

[3 + 3] Cycloaddition by 1,3-Dipoles

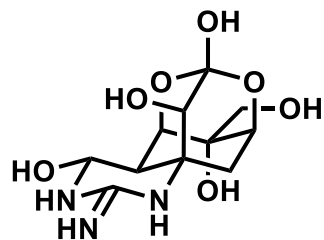
~ new method for cyclization reaction ~

2015. 2. 21.

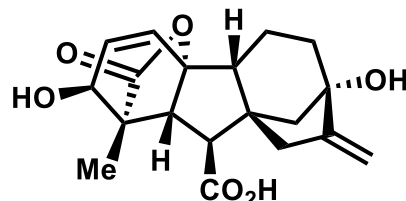
Nagashima Nozomu

1. Introduction

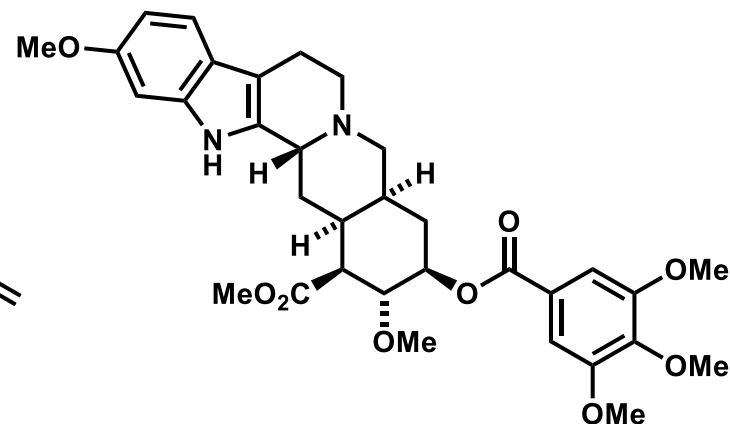
Six membered ring in natural products



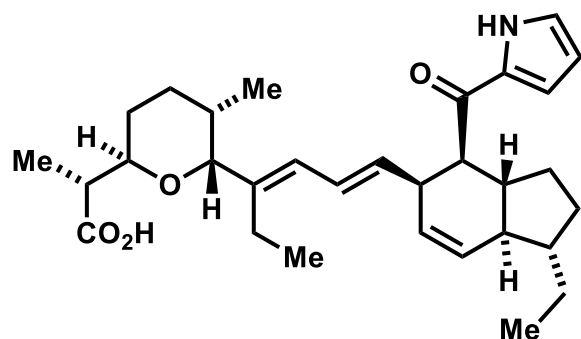
tetrodotoxin



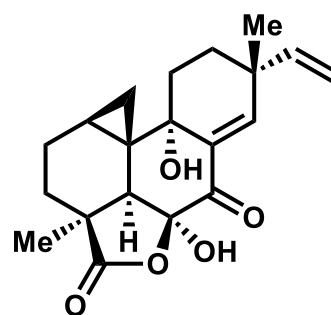
gibberellic acid



reserpine



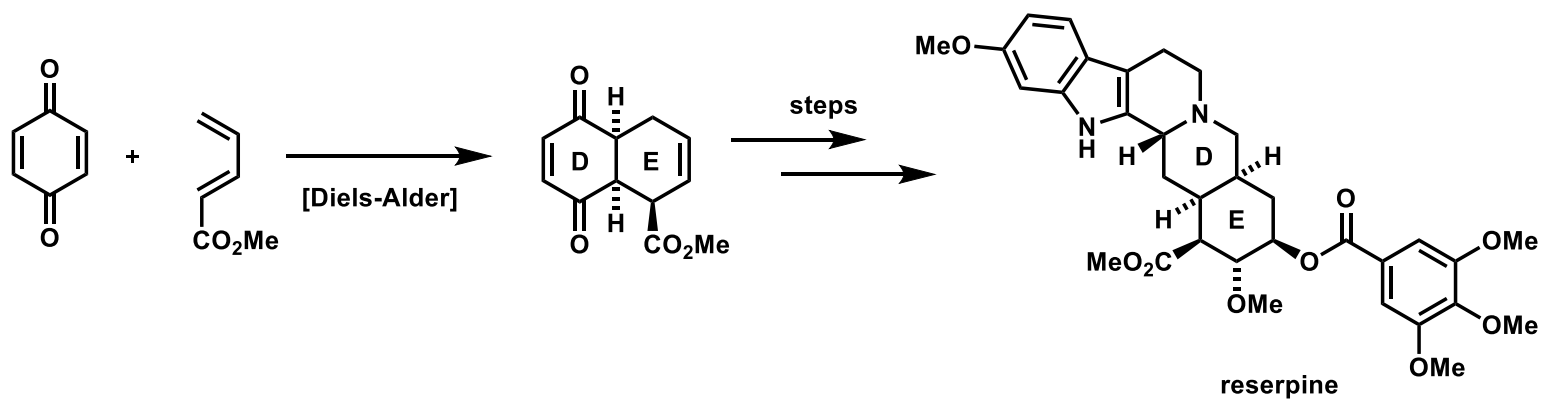
antibiotic X-14547 A



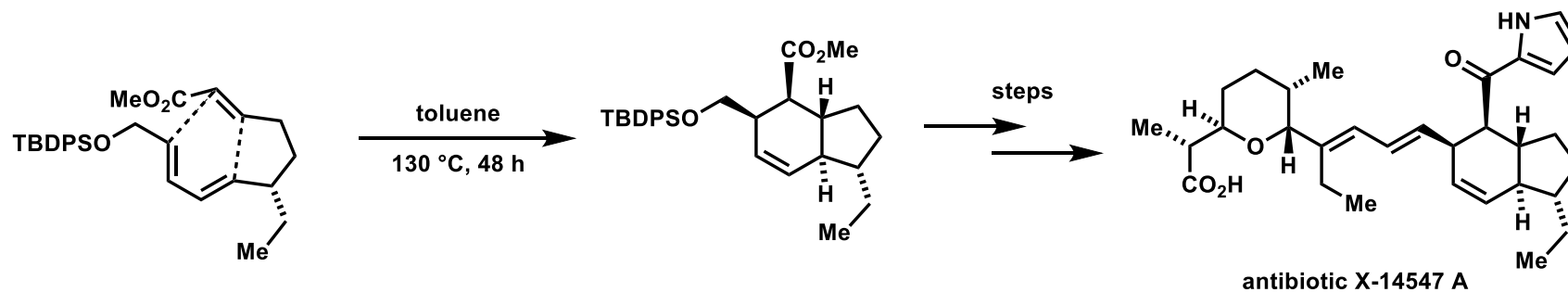
myrocin C

- Many natural products contain six-membered rings.
- Formation of six-membered rings would be a key step in synthesis.

Diels Alder Reaction



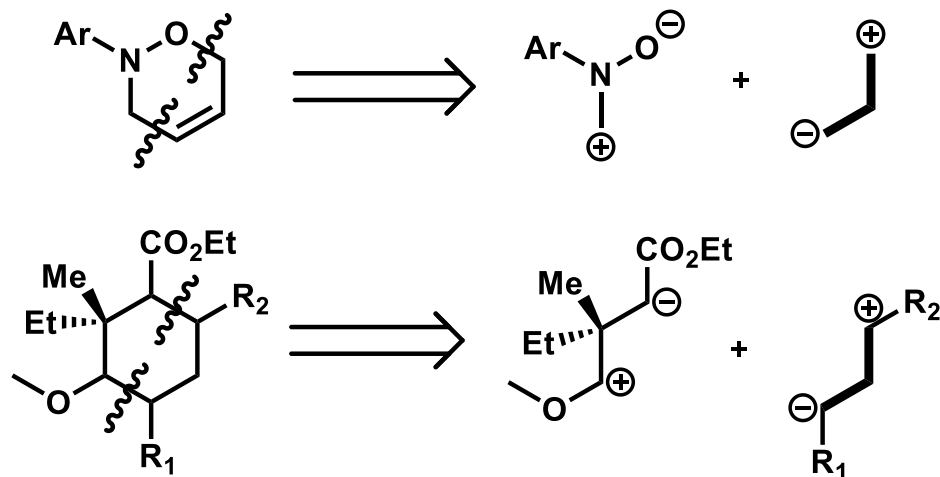
R. B. Woodward *et al.* *J. Am. Chem. Soc.* **1952**, 74, 4223.



K. C. Nicolaou *et al.* *J. Org. Chem.* **1985**, 50, 1440.

- Diels-Alder reaction is one of certificated methods for six membered ring.

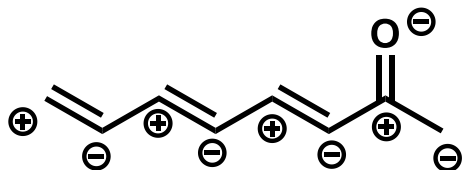
New method for synthesis of 6 membered ring



□ Feature of [3 + 3] dipole cycloaddition

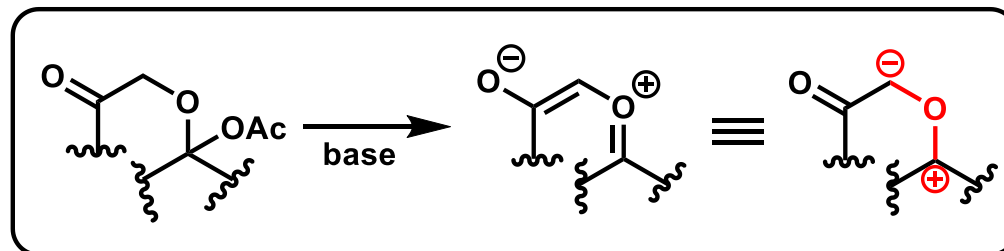
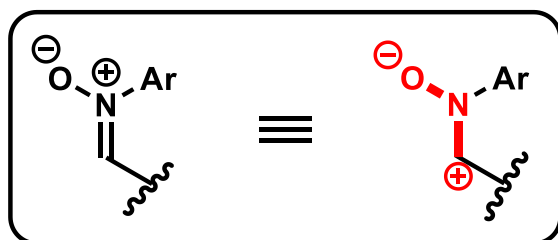
1. Some substrates would be more suitable for [3 + 3] cycloaddition
2. Quaternary carbon could be introduced before cyclization.
3. Stepwise reaction.

How to make 1,3-dipole?

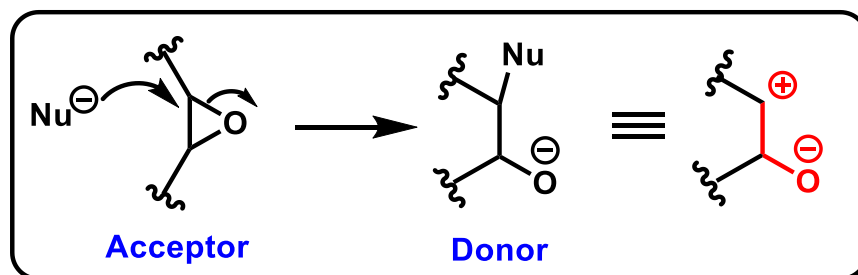


Normal molecule: negative charge and positive charge emerges alternately.

1. Contain hetero atoms at center

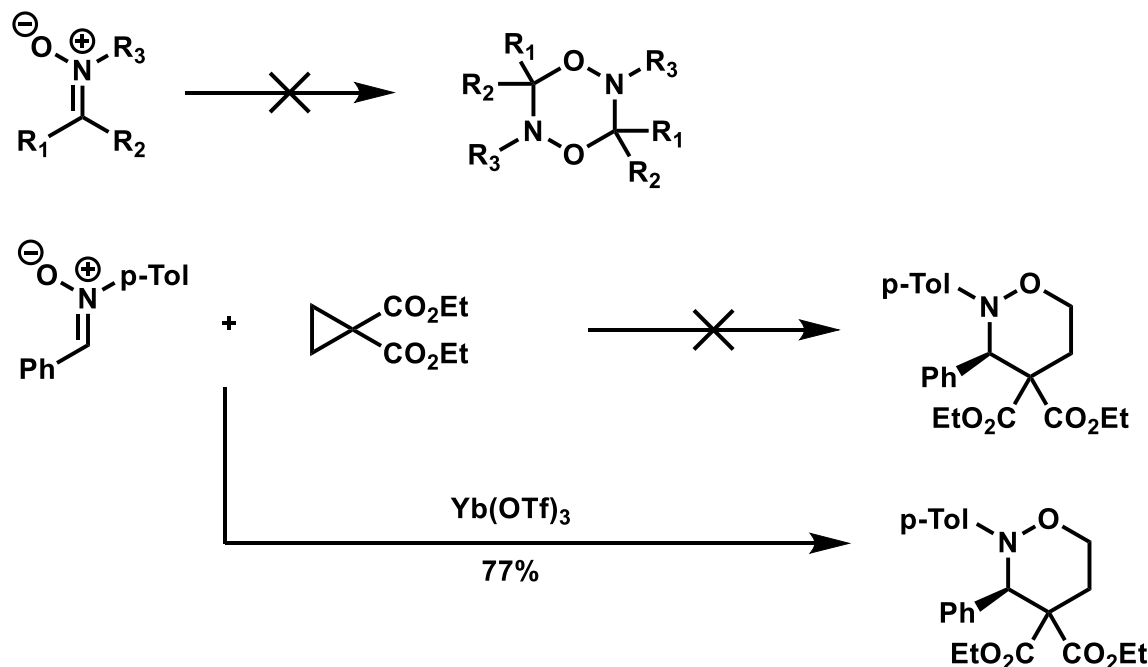


2. Molecule changes acceptor to donor stepwise. (or donor to acceptor)

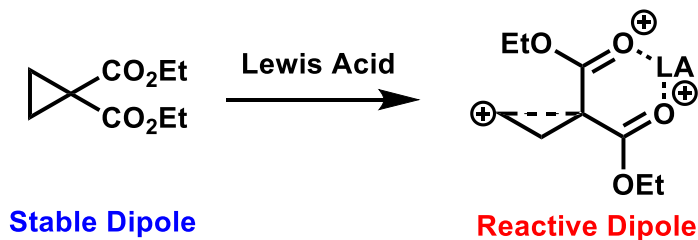


How to make 3-carbon unit dipoles?

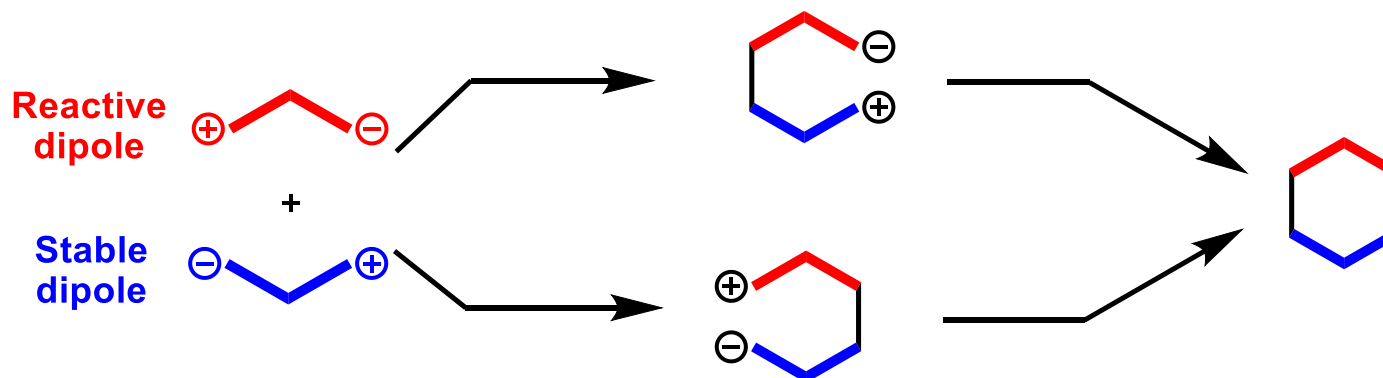
Reactive dipole and Stable dipole (1)



- 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

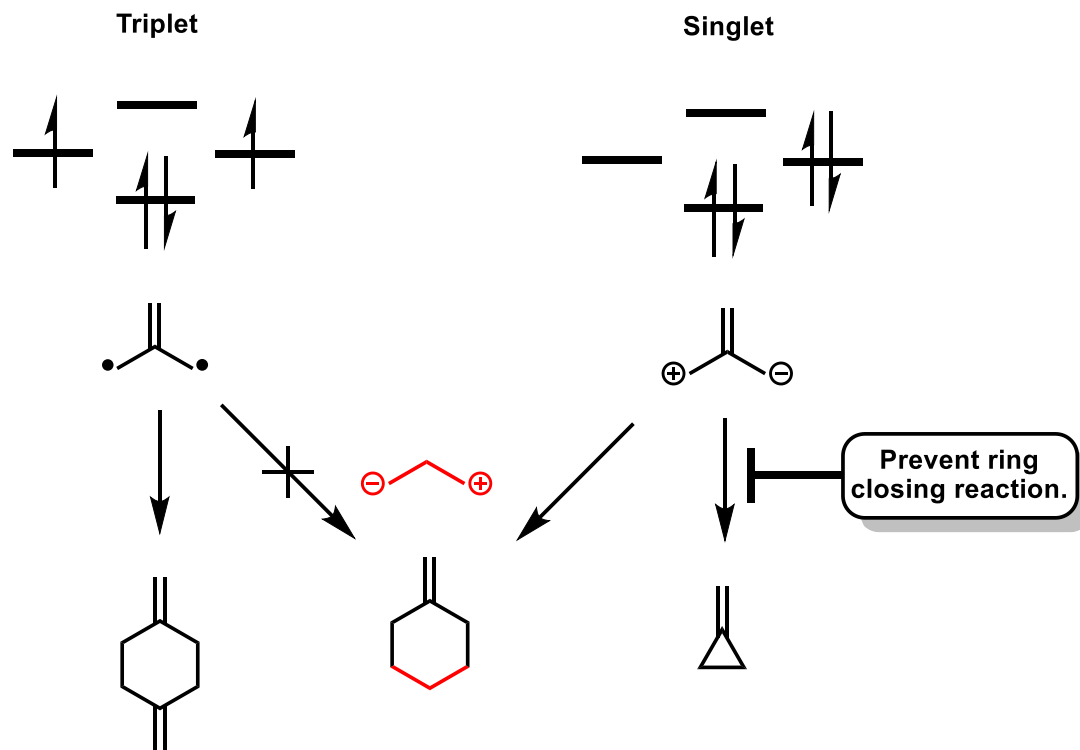
(2-1) Normal 1,3-dipole species

- *Trimethylenemethane*

(2-2) Stepwise 1,3-dipole species

- *NHC conjugated unsaturated aldehyde*
- *Phosphine conjugated allene*
- *Vinylcarbene*

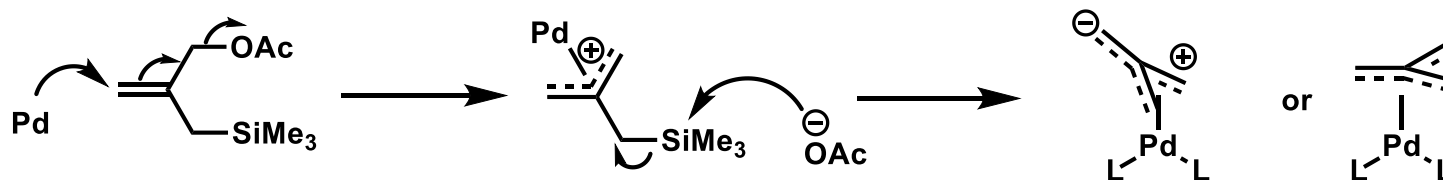
Nature of TMM (1)



- 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?

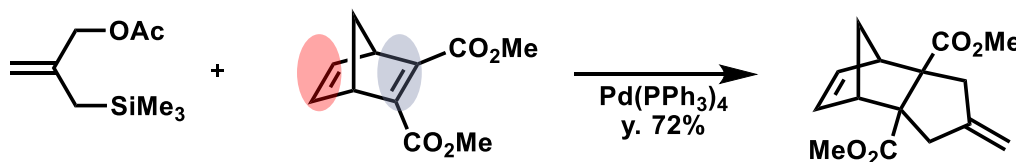
Nature of TMM (2)



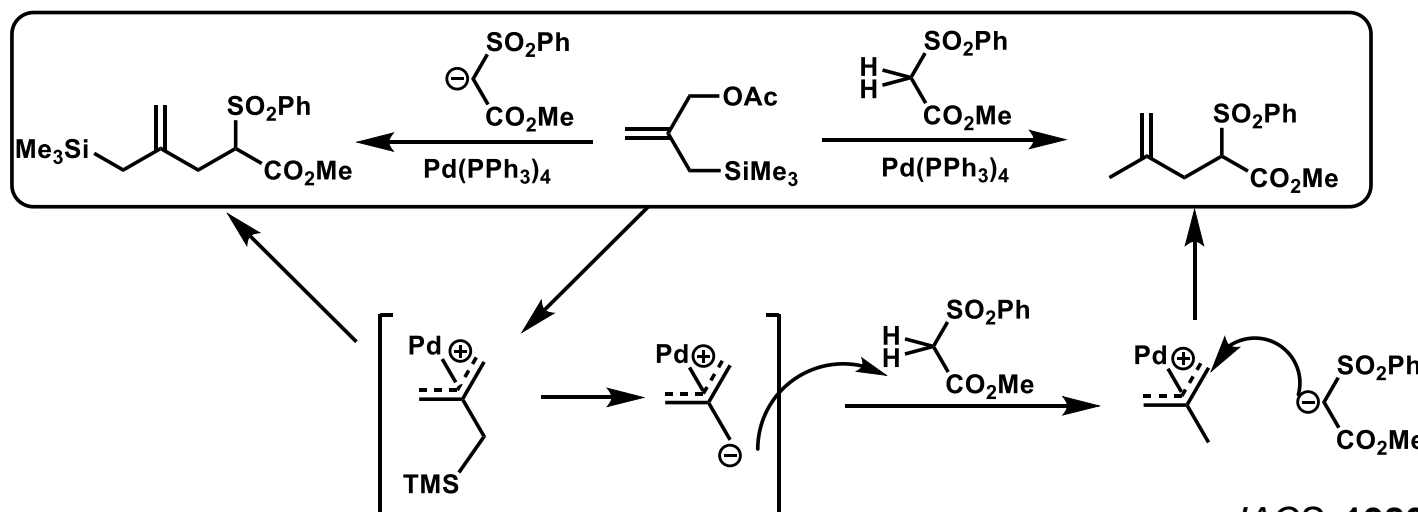
Barry M. Trost *et. al.* *JACS*, **1979**, *101*, 6429.

- Cation is stabilized by palladium and prevents ring closing.

- Nucleophilic / Basic character of TMM



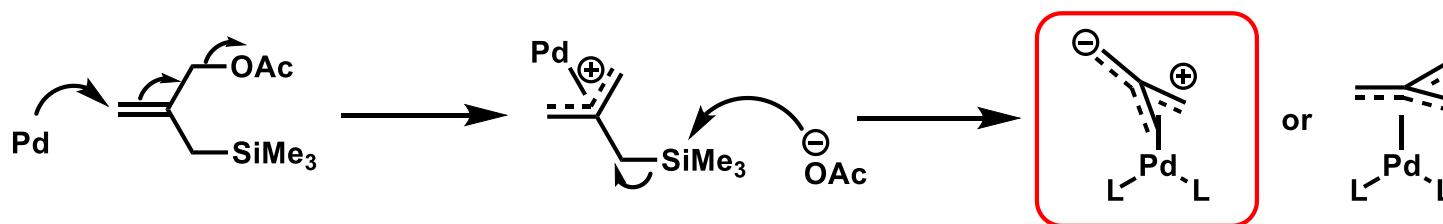
Pd-TMM complex reacts with only electron-deficient alkene. (Nucleophilic character)



Pd-TMM complex acts as base. (Basic character)

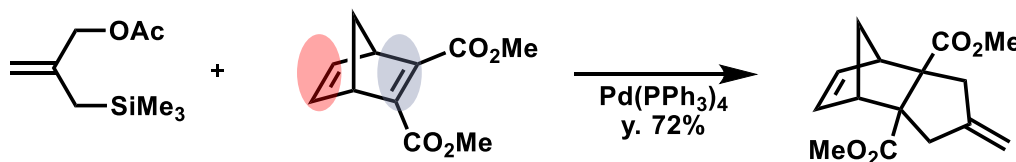
JACS, **1980**, *102*, 6359.

Nature of TMM (2)

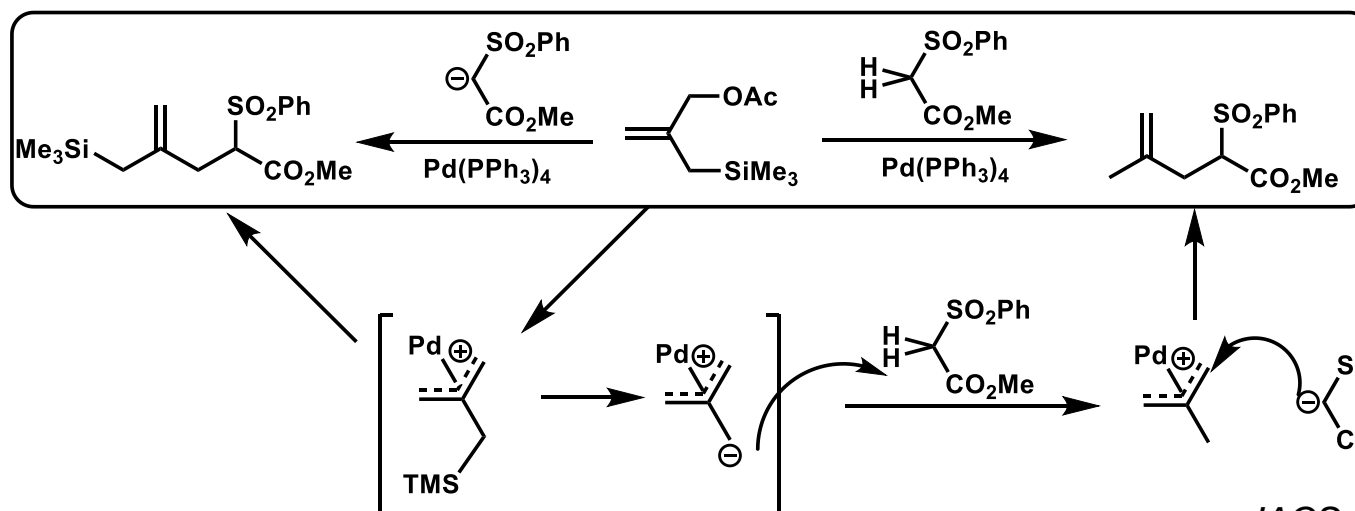


B. M. Trost *et. al.* *JACS*, **1979**, *101*, 6429.

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



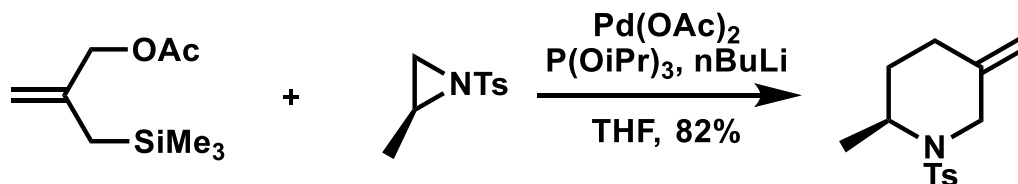
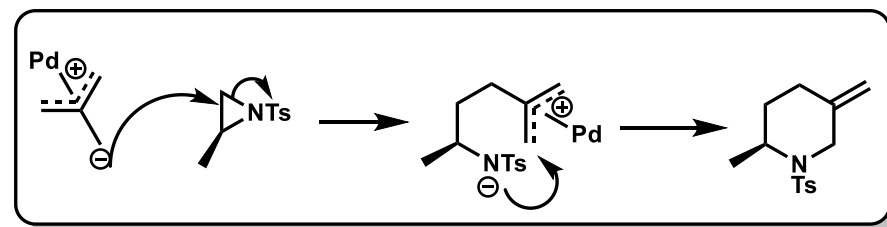
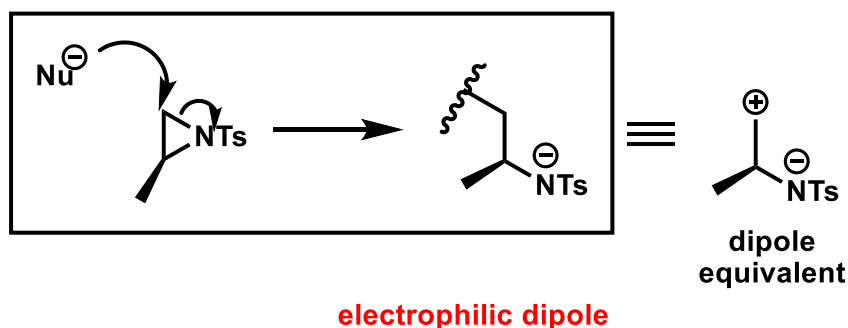
Pd-TMM complex reacts with only electron-deficient alkene. (Nucleophilic character)



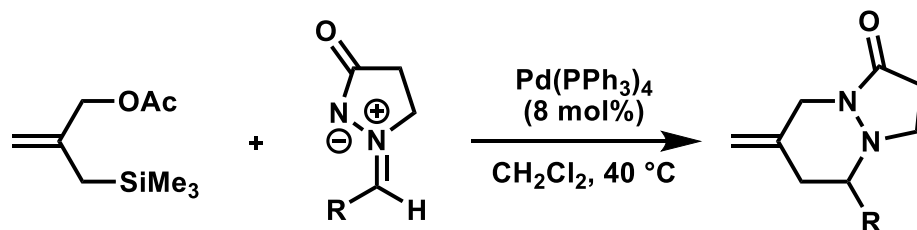
Pd-TMM complex acts as base. (Basic character)

JACS, **1980**, *102*, 6359.

2. Three carbon unit 1,3-dipole

Pd-TMM [3 + 3] cycloadditionJoseph P. A. Harrity *et al.* *JOC*, **2003**, 68, 4286.

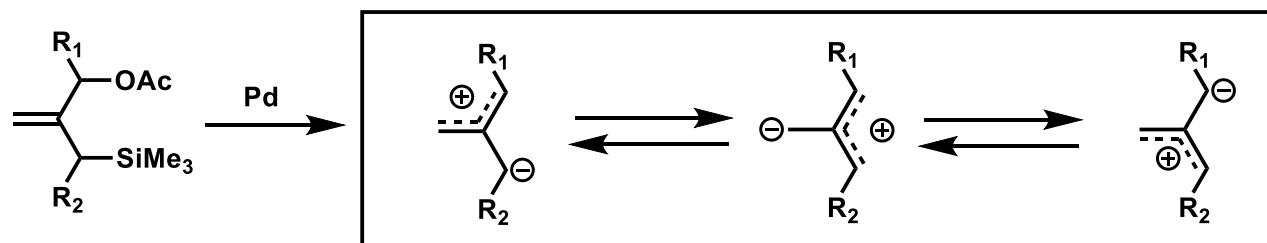
- Reaction between TMM and dipole equivalent was reported.



- TMM also reacts with azomethine imine.

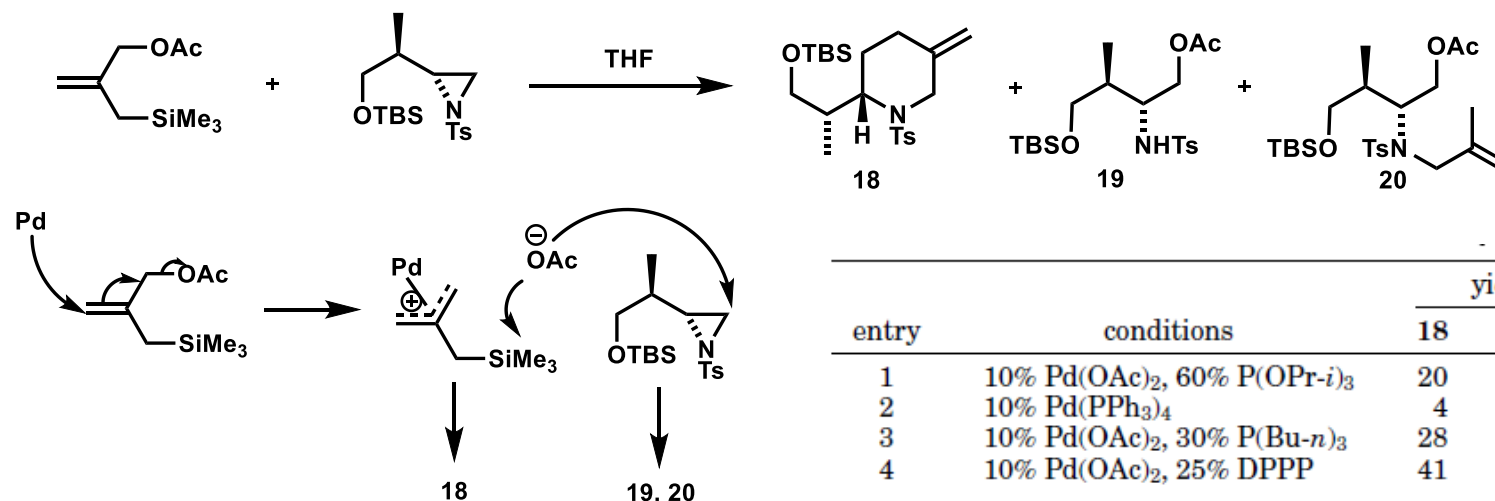
entry	R	product	yield (%) ^a
1	Ph (2a)	3a	81
2	4-MeC ₆ H ₄ (2b)	3b	74
3	4-CF ₃ C ₆ H ₄ (2c)	3c	92
4	3-ClC ₆ H ₄ (2d)	3d	90
5	2-FC ₆ H ₄ (2e)	3e	88
6	2-MeC ₆ H ₄ (2f)	3f	70
7	3-pyridyl (2g)	3g	75
8	1-cyclohexenyl (2h)	3h	71
9	<i>t</i> -Bu (2i)	3i	20

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

TMM problems

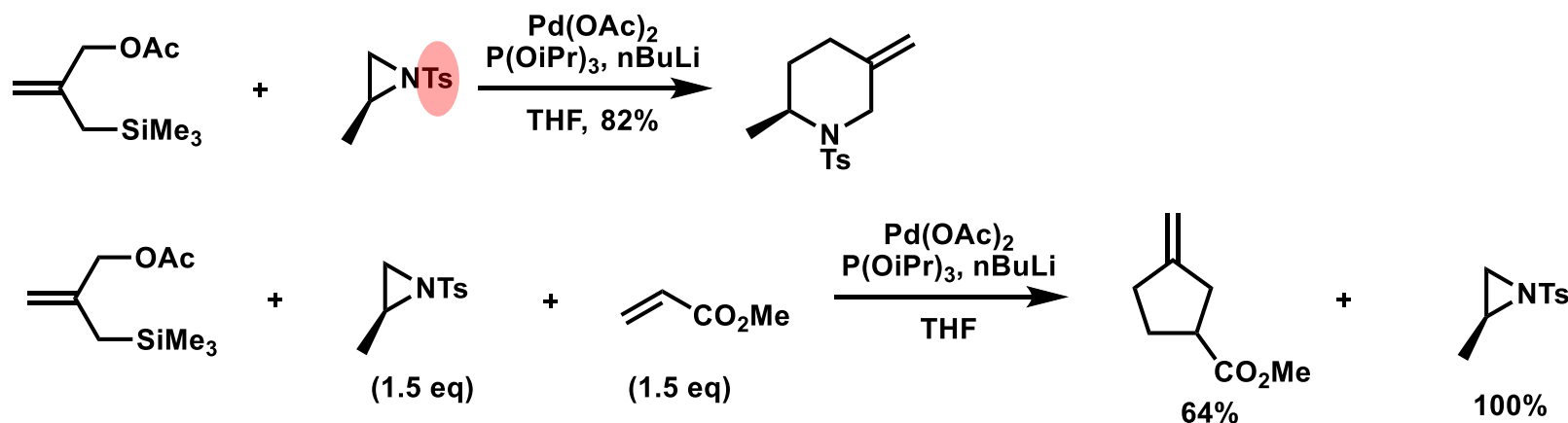
Controlling substituent position would be difficult.

→ The synthesis is limited to cycloaddition from simple trimethylenemethane.



- Acetoxy group also attacks as nucleophile.

Sluggish reaction of TMM [3 + 3] cyclization

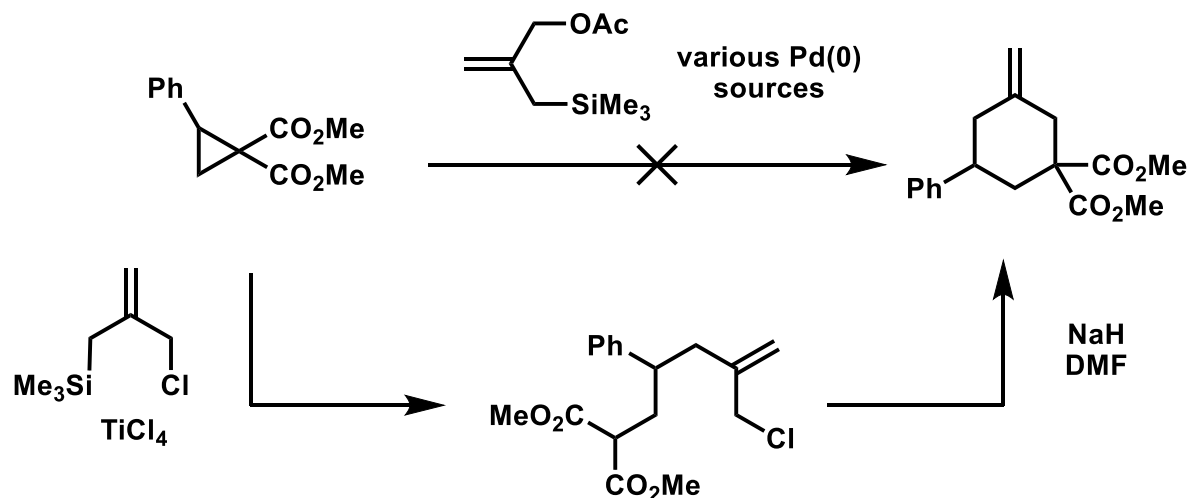


- Cycloaddition with aziridines which doesn't have arylsulfoneamide didn't proceed.
- This reaction is sluggish reaction.

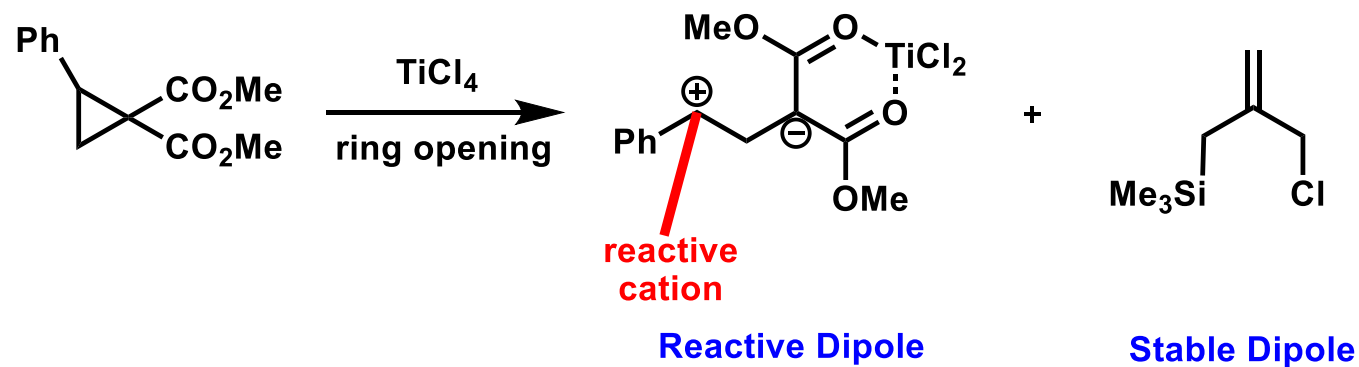
Joseph P. A. Harrity *et al.* *JOC*, **2003**, 68, 4286.

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

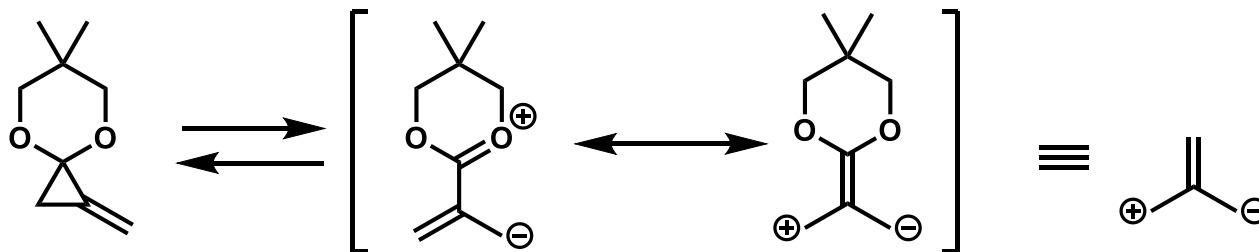
Stable TMM dipole



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



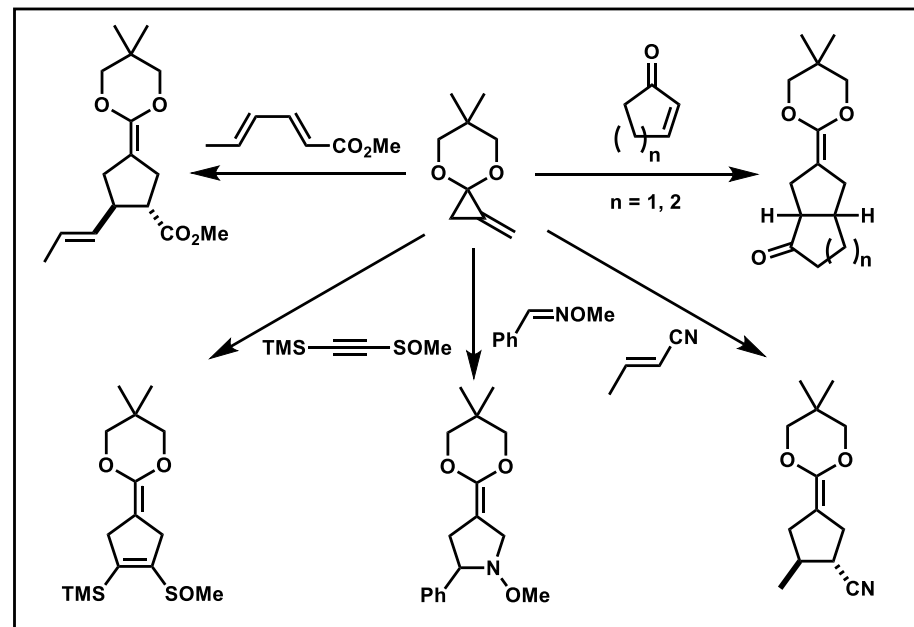
Other TMM (Nakamura TMM)



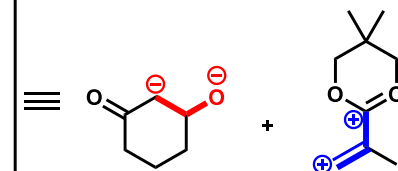
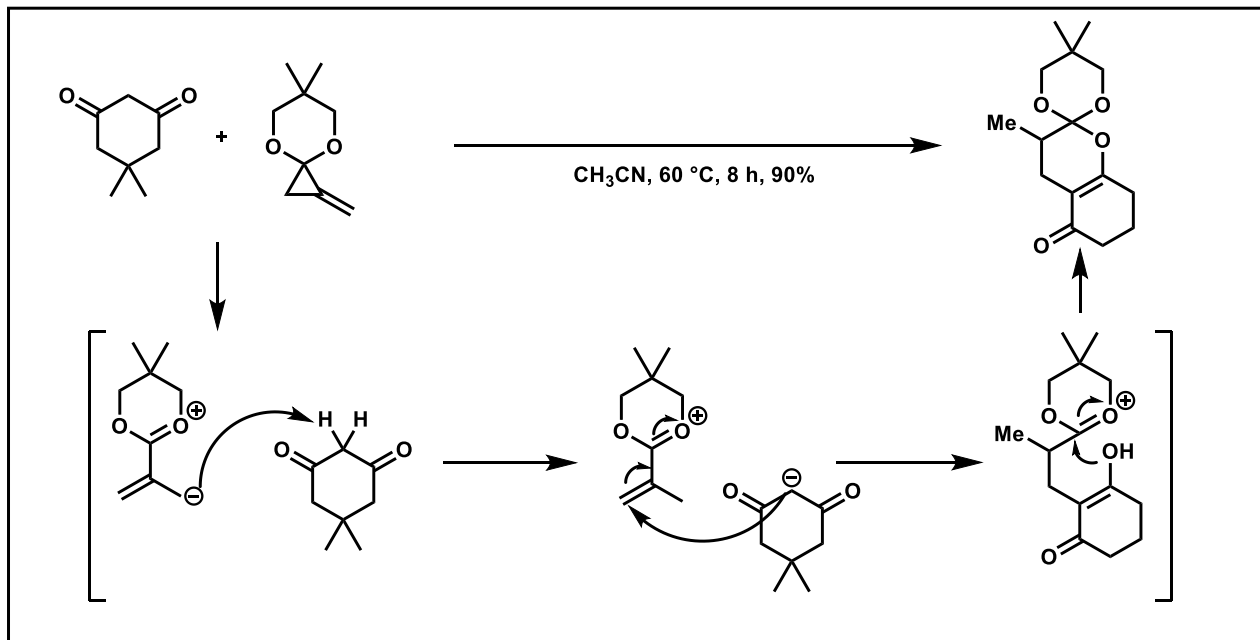
- Acetal substituent promotes ring cleavage.
- The reactivity of TMM doesn't decrease.

[3 + 2] cycloaddition by Nakamura TMM

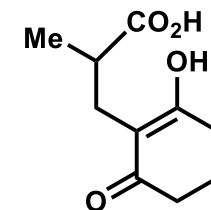
- This TMM is suitable for [3 + 2] cycloaddition
- This five-membered product would lead to carboxylic acid in acidic condition.



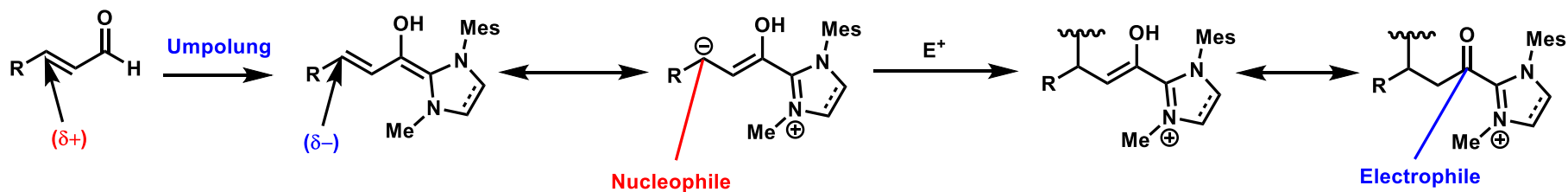
[3 + 3] cycloaddition by Nakamura TMM



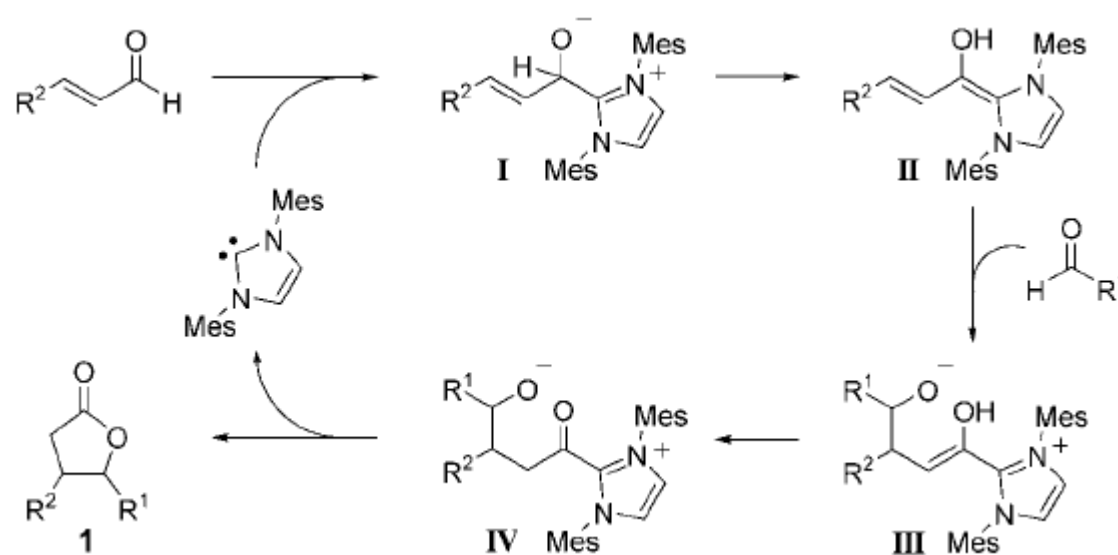
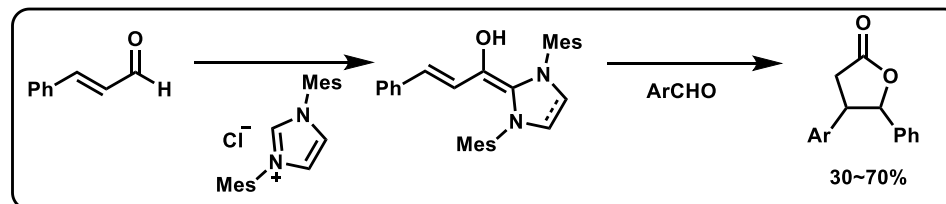
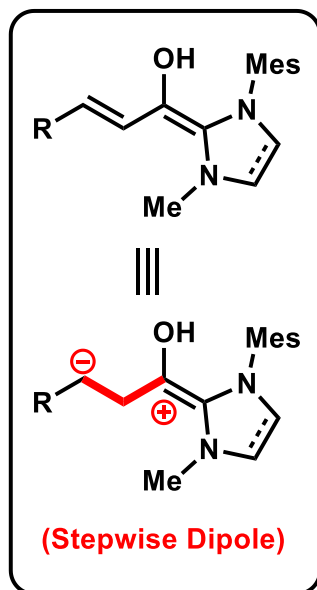
- [3 + 3] cycloaddition with 1,3-dipole is not reported (doesn't proceed?)
- 6-membered ring is cleaved in acidic condition.
- Nakamura TMM is not useful for [3 + 3] dipole cycloaddition today.



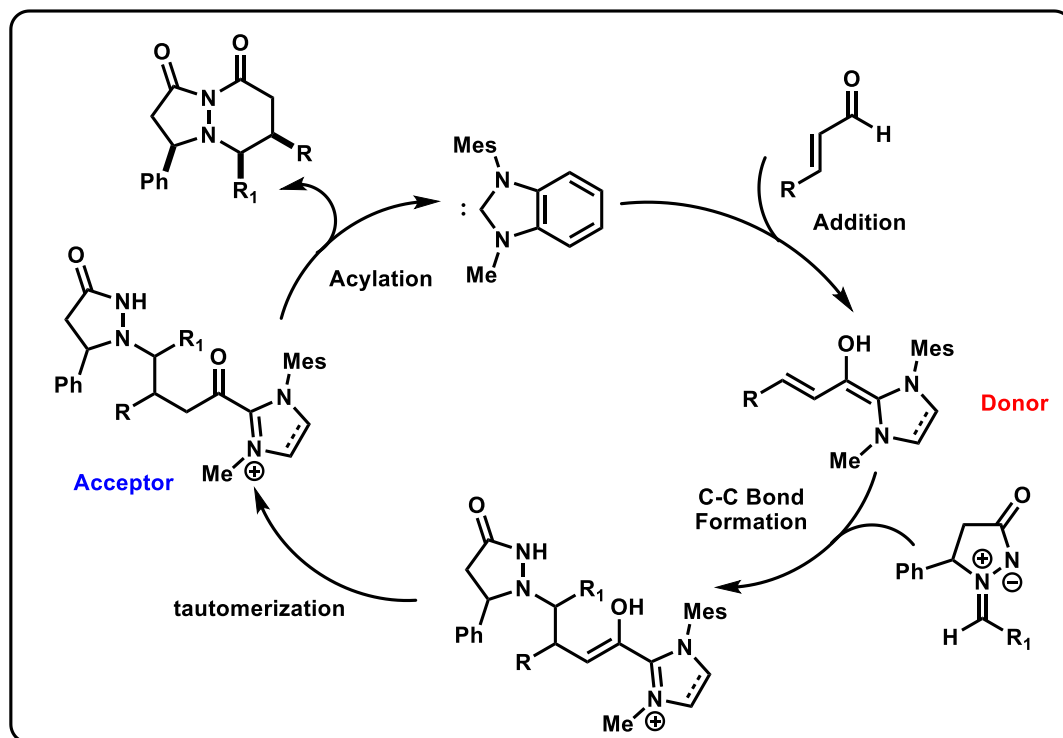
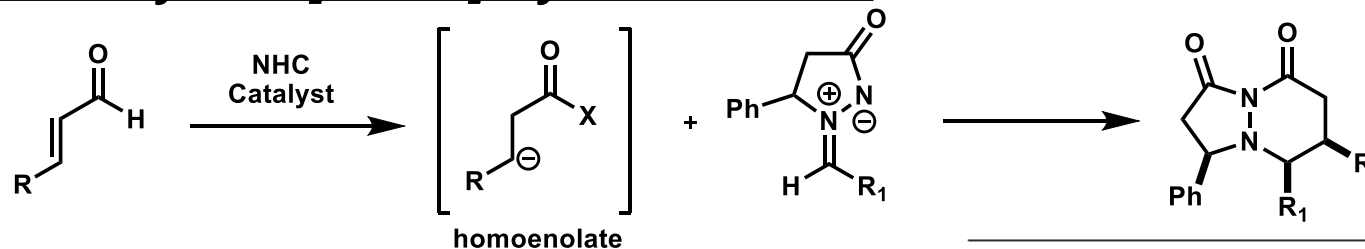
Nature of enal with NHC



□ NHC conjugated unsaturated aldehyde



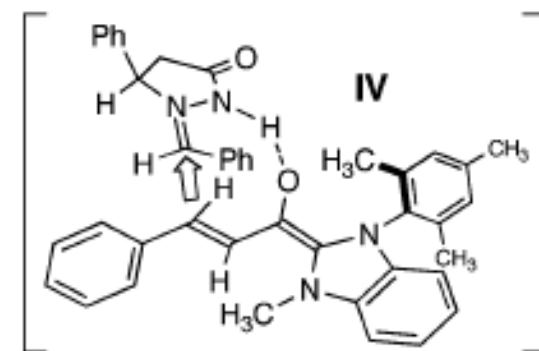
NHC catalyzed [3 + 3] cycloaddition



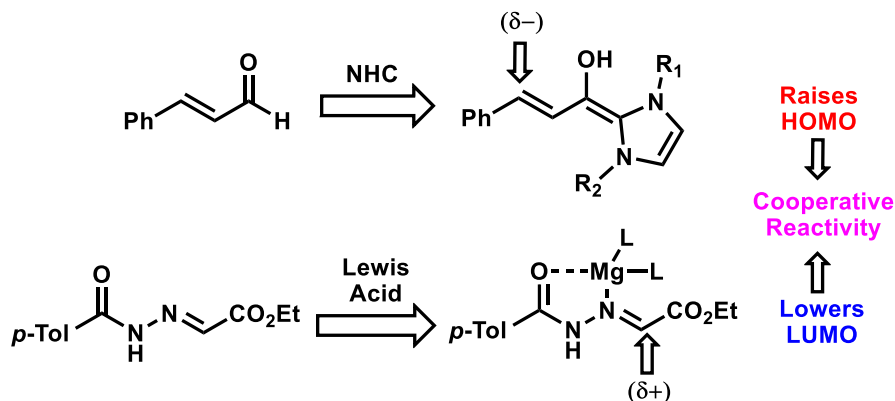
2. Three carbon unit 1,3-dipole

entry	R	R ¹	product	yield (%) ^b	d ^r
1	Ph (1a)	Ph (2a)	4	79	>20:1
2	4-OMePh (1b)	Ph (2a)	5	76	>20:1
3	3-OMePh (1c)	Ph (2a)	6	79	>20:1
4	2-OMePh (1d)	Ph (2a)	7	94	>20:1
5	2-naphthyl (1e)	Ph (2a)	8	77	>20:1
6	CH ₂ CH ₂ CH ₃ (1f)	Ph (2a)	9	67	>20:1
7	HC=CHCH ₃ (1g)	Ph (2a)	10	51	>20:1
8	4-ClPh (1h)	Ph (2a)	11	0	
9	Ph (1a)	4-BrPh (2b)	12	87	>20:1
10	Ph (1a)	4-FPh (2c)	13	82	>20:1
11	Ph (1a)	3-CF ₃ Ph (2d)	14	93	>20:1
12	Ph (1a)	3-BrPh (2e)	15	78	>20:1
13	Ph (1a)	3-CH ₃ Ph (2f)	16	76	>20:1
14	Ph (1a)	3-OMePh (2g)	17	67	>20:1
15	Ph (1a)	cyclohexyl (2h)	18	0	

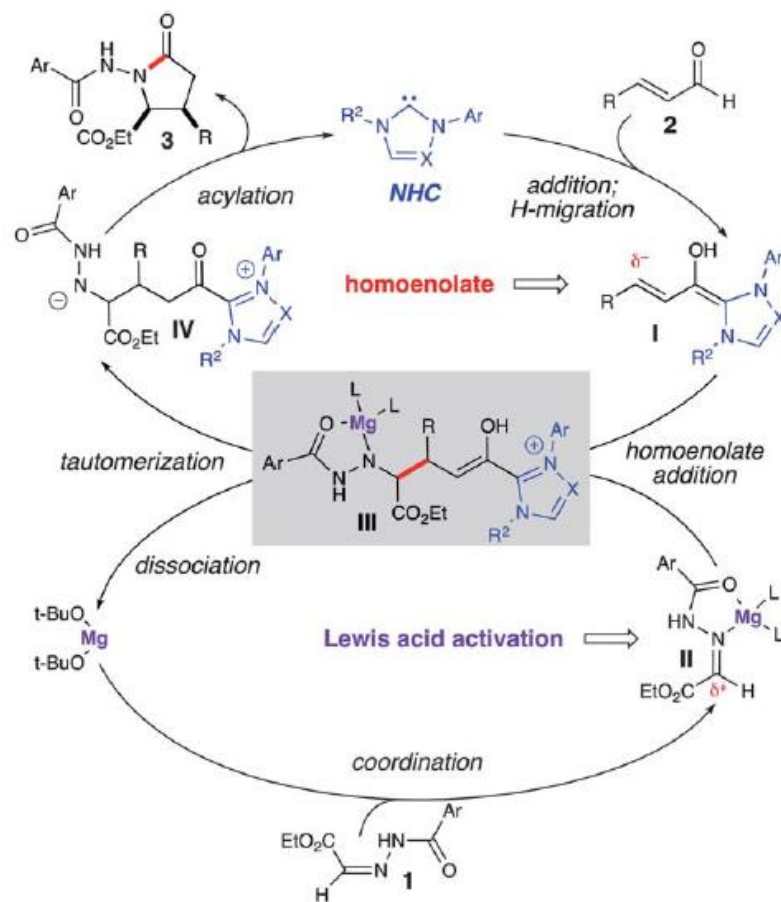
Stereoselectivity of cyclization



NHC application with Lewis acid



2. Three carbon unit 1,3-dipole



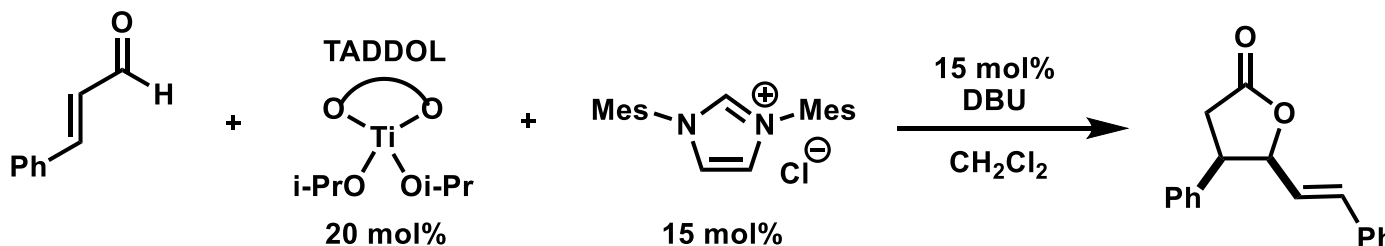
K. A. Scheidt *et al.* *Nature. Chem.* **2010**, *2*, 766.

K. A. Scheidt *et al.* *Chem. Sci.* **2012**, *3*, 53.

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

NHC problems

□ Possibility of dimerization



K. A. Scheidt *et al.* *JACS*, **2010**, 132, 5345.

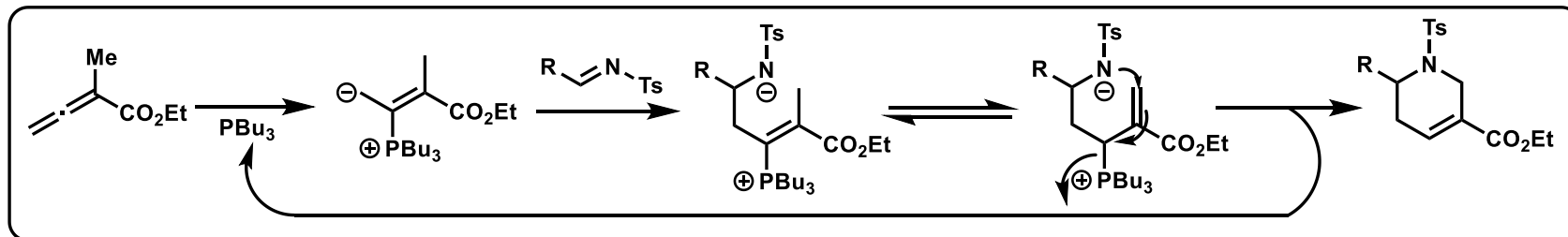
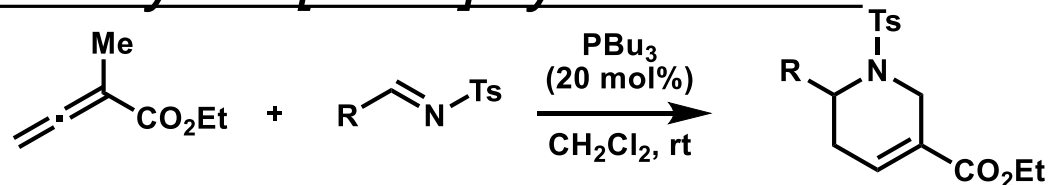
- Dimerization between NHC conjugated aldehyde and not conjugated aldehyde would occur.
- Aldehyde is also activated by Lewis Acid.
 - The reaction is limited to the stable dipole which is more reactive than starting α,β -unsaturated aldehydes

□ Lacking certifiable examples

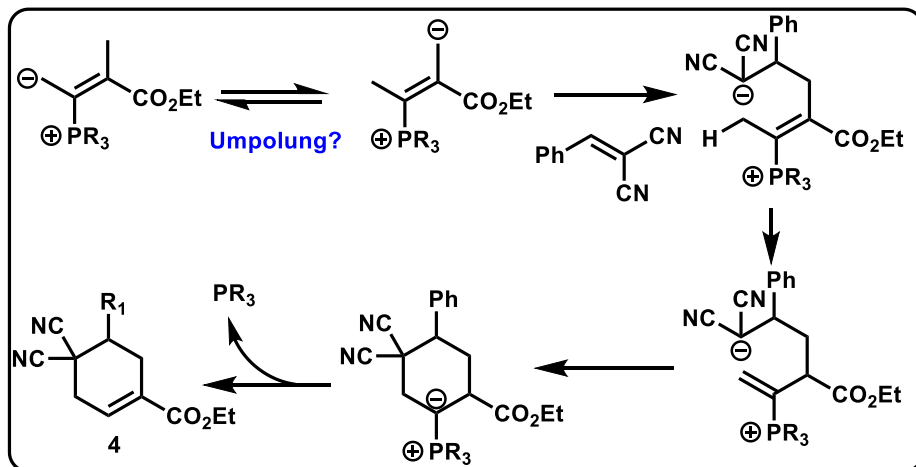
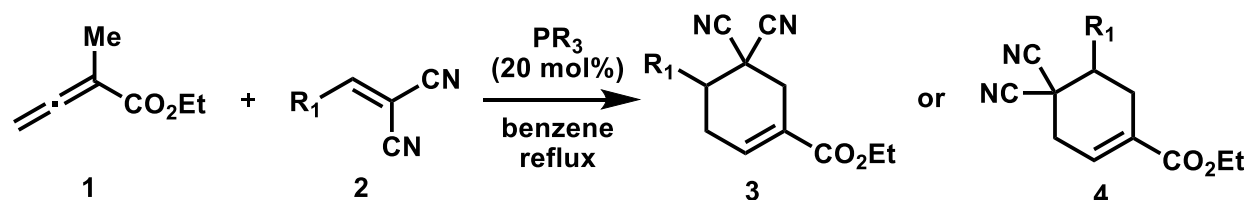
- Cycloaddition partner is limited to azomethine imine. (Only 1 example)
 - Reactivity is low and other dipoles can't react with this dipole?

Phosphine catalyzed [4 + 2] cycloaddition

2. Three carbon unit 1,3-dipole



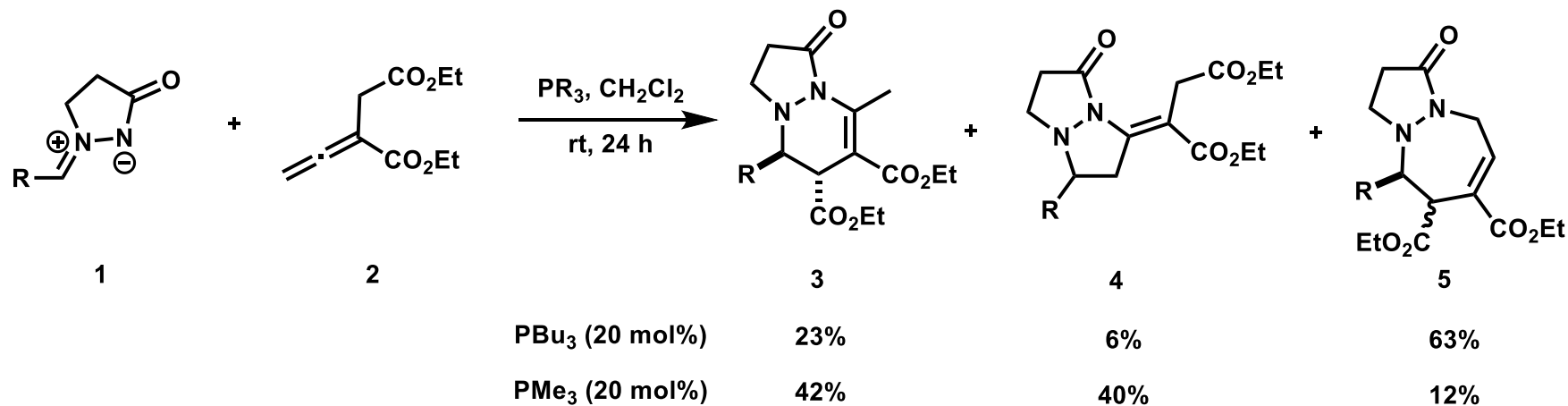
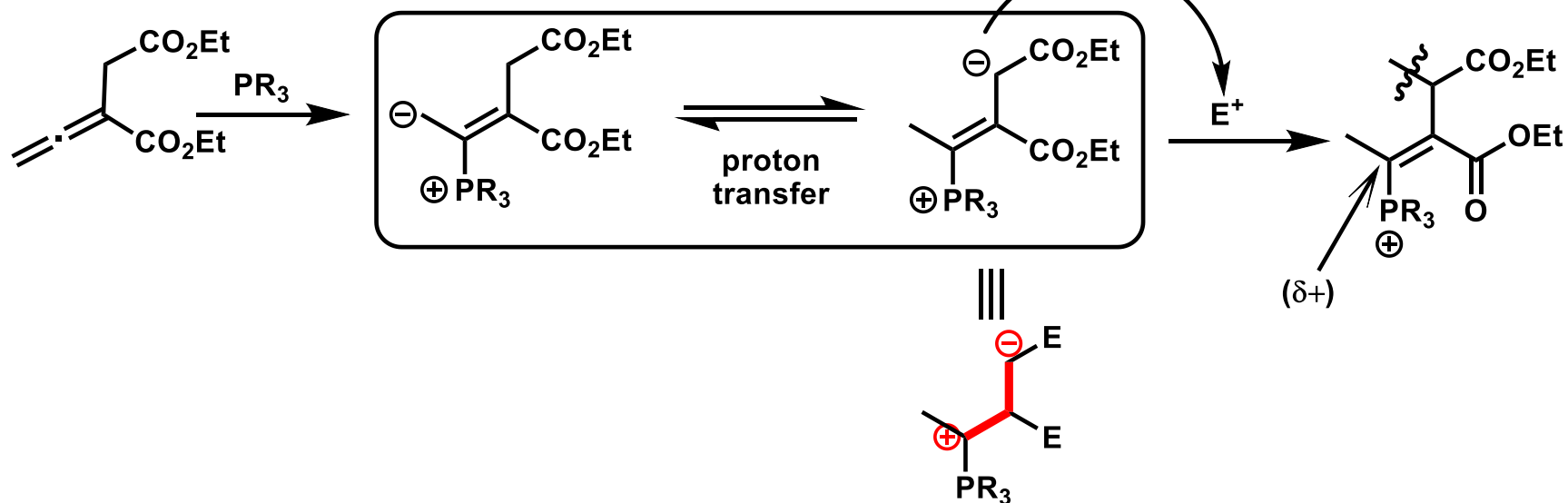
O. Kwon *et al.* JACS, **2003**, 125, 4716.



entry	R ¹	phosphine	product	% yield ^b
1	Ph (2a)	P(NMe ₂) ₃	3a	98
2	4-MeOC ₆ H ₄ (2b)	P(NMe ₂) ₃	3b	94
3	4-BrC ₆ H ₄ (2c)	P(NMe ₂) ₃	3c	86
4	Ph (2a)	P(4-FC ₆ H ₄) ₃	4a	93
5	4-MeOC ₆ H ₄ (2b)	P(4-FC ₆ H ₄) ₃	4b	90
6	4-BrC ₆ H ₄ (2c)	P(4-FC ₆ H ₄) ₃	4c	85
7	2-furyl (2d)	P(4-FC ₆ H ₄) ₃	4d	88
8	3-pyridyl (2e)	P(4-FC ₆ H ₄) ₃	4e	80
9	N-Me-2-indolyl (2f)	P(4-FC ₆ H ₄) ₃	4f ^c	91

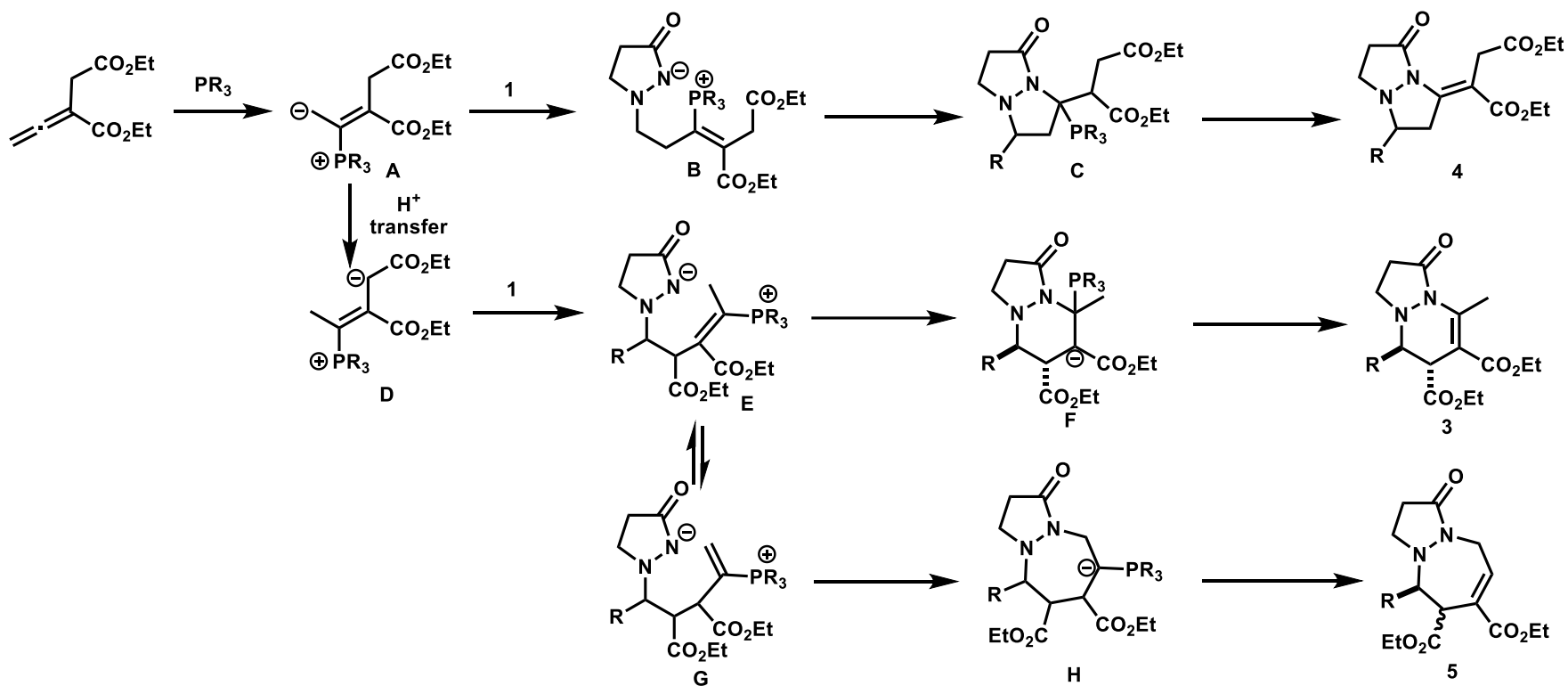
O. Kwon *et al.* JACS, **2007**, 129, 12632.

Phosphine catalyzed [3 + 3] cyclization



Reaction Mechanism

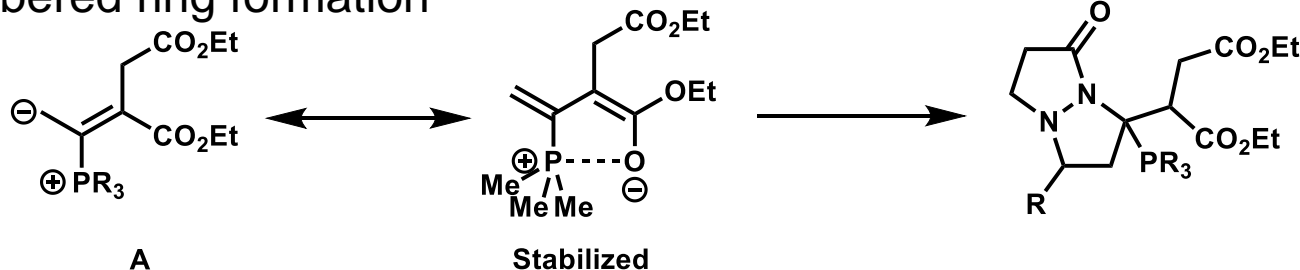
2. Three carbon unit 1,3-dipole



- Proton transfer (A to D) is promoted by PBU_3 .
- 6-endo cyclization of E is less efficient and proton transfer (E to G) proceeds when PBU_3 is catalyst.
- Control other cyclizations and promote only [3 + 3] cycloaddition is difficult.
- e.e. or d.r. is not discussed in this paper

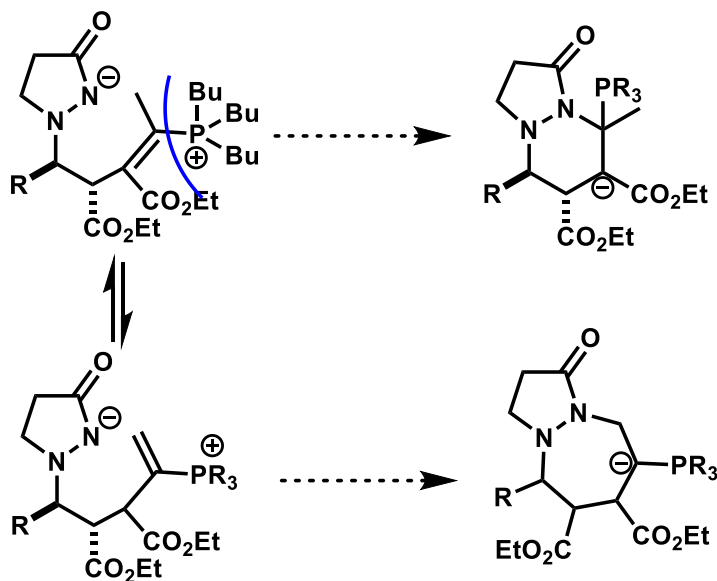
Phosphine catalyzed cyclization problems

□ 5 membered ring formation



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

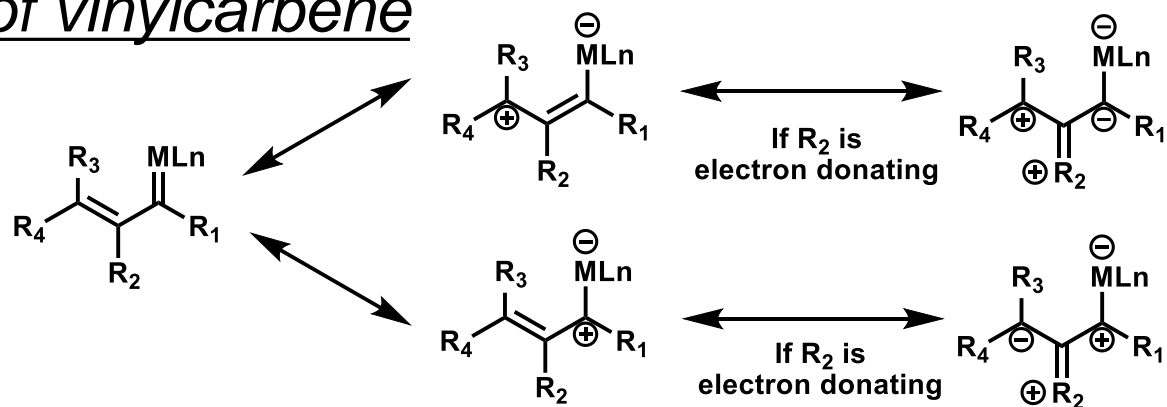
□ 7 membered ring formation



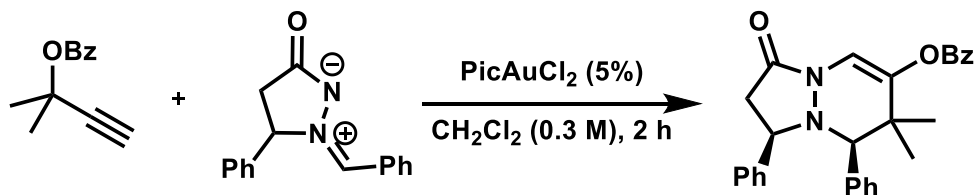
- Steric hindrance of Bu substituents prevents the 6 membered cyclization

It is difficult to prevent other cyclizations.

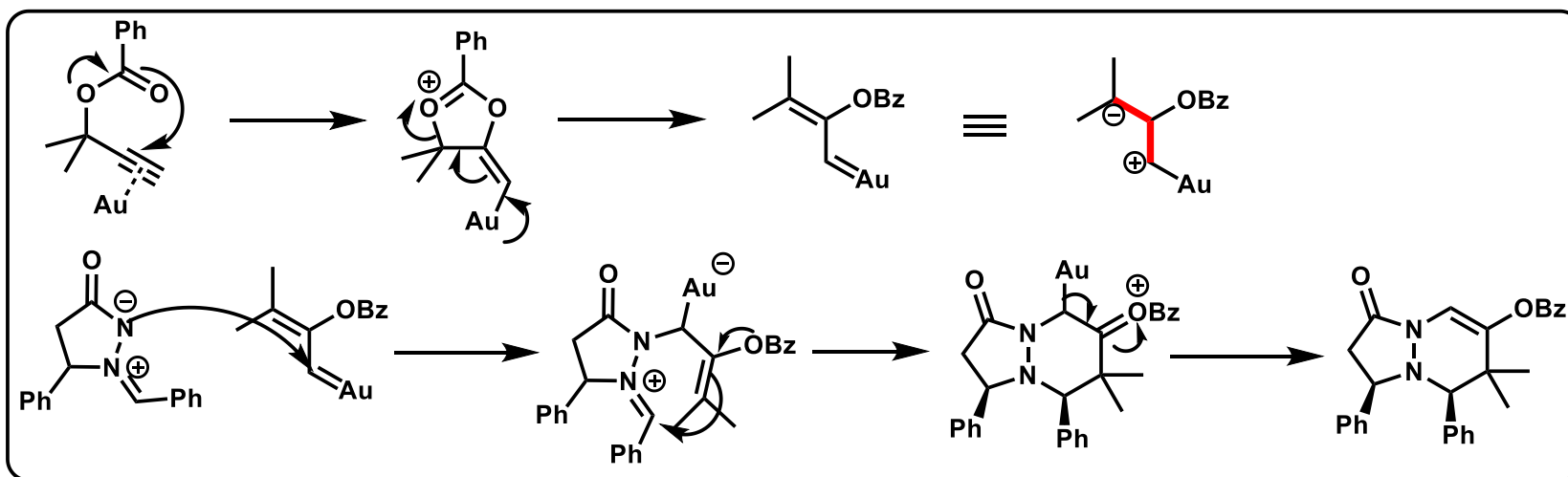
Nature of vinylcarbene



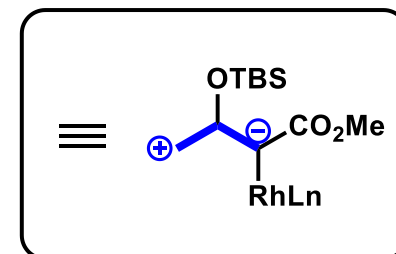
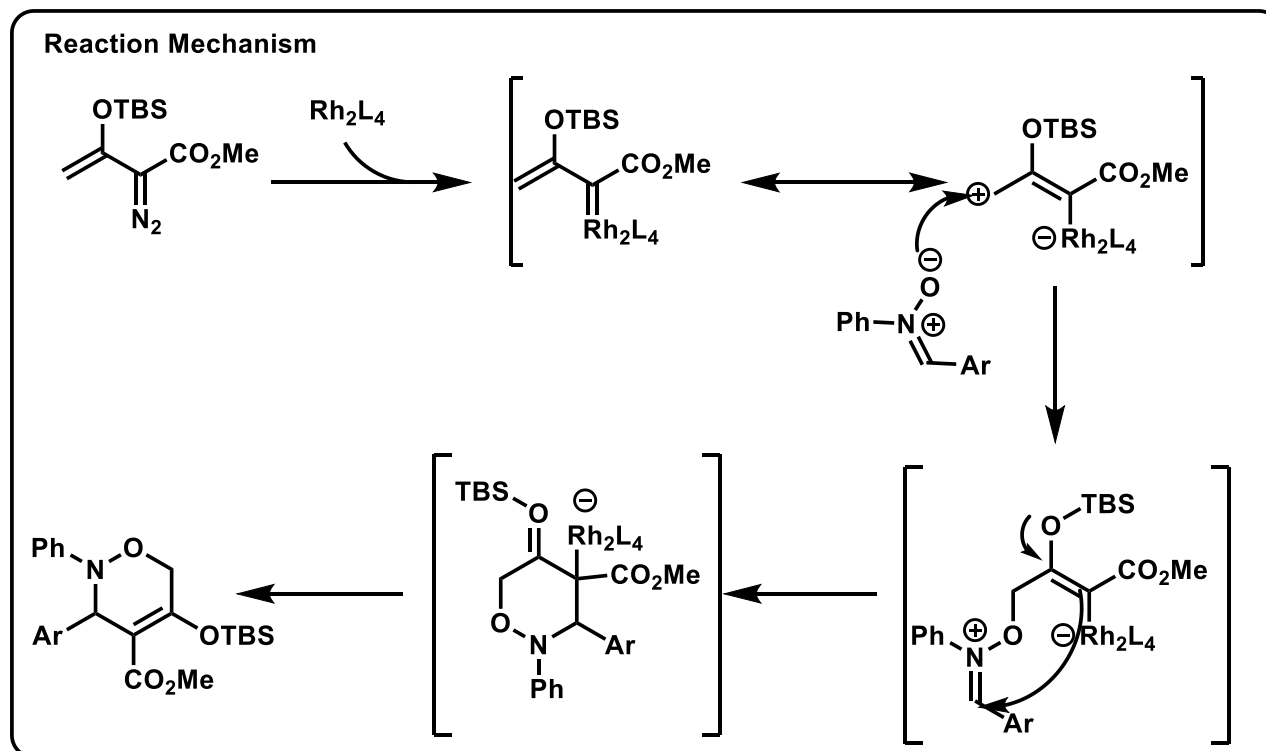
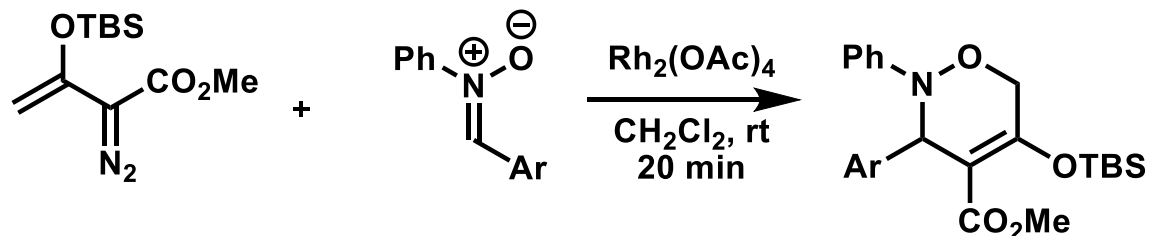
□ Vinyl-gold-carbene



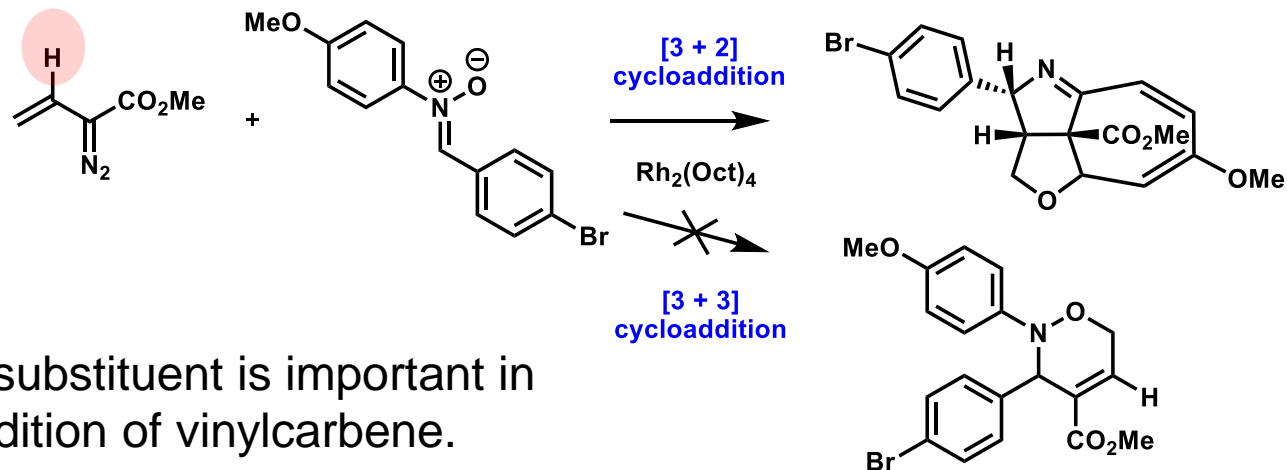
F. D. Toste *et al.* *JACS*, 131, 11654.



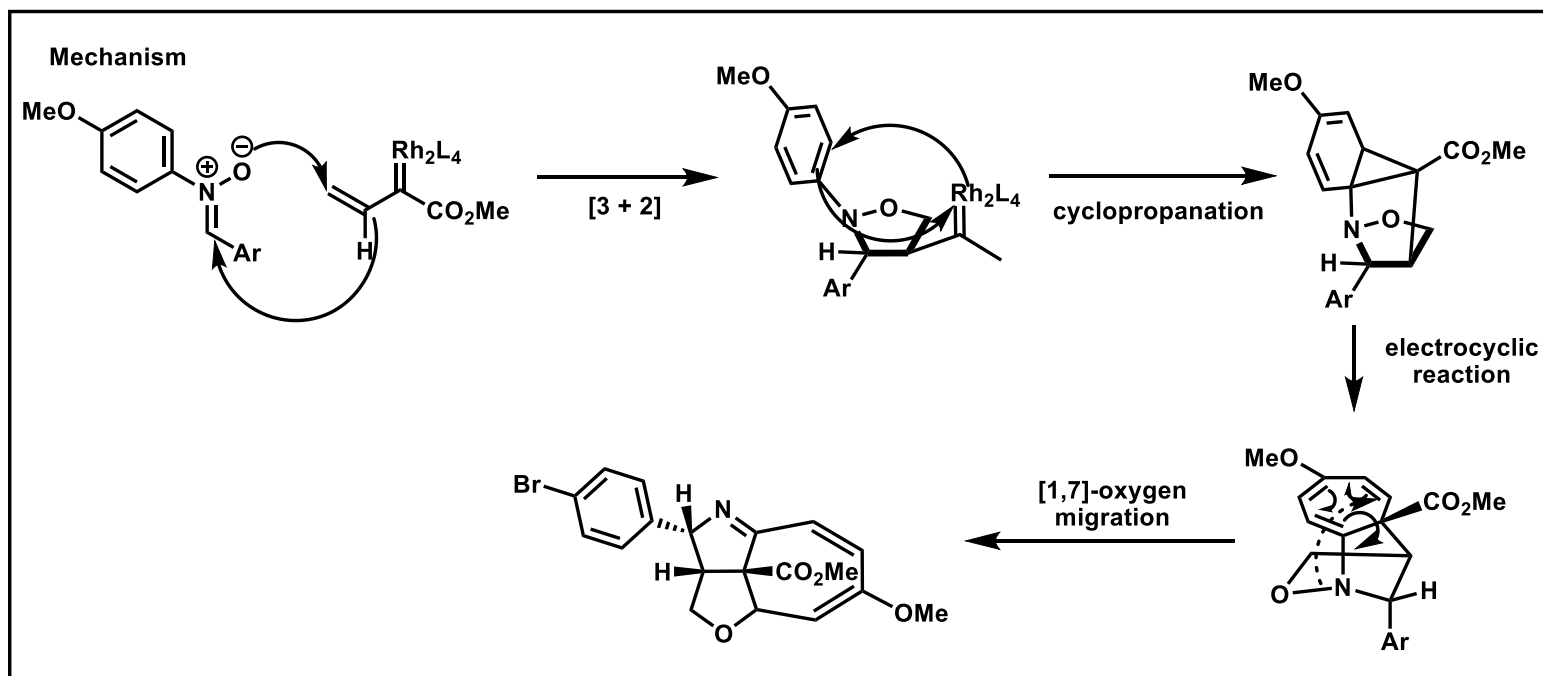
Vinylrhodiumcarbene



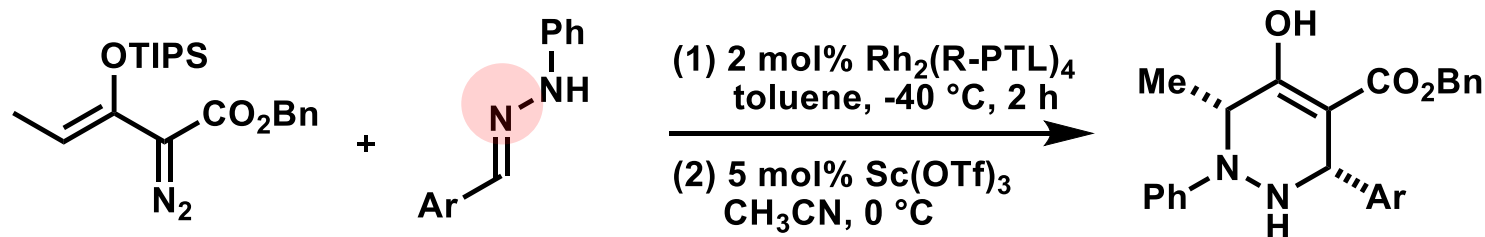
2. Three carbon unit 1,3-dipole

Effect of Substituents

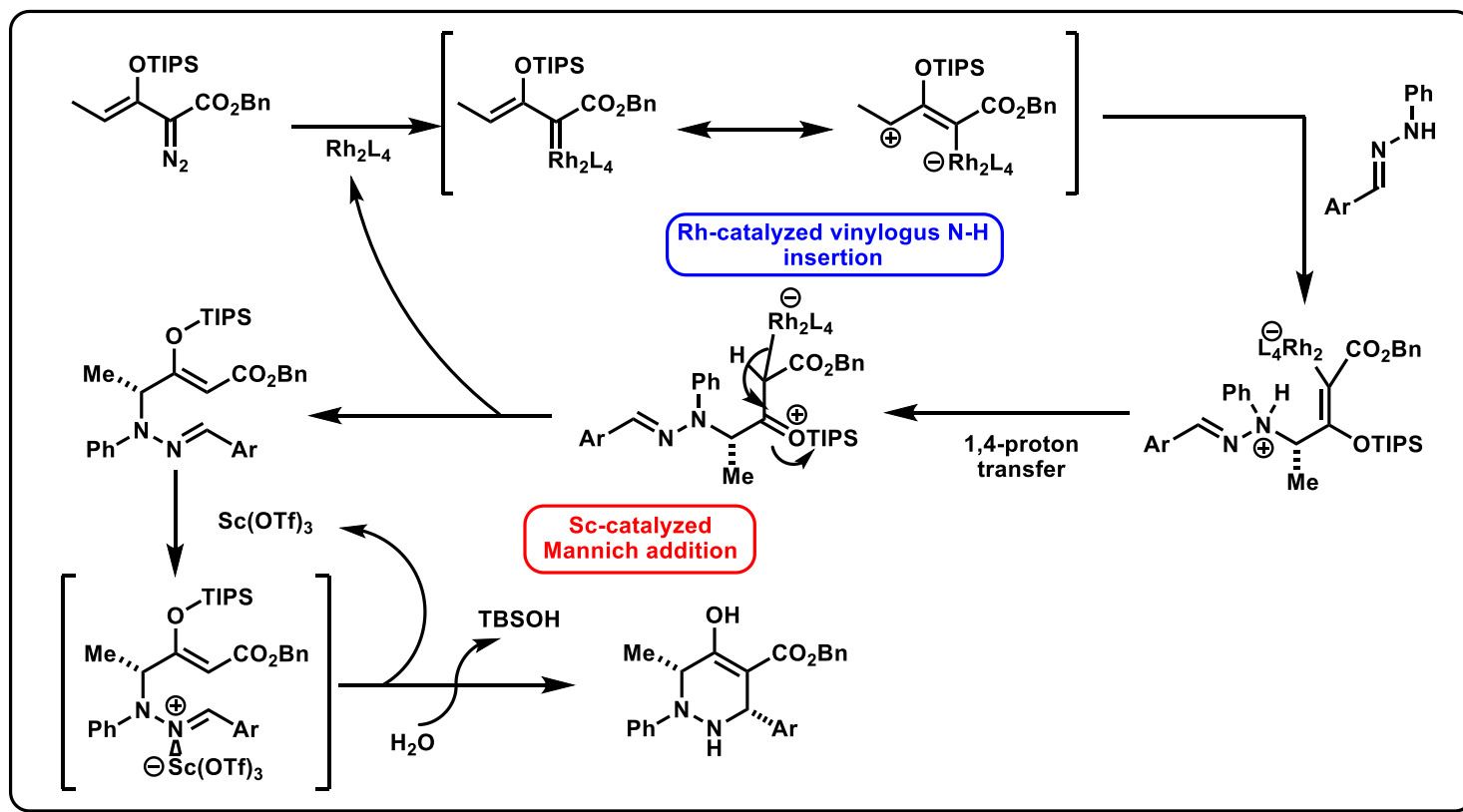
- TBSO- substituent is important in cycloaddition of vinylcarbene.



2. Three carbon unit 1,3-dipole

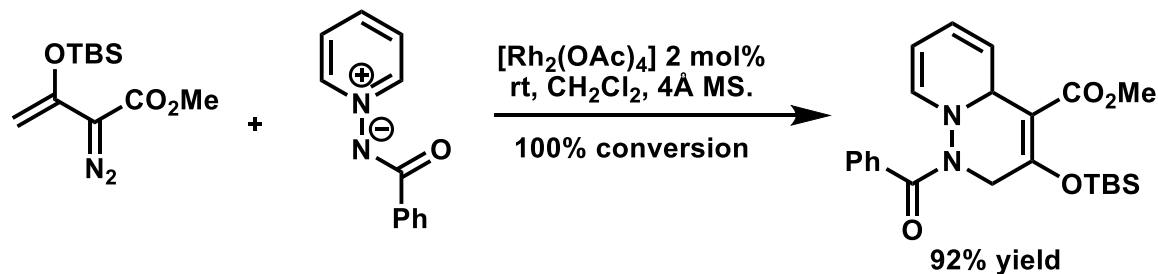
Combination with Lewis acid

M. P. Doyle et. al. *Angew. Chem. Int. Ed.* **2012**, 51, 9829

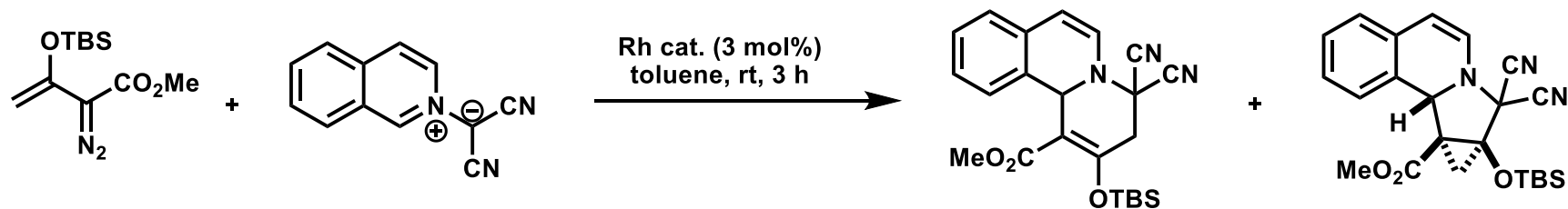


- Reaction does not proceed without activation of hydrazone.

Dearomatization [3 + 3] cycloaddition by vinylcarbene



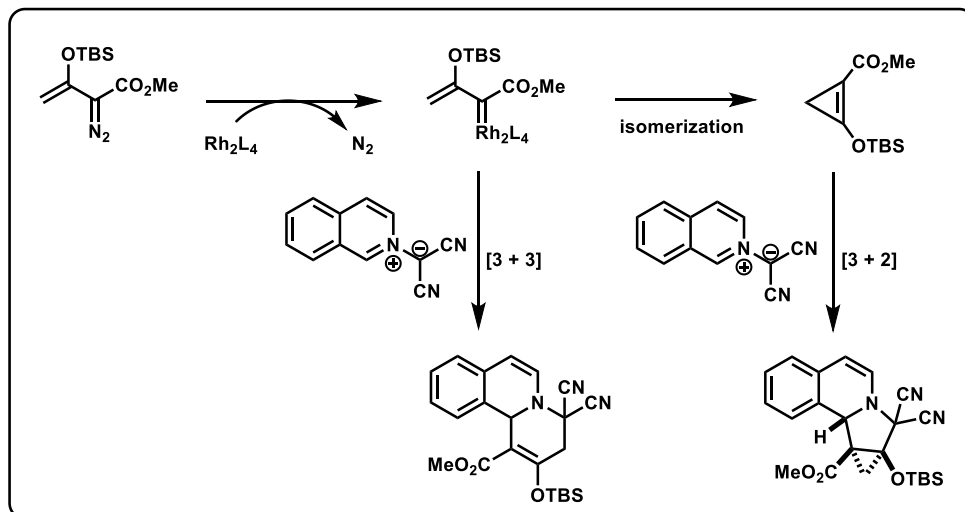
M. P. Doyle *et. al.* *ACIE*, **2013**, *52*, 12664



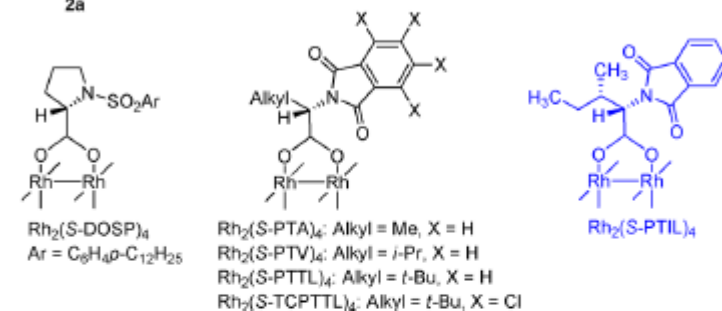
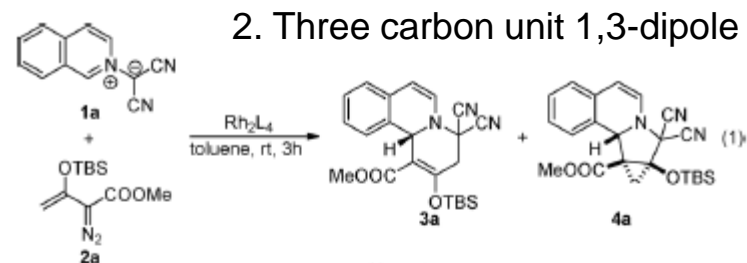
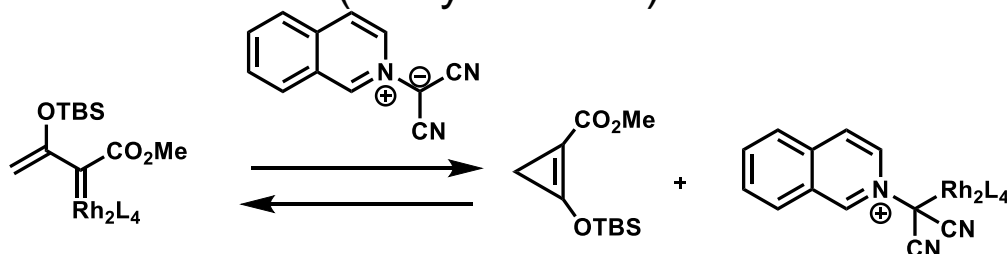
M. P. Doyle *et. al.* *JACS*, **2013**, *135*, 12439

What promotes side reaction?

Reaction mechanism (1)

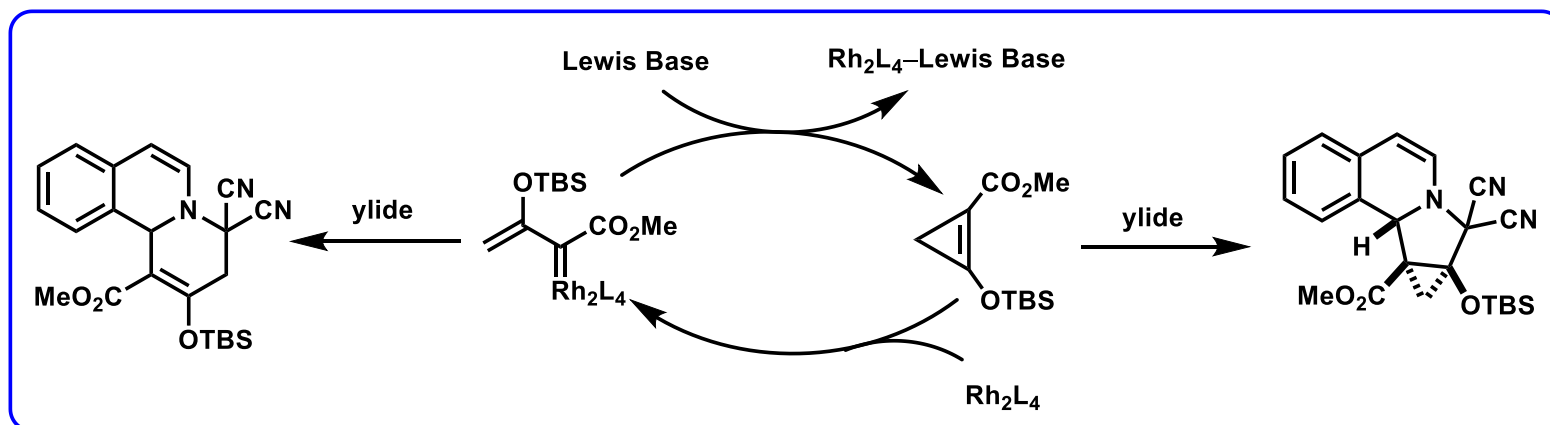
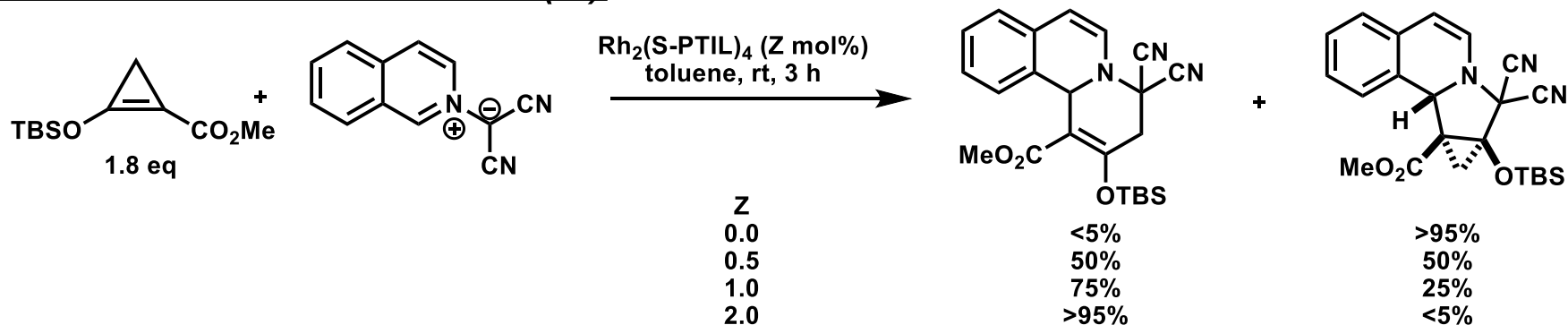


1. Lewis acidic dirhodium compound promotes [3 + 2] cycloaddition (Entry 2, 4, 10)
2. Lewis base additives promotes [3 + 2]
3. Cyclopropene was also demonstrated to be a precursor of the same metal carbene intermediate (Entry 11 to 15)



entry ^a	catalyst (y mol %)	3a:4a ^{b,c}	yield (%) ^d	ee (%) of 3a ^e
1	$Rh_2(Oct)_4$ (1.0 mol %)	2.0:1	85	
2	$Rh_2(S-DOSP)_4$ (1.0 mol %)	1:4.2	83	-20
3	$Rh_2(S-PTA)_4$ (1.0 mol %)	3.7:1	81	49
4	$Rh_2(S-PTV)_4$ (1.0 mol %)	1:1.7	79	90
5	$Rh_2(S-PTTL)_4$ (1.0 mol %)	10:1	69	89
6	$Rh_2(S-PTIL)_4$ (1.0 mol %)	1.6:1	83	93
7 ^f	$Rh_2(S-PTIL)_4$ (1.0 mol %)	1.9:1	49	94
8 ^g	$Rh_2(S-PTIL)_4$ (1.0 mol %)	1:2.1	70	90
9 ^h	$Rh_2(S-TCPTTL)_4$ (1.0 mol %)	1:>20	49	nd
10 ^h	$Rh_2(tfa)_4$ (1.0 mol %)	1:>20	71	
11	$Rh_2(S-PTIL)_4$ (0.5 mol %)	1:1.5	69	93
12	$Rh_2(S-PTIL)_4$ (1.5 mol %)	4.3:1	82	93
13	$Rh_2(S-PTIL)_4$ (2.0 mol %)	15:1	85	93
14	$Rh_2(S-PTIL)_4$ (2.5 mol %)	>20:1	89	93
15	$Rh_2(S-PTIL)_4$ (3.0 mol %)	>20:1	90	93
16	$Rh_2(S-PTV)_4$ (3.0 mol %)	>20:1	88	90

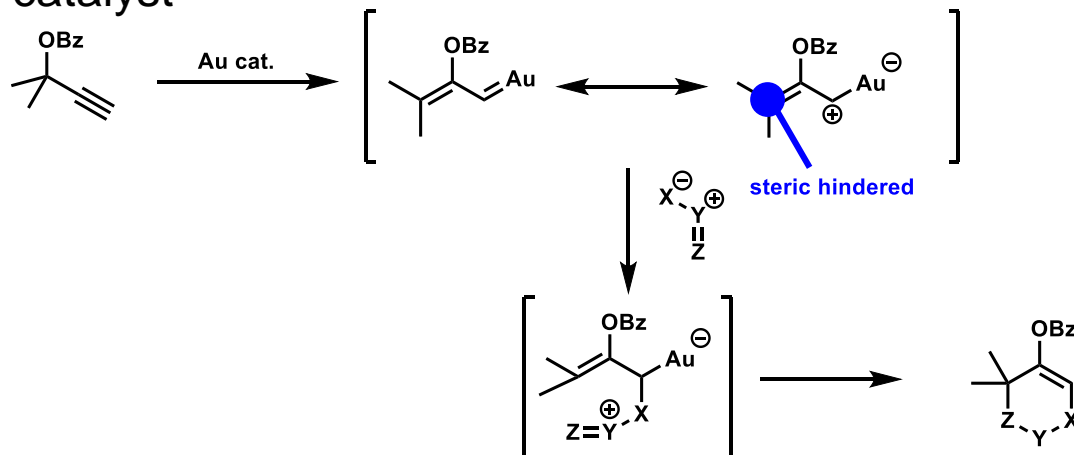
2. Three carbon unit 1,3-dipole

Reaction mechanism (2)

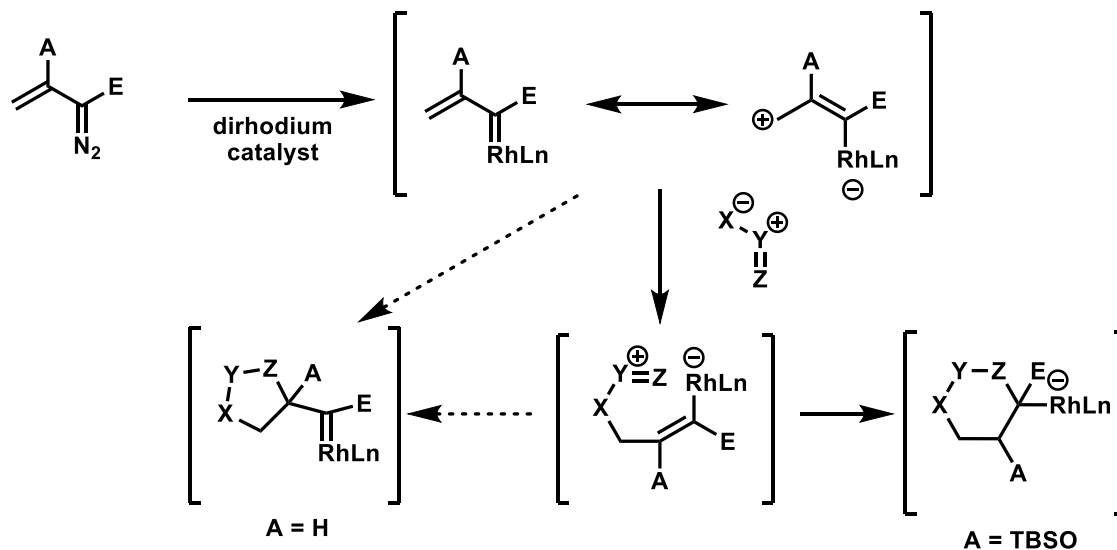
- Stable dipoles which were not sufficiently basic don't cause inhibition of dirhodium catalysts toward metal carbene formation.
- Dirhodium compounds are mild Lewis acids that coordinate with Lewis bases (Isoquinolinium/ pyridinium methylylides are readily accessible nucleophiles) .

Vinylcarbene reactivity

□ Gold catalyst



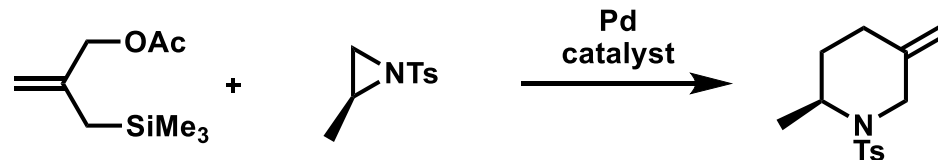
□ Rhodium catalyst



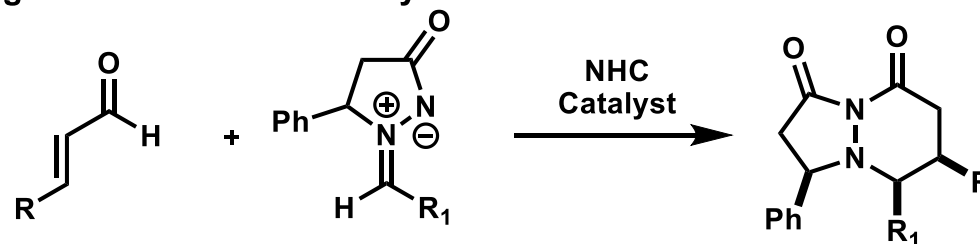
3. Summary

1,3-dipole cycloaddition methods

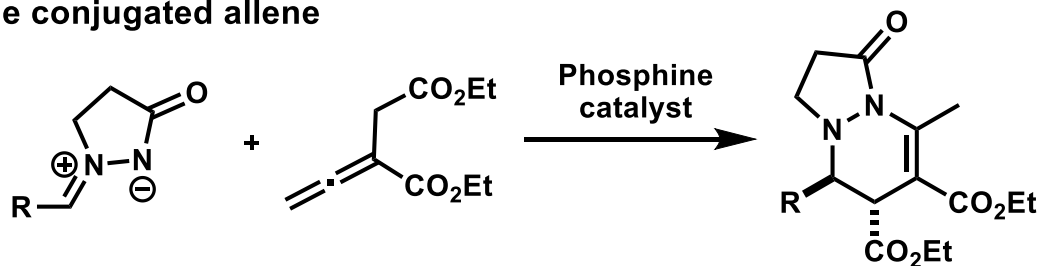
Pd-TMM complex



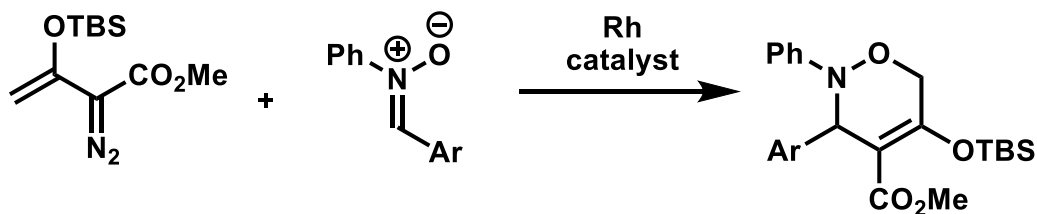
NHC conjugated unsaturated aldehyde



Phosphine conjugated allene



Vinylcarbene



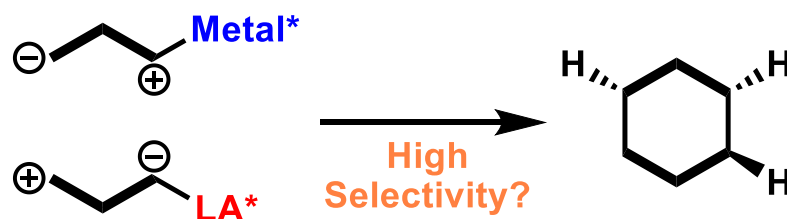
Comparison of 1,3-dipole cycloaddition methods

	Feature	Disadvantage
TMM	<ul style="list-style-type: none"> · Synthesized easily · Used as both reactive dipole and stable dipole 	<ul style="list-style-type: none"> · AcO group also acts as nucleophile. · Difficult to control enantioselectivity. (From less hindered side)
NHC	<ul style="list-style-type: none"> · Umpolung · Stereoselectivity is determined by ligand of NHC 	<ul style="list-style-type: none"> · Possibility of dimerization. · Partner is limited to azomethine imine. (Other partners are less reactive than aldehyde?)
Phosphine	<ul style="list-style-type: none"> · Umpolung · Allene can be applied for this method. 	<ul style="list-style-type: none"> · Other cyclizations ([3 + 2] or [3 + 4]) also proceed. · Low yields · Stereoselectivity is difficult to be controlled?
Vinylcarbene	<ul style="list-style-type: none"> · Many examples are reported. · Can be used with Lewis acid (but 2 steps) 	<ul style="list-style-type: none"> · Reaction is supported by Ester or ether substituents.

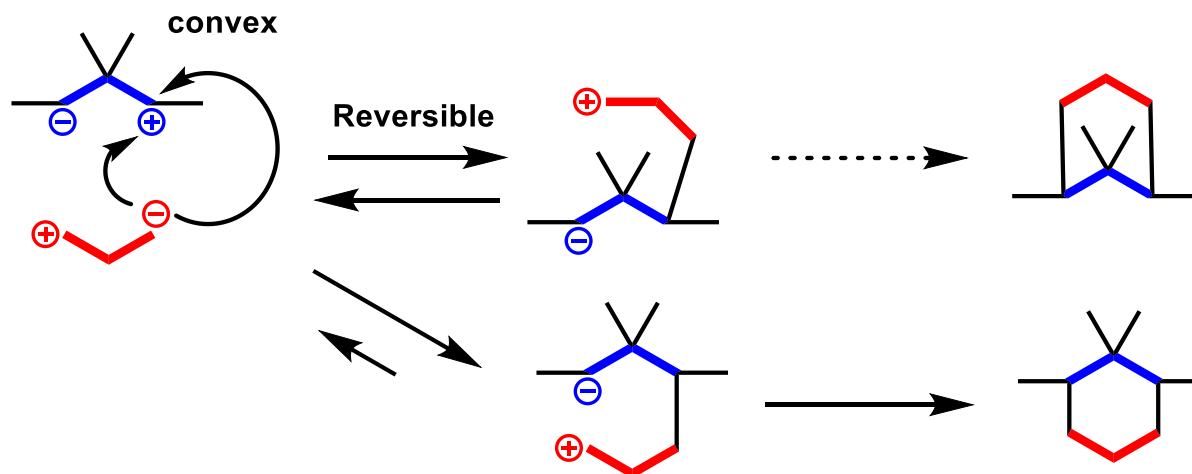
Future of [3 + 3] cycloaddition

□ 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?