

# Literature Report 1

## Total Syntheses of Disorazoles A<sub>1</sub> and B<sub>1</sub> and Full Structural Elucidation of Disorazole B<sub>1</sub>

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Checker: Xiao-Yong Zhai

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*J. Am. Chem. Soc.* **2017**, *139*, 15636–15639

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# CV of Prof. Nicolaou, K. C.

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## Background:

- ❑ 1966-1969 B.Sc., Bedford College
- ❑ 1969-1972 Ph.D., University College London
- ❑ 1972-1973 Postdoc., Columbia University
- ❑ 1973-1976 Postdoc., Harvard University
- ❑ 1976-1989 Prof., University of Pennsylvania
- ❑ 1989-2013 Prof., University of California, San Diego  
and Scripps Research Institute
- ❑ 2013-Now Prof., Rice University

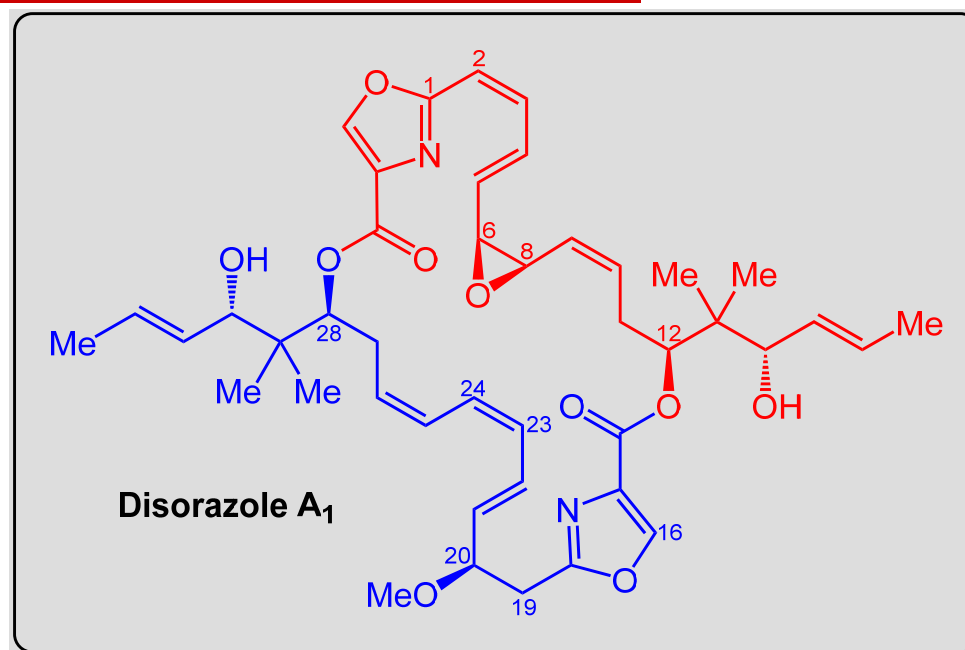
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## Research Interests:

The group's research activities are centered around the total synthesis of architecturally novel and biologically important natural products which serve as opportunities for discovery and invention of novel synthetic strategies, methods, and enabling technologies for biology and medicine.

# Introduction of Disorazoles

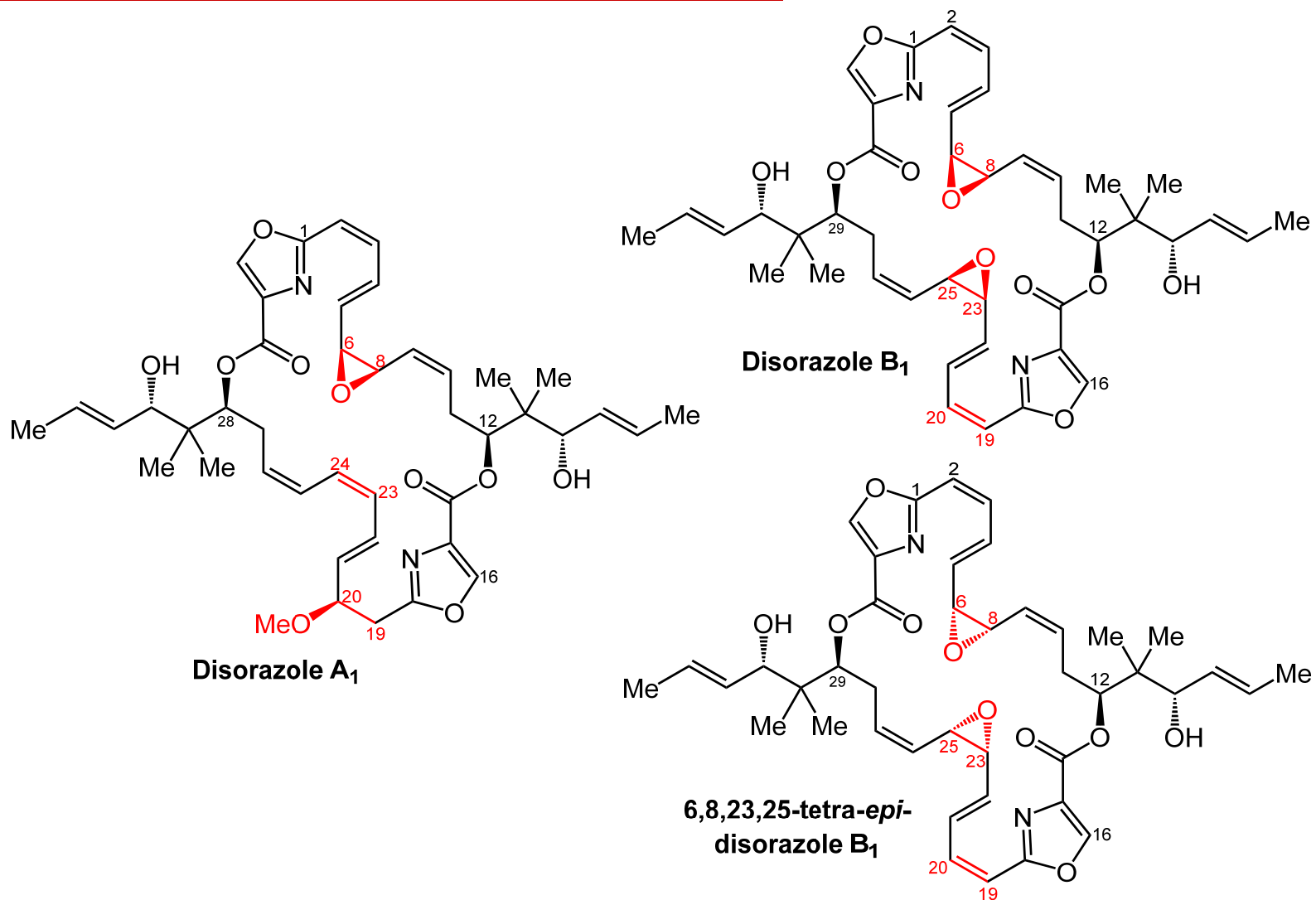
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- Twenty-nine disorazoles were isolated from *Sorangium cellulosum* in 1993.
- The disorazoles are macrocyclic dilactones of two 2-pentadecyloxazol-4-carboxylic acids.
- The disorazoles proved to be highly cytotoxic and active against fungi.

Jansen, R. *et al. Liebigs Ann. Chem.* **1994**, 759-773

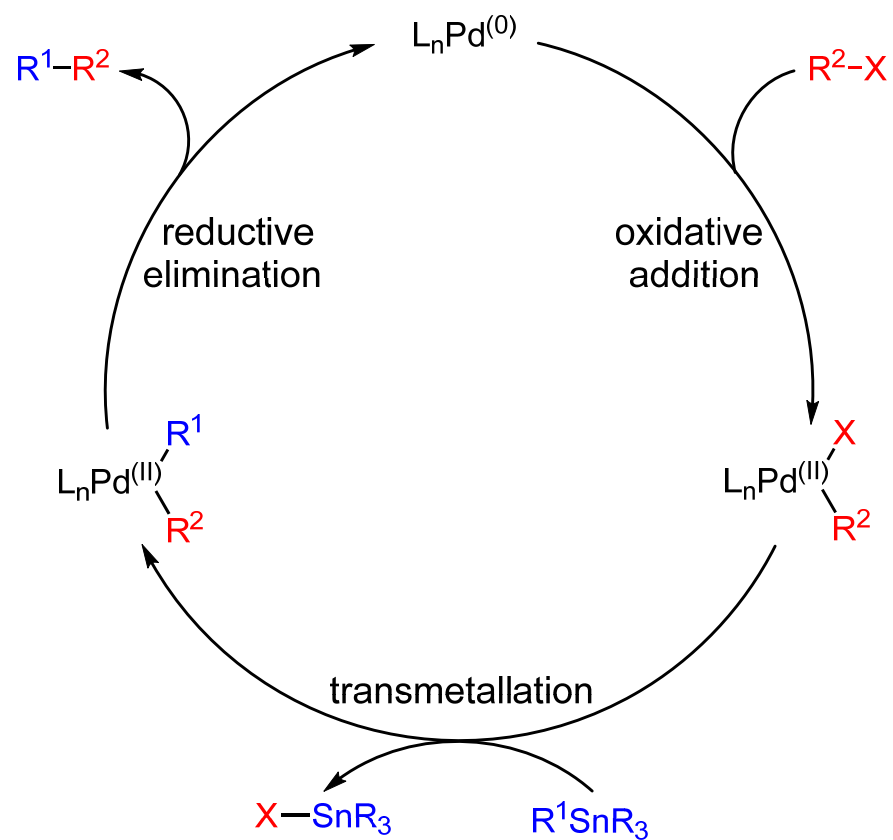
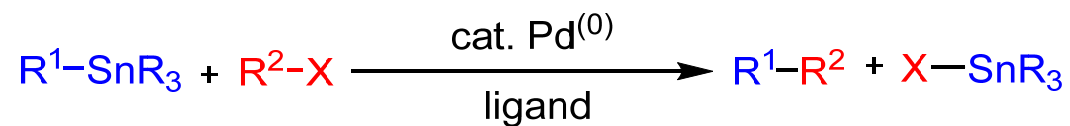
# Introduction of Disorazoles



