Asymmetric Total Synthesis of (+)-Waihoensene

Reporter: **Bo Wu**
Checker: **Yang Zhao**
Date: **2020/09/07**

Qu, Y.; Yang, Z. *et al*. *J. Am. Chem. Soc.* **2020**, *142,* 6511.
Lee, H.; Lee, H.-Y. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 8254.

Contents

CV of Prof. Zhen Yang

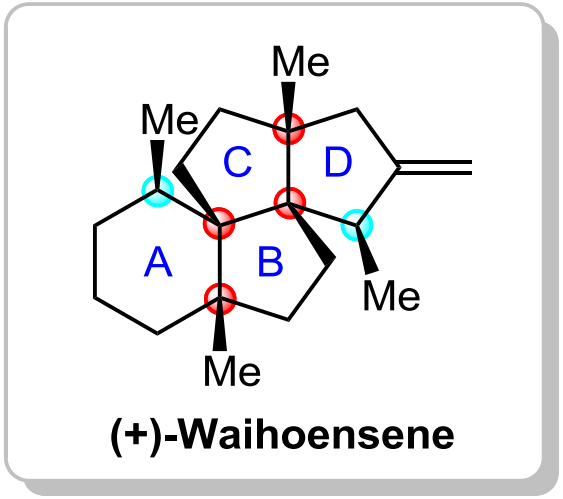
Background:

- **1978-1986** B.S. & M.S., Shenyang College of Pharmacy
- **1989-1992** Ph. D., The Chinese University of Hong Kong
- **1992-1998** Postdoc & Assistant Professor, The Scripps Research Institute
- **1998-2001** Institute fellow, Harvard University
- **2001-present** Professor, Peking University

Research Interests:

- ✓ Development of synthetic methods for the synthesis of complex natural product molecules and application of synthetic chemistry for drug discovery.

Introduction



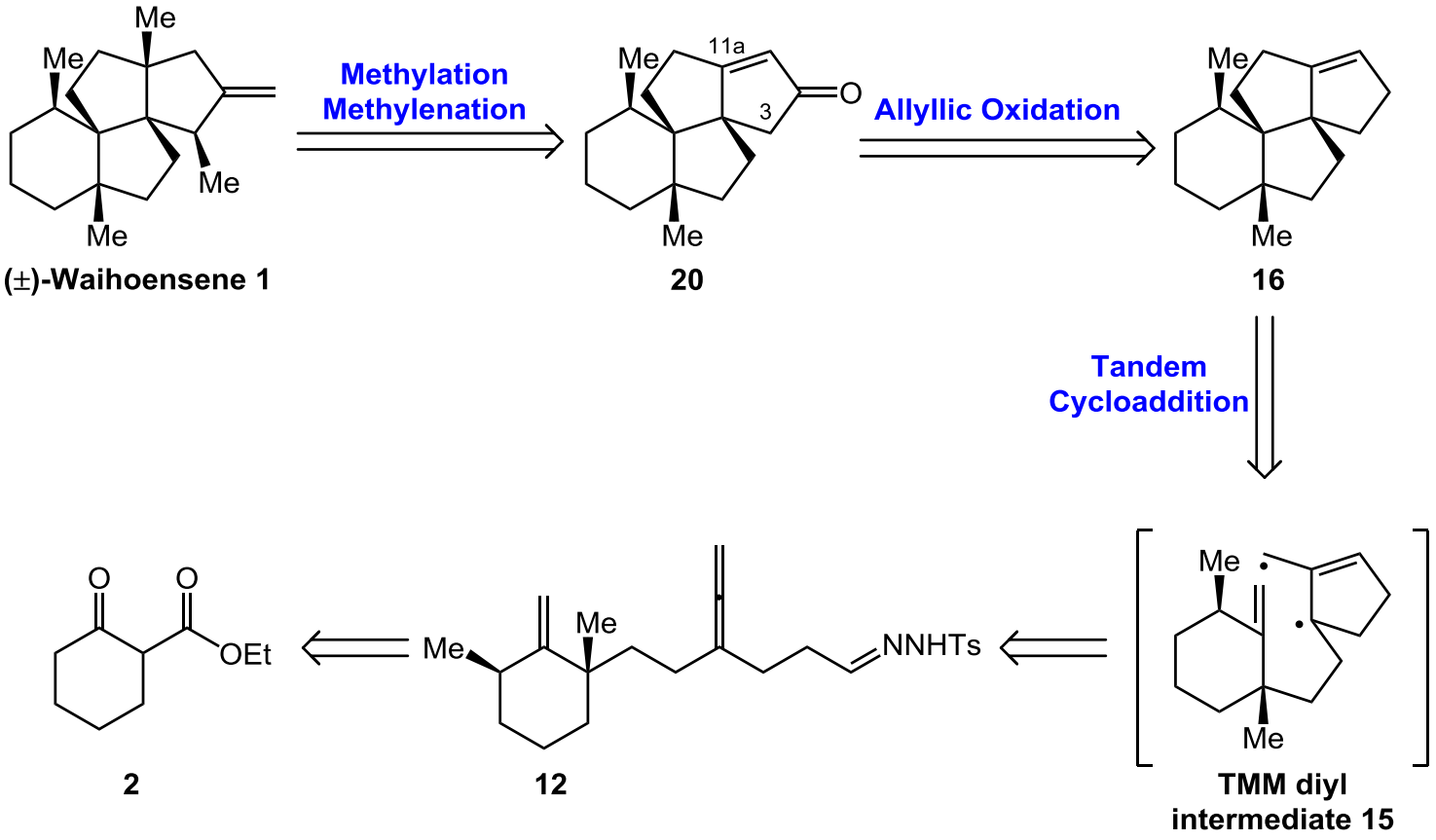
(+)-Waihoensene

Podocarpus totara var. waihoensis

- Isolated from the New Zealand podocarp, *Podocarpus totara var. waihoensis* in 1997.
- A highly congested and *cis*-fused tetracyclic core decorated with six contiguous stereogenic centers, among them, four are contiguous all-carbon quaternary carbon atoms.

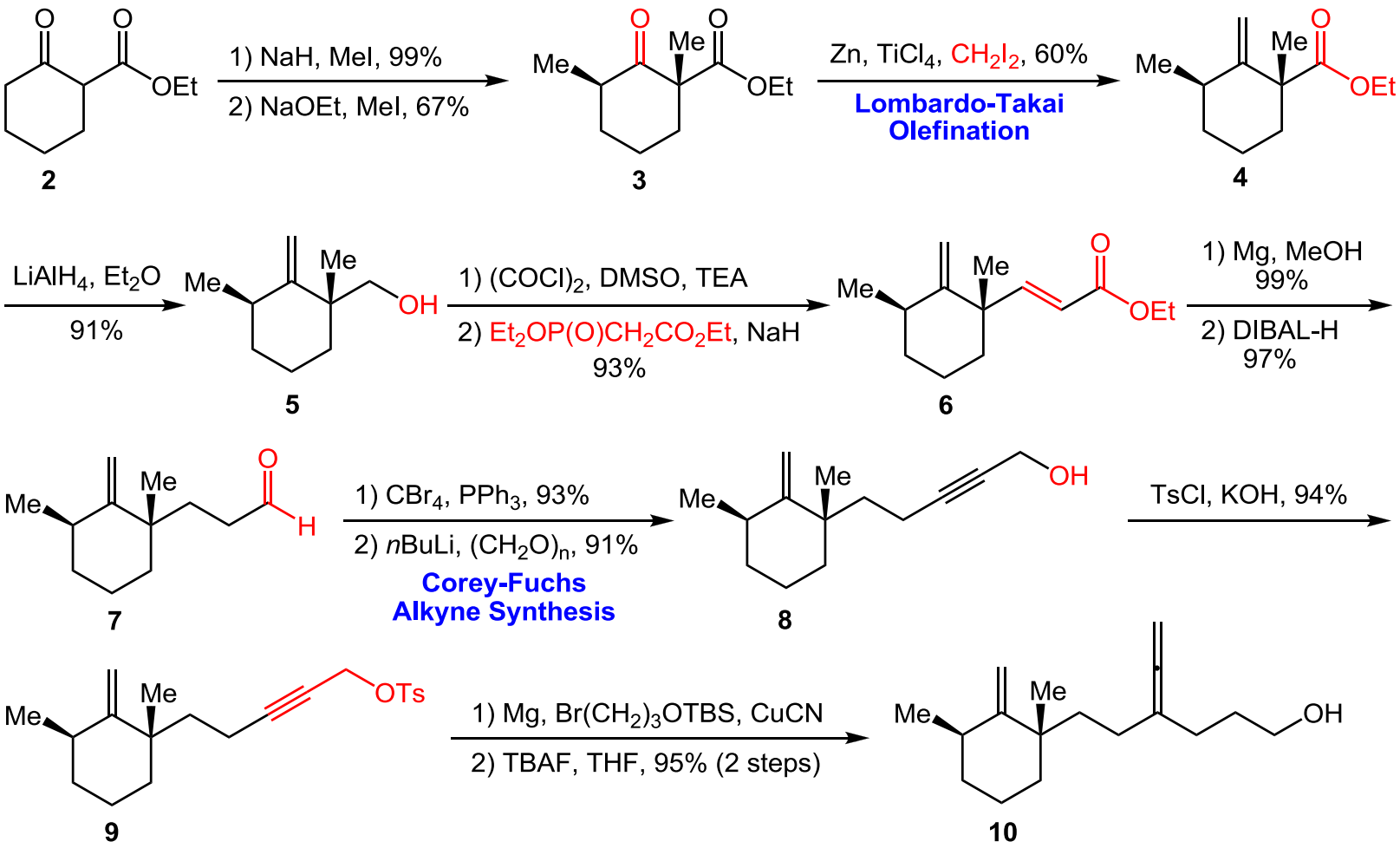
Weavers, R. T. *et al. Tetrahedron Lett.* **1997**, *38*, 4297.

Retrosynthetic Analysis

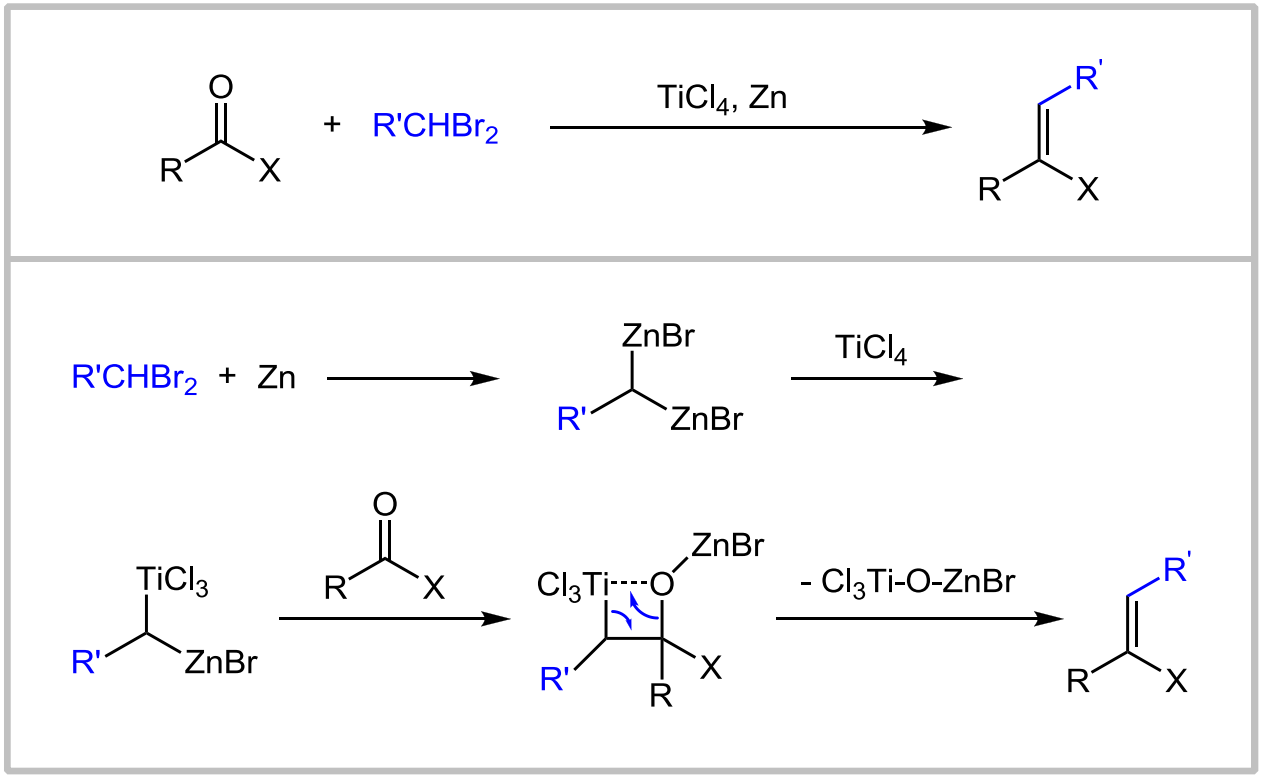


Lee, H.-Y. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 8254.

Synthesis of Compound 10

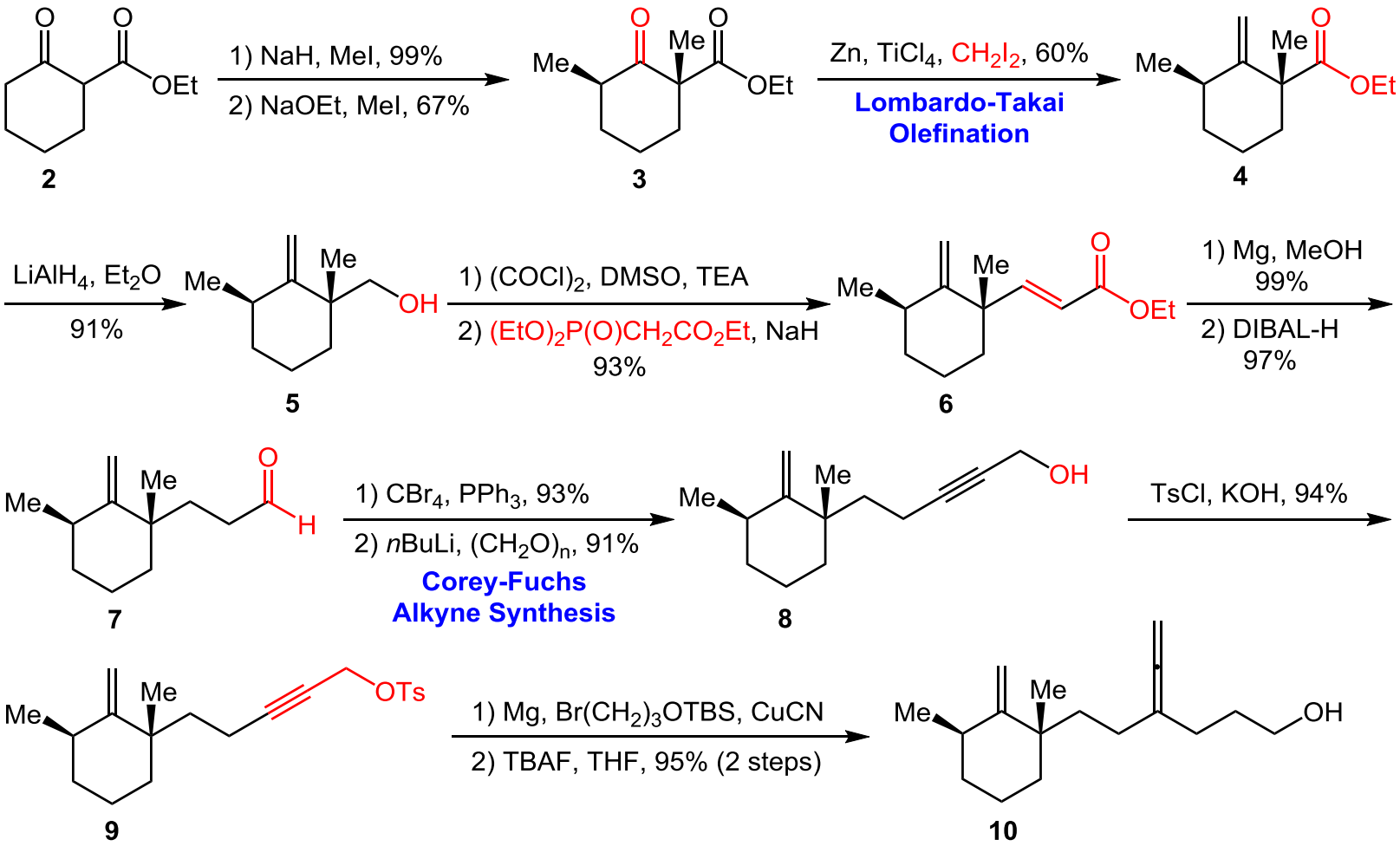


Lombardo-Takai Olefination

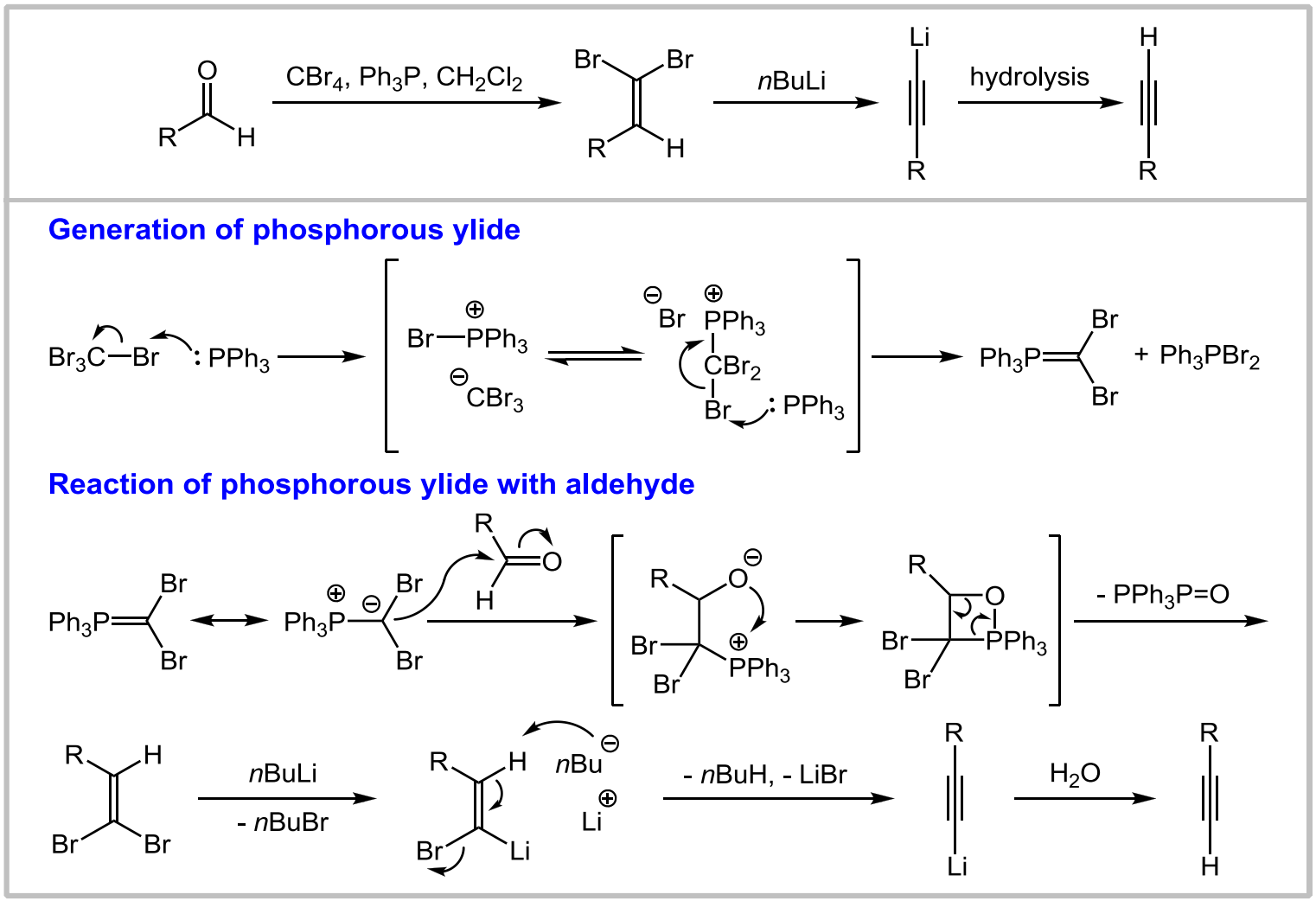


Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293;
Takai, K. *et al. Tetrahedron Lett.* **1978**, *19*, 2417.

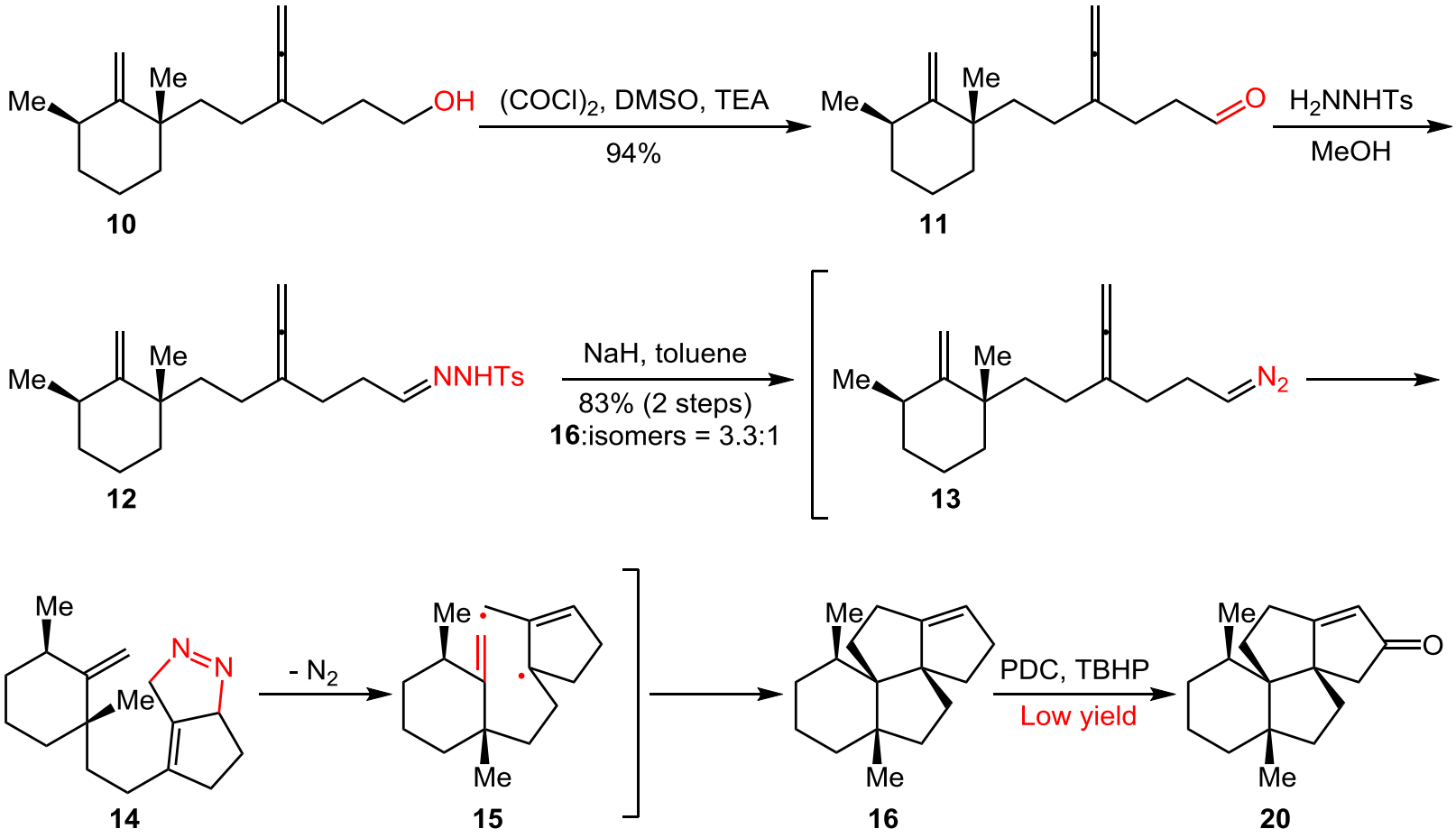
Synthesis of Compound 10



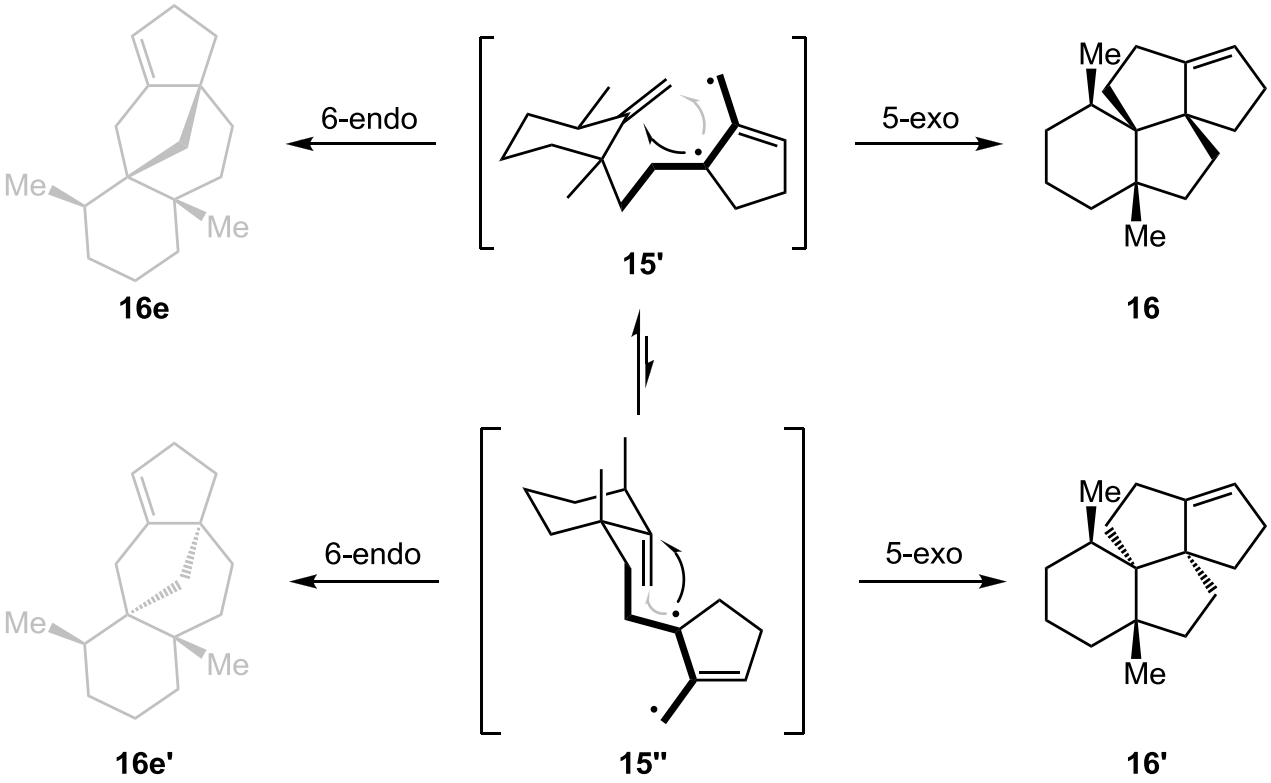
Corey-Fuchs Alkyne Synthesis



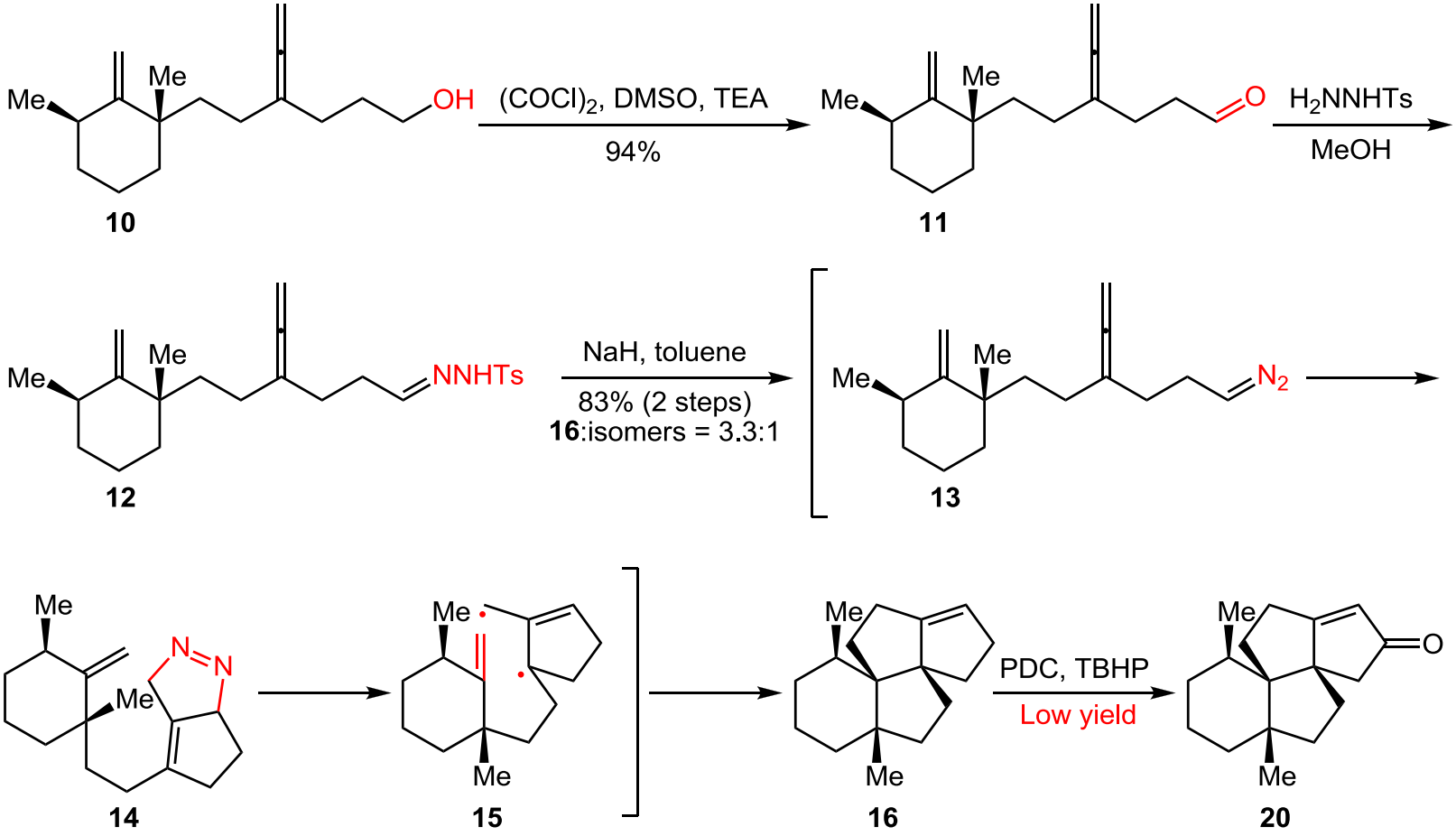
Synthesis of Compound 16



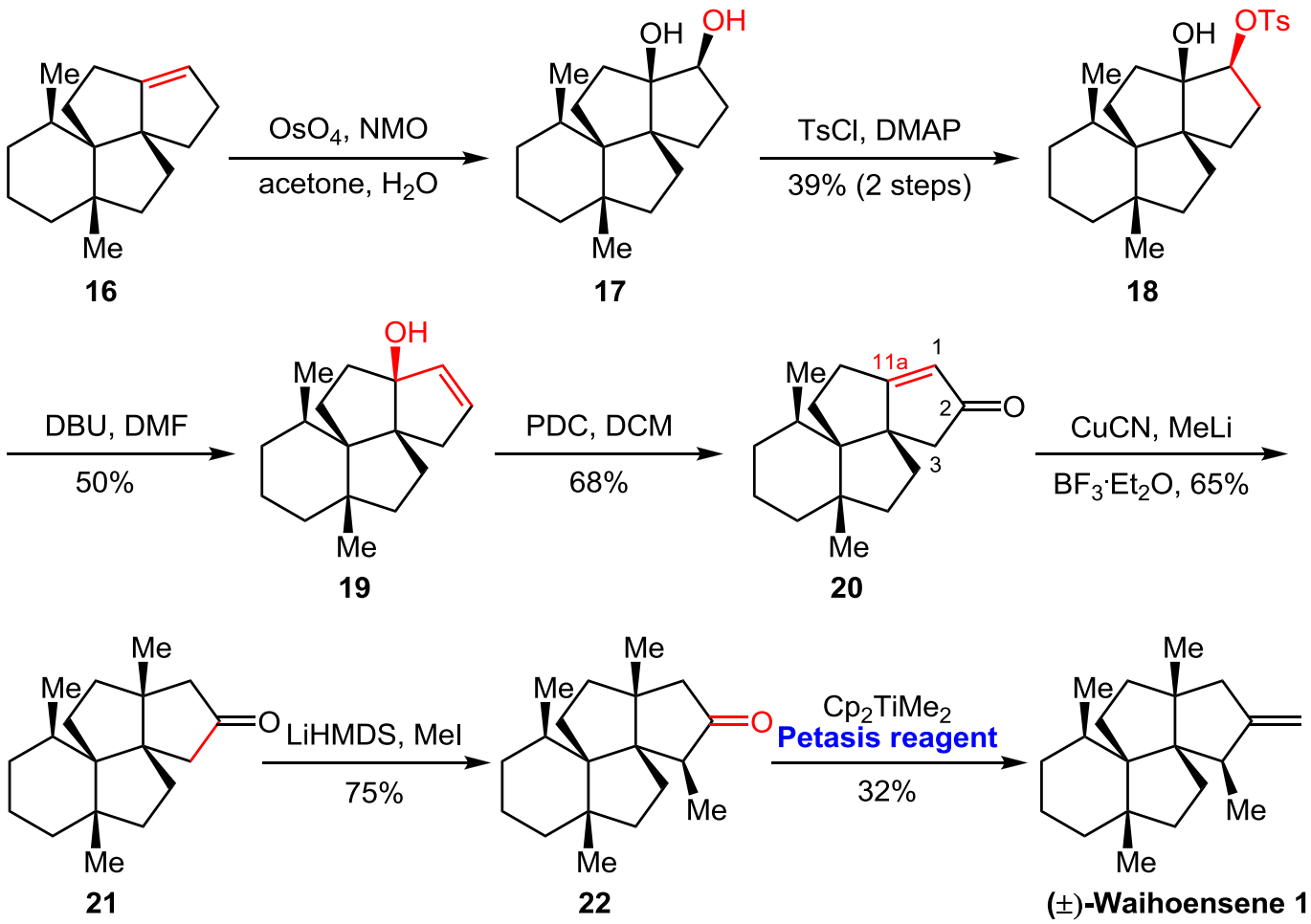
Possible Products From 15’ and 15”



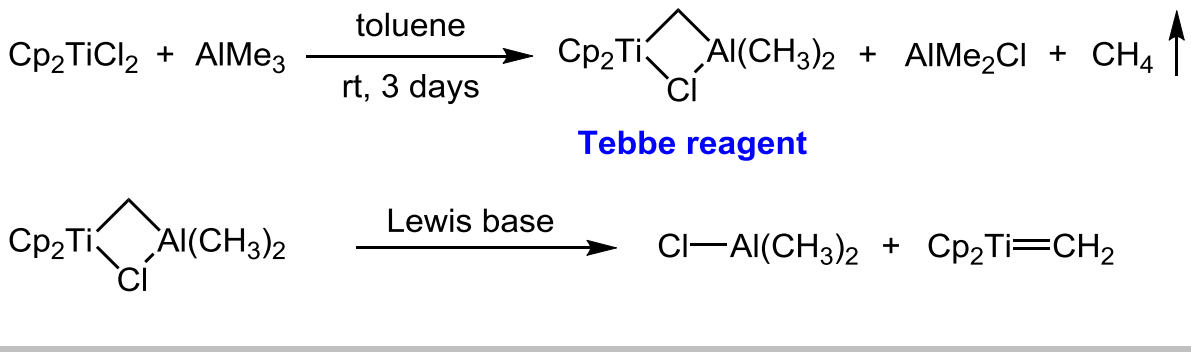
Synthesis of Compound 16

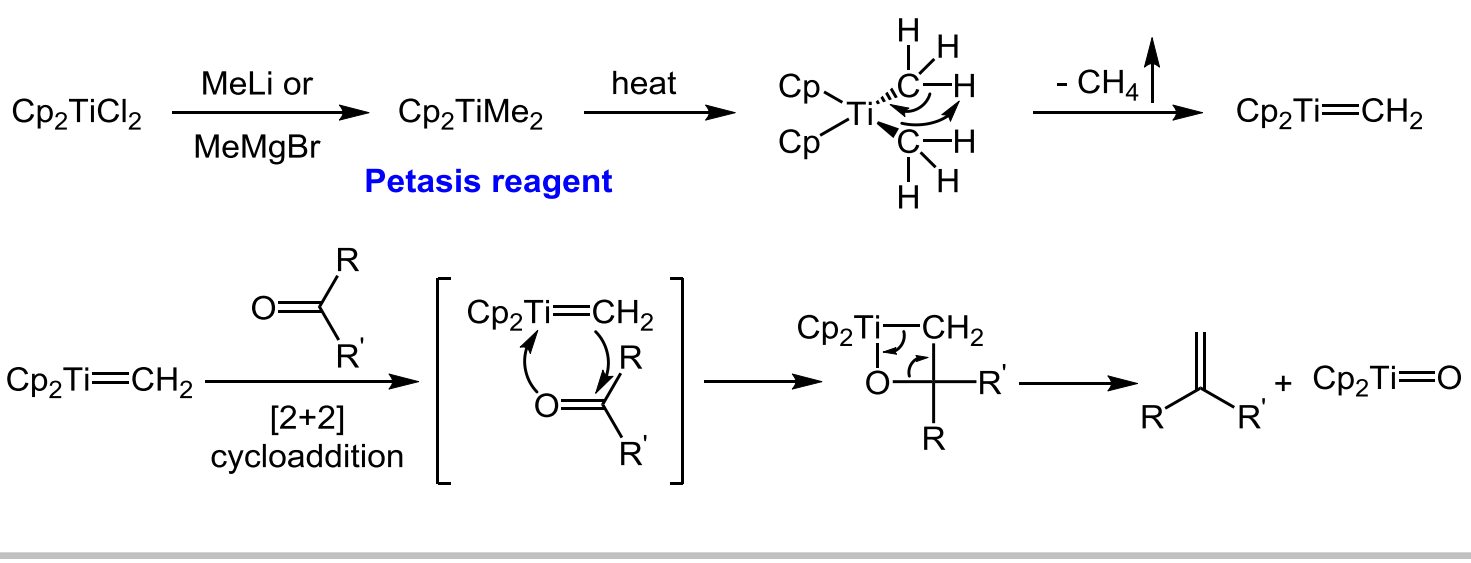


Synthesis of (±)-Waihoensene 1

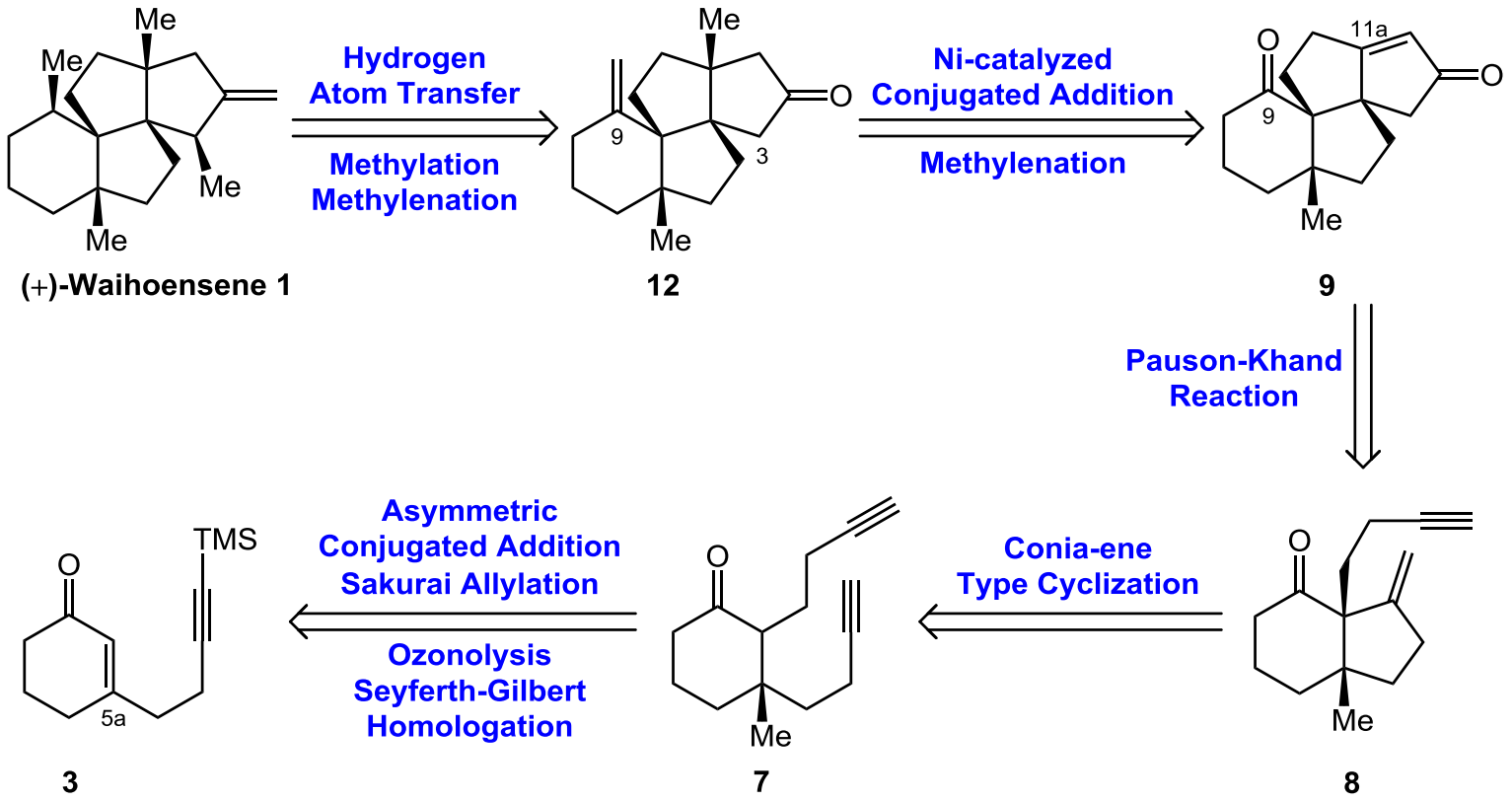


Tebbe Reagent and Petasis Reagent





Retrosynthetic Analysis



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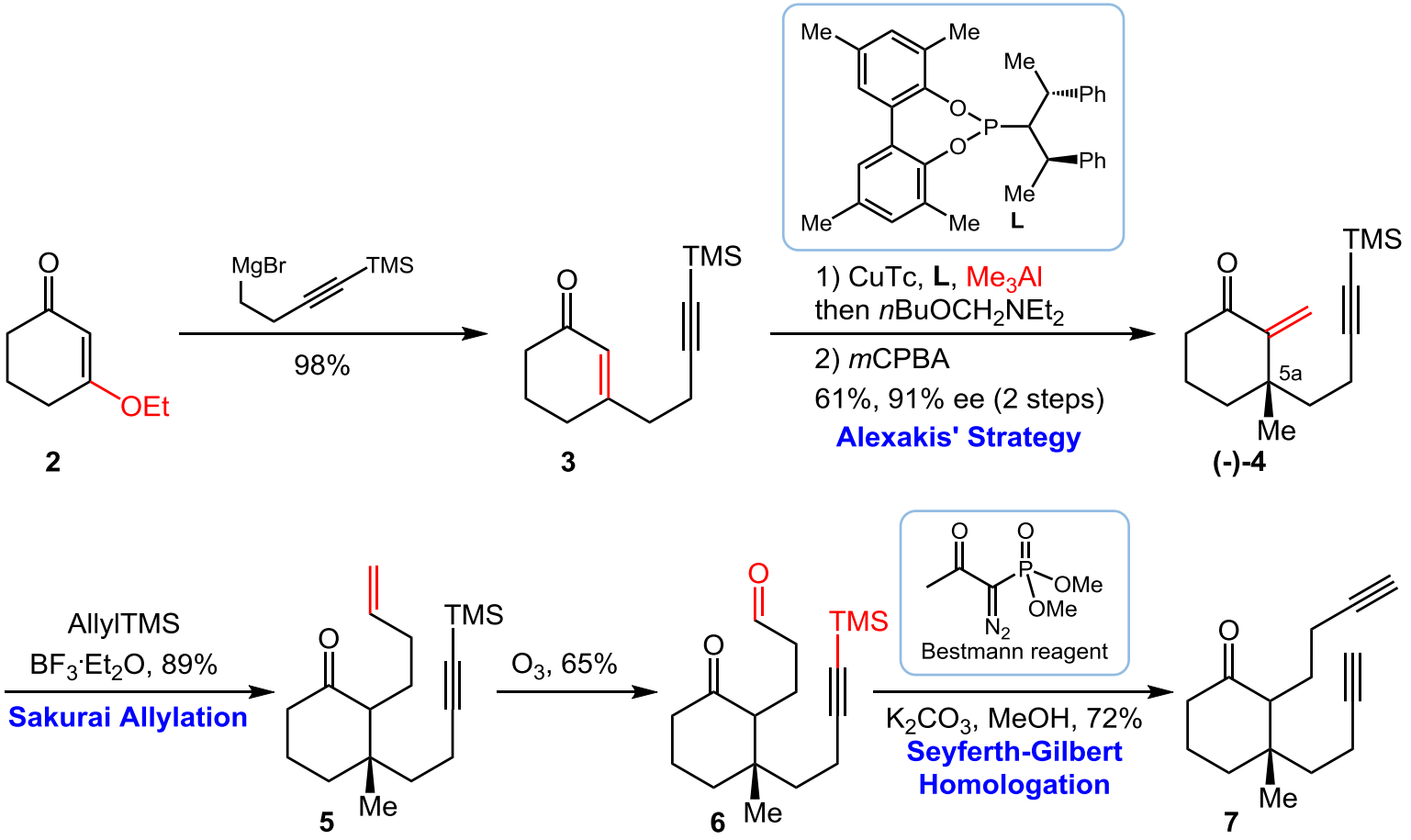
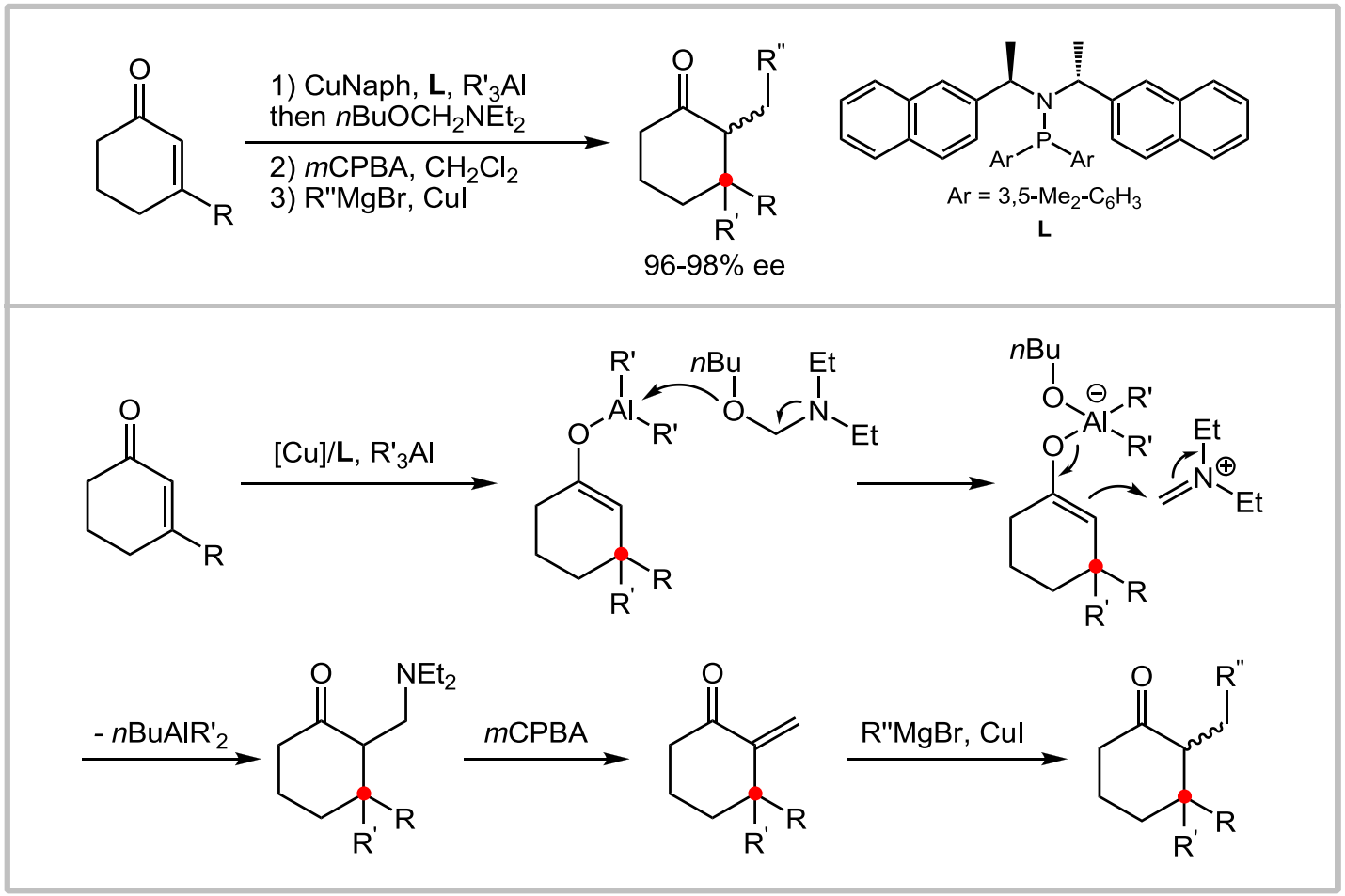
Synthesis of Compound 7

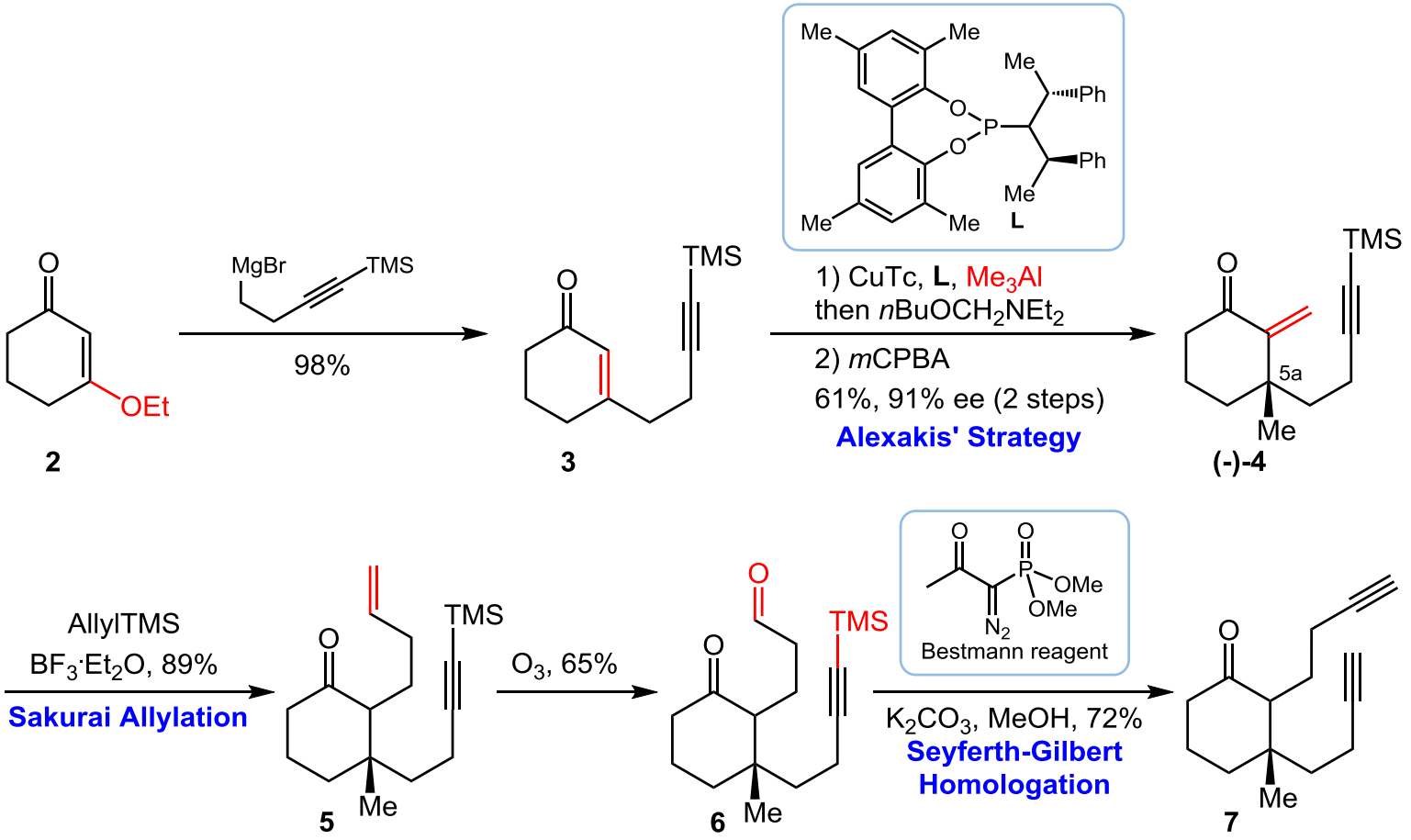


Alexakis' strategy

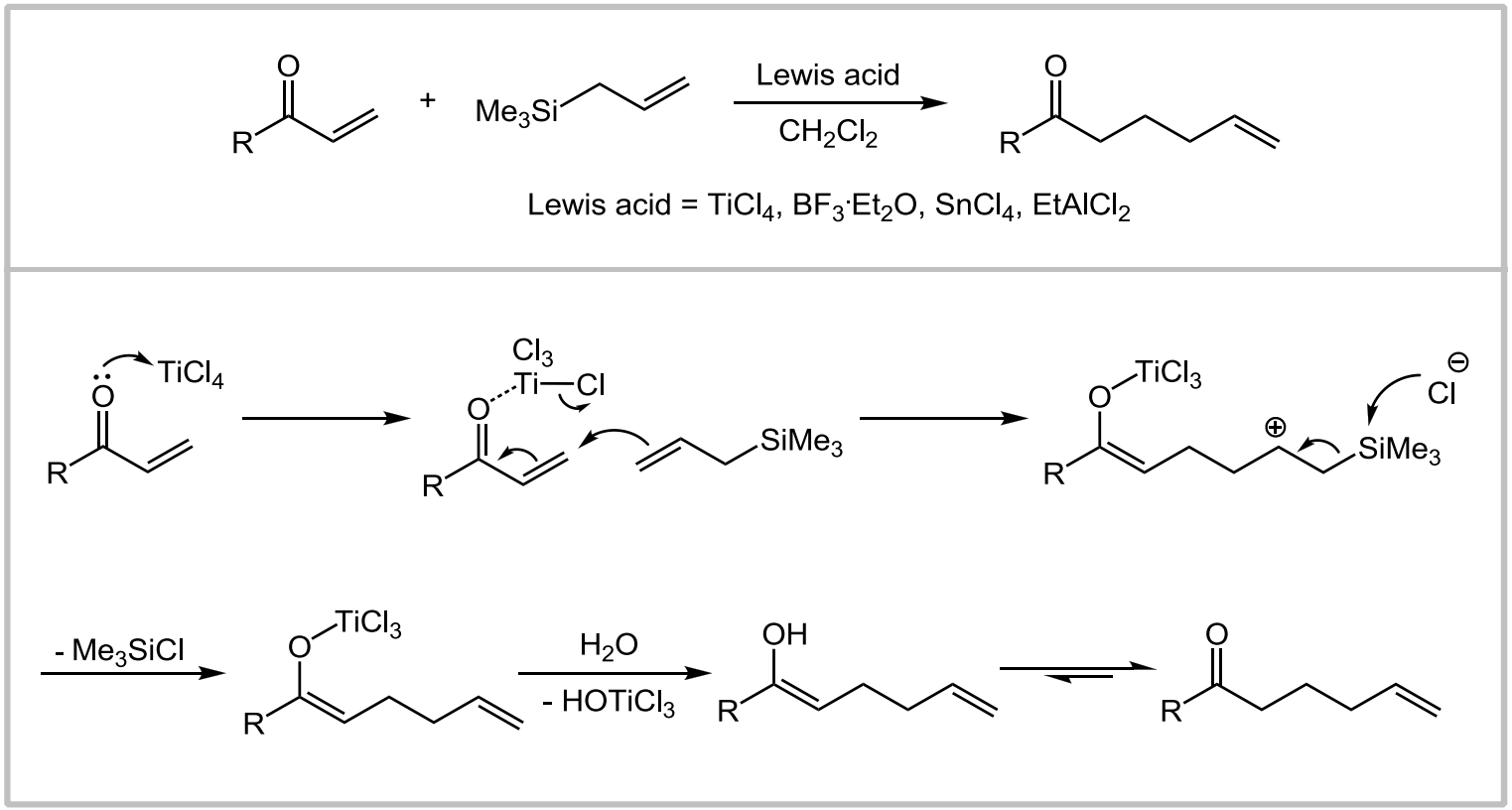


Alexakis, A. *et al*. *Org. Lett.* **2013**, *15*, 2152.

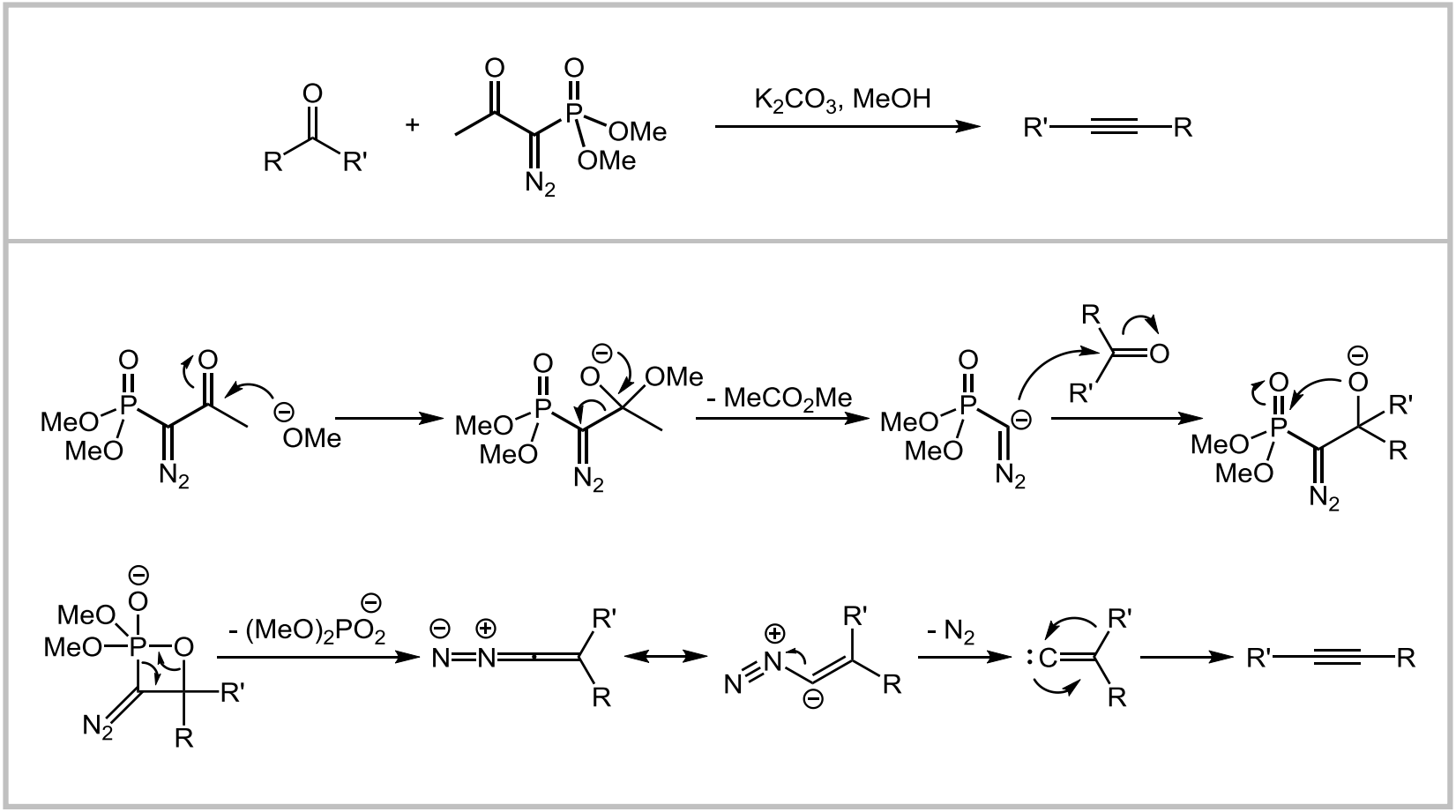
Synthesis of Compound 7



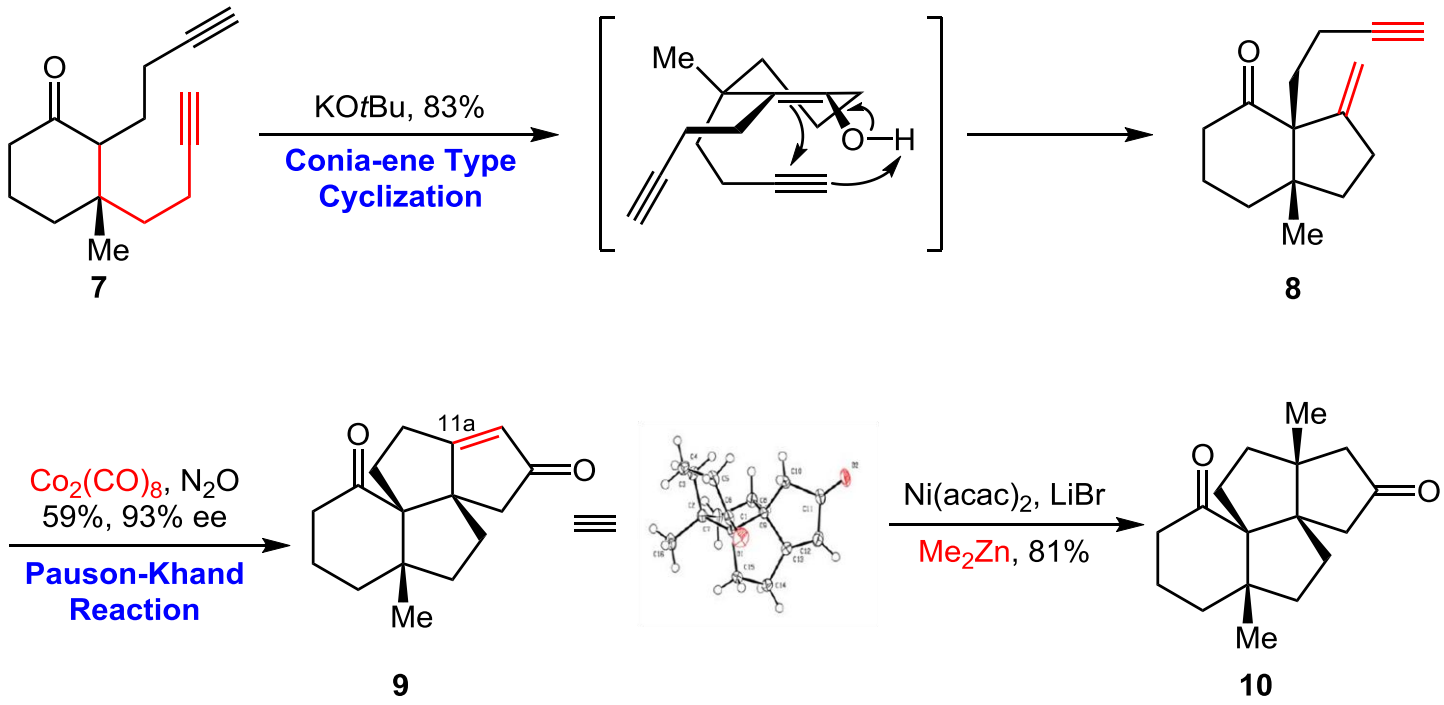
Sakurai Allylation



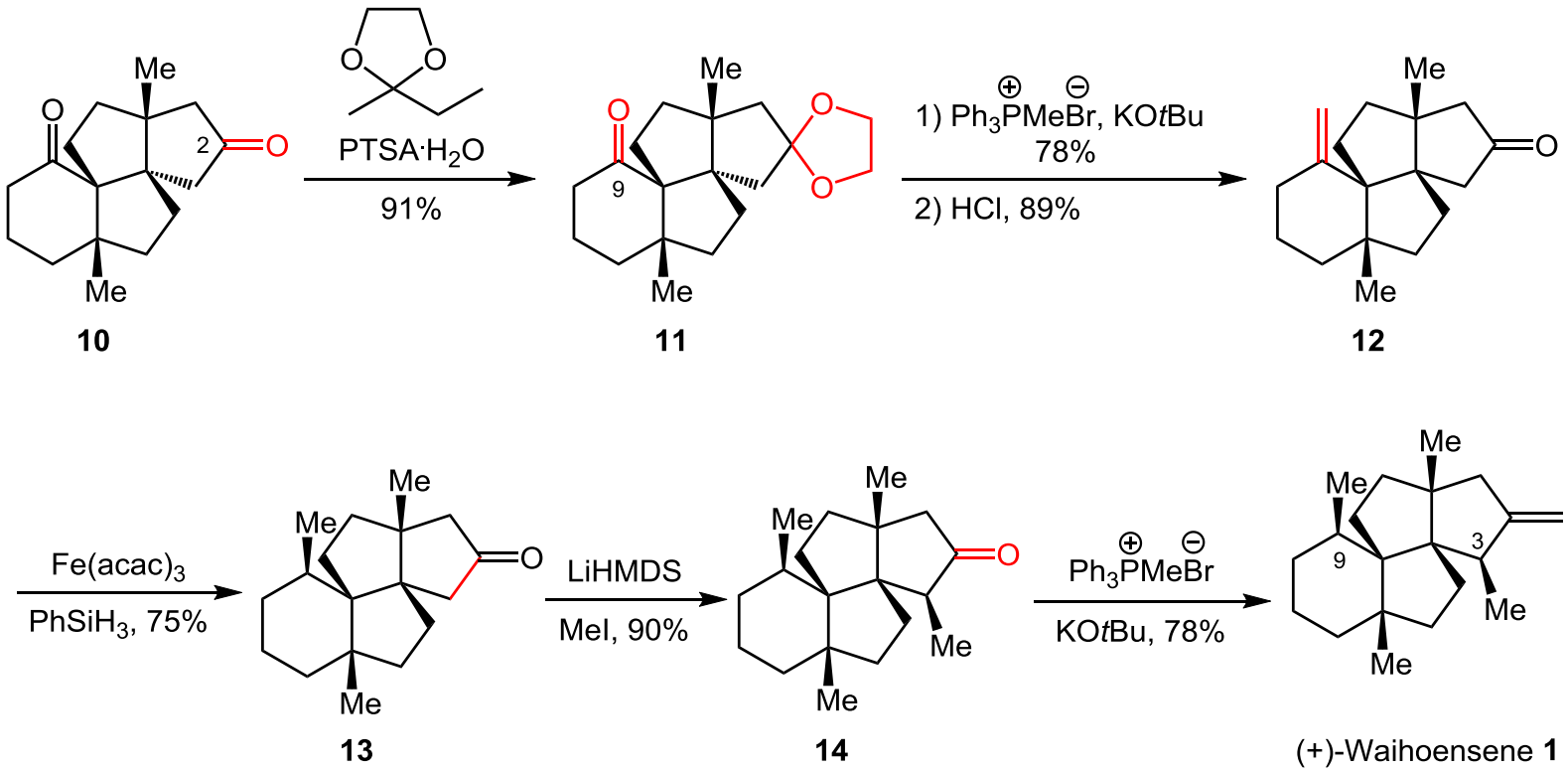
Seyferth-Gilbert Homologation



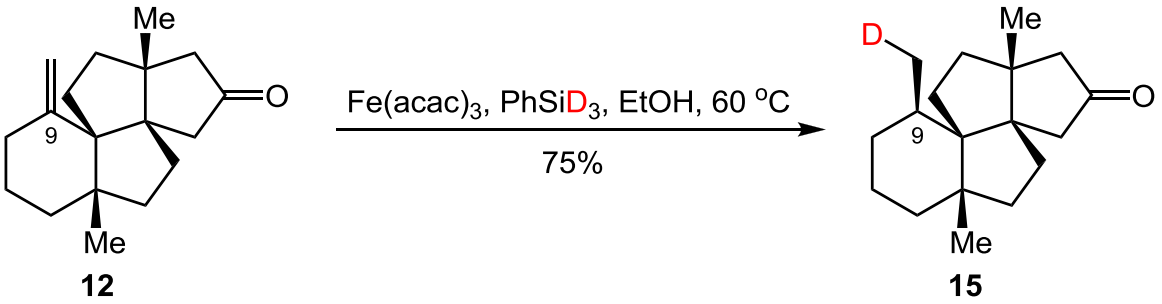
Synthesis of Compound 10

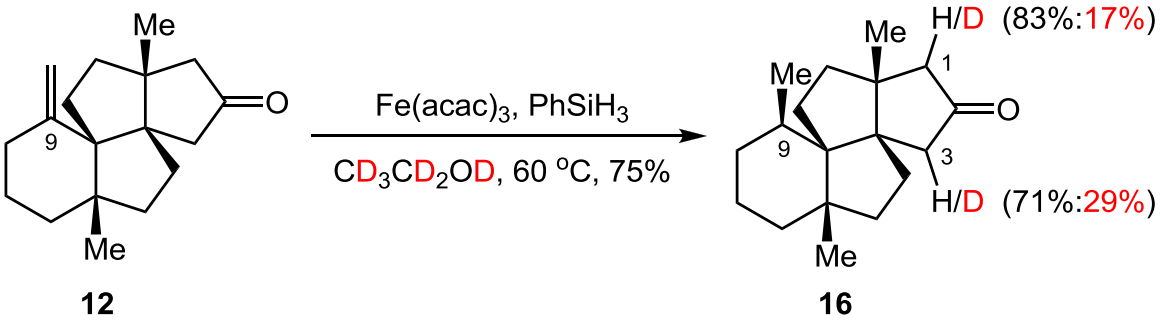


Synthesis of (+)-Waihoensene 1



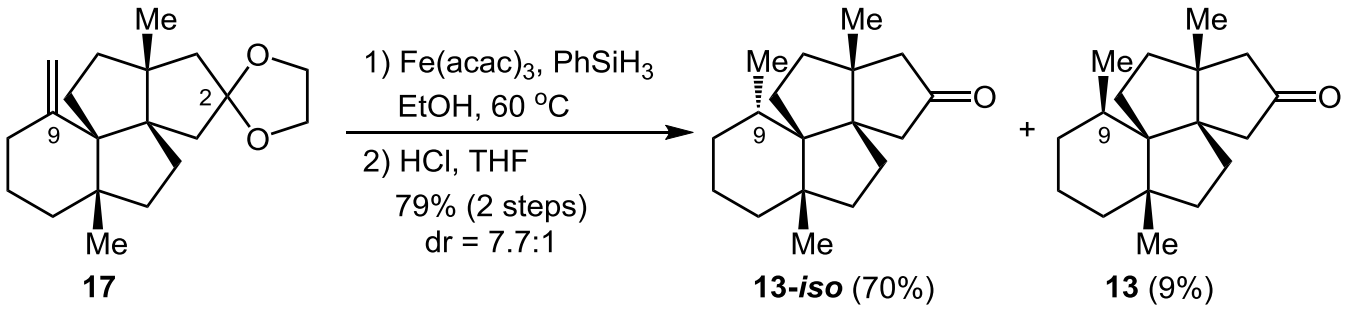
Deuterium Labeling Studies



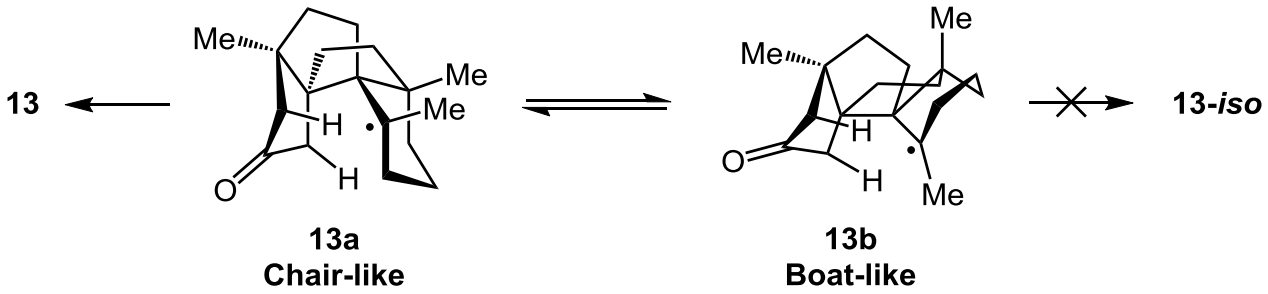


Control Experiment and Conformation 13a

Control Experiment

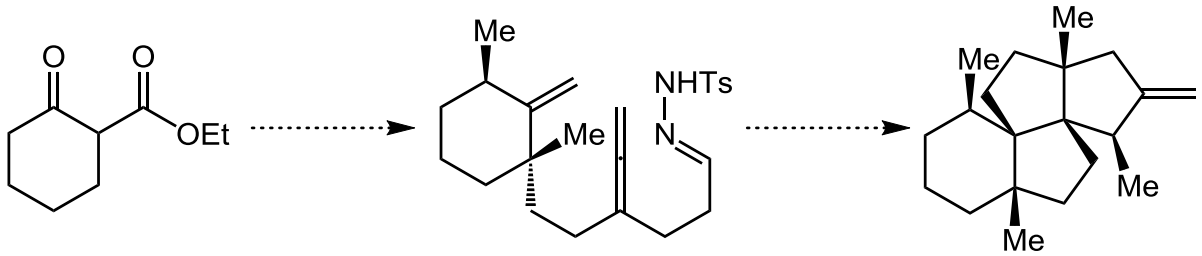


Conformational Isomerization of 13a



Summary

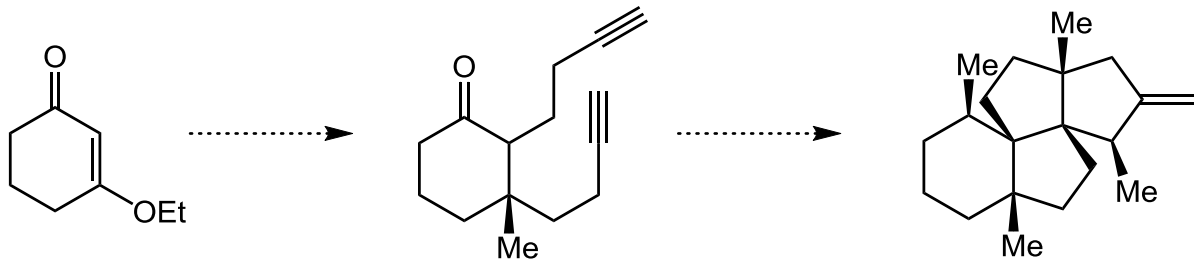
Lee's Group in 2017



(±)-Waihoensene

- First total synthesis, 18 steps, 0.3% overall yield
- **Intramolecular tandem [2+3] cycloaddition**

Yang's Group in 2020



(+)-Waihoensene

- Asymmetric total synthesis, 15 steps, 3.8% overall yield
- **Cu-catalyzed asymmetric conjugated addtion; Conia-ene type reaction; Intramolecular Pauson-Khand reaction; Radical-initiated intramolecular hydrogen atom transfer**

The First Paragraph

Writing Strategy

The importance of polyquinanes

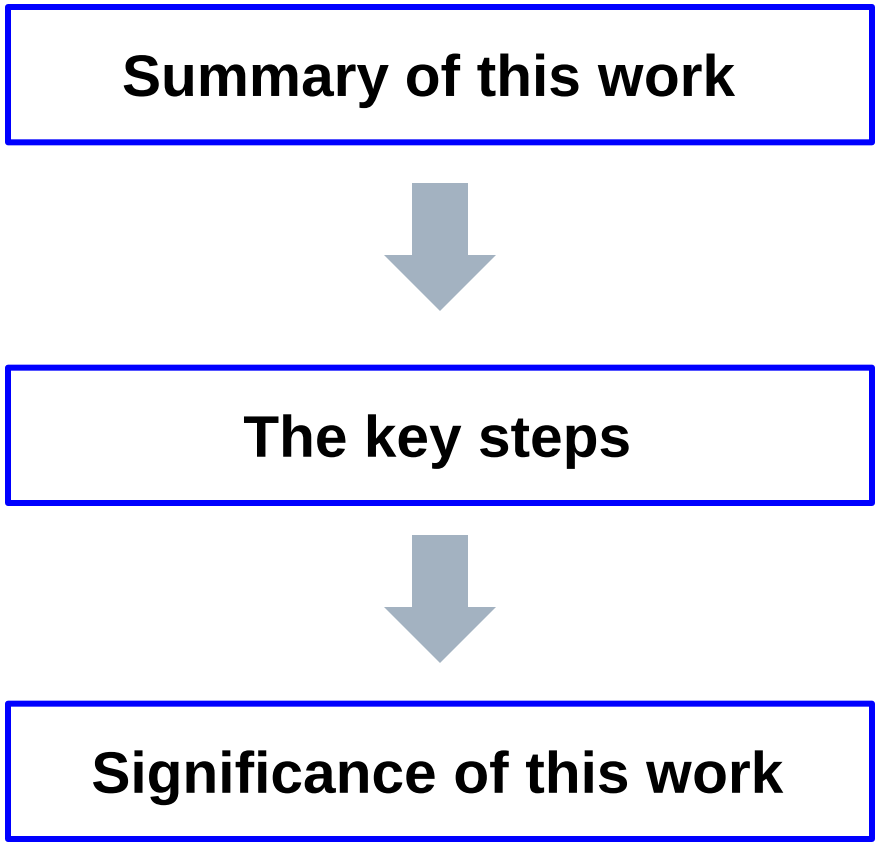
The isolation and structural features of (+)-waihoensene

The First Paragraph

Polyquinanes constitute an important class of carbocyclic frame-works containing fused 5-membered rings and are found in various natural products, such as terpenoids and steroids. In 1997, Weavers and co-workers isolated (+)-waihoensene (**1**) from the New Zealand podocarp, Podocarpus totara var. waihoensis. Structurally, **1** contains a highly congested and cis-fused tetracyclic core decorated with six contiguous stereogenic centers; among them, four are contiguous all-carbon quaternary carbon atoms (C3a, C5a, C9a, and C11a). Thus, **1** was widely regarded as a challenging target for total synthesis.

The Last Paragraph

Writing Strategy



The Last Paragraph

In summary, the asymmetric total synthesis of (+)-waihoensene has been achieved for the first time in 15 steps and 3.8% overall yield. The key step in this total synthesis was identification of the $Fe(acac)_3/PhSiH_3$-mediated intramolecular HAT reaction, which enabled the diastereoselective saturation of the exocyclic double bond of C9−C15 in **12** via both [1,4]- and [1,5]-HAT processes. The total synthesis also features an enantioselective construction of the angular triquinane core bearing four contiguous quaternary stereogenic centers via key steps: (1) a Cu-catalyzed asymmetric conjugate addition; (2) a Conia-ene type reaction; (3) a Co-mediated intramolecular PK reaction; and (4) a Ni-catalyzed alkylation. Application of this synthetic strategy to the total synthesis of other complex natural products is currently underway in our laboratories and will be reported in due course.

Representative Examples

Given its structural complexity, **1** has been a focus of the synthetic community for many years. (描述化合物的重要性)

In 2017, Lee and coworkers published an impressive synthesis of (±)-waihoensene for the first time in 18 steps, featuring a tandem [2+3] cycloaddition to construct the BCD tricyclic ring with two contiguous quaternary stereogenic centers. (阐述他人工作)

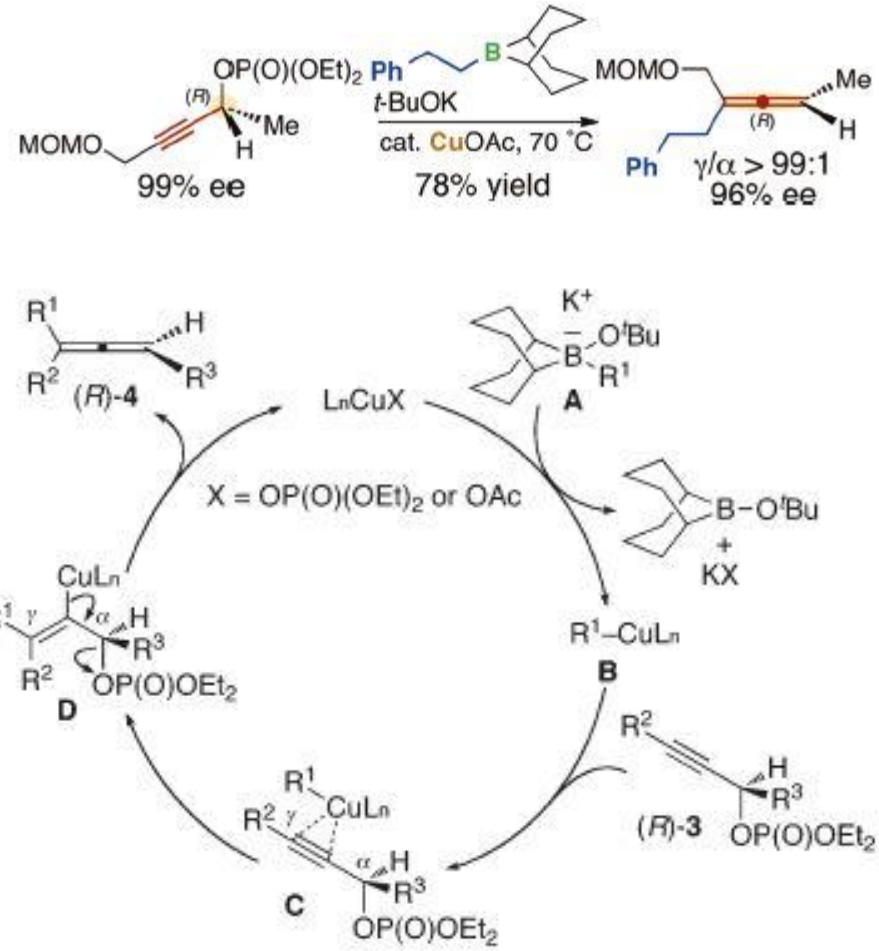
To this end, we initially profiled several typical PK reaction conditions. (条件优化)

We conjectured that the newly formed C9 carbon radical in **13a**, derived from a radical-mediated reductive reaction from **12**, could abstract a proton through an intramolecular HAT from the C3, due to the close proximity (2.4 Å) between the H atoms of C3 and C9 and their position next to the C2 carbonyl group. (提出设想)

Acknowledgement

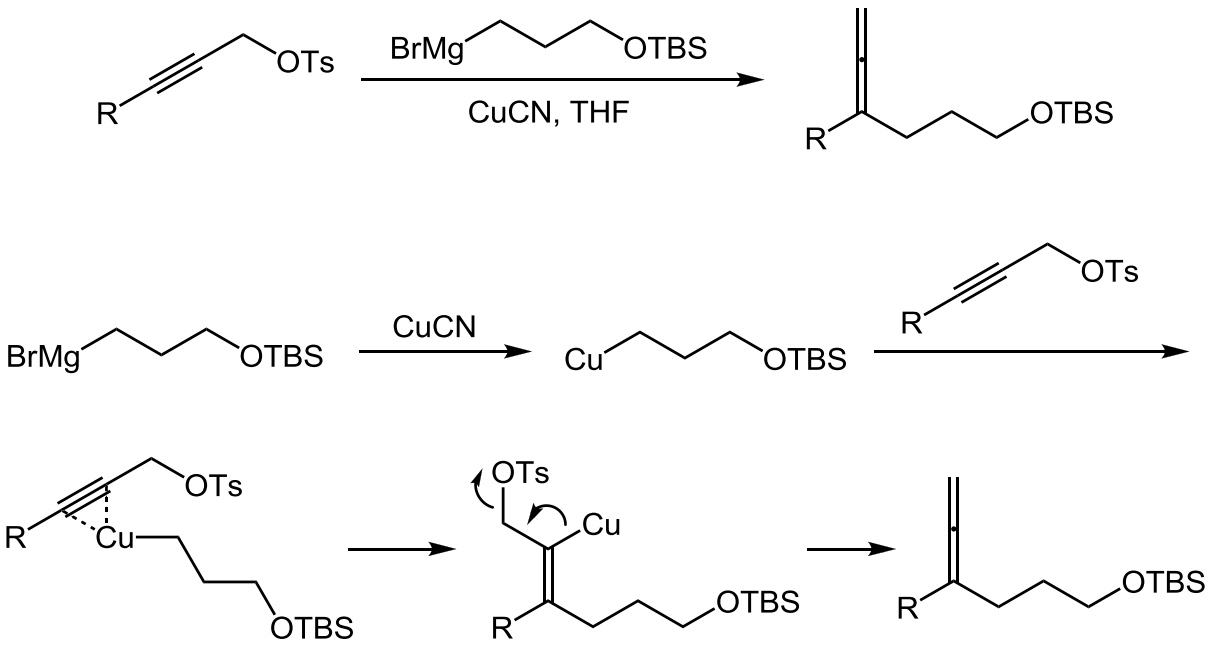
Thanks
for your attention

Copper(I)-catalyzed S_N2' Reaction

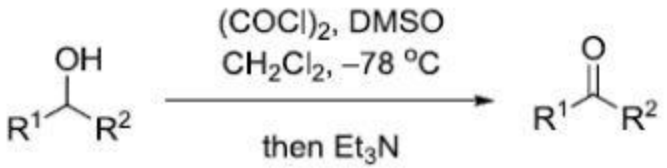


Sawamura, M. *et al*. *Org. Lett.* **2011**, *13*, 6312.

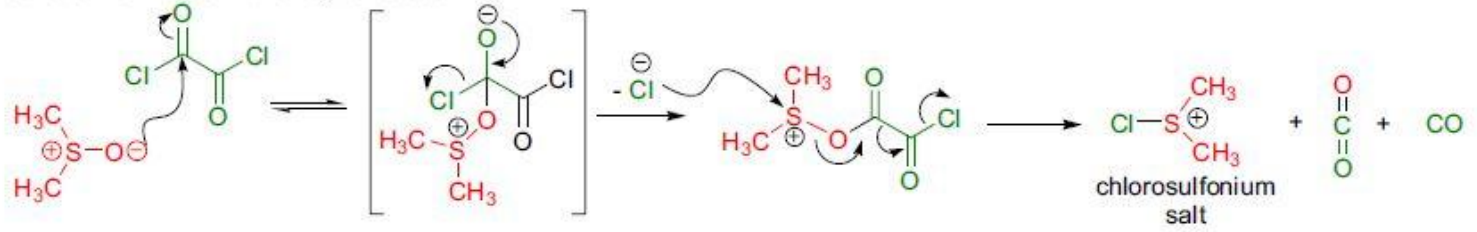
Copper(I)-catalyzed S_N2' Reaction



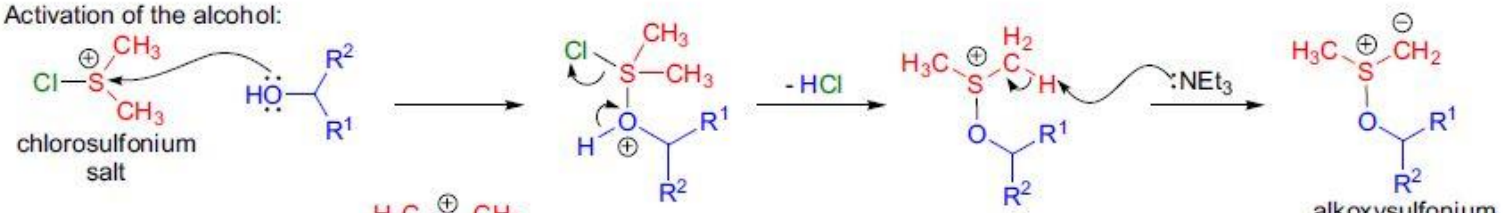
Swern Oxidation



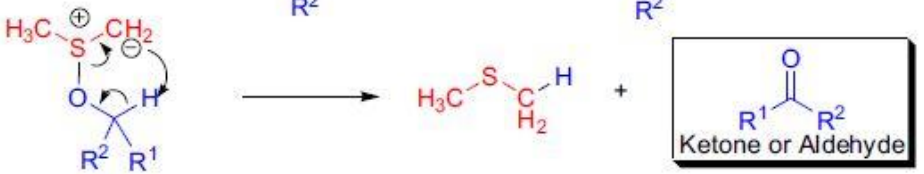
Activation of DMSO with oxalyl chloride:



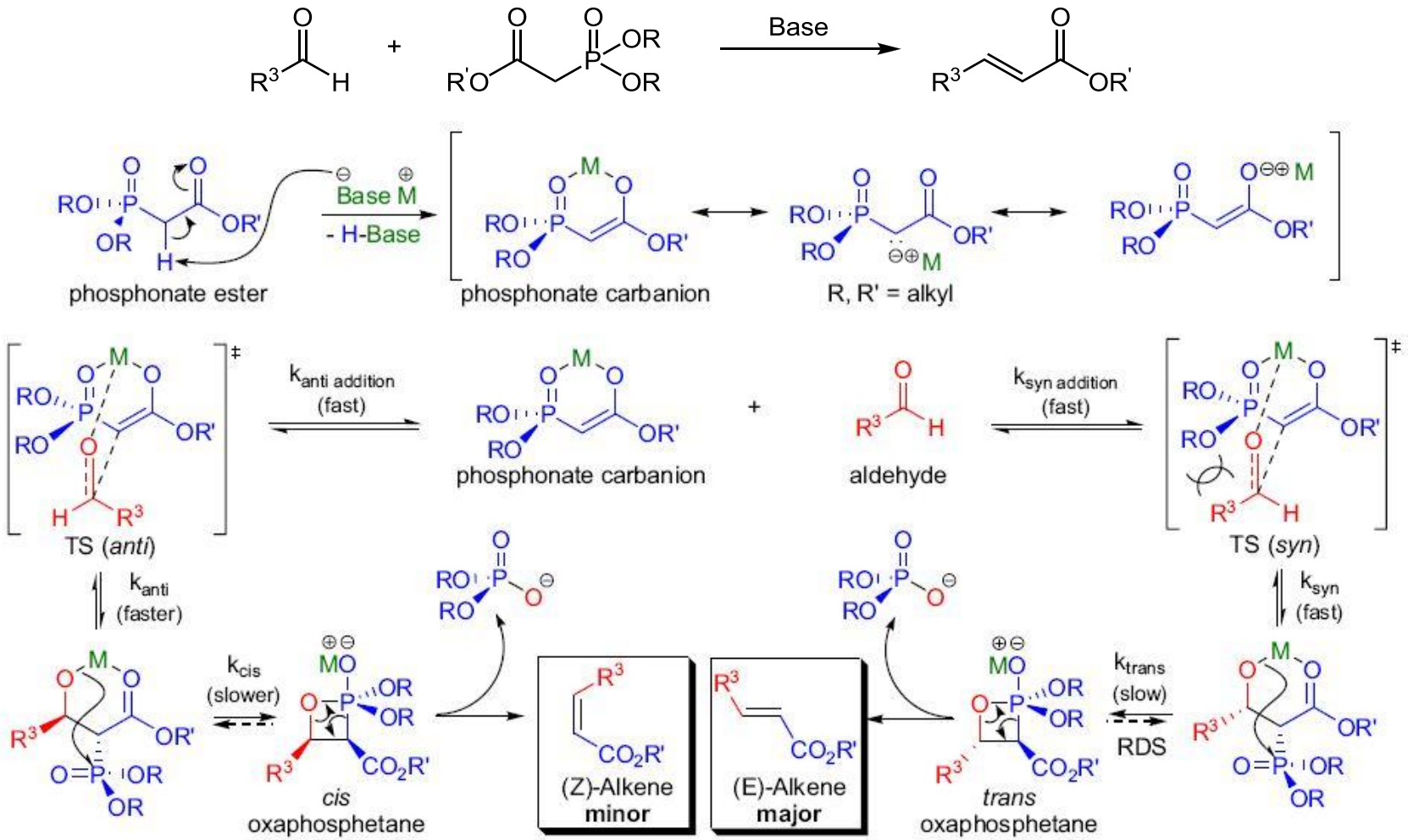
Activation of the alcohol:



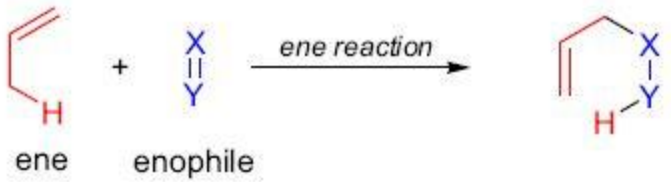
Formation of the product:

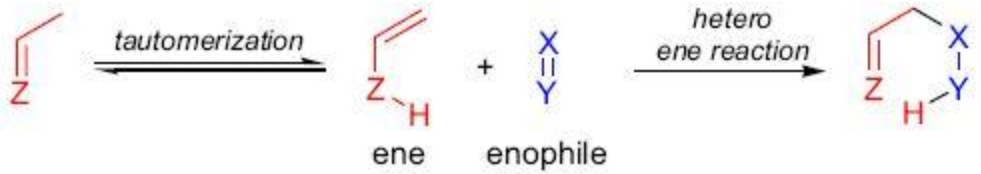


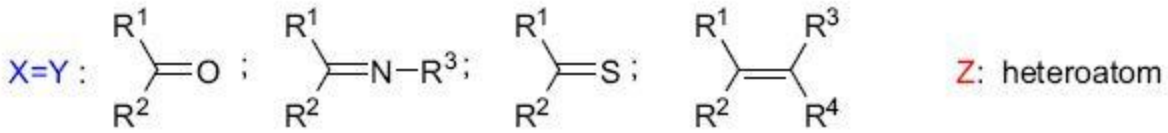
Horner-Wadsworth-Emmons Olefination

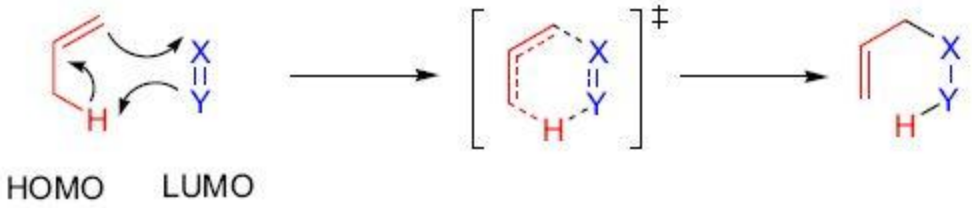


Ene Reaction

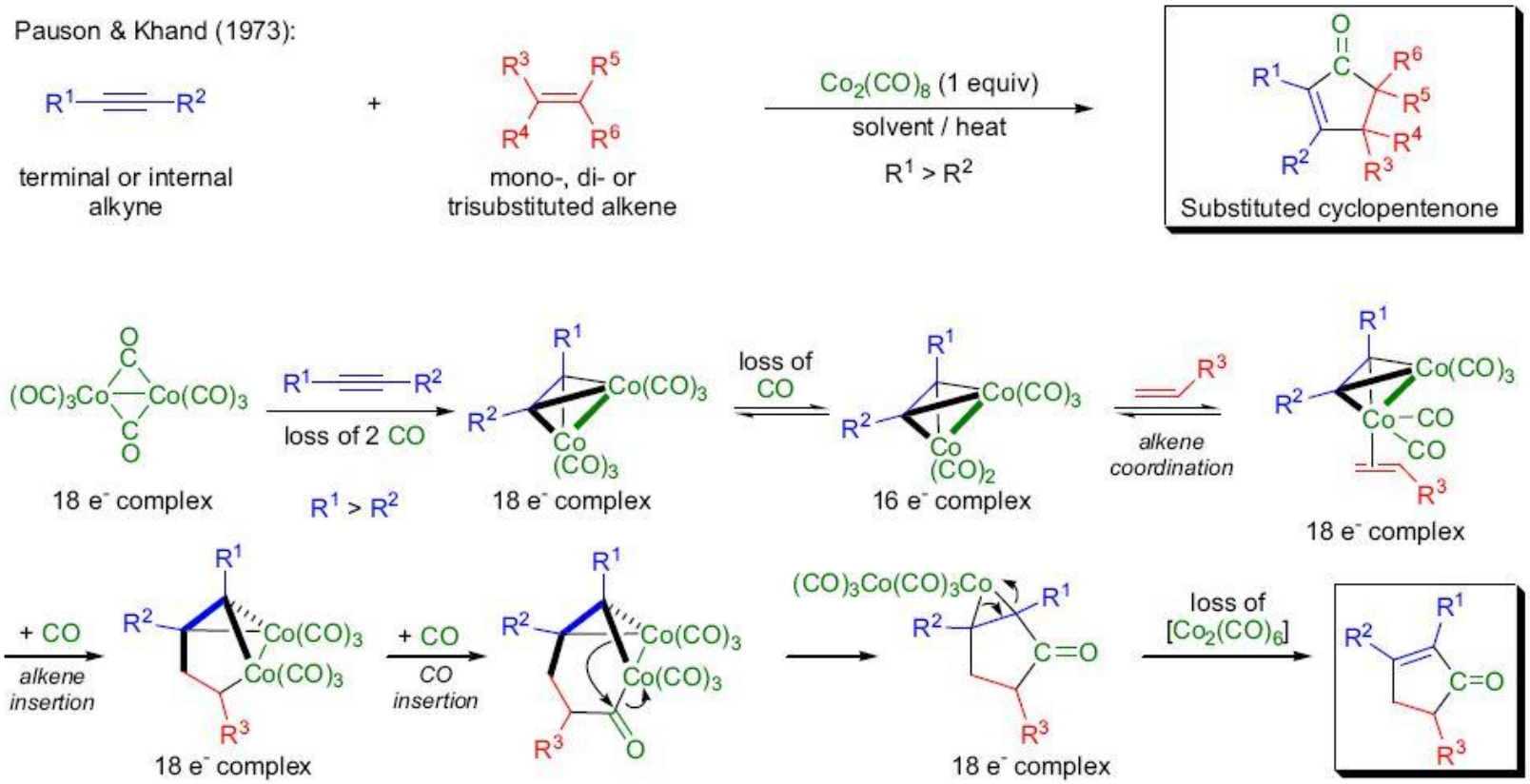




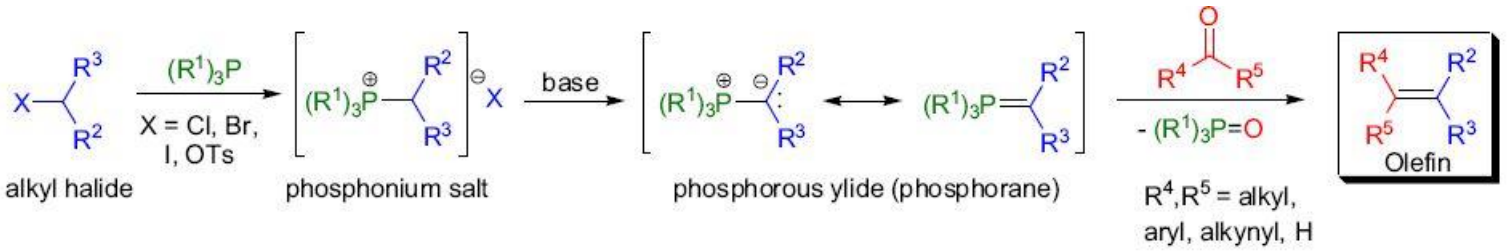




Pauson-Khand Reaction



Wittig Reaction



if R^1 = aryl and R^2, R^3 = alkyl, H ⟹ "nonstabilized" ylide

if R^1 = aryl and R^2, R^3 = aryl, alkenyl, benzyl, allyl, H ⟹ "semi-stabilized" ylide

if R^1 = aryl and R^2, R^3 = $-CO_2R$, $-SO_2R$, $-CN$, $-COR$ ⟹ "stabilized" ylide