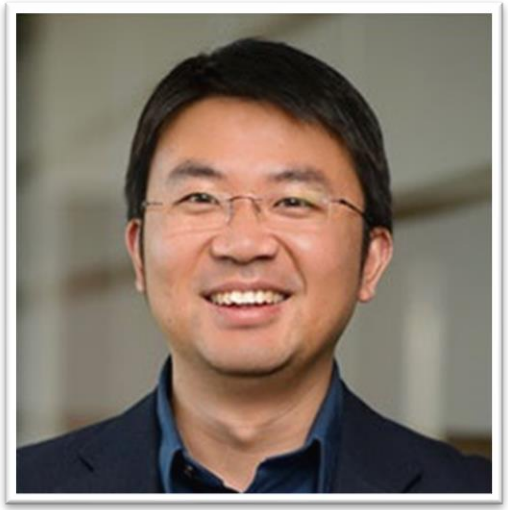
Literature Report 11

Convergent and Efficient Total Synthesis of (+)-Heilonine Enabled by C-H Functionalizations

Reporter: Han Wang
Checker: Shan-shan Xun
Date: 2024.05.06

Jin, Y.; Hok, S.; Bacsa, J.; Dai. M.* *J. Am. Chem. Soc.* **2024**, *146*, 1825-1831.

CV of Dr. Mingji Dai (代明骥)



Background:

- **1998-2002** B.S., Peking University
- **2002-2004** Research Assistant, Peking University
- **2004-2009** Ph.D., Columbia University (Prof. S. J. Danishefsky)
- **2009-2012** Postdoc., Harvard University (Prof. S. L. Schreiber)
- **2012-2022** Professor, Purdue University
- **2022-present** Asa Griggs Candler Prof., Emory University

Research:

- ✓ **Developing efficient and novel synthesis methods and strategies**
- ✓ **Total synthesis of natural products with complex structures and biological activity**
- ✓ **Pharmaceutical chemistry and chemical biology research**

Contents

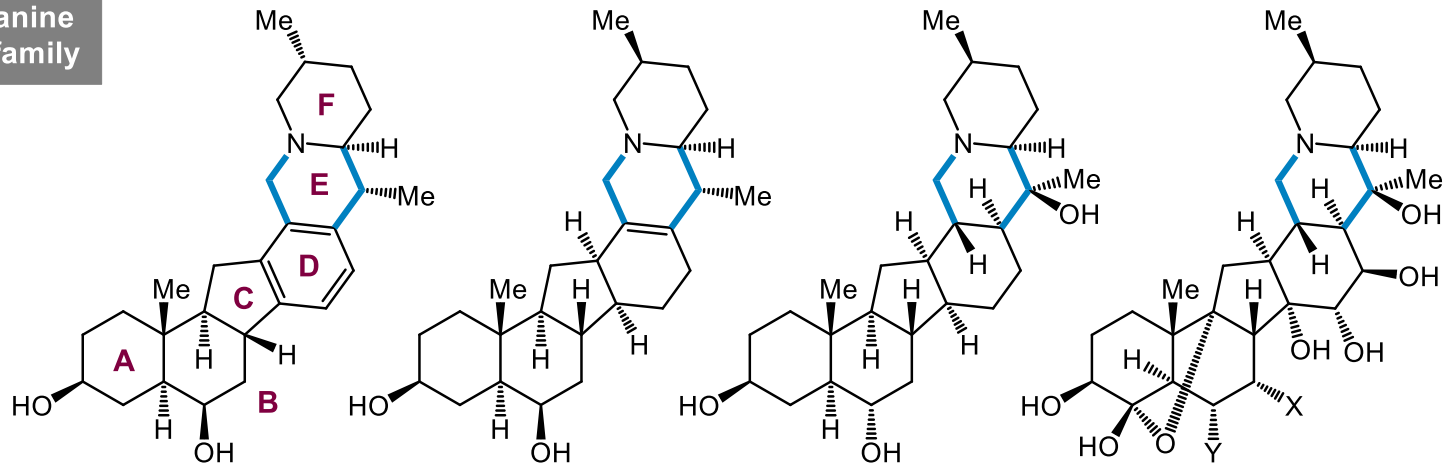
Introduction

(+)-Heilonine

Fritillaria ussuriensis Maxim.

- ♣ First isolated from the *Fritillaria ussuriensis* Maxim. in 1989
- ♣ Used as an effective antitussive, sedative, and expectorant
- ♣ The first example of a cevanine alkaloid with an aromatic D-ring
- ♣ A hexacyclic ring system including a *trans*-hydrindane

cevanine subfamily



Heilonine (**1**)

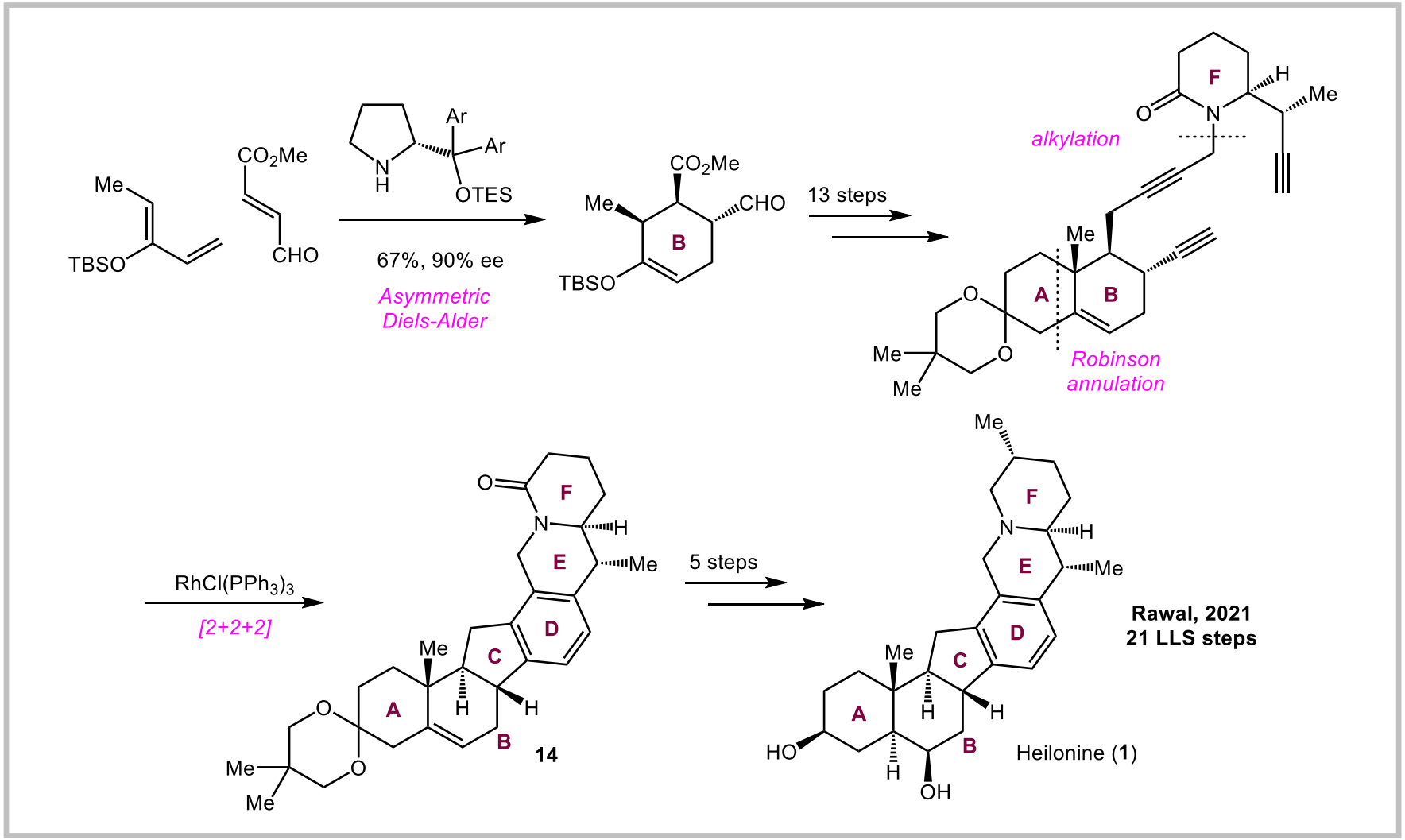
Ebeienine (**2**)

Verticine (**3**)

Germine (**4**: X, Y = OH, H)
Zygadenine (**5**: X, Y = H, OH)

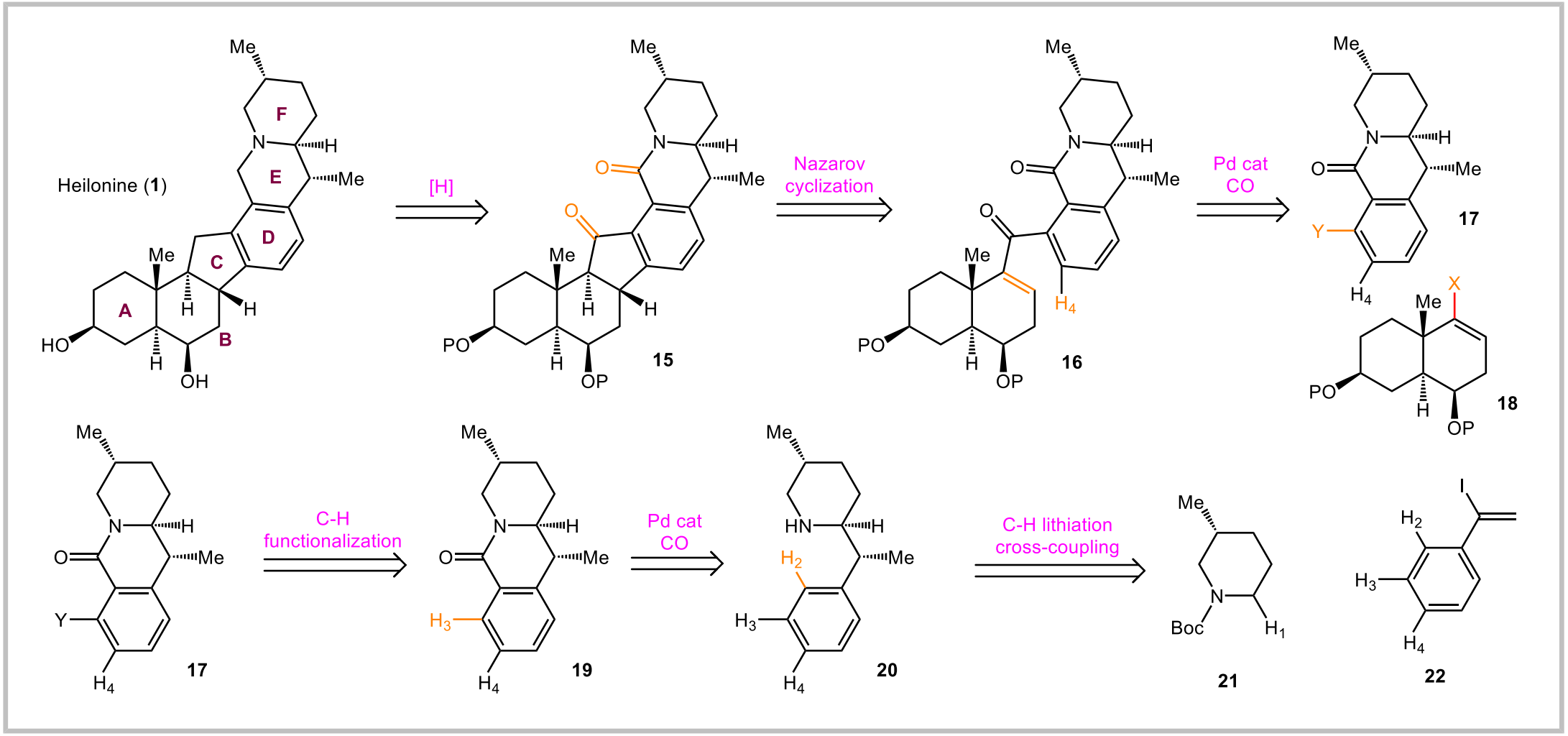
Kaneko, K. *et al. Tetrahedron* **1989**, *45*, 7281.

Rawal's work

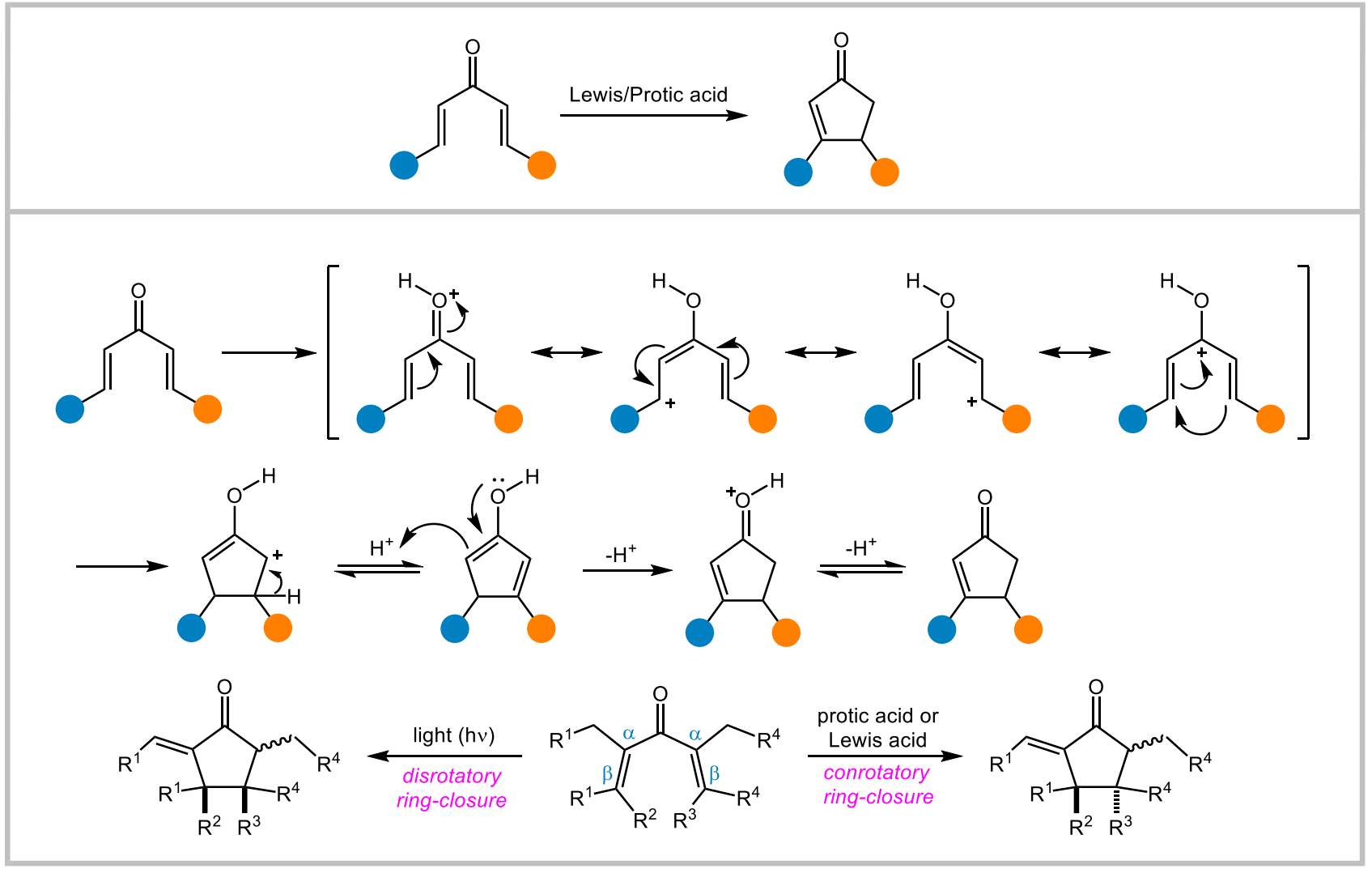


Rawal, V. H. *et al. J. Am. Chem. Soc.* **2021**, *143*, 16394.

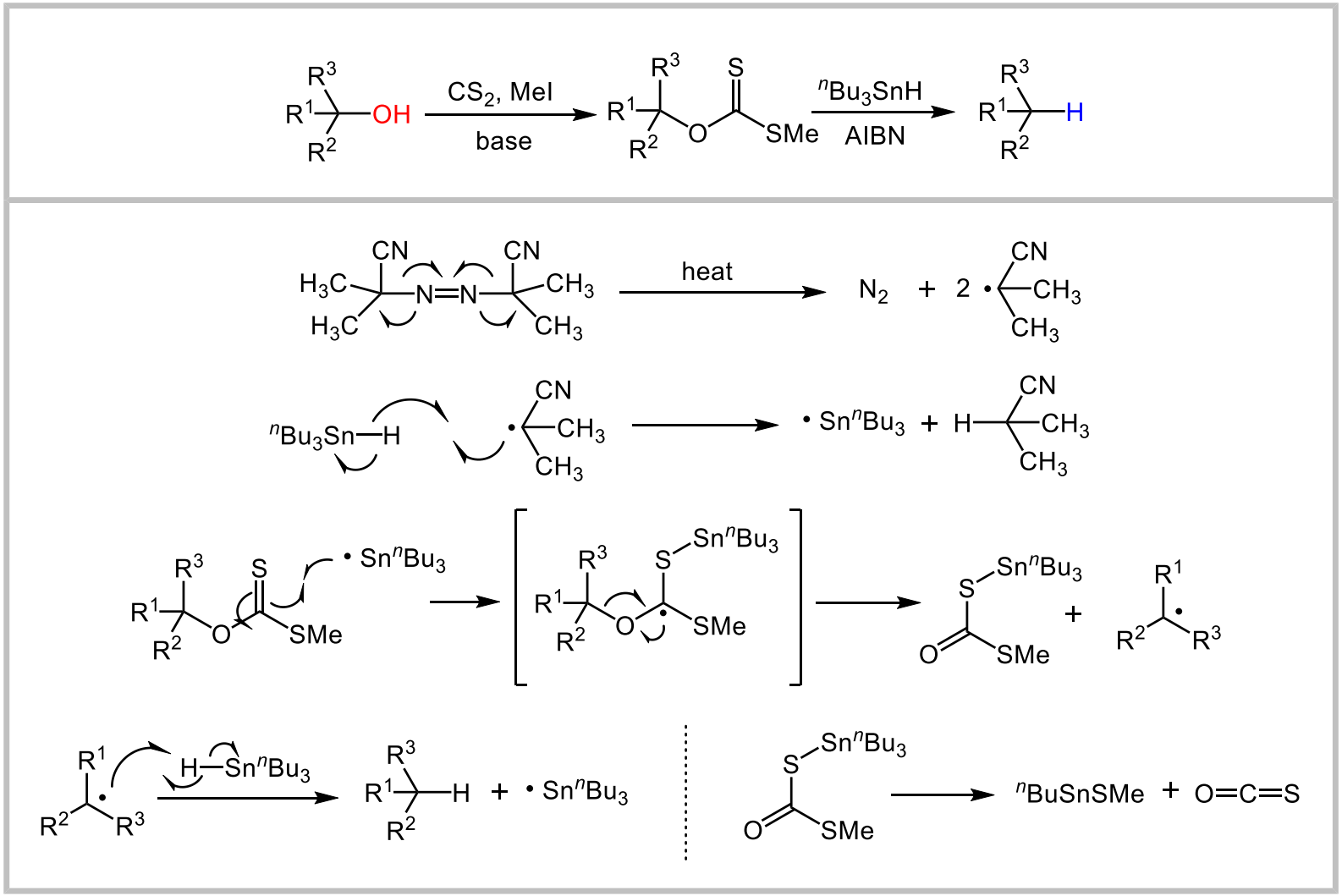
Retrosynthetic Analysis (Dai's work)



Nazarov Cyclization

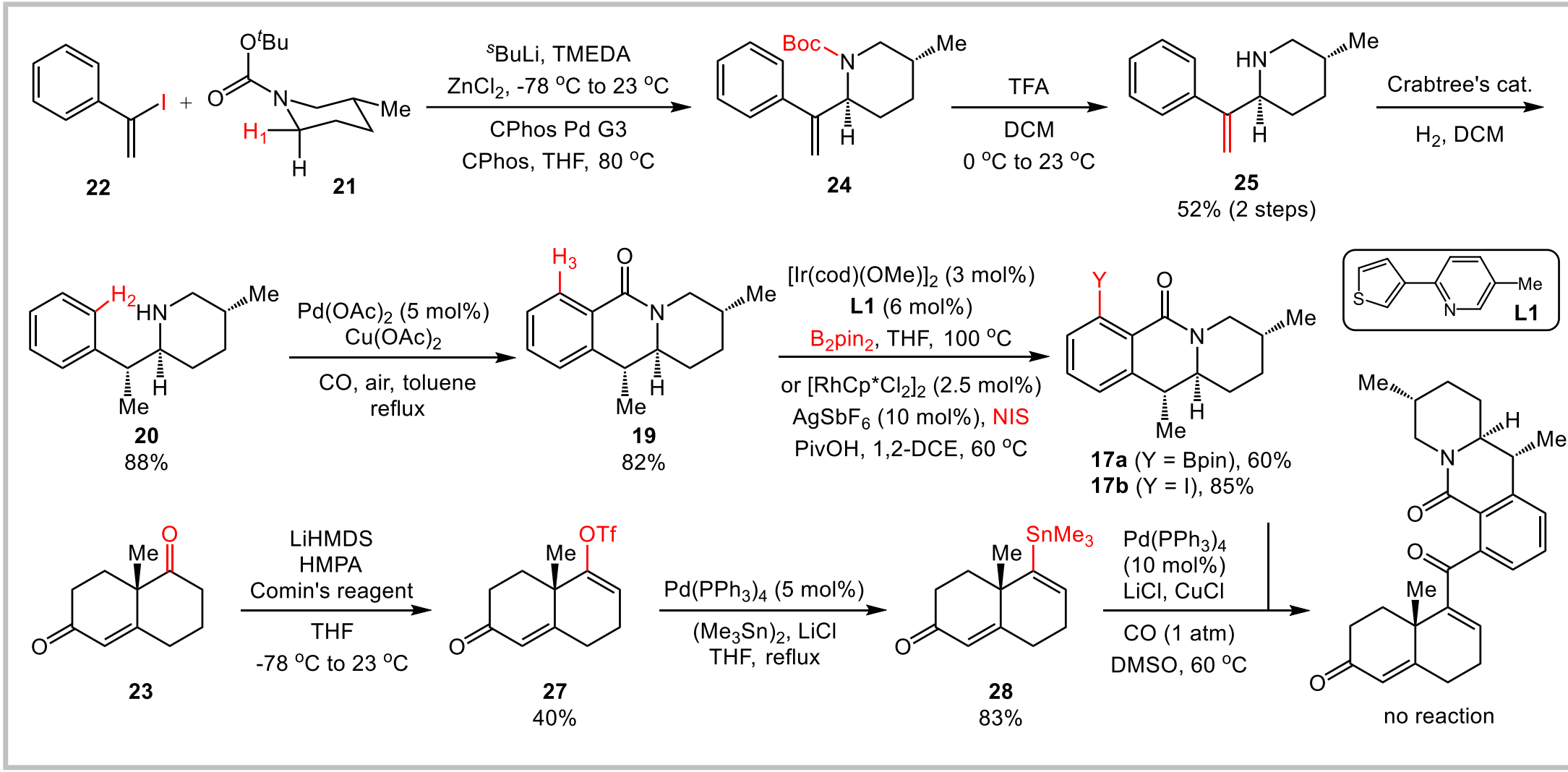


Barton-McCombie Reaction



From Name Reaction

Synthesis of 17&28



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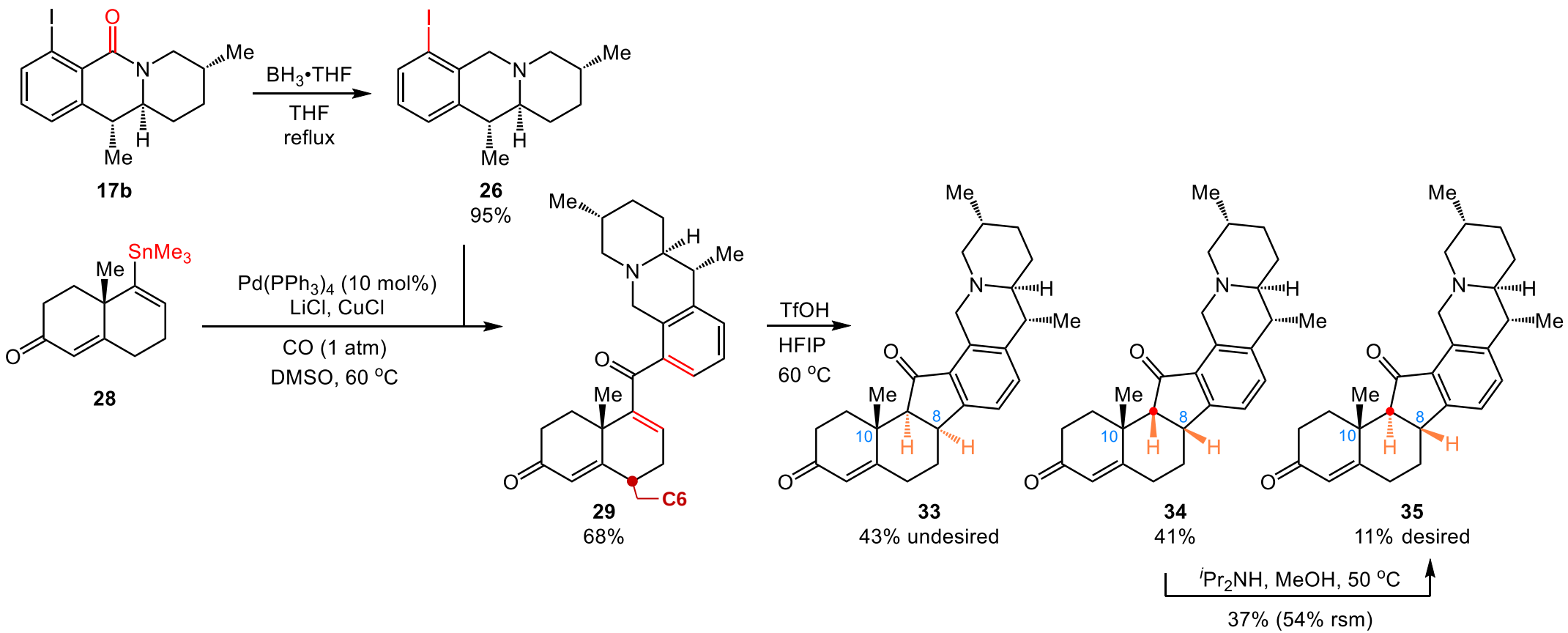
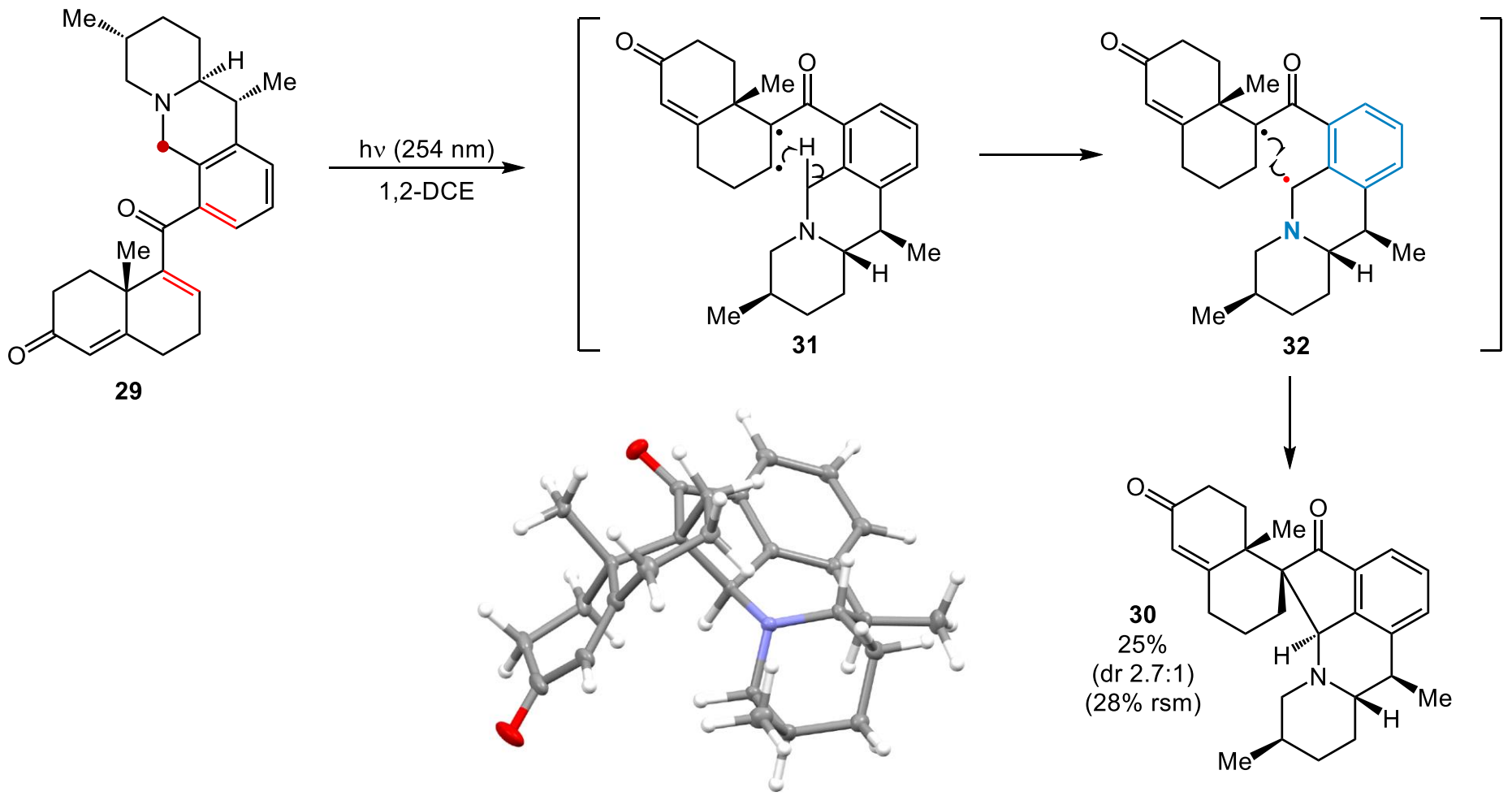
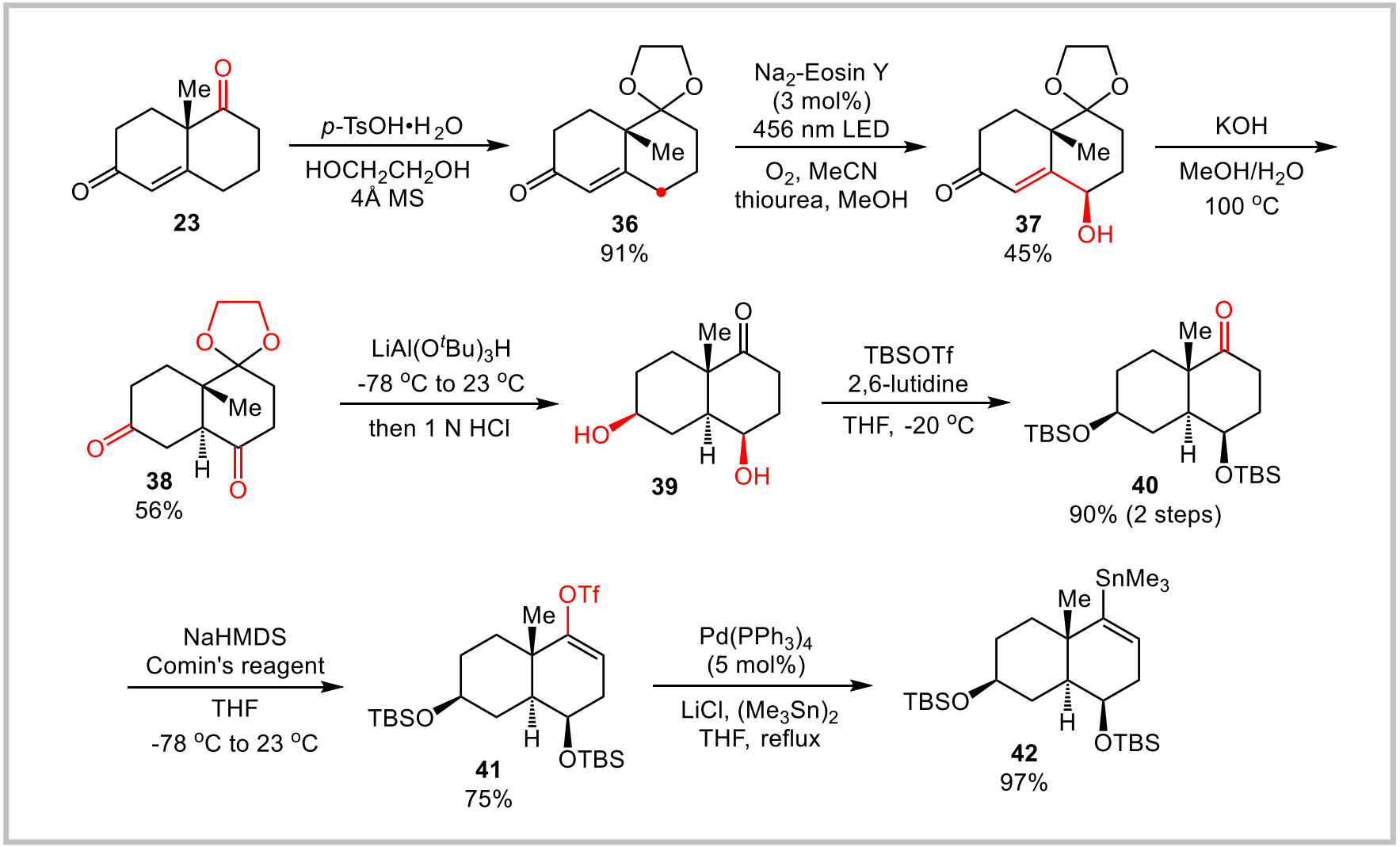


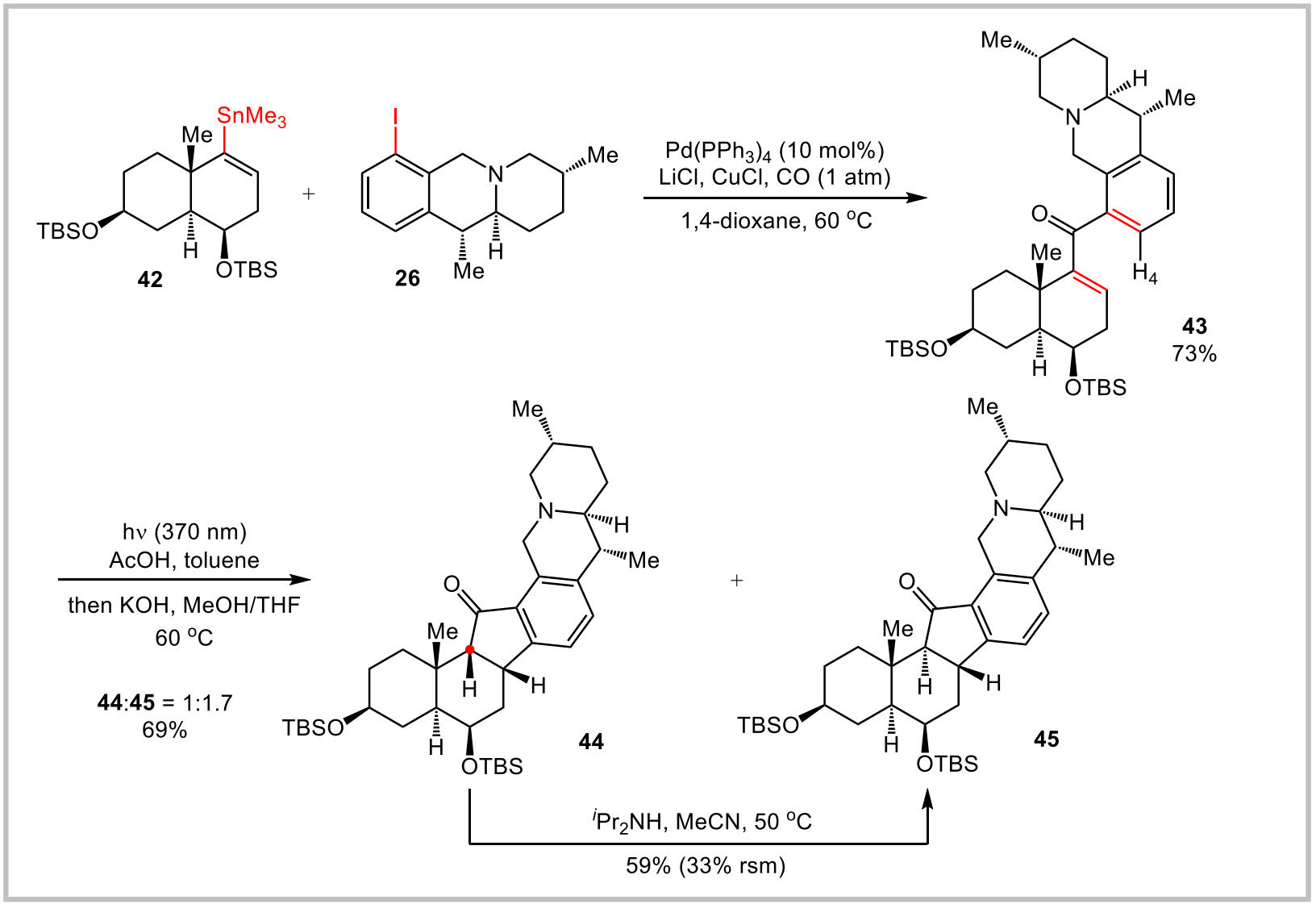
Nazarov Cyclization



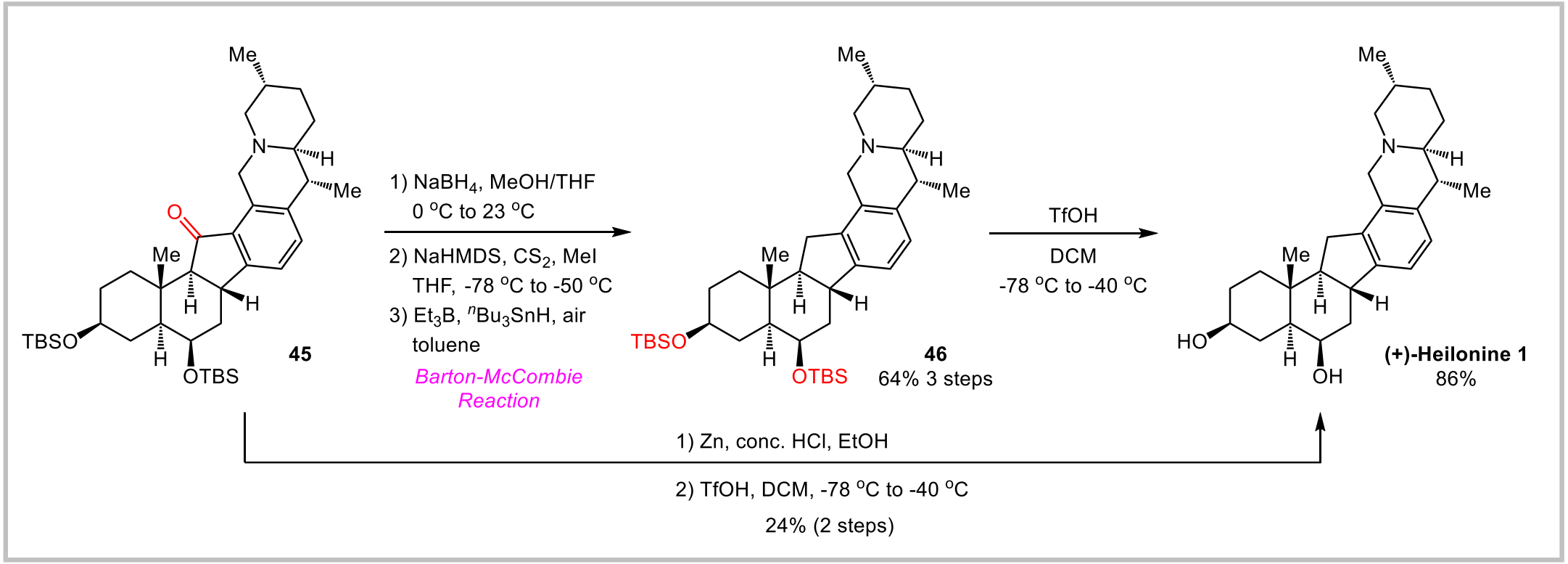
Synthesis of 42



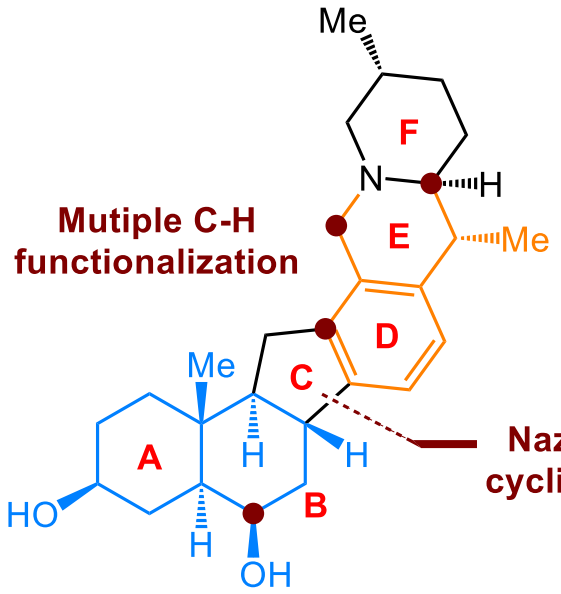
Synthesis of (+)-Heilonine (1)



Synthesis of (+)-Heilonine (1)



Summary



Mutiple C-H functionalization

Nazarov cyclization

- Four well-orchestrated C-H functionalizations
- Photochemical Nazarov cyclization

(+)-Heilonine

- C-H functionalization/Nazarov cyclization;
- Consecutive bond constructions around to produce the tetrasubstituted aromatic core
- Total synthesis of (+)-Heilonine: 11 or 13 LLS steps, 4.1 or 8.4% overall yield.

Writing Strategy

➢ Introduction

The source and utility of (+)-Heilonine

The investigation of (+)-Heilonine and related steroidal alkaloids

- Heilonine was isolated by Kaneko et al. in 1989 from *Fritillaria ussuriensis* Maxim. cultivated in the Hei-Long-Jiang province in China, from which its name was given. *Fritillaria ussuriensis* Maxim. (also called Ping-bei-mu) is part of the Chinese herbal drug “Bei-mu”, which has been used as an effective antitussive, sedative, and expectorant. “Beimu” is a rich source of steroidal alkaloids with broad therapeutic potential.

- Heilonine belongs to the Veratrum steroidal alkaloid family whose members feature a common C-*nor* D-*homo* steroidal skeleton. Based on the connectivity patterns around the piperidine E ring, the Veratrum steroidal alkaloids can be further divided into three subfamilies: cevanine, jervine, and veratramine. Among them, cyclopamine is arguably the most notable and investigated one. It was identified as a Hedgehog signaling pathway inhibitor, and its analogue patidegib is currently in human clinical trials for cancer treatment.

Writing Strategy

➢ The Last Paragraph

Highlight of the work

Summary of the work

- In summary, this work highlights how transition metal catalysis and C-H functionalization chemistry can impact the efficiency of natural product synthesis. Four well-orchestrated C-H functionalizations, namely, Boc-directed C-H lithiation-Negishi cross-coupling, palladium-catalyzed carbonylative C-H lactamization, lactam directed rhodiumcatalyzed C-H iodination, and Na_2-Eosin Y-catalyzed visible light-induced C-H hydroxylation enabled rapid syntheses of building blocks **26** and **42**, which were then linked together with a palladium-catalyzed Stille carbonylation for the subsequent photochemical Nazarov cyclization to build the hexacyclic skeleton.
- These enabling transformations allowed consecutive bond constructions around a monosubstituted aromatic starting material to produce the tetrasubstituted aromatic core of heilonine. Overall, total synthesis of (+)-heilonine was achieved in a highly convergent manner with 11 or 13 LLS steps.

Representative Examples

- The addition of the ketone group on the five-membered C ring would enable a Nazarov cyclization to close the five membered C ring and a highly convergent carbonylative cross-coupling strategy to bring together the AB and DEF ring systems and access **16** rapidly with carbon monoxide as a one carbon **linchpin**. (关键人物，关键事物)
- Our continued interest in using carbonylation chemistry and C-H functionalization to **streamline** total synthesis of medicinally important natural products prompted us to embark on the total synthesis of heilonine with the goal to establish a general and efficient approach to access both natural and synthetic analogs for comprehensive biological evaluations. (流线型;使流畅，优化条件使用)

Acknowledgement

Thanks
for your attention