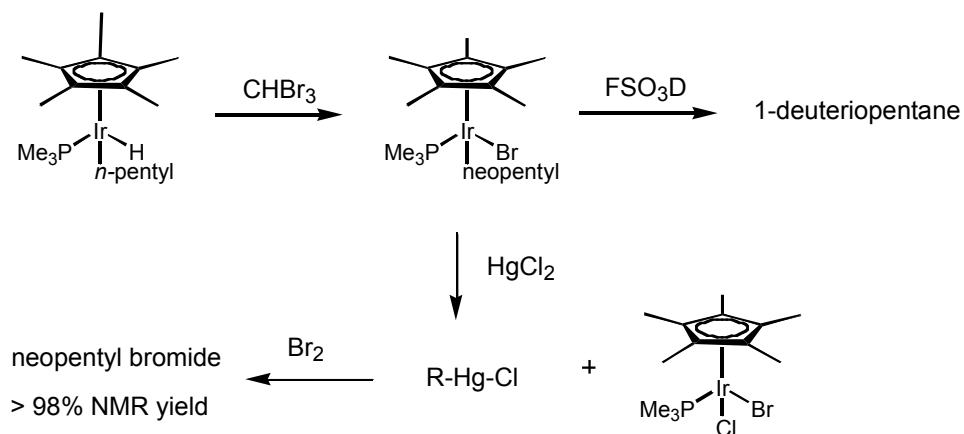
Suggests that a combination of photolysis followed by thermal equilibration will allow exclusive functionalization of primary linear alkanes

Wax, M.J.; Stryker, J.M.; Buchanan, J.M.; Kovac, C.A.; Bergman, R.G. *JACS*, **1984**, *106*, 1121

Functionalization of the Hydrido Alkyl Insertion Products

■ Treatment with reagents such as ZnBr_2 , H_2O_2 , Br_2 , HBF_4 or O_2 results in reductive elimination of RH .

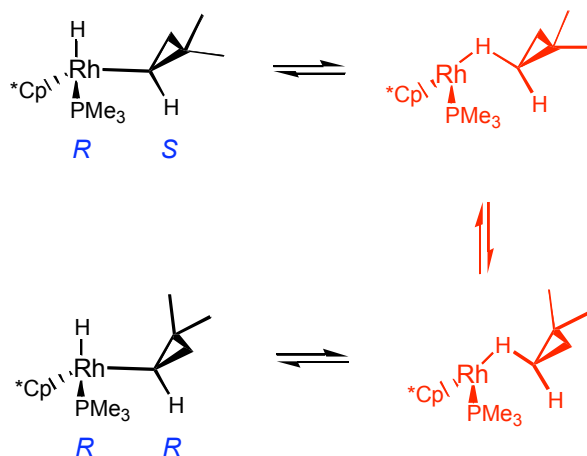
■ Solution was to replace the hydride ligand with bromide:



Janowicz, A.H.; Bergman, R.G. *JACS*, **1983**, *105*, 3929

Stereochemistry of Oxidative Addition of C-H Bonds

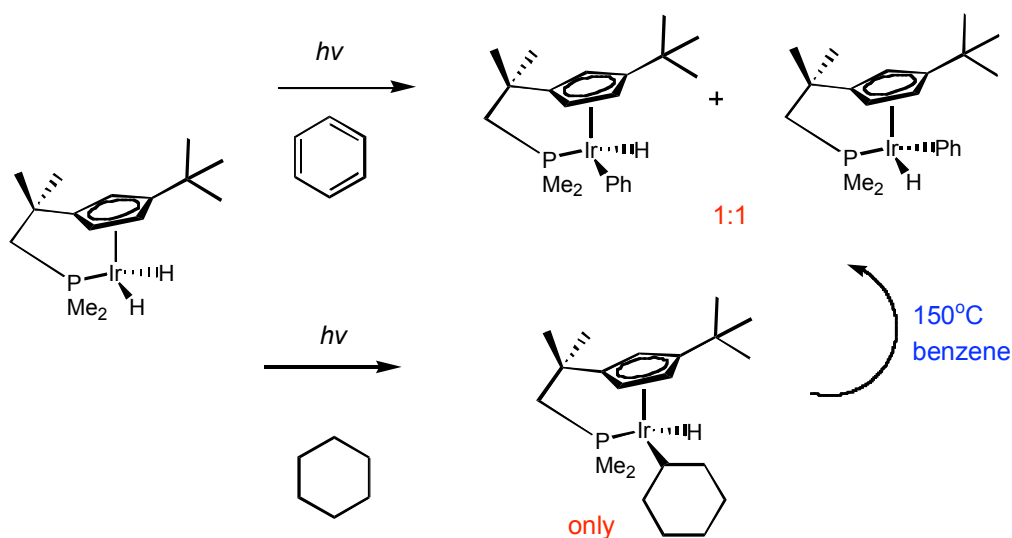
Examination of the rearrangement of a gem-dimethylcyclopropane adduct



Inversion of the carbon center was effected by way of isomerization to an **alkane sigma complex** which rearranged to a second complex before reinserting into the C-H bond

Mobley, T. A.; Bergman, R.G. *JACS*, **1995**, *117*, 7822

Recent Example of C-H Activation with Asymmetric Induction



Differences reflect kinetic selectivities due to the greater steric demands of the cyclohexane ring

Mobley, T.A.; Bergman, R.G. *JACS*, **1998**, *120*, 3253

Quest to Understand C-H Activation

Previous Studies:

spectroscopic techniques with microsecond time resolution required study in the gas phase, liquified noble gases or in low temperature matrices to slow down the reaction.

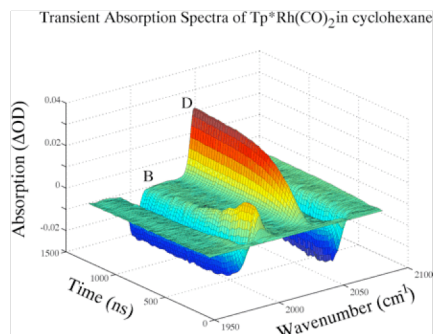
Bengali, A.A.; Moore, C.B.; Bergman, R.G. *Science* **1992**,255,315

In contrast to earlier work:

goal is to study the reaction under the most relevant conditions: rt in alkane solution

Technique:

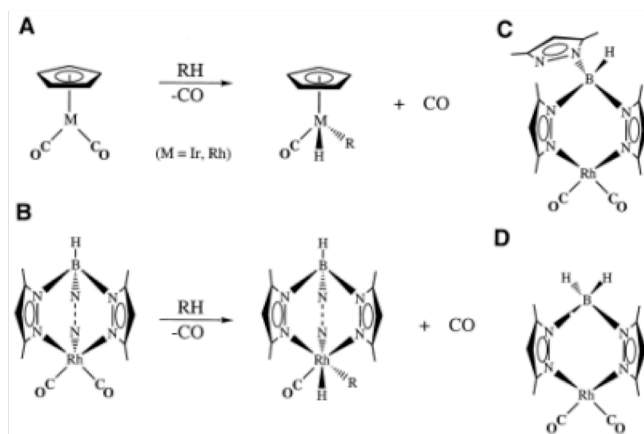
time resolved infrared experiments:
ultrafast spectroscopy with picosecond
and femtosecond time resolution
(faster time scales than diffusion)



Bergman, R.G. *et. al. Science*, **1997**, 278, 189

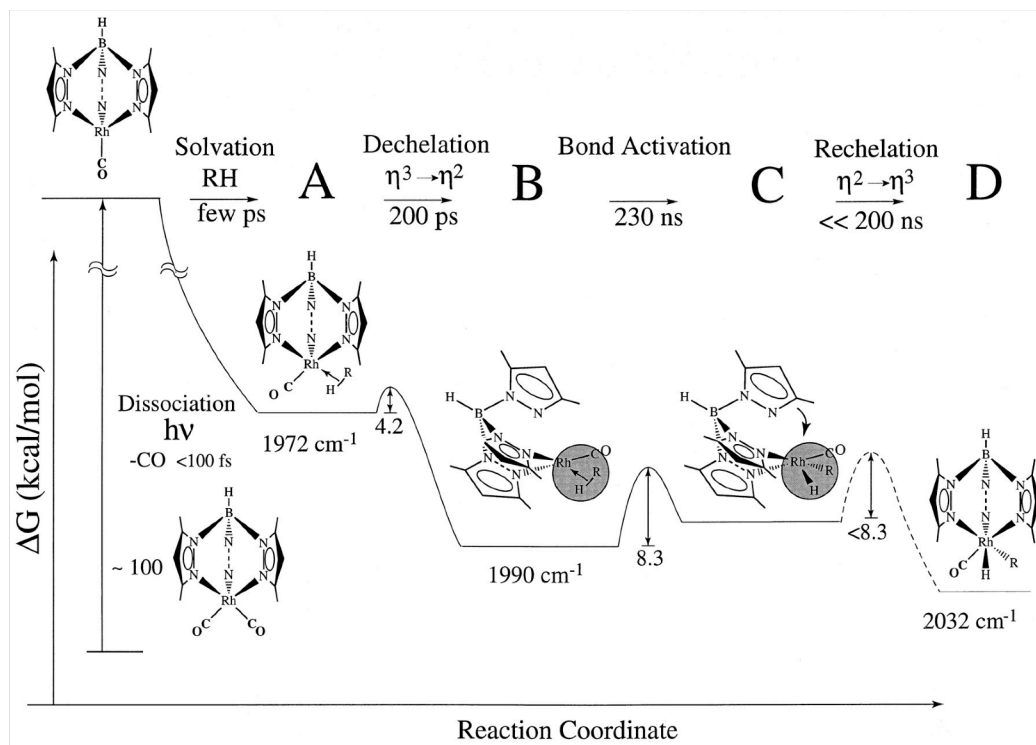
The C-H Activation Chosen For Study Based on Quantum Yield

