

'Carbon has the unique ability to bind four atoms and form stable tetravalent structures that are prevalent in nature. The lack of one or two valences leads to a set of species—carbocations, carbanions, radicals and **carbenes**—that is fundamental to our understanding of chemical reactivity.'

---[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 σ -bonds extending from the central carbon and two nonbonding electrons.

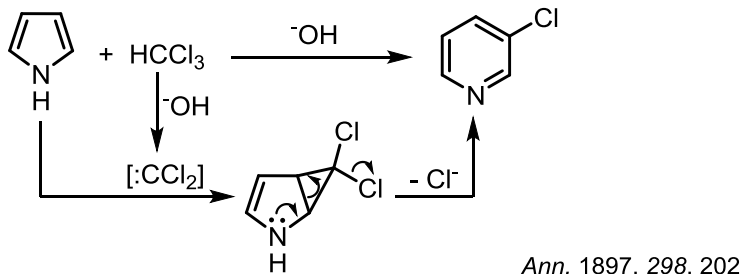
1.1 A brief history:

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



Liebigs Ann. Chem. **1855**, 95, 211

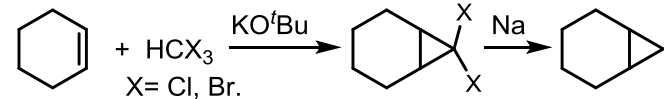
1897, **Nef** proposed the same intermediate for *Ciamician-Dennstedt Rearrangement*:



α -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-

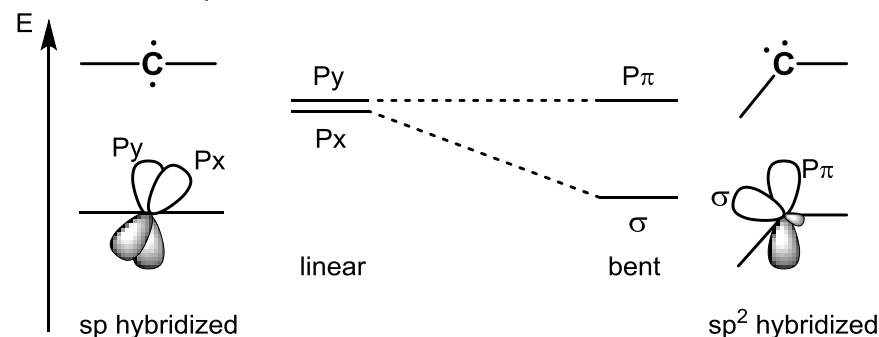
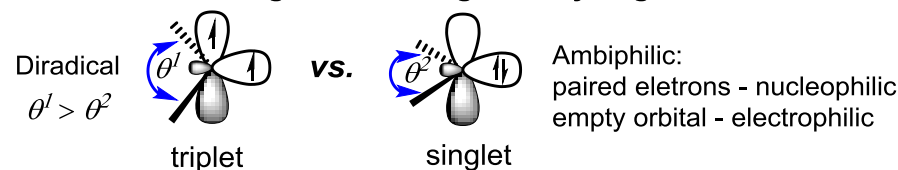
Coordin. Chem. Rev. **2009**, 253, 862

1954, Doering demonstrated the synthetic utility of dihalogencarbenes:



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

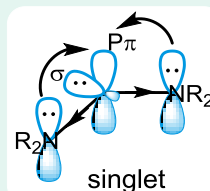
1.2 Electronic configuration and geometry at ground state:



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:

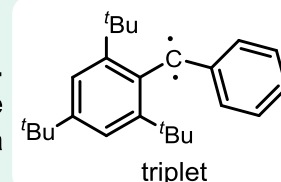


a. The energy gap between $\text{P}\pi$ and σ orbital.

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

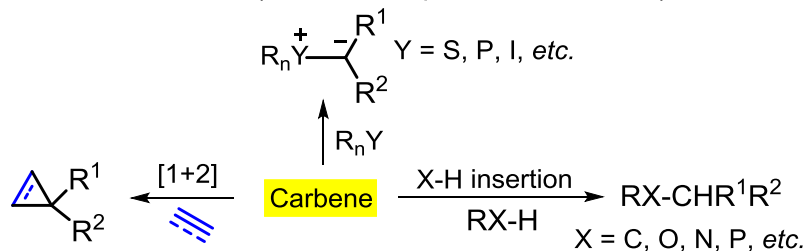
b. The steric hindrance of the substituents.

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

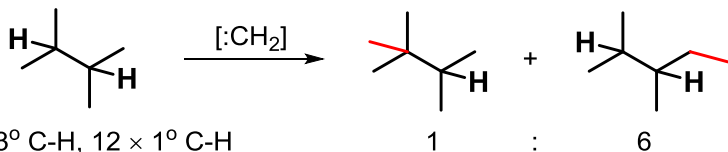


1.3 Reactivity of free carbenes:

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.



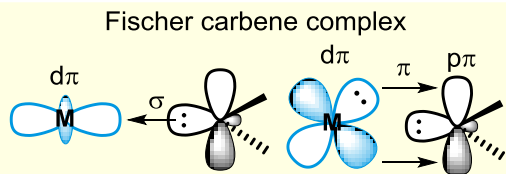
'Methylene must be classified as the most indiscriminate reagent known in organic chemistry.'

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:

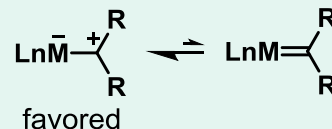
Typically carbenoid is formed from diazo compounds. The reactivity can be modified by the metal itself, the diazo compounds and the ligands associated with the metal center.

a. Different Transition metals give different types of carbenes.



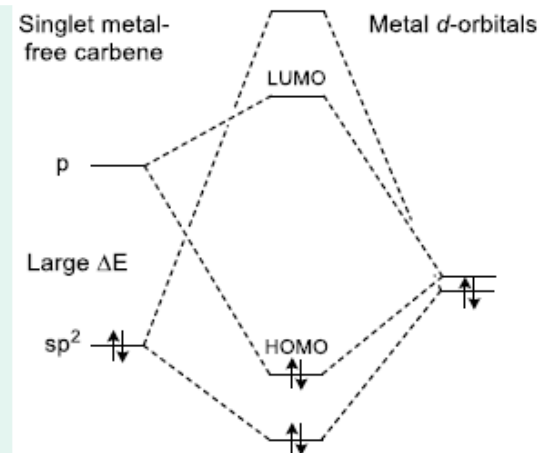
- ◆ Formed by a singlet free carbene and a late TM with a low oxidation state (a low energy d orbital).
- ◆ Electrophilic carbene

Fischer carbene complex



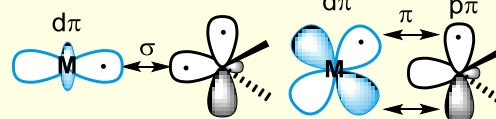
$$\Delta E \approx 8 - 10 \text{ kcal/mol}$$

In Fischer carbene, LUMO is closer in energy to carbene, so the carbon center of the carbene is more electrophilic than the metal.



J. Am. Chem. Soc. **1984**,106, 1576

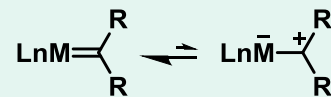
Schrock carbene complex



- ◆ 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).

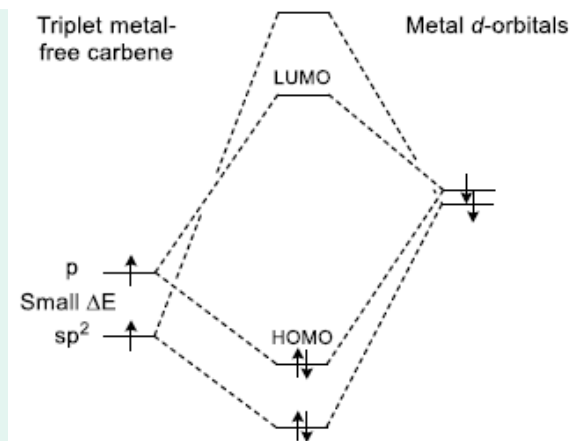
- ◆ Nucleophilic carbene

Schrock carbene complex



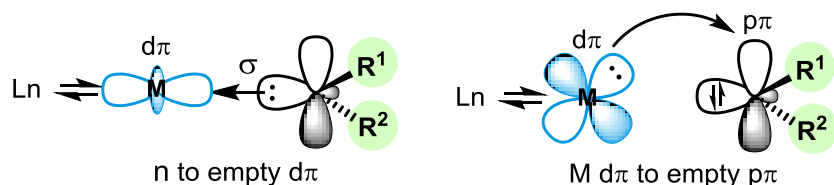
$$\Delta E \approx 19 \text{ kcal/mol}$$

In Schrock carbene, LUMO is closer in energy to metal, so the metal is more electrophilic than carbene carbon.

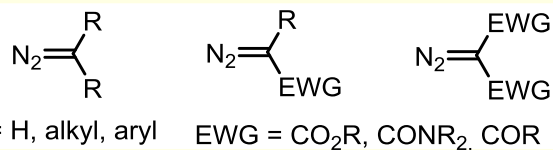


J. Am. Chem. Soc. **1984**,106, 1576

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

Beilstein J. Org. Chem. **2016**, 12, 882

c. 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 $d\pi$ orbitals, enhance or decrease the electron density, in some cases lowering the energy of the $d\pi$ 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 create a chiral environment for TM mediated/catalyzed carbene reactions.

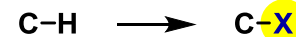
Nature **2008**, 451, 417

Angew. Chem. Int. Ed. **1994**, 33, 1797

2 'Carbene' insertion in C-H bond functionalization:

C-H bond is a very strong covalent bond (BDE \approx 110 kcal/mol), direct transformation (selectively) from C-H bond to C-X bond is challenging.

2.1 General introduction of C-H functionalization



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.

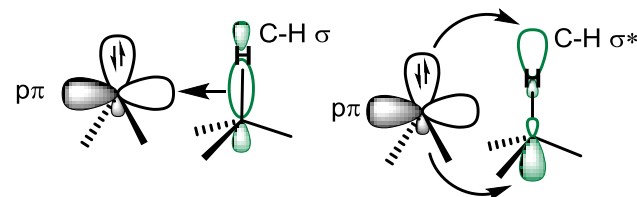
a. For a TM reacts directly with a C-H bond:



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?)

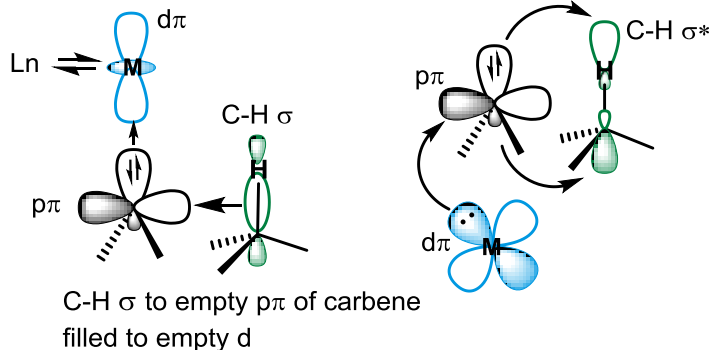
M $d\pi$ to C-H σ^* from the carbon atom, when it's a tertiary C-H bond, it can be quite sterically hindered

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



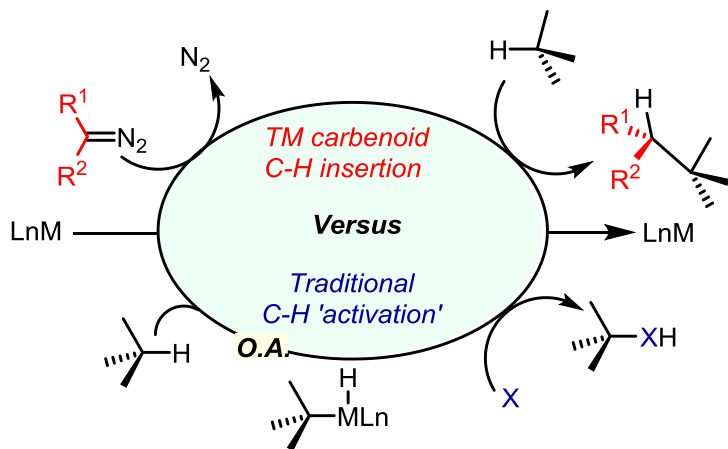
The frontier orbitals of carbene carbon center and the C-H bond were both 2p or 2p-hybridized orbitals, which matched perfectly with each other at energy level. Besides, their frontier orbitals were also symmetrically matched, offering them possibility to get a very good overlap.

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 an electrophilic carbene species.

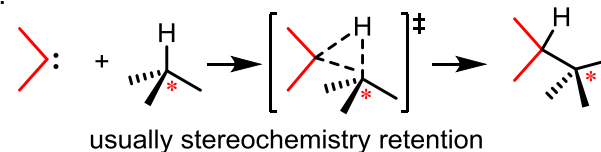
Electron rich, low valent late TM (eg. Re, Fe, Ru, Os, Rh, Ir, Pt, etc.) has close interaction with the targeted C-H bond during the **C-H 'activation'** through oxidative addition.

Nature **2008**, 451, 417

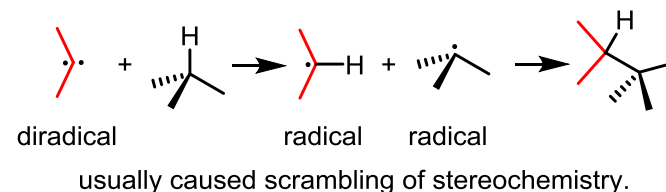
2.2 C-H functionalization by free carbene insertion

a. Singlet carbene

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



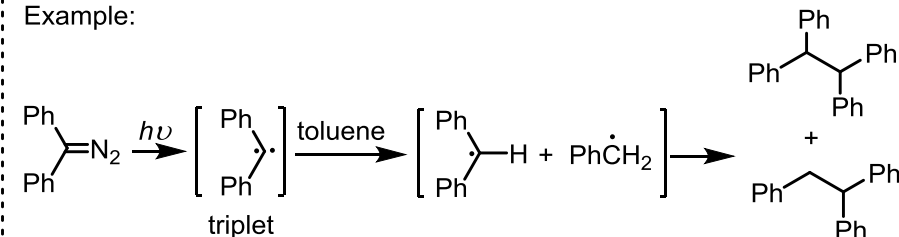
b. Triplet carbene



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:



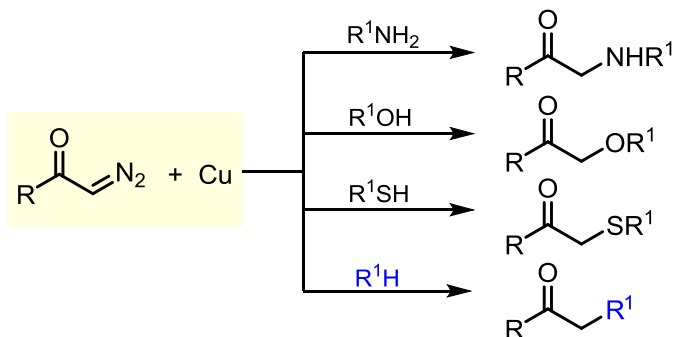
Note: Usually triplet carbenes can be obtained from photolysis of diazo compounds. Singlet carbenes can be obtained from thermolysis of diazo compounds.

J. Am. Chem. Soc. **1969**, 91, 4549

2.3 C-H functionalization by TM carbene insertion.

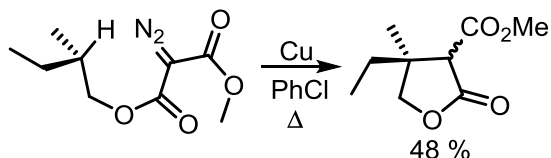
2.3.1 History (mostly is about Cu and Rh)

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'.



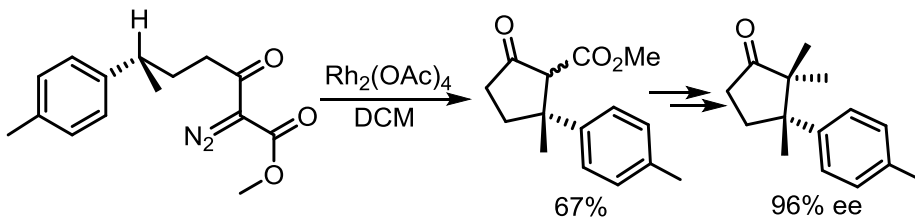
J. Am. Chem. Soc. **1952**, 74, 5376

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



Tetrahedron Lett. **1973**, 14, 25

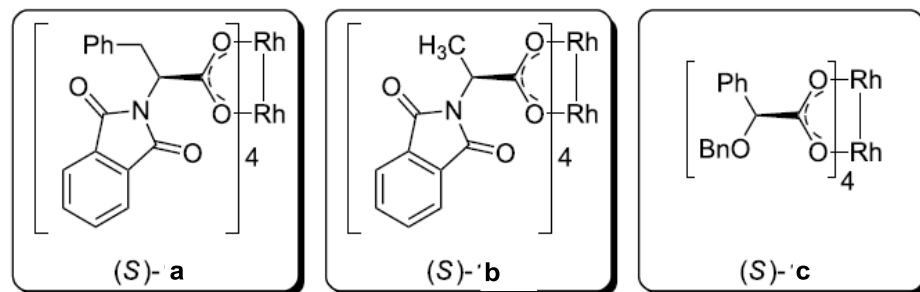
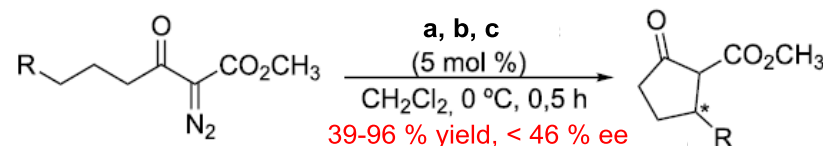
1985, **Taber** reported Rh₂(OAc)₄ catalyzed enantioselective carbenoid insertion for the synthesis of (+)- α -cuparenone.



J. Am. Chem. Soc. **1985**, 107, 196

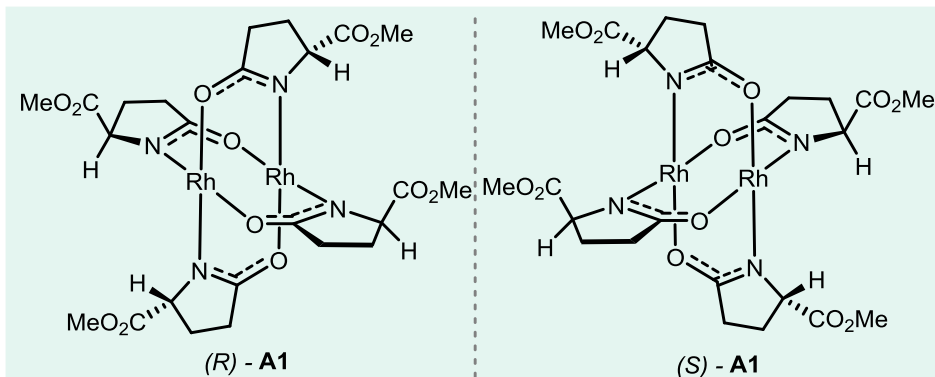
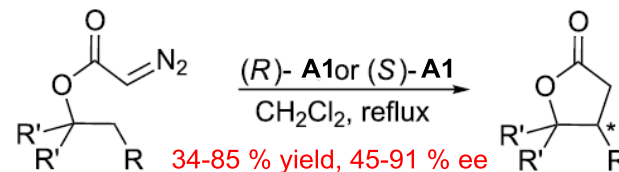
These are stereochemistry retention reactions.

1990, **Ikegami** developed the **chiral Rh carboxylate catalysts**.



Tetrahedron Lett. **1990**, 31, 5173

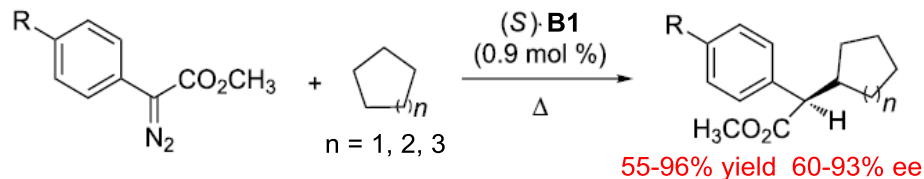
1991, **Doyle** developed the **chiral Rh carboxamide catalysts**.



J. Am. Chem. Soc. **1991**, 113, 8982

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



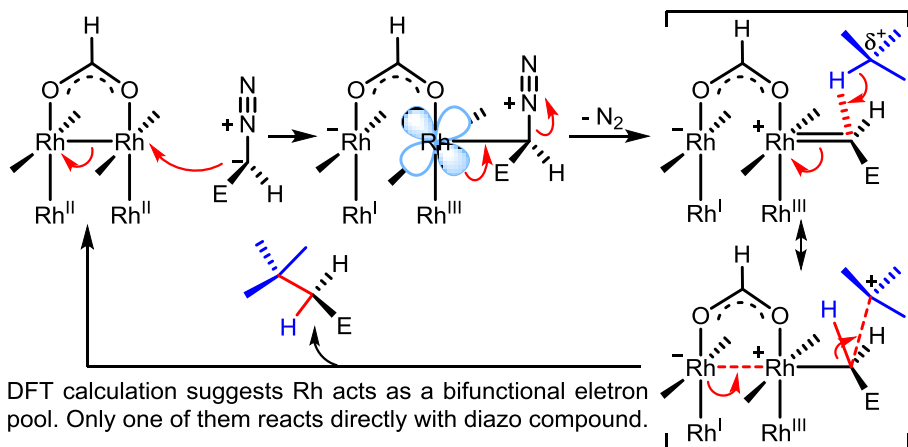
Note: with this chiral ligand, the new stereogenic center is formed on the carbene carbon coordinated to the Rh center and not on carbon-containing the C(sp³)-H bond activated by the carbene moiety.

(S)-B1 gives (R)-product.

J. Am. Chem. Soc. **1997**, 119, 9075

This is the intermolecular enantioselective reaction.

Doyle (1993) & **Nakamura** (2002) were the first to do important contribution to the understanding of the reaction mechanism. Generally believed to occur through concerted (though asynchronous), three-centered transition state.

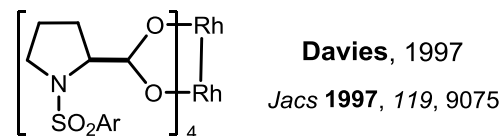


J. Am. Chem. Soc. **2002**, 124, 7181

J. Am. Chem. Soc. **1993**, 115, 958

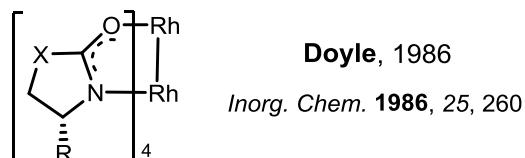
Later, a lot of chiral ligands was developed...

Rh(II) carboxylates

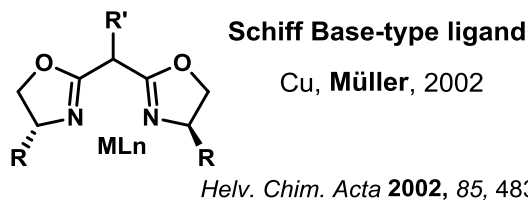


- Very active at decomposing diazo compounds
- Optimal for intermolecular C-H insertion reactions
- Later generations possess rigid bridged structure

Rh(II) carboxamides



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

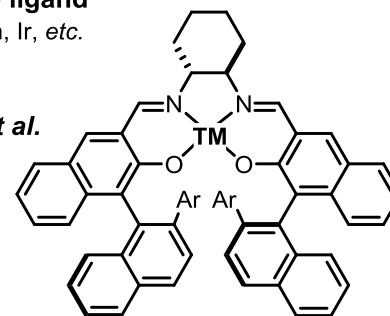


Salen-type ligand

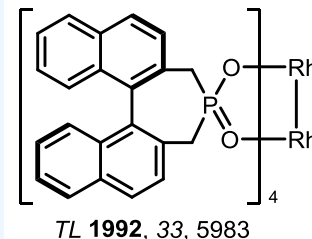
TM = Cu, Rh, Ir, etc.

Suematsu

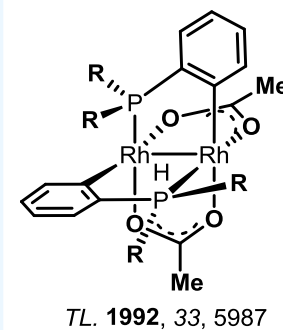
&
Katsuki, et al.



Rh(II) phosphates

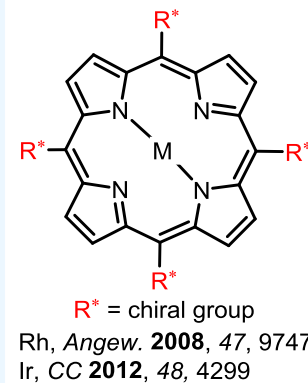


Rh(II) orthometallated phosphines



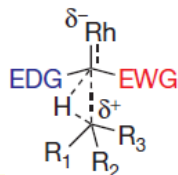
TM Porphyrin

Che, 2008



2.3.2 General Trends in Carbenoid C-H Activation Chemistry

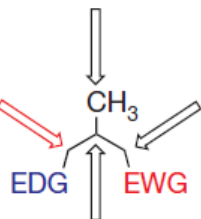
Facile C-H insertion at activated sites positive charge buildup at insertion site stabilized when R = N, O, aryl, vinyl. And an EWG adjacent to the C-H bond will deactivate it.



- intramolecular C-H insertion > intermolecular C-H insertion
- 5-membered ring formation > other size ring formation
- 3° C-H > 2° C-H > 1° C-H when sterically accessible

1° C-H sterically favoured
electronically disfavoured

2° C-H sterically favoured
electronically favoured



2° C-H sterically favoured
electronically disfavoured

3° C-H sterically disfavoured
electronically favoured

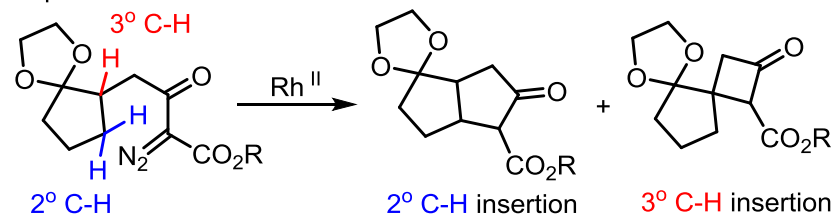
Nature **2008**, 451, 417

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.

2.3.3 Ligand Effect

a. Usually 3° C-H > 2° C-H > 1° C-H due to higher electron density σ orbital of the C-H bond would more likely react with electrophilic TM carbene complex. However, if the **steric hindrance of the ligand** increased, then 3° C-H might not be favored at all.

Example:



Note:

acam: acetamide
TPA: triphenylacetate
Piv: pivalate $t\text{Bu}_3\text{CO}_2\text{H}$
BzO: benzoic acid
TPA: OCOCPh_3

Catalyst

$[\text{Rh}_2(\text{OAc})_4]$	37 : 63
$[\text{Rh}_2(\text{TFA})_4]$	56 : 44
$[\text{Rh}_2(\text{acam})_4]$	14 : 86
$[\text{Rh}_2(\text{Piv})_4]$	37 : 63
$[\text{Rh}_2(\text{OBz})_4]$	54 : 46
$[\text{Rh}_2(\text{OCOCPh}_2)_4]$	64 : 36
$[\text{Rh}_2(\text{OCOCMePh}_2)_4]$	82 : 18
$[\text{Rh}_2(\text{TPA})_4]$	96 : 4

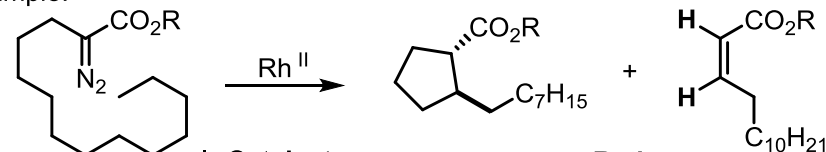
bulkier

less hindered C-H favored

Angew. Chem. Int. Ed. **1994**, 33, 1797

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:



Catalyst

$[\text{Rh}_2(\text{OCO}-n\text{-C}_8\text{H}_{17})_4]$	85 : 15
$[\text{Rh}_2(\text{Piv})_4]$	78 : 22
$[\text{Rh}_2(\text{OBz})_4]$	78 : 22
$[\text{Rh}_2(\text{OAc})_4]$	66 : 34
$[\text{Rh}_2(\text{TFA})_4]$	52 : 48

more electron deficient

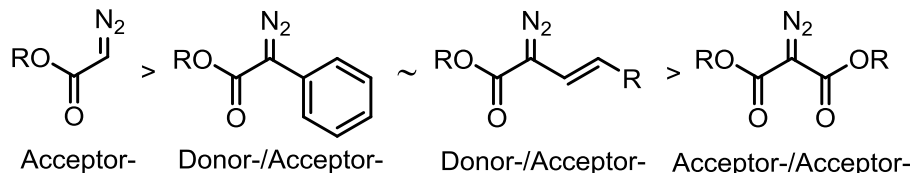
Angew. Chem. Int. Ed. **1994**, 33, 1797

Carbene and C-H Functionalization

Yaya Duan

2.3.4 Influence from diazo compound

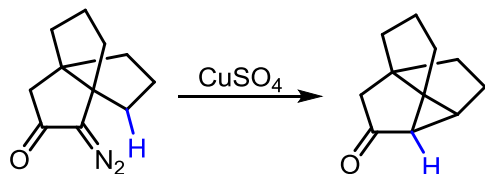
a. **Electronically** deficient diazo compounds was highly reactive towards transition metal compounds, generating electrophilic carbene carbon center. Reactivity trend is as the followed order:



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.

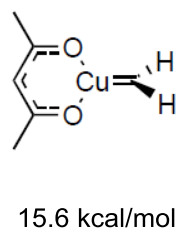
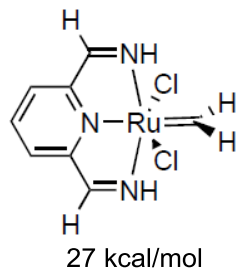
Example:



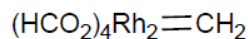
J. Org. Chem. **1983**, *48*, 139.

2.3.5 The nature of the metal

C-H insertion is enhanced when activated energy is decreased. Rh-carbenoid, compared to Cu-carbene and Ru-carbene, energy of C-H insertion to carbenoid is lower (diazomethane-methane).



DFT calculation

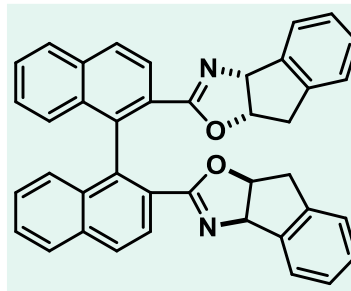
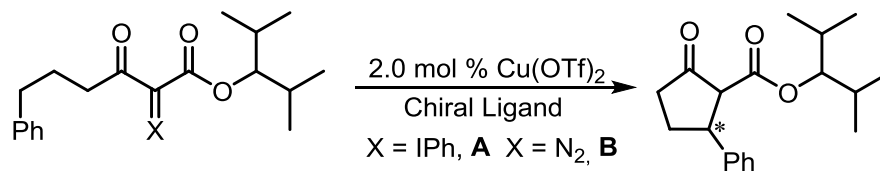


5.7 kcal/mol

Jacs, **2002**, *124*, 7181

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.



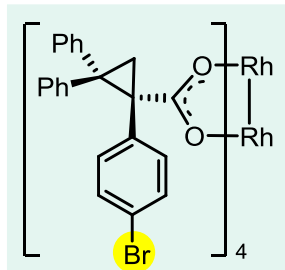
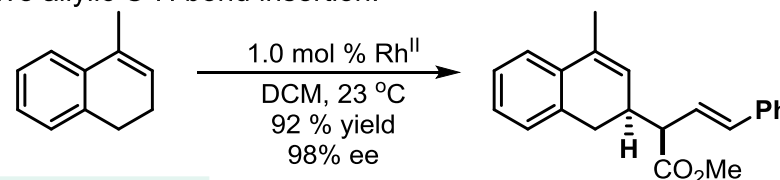
Substrate	Conditions	Yield	ee
A	DCE, 60 °C, 3 h	54%	> 98%
B	DCM, 0 °C, 3 h	36%	> 98%

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...

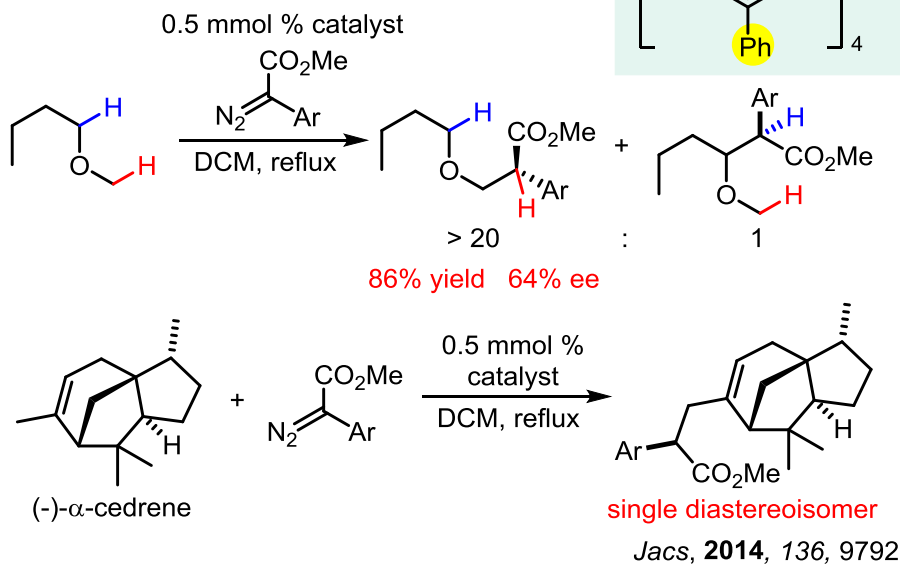
b. Usually benzylic C-H is more reactive than allylic C-H. 2011, **Davies** developed a bulky dirhodium cyclopropylcarboxylate catalyst for a selective allylic C-H bond insertion.



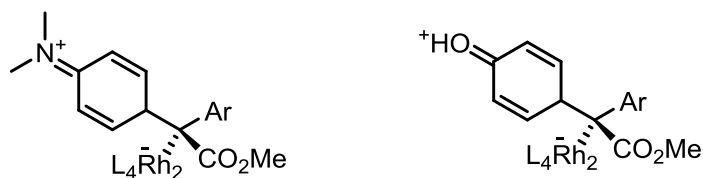
The cyclopropylcarboxylate-based Rhodium catalyst has a increased steric hindrance when access to the C-H bond. So a less hindered secondary allylic C-H is favored over a benzylic C-H bond.

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.

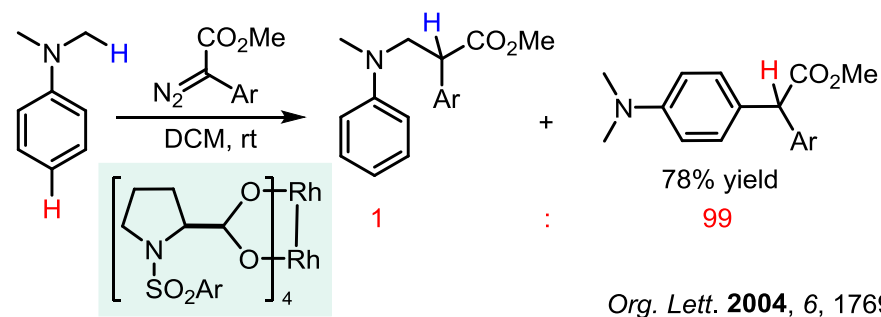


d. An aromatic electrophilic substitution occurs via the zwitterionic intermediate was proposed by **Davies** in 2004. From the result, it can be regarded as a C(sp²)-H bond insertion reaction. Then followed by Cu, Au, etc. catalyzed C(sp²)-H bond functionalizations as well.

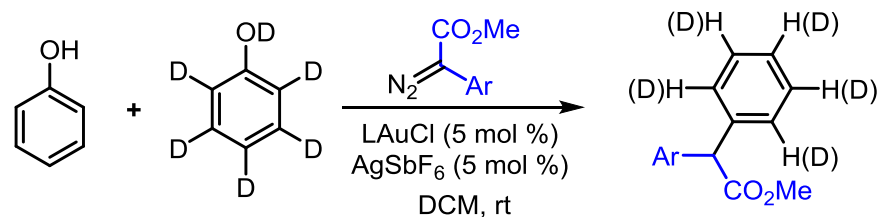
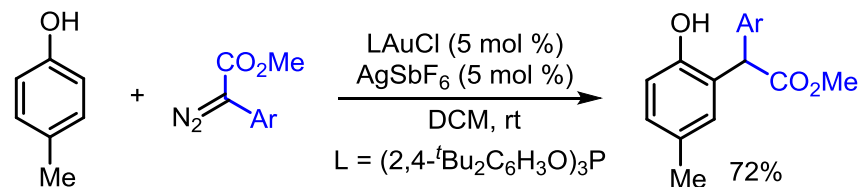
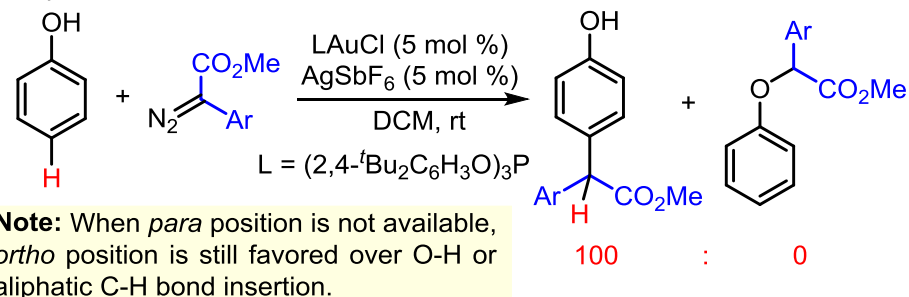


Note: Zwitterionic intermediate is a electrically neutral molecule with at least one positive charge and one negative charge at the same time, also called inner salts.

Example:



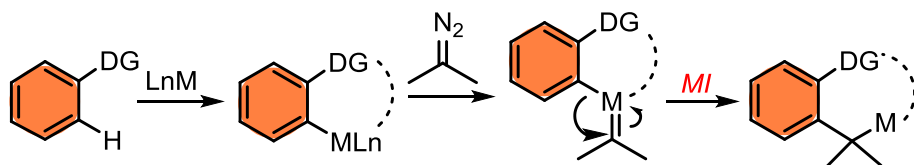
Example:



$$K_H/K_D = 1.0$$

Jacs, **2014**, 136, 6904

e. 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 activate the C-H bond first, then generate the carbenoid, followed by the migratory insertion, further get hydrolysis to give the final product.

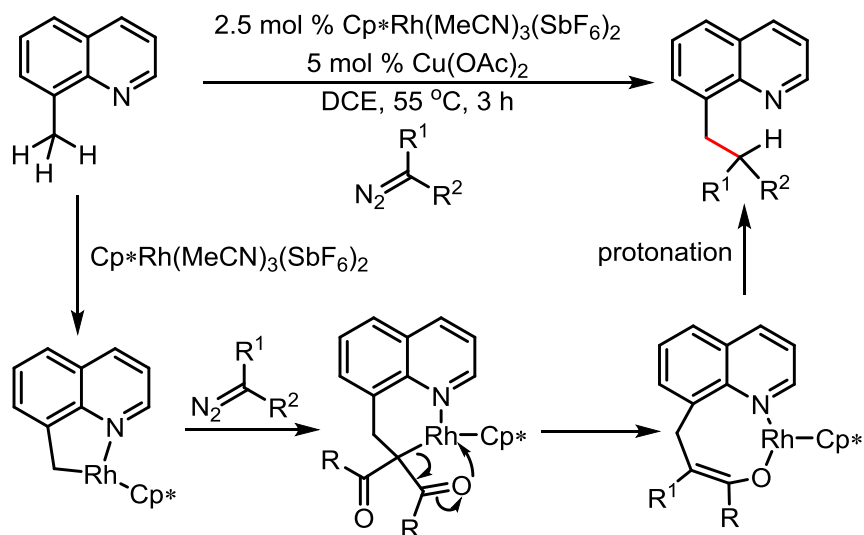
Reviews:

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

Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, 117, 13810

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.

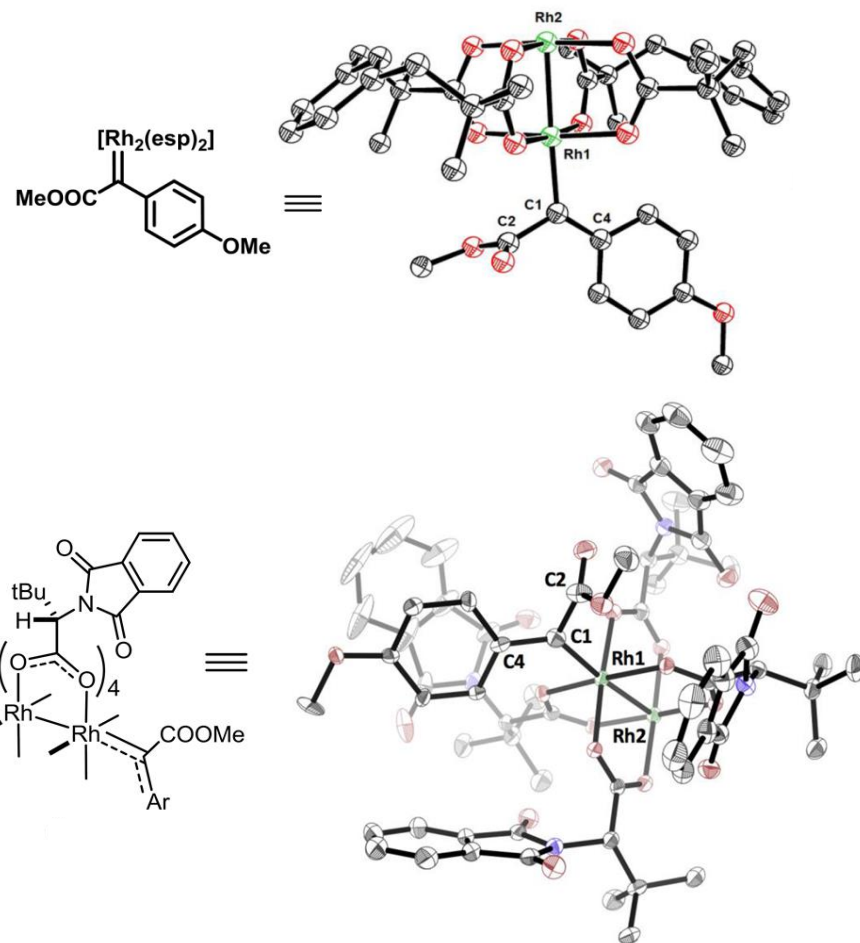
Example:



Chem. Commun., **2016**, 52, 9672

f. The structure determination of the key Rh-carbenoid intermediate.

2013, **Davies** initially reported the direct spectroscopic characterization of transition metal donor-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

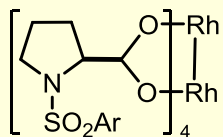
J. Am. Chem. Soc. **2016**, 138, 3797



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:

Chem. Rev., **2003**, 103, 2861.
ACIE, **2006**, 45, 6422.
Nature, **2008**, 451, 417.
Chem. Soc. Rev., **2009**, 38, 3061.

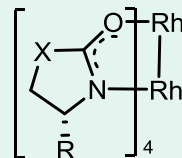


Michael P. Doyle was born in Minneapolis, MN. He received his B.S. degree from the College of St. Thomas in St. Paul, MN, and obtained his Ph.D. degree from Iowa State University. Following a postdoctoral engagement at the University of Illinois at Chicago Circle, he joined the faculty at Hope College 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
- Optimal for intramolecular C-H insertion reactions

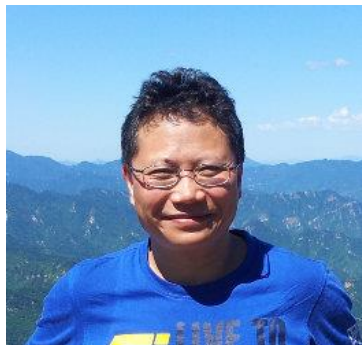


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Ph.D., Hokkaido University, 1987-1990 (with Professor Hiroshi Suginome)

Postdoctoral: University of Geneva, Switzerland, 1990-1993

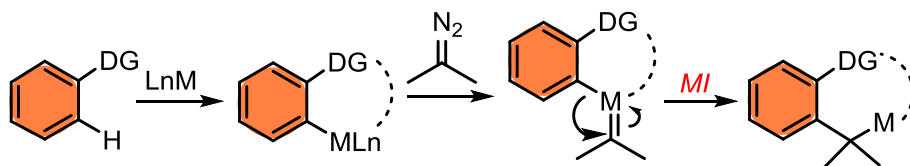
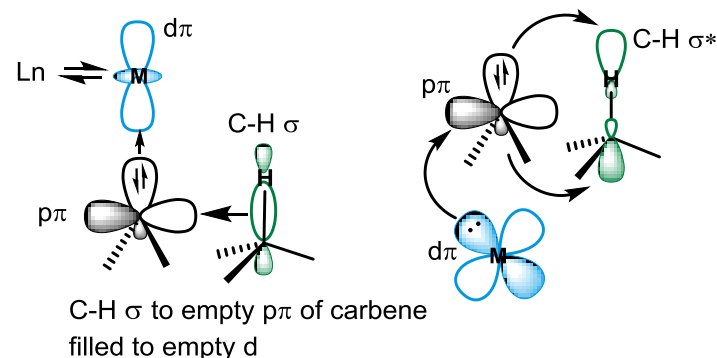
(with Professor C. W. Jefford)

Postdoctoral: University of Wisconsin-Madison, USA, 1993-1995

(with Professor H. E. Zimmerman and Professor L. A. Fahien)

Associate Professor, Peking University, 1995- 1999

Professor, Peking University, 1999-

The metal carbene migratory insertion (*MI*) type reaction.**Reviews:**F. Hu, Y. Xia, C. Ma, Y. Zhang, J. Wang, *Chem. Commun.* **2015**, 51, 7986Y. Xia, D. Qiu, J. Wang, *Chem. Rev.* **2017**, 117, 13810**Outlooks in this area**

More environmental friendly metal catalysts developing ?

Simple chiral ligands applying into enantioselective C-H insertion?

Predictable selectivity by new catalysts designing ?

Further investigation into the reaction mechanism studies ?

New mechanism of C-H insertion of carbenoid ?