C–H Functionalization in organic synthesis

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Topics in this series of reviews

• History & logic of C-H functionalization
• Recent C-H in total synthesis
• Stereoselectivity
• Enzymatic C–H functionalization
• Metalloporphyrin complex in C–H
• Oxidation and mechanistic study
Topics in this series of reviews

The papers I will focus on:

• alpha-C–H functionalization of ethers and alcohols (page 1937–1949)
• Diastereocontrol in C-H of Methylene group (page 2022-2038)
Classification

• sp2 C–H functionalization
• Activated sp3 C–H functionalization (allyl, benzyl, propargyl and carbonyl; alpha heteroatomic Hydrogen)
• Deactivated sp3 C–H functionalization (beta heteroatomic Hydrogen). Importantly but rarely.
Alpha H Vs. Beta H

• The heteroatom can stabilized the positive charge (radical) at alpha position.

• The inductive effect of oxygen destabilized the positive charge (radical) at beta position.

• Therefore to achieve the C-H activation at beta position, the directing group is usually required.
Alpha H Vs. Beta H

72%
C–H activation reactions at methylene groups

• Insertion of transition metal stabilized carbenes and nitrenes into diastereotopic CH2 groups

• Transition metal catalysed diastereoselective C–H activation reactions
Metal carbenoid insertions

Scheme 1
Asymmetric synthetic method

- Davies and coworkers (page 1857-1869, explain the stereochemistry)

**Chemical Reaction**

```
22 \[\text{Rh}_2(\text{S-DOSP})_4\] \rightarrow 23
```

- Catalyst: \(\text{Rh}_2(\text{S-DOSP})_4\)
- Reaction conditions: hexane, -50 °C, 72h
- Yield: 98%
- ee: 94%

Catalyst will be shown in the next slide.
Typically catalyst loadings of 1 mol% are employed. A recent study has shown, however, that the catalyst is efficient at loadings as low as 0.0001 mol%.
Metal Carbene C–H Functionalization

$\text{L}_n\text{M}$

$\text{N}_2$

$\text{R}^1\text{C} = \text{ML}_n$

$\text{H–C}$

$\text{R}^1\text{C} = \text{C}$

$\text{EWG}$

$\text{EDG}$

$\text{Rh}_2(\text{S-DOSP})_4$

$\text{Rh}_2(\text{R-DOSP})_4$
Reactions

• The first example of a diastereoselective intramolecular carbene insertion into a methylene group was observed as early as 1982 by Wenkert and co-workers.
Iron Carbenoid

\[
\begin{align*}
\text{Fe(CO)\textsubscript{2}Cp} & \quad \text{(CH\textsubscript{3})\textsubscript{3}O\textsuperscript{+}BF\textsubscript{4}\textsuperscript{-}} \\
\text{0-25 °C (CH\textsubscript{2}Cl\textsubscript{2})} & \quad 90-92\% \\
\Rightarrow & \quad \text{rac-39}
\end{align*}
\]
Metal nitrenoid insertions

Scheme 6
There is a question on next slide!
Reactions of Carbamates

Scheme 7

What is the purpose of the MgO?
• Changing the solvent to benzene and heated up to 80 degree led to complete conversion.
Reactions of Sulfamate esters

Reactions of $\alpha,\gamma$-substituted sulfamate esters

$$\text{Reactions of } \alpha,\gamma\text{-substituted sulfamate esters}$$

$$\begin{align*}
\text{ rac-50 } & \xrightarrow{[\text{Rh}_2(\text{oct})_4] \ \text{PhI(OAc)}_2, \text{MgO}} \\
& \quad 40 \degree \text{C (CH}_2\text{Cl}_2) \\
& \quad 51\text{--}91\% \\
\text{ rac-51 }
\end{align*}$$

Reactions of $\beta,\gamma$-substituted sulfamate esters

$$\begin{align*}
\text{Reactions of } \beta,\gamma\text{-substituted sulfamate esters} \\
\text{ rac-52 } & \xrightarrow{[\text{Rh}_2(\text{oct})_4] \ \text{PhI(OAc)}_2, \text{MgO}} \\
& \quad 40 \degree \text{C (CH}_2\text{Cl}_2) \\
& \quad 65\text{--}85\% \\
\text{ rac-53 }
\end{align*}$$

A rough reaction rate scale was drawn: $3^\circ >$ ethereal $\approx$ benzylic $> 2^\circ \gg 1^\circ$. 
Intermolecular nitrene

![Chemical reaction diagram](image)

(16)
Intermolecular nitrene

Tces=1,1,1-trichloroethoxysulfamate

bis[rhodium(α,α,α',α'-tetramethyl-1,3-benzenedipropionic acid)]

![Chemical structures and reaction scheme]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>R</th>
<th>rac-108/rac-109</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rac-107a</td>
<td>COOMe</td>
<td>82 : 18</td>
<td>81</td>
</tr>
<tr>
<td>rac-107b</td>
<td>PO(OEt)_2</td>
<td>&gt; 95 : 5</td>
<td>65</td>
</tr>
<tr>
<td>rac-107c</td>
<td>SO_2Ph</td>
<td>&gt; 95 : 5</td>
<td>56</td>
</tr>
<tr>
<td>rac-107d</td>
<td>NO_2</td>
<td>91 : 9</td>
<td>63</td>
</tr>
<tr>
<td>rac-107e</td>
<td>CN</td>
<td>80 : 20</td>
<td>86</td>
</tr>
<tr>
<td>rac-107f</td>
<td>OAc</td>
<td>86 : 14</td>
<td>40</td>
</tr>
</tbody>
</table>
Directed metal C-H insertions

Scheme 18
Sp3-CH2-activation

- Sanford

\[ \text{rac-110a} \quad R = \text{OMe} \]
\[ \text{rac-110b} \quad R = \text{OH} \]

\[
\begin{align*}
\text{[Pd(OAc)\textsubscript{2}]} \\
\text{Phl(OAc)\textsubscript{2}} \\
80 \degree \text{C} (\text{AcOH}/\text{Ac}_2\text{O} 1:1) \\
81\% \ (111\text{a}) \\
41\% \ (111\text{b}) \\
\end{align*}
\]
Sp3-CH2-activation

Mn(OAc)$_2$ is responsible for the reaction rate acceleration. It is oxidised in the reaction mixture to Mn$_3$O(OAc)$_7$ which is Lewis-acidic and presumably lowers the barrier for C–H insertion by enhancing the electrophilicity of the palladium species.

- Corey

\[
\begin{align*}
\text{[Pd(OAc)$_2$]} & \rightarrow \text{Mn(OAc)$_2$} \\
\text{Oxone} & \rightarrow \text{Ac$_2$O} \\
80 \degree \text{C (CH$_3$NO$_2$)} & \rightarrow \\
\rightarrow & \text{51-63%} \\
R^1 = \text{Me, 51\%, d.r. = 83:17} \\
R^1 = \text{Et, 56\%, d.r. = 89:11} \\
R^1 = \text{Ph, 63\%, d.r. = 100:0} \\
potassium \text{ peroxymonosulfate, KHSO}_5
\end{align*}
\]
Sp3-CH2-activation

• Yu

\[
\text{Me} \quad \text{Me} \quad \text{Me} \\
\text{Me} \quad \text{Oxa} \\
\text{116}
\]

\[
\text{Me} \quad \text{Oxa} \\
\text{117}
\]

\[
\text{Me} \quad \text{Oxa} \\
\text{118}
\]

\[
\text{Me} \quad \text{Oxa} \\
\text{119}
\]
Sp3-CH2-activation

- Murai
Sp3-CH2-activation

- Murai

\[
\text{N}
\]
\[
\text{N} \quad \text{Py}
\]

\[
\begin{align*}
\text{[Ru}_3\text{(CO)}_{12}] & \quad \text{CH}_2=\text{CH}_2 \\
& \quad 140 \degree \text{C} (\text{'PrOH}) \\
& \quad 75\%
\end{align*}
\]

\[
\text{N}
\]
\[
\text{N} \quad \text{Py}
\]

\[
\begin{align*}
\text{Ph-}
\text{N} & \quad \text{N} \\
\text{Ph} & \quad \text{N} \\
& \quad \text{N} \\
& \quad \text{N}
\end{align*}
\]
\[
\begin{align*}
\text{O} & \quad \text{B} & \quad \text{O} \\
\text{O} & \quad \text{B} & \quad \text{O}
\end{align*}
\]

\[
\begin{align*}
\text{[Ru}_3\text{(CO)}_{12}] & \quad \text{tBuCOMe} \\
& \quad 150 \degree \text{C neat} \\
& \quad 70\%
\end{align*}
\]

\[
\text{Ph} \quad \text{N}
\]
\[
\text{N} \quad \text{Ph}
\]

\[
rac-124
\]
\[
rac-125 \quad \text{d.r.} = 80:20
\]
Summary

- Directing group

Sanford  Corey  Yu  Murai
alpha-C–H functionalization of ethers and alcohols

- Radical-mediated C-H functionalization
- Metal mediated carbenoid insertion
- Cross-dehydrogenative coupling (CDC)
- Intramolecular annulation
- Transfer hydrogenative coupling (THC)
- Transition metal-catalyzed coupling
Radical-mediated addition and elimination

\[ R\text{-C}=-\text{C SO}_2\text{CF}_3 (1) \]
\[ R = \text{alkyl or aryl} \]

AIBN or hv
59-92 %

- \text{HCF}_3 \rightarrow \cdot \text{CF}_3

- \text{SO}_2 \rightarrow \cdot \text{SO}_2\text{CF}_3

\begin{align*}
\text{A} & \quad \text{B} \\
\text{C} & \quad \text{D}
\end{align*}

AIBN
2,2'-azo bisisobutyronitrile
Metal mediated carbenoid insertion

- Stereoselective method
Brook rearrangement

\[
\begin{align*}
\text{O} & \quad \text{Li} \\
R & \quad \text{SiMe}_3 \quad \text{R} \quad \text{Li} \quad \text{R}'
\end{align*}
\]

\[
\begin{align*}
\text{R} & \quad \text{SiMe}_3 \\
\text{R}' & \quad \text{R}'
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{Li} \\
\text{R} & \quad \text{R}'
\end{align*}
\]

\[\text{pentacordinate silicon intermediate}\]

\[
\begin{align*}
\text{Me}_3\text{Si} & \quad \text{O} \\
\text{R} & \quad \text{R}' \quad \text{Li}
\end{align*}
\]
Oxidative CDC reaction of ether with carbonyl compounds

Scheme 16  Single-electron transfer mechanism for oxidative CDC reaction of ether with ketone.
Intramolecular annihilation of ether via 1,5-hydride migration

Scheme 18 Intramolecular annihilation process of ether with C=C moiety via 1,5-H migration.
Transfer hydrogenative coupling (THC) of alcohols with alkene and alkyne

Scheme 25 General process of THC reactions of alcohol with unsaturated species.

Feel familiar?
Transition metal-catalyzed coupling of alcohols with alkenes via C–H insertion

\[
\begin{align*}
89 & \quad \text{up to 78\% yield} \\
{\text{eq. 1}} & \\
\text{RhCl(PPh}_3\text{)}_3 & \quad (\text{cat.}) \\
\text{BF}_3\cdot \text{OEt}_2, \text{ n-BuBr} & \\
88 & \\
R^1 & \quad \text{or} \quad R^2 & \\
\text{eq. 2} & \\
Pd(\text{OTFA})_2 & \quad (\text{cat.})/\text{PPh}_3 \\
\text{BF}_3\cdot \text{OEt}_2, \text{ CH}_3\text{NO}_2 & \\
90 & \\
88 & + \\
R^2 & \quad \text{or} \quad R^1 \\
\text{eq. 3} & \\
\text{RuCl}_2(PPh}_3\text{)}_3 & \quad (\text{cat.}) \\
\text{BF}_3\cdot \text{OEt}_2, \text{ DCE} & \\
92 & \\
OH & \\
93 & \quad \text{up to 98\% yield} \\
\text{syn:anti} & \quad >99:1 \\
\text{eq. 4} & \\
\text{FeCl}_3 & \quad (\text{cat.}) \\
\text{DCE} & \\
94 & \\
95 & \quad \text{up to 93\% yield} \\
R & \quad \text{alkyl} ; \quad R^1, R^2 & \quad \text{aryl, alkyl}
\end{align*}
\]
Scheme 30  Mechanism of RhCl(PPh$_3$)$_3$/BF$_3$·OEt$_2$-copromoted coupling of alcohol with alkene.
### Summary for the second half

<table>
<thead>
<tr>
<th>Type</th>
<th>Radical</th>
<th>Carbene</th>
<th>CDC</th>
<th>Annulation</th>
<th>THC</th>
<th>T. S. Metal coupling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good at making</td>
<td>Sub-furan</td>
<td>2°, 3° ether</td>
<td>Conbonyl Beta-H</td>
<td>Pyran like</td>
<td>1,3 diol 2° alcohol</td>
<td>2° alcohol</td>
</tr>
<tr>
<td>Catalyst</td>
<td>Rh (Davies)</td>
<td>DDQ, In, Cu, Fe</td>
<td>BF3, Sc(oTf)3, LA</td>
<td>Ru, Ir</td>
<td></td>
<td>Rh, Ru, Pd, Fe</td>
</tr>
<tr>
<td>Difference</td>
<td>Radical</td>
<td>diazo</td>
<td>Dehydrogenative (oxidation)</td>
<td>Migration</td>
<td>Hydrogenative (reduction)</td>
<td>Radical</td>
</tr>
</tbody>
</table>