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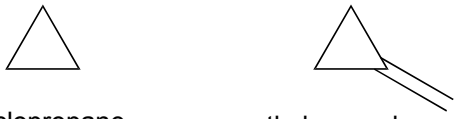
Lit. Seminar 080618

Strained Molecules in Organic Synthesis

~ featuring on three-membered rings ~

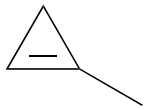
for cyclobutadienes : see Mr. Yamatsugu's Lit. Sem. 061129

0. Introduction



cyclopropane
SE = 27.5 kcal/mol

methylenecyclopropane
SE = 40.9 kcal/mol



1-methylcyclopropene
SE = 51.1 kcal/mol

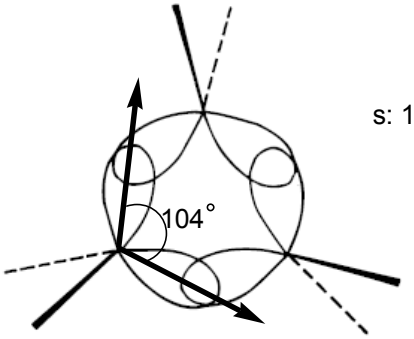
← stable up to 200℃

Heat of Formation

$3C + 3H_2(gas) \rightarrow$ cyclopropane + 12.7 kcal/mol
$6C + 6H_2(gas) \rightarrow$ cyclohexane - 29.6 kcal/mol

→ Strain Energy (SE) : 12.7 - (-29.6/2) = 27.5 kcal/mol
(cf. cyclobutane : 26.5 kcal/mol)

The introduction of each trigonal carbon center into a three-membered ring introduces an additional 12 - 14 kcal/mol of ring strain.



orbital of cycloproane

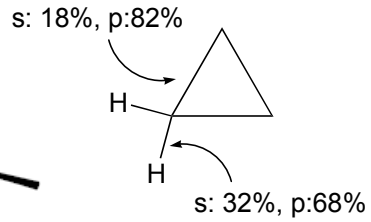
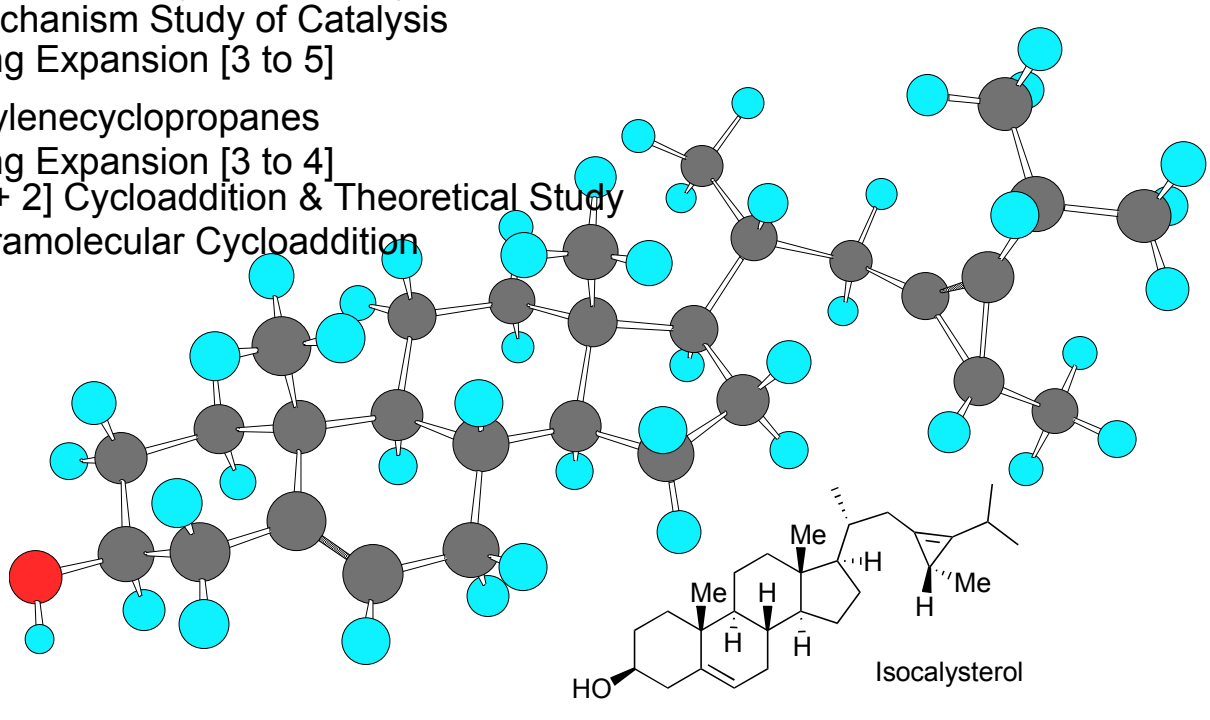


Table 1. Acidities, Bond Energies, and Hybridizations of Simple Hydrocarbons[a]

cmpd	hybridization	acidity		BDE
	(J, Hz)[b]	$\Delta H°_{acid}$ (gas)	pK_A (liq.)	$\Delta H°$ (gas)
CH_4	125	416.8 ± 0.7	48	104.99 ± 0.03
$CH_2{=}CH_2$	156	408.8 ± 0.3	44	110.7 ± 0.6
$HC{\equiv}CH$	249	376.86 ± 0.14	24	133.32 ± 0.07
c-C_3H_6	161	411.5 ± 2.0	46	106.3 ± 0.3
	202	398.0 ± 2.0	35 - 37	
	166[c]	409.7 ± 2.0		109.7 ± 3.3
1 	228	382.7 ± 1.3	30	106.7 ± 3.7

[a] All energies are in kcal mol^{-1}. See refs 1 and 6 for the cited quantities. [b] $^{13}C-H$ coupling constant. [c] This value is for the parent compound.

Contents

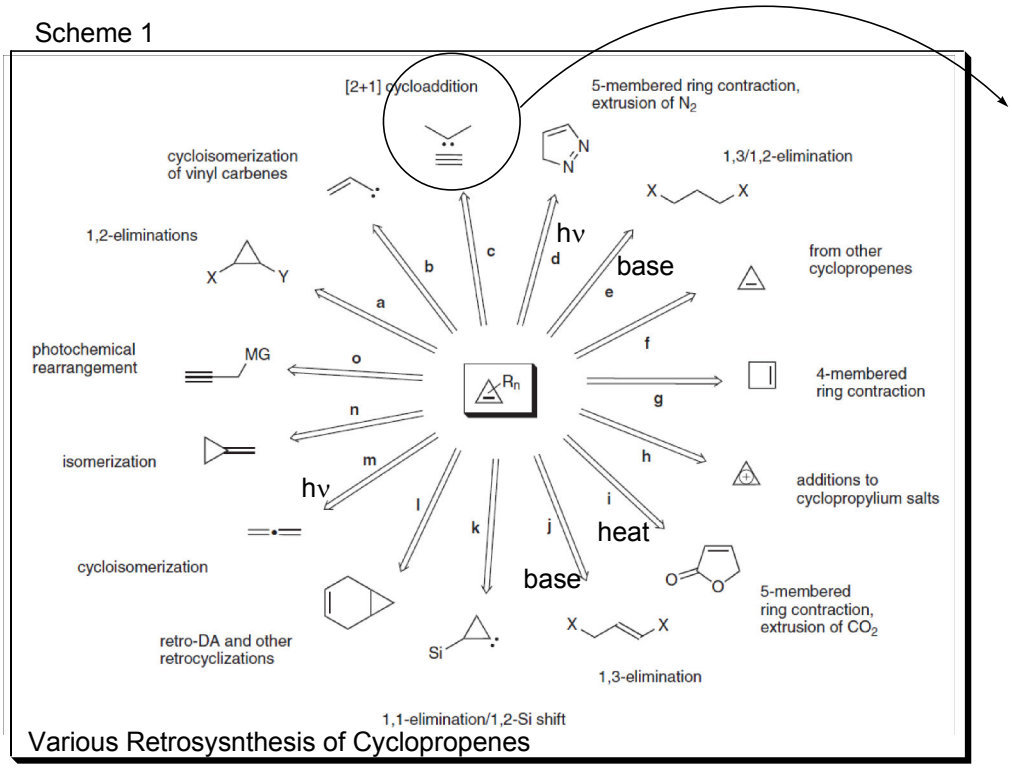


Isocalysterol

1. Cyclopropenes

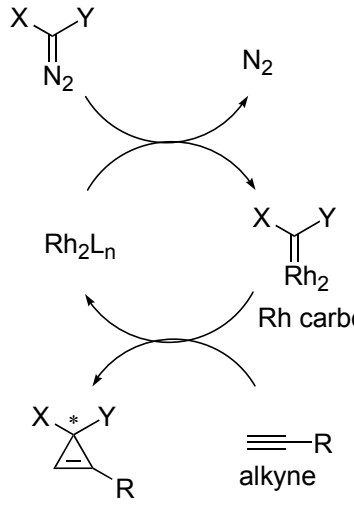
1-1. Asymmetric Synthesis of Cyclopropenes

Scheme 1



Various Retrosysnthesis of Cyclopropenes

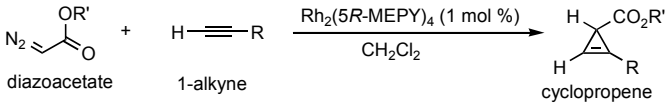
Rh catalyzed cyclopropenation



(about Rh catalyzed C-H activation; see Mr. Yamaguchi & Tanaka Lit. Sem. 060909 & 070207)

Figure 1

Doyle et al. *JACS*, **1992**, *114*, 2755

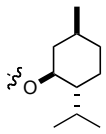


diazoacetate 1-alkyne cyclopropene

Table I. Enantioselective Cyclopropenation of Representative Alkynes Catalyzed by $Rh_2(5R\text{-MEPY})_4$[a]

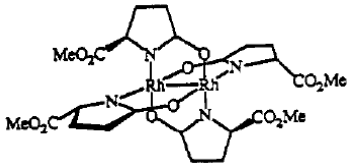
	diazoacetate, R′ =	1-alkyne, R =	cyclo-propene	yield, %[b]	ee, %[c]
1	Et	CH_3OCH_2	**1a**	73 (65)	69
2	*t*-Bu	CH_3OCH_2	**1b**	56 (38)	78
3	*d*-menthyl	CH_3OCH_2	**1c**	43 (28)	98
4	*l*-menthyl	CH_3OCH_2	**1d**	45	43
5	Et	*n*-Bu	**2a**	70 (58)	54
6	*t*-Bu	*n*-Bu	**2b**	69 (60)	53
7	*d*-menthyl	*n*-Bu	**2c**	46 (32)	86
8	*l*-menthyl	*n*-Bu	**2d**	46	20
9	Et	*t*-Bu	**3a**	85 (69)	57
10	*t*-Bu	*t*-Bu	**3b**	57 (37)	70
11	*d*-menthyl	*t*-Bu	**3c**	51 (30)	77
12	*l*-menthyl	*t*-Bu	**3d**	50 (29)	56

[a] Reactions were performed by the addition of the diazo compound (1.0 mmol) in 5 mL of CH_2Cl_2 over a 5-h period to a solution of the alkyne (10.0 mmol) and catalyst (0.01 mmol) in 10 mL of CH_2Cl_2. Average values from 2–4 separate experiments are reported. [b] Yield of product following chromatographic separation of catalyst and, in parentheses, product yield of the homogeneous sample after distillation (**2a**) or column chromatography (silica gel: hexane/ethyl acetate). [c] Determined from integration of the olefinic proton with use of chiral NMR shift reagent $Eu(tfc)_3$[10a] and for **2a** and **1b–3b** also by chromatographic separation on a Chiraldex γ-cyclodextrin trifluoroacetate column (±2% from separate experiments). Diastereomeric excesses for **1c–3c** and **1d–3d** were obtained by direct NMR analysis (±3%).

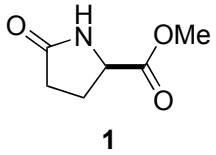


d-menthyl

$Rh_2(5R\text{-MEPY})_4$

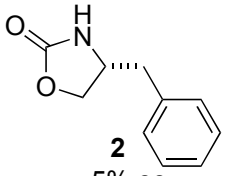


4(*R*)-bezyloxazolidinone



1

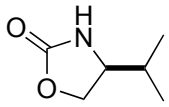
4(*S*)-isopropyloxazolidinone



2

5% ee

same condition



3

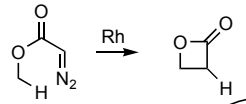
6% ee

It seems that dipolar influences from $Rh_2(5R\text{-MEPY})_4$ ligand's carboxylate substituents are primary determinants of enatiocontrol in these reacton.

Carbene dimer is major byproduct.

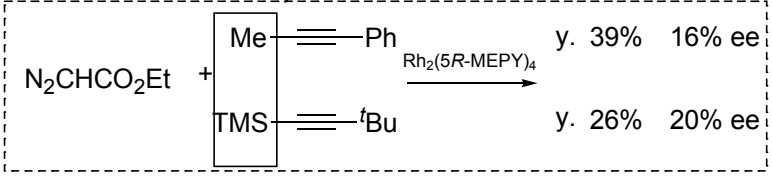
⟹ Slow addition & higher aklyne ratio suppress it.

In reactions with methyldiazoacetate, intramolecular C-H insertion compete with cyclopropanation.



disubstituted alkynes

Scheme 2



Doyle, Muller and Shapiro, *JACS*, **1994**, *116*, 8492

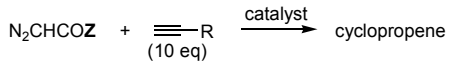


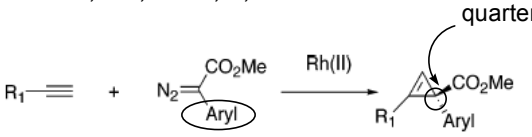
Table 2. Enantioselective Cyclopropenation of Representative 1-Alkynes by Diazoacetate Esters and *N,N*-Dimethyldiazoacetamide Catalyzed by $Rh_2(5S\text{-MEPY})_4$ and $Rh_2(5R\text{-MEPY})_4$

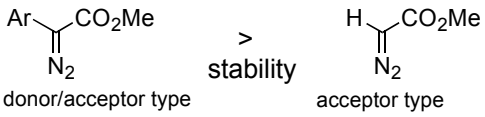
	catalyst	N_2CHCOZ, Z =	R	cyclopropene[a]	yield, %[b]	ee, %[c]	absolute config[d]
1	$Rh_2(5S\text{-MEPY})_4$	OMe	$CH(OEt)_2$	**8a*S***	42	≥98	*S*
2	$Rh_2(5S\text{-MEPY})_4$	O-*t*-Bu	CH_2OMe	**9c*S***	52	78	*S*
3	$Rh_2(5R\text{-MEPY})_4$	OEt	CH_2OMe	**9b*R***	73	69	*R*
4	$Rh_2(5R\text{-MEPY})_4$	O-*t*-Bu	CH_2OMe	**9c*R***	56	78	*R*
5	$Rh_2(5R\text{-MEPY})_4$	NMe_2	CH_2OMe	**9d*R***	22	≥94	*R*
6	$Rh_2(5R\text{-MEPY})_4$	OEt	*n*-Bu	**10b*R***	70	54	*R*
7	$Rh_2(5R\text{-MEPY})_4$	O-*t*-Bu	*n*-Bu	**10c*R***	69	53	*R*
8	$Rh_2(5R\text{-MEPY})_4$	NMe_2	*n*-Bu	**10d*R***	49	78	*R*
9	$Rh_2(5S\text{-MEPY})_4$	OEt	*n*-Bu	**10b*S***	60	51	*S*
10	$Rh_2(5R\text{-MEPY})_4$	OEt	*t*-Bu	**11b*R***	85	57	*R*
11	$Rh_2(5R\text{-MEPY})_4$	O-*t*-Bu	*t*-Bu	**11c*R***	57	70	*R*
12	$Rh_2(5R\text{-MEPY})_4$	NMe_2	*t*-Bu	**11d*R***	47	89	*R*
13	$Rh_2(5S\text{-MEPY})_4$	OMe	*n*-pentyl	**12a*S***	83	48	*S*

[a] *R* or *S* is the catalyst configuration. [b] Yield of the chromatographically purified cyclopropene. [c] From GC or ^1H NMR analyses. Results confirmed with duplicate runs. [d] For assignment see section on absolute configurations of cyclopropenes.

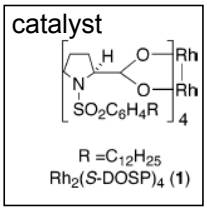
Davies, *OL*, **2004**, *6*, 1233

quarternally carbon center forming





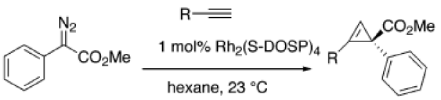
donor/acceptor type — acceptor type

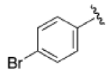
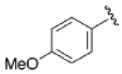
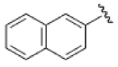
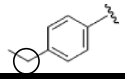


The donor/acceptor-type carbenoids are more stabilizedthan the conventional carbenoids derived from diazoacetate.

substituent on alkyne

Table 1. $Rh_2(S\text{-DOSP})_4$-Catalyzed Enantioselective Cyclopropenation with Methyl Phenyldiazoacetate[a]



entry	R	product	yield, %	ee, %
1		**2**	62	90
2		**3**	63	92
3		**4**	67	86
4		**5**	60	96
5		**6**	48	87
6		**7**	74	92
7	$(CH_2)_3CH_3$	**8**	51	84

[a] Reactions were performed by the addition of the diazo compound (1.0 mmol) in 5 mL of hexanes over a 5-h period to a solution of the alkyne (10.0 mmol) and catalyst (0.01 mmol) in 10 mL of hexanes. See the Supporting Information for details.

The reactions proceed without regard to EWG or EDG .

Too stable to react ...?

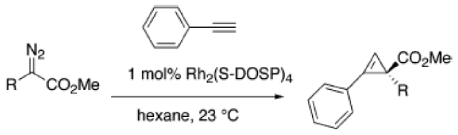
Cyclopropenation is favored over benzylic C-H insertion.

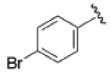
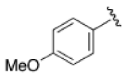
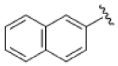
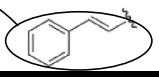
Cyclopropenation precede cyclopropanation.

This substrate reacts with styrene and gives 90% ee. Then the failure may be due to the instability of the product.

substituent on diazoacetate

Table 2. $Rh_2(S\text{-DOSP})_4$-Catalyzed Enantioselective Cyclopropenation of Phenylacetylene with Various Aryl- and Vinyldiazoacetates[12]



entry	R[a]	product	yield (%)	ee (%)
1		**2**	62	90
2		**10**	62	86
3		**11**	24[b]	66[b]
4		**12**	55	86
5		**13**	57	88
6		**14**	0	-

[a] 2.5−10 equiv of alkyne was used. See the Supporting Information for details. [b] 2 mol % catalyst was used.

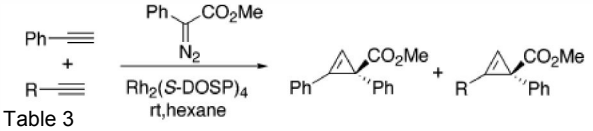


Table 3

R	relative rate vs phenylacetylene
p-$MeOC_6H_4$	5.9
p-EtC_6H_4	1.9
p-ClC_6H4	1.1
n-Bu	0.06

Electron rich alkynes react faster than normal alkyne.

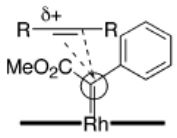
Does the reaction mechanism have a close relation to electron density of alkynes ?

1-2. Mechanism Study of Catalysis

Electron rich alkynes react faster. ⟹ Stabilized cationic species at transition state concern ...?
The author proposed that the alkynes and olefins react by side-on mannar.
For olefins, the reaction proceeds with retention of stereochemistry.

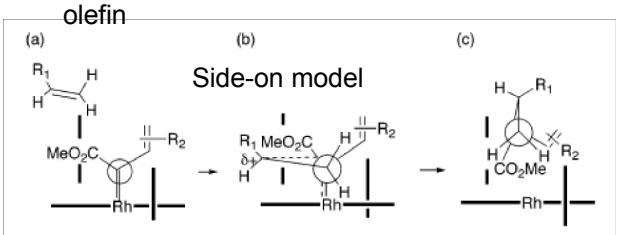
Davies, *JACS*, **1996**, *118*, 6897

alkyne



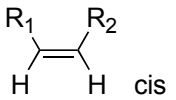
side-on

olefin

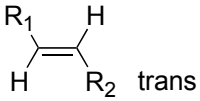


Side-on model

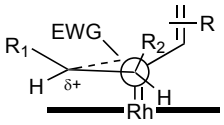
Figure 1. (a) Alkene approach at the top face of the carbenoid from a sideways trajectory (least encumbered approach). (b) "Side-on" transition state for cyclopropanation. (c) Cyclopropane formed with absolute stereochemistry set.

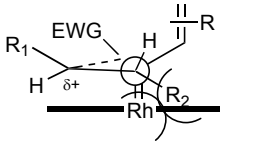


cis



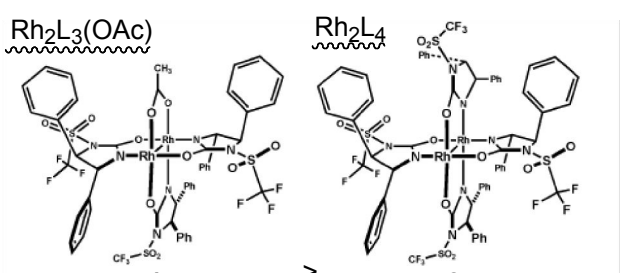
trans





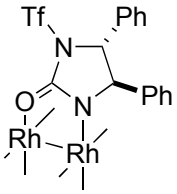
sterically hindered

Novel Catalyst Corey, *JACS*, **2004**, *126*, 8916

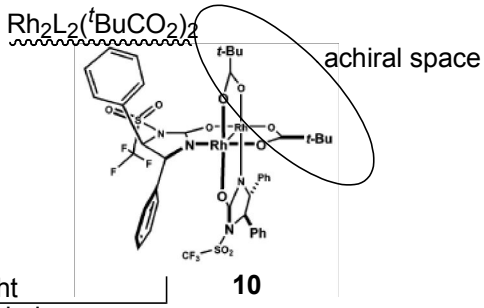


1 > activity **2**

Figure 2



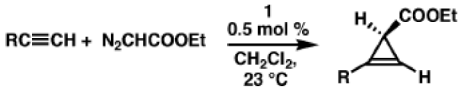
≡

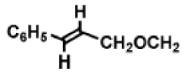


10

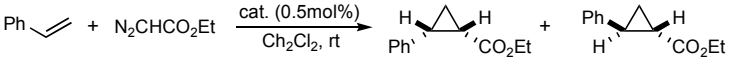
the upper right quadrant is achiral however...

Table 1. Catalyzed Enantioselective Addition of Ethyl Diazoacetate to Terminal Acetylenes



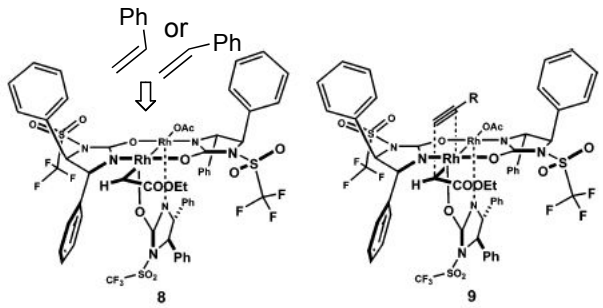
entry	R	yield, %	ee, %[a]	cat. 2	cat. 10
1	$CH_3(CH_2)_4$	90	95		
2	$CH_3(CH_2)_5$	90	93	⇨ 86% ee	91% ee
3	*t*-Bu	81	92		
4	$(CH_3CH_2O)_2CH$	64	92		80% ee
5	$BnOCH_2$	86	92		88% ee
6	$MeOCH_2$	78	92		
7	$BrCH_2$	62	95		
8[b]		76	95		

[a] Enantiomeric purity for entries 1−7 was determined by GC analysis using either a Cyclosil B or γ-TA column; for entry 8, ee was determined by HPLC analysis using a Chiracel OJ column. Absolute configurations were assigned from comparison of rotation with literature values except for entries 2, 5, 7, and 8 for which the assignment followed from the observed dextrorotation. [b] Pentane was used as a solvent.

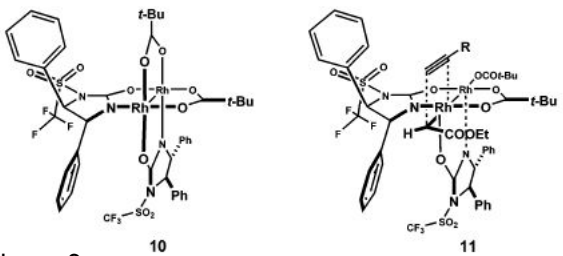


cat. **1**	y. 84%	99%ee	(~2:1)	94%ee
cat. **10**		97%ee		91%ee

The rate determing step is nucleophilic addition of diazoacetate to Rh_2L_4.
high face-selectivity for carbenoid
low(only 2:1) π-facial selectivity



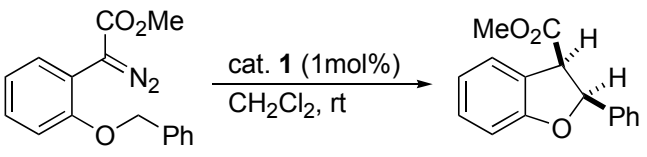
8 **9**



10 **11**

Figure 3

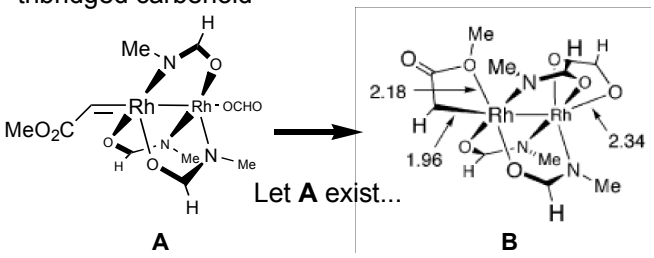
Scheme 3. available for C-H insertion



y. 51%, ee. 96%

Theoretical calculation

tribridged carbenoid



21.5 kcal/mol higher than tetrabridged one

Figure 1

Davies, *JACS*, **2003**, *125*, 15902
Singleton, *JACS*, **2005**, *127*, 6190

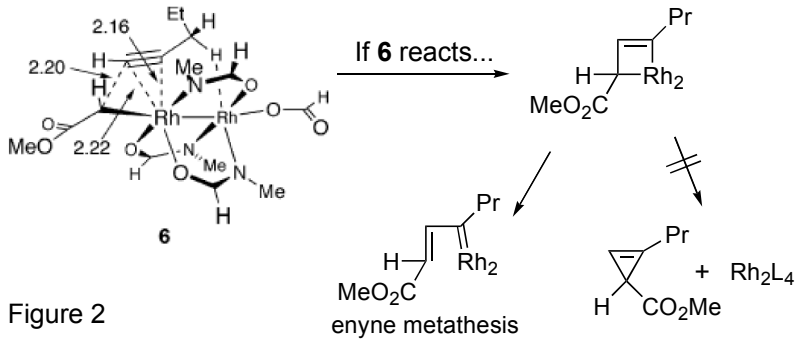


Figure 2

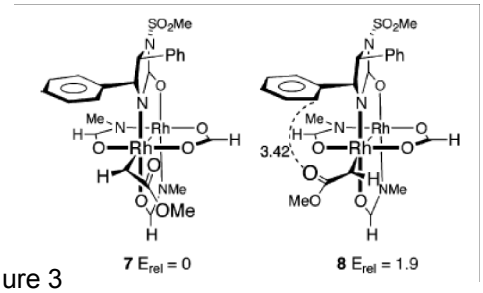


Figure 3

End-on model

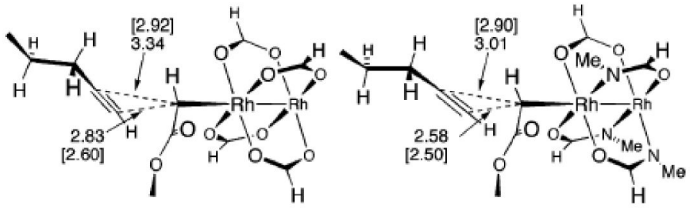
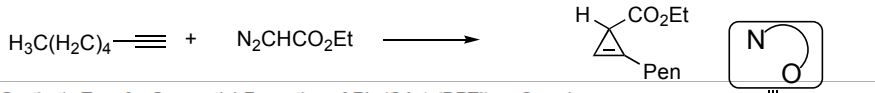
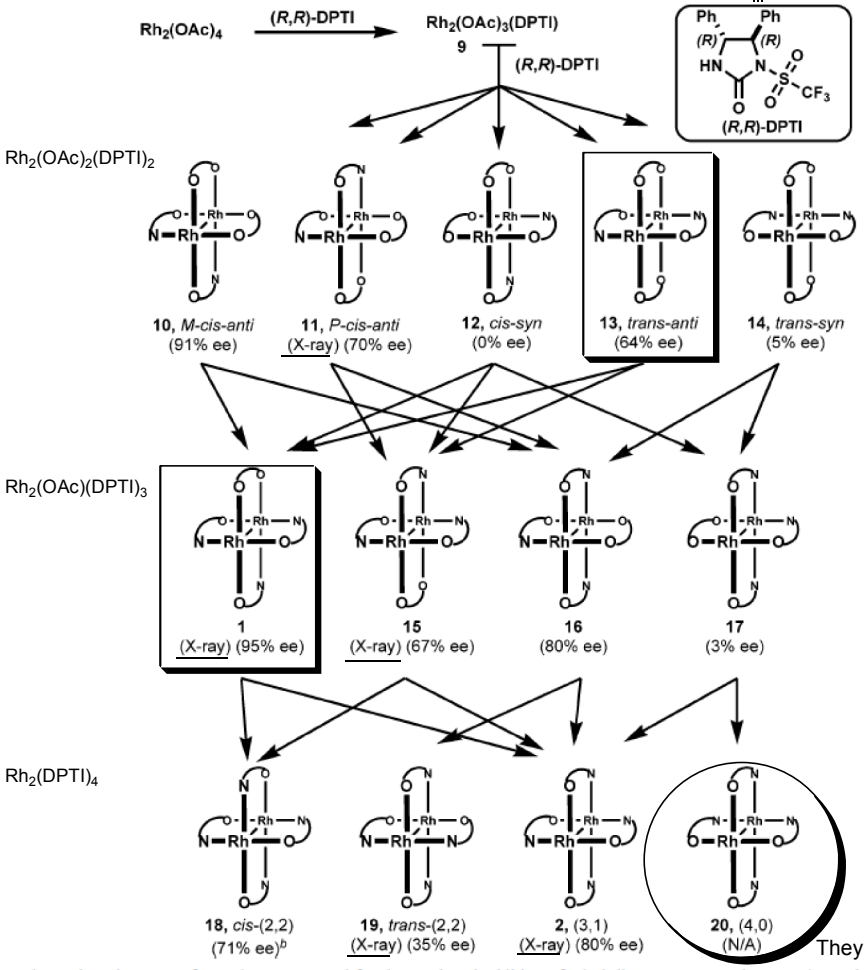


Figure 4. Calculated transition structures for reaction of 1-pentyne with rhodium carbenoids. Distances outside brackets are for the potential energy saddle points, while distances in brackets refer to the approximate canonical variational transition structures.

Corey et al. *JACS*, **2005**, *127*, 14223



Scheme 1. Synthetic Tree for Sequential Formation of $Rh_2(OAc)_n(DPTI)_{4-n}$ Complexes[a]



[a] The ee values shown in Scheme 1 refer to those measured for the catalyzed addition of ethyl diazoacetate to 1-heptyne (CH_2Cl_2 at 23 °C). [b] At 40 °C in CH_2Cl_2.

Table 1. Anionic Ligand Displacement of Acetate by DPTI Anion in THF: Observed Ratio of Product to Remaining Starting Material (**9**) as a Function of Time

t, min	9	10	11	12	13	14
10	1	0	0	0	0	0
30	1	0.02	0.03	0.02	0	0
60	1	0.04	0.05	0.03	0	0
120	1	0.09	0.12	0.05	0	0
180[a]	1	0.13	0.19	0.06	0.03	0.15
600[b]	1	0.31	0.53	0.10	0.20	0.49

[a] **1** (0.36) and **16** (0.03) also formed. [b] **1** (0.61) and **16** (0.16) also formed.

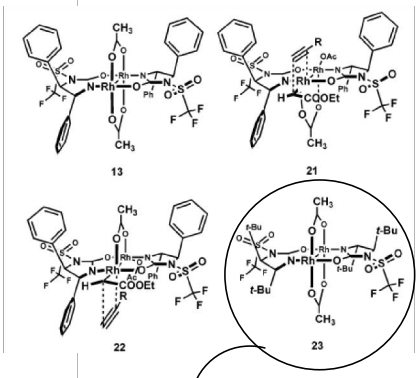
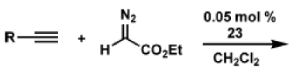


Table 3. Cyclopropenation of Ethyl Diazoacetate and Terminal Alkynes Catalyzed by **23**



entry	R	*T*, °C	yield, %	ee, %[a]
1	$CH_3(CH_2)_4$	23	87	89
2	$CH_3(CH_2)_4$	0	84	91
3	*t*-Bu	0	81	90
4	$MeOCH_2$	0	78	93

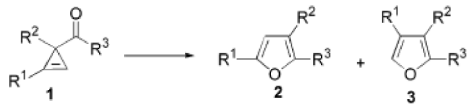
[a] Enantiomeric excess was determined by GC using a γ-TA column.[10]

They can't synthesize.

