A Mechanistic Presentation of the Total Synthesis of Galanthamine by Yu Feng and Zhi-Xiang Yu

Cameron McConnell

The Liu Lab

Abstract

Formal Synthesis of (+/–)-Galanthamine and (+/–)-Lycoramine Using Rh(I)-Catalzed [(3 + 2) + 1] Cycloaddition of 1-Ene-Vinylcyclopropane and CO

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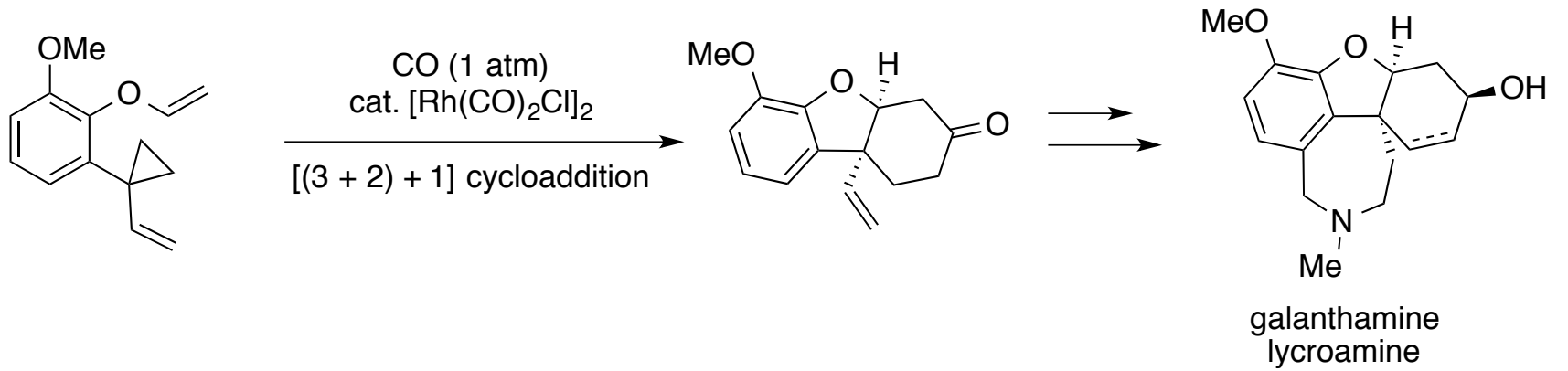
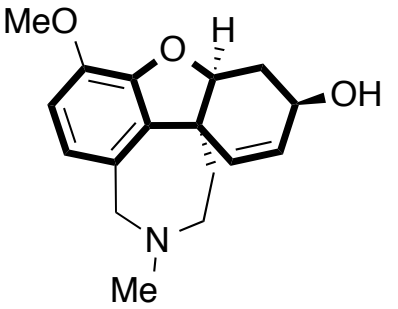


ABSTRACT: An efficient strategy using Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition of 1-ene-vinylcyclopropane and CO as a key step to build the *cis*-hydrobenzofuran skeleton has been developed and applied for the formal synthesis of (+/–)-galanthamine and (+/–)-lycoramine.

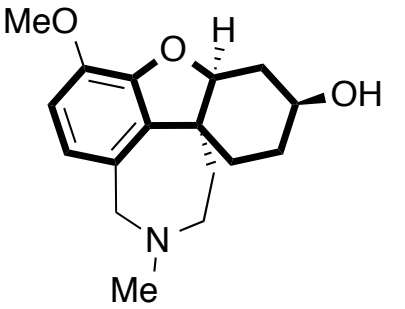
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Introduction

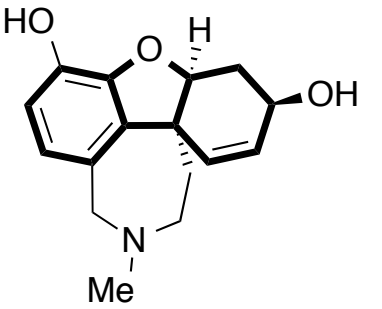
INTRODUCTION: Galanthamine is an alkaloid part of a broader family of galanthamine and morphine-like alkaloids. These alkaloids are isolated from bulbous flowering plants; galanthamine in particular is isolated from the bulb of the Amaryllidaceae family. Galanthamine has demonstrated activity as a reversible and competitive acetylcholine esterase inhibitor. Researchers have used galanthamine in the early treatment of Alzheimer's disease.



galanthamine **1a**

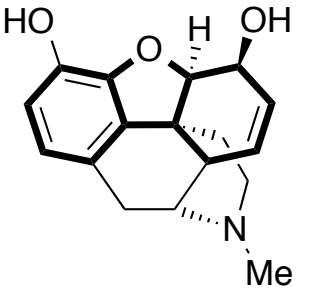


lycoramine **1b**

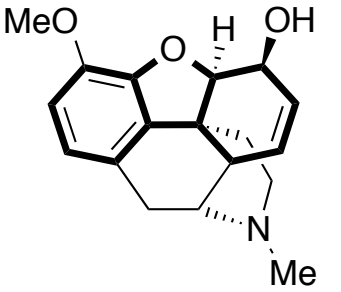


saunginine

SYNTHETIC CONSIDERATIONS: The morphine and galanthamine-like alkaloids all feature a tetracyclic structure with an azepane ring (highlighted in **Figure 1)** and an all-carbon quaternary, stereogenic center. Galanthamine has already been synthesized by several groups using a number of strategies, nearly all of which approach the problem by tethering the two six-membered rings through the amine and then fusing them through the central furan ring at a late state of the synthesis. The authors of this total synthesis took a different approach whereby they construct the azepane skeleton in a single Rh(I)-catalyzed [(3 + 2) + 1] cycloaddition step. The authors synthesize galanthamine in 15 steps.



morphine

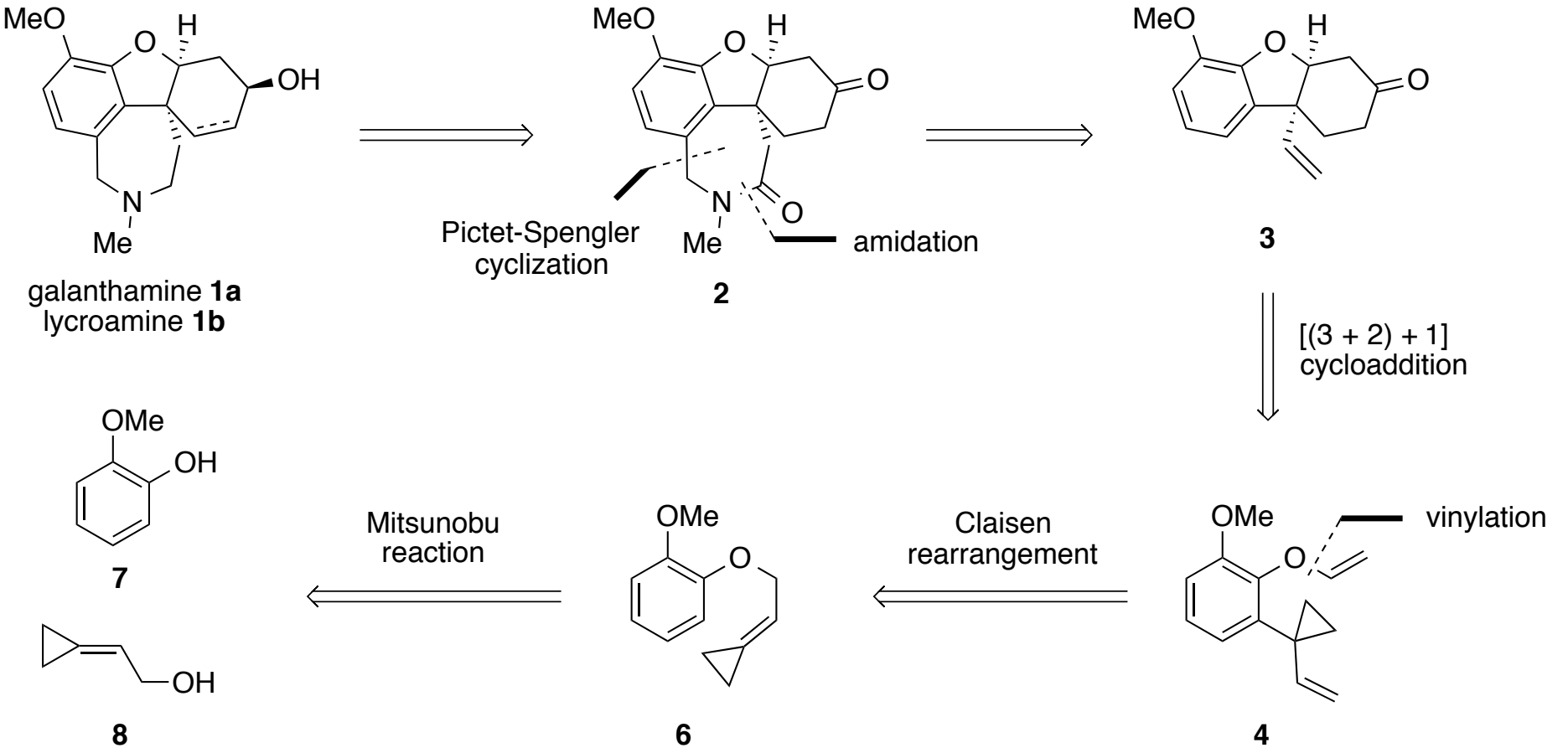


codeine

Figure 1

Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

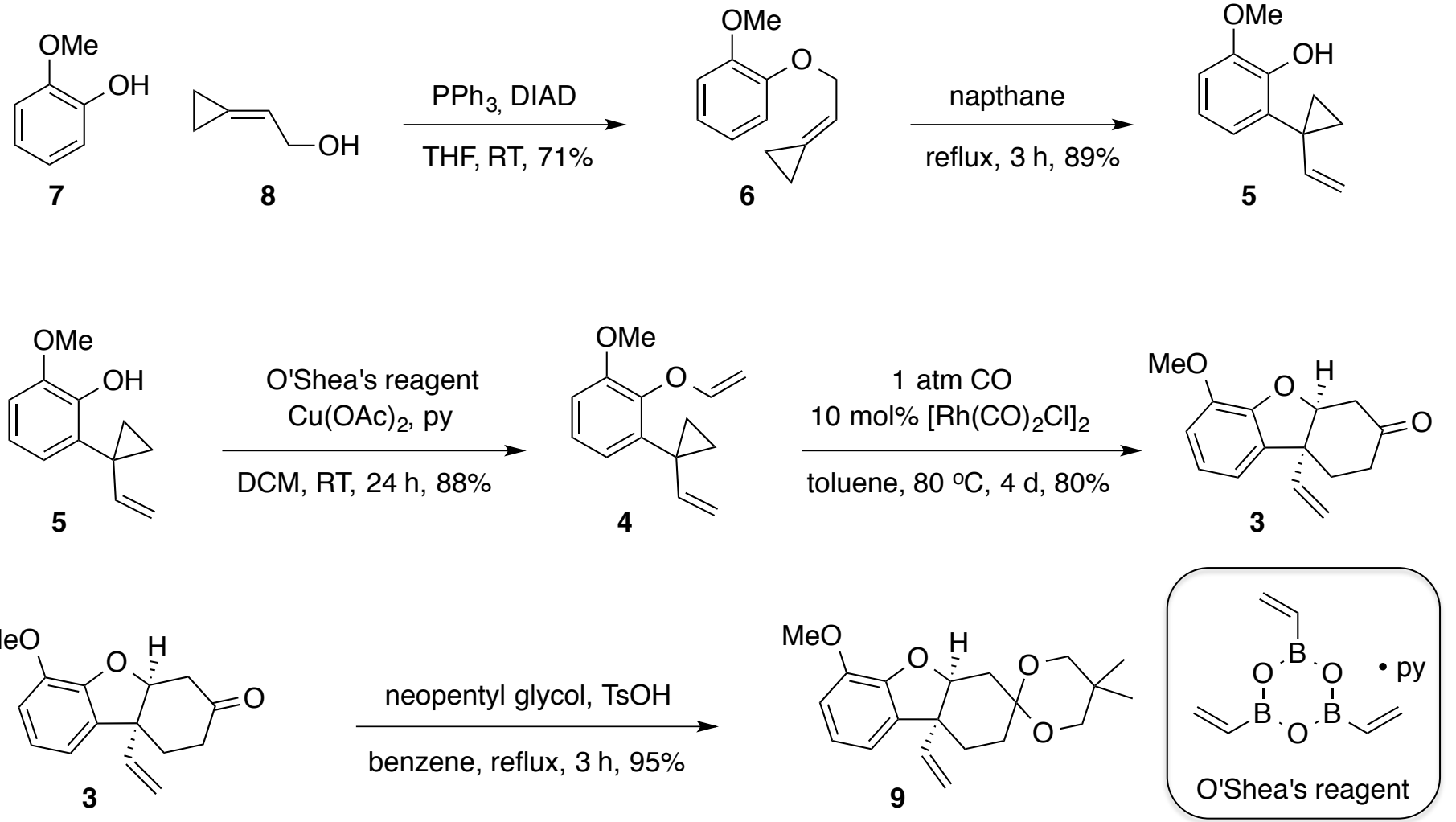
Retrosynthetic Analysis



Scheme 1. Synthetic Strategy for (+/–)-Galanthamine and (+/–)-Lycoramine

Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

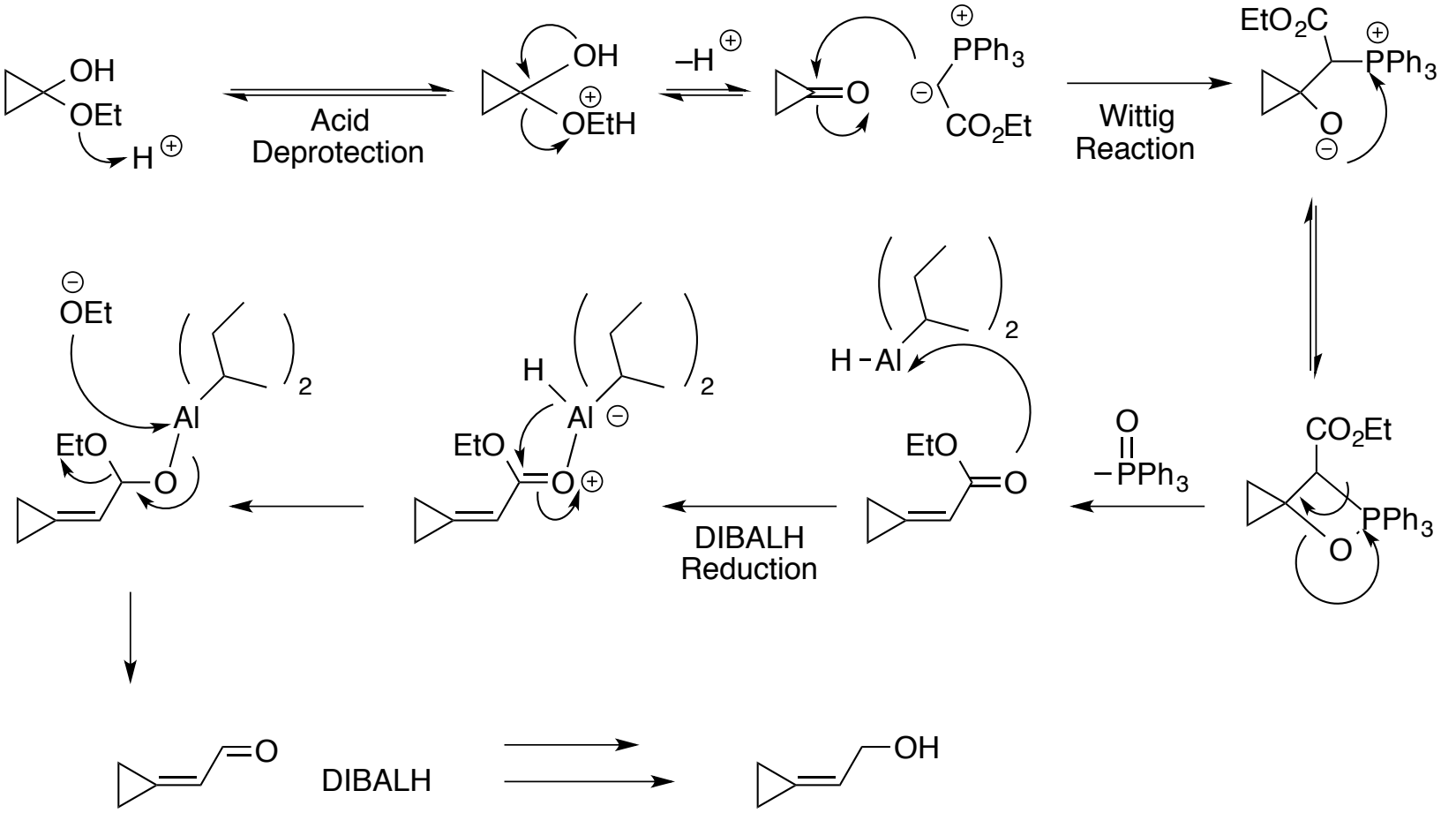
Forward Synthesis



Scheme 2. Formal Synthesis of (+/–)-Galanthamine and (+/–)-Lycoramine

Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Preparation of Compound 8



