A Review of Three Total Syntheses of Quinine and Quinidine

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Organic Chemistry Supergroup Meeting
Princeton University
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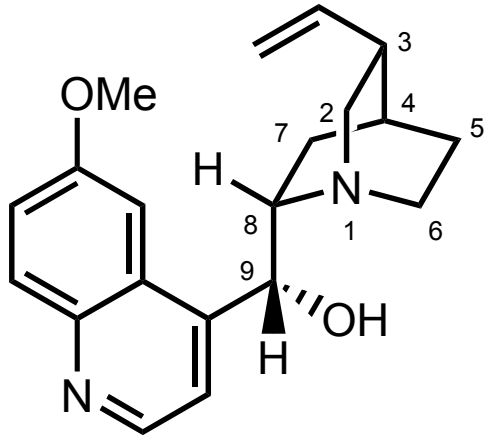
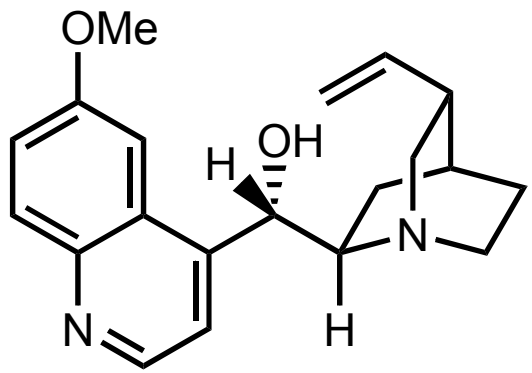
Quinine and Quinidine

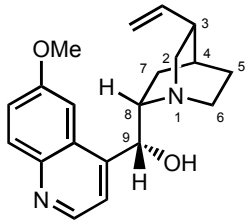


Quinine

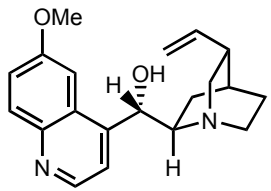


Quinidine

Quinine and Quinidine



Quinine



Quinidine

Biology[1]

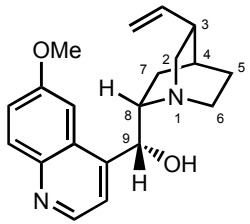
- Antimalarial
- Isolated from bark of trees of *Cinchona* spp.
- Native of Peru and Bolivia
- Cultivated mainly in Java
- Cultivated bark contains 7-10% alkaloids, 70% of which is quinine

Availability

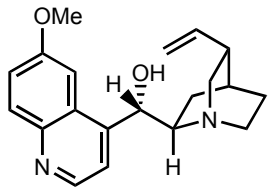
- U.S. imported 68 tons of quinine in 1999[2]
- Quinine (anhydrous, 99%): 50g for $129 Acros[3]
- Quinidine (anydrous, 99%): 5g for $34 Acros[3]

1. *The Merck Index*, 12th ed.; Budavari, S., Ed.; Merck: Whitehouse Station, NJ, 1996; pp 383-384.
2. U.S. Department of Commerce, *U.S. imports of organic chemicals for consumption*; Chapter 29, subheading 293921.
3. Acros Organics; *Catalog of Organics and Fine Chemicals*, 2004-2005, pp 1837-1838.

Quinine and Quinidine



Quinine



Quinidine

Chemistry

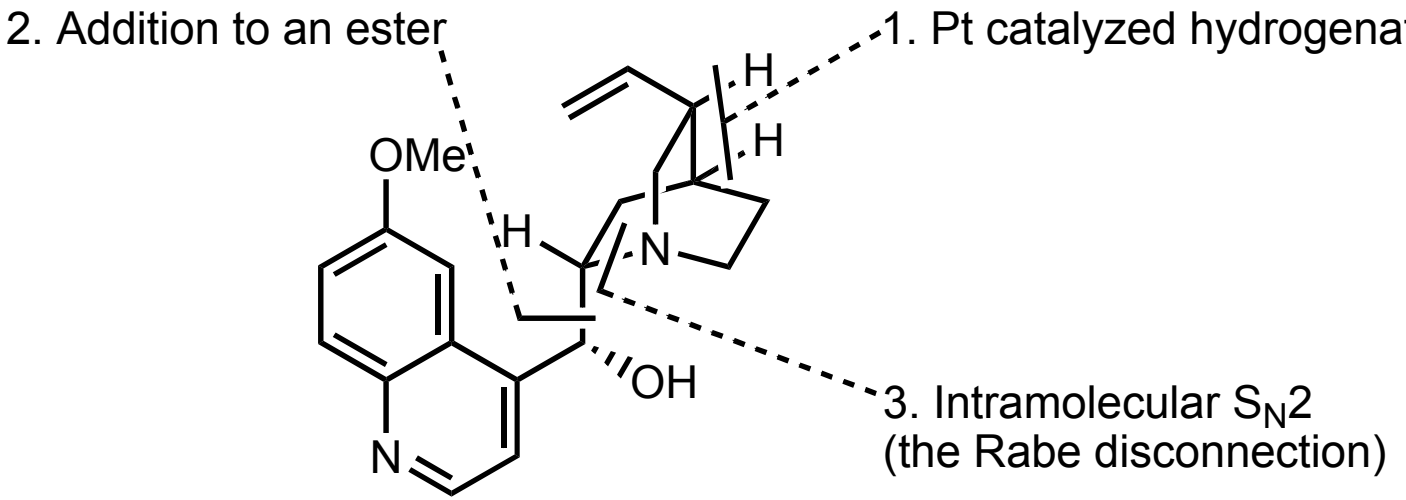
- 4 stereocenters: C3, C4, C8, C9
- Quinuclidine substructure
- Quinoline substructure
- Structure of quinine reported by German chemist paul Rabe in 1907.[1]
- Privileged ligand and catalyst for asymmetric catalysis[2]

Synthesis

- First partial synthesis reported by Rabe in 1918[3]
- Partial synthesis by Prelog and Prostenik in 1943[4]
- First formal total synthesis by Woodward and Doering in 1944[5]
- First stereoselective synthesis of quinidine by Uskokovic and Gutