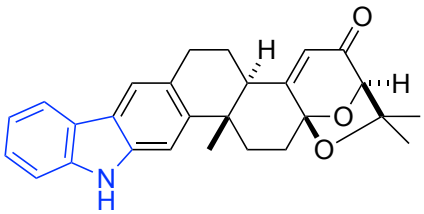
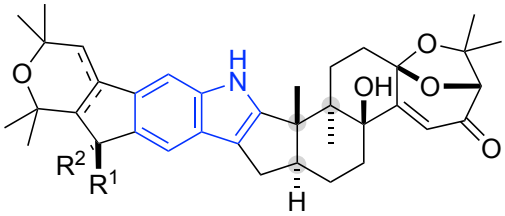
Problem Session (4)

23/06/23 Junhao Fu

Topic: Total synthesis of indole diterpenoid natural products



(+)-shearillicine



shearinine D: R^1 = OH, R^2 = H
shearinine G: R^1, R^2 = O

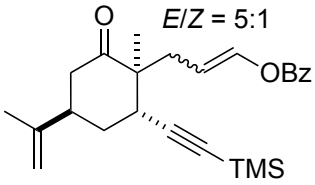
Isolation[1]
endophytic *Penicillium* sp.
Structural features
- highly oxidized terminal ring
- carbazole moiety

Biological activities
anticancer activity
Total synthesis[2]
Newhouse *et al.* **2023** ⟸ probelm 1

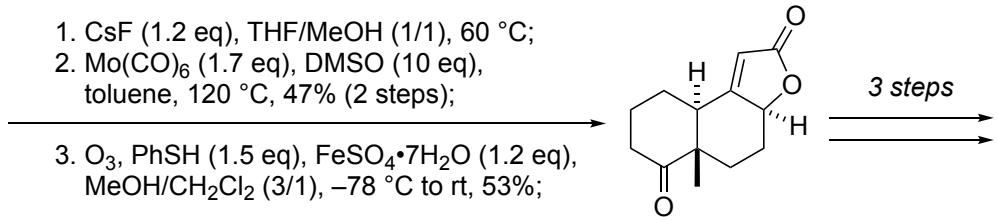
Isolation[3]
endophytic *Penicillium* sp.
Structural features
- *trans*-hydrindane with two vicinal quaternary stereocenters
- indole moiety

Biological activities
BK_{Ca} channel inhibition
Total synthesis[4]
Carreira *et al.* **2022** ⟸ probelm 2

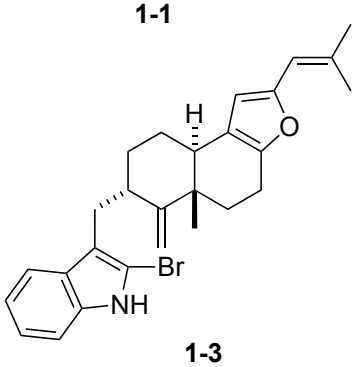
Problem 1



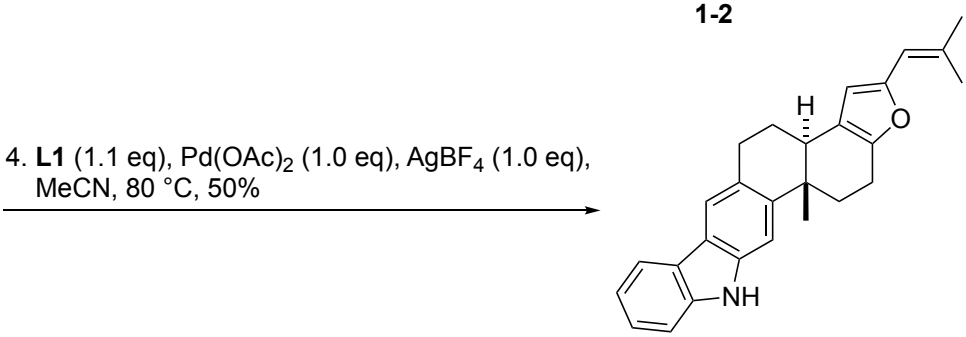
1-1



1-2



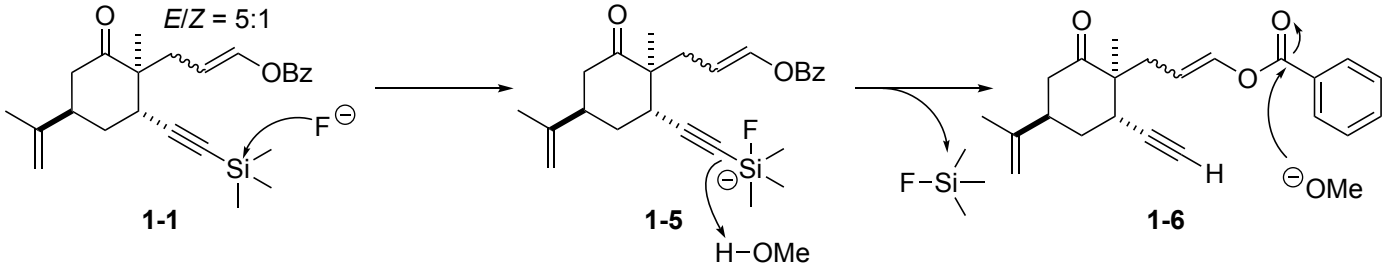
1-3



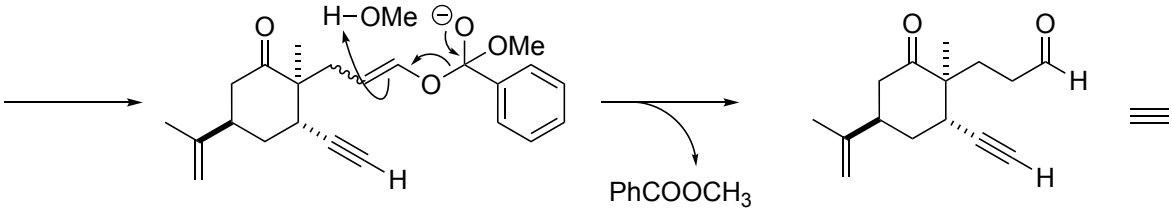
1-4

J. Am. Chem. Soc. **2023**, *145*, 4394-4399.

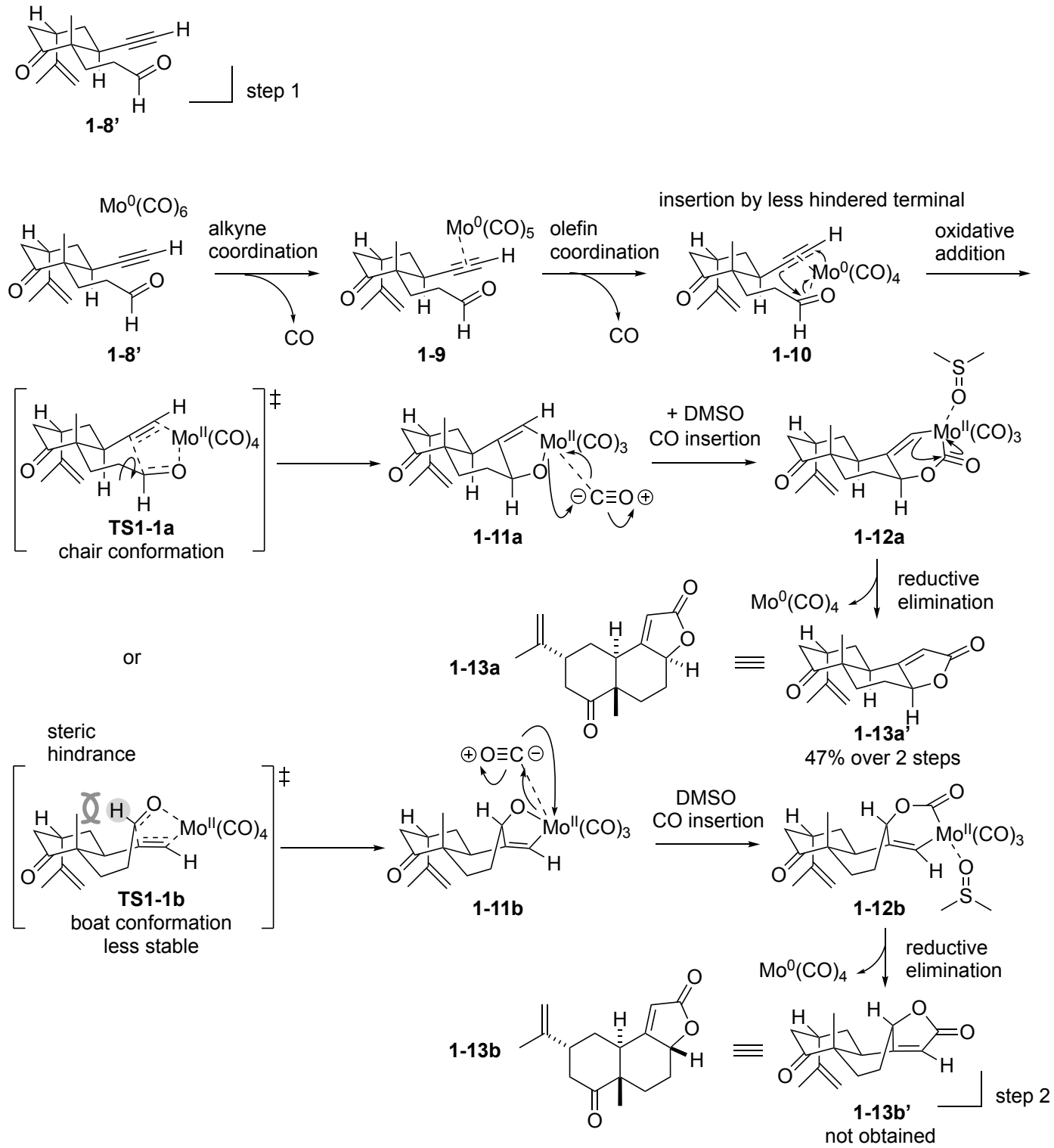
Mild basicity and high solubility of CsF in MeOH/THF contributes to the effective one-pot deprotection reaction.



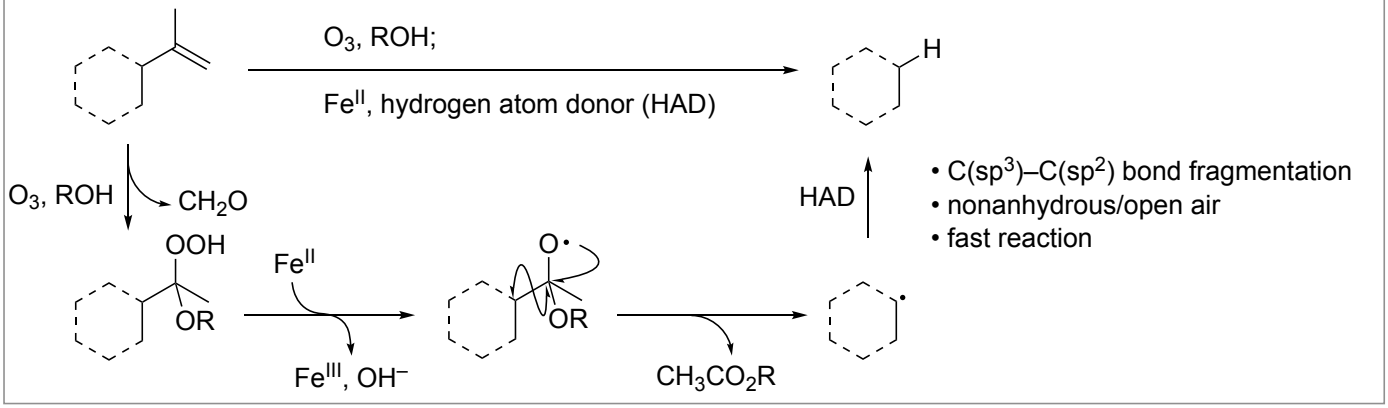
1-1 **1-5** **1-6**



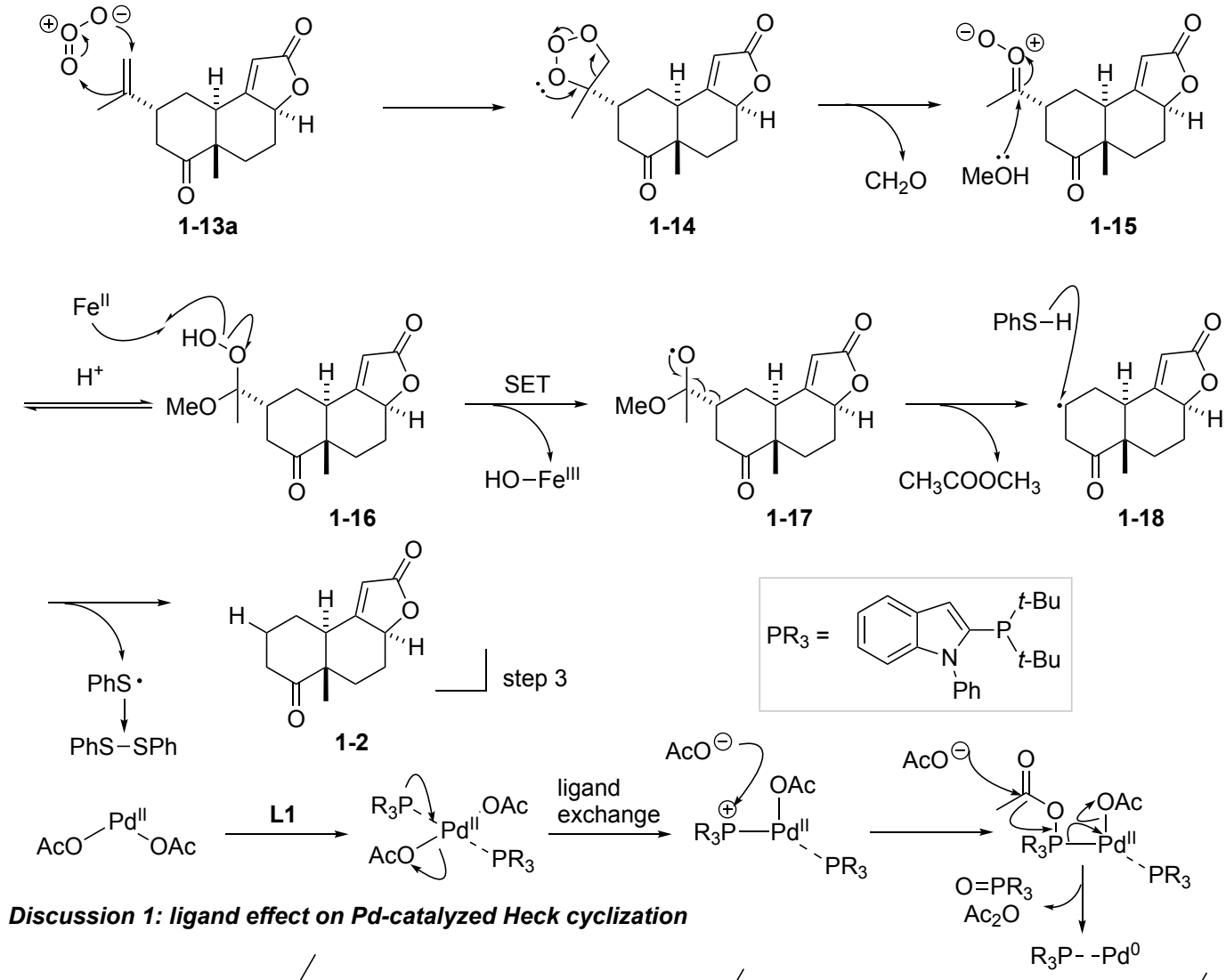
1-7 **1-8**



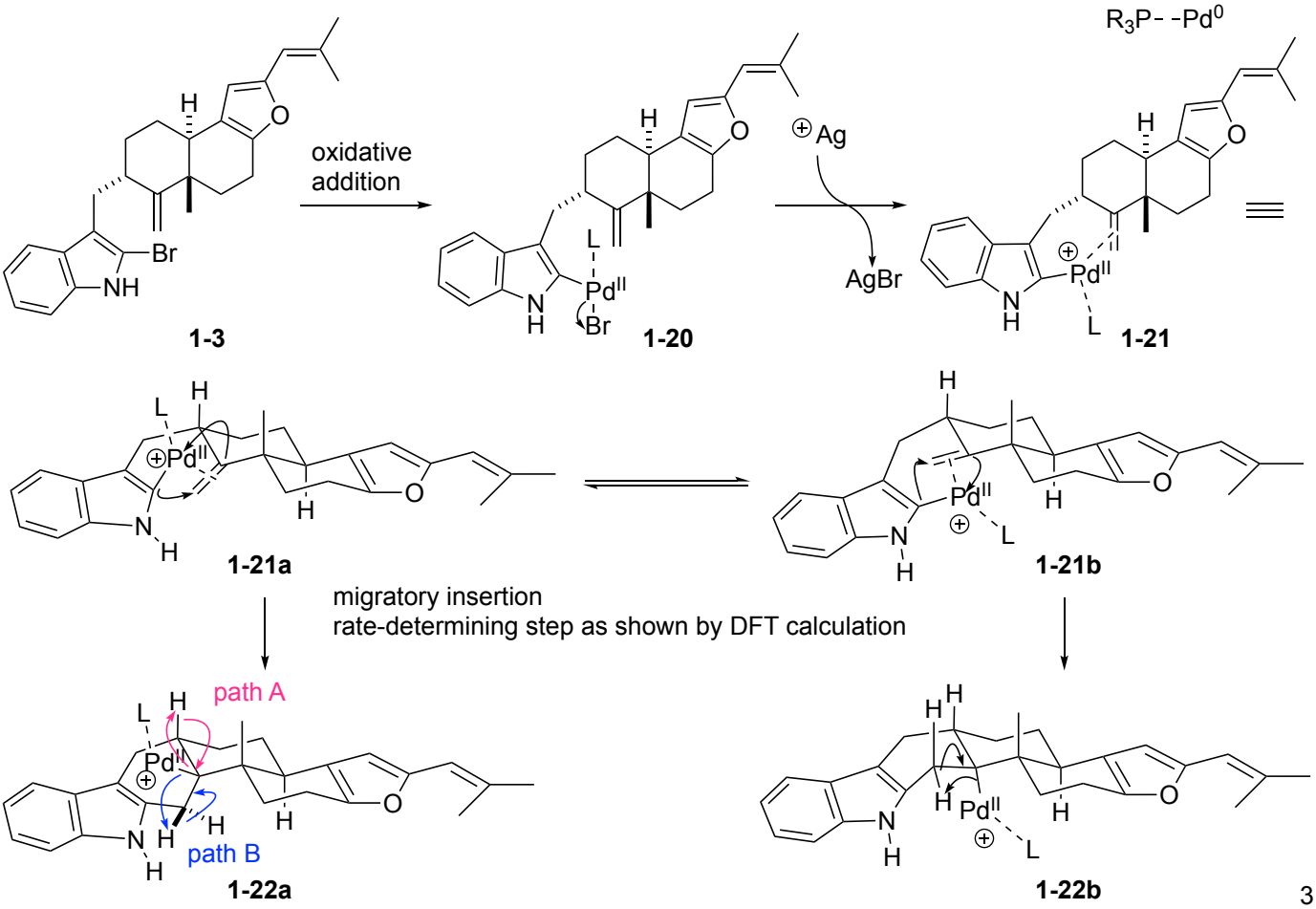
hydrodealkenylation[5]: Kwon *et al.* **2019**

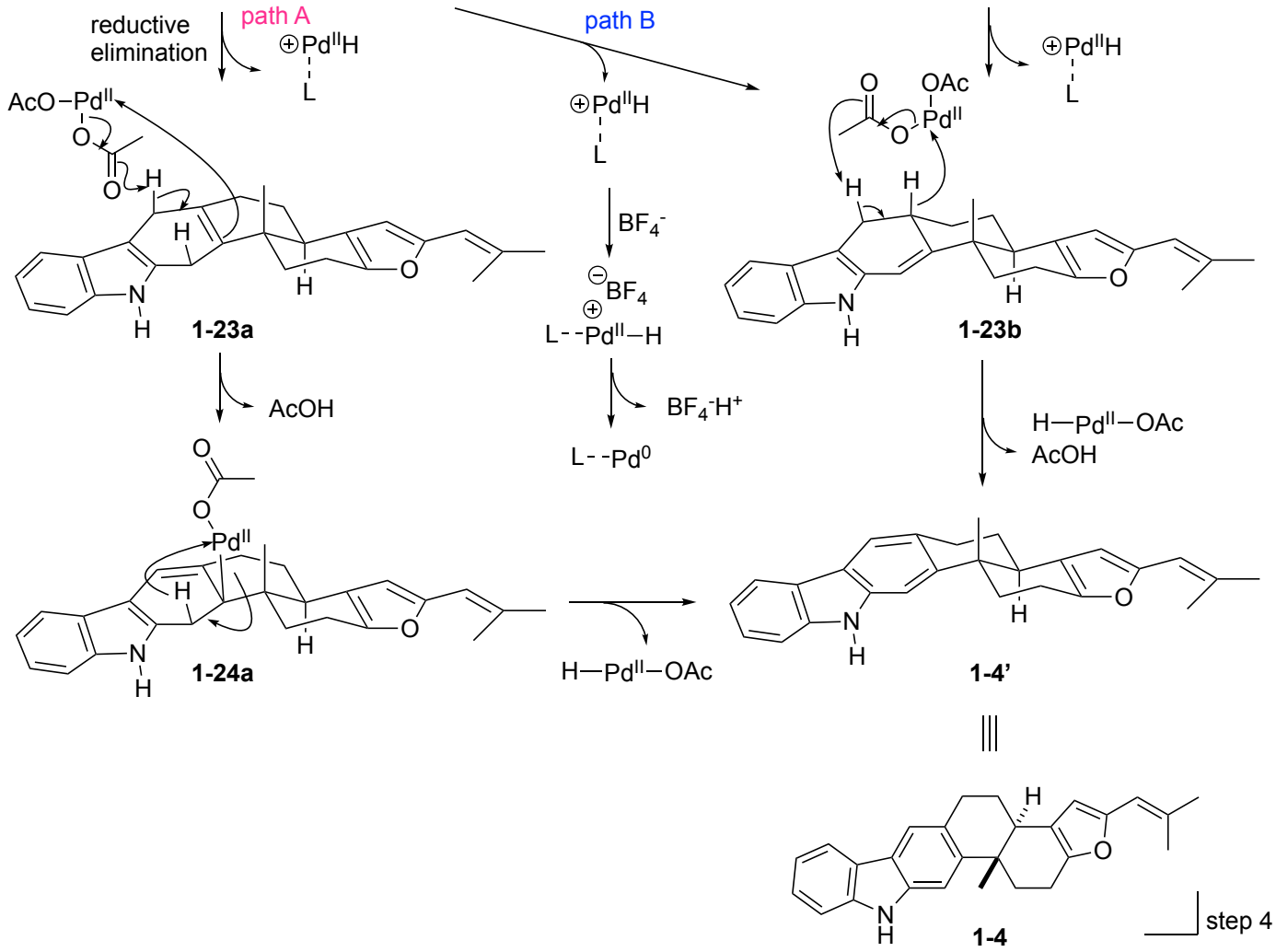


regioselective oxidation to electron-rich olefin



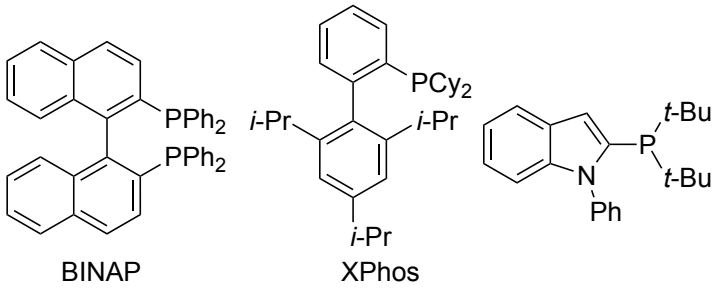
Discussion 1: ligand effect on Pd-catalyzed Heck cyclization





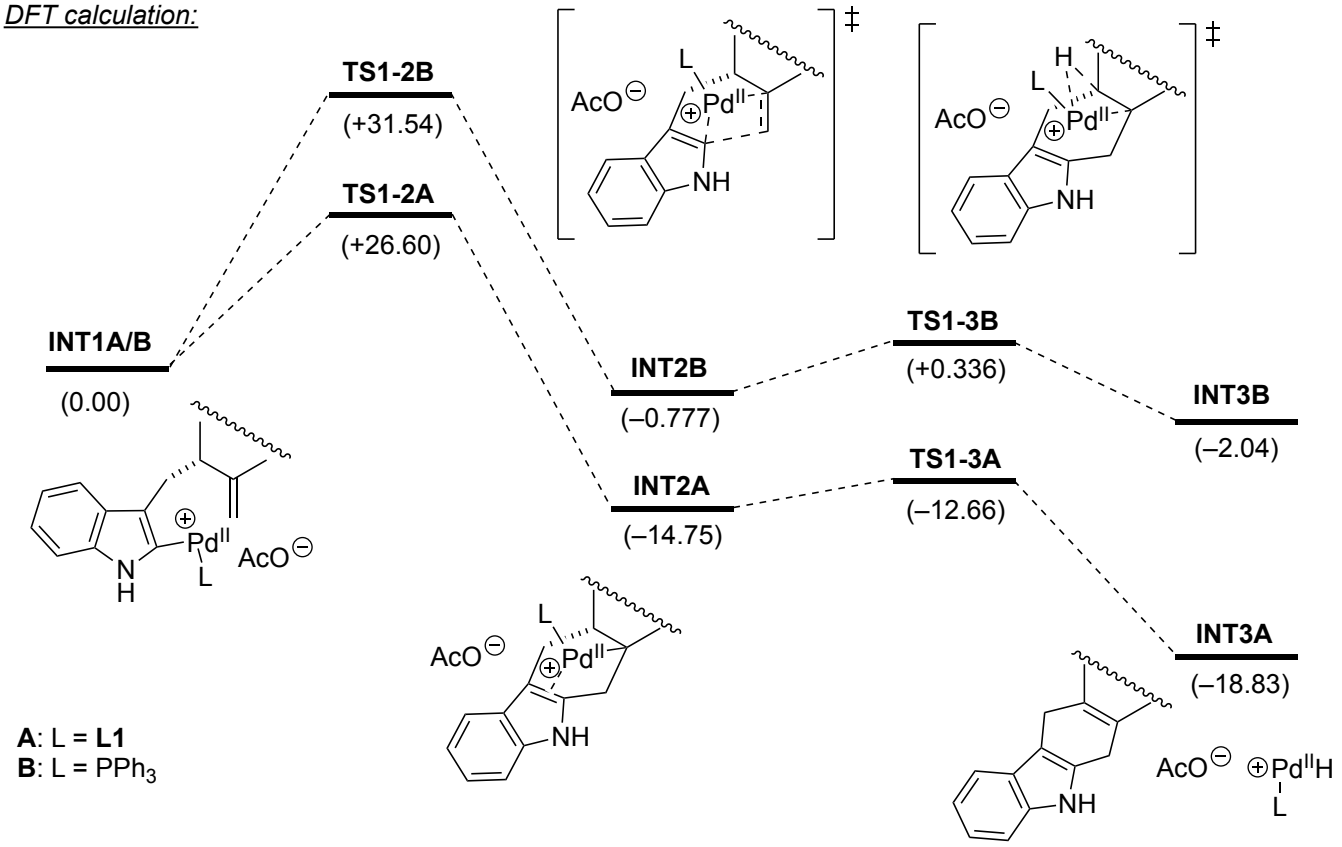
Discussion 1-1: ligand effect on Pd-catalyzed Heck cyclization

entry	ligand	yield (%)
1	–	0
2	PPh_3	8
3	BINAP	6
4	$PBn(Ad)_2$	12
5	XPhos	28
6	**L1**	50



- The ligand-free condition and generally utilized ligands all failled to afford **1-4** in ideal yields.
- Compared to the generally utilized ligands, **L1** seems to afford higher yield.

DFT calculation:



The results of DFT calculation revealed roughly 5 kcal/mol stabilization effect of **TS1-2A** than **TS1-2B**, which are at the highest energy level and are possibly the energy barrier for this Heck reaction.

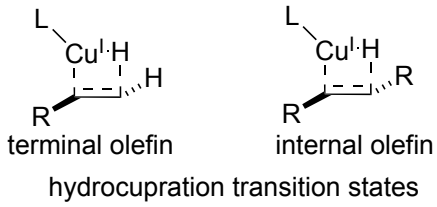
Rationale for the difference in energy of the two TSs:

1. Electron density of phosphine ligand

Comparing to the triarylphosphine ligand PPh_3, the two electron rich alkyl *t*-Bu substitutions of **L1** greatly contributes to the stabilization of the cationic Pd center.

2. Ligand-substrate **London dispersion forces**: formation of instantaneous dipoles that attract each other[6] (proposed by the author, minor effect)

Liu, P. et al. *J. Am. Chem. Soc.* **2017**, *139*, 16548–16555.



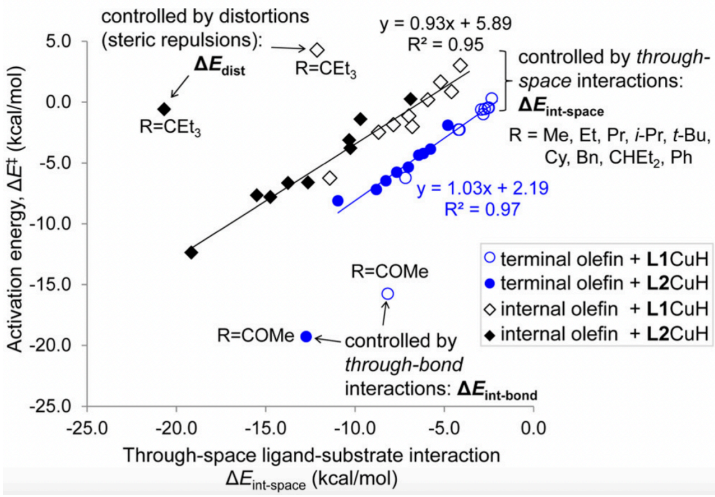
$$\Delta E^{\ddagger} = \Delta E_{\text{int-space}} + \Delta E_{\text{int-bond}} + \Delta E_{\text{dist}}$$

$\Delta E^{\ddagger}$: activation energy

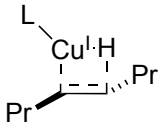
$\Delta E_{\text{int-space}}$: through space interaction energy

$\Delta E_{\text{int-bond}}$: through bond interaction energy

ΔE_{dist}: distortion energy (steric repulsion)

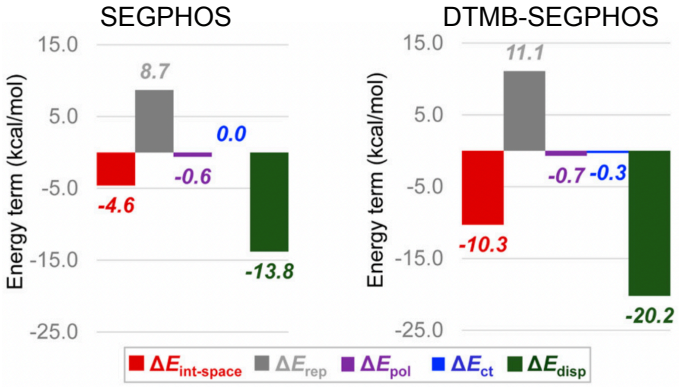


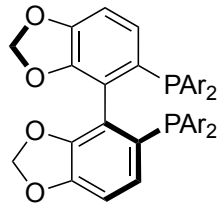
Except for extreme cases, linear correlation between $\Delta E^{\ddagger}$ and $\Delta E_{\text{int-space}}$ is observed. Through-bond interaction and steric repulsion are insignificant in this case.



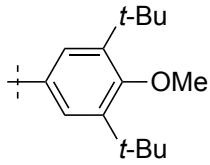
L = SEGPHOS:
$\Delta G^{\ddagger}$ = 26.4 kcal/mol
$\Delta E^{\ddagger}$ = 0.8 kcal/mol

L = DTMB-SEGPHOS:
$\Delta G^{\ddagger}$ = 21.3 kcal/mol
$\Delta E^{\ddagger}$ = –3.8 kcal/mol





SEGPHOS: Ar = Ph
DTMB-SEGPHOS: Ar =



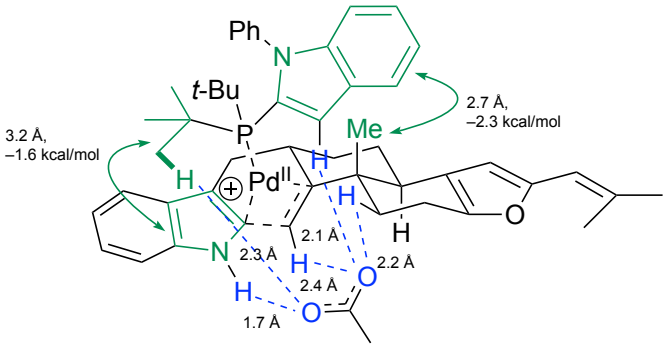
$\Delta E_{int\text{-}space} = \Delta E_{rep} + \Delta E_{pol} + \Delta E_{ct} + \mathbf{\Delta E_{disp}}$

Dispersion energy dominates $\Delta E_{int\text{-}space}$, stabilizing the transition state.

ΔE_{rep}: electrostatistic repulsion energy
ΔE_{pol}: intrafragment polarization energy
ΔE_{ct}: ligand-substrate charge-transfer energy
ΔE_{disp}: dispersion energy

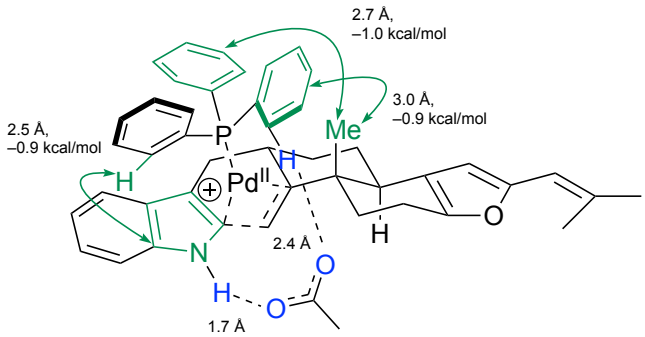
TSs of Heck reaction of this problem (dispersion forces shown in green):

a. total stabilization: –3.9 kcal/mol



TS1-2A
$\Delta G^{\ddagger}$ = 26.6 kcal/mol

b. total stabilization: –2.8 kcal/mol



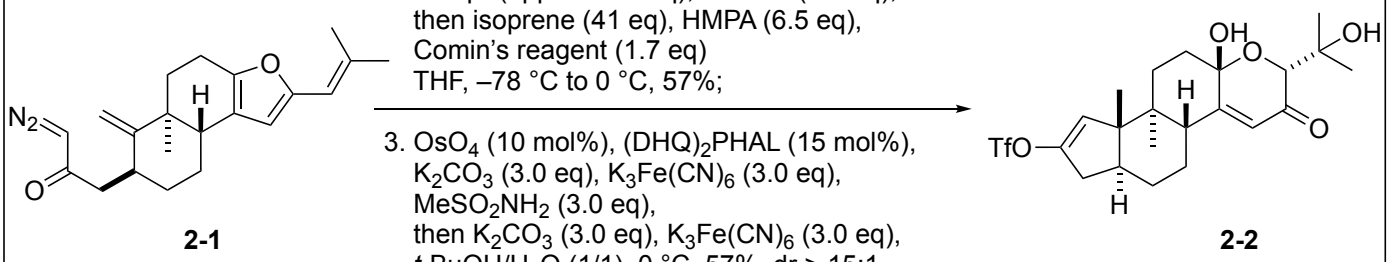
TS1-2B
$\Delta G^{\ddagger}$ = 31.5 kcal/mol

Since London dispersion forces contributes to only 1.1 kcal/mol stabilization effect, the major contribution seems to be originated from the electronic properties of the ligands as stated above.

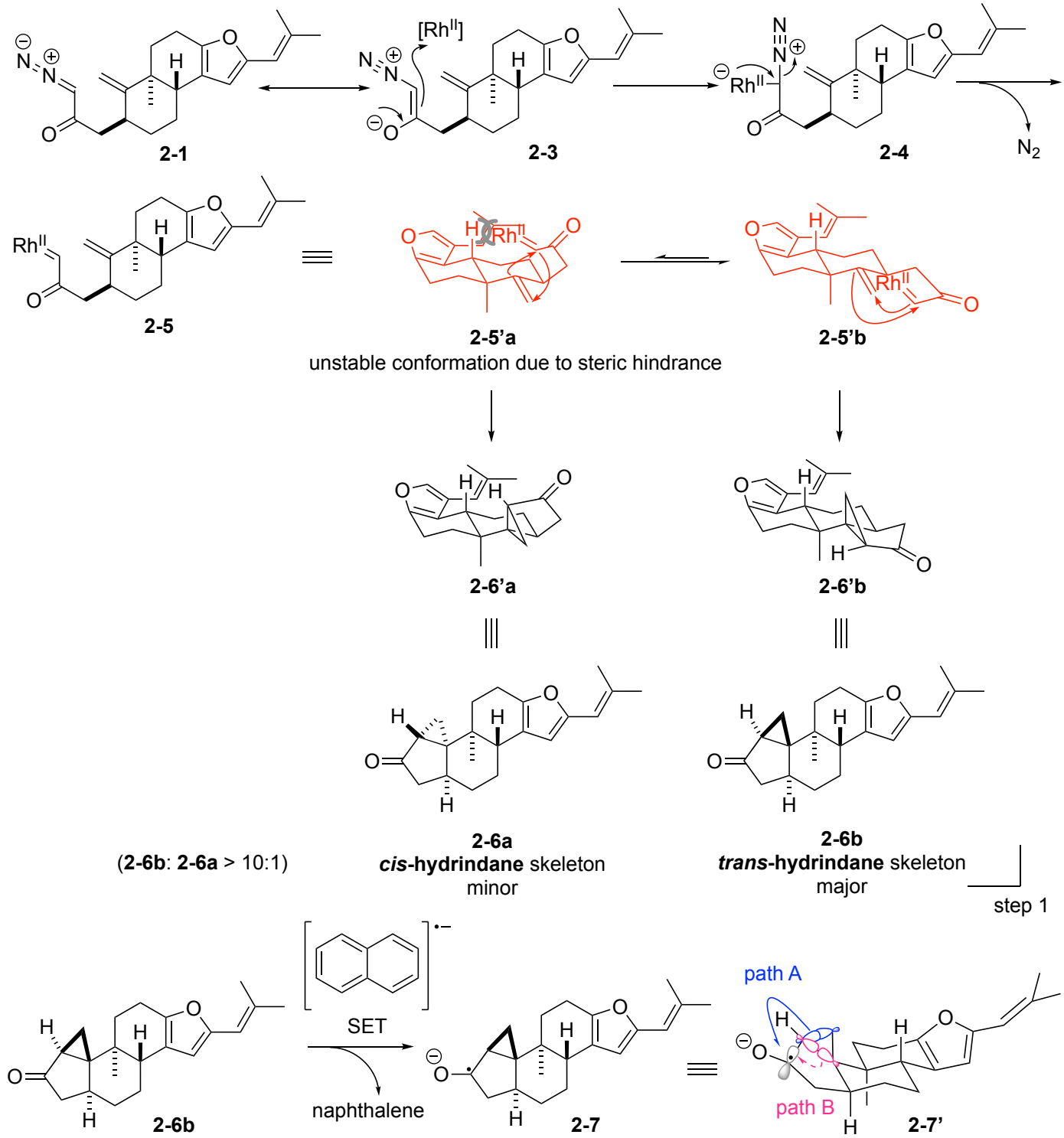
<u>3. Counter anion-ligand/substrate interaction</u>

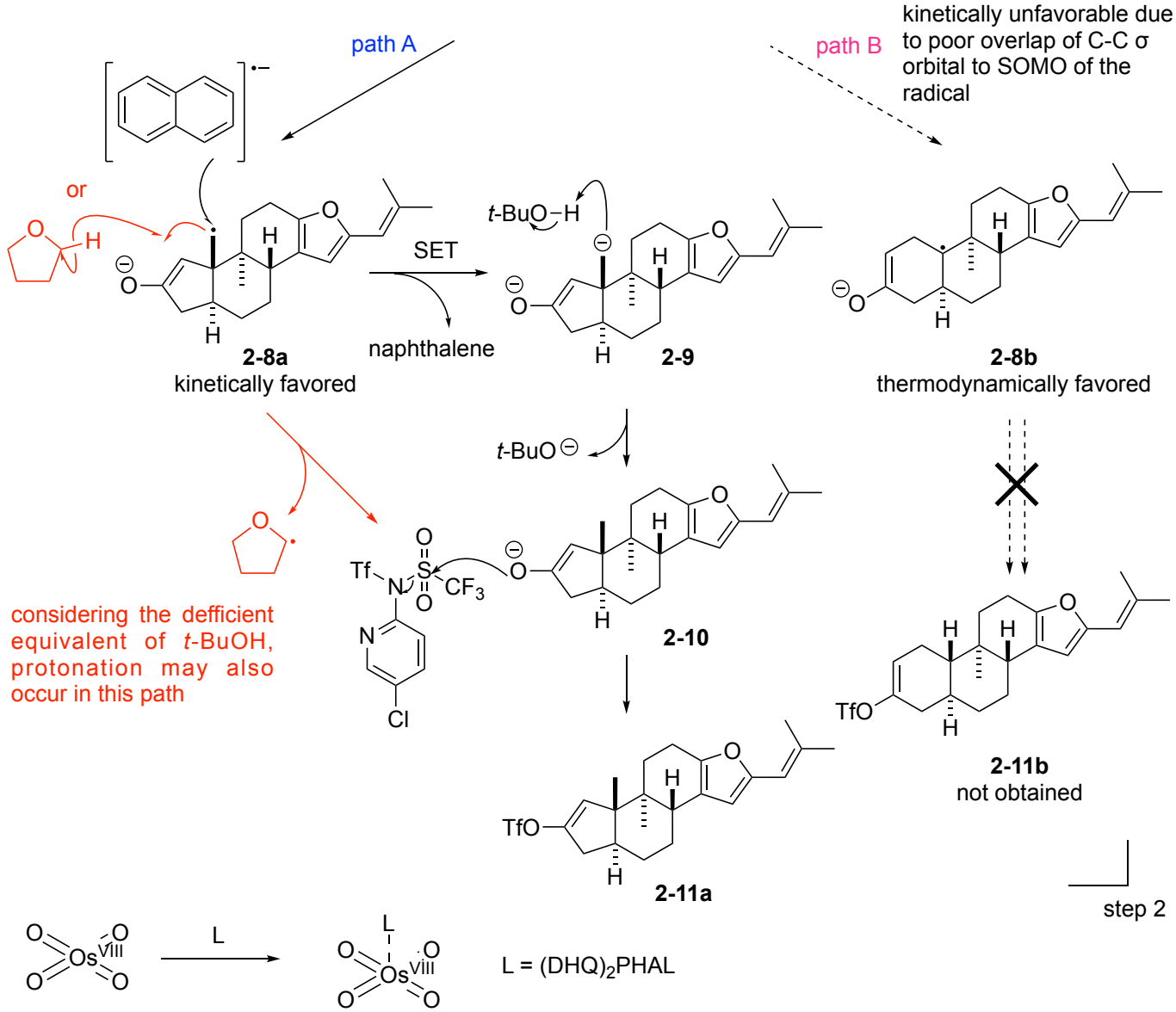
Due to larger steric repulsion, acetate anion coordinates more distantly from Pd center in **TS1-2A** than in **TS1-2B**, allowing more counter anion-ligan/substrate interactions that stablize the transition state.

Problem 2

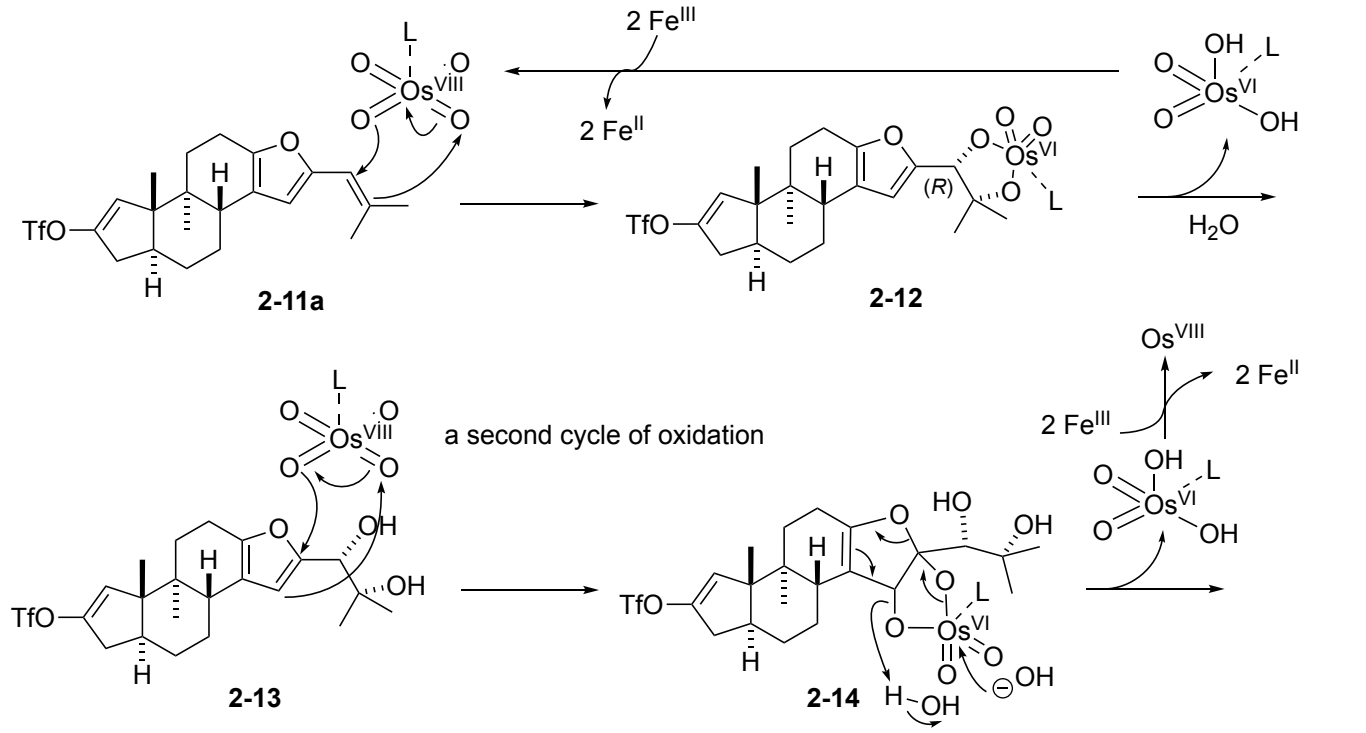


Angew. Chem. Int. Ed. **2022**, *61*, e202112838.

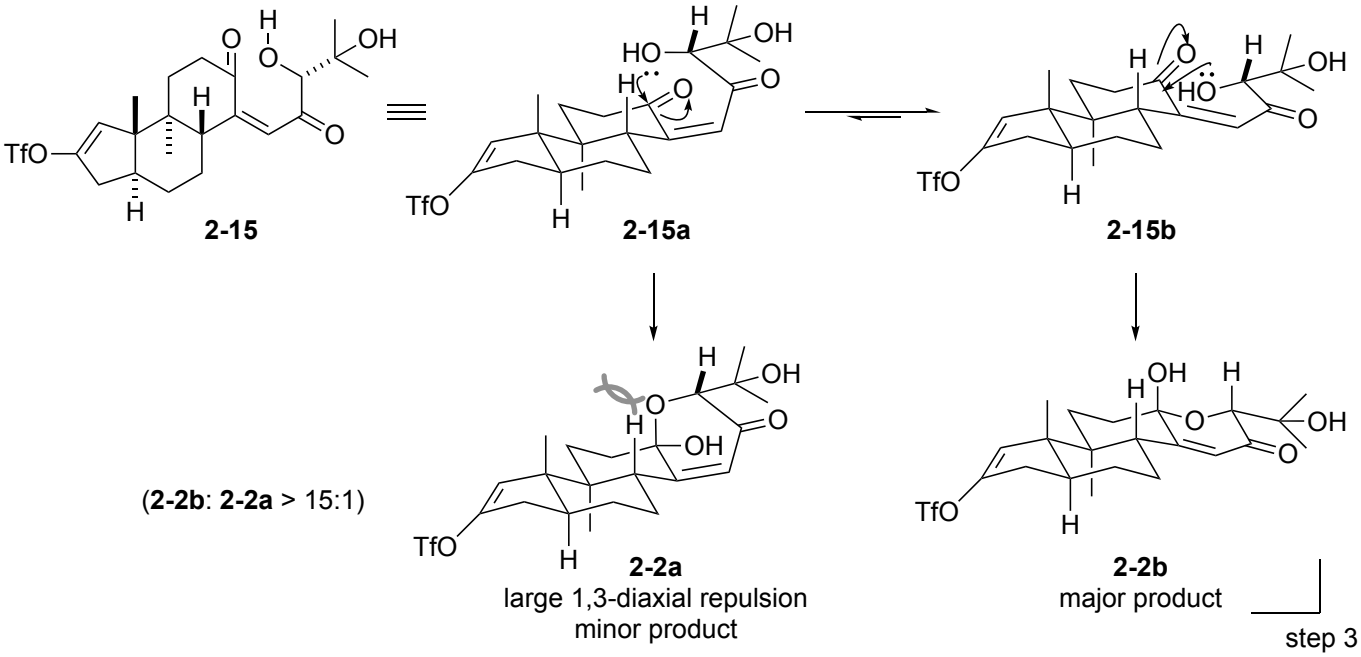




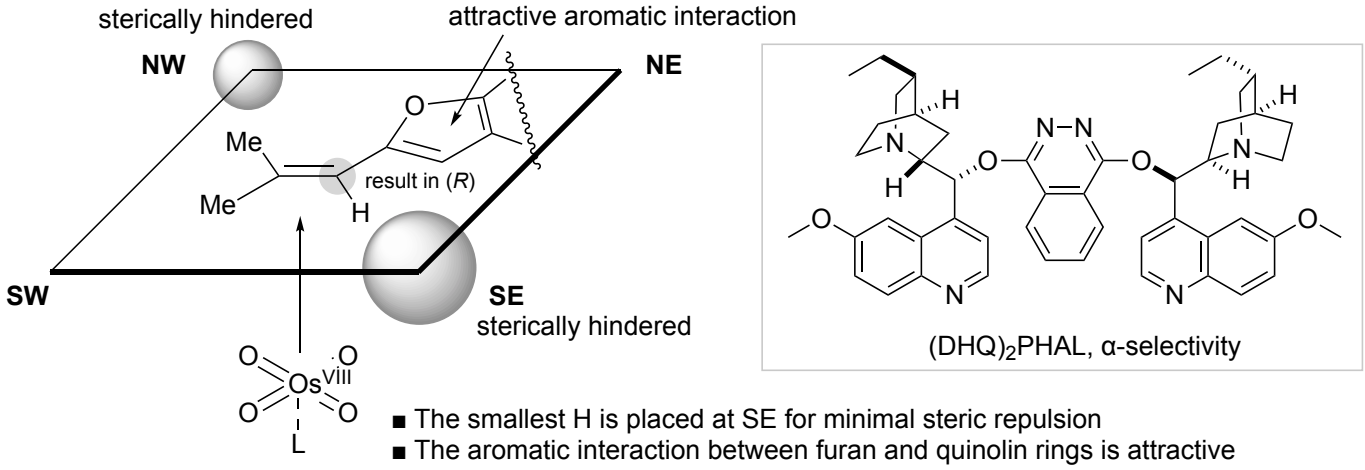
Discussion 2: face selectivity of Sharpless asymmetric dihydroxylation



Achmatowicz rearrangement



Discussion 2: face selectivity of Sharpless asymmetric dihydroxylation



References:

1. Ariantari, N. P.; Ancheeva, E.; Wang, C.; Mandi, A.; Knedel, T. O.; Kurtan, T.; Chaidir, C.; Muller, W. E. G.; Kassack, M. U.; Janiak, C.; Daletos, G.; Proksch, P. *J. Nat. Prod.* **2019**, *82*, 1412–1423.
2. Kim, D. E.; Zhu, Y.; Harada, S.; Aguilar, I.; Cuomo, A. E.; Wang, M.; Newhouse, T. R. *J. Am. Chem. Soc.* **2023**, *145*, 4394–4399.
3. Xu, M.; Gessner, G.; Groth, I.; Lange, C.; Christner, A.; Bruhn, T.; Deng, Z.; Li, X.; Heinemann, S. H.; Grabley, S.; Bringmann, G.; Sattler, I.; Lin, W. *Tetrahedron* **2007**, *63*, 435–444.
4. Hauser, N.; Imhof, M. A.; Eichenberger, S. S.; Kündig, T.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2022**, *61*, e202112838.
5. Smaligo, A. J.; Swain, M.; Quintana, J. C.; Tan, M. F.; Kim, D. A.; Kwon, O. *Science* **2019**, *364*, 681–685.
6. Lu, G.; Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D S.; Buchwald, S. L.; Liu, P. *J. Am. Chem. Soc.* **2017**, *139*, 16548–16555.