Asymmetric Total Synthesis of (+)-Alstonlarsine A

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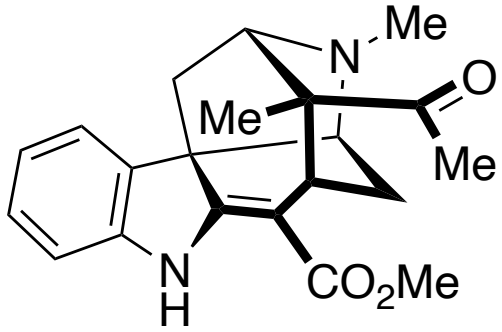
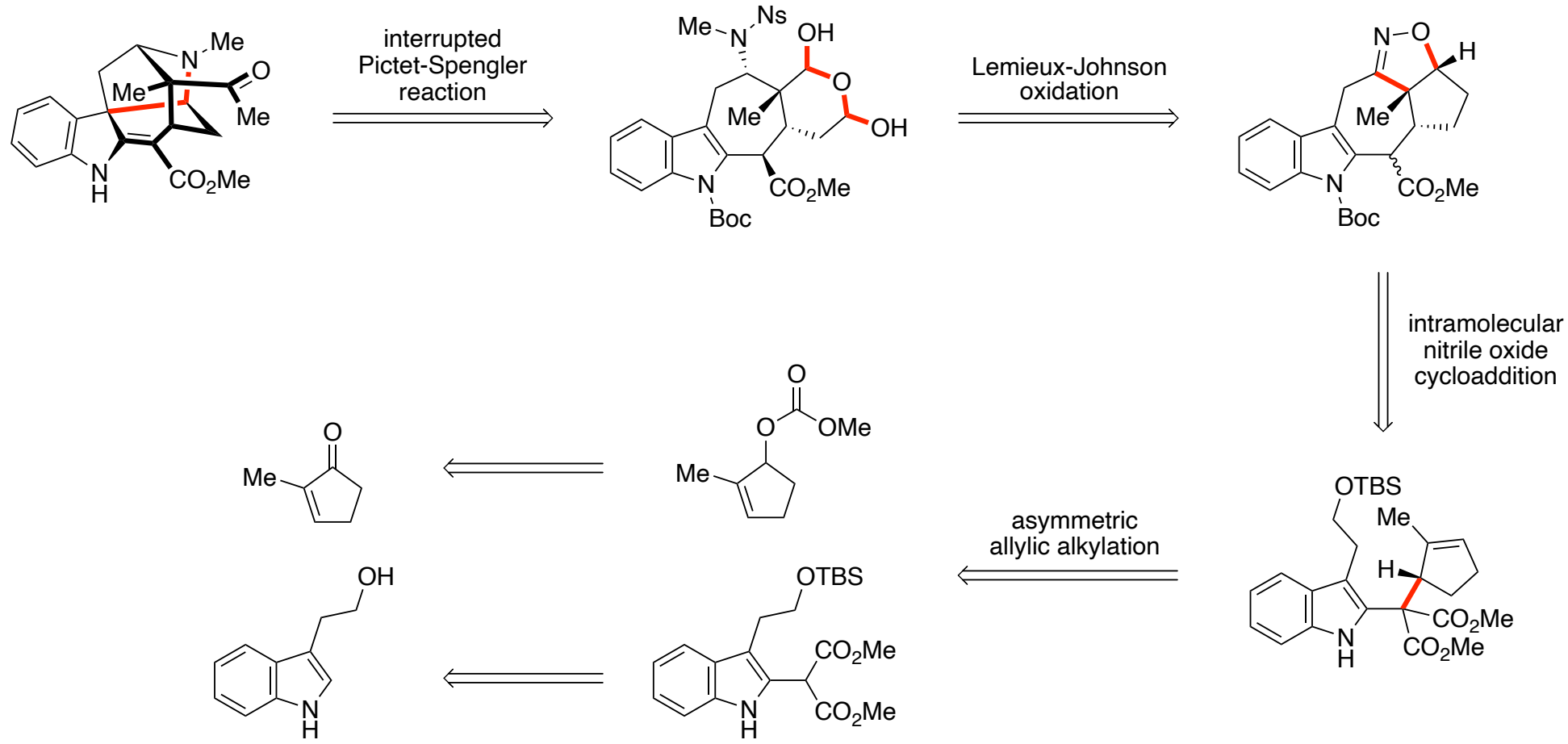