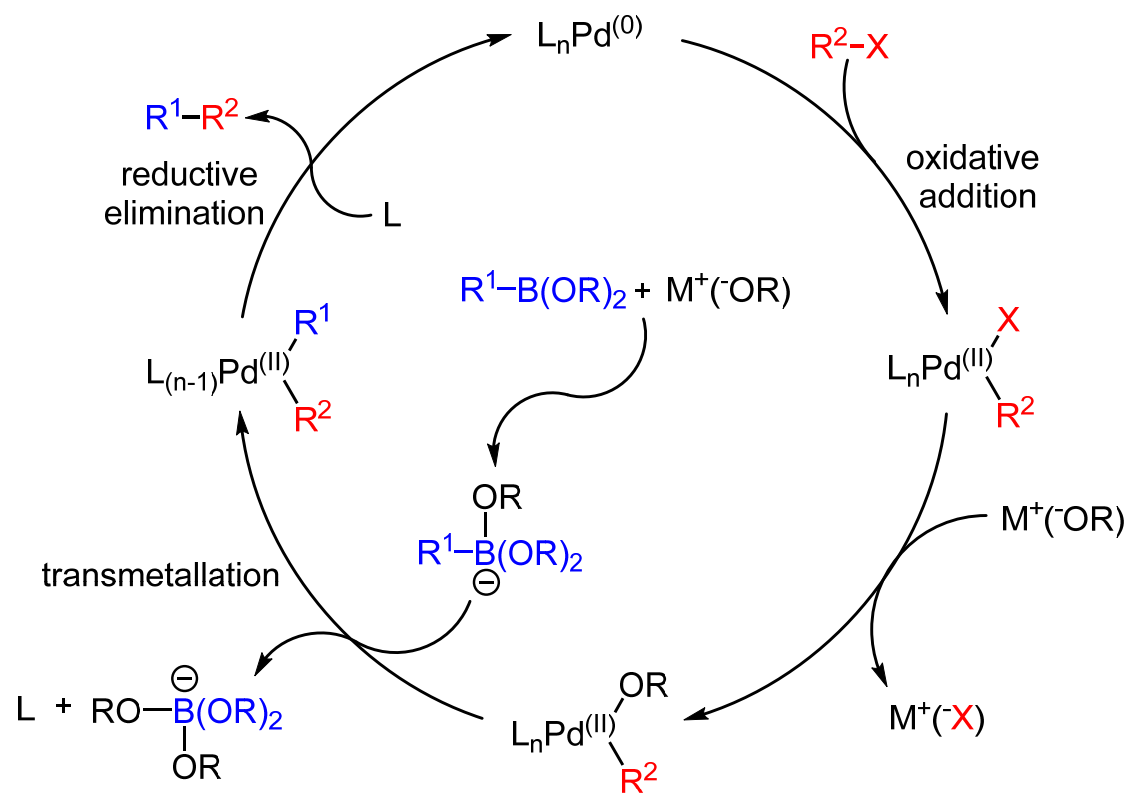
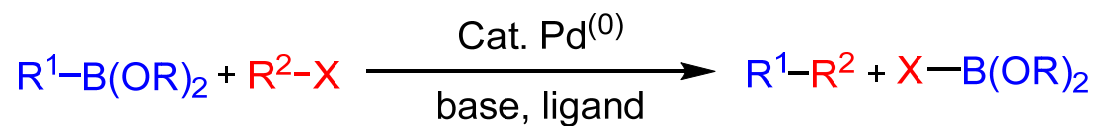
Jansen, R. *et al.* *Liebigs Ann. Chem.* **1994**, 759-773

# Stille Cross-Coupling

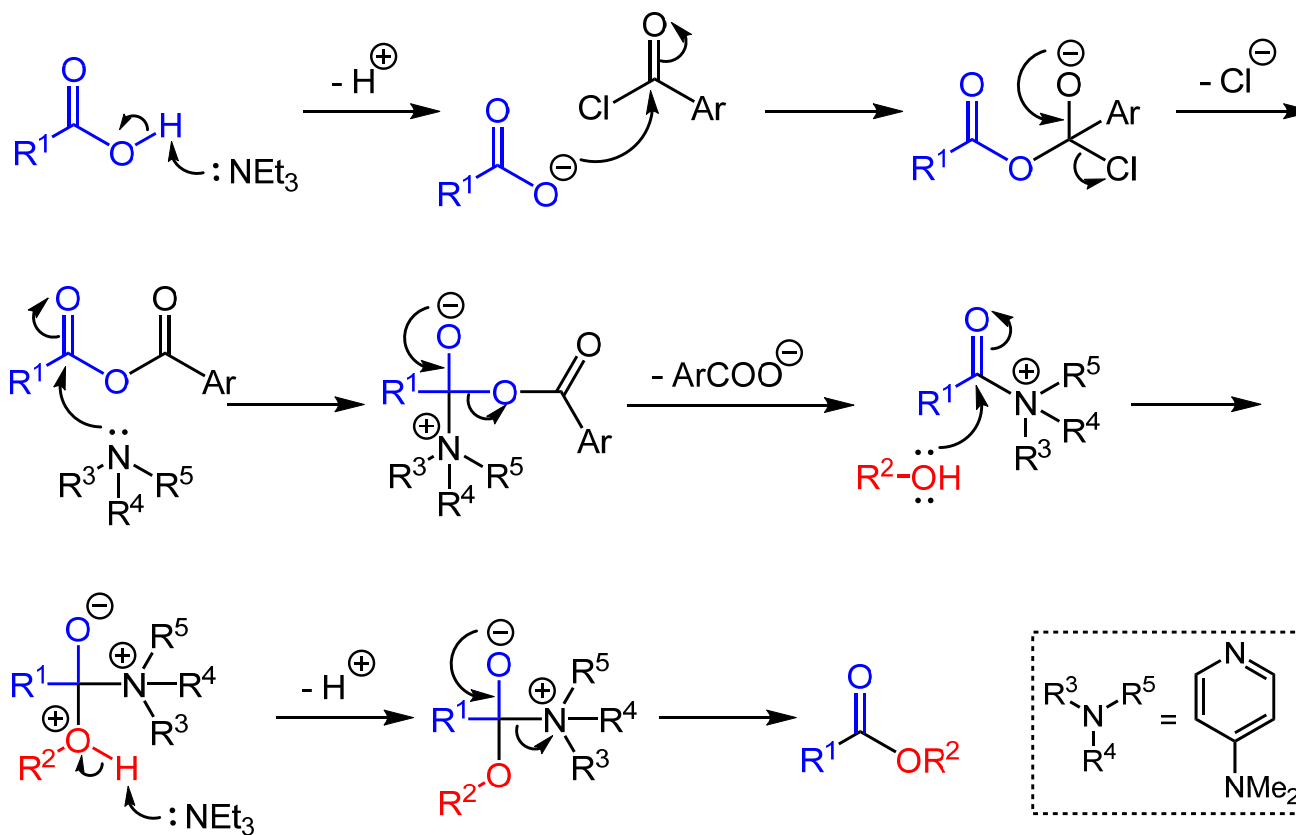
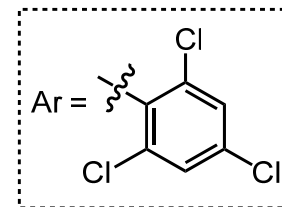
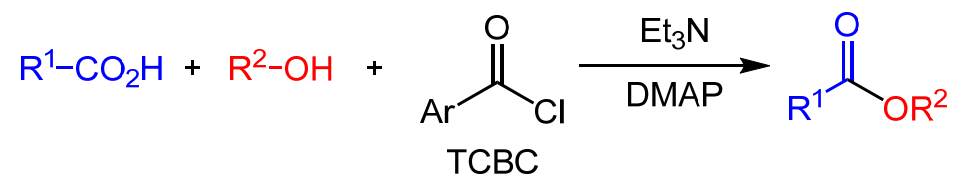
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# Suzuki Cross-Coupling

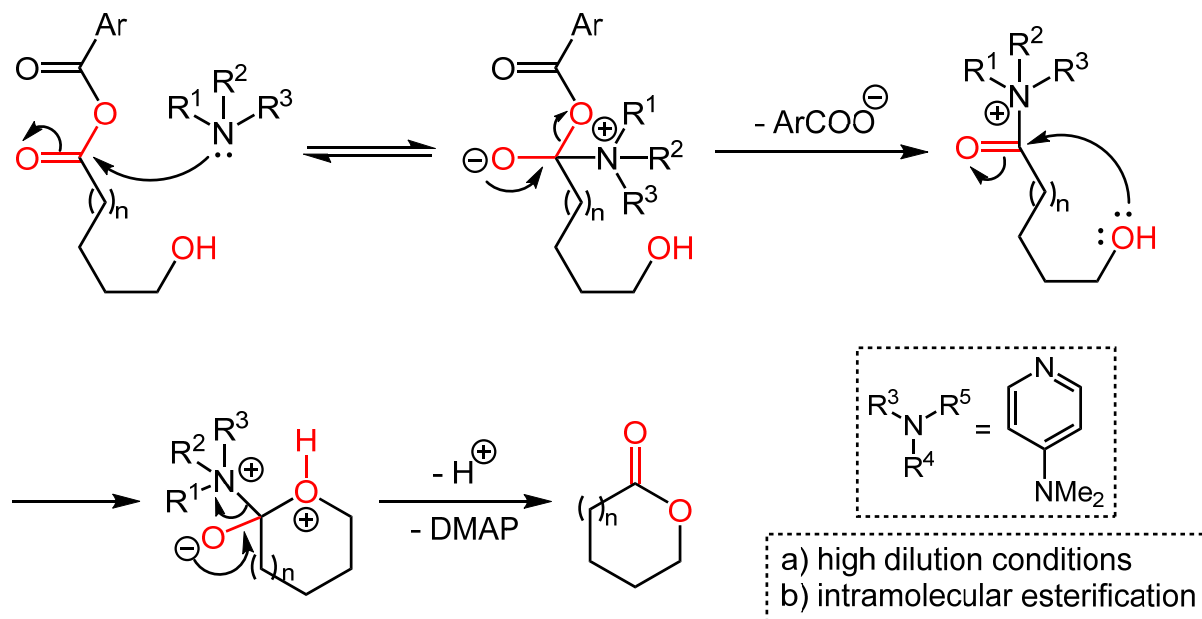
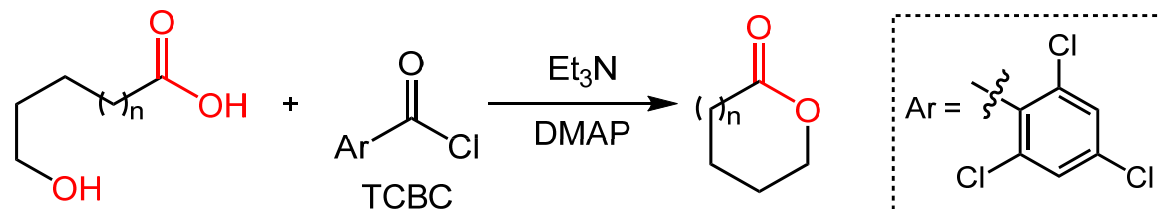


# Yamaguchi Esterification

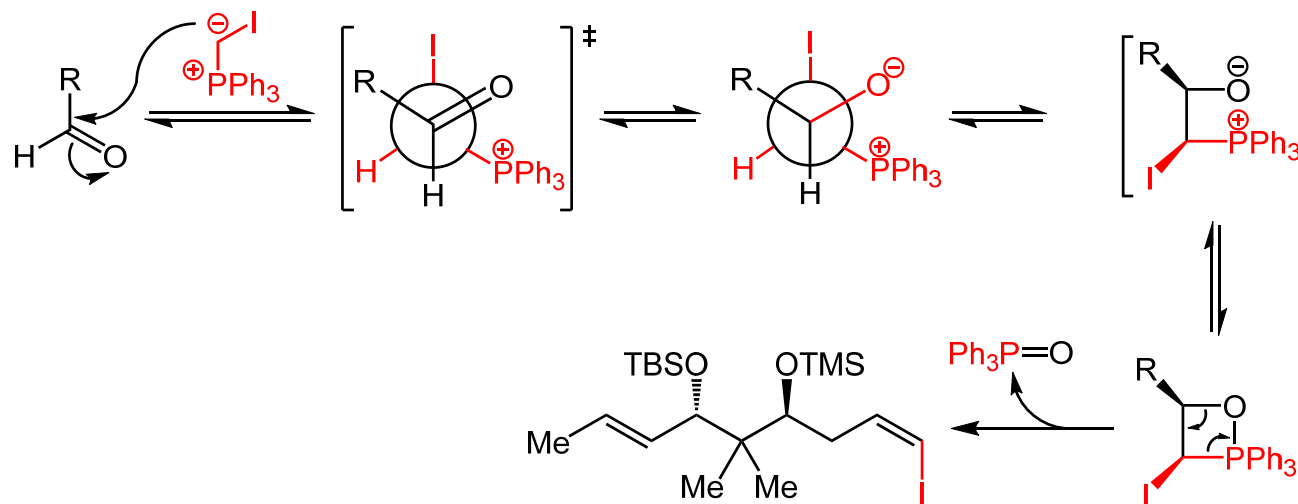
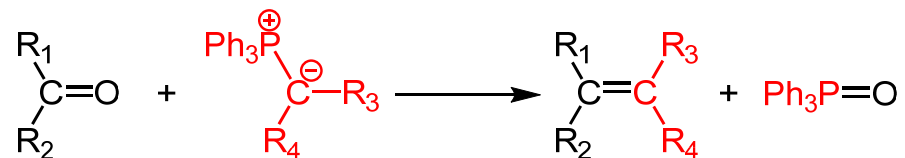




# Yamaguchi Macrolactonization

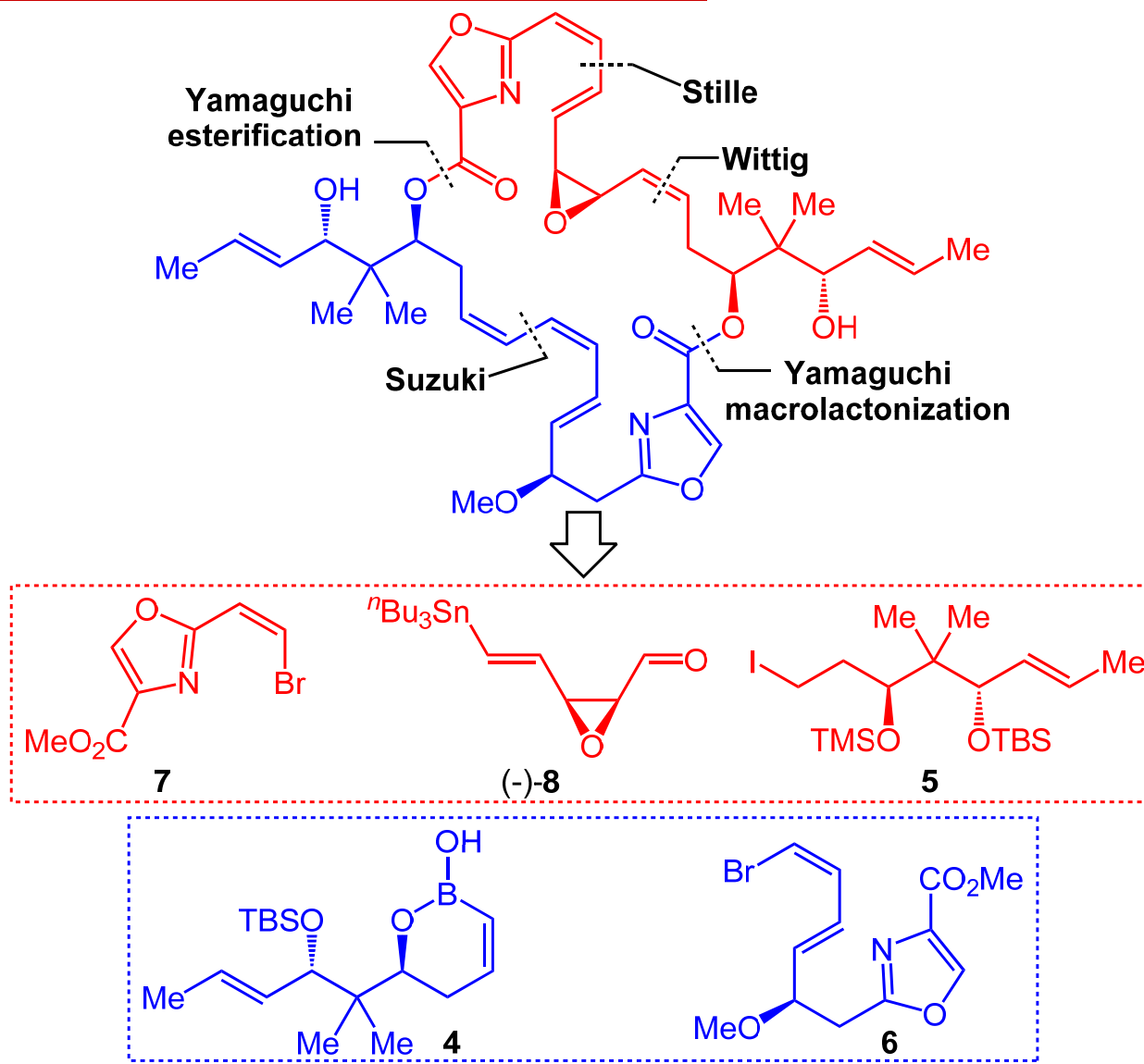


# Wittig Reaction

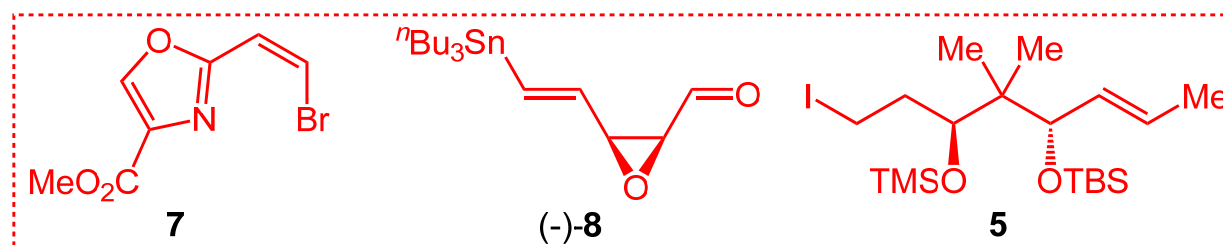
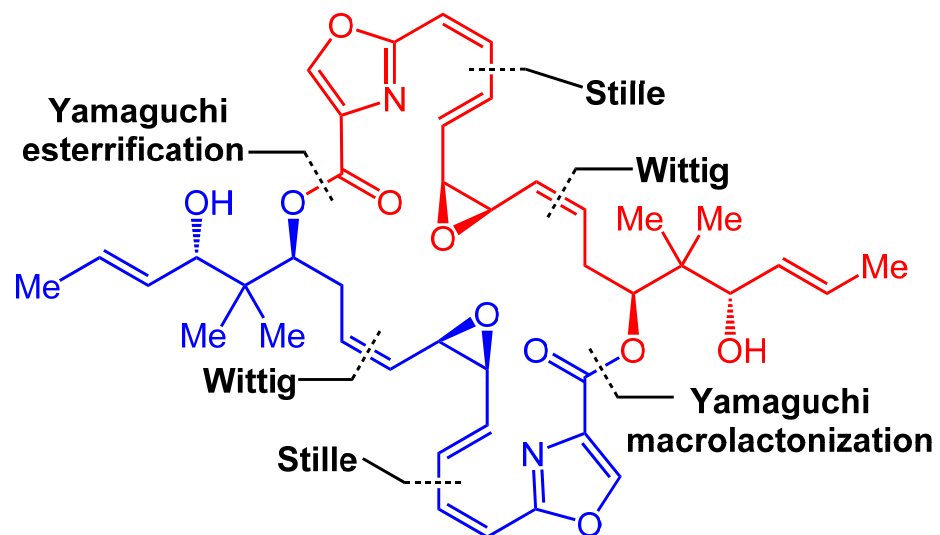


Unstabilized ylides give predominantly (Z)-Olefins  
Stabilized ylides give predominantly (E)-Olefins  
Semi-stabilized ylides give alkenes with poorer stereoselectivity

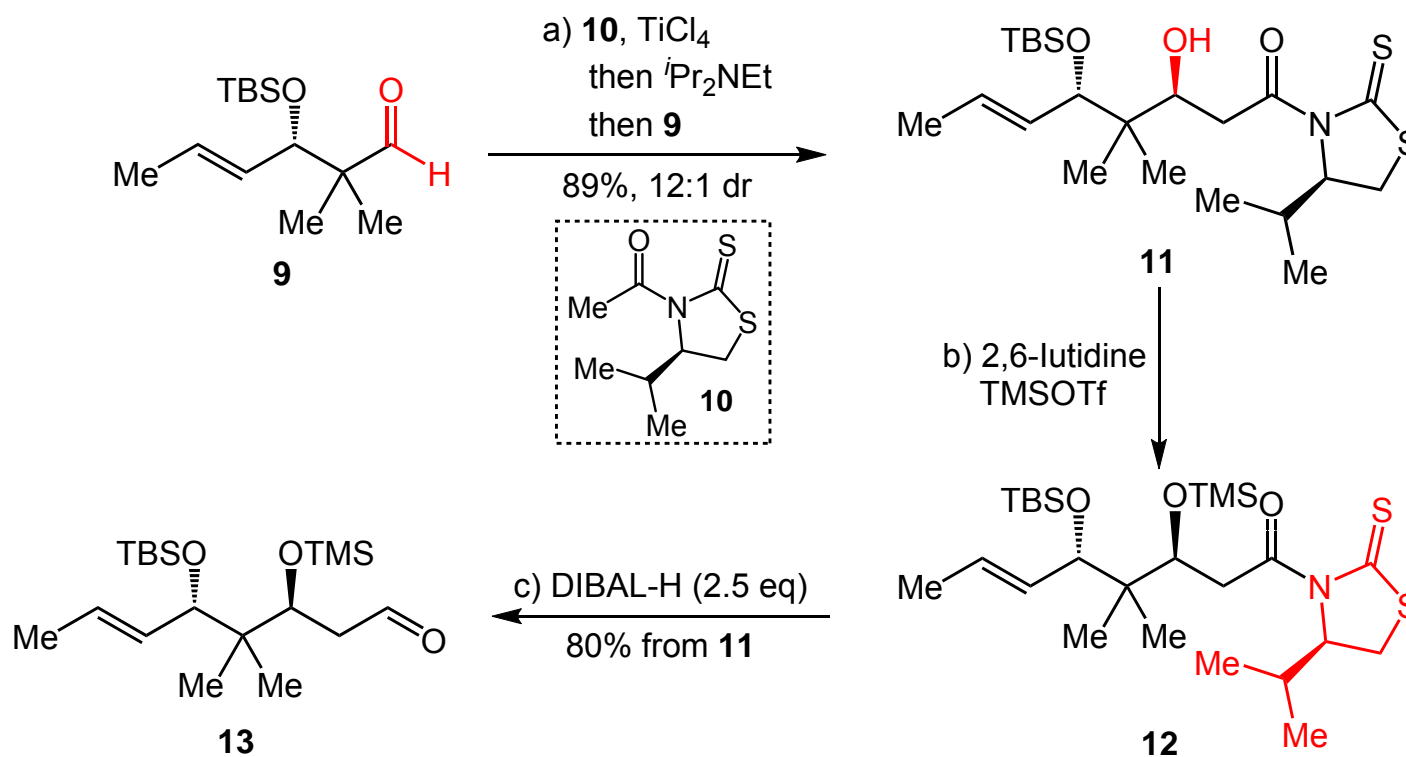
# Retrosynthetic Analysis of Disorazole A<sub>1</sub>



