Problem Session (1) -Answer-

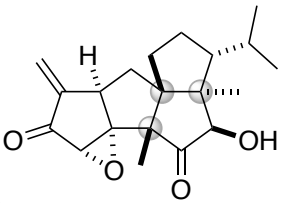
2020. 2. 8. Yuto Hikone

Topic: Total Syntheses of Crinipellins

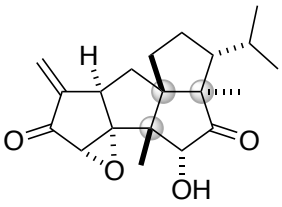
0. Introduction

0-1. Crinipellin

Isolation: fungus *Crinipellis stipitaria*
Structure: unique tetraquinane core
three contiguous all-carbon quaternary carbon atoms
Biolactivity: antibiotic
Total synthesis of (±)-crinipellin B: Piers (1993)
(-)-crinipellin A: Lee (2014) -> **problem 2**
(-)-crinipellin A/B: Yang (2018) -> **problem 1**



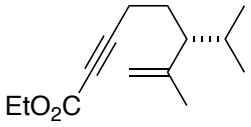
crinipellin A



crinipellin B

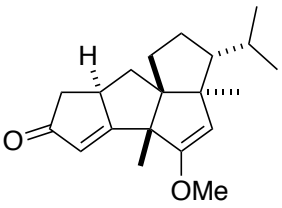
1. Answer

1.

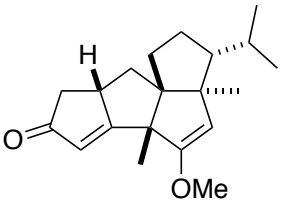


1-1

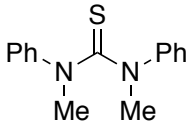
1. $Co_2(CO)_8$ (1.05 eq.), NMO (3.5 eq.), CO (1 atm)
   $ClCH_2CH_2Cl$, rt to 76 ºC, 66%
2. AllylMgCl (1.5 eq.), TMSCl (1.1 eq.)
   CuBr•Me_2S (1.5 eq.), THF, -78 ºC;
   Me_2SO_4 (4.0 eq.), Cs_2CO_3 (4.0 eq.), 0 ºC to rt;
   TBAF (0.75 eq.), Me_2SO_4 (4.0 eq.), rt, 81%
3. $LiN(TMS)_2$ (4.0 eq.), HMPA, THF, -15 ºC;
   MeI (15 eq.), rt, 55%
4. DIBAL-H (2.5 eq.), CH_2Cl_2, 0 ºC;
   ^{t}BuOH (10 eq.);
   $NaHCO_3$ (10 eq.), DMP (3.5 eq.), 0 ºC, 95%
5. Bestmann-Ohira reagent (2.5 eq.), K_2CO_3 (5.0 eq.)
   MeOH, rt, 66% (94% brsm)
6. $PdCl_2$ (30 mol%), **1-2** (30 mol%), CO (1 atm)
   $NaHCO_3$ (1 eq.), THF, 50 ºC



1-3 (61%)



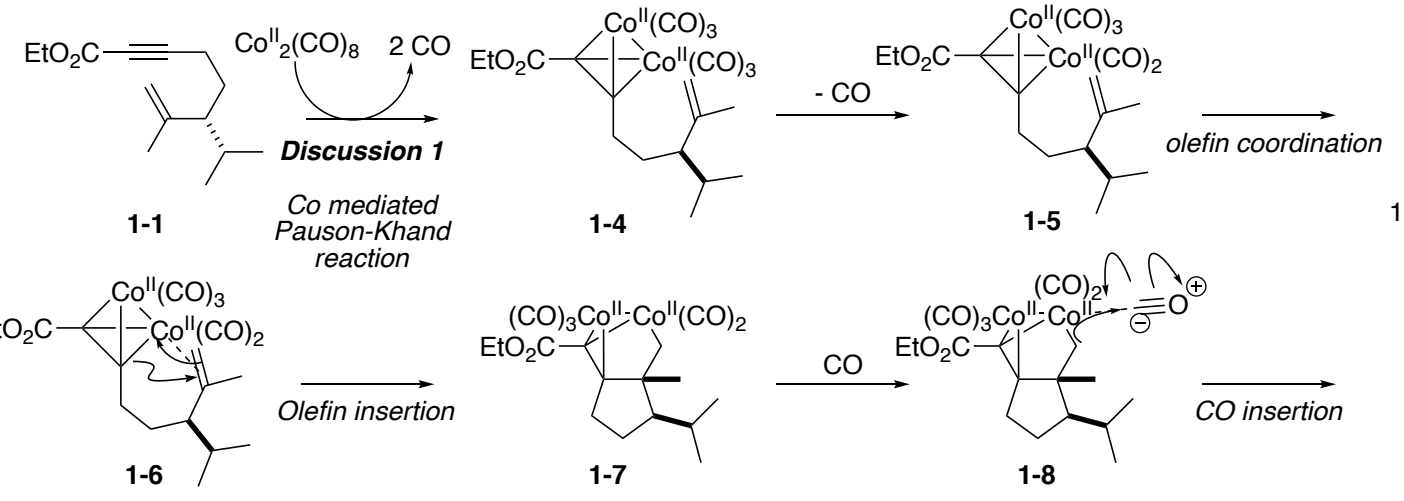
1-3' (16%)

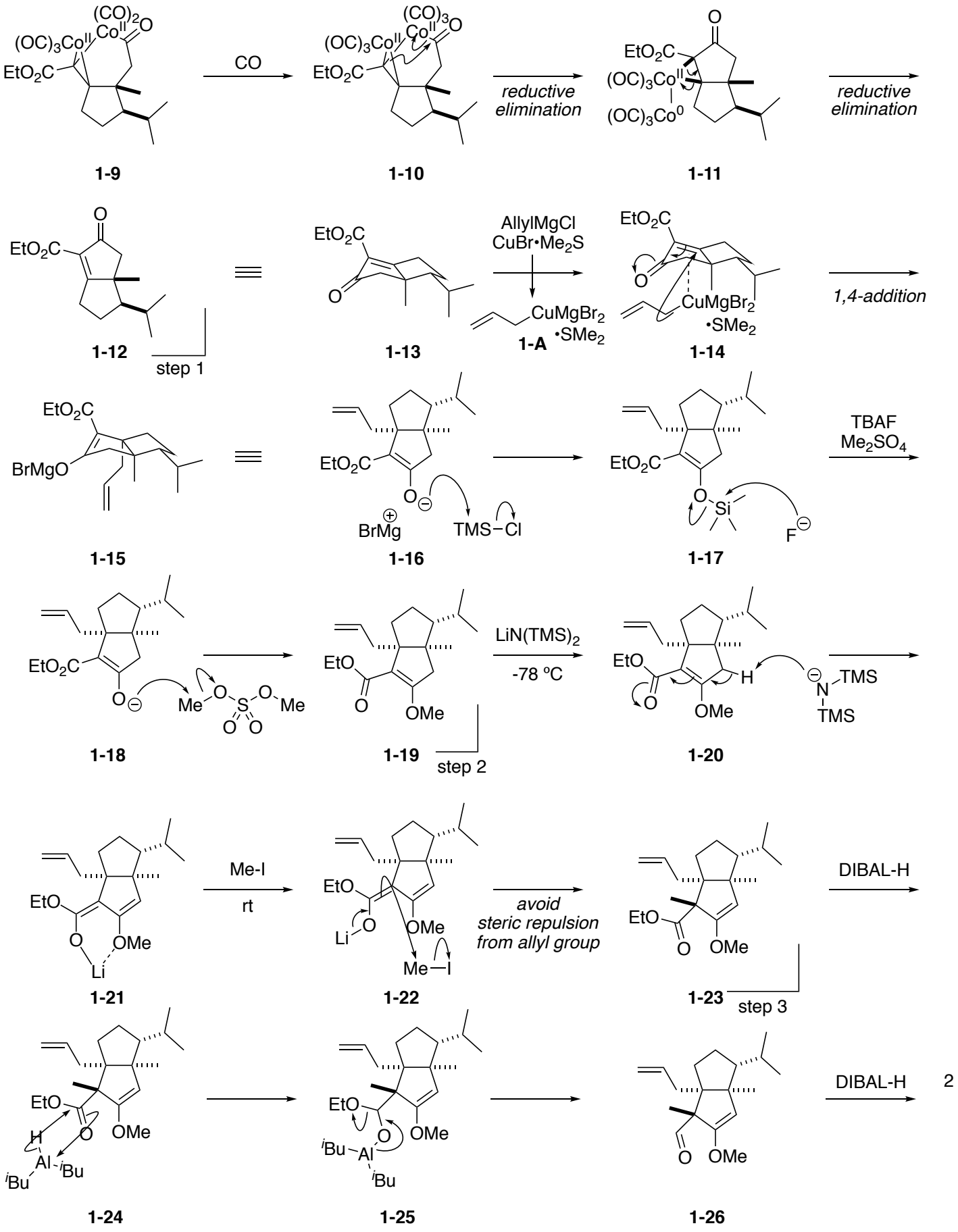


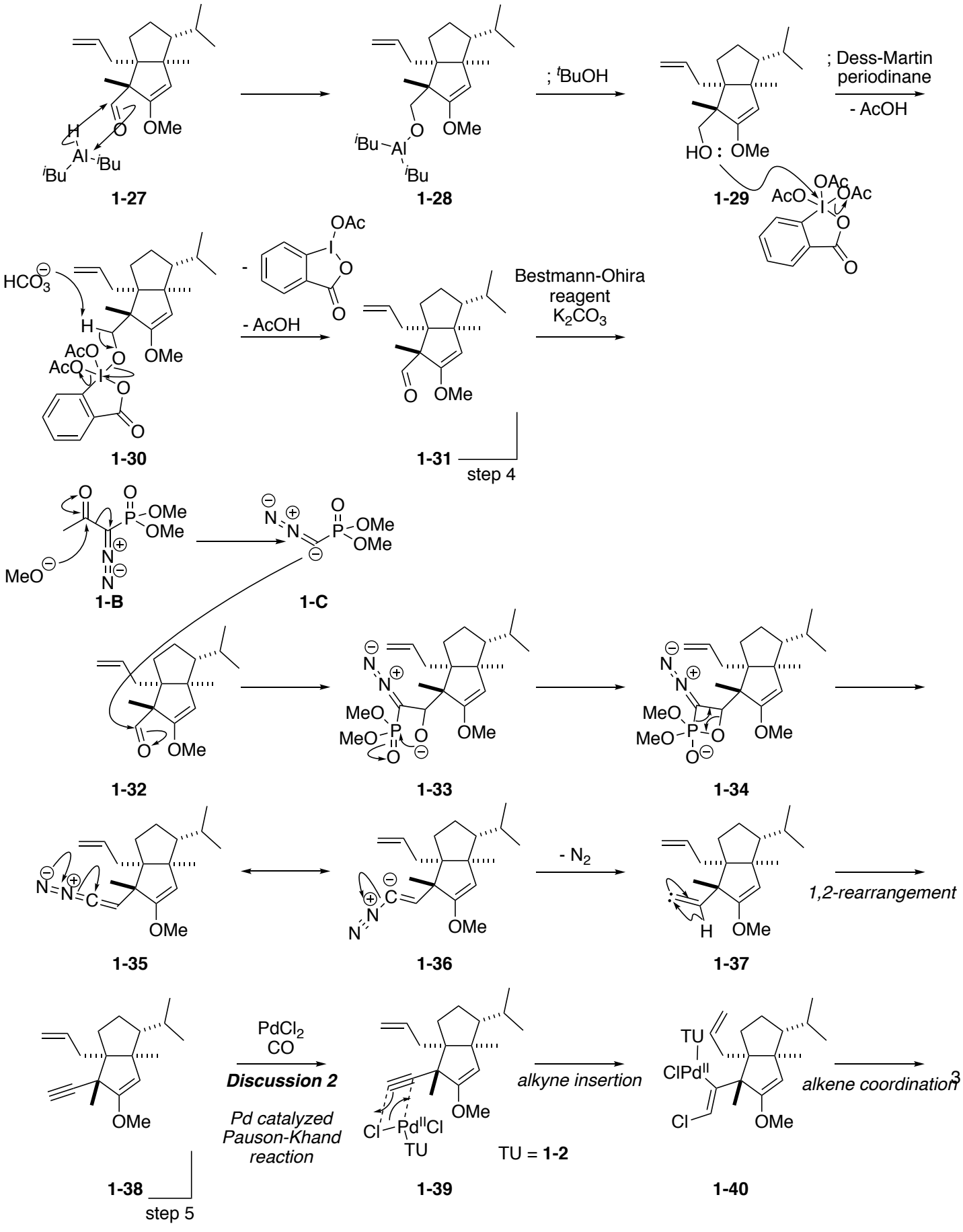
1-2

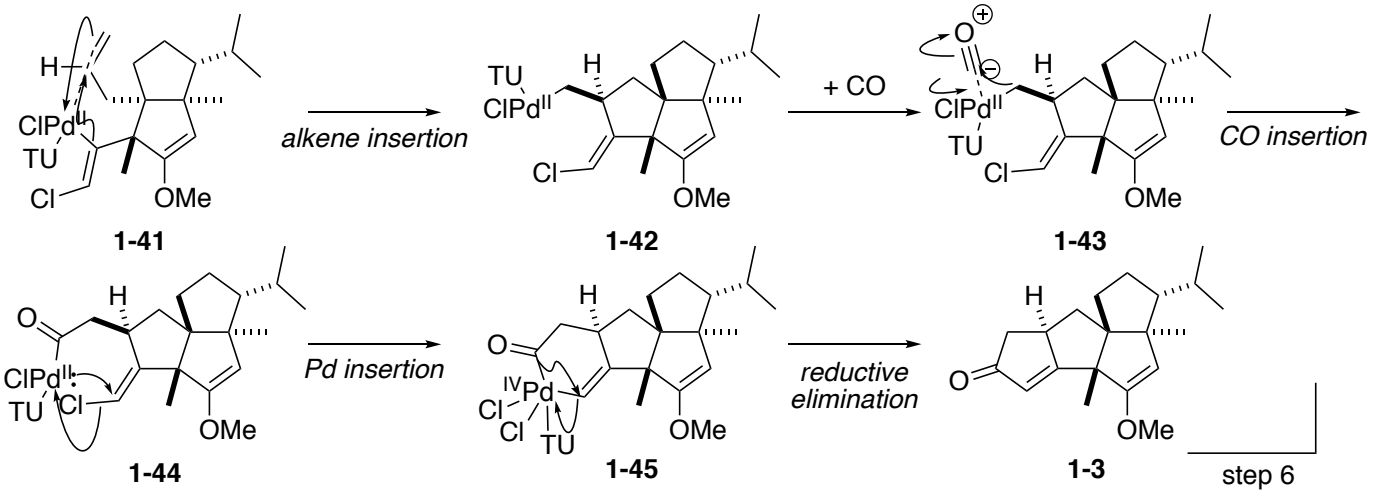
Z, Huang.; J, Huang.; Y, Qu.; W, Zhang.; J, Gong.; Z, Yang. *Angew. Chem.* **2018,** 130, 8880.

Answer




CO
reductive elimination
reductive elimination
1-9
1-10
1-11
AllylMgCl
CuBr•Me2S
1,4-addition
1-12
step 1
1-13
1-A
1-14
TBAF
Me2SO4
1-15
1-16
1-17
LiN(TMS)2
-78 °C
1-18
1-19
step 2
1-20
Me-I
rt
avoid
steric repulsion
from allyl group
DIBAL-H
1-21
1-22
1-23
step 3
DIBAL-H
2
1-24
1-25
1-26


; tBuOH
; Dess-Martin periodinane
- AcOH
1-27
1-28
1-29
1-30
1-31
step 4
Bestmann-Ohira reagent
K2CO3
- AcOH
1-B
1-C
1-32
1-33
1-34
1-35
1-36
1-37
- N2
1,2-rearrangement
PdCl2
CO
Discussion 2
Pd catalyzed Pauson-Khand reaction
alkyne insertion
alkene coordination
TU = 1-2
1-38
step 5
1-39
1-40

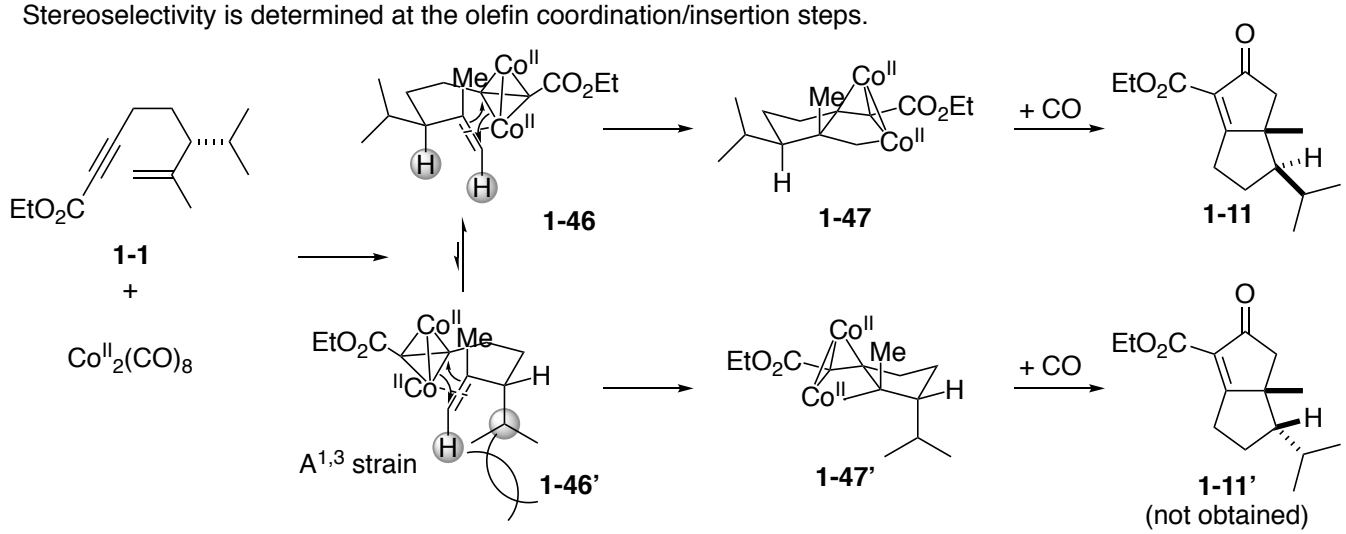


1-41 **1-42** **1-43** **1-44** **1-45** **1-3**

Discussion 1: Co mediated Pauson-Khand reaction (Co-PKR)

1. Stereoselectivity

Stereoselectivity is determined at the olefin coordination/insertion steps.



1-1 + $Co^{II}_2(CO)_8$ **1-46** **1-47** **1-11** **1-46'** **1-47'** **1-11'** (not obtained)

Discussion 2: Pd catalyzed Pauson-Khand reaction (Pd-PKR)

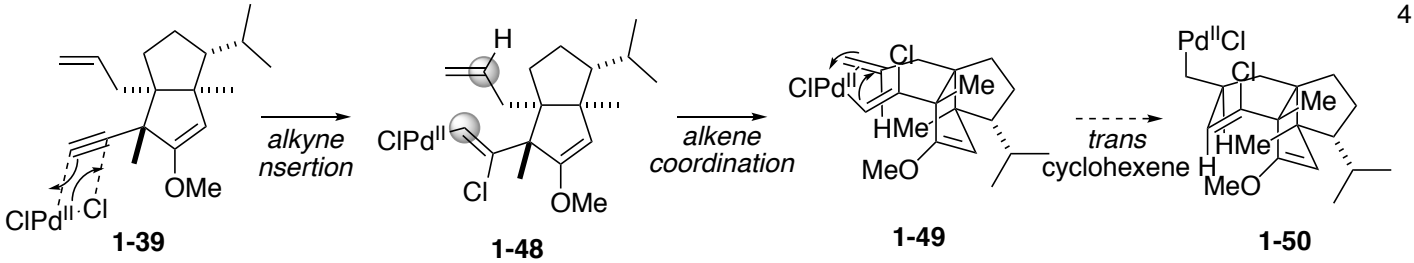
2-1: Regioselectivity and stereoselectivity

2-1-1. Regioselectivity; Halometallation

There are two possible regiochemistries for the insertion with either the Pd or the Cl adding to the terminal position of the alkyne. DFT calculation shows that $PdCl_2$ inserts to the alkyne in the way the Cl is attached to the terminal position*.

* Y, Lan.; L, Deng.; J, Liu.; C, Wang.; O, Wiest.; Z, Yang.; Y, D. Wu. *J. Org. Chem.* **2009**, 74, 5049.

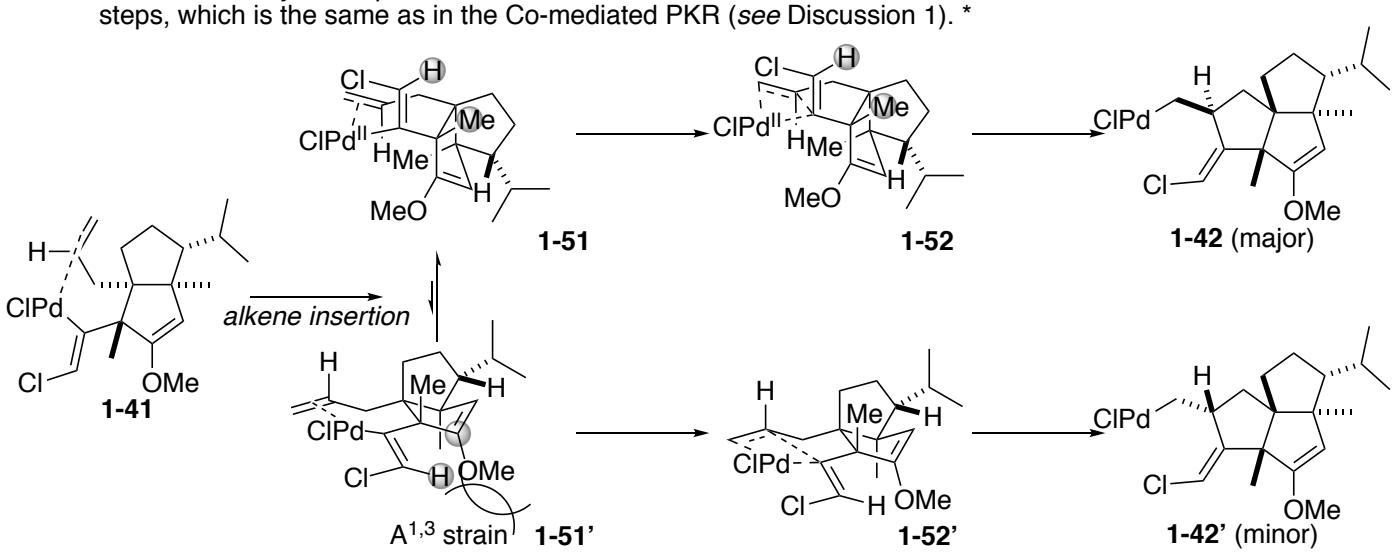
Insertion of Pd at the terminal position of the alkyne affords **1-48**. It seems that alkene coordination to **1-48** is difficult because Pd and olefin are away from each other. Even if alkene coordination proceeds, alkene insertion will not occure due to a lack of orbital interaction between Pd-C σ bond and π orbital of the olefin. In addition, product will be *trans* cyclohexene, **1-50**, suggesting the low possibility of this pathway.



1-39 **1-48** **1-49** **1-50**

2-1-2. Stereoselectivity

Stereoselectivity of the product in the Pd-mediated PKR is determined at the olefin coordination/insertion steps, which is the same as in the Co-mediated PKR (*see* Discussion 1). *



* Y, Lan.; L, Deng.; J, Liu.; C, Wang.; O, Wiest.; Z, Yang.; Y, D. Wu. *J. Org. Chem.* **2009**, 74, 5049.

2-2. Different stereoselectivity between Co-PKR and Pd-PKR

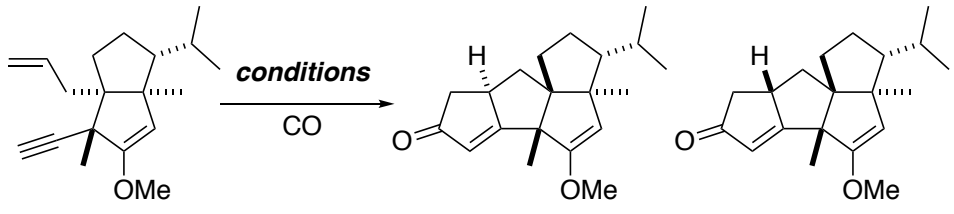
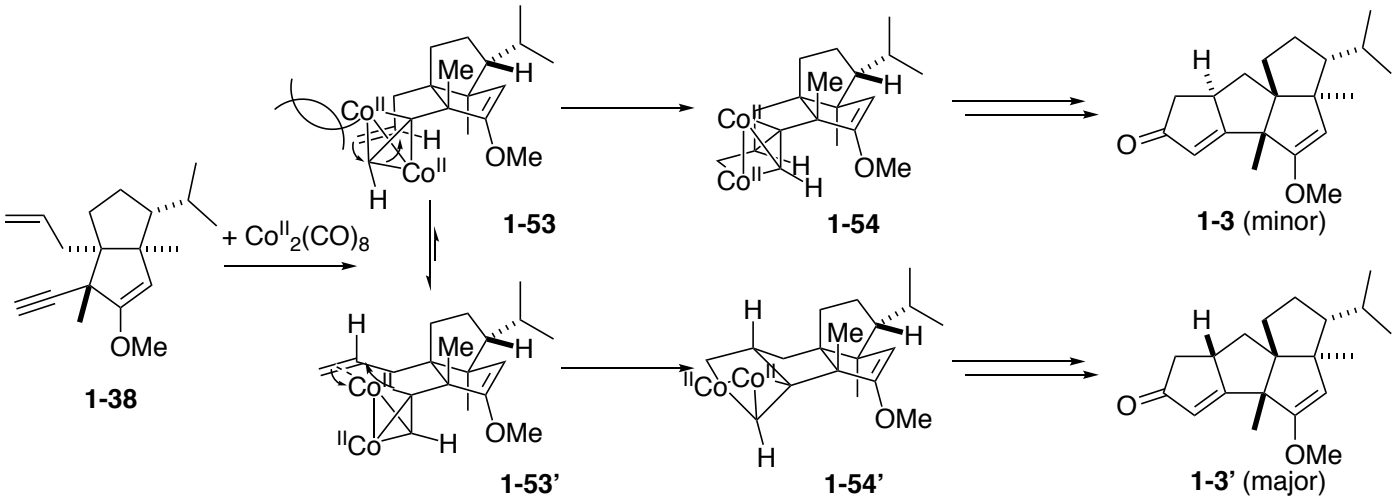


Table 1 **

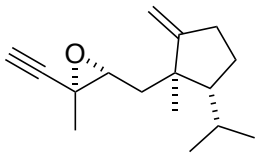
entry	***conditions***	**1-3 : 1-3'**
1	$PdCl_2$	4 : 1
2	$Co_2(CO)_8$	1 : 2
3	$[Rh(CO)_2Cl]_2$	1 : 5



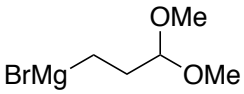
** Z, Huang.; J, Huang.; Y, Qu.; W, Zhang.; J, Gong.; Z, Yang. *Angew. Chem.* **2018,** 130, 8880.

2.

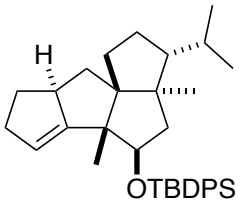
1. **2-2** (3 eq.) $Fe(acac)_3$ (10 mol%), THF, toluene, -15 ºC, 94%
2. TBDPSCl (2.2 eq.), imidazole (3 eq.)
   DMAP (0.3 eq.), CH_2Cl_2, 0 ºC to rt, 96%
3. *p*-TsOH•H_2O (1.0 eq.)
   HCHO (37 wt% in H_2O), THF, H_2O, rt, 93%
4. $TsNHNH_2$ (1.2 eq.), MeOH, 0 ºC to rt, 97%
5. NaH (1.2 eq.), toluene, reflux, 87%



2-1



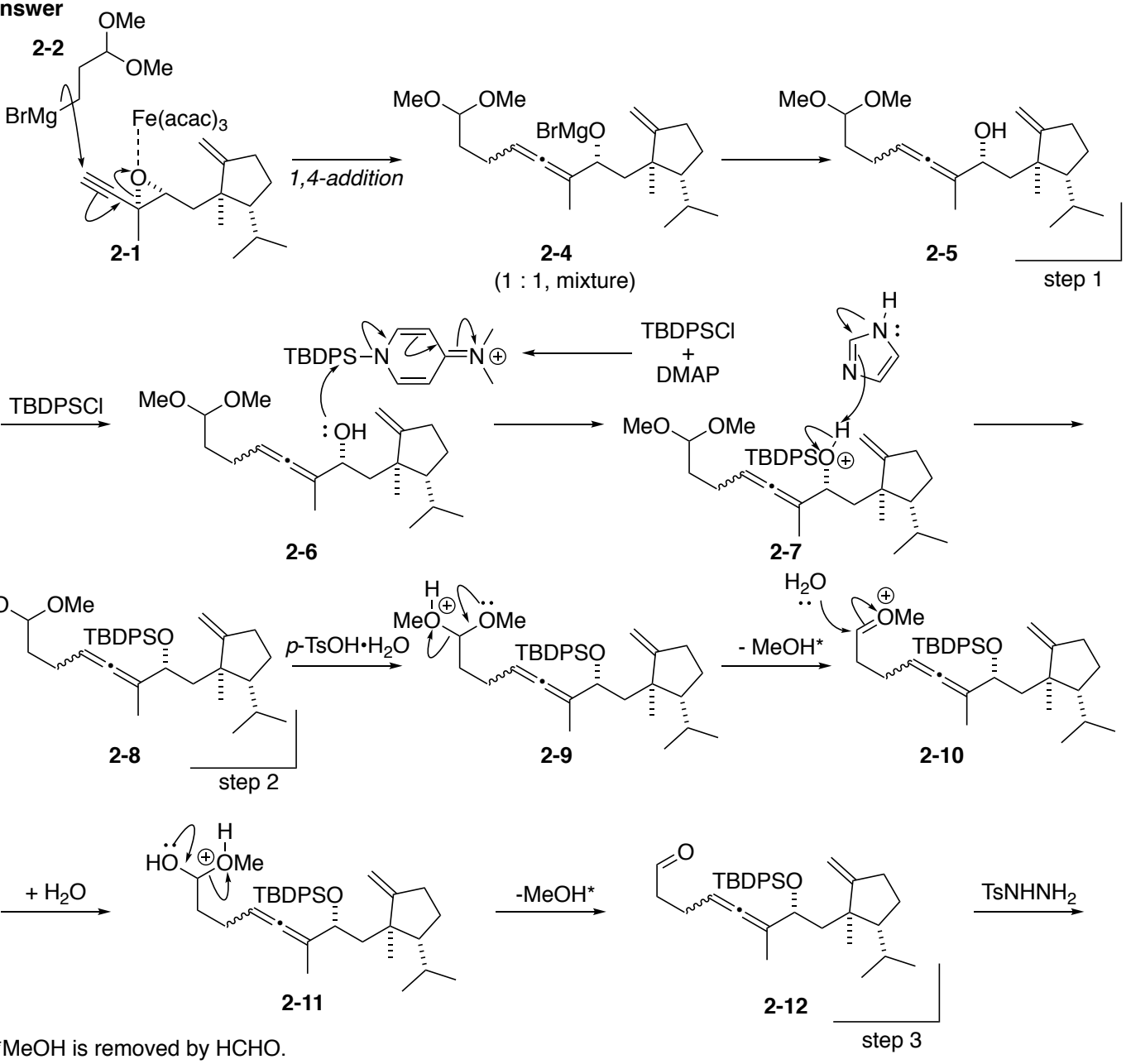
2-2



2-3

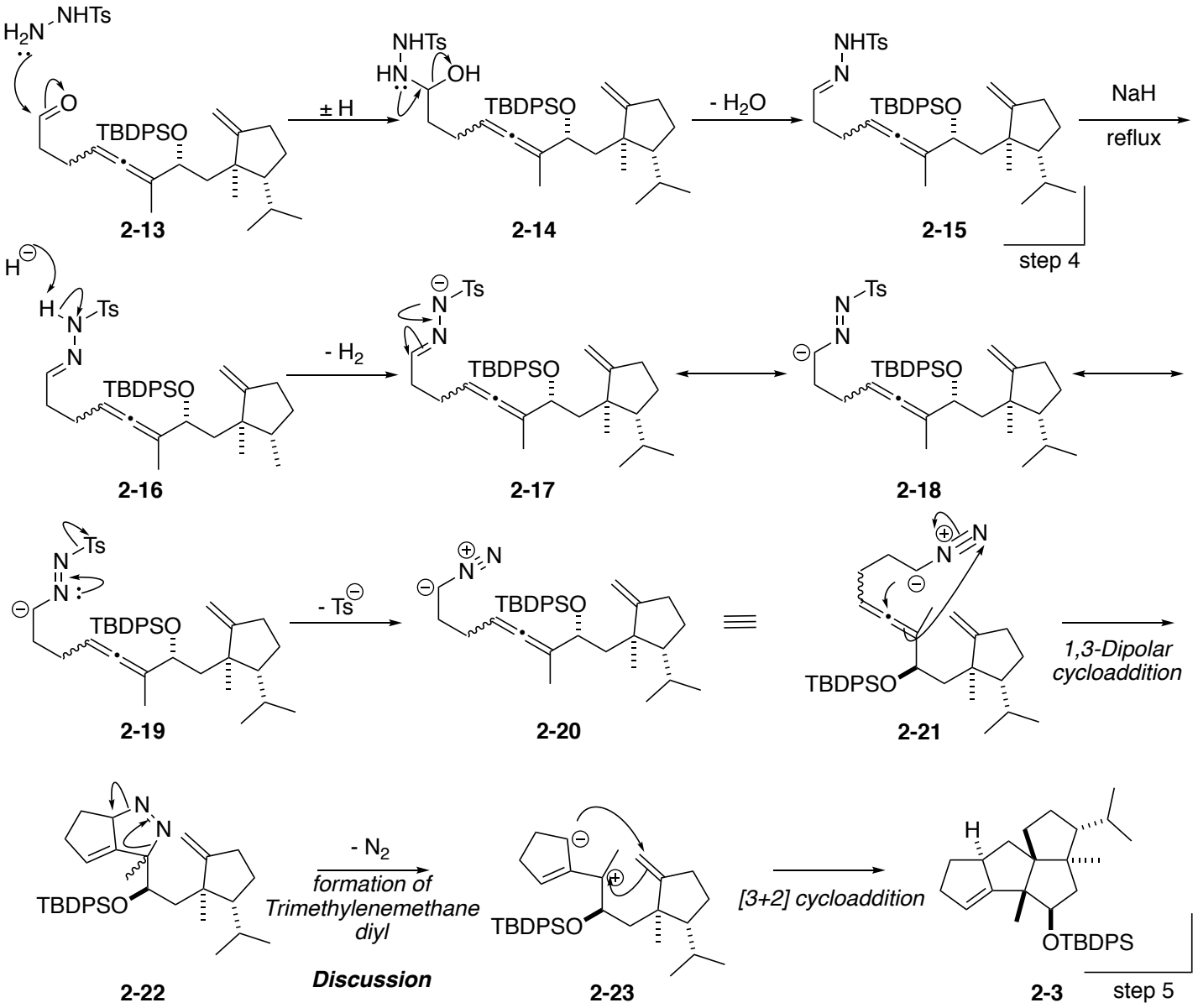
T, Kang.; S, B, Song.; W, Y, Kim.; B, G, Kim.; H, Y, Lee. *J. Am. Chem.* **2014**, 136, 10274.

Answer



*MeOH is removed by HCHO.

$$2\ MeOH + HCHO \longrightarrow MeO\diagup\!\!\diagdown OMe + 2\ H_2O$$



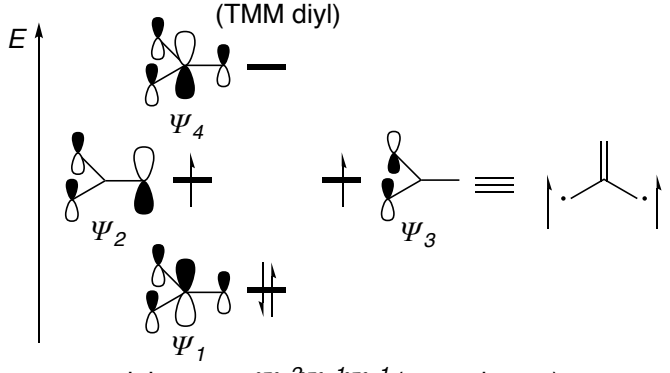
Discussion : Formation of Trimethylenemethane diyl

1-1. Trimethylenemethane diyl (TMM diyl)

R, D, Little. *Chem. Rev.* **1996**, 96, 93.

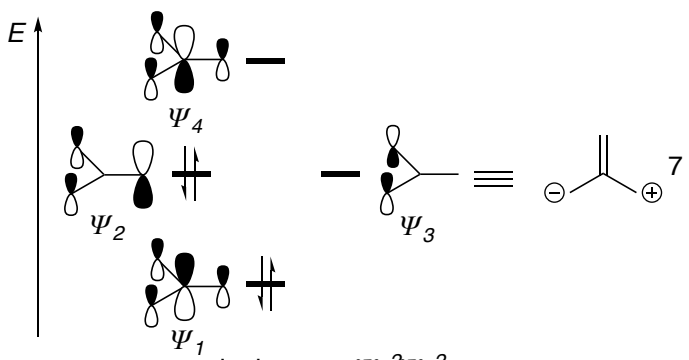
trimethylenemethane diyl
(TMM diyl)

- electron-rich system
- two electronic states: triplet and singlet (shown below)



triplet state: $\Psi_1^2\Psi_2^1\Psi_3^1$ (ground state)

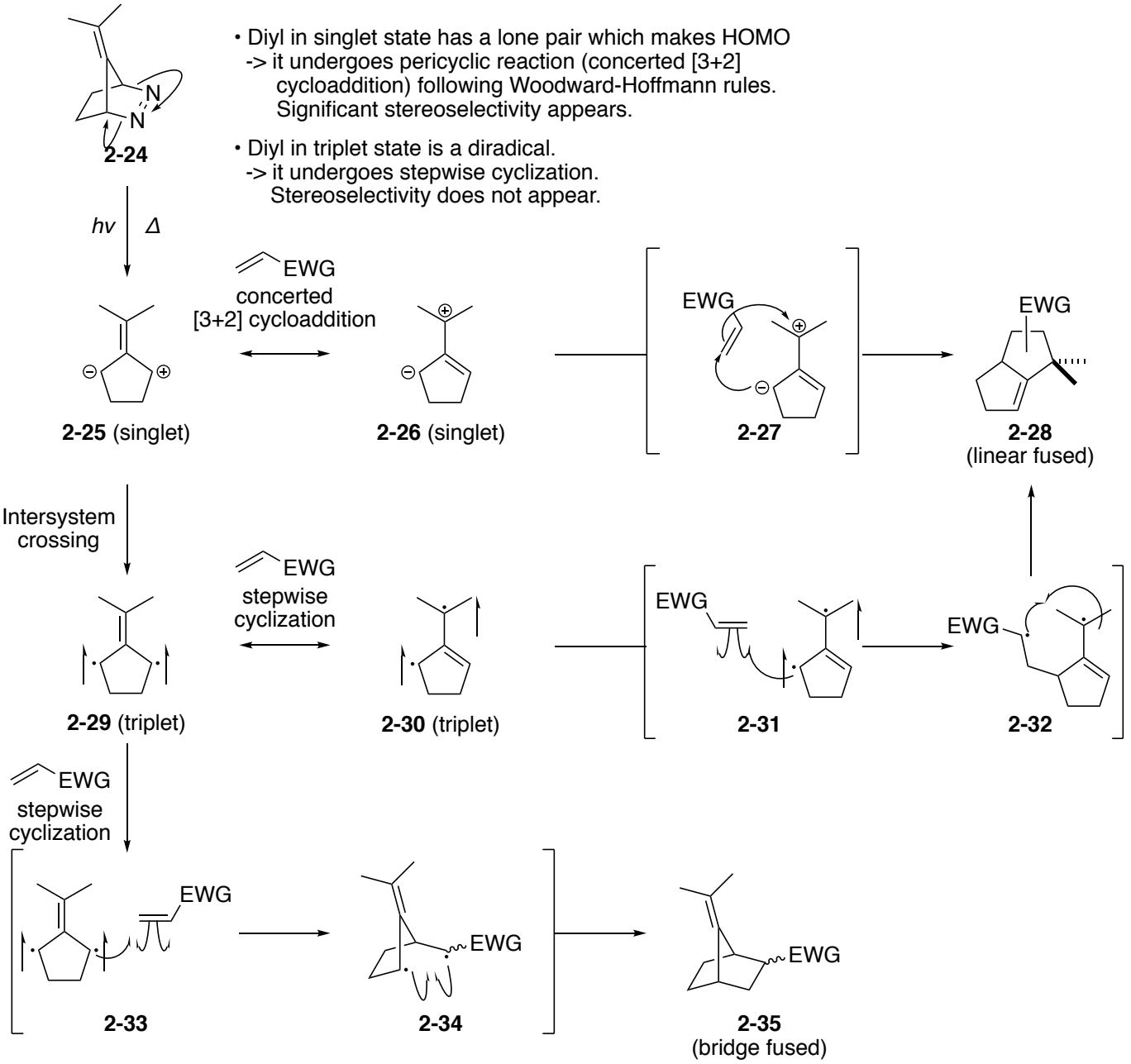
- behave as a diradical



singlet state $\Psi_1^2\Psi_2^2$

- behave in accordance with Woodward-Hoffmann rules. Ψ_2 corresponds to HOMO and Ψ_3 does to LUMO.

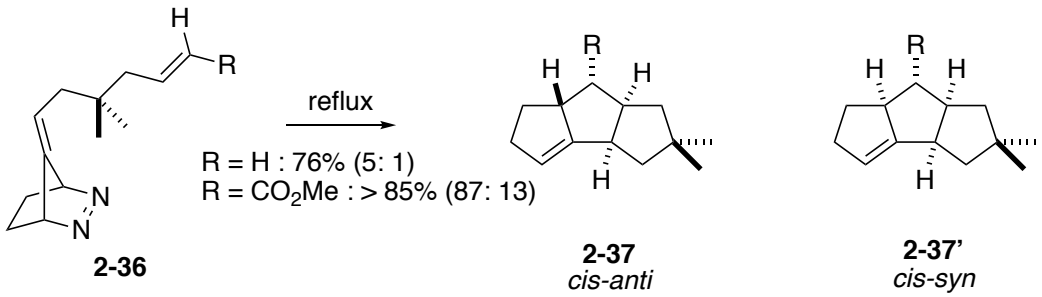
The different reactivities between singlet and triplet TMM diyl analogue.



R, D, Little. *Chem. Rev.* **1996**, 96, 93.

1-2. Stereoselectivity

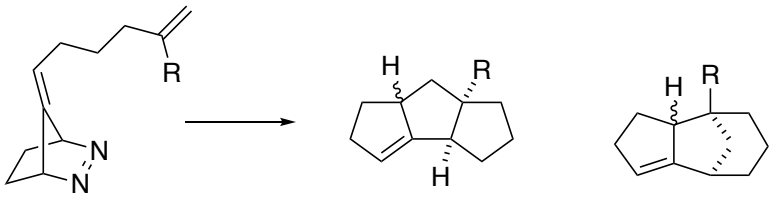
1-2-1. Singlet state: pericyclic reaction (concerted [3+2] cycloaddition)*,**



* R, D, Little.; R, G, Higby.; K, D, Moeller. *J. Org. Chem.* **1983**, 48, 3139.
** R, D, Little.; A, Bukhari.; M, G, Venegas. *Tetrahedron Lett.* **1979**, 305.

- *cis-anti* product is preferentially obtained.
- Electorn withdrawing group makes LUMO of diylophile lower, decreasing HOMO-LUMO gap to contribute to the increase in yield.

1-2-2. Triplet state: stepwise cyclization



2-38 **2-39** linear-fused **2-40** bridge-fused

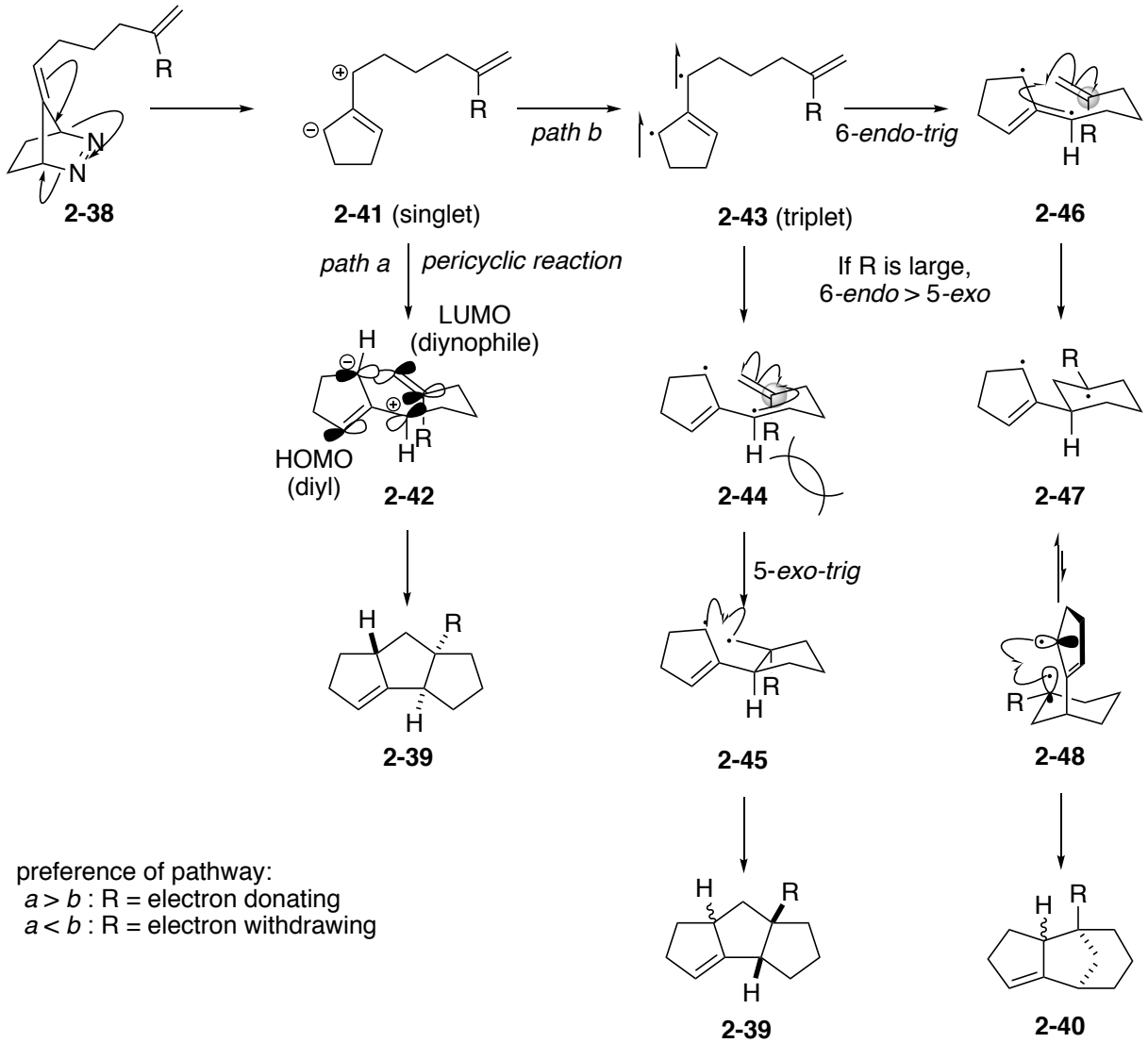
Table 2 *

entry	R	result
1	CO_2Me	**2-39**: **2-40** = 19 : 1
2	CH_2OH	**2-39**: **2-40** = 1 : 2
3	$CH(OMe)_2$	**2-39**: **2-40** = 1 : 19

* R, D, Little.; M, R, Masjedizadeh.; I, Dannecker-Doerig. *J. Org. Chem.* **1990**, 55, 2724

• When electron withdrawing group is attached to olefin, reaction proceeds based on HOMO-LUMO interaction (*see* 2-2-1). -> entry 1
• When electron donating group is attached to olefin, HOMO-LUMO gap gets large, making concerted cycloaddition difficult. This event provides time for intersystem crossing to become competitive, making formation diyl in triplet state possible. -> entry 2 and 3
• Triplet can choose either a stepwise 5-*exo-trig* cyclization or a 6-*endo-trig* cyclization. The former pathway gives linear-fused product while the latter pathway gives bridge-fused product. If bulky R group is attached at a vinyl position, 6-*endo-trig* cyclization proceeds in preference to 5-*exo-trig* cyclization.**

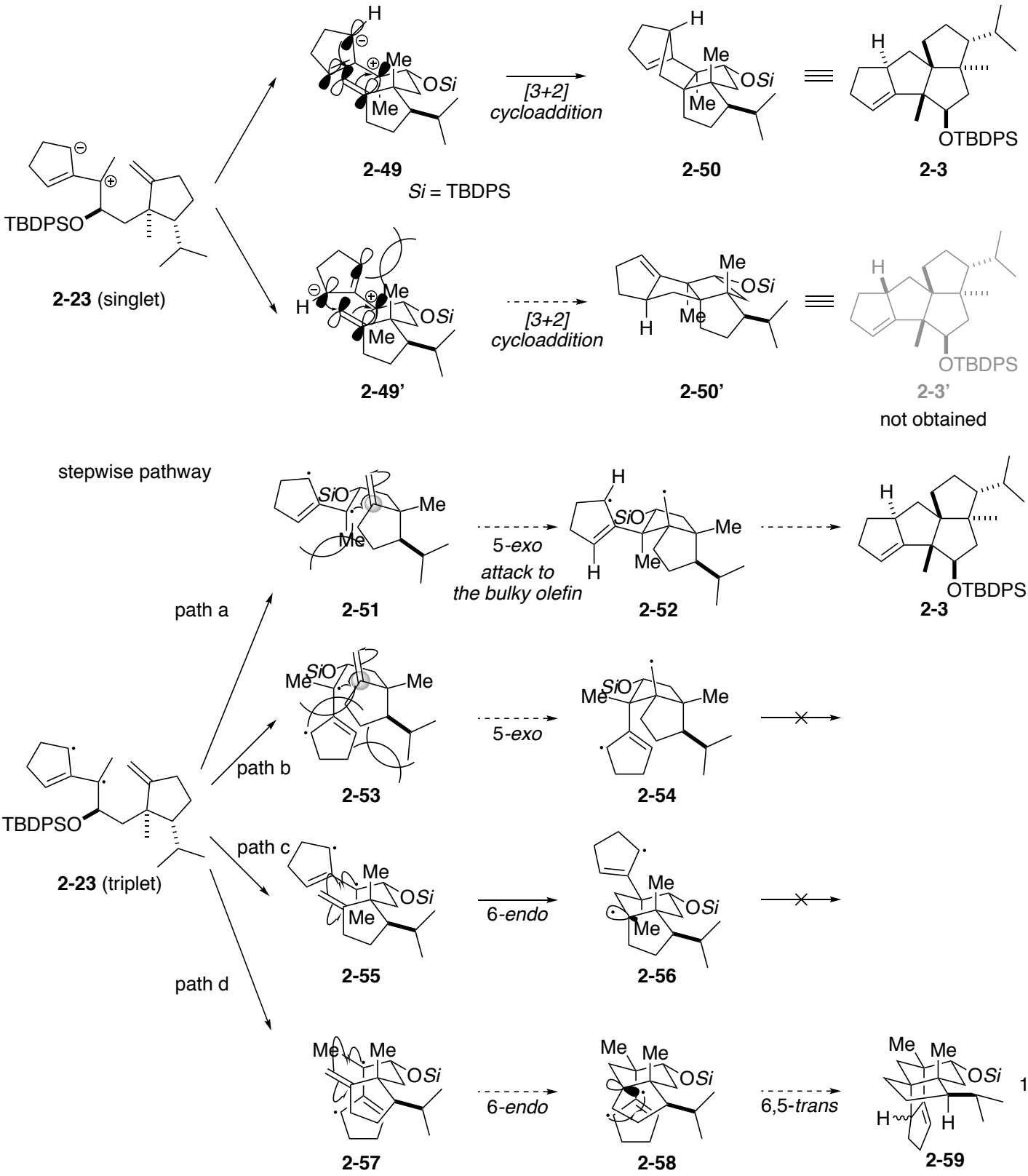
** D, C, Spellmeyer.; K, N, Houk. *J. Org. Chem.* **1987**, 52, 959.



preference of pathway:
a > *b* : R = electron donating
a < *b* : R = electron withdrawing

1-3. Stereoselectivity in real substrate

pericyclic reaction (concerted [3+2] cycloaddition)



There are problems which makes some pathways difficult to proceed.

- addition of the tertiary radical to the substituted olefin (path a and b)
- steric hinderance between 5 membered rings (path b and d)

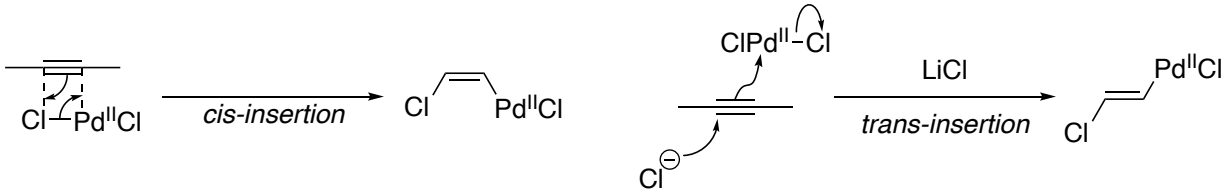
- > Path c is the most reasonable among these pathways, but further conversion would not proceed beacuse reaction sites are away from each other .

Problem Session (1) - Appendix-

1. Stereo/Regioselectivity of Alkyne insertion to $PdCl_2$

1-1. Stereoselectivity

Stereoselective insertion of alkyne to $PdCl_2$ is determined by the existence of LiCl. While *cis*-insertion of alkyne proceeds in the absence of LiCl, *trans*-insertion proceeds in its presence[1)].

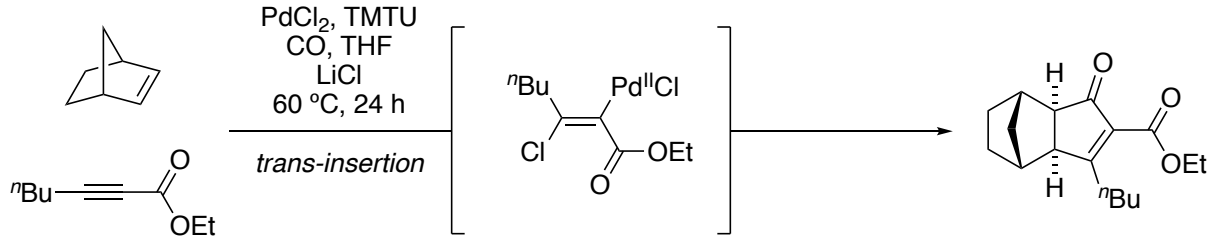


1-2. Regioselectivity

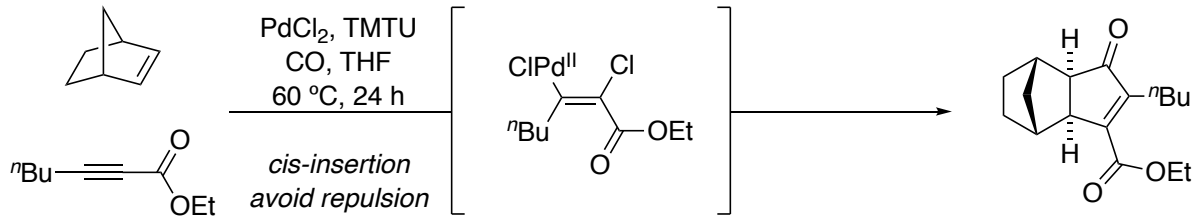
• Existence of LiCl

In the presence of LiCl, insertion of alkyne to $PdCl_2$ proceeds in such a way that chloride ion attacks electron-deficient position of the alkyne. In the absence of LiCl, Pd^{II} is attached to electron-rich position of the alkyne, but the regioselectivity seems to be dependent on substrates. When a substrate has an enyne system, Pd^{II} is added to the inner position of the alkyne (*see next page*).

• In the presence of LiCl

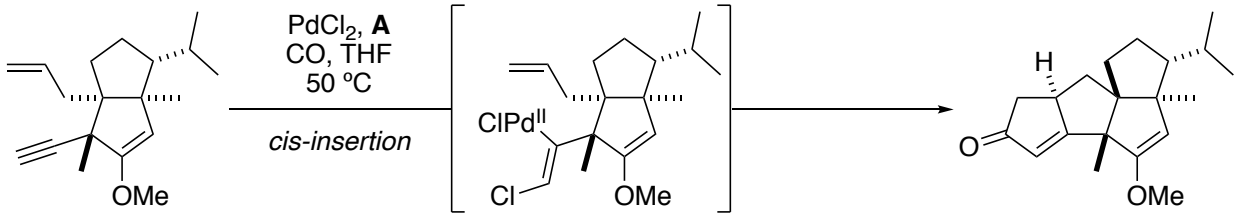


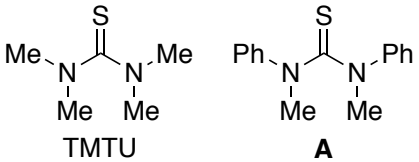
• In the absence of LiCl
intermolecular Pauson Khand reaction



N, Wu.; L, Deng.; L, Liu.; Q, Liu.; C, Li.; Z, Yang. *Chem. Asian J.* **2013**, 8, 65.

intramolecular Pauson Khand reaction

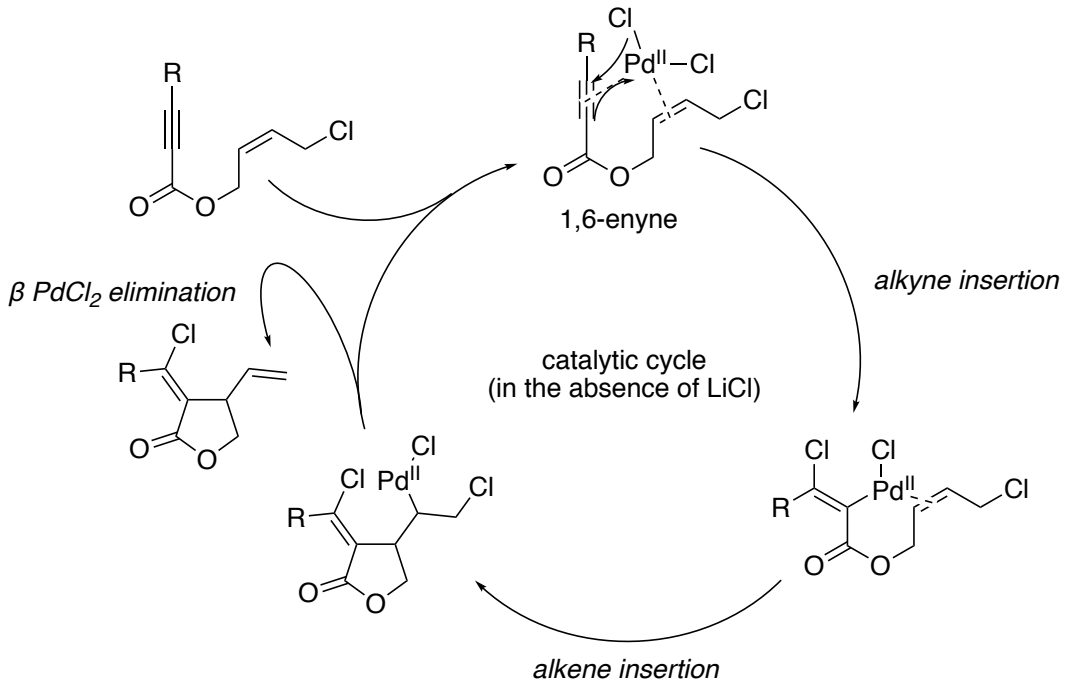




Z, Huang.; J, Huang.; Y, Qu.; W, Zhang.; J, Gong.; Z, Yang. *Angew. Chem.* **2018,** 130, 8880.

• Enyne system

In the enyne system, coordination of enyne to $PdCl_2$ may lead to the formation of vinylic adducts in such a way that the Pd^{II} is added to the inner position of the alkyne [2].



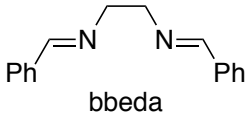
G. Zhu.; Z. Zhang. *J. Org. Chem*, **2005**, 70, 3339.

2. Carbopalladium(IV) intermediate

2-1.Cycloisomerization

Cycloisomerization proceeds under the catalytic amount of $Pd^{II}(OAc)_2$, $Pd^{II}(OAc)_2$/bbeda and $Pd^0{}_2(dba)_3$•$CHCl_3$/AcOH [3] using AcOH as a solvent. There seems to be few examples of the use of $PdCl_2$ in enyne cycloisomerization.

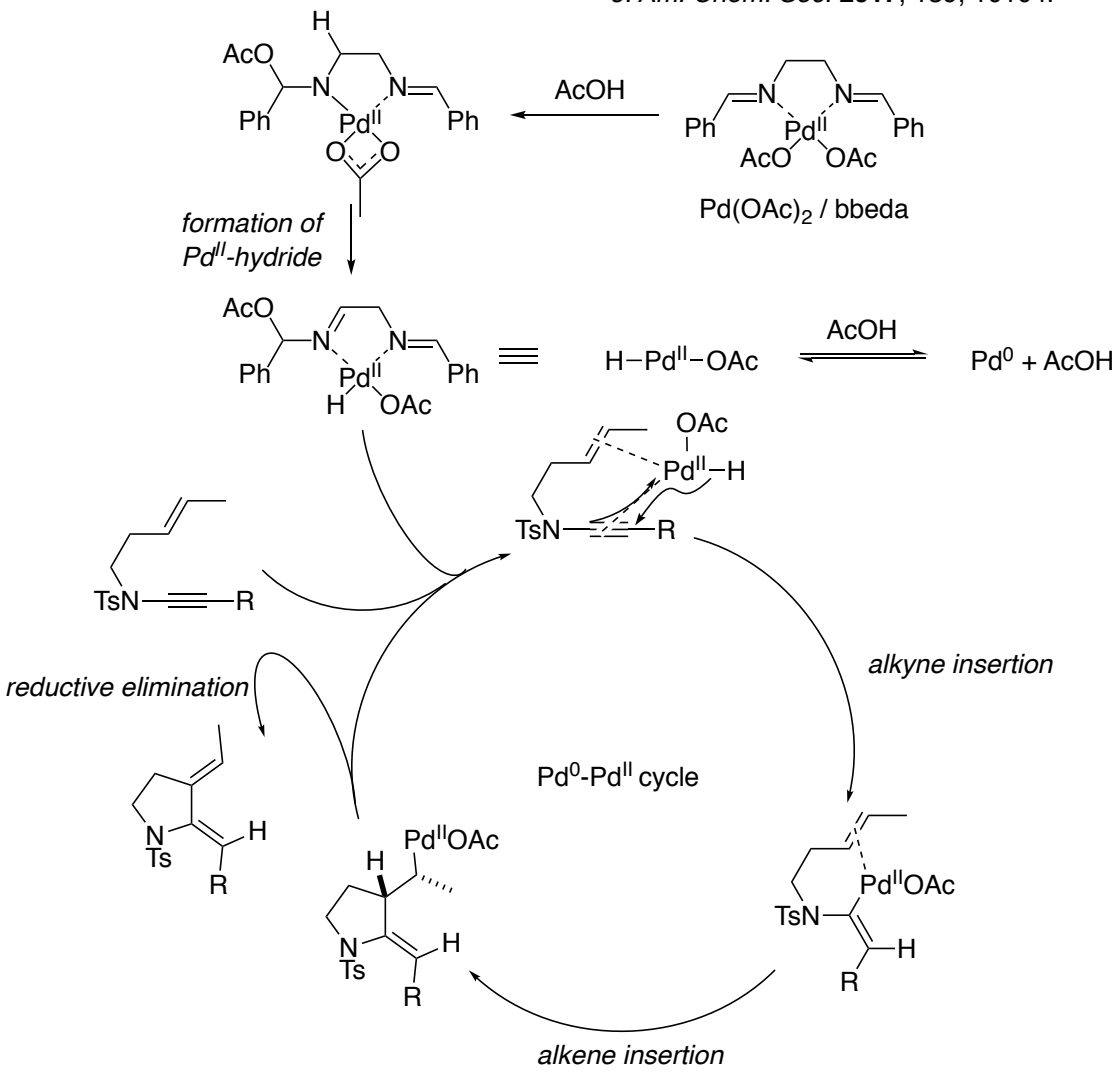
There are two possible mechanisms for cycloisomerization: 1. Pd^0-Pd^{II} cycle or 2. Pd^{II}-Pd^{IV} cycle. When $Pd^{II}(OAc)_2$/bbeda and $Pd^0{}_2(dba)_3$•$CHCl_3$/AcOH are employed, reaction proceeds through mechanism 1. In the $Pd^{II}(OAc)$/bbeda system, Pd^{II} is reduced by bedda to afford Pd^0. Pd^0 inserts to AcOH, forming active species Pd^{II}-hydride (Pd^{II}-H) [3]. When $Pd^{II}(OAc)$ is employed, it is considered that reaction proceeds through mechanism 2, because there is no reagent to reduce Pd^{II} [4].



bbeda
(bis-benzylidene ethylenediamine)

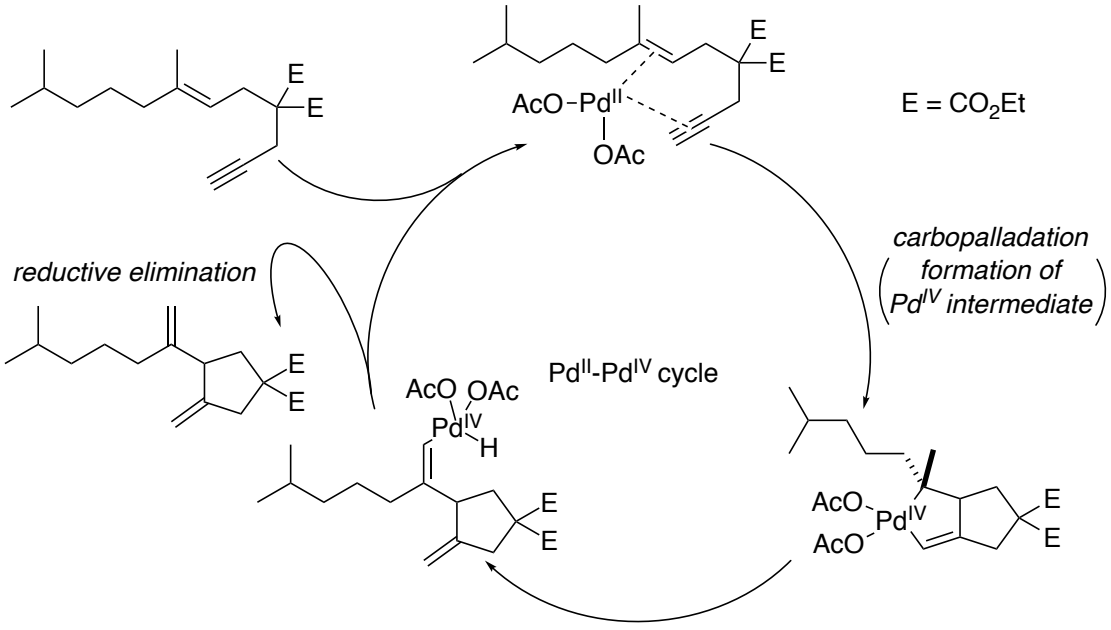
• mechanism 1: Pd^0-Pd^{II} cycle

A, Mekarreya.; P, R, Walker.; A, Couce-Rios.; C, D, Campbell.; A, Steven.; R, S, Paton.; E, A, Anderson. *J. Am. Chem. Soc.* **2017**, 139, 10104.



• mechanism 2: Pd^{II}-Pd^{IV} cycle

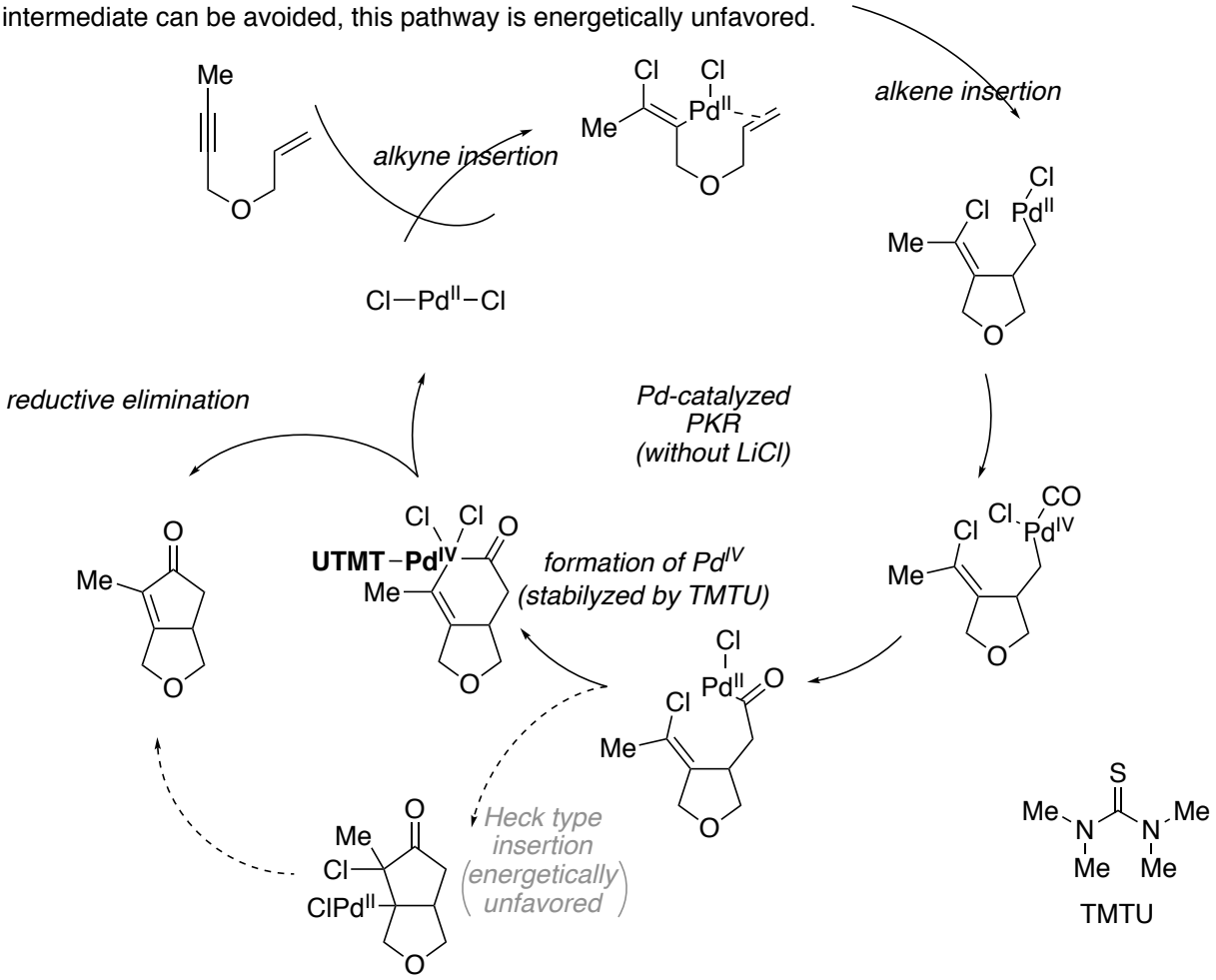
Trost, B. M.; Lautens, M. *Tetrahedron Lett.* **1985**, 26, 4887



2-2. Pd catalyzed Pauson-Khand reaction

In contrast to cycloisomerization, neither $Pd(OAc)_2$ nor $Pd_2(dba)_3$ catalyzes the Pauson-Khand reaction. Only $PdCl_2$ can work as a catalyst in this reaction. In this system, thiourea is frequently used as a ligand to Pd [1].

In Pd catalyzed Pauson-Khand reaction [5], alkyne insertion to $PdCl_2$ occures at first. Stereo/ regioselectivity are determined in the same way as described in section 1. Next, alkene insertion to Pd-complex proceeds to afford 5-membered ring system. After the insertion of CO to Pd-C, cyclopalladation occures to form Pd^{IV} intermediate. DFT calculation shows that the Pd^{IV} intermediate is stabilized by thiourea, an electron donating ligand. Although an alternative pathway involving Heck type alkene insertion seems to be reasonable in that the formation of Pd^{IV} intermediate can be avoided, this pathway is energetically unfavored.



Y. Lan.; L, Deng.; J, Liu.; C, Wang.; O, Wiest.; Z, Ynag.; Y, D, Wu. *J. Org. Chem.* **2009**, 74, 5049.

Reference

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3. A, Mekarreya.; P, R, Walker.; A, Couce-Rios.; C, D, Campbell.; A, Steven.; R, S, Paton.; E, A, Anderson. *J. Am. Chem. Soc.* **2017**, 139, 10104.
4. Trost, B. M.; Lautens, M. *Tetrahedron Lett.* **1985**, 26, 4887
5. Y. Lan.; L, Deng.; J, Liu.; C, Wang.; O, Wiest.; Z, Ynag.; Y, D, Wu. *J. Org. Chem.* **2009**, 74, 5049.