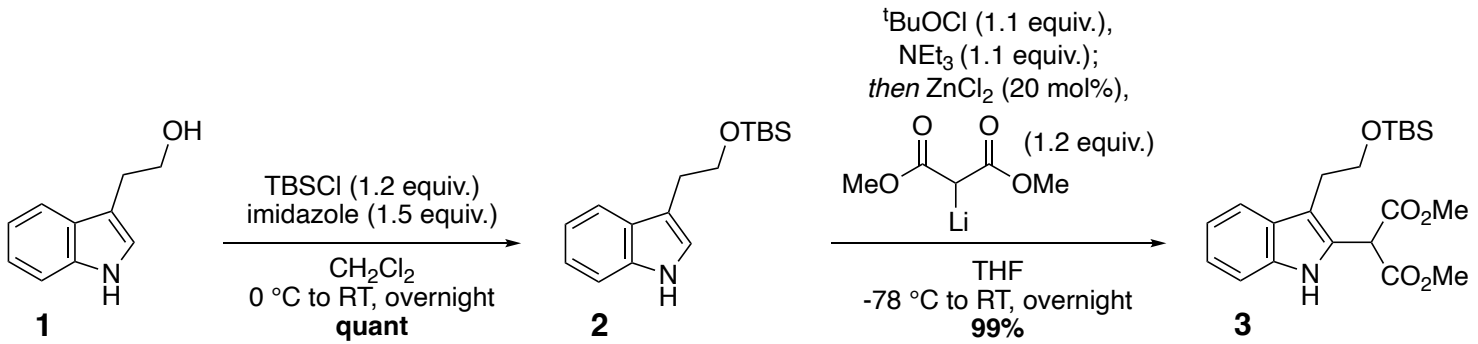
(+)-Alstonlarsine A

Kevin Byrne
Liu/Chatterjee Research Groups
September 21st, 2022

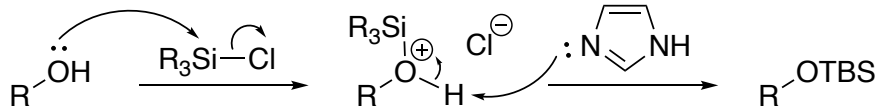
- Found in the bark and roots of the *Alstonia scholaris* tree ("Devil's Tree" from the Asia-Pacific region)
  - Plant itself exhibits toxicity to rats and mice; level of toxicity depends on the season it's harvested
  - Yue and Coworkers first isolated the monoterpene indole alkaloid (MIA) in 2019 => (4 mg/20 kg plant)
  - (+)-Alstonlarsine A has shown to be a moderate DRAK2 inhibitor
    - DRAK2: protein responsible for regulating apoptosis in white blood cells (T cells)
- Challenging due to unique, densely-functionalized 7/6/5 tricyclic core
  - Five stereogenic centers, two of which are all-carbon quaternary centers
- This work: first asymmetric total synthesis of (+)-alstonlarsine in 13 steps from readily accessible compounds

Retrosynthetic Analysis:

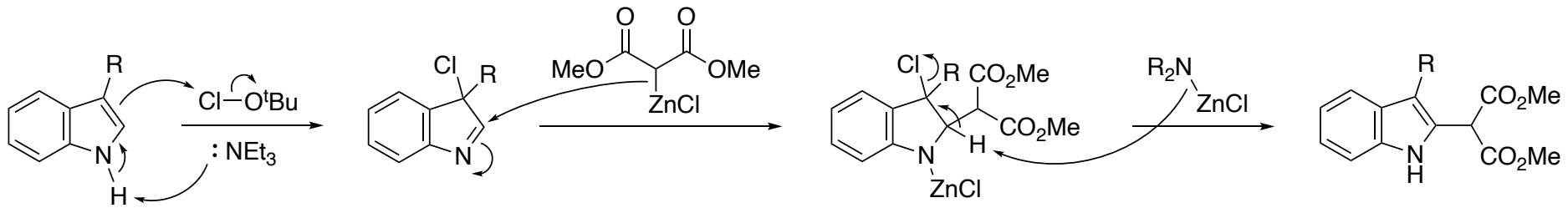


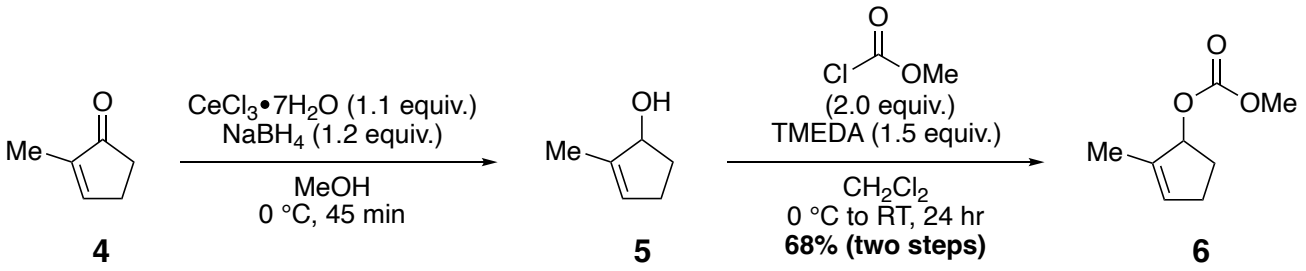


Alcohol TBS-Protection:

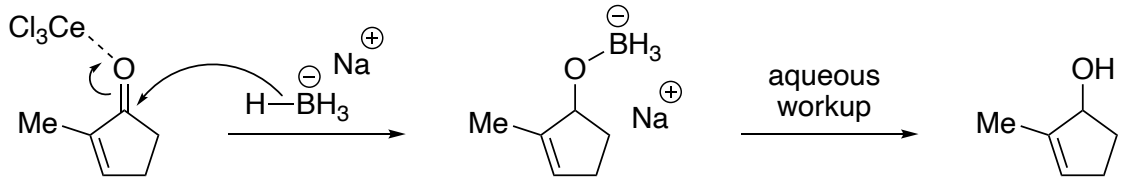


Indole
C2-Functionalization:

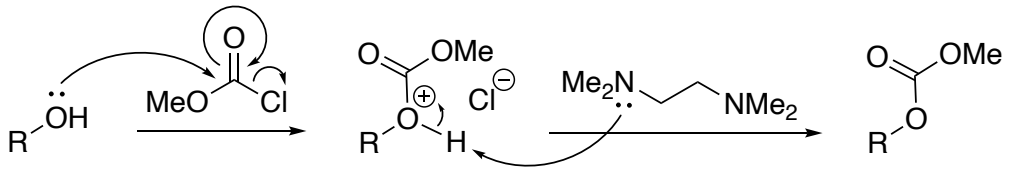


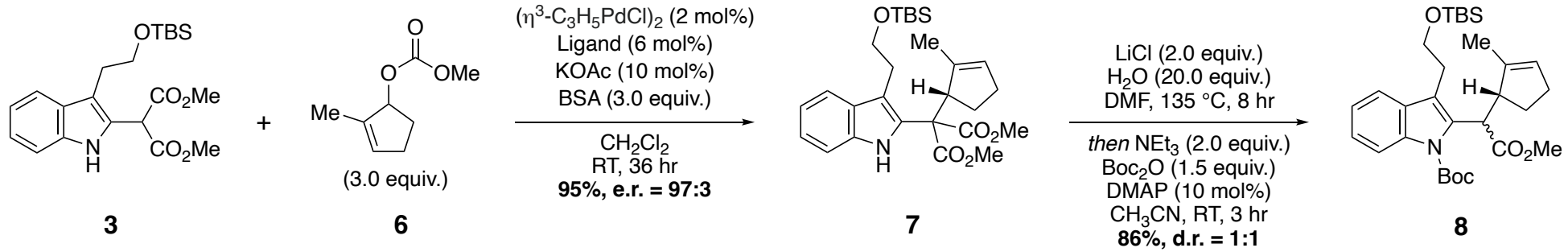


Luche Reduction:

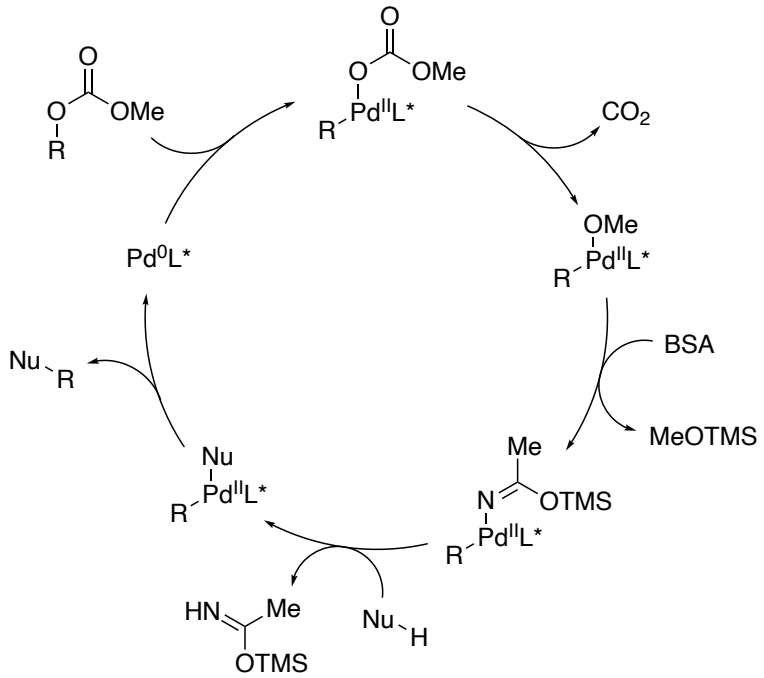


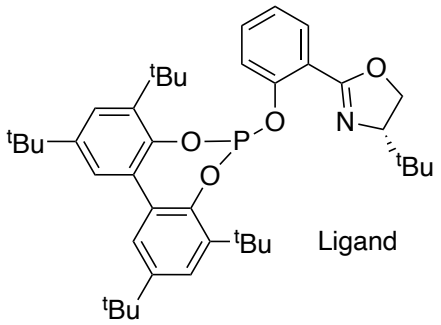
Acylation:

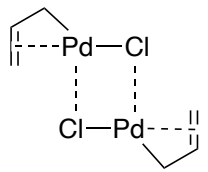


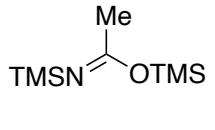


Asymmetric Allylic Alkylation:

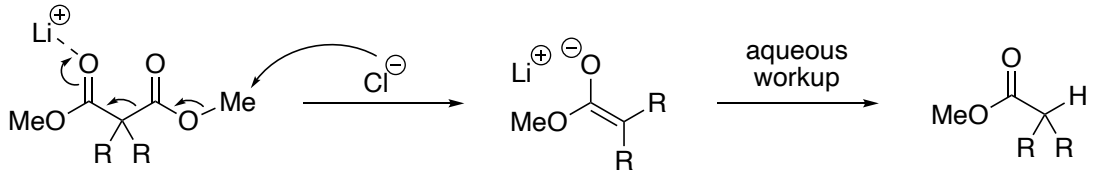




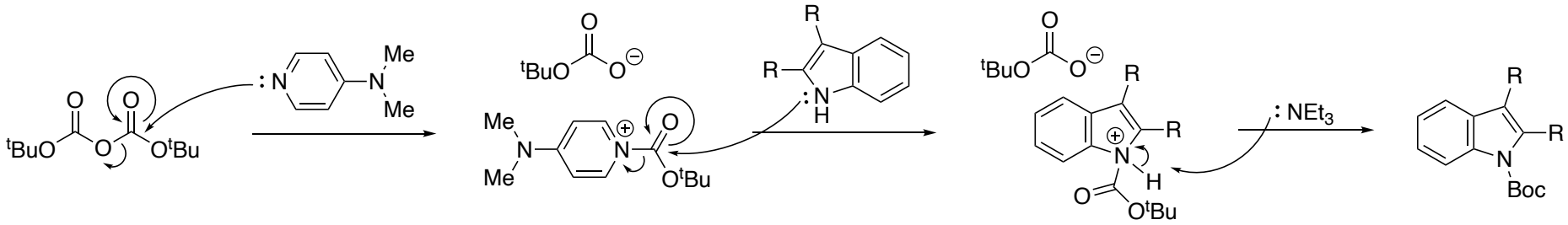


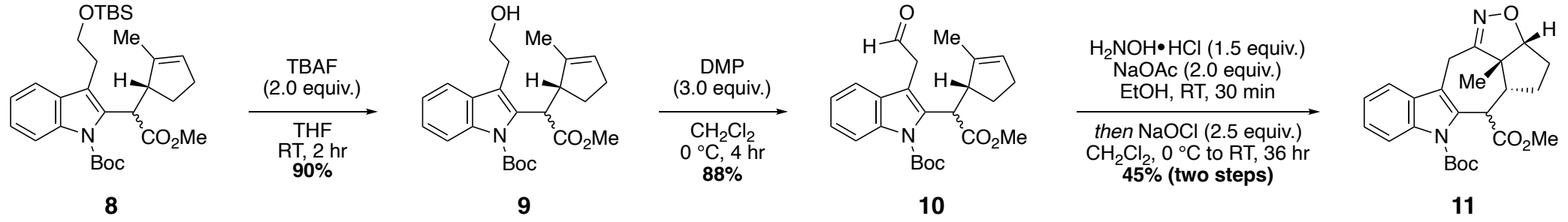


Krapcho Decarboxylation:

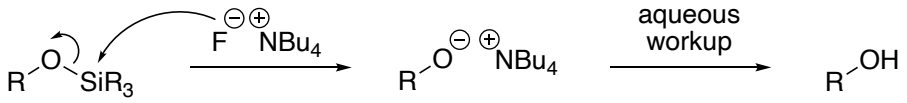


Amine Boc-Protection:

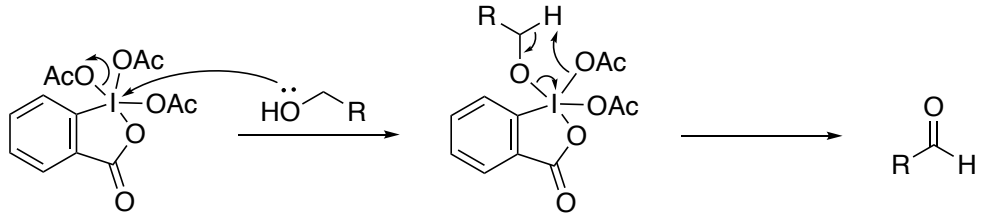




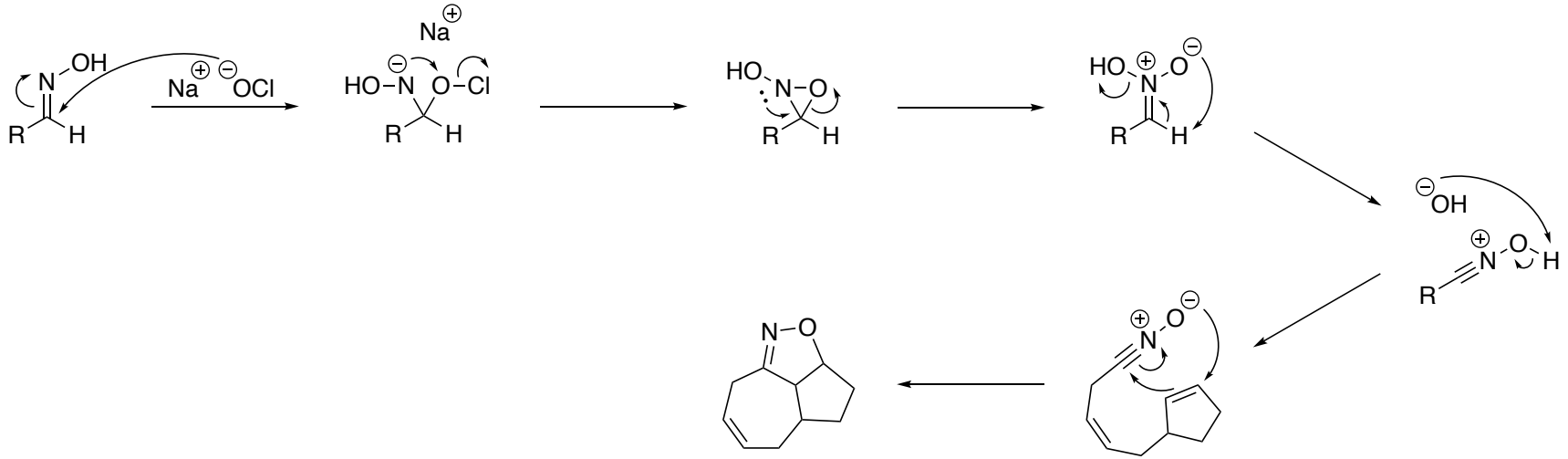
Alcohol TBS-Deprotection:

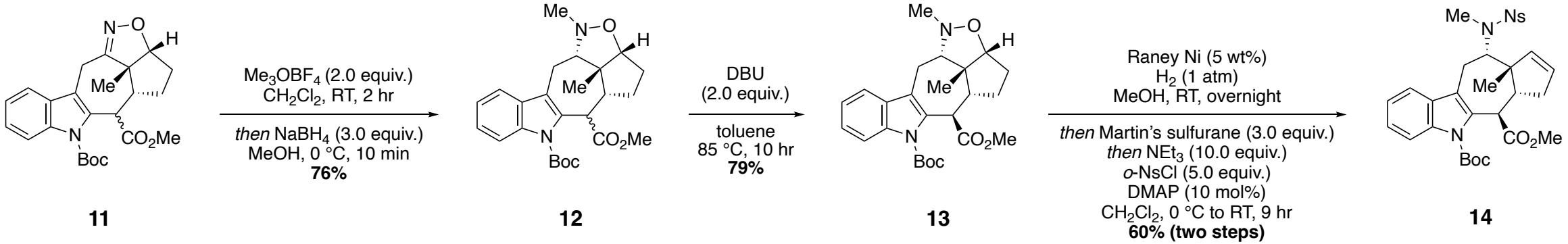


Dess-Martin Periodinane Oxidation:

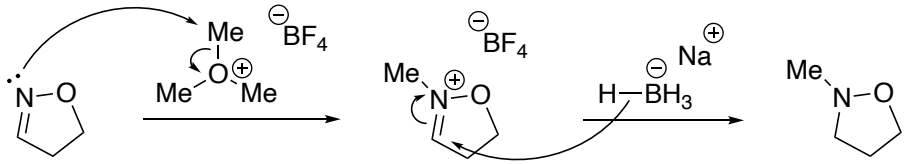


Intramolecular Nitrile Oxide Cycloaddition:

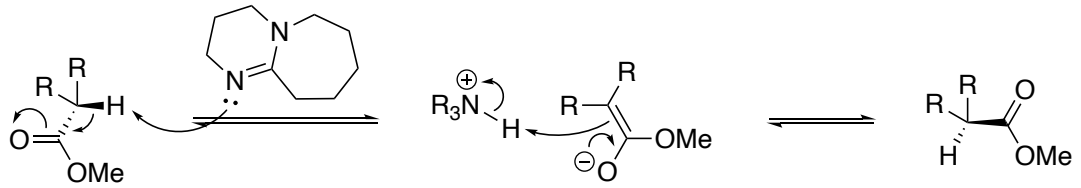




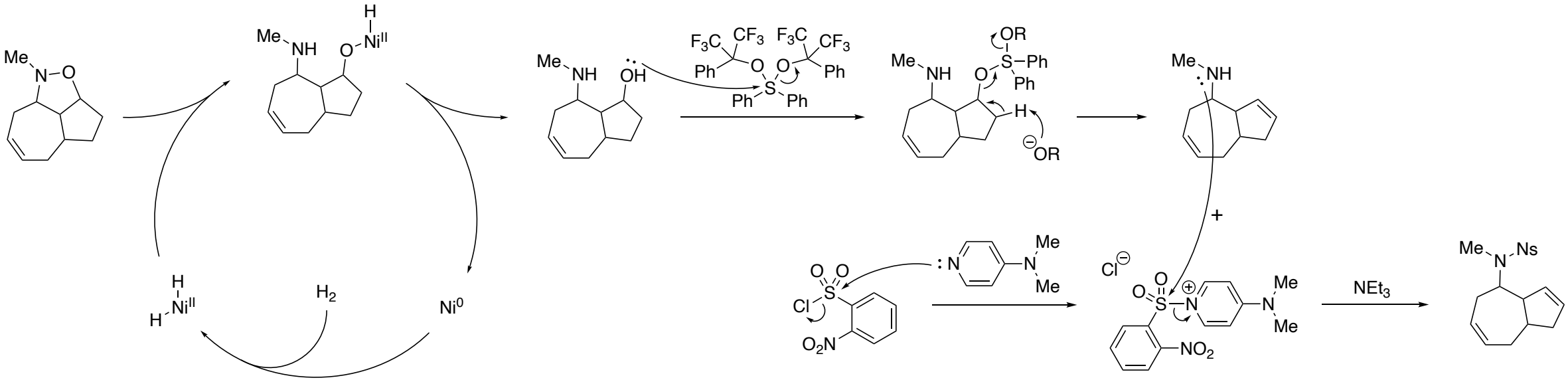
Oxime Alkylation and Reduction:

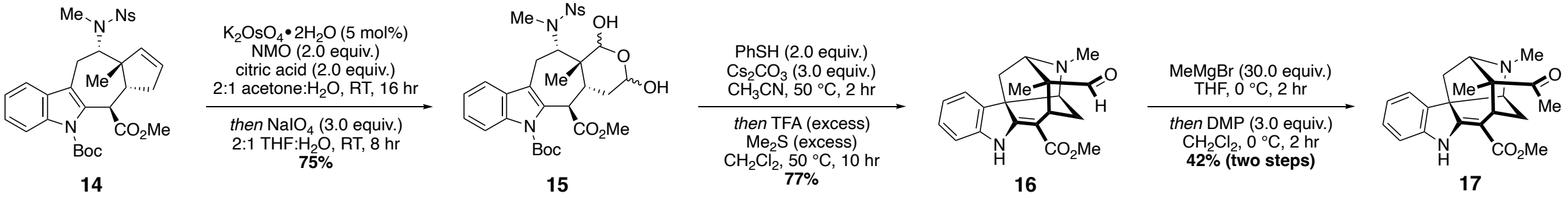


Base-Promoted Isomerization:

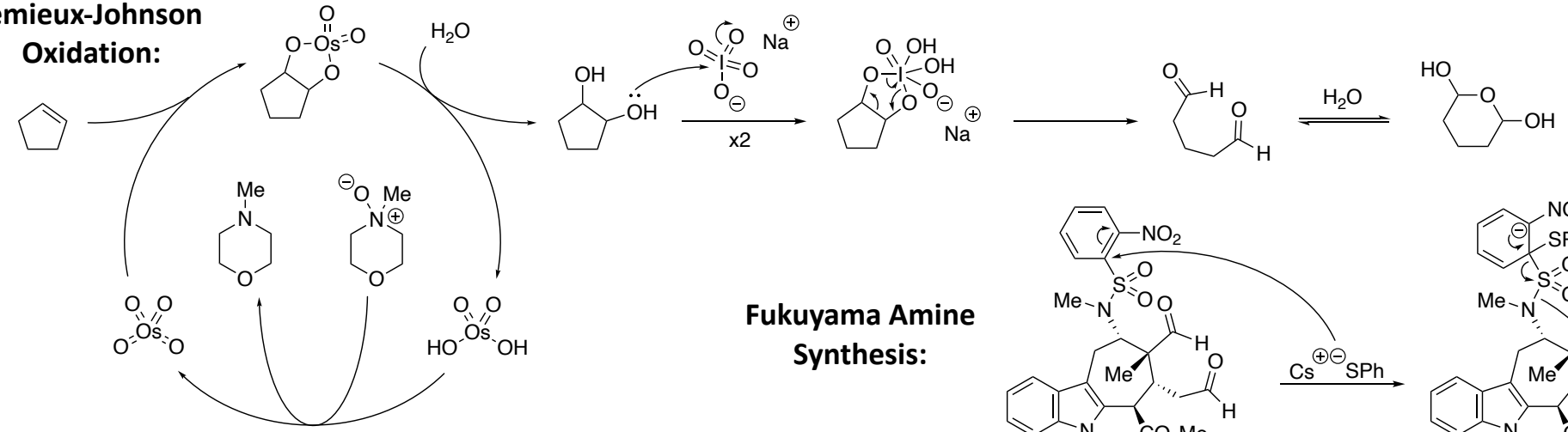


Raney Ni Hydrogenolysis/Dehydration/Amine *o*-Nosyl-Protection:

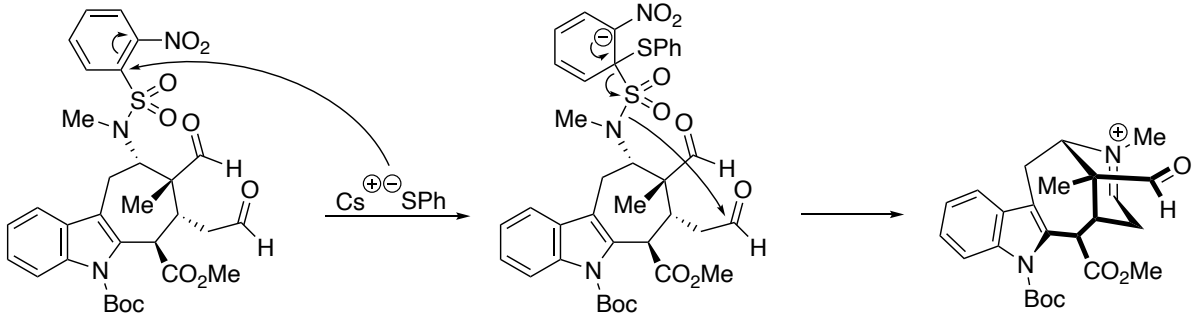




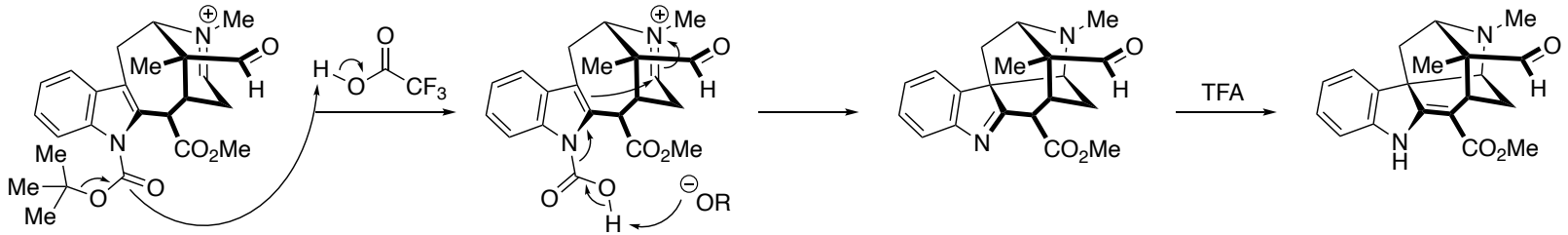
Lemieux-Johnson Oxidation:



Fukuyama Amine Synthesis:



Interrupted Pictet-Spengler Reaction:



Grignard Addition/DMP Oxidation: