Concise Enantioselective Total Synthesis of Daphenylline Enabled by an Intramolecular Oxidative Dearomatization

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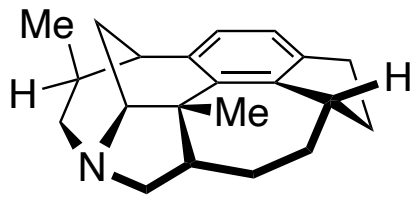
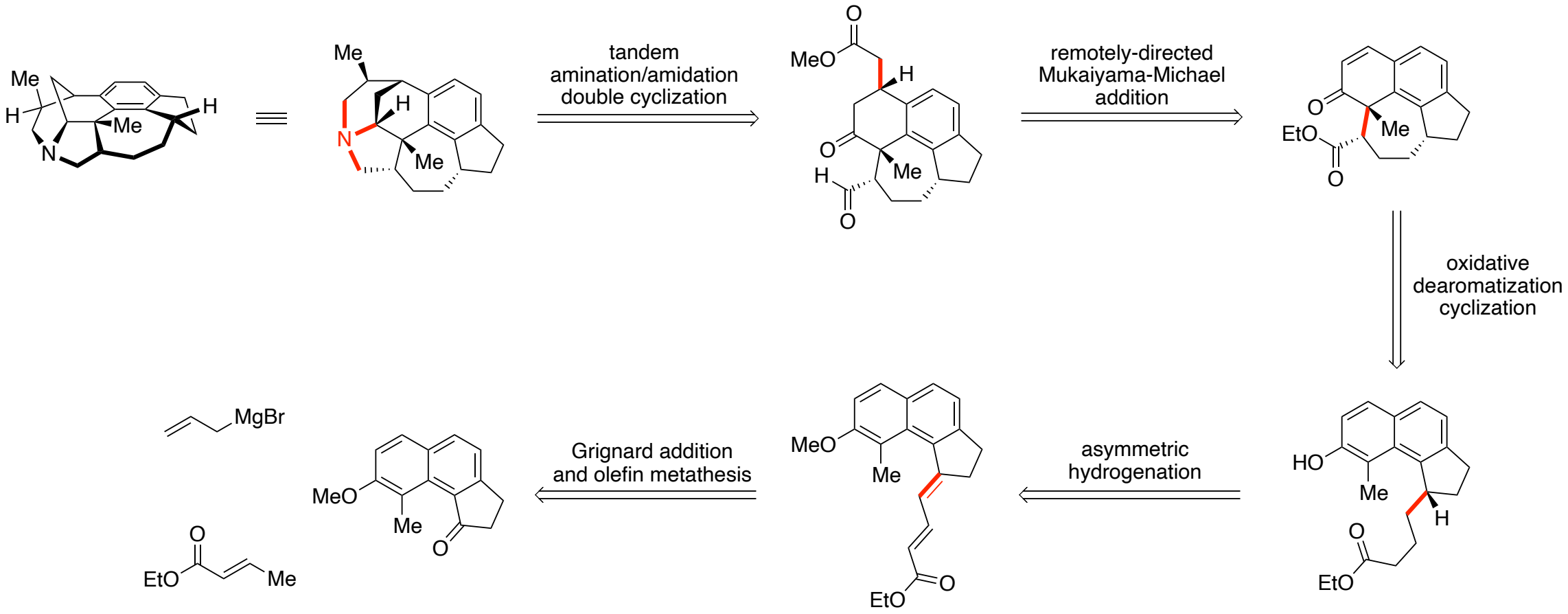


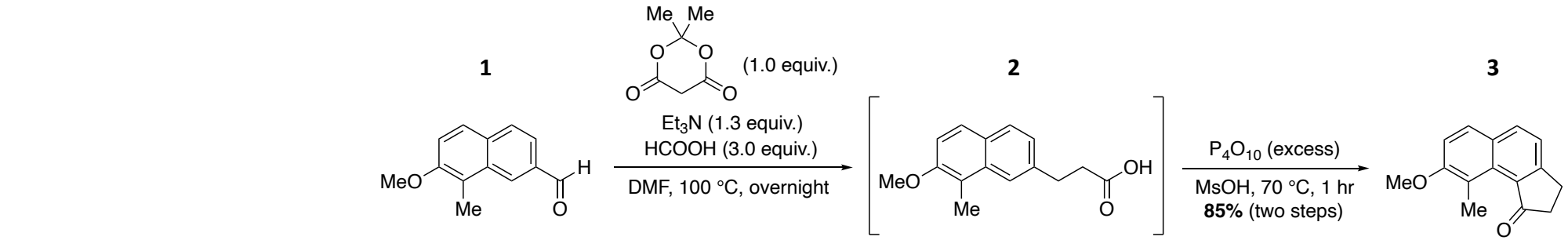
(-)-daphenylline

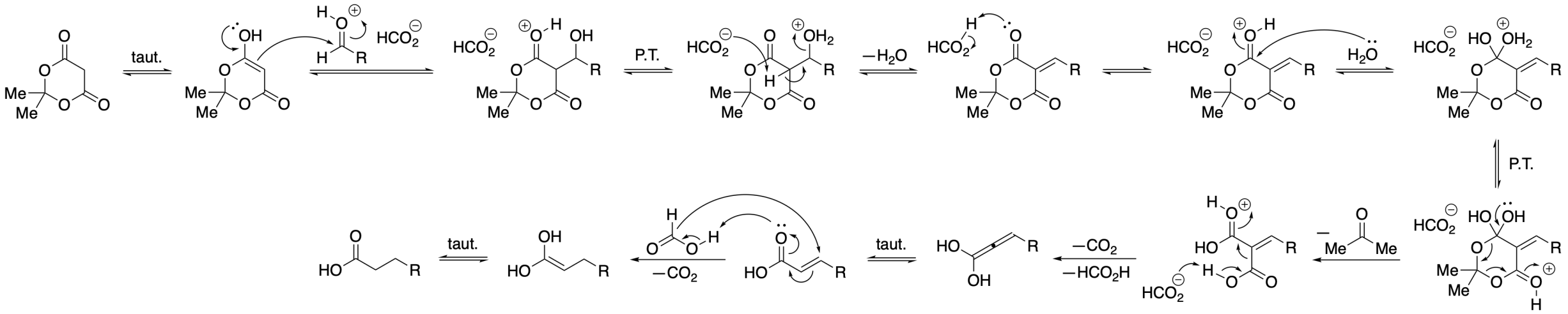
Kevin Byrne
Liu/Chatterjee Research Groups
April 15th, 2022

- Found in plants of the *Daphniphyllum* genus (evergreen trees/shrubs from Asia-Pacific region)
  - Chinese herbal medicine for treating asthma, rheumatism, and snakebites
  - *Daphniphyllum* alkaloids have shown vasorelaxant, neurotrophic, cytotoxic, and antioxidant activity
- Challenging due to unique benzene ring with four contiguous carbon substituents, three of which are chiral
- First synthesized by Li in 2013, with five additional total syntheses reported since then
  - All rely on aromatization strategies and surplus redox/functional group interconversions
- This work: concise enantioselective total synthesis through an unconventional dearomative approach and a novel tandem reductive amination/amidation double cyclization step.

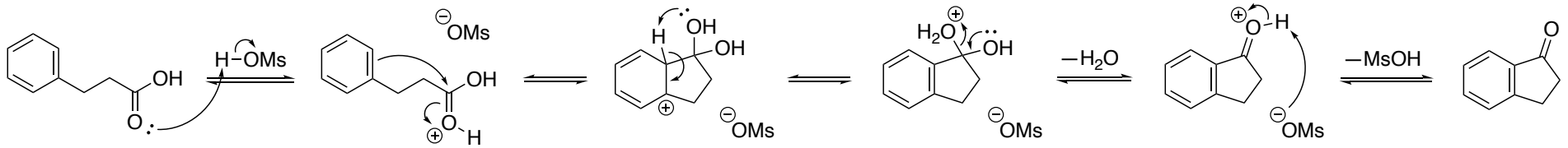
Retrosynthetic Analysis:

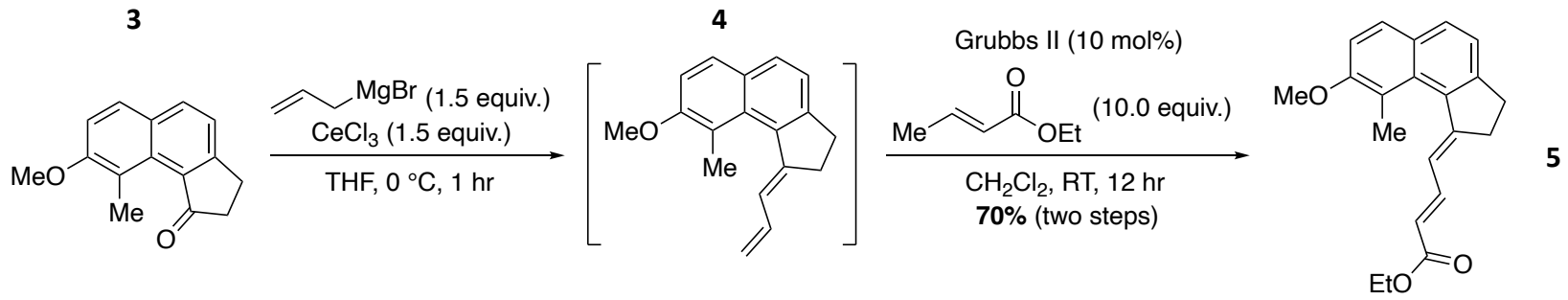




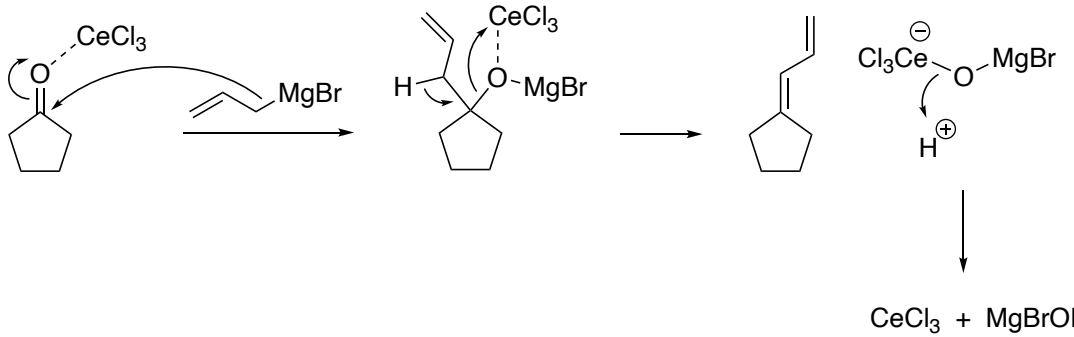


Friedel-Crafts Cyclization:

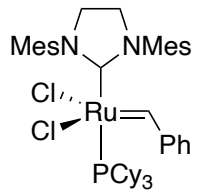




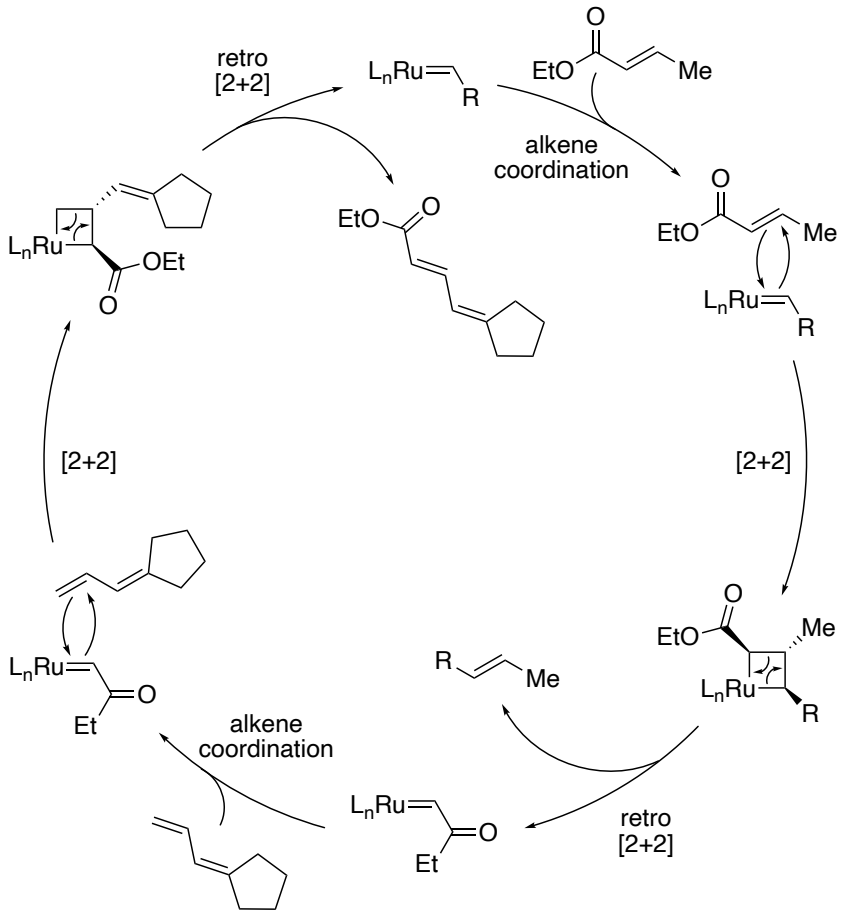
Grignard Condensation:

