Rhodium Carbenoids and C-H Insertion



<u>Outline</u>

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

General References:

Modern Catalytic Methods for Organic Synthesis with Diazo Compounds: 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:



2 possible electronic structures: singlet and triplet



 \bullet resembles carbocation and carbanion united on same carbon \bullet "sp^2" filled orbital with empty "p" oribtal

- many R groups (with unshared electrons) can stabilize singlet more than triplet



I. What is a Carbene: Formation from Diazo Decomposition



Driving force for decomposition of diazo compounds: formation of N₂ activation energy for diazoalkane 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

Free carbenes undergo insertion reactions

<u>singlet carbene</u>

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)



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

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



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)



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)



II. What is a Carbenoid: *Structure and Formation*

Then homogeneous Cu complexes were utilized



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 RCOC: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)



Diazo compounds are unstable to acid promoted decomposition:

$$H_3C - N_2 \longrightarrow H_2C = N_2 + H^+$$

Site of protonation:



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



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:



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:



Cu: J. Organomet. Chem. 1975, 88, 15

BF3: JOC 1980, 45, 3657

III. Carbenoid Formation from Diazo Compounds: Effect of Lewis Bases



But sometimes a Lewis base (B:) substrate can associate with the coordinatively usaturated transition metal complex and *inhibits* diazo decomposition:

$$B-ML_n \xrightarrow{-B:} ML_n \xrightarrow{+R_2C=N_2} L_n \xrightarrow{-R_2C=N_2} I_n$$

Effective inhibitors for diazo decomposition: amines, sulfides, nitriles, (sometimes alkenes, aromatics) (*Inorg. Chem.* **1982**, *21*, 2196)

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

III. Carbenoid Formation from Diazo Compounds: *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) carboxylates:

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



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

Electron-withdrawing capabilities of carboxylate ligands affect properties of the catalyst (eg. $Rh_2(OAc)_4$ does not form olefin complexes in solution, but $Rh_2(TFA)_4$ does form olefin complexes in solution) Inorg. Chem. **1984**, 23, 3684

Other ligands used in dirhodium (II) complexes:



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



IV. C-H Insertion with Rh Carbenoids: Introduction

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 Heteroatom-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):



IV. C-H Insertion with Rh Carbenoids: Mechanism of C-H Insertion



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

• C-C and C-H bond formation with carbonoid 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 (*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 \square catalyst displays poor selectivity because of high reactivity, and it is susceptible to undesired competing reactions

• If the metal center is not electrophilic enough 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

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)



 $k = 3.0 - 12 \times 10^{-4} \text{ s}^{-1}$ (reaction is first order in ethyl diazoacetate)

Tetrahedron 1989, 45, 69

IV. C-H Insertion with Rh Carbenoids: Trends in Selectivity for <u>Intra</u>molecular 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)



• alkoxy groups activate adjacent C-H bonds:



Tetrahedron 1991, 47, 1765

IV. C-H Insertion with Rh Carbenoids: Trends in Selectivity for <u>Intra</u>molecular C-H Insertion

• electron-withdrawing groups (eg. CO2Me) inhibit adjacent C-H bonds (TL 1988, 29, 2283)



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



Model for explaining diastereoselectivity: pseudo-chair transition state (*JACS* **1996**, *118*, 547 & *Tetrahedron* **1996**, *52*, 3879)



V. Enantioselective C-H Insertion with Rh Carbenoids: Classification of Carbenoid Intermediates

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:



V. Enantioselective C-H Insertion with Rh Carbenoids: Acceptor Substitutd Carbenoids







JACS 1991, 113, 8982



V. Enantioselective C-H Insertion with Rh Carbenoids: Acceptor/Acceptor Substitutd Carbenoids





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



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