Syntheses of Crinine Type Alkaloids

Outline

1. **Condensation**
   - **(±)-Crinine Whitlock (1967)**
   - **(±)-Haemanthamine Core Pierce (2021)**
   - **(±)-Powelline Dixon (2010)**
2. **Cycloadditions**
   - **(-)-Augustamine Pearson (1998)**
   - **(±)-Crinane Padwa (2001)**
   - **(±)-Crinane Pearson (1996)**
3. **Ene reactions**
   - **(±)-Hamayne Banwell (2011)**
   - **(±)-Crinine Lautens (2012)**
4. **Dearomative methods**
   - **(-)-Crinine Tang (2017)**
   - **(±)-Epicrinine Node (2004)**
   - **(±)-Crinine Guillou (2006)**
5. **Strategies using crinine intermediates**
   - **(±)-Gracilamine Ma (2012)**
   - **(+)-Gracilamine Xie (2017)**

Reviews and books

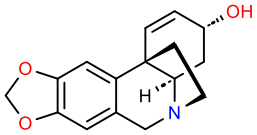
1. **Synthesis of crinine alkaloids**
   - **https://doi.org/10.3390/molecules26030765**
2. **Synthesis of gracilamine**
   - **https://doi.org/10.1039/C8CC07799A**
3. **Synthesis & biosynthesis of Amaryllidaceae alkaloids**
   - **https://doi.org/10.1039/C8NP00055G**
4. **Biological activity of Amaryllidaceae alkaloids**
   - **https://doi.org/10.1039/C4RA14666B**

This is not a historical account of the synthesis of crinine type alkaloids. See the Banwell review for a more “historical”/ all encompassing review of strategies towards this class of alkaloids.

While crinine type alkaloids fall under the large family of Amaryllidaceae alkaloids, specifically approaches to crinine type and two synthesis of gracilamine that utilize known crinine intermedites are shown in this topic

For a topic on Isocarbostyril alkaloids see Daniel Holycross’s topic https://8cf9eb7e-b5ec-48cd-9fdd-580cfdeede43.filesusr.com/ugd/31ec9c_4e7c01cea19942f8bc559761d6c09969.pdf

Introduction

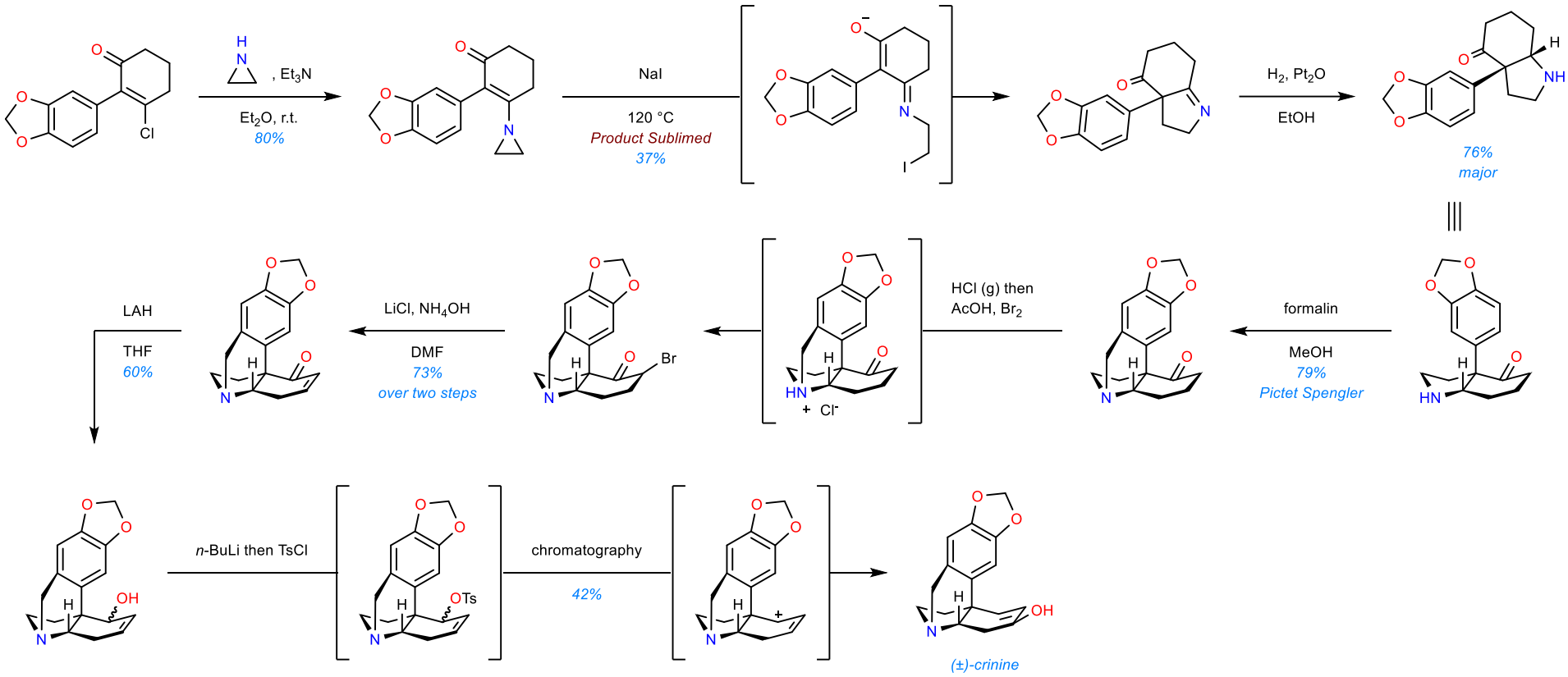


(-)-crinine

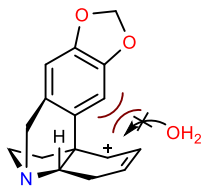
- (-)-Crinine was isolated in 1955 by Wildman from *Amaryllis belladonna L.*. It was shown to cause respiratory paralysis in animals, thereby killing them.
- It is comprised of a pentacyclic scaffold, containing one quaternary center, and a tertiary nitrogen
- Since crinine’s original isolation a number of other crinine type alkaloids have been isolated, containing different oxidation levels on the pentacyclic scaffold
- Many of the crinine and related Amaryllidaceae alkaloids have very interesting pharmaceutical properties including, but not limited to, anti-malarial, anti-proliferative, and the ability to induce apoptosis.

Wildman, W. *J. Am. Chem. Soc.* **1955**, 77, 1253–1256. https://doi.org/10.1021/ja01610a046

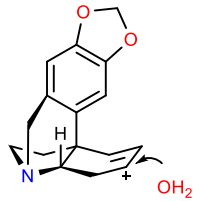
(±)-Crinine Whitlock (1967)



- Attempting unsaturation of the carbonyl with DDQ lead to decomposition due to 1) steric hinderance around the ketone, 2) the Enon is highly susceptible to further oxidation and can easily eliminate the amine group. This is supported by the fact that after treating the product from DDQ with base r.s.m. is obtained.
- The arene is not brominated since the quaternized nitrogen is closer to the arene, which in a way deactivates it to electrophilic attack



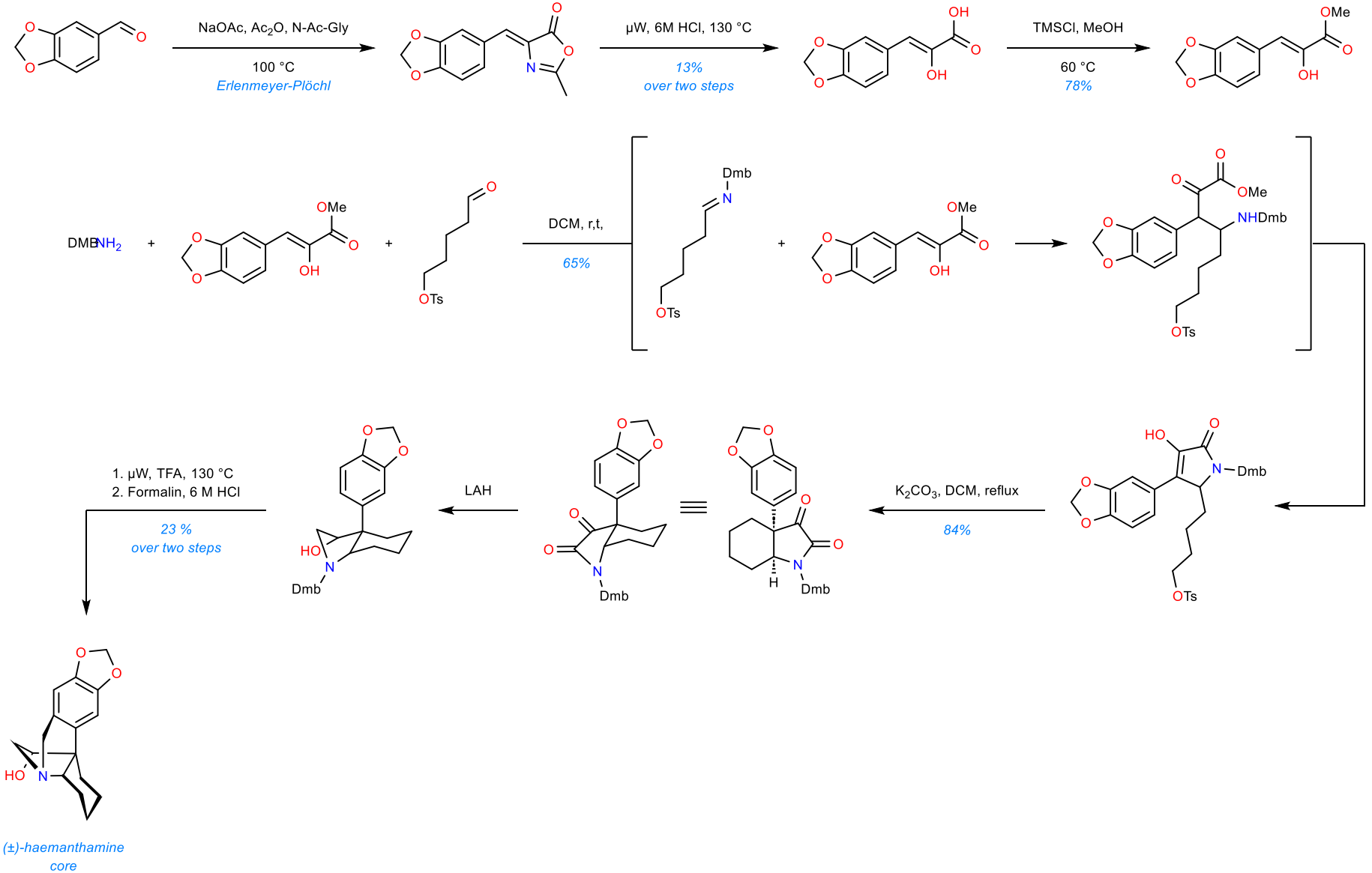
Steric Repulsion From Arene



No Steric Repulsion From Arene

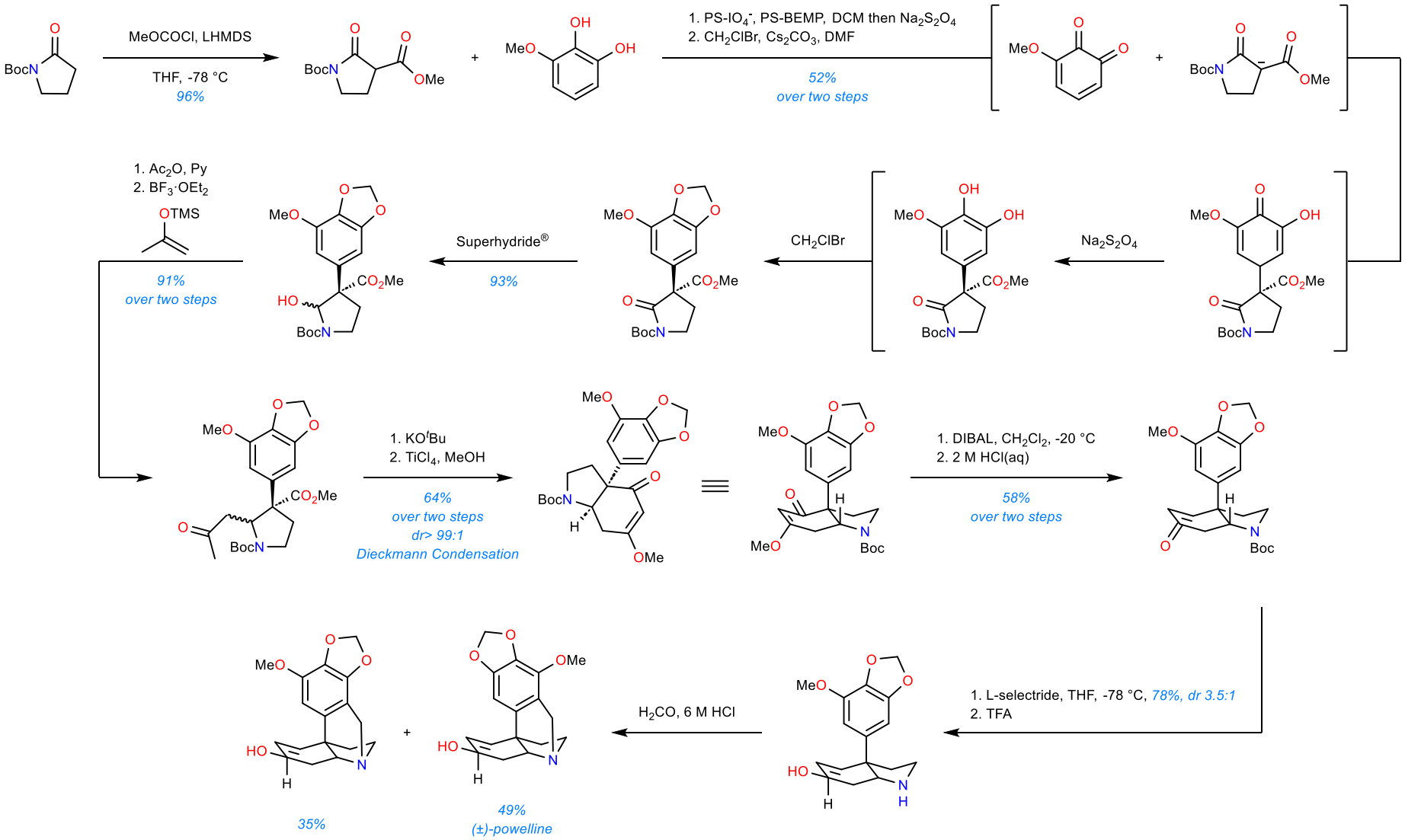
Whitlock, H. *J. Am. Chem. Soc.* **1967**, 89, 3600–3606. https://doi.org/10.1021/ja00990a045

(±)-Haemanthamine Core Pierce (2021)



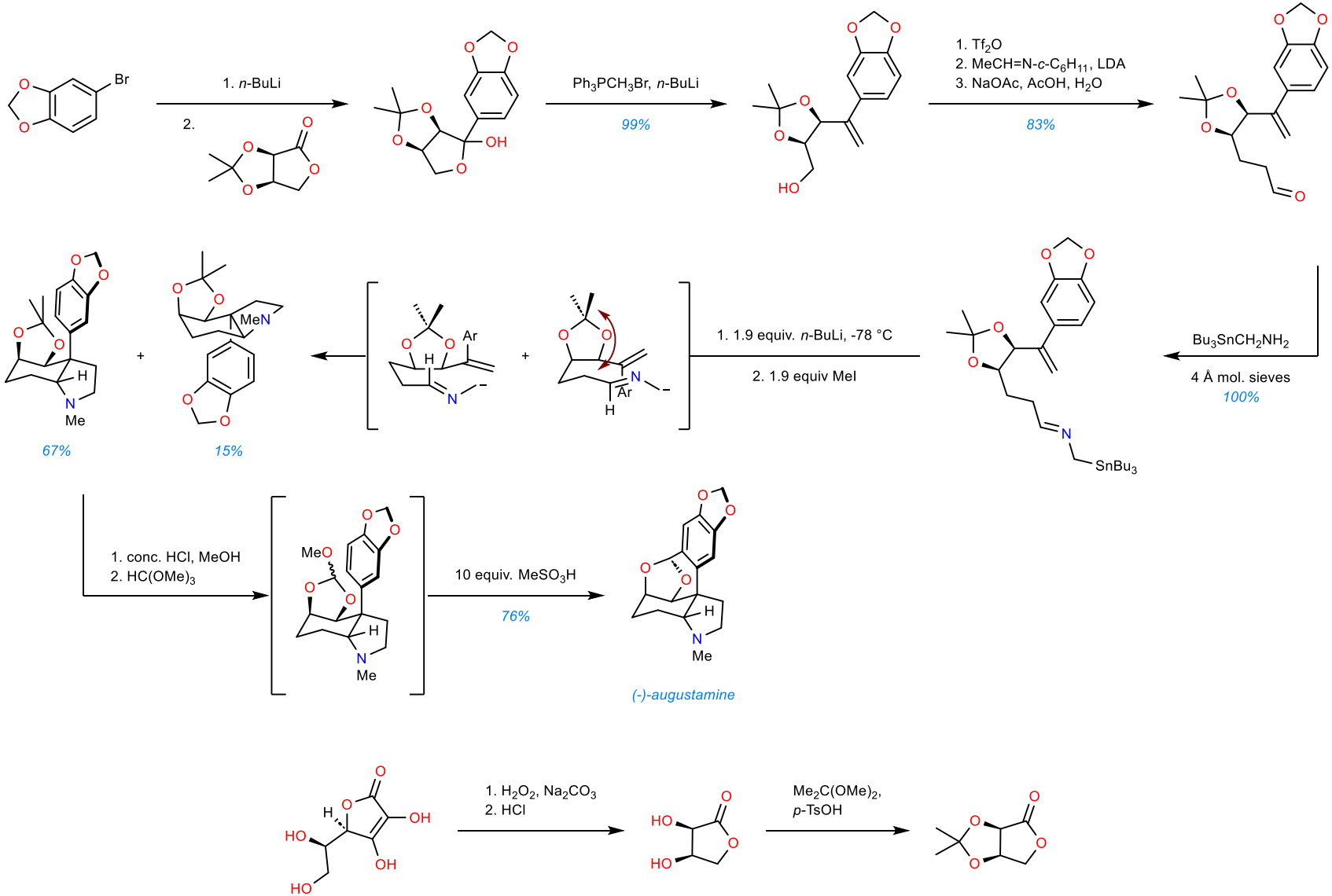
Pierce, J. *Tetrahedron Lett.* **2021**, 75, 153201. https://doi.org/10.1016/j.tetlet.2021.153201

(±)-Powelline Dixon (2010)



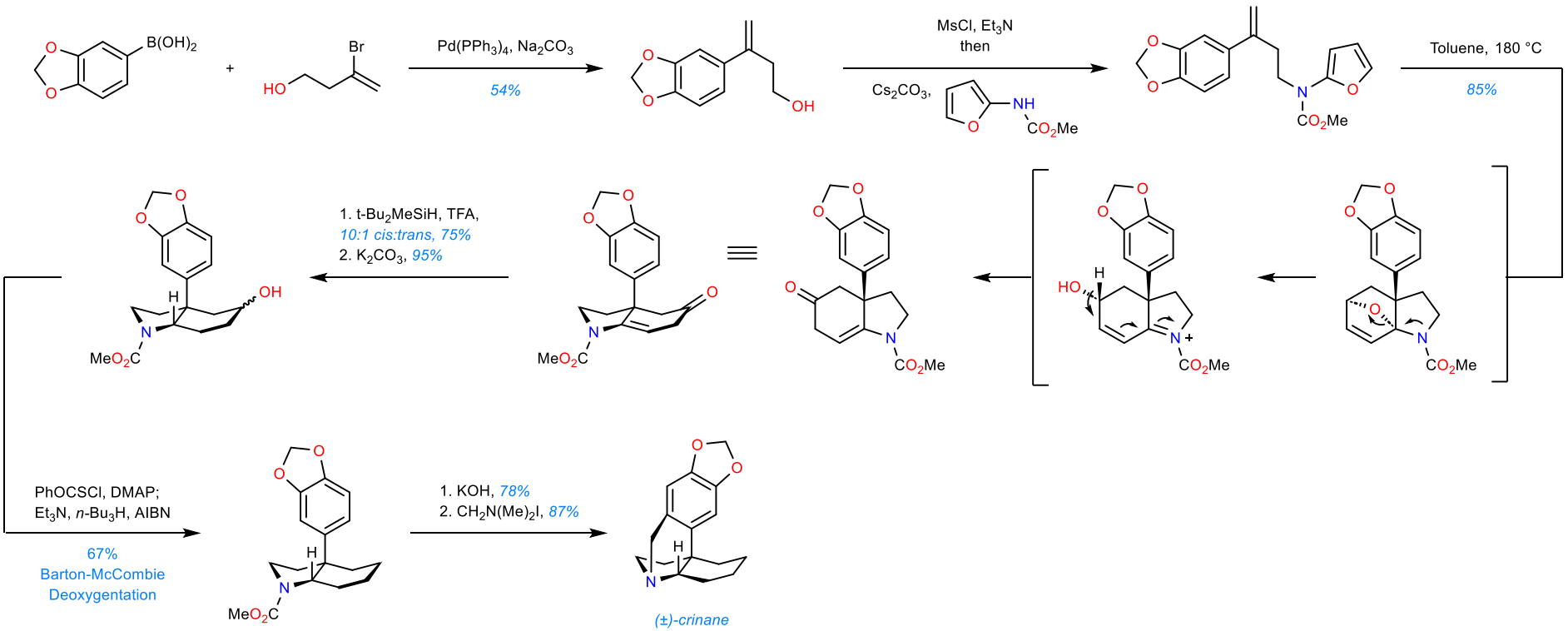
Dixon, D. *Org. Lett.* **2010**, 12, 1252-1254. https://doi.org/10.1021/ol1000654

(-)-Augustamine Pearson (1998)



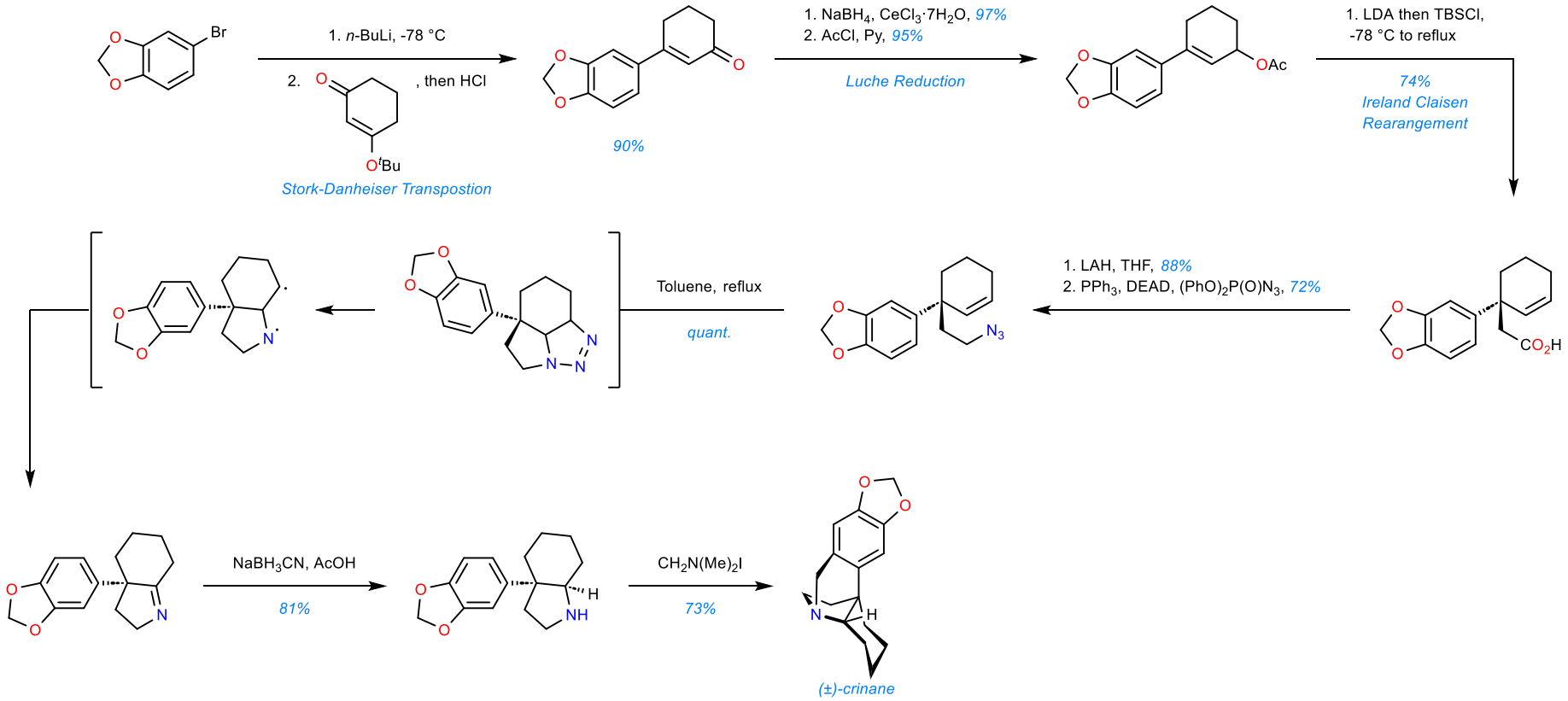
Pearson, W. *J. Org. Chem.* **1998**, 63, 3607-3617. https://doi.org/10.1021/jo972255+
Carozza, L. *Org. Synth*. **1985**, 63, 127. DOI: 10.15227/orgsyn.063.0127

(±)-Crinane Padwa (2001)



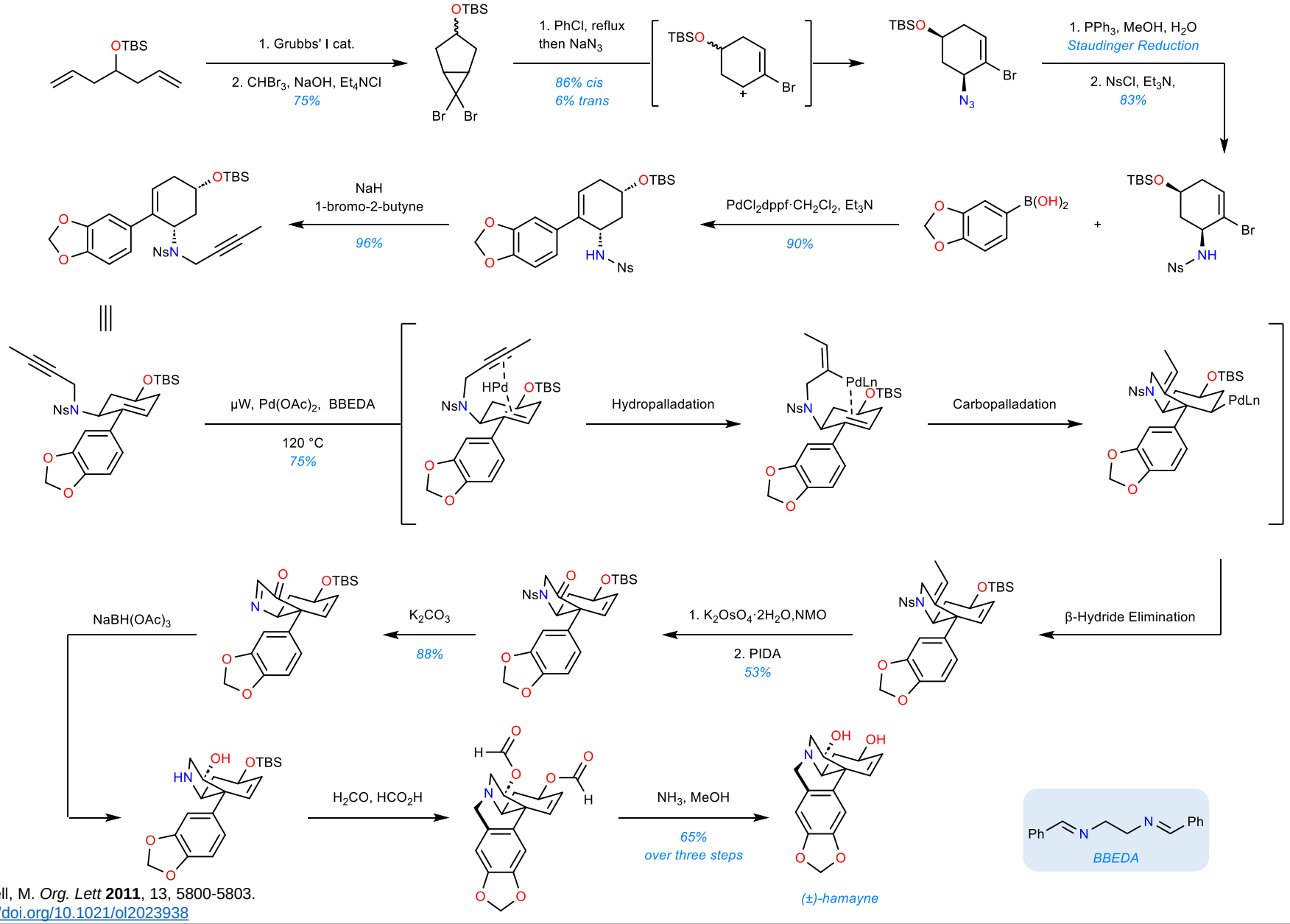
Padwa, A. *J. Org. Chem.* **2001**, 66, 3119-3128. https://doi.org/10.1021/jo010020z

(±)-Crinane Pearson (1996)



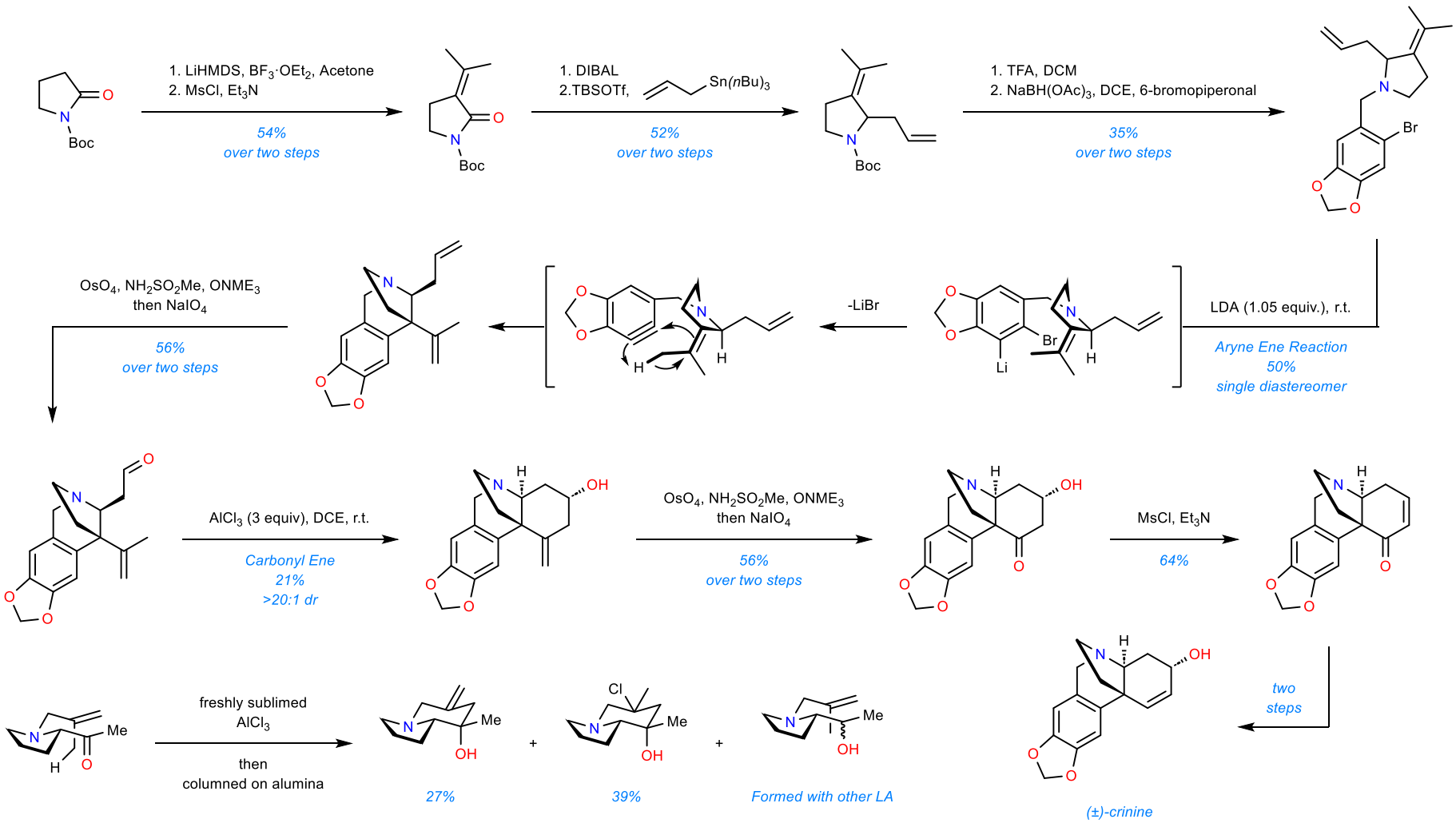
Pearson, W. *Tetrahedron* **1996**, 52, 3107-3116. https://doi.org/10.1016/0040-4020(95)01098-X

(±)-Hamayne Banwell (2011)



Banwell, M. *Org. Lett* **2011**, 13, 5800-5803.
https://doi.org/10.1021/ol2023938

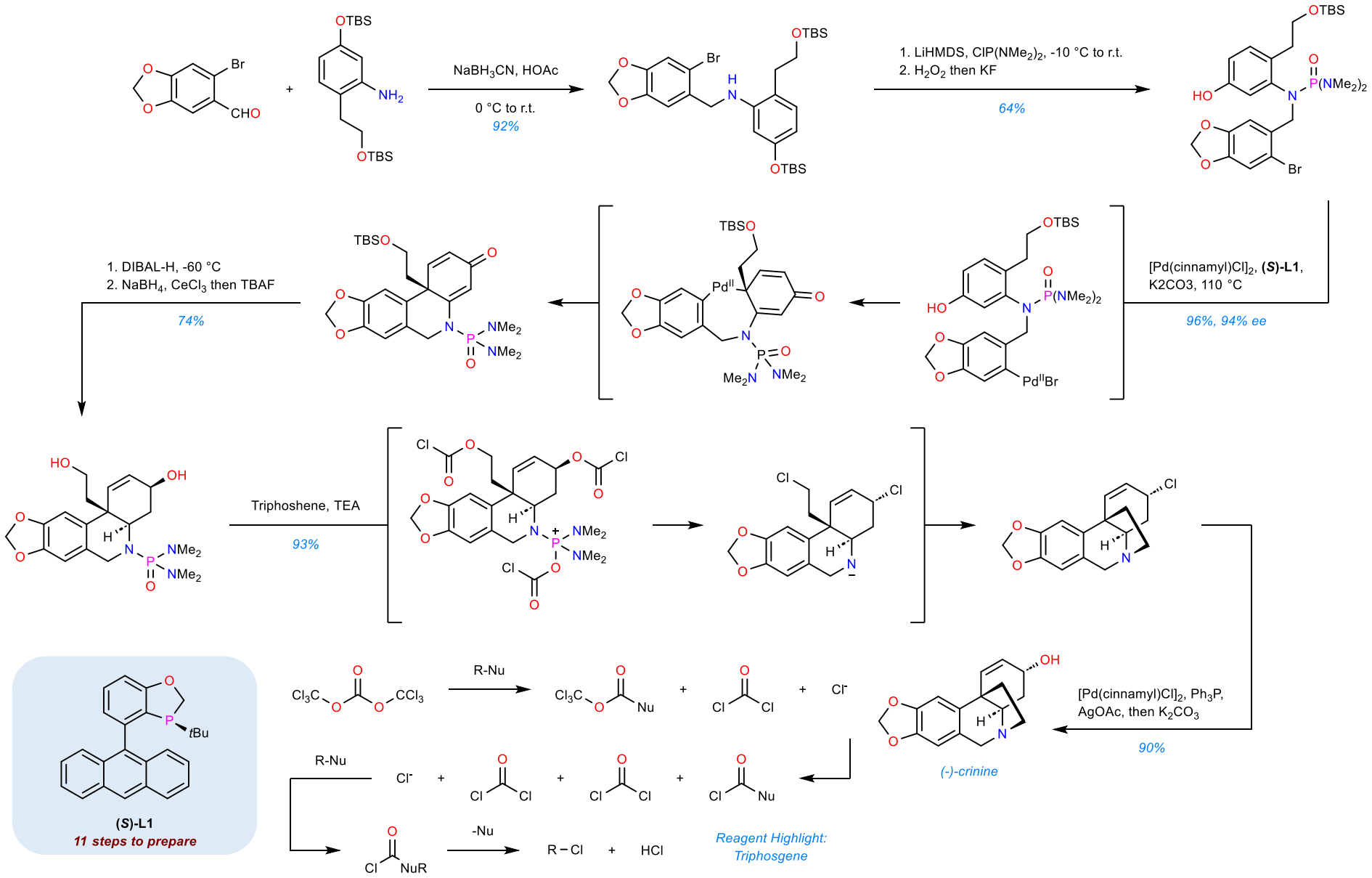
(±)-Crinine Lautens (2012)



The following carbonyl ene in the presence of a tertiary amine was found to be challenging. Several Lewis acids were screened, but only an excess of $AlCl_3$ was found to give the desired product.

Lautens, M. *J. Am. Chem. Soc.* **2012**, 134, 15572-15580. https://doi.org/10.1021/ja306881u
Overman, L. *Tetrahedron Lett.* **1985**, 26, 4167-4170. https://doi.org/10.1016/S0040-4039(00)98981-0

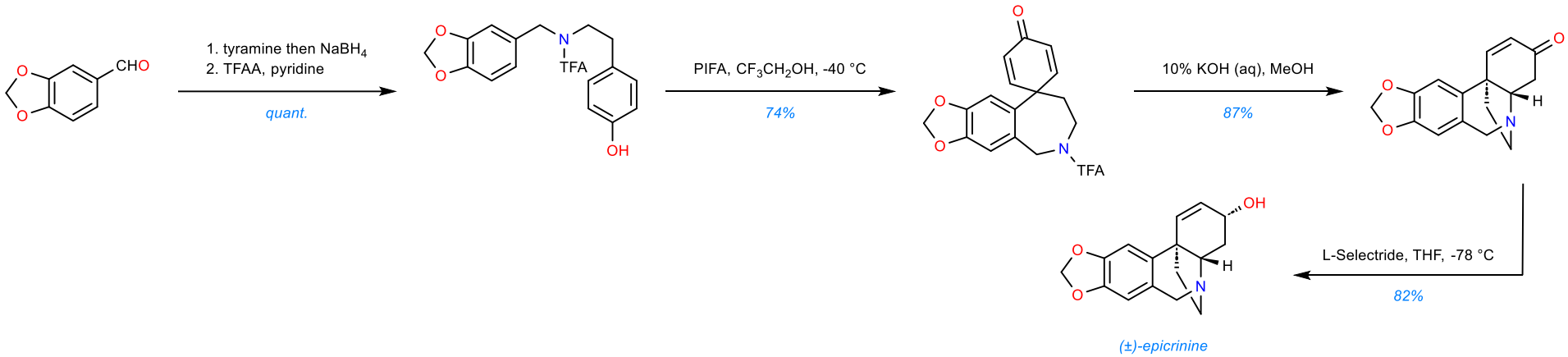
(-)-Crinine Tang (2017)



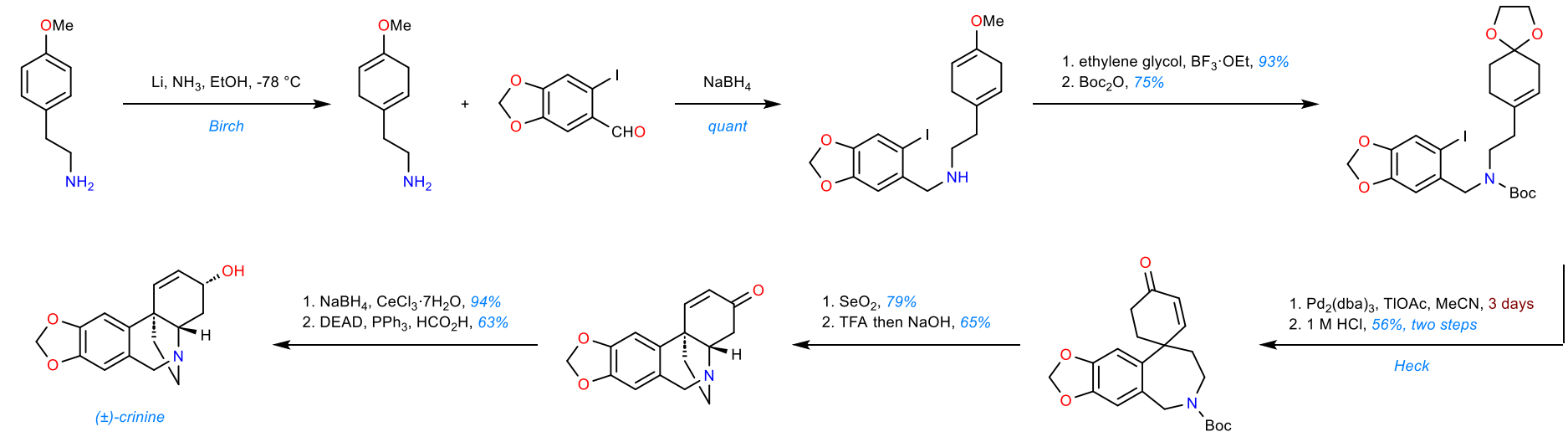
Tang, W. *Chem. Sci.* **2017**, 8, 6247-6256. https://doi.org/10.1039/C7SC01859B

Eckart, H. *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 894-859. https://doi.org/10.1002/anie.198708941

(±)-Epicrinine Node (2004) and (±)-Crinine Guillou (2006)

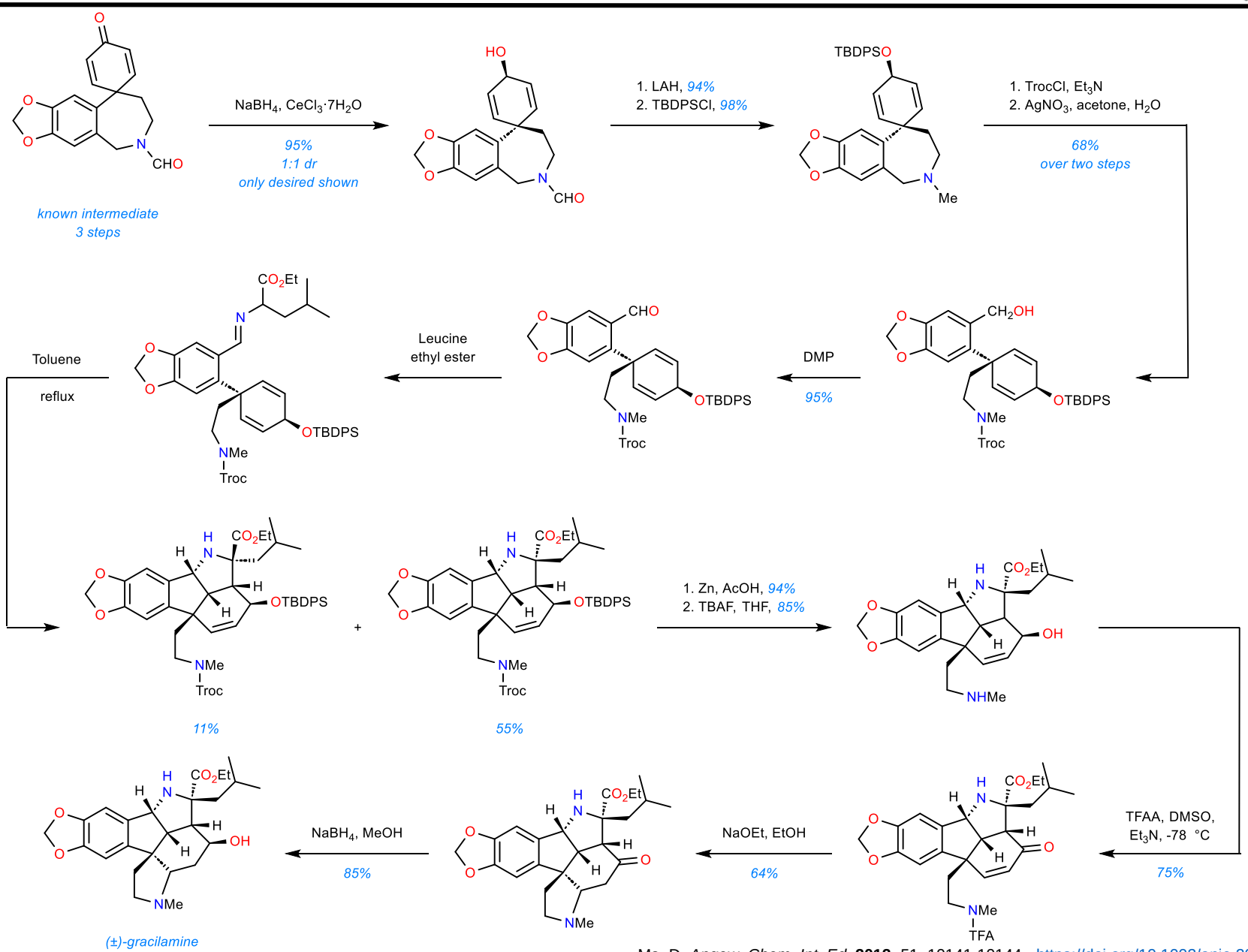


Node, M. *Tetrahedron* **2004**, 22, 4901-4907. https://doi.org/10.1016/j.tet.2004.03.087



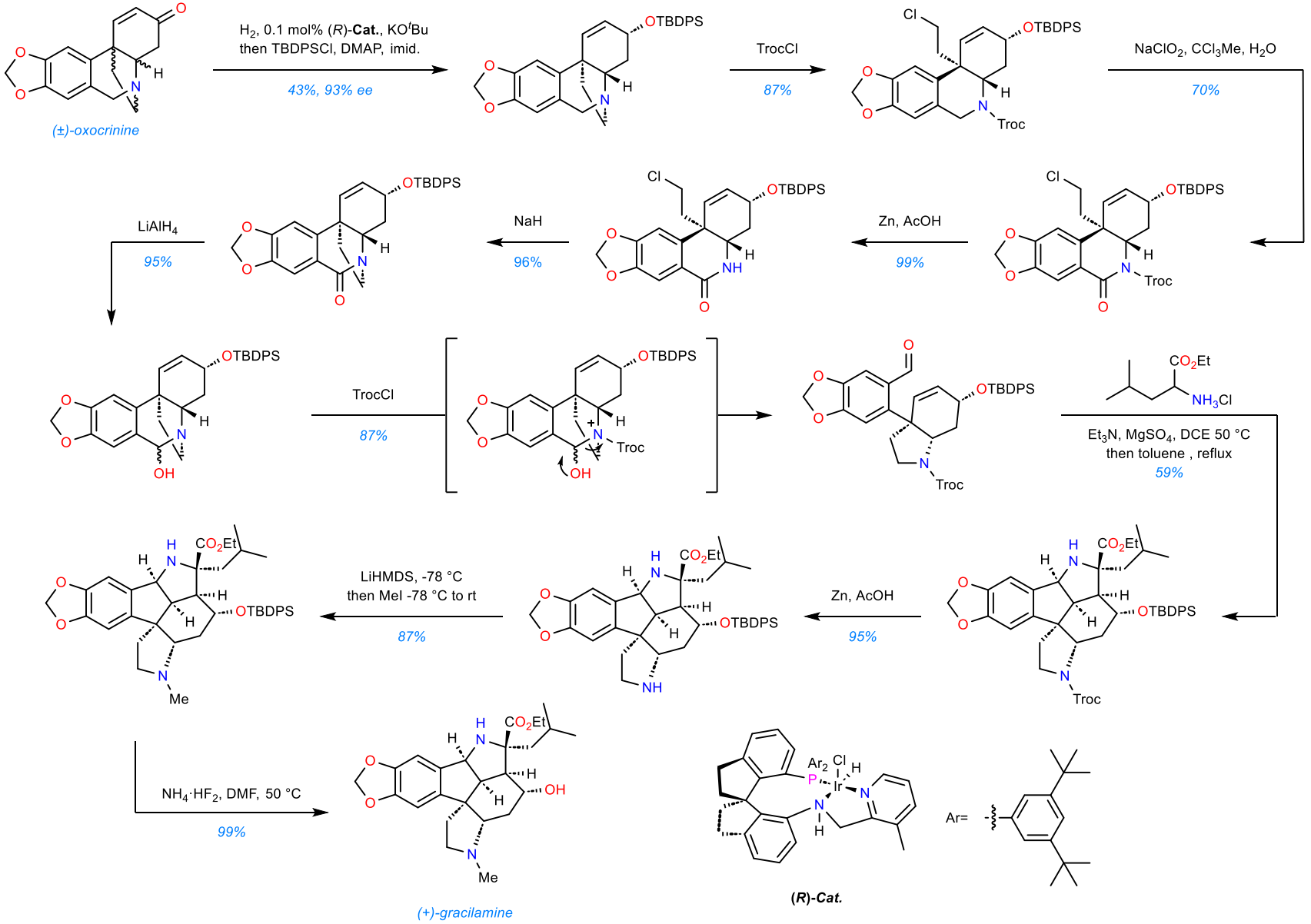
Guillou, C. *Tetrahedron* **2006**, 38, 9043-9048. https://doi.org/10.1016/j.tet.2006.07.005

(±)-Gracilamine Ma (2012)



Ma, D. *Angew. Chem. Int. Ed.* **2012**, 51, 10141-10144 https://doi.org/10.1002/anie.201205711

(+)-Gracilamine Xie (2017)



Xie, J. *Org. Lett* **2017**, 19, 5240-5243 https://doi.org/10.1021/acs.orglett.7b02517