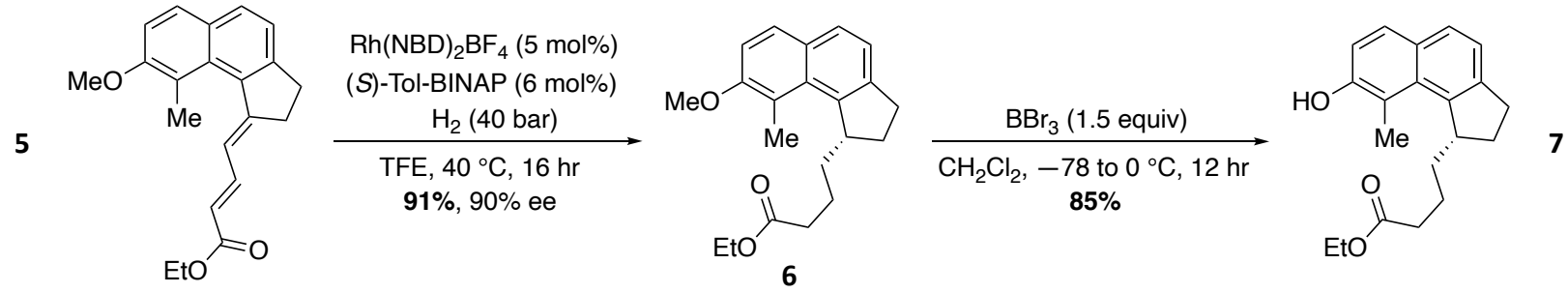


Olefin Metathesis:

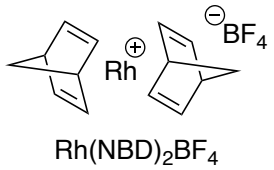


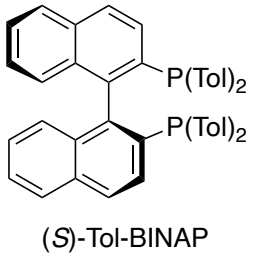
Grubbs II

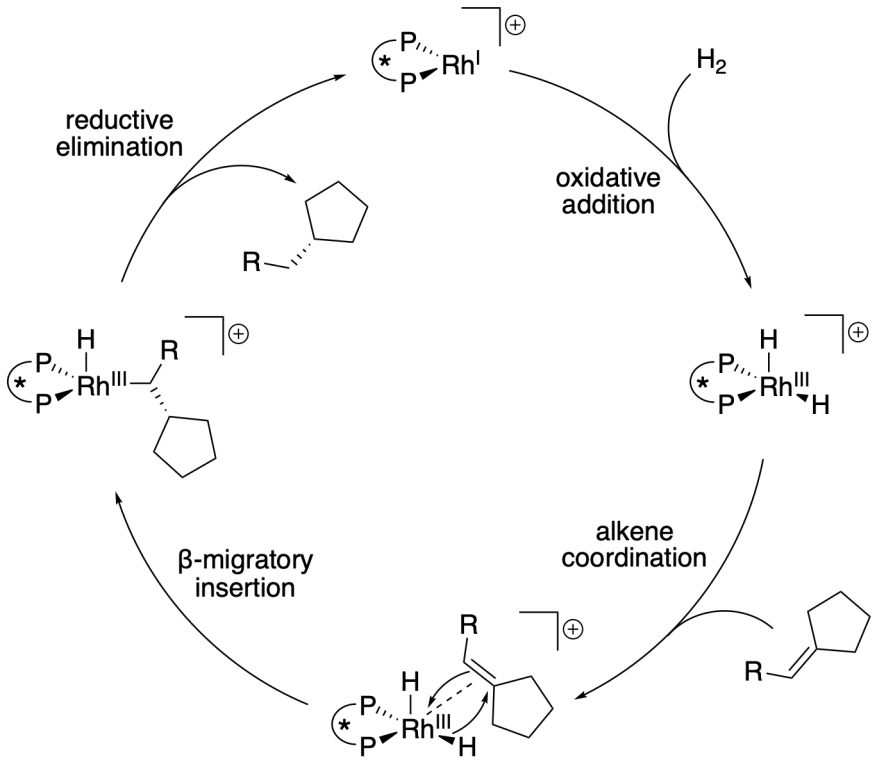




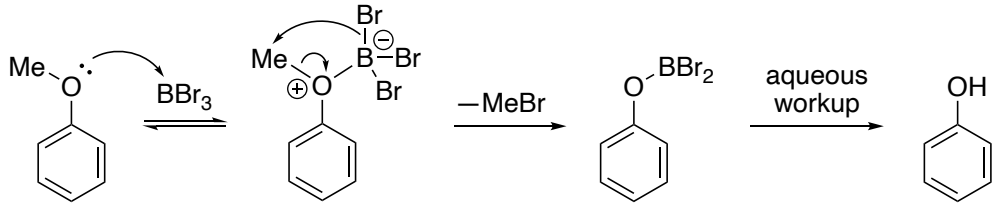
Rh-Catalyzed Enantioselective Hydrogenation:

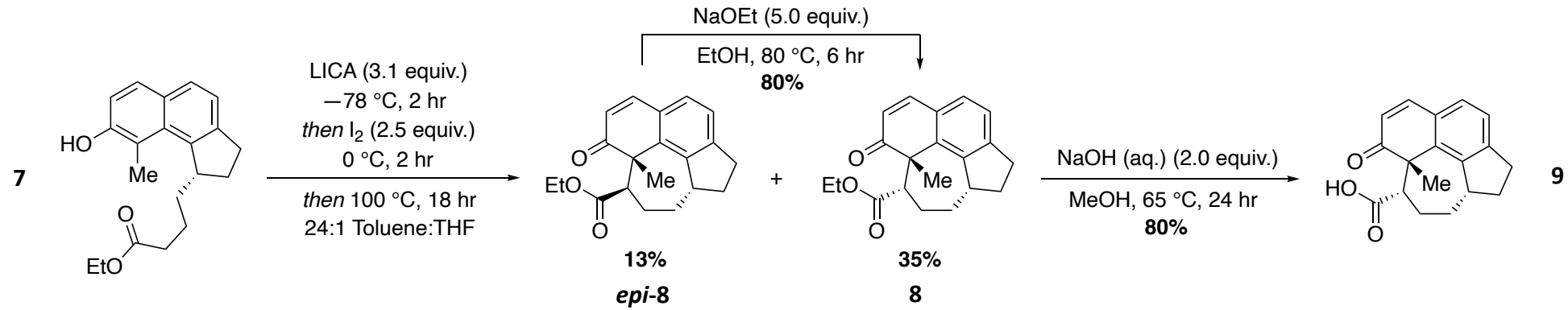




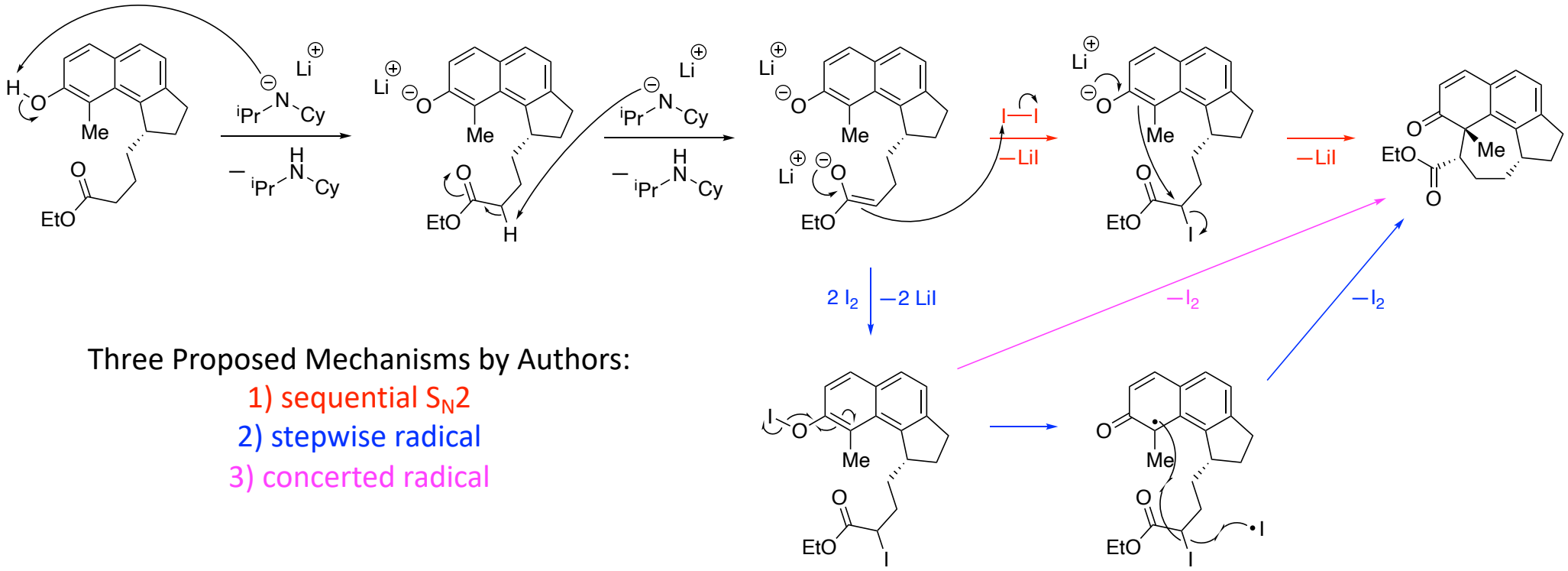


BBr_3 Demethylation:





Oxidative Dearomative Cyclization:

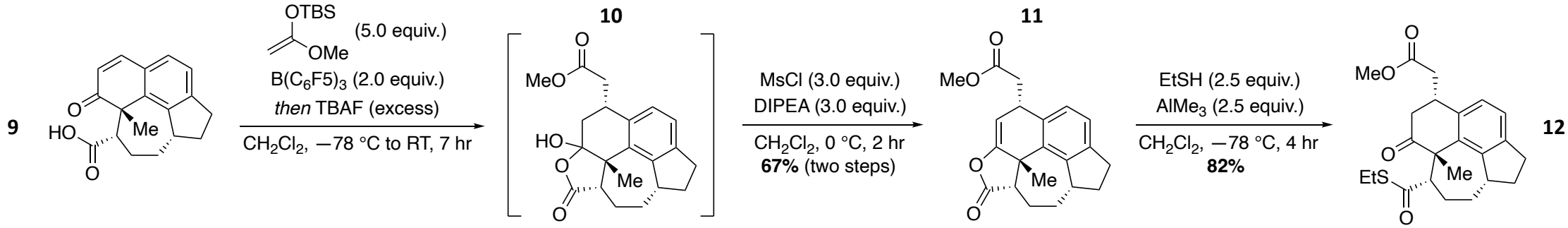


Three Proposed Mechanisms by Authors:

