Rhodium Carbenoids and C-H Insertion

Outline

I. What is a Carbene?
II. What is a Carbenoid?
III. Carbenoid Formation from Diazocompounds
IV. C-H Insertion with Rhodium Carbenoids
V. Enantioselective C-H Insertion with Rhodium Carbenoids

General References:
Modern Catalytic Methods for Organic Synthesis with Diazocompounds: From Cyclopropanes to Ylides (Doyle)
Chem Rev. 1986, 86, 919 (Doyle)
Chem Rev. 2003, 103, 2861 (Davies)
Advanced Organic Chemistry: Reactions and Mechanisms (Bernard Miller)
Carey & Sundberg, Part B, Chapter 10

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I. What is a Carbene: 
*Structure*

Carbenes are neutral molecules containing divalent carbon atoms with 2 unshared electrons:

\[
\begin{array}{c}
\text{H} \\
\text{C} \\
\text{H}
\end{array}
\]

2 possible electronic structures: *singlet* and *triplet*

**Singlet**
- resembles carbocation and carbanion united on same carbon
- "sp^2" filled orbital with empty "p" orbital
- many R groups (with unshared electrons) can stabilize singlet more than triplet

**Triplet**
- resembles diradical
- R groups in "sp" orbital, 2 partially filled orthogonal "p" orbitals
- usually more stable than singlet form (Hund's rule)

I. What is a Carbene: 
*Formation from Diazocomposition*

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{H}
\end{array}
\begin{array}{c}
\Delta \text{ or hf} \\
\rightarrow
\end{array}
\begin{array}{c}
\text{N}_2 \\
\text{C} \\
\text{O} \\
\text{H}
\end{array}
\]

Driving force for decomposition of diazo compounds: formation of N\(_2\)
activation energy for diazooalkane decomposition = 30 kcal/mol (thermal or photochemical energy)

*Usually it is difficult to know if a "carbene" reaction in solution involves a free carbene or some pseudo-carbene species that behaves like a carbene*
I. What is a Carbene: Reactivity

Free carbenes undergo insertion reactions

**Singlet carbene**
- Direct (one-step) insertion into C-H bonds, which leads to retention of stereochemistry at carbon
- No selectivity between different types of C-H bonds in intermolecular reactions (only some selectivity in intramolecular reactions)

\[ \text{singlet carbene} \]

(a) \[
\begin{array}{c}
\cdot \text{CH} \_2 \\
\end{array}
\]

\[ + 
\]

\[ \begin{array}{c}
\cdot \\
\end{array}
\]

\[ \rightarrow 
\]

\[ \begin{array}{c}
\cdot \\
\end{array}
\]

\[ + 
\]

\[ \begin{array}{c}
\cdot \\
\end{array}
\]

\[ JACS 1956, 78, 3224 \]

(b) Photolysis of diazomethane in heptane:

\[ \text{photolysis of diazomethane in heptane:} \]

\[ \begin{array}{c}
\text{CH}_2N_2 \\
\end{array}
\]

\[ \rightarrow 
\]

\[ \begin{array}{c}
\text{38\%} \\
\end{array}
\]

\[ \begin{array}{c}
\text{24\%} \\
\end{array}
\]

\[ \begin{array}{c}
\text{25\%} \\
\end{array}
\]

\[ \begin{array}{c}
\text{13\%} \\
\end{array}
\]

\[ JACS 1961, 83, 1934 \]

"Methylene must be classified as the most indiscriminate reagent known in organic chemistry." (JACS 1956, 78, 3224)

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I. What is a Carbene: Reactivity

Free carbenes undergo insertion reactions

**Triplet carbene**
- Multi-step process (involving radical pairs), which can lead to scrambling of stereochemistry

\[ \text{triplet carbene} \]

\[ \begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\]

\[ \rightarrow 
\]

\[ \begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\]

\[ \text{Ph-Me} \]

\[ \left\{ \begin{array}{c}
\cdot \\
\end{array}\right. 
\]

\[ + 
\]

\[ \begin{array}{c}
\cdot \text{CH}_2 \\
\end{array}
\]

\[ \rightarrow 
\]

\[ \begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\]

\[ \begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\]

\[ \text{Ph} \\
\]

\[ JACS 1969, 91, 4549 & 4554 \]
II. What is a Carbenoid: 
Structure and Formation

Carbenoid is a vague term used for a molecule in which all carbons are tetravalent but still has properties resembling those of a carbene (usually the carbene-like carbon has multiple bonds with a metal)

\[
\text{C} = \text{ML}_n
\]

Carbenoids can be formed by reacting salts of transition metals (eg. Cu, Pd, Rh) with diazo compounds

Initially the transition metal complexes used to decompose diazo compounds were heterogenous Cu complexes (*JCS* 1906, 89, 179)

\[\text{EtO} \cdots \text{N}_2 \xrightarrow{\text{Copper dust}} \text{EtO} \cdots \text{OEt} \xrightarrow{\text{N}_2} \text{EtO} \cdots \text{N} \cdots \text{OEt}\]

II. What is a Carbenoid: 
Structure and Formation

Then homogeneous Cu complexes were utilized

\[\text{Ph} \cdots \text{Cu} \cdots \text{O} \cdots \text{O} + \text{Ph} \cdots \text{N}_2 \xrightarrow{\text{PhH}} \text{Ph} \cdots \text{Ph} \xrightarrow{\Delta} \text{Ph} \cdots \text{Ph}\]

*TL 1966, 59*

\[\text{EtO} \cdots \text{N}_2 + \text{Ph} \xrightarrow{(\text{RO})_3\text{CuCl}} \text{CO}_2\text{Et} + \text{Ph} \cdots \text{CO}_2\text{Et}\]

*JACS 1969, 91, 1135 & 1141*

In 1952 Yates postulated that the reaction of transition metal complexes with diazo compounds led to the generation of transient electrophilic metal carbenes: "reaction of ROC:H (or of the ROCH:C:H-copper complex) probably involves an attack by the unshared pair of electrons on oxygen, nitrogen or sulfur at the electron-deficient methine carbon followed by a prototropic shift" (*JACS* 1952, 74, 5376)
III. Carbenoid Formation from Diazo Compounds:
Lewis Acid Promoted Decomposition of Diazo Compounds

Diazo compounds are unstable to acid promoted decomposition:

\[
\begin{align*}
\text{H}_3\text{C} &= \text{N}_2 \\
\text{H}_2\text{C} &= \text{N}_2 + \text{H}^+
\end{align*}
\]

Site of protonation:

\[
\begin{align*}
\text{H}_2\text{C} &= \text{N} = \text{N} + \text{H}^+ \\
\text{H}_2\text{C} &= \text{N} = \text{N} + \text{H}^+ \\
\text{H}_2\text{C} &= \text{N} = \text{N} + \text{H}^+
\end{align*}
\]

*kinetic product*

*thermodynamic product*

This instability of diazo compounds towards acids models their reactivity with lewis acidic transition metal complexes:

\[
\begin{align*}
\text{H}_2\text{C} &= \text{N} = \text{N} + \text{LA} \\
\text{H}_2\text{C} &= \text{N} = \text{N} + \text{LA}
\end{align*}
\]

---

III. Carbenoid Formation from Diazo Compounds:
Mechanism of Transition Metal Promoted Decomposition of Diazo Compounds

Lewis acidic transition metal complexes, like Rh(II) complexes, are effective catalysts for diazo decomposition. Activity of transition metal complexes depends on coordinative unsaturation at metal center, which allows them to react as "electrophiles" for diazo compound:

\[
\text{JACS 1996, 118, 8162}
\]

Some eccentric metal mediated diazo decomposition reactions do not yield carbenoids, and these reactions are often catalyzed by non-transition metal lewis acids as well:

\[
\begin{align*}
\text{Cu(O} \text{O})_2 \\
\text{BF}_3 \cdot \text{OEt}_2
\end{align*}
\]

BF$_3$: *JOC 1980, 45, 3657*
III. Carbenoid Formation from Diazocompounds:
*Effect of Lewis Bases*

An electron rich substrate (S:\_) can react with the electrophilic metal carbenoid, which results in the regeneration of the transition metal complex (important for catalysis)

Sometimes the reaction between the electrophilic carbenoid and a Lewis basic substrate (S:\_) is desirable

But sometimes a Lewis base (B:\_) substrate can associate with the coordinatively unsaturated transition metal complex and inhibit diazo decomposition:

\[
B - ML_n + R_2C=\text{N}_2 + R_2C'=\text{N}_2 \rightarrow ML_n + \text{N}_2
\]


Ineffective inhibitors for diazo decomposition: halogenated hydrocarbons, eg. DCM, DCE (great solvents for diazo decomposition)

III. Carbenoid Formation from Diazocompounds:
*Rh(II) Catalysts*

Carbene C-H insertions are highly non-selective

Carbenoid C-H insertions are much more selective because of the reduced reactivity of carbenoids

*Rh Carbenoids* (generated from Rh(II) dimer complexes) have become the most common catalysts for C-H insertion reactions because of their selectivity and the ease with which ligands are modified

*Dirhodium (II) Carbylates:*

- First example of Rh carbenoid generation from diazo decomposition: (*TL* 1973, 2233)

\[
\text{EtO}_2\text{C}=\text{N}_2 + \text{ROH} \xrightarrow{\text{Rb}_2(\text{OAc})_4} \text{EtO}_2\text{C} \text{OR} + \text{N}_2
\]

- D\text{d}_5 symmetry with 4 bridging acetate ligands and 1 vacant coordinate site per metal atom presents an octahedral geometry resembling a circular wall with an electron rich circumference and electron deficient core:

- Complexes are air stable and easy to work with
III. Carbenoid Formation from Diazo Compounds: 
*Rh(II) Catalysts*

Electron-withdrawing capabilities of carboxylate ligands affect properties of the catalyst (e.g., Rh$_2$(OAc)$_2$ does not form olefin complexes in solution, but Rh$_2$(TFA)$_2$ does form olefin complexes in solution) 

Other ligands used in dirhodium (II) complexes:

![Carboxamidates](image1)
![Phosphates and orthometallated phosphines](image2)
![Porphyrins](image3)

*TL* 1992, 33, 5983
*TL* 1992, 33, 5987
*TL* 1980, 21, 3489
*TL* 1981, 22, 1783

---

III. Carbenoid Formation from Diazo Compounds: 
*Stability of Rh carbenoid complexes*

The use of dirhodium (II) catalysts for intramolecular C-H insertion of diazo carbonyls has developed into a significant synthetic achievement because of the stability of these intermediates

*increasing stability*

![Stability Diagram](image4)

*increasing reactivity*

A stable dirhodium tetracarboxylate carbenoid was isolated recently by Padwa: 
*JACS* 2001, 123, 11318
IV. C-H Insertion with Rh Carbenoids:

Different Types of Insertion Reactions:

Rh (II) complexes are used for C-H, Si-H, and Heteratom-H insertion reactions.

C-H and Si-H insertions are unique because of the low polarity of the bonds, so their mechanisms are distinct from Heteratom-H insertions.

C-H Insertion via Metal Carbenoids vs. C-H Activation via Oxidative Addition:

In metal carbenoid induced C-H activation the metal atom is not thought to interact directly with the alkane C-H bond (this is different than most other C-H activation reactions, which involve oxidative addition of the metal across the alkane C-H bond):

\[
\text{N}_2 \quad \text{C} = \text{ML}_n \quad \text{C-H} \quad \text{C} = \text{ML}_n
\]

\[
\text{C-H Insertion via Metal Carbenoids} \quad \text{vs.} \quad \text{C-H Activation via Oxidative Addition}
\]

IV. C-H Insertion with Rh Carbenoids:

Mechanism of C-H Insertion

\[
\begin{array}{c}
\text{A} \quad \text{B} \\
\text{H} \quad \text{D} \\
\end{array}
\begin{array}{c}
\text{x} \\
\text{y} \\
\text{Rh}_2\text{L}_4
\end{array}
\]

\[
\begin{array}{c}
\text{A} \quad \text{B} \\
\text{H} \quad \text{D} \\
\end{array}
\begin{array}{c}
\text{x} \\
\text{y} \\
\text{Rh}_2\text{L}_4
\end{array}
\]

or

\[
\begin{array}{c}
\text{A} \quad \text{B} \\
\text{H} \quad \text{D} \\
\end{array}
\begin{array}{c}
\text{x} \\
\text{y} \\
\text{Rh}_2\text{L}_4
\end{array}
\]

\[
\begin{array}{c}
\text{A} \quad \text{B} \\
\text{H} \quad \text{D} \\
\end{array}
\begin{array}{c}
\text{x} \\
\text{y} \\
\text{Rh}_2\text{L}_4
\end{array}
\]

• Carbenoid's empty p-orbital overlaps with the α-orbital of the C-H bond.

• C-C and C-H bond formation with carbenoid carbon proceeds as ligated metal dissociates (1).

• Taber prefers a transition state in which there is a more pronounced interaction/transfer of hydrogen to rhodium (2), followed by a reductive elimination. 
  \textit{(JACS 1996, 118, 547)}
IV. C-H Insertion with Rh Carbenoids:  
*General Characteristics of a Good Rh Complex for C-H Insertion*

**Proficient C-H insertion requires an appropriate level of electrophilic character at the metal center**

- If the metal center is too electrophilic ➔ catalyst displays poor selectivity because of high reactivity, and it is susceptible to undesired competing reactions
- If the metal center is not electrophilic enough ➔ catalyst is not reactive enough to insert C-H bond

**Solutions:**

- Electron-withdrawing groups on metal or adjacent to carbenoid carbon increase the electrophilicity of the carbenoid intermediate
- The best metal complexes bind to the carbenoid carbon through strong σ-donation and weak π-back donation, which stabilizes the carbenoid carbon somewhat but still ensures electrophilicity

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**IV. C-H Insertion with Rh Carbenoids:  
Trends in Selectivity for Intermolecular C-H Insertion**

Intermolecular C-H insertion has mechanistic value, but it is not always synthetically useful (because of low selectivity)

\[
\text{EtO} = \text{N} \quad + \quad \text{Rh}_2(\text{OAc})_4 \quad \rightarrow \quad \text{Rh}_2(\text{OAc})_4
\]

\[
k = 3.0 \times 12 \times 10^{-4} \text{ s}^{-1}
\]

(reaction is first order in ethyl diazoacetate)

*Tetrahedron* 1989, 45, 69
IV. C-H Insertion with Rh Carbenoids: Trends in Selectivity for Intramolecular C-H Insertion

C-H insertion occurs preferably at a carbon that can stabilize positive charge (electronic effects)

- tertiary carbon > secondary carbon > primary carbon  
  (because of the availability of the electron density in the C-H bond)

\[
\begin{align*}
\text{Rh}_2(OAc)_4 & \quad \text{O} \\
\text{N}_2 & \quad \text{E} \\
\text{O} & \quad \text{E}
\end{align*}
\]

\textit{JACS 1986, 108, 7686}

- alkoxy groups activate adjacent C-H bonds:

\[
\begin{align*}
\text{O} & \quad \text{N}_2 \\
\text{OBn} & \quad \text{OBn}
\end{align*}
\]

\textit{Tetrahedron 1991, 47, 1765}

- electron-withdrawing groups (eg. \text{CO}_2\text{Me}) inhibit adjacent C-H bonds (\textit{TL 1988, 29, 2283})

\[
\begin{align*}
\text{N}_2 & \quad \text{O} \\
\text{C} & \quad \text{O} \\
\text{N}_2 & \quad \text{O} \\
\text{N}_2 & \quad \text{O}
\end{align*}
\]

Sometimes electronic effects are outweighed by steric or conformational factors

- 5 membered rings > 6 membered rings
**IV. C-H Insertion with Rh Carbenoids:**
*Diastereoselectivity in Intramolecular C-H Insertion*

Although dirhodium (II) catalysts provide the highest levels of asymmetric induction for C-H insertion, there is no one class of chiral rhodium (II) complex that is effective for all C-H insertion reactions.

This is because different types of carbenoid intermediates display very different reactivities.

3 *main categories of carbenoids:*

- **acceptor substituted carbenoid**
  - Substituent at the acceptor site

- **acceptor/acceptor substituted carbenoid**
  - Both acceptor sites are substituted

- **donor/acceptor substituted carbenoid**
  - One acceptor and one donor site are substituted

Model for explaining diastereoselectivity:
pseudo-chair transition state
(ACS 1996, 118, 547 & Tetrahedron 1996, 52, 3879)
V. Enantioselective C-H Insertion with Rh Carbenoids:

\textit{Acceptor Substituted Carbenoids}

\[ \text{acceptor substituted carbenoid} \xrightarrow{\text{catalyst}} \text{L}_nM=H \]

\[ \text{EWG} \]

Example of a catalyst for enantioselective intramolecular C-H activation:

\[
\begin{array}{cccc}
\text{RO} & \text{RO}_2 & \text{Me} & 73 \\
\text{N}_2 & \text{N}_2 & \text{Et} & 64 \\
\text{CH}_2\text{Cl}_2 & \text{CH}_2\text{Cl}_2 & \text{Bn} & 64 \\
\end{array}
\]

\[ \% \text{ Yield} \quad \% \text{ ee} \]

\[ \text{Me} \quad 91 \]

\[ \text{Et} \quad 89 \]

\[ \text{Bn} \quad 87 \]

\[ JACS \ 1991, 113, 8982 \]

V. Enantioselective C-H Insertion with Rh Carbenoids:

\textit{Acceptor/Acceptor Substituted Carbenoids}

\[ \text{acceptor/acceptor substituted carbenoid} \xrightarrow{\text{catalyst}} \text{L}_nM=H \]

\[ \text{EWG} \]

Example of a catalyst for enantioselective intramolecular C-H activation:

\[ T\text{L.} \ 1990, 31, 5173 \]

\[
\begin{array}{cccc}
\text{R} & \% \text{ Yield} & \% \text{ ee} \\
\text{Me} & 76 & 24 \\
n\text{-Pn} & 43 & 29 \\
\text{CH}_2\text{=}\text{CH}_2 & 44 & 38 \\
\text{Ph} & 96 & 46 \\
\end{array}
\]
V. Enantioselective C-H Insertion with Rh Carbenoids:
Donor/Acceptor Substituted Carbenoids

Example of a catalyst for enantioselective intermolecular C-H activation:

<table>
<thead>
<tr>
<th>R</th>
<th>% Yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>86</td>
<td>67</td>
</tr>
<tr>
<td>H</td>
<td>83</td>
<td>81</td>
</tr>
<tr>
<td>Cl</td>
<td>91</td>
<td>86</td>
</tr>
</tbody>
</table>

Outlook for the Future

- Rh (II) carbenoids have become the most widely used catalysts for selective C-H insertion reactions
- Both the catalyst design and carbenoid structure can affect reactivity and selectivity (chemoselectivity, regioselectivity, diastereoselectivity, and enantioselectivity)
- C-H insertion with Rh carbenoids is now becoming a powerful and widely applicable synthetic strategy for total synthesis (avoidance of functional group manipulations)
- A major area of future research will be to broaden the range of carbenoid systems that can undergo selective C-H insertion reactions
- Recent computational studies to study the mechanism may help make the design of future systems more rational and predictable