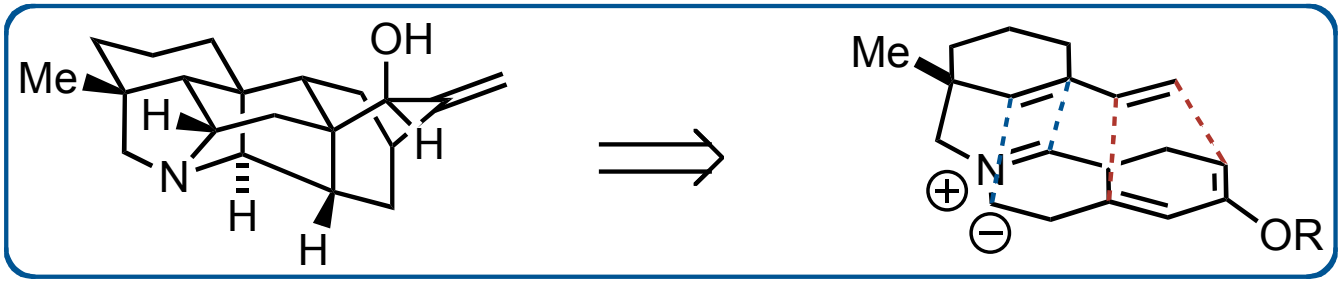
Asymmetric Synthetic Access to the Hetisine Alkaloids:Total Synthesis of (+)-Nominine



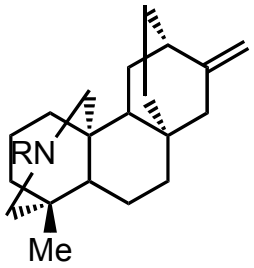
Kevin M. Peese and David Y. Gin

Chem. Eur. J. **2008**, *14*, 1654 - 1665
J. Am. Chem. Soc. **2006**, *128*, 8734

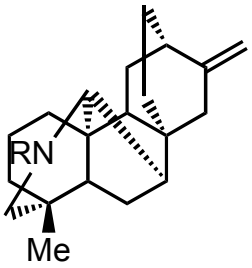
C20 - Diterpenoid Alkaloids

C_{20} - diterpenoids

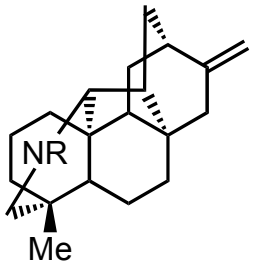
atisane class



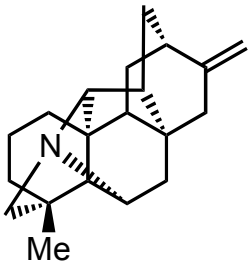
atisine type



danudatine type

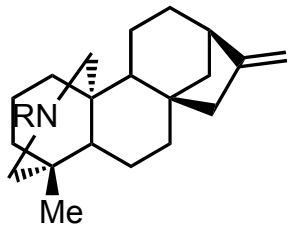


hetidine type

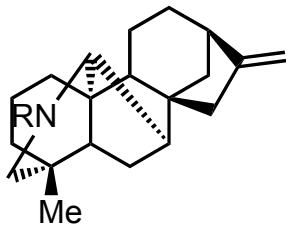


hetisine type

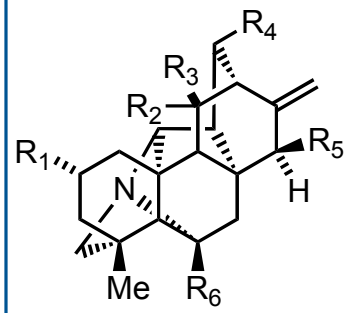
kaurane class



veatchine type



napelline type



Nominine
R_1, R_2, R_3, R_4, R_6 = H, R_5 =OH

Kobusine
R_1, R_2, R_4, R_6 = H, R_3, R_5 = OH

Pseudokobusine
R_1, R_2, R_4 = H, R_3, R_5, R_6 = OH

Hetisine
R_3, R_5, R_6 = H, R_1, R_2, R_4 = OH

Wang, Liang *The Alkaloids* **2002**, *59*, 1

Hetisine Alkaloids

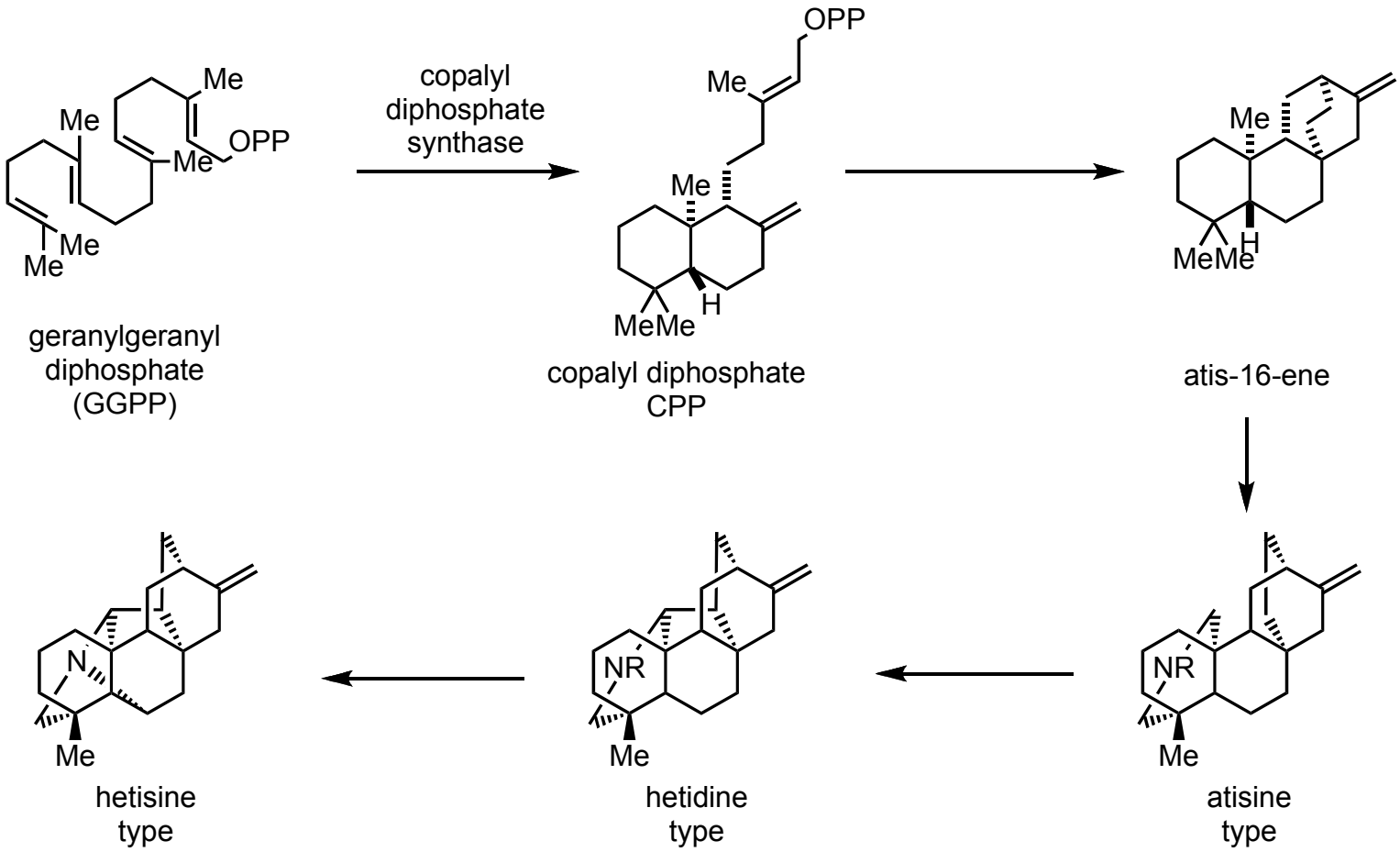
- A subclass of C_{20}-diterpenoid alkaloids consisting of >100 members.

- Isolated predominantly from *Aconitum* and *Delphinium* genera, but also *Rumex*, *Consolidia*, and *Spirea*.

- Pharmacological Activity:
  - vasodialating
  - antiarrhythmic
  - immunomodulatory
  - analgesic

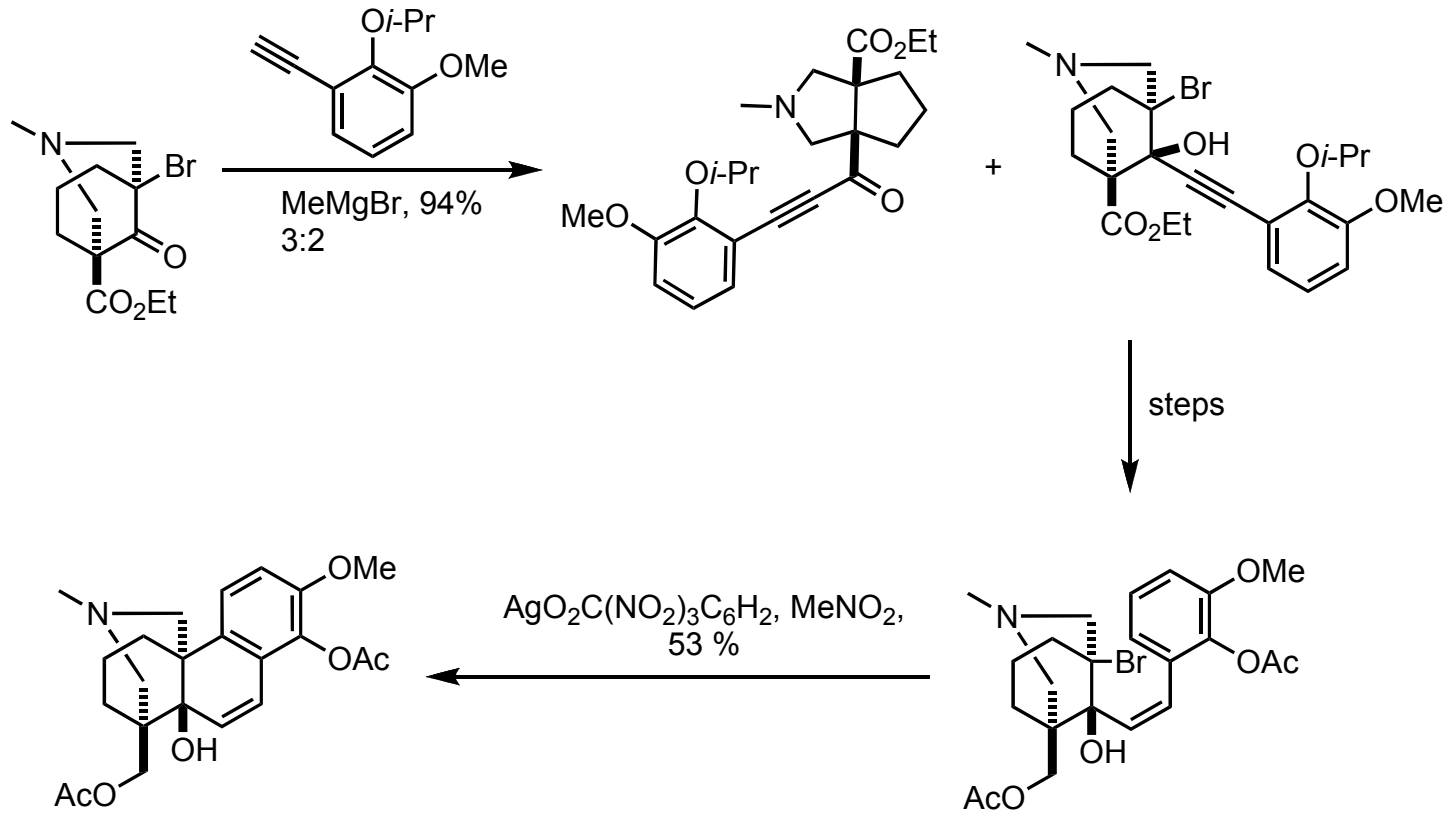
Wang, Liang *The Alkaloids* **2002**, *59*, 1

Proposed Biosynthesis of Hetisine Alkaloids



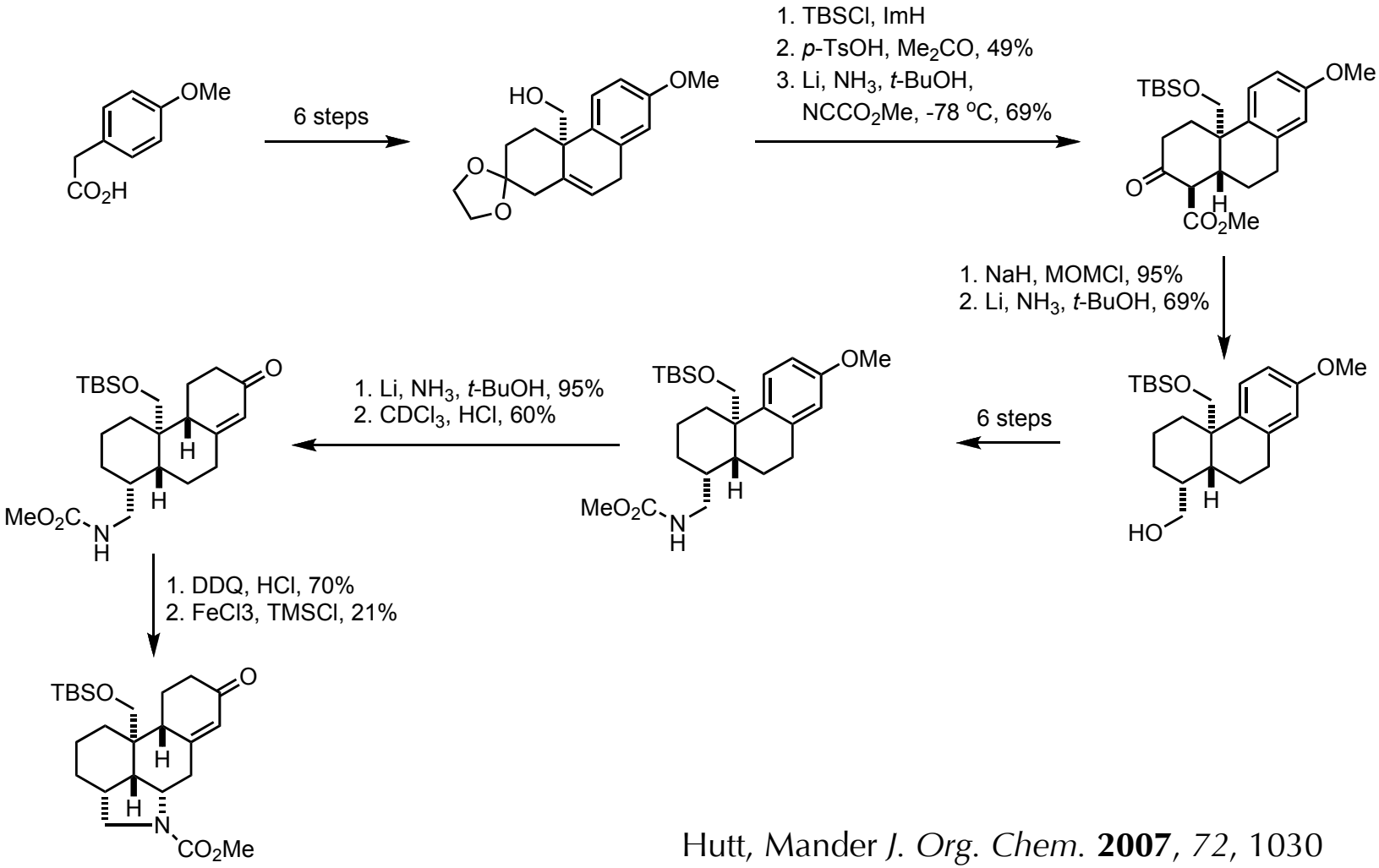
Wang, Liang *The Alkaloids* **2002**, *59*, 1

