Literature Report II

Convergent Total Synthesis of (−)-Cyclopamine

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Checker: Jian Chen
Date: 2024-04-01

Sofiadis, M.; Xu, D.; Rodriguez, A. J.; Nissl, B.; Clementson, S.; Petersen, N. N.;
Baran, P. S.* *J. Am. Chem. Soc.* **2023**, *145*, 21760

CV of Prof. Phil S. Baran

Background:

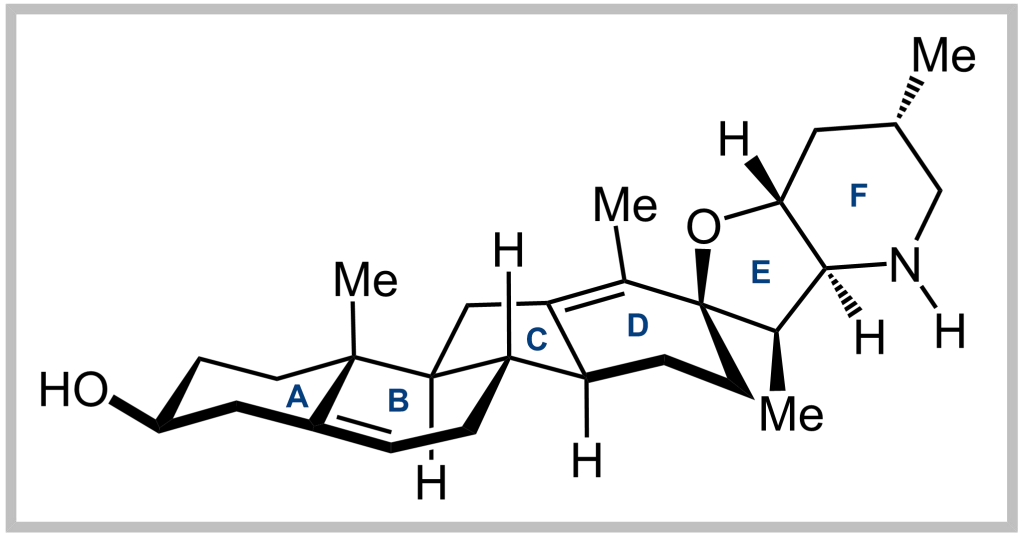
- **1995-1997** B.S., New York University
- **1997-2001** Ph.D., The Scripps Research Institute (K. C. Nicolaou)
- **2001-2003** Postdoc., Harvard University (E. J. Corey)
- **2003-2006** Assistant Professor, The Scripps Research Institute
- **2006-now** Professor, The Scripps Research Institute

Research:

- **Total Synthesis of Natural Products**
- **Efficient Methods for Constructing C-C and C-N Bonds**

Contents

Introduction



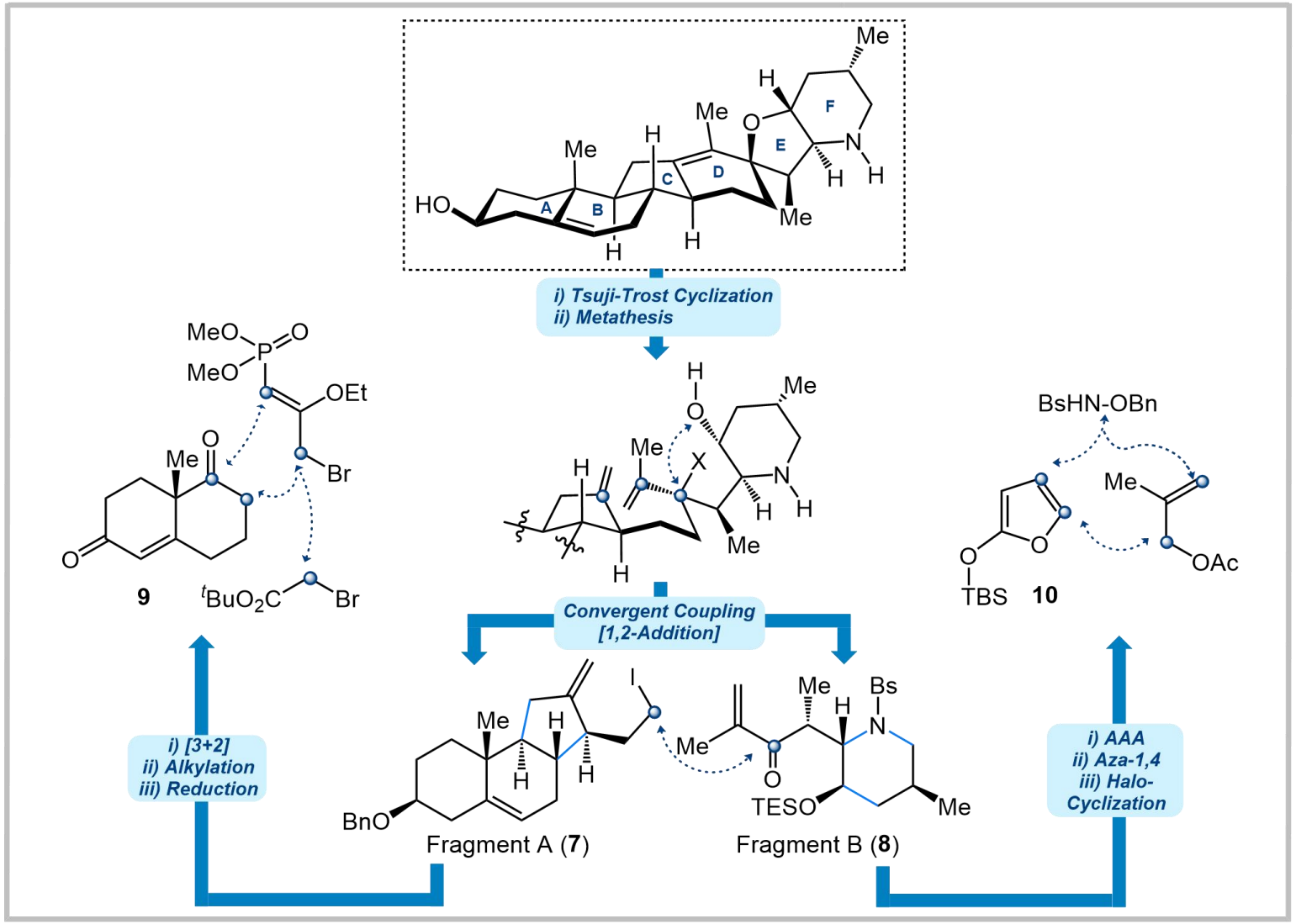
(−)-Cyclopamine

California corn lily

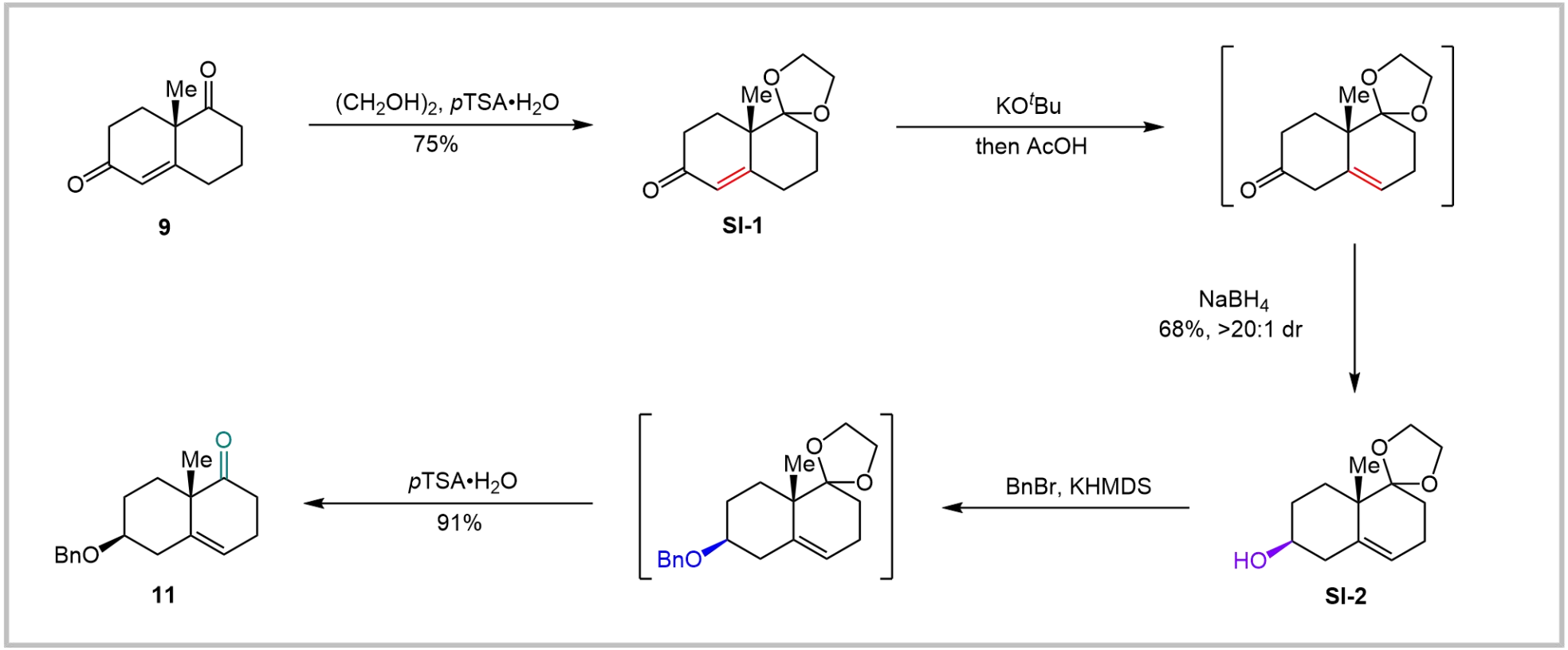
- Isolated from the *Veratrum californicum* (California corn lily) in 1968;
- Belongs to the *Veratrum* alkaloid family;
- Cyclopamine is a potent inhibitor of the highly conserved hedgehog signaling pathway;
- Cyclopamine has been recognized as a promising lead compound for anticancer agents.

Tremblay, M. R. *et al*. *J. Med. Chem.* **2009**, *52*, 4400

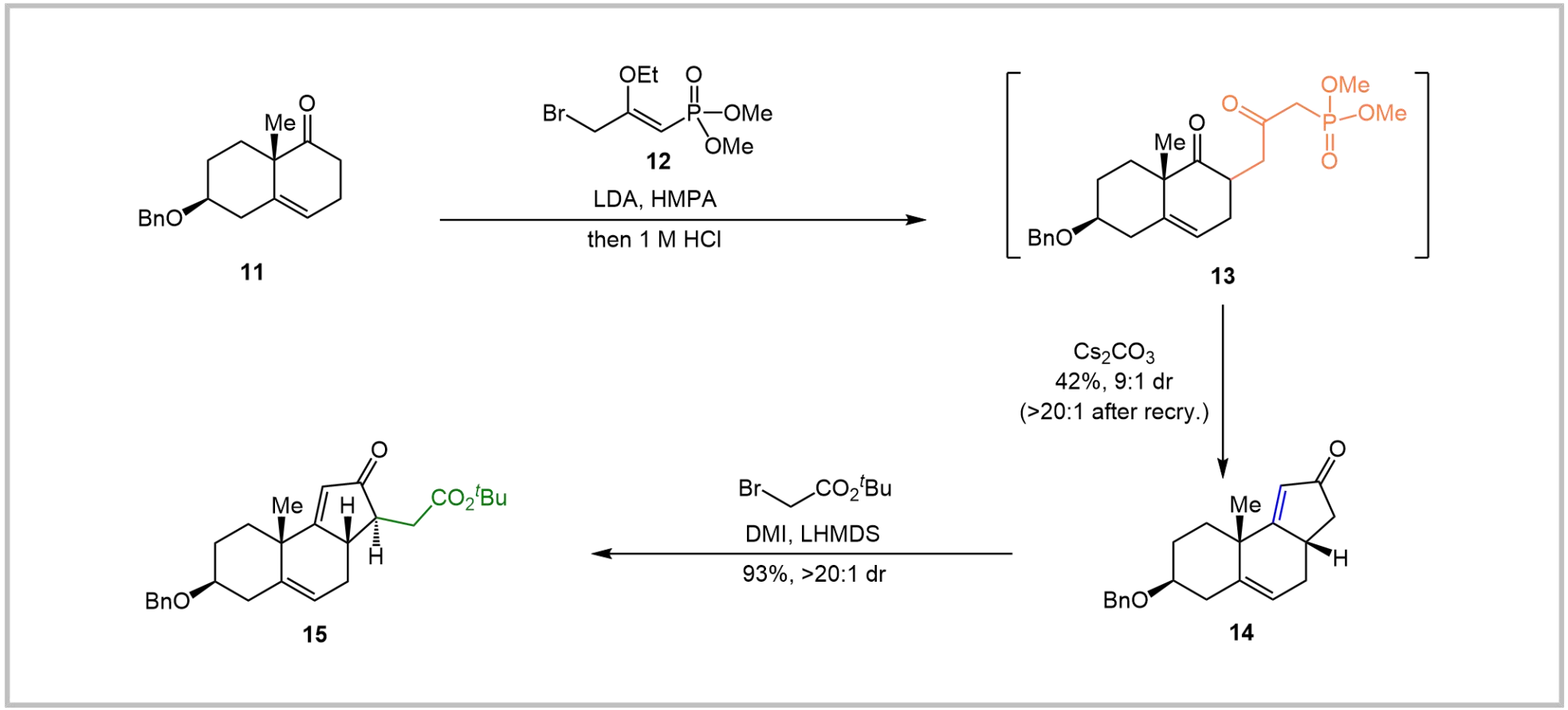
Retrosynthetic Analysis



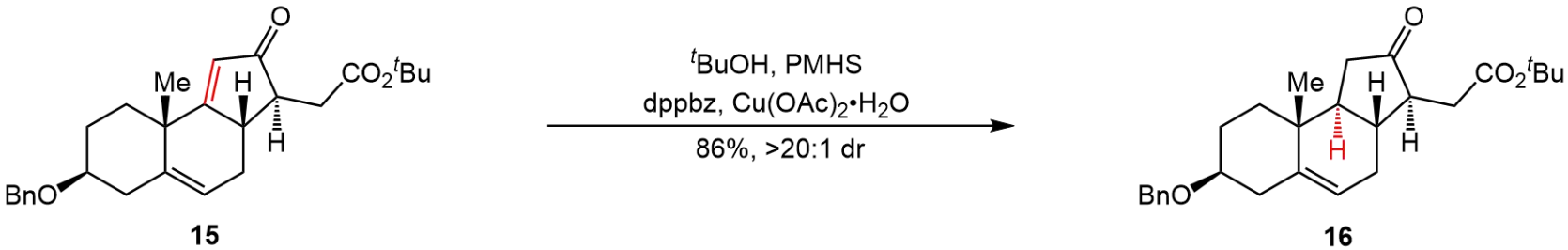
Stage 1——Synthesis of 11



Stage 1——Synthesis of 15

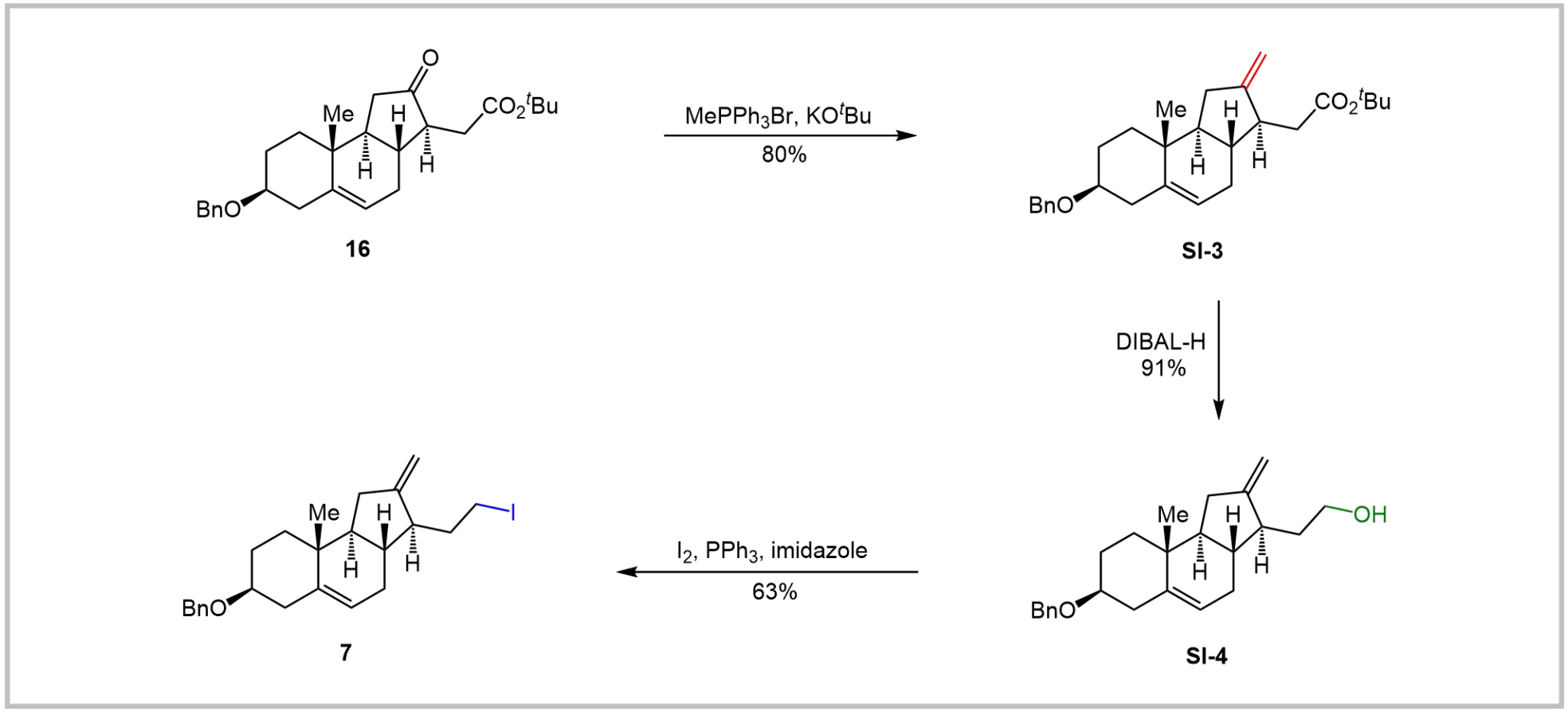


Stage 1——Synthesis of 16

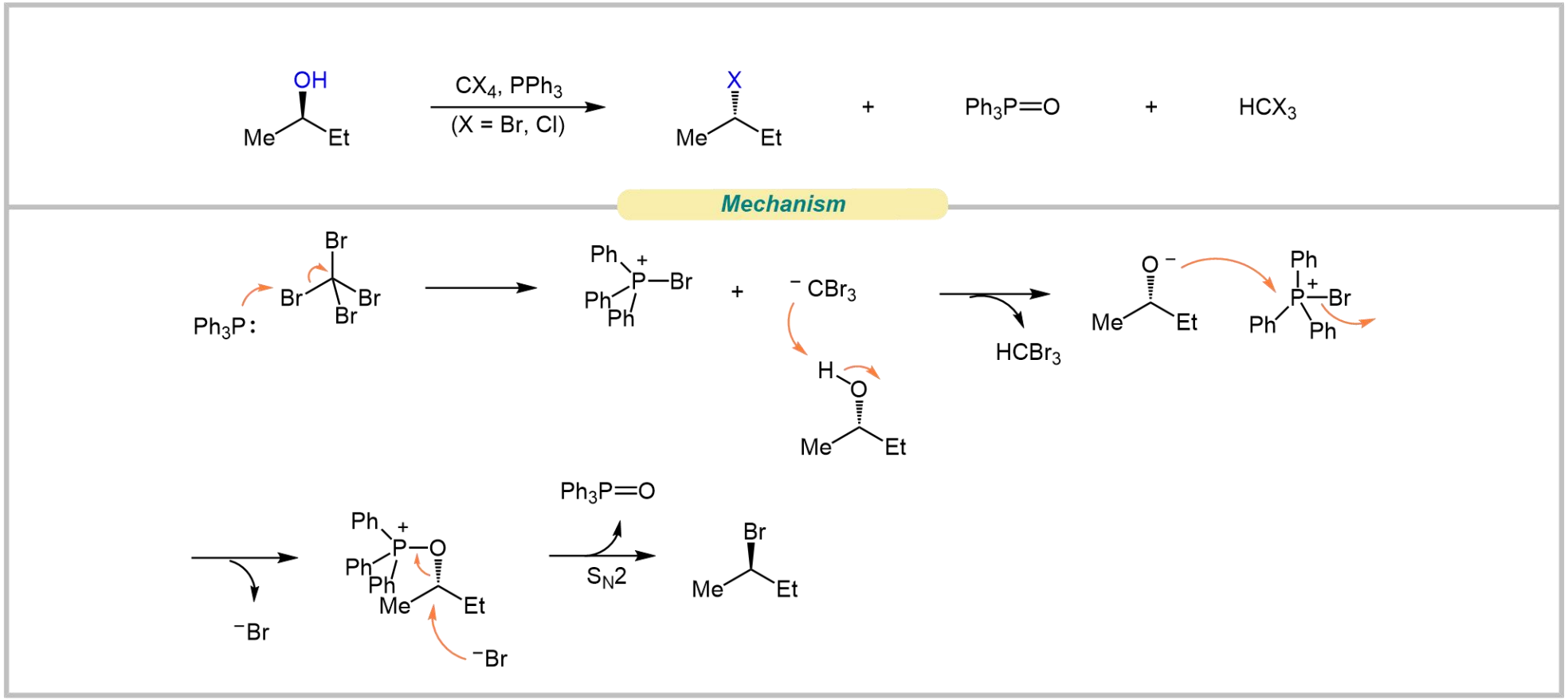


Conditions	Results
$[Cu(PPh_3)H]_6$ (1.0 eq.), MePh, 130 °C, 12 h	no reaction
$Mn(dpm)_3$ (20 mol%), $PhSiH_3$ (1.5 eq.), THF, 60 °C, 12 h	decompose
SmI_2 (2.0 eq.), ^{i}PrOH (10 eq.), THF, rt, 12 h	no reaction
$Cu(OAc)_2•H_2O$ (0.2 eq.), dppbz (0.1 eq.), PMHS (4.0 eq.), ^{t}BuOH (4.0 eq.), MePh, 40 °C, 16 h	86% yield

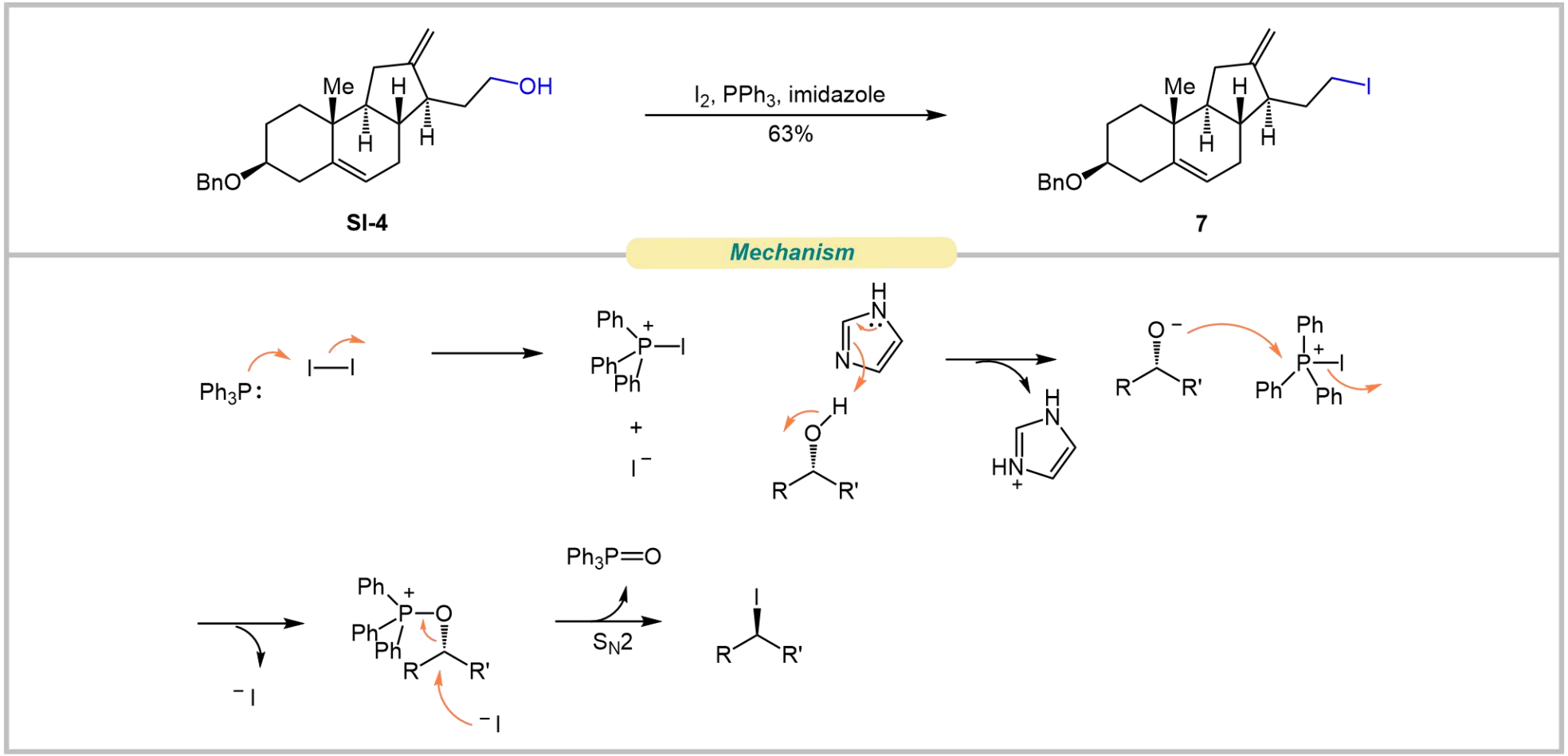
Stage 1——Synthesis of 7



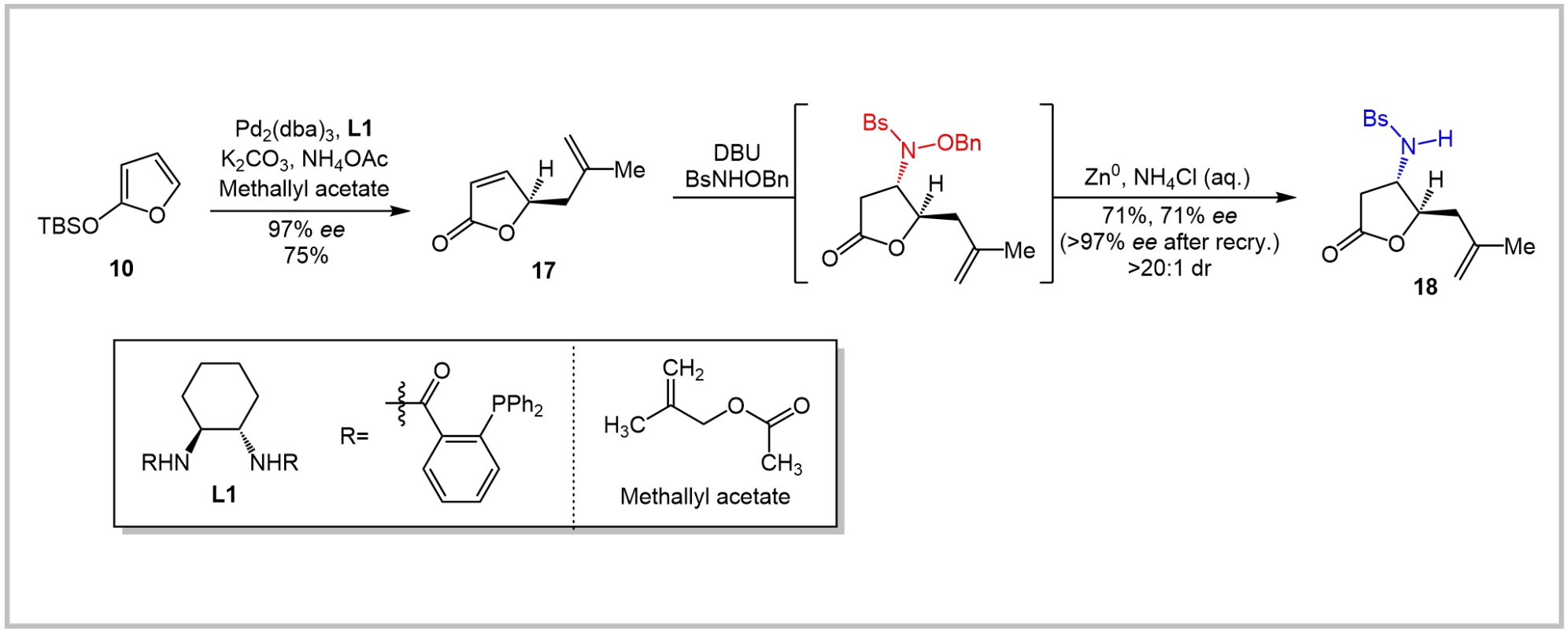
Appel Reaction



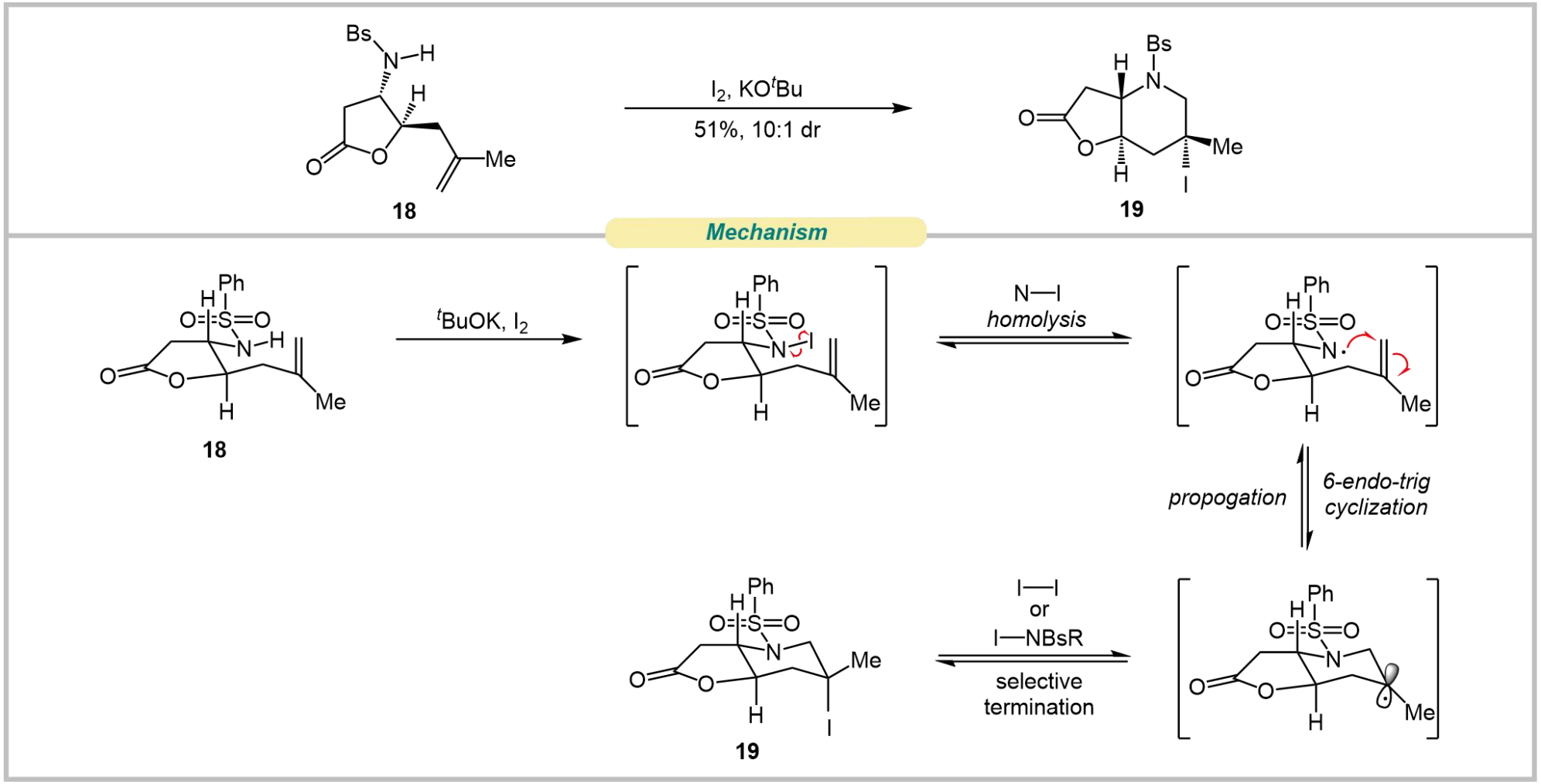
The Reaction Mechanism of SI-4 to 7



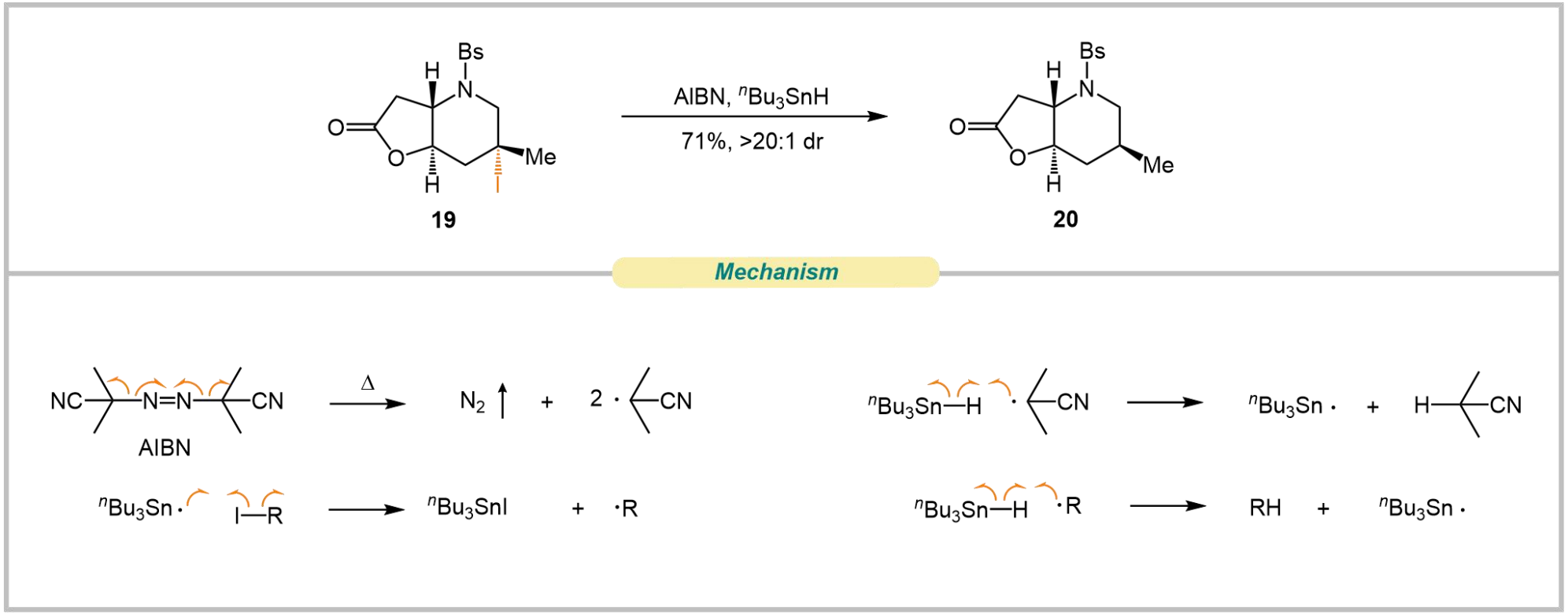
Stage 2——Synthesis of 18



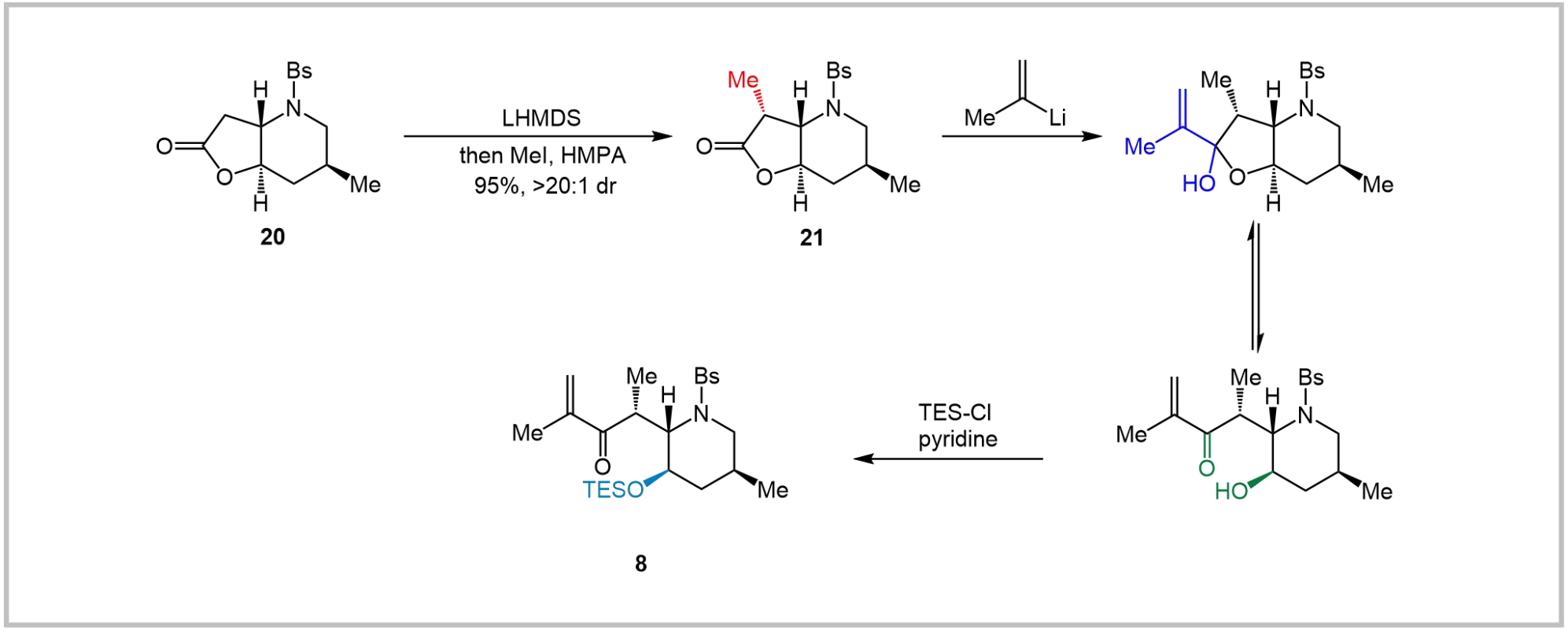
Stage 2——Synthesis of 19



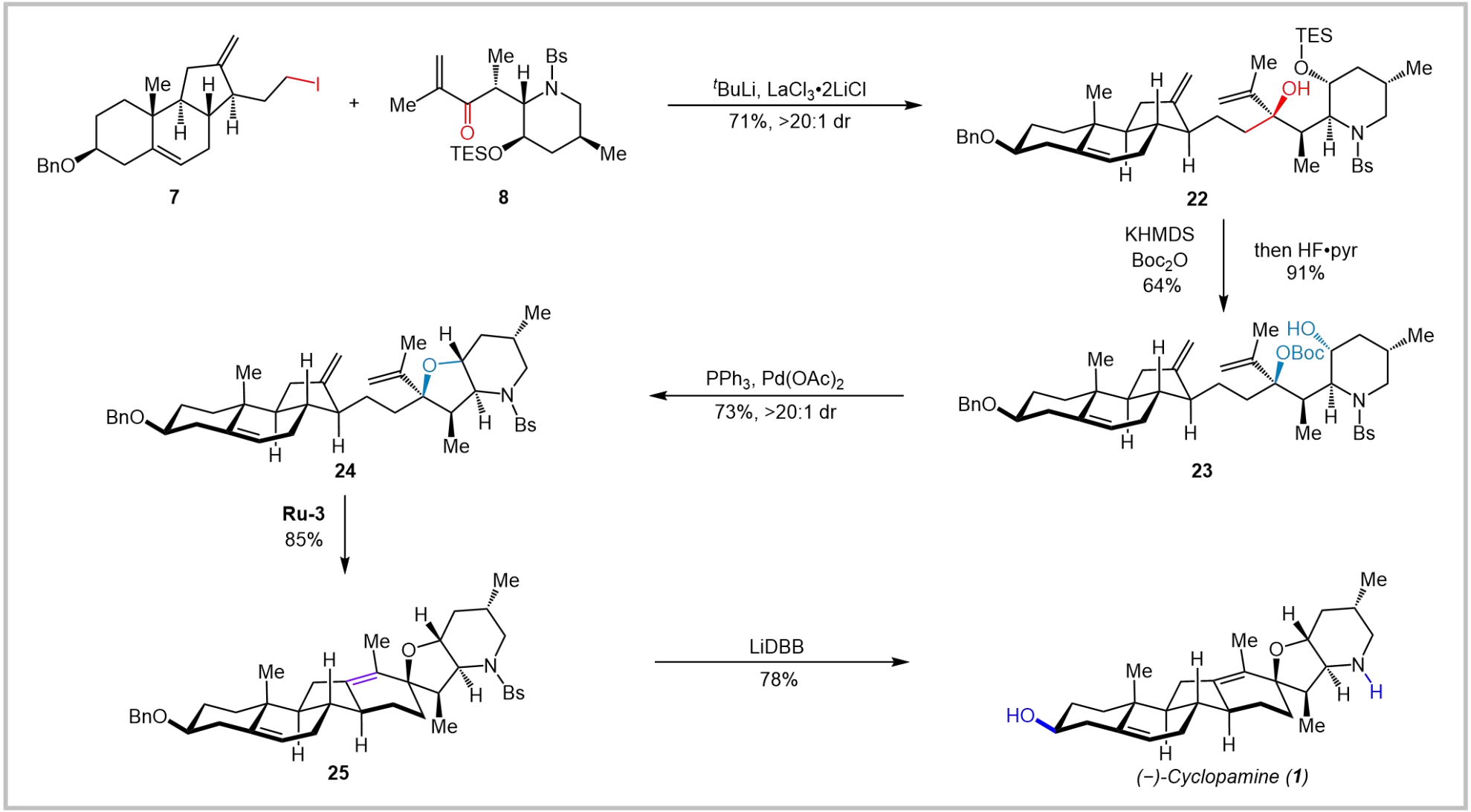
Stage 2——Synthesis of 20



Stage 2——Synthesis of 8

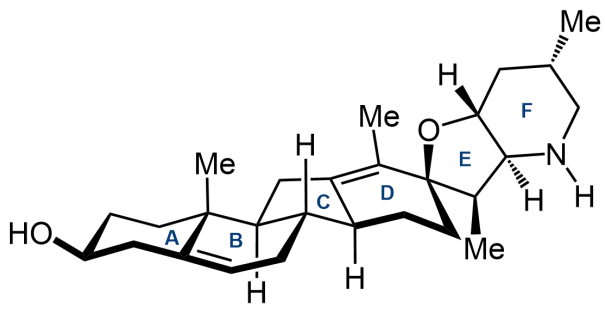


Stage 3——Synthesis of (−)-Cyclopamine



Summary

Total Synthesis of (−)-Cyclopamine (1)



(−)-Cyclopamine (1)

» ***The First Enantioselective Total Synthesis of (−)-Cyclopamine (1), 1.4% Overall Yield***

» ***Synthesize ABC-Ring Through Annulation/CuH Reduction***

» ***Synthesize DEF-Ring System via AAA/Aza-Michael/Halocyclization/Tsuji-Trost/RCM***

Writing Strategy

Introduction

Source and Physiological Activity

↓

Structural Features

↓

Examples of Synthesis

- Cyclopamine (**1**), first isolated from *Veratrum californicum*, is a notable member of the *Veratrum* alkaloid family. Studies from Beachy *et al*. revealed that cyclopamine is a potent inhibitor of the highly conserved hedgehog signaling pathway, which is critical for the correct differentiation and symmetry development of embryos.
- With respect to cyclopamine, the rare C-*nor*-D-*homo* steroid skeleton is further complicated by the fully substituted, spirocyclic THF motif, the unique *trans*-6,5-EF ring system, and the central tetrasubstituted olefin, all of which pose unique challenges to its synthesis.
- A pioneering synthesis of the closely related jervine (**2**) by the Masamune group involves an 18-step sequence starting from the advanced intermediate **6**, which in turn must be prepared in 25 steps from Hagemann's ester or obtained from degradation of hecogenin.

Writing Strategy

➢ **Last paragraph**

Summary

Highlights of This Work

Committed Steps

- To conclude, a convergent total synthesis of (−)-cyclopamine (**1**) was achieved with a 16-step LLS (1.4% overall yield).
- Unlike the semisynthetic routes that predate this disclosure, the strategy outlined herein should be amenable to exploring deep-seated structural modifications for further SAR studies of this promising class of natural products.
- Key areas for improvement for which there are methodological gaps include a more direct conversion of 18 to 20 and a more concise fragment coupling that can minimize protecting group manipulations.

Representative Examples

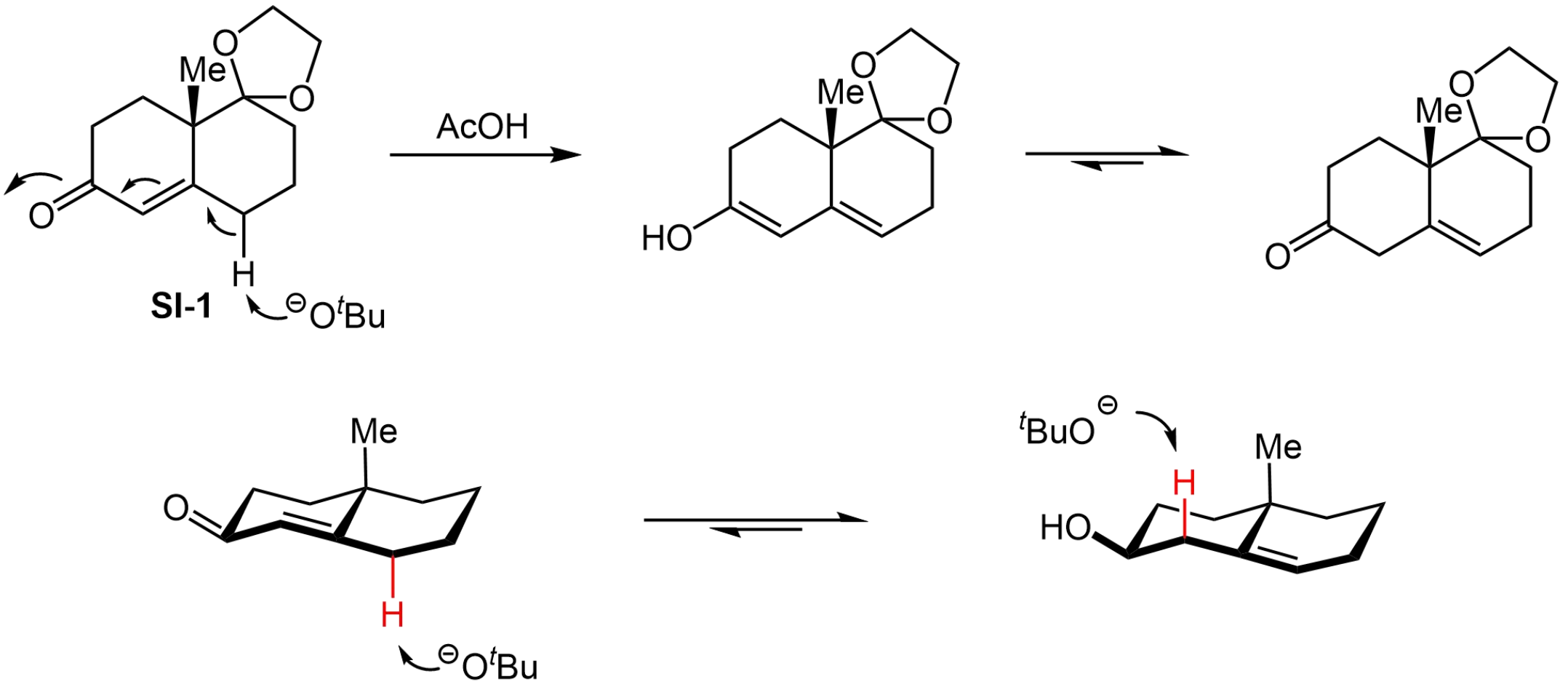
- It is known *ex post facto* for inducing the cyclopia birth defect in sheep where the affected newborn lambs only had one eye and were reminiscent of the cyclops from Greek mythology. (让人想起)

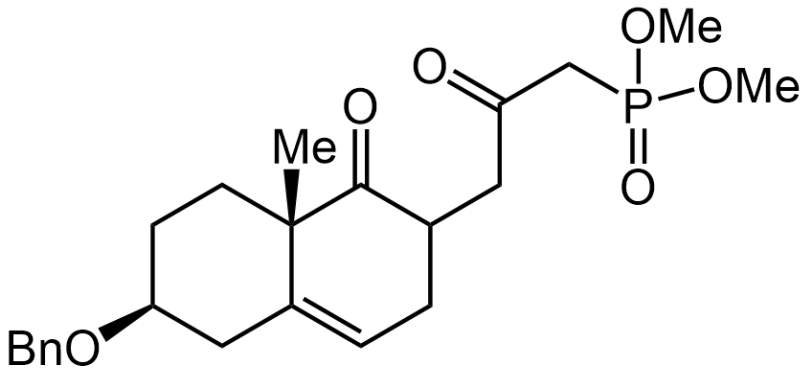
- Conventional metathesis catalysts, such as Hoveyda−Grubbs second generation catalyst (**Ru-1**), gave low conversions even at elevated temperatures, and the less sterically encumbering *o*-tolyl variant **Ru-2** only led to slightly improved results. (*v*. 阻碍)

- Attempts to suppress this process by running the reaction at ambient temperature instead of 100 °C surprisingly exacerbated the ring opening. (*n*. 环境温度)

Acknowledgement

Thanks for your attention


Me
O
O
O
H
SI-1
$^{\ominus}$O^{t}Bu
AcOH
HO
Me
O
O
Me
O
O
Me
O
H
$^{\ominus}$O^{t}Bu
^{t}BuO$^{\ominus}$
Me
H
HO



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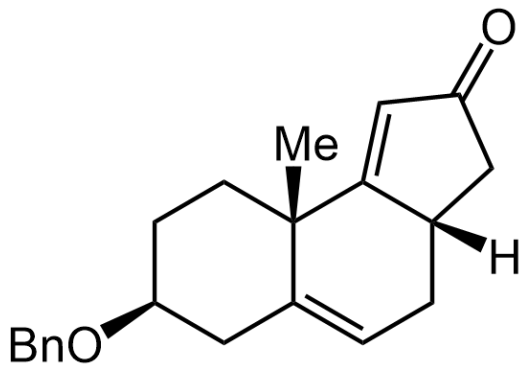

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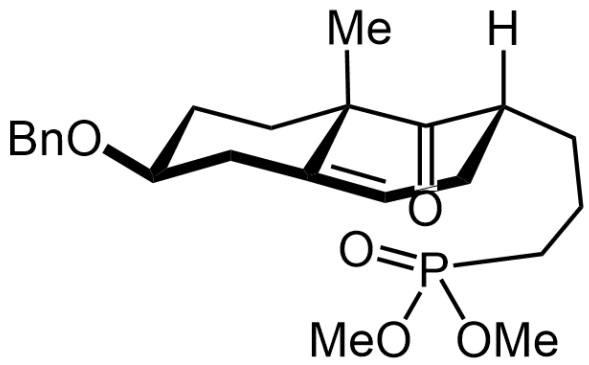

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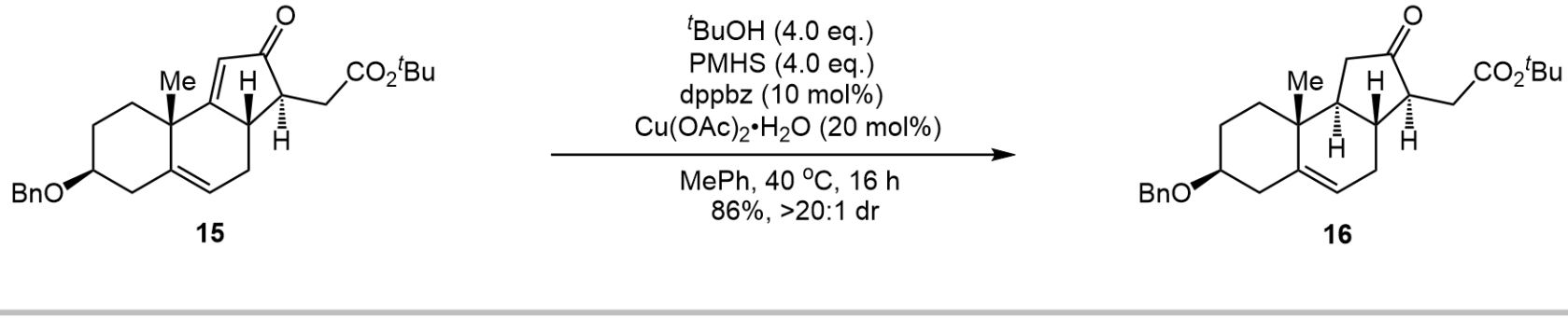
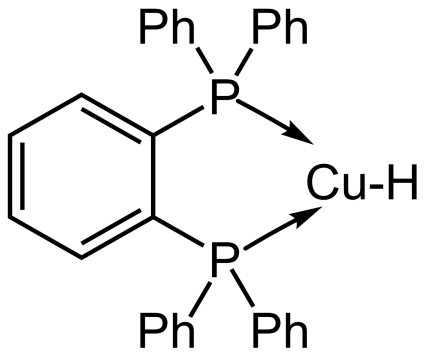
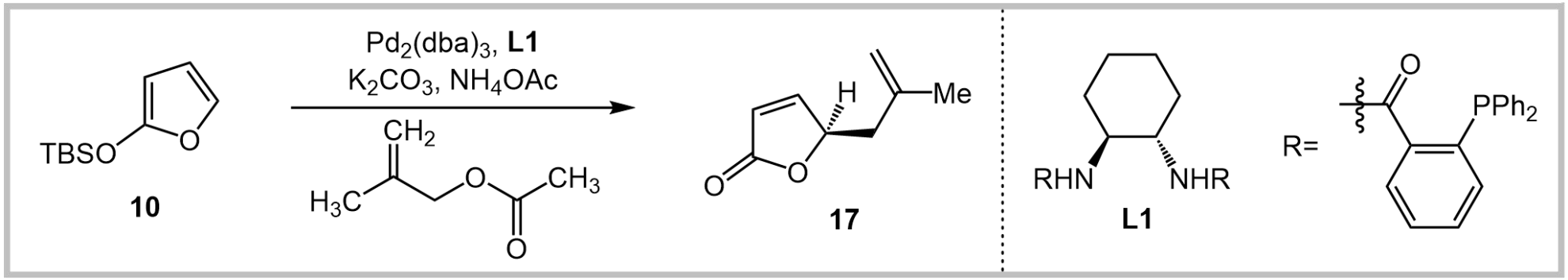
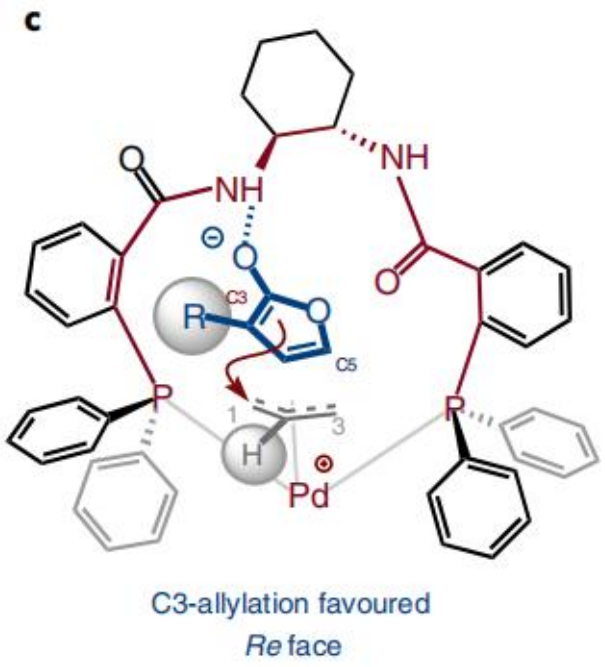

Me
H
O
CO2tBu
H
BnO
15
tBuOH (4.0 eq.)
PMHS (4.0 eq.)
dppbz (10 mol%)
Cu(OAc)2•H2O (20 mol%)
MePh, 40 °C, 16 h
86%, >20:1 dr
Me
H
O
CO2tBu
H
H
BnO
16

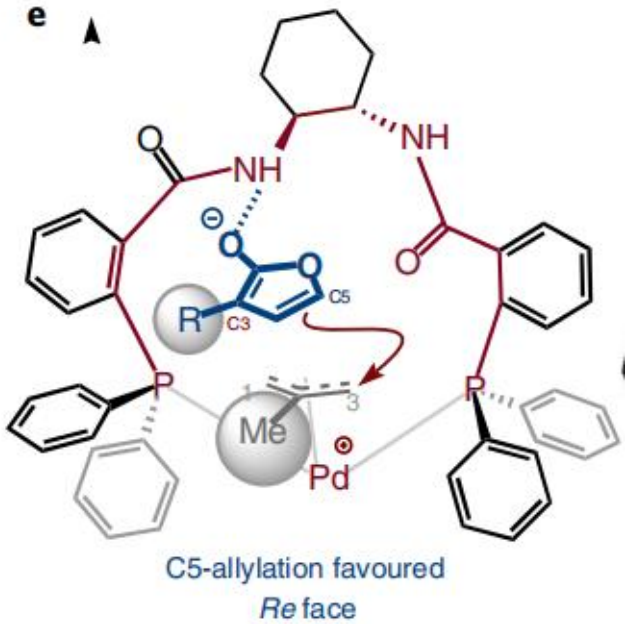

Ph
Ph
P
Cu-H
P
Ph
Ph

(BDP)CuH

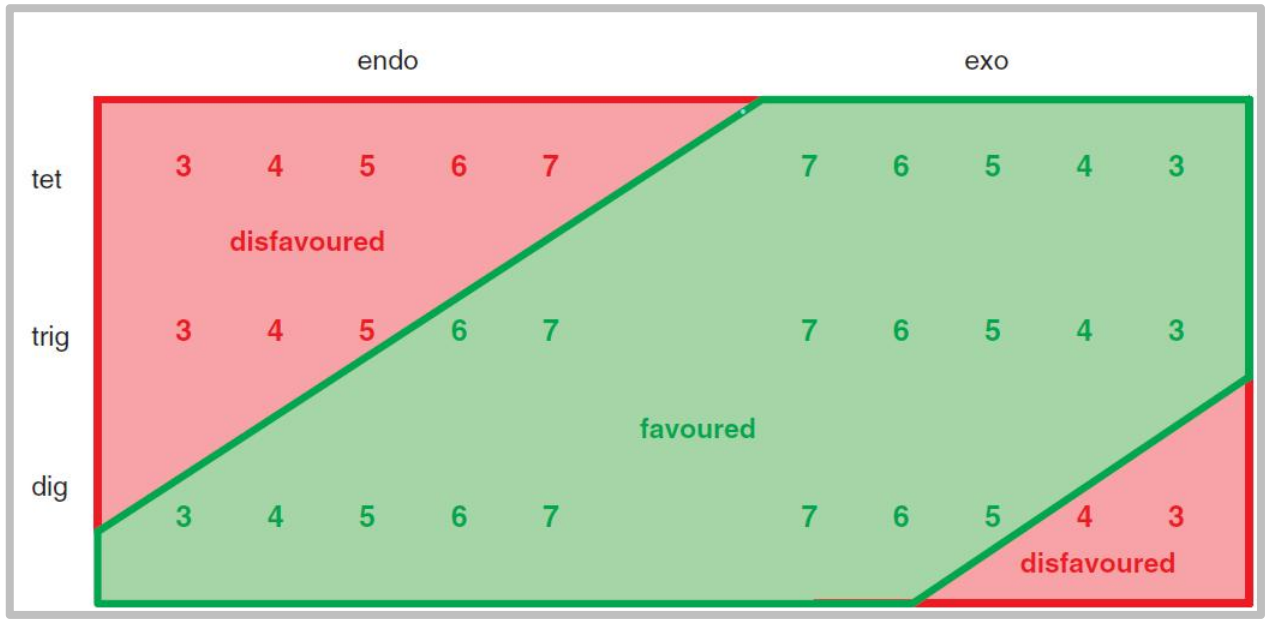


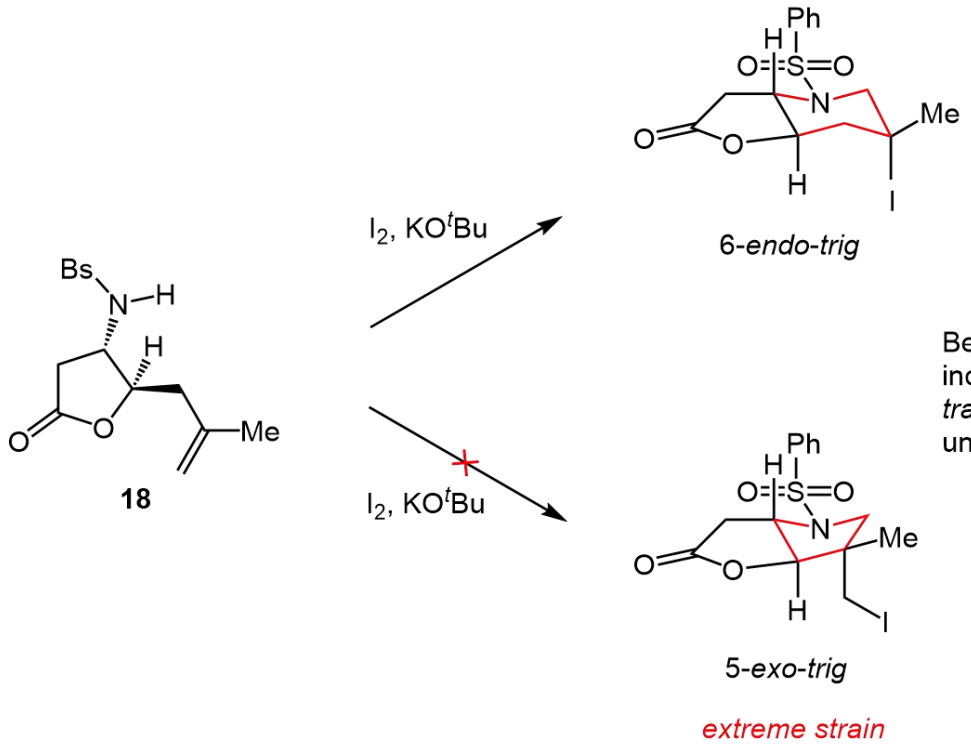


C3-allylation favoured
Re face



C5-allylation favoured
Re face


endo
exo
tet
trig
dig
3 4 5 6 7
7 6 5 4 3
disfavoured
3 4 5 6 7
7 6 5 4 3
favoured
3 4 5 6 7
7 6 5 4 3
disfavoured

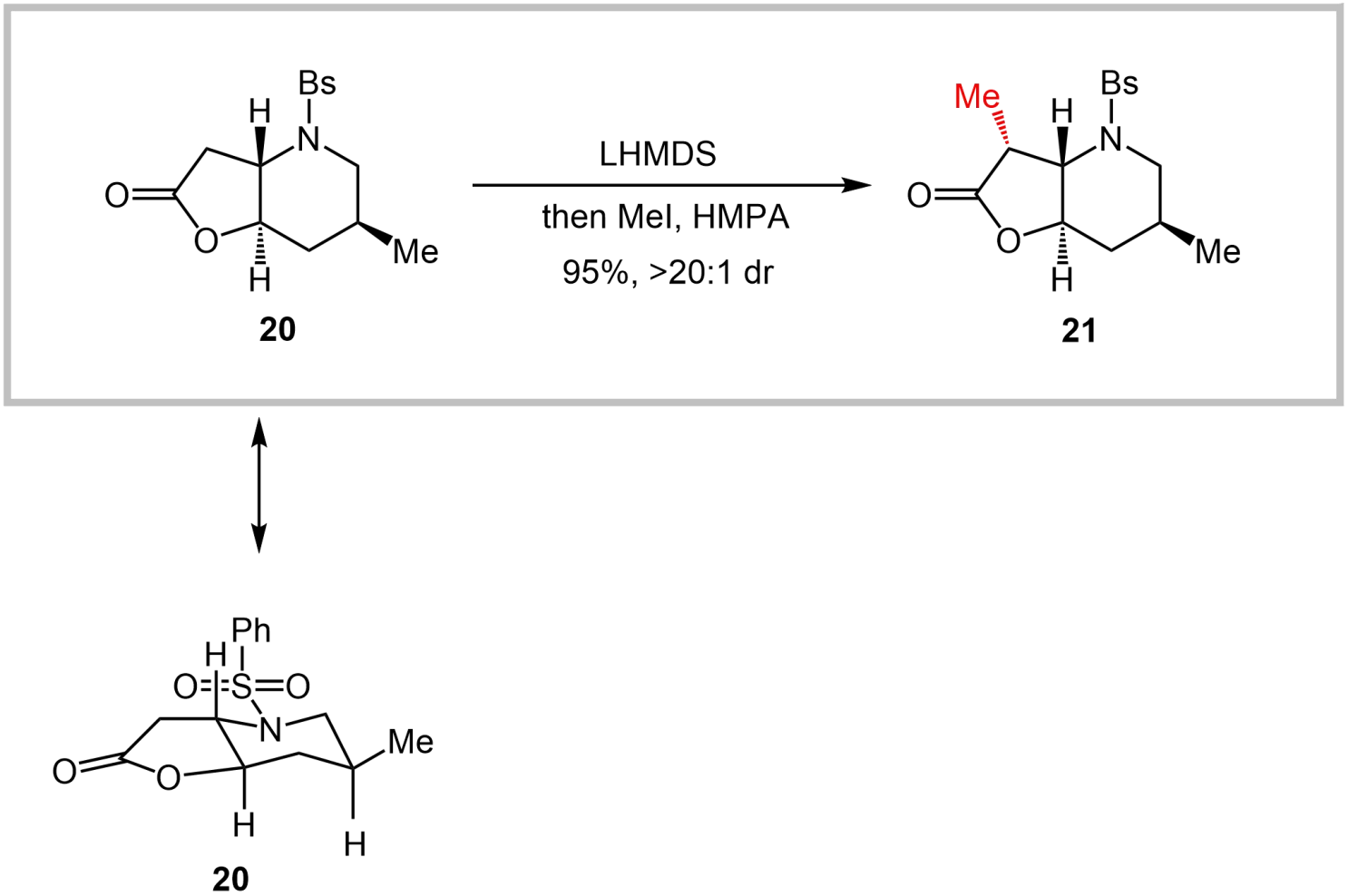


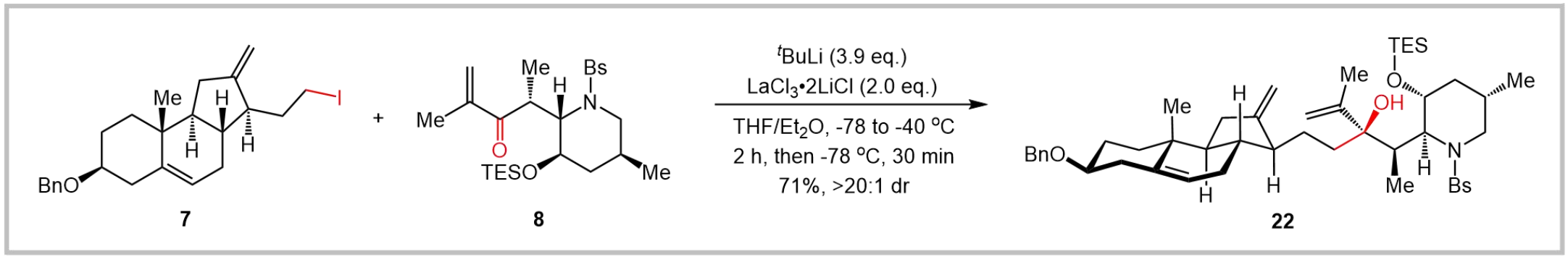
Because of the extreme strain that would be incurred through a 5-*exo-trig* cyclization to deliver a *trans*-5,5-ring system, it was rationalized that an unusual 6-*endo-trig* cyclization would be preferred.

表 3-2　常见基团的一取代环己烷直键取代与平键取代构象的势能差(25℃)

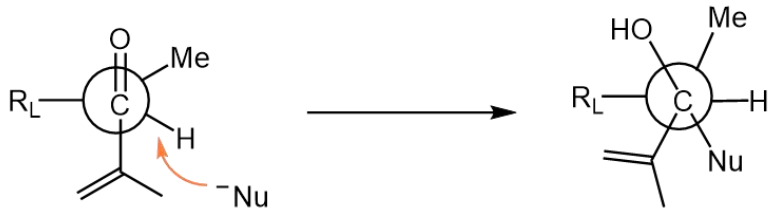
取代基	势能差(直键⇌平键) /(kJ·mol^{-1})	取代基	势能差(直键⇌平键) /(kJ·mol^{-1})	取代基	势能差(直键⇌平键) /(kJ·mol^{-1})
$-CH_3$	7.1	$-Cl$	1.7	$-C_6H_5$	13.0
$-CH_2CH_3$	7.5	$-Br$	1.7	$-CN$	0.8
$-CH(CH_3)_2$	8.8	$-I$	1.7	$-COOH$	5.0
$-C(CH_3)_3$	>18.4	$-OH$*	≈3.3	$-NH_2$*	≈6.3
$-F$	0.8	$-OCH_3$	2.9		

* 其值可受溶剂的影响，特别是氢键。


Bs
H
N
O
O
H
Me
20
LHMDS
then MeI, HMPA
95%, >20:1 dr
Me
Bs
H
N
O
O
H
Me
21
Ph
H
O
S
O
N
Me
O
O
H
H
20

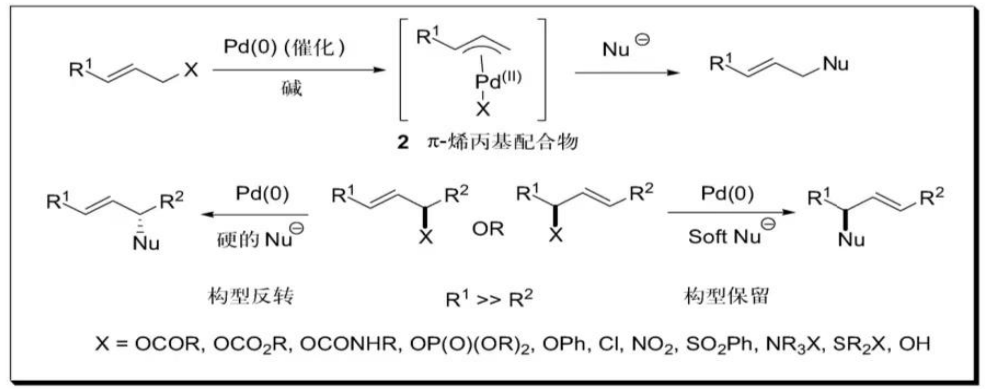


Felkin–Anh 模型:

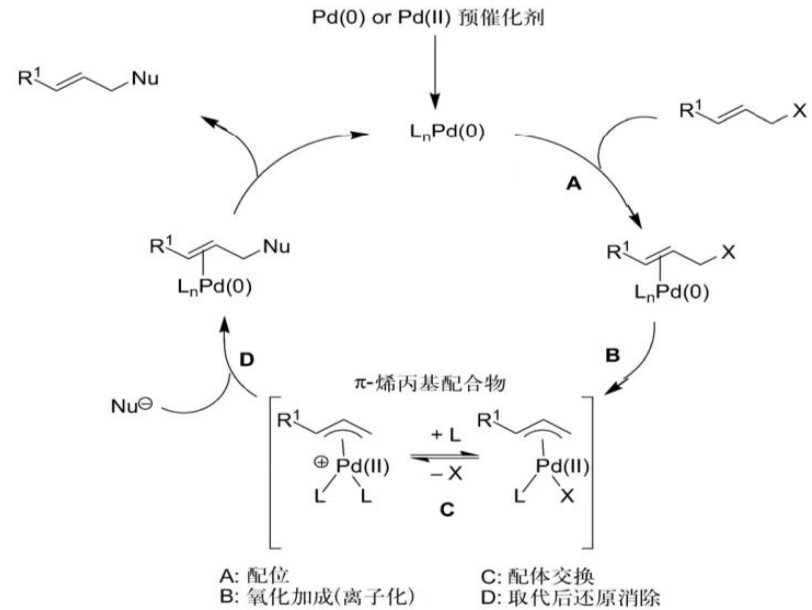


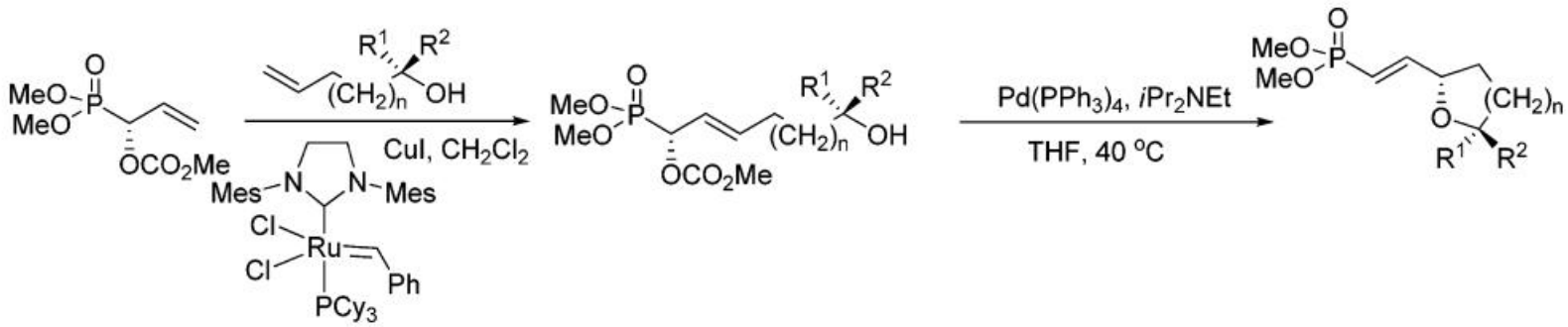
Tsuji-Trost 反应

Tsuji-Trost反应是Pd催化下碳亲核物种在烯丙基位上的取代反应。这些反应经过 π-烯丙基钯中间体过程。

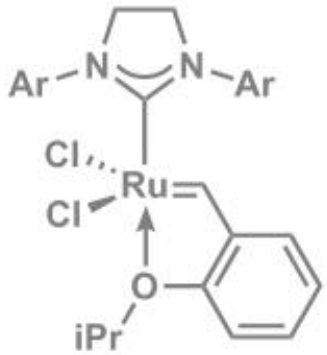


催化循环：

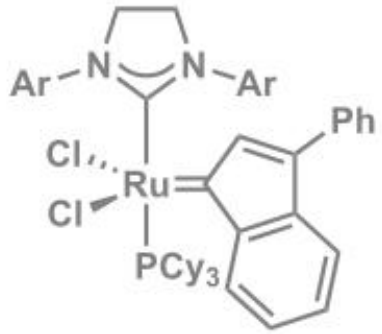




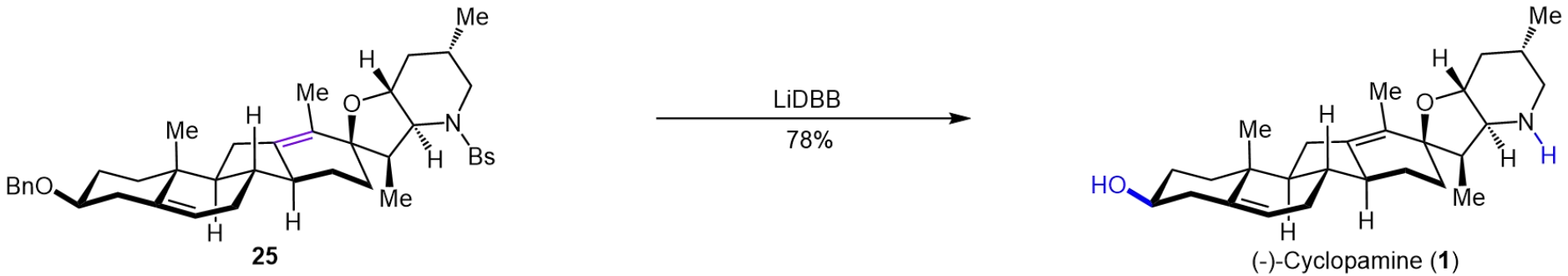
He, A. Y. Sutivisedsak, N. Spilling, C. D. *Org. Lett.* **2009**, *11*, 14

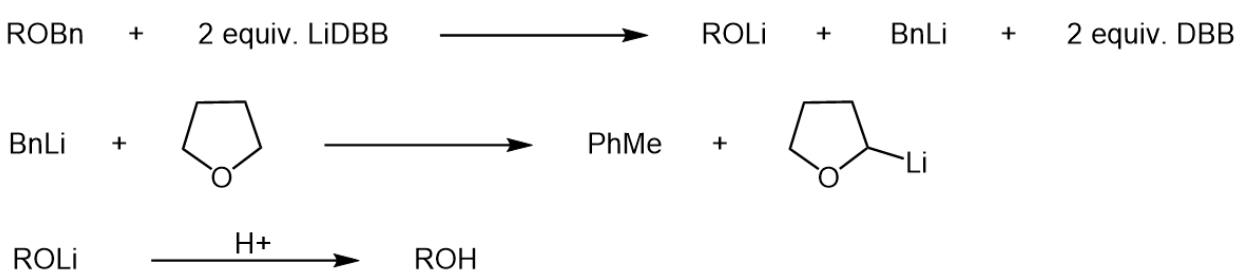


Ru-1: Ar = mesityl
Ru-2: Ar = o-tolyl

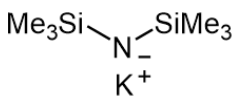


Ru-3: Ar = mesityl

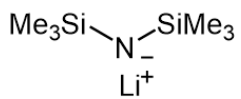

Me
H
Me
O
N
Bs
H
Me
BnO
Me
H
H
H
25
LiDBB
78%
Me
H
Me
O
N
H
H
HO
Me
H
H
Me
H
(-)-Cyclopamine (1)


ROBn + 2 equiv. LiDBB
ROLi + BnLi + 2 equiv. DBB
BnLi +
O
PhMe +
O
Li
ROLi
H+
ROH

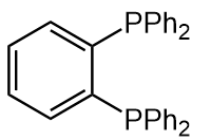
KHMDS: 双(三甲基硅基)氨基钾



LHMDS: 双(三甲基硅基)氨基锂



dppbz: 1,2-双(二苯基膦基)苯



LiDBB: