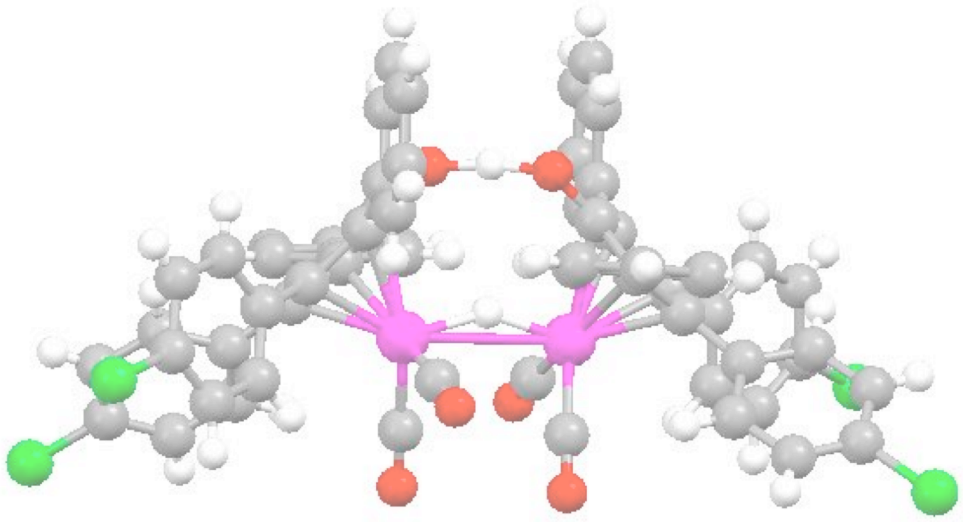
A Long Standing Argument Over the Transfer of a Hydride: Inner versus Outer Sphere Mechanisms Involving Imines

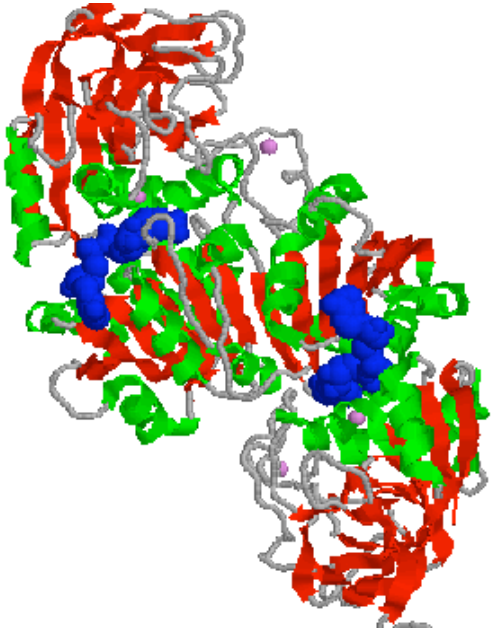


Russell C. Smith

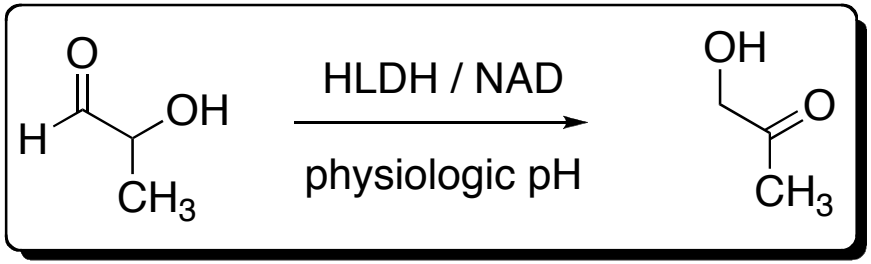
Denmark Group Meeting

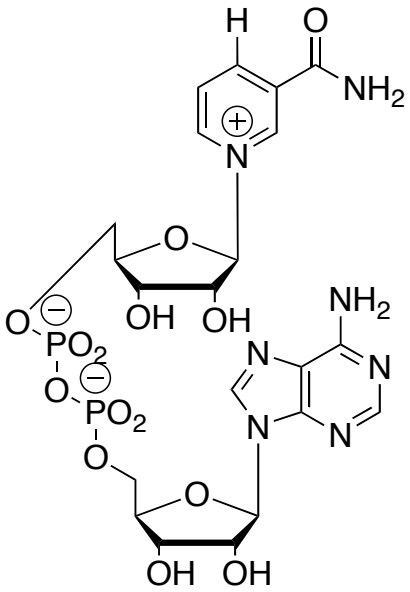
10-16-2007

Nature's Transfer Hydrogenation



- Horse Liver Dehydrogenase
  - Symmetrical dimer containing 2 Zn metals
  - Enzyme uses NAD as coenzyme to shuttle hydride
  - Number of studies have studied the kinetics and specific binding of this enzyme (NAD binds to two specific sites)





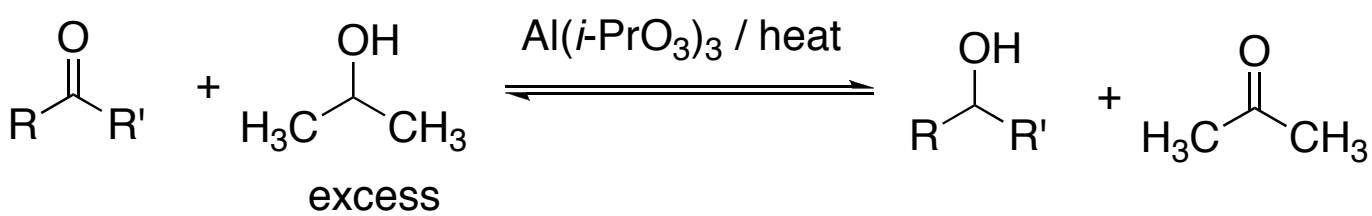
NAD

J. Biolog. Chem. **1961**, *236*, 1531-1533.

http://chemistry.umeche.maine.edu/CHY252/Enzyme7.html

Meerwein-Ponndorf-Verley Reduction

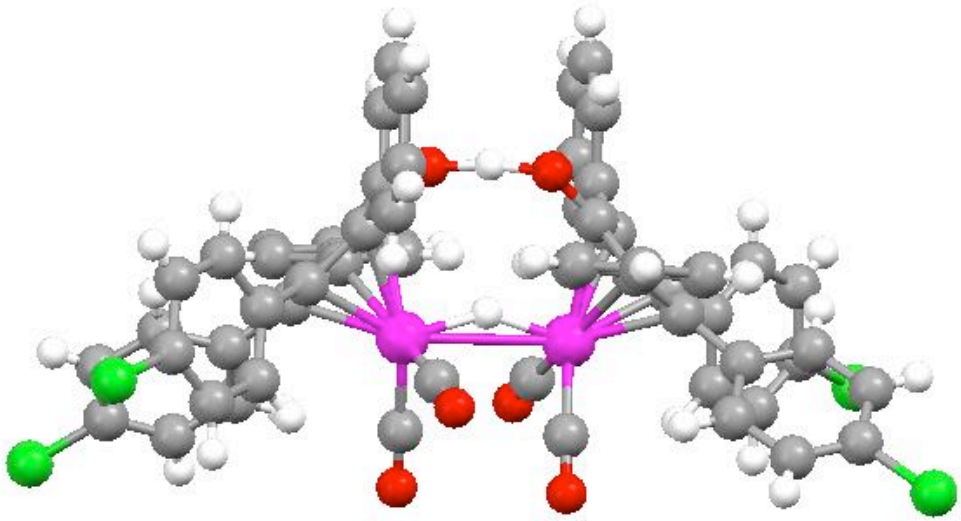
- Almost simultaneously discovered in the mid-1920s
- Used stoichiometric amounts of metals alkoxides
- Discovered that reaction is reversible (Oppenauer Oxidation)



* Crucial aspect was the recognition that a hydride could be delivered from an organic molecule

Oxidation / Reduction Goes Catalytic

- In 1984, Shvo and coworkers determined that cat. of formula $[(Ph_4C_4C{=}O)(CO)_2Ru]_2$ promoted similar ox/red transformations
- Identified structure through x-ray analysis

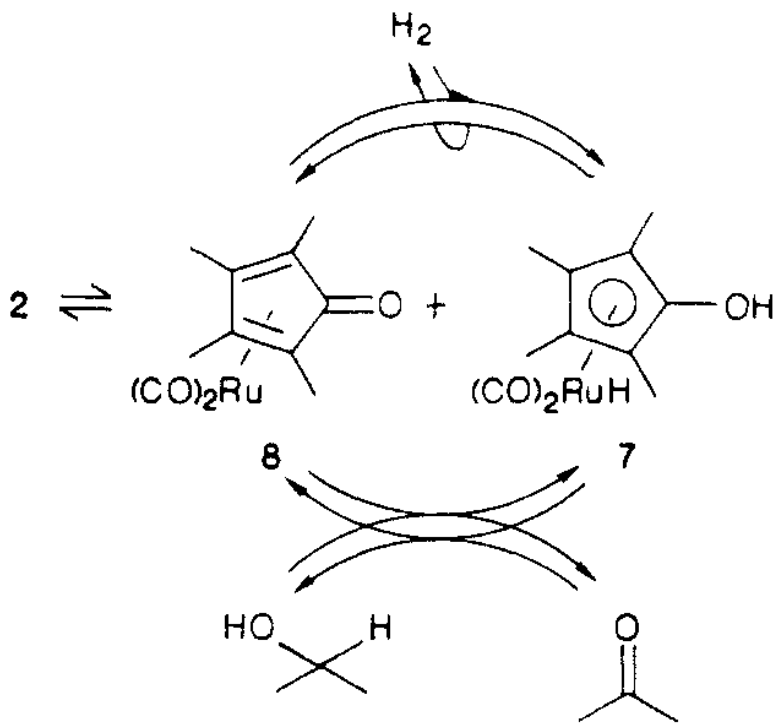


Initial kinetics of hydrogenation of cyclohexanone displayed $[Ru]^{0.5}$

J. Am. Chem. Soc. **1986**, *108*, 7400-7402

Oxidation / Reduction Goes Catalytic

- Used both IR and NMR to determine structures from dimer breaking

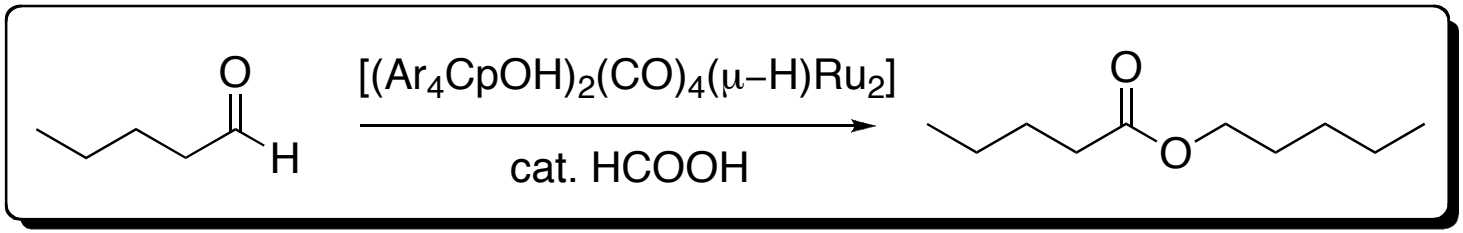


Most of the π-character in IR stretch was lost (band @ 1550 cm^{-1})

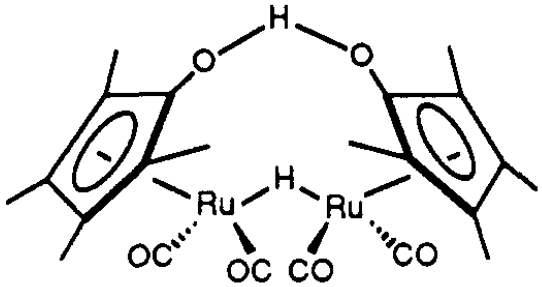
^{13}C NMR of hydrogenated 2 shows a signal @ 137.3 ppm ==> indicative of increased aromaticity

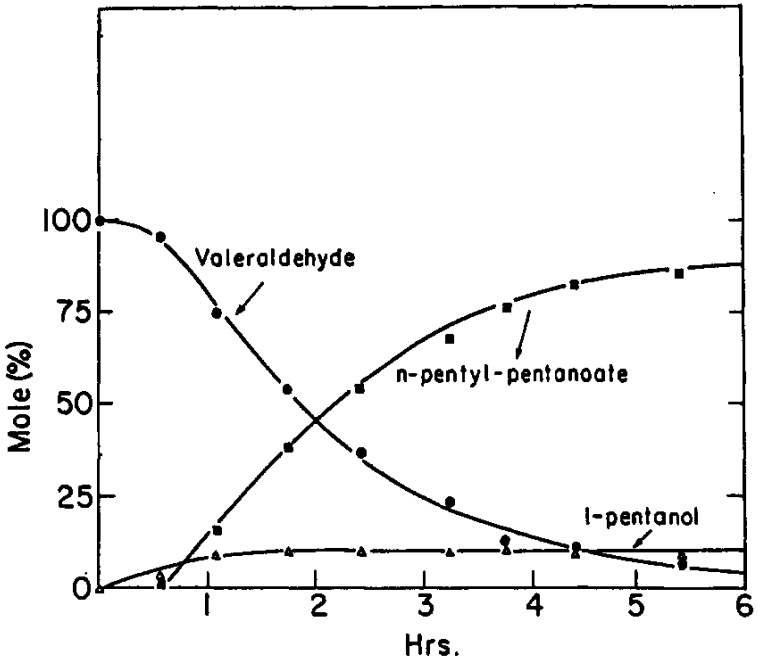
J. Am. Chem. Soc. **1986**, *108*, 7400-7402

Difference in Reactivity using Aldehydes



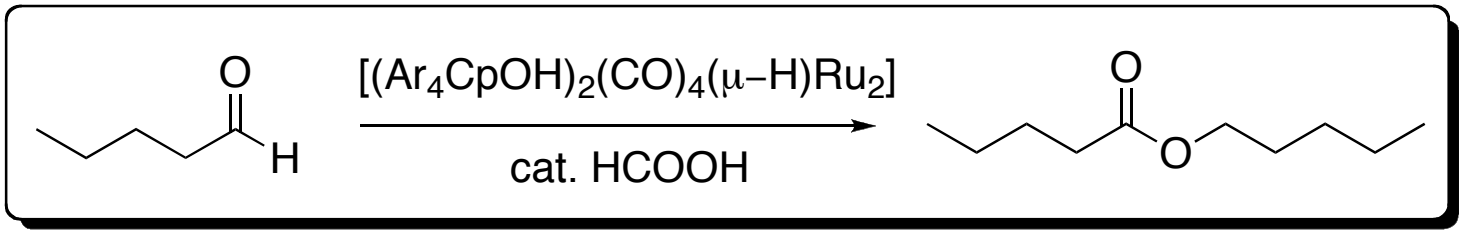
- Determined rate = $k[cat]^{0.5}[CHO]$



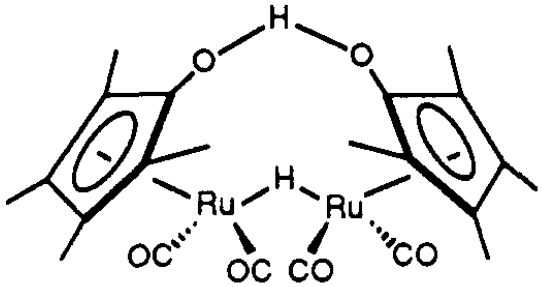


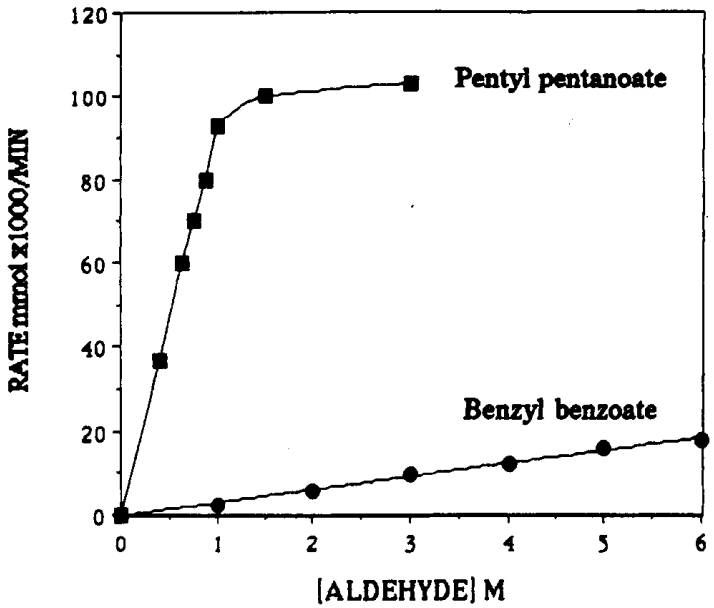
Organometallics. **1991**, *10*, 3885-3891

Difference in Reactivity using Aldehydes



- Different behaviors were noted with aliphatic and aromatic CHO



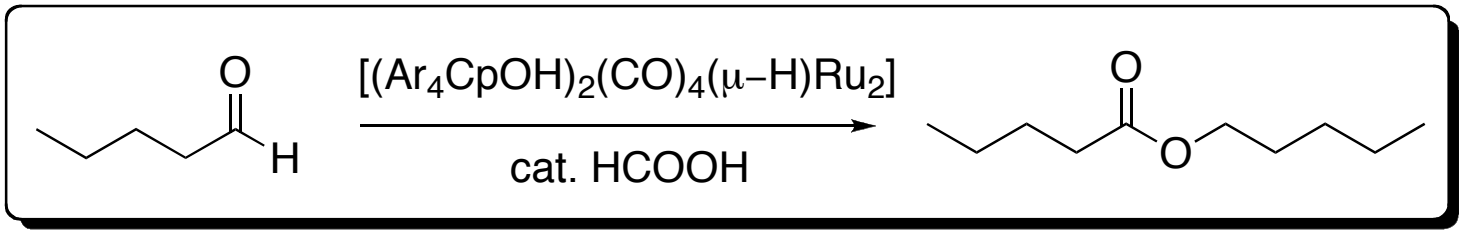


Deuterium Labeling Exp:

PhCOD + DCOOH -> $PhCOOCD_2Ph$

Organometallics. **1991**, *10*, 3885-3891

Difference in Reactivity using Aldehydes



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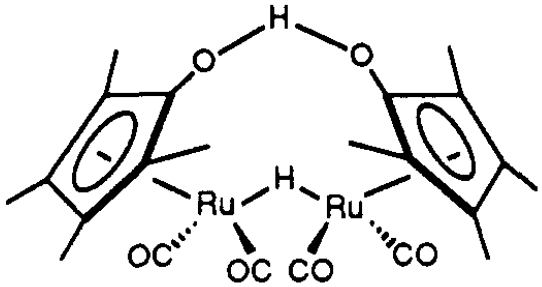
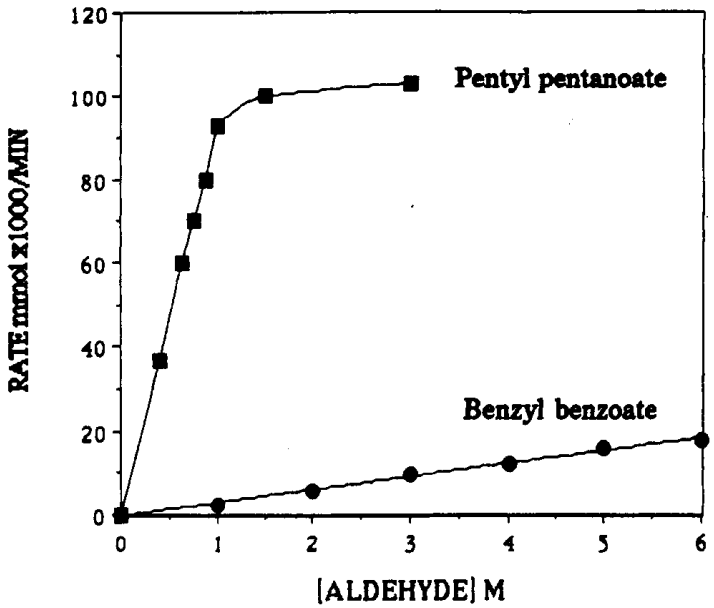
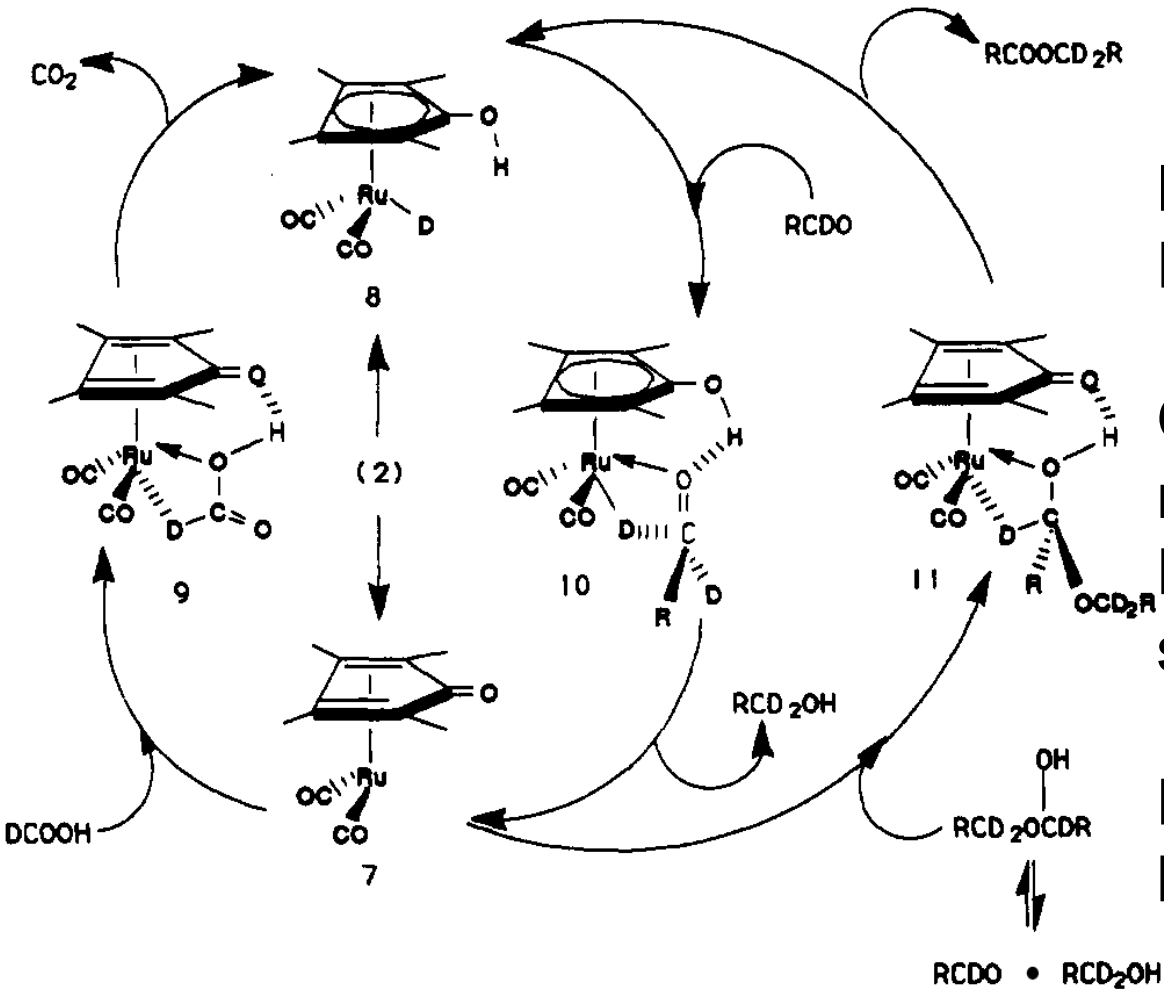




Based on these findings… propose a basic mechanism that accounts for the observed data!!

Hemiacetal serves as reactive intermediate



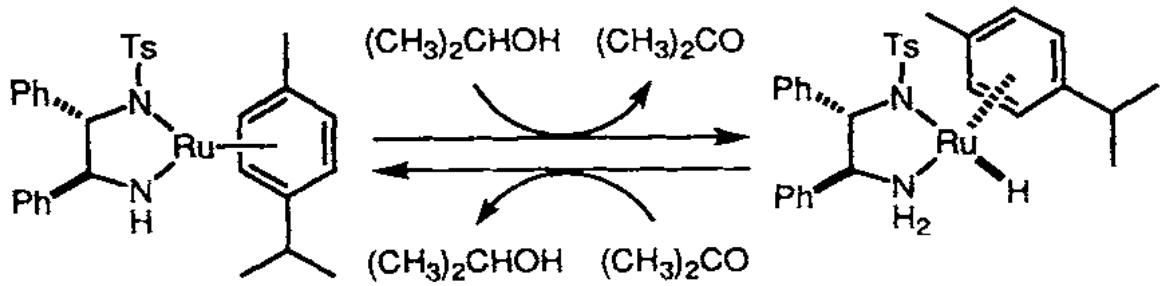
Both acidic and hydridic H atoms are well defined

Oxidation of hemiacetal must serve as RDS…additionally lack of sig. KIE suggests binding

No Ru-O species could be isolated

Ru catalyzes the oxidation/reduction of aldehydes through a discrete monohydride intermediate

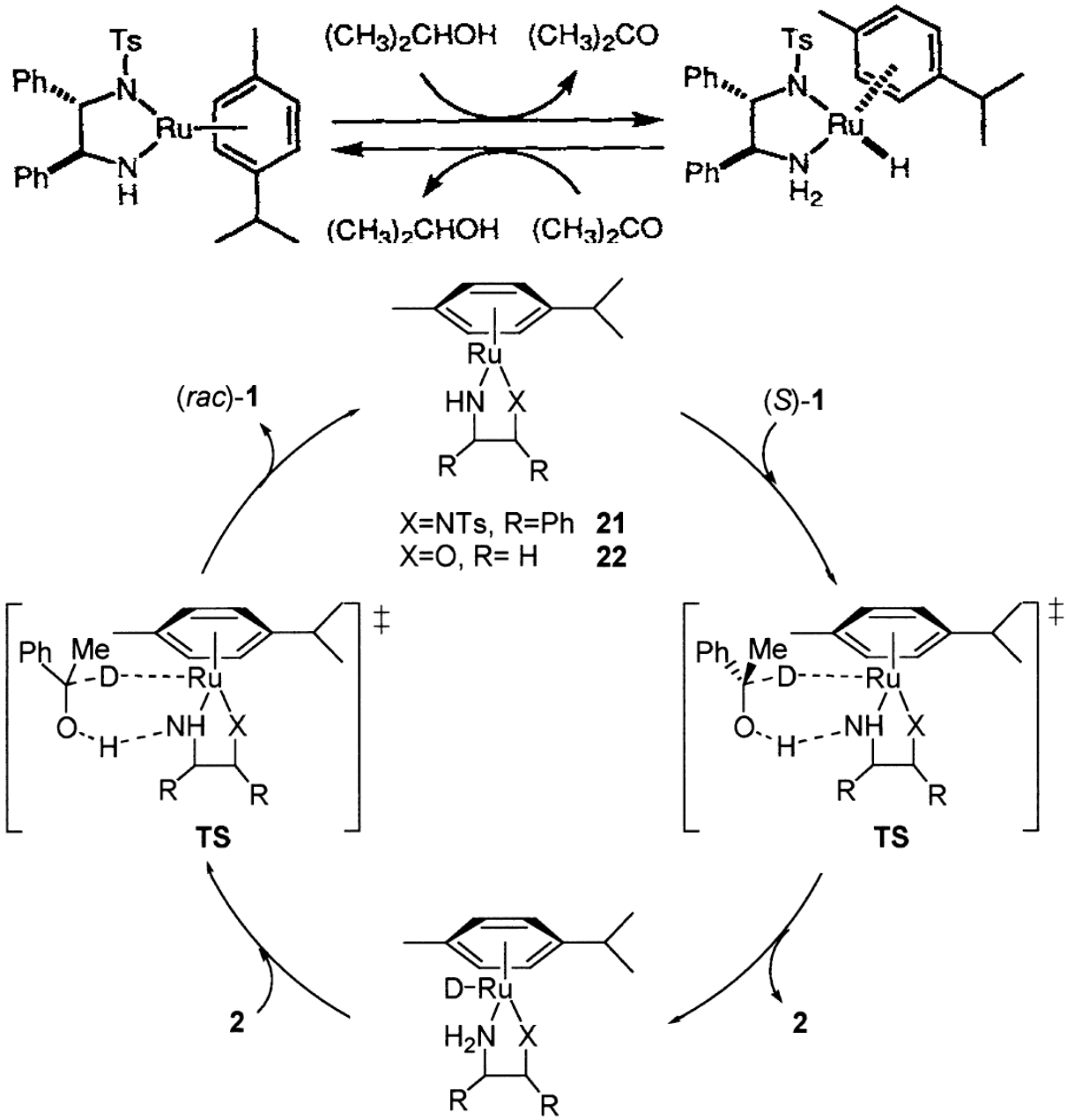
Dual Function of Ru-diamine catalyst



- Independently isolated the two intermediates and have shown catalytic competency
- Second order kinetics observed
- Computational support has also provided support for this mechanism

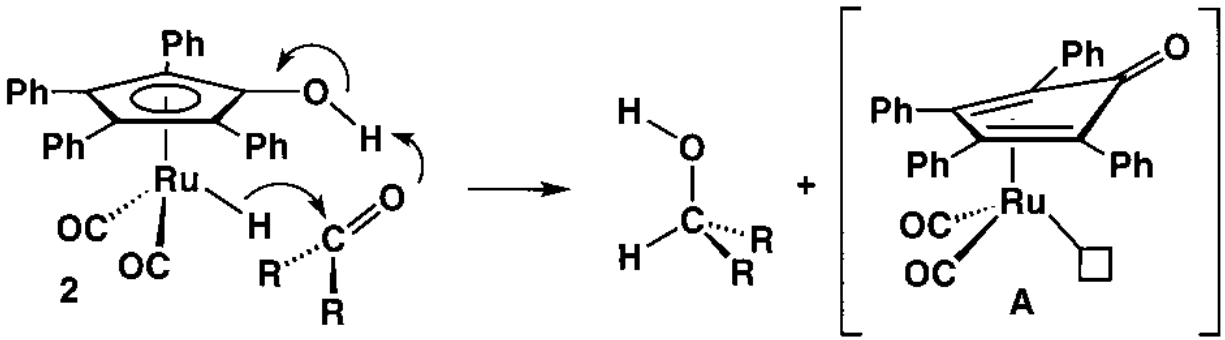
Angew. Chem. Int. Ed. **1997**, *36*, 285-288

Dual Function of Ru-diamine catalyst

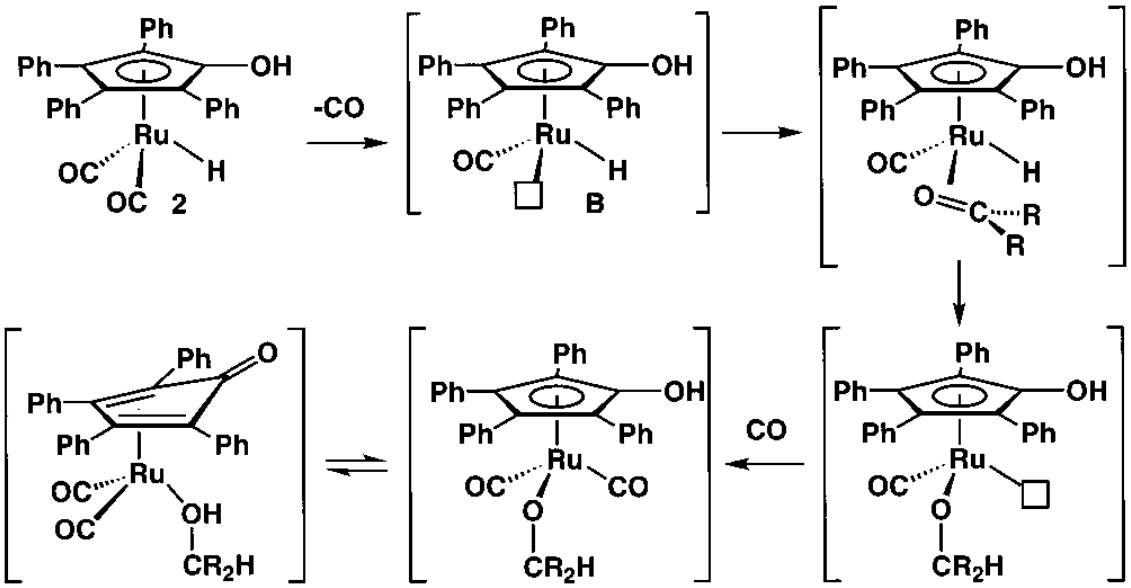


What are the possible mechanisms using the Shvo-type catalyst?

- Similar to Noyori's mechanism: concerted, outer sphere process

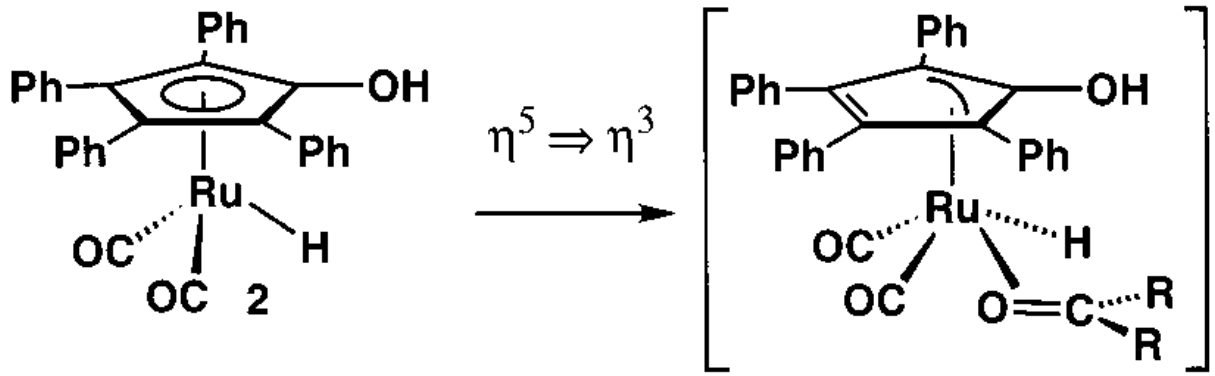


- Loss of CO, followed by carbonyl coordination



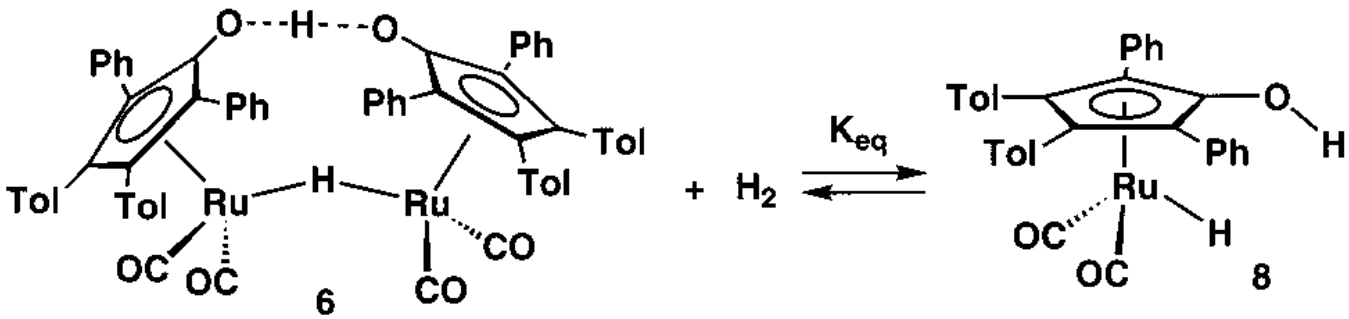
What are the possible mechanisms using the Shvo-type catalyst?

- η^5–>η^3 Ring slippage concurrent with CHO complexation



What would be some possible experiments to distinguish these three mechanisms?

Kinetics of PhCHO Reduction



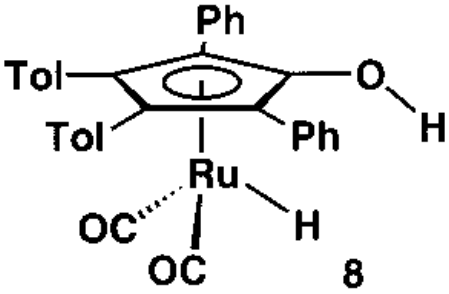
- Intermediate 8 was mixed with an excess of PhCHO (4 different [CHO])
  - Rate = $2k_2$[8][PhCHO]
- Zeroth order dependence on [CO]

- Measured temp dependence (0 to -15 °C) on rate
  - Erying plot gave ΔH = 12 kcal/mol and ΔS = -28 kcal/mol

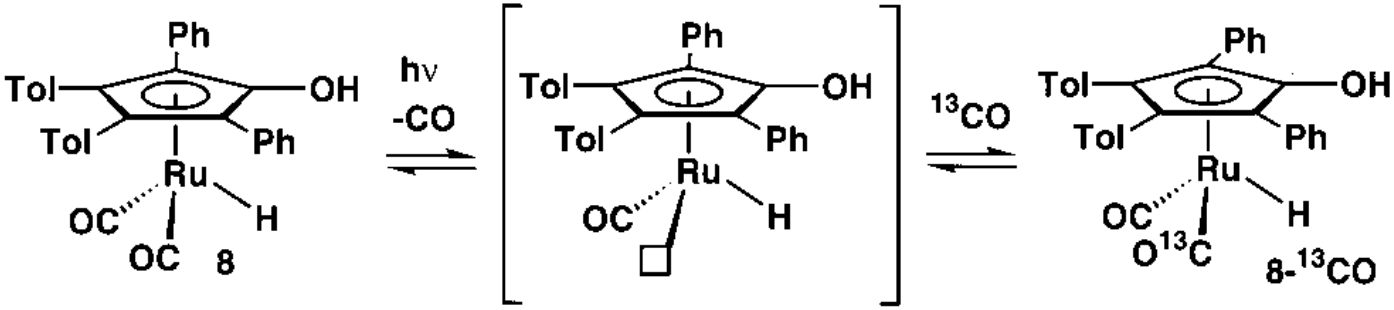
TS is highly ordered, consistent with an associative mechanism

Effects of Various Isotope Substitutions

k_{OHRuH}/k_{OHRuD}	1.5 ± 0.2
k_{OHRuH}/k_{ODRuH}	2.2 ± 0.1
k_{OHRuH}/k_{ODRuD}	3.6 ± 0.3
k_{ODRuH}/k_{ODRuD}	1.6 ± 0.2
k_{OHRuD}/k_{ODRuD}	2.3 ± 0.4



- Added D_2O to eliminate adventitious H sources

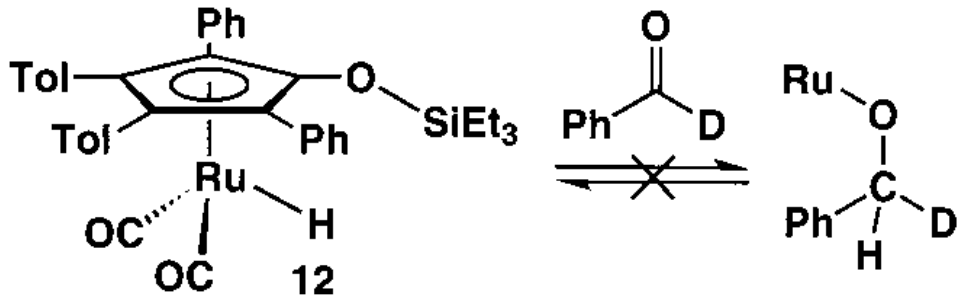


- CO excnange required light
  - In absence of light, < 5 % exchange occurred

In combination with [CO] dependence, CO dissociation unlikely

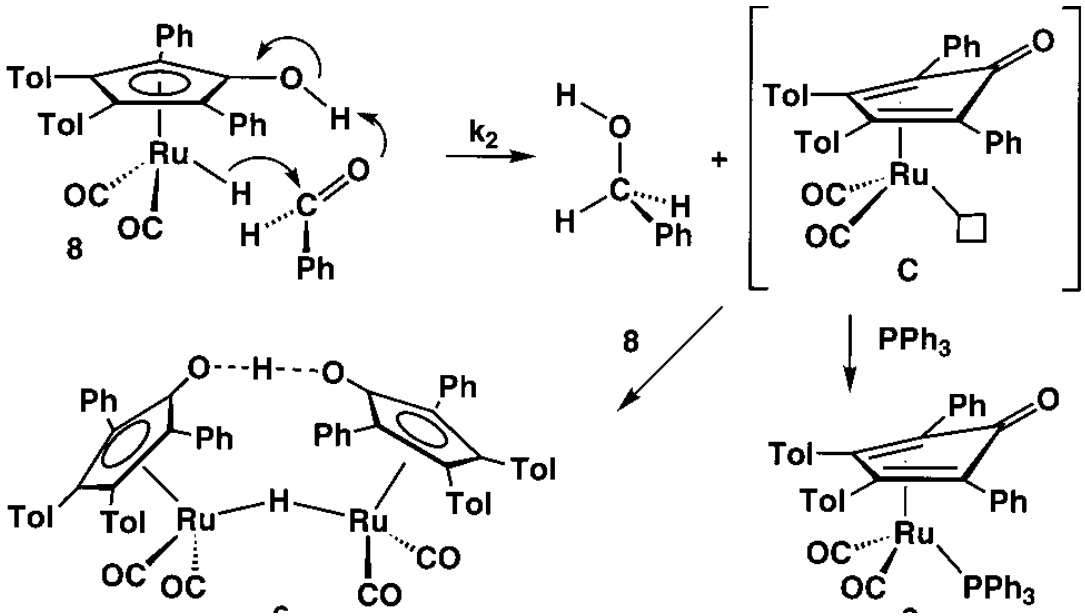
Studies on Ruthenium Complexes

- Importance of protic H atom on Cp ring

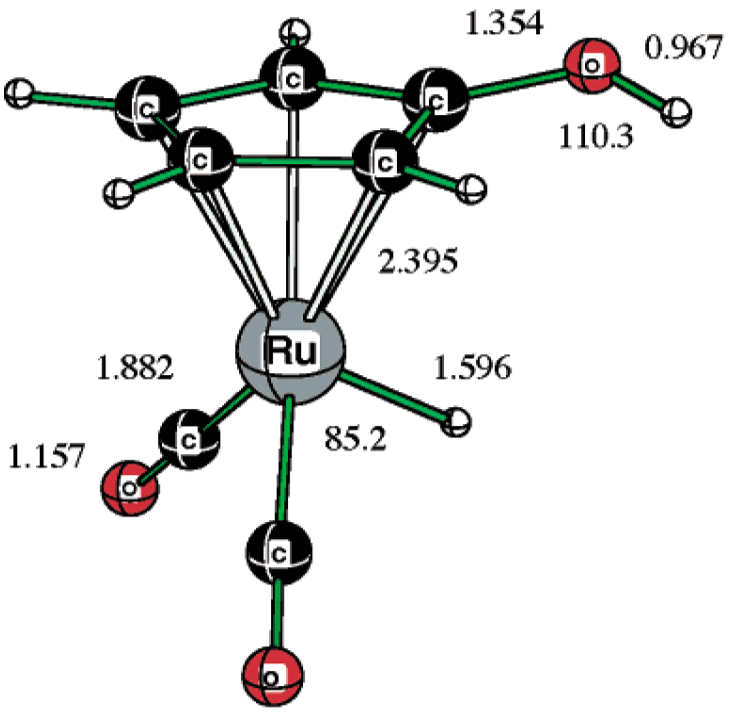


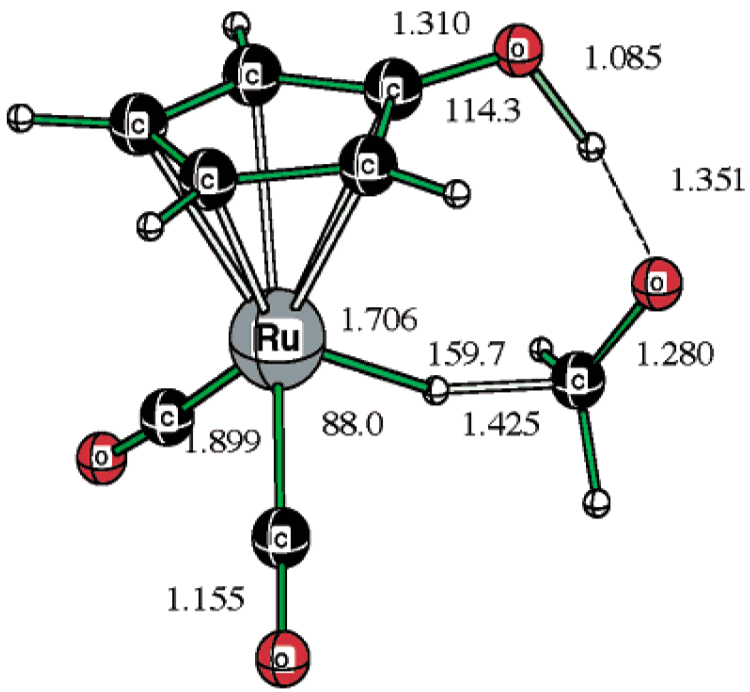
  – No loss in hydride signal was observed

- Outer sphere mechanism leads to coordinatively unsaturated Ru intermediate



Simple Model Calculations



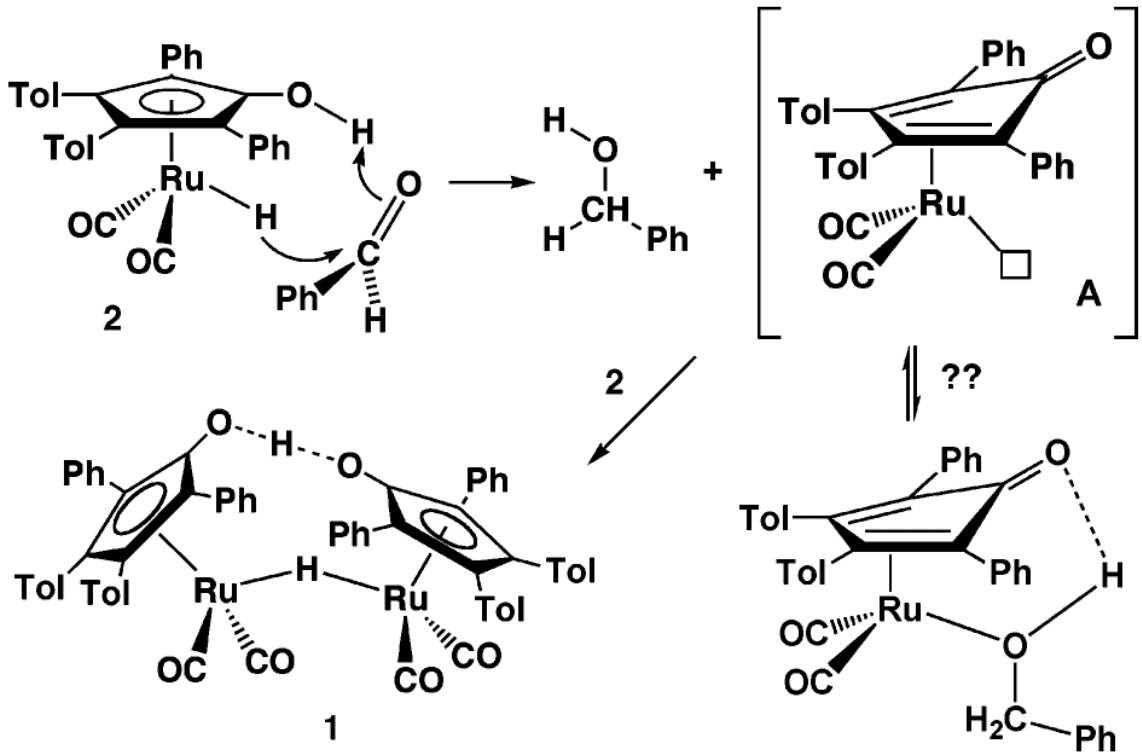


- DFT using B3LYP/LANl2DZ level of theory
- Concerted lengthening of OH and Ru-H was found

- Calc activation barrier of 13.8 kcal/mol (experimental ΔH = 12 kcal/mol)

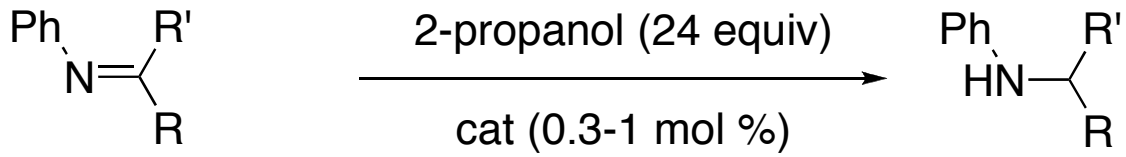
J. Am. Chem. Soc. **2005**, *127*, 14062-14071

Current Accepted Mechanism Involving Aldehydes and Ketones



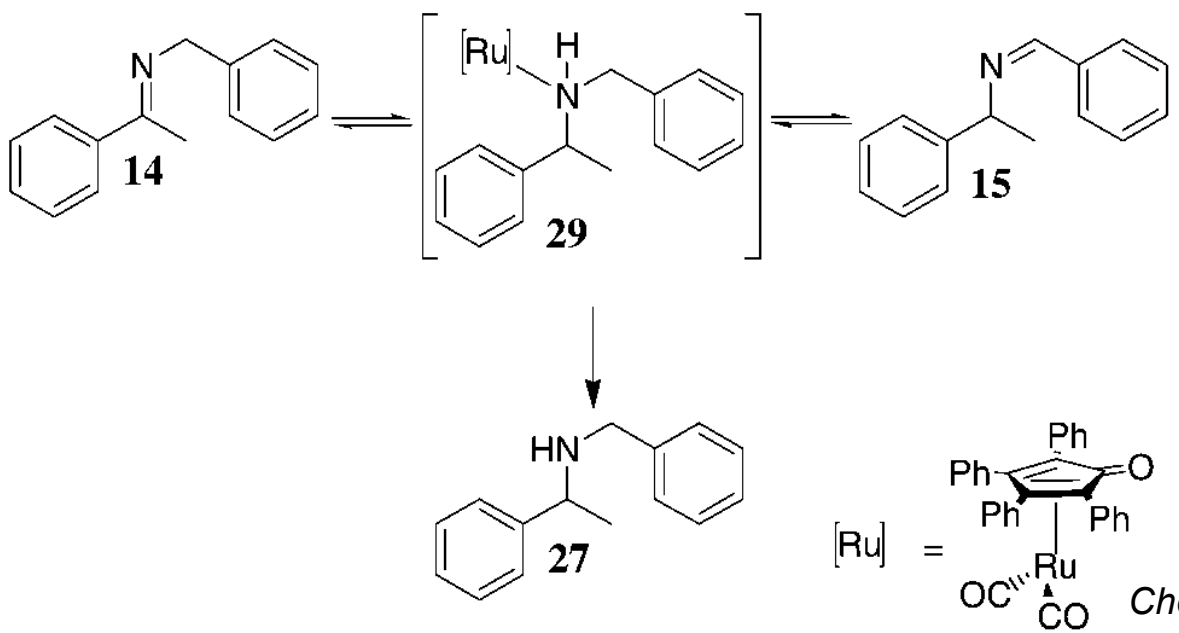
- Presence of -OTES on Cp ring should not effect C=O binding ==> ring-slippage less likely
- All data is consistent with outer sphere mechanism

Transfer Hydrogenation of Imines



where R = Aryl, one ex alkyl
R' = H, Me, Et
also benzyl imines studied

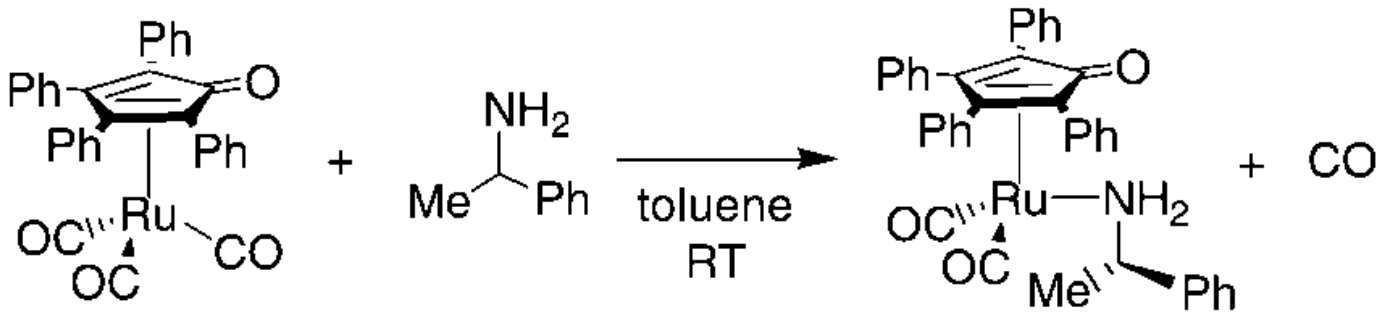
- Solvent study: THF (TOF 140) vs benzene (TOF 700)
- Electronic study on R= Aryl showed rate enhancement using e^--rich systems



Chem. Eur. J. **2002**, *8*, 2955-2961

Mechanistic Insights: Ru-amine complex

Independently Synthesized:



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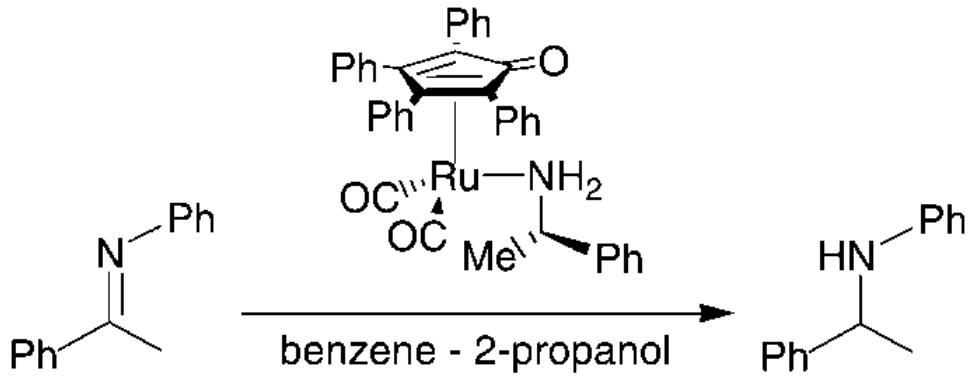

4 **17**

Ru-amine complex was shown to have catalytic activity

Disparities between Imine Reduction Compared to Aldehyde / Ketone Red.

- Shvo (1985)
  - Proposed that Ru-alkoxides were intermediates based upon isolation of Ru-amine complexes
- Casey (2001)
  - Fast reaction with MeN=CHPh, 26x times faster compared to PhCHO
- Bäckvall (2002)
  - Ru-amine complex shown to be competent catalyst
  - Strong electron effect on substitution off imine

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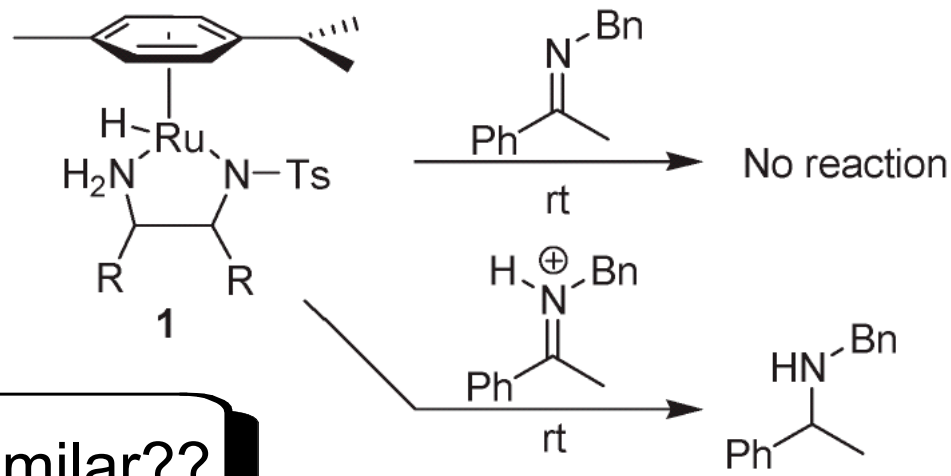
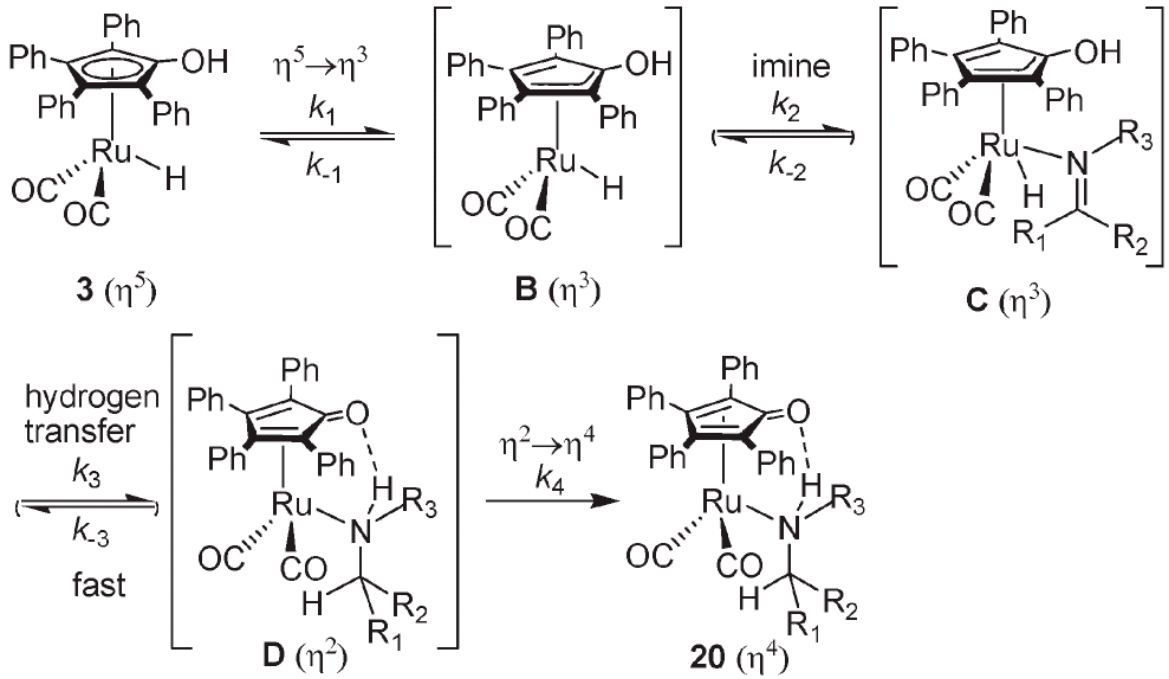
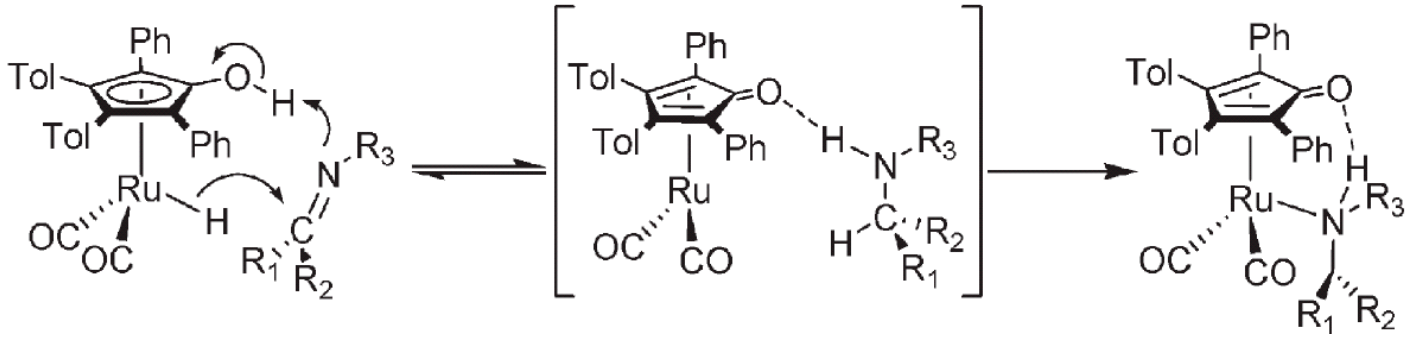


Are the mechanisms similar??

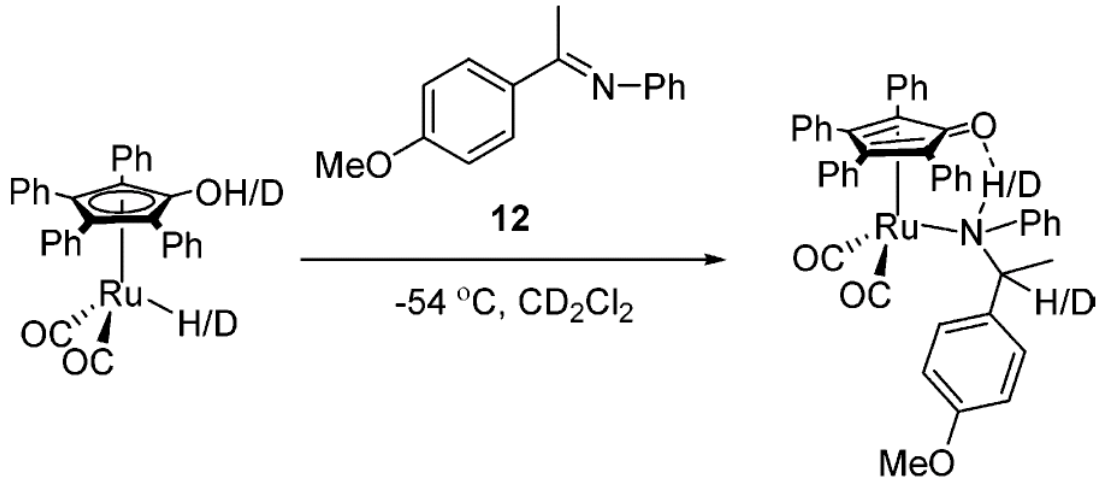
The Debate Begins…Inner versus Outer Sphere

- Inner
- Outer



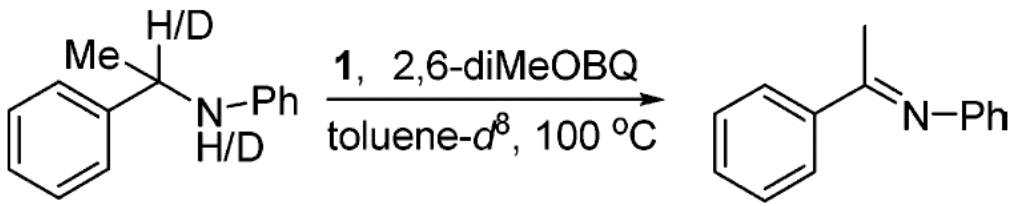


Initial Isotope Effects Support Inner Sphere



$K_{RuHOH}/K_{RuDOD} = 1.05$

- Absence of KIE suggests that RDS is not hydride transfer



4 **8**

KIE

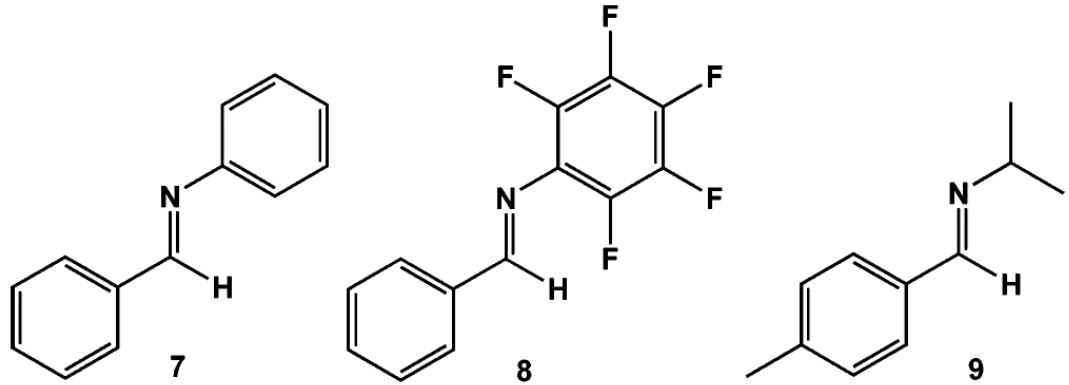
$k_{CHNH/CDND} = 3.26$

$k_{CHNH/CDNH} = 3.24$

- Use of benzoquinone allowed for catalytic isotope monitoring

Chem. Soc. Rev. **2006**, *35*, 237-248.

Change in Mechanism of Various Imines

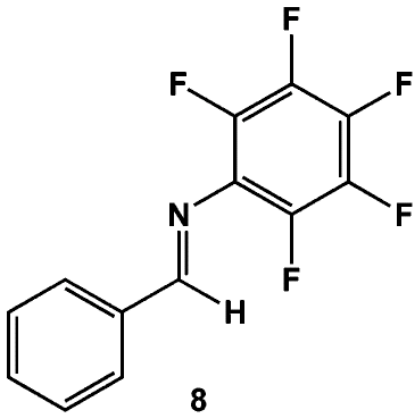


- Overall rate = k[monomer][imine]
- Erying plot: ΔH = 9.9 kcal/mol and ΔS = -26 kcal/mol (determined from imine **7**)
  - Associative process between the Ru-H and imine
  - Similar process assumed for other imines

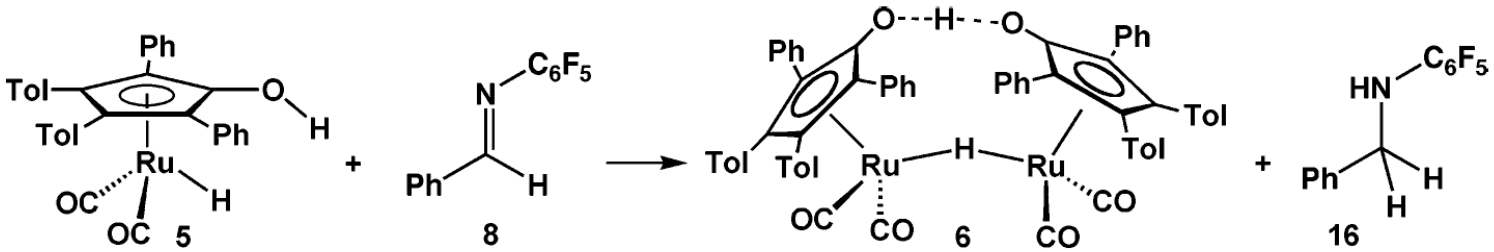
How can the outer sphere mechanism explain each imine?

J. Am. Chem. Soc. **2005**, *127*, 1883-1894

Electron-Deficient Imine



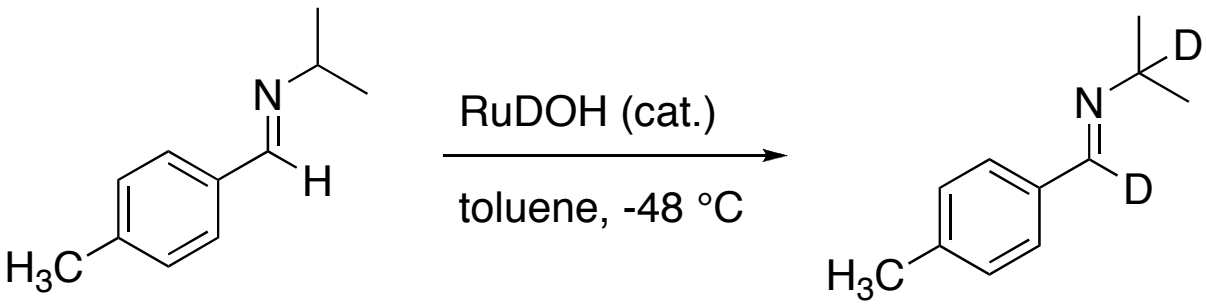
k_{RuHOH}/k_{RuHOD}	1.57 ± 0.07
k_{RuDOH}/k_{RuDOD}	1.66 ± 0.08
k_{RuHOH}/k_{RuDOH}	1.99 ± 0.13
k_{RuHOD}/k_{RuDOD}	2.11 ± 0.04
k_{RuHOH}/k_{RuDOD}	3.32 ± 0.14



- Ru-amine complex could not be isolated
- Results similar to those from aldehyde / ketone reduction (KIE, indiv and combined)

Consistent with concerted proton / hydride transfer = OUTER SPHERE

Alkyl Substituted Imines

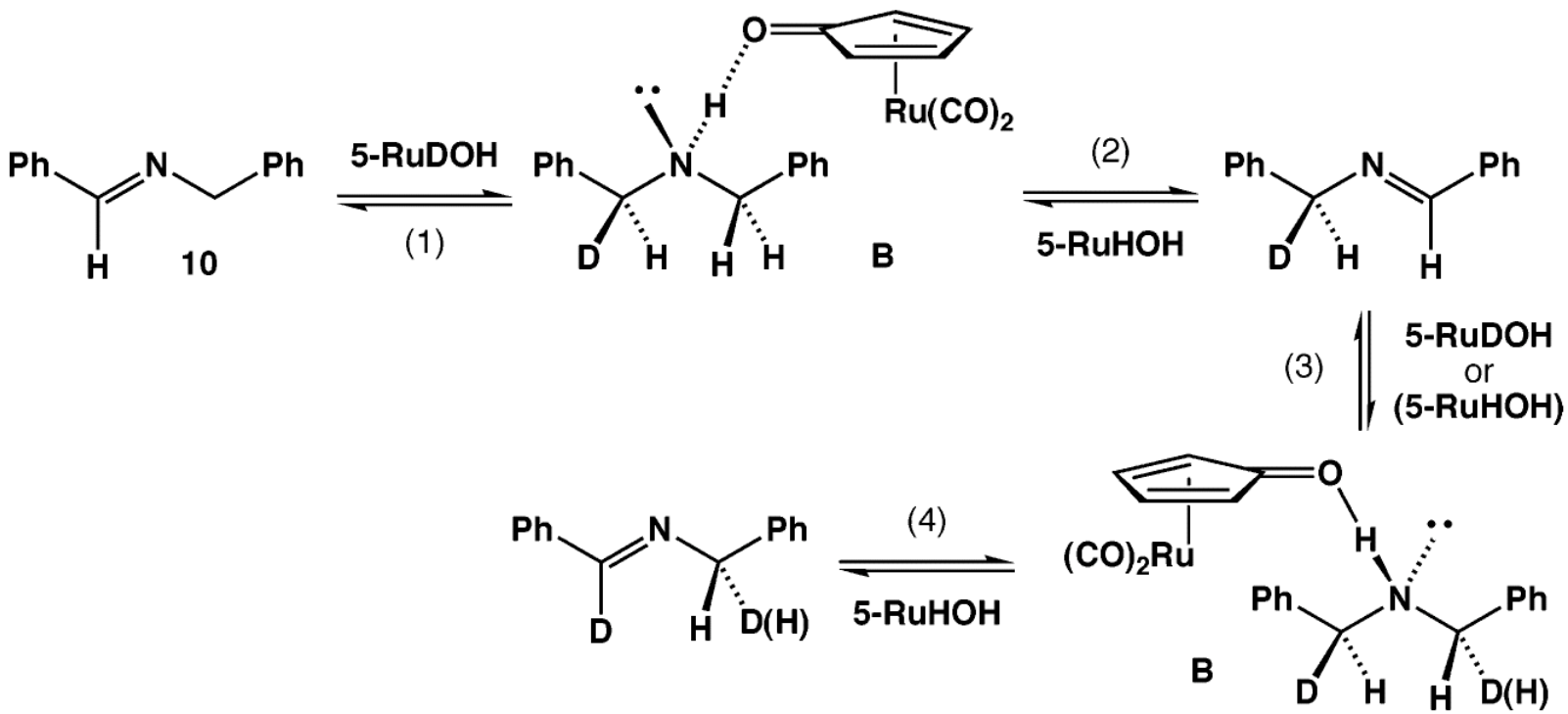


Reaction was performed with 5-fold excess of imine compared to cat.

Based on knowledge from carbonyl mechanism, propose a mechanism that accounts for the observed D incorporation.

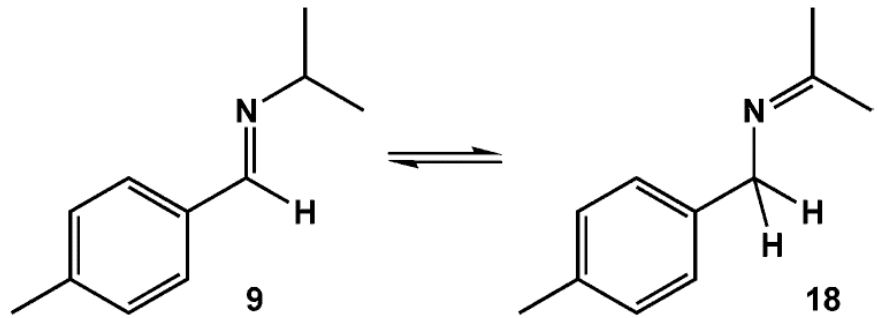
Additionally, predict the outcome your mechanism plays on the observed isotope effects!
(Stereochemistry is important!!)

Trans addition of deuterium



Intermediate formation of a second imine leads to a reversible rxn

Electron Rich Imines Yield Isomerization

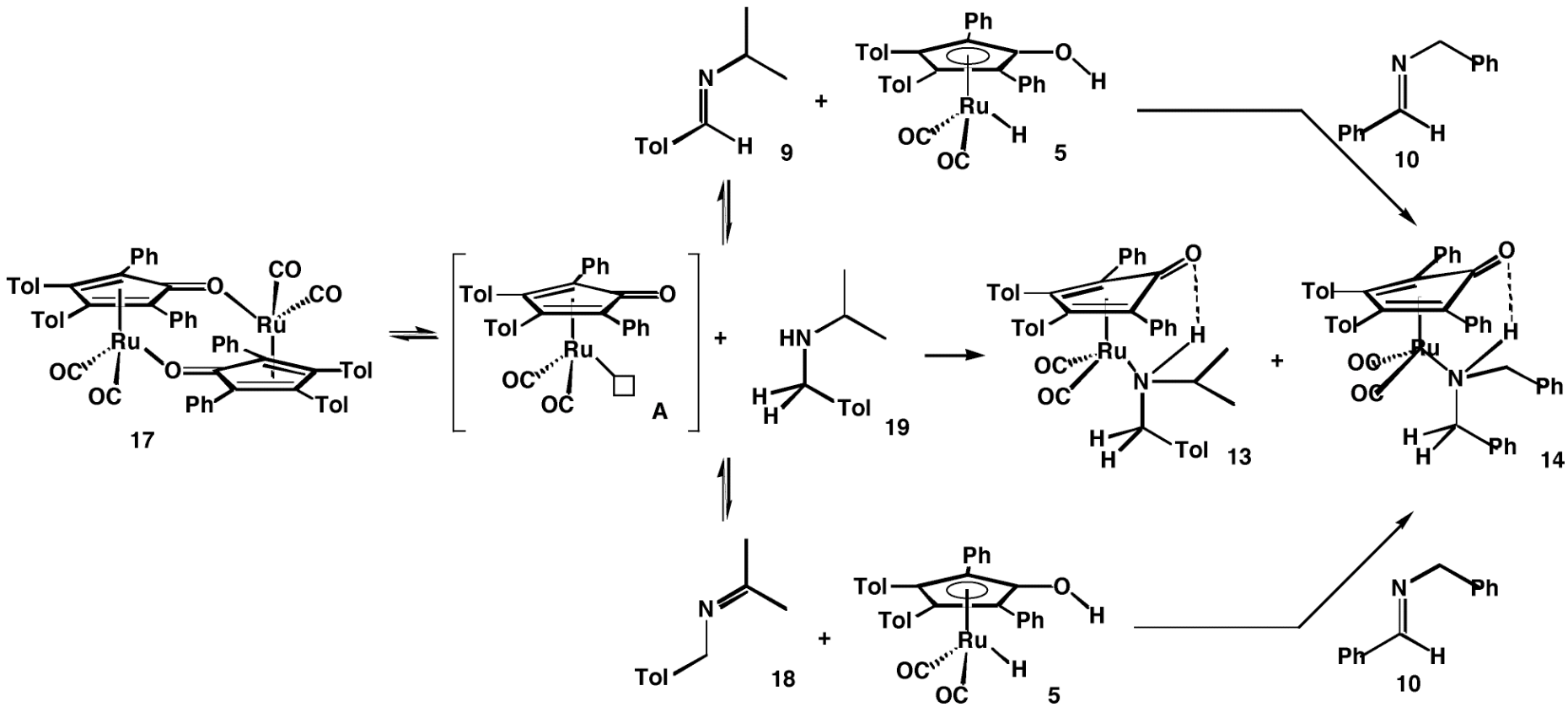


k_{RuHOH}/k_{RuHOD}	0.92 ± 0.09
k_{RuDOH}/k_{RuDOD}	0.91 ± 0.07
k_{RuHOH}/k_{RuDOH}	1.03 ± 0.08
k_{RuHOD}/k_{RuDOD}	1.02 ± 0.07
k_{RuHOH}/k_{RuDOD}	0.94 ± 0.08

- Deuterium gets incorporated into both α-carbons!!

J. Am. Chem. Soc. **2005**, *127*, 1883-1894

Electron Rich Imines Yield Isomerization



- Aldimine / Ketenimine ratio = 7 / 1
- Analysis of deuterium isotope effect difficult, however isomerization to aldimine is 25x faster than coordination

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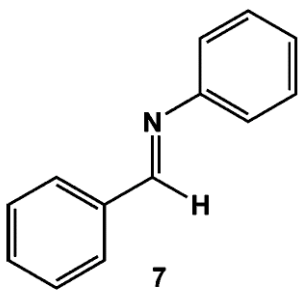
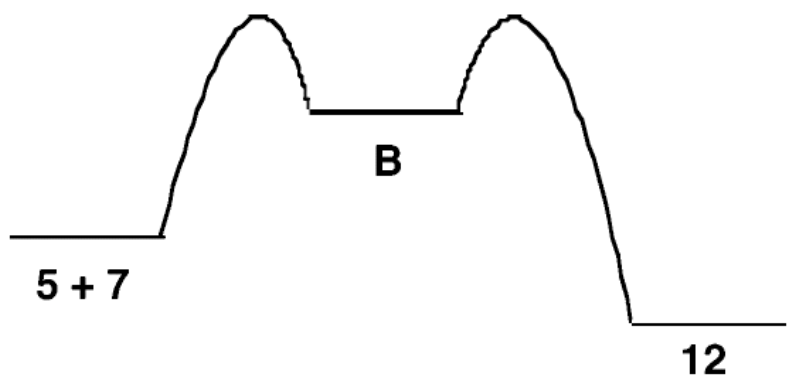
Simple Phenyl Substituted Imine

- Expected to behave similar to e^--deficient imines



k_{RuHOH}/k_{RuHOD}	1.30 ± 0.13
k_{RuDOH}/k_{RuDOD}	1.31 ± 0.12
k_{RuHOH}/k_{RuDOH}	1.23 ± 0.12
k_{RuHOD}/k_{RuDOD}	1.24 ± 0.12
k_{RuHOH}/k_{RuDOD}	1.60 ± 0.17

Results fall between an inverse KIE and a concerted process



Casey, et al. proposes that coordination becomes RDS, therefore both a kinetic and equilibrium isotope affect are seen

J. Am. Chem. Soc. **2005**, *127*, 1883-1894

Simple Phenyl Substituted Imine

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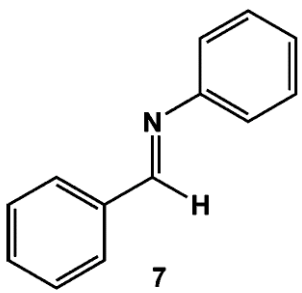

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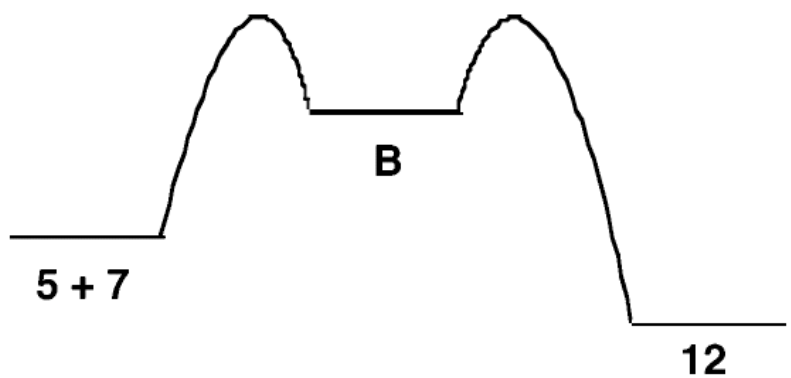

However, although evidence gives support for outer sphere mech…data can also be loosely explained with inner sphere!

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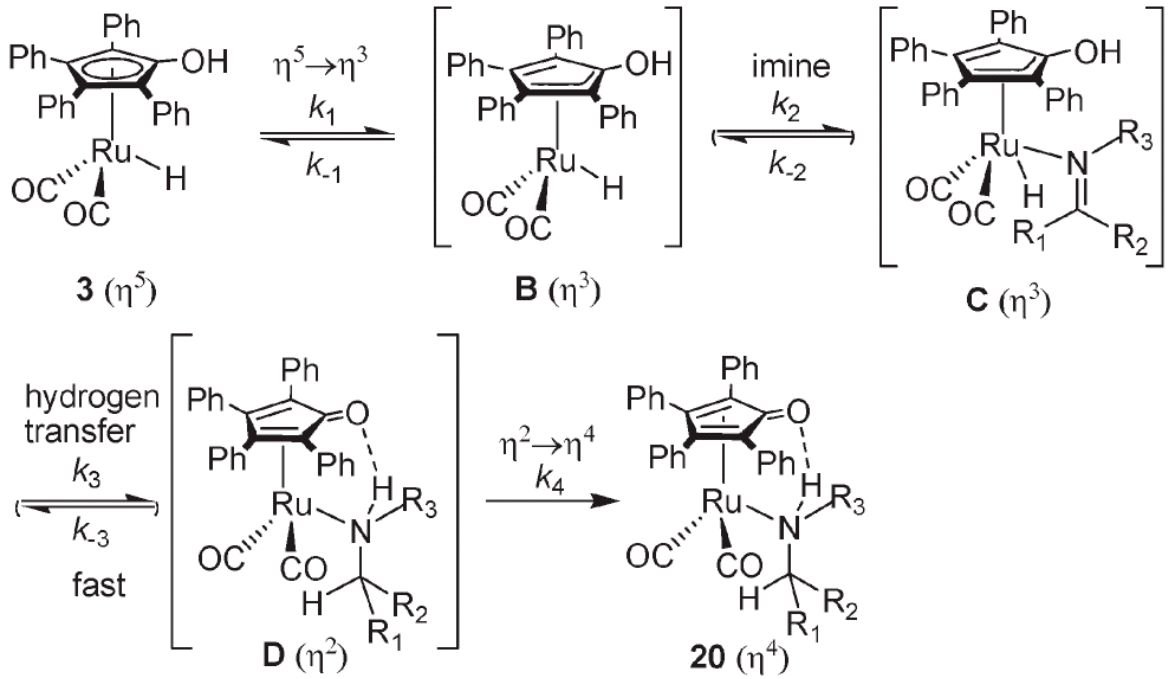
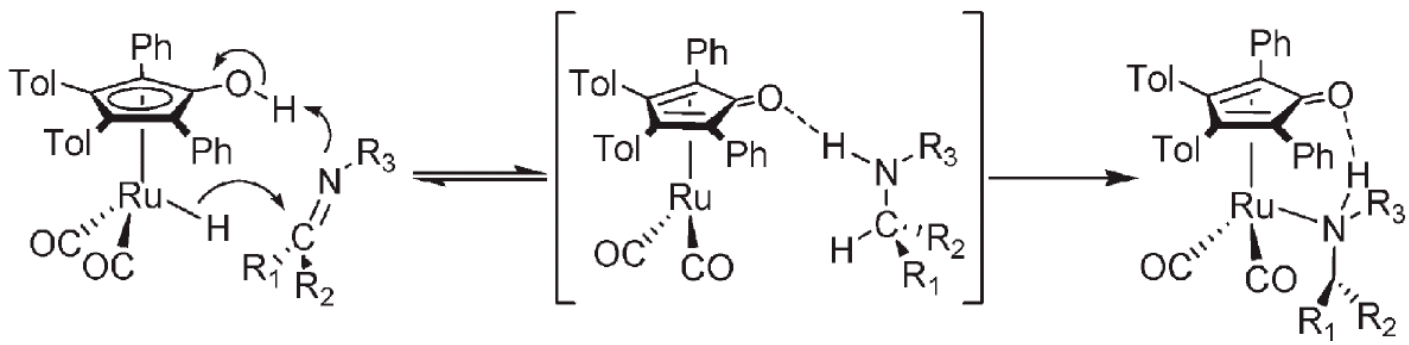
Inner versus Outer Sphere Revisited

What would be the outcome if an external amine were added?

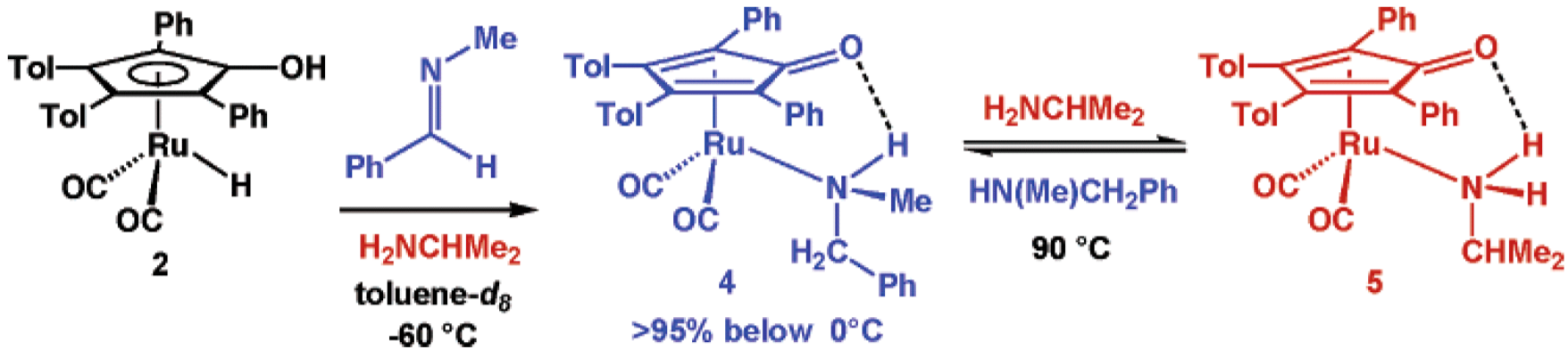
- Inner



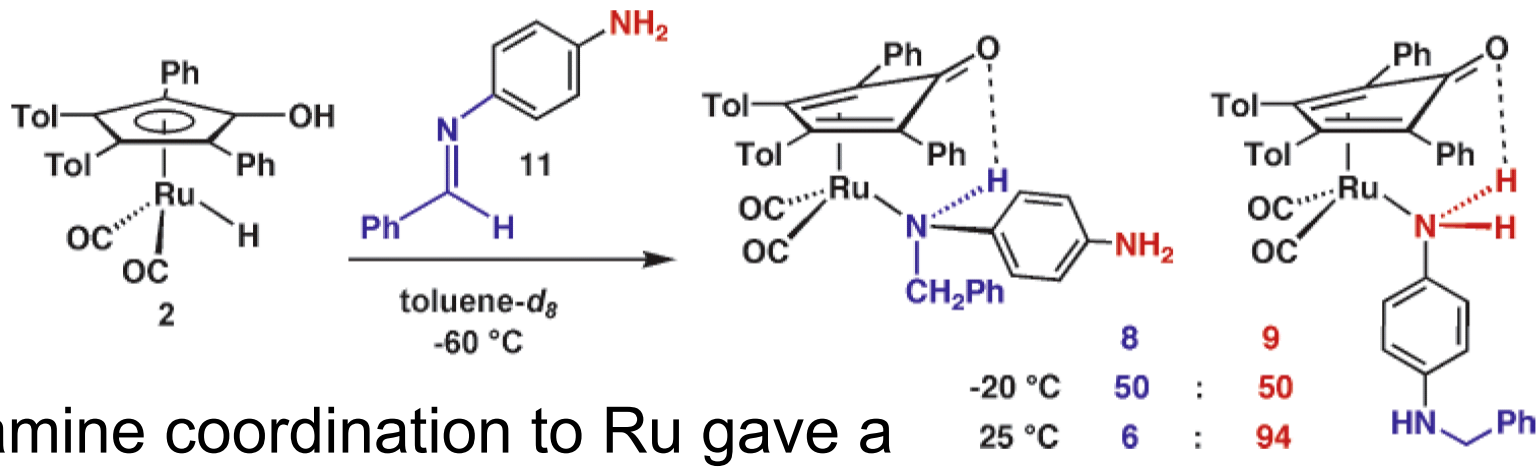
- Outer



Amine Trapping Experiments



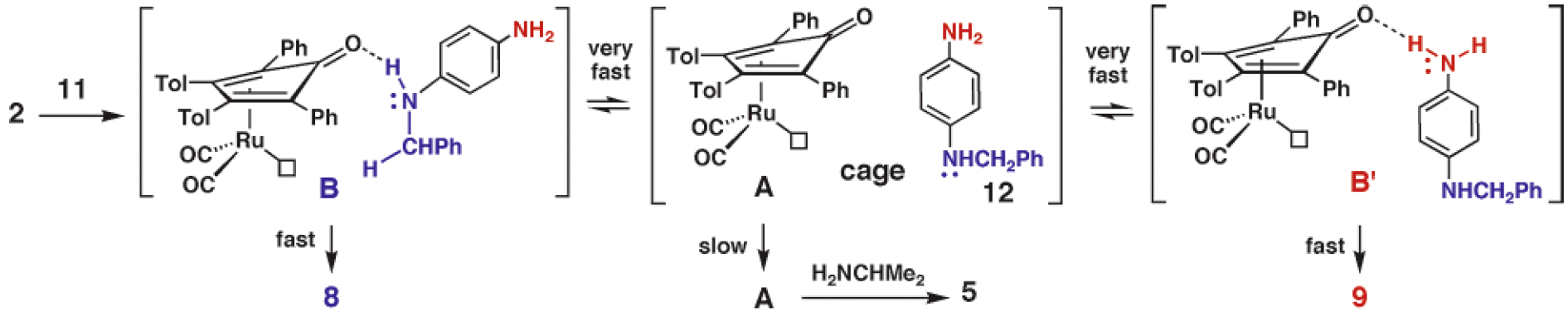
- Also performed exchange study with PPh_3
- Took temperatures upward of 90 °C to promote exchange
- Dissociative mechanism is required



Diamine coordination to Ru gave a 20:80 ratio of 8:9

J. Am. Chem. Soc. **2005**, *127*, 14062-14071

Alternative Outer Sphere Mechanism



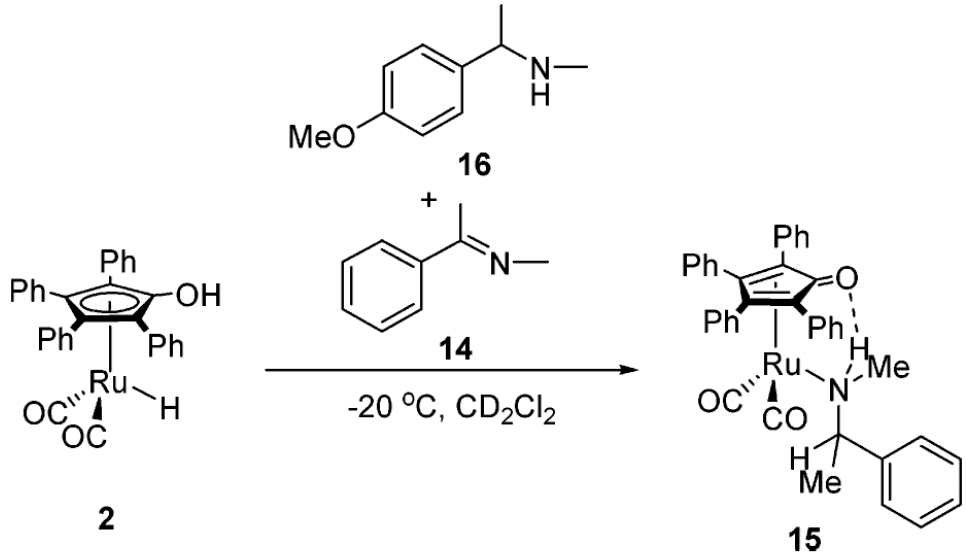
Ring slippage mechanism would solely produce 8

Solvation by solvent cage also explains the relative isomerization seen for β-H containing imines

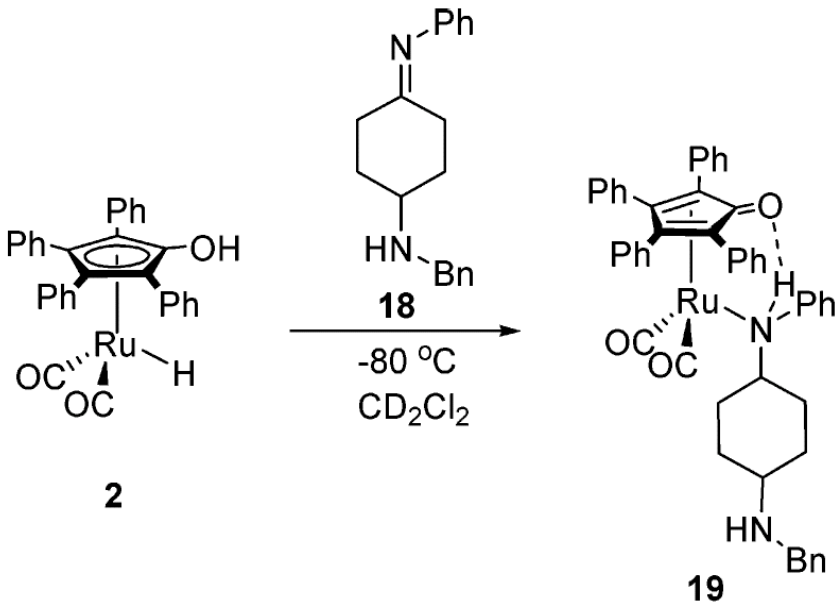
Overall, evidence provides strong support for outer sphere mechanism

Rebuttal with Another Trapping Experiment

- External amine trap
  - Similar result compared to work from Casey
  - Ratio found to be 90:10



- Non-aromatic Internal trapping
  - Above -8 °C see isomerization



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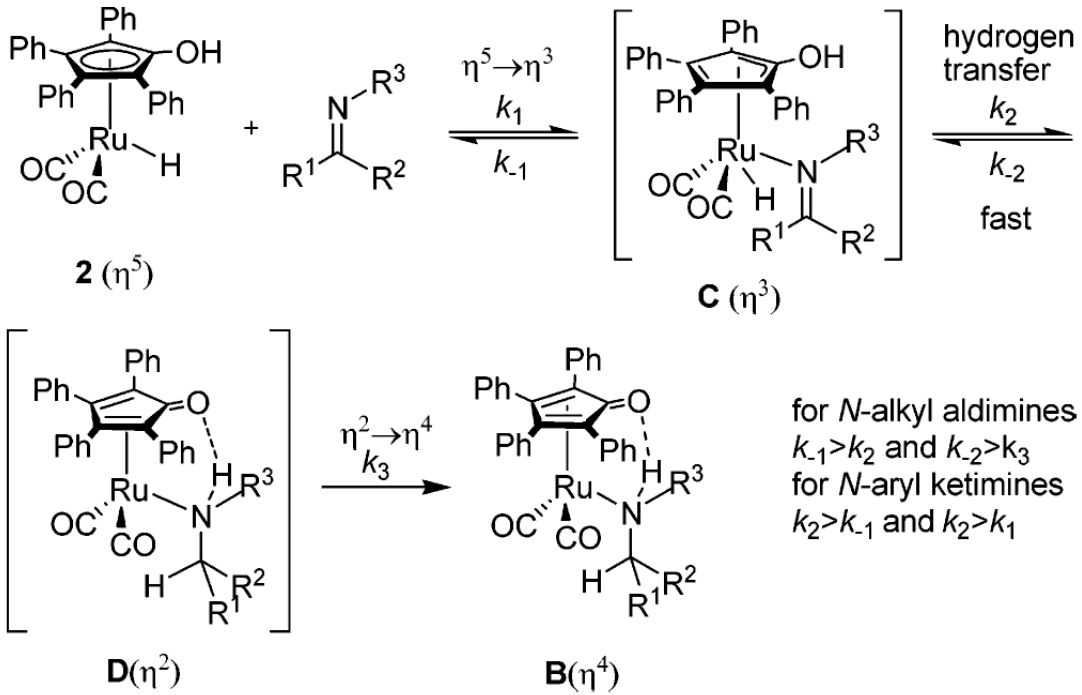
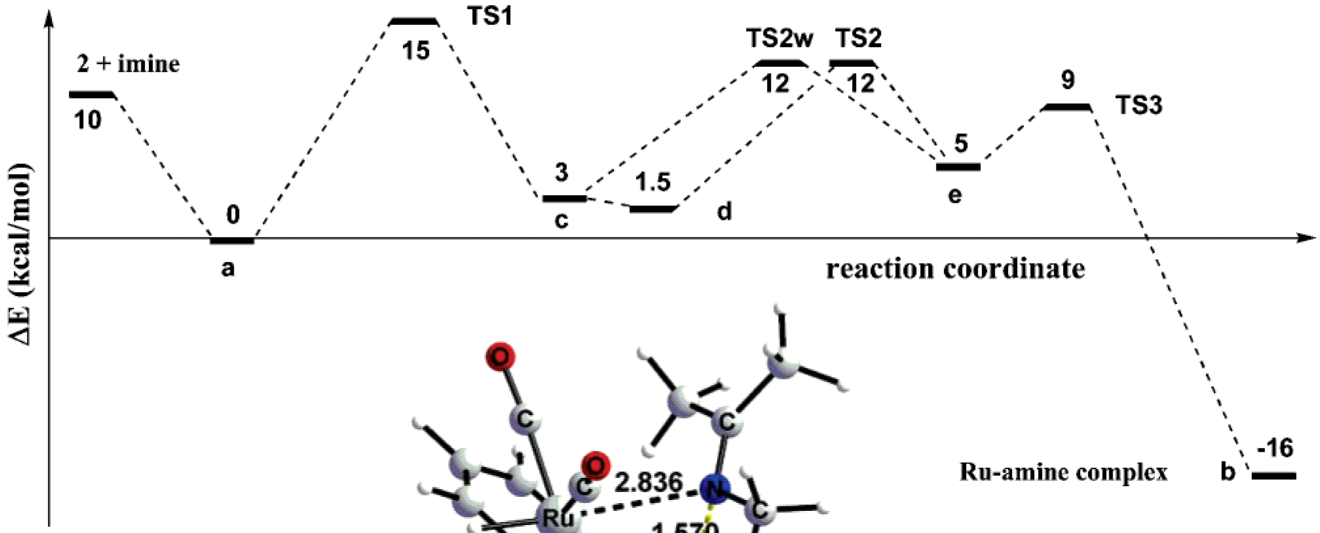
Inner Sphere Mechanism Can Explain All

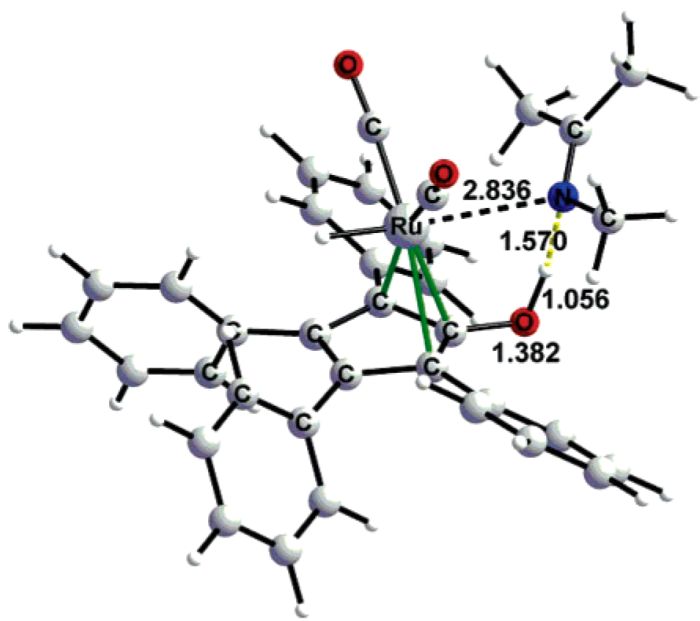


- Electron deficient imines: RDS = slow transfer of H^-
- Observed change in mechanism => rel. binding of imine
- Electron rich imines favors slipped η^3 intermediate
  - Therefore explains rate effects for imines

Use of PCM Achieves Stability in Computational Model

- PCM = Polarizable Continuum Solvent Model
- Environmental effects in catalytic reactions are crucial
- e.g. large solvent effect observed for reduction of carbonyl / imines



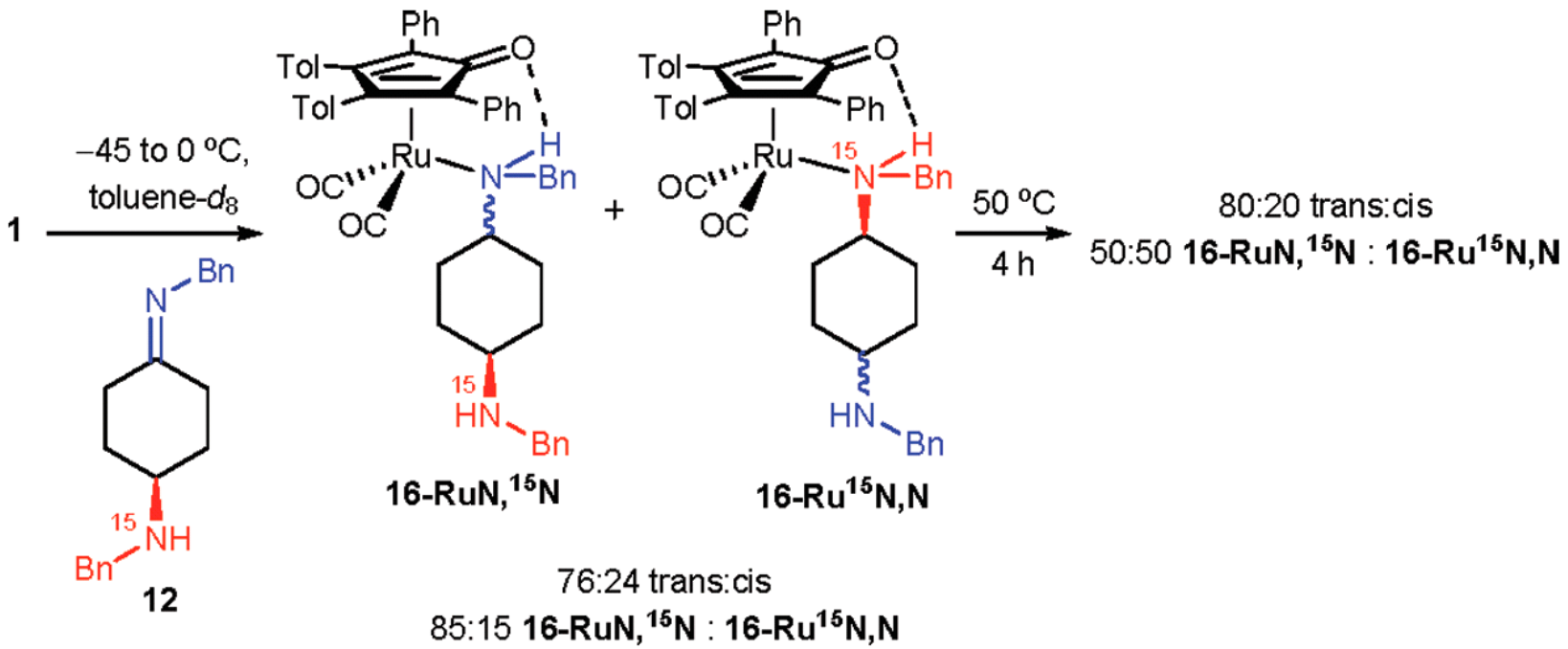


Complete computational model provides a complete reaction pathway including TS for the INNER SPHERE mechanism

Organometallic **2007**, *26*, 2840-2848

Along Comes Another Trapping Dispute

- Problems associated with previous trapping exp
  - Presence of π-system
  - Difference in electronic nature
  - Alkyl versus aryl amines



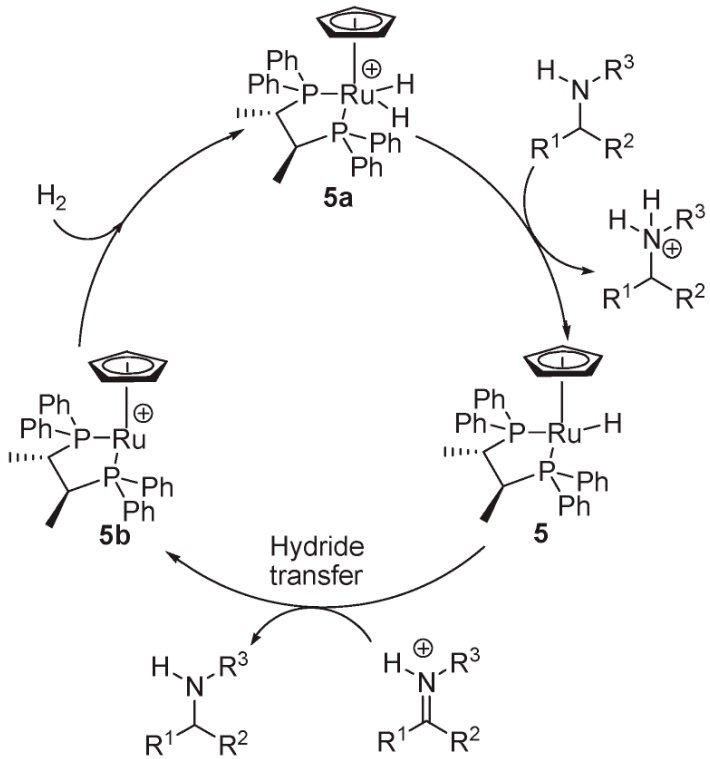
Temperature dependence indicates trapping is kinetically controlled

J. Am. Chem. Soc. **2007**, *129*, 11821-11827.

Conclusions - What are Your Thoughts?

- Aldehyde / Ketone reduction occurs via a concerted, outer sphere transfer of H^+/H^-
- Imines are a whole different system!!
  - Kinetics unequivocally demonstrate second order rates
  - Isotope Effects - TIE:
    - For both systems, certain constraints must be made
  - Computational - Inner Sphere
    - The solvent model allowed for a simple imine to be used
    - Calculated both TS and ground state energies
    - Decrease in hapticity is stabilized by presence of solvent
  - Trapping Studies - Outer Sphere
    - Kinetic trapping of electronically similar reagent gave striking evidence for outer sphere

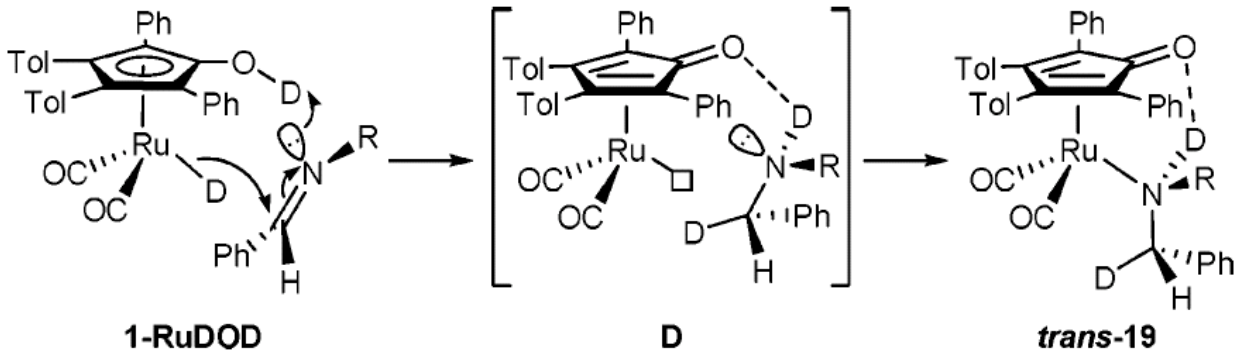
Items Not Covered



- Anionic-type mechanisms

- Dynamic Kinetic Resolution
- Kinetics of Dehydrogenation
- Other transition metals (Ir, Rh)

- Stereochemistry of hydride delivery



References

- Horse Liver Dehydrogenase
  - *J. Biological Chem.* **1961**, *236*, 1531-1532.
  - *J. Biological Chem.* **1972**, *247*, 267-272.
- Meerwein-Ponndorf-Verley Reduction
  - *Ann.* **1925**, *444*, 221-238.
  - *Bull. Soc. Chim.* **1925,** *37*, 871-874
  - *Angew. Chem.* **1926**, *39*, 138-143.
- Ruthenium Catalyzed Hydrogenation of Aldehydes and Ketones
  - *J. Am. Chem. Soc.* **1986**, *108*, 7400-7402.
  - *Organometallics* **1991**, 10, 3885-3891.
  - *Chem. Eur. J.* **2001**, *7*, 5052-5058.
  - *Chem. Commun.* **2003**, 1652-1653.
- Mechanistic Studies
  - *J. Am. Chem. Soc.* **2001**, *123*, 1090-1100.
  - *Can. J. Chem.* **2005,** *83*, 1339-1346.
  - *J. Org. Chem.* **2003**, *68,* 7681-7684.
  - *Chem. Soc. Rev.* **2006**, *35,* 237-248.
- Ruthenium Catalyzed Hydrogenation of Imines
  - *Chem. Eur. J.* **2002**, *8*, 2955-2961.
  - *Can. J. Chem.* **2005,** *83*, 909-916. *J. Chem. Soc. Chem. Commun*, **1992**, 980-982.
- Mechanistic Aspects:
- Inner Sphere
  - *J. Am. Chem. Soc.* **2006**, *128*, 14293-14305
  - *Organometallics* **2007**, 26, 2840-2848.
- Outer Sphere
  - *J. Am. Chem. Soc.* **2007**, *129*, 11821-11827.
  - *J. Am. Chem. Soc.* **2006**, *128*, 2286-2293.
  - *J. Am. Chem. Soc.* **2005**, *127*, 14062-14071.
  - *J. Am. Chem. Soc.* **2005**, *127*, 1883-1894.