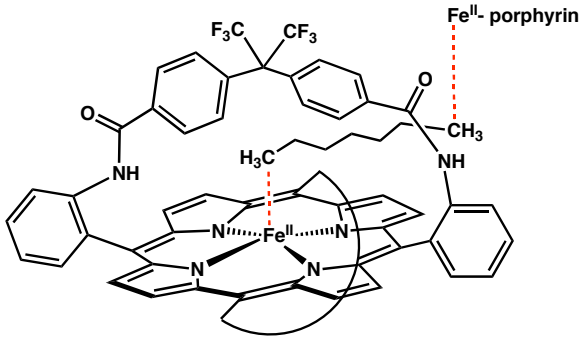
Catalytic C-H Activation and Functionalization: Some Applications in Organic Synthesis

Yeeman Ramtohul
Literature Presentation
May 24, 2004
8 pm, 147 Noyes



Outline

I. Introduction

II. Types of C-H Activation

III. Oxidation of Alkanes

IV. Ru and Rh Addition of C-H Bond to Double Bonds

V. Ru and Rh Hydroacylation of Aldehydes

VI. Hydroiminoacylation

R. H. Crabtree, Yale

R. G. Bergman, UC Berkley

Shinji Murai, Osaka University

• General referrences

- Kakiuchi and Chatani *Adv. Synth. Catal.* **2003**, *345*, 1077

- Jun et. al. *Chem. Eur. J.* **2002,** *8,* 2423

- Sen and Remias *J. Mol. Cat. A: Chemical* **2002**, *189*, 33

- Crabtree *J. Chem. Soc., Dalton Trans.*, **2001**, *17*, 2437

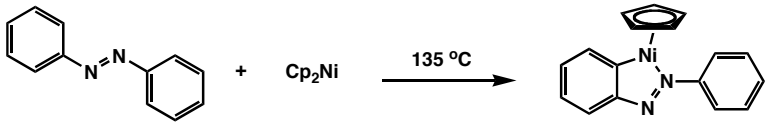
- Sen A. *Topics in Organomet. Chem.,* Vol 3, **1999** (whole issue)

- Shul'pin and Shilov *Chem Rev.* **1997**, *97*, 2879

C-H Bond Activation

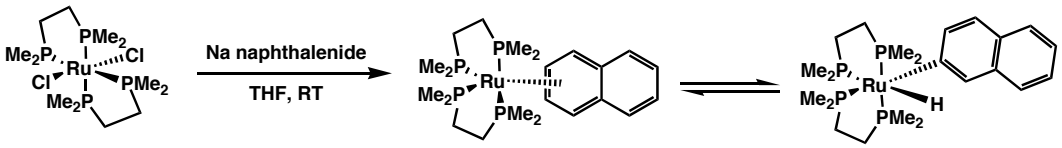
• C-H bonds are ubiquitous in organic compounds. If can be used as functional group similar as C-X bond, it would become a powerful tool for producing C-C bond.

• First example of C-H activation
- C-H bond cleavage in azobenzene by Cp_2Ni complex



Kleiman, Dubeck *JACS* **1963**, *85*, 1544

• Oxidative addition of a C-H bond to Ru(0) complex



Chatt and Davidson *J. Chem Soc.* **1965**, 843
Kakiuchi and Chatani A*dv. Synth. Catal.* **2003**, *345*, 1077

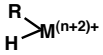
Types of C-H bond Cleavage

• Three main types of C-H bond cleavage based on their mechanism

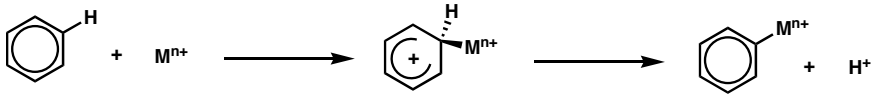
1) "True"Activation

- Processes where an organometallic, i.e. M-C σ-bond is formed as an intermediate or final product. This involves oxidative addition of the C-H bond to low-valent metal center or an electrophilic substitution.

- Promoted by transition metal whose most stable oxidation state differ by $2e^-$

Oxidative addition $RH + M^{n+} \longrightarrow$ 

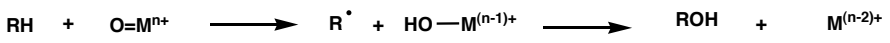
Electrophilic substitution $RH + M^{n+} \longrightarrow R{-}M^{n+} + H^+$



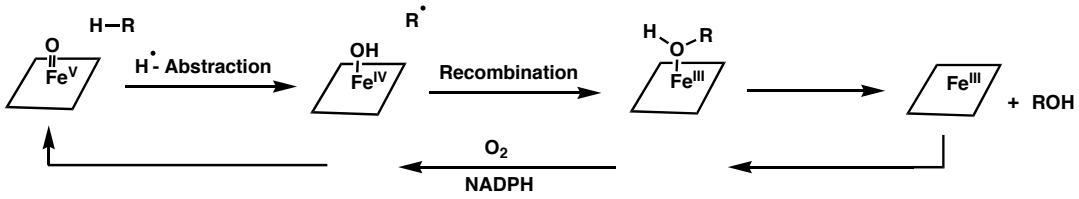
Shul'pin and Shilov *Chem Rev.* **1997**, *97*, 2879

Types of C-H bond Cleavage

2) No direct contact between the metal and the C-H bond, i.e. metal complex cleaves a C-H bond but no σ-C-M bond is directly generated at any stage.
- The metal complex abstracts an e^- or a H atom to form radical ions $RH^{\bullet}$ or $R^{\bullet}$ which interact with other species such as oxygen.
- E.g. Hydroxylation of an alkane by an oxo complex, MnO_4^- and CrO_4^{2-}, not very selective because involves free radicals



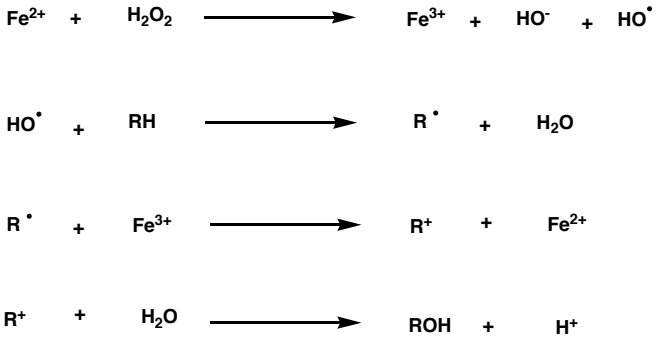
- Nature's preferred route to alkane oxidation using cytochrome P_{450}, believed to proceed through porphyrino-Fe(IV)-O$^{\bullet}$ complex
- High specificity observed in enzymatic system is presumably due to steric restrains
- Plausible mechanism



Shul'pin and Shilov *Chem Rev.* **1997**, *97*, 2879

Types of C-H bond Cleavage

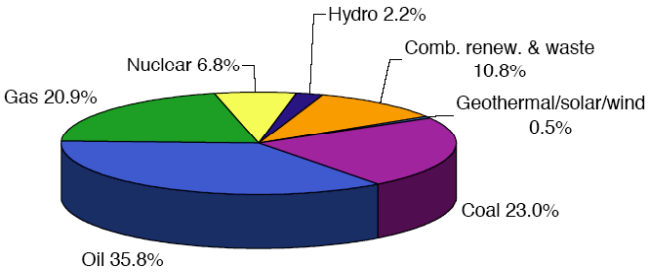
3) When a metal complex promotes the formation of a reactive species which then attacks the C-H bond
- Metal compex activates some other reactants (e.g. O_2 or H_2O_2) to form a reactive species usually a radical, such as hydroxyl radical which then attacks the hydrocarbon independent of any participation of the metal complex.
- E.g. Oxidation of alkanes by Fenton's reagent
- Fenton's reaction is one of the most powerful oxidizing reaction known.



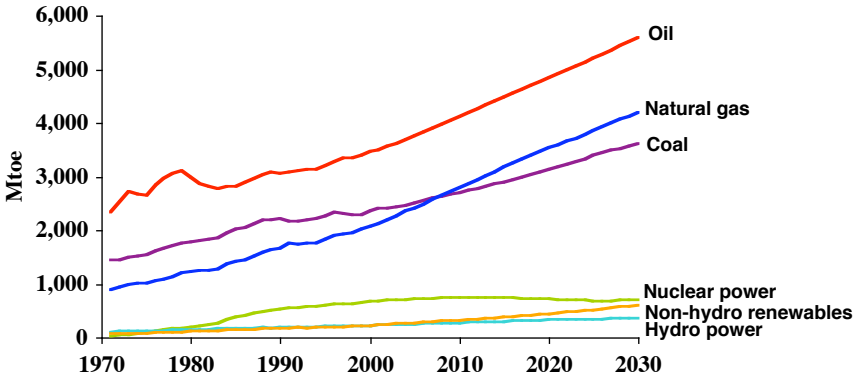
- If reaction is carried to completion, then CO_2 and H_2O are usually obtained

Sen and Remias *J. Mol. Cat. A: Chemical* **2002**, *189*, 33

World Energy Production 2001



- **World primary energy demand**



Courtesy of Jonathan Owen **International Energy Association, 2004**

Natural Gas Transportation is Costly

- CH_4 major constituent of natural gas with 5-10% ethane
- The energy efficiency of natural gas liquefaction and regasification add to the cost of methane production.
- Pipelines are roughly $1M/km to build.

- **Industrial Methane Reforming**

$$CH_{4(g)} + H_2O_{(g)} \xrightarrow{[Ni],\ \Delta} CO_{(g)} + 3\ H_{2(g)} \qquad \Delta H^\circ = 49.3 \text{ kcal/mol}$$

$$CO_{(g)} + 2\ H_{2(g)} \xrightarrow{[Cu/ZnO]} CH_3OH_{(g)} \qquad \Delta H^\circ = -21.7 \text{ kcal/mol}$$

$$nCO + n{+}1\ H_2 \xrightarrow{[M]} C_nH_{2n+2}$$

$$CH_3OH \xrightarrow{[O]} CH_3CO_2H$$

Multistep processes as well as high capital costs make these processes inefficient.

$$CH_{4(g)} + 1/2\ O_{2(g)} \longrightarrow CH_3OH_{(l)} \qquad \Delta H^\circ = -30.7 \text{ kcal/mol}$$

- **Direct and low temperature transformation of methane or other hydrocarbons to their oxygenates (via C-H activation and functionalization) is of considerable interest and remains a challenge to chemists.**

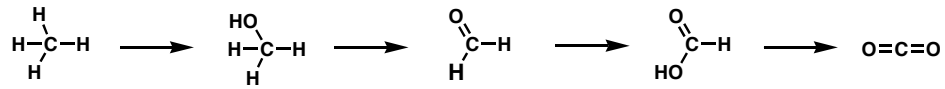
Sen A. *Topics in Organomet. Chem.,* Vol 3, **1999,** 81

Aerobic Methane Oxidation

- Inertness of alkanes - old name "paraffins" - latin name *parum affinis* (without affinity)

- Bergman "Referred to the selective activation of C-H bonds of saturated alkanes as one of the last remaining Holy Grails of synthetic chemistry."

- Main limitation is the high bond energy of C-H bonds, methane (104 Kcal/mol) and benzene (110 Kcal/mol)



104 Kcal/mol 94 Kcal/mol 87 Kcal/mol

- Selectivity is usually low due to overoxidation, intermediates are more reactive than the alkane and high temperature used promotes oxidation of the intermediates

- C–H BDE energies parallel relative reactivity in H-atom abstraction reactions, 3° > 2° > 1°

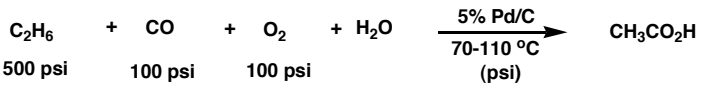
- Low temperature process and metal catalyzed oxidation procedures are desired

- Transition metals whose stable oxidation states differ by $2e^-$ often promote non-radical pathway even in the presence of dioxygen

Sen A. *Topics in Organomet. Chem.,* Vol 3, **1999,** 81
Wolff *ACIE* **1998**, *37,* 33

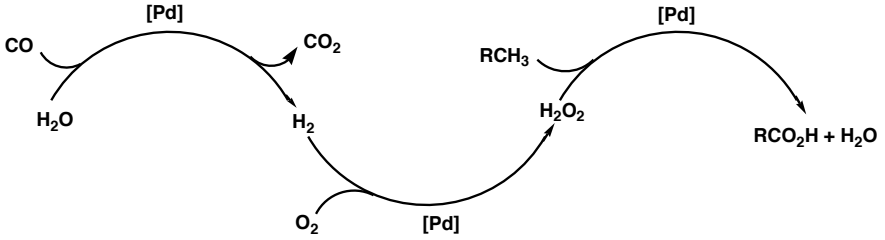
Palladium-Catalyzed Aerobic Oxidation of Alkanes

- Palladium mediated aerobic oxidation of methane to formic acid in the presence of CO
- Also oxidation of ethane to acetic acid
- $CuCl_2$ and TFA as additive - the alcohol and its ester became the major products
- CuCl was detected in the reaction mixture



C_2H_6 (500 psi) + CO (100 psi) + O_2 (100 psi) + H_2O → CH_3CO_2H (5% Pd/C, 70-110 °C (psi))

- Initial step involves water gas shift reaction
- Oxidation of Pd(0) to Pd(II) generates free peroxide oxidant (O_2^{2-} or H_2O_2)
- No oxidation in the absence of CO
- CO can be replaced by H_2
- Slow Pd-catalyzed oxidation of ethane to ethanol, acetic acid and formic acid by H_2O_2 at 30 °C



Sen and Li *JACS* **1992**, *114*, 7307
Sen et.al. *JACS* **1997**, *119*, 6048

C-H Bond Activation of Methane to Methanol

- Highly efficient process with 90% conversion and 81% selectivity into methyl hydrogensulfate in 102% H_2SO_4 at 220 °C

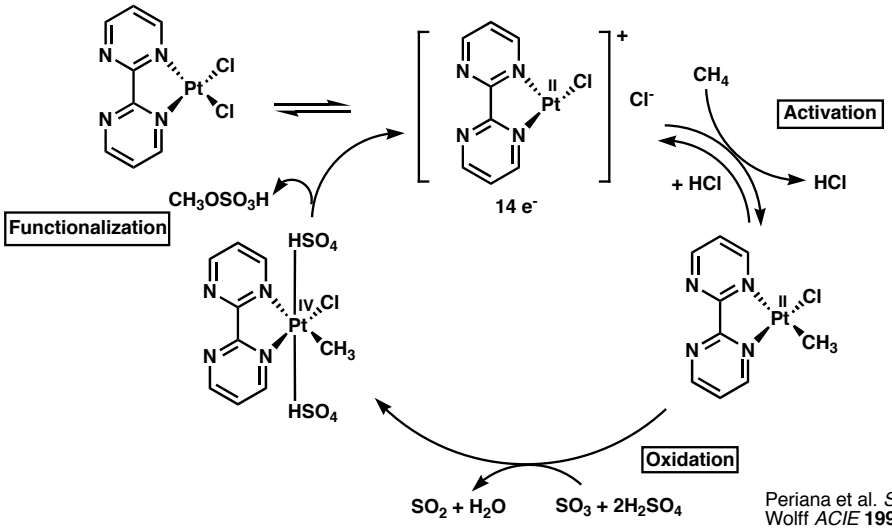
$$CH_4 + H_2SO_4 + SO_3 \xrightarrow{\text{Pt(II) cat}} CH_3OSO_3H + H_2O + SO_2$$

$$CH_3OSO_3H + H_2O \longrightarrow CH_3OH + H_2SO_4$$

$$SO_2 + 1/2O_2 \longrightarrow SO_3$$

$$\text{Net reaction} \quad CH_4 + 1/2O_2 \longrightarrow CH_3OH$$

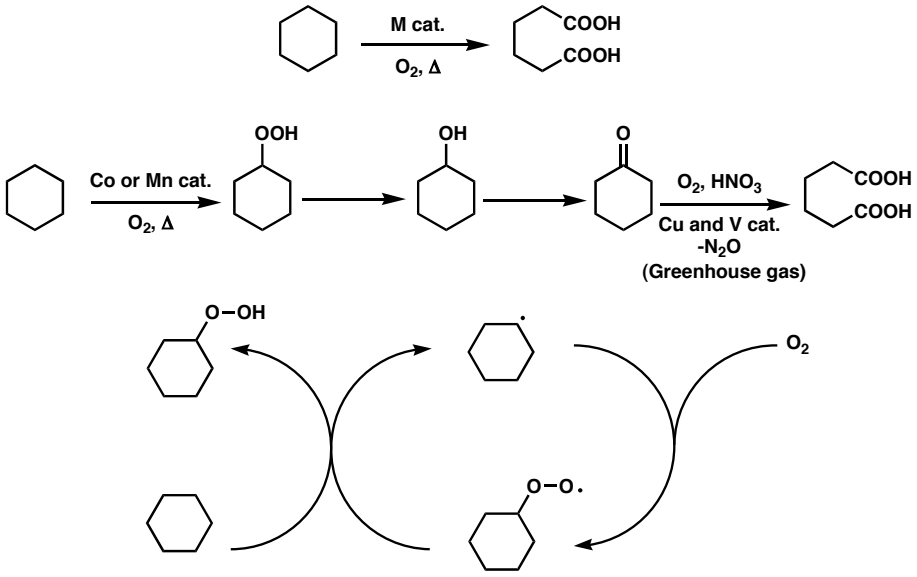
- Reaction mechanism
- Pt complex remains stable for over 50 h at 200 °C in oleum

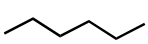


Periana et al. *Science* **1998**, *280*, 560
Wolff *ACIE* **1998**, *37*, 3351

Aerobic Oxidation of Cyclohexane to Adipic Acid

- Adipic acid in the production of nylon 6,6
- ~2.3 million metric tons of adipic acid produced anually worldwide, 42% produced in the US



- What about oxidation of  [O] → Adipic acid ?

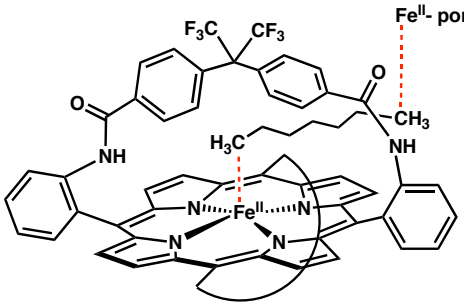
Reimer et. al. *Environmental Progress* **1994**, *9*, 237

The Barton Challege

- Devised by John D. Roberts in honor of the late Derek Barton
- It consists of $5,000 prize for a chemical systems that converts *n*-hexanes to adipic acid with 85% yield based on alkane consumption

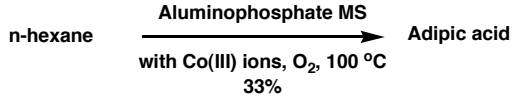
Chem. Eng. News. **1999**, Jan 4, 24

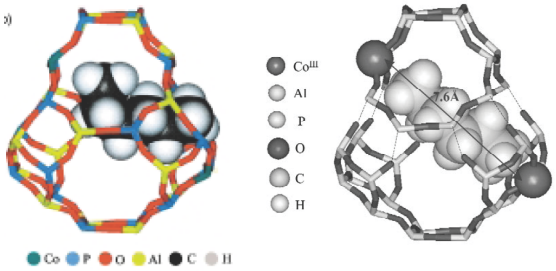
- σ-Complex of Heptane and Fe(II) porphyrin
- C-H bond is an electron pair donor in a 3-center 2e⁻ M-H-C bond referred as an agostic interaction



Reed et. al. *JACS* **1997**, *119*, 7521

- Space selective aerobic oxidation



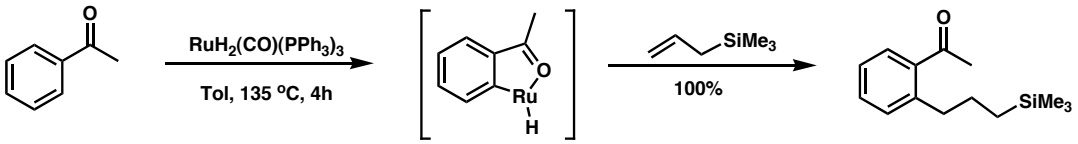


JDR - " The work is very nice, beautifully presented, and represents real progress toward meeting the Barton Challenge"

Chem. Eng. News. **2000**, Jul 3, 7
Thomas J. et. al. *ACIE* **2000**, *39*, 2314
Thomas J. et. al. *Pure Appl. Chem.* **2001**, *7*, 1087

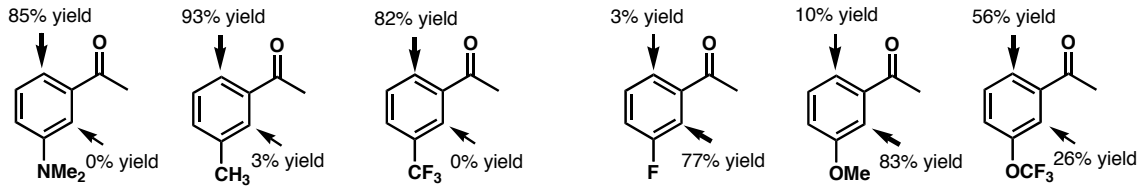
Addition of C-H bond to C=C bonds

- 1993 Murai reported the first highly efficient and selective functionalization of C-H bonds in aromatic ketones with a Ru complex via chelation assistance



- Other directing groups include esters, aldehydes, aldimines, ketimines, amidinates, hydrazones and nitriles
- Reaction tolerant of a variety of functional group, NMe_2, OMe, F, NEt, C(O)Me, CF_3, CO_2Et, CN, acetals

- Regioselectivity is generally controlled by steric factor

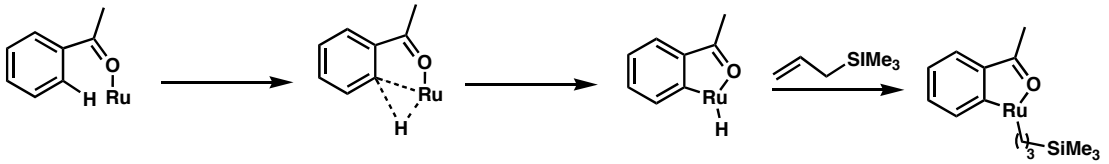


Murai et. al. *Nature* **1993**, *366*, 529
kakiuchi et. al. *Adv. Synth. Catal.* **2003**, *345*, 1077

Addition of C-H bond to C=C bonds

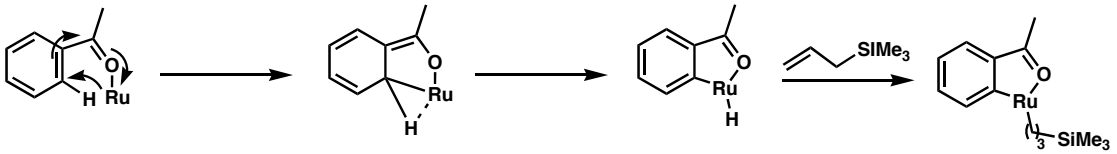
• 2 plausible mechanism of C-H bond cleavage

- Usual oxidative addition: concerted pathway



E_A = 20.1 Kcal/mol

- Unusual oxidative addition: stepwise pathway

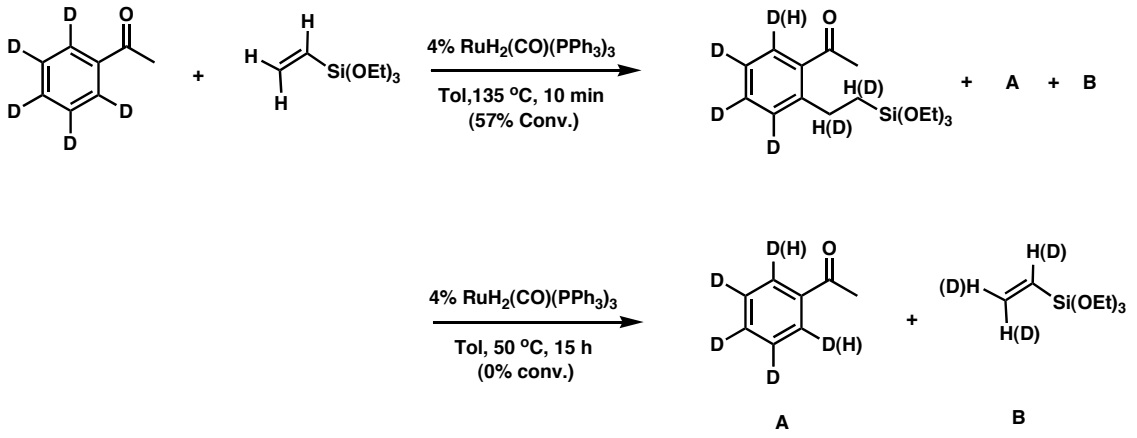


E_A = 1.8-3.0 Kcal/mol

Murai et. al. *Bull Chem Soc. Jpn* **1995**, *68*, 62

Addition of C-H bond to C=C bonds

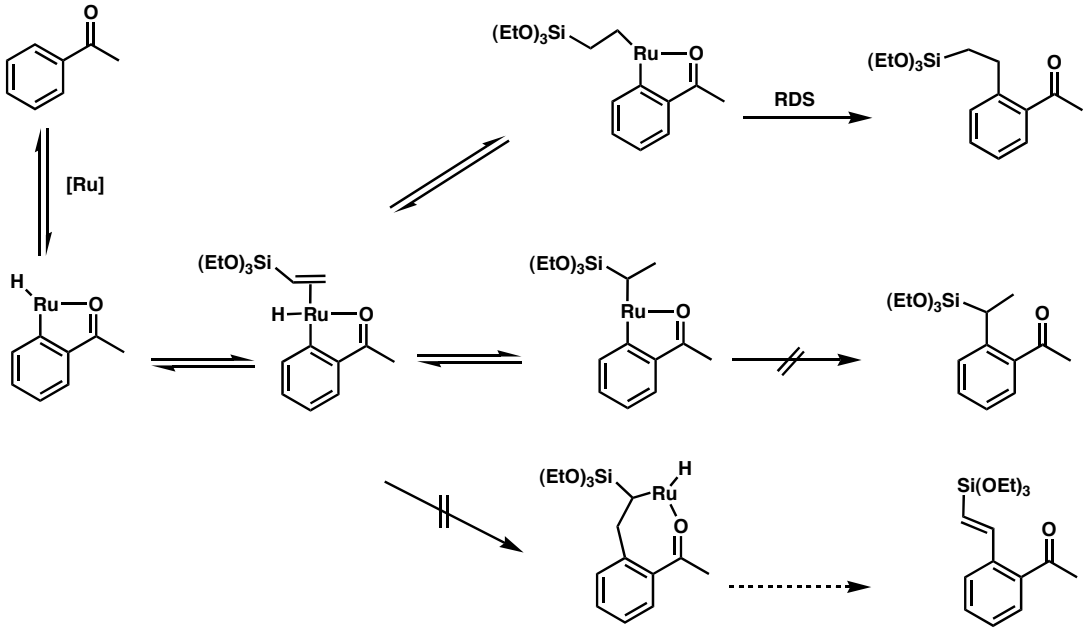
• Deuterium-labeling experiment provides information about the rate determining step
- Higher temperature, complete scrambling D/H 2 *ortho* and 3 olefinic positions
- Lower temperaure, no product formed, some D/H scrambling
- C-H bond cleavage is facile and not rate limiting step
- Chelation of Ru with carbonyl promotes C-H activation



Murai et. al. *Bull Chem Soc. Jpn* **1995**, *68*, 62

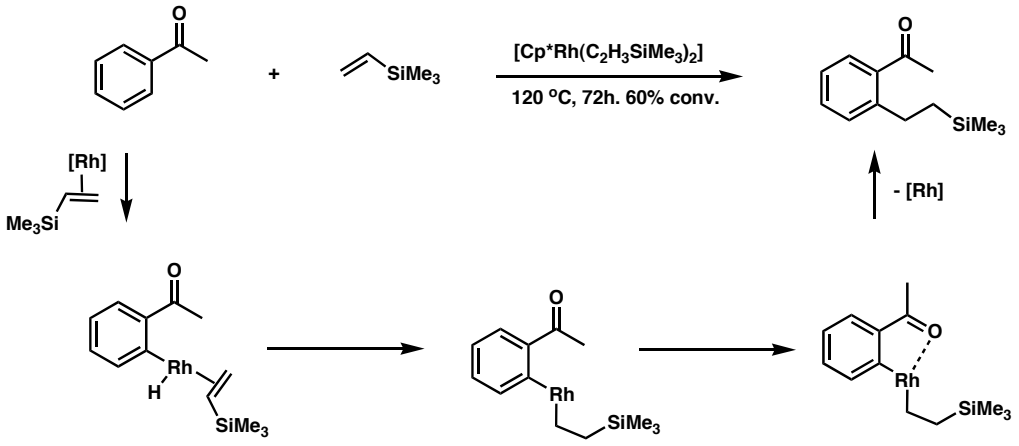
Addition of C-H bond to C=C bonds

- H/D scrambling suggests a rapid equilibrium prior to reductive elimination
- C-H bond cleavage is facile
- reductive elimination is the rate-determining step
- β-Hydride elimination step is fast and reversible



Addition of C-H bond to C=C bonds

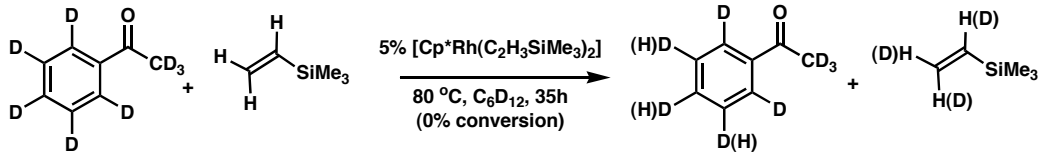
- C-H insertion with Rh complex proceeds without coordination with the carbonyl group
- C-C bond formation occured only at the *ortho* position



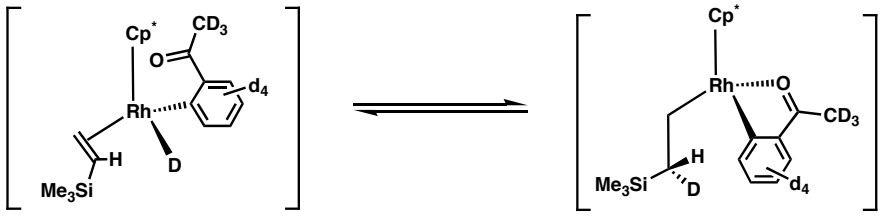
Brookhart and Lenges *JACS* **1999**, *121*, 6616

Addition of C-H bond to C=C bonds

- Deuterium-labeling experiment provides mechanistic information
- H/D exchange occured only at *meta* and *para* positions
- Chelation of Rh with carbonyl not a requirement for C-H activation
- Plausible explanations - activation of the *meta* and *para* C-H bonds followed by olefin insertion is reversible
- Energy barrier for the oxidative addition of the *ortho* C-H is much higher than *meta* or *para*
- Barrier for reductive elimination is apparently reduced by chelation with the carbonyl



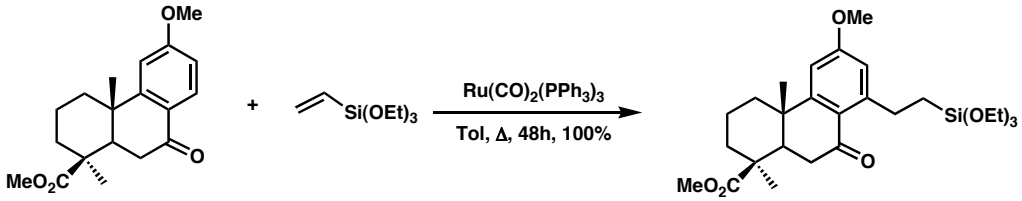
- Oxidative addition/migratory insertion occurs reversibly but a chelate of the carbonyl with Rh renders the methylene hydrogens diastereotopic and therefore the deuterium which migrates to the olefin must, by microscopic reversibility, also return to the Rh in the reverse β-hydride elimination step.



Brookhart and Lenges *JACS* **1999**, *121*, 6616

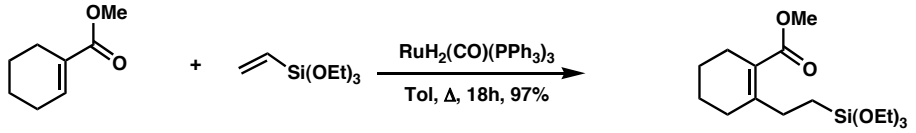
Addition of C-H bond to C=C bonds

- Application to natural product synthesis - diterpenoid analogue



Harris and Woodgate *J. Organomet. Chem.* **1996**, *506*, 339

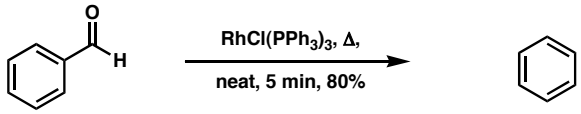
- β-Olefinic C-H of enones also reacts



Trost et. al. *JACS* **1995**, *117*, 5371

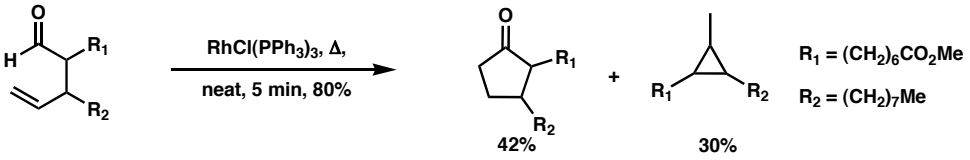
Hydroacylation of aldehydes via C-H Activation

• Hydroacylation of aldehydes
- Tsuji observed that aldehydes are decarbonylated by stoichiometric $RhCl(PPh_3)_3$



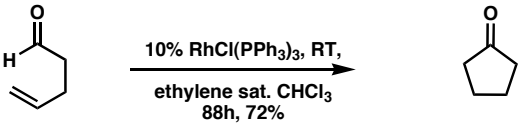
Tsuji *TL* **1965**, 3969

• Sakai discovered intramolecular hydroacylation of enals
- Reaction required stoichiometric amount of Rh complex



Sakai *TL* **1972**, 1287

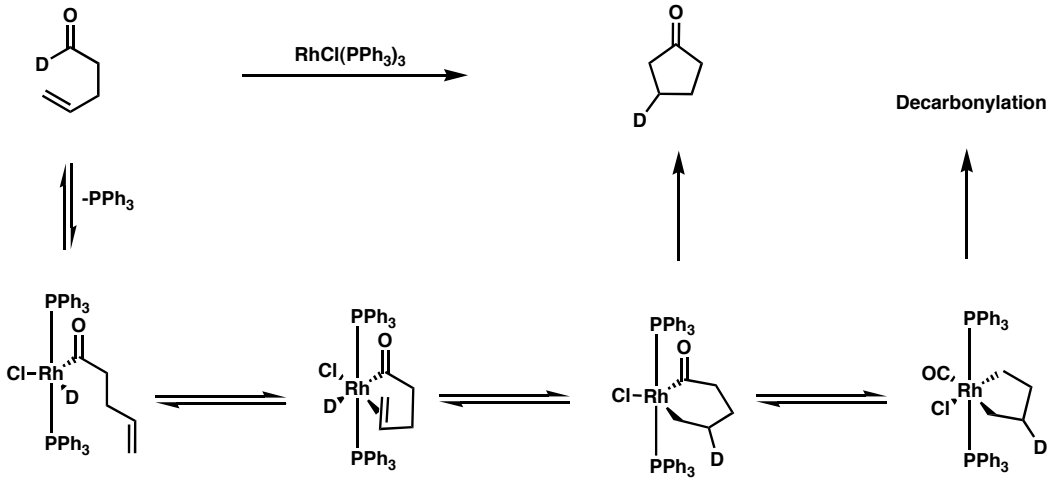
• Miller - discovered first catalytic intramolecular acylation of olefin
- Higher yields are obtained in ethylene saturated chloroform
- Catalyst deactivation may occur by competing decarbonylation, $RhCl(CO)(PPh_3)_2$ isolated



Miller *JACS* **1976**, *98*, 1281

Hydroacylation of aldehydes via C-H Activation

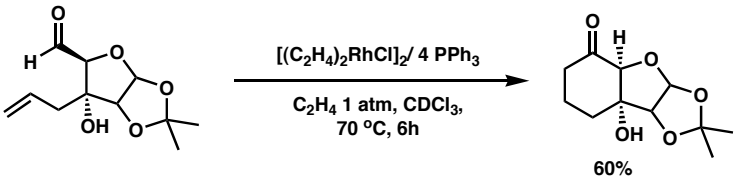
• Mechanism of hydroacylation of aldehydes



Miller *JACS* **1980**, *102*, 5824

Hydroacylation of aldehydes via C-H Activation

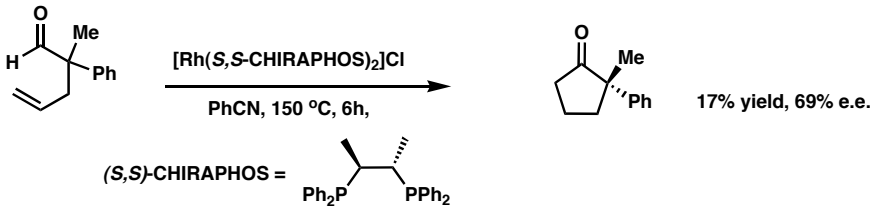
・Application to carbohydrate analogue synthesis



60%

Gable and Benz *TL*, **1991**, 3473

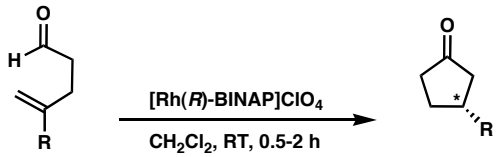
・Resolution of racemic enals
- Attempted decarbonylation of the racemic aldehydes to chiral hydrocarbons gave cyclized product

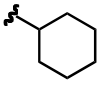
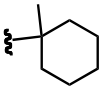


James and Young *Chem. Commun.* **1983**, 1215

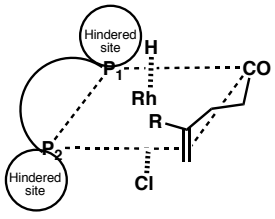
Hydroacylation of aldehydes via C-H Activation

・Asymmetric cyclization of 4-pentenals
- Reaction works better with cationic Rh complex.



R	Yield	e.e.
	90	67
	79	78
	92	92
	86	99
	92	99

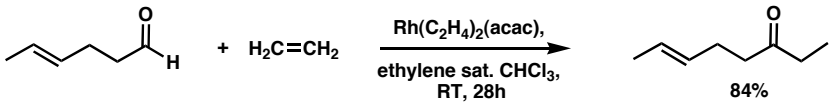
- Steric repulsion between R and H is smaller than R and Cl
- Steric repulsion between R and the phosphine ligands controls the enantiofacial selection



Sakai et. al. *TL* **1992**, *33*, 6331

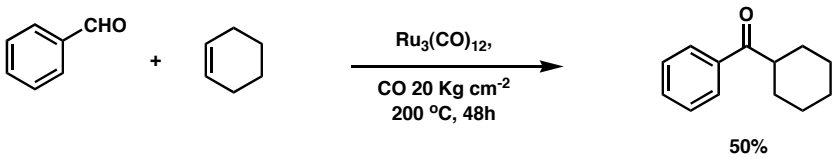
Hydroacylation of aldehydes via C-H Activation

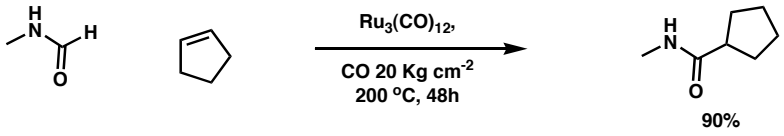
• Intermolecular hydroacylation of olefins
- Intra- and intermolecular reactions depend on the choice of the catalyst used



Miller *J. Organomet. Chem.* **1980**, *192*, 257

• Ru complex also works
- CO atm is used to stabilize the catalyst and suppress decarbonylation



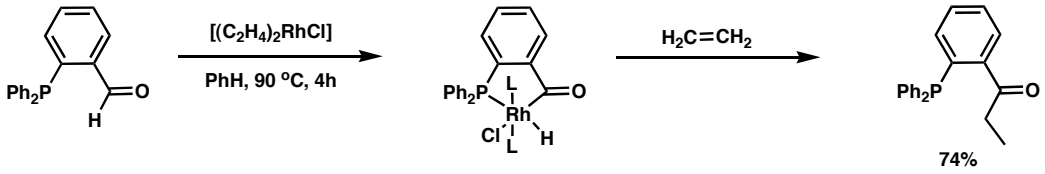


Watanabe *JOC* **1990**, *55*, 1286

Hydroacylation of aldehydes via C-H Activation

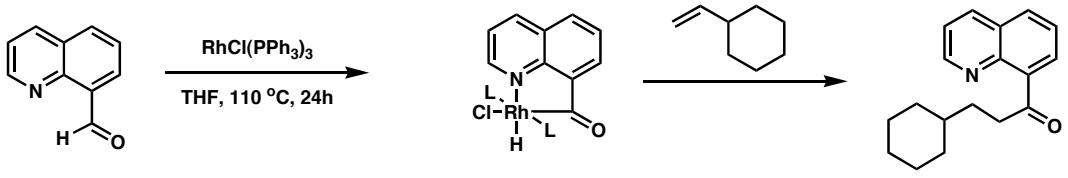
• Intermolecular hydroacylation of olefins not always high yielding due to competing decarbonylation
- High pressure of CO and ethylene are usually used to stabilize the acyl metal hydride complex
- Reaction lack generality due to reaction conditions and limitations of olefins that can be used

• 2-(Diphenyl phosphino) benzaldehyde
- Chelation-assisted C-H activation - requires coordination site to facilitate access of the metal to the C-H bond



Jun et. al. *Bull. Korean Chem. Soc.* **1995,** *16*, 66

- 8-Quinolinecarboxaldehyde

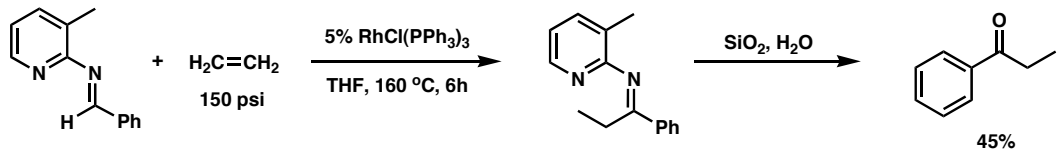


10% Cat. - 32%
Stoichiometric - 78%

Jun et. al. *Bull. Korean Chem. Soc.* **1994,** *15*, 204
Jun et. al. *Chem. Eur. J.* **2002,** *8*, 2423

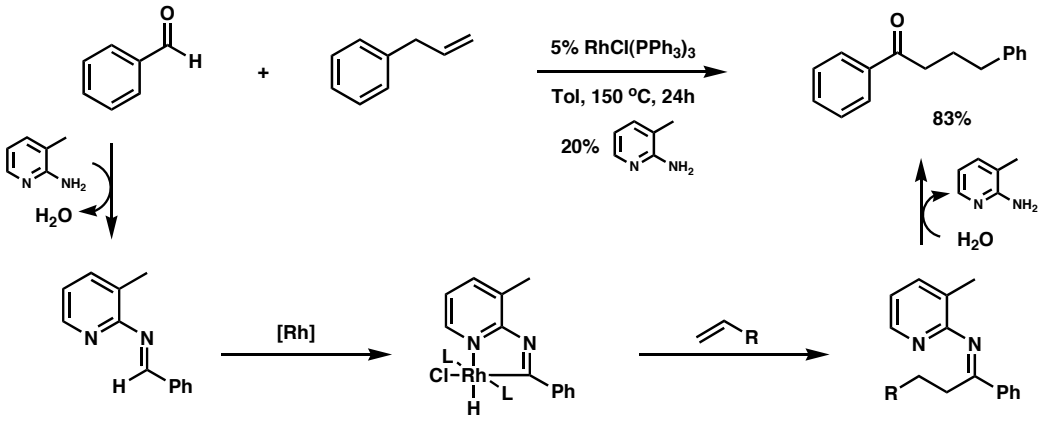
Hydroacylation of aldehydes via C-H Activation

• **Hydroacylation utilizing 2-amino-3-picoline as chelation auxiliary**



Suggs *JACS* **1979**, *101*, 489

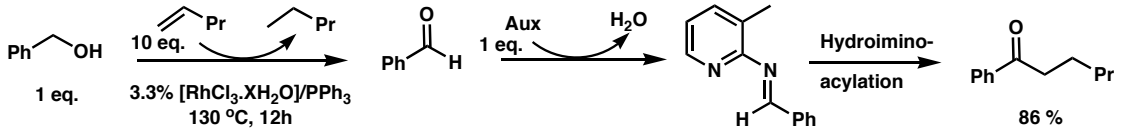
• **2-amino-3-picoline as catalyst**



Jun et. al. *JOC* **1997,** *62*, 1200

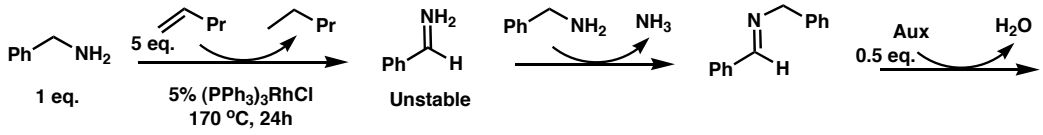
Hydroacylation with 1° Alcohols and Amines

• **Primary alcohols can be oxidized *in situ* to the aldehydes by hydrogen transfer**



Jun et. al. *ACIE* **1998,** *37*, 145

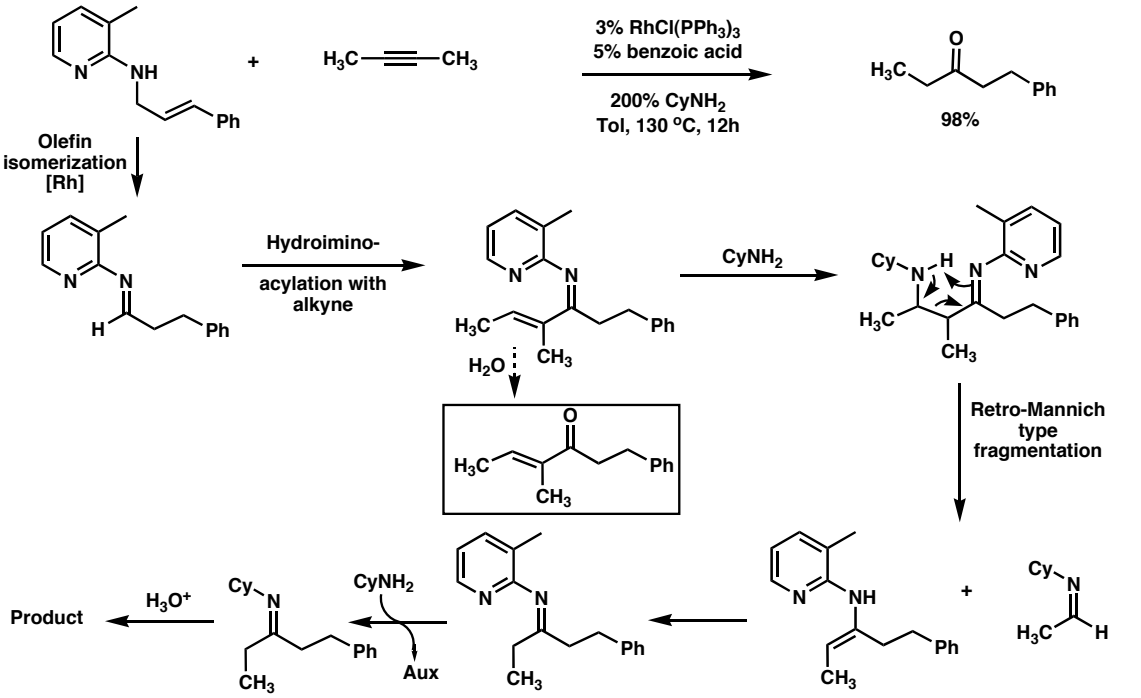
• **Dehydrogenation and transimination of primary amines**



Jun et. al. *Org. lett.* **2001,** *5*, 785

Cleavage of Triple bonds via Hydroiminoacylation

- Hydroacylation of aliphatic aldehydes to dialkyl ketones is problematic presumably due to aldol side reactions
- An alternative is Allyamine derivative of 2-amino-3-picoline which can readily be isomerized by a metal to its aldimine



Jun et. al. *JACS* **2001,** *123*, 8600

Summary

- **Catalytic C-H functionalization is one of the simplest and most powerful methods in organic chemistry**
- **C-H/olefin, C-H/acetylene, C-H/CO/olefin, C-H aldehyde couplings exhibit high selectivity and efficiency and are valuable synthetic tool in organic chemistry**
- **Rapid growth of this research area, but the application to complex molecule synthesis is slow**