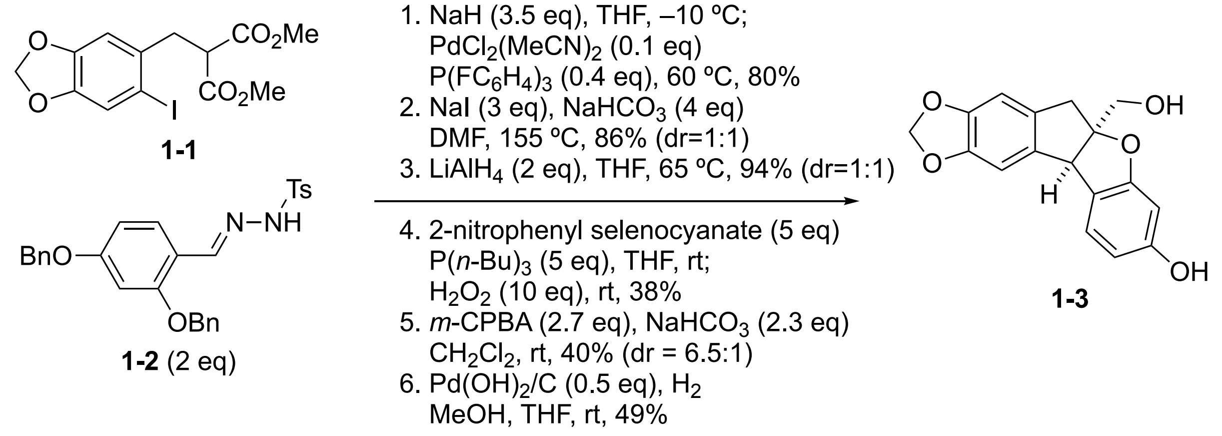
Problem Session (2) -Answer-

2025/05/24 Kaede Ono

Topic: Ring Opening Reaction of Epoxide

Problem 1: Synthetic Study to Brazilin

1 Please provide the reaction mechanisms.



1-1

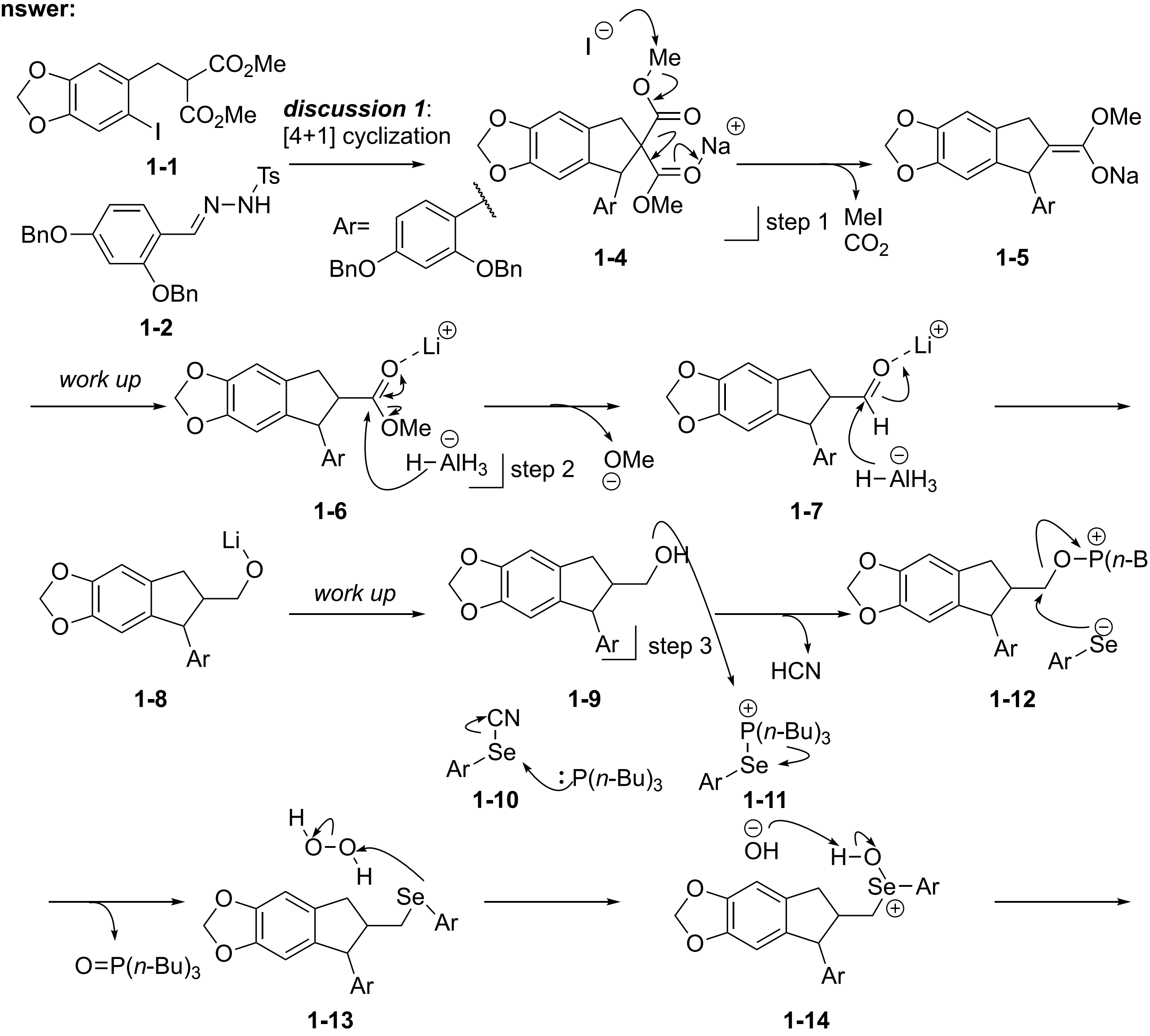
1-2 (2 eq)

1-3

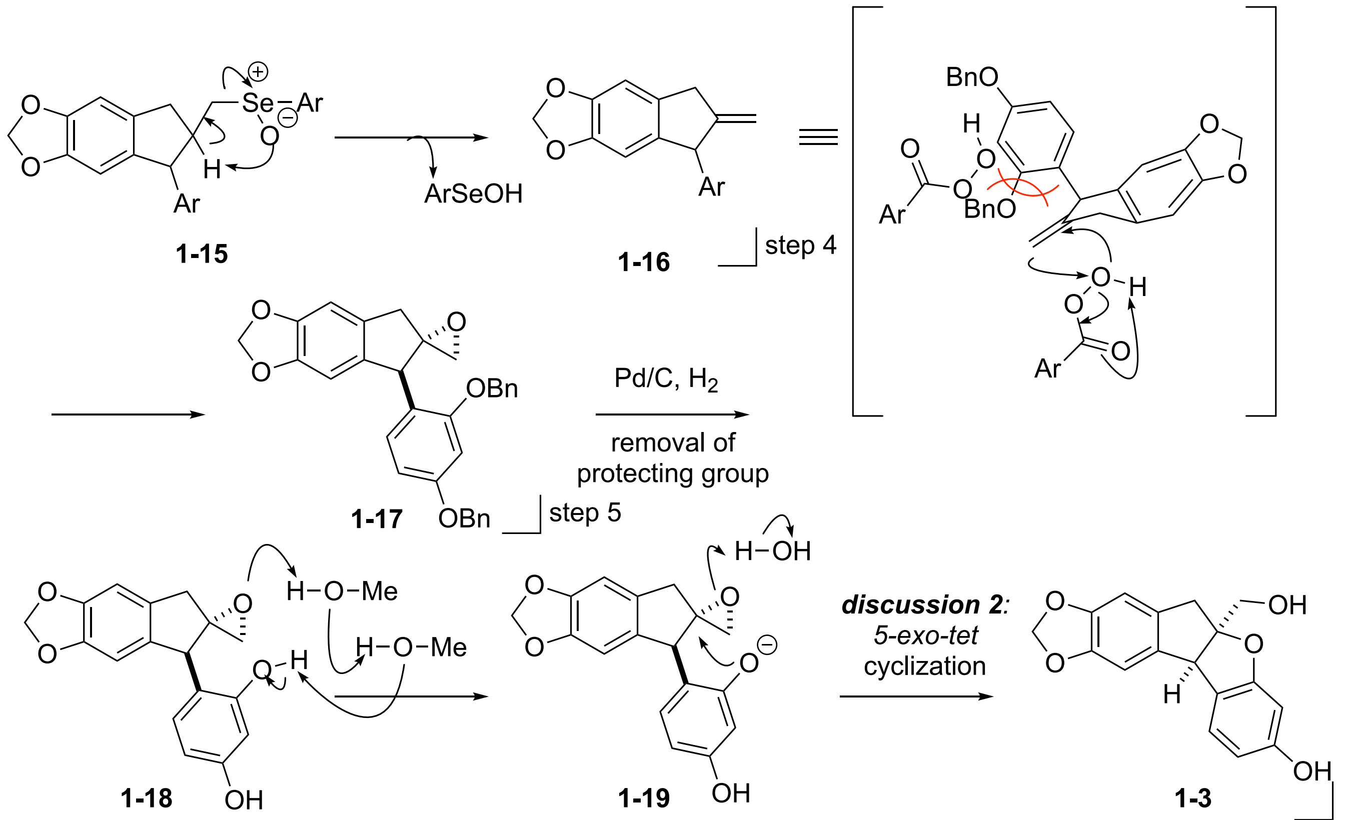
1. NaH (3.5 eq), THF, –10 ºC; $PdCl_2(MeCN)_2$ (0.1 eq) $P(FC_6H_4)_3$ (0.4 eq), 60 ºC, 80%
2. NaI (3 eq), $NaHCO_3$ (4 eq) DMF, 155 ºC, 86% (dr=1:1)
3. $LiAlH_4$ (2 eq), THF, 65 ºC, 94% (dr=1:1)
4. 2-nitrophenyl selenocyanate (5 eq) $P(n\text{-}Bu)_3$ (5 eq), THF, rt; H_2O_2 (10 eq), rt, 38%
5. *m*-CPBA (2.7 eq), $NaHCO_3$ (2.3 eq) CH_2Cl_2, rt, 40% (dr = 6.5:1)
6. $Pd(OH)_2/C$ (0.5 eq), H_2 MeOH, THF, rt, 49%

