

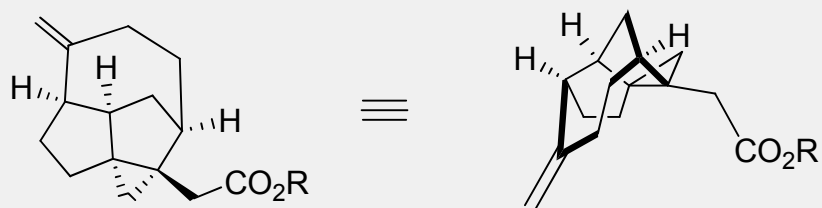
A Synthesis of Echinopine B

C. D. Vanderwal *et al.*, *Angew. Chem., Int. Ed.* **2012**, *51*, 7572-7576.

Introduction

Echinopines A and B

- Isolated from the root of *Echinops spinosus* in 2008



R = H: echinopine A

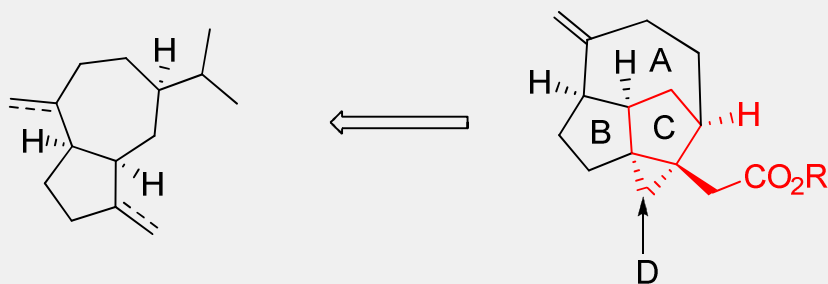
R = Me: echinopine B

- Unique carbocyclic [3.5.5.7] framework
- Presence of an exocyclic methylene double bond and a methylester
- Lack of reported biological activity

Introduction

Echinopines A and B

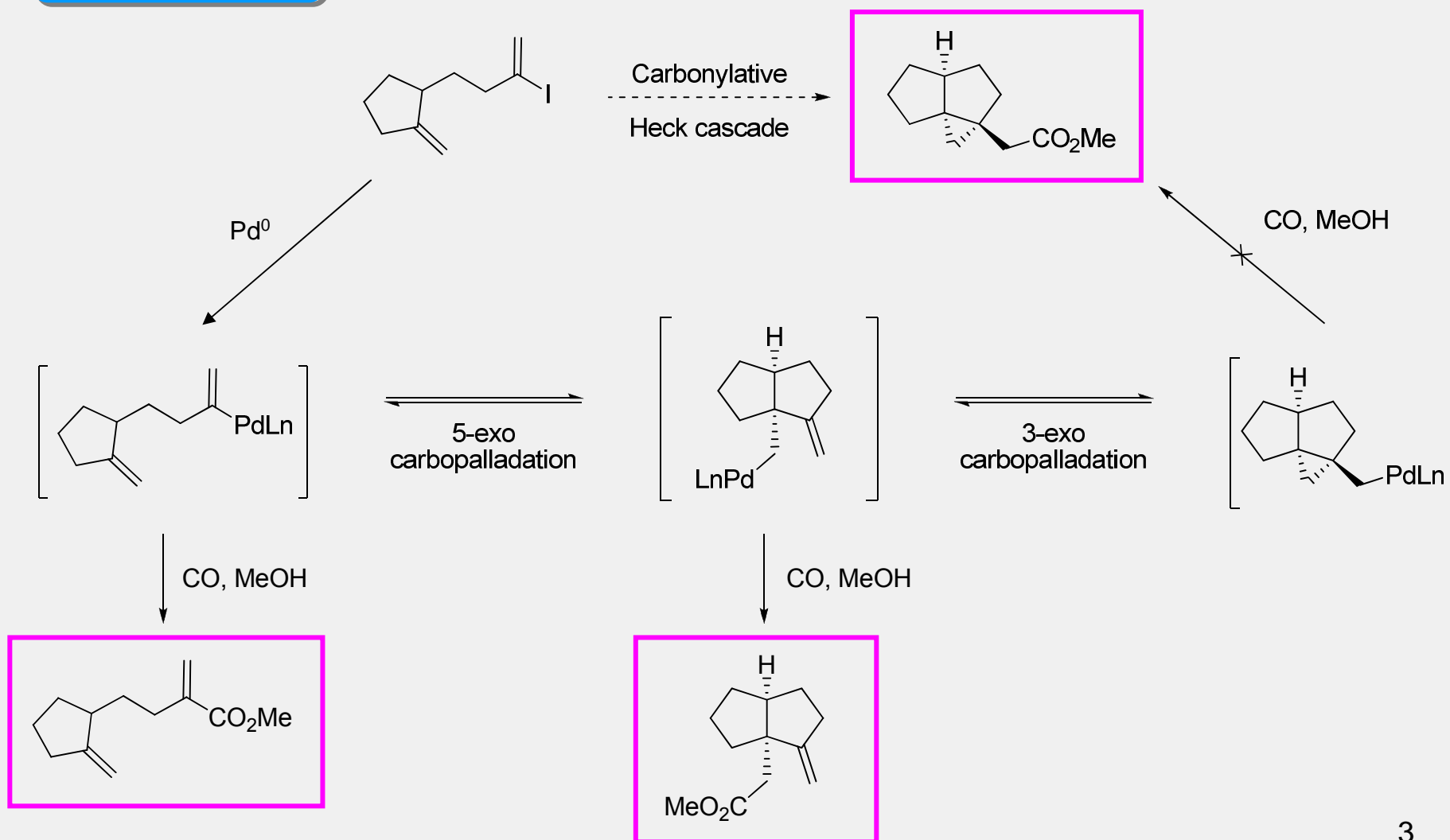
- Mulzer achieved the first enantioselective total synthesis in 2009 (20 steps), followed by Nicolaou (2010, 39 steps) and Chen (2011, 25 steps)
- Presumed biogenesis: from *cis*-guaiane



- Transition-metal catalyzed bicyclization from guaiane-like precursor
- Choice of the method: tests on mimetic substrates

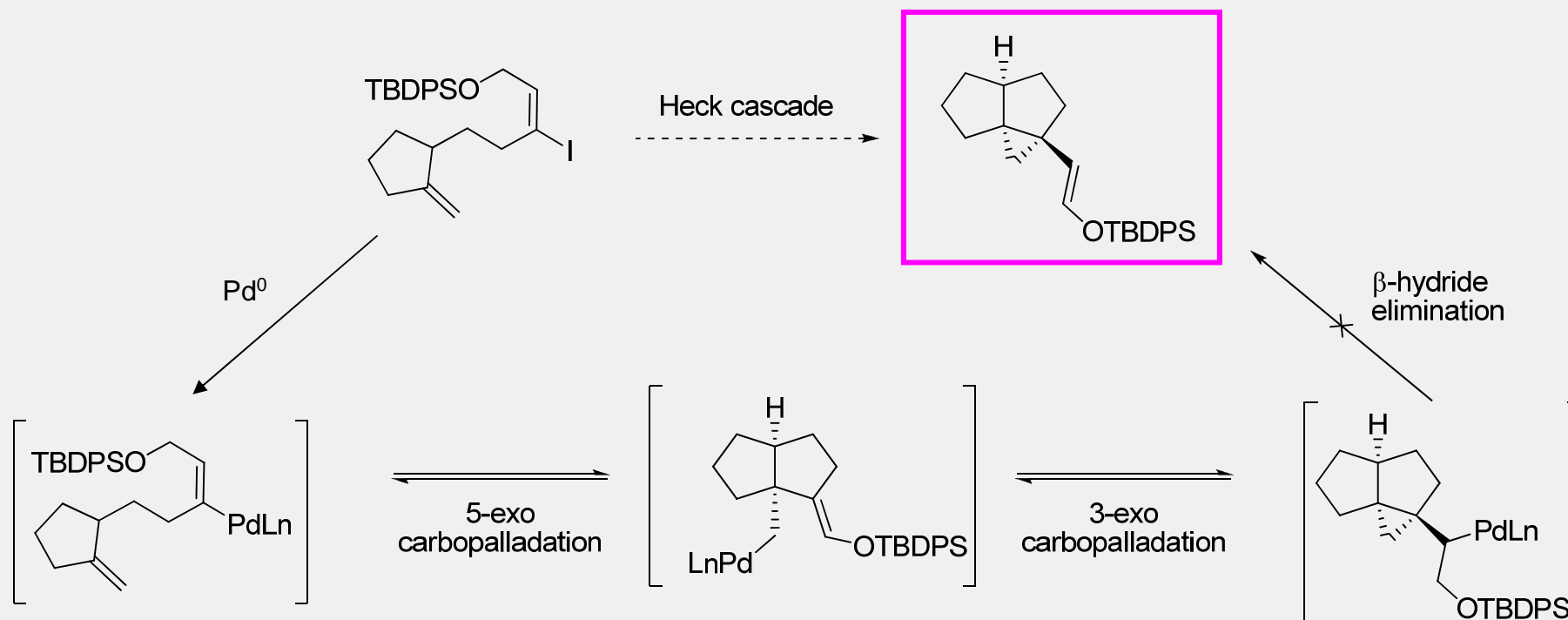
Synthetic strategy

Heck Cascades : Test substrate



Synthetic strategy

Heck Cascades

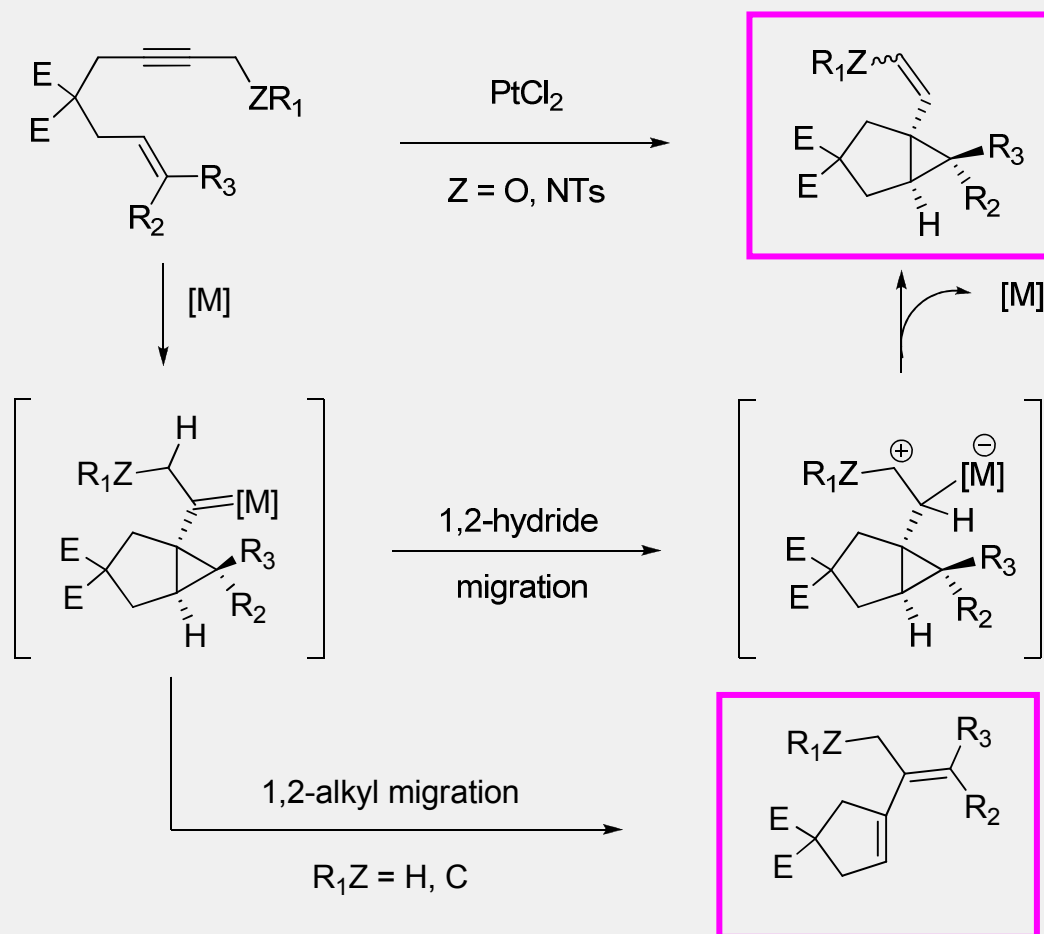


- Change the strategy

Synthetic strategy

1,6-enyne cycloisomerization

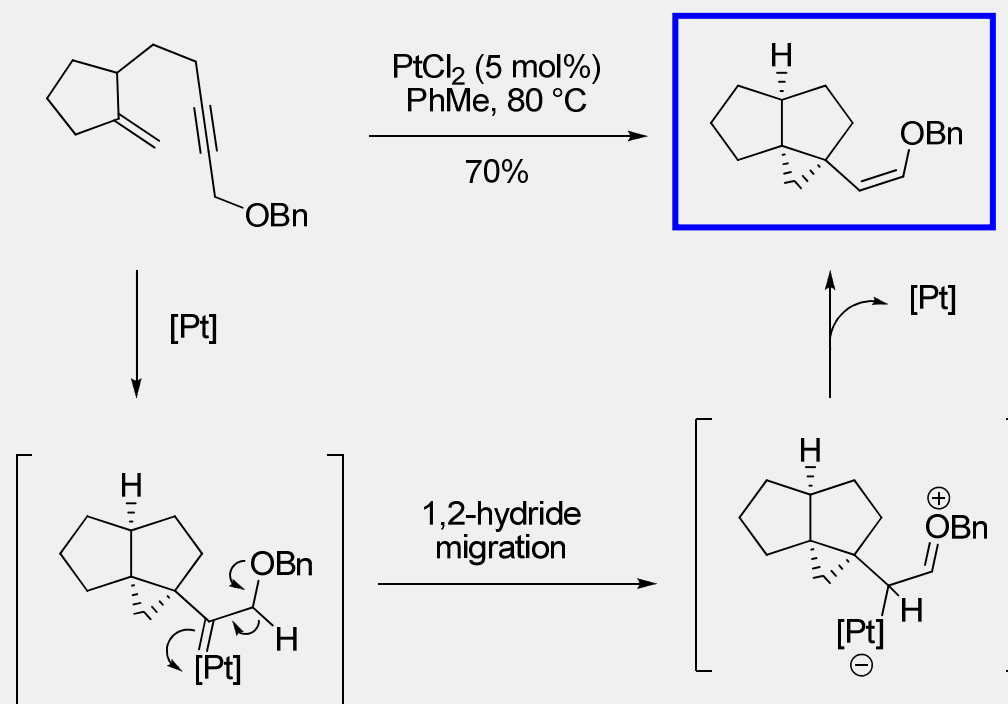
- Presence of the heteroatom at the propargylic position



Synthetic strategy

1,6-enyne cycloisomerization

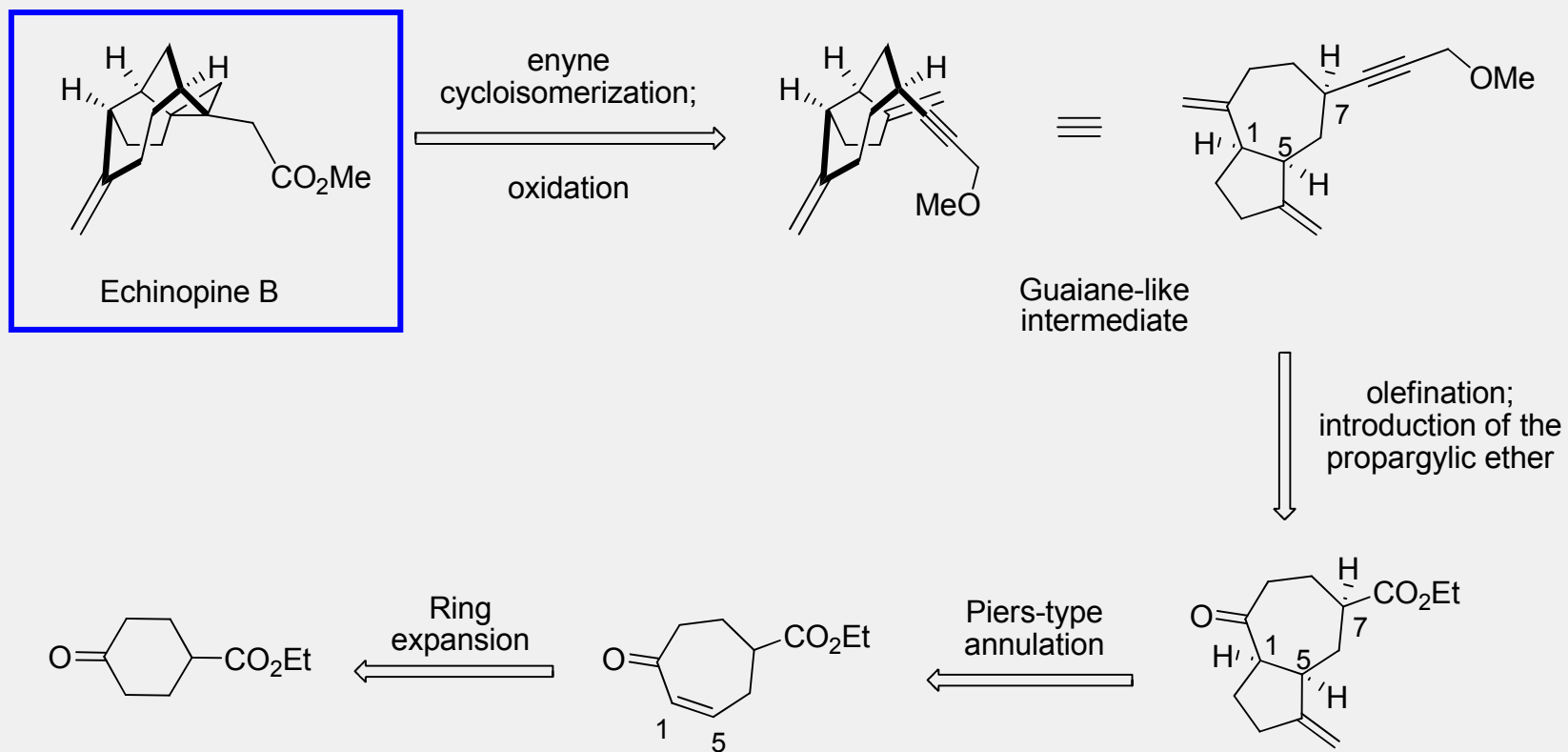
- Test on a mimetic substrate:



- The ether could be further transformed into ester

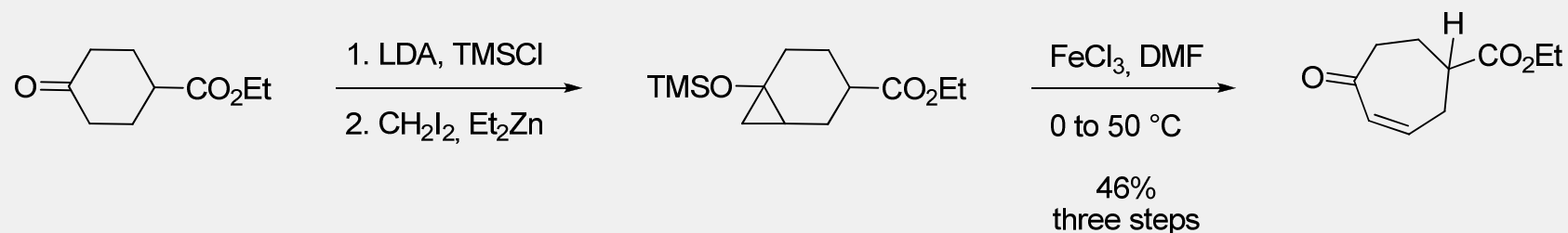
Synthetic strategy

Retrosynthetic approach



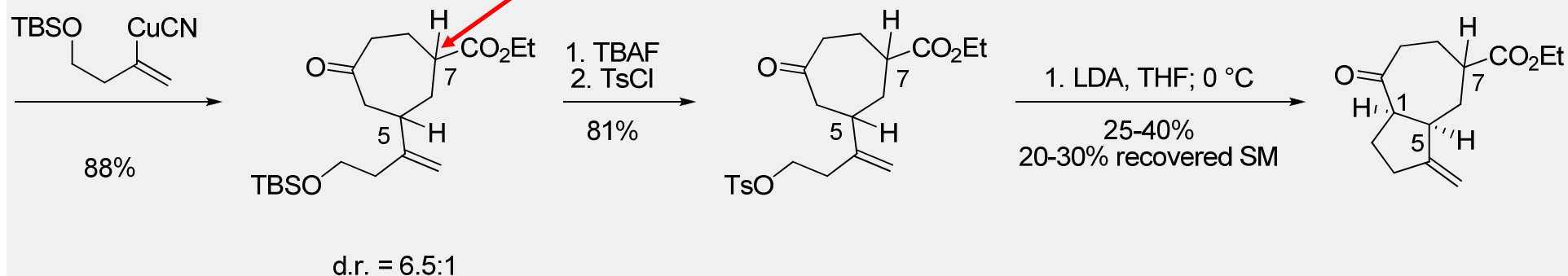
Synthesis of Echinopine B

Ring expansion



Piers-type annulation

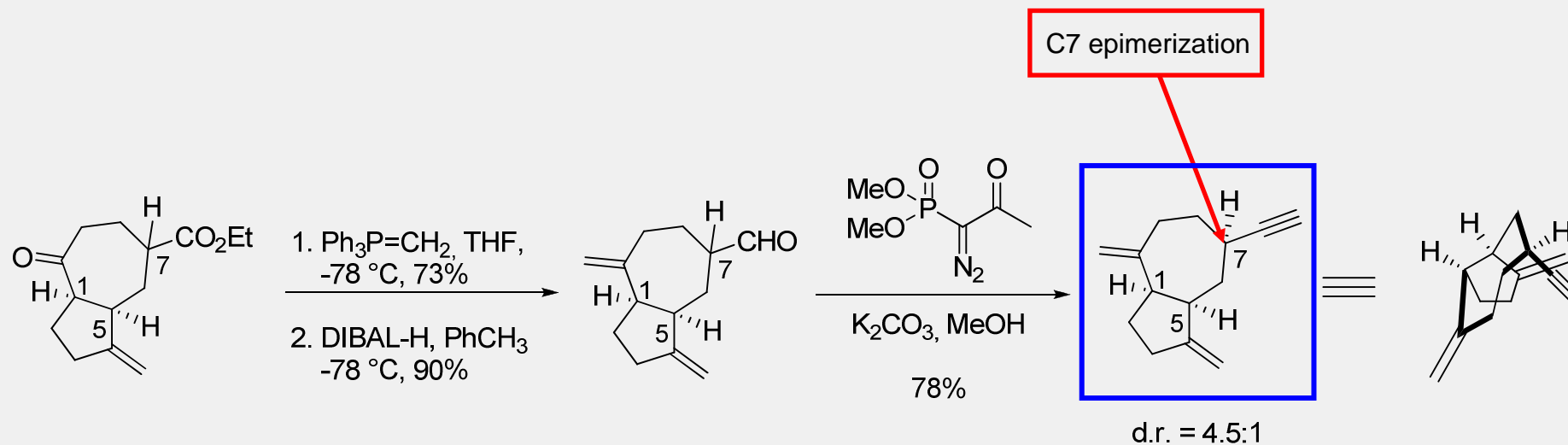
Unknown configuration!



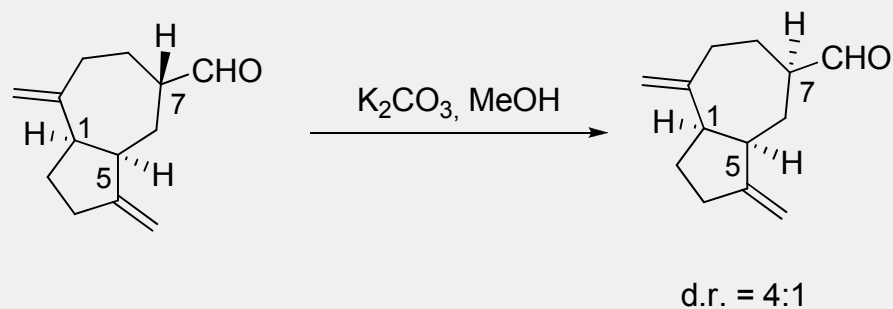
- Cyclization not run to complete conversion to avoid C1 epimerization

Synthesis of Echinopine B

Preparation of the guaiane-like precursor

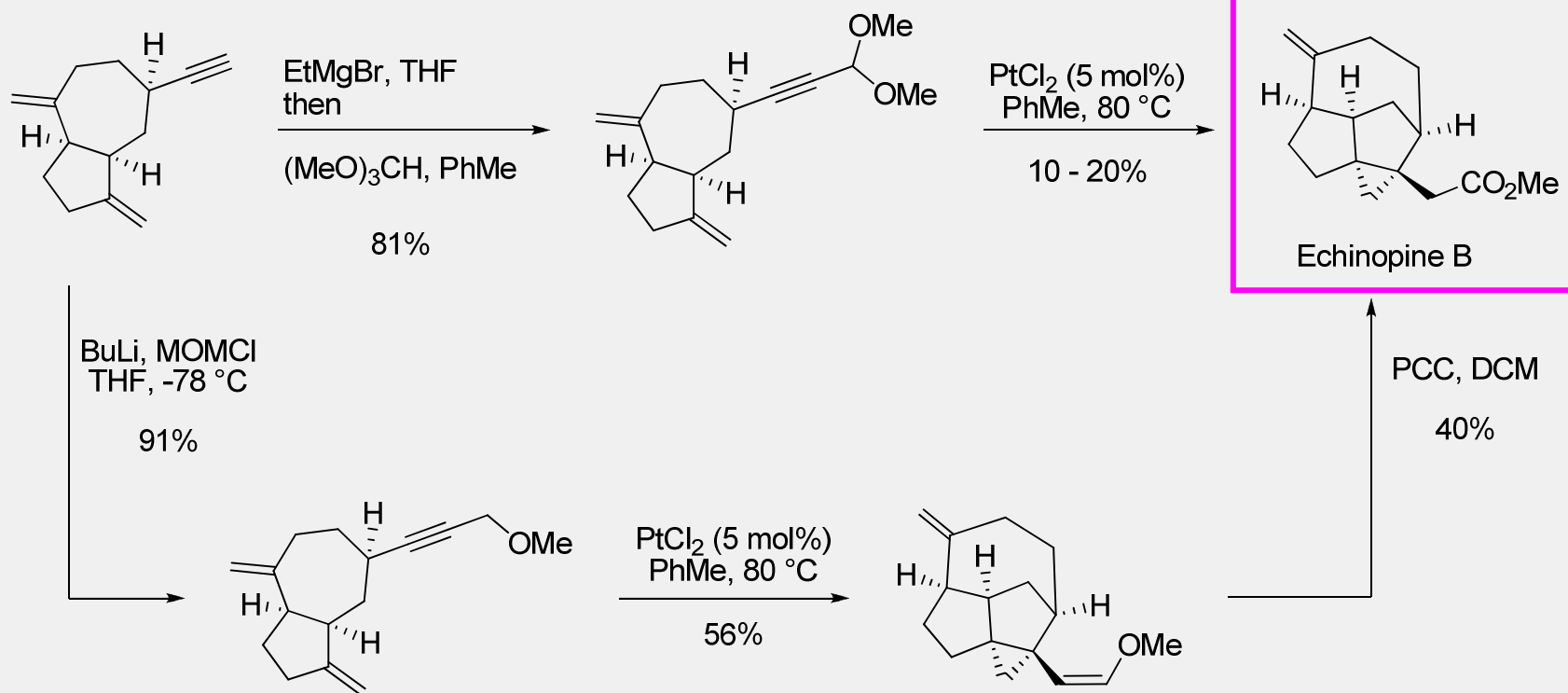


- Epimerization during Ohira-Bestmann reaction



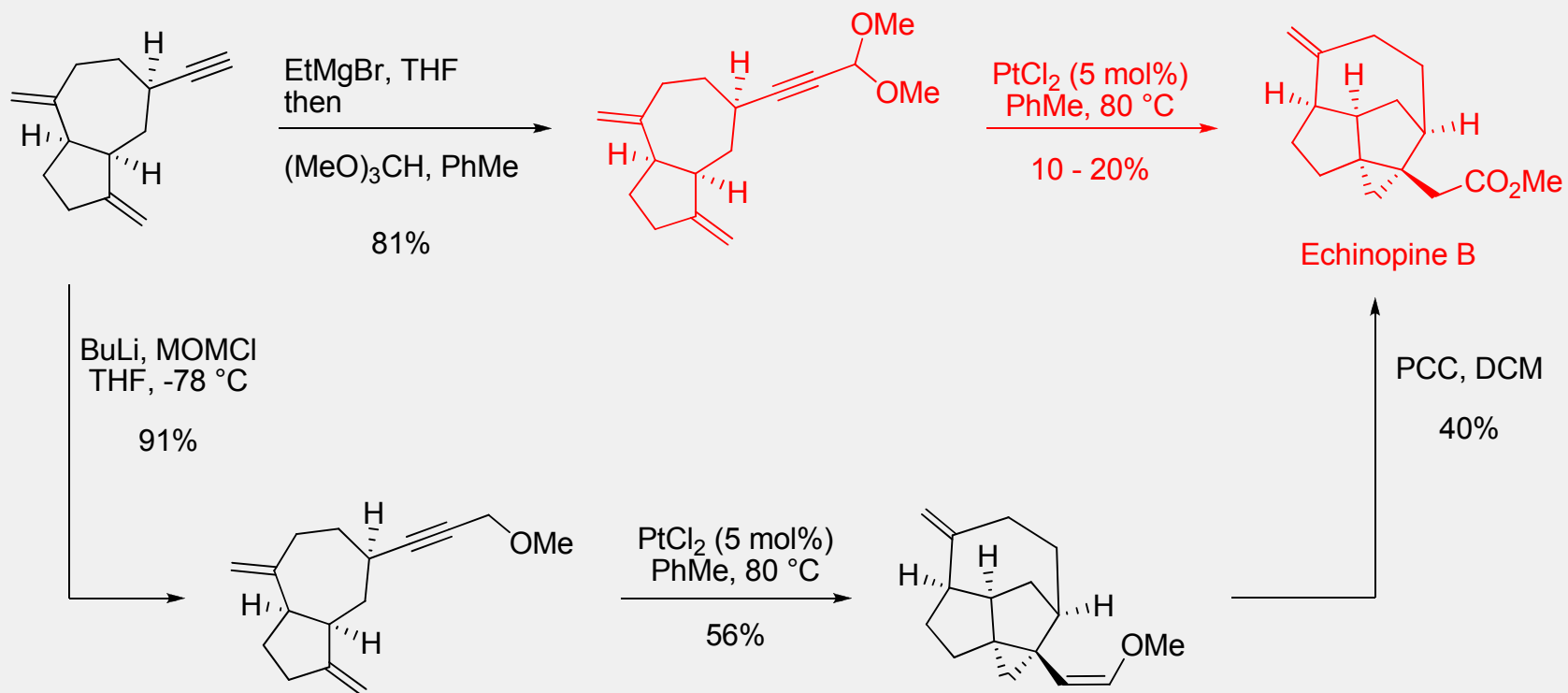
Synthesis of Echinopine B

Platinum-catalyzed cycloisomerizations



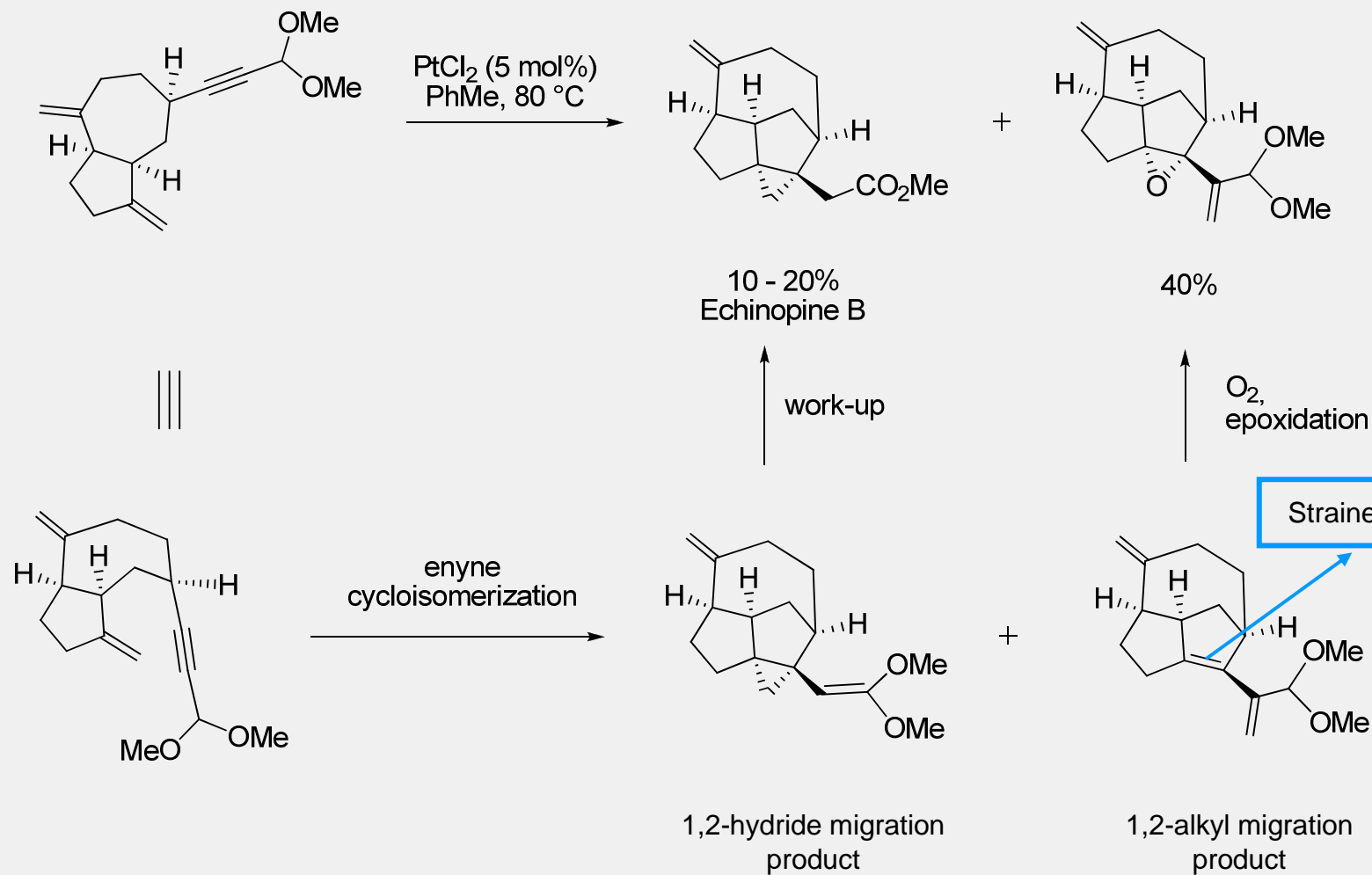
Synthesis of Echinopine B

Platinum-catalyzed cycloisomerizations



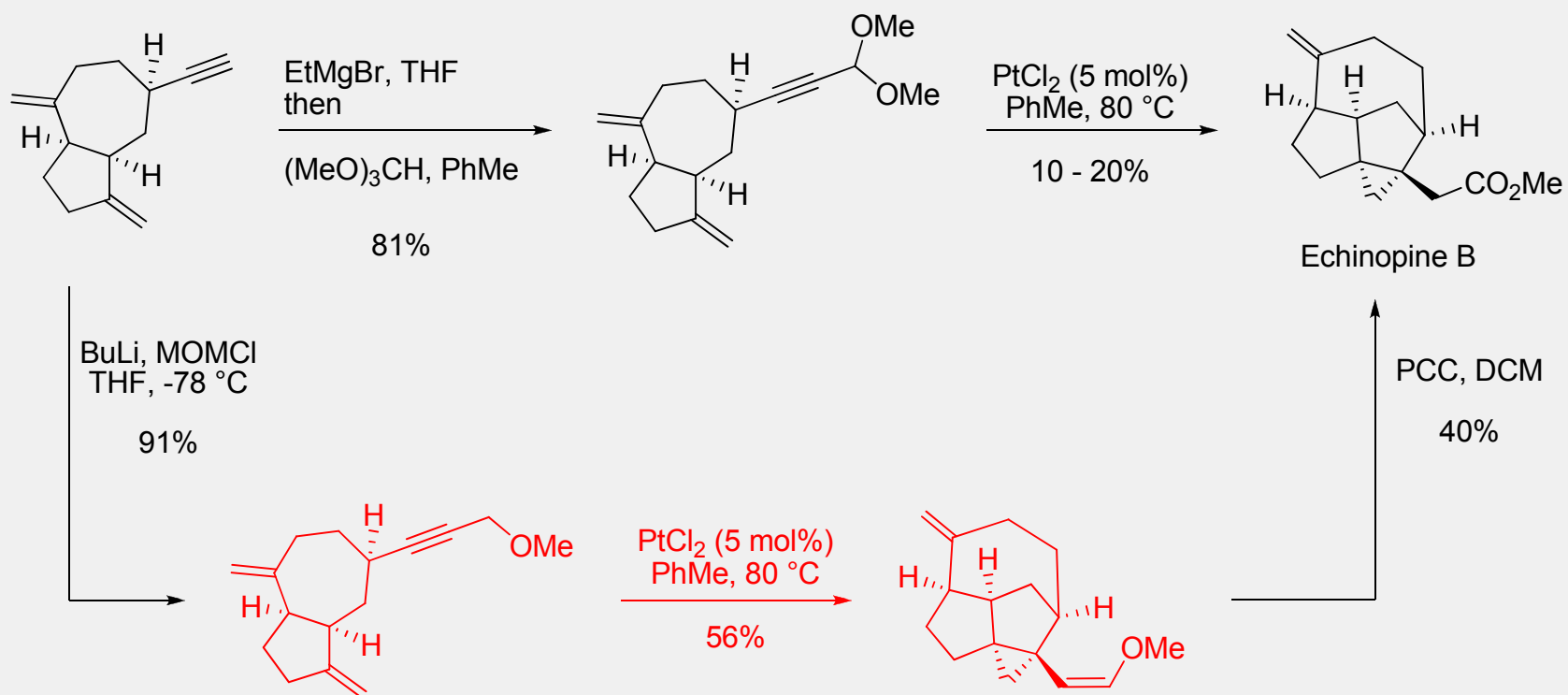
Synthesis of Echinopine B

Platinum-catalyzed cycloisomerizations



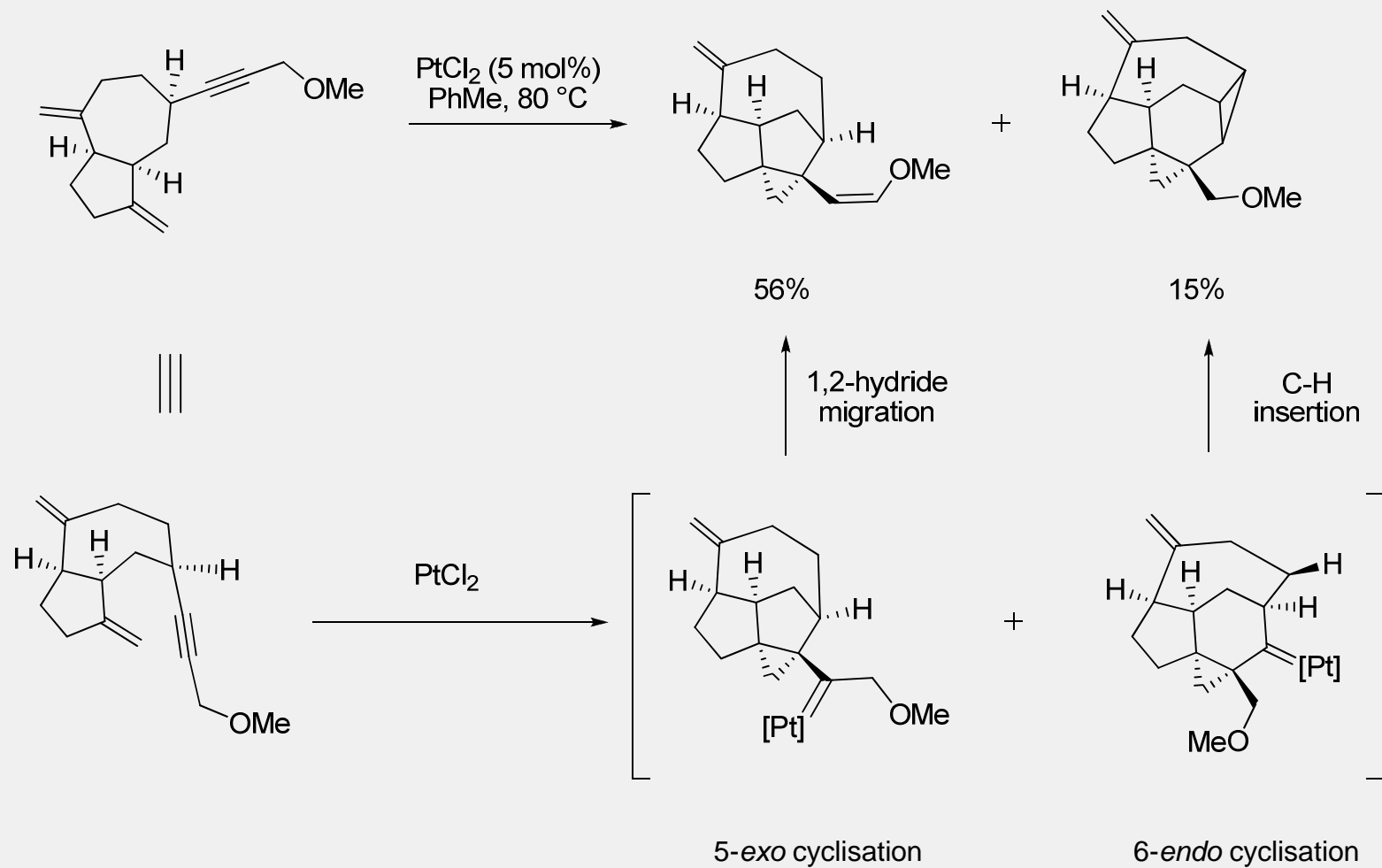
Synthesis of Echinopine B

Platinum-catalyzed cycloisomerizations



Synthesis of Echinopine B

Platinum-catalyzed cycloisomerizations



Conclusion

- Shortest synthesis ever reported of Echinopine B: 12 or 13 steps
- Utilization of recently developed methodologies
- Racemic synthesis: access to enantioenriched cycloheptenone?
- Low yielding Piers-type annulation

Thanks for your attention

PCC oxidation

Proposed mechanism

