

# Literature Report VI

## Asymmetric Total Synthesis of Alstroline G Utilizing a Catalytic Asymmetric Desymmetrization Strategy

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Reporter: Bao-Qian Zhao

Checker: Tong Niu

Date: 2024-10-14

Zhang, N.; Wang, C.; Xu, H.; Jiang, H.; Chen, K.; [Ma, Z.](#) *Angew. Chem. Int. Ed.* **2024**, *62*, e202407127

# CV of Prof. Zhiqiang Ma (马志强)

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## Research:

Natural Product Synthesis & Target-oriented Methodology Development & Medicinal Chemistry

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## Background:

- ❑ **1997-2001** B.S., Lanzhou University
- ❑ **2001-2007** Ph.D., Shanghai Institute of Organic Chemistry, CAS
- ❑ **2007-2015** Postdoc., UT Southwestern Medical Center
- ❑ **2016-Now** Professor, South China University of Technology

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## 2 Copper-Catalyzed Enantioselective Monobenzylation of 1,3-Diol

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## 3 Total Synthesis of (+)-Alstroline G (1)

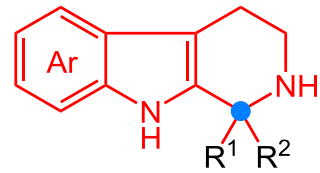
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## 4 Summary

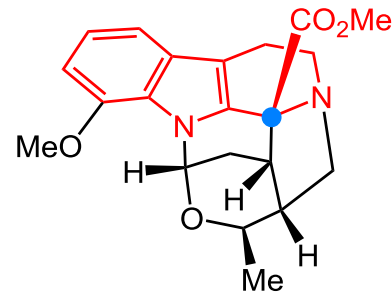
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# Introduction

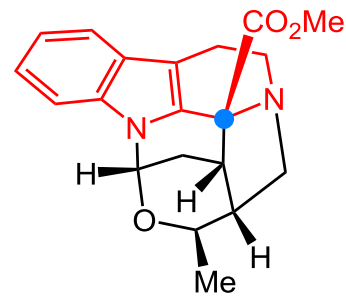
## Indoline Alkaloids with 1,1-Disubstituted THBC Nucleus



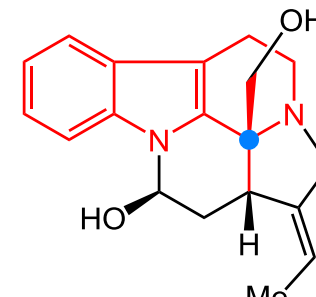
1,1-disubstituted  
tetrahydro- $\beta$ -carboline  
(THBC)



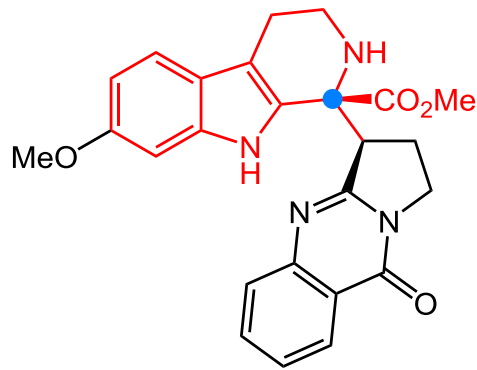
alstroisine G (1)



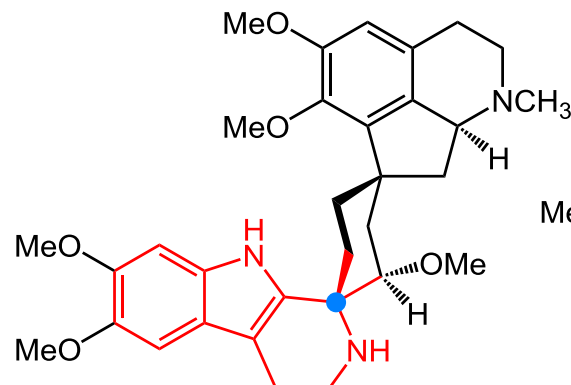
alstratine A (2)



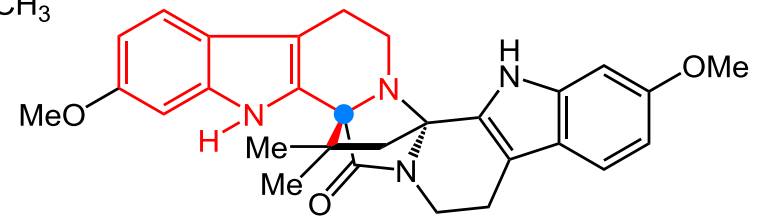
arbornamine (3)



peharmaline A (4)

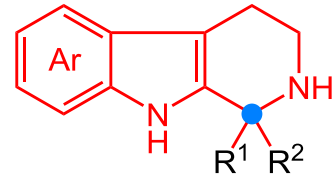


roemeridine (5)

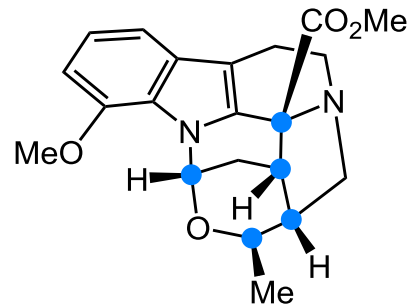


peganumine A (6)

# Introduction



1,1-disubstituted  
tetrahydro- $\beta$ -carboline  
(THBC)



alstrostine G (1)

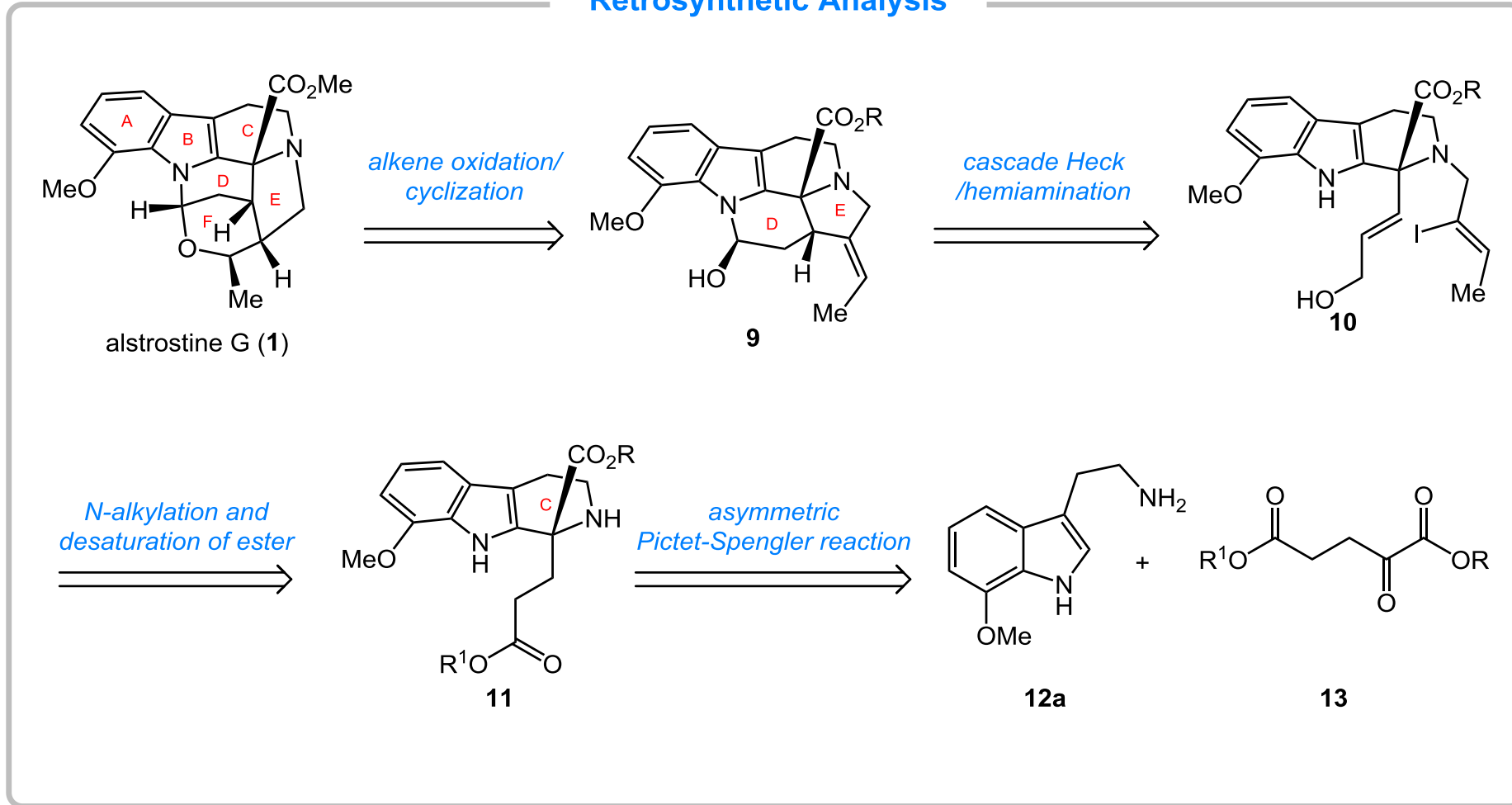


- First isolated from the *Alstonia rostrata* by the Cai group in 2017
- Unusual 6/5/6/6/5/6 hexacyclic ring system and five stereocenters
- Total synthesis of alstrostine G (1) has not been disclosed

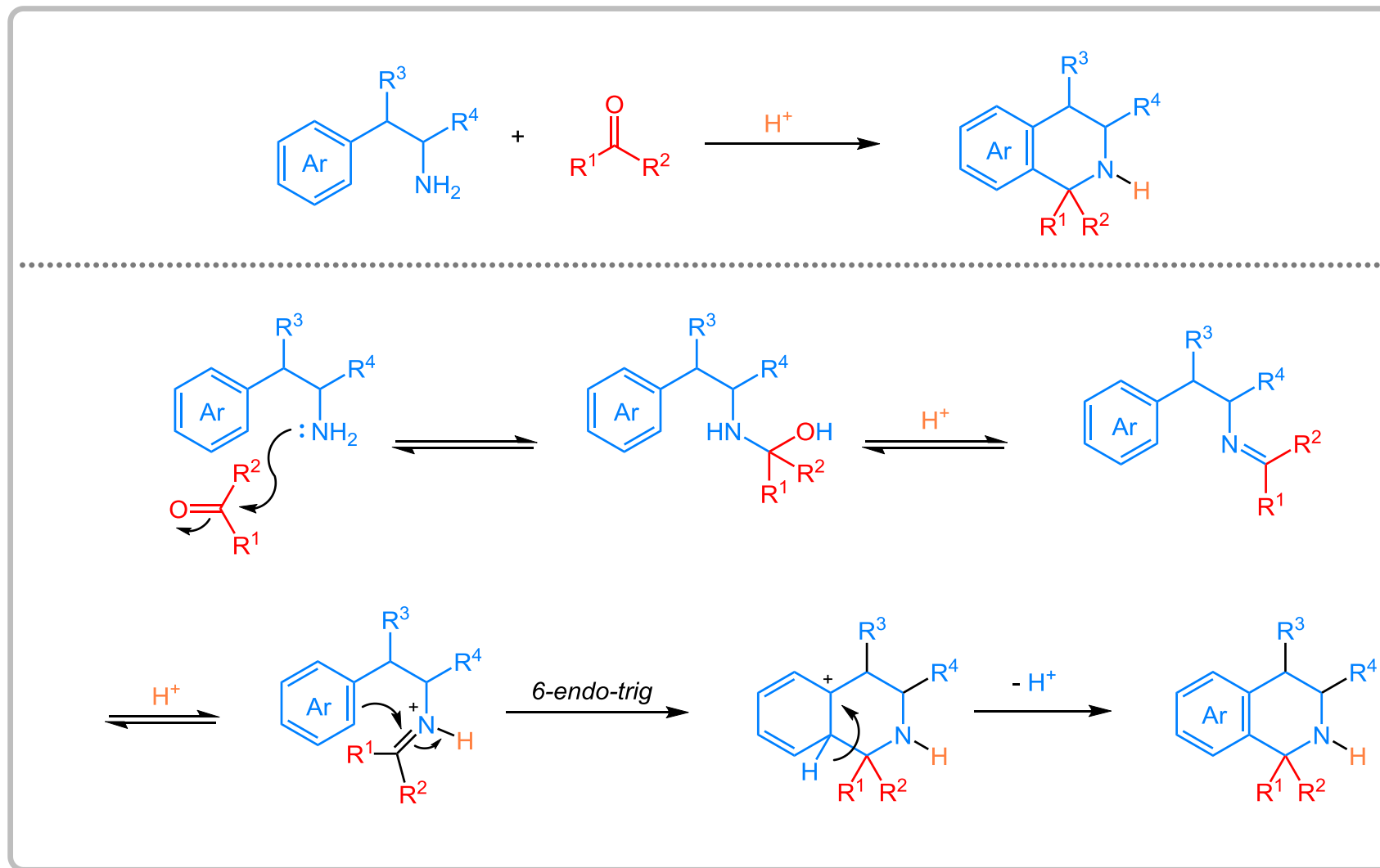
Zhong, X.; Bao, M.; Zeng, C.; Zhang, B.; Zhang, Y.; Cai, X. *Phytochem. Lett.* **2017**, *20*, 77

# Retrosynthetic Analysis

## Retrosynthetic Analysis

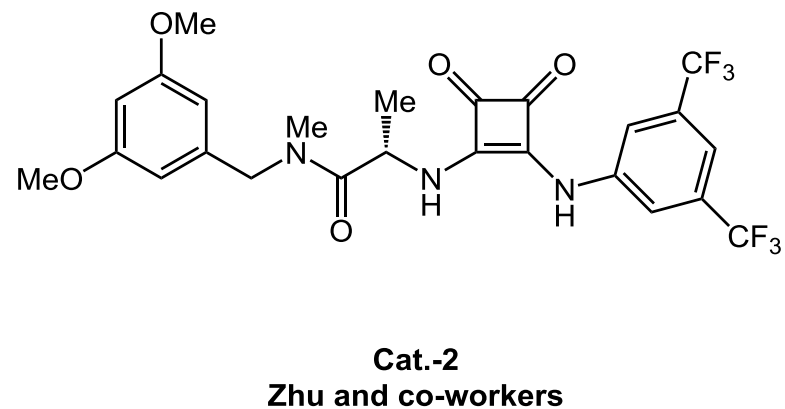
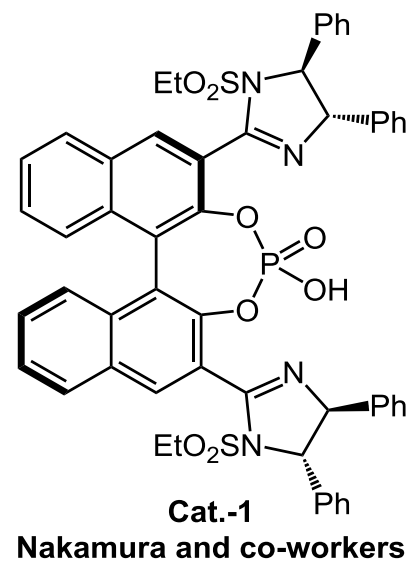
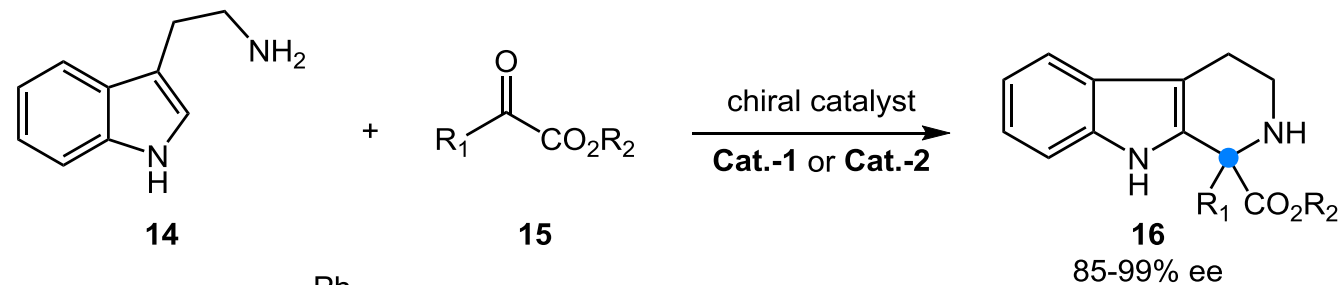


# Pictet–Spengler Reaction



# Asymmetric Pictet–Spengler Reaction

## Previous Studies

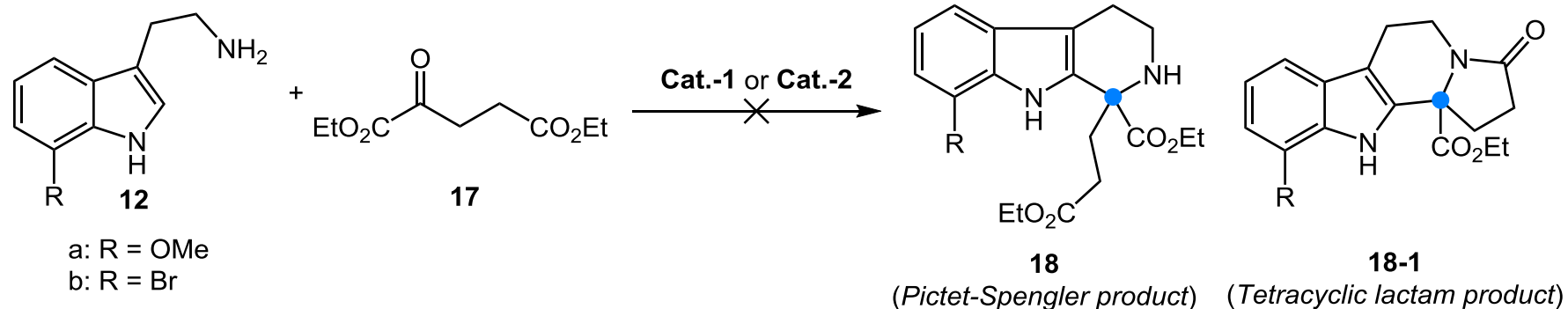


Nakamura, S.; Matsuda, Y.; Takehara, T.; Suzuki, T. *Org. Lett.* **2022**, 24, 1072  
Andres, R.; Sun, F.; Wang, Q.; Zhu, J. *Angew. Chem. Int. Ed.* **2023**, 62, e202213831

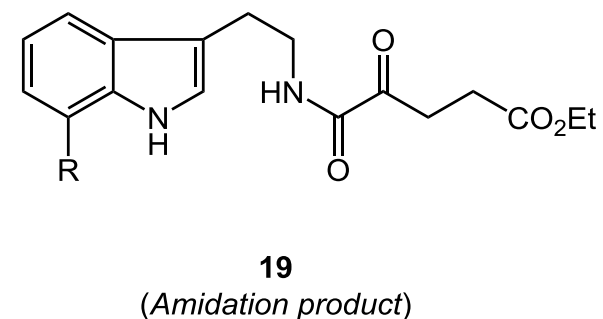


# Asymmetric Pictet–Spengler Reaction

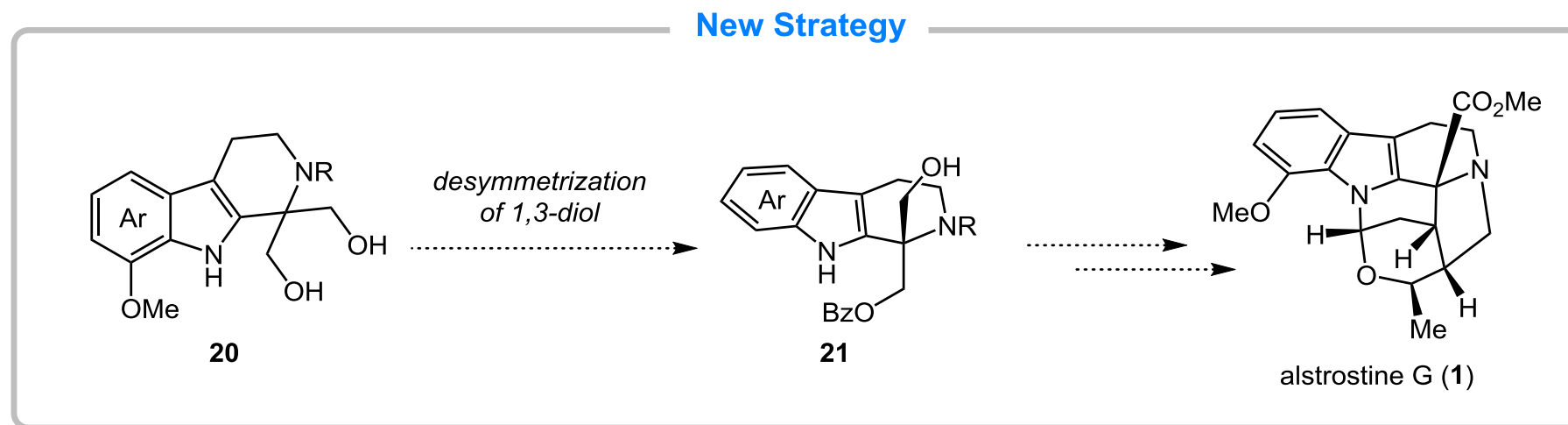
## Reaction of 7-Substituted Tryptamines 12 with 17



Entry	Substrates	Cat.	Yield (%) of					
			18a	18-1a	19a	18b	18-1b	19b
1	12a+17	Cat.-1	0	15	12	-	-	-
2		Cat.-2	0	0	14	-	-	-
3	12b+17	Cat.-1	-	-	-	0	0	0
4		Cat.-2	-	-	-	0	0	19

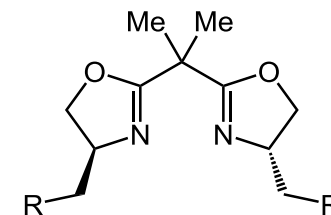
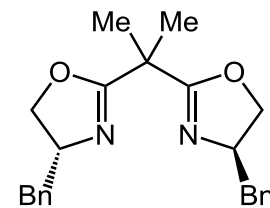
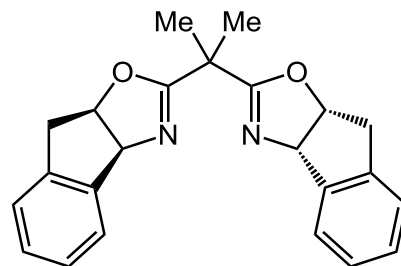
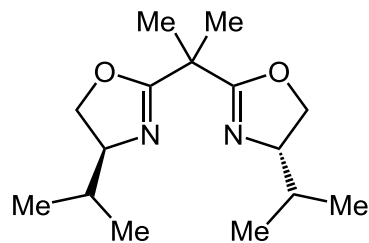
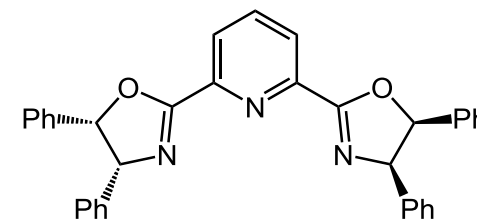
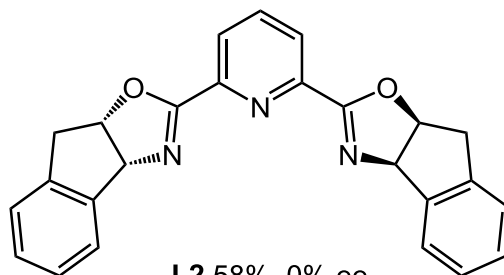
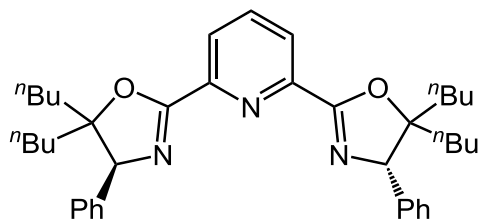
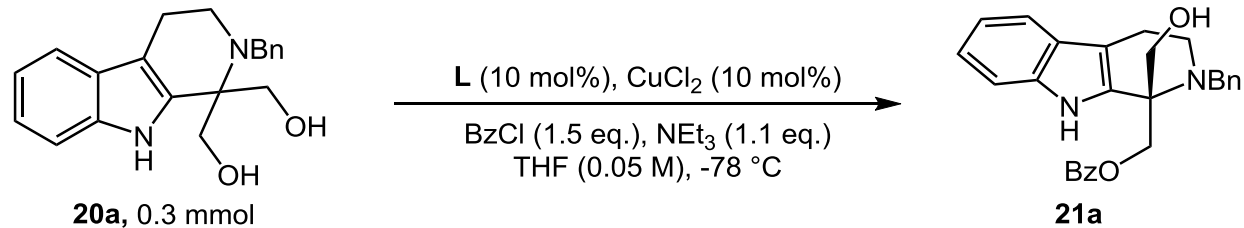


# Desymmetrization of 1,3-Diol



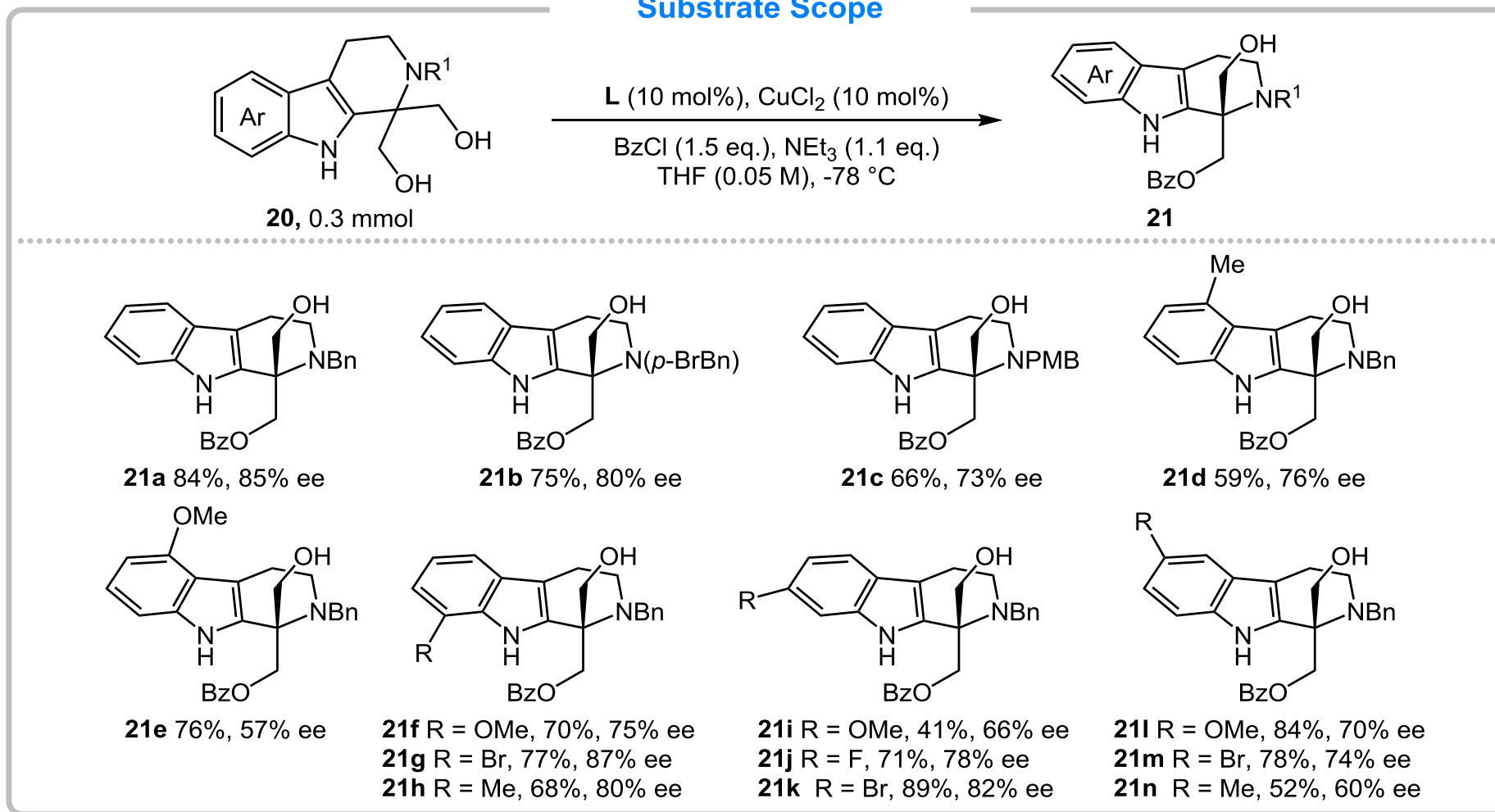
# Desymmetrization of 1,3-Diol

## Optimization of the Enantioselective Monobenzoylation Reaction



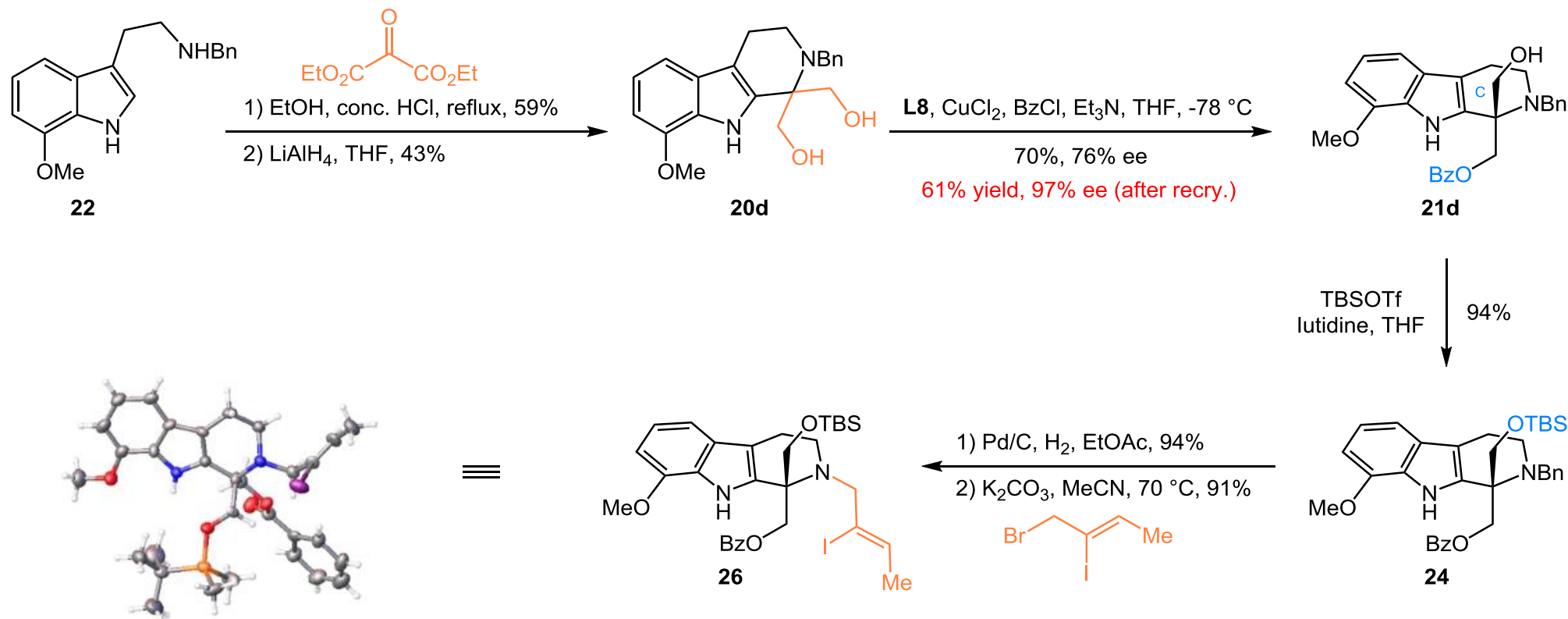
# Desymmetrization of 1,3-Diol

## Substrate Scope



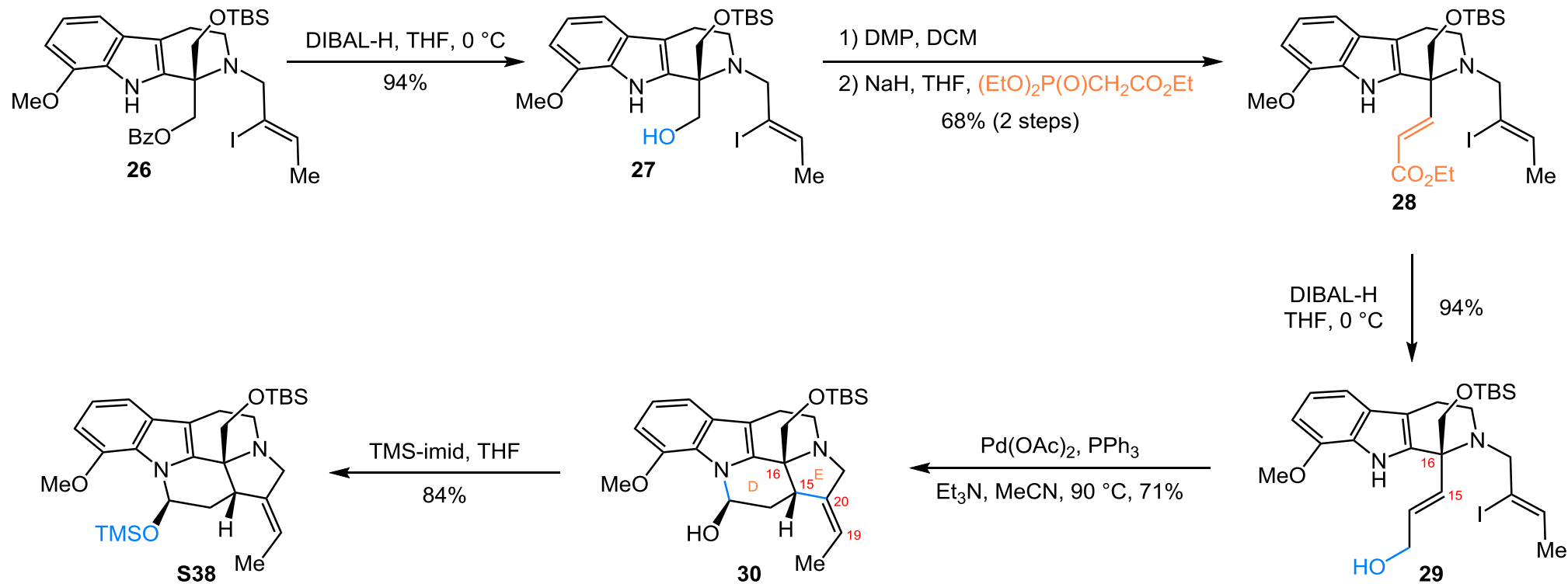
# Total Synthesis of (+)-Alstroline G

## Synthesis of 26



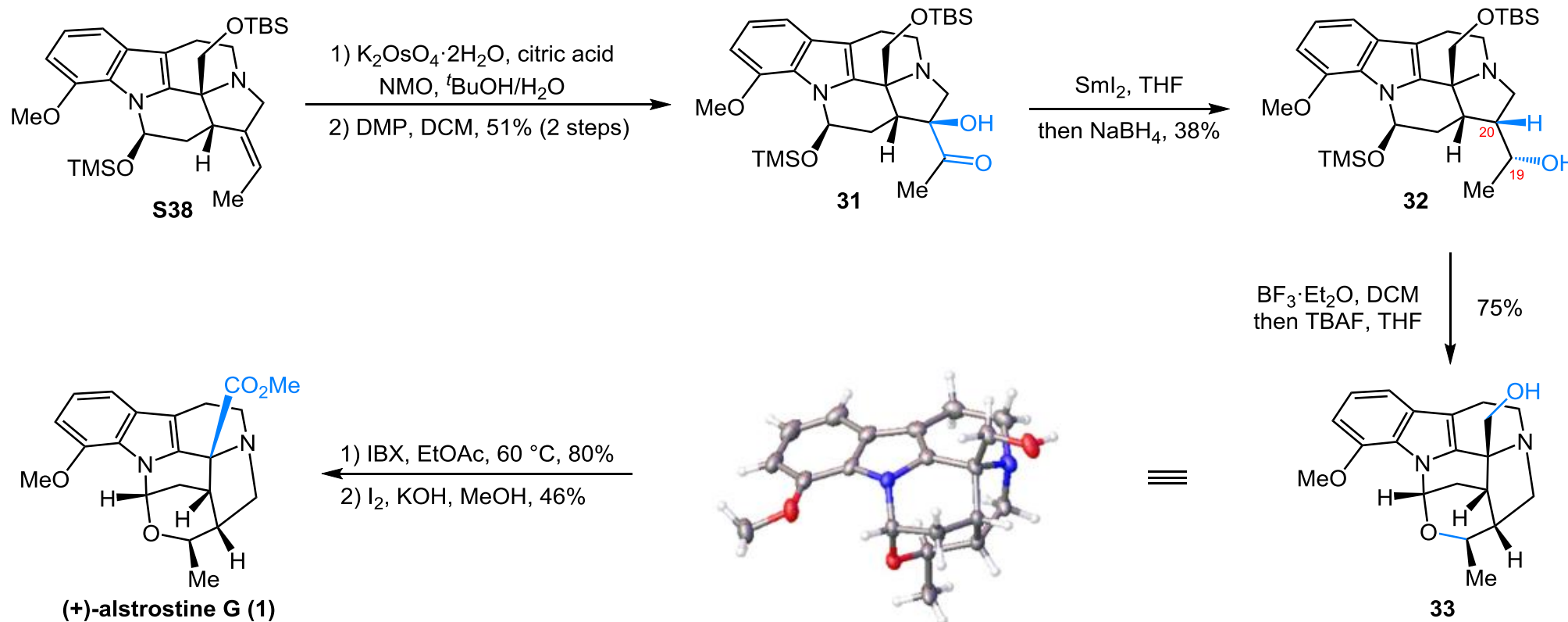
# Total Synthesis of (+)-Alstroline G

## Synthesis of S38

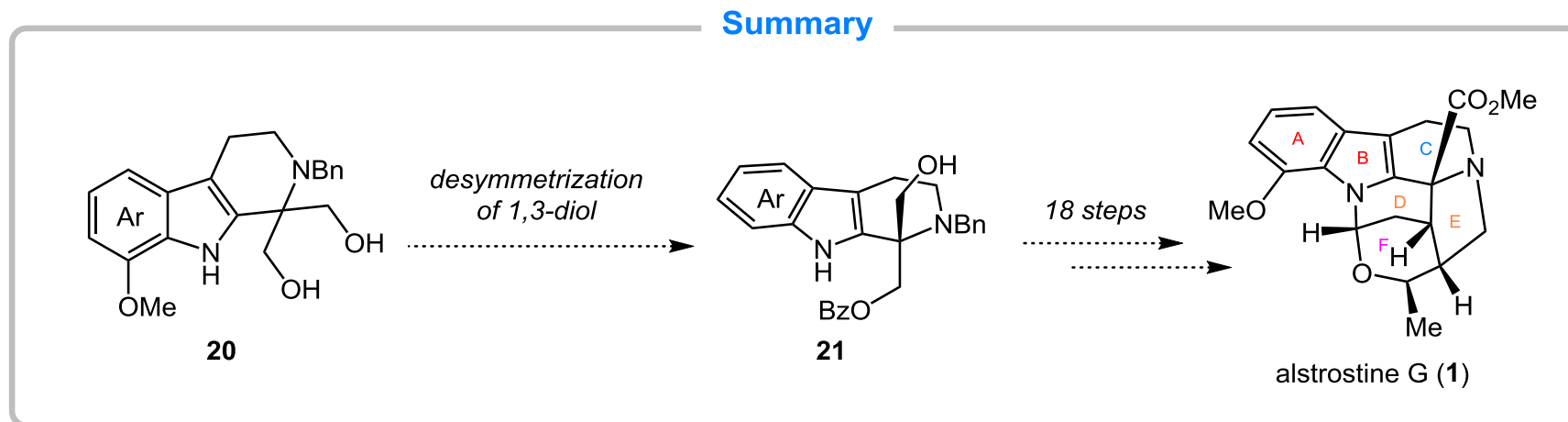


# Total Synthesis of (+)-Alstroline G

## Synthesis of (+)-alstroline G



# Summary



- Enantioselective monobenzoylation of the polycyclic 1,3-diol
- Cascade intramolecular Heck-hemiamination reaction
- The first asymmetric total synthesis of (+)-alstrofine G (1) in 18 steps.



# Writing Strategies

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## □ The First Paragraph

Natural products  
containing **THBC core**



Methods toward  
**THBC core were limited**



Main Content  
of **This Work**

- ✓ Indole alkaloids with a characteristic 1,1-disubstituted tetrahydro- $\beta$ -carboline (THBC) core, such as alstrostine G (1), alstratine A (2), arbornamine (3), peganumine A (4), and voacafricine A are an important group of compounds exhibiting interesting bioactivity.
- ✓ Although many effective synthetic strategies have been developed for the asymmetric synthesis of C1 monosubstituted THBC, the enantioselective synthesis of 1,1-disubstituted THBC has proven to be far more challenging.
- ✓ Herein, we report the development of an efficient asymmetric synthesis of 1,1-disubstituted THBC by Cu-catalyzed enantioselective desymmetrization. We also describe the details of our use of such a strategy to complete the first asymmetric total synthesis of alstrostine G (1).

## □ The Last Paragraph

**Summary**  
of this work



**Highlights** of  
the current method



**Outlook**  
of this work

- ✓ In conclusion, we have accomplished **the first asymmetric total synthesis** of monoterpene indole alkaloid (+)-alstroline G (**1**) from tryptamine **22** in 18 steps.
- ✓ An efficient **enantioselective monobenzylation** of the characteristic polycyclic 1,3-diols has been developed, which offers a general method for the assembly of the enantioenriched THBC scaffold. A double cyclization through cascade **intramolecular Heck-hemiamination reaction** was further used to rapidly establish the pentacyclic core of **1**.
- ✓ We envision that the developed strategy could be **extended to the construction of the core structures of other related alkaloids**, such as those listed in Figure 1, thus providing more facile access to those natural products.

# Representative Examples

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- ✓ **In stark contrast** (形成鲜明对比的是), basic conditions  $K_2CO_3/MeOH$  resulted in significant erosion of the ee, the observed racemization could be presumably attributed to the facile silyl-transferring reaction.
- ✓ We **postulated** (v. 假设, 假定) that such an adjustment would not only enhance the activity of C15 carbonyl group but also improve the structural flexibility of the precursor compared to **19a**.
- ✓ Trials with quinine-derived catalyst **L1** furnished an inseparable mixture of the desired **11a** and its epimer **11b** in favor of **11a**, **albeit** (然而, 但是, 尽管, 表转折) with poor diastereo- and enantioselectivity.

# Acknowledgment

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***Thanks for your attention !***