

# *C-H Bond Activation Using Homogeneous Transition Metal Catalysts*

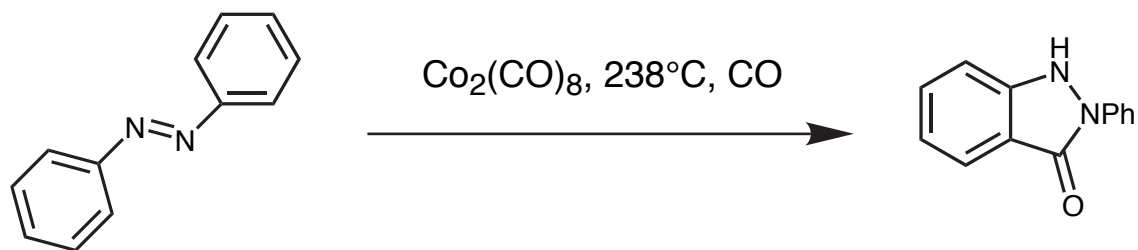
Kevin Campos

March 1, 1996

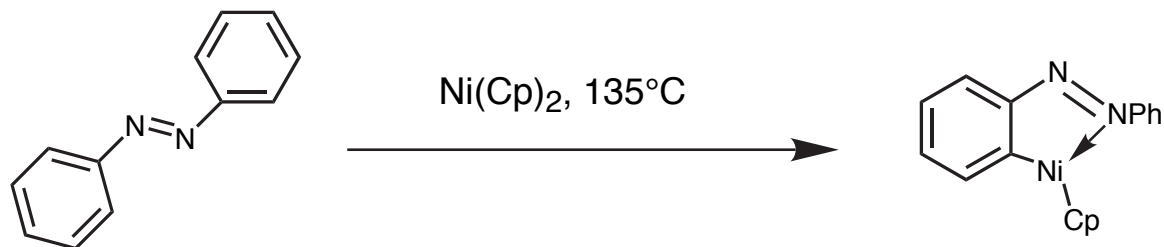
## Reviews:

- R. Bergman, *Acc. Chem. Res.*, **1995**, 28, 154
- R. Crabtree, *Chem. Rev.*, **1985**, 245
- M. Brookhart, *J. Organomet. Chem.*, **1983**, 250, 395

## Some Interesting Early Examples

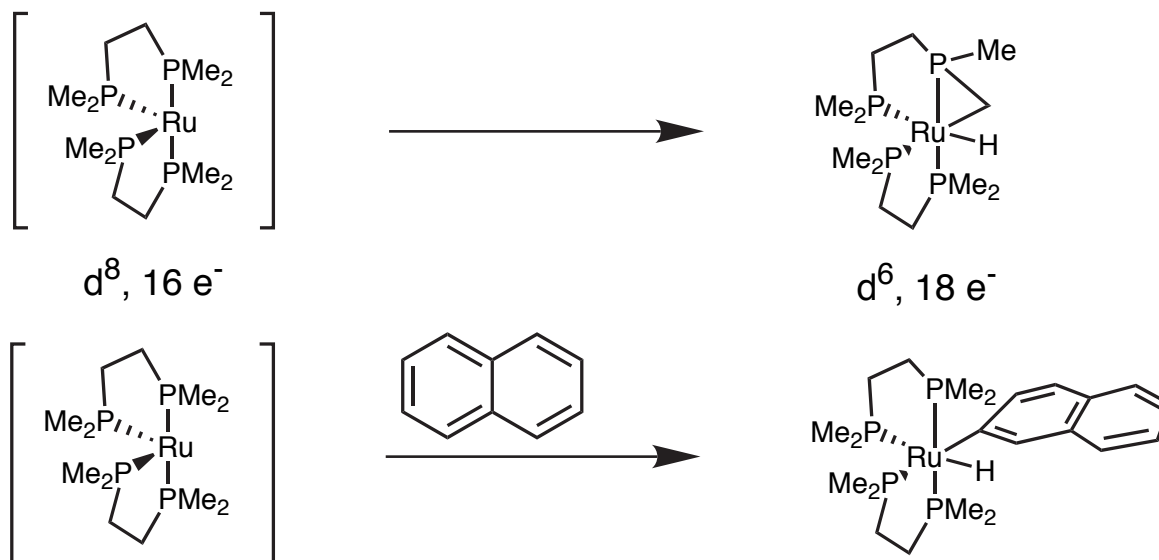


□ S. Horii, *Bull. Chem. Soc. Jpn.* **1960**, 23, 247

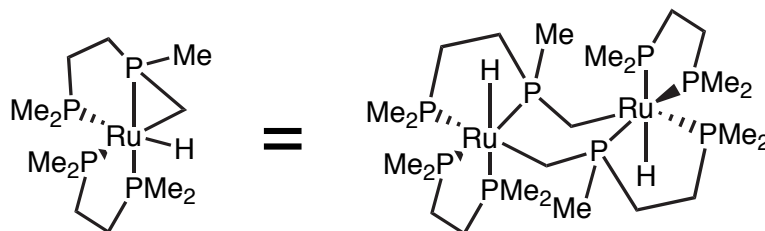


□ J. Kilman, M. Dubeck, *JACS* **1963**, 85, 1544

## Early Examples of Oxidative Addition



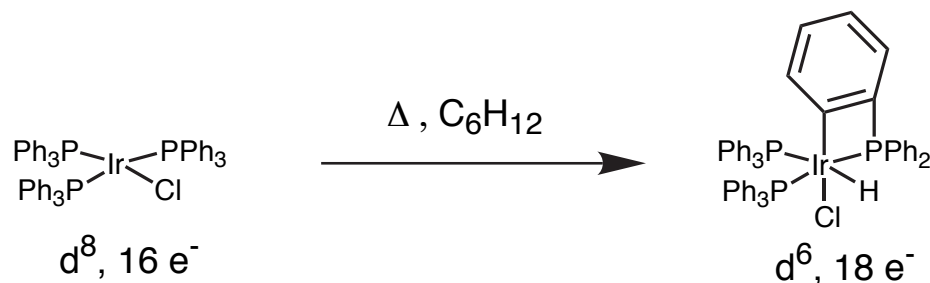
□ J. Chatt, J. Davidson, *JCS* **1965**, 843



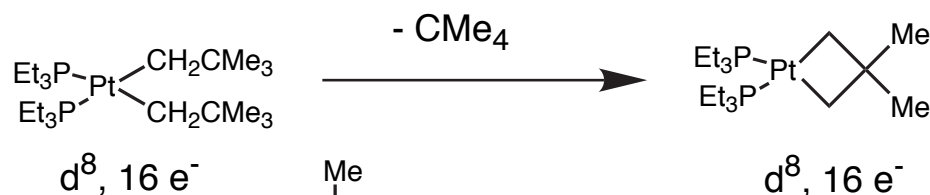
Intramolecular cyclometallated product determined to be a dimer by X-ray crystallography

□ F. Cotton, *JCS CC*, **1974**, 755

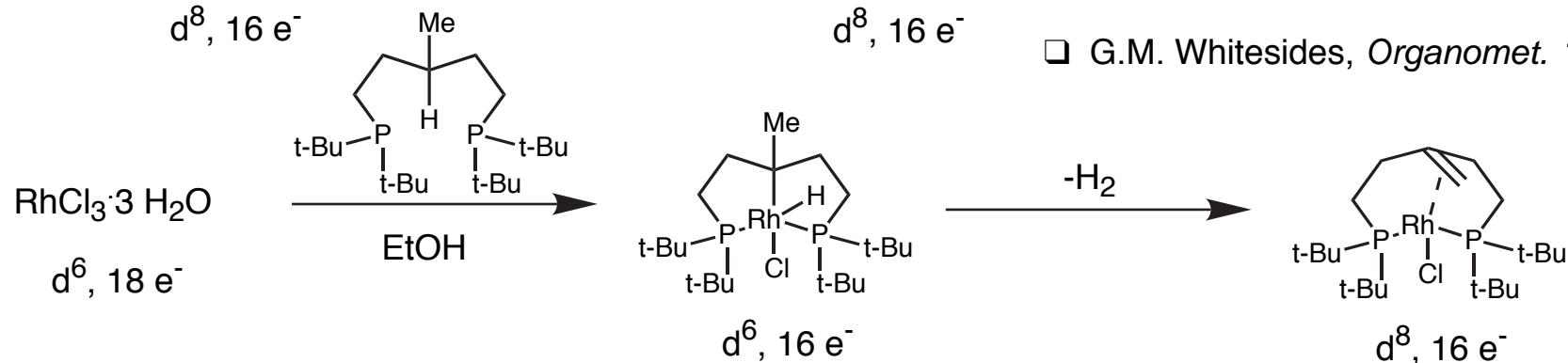
## Intramolecular C-H Bond Activation



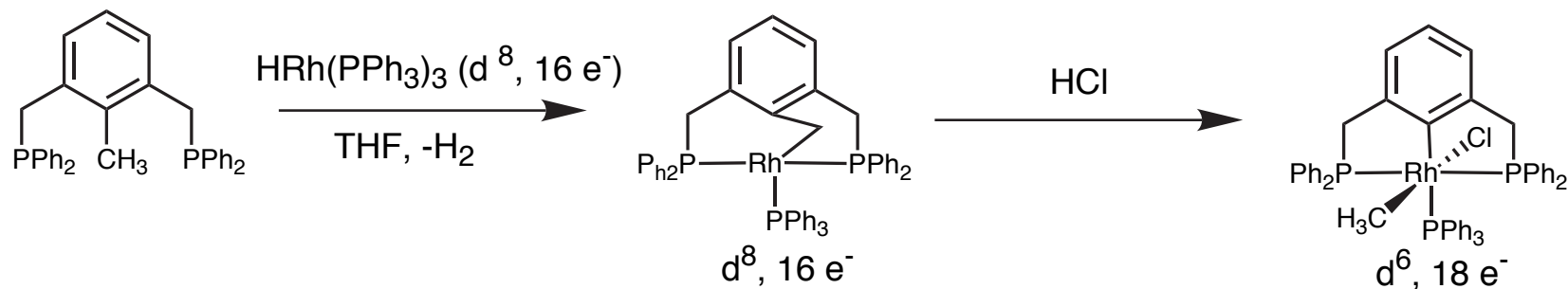
□ M. Bennet, *JCS CC* **1967**, 581



□ G.M. Whitesides, *Organomet.* **1982**, 1, 13



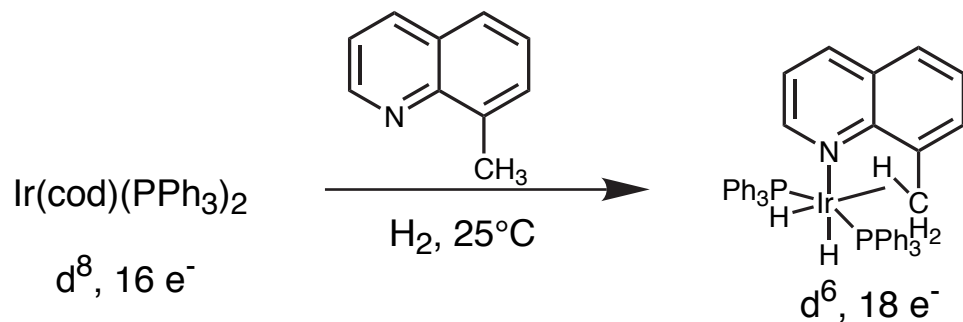
□ C. Crocker, *JCS CC* **1979**, 498



□ D. Milstein, *Nature*, **1993**, 364, 699

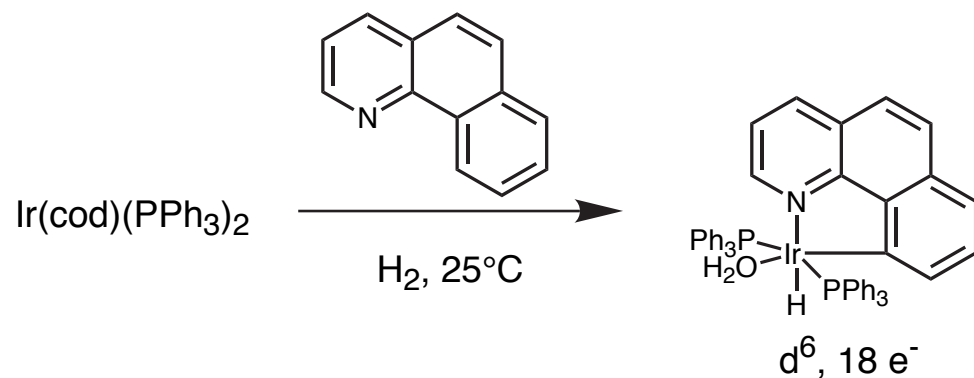
## Intramolecular C-H Bond Activation

- C-H agostic interaction observed in X-ray structure of iridium-methylquinoline complex:



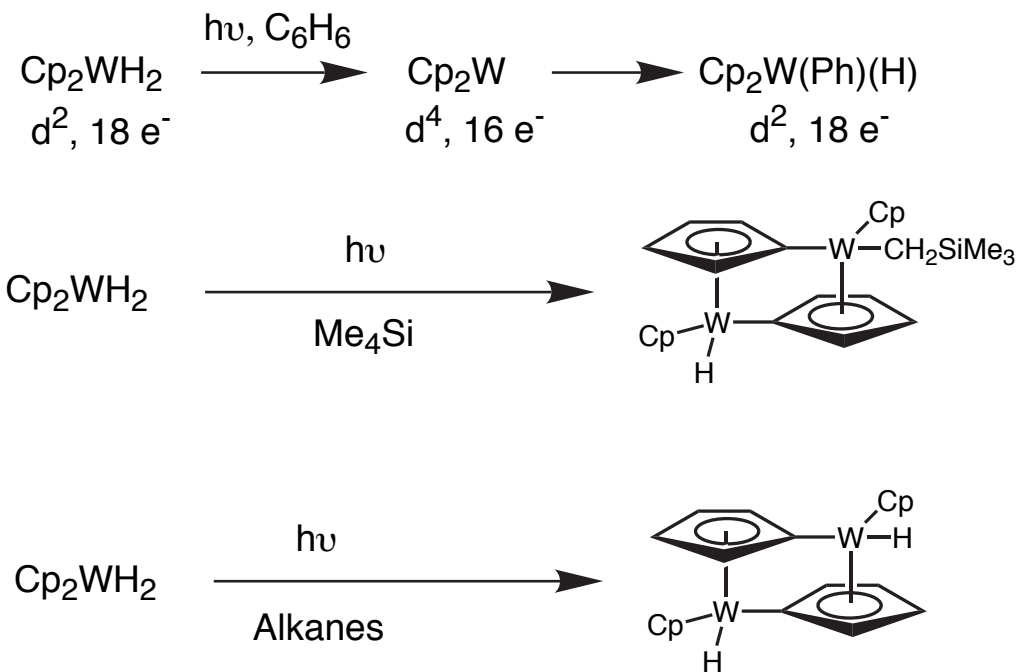
- R. Crabtree, *Inorganic Chem* **1985**, 24, 1986

- Oxidative addition was observed in X-ray structure when benzoquinoline was used:



- R. Crabtree, *JCS CC* **1985**, 194

## Potential Difficulties in Intermolecular C-H Bond Activation

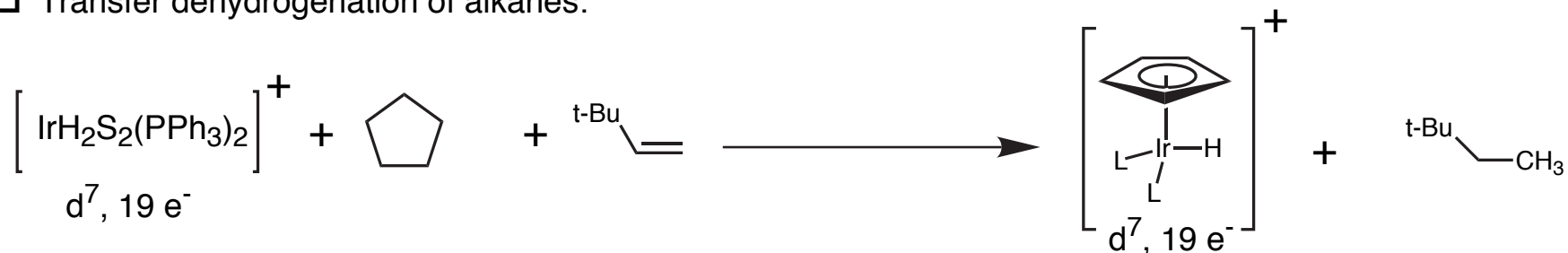


Oxidative addition into a variety of aryl C-H bonds was observed  
 Stronger C-H bonds were unreactive, causing oxidative addition into Cp-H

- Green, *JCS CC* **1972**, 1114
- Green, *JCS Dalton Trans.* **1979**, 1157

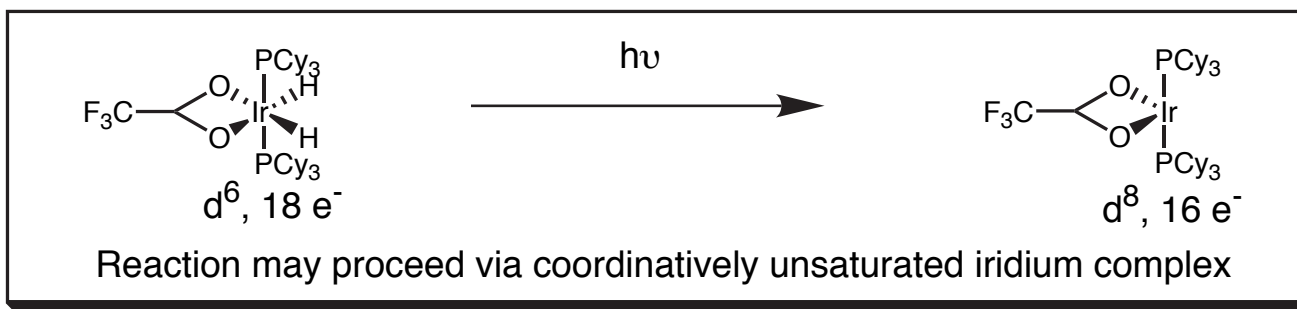
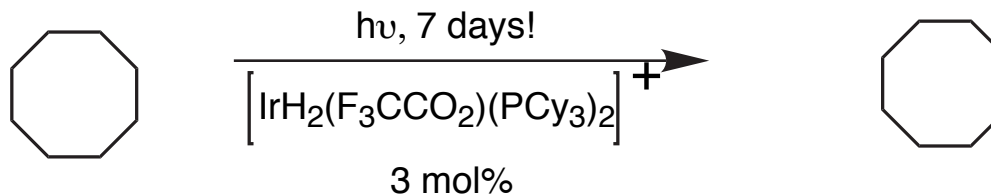
## Dehydrogenation of Alkanes

□ Transfer dehydrogenation of alkanes:



