

Problem Session (4) -Answer-

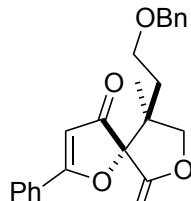
2022.5.28. Yuto Hikone

1



1. lithium acetylide (0.5 M THF solution, 2.8 eq)
THF, -78 °C, 92% (dr = 3:1)*

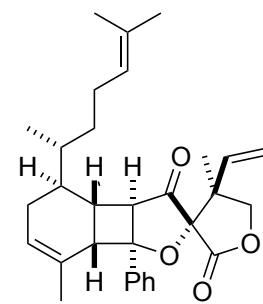
2. PhI (1.2 eq), Pd(PPh₃)₄ (5 mol%)
CO (14 atm), CO₂ (14 atm)
Et₃N (1.2 M), 100 °C, 79%



* Major diastereomer was used at the next step.

1-1

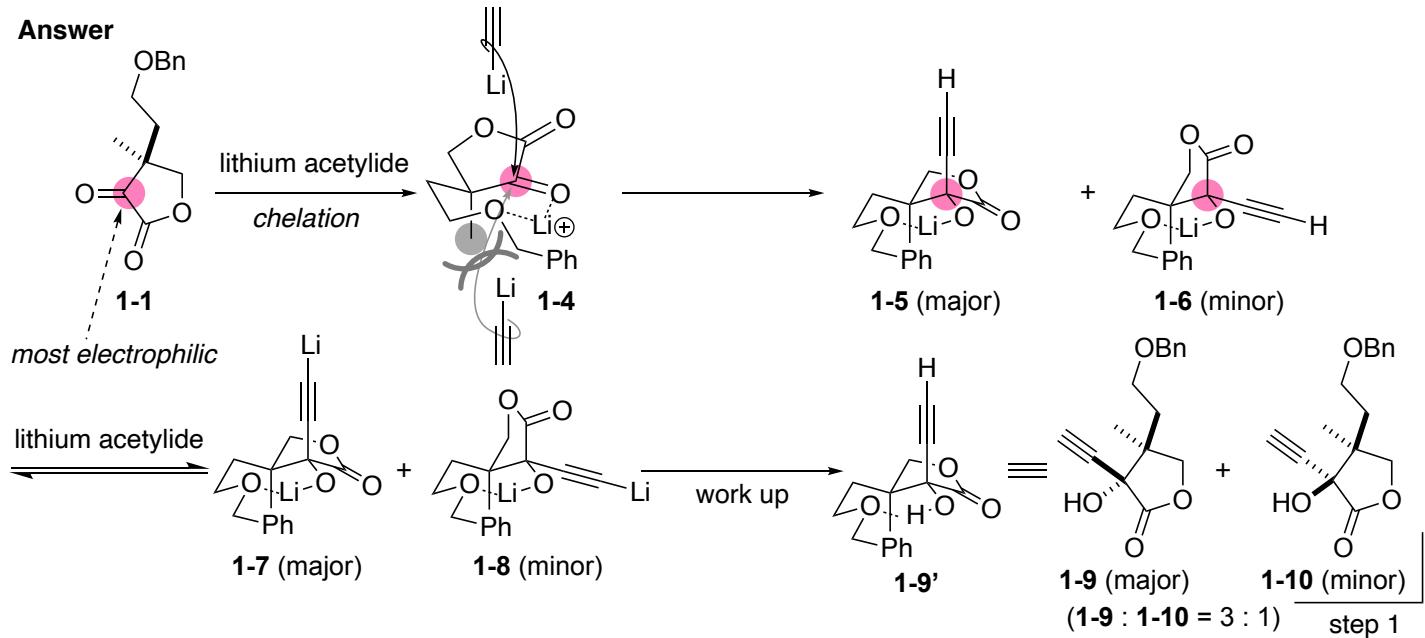
1-2



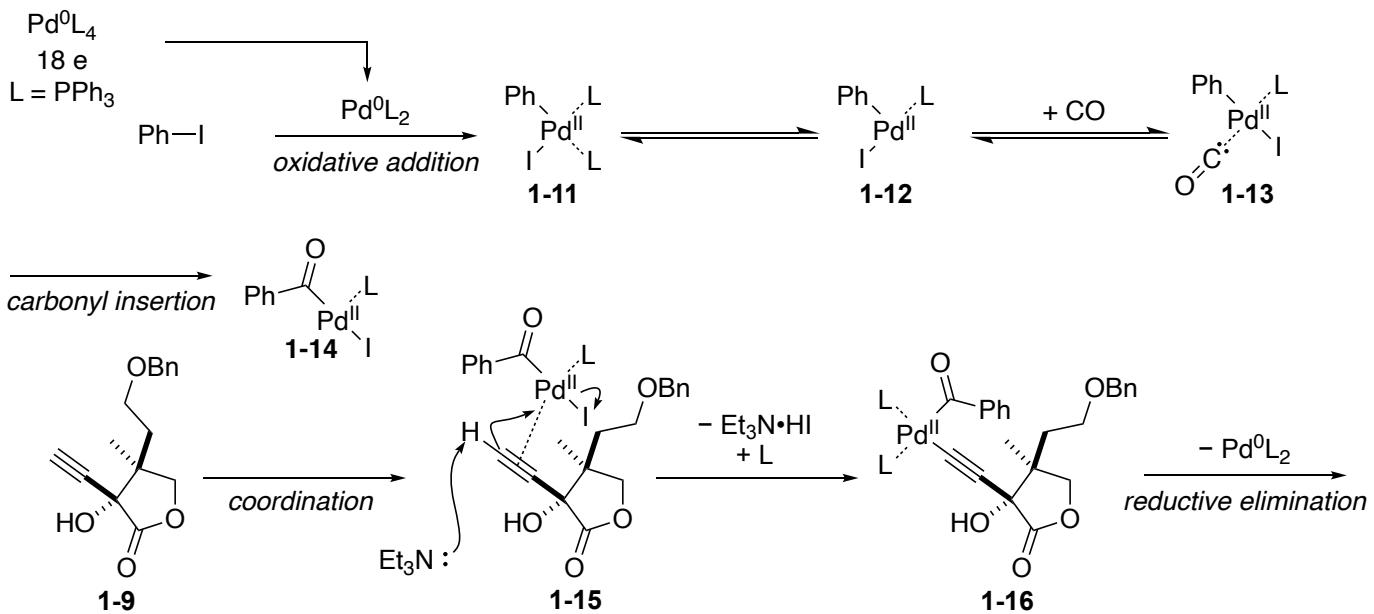
1-3
biyouyanagin A

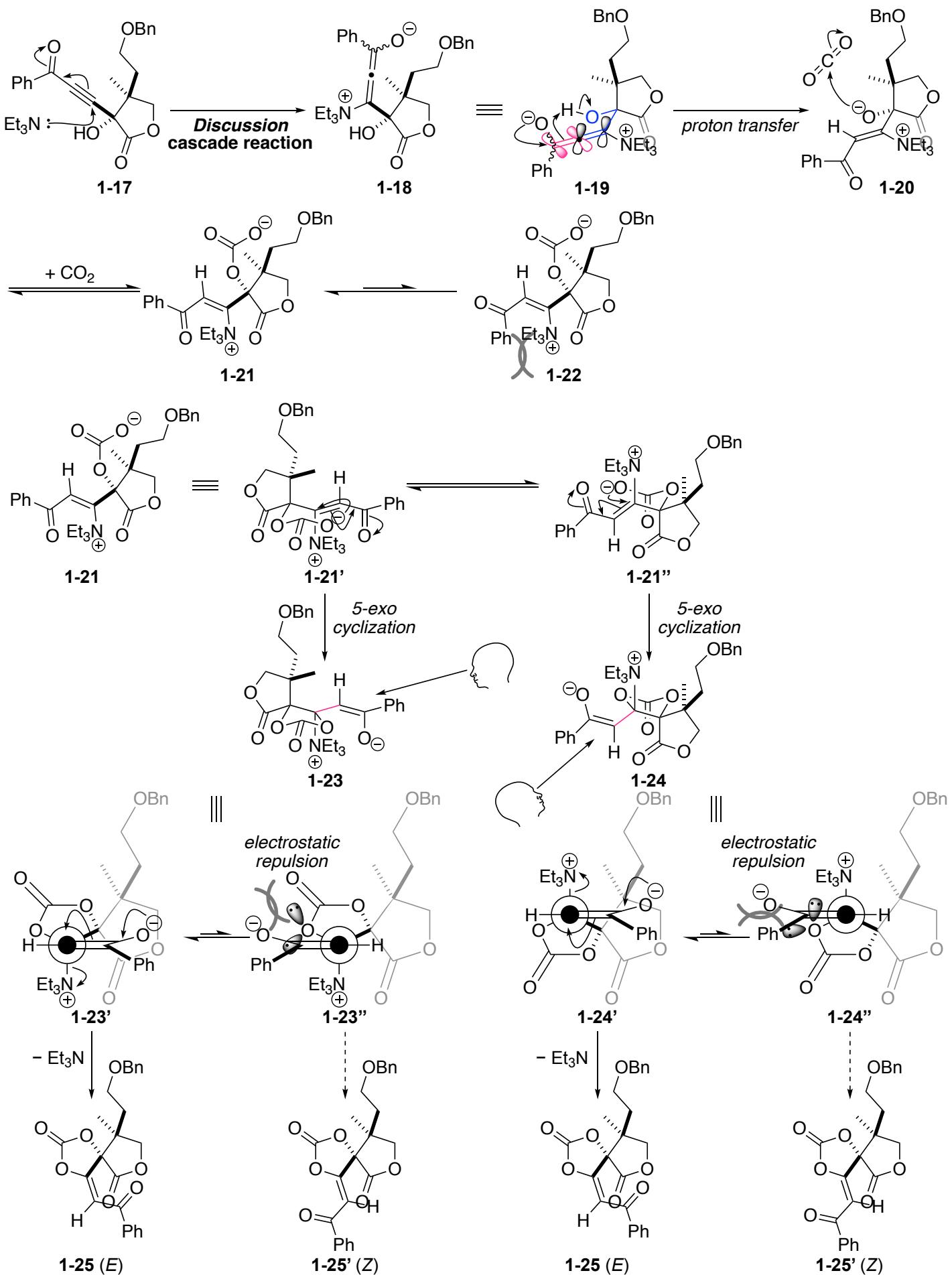
Nicolaou, K. C.; Wu, T. R.; Sarlah, D.; Shaw, D. M.; Rowcliffe, E.; Burton, D. R.
J. Am. Chem. Soc. **2008**, *130*, 11114–11121.

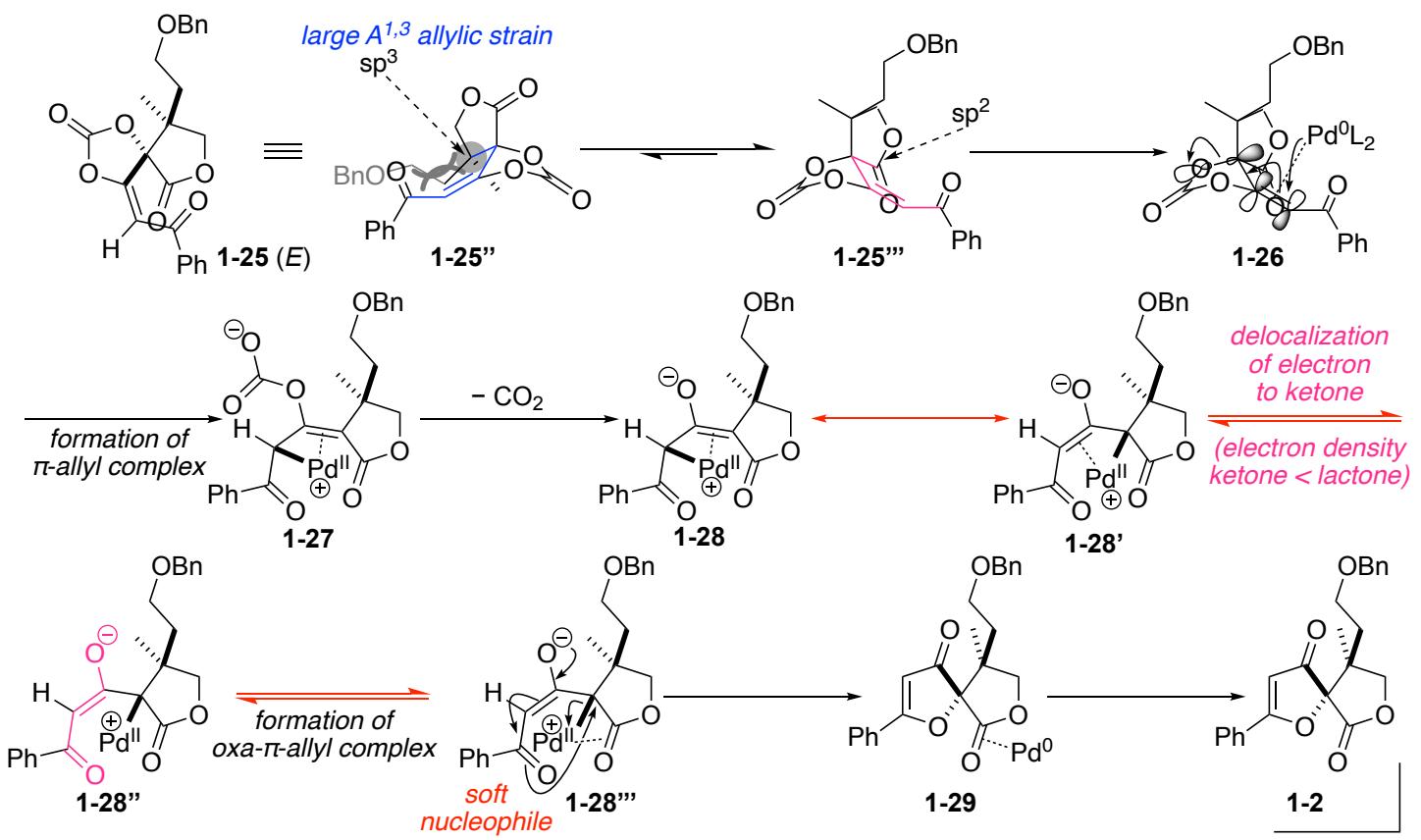
Answer



If chelation control were not considered, no stereoselectivity would be observed.

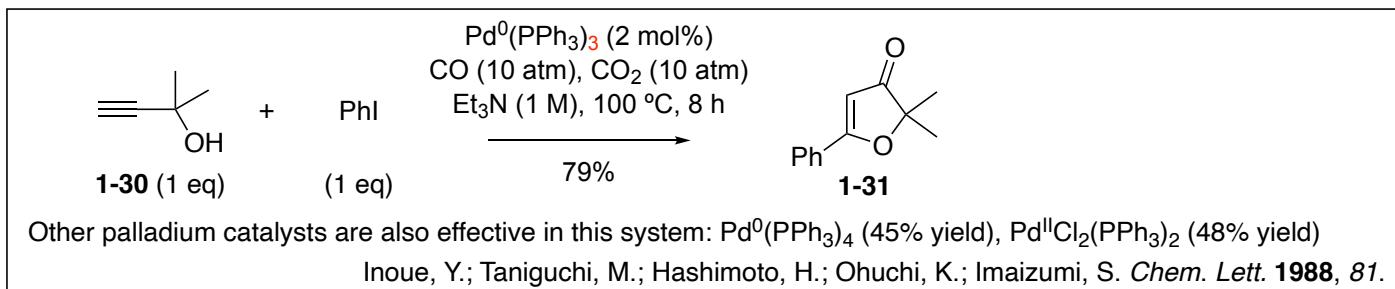






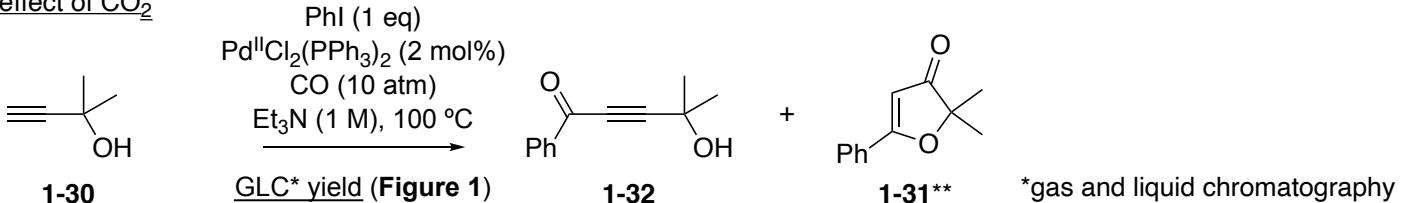
Discussion : cascade reaction

1. original reaction

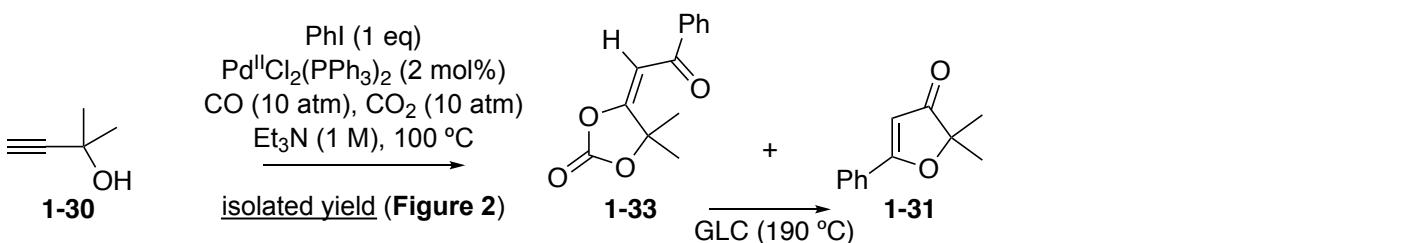


2. elucidation of the reaction mechanism^{ref 1}

• effect of CO_2



** It was assumed that catalytic amount of CO_2 was generated via the water-gas shift reaction:
 $\text{CO} + \text{H}_2\text{O} \rightleftharpoons \text{CO}_2 + \text{H}_2$



- **1-30** was converted to carbonate **1-33** in the presence of CO_2 .
- It was found that isolated carbonate **1-33** was completely converted to **1-31** in gaseous phase (190 °C).

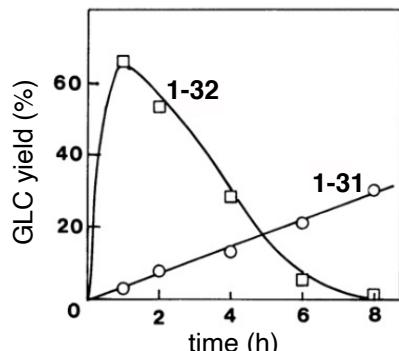


Figure 1

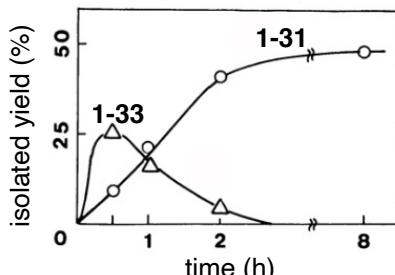
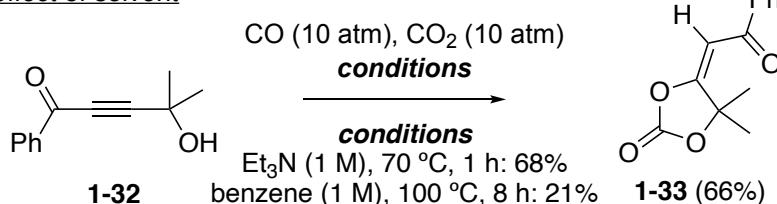
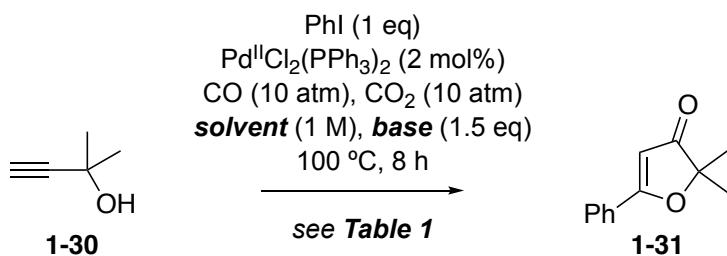


Figure 2

• effect of solvent

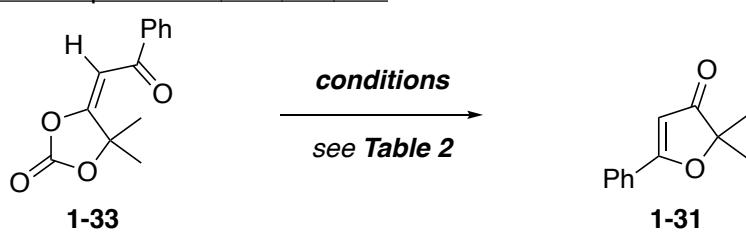


- Acetylenic ketone **1-32** was converted to carbonate **1-33**.
- Et_3N accelerated the formation of **1-33** (also see right table).
- Palladium catalyst was not involved in this step.



- Inorganic bases, which can be used in the carbonyl Sonogashira coupling, were not effective in this reaction. Thus it was suggested that Et_3N acted not only as a base, but also a nucleophile.

• relationship between **1-33** and **1-31**



- Cyclohexenone **1-31** was converted to **1-29** with the extrusion of CO_2 .
- Pd was not necessary in this reaction in a harsh conditions.

