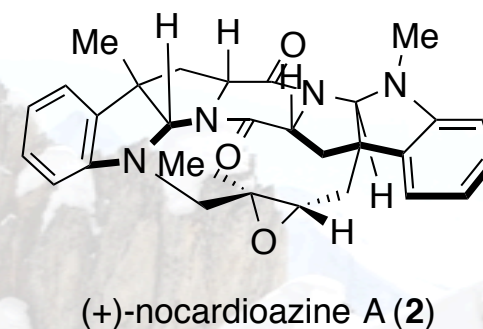
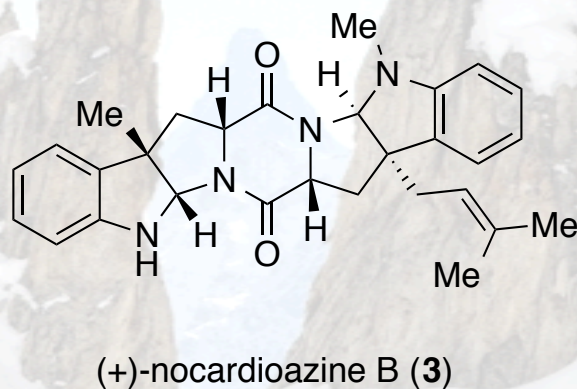
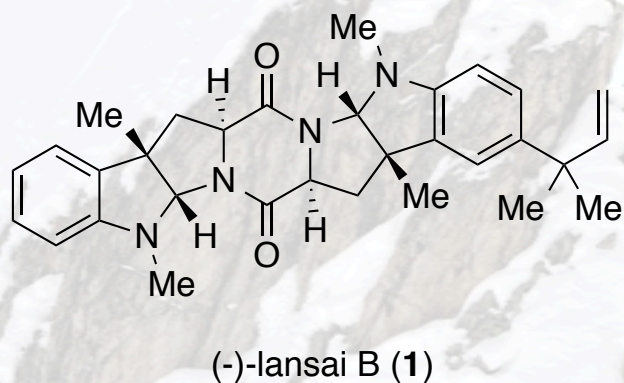


Enantioselective Total Synthesis of (-)-Lansai B and (+)-Nocardioazines A and B



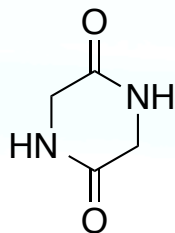
H. Wang, S. E. Reisman*

Angew. Chem. **2014**, *126*, 6320 - 6324

California Institute of Technology (CALTEC)

Introduction

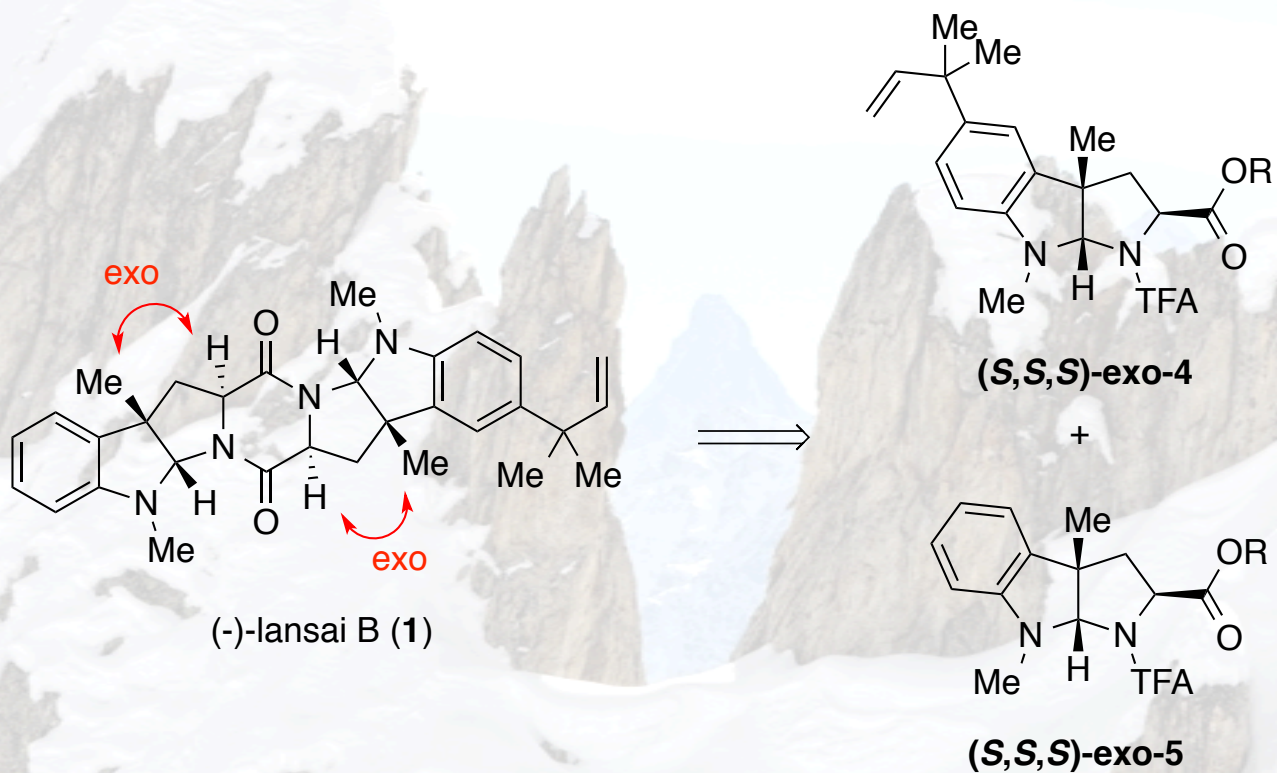
- diketopiperazine (DKP) ring:

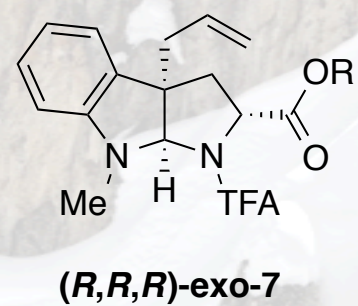
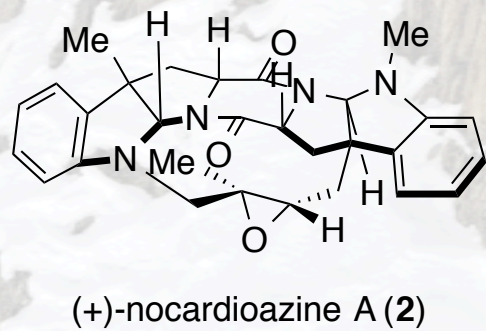
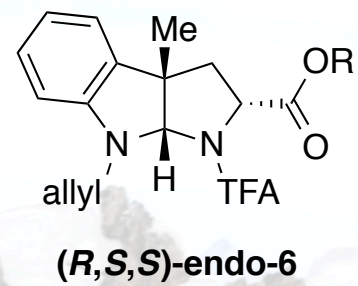
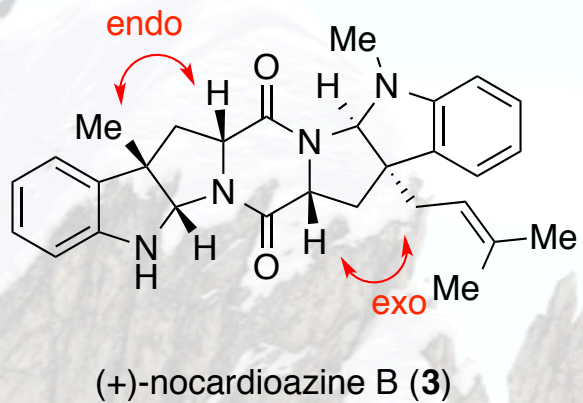


- **(-)-Lansai B** isolated as secondary metabolite from *streptomyces sp. SUC1* from the roots of *ficus benjamina*
- **(+)-nocadiozine A**: inhibitor of P-glycoprotein (transmembrane protein overexpressed in many multidrugresistant tumors)
- **(+)-nocadiozine A** and **B** were isolated from a marine bacetria *nocardiopsis sp.*
- Diastereoselective synthesis of **nocardiozine B** by group of Ye in 2012
- No total syntheses of **(-)-lansai B** and **(+)-nocadiozine A**



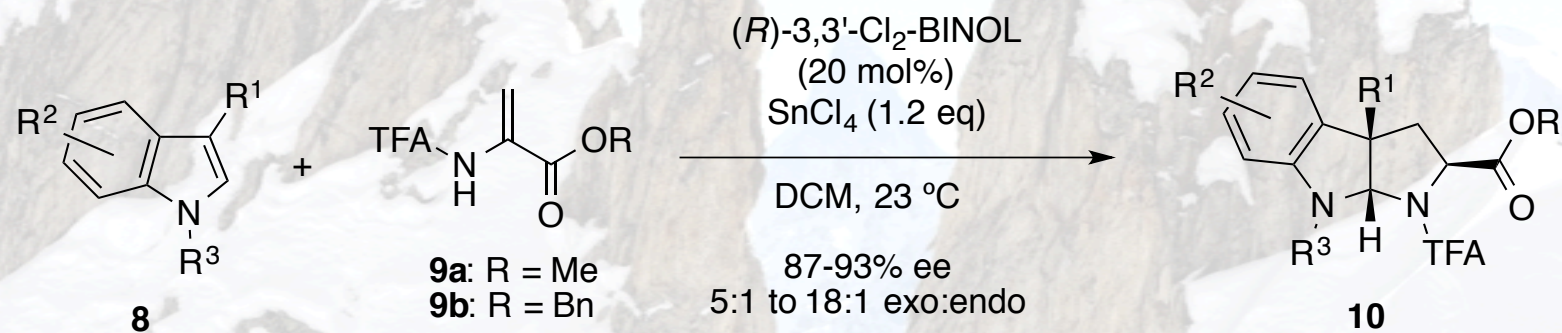
Retrosynthesis

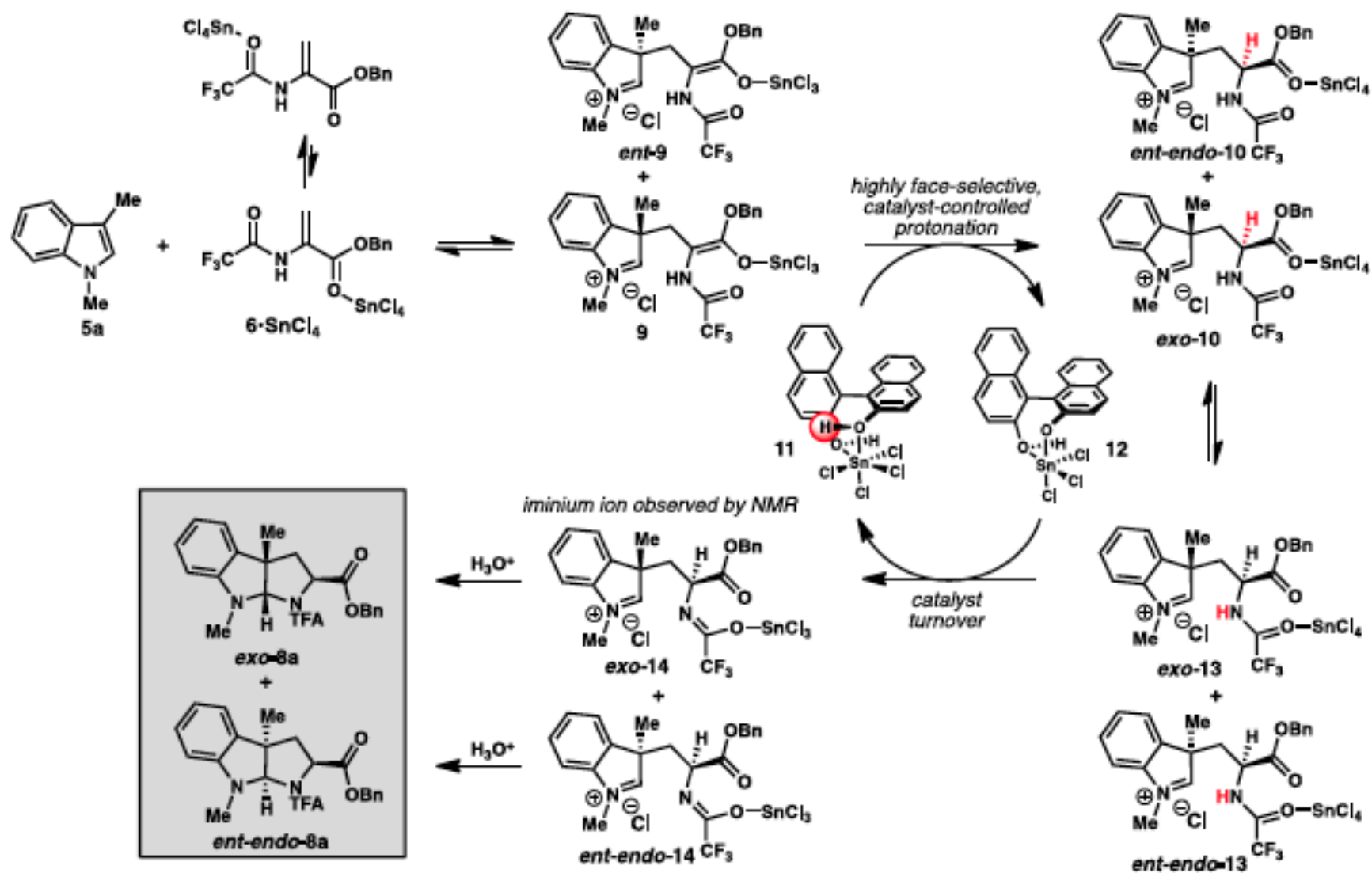




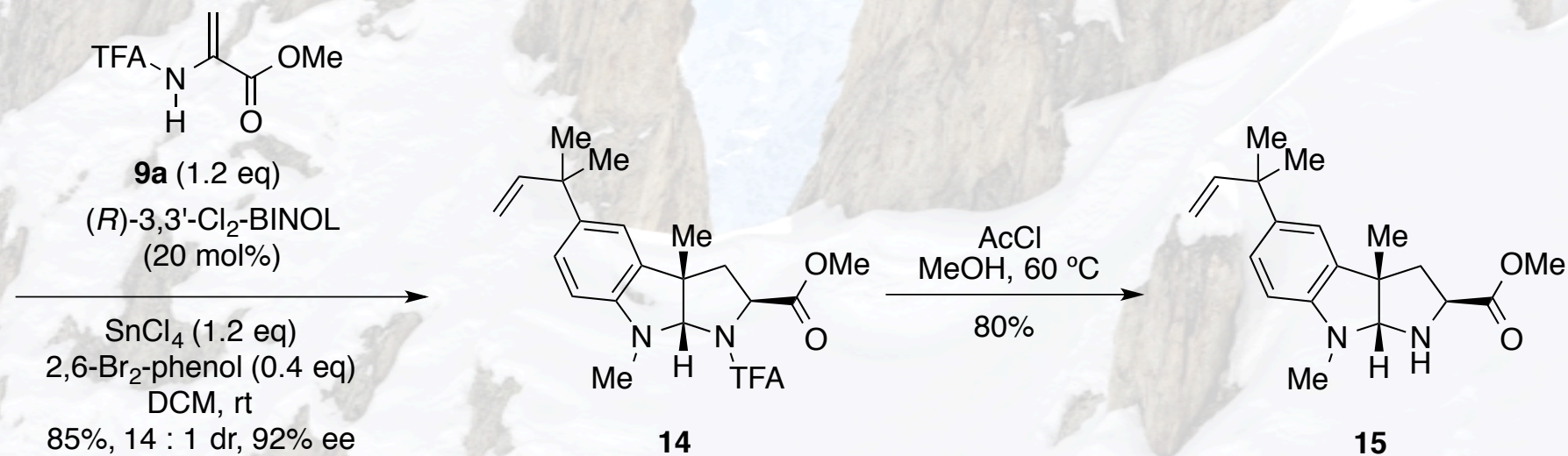
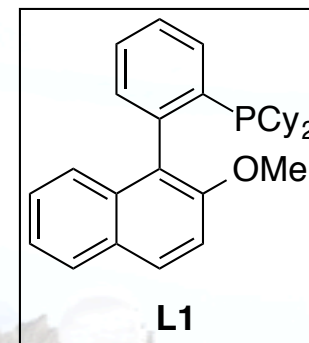
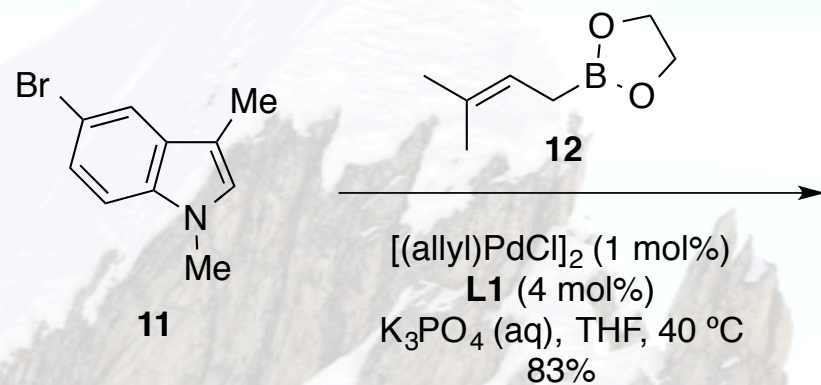
Enantioselective pyrroloindoline synthesis

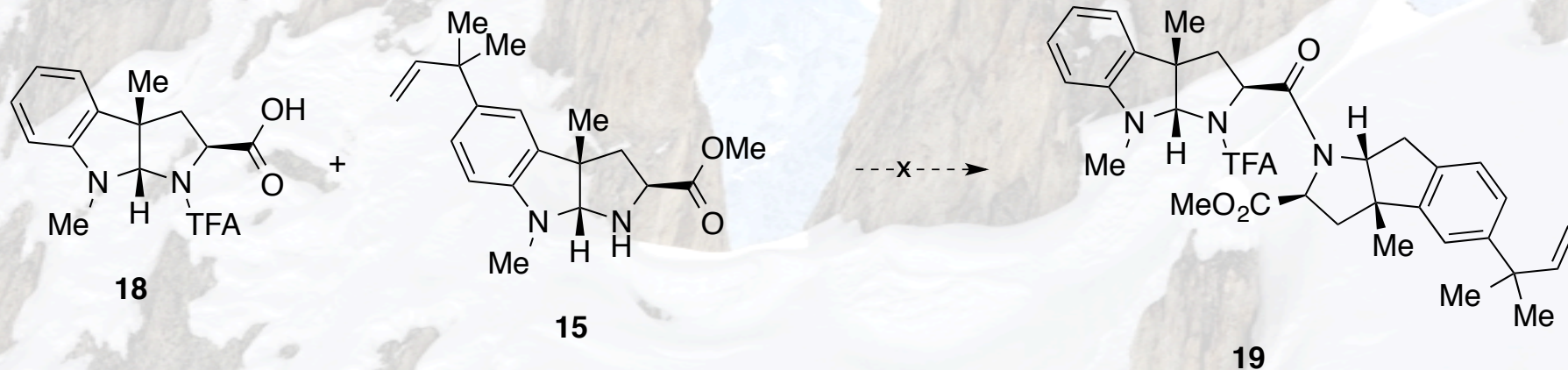
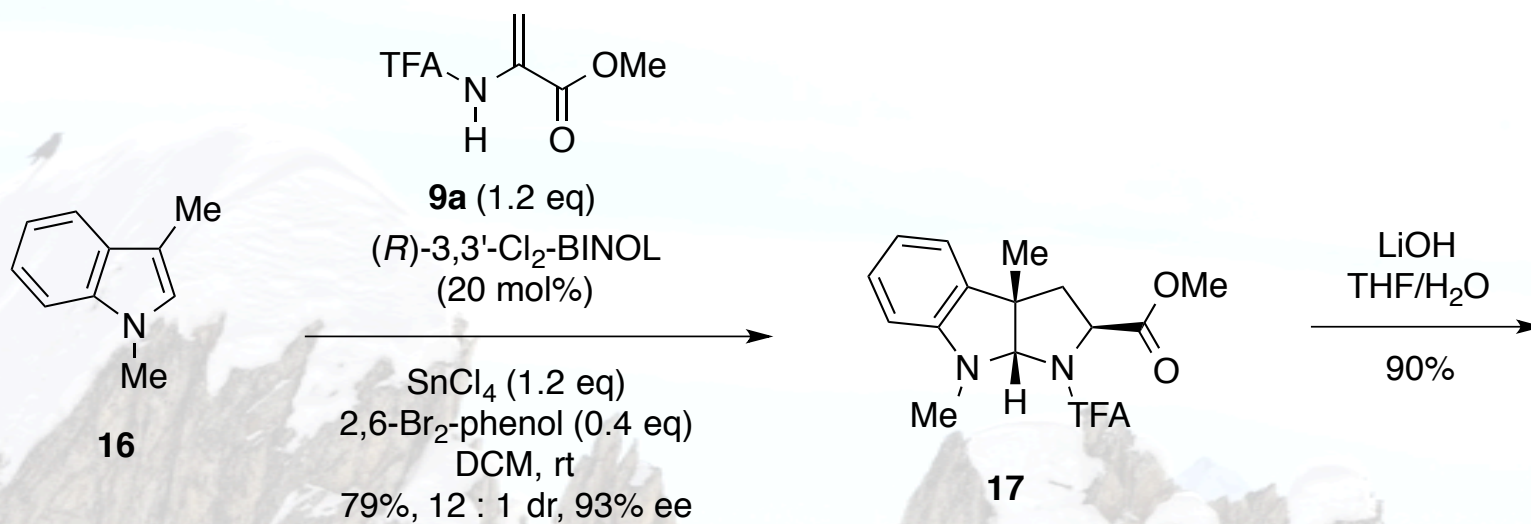
formal [3+2] cycloaddition reaction



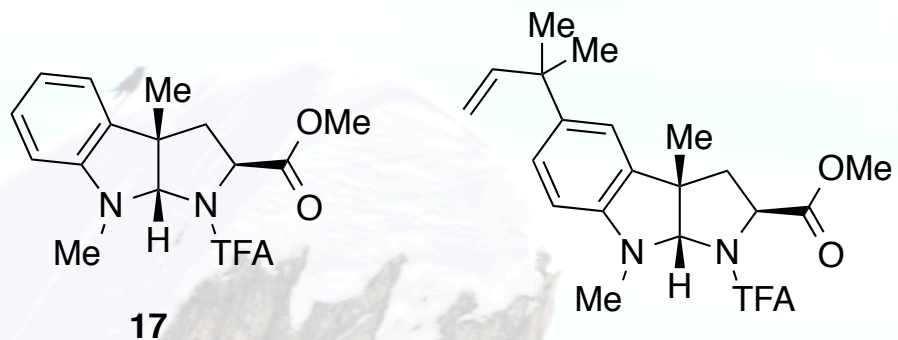


Synthesis of (-)-lansai B:





Problem: N substitution significantly influences stability of activated ester

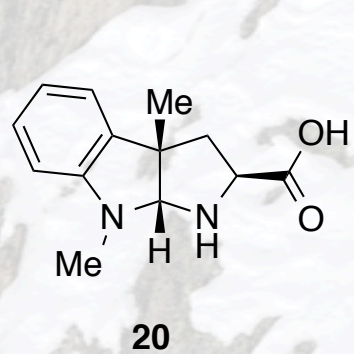


17

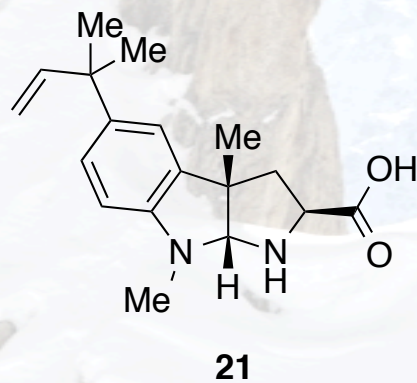
14

1) AcCl, MeOH
2) LiOH, THF/H₂O
87%

1) AcCl, MeOH
2) LiOH, THF/H₂O
76%

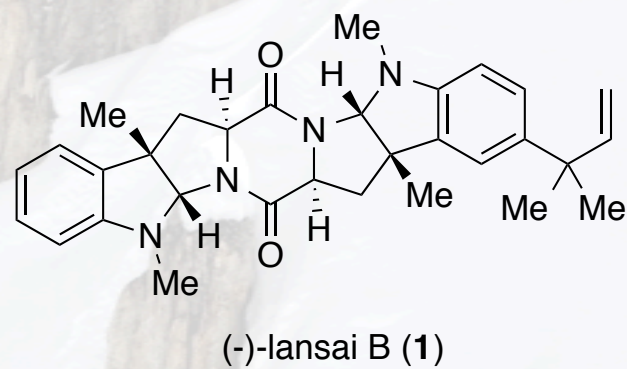


+

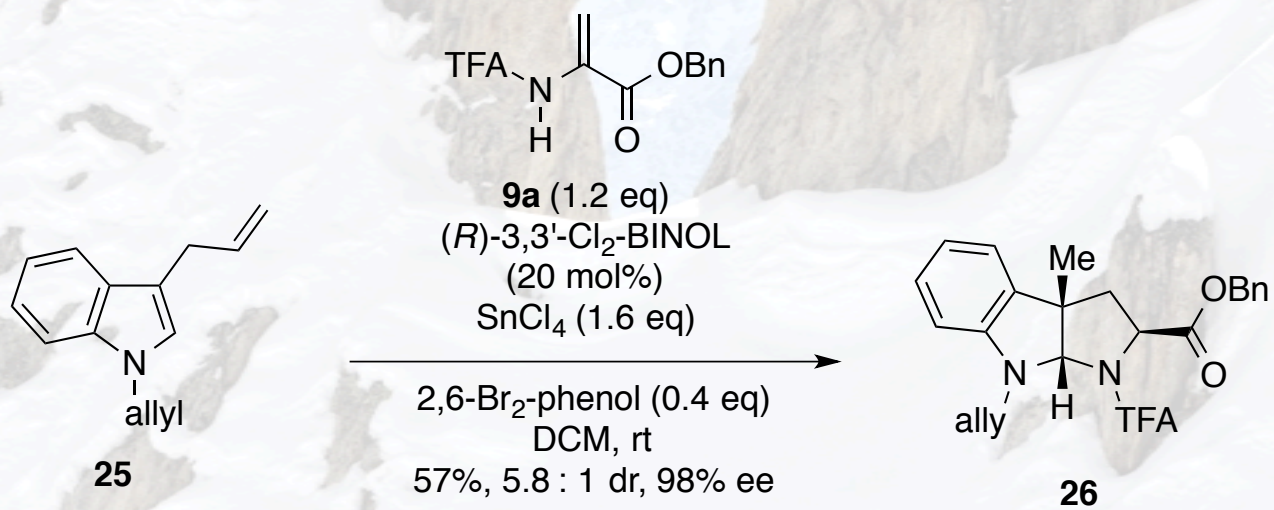
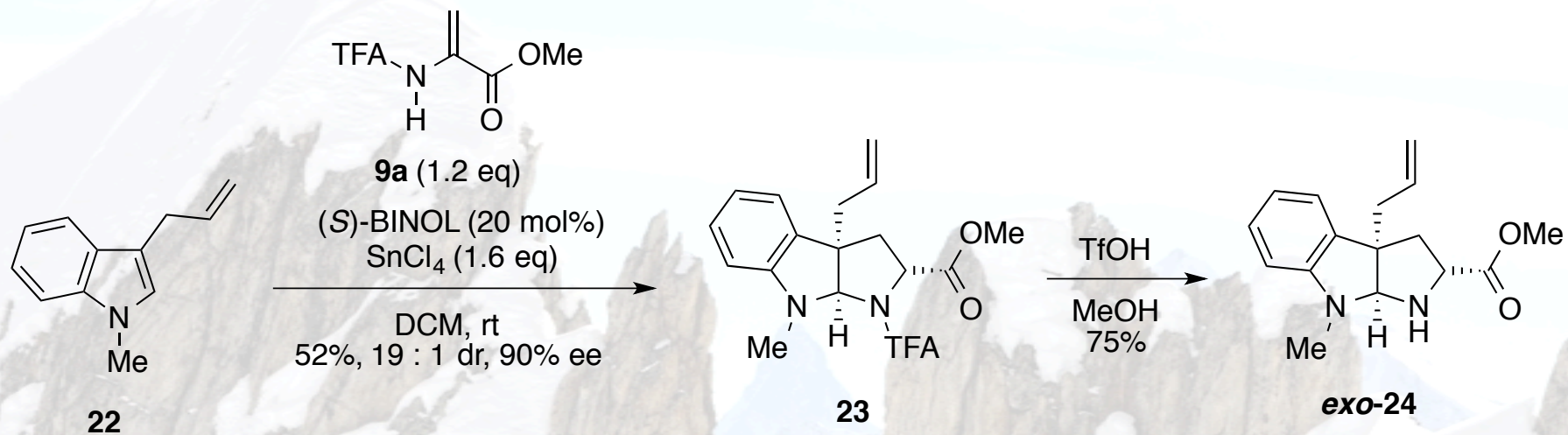


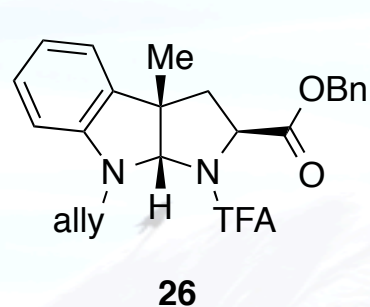
BOP-Cl
DIPEA

DCM
0 °C to rt
38%

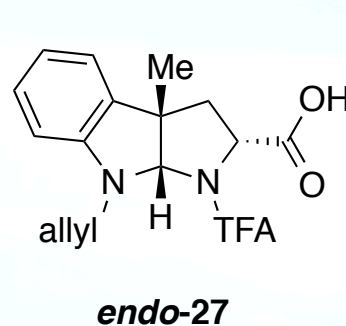


Synthesis of (+)-nocardioazine B:

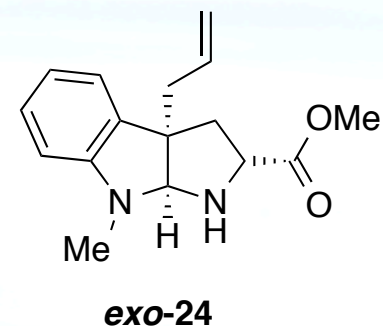




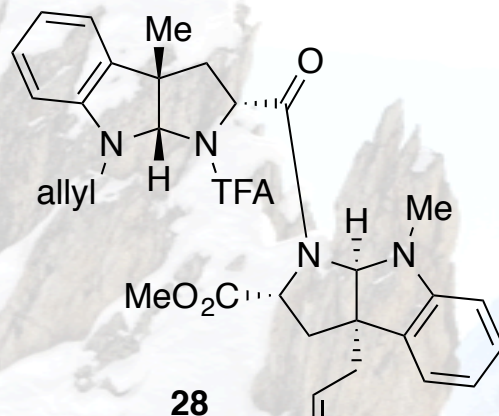
1) MeOH, K₂CO₃
 2) LiHMDS, -78 °C;
 AcOH
 3) BBr₃, -78 °C to rt;
 then H₂O
 79% (3 steps)



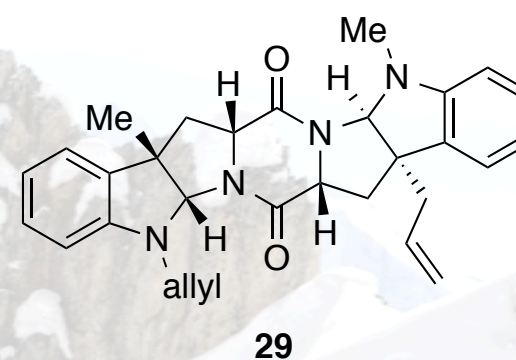
+



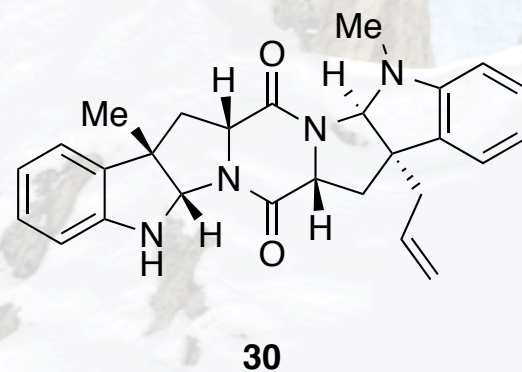
BOP-Cl
 collidine,
 slow addition
 of **27**
 DCM, 0.02 M
 84%



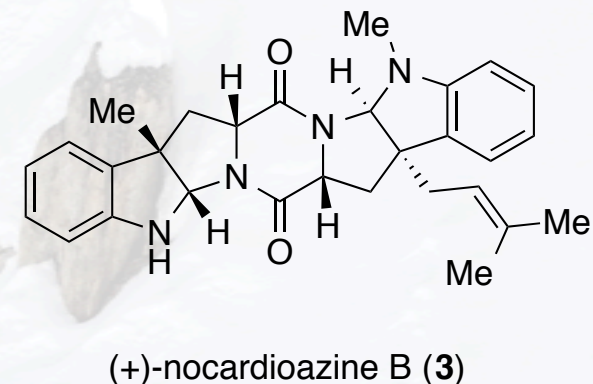
LiOH
 THF/H₂O
 then 1M HCl
 74%



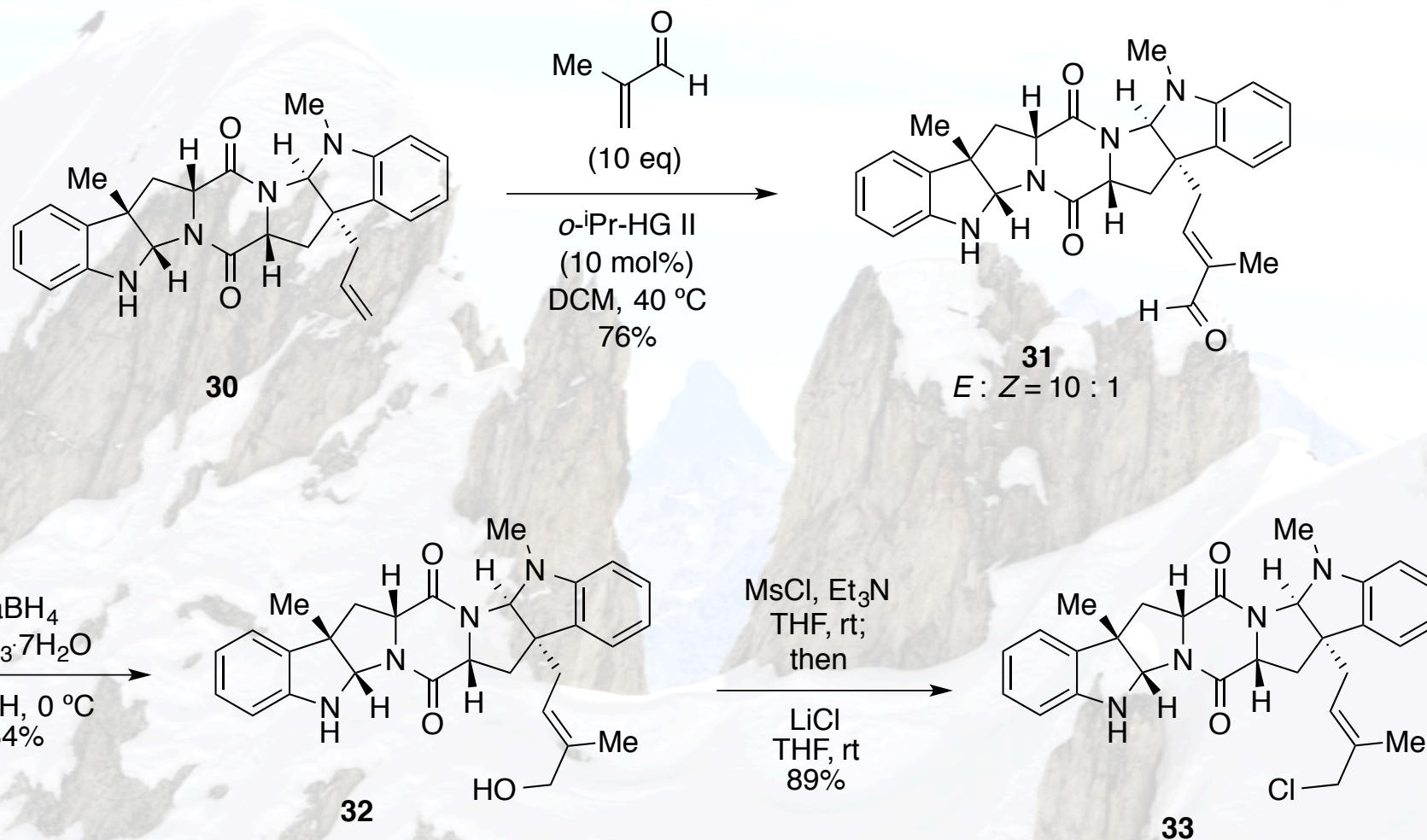
Pd₂(dba)₃ (10 mol%)
 dppb (20 mol%)
 DMBA
 DCE, 80 °C, 0.25 M
 (quantitative yield)

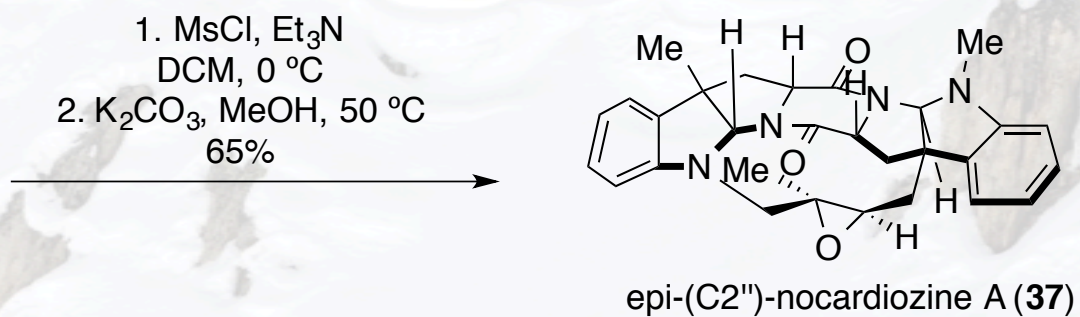
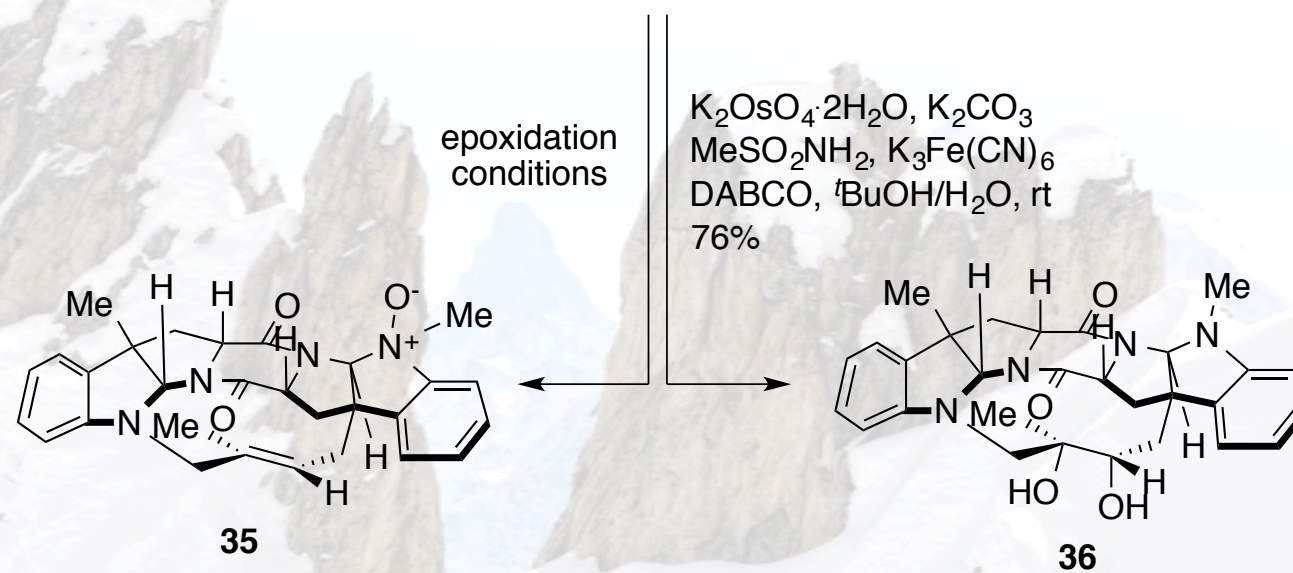
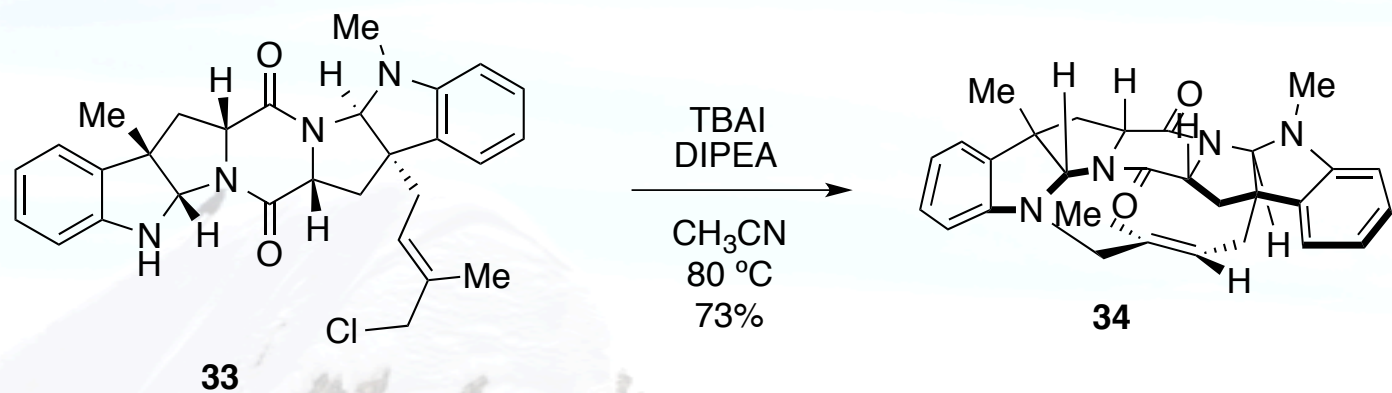


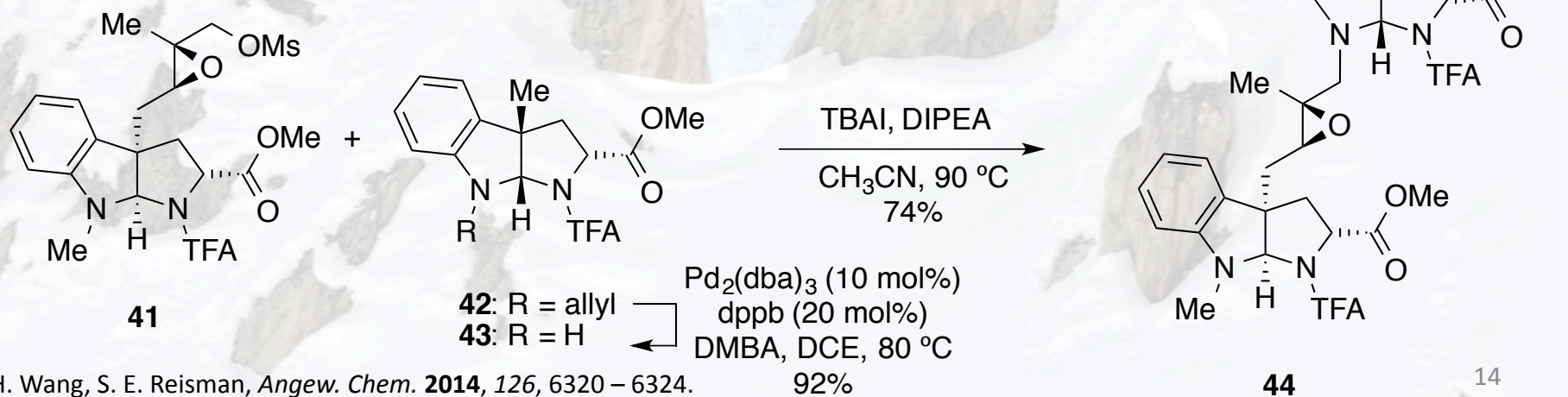
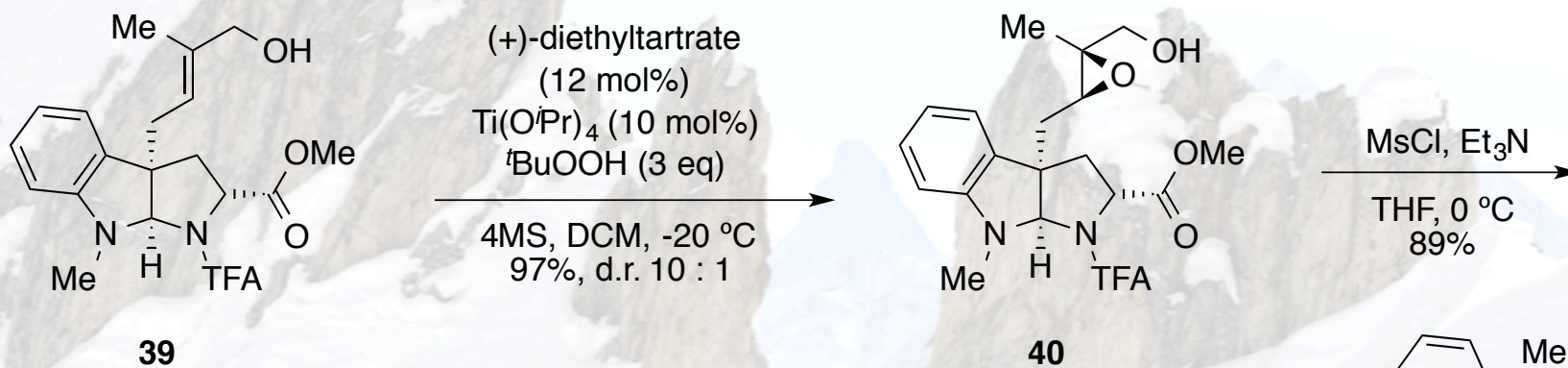
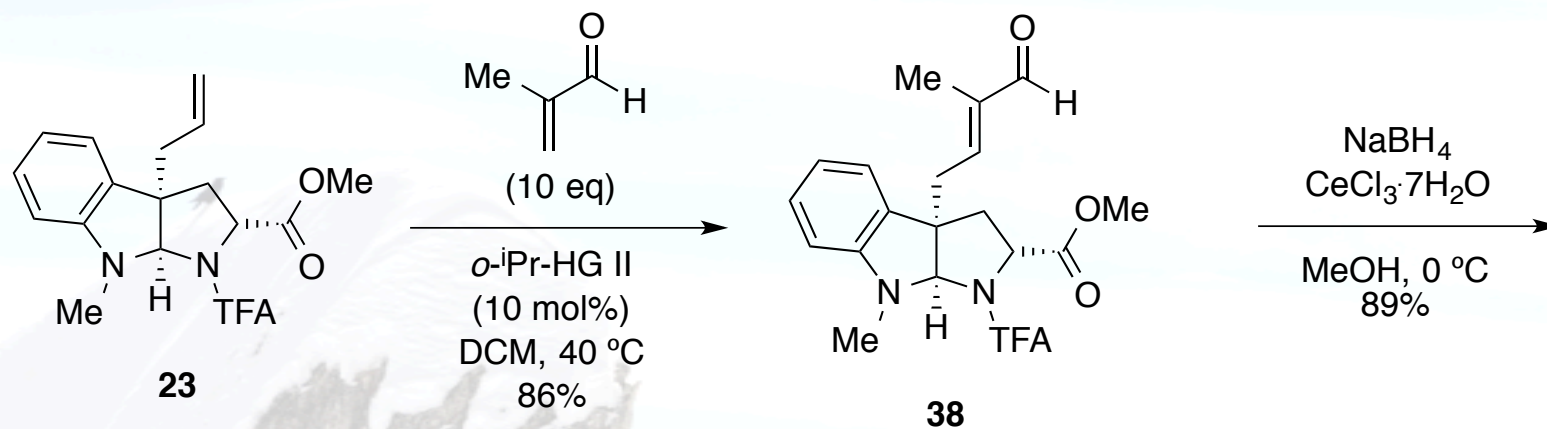
HG-II
 (10 mol%)
 38 °C
 85%

