Versatile Construction of 6-Substituted *cis*-2,8-Dioaxabicyclo[3.3.0]octan-3-ones: Short Enantioselective Total Synthesis of Cheloviolenes A and B and Dendrillolide

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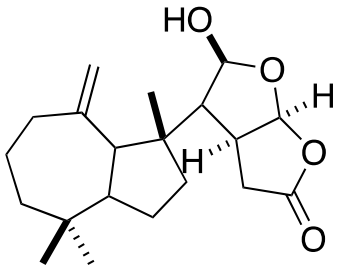
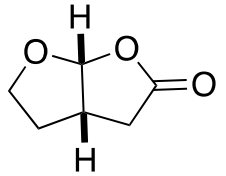
Total Synthesis Presentation
Sophia Staerz

Background:

- Class of rearranged diterpenoids
  - Large group isolated in marine sponges
- Have a *cis*-2,8-dioxabicyclo[3.3.0]octan-3-one ring system
- Structural subtypes differ in whether the hydrocarbon fragment resides on the concave or convex face
  - Cheloviolene A is on the convex face



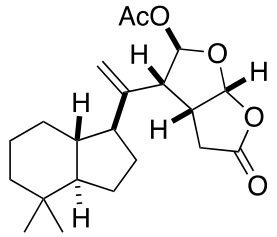
cheloviolene A



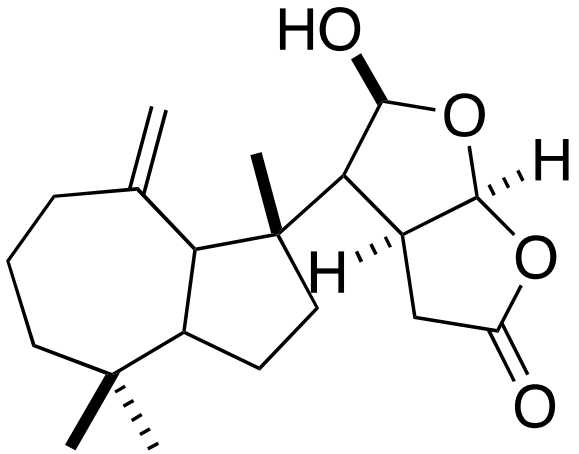
cis-3,8-dioxabicyclo[3.3.8]octan-3-one

Biological Activity

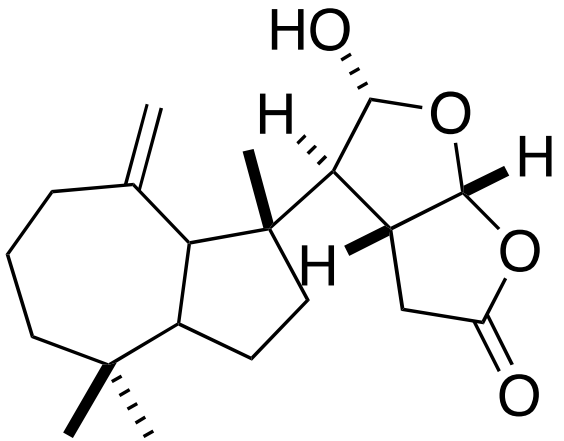
- Diterpenoids effect the structure of the Golgi apparatus
  - Most block protein transport from the Golgi apparatus to the plasma membrane
  - Norrisolide induces irreversible fragmentation and delocalization of Golgi membrane throughout the cytosol
  - Thought that diterpenoids react with primary amines, like in lysine side chains in a class of enzymes, to form pyrroles- which could account for the Golgi apparatus effects observed



norrisolide

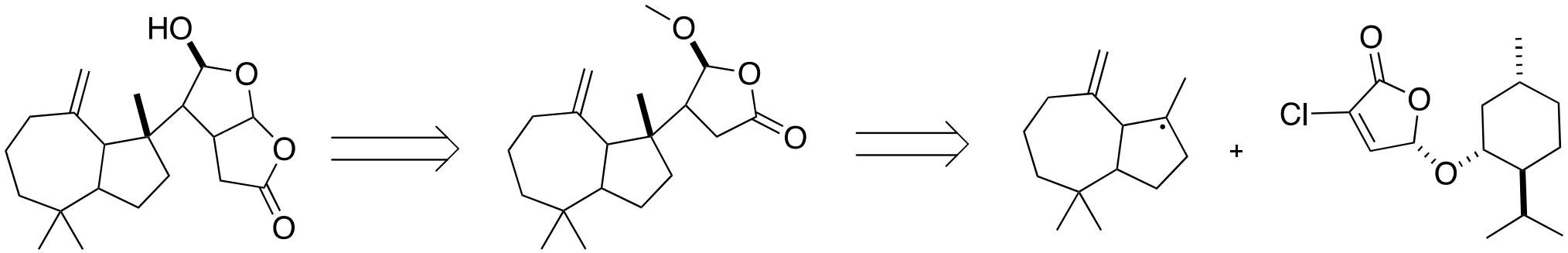


cheloviolene A

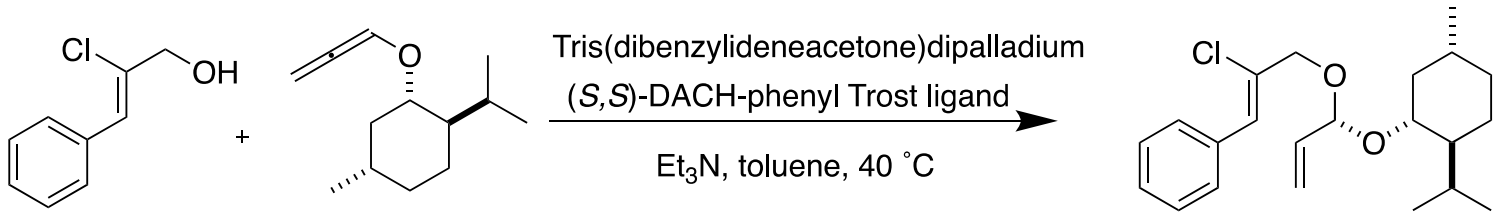


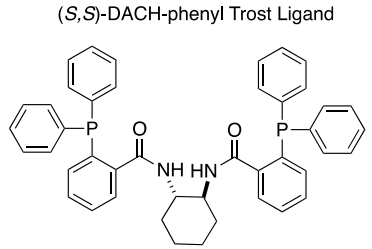
cheloviolene B

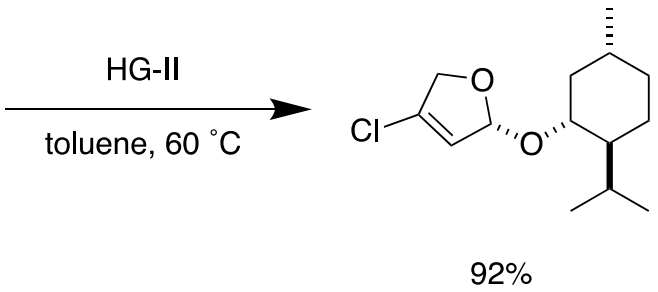
Retro-Synthesis

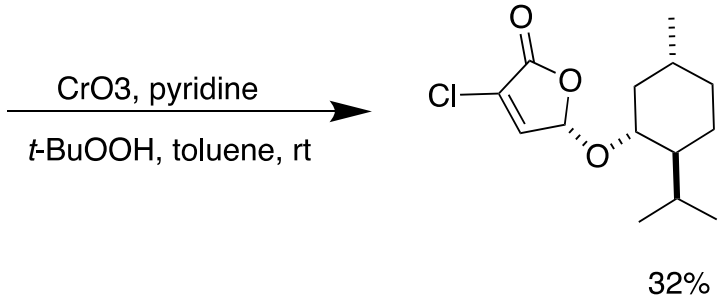


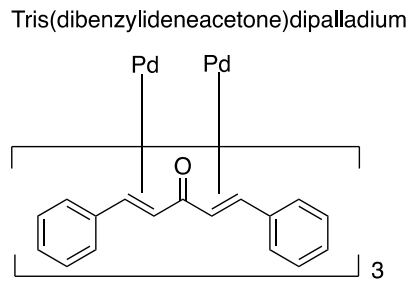
Synthesis of 3-chloro-5-alkoxybutenolide



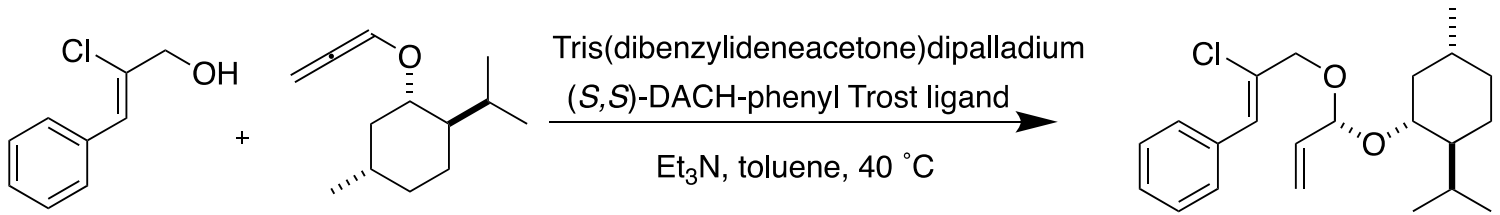


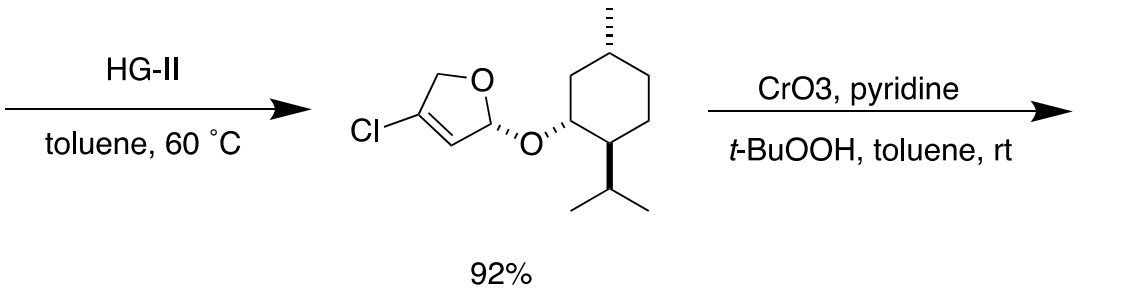




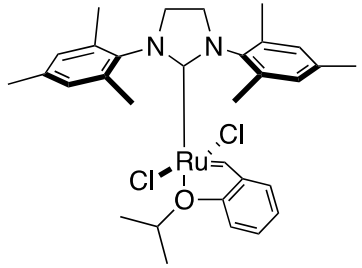


Synthesis of 3-chloro-5-alkoxybutenolide

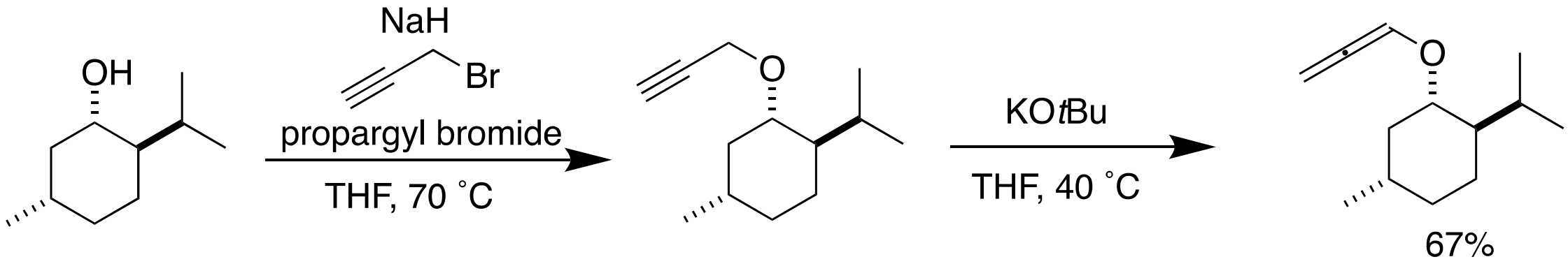




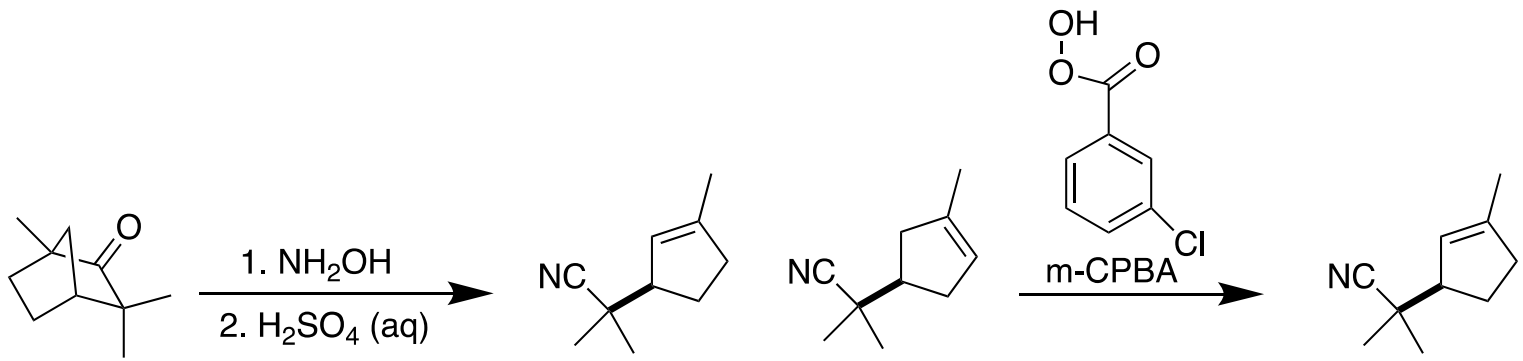
Hoveyda-Grubbs II



Starting Material Synthesis: Allene



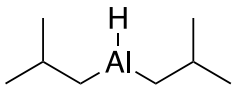
Synthesis of *cis*-perhydroazulene tertiary radical



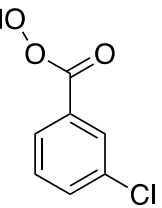
(+)-fenchone

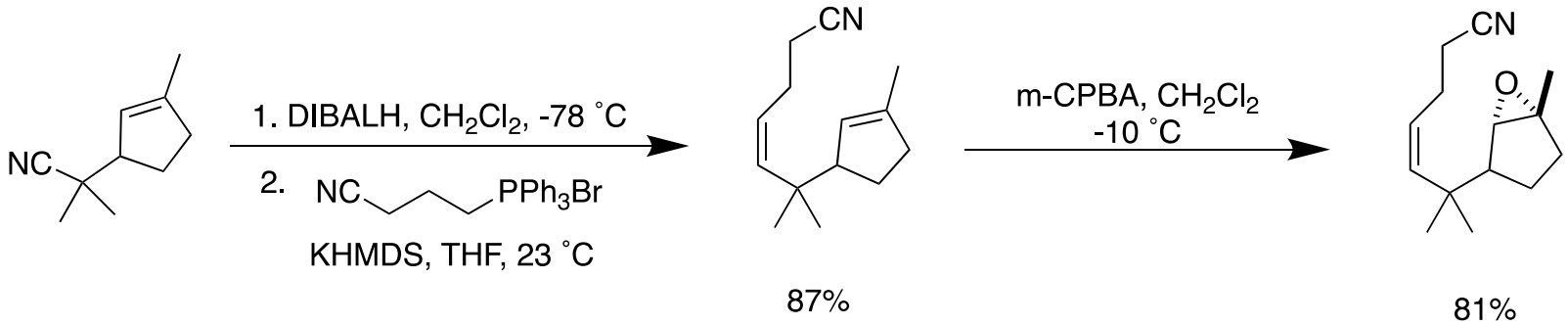
33%

Diisobutyl Aluminum Hydride



meta-Chloroperoxybenzoic Acid

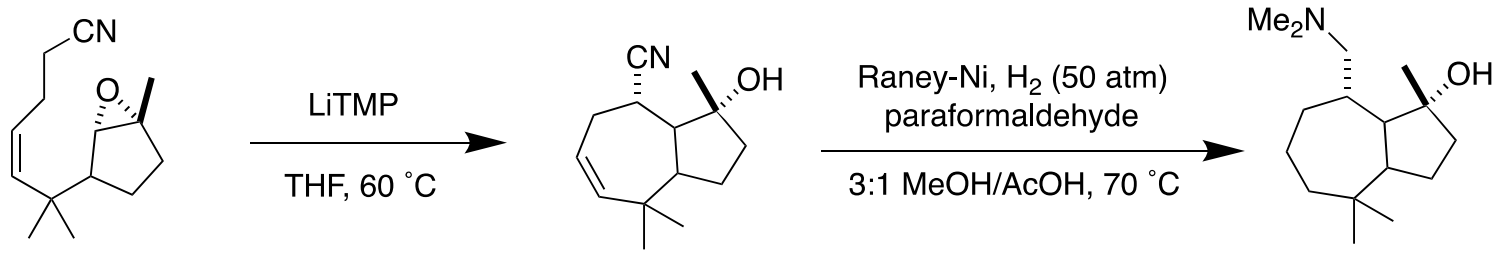




87%

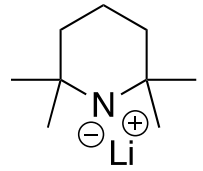
81%

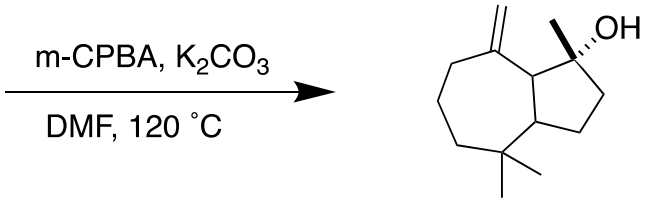
Synthesis of *cis*-perhydroazulene tertiary radical



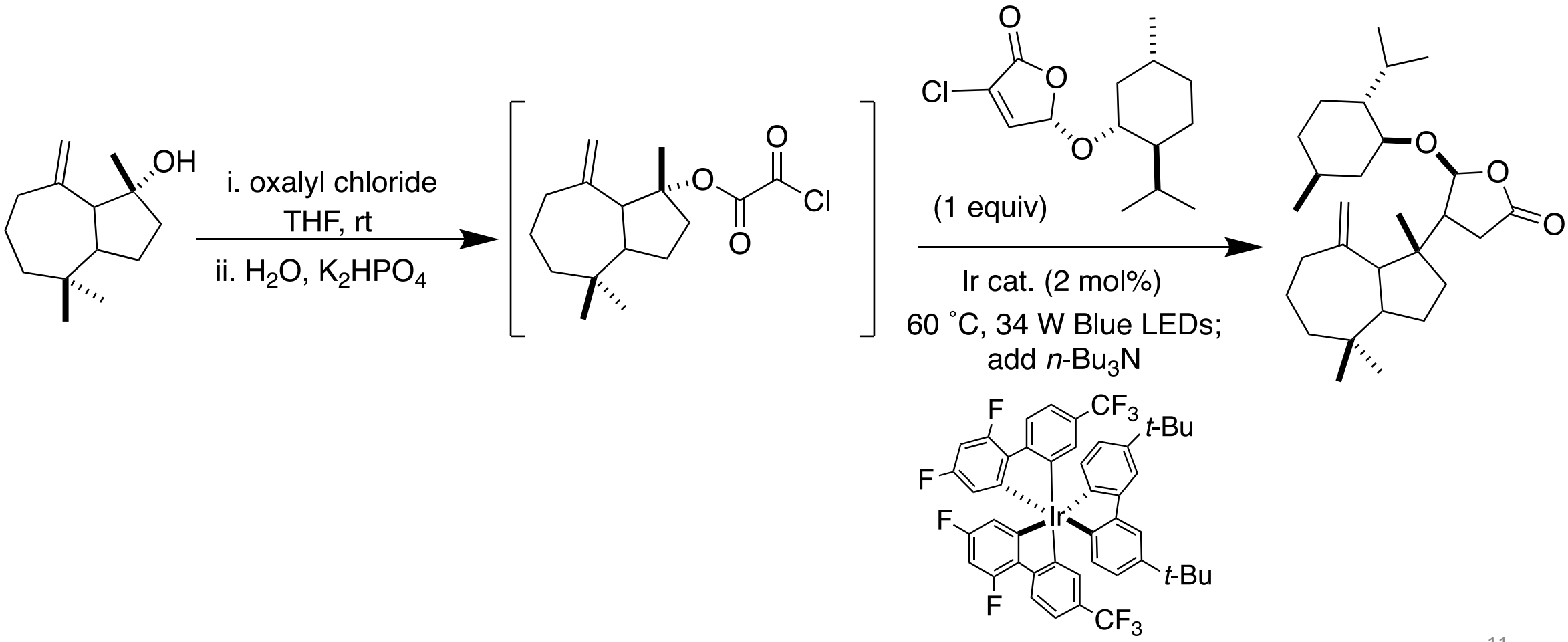
85%

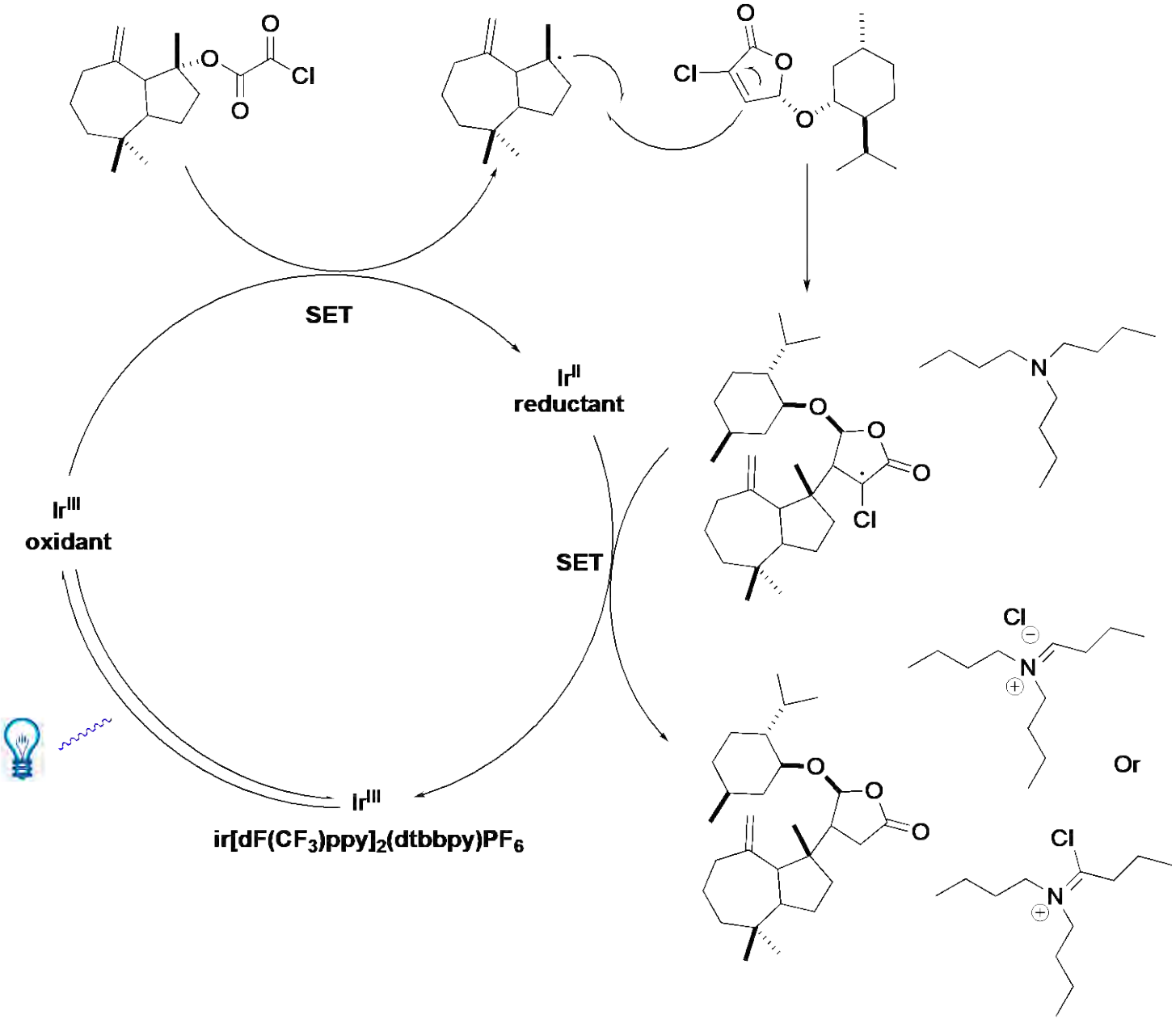
Lithium tetramethylpiperidide





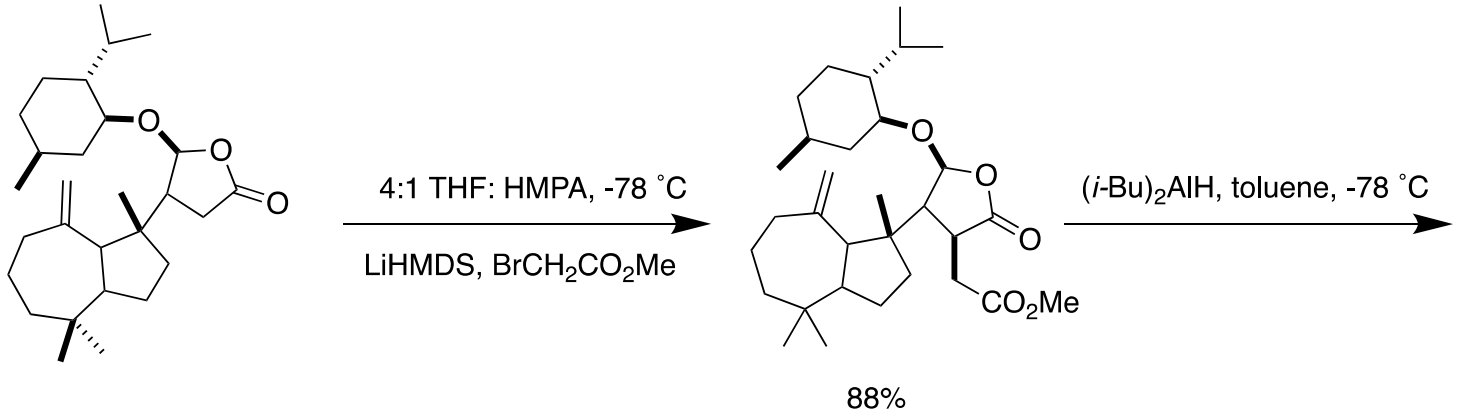
Radical Coupling

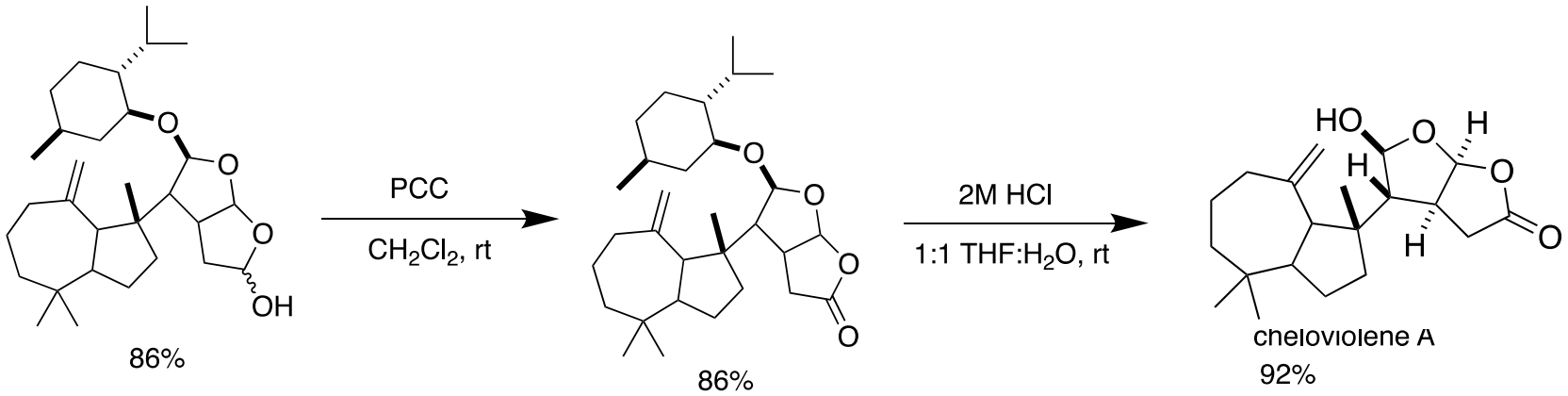




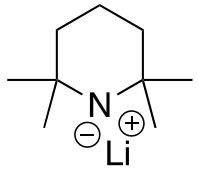
Single Electron transfer= SET

Final Steps to (+)-Cheloviolene A

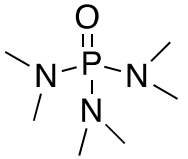




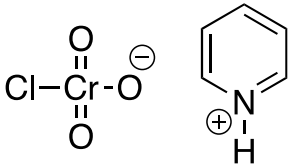
Lithium tetramethylpiperidide



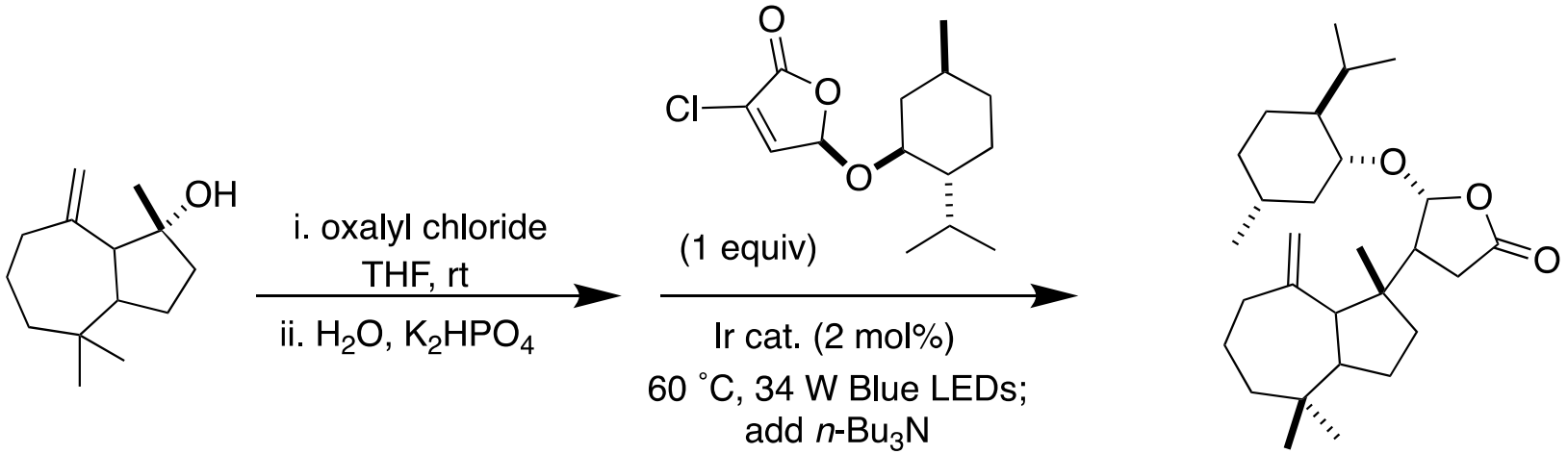
Hexametylphosphoramide

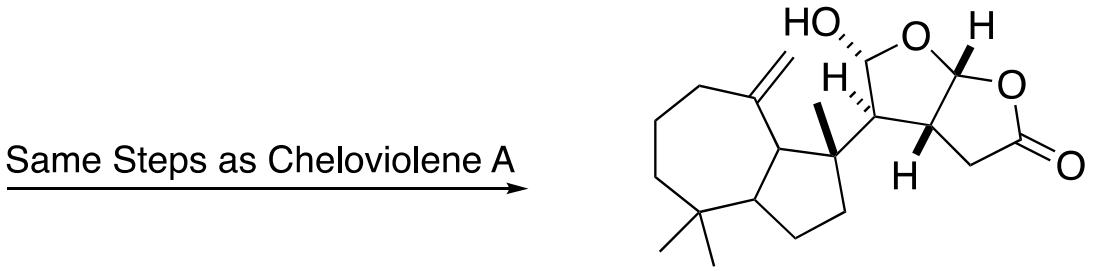


Pyridinium Chlorochromate



Synthesis of Cheloviolene B



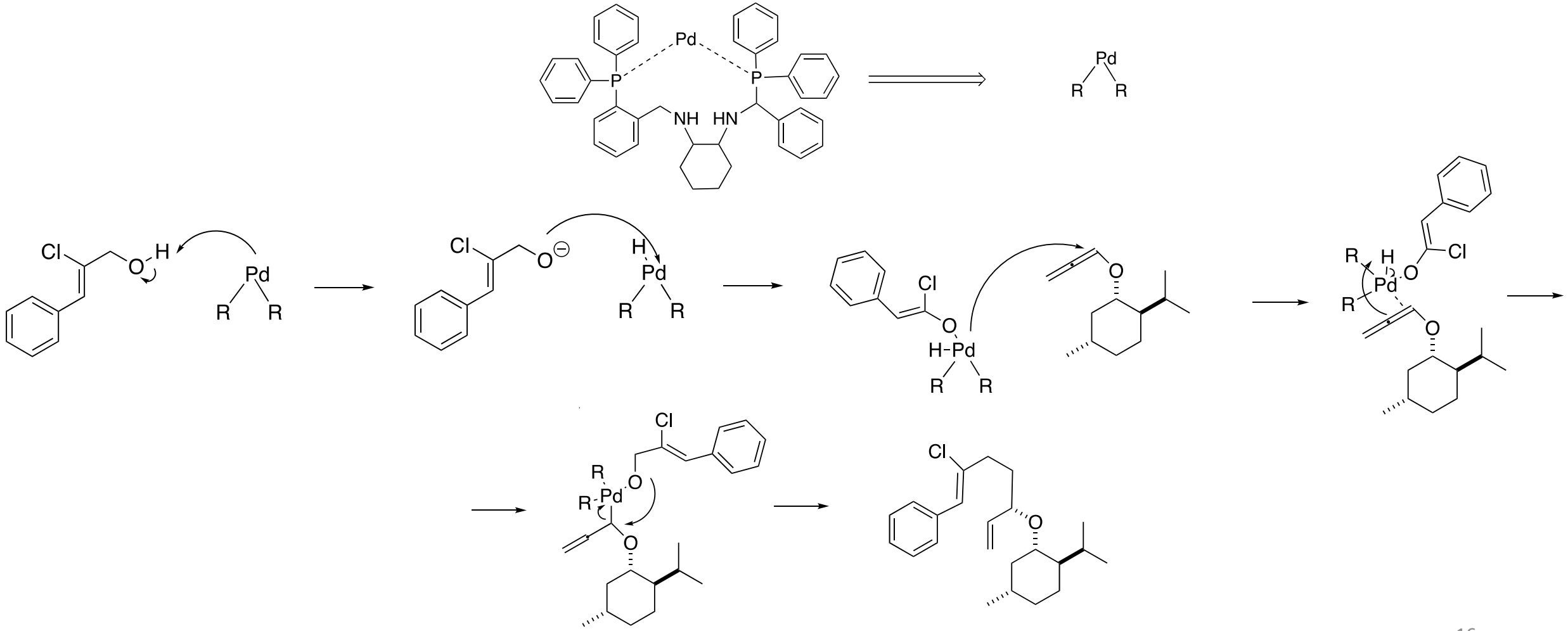


62%

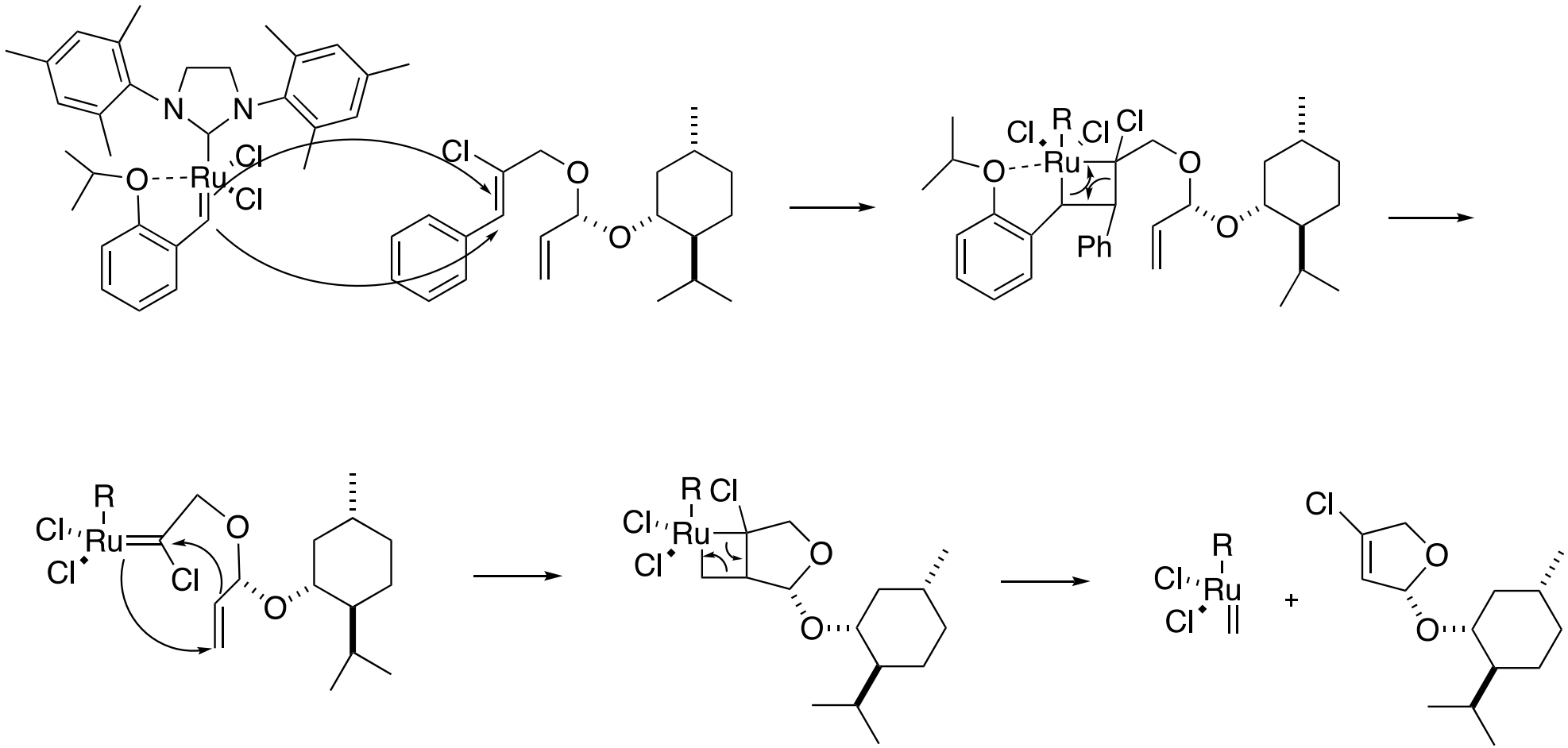
Thank you!

Mechanism:

Palladium goes through a ligand exchange:



Mechanism: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