Reaction A: Quantum yield (1%) for this widely studied reaction was too low to observe reactive intermediates.



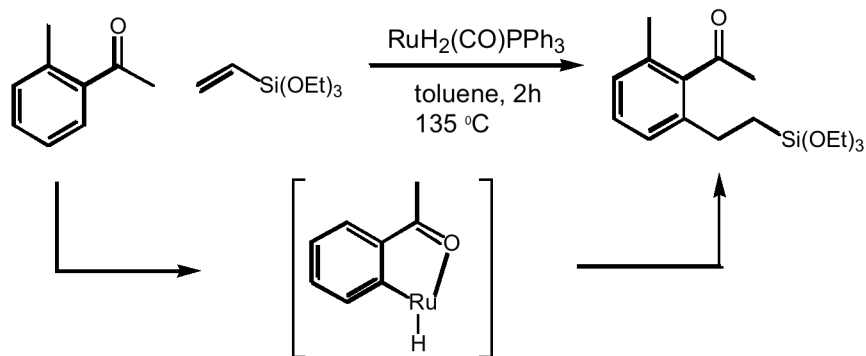
Reaction B: Larger quantum yield (30%) allows for the detection of intermediates.

Proposed Mechanism and Energy Diagram



Early Example of Synthetic Applications of Transition Metal-Mediated C-H Activation

Ruthenium-catalyzed *ortho* alkylation of aromatic ketones and alkenes

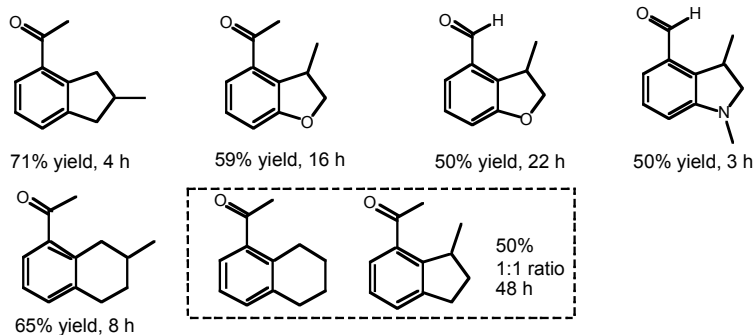
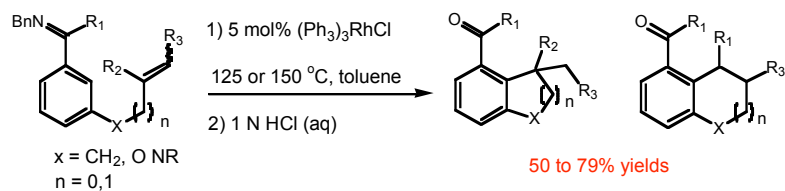


First example of a highly efficient and selective C-H/olefin coupling reaction

Functional group tolerant (NMe_2 , OMe , F , ETC(O)Me , CO_2Et , CN)

C-H bond cleavage is not rate determining

Annulation of Aromatic Imines via Directed C-H Activation



Thalji, R.K.; Ahrendt, R.G.; Bergman, R.G.; and Ellman, J.A. *JACS*, **2002**, 123,9692

Outlook on the Activation and Functionalization of C-H Bonds

In past decade, chemistry of the catalytic functionalization of CH bonds has rapidly expanded

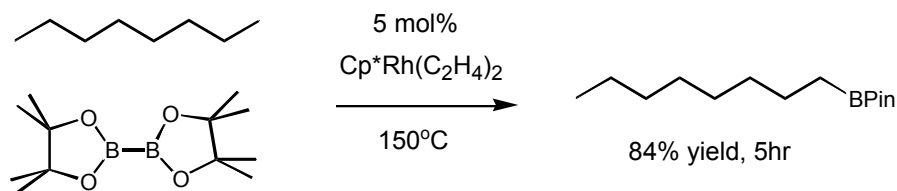
C-H/olefin, C-H/acetylene, C-H/CO/olefin couplings

Hydroacylations of olefins and acetylenes to provide ketones

Transition metal-catalyzed aldol and Michael addition reactions (enantioselective and diastereoselective).

Kakiuchi, F.; Murai, S. *Topics in Organometallic Chemistry* **1999**, 48

Regioselective and Catalytic Functionalization Achieved:

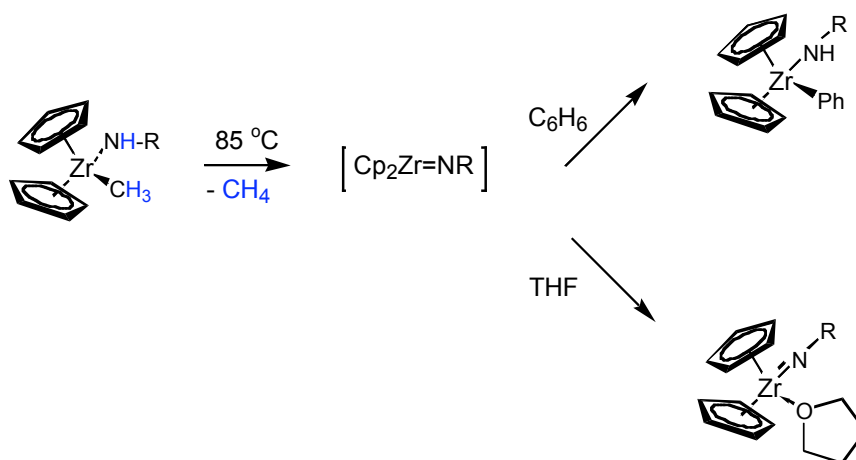


Hartwig, J.F. *et. al. Science*, **2000**, 1995

Field is still young and exciting new discoveries expected in the next decade

Addition of C-H Bonds Across M=X Bonds

Zirconium-nitrogen double bond



No reactions with alkanes have yet been reported

Walsh, P.J.; Hollander, F.J.; Bergman, R.G. *JACS*, **1988**, *110*, 8729

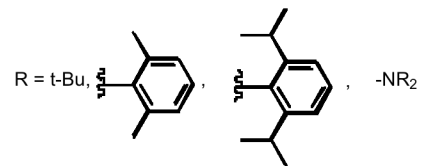
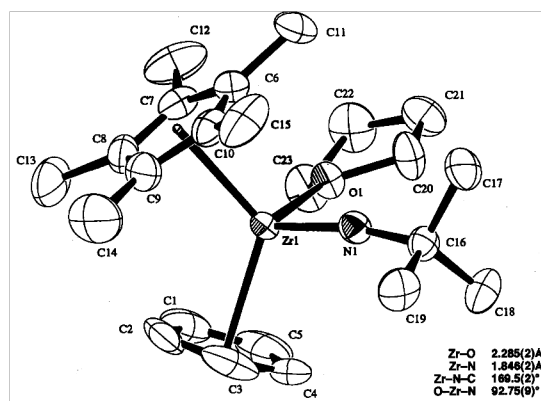
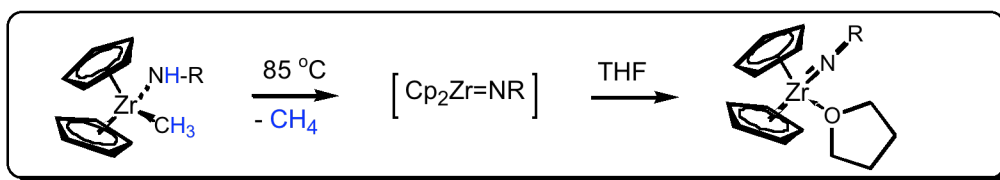
III. Chemistry of Zirconocene Imido Complexes

Organometallics **1993**, *12*, 3705

JACS **1998**, *110*, 8729

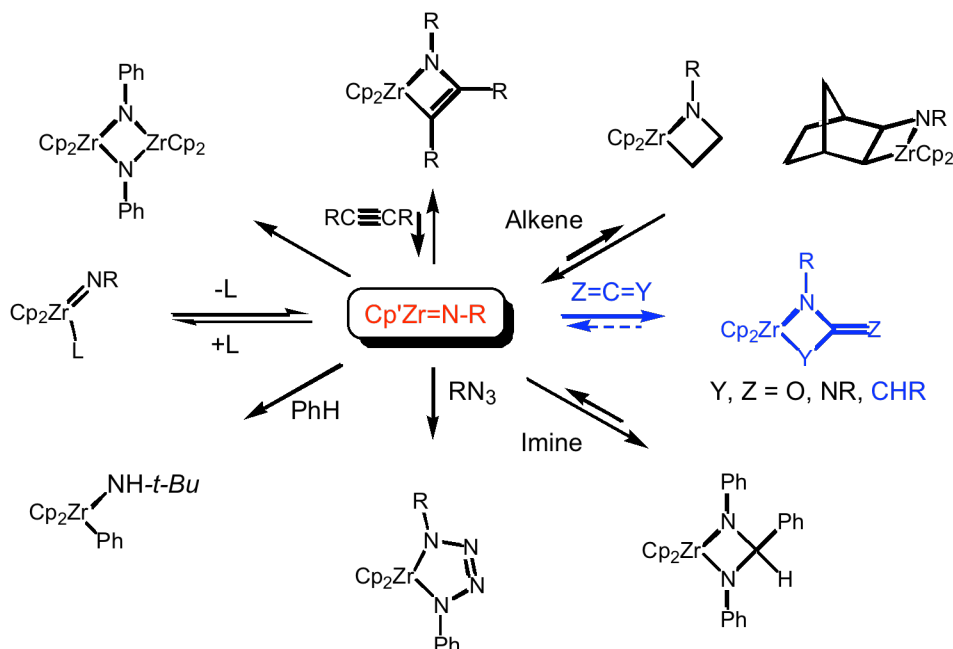
ACIEE **2000**, *39*, 233₉

Synthesis and Structure of Imidozirconocene Complex



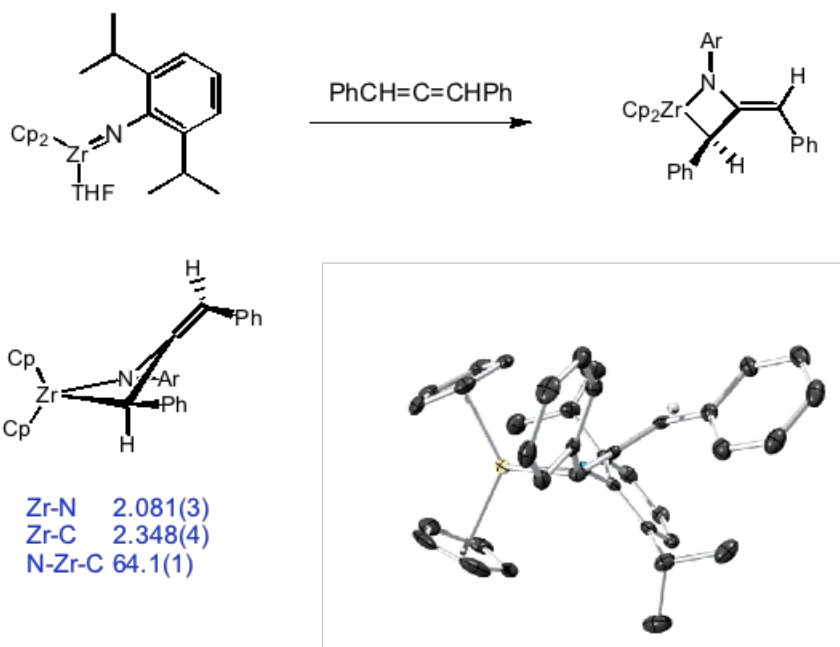
Zr-O 2.285(2) Å
 Zr-N 1.846(2) Å
 Zr-N-C 169.5(2) Å
 O-Zr-N 92.65(9) Å

Reactivity of Group (IV) Metallocene Imido Complexes



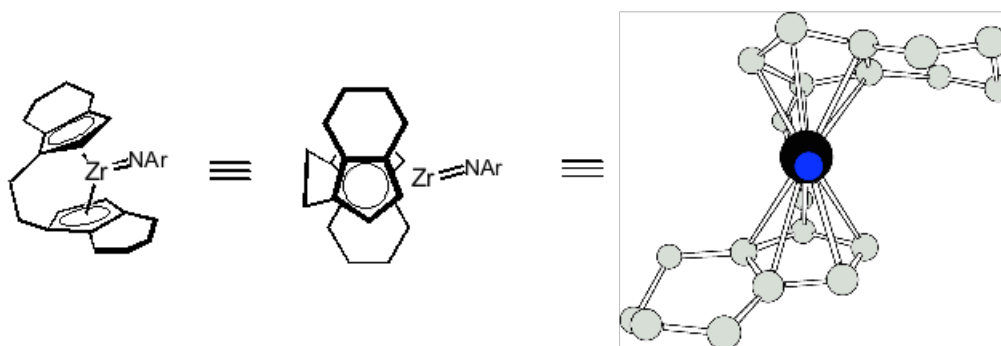
Regioselectivity of the Cycloaddition with 1,3-Diphenylallene

Formation of a Bent Metallacycle:



Ethylene-bis-tetrahydroindenyl (EBTHI) as a Chiral Ancillary Ligand

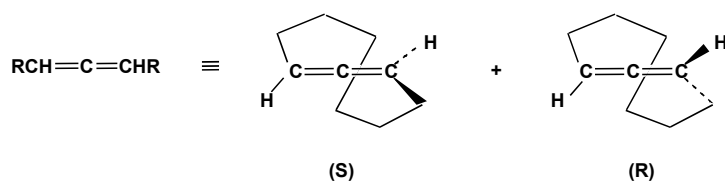
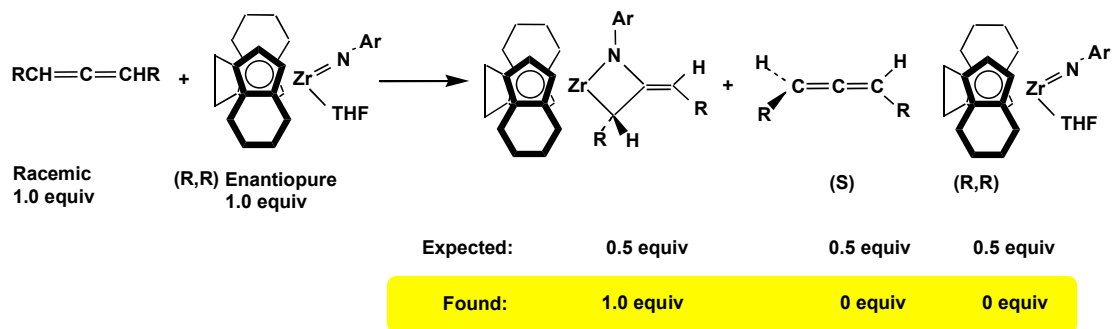
Used in catalytic carbomagnesations (Hoveyda), stoichiometric synthesis of amino acids, allylic amines (Buchwald, Norton)



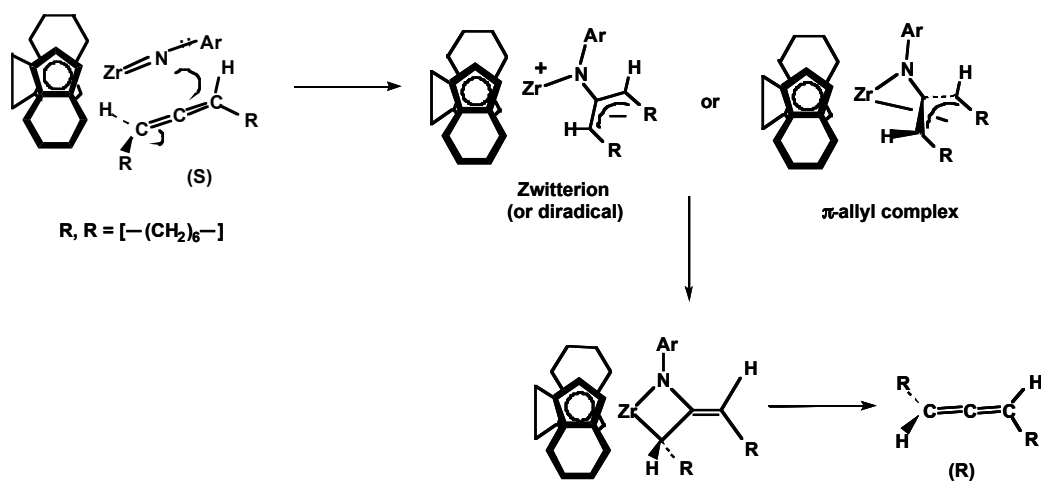
Approximate C₂ symmetry

side on attack controlled by the bulky cyclohexyl substituents
bulky imido substituent provides extra control element

