Diazommediated 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.

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1. Carbenoid

1-1. Carbone

Carbone is a molecule containing a neutral carbon with 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 ($\sigma$ orbital) and empty p orbital
  - resembles carboxylation 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 $\theta$ (calculated): 100–110°

- Triplet
  - 2 electron was shared with p orbital and $\sigma$ orbital
  - resembles biradical
  - Typical angle $\theta$ (calculated): 130–150°

One of the typical carbene formation: diazo decomposition

$$\text{N}_2\text{H}_3\text{CO}_2\text{R} \xrightarrow{\Delta \text{ or h} \text{v} \text{ or Metal}} \text{CO}_2\text{R} \quad \text{C-H Insertion}$$

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

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 posse 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 carbenoid precursor, typically diazo compound.

Kind of Diazo Compound (Carbenoid Precursor)

Carbenoid can be controlled 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

$$\text{O} \quad \text{X}_2 \quad \text{N}_2 \quad \text{H}$$

Acceptor/Acceptor

$$\text{O} \quad \text{X}_2 \quad \text{N}_2 \quad \text{Y}$$

Acceptor/Donor

$$\text{O} \quad \text{X}_2 \quad \text{N}_2 \quad \text{Y}$$

- Acceptor/Acceptor and Acceptor/Donor types stabilize diazo compound (so more active catalyst needed for decomposition).
- Donor substituent stabilized carbene 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 $\sigma$ bond
- d electrons to p orbital on carbon: weak–moderate $\pi$ bond, stabilize carbene a little but still maintain its enough electrophilicity
- Desired metal: bind to the carbene through strong $\sigma$-acceptor interactions and weak (appropriate) back donation interaction.
**Observation of Carbenoid**

- **Cu-Carbenoid**
  
  \[
  \text{\textprime Bu}^+\text{P}^\text{NMS} \text{Cu-\textprime Bu}^+ + \text{N}_2 = \text{CO}_2\text{Me} \rightarrow \text{\textprime Bu}^+\text{P}^\text{NMS} \text{Cu} = \text{CO}_2\text{Me}
  \]

  In toluene-d8 or benzene-d6 at rt, 15-25% Cu-complex was detected. Caracterization from \(^1\text{H} NMR\) (Figure 2), \(^{13}\text{C} NMR\) (229.9 ppm (C=N)), 177.9 ppm (C=O), MS (FAB: 531.2, [M\textsuperscript+]).

  (At -33°C, this complex was maintained for several hours without significant evolution of nitrogen.)

- **Rh\textsubscript{2}-Carbenoid**
  
  \[
  \text{Rh}(\text{OCO'Bu})_4 + :\text{N} = \text{H} \rightarrow \text{Rh}(\text{OCO'Bu})_4 \text{Nu} = \text{RO, RS, R}_2\text{N}
  \]

  In this paper, other example, characterization from \(^1\text{H} NMR\) (Figure 2), \(^{13}\text{C} NMR\) (229.9 ppm (C=N)), 177.9 ppm (C=O), MS (FAB: 531.2, [M\textsuperscript+]).

  (At -33°C, this complex was maintained for several hours without significant evolution of nitrogen.)

**1-3. Early Example of Metal-Carbenoid Reaction**

- **Insertion**
  
  \[
  \text{R} = \text{N}_2 \quad \text{Cu} \quad \text{Nu} = \text{RO, RS, R}_2\text{N}
  \]

  P. Yate, *JACS*, 1952, 74, 5376.

- **Cyclopropanylation**
  
  \[
  \text{Cl} = \text{C} \rightarrow \text{Cl} \quad \text{Metal} \quad \text{N}_2\text{HC} = \text{CO}_2\text{R}
  \]


- **Dimerization (Homometathesis)**
  
  \[
  \text{O} \quad \text{Cu} \quad \text{O} + \text{Ph} = \text{N}_2 \quad \text{toluene} \quad \Delta \quad 86\%
  \]


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

**Dirhodium carboxylate (Rh\textsubscript{2}L\textsubscript{4})**


First example of Rhodium carbenoid generation from diazo decomposition.

\[
\text{R-} \text{OH} + \text{N}_2 = \text{CO}_2\text{Et} \quad \text{catalyst} \quad 25^\text{oC} \rightarrow \text{RO} = \text{CO}_2\text{Et}
\]

Reactivity using Rh\textsubscript{2}(OAc)\textsubscript{4} (Rh(II)) was higher than Rh(I), Rh(III).

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>diazo/Catalyst</th>
<th>R</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh\textsubscript{2}(OAc)\textsubscript{4}</td>
<td>600</td>
<td>Et</td>
<td>88</td>
</tr>
<tr>
<td>Rh\textsubscript{2}(OAc)\textsubscript{4}</td>
<td>600</td>
<td>'Pr</td>
<td>83</td>
</tr>
<tr>
<td>Rh\textsubscript{2}(OAc)\textsubscript{4}</td>
<td>600</td>
<td>'Bu</td>
<td>82</td>
</tr>
<tr>
<td>Rh\textsubscript{2}(OAc)\textsubscript{4}</td>
<td>600</td>
<td>H</td>
<td>80</td>
</tr>
<tr>
<td>Rh\textsubscript{2}(OAc)\textsubscript{4}</td>
<td>600</td>
<td>Ac</td>
<td>93</td>
</tr>
<tr>
<td>RhCl\textsubscript{2}3\textsubscript{H}_2O</td>
<td>125</td>
<td>Et</td>
<td>64</td>
</tr>
<tr>
<td>RhCl\textsubscript{2}3\textsubscript{H}_2O</td>
<td>125</td>
<td>'Bu</td>
<td>58</td>
</tr>
<tr>
<td>RhCl(PPPh\textsubscript{3})\textsubscript{3}</td>
<td>125</td>
<td>Et</td>
<td>49</td>
</tr>
</tbody>
</table>
2. Rhodium Carbenoid Induced Reaction

2-1. C-H Insertion

**Trend in Selectivity**

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


\[
\text{R}^1\text{R}_2\text{O} = \text{CO}_{2}\text{Et} \xrightarrow{\text{Rh}_2(\text{OAc})_4} \text{R}^1\text{R}_2\text{O} = \text{CO} \text{Et}^1 \text{R}_2\text{O} = \text{CO} \text{Et}^2 \text{R}_2\text{O} = \text{CO} \text{Et}^3
\]

| R^1 = Me, R^2 = Me, R^3 = Me (3° vs 2°) | 23 : 1 |
| R^1 = Me, R^2 = H, R^3 = tBu (2° vs 2°bulky) | 34 : 1 |

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


\[
\text{COCH}_2\text{Et} \xrightarrow{\text{Rh}_2(\text{OAc})_4} \text{COCH}_2\text{Me} \xrightarrow{\text{Rh}_2(\text{OAc})_4} \text{COCH}_2\text{Me}
\]

| \text{COCH}_2\text{Et} (81%) | \text{COCH}_2\text{Me} (64%)
| \text{COCH}_2\text{Me} (0% dimer: 33%)
| \text{COCH}_2\text{Me} (0% dimer: 31%)

: **electron-withdrawing groups inhibit adjacent C-H bond**

**Mechanism**


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)

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


DFT using B3LYP on Rh_{2}(O_{2}CR)_{4} C-H activation/C-C bond formation reaction.

- calculated for [Rh_{2}(O_{2}CH)_{4} - CH_{2}N_{2} - metane or propane] and [Rh_{2}(O_{2}CH)_{4} - N_{2}CHO_{2}Et - metane 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\textsuperscript{1} has positive charge which increases the electrophilicity of carbon center
- electron donation from Rh_{2} to Rh\textsuperscript{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).

\[
\begin{align*}
\text{N}_2(\text{HCO})_4\text{Rh}_2\text{CH}_2 & > 27.6 \text{ kcal/mol} > 15.6 \text{ kcal/mol} > 5.7 \text{ kcal/mol}
\end{align*}
\]
Stereo-/Chemo-Selective Reaction

**Intramolecular reaction**

<table>
<thead>
<tr>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Reaction Diagram" /></td>
</tr>
<tr>
<td><img src="image2" alt="Reaction Diagram" /></td>
</tr>
</tbody>
</table>

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.

**Proposed mechanism:**

- 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:**

**TABLE 3. Carbon–Hydrogen Insertion Reaction of Cyclohexyl Diazoacetate**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Yield (%)</th>
<th>cis/ trans</th>
<th>% ee cis</th>
<th>% ee trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh₂(4S-MPPIM)₄, 1</td>
<td>71</td>
<td>100/0</td>
<td>92</td>
<td>na</td>
</tr>
<tr>
<td>Rh₂(4S,2'S,3'S-MCPIM)₄, 11</td>
<td>78</td>
<td>99/1</td>
<td>97</td>
<td>nd</td>
</tr>
<tr>
<td>Rh₂(4S,2'R,3'R-MCPIM)₄, 12</td>
<td>63</td>
<td>80/20</td>
<td>72</td>
<td>13</td>
</tr>
<tr>
<td>Rh₂(4S,2'S-BSPIM)₄, 15</td>
<td>88</td>
<td>97/3</td>
<td>&gt;99</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Rh₂(4S,2'R-BSPIM)₄, 16</td>
<td>89</td>
<td>98/2</td>
<td>74</td>
<td>33</td>
</tr>
</tbody>
</table>

*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 the cases of other type ligands, they are expected by similarly catalysis model.
• Model for asymmetric induction in β-lactam formation with Hashimoto’s catalyst.

- In the case of $R_2$ is alkyl group, β-lactam is obtained, but in $R_2^2$ 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 $R_1^1 = \text{Ar}$, 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 ($\text{Rh}_2(\text{S-DOSP})_4$).

\[ \text{Mannich type products.} \]

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

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

**Table 1.** Asymmetric C–H Activation of Cycloalkanes

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Ar} & \text{yield, %} & \text{ee, %} & \text{ee, %} \\
\hline
\text{a} & \text{Ph} & 72 & 94 & 92 \\
\text{b} & \text{p-Me-Ph} & 70 & 94 & 94 \\
\text{c} & \text{p-Me-Ph} & 67 & 94 & 94 \\
\text{d} & \text{2-Naphthyl} & 49 & 93 & 92 \\
\hline
\end{array}
\]

\[ \text{3 mol% of catalyst was used. At 80°C, 85%, 67%ee.} \]
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

previous work

normal C-C bond formation


Ph → Et

Proposed mechanism

C-H activation as a surrogate of classic reactions of organic synthesis.

C-H activation at adjacent to N

JOC, 2005, 70, 10737.

C-H activation at adjacent to O

C-H activation as a surrogate of classic reactions of organic synthesis.

...
2-2. Cyclopropanation
diastereoselective cyclopropanation

\[
\text{Ph} + \text{N}_2 + \text{CO}_2 \text{Me} \xrightarrow{\text{Rh}_2(\text{OAc})_4 \text{ (1 mol%)}} \text{Ph} + \text{CO}_2 \text{Me}
\]


\[\text{Ph} \rightarrow \text{Me}\]

enantio/diastereoselective cyclopropanation

\[
\text{R} + \text{N}_2 + \text{CO}_2 \text{Me} \xrightarrow{\text{Rh}_2(\text{S-DOSP})_4 \text{ (1 mol%)}} \text{Rh}_{\text{penentane, -78°C}} \text{R}
\]

H. M. L. Davies et al., JACS, 1996, 118, 6897.

\[\text{R} = \text{H}, \text{Et}, \text{Pr}, \text{Bu}, \text{allyl}\]

\[\text{R} = \text{H}, \text{Et}, \text{Pr}, \text{Bu}, \text{allyl}\]

\[\text{R} = \text{H}, \text{Et}, \text{Pr}, \text{Bu}, \text{allyl}\]

\[\text{R} = \text{H}, \text{Et}, \text{Pr}, \text{Bu}, \text{allyl}\]

\[\text{R} = \text{H}, \text{Et}, \text{Pr}, \text{Bu}, \text{allyl}\]

Enantioselective Cyclopropanation of Allenes

Table 1. Cyclopropanation of Monosubstituted Allenes

<table>
<thead>
<tr>
<th>allene</th>
<th>R</th>
<th>product</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Ph</td>
<td>2a</td>
<td>76</td>
<td>90</td>
</tr>
<tr>
<td>1b</td>
<td>p-ClC_6H_4</td>
<td>2b</td>
<td>61</td>
<td>84</td>
</tr>
<tr>
<td>1c</td>
<td>C_6H_5</td>
<td>2c</td>
<td>60</td>
<td>88</td>
</tr>
<tr>
<td>1d</td>
<td>CH_2Ph</td>
<td>2d</td>
<td>54</td>
<td>&gt;80^2</td>
</tr>
</tbody>
</table>

Table 2. Cyclopropanation of 1,1-Disubstituted Allenes

<table>
<thead>
<tr>
<th>allene</th>
<th>R</th>
<th>R'</th>
<th>product</th>
<th>% yield</th>
<th>% ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>Ph</td>
<td>CH_3</td>
<td>3a</td>
<td>33</td>
<td>86</td>
</tr>
<tr>
<td>5b</td>
<td>CH_3</td>
<td>CH_3</td>
<td>3b</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>5c</td>
<td>(CH_3)_2Si</td>
<td>CH_3</td>
<td>3c</td>
<td>79</td>
<td>85</td>
</tr>
</tbody>
</table>

\[\text{R} = \text{H}, \text{Et}, \text{Pr}, \text{Bu}, \text{allyl}\]

\[\text{R} = \text{H}, \text{Et}, \text{Pr}, \text{Bu}, \text{allyl}\]

\[\text{R} = \text{H}, \text{Et}, \text{Pr}, \text{Bu}, \text{allyl}\]

\[\text{R} = \text{H}, \text{Et}, \text{Pr}, \text{Bu}, \text{allyl}\]

positive charge

In toluene solvent, trace product is obtained. Maybe cyclopropanation of aromatic rings and \(\alpha\)-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


\[
\text{Ph} + \text{N}_2 + \text{CH}_2\text{Cl}_2, \text{heat} \xrightarrow{\text{Rh}_2(\text{OAc})_4} \text{Ph}
\]

R = H, Et, Pr, 'Pr, 'Bu, 'Bu, allyl

allyl : 49% (byproduct : cyclopropanation of allyl olefin, other alkyl substrate : 59-79%)

Benzen ring is reacted with metal-carbenoid species.

In this case, R groups sterically block, diastereoselectivity is appeared.

steric effect of cyclization

model of diastereoselectivity

\[\text{R}^1 \text{ is saturated alkyl group (not shown, TL paper) : diastereoselectivity is decreased.} \]

\[\text{R}^2 \text{ is donor group (Ar, allyl) \rightarrow diastereoselectivity is increased.} \]

\[\text{R}^2 = \text{ acceptor (e.g. ester) : selectivity is decreased, acceptor/acceptor type carbenoid is too much reactivity.} \]

\[\text{using chiral Rh catalyst, high ee was obtained.} \]
**Entantoselective Cyclopropanation of Alkyne**


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** Allyl diazoester**

```
entry  R  product  yield (%)  ee (%)  
1  16a  88  96  
2  16b  79  96  
3  16c  86  97  
4  17a  87  --  
5  17b  78  --  
```

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

---

**With simple diene**


---

**With heteroaromatic**


---

**Mechanistic hypothesis of cyclopentadiene**

---

 menos substituted olefin is preferentially proceeded first cyclopropanation
2-4. Other C-C Bond Formation

**[3+2] Annulation of Indole**


In simple N-methylindole, 2 isomers are obtained. Initial reaction at C2 or C3 position of indole??

- 2-methylindole: endo compound is obtained.
- 3-methylindole: exo compound is obtained.

Reactivity is stability of 2 or 3-position? So author's said, this reaction is step-by-step reaction, stable 3° carbocation is generated in transition state, maybe not concerted reaction.

**Proposed mechanism:**

Ylide Formation  
H. M. L. Davies et al., JACS, 2009, 131, 1101.

Carbenoid can generate ylide with appropriate carbonyls or imines.

Three-Component Cycloaddition

- Rh₂(Piv)₄ is most suitable.
- Rh₂(OAc)₄ yield is decreased.
- regioselective reaction
- endo selective reaction
2-5. Heteroatom-H Insertion

○Si-H Insertion


2-6. Total Synthesis using Rhodium Carbenoid

R. Sarpong

stereoselective diastereoselective intermolecular [4+3] to diterpenes.

○N-H Insertion

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

○O-H Insertion


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.

When racemic SM was employed, 41 and 44 (diastereomer) was mainly obtained (depend of chiral ligand).

Although they have inverse absolute configuration at reactive site, using Rh2(R-DOSP)₄, [4+3] cyclization was proceeded in 'same' stereochemistry so diastereomers are obtained.

↓ 'pallarel kinetic resolution'
3. Copper Carbenoid Induced Reaction

Copper carbenoid is shown the similar reaction for Rhodium carbeoid 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 improved of ee compared for Rhodium carbenoid.

- Counter anion effect is so high, the smaller and slightly coordinating OTf is inferior to the PF$_6$ 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.


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

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

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>[Cu]</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S,S,S)-1a CuP(t-Bu)CN$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>2</td>
<td>78</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(R,S,S)-1a CuP(4-MeCN)$_4$</td>
<td>CH$_2$Cl$_2$</td>
<td>2</td>
<td>95</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(S,S,S,1a CuOTf(Tol)$_2$</td>
<td>CH$_2$Cl$_2$</td>
<td>2</td>
<td>83</td>
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<tr>
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<td>(S,S,S)-1a CuClNaBARF</td>
<td>CH$_2$Cl$_2$</td>
<td>2</td>
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<td>(S,S,S)-1a CuClNaBARF</td>
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<tr>
<td>14</td>
<td>(S,S,S)-Ph-Boc-cis-CuClNaBARF-1b</td>
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<td>2</td>
<td>66</td>
<td>5</td>
<td></td>
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</table>

$^a$ 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-diazopropanoate (0.2 mmol) were introduced and stirred at 25 °C. Isolated yield. Determined by chiral HPLC using a Chiralpak A3 column. $^b$ With 1 mol % of catalyst, refluxed.


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.

\[
\text{Ph CO}_2\text{Me} + \text{H}_2\text{O} \rightarrow \text{Ph CO}_2\text{Me}
\]

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

- TS-O : 2 H_2O and metal-coordinated TS before product
- TS-F : only 2 H_2O 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
  - Ligand affects protonation step determining ee.


**Table 2** Cu-catalyzed asymmetric S-H bond insertion of α-diazooesters with alkythioethylenes mercaptoates

- 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
Palladium carbenoid shows different behavior for other metal carbenoid.

Early report
D. F. Taber et al., JOC, 1986, 51, 3382.

\[
\begin{align*}
\text{CO}_3\text{Me} & \xrightarrow{\text{PhCN, reflux, 5 h}} \text{CO}_3\text{Me} + \text{CO}_3\text{Me} \\
\text{CO}_3\text{Me} & \xrightarrow{\text{PdL}_n} \text{PdL}_n
\end{align*}
\]

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

\[\text{Pd-Carbonenoid can perform other type reaction??}\]

Insertion of Palladium Carbenoid

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

Nucleophilic Addition
D. L. V. Vranken et al., OL, 2007, 9, 2047. \(X = \text{TMSCH}_2\text{N}_2\)
D. L. V. Vranken et al., ACIE, 2009, 48, 3677. \(X = \text{CO}_3\text{Et}\)

\[\text{This substituent is hydrogen, this reaction is occurred.}\]

In other groups, coupling of carbenoid with Aryl halide. (I show next.)