Arredondo, V.; Roa, D. E.; Gutman, E. S.; Huynh, N. O.; Van Vranken, D. L. *J. Org. Chem.* **2019**, *84*, 14745.

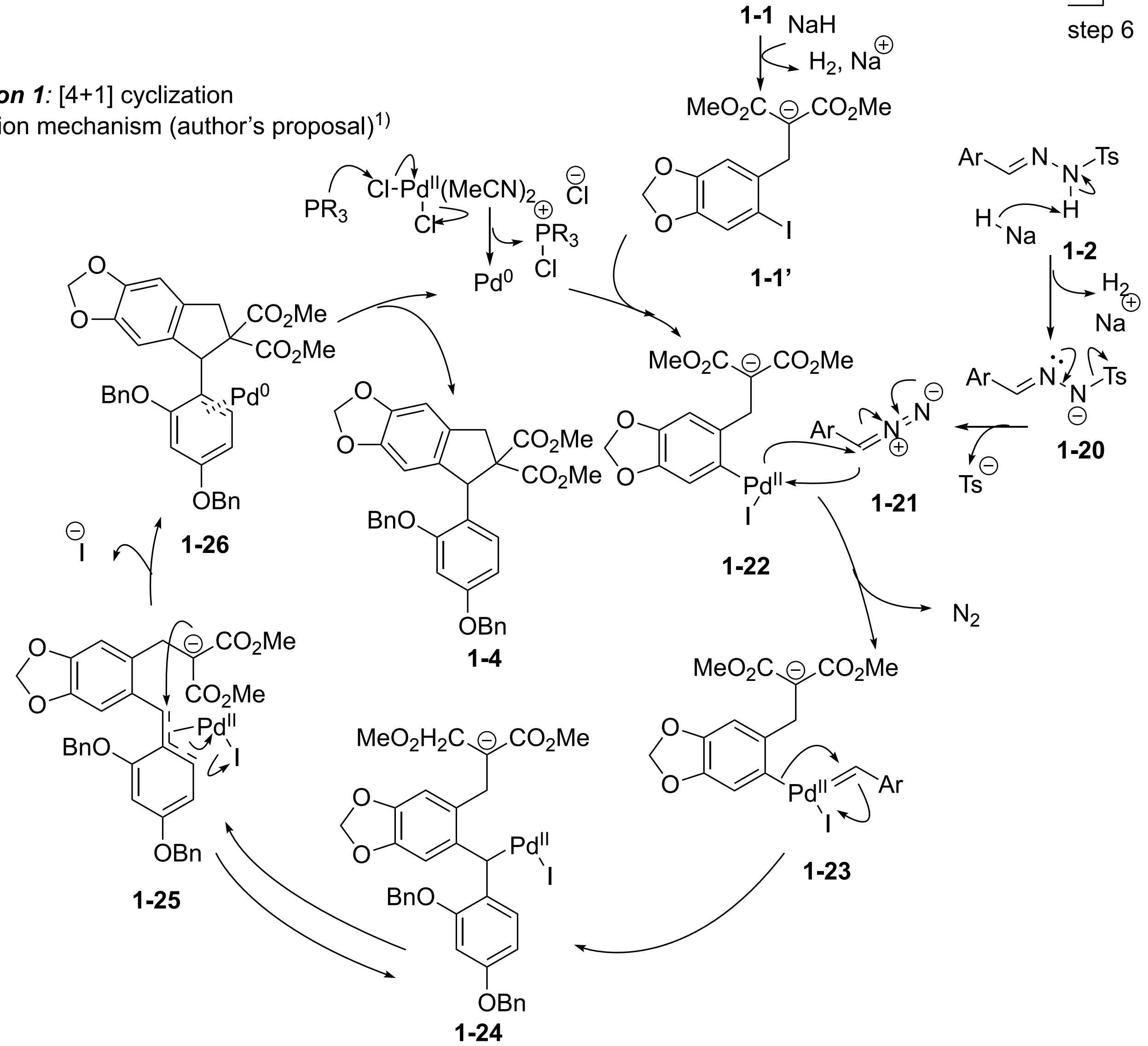
Answer:



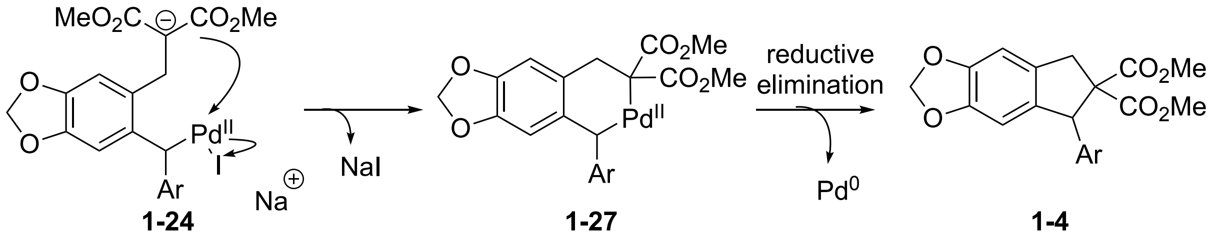
1-1 **1-2** **1-4** **1-5** **1-6** **1-7** **1-8** **1-9** **1-10** **1-11** **1-12** **1-13** **1-14**

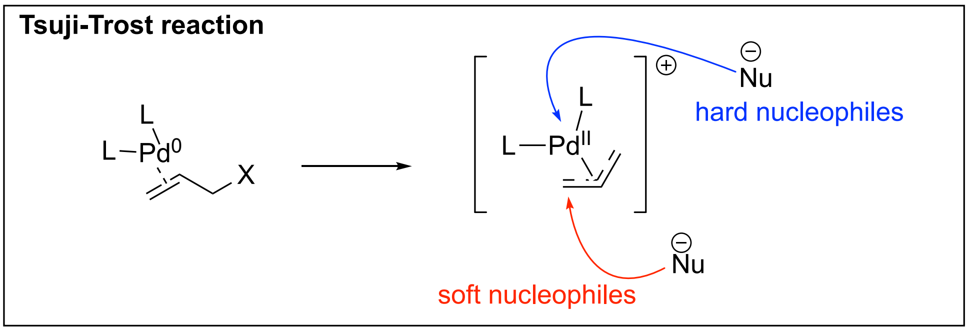


Discussion 1: [4+1] cyclization
1-1: reaction mechanism (author's proposal)1)



1-2: Another possible way

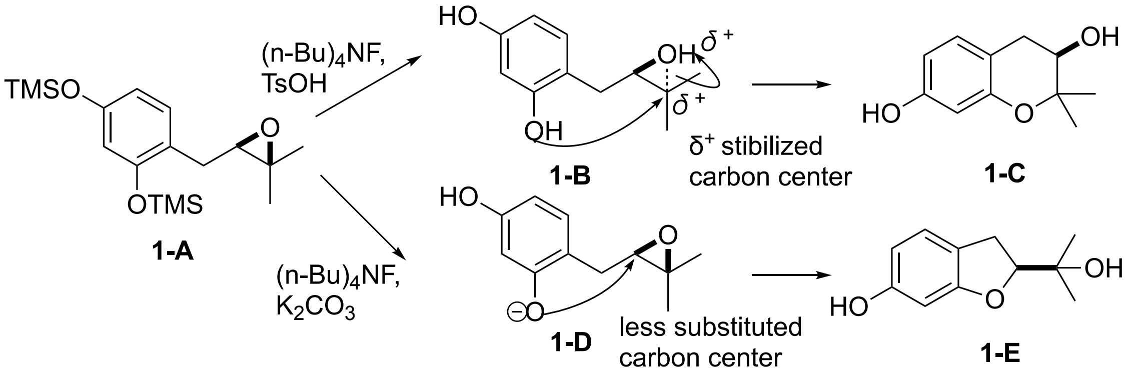




It is known that nucleophile spicies affects the regioselectivity in Tsuji-Trost reactions.
Specifically, soft nucleophiles attack the carbon of the π-allyl complex, while hard nucleophiles causes a kinetic reaction that attacks the Pd directly.
In this case, the soft nucleophile is used, so nucleophilic addition to the carbon seems to be a reasonable pathway.
However, aromatic ring decomposes when the substrate takes π-allyl complex. Thus, it is hard to determine which pathway is better.

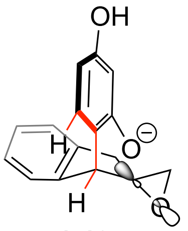
discussion 2*:* 5-*exo*-*tet* cyclization

1-0. general epoxide opening reaction2)

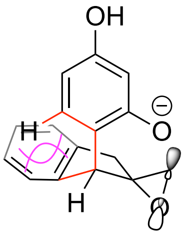


Under basic conditions nucleophile attacks less substituted carbon center.
In contrast, under acidic condition, it attacks more substituted carbon, where δ^+ is stibilied.
Due to the acidic activation, 6-endo-tet become more favorable than the typically favorable 5-exo-tet.

2-1. chemselectivity



1-19’

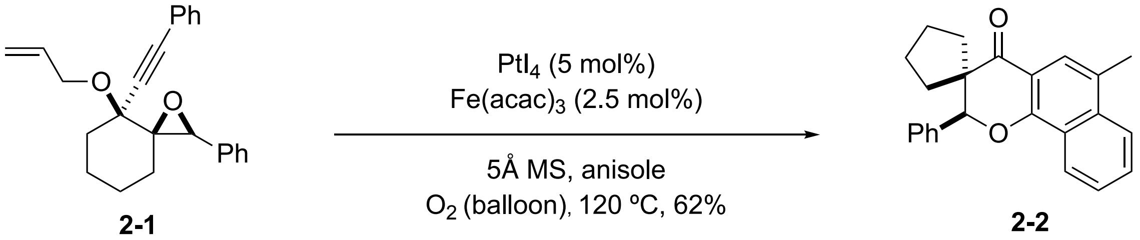


1-19”

In this reaction nucleophile attacks the more substituted carbon, even in the presence of base.
The kinetically favorable 5-exo-tet cyclization proceeds, despite potential steric hindrance associated with attacking a polysubstituted carbon.
The selectivity may also be influenced by the transition-state structure that minimizes 1,3-allylic strain in the 5-exo-tet transition state.

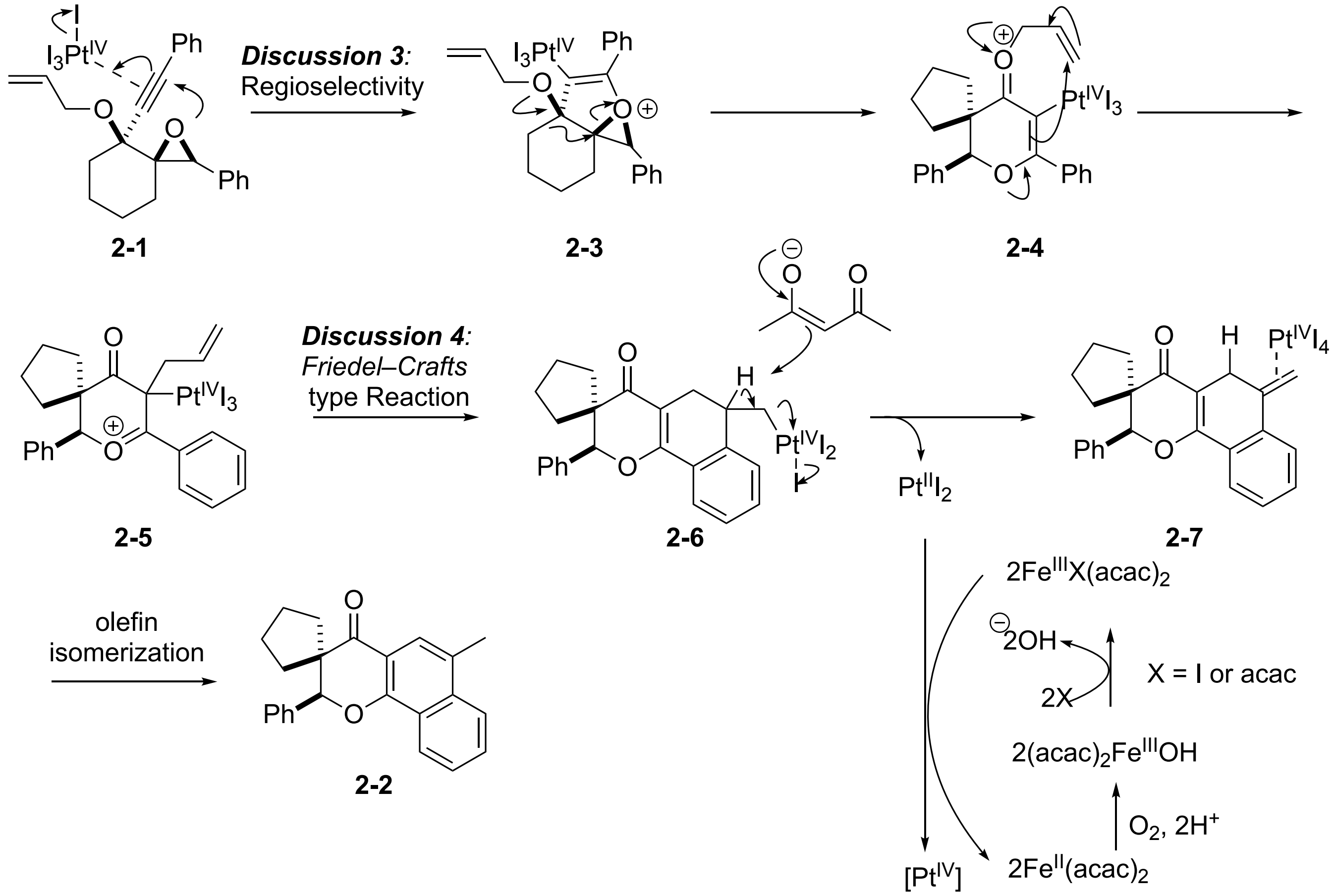
Problem 2: Platinum-Catalyzed Cascade Raction

2 Please provide the reaction mechanisms.



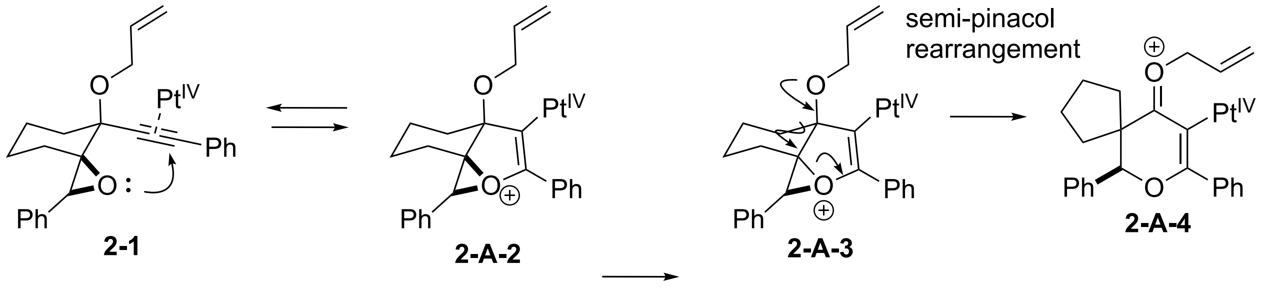
Li, W.; Li, Y.; Zhou, G.; Wu, X.; Zhang, J. *Chem. Eur. J.* **2012**, *18*, 15113.

Answer:



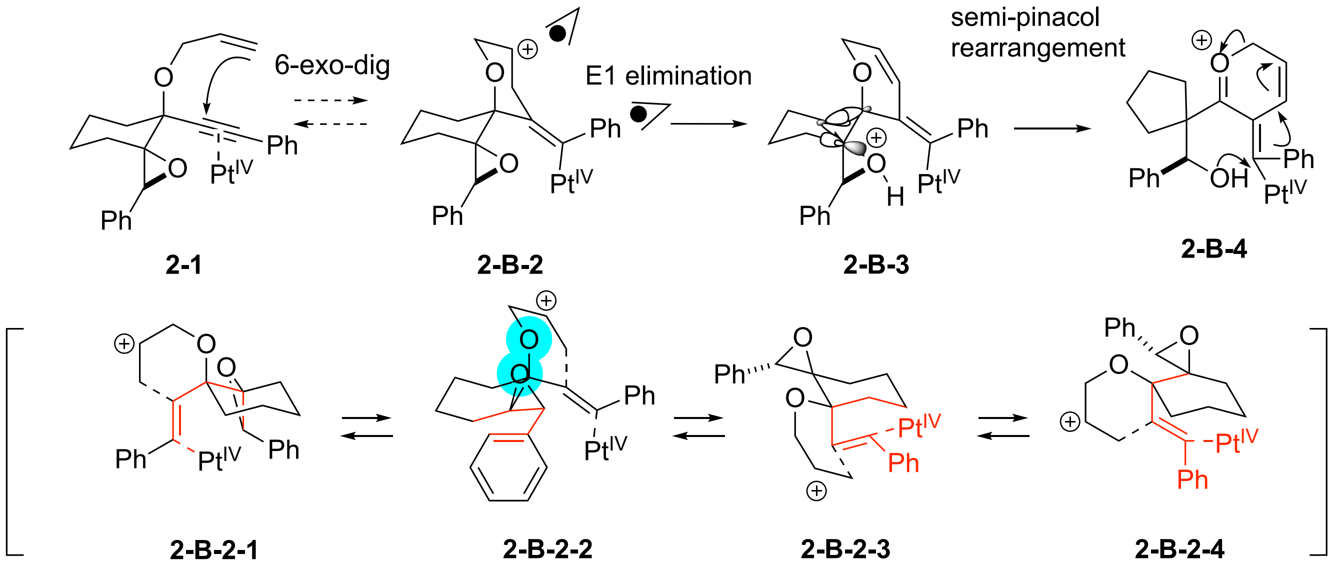
Discussion 3: Regioselectivity toward construction of spiro compound

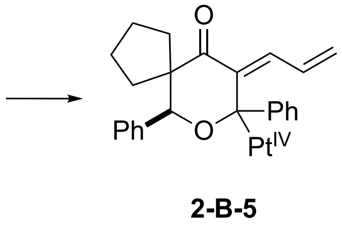
A: Alkyne → Epoxide



The most electronically favorable cyclization occur where the lonepair on the epoxide stabilizes the activated alkene. Thus, this reaction seems to be faster.
Although oxonium cation is produced in rearrangement, the reaction may proceed driven by activated epoxide.

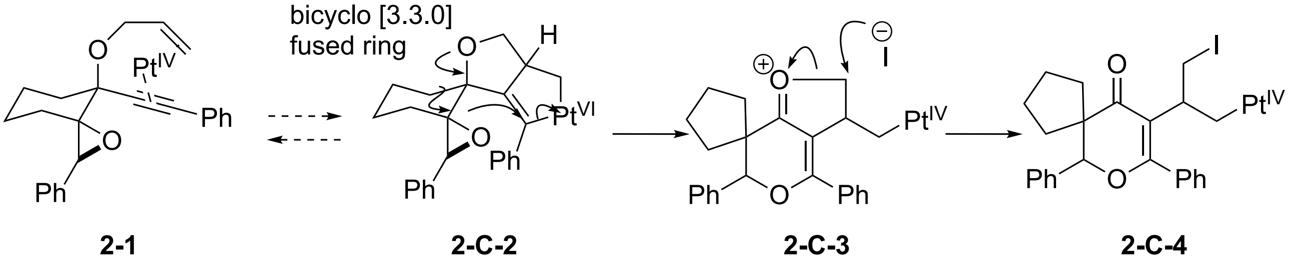
B: Alkyne → Alkene





Electron donation from the non-electron-rich exo-olefin occurs, resulting in an unstable secondary cation.
In addition, **2-B-2** is a sterically unfavorable in any conformations because of the allylic strain.

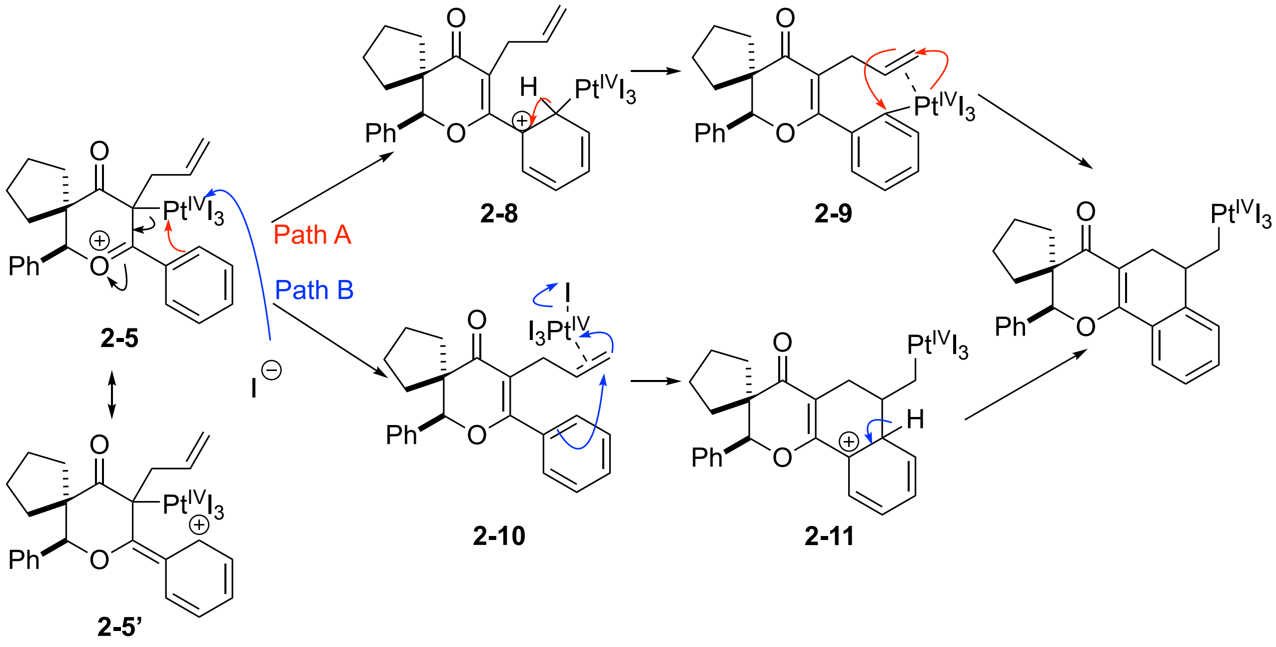
C: Enyne cyclization



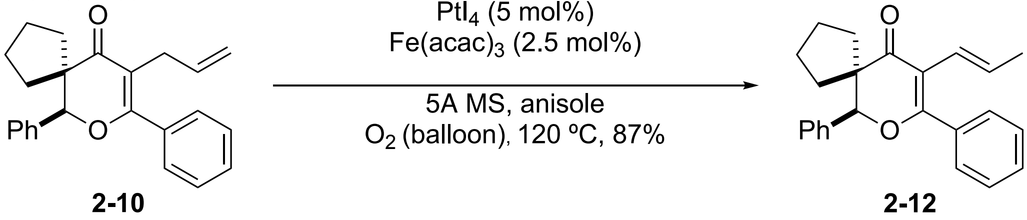
Alkynes and alkenes are in close proximity and react easily regardless of their conformation.
However, in this reaction, Pt^{IV} should turn to Pt^{VI}, despite Platinum generally exhibits a +2 or +4 oxidation state.
So this type reaction does not occur.

***Discussion 4**:* Friedel–Crafts type Reaction

2-1. Two possible way of cyclization (author's proposal)



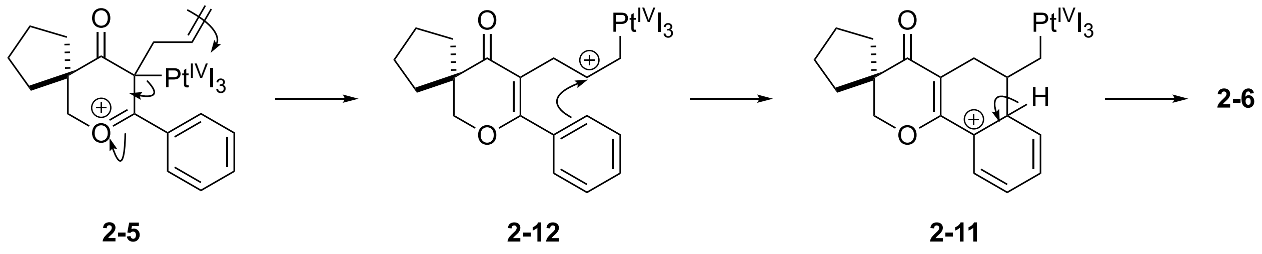
Experimental result



Cyclization did not occur but olefin isomerization was observed.

This result shows once Pt is removed, the reaction does not proceed.
Friedel-Craft-Type reaction seems to require driving force to resolve the cation.
Therefore, the reaction does not proceed in path B through intermediate **2-10**.
In contrast, Path A proceeds via an intramolecular reaction.
However, aromatic ring of **2-5** is electron deficient due to resonance stabilization as **2-5'**, thus Friedel–Crafts-Type reaction seems to be disfavored reaction.

2-2. My proposal



In this pathway, unstable cation **2-12** is formed, so the first step is disfavorable.
However, in the Friedel-Crafts reaction, conjugated cation is generated, this can be the driving force of cyclization.

Reference:

1. Gutman, E. S.; Arrendondo, V.; Van Vranken, D. L. *Org. Lett*. **2014**, *16*, 5498.
2. Ren, X.-D.; Zhao, N.; Xu, S.; Lü, H.-N.; Ma, S.-G.; Liu, Y.-B.; Li, Y.; Qu, J.; Yu, S.-S. *Tetrahedron* **2015**, *71*, 4821.