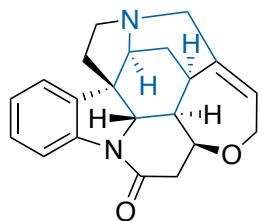


# Total Synthesis of (-)-Himalensine

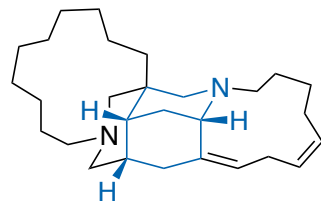
Emma Huang  
Liu Group  
03/20/2024

# Introduction

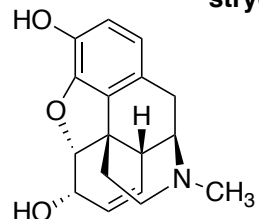
## (A) Morphan core in natural products



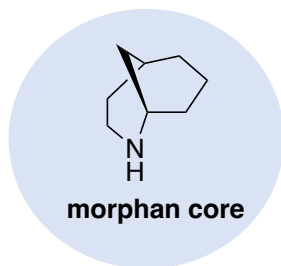
strychnine



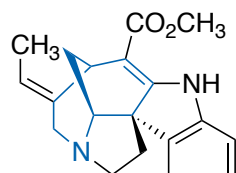
madangamine E



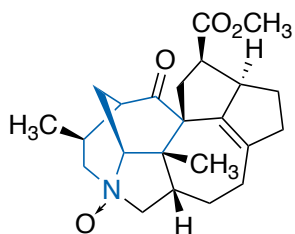
morphine



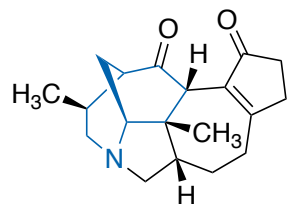
morphan core



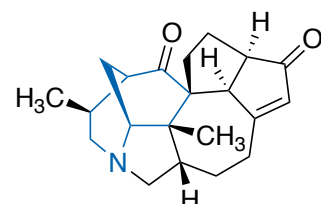
akuammicine



calyciphylline A



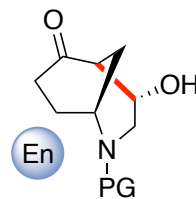
himalensine A



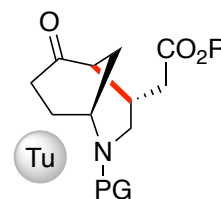
longeraciphylline A

Dixon *et al.*, *J. Am. Chem. Soc.* **2023**, 145, 5422–5430.

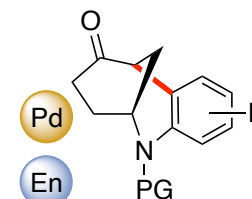
## (B) Synthesis of morphan core



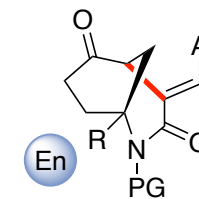
aldol reaction  
Bonjoch (2009)



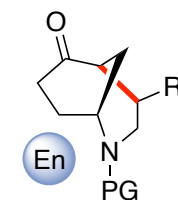
Michael addition  
Dixon (2015)



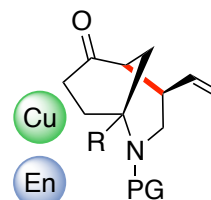
ketone arylation  
Jia (2016)



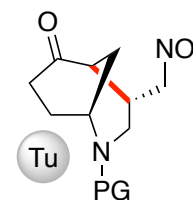
$\alpha$ -addition  
Jia (2019)



$\alpha$ -addition  
Ye (2019)



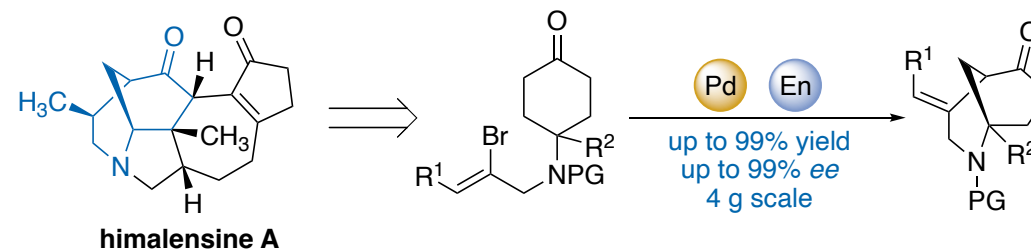
ketone allylation  
Dixon (2020)



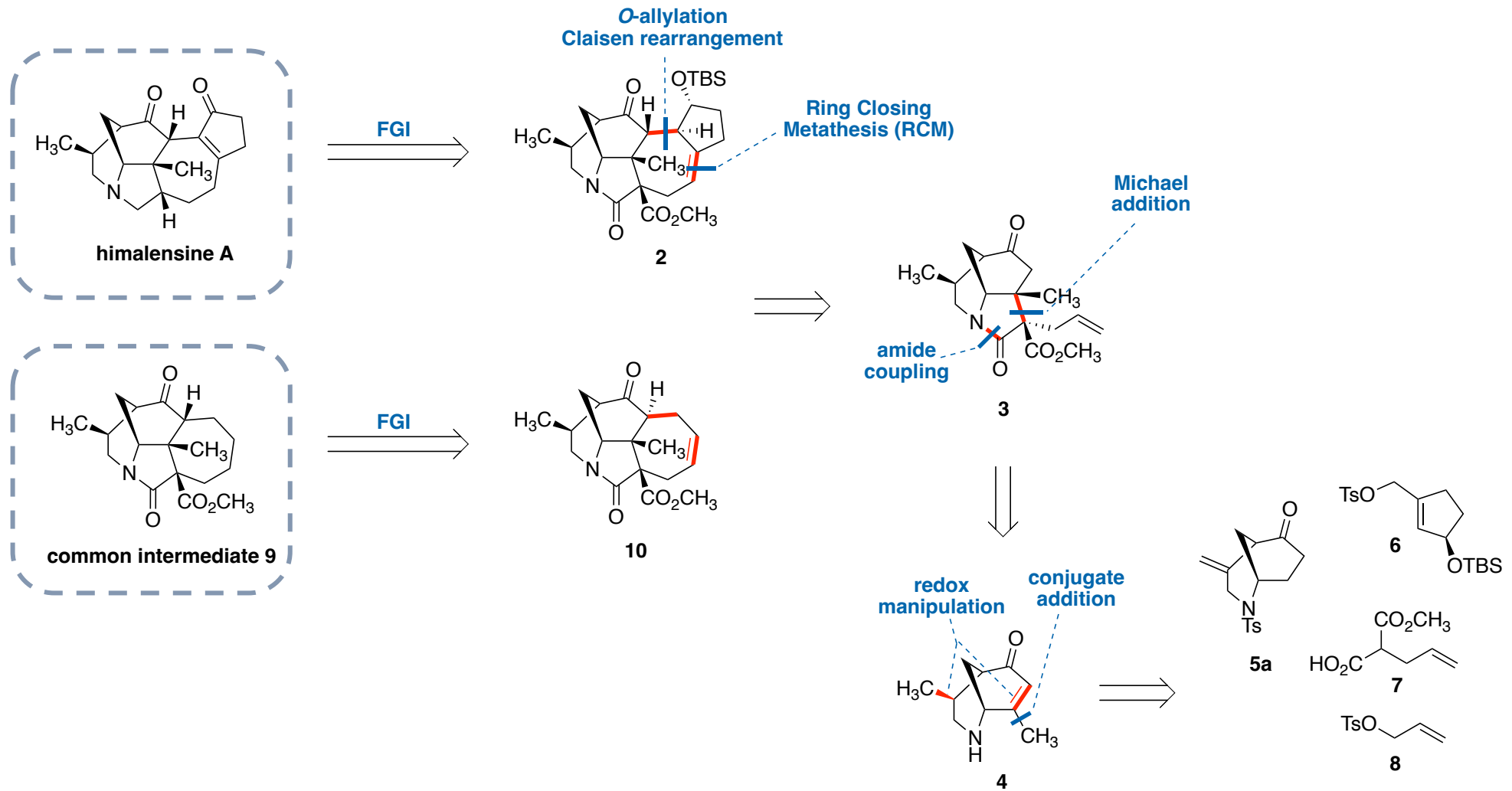
Michael addition  
Dixon (2022)

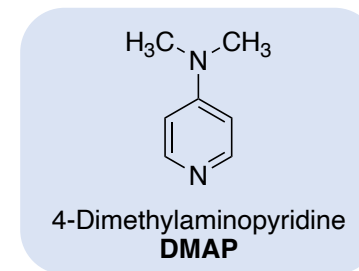
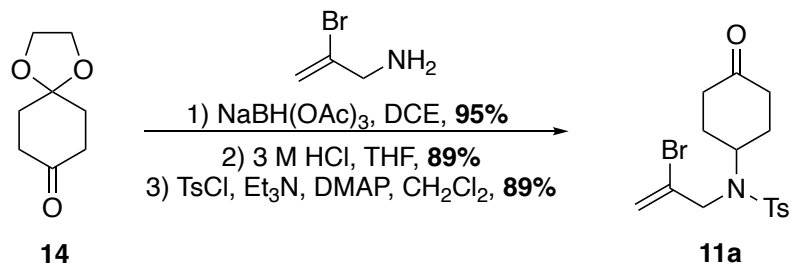
Tu = Thiourea Catalyst  
En = Enamine Catalyst

## (C) Total synthesis of (-)-himalensine A via a novel vinylation

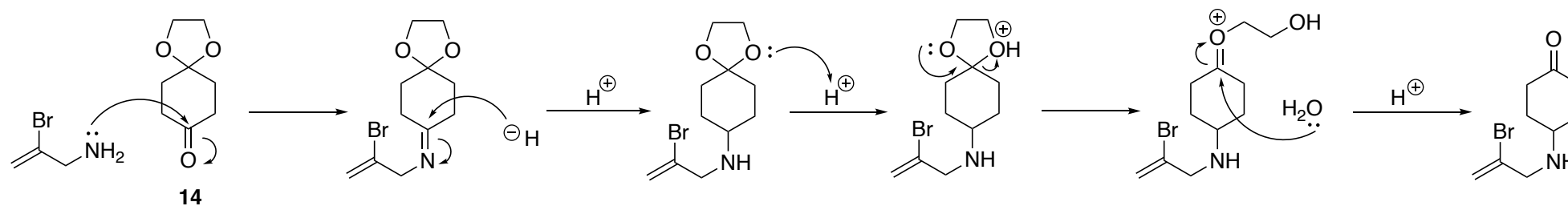


# Retrosynthesis

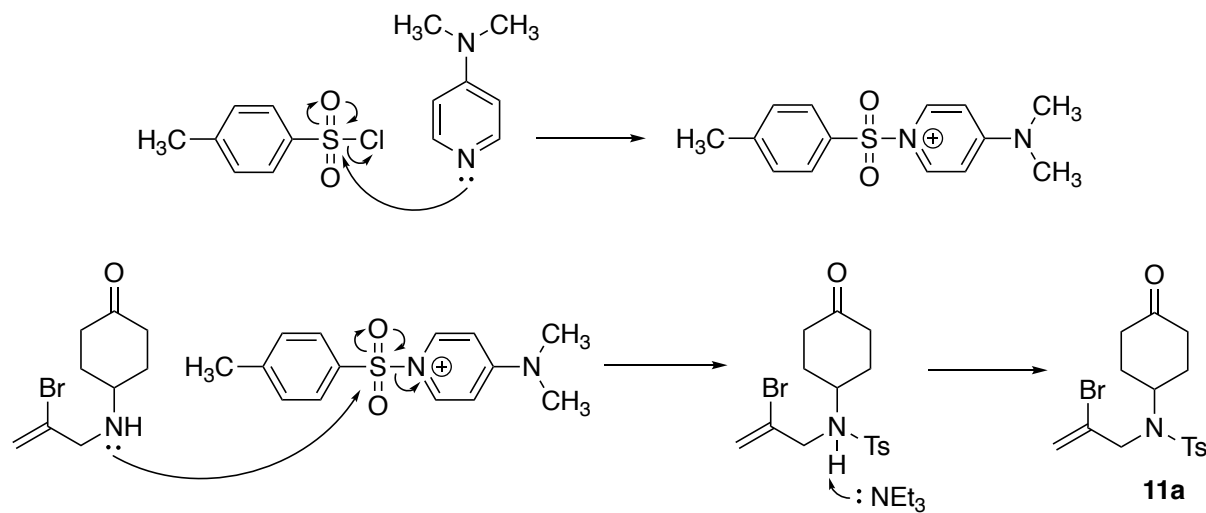


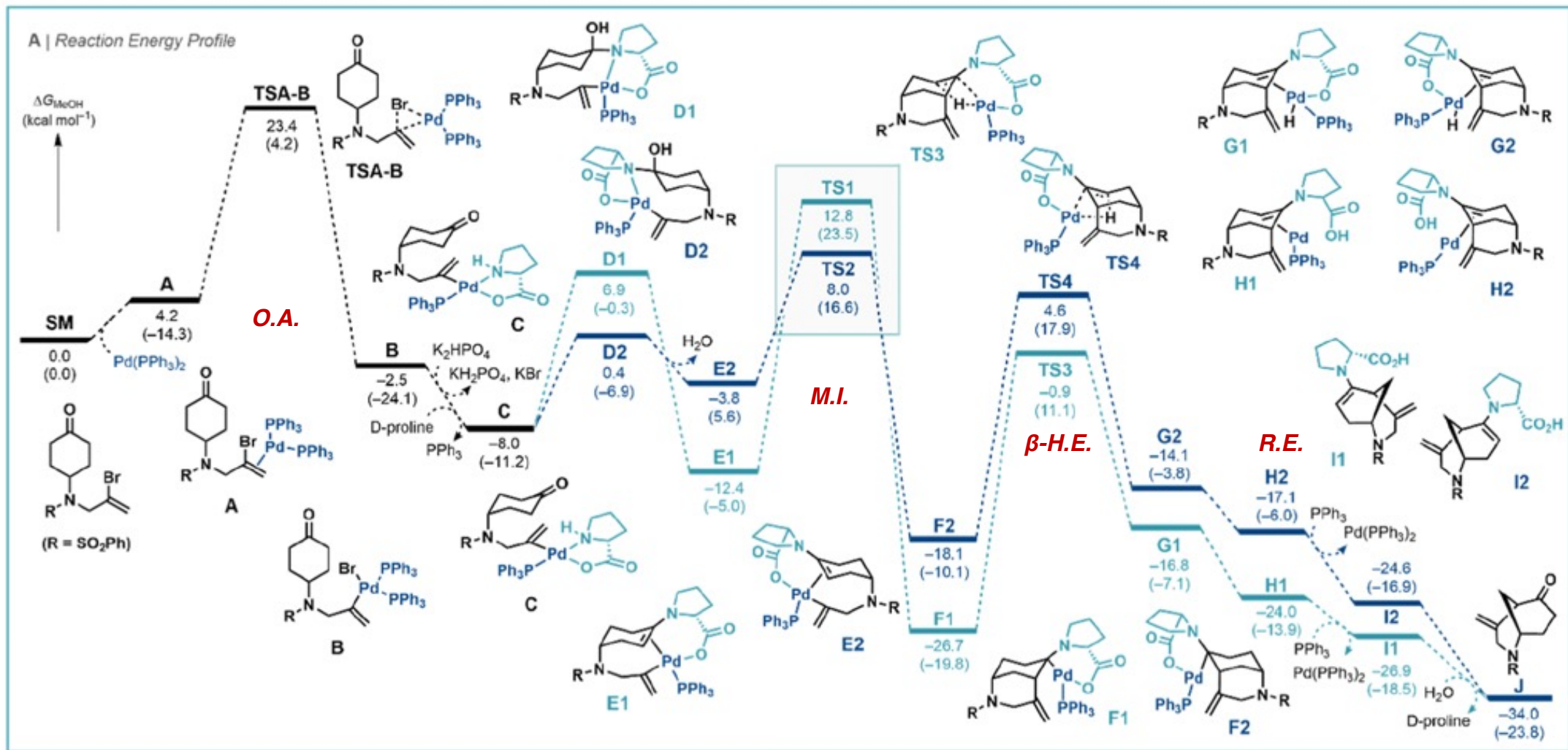
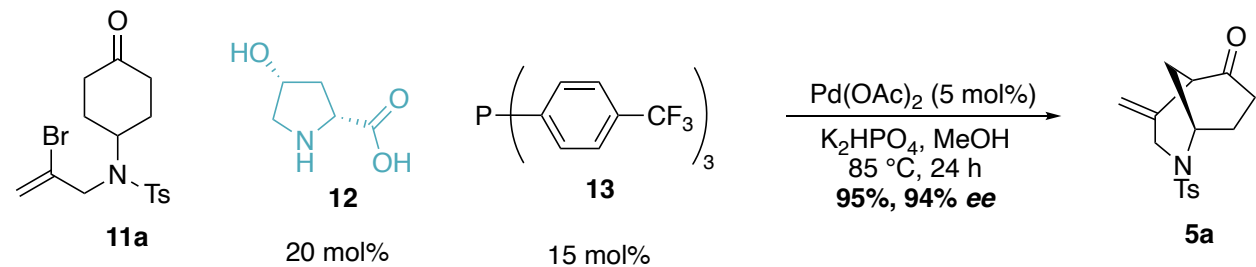


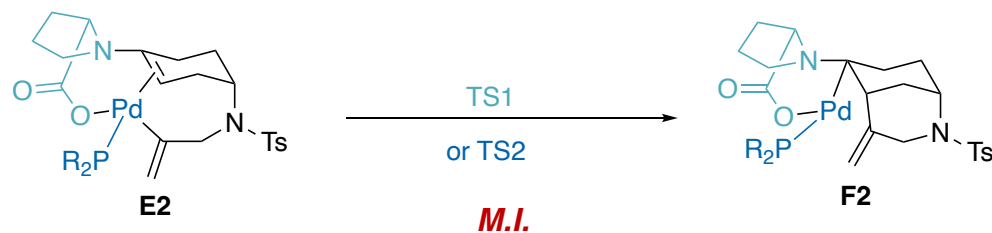
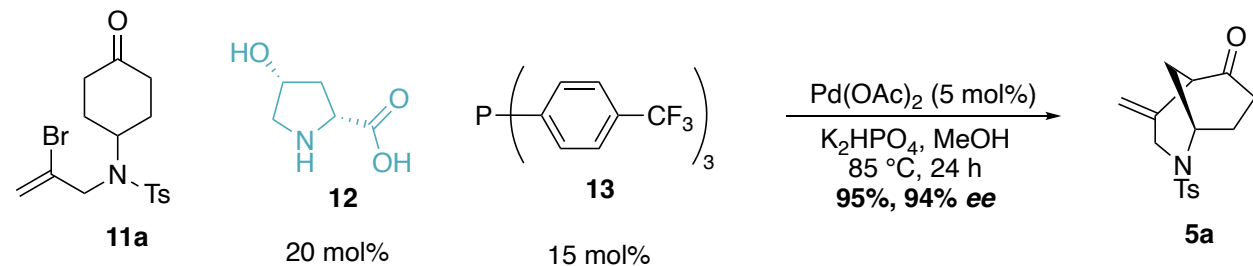
**Reductive amination followed by ketol hydrolysis:**



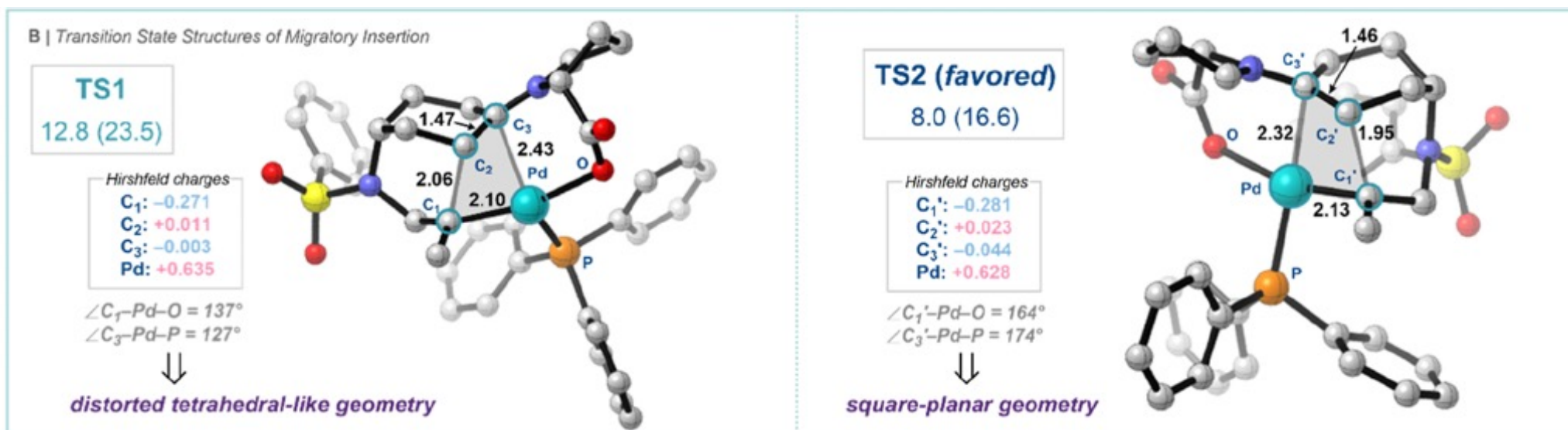
**Amine tosylation:**

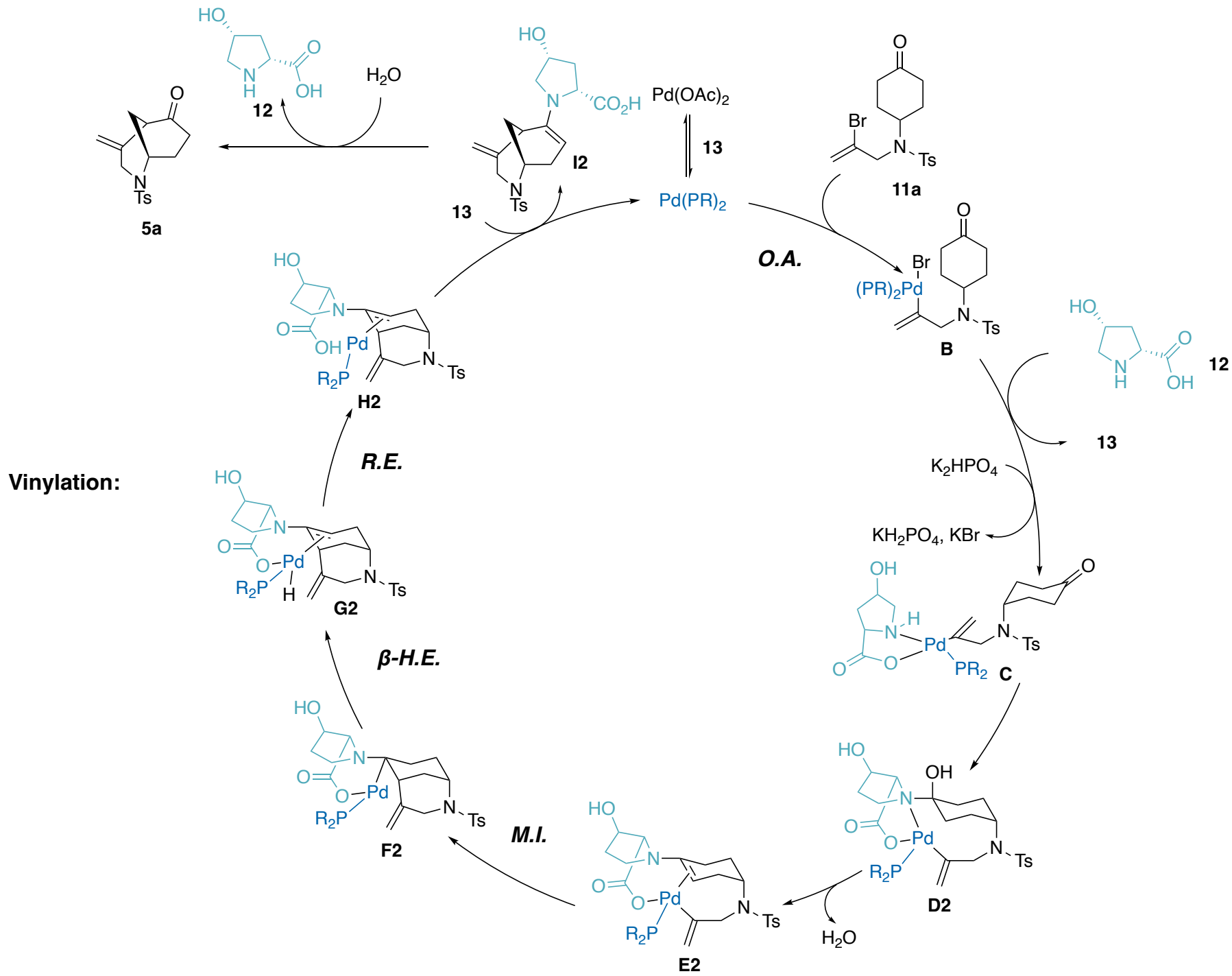


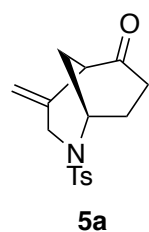




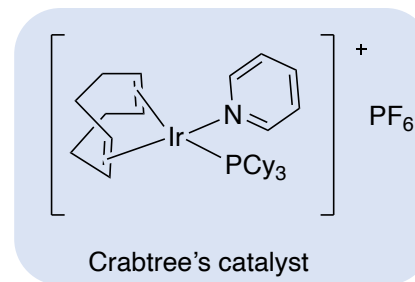
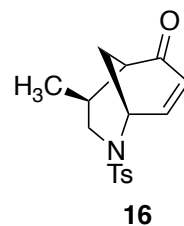
“The origin of the kinetic preference for TS2 likely originates from the smaller interatomic distances between the positively charged Pd atom and the negatively charged atoms of the substrate to which it is bound, which maximizes the stabilizing electrostatic interactions compared to TS1”



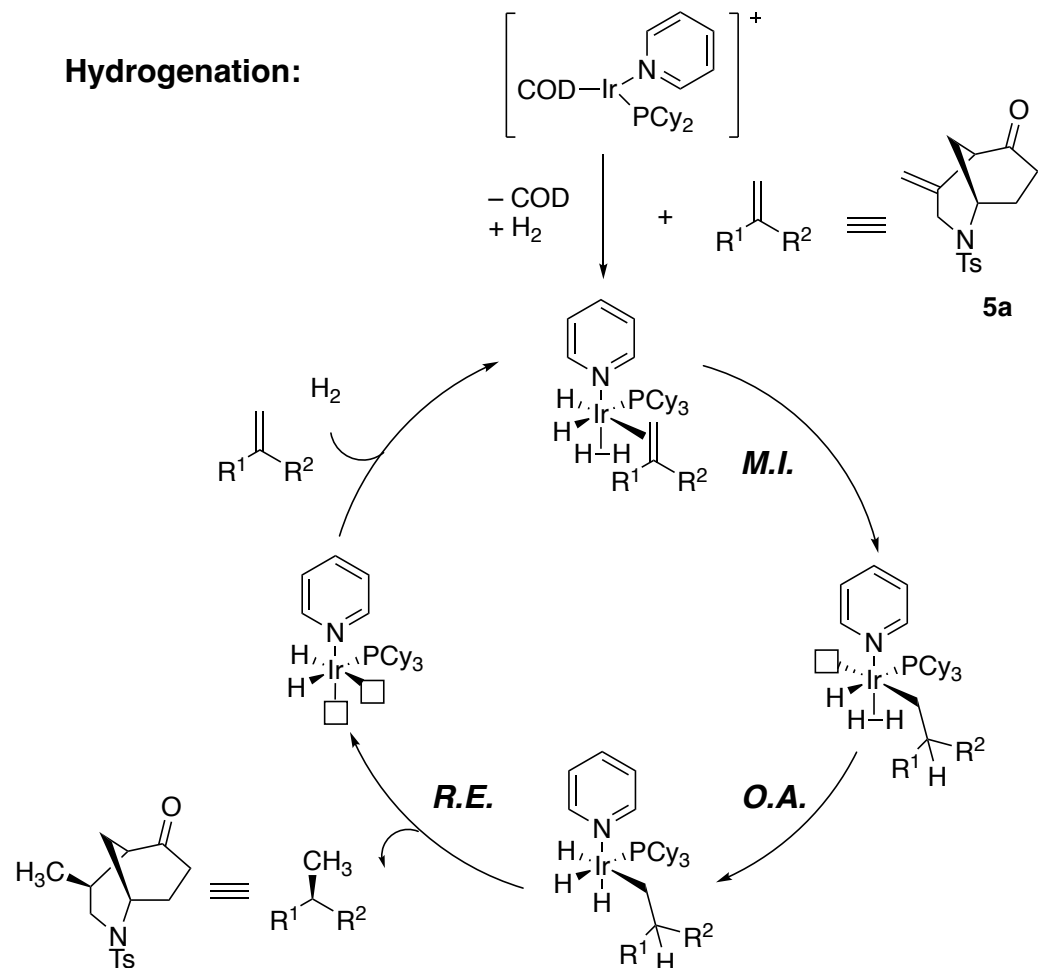




1) Crabtree's cat. (1.5 mol)  
 $H_2$  (58 bar),  $CH_2Cl_2$   
**96%, > 20:1 d.r.**  
 2)  $Pd(TFA)_2$ ,  $O_2$  (balloon)  
 $DMSO$ ,  $AcOH$ ,  $80\text{ }^\circ C$   
**91%**

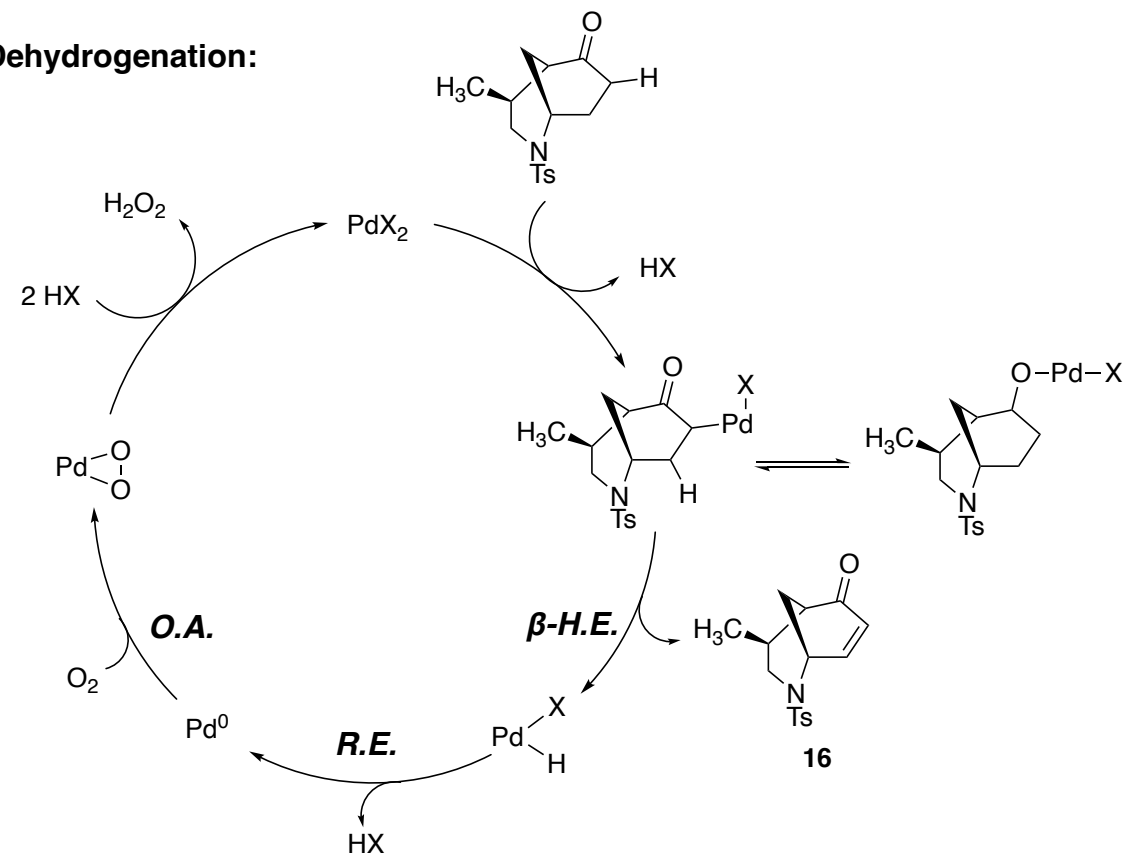


**Hydrogenation:**



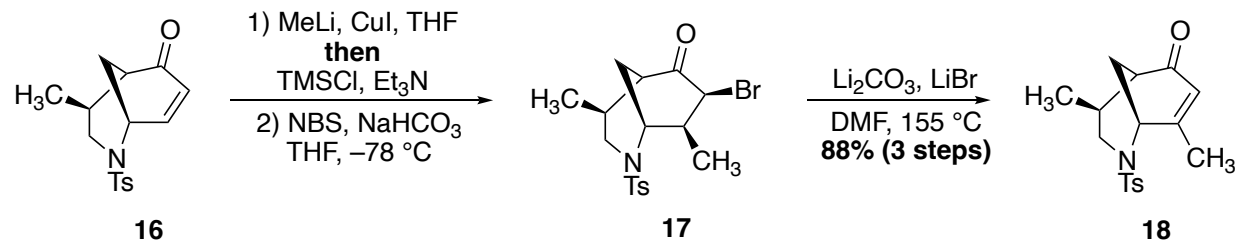
Crabtree et al., *Acc. Chem. Res.* **1979**, *12*, 331.

**Dehydrogenation:**

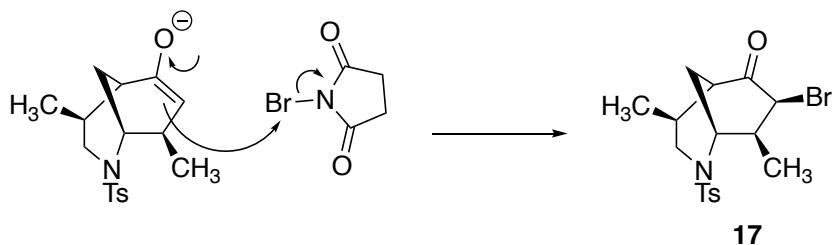
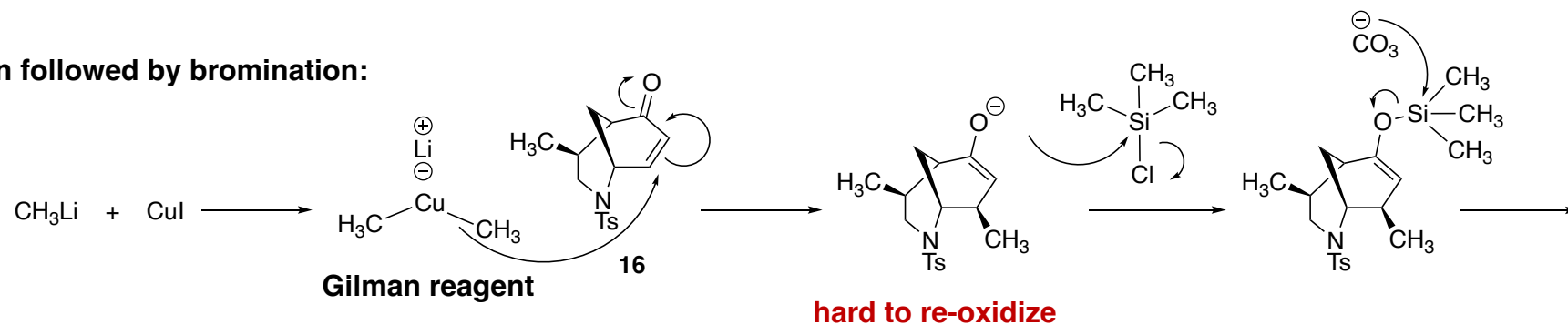


Stahl et al., *J. Am. Chem. Soc.* **2011**, *133*, 37, 14566–14569



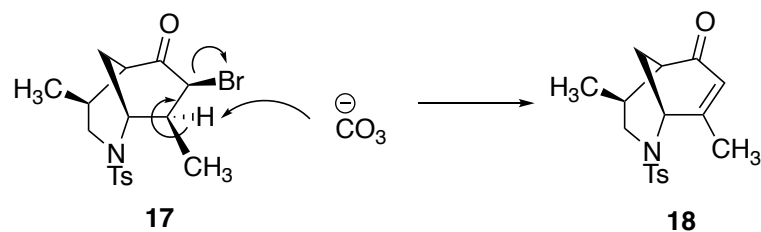


**Cuprate addition followed by bromination:**

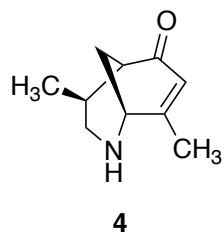
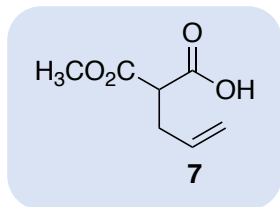


Woods *et al.*, *J. Org. Chem.* **1952**, 17, 12, 1630–1634.

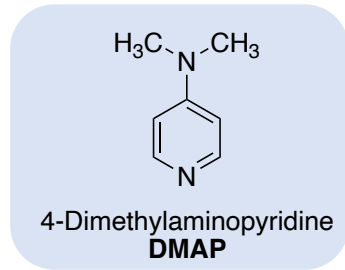
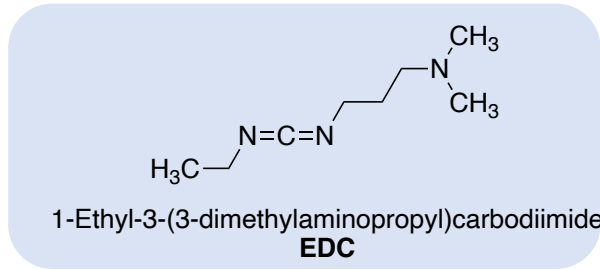
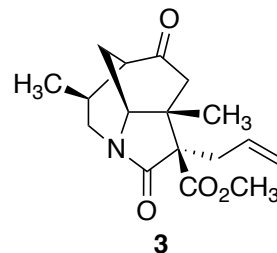
**Dehydrobromination:**



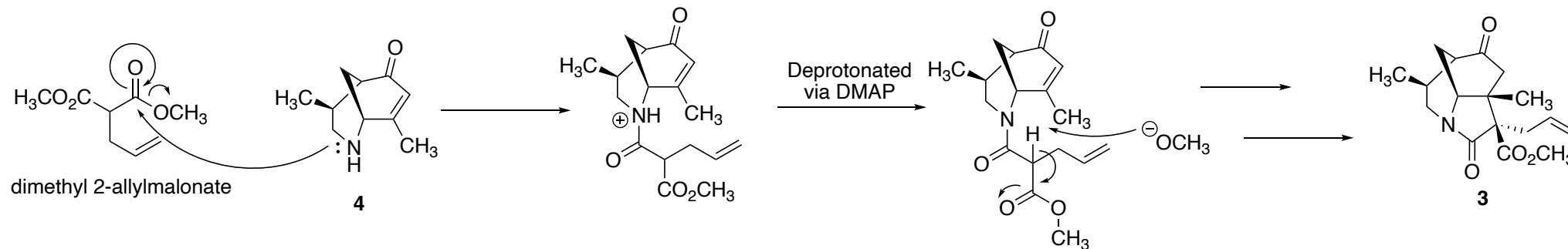
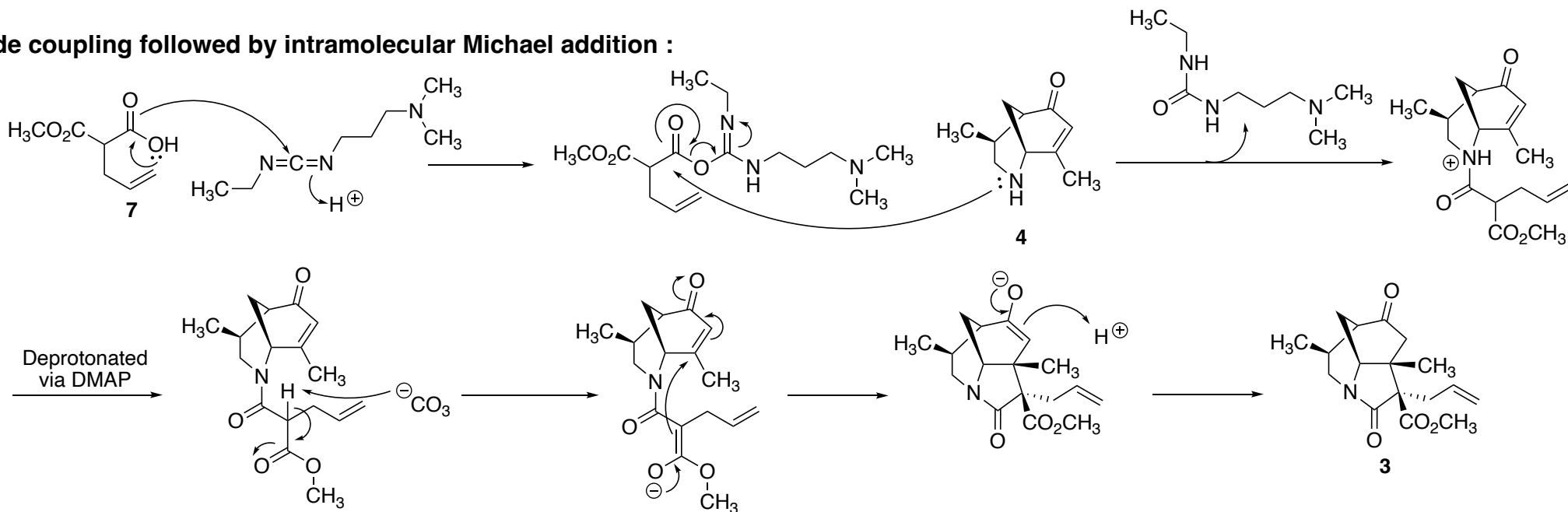




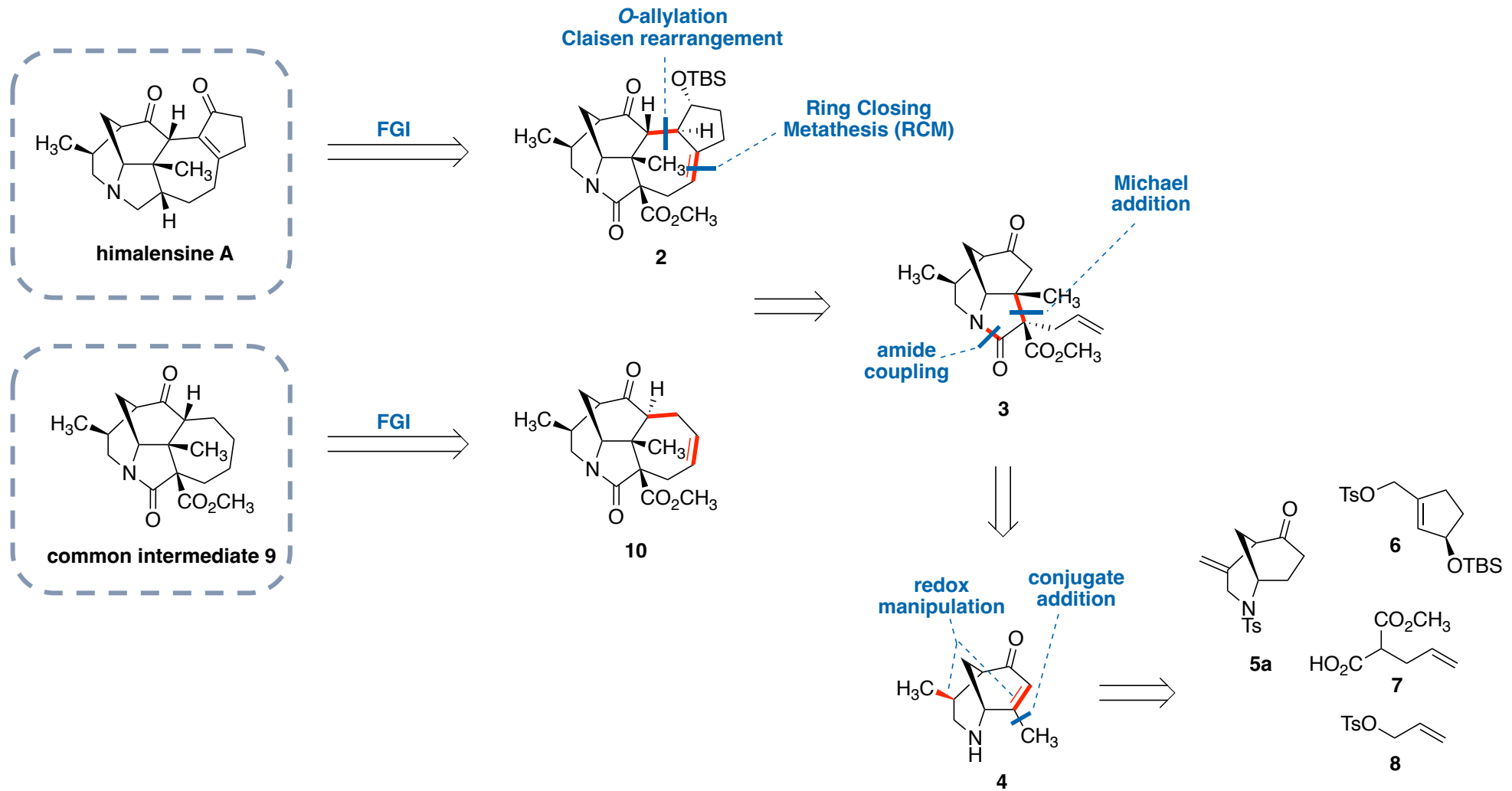
1) 7, EDC, HCl, DMAP, 99%  
 2) K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN, reflux  
**>10:1 d.r., 85%**  
 or  
 dimethyl 2-allylmalonate  
 DMAP, PhCH<sub>3</sub>, reflux  
**7:3 d.r., 71%**

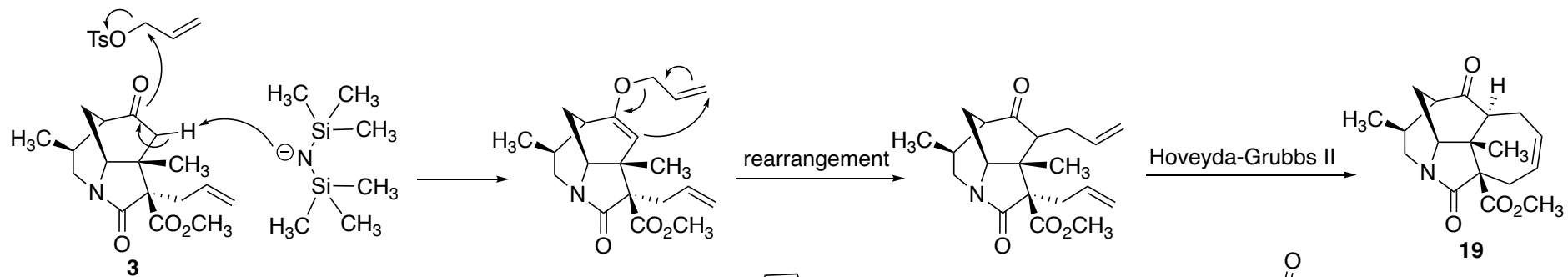
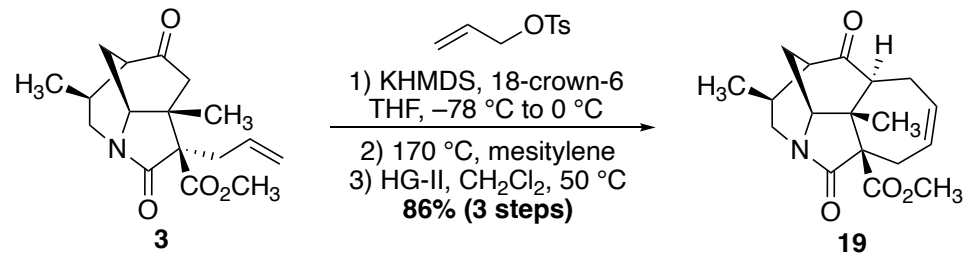


**Amide coupling followed by intramolecular Michael addition :**

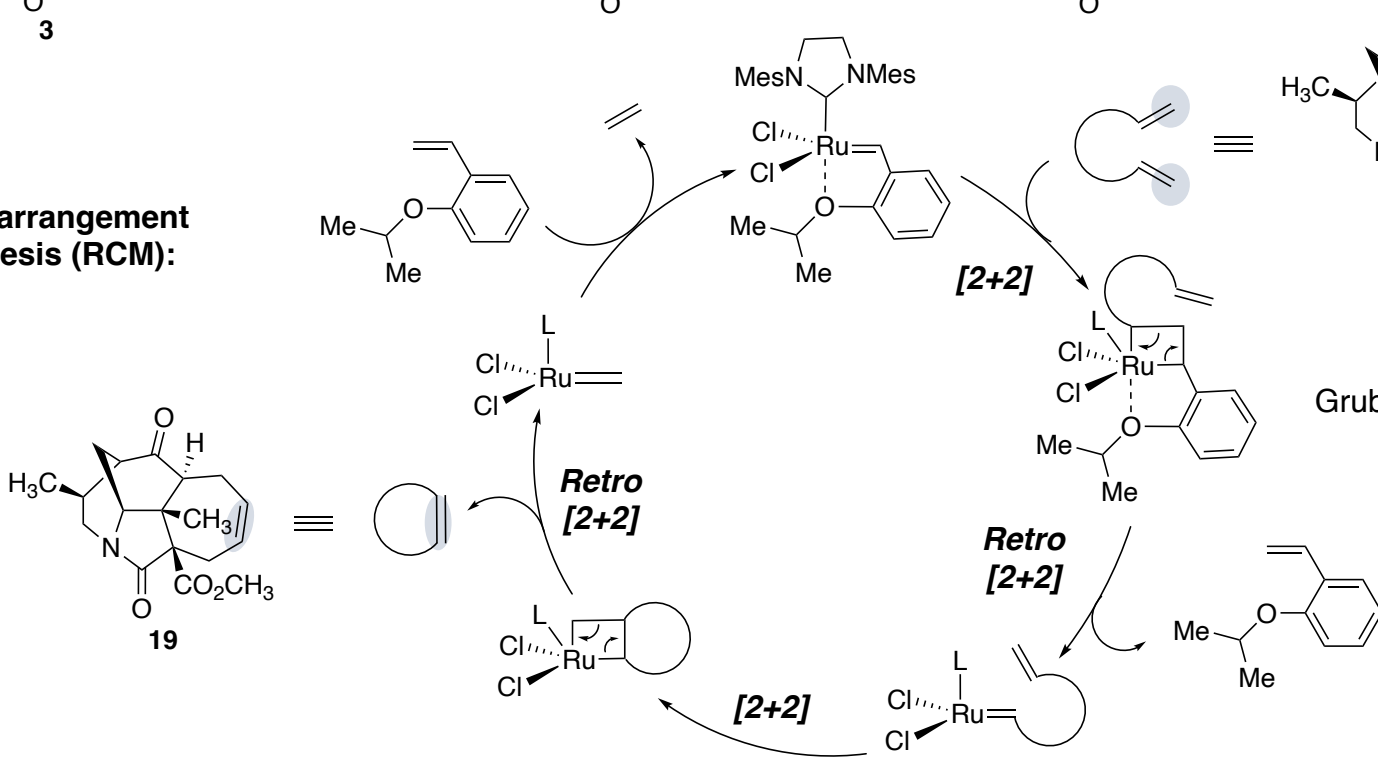


# Retrosynthesis





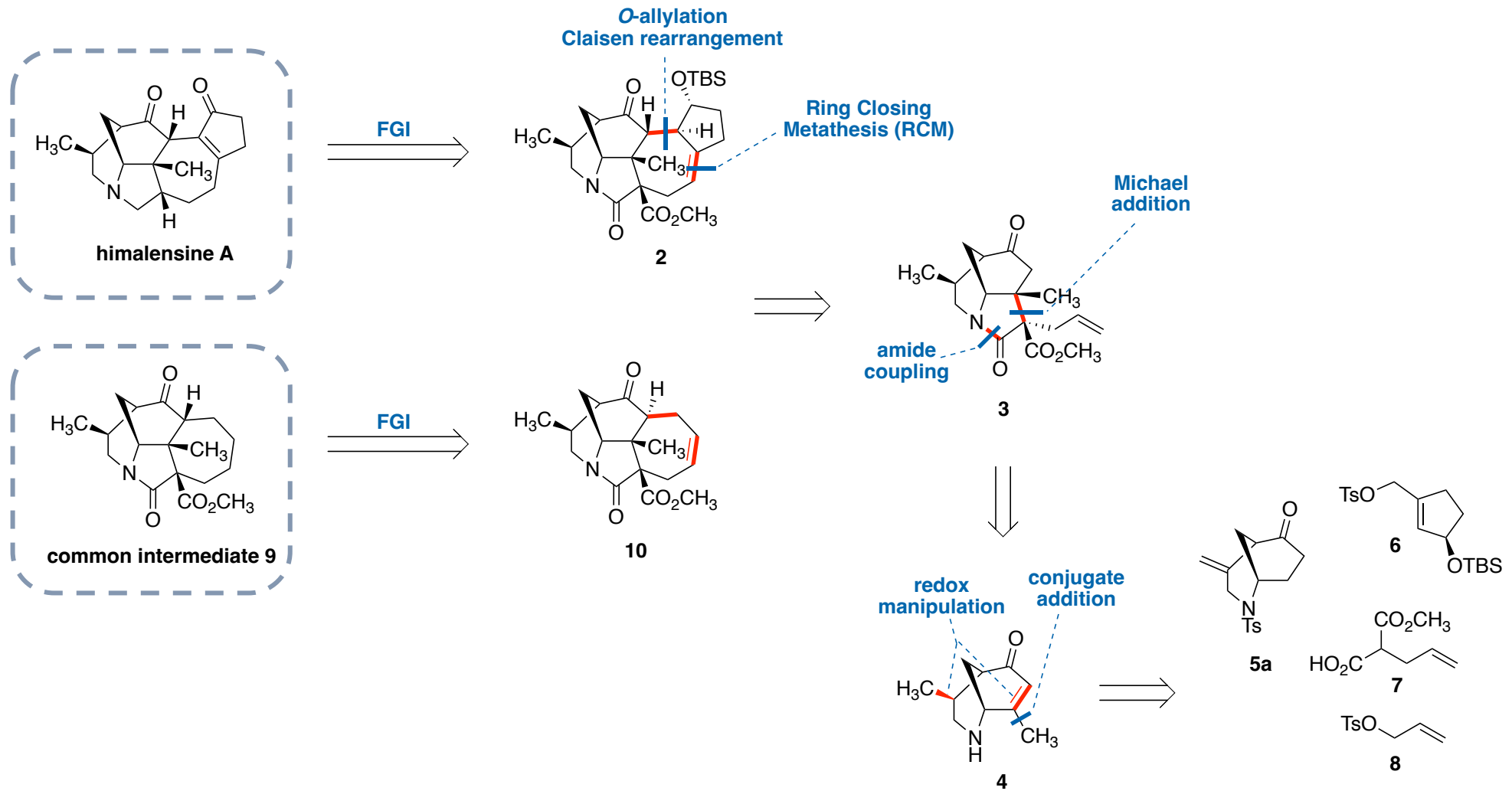
**Allylation / Claisen rearrangement  
/ Ring Closing Metathesis (RCM):**

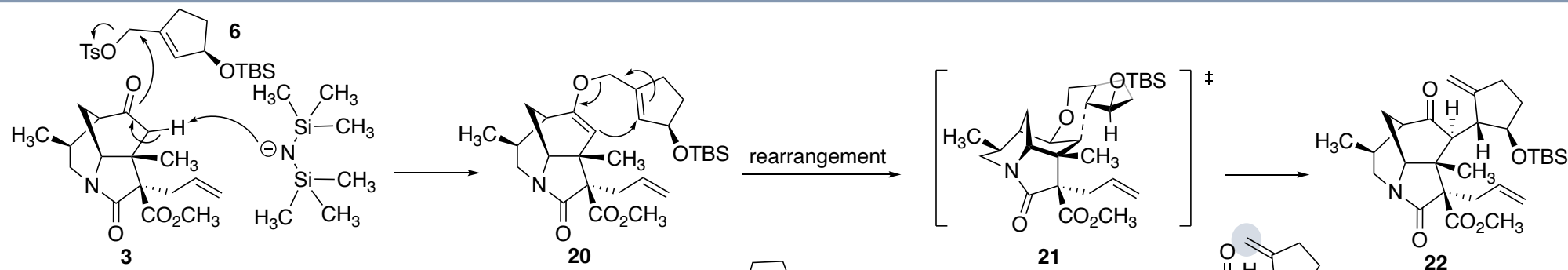
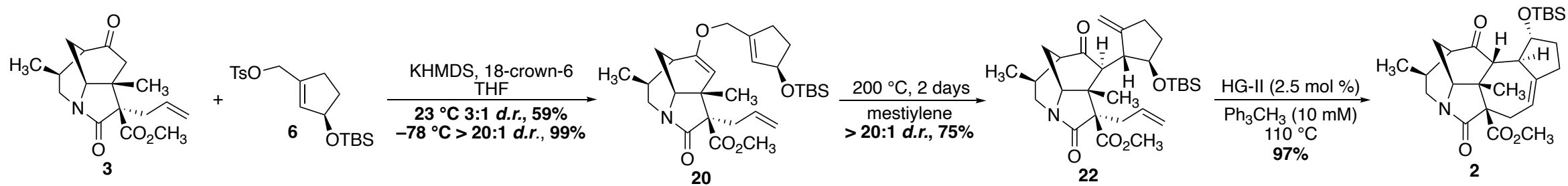


Grubbs *et al.*, *Tetrahedron* **2004**, 60, 7117–7140.

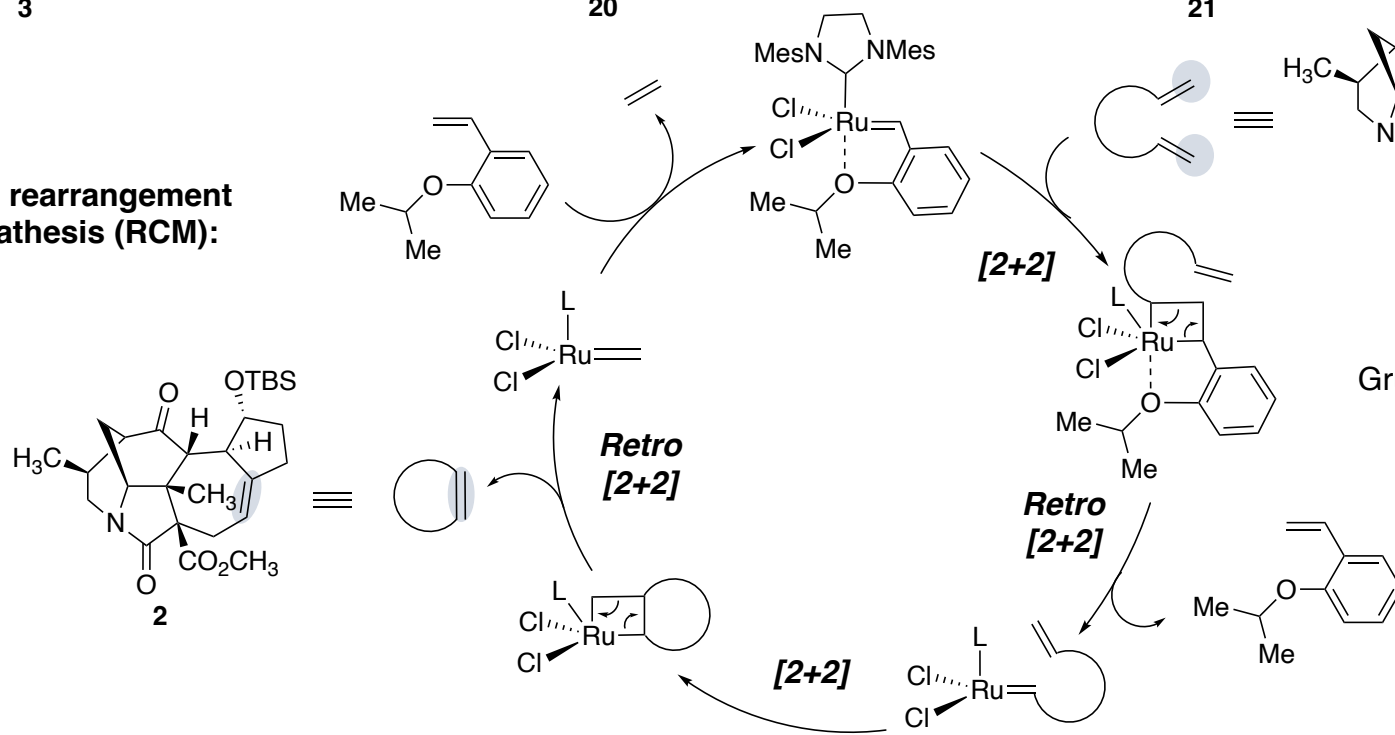


# Retrosynthesis



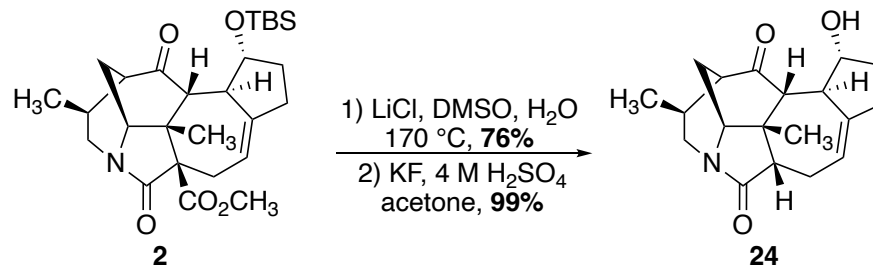


**Allylation / Claisen rearrangement / Ring Closing Metathesis (RCM):**

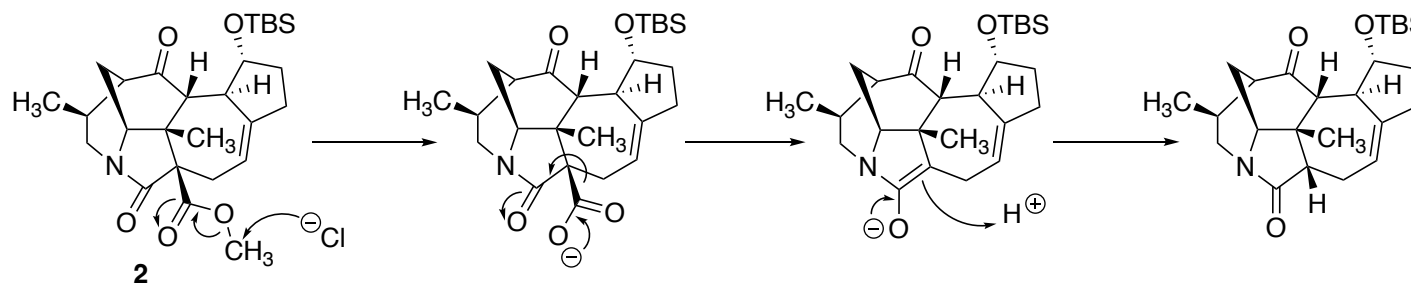


Grubbs *et al.*, *Tetrahedron* **2004**, *60*, 7117–7140.



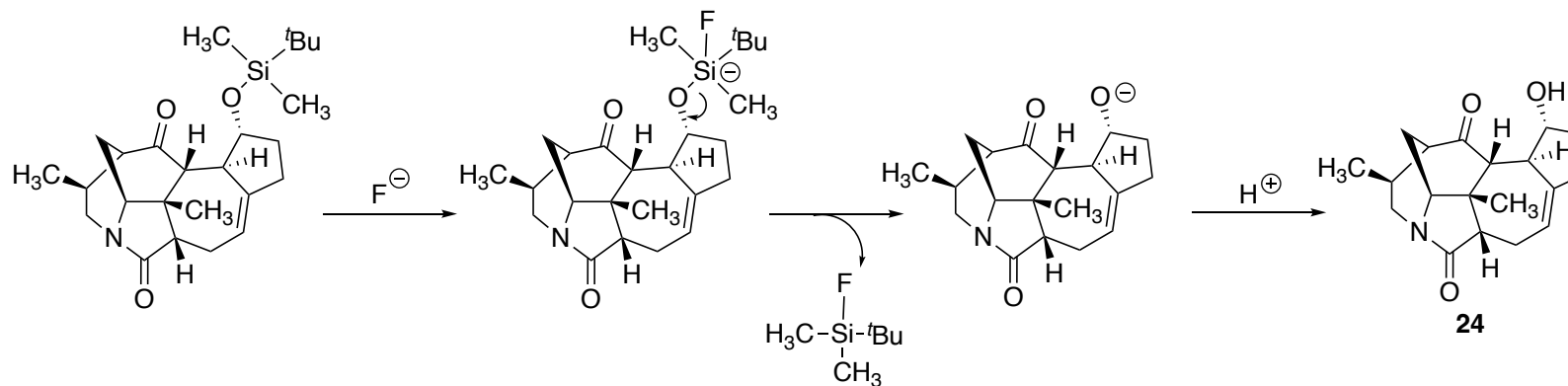


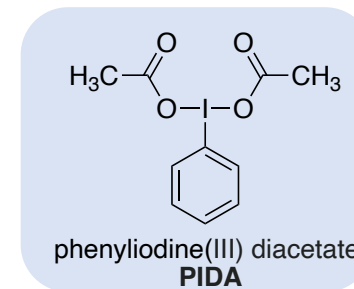
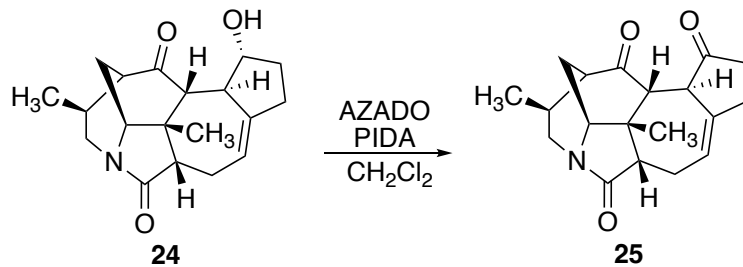
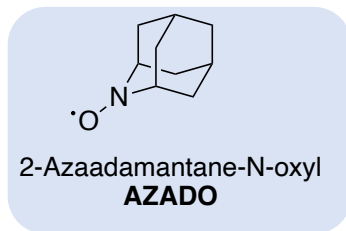
**Krapcho decarboxylation:**



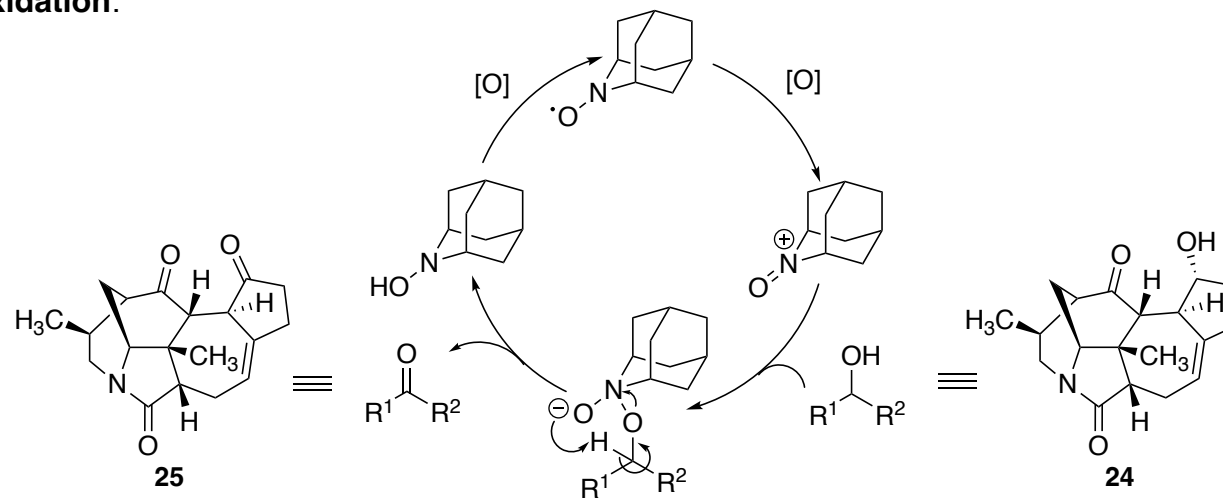
Short *et al.*, *Tetrahedron Lett.* **1974**, 15, 1091.

**TBS deprotection:**

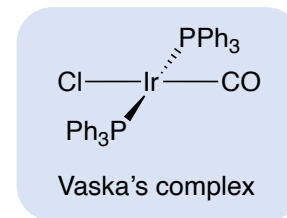
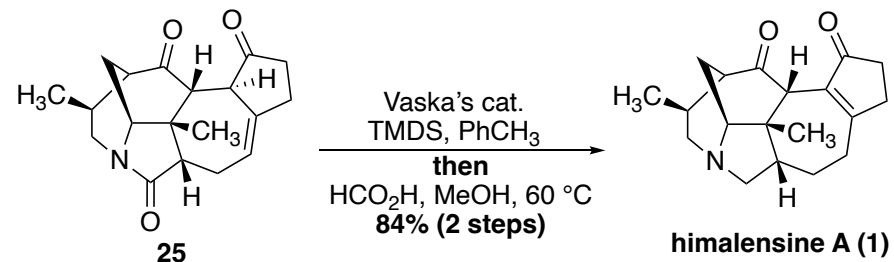




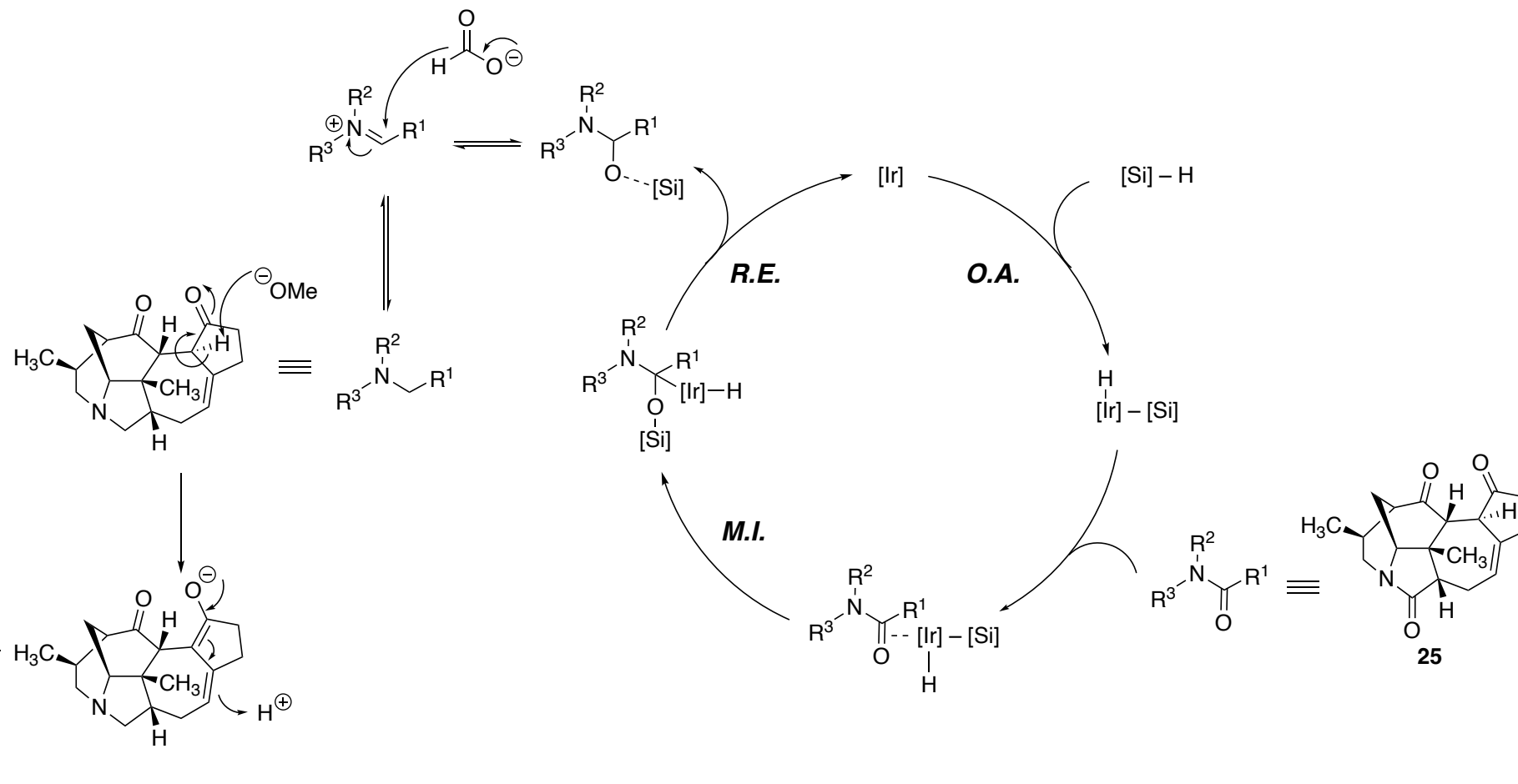
**Oxidation:**



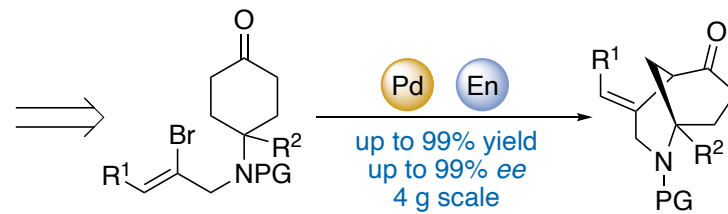
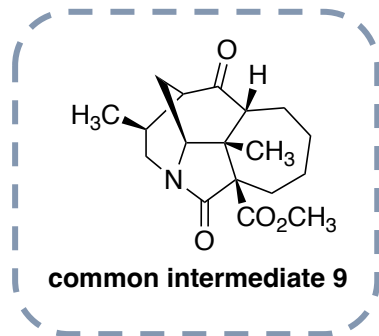
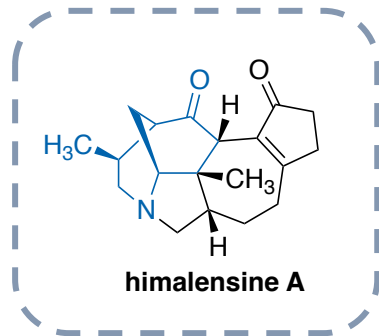
Iwabuchi *et al.*, *J. Am. Chem. Soc.* **2006**, 128, 26, 8412–8413



Reduction:



# Conclusion



- Development of a novel highly enantioselective desymmetrizing  $\alpha$ -vinylation of cyclohexanones
- Total Synthesis of himalensine A in 20 steps and 10% overall yield
- Synthesis of a common intermediate in synthesis of natural products

Thank you!