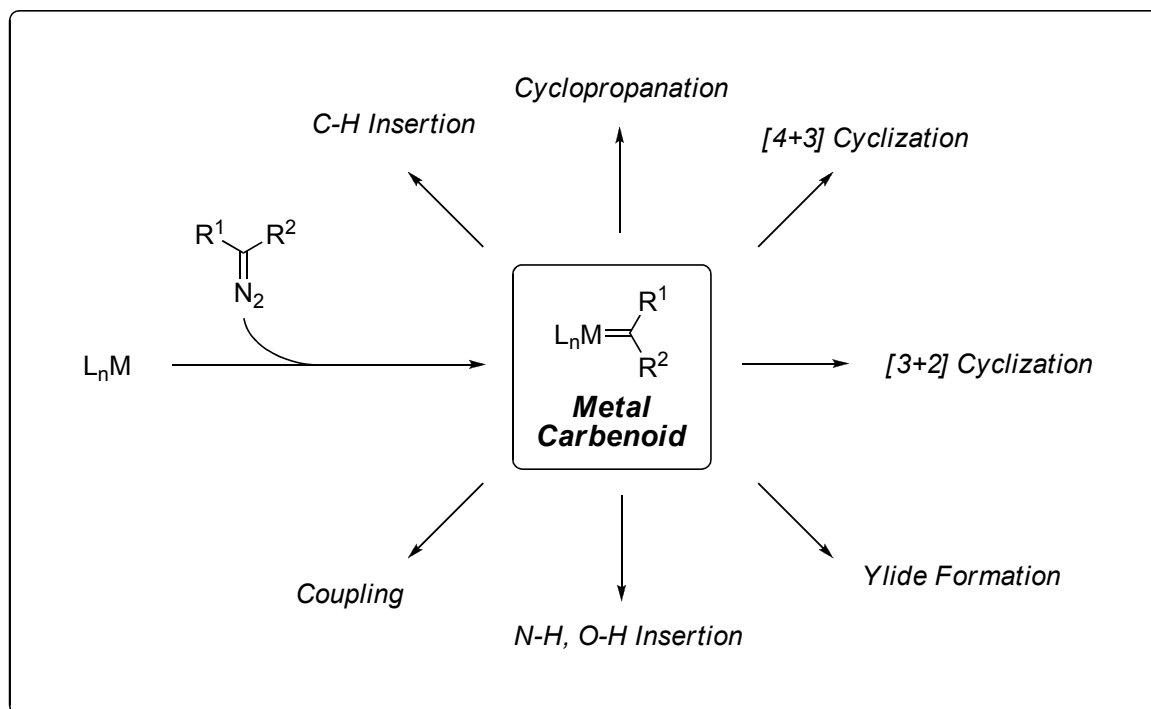


Diazo-mediated Metal Carbenoid Chemistry

~Recent Developments of Variety Bond Formation Methods~



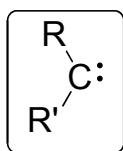
Recently, many metal catalyzed C-H activation reactions have been reported, but many reactions have not become reaction using wide range (selectivity, functional group tolerance). The metal-carbenoid intermediates are capable of undergoing a range of unconventional reactions, and due to their high energy, they are ideal for initiating cascade sequences leading to the rapid generation of structural complexity. These species are using for many type C-H activated reactions, C-C or C-heteroatom bond formations, and skeletal constructions. In this seminar, I talk about many type metal-carbenoid reactions from various metal.

Contents

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2. Rhodium Carbenoid Induced Reaction (P.3-10)
3. Copper Carbenoid Induced Reaction (P.11-12)
4. Palladium Carbenoid Induced Reaction (P.13-14)
5. Other Metal Carbenoid Induced Reaction (P.15-16)
6. Summary & Perspective (P.17)

1. Carbenoid

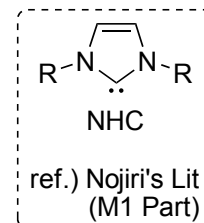
1-1. Carbene



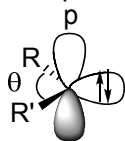
Carbene is a molecule containing a neutral carbon with a 2 valences and 2 unshared electrons.

Carbenes are classified as either singlets or triplets depending upon their electronic structure.

Most carbenes are very short lived, although persistent carbenes are known (example of stable carbene: N-Heterocyclic carbene; NHC).

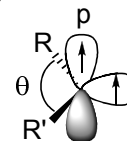


Singlet



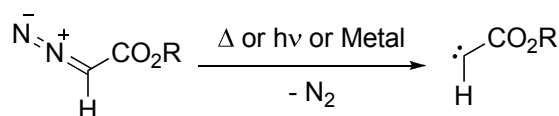
- unshared electron pair (σ orbital) and empty p orbital
- resembles carbocation and carboanion united on same carbon, so have nucleophilicity and electrophilicity (reactivity depends on substituted groups).
- many R and R' groups can stabilize singlet carbene (more than triplet carbene).
- Typical angle θ (calculated) : 100~110°

Triplet



- 2 electron was shared with p orbital and σ orbital
- resembles biradical
- Typical angle θ (calculated) : 130~150°

One of the typical carbene formation : diazo decomposition



Diazo compounds readily decompose thermally or photochemically driving force : formation of N₂ bond and generation of N₂ gas
Generated carbene is high reactivity.

In the case of using transition metal to generated carbene
⇒ **Metal-Carbenoid species is generated**

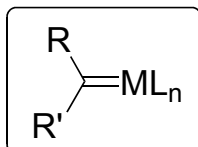
C-H Insertion
1,2-migration of alkyl
Cyclopropanylation
and other reaction...

1-2. Metal-Carbenoid

Carbenoid is a vague term used for a molecule in which all carbons are tetravalent but still has properties resembling those of a carbene, typically **the carbene-like carbon has multiple bonds with a metal**. Carbene is stabilized by Metal.

Carbenoid has unique reactivity that carbene has not, keeping the reactivity of free carbene.

Carbenoid is structurally related to **singlet carbenes** and posses similarly reactivity.



Carbenoids can be formed by reacting salts of **transition metals**.

e.g. Cu, Rh, Pd, etc... many metals can be formed.

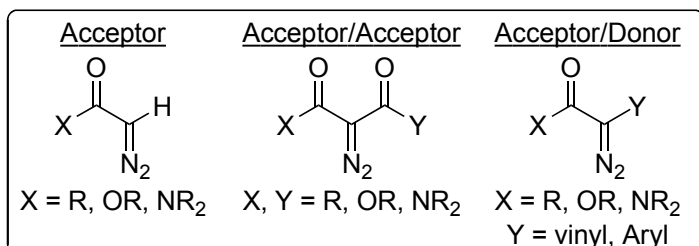
These are formed by metal with carbene precursor, typically **diazo compound**.

Kind of Diazo Compound (Carbenoid Precursor)

Carbenoid can be controled carbene reactivity through substituent (acceptors and donors).

Not enough electrophilicity causes less reactivity, and too much electrophilicity causes side-reaction, so control of electrophilicity is important.

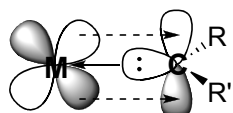
Metal-carbenoid reaction requires appropriate level of electrophilic ability at the carbenoid carbon center.



- **Acceptor/Acceptor** and **Acceptor/Donor** types stabilize diazo compound (so more active catalyst needed for decomposition).
- Donor substituent stabilized carbenoid through resonance.
- Almost metal-carbenoids have **electrophilicity**.
- Carbenoids formed from Acceptor/Acceptor compounds has high electrophilicity.

too much electrophilicity causes side-reaction, so control of electrophilicity is important.

Electron Feature of This Type Metal-Carbenoid



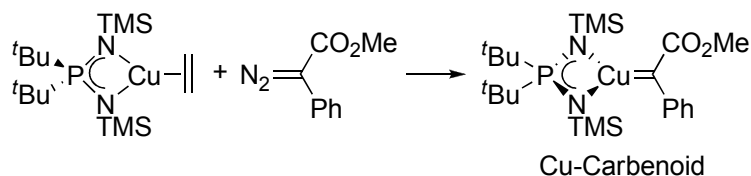
lone pair on carbon to M : strong C-M σ bond

d electrons to p orbital on carbon : weak~moderate π bond, stabilize carbene a little but still maintain its enough electrophilicity

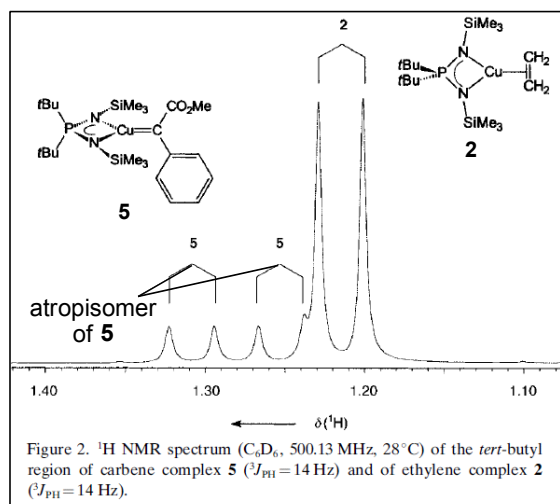
desired metal : bind to the carbene through strong σ -acceptor interactions and weak (appropriate) back donation interaction.

Observation of Carbenoid

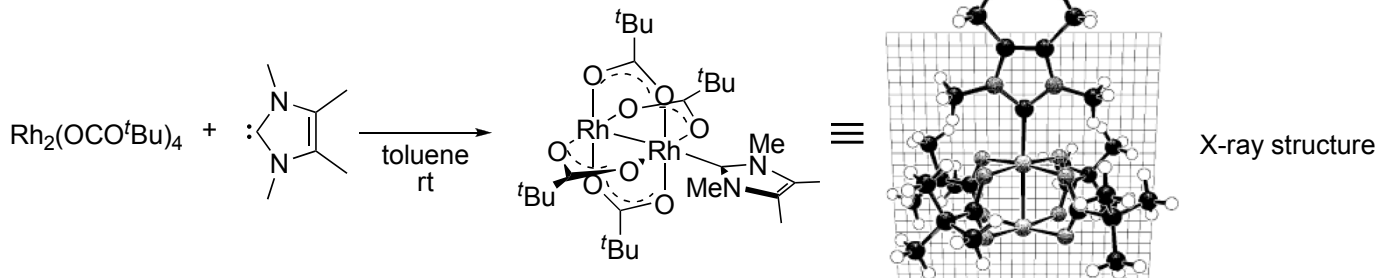
○ **Cu-Carbenoid** P. Hofmann *et al.*, *ACIE*, **2001**, *40*, 1288.



In toluene-d₈ or benzene-d₆ at rt, 15-25% Cu-complex was detected. Characterization from ¹H NMR (Figure 2), ¹³C NMR (229.9 ppm (C=N₂), 177.9 ppm (C=O)), MS (FAB; 531.2, [M⁺]). (At -33°C, this complex was maintained for several hours without significant evolution of nitrogen.)

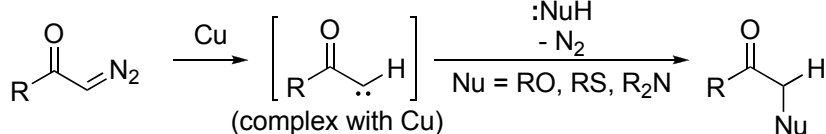


○ **Rh₂-Carbenoid** J. P. Snyder *et al.*, *JACS*, **2001**, *123*, 11318.

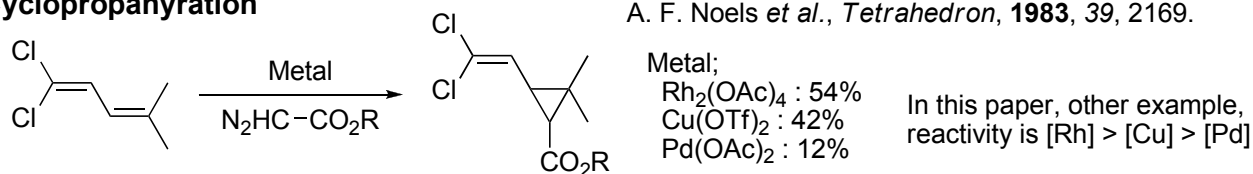


1-3. Early Example of Metal-Carbenoid Reaction

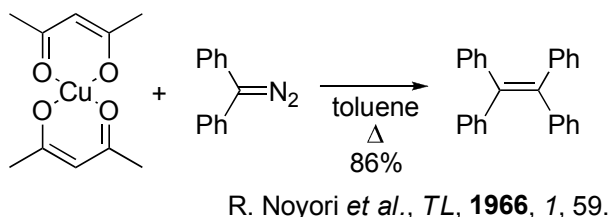
○ **Insertion** P. Yates, *JACS*, **1952**, *74*, 5376.



○ **Cyclopropanation**



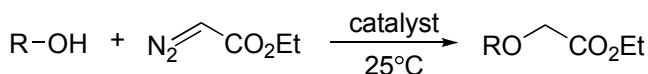
○ **Dimerization (Homometathesis)**



general metal of metal-carbenoid reaction : Rh, Cu, Pd ; most useful metal is **Rhodium**.

Dirhodium carboxylate (Rh₂L₄) H. Reimlinger *et al.*, *TL*, **1973**, *24*, 2233.

First example of Rhodium carbenoid generation from diazo decomposition.



Reactivity using Rh₂(OAc)₄ (Rh(II)) was higher than Rh(I), Rh(III).

Catalyst	diazo/Catalyst	R	Yield
Rh ₂ (OAc) ₄	600	Et	88
Rh ₂ (OAc) ₄	600	<i>i</i> Pr	83
Rh ₂ (OAc) ₄	600	<i>t</i> Bu	82
Rh ₂ (OAc) ₄	600	H	80
Rh ₂ (OAc) ₄	600	Ac	93
RhCl ₃ ·3H ₂ O	125	Et	64
RhCl ₃ ·3H ₂ O	125	<i>t</i> Bu	58
RhCl(PPh ₃) ₃	125	Et	49

2. Rhodium Carbenoid Induced Reaction

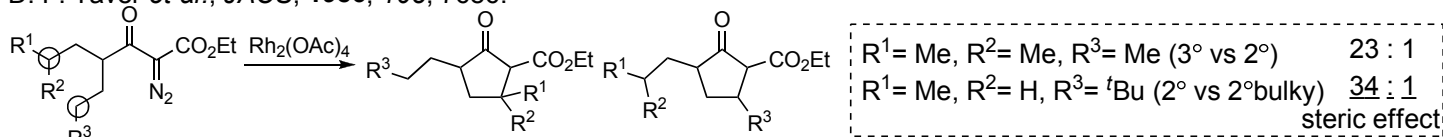
2-1. C-H Insertion

ref.) Yamaguchi's Lit (M1 Part)

Trend in Selectivity

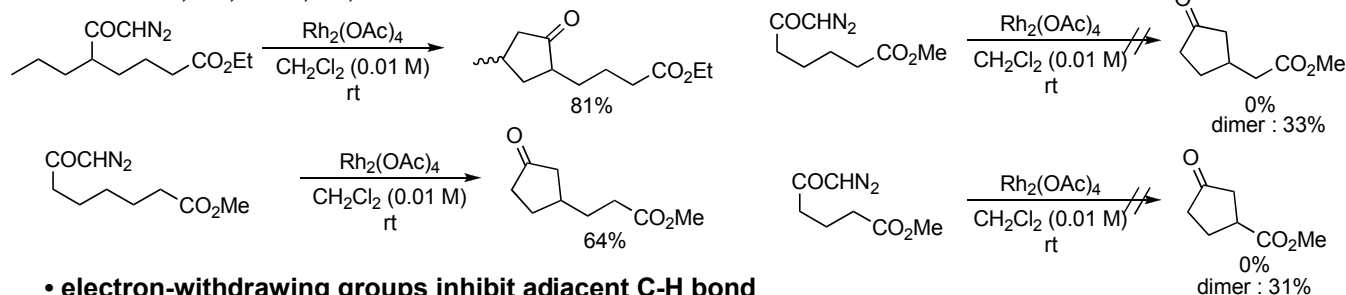
In simple case, Reactivity is determined with both electric effect and steric effect.

D. F. Taver *et al.*, *JACS*, **1986**, *108*, 7686.



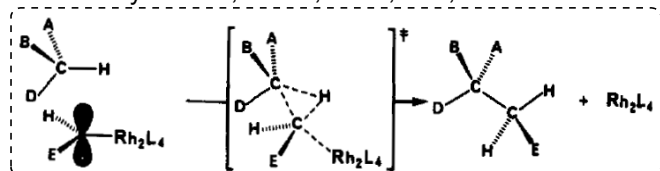
tertiary > secondary > primary (electric effect; electron density in the C-H bond)

G. Stork *et al.*, *TL*, **1988**, *29*, 2283.



Mechanism

M. P. Doyle *et al.*, *JACS*, **1993**, *115*, 958.

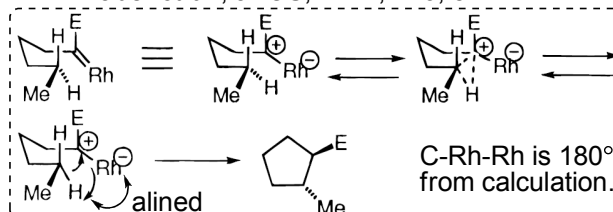


They didn't perform DFT calculation, but they expected from ligand (L) effect of C-H insertion.

low EWG : general selectivity

high EWG : selectivity is decreased (attack low steric barrier)

D. F. Taber *et al.*, *JACS*, **1996**, *118*, 547.

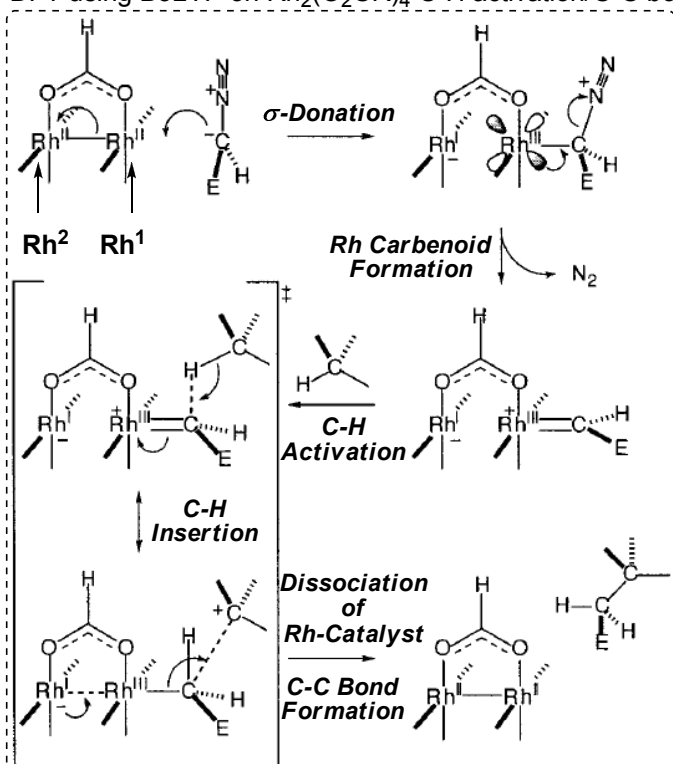


This mechanism was expected from experiments results, and ZINDO calculation was performed to ylide intermediate.

These mechanisms were plausible and widely accepted, but additional analysis of mechanism was performed for further development of the C-H activation chemistry.

○ **Proposed mechanism from DFT calculation** E. Nakamura *et al.*, *JACS*, **2002**, *124*, 7181.

DFT using B3LYP on $\text{Rh}_2(\text{O}_2\text{CR})_4$ C-H activation/C-C bond formation reaction.

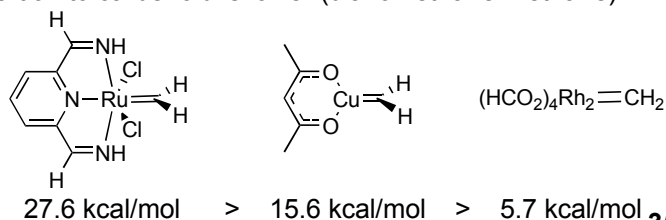


calculated for $[\text{Rh}_2(\text{O}_2\text{CH})_4 - \text{CH}_2\text{N}_2 - \text{methane or propane}]$ and $[\text{Rh}_2(\text{O}_2\text{CH})_4 - \text{N}_2\text{CHCO}_2\text{Et} - \text{methane or propane}]$

- carboxylate groups serves as anchors of the Rh^2 atom
- electron-withdrawing group (E) enhances the electrophilicity of the carbene carbon center
- Rh^1 has positive charge which increases the electrophilicity of carbon center
- electron donation from Rh^2 to Rh^1 assist the C-C bond formation and catalyst regeneration.
- If chiral ligand was used, it also serves as the site to harness chirality.

Activated energy is decreased, so C-H Insertion is enhanced.

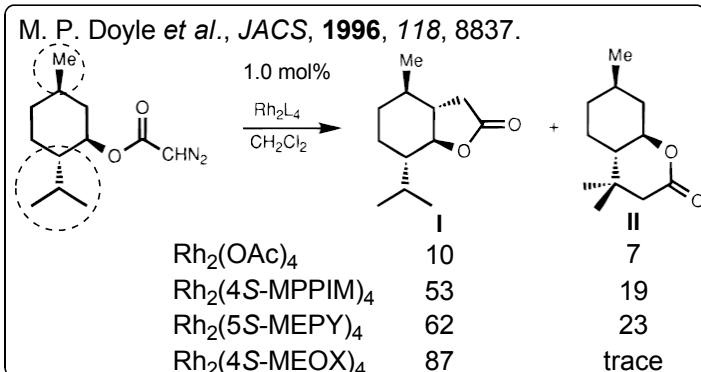
compared to Cu-carbenoid and Ru-carbenoid, energy of C-H insertion to carbenoid is lower (diazomethane-methane).



Stereo-/Chemo-Selective Reaction

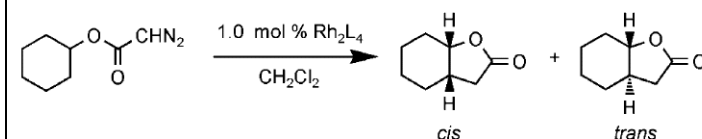
Review; H. M. L. Davies *et al.*, *Chem. Rev.*, **2003**, 103, 2861.
 H. M. L. Davies, *ACIE*, **2006**, 45, 6422.
 H. M. L. Davies *et al.*, *Nature*, **2008**, 451, 417.
 H. M. L. Davies *et al.*, *Chem. Soc. Rev.*, **2009**, 38, 3061.

○ Intramolecular reaction



M. P. Doyle *et al.*, *JOC*, **2005**, 70, 5291.

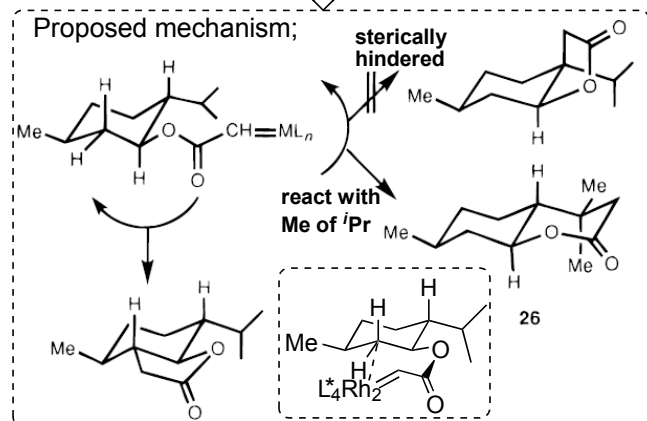
TABLE 3. Carbon-Hydrogen Insertion Reaction of Cyclohexyl Diazoacetate^a



catalyst	yield (%) ^b	cis/trans ^c	% ee cis ^c	% ee trans ^c
Rh ₂ (4S-MPPIM) ₄ , 1	71	100/0	92	na
Rh ₂ (4S,2'S,3'S-MCPIM) ₄ , 11	78	99/1	97	nd
Rh ₂ (4S,2'R,3'R-MCPIM) ₄ , 12	63	80/20	72	13
Rh ₂ (4S,2'S-BSPIM) ₄ , 15	88	97/3	>99	>99
Rh ₂ (4S,2'R-BSPIM) ₄ , 16	89	98/2	74	33

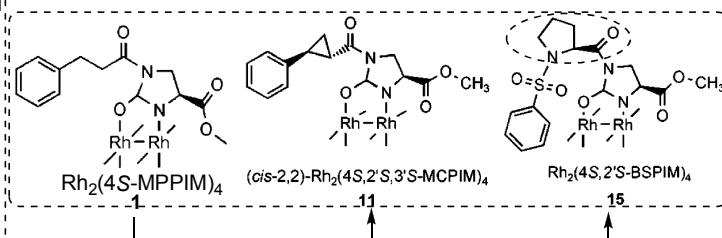
^a Reactions performed in refluxing CH₂Cl₂ using 1.0 mol % catalyst. ^b Reported as isolated yields after column chromatography. ^c cis/trans ratios and enantiomeric excesses were determined by gas chromatography.

In this type reaction, it was thought that Rh-carbenoid reacts with equatorial C-H, because access to axial C-H is prevented by crowding of the cyclohexane ring.



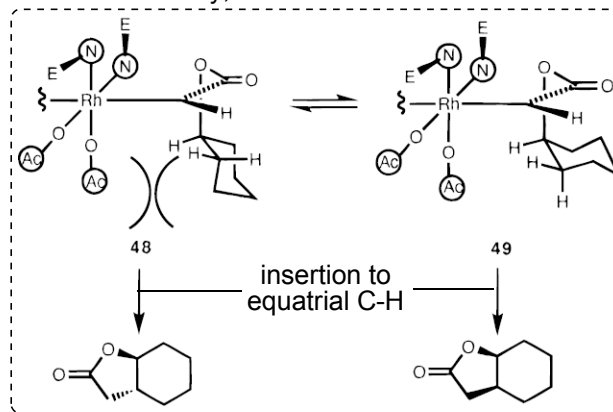
conformation should be locked as all the substituents are placed at equatorial position

- Equilibrium depends on the ligand (catalyst) (whether the substituent is at axial or equatorial).
- Small ligand leads to low diastereoselectivity. (L=OAc, 40:60; *JACS*, **1994**, 116, 4507.)
- Rh-carbenoid reacts with equatorial C-H, so in appropriate ligand, reaction is *cis* selectivity.

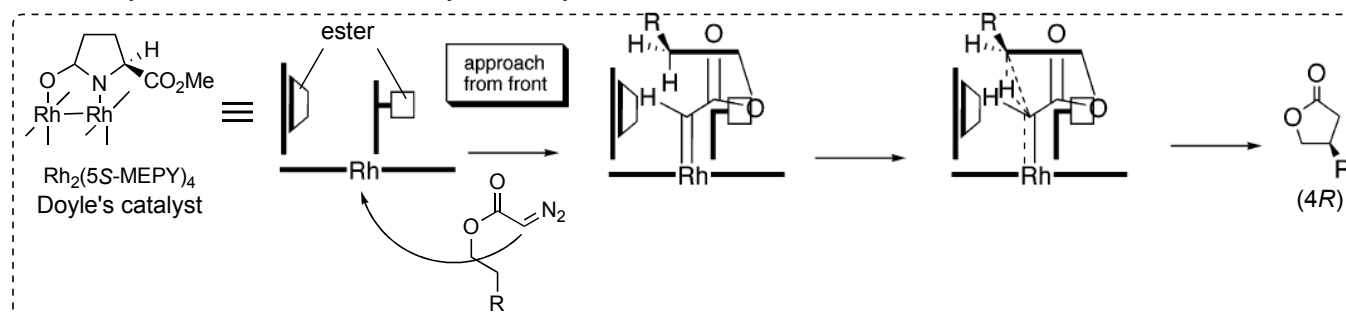


additional chiral attachment, so ee was increased.

- **12, 16**: direction of additional chiral attachment is mismatched.
- diastereoselectivity;



- Model for asymmetric induction with Doyle's catalysts;



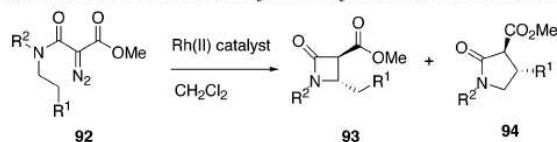
In the cases of other type ligands, they are expected by similarly catalysis model.

• lactam formation

S. Hashimoto *et al.*, *Synlett*, **1994**, 12, 1031.

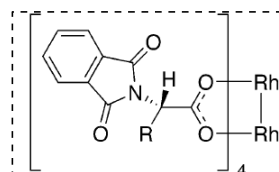
H. M. L. Davies *et al.*, *Chem. Rev.*, **2003**, 103, 2861.

Table 17. Intramolecular C–H Activation of α -Methoxycarbonyl- α -diazoacetamides

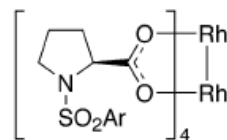


compd	catalyst	R ¹	R ²	product ^a	yield, %	de, %	ee, %
a	Rh ₂ (S-PTPA) ₄	CO ₂ Et	^t Bu	93	98	>98	56
b	Rh ₂ (S-PTPA) ₄	C ₂ H ₅	^t Bu	93	97	>98	60
c	Rh ₂ (S-PTPA) ₄	C ₆ H ₅	^t Bu	93	>90	>98	74
d	Rh ₂ (S-PTPA) ₄	C ₆ H ₅	<i>p</i> -MeOC ₆ H ₄	94	<5 ^b		
e	Rh ₂ (S-PTPA) ₄	C ₆ H ₅	<i>p</i> -NO ₂ C ₆ H ₄	94	82	>98	47
e	Rh ₂ (S-PTA) ₄	C ₆ H ₅	<i>p</i> -NO ₂ C ₆ H ₄	94	83	>98	47
e	Rh ₂ (S-PTV) ₄	C ₆ H ₅	<i>p</i> -NO ₂ C ₆ H ₄	94	82	>98	26
e	Rh ₂ (S-PTTL) ₄	C ₆ H ₅	<i>p</i> -NO ₂ C ₆ H ₄	94	80	>98	74
e	Rh ₂ (S-TBSP) ₄	C ₆ H ₅	<i>p</i> -NO ₂ C ₆ H ₄	94	87	>98	6
f	Rh ₂ (S-PTTL) ₄	CH ₃	<i>p</i> -NO ₂ C ₆ H ₄	94	82	>98	33
g	Rh ₂ (S-PTTL) ₄	C ₂ H ₅	<i>p</i> -NO ₂ C ₆ H ₄	94	84	>98	34
h	Rh ₂ (S-PTTL) ₄	C ₆ H ₅	<i>p</i> -NO ₂ C ₆ H ₄	94	80	>98	74
i	Rh ₂ (S-PTTL) ₄	<i>p</i> -MeOC ₆ H ₄	<i>p</i> -NO ₂ C ₆ H ₄	94	72	>98	81
j	Rh ₂ (S-PTTL) ₄	<i>p</i> -NO ₂ C ₆ H ₄	<i>p</i> -NO ₂ C ₆ H ₄	94	81	>98	73

^a Exclusive product. ^b Major product arose from electrophilic addition to aryl ring of *p*-methoxyphenyl.



R = Bn Rh₂(S-PTPA)₄
 R = Me Rh₂(S-PTA)₄
 R = ⁱPr Rh₂(S-PTV)₄
 R = ^tBu Rh₂(S-PTTL)₄
 R = Ph Rh₂(S-PTPG)₄



Ar = ^tBuC₆H₄ Rh₂(S-TBSP)₄

- In the case of R₂ is alkyl group, β -lactam is obtained, but in R² is Aryl groups, γ -lactam is obtained.

⇒ Electron density of nitrogen atom is important.

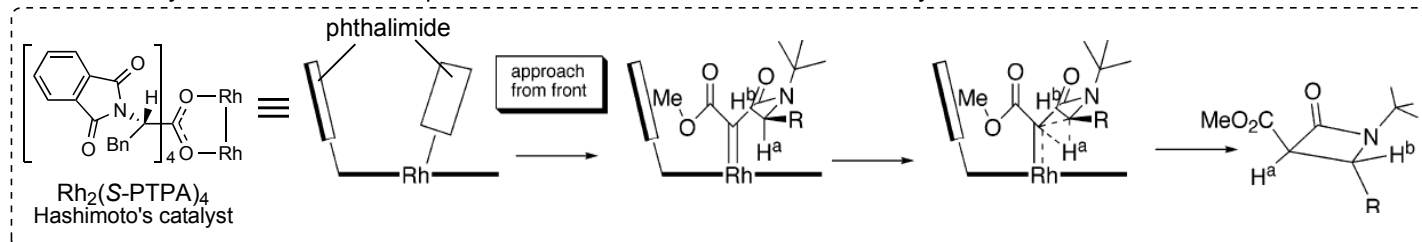
When N has electron-enough, C-H insertion at adjacent to N is enhanced (in insertion mechanism, C-H insertion process is activated by push of unshared-electron pair).

When N has electron-withdrawing group (Ar, carbonyl), β -lactam cyclization is inactivated, and γ -lactam is obtained.

- This is acceptor/acceptor type, reactivity is so high. So enantioselectivity is low, but R¹ = Ar, selectivity is increased.

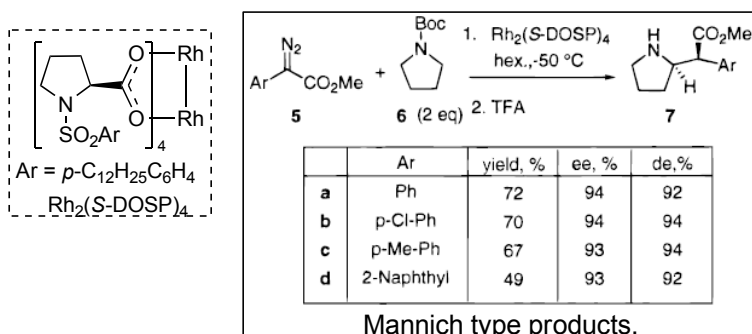
⇒ Benzyl position is slightly lower reactivity than saturated aliphatic C-H because of electron-withdrawing nature of Ph group, so reactivity is controlled, and enantioselectivity is increased.

- Model for asymmetric induction in β -lactam formation with Hashimoto's catalyst.

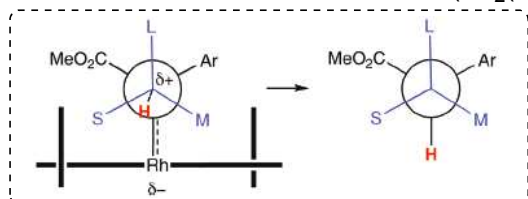


○ Intermolecular reaction

- Simple reaction system and chemoselectivity



Newmann model of intermolecular reaction (Rh₂(S-DOSP)₄).



H. M. L. Davies *et al.*, *JOC*, **2009**, 74, 6555.



diastereoselectivity is depended on size of substituents.

H. M. L. Davies *et al.*, *JACS*, **2000**, 122, 3063.

H. M. L. Davies *et al.*, *JACS*, **1999**, 121, 6509.

H. M. L. Davies *et al.*, *JACS*, **1997**, 119, 9075.

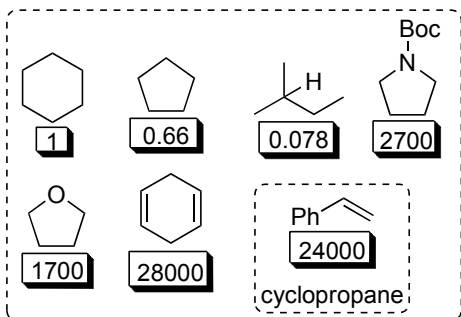
Table 1. Asymmetric C–H Activation of Cycloalkanes

diazo	Ar	n	product	yield, %	ee, %
3a	C ₆ H ₅	2	4a	80	95
3b	<i>p</i> -BrC ₆ H ₄	2	4b	64	95
3c	<i>p</i> -ClC ₆ H ₄	2	4c	76	94
3d	<i>p</i> -(MeO)C ₆ H ₄	2	4d	23 ^a	88
3e	<i>o</i> -ClC ₆ H ₄	2	4e	81	90
3f	<i>m</i> -ClC ₆ H ₄	2	4f	47	94
3g	<i>p</i> -CF ₃ C ₆ H ₄	2	4g	78	94
3h	<i>p</i> -MeC ₆ H ₄	2	4h	63	93
3i	<i>o</i> -BrC ₆ H ₄	2	4j	72	90
3j	<i>m</i> -BrC ₆ H ₄	2	4k	62	95
3a	C ₆ H ₅	1	5a	72	96
3c	<i>p</i> -ClC ₆ H ₄	1	5c	70	95

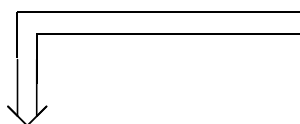
^a 3 mol% of catalyst was used. At 80°C, 85%, 67%ee.

- enantioselective reaction
- electron-donating groups on Ar decrease reactivity, probably because of the lower electrophilicity.
- adjacent to heteroatom, reactivity is increased.

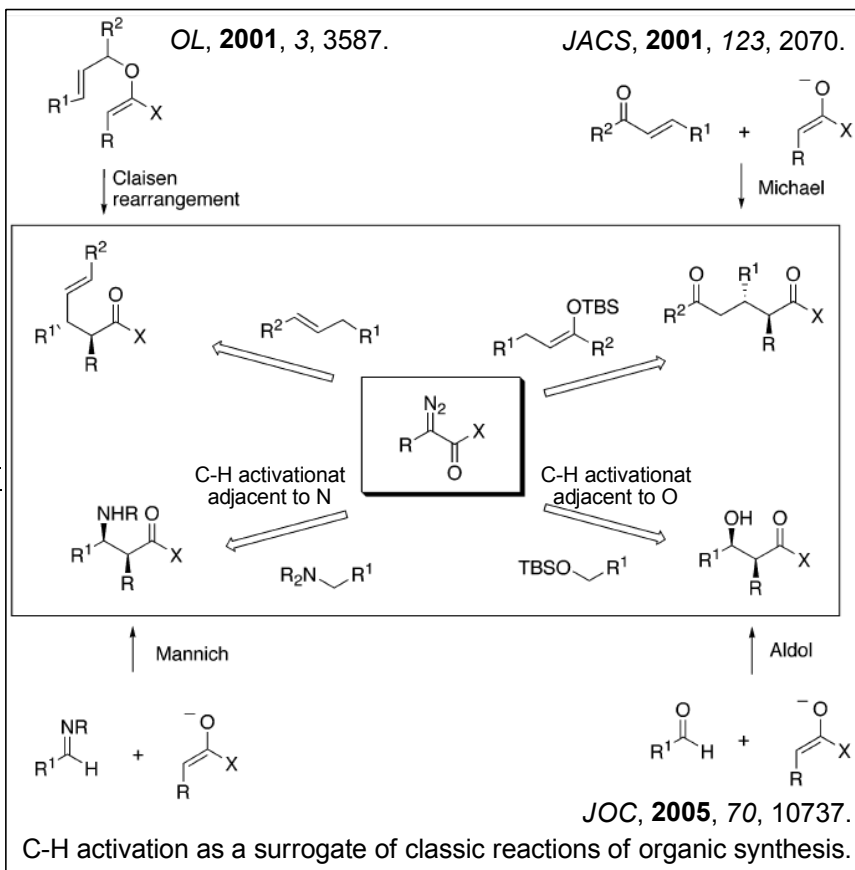
Relative rates of reaction various substrates.



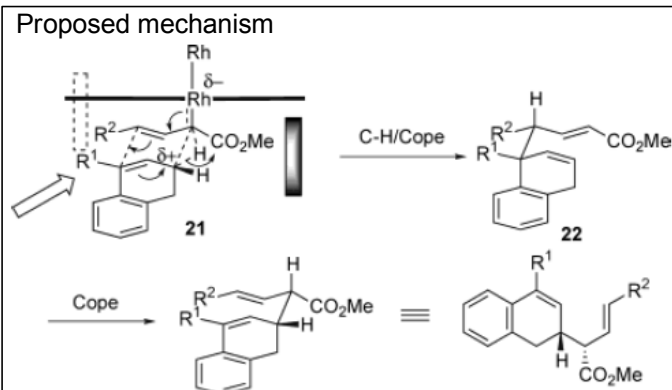
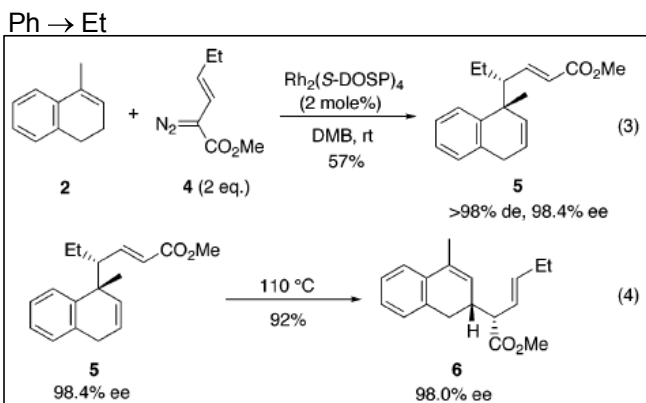
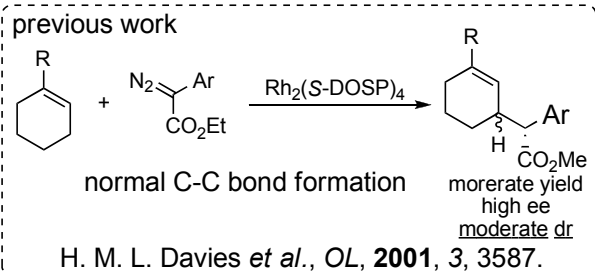
reaction rate is so different with respect to substrates (functional groups), so selective reaction is possible.



