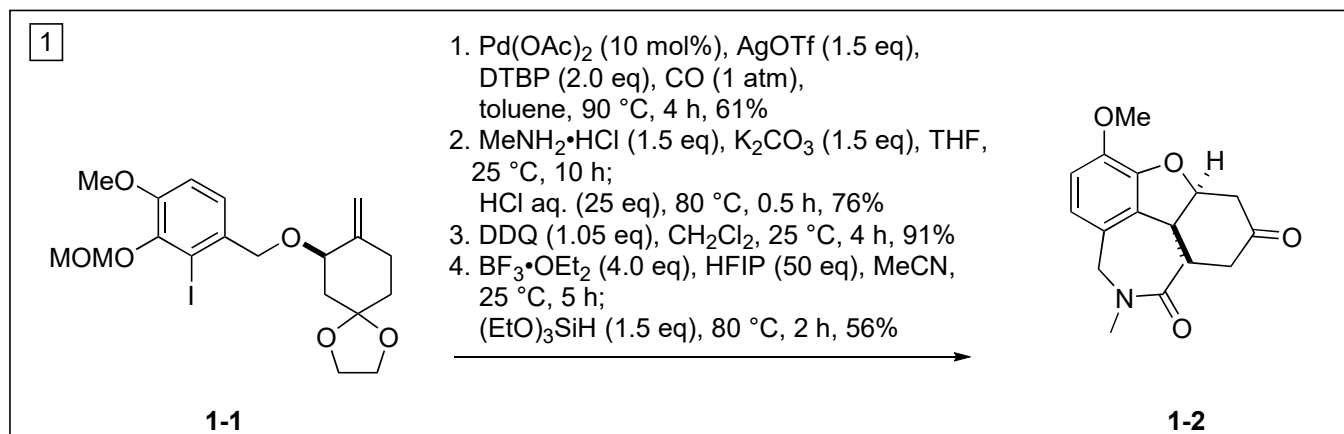
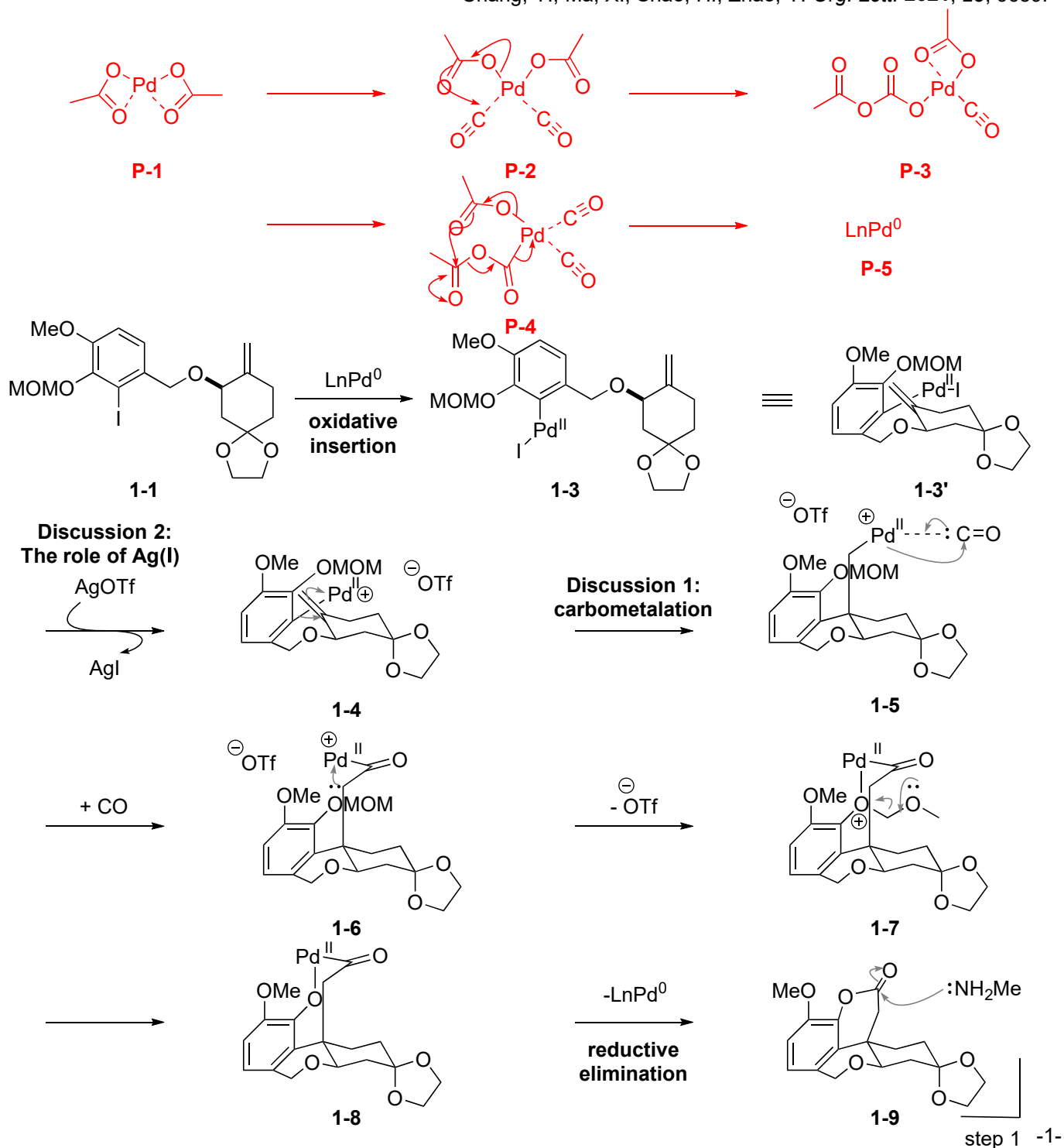
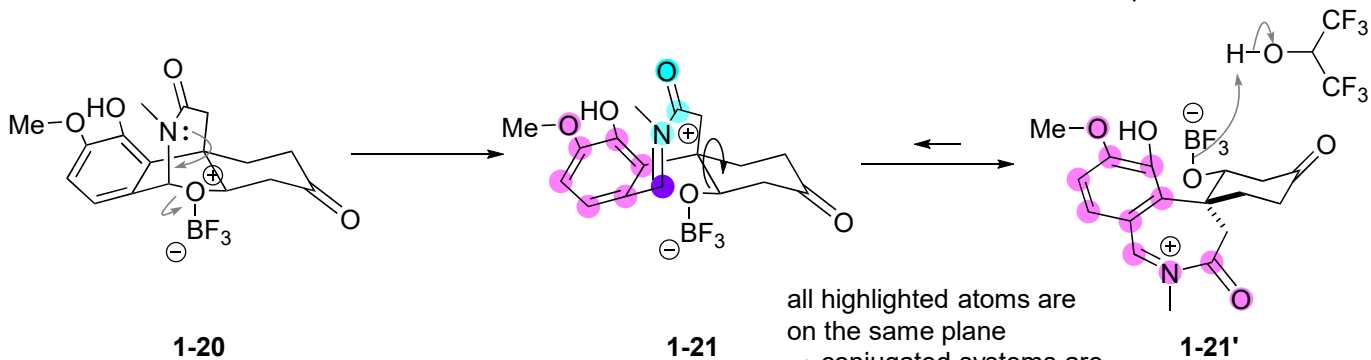
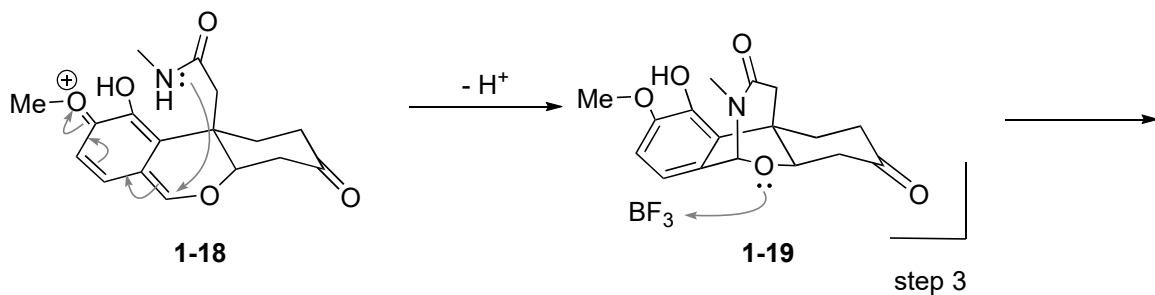
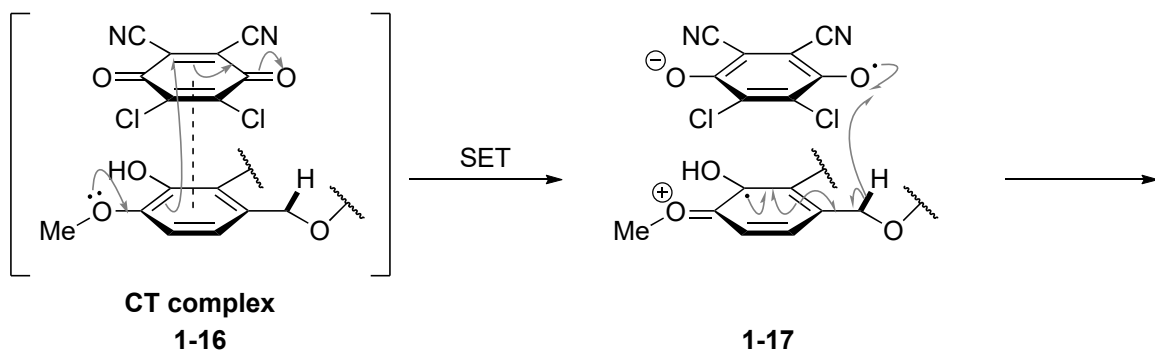
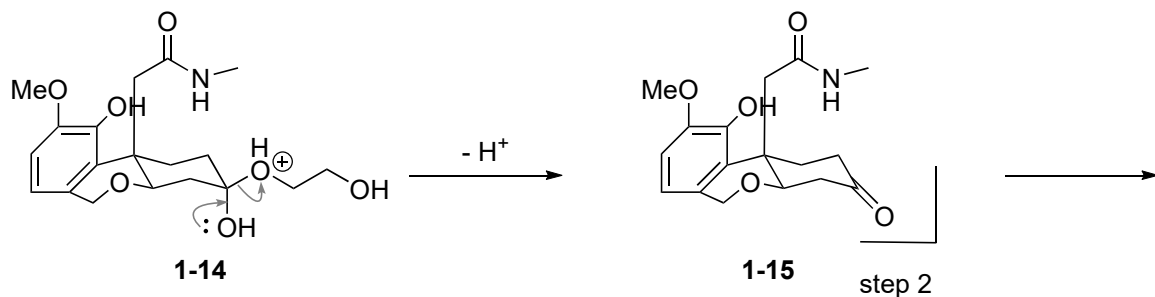
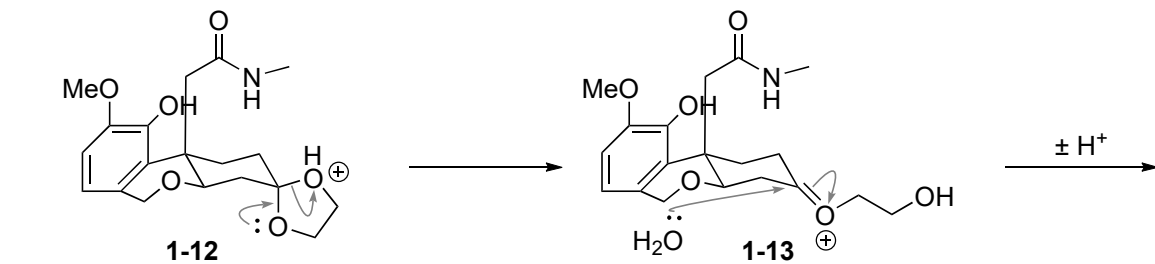
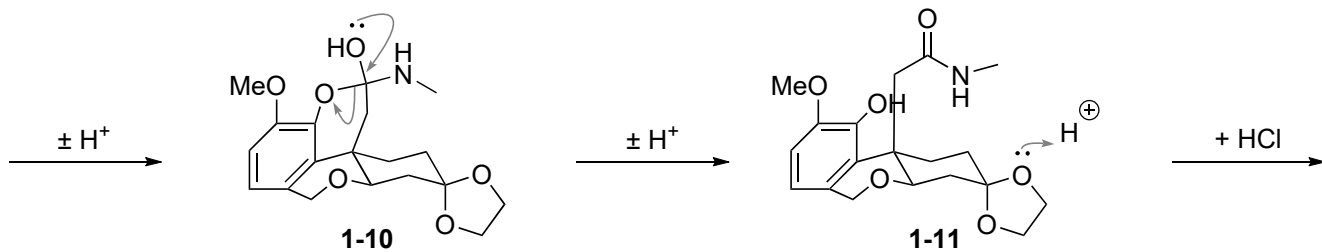


1-1. Reaction mechanism

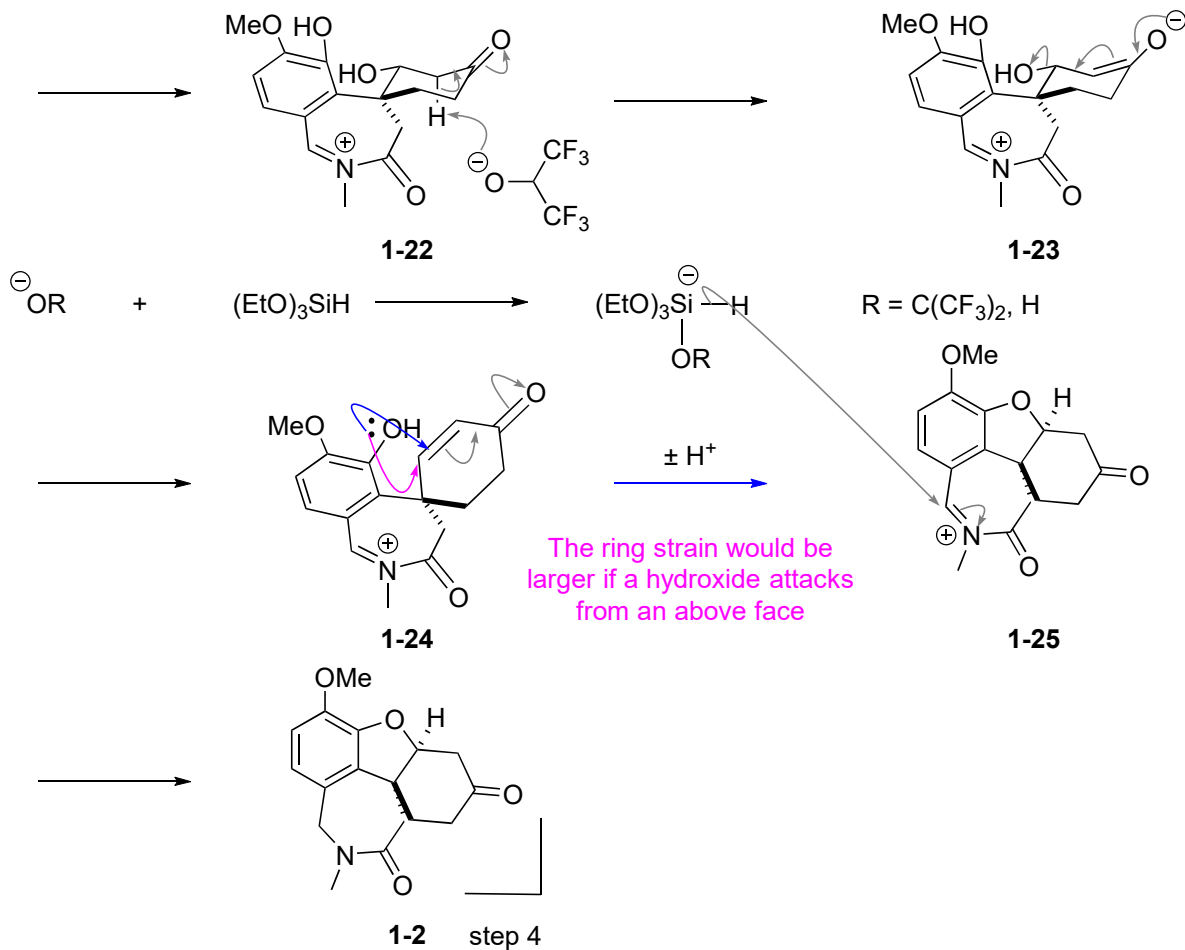


Chang, Y.; Ma, X.; Shao, H.; Zhao, Y. *Org. Lett.* **2021**, *23*, 9659.

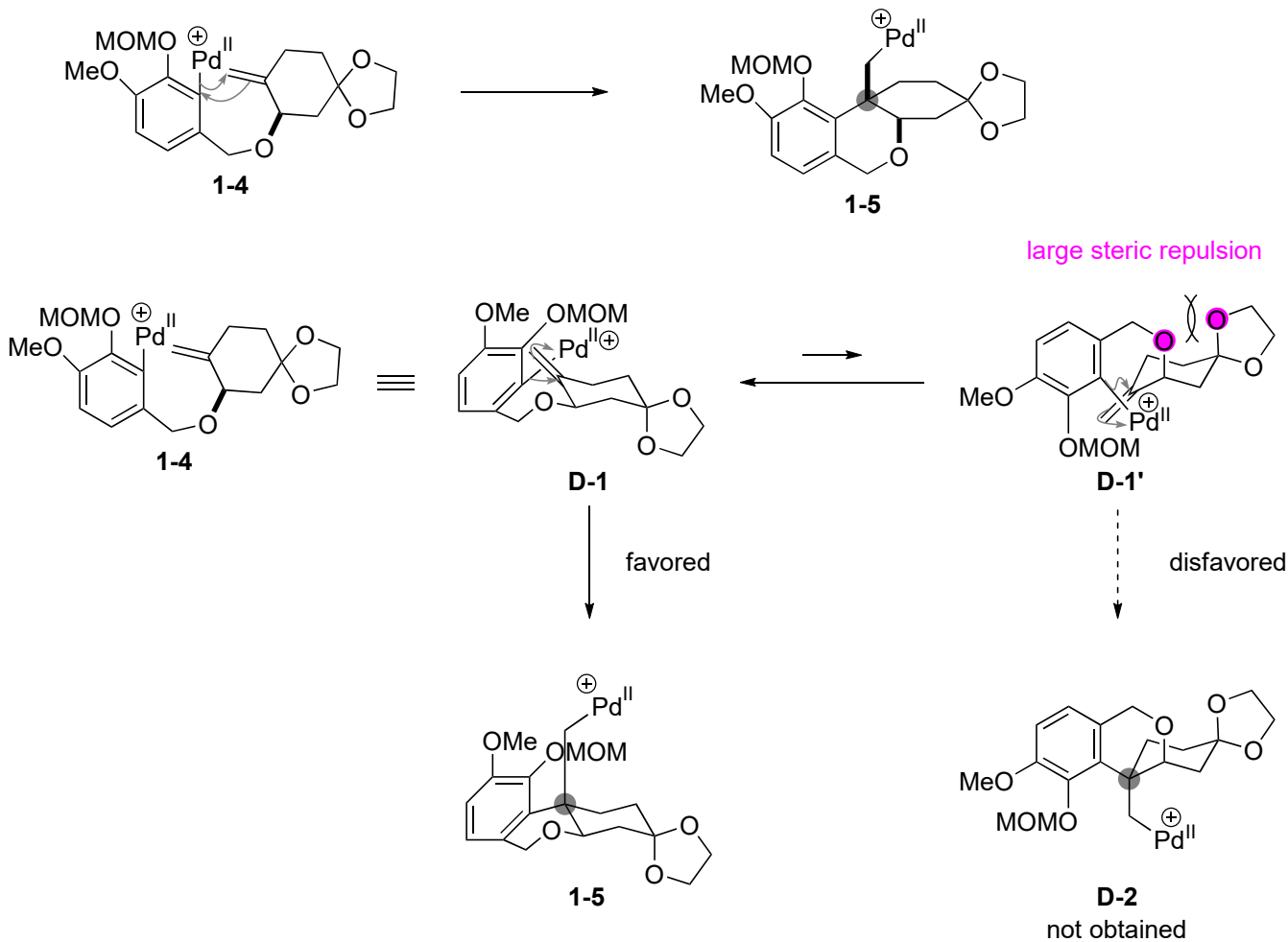




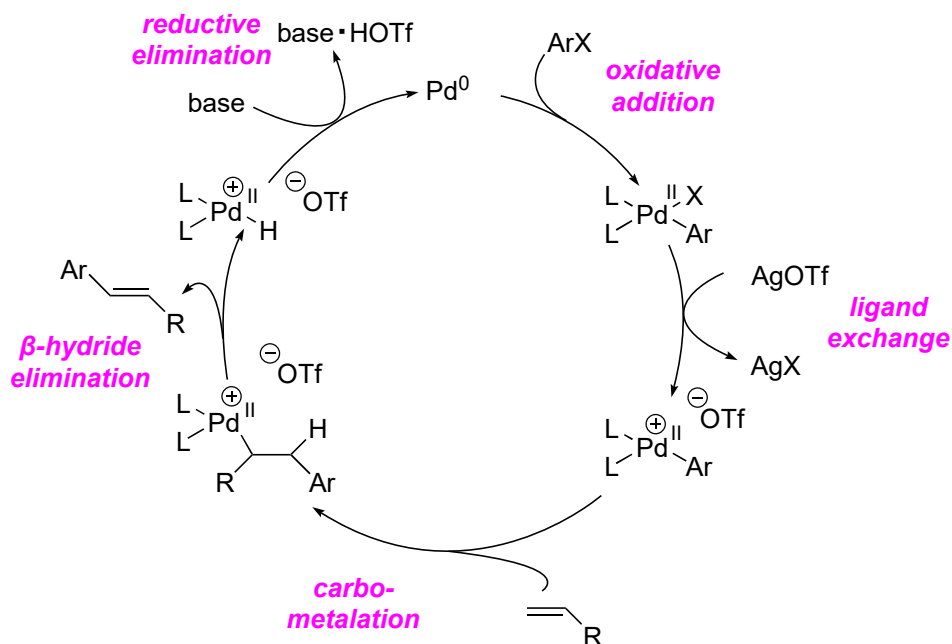
all highlighted atoms are
 on the same plane
 → conjugated systems are
 extended
 → more stable



1-2. Discussion 1: carbometalation



1-3. Discussion 2: The role of Ag(I)



Generally, Ag(I) additives give us three benefits.

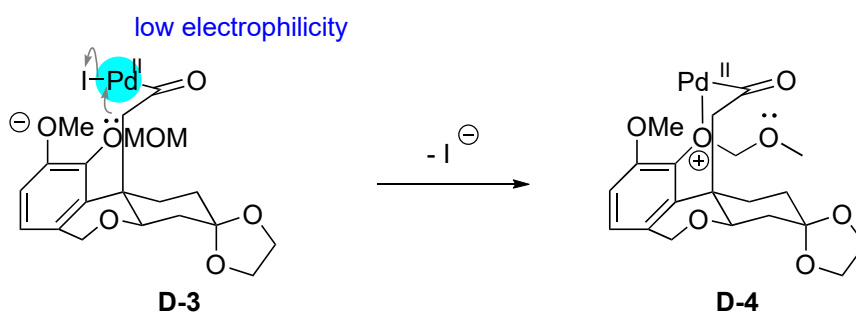
- ① To increase the reaction rates
- ② To prevent deactivation of the palladium catalyst
- ③ To minimize alkene isomerization of the product

①~③ : due to the acceleration of reductive elimination

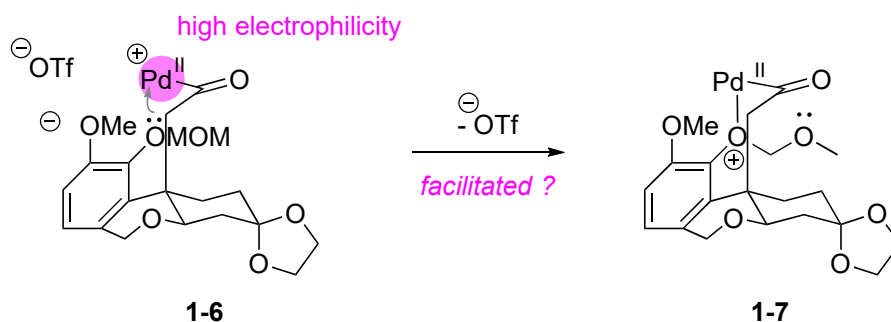
Dounay, B.; Overman, L. *Chem. Rev.* **2003**, *103*, 2945

In addition to general benefits, it is thought that AgOTf worked to facilitate the nucleophilic addition in this case.

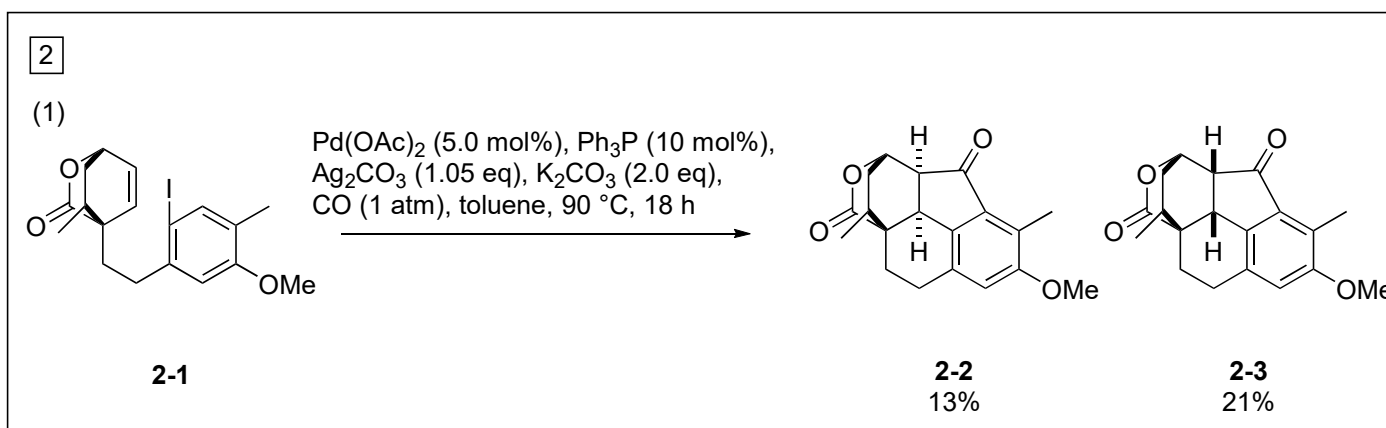
Without AgOTf (neutral pathway)



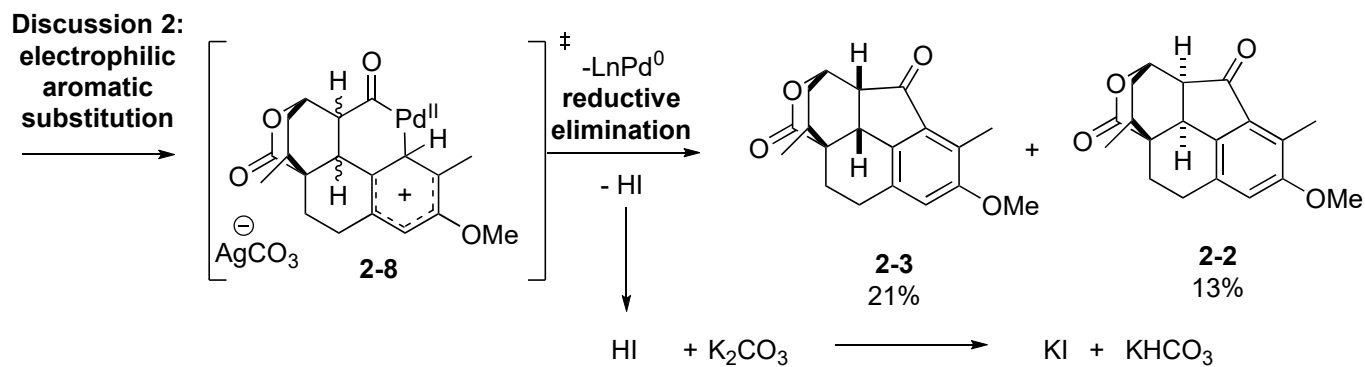
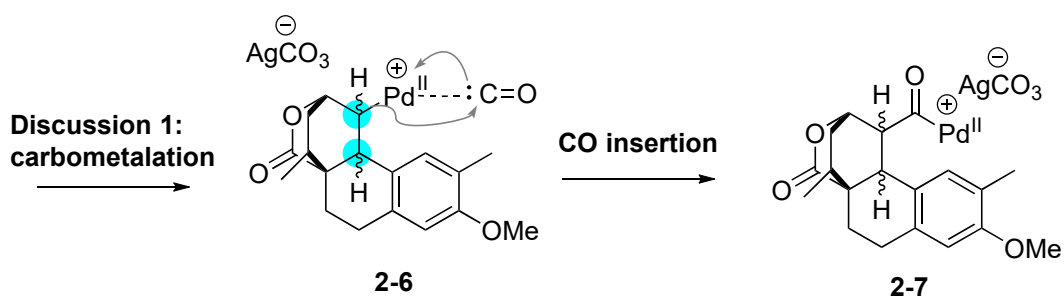
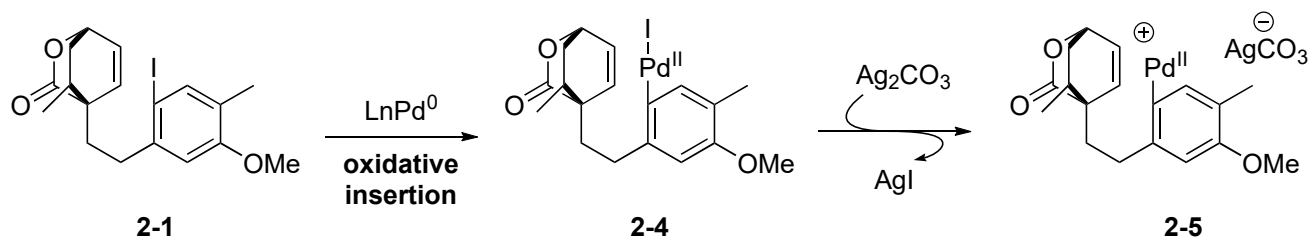
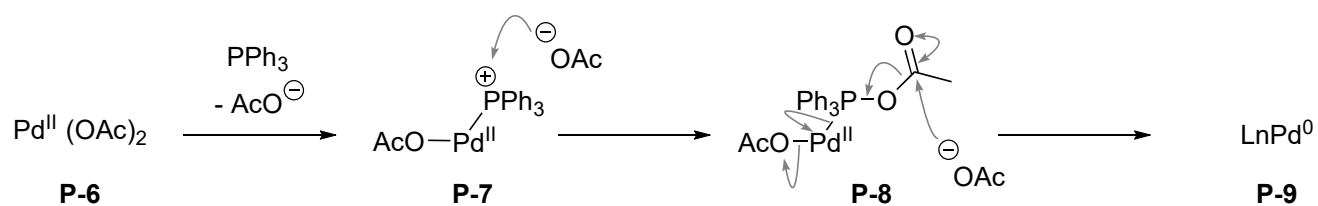
With AgOTf (cationic pathway)

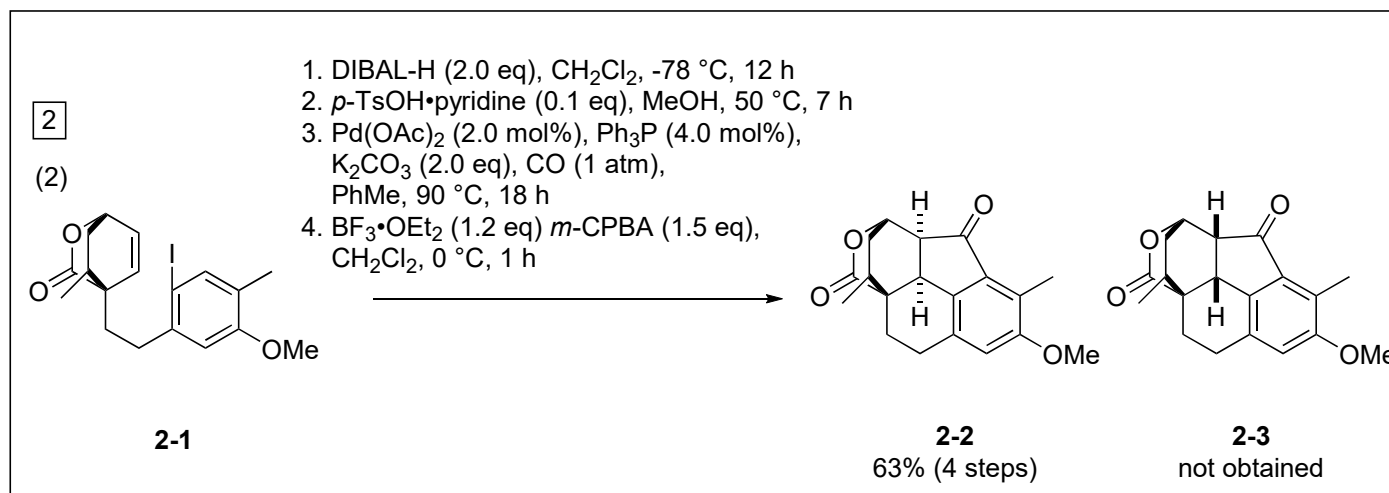


2. Reaction mechanism

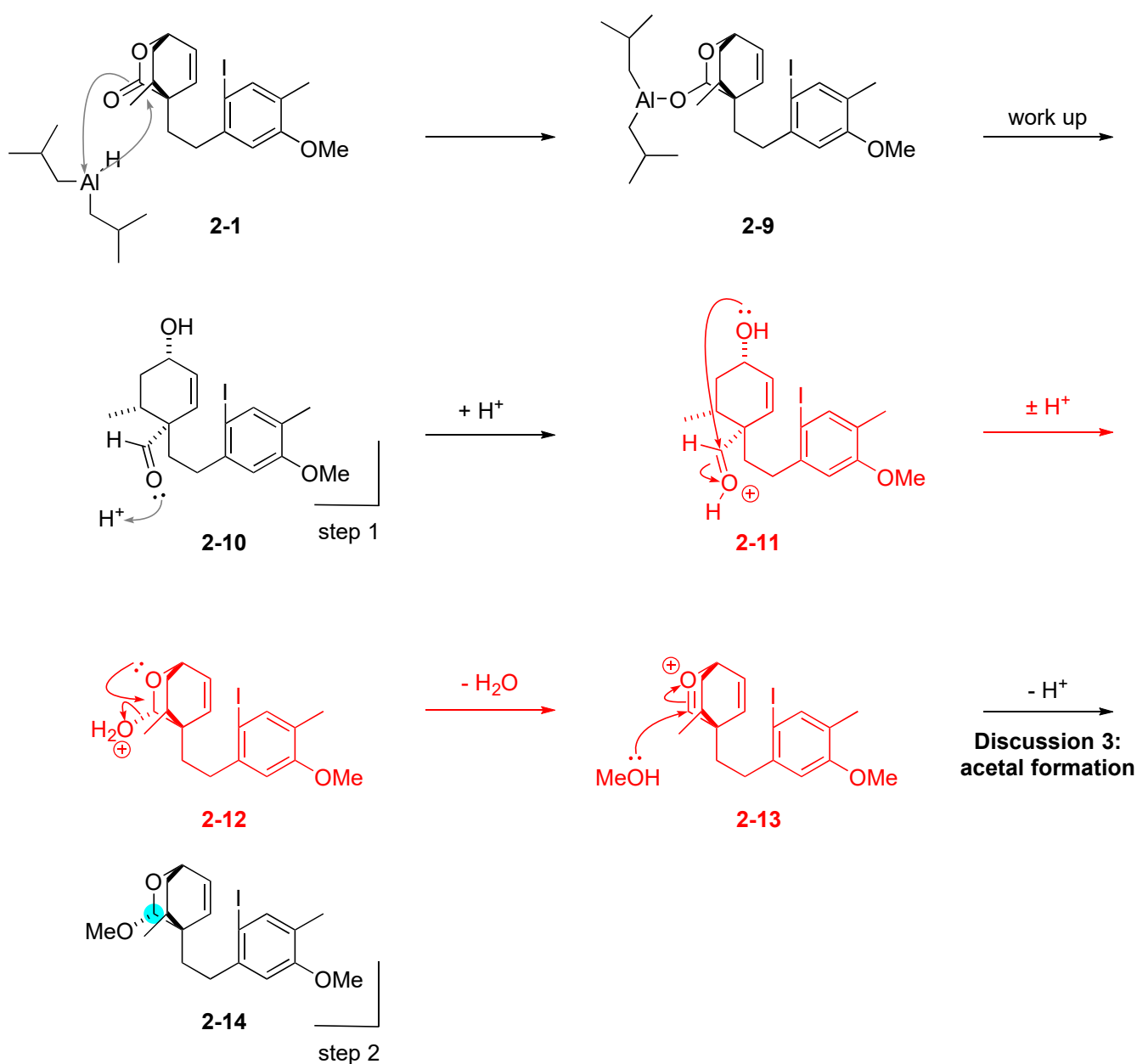


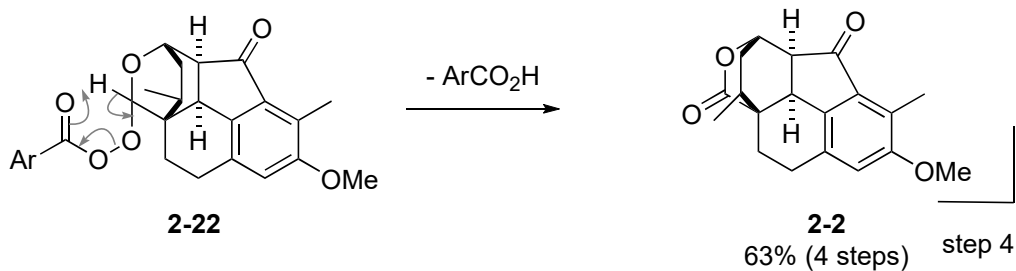
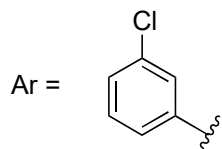
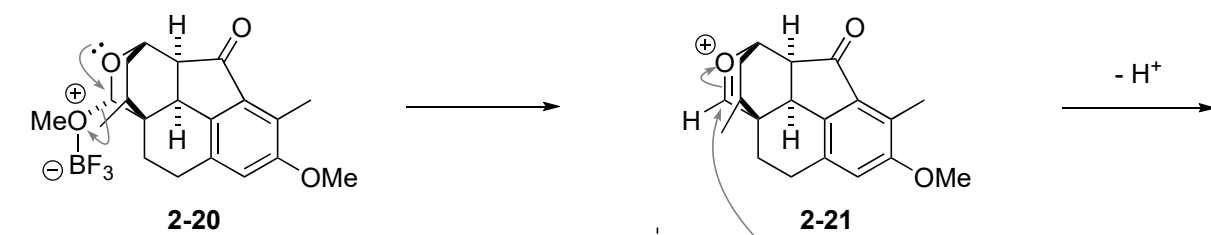
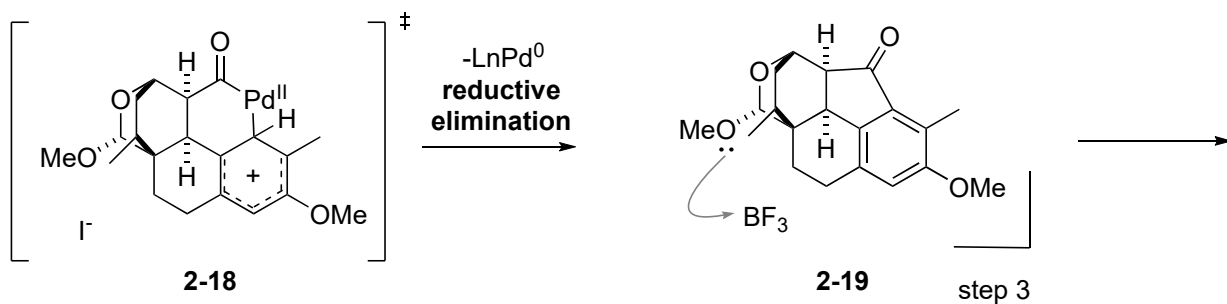
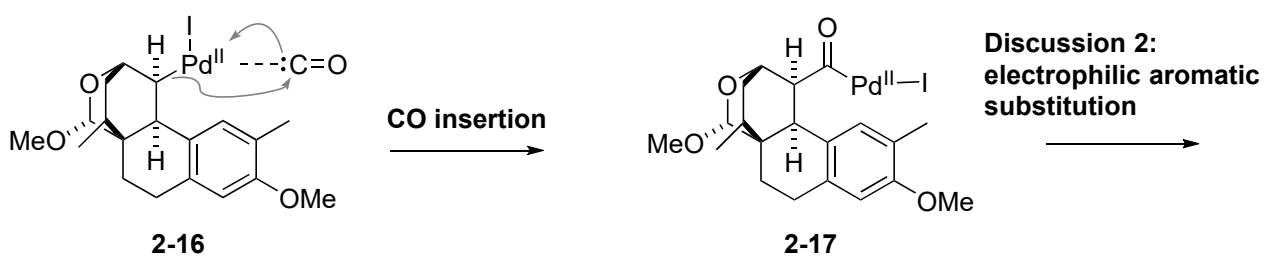
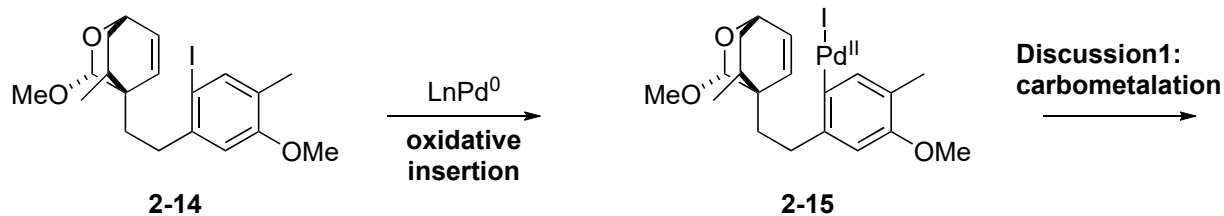
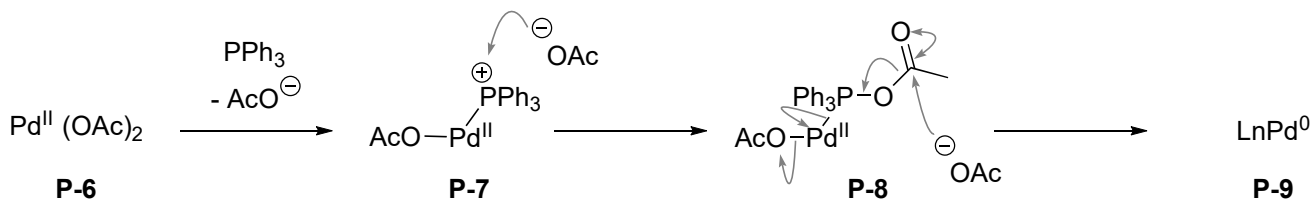
Xu, L.; Wang, C.; Gao, Z.; Zhao, Y. *J. Am. Chem. Soc.* **2018**, *140*, 5653.





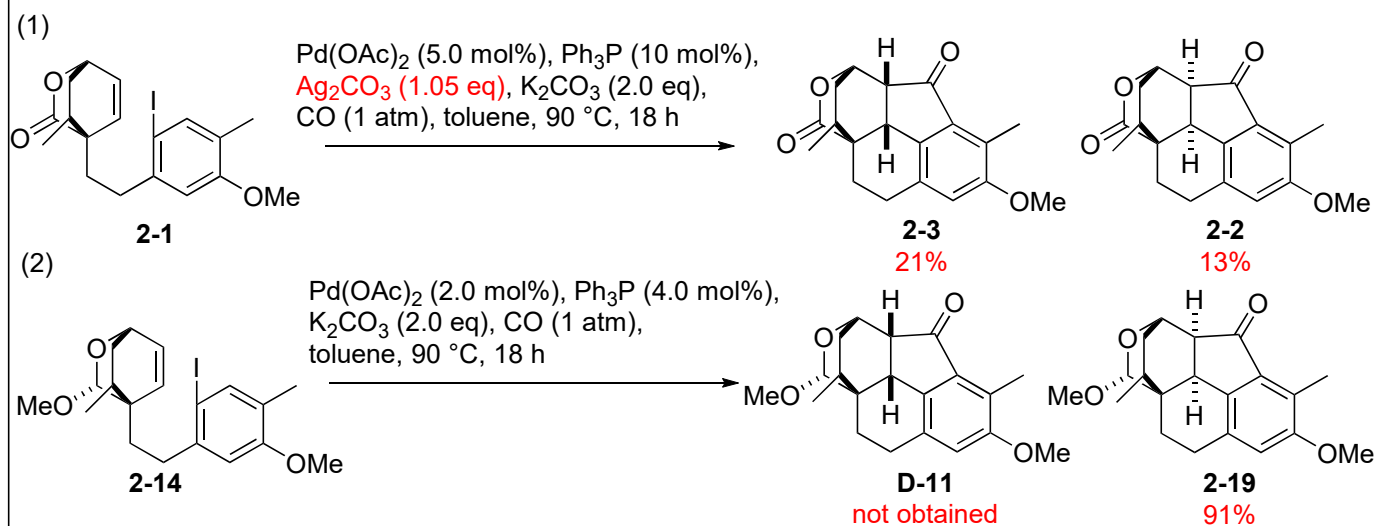
Xu, L.; Wang, C.; Gao, Z.; Zhao, Y. *J. Am. Chem. Soc.* **2018**, *140*, 5653.





2-2. Discussion 1: carbometalation

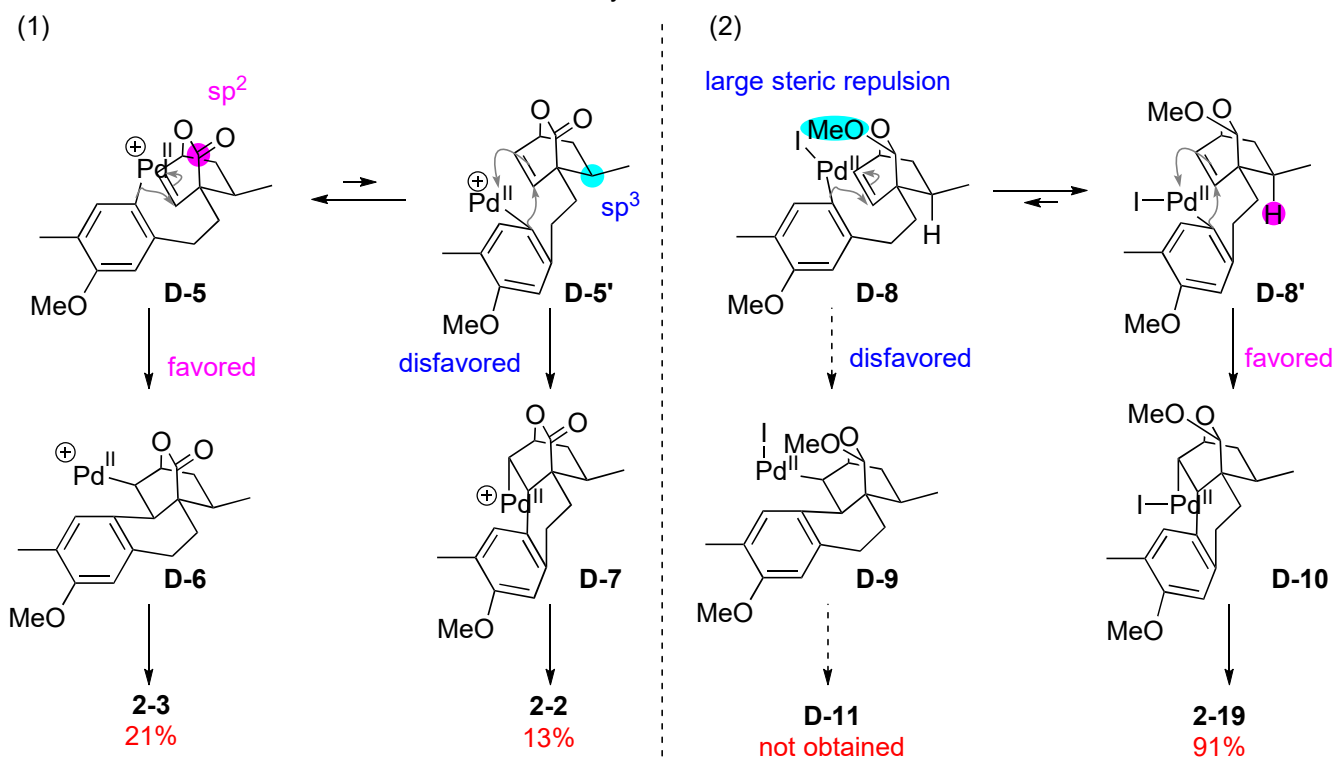
The comparison of two palladium-catalyzed cascade cyclizations



→ From this comparison, three questions arise.

- Question A: What controls the stereoselectivity?
 Question B: What makes the material balance of (1) worse?
 Question C: What is the role of Ag_2CO_3 in (1)?

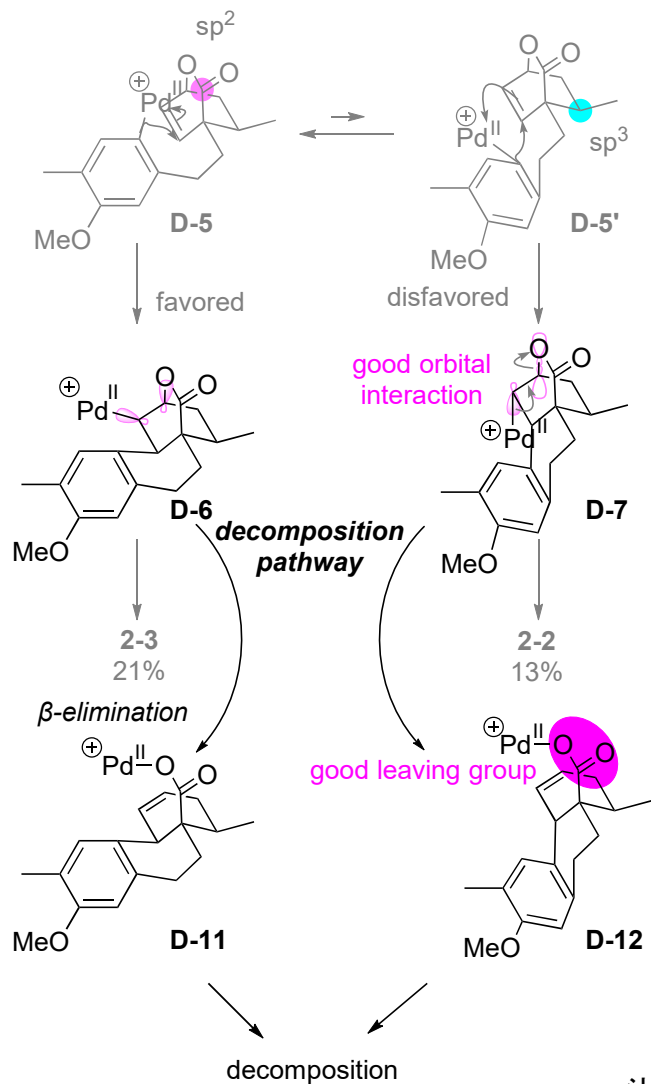
2-2-1, Question A: What controls the stereoselectivity?



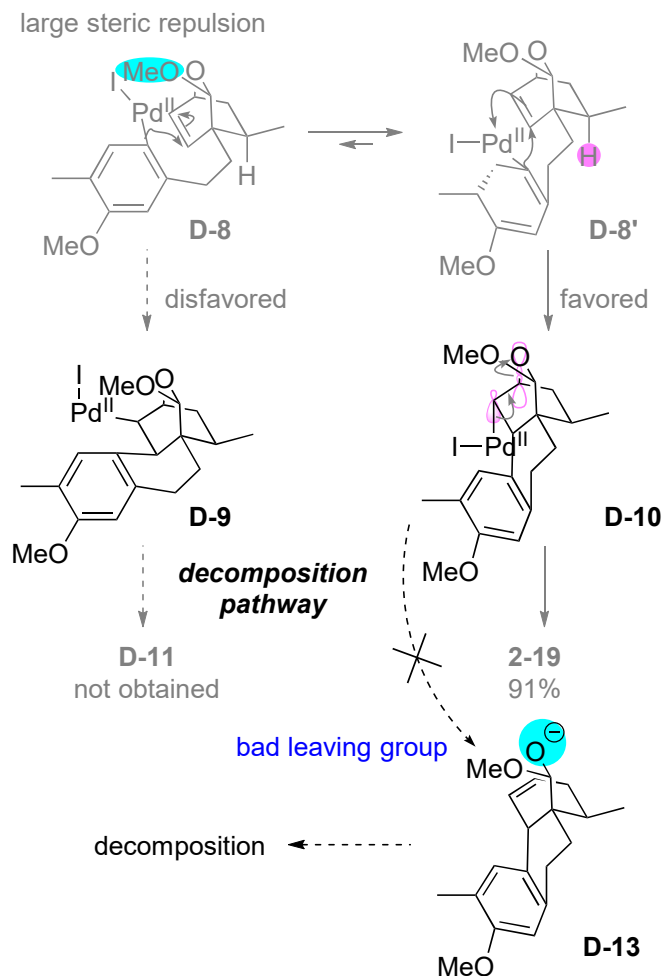
- Question A: What controls the stereoselectivity?
 → The steric constraints surrounding the alkene diastereofaces.

2-2-2, Question B: What makes the material balance of (1) worse?

(1)

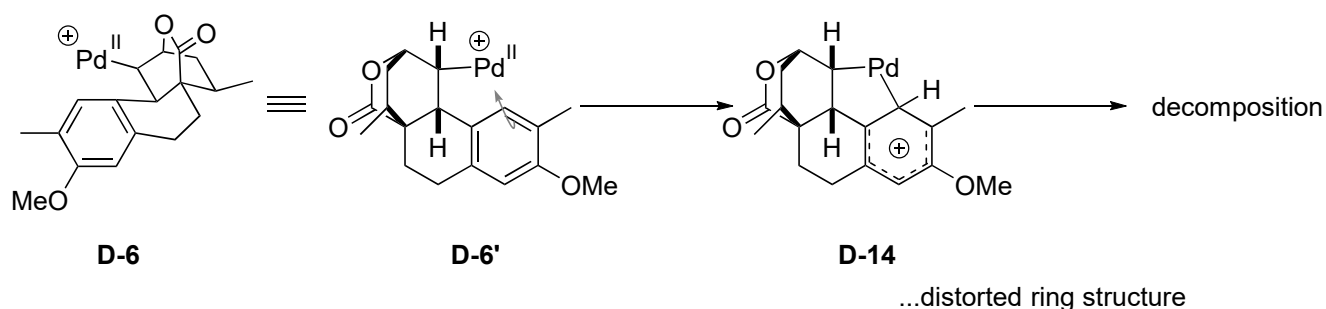


(2)



辻二郎; 有機合成化学協会誌, 2005, vol.63, No.5, 539

Another decomposition pathway from D-6

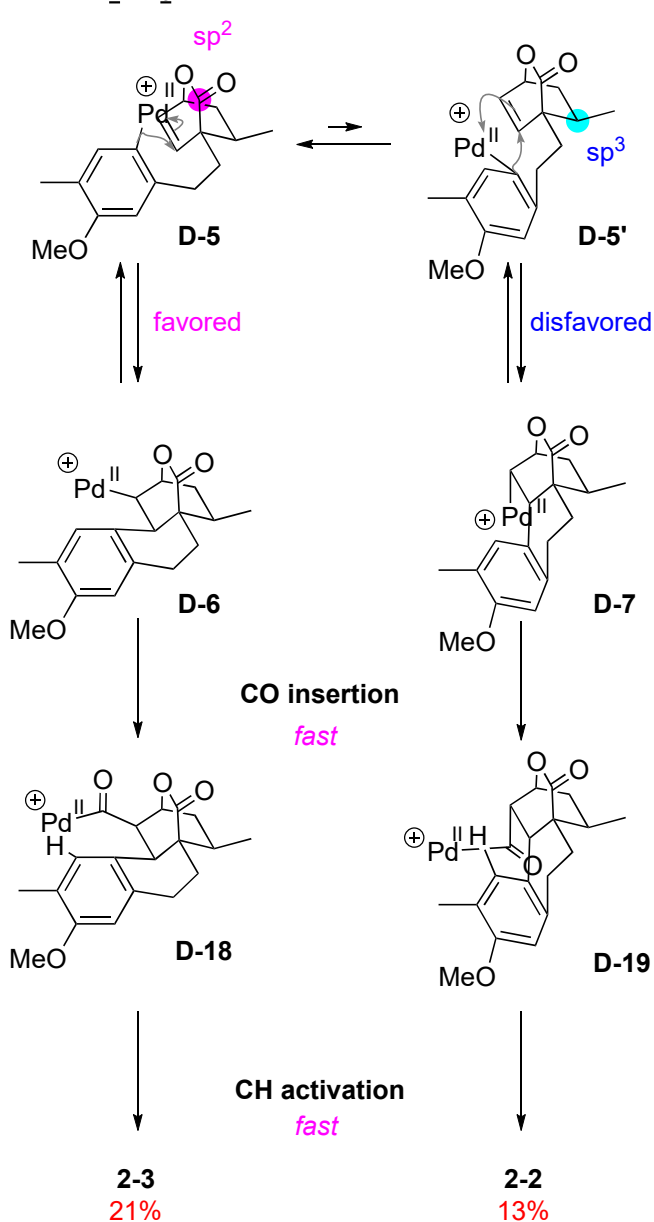


Question B: What makes the material balance of (1) worse?
 →The intermediate **D-6**, **D-7** are decomposable due to its good leaving group.

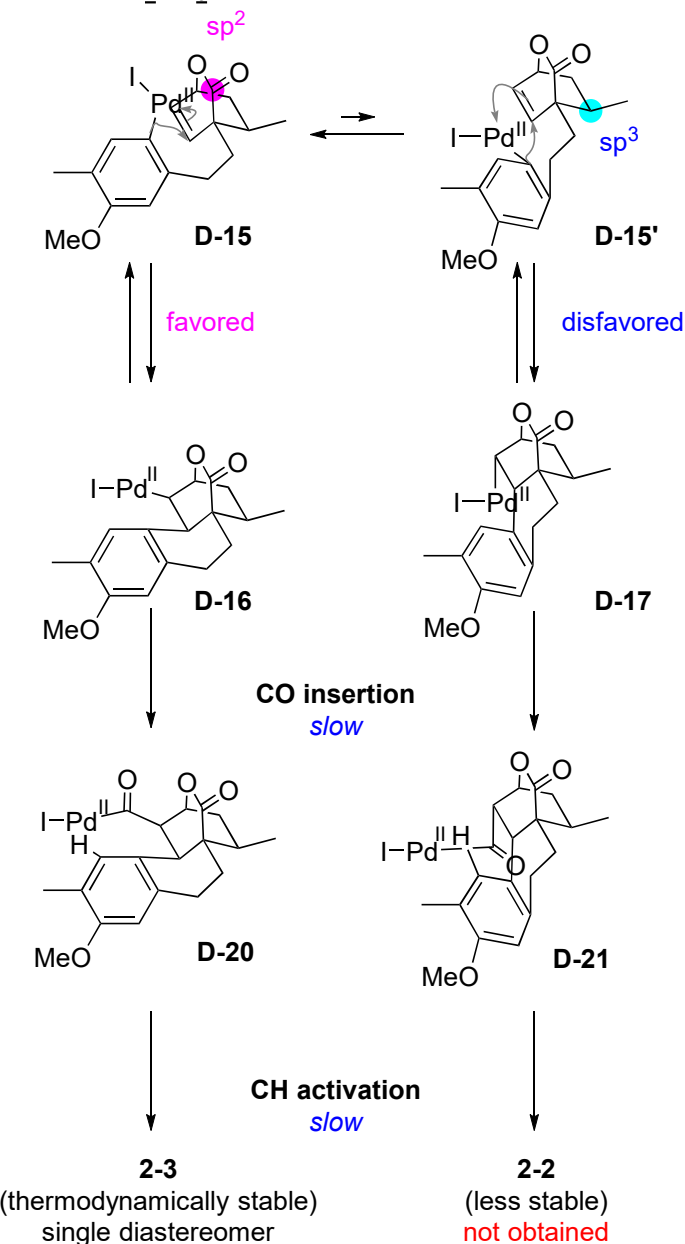
2-2-3, Question C: What is the role of Ag_2CO_3 in (1)?

The authors reported that standard palladium-catalyzed conditions (without Ag_2CO_3) were examined, but only **2-3** was obtained (the yield was not reported).

with Ag_2CO_3 (cationic pathway)



without Ag_2CO_3 (neutral pathway)



Ag divers the heck reaction from a neutral pathway to a cationic one. In the cationic pathway, CO insertion and CH activation were facilitated.

CO insertion and CH activation were slow. Therefore, the equilibrium between **D-16** and **D-17** shifted completely toward **D-16**.

Dounay, B.; Overman, L. *Chem. Rev.* **2003**, *103*, 2945
Kashiki, Y.; Shimizu, I.; Yamamoto, A.; *Bull. Chem. Soc. Jpn.* **1997**, *70*, 917

Question C: What is the role of Ag_2CO_3 in (1)?

→ Ag_2CO_3 contributes to facilitate CO insertion and CH activation, to obtain **2-2**.

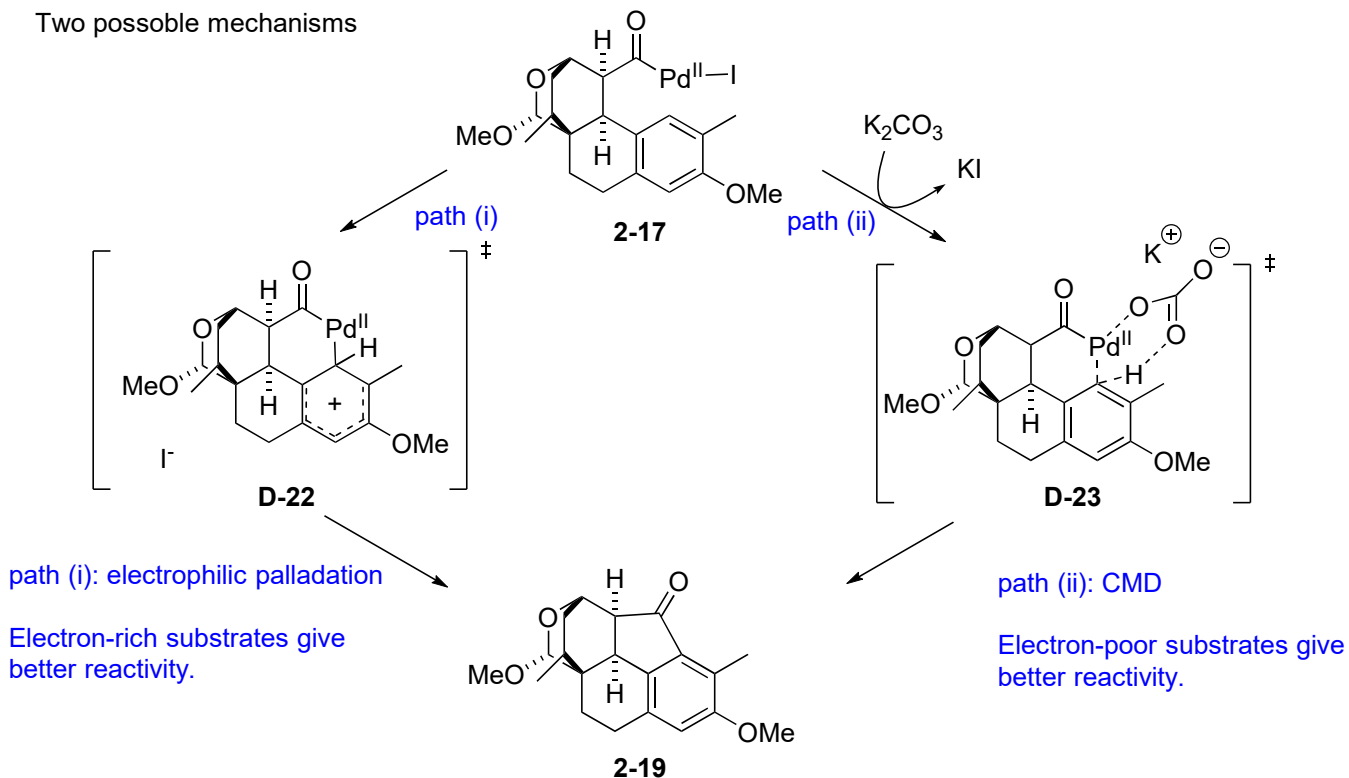
2-3. Discussion 2: electrophilic aromatic substitution

Generally, there are two potential mechanisms in the reaction of palladium-catalyzed aryl $\text{Csp}_2\text{-H}$ bond functionalization.

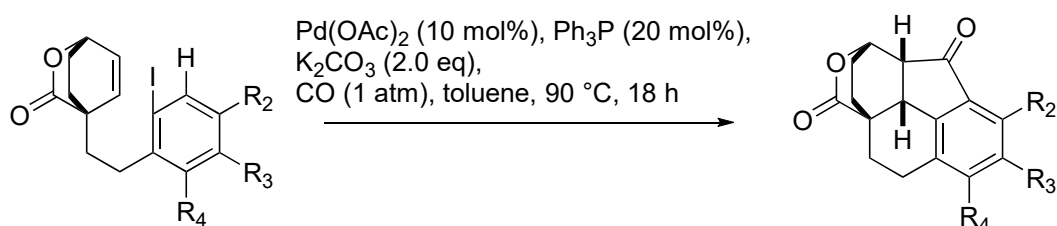
- (i) Electrophilic Palladation
- (ii) Concerted-Metallation Deprotonation (CMD)

→ Question = Which reaction mechanism is appropriate?

Two possible mechanisms



• Substrate Scope of Palladium-Catalyzed Cascade Annulation



entry	substrates	products	yield
1	 D-24	 D-25	62%
2	 D-26	 D-27	50%
3	 D-28	 D-29	31%

Author's opinion

Electron-withdrawing groups on the aromatic ring dramatically reduced the yield.
 ⇒ path (i) electrophilic palladation is thought to be appropriate.

2-4. Discussion 3: acetal formation

(2) step 2