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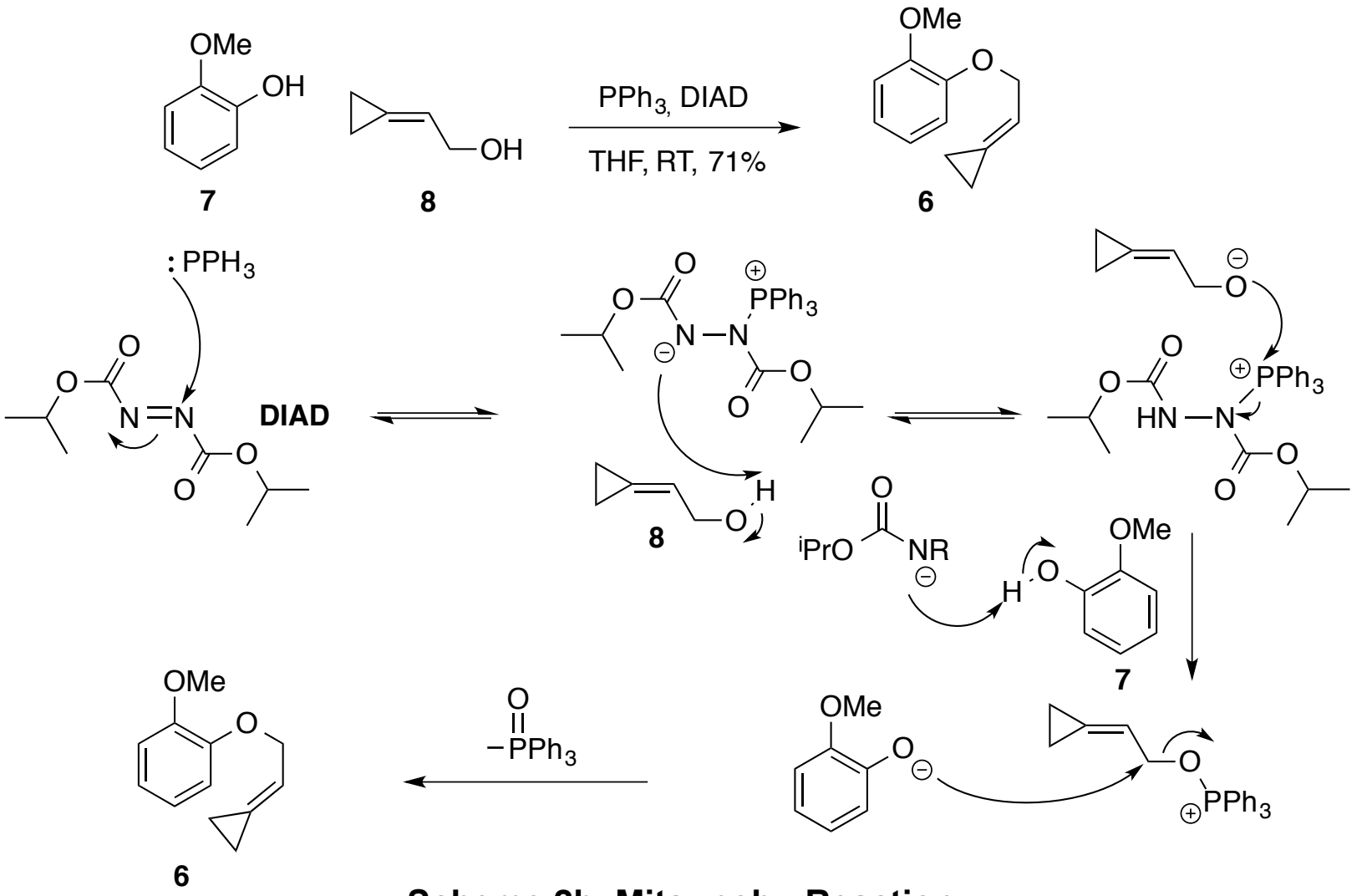
Scheme 2a. Synthesis of Compound 8

Wittig, G.; Schöllkopf, U. *Chemische Berichte* **1954**, *87*, 1318.
Stolle, A. et al. *J. Am. Chem. Soc.***1992**, 114, 4051.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

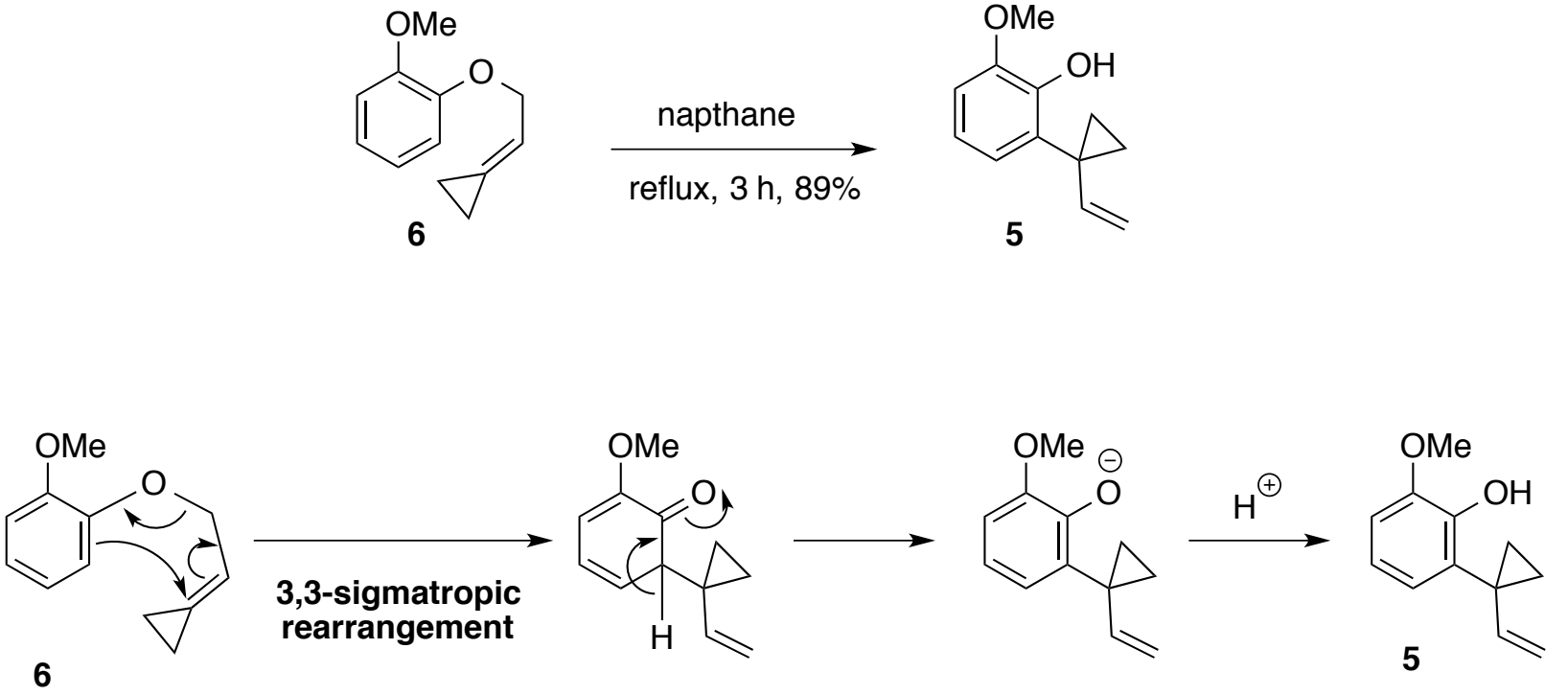
Mitsunobu Reaction



Scheme 2b. Mitsunobu Reaction

Mitsunobu, O. *Synthesis* **1981,** 1, 1-28.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

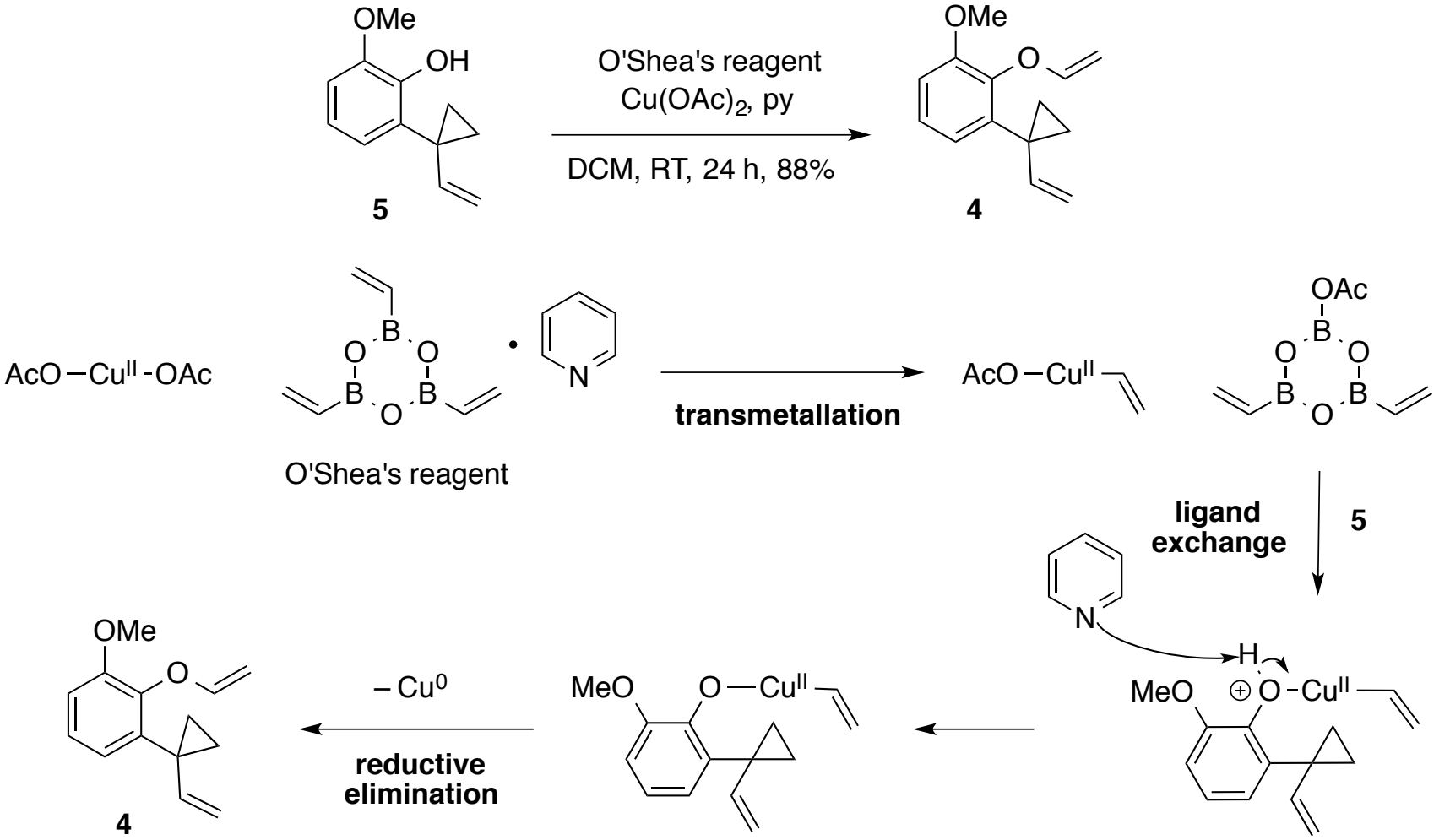
Claisen Rearrangement



Scheme 2c. Claisen Rearrangement

Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

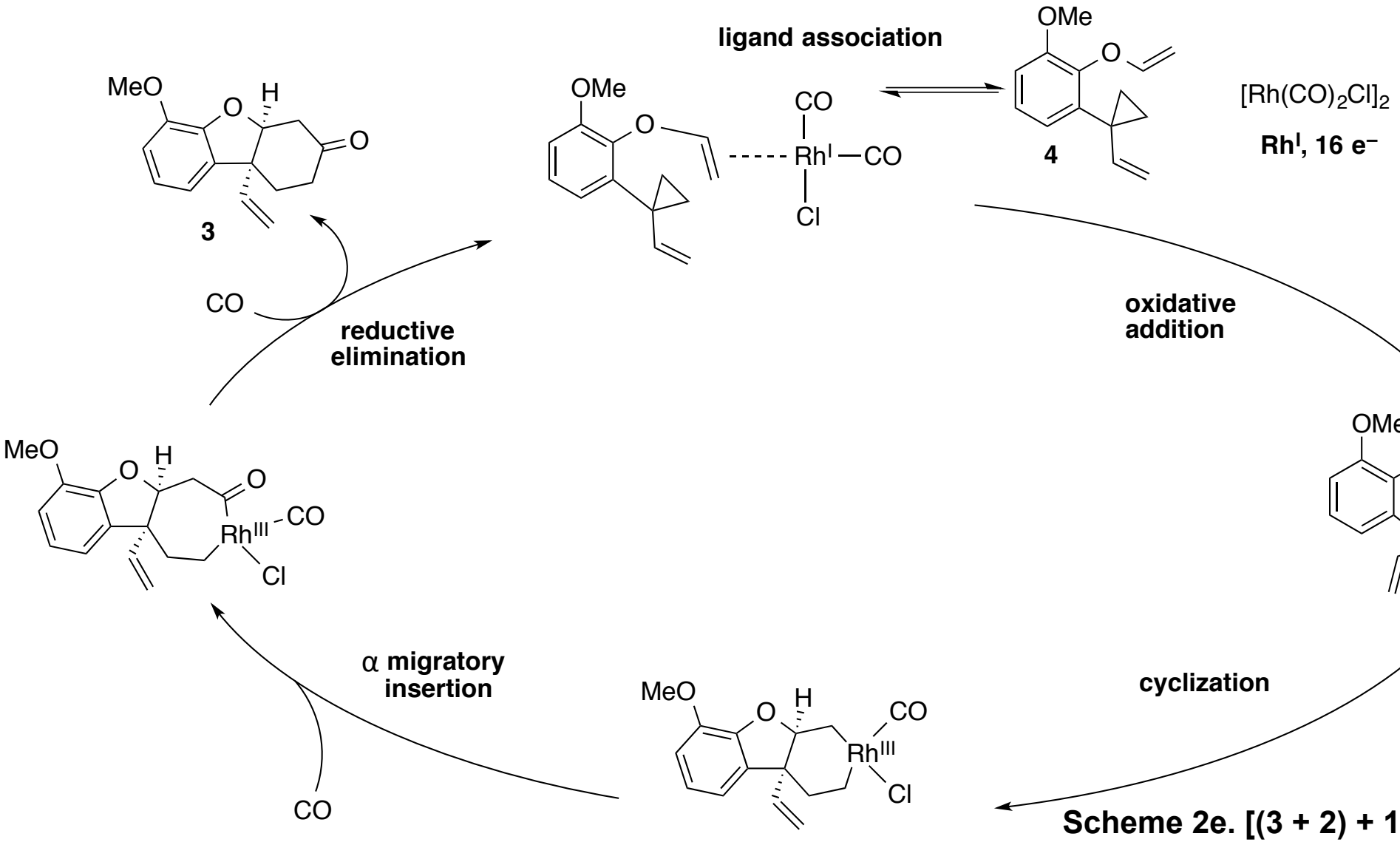
Vinylation with O'Shea's Reagent



Scheme 2d. Vinylation with O'Shea's Reagent

McKinley, N. F.; O'Shea, D. F. *J. Org. Chem.* **2004**, 69, 5087.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

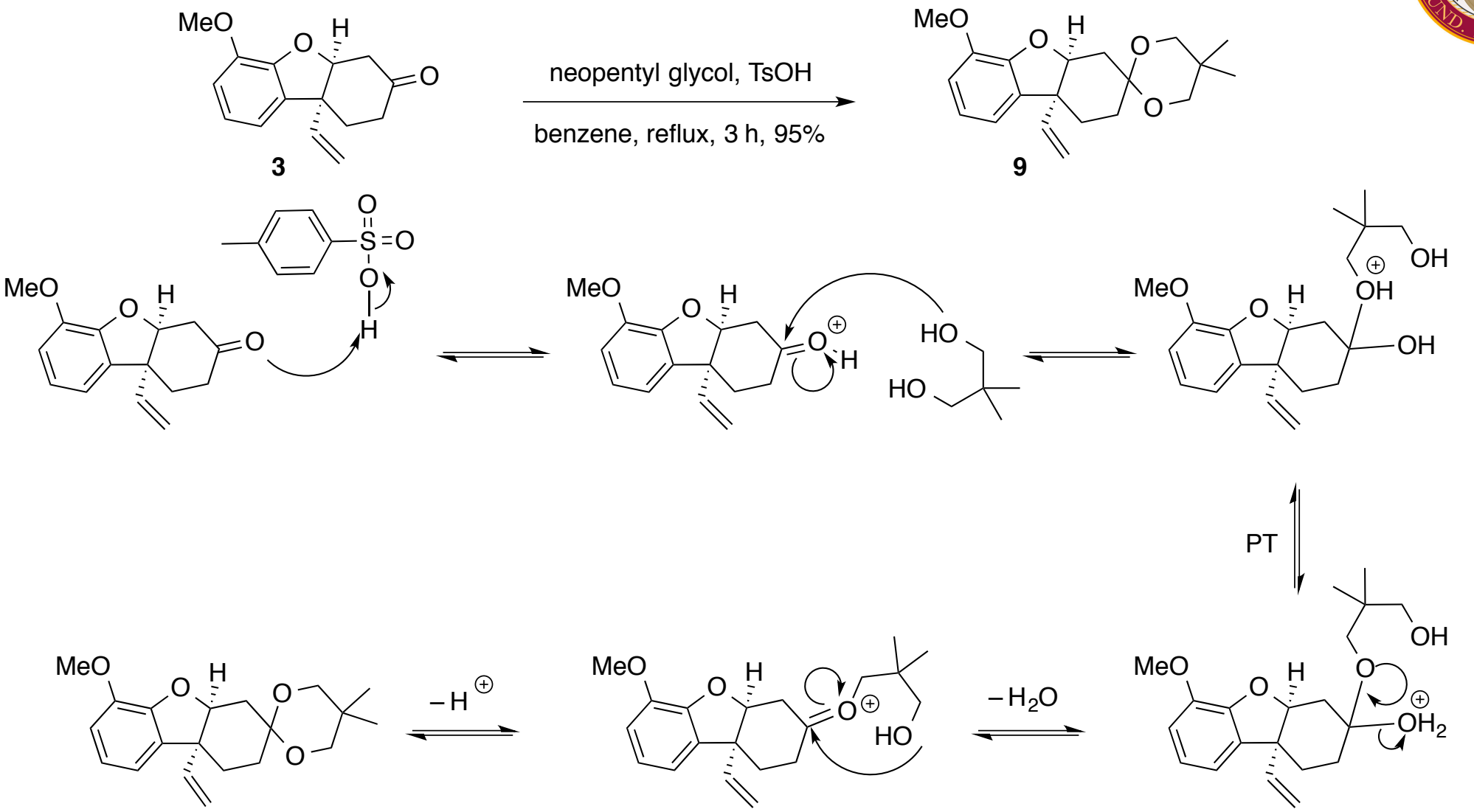
Key Step: [(3 + 2) + 1] Cycloaddition



Scheme 2e. [(3 + 2) + 1] Cycloaddition

Jiao, L.; Lin, M.; Zhuo, L.-G.; Yu, Z.-X. *Org. Lett.* **2010**, 12, 2528.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

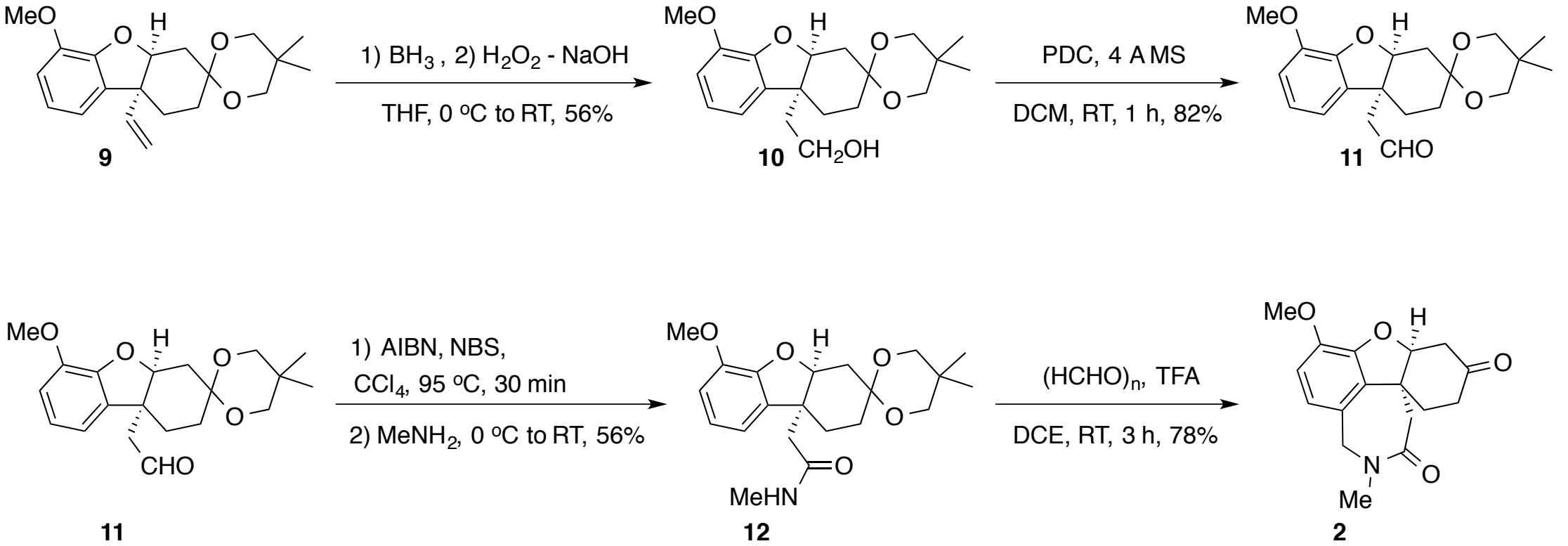
Ketal Protection



Scheme 2f. Ketal Protection

Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

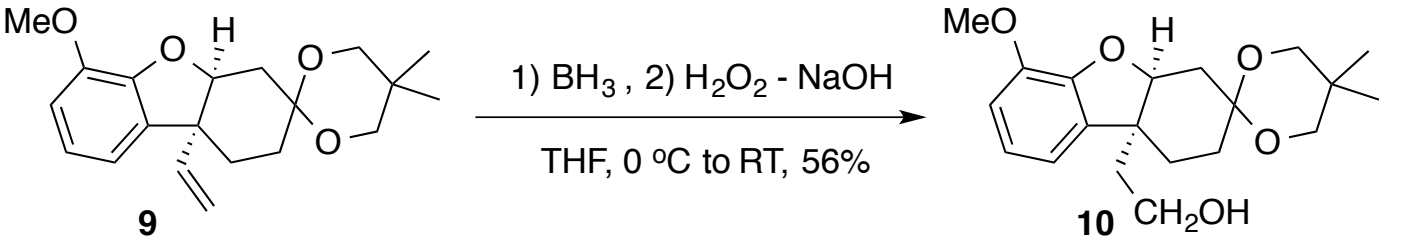
Forward Synthesis Continued

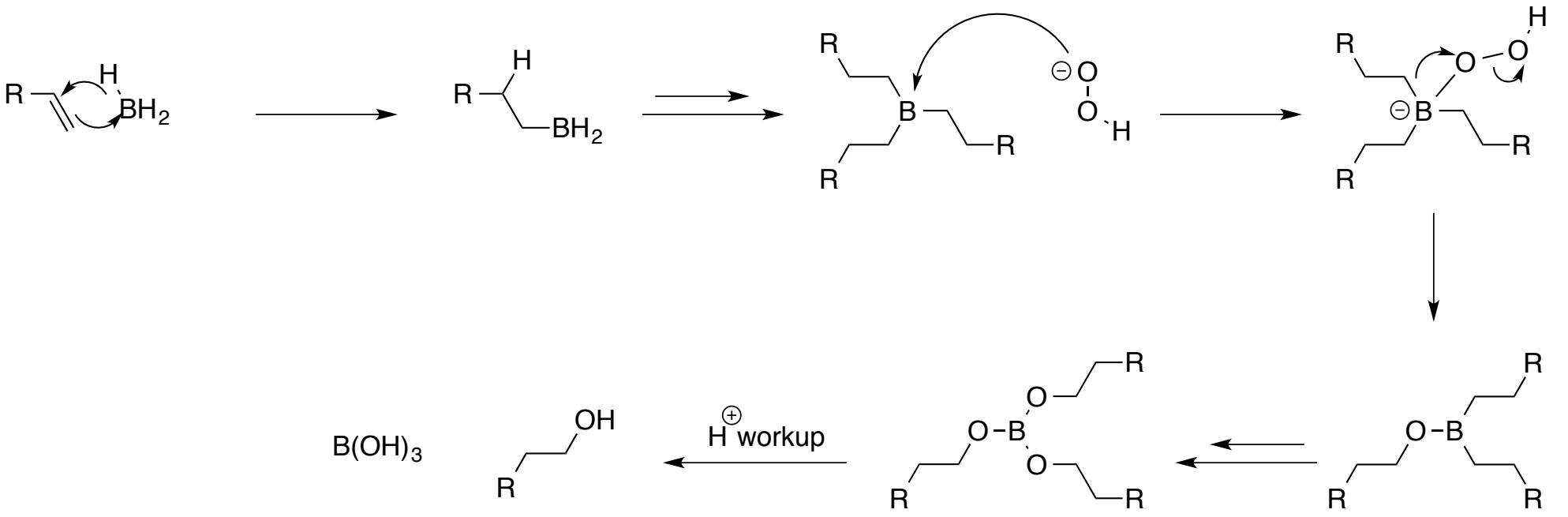


Scheme 3. Formal Synthesis of (+/–)-Galanthamine and (+/–)-Lycoramine

Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Hydroboration, Oxidation

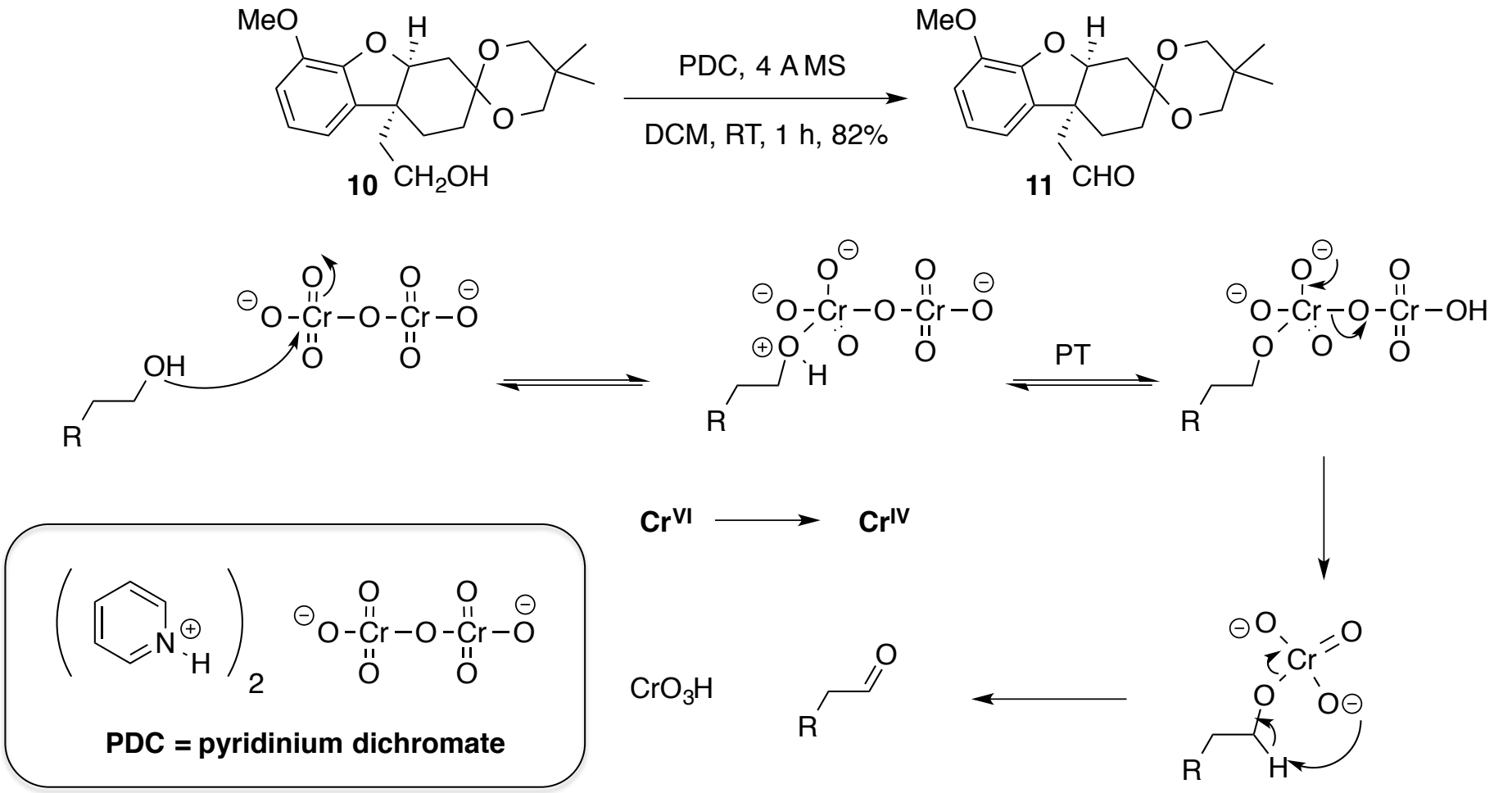




Scheme 3a. Hydroboration, Oxidation

Brown, H. C. *Tetrahedron* **1961**, *12*, 117.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

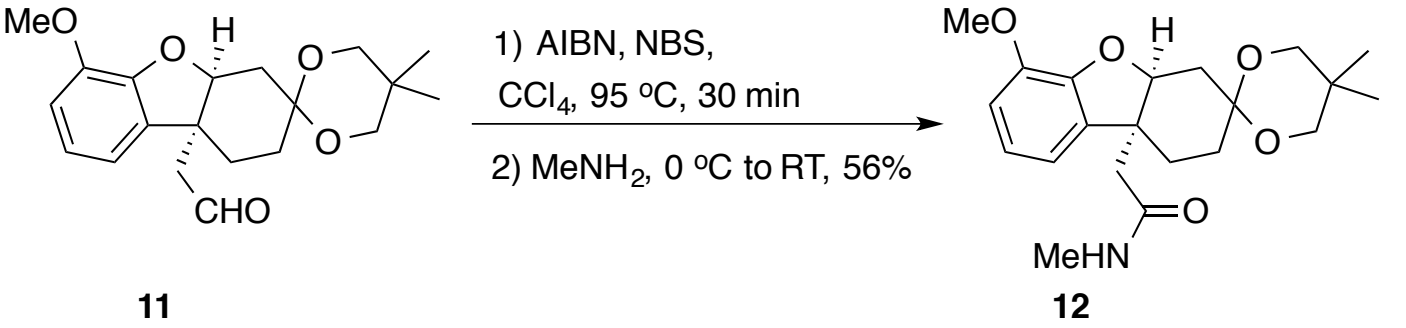
Pyridinium Dichromate Oxidation



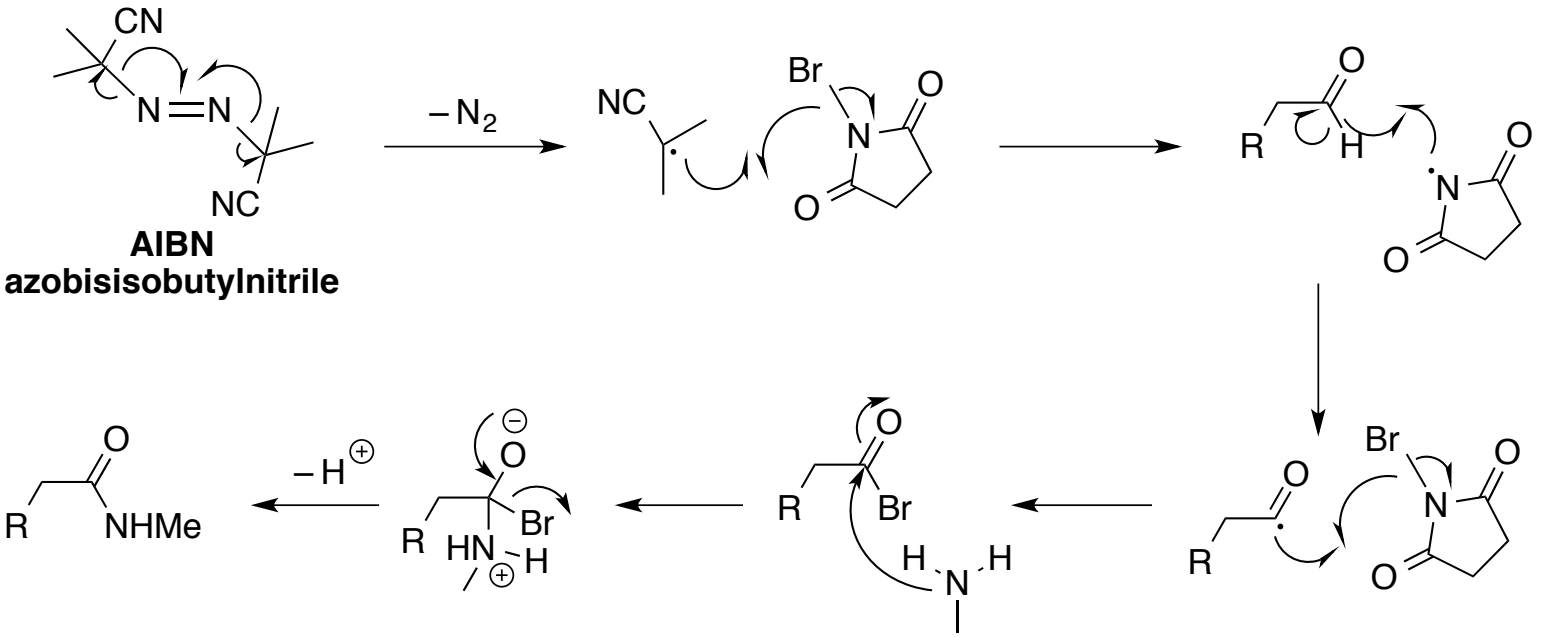
Scheme 3b. PDC Oxidation (Cornforth Reagent)

Cornforth, R. H.; Cornforth, J. W.; Popják, G. *Tetrahedron* **1962**, *18*, 1351.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Amidation via Acyl Bromide



11 **12**

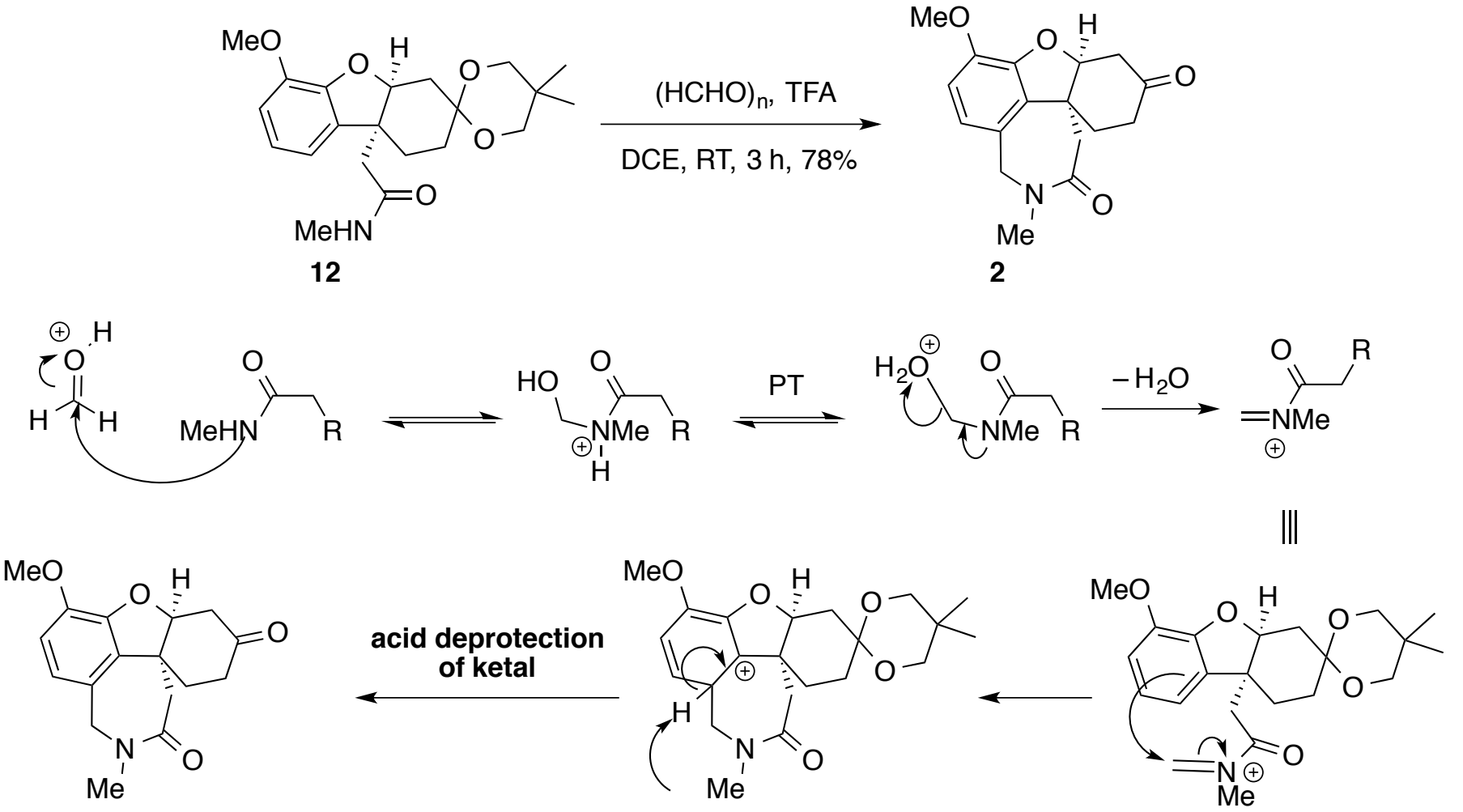


AIBN
azobisisobutylnitrile

Scheme 3c. Amidation via Acyl bromide

Markó, I. E.; Mekhalfia, A. *Tet. Lett.* **1990**, *31*, 7237.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

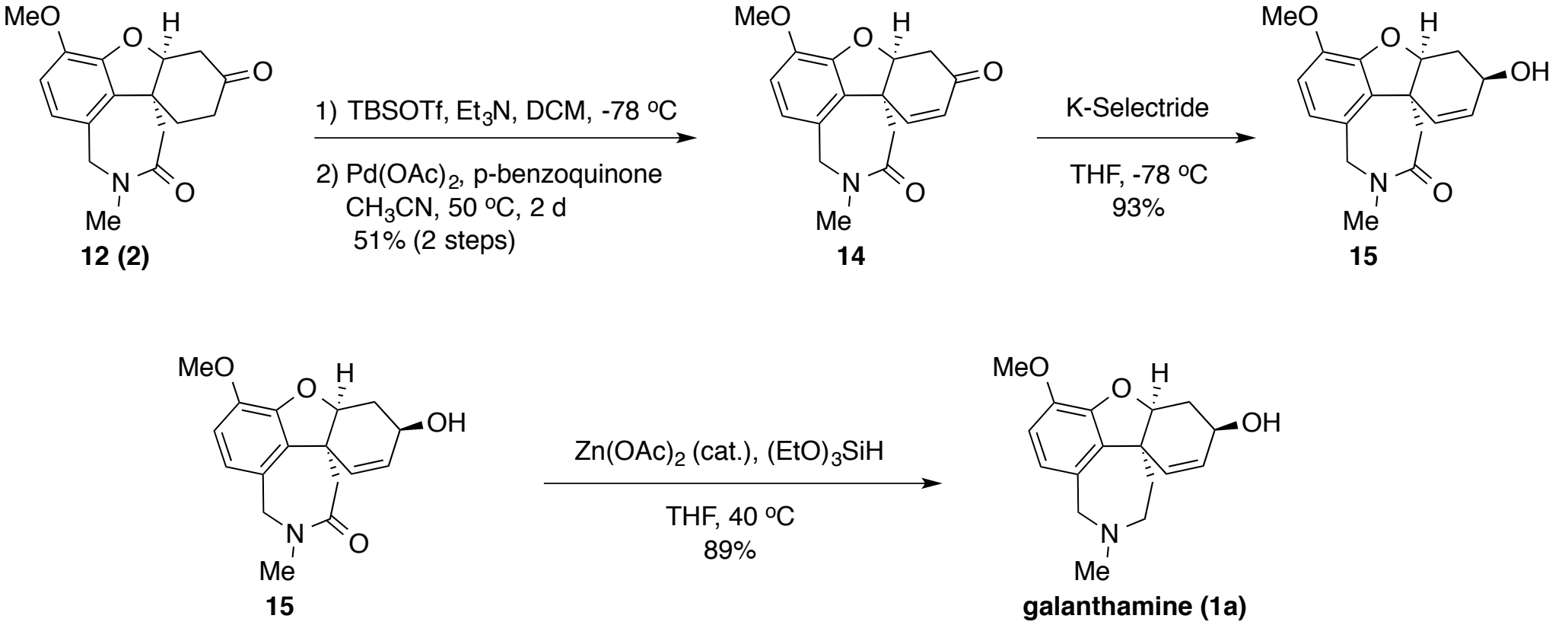
Pictet-Spengler Reaction



Scheme 3d. Pictet-Spengler Reaction

Pictet, A.; Spengler, T. *Berichte der deutschen chemischen Gesellschaft* **1911**, *44*, 2030.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

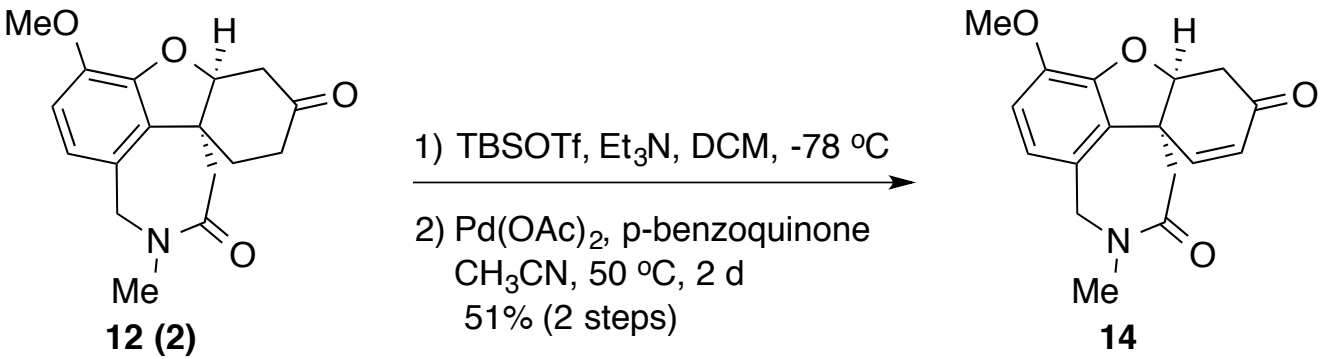
Final Steps to Galanthamine

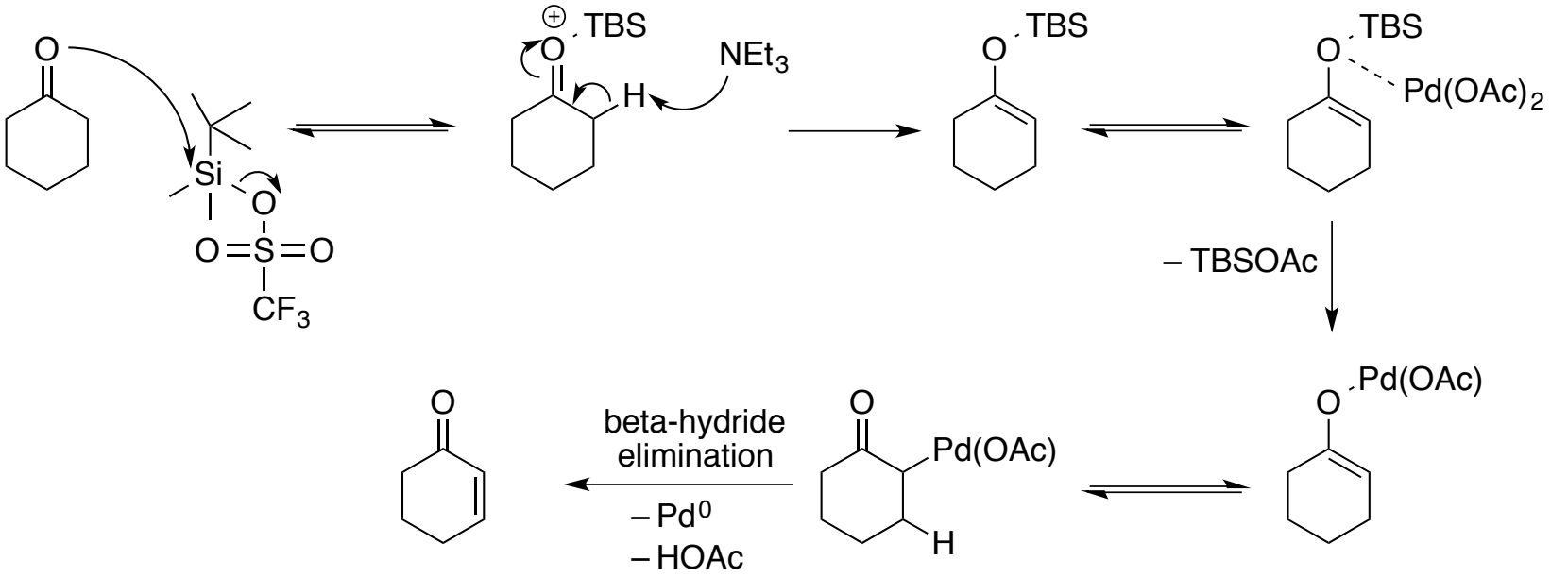


Scheme 4. Formal Synthesis of (+/–)-Galanthamine and (+/–)-Lycoramine

Chen, J.-Q.; Xie, J.-H.; Bao, D.-H.; Liu, S.; Zhou, Q.-L. *Org. Lett.* **2012**, 14, 2714.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Saegusa-Ito Oxidation

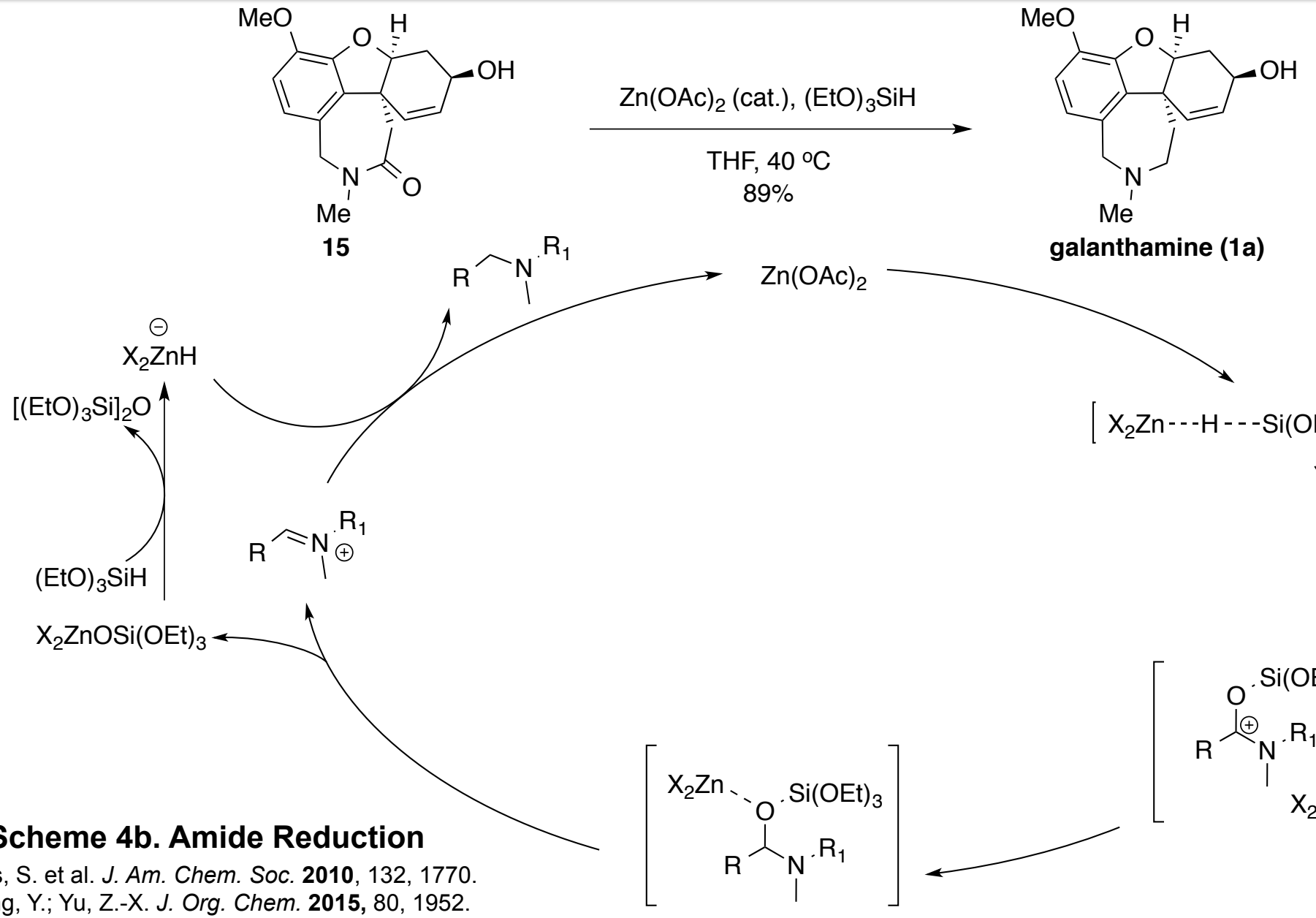




Scheme 4a. Saegusa-Ito Oxidation

Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
Chen, J.-Q.; Xie, J.-H.; Bao, D.-H.; Liu, S.; Zhou, Q.-L. *Org. Lett.* **2012**, 14, 2714.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

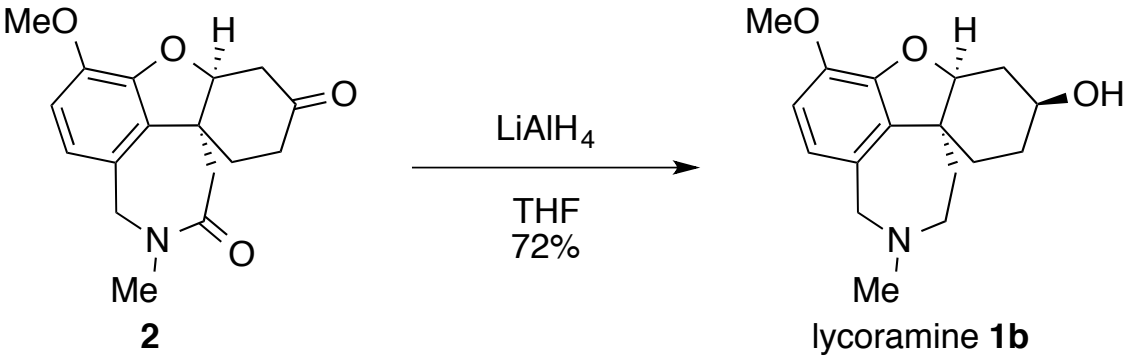
Amide Reduction



Scheme 4b. Amide Reduction

Das, S. et al. *J. Am. Chem. Soc.* **2010**, 132, 1770.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.

Final Step to Lycoramine



Scheme 5. Formal Synthesis of (+/–)-Galanthamine and (+/–)-Lycoramine

Ishizaki, M.; Ozaki, K.; Kanematsu, A.; Isoda, T.; Hoshino, O. J. *Org. Chem.* **1993**, 58, 3877.
Feng, Y.; Yu, Z.-X. *J. Org. Chem.* **2015,** 80, 1952.