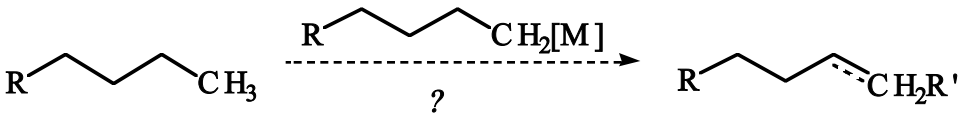
# *The Holy Grail of Catalysis*



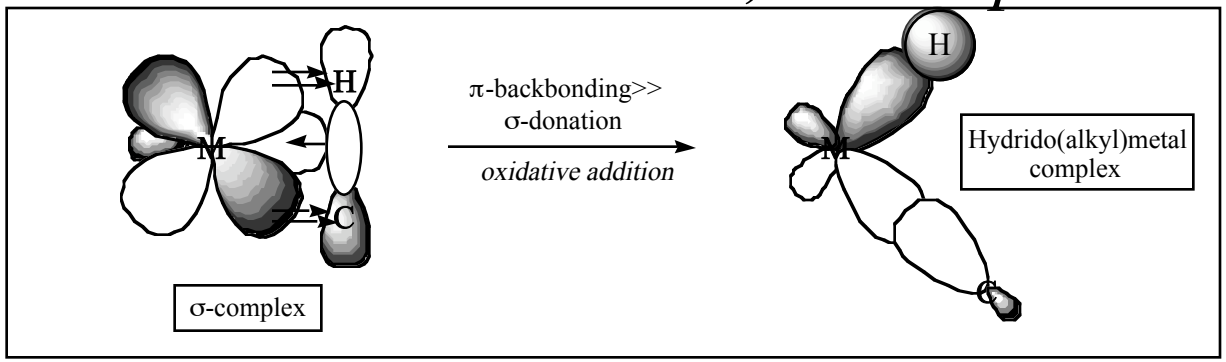

**C-H activation** Process where a strong C-H bond (90-105 kcal/mol) undergoes substitution to produce a weaker C-M bond (50-80 kcal/mol).
**Functionalization** Metal-C bond is replaced by any bond except C-H.

Methods have been identified to regioselectivity effect ***C-H activation***. Recall that there is both a kinetic and thermodynamic preference to form the less sterically hindered $1^{o}$ C-M intermediate (see Structure & Bonding; pg. 32). The *challenge* lies in finding ways to selectively form the C-M intermediate under synthetically useful, mild conditions that enable ***functionalization*** and catalyst renewal.

**ARTHUR**: Yes we seek the Holy Grail (clears throat very quietly). Our quest is to find the Holy Grail.
**KNIGHTS**: Yes it is.
**ARTHUR**: And so we're looking for it.
**KNIGHTS**: Yes we are.
**BEDEVERE**: We have been for some time.
**KNIGHTS**: Yes.
**ROBIN**: Months.
**ARTHUR**: Yes…and any help we get is…is very…helpful.

**Bergman** *Acc. Chem. Res.* **1995** (28) 154. Exerpt from "Monty Python and the Holy Grail"; 1974.

# *Bergman: C-H Activation via Late, Nucleophilic Complexes*




**regioselectivity** $sp^2$ C-H > 1° $sp^3$C-H> 2° $sp^3$ C-H >>> 3° $sp^3$ C-H. There is both a kinetic and thermodynamic preference to form the least sterically hindered C-M σ bond. Kinetic preference: activation barrier to σ-complex formation is lower for less sterically hindered C-H bonds and bonds with more s character. Thermodynamic preference: stronger C-M bonds are formed (see Structure and Bonding, pg. 32).

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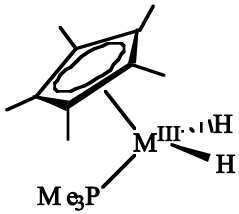
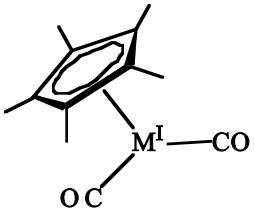



M = Ir, **1**
Rh, **2**




18 e-

M = Ir, **3**
Rh, **4**

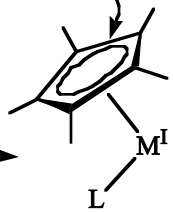
*h v* or Δ → $H_2$

*ligand dissociation*

*h v* or Δ → CO

low OS metals capable of donating electrons in σ-bond formation. Highly prone to air oxidation.

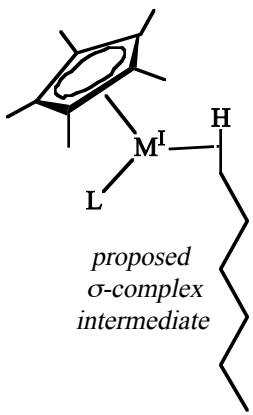
π-donor




16 e-

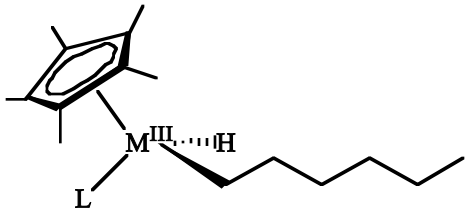
*coordinatively and electronically unsaturated intermediate*

*oxidative addition*




*proposed σ-complex intermediate*

These hydrido(alkyl)metal complexes are prone to non-productive reductive elimination in the presence of oxidants and non-productive protonolysis in the presence of protic reagents




18 e-

Relative rate constants for attack at a single C-H bond by **1** and **2** at -60°C.

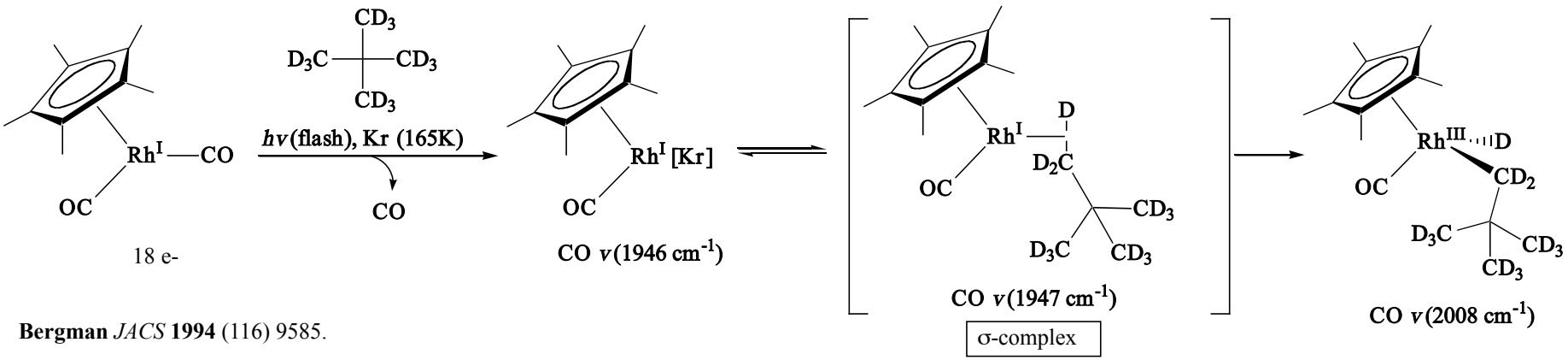
| C-H bond | $k_{rel}$ (Rh, 2) | $k_{rel}$ (Ir, 1) |
|---|---|---|
| benzene | 19.5 | 3.9 |
| cyclopropane | 10.4 | 2.1 |
| *n*-hexane (1°) | 5.9 | 2.7 |
| *n*-hexane (2°) | 0 | 0.2 |
| propane (1°) | 2.6 | 1.5 |
| propane (2°) | 0 | 0.3 |
| cyclopentane | 1.8 | 1.1 |
| cyclohexane | 1.0 | 1.0 |

with acyclic substrates the Rh complex inserts only into 1° C-H bonds

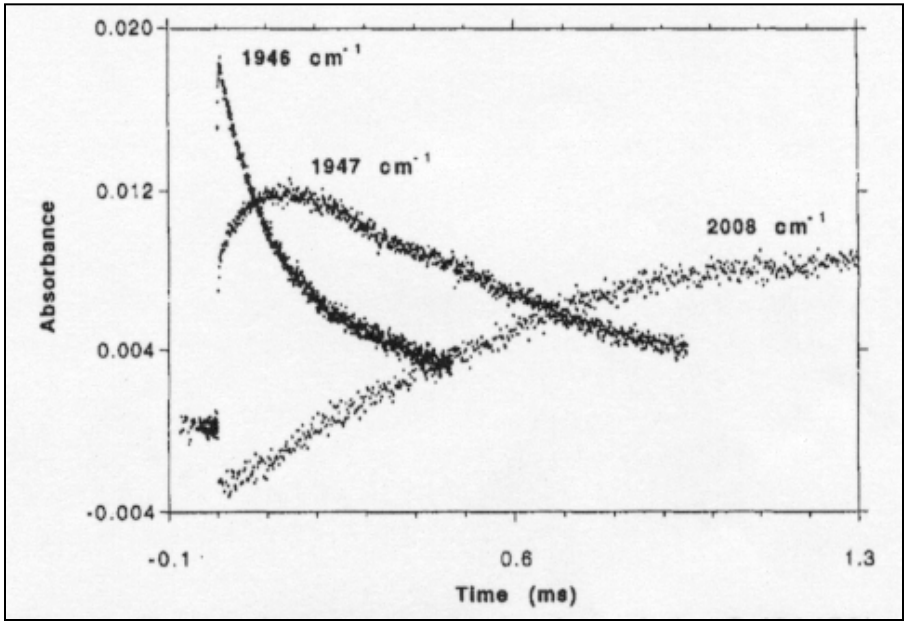
arbitrarily set at 1

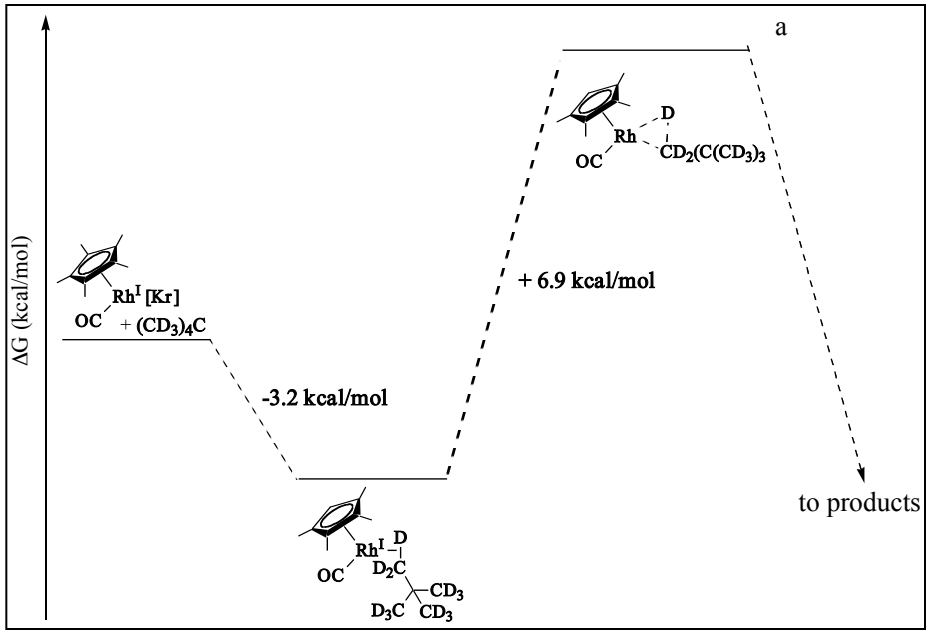
**Bergman** *JACS* **1982** (104) 352 (Cmp. **1**).
**Bergman** *OM* **1984** (3) 508 (competition exp).
**Graham** *JACS* **1983** (105) 7190 (Cmp. **3**).
**Bergman** *JACS* **1994** (116) 9585 (Cmp. **4**).

# *Evidence for intermolecular σ-complex formation*




**Bergman** *JACS* **1994** (116) 9585.

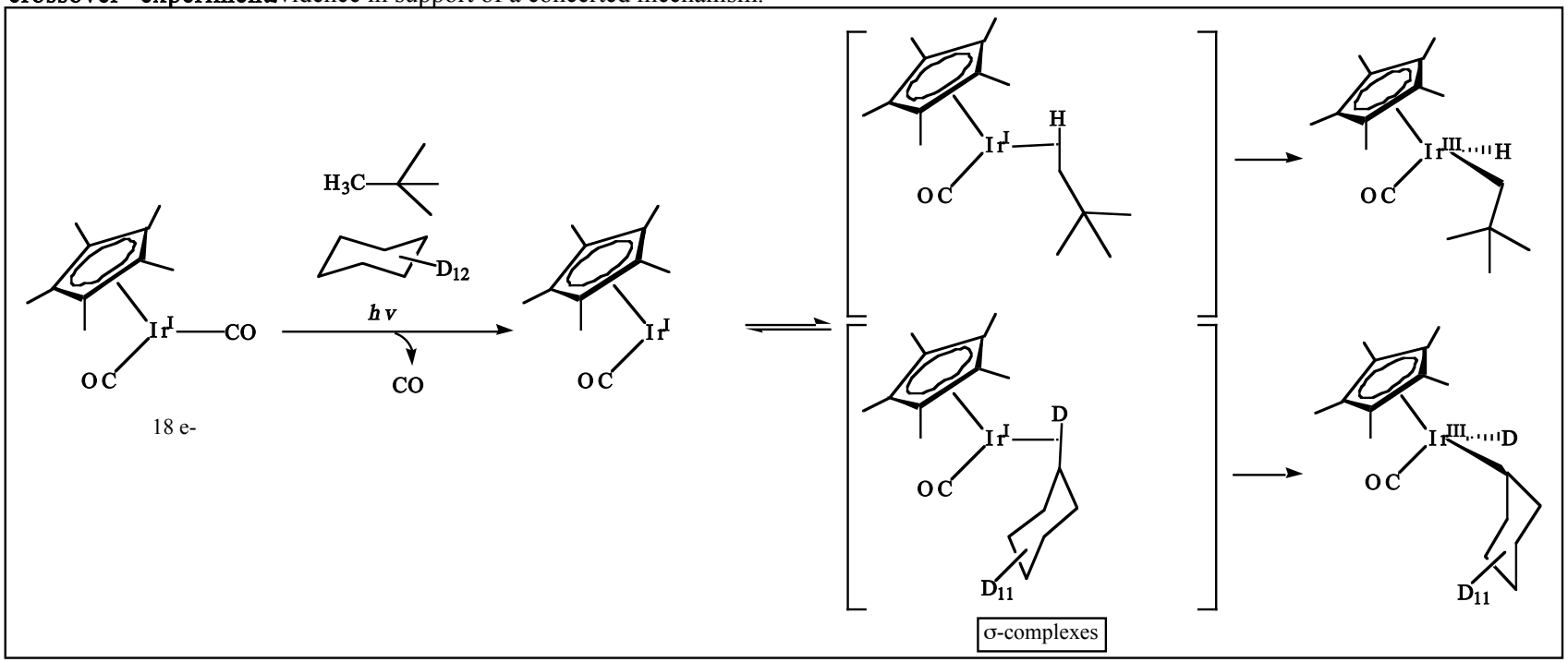


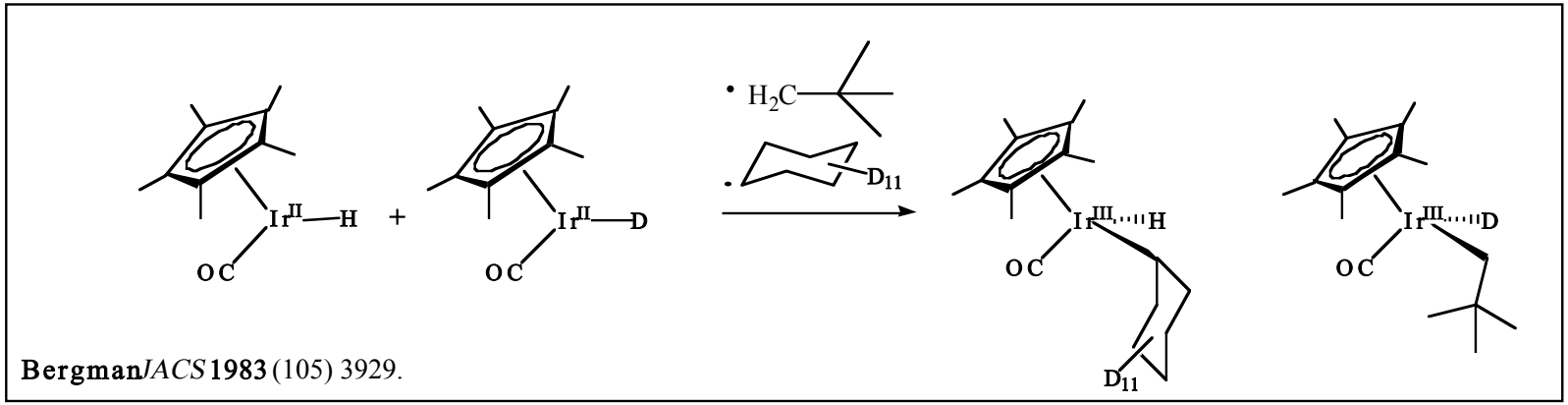

The reaction of $Cp^*Rh(CO)_2$ with neopentane-$d_{12}$ was monitored using **low-temperature IR flash kinetic spectroscopy**. The CO stretch at 1946 $cm^{-1}$ was assigned to the initial intermediate Cp*Rh(CO)(Kr) complex, which after photolysis-mediated formation shows rapid decay. During this time, a second CO stretch at 1947 $cm^{-1}$ grows in and then decays; this absorption is assigned to a transient intermediate Rh---CD σ-complex. The absorption at 2008 $cm^{-1}$ is known to correspond to the product $Cp^*Rh(CO)(D)(C_5D_{11})$, which increases steadily throughout the course of the reaction. Note that this entire process occurs in less than 1.5 ms.

# *Evidence for concerted C-H oxidative addition*

**crossover experiment:** evidence in support of a concerted mechanism.

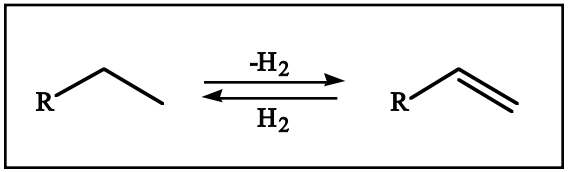



Less than 7% of the crossover products were observed by $^1$HNMR. This may be indicative of a minor radical pathway.

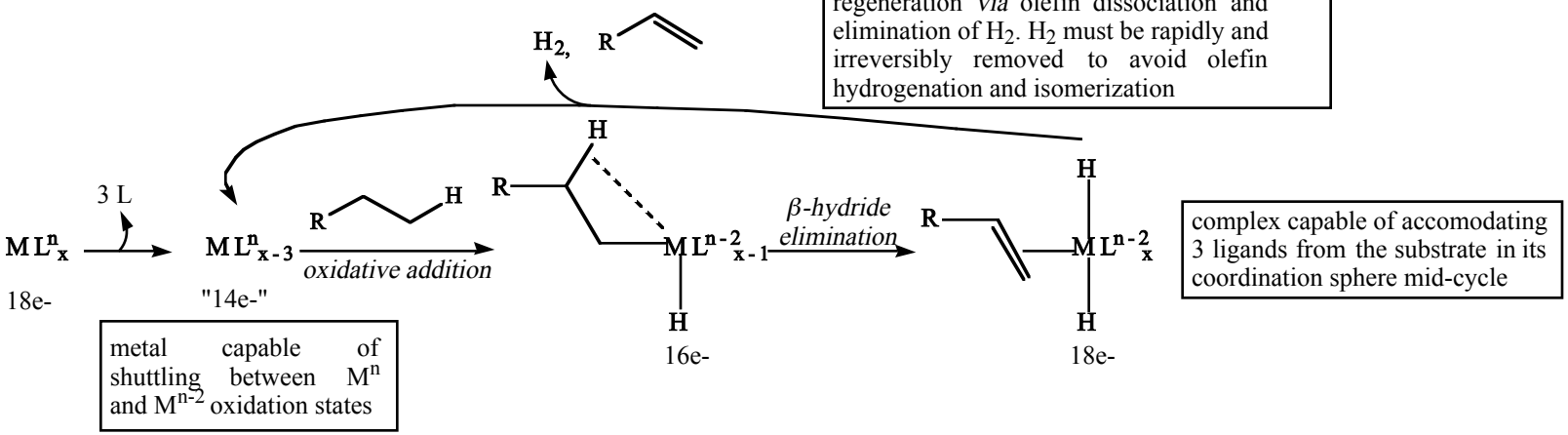



**Bergman** *JACS* **1983** (105) 3929.

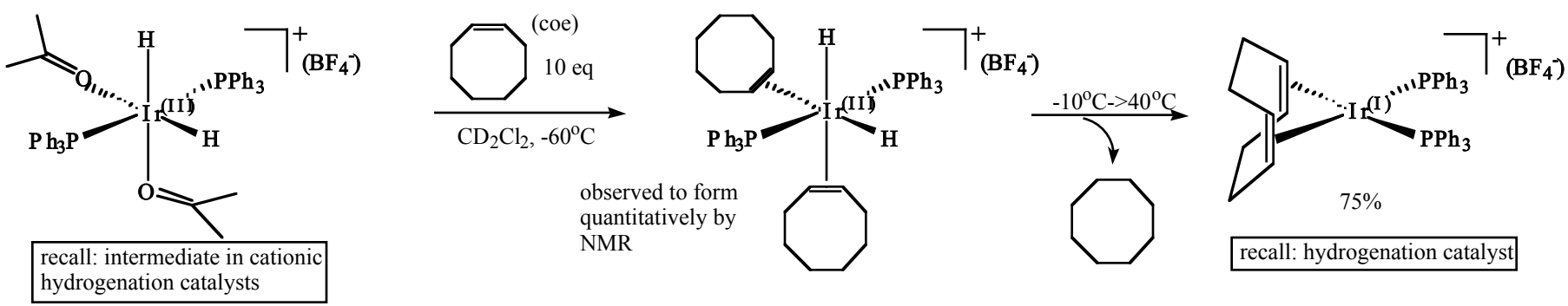
# *Dehydrogenation of alkanes to alkenes*




***Catalyst requireme***

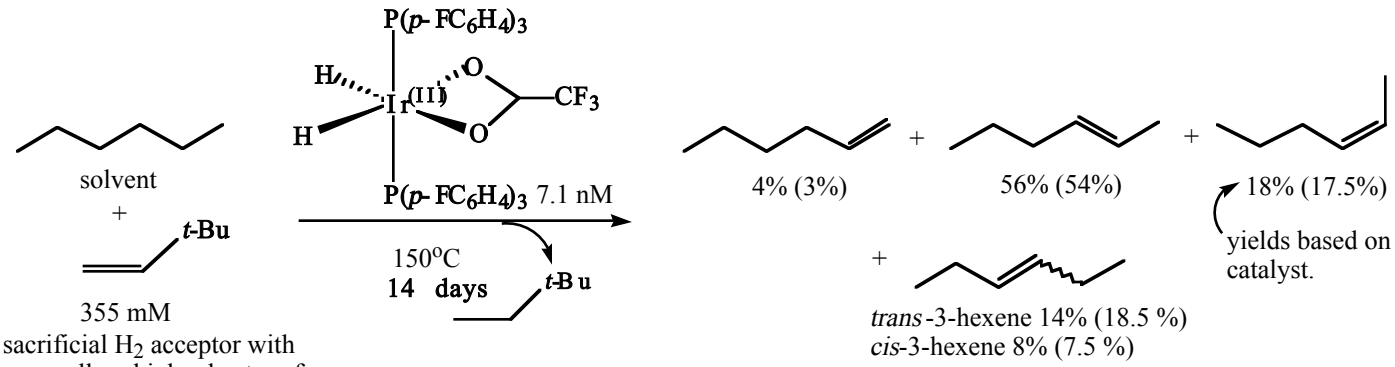



*The first report:*

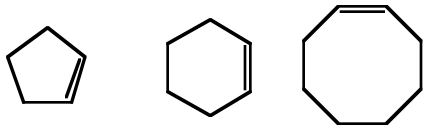



Crabtree*JACS*1979 (101) 7738.

# *Crabtree:thermal dehydrogenation of alkanes to alkenes*

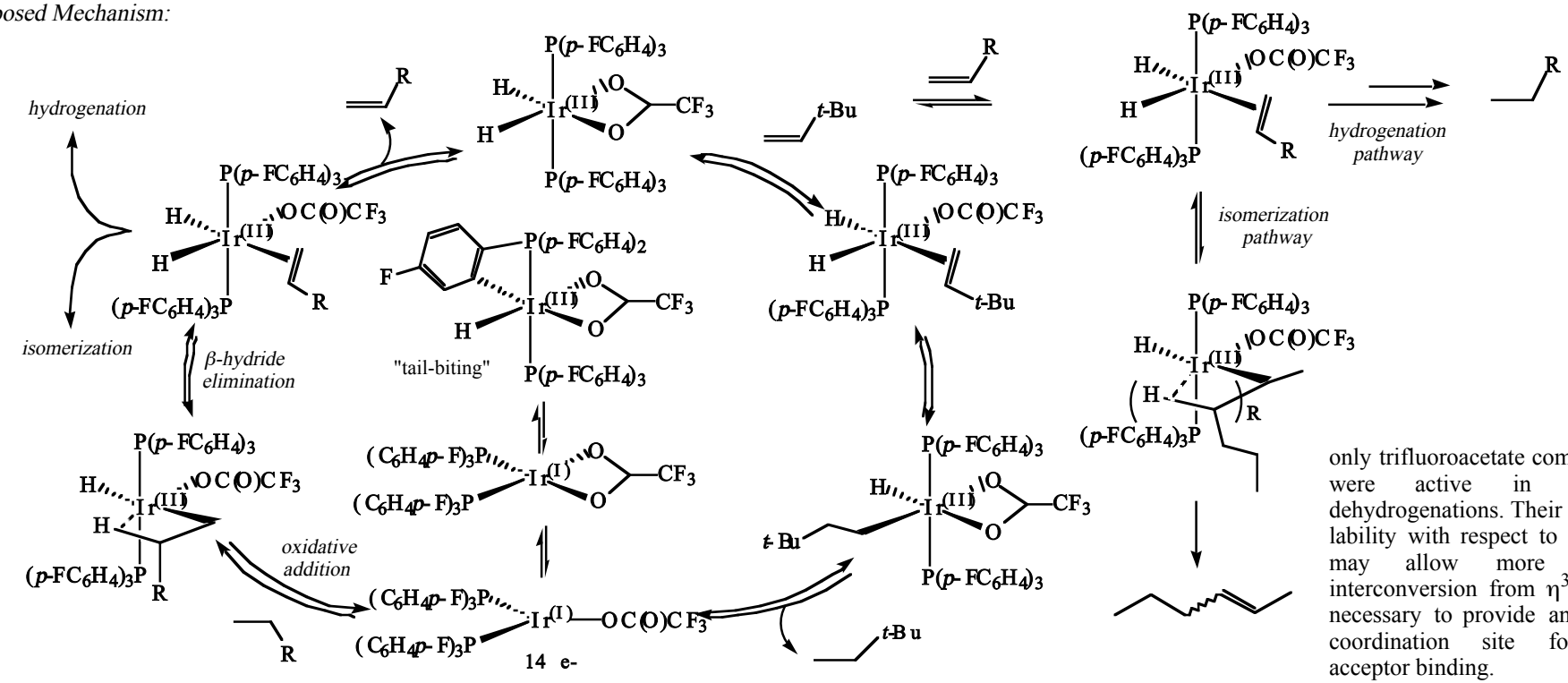



Product distributions of linear alkenes are thought to result from isomerization of the initial kinetic 1-ene product *via* intermediate Ir hydride species. Subjecting 1-hexene to the reaction conditions gives similar olefin distributions (in parentheses).



2d, 1.4 tn 2d, 3 tn 2d, 9 tn
tn = turnover #

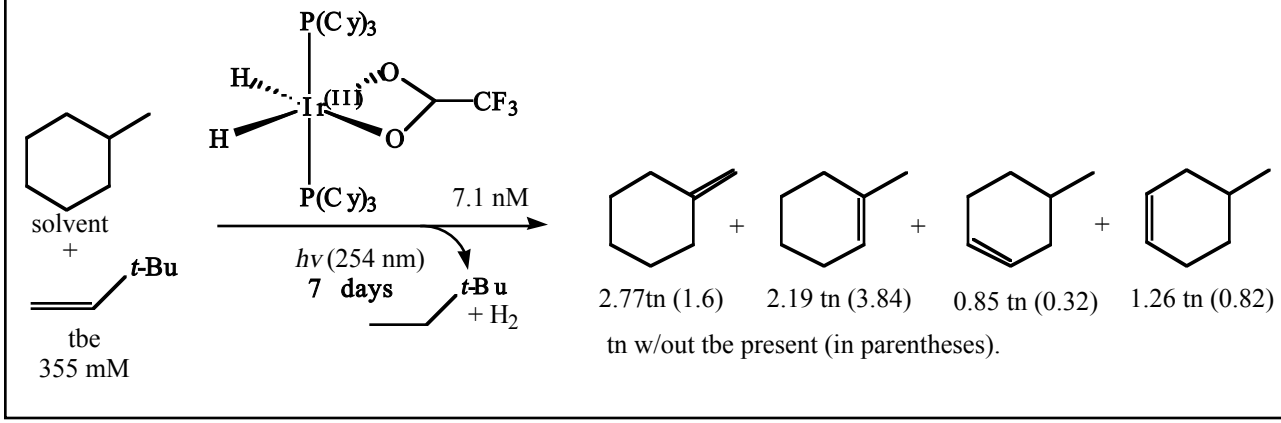
*Proposed Mechanism:*




only trifluoroacetate complexes were active in alkene dehydrogenations. Their greater lability with respect to acetate may allow more facile interconversion from $\eta^3$ to $\eta^1$ necessary to provide an open coordination site for $H_2$ acceptor binding.

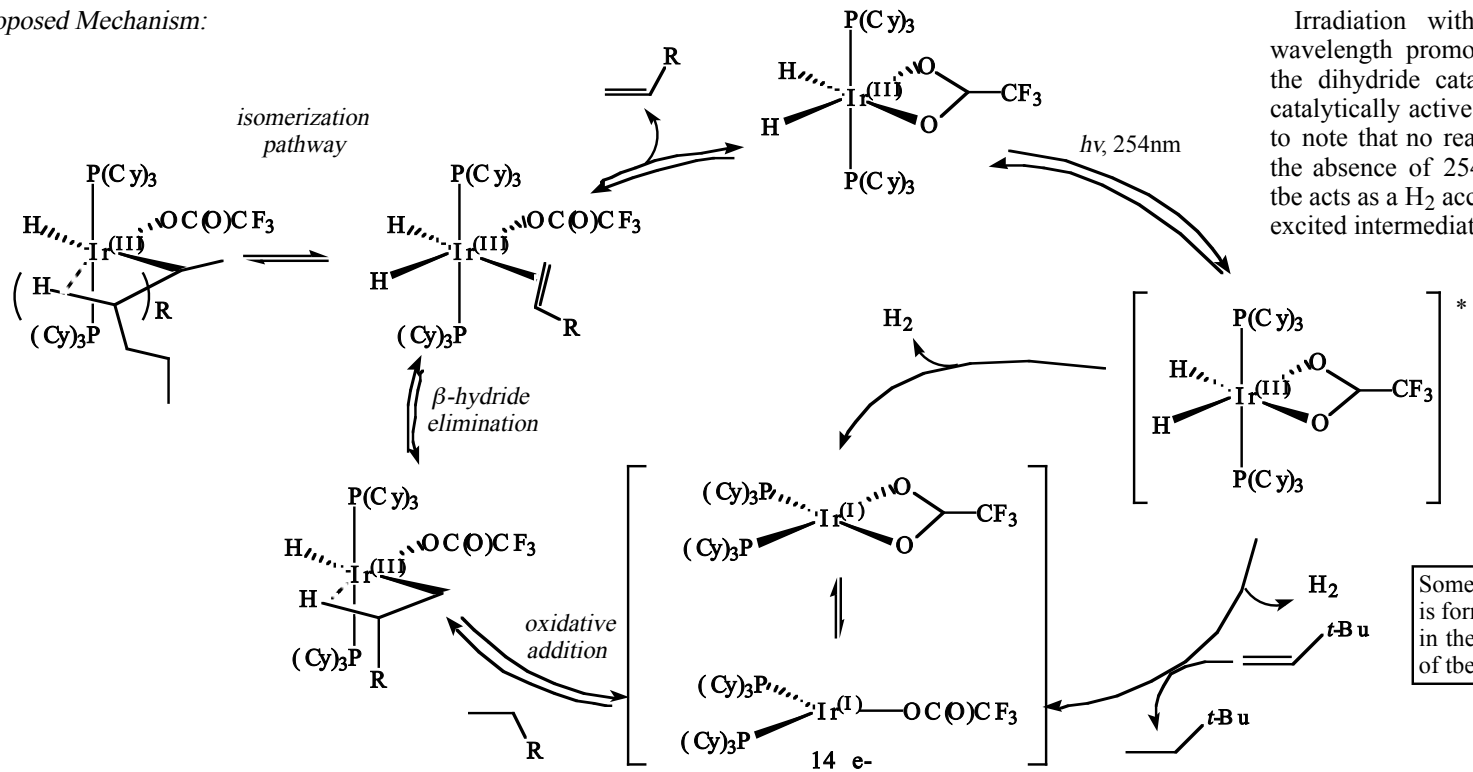
Crabtree *JACS* 1987 (109) 8025.

# *Crabtree:photochemical dehydrogenation of alkanes to alkenes*




Under conditions of *hv* and tbe, methylcyclohexane is the preferred product. This is thought to result from a kinetic preference to form the sterically less hindered M-C bond. Methylenecyclohexane subjected to the reaction conditions results in only 25% conversion to the thermodynamically more stable 1-methylcyclohexene. Although the reaction proceeds w/out tbe, the product ratios reflect more isomerization activity.

*Proposed Mechanism:*

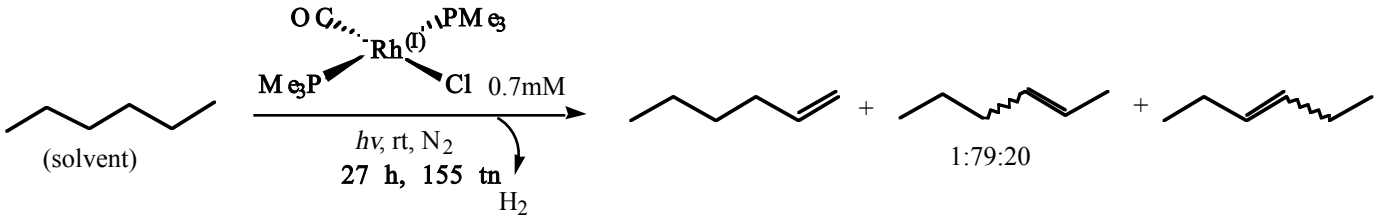


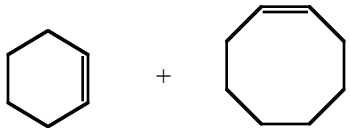

Irradiation with light of the appropriate wavelength promotes reductive elimination of the dihydride catalyst leading directly to the catalytically active 14e- complex. It's interesting to note that no reaction takes place with tbe in the absence of 254 nm light. This implies that tbe acts as a $H_2$ acceptor from a photochemically excited intermediate.

Some free $H_2$ is formed even in the presence of tbe.

Crabtree *JACS* 1987 (109) 8025.

# *Tanaka: photochemical dehydrogenation*




138 tn, 17 h
A theoretical amount of $H_2$ was detected in the gas phase.
When a $N_2$ stream was used, tn increased to 195 tn.

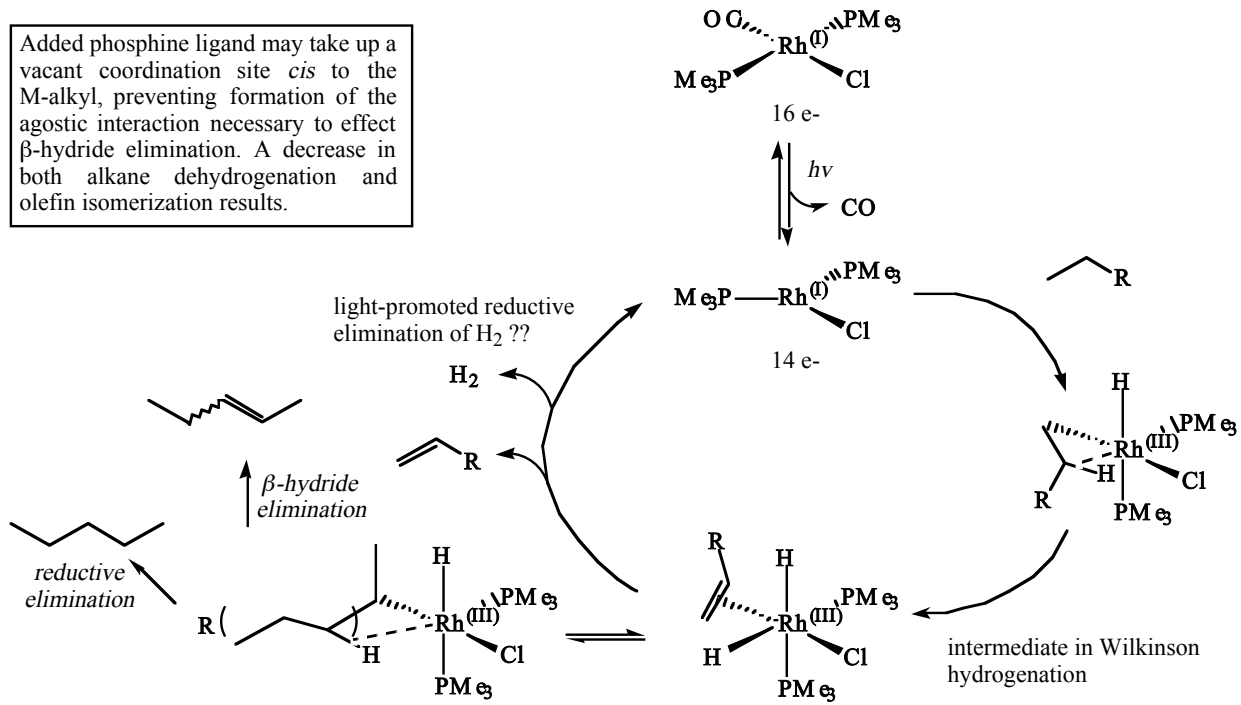
930 tn, 69h
$N_2$ stream

| $PMe_3$/Rh | time (h) | hexenes 1- | 2- | 3- | TN |
|---|---|---|---|---|---|
| 2 | 1 | 1 | 11 | 2 | 5.4 |
| 5 | 3 | 12 | 4 | 1 | 4.0 |
| 5 | 22 | 6 | 4 | 1 | 18.7 |
| 10 | 3 | 28 | 4 | 1 | 0.6 |
| 10 | 22 | 10 | 3.4 | 1 | 7.2 |

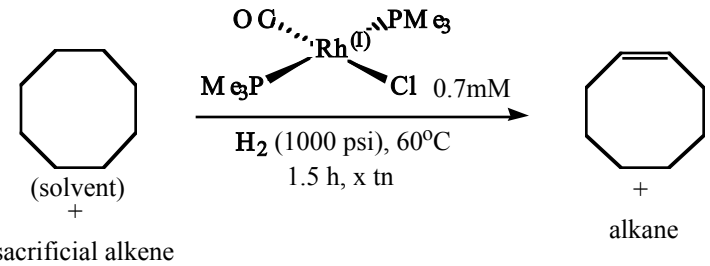
Added phosphine ligand decreases the efficiency of the reaction but increases the regioselectivity towards formation if 1-hexene. Within the same $PMe_3$/Rh ratio, an erosion in regioselectivity is observed upon prolonged reaction times. This is indicative of catalyst mediated alkene isomerization. Could this ratio also be reflective of the rates of olefin hydrogenation? Exposure of 1-hexene to the reaction conditions results in 2-hexene (35%) and hexane (63%) after 22 h.

*Proposed Mechanism:*

Added phosphine ligand may take up a vacant coordination site *cis* to the M-alkyl, preventing formation of the agostic interaction necessary to effect β-hydride elimination. A decrease in both alkane dehydrogenation and olefin isomerization results.

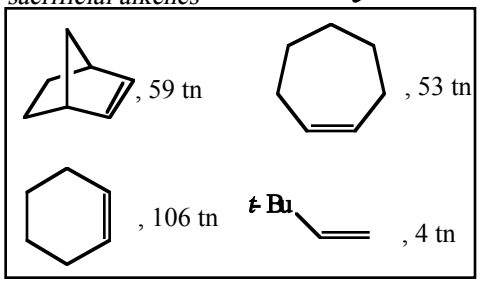


# *Goldman: Wilkinson's Catalyst Varient*




*n*-hexane gave hexenes in modest tn (9.6) with norbornene as the $H_2$ acceptor. No mention was made to the isomer distributions.

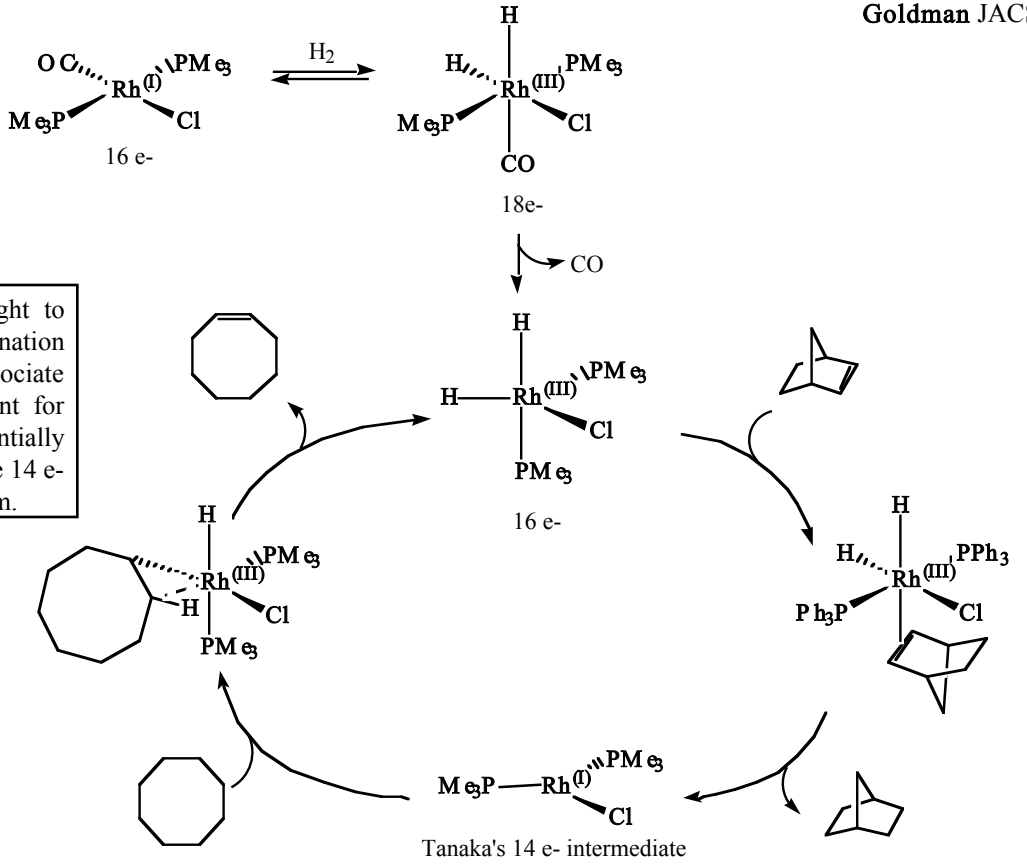
*sacrificial alkenes*




A variety of sacrificial alkenes work in the dehydrogenation of cyclooctane, an especially reactive substrate. Cyclooctene has a very low heat of hydrogenation probably resulting from transannular steric repulsions in cyclooctane which are less severe in cyclooctene.

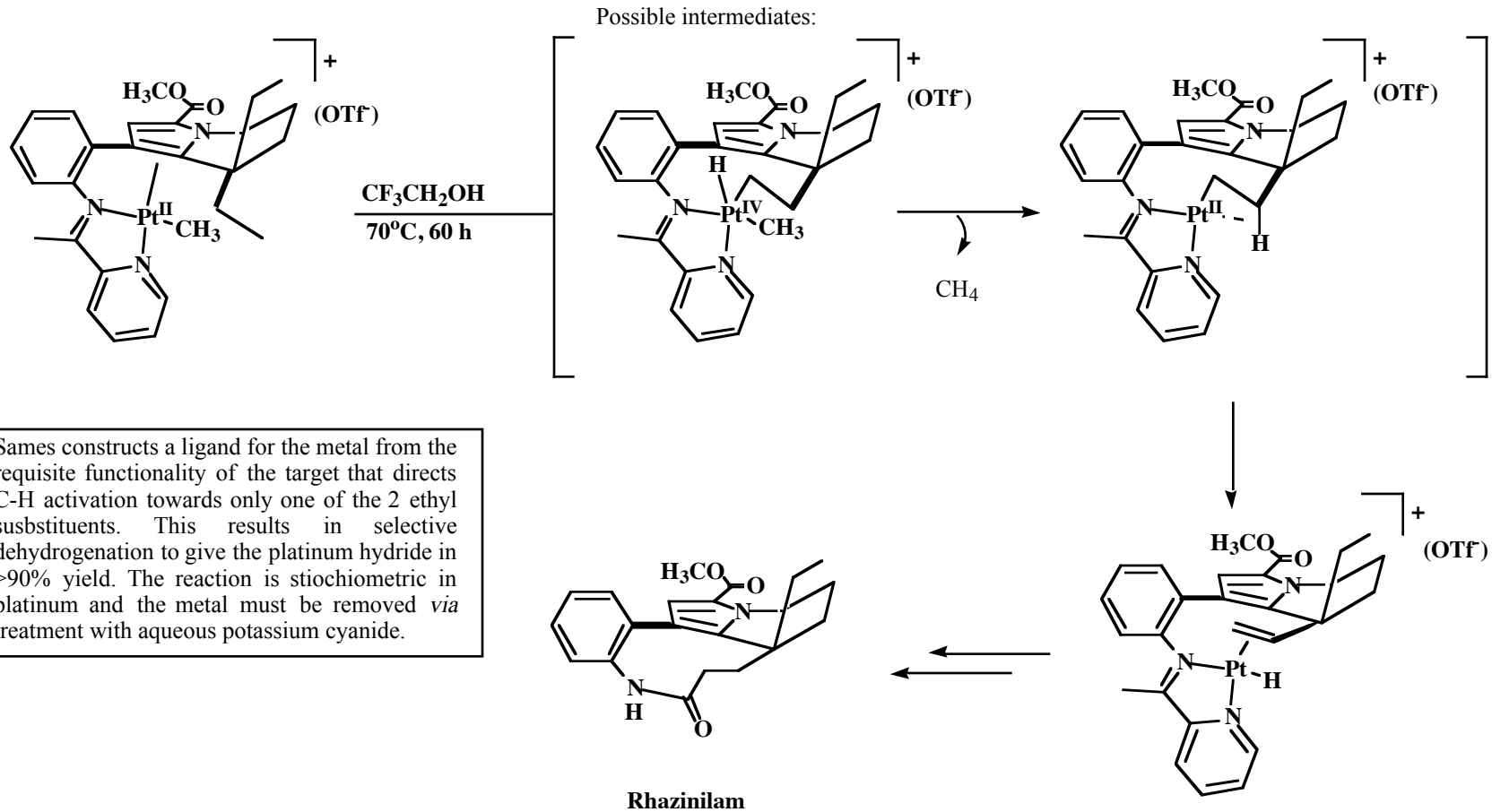
**Goldman** JACS **1992** (114) 9492.

*Proposed Mechanism:*




Formation of octahedral dihydride complex is thought to initiate ligand dissociation. Wilkinson's hydrogenation catalyst (see hydrogenation, pg. 142), known to dissociate $PPh_3$ upon $H_2$ oxidative addition, is cited as precedent for this. There is no evidence that CO dissociates preferentially over $PMe_3$. The authors invoke this to arrive at the same 14 e- intermediate proposed in Tanaka's photochemical system.

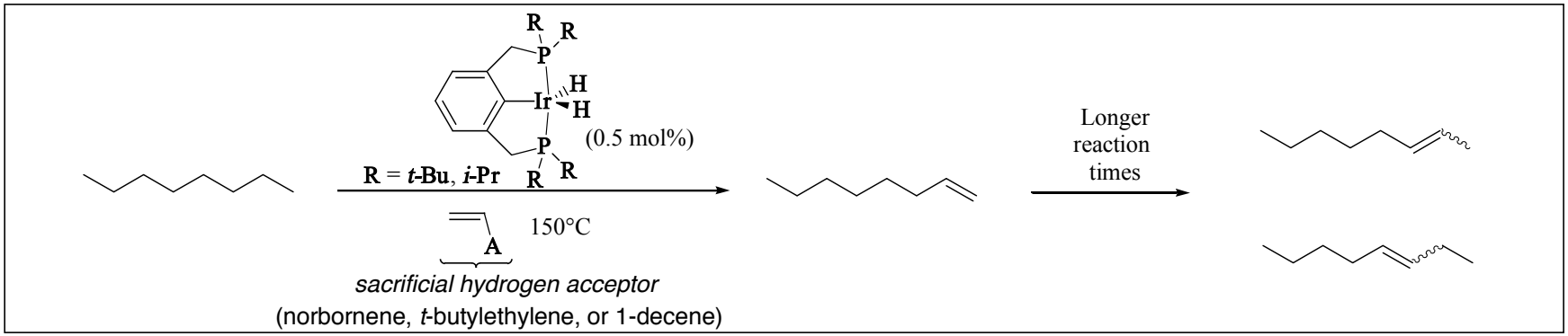
# *Substrate directed dehydrogenation via C-H activation*



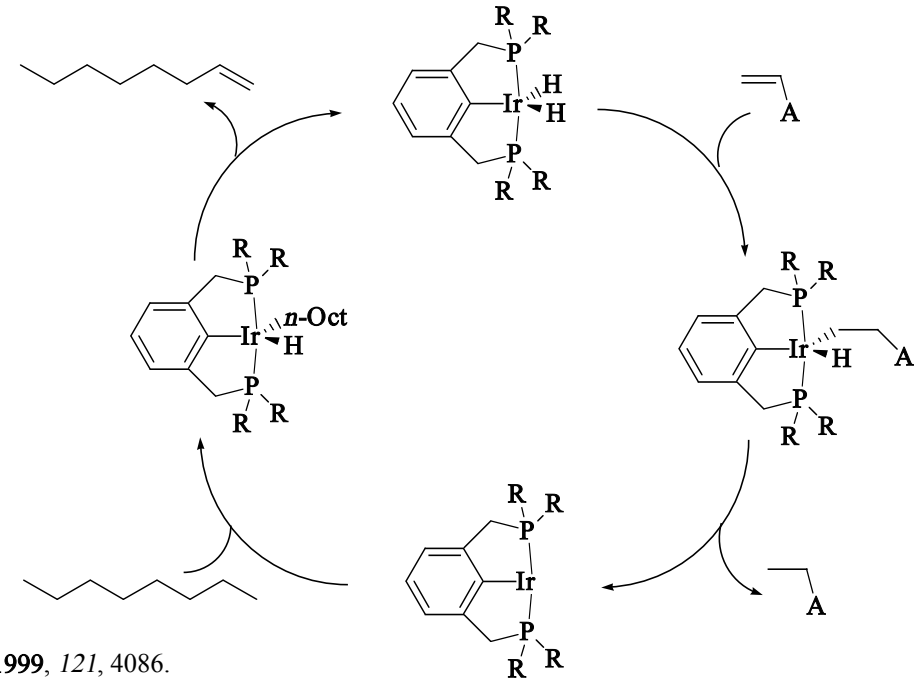

Sames constructs a ligand for the metal from the requisite functionality of the target that directs C-H activation towards only one of the 2 ethyl susbstituents. This results in selective dehydrogenation to give the platinum hydride in >90% yield. The reaction is stiochiometric in platinum and the metal must be removed *via* treatment with aqueous potassium cyanide.

Sames *JACS* 2000 (122) 6321.

# *Dehydrogenation of n-alkanes to terminal olefins*




At low conversions, 1-octene is the major product of the dehydrogenation reaction (90 to >95% selectivity at 5% conversion, depending upon the acceptor used). Ethylene was not a suitable acceptor, resulting in inhibition of catalysis due to formation of a stable Ir-ethylene complex. As the reaction proceeds, olefin isomerization via sequential hydrometallation and β-hydride elimination erodes the kinetic selectivity, resulting in a mixture of olefin isomers.

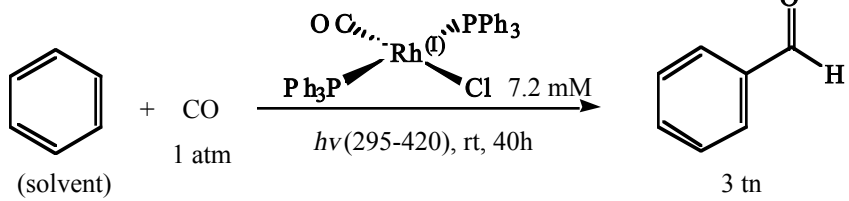



Although the nature and the concentration of the sacrificial hydrogen acceptor had little effect on the reaction rate, these factors had a large effect on the observed distribution of double bond isomers in the product. The authors propose that the observed isomer distribution is largely determined by the competition between the sacrificial acceptor and the product olefin for insertion into the Ir-H bond of the dihydride intermediate.

Goldman, A. *JACS* 1999, *121*, 4086.

# *Direct carbonylation of benzene*

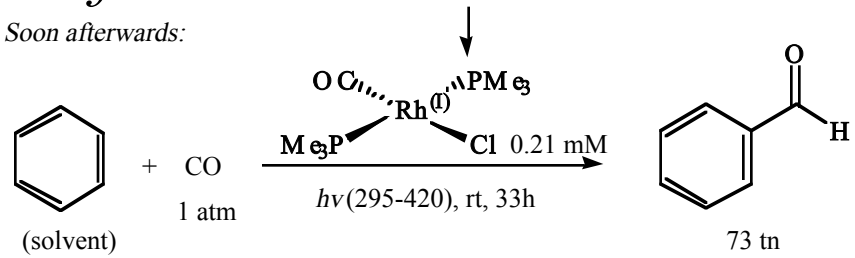
*The first report:*




$RhCl(CO)(PPh_3)_2$ is a photochemical decarbonylation catalyst at rt.

Eisenberg *JACS* 1986 (108) 535.

*Soon afterwards:*

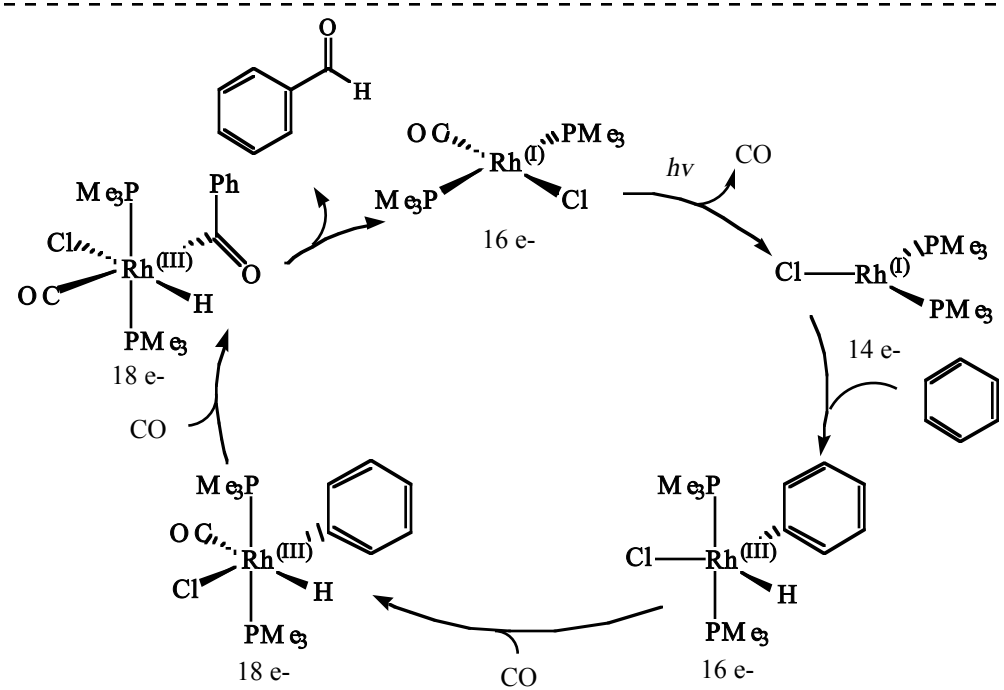



| Phosphine | CO ($cm^{-1}$) | TN |
|---|---|---|
| $PMe_3$ | 1970 | 73 |
| $PBu_3$ | 1955 | 19 |
| $PEt_3$ | 1957 | 17 |
| $P(i\text{-}Pr)_3$ | 1947 | 2 |
| $P(p\text{-tolyl})_3$ | 1979 | 3 |
| $PPh_3$ | 1982 | 2 |
| $P(OMe)_3$ | 2011 | 2 |

$PMe_3$ is thought to increase the effectiveness of the Rh catalyst both by increasing electron density at the metal thereby promote oxidative addition and by decreasing tail-biting of the complex.

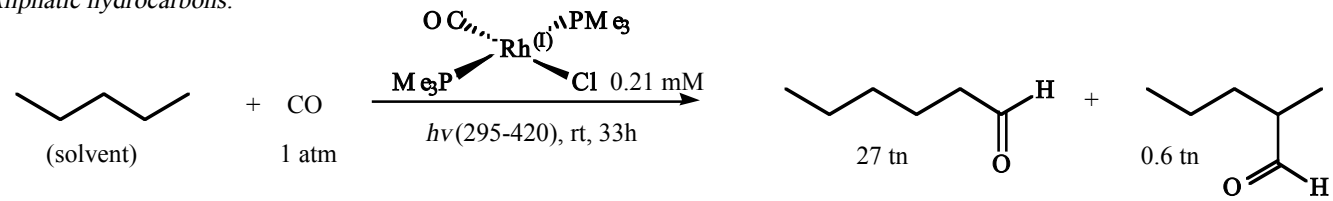
Tanaka *Chem. Lett.* 1987 249.
Tanaka *JACS* 1990 (112) 7221.

*Postulated mechanism:*



# *Direct carbonylation of alkanes*

*Aliphatic hydrocarbons:*

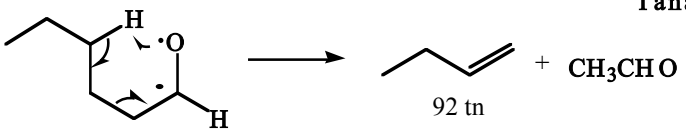



The carbonylation reaction is highly regioselective towards primary C-H bonds to give linear aldehydes with high selectivities. Unfortunately, the aldehydes formed readily undergo a secondary photochemical reaction (Norrish Type II) to give a dehomologated terminal alkene and acetaldehyde in large quantities.

**Tanaka** *Chem. Comm.* **1987** 758.

Effects of irradiation wavelength: Flash photolysis revealed loss of CO (thought to lead to the catalytically active 14e- species for C-H oxidative addition) is the dominant photoreaction of $RhCl(CO)(PPh_3)_2$ at >330 nm. Metal-to-ligand charge transfer band of Rh-CO @ 365 nm. **Ford** *JACS* **1989** (111) 1932. Absorption of non-conjugated aldehydes appear at ~285 nm. It was hypothesized by Tanaka that cutting of the short-wavelength region capable of aldehyde excitation would improve yields of the desired aldehyde.

*Photo-induced Norrish Type II Chemistry*

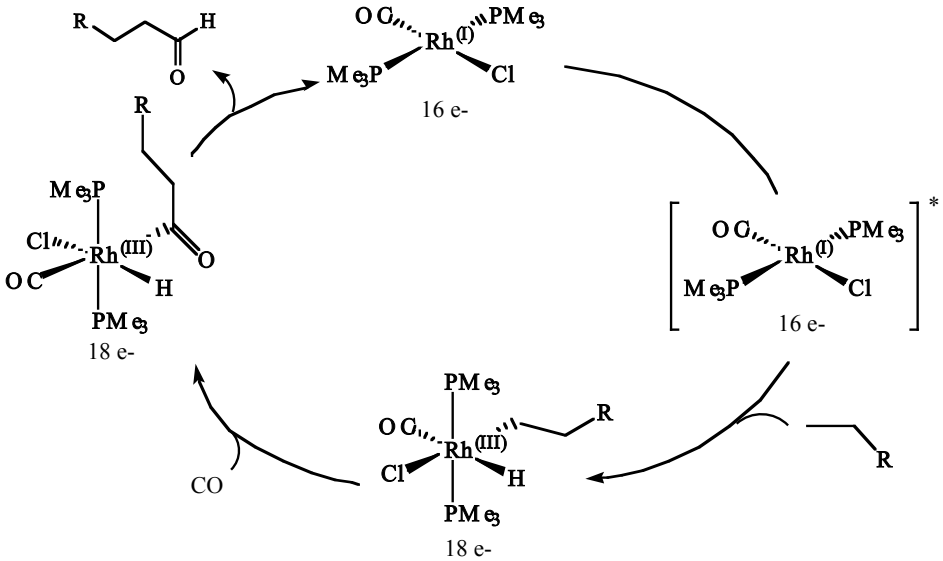



| wavelength (nm) | aldehyde tn (1-decanal, 2-, 3-, 4-) | nonene tn |
|---|---|---|
| 295-420 | 610 (85:5:4:2:3) | 319 |
| >325 | 126 (8:45:17:15:16) | 0 |

While Norrish Type II reactions leading to dehomologated terminal alkenes were suppressed by going to a longer wavelength, carbonylation selectivity towards the $1^o$ position of the alkane was lost and catalytic activity was diminished. These results imply that photo-induced CO dissociation may not be the major pathway in this system for generating the complex capable of C-H activation of linear aliphatic alkanes.

**Tanaka** *JACS* **1990** 7221.

*Revised proposed catalytic cycle:*

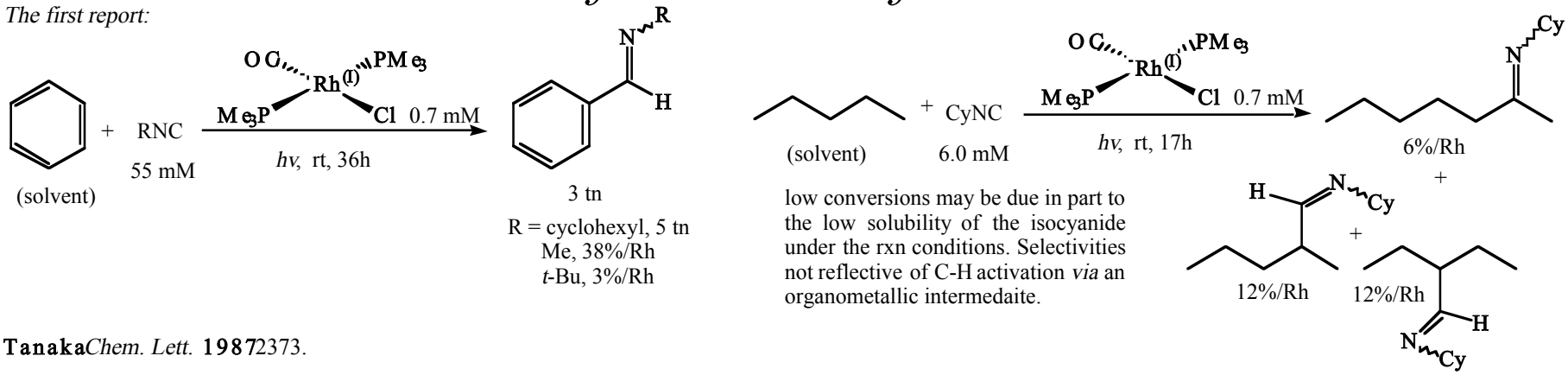



The rate of benzene carbonylation catalyzed by $RhCl(CO)(PMe_3)_2$ irradiated at >290 nm (ca. 314 nm, a wavelength where Rh-CO does not absorb) is proportional to CO pressure. Goldman proposes a photoelectronically excited intermediate as the species effecting C-H activation. **Goldman** *JACS* **1994** (116) 9498.

Irradation of a solution of $RhCl(CO)(PMe_3)_2$ /$C_6H_6$ in the absence of CO at -40°C afforded two isomers of the 18 e- alkylhydrido complexes which were fully characterized by NMR ($^1H$, $^{31}P$, $^{13}C$ NMR). **Fields** *JACS* **1994** (116) 9492.

# *Direct formation of aldimines*

*The first report:*




low conversions may be due in part to the low solubility of the isocyanide under the rxn conditions. Selectivities not reflective of C-H activation *via* an organometallic intermedaite.

Tanaka *Chem. Lett.* 1987 2373.

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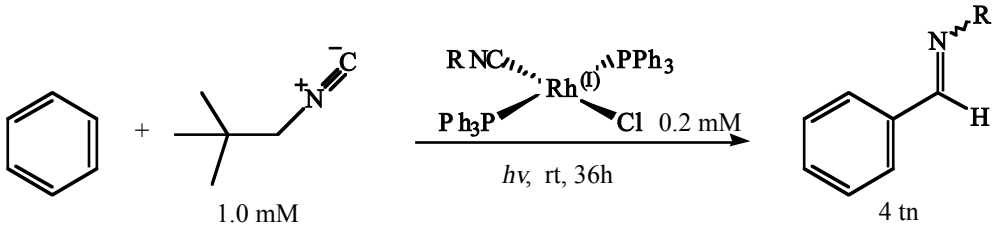
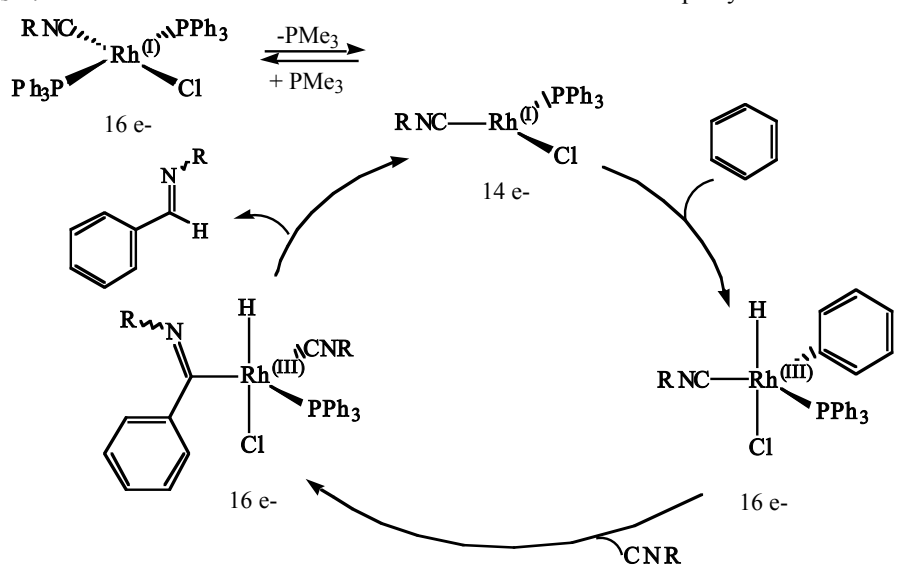


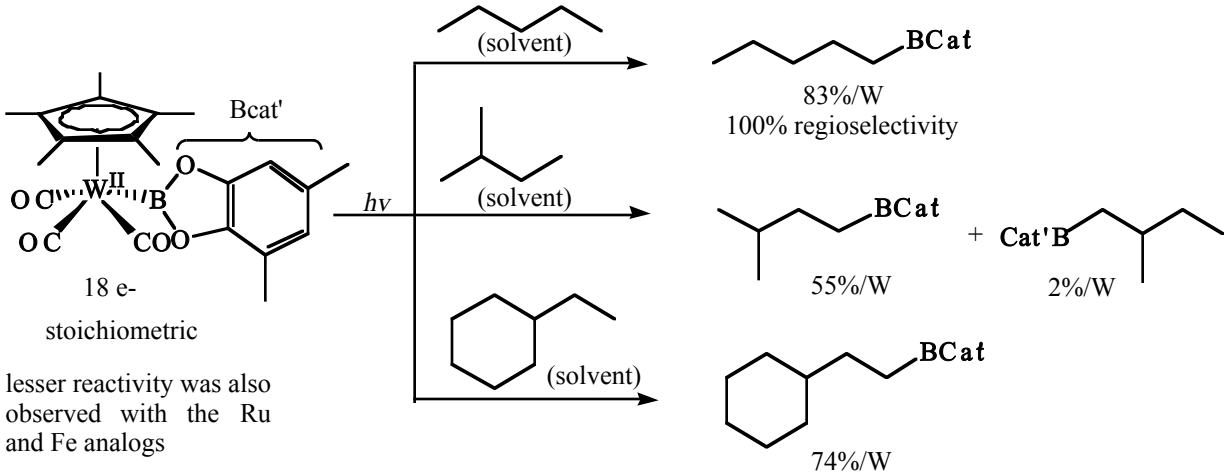

Jones notes that this system (unlike the one reported by Tanaka) is completely ineffective at aldimine formation from aliphatic hydrocarbons.

*Proposed mechanism:*




Jones *OM* 1990 (9) 718.

# *Direct Borylation of Alkanes: Stoichiometric*

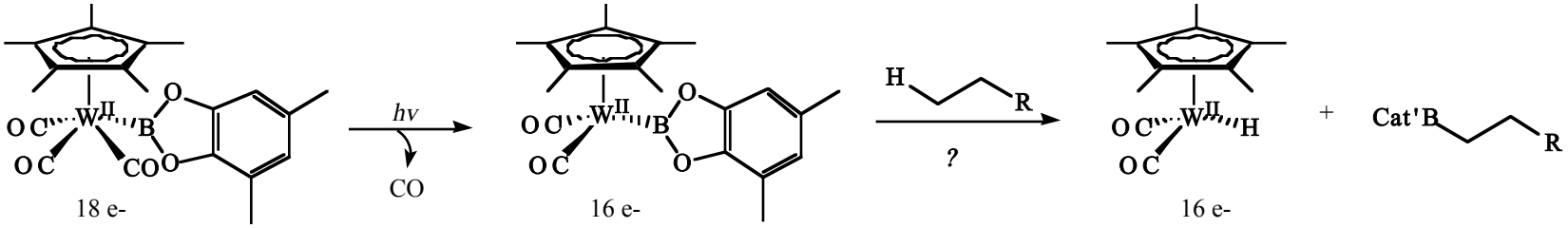



lesser reactivity was also observed with the Ru and Fe analogs

Selectivity between activation/ functionalization of 1° *vs.* 2° C-H bonds is high. Reactions of the tungsten complex with cyclohexane resulted in 22% yield based on W. This system appears to be highly sensitive to sterics as demonstrated in it's ability to discriminate between the linear and branched 1° C-H bonds of isopentane.

*Proposed mechanism:*

The exact mechanism of C-H activation/functionalization is unclear. Two possibilities are likely: 1. oxidative addition followed by reductive elimination, 2. σ-bond metathesis. The first possibility would requires an increase in the oxidation state of the W to +4, a high energy oxidation state for an organometallic W complex. Alternatively, σ-bond methathesis could occur with no oxidation state change. Alkane dehydrogenation followed by anti-Markovnikov hydroboration is excluded since aliphatic alkenes result in vinylborates rather than the observed alkylborate esters.

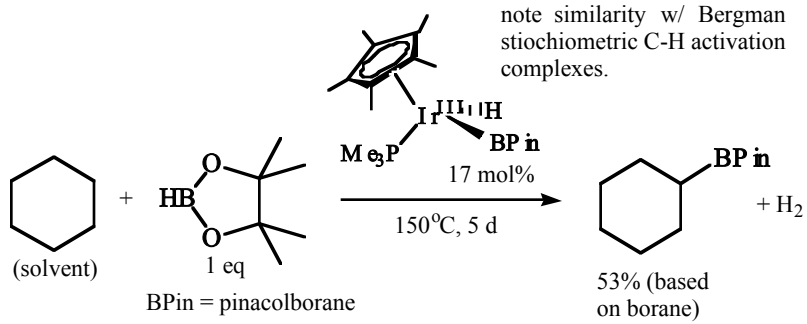



Photolysis in the presence of $PMe_3$ results in the formation of $Cp^*W(CO)_2(PMe_3)Bcat'$. This was taken as evidence for the photo-induced loss of CO to generate coordinatively unsaturated 16 e- intermediate that may interact with the alkane.

Hartwig *Science* 1997 (277) 211.

# *Direct Borylation of Alkanes: Catalytic*

*The first catalytic report:*




Smith *JACS* 1999 (121) 7696.

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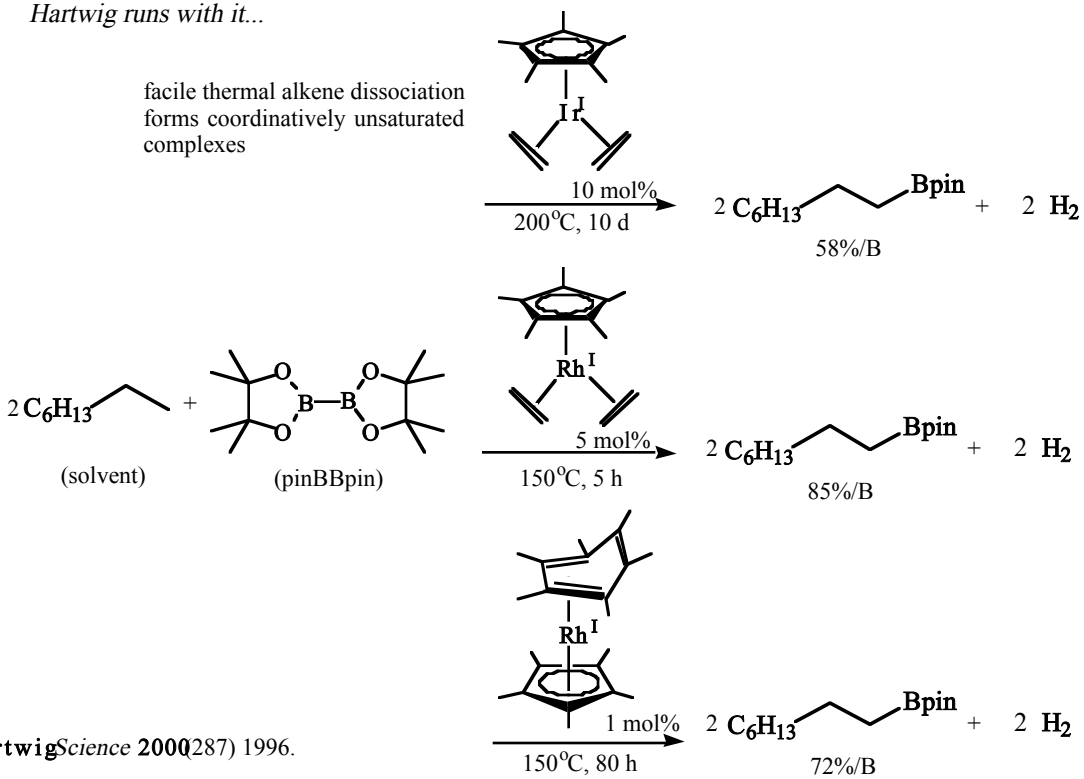
*Hartwig runs with it...*

facile thermal alkene dissociation forms coordinatively unsaturated complexes

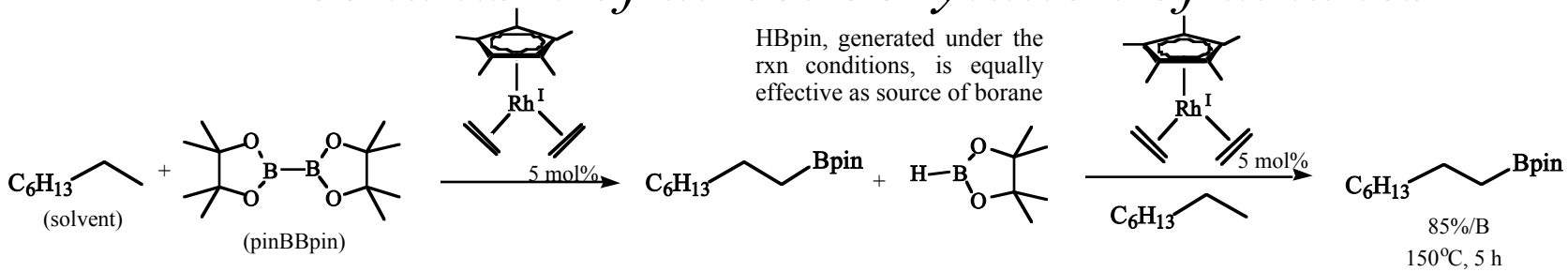



The rate acceleration observed in going from a 3rd row metal complex to an analogous 2nd row complex may be accounted for by a weakening of M-C bonds which may promote turnover steps in the catalytic cycle.

100% regioselectivity for the terminal borane was consistently observed. The linear borane is thought to be the kinetic product. Exposure of secondary alkyl boranes to reaction conditions does not result in isomerization. 2-Methylheptane resulted exclusively in products formed from primary C-H bond activation with the less sterically hindered terminal methyl group becoming functionalized selectively.

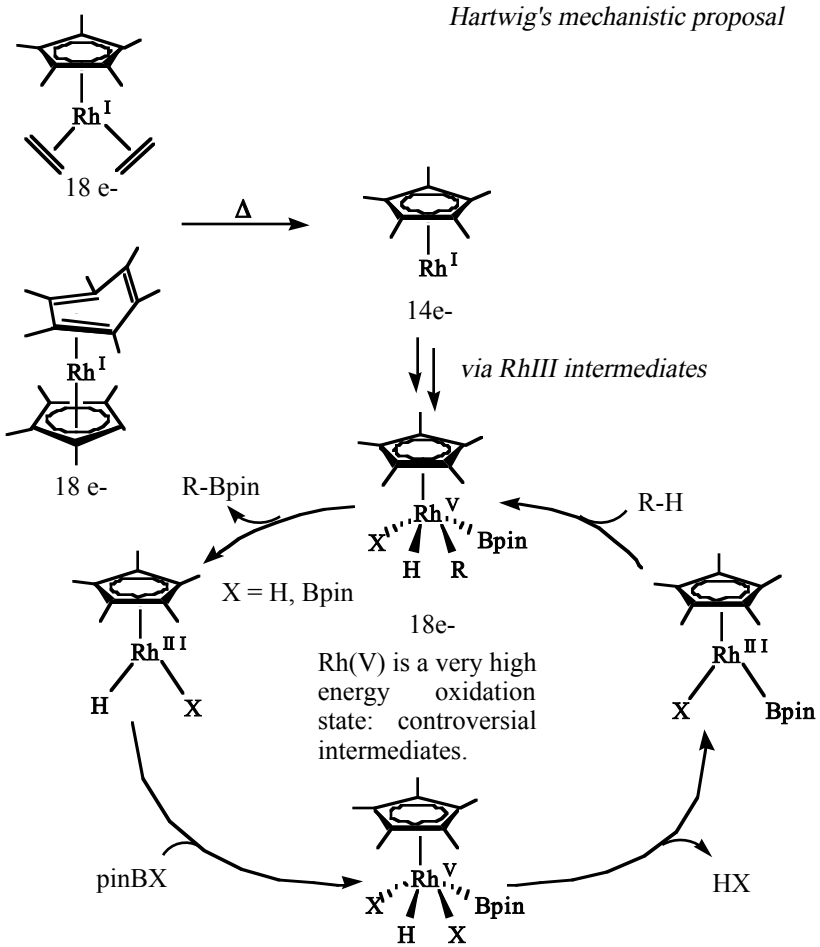
Hartwig *Science* 2000 (287) 1996.

# *Mechanism of direct borylation of alkanes*

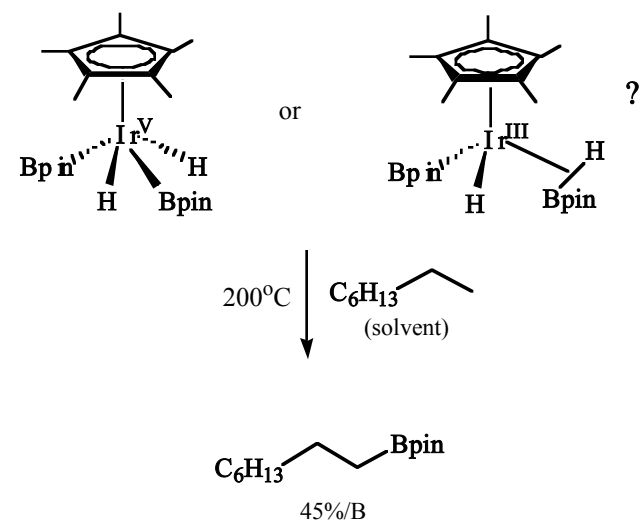



Hartwig *Science* 2000(287) 1996.

*Hartwig's mechanistic proposal*




To validate his mechanistic proposal that invokes high energy Rh(V) intermediates, Hartwig synthesizes what he claims is an Ir(V) dihydrido bisboryl species (the high reactivity of the Rh complex has precluded its isolation/characterization). Although Hartwig argues against a σ-complexed borane Ir(III) species, his evidence does not conclusively eliminate it as a possibility. The independently synthesized intermediate was an effective alkane borylation reagent, resulting in similar yields and the same selectivities observed in the catalytic system.

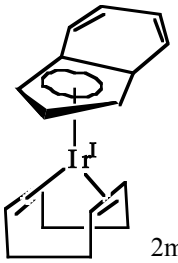



Hartwig *JACS* 2001(123) 8422.

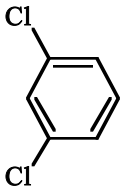
# *Direct Arene borylation: Suzuki precursors*

*Towards synthetic utility...*

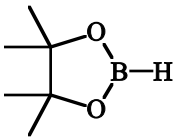
In several examples the authors were able to achieve intermolecular C-H activation/functionalization without using the substrate as the solvent. Some substrates were borylated under neat conditions while others employed cyclohexane as solvent.




$\eta^5$-indenyl complex capable of rearranging to $\eta^3$ and $\eta^1$




1 eq

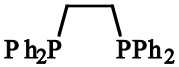



1.5 eq

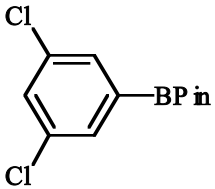
2mol%

dpp e 2mol%, 100°C

16h

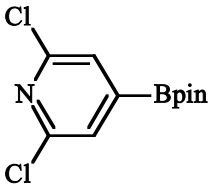



dppe

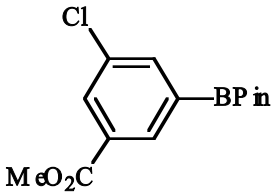



89% based on arene

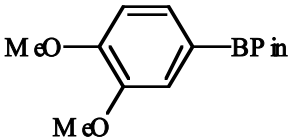
excellent regioselectivities for functionalization of sterically less hindered sites




aryl-H: HBpin (1:2)
69% yield, 4h




aryl-H: HBpin (1:2)
95% yield, 25h




aryl-H: HBpin (1:3)
62% yield, 95h, dmpe

Recall that, in general, Ir complexes are less reactive than the corresponding Rh complexes towards alkane borylation. Aryl C-H bonds are more reactive towards C-H activation than alkyl C-H. The factors favoring activation of aryl C-H bonds are the high degree of s character in the $C_{sp2}$-H bond which favors σ-complexation to the metal and the strength of the resulting aryl $C_{sp2}$-M bond after oxidative addition.

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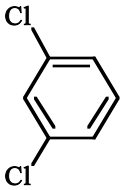
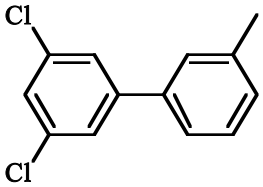
*Consecutive aryl borylation/Suzuki:*




1 eq

1).HBpin, 2 mol% (Ind)Ir(COD), 2 mol% dppe, 100°C, 16 h

2). 3-bromotoluene, 2 mol% $Pd(PPh_3)_4$, $K_3PO_4$, DME, 80°C, 17 h.

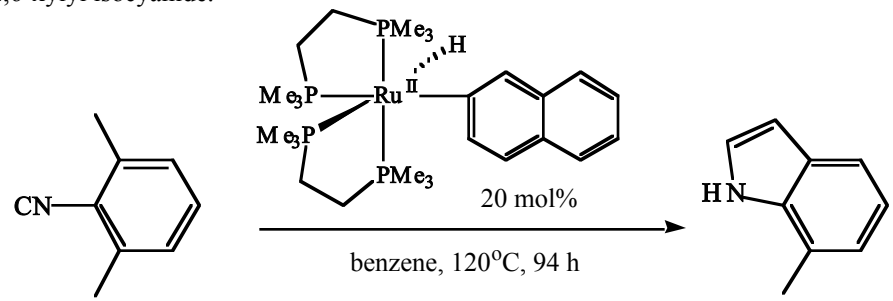



80% yield based on dichlorobenzene

Smith *Science* **2002**(295) 305.
A related study that uses the bpy ligand in conjunction with IrI: Hartwig *JACS* **2002**(124) 390.

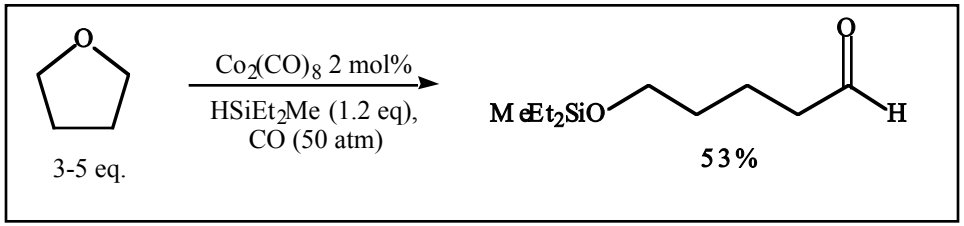
# *Question 1: Catalytic Indole Production*

Propose a catalytic cycle for the following Ru system that affords indoles in good yields from 2,6-xylyl isocyanide.

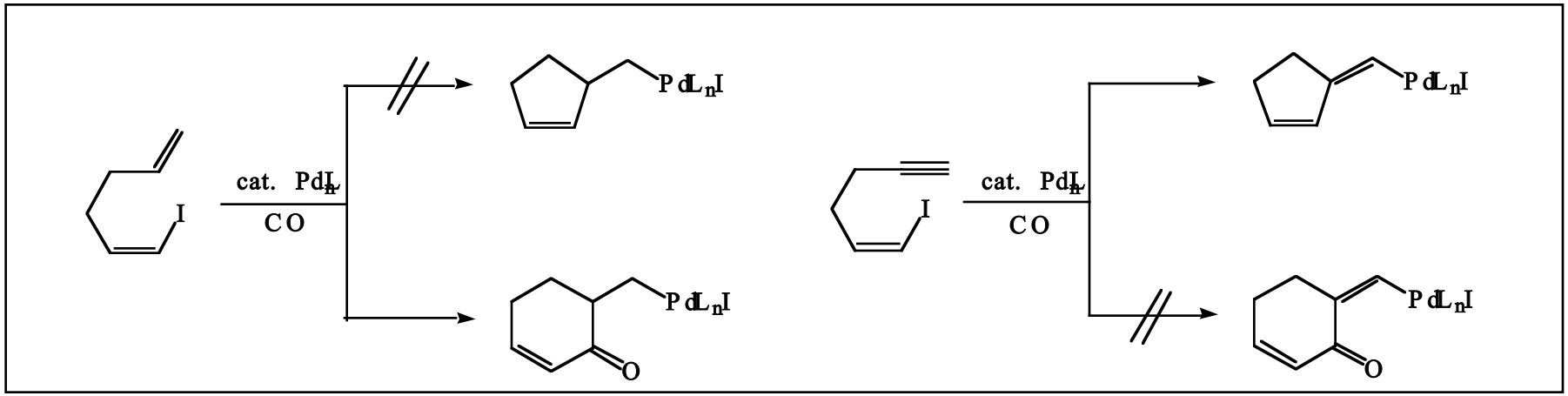


# *Question 2*

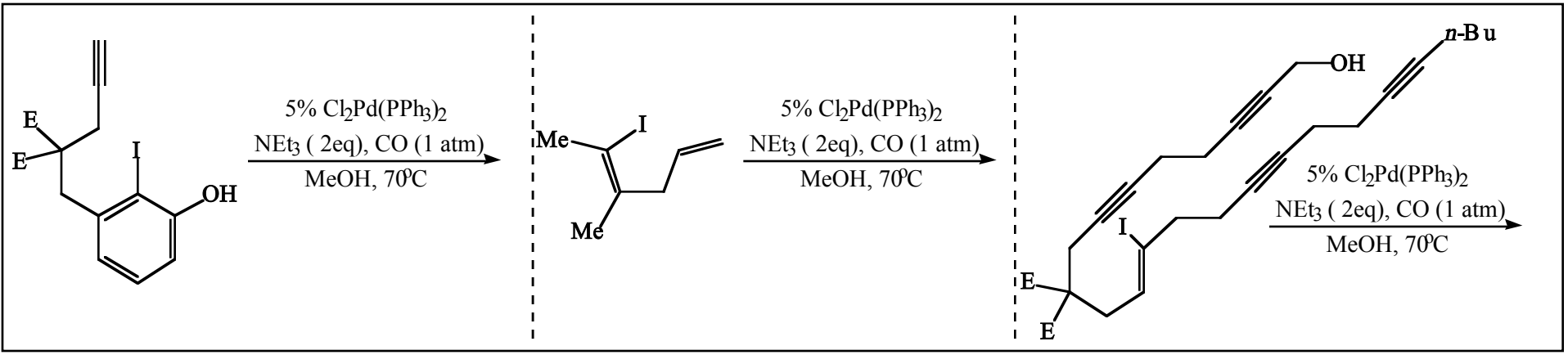
Provide a detailed mechanism for the following transformation.



# *Question 3*

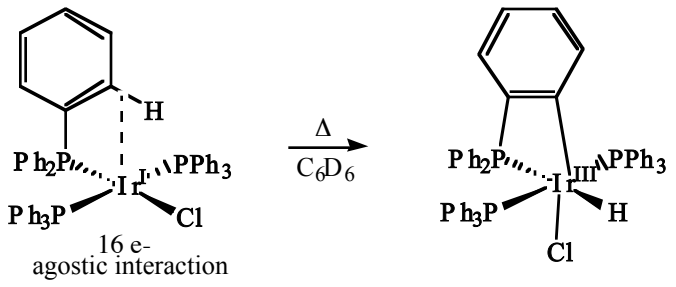



When a competition exists between cyclic acylpalladation and cyclic carbopalladation, the preferred outcome is different for alkenyl and alkynyl substrates. For alkenyl substrates, cyclic acylpalladation is favored over cyclic carbopalladation, and for alkynyl substrates, this preference is reversed. Given these empirical observations, predict the products of the following transformations:

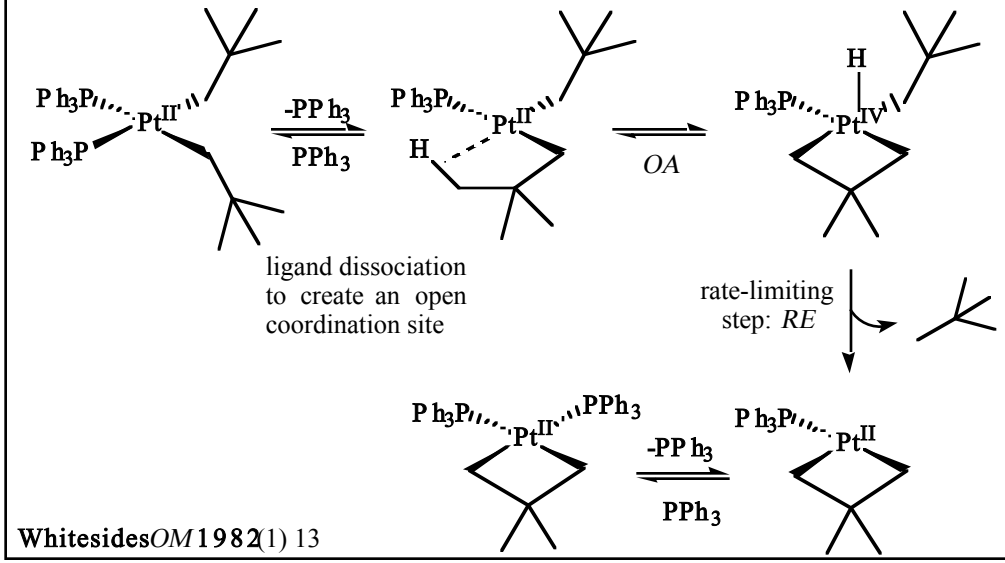


# *Cyclometallation*

*Cyclometallation: intramolecular C-H activation of supporting metal ligands (a.k.a. "tail-biting")...*



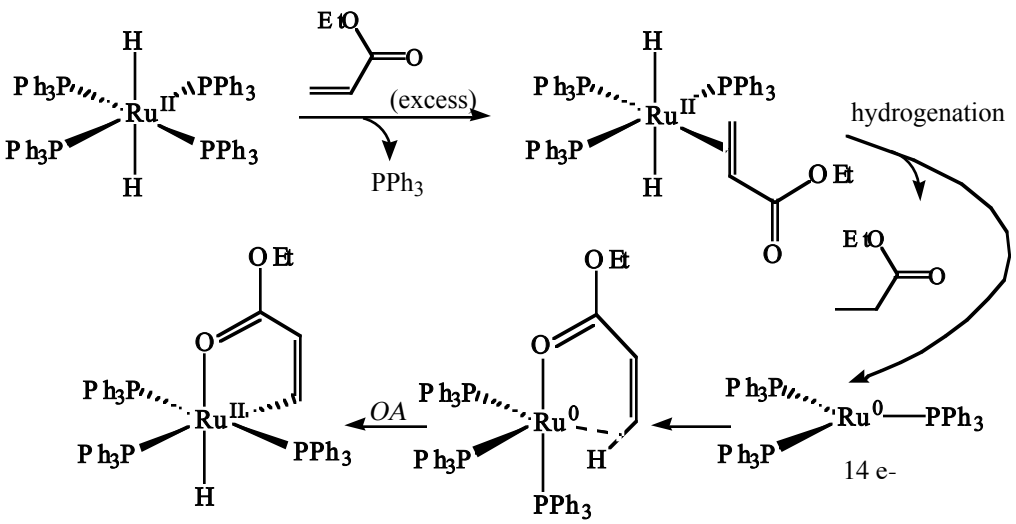

Bennnett *JACS* (91) 1969 6983.

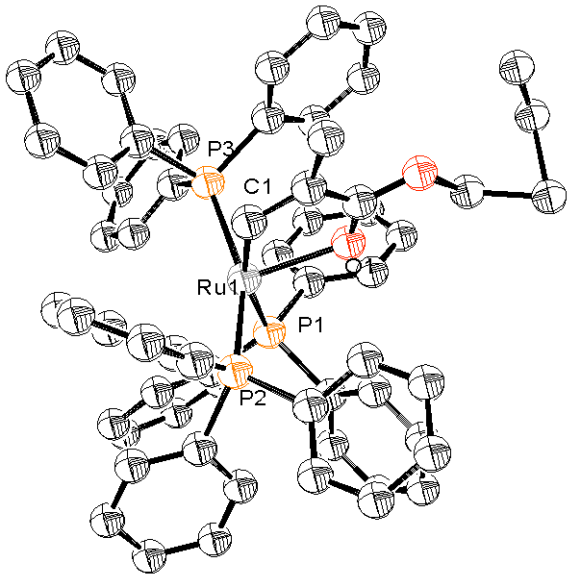



Whitesides *OM* 1982 (1) 13

*Chelate-assisted C-H activation:*

Substrates with Lewis basic functionality can temporarily become appended to a site of coordinative unsaturation on a metal and undergo chelate assisted C-H activation.

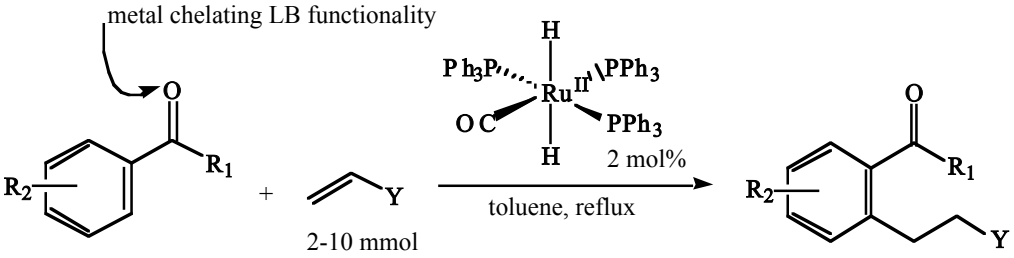



Ibers *JACS* **1976** (98) 3874.

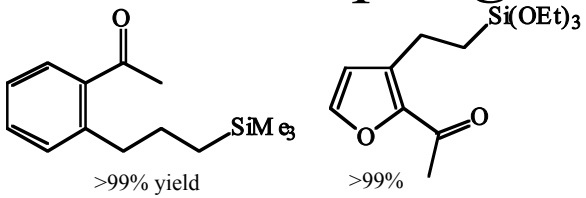
# *Chelate assisted $Csp_2$-H-olefin reductive coupling*

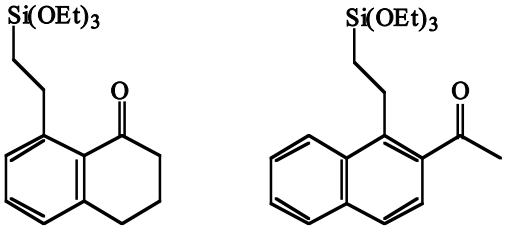
*Murai's breakthrough system...*




$C_{sp2}$-H 4 atoms from LB functionality results in 5-membered ring metal chelate

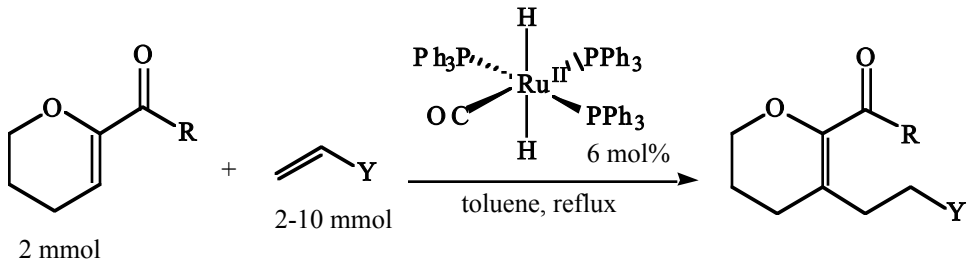
Y = H (ethylene)
$Si(OEt)_3$ ← "privileged olefin"
$CH_2SiMe_3$
*t*-Bu

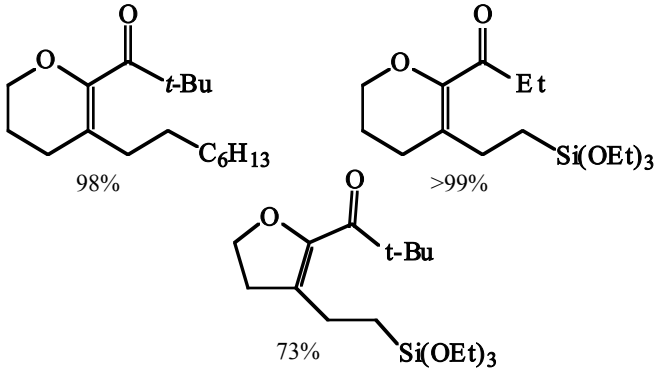



**Murai** *Nature* **1993**(366) 529.

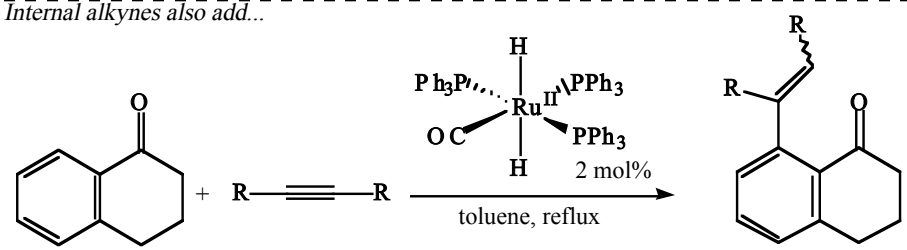
*Many other examples follow:*




**Murai** *Chem. Lett.* **1995**679.

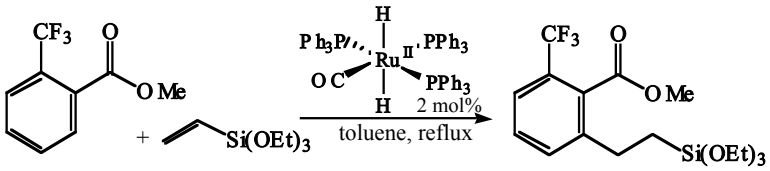
*Internal alkynes also add...*




R = Pr (72%), E/Z = 16/1
Ph (85%), E/Z = 9/1

**Murai** *Chem. Lett.* **1995**681.

*Aryl esters:*

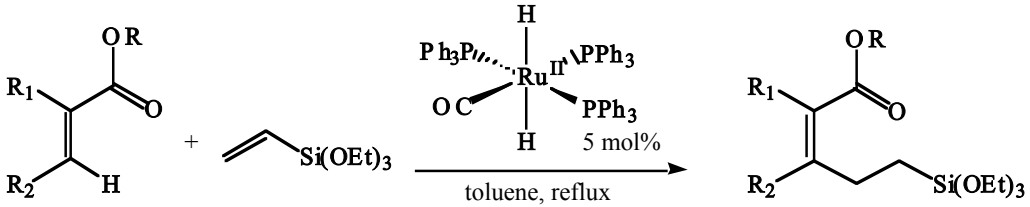



Only aromatic esters substituted with $CF_3$ or F groups (*m*,*p*,and *o*) resulted in coupled product. Other benzoates w/electron withdrawing substituents *o*-$NO_2$, *p*-$NO_2$, *o*-CN, *o*-$CO_2Me$ failed to give coupled product.

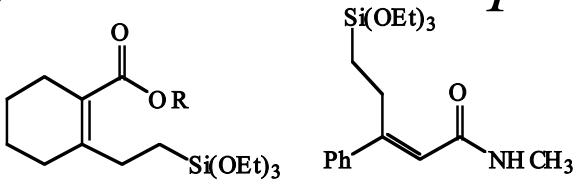
**Murai** *Chem. Lett.* **1996**109.

# *Oxygen chelate assisted $Csp_2$-H-olefin reductive coupling*

*Cyclic and acyclic vinyl esters :*



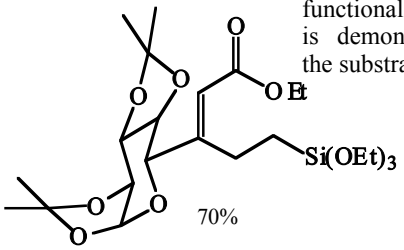

A lack of reactivity is observed when the β $C_{sp2}$-H bond is *trans* to the ester carbonyl




R = $(CH_2)_5CH_2OAc$, 85%
$(CH_2)_5CH_2OTBS$, 91%
$(CH_2)_5CH_2Br$, 54%

80%

A high degree of functional group tolerance is demonstrated through the substrates tested.

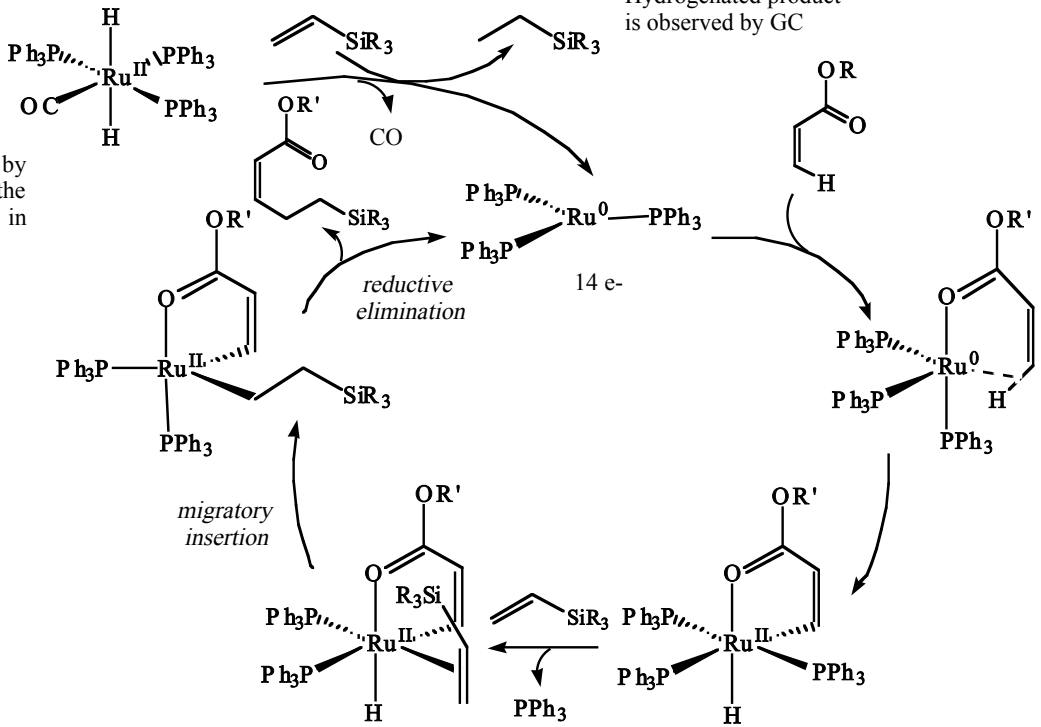



70%

Trost *JACS* **1995**(117) 5371.

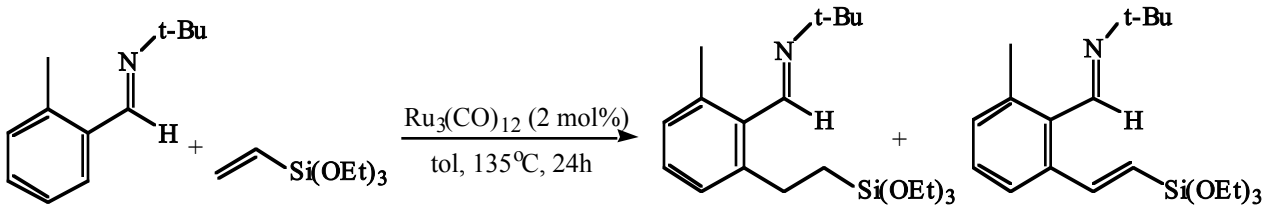
*Proposed mechanism:*

Hydrogenated product is observed by GC




CO loss is supported by the observation that the reaction is inhibited in the presence of CO.

# *Nitrogen chelate assisted $Csp_2$-H-olefin reductive coupling*




81% 10%

$RuH_2(CO)(PPh_3)_3$ (2 mol%) 26% 8%

Some Ru-H is formed *via* the dehydrogenative coupling.

Muria *Chem. Lett.* 1996 111.

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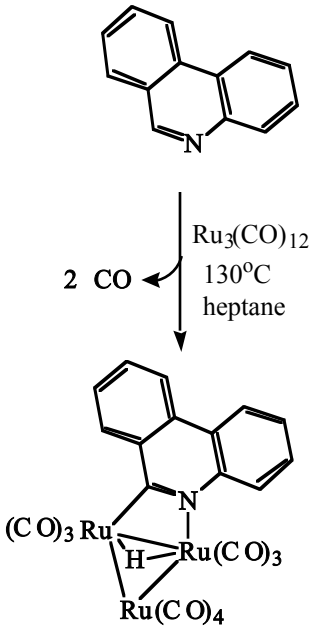
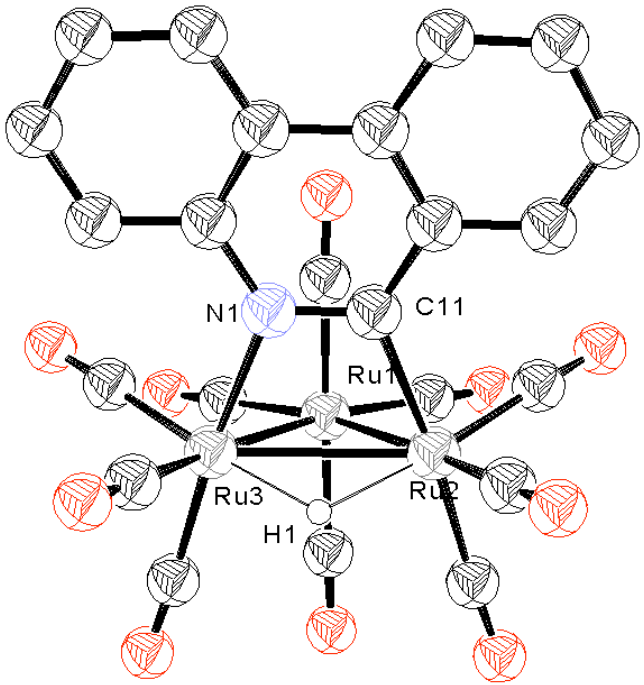



1

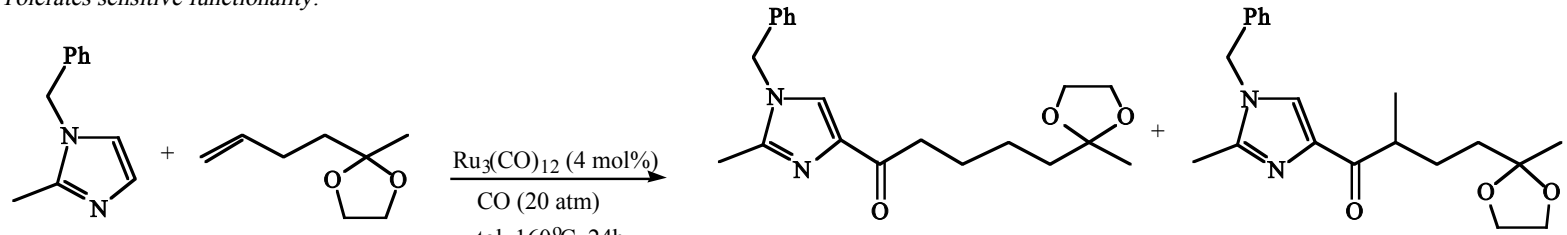
$Ru_3(\mu\text{-}H)(m\text{-}C_{13}H_8N)(CO)_{10}$

Fish *OM* 1986 (5) 2193.



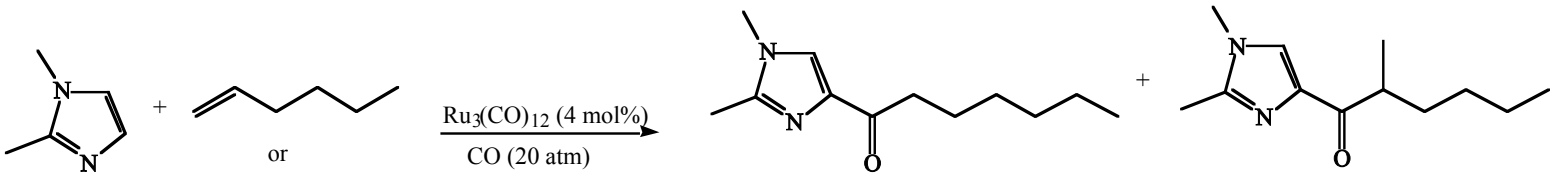
# *Nitrogen chelate assisted $Csp_2$-H/CO/olefin reductive coupling*

*Tolerates sensitive functionality:*



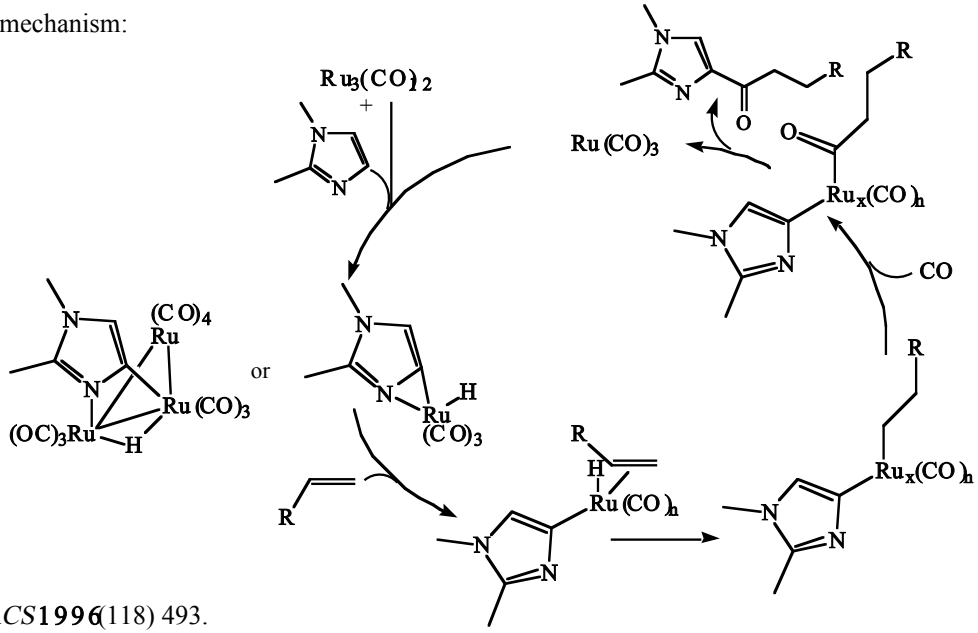

72% (linear:branched; 97:3)

*Olefin isomerization occurs under the reaction conditions:*




1-hexene; 68% (linear:branched; 94:6)
2-hexene; 41% (linear:branched; 94:6)

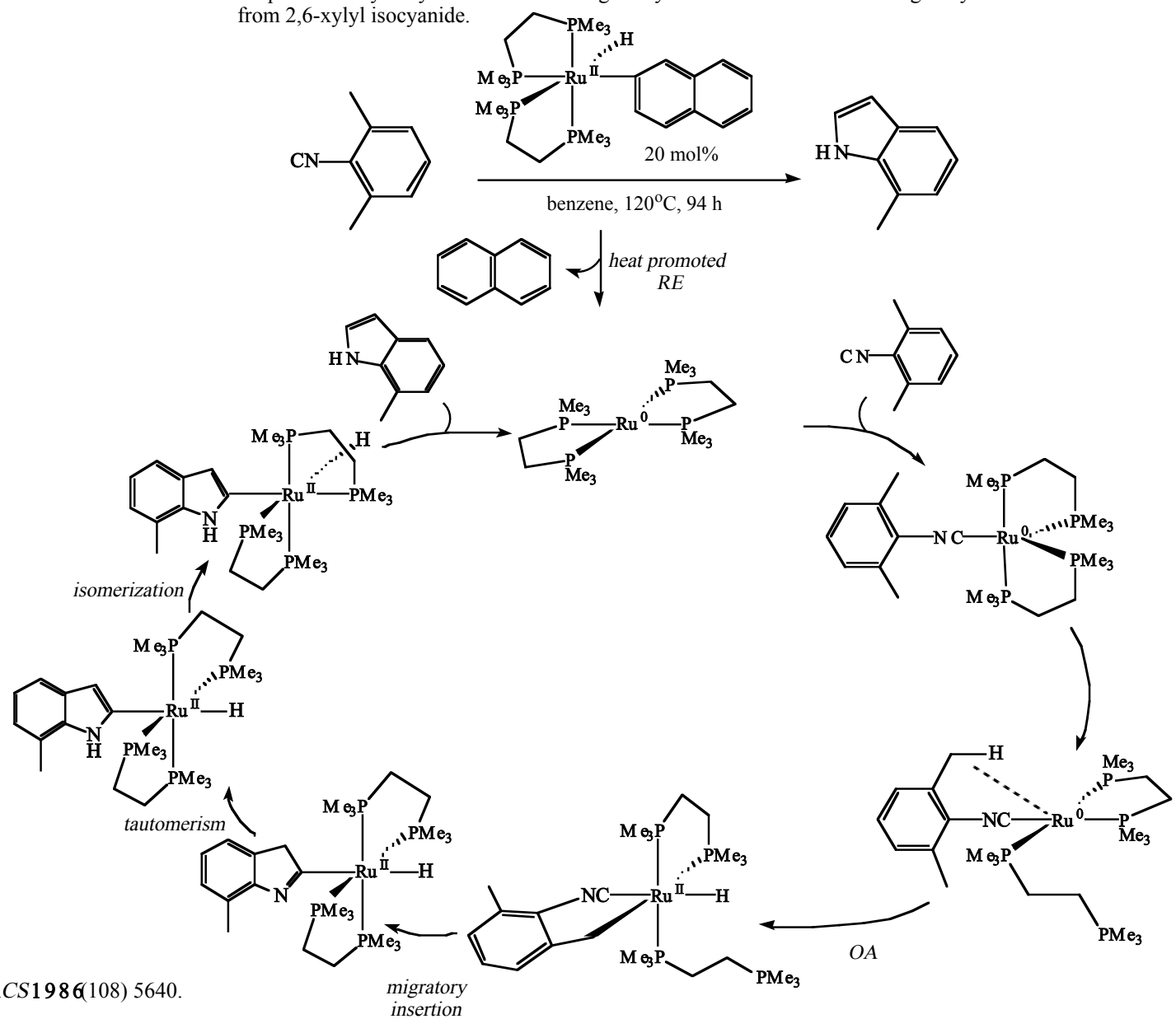
Proposed mechanism:




Murai *JACS* **1996** (118) 493.

# *Indole synthesis via isonitrile chelation/ C-H bond activation*

Propose a catalytic cycle for the following Ru system that affords indoles in good yields from 2,6-xylyl isocyanide.




Jones *JACS* 1986 (108) 5640.

# *Oxidative functionalization of alkanes*

*The methane to methanol challenge: Synthesizing "liquid gold":*

Current industrial process consumes significant amounts of energy:

$$CH_4\,(g) + H_2O\,(g) \xrightarrow[700^oC]{Ni/Al_2O_3} CO\,(g) + H_2 \qquad \Delta H^o = 49.3 \text{ kcal/mol}$$

$$CO\,(g) + 2\,H_2(g) \xrightarrow[\Delta]{\text{zeolite cat}} CH_3OH \qquad \Delta H^o = -21.7 \text{ kcal/mol}$$

Direct oxidation is thermodynamically favorable.

$$CH_4\,(g) + 1/2\,O_2\,(g) \xrightarrow{\text{catalyst ?}} CH_3OH \qquad \Delta H^o = -30.7 \text{ kcal/mol}$$

overoxidation to $CO_2$ is major problem w/methane oxidation

---

*Nature does it:*

***Methane Mono-Oxygenase (MMO):***

MMO oxidizes methane to methanol with 100% chemoselectivity (no overoxidized product results).

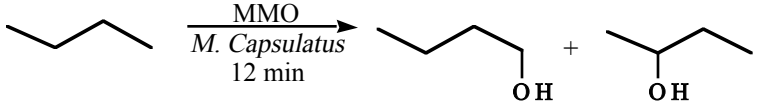
$$CH_4 + O_2 + NADPH + H^+ \xrightarrow[\text{M. Capsulatus}]{\text{MMO}} CH_3OH + NADP^+ + H_2O$$

12 min

84 tof

tof = nmol product/min/mg enzyme

Higher hydrocarbons are oxidized with poor regioselectivities




1.3 : 1

**Lipscomb** *J. Biol. Chem.* **1992** (267) 17588.

***Pseudomonos Oleovorans Mono-Oxygenase (POM):***

Oxidizes linear alkanes with 100% regio- and chemoselectivity

$$n\text{-alkanes} + O_2 + NADPH + H^+ \xrightarrow{POM} \text{1-alcohols} + NADP^+ + H_2O$$

$C_6$-$C_{12}$

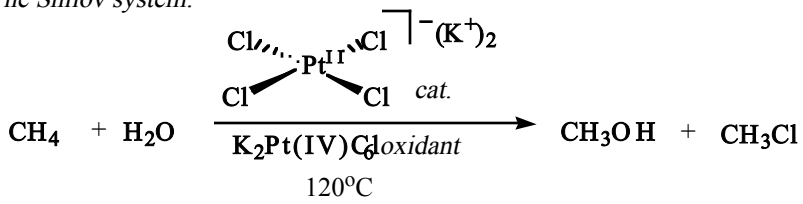
1-octanol, 590 tof

**Coon** *Biochem. Biophys. Res. Comm.* **1974** (57) 1011.
**Munck** *PNAS* **1997** (94) 2981.

---

*A beginning...*

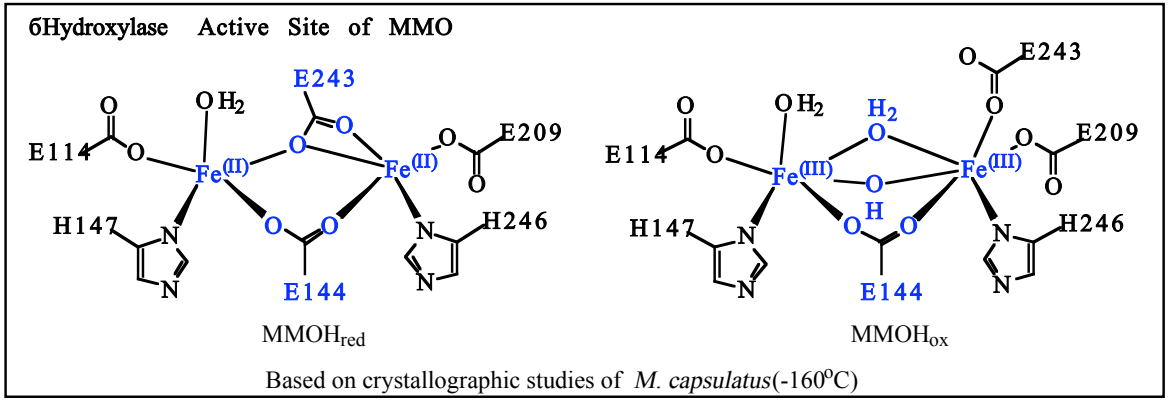
*The Shilov system:*




In 1972 Shilov and coworkers demonstrated that a combination of chloroplatinum(II) and (IV) salts in aqueous solutions at elevated temperatures effects the oxidation of alkanes to mixtures of alcohols and alkyl chlorides. The regio- and chemoselectivity of the Shilov system reflects those of other organometallic systems in that the stronger $1^o$ methyl hydrogens of propane and even ethanol are more reactive than the methylene hydrogens. Unfortunately only modest selectivites are observed. Some overoxidized products and regioisomeric mixtures of alcohols are observed because the product alcohols are more soluble in the aqueous reaction media than the hydrocarbon.

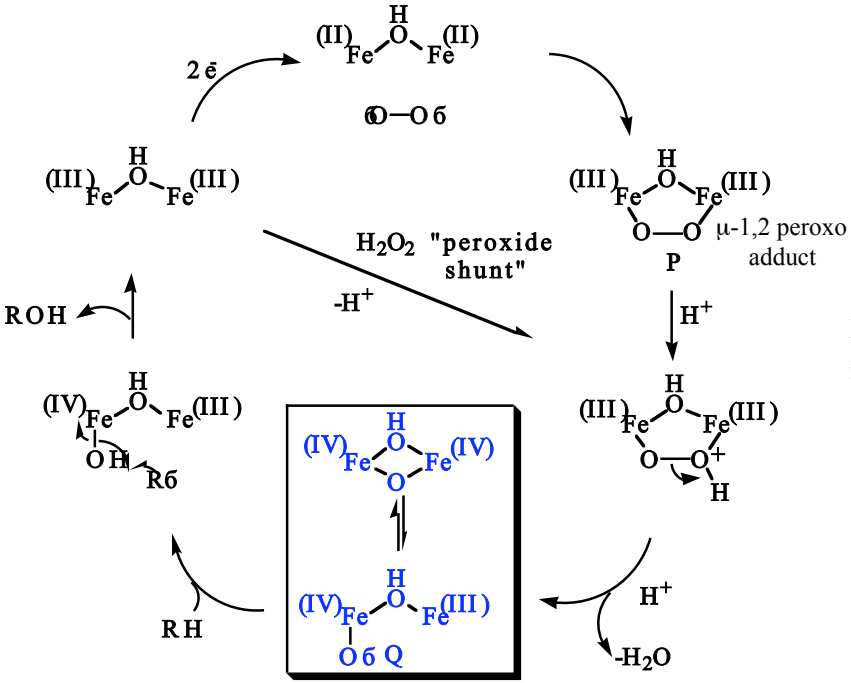
**Shilov** *Zh. Fiz. Khim. (Engl. Trans.)* **1972** (46) 785.
regioselectivities: **Bercaw** *JACS* **1990** (112) 5628.

# *MMO*



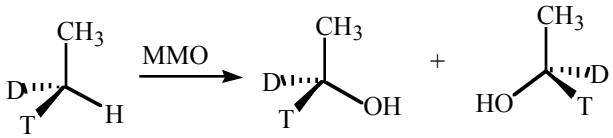

Lippard *Nature* **1993**(366) 537.

*Proposed mechanism (thought to be operating for POM as well):*



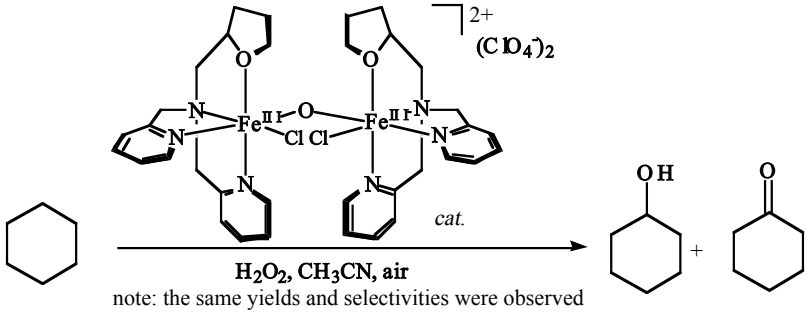

The second iron in MMO transiently stabilzes intermediate Q by supplying an e⁻ to fill the oxygen atom's octet. This avoids energetically unfavorable Fe(V) intermediates.

Key piece of evidence supporting substrate radical intermediate:



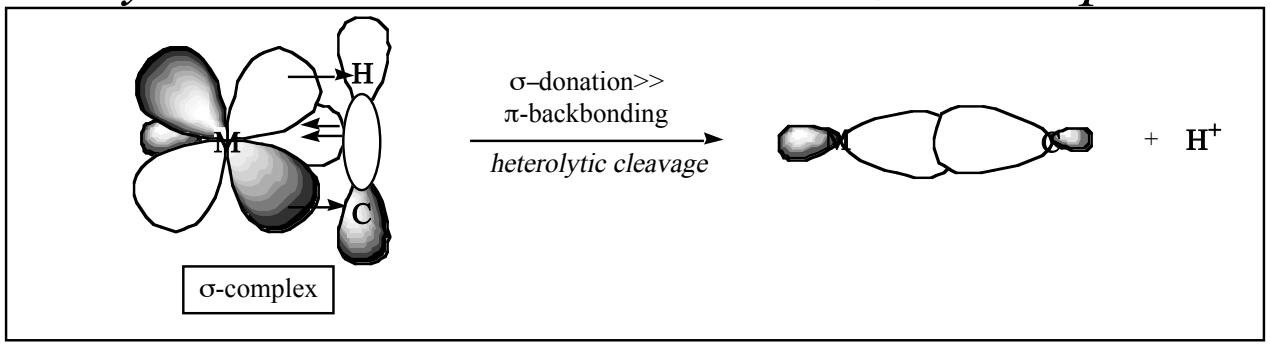

Lipscomb *Chem. Reviews* **1996**(96) 2625.

Attempts to mimic Nature's solution have failed. The key to chemo- and regioselectivity in these radical systems may be MMO and POM's protein suprastructure which thus far have not been mimicked in solution.



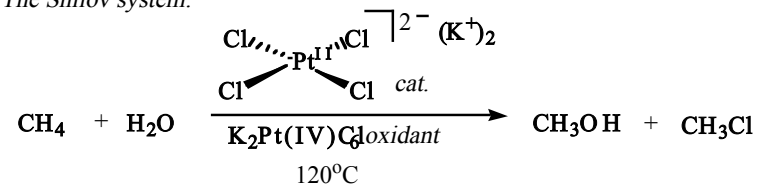

note: the same yields and selectivities were observed when the reactions were run under an inert atmosphere (Ar) or in air. This indicates that free radicals, propagated with $O_2$, are not acting as the oxidant. Nishida *Chem. Lett.* **1995** 885.

# *The Shilov System/C-H activation via late, electrophilic complexes*



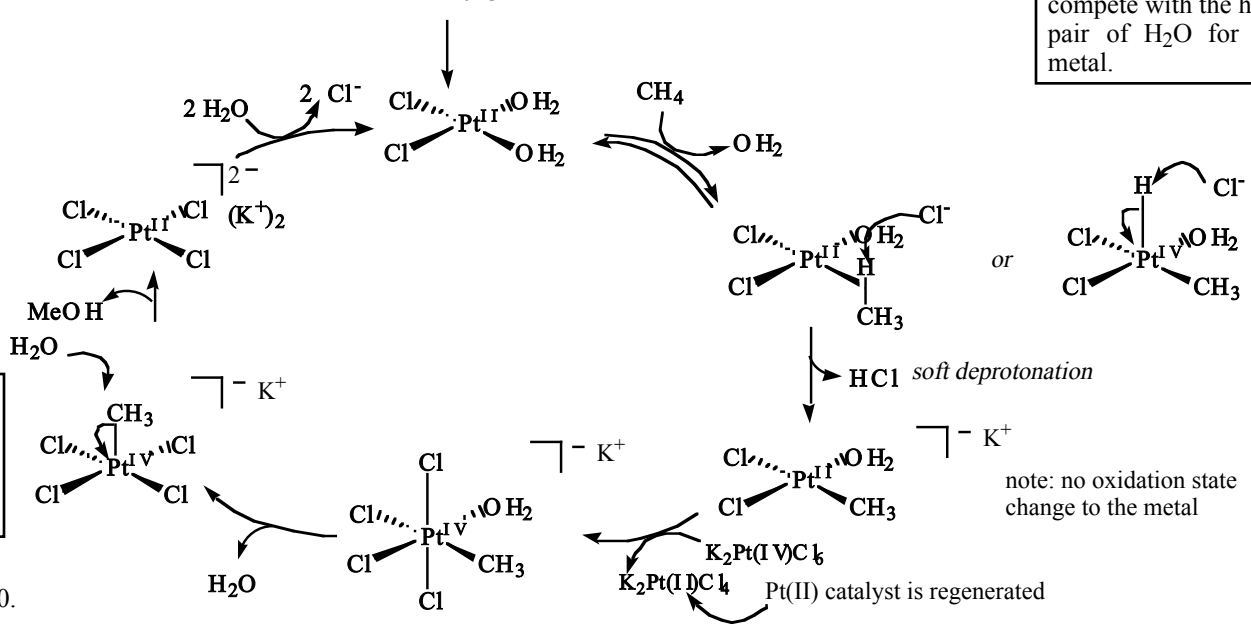

C-H activation processes that occur *via* heterolytic cleavage result in no oxidation state change at the metal. Generally, electrophilic metal complexes are used that incorporate metals in their highest stable oxidation states. Unlike the Bergman nucleophilic complexes, electrophilic complexes are compatable with oxidants and provide a route to oxidative functionalization of hydrocarbons (the most desirable form of functionalization).

*The Shilov system:*




Because Pt is a late "soft" metal, the relatively diffuse alkane C-H bond is able to intermolecularly compete with the hard oxygen lone pair of $H_2O$ for binding to the metal.

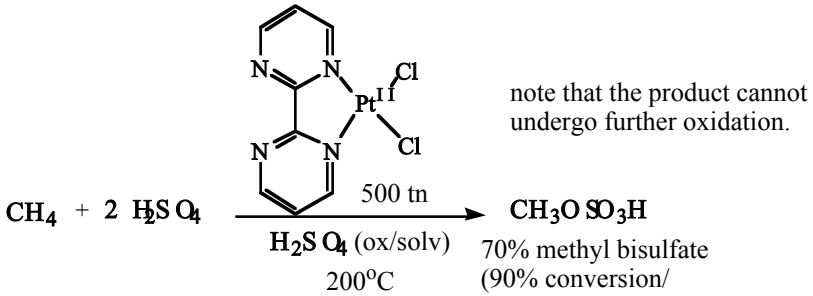
*Proposed mechanism:*




Inversion of stereochemistry at the platinum bound C using deuteruim labeled substrates provided strong evidence for $S_N2$ functionalization pathway

Bercaw *ACIEE* **1998**(37) 2180.

# *C-H activation via late, electrophilic complexes in highly acid media*

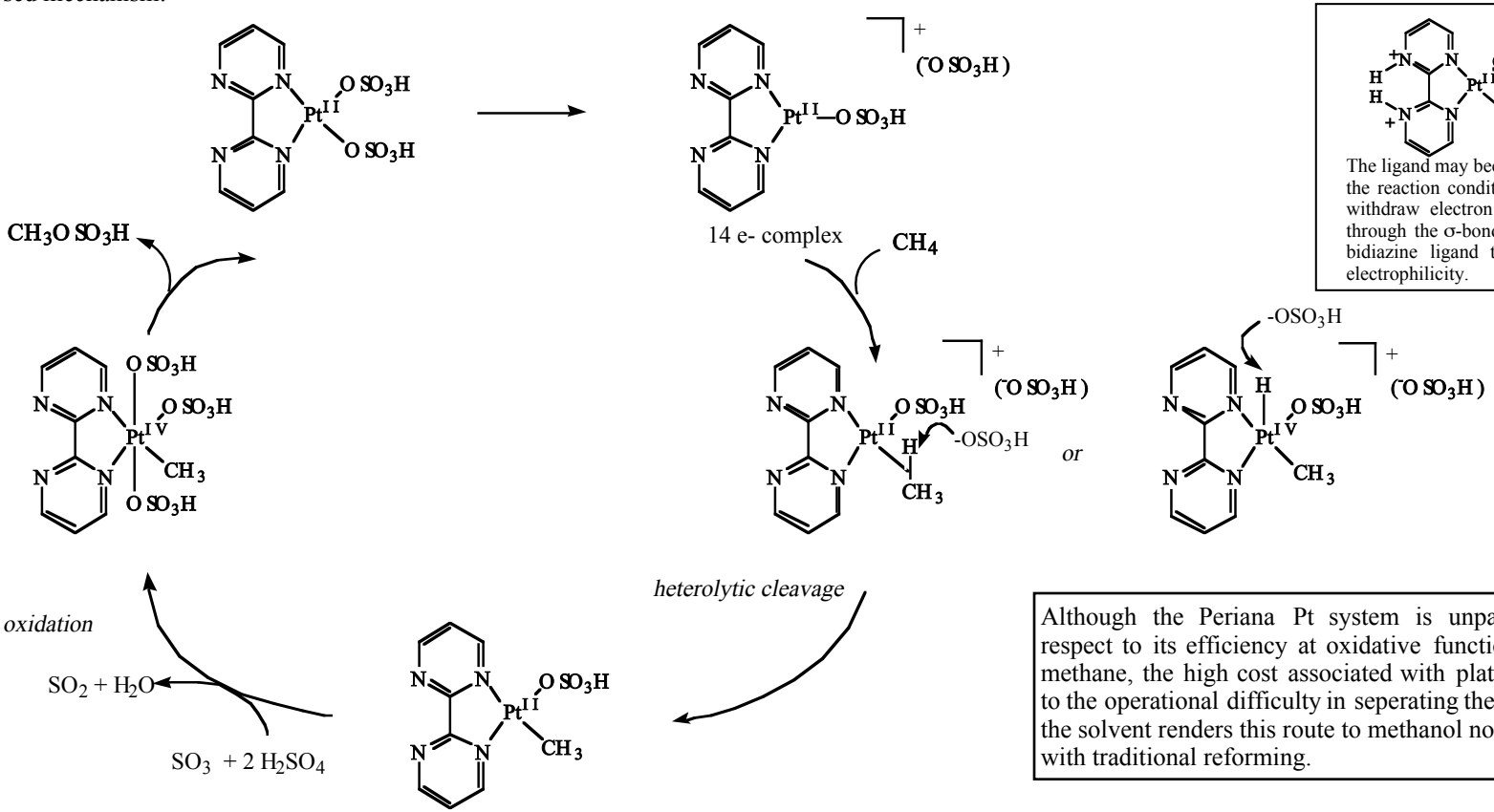



note that the product cannot undergo further oxidation.

70% methyl bisulfate (90% conversion/ 80% selectivity) based on methane.

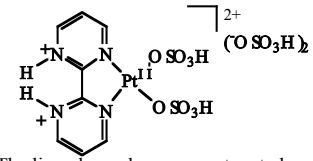
Periana *Science* 1998 (280) 560.

*Proposed mechanism:*




| | | |
|---|---|---|
| $CH_4$ + 2 $H_2SO_4$ | $Hg^{(II)}(OSO_3H)_2$ cat. / $H_2SO_4$ (ox/solv) 200°C | $CH_3OSO_3H$ 50% yield (based on $CH_4$) Periana *Science* 1993 (259) 340 |
| $CH_4$ + $CF_3CO_2H$ | $Pd(OAc)_2$ stoic. / $CF_3CO_2H$ (solv) | $CH_3O_2CF_3$ + Pd (0) Sen *JACS* 1987 (109) 8109 |

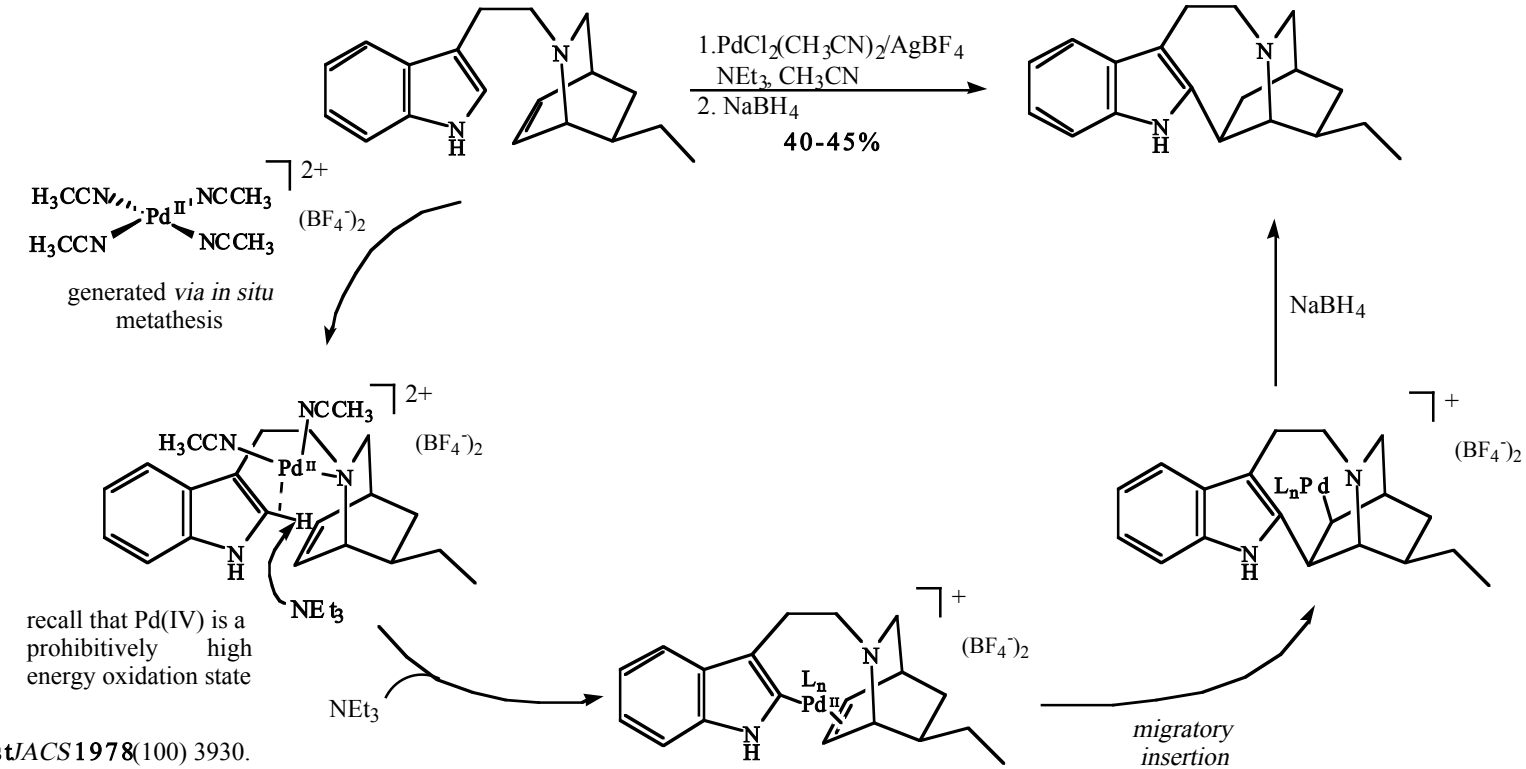
Heterolytic cleavage directly from the σ-complex is clearly operating for Pd(II) and Hg(II) systems where the $M^{(n+2)}$ oxidation state of the alkyl(hydrido)metal intermediate is prohibitively high in energy.



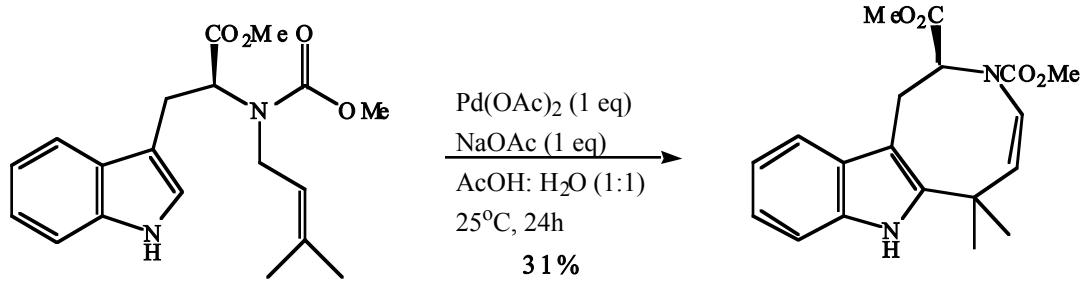
The ligand may become protonated under the reaction conditions. Protonation will withdraw electron density from the Pt through the σ-bonding framework of the bidiazine ligand thereby enhancing its electrophilicity.

Although the Periana Pt system is unparalleled with respect to its efficiency at oxidative functionalization of methane, the high cost associated with platinum coupled to the operational difficulty in seperating the product from the solvent renders this route to methanol non-competitive with traditional reforming.

# *Substrate-directed vinyl alkylation via electrophilic C-H activation*



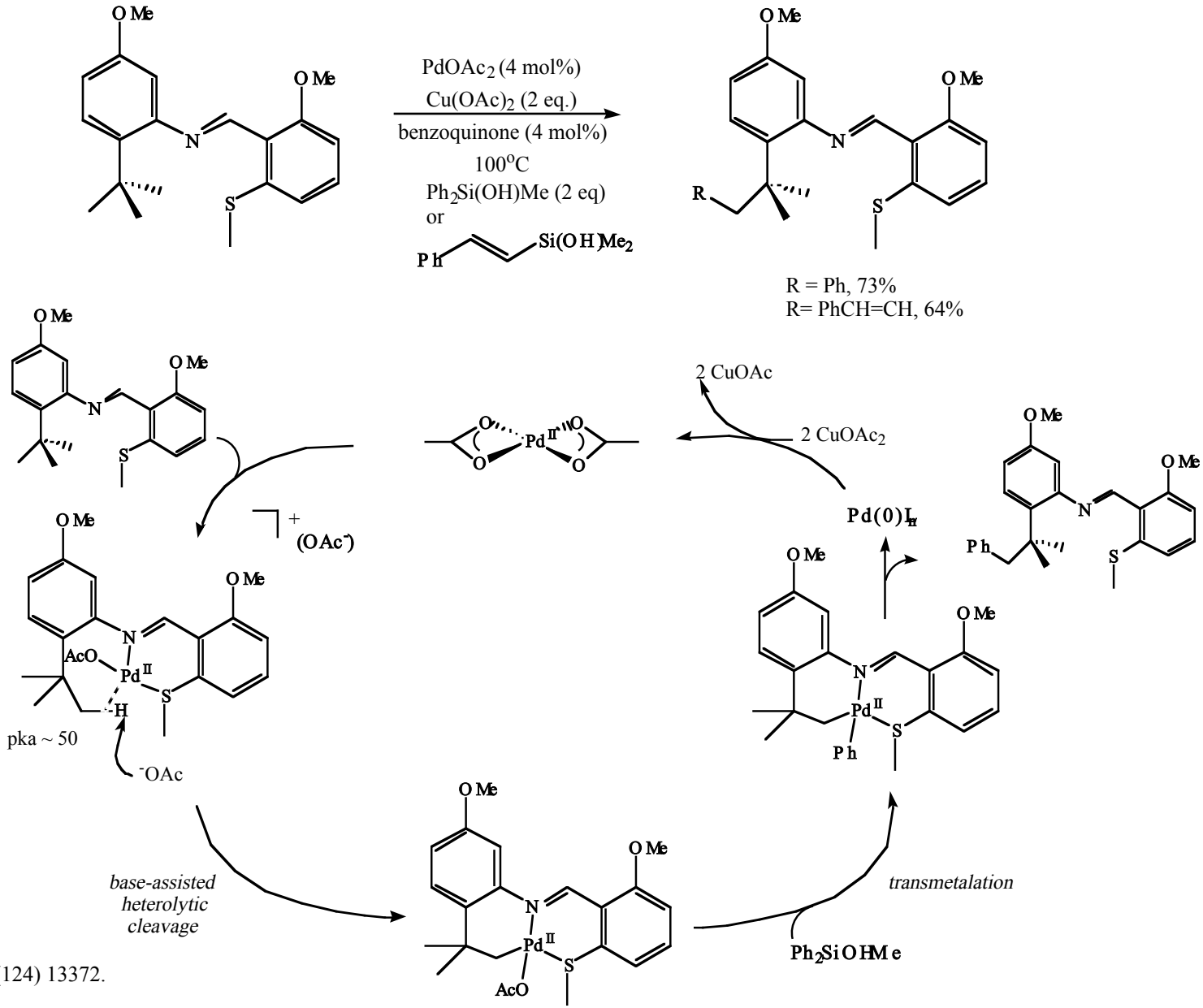

Trost *JACS* 1978 (100) 3930.




model system for key cyclization step in (+)-Austamide synthesis

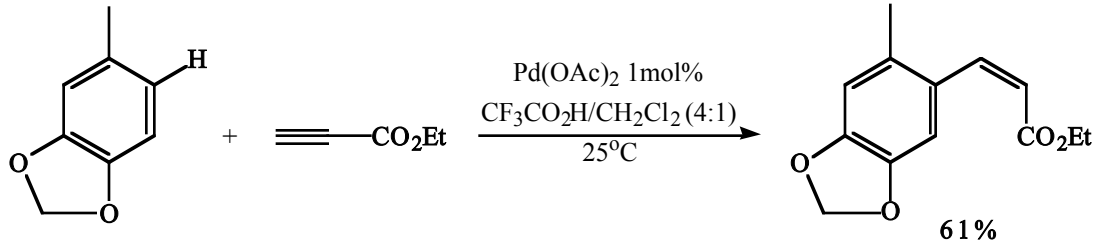
Corey *JACS* 2002 (124) 7904.

# *Substrate-directed alkane arylation via electrophilic C-H activation*



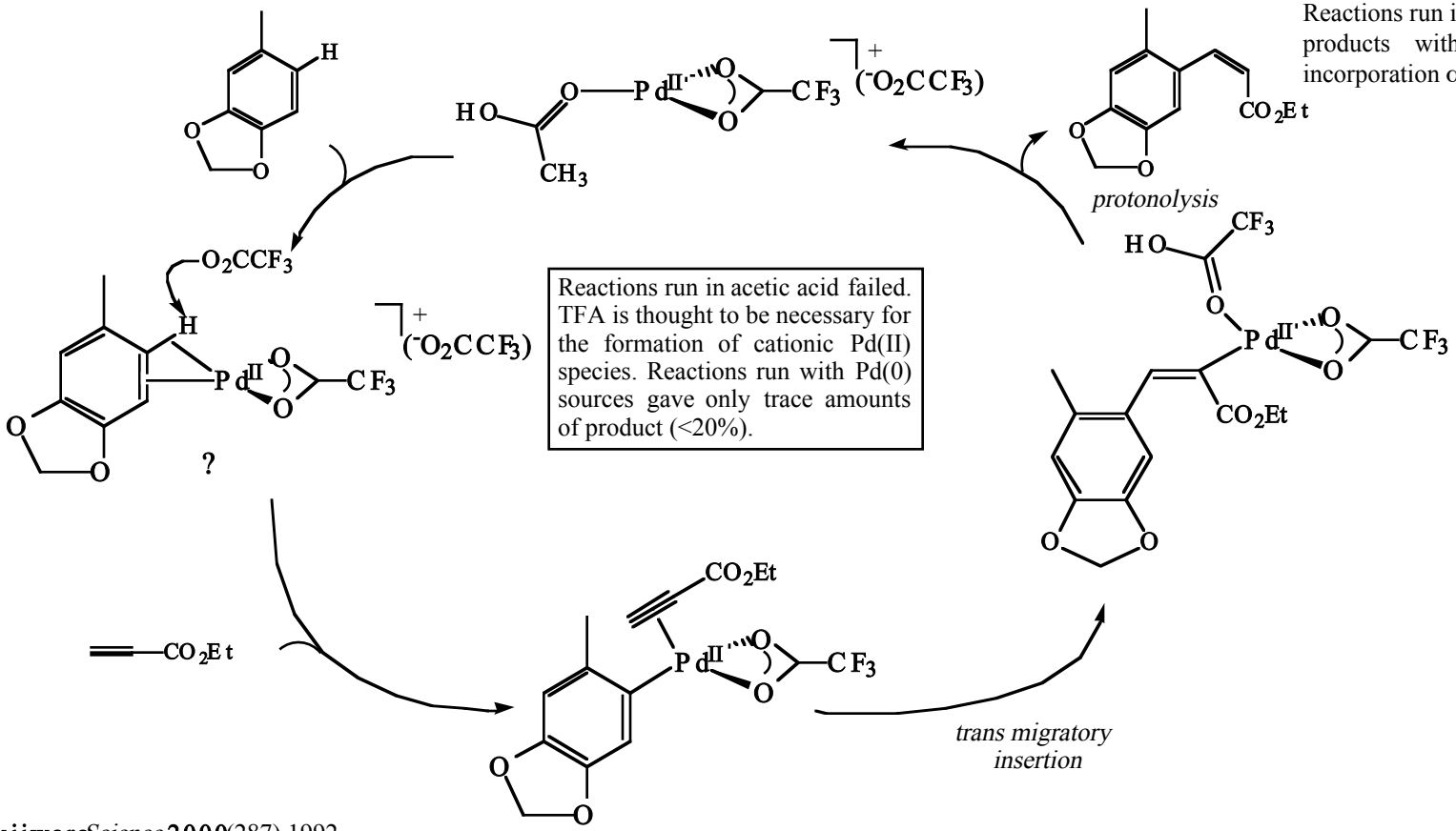

Sames *JACS* 2002 (124) 13372.

# *Intermolecular arene vinylation via electrophilic C-H activation*




Reaction exhibits excellent functional group tolerance with unprotected OH, Br, and acetals tolerated in the arene. Coupling to activated alkenes (vinyl esters) was also effected in high yields (65-96%).

Reactions run in $CF_3CO_2D$ yielded products with vinyl deuterium incorporation α to the ester.

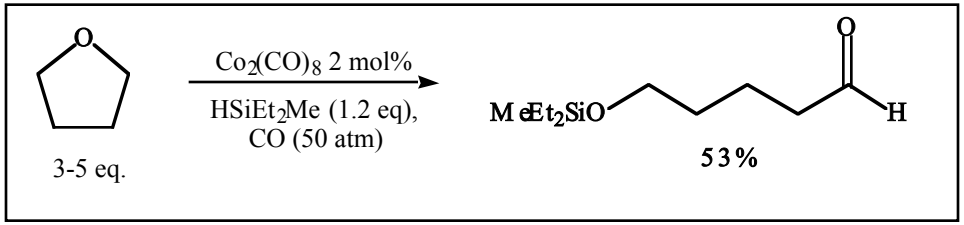



Reactions run in acetic acid failed. TFA is thought to be necessary for the formation of cationic Pd(II) species. Reactions run with Pd(0) sources gave only trace amounts of product (<20%).

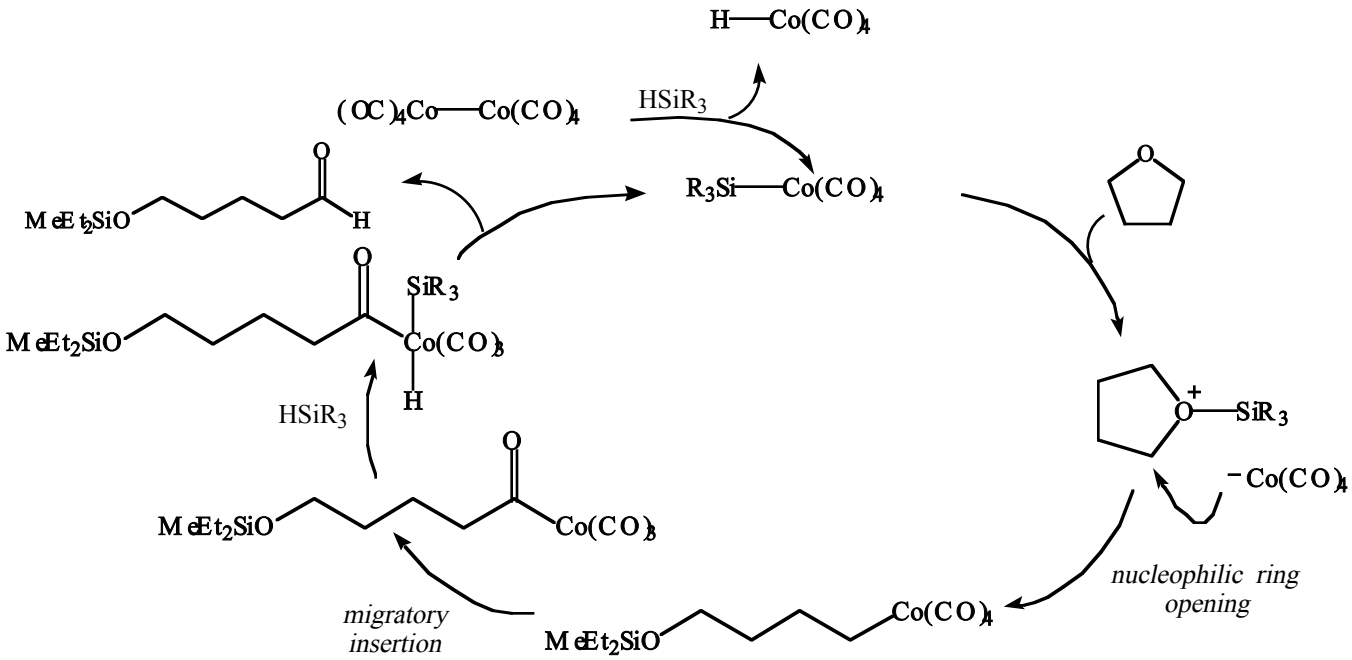
Fujiwara *Science* 2000 (287) 1992.

# *Silylformylation*

Provide a detailed mechanism for the following transformation reported in the literature.

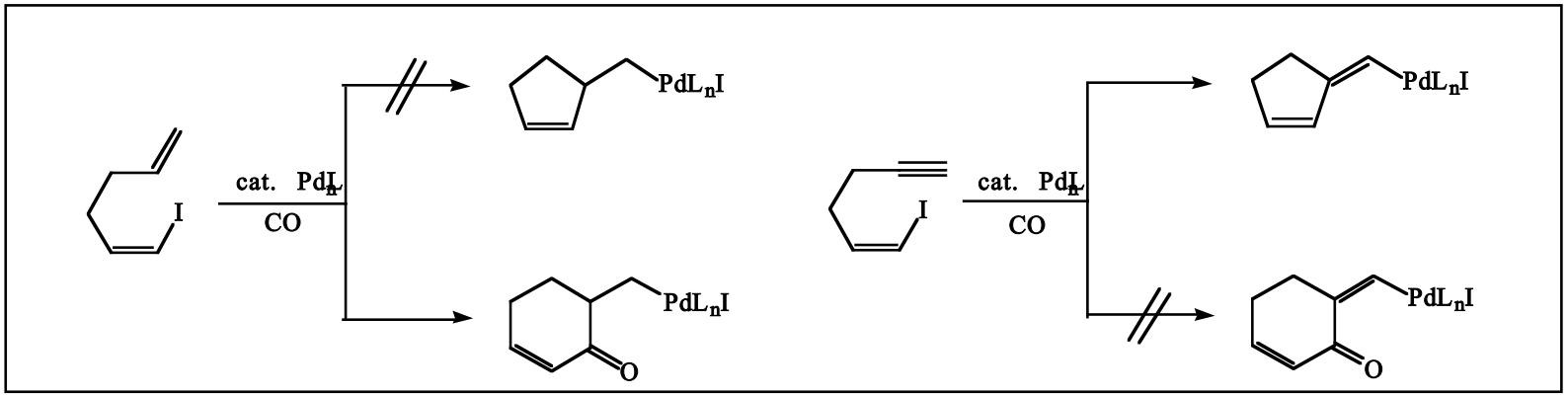



Reaction works for 3,4, and 5 membered cyclic ethers. Ring strain may promote the nucleophilic ring opening reaction. Neither tetrahydropyran or diethyl ether react under these conditions. The high affinity of silicon for oxygen is used to account for the fact that $R_3SiCo(CO)_4$ and not $HCo(CO)_4$ interacts with the cyclic ether.

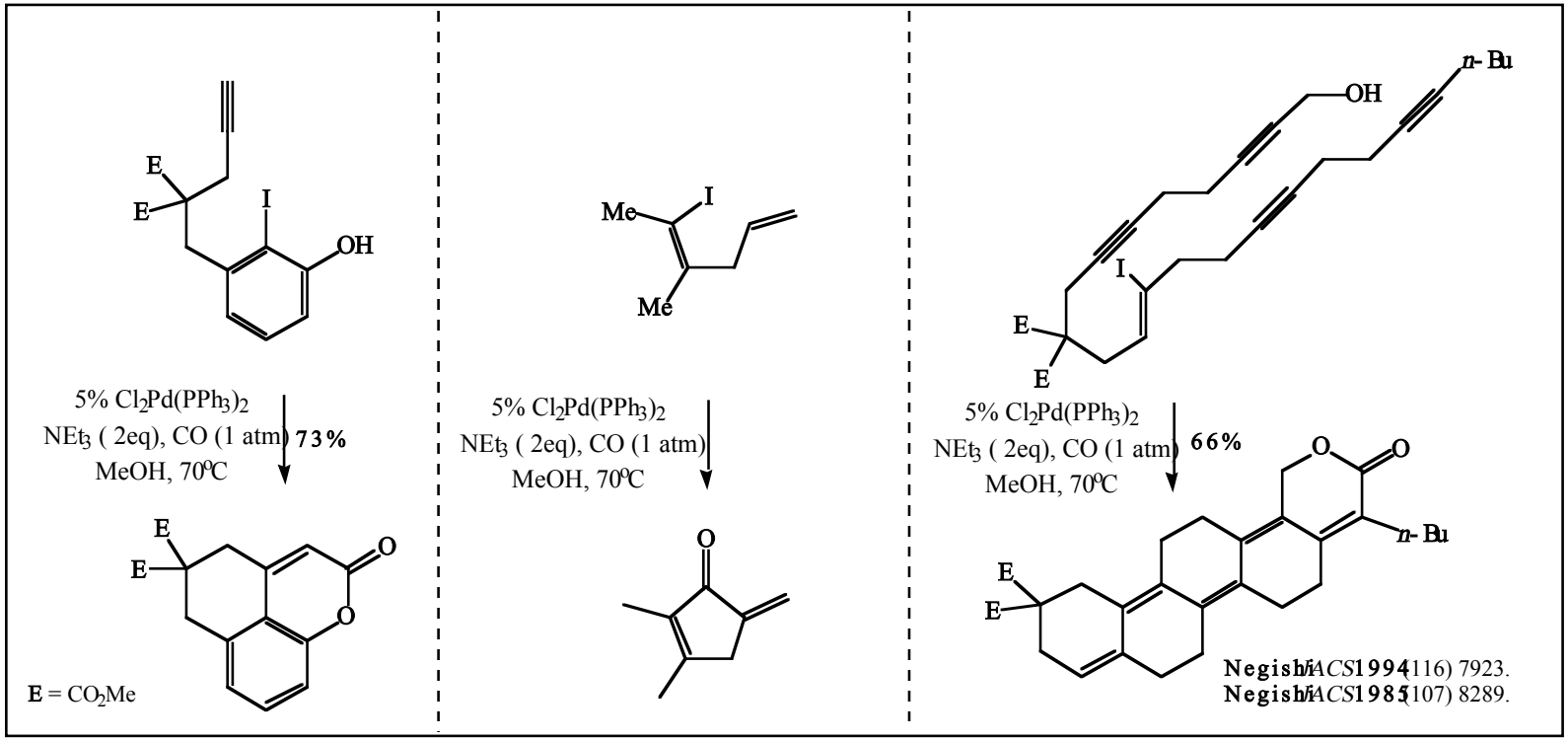



Murai *ACIEE* 1977 (16) 789.
Murai *ACIEE* 1979 (18) 837.

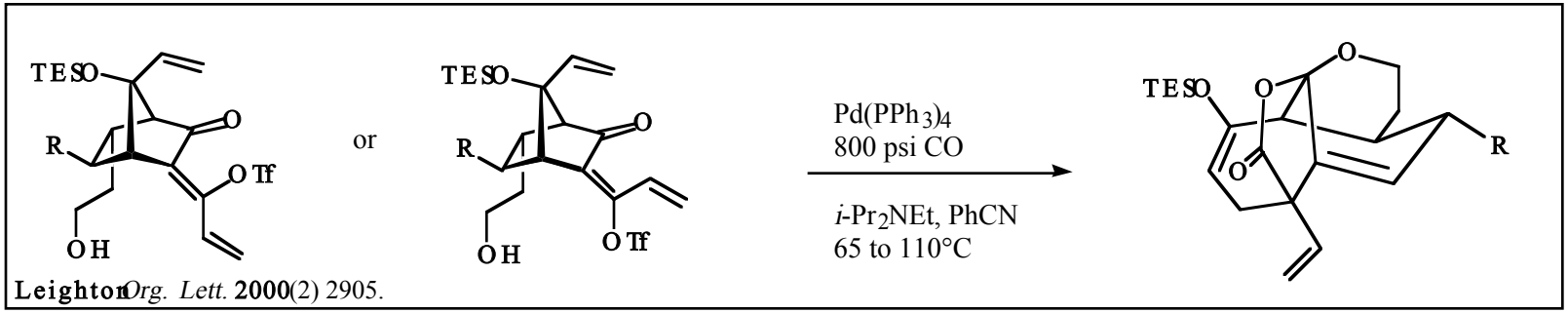
# *Carbonylation*




When a competition exists between cyclic acylpalladation and cyclic carbopalladation, the preferred outcome is different for alkenyl and alkynyl substrates. For alkenyl substrates, cyclic acylpalladation is favored over cyclic carbopalladation, and for alkynyl substrates, this preference is reversed. Given these empirical observations, predict the products of the following transformations:

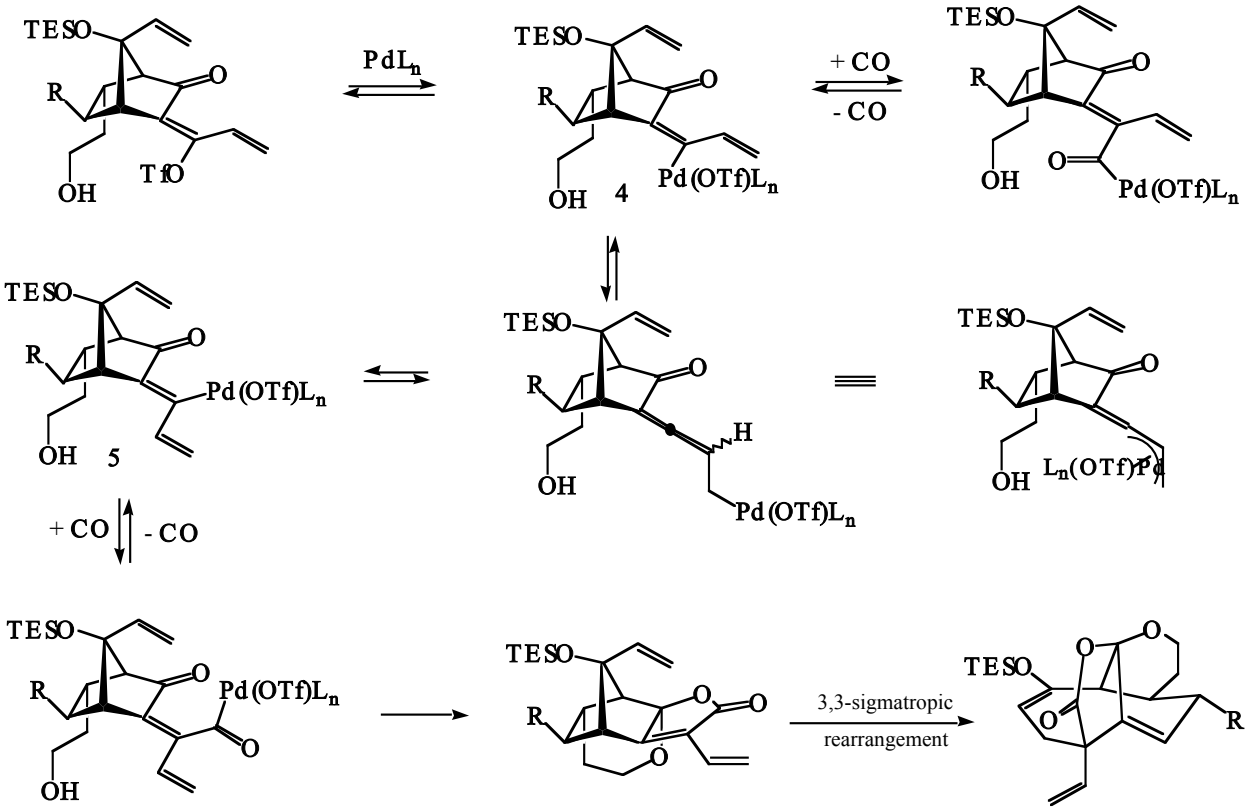



Negishi *JACS* 1994 (116) 7923.
Negishi *JACS* 1985 (107) 8289.



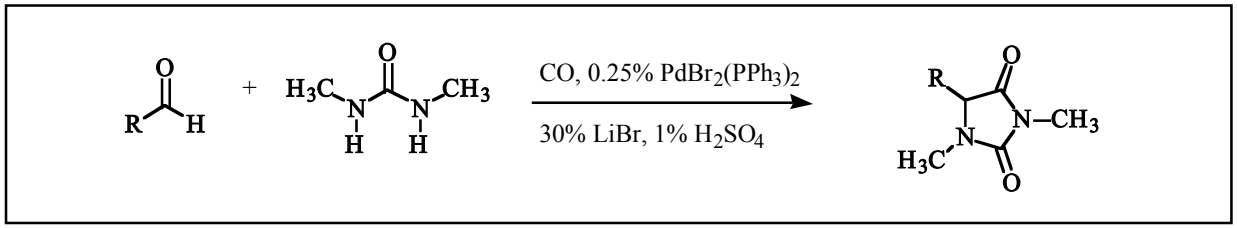

Leighton *Org. Lett.* **2000**(2) 2905.

Provide a mechanism for this one-pot transformation. Explain why both the *E*- and *Z*-tetrasubstituted enol triflates react to form the desired product in comperable yields.

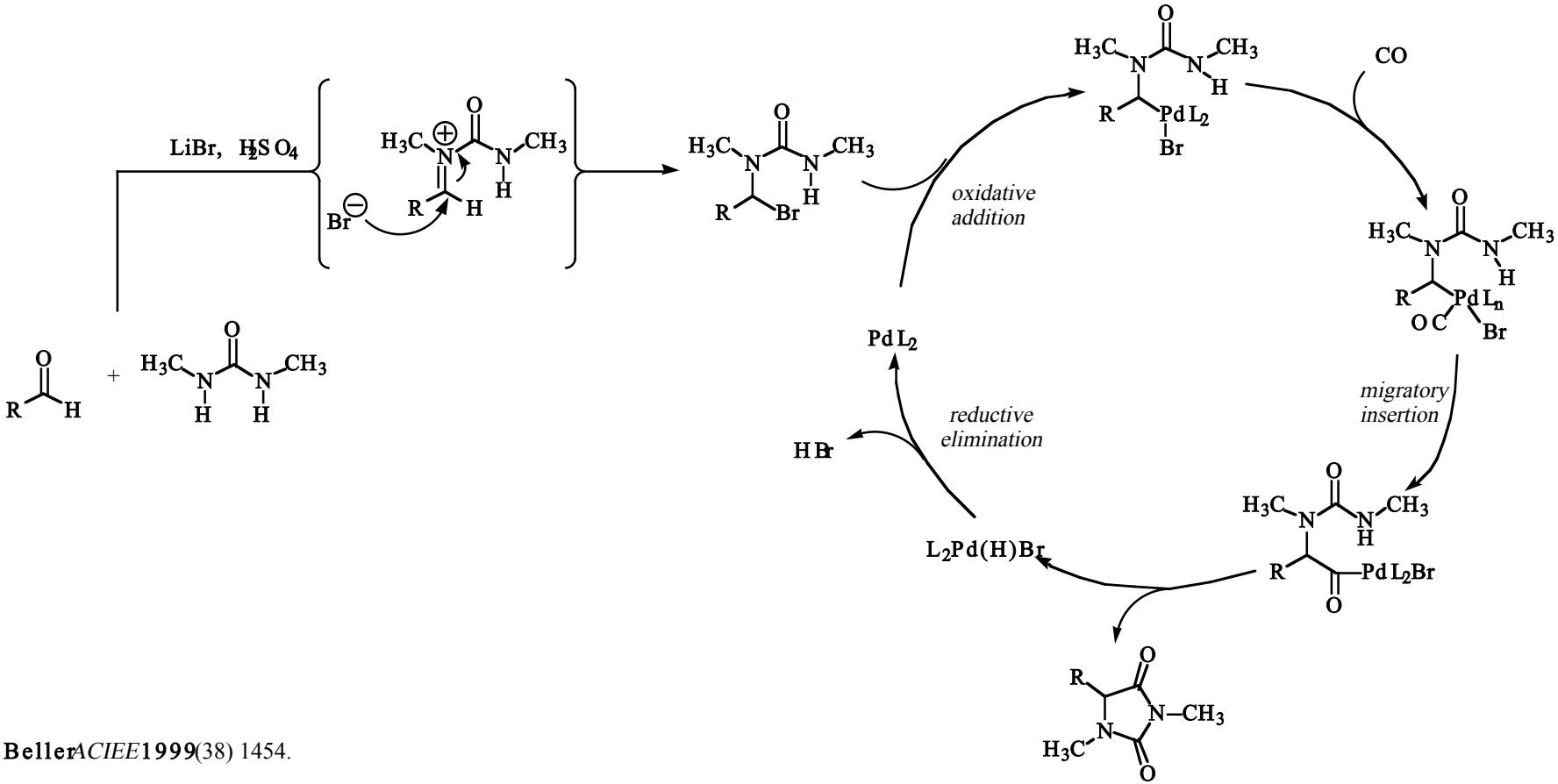



Oxidative addition into the Z-tetrasubstituted enol triflate leads directly to intermediate **5** which can continue on the path to the desired product. Oxidative addition into the E-tetrasubstituted enol triflate leads to intermediate **4** which can isomerize to **5** via a ϵ-allenyl intermediate.

# *Carbonylation*



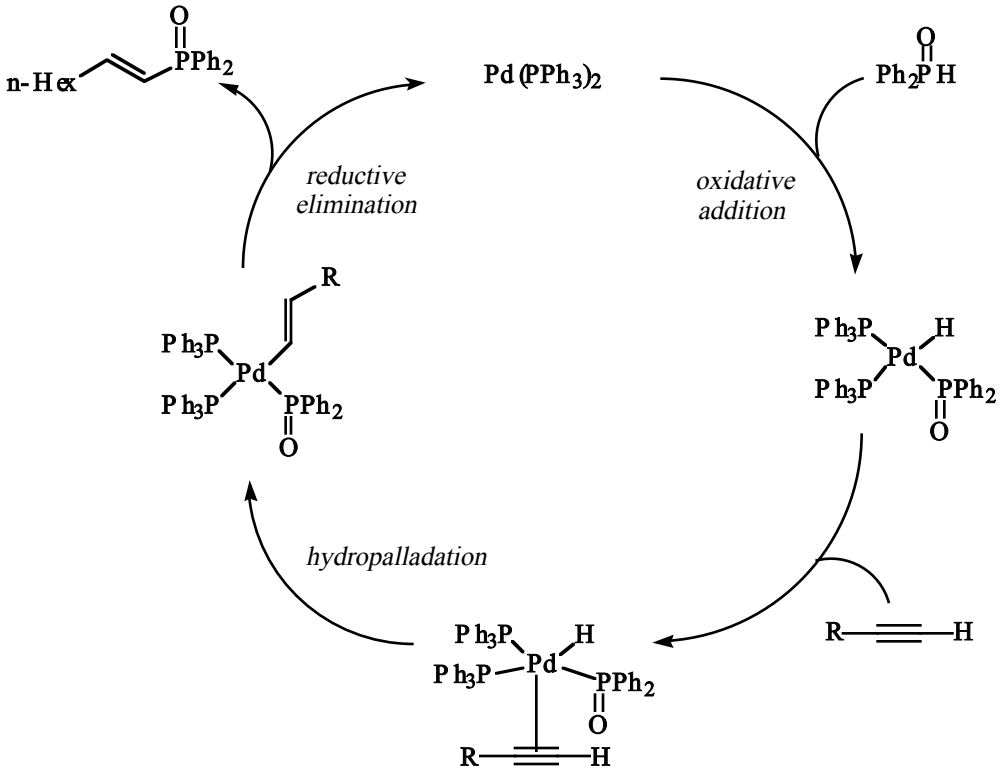

Substituted hydantoins can be prepared by the ureidocarbonylation of an aldehyde in presence of LiBr and $H_2SO_4$. Propose a mechanism for this transformation.




Beller *ACIEE* **1999**(38) 1454.

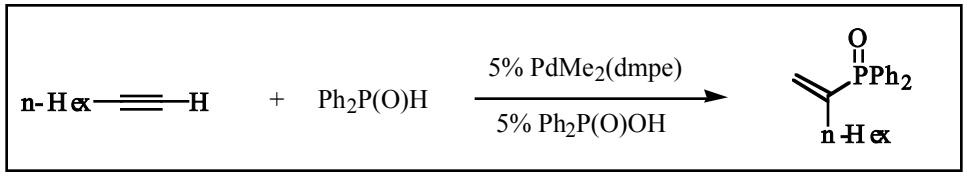
# *Hydrophosphinylation*

1a) Hydrophosphinylation of internal and terminal alkynes with $Ph_2P(O)H$ can be catalyzed by a variety of palladium sources. $Pd(PPh_3)_4$ is selective for the *anti*-Markovnikov product. Propose a mechanism for the hydrophosphinylation of 1-octyne below.



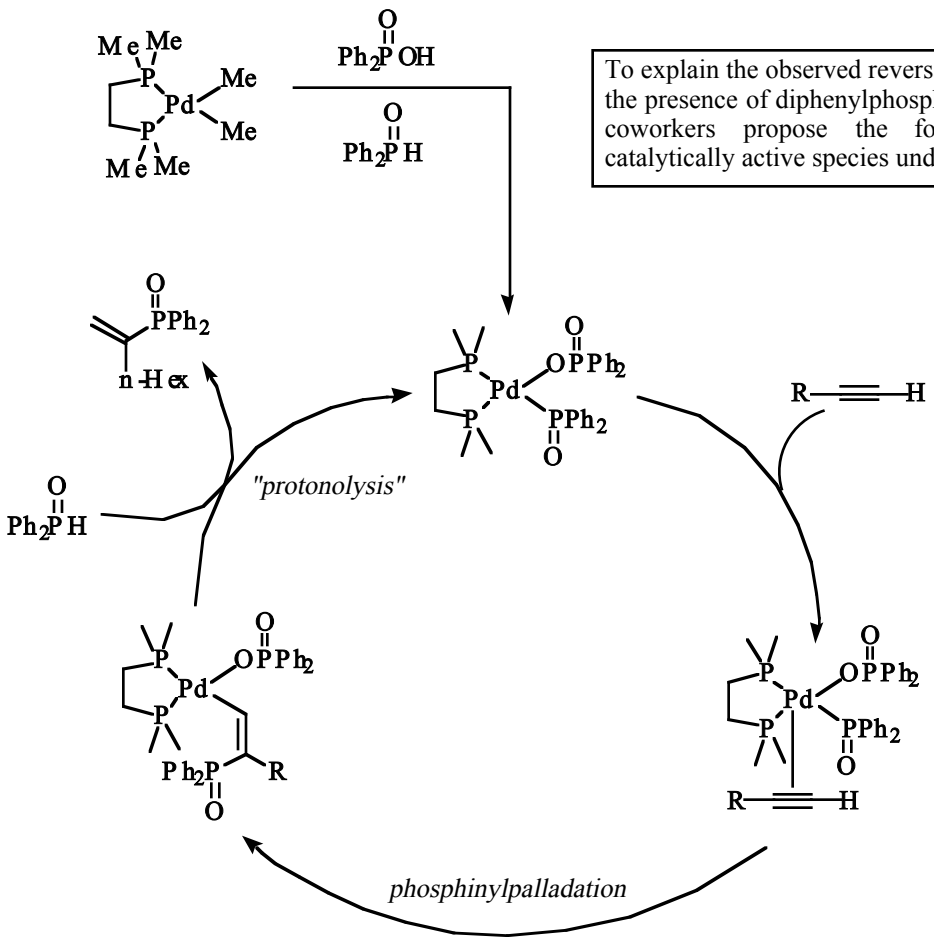

Tanaka, M. *ACIEE* **1998**, *37*, 94-96.
Tanaka, M. *OM* **1996**, *15*, 3259-3261.

# *Hydrophosphinylation*




b) The regioselectivity of the hydrophosphinylation can be completely reversed by using $PdMe_2$(dmpe) (dmpe = dimethylphosphinoethane) and the phosphinic acid, $Ph_2P(O)OH$. Propose a mechanism for the formation of the Markovnikov product under these conditions.

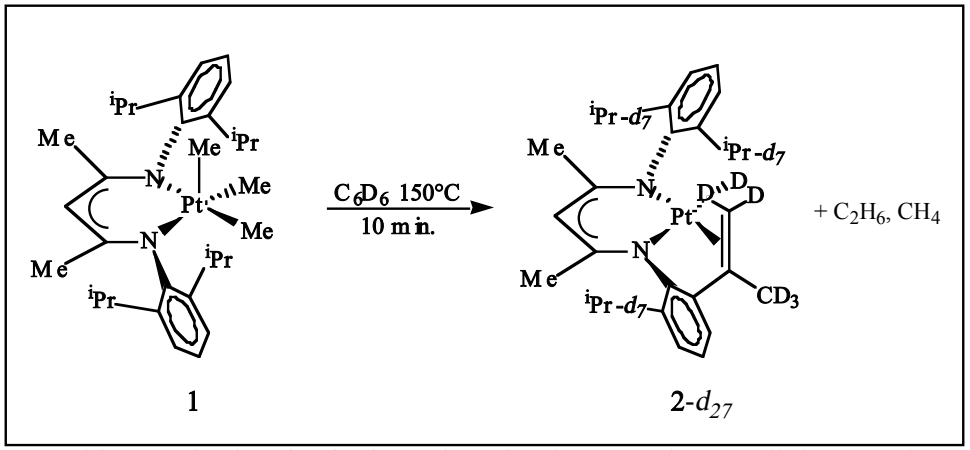
To explain the observed reversal in regioselectivity in the presence of diphenylphosphinic acid, Tanaka and coworkers propose the formation of a new catalytically active species under these conditions.




Tanaka, M. *ACIEE* **1998** *37*, 94-96.
Tanaka, M. *OM* **1996** *15*, 3259-3261.

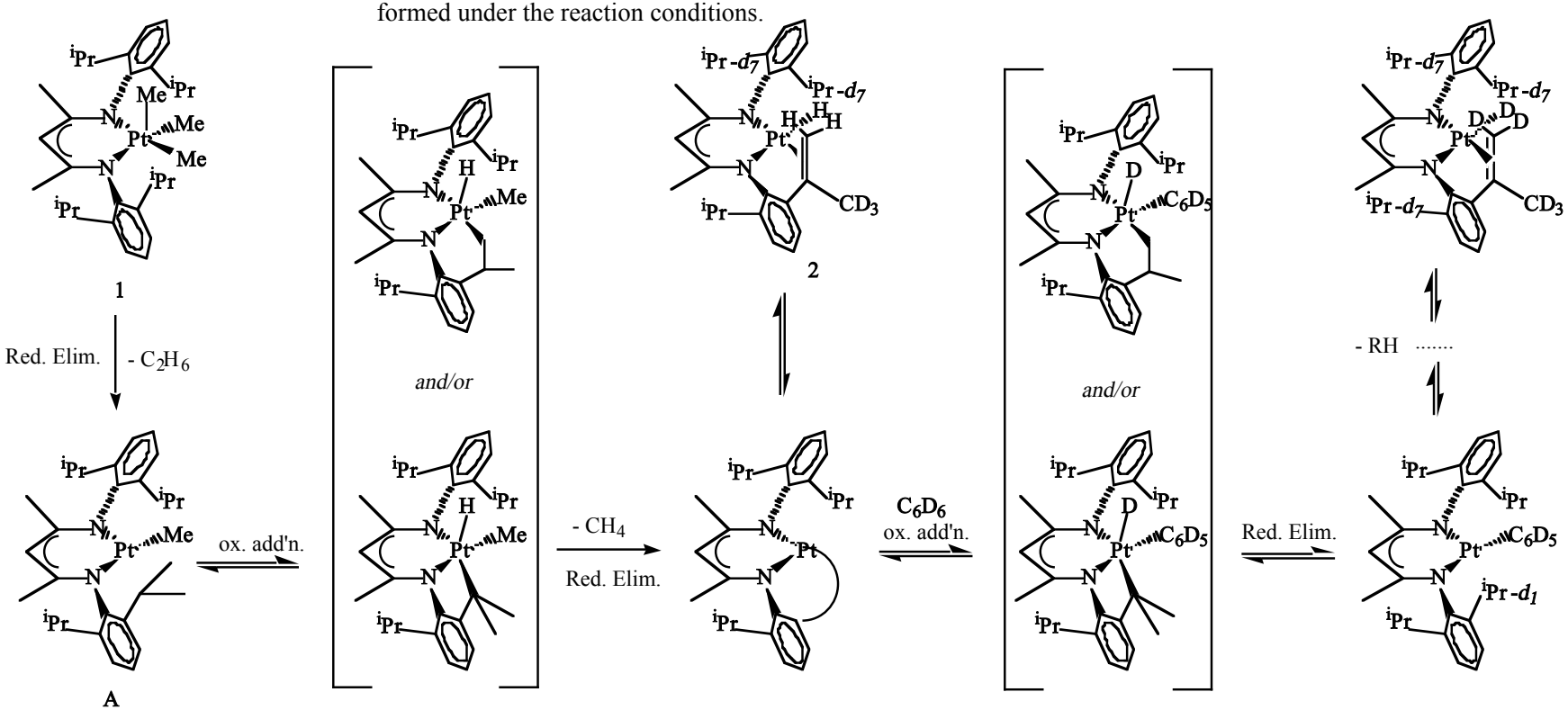
# *Carbometallation*

Since very little $CH_3D$ is observed, oxidative addition of a C-H from the ligand isopropyl group in intermediate **A** must be much faster than oxidative addition of $C_6D_6$ to **A**.



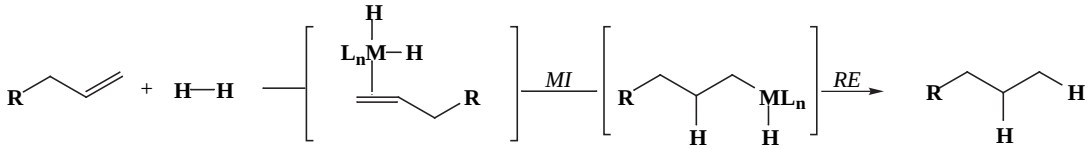

**Goldberg** *JACS* **2002** (124) 6804.

Provide a mechanism for the formation of **2**-$d_{27}$. Note that very little $CH_3D$ is formed under the reaction conditions.

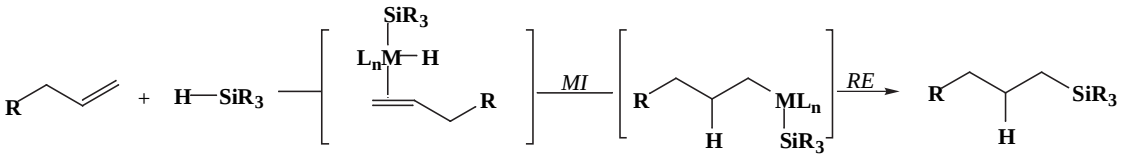


# *Functionalization of terminal olefins via H migratory insertion /reductive elimination sequence*

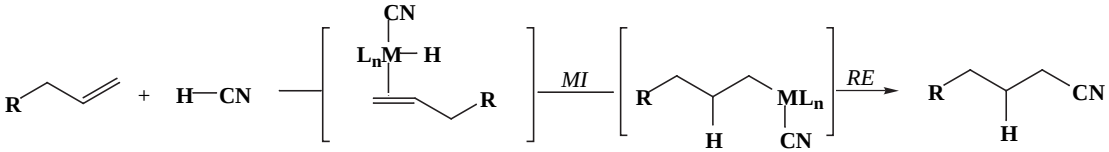
*Hydrogenation*



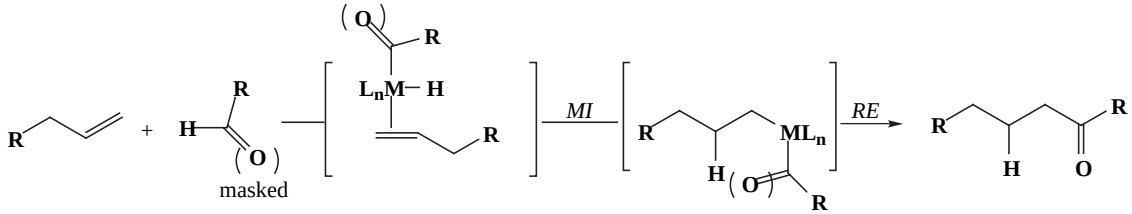

*Hydrosilylation*



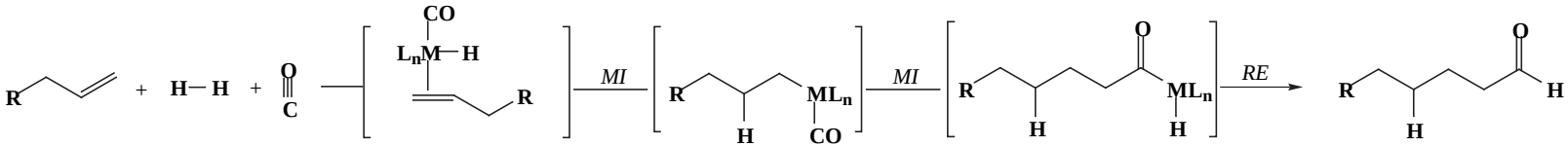

*Hydrocyanation*




*Hydroacylation*

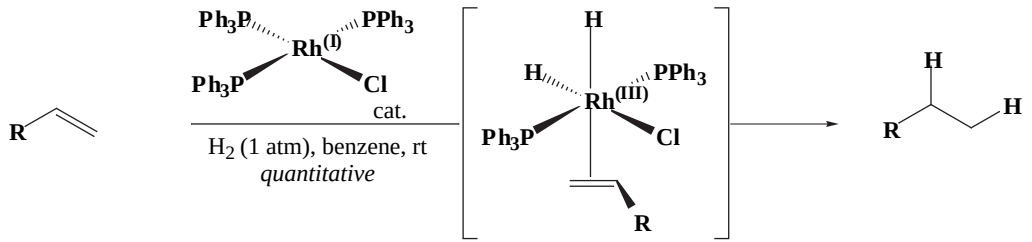



*Hydroformylation*

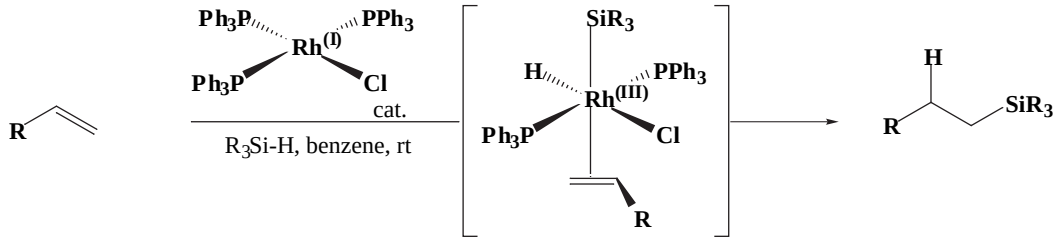


# *Wilkinson's Catalyst*

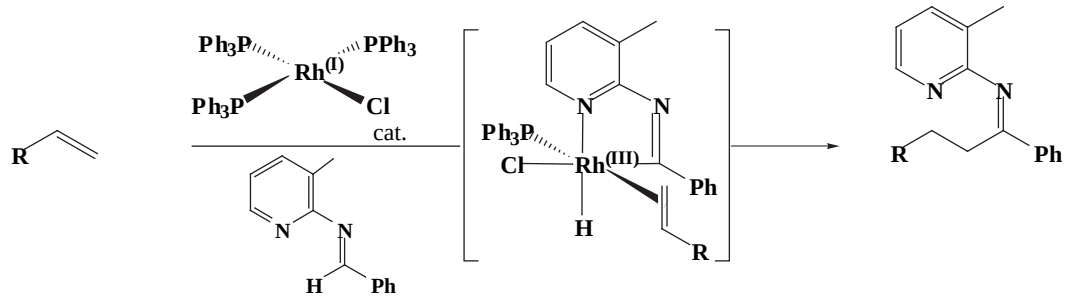
*Hydrogenations: OA of $H_2$*



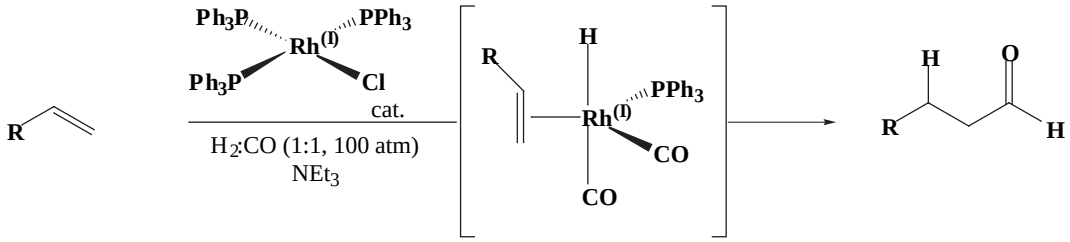

*Hydrosilylations: OA of $R_3Si$-H*




*Hydroacylation: OA of RC("O")-H*



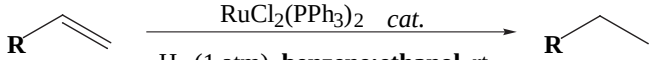

*Hydroformylation*



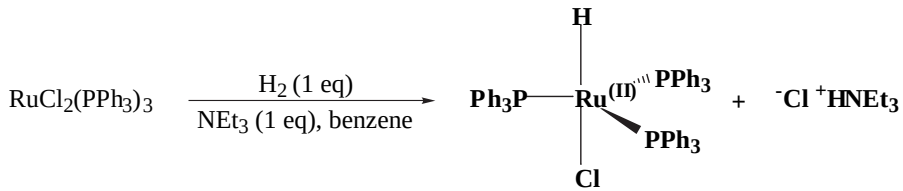

Rapid $PR_3$/CO ligand exchange occurs with Wilkinson's catalyst under a CO atmosphere (Rh has a high affinity for CO). CO's are strong $\pi$-acids and may serve to disfavor OA of $H_2$ to generate a Rh(III) dihydride.

# *Hydrogenation via σ-bond metatheses: Ru(II) catalysts*

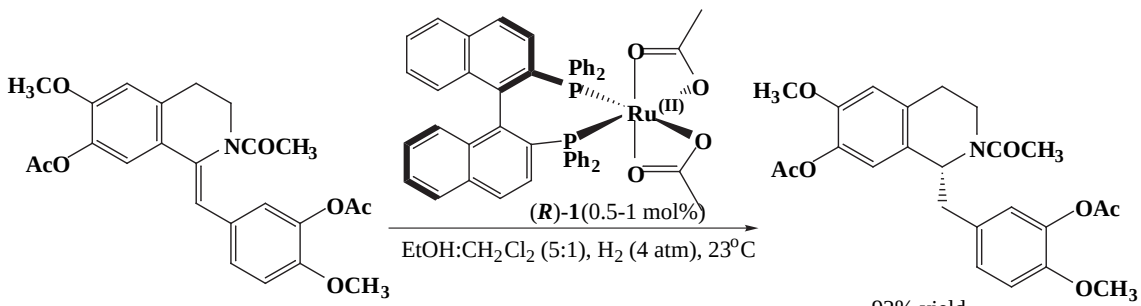
*Wilkinson's Ru catalyst*




*Monohydride identified as active catalyst*: Formation of Ru(IV) dihydride is prohibitively high in energy.




*Noyori's Ru catalyst*

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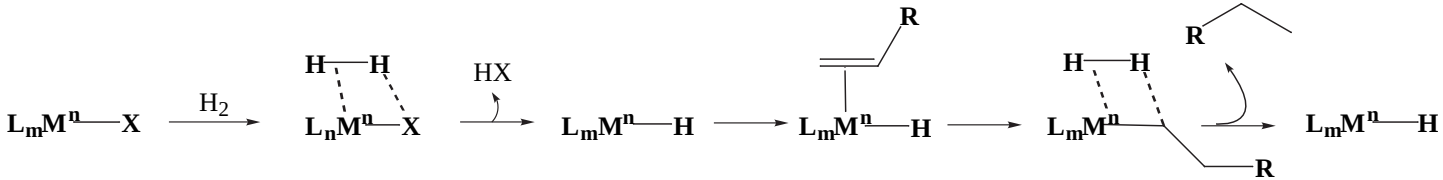
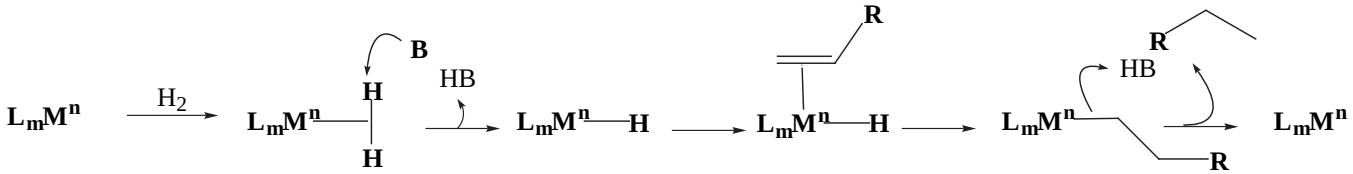
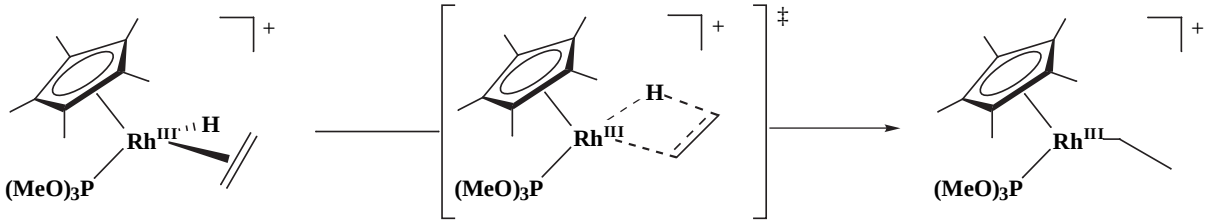
*Possible monohydride hydrogenation mechanisms* (Hydrogenations, pg. 156).

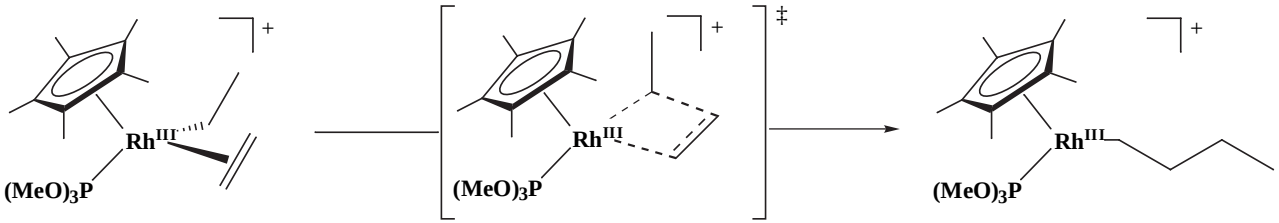


# *Rate of migratory insertion into olefin: M-H>>M-C*



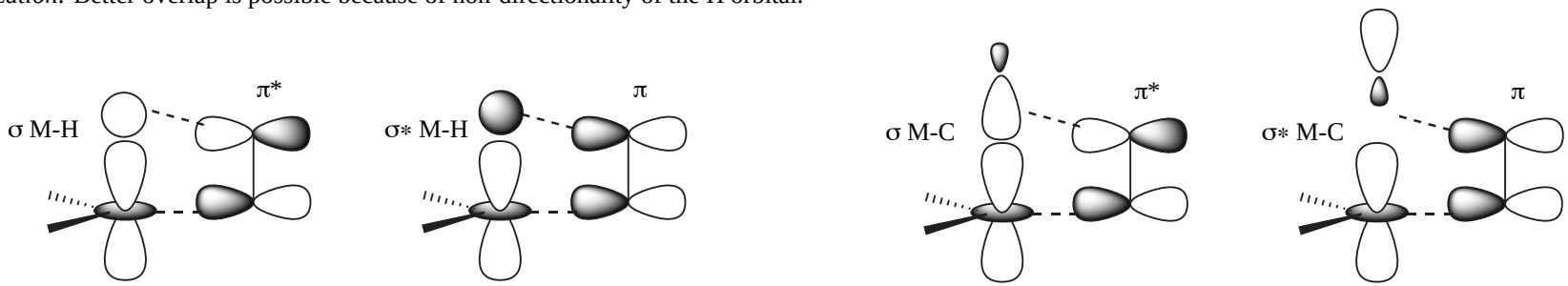

$\Delta G^{\ddagger}$ = 12.0 kcal/mol




$\Delta G^{\ddagger}$ = 22.3 kcal/mol

The difference of 10.3 kcal/mol in the free energy of activation of ethyl *vs* hydride migratory insertion into ethylene in these systems corresponds to a rate ratio of $k_{H\,MI}/k_{Et\,MI}$ of $10^7$-$10^8$. The effect is thought to be kinetic in nature. **Brookhart** *JACS* **1985** (107) 1443.

*Rationalization:* Better overlap is possible because of non-directionality of the H orbital.




Trigonal-bipyramidal structure

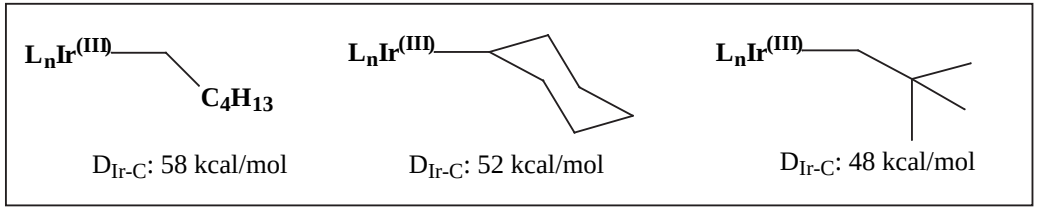
Note: at the TS of olefin insertion, both σM-H to π*C=C back-donation and πC=C to σ* M-H donation are necessary for bond exchange.

**Morokuma** *JACS* 1988 (110) 3417.
**Morokuma** *OM* **1997** (16) 1065.

# *Regioselectivity of hydrometallation*

**Aliphatic terminal olefins**: *For aliphatic terminal olefins, there is both a strong thermodynamic preference to form the sterically less hindered M-C bond.*

Structure & Bonding, pg. 32: As seen for C-H σ bonding, there is a general trend towards weaker M-C σ bonds with increased substitution.

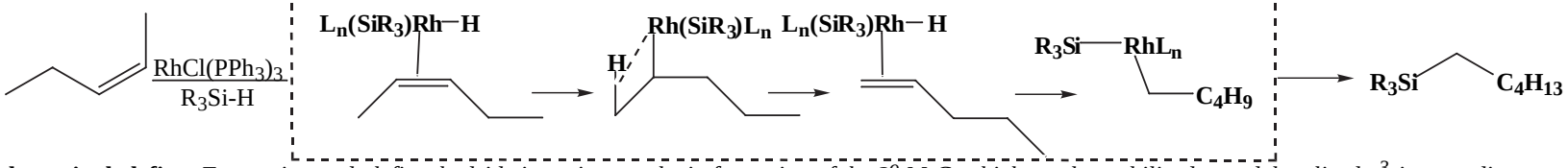



$D_{Ir-C}$: 58 kcal/mol $D_{Ir-C}$: 52 kcal/mol $D_{Ir-C}$: 48 kcal/mol

If an equilibration mechanism exists, M-alkyls will isomerize to the least sterically hindered $1^o$ product. For more examples of this see: Hydroformylation, pg.205 and 206.

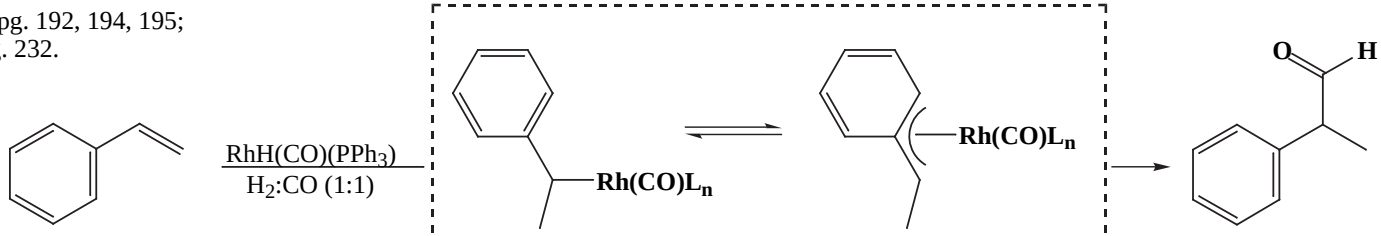
Hydrosilylation, pg. 183

olefin isomerization to terminal olefin leads to $1^o$ metal alkyl that undergoes RE to product.



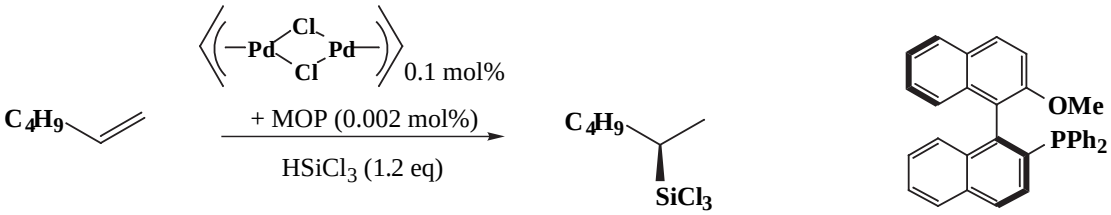

**Conjugated terminal olefins**: *For conjugated olefins, hydride insertion results in formation of the $2^o$ M-C which can be stabilized as a delocalized $\eta^3$-intermediate.*

Hydroformylation, pg. 192, 194, 195;
Hydrocyanation, pg. 232.




branched: linear (11:0)

**Ligand Effects?** Hayashi's observed hydrosilylation regioselectivities with aliphatic terminal olefins cannot be rationalized using our models (Hydrosilylation, pg. 189).

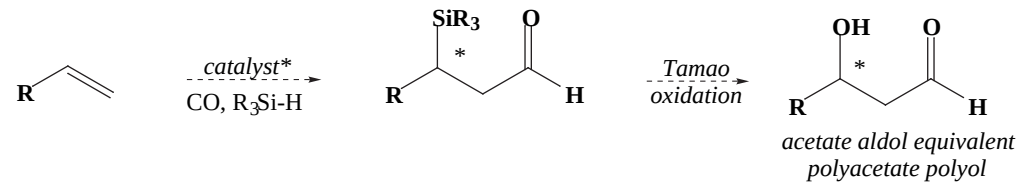



regioselectivity (87:13)

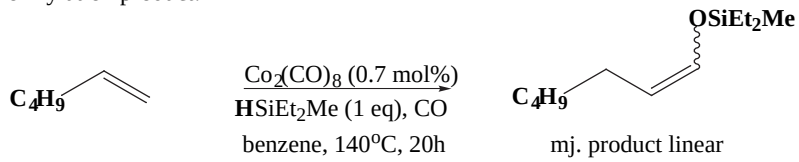
MOP

# *Unsolved problem: intermolecular silylformylation of terminal olefins*

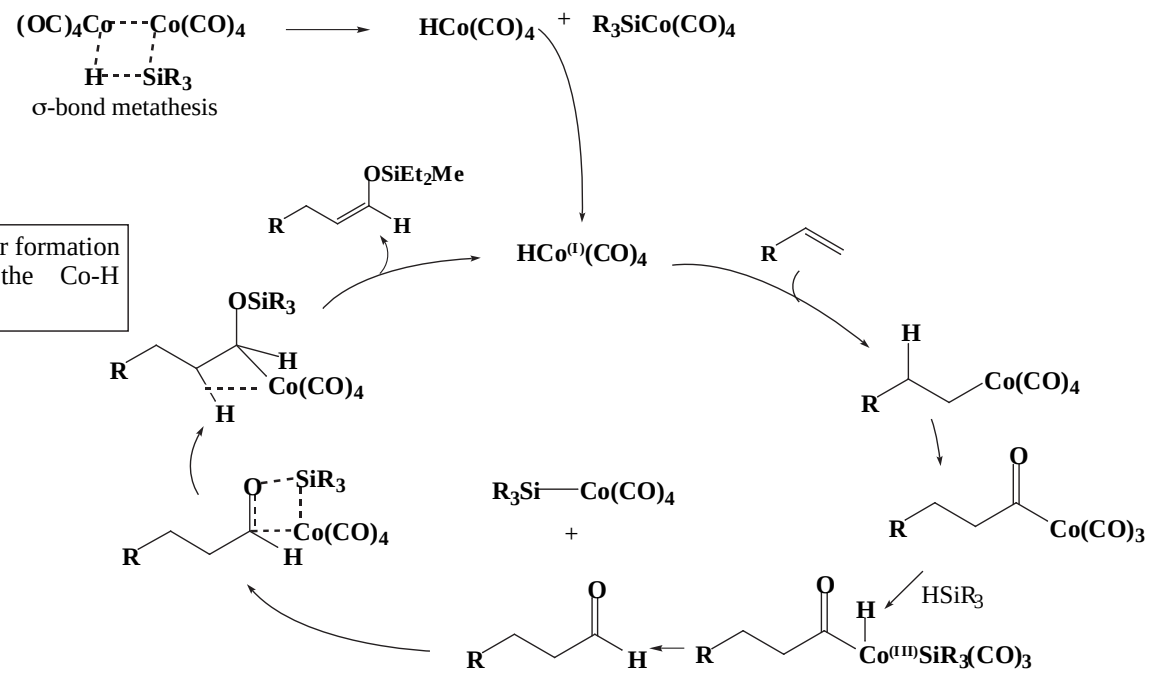
*Desired silylformylation product:*




Observed silylformylation product:



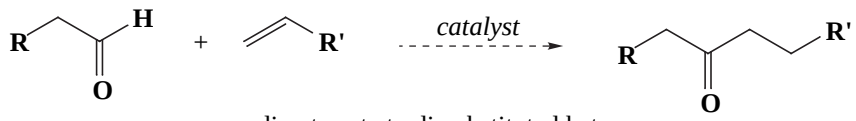

*Route of the problem?* One hypothesis is that hydrometalation of terminal olefins with Co-H occurs at a faster rate than silylmetalation with Co-$SiR_3$. The overall result is the hydroformylated aldehyde product which can further react with Co-$SiR_3$ (recall Si is oxophilic) to give the silylenol ether. See Silylformylation, pg. 211.




Silylenol ether formation regenerates the Co-H species.

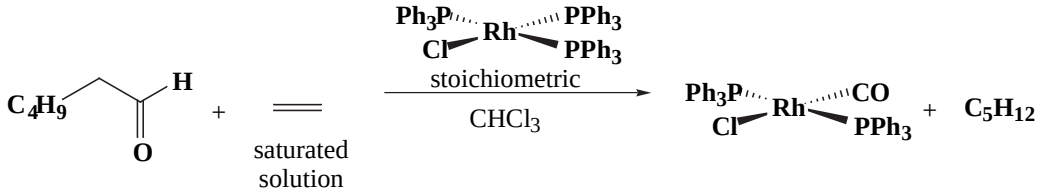
# *Unsolved problem: direct hydroacylation of terminal olefins*

*Desired hydroacylation product*

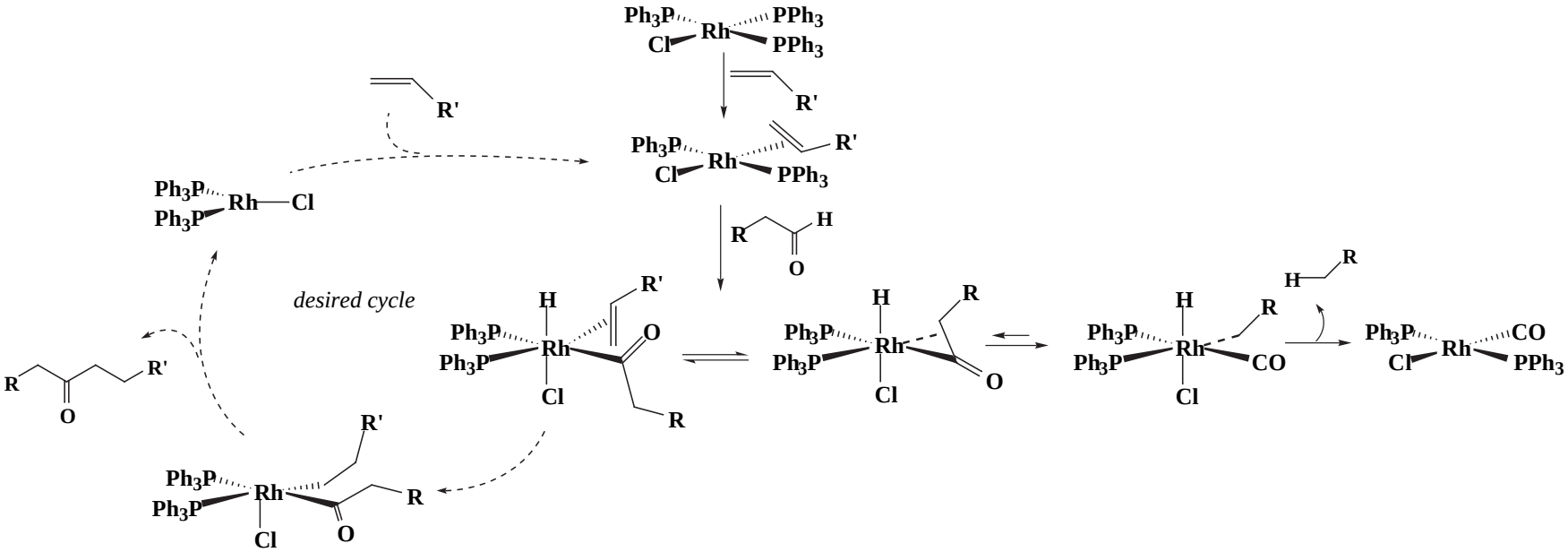



direct route to di-substituted ketones
from unactivated precursors

Observed intermolecularly: decarbonylation

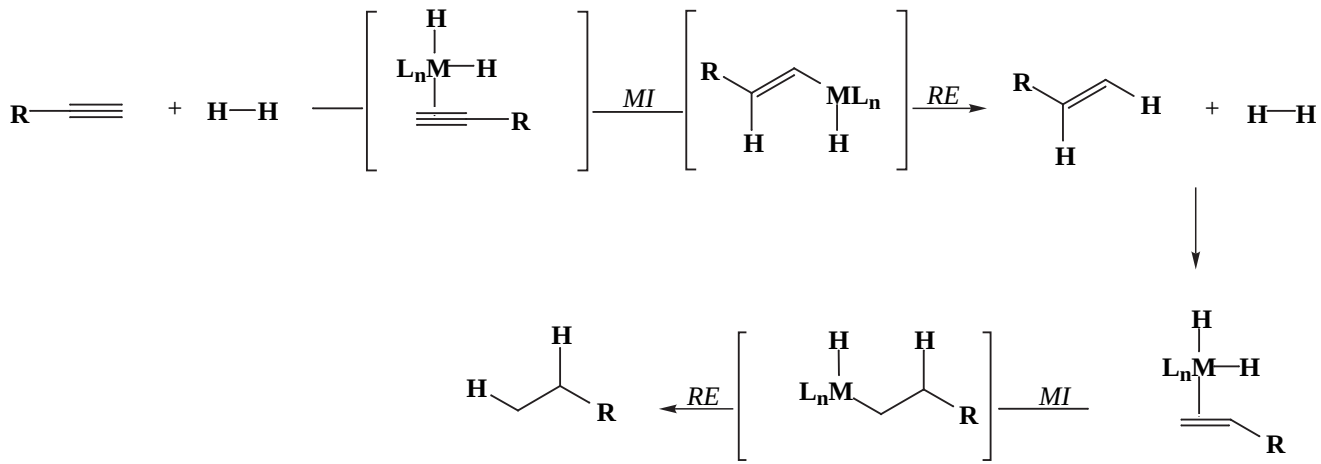



Route of the problem? One hypothesis is as follows: The catalyst must have three "open" and adjacent coordination sites for the acyl, hydride, and olefin moieties to effect successful hydroacylation. Upon oxidative addition of the aldehyde to give the hydridoacyl metal species, intramolecular binding of the acyl alkyl substituent to the syn open site competes effectively with intermolecular olefin binding and results in decarbonylation.

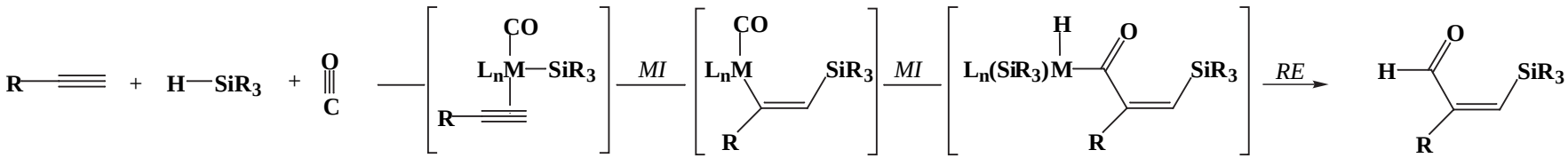


# *Functionalization of terminal alkynes via migratory insertion /reductive elimination sequence?*

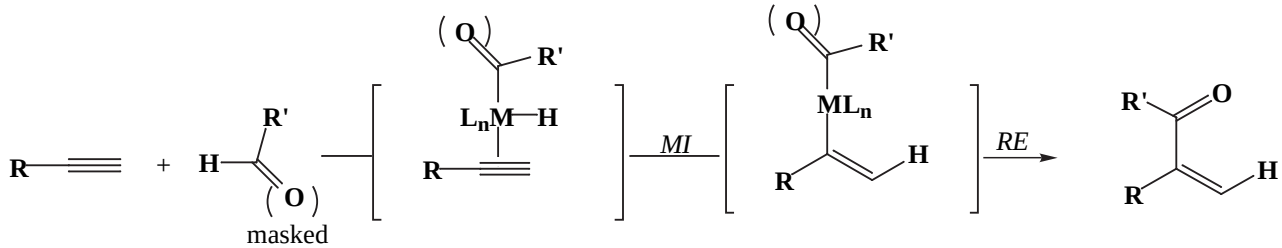
*Hydrogenation*




*Silylformylation*

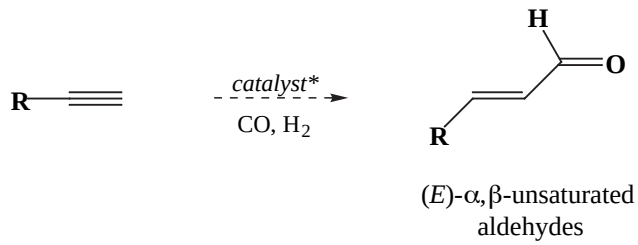



*Hydroacylation*

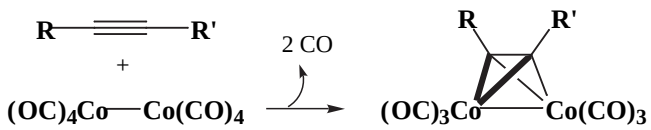


# *Unsolved problem: hydroformylation of terminal alkynes*

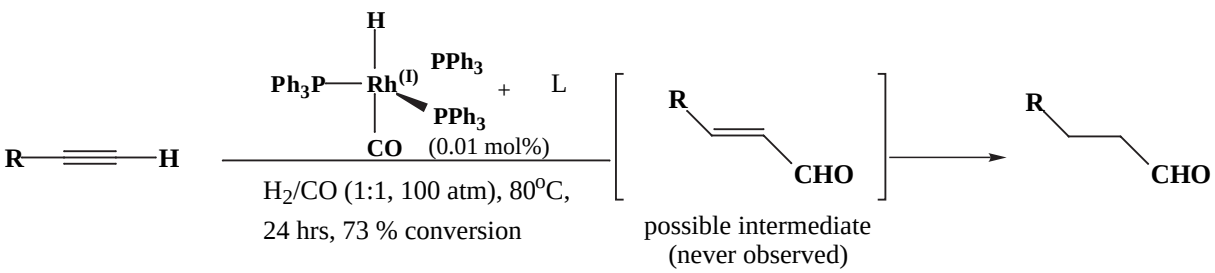
*Desired hydroformylation product:*




Route of the problem: acetylenes form stable metallocyclopropane/propene complexes that resist hydroformylation under mild conditions.

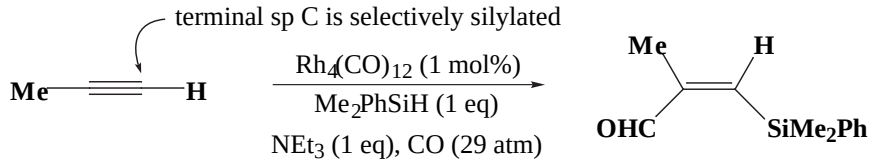



Under forcing conditions of high $CO/H_2$ pressure and high temperatures, terminal acetylenes are converted to fully saturated linear aldehydes.



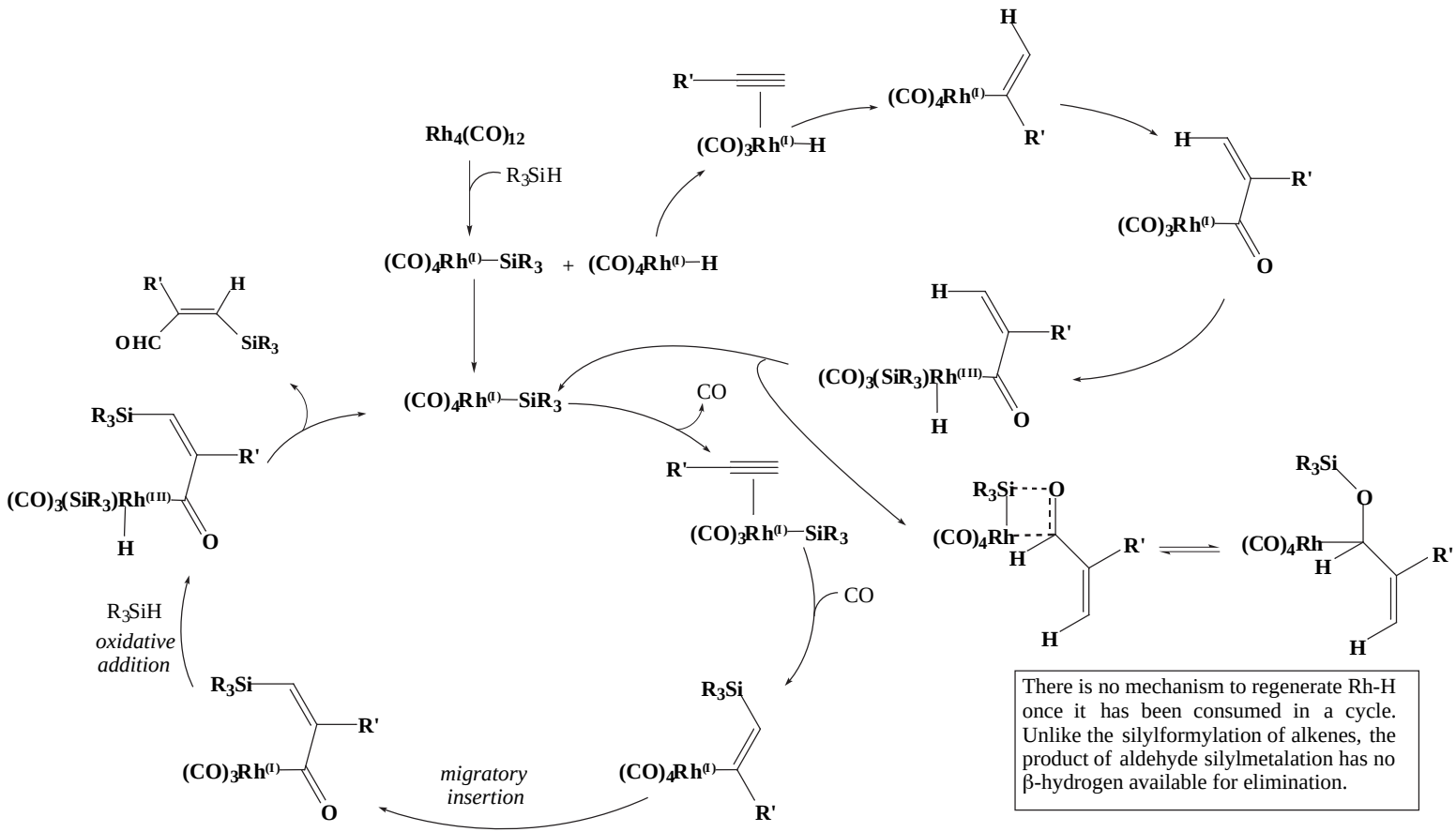
# *Silylformylation of alkynes*

*terminal alkynes:*




99% yield
*Z*:*E* (80:20)

*Z*-isomer is the kinetic product. *E*-isomer arises from isomerization under the carbonylation conditions.




There is no mechanism to regenerate Rh-H once it has been consumed in a cycle. Unlike the silylformylation of alkenes, the product of aldehyde silylmetalation has no β-hydrogen available for elimination.