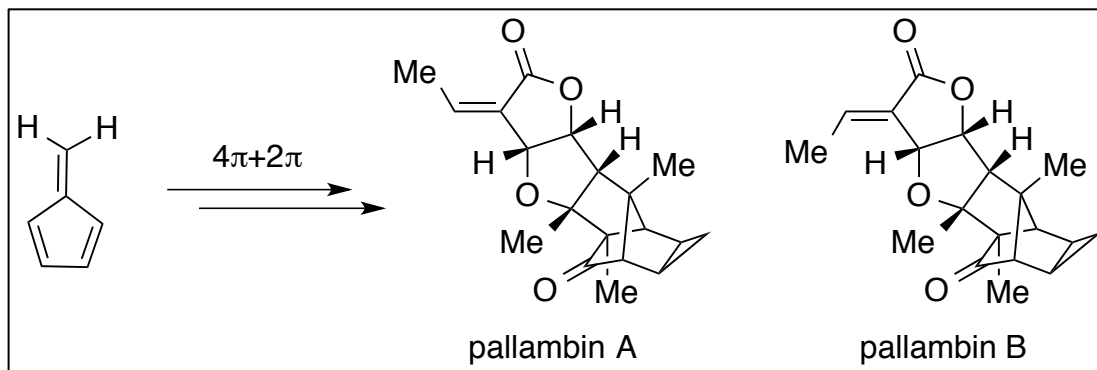


# Pentafulvene for the Synthesis of Complex Natural Products: Total Syntheses of ( $\pm$ )-Pallambins A and B



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# Erick M. Carreira

## Biography

- **1963:** Born in Havana, Cuba
- **1984:** B.S. degree, University of Illinois, Scott Denmark
- **1990:** PhD degree, Harvard University, David A. Evans
- **1992:** Post-Doc, California Institute of Technology, Peter Dervan
- **1993:** Assistant Professor, California Institute of Technology
- **1996:** Associate Professor, California Institute of Technology
- **1997:** Full Professor, California Institute of Technology
- **1998:** ETH Zurich

### Research Interest

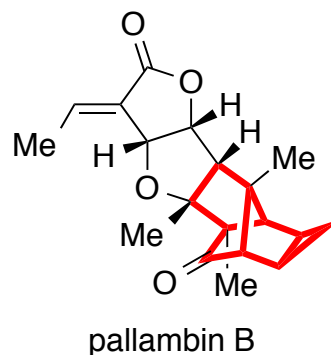
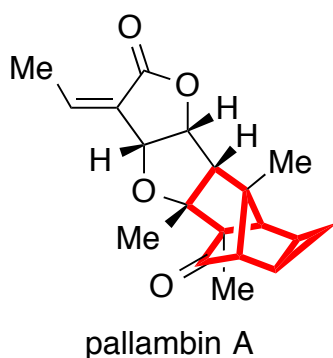
- Asymmetric synthesis of biologically active, stereochemically complex, natural products
- Unique challenges in asymmetric bond construction
- Developing catalytic and stoichiometric reagents for asymmetric stereocontrol



# (±)-Pallambin A and B

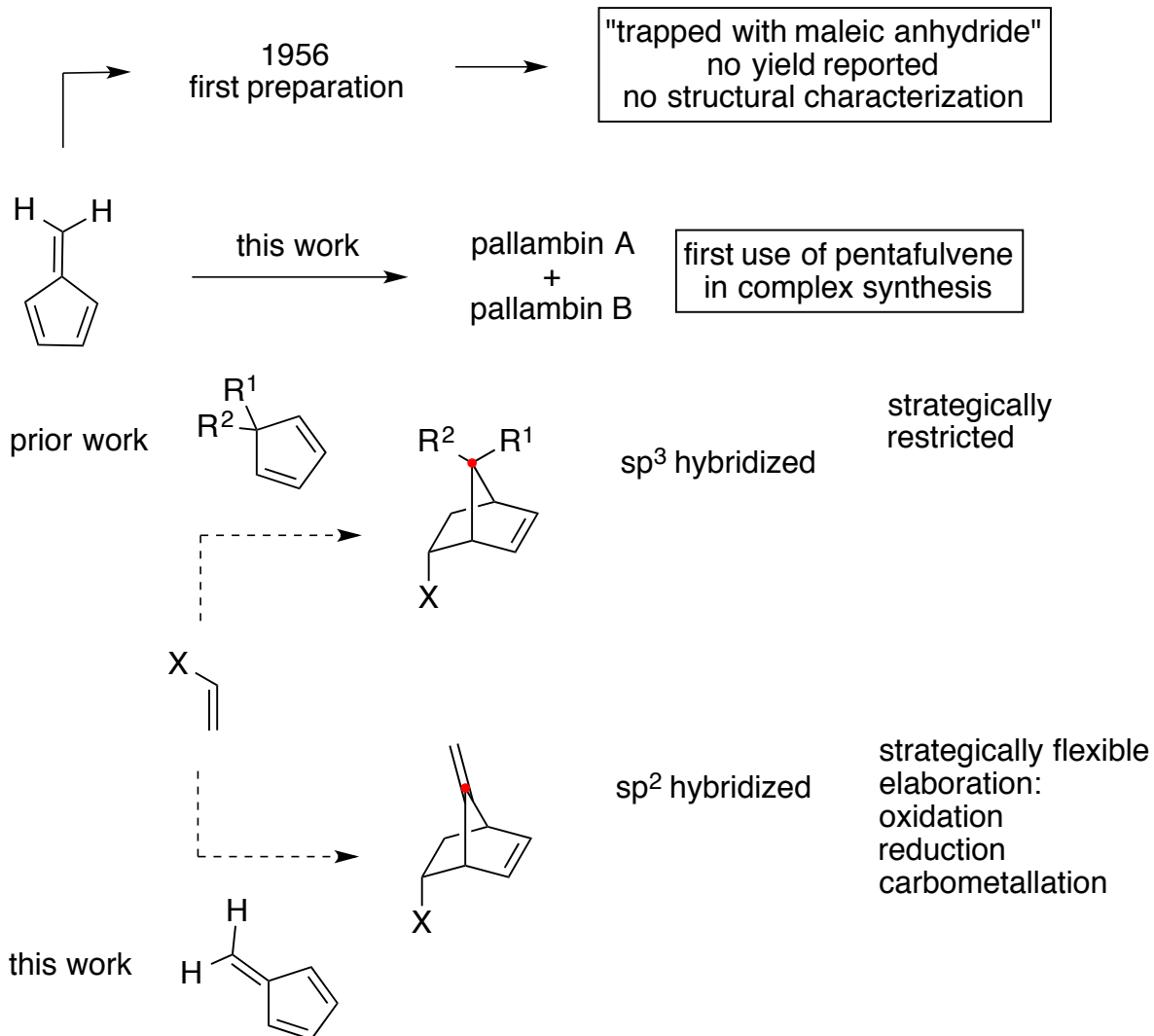
## General Information

- Isolated from liverwort *Pallavicinia ambigua*
- Cyclopropane containing diterpenoid (C<sub>19</sub>)
- Unprecedented and highly congested tetracyclo[4.4.0<sup>3,5</sup>.0<sup>2,8</sup>]decane core
- Ten contiguous stereocenters, two quaternary



# Fulvene

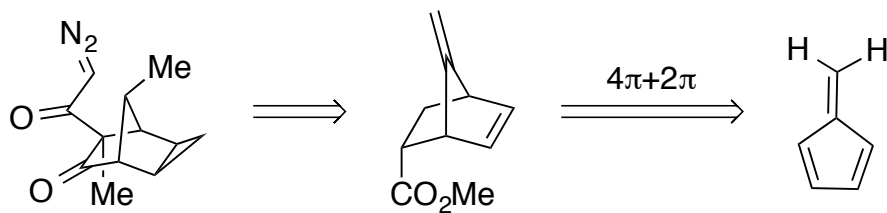
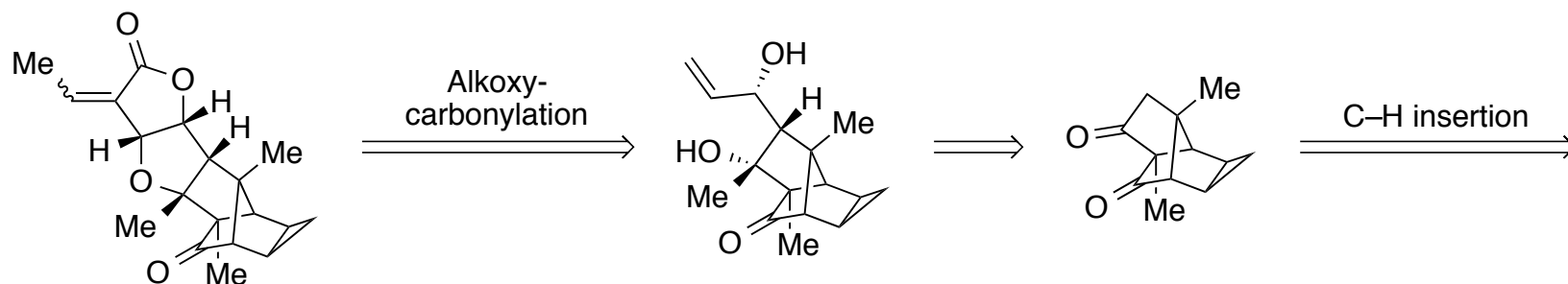
## Rule of Fulvene; Synthetic Strategy



# Total Synthesis from Fulvene

## Retrosynthesis

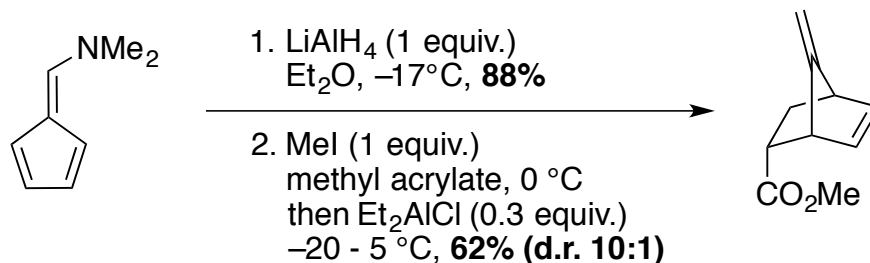
- Pentafulvene **not susceptible to isomerisation** ( $\neq$  cyclopentadiene)
- $sp^2$  bridge carbon atom  $\rightarrow$  wide variety of transformations



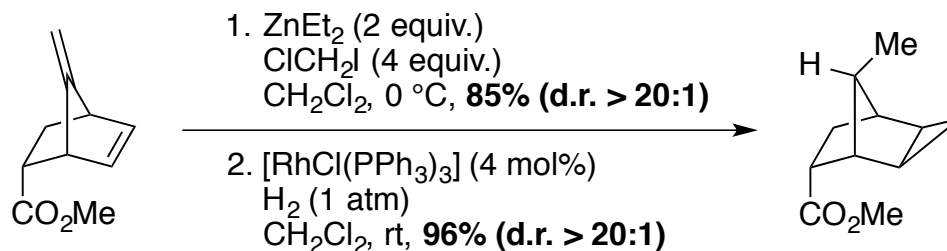
# Synthesis I

## Diels-Alder; Early Installation of Cyclopropane

- Starting from fulvene
  - Known to undergo facile light- or heat-induced **polymerization**
  - **Acid- and base-sensitive**
  - Stable in neat form only **below  $-70\text{ }^{\circ}\text{C}$**

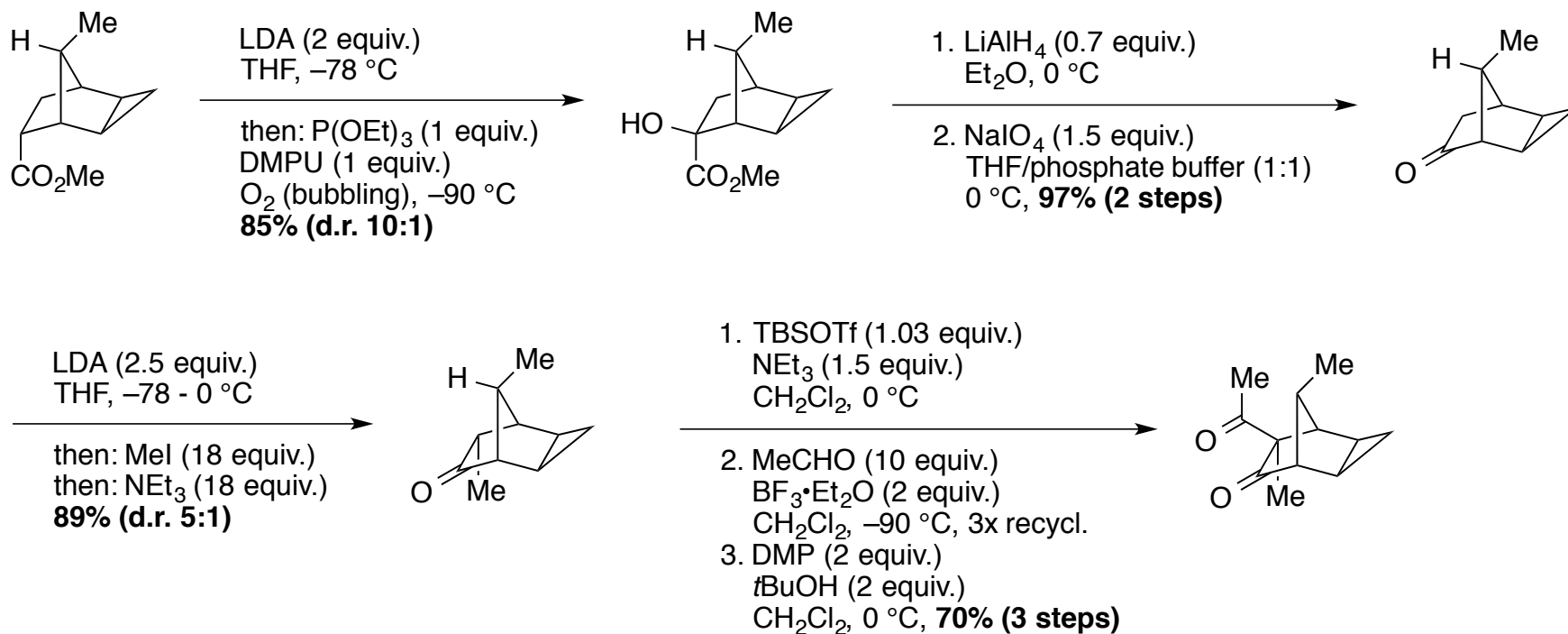


- Established cyclopropanation-protocols  $\rightarrow$  low conversion, poor chemoselectivity



# Synthesis II

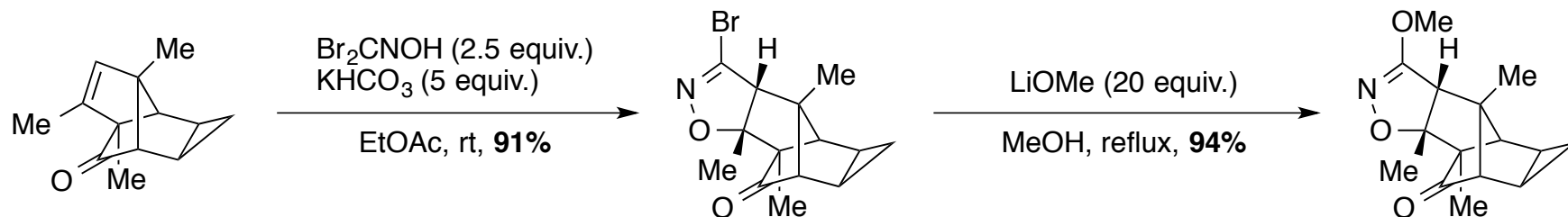
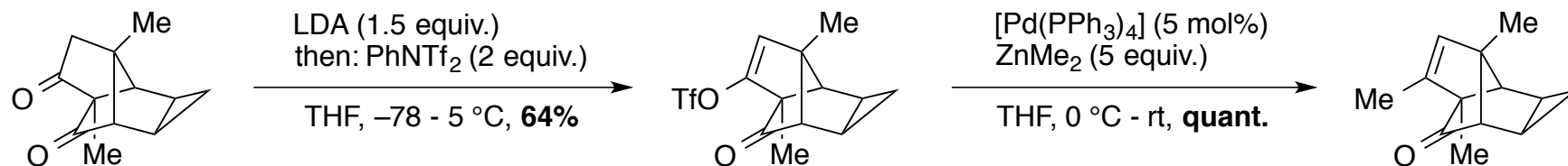
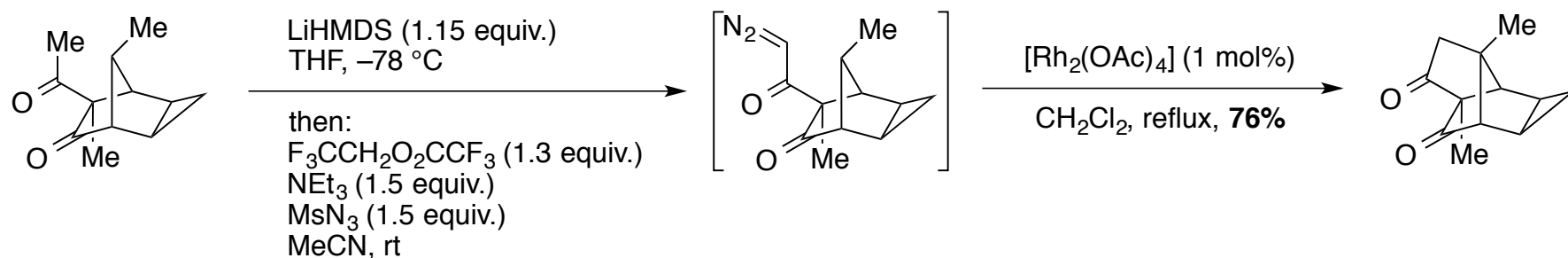
## Carbene Precursor



- Intermediate  **$\beta$ -hydroxy ketone** unstable  $\rightarrow$  Retro aldol (DM oxidation, LA nature)
- DMP/ $t\text{BuOH}$   $\rightarrow$  increase **rate** of oxidation

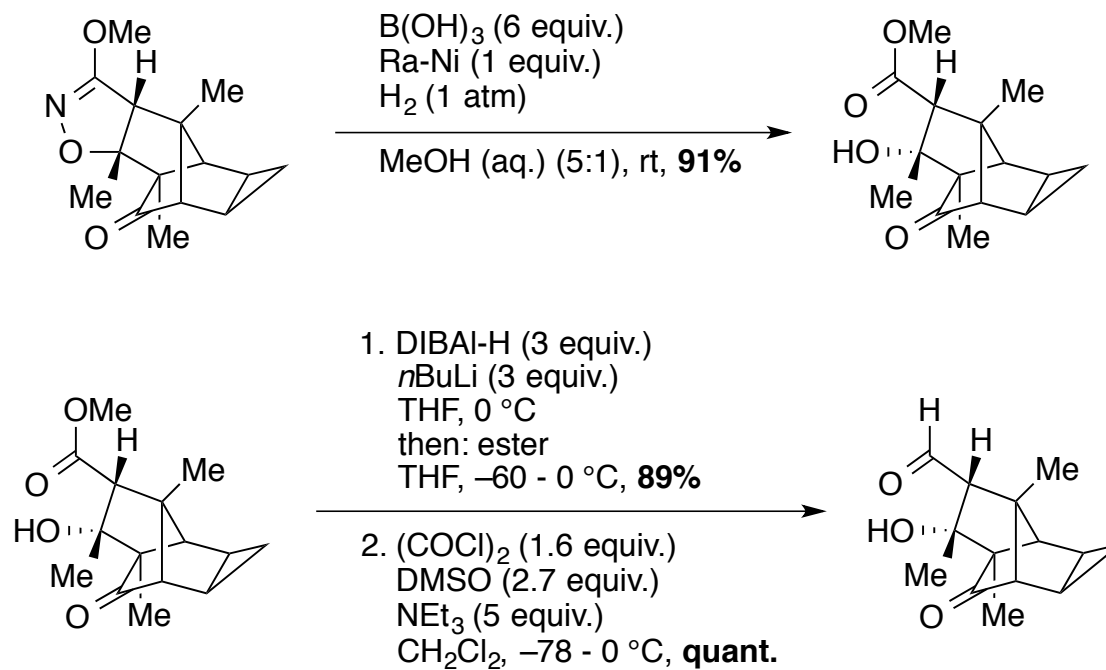
# Synthesis III

## C-H Insertion





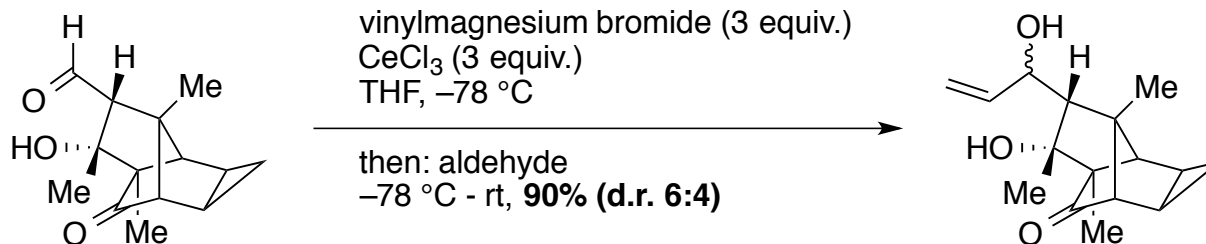
# Synthesis IV



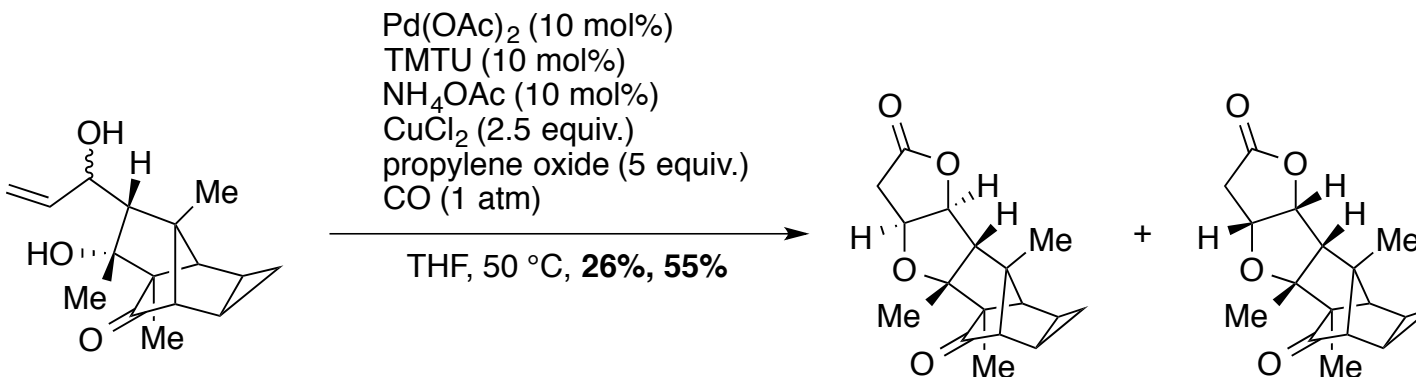
- DIBAL-H and  $n\text{BuLi} \rightarrow$  non-Lewis-acidic  $\text{Li}(i\text{Bu})_2(n\text{Bu})\text{AlH}$

# Synthesis V

## Introduction of the Tetrahydrofuran and the $\gamma$ -Lactone



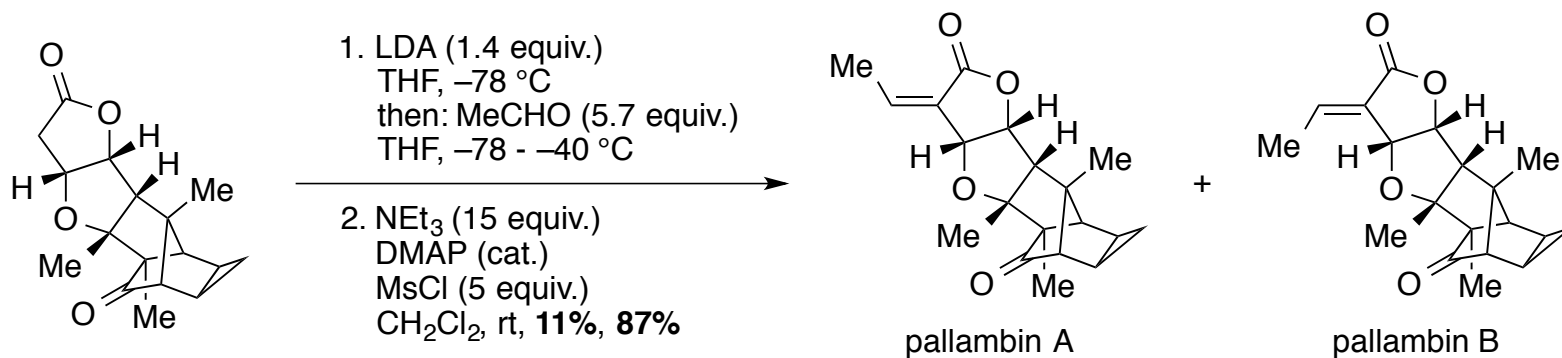
- Separation of diastereoisomers unsuccessful  $\rightarrow$  mixture used



# Synthesis VI

## Synthesis of Pallambin A and B

- Generation of the  $\beta$ -phosphonate (for HWE) failed
- Two-step aldol condensation



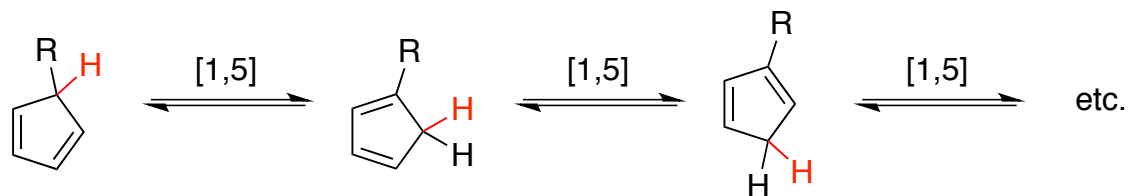
# Conclusion

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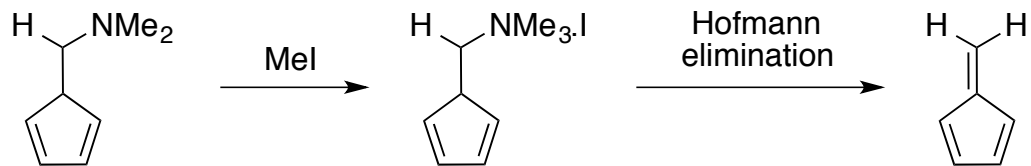
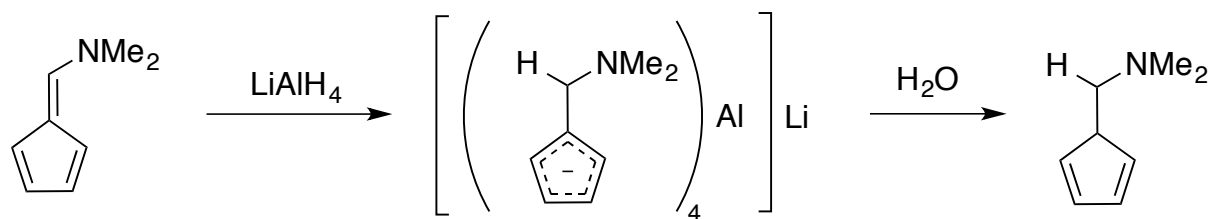
- First total syntheses of pallambins A and B (3.3% overall yield, 20 steps)
- Synthetic strategy centered around use of fulvene in a DA reaction
- Highly chemo- and diastereoselective cyclopropanation
- Efforts to expand use of the fulvene DA reaction are ongoing

**Thank you for your attention**

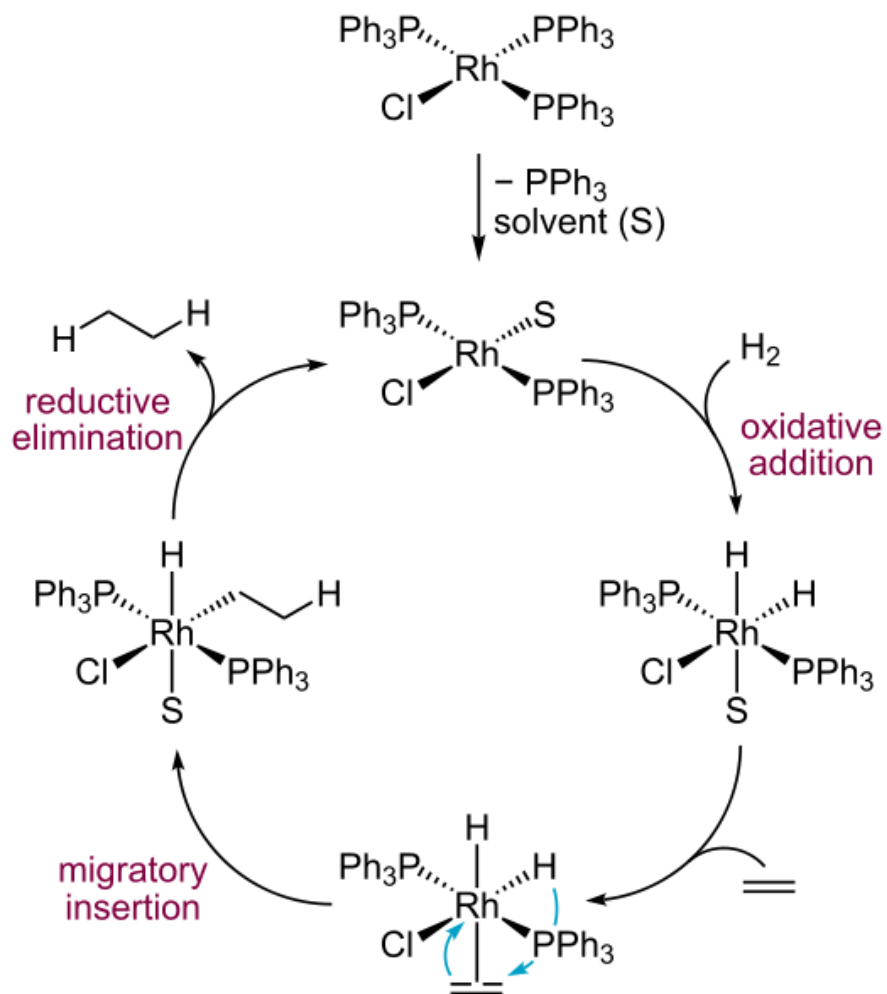
# [1,5]-shift of Substituted Cyclopentadienes



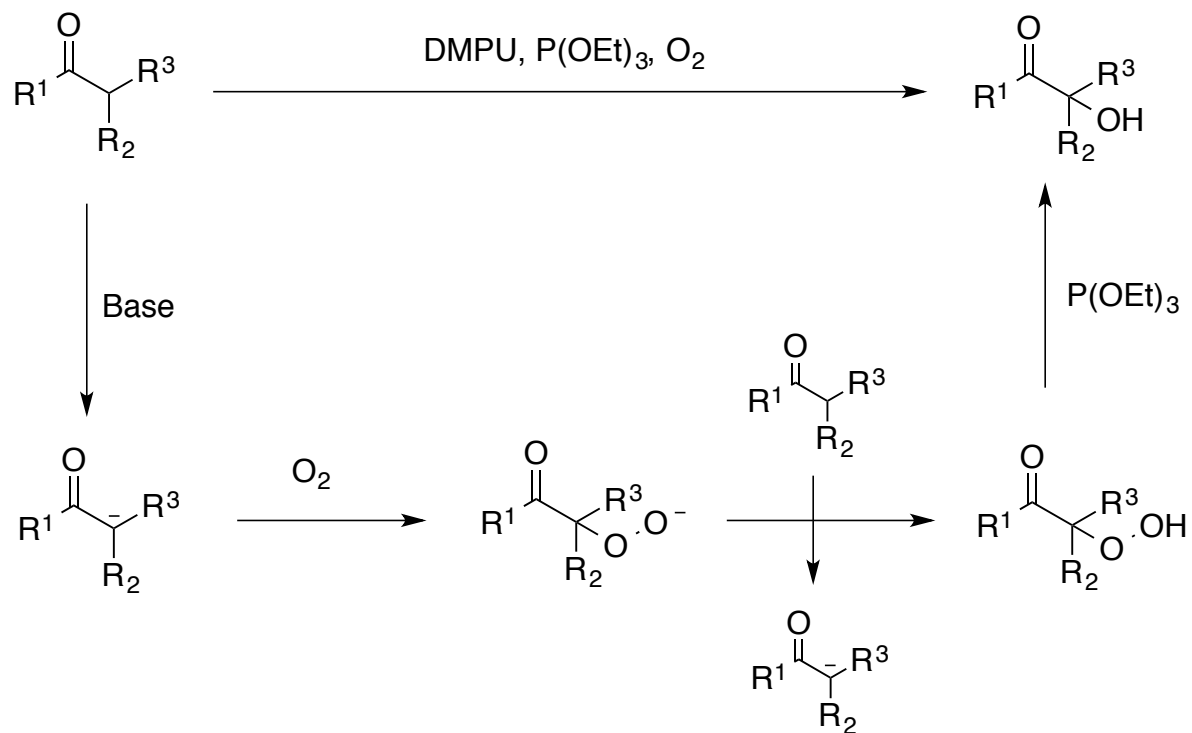
# Preparation of Pentafulvene



# Wilkinson's Catalyst $[\text{RhCl}(\text{PPh}_3)_3]$



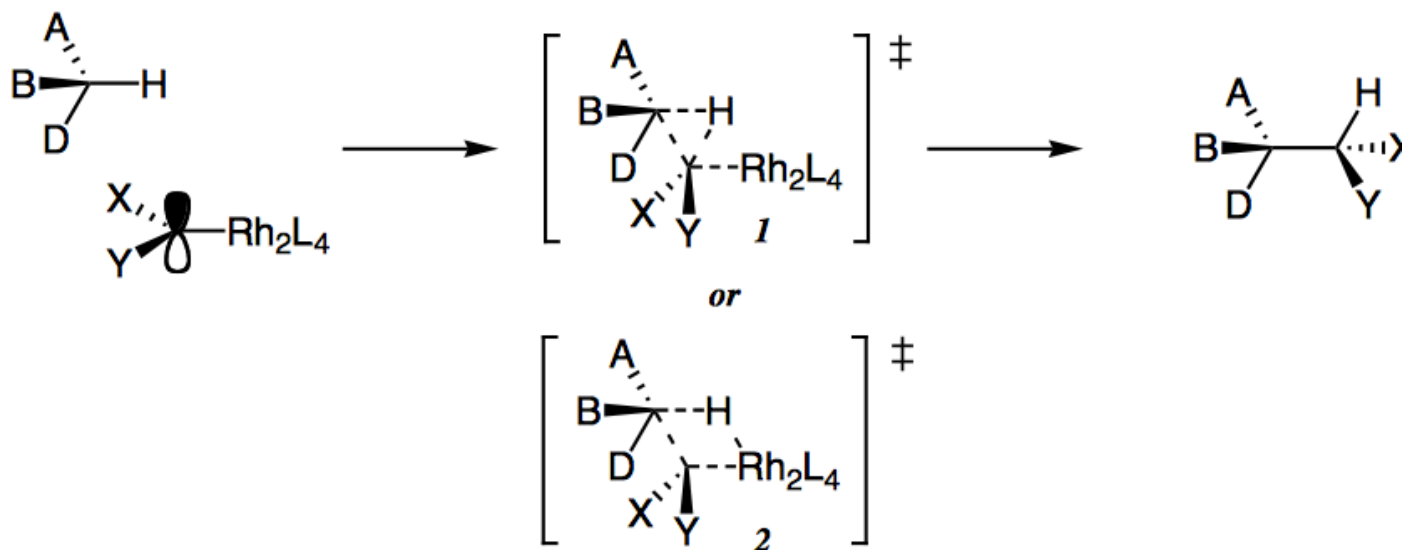
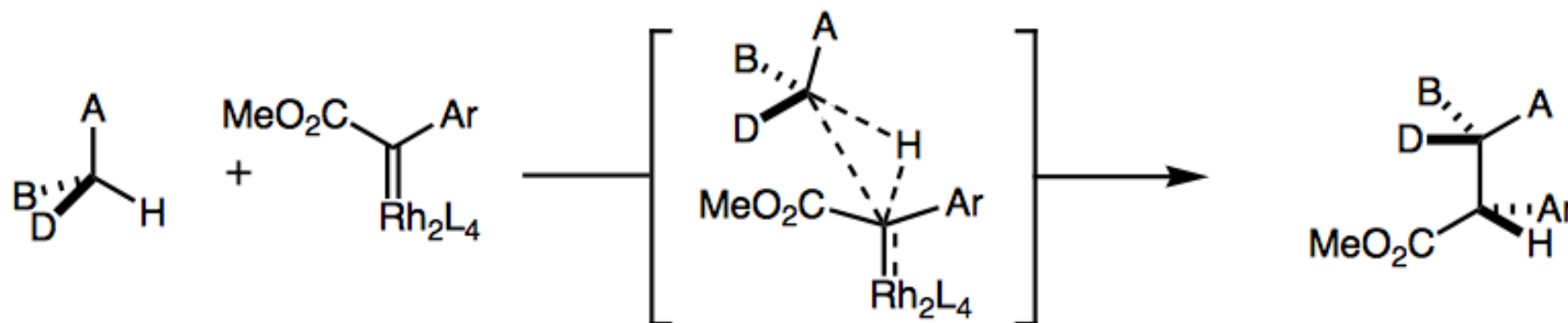
# Hydroxylation with O<sub>2</sub>, P(OEt)<sub>3</sub>





# Carbene, C–H insertion

Mechanism not well Understood, Source of Dispute

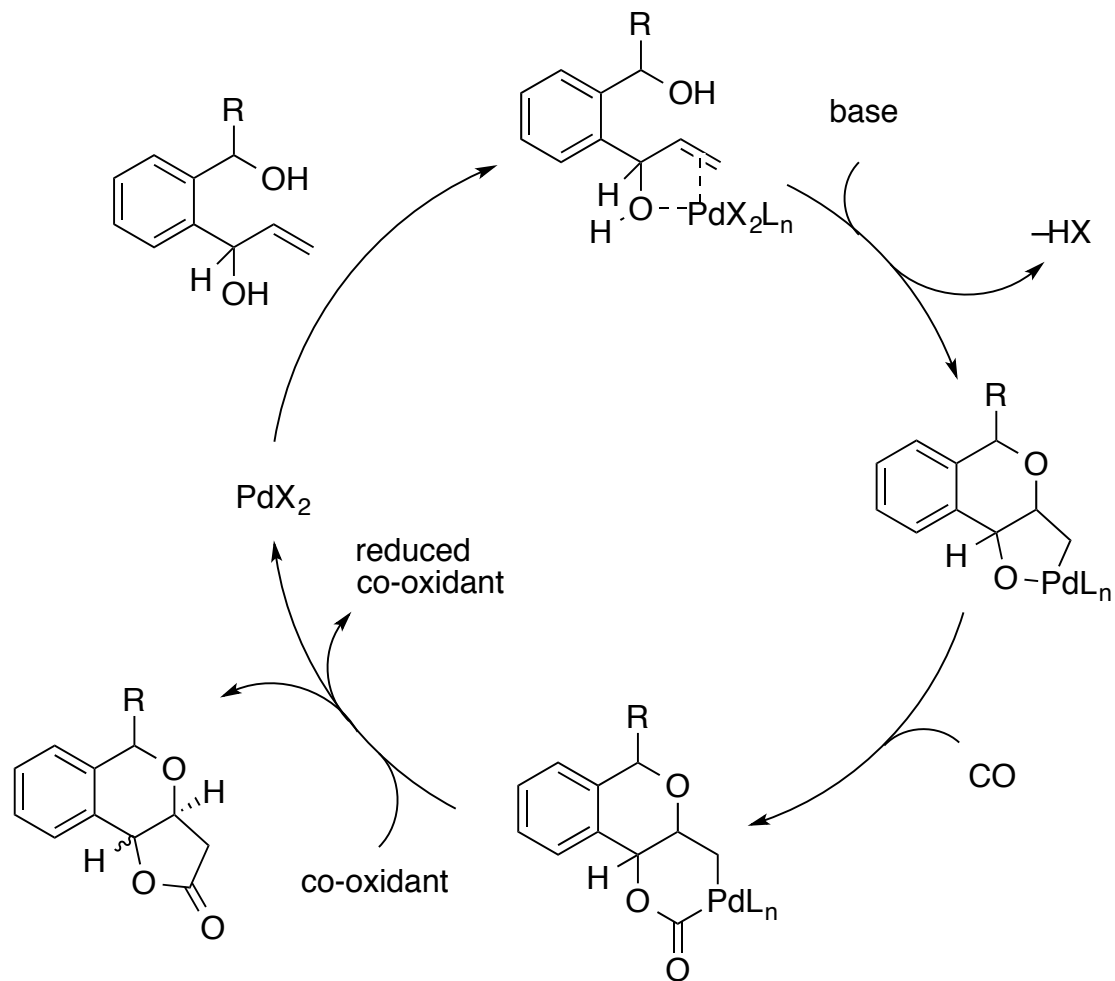


H. M. L. Davies, T. Hansen, M. R. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063

D. F. Taber, K. K. You, A. L. Rheingold, *J. Am. Chem. Soc.* **1996**, *118*, 547

# Carbene, C–H insertion

Mechanism not well Understood, Source of Dispute



# Biosynthesis