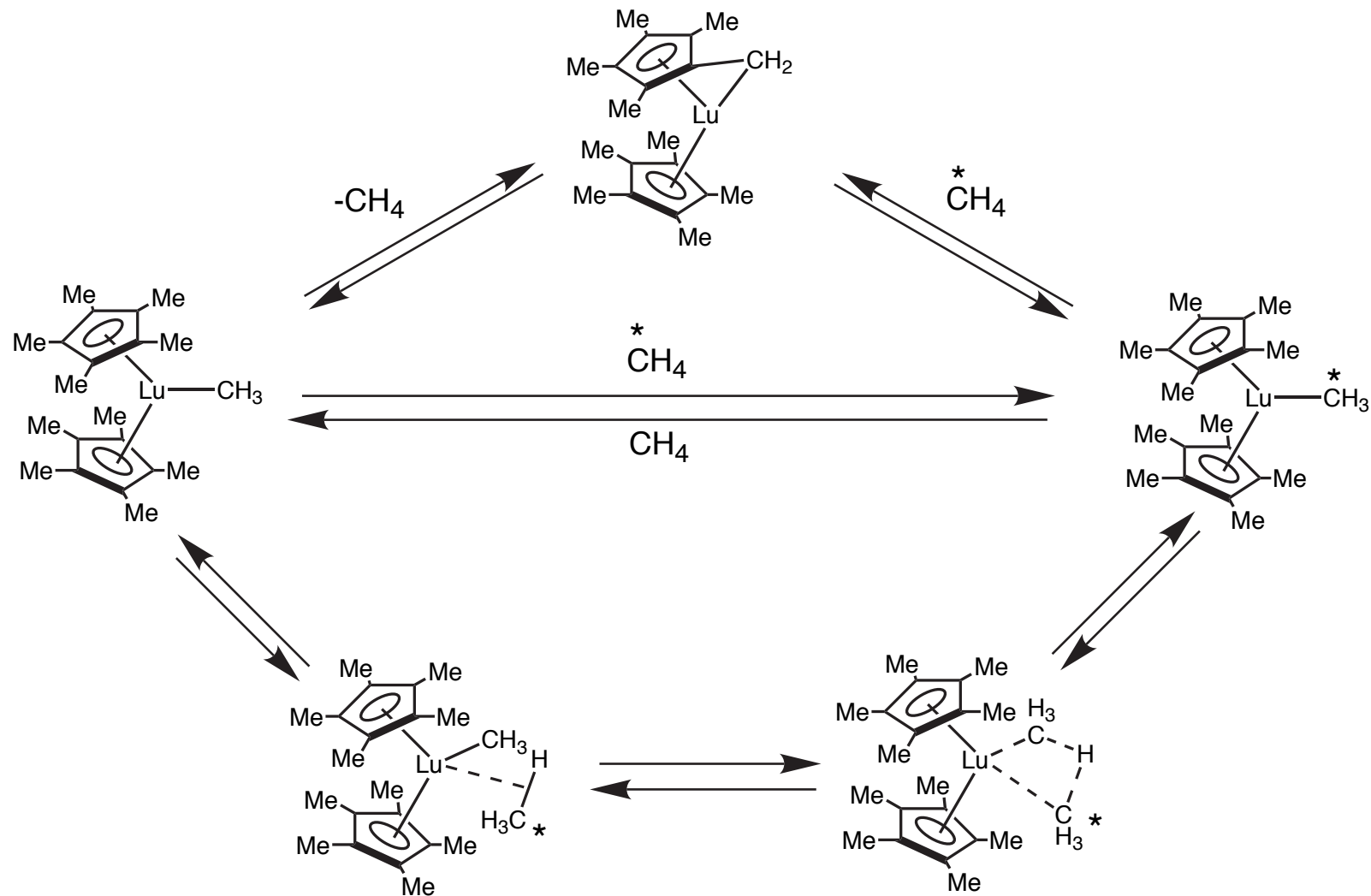
- R. H. Crabtree, *JACS* **1979**, *101*, 7738
- R. H. Crabtree, *JACS* **1982**, *104*, 6994

□ Catalytic dehydrogenation of alkanes:



- R. H. Crabtree, *JCS CC* **1985**, 1829
- R. H. Crabtree, *JACS* **1987**, *109*, 8025

## $\sigma$ -Bond Metathesis Proposed for Some Organolanthanide Complexes

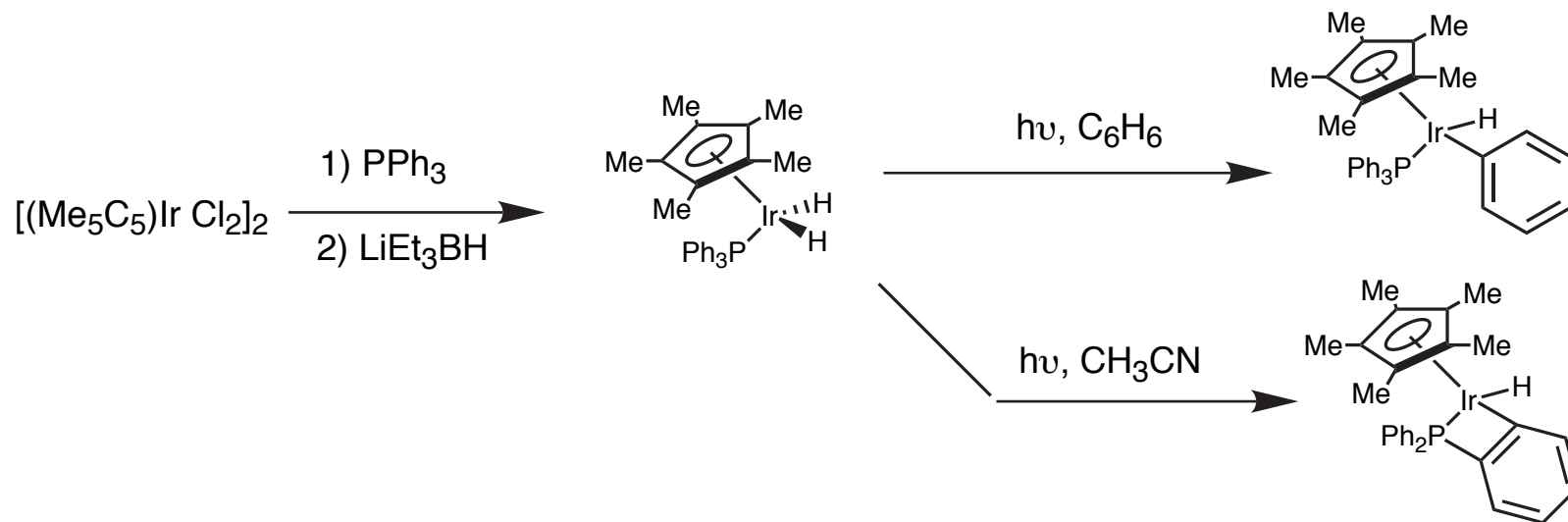


□ Other straight-chain alkanes were also added, but quickly decomposed to yield the alkene and metal hydride

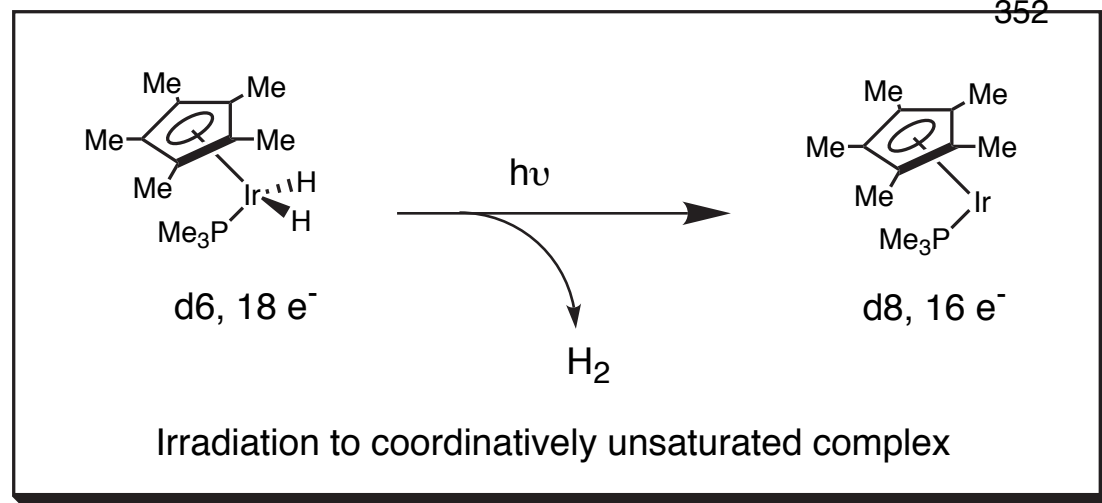
□ G.Parshall, P. Watson, *Acc. Chem. Res.* **1985**, 18, 51



## Intermolecular Oxidative Additions via Photochemically Induced Complex

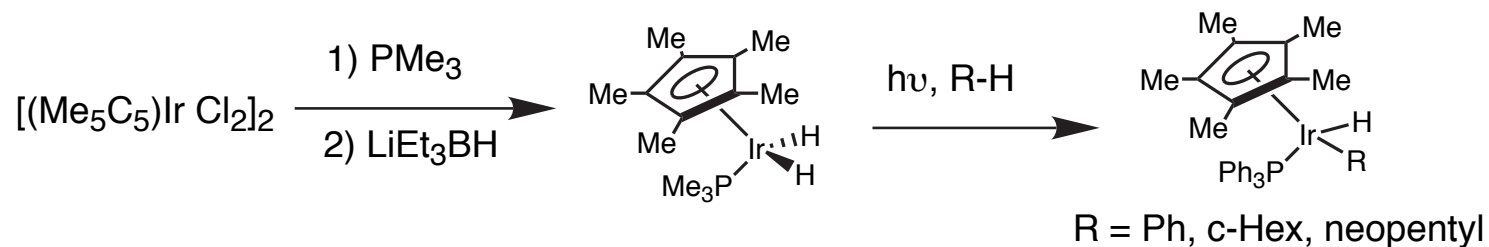


□ R. Bergman, *JACS* **1982**, *104*, 352

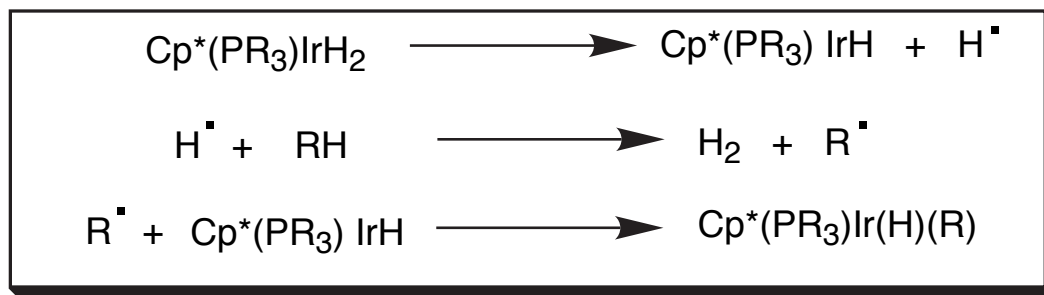


Similar photolysis/oxidative addition has been reported for  $\text{Cp}^* \text{Ir}(\text{CO})_2$  - W. Graham, *JACS* **1982**, *104*, 3723

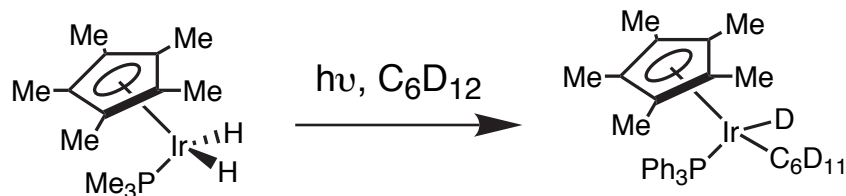
## Mechanistic Studies



- Characterization of complexes by NMR (Ir-H @ -18 ppm) and mass spectrometry
- Ruling out Free Radical Mechanisms:

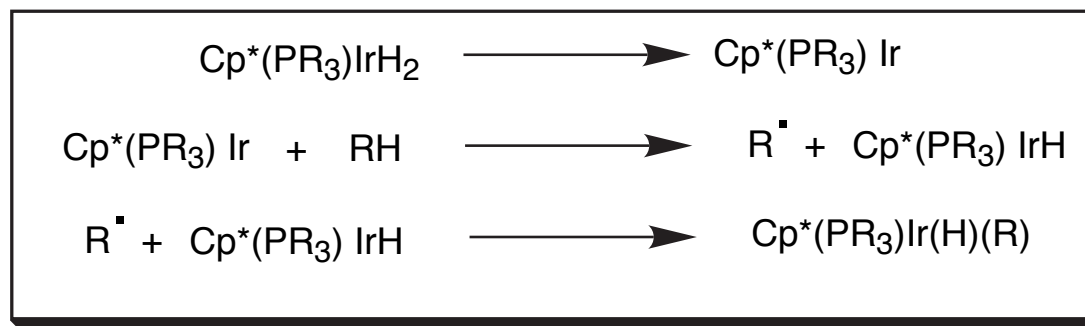


- No H(D) exchange observed between iridium-hydride and  $\text{C}_6\text{D}_{12}$

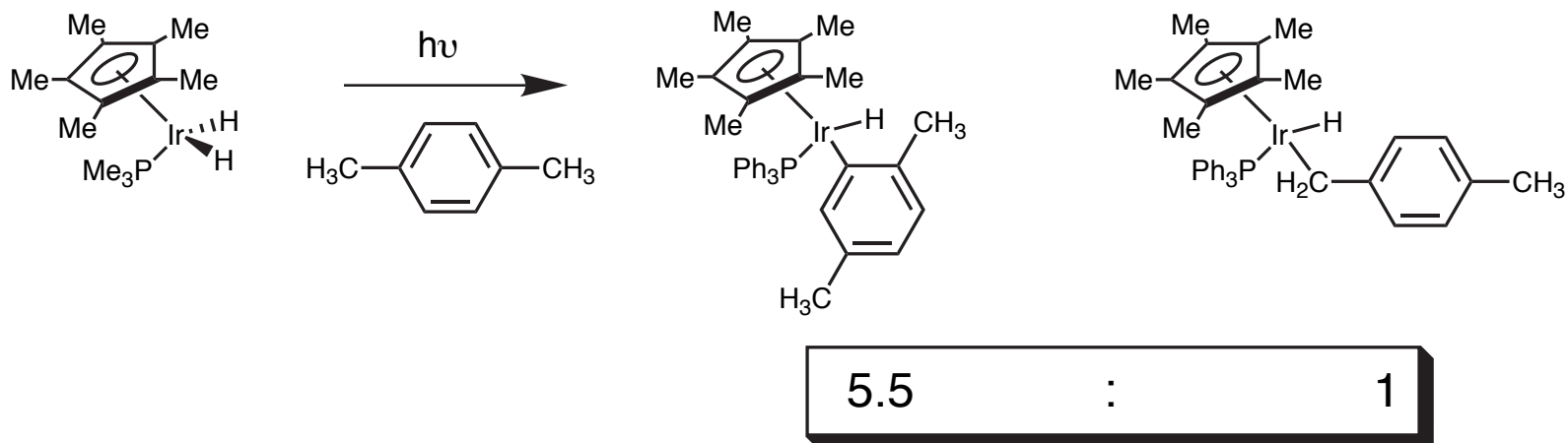


□ R. Bergman, *JACS* **1983**, 105, 3929

## Mechanistic Studies: Lending Proof Against a Free Radical Mechanism



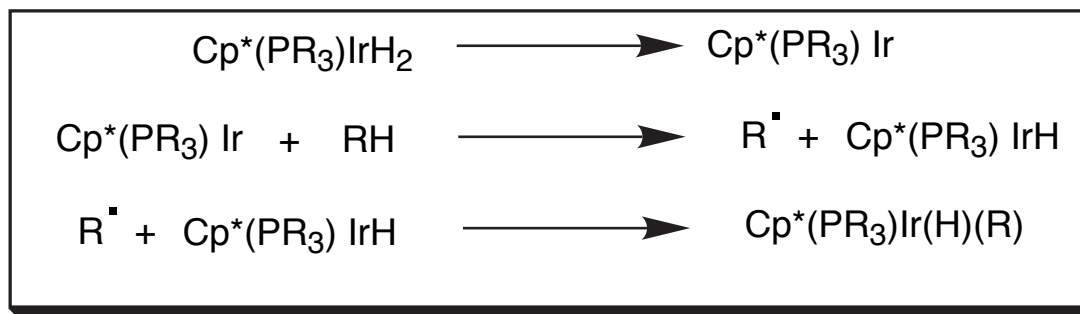
□ Iridium complex reacts three times as fast with Ar-H than with Ar-CH<sub>3</sub>



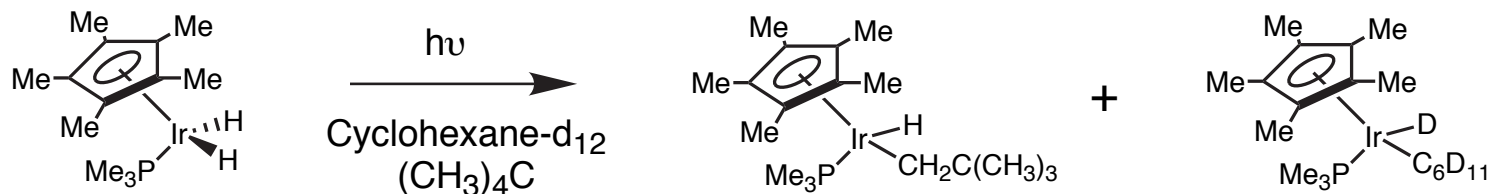
□ R. Bergman, *JACS* **1982**, *104*, 352

