[3 + 3] Cycloaddition by 1,3-Dipoles
~ new method for cyclization reaction ~

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Nagashima Nozomu
1. Introduction
Six membered ring in natural products

- Many natural products contain six-membered rings.
- Formation of six-membered rings would be a key step in synthesis.
Diels-Alder reaction is one of certificated methods for six membered ring.


New method for synthesis of 6 membered ring

Feature of [3 + 3] dipole cycloaddition

1. Some substrates would be more suitable for [3 + 3] cycloaddition
2. Quaternary carbon could be introduced before cyclization.
3. Stepwise reaction.
How to make 1,3-dipole?

Normal molecule: negative charge and positive charge emerges alternately.

1. Contain hetero atoms at center

2. Molecule changes acceptor to donor stepwise. (or donor to acceptor)

How to make 3-carbon unit dipoles?
**Reactive dipole and Stable dipole (1)**

These dipoles are stable dipoles and the reaction between stable dipoles wouldn’t proceed.

Stable dipoles react with “Reactive dipoles”
**Reactive dipole and Stable dipole (2)**

- First covalent bond formation step is important and second cyclization step would be supported by entropic effect.
- The reactive dipole is catalytically formed in the reaction.

**How to make the “reactive dipole”?**
2. Three carbon unit 1,3-dipole

(2-1) Normal 1,3-dipole species
● Trimethylenemethane

(2-2) Stepwise 1,3-dipole species
● NHC conjugated unsaturated aldehyde
● Phosphine conjugated allene
● Vinylcarbene
**Nature of TMM (1)**

Dimerization of TMM is proceeded from triplet TMM. (CIDNP analysis)

- [3 + 3] cycloaddition would be difficult by using triplet TMM

How prevent the ring closing and stabilize the ring open state of singlet TMM?
**Nature of TMM (2)**

- Cation is stabilized by palladium and prevents ring closing.
- Nucleophilic / Basic character of TMM

Pd-TMM complex reacts with only electron-deficient alkene. (Nucleophilic character)

Pd-TMM complex acts as base. (Basic character)
**Nature of TMM (2)**

- Cation is stabilized by palladium and prevents ring closing.
- Nucleophilic / Basic character of TMM

Pd-TMM complex reacts with only electron-deficient alkene. (Nucleophilic character)


2. Three carbon unit 1,3-dipole

Pd-TMM complex acts as base. (Basic character)
Pd-TMM [3 + 3] cycloaddition

TMM also reacts with azomethine imine.

T. Hayashi et al. JACS, 2006, 128, 6330.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (2a)</td>
<td>3a</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>4-MeC₆H₄ (2b)</td>
<td>3b</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>4-CF₃C₆H₄ (2c)</td>
<td>3c</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>3-ClC₆H₄ (2d)</td>
<td>3d</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>2-FC₆H₄ (2e)</td>
<td>3e</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>2-MeC₆H₄ (2f)</td>
<td>3f</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>3-pyrdyl (2g)</td>
<td>3g</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>1-cyclohexenyl (2h)</td>
<td>3h</td>
<td>71</td>
</tr>
<tr>
<td>9</td>
<td>t-Bu (2i)</td>
<td>3i</td>
<td>20</td>
</tr>
</tbody>
</table>

2. Three carbon unit 1,3-dipole

- Reaction between TMM and dipole equivalent was reported.

- TMM also reacts with azomethine imine.
Controlling substituent position would be difficult.

→ The synthesis is limited to cycloaddition from simple trimethylenemethane.

- Acethoxy group also attacks as nucleophile.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10% Pd(OAc)$_2$, 60% P(OPr-i)$_3$</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>10% Pd(PPh$_3$)$_4$</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>10% Pd(OAc)$_2$, 30% P(Bu-$n$)$_3$</td>
<td>28, 20, 50</td>
</tr>
<tr>
<td>4</td>
<td>10% Pd(OAc)$_2$, 25% DPPP</td>
<td>41, 20, 30</td>
</tr>
</tbody>
</table>
Cycloaddition with aziridines which doesn’t have arylsulfoneamide didn’t proceed.

This reaction is sluggish reaction.

Sluggish reaction of TMM [3 + 3] cyclization

- Reaction is limited to less-hindered dipoles which have some reactivity?

**Stable TMM dipole**

TMM is used as stable dipole and cyclopropane is used as reactive dipole.

Other TMM (Nakamura TMM)

- Acetal substituent promotes ring cleavage.
- The reactivity of TMM doesn’t decrease.

[3 + 2] cycloaddition by Nakamurra TMM

- This TMM is suitable for [3 + 2] cycloaddition
- This five-membered product would lead to carboxylic acid in acidic condition.
[3 + 3] cycloaddition by Nakamura TMM

- [3 + 3] cycloaddition with 1,3-dipole is not reported (doesn’t proceed?)
- 6-membered ring is cleaved in acidic condition.
- Nakamura TMM is not useful for [3 + 3] dipole cycloaddition today.

**Nature of enal with NHC**

NHC catalyzed [3 + 3] cycloaddition

2. Three carbon unit 1,3-dipole

Stereoselectivity of cyclization

**NHC application with Lewis acid**

![Chemical structures and mechanisms](image)

Can this mechanism apply for [3 + 3] cycloaddition??

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NHC problems

- Possibility of dimerization

![Chemical reaction diagram]

- Dimerization between NHC conjugated aldehyde and not conjugated aldehyde would occur.
- Aldehyde is also activated by Lewis Acid.
  → The reaction is limited to the stable dipole which is more reactive than starting \( \alpha,\beta \)-unsaturated aldehydes

- Lacking certifiable examples
  - Cycloaddition partner is limited to azomethine imine. (Only 1 example)
  → Reactivity is low and other dipoles can’t react with this dipole?
Phosphine catalyzed [4 + 2] cycloaddition

\[
\text{Me}\text{CO}_2\text{Et} + \text{R} = \text{N} - \text{Ts} \xrightarrow{\text{PBu}_3 (20 \text{ mol\%})} \text{CH}_2\text{Cl}_2, \text{rt}} \rightarrow \text{R} - \text{N} - \text{Ts} \text{CO}_2\text{Et}
\]

2. Three carbon unit 1,3-dipole

O. Kwon et al. JACS, 2003, 125, 4716.

<table>
<thead>
<tr>
<th>entry</th>
<th>R(^1)</th>
<th>phosphine</th>
<th>product</th>
<th>% yield(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (2a)</td>
<td>P(NMe(_2))(_3)</td>
<td>3a</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC(_6)H(_4) (2b)</td>
<td>P(NMe(_2))(_3)</td>
<td>3b</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>4-BrC(_6)H(_4) (2c)</td>
<td>P(NMe(_2))(_3)</td>
<td>3c</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>Ph (2a)</td>
<td>P(4-FC(_6)H(_4))(_3)</td>
<td>4a</td>
<td>93</td>
</tr>
<tr>
<td>5</td>
<td>4-MeOC(_6)H(_4) (2b)</td>
<td>P(4-FC(_6)H(_4))(_3)</td>
<td>4b</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>4-BrC(_6)H(_4) (2c)</td>
<td>P(4-FC(_6)H(_4))(_3)</td>
<td>4c</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>2-furyl (2d)</td>
<td>P(4-FC(_6)H(_4))(_3)</td>
<td>4d</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>3-pyridyl (2e)</td>
<td>P(4-FC(_6)H(_4))(_3)</td>
<td>4e</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>N-Me-2-indolyl (2f)</td>
<td>P(4-FC(_6)H(_4))(_3)</td>
<td>4f(^*)</td>
<td>91</td>
</tr>
</tbody>
</table>

**Phosphine catalyzed [3 + 3] cyclization**

2. Three carbon unit 1,3-dipole

\[ \text{CO}_2\text{Et} \rightarrow \text{CO}_2\text{Et} \]

24

Proton transfer (A to D) is promoted by PBu3.
6-endo cyclization of E is less efficient and proton transfer (E to G) proceeds when PBu3 is catalyst.
Control other cyclizations and promote only [3 + 3] cycloaddition is difficult.
e.e. or d.r. is not discussed in this paper ....

O. Kwon et al. JACS, 2011, 133, 13337.
Phosphine catalyzed cyclization problems

- 5 membered ring formation

- 7 membered ring formation

P-O interaction would be weaker when R = Bu because of steric hindrance.

- Steric hindrance of Bu substituents prevents the 6 membered cyclization

It is difficult to prevent other cyclizations.
Nature of vinylcarbene

Vinyl-gold-carbene

F. D. Toste et al. JACS, 131, 11654.
Vinylrhodium carbene

2. Three carbon unit 1,3-dipole

M. P. Doyle et. al. JACS, 2011, 133, 16402
Effect of Substituents

TBSO- substituent is important in cycloaddition of vinylcarbene.

Combination with Lewis acid


Reaction does not proceed without activation of hydrazone.

2. Three carbon unit 1,3-dipole
Dearomatization $[3 + 3]$ cycloaddition by vinylcarbene

$\text{OTBS\ CO}_2\text{Me} + \text{PhN=O} \xrightarrow{[\text{Rh}_2(\text{OAc})_4] 2 \text{ mol\%} \text{ rt, CH}_2\text{Cl}_2, 4\text{A MS.}} \xrightarrow{100\% \text{ conversion}} \text{PhCO}_2\text{Me}$

92% yield

What promotes side reaction?

M. P. Doyle et. al. ACIE, 2013, 52, 12664

$\text{OTBS\ CO}_2\text{Me} + \text{N=O-CN} \xrightarrow{\text{Rh cat. (3 mol\%) toluene, rt, 3 h}} \text{MeO}_2\text{C} \text{OTBS}$

+ $\text{MeO}_2\text{C} \text{OTBS}$

M. P. Doyle et. al. JACS, 2013, 135, 12439
**Reaction mechanism (1)**

1. Lewis acidic dirhodium compound promotes [3 + 2] cycloaddition (Entry 2, 4, 10)
2. Lewis base additives promotes [3 + 2]
3. Cyclopropene was also demonstrated to be a precursor of the same metal carbene intermediate (Entry 11 to 15)

M. P. Doyle *et. al.* JACS, **2013**, *135*, 12439
Stable dipoles which were not sufficiently basic don’t cause inhibition of dirhodium catalysts toward metal carbene formation.

Dirhodium compounds are mild Lewis acids that coordinate with Lewis bases (Isoquinolinium/ pyridinium methylylides are readily accessible nucleophiles).
Vinylcarbene reactivity

- **Gold catalyst**
  
  ![Gold catalyst diagram]

- **Rhodium catalyst**
  
  ![Rhodium catalyst diagram]
3. Summary
1,3-dipole cycloaddition methods

Pd-TMM complex

\[
\text{CH}_2=\text{SiMe}_3\text{OAc} + \text{NTs} \xrightarrow{\text{Pd catalyst}} \text{N}_2\text{Ts}
\]

NHC conjugated unsaturated aldehyde

\[
\text{R}^1\text{CH}=\text{H} + \text{PhN}^+\text{N}^-\text{R} \xrightarrow{\text{NHC Catalyst}} \text{R}^1\text{N}=\text{N}^+\text{Ph}
\]

Phosphine conjugated allene

\[
\text{R}^1\text{N}^+\text{N}^-\text{R} + \text{CO}_2\text{Et} \xrightarrow{\text{Phosphine catalyst}} \text{R}^1\text{N}=\text{N}^+\text{R}^2\text{CO}_2\text{Et}
\]

Vinylcarbene

\[
\text{CO}_2\text{Me} + \text{PhN}^+\text{N}^-\text{Ar} \xrightarrow{\text{Rh catalyst}} \text{Ph}^+\text{N}^-\text{ArCO}_2\text{Me}
\]
### Comparison of 1,3-dipole cycloaddition methods

<table>
<thead>
<tr>
<th></th>
<th>Feature</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMM</td>
<td>· Synthesized easily</td>
<td>· AcO group also acts as nucleophile.</td>
</tr>
<tr>
<td></td>
<td>· Used as both reactive dipole and stable dipole</td>
<td>· Difficult to control enantioselectivity. (From less hindered side)</td>
</tr>
<tr>
<td>NHC</td>
<td>· Umpolung</td>
<td>· Possibility of dimerization.</td>
</tr>
<tr>
<td></td>
<td>· Stereoselectivity is determined by ligand of NHC</td>
<td>· Partner is limited to azomethine imine. (Other partners are less reactive than aldehyde?)</td>
</tr>
<tr>
<td>Phosphine</td>
<td>· Umπpolung</td>
<td>· Other cyclizations ([3 + 2] or [3 + 4]) also proceed.</td>
</tr>
<tr>
<td></td>
<td>· Allene can be applied for this method.</td>
<td>· Low yields.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>· Stereoselectivity is difficult to be controlled?</td>
</tr>
<tr>
<td>Vinylcarbene</td>
<td>· Many examples are reported.</td>
<td>· Reaction is supported by Ester or ether substituents.</td>
</tr>
</tbody>
</table>
**Future of [3 + 3] cycloaddition**

- Possibility of high stereoselectivity or enantioselectivity
  - Stereoselectivity or enantioselectivity is controlled by chiral auxiliary.
    → Selectivity will be more strengthened by 2 chiral auxiliary??

- First addition step could be reversible?

If first step is reversible, compounds attacked from concave side are obtained selectively?