

Career Overview of David W. C. MacMillan

Christina S. Stauffer
Wednesday Group Meeting
April 18, 2007

Introduction

- **1968:** Born in Scotland.
- **1990:** Began graduate studies with Overman at UC Irvine – total synthesis of (7)-(-)-deacetoxyalcyonin acetate... A member of the eunicellin family of natural products.
- **1996:** Postdoc with David Evans at Harvard – worked on enantioselective catalysis of Sn(II)-derived bisoxazoline complexes.
- **1998:** Began career at UC Berkeley.
- **2000:** Moved to Caltech – appointed Earle C. Anthony Professor of Chemistry in 2004.
- **2006:** Recently completed move to Princeton University – A. Barton Hepburn Prof. of Org. Chemistry.

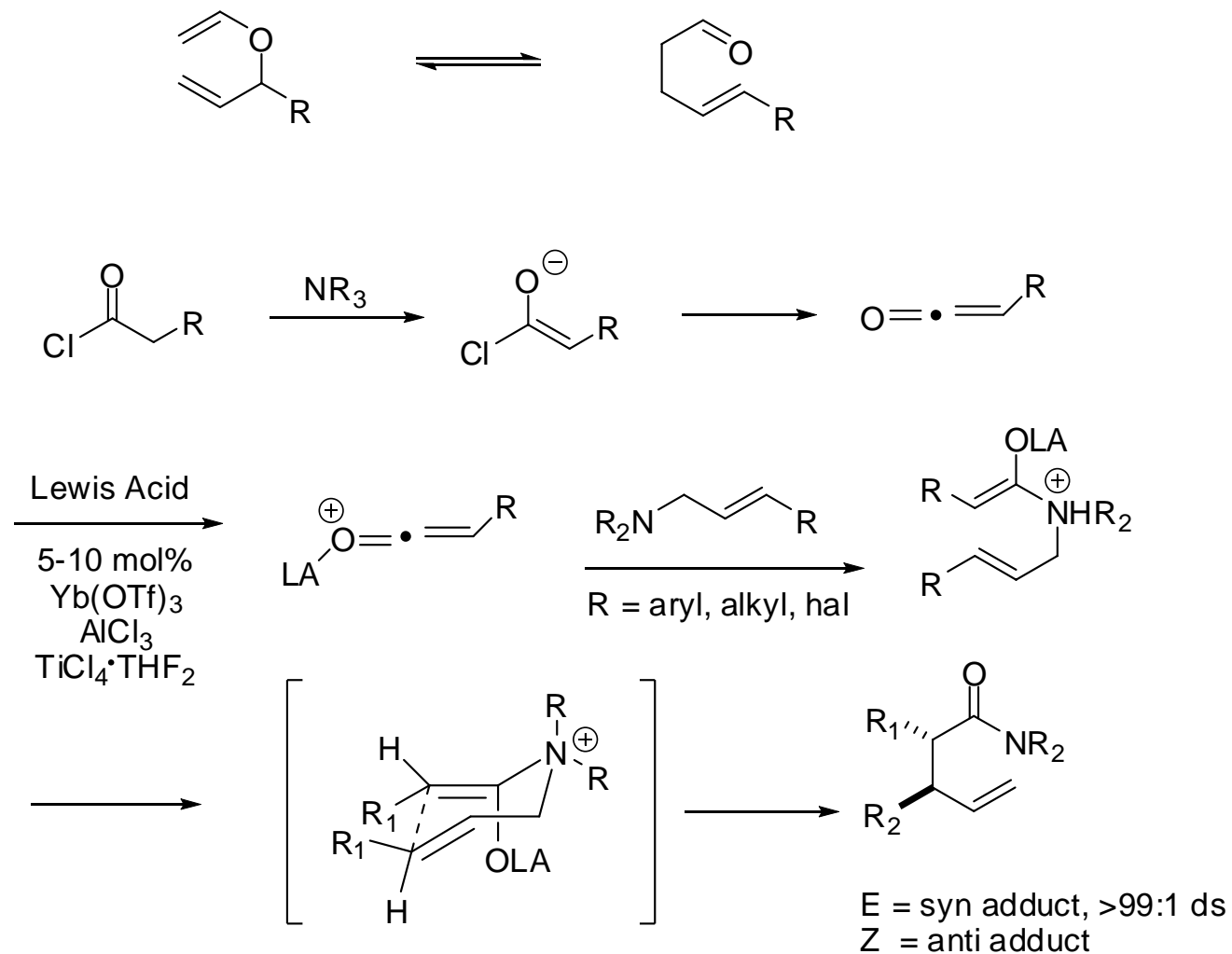
Awards, etc.

- **2006:** Arthur C.Cope Scholars Award
Mukaiyama Award
- **2005:** E.J. Corey Award for Young Investigator
- Numerous other awards from industry: BMS, Pfizer, GSK, Eli Lilly.
- Serves on the scientific advisory boards of several companies and as a scientific consultant to several pharma companies.

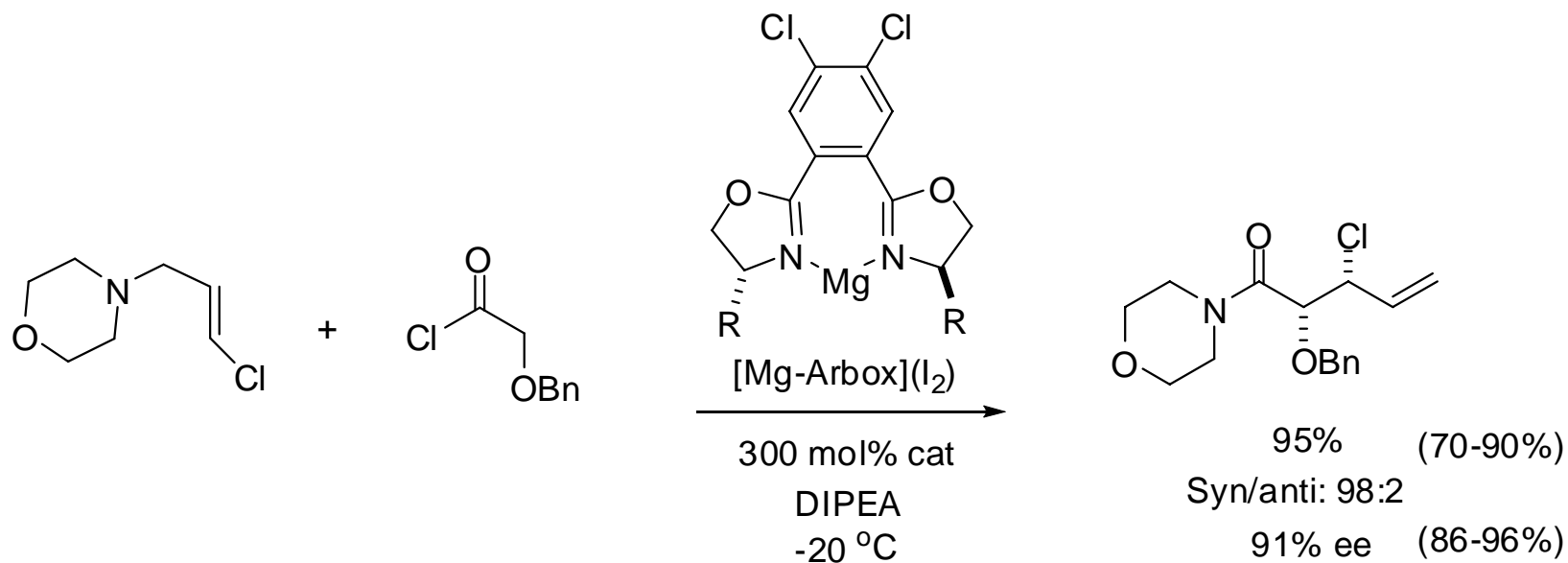
Research Interests

1. Enantioselective catalysis
2. New reaction methodology
3. Natural product synthesis

Catalytic acyl-Claisen rearrangement

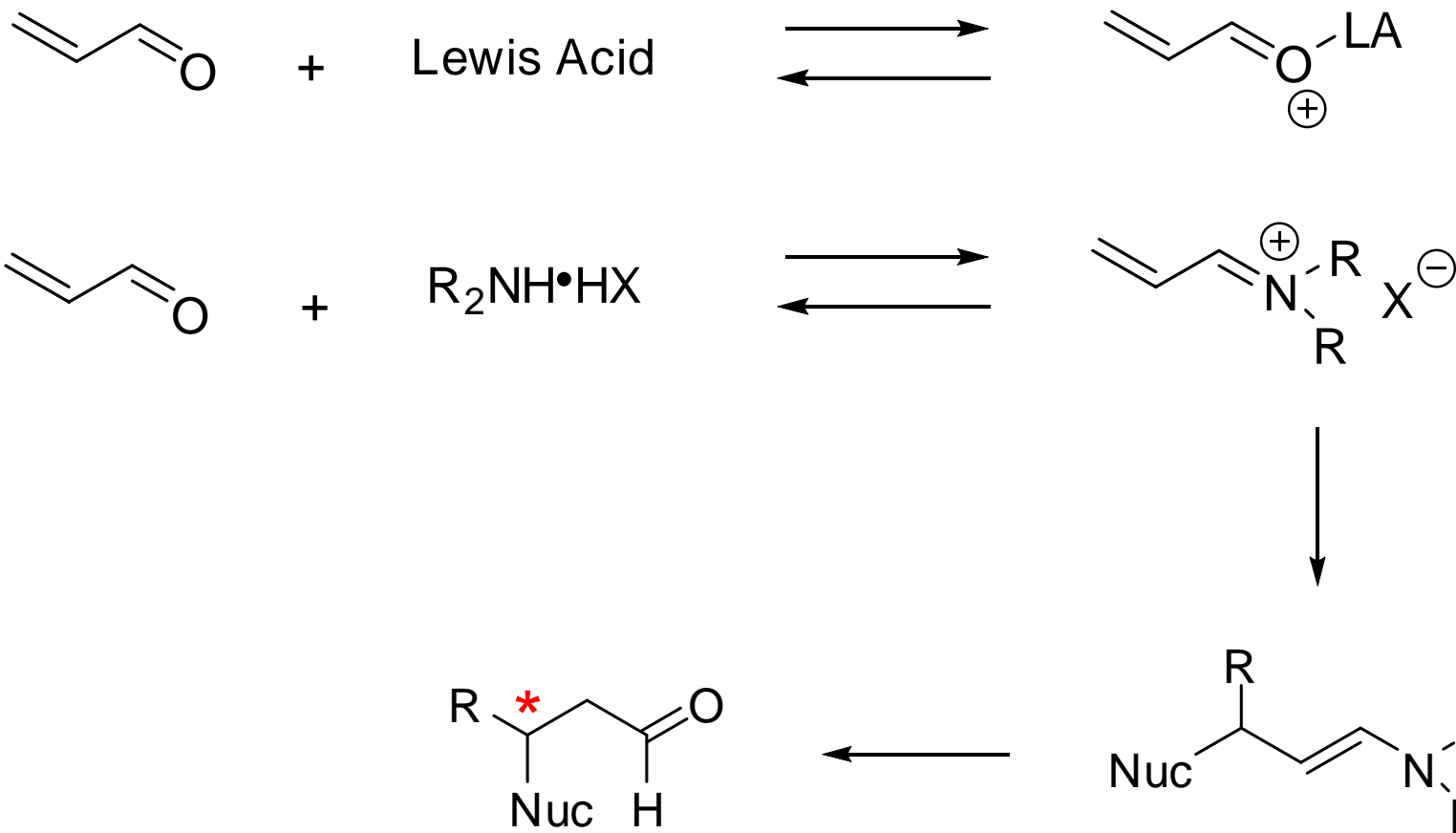


Acyl-Claisen rearrangement with allyl morpholines



1st enantioselective acyl-Claisen methodology

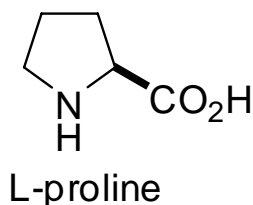
Iminium Activation: Concept Development



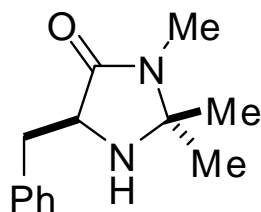
- Use chiral amines as LUMO-lowering catalysts instead of Lewis acids.
- Trying to emulate the equilibrium dynamics and pi-orbital electronics of L.A.'s with a carbogenic system.

Requirements for effective organocatalysis

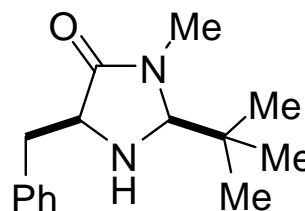
1. Increase reactivity of substrate.
2. Efficient and reversible iminium ion formation.
3. Control enantiofacial selectivity of the olefin.
 - thru organized T.S.
 - predictable d.b. geometry
4. Ease of catalyst preparation and implementation.



List, Barbas, MacMillan, etc.



MacMillan 1st gen.
Imidazolidinone catalyst



MacMillan 2nd gen.
Imidazolidinone catalyst

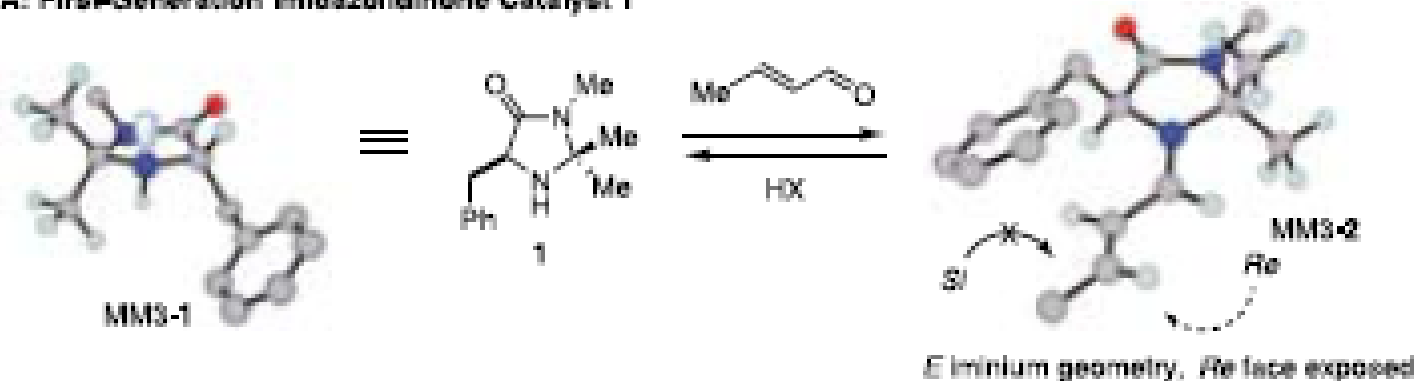
Applications

- cycloadditions
- conjugate additions
- Friedel-Crafts alkylations
- cascade reactions

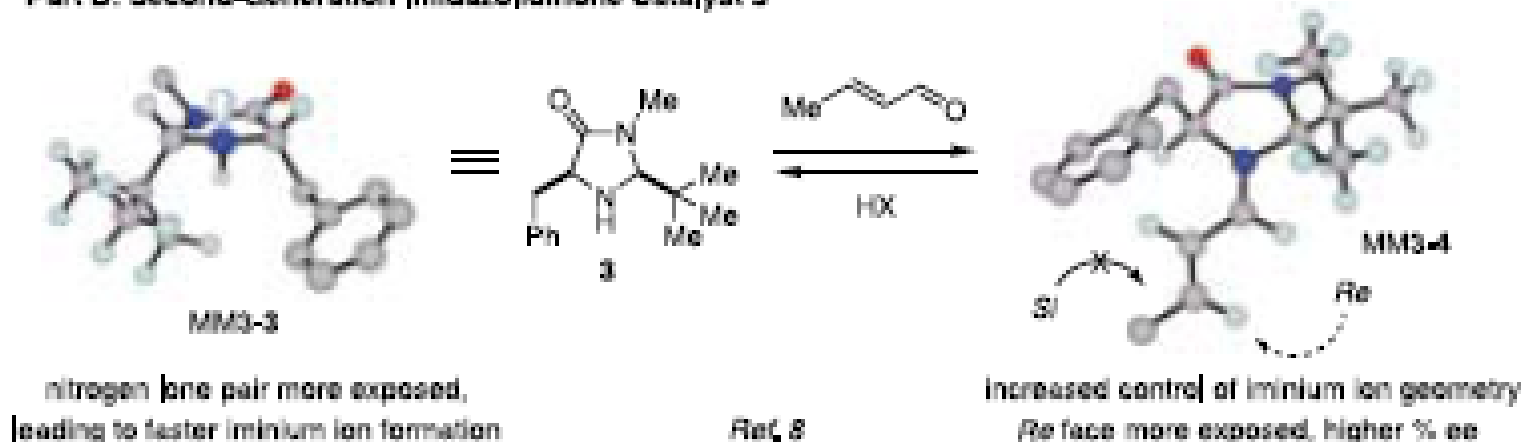
Alrichimica ACTA, **2006**, 39, 79-87
JACS, **2000**, 122, 4243
JACS, **2002**, 124, 1172

Computational Models of the Imidazolidinone Catalysts

Part A: First-Generation Imidazolidinone Catalyst 1

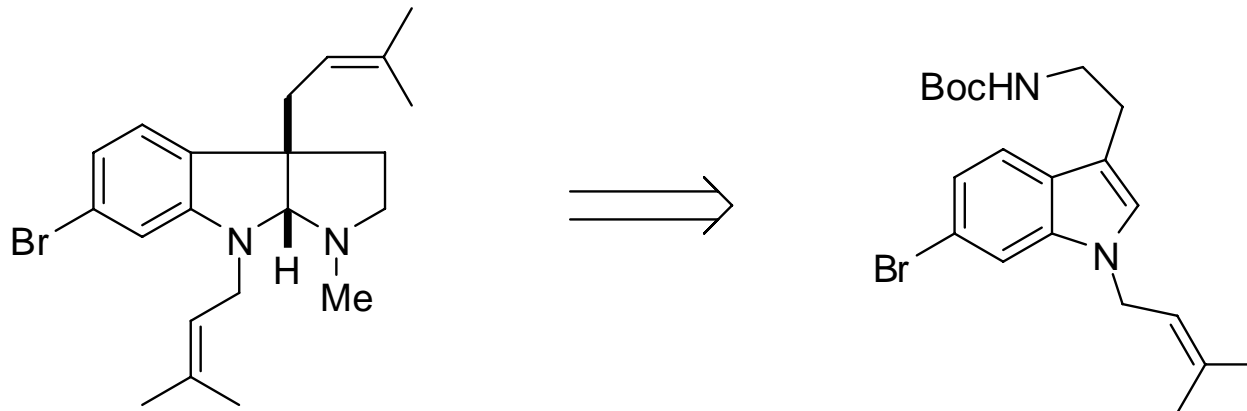
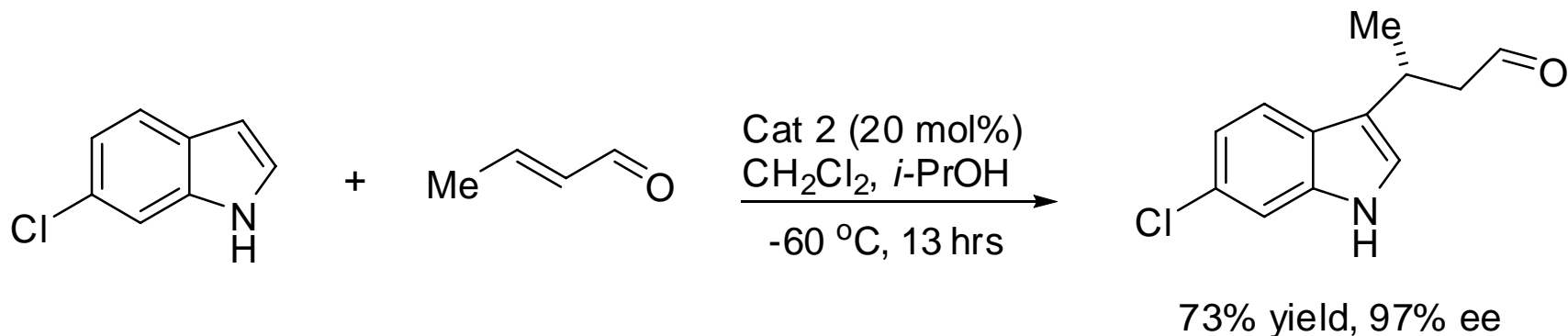


Part B: Second-Generation Imidazolidinone Catalyst 3



- *E*-iminium geometry favored to avoid nonbonding interactions between the substrate olefin and the *gem*-dimethyl substituents.

Organocatalyzed Friedel-Crafts Indole Alkylation

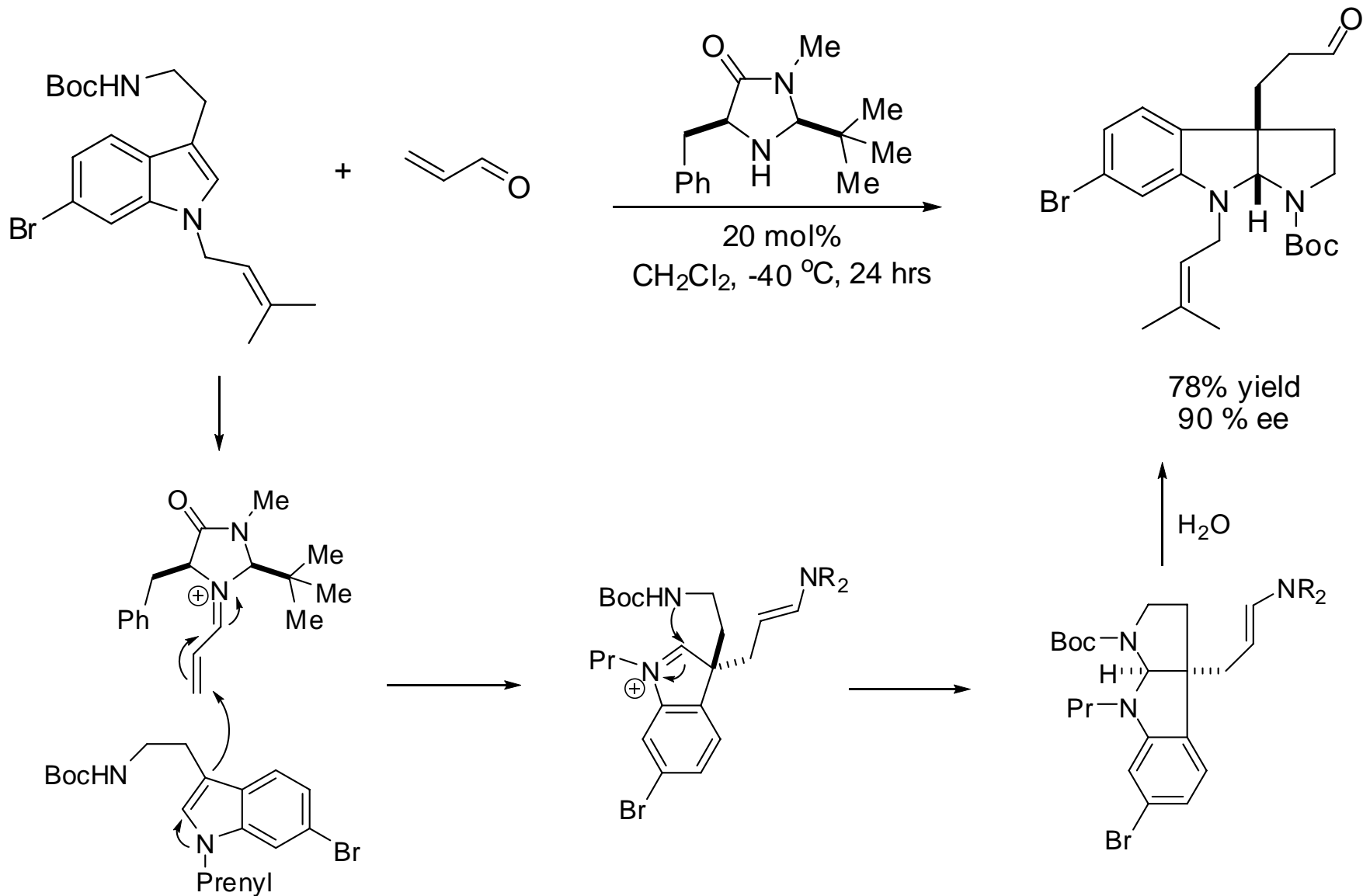


(-)-Flustramine B

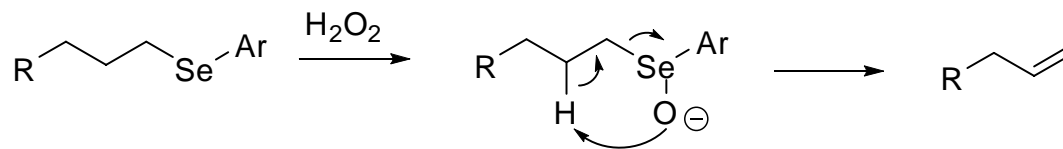
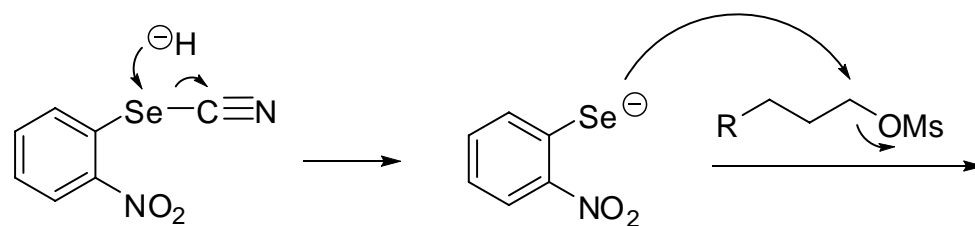
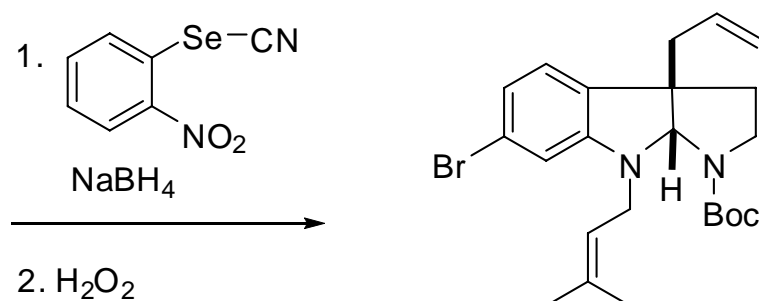
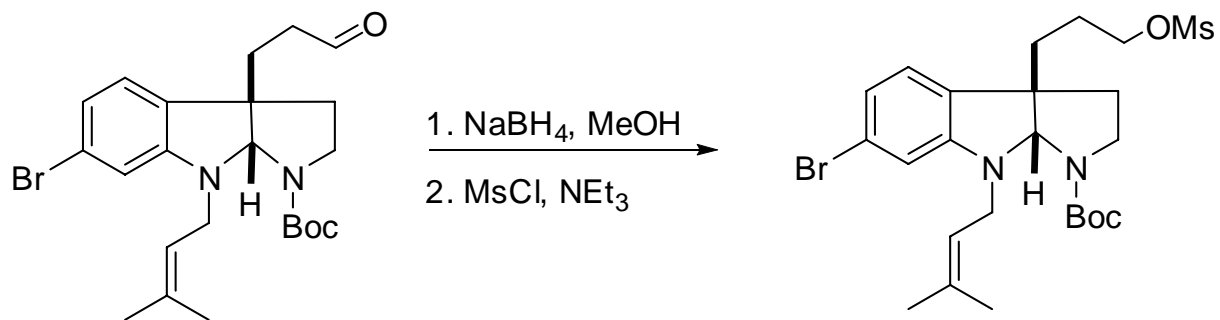
- pyrroloindoline marine alkaloid
- blocks voltage-gated K⁺ channels

JACS, **2002**, *124*, 1172
PNAS, **2004**, *101*, 5482

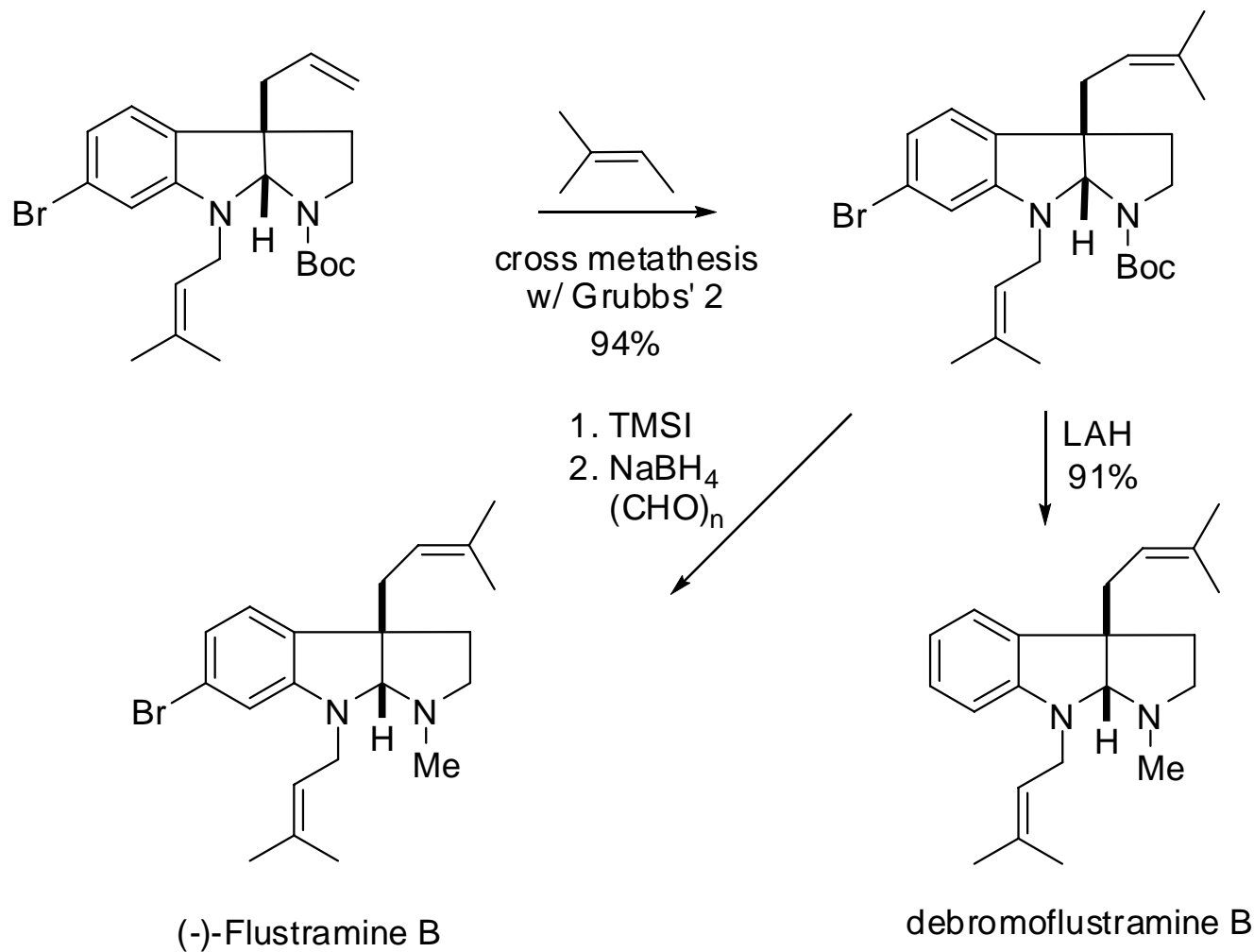
Synthesis of (-)-Flustramine B



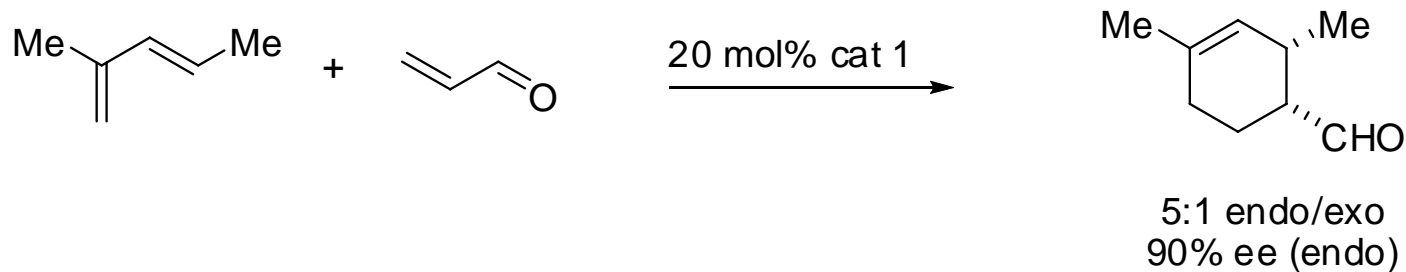
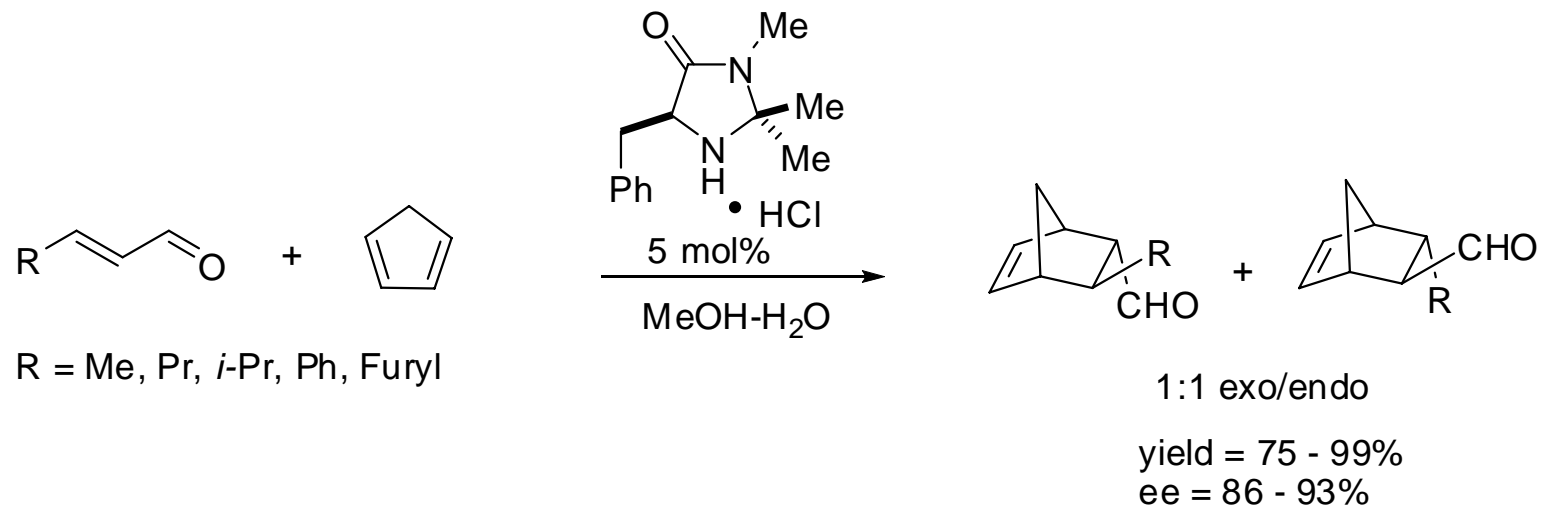
Synthesis of (-)-Flustramine B Continued



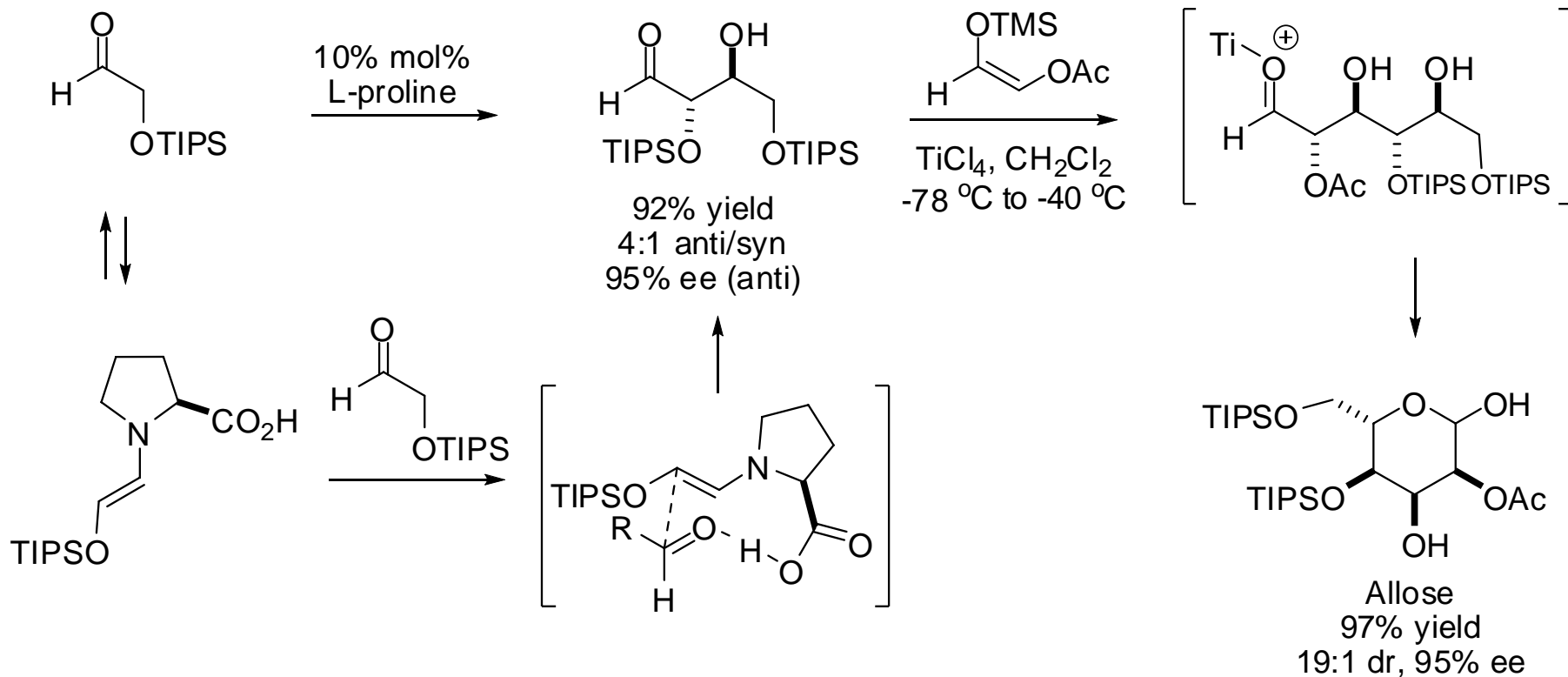
Completion of (-)-Flustramine B



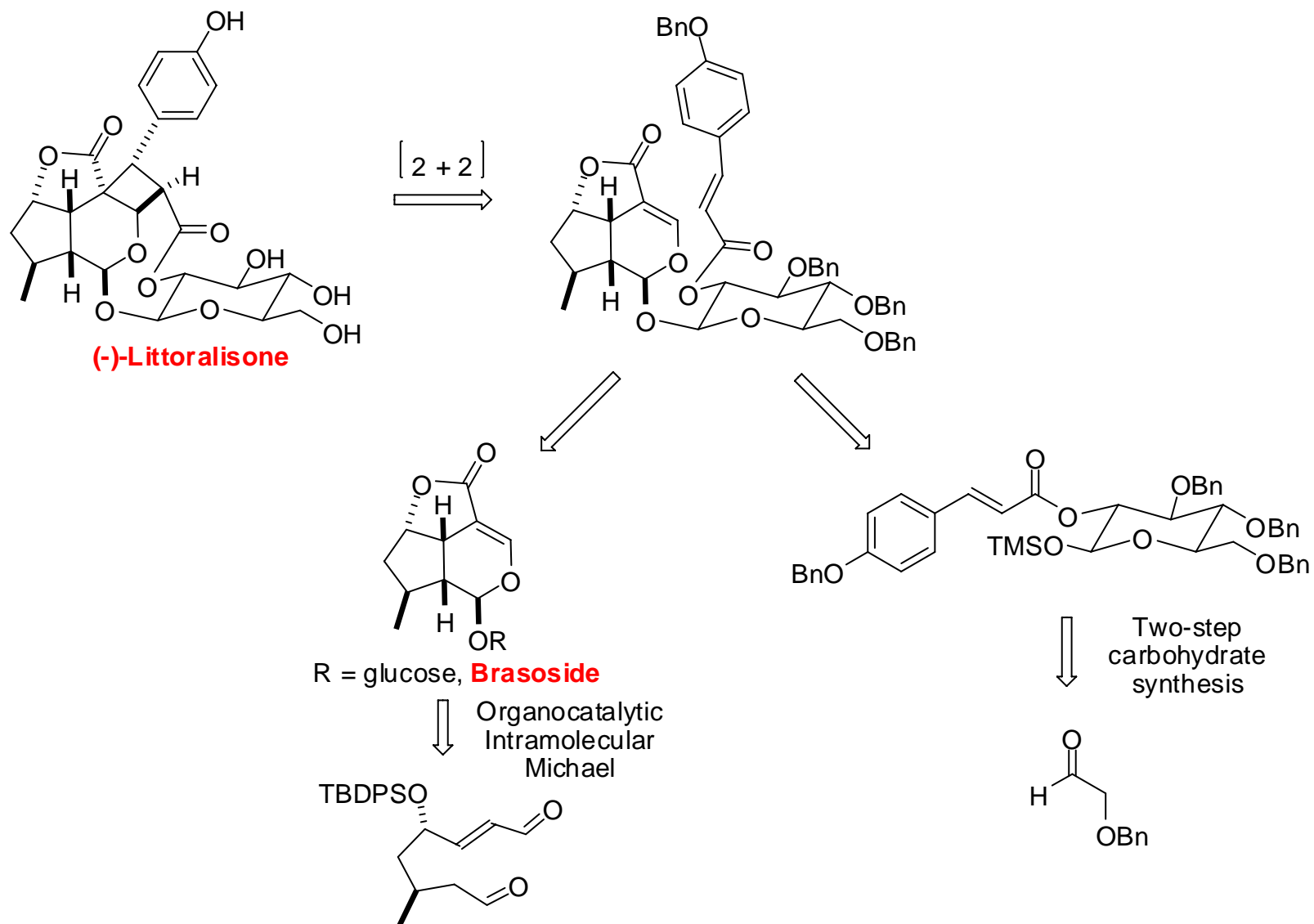
Enantioselective Organocatalytic Diels-Alder Reaction



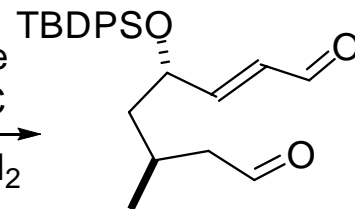
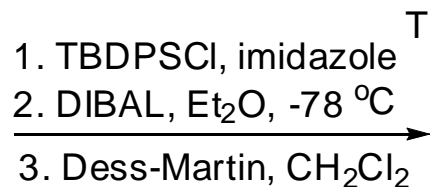
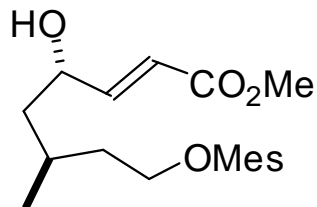
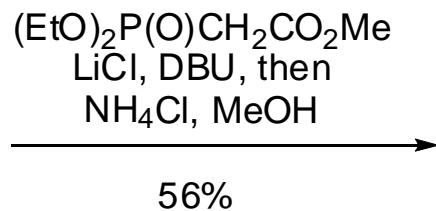
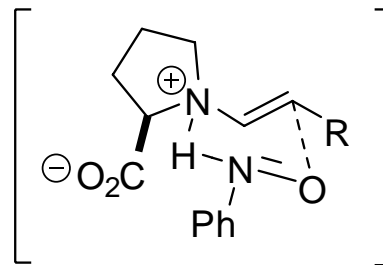
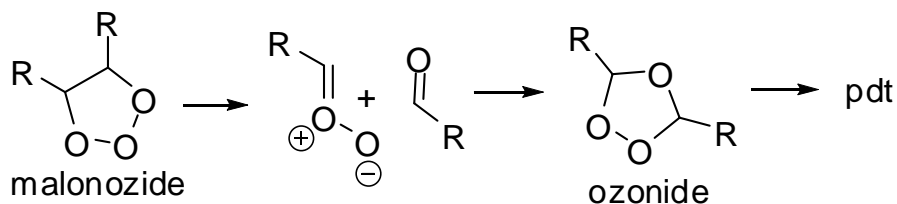
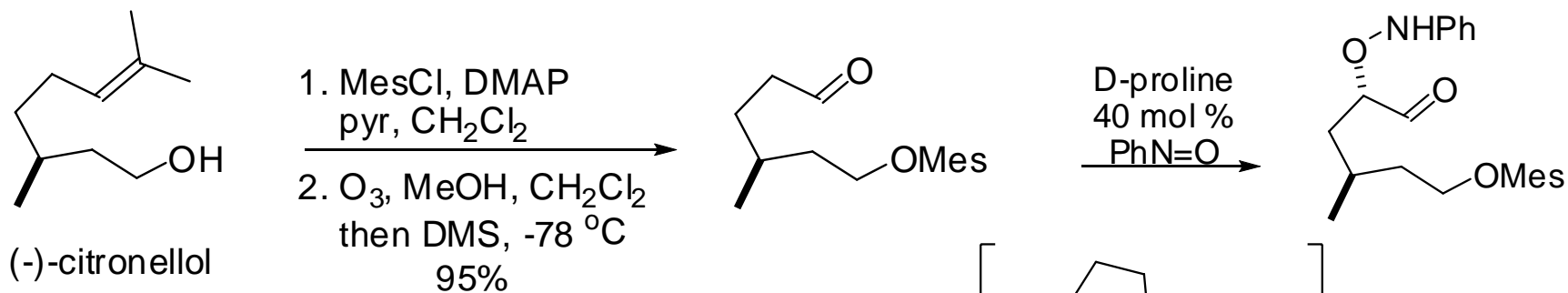
Two-step carbohydrate synthesis utilizing aldol reactions



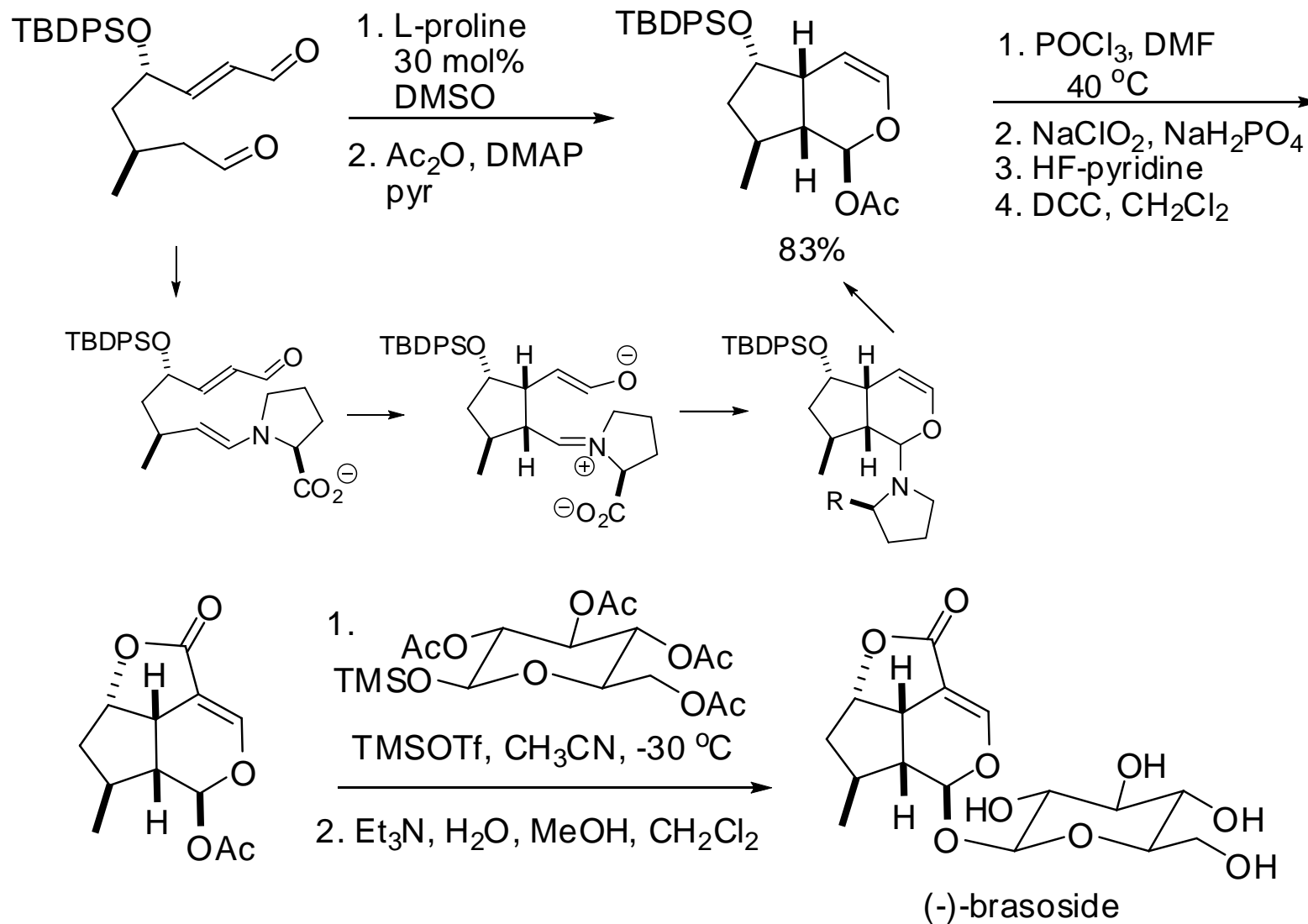
Retrosynthetic strategy for Brasoside and Littoralisone



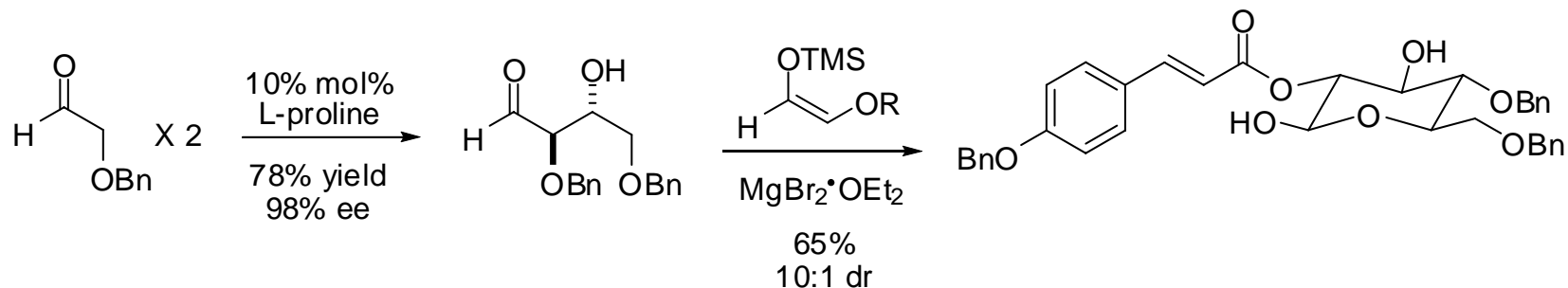
Synthesis of Brasoside



Synthesis of Brasoside cont.



Synthesis of Littoralisone



1. Ag_2O , BnBr
2. $\text{Pd}/\text{Al}_2\text{O}_3$, HCO_2NH_4
3. TMSCl , Et_3N , 80°C