## Mechanistic Studies: Lending Proof Against a Free Radical Mechanism

### □ Ruling out Free Radical Mechanisms:

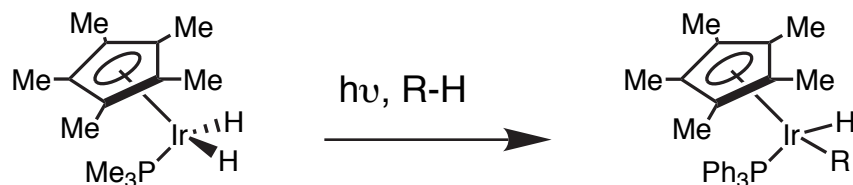


### □ No crossover observed between deuterated and non-deuterated hydrocarbons



□ R. Bergman, *JACS* **1983**, *105*, 3929

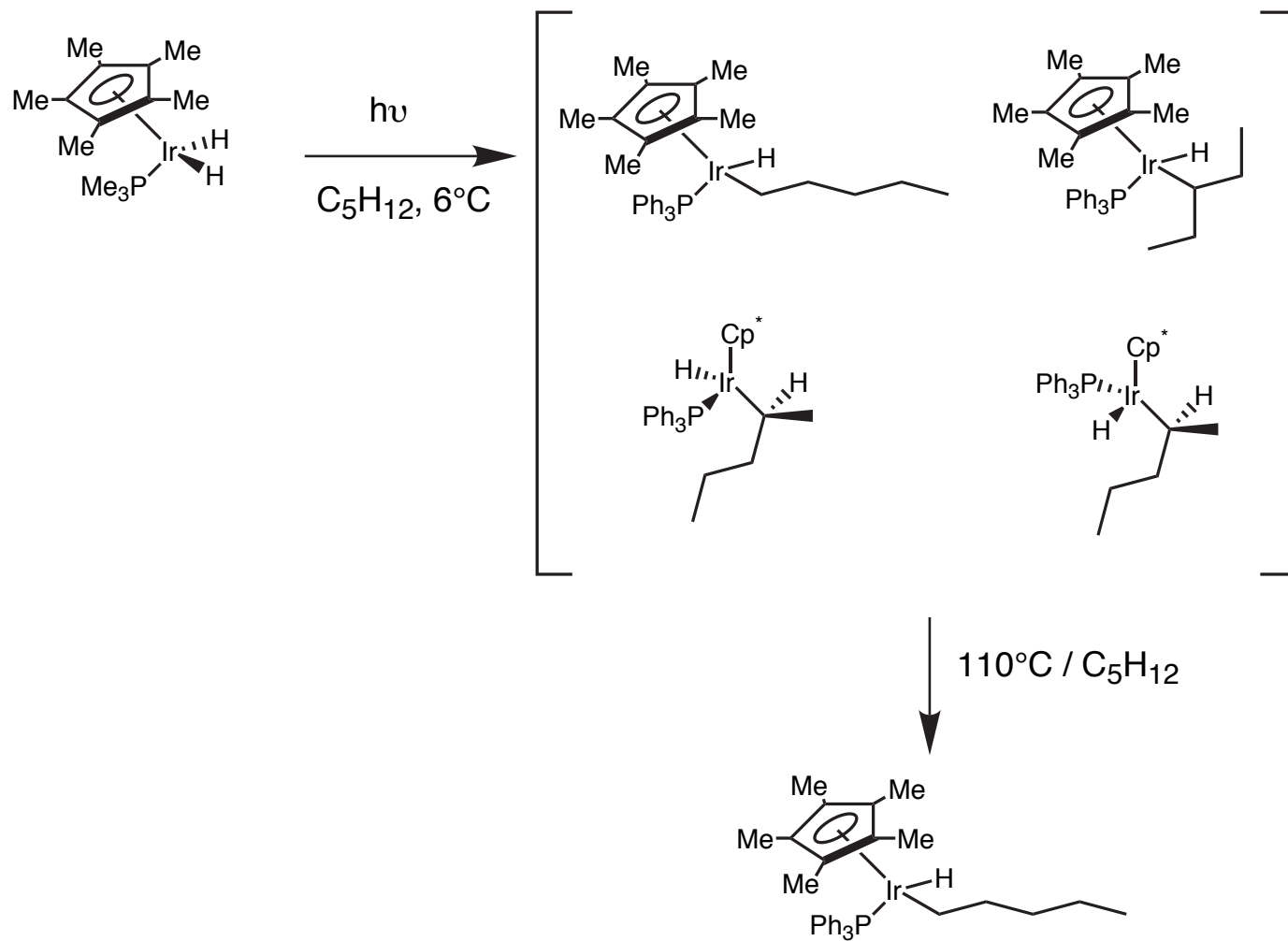
*Relative Rates of Reaction with  
Various Hydrocarbons*



Hydrocarbon	Rel. Rate (Ir)	Rel. Rate (Rh)
Benzene	4.0	19.5
Cyclopropane	2.65	10.4
Cyclopentane	1.6	1.8
Neopentane	1.14	-
Cyclohexane	1.0	1.0
Cyclodecane	0.23	-
Cyclooctane	0.09	0.06
Ethylene	-	2.4
Propane (1°:2°)	4.5 : 1	25 : 1
Pentane (1°:2°)	10 : 1	59 : 1

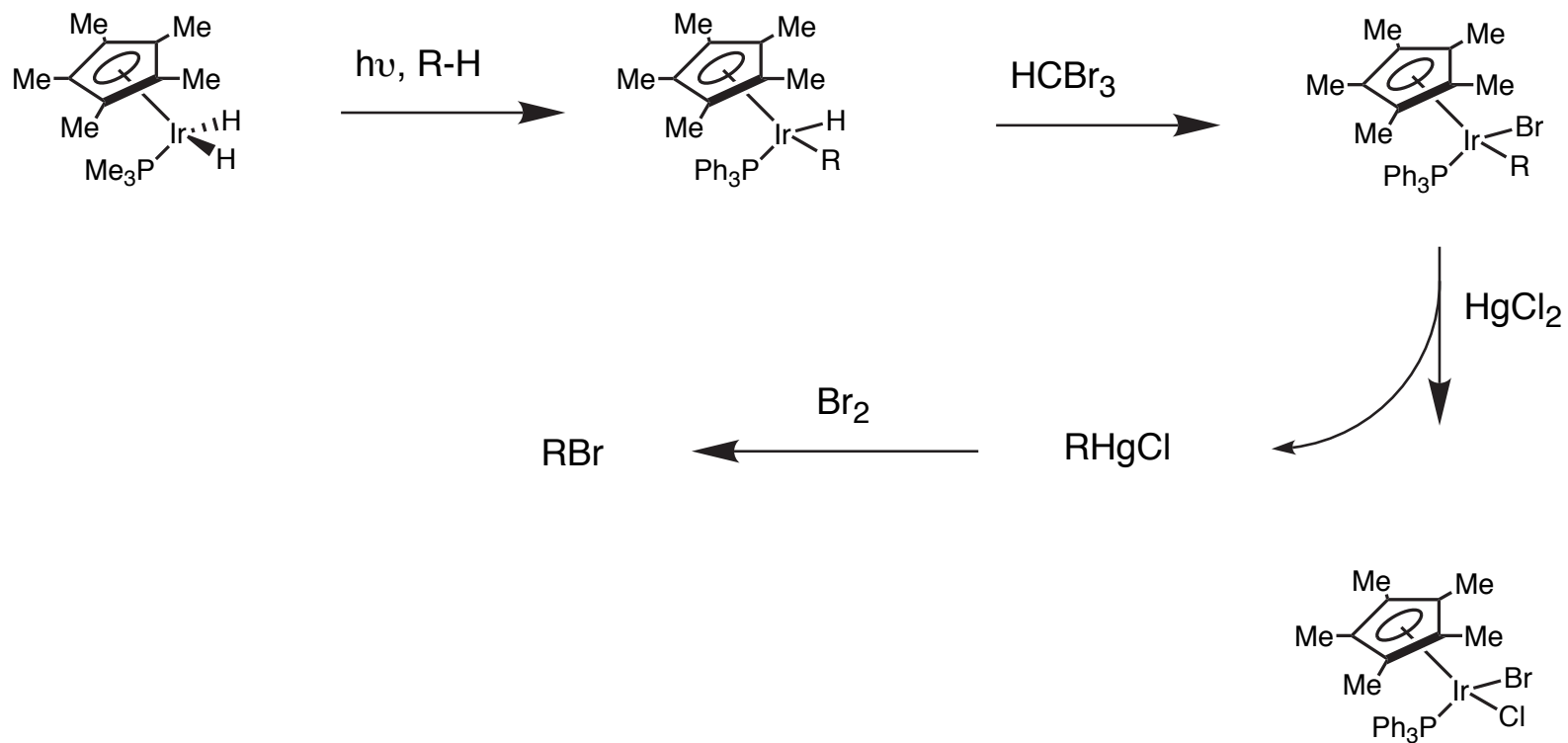
□ R. Bergman, *JACS* **1983**, *105*, 3929

*Little Kinetic Selectivity, But High  
Thermodynamic Selectivity*



□ R. Bergman, *JACS* **1983**, *105*, 3929

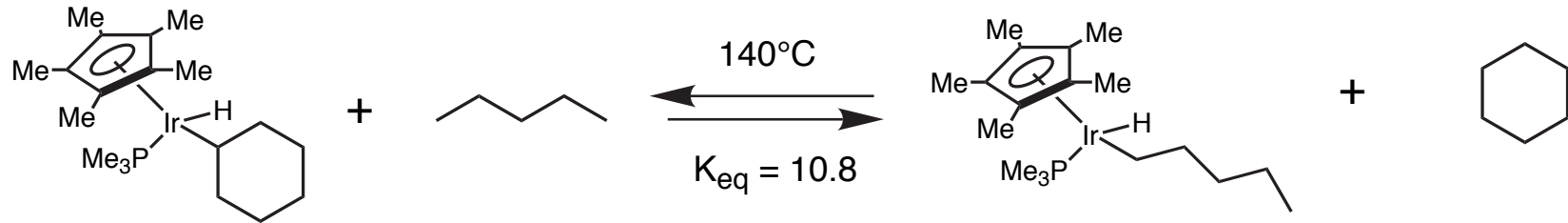
*We Can Activate the C-H Bond, But  
Can We Functionalize the Alkane?*



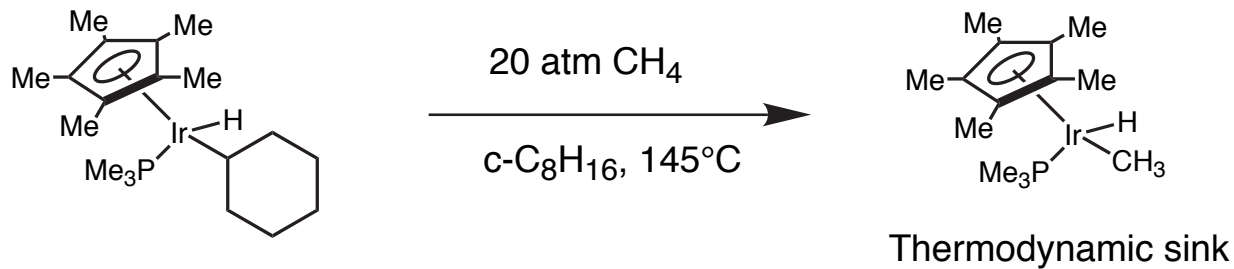
□ R. Bergman, *JACS* **1983**, *105*, 3929

## Can We Activate Methane?

- Oxidative Additon Reversible at 140°C:



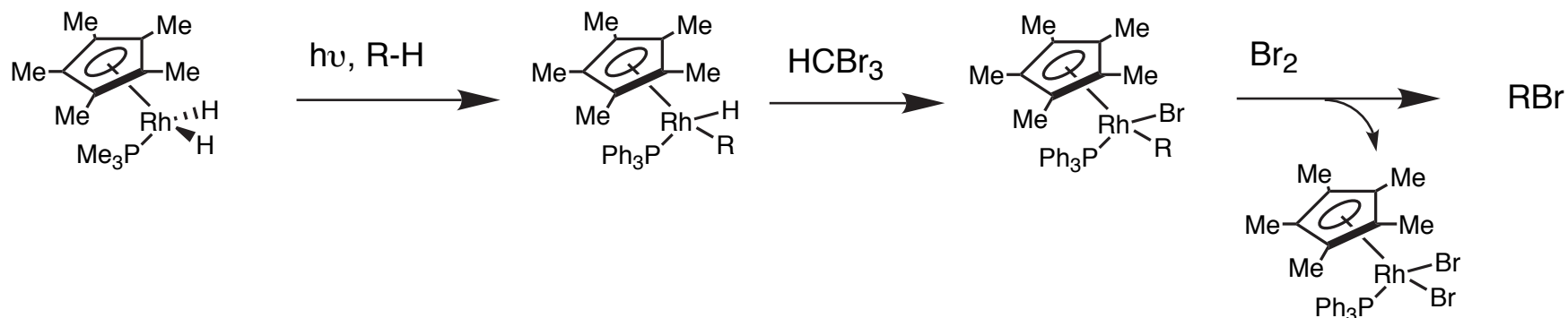
- Applications Towards Activation of Methane:



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



## Similar Chemistry Observed With Rhodium



### ❑ The Advantages

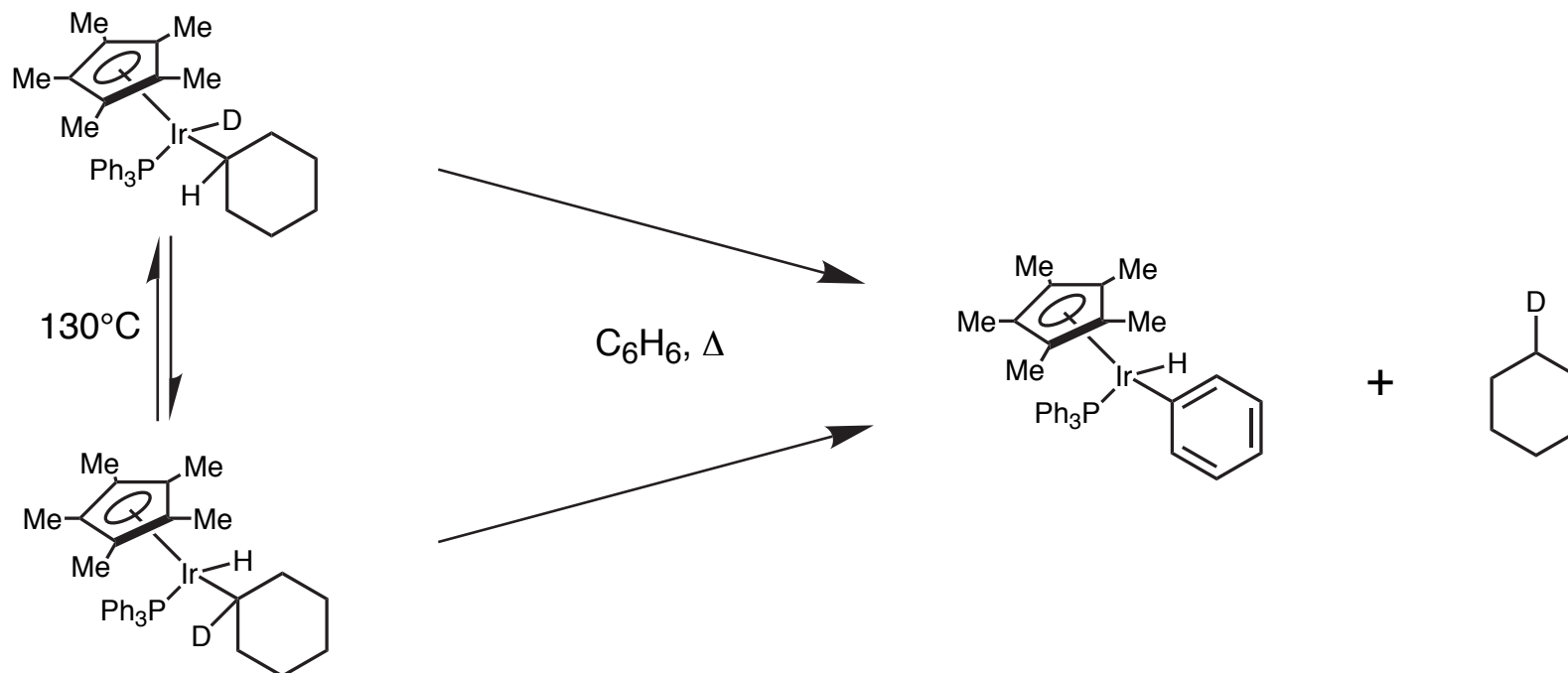
Higher selectivities for  $1^\circ$  vs  $2^\circ$  C-H bonds observed  
Direct conversion to alkylhalides from haloalkyl complexes by treatment with  $\text{Br}_2$

### ❑ The Disadvantages

Hydridoalkyl complexes only stable at temperatures below  $-20^\circ\text{C}$

❑ R. Bergman, *Pure & Appl. Chem.* **1984**, 56, 13

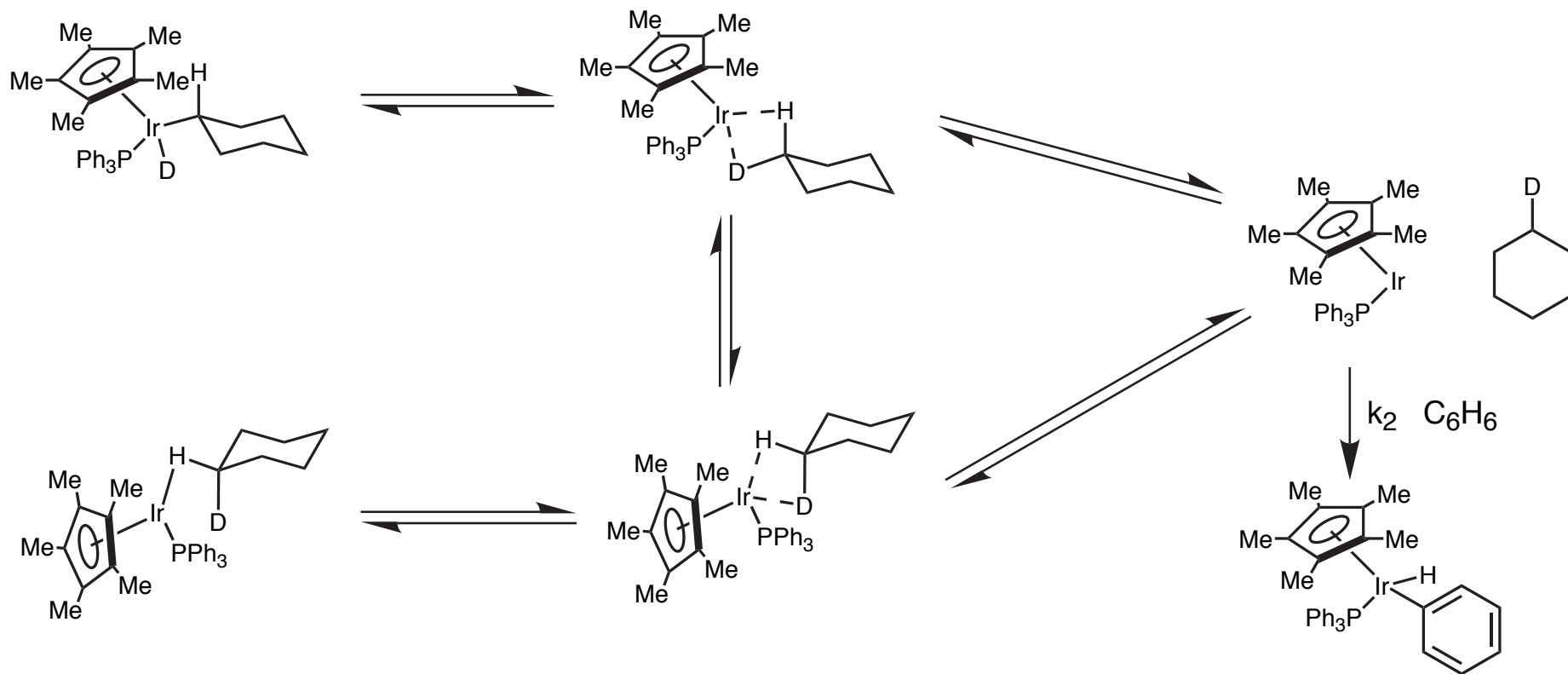
## An Interesting H(D) Exchange Observed in Alkyliridiumdeuterides



- ❑ Deuterium exchange was observed between hydride position and  $\alpha$ -position of cyclohexane
- ❑ As the reaction progressed, the rate of combined disappearance of cyclohexyl complexes decreased
- ❑ For reductive elimination,  $k_{\text{obs}}(\text{C}_6\text{H}_{11}) / k_{\text{obs}}(\text{C}_6\text{D}_{11}) = 0.7$  (Inverse Isotope effect)
- ❑ Similar scrambling was observed in hydridomethyl iridium complex

❑ R. Bergman, *JACS* **1986**, *108*, 1537

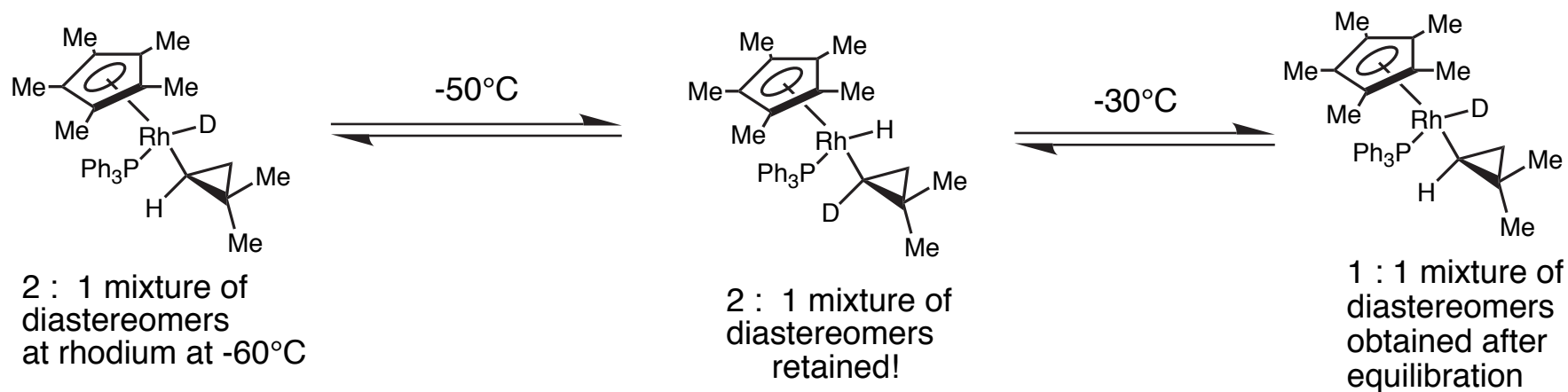
## Inverse Isotope Effect?



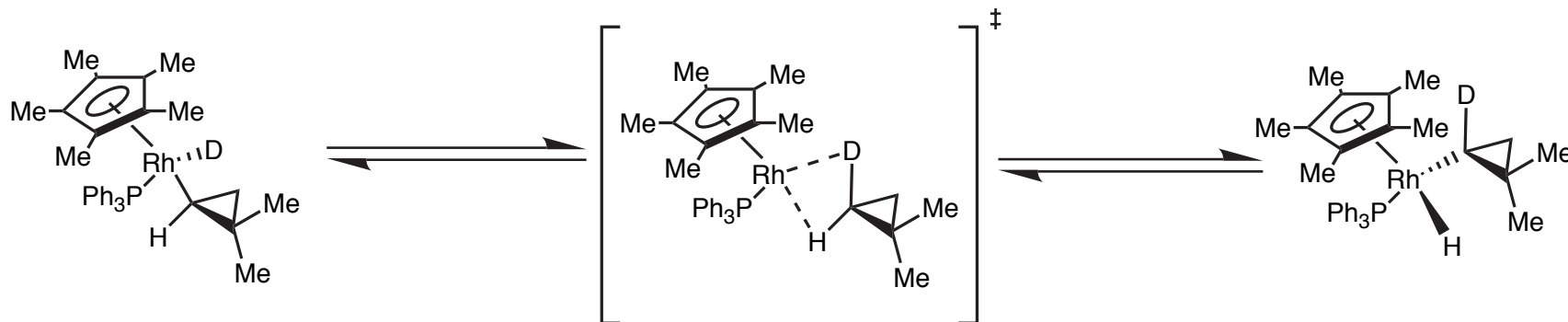
- Reductive elimination/oxidative addition consistent with observed kinetic data except for inverse isotope effect
- Intermediate  $\sigma$ -complex postulated to explain both inverse isotope effect AND deuterium exchange
- Inverse isotope effect observed for various alkyl/aryl hydride complexes

- W.D. Jones, *JACS* **1985**, *107*, 620
- J. Norton, *JACS* **1989**, *111*, 3897
- D. Heineky, *JACS* **1989**, *111*, 5502
- R. Bergman, *JACS* **1986**, *108*, 1537

## Attempts to Identify the Intermediate in $\alpha$ -C-H Exchange

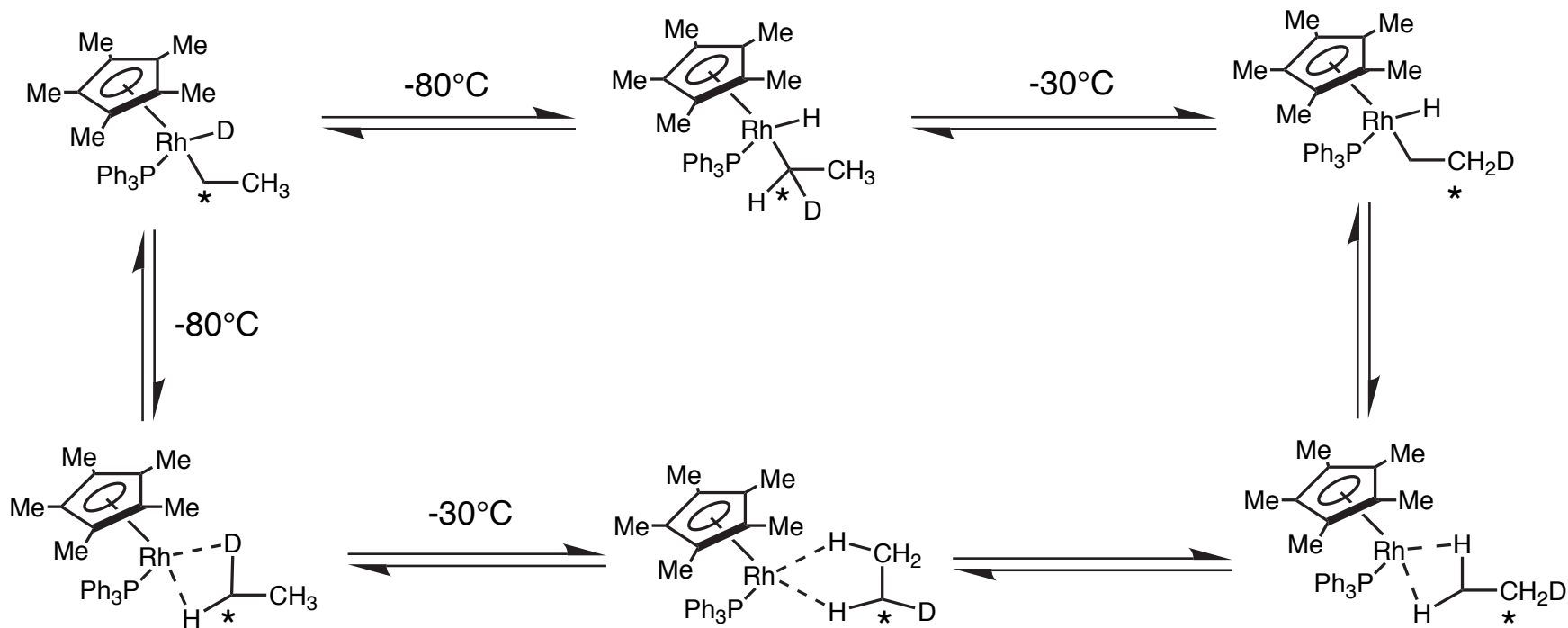


□ Proposed explanation for stereospecific exchange



□ R. Bergman, *JACS* **1986**, *108*, 7332

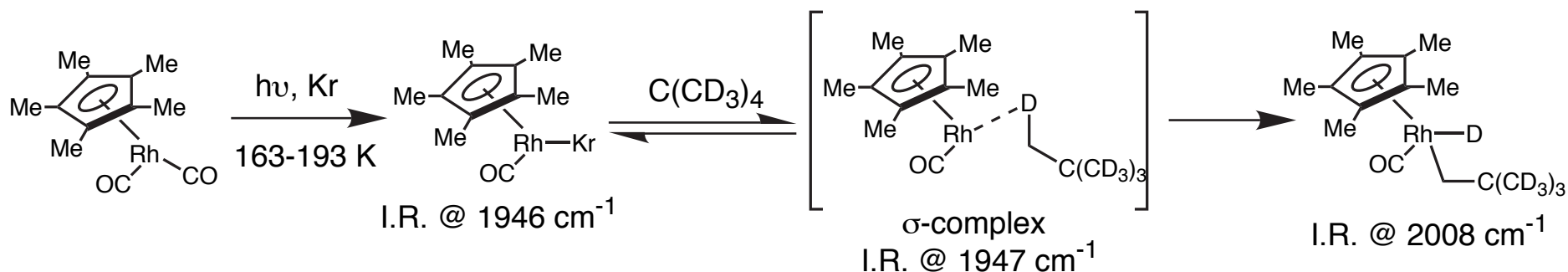
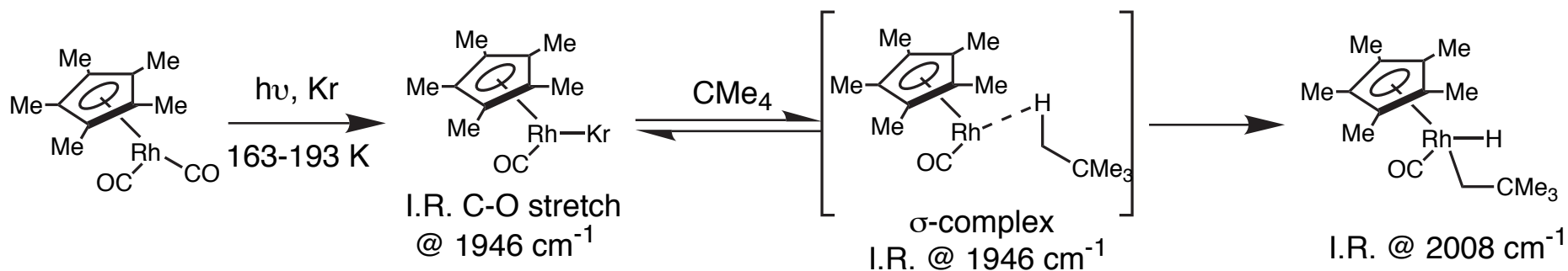
## Can We Observe $\beta$ -C-H Exchange?



- Reactions run at 0.025M in toluene- $\text{d}_8$
- Perdeuterated ethyl deuteride complex was doped with ethane in toluene- $\text{d}_8$  to show no ethyl hydride
- Perdeuterated ethyl deuteride complex and ethyl hydride complex mixed together showed no crossover products

R. Bergman, *JACS* **1986**, *108*, 7332

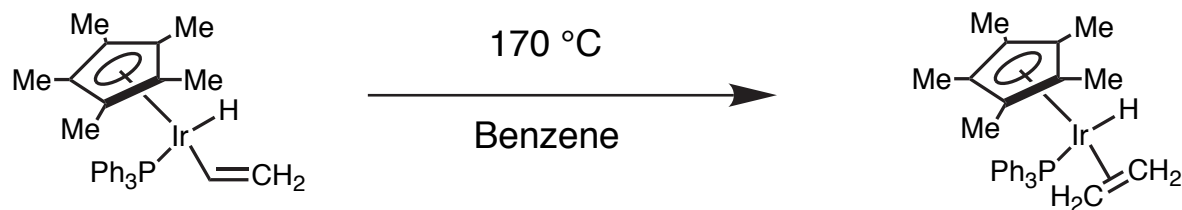
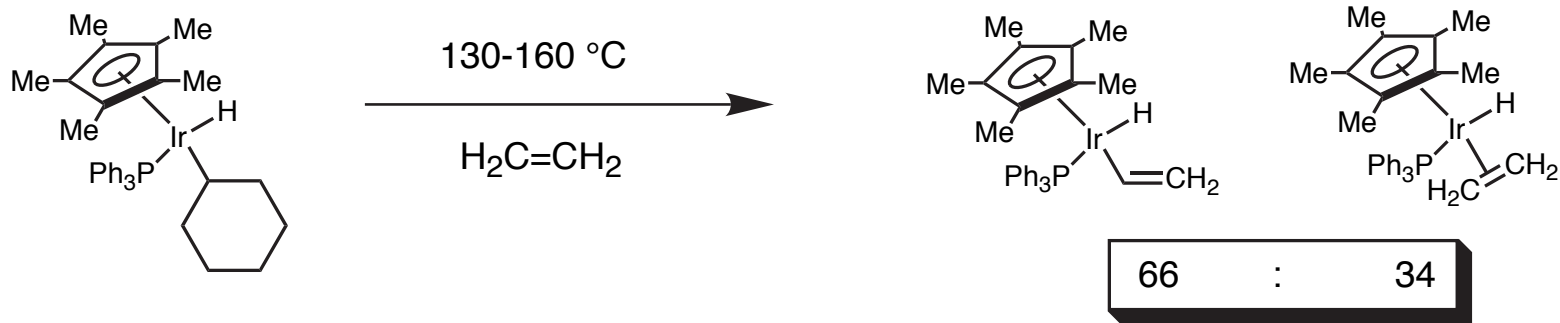
*Transient Metal-Alkane  $\sigma$ -complex  
Observed Using IR Flash Kinetic  
Spectroscopy*



- Metal-alkane intermediate grows at a rate equal to the decay of the metal-krypton complex
- Intermediate decays at a rate equal to the decay of the metal-krypton complex and growth of the product
- $k_{\text{H}} / k_{\text{D}} = 4.4$  @  $25^\circ\text{C}$  for oxidative addition
- $K_{\text{eq}}(\text{H}) / K_{\text{eq}}(\text{D}) = 0.1$
- Similar results observed for cyclohexane- $\text{d}_0$ ,  $\text{d}_{12}$

R. Bergman, *JACS* **1994**, *116*, 7369 + 9587

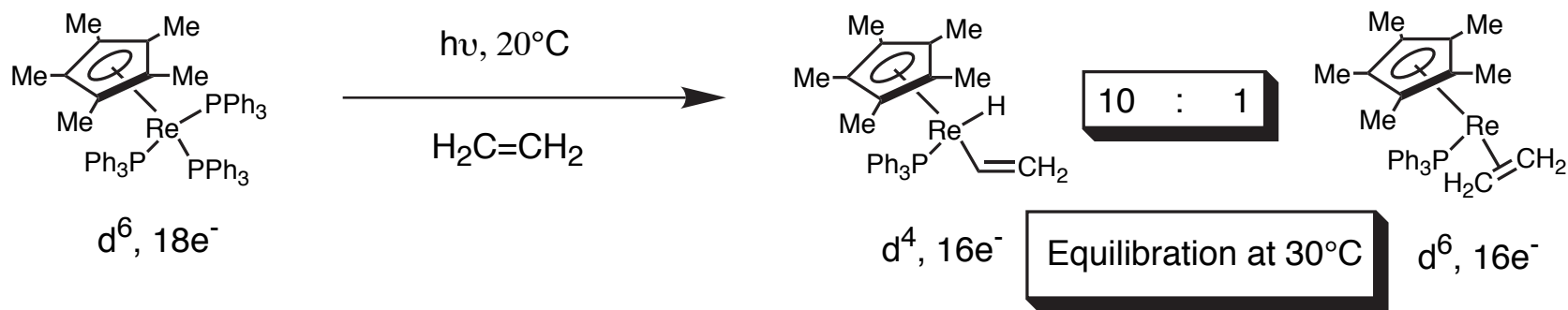
## C-H Bond Activation of Alkenes



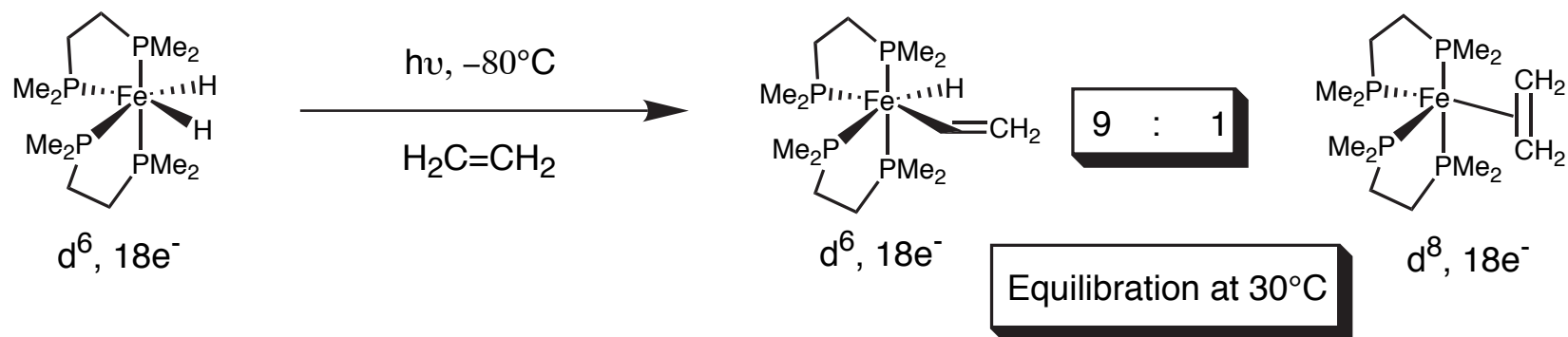
- 66 : 34 represents a kinetic product ratio of coordinatively unsaturated iridium complex with ethylene
- $\eta^2$ -ethylene complex is thermodynamic product of the reaction
- $\eta^2$ -ethylene complex cannot be an intermediate to the formation of the C-H inserted complex
- The reaction proceeds without reversion to ethylene and the reactive iridium intermediate
- The  $\eta^2$ -ethylene complex and the C-H inserted complex are formed through unique transition states
- Interconversion between the two complexes proceeds through a third unique transition state

R. Bergman, *JACS* **1985**, *107*, 4581

Similar Kinetic Results Were  
Observed with Other Metal Systems



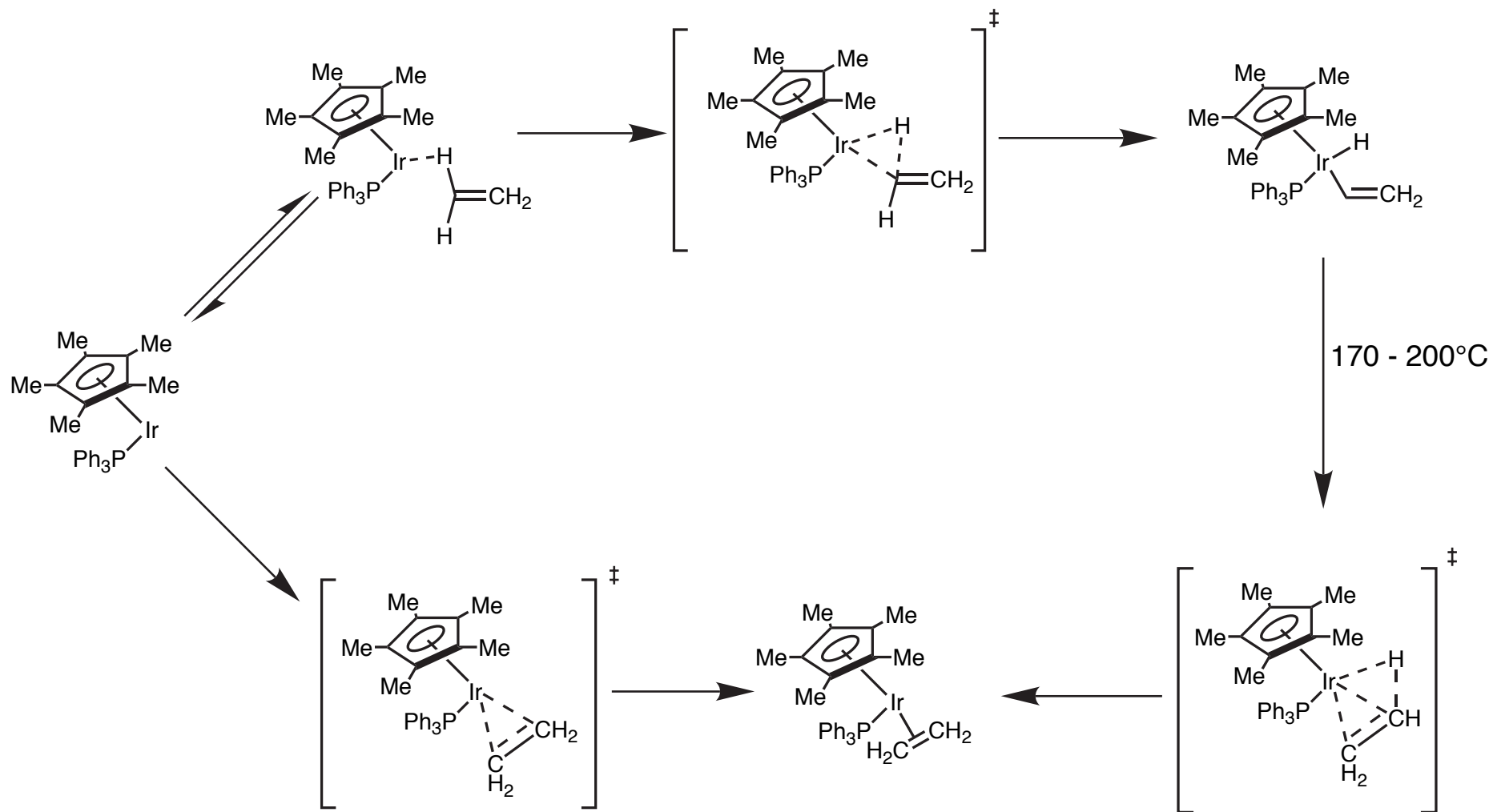
□ R. Bergman, *JACS* **1986**, *108*, 4856



□ M. Baker, L. Field, *JACS* **1986**, *108*, 7433

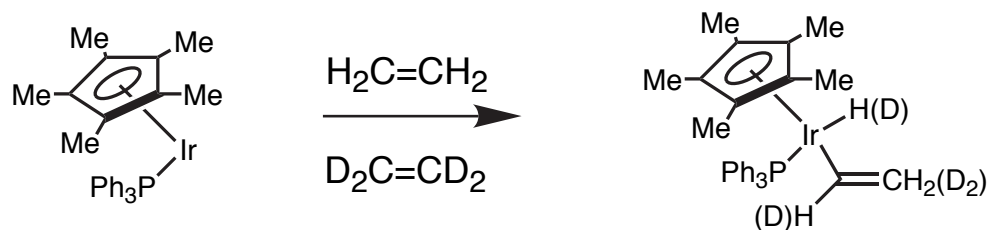


*Two Distinct Mechanisms are Proposed*



□ R. Bergman, *JACS* **1985**, *107*, 4581

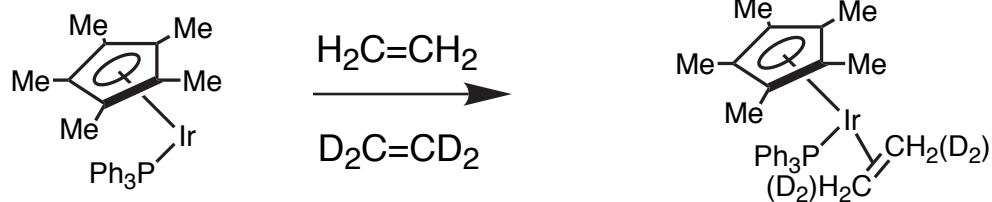
## Isotope Studies to Define Mechanism



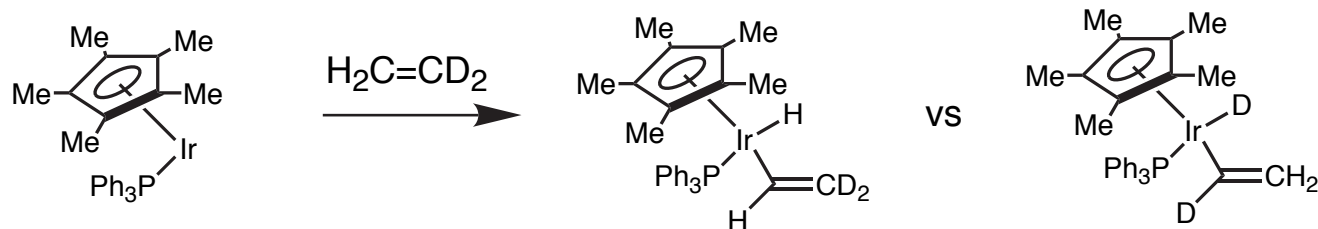
$$k_{\text{H}} / k_{\text{D}} = 1.49$$

$$k_{\text{H}} / k_{\text{D}} = 1.38 \text{ (Cyclohexane)}$$

$$k_{\text{H}} / k_{\text{D}} = 1.05 \text{ (Benzene)}$$



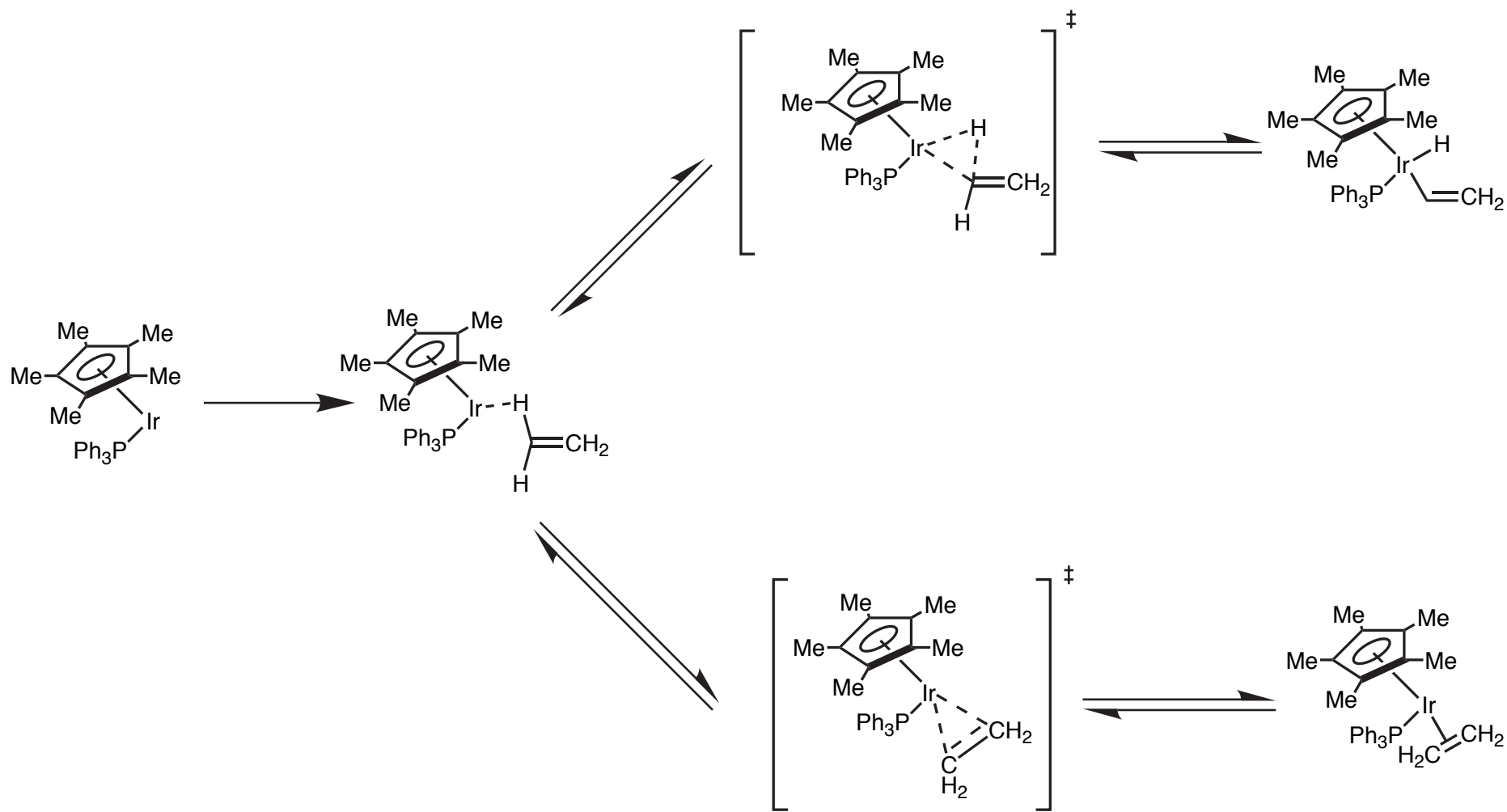
$$k_{\text{H}} / k_{\text{D}} = 0.95$$



$$k_{\text{H}} / k_{\text{D}} = 1.20$$

□ R. Bergman, *JACS* **1988**, *110*, 5732

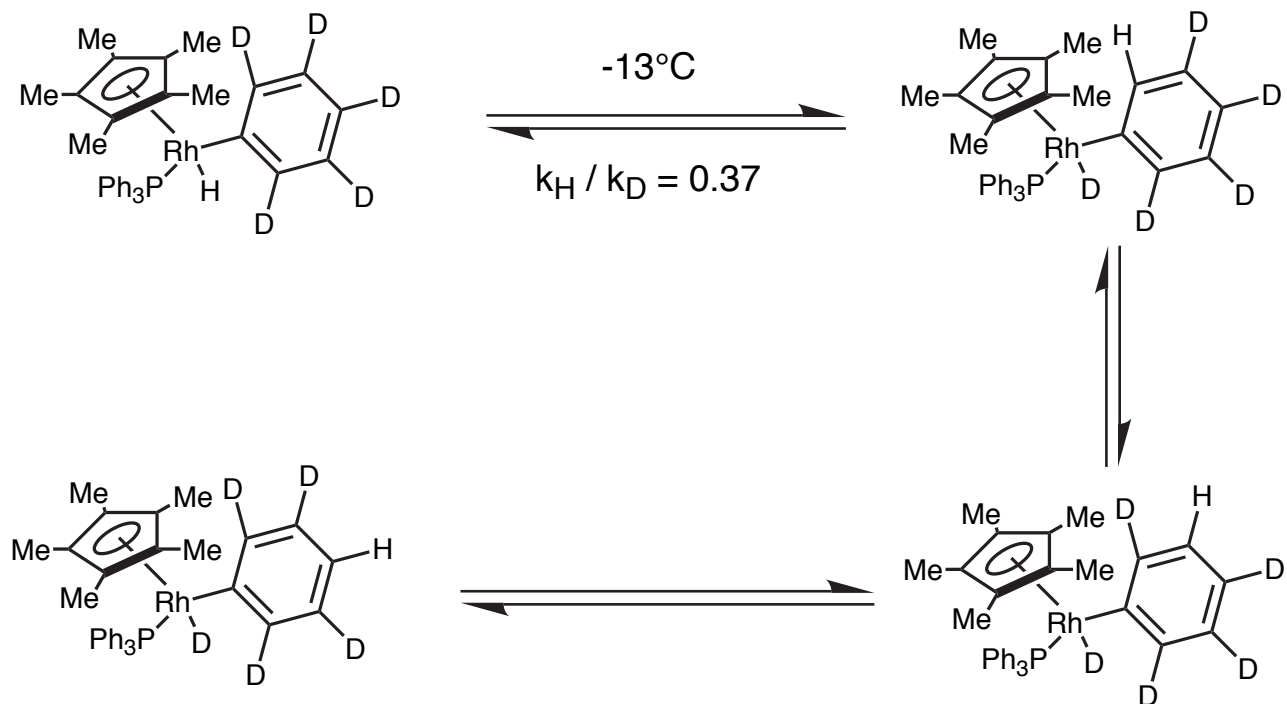
*Revised Mechanism  
Based on Isotope Studies*



□ R. Bergman, *JACS* **1988**, *110*, 5732

## An Interesting Contrast to Bergman's Ethylene Activation Studies

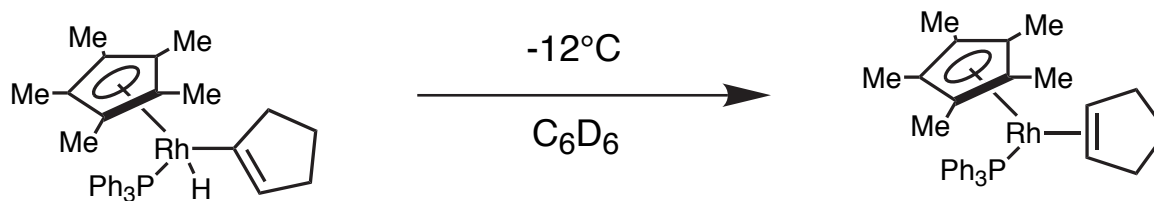
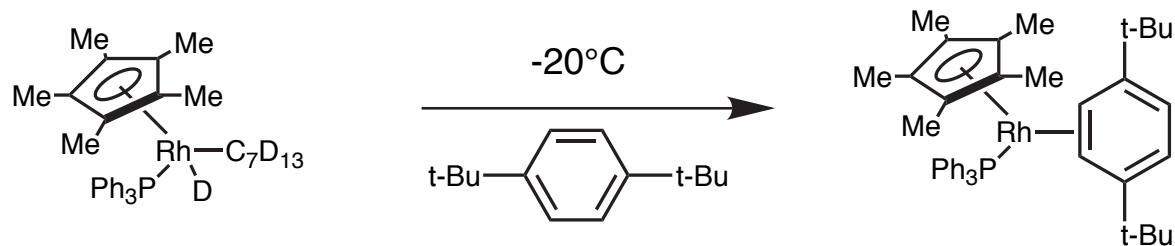
□ [1,2] shift observed in rhodium aryl hydride complex:



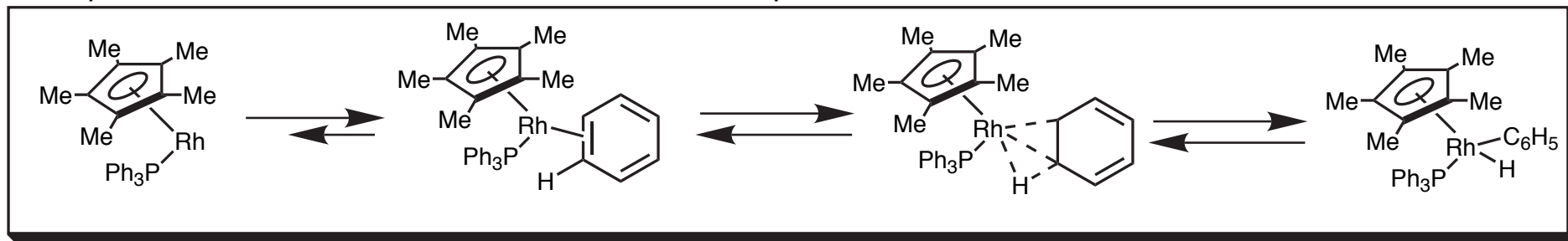
□ W. Jones, *JACS* **1984**, *106*, 1650

## $\eta^2$ -Arene Postulated as the Intermediate in Aryl-H Oxidative Addition

- Two examples of an  $\eta^2$ -arene-metal complex

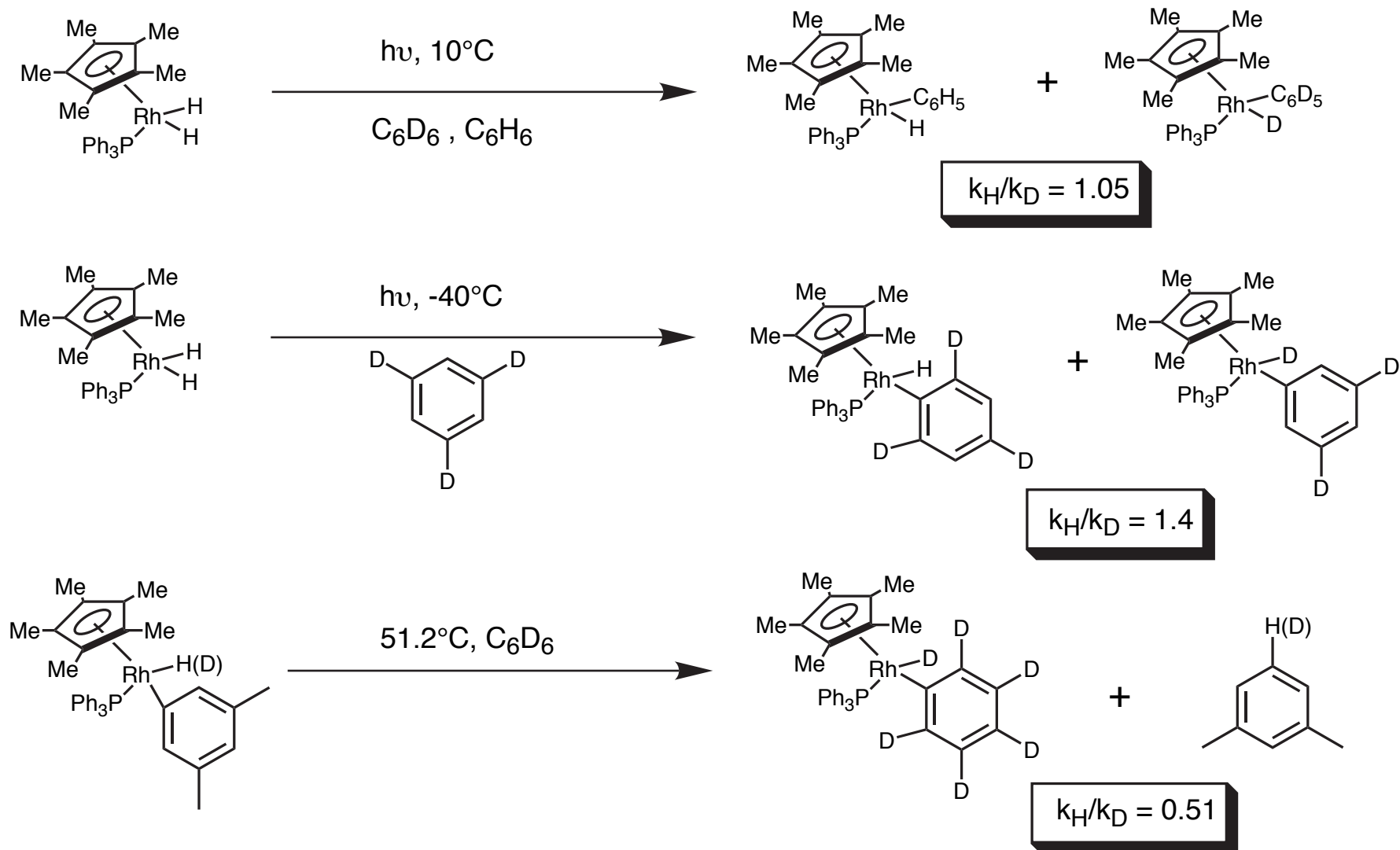


- Proposed mechanism for Ar-H activation based on experimental results:

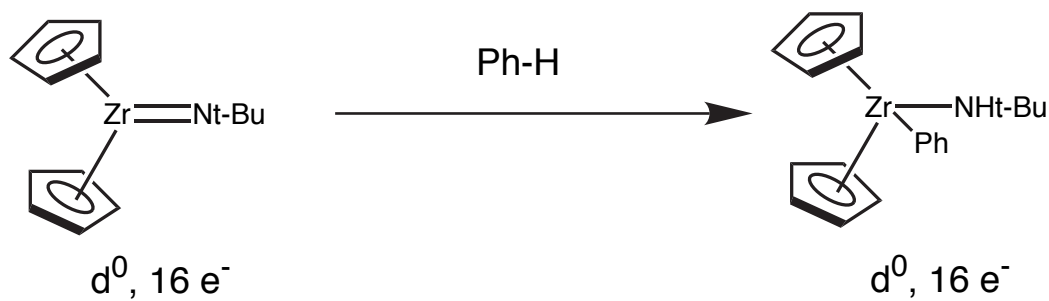


□ W. Jones, *JACS* **1984**, *106*, 1650

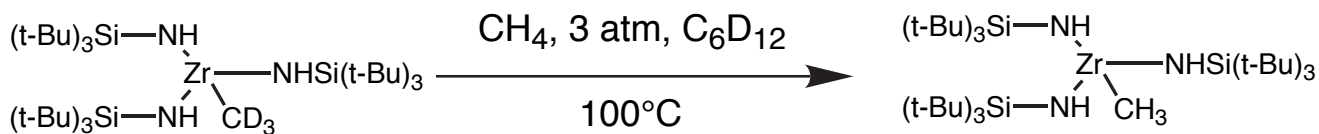
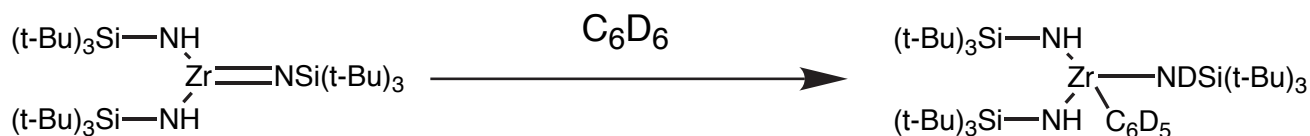
## Isotope Studies Lend Proof Toward an $\eta^2$ -Arene Intermediate



## C-H Activation Using Imidozirconocene Complexes



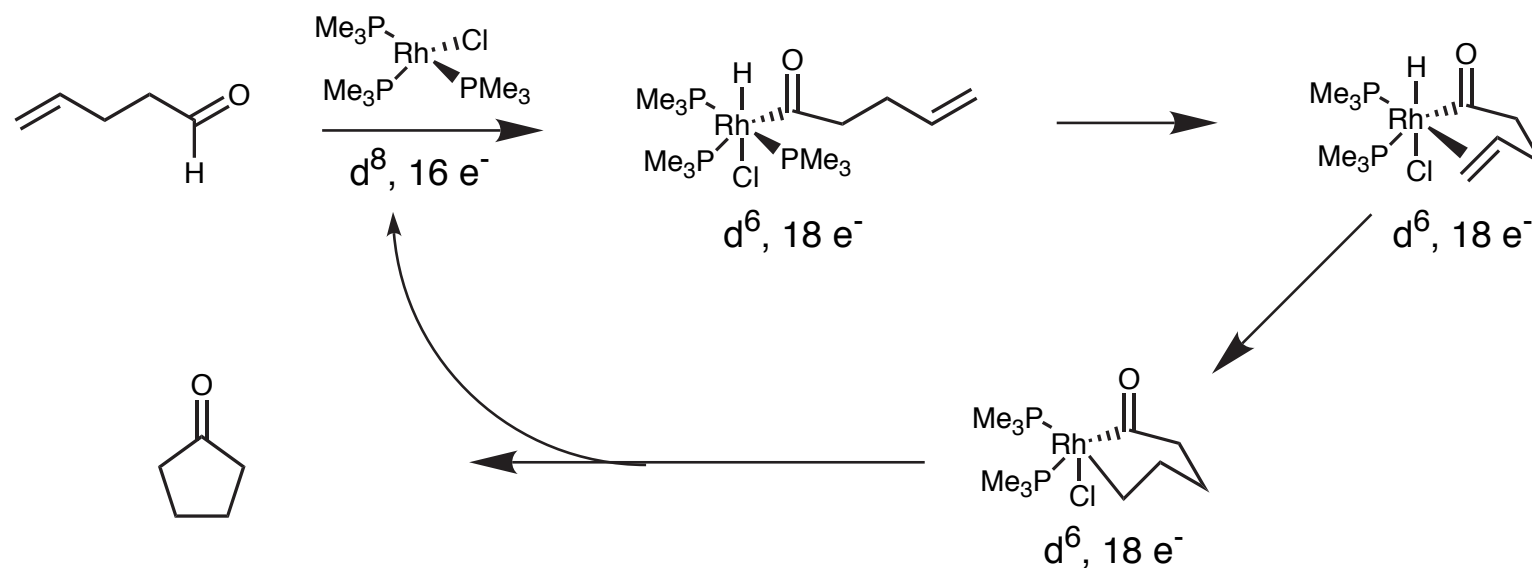
□ R. Bergman, *JACS*, **1988**, *110*, 8729



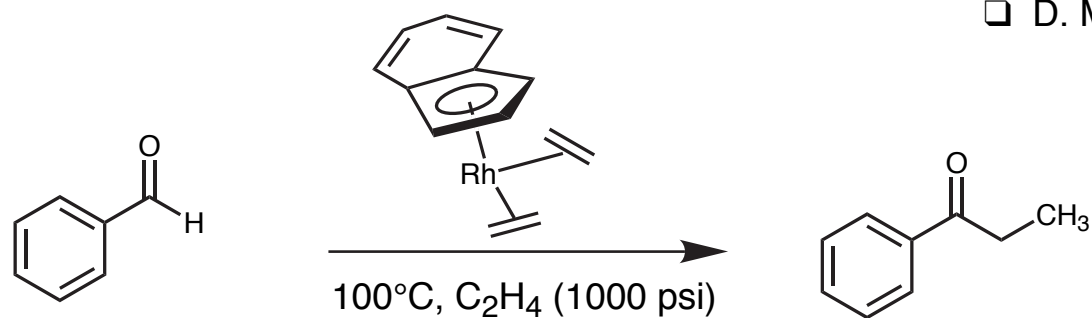
- Extrusion of alkane correlates with C-H bond strength
- $k_H(\text{CH}_3) / k_D(\text{ND}_3/\text{CH}_3) = 7.3$ ,  $k_H(\text{CH}_3) / k_D(\text{NH}_3/\text{CD}_3) = 1.32$
- Methane binding not detected in this system
- Standard  $\beta$ -elimination mechanism?

- C. Cummins, P. Wolczanski, *JACS* **1988**, *110*, 8731
- C. Cummins, P. Wolczanski, *JACS* **1991**, *113*, 2985
- P. Wolczanski, *JACS* **1994**, *116*, 4113

## Intermolecular Hydroacylation: C-H Bond Activation / C-C Bond Formation



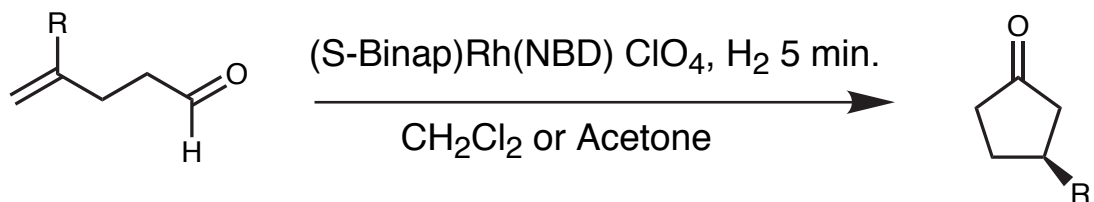
- Sakai, *Tet. Lett.* **1972**, 1287
- D. Milstein, *JCS CC*, **1982**, 1357



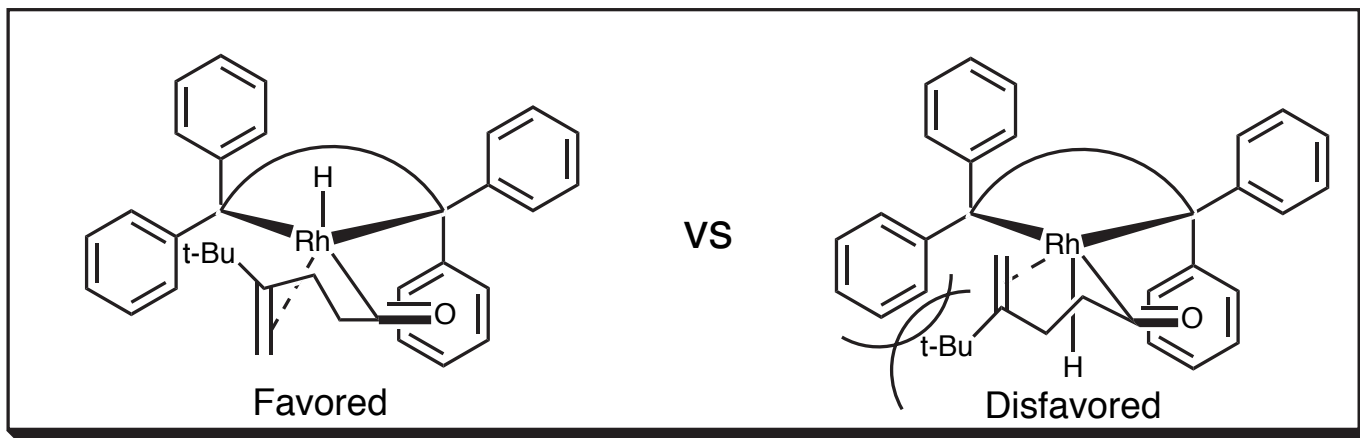
- D. Milstein, *Organomet.*, **1988**, 1451



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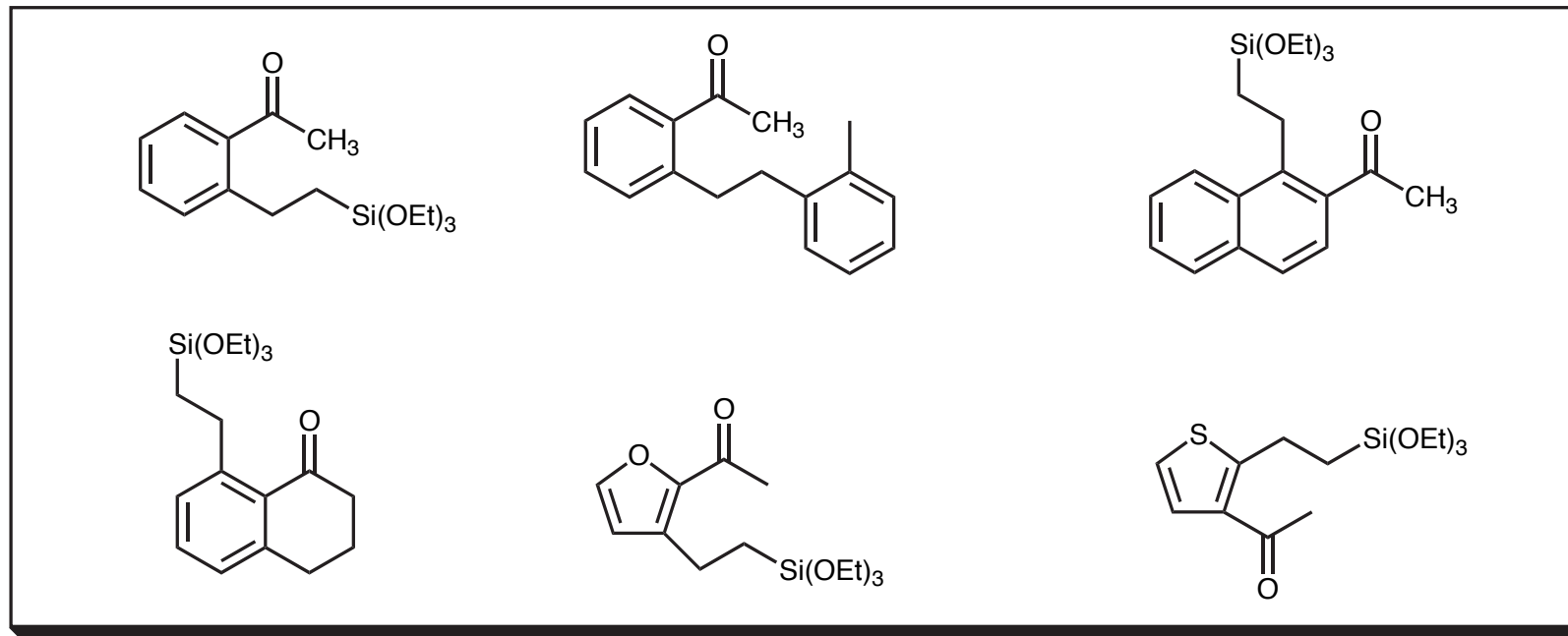
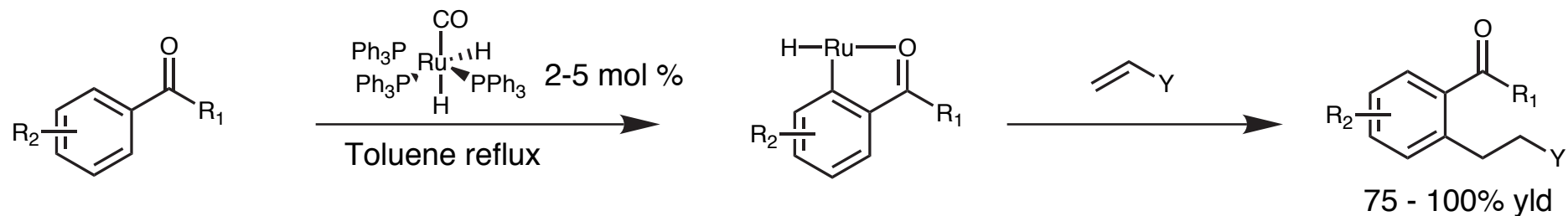


R	e.e.
Me	78
Ph	70
t-Bu	99
Me <sub>3</sub> Si	99
MeOC(CH <sub>3</sub> ) <sub>2</sub>	94
PhC(O)	94
t-BuC(O)	99
EtOC(O)	



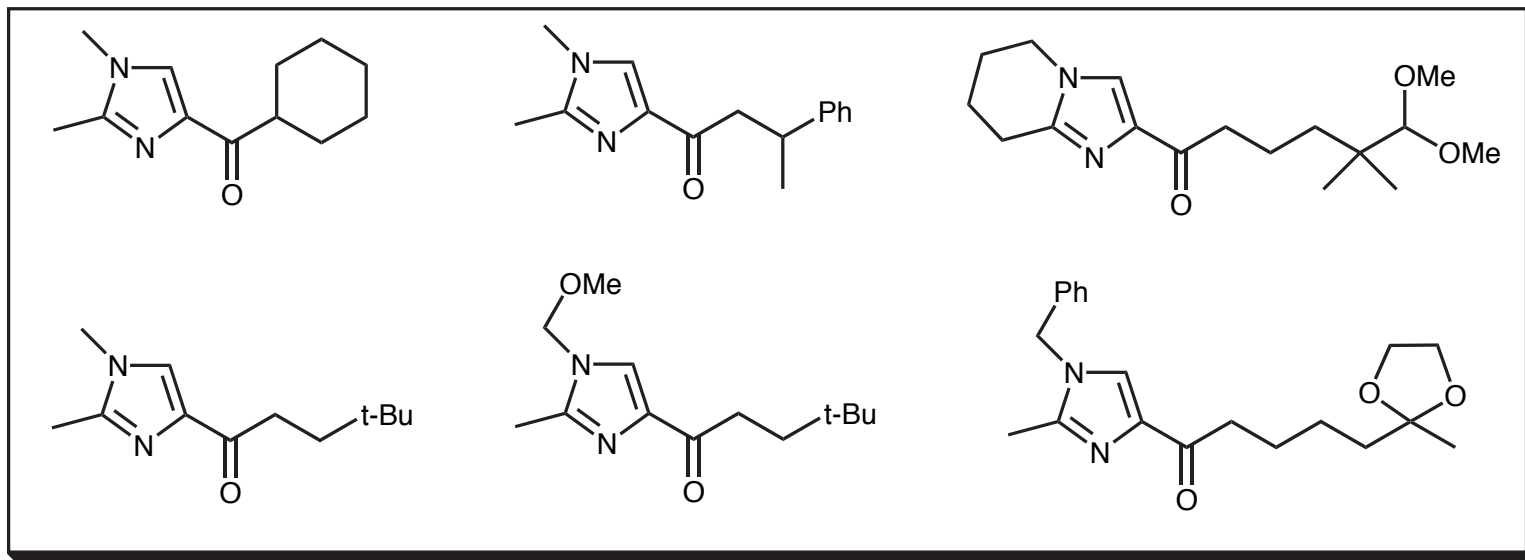
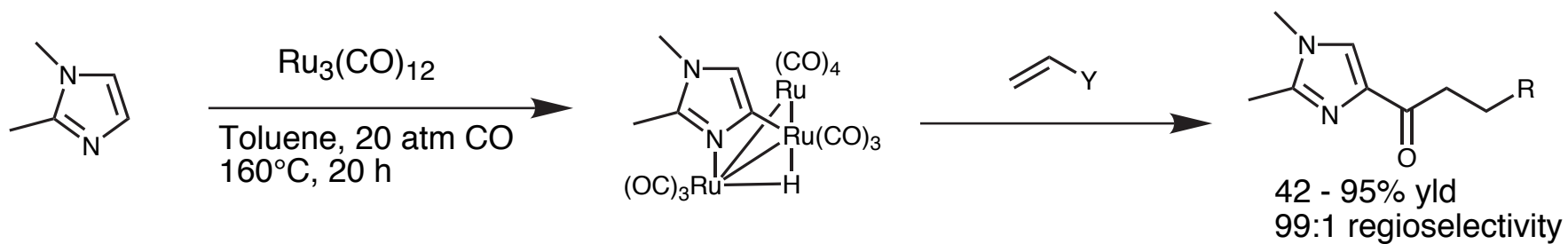
□ B. Bosnich, *JACS*, **1994**, 116, 1821

## Directed Functionalization of Aromatic C-H Bonds Using Catalytic Ruthenium



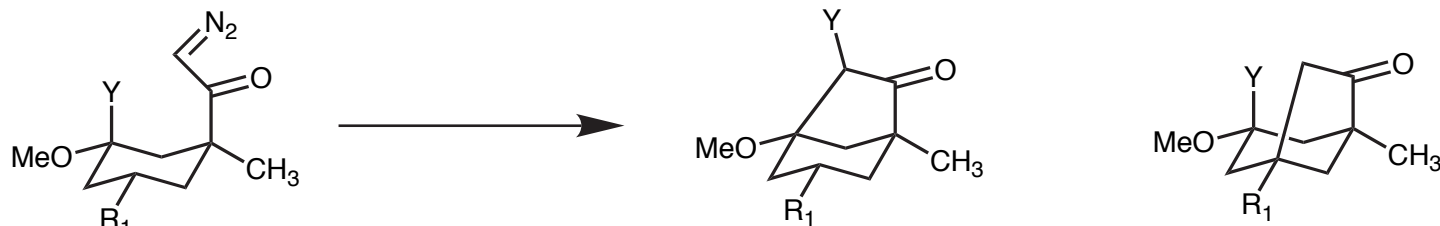
□ Murai, *Nature*, **1993**, 366, 529

## Shinji Murai Does It Again



□ Murai, *JACS*, **1996**, *118*,  
493

## Trends in the Rh(II) Catalyzed C-H Insertion

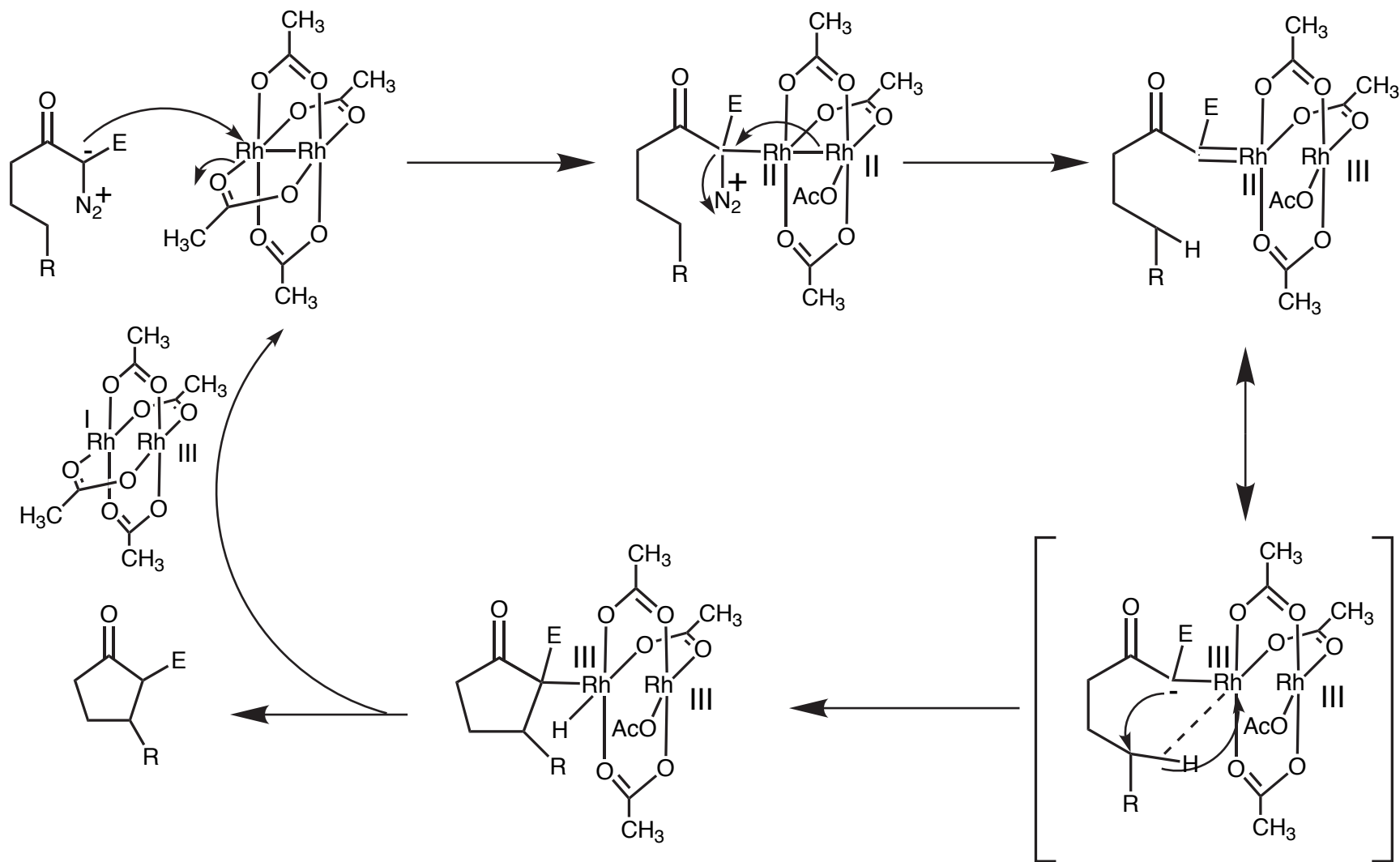


Rh <sub>2</sub> (X) <sub>4</sub>	R <sub>1</sub>	Y	Ratio
Rh <sub>2</sub> (OAc) <sub>4</sub>	OAc	H	99 : 1
Rh <sub>2</sub> (OAc) <sub>4</sub>	N <sub>3</sub>	H	1 : 8
Rh <sub>2</sub> (Cap) <sub>4</sub>	N <sub>3</sub>	H	1 : 30
Rh <sub>2</sub> (OAc) <sub>4</sub>	OMe	D	1 : 1.2
Rh <sub>2</sub> (Cap) <sub>4</sub>	OMe	D	1 : 2.0

- 3°H > 2°H ~ Ar-H > 1°H
- Alkyl > allyl ~ aryl
- C-H α to heteroatoms are activated towards C-H insertion
- C-H α and β to electron withdrawing groups are deactivated towards C-H insertion
- More hindered sites undergo slower rates of C-H insertion
- The reaction proceeds with retention of configuration at the reacting site
- Five-member rings are preferentially formed
- More basic ligands on rhodium will increase the aforementioned selectivity

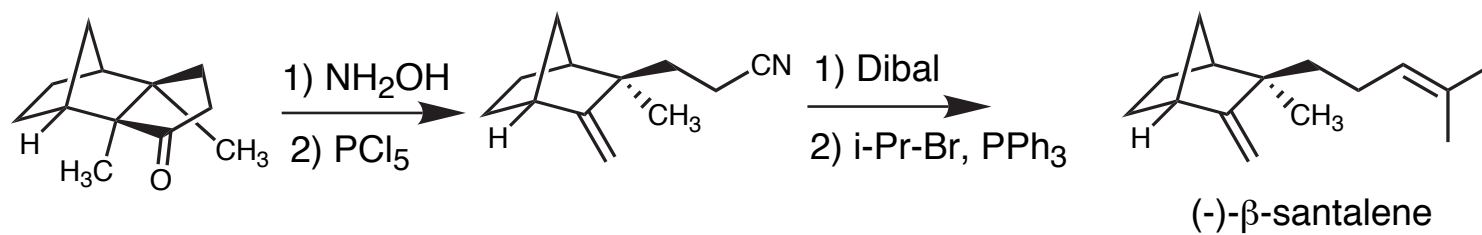
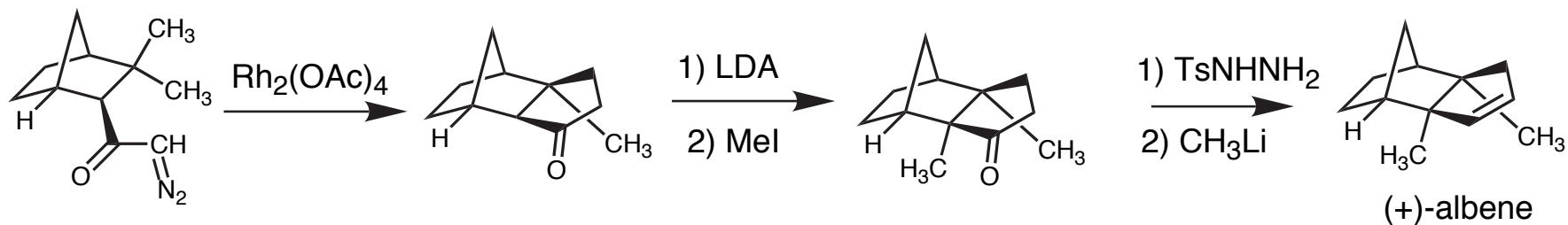
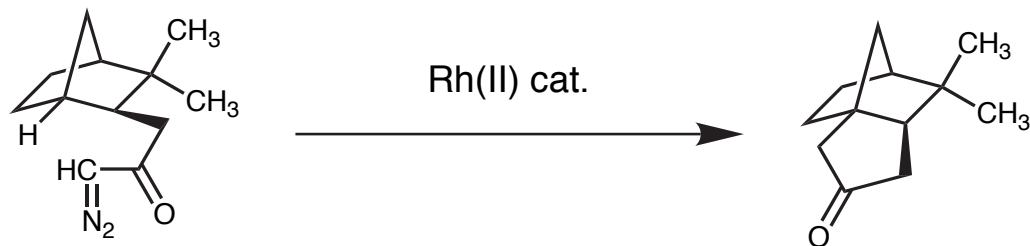
- J. Adams, *Tet. Letters*, **1989**, 30, 1749
- G. Stork, *Tet. Letters*, **1988**, 29, 2283
- M. Doyle, *Tet. Letters*, **1989**, 30, 7001
- J. Adams, *JACS*, **1994**, 116, 3296

## Mechanism of Rh(II) Catalyzed C-H Insertion



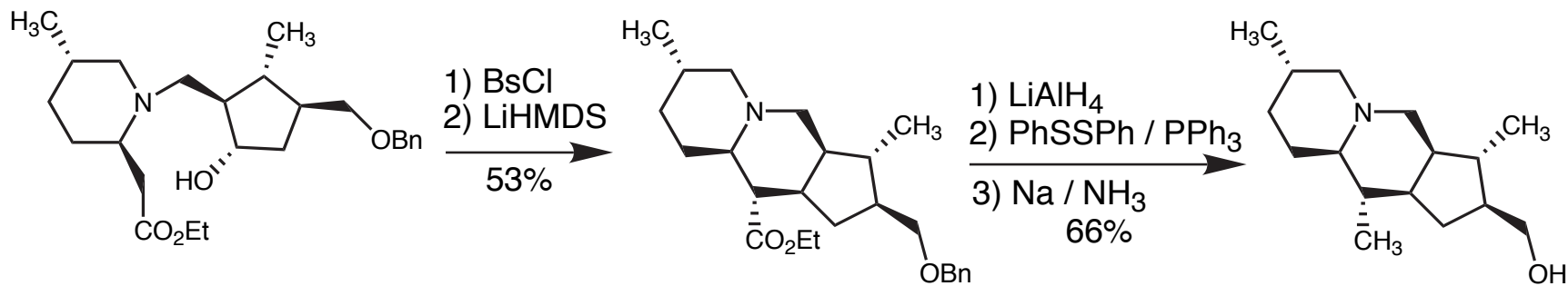
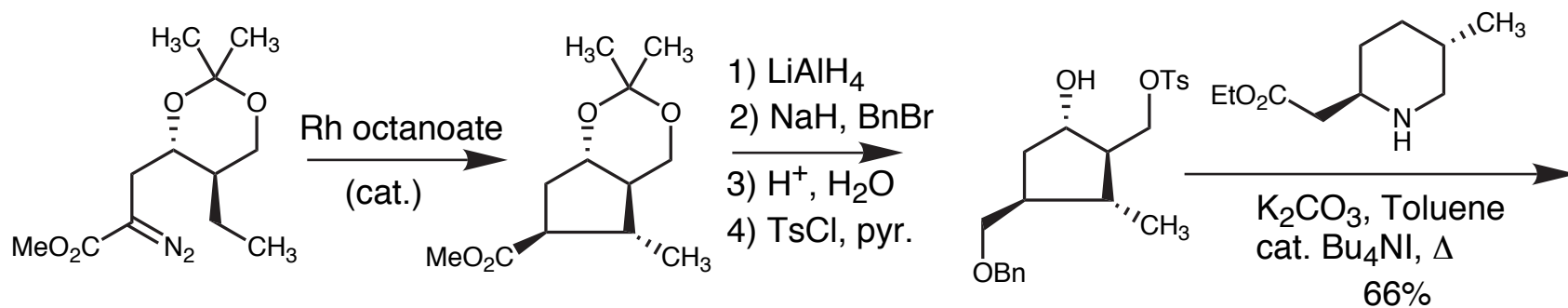
Speculation by K. Campos based on  
 □ J. Adams, *Tetrahedron*, **1991**, *47*, 1765

## *C-H Insertion Reactions: Applications to Synthesis*

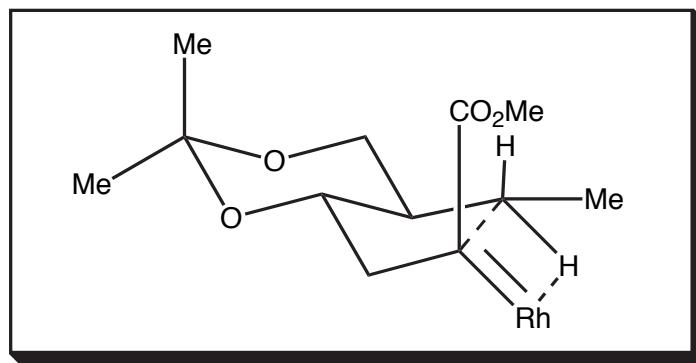


□ H. Sonawa, *J. Org. Chem.* **1991**, *56*, 1434

*Asymmetric C-H Insertion Reactions:  
Applications to Synthesis  
Dendrobatid Alkaloid (251F)*



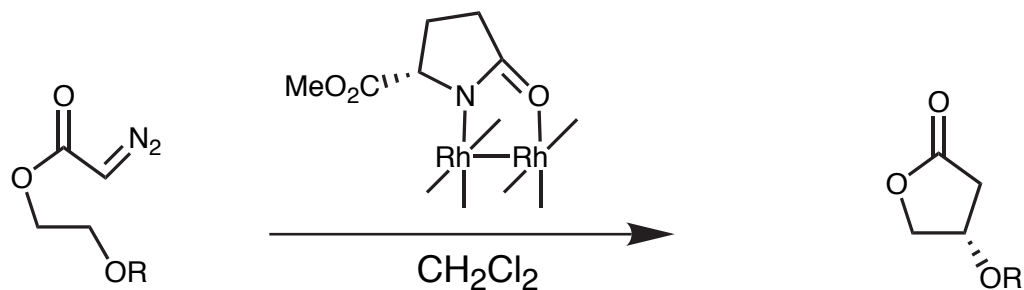
□ D. Taber, *JACS*, **1995**, 5757



Some insight on the stereochemical outcome

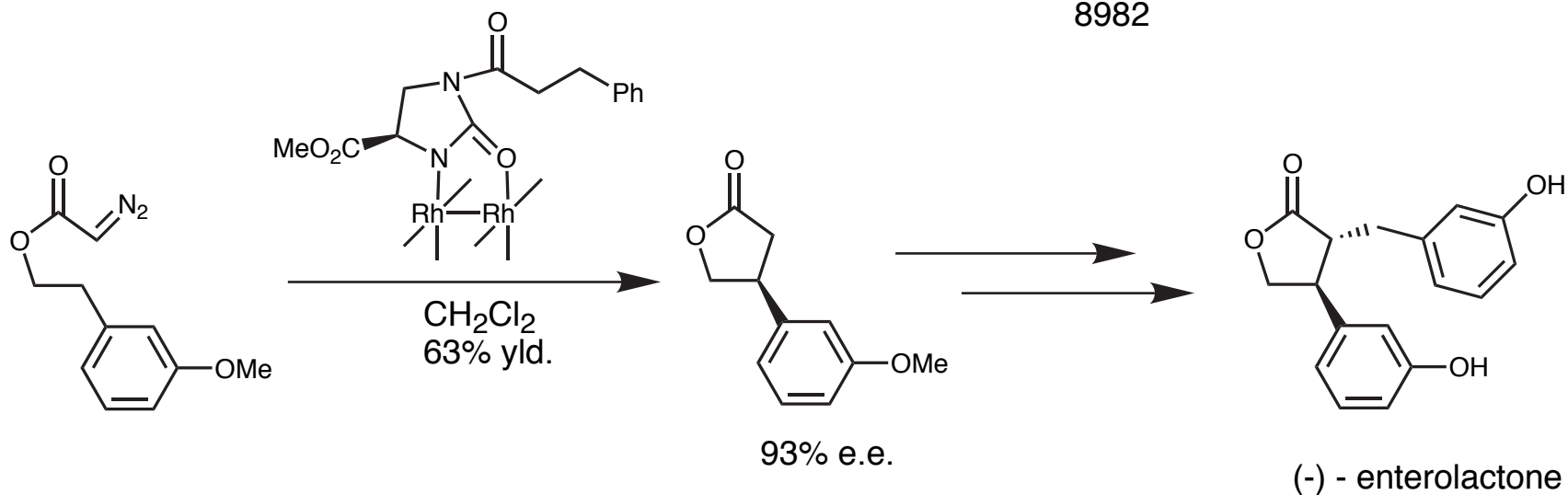
□ D. Taber, *JACS*, **1996**, 118,

## Asymmetric C-H Insertion Reactions: Synthesis of Dibenzylbutyrolactone Lignans



R = Me 91% e.e.  
Et 89% e.e.  
Bn 87% e.e.

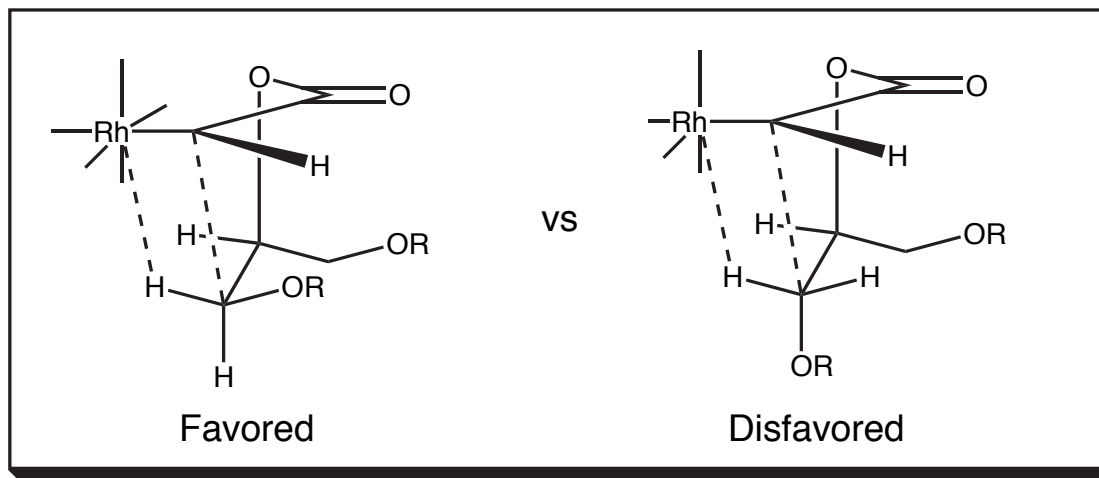
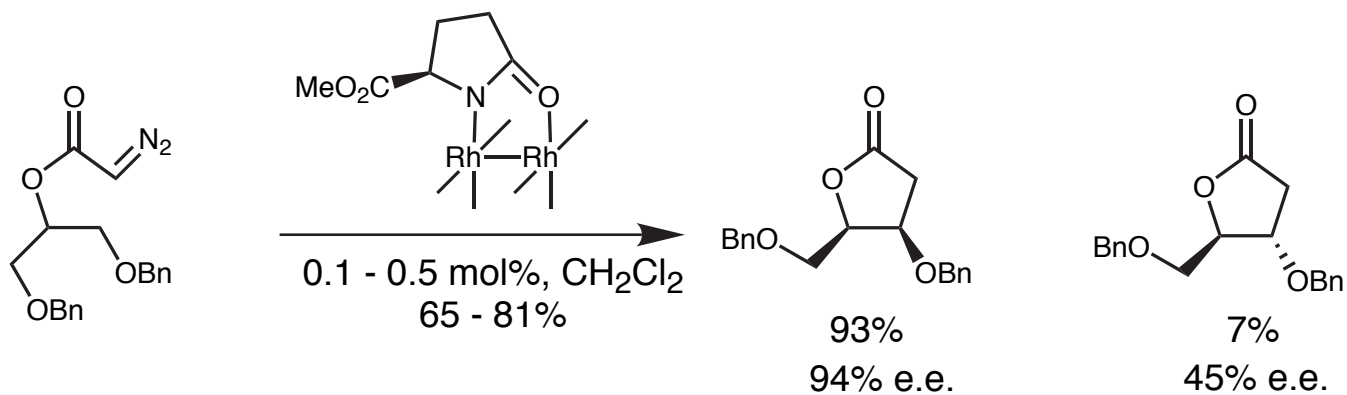
□ M. Doyle, *JACS* **1991**, *113*, 8982



□ M. Doyle, *J. Org. Chem.* **1995**, *60*, 6654



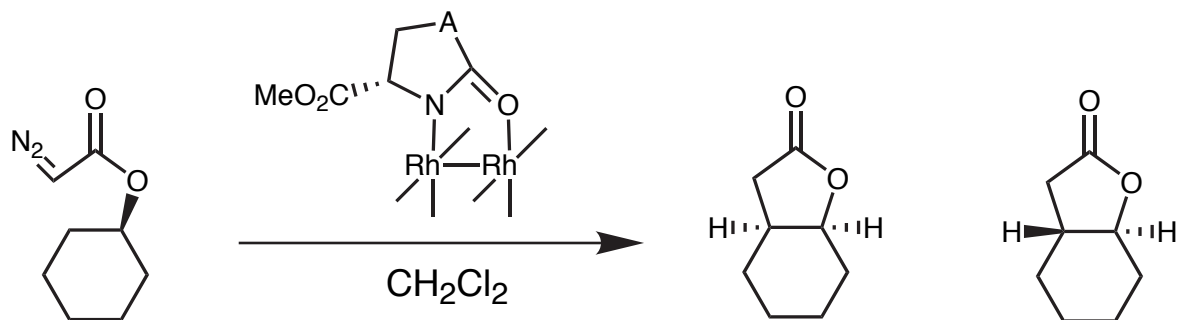
## Asymmetric C-H Insertion Reactions: Synthesis of Deoxyxylolactone



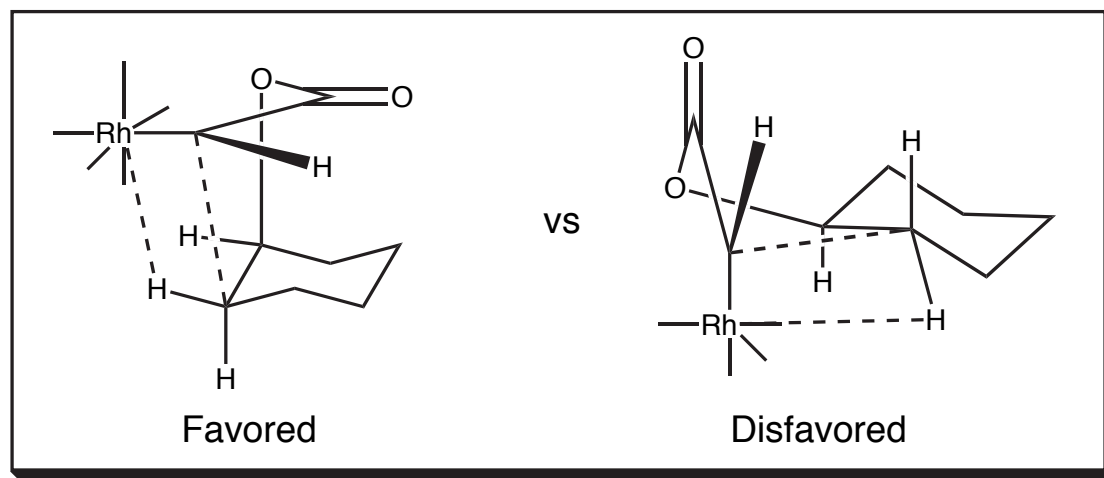
Postulated Conformation Leading to Observed Product

□ M. Doyle, A. Dyatkin, J. Tedrow, *Tet. Letters*, **1994**, *35*, 3853

## Asymmetric C-H Insertion Reactions: More Doyle Results

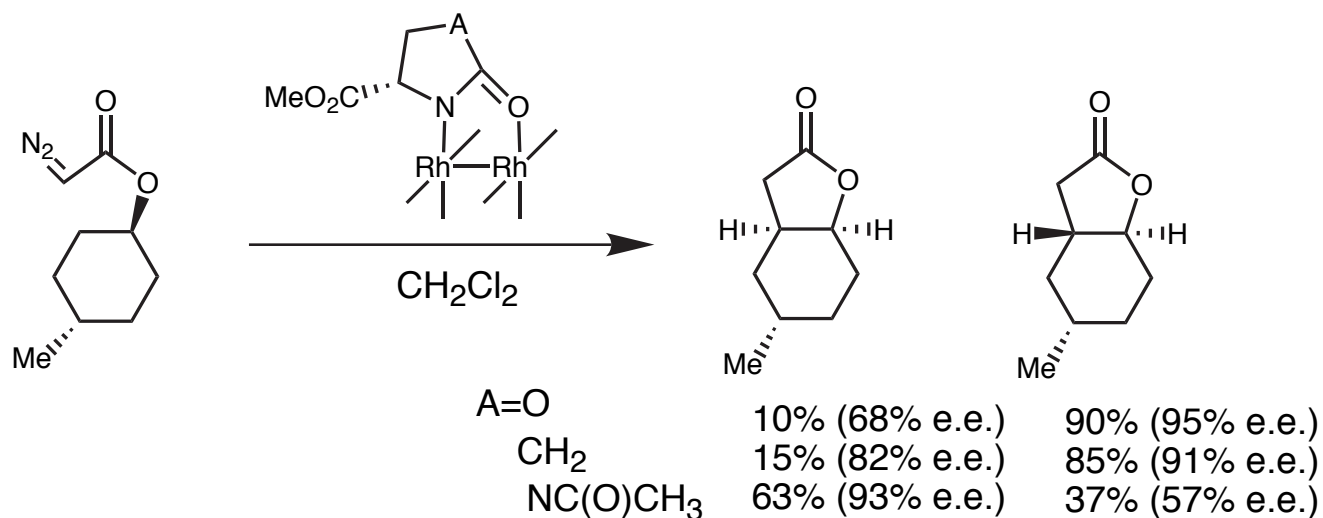
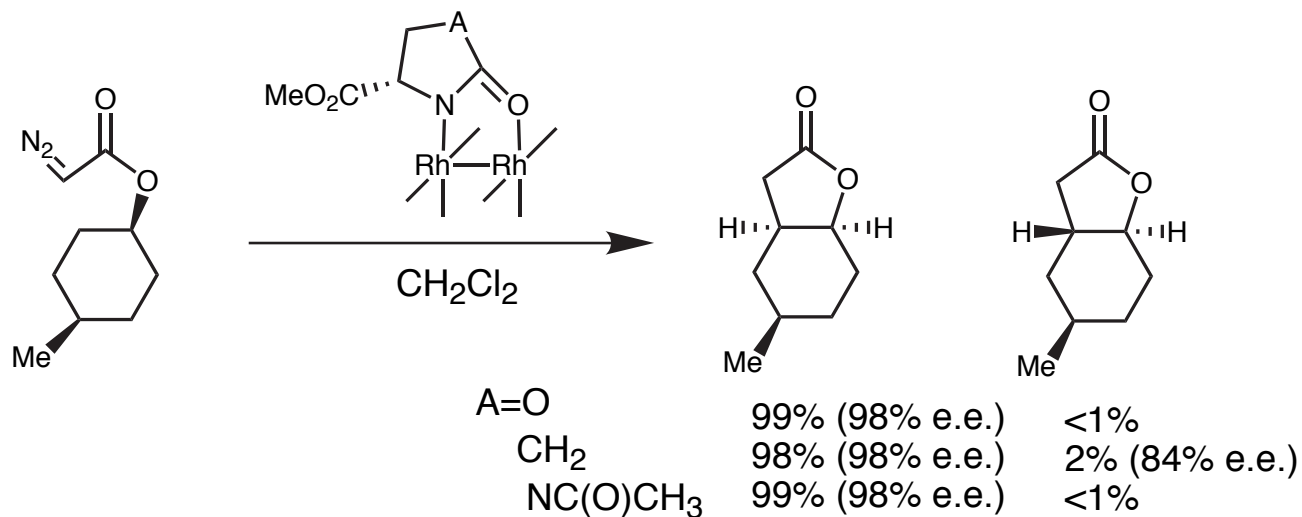


A=O	55% (96% e.e.)	45% (95% e.e.)
CH <sub>2</sub>	75% (97% e.e.)	25% (91% e.e.)
NC(O)CH <sub>3</sub>	99% (97% e.e.)	1% (65% e.e.)

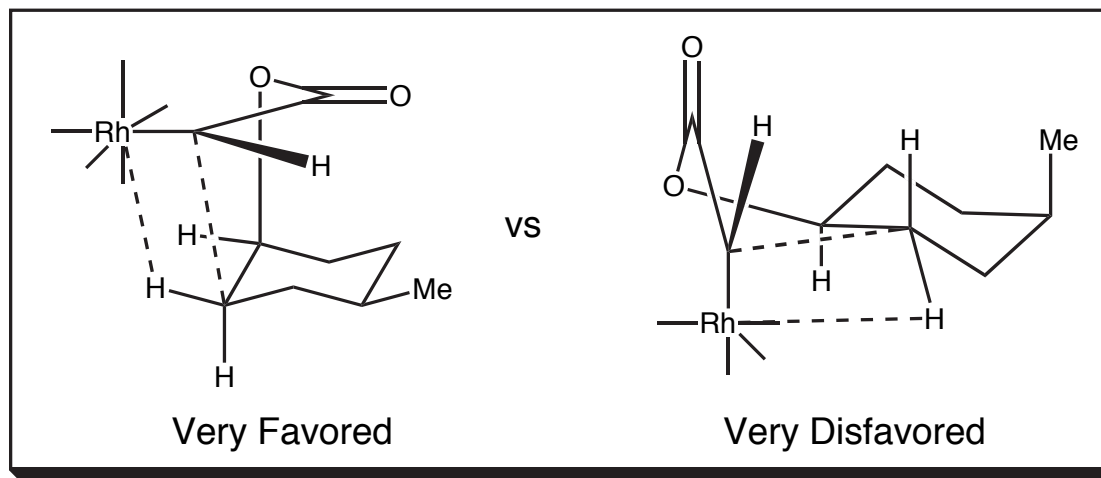


Postulated Conformation Leading to Observed Diastereomer

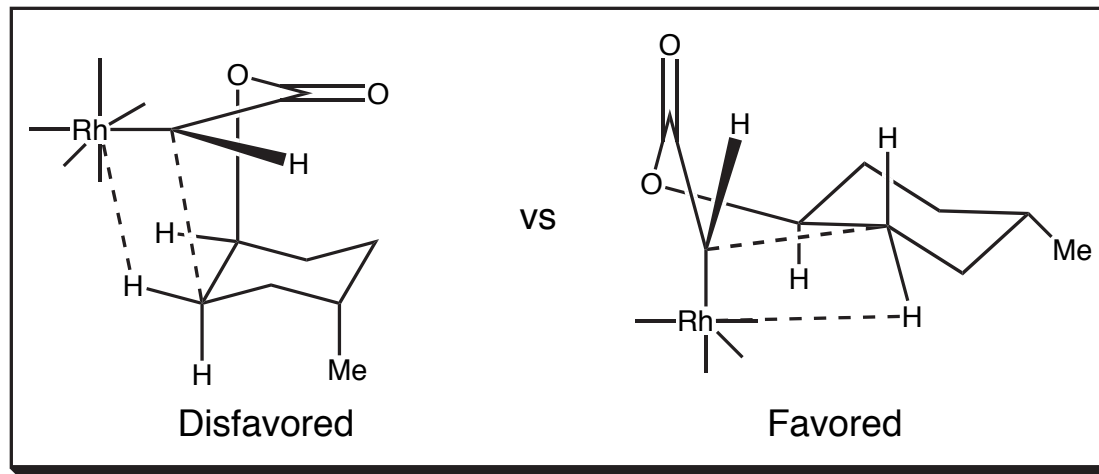
## Asymmetric C-H Insertion Reactions: Double Stereodifferentiation Observed



## Asymmetric C-H Insertion Reactions: More Doyle Results

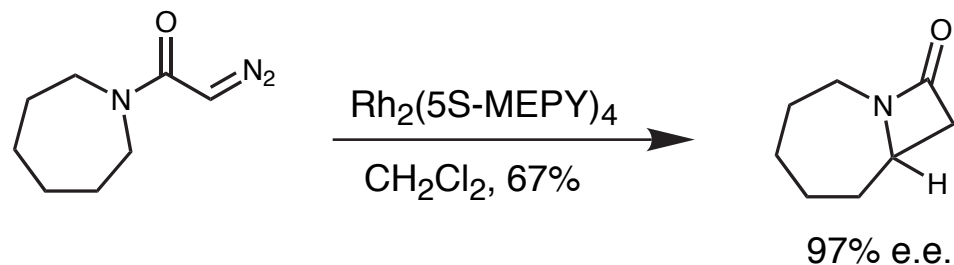


The Matched Case

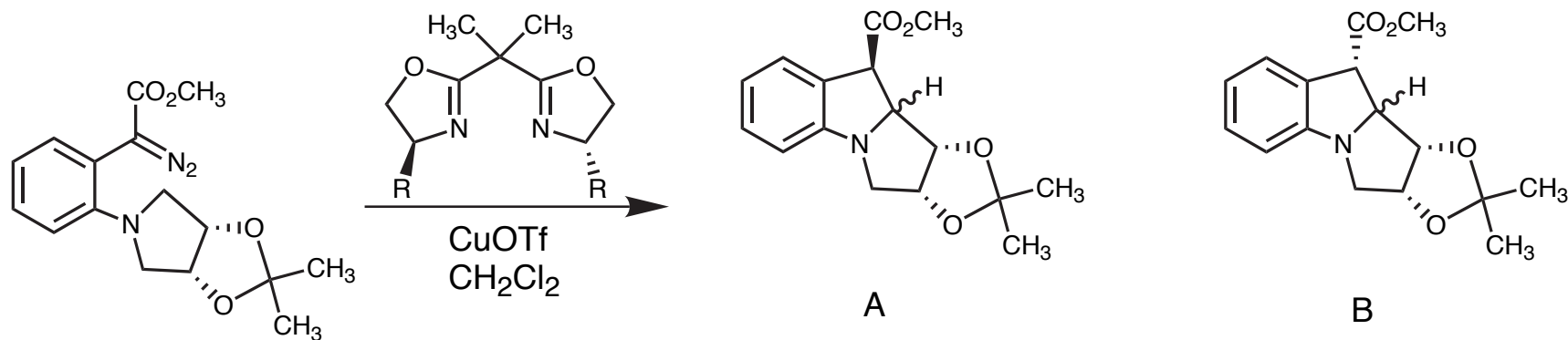


The Mismatched Case

## Asymmetric C-H Insertion Reactions: Insertion $\alpha$ to Nitrogen



M. Doyle



Catalyst	%A (trans : cis)	%B (trans : cis)
$\text{Rh}_2(\text{OAc})_4$	50% (3:1)	50% (10:1)
$\text{Rh}_2(5(\text{S})\text{-MEPY})_4$	38% (5:95)	62% (5:95)
$\text{CuOTf}$ , R = iPr	33% (1:1)	67% (2:1)
$\text{CuOTf}$ , R = t-Bu	33% (9:1)	67% (1:1)
$\text{CuOTf}$ , R = Ph	33% (13:1)	67% (1:2)