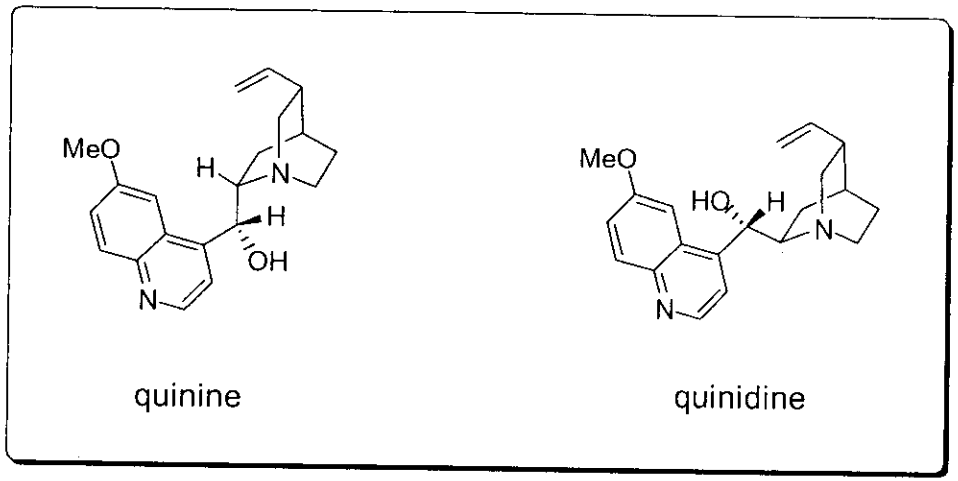
Catalytic Asymmetric Total Syntheses of Quinine and Quinidine

Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N.

J. Am. Chem. Soc. ASAP



Quinine Timeline

1853 - Pasteur conducts degradation experiments on cinchona alkaloids

1856 - Perkin helps settle the debate over the emperical formula of quinine ($C_{20}H_{24}N_2O_2$)

1908 - Rabe proposes the correct structure of quinine

1944 - Woodward and Doering publish the first total synthesis of quinine

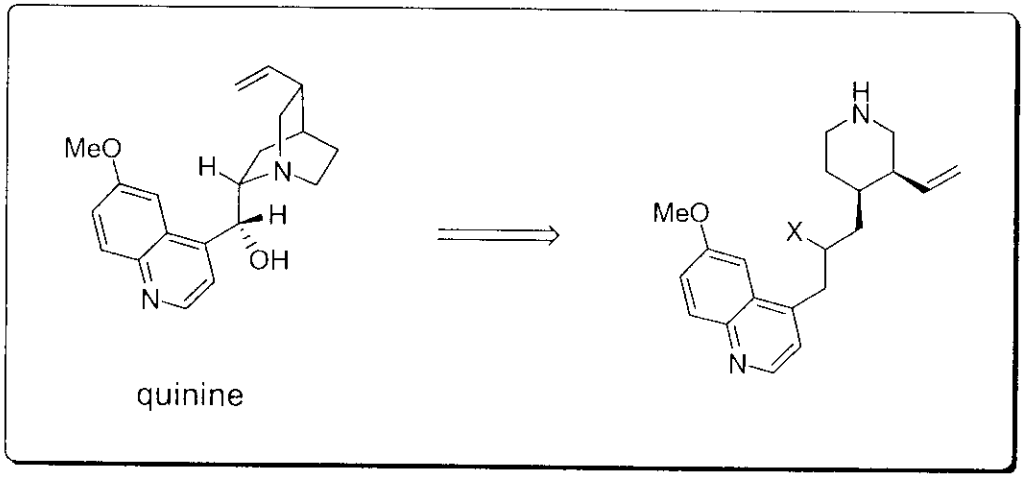
1946 - Stork begins studies toward a stereoselective quinine synthesis

1970 - Uskokovic (Hoffmann-LaRoche) reports several different syntheses of quinine in which 3 of the 4 asymmetric centers were established stereoselectively

2001 - Stork reports the first stereoselctive total synthesis of quinine

2003 - Jacobsen reports the first catalytic asymmetric total synthesis of quinine

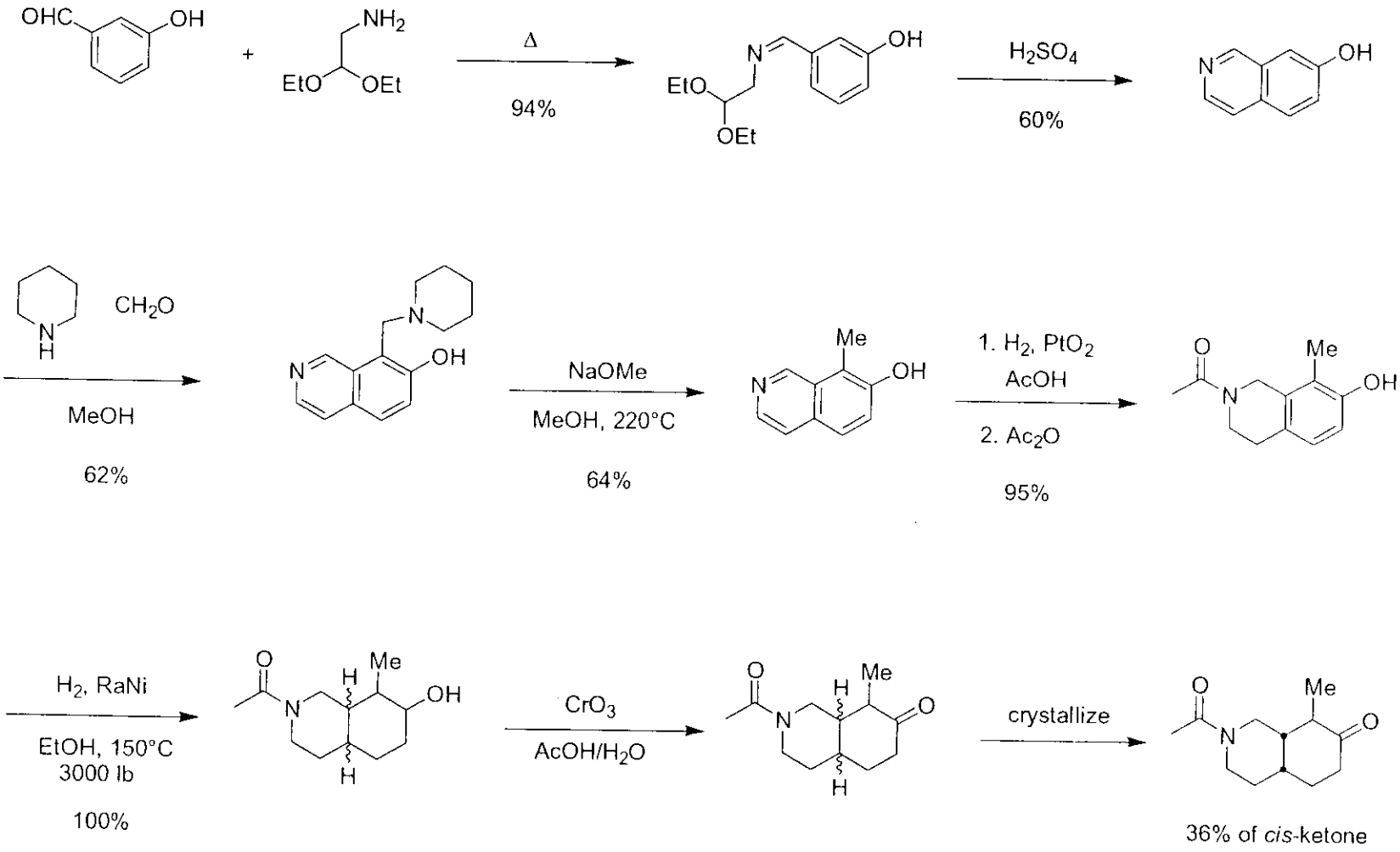
Malaria caused over 1 million deaths in 1999 (World Health Organization report 2000)



Woodward/Doering (**1944**) and Jacobsen (**2003**) had same general disconnection

How do these syntheses compare?

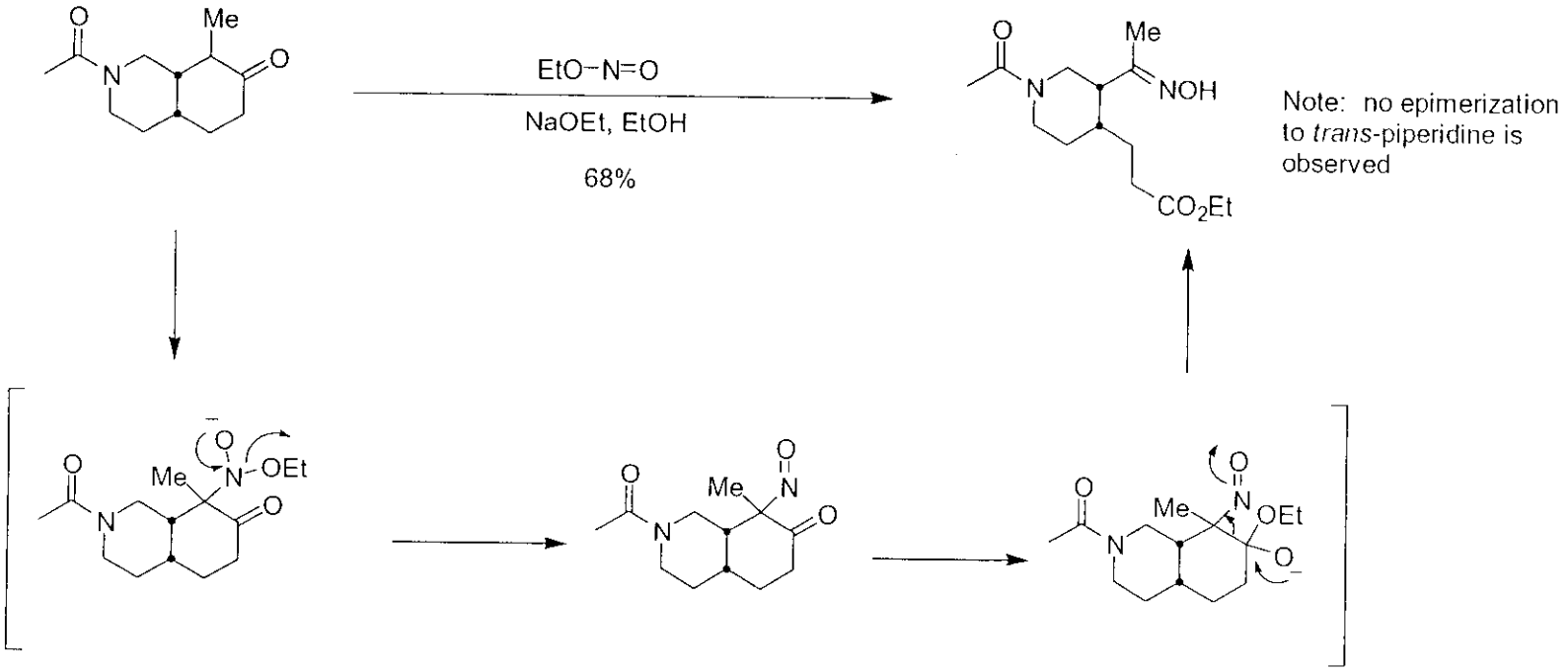
Woodward/Doering Approach



Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1944**, *66*, 849.

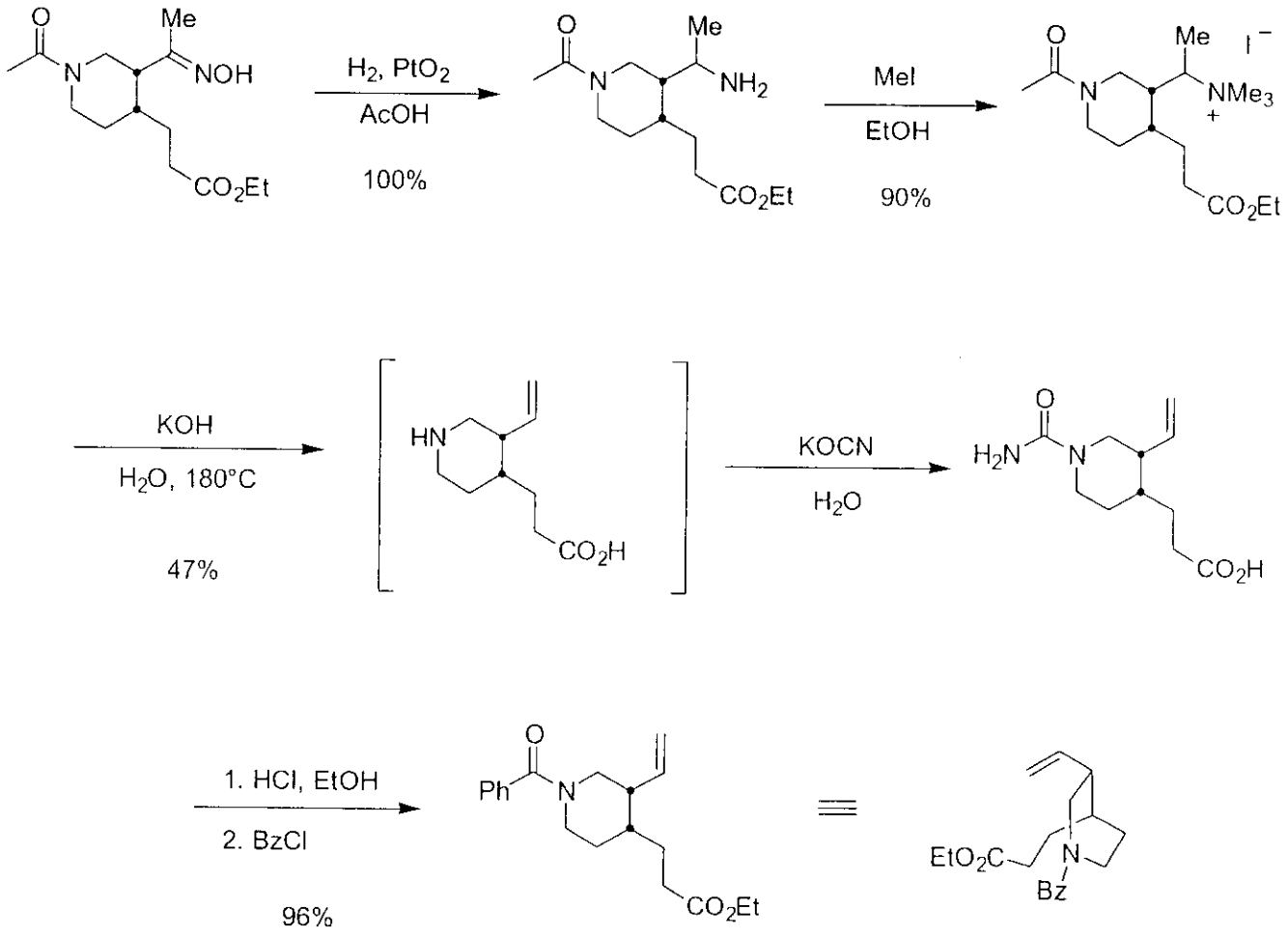
Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 860.

Woodward/Doering Approach

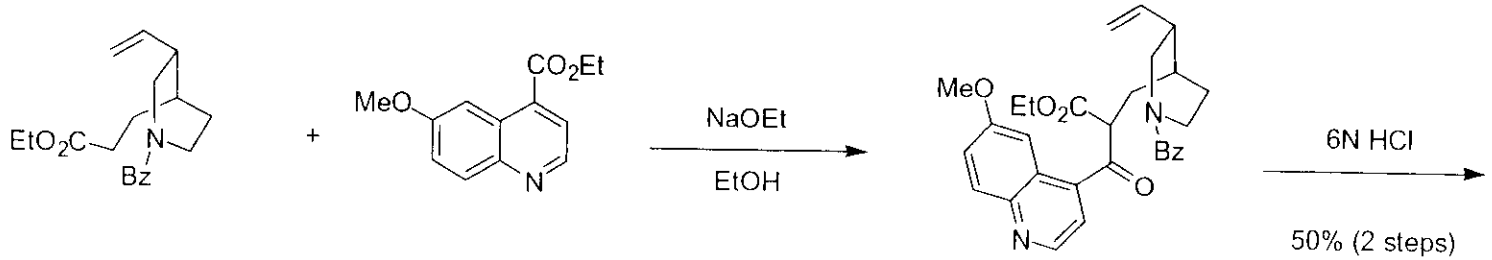


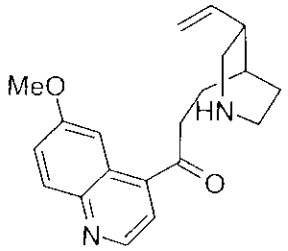
Note: no epimerization to *trans*-piperidine is observed

Woodward/Doering Approach



Woodward/Doering Approach

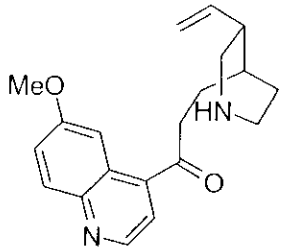




dl-quinotoxine

dibenzoyl-*d*-tartrate

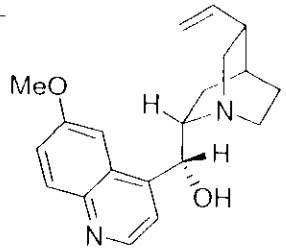
crystallize



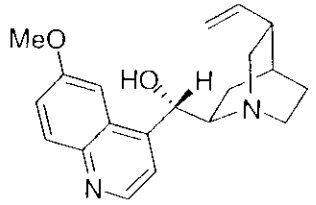
d-quinotoxine

15 steps
5% yield

1. NaOBr
2. NaOEt
3. Al powder
EtOH

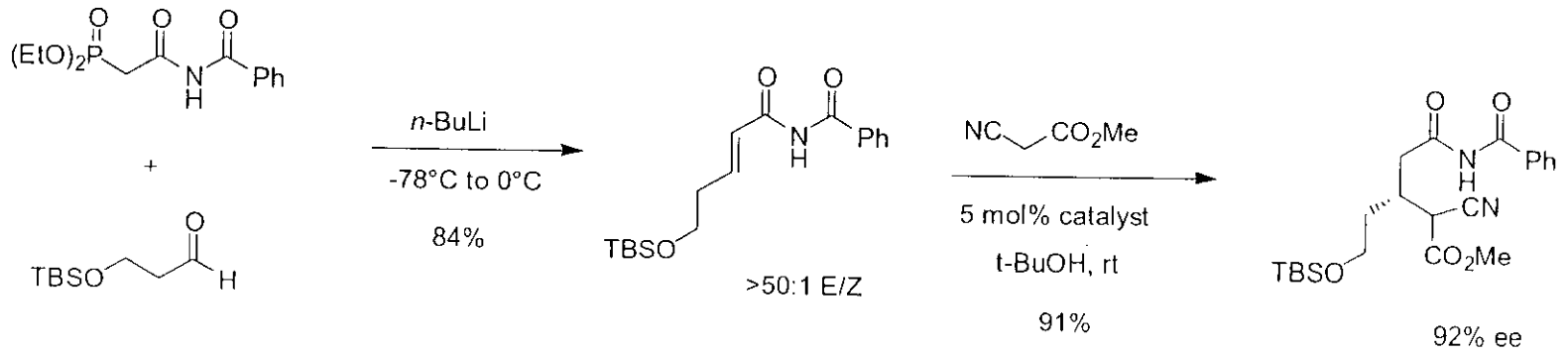


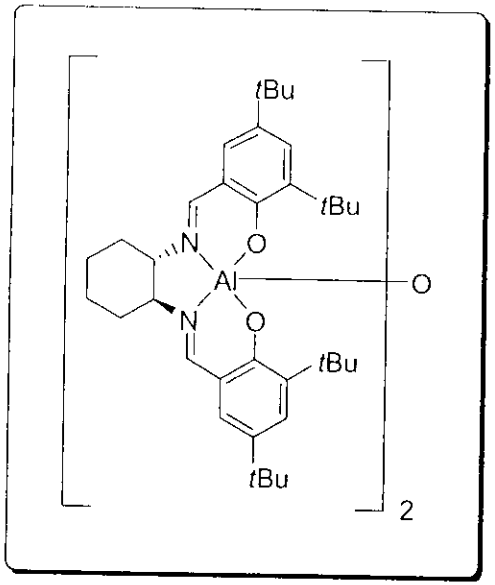
quinine

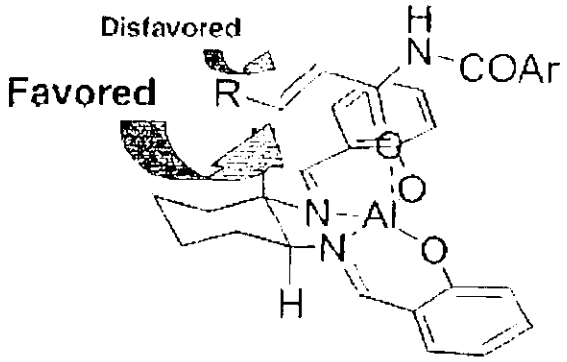


quinidine

Jacobsen Approach

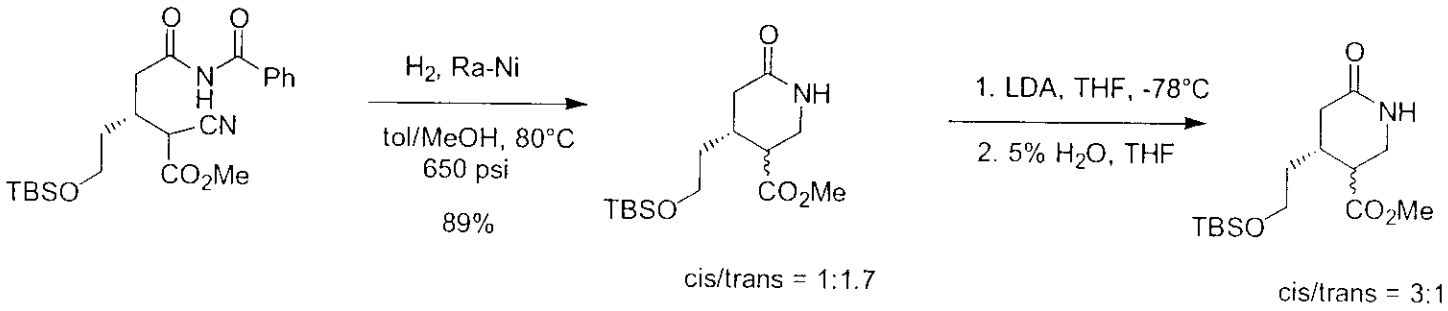


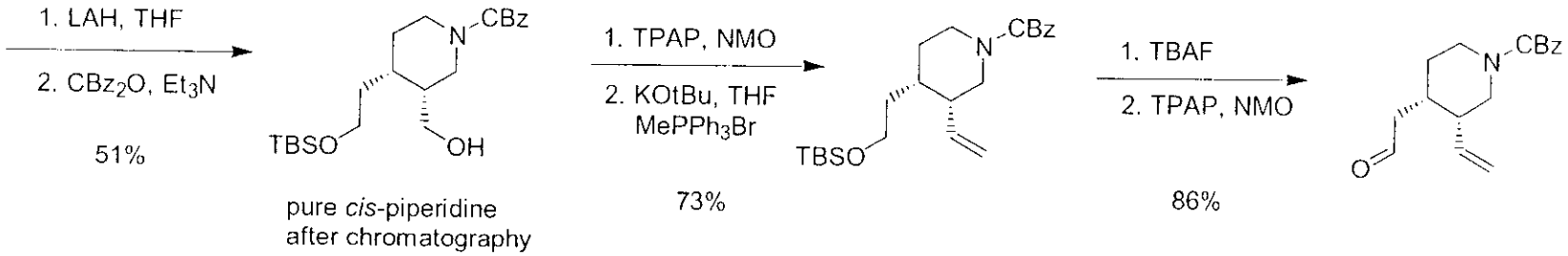




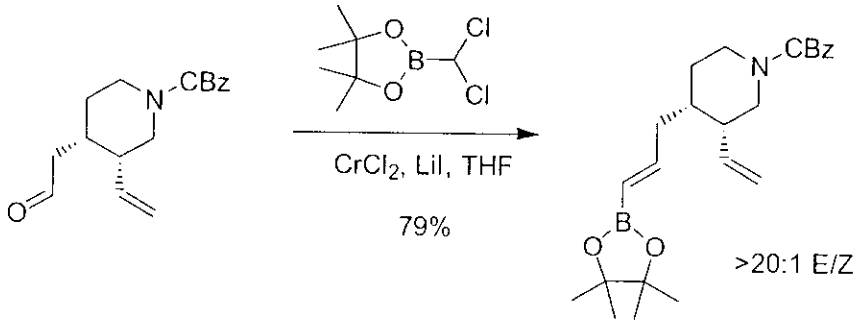
Steve Lynch @ Wipf Group Taylor, M. S.; Jacobsen, E. N. *J8Am. Chem. Soc.* **2003**, *125*, 11204. 1/10/04

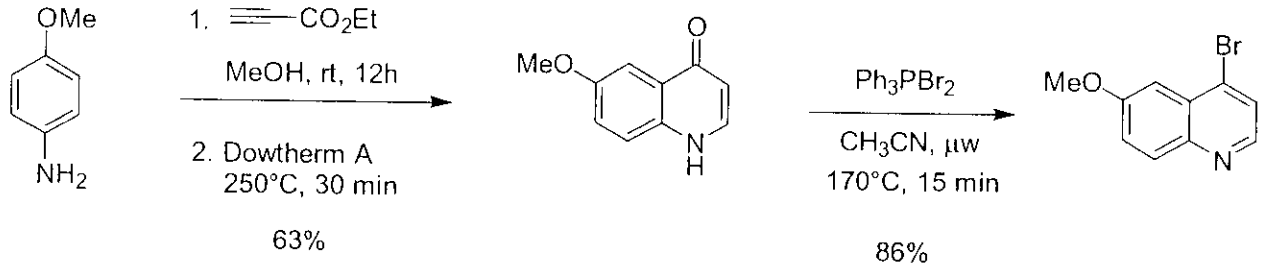
Jacobsen Approach



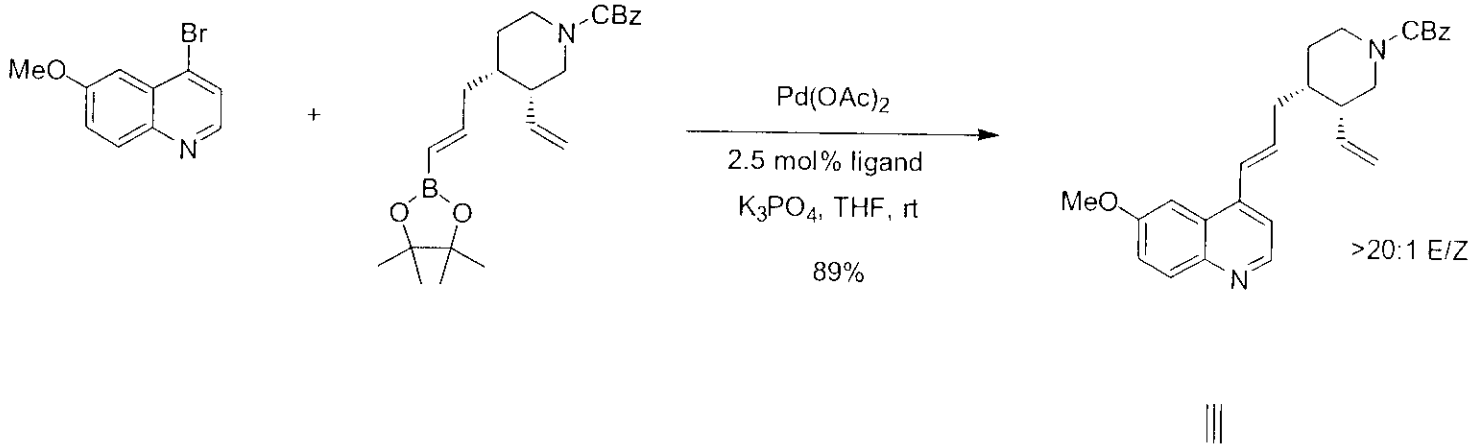


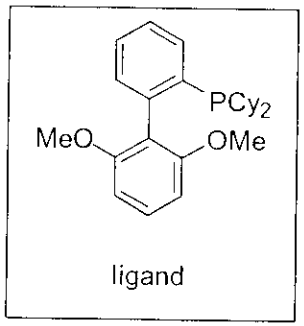
Jacobsen Approach

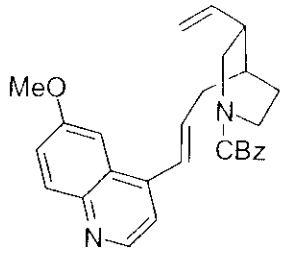




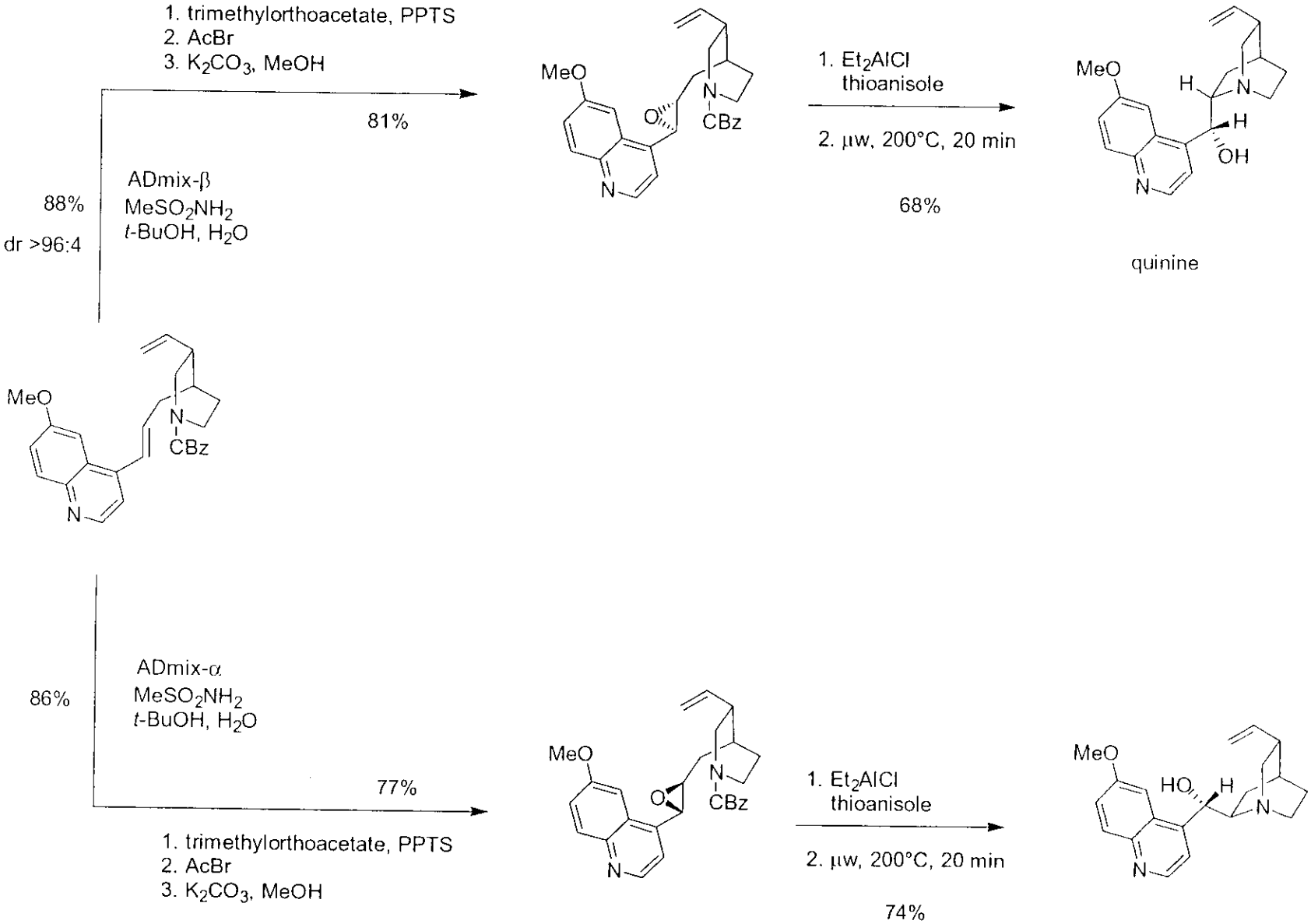
Jacobsen Approach







Jacobsen Approach



Summary

Woodward/Doering Approach - 15 steps (5% yield)

Jacobsen Approach - 16 steps (5% yield)

The catalytic asymmetric total synthesis of quinine highlights the power of modern chemical methodology.

Fundamental classical techniques still remain useful in organic synthesis.