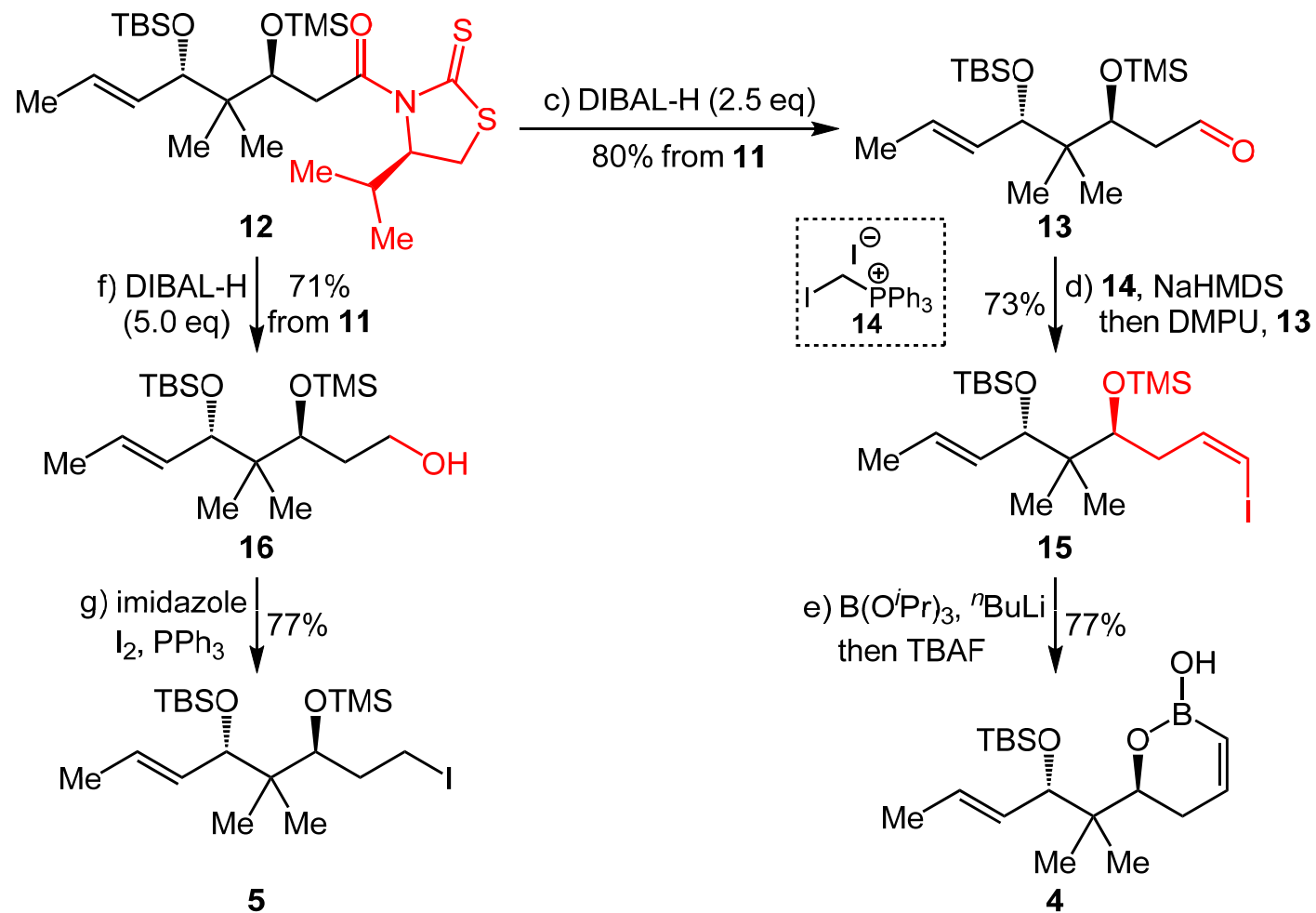
# Retrosynthetic Analysis of Disorazole B<sub>1</sub>



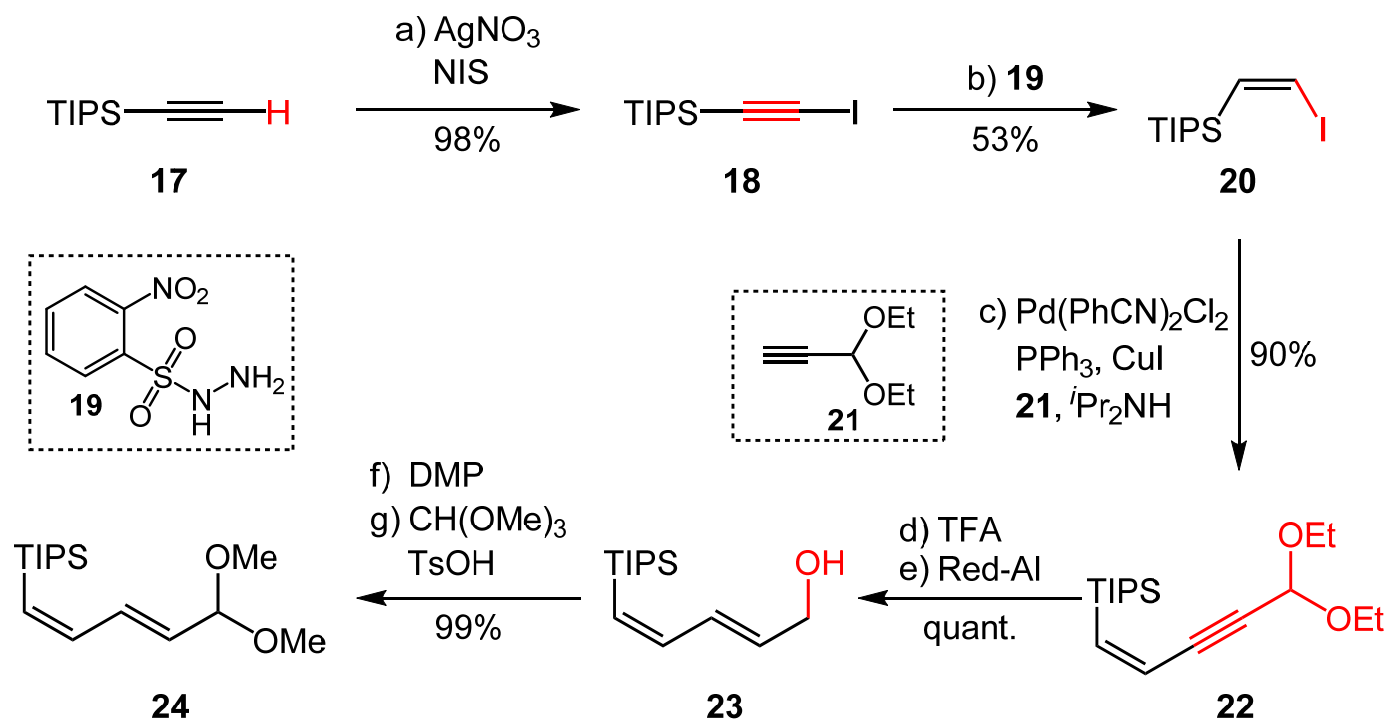
# Synthesis of Vinyl Boronic Acid 4 and Iodide 5



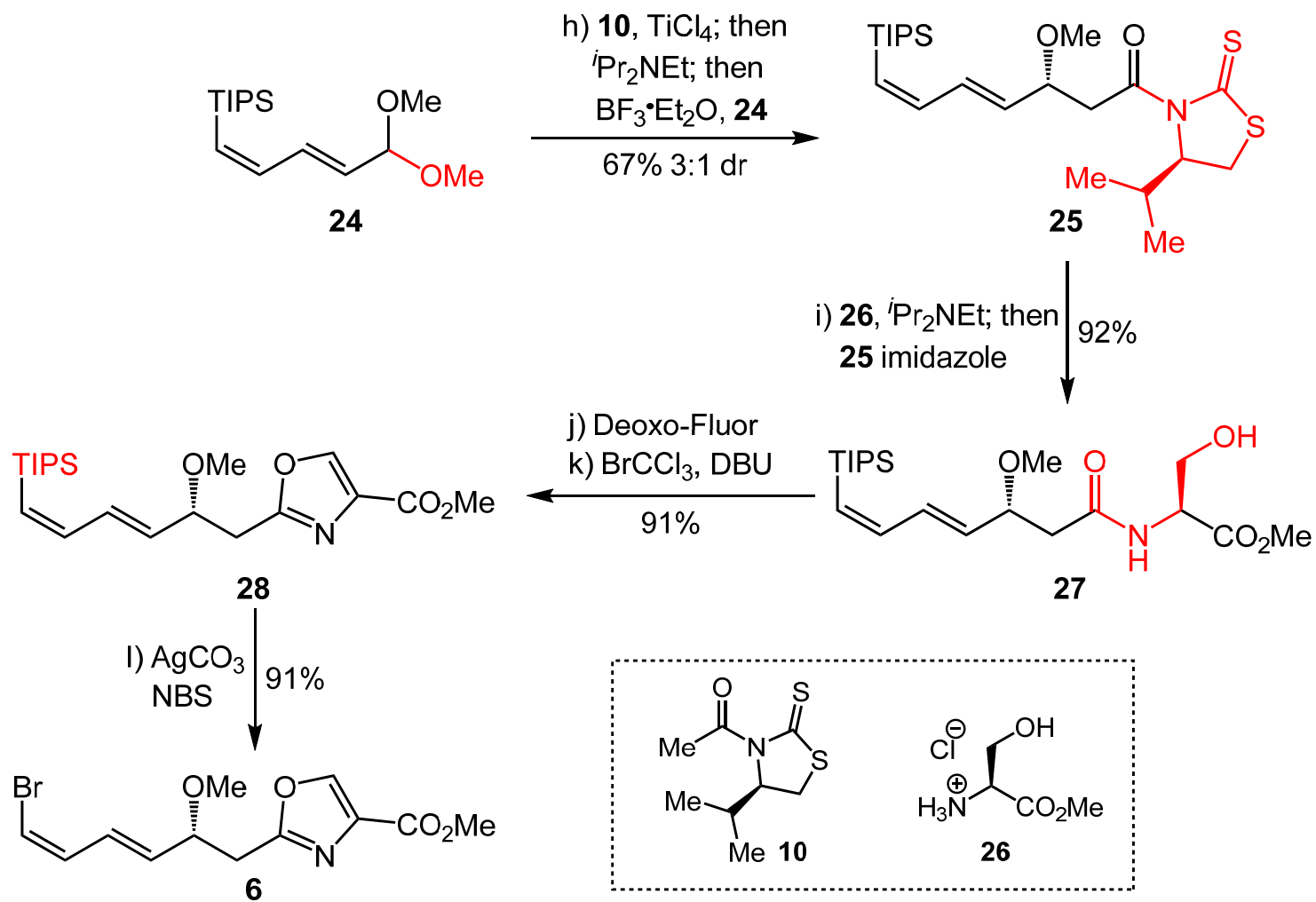
# Synthesis of Vinyl Boronic Acid **4** and Iodide **5**



# Synthesis of Vinyl Bromide 6

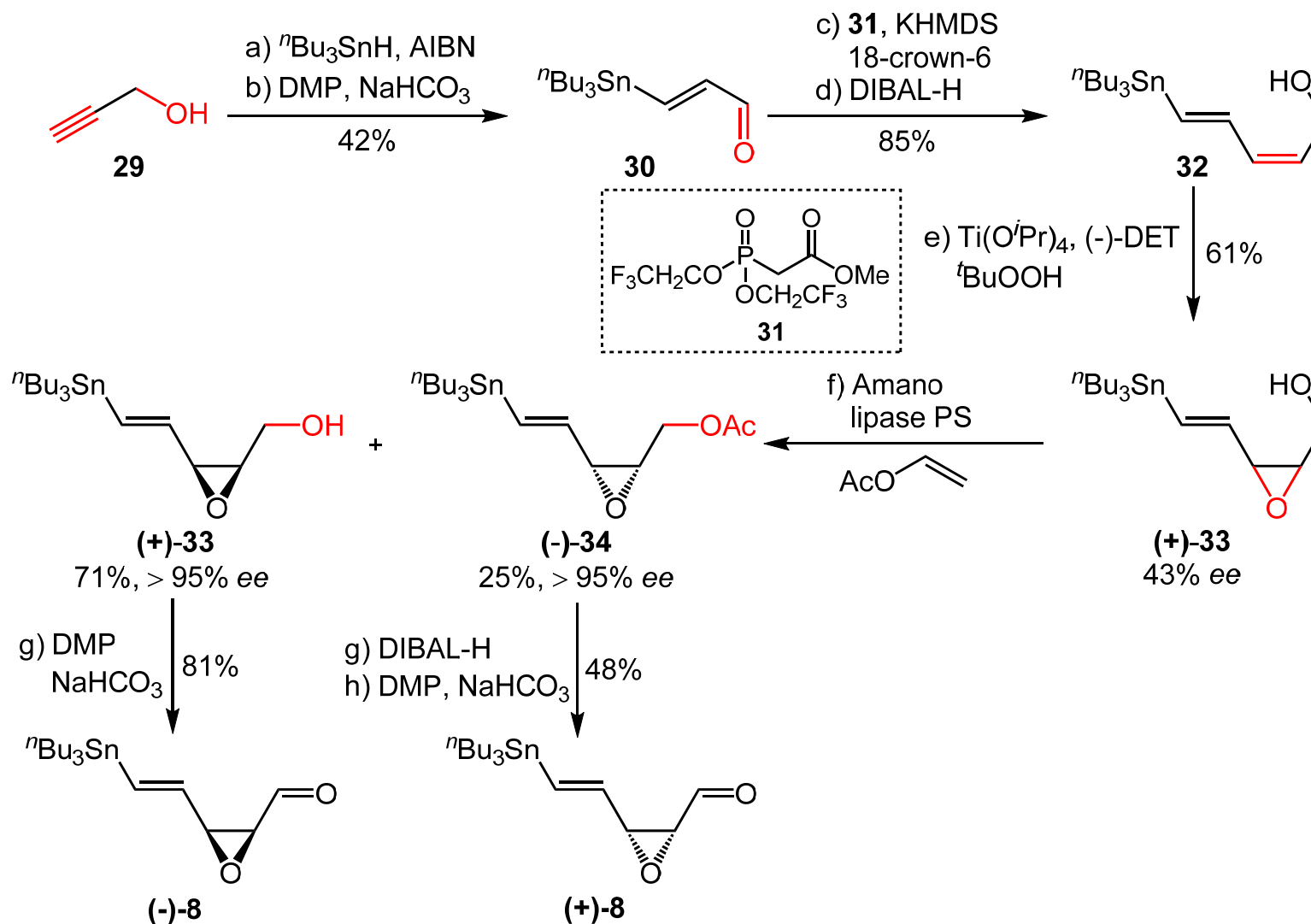


# Synthesis of Vinyl Bromide 6

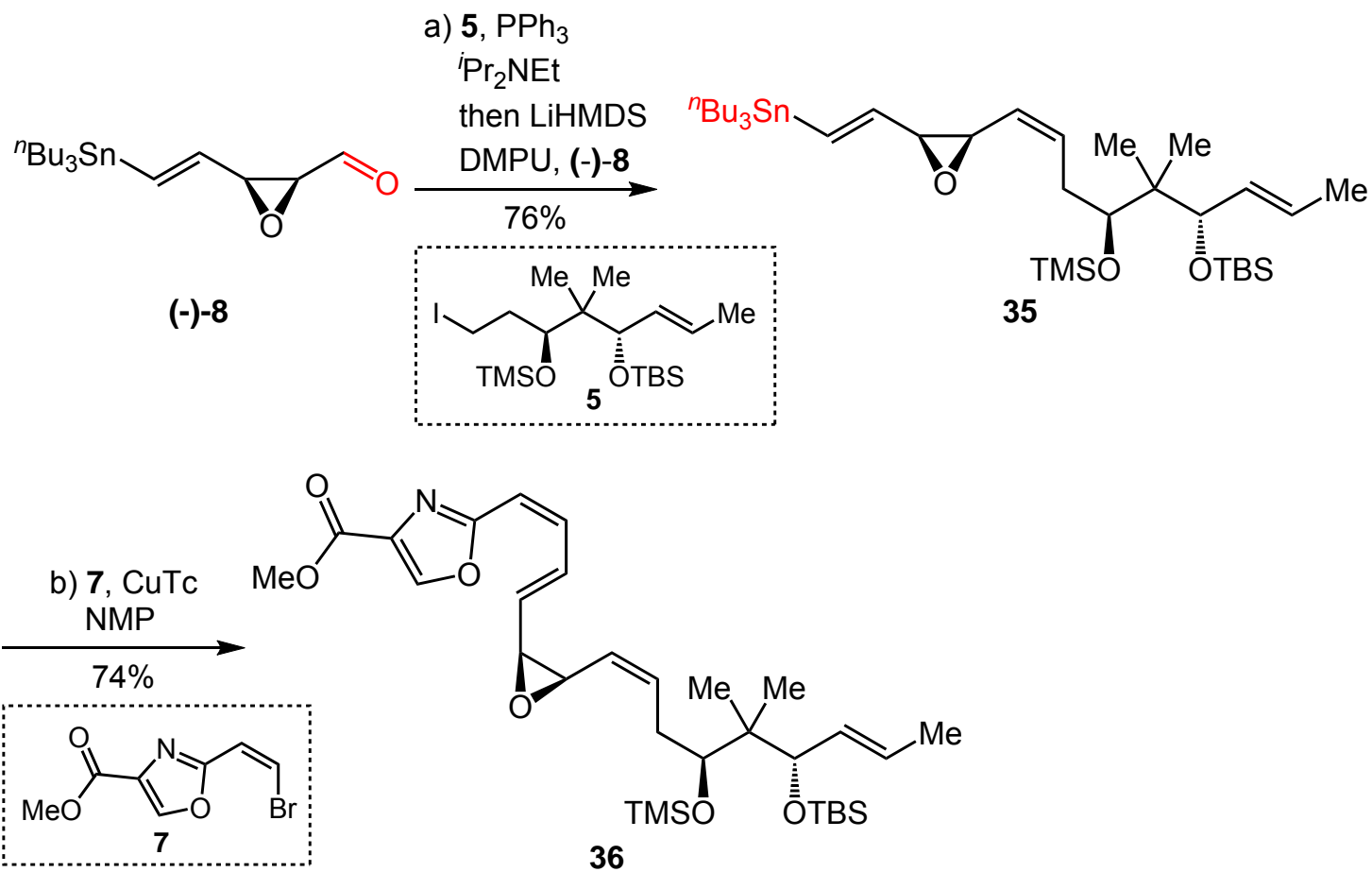




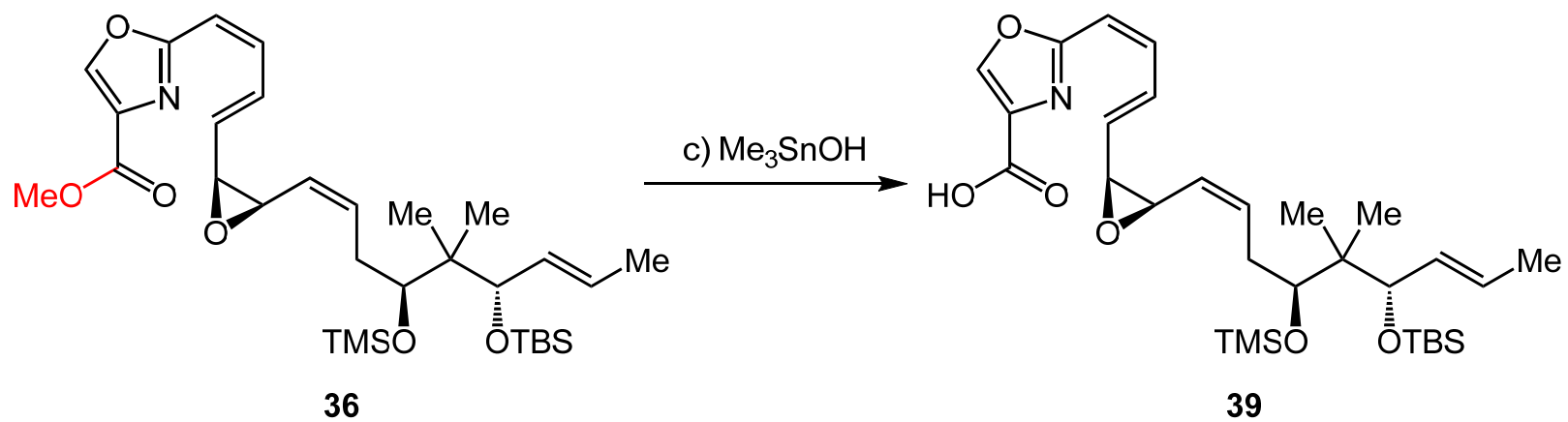
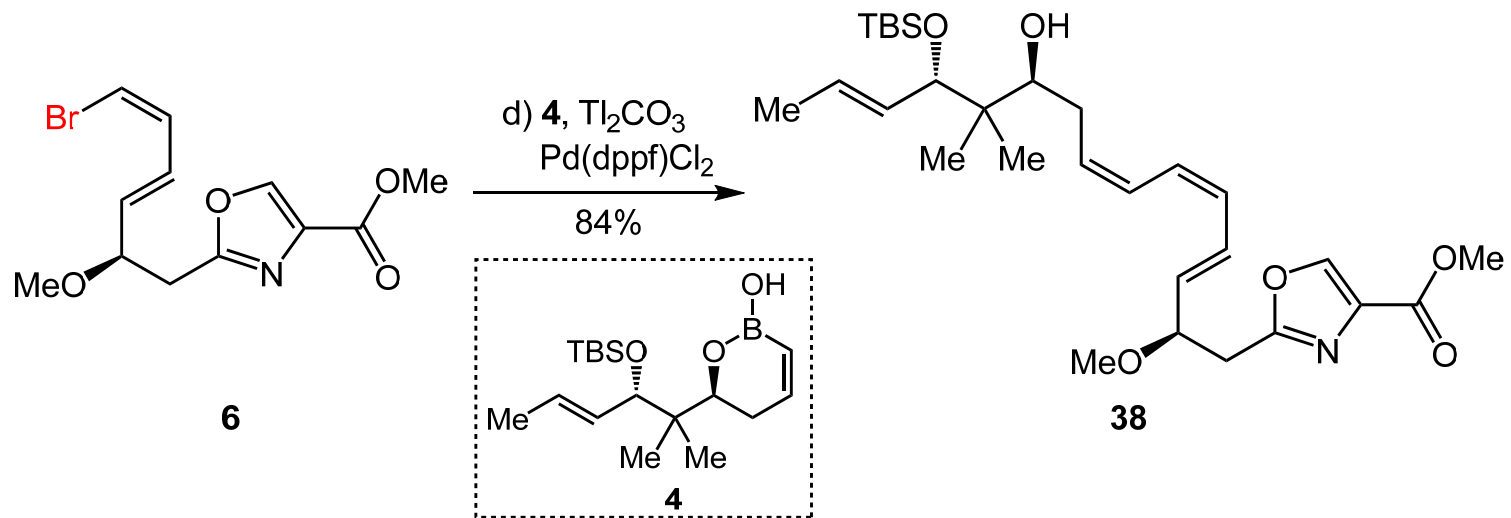
# Synthesis of Aldehyde 8



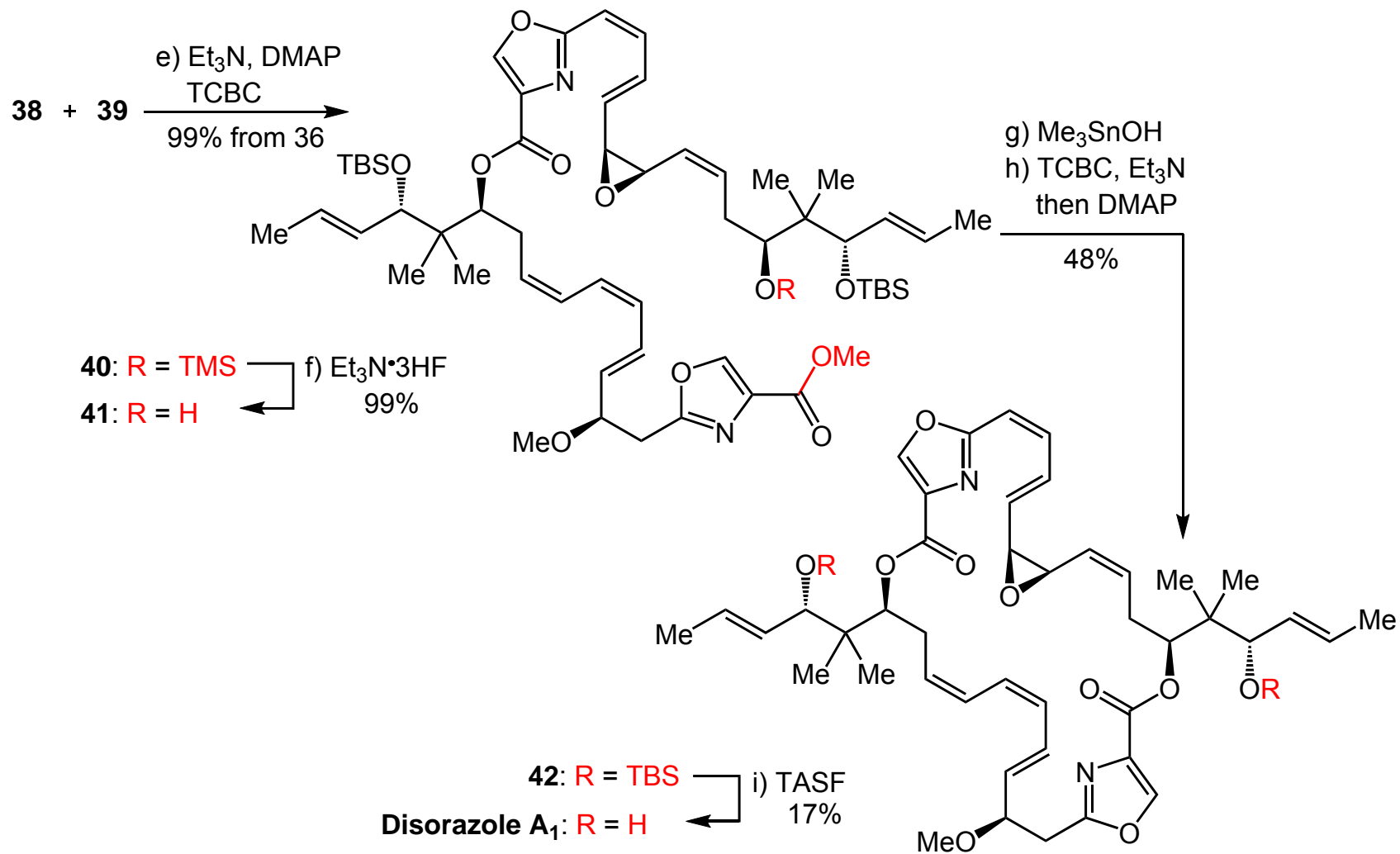
# Total Synthesis of Disorazole A1



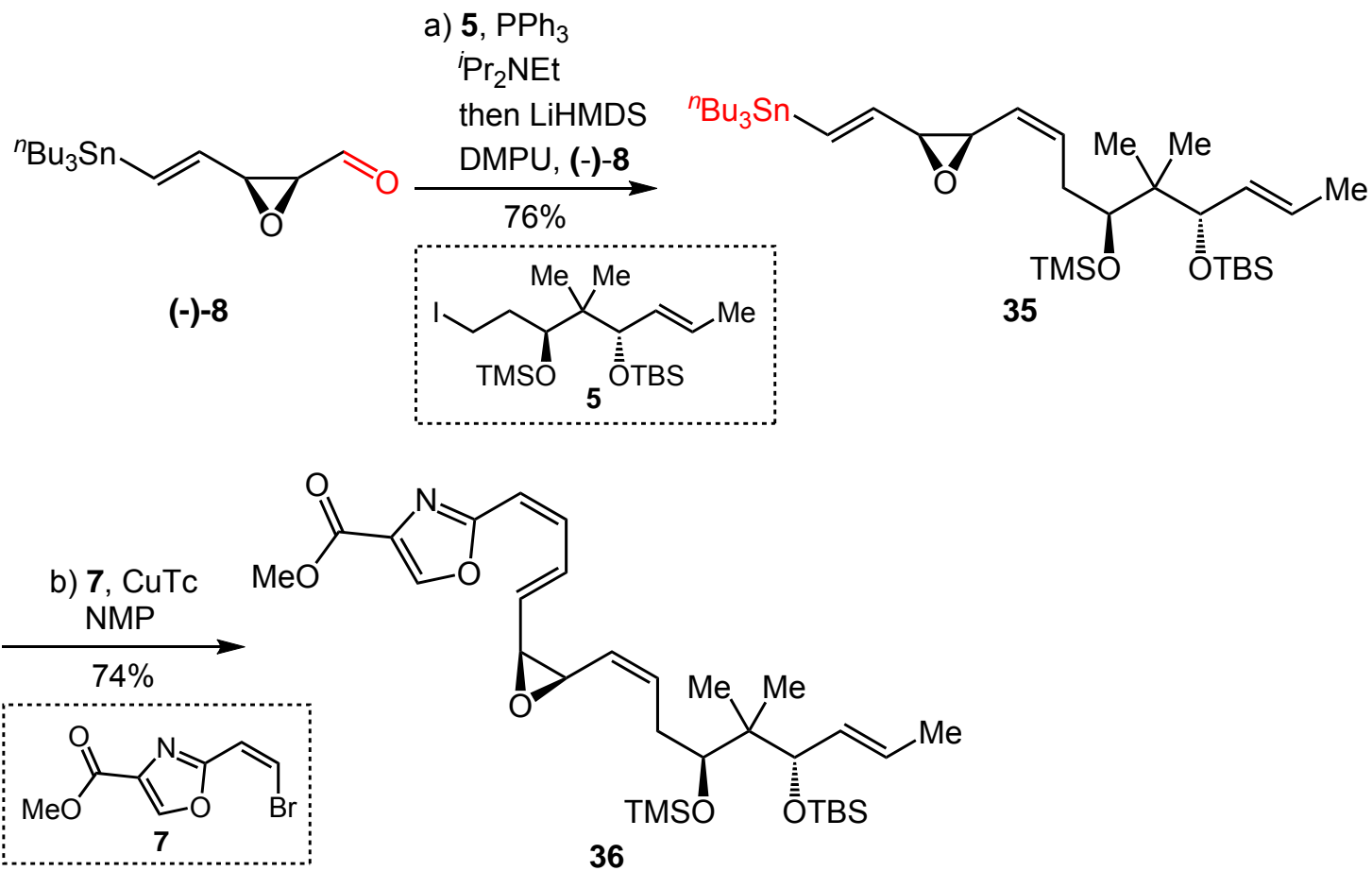
# Total Synthesis of Disorazole A<sub>1</sub>



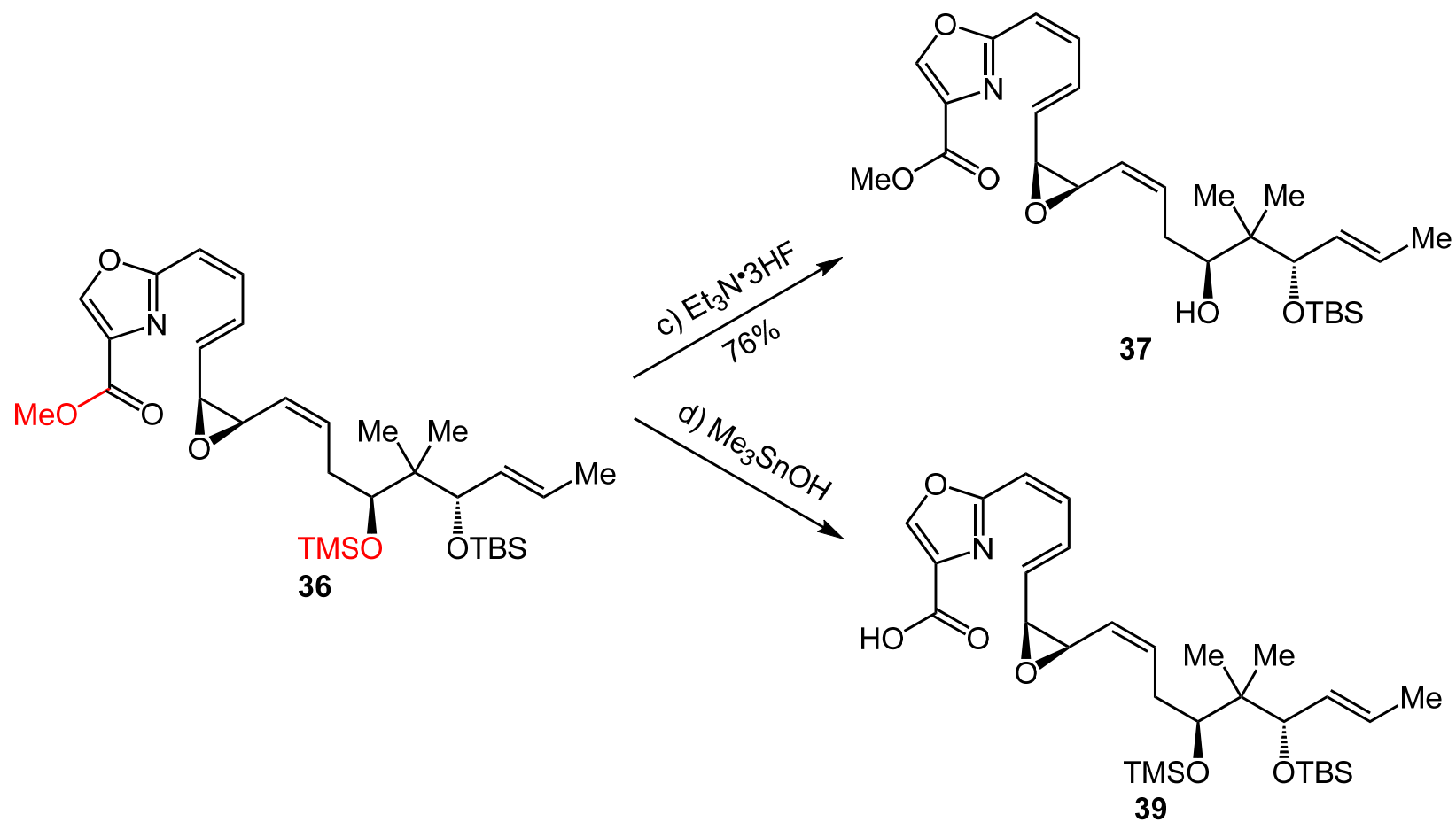
# Total Synthesis of Disorazole A<sub>1</sub>



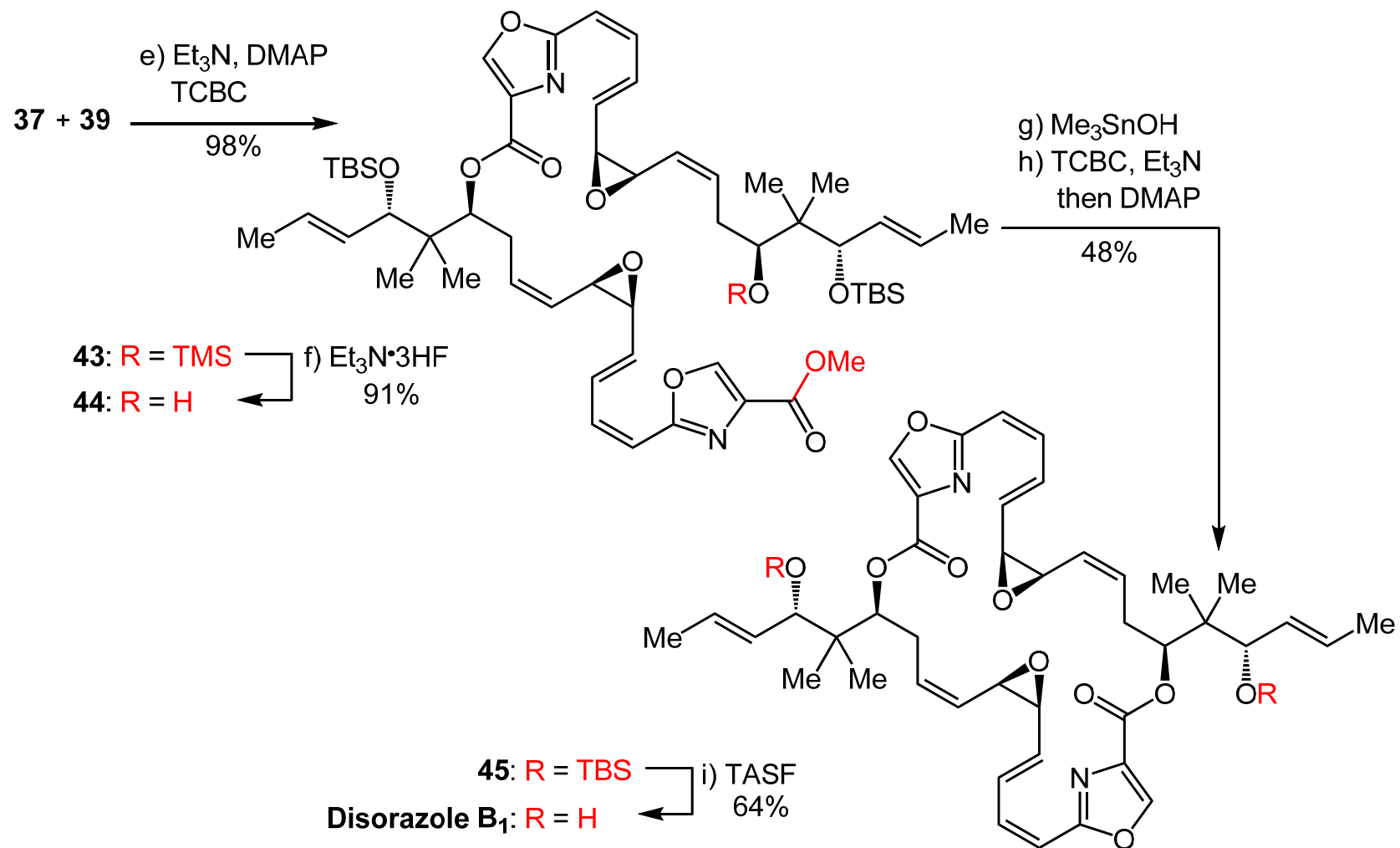
# Total Synthesis of Disorazole B1



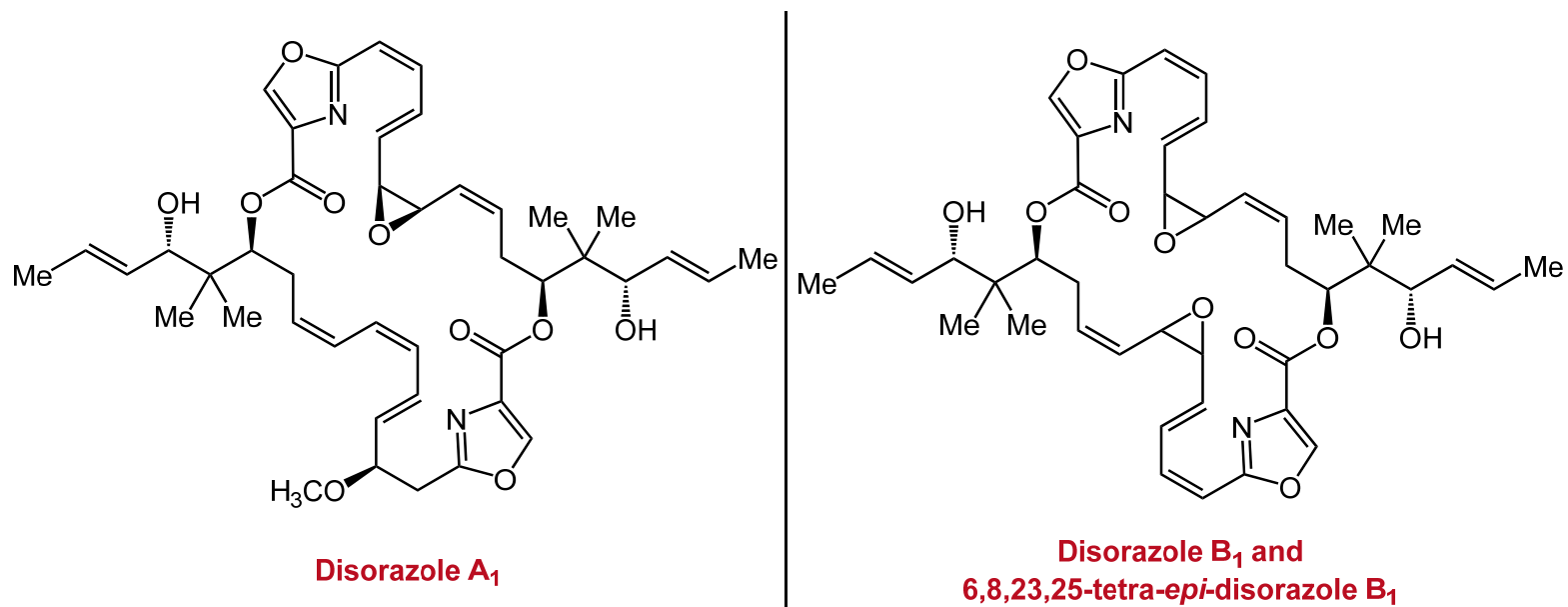
# Total Synthesis of Disorazole B<sub>1</sub>



# Total Synthesis of Disorazole B<sub>1</sub>



# Summary



- Disorazole A<sub>1</sub>: 18 steps, 1.59% overall yield  
Disorazole B<sub>1</sub>: 15 steps, 14.66% overall yield  
6,8,23,25-tetra-*epi*-disorazole B<sub>1</sub>: 16 steps, 0.12% overall yield
- The first total syntheses of disorazoles A<sub>1</sub> and B<sub>1</sub>
- The syntheses were achieved through a series of coupling reactions, including Wittig reaction, Suzuki cross-coupling, Stille cross-coupling, Yamaguchi esterification and Yamaguchi macrolactonization



## The First Paragraph

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该类化合物的来源和生物活性

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graph TD; A[该类化合物的来源和生物活性] --> B[分析该类化合物在合成上的挑战]; B --> C[概括本文的工作内容];
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分析该类化合物在合成上的挑战

概括本文的工作内容

## The First Paragraph

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The disorazoles are a distinguished class of tubulin binding antitumor agents due to their unique mode of action and high potencies against a broad range of cancer cell lines. Although too cytotoxic to be used as anticancer drugs, these natural products may become powerful payloads for antibody–drug conjugates (ADCs), a hotly pursued paradigm for targeted personalized cancer therapies. Elegant total syntheses of disorazole C1 and related synthetic studies have been reported. From the members of this family of compounds, disorazole A1 (1, Figure 1) stands as the flagship, not only because it is the most studied, but also due to its single digit picomolar potencies and synthetically challenging structure.

## The First Paragraph

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Indeed, a total synthesis of disorazole A<sub>1</sub> has not been reported, despite several studies directed toward this goal. Disorazole B<sub>1</sub> whose structure has only been partially assigned as 2 (C<sub>2</sub> symmetric) or 3 (6,8,23,25-tetra-*epi*-disorazole B<sub>1</sub>, Figure 1) presents another challenging calling to both structural elucidation and total synthesis. In this communication, we report: (a) total synthesis of disorazole A<sub>1</sub> (1); (b) total synthesis of disorazole B<sub>1</sub> (2) and 6,8,23,25-tetra-*epi*-disorazole B<sub>1</sub> (3); and (c) full assignment of disorazole B<sub>1</sub> as structure 2.

# The Last Paragraph

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概述本文的工作内容



表明工作意义及潜在应用

## The Last Paragraph

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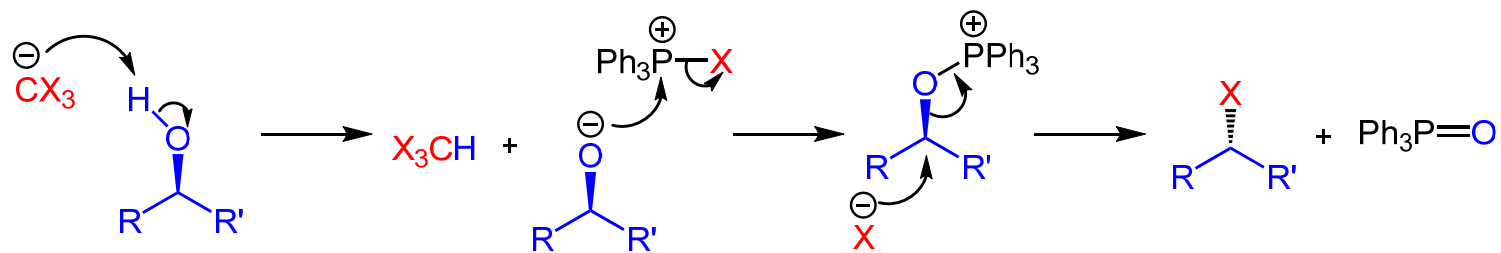
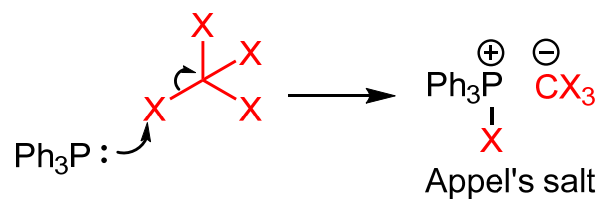
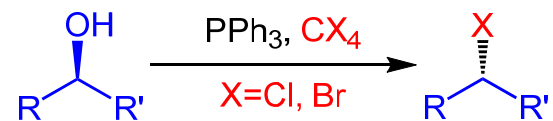
Representing the first total syntheses of disorazoles A1 (1) and B1 (2), and revealing the full structural assignment of disorazole B1, the described chemistry could lead to wide scope explorations of structure–activity relationships (SARs) through analogue design, synthesis and biological evaluation within the disorazole family of compounds, from which highly potent cytotoxic agents may emerge as potential payloads for antibody–drug conjugates (ADCs).

## Acknowledgement

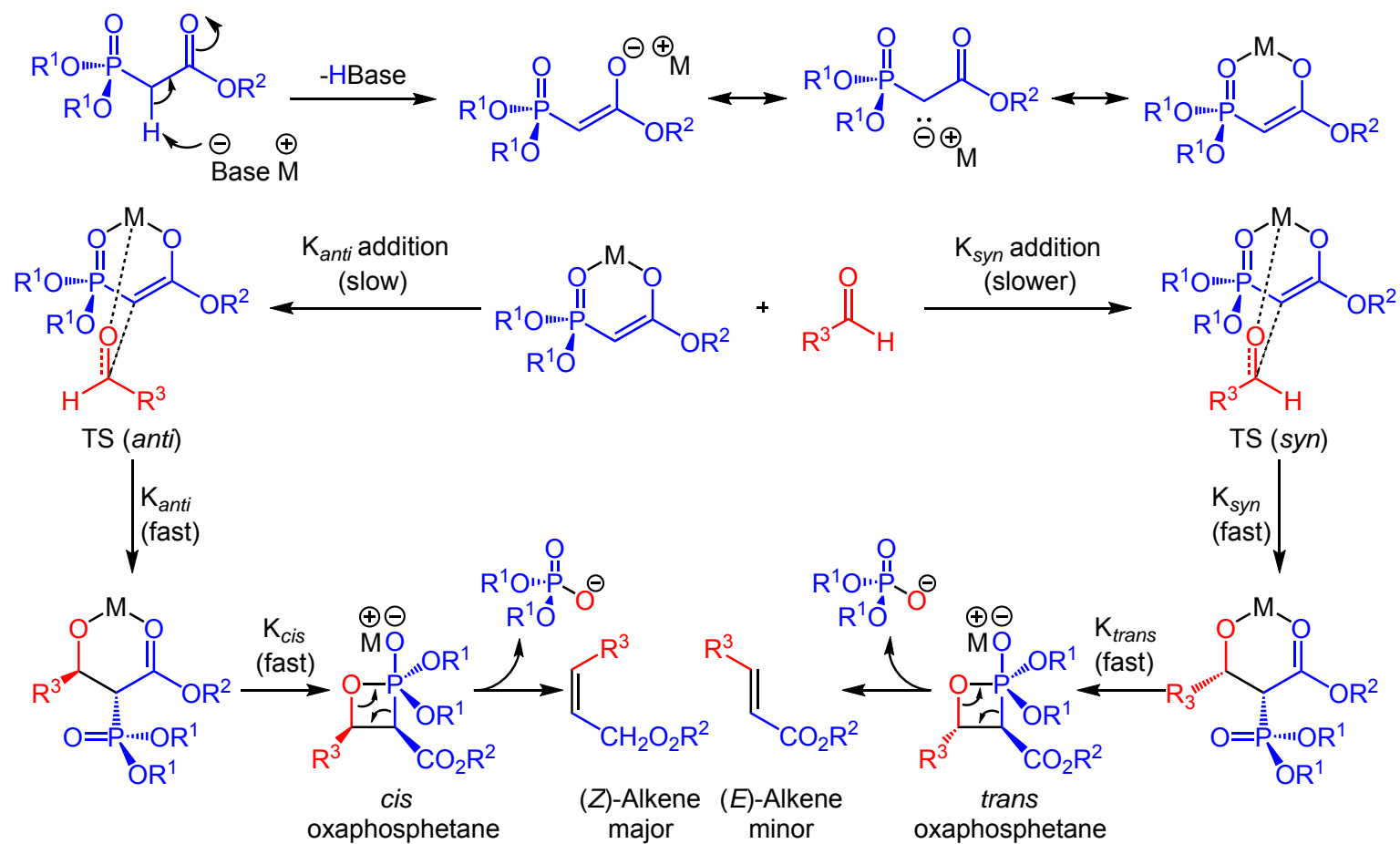
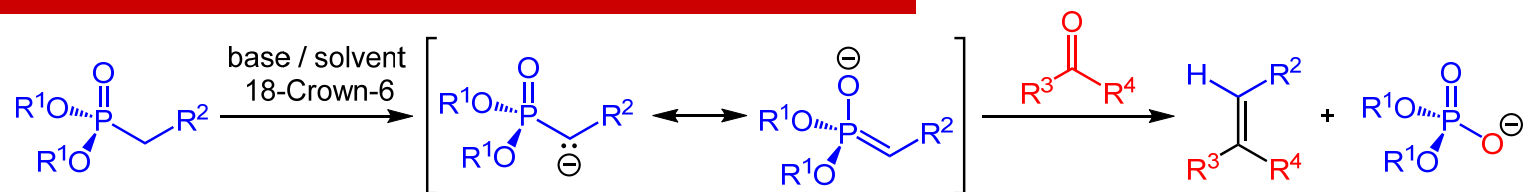
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***Thanks  
for your attention***

# Appel Reaction

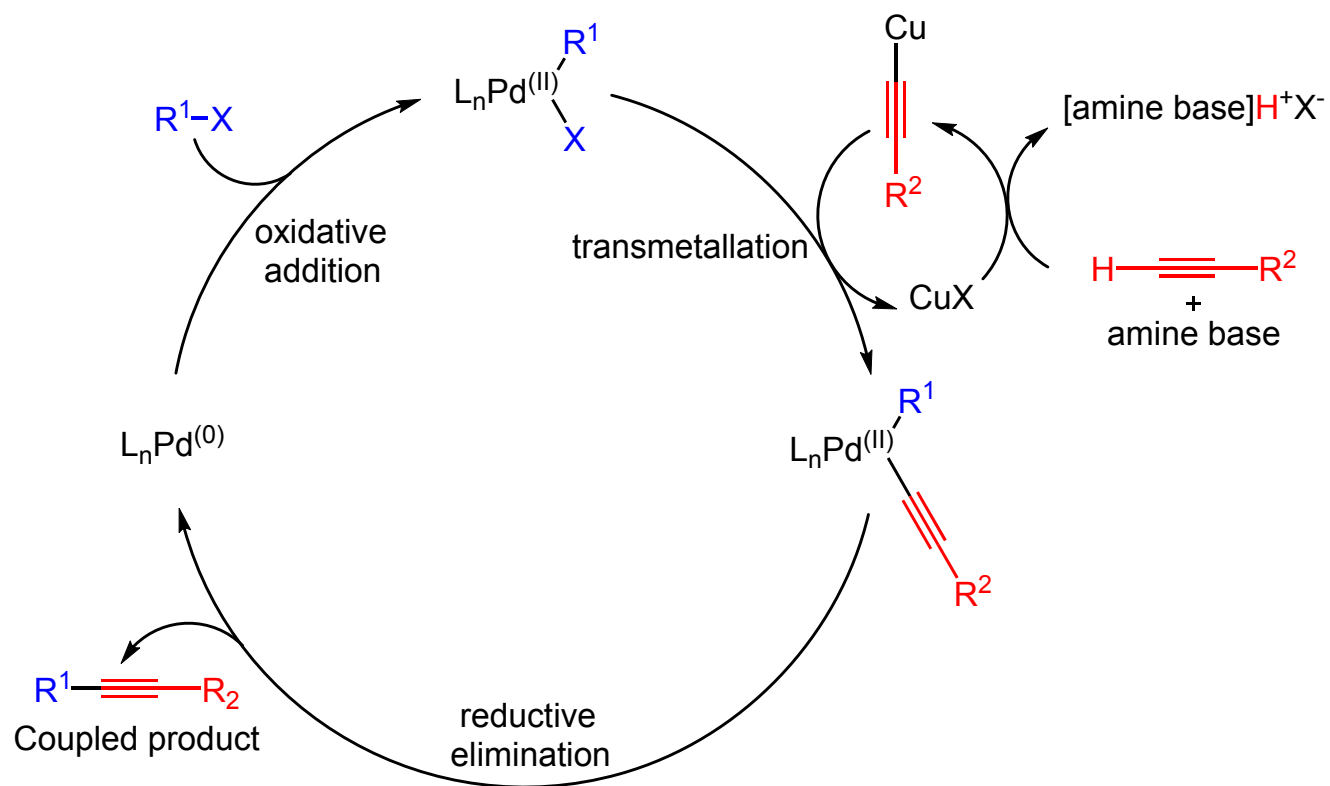
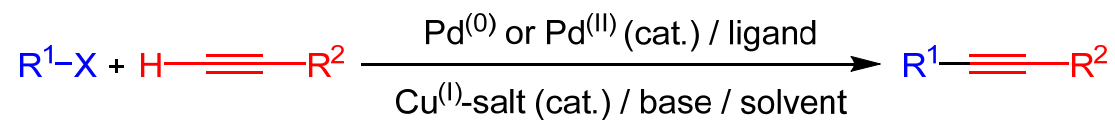


# Still-Gennari Reaction



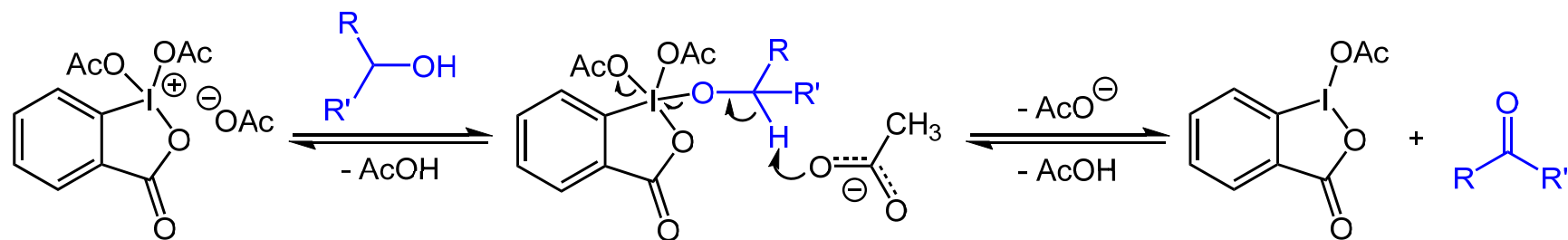
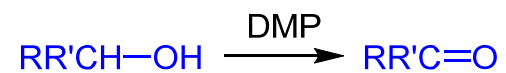


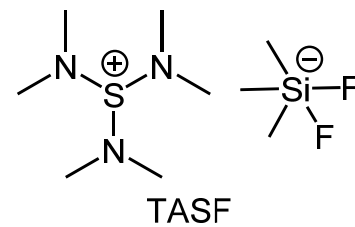
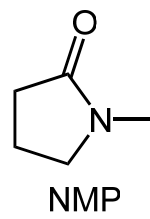
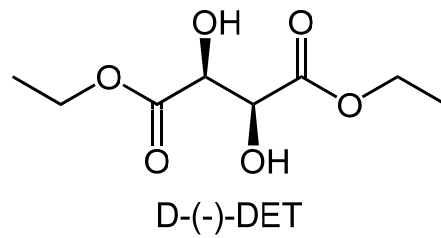
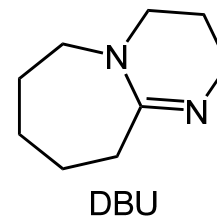
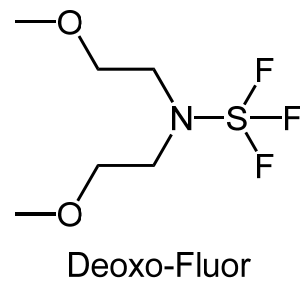
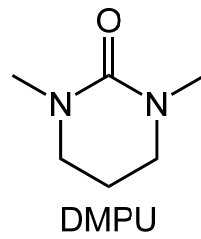
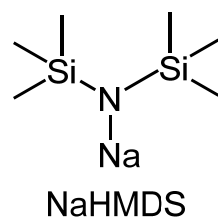
# Sonogashira Cross-Coupling



# Dess-Martin Oxidation

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