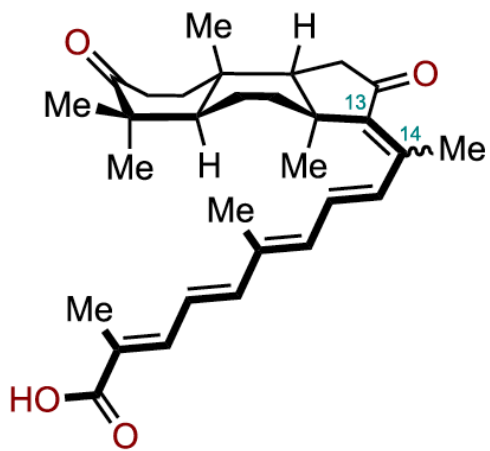


Total Synthesis of Isomalabaricane Triterpenoids

Yaroslav D. Boyko,[‡] Christopher J. Huck,[‡] and David Sarlah^{*†}



$\Delta^{13(14)} = E$, **rhabdastrellic acid A (1)**

$IC_{50} = 1.46 \mu M$ (HL-60)

$\Delta^{13(14)} = Z$, **stellatin E (2)**

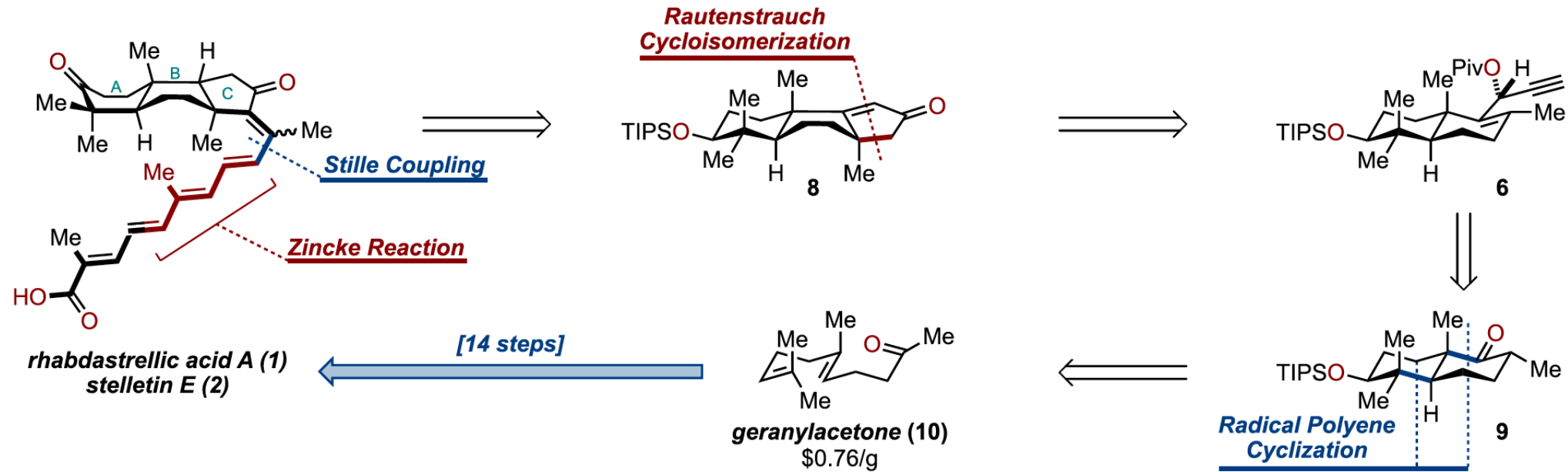
$IC_{50} = 3.9 nM$ (HCT-116)

Rhabdastrellic acid A (1) and stelletin E (2) are among the flagship members of the isomalabaricane triterpenoids, a rare family of marine natural products that continue to attract attention for their remarkably specific antitumor properties.

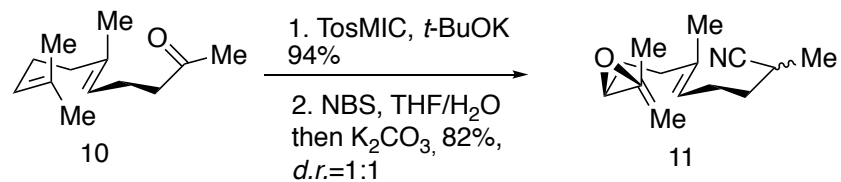
Nonetheless, and despite several impressive efforts, the isomalabaricanes have yet to succumb to total synthesis in the 38 years since their first isolation.

This is perhaps due to the complexity of their trans-syn-trans perhydrobenzindene core, whose imposing strain and unorthodox boat–boat conformation stymies many of the traditional synthetic techniques for constructing polycyclic terpene systems.

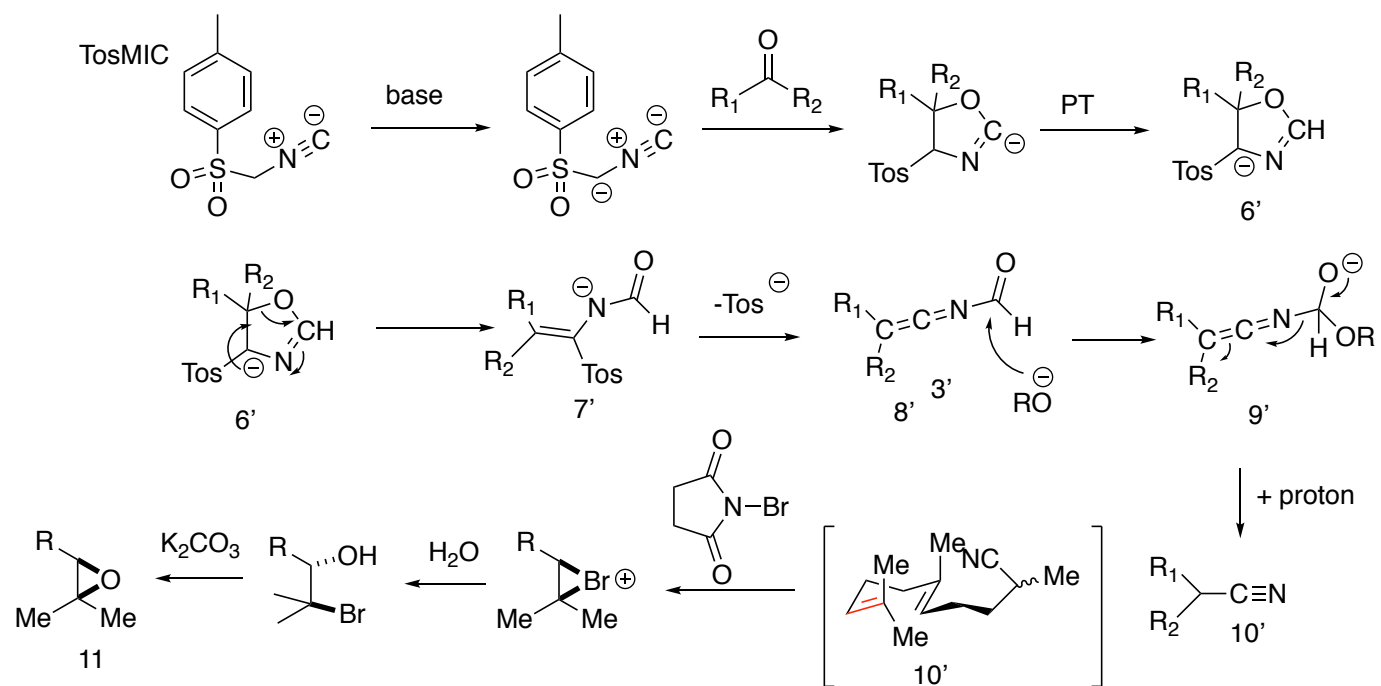
Retrosynthetic Analysis



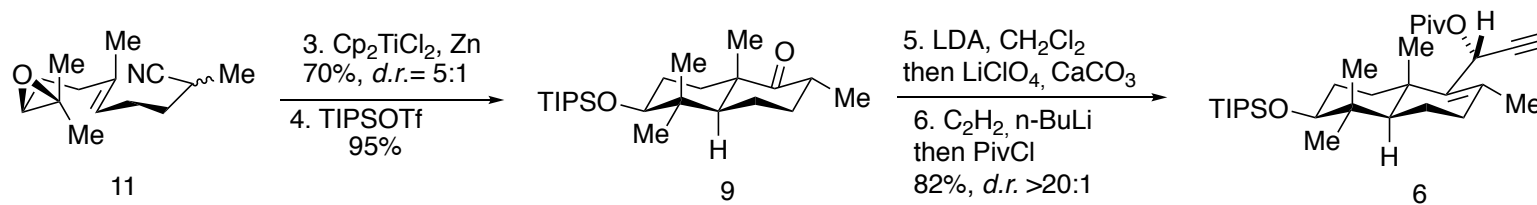
Forward Synthesis: Constructing enyne 6



Van Leusen Reductive Cyanation of Ketone followed by Epoxidation

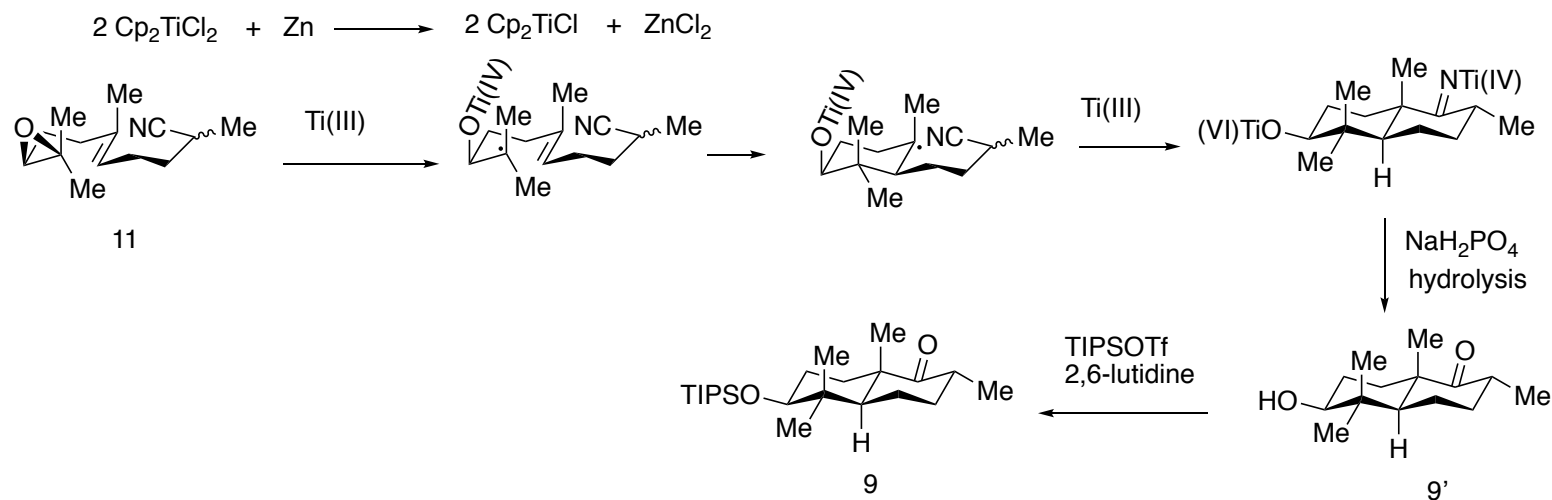


Forward Synthesis: Constructing enyne 6

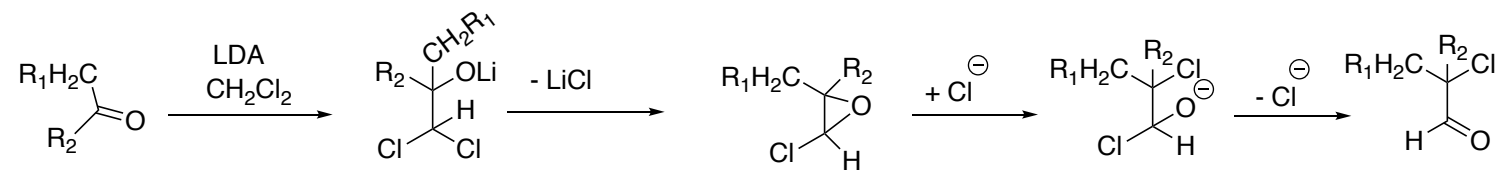


Forward Synthesis: Constructing enyne 6

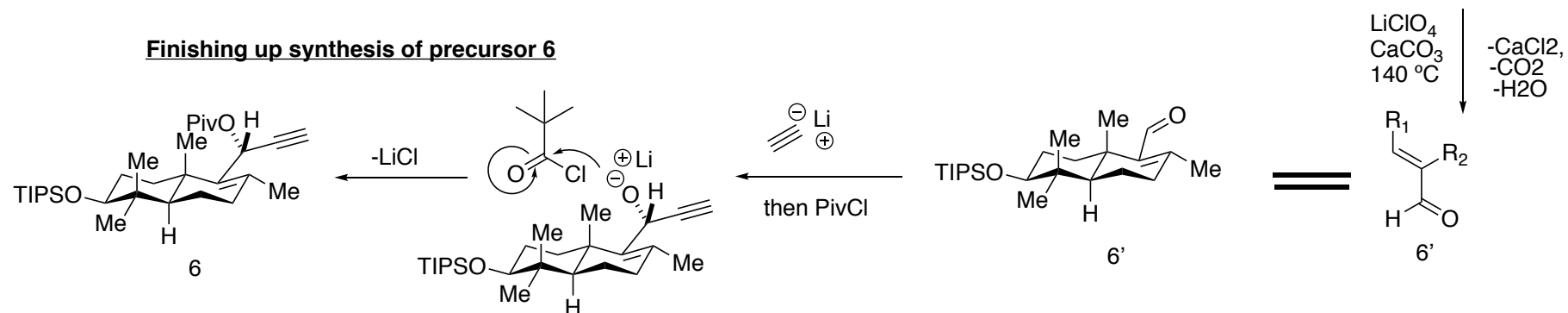
Ti-Mediated Reductive Radical Polyene Cyclization



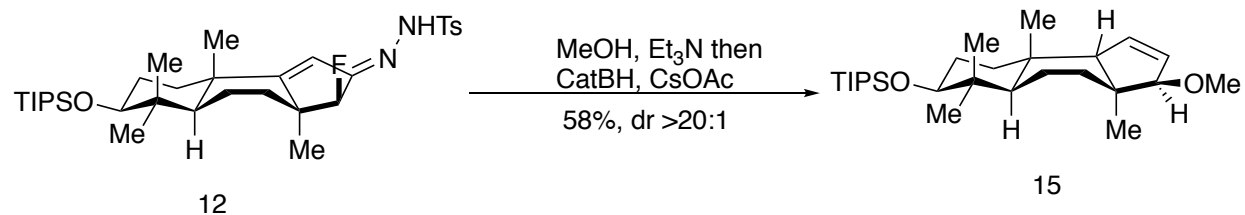
Homologation of Ketone to α,β -unsaturated aldehyde



