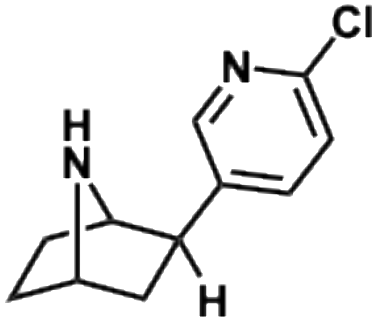
Total Synthesis of Epibatidine



Krishna P Kaliappan

Professor of Chemistry, IIT Bombay

Epibatidine

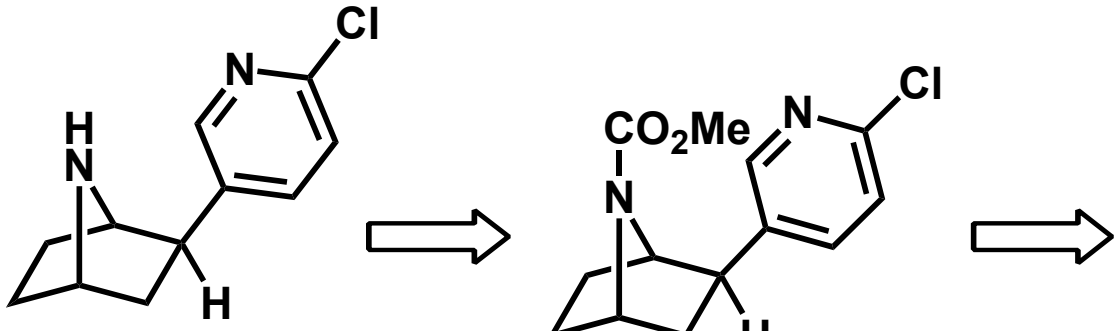


(±)-Epibatidine

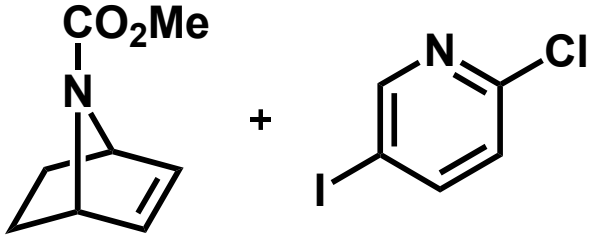
- Epibatidine is an alkaloid which was isolated from the Ecuadoran poison frog *Epipedobates tricolor*
- Its structure is unusual among alkaloids in containing a chloropyridine, and it appears to be unique in possessing the 7-azabicyclo[2.2.1]heptane ring system
- It shows analgesic activity at 1/200th dose of morphine

Daly, J.W., co-workers. *J. Am. Chem. Soc.*, **1992**, *114*, 3475-3478

Regan's Retrosynthesis of Epibatidine

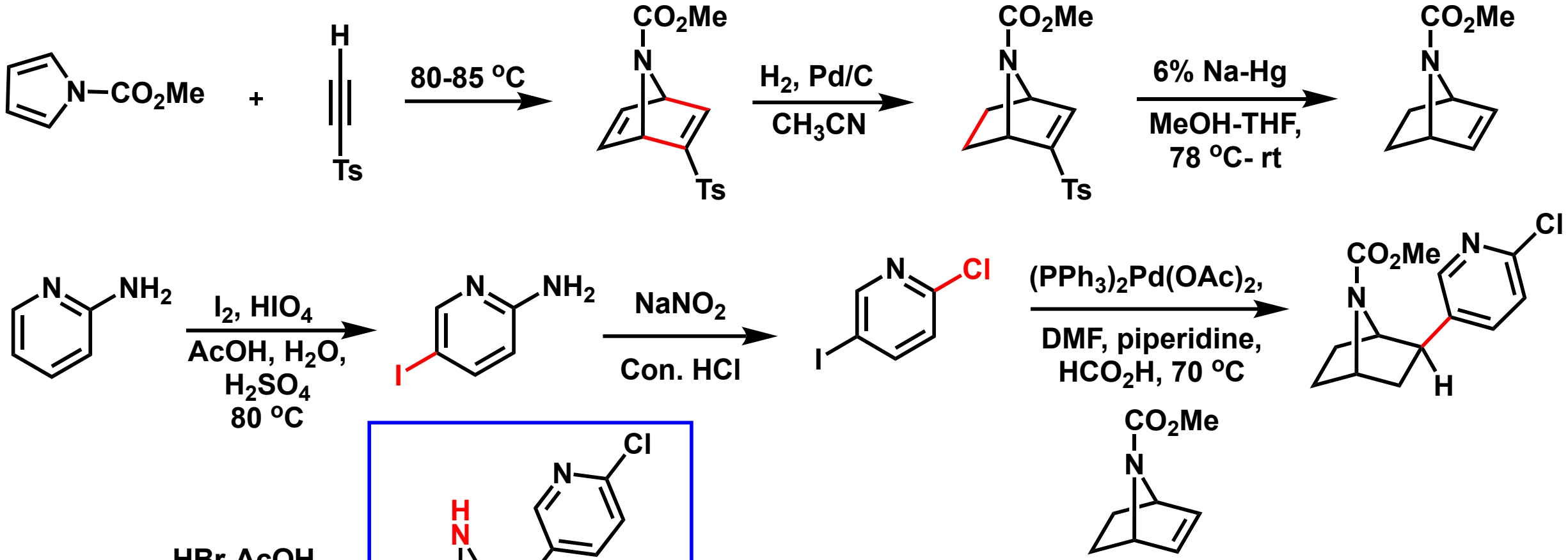


(±)-Epibatidine



- A concise, highly convergent total synthesis of epibatidine was reported by Regan and co-workers in 1993, using a reductive palladium-catalysed Heck-type coupling as the key step

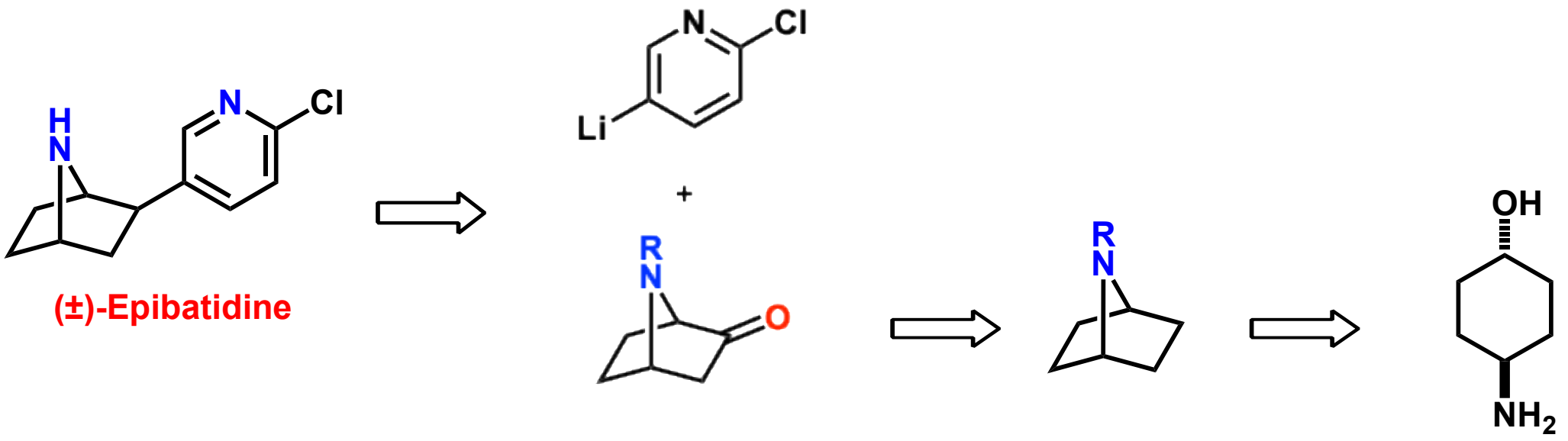
Regan's Total Synthesis of Epibatidine



Regan, A.C. and co-workers. *Tetrahedron Lett.* **1993**, *34*, 7493-7496

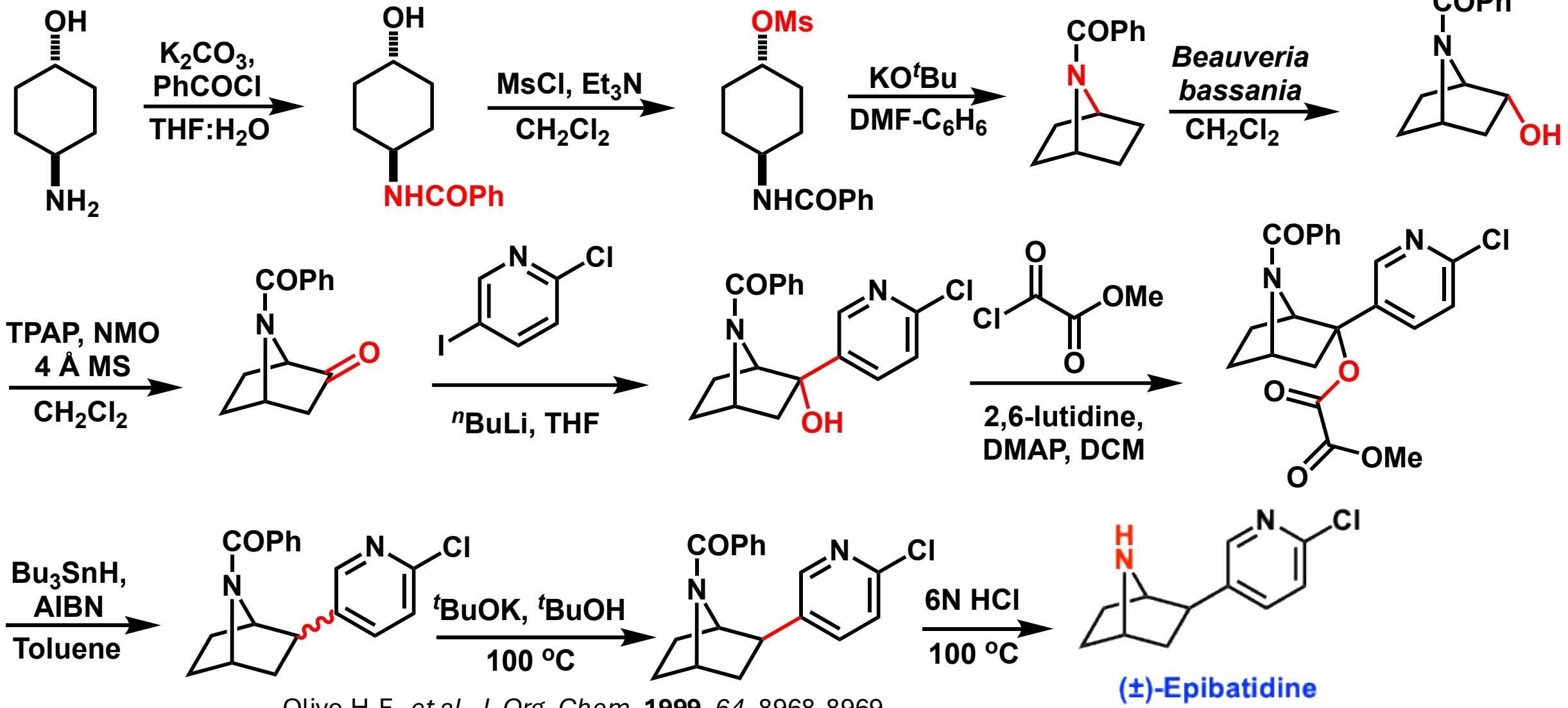
Olivo's Total Synthesis of Epibatidine

- Total synthesis of (±)-epibatidine using a biocatalytic approach was reported by Olivo *et al* in 1999
- This work demonstrates how preparative biotransformations can be successfully blended with modern synthetic organic chemistry to prepare a molecule of great biological interest



Olivo,H.F., *et al*. *J. Org. Chem*. **1999**, *64*, 8968-8969

Olivo's Total Synthesis of Epibatidine

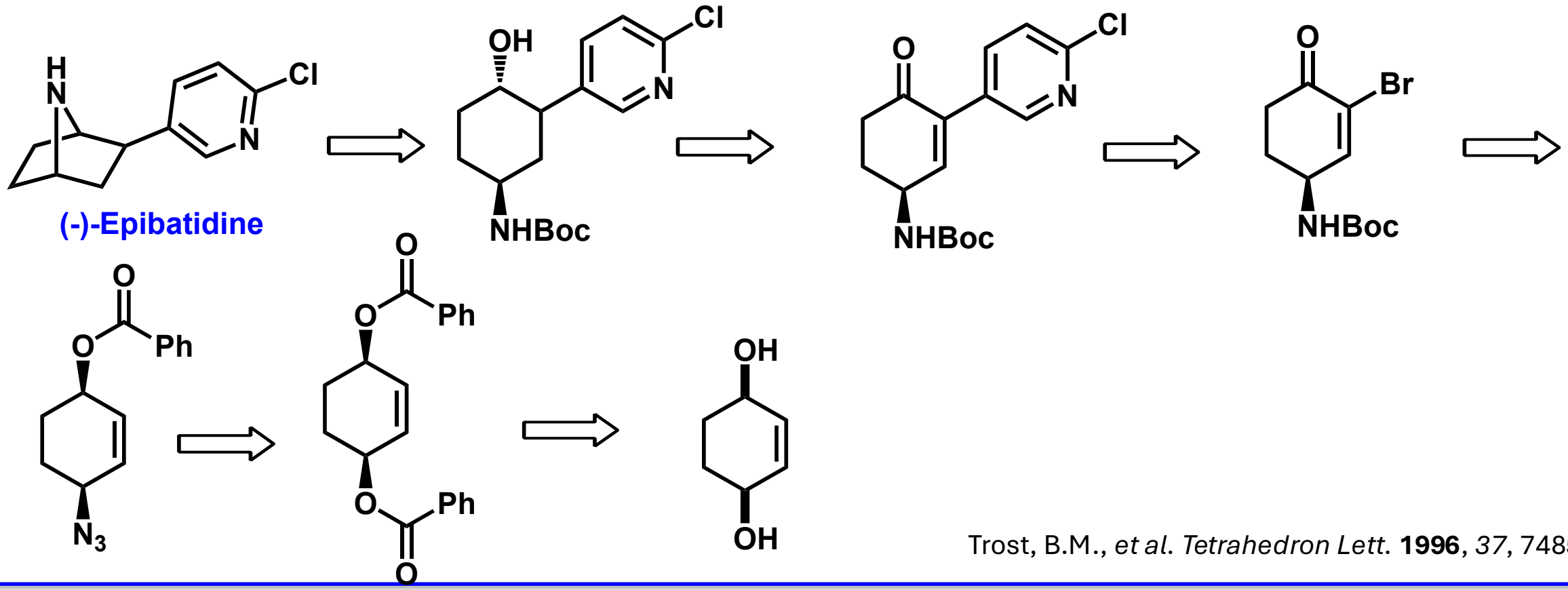


Olivo,H.F., *et al. J. Org. Chem.* **1999**, *64*, 8968-8969

Asymmetric Synthesis of Epibatidine

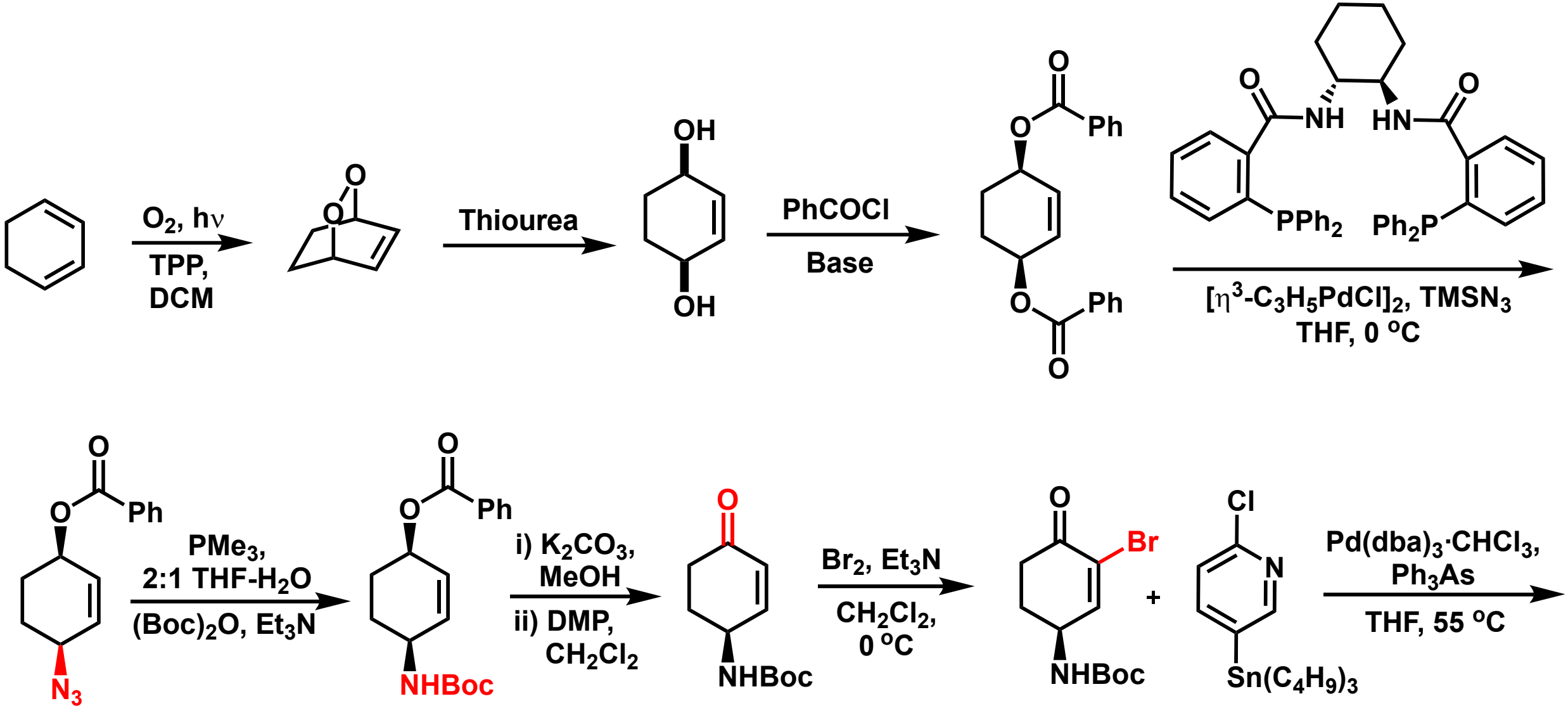
- Trost *et al.* reported the first asymmetric total synthesis of (-)-epibatidine in 1996

- A Pd-catalyzed desymmetrization of cis-3,6-dibenzoyloxy-2-cyclohexene and a Pd-catalyzed crosscoupling constitute key reactions in this synthesis

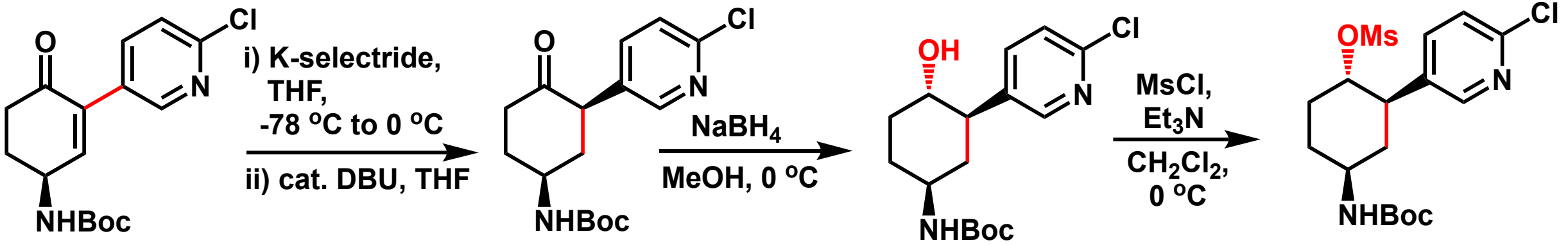


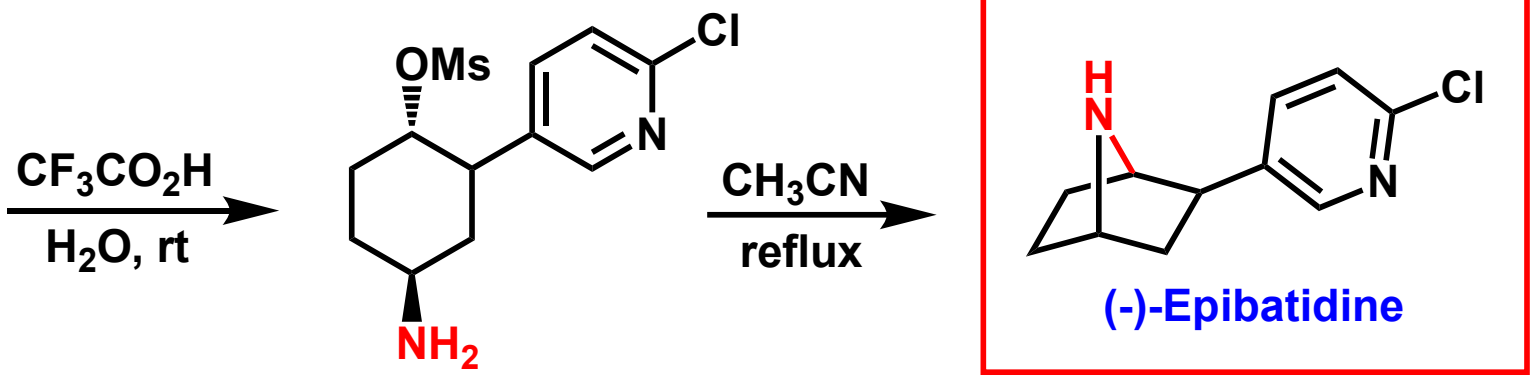
Trost, B.M., *et al. Tetrahedron Lett.* **1996**, *37*, 7485-7488

Trost's Asymmetric Synthesis of Epibatidine



Trost's Asymmetric Synthesis of Epibatidine





- Trost *et al.* reported the first asymmetric total synthesis of (-)-epibatidine in 1996
- A Pd-catalyzed desymmetrization of cis-3,6-dibenzoyloxy-2-cyclohexene and a Pd-catalyzed crosscoupling constitute key reactions in this synthesis
- The reaction was commenced from dibenzoate and the total synthesis was accomplished in 10 steps with an overall yield of 13.36%

Trost, B.M., *et al. Tetrahedron Lett.* **1996**, *37*, 7485-7488