Literature Report VIII

Total Synthesis of Aleutianamine

Reporter: Tong Niu

Checker: Bao-Qian Zhao

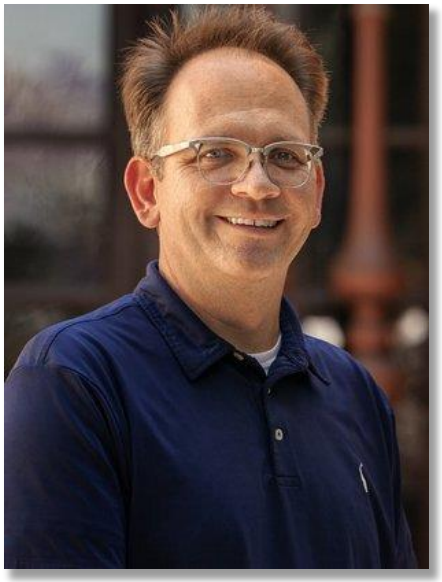
Yu, H.; Sercel, Z. P.; Rezgui, S. P.; Farhi, J.; Virgil, S. C.; Stoltz, B. M.,
***J. Am. Chem. Soc.* 2023, *145*, 25533**

2024.01.15

CV of Prof. Brian M. Stoltz

Research:

- Discovering new ways to make complex molecules
- Development of effective catalysts for enantioselective reactions

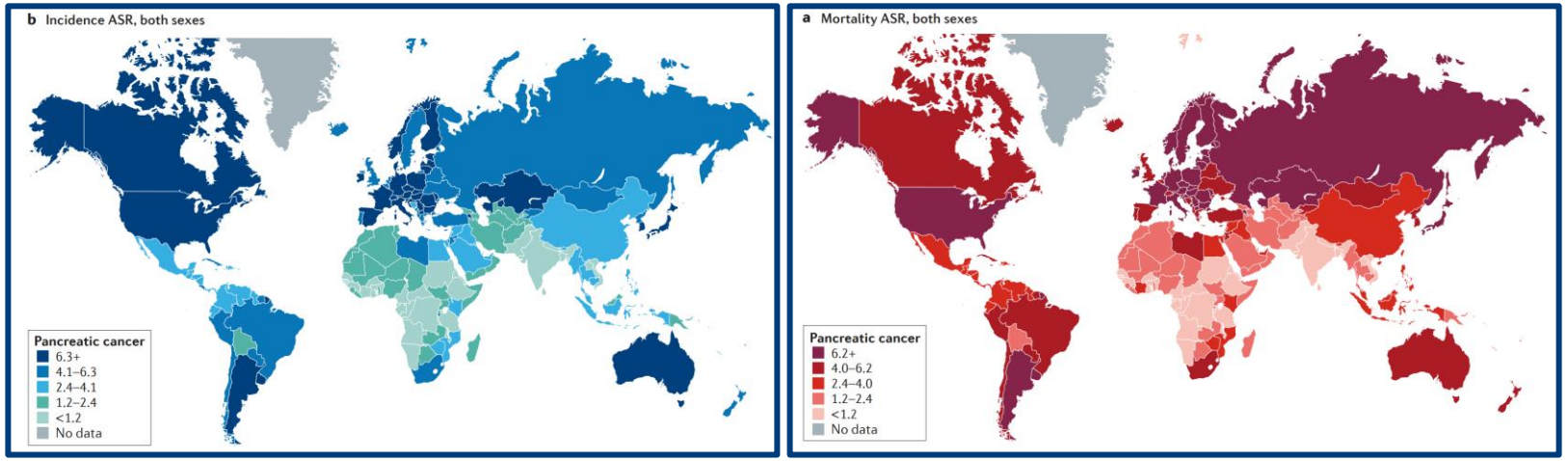


Education & Professional Experience:

- **1993** B.S., Indiana University of Pennsylvania
- **1997** Ph.D., Yale University (Prof. John L. Wood)
- **1998-2000** Postdoc., Harvard (Prof. E. J. Corey)
- **2000-2006** Assistant Professor, Caltech
- **2006-2007** Associate Professor, Caltech
- **2007-** Professor, Caltech

Contents

Introduction



Pancreatic Cancer (胰腺癌): Mortality rates closely parallel incidence rates

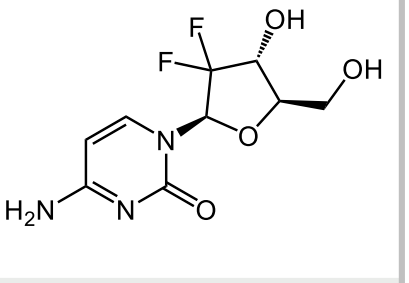
» **Difficulties in Early Disease Detection** » **Overall Ineffective Treatment Options**

» **Lack of Common Genetic Mutations Associated with the Disease**

***Natural products** have contributed significantly toward **drug discovery** and novel therapeutics, particularly in the areas of **cancer** and **infectious** disease.*

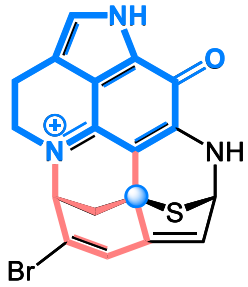
Kleeff, J.; Korc, M.; Neoptolemos, J. P., *Nat. Rev. Dis. Primers* **2016**, *2*, 16022

Introduction



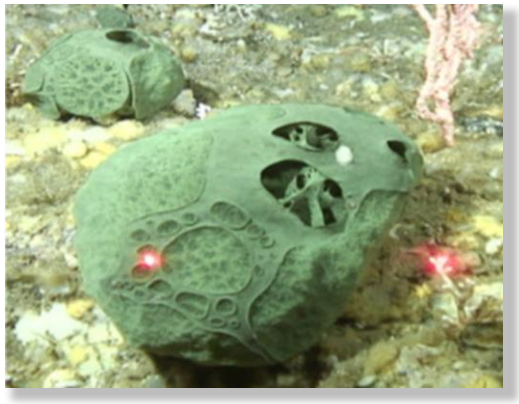
Gemcitabine (吉西他滨)

FDA-Approved Chemotherapeutic Agent



Aleutianamine (1)

IC50 against PANC-1 160 times larger



» *First Isolated in **2019** from Alaska's Deep Ocean by **Hamann** and Co-workers*

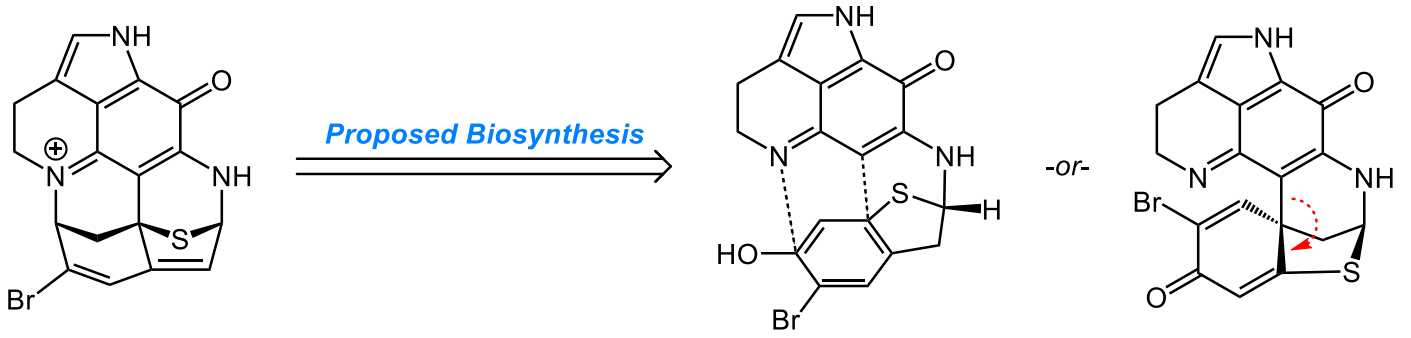
» *Belongs to **Pyrroloiminoquinone** Alkaloid Family* » *A **Heptacyclic** ring system*

» *A Bridged **Azabicyclo[3.3.1]nonane** Ring* » *A Congested **Tertiary** Alkyl Sulfide*

Zou, Y.; Wang, X.; Hamann, M. T., *J. Am. Chem. Soc.* **2019**, *141*, 4338

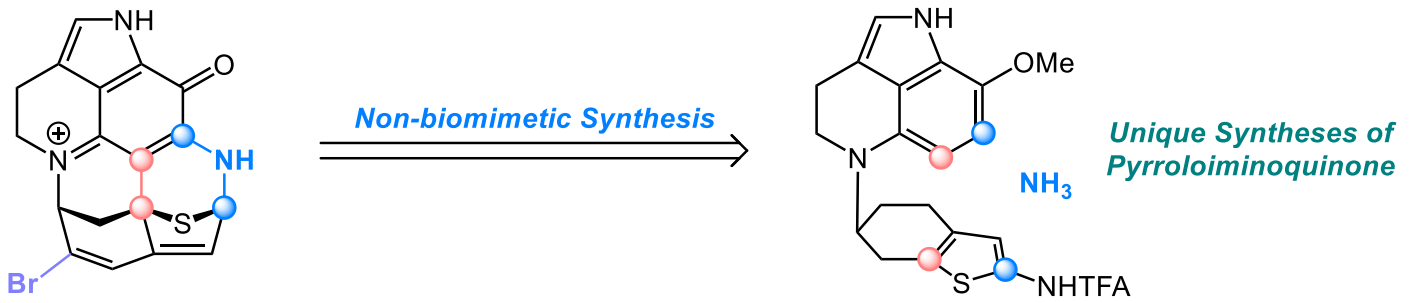
Introduction

Proposed Biosynthesis from Related Alkaloids



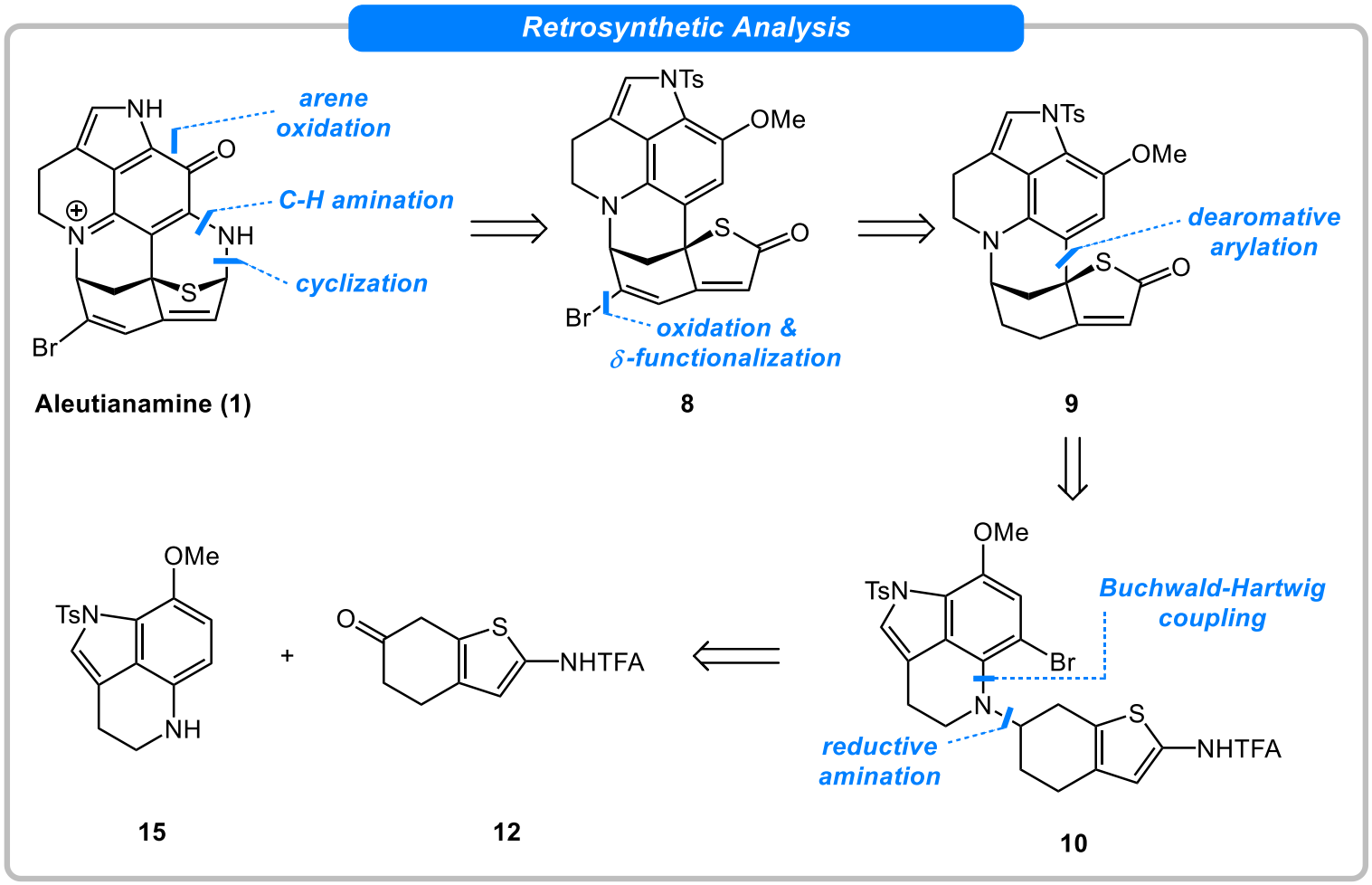
Aleutianamine (1) **Makaluvamine F (2)** **Discorhabdin B (3)**

Retrosynthetic Logic

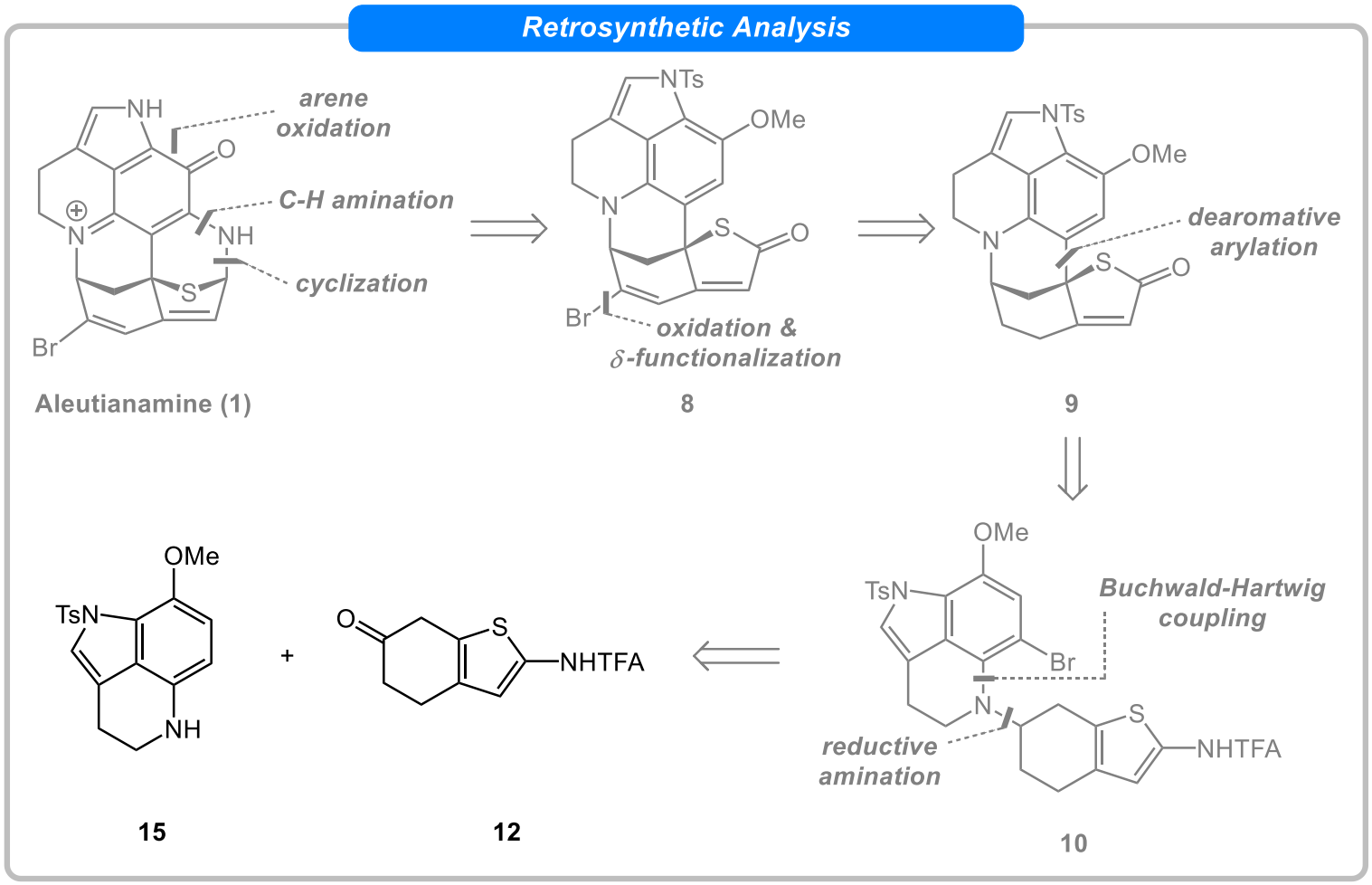


Shimomura, M.; Ide, K.; Sakata, J.; Tokuyama, H., *J. Am. Chem. Soc.* **2023**, *145*, 18233

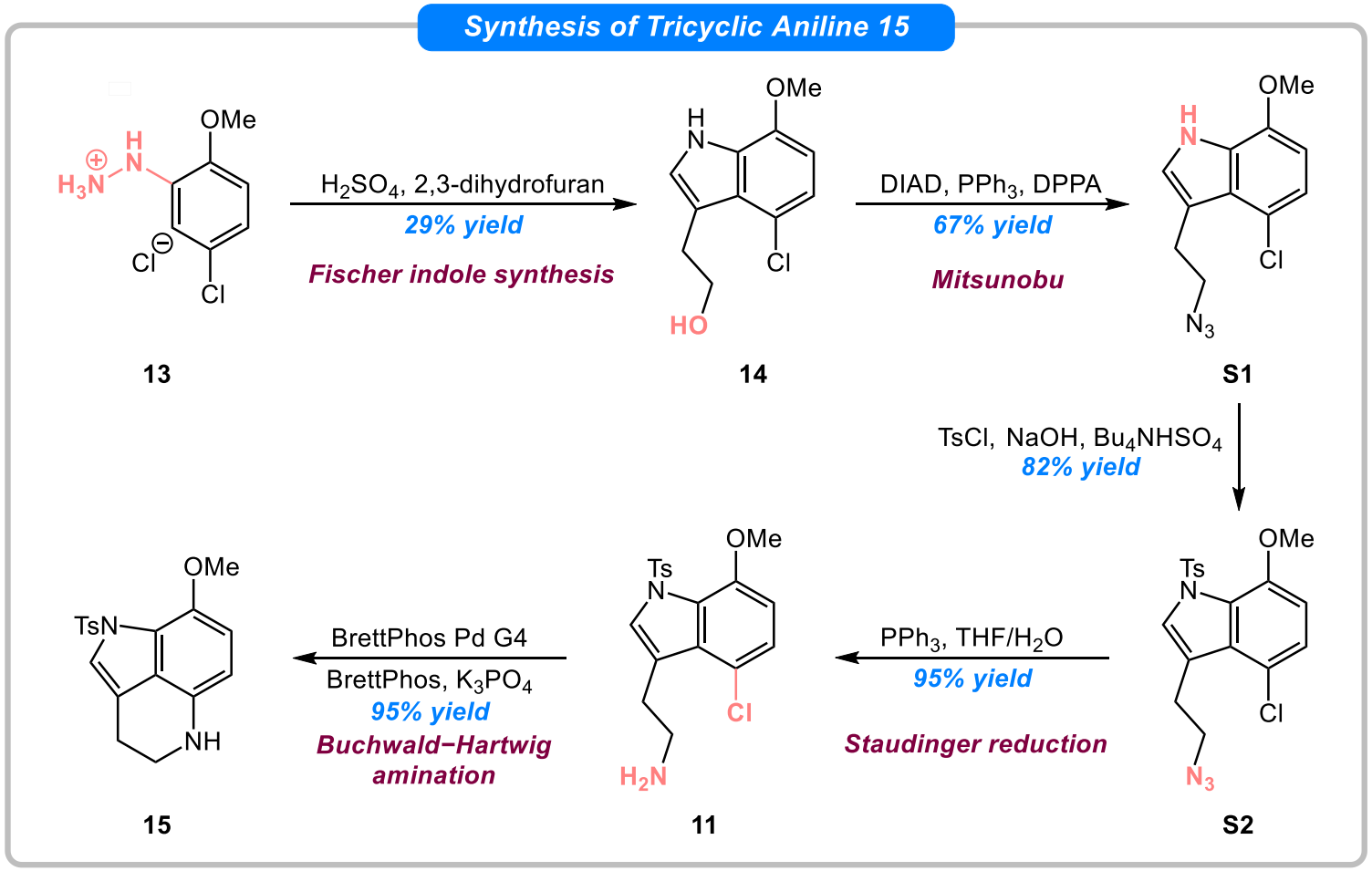
Retrosynthetic Analysis



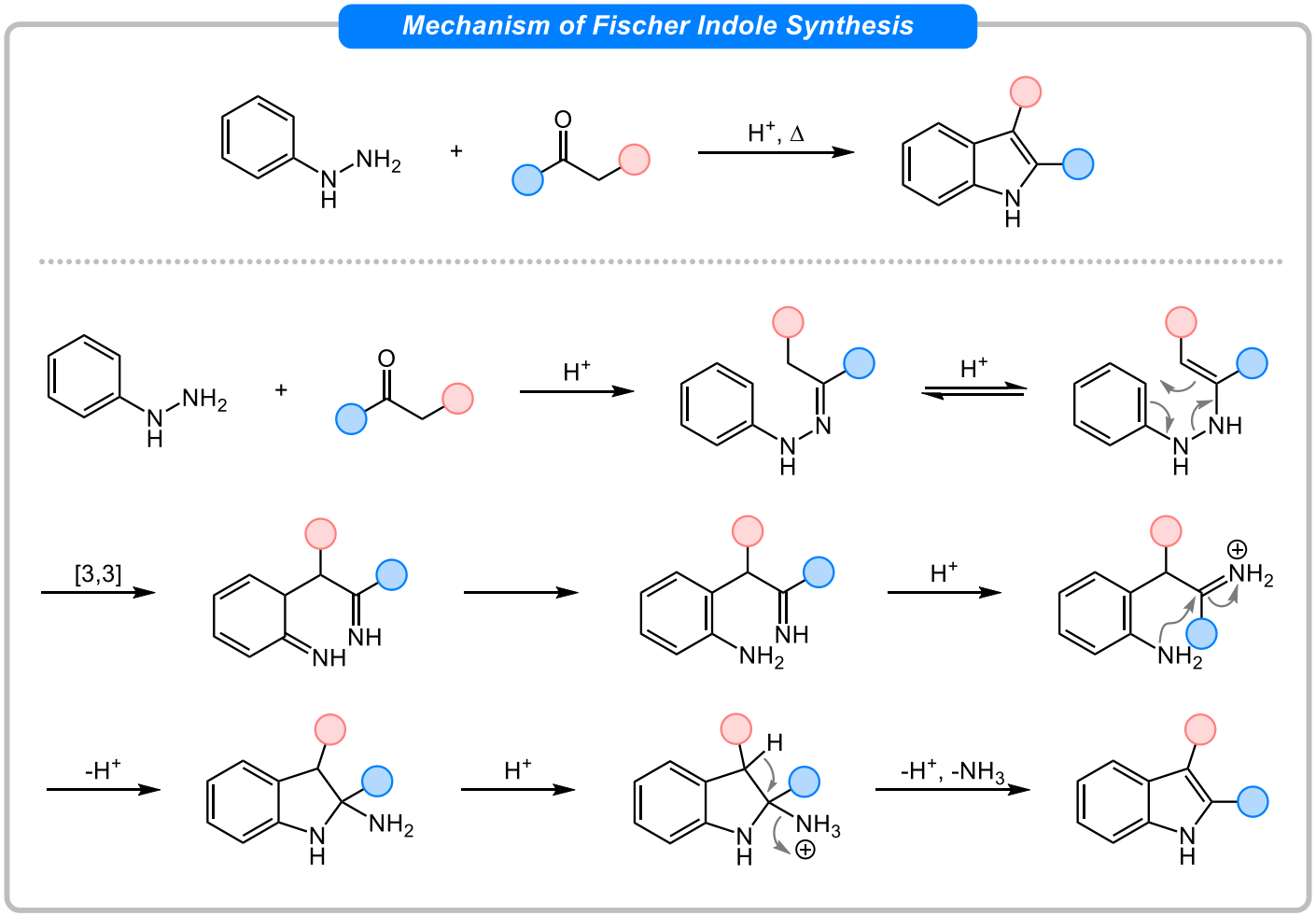
Stage 1—Synthesis of 15 and 12



Stage 1—Synthesis of 15 and 12

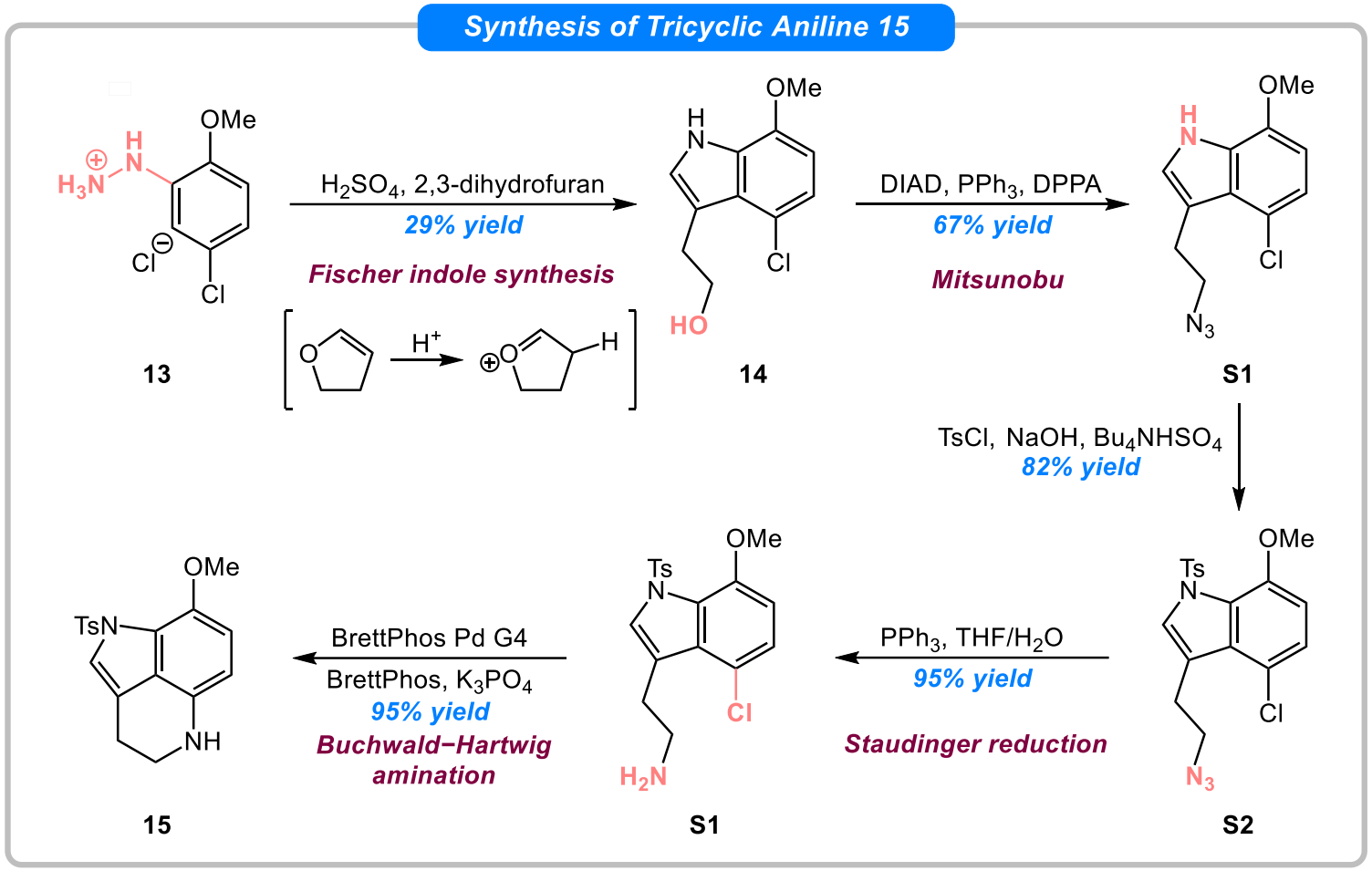


Fischer Indole Synthesis

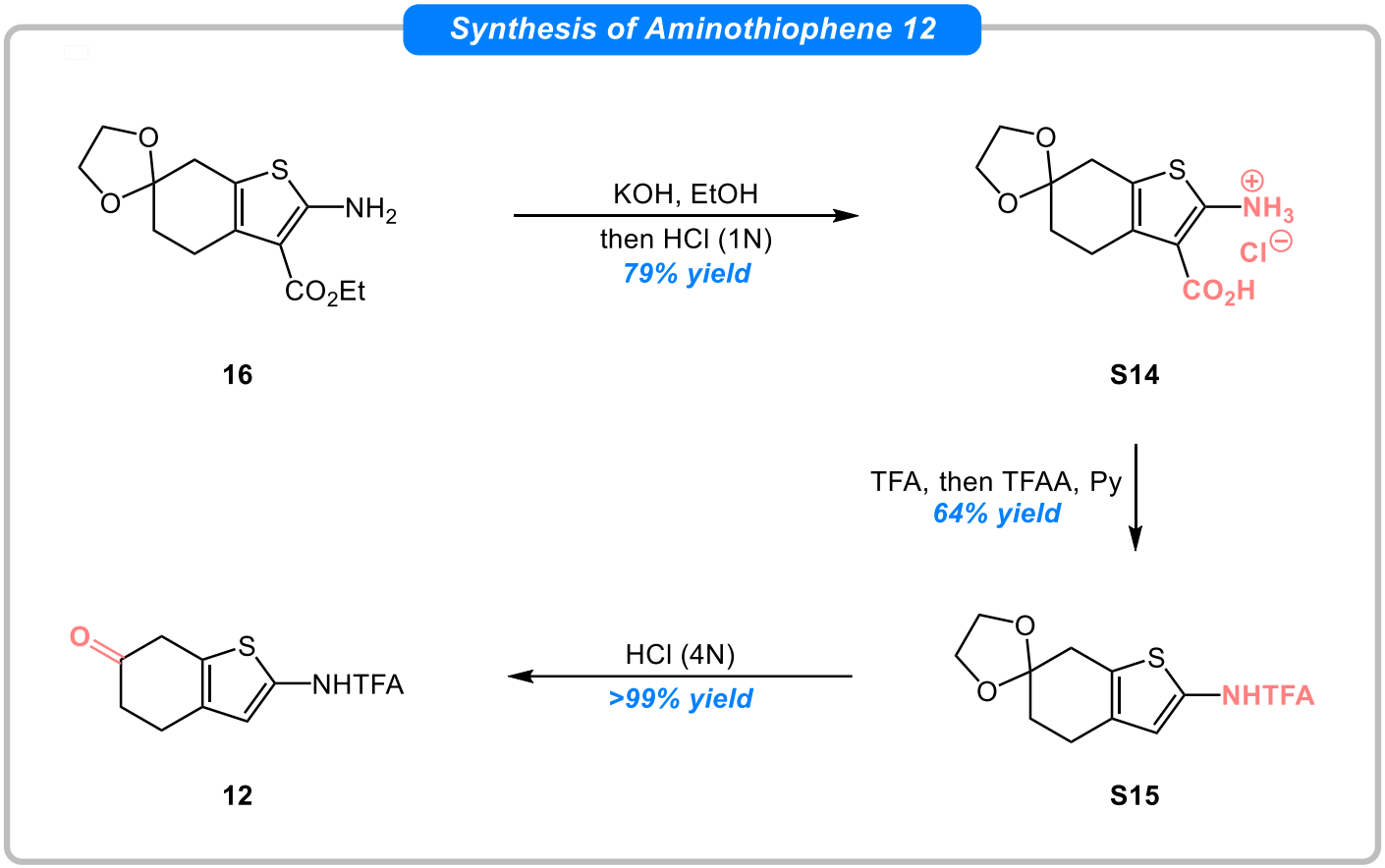


