Literature Report 3

Total Synthesis of (+)-Arboridinine

Reporter: Han Wang
Checker: Bo Wu
Date: 2019.7.22

Gan, P.; Pitzen, J.; Qu, P.; Snyder, S. A.* *J. Am. Chem. Soc*. **2018**, *140*, 919.
Zhang, Z.; Xie, S.-J.; Cheng, B.; Zhai, H.-B.* *J. Am. Chem. Soc.* **2019**, *141*, 7147.

CV of Hongbin Zhai

Background:

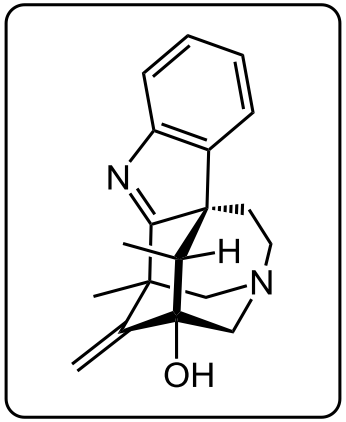
- **1981-1985** B. S., Peking University
- **1985-1988** M. S., Peking Union Medical College
- **1989-1995** Ph. D., The Ohio State University
- **1996-1997** Postdoc., The Ohio State University (Albert Soloway)
- **1998-2000** Postdoc., UC, Berkeley (Henry Rapoport)
- **2000-2010** Prof., Shanghai Institute of Organic Chemistry
- **2010-2015** Prof., Lanzhou University
- **2015-now** Prof., Peking University Shenzhen Graduate School

Research:

- Total synthesis of natural products
- Heterocyclic chemistry/medicinal chemistry
- Synthetic methodology development

Contents

Introduction



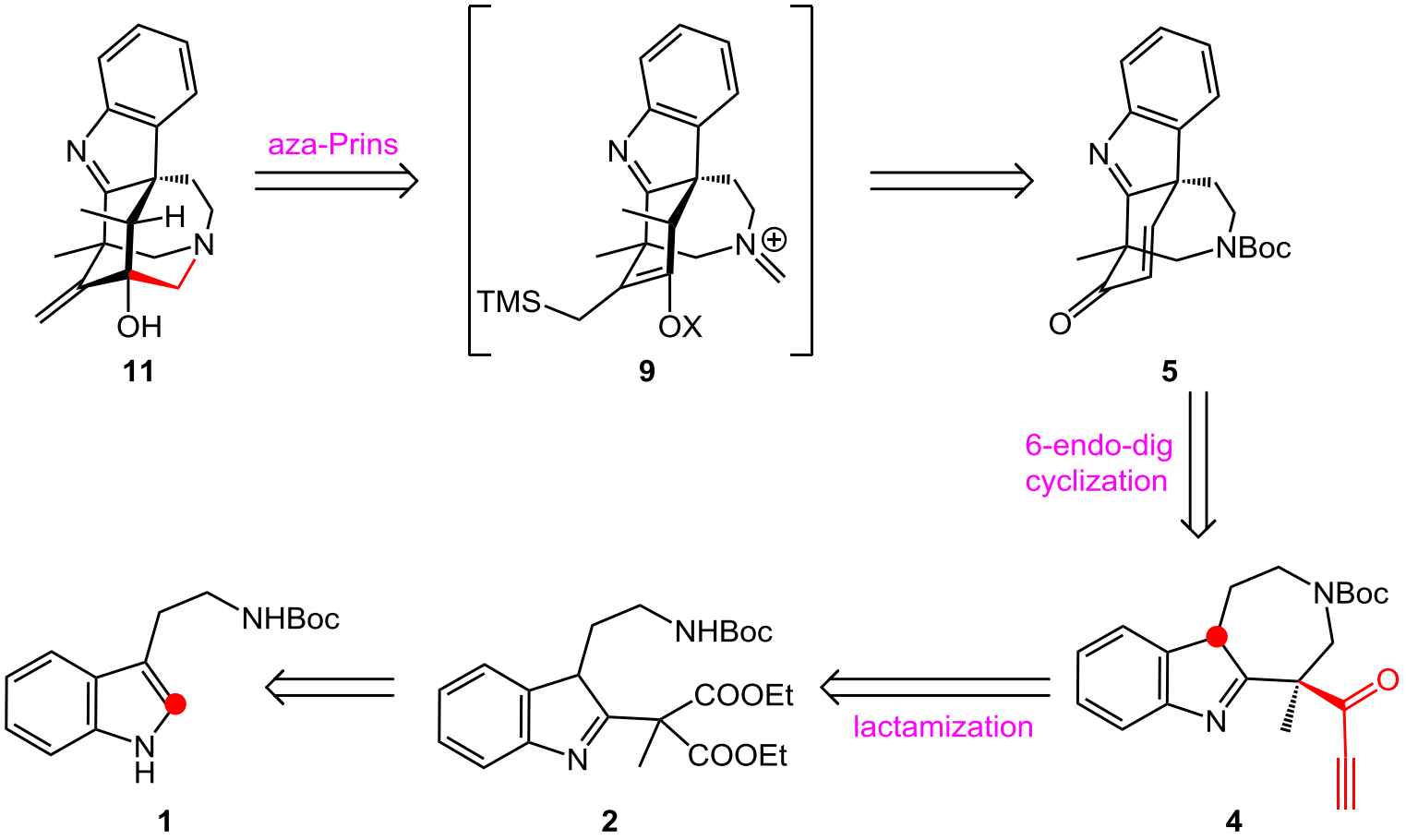
(+)-Arboridinine

Kopsia

- Isolated from the *Kopsia*, belonging to the family of Apocynaceae
- A cage-like indolenine skeleton which contains four stereocenters
- Two quaternary carbons along with one bridgehead tertiary alcohol

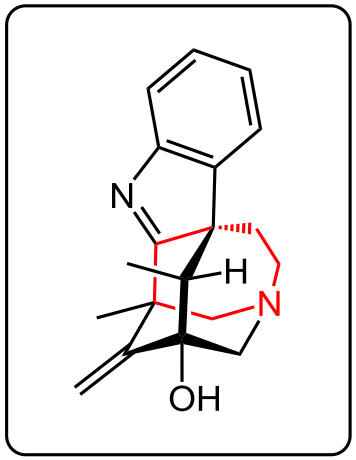
Kam, T.-S. *et al. Org. Lett.* **2015,** *17*, 3628.

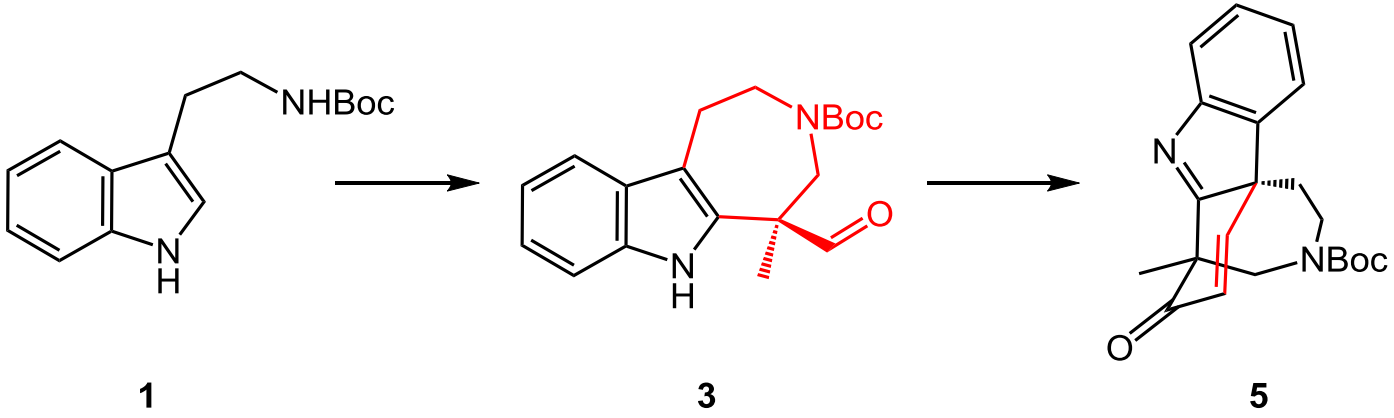
Retrosynthetic Analysis of Arboridinine



Snyder, S. A. *et al. J. Am. Chem. Soc.* **2018,** *140*, 919.

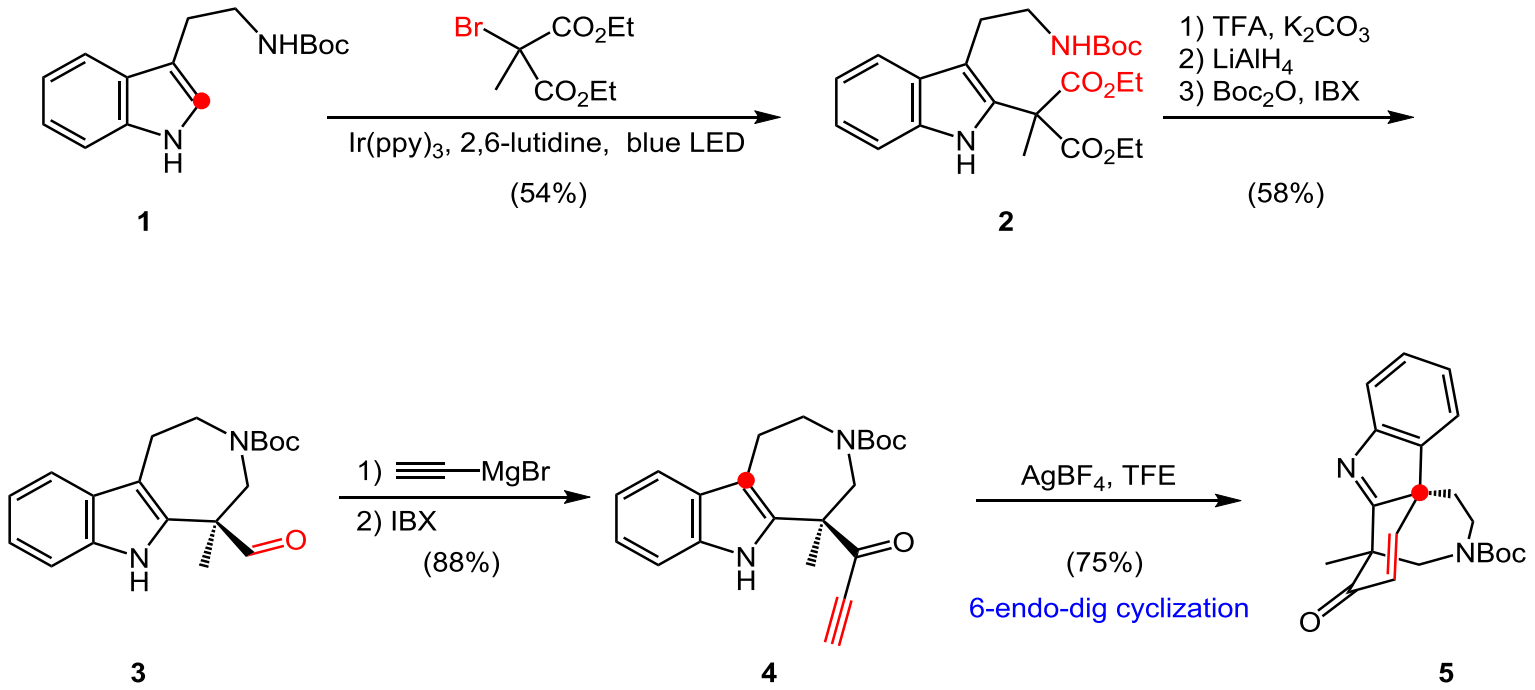
Stage 1



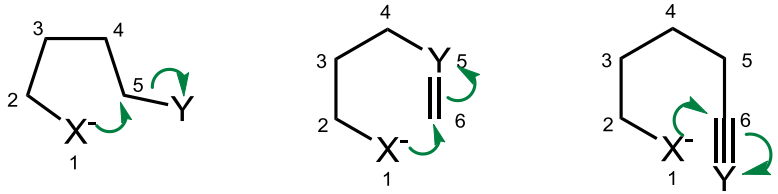


1 **3** **5**

Total Synthesis of Arboridinine



Baldwin's Rules

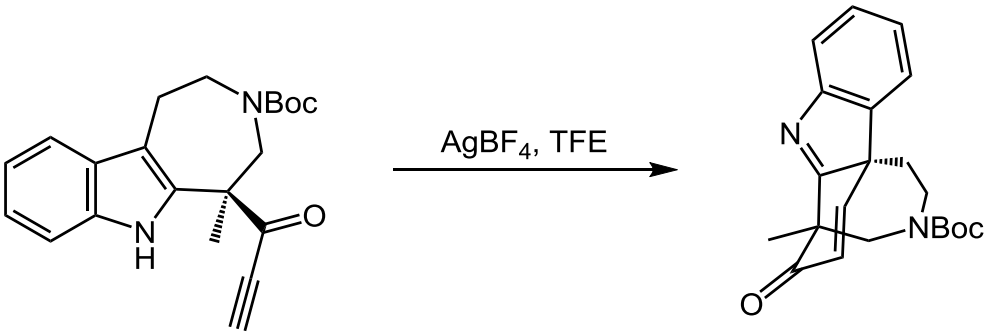


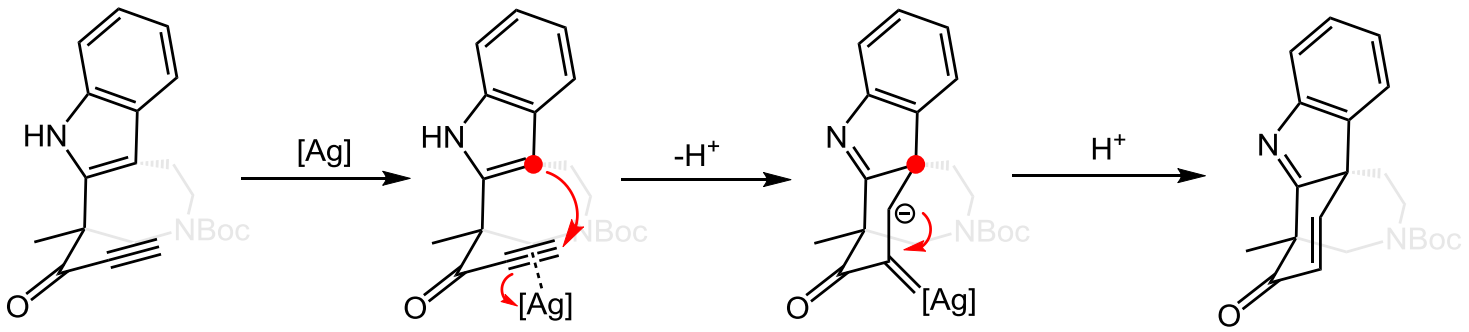
5-exo-tet　　6-endo-trig　　6-exo-dig

- 环中原子个数一般为**3-8**
- 以**exo**和**endo**表示闭环时断键位置，**exo-环外**，**endo-环内**
- 以**tet**、**trig**和**dig**表示亲电碳的杂化方式，**tet-sp^3**，**trig-sp^2**，**dig-sp**。

	3		4		5		6		7	
	exo	endo	exo	endo	exo	endo	exo	endo	exo	endo
Tet										
Trig										
dig										

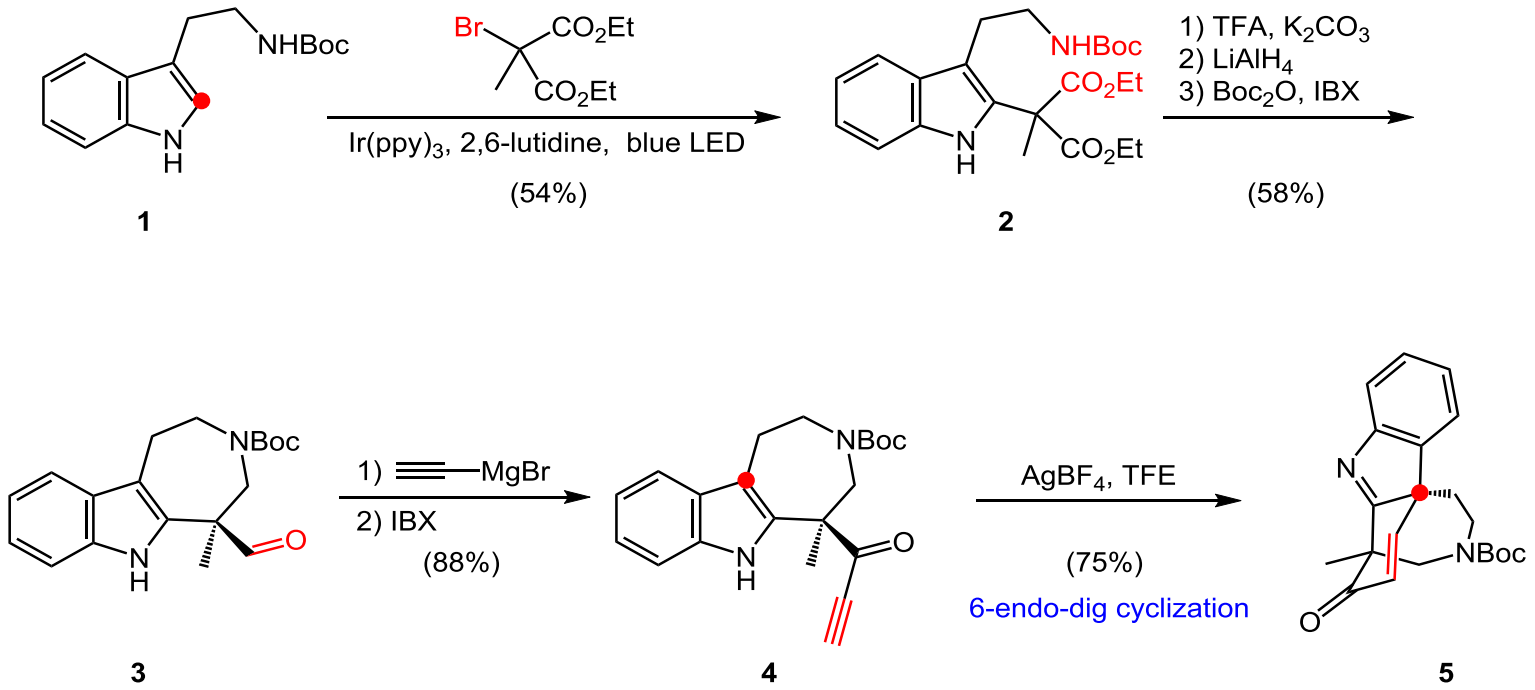
6-endo-dig Cyclization



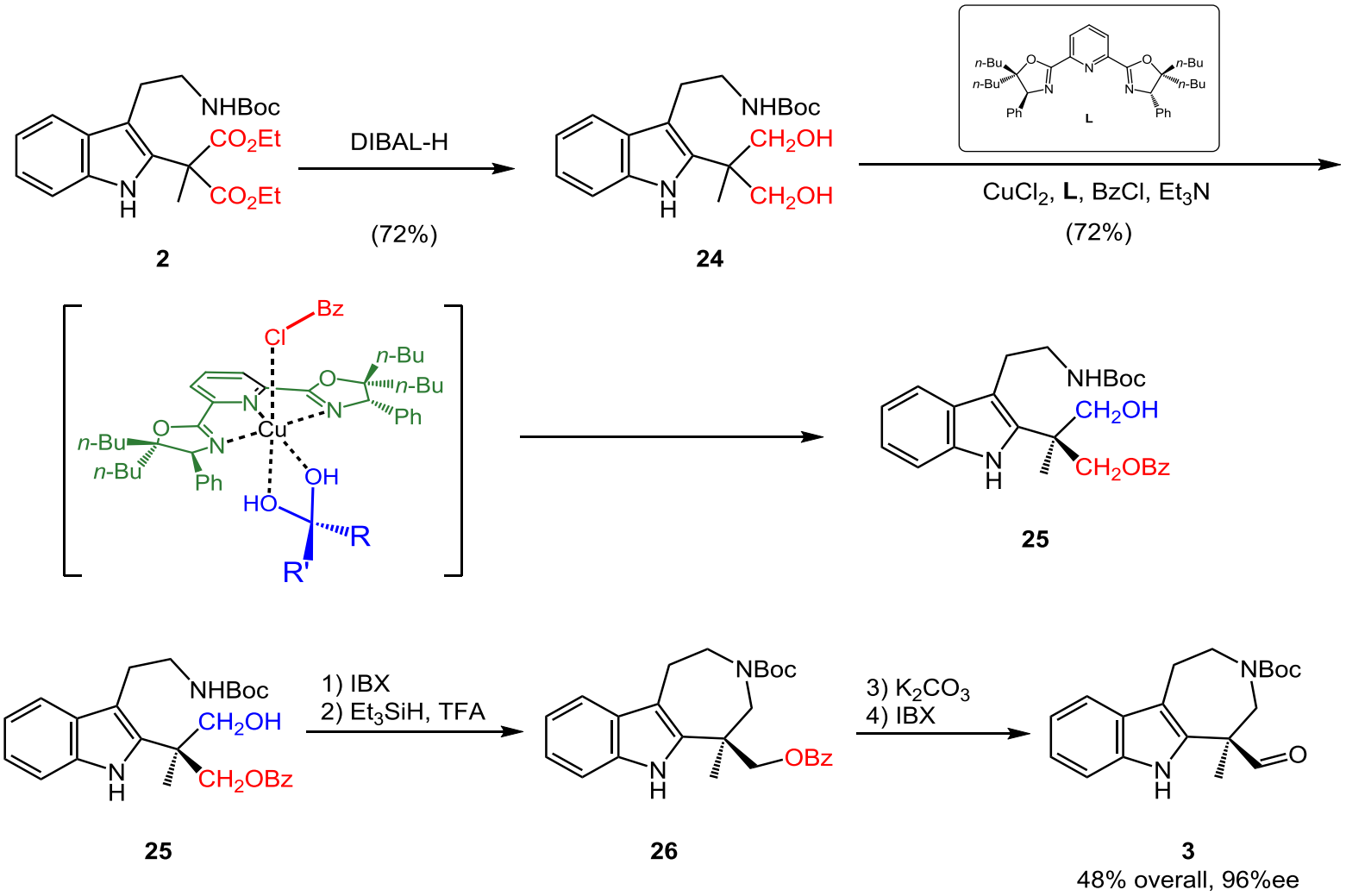


Xu, X.-F. *et al. Adv. Synth. Catal.* **2019,** *361*, 826.

Total Synthesis of Arboridinine

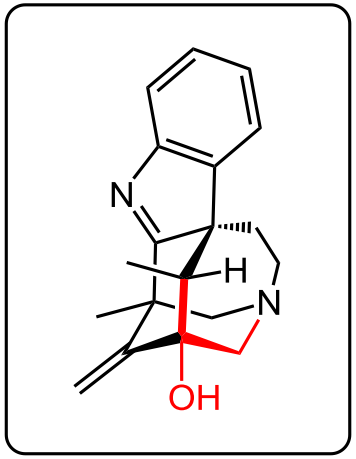


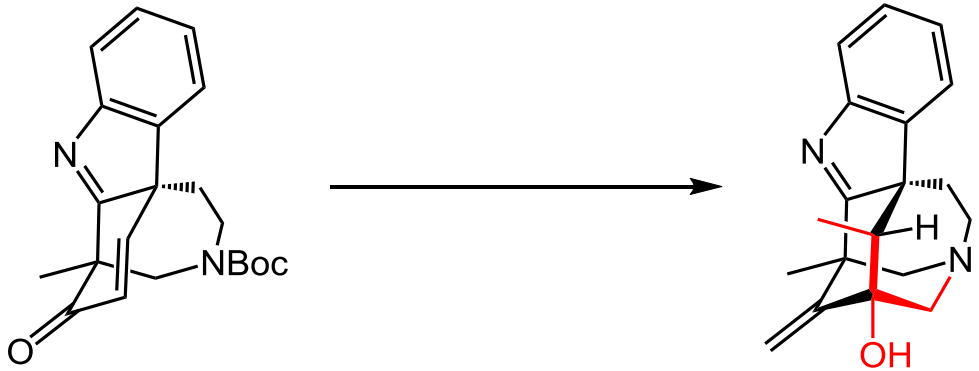
Asymmetric Sythesis of Compound 3



Kang, S. H. *et al. J. Am. Chem. Soc.* **2011,** *133,* 1772.

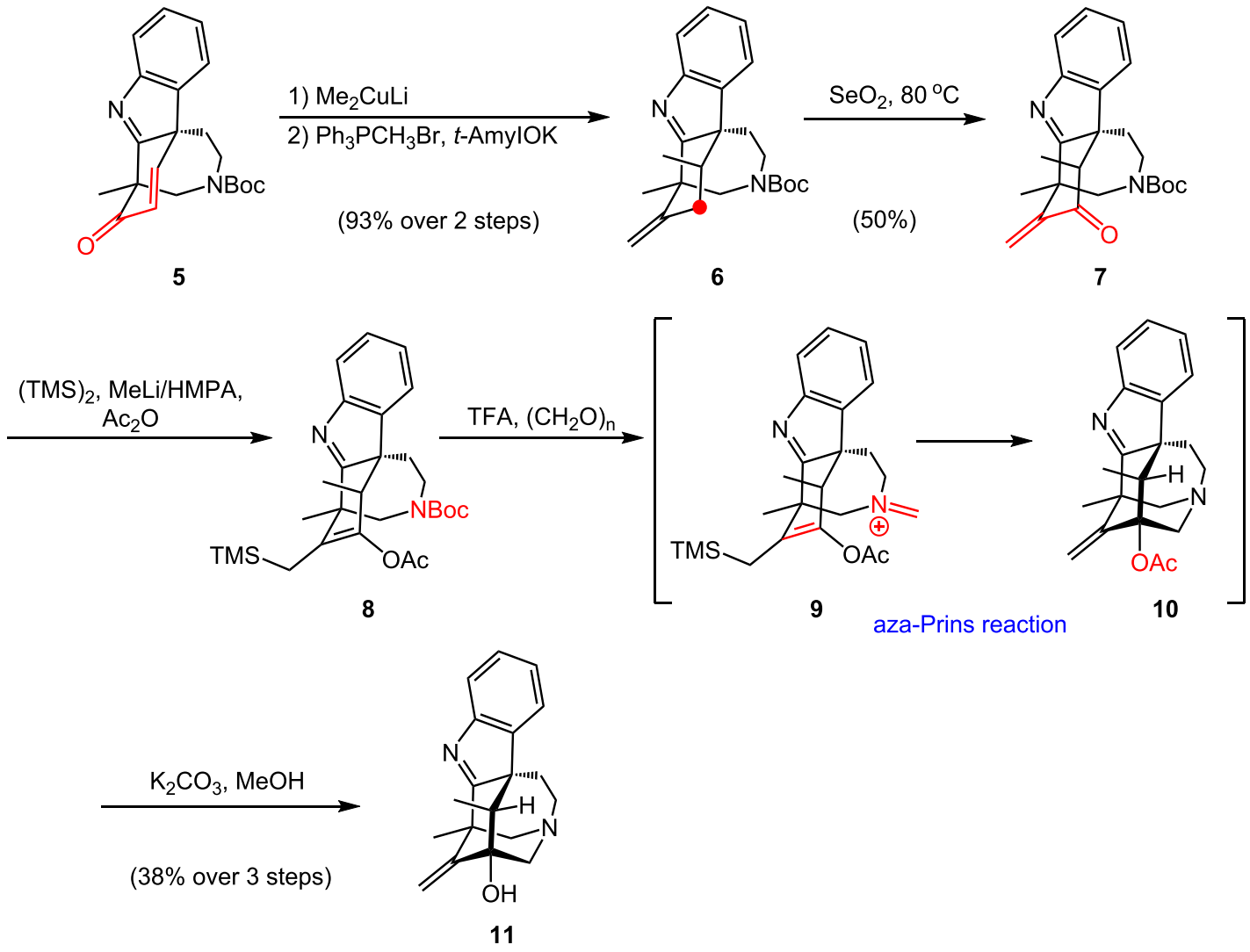
Stage 2



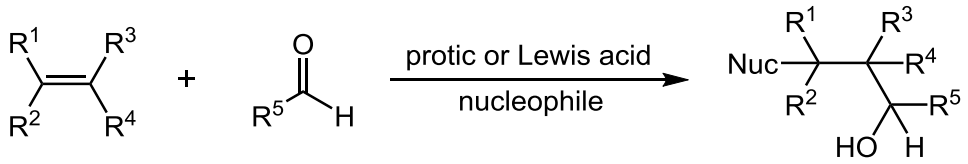


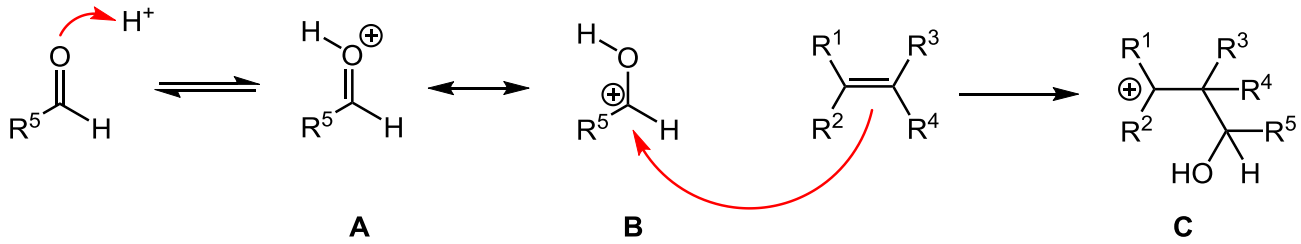
5 **11**

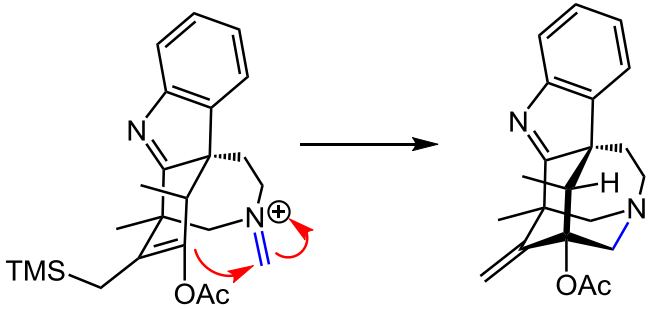
Total Synthesis of Arboridinine



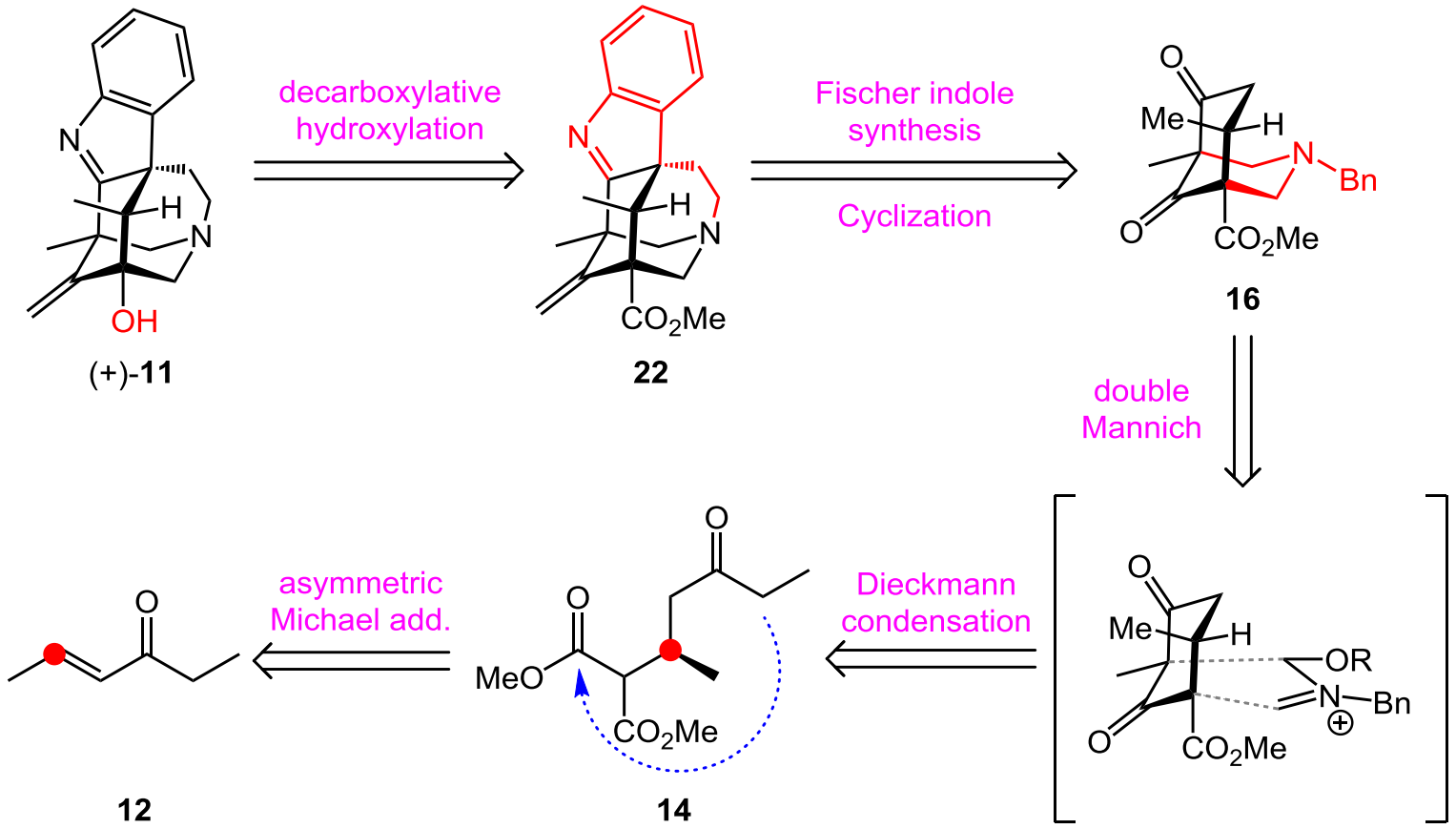
aza-Prins Reaction





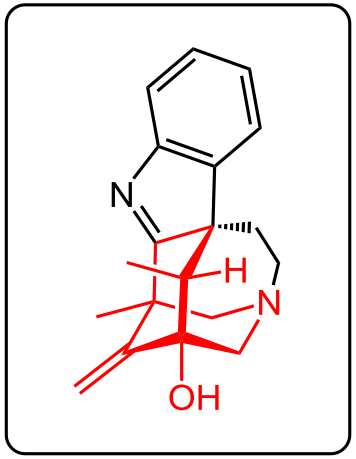


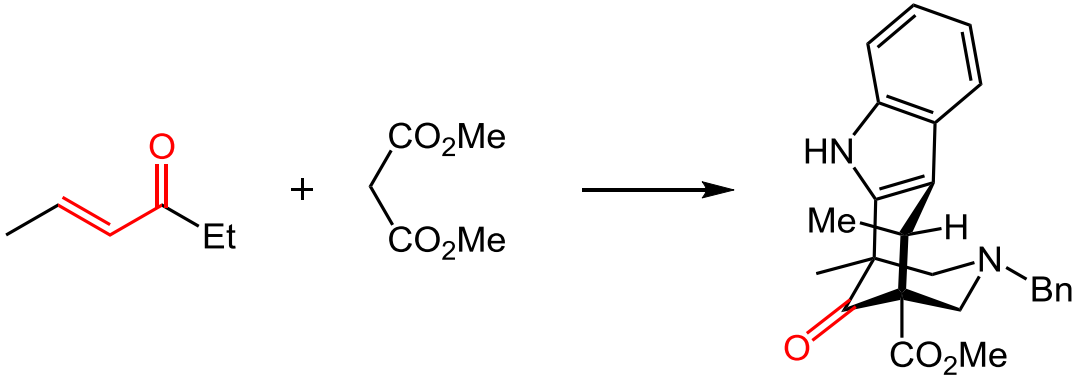
Retrosynthetic Analysis of (+)-Arboridinine



Zhai, H.-B. *et al. J. Am. Chem. Soc.* **2019,** *141*, 7147.

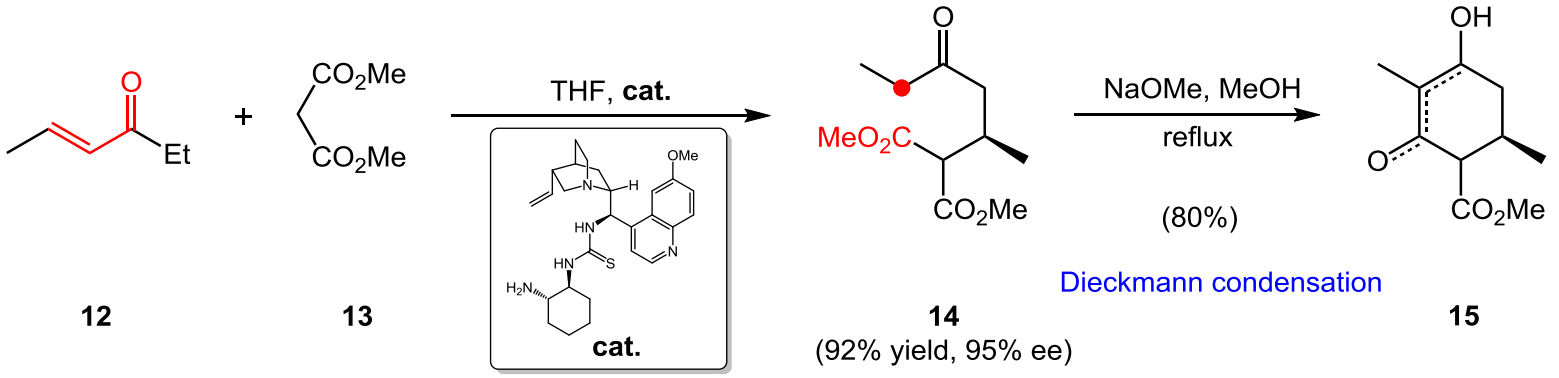
Stage 1





12 **13** **18**

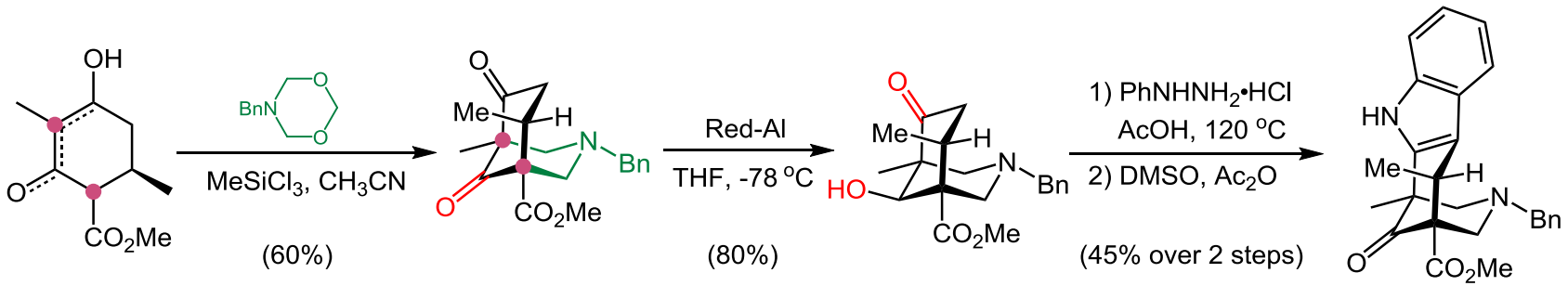
Total synthesis of (+)-Arboridinine



12 13 14 15

(92% yield, 95% ee)

Dieckmann condensation



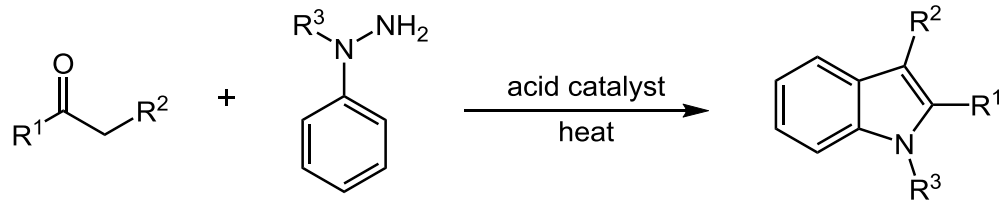
15 16 17 18

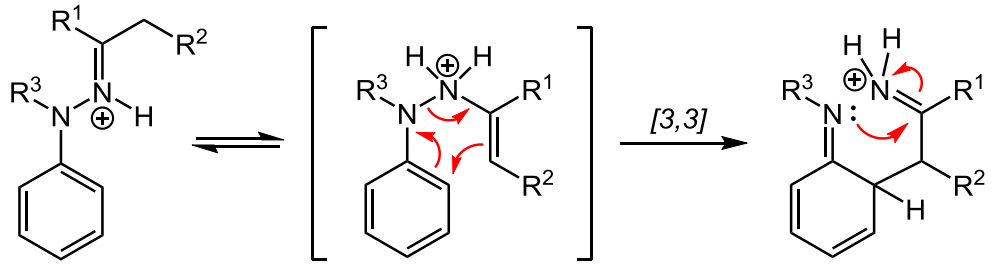
double Mannich reaction

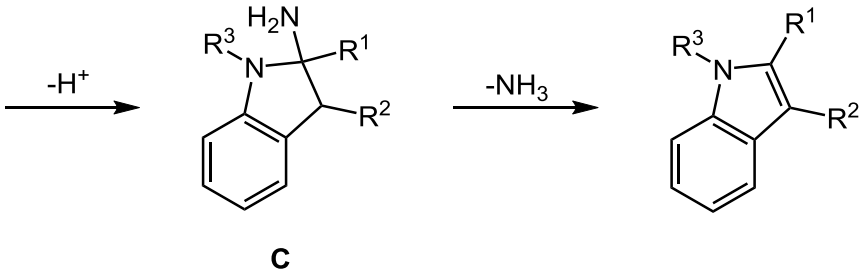
Fischer indole synthesis

recrystallize to 98% ee

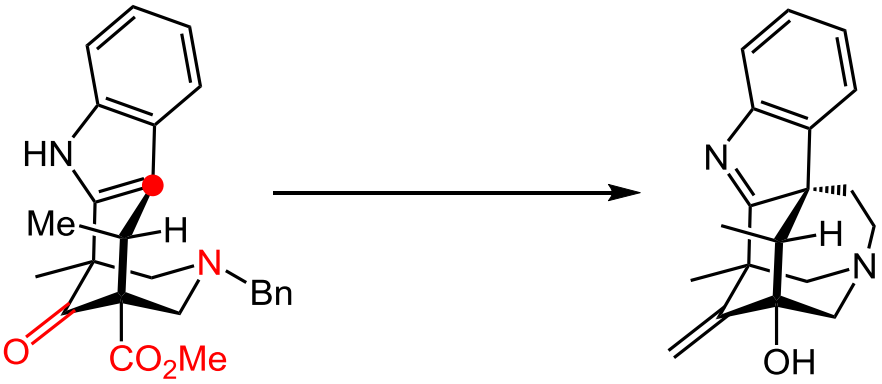
Fischer Indole Synthesis





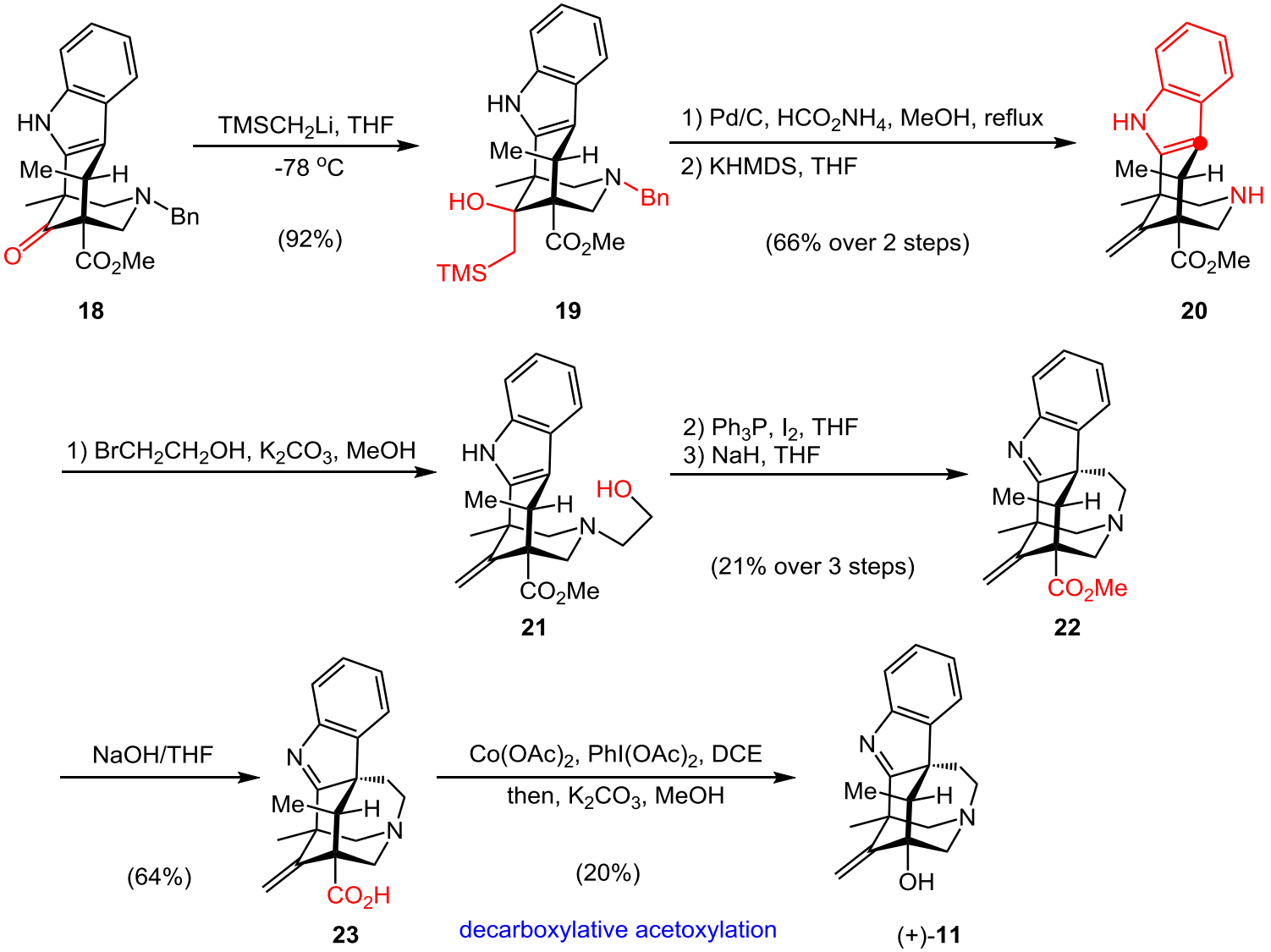


Stage 2

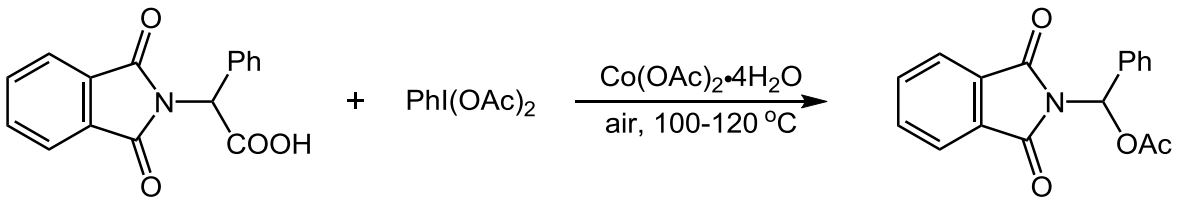


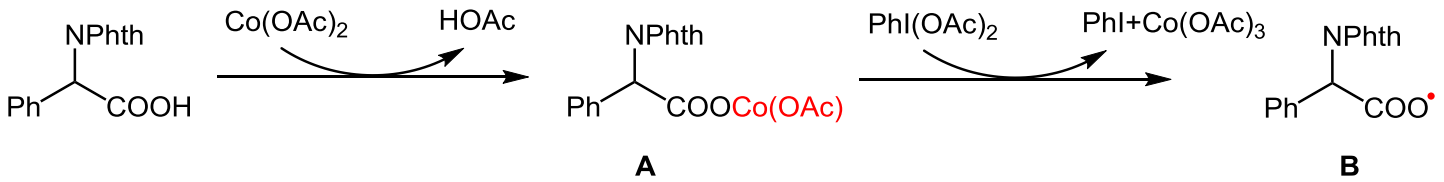
18 (+)-**11**

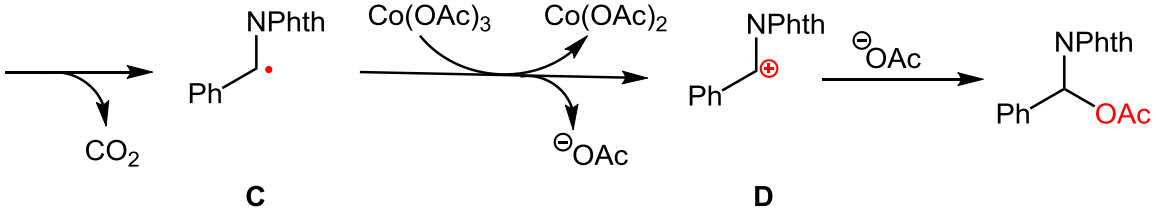
Total synthesis of (+)-Arboridinine



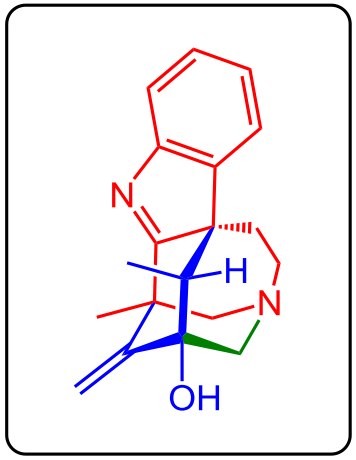
Decarboxylative Acetoxylation Reaction





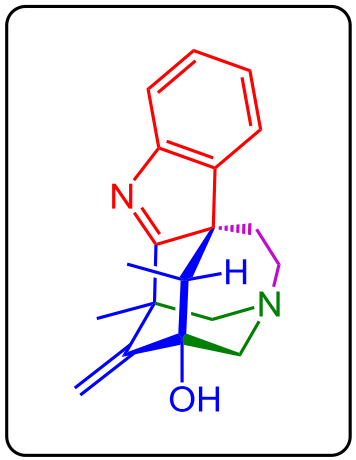


Summary



- 5.8% Overall yield, 13 steps
- *6-endo-dig* cyclization
- *aza*-Prins reaction

Snyder, S. A. *et al. J. Am. Chem. Soc.* **2018,** *140*, 919.



- 0.3% Overall yield, 17 steps, large scale
- Enantioselective Michael addition
- Double-Mannich reaction
- Cobalt-catalyzed decarboxylative acetoxylation

Zhai, H.-B. *et al. J. Am. Chem. Soc.* **2019,** *141*, 7147.

The First Paragraph

The genus *Kopsia*, belonging to the family of Apocynaceae, has proven to be an abundant source of monoterpenoid indole alkaloids which possess structural diversities and significant biological activities. As shown in Figure 1, arboridinine, which contains an unusual pentacyclic framework, was isolated from the *Kopsia* genus of Malaysia in 2015 by Kam and coworkers. The highly congested structure features a cage-like indolenine skeleton which contains four stereocenters and two quaternary carbons along with one bridgehead tertiary alcohol. The intriguing structure together with the densely substituted caged skeleton presents a veritable challenge for its synthesis.

The First Paragraph

Due to the paucity of material, the specific biological properties of arboridinine, however, remain unexplored. On the other hand, alkaloids possessing a cage-shaped framework while containing an indolenine motif constitute a large class of monoterpenoid indole alkaloids. As some representative examples shown in Figure 1, arborisidine, strictamine, scholarisine A, koumine, perakine, and alsmaphorazine B, display a great deal of complexity and structural diversity.

The Last Paragraph

In conclusion, the enantioselective total synthesis of (+)-arboridinine has been achieved in 14 steps from readily available starting materials. This efficient synthesis relies on an asymmetric Michael addition reaction to establish the first chiral center, the high stereoselective double-Mannich reaction to construct the tricyclic framework, and a cobalt-catalyzed decarboxylative acetoxylation reaction to incorporate the bridgehead hydroxyl group in (+)-arboridinine. The robustness of the developed synthesis was demonstrated by a series of practical transformations that are easily conducted on decagram scale.

Acknowledgement

Thanks
for your attention