Literature Report III

Enantioselective Total Synthesis of Bipolarolides A and B

Reporter: Shui-Long Lei

Checker: Xin-Yang Li

Liu, Y.; Sun, K.; Wei, Q.; Chen, J.; Sun, S.; Lu, Z.* *J. Am. Chem. Soc*. **2025**, *147*, 27219

2025-08-25

CV of Prof. Zhaohong Lu (陆钊洪)

Background:

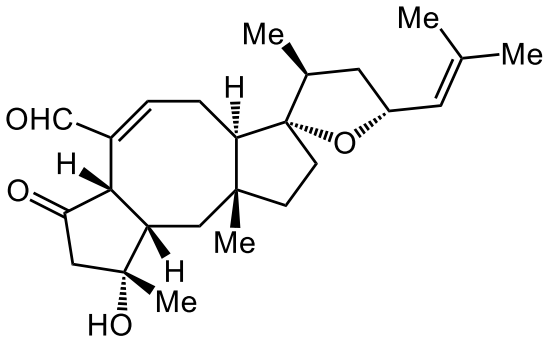
- **2006-2010** B.S., Sun Yat-sen University
- **2011-2016** Ph.D., Shanghai Institute of Organic Chemistry
- **2017-2020** Postdoctor, Massachusetts Institute of Technology
- **2020-Now** Assistant Professor, Professor, Xiamen University

Research Field:

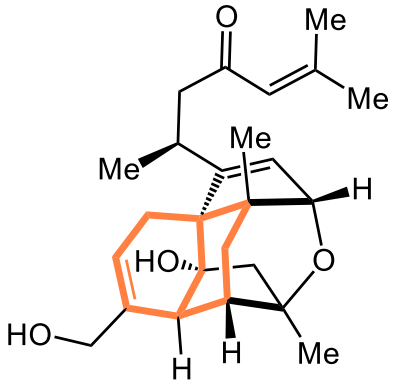
- Total Synthesis of Highly Bioactive Natural Product
- Organic Electrochemical Synthesis

Contents

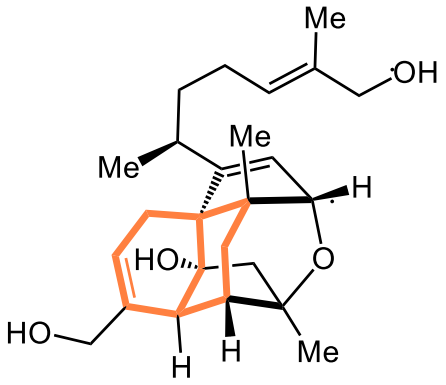
Introduction



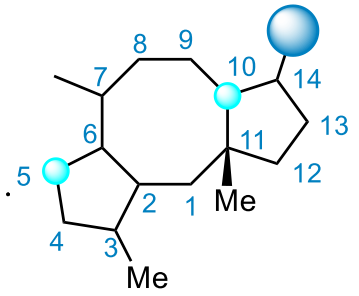
Ophiobolin A



Bipolarolide A



Bipolarolide B

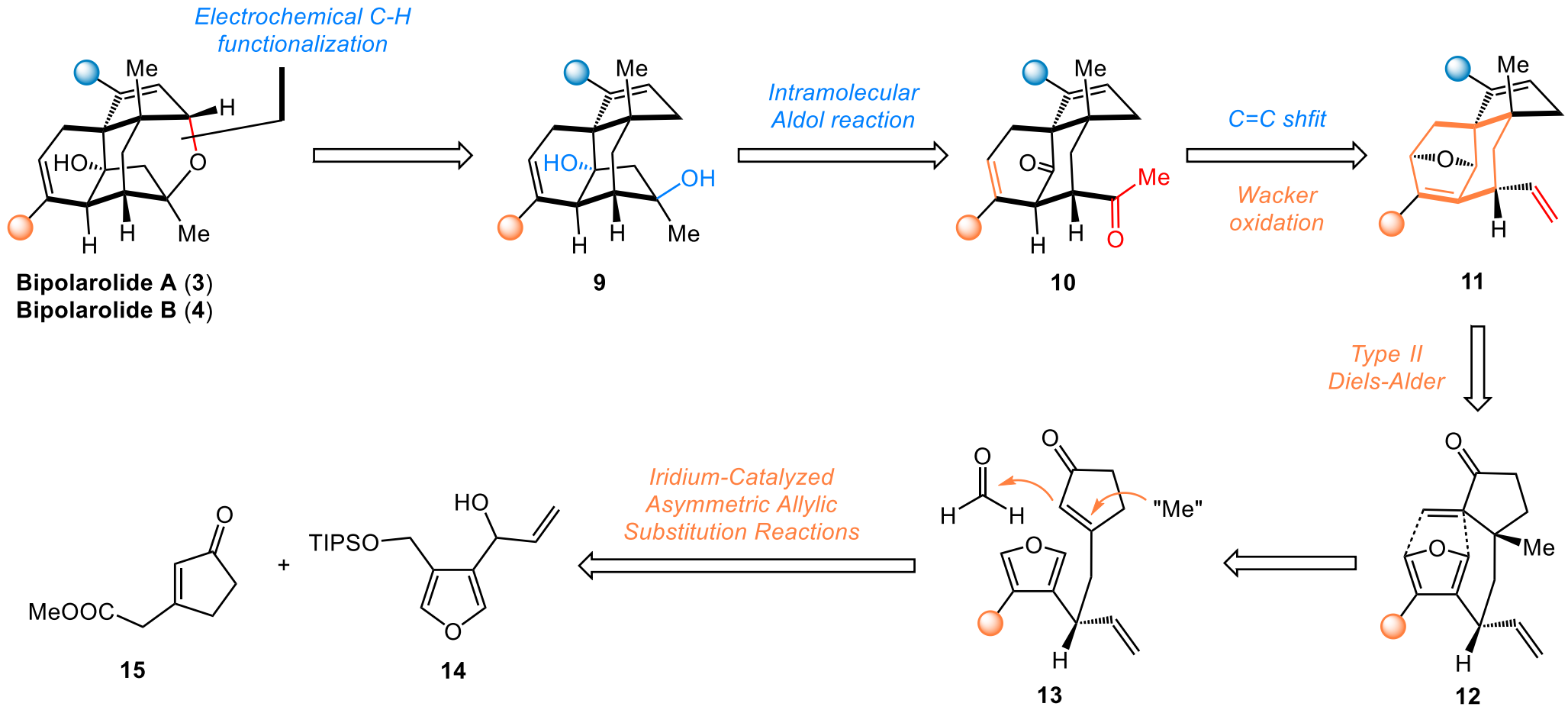


5/8/5 ring system ophiobolin core

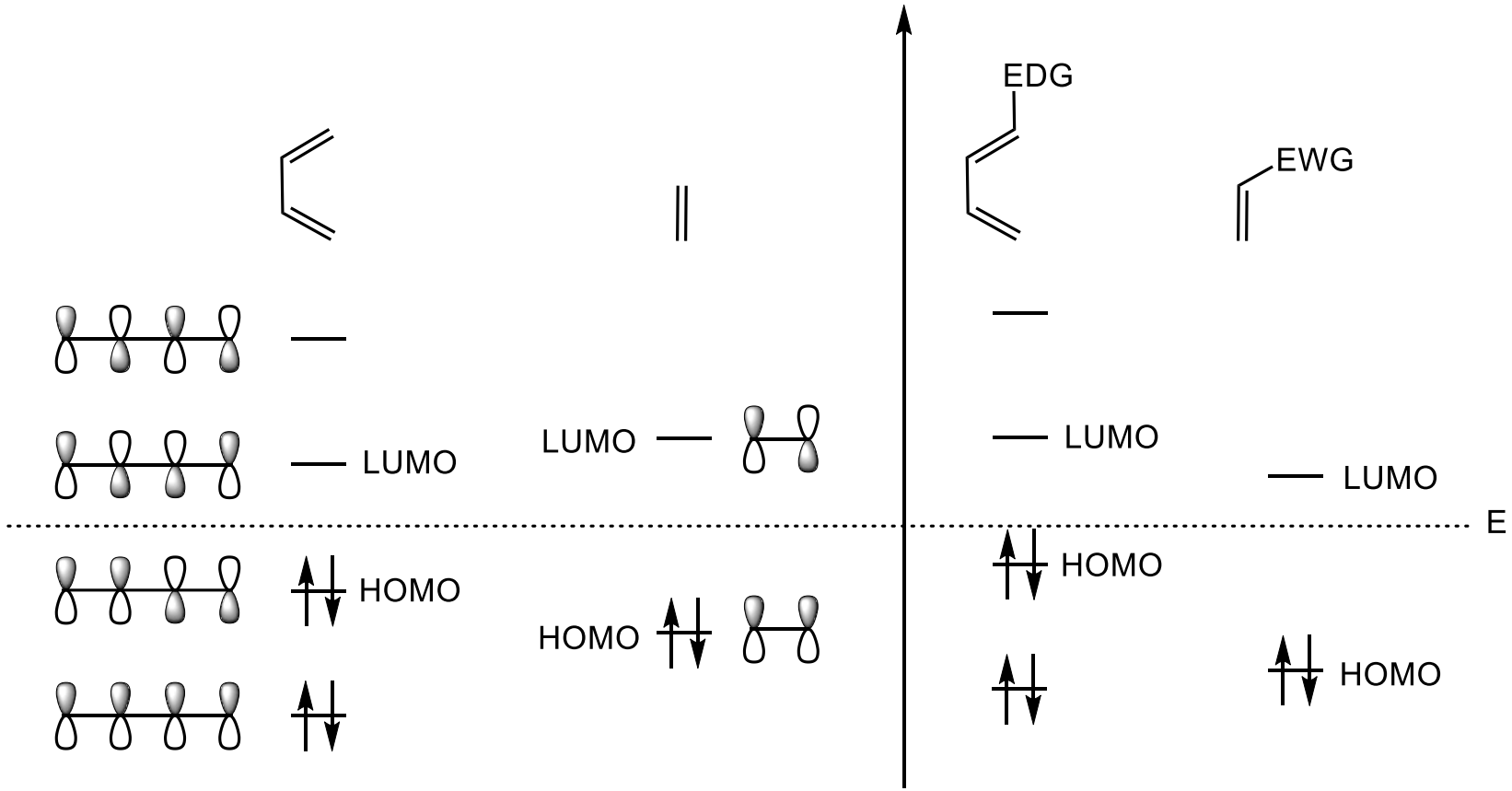
- Bipolarolides A and B derived from ophiobolin were first isolated in 2019.
- They have a novel skeletal framework characterized by a [3.3.1] bridged ring system adorned with three contiguous quaternary carbon centers.
- Bipolarolide A has been shown to exhibit significant cholesterol-lowering activity.