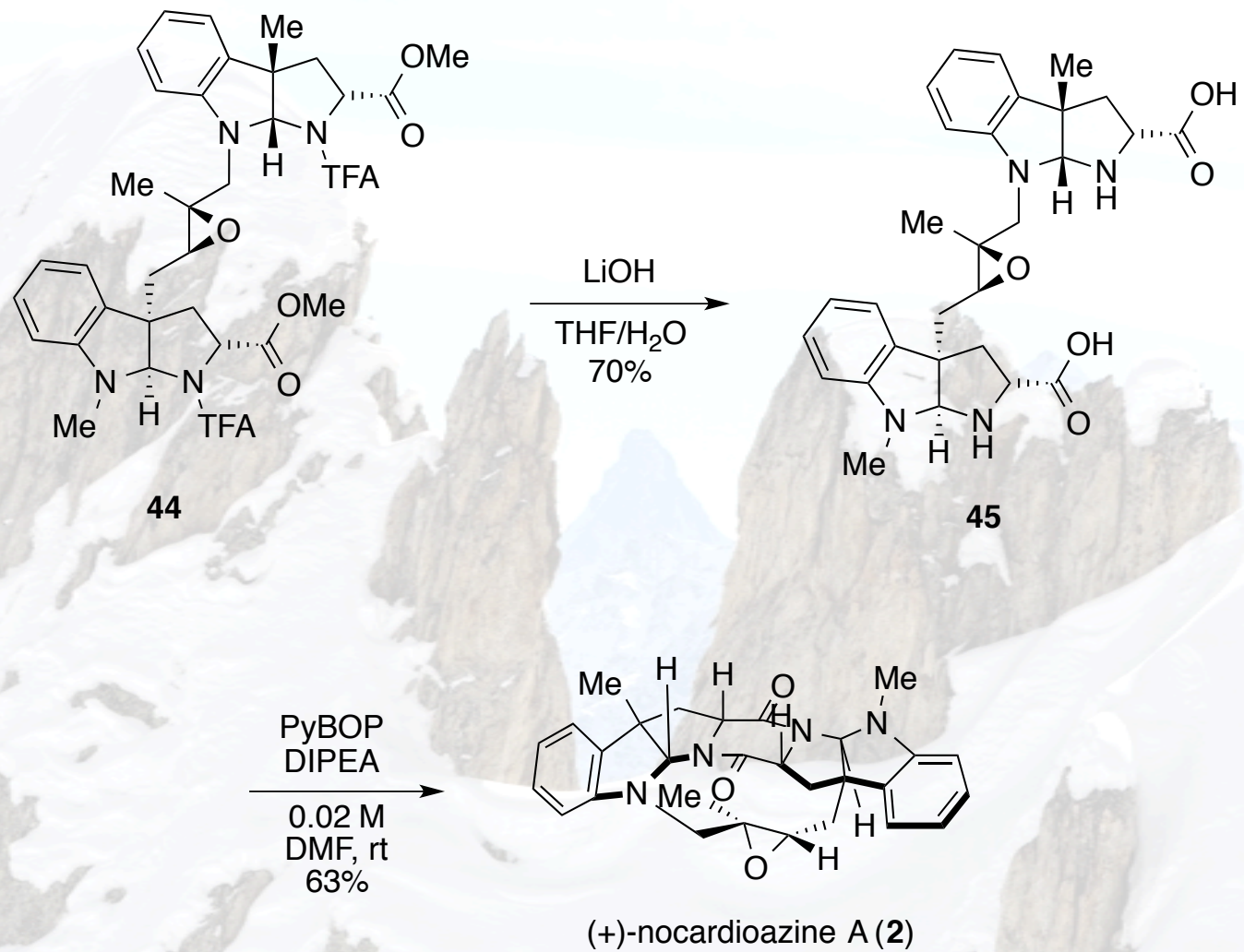


Synthesis of (+)-nocardioazine A:



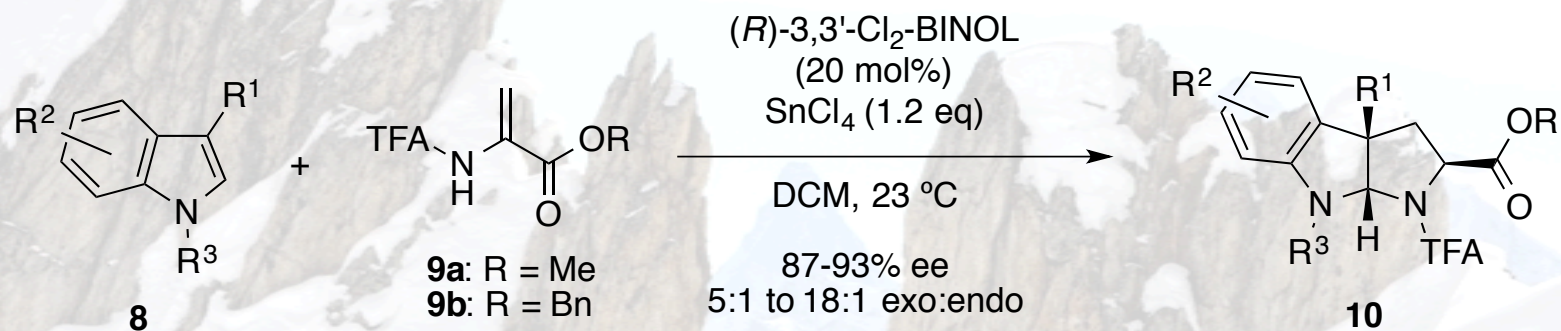







Conclusion

- method to enantioenriched pyrroloindolines from C3-substituted indoles



- (-)-lansai B: 6 steps (longest linear sequence) and 20% overall yield
- (+)-nocardioazine B: 9 steps (longest linear sequence) and 21% overall yield
- (+)-nocardioazine A: 9 steps (longest linear sequence) and 11% overall yield

A high-altitude mountain landscape covered in snow. In the foreground, a snowfield is dotted with dark, jagged rock formations. In the middle ground, a prominent, sharp rock peak rises from the snow. To the left, a person is visible on a snow-covered ridge. The background shows more snow-covered mountain ranges under a pale, overcast sky. The word "End" is superimposed in large, bold, black letters across the center of the image.

End

Pd-catalyzed deallylation with DMBA (dimethylbarbituric acid):