1-3. Ring Expansion [3 to 5]

Ma , *JACS*, **2003**, *125*, 12386
Battiste , *TL*, **1975**, *1*, 45

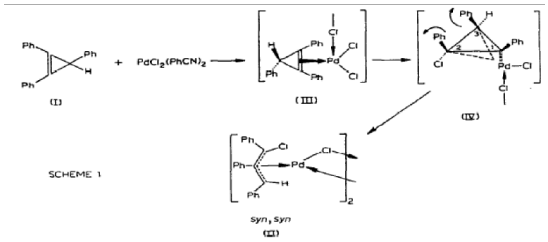
Table 2. Regioselective Cycloisomerization of Cyclopropene Ketones **1** under Conditions A and B

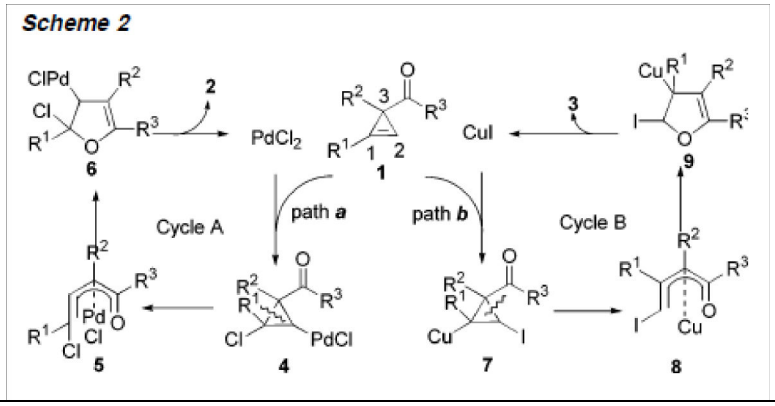


Conditions A: $[PdCl_2(CH_3CN)_2]$ (5 mol%), $CHCl_3$, reflux;
Conditions B: [CuI] (5 mol%), CH_3CN, reflux.

entry	cyclopropenyl ketones **1** $R^1/R^2/R^3$	cond./*t*(h)	yield[a] (**2**:**3**)[b]
1	$TBSO(CH_2)_2/CO_2Et/CH_3$ (**1b**)	A[c]/3	(**2b**) 65 (95:5)
2	**1b**	B/10	(**3b**) 85 (<1:99)
3	$TBSOCH_2/CO_2Et/CH_3$ (**1c**)	A/3	(**2c**) 60 (96:4)
4	**1c**	B/10	(**3c**) 83 (<1:99)
5	*t*-Bu/CO_2Et/CH_3 (**1d**)	A/13	(**2d**) 66 (98:2)
6	**1d**	B/4.5	(**3d**) 80 (<1:99)
7	$Ph/CO_2Et/CH_3$ (**1e**)	A/10	(**2e**) 73 (99:1)
8	**1e**	B/2.5	(**3e**) 89 (1:99)
9	$n\text{-}C_5H_{11}/CO_2Et/Ph$ (**1f**)	A[c]/24	(**2f**) 50 (98:2)[d]
10	**1f**	B/10	(**3f**) 80 (<1:99)
11	$n\text{-}C_4H_9/COMe/CH_3$ (**1g**)	A[c]/3	(**2g**) 78 (95:5)
12	**1g**	B/6	(**3g**) 80 (<1:99)
13	$n\text{-}C_4H_9/SO_2Ph/CH_3$ (**1h**)	A[c]/5	(**2h**) 88 (99:1)
14	**1h**	B/10	(**3h**) 96 (<1:99)

[a] Isolated yield of the major isomer. [b] The ratio was determined by ^1H NMR analysis of the crude reaction mixture. [c] CH_2Cl_2 was used as the solvent. [d] Unidentified product was also formed.





2. Methylenecyclopropanes (MCPs)

2-1. Ring Expansion [3 to 4]

Furstner et al, *JACS*, **2006**, *128*, 6306

Scheme 1. $PtCl_2$-Catalyzed Cyclobutene Formation

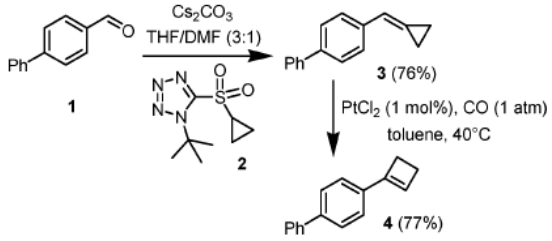
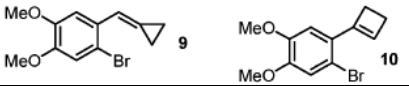
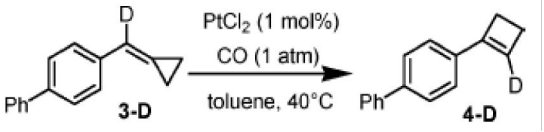


Table 1. Cyclobutenes by $PtCl_2$-Catalyzed Rearrangement of Alkylidenecyclopropanes[a]

Nr	Product	Yield
1		90%
2		80%
3		61%
4		50%[b]
5		93%
6		95%

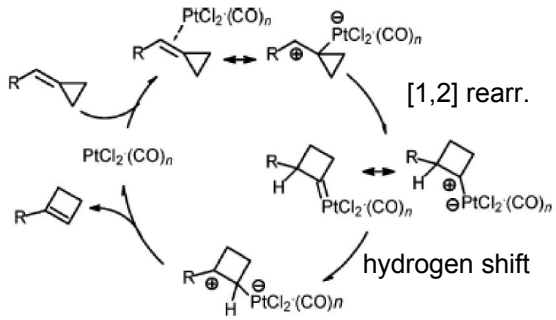
[a] All reactions were performed with $PtCl_2$ (5 mol %) in toluene (0.1 M) at 80 °C under CO (1 atm) unless stated otherwise. [b] $c = 0.02$ M.

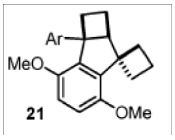
Scheme 3. Deuterium-Labeling Experiment



> 97% D-labeled

Scheme 2. Proposed Mechanism



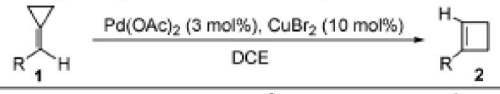


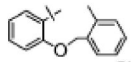
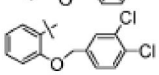
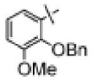
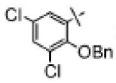
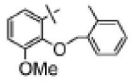
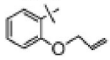
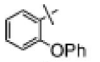
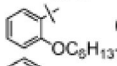
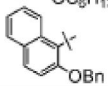
For entry3 and 4, high concentration causes dimerization.

Alkyl substituted MCPs also undergo ring expansion.

Shi, *JACS*, **2006**, *128*, 7430

Table 2. Ring Enlargement of MCPs 1 to Cyclobutenes[a]



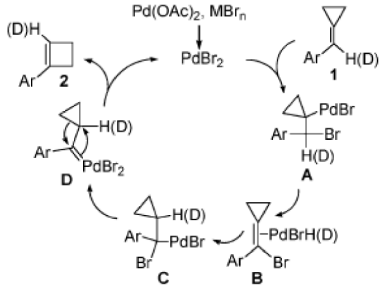
entry	R	temp./°C	time/h	yield/[%][b] (conv./[%])[c]
1	C_6H_5 (**1b**)	80	24	**2b**, 46 (68)
2	p-$CH_3C_6H_4$ (**1c**)	r.t.	3	**2c**, 52 (>99)
3	p-$CH_3OC_6H_4$ (**1d**)	r.t.	1	**2d**, 60 (>99)
4	o,p-$(CH_3O)_2C_6H_3$ (**1e**)	r.t.	3	**2e**, 74 (>99)
5	p-ClC_6H_4 (**1f**)	80	24	**2f**, 41 (60)
6	m-ClC_6H_4 (**1g**)	80	24	**2g**, 38 (62)
7	 (**1h**)	r.t.	3	**2h**, 89 (>99)
8	 (**1i**)	80	10	**2i**, 91 (>99)
9	 (**1j**)	r.t.	3	**2j**, 91 (>99)
10	 (**1k**)	80	24	**2k**, 64 (82)
11	 (**1l**)	r.t.	3	**2l**, 93 (>99)
12	 (**1m**)	r.t.	3	**2m**, 91 (>99)
13	 (**1n**)	r.t.	3	**2n**, 85 (>99)
14	 (**1o**)	r.t.	3	**2o**, 83 (>99)
15	 (**1p**)	r.t.	3	**2p**, 90 (>99)

[a] Reactions were carried out by use of MCP 1 (0.3 mmol) in 1,2-dichloroethane (DCE) (2.0 mL) with palladium acetate (2.0 mg, 3 mol %) and copper(II) bromide (7.0 mg, 10 mol %). [b] Isolated yields. [c] Starting material consumed after column chromatography.

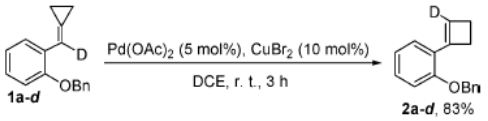
R are aromatic substituents. Substrates which have EDG at ortho-position give better yield.

When R are aklyl substituents, reaction doesn't proceed.

Scheme 1. Proposed Mechanism for the Pd-Catalyzed Ring Enlargement of MCPs to Cyclobutenes

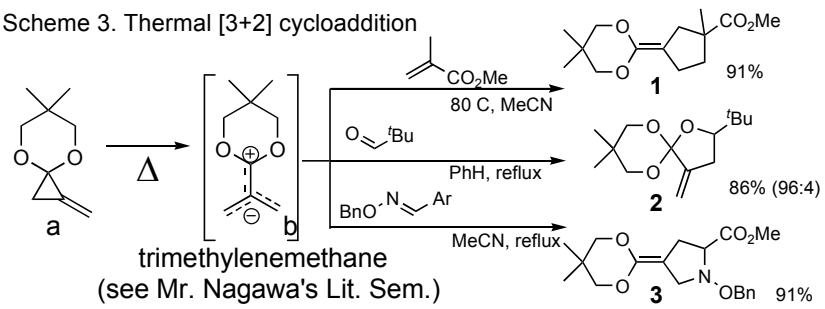


Scheme 2. Deuterium Labeling Experiment of the Ring Enlargement Reaction



2-2. [3 + 2] Cycloaddition & Theoretical Study

Scheme 3. Thermal [3+2] cycloaddition

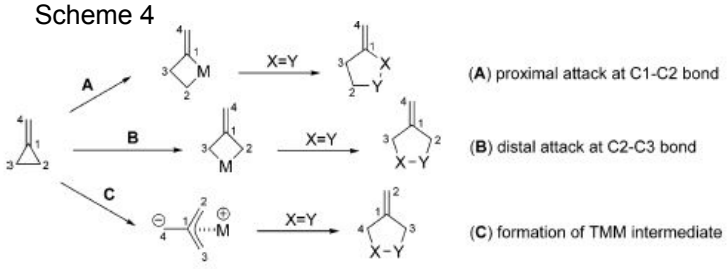


trimethylenemethane
(see Mr. Nagawa's Lit. Sem.)

E. Nakamura, *JACS*, **1989**, *111*, 7285
JOC, **1990**, *55*, 5553 *JOC,* **1998**, *63*, 1694

Metal catalyzed hetero [3+2] cycloaddition

Scheme 4



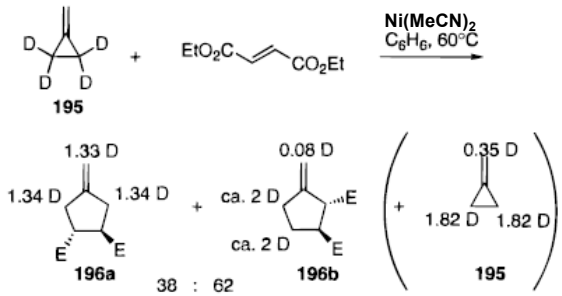
Lautens, *JACS*, **1996**, *118*, 9597
from previous studies...

Ni^0 : 1. parent MCP undergoes proximal ring opening
2. monosubstituted MCPs undergo proximal and distal ring opening
3. MCPs which bear dialkyl substituents at cyclopropyl or vinylic carbon undergo distal ring opening preferentially

Pd^0 : all types of MCPs undergo distall ring opening regardless of the substitution pattern

Noyori, *JACS*, **1970**, *92*, 5780 & *TL*, **1978**,*48*, 4823

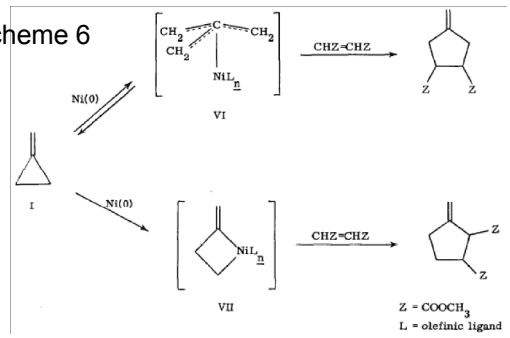
Scheme 5



$Ni(COD)_2$: proximal attack (**A**)
with phosphine or phosphite : distal attack (**B**)

$Ni(MeCN)_2$: distal attack (**B**)

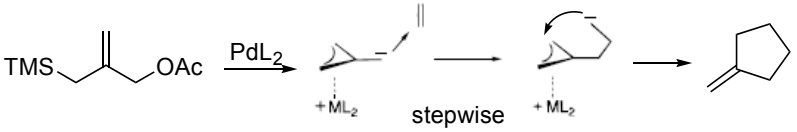
Scheme 6



Theoretical Study of Pd Insertion & [3+2] Cycloaddition Mechanisms

Fujimoto et al, *Inorg. Chem.* **1996**, *35*, 231
Inorg. Chem. **2000**, *39*, 1113

Scheme 1

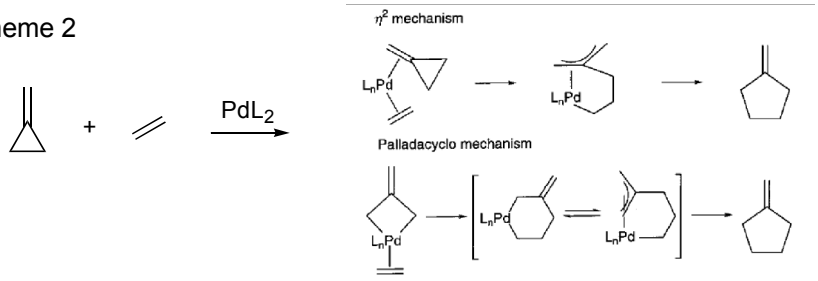


Theoretical works on d^{10} matal-TMM have revealed that they have a zwitterionic charge distribution.

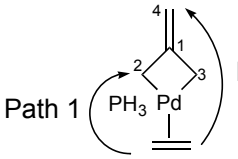
Experimental results support this mechanism: TMM-PdL_2 complexes demand that olefin has electron-deficient groups.

On the other hand... MCP-Pd complexes react both with electron-rich olefins and electron-poor olefins.

Scheme 2



distal bond insertion



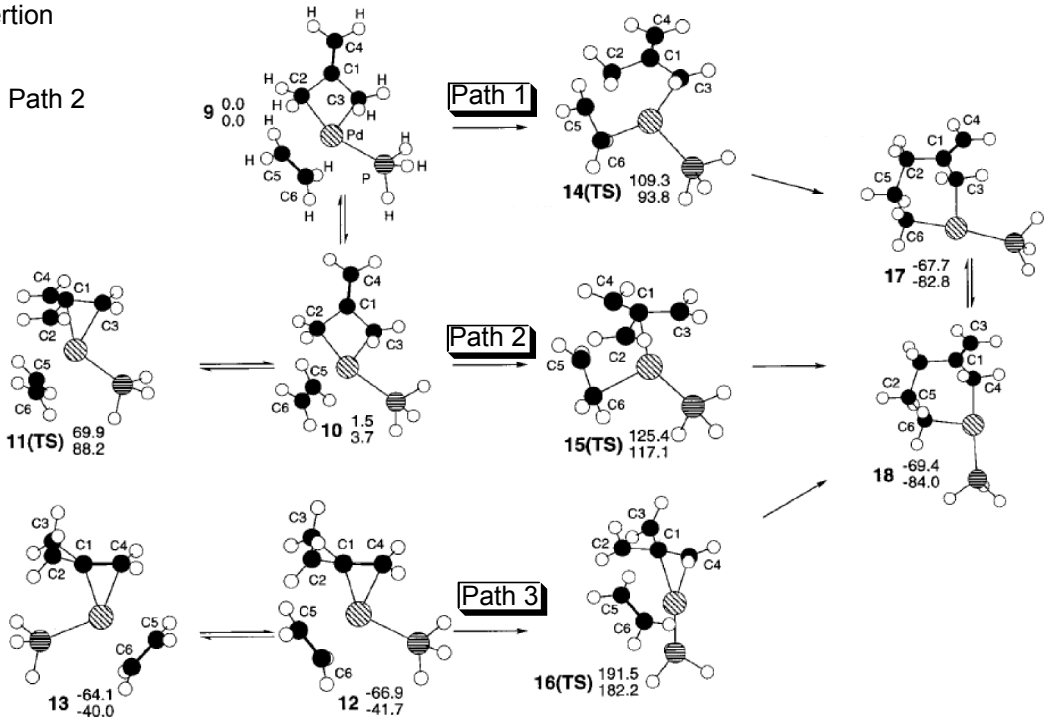
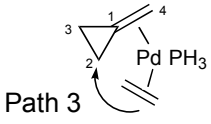
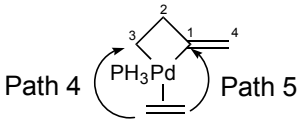


Figure 2. Structures of the ground and transition states of the species on the paths for the [3 + 2] cycloaddition reaction between methylenecyclopropane and ethylene, involving the cleavage of the distal bond of the cyclopropane ring or an η^2 complex. Bond lengths (in Å) have been calculated at the MP2 level of theory. Relative energies (kJ/mol) are given for the MP4/BS2//MP2/BS1 (above) and B3LYP/BS2//B3LYP/BS1 (below) calculations, by taking **9** as the reference. Bond lengths in parentheses are the B3LYP/BS1 optimized values.

η^2(with MCP) mechanism



proximal bond insertion



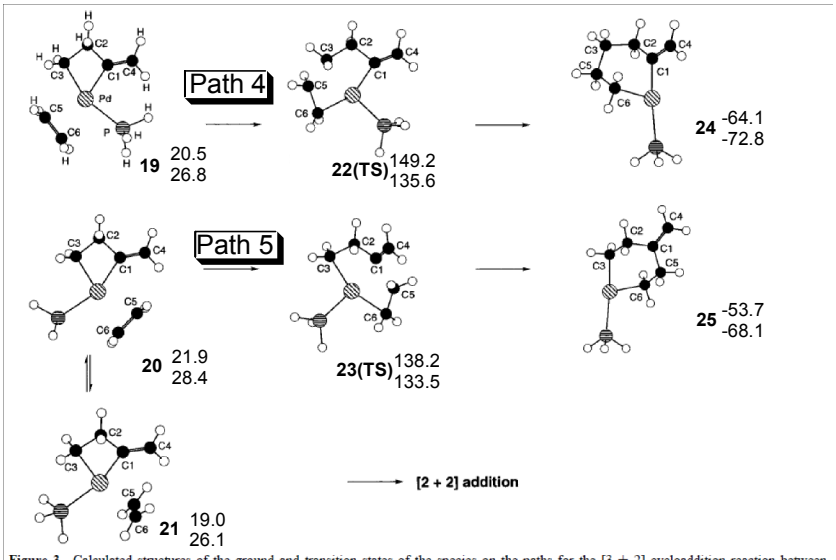
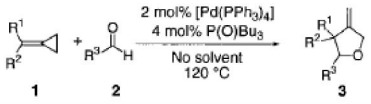


Figure 3. Calculated structures of the ground and transition states of the species on the paths for the [3 + 2] cycloaddition reaction between methylenecyclopropane and ethylene, involving the cleavage of a proximal bond of the cyclopropane ring.

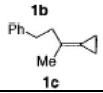
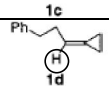
Pd catalyzed [3+2] cycloaddition of aldehydes and imines

Y. Yamamoto et al. *ACIE*, **2001**, *40*, 7
Y. Yamamoto et al. *TL*, **2001**, *42*, 6203

Table 1. Palladium-catalyzed cycloaddition of alkylidenecyclopropanes **1** with aldehydes **2**.[a]



1 **2** **3**

Entry	1	2	Time [h]	3	Yield [%][b]
1	 **1a**	 **2a**	5	**3a**	75
2	 **1b**	**2a**	11	**3b**	71
3	 **1c**	**2a**	16	**3c**	86 (53:47)[c]
4	 **1d**	**2a**	20	**3d**	42 (54:46)[c]
5	**1a**	 **2b**	6	**3e**	65
6[d]	 **1e**	**2b**	20	**3f**	77
7	**1a**	 **2c**	12	**3g**	51
8	**1a**	 **2d**	19	**3h**	64
9	**1a**	 **2e**	19	**3i**	43
10[d]	**1a**	 **2f**	32	**3j**	38

[a] The reaction of **1** (0.5 mmol) with **2** (1.5 mmol) was carried out in the presence of 2 mol% of $[Pd(PPh_3)_4]$ and 4 mol% of tributylphosphane oxide without solvent at 120°C. [b] Isolated yield based on **1**. [c] The diasteromeric ratio of **3**. [d] Compound **1** (1 mmol) was treated with **2** (0.5 mmol), and the yield is based on **2**.

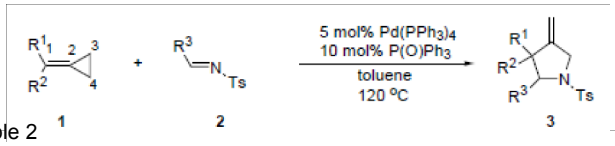
Other Pd, Pt sources didn't catalyze the reaction.

additive:
PPh_3, PBu_3, $P(OPh)_3$
→ slow and low yield

no reaction

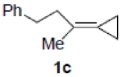
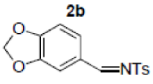
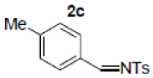
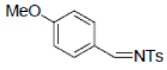
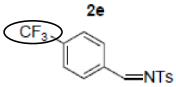
additive:
PPh_3, OP^tBu_3, P(*o*-tolyl)$_3$
→ good to high yield
bidentate ligands
→ trace

solvent:
THF, MeCN, Diox, DMF
→ good to moderate yield
CH_2Cl_2 → no reaction



1 **2** **3**

Table 2

entry	1	2	time / h	3	yield / %[b]
1	 **1a**	 **2a**	16	**3a**	89
2	 **1b**	**2a**	18	**3b**	88
3	 **1c**	**2a**	13	**3c**	91 (56:44)[c]
4	 **1d**	**2a**	20	**3d**	71
5	**1a**	 **2b**	17	**3e**	91
6	**1a**	 **2c**	16	**3f**	93
7	**1a**	 **2d**	12	**3g**	91
8	**1a**	 **2e**	9	**3h**	94
9	**1a**	 **2f**	24	**3i**	88

[a]The reaction of **1** (1 mmol) and **2** (0.5 mmol) was carried out in the presence of 5 mol% of $Pd(PPh_3)_4$ and 10 mol% of triphenylphosphine oxide in toluene at 120 °C. [b]Isolated yield based on **2**. [c]The diastereomeric ratio of **3c**.

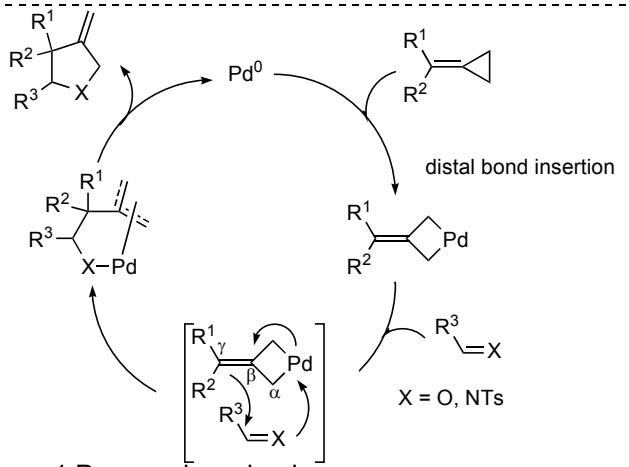
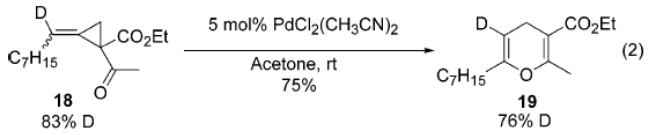
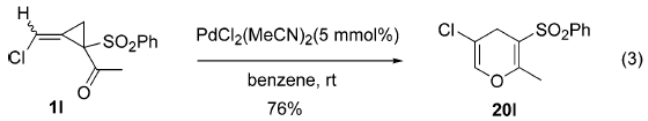


Figure 1 Proposed mechanism

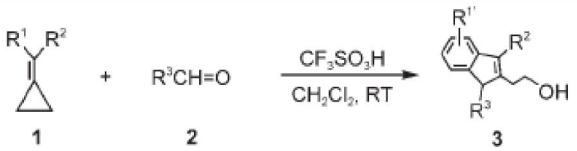
Other Reactions

Ma, *JACS*, **2004**, *126*, 9645





Shi, *Chem. Eur. J.*, **2006**, *12*, 510

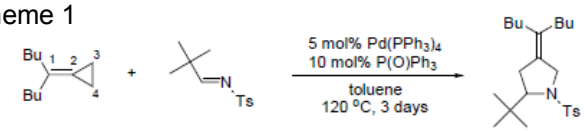


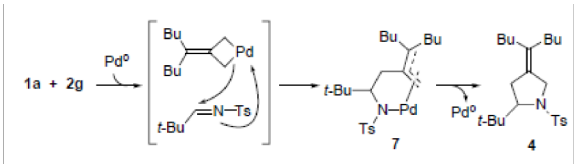
Isolated Yield [%]

1b: $R^1 = R^2$ = 4-$MeOC_6H_4$ **2e**: R^3 = 4-ClC_6H_4 **3h**: 50
1c: $R^1 = R^2$ = 4-MeC_6H_4 **2j**: R^3 = 4-BrC_6H_4 **3i**: 58

Scheme 10. Reaction of MCPs **1** (0.5 mmol) with aldehydes (1.0 mmol) in the presence of CF_3SO_3H (0.1 mmol) at room temperature.

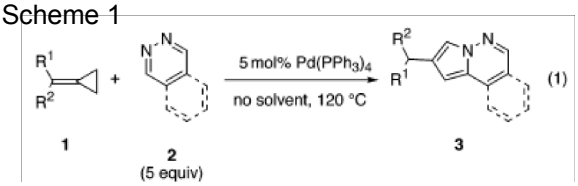
Scheme 1

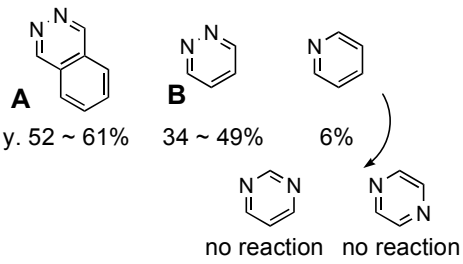


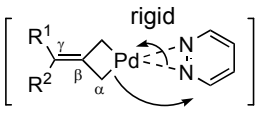


Y. Yamamoto, *JOC*, **2004**, *69*, 3202

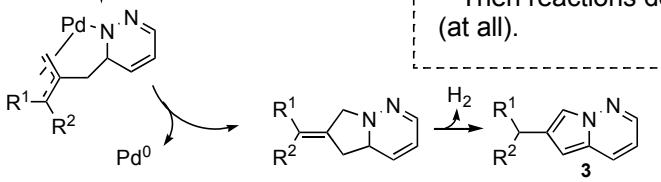
Scheme 1

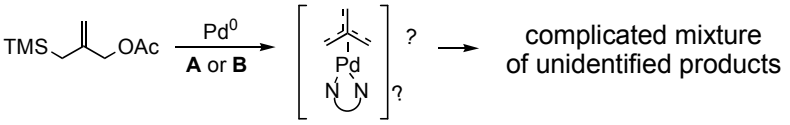


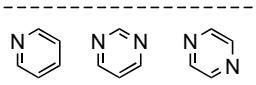




different reaction position







These heteroaromatics can't make rigid coordination to Pd.
Then reactions don't proceed (at all).

2-3. Intramolecular Cycloaddition

E. Nakamura, *Tetrahedron*, **1989**, *45*, 3088

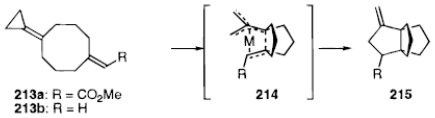


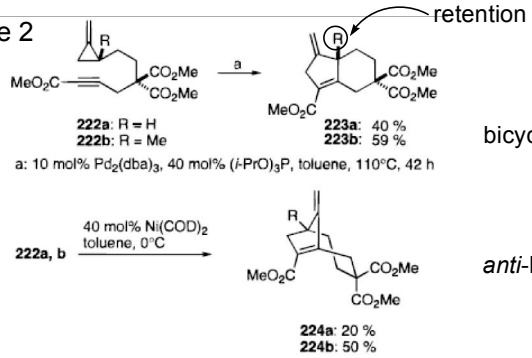
Table 1

diene	catalyst (20 mol %)[a]	temperature	yield of **215**
213a	$Ni(COD)_2$, PPh_3	110°C	74 %
213a	$(PPh_3)_2PdCl_2$, DIBAL	130°C	98 %
213b	$(PPh_3)_2PdCl_2$, DIBAL	90°C	74 %

a: reaction procedure: the catalyst in degassed toluene was treated with DIBAL and **213** at -78°C, then heated at the indicated temperature

Motherwell, *TL*, **1989**, *30*, 7107

Scheme 2



bicyclo [4,3,0]

anti-Bredt rule

Stereospecificity of the Cycloaddition — bicyclo [3,3,0]

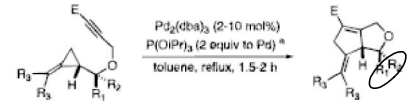


Table 2

Entry		Substrate[b]	Cycloadduct	Yield (%)
1	**3a**	$R_1 = C_6H_{11}$, $R_2 = H$, $R_3 = H$, E = $COOCH_3$	**11a**	75
2	**3b**	$R_1 = C_6H_{11}$, $R_2 = H$, $R_3 = H$, E = CH_2OH	**11b**	85[c]
3	**4**	$R_1 = H$, $R_2 = C_6H_{11}$, $R_3 = H$, E = $COOCH_3$	**12**	72
4	**5**	$R_1 = C_7H_{15}$, $R_2 = H$, $R_3 = H$, E = $COOCH_3$	**13**	71
5	**6a**	$R_1 = H$, $R_2 = C_7H_{15}$, $R_3 = H$, E = $COOCH_3$	**14a**	70 (83)[d]
6	**7**	R_1 , $R_2 = (CH_2)_5$, $R_3 = H$, E = $COOCH_3$	**15**	68
7	**8**	$R_1 = C_6H_{11}$, $R_2 = H$, $R_3 = nPr$, E = $COOCH_3$	**16**	58

[a] P/Pd = 2/1; typically 2−10 mol % of $Pd_2(dba)_3$ was used. See experimental for details. [b] C_6H_{11} refers to cyclohexyl and C_7H_{15} refers to n-heptyl. [c] Reflux for 4 h. [d] 10 mol % of $Pd(PPh_3)_4$ was used at reflux in toluene for 2 h.

Substitution at R_1 and R_2 have little effect on stereoselectivity.

Lautens, *JACS*, **1996**, *118*, 9597

Effect of Substituent on the Cyclopropane Carbon

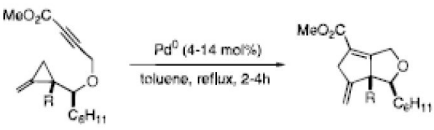


Table 3

Entry	Substrate [a]	R	Catalyst [b]	Cycloadduct	Yield (%)
1	**3a**	H	$Pd_2(dba)_3$ / $P(OiPr)_3$	**11a**	75
2	**9**	OCH_3	$Pd_2(dba)_3$ / $P(OiPr)_3$	**17**	75
3	**10**	CH_3	$Pd_2(dba)_3$ / $P(OiPr)_3$	**18**	complex mixture
4	**10**	CH_3	**$Pd(PPh_3)_4$**	**18**	**43**

[a] C_6H_{11} refers to cyclohexyl. [b] P/Pd = 2/1; typically 2−12 mol % of Pd^0 was used.

Effect of Substituent on the Acetylene

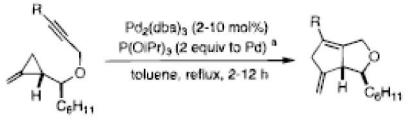
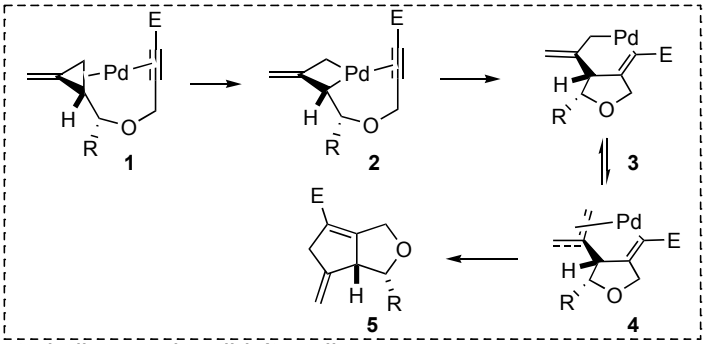


Table 4

Entry	Substrate [b]	R	Catalyst	Cycloadduct	Yield (%)
1	**3a**	$COOCH_3$	$Pd_2(dba)_3$ / $P(OiPr)_3$	**11a**	75
2	**3b**	CH_2OH	$Pd_2(dba)_3$ / $P(OiPr)_3$	**11b**	85
3	**3c**	$CH_2OTBDMS$	$Pd_2(dba)_3$ / $P(OiPr)_3$	**11c**	100
4	**3e**	$COCH_3$	$Pd_2(dba)_3$ / $P(OiPr)_3$/ 4Å MS	**11e**	52 (92) [c]
5	**3g**	CH_3	$Pd_2(dba)_3$ / $P(OiPr)_3$	**11g**	< 5 [d]

[a] P/Pd = 2/1; typically 2−10 mol % of $Pd_2(dba)_3$ was used. See experimental for details. [b] C_6H_{11} refers to cyclohexyl. [c] 11 mol % of $Pd(PPh_3)_4$ was used at reflux in toluene for 1.5 h. [d] A similar result was observed when $Pd(PPh_3)_4$ was used as the catalyst.

Scheme 3



Si subsutituted alkynes also didn't cyclize.