

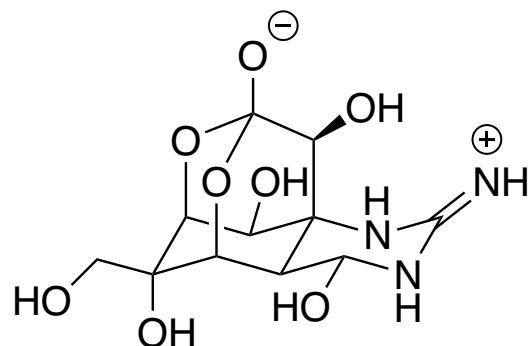
# A concise synthesis of tetrodotoxin

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Science

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Liu/Chatterjee Research Groups  
November 15<sup>th</sup>, 2023



tetrodotoxin



*Aeromonas*



pufferfish



blue-ringed octopus

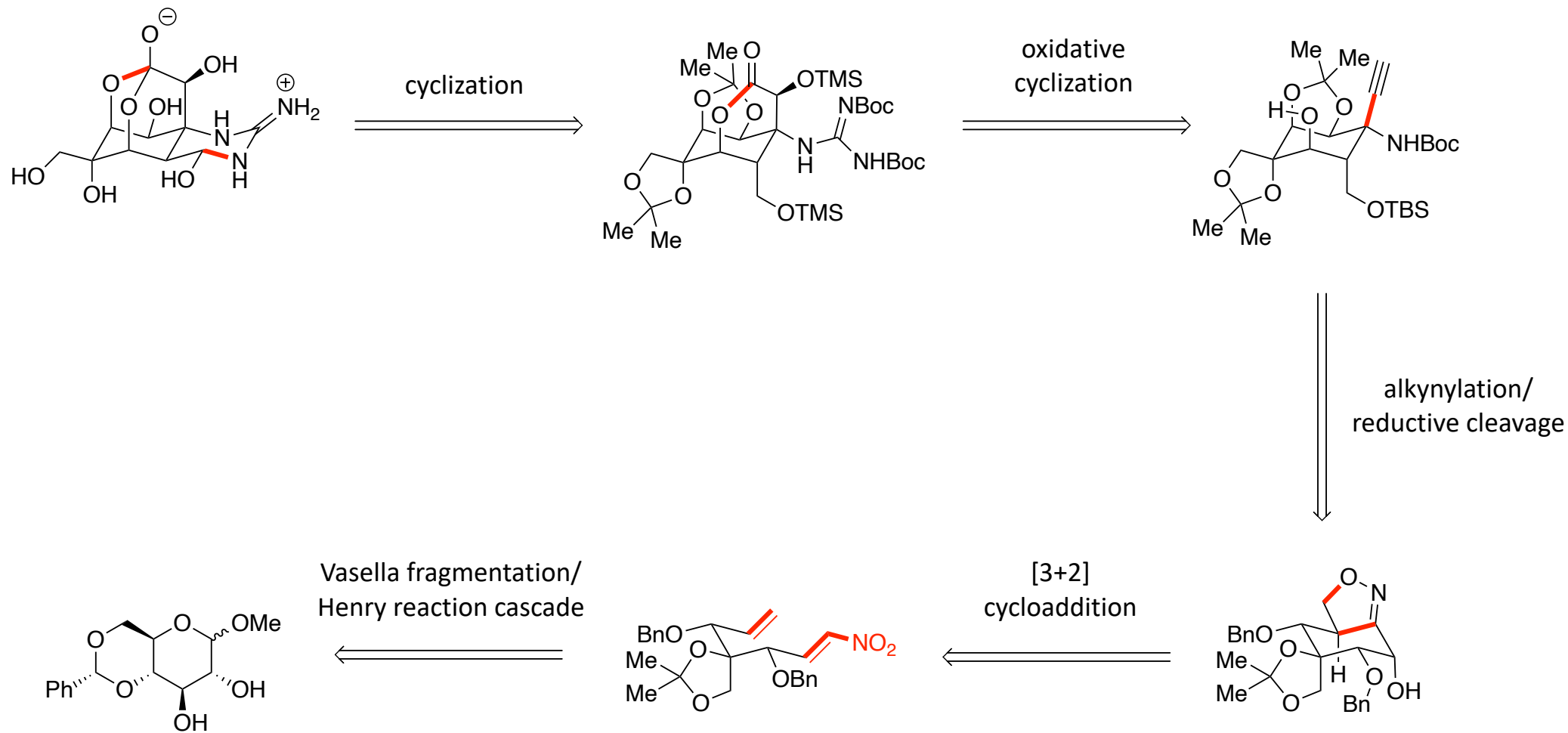
## Background

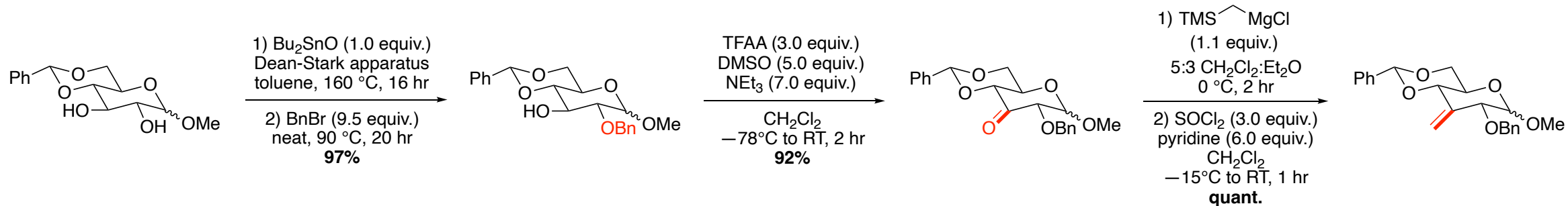
- Potent neurotoxin (25X lower LD<sub>50</sub> than KCN) that blocks voltage-gated sodium channels
- Produced by *Actinomyces*, *Aeromonas*, *Alteromonas*, *Bacillus*, *Pseudomonas*, and *Vibrio* genera of bacteria
- Accumulates in many metazoan animals as a defense mechanism against predation

## Synthetic Challenges

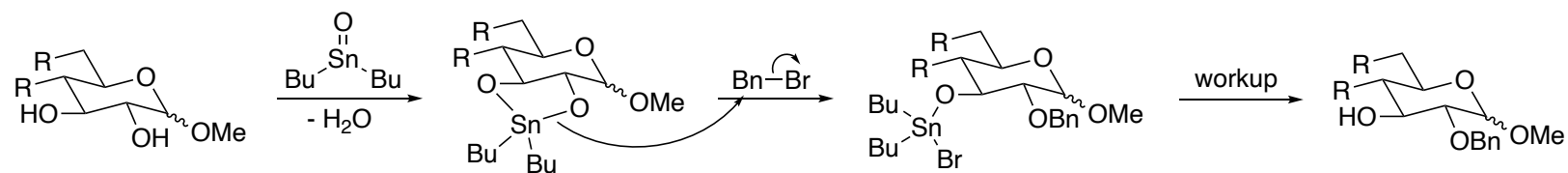
- Challenging due to high density of polar functional groups, despite relatively simple carbon framework
  - Hemi-*ortho*-ester, hemiaminal, cyclic guanidinium, multiple alcohols, four rings, and 9 contiguous stereocenters
- First racemic total synthesis by Kishi and Fukuyama in 1972
- First asymmetric total synthesis by Isobe in 2003; multiple synthetic routes have been published since
- This synthesis is the shortest (22 steps) and most efficient (~11% overall yield) reported to date

# Retrosynthesis:

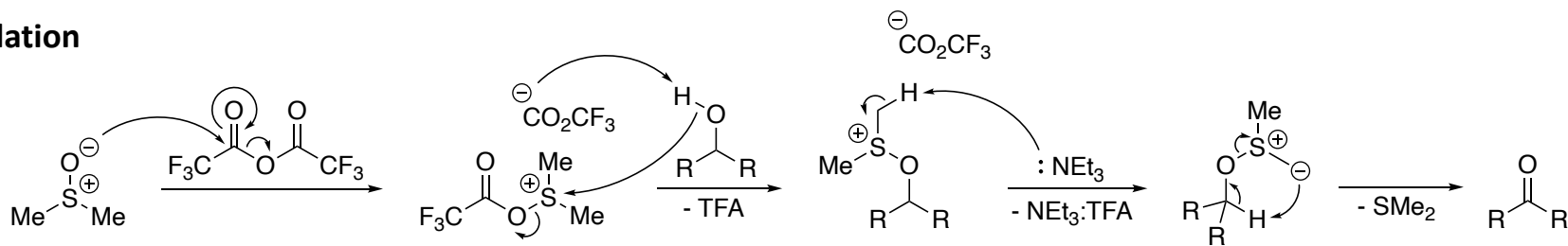




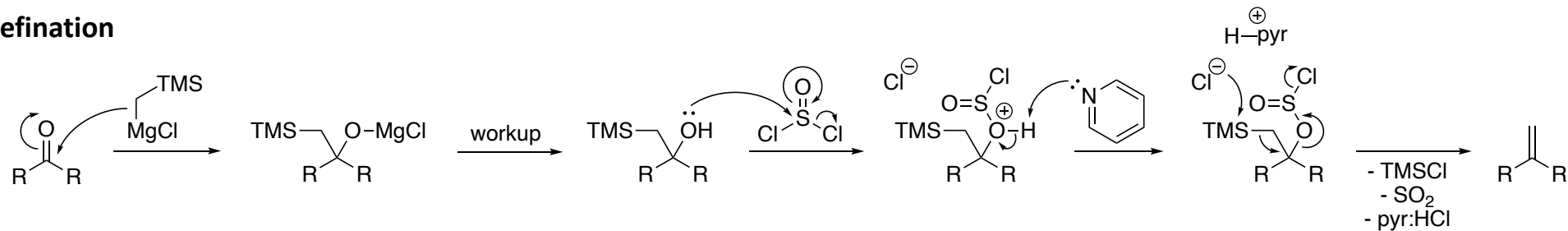
### Regioselective Benzylation

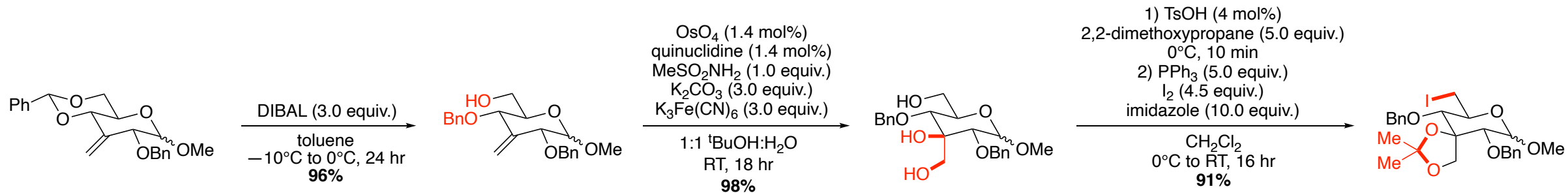


### Swern Oxidation

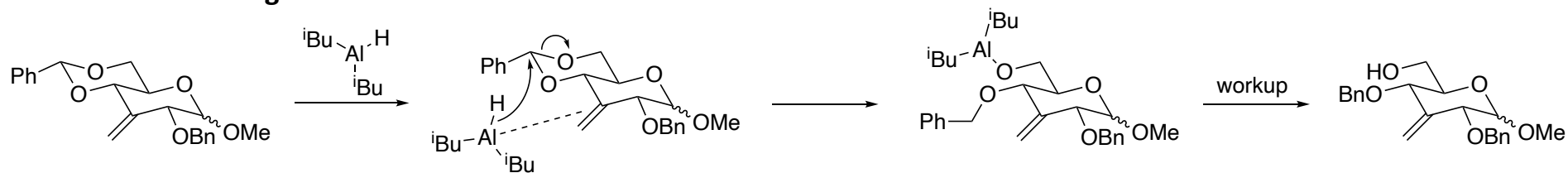


### Peterson Olefination

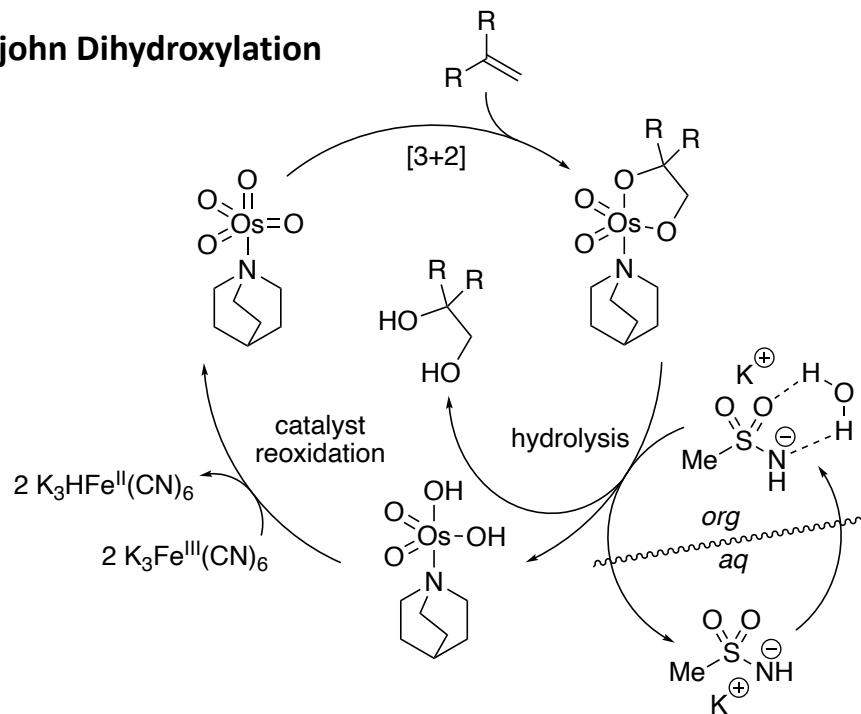




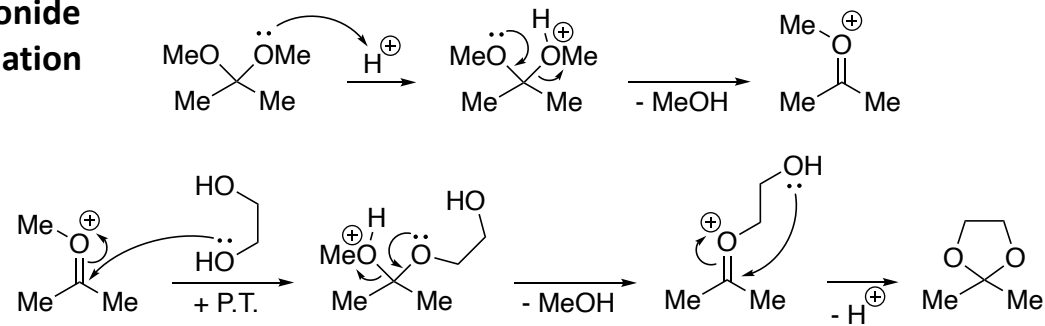
### Regioselective Reductive Cleavage



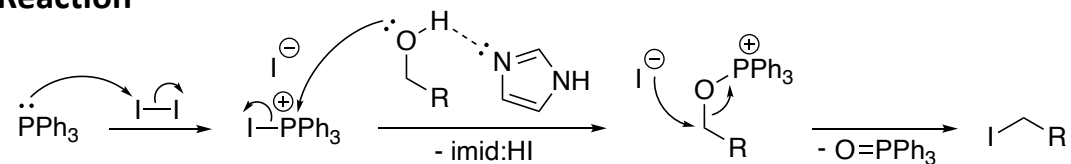
### Upjohn Dihydroxylation

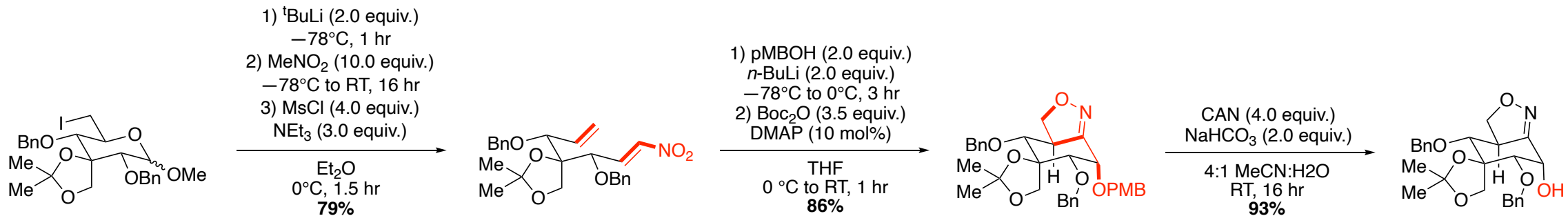


### Acetonide Formation

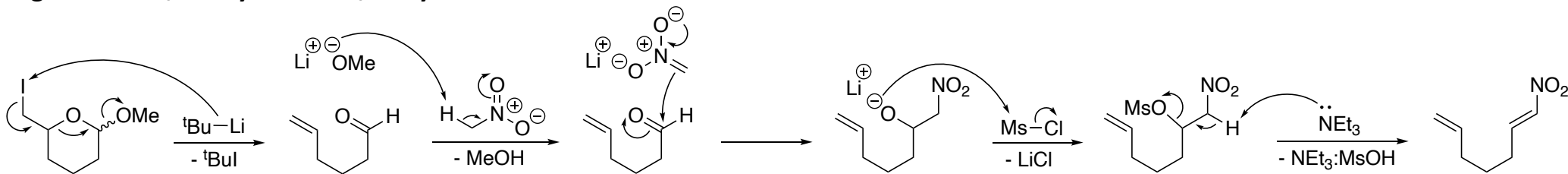


### Appel Reaction

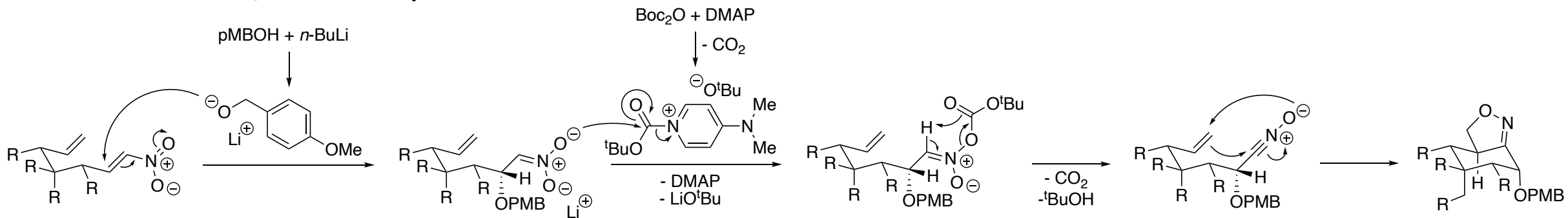




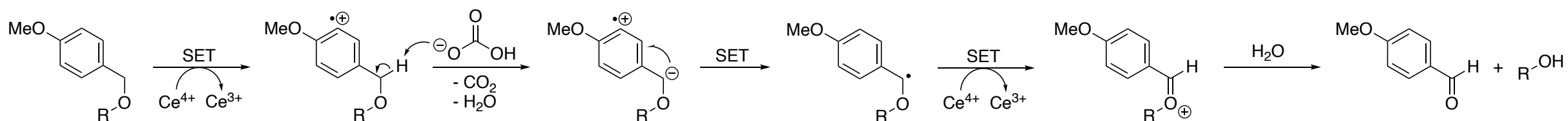
### Vasella Fragmentation/Henry Reaction/Dehydration Cascade

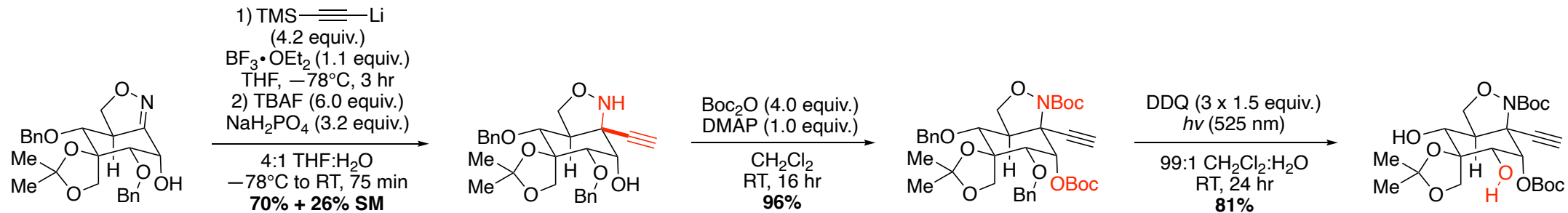


### Oxa-Michael Addition/Nitrile Oxide Cycloaddition Cascade

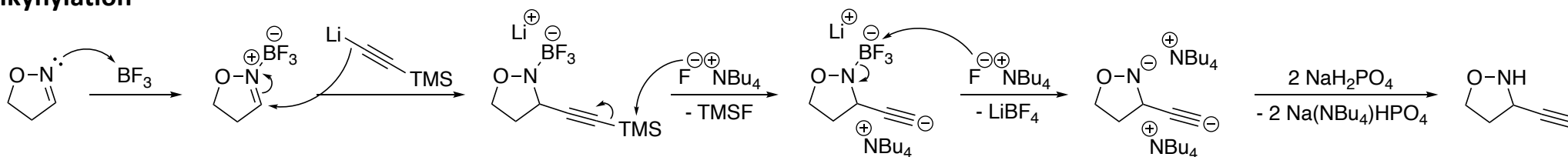


### PMB Deprotection

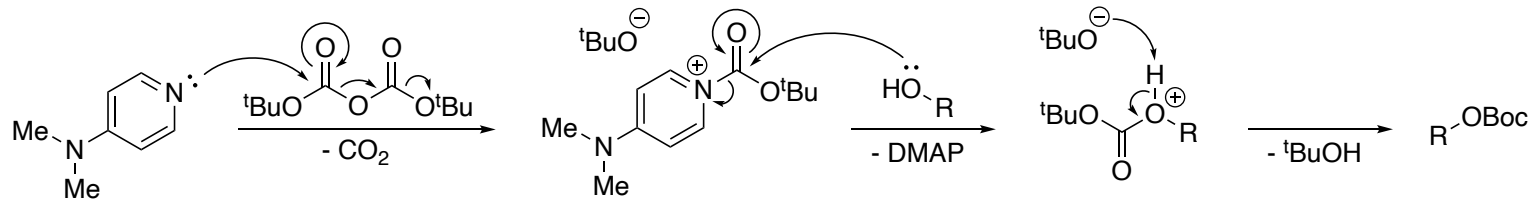




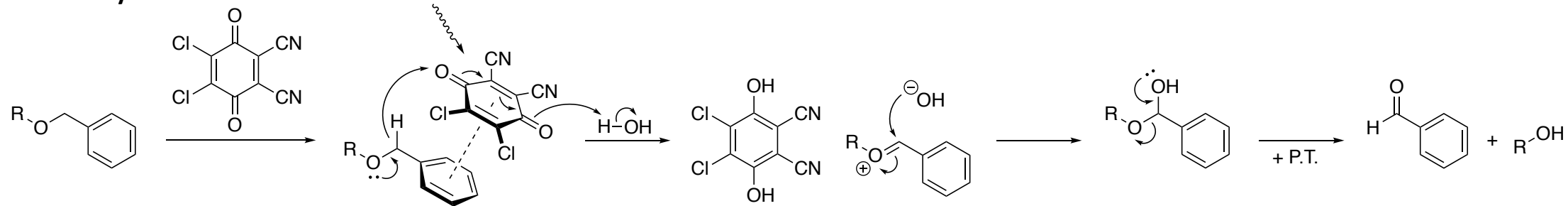
### Alkynylation

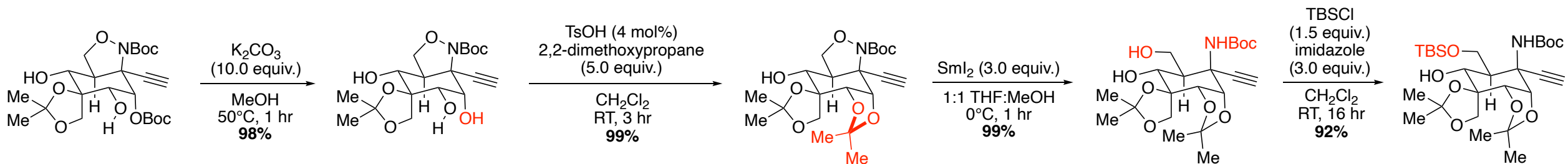


### Boc Protection

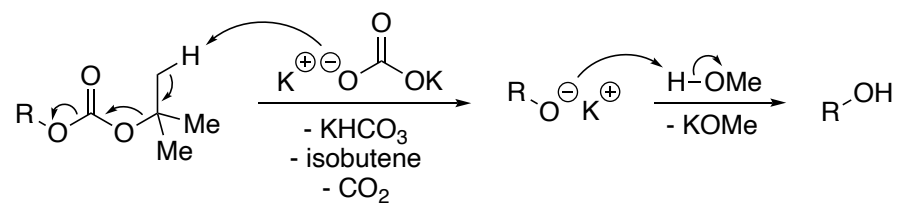


### Photochemical Debenzylation

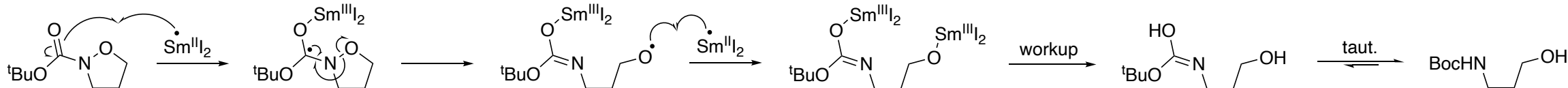




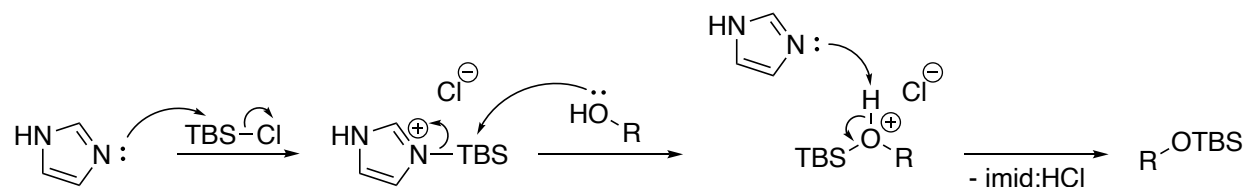
### Boc Deprotection (Basic)



### Reductive Isoxazolidine Cleavage

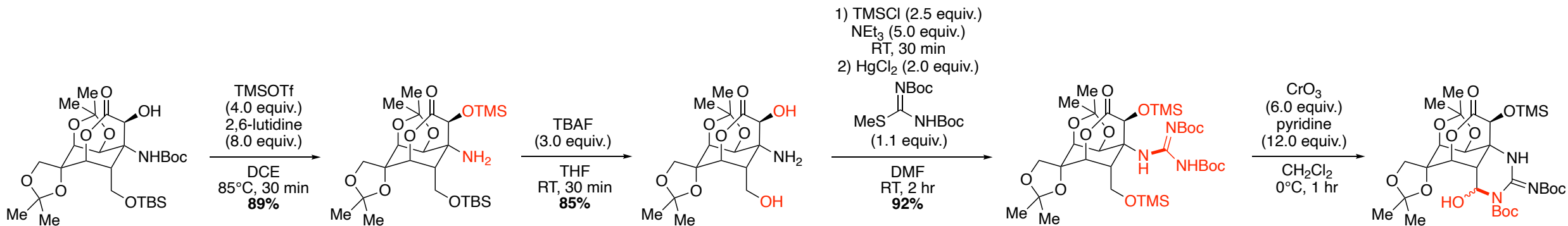


### TBS Protection

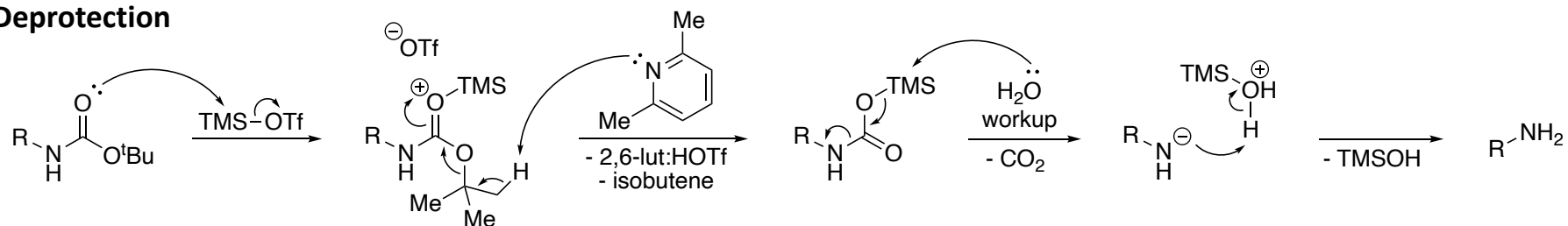




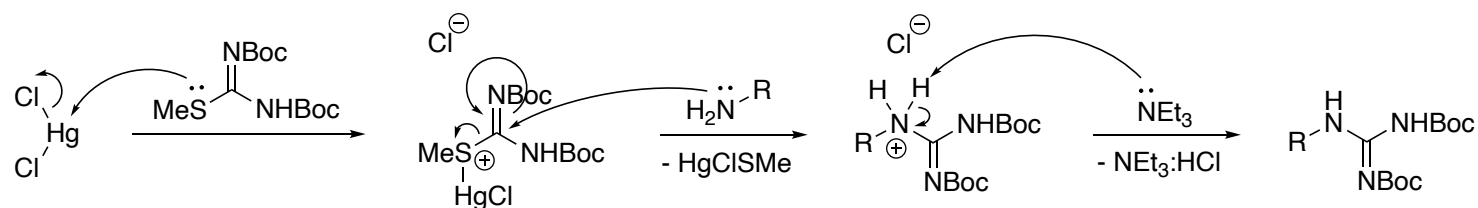




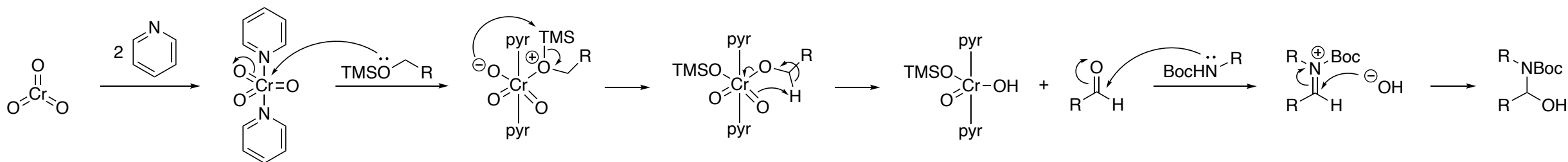
### Boc Deprotection

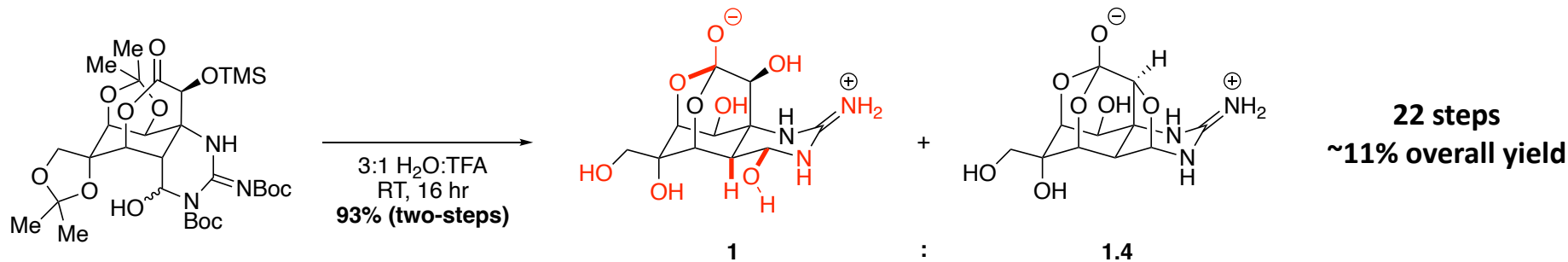


### Kishi Guanylation

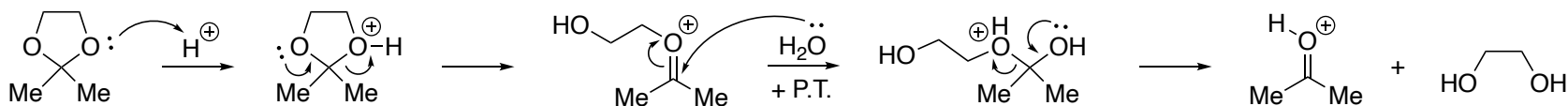


### Collins Oxidation





**Acetonide Deprotection**



**Hemi-ortho-Ester Formation**

