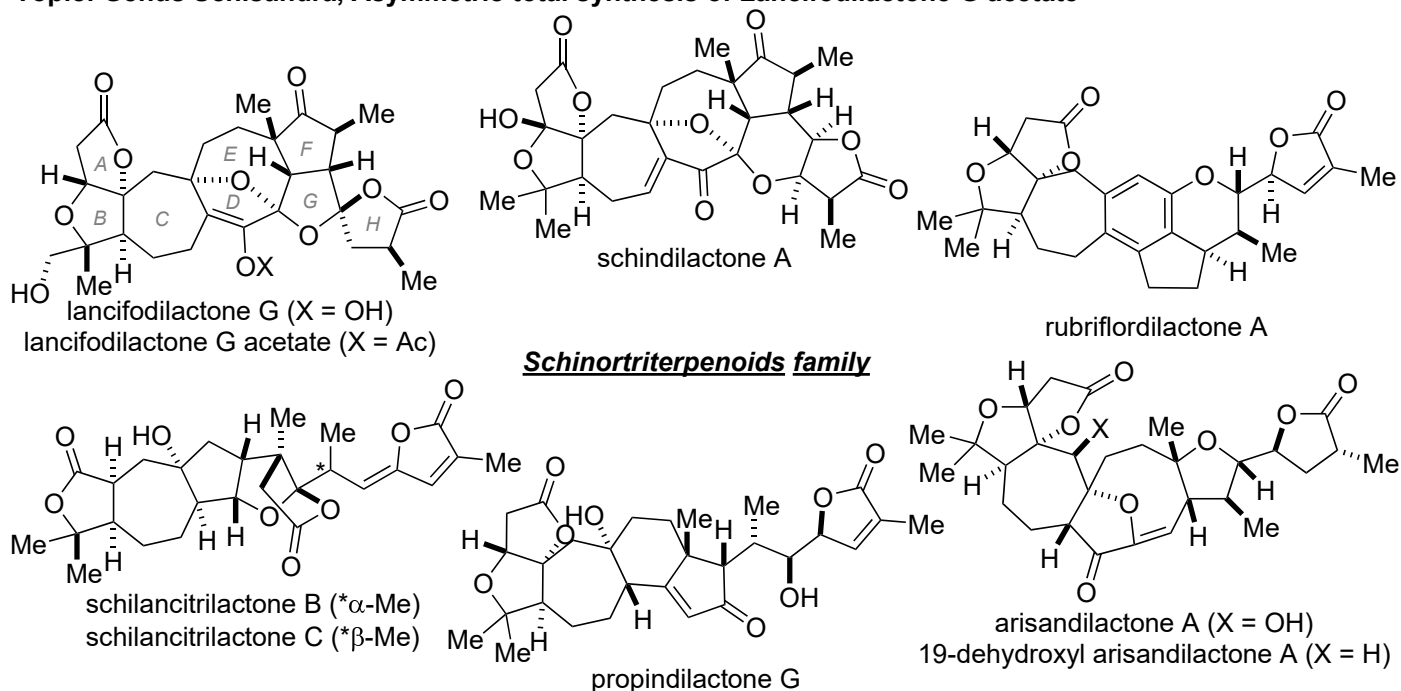


## Problem session (5) - Answer

Topic: Genus *Schisandra*, Asymmetric total synthesis of Lancifodilactone G acetate



### Isolation of lancifodilactone G:

from the medical plant *Schisandra lancifolia*.

(Zheng, Q.-T. *et al. Org. Lett.* **2005**, 7, 2145.)

the original structural assignment has been revised by X-ray crystallographic analysis.

(Zheng, Q. T. *et al. Org. Lett.* **2006**, 8, 801.)

### Structural features of lancifodilactone G:

· unusual 7/5/7-tricyclic ring (CDE), highly congested FGH tricyclic ring, 12 stereocenters

### Bioactivity of Schinortriterpenoids:

exhibit antihepatitis, antitumor, and anti-HIV agents.

(Shi, Y.-M.; Xiao, W.-L.; Pu, J.-X.; Sun, H.-D. *Nat. Prod. Rep.* **2015**, 32, 367.)

### Total synthesis of Schinortriterpenoids:

· (±)-schindilactone A (Yang, Z. *et al. Angew. Chem. Int. Ed.* **2011**, 50, 7373.)

(160123\_LS\_Yinghua\_Wang)

· Rubriflorldilactone A (Li, A. *et al. J. Am. Chem. Soc.* **2014**, 136, 16477.)

(160123\_LS\_Yinghua\_Wang)

· Rubriflorldilactone A (Anderson, E. A. *et al. Angew. Chem. Int. Ed.* **2015**, 54, 12618.)

(160123\_LS\_Yinghua\_Wang)

· Propindilactone G (Yang, Z. *et al. J. Am. Chem. Soc.* **2015**, 137, 10120.)

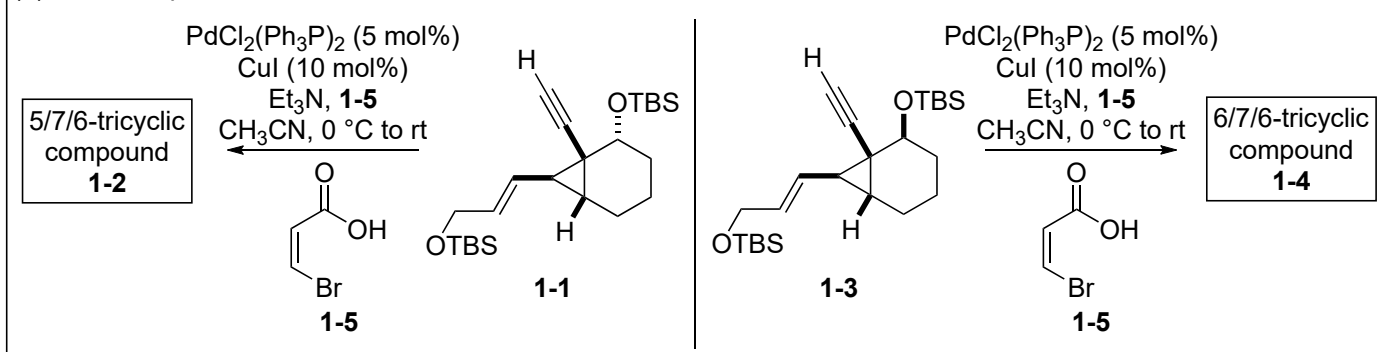
· Schilancitrilactone B and C (Tang, P. *et al. Angew. Chem. Int. Ed.* **2015**, 54, 5732.)

(170506\_PS\_Haruka\_Fujino)

· 19-dehydroxyl arisandilactone A (Yang, Z. *et al. Nat. Commun.* **2017**, 8, 14233.)

(170506\_PS\_Haruka\_Fujino)

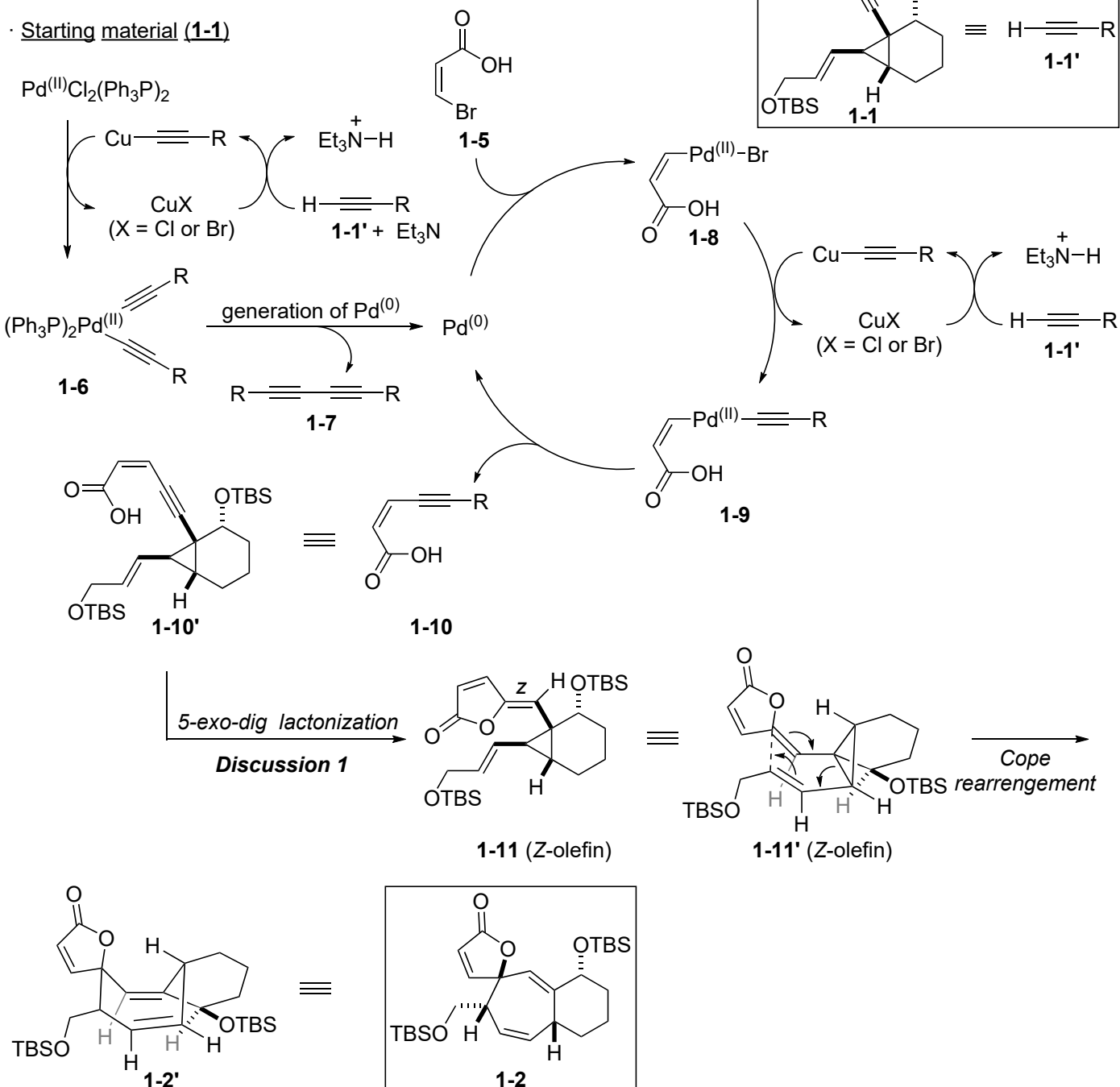
(1) Please expect the structure of **1-2** and **1-4**



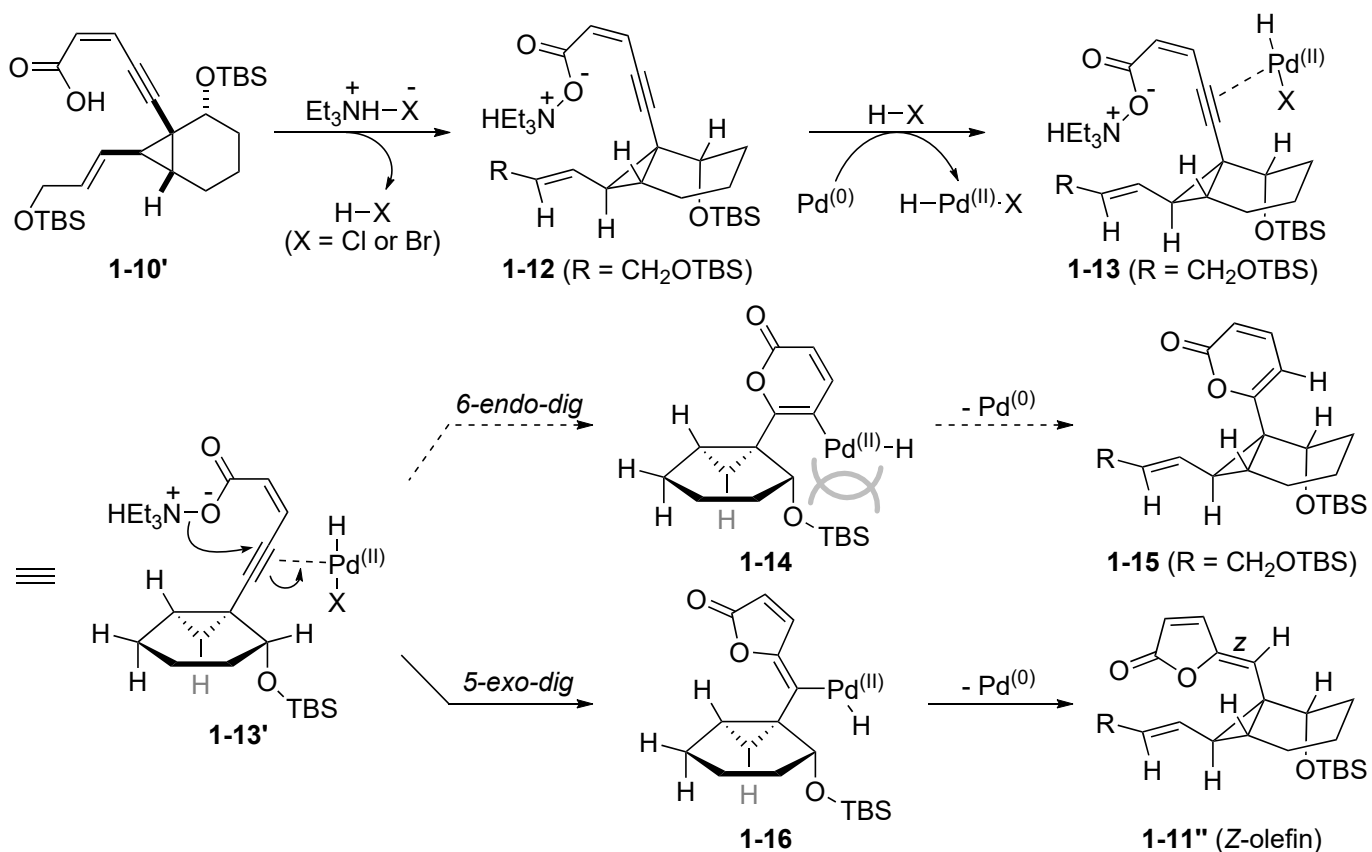
Answer

Sonogashira cross coupling / lactonization / Cope rearrangement

· Starting material (**1-1**)

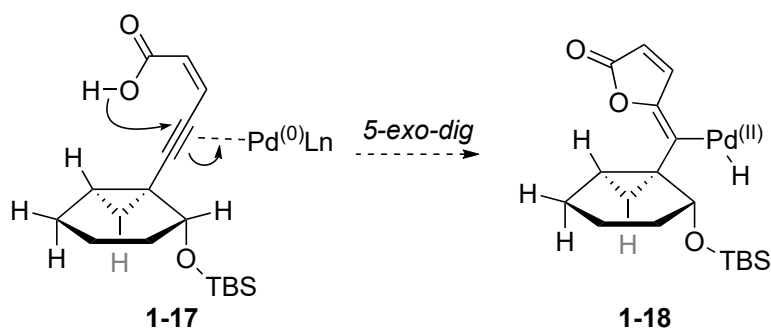


**Discussion 1 (5-exo-dig lactonization)**

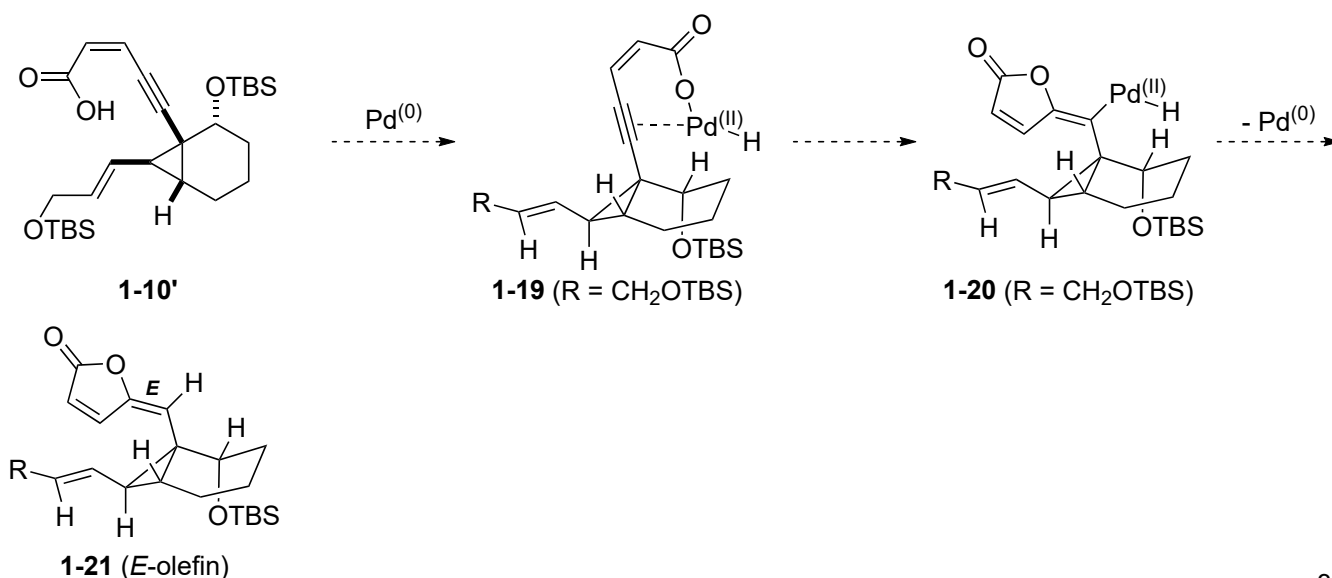


The reaction mechanism which Pd<sup>(II)</sup> is generated is proposed because....

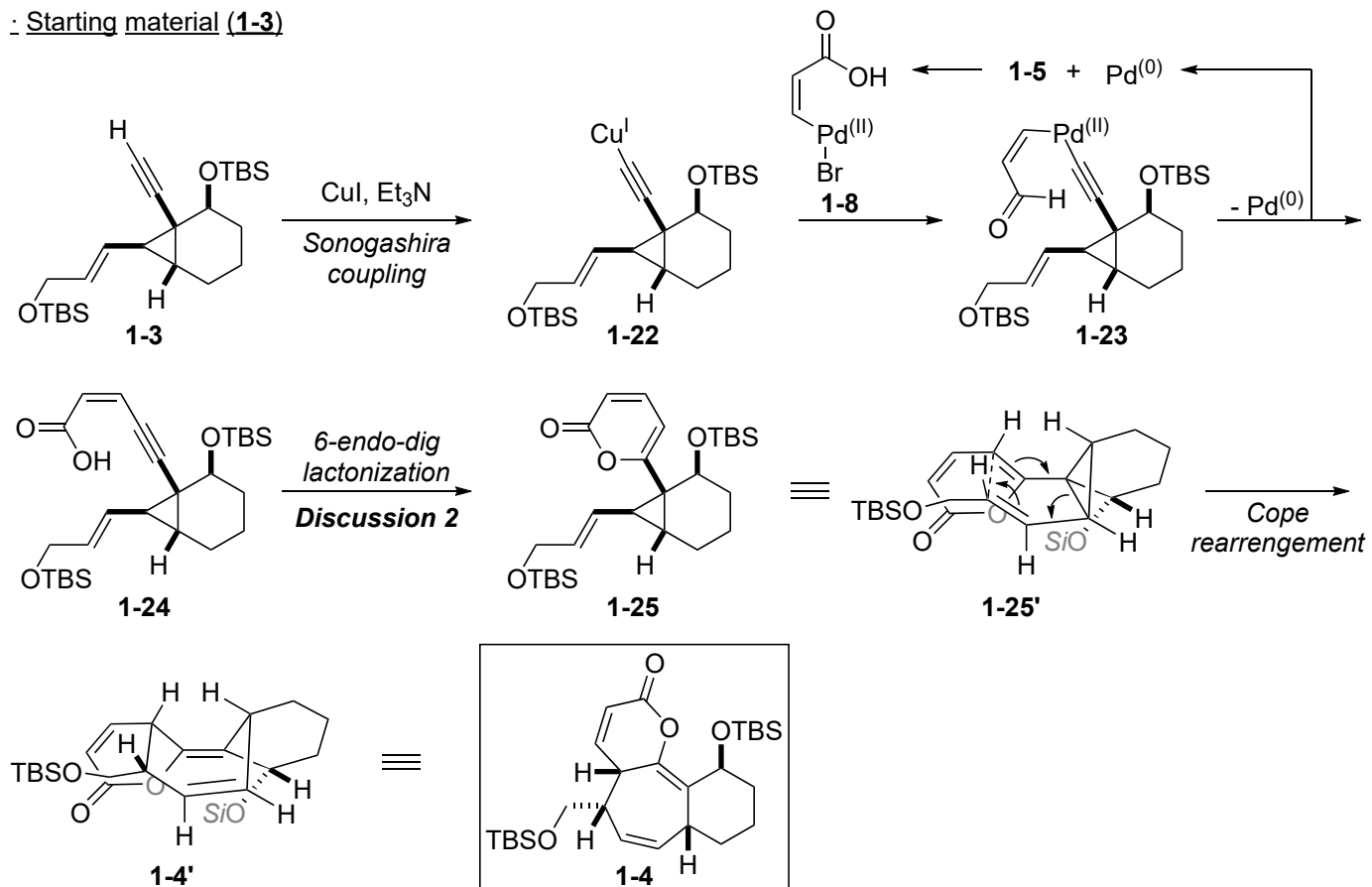
(1) Pd<sup>(0)</sup> is difficult to behave like Lewis acid



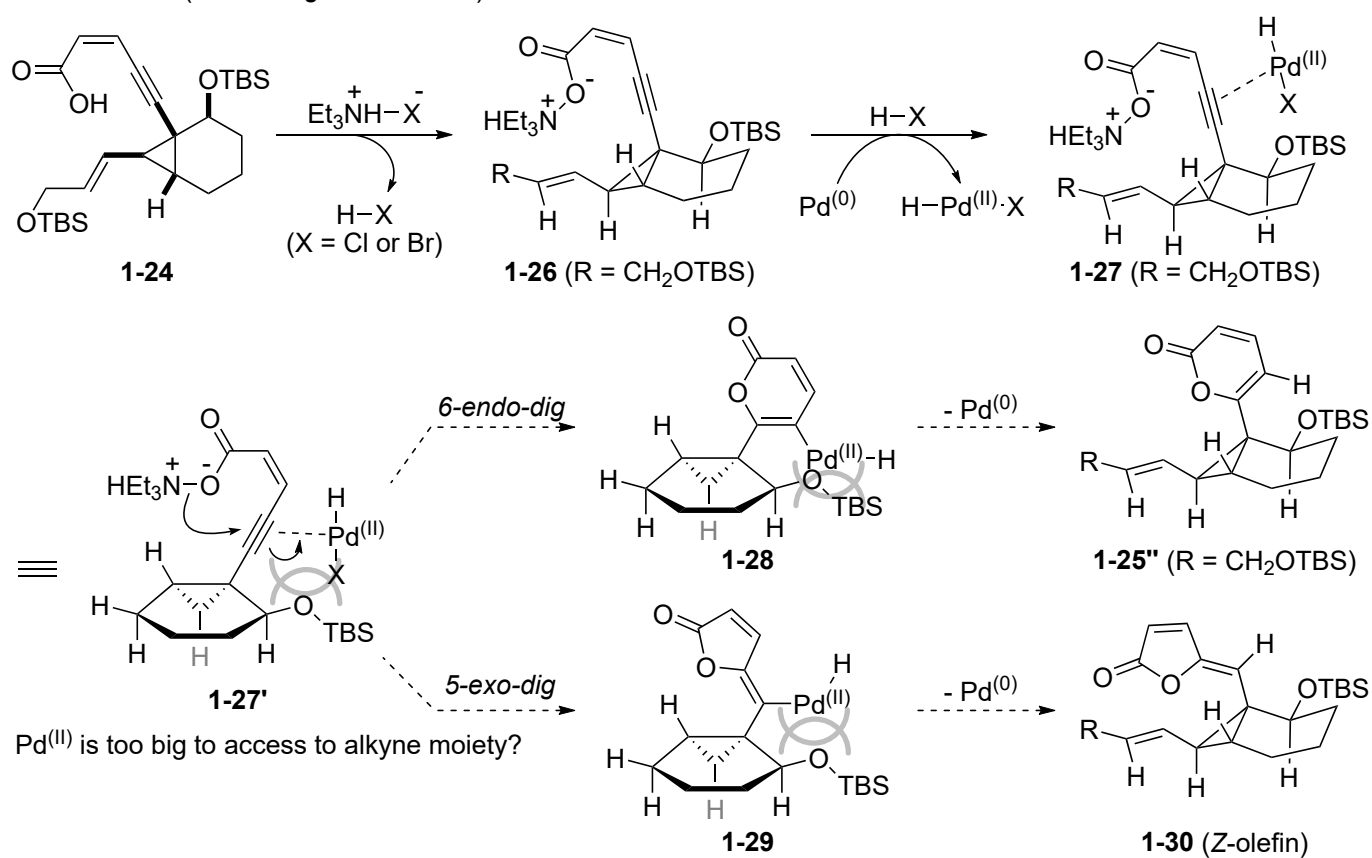
(2) If the oxidative addition to carboxylic group proceed....  
after lactonization, compound **1-X** (E-olefin) must be obtained.



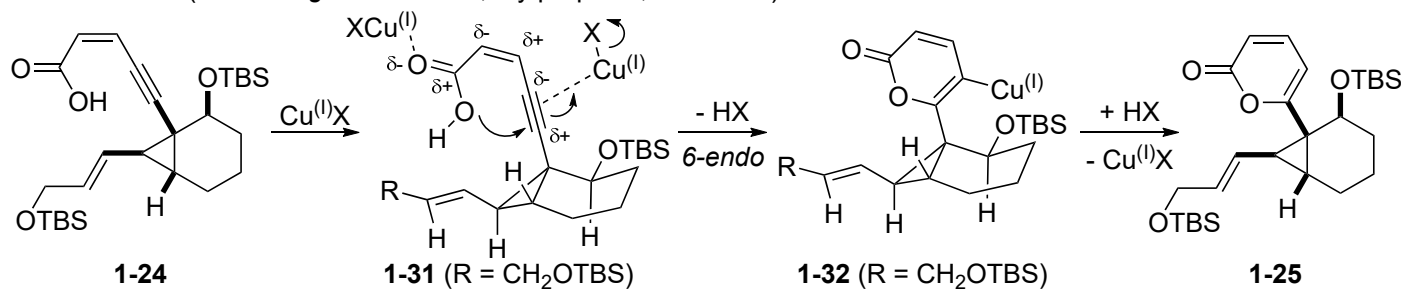
: Starting material (1-3)



**Discussion 2** (6-endo-dig lactonization)



**Discussion 2 (6-endo-dig lactonization, my proposal, continued)**



· Cu(I)-catalyzed 6-endo lactonization

1. Effect of Copper iodide (NOT carboxylic acid)

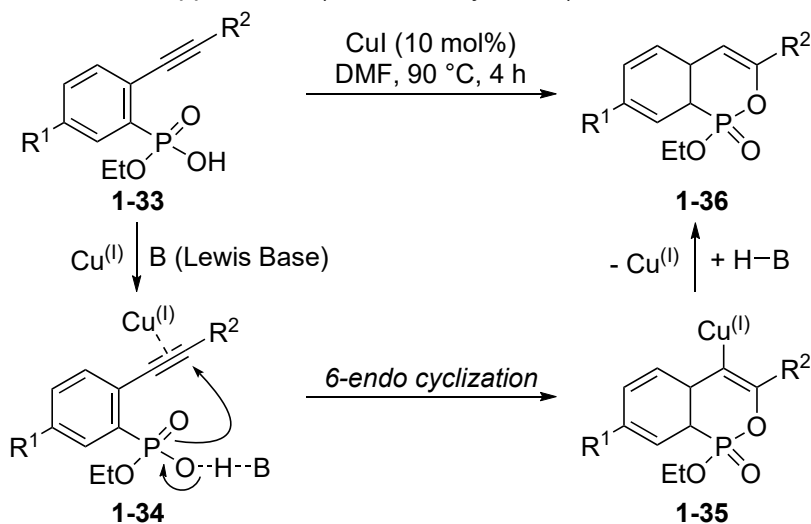
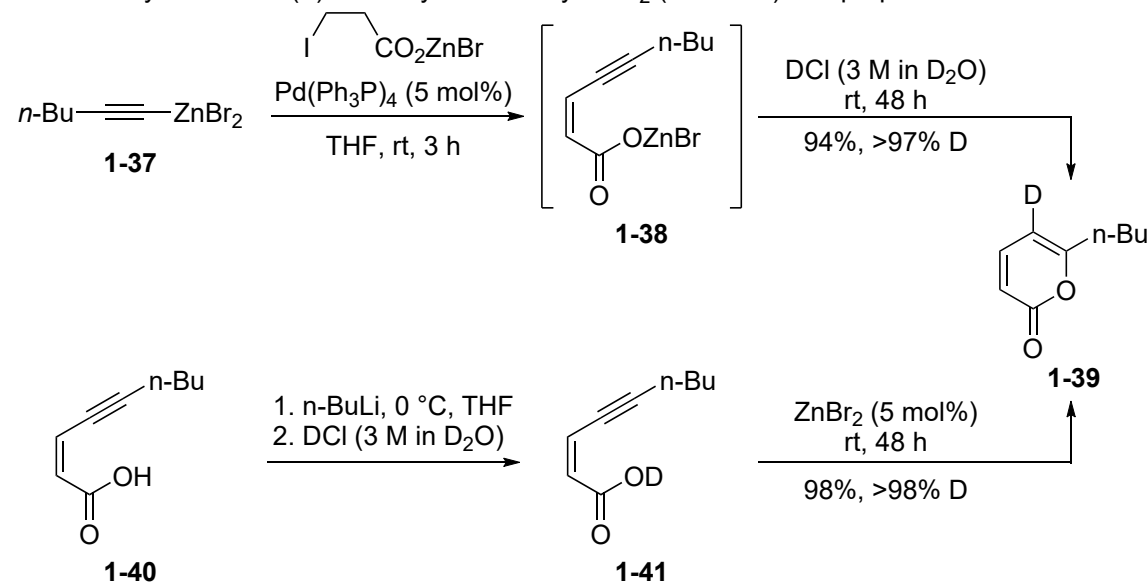


Table 1 (Cu(I)-catalyzed lactonization)

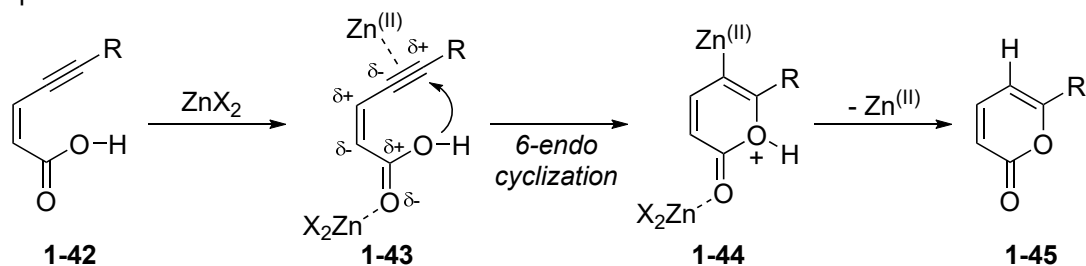
entry	R <sup>1</sup>	R <sup>2</sup>	yield
1	H	<i>n</i> -Bu	79%
2	OMe	C <sub>6</sub> H <sub>5</sub>	88%
3	NO <sub>2</sub>	<i>p</i> -CH <sub>3</sub> CH <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	60%

Peng, A-Y.; Ding, Y-X. *J. Am. Chem. Soc.* **2003**, *125*, 15006.

2. 6-endo cyclization of (Z)-2-en-4-ynoic acid by ZnBr<sub>2</sub> (NOT CuI) and proposed mechanism in acidic condition.

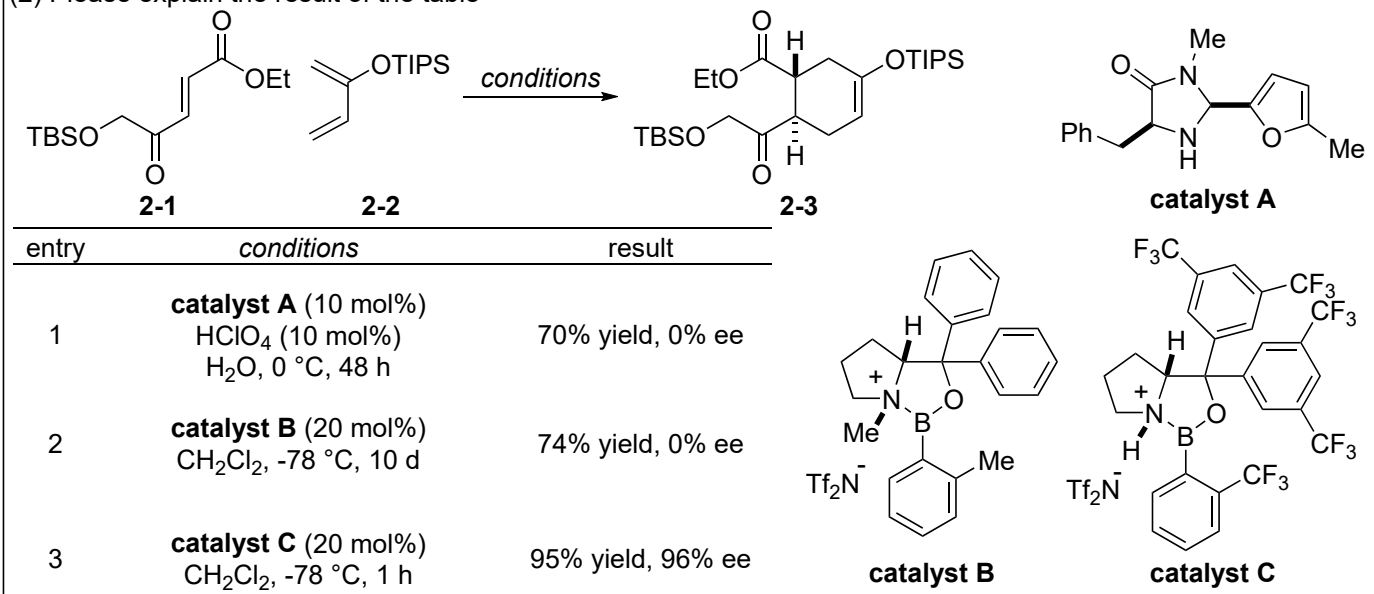


Proposed mechanism in acidic condition.

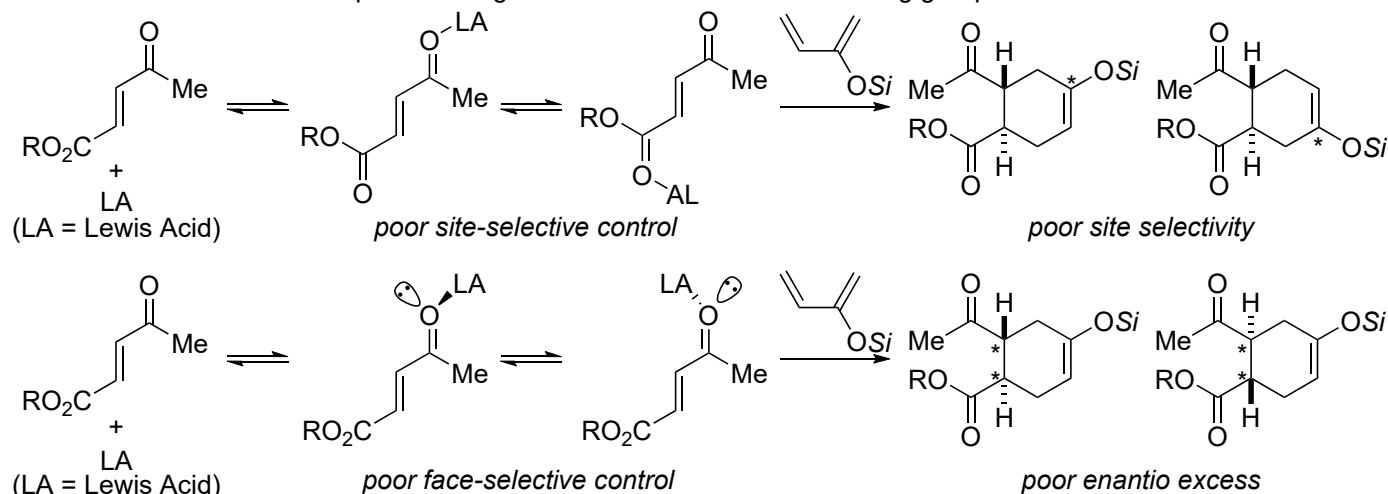


Anastasia, L.; Xu, C.; Negishi, E. *Tetrahedron Lett.* **2002**, *43*, 5673.

(2) Please explain the result of the table



Diels-Alder reaction of dienophile bearing two different electron-withdrawing groups



Entry 1 (MacMillan's catalyst, cf. 110618\_LS\_Ken\_Mukai)

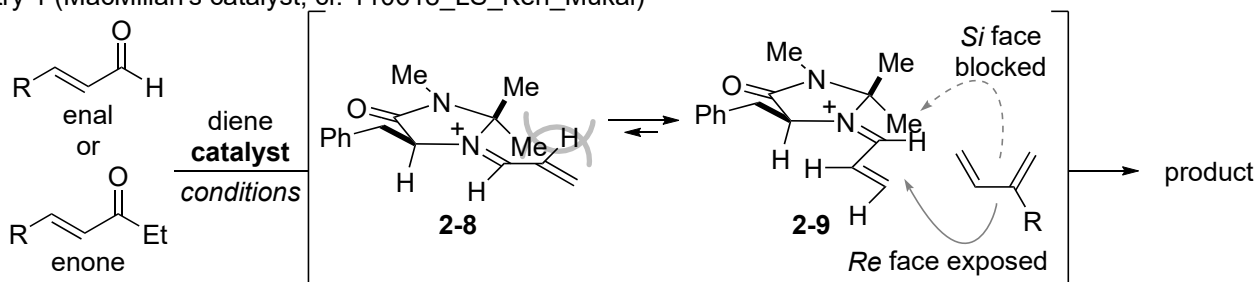


Table 2 (Example of Diels-Alder reaction with MacMillan's catalyst)

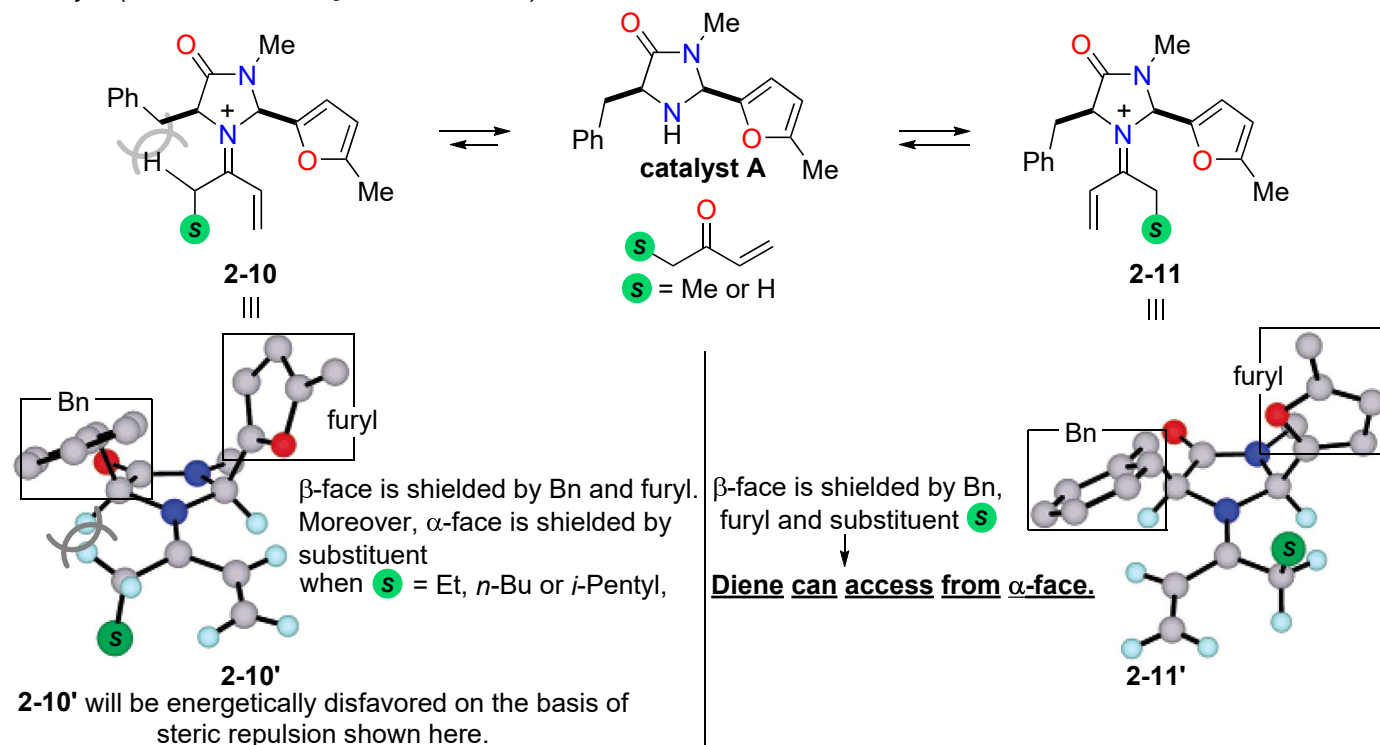
entry	dienophile	diene	conditions	result
1			<b>catalyst 2-M</b> (20 mol%) MeOH/H <sub>2</sub> O 23 °C, 31 h	 75% yield, 90% ee
2			<b>catalyst A</b> (20 mol%) HClO <sub>4</sub> (20 mol%) EtOH, -40 °C, 10 h	 92% yield, 90% ee

Chemical structure of **catalyst 2-M** is shown in a separate box.

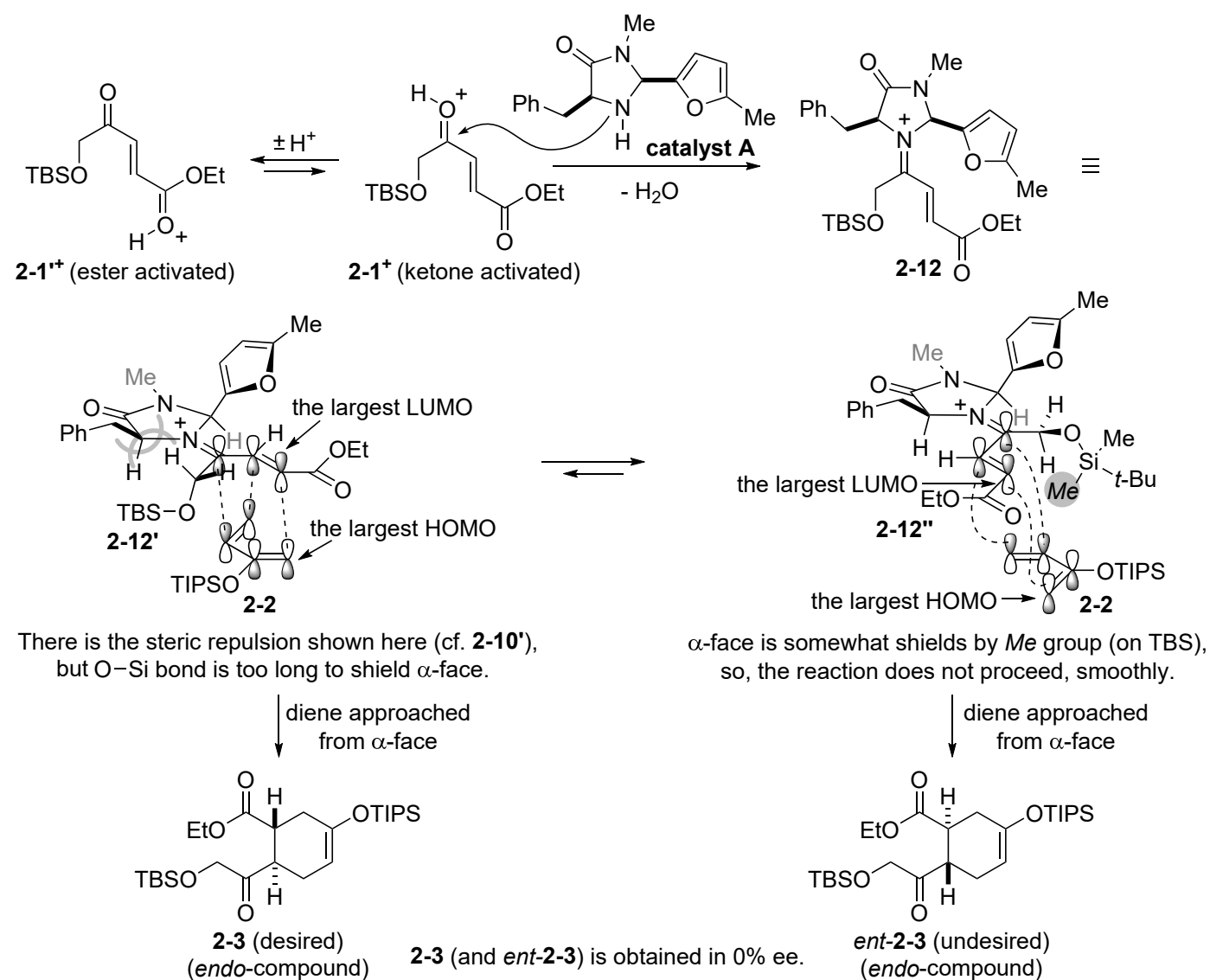
Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243.

Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458. - 6 -

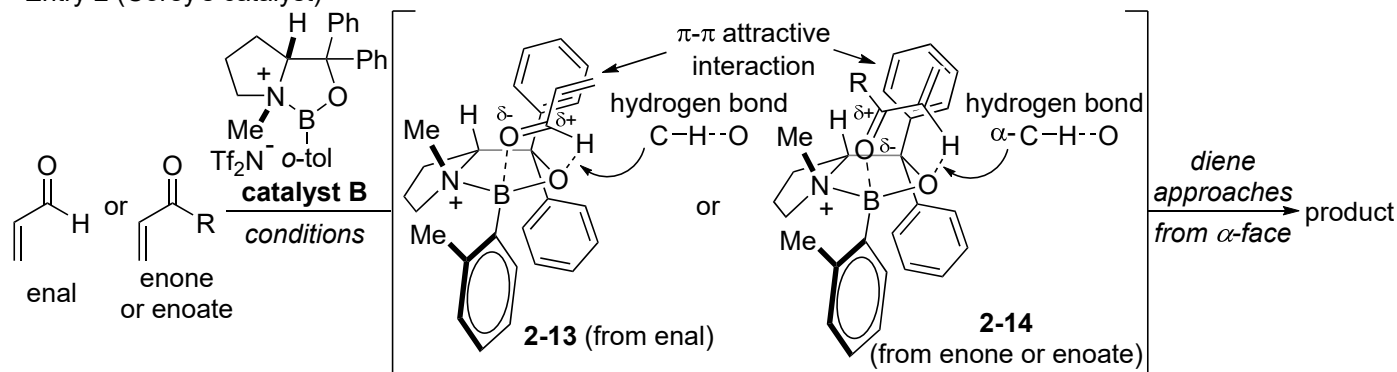
· Entry 1 (MacMillan's **catalyst A**, continued)



· Answer of Entry 1 (MacMillan's **catalyst A**)



· Entry 2 (Corey's catalyst)



If the positivity ( $\delta^+$ ) of the carbonyl carbon is higher (in this case)...

pKa value of  $\alpha$ -H becomes smaller.

Hydrogen bond  $\alpha$ -C-H...O becomes shorter (stronger)

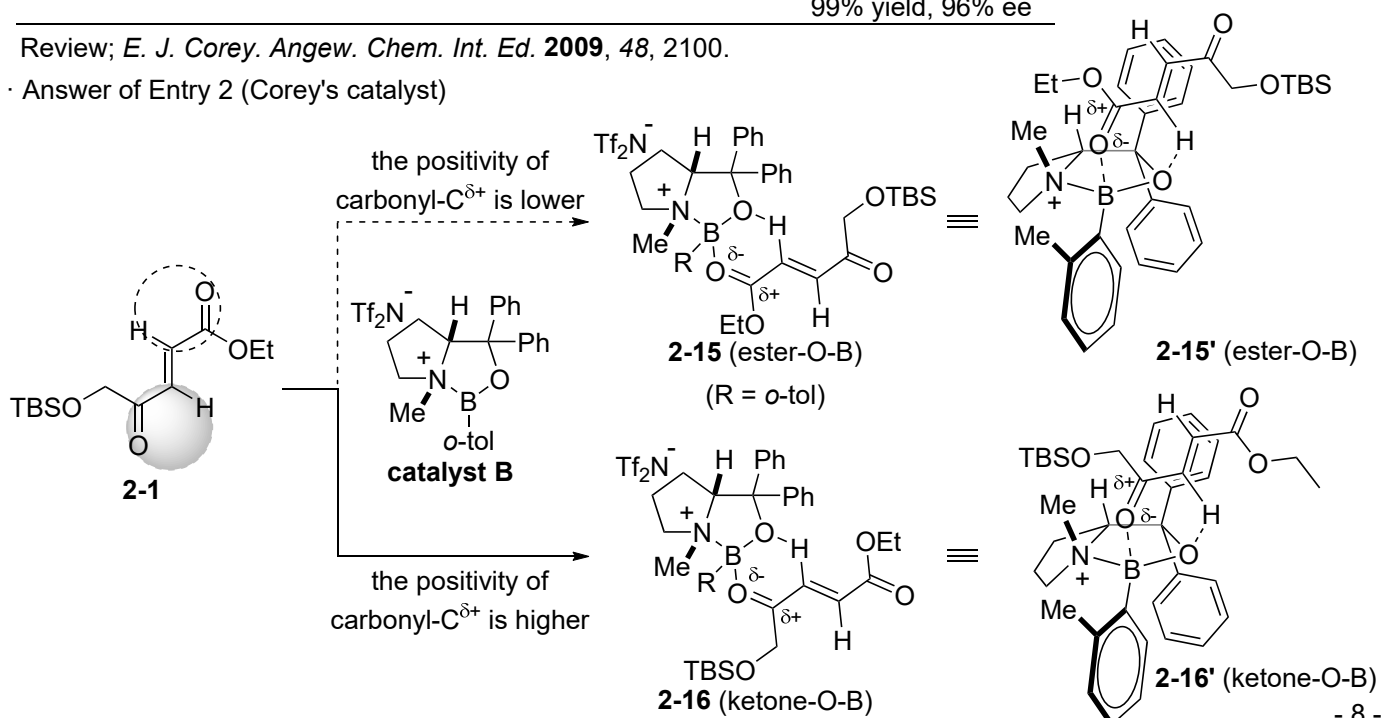
my proposal:  $\pi$ - $\pi$  attractive interaction (from Ph to  $C^{\delta+}$ ) becomes stronger. The stacking becomes rigid. Higher ee can be expected?

Table 3 (Example of Diels-Alder reaction with Corey's **catalyst B**)

entry	dienophile	diene	conditions	result
1			<b>catalyst B</b> (10 mol%) CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 1.5 h	 96% yield, 90% ee
2*			<b>catalyst B</b> (10 mol%) CH <sub>2</sub> Cl <sub>2</sub> , -78 °C, 1 h	 97% yield, 98% ee *entry 2 cf. (151016_PS_Kotaro_TOKUMOTO)
3			<b>catalyst B</b> (10 mol%) CH <sub>2</sub> Cl <sub>2</sub> , -60 °C, 8 h	 99% yield, 96% ee

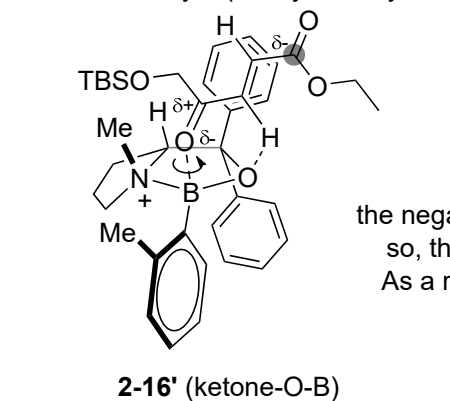
Review; E. J. Corey. *Angew. Chem. Int. Ed.* **2009**, 48, 2100.

· Answer of Entry 2 (Corey's catalyst)

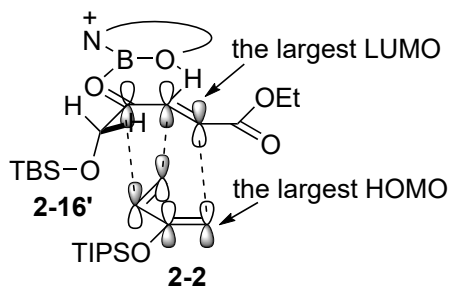
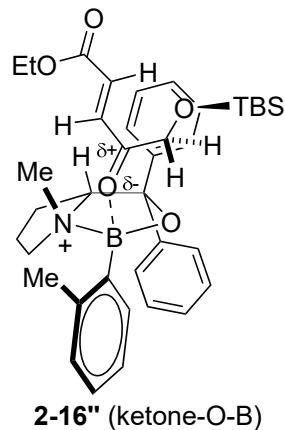




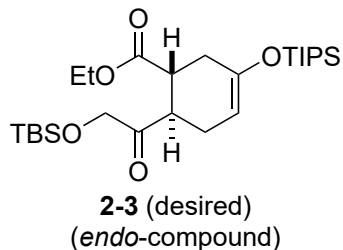
· Answer of Entry 2 (Corey's catalyst, continued)



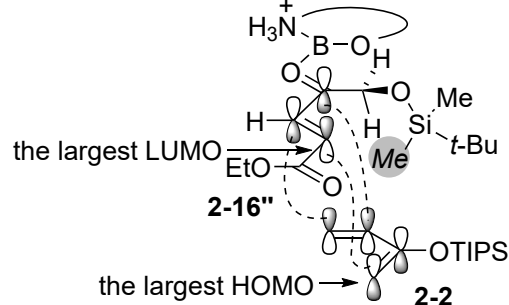
the negativity of carbonyl-C of ester moiety is high, so, the rigidity of  $\pi$ - $\pi$  stacking becomes weak. As a result, B-O coordinated bond can rotate.



diene approached from  $\alpha$ -face

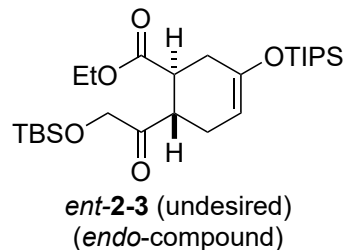


**2-3** (and *ent*-**2-3**) is obtained in 0% ee.

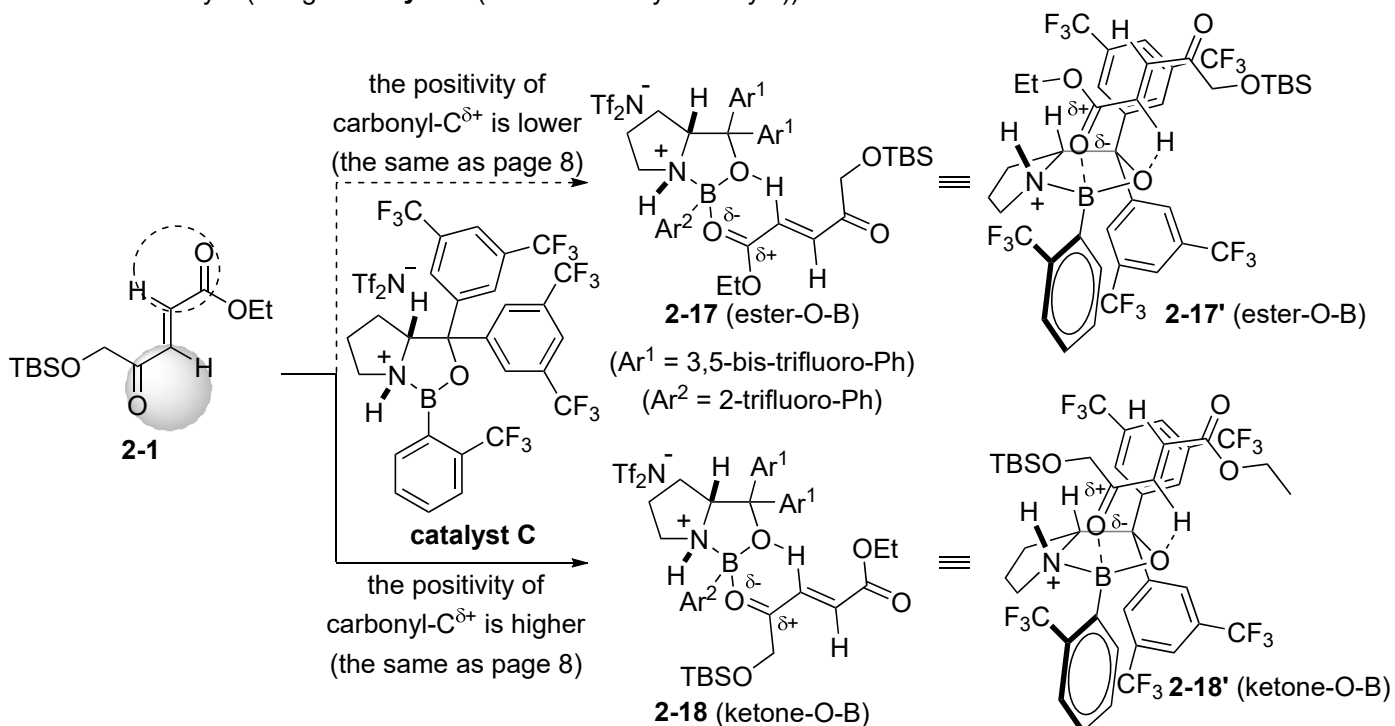


$\alpha$ -face is somewhat shields by Me group, so, the reaction does not proceed, smoothly

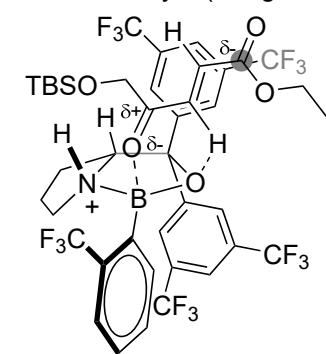
diene approached from  $\alpha$ -face



· Answer of Entry 3 (Yang's **catalyst C** (modified Corey's catalyst))



· Answer of Entry 3 (Yang's **catalyst C**, continued)

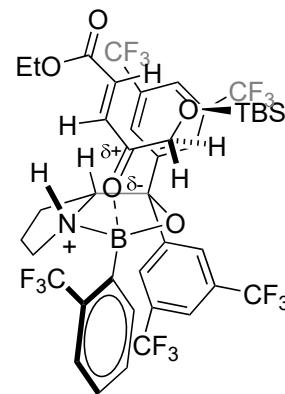


**2-18'** (ketone-O-B)

Because of the effect of electron withdrawing CF<sub>3</sub> groups, the electron density on the aryl rings is decreased.

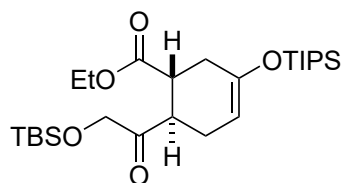
As a result,

1. enhance coordination of B-O=C
2. the effect of  $\alpha$ -C-H-O hydrogen bond increases.
3.  $\pi$ - $\pi$  stacking becomes strong from ester C $\delta^-$  to Ar

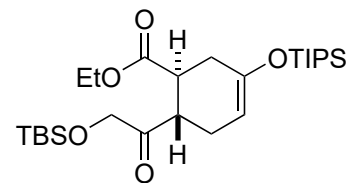


**2-18''** (ketone-O-B)

↓ diene approached from  $\alpha$ -face



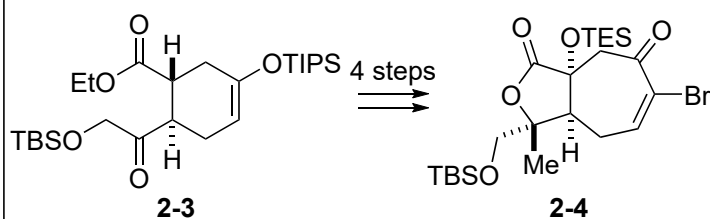
**2-3** (desired)  
(endo-compound)



**ent-2-3** (undesired)  
(endo-compound)

**2-3** is obtained in 96% ee.

(2) Please fill in the blank (continued).



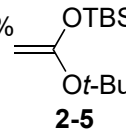
1) **2-5**  
PdCl<sub>2</sub>[P(o-tol)<sub>3</sub>]<sub>2</sub> (cat.)  
CuF<sub>2</sub>, THF, reflux, 77%

2) Pd/C, H<sub>2</sub>, EtOAc  
50 °C, 97%

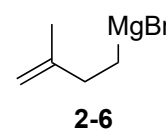
3) **2-6**  
THF, -78 to 0 °C, 84%

4) LiN(TMS)<sub>2</sub>, LiCl  
MoOPH, THF  
-78°C, 85%

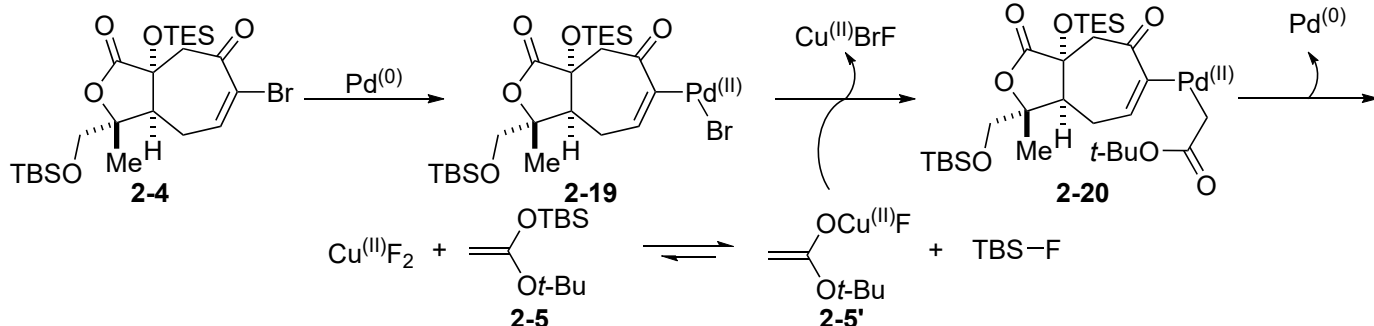
tricyclic compound  
**2-7**



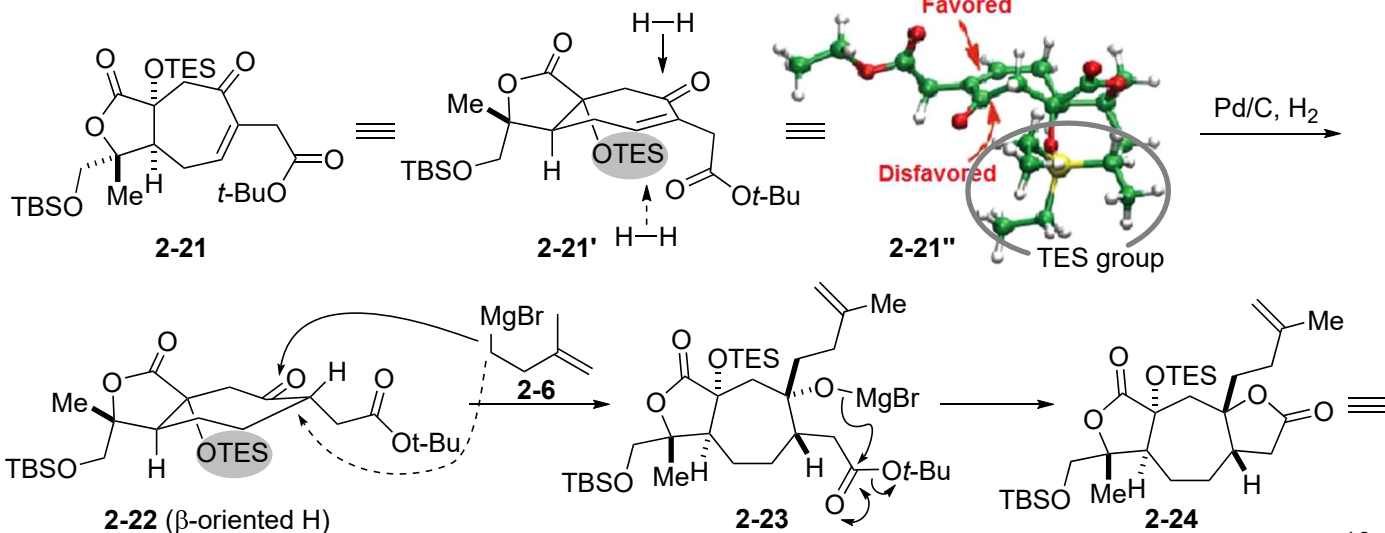
**2-5**



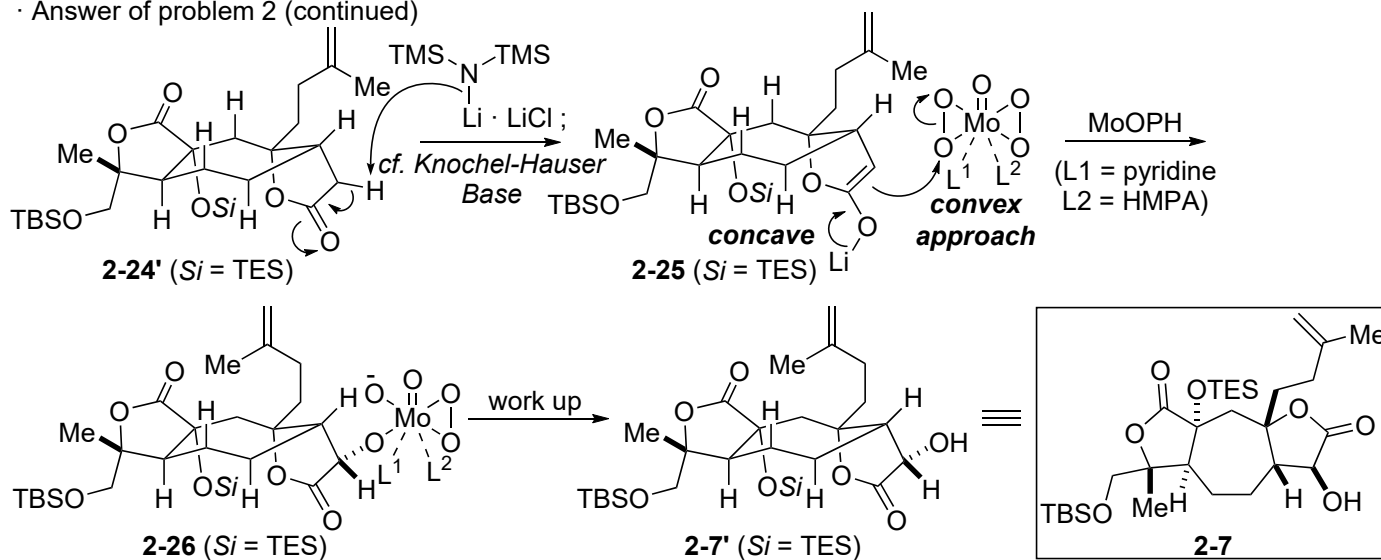
**2-6**



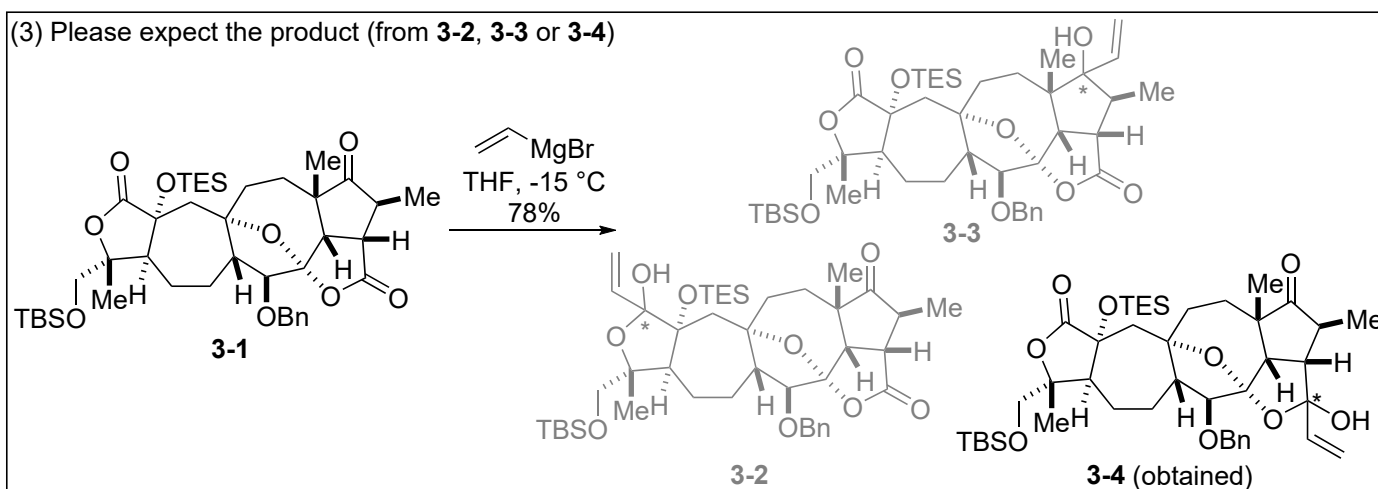
Agnelli, F.; Sulikowski, G. A. *Tetrahedron Lett.* **1998**, *39*, 8807.



· Answer of problem 2 (continued)



(3) Please expect the product (from 3-2, 3-3 or 3-4)

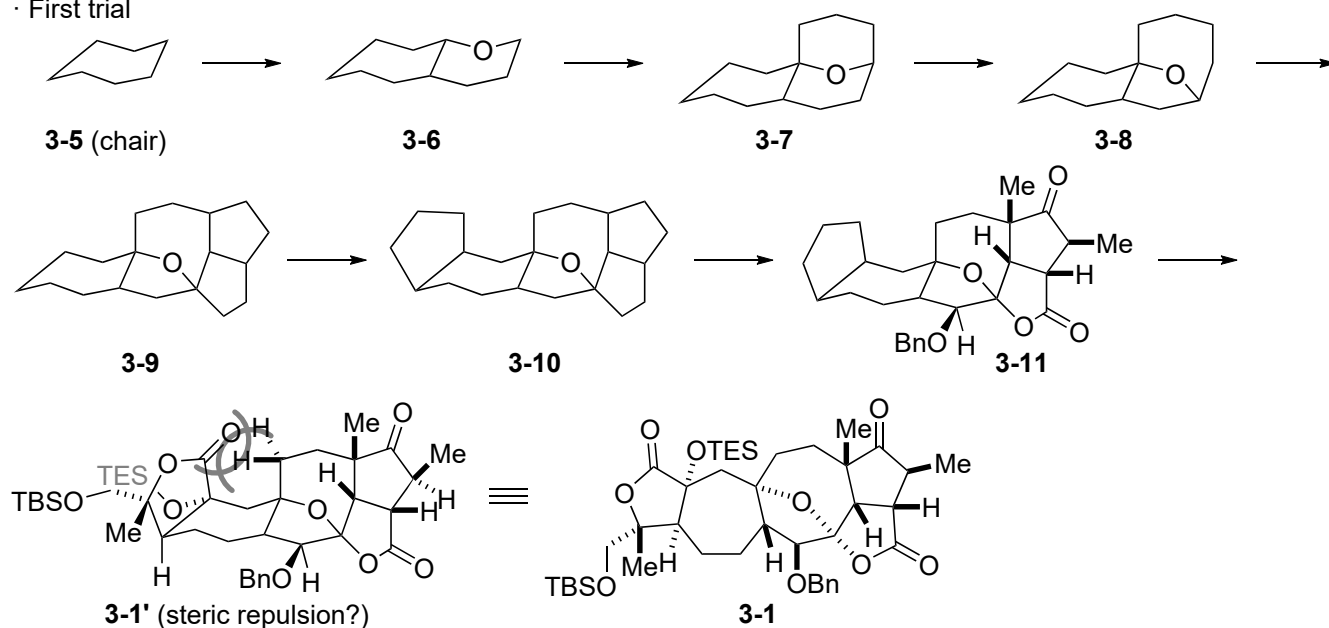


· Answer (proposed way of drawing)

First of all, I wrote chair-form 7-membered ring because...

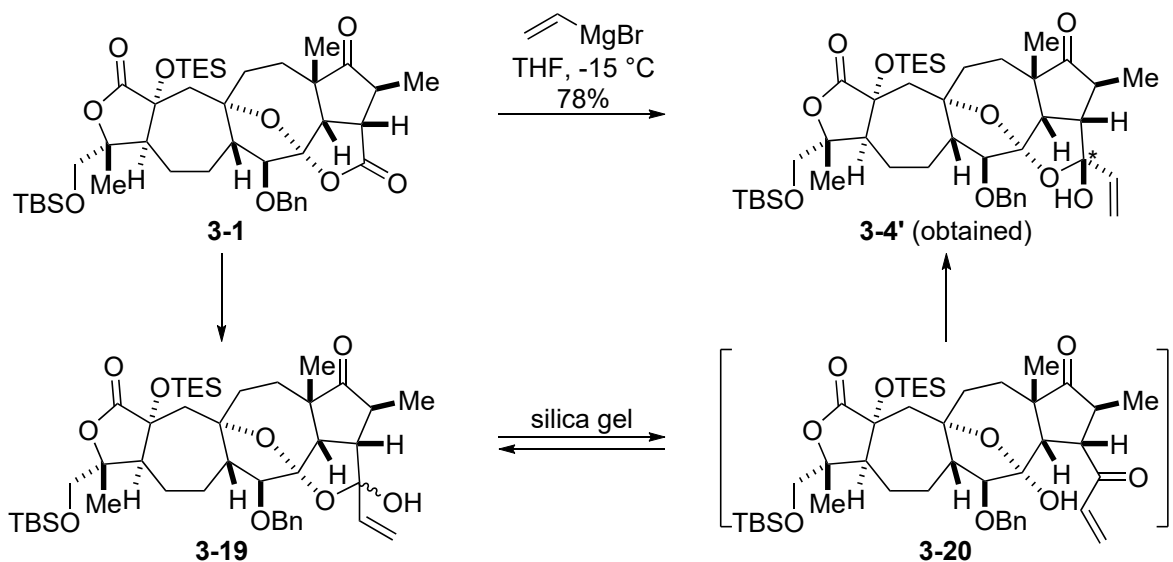
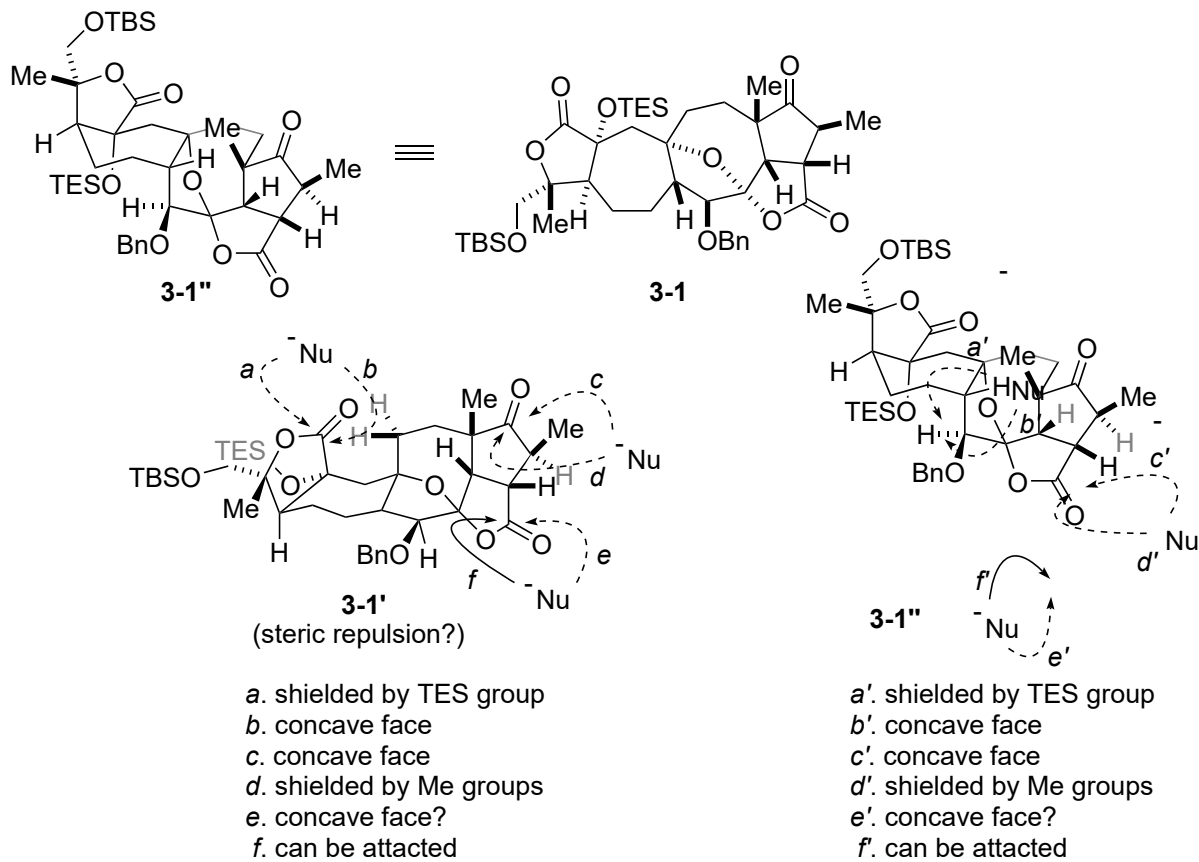
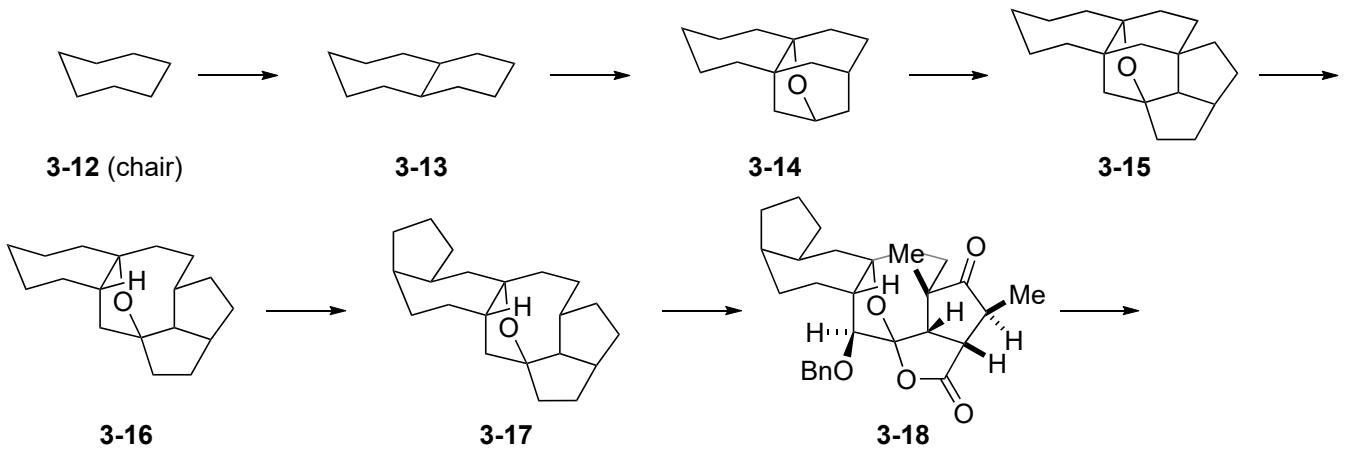
1. the ring locates in the middle of the structure of 3-1
2. the bigger the ring is, the more we need to consider the most stable conformations.

· First trial

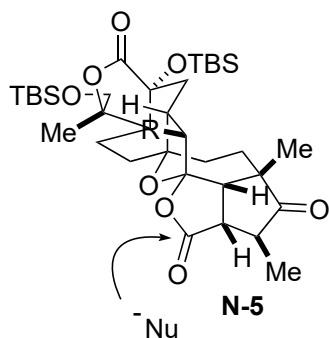
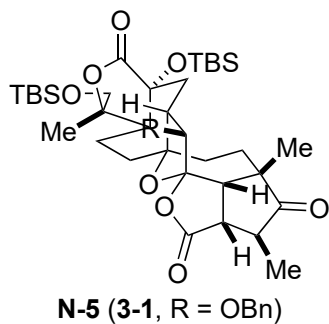
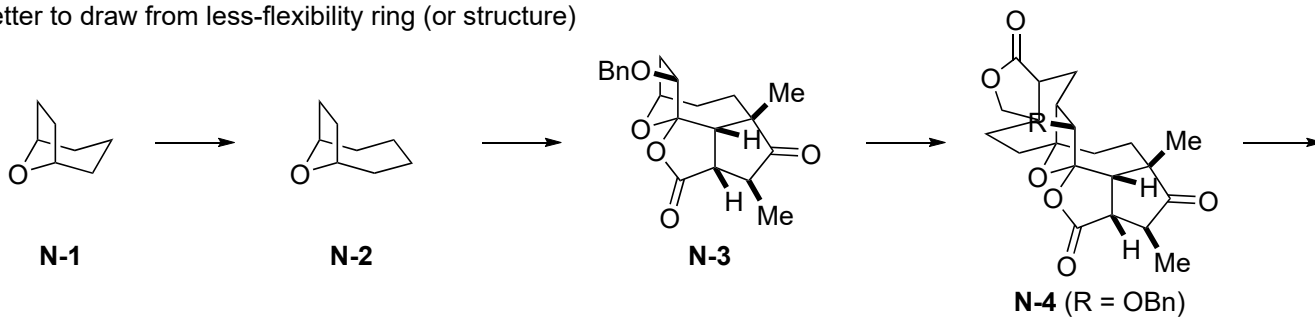


· Answer of problem 3 (continued)

· Second trial



· Nagatomo-san's proposal  
Better to draw from less-flexibility ring (or structure)



easy to access from convex face