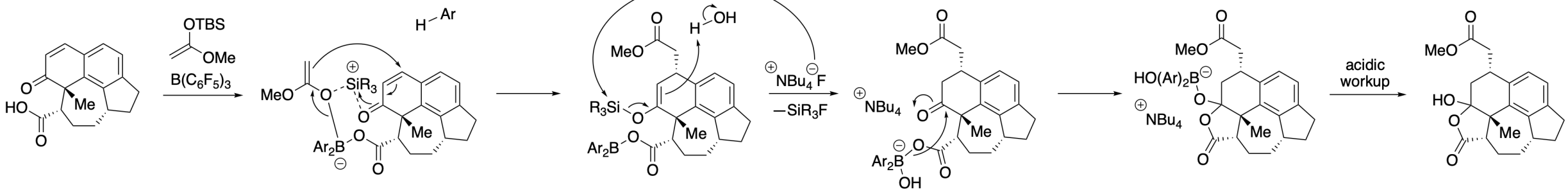
1) sequential S_N2

2) stepwise radical

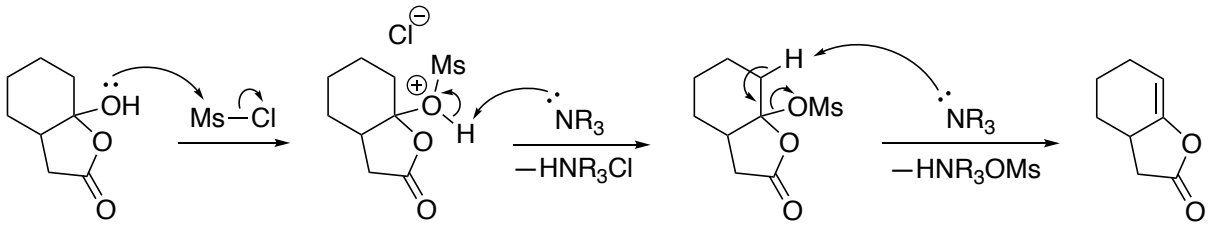
3) concerted radical



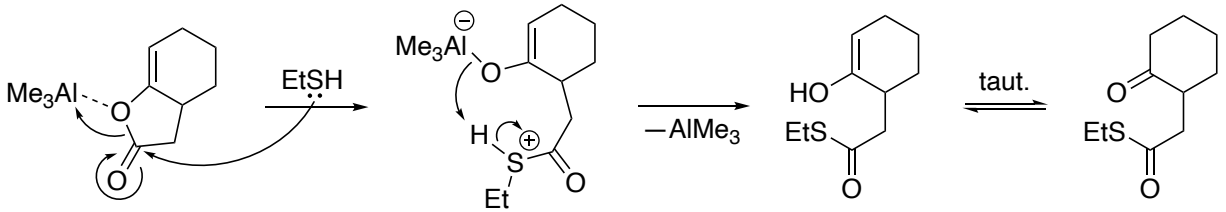
Mukaiyama-Michael Addition:

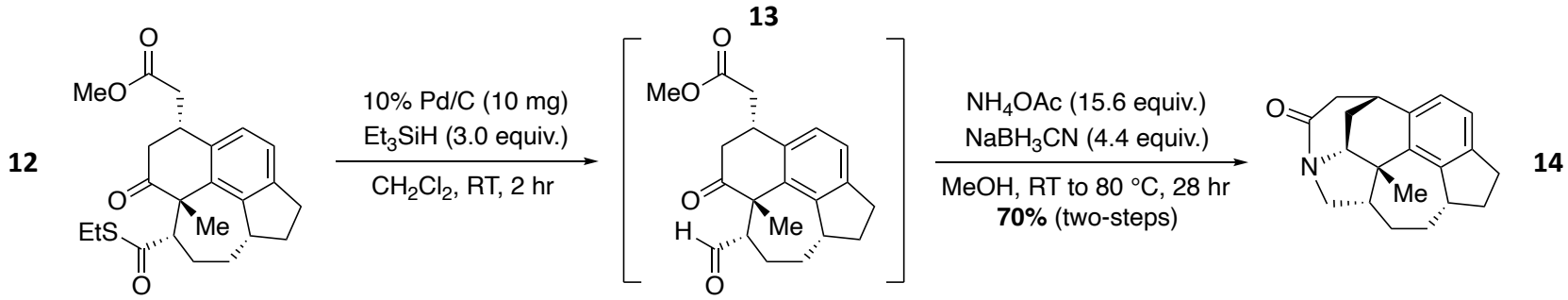


Dehydration:

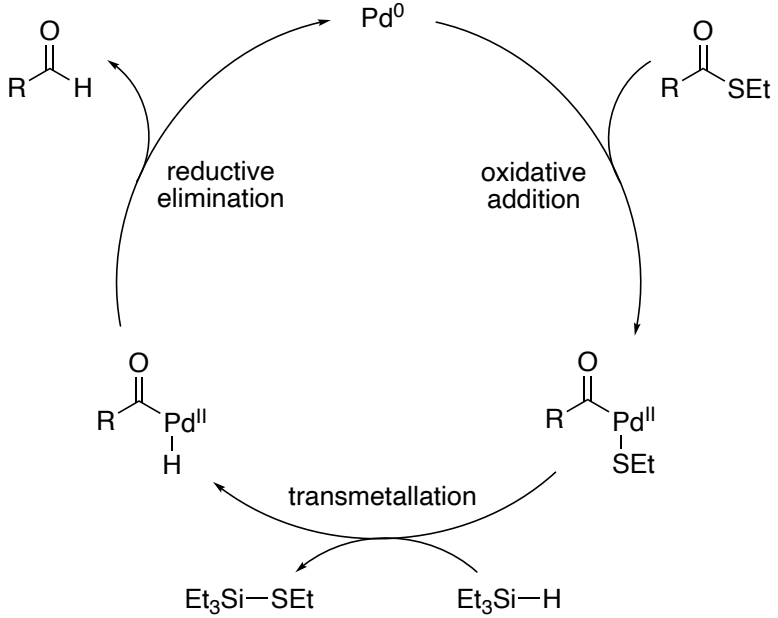


Thioester Formation:

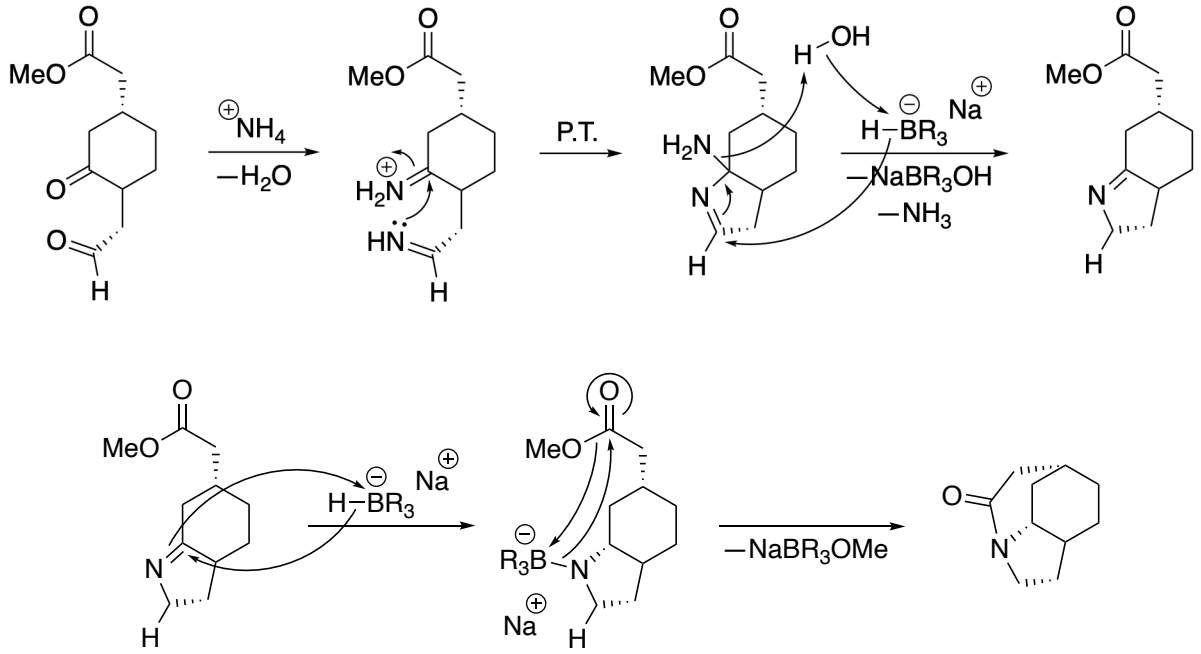


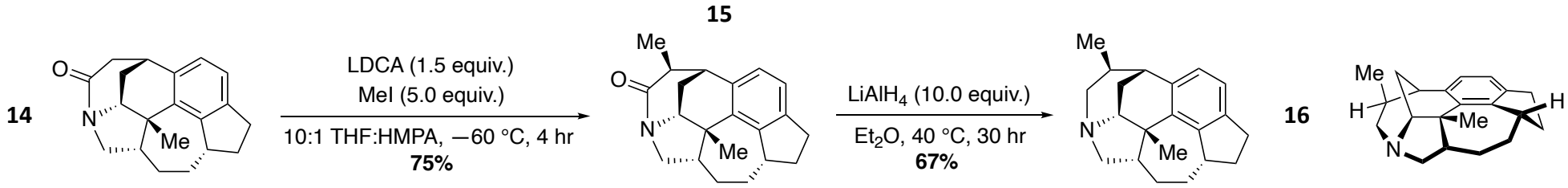


Fukuyama Reduction:

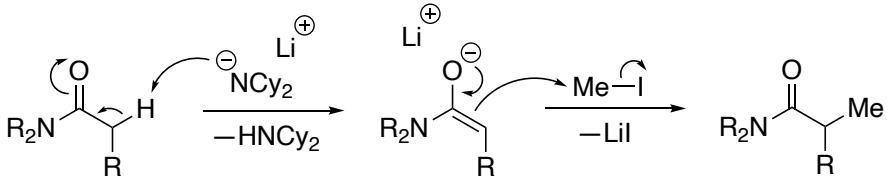


Tandem Reductive Amination/Amidation Double Cyclization:





Methylation:



LAH Amide Reduction: