Carbene and C-H Functionalization

1954, Doering demonstrated the synthetic utility of dihalogencarbenes:

\[
\text{Cyclopropane} + \text{HCX}_3 \xrightarrow{\text{KOH} \cdot \text{Bu}} \xrightarrow{\text{Na}} \xrightarrow{\text{X}} \text{Carbene}
\]

\[X = \text{Cl, Br.}\]

*J. Am. Chem. Soc. 1954, 76, 6162*

1.2 Electronic configuration and geometry at ground state:

Diradical \[\theta^1 > \theta^2\] vs. Ambiphilic: paired electrons - nucleophilic empty orbital - electrophilic

triplet vs. singlet

Note: the linear geometry is an extreme case.

The ground-state spin multiplicity is a fundamental feature of carbenes that dictates their reactivity.

General considerations to classify a singlet or a triplet carbene:

a. **The energy gap between \(P_\pi\) and \(\sigma\) orbital.**

If the gap is big enough to overcome the electron repulsion between two paired electrons, then the carbene species is singlet state favored.

b. **The steric hindrance of the substituents.**

With bulky groups broadening the angle \(\theta\), the geometry is more linear than bent, thus, a triplet ground state is favored.

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Generating carbyne equivalents with photoredox catalysis

This presentation will cover: carbene, carbenoid and C-H bond insertion with carbene or carbenoid.

1. **Carbene**: is a species containing a neutral carbon atom with only six valence electrons: two associated with the two \(\sigma\)-bonds extending from the central carbon and two nonbonding electrons.

1.1 A brief history:

First discovered in 1855 by **Geuther** and **Hermann**:

\[\text{CHCl}_3 + \cdot \text{OH} \rightarrow \text{[:CCl]_2} + \text{Cl}^- + \text{H}_2\text{O}\]

*Liebig's Ann. Chem. 1855, 95, 211*

1897, **Nef** proposed the same intermediate for **Ciamician-Dennstedt Rearrangement**:

\[\text{PyH} + \text{HCl} \rightarrow \text{[:CCl]_2} \rightarrow \text{PyHCl} \rightarrow \text{PyCl}\]

*Ann. 1897, 298, 202*

\(\alpha\)-chloropyridine in chloroform [3]. They both showed a lot of intuition and courage for their postulations considering that most chemists did not even believe in the existence of free radicals at that time. Indeed, it was only 3 years later that Gomberg character-
1.3 Reactivity of free carbenes:

Cyclopropanation, dimerization, ylide formation, X-H bond insertion, etc. Generally, for singlet carbene, usually a concerted mechanism, however, for triplet carbenes, usually nonstereospecific results were obtained (diradical stepwise mechanism).

Free carbenes: great reactivity but poor selectivity.

The way to modify the reactivity and the selectivity of carbene is to combine carbene with a metal, consequently gives a vague concept for a species in which all carbon atoms are tetravalent but still has the properties of carbene.

1.4 Metal-carbene Complexes:

Typically carbenoid is formed from diazo compounds. The reactivity can be modified by the metal itself, the diazo compounds and the ligands associated with the metal center.

a. Different Transition metals give different types of carbenes.

Fischer carbene complex

- Formed by a singlet free carbene and a late TM with a low oxidation state (a low energy d orbital).
- Electrophilic carbene

Schrock carbene complex

- Formed by a triplet free carbene and a early or middle TM (Group 3 to 6) with a high oxidation state (a high energy d orbital).
- Nucleophilic carbene
b. The influence of the diazo compounds.

Appropriate electrophilicity at the carbene carbon center is crucial in metal-carbene reactions.

Increased stability & selectivity

Increased reactivity

R = H, alkyl, aryl

EWG = CO₂R, CONR₂, COR

Theoretically, in a two-electron pathway, in order to activate a C-H bond, an empty orbital (close in energy to the low energy C-H σ orbital) is needed to receive the electron donation from the C-H σ orbital. In turn, suitable filled orbital to backdonate electrons to the C-H σ* orbital.

