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

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Literature Presentation
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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. Hydroiminocyclation

• General references
  - Sen and Remias J. Mol. Cat. A: Chemical 2002, 189, 33
  - 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 Cp₂Ni complex

\[
\text{Cleavage of C-H bond in azobenzene under Cp₂Ni catalyst.}
\]

Kleiman, Dubeck JACS 1963, 85, 1544

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

\[
\text{Oxidative addition of a C-H bond to Ru(0) complex under Na naphthalenide catalysis.}
\]

Chatt and Davidson J. Chem Soc. 1965, 843

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 α-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⁻

\[
\begin{align*}
\text{Oxidative addition} & \quad \text{RH} + M^{n+} \rightarrow R - H^+ + M^{(n+2)+} \\
\text{Electrophilic substitution} & \quad \text{RH} + M^{n+} \rightarrow R - M^{n+} + H^+
\end{align*}
\]

\[
\text{Electrophilic substitution of C-H bond under M^{n+} catalysis.}
\]

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 α-C-M bond is directly generated at any stage.
- The metal complex abstracts an e⁻ or a H atom to form radical ions RH⁺ or R⁻ which interact with other species such as oxygen.
- E.g. Hydroxylation of an alkane by an oxo complex, MnO₄⁻ and CrO₄²⁻; not very selective because involves free radicals

\[
\begin{align*}
\text{RH} + \text{O}_2 & \rightarrow \text{R}^+ + \text{HO}_2^- + \text{ROH} + \text{M}^{(n-2)+} \\
\end{align*}
\]

- Nature's preferred route to alkane oxidation using cytochrome P₄₅₀, believed to proceed through porphyrino-Fe(IV)-O complex
- High specificity observed in enzymatic system is presumably due to steric restraints
- 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 complex activates some other reactants (e.g. O₂ or H₂O₂) 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.

\[
\begin{align*}
\text{Fe}^{2+} + \text{H}_2\text{O}_2 & \rightarrow \text{Fe}^{3+} + \text{HO}^- + \text{HO}^+ \\
\text{HO}^- + \text{RH} & \rightarrow \text{R}^- + \text{H}_2\text{O} \\
\text{R}^- + \text{Fe}^{3+} & \rightarrow \text{R}^+ + \text{Fe}^{2+} \\
\text{R}^+ + \text{H}_2\text{O} & \rightarrow \text{ROH} + \text{H}^+ \\
\end{align*}
\]

- If reaction is carried to completion, then CO₂ and H₂O are usually obtained

Sen and Remias J. Mol. Cat. A: Chemical 2002, 189, 33
World primary energy demand

- $\text{CH}_4$ 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 $1\text{M/km}$ to build.

Industrial Methane Reforming

\[
\text{CH}_4(g) + \text{H}_2\text{O}(g) \xrightarrow{[\text{Ni}], \Delta} \text{CO}(g) + 3 \text{H}_2(g) \quad \Delta H^\circ = 49.3 \text{ kcal/mol}
\]

\[
\text{CO}(g) + 2 \text{H}_2(g) \xrightarrow{[\text{Cu/ZnO}]} \text{CH}_3\text{OH}(g) \quad \Delta H^\circ = -21.7 \text{ kcal/mol}
\]

\[
n\text{CO} + n+1 \text{H}_2 \xrightarrow{[\text{M}]} \text{C}_n\text{H}_{2n+2}
\]

\[
\text{CH}_2\text{OH} \xrightarrow{[\text{O}]} \text{CH}_3\text{CO}_2\text{H}
\]

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

\[
\text{CH}_4(g) + \frac{1}{2} \text{O}_2(g) \xrightarrow{} \text{CH}_3\text{OH}(g) \quad \Delta H^\circ = -30.7 \text{ kcal/mol}
\]

- 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.

**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)

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

- 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 2' 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

- CuCl₂ and TFA as additive - the alcohol and its ester became the major products

- CuCl was detected in the reaction mixture

\[
\begin{align*}
\text{C}_2\text{H}_6 & \quad \text{CO} & \quad \text{O}_2 & \quad \text{H}_2\text{O} & \quad 5\% \text{ Pd/C} \\
500 \text{ psi} & \quad 100 \text{ psi} & \quad 100 \text{ psi} & \quad 70-110 \text{ °C} & \quad \text{CH}_3\text{CO}_2\text{H} \\
& \quad \text{(psi)} & & & \\
\end{align*}
\]

- Initial step involves water gas shift reaction

- Oxidation of Pd(0) to Pd(II) generates free peroxide oxidant (O₂³⁻ or H₂O₂)

- No oxidation in the absence of CO

- CO can be replaced by H₂

- Slow Pd-catalyzed oxidation of ethane to ethanol, acetic acid and formic acid by H₂O₂ 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 hydrosulfate in 102% H₂SO₄ at 220 °C

\[
\begin{align*}
\text{CH}_4 & \quad + \quad \text{H}_2\text{SO}_4 & \quad + \quad \text{SO}_3 & \quad \text{Pt(II) cat} & \quad \rightarrow & \quad \text{CH}_2\text{OSO}_3\text{H} & \quad + \quad \text{H}_2\text{O} & \quad + \quad \text{SO}_2 \\
\text{SO}_2 & \quad + \quad \frac{1}{2}\text{O}_2 & \quad \rightarrow & \quad \text{SO}_3 & \quad + \quad \text{H}_2\text{SO}_4 \\
\text{Net reaction} & \quad \text{CH}_4 & \quad + \quad \frac{1}{2}\text{O}_2 & \quad \rightarrow & \quad \text{CH}_3\text{OH}
\end{align*}
\]

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

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 annually worldwide, 42% produced in the US

\[
\begin{align*}
\text{M cat.} & \quad \text{O}_2, \Delta & \quad \rightarrow & \quad \text{COOH} & \quad \text{COOH} \\
\text{O}_2, \Delta & \quad \rightarrow & \quad \text{OH} & \quad \rightarrow & \quad \text{O} & \quad \text{O}_2, \text{HNO}_3 & \quad \rightarrow & \quad \text{COOH} & \quad \text{COOH} \\
\text{Cu and V cat.} & \quad \text{N}_2\text{O} & \quad \rightarrow & \quad \text{COOH} & \quad \text{COOH} \\
\text{Greenhouse gas}
\end{align*}
\]

- What about oxidation of Adipic acid?

Reimer et. al. Environmental Progress 1994, 9, 237
The Barton Challenge
- Devised by John D. Roberts in honor of the late Derek Barton
- It consists of $5,000 prize for a chemical system that converts n-hexanes to adipic acid with 85% yield based on alkane consumption


- α-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

n-hexane Aluminophosphate MS
with Co(II) ions, O2, 100 ºC
33%

Adipic acid

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

Thomas J. et. al. ACIE 2000, 39, 2314

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

\[
\text{RuH}_2(\text{CO})(\text{PPh}_3)_3 
\quad \text{Tol, 135 ºC, 4h} 
\quad \begin{array}{c}
\text{Ph} \\
\text{SiMe}_3 \\
\end{array} 
\quad \text{100% yield} 
\quad \begin{array}{c}
\text{Ph} \\
\text{SiMe}_3 \\
\end{array} 
\]

- 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

85% yield 93% yield 82% yield 3% yield 10% yield 56% yield

Addition of C-H bond to C=C bonds

- 2 plausible mechanism of C-H bond cleavage
  - Usual oxidative addition: concerted pathway
    \[
    \begin{align*}
    &\text{Ru} &\xrightarrow{E_A = 20.1 \text{ Kcal/mol}} &\text{Ru} &\xrightarrow{\text{SiMe}_3} &\text{Ru} \\
    &\text{Ru} &\xrightarrow{E_A = 1.8-3.0 \text{ Kcal/mol}} &\text{Ru} &\xrightarrow{\text{SiMe}_3} &\text{Ru}
    \end{align*}
    \]
  - Unusual oxidative addition: stepwise pathway


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 temperature, 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

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 occurred only at the ortho position
Addition of C-H bond to C=C bonds

- Deuterium-labeling experiment provides mechanistic information
- H/D exchange occurred 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

\[ \text{[Cp}^*\text{Rh(C}_2\text{H}_5\text{SiMe}_3)_2] \rightarrow \text{[Cp}^*\text{Rh(CH}_2\text{CD}_3]} \]
80 °C, C\(_6\)D\(_{12}\), 35h (0% conversion)

- 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 \(\beta\)-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

\[ \text{OMe} \quad + \quad \text{Me}_3\text{Si} \]
Ru(CO\(_2\))(PPh\(_3\))\(_2\) Tol, \(\Delta\), 48h, 100%


- \(\beta\)-Olefinic C-H of enones also reacts

\[ \text{OMe} \quad + \quad \text{Me}_3\text{Si} \]
RuH\(_2\)(CO)(PPh\(_3\))\(_2\) Tol, \(\Delta\), 18h, 97%

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(PPh₃)₃

  \[
  \text{RhCl(PPh₃)₃, \Delta, neat, 5 min, 80\%} \\
  \text{C₆H₅CHO} \rightarrow \text{C₆H₅CH₂O} \\
  \]

  Tsuji TL 1965, 3969

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

  \[
  \text{RhCl(PPh₃)₃, \Delta, neat, 5 min, 80\%} \\
  \text{H₂C=CH-CO₃Me} \rightarrow \text{C₆H₅CH₂O} \\
  \]

  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)(PPh₃)₂ isolated

  \[
  \text{10\% RhCl(PPh₃)₃, RT, ethylene sat. CHCl₃} \\
  \text{C₆H₅CHO} \rightarrow \text{C₆H₅CH₂O} \\
  \]

  Miller JACS 1976, 98, 1281

Hydroacylation of aldehydes via C-H Activation

- Mechanism of hydroacylation of aldehydes

  \[
  \text{RhCl(PPh₃)₃} \rightarrow \text{C₆H₅CH₂O} \\
  \]

  Miller JACS 1980, 102, 5824
**Hydroacylation of aldehydes via C-H Activation**

- Application to carbohydrate analogue synthesis

\[
\text{[C}_2\text{H}_2\text{RhCl]}_2 / 4 \text{ PPh}_3
\]

\[
\text{C}_2\text{H}_4 \text{ 1 atm, CDCl}_3, 70 \degree \text{C, 6h}
\]

\[
60\%
\]

Gable and Benz TL, 1991, 3473

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

\[
\text{[Rh(S,S-CHIRAPHOS)]Cl}
\]

\[
\text{PhCN, 150 \degree \text{C, 6h}, (S,S)-CHIRAPHOS = Ph}_3\text{P}
\]

\[
\text{Me}
\]

\[
\text{Ph}
\]

\[
17\% \text{ yield, 69\% e.e.}
\]

James and Young Chem. Commun. 1983, 1215

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

\[
\text{[Rh(R)-BINAP]ClO}_4
\]

\[
\text{CH}_2\text{Cl}_2 \text{ RT, 0.5-2 h}
\]

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>e.e.</th>
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<tbody>
<tr>
<td></td>
<td>90</td>
<td>67</td>
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<td>99</td>
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<tr>
<td></td>
<td>92</td>
<td>99</td>
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</tbody>
</table>

- Steric repulsion between R and H is smaller than R and Cl
- Steric repulsion between R and the phospine 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

\[
\text{vinyl} + H_2C=CH_2 \xrightarrow{\text{Rh(C}_2\text{H}_4)_2(\text{acac})_2, \text{ethene sat. CHCl}_3, \text{RT, 28h}} \text{acetyl} \quad 84\%
\]

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

\[
\text{phenylCHO} + \text{cyclohexene} \xrightarrow{\text{Ru}_3(\text{CO})_{12}, \text{CO 20 Kg cm}^{-2}, 200 \degree \text{C}, 48h}} \text{benzophenone} \quad 50\%
\]

\[
\text{aniline} + \text{cyclohexene} \xrightarrow{\text{Ru}_3(\text{CO})_{12}, \text{CO 20 Kg cm}^{-2}, 200 \degree \text{C}, 48h}} \text{anilide} \quad 90\%
\]

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

\[
\text{[C}_2\text{H}_4\text{H}]_2\text{RhCl}] \xrightarrow{\text{PhH, 90} \degree \text{C, 4h}} \text{[C}_2\text{H}_4\text{H}]_2\text{RhCl} \xrightarrow{\text{H}_2\text{C}=\text{CH}_2} \text{acetylene} \quad 74\%
\]


- 8-Quinolinecarboxaldehyde

\[
\text{8-quinolinecarboxaldehyde} \xrightarrow{\text{RhCl}(\text{PPh}_3)_3, \text{THF, 110} \degree \text{C, 24h}} \text{8-quinolinecarboxylate} \quad 10\% \text{ Cat, - 32}\%
\]

10% Cat. - 32%
Stoichiometric - 78%

**Hydroacylation of aldehydes via C-H Activation**

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

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{H}_2\text{C=CH}_2 \\
& \quad \quad \quad \quad \quad \quad \text{150 psi} \\
& \quad \quad \quad \quad \quad \quad \text{THF, 160 °C, 6h} \\
& \quad \quad \quad \quad \quad \quad \text{SiO}_2, \text{H}_2\text{O} \\
\end{align*}
\]

\[
\text{PhCHCH}_2\text{Ph} \quad \xrightarrow{5\% \text{RhCl(PPh}_3)_3} \quad \text{PhCHCH}_2\text{Ph} \quad \xrightarrow{45\%}
\]

Suggs *JACS* 1979, 101, 489

- 2-amino-3-picoline as catalyst

\[
\begin{align*}
\text{PhCHO} & \quad + \quad \text{Ph} & \text{CH} \quad \xrightarrow{5\% \text{RhCl(PPh}_3)_3} \\
& \quad \quad \quad \quad \quad \quad \text{Tol, 150 °C, 24h} \\
& \quad \quad \quad \quad \quad \quad \text{20\%}
\end{align*}
\]


**Hydroacylation with 1° Alcohols and Amines**

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

\[
\begin{align*}
\text{PhCH}_2\text{OH} & \quad \xrightarrow{10 \text{ eq.}} \quad \text{Pr} & \quad \text{Pr} & \quad \xrightarrow{1 \text{ eq.}} \quad \text{H}_2\text{O} \\
& \quad \quad \quad \quad \quad \quad \text{3.3\% [RhCl}_3\text{XH}_2\text{O}]\text{PPh}_3 \\
& \quad \quad \quad \quad \quad \quad \text{130 °C, 12h} \\
\end{align*}
\]

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

- Dehydrogenation and transimination of primary amines

\[
\begin{align*}
\text{PhCH}_2\text{NH}_2 & \quad \xrightarrow{5\% \text{PPh}_3\text{RhCl}} \\
& \quad \quad \quad \quad \quad \quad \text{170 °C, 24h} \\
\end{align*}
\]

**Cleavage of Triple bonds via Hydroiminoacylation**

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

![Chemical reaction diagram]

**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.