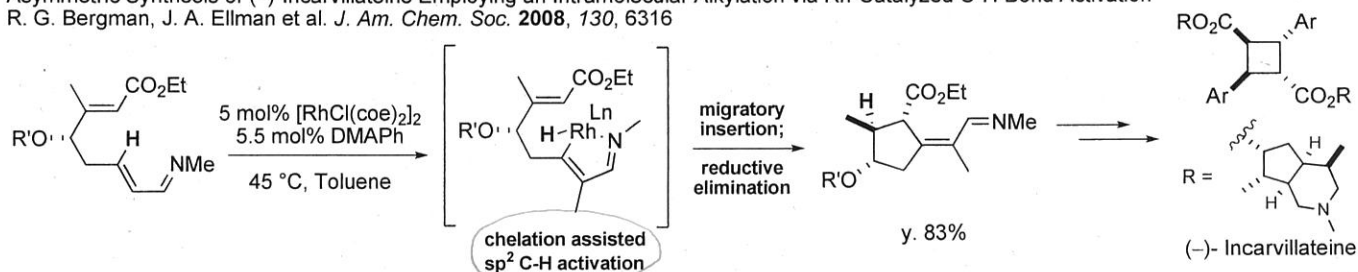


## Functionalization of Inert $sp^3$ Carbon-Hydrogen Bonds with a Soft Transition Metal

- Exploring Organometallics with D. Sames' Work as Central Themes -

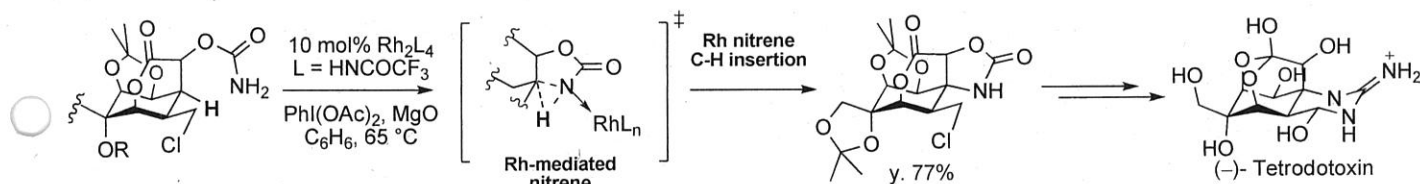
Asymmetric Synthesis of (-)-Incarvilleine Employing an Intramolecular Alkylation via Rh-Catalyzed C-H Bond Activation  
R. G. Bergman, J. A. Ellman et al. *J. Am. Chem. Soc.* **2008**, *130*, 6316



A Stereoselective Synthesis of (-)-Tetrodotoxin

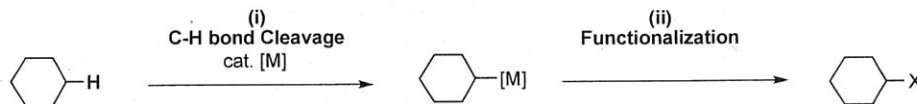
J. Du. Bois et al. *J. Am. Chem. Soc.* **2003**, *125*, 11510

Ref.) Mr. Tanaka's Lit. Seminar (B4)



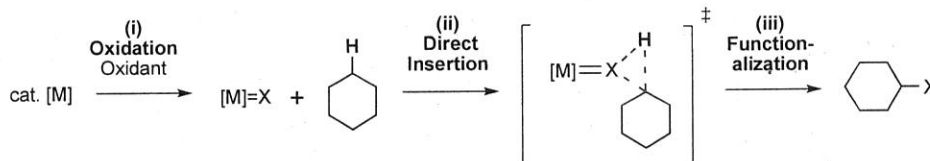
### Inner-sphere mechanism

Formation of discrete organometallic intermediate



### Outer-sphere mechanism

Substrate does not interact directly with transition metal center

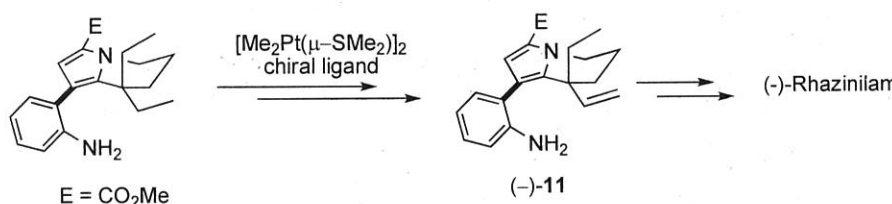


M. S. Sanford et al. *Tetrahedron* **2006**, *62*, 2439

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### (1) C-H Bond Activation of Hydrocarbon Segments in Complex Organic Molecule: Total Synthesis of (-)-Rhazinilam

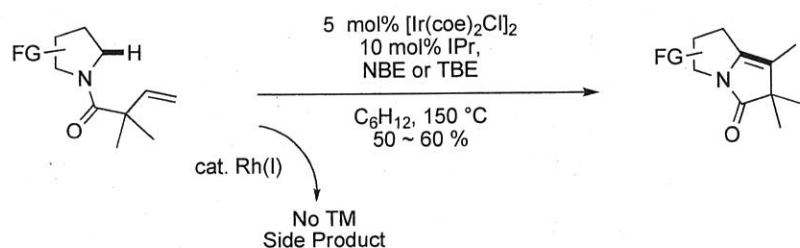
D. Sames et al. *J. Am. Chem. Soc.* **2000**, *122*, 6321.  
*J. Am. Chem. Soc.* **2002**, *124*, 6900



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| (1-2) Reaction Mechanism   | 3, 4 |
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### (2) Cross-Coupling of $sp^3$ C-H Bonds and Alkenes: Catalytic Cyclization of Alkene-Amide Substrates

D. Sames et al. *J. Am. Chem. Soc.* **2004**, *126*, 6556.

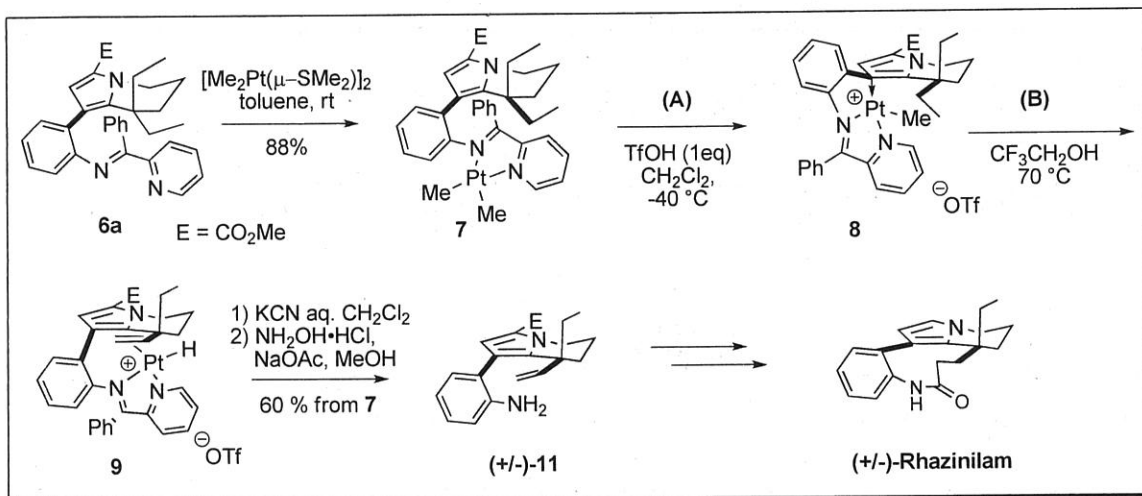


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# (1) C-H Bond Activation of Hydrocarbon Segments in Complex Organic Molecules Total Synthesis of Antimitotic (-)-Rhazinilium

D. Sames et al.  
*J. Am. Chem. Soc.* **2000**, 122, 6321.  
*J. Am. Chem. Soc.* **2002**, 124, 6900.

Overview of the Key Conversion:



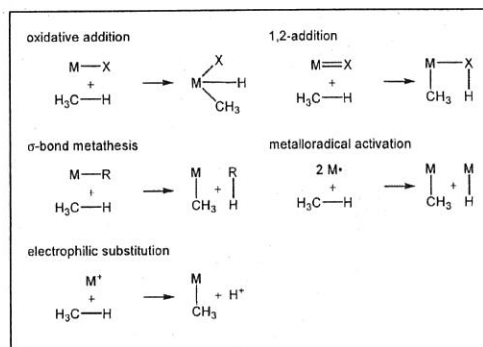
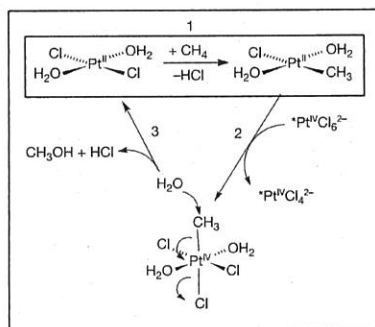
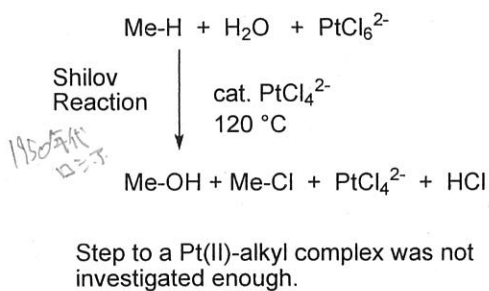
Remarkable points of this overall conversions:

- (A) Liberation of CH<sub>4</sub> from the complex to afford reactive Pt(II) center
- (B) Dehydrogenation of ethyl group via C-H bond activation

## Ref 1-1

### Intramolecular and intermolecular C-H activation at Cationic Pt<sup>II</sup> center

J. A. Labinger et al.  
*Inorg. Chim. Acta.* **1998**, 270, 467  
*J. Am. Chem. Soc.* **1997**, 119, 848



Labinger's initial model study with ether solvent

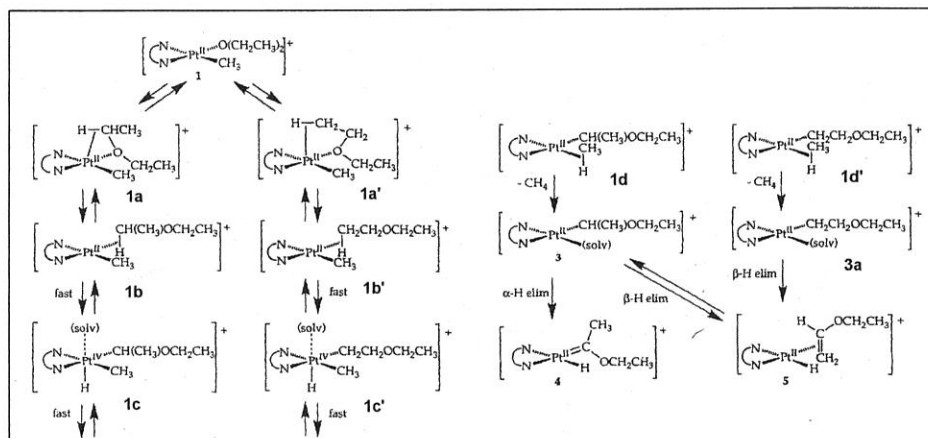


Ethers coordinate strongly to the platinum center and offer their own C-H bonds

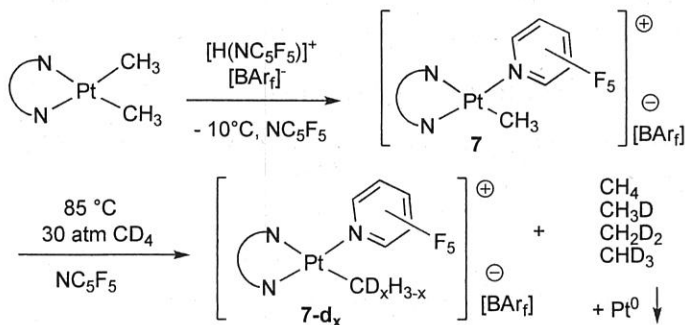
Mechanism:  
 initiated by an agostic interaction with a metal center

reversibility and irreversibility speculated from several deuteration experiments

cf. Protonation of 0 in CH<sub>2</sub>Cl<sub>2</sub>:  
 Cl<sup>-</sup> abstraction from CH<sub>2</sub>Cl<sub>2</sub>



- Pentafluoropyridine (NC<sub>5</sub>F<sub>5</sub>) weakly donor solvent, lack of C-H bonds, dissolve cationic Pt(II) complex

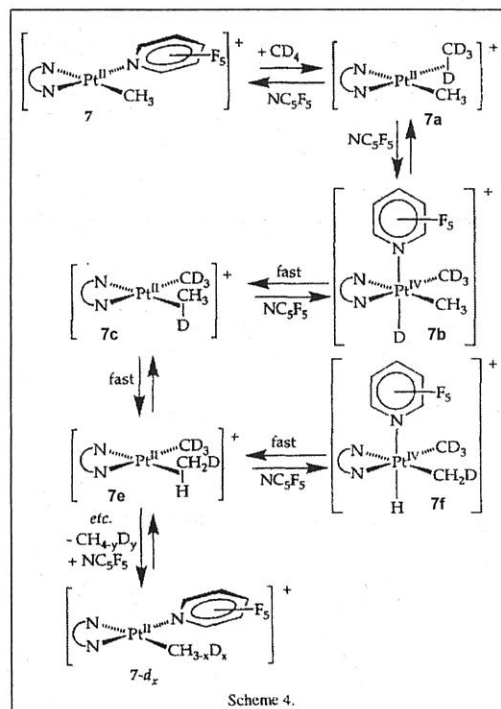


Proposed Reaction Mechanism (in Scheme 4)

Formation of multiple deuterated methane  
Rapid reversible equilibria between  
"Pt<sup>IV</sup> dialkyl hydride cation" and "Pt<sup>II</sup> C-H σ complexes"

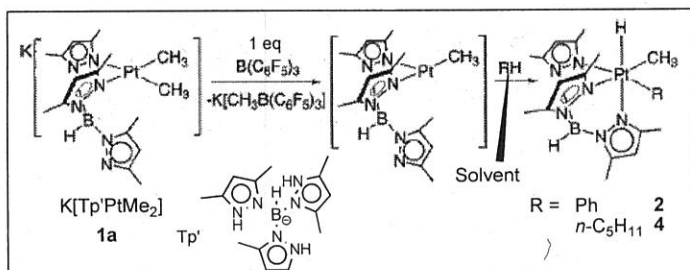
Sufficiently electrophilic Pt(II) complex can activate alkane C-H Bond

Success of the C-H activation process can be attributed to:  
the use of **weakly donor solvent** that can accommodate  
the ligand exchange between solvent and methane



### Ref 1-2 C-H Activation at Pt(II) to Form Stable Pt(IV) Alkyl Hydrides

First example of the intermolecular oxidative addition of arene and alkane C-H bonds by Pt(II) species **resulting in Pt(IV) compounds**

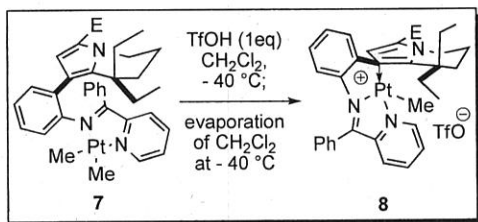


K. I. Goldberg et al.  
*J. Am. Chem. Soc.* **1997**, 119, 10235

Generation of a 3-coordinate 14e/Pt(II) species  
followed by Oxidative addition to R-H bond

Rapid trapping of the  
five-coordinate Pt(IV) species

Success of  
C-H activation process and  
isolation of oxidative addition product :  
primarily due to flexible nature of ligand

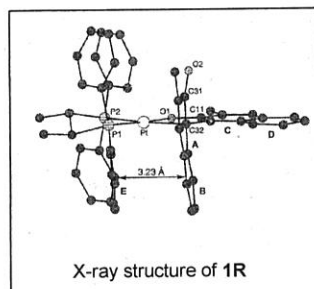
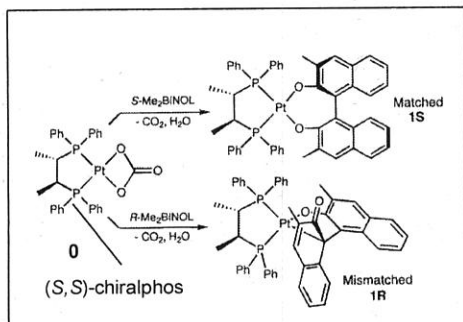


### (A) Liberation of 1 eq CH<sub>4</sub> to afford electrophilic Pt<sup>II</sup> center

Unusual coordination mode observed in **8**:  
one pyrrole carbon becomes sp<sup>3</sup>-like to coordinate Pt<sup>II</sup>

This ligation should not be so strong,  
making the following ethyl C-H coordination easier.

### Ref 1-3 Unorthodox C,O Binding Mode of Me<sub>2</sub>BINOL in Pt(II) Complexes

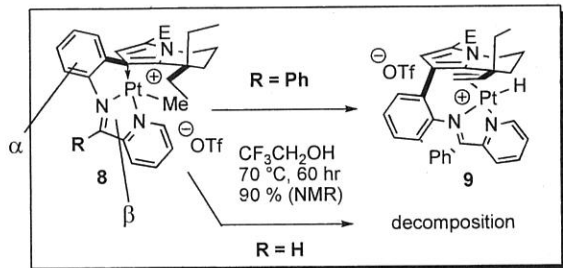


M. R. Gagne et al.  
*J. Am. Chem. Soc.* **1998**, 120, 11002

PtCO<sub>3</sub>(S,S-chiralphos) **0**:  
five membered ring (Pt and chiralphos),  
square planar Pt(II) complex  
diMe at pseud-equatorial,  
constituting fixed chiral space

Unusual C-O binding mode  
observed in mismatched pair of  
chiralphos and Me<sub>2</sub>BINOL (**1R**)

5 membered ring around Pt rather than 7  
soft nature of Pt(II)

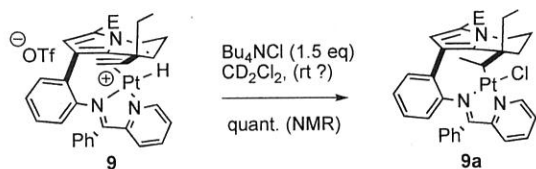


## (B) Dehydrogenation via C-H bond activation

**8** ( $\text{R} = \text{H}$ ) did not afford target molecule

importance of weakly coordinating ligand?

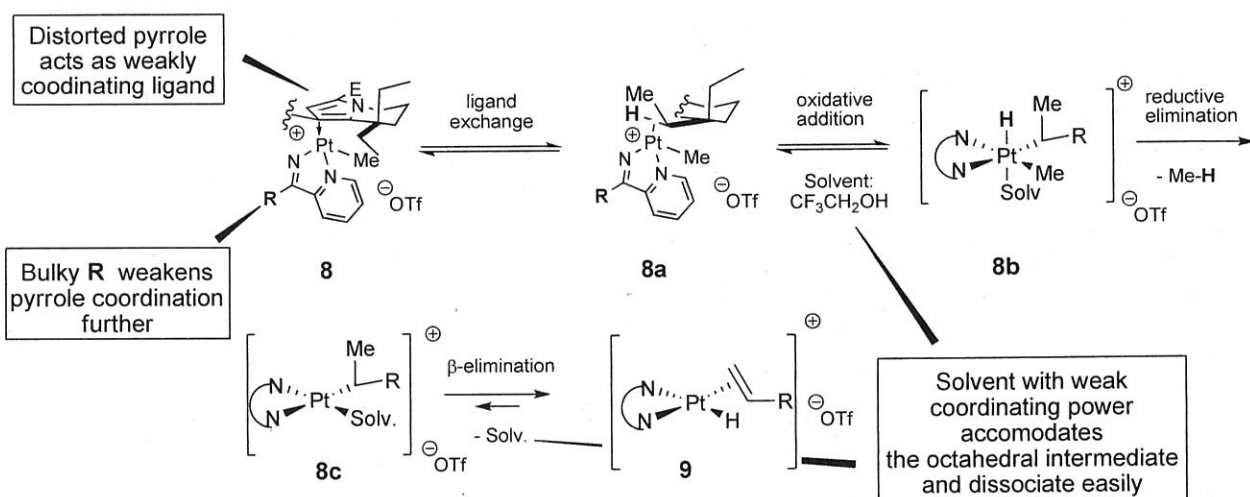
installation of bulky  $\text{R}$  to disfavor coplanarity of 2 rings ( $\alpha$  and  $\beta$ ) resulting in **weaker pyrrole complexation**



Addition of  $\text{Cl}^-$  to the olefin complex **9**

complex wherein Pt is bonded to methylene carbon, suggesting initial C-H activation at methylene carbon

## Mechanism speculated from the results



## Asymmetric C-H Activation

Differentiating the two enantiotropic ethyl group via the introduction of a chiral ligand

Pt chemistry proved to be robust and insensitive to air and moisture: likely to accommodate a broader range of ligands

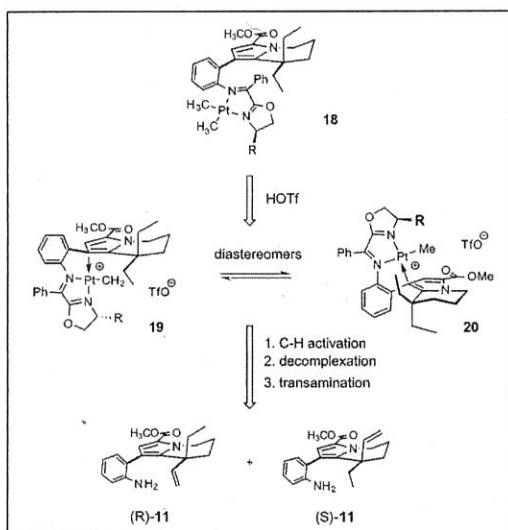


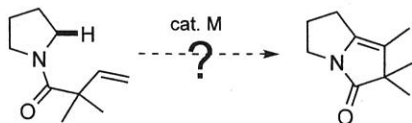
Table 1. Diastereoselective Directed C-H Bond Functionalization Studies

| entry | LIGAND | T(°C) | ds ratio <sup>a</sup> | conversion (%) <sup>b</sup> | isolated yields (%) |
|-------|--------|-------|-----------------------|-----------------------------|---------------------|
| 1     | 13     | 60    | 6:1                   | 20                          | 15                  |
|       |        | 65    | 4:1                   | 60                          | 35                  |
|       |        | 70    | 3:1                   | 63                          | 40                  |
| 2     | 14     | 60    | 5.5:1                 | 16                          | 10                  |
|       |        | 65    | 4:1                   | 60                          | 36                  |
|       |        | 70    | 3:1                   | 65                          | 40                  |
| 3     | 15     | 60    | 7.5:1                 | 30                          | 20                  |
|       |        | 65    | 5.5:1                 | 58                          | 35                  |
|       |        | 70    | 4.4:1                 | 66                          | 42                  |
| 4     | 16     | 60    | >20:1                 | <10 <sup>c</sup>            |                     |
| 5     | 17     | 70    | 1.1:1                 |                             |                     |

<sup>a</sup> Determined by  $^1\text{H}$  NMR (platinum hydride, not shown), and HPLC (Schiff base 12). <sup>b</sup> Determined by HPLC. <sup>c</sup> Low conversion is due to the low yield of the complexation step. The crude mixture was submitted to the reaction sequence since the corresponding complex could not be purified. cHex = cyclohexyl; reaction and purification conditions are detailed in the Supporting Information.

## (2) Cross-Coupling of $sp^3$ C-H Bonds and Alkenes Catalytic Cyclization of Alkene-Amide Substrates

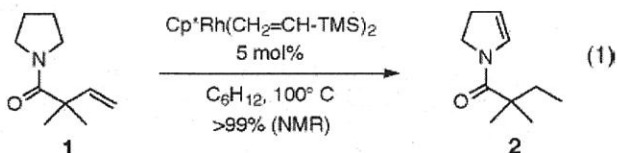
D. Sames et al.  
*J. Am. Chem. Soc.*  
2004, 126, 6556



Direct cross coupling of  $sp^3$  C-H bonds and alkenes

Few examples of  $sp^3$  C-H bond activation followed by C-C bond formation

### Initial trial



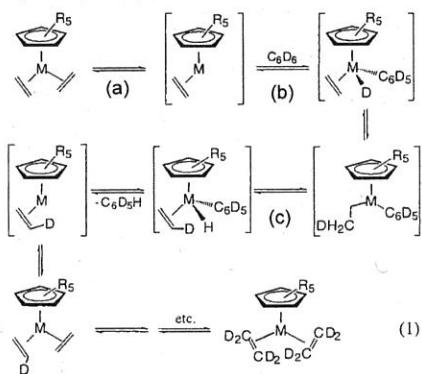
Initial trial using cat.  $Cp^*Rh(CH_2=CH-TMS)_2$  which was already known to activate some kinds of  $sp^2$  and  $sp^3$  C-H bond

Complete intramolecular transfer hydrogenation

### Ref 2-1 Hydrogen/Deuterium Exchange Reactions and Transfer Hydrogenations Catalyzed by $[C_5Me_5Rh(olefin)_2]$ Complexes: Conversion of Alkoxysilanes to Silyl Enolates

M. Brookhart et al.  
*J. Am. Chem. Soc.*  
1999, 121, 4385

Scheme 1. Reversible C-H Bond Activation of Benzene- $d_6$  with  $[C_5R_5M(C_2H_4)_2]$  ( $M = Co, Rh$ ) and H/D Exchange



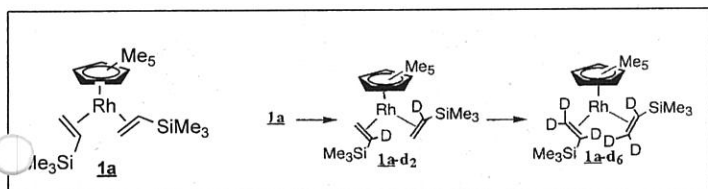
Early work by Seiwell (*J. Am. Chem. Soc.* 1974, 96, 7134)

Heating  $[CpRh(C_2H_4)_2]$  at 130 °C in  $C_6D_6$

- (a) dissociation of olefin ligand to generate reactive 16e fragment
- (b) oxidative addition to aromatic C-D bond of solvent
- (c) reversible olefin insertion-deinsertion sequence



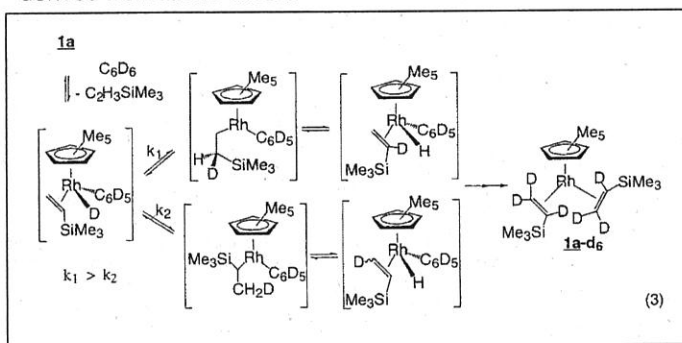
use of bulkier olefin ligand (eg. **1a**) would lead more efficient system?



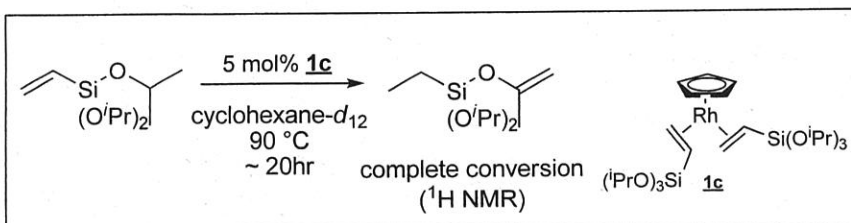
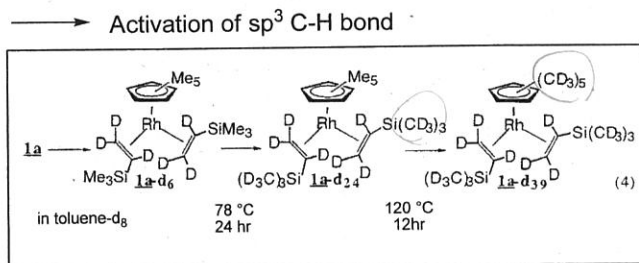
Reaction at 50 °C  
time for 50 % reduction in signal intensity ( $^1H$  NMR)

Solvent  
 $C_6D_6$   $\alpha$ : 115 min,  $\beta$ : 250 min  
 $(CD_3)_2CO$   $\alpha$ : 120 min,  $\beta$ : 250 min

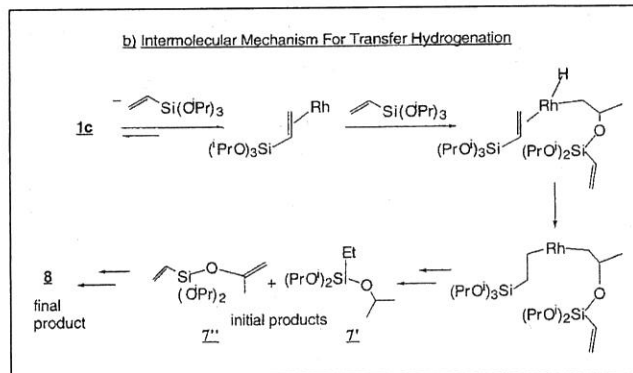
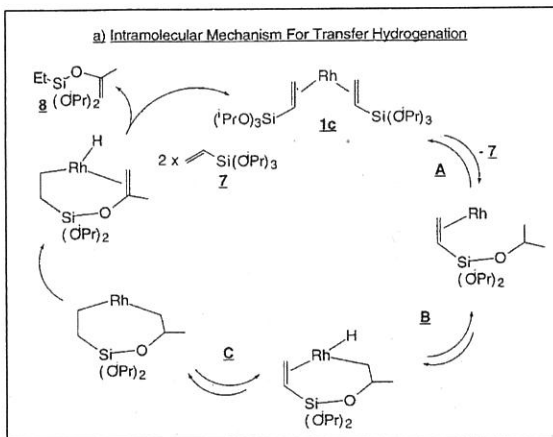
Kinetic preference for deuteration at  $\alpha$  position:  
derived from steric effect?



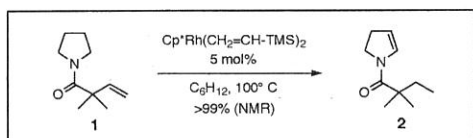
Further heating at higher temperature resulted in deuteration other parts than olefin



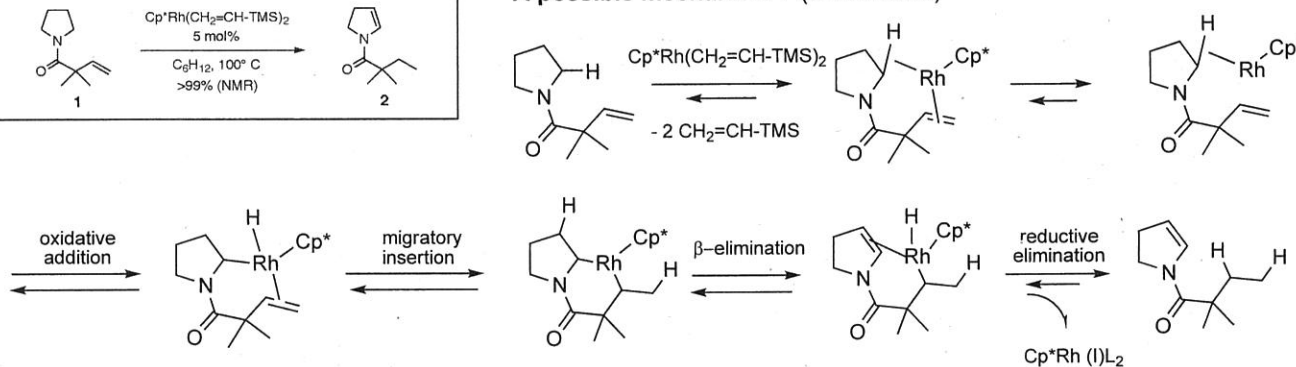
Alkoxysilane Isomerization: Transfer Hydrogenation  
Catalytic conversion of alkoxysilane to silyl enolate



No observation of  $Z'$ ,  $Z''$  in  $^1\text{H}$   $^{13}\text{C}$  NMR  
 → Intramolecular Mechanism?



A possible mechanism? (abbreviated)



### Investigations with Ir(I) catalyst: Introduction

Table 1. Catalytic Oxidative Cyclization, Lead Discovery

| entry | complex  | NMR yields <sup>a</sup> |
|-------|--|-------------------------|
| 1     | $[\text{Ir}(\text{COE})_2\text{Cl}]_2 / \text{PCy}_3$ (2 eq)             |                         |
| 2     | $[\text{Ir}(\text{COE})_2\text{Cl}]_2 / \text{IPr}$ (2 eq)               |                         |
| 3     | $[\text{Ir}(\text{COE})_2\text{Cl}]_2 / \text{IPr}$ (2 eq) + 4 eq NBE    | ?                       |
| 4     | $(\text{Cy}_3\text{P})_2\text{Ir}(\text{Cl})\text{H}_2$ , 6              |                         |
| 5     | $(\text{Cy}_3\text{P})_2\text{Ir}(\text{CF}_3\text{CO}_2)\text{H}_2$ , 7 |                         |

IPr: R = *i*Pr  
 NHC Ligand

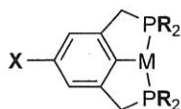
Table 1 (continued)

| Entry | complex   | NMR yields             |
|-------|---|------------------------|
| 6     | $\text{Cl}-\text{Ir}(\text{H})_2-\text{IPr}$ , 8  | Pincer complex (PCP) ? |
| 7     | $\text{MeO}-\text{C}_6\text{H}_4-\text{P}(\text{t-Bu})_2-\text{Ir}(\text{H})_2-\text{P}(\text{t-Bu})_2$ , 9 |                        |

<sup>a</sup> Reported yields were determined by NMR using an internal standard (average of three runs). NBE, norbornene. Total loading of Ir catalyst was 10 mol %.

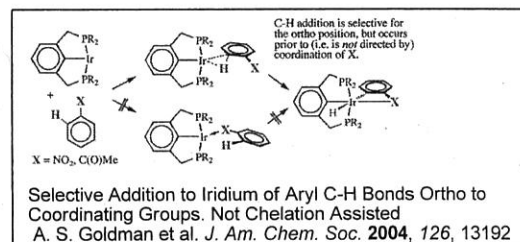
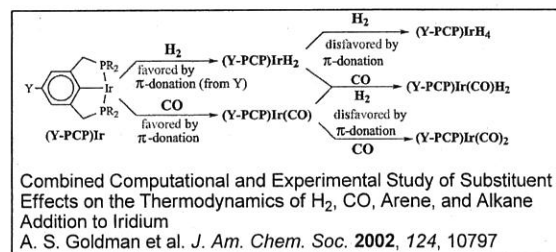
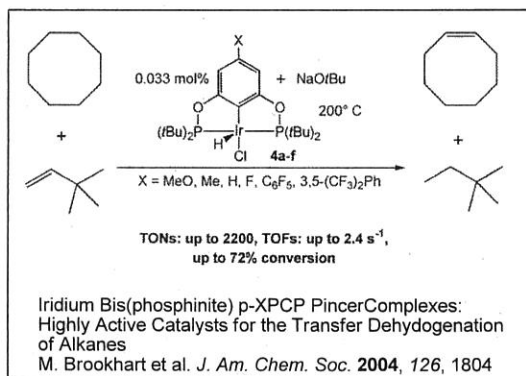
### PCP Ligands: Overview

J. T. Singleton  
*Tetrahedron*  
 2003, 59, 1837



stability to air, moisture, high temp.

fine tuning at R and X



**Ref 2-2**  
**Heterocyclic Carbenes: Synthesis and Coordination Chemistry**  
**Understanding the M-(NHC) bond**

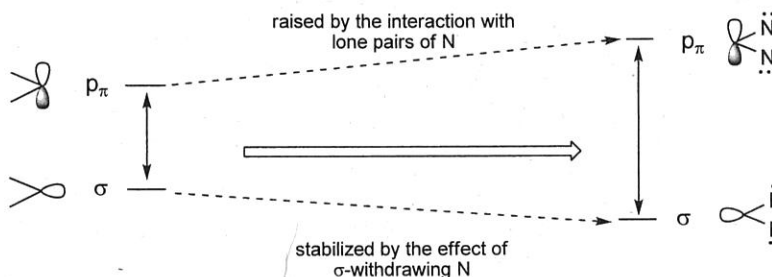
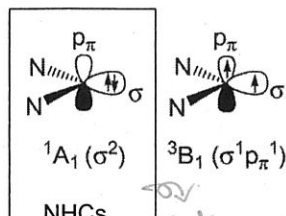
F. E. Hahn et al. *Angew. Chem. Int. Ed.* **2008**, 47, 3122  
 L. Cavallo et al. *Coord. Chem. Rev.* **2009**, 253, 687



strong  $\sigma$ -donor  
 poor  $\pi$ -acceptor  
 bulkiness of R

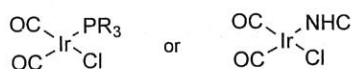
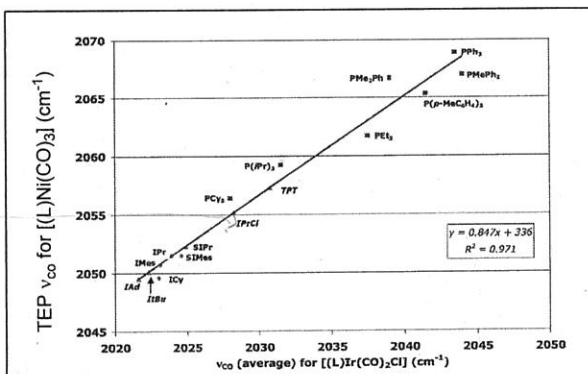
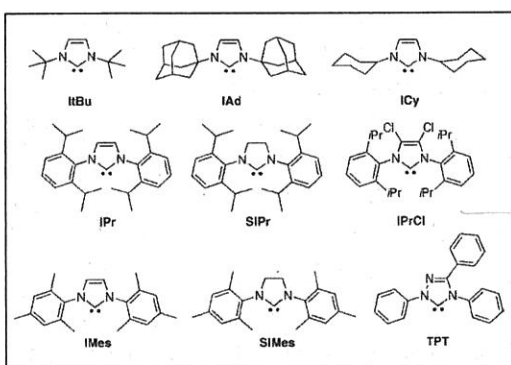
Features (compared with  $PR_3$ )

- 1) reduced need for excess ligand
- 2) improved stability to air and moisture of TM-NHC complex
- 3) remarkable activity in catalysis



**Ref 2-3**  
**Determination of N-Heterocyclic Carbene (NHC) Steric and Electronic Parameters**  
**using the [(NHC)Ir(CO)<sub>2</sub>Cl] System**

P. Nolan et al.  
*Organometallics*  
**2008**, 27, 202



IR Carbonyl  
 Stretching Frequency  
 Analysis

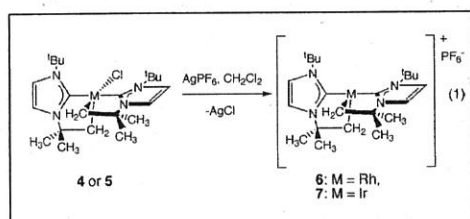
NHCs are much more strongly donating ligands than the strongest tertiary phosphines

Little difference between the NHCs  
 (weak influence of N-substituents on electronic properties)

Modifications on imidazole ring allow for effective tuning of electronic properties

**Ref 2-4**  
**Interaction of a Bulky N-Heterocyclic Carbene Ligand with Rh(I) and Ir(I).**  
**Double C-H Activation and Isolation of Bare 14-Electron Rh(III) and Ir(III) Complexes**

P. Nolan et al.  
*J. Am. Chem. Soc.*  
**2005**, 127, 3516



Unusual 14e M(III)L<sub>4</sub> complex (M = Rh, Ir)  
 (No  $\sigma$ -C-H agostic interaction to Metal)

DFT calculation of complex 7

HOMO strong  $d_{z^2}$  character  
 HOMO-1 mainly  $d_{xz}$   
 HOMO-2 mainly  $d_{yz}$

HOMO-3 interaction between  
 HOMO-4 filled highest  $\pi$ -MO(NHC)  
 and d(metal)

NHCs

normally considered as pure  $\sigma$ -donor

can also donate electron density through  
 $\pi$  to d interaction

can even stabilize bare 14e/M(III) complex  
 (M = Rh, Ir)

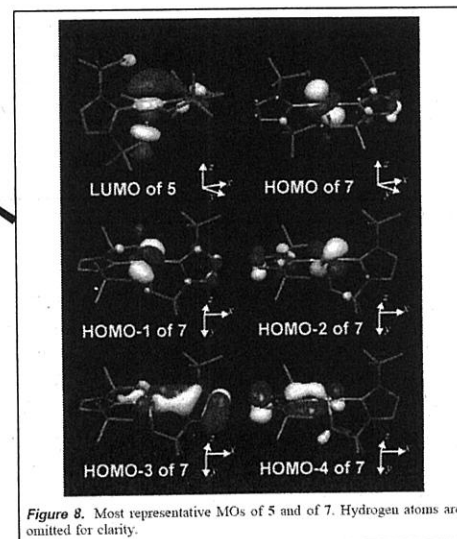
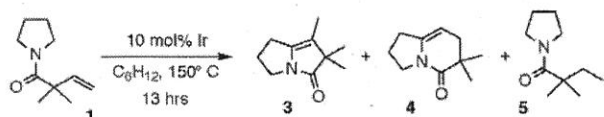


Figure 8. Most representative MOs of 5 and of 7. Hydrogen atoms are omitted for clarity.

Qualitative MO Analysis of **12**  
 highest filled  $\pi$ -orbital (NHC)<sub>2</sub>-12A  
 match well metal empty  $d_{xy}$  orbital

# Investigations with Ir(I) Catalyst: Result

**Table 1. Catalytic Oxidative Cyclization, Lead Discovery**



| entry | complex   | NMR yields <sup>a</sup> |    |    |
|-------|---|-------------------------|----|----|
| 1     | [Ir(COE) <sub>2</sub> Cl] <sub>2</sub> / PCy <sub>3</sub> (2 eq)                        | 26                      | 11 | 25 |
| 2     | [Ir(COE) <sub>2</sub> Cl] <sub>2</sub> / IPr (2 eq)                                     | 41                      | 4  | 41 |
| 3     | [Ir(COE) <sub>2</sub> Cl] <sub>2</sub> / IPr (2 eq) + 4 eq NBE                          | 66                      | 17 | 10 |
| 4     | (Cy <sub>3</sub> P) <sub>2</sub> Ir(Cl)H <sub>2</sub> , 6                               | 9                       | 0  | 20 |
| 5     | (Cy <sub>3</sub> P) <sub>2</sub> Ir(CF <sub>3</sub> CO <sub>2</sub> )H <sub>2</sub> , 7 | 0                       | 0  | 24 |

**Table 1 (continued)**

| Entry | complex | NMR yields |   |       |
|-------|---------|------------|---|-------|
| 6     |         | trace      | 0 | trace |
| 7     |         | 0          | 0 | 0     |

<sup>a</sup> Reported yields were determined by NMR using an internal standard (average of three runs). NBE, norbornene. Total loading of Ir catalyst was 10 mol %.

Entry 1: Ir(I)/PCy<sub>3</sub> afforded TM

Entry 2: NHC ligand; increased efficiency

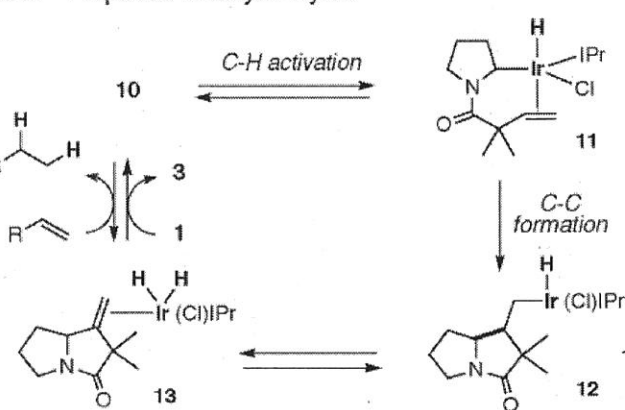
Entry 3; NBE as a hydrogen acceptor added; prevented the formation of 5

Initial thoughts of active complex: L<sub>2</sub>IrX?

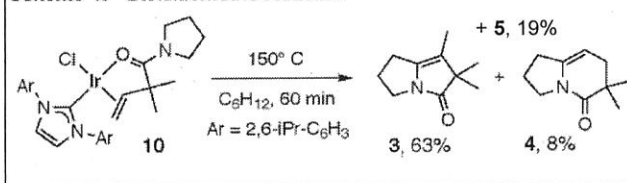
This idea was denied by the results of entries 4 ~ 7

IPr-Ir-Cl is an active complex? : Scheme 1 providing identical yields and kinetics

**Scheme 2. Proposed Catalytic Cycle**

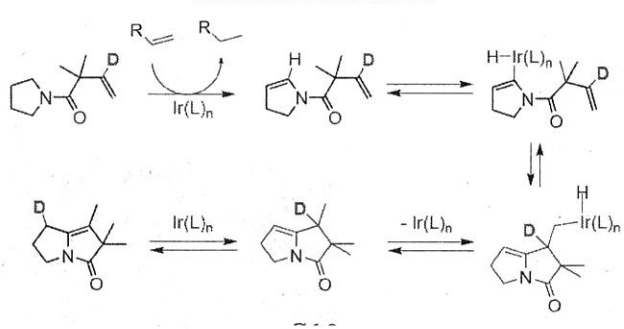


**Scheme 1. Stoichiometric Reaction**



Formation of 11 via Ir(I)/14e complex which would be stabilized by strong NHC donation?  
 Competition of 3/4 at C-C formation  
 Isomerization of 13 affords 3

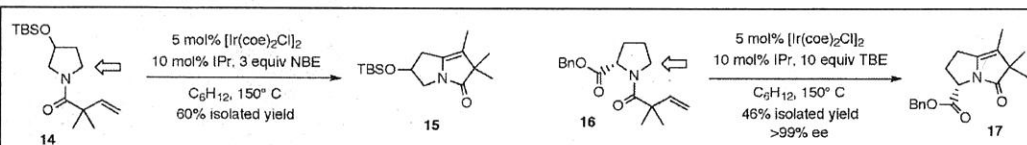
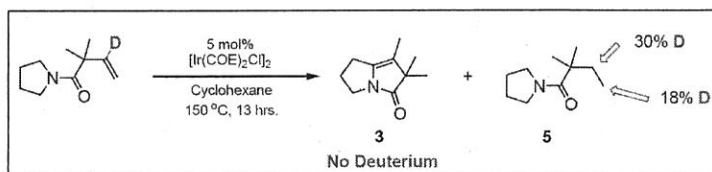
**Alternative Mechanism**



Alternatively Possible Mechanism

Transfer dehydrogenation followed by sp<sup>2</sup> C-H Activation

Denied by deuterium labeling experiments



Examples showing functional group compatibility