2.1 General introduction of C-H functionalization

C-H            C-X

a. For a TM reacts directly with a C-H bond:

The energy of C-H σ orbital is at very low level, it's not easy to find a suitable TM to match the energy. (3d with 2p?)

b. For a free carbene interacting with a C-H bond:

The frontier orbitals of carbene carbon center and the C-H bond were both 2p or 2p-hybridized orbitals, which matched perfectly with each other at energy level. Besides, their frontier orbitals were also symmetrically matched, offering them possibility to get a very good overlap.

b. The influence of the ligands.

The ligands can influence the metal center both electronically and sterically.

Electronically

Since some of the ligands could also interact with the dₓ orbitals, enhance or decrease the electron density, in some cases lowering the energy of the dₓ orbital. In this way, the electrophilicity of the carbene center can be modified.

Sterically

Bulky ligands can improve both the stability and the selectivity of the species. In another aspects, introduce chiral ligands to the metal center could creat a chiral environment for TM mediated/catalyzed carbene reactions.
c. For a TM carbene interacting with a C-H bond:

According to those electronic configurations, traditional C-H 'activation', free carbenes and also the TM carbene complexes seem to be capable to interact with C-H bonds.

d. The difference of TM carbene insertion & traditional C-H activation.

In the C-H insertion reaction, TM was mainly used to decompose the diazo compound and form a electrophilic carbene species.

Electron rich, low valent late TM (eg. Re, Fe, Ru, Os, Rh, Ir, Pt, etc.) has close interaction with the targeted C-H bond during the C-H 'activation' through oxidative addition.

2.2 C-H functionalization by free carbene insertion

a. Singlet carbene

For a singlet free carbene, the C-H insertion process as a concerted mechanism:

\[ \begin{array}{c}
\text{H} + \text{H} \\
\text{diradical}
\end{array} \rightarrow \begin{array}{c}
\text{H} + \text{radical} \\
\text{radical}
\end{array} \rightarrow \text{product} \]

usually stereochemistry retention

b. Triplet carbene

For a triplet free carbene, the C-H insertion process as a stepwise mechanism. Due to their diradical nature, triplet carbenes are expected to be much more reactive than their singlet analogues. Triplet carbenes generally have half-lives in the ps or ms ranges and are able to react with many compounds that are often considered inert.

Chem. Rev. 2000, 100, 39
J. Am. Chem. Soc. 1993, 115, 10237

Example:

\[ \text{Ph}_{2}N_{2} \rightarrow [\text{Ph}_{2}N] \rightarrow \text{PhCH}_{2} + \text{Ph} \]

Note: Usually triplet carbenes can be obtained from photolysis of diazo compounds. Singlet carbenes can be obtained from thermolysis of diazo compounds.

Nature 2008, 451, 417
J. Am. Chem. Soc. 1969, 91, 4549
2.3 C-H functionalization by TM carbene insertion.

2.3.1 History (mostly is about Cu and Rh)

1952, Yates applied Cu to decompose the diazoketones for the X-H bond insertion. He suggested 'Cu-carbene complex' formation, but Cu only help release N₂ to generate 'free carbenes'.

\[
\text{R}^1\text{NH}_2 \quad \text{R}^1\text{OH} \quad \text{R}^1\text{SH} \quad \text{R}^1\text{H}
\]

1973, Ledon used the term 'carbenoid' for Cu catalyzed C-H bond insertion reaction, but suggests Cu was the diazo compound activating reagent.

1985, Taber reported Rh₂(OAc)₄ catalyzed enantioselective carbenoid insertion for the synthesis of (+)-α-cuparenone.

1990, Ikegami developed the chiral Rh carboxylate catalysts.

1991, Doyle developed the chiral Rh carboxamide catalysts.

These are stereochemistry retention reactions.

These are intramolecular enantioselective reactions.
1997, Davies and Hansen reported the intermolecular carbene insertion into C(sp3)−H catalyzed by chiral Rh carboxylate with good to excellent enantioselective control

\[
\begin{align*}
\text{Ar} = & p-C_{12}H_{25} \\
\text{(S)-B1} & \\
\end{align*}
\]

\[(S)\text{ B1} \quad \text{(0.9 mol %)} \quad \Delta \quad \text{Rh carboxylates} \quad \text{(S)-B1 gives (R)-product.}
\]

This is the intermolecular enantioselective reaction.

Davies (1997) & Nakamura (2002) were the first to do important contributions to the understanding of the reaction mechanism. Generally believed to occur through concerted (though asynchronous), three-centered transition state.

Later, a lot of chiral ligands was developed...

Rh(II) carboxylates

\[
\begin{align*}
\text{Rh(II) carboxylates} & \\
\text{Davies, 1997} \quad \text{Jacs 1997, 119, 9075} \\
\end{align*}
\]

- Very active at decomposing diazo compounds
- Optimal for intermolecular C-H insertion reactions
- Later generations possess rigid bridged structure

Rh(II) carboxamides

\[
\begin{align*}
\text{Rh(II) carboxamides} & \\
\text{Doyle, 1986} \quad \text{Inorg. Chem. 1986, 25, 260} \\
\end{align*}
\]

- Generally much more rigid than Rh carboxylates
- Optimal for intramolecular C-H insertion reactions

Schiff Base-type ligand

\[
\begin{align*}
\text{Cu, Müller, 2002} \quad \text{Helv. Chim. Acta 2002, 85, 483} \\
\end{align*}
\]

Salen-type ligand

\[
\begin{align*}
\text{TM Porphyrin} \quad \text{Che, 2008} \\
\text{TM = Ir, Jacs 2009, 131, 14218} \\
\end{align*}
\]

R* = chiral group

Rh, Angew. 2008, 47, 9747
Ir, CC 2012, 48, 4299
2.3.2 General Trends in Carbenoid C-H Activation Chemistry

Facile C–H insertion at activated sites positive charge buildup at insertion site stabilized when R = N, O, aryl, vinyl. And an EWG adjacent to the C-H bond will deactivate it.

- intramolecular C-H insertion > intermolecular C-H insertion
- 5-membered ring formation > other size ring formation
- \(3^\circ\) C-H > \(2^\circ\) C-H > \(1^\circ\) C-H when sterically accessible

2.3.3 Ligand Effect

**b.** With electron deficient group substituted ligands (*the electronic effect*) will increase the electrophilicity of the TM center, which will lead to a very reactive TM carbenoid favors the entropically less demanding pathway.

**Example:**

```
$\text{EDA} \quad \text{EWG}$
```

$\begin{align*}
\text{EDA} & = \text{electronic donor atom} \\
\text{EWG} & = \text{electronic wither group} \\
\end{align*}$

**Note:**
- acam: acetamide
- TPA: triphenylacetate
- Piv: pivalate
- Bu₃CO₂H
- BzO: benzoic acid
- TPA: OCOCPh₃

**Catalyst**

- \([\text{Rh}_2(\text{OAc})_4]\)
- \([\text{Rh}_2(\text{TFA})_4]\)
- \([\text{Rh}_2(\text{acam})_4]\)
- \([\text{Rh}_2(\text{Piv})_4]\)
- \([\text{Rh}_2(\text{OBz})_4]\)
- \([\text{Rh}_2(\text{OCOCPh}_2)_4]\)
- \([\text{Rh}_2(\text{OCOCMePh}_2)_4]\)
- \([\text{Rh}_2(\text{TPA})_4]\)

**Ratio.**

- 37 : 63
- 56 : 44
- 14 : 86
- 37 : 63
- 54 : 46
- 64 : 36
- 82 : 18
- 96 : 4


**Nature 2008, 451, 417**

**Steric** as well as **electronic** factors and the chemical properties of the diazo compound, the steric, electronic properties of the ligands around the metal center also the metal itself will determine significantly the type of insertion performed by the carbenoid intermediate. In general, the reactivity and selectivity is a balance between electronic and steric control.
2.3.4 Influence from diazo compound

a. **Electronically** deficient diazo compounds were highly reactive towards transition metal compounds, generating electrophilic carbene carbon center. Reactivity trend is as the followed order:

\[
\text{RO}_2 N_2 > \text{RO}_2 C=\text{N} \sim \text{RO}_2 C=\text{CPh} > \text{RO}_2 C=\text{OCR}
\]

An acceptor group (EWG) will tend to make the carbenoid more electrophilic and reactive, whereas a donor group (EDG) will make the carbenoid more stable and chemoselective.

b. **Geometrically** rigid structures favor intramolecular insertions. In some special cases C-H insertion results in three-membered ring compounds.

Example:

\[
\text{CuSO}_4 \rightarrow \text{CuSO}_4
\]


2.4 Selected recent developments in this area

a. For most of the C(sp3)-H bond insertion were catalyzed by Rh catalysts. 2002, **Müller & Boléa** reported the first Cu catalyzed enantioselective C-H insertion.

\[
\text{Substrate} \quad \text{Conditions} \quad \text{Yield} \quad \text{ee}
\]

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Conditions</th>
<th>Yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>DCE, 60 °C, 3 h</td>
<td>54%</td>
<td>&gt; 98%</td>
</tr>
<tr>
<td>B</td>
<td>DCM, 0 °C, 3 h</td>
<td>36%</td>
<td>&gt; 98%</td>
</tr>
</tbody>
</table>

With other ligands, the reaction with B usually gives better enantioselectivity than A (might because of the generation of carbene from B can be performed at lower temperature). *Helv. Chim. Acta 2002, 85, 483*

Later, a lot of Cu catalyzed C-H insertion with chiral ligands was obtained...

b. Usually benzylic C-H is more reactive than allylic C-H. 2011, **Davies** developed a bulky dirhodium cyclopropylcarboxylate catalyst for a selective allylic C-H bond insertion.

\[
\begin{align*}
\text{DCM, 23 °C} \\
92 \% \text{ yield} \\
98\% \text{ ee}
\end{align*}
\]

The cyclopropylcarboxylate-based Rhodium catalyst has a increased steric hindrance when access to the C-H bond. So a less hindered secondary allylic C-H is favored over a benzylic C-H bond. *Acc. Chem. Res. 2012, 45, 923*
c. 2014, Davies developed a more bulkier cyclopropylcarboxylate-based Rhodium catalyst which favored the insertion into the primary C-H bond even in the presence of activated secondary C-H bonds.

\[ \text{Ar} + \text{N}_{2} \rightarrow \text{Ar} + \text{N}_{2} \]

0.5 mmol % catalyst

DCM, reflux

> 20

86% yield 64% ee

Example:

\[ \text{N}_{2} \text{Ar} \overset{\text{DCM, rt}}{\rightarrow} \text{N}_{2} \text{Ar} \]

78% yield 99%

Example:

\[ \text{OH} \rightarrow \text{OH} \]

LAuCl (5 mol %)

AgSbF\(_{6}\) (5 mol %)

DCM, rt

L = (2,4,6\(\text{Bu}_{2}\)C\(_{6}\)H\(_{3}\))\(_{3}\)P

100 : 0

Note: When \textit{para} position is not available, \textit{ortho} position is still favored over O-H or aliphatic C-H bond insertion.

d. An aromatic electrophilic substitution occurs via the zwitterionic intermediate was proposed by Davies in 2004. From the result, it can be regard as a C(sp\(^2\))-H bond insertion reaction. Then followed by Cu, Au, etc. catalyzed C(sp\(^2\))-H bond functionalizations as well.

Note: Zwitterionic intermediate is a electrically neutral molecule with at least one positive charge and one negative charge at the same time, also called inner salts.

\[ \text{L}_{4}\text{Rh}_{2} \overset{\text{N}_{2}}{\rightarrow} \text{L}_{4}\text{Rh}_{2} \]

\[ \text{OH} \overset{\text{LAuCl (5 mol %)}}{\rightarrow} \text{Ar} \]

72%

\[ \text{OH} \overset{\text{LAuCl (5 mol %)}}{\rightarrow} \text{Ar} \]

50% H

\[ K_{H}/K_{D} = 1.0 \]

\[ \text{Ar} \overset{\text{LAuCl (5 mol %), AgSbF}_{6} \text{ (5 mol %)}}{\rightarrow} \text{Ar} \]

\[ Jacs, 2014, 136, 9792 \]

\[ Org. Lett. 2004, 6, 1769 \]

\[ Jacs, 2014, 136, 6904 \]
Carbene and C-H Functionalization

Yaya Duan

The metal carbene migratory insertion (MI) type reaction.

Chem. Commun. 2015, 51, 7986

It's a completely different mechanism compared to the former C-H bond insertion mechanism been discussed so far. Transition metal will activation the C-H bond first, than generate the carbenoid, followed by the migratory insertion, further get hydrolysis to give the final product.

Reviews:
F. Hu, Y. Xia, C. Ma, Y. Zhang, J. Wang, Chem. Commun. 2015, 51, 7986

Mostly was C(sp2)-H bond functionalization through this MI type reaction. But recently a lot of directing C(sp3)-H bond functionalization reactions were reported.

Example:

Chem. Commun., 2016, 52, 9672

f. The structure determination of the key Rh-carbenoid intermediate. 2013, Davies initially reported the direct pectroscopic characterization of transition metal doner-acceptor carbene complex (13C NMR and EXAFS spectrum). Later, Fürstner reported the X-ray structure of the key Rh-carbenoid intermediates, which helps better understanding the stereochemistry control by the chiral Rh catalyst in C-H insertions.

Science, 2013, 342, 351
Angew. Chem. Int. Ed. 2015, 54, 15452
Huw M. L. Davies was born in Aberystwyth, Wales. He received his B.Sc. degree from University College Cardiff, Wales in 1977 and his Ph.D. degree from the University of East Anglia, England in 1980. After a post-doctoral position at Princeton University, he joined the faculty at Wake Forest University. He holds the position of Larkin Professor of Organic Chemistry in 1995 at the State University of New York. In 2008, he moved to Emory University as the Asa Griggs Candler Professor of Organic Chemistry.

His research interests include: catalytic asymmetric C-H activation, new synthetic methodology based on carbenoid intermediates, chiral catalysts for asymmetric synthesis, total synthesis of biologically active natural products, and development of medications for cocaine addiction and other CNS diseases.

Rh(II) carboxylates

- Very active at decomposing diazo compounds
- Optimal for intermolecular C-H insertion reactions
- Later generations possess rigid bridged structure

Reviews:
ACIE, 2006, 45, 6422.

Michael P. Doyle was born in Minneapolis, MN. He received his B.S. degree from the College of St. Thomas in St. Paul, MN, and obtained his Ph.D. degree from Iowa State University. Following a postdoctoral engagement at the University of Illinois at Chicago Circle, he joined the faculty at Hope College in 1968 where he rose to full professor and was appointed the first Kenneth Herrick Professor in 1982.

In 1984, he moved to Trinity University in San Antonio, TX, as the Dr. D. R. Semmes Distinguished Professor of Chemistry, and in 1997 he came to Tucson, AZ, as Vice President, then President, of Research Corporation and Professor of Chemistry at the University of Arizona. In 2003 he moved to the University of Maryland, College Park, as Professor and Chair of the Department of Chemistry and Biochemistry.

His research interests are in catalysis, especially reactions catalyzed by paddlewheeled dirhodium compounds, and in the diverse chemistries that surround the dirhodium framework.

Rh(II) carboxamides

- Generally much more rigid than Rh carboxylates
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Carbene and C-H Functionalization

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The metal carbene migratory insertion (MI) type reaction.

Outlooks in this area
More environmental friendly metal catalysts developing?
Simple chiral ligands applying into enantioselective C-H insertion?
Predicable selectivity by new catalysts designing?
Further investigation into the reaction mechanism studies?
New mechanism of C-H insertion of carbenoid?

Reviews:
F. Hu, Y. Xia, C. Ma, Y. Zhang, J. Wang, Chem. Commun. 2015, 51, 7986