

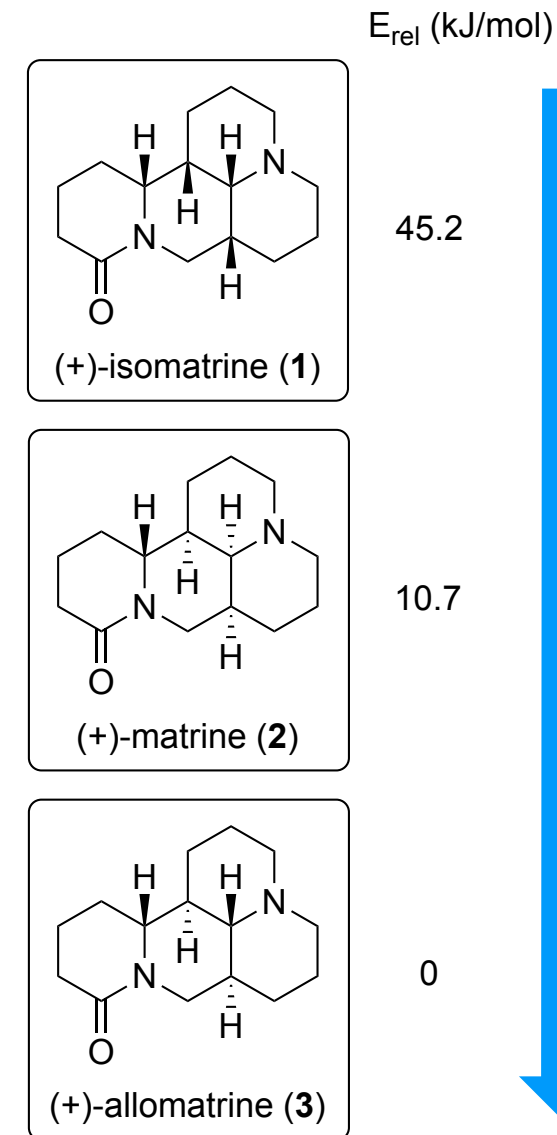
Total Synthesis of Matrine-Type Alkaloids

S. E. Reisman *et al.* *JACS*, **2022**, *144*, 15938. M. S. Sherburn, *JACS*, **2022**, *144*, 19695.

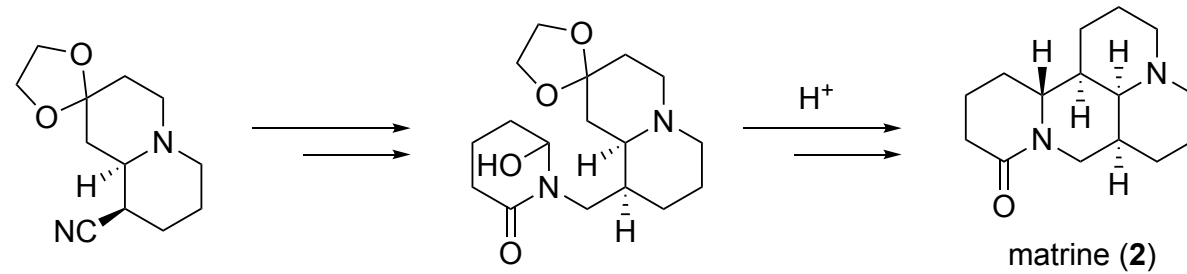
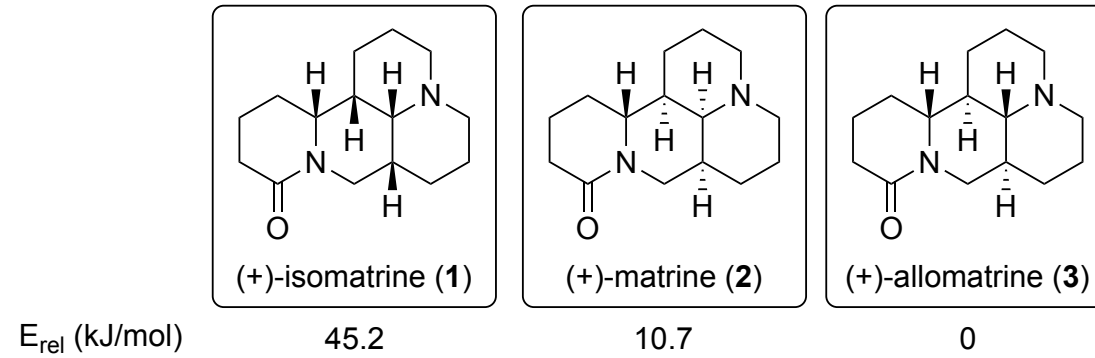
Reisman's work: *ChemRxiv* May 27, 2022, *JACS* August 25, 2022

Sherburn's work: *ChemRxiv* June 7, 22, *JACS* October 19, 2022

- (+)-isomatrine and (+)-matrine are tetracyclic lupin alkaloids isolated from the plant *Sophora flavescens*. While little is known about the pharmacological properties of (+)-isomatrine, (+)-matrine has shown anticancer activity and have also been used for the clinical treatment of hepatitis B.
- Most of the total synthesis had focused on matrine to date. 4 reports for matrine (**2**), 2 reports for allomatrine (**3**), and no report for isomatrine (**1**)
Isomatrine (**1**) is the least thermodynamically stable isomer and its isomerization to matrine (**2**) and (**3**) has been previously reported.
- In 2022, both Reisman group and Sherburn group reported the total synthesis of these diastereomers simultaneously. Both synthetic routes take advantage of the thermodynamic stability trends of these three molecules.

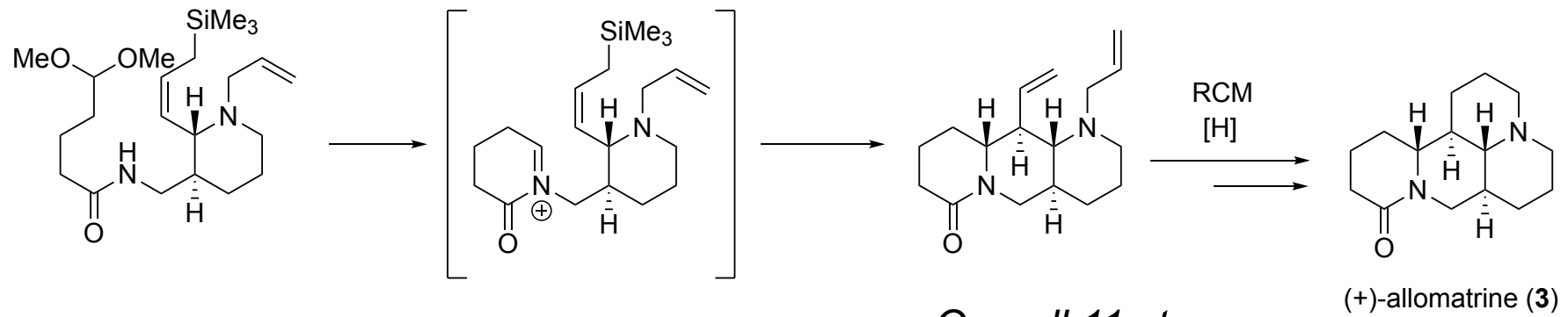


Previous Synthesis



J. Chen *et al.*, *J. Chem. Soc., Chem. Commun.* **1986**, 905.

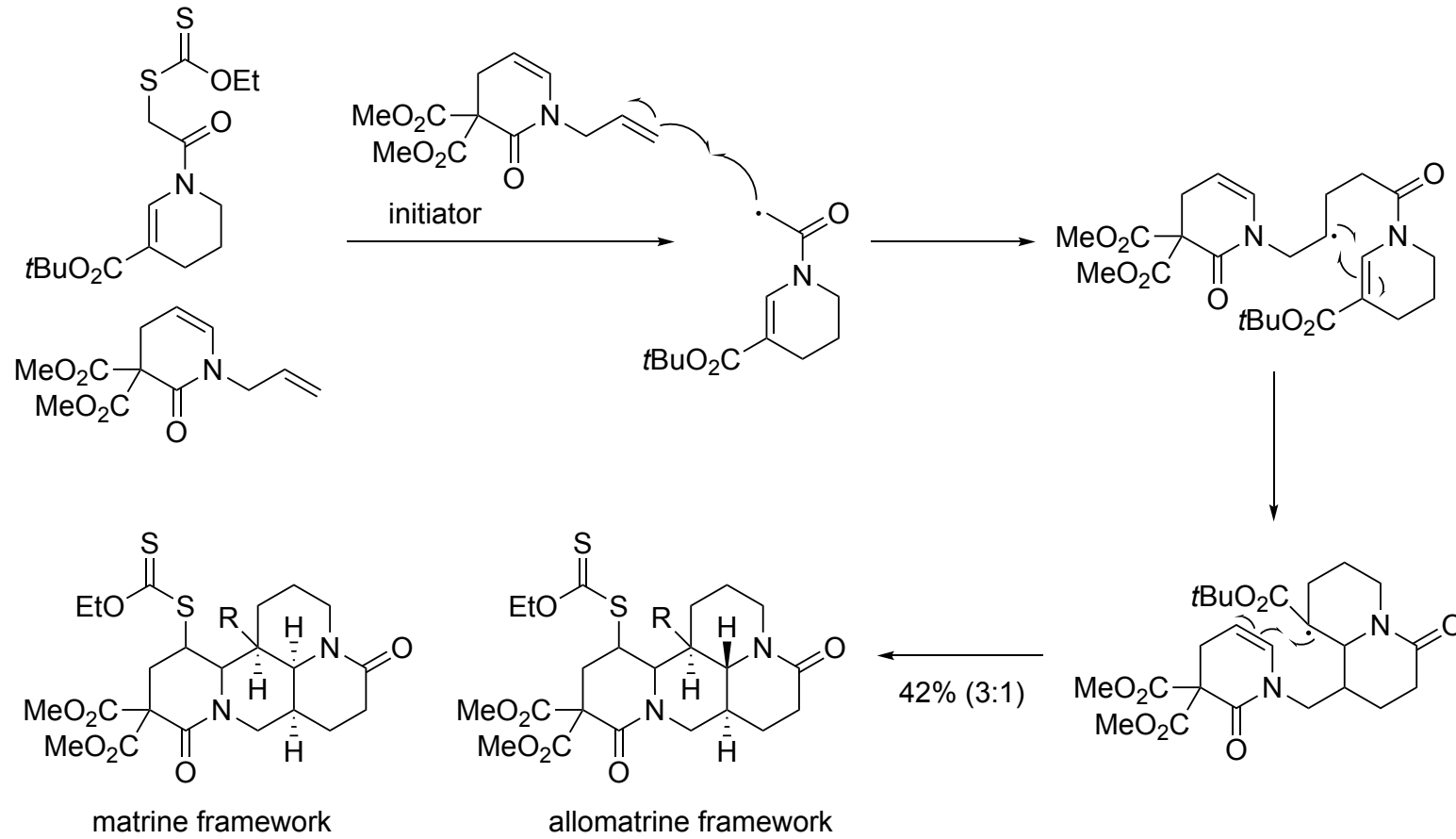
6 steps from relatively complex molecule



R. C. D. Brown, *Org. Lett.*, **2013**, 15, 4596.

Overall 11 steps

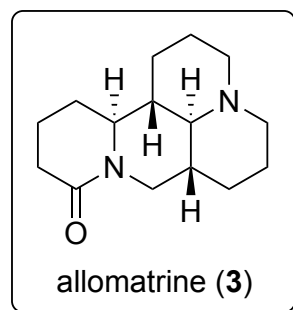
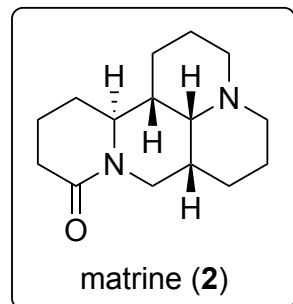
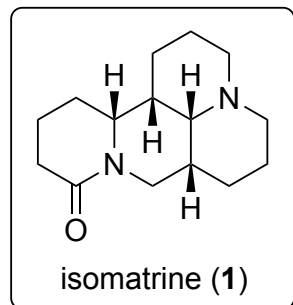
Previous Synthesis



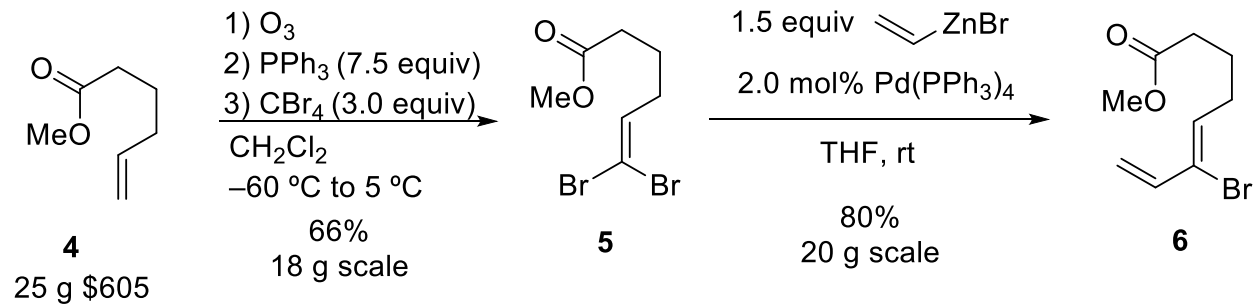
S. Z. Zard et al., *ACIE*. 1998, 37. 1128.

Overall 10 steps

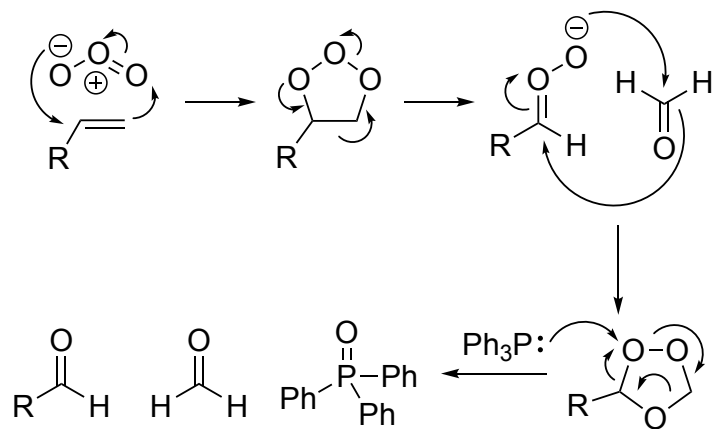
Retrosynthetic Analysis (Sherburn's work)



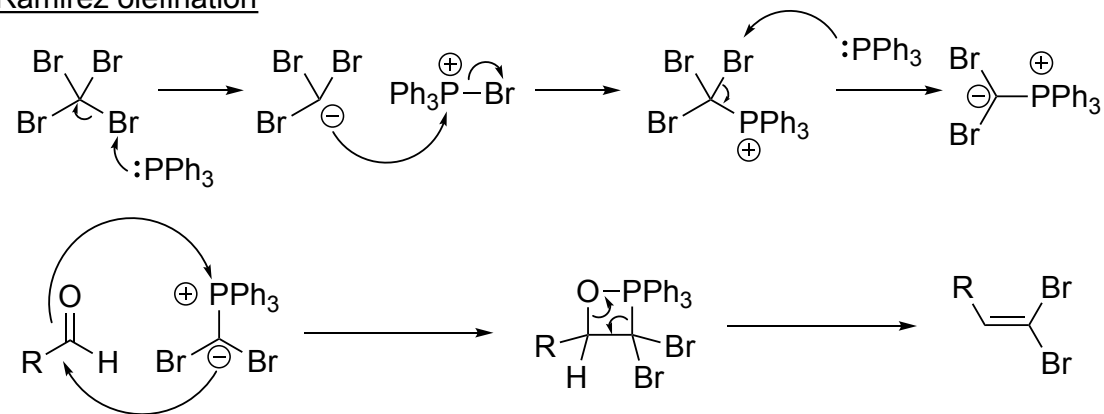
10 steps (Overall)
8 steps (LLS)



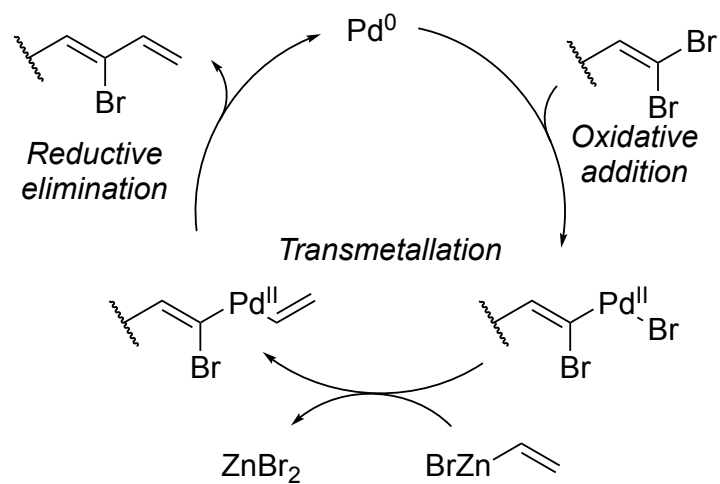
Ozonolysis

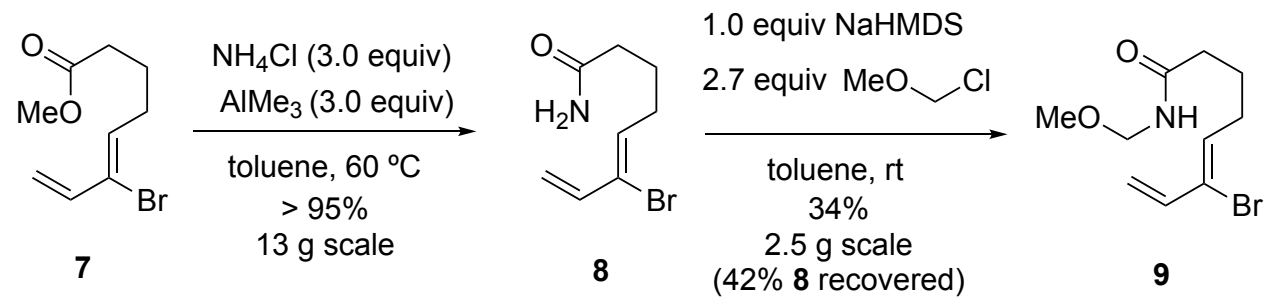


Ramirez olefination

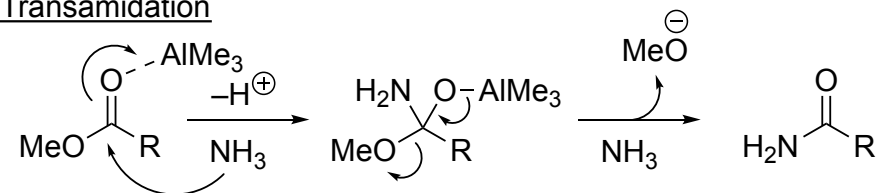


Negishi Coupling

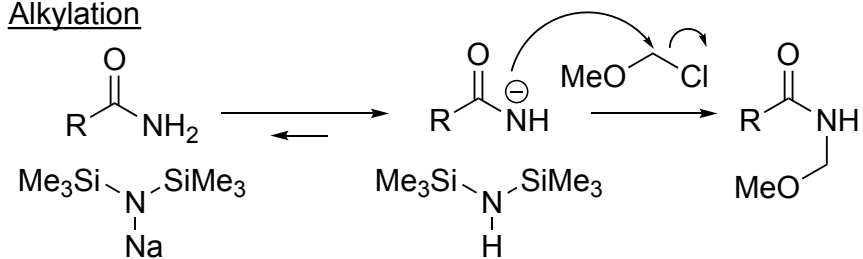


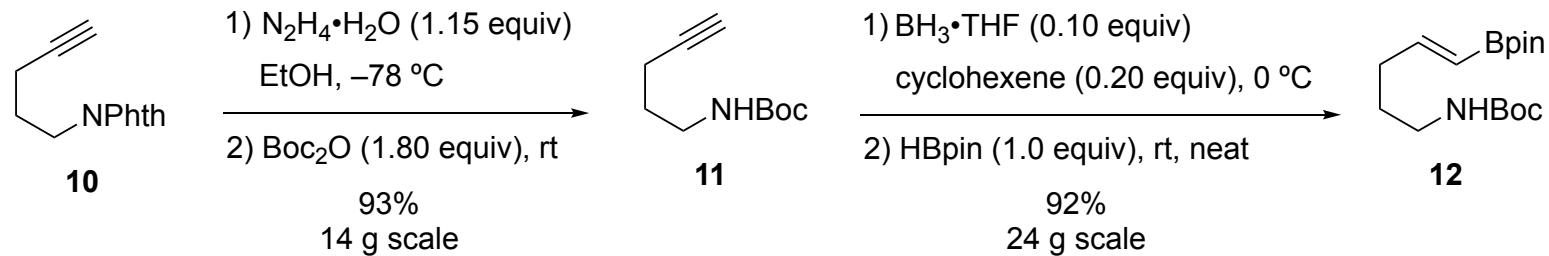


Transamidation

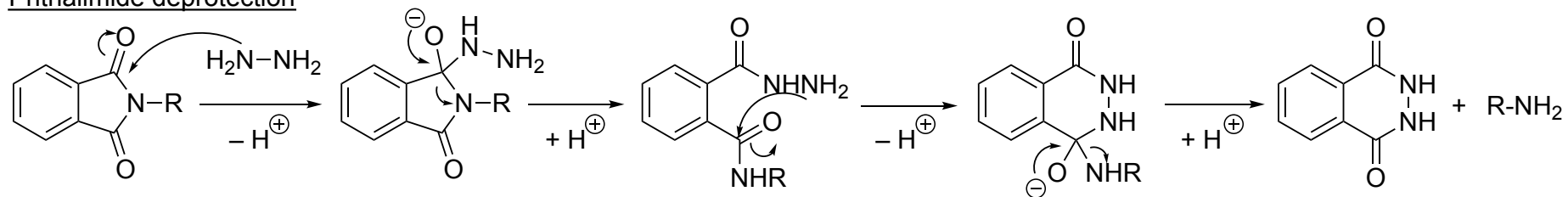


Alkylation

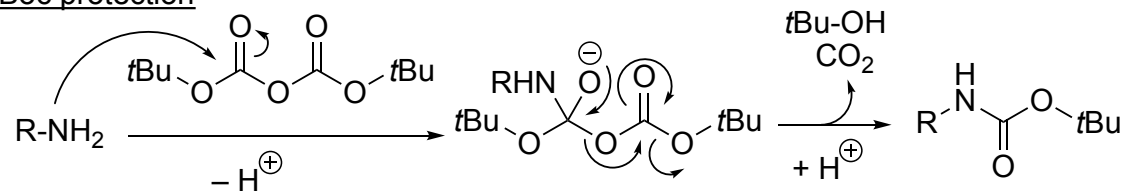




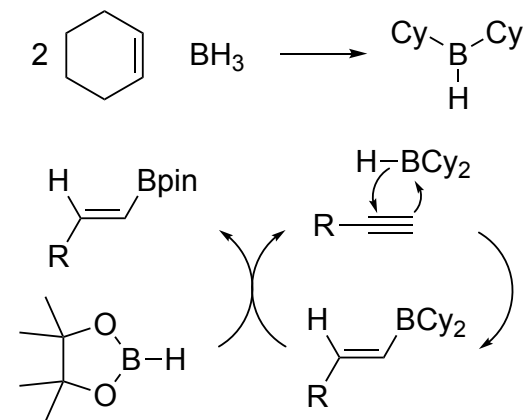
Phthalimide deprotection



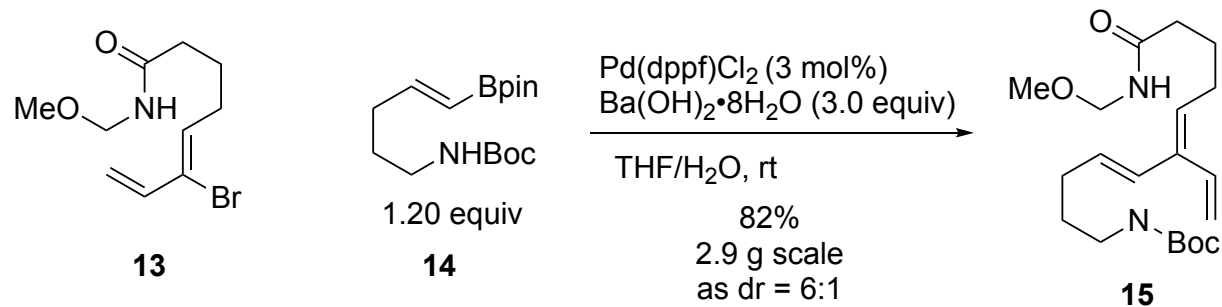
Boc protection



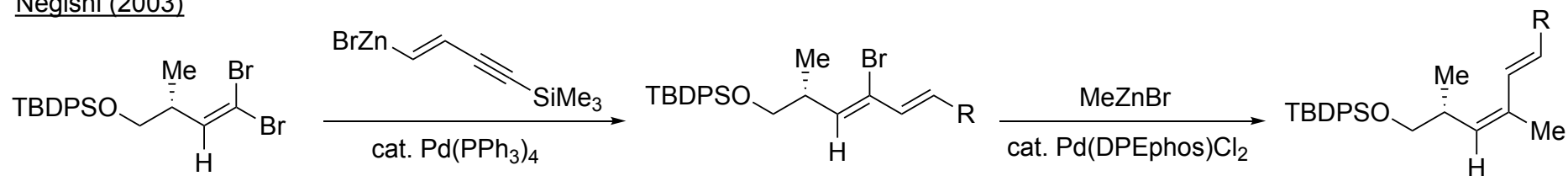
Hydroboration of Alkyne



M. Hoshi *et al.*, *Synthesis*, **2004**, *11*, 1814.



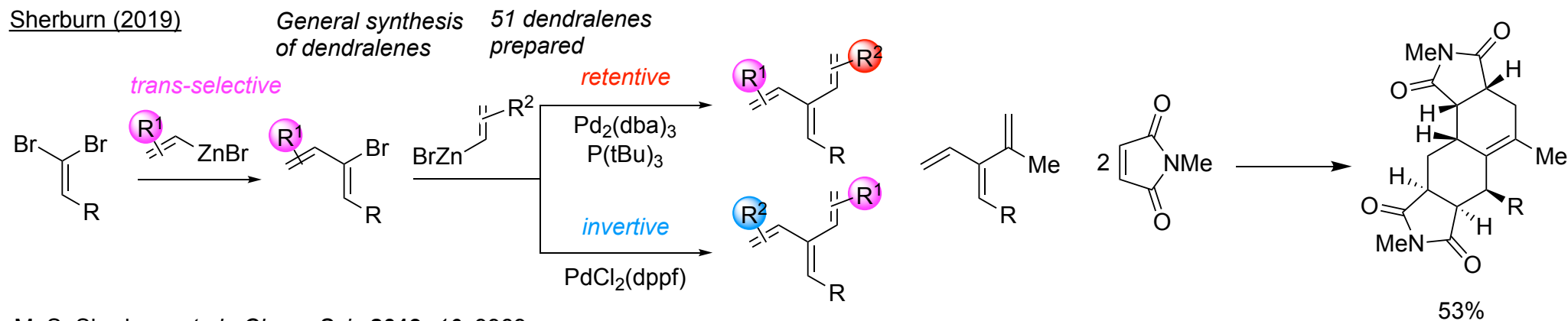
Negishi (2003)



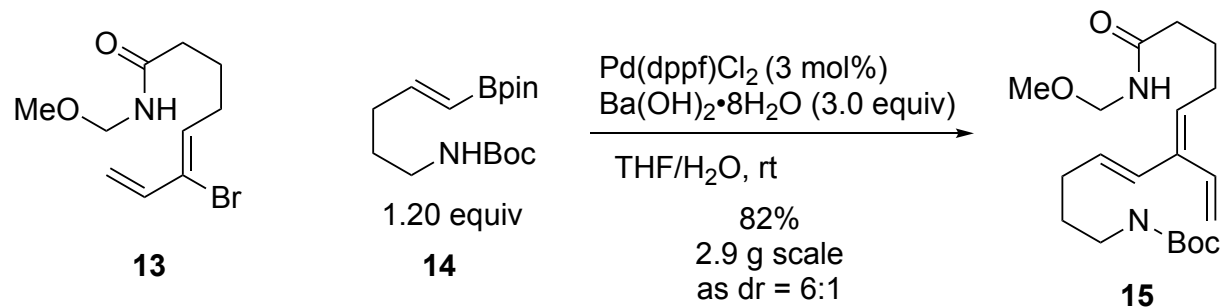
- 1) First cross-coupling partner has to be (E)-alkenylzinc derivatives
- 2) Geometries of (E)-alkenylzinc derivatives remains intact.

E. Negishi *et al.*, *JACS*, **2003**, 125, 13636.

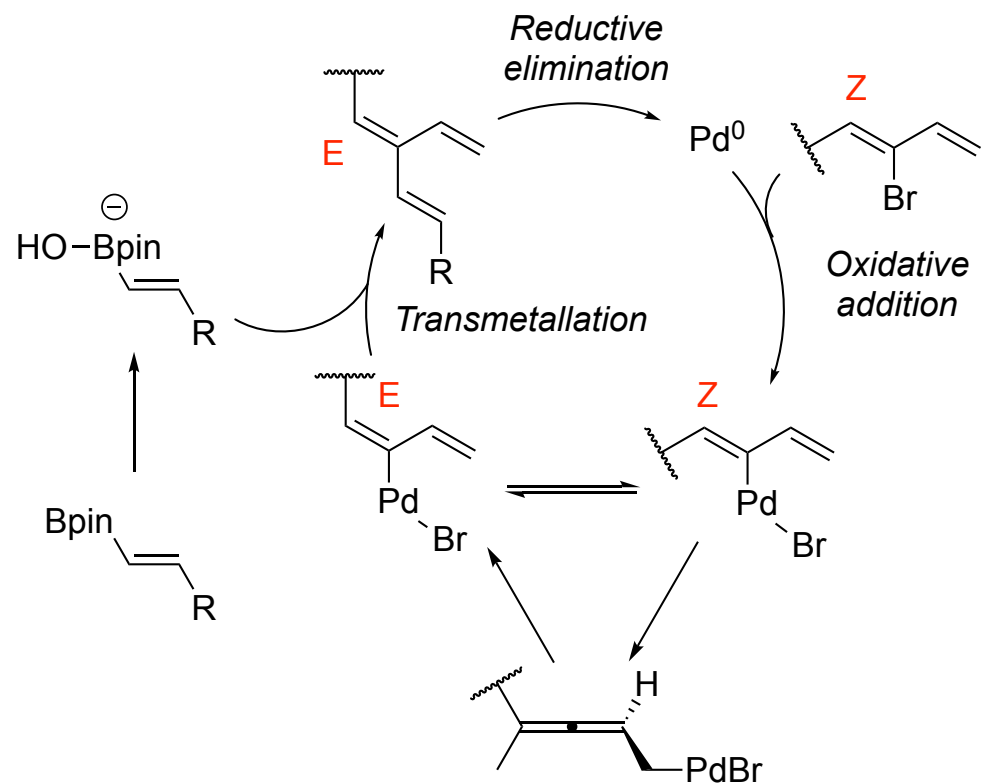
Sherburn (2019)



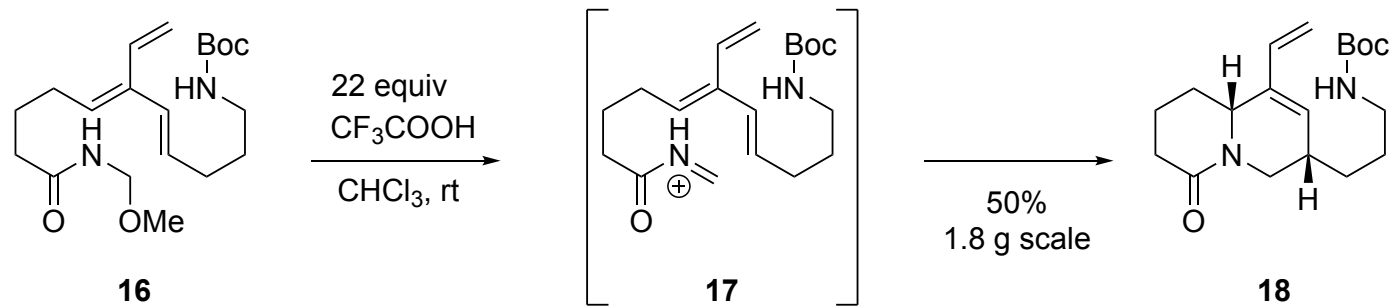
M. S. Sherburn *et al.*, *Chem. Sci.*, **2019**, 10, 9969.



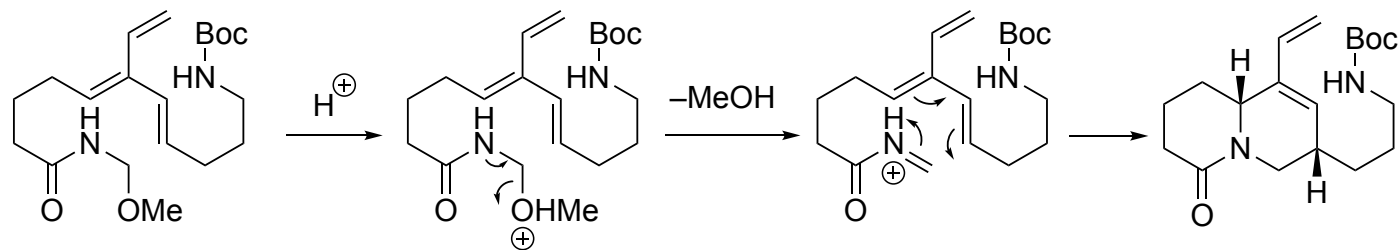
Stereoinvertive Suzuki coupling

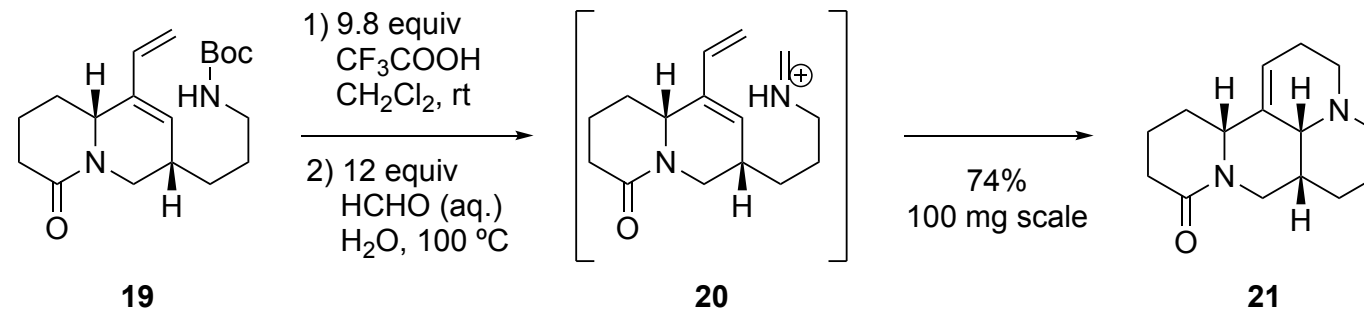


“This process, which was guided by our experience with related Negishi methodology, is to our knowledge the **first example** of a stereoinvertive Suzuki–Miyaura cross-coupling”

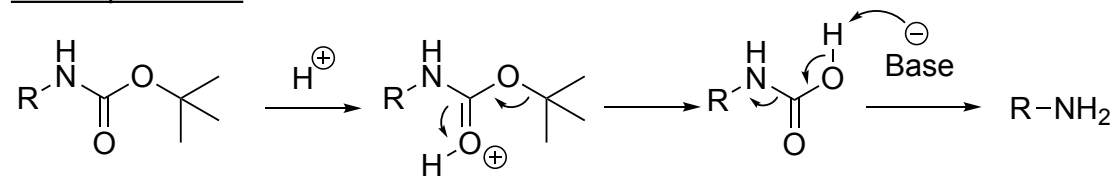


First hetero-Diels-Alder

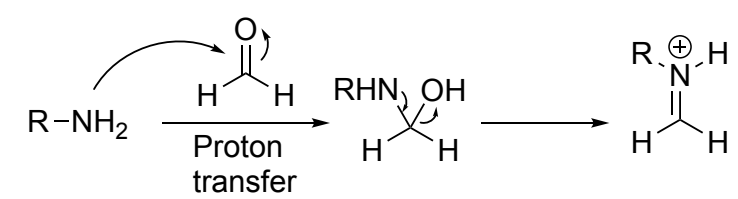




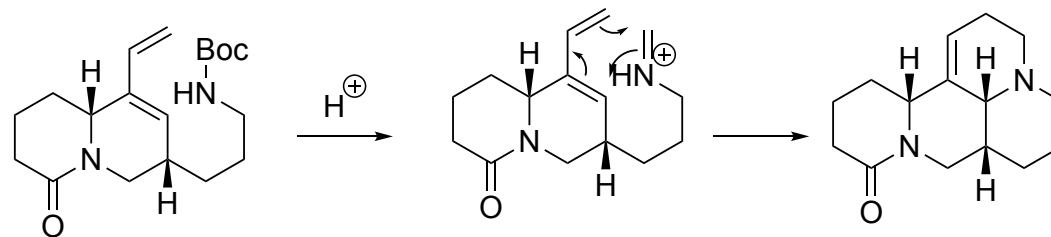
Boc deprotection

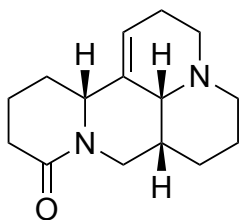


Iminium formation



Second hetero-Diels-Alder

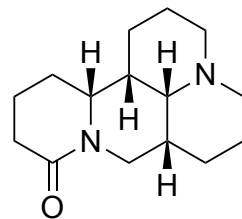




21

Condition 1:
 5% Pd/C, H₂
 Et₃N/EtOH, 70 °C
 dr (1):(2):(3) = 1:4:1
 38% (2) isolated
 29% **21** recovered

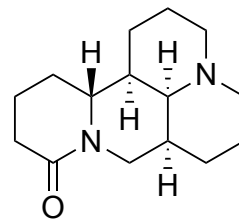
Condition 2:
 PtO₂ (17 mol%),
 H₂, AcOH, 25 °C
 dr (1):(2):(3) = 2:1:0
 25% (1) isolated
 53% **21** recovered



isomatrine (1)

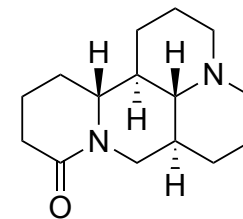
E_{rel} (kJ/mol)

45.2



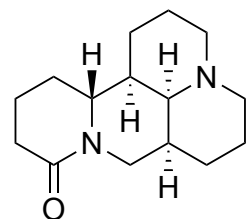
matrine (2)

10.7

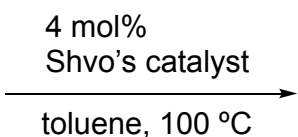


allomatrine (3)

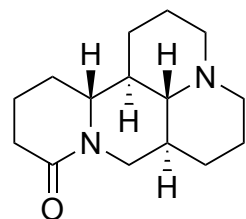
0



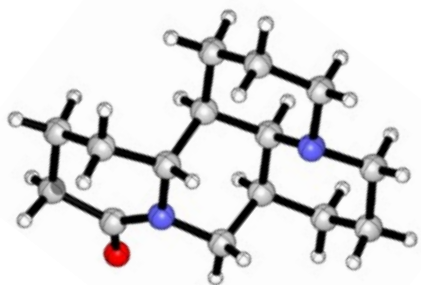
matrine (2)



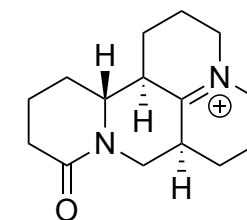
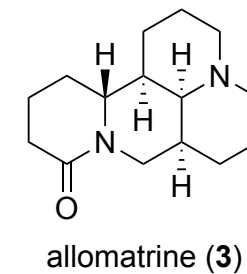
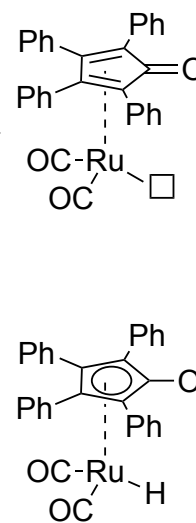
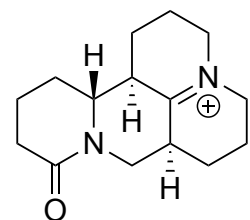
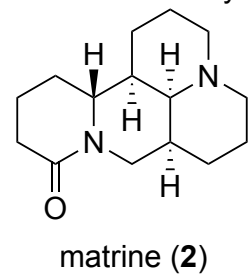
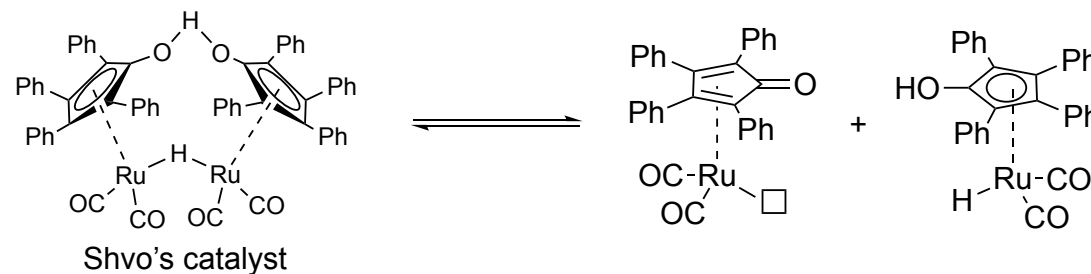
95%



allomatrine (3)

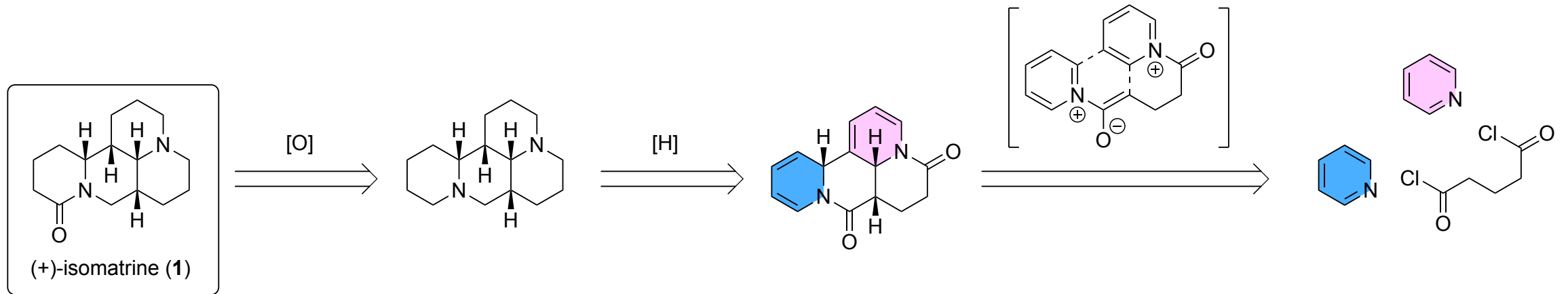
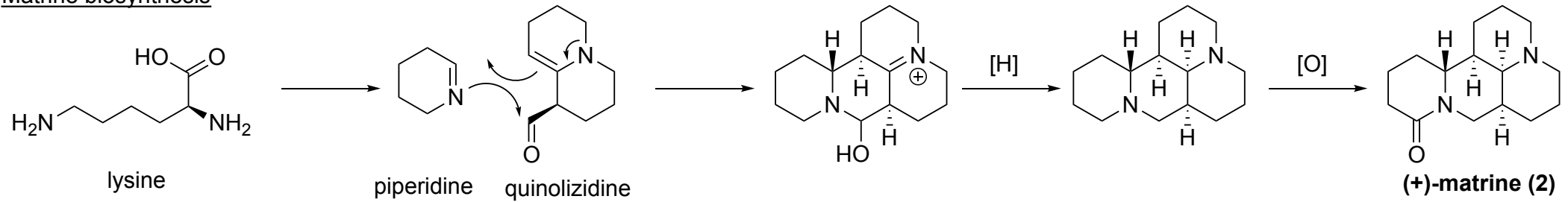


Isomerization from 2 to 3

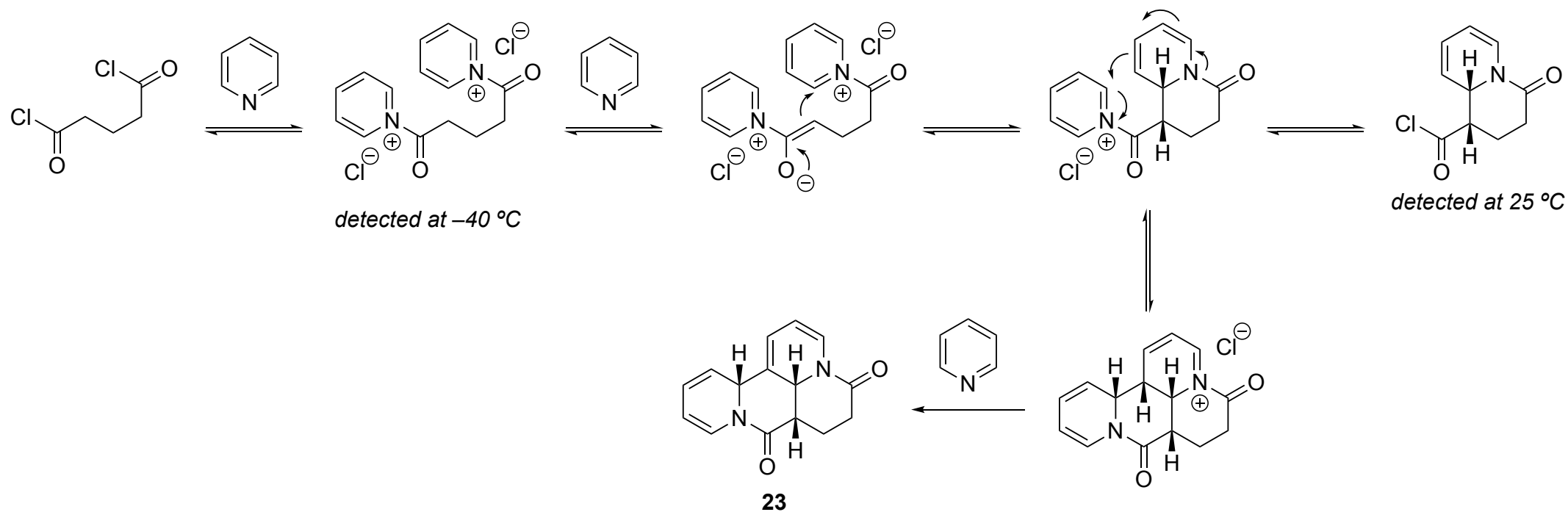
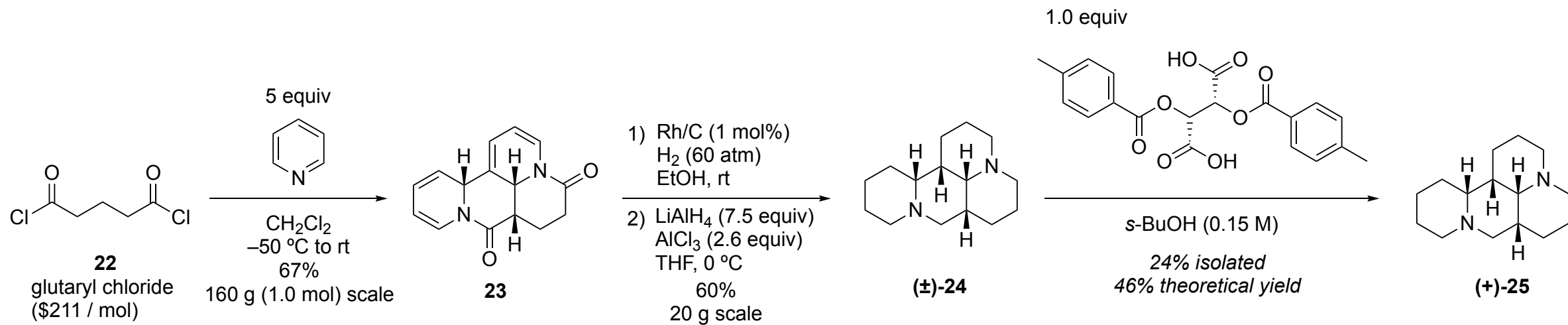


Retrosynthetic Analysis (Reisman's work)

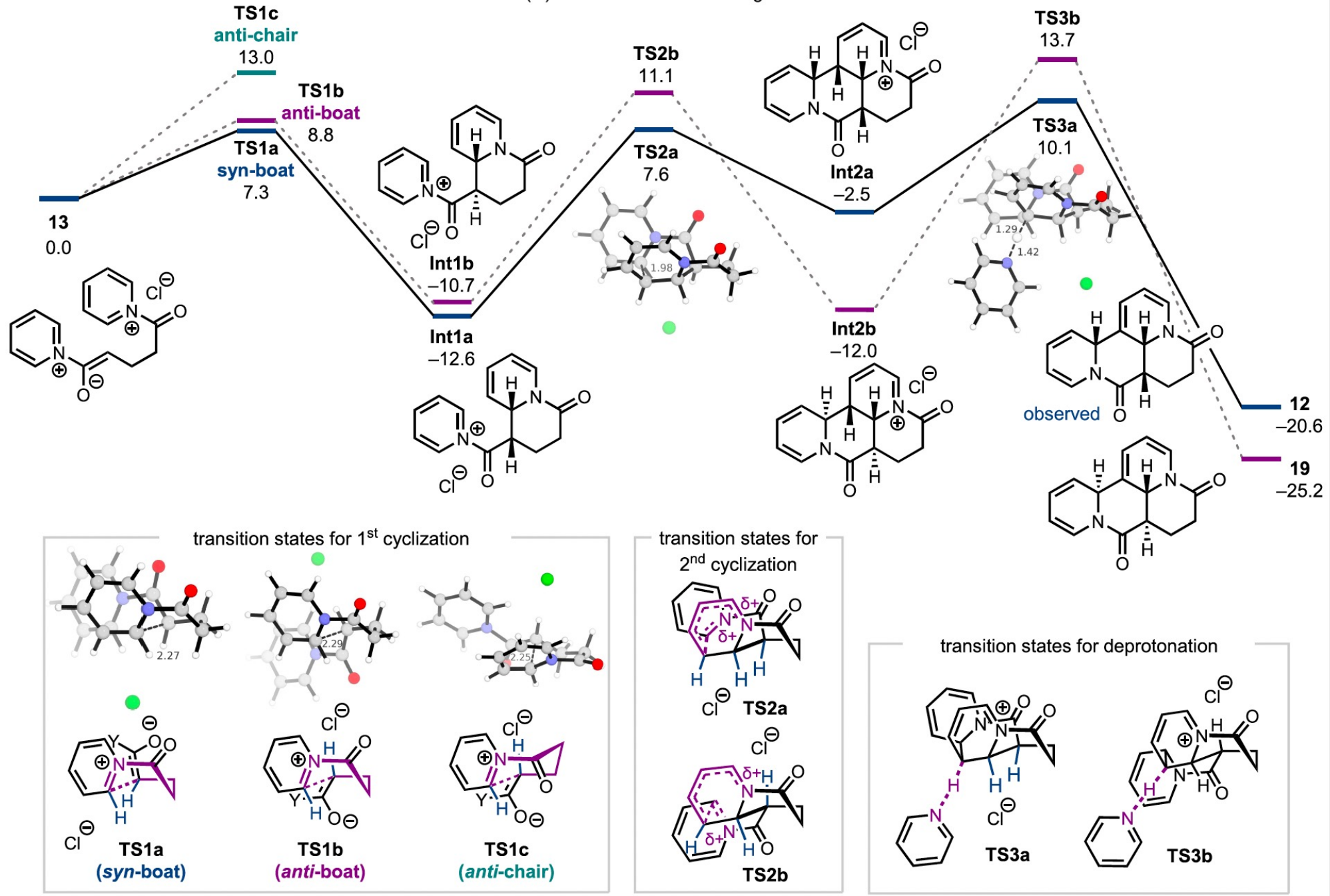
Matrine biosynthesis

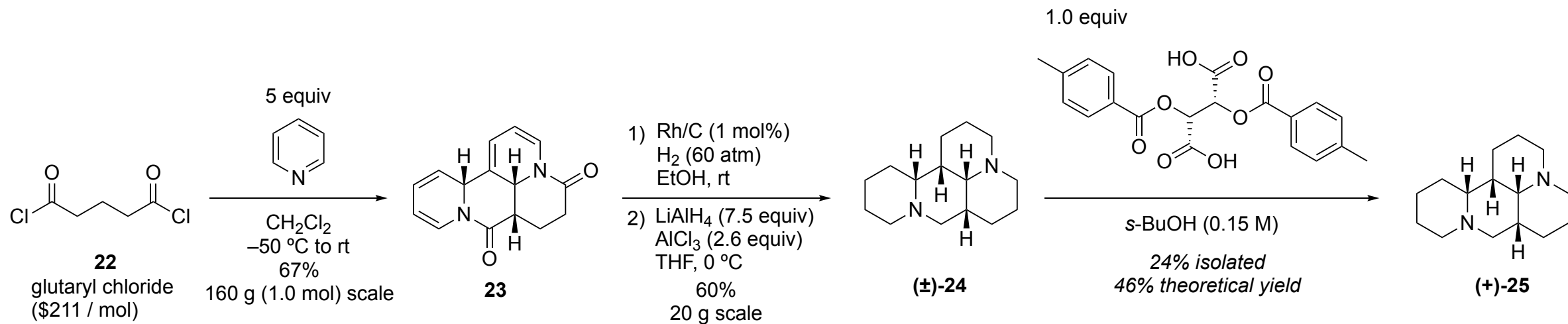


4 steps (Overall)!!

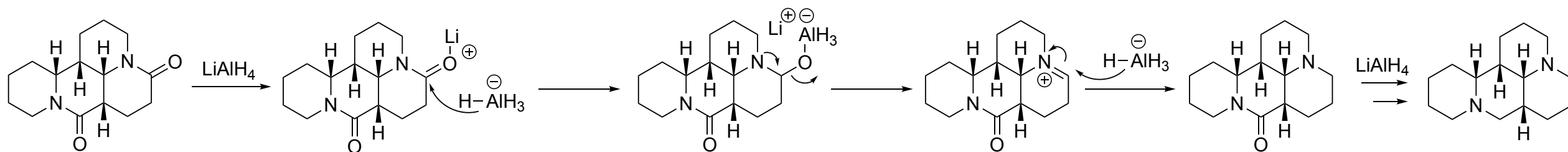


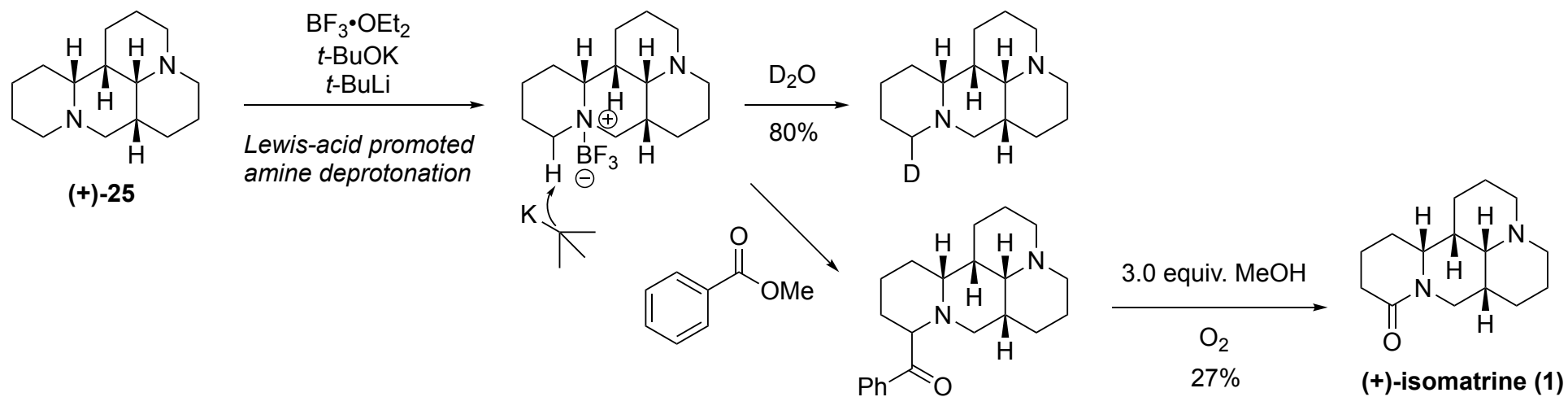
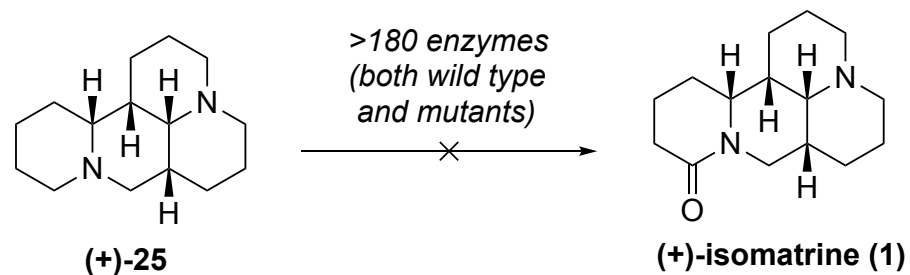
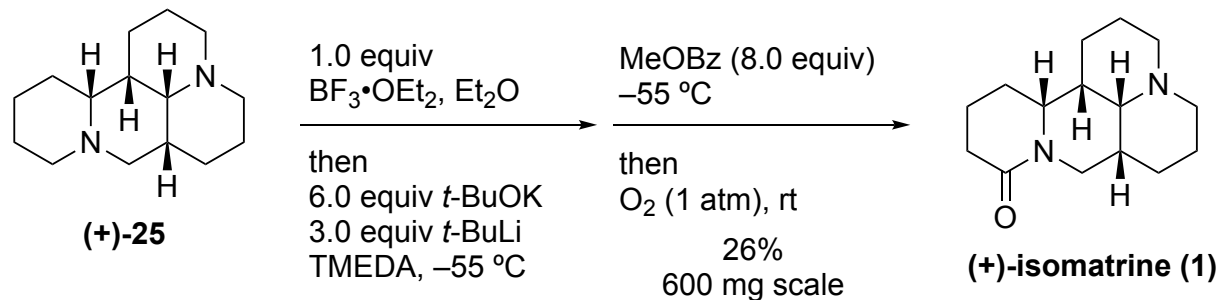
(D) Reaction coordinate diagram



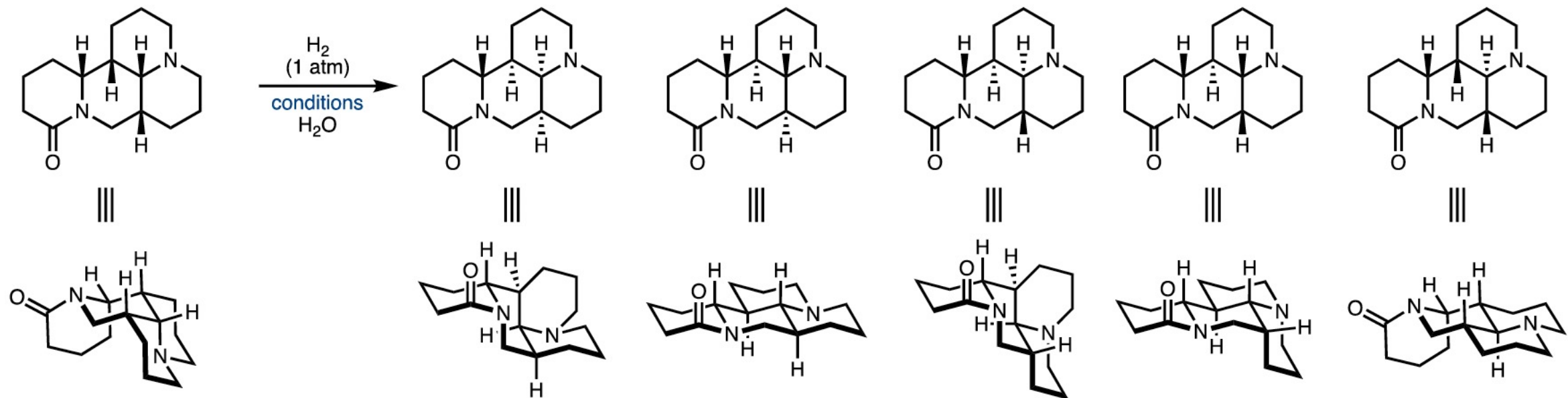


LiAlH_4 reduction of amide





Isomerization studies



1
(+)-isomatrine

conditions

2
(+)-matrine

3
(+)-allomatrine

4
(-)-sophoridine

5
(+)-isosophoridine

26
(-)-unnatural product

10 mol% Rh/C, 98 °C, 1 h	32%	60%	0%	0%	0%
10 mol% Pd/C, 98 °C, 2 h	15%	83%	0%	0%	0%
110 mol% PtO ₂ , 98 °C, 15 min	6%	10%	10%	29%	14%
10 mol% Pt/C, 98 °C, 15 min	0%	11%	0%	55%	19%
110 mol% PtO ₂ , 80 °C, 24 h	0%	18%	0%	33%	40%

“the first total synthesis of the lupin alkaloid (-)-sophoridine, and the shortest syntheses of (+)-isomatrine, (+)-matrine, (+)-allomatrine, and (+)-isosophoridine reported to date”