Inman, M.; Moody, C. J., *Chem. Sci.* **2013**, *4*, 29

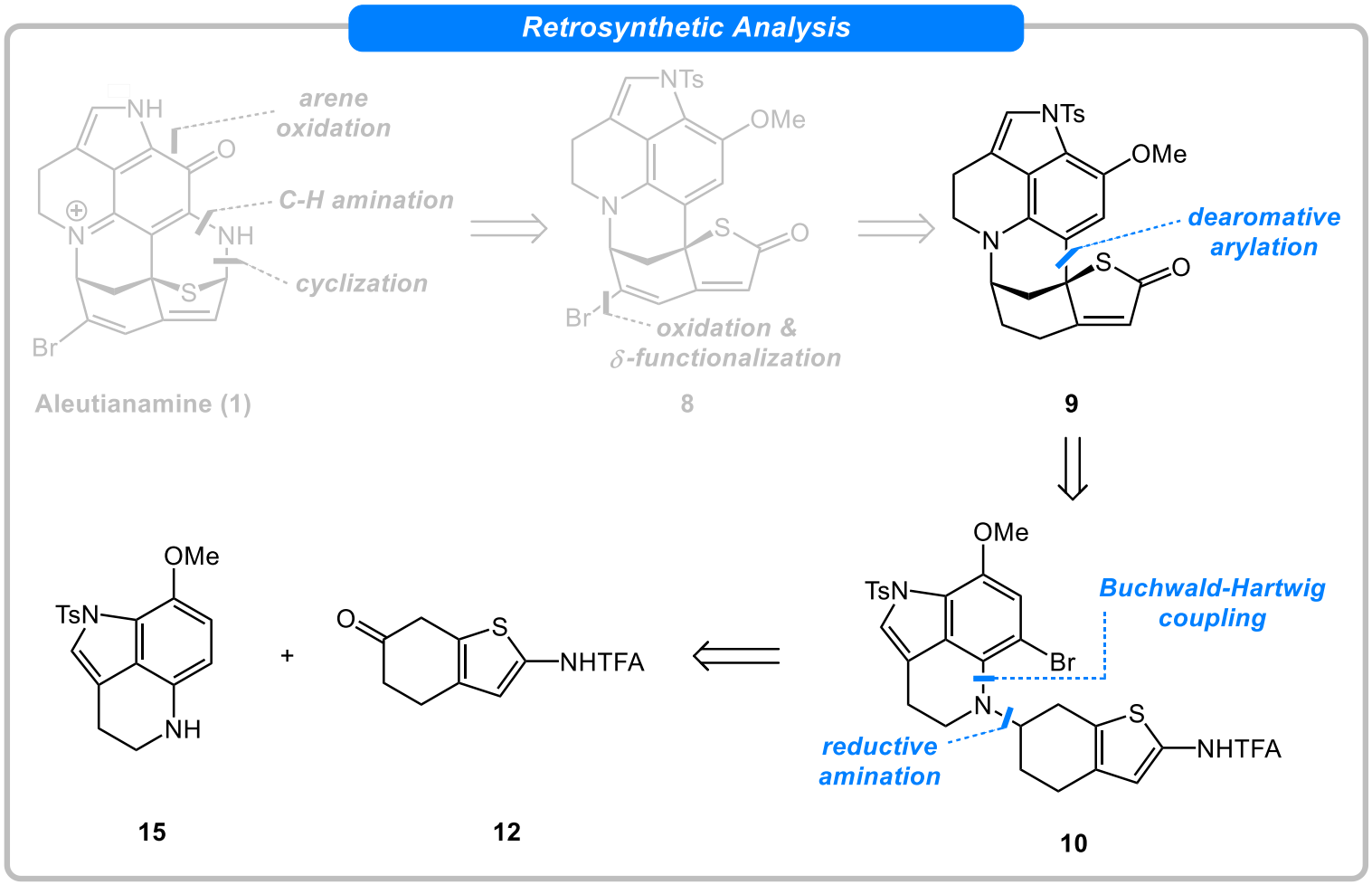
Stage 1—Synthesis of 15 and 12



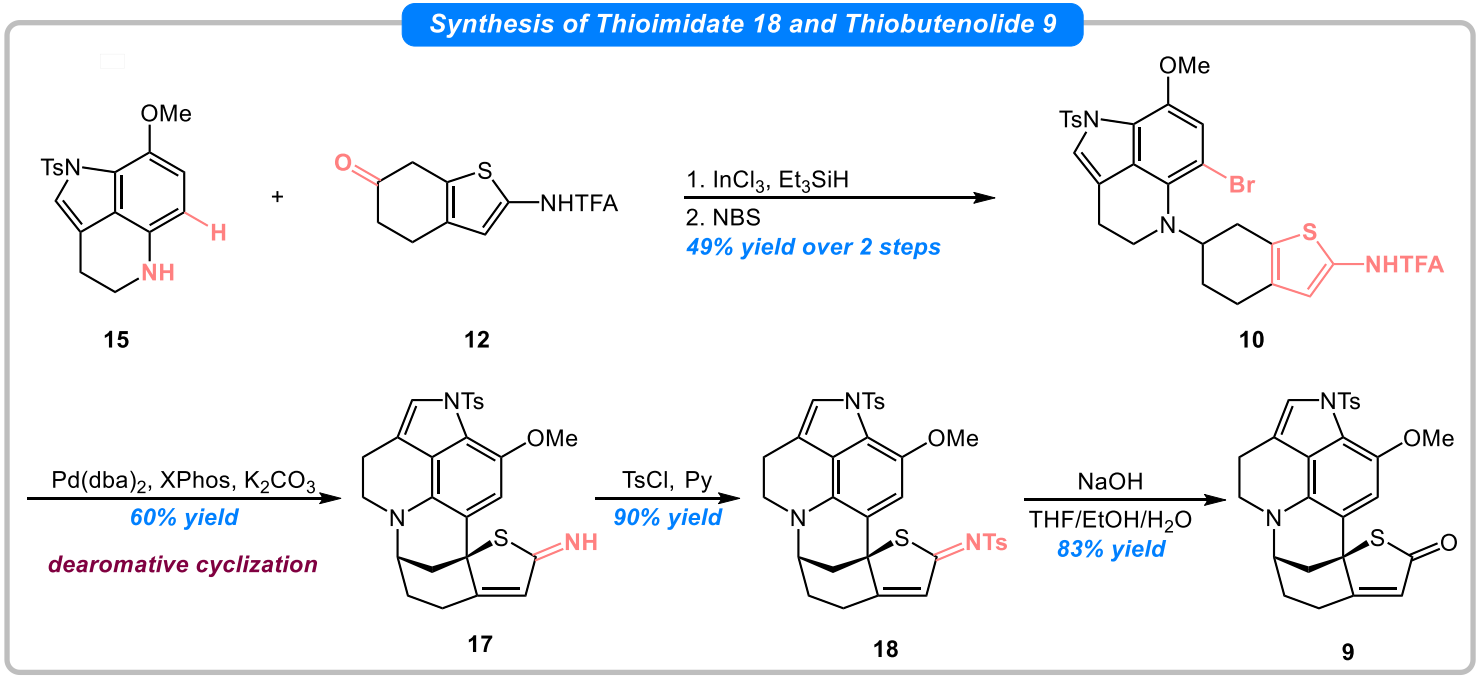
Stage 1—Synthesis of 15 and 12



Stage 2—Synthesis of 9

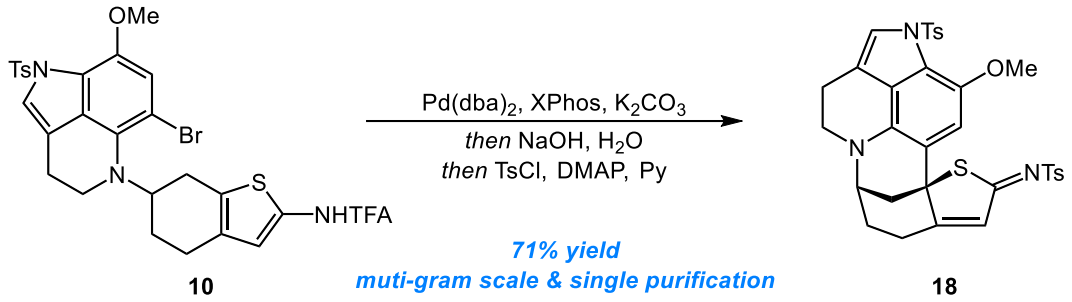


Stage 2—Synthesis of 9

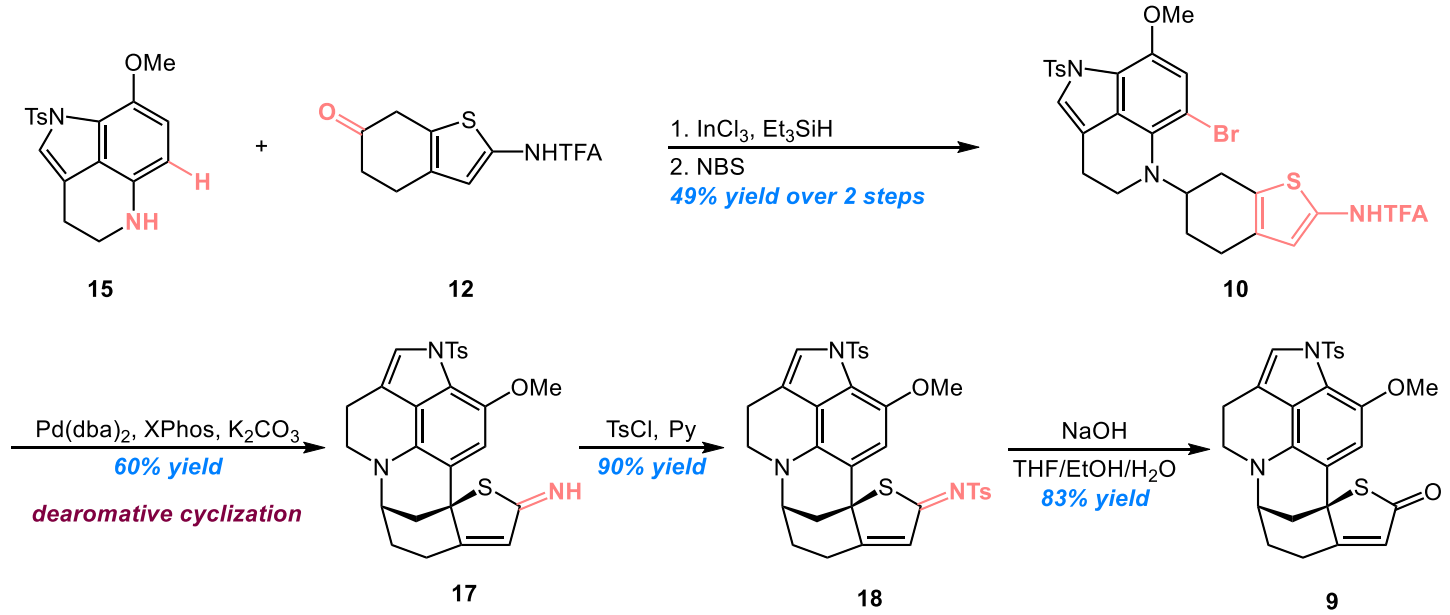


Stage 2—Synthesis of 9

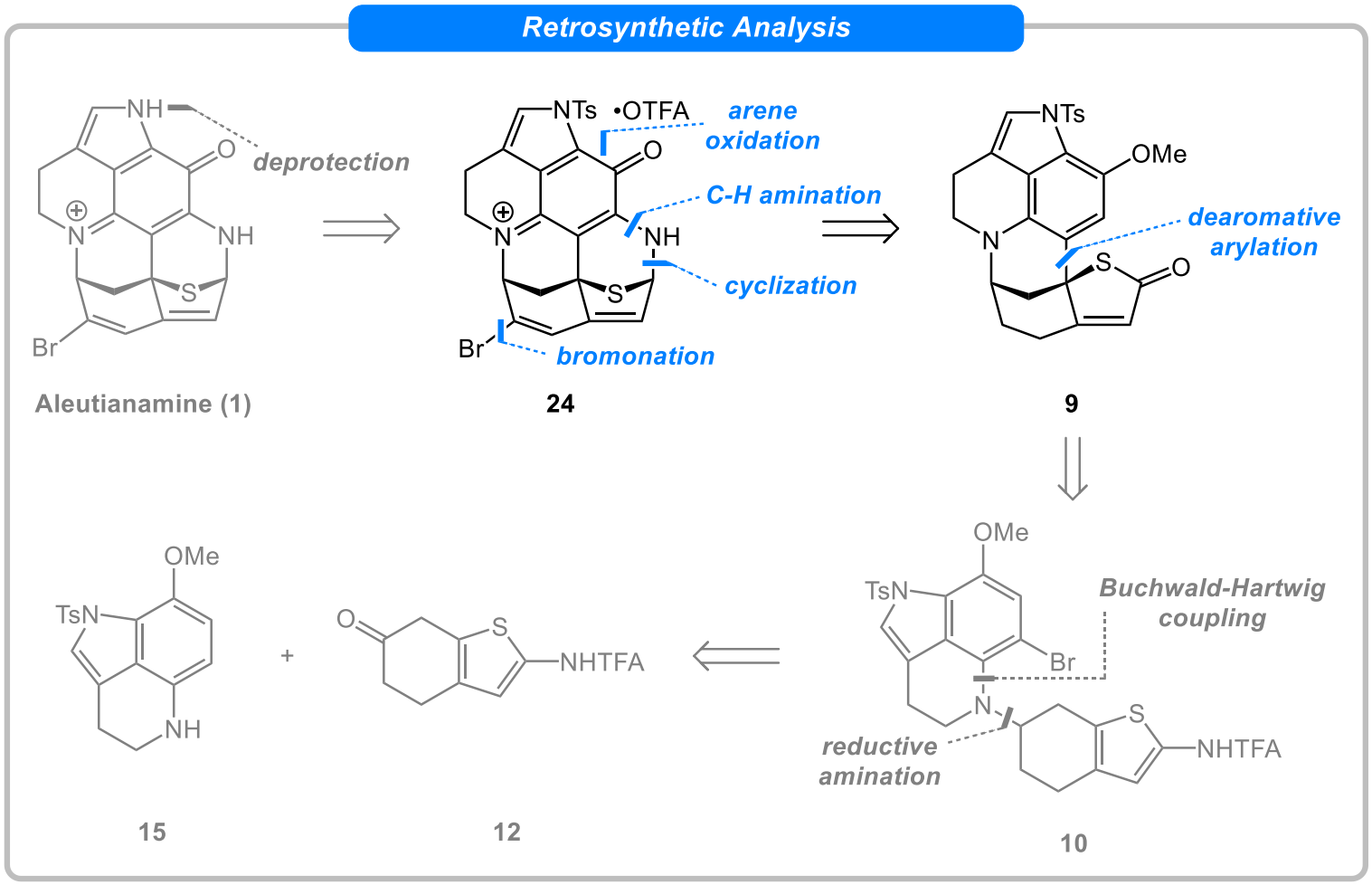
Telescoped Sequence



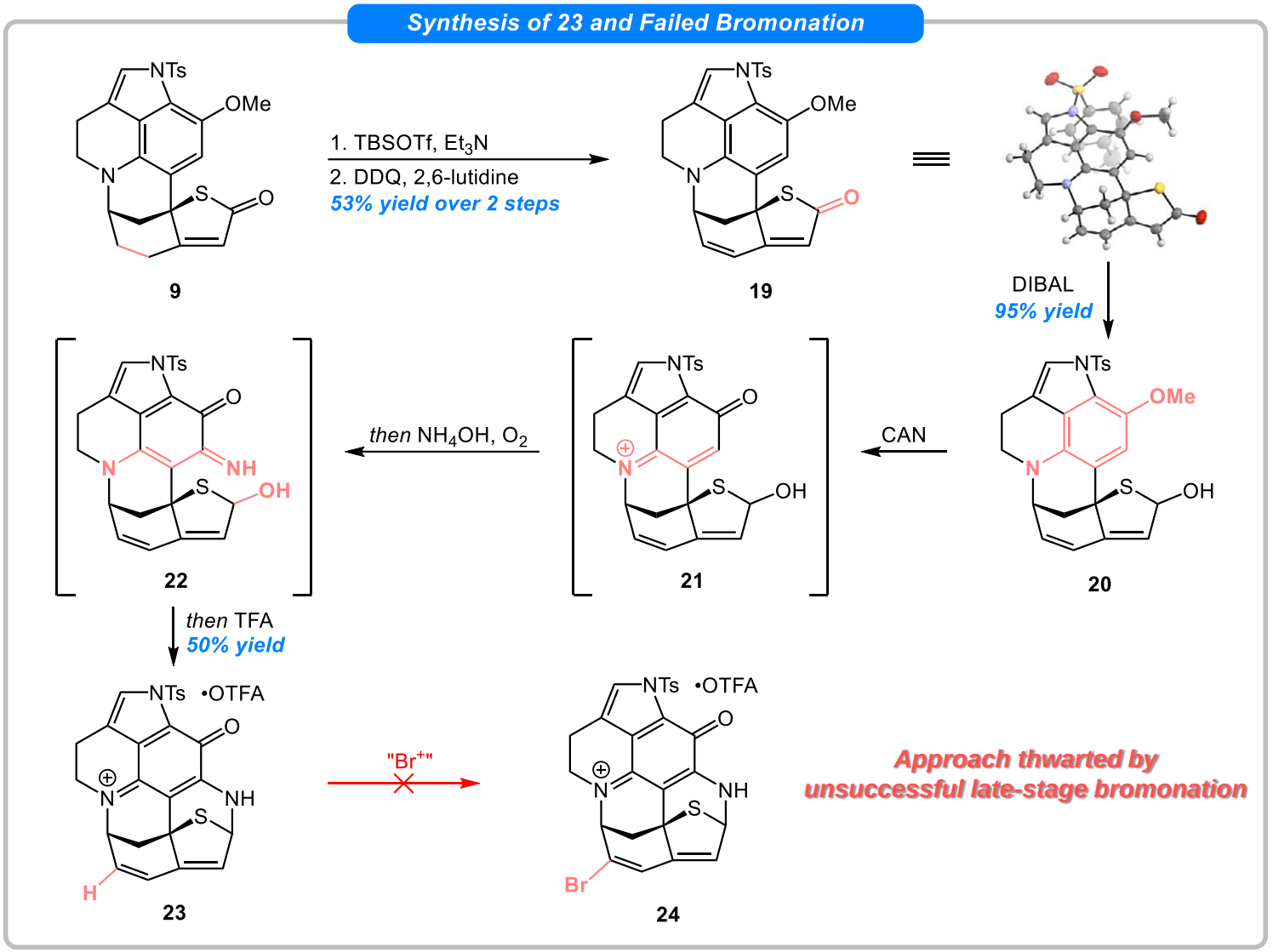
Synthesis of Thioimidate 18 and Thiobutenolide 9



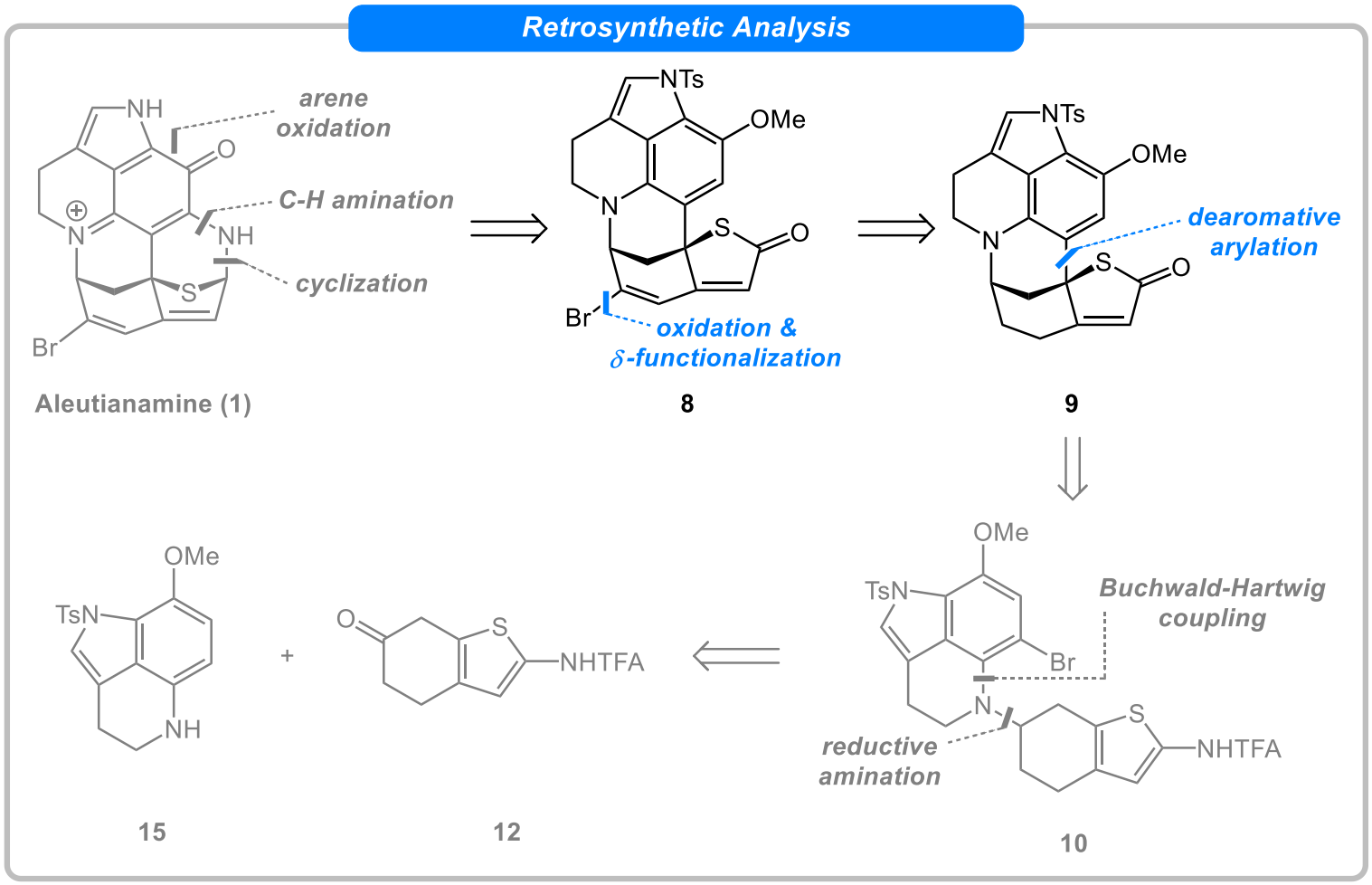
Stage 3—Attempt to Synthesis 24



Stage 3—Attempt to Synthesis 24

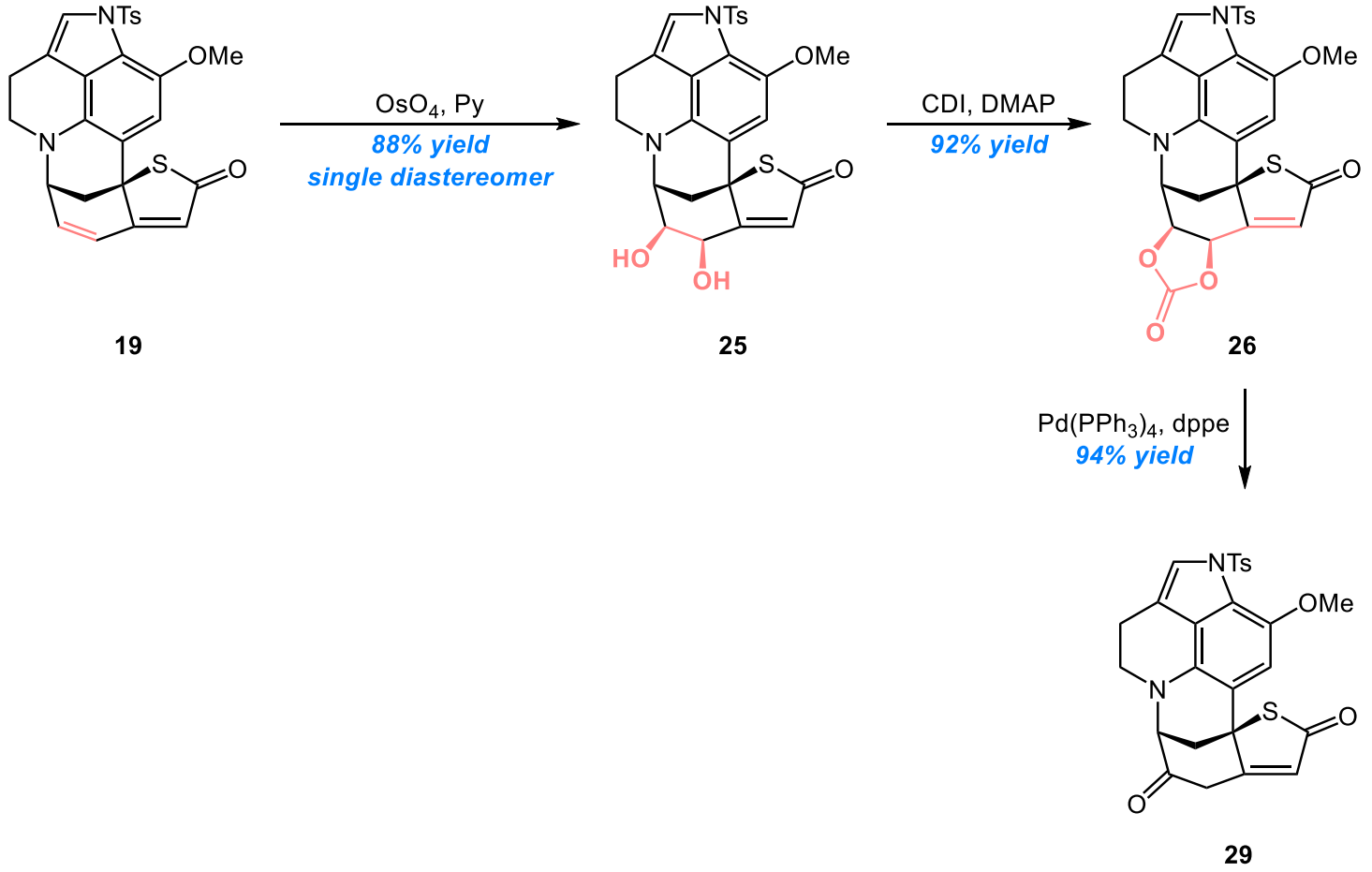


Stage 3—Synthesis of 8



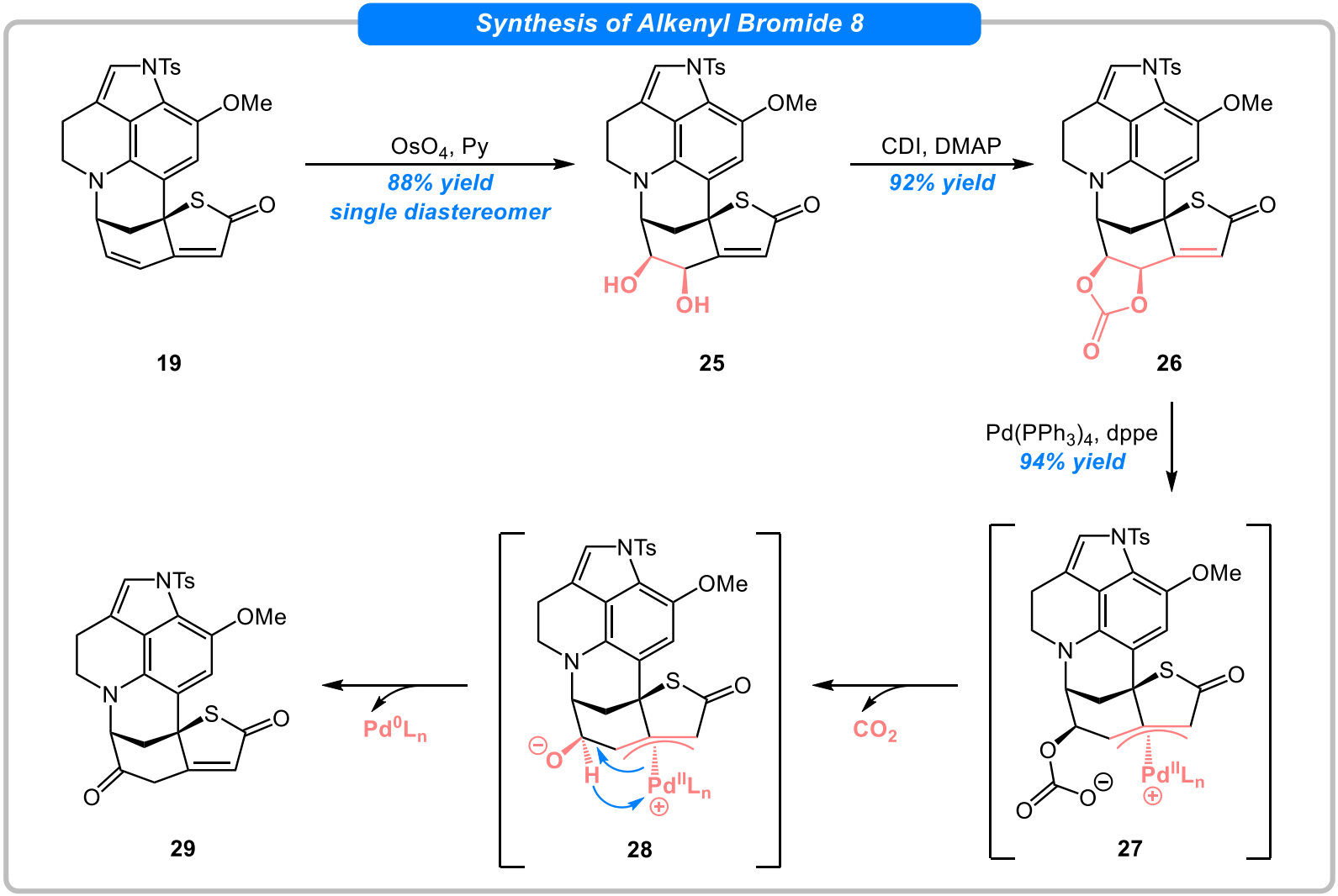
Stage 3—Synthesis of 8

Synthesis of Alkenyl Bromide 8

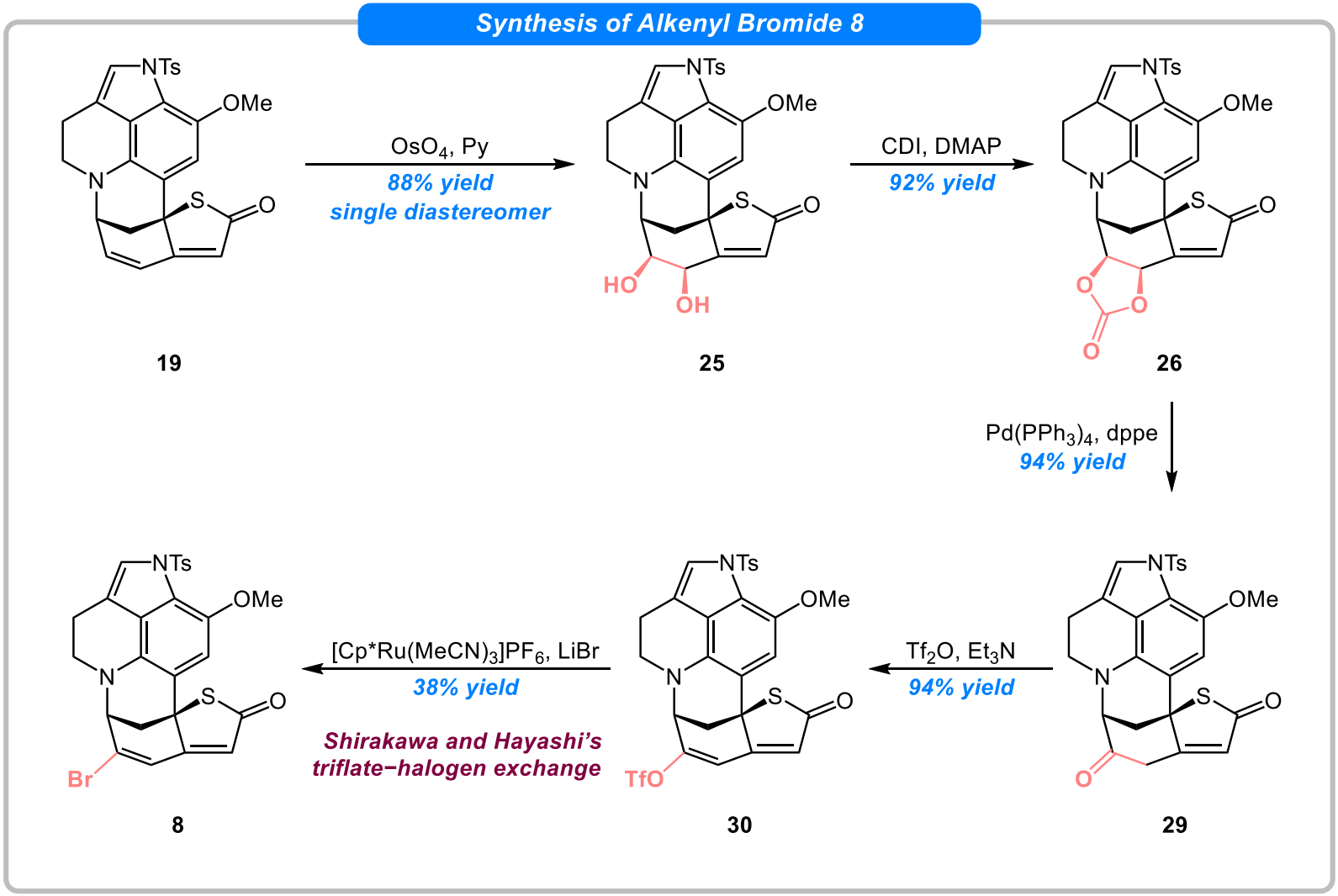


19 **25** **26** **29**

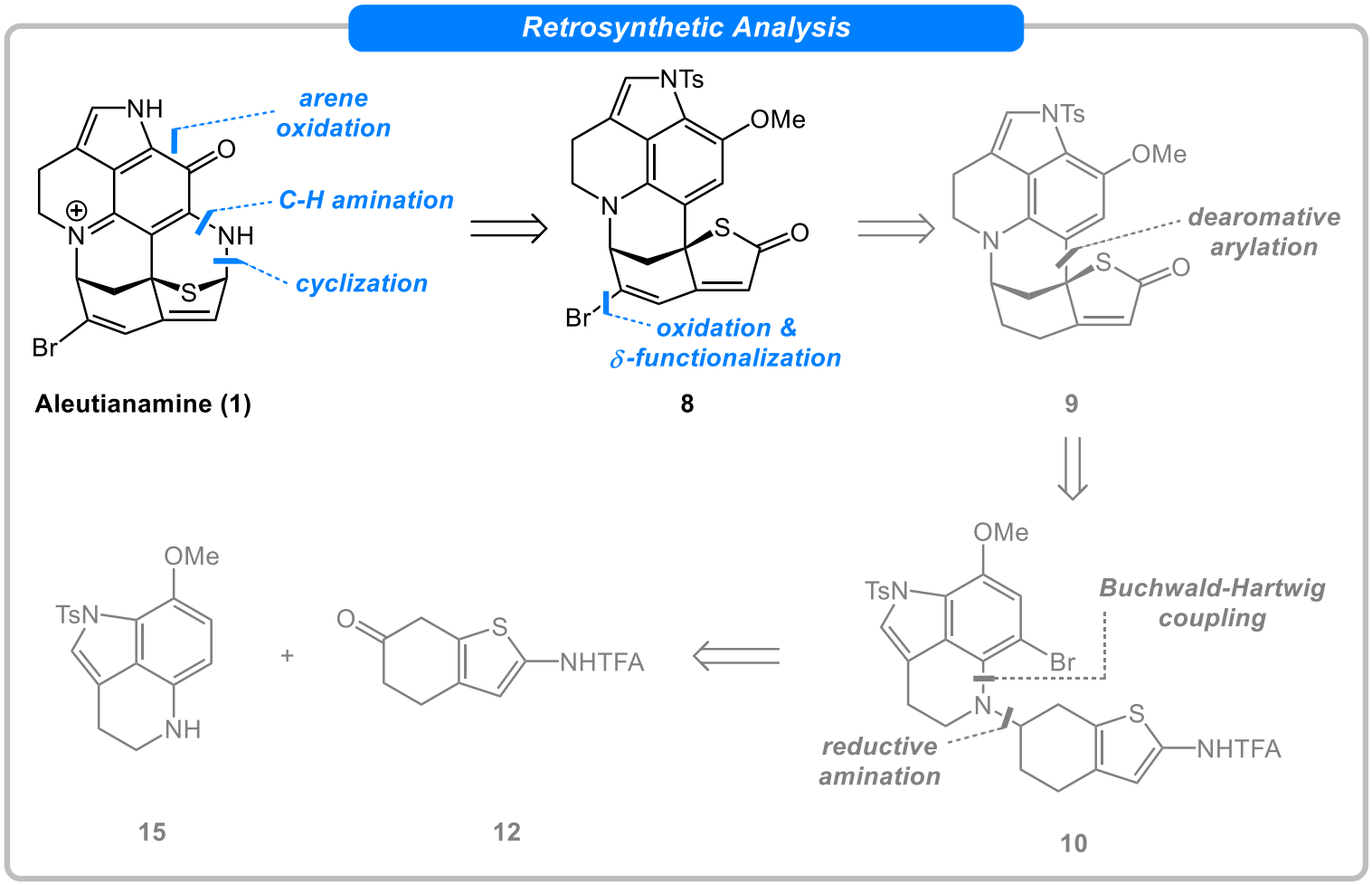
Stage 3—Synthesis of 8



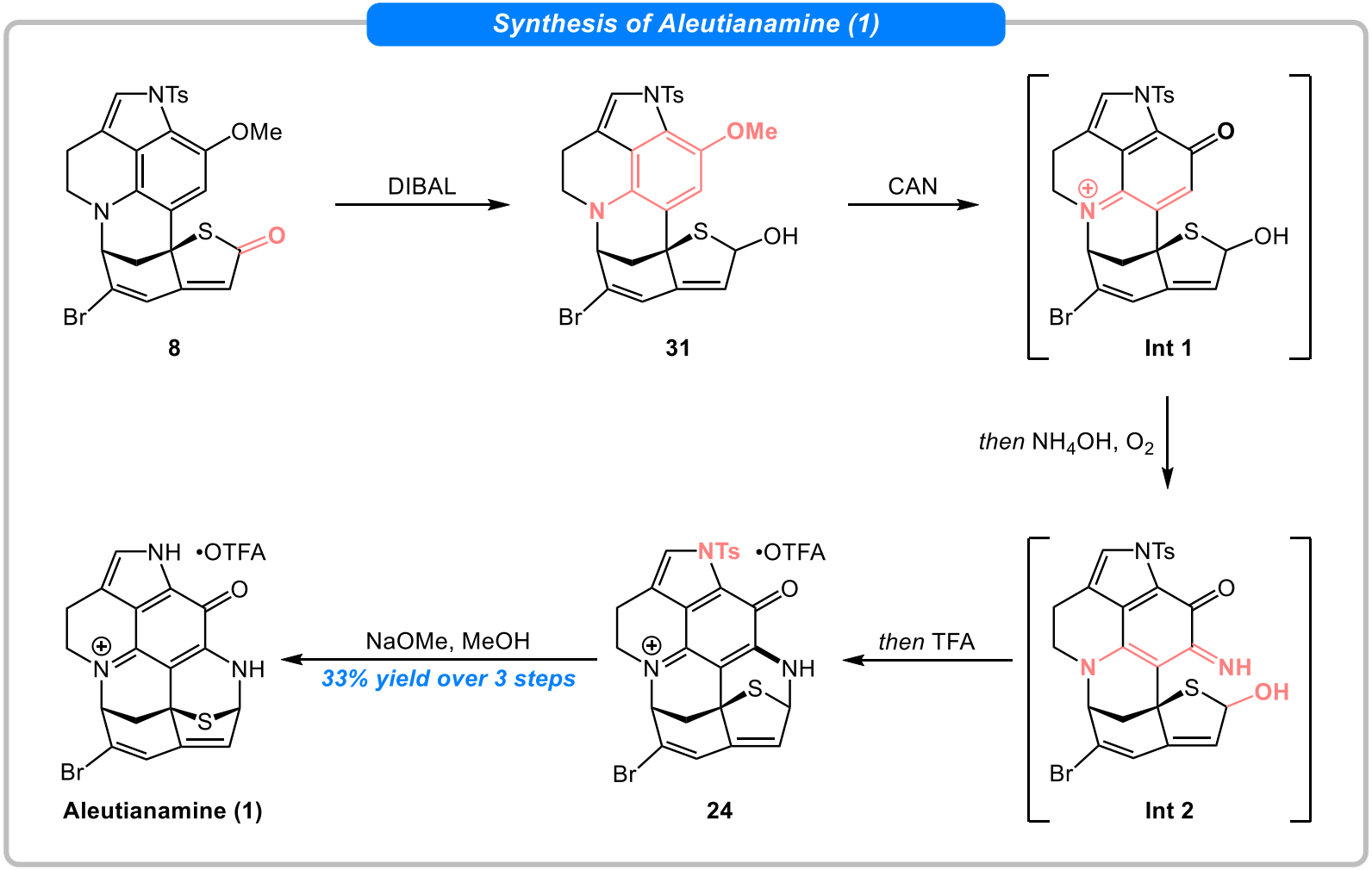
Stage 3—Synthesis of 8



Final Stage—Synthesis of Aleutianamine (1)

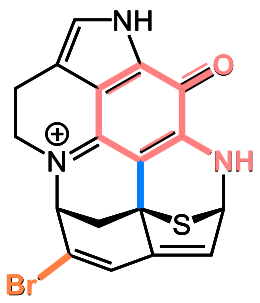


Final Stage—Synthesis of Aleutianamine (1)



Summary

Total Synthesis of Aleutianamine (1)



- ***Nonbiomimetic* Synthetic Approach to Aleutianamine**
- ***Longest Linear Sequence of 20 Steps***
- ***0.14% Overall Yield***

» ***Pd-Catalyzed Intramolecular Dearomative Arylation***

» ***Pd-Catalyzed Pinacol-Type Rearrangement of Cyclic Carbonate***

» ***Late-Stage Arene Oxidative Amination and Cyclization***

Writing Strategies

☐ The First Paragraph

The High Lethality of Pancreatic Cancer

Difficulty in Treating Pancreatic Cancer

The Therapeutic Potential of Aleutianamine

✓ Pancreatic cancer is the third leading cause of cancer death and is projected to be the second deadliest cancer by 2040, exemplified by a dismal 12% five year survival rate for patients with the disease.

✓ These alarming statistics can be attributed to difficulties in early disease detection, the lack of common genetic mutations associated with the disease, and overall ineffective treatment options.

✓ Historically, natural products have contributed significantly toward drug discovery and novel therapeutics, particularly in the areas of cancer and infectious disease. Aleutianamine (**1**), isolated in 2019 by Hamann and co-workers, is a marine derived alkaloid that possesses potent and selective cytotoxicity toward solid tumor cell lines.

Writing Strategies

☐ The Last Paragraph

Summary of this Work

- ✓ This total synthesis represents a nonbiomimetic synthetic approach to aleutianamine.

Highlights of this Work

- ✓ Key to the synthetic approach were the Pd-catalyzed intramolecular dearomative arylation of an aminothiophene, ketone installation by the Pd-catalyzed pinacol-type rearrangement of a cyclic carbonate, and latestage arene oxidative amination

Outlook of this Work

- ✓ Efforts to prepare analogues of aleutianamine with related sequences and to establish a structure-activity relationship against biologically relevant cancer cell lines are ongoing.

Representative Examples

- ✓ Despite advances in new therapeutics for pancreatic cancer, patient survival has only **marginally** (*adv.* **少量地，轻微地，微不足道地**) increased in the past several decades.

- ✓ We devised an alternative nonbiomimetic approach **centered around** (**围绕…，以…为中心**) formation of the bridging [3.3.1] ring system followed by late-stage arene oxidation, a strategy that is unique in comparison to previous pyrroloiminoquinone syntheses

- ✓ Reasoning that the electronics of diene **19** would promote bromination at the undesired C1 position, we **opted** (*vi.* **选择，挑选**) to delay the installation of the alkenyl bromide until the final stage of the synthesis.

Acknowledgement

Thanks for your attentions!