Studies towards the Total Synthesis of Hetisine Alkaloids



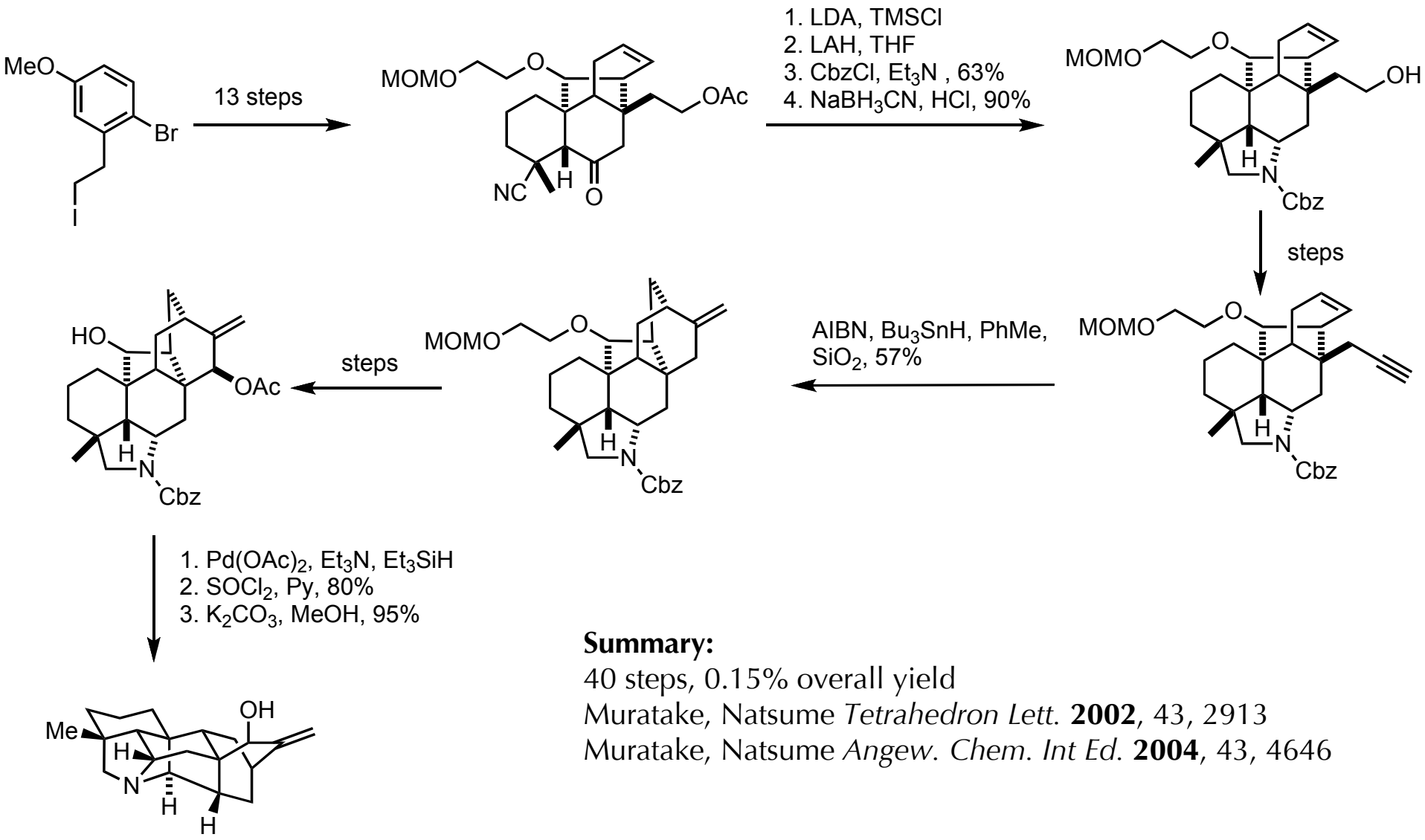
Williams, Mander *Org. Lett.* **2003**, *5*, 3499
Williams, Mander, Bernhardt, Willis
Tetrahedron **2005**, *61*, 3759

Studies towards the Total Synthesis of Hetisine Alkaloids



Hutt, Mander *J. Org. Chem.* **2007**, *72*, 1030

Total Synthesis of (±)-Nominine



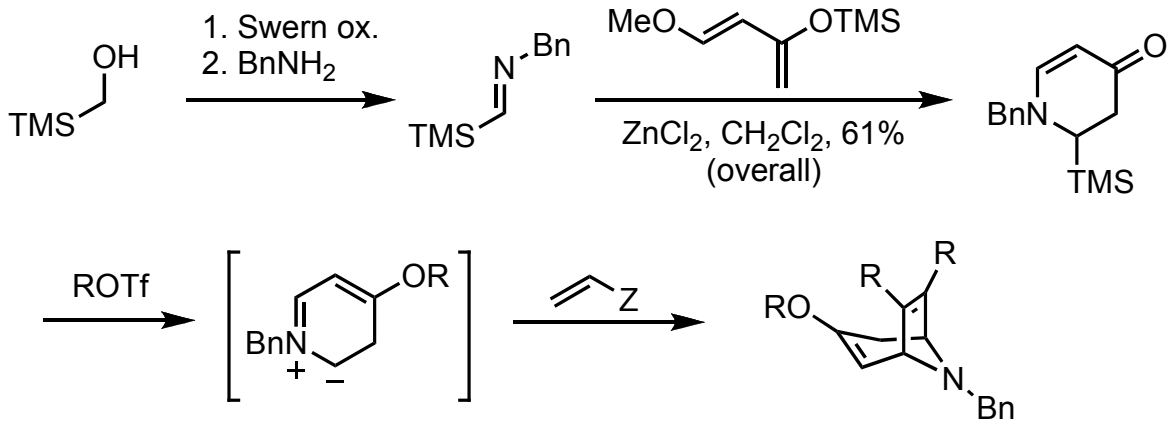
Summary:

40 steps, 0.15% overall yield

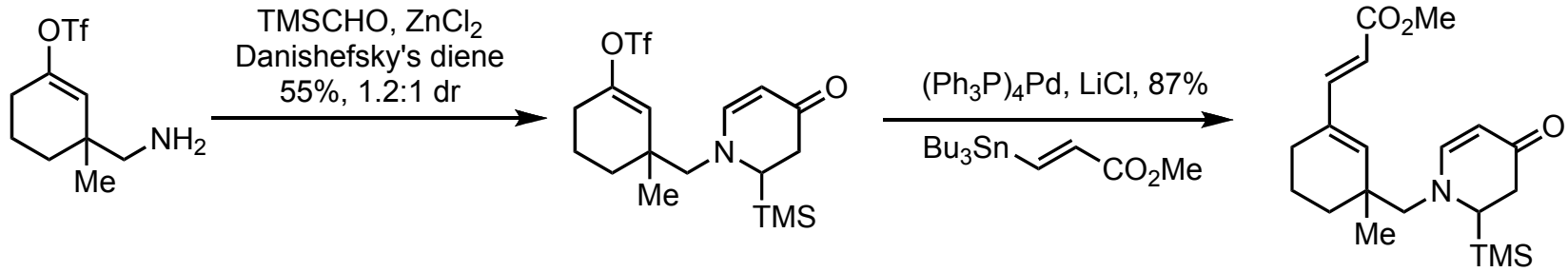
Muratake, Natsume *Tetrahedron Lett.* **2002**, 43, 2913

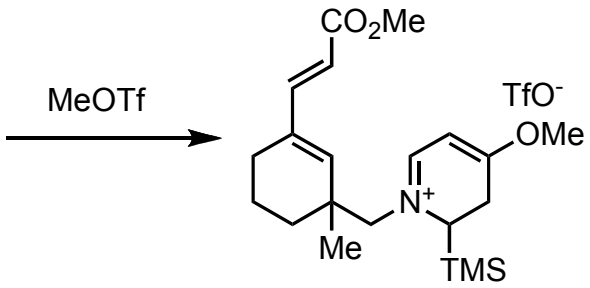
Muratake, Natsume *Angew. Chem. Int Ed.* **2004**, 43, 4646

Model Studies



R = H, CO_2Me, SO_2Ph
Yields: 20-43 %



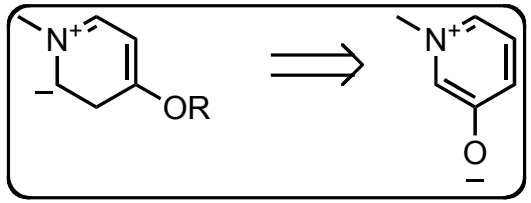


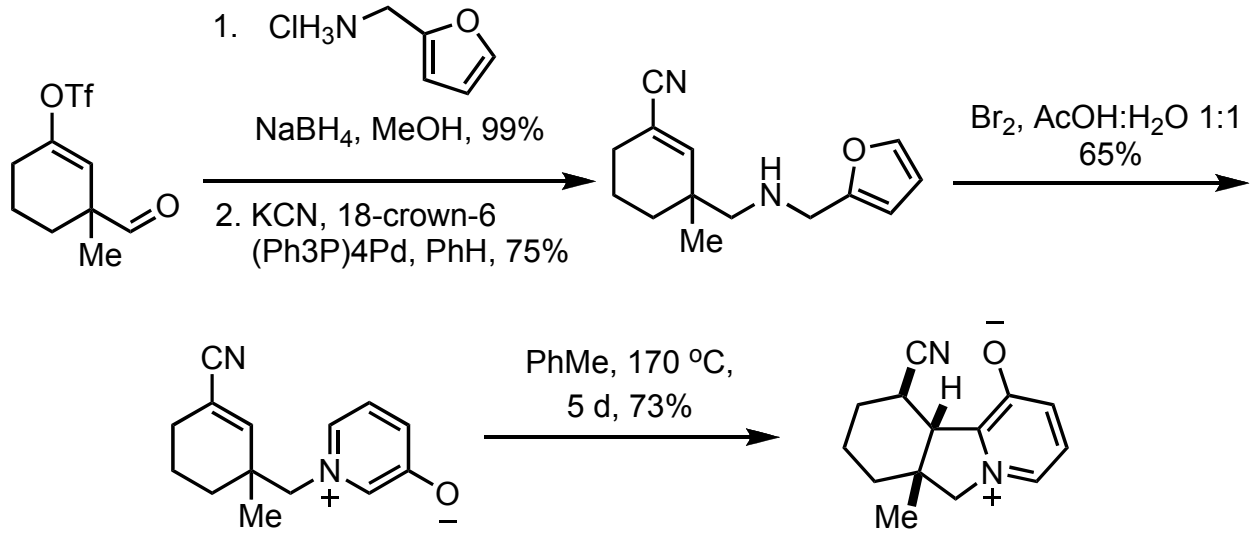
- stable and unreactive towards *intra*molecular cycloaddition

- underwent *inter*molecular addition with DMAD

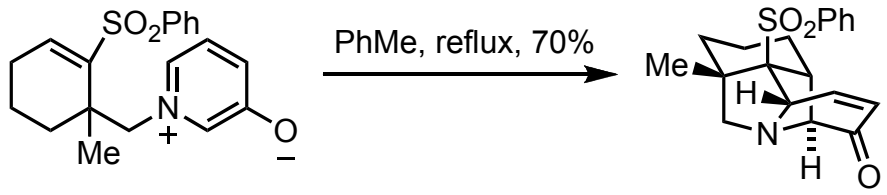
Model Studies - 3-Oxidopyridinium Betains

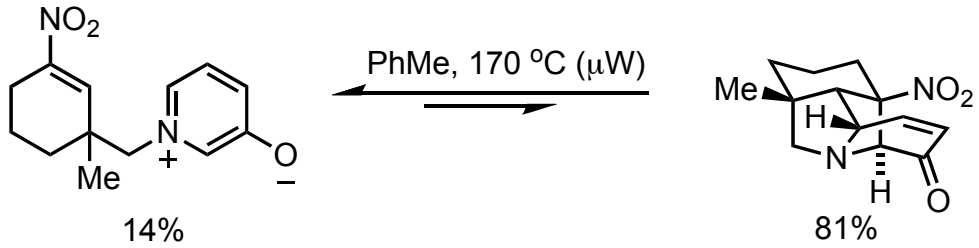
3-Oxidopyridinium betains, introduced by Katritzky, are stable and isolable 1,3-dipoles undergoing cycloaddition reactions at positions 2 and 6.

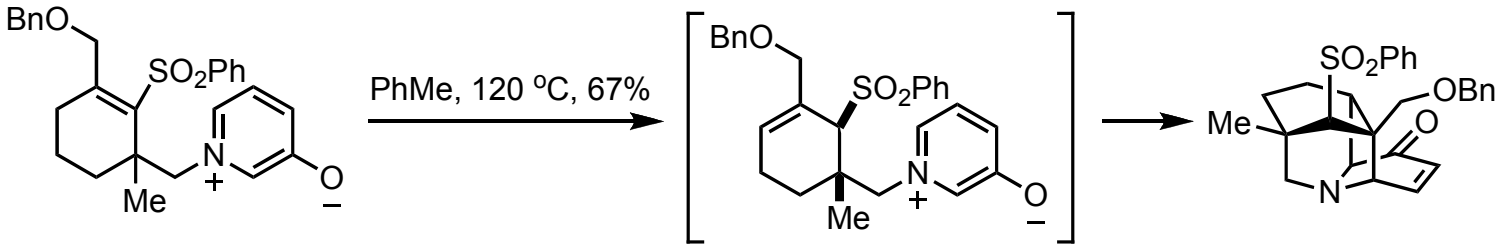




Model Studies - 3-Oxidopyridinium Betains

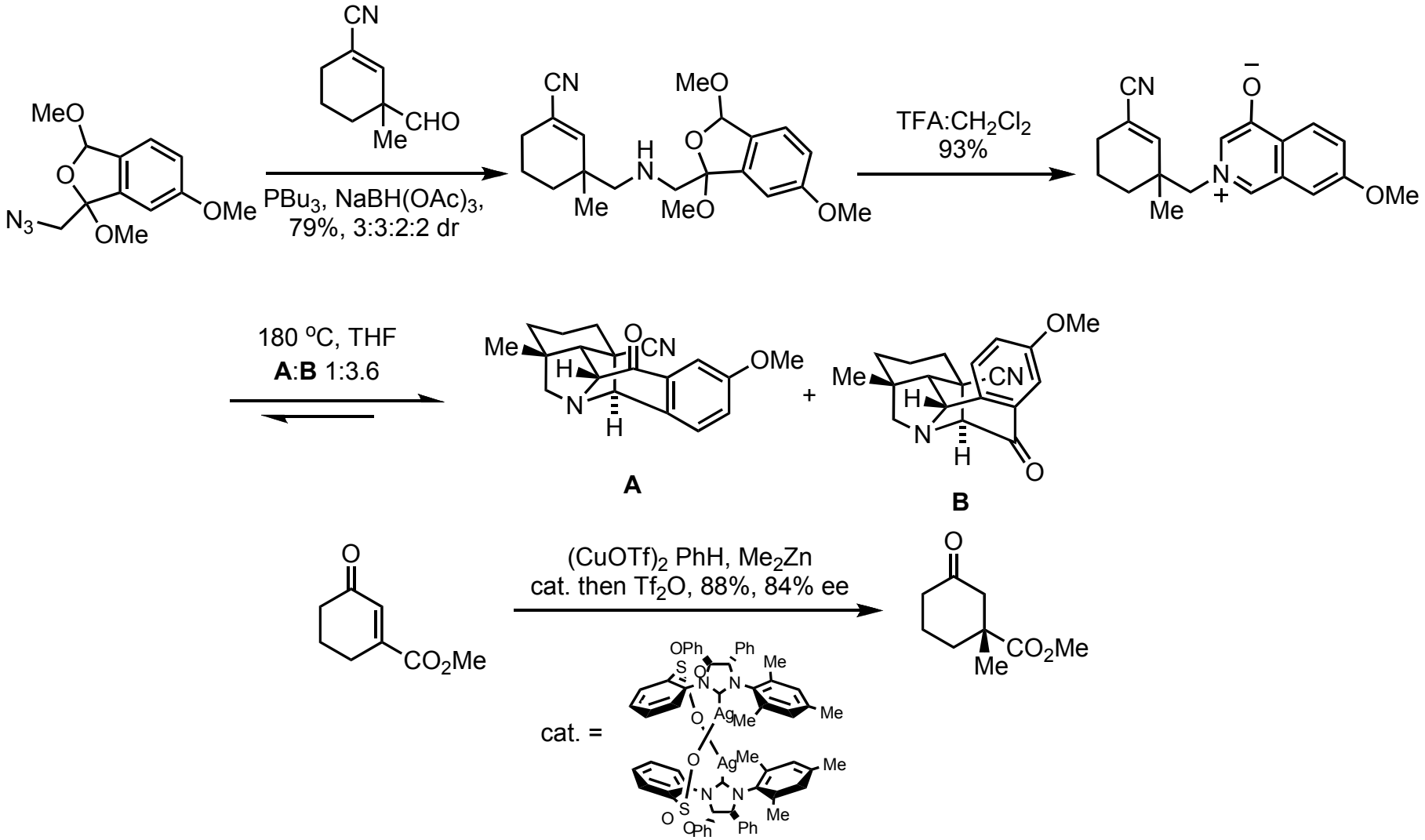






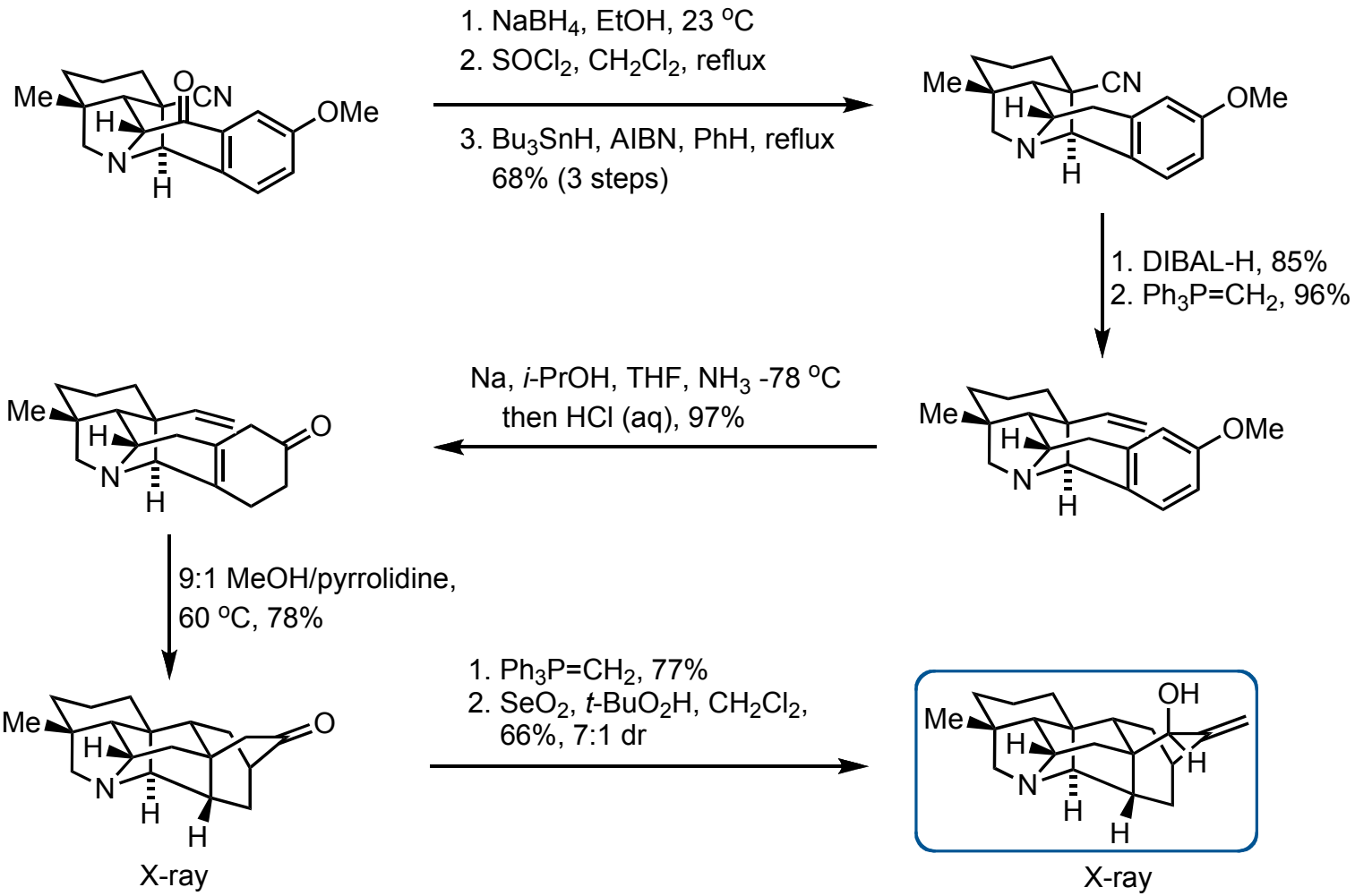
Intramolecular Cycloaddition

Due to lower Resonance Stabilization Energies (RSEs), 3-oxoisoquinolines are ideal partners for the cycloadditions reactions. Ground-state destabilization of the substrate may facilitate formation of the desired pentacycle.



Completion of Synthesis

Completion of the synthesis involved adjustment of the oxidation state followed by Diels-Alder cyclization. Notably, the non-conjugate enone proved to be more stable thermodynamic isomer.



Summary

- Gin and Peese completed a total synthesis of (±)-nominine in 15 steps (longest linear sequence) and 6.1 % overall yield.
- Introduction of a chiral center via asymmetric conjugate addition allowed for completion of a synthesis of (+)-nominime in 16 steps and 1.3% overall yield.
- Convergent construction of the polycyclic core relied on a series of cycloadditon (3+2 and 4+2) reactions demonstrating power of a well-planned synthesis.