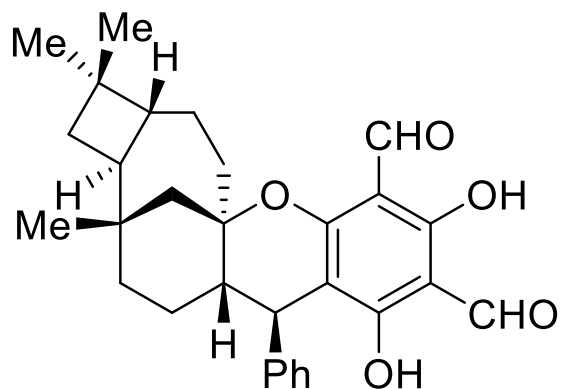


# Enantioselective Total Synthesis of (+)-Psiguadial B

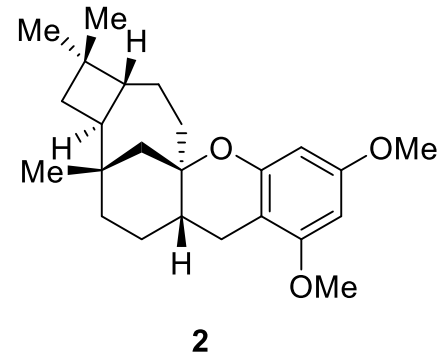
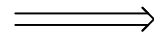
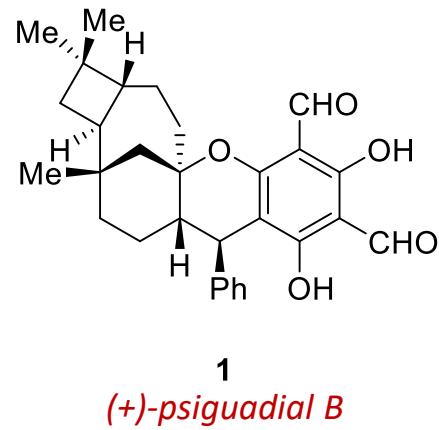
Lauren M. Chapman, Jordan C. Beck, Linglin Wu, and Sarah E. Reisman



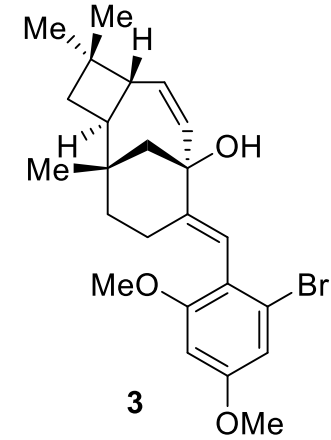
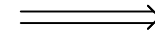
**(+)-Psiguadial B (1)**

- Isolated from leaves of *Psidium guajava*;
- Displays antiproliferative activity against human hepatoma cells;
- Sesquiterpenoid fragment of **1** arises biosynthetically from  $\beta$ -caryophyllene;
- 15 step synthesis

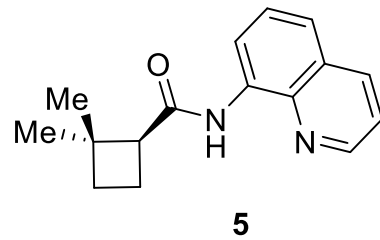
# Retrosynthesis:



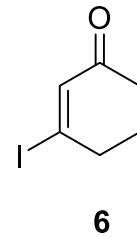
*C-O bond  
formation*



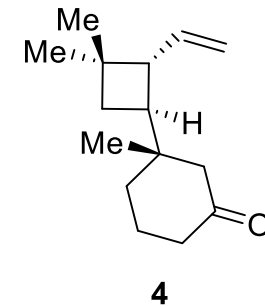
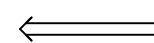
*Ring closing metathesis,  
aldol*



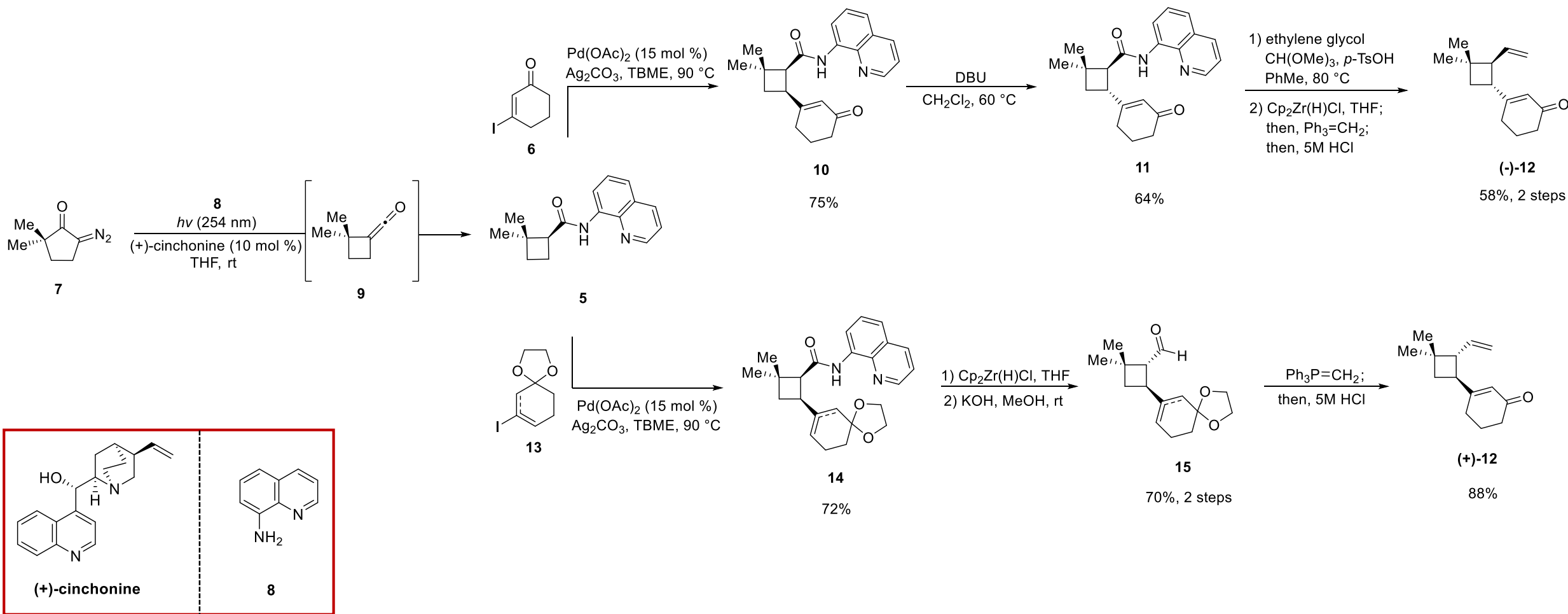
+



*C(sp<sup>3</sup>)-H  
alkenylation*

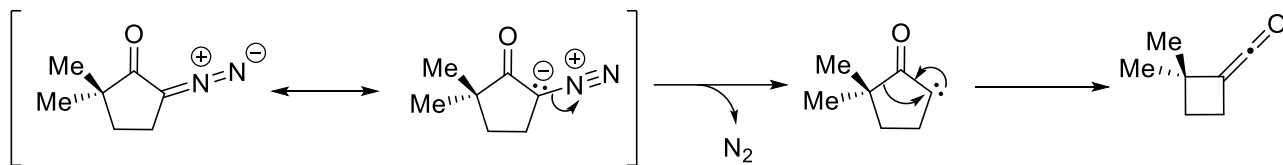


# C(sp<sup>3</sup>)-H Alkenylation and Epimerization Strategies:

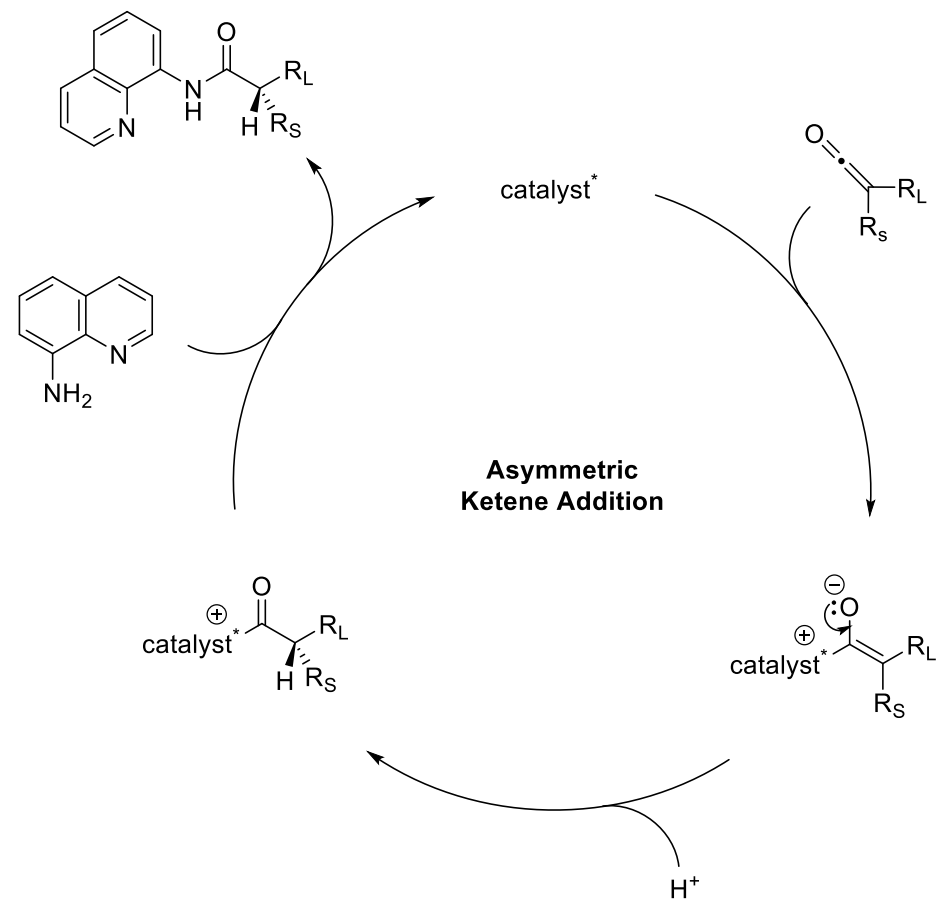


# C(sp<sup>3</sup>)-H Alkenylation and Epimerization Strategies:

## 7 to 9: Wolff Rearrangement

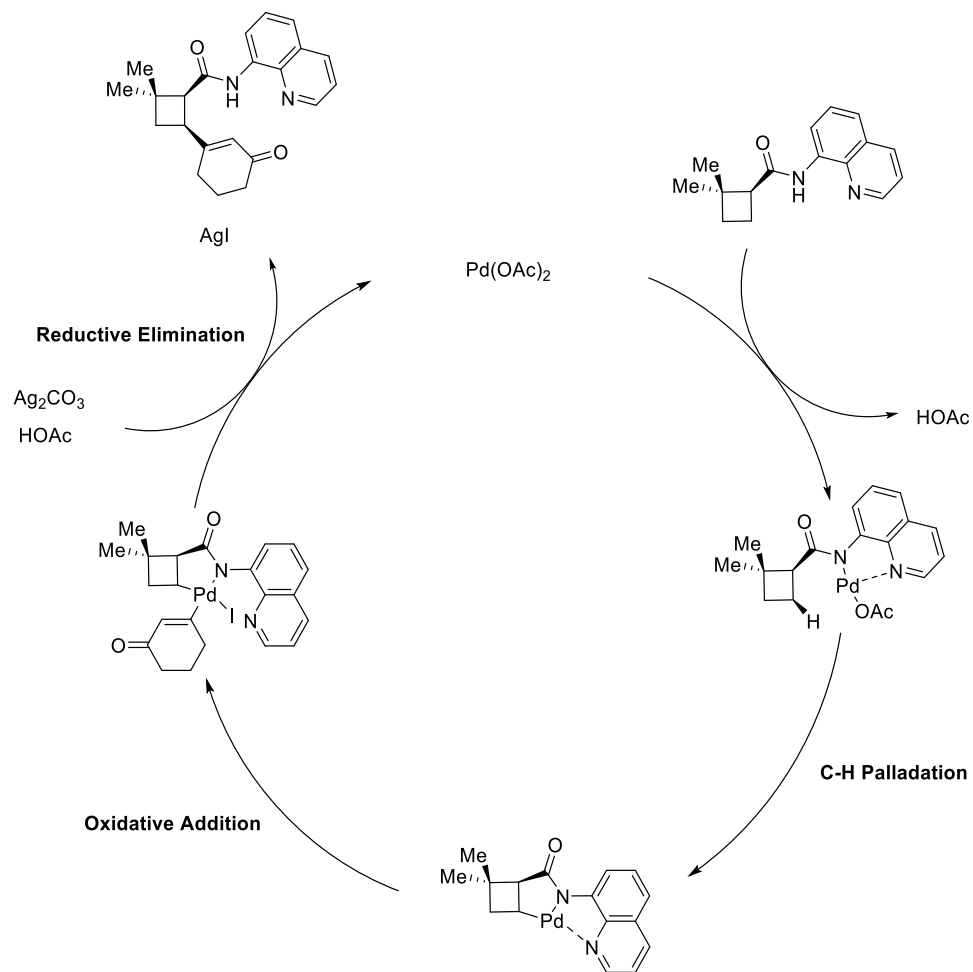


## 9 to 5: Catalytic Asymmetric Ketene Addition

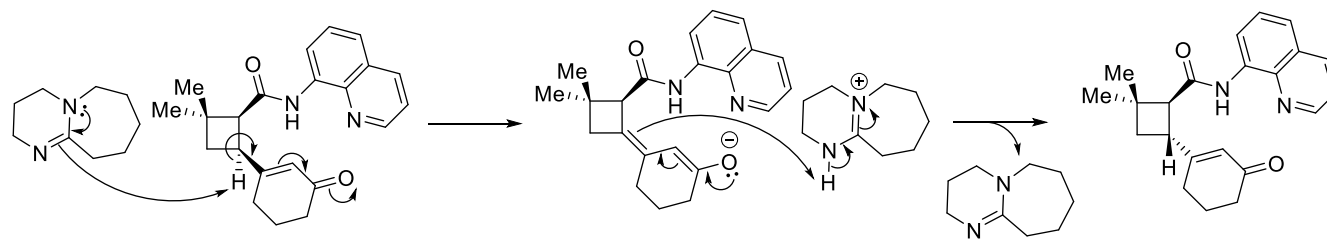


# C(sp<sup>3</sup>)-H Alkenylation and Epimerization Strategies:

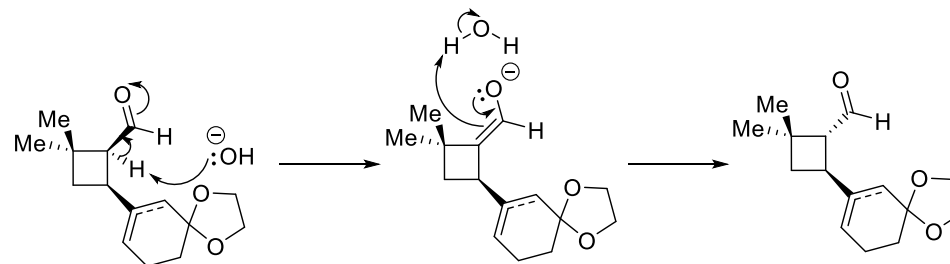
## 5 to 10/ 5 to 14: C(sp<sup>3</sup>)-H Alkenylation



## 10 to 11: C-2 Base-catalyzed Epimerization

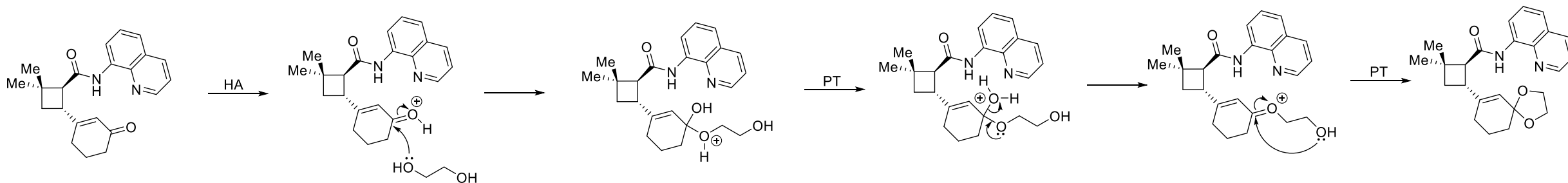


## 14 to 15: C-5 Base-catalyzed Epimerization

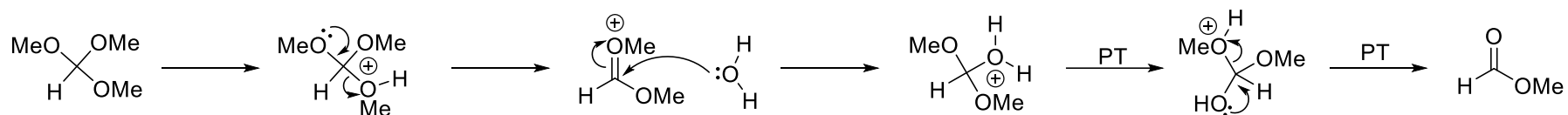


# C(sp<sup>3</sup>)-H Alkenylation and Epimerization Strategies:

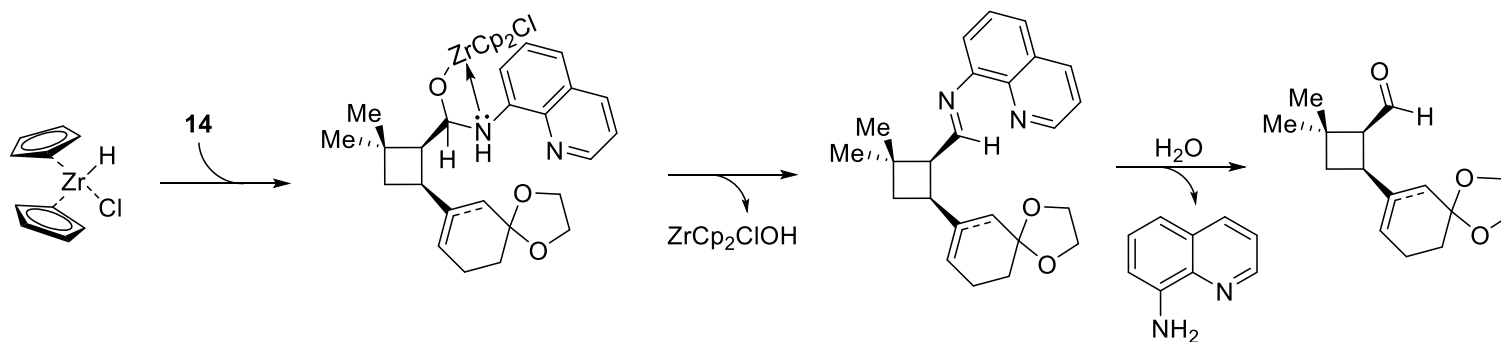
## 11 to (-)-12: Carbonyl Protection



## 11 to (-)-12: Methyl Orthoformate as a H<sub>2</sub>O Scavenger

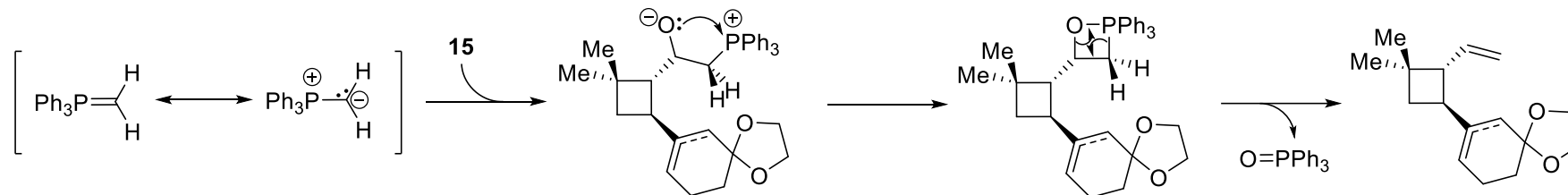


## 11 to (-)-12: Amide Reduction

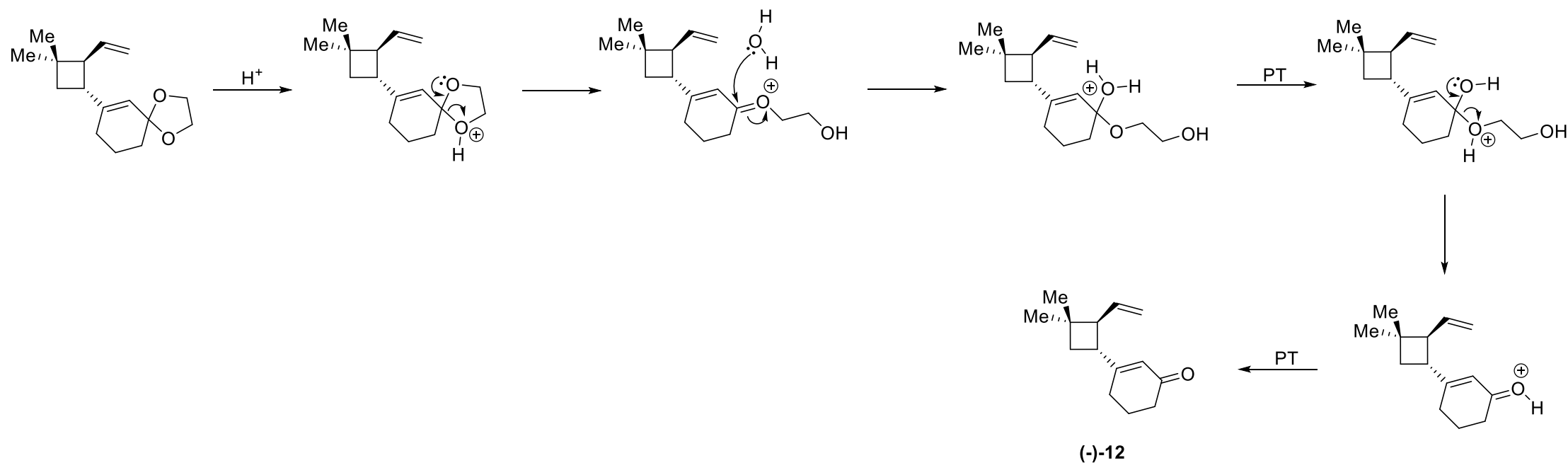


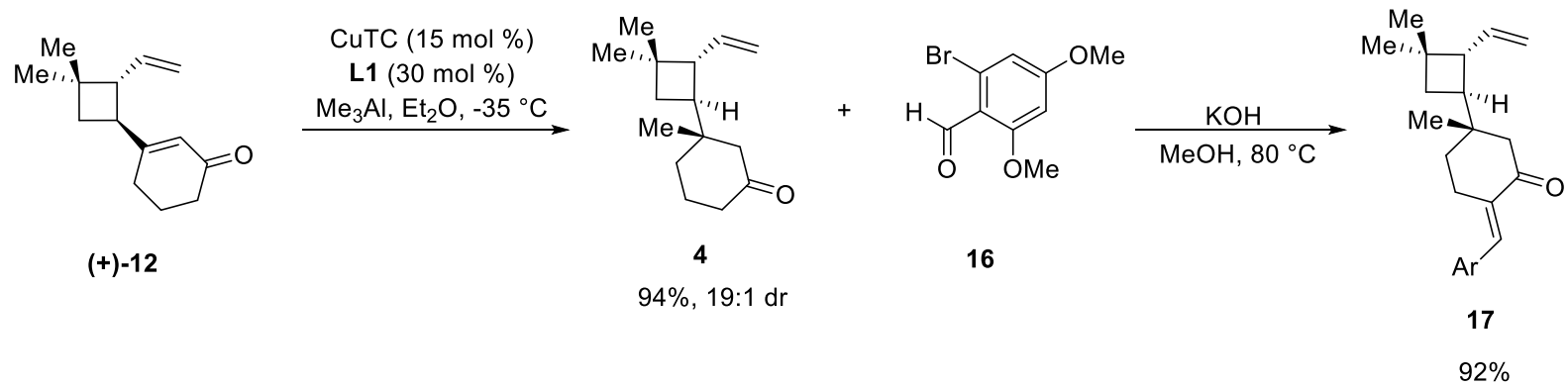
# C(sp<sup>3</sup>)-H Alkenylation and Epimerization Strategies:

## 15 to (+)-12: Wittig Olefination

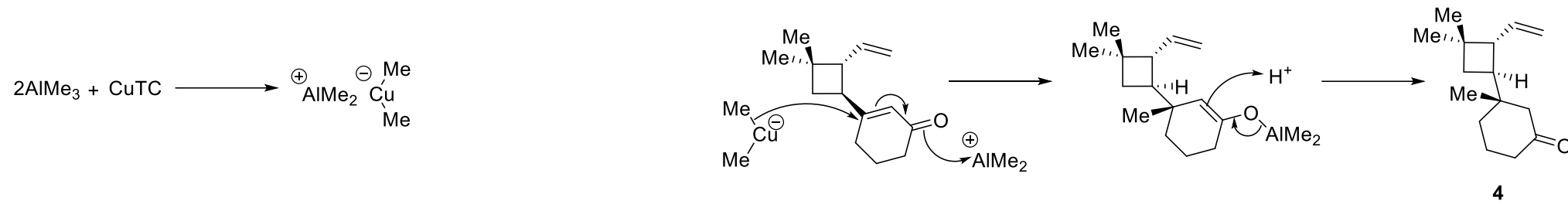


## 11 to (-)-12: Carbonyl Deprotection

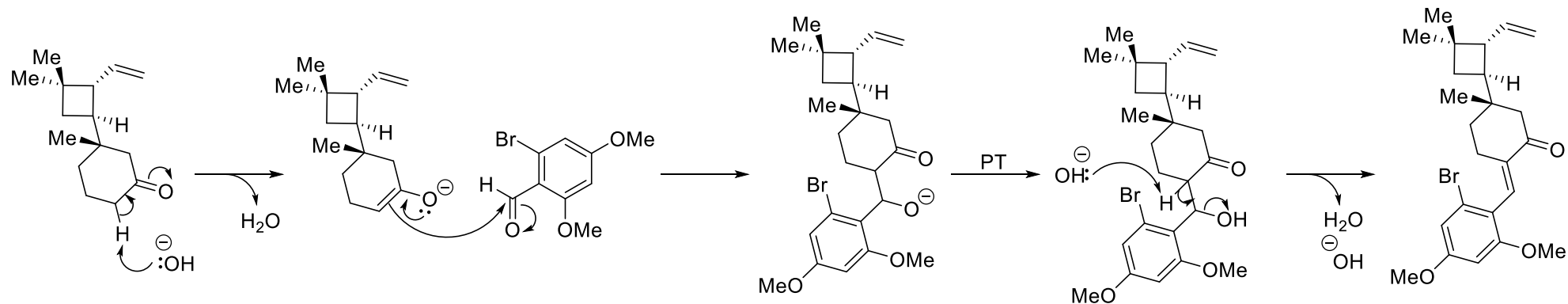
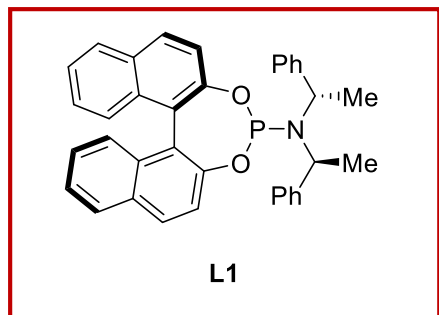




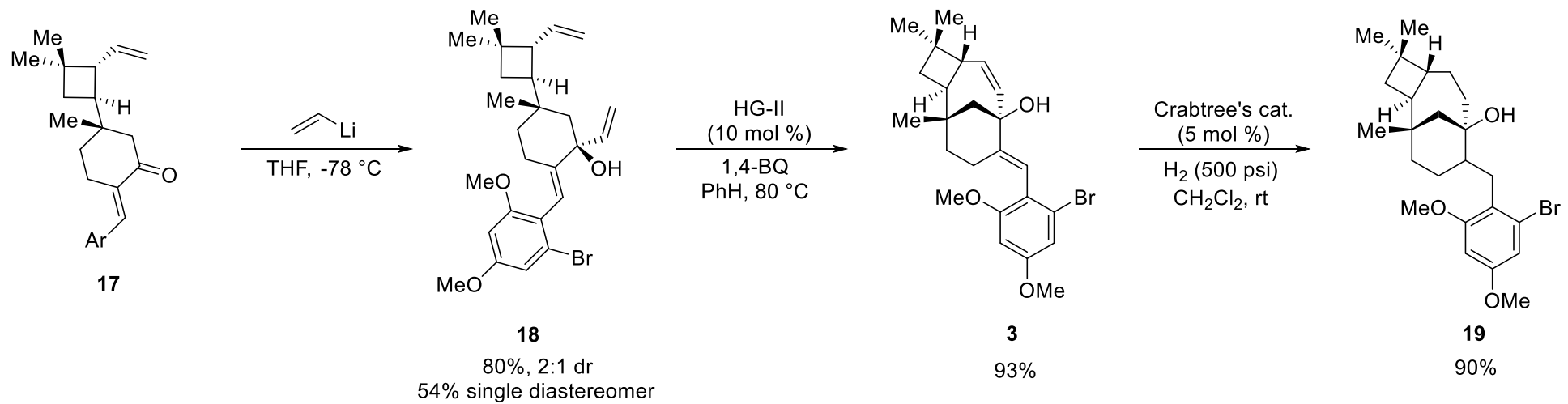
### (+)-12 to 4: 1, 4 Conjugate Addition



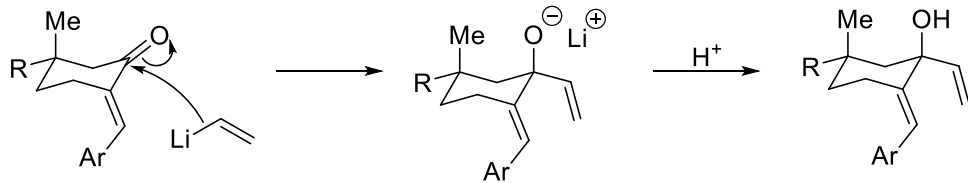
### 4 to 17: Aldol Condensation



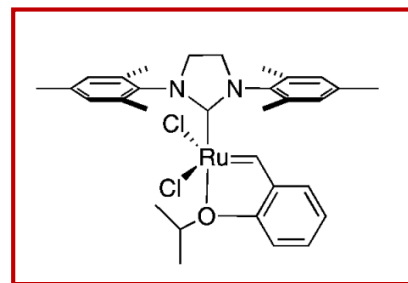
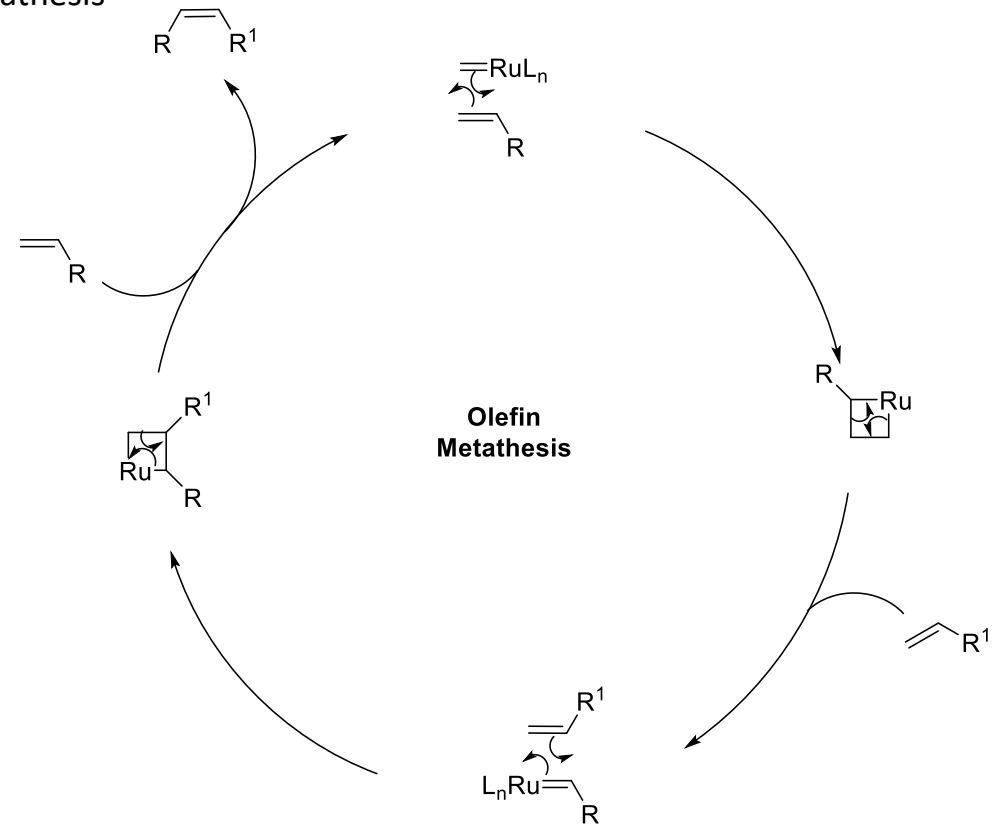




### 17 to 18: 1,2 Carbonyl Addition

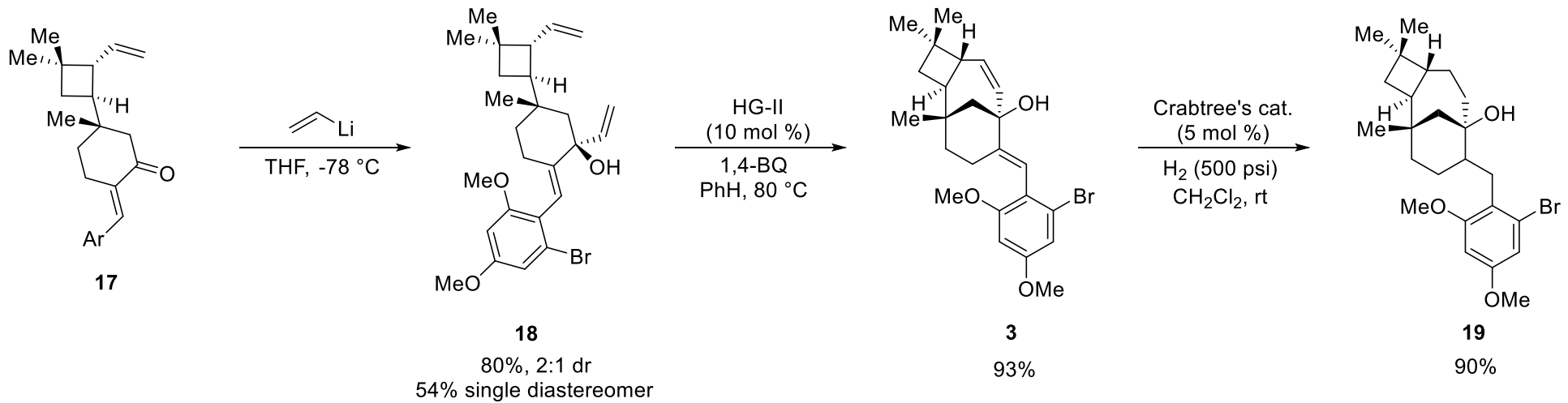


### 18 to 3: Ring-Closing Metathesis

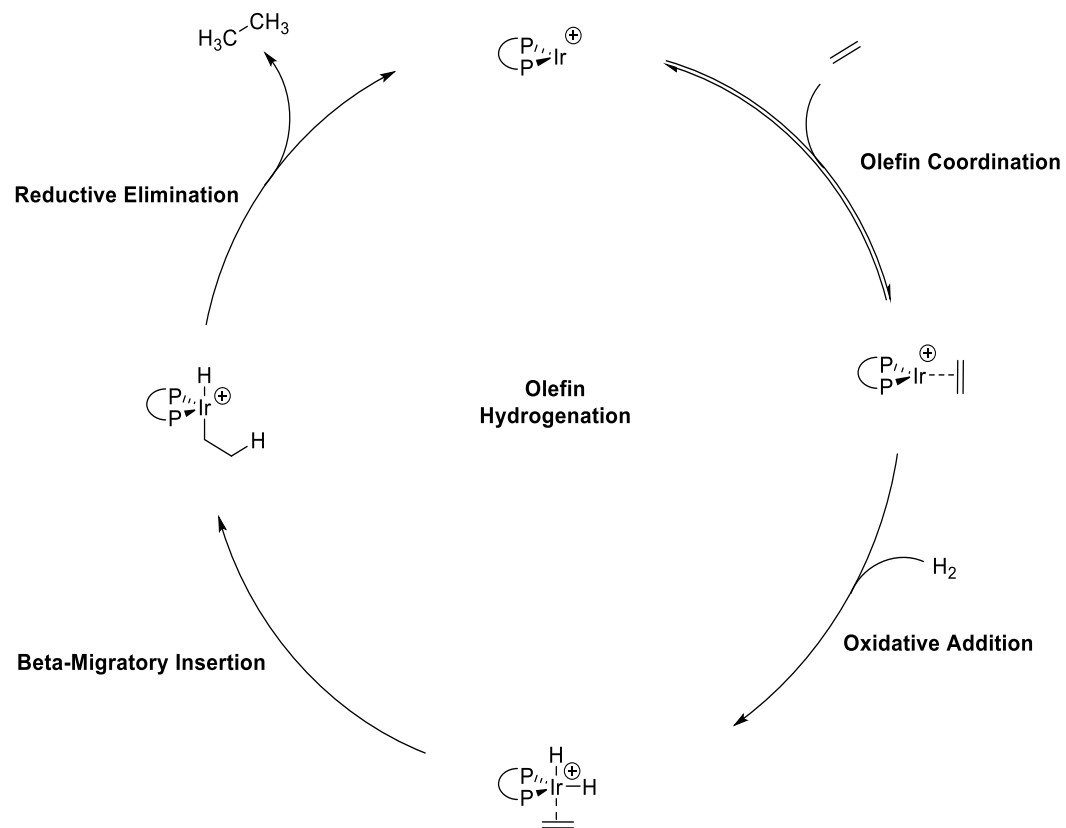
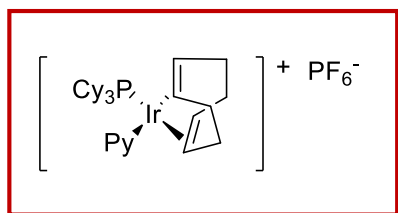


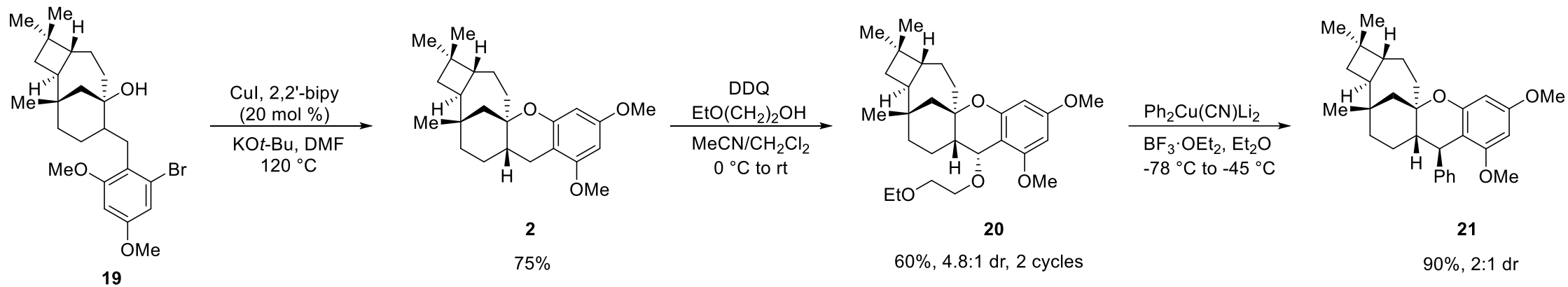
**Hoveyda-Grubbs II**

Addition of 1,4-BQ prevents olefin isomerization: Grubbs et al. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

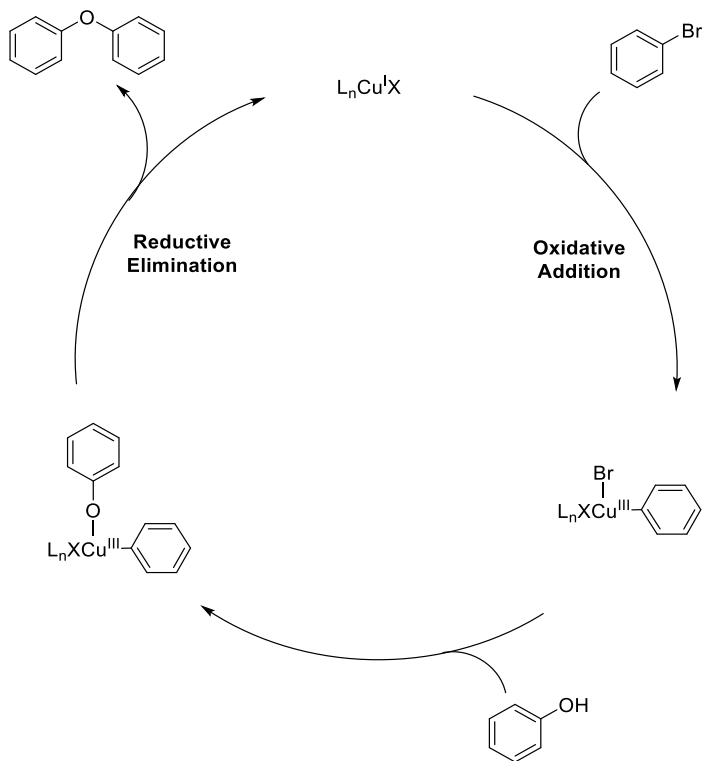


### 3 to 19: Olefin Hydrogenation

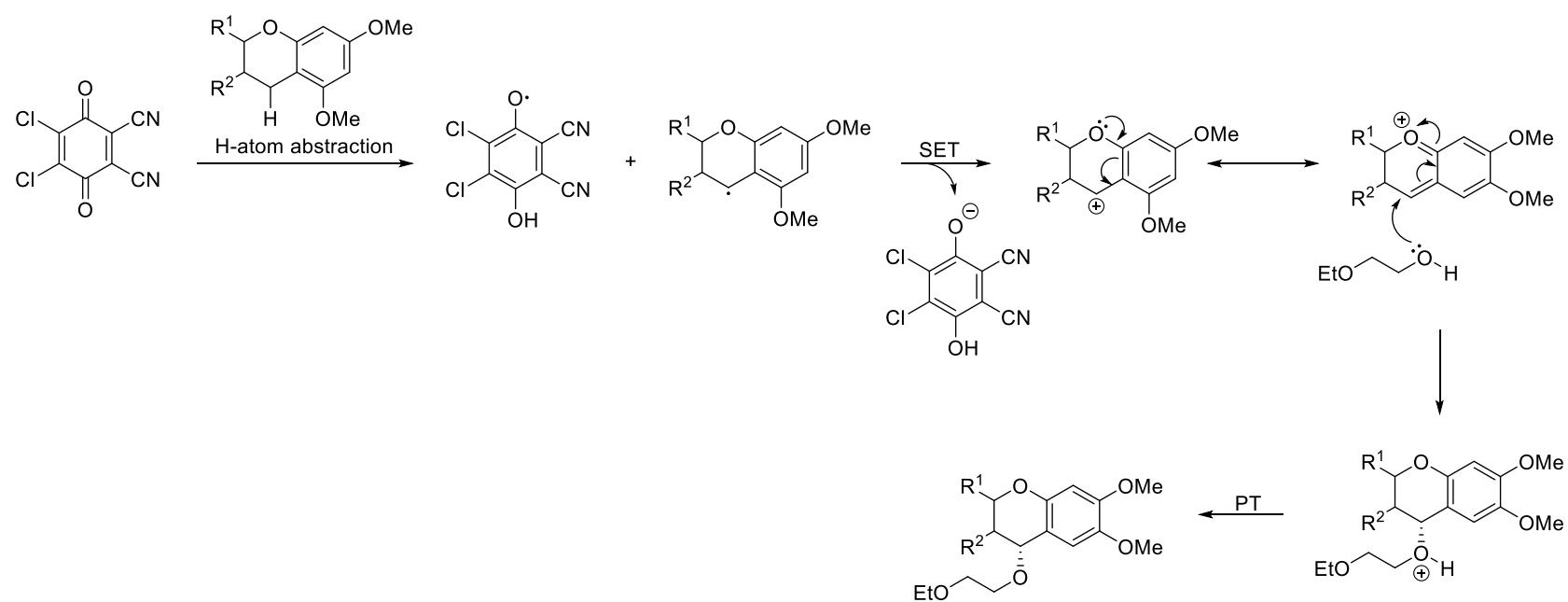


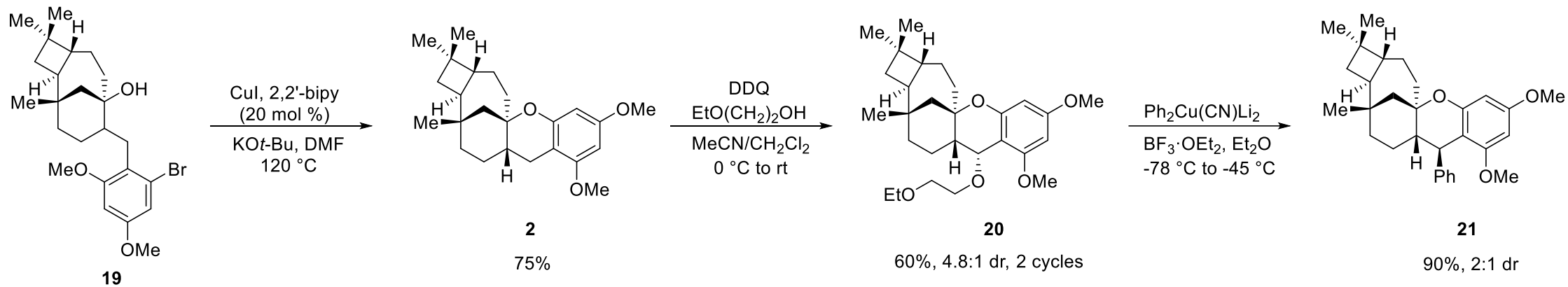


### 19 to 2: Copper-Catalyzed C–O Bond Formation

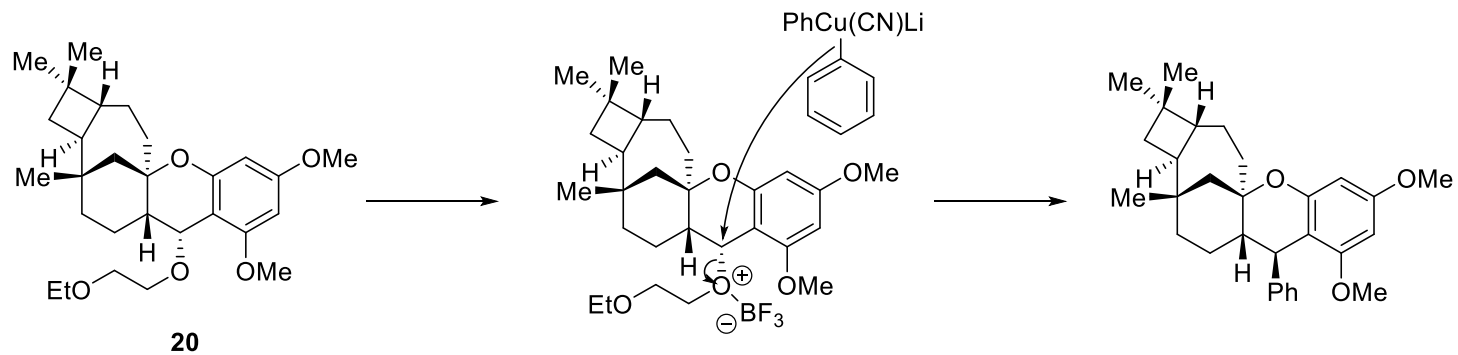


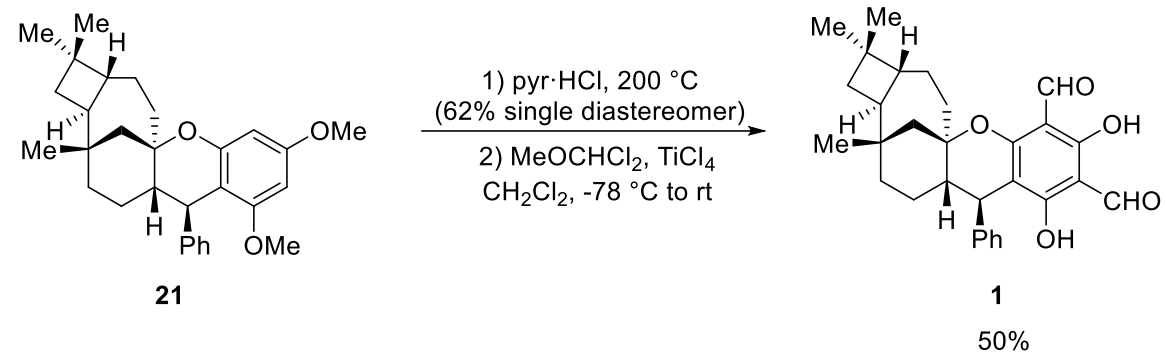
### 2 to 20: Benzylic Oxidation/ Addition



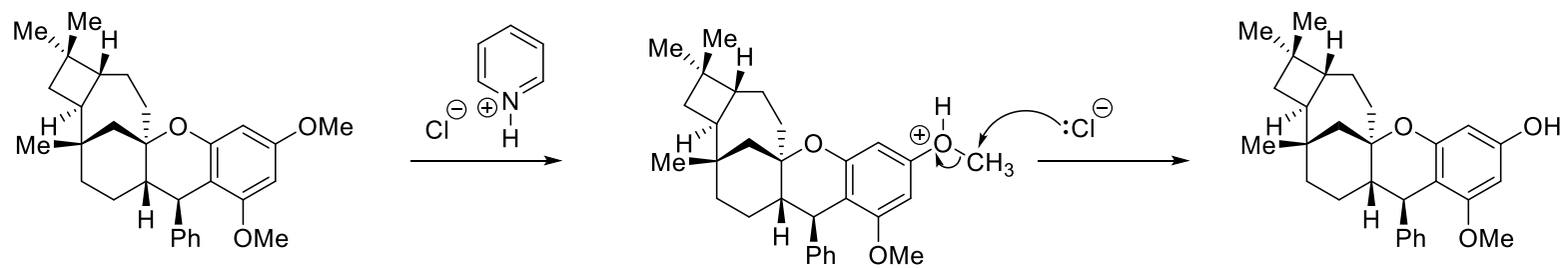


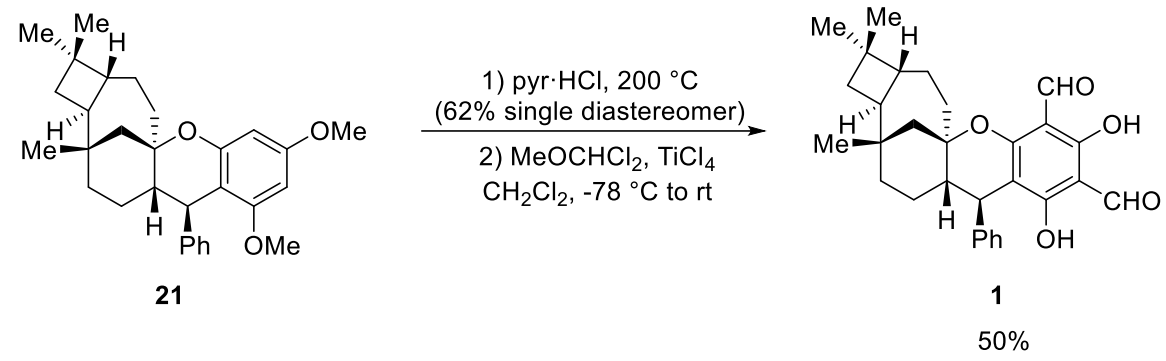
### 20 to 21: Cuprate Addition





**21 to 1: Demethylation**





**21 to 1: Rieche Formylation**