Cross-Coupling with Diazoacetate
J. Wang et al., JACS, 2007, 129, 8708.

[Chemical structures and mechanisms are depicted in the diagram, including reactions with various substituents and mechanisms for the reaction pathways.]

13/17
Cross Coupling with Aryl Group

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

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

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

CO Insertion

Pd₂dba (1 mol%) & Xphos (2 mol%) & LiO'Bu (2.2 eq.) in dioxane

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.
5. Recent Other Metal Carbenoid Induced Reaction

**Iridium Carbenoid**

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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>T</th>
<th>Yield [%]</th>
<th>cis/trans [%]</th>
<th>ee[ci] [%]</th>
<th>ee[trans] [%]</th>
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<td>RT</td>
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</table>

Table 1: Asymmetric cyclopropanation of styrene and its derivatives with tert-butyl α-diazocetate.

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

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

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<th>Entry</th>
<th>Rᵣ-Si–H</th>
<th>(1.2 equiv)</th>
<th>N₂ (1.0 equiv)</th>
<th>R²</th>
<th>CO₂Me</th>
<th>80°C, 4h</th>
<th>ArMe₂Si–H</th>
<th>(3.0 equiv)</th>
<th>N₂ (1.0 equiv)</th>
<th>R²</th>
<th>CO₂R²</th>
<th>80°C, 4h</th>
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<td>97</td>
<td>&gt;99</td>
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<td>-</td>
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</table>

Table 2: Asymmetric Si–H Insertion with α-Alkyl-α-Diazocetates.

- in aryl diazoacetate, normal salen complex (R=C₆H₅) gives high yield and enantioselectivity.
- in alkyl diazoacetate, salen complex 4 (R=p-TBDPS-C₆H₄) gives high yield and enantioselectivity.

(the complexes having a higher molecular recognition ability would serve as an efficient catalyst for this reaction.)
Iron Carbenoid

Iron is so cheap metal, but reaction example is not enough...
Y. Tang et al., JACS, 2009, 131, 4192.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclopropane</th>
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<th>Z/E (%)</th>
<th>ee (%)</th>
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<td>Et</td>
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<td>94</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>87</td>
<td>&gt;99:1</td>
<td>94</td>
<td>19%</td>
<td>Et</td>
<td>91:06</td>
<td>94</td>
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<tr>
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<td>Bu</td>
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<td>&gt;99:1</td>
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<td>Et</td>
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<td>&gt;99:1</td>
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<td>19%</td>
<td>Et</td>
<td>91:06</td>
<td>94</td>
<td>83</td>
</tr>
</tbody>
</table>

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.

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. Summary & 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.

$$\begin{align*}
\text{N}_2 & \quad \text{ML}_n \\
R^1 & \quad \text{R}^2 \\
\text{Various Bond Formations} & \quad \text{stereoselective} \\
R^1 & \quad \text{R}^2 \\
\text{Natural Products} & \\
\text{further transformations} & \\
\end{align*}$$

Further 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

$$\begin{align*}
\text{R}^1 & \quad \text{O} \\
\text{R}^2 & \quad \text{O} \\
\text{TsN}_3 & \quad \text{or p-ASBA} \\
\text{Ar} & \\
\text{NHAc} & \\
\end{align*}$$
```

- **Carbenoid generation method not using diazo precursor??**

available substrate and useful additive, easy conditions...

\[ \text{e.g.) substrate (dihalogen, monohalogen, active methylene (benzylic, allylic, } \alpha \text{-position of carbonyl), directing group, alkene, or alkane), additive (base, oxidant), ligand effect of metal (steric, other several character), and the other additive and conditions...} \]

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