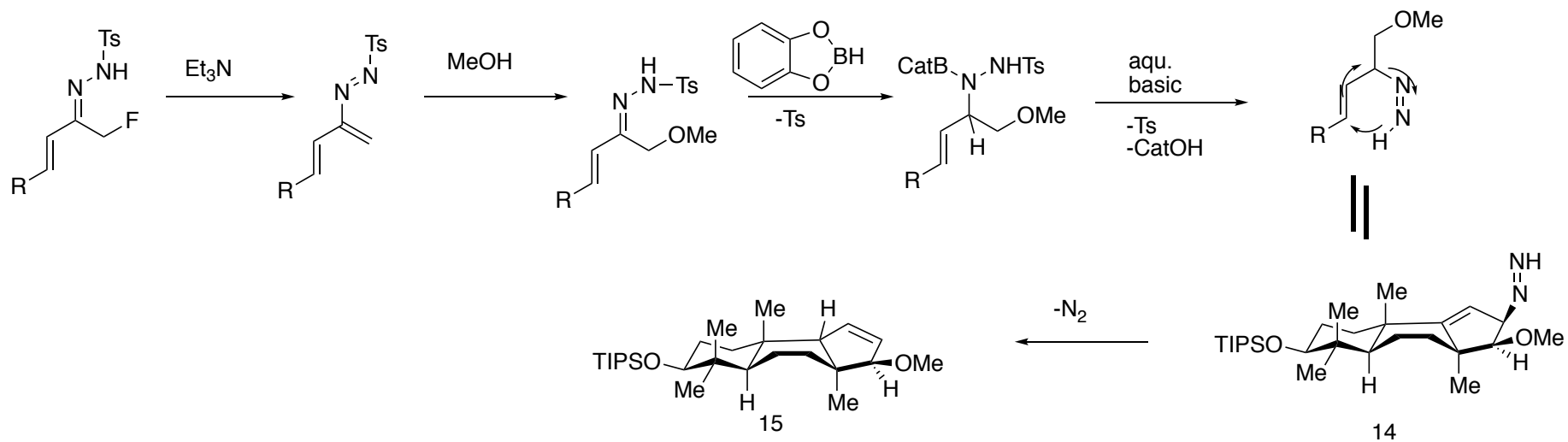
Finishing up synthesis of precursor 6

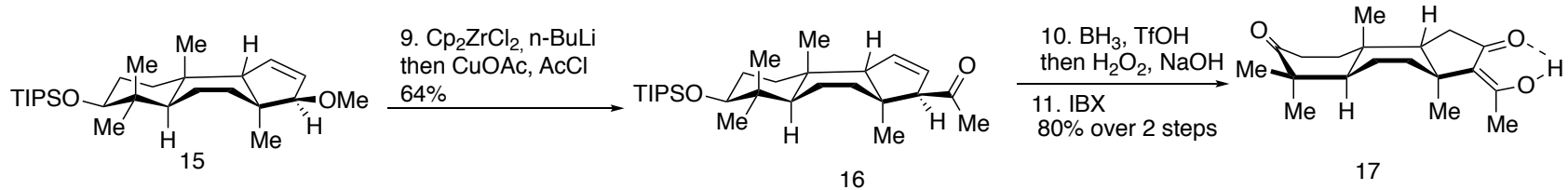


Forward Synthesis: Constructing key trans-syn-trans intermediate 15

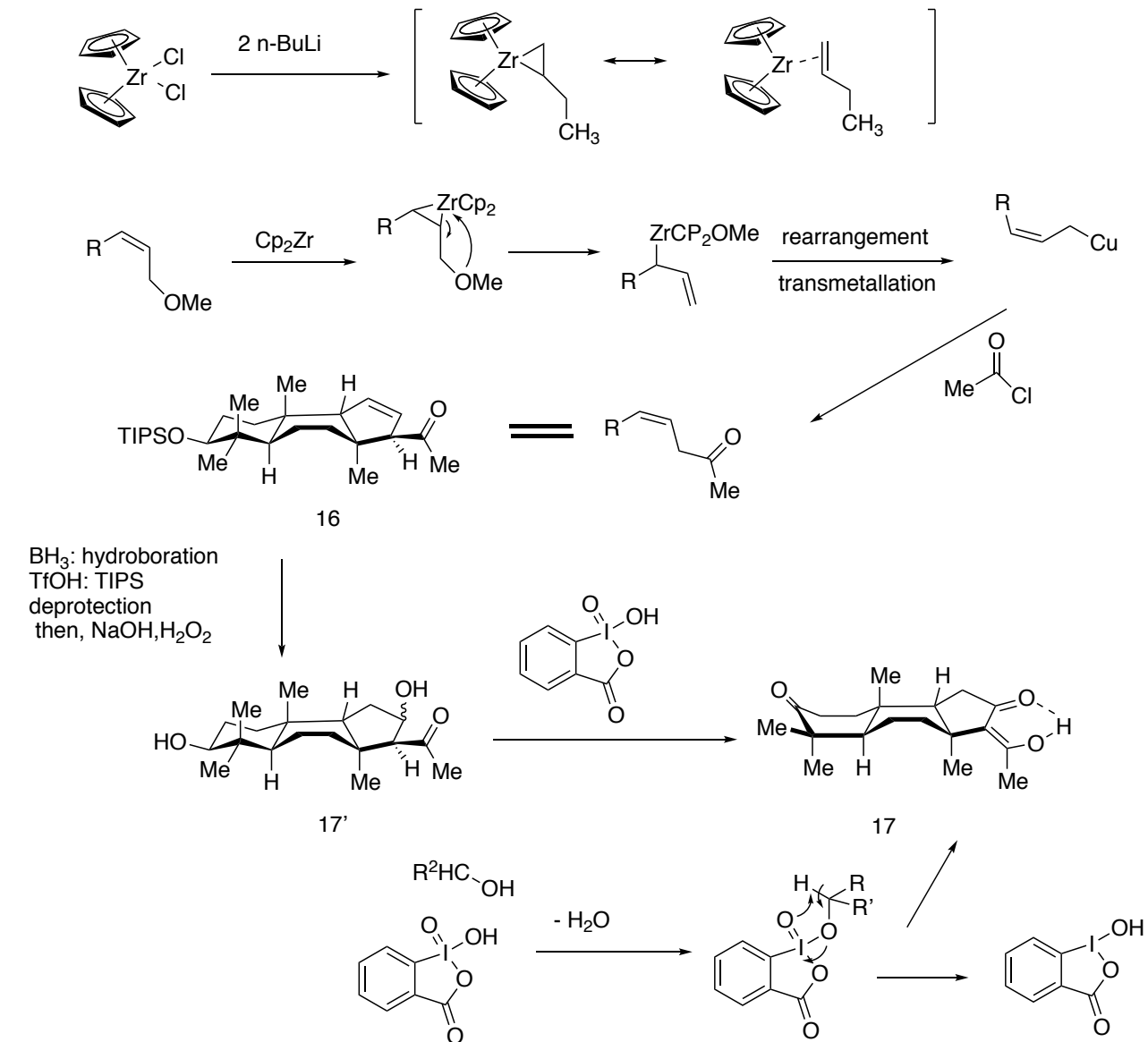


Azoalkene formation then retro-ene rearrangement of allylic diazene

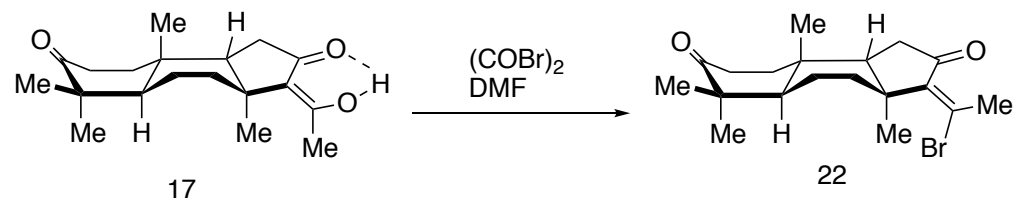




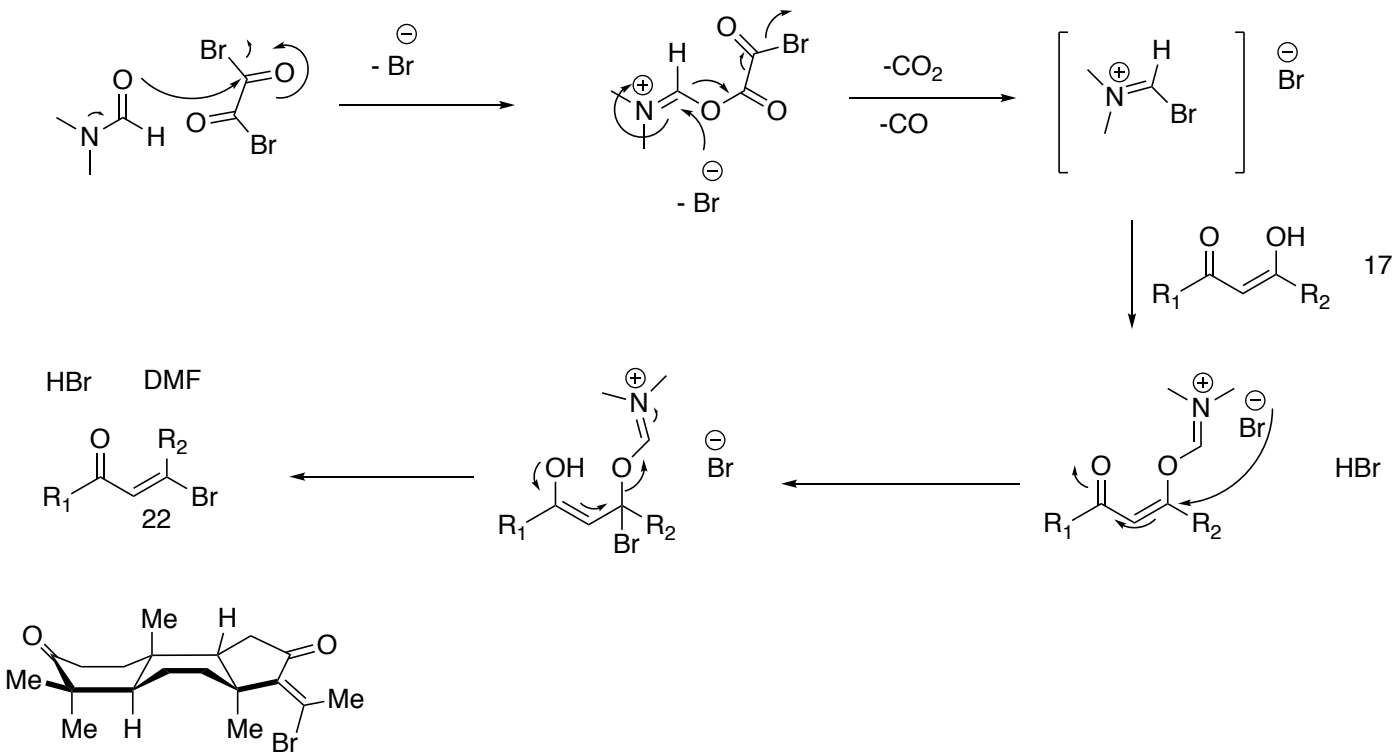
Reductive Zirconation and Copper Cat. Cross-Coupling



Forward Synthesis: Accessing vinyl bromide 22 for late-stage coupling

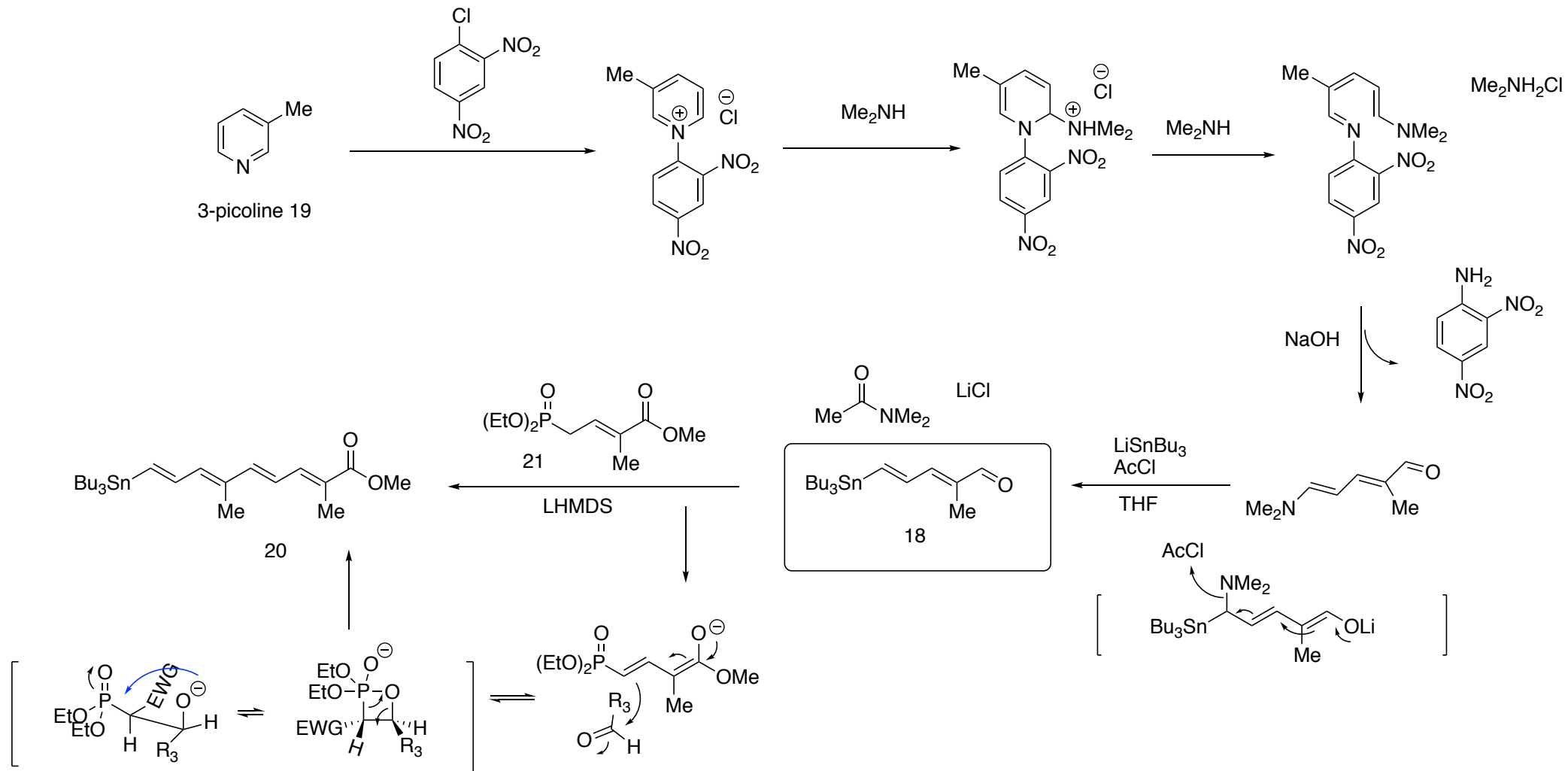


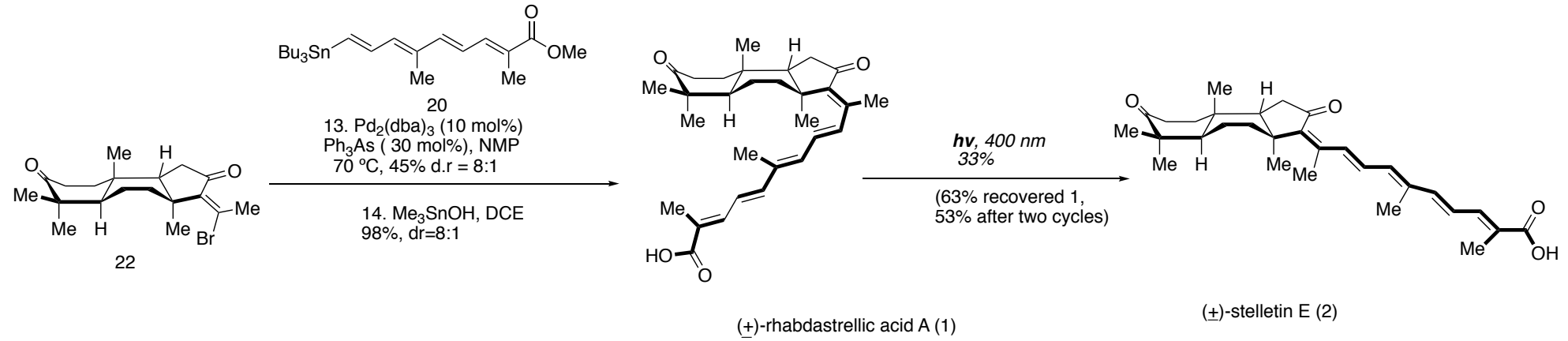
Bromination using Vilsmeier Reagent



Forward Synthesis: Building up coupling partners 20

Zincke Reaction followed by Horner-Wadsworth-Emmons





Stille Coupling, Saponification, Photoisomerization