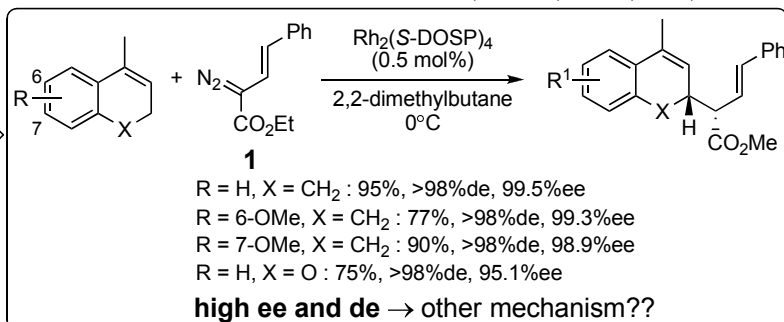
Intermolecular metal-carbenoid C-H insertion can replace with classical C-C bond formation, in high stereoselectivity.



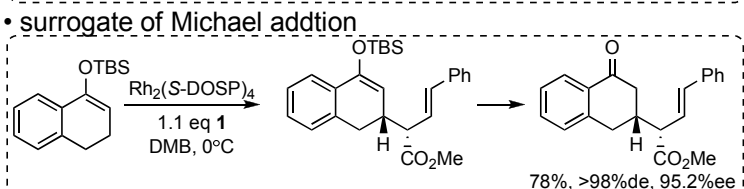
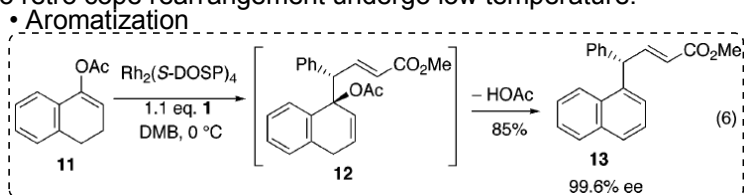
C-H Insertion/Cope Rearrangement



H. M. L. Davies *et al.*, JACS, 2004, 126, 10862.

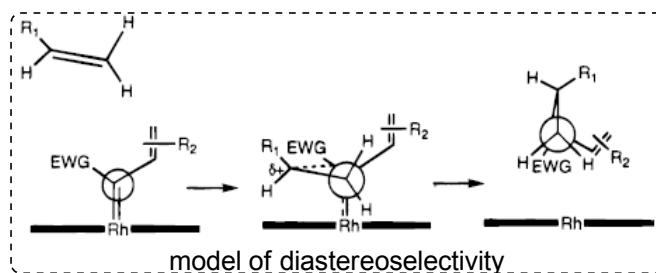
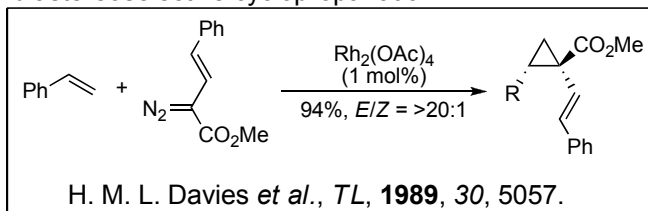


- first step: C-C bond formation of benzyl position (olefin side) (3) high stereoselective reaction by Rh₂(S-DOSP)₄ ⇒ **C-H activation/Cope rearrangement**
 - second step: cope rearrangement
- consecutive 2 steps reaction, apparent direct C-H activation
- using diazo 4, second retro cope rearrangement is unfavored, so high temperature is required.
- Et → Ph, because of conjugated with Ph after rearrangement, so retro cope rearrangement undergo low temperature.

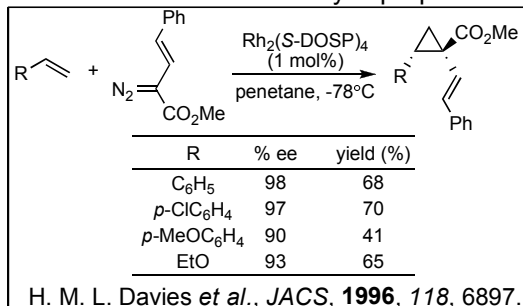


2-2. Cyclopropanation

diastereoselective cyclopropanation



enantio/diastereoselective cyclopropanation



- R¹ is saturated alkyl group (not shown, TL paper) : diastereoselectivity is decreased.
→ intermediate is not stabilized??
(but when bulky ligand is used, it is improved (JACS paper).)
- R² is donor group (Ar, allyl) → diastereoselectivity is increase.
(R² = acceptor (e.g. ester) : selectivity is decreased, acceptor/acceptor type carbenoid is too much reactivity)
- using chiral Rh catalyst, high ee was obtained.

Enantioselective Cyclopropanation of Allenes

H. M. T. M. Gregg *et al.*, *OL*, **2009**, *11*, 4434.

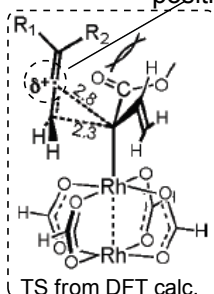
Table 1. Cyclopropanation of Monosubstituted Allenes

allene	R	product	% yield	% ee
1a	Ph	3a	76	90
1b	<i>p</i> -ClC ₆ H ₄	3b	61	84
1c	C ₅ H ₁₁	3c	60	88
1d	CH ₂ Ph	3d	54	>80 ^a

Table 2. Cyclopropanation of 1,1-Disubstituted Allenes

allene	R	R'	product	% yield	% ee
5a	Ph	CH ₃	6a	33	86
5b	CH ₃	CH ₃	6b	30	90
5c	(CH ₃) ₃ Si	CH ₃	6c	79	85

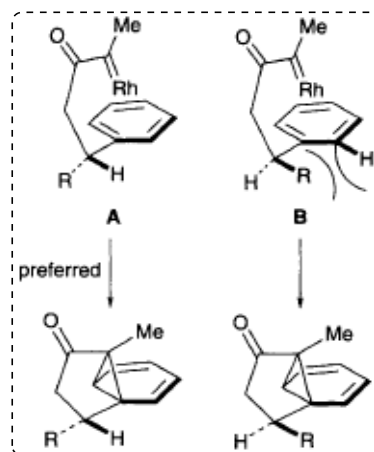
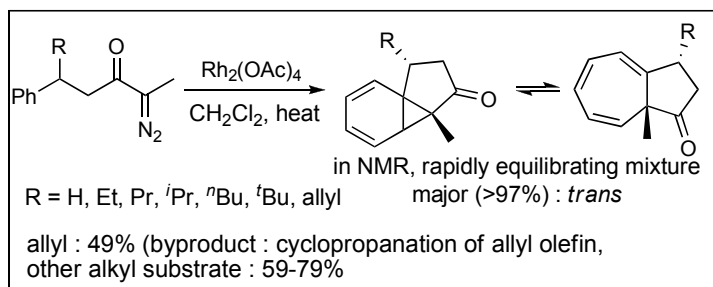
positive charge



- In toluene solvent, trace product is obtained. Maybe cyclopropanation of aromatic rings and α -methyl C-H insertion is proceeded, so it is suggested that cyclopropanation of allene is slowly.
- Reaction is proceeded at only indicated no substituted olefin.
- Aryl allene and aliphatic allene are succeeded moderate~good yield and ee.
- Disubstituted allenes are decreased reactivity because of sterically barrier (see TS).
- In TS, there is positive carbon on the central carbon of the allene, so stabilized substituents give high reactivity (e.g. silyl).

Buchner ring expansion

A. R. Maguire *et al.*, *Chem. Comm.*, **1996**, 2595.



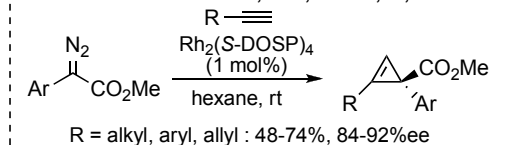
steric effect of cyclization

- Benzen ring is reacted with metal-carbenoid species.
- In this case, R groups stericallyblock, diastereoselectivity is appeared.

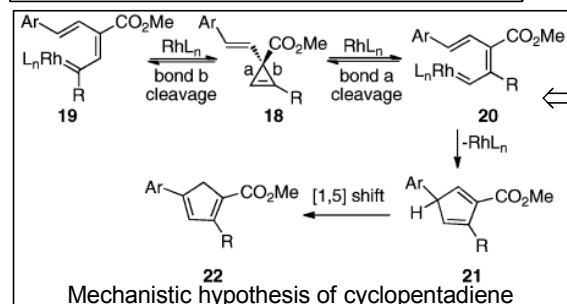
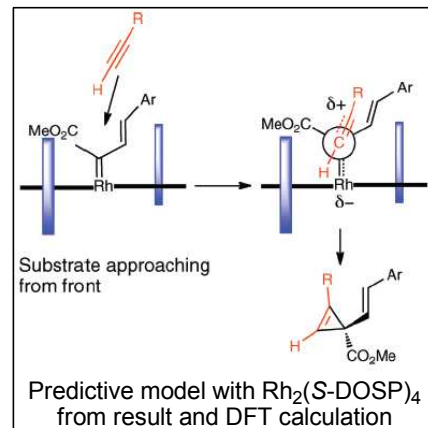
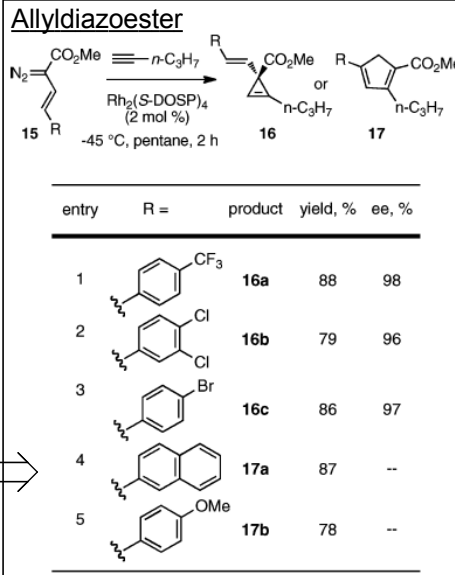
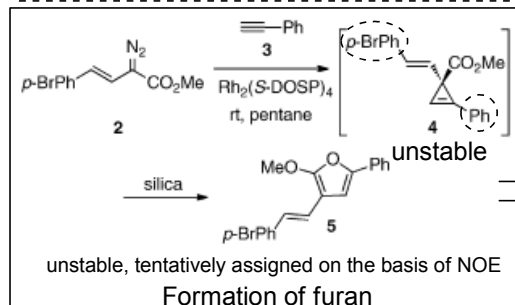
Enantioselective Cyclopropanation of Alkyne

H. M. L. Davies *et al.*, *JACS*, 2010, 132, 17211.

H. M. L. Davies *et al.*, *OL*, 2004, 6, 1233.



Ar = EWG, heteroaromatic : moderate yield and high ee
 EDG : low yield and moderate ee
 → lower reactivity of *p*-methoxyphenyl carbenoid.
allylic : not obtained (can't isolate)

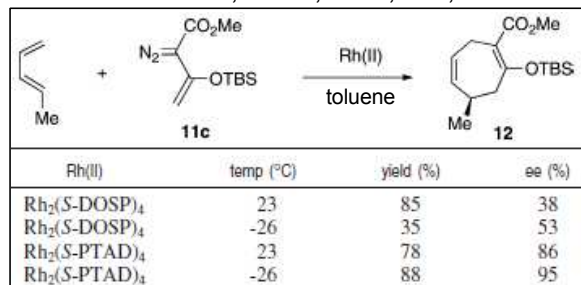


- At low temperature, cyclopropene is generally obtained in high enantioselectivity.
- When Ar has EDG, **cyclopentadiene** is generated.
- At reflux, cyclopropene is not observed, cyclopentadiene is obtained.
- Disubstituted alkynes are no reaction : sterically barrier (in TS)

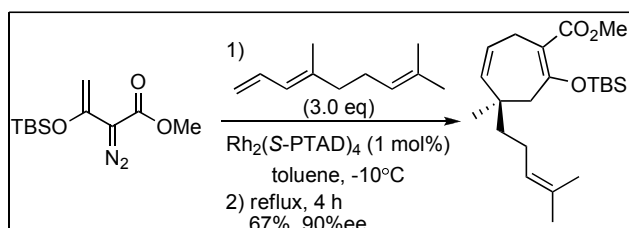
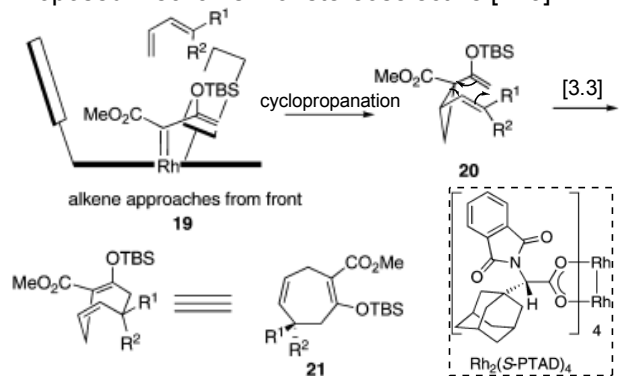
[4+3] Cyclization : Tandem Cyclopropanation/Cope Rearrangement (for diene)

○ With simple diene

H. M. L. Davies *et al.*, *JACS*, 2009, 131, 8329.

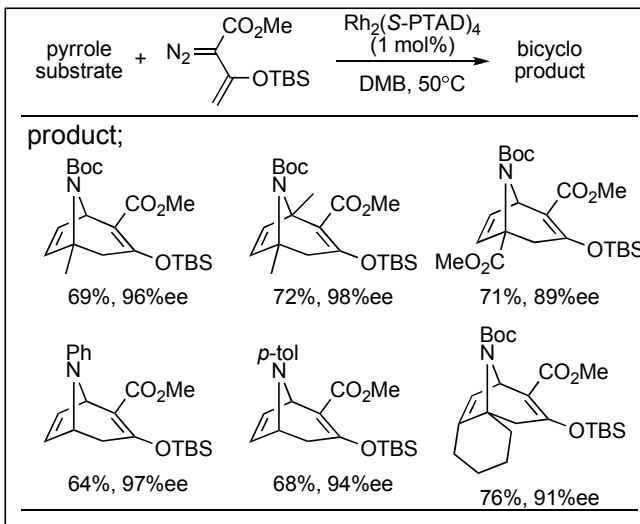
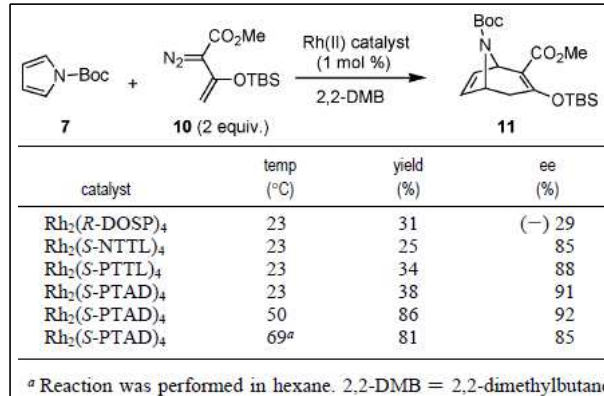


Proposed mechanism of stereoselective [4+3]



○ With heteroaromatic

H. M. L. Davies *et al.*, *JACS*, 2007, 129, 10312.

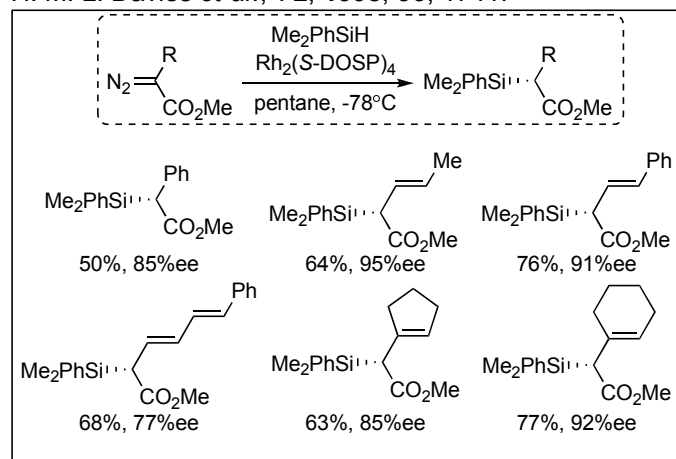


less substituted olefin is preferentially proceeded first cyclopropanation

2-5. Heteroatom-H Insertion

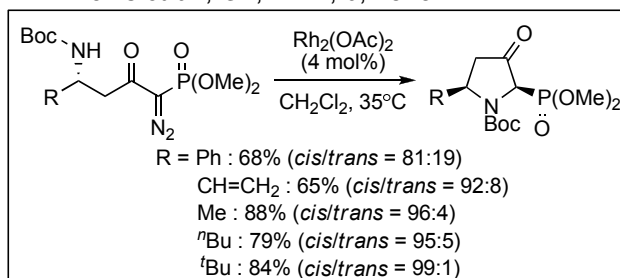
○Si-H Insertion

H. M. L. Davies *et al.*, *TL*, **1998**, *38*, 1741.



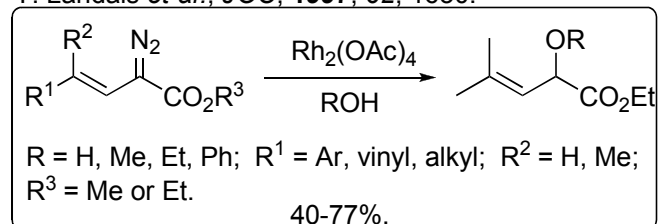
○N-H Insertion

F. A. Davis *et al.*, *OL*, **2004**, *6*, 4523.



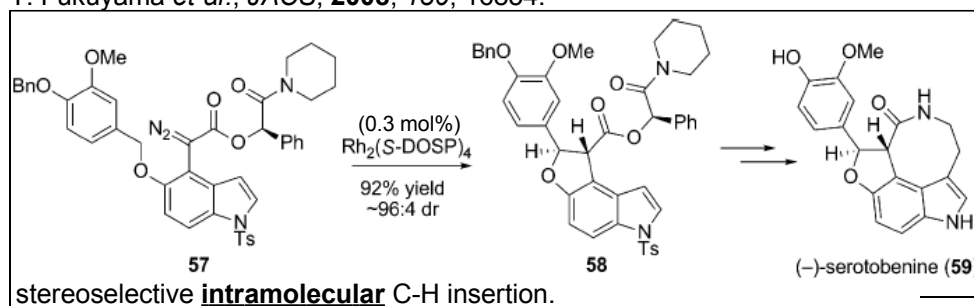
○O-H Insertion

Y. Landais *et al.*, *JOC*, **1997**, *62*, 1630.

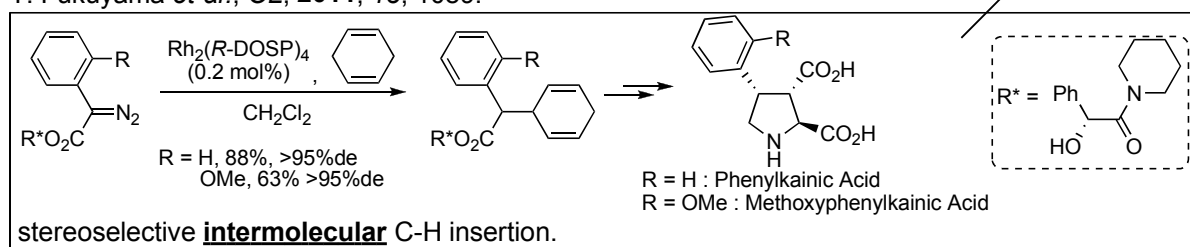


2-6. Total Synthesis using Rhodium Carbenoid

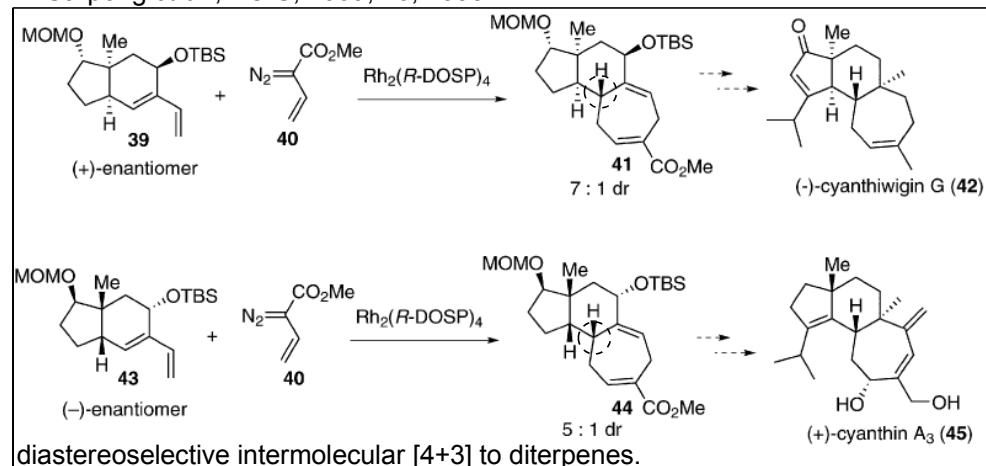
T. Fukuyama *et al.*, *JACS*, **2008**, *130*, 16854.



T. Fukuyama *et al.*, *OL*, **2011**, *13*, 1089.



R. Sarpong *et al.*, *ACIS*, **2009**, *48*, 2398.

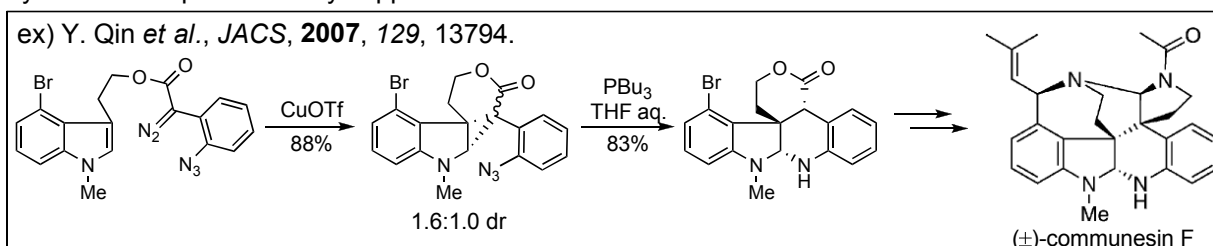


3. Copper Carbenoid Induced Reaction

Copper carbenoid is shown the similar reaction for Rhodium carbenoid reaction.

But to manipulate reagents and conditions, higher reactivity and selectivity can be afforded.

Copper carbenoid can be proceeded main metal-carbenoid reaction, C-H insertion and cyclopropanation, and total synthesis was performed by copper carbenoid induced reaction.



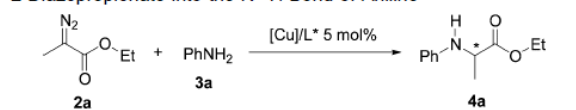
Reactivity of many C-H insertion or cyclopropanation using Copper carbenoid is lower or same for Rhodium carbenoid. But heteroatom(N, O, Si, S)-H insertion reaction is significantly improvement of ee compared for Rhodium carbenoid.

N-H Insertion

Q.-L. Zhou *et al.*, *JACS*, **2007**, *129*, 5834.

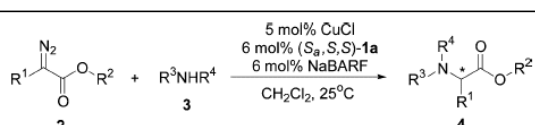
α -amino acid derivative (N-Ar) synthesis.

Table 1. Cu-Catalyzed Asymmetric Insertion of Ethyl 2-Diazoacetate into the N-H Bond of Aniline^a



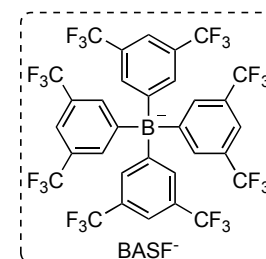
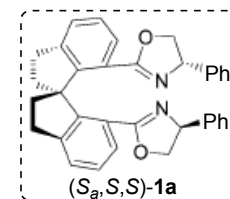
entry	ligand	[Cu]	solvent	time (h)	yield (%) ^b	ee (%) ^c
1	(S _a ,S,S)-1a	CuPF ₆ (MeCN) ₄	CH ₂ Cl ₂	2	78	43
2	(R _a ,S,S)-1a	CuPF ₆ (MeCN) ₄	CH ₂ Cl ₂	2	95	5
3	(S _a ,S,S)-1a	CuOTf(Tol) _{11/2}	CH ₂ Cl ₂	2	83	5
4	(S _a ,S,S)-1a	CuCl	CH ₂ Cl ₂	24	15	rac
5	(S _a ,S,S)-1a	CuCl/NaBARF	CH ₂ Cl ₂	2	94	98
6 ^d	(S _a ,S,S)-1a	CuCl/NaBARF	CH ₂ Cl ₂	2	90	95
7	(S _a ,S,S)-1a	CuCl ₂ /NaBARF	CH ₂ Cl ₂	2	80	85
8	(S _a ,S,S)-1a	CuCl/NaBARF	CHCl ₃	2	89	98
9	(S _a ,S,S)-1a	CuCl/NaBARF	C ₆ H ₆	6	80	85
10	(S _a ,S,S)-1a	CuCl/NaBARF	MeCN	72	45	rac
11	(S _a ,S,S)-1b	CuCl/NaBARF	CH ₂ Cl ₂	2	83	61
12	(S _a ,S,S)-1c	CuCl/NaBARF	CH ₂ Cl ₂	2	90	79
13	(S _a ,S,S)-1d	CuCl/NaBARF	CH ₂ Cl ₂	2	75	85
14	(S,S)-Ph-Box	CuCl/NaBARF	CH ₂ Cl ₂	2	66	5

^a Reaction conditions: [Cu] (0.01 mmol), ligand (0.012 mmol), and NaBARF (0.012 mmol) (entries 5–14) were mixed in solvent (2 mL) for 2 h at 25 °C, then aniline (0.2 mmol) and ethyl 2-diazoacetate (0.2 mmol) were introduced and stirred at 25 °C. ^b Isolated yield. ^c Determined by chiral HPLC using a Chiralpak AS column. ^d With 1 mol % of catalyst, refluxing.



entry	R ¹	R ²	R ³	R ⁴	product	yield (%)	ee (%)
1	Me	Et	Ph	H	4a	94	98
2	Me	Et	<i>p</i> -MePh	H	4b	94	91
3	Me	Et	<i>p</i> -MeOPh	H	4c	96	85
4	Me	Et	<i>p</i> -ClPh	H	4d	92	98
5	Me	Et	<i>p</i> -BrPh	H	4e	95	98
6	Me	Et	<i>m</i> -MePh	H	4f	92	96
7	Me	Et	<i>m</i> -ClPh	H	4g	95	97
8	Me	Et	<i>m</i> -BrPh	H	4h	96	98
9	Me	Et	<i>o</i> -MePh	H	4i	95	98
10	Me	Et	<i>o</i> -MeOPh	H	4j	86	98
11	Me	Et	<i>o</i> -ClPh	H	4k	95	88
12	Me	Et	1-naphthyl	H	4l	89	98
13	Me	Et	2-naphthyl	H	4m	91	98
14	Me	Me	Ph	H	4n	78	96
15	Me	^t Bu	Ph	H	4o	93	96
16 ^b	Et	Et	Ph	H	4p	51	94
17	Ph	Et	Ph	H	4q	85	8
18	Me	Et	Ph	Me	4r	93	rac
19 ^c	Me	Et	Bz	H	4s	55	rac
20	Me	Et	<i>c</i> -C ₆ H ₁₁	H			NR ^d

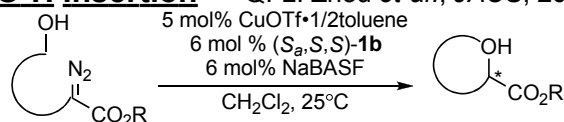
^a Reaction conditions were the same as those in Table 1, entry 5. For the characterization and analysis of ee values of insertion products, see Supporting Information. ^b Reaction time: 48 h. ^c Reaction time: 16 h. ^d No reaction.



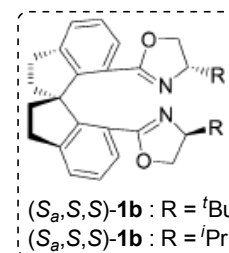
- Counter anion effect is so high, the smaller and slightly coordinating OTf is inferior to the PF₆ in the enantiocontrol.
- with the larger and non-coordination ion BARF⁻, reactivity and enantioselectivity is significantly increased.
- steric-hindrance diazoacetate (Entry 17), secondary amine (Entry 18), amide (Entry 19) → enantioselectivity is so low.

O-H Insertion

Q.-L. Zhou *et al.*, *JACS*, **2010**, *132*, 16374.



entry	α -diazo compound 2	product 3	yield (%)	ee (%)	entry	α -diazo compound 2	product 3	yield (%)	ee (%)
1	2a	3a	80	93	7	2g	3g	98	97 (R)
2	2b	3b	89	90	8	2h	3h	94	95
3	2c	3c	77	88	9	2i	3i	63	93
4	2d	3d	95	92	10	2j	3j	81	88
5	2e	3e	96	92	11	2k	3k	80	95
6	2f	3f	97	82	12	2l	3l	79	97
					13	2m	3m	14 (70) ^b	95 (83) ^b



high yield and high selective reaction for pyran rings and furan rings. In seven-membered ring, reactivity is so decreased, but using ligand 1c, good yield and selectivity is obtained.

○ Calculated Study for O-H Insertion into Water, Cu vs. Rh

Z.-X. Yu *et al.*, *JACS*, **2009**, *131*, 17783.

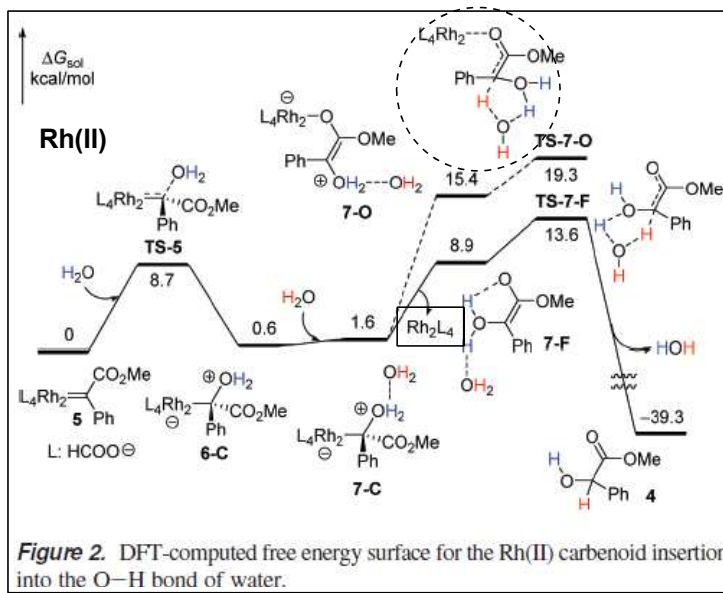
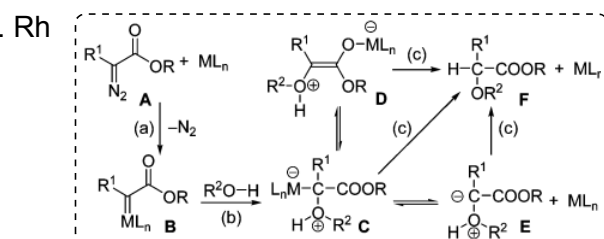
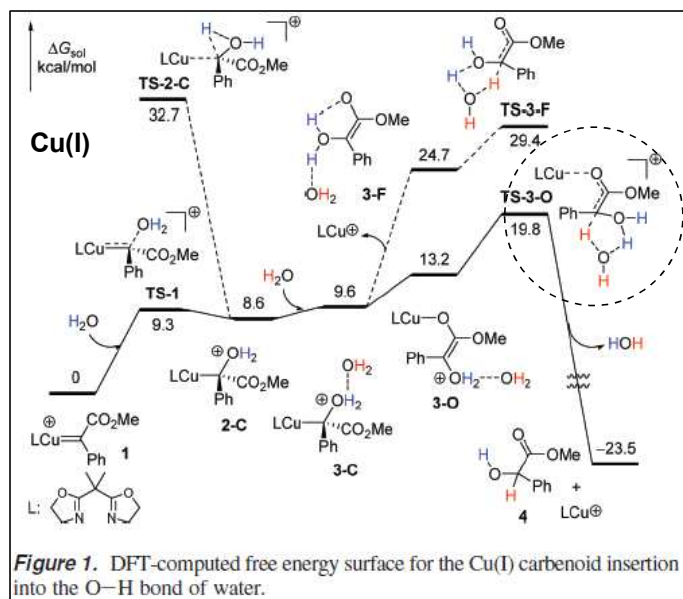
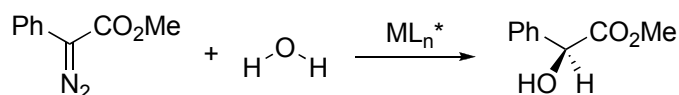
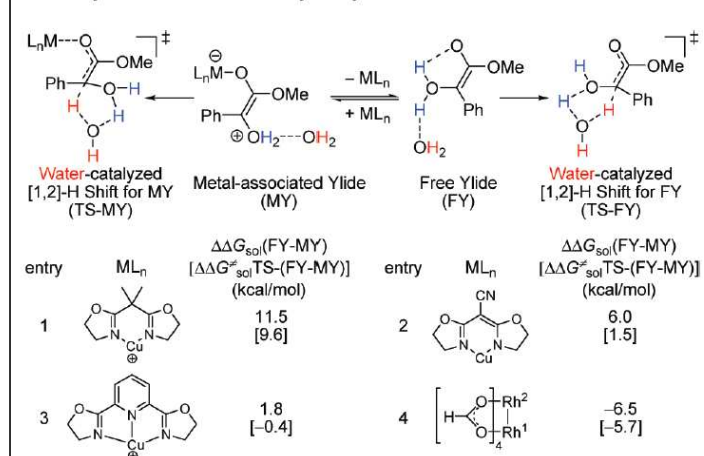


Figure 1. DFT-computed free energy surface for the Cu(I) carbenoid insertion into the O-H bond of water.

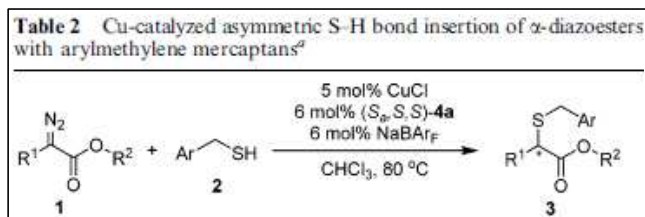
Figure 2. DFT-computed free energy surface for the Rh(II) carbenoid insertion into the O-H bond of water.

Scheme 4. Relative Free Energies of the Two Competing Pathways for Various Catalyst Systems

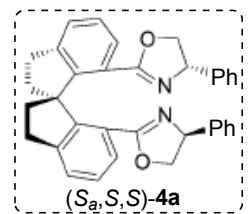


- TS-O : 2 H₂O and metal-coordinated TS before product
- TS-F : only 2 H₂O coordinated TS before product
- In DFT calculation;
 - Cu : TS-3-O is more favor than TS-3-F (Figure 1)
 - Rh : TS-7-O is more unfavor than TS-7-F (Figure 2)
- Scheme 4 , FY : metal is not coordinated at protonation step
- MY : metal is coordinated at protonation step
- ΔΔG(FY-MY) (ΔΔG_{sol}TS-(FY-MY)) > 0
 - Ligand affects protonation step determining ee.
- in Rh₂L₄, ΔΔG(FY-MY) < 0, so ligand effect is decreased.
- in CuL_n, ΔΔG(FY-MY) > 0, so ligand effect is significantly obtained.
- ⇒ in O-H insertion Cu prefers to Rh.

S-H Insertion Q.-L. Zhou *et al.*, *Chem. Comm.*, **2009**, 5362.



Entry	R ¹	R ²	Ar	Product	Yield (%)	ee (%)
1	Me	Bn	C ₆ H ₅	3a	82	81
2	Me	Et	C ₆ H ₅	3b	91	73
3	Me	^t Bu	C ₆ H ₅	3c	62	83
4	Me	Bn	4-MeOC ₆ H ₄	3d	73	85
5	Me	Bn	4-ClC ₆ H ₄	3e	86	83
6	Me	Bn	2-MeC ₆ H ₄	3f	87	68
7	Me	Bn	2-ClC ₆ H ₄	3g	70	78
8	C ₆ H ₅	Me	C ₆ H ₅	3h	59	44
9	2-MeC ₆ H ₄	Me	C ₆ H ₅	3i	64	77
10	2-ClC ₆ H ₄	Me	C ₆ H ₅	3j	83	73
11	2-MeOC ₆ H ₄	Me	C ₆ H ₅	3k	88	77
12	3-MeOC ₆ H ₄	Me	C ₆ H ₅	3l	71	52
13	4-MeOC ₆ H ₄	Me	C ₆ H ₅	3m	61	61



moderate~good yield was obtained, but enantioselectivity was moderate.

other heteroatom-H insertion;

Si-H : **high yield and high enantioselectivity** for the similar ligand ; Q.-L. Zhou *et al.*, *ACIE*, **2008**, *47*, 8496.

4. Palladium Carbenoid Induced Reaction

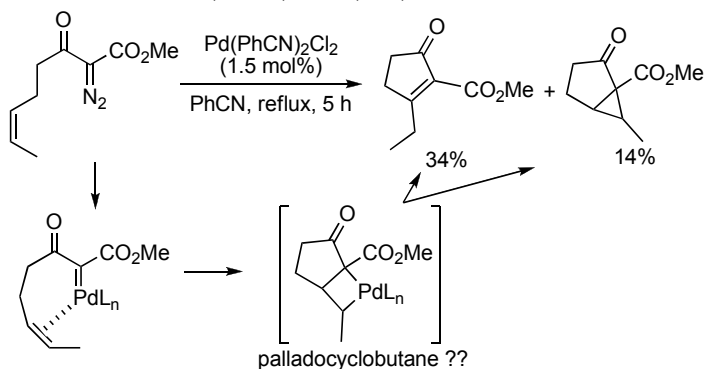
Review : Y. Zhang *et al.*, *EurJOC*, **2011**, 1015.

Palladium carbenoid shows different behavior for other metal carbenoid.

L. Wang *et al.*, *TL*, **2008**, 6781.

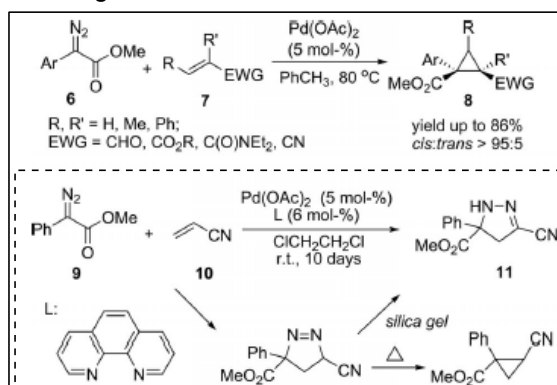
Early report

D. F. Taber *et al.*, *JOC*, **1986**, *51*, 3382.



Authors believed to proceed through a palladocyclobutane which partitions to the enone or the cyclopropane.

\Rightarrow Pd-Carbenoid can perform other type reaction ??



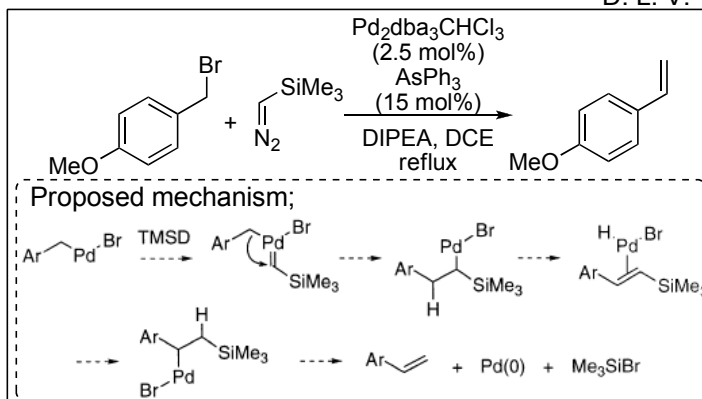
in reactive olefin, even $\text{Rh}_2(\text{OAc})_4$ was not reacted. Mechanism is different from other metal carbenoid. In after report, enantioselective reaction was failed.

S. E. Denmark *et al.*, *JOC*, **1997**, *62*, 3375.

Insertion of Palladium Carbenoid

D. L. V. Vranken *et al.*, *TL*, **1999**, *40*, 1617.

D. L. V. Vranken *et al.*, *Tetrahedron*, **2001**, *57*, 5219.



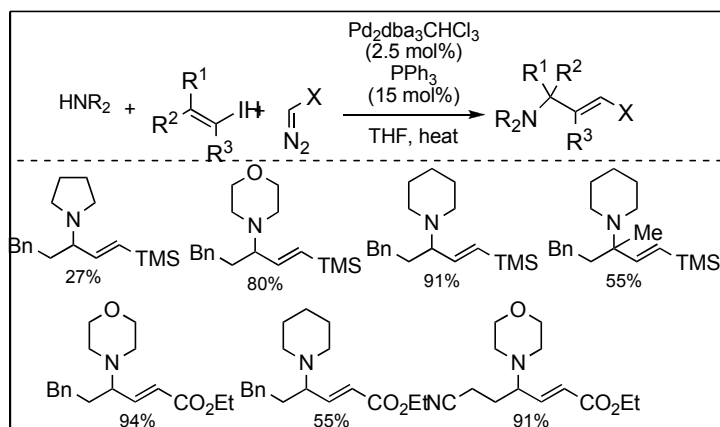
Oxidative addition \rightarrow Migratory insertion
 \rightarrow β -Hydride elimination \rightarrow Insertion to olefin
 \rightarrow Elimination of TMS and regeneration of $\text{Pd}(0)$

$\text{Pd}(0)$ reacts with diazo compounds to rapidly form a Pd-carbenoid, and $\text{Pd}(\text{II})$ can be formed *in situ* from $\text{Pd}(0)$.

Nucleophilic Addition

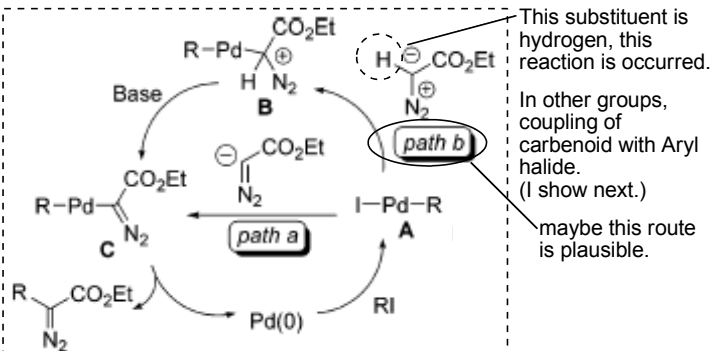
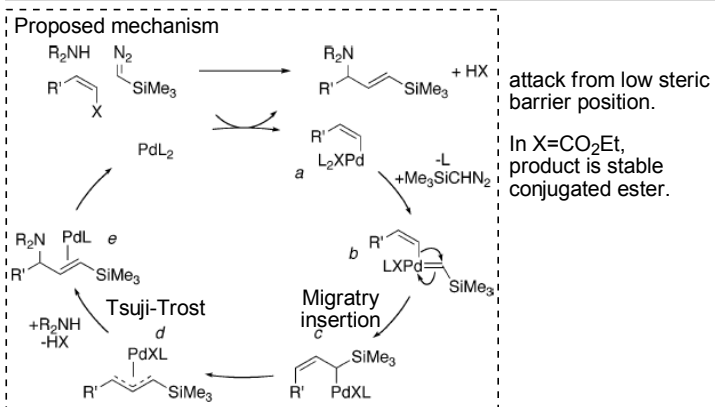
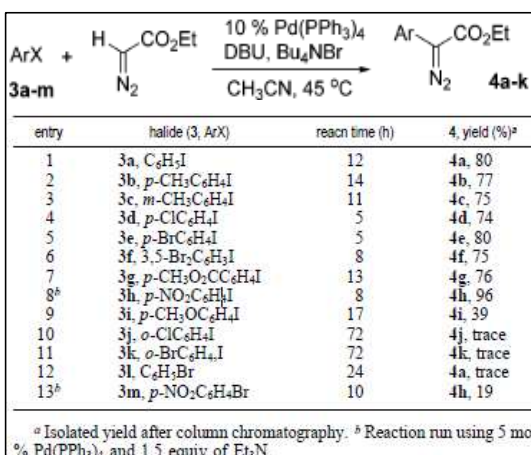
D. L. V. Vranken *et al.*, *OL*, **2007**, *9*, 2047. X = TMSCH_2N_2

D. L. V. Vranken *et al.*, *ACIE*, **2009**, *48*, 3677. X = CO_2Et



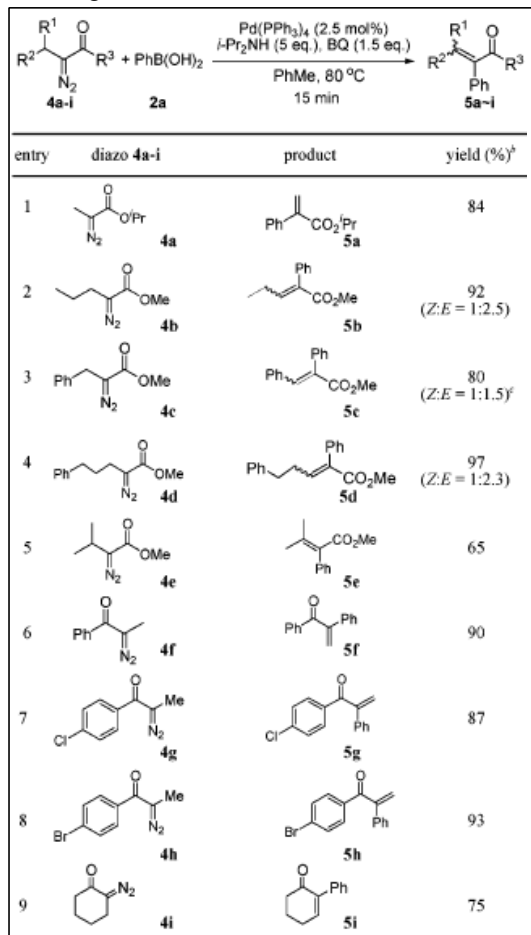
Cross-Coupling with Diazoacetate

J. Wang *et al.*, *JACS*, **2007**, *129*, 8708.

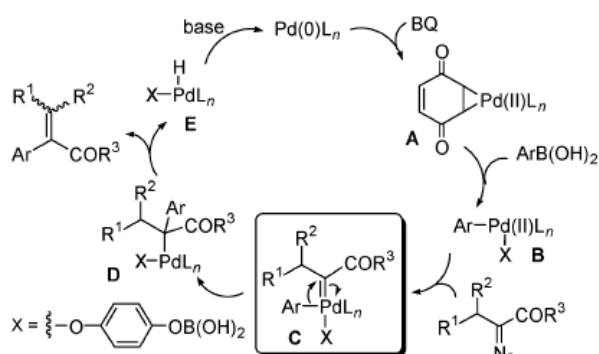


Cross Coupling with Aryl Group

J. Wang *et al.*, *JACS*, **2008**, *130*, 1566. **PhB(OH)₂**



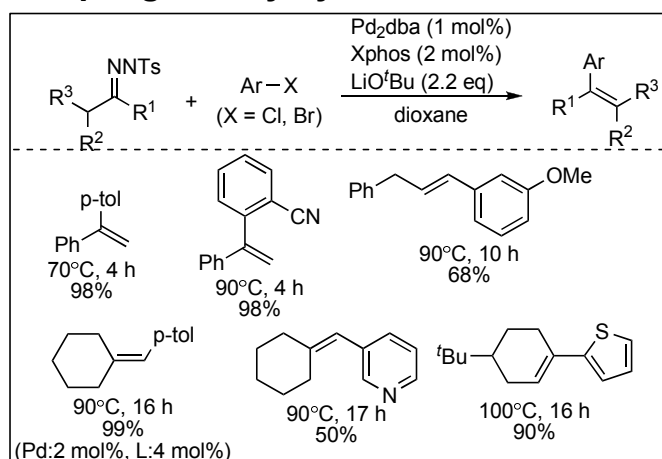
Scheme 1. Mechanistic Rationale



Using CuCl (10 mol%) & O₂, reaction was proceeded.
(From tosylhydrazone; shown below.)

J. Wang *et al.*, *Chem. Comm.*, **2010**, *46*, 1724.

Coupling of tosylhydrazone



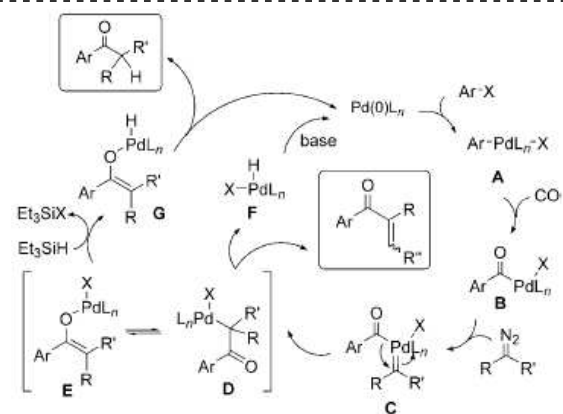
in situ, diazo intermediate is generated from tosylhydrazone with base, and next carbenoid generation, migratory → β-elimination.

J. Wang *et al.*, *JACS*, **2010**, *49*, 1139. **CO Insertion**

Table 2: [Pd(PPh₃)₄]-catalyzed reactions of CO with 1a-i and 2a-j.^[a]

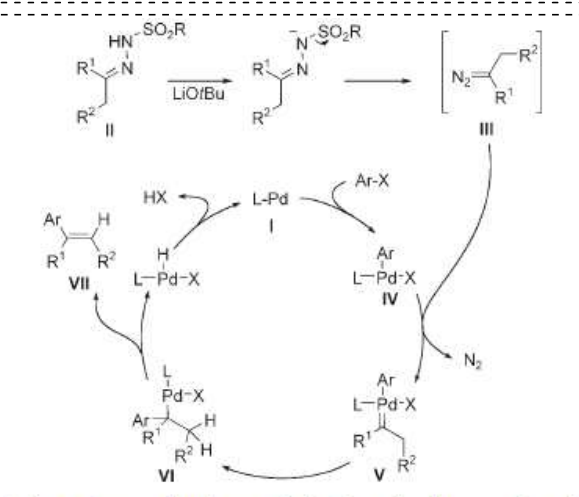
Entry	1: Ar	2: R, R'	t [h]	Yield of 4, [%] ^[b]
1	1a: C ₆ H ₅	2a: Me, Me	10	4a: 88
2	1b: o-MeC ₆ H ₄	2a: Me, Me	11	4b: 43 ^[d]
3	1c: p-MeC ₆ H ₄	2a: Me, Me	9	4c: 80
4	1d: p-MeOC ₆ H ₄	2a: Me, Me	9	4d: 85
5	1e: p-NO ₂ C ₆ H ₄	2a: Me, Me	17	4e: 61
6	1f: p-MeO ₂ CC ₆ H ₄	2a: Me, Me	14	4f: 74
7	1g: p-ClC ₆ H ₄	2a: Me, Me	10	4g: 80
8	1a: C ₆ H ₅	2b: Me, iPr	7	4h: 87
9	1a: C ₆ H ₅	2c: Ph(CH ₂) ₃ , Me	12	4i: 77
10	1a: C ₆ H ₅	2d: Ph, Me	9	4j: 57
11	1a: C ₆ H ₅	2e: p-MeOC ₆ H ₄ , Me	8	4k: 75
12	1h: m-CH ₃ C ₆ H ₄	2a: Me, Me	10	4l: 64
13	1i: p-BrC ₆ H ₄	2a: Me, Me	10	4m: 75
14	1a: C ₆ H ₅	2f: Me, tBu	12	4n: 82
15	1a: C ₆ H ₅	2g: Me, Bn	12	4o: 79
16	1a: C ₆ H ₅	2h: nPr, Me	10	4p: 66
18	1a: C ₆ H ₅	2i: Bn, Me	20	4q: 62
19	1a: C ₆ H ₅	2j: p-O ₂ NC ₆ H ₄ , Me	12	- ^[d]

[a] Reaction conditions: 1a-i (1.0 equiv), 2a-j (2.0 equiv), and 3 (1.1 equiv). [b] Yield of the isolated products. [c] The product was a mixture of keto and enol. [d] No reaction.



Scheme 3. Mechanistic rationale.

Et₃SiH is hydrogen source, halogen-hydrogen exchange process promotes reaction.



Scheme 3. Proposed mechanism for the Pd-catalyzed cross-coupling of N-tosylhydrazones.

5. Recent Other Metal Carbenoid Induced Reaction

Iridium Carbenoid

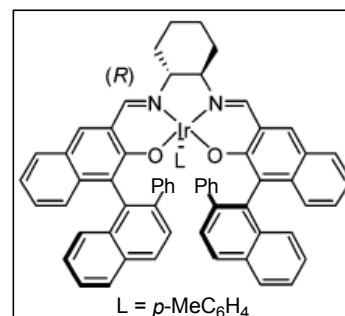
Recently, Iridium-salen complexes are employed for metal-carbenoid reactions, by Katsuki's group.

Cyclopropanation ; *ACIE*, **2007**, *46*, 3889.
JACS, **2008**, *130*, 10327.
ACIE, **2009**, *48*, 3121.
 C-H Insertion ; *JACS*, **2009**, *131*, 14218.
 Si-H Insertion ; *JACS*, **2010**, *132*, 4510.
 Cyclopropanation ; *JACS*, **2011**, *133*, 170.

ACIE, **2007**, *46*, 3889 ; Cyclopropanation

Table 1: Asymmetric cyclopropanation of styrene and its derivatives with *tert*-butyl α -diazooacetate.^[4]

Entry	Ar	T [°C]	Yield [%] ^[b]	cis/trans ^[c]	ee _{cis} [%] ^[d]	ee _{trans} [%] ^[d]
1 ^[4]	Ph	RT	40	40:60	76 ^[f]	96 ^[f]
2	Ph	RT	87	55:45	84 ^[f]	96 ^[f]
3 ^[4]	Ph	RT	43	58:42	-37 ^[f]	70 ^[f]
4 ^[4]	Ph	RT	36	66:34	64 ^[f]	18 ^[f]
5	Ph	-20	87	87:13	93 ^[f]	96 ^[f]
6	Ph	-40	85	96:4	96 ^[f]	93 ^[f]
7	Ph	-78	>99	>99:1	99 ^[f]	92 ^[f]
8 ^[5]	Ph	-78	>99	>99:1	99 ^[f]	-
9 ^[7]	Ph	-78	>99	>99:1	98 ^[f]	-
10 ^[7]	<i>o</i> -MeOC ₆ H ₄	-78	90	97:3	99 ^[a]	-
11 ^[7]	<i>m</i> -MeOC ₆ H ₄	-78	88	>99:1	97 ^[a]	-
12 ^[7]	<i>p</i> -MeOC ₆ H ₄	-50	>99	>99:1	97 ^[a]	-
13 ^[5,8]	<i>o</i> -ClC ₆ H ₄	-78	90	99:1	98 ^[a]	-
14 ^[5]	<i>m</i> -ClC ₆ H ₄	-78	91	>99:1	98 ^[a]	-
15 ^[5]	<i>p</i> -ClC ₆ H ₄	-78	>99	>99:1	98 ^[a]	-
16 ^[5,m]	Ph	-78	90 ^[a]	>99:1	99 ^[a]	-
17 ^[5,o]	Ph	-78	>99	>99:1	97 ^[f]	-



- at -78°C, in THF, high yields and high stereoselectivity.
- cis selective reaction.

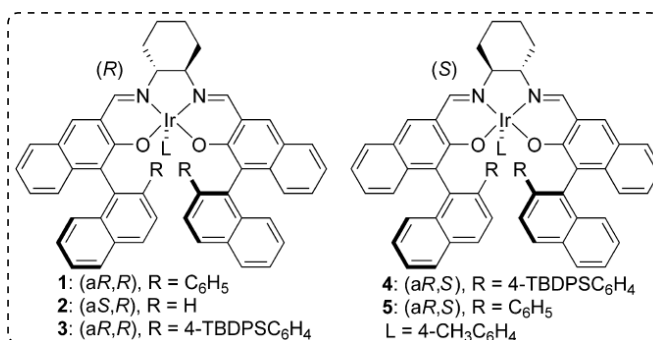
JACS, **2010**, *132*, 4510 ; Si-H Insertion

Table 3. Asymmetric Si-H Insertion with α -Aryl- α -Diazooacetates^a

entry	cat.	prod.	R ¹	R ²	% yield ^{b,c}	% ee ^d
1	1	6i	PhMe ₂	Ph	93	>99
2	5	6i	PhMe ₂	Ph	91	50 ^e
3	1	6j	Et ₃	2-MeOC ₆ H ₄	92	99
4	1	6k	Et ₃	2-ClC ₆ H ₄	95	>99
5	1	6l	Et ₃	3-MeOC ₆ H ₄	95	>99
6	1	6m	Et ₃	3-ClC ₆ H ₄	97	>99
7 ^f	1	6n	Et ₃	4-MeOC ₆ H ₄	94	>99
8	1	6o	Et ₃	4-ClC ₆ H ₄	97	>99

Table 1. Asymmetric Si-H Insertion with α -Alkyl- α -Diazooacetate^a

entry	cat.	prod.	Ar	R ¹	R ²	% yield ^b	% ee ^c
1 ^d	1	6a	Ph	Me	Et	71(86)	41 ^e
2 ^f	1	6a	Ph	Me	Et	83(96)	37 ^e
3	1	6a	Ph	Me	Et	89(98)	51 ^e
4	3	6a	Ph	Me	Et	85	73 ^e
5	4	6a	Ph	Me	Et	85	97
6	4	6b	Ph	Me	<i>t</i> Bu	88	97
7	4	6c	<i>o</i> -tol	Me	Et	85	98
8	4	6d	Ph	Et	<i>t</i> Bu	47	97



- in aryldiazooacetate, normal salen complex (R=C₆H₅) gives high yield and enantioselectivity
- in alkyl diazoacetate, salen complex 4 (R=*p*-TBDPSC₆H₄) gives high yield and enantioselectivity. (the complexes having a higher molecular recognition ability would serve as an efficient catalyst for this reaction.)

Cobalt Carbenoid

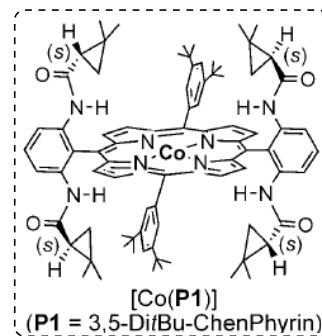
There are a few examples.

X. P. Zhang *et al.*, *ACIE*, **2008**, *47*, 8460.

Reaction scheme: $R'CH=CH_2 + N_2=C(CO_2Et)NO_2 \xrightarrow{[Co(P1)] (1 \text{ mol}\%), \text{hexane, rt, 24 h}} R'CH_2-CH_2-CO_2R$

Table 2: [Co(P1)]-catalyzed diastereo- and enantioselective cyclopropanation of different alkenes with α -nitrodiazoacetates.^[a]

Entry	Cyclopropane	R	Yield [%] ^[b]	Z/E ^[c]	ee [%] ^[d]	[α] ^[e]	Entry	Cyclopropane	R	Yield [%] ^[b]	Z/E ^[c]	ee [%] ^[d]	[α] ^[e]
1		Et	87	92:08	89	(-)	16		Et	90	91:09	94	(-) ^[f]
2 ^[g,h]		Et	93	92:08	92	(-)	17 ^[g,h]		Et	81	93:07	95	(-) ^[f]
3		tBu	91	>99:1	91	(-)							
4 ^[g,h]		tBu	97	>99:1	94	(-)							
5 ^[g,h]		Et	86 ^[i]	93:07	90	(-)	18 ^[h,i]		Et	51	90:10	82	(-)
6 ^[h]		tBu	90	>99:1	92	(-)							
7 ^[g,h]		Et	91	96:04	91	(-)	19		Et	70 ^[k]	94:06	83	(-)
8 ^[g,h]		Et	82	92:08	91	(-)	20 ^[h,m]		tBu	45	92:08	≥80 ^[n]	(-)
9 ^[g,h]		Et	83	92:08	90	(-)	21 ^[h,m]		tBu	43	92:08	≥86 ^[n]	(+)
10 ^[h]		tBu	87	>99:1	92	(-)							
11 ^[g,h]		Et	84	91:09	90	(-)	22 ^[h,il]		Et	42	53:47	88	(-)
12 ^[g,h]		Et	82	91:09	90	(-)	23 ^[h,il]		Et	62	56:44	88	(-)
13 ^[g,h]		Et	87	91:09	90	(-)	24 ^[h,il]		Et	92	63:37	75	(-)
14 ^[g,h]		Et	88	92:08	90	(-)							
15 ^[h]		tBu	98	96:04	88	(-)							



• [h] 5 mol% catalyst.

• enantioselective cyclopropanation of **acceptor/acceptor type** (Hydrogen bond of N-H of amide vs NO₂ and ester of diazosubstrate, reactive face is determined.)

Iron Carbenoid

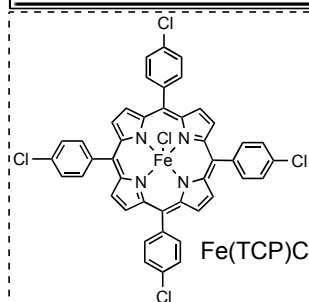
Iron is so cheap metal, but reaction example is not enough...

Y. Tang *et al.*, *JACS*, **2009**, *131*, 4192.

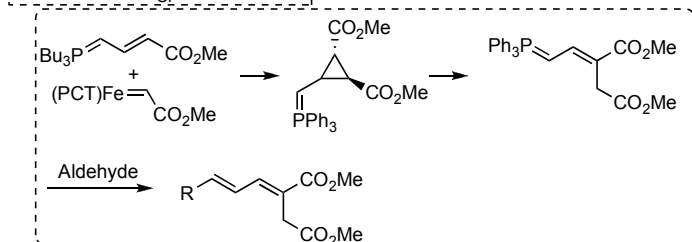
Table 1. One-Pot Synthesis of 1,3-Butadienes via Catalytic Carbenoid Insertion of Allylic Ylide^a

Reaction scheme: $Bu_3P^+CH_2CH=CHCO_2Me + 1) LiHMDS, PhMe; 2) MDA, Fe(TCP)Cl; 3) RCHO \rightarrow RCH=CH-CH=CHCO_2Me$

entry	R	Time (h)	6 (%) ^b	3E,5E/3E,5Z
1	4-ClC ₆ H ₄	6	62 (6a)	92/8
2	4-BrC ₆ H ₄	7	61 (6b)	94/6
3	4-NO ₂ C ₆ H ₄	7	54 (6c)	97/3
4	4-CNC ₆ H ₄	6	53 (6d)	92/8
5	C ₆ H ₅	7	61 (6e)	95/5
6	4-MeC ₆ H ₄	20	67 (6f)	94/6
7	E-PhCH=CH	23	45 (6g)	90/10
8	Cy	25	72 (6h)	92/8
9	Ph(Me)CH	24	66 (6i)	94/6
10 ^d		4	65 (6j)	75/25
11	C ₅ H ₁₁	24	69 (6k)	87/13



tandem carbenoid reaction/ Wittig reaction.
good E/Z selectivity for Wittig reaction.



Other example of iron carbenoid, asymmetric cyclopropanation using porphyrin complex, moderate yield (up to 67%), good diastereoselectivity (up to 96:4) and moderate enantioselectivity (up to 80%ee), further improvements are required...

G. Simonneaux *et al.*, *TL*, **2009**, *50*, 5149.

Ruthenium Carbenoid

Y. Tang *et al.*, *JACS*, **2010**, *12*, 604.

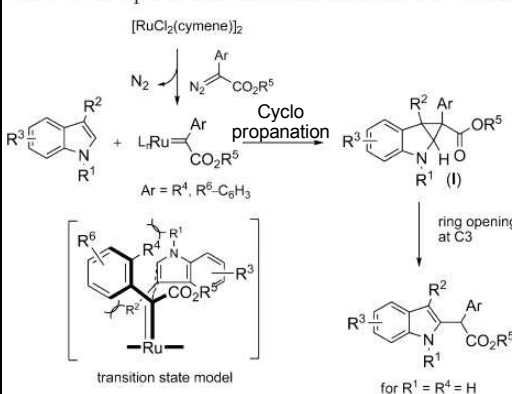
Reaction scheme: $1a + Ar-CO_2R + N_2 \xrightarrow{[RuCl_2(p-cymene)]_2 (2 \text{ mol}\%), N_2, CH_2Cl_2, rt} 3$

entry	Ar	R	product	time (h)	yield (%) ^b
1	Ph	Me (2a)	3aa	0.5	96
2	4-MeC ₆ H ₄	Me (2b)	3ab	0.5	87
3	4-FC ₆ H ₄	Me (2c)	3ac	0.5	92
4	4-ClC ₆ H ₄	Me (2d)	3ad	0.5	80
5	4-BrC ₆ H ₄	Me (2e)	3ae	0.5	90
6	4-CF ₃ C ₆ H ₄	Me (2f)	3af	0.5	77
7	4-NO ₂ C ₆ H ₄	Me (2g)	3ag	2	48
8	4-MeOC ₆ H ₄	Me (2h)	3ah	0.5	83
9	3-MeOC ₆ H ₄	Me (2i)	3ai	0.5	84
10	2-MeOC ₆ H ₄	Me (2j)	3aj	18	trace ^c
11	4-MeOC ₆ H ₄	CH ₂ CH=CH ₂ (2k)	3ak	2	50
12	2-naphthyl	Me (2l)	3al	72	74
13	1-naphthyl	Me (2m)	3am	72	22
14	Ph	tert-butyl (2n)	3an	24	12
15		Me (2o)	3ao	0.5	65
16		Me (2p)	3ap	0.5	91
17		Me (2q)	3aq	18	61

sterically barrier is critically affected.

Entry 10, 13, 14.

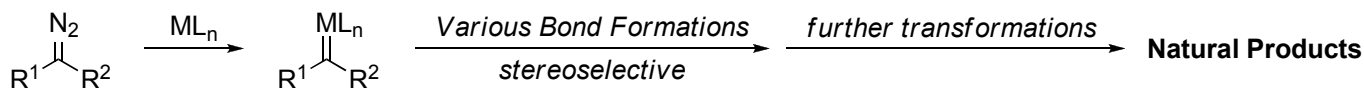
Scheme 1. Proposed Mechanism and Transition State Model



Ruthenium is the similar reactivity for Rhodium, many high efficient examples of Ruthenium are reported, but enantioselective reaction is a few report. (See Review ; Enantioselective Ruthenium-porphyrin-carbenoid ; C.-M. Che *et al.*, *Synlett*, **2010**, 2681.)

6. Sammury & Perspective

Metal-carbenoid-mediated-reactions are so useful reactions for several type bond formation and skeletal construction. C-H Insertion, cyclopropanation, ylide formation, and others.... These reaction was used for several total syntheses.



Futher Improvement

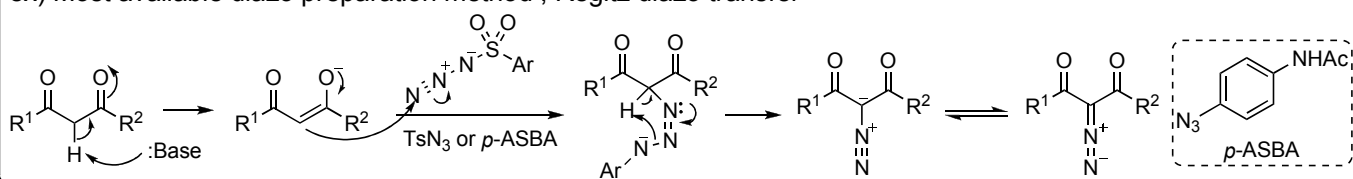
- Main metal of carbenoid reaction is Rhodium, that is so expensive.

⇒ We would like to use other cheap and available metal ; Cu, Fe, Co, Ni, Mn,

Recently, several cheap metals is used for metal-carbenoid reaction (further improvements were required).

- Usually, many type diazo compounds are thermally and photochemically unstable, and diazo precursor is unstable, explosive, and toxic.

ex) Most available diazo preparation method ; Regitz diazo transfer



⇒ Carbenoid generation method not using diazo precursor ??

available substrate and useful additive, easy conditons...

e.g.)

substrate (dihalogen, monohalogen, active methylene (benzylic, allylic, α-position of carbonyl), directing group, alkene, or alkane), additive (base, oxidant), ligand effect of metal (steric, other several character), and the other additive and conditions...

If these reactions will be achieved, metal-carbenoid reactions is sure to become more general and conventional reaction.