Chapter 18: Catalytic C-H Functionalization

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18.1. Overview

**C-H activation:** Catalytic or stoichiometric reactions of transition metal complexes with the unreactive C-H bonds of alkanes, arenes, or alkyl chains to form products containing a new metal-carbon bond. (Fiedel-Crafts reaction or ortho lithiation are not C-H activation.)

**major challenge:**
- selective activation
- catalytic process
- terminal C-H bond functionalization (sec. or tert. C-H: radical approach)
- methane to methanol

**Difficulties**
- The reactions are thermodynamically unfavored in many cases.
- Oxidation by many oxidizing reagents is downhill.

\[
\Delta H = 1.7 \text{ kcal/mol}
\]

\[
R - H + HX \rightarrow RX + H_2 \quad \Delta H = 22 \text{ kcal/mol}
\]

(for \( R = C_6H_{11}, X = OH \))

\[
RCH_2CH_3 \rightarrow RCH + H_2 \quad \Delta H = 30 \text{ kcal/mol}
\]

(for \( R = C_6H_{13} \))

- The products are typically more reactive than the reactants.

**18.2. Oxidations**

Platinum catalyst

Shilov's system

**H-D exchange**

\[ R - H \xrightarrow{K_2PtCl_6, 12 \text{ mol } \%} \text{ DClO}_4, \text{CH}_3\text{CO}_2\text{D, D}_2\text{O} \rightarrow R - \text{D} \]

<table>
<thead>
<tr>
<th>Alkane</th>
<th>Time (h)</th>
<th>D found (%)</th>
<th>Me- (%)</th>
<th>–CH₂- (%)</th>
<th>–CH- (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methane</td>
<td>95</td>
<td>25</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ethane</td>
<td>137</td>
<td>91</td>
<td>91</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Pentane</td>
<td>137</td>
<td>75</td>
<td>92</td>
<td>57</td>
<td>–</td>
</tr>
<tr>
<td>2-Methylbutane</td>
<td>137</td>
<td>69</td>
<td>83</td>
<td>37</td>
<td>9</td>
</tr>
</tbody>
</table>

- primary C-H selective

**functionalization**

\[ \text{H}_2\text{PtCl}_6 \xrightarrow{\text{Cat. Na}_2\text{PtCl}_4, \text{Water}} \text{Cl} \]

\[ 56 : 44 \]

**Periana's improvement**

\[ \text{CH}_4 + 2\text{H}_2\text{SO}_4 \xrightarrow{\text{Cat. (bpym)PtCl}_2} \text{CH}_3\text{OSO}_3\text{H} + 2\text{H}_2\text{O} + \text{SO}_2 \]

\[ \text{TOF} = 10^{-2.5} \text{ s}^{-1} \]

\[ \text{TON} > 500 \]

**remarkable stability**

**EWG:** prevent the further reaction

**cf.** Polyoxometallate \((\text{H}_4\text{PV}_2\text{Mo}_{10}\text{O}_{40})\) can act as a mediator of oxidation by \( \text{O}_2 \).
Directed functionalizations

Role of directing group
- trigger C-H bond cleavage
- regioselective functionalization

<table>
<thead>
<tr>
<th>Catalyst/oxidant</th>
<th>Yield</th>
<th>Syn : ant</th>
</tr>
</thead>
<tbody>
<tr>
<td>16% K$_2$PtCl$_4$/K$_2$PtCl$_6$</td>
<td>21%</td>
<td>5 : 1</td>
</tr>
<tr>
<td>10% K$_2$PtCl$_4$/CuCl$_2$</td>
<td>67</td>
<td>3 : 1</td>
</tr>
<tr>
<td>1% K$_2$PtCl$_4$/5%CuCl$_2$</td>
<td>20</td>
<td>3 : 1</td>
</tr>
</tbody>
</table>

Sames (Shilov's system)

- **Acetoxylation**
  - $\text{MeO} \quad \text{N} \quad \text{MeO}$
  - $\text{Pd(OAc)}_2$

- **Amination**
  - $\text{CH}_3 \quad \text{N} \quad \text{OCH}_3$
  - $\text{Pd(OAc)}_2 (5 \text{ mol } %)$

- **Halogenation**
  - $\text{Bu}^\prime \quad \text{Bu}^\prime$
  - $\text{Pd(OAc)}_2 10 \text{ mol } %$

Mechanistic insight

- **Pd(II)** oxidation
- **Pd(IV)** reductive elimination
- **Pd(III) species** alternatively
  - C-H activation
  - Oxidation
  - Reductive elimination

Backside attack on a palladium methyl

via α-complex

see chapter 6
18.4. Carbonylation of Arenes and Alkanes

oxidative carbonylation

stoichiometric in Pd by Fujiwara

\[
\begin{align*}
\text{Ar-H} & \xrightarrow{\text{Pd(OAc)}_2, \text{H}^+} \text{Ar-Pd-OAc} + \text{CO} + \text{HOAc} \rightarrow \text{Ar-Pd-OAc} + \text{H}^+ \\
\text{Ar-H} & \xrightarrow{\text{Pd(OAc)}_2, \text{H}^+} \text{Ar-Pd-OAc} + \text{CO} + \text{HOAc} \rightarrow \text{Ar-Pd-OAc} + \text{H}^+ \\
\end{align*}
\]

\[\text{ArH:} \text{aromatic} \text{and} \text{heterocyclics}\]

\[\text{sp}^2 \text{C-H} \rightarrow \text{sp}^3 \text{C-H}\]

[Chemical structures and reactions]

Catalytic in Pd

alkylative carbonylation

mainly by Ru

[Chemical structures and reactions]

linear selective

directed reaction

[Chemical structures and reactions]

direct carbonylation to aldehyde

endothermic process (thermal conditions were inefficient)

Photochemical processes partially succeeded the reaction.

\[\begin{align*}
\text{RhCl}(\text{CO})(\text{PMe}_3)_3 \rightarrow \text{CHO} \rightarrow \text{CHO} \rightarrow \text{CHO} \rightarrow \text{CHO} \\
\text{CO} \rightarrow \text{CHO} \rightarrow \text{CHO} \rightarrow \text{CHO} \rightarrow \text{CHO} \\
\text{RhCl}(\text{CO})(\text{PMe}_3)_3 \rightarrow \text{CHO} \rightarrow \text{CHO} \rightarrow \text{CHO} \rightarrow \text{CHO} \\
\end{align*}\]

A radical trap inhibited the formation of the branched aldehyde.

alternative use of isocyanide (weaker multiple bond)

[Chemical structures and reactions]
18.5. Dehydrogenation

Early works by Crabtree and Felkin

Crabtree: Catalyst = [{Ir(PR3)2(η6-2,3-C2H3-4-F-F-C6-H5)}]+ R = Cy or C6H4CF3
35 turnovers with acceptor; 35 turnovers without acceptor in open reflux
Felkin: Catalyst = [(η3-Pr3P)2IrH6], [(η-FC6H4)2P]2IrH6, or [(η3-FC6H4)2P]2RuH4
45–70 turnovers with acceptor

Pincer complex

\[
\text{(PCP)IrH}_2 \xrightarrow{\Delta} \text{trans isomer} \rightarrow 300-900 \text{ turnovers}
\]

Thermally stable complex

Applicable to polymers and amines

Mechanism

Most stable species for PCP cat. (resting state)

Most stable species for POCOP cat. (resting state)

Dehydrogenation cat. + olefin metathesis cat. = alkane metathesis

Schrock's metathesis catalyst:

\[
\text{Schrock's metathesis catalyst:}
\]
18.6. Hydroarylation overview

Murai et al. 1993

**synthesis of lithospermic acid**

- Reaction steps:
  1. 
  2.

- C-H activation

- Mechanism:
  - Reversible
  - Insertion
  - Ortho EWG accelerates the process
  - Resembles to migration process (by calc.)

**Scope**

**DG part:** imine, pyridine, carbonyl, heterocycles

**imine**

**ketone**

**heterocycle**

**pyridine**

**catalyst**

- Ketone DG: RuH_2(CO)(PPh_3)_3, [RuH_2(H_2)(PCy_3)_2], [Cp*Rh(C_2H_5SiMe_3)_2]
- Imine DG: Ru_3(CO)_12, [Rh(PPh_3)_3Cl]
- Pyridine DG: [RhCl(COE)] + PCy_3

**alkynes**

- More likely via electrophilic substitution
without directing group
hydroarylation

oxidative arylation

mechanism

oxidative hydrogen migration
18.7. Functionalization of Alkanes and Arenes with Main Group Reagents

Borylation of Alkanes

Hartwig's landmark reaction

\[ \text{sp}^3 \quad \text{arene} + \text{Bpin}_2 \rightarrow \text{Bpin} + \text{H}_2 \]

\[ \text{sp}^2 \quad \text{arene} + \text{Bpin}_2 \rightarrow \text{Bpin} + \text{H}_2 \]

terminal C-H selective
less hindered position
not at the \( \alpha \) position of heteroatom

Ir catalyzed borylation of arenes

Ir cat. isolated (catalytically active)

Mechanism

Rh cat. isolated (catalytically active)

Ir cat. turnover limiting step

\[ \begin{align*}
\text{Bpin}_2 + 2 \text{H}^+ &\rightarrow 2 \text{Ac} + \text{Bpin} + \text{H}_2 \\
\text{Hexane} &\rightarrow \text{Room temperature}
\end{align*} \]

little electronic preference
controlled by steric effects
complements to electrophilic substitutions

\( \rho \)-orbital on boron assists in the C-H bond cleavage step (chapter 6)

Silylation of C-H bonds

With DG

hydrogen acceptor

without DG

via \( \text{Cp}^*\text{Rh(SiEt}_3)_2 \)

via \( \sigma \)-bond metathesis
18.8. Hydroacylation

**mechanism**

\[
\begin{align*}
\text{Rh cat.} & \quad \text{Cat. } \text{Rh}
\end{align*}
\]

\[
\begin{align*}
\text{Co cat.} & \quad \text{Cat. } \text{Co}
\end{align*}
\]

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

\[
\begin{align*}
\text{directing group} & \quad \text{Cat. } \text{Rh}
\end{align*}
\]

\[
\begin{align*}
\text{imine derivative} & \quad \text{Cat. } \text{Rh}
\end{align*}
\]

18.9. Functionalization of C-H Bonds by Carbene Insertions

- secondary C-H > tertially C-H > primary C-H
- favorable at sites that stabilize a buildup positive charge (favored: $\alpha$ to O, N disfavored: $\alpha$ to ester, OAc)
- aliphatic C-H > aromatic C-H

\[
\begin{align*}
\text{The use of cationic Rh complex containing chelating ligand suppresses poisoning of the catalyst by decarbonylation.}
\end{align*}
\]

\[
\begin{align*}
\text{stable metallacycle}
\end{align*}
\]

\[
\begin{align*}
\text{stable metallacycle} + \text{less favorable de-insertion of an isocyanide}
\end{align*}
\]
Cu catalyst
The first work was conducted with copper complexes.

intramolecular

<table>
<thead>
<tr>
<th>n</th>
<th>H</th>
<th></th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n = 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>n = 2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

intermolecular

$$\begin{align*}
\text{O} + \text{N}_2 & \rightarrow \text{Tp}^- \text{Cu} \rightarrow \text{CO}_2 \text{Et} \\
\text{R} & \rightarrow \text{Tp}^- \text{Cu} \rightarrow \text{CO}_2 \text{Et} \\
\text{R} & \rightarrow \text{Tp}^- \text{Cu} \rightarrow \text{CO}_2 \text{Et}
\end{align*}$$

98% yield

Rh catalyst

intramolecular reaction

asymmetric reaction

$$\text{R}_2 \rightarrow \text{R}_2 + \text{Rh}_2 \rightarrow \text{R}_2$$

For $\text{R} = \text{Br}$:
- $\text{Rh}_2(\text{S-MEPY})_4$: 51% ee
- $\text{Rh}_2(\text{S-MEPY})_4$: 72% ee
- $\text{Rh}_2(\text{N-MEPY})_4$: 91% ee

for total synthesis

$$\begin{align*}
\text{R}_2(\text{S-MEPY})_4 & \rightarrow \text{R}_2(\text{S-MEPY})_4 \\
\text{CH}_2O & \rightarrow \text{CH}_2O
\end{align*}$$

67% yield, 95% ee

(+)-isocorynocephalophytoxin

intermolecular reaction (see Mr. Takasu's lit. seminar (D2))

major problem: self coupling to form olefins

$$\begin{align*}
\text{Ar} & \rightarrow \text{CO}_2 \text{R} \\
\text{Donor} & \rightarrow \text{Acceptor}
\end{align*}$$

$\pi$-Donor-$\pi$-acceptor type carbenoids have moderate reactivity.
It worked well for intermolecular C-H functionalization.

$\alpha$ to heteroatom

$$\begin{align*}
\text{N}_2 & \rightarrow \text{CO}_2 \text{Me} \\
\text{N}_2 & \rightarrow \text{CO}_2 \text{Me}
\end{align*}$$

56-70% yield 50-60% do 85-100% ee

for total synthesis

$$\begin{align*}
\text{OTBS} & \rightarrow \text{OTBS} \\
\text{MeO} & \rightarrow \text{MeO}
\end{align*}$$

18.10. H/D Exchange

Label compounds directly from natural products or synthetic products.