Equimolar Reaction of Enantiopure Imido Complex with Racemic 1,2 Cyclononadiene



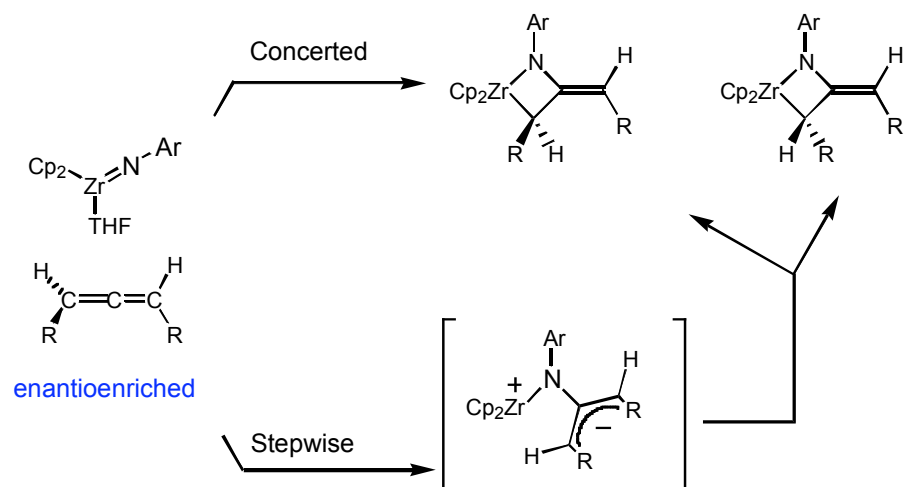
Possible Mechanism for Allene Stereoconversion



Allene chirality is destroyed in forming the intermediate

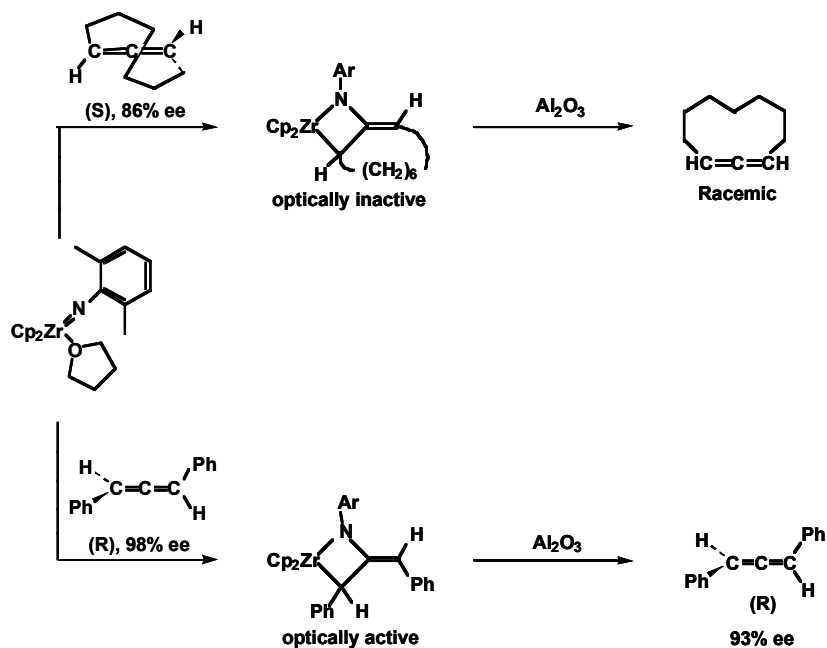
Probing the Stepwise Mechanism

Reaction of the achiral $\text{Cp}_2\text{Zr}=\text{N}=\text{R}$ and Optically Active Allene

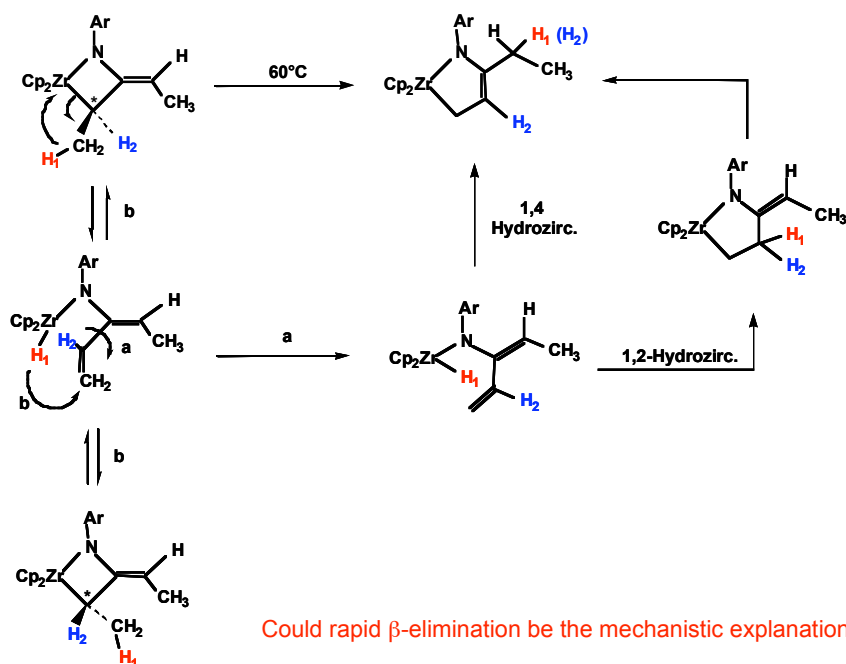


Stepwise mechanism should result in racemization of the starting allene

Results Depend Dramatically on the Allene Substituents

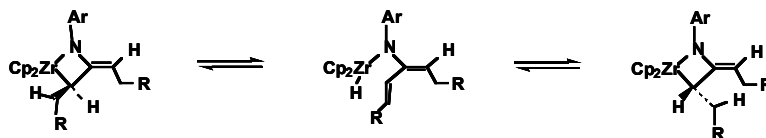


Thermal Metallacycle Rearrangement Observed

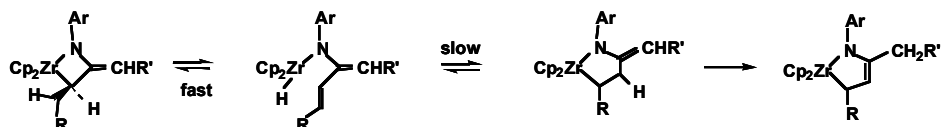


The β -Elimination Pathway Accounts For the Puzzling Observations

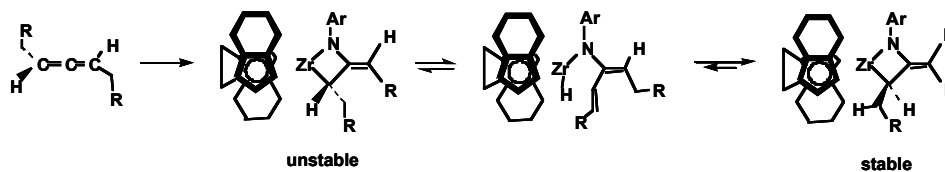
(a) Racemization in the reaction of alkyl- but not arylallenes with $\text{Cp}_2\text{Zr}=\text{NR}$:



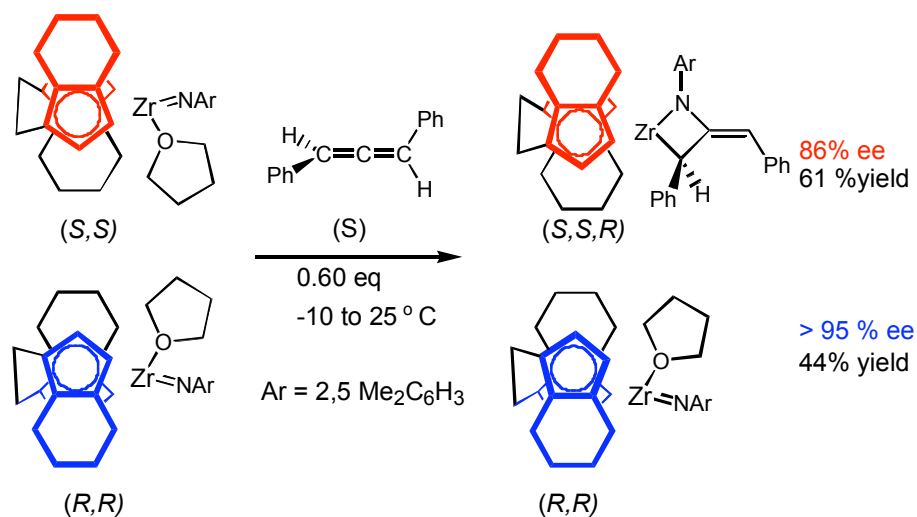
(b) Formation of azadiene complexes:



(c) Inversion of configuration in the (EBTHI)Zr + 1,3-dialkylallene reactions:



Use of Enantiopure Diphenylallene to Resolve Imidozirconium Complexes



Resolved imido complex cleanly separated by wasing with cold Et₂O

Robert G. Bergman Research

Best known for:

1972 Discovery of thermal rearrangement of cis-1,5-hexadiyne-3-enes to 1,4-dehydrobenzenes, the "[Bergman cyclization](#)"

1982 Discovery of the first soluble organometallic complexes that undergo intermolecular insertion of [transition metals into C-H bonds of alkanes](#)

Major Areas of Current Research

New Stoichiometric and Catalytic C-H activation and Si-H activation Methods

Stoichiometric and Catalytic Chemistry of Group IV Imido Complexes

Fundamental Chemistry of Late Metal Alkoxo and Amido Complexes

New Catalytic Ligands for Use in Asymmetric Carbene Transfer Reactions

Over 350 publications