Table 1

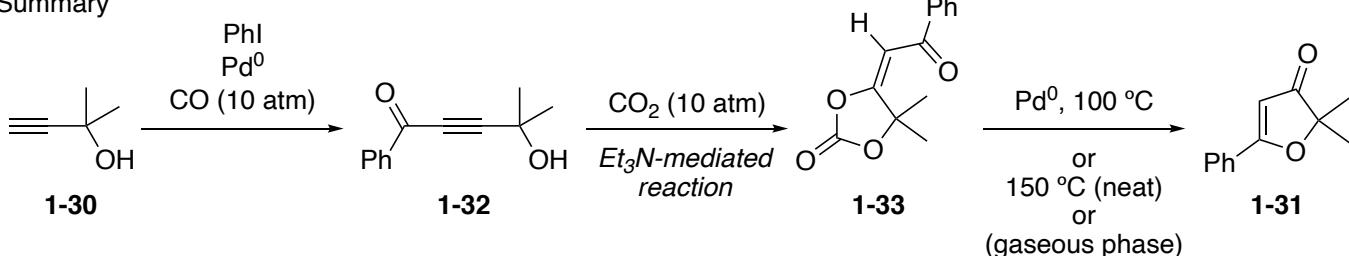
entry	solvent	base	result ^a
1	Et_3N	-	48%
2	DMF	Na_2CO_3	18%
3	CH_3CN	K_2CO_3	20%
4	CH_3CN	Li_2CO_3	trace
5	CH_3CN	Et_3N	69%

a) GLC yield

Table 2

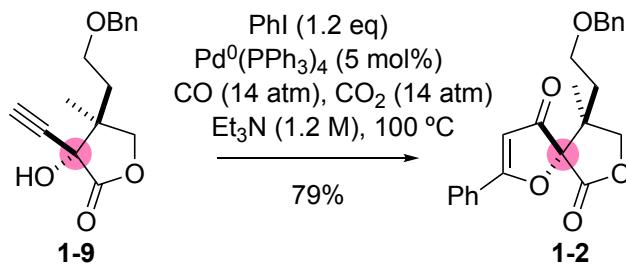
entry	conditions	result
1	$\text{Pd}^0(\text{PPh}_3)_4$ (2 mol%), CO (10 atm), Et_3N (1 M), 100 °C, 1 h	73%
2	$\text{Pd}^0(\text{PPh}_3)_4$ (2 mol%), CO_2 (10 atm), Et_3N (1 M), 100 °C, 1 h	75%
3	neat, 150 °C, 20 min	100%

Summary



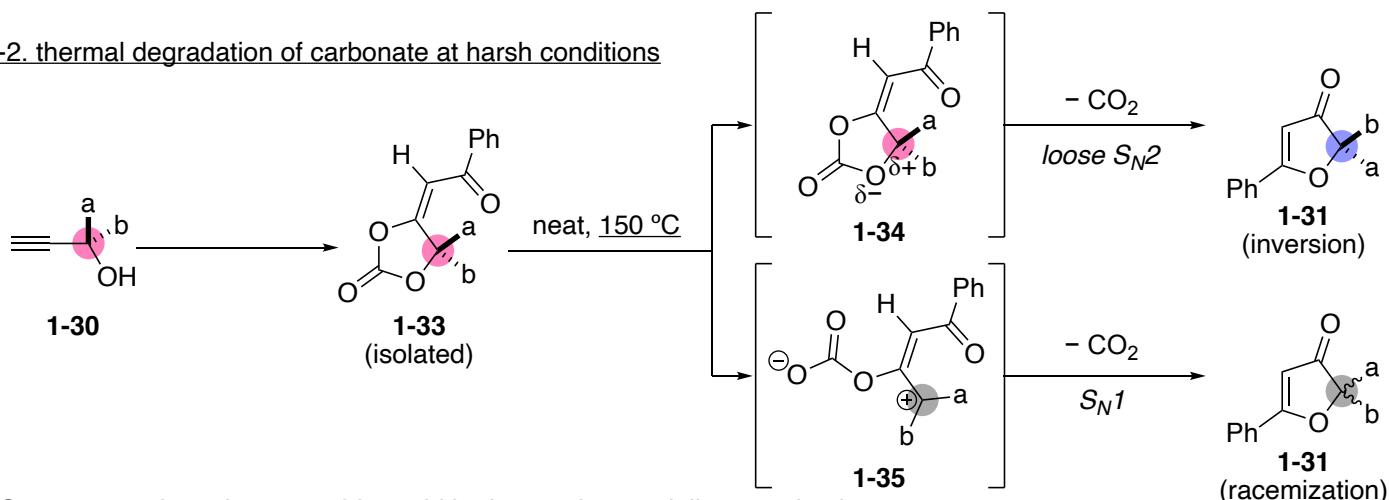
4. insight into the reaction mechanism of the decarboxylation from carbonate (last step)

4-1. palladium catalyzed pathway



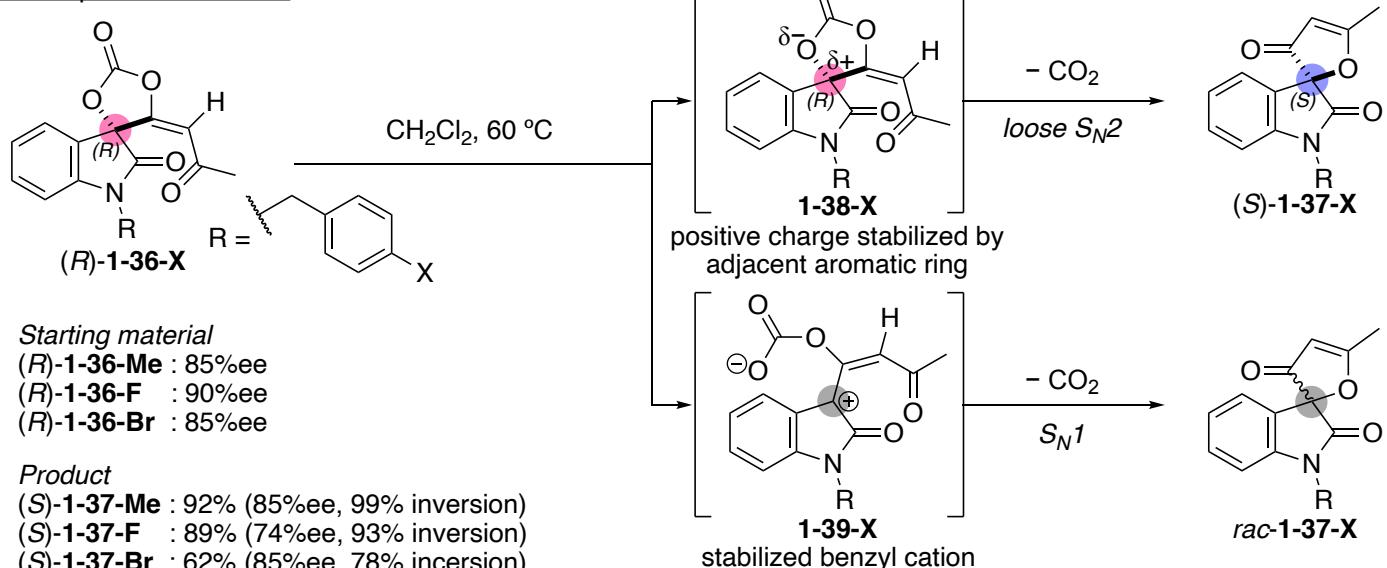
In palladium catalyzed pathway, stereocenter highlighted in **1-2** was retained.

4-2. thermal degradation of carbonate at harsh conditions

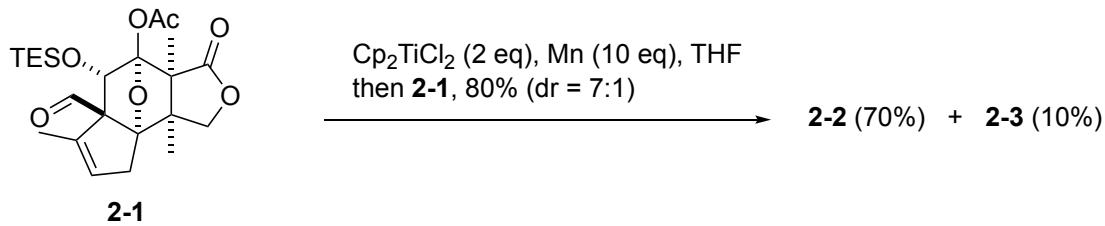


Stereocenter in carbonate **1-33** would be inverted or partially racemized.

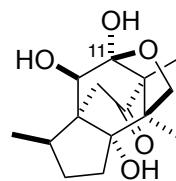
4-3. experimental results^{ref2}



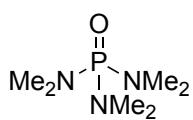
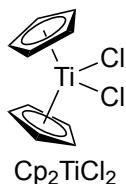
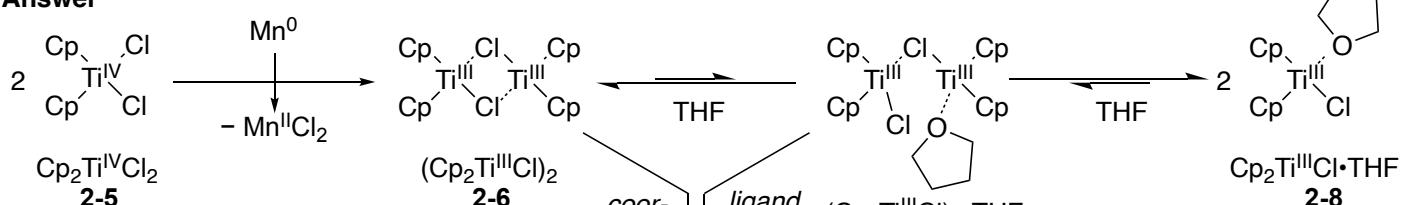
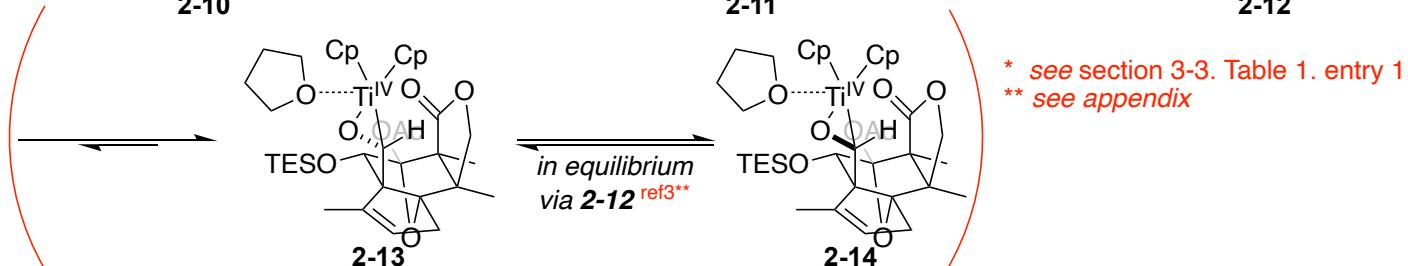
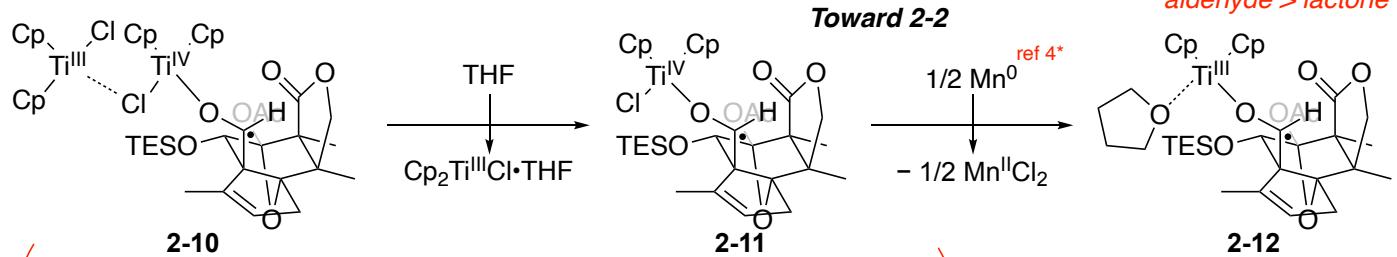
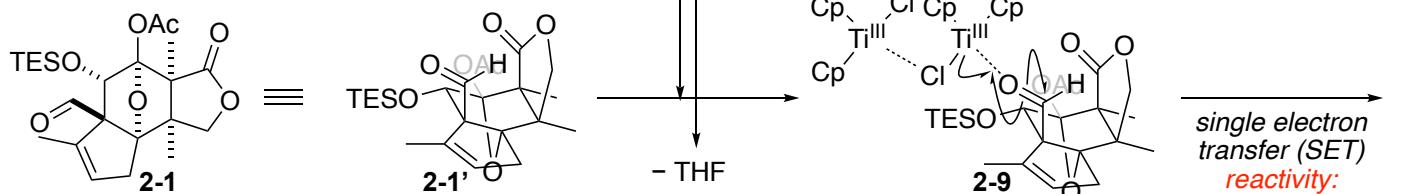
2.