Liu, M.; Sun, W.; Shen, L.; He, Y.; Liu, J.; Hu, Z.;* Zhang, Y.* *Angew. Chem. Int. Ed.* **2019**, *58*, 12091

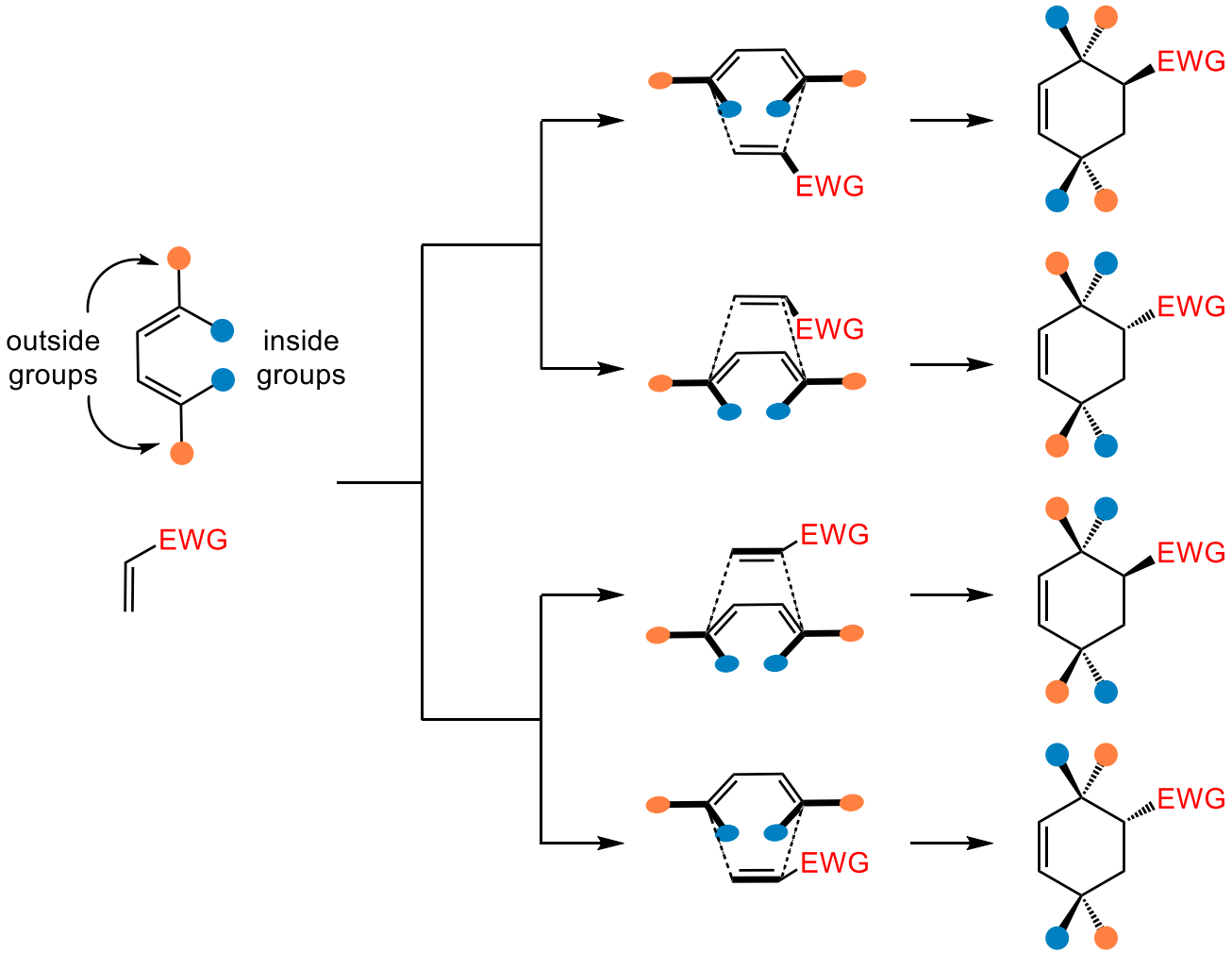
Retrosynthetic Analysis



Diels-Alder Reaction



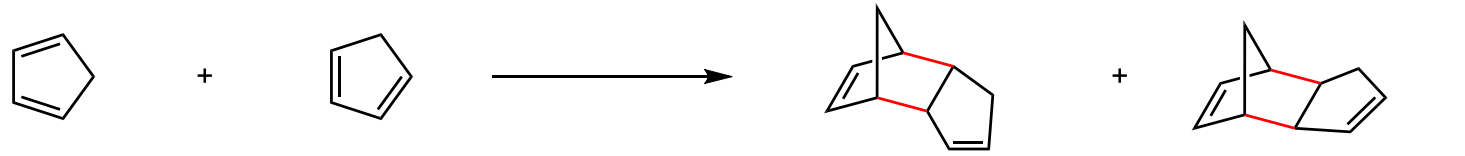
The “endo” and “exo” Products in Diels-Alder Reaction



exo: ● is on the opposote side of the ring as EWG

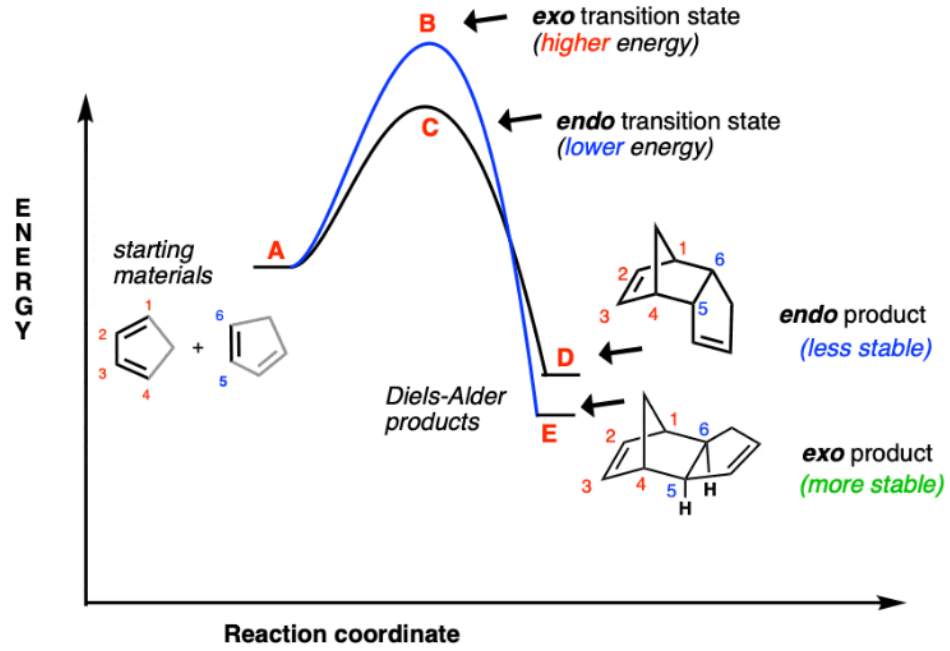
endo: ● is on the same side of the ring as EWG

The “endo” and “exo” Products in Diels-Alder Reaction

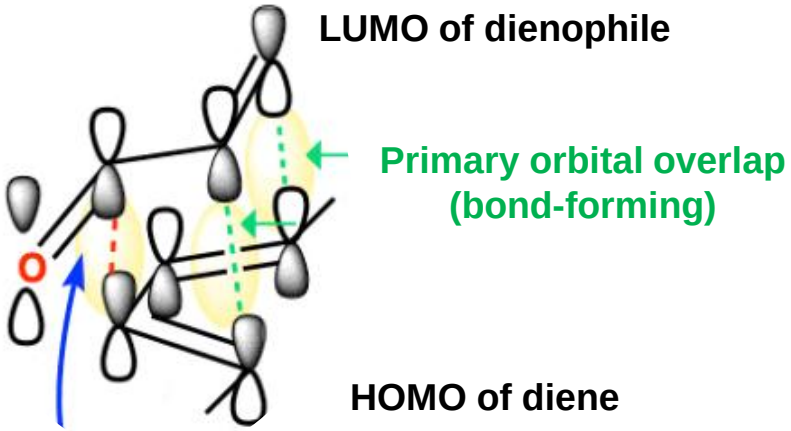


endo
Kinetic product

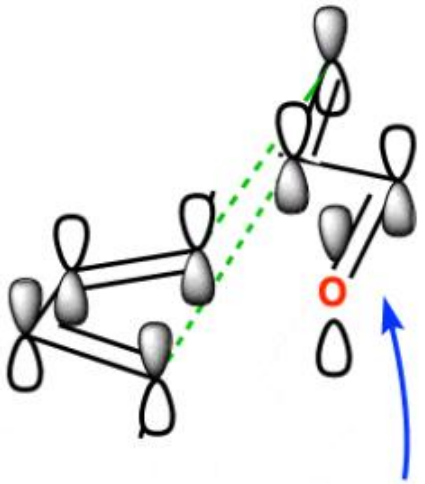
exo
Thermodynamic product



The “endo” and “exo” Products in Diels-Alder Reaction

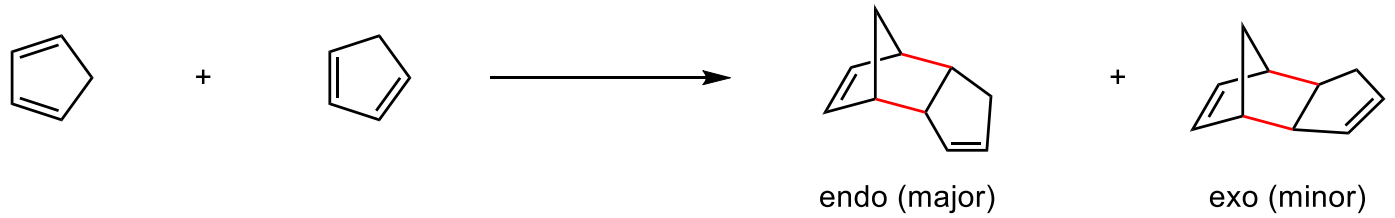


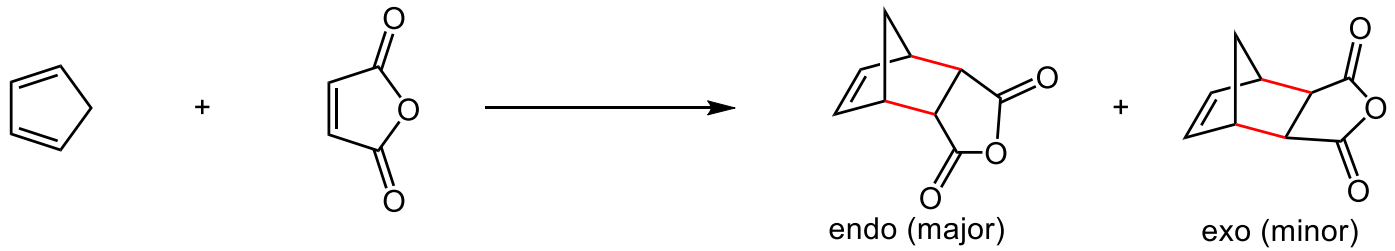
“Secondary orbital overlap”
In endo transition state
Not bond-forming, but stabilizing nonetheless

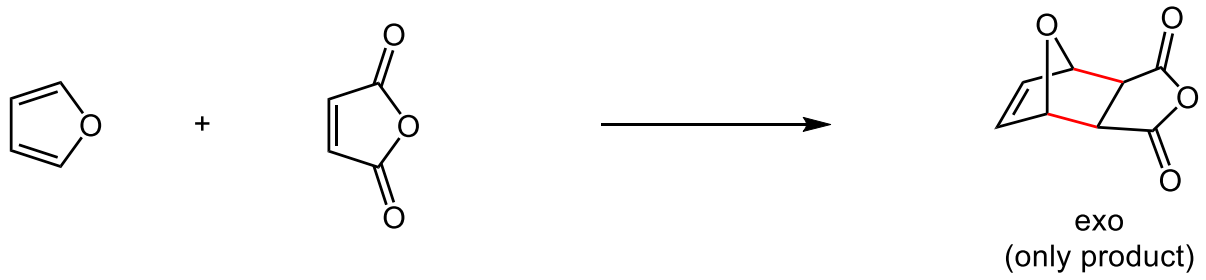


Exo transition state
Secondary overlap not possible
π orbitals are too far away

The “endo” and “exo” Products in Diels-Alder Reaction

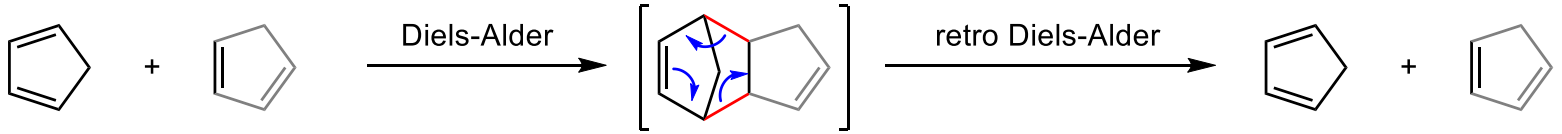


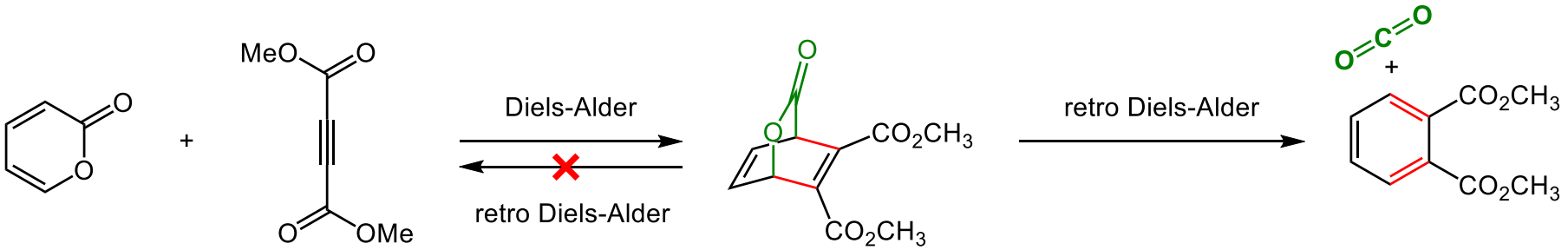




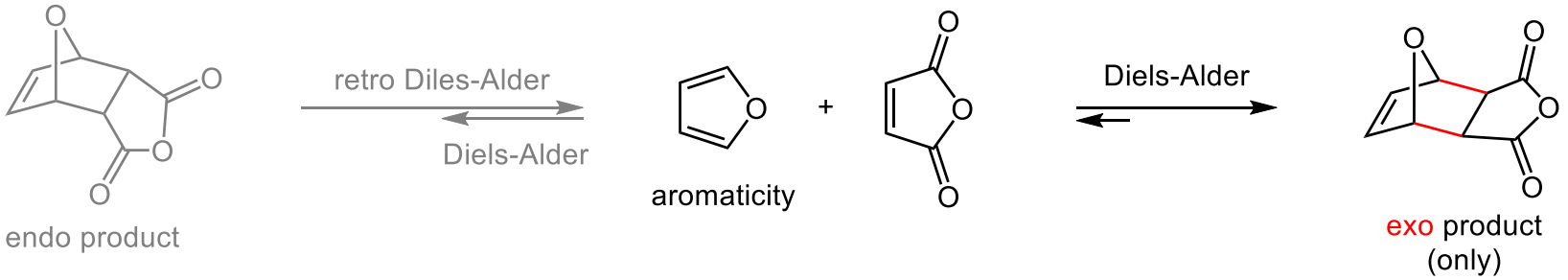
Retro Diels-Alder Reaction

Reverse ("retro") Diels-Alder Reaction





Molecules such as N_2, CO_2, and CO can also be extruded from bicyclic molecules through a retro Diles-Alder processs.

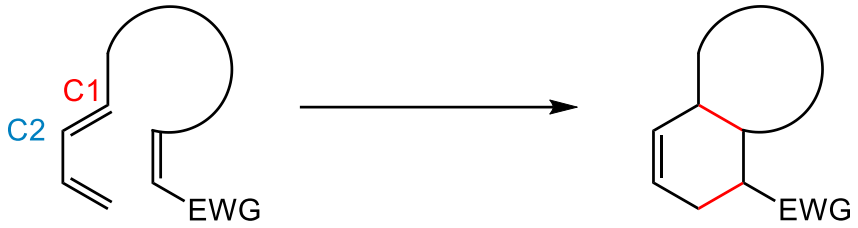


endo product

exo product
(only)

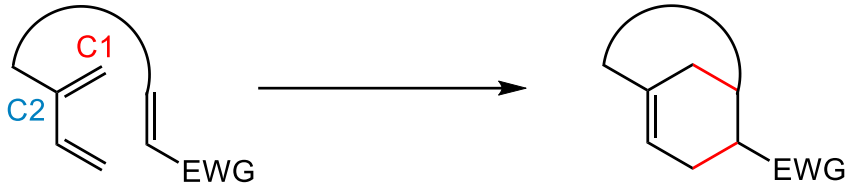
Intramolecular Diels-Alder Reactions

♦ "Type I" Intramolecular Diels Alder Reactions



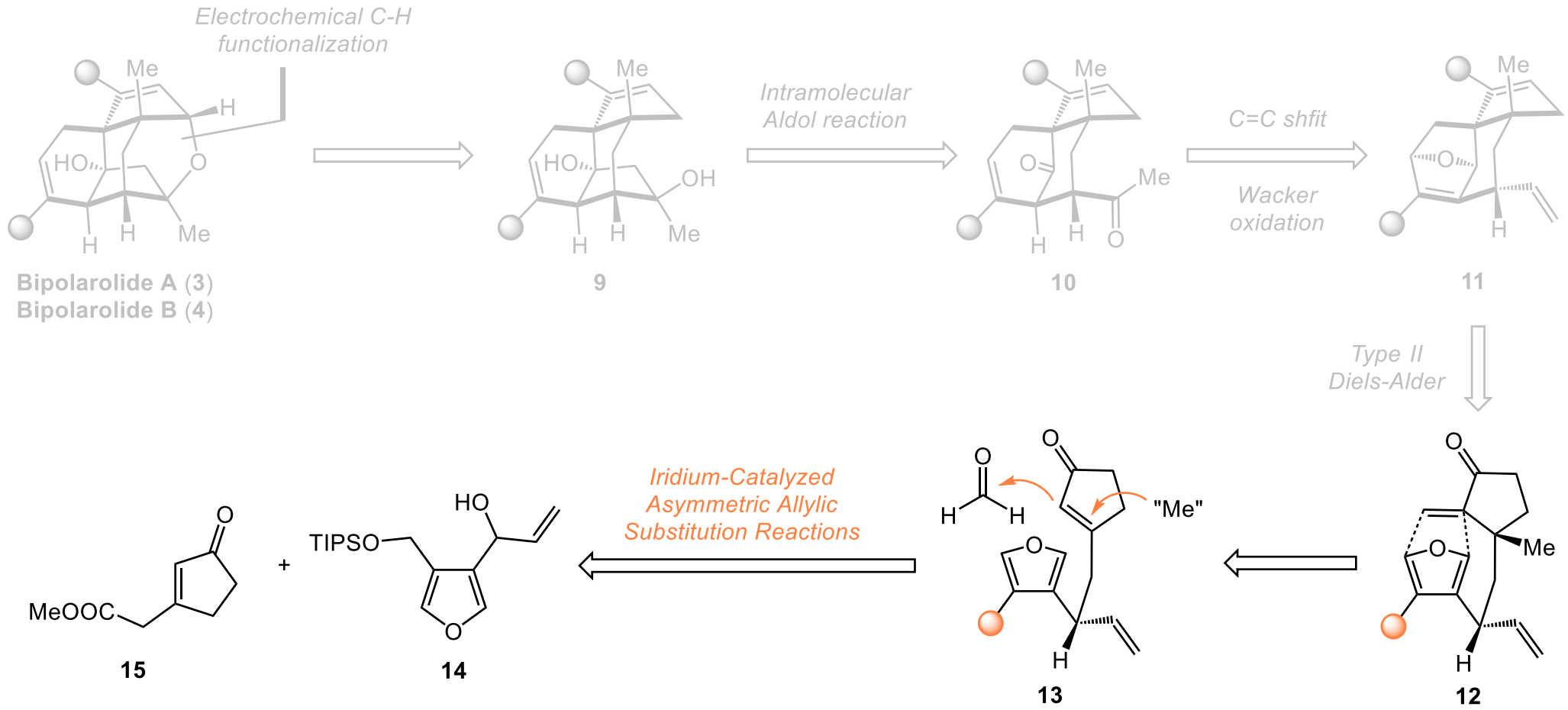
[n.4.0] fused bicyclic ring systerm

♦ "Type II" Intramolecular Diels Alder Reactions



[n.3.1] brigded bicyclic ring systerm

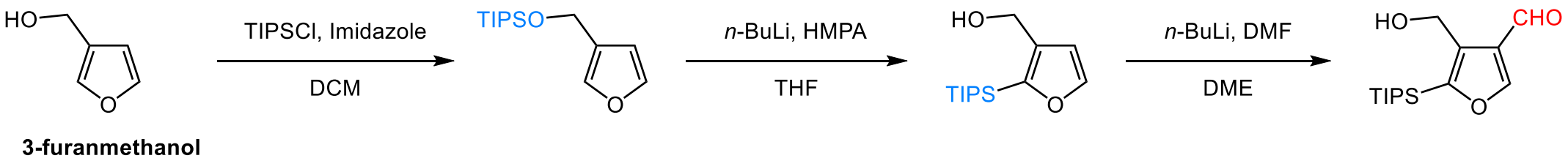
Retrosynthetic Analysis



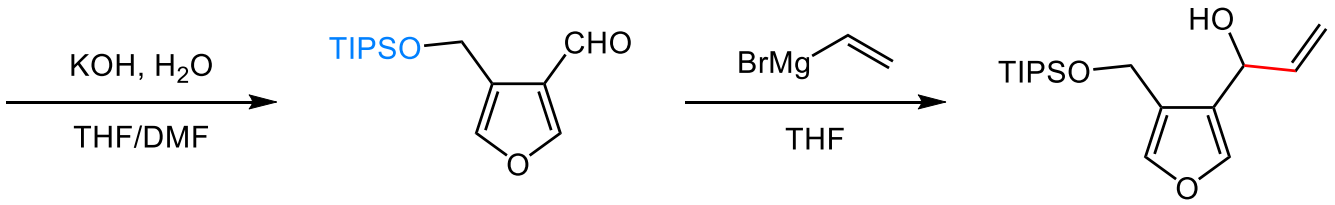
Bipolarolide A (3)
Bipolarolide B (4)

9 **10** **11** **12** **13** **14** **15**

Synthesis of Compound 14



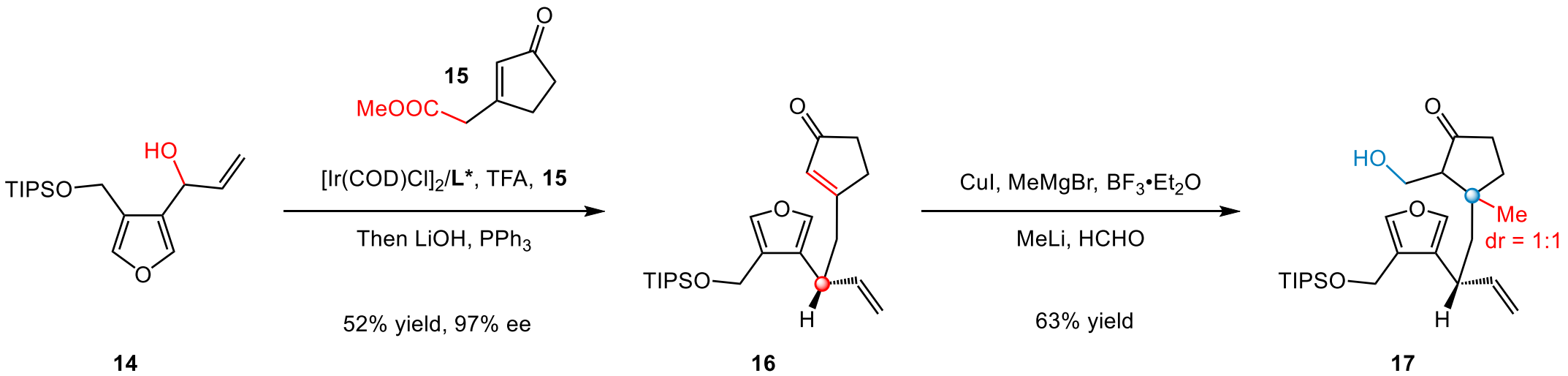
3-furanmethanol



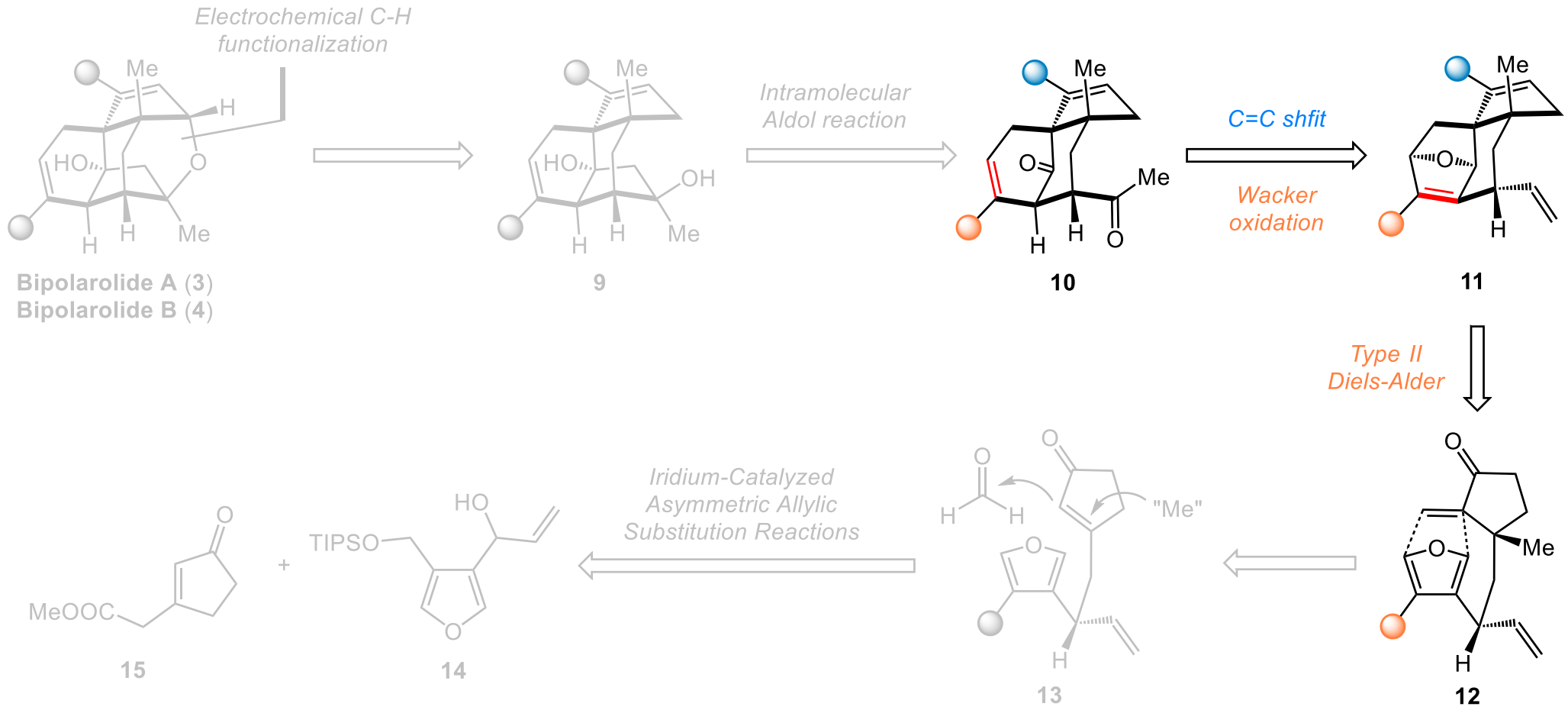
14

67% yield over 5 steps

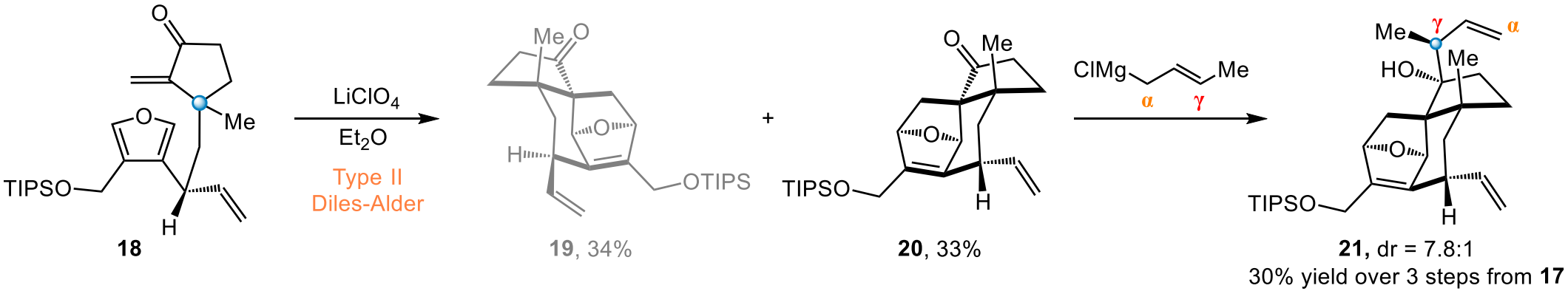
Synthesis of Compound 18



Retrosynthetic Analysis

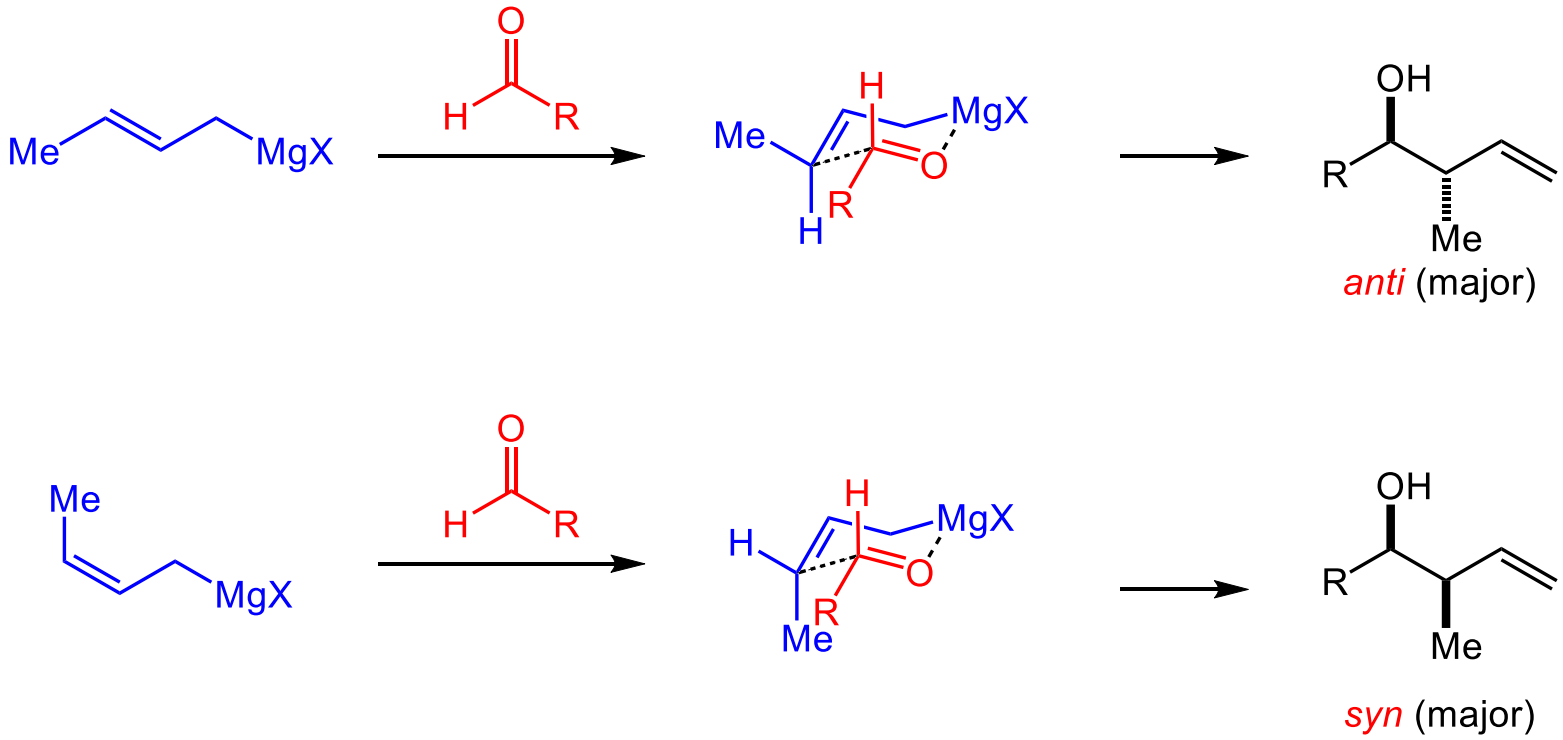


Synthesis of Compound 21

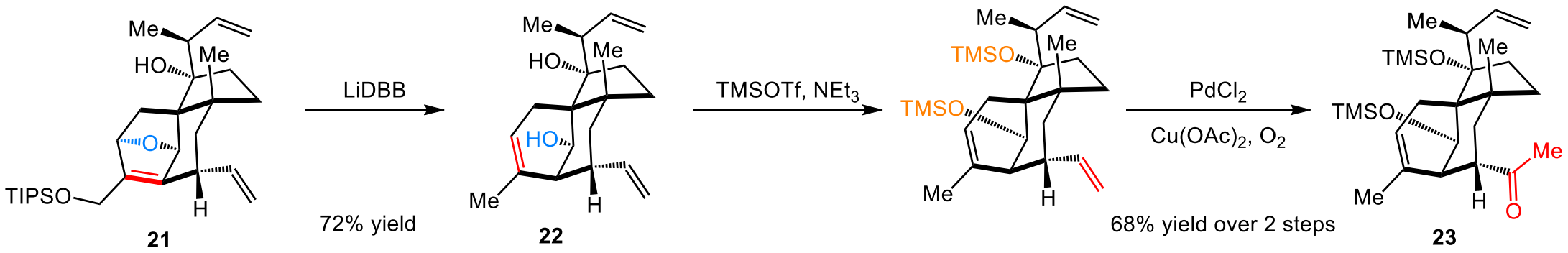


Addition Reaction of Allylmetals to Carbonyl Compounds

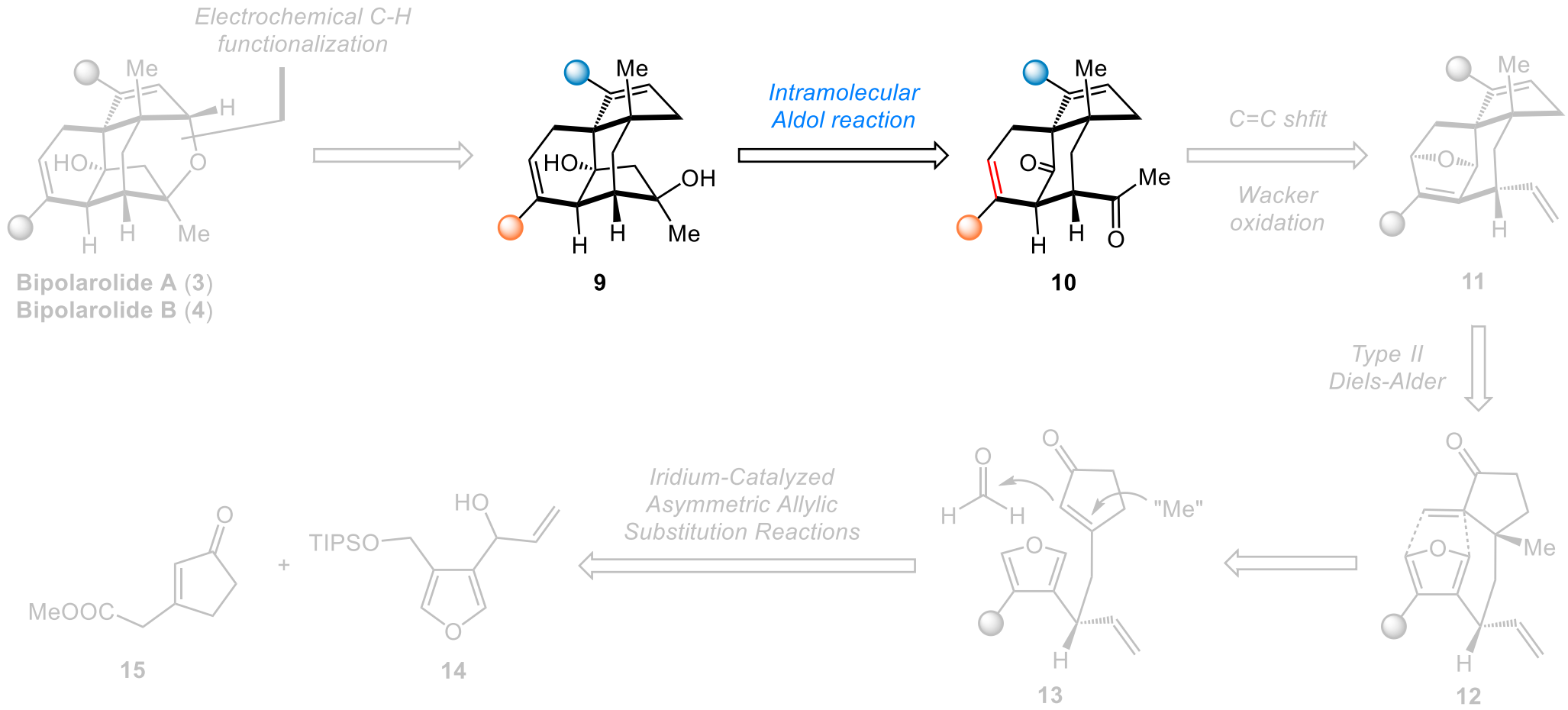
"Regioselective (γ-) Addition *via* 6-Membered Ring Transition State"



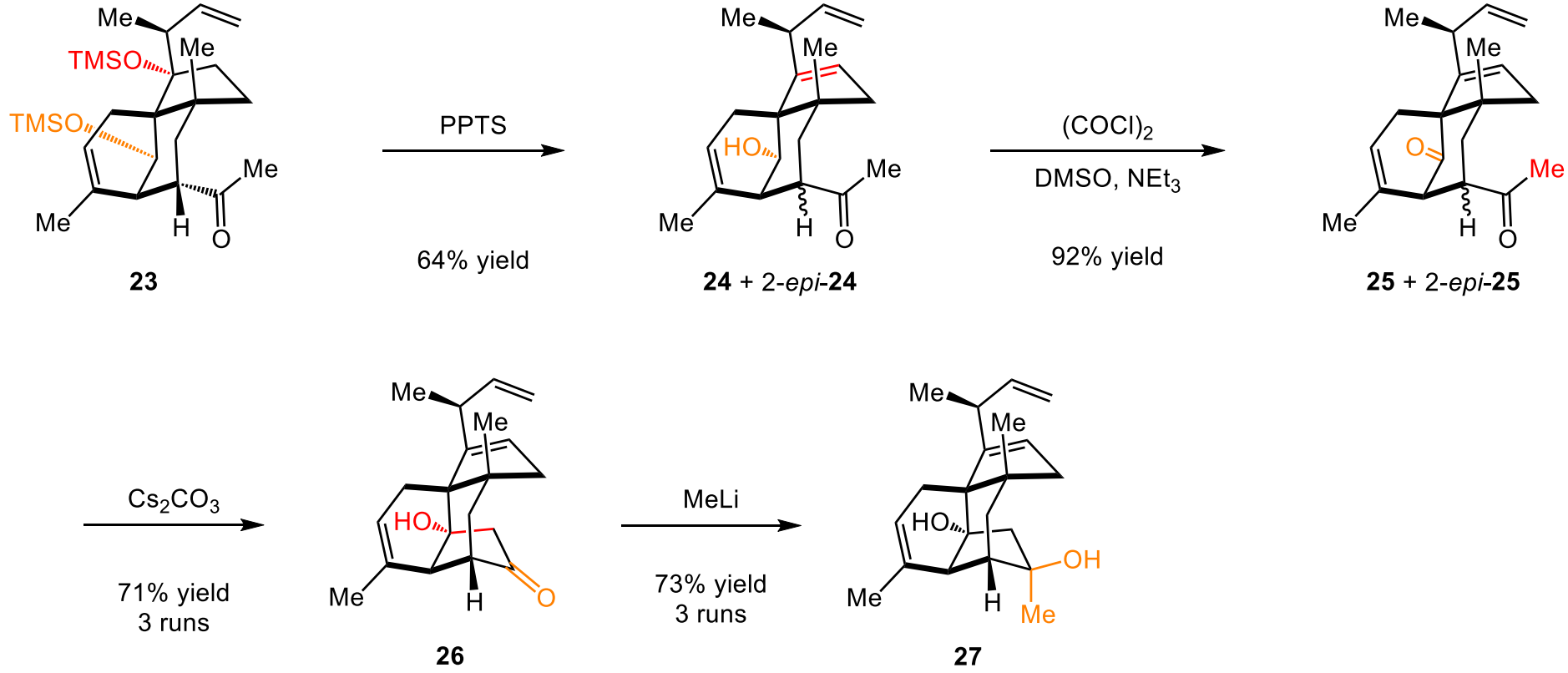
Synthesis of Compound 23



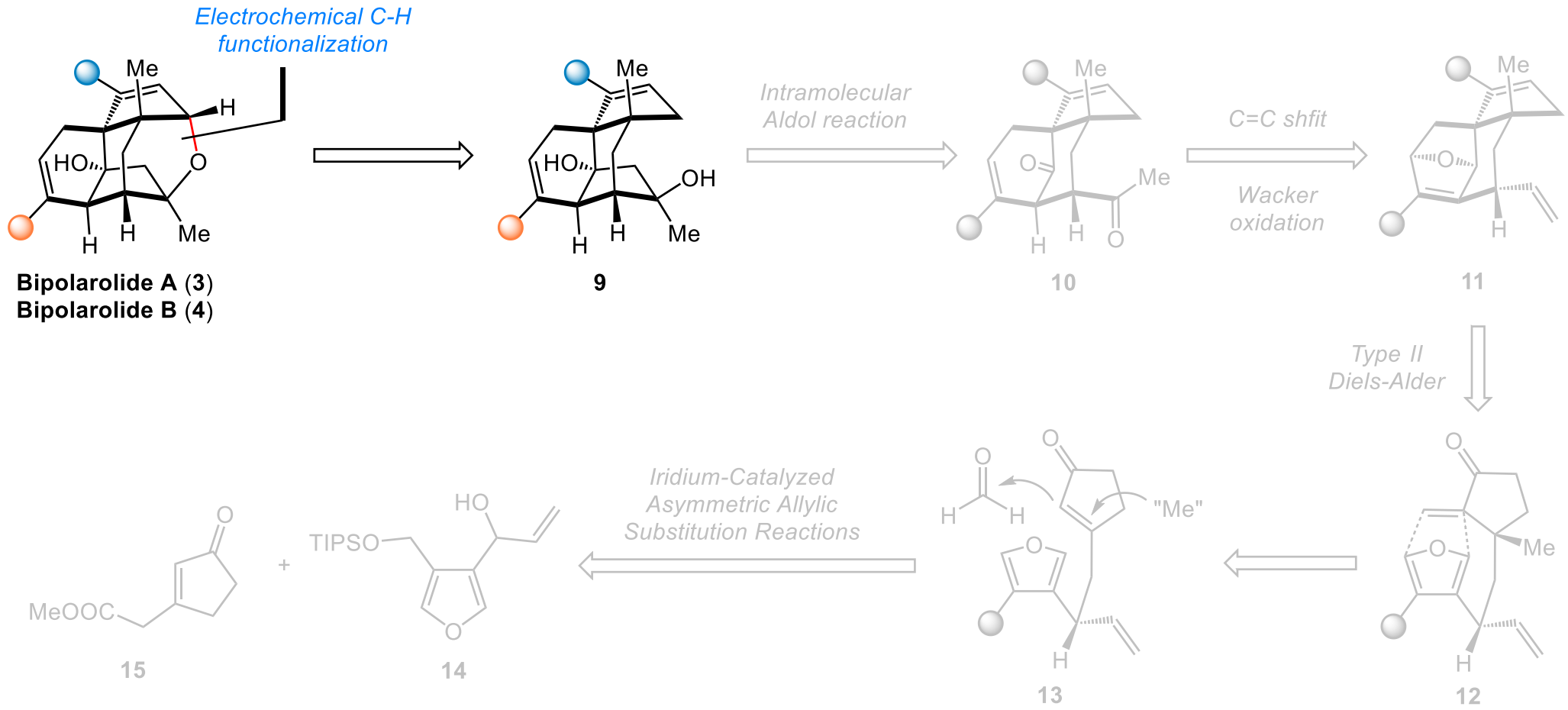
Retrosynthetic Analysis



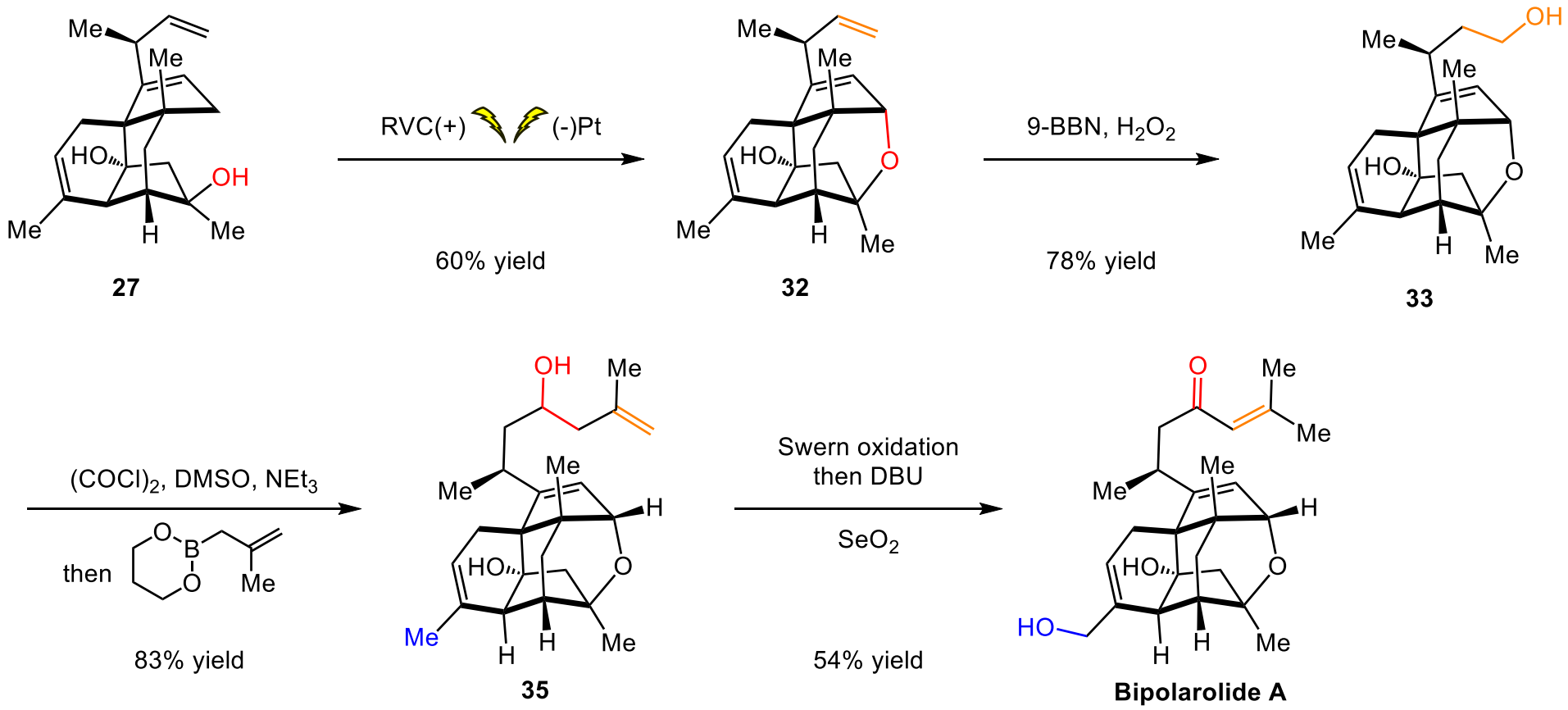
Synthesis of Compound 27



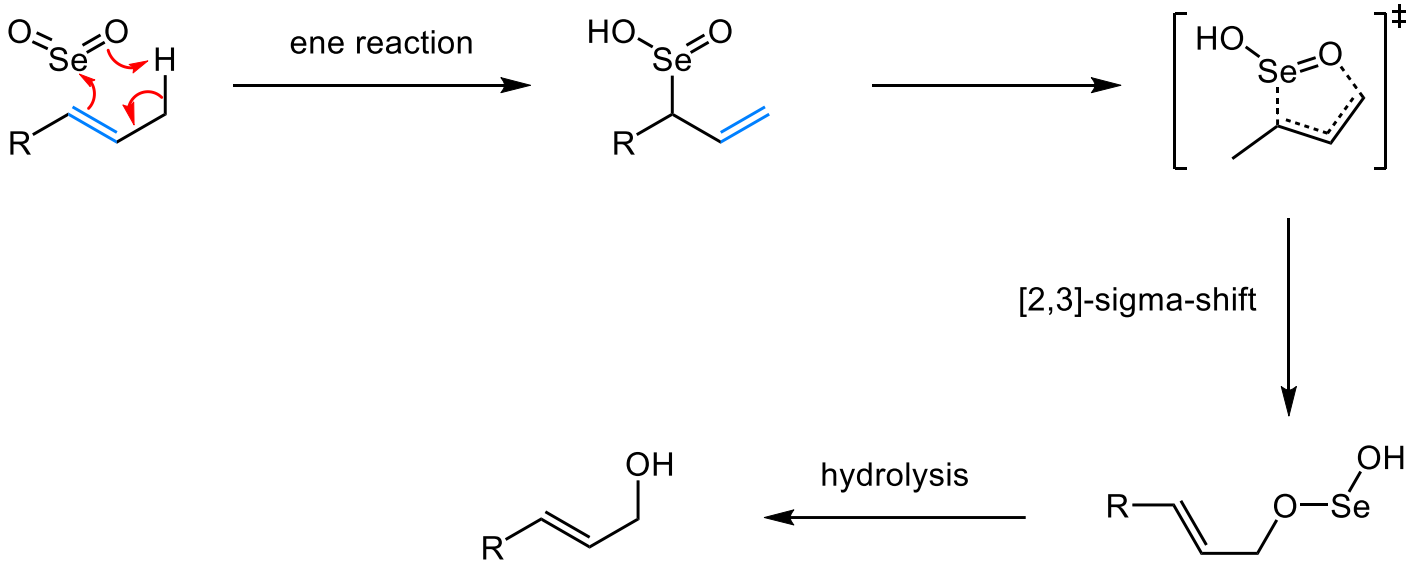
Retrosynthetic Analysis



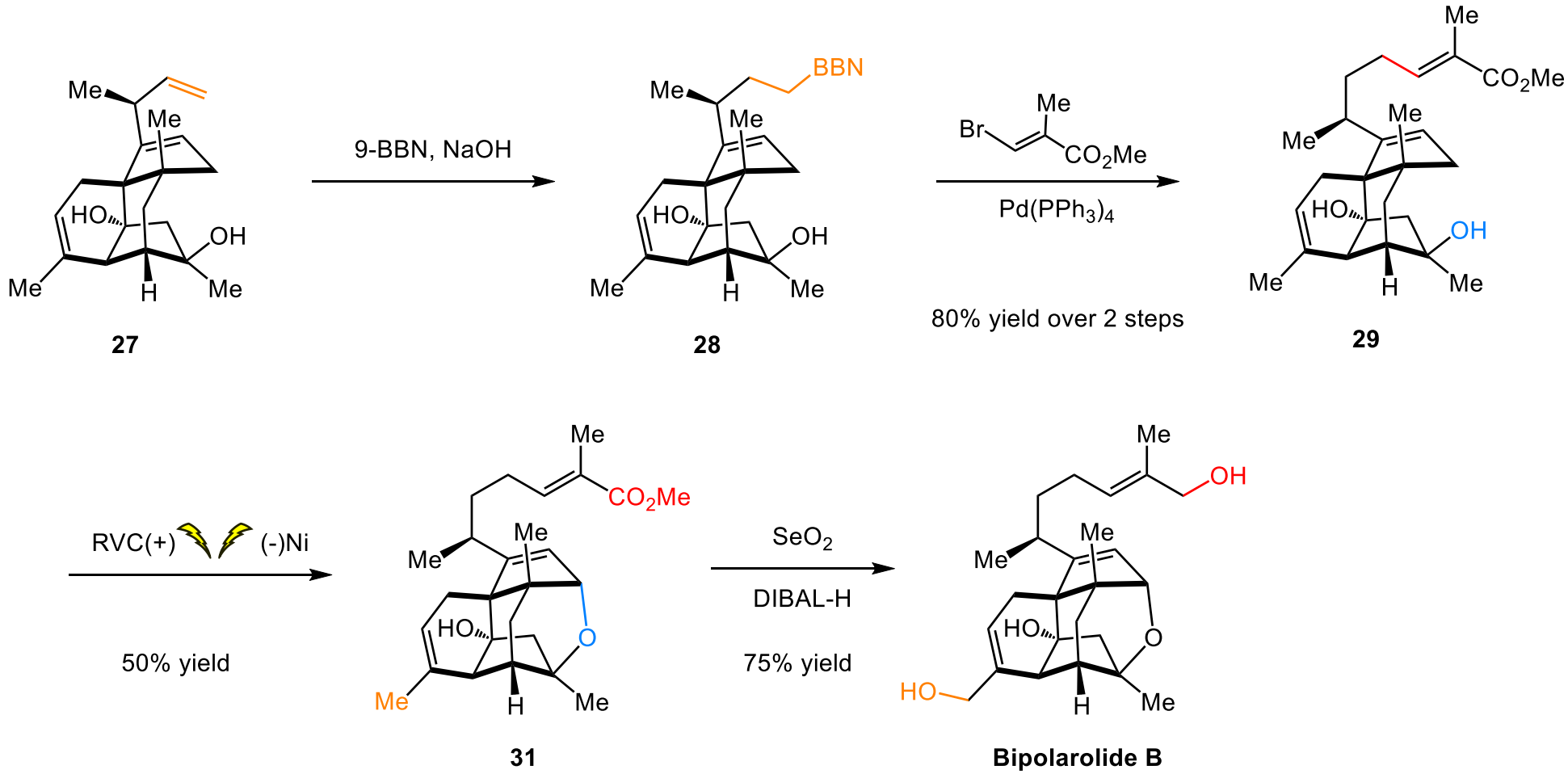
Synthesis of Bipolarolide A



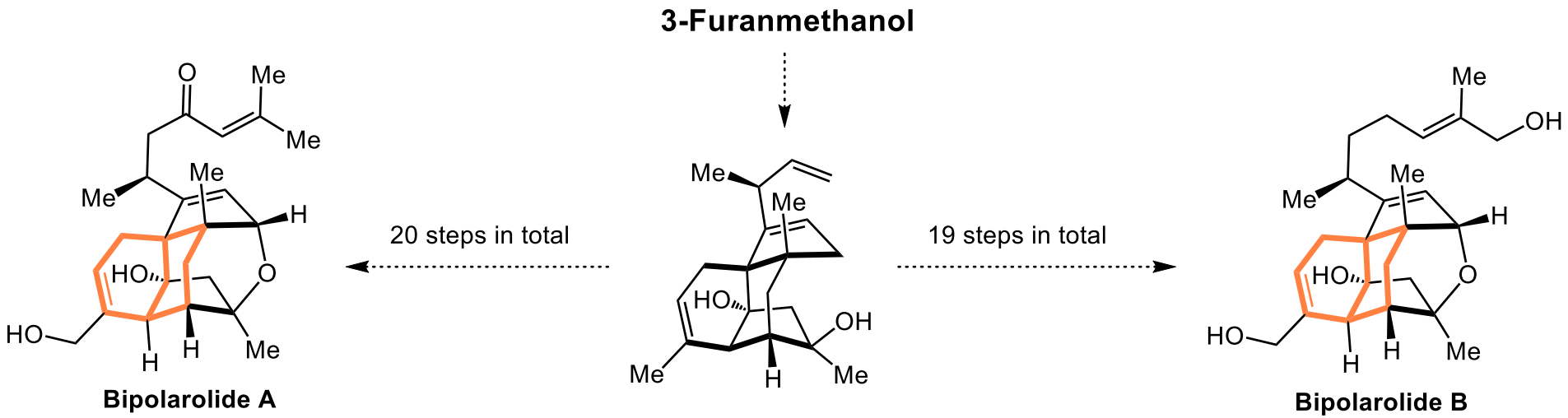
Riley Oxidation



Synthesis of Bipolarolide B



Summary



- Total syntheses of bipolarolides A and B in 20 steps and 19 steps (the longest linear steps);
- Electrochemical oxidation for ether ring cyclization;
- Establishment of the first chiral center *via* Ir-catalyzed asymmetric allylic alkylation.;
- Efficient assembly of the [3.3.1] bridged ring system *via* type-II Diels-Alder reaction.

Writing Strategy

First paragraph

Introduction

Ophiobolins are a class of sesterterpenoid natural products, with over 100 family members isolated to date, and have attracted widespread attention from synthetic chemists. Among them, bipolarolides A and B, derived from ophiobolin and featuring a novel skeletal architecture, were first isolated by Zhang's research group in 2019.

Biosynthesis

Bipolarolide A has been shown to exhibit significant cholesterol-lowering activity (IC50 = 2.5 μM). Biosynthetically, bipolarolides A and B are formed through C5–C10 bond formation within the 5/8/5 fused ring system of ophiobolin. This process generates a novel skeletal framework characterized by a [3,3,1] bridged ring system adorned with three contiguous quaternary carbon centers.

Synthesis Examples

Inspired by this biosynthetic pathway, Jia and co-workers pioneered the asymmetric synthesis of bipolarolides A and B using a bioinspired Prins cyclization strategy. Recently, Fan's group achieved the racemic synthesis of bipolarolide B and bipoladien B via bridgehead enone chemistry.

Writing Strategy

- **Last paragraph**

Summary

In summary, the enantioselective total syntheses of 3 and 4 were efficiently achieved. Key steps include (1) establishment of the first chiral center via Ir-catalyzed asymmetric allylic alkylation with 97% ee; (2) efficient assembly of the bridged ring system via type-II Diels–Alder reaction; (3) site-selective Wacker oxidation enabling precise conversion of olefin to methyl ketone; (4) formation of the D-ring structure through intramolecular aldol condensation; (5) electrochemical oxidation for ether ring cyclization; and (6) divergent modification of side chains in the late-stage synthesis to achieve targeted synthesis of **3** and **4**.

Prospect

This synthetic route, characterized by powerful cycloaddition and precise stereochemical control, provides crucial compounds for subsequent bioactivity investigations.

Representative Examples

- This process generates a novel skeletal framework characterized by a [3,3,1] bridged ring system adorned with (佩戴，装饰。 adorn *vt* 装饰，使声色) three contiguous quaternary carbon centers.
- Intriguingly (*adv*. 有趣地，引起好奇心地), **18** spontaneously produced trace DA adducts at ambient temperature, yet heating paradoxically (*adv*. 矛盾地，事与愿违地，出乎意料地) diminished adduct formation due to *retro*-DA dominance, likely driven by furan aromatic stabilization and bridged olefin strain.

Acknowledgement

Thank You for Your Attention!