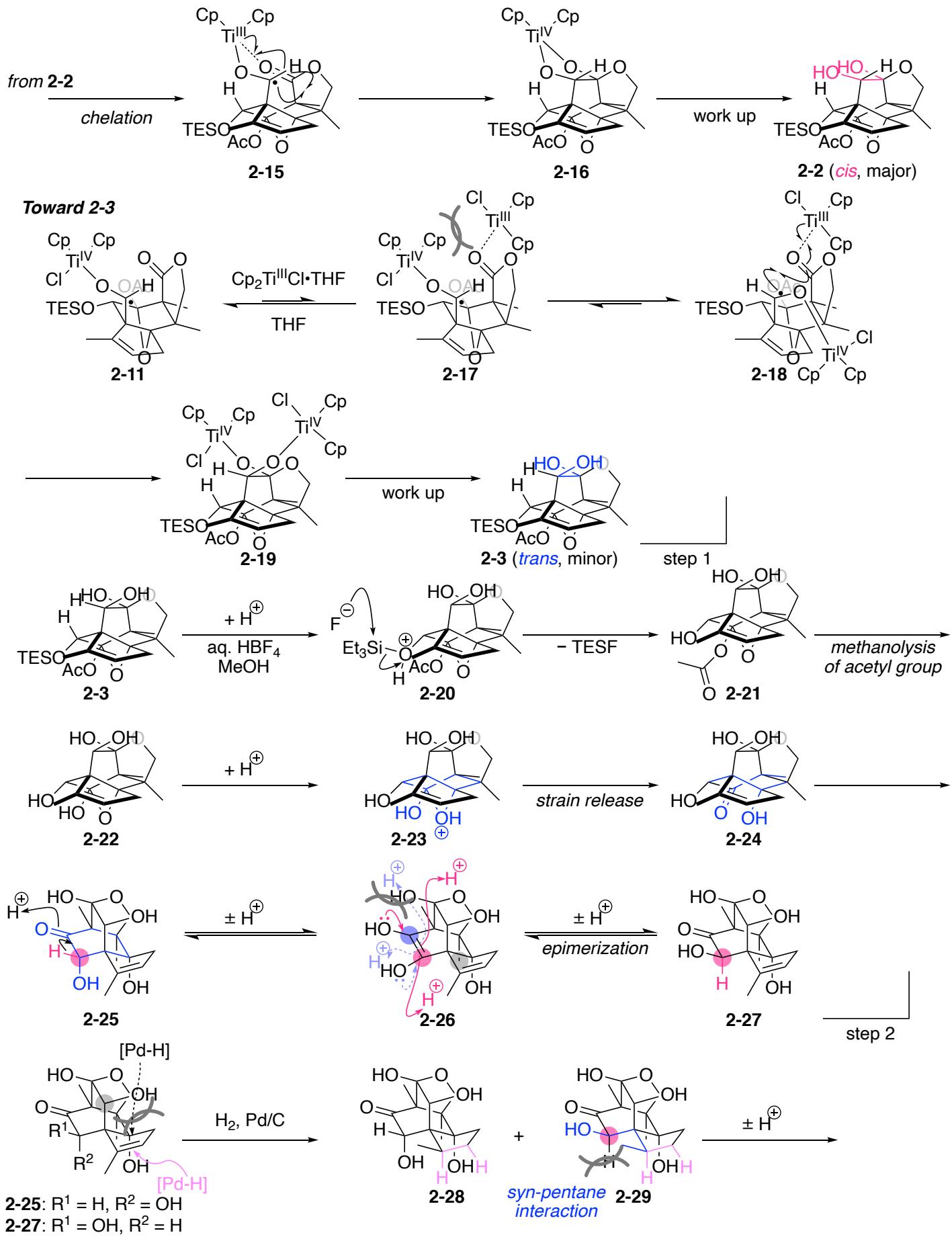
**2-3**

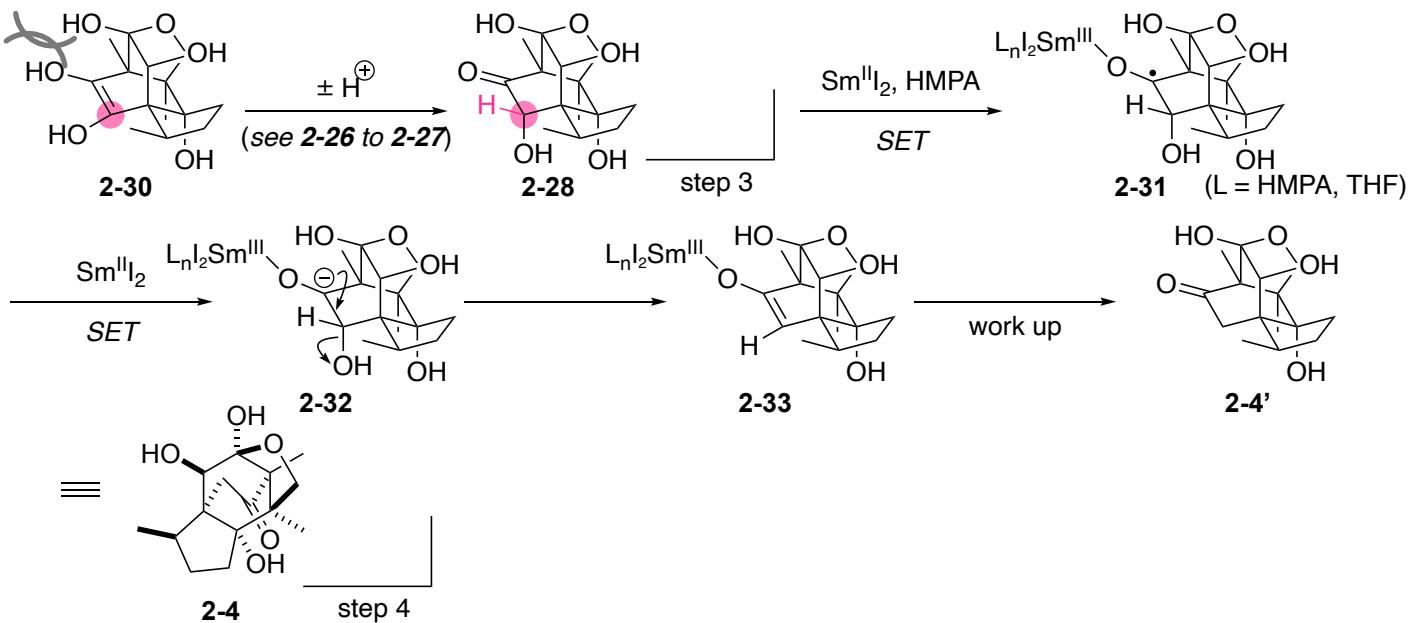
1. 48 wt% aq. HBF_4 (3 eq)
MeOH, 40 °C, 86% (dr = 2:1)*
2. H_2 (1 atm)
Pd/C (10 wt% Pd on carbon, 50 wt%)
MeOH, 90%
3. SmI_2 (2 eq), HMPA (2 eq)
THF, -78 °C, 93%

**11-O-debenzoyltashironin*** Judged from ^1H NMR.

It cannot be determined which diastereomer is the major one.

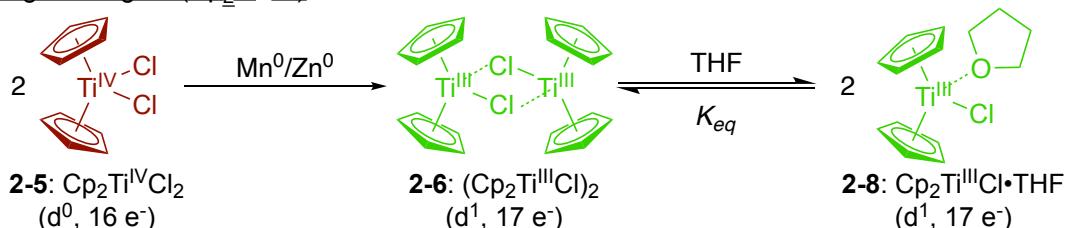
Tong, J.; Xia, T.; Wang, B. *Org. Lett.* **2020**, 22, 2730–2734.**Answer****Discussion: titanocene-mediated pinacol coupling**





Discussion: titanocene-mediated pinacol coupling

1. Nugent reagent ($\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}$)



- Cyclic voltammetry showed that $(\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl})_2$ (2-6) and $\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}\cdot\text{THF}$ (2-8) are in equilibrium in THF.^{ref1}
- K_{eq} was independent of the metal (Mn^0 , Zn^0) used.

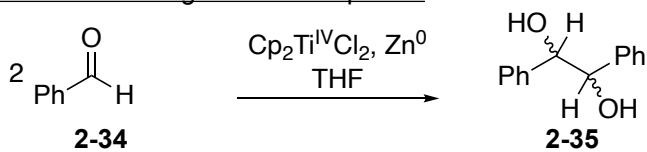
$$K_{\text{eq}} = [(\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl})_2]/[\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}]^2 = 3 \times 10^3 \text{ M}^{-1}$$

The distribution of Ti^{III} species in solution will be calculated as follows:

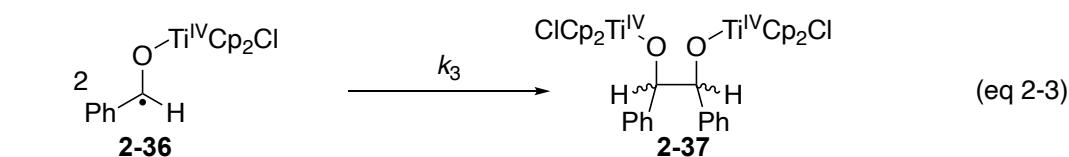
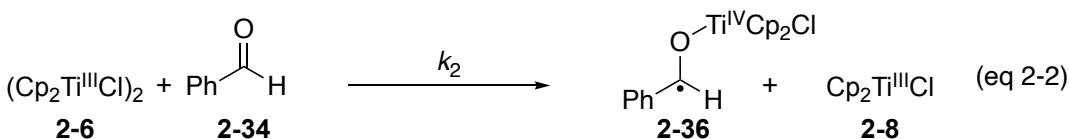
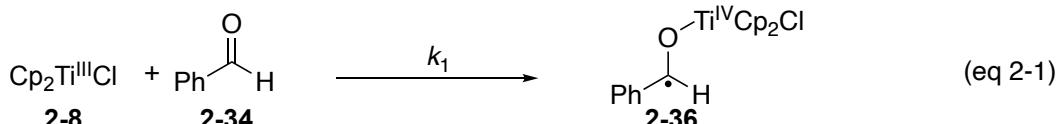
$$0.005 \text{ M} : [(\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl})_2] = 0.14 \text{ mM}, [\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}] = 0.22 \text{ mM}$$

$$0.1 \text{ M} : [(\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl})_2] = 0.048 \text{ M}, [\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}] = 0.004 \text{ M}$$

2. revelation of the reducing titanocene species^{ref1}

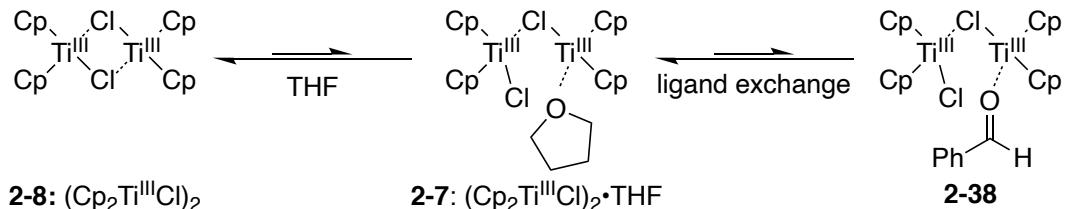


Kinetic traces were recorded for the decay of Ti^{III} at $\lambda = 800 \text{ nm}$ for PhCHO (0.015 M) in THF solutions of $\text{Cp}_2\text{Ti}^{\text{IV}}\text{Cl}_2/\text{Zn}^0$ (1, 2, and 5 mM) at 20 °C.



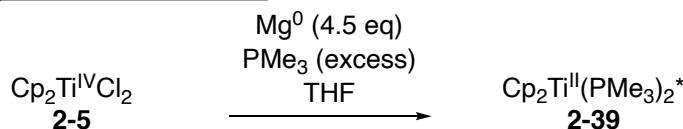
From kinetic measurements, k_1 and k_2 were determined as follows: $k_1 < 2 \text{ M}^{-1}\text{s}^{-1}$, $k_2 = 70 \text{ M}^{-1}\text{s}^{-1}$.

This result suggested that dimeric titanocene ($\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}_2$) would be the species responsible for the reduction of PhCHO. Thus half-open type dimeric species ($\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}_2 \cdot \text{THF}$ **2-7** and **2-38**) would be a tentative structure.



3. more detailed mechanism

3-1. synthesis of titanoxirane^{ref2,3}



cf: redox potential

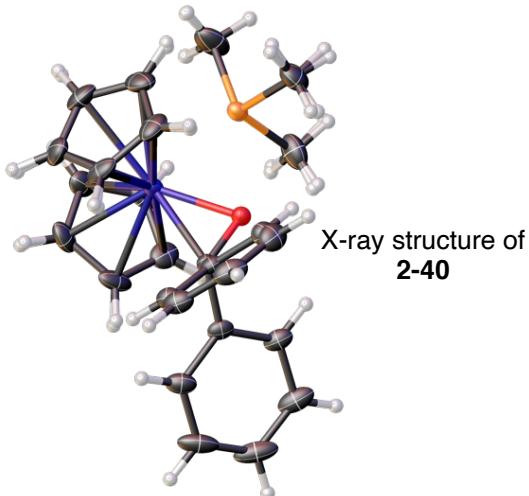
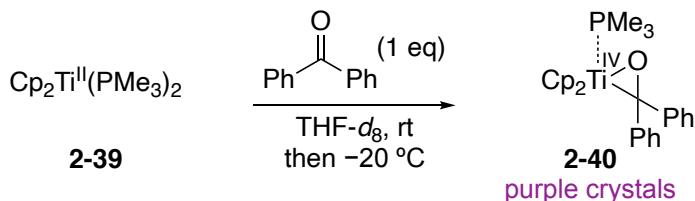
$\text{Mg}^0: E^\circ = -2.36 \text{ V vs. SHE}$

$\text{Mn}^0: E^\circ = -1.18 \text{ V vs. SHE}$

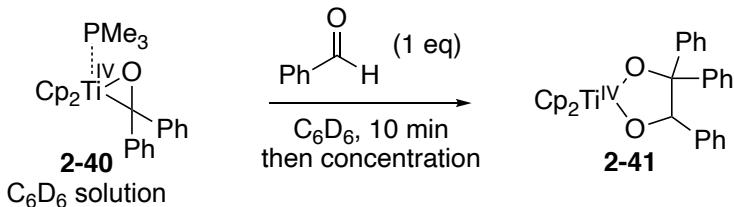
$\text{Zn}^0: E^\circ = -0.76 \text{ V vs. SHE}$

$\text{Cp}_2\text{Ti}^{\text{III}}\text{Cl}: E^\circ = -0.8 \text{ V vs. Fc}^+/\text{Fc}$

* In solution **2-39** is in equilibrium with $\text{Cp}_2\text{Ti}^{\text{II}}(\text{PMe}_3) + \text{PMe}_3$, with **2-39** favoured at room temperature.

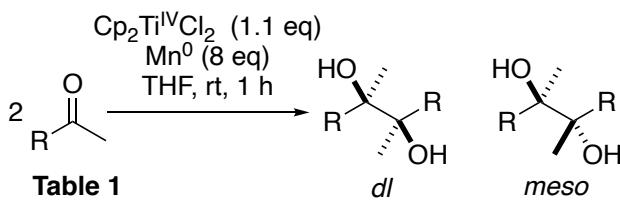


3-2. pinacolized product from titanoxirane

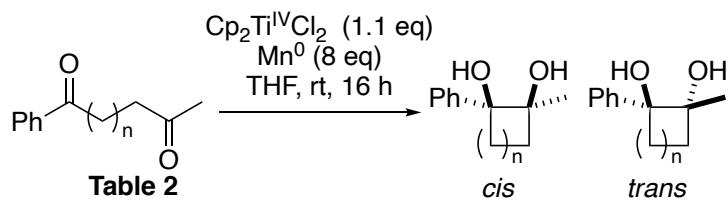


Titanoxirane **2-40** was an intermediate in the titanocene-mediated pinacol coupling.

3-3. necessity of Mn^0 and chelation control^{ref4}

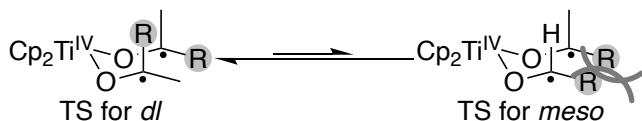


entry	R	yield (dl:meso)
1*	R = Ph	10% (2:1)
2	R = Ph	81% (9:1)
3	R =	91% (85:15)



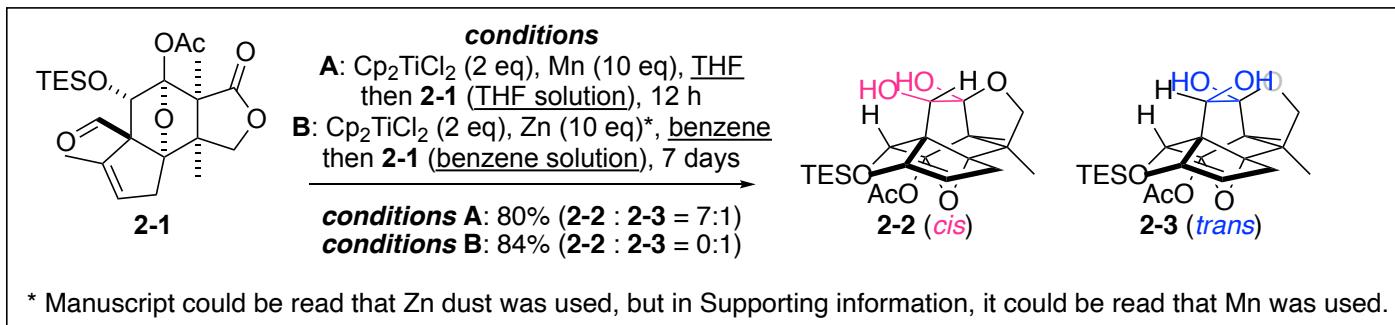
entry	R	yield (cis:trans)
1*	n = 1	50% (cis only)
2*	n = 2	80% (1:1)
3	n = 3	67% (3:1)

* Zn^0 (8 eq) was used.



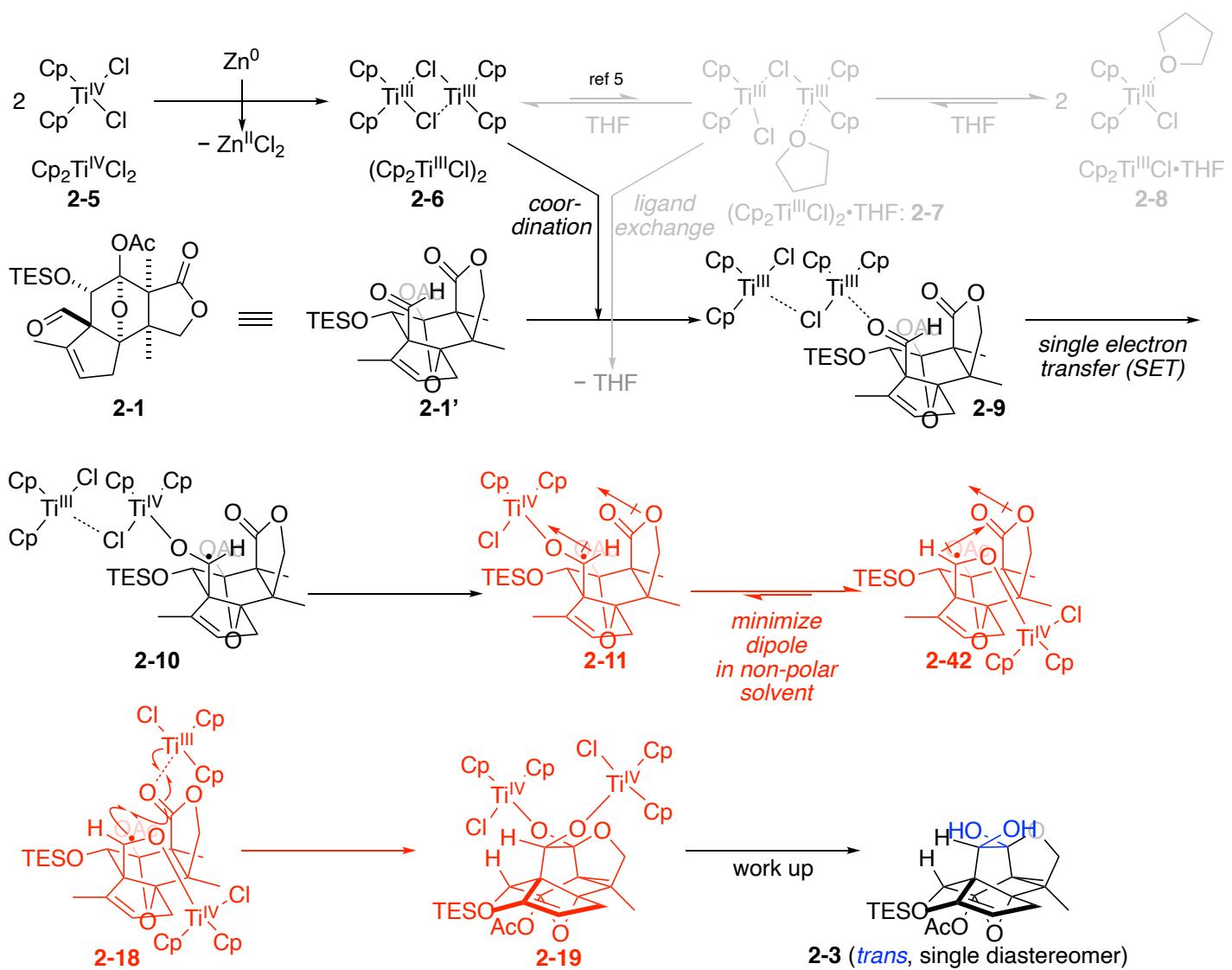
These results supported the chelation mechanism in the titanocene mediated pinacol coupling in THF (see page 6-7).

4. effect of the solvent



* Manuscript could be read that Zn dust was used, but in Supporting information, it could be read that Mn was used.

Above results showed that the choice of the solvent had an great influence on the stereoselective outcome. This difference can be attributed to the polarity of the solvent.



Reference

Problem 1

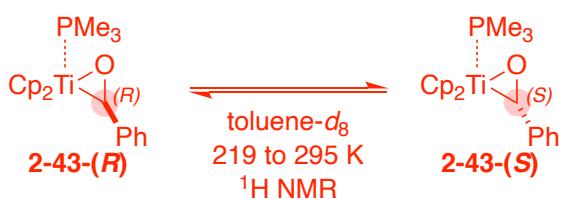
- 1) Inoue, Y.; Ohuchi, K.; Yen, I.-F.; Imaizumi, S. *Bull. Chem. Soc. Jpn.* **1989**, 62, 3518–3522.
- 2) Sun, Y.-L.; Wei, Y.; Shi, M. *Org. Chem. Front.* **2019**, 6, 2420–2429.

Problem 2

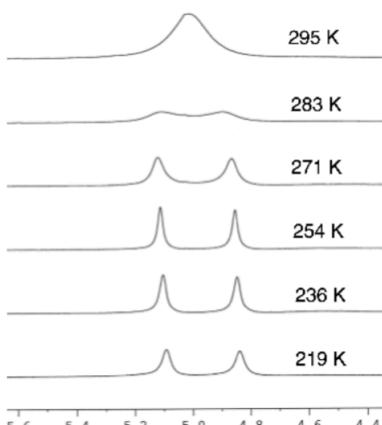
1. Enemærke, R. J.; Larsen, J.; Skrydstrup, T.; Daasbjerg, K. *J. Am. Chem. Soc.* **2004**, 126, 7853–7864.
2. (a) Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Thewalt, U.; Wolf, B. *Angew. Chem., Int. Ed.* **1985**, 24, 394.
(b) Kool, L. B.; Rausch, M. D.; Alt, H. G.; Herberhold, M.; Honold, B.; Thewalt, U. *J. Organomet. Chem.* **1987**, 320, 37.
3. Li, L.; Kristian, K. E.; Han, A.; Norton, J. R.; Sattler, W. *Organometallics* **2012**, 31, 8218–8224.
4. Paradas, M.; Campaña, A. G.; Estevez, R. E.; Cienfuegos, L. A.; Jiménez, T.; Robles, R.; Cuerva, J. M.; Oltra, J. E. *J. Org. Chem.* **2009**, 74, 3616–3619.
5. Coutts, R. S. P.; Wailes, P. C.; Martin, R. L. *J. Organomet. Chem.* **1973**, 47, 375–382.

Appendix

1. Interconversion of the enantiomers of titnoxirane **2-43**^{ref3}



At 295 K, there is a single Cp peak, indicating that titnoxiranes **2-43-(R)** and **2-43-(S)** are in a fast enantiomer interconversion.



temperature dependence of the C₅H₅ of **2-43**
¹H NMR (300 MHz, toluene-*d*₈)

2. X-ray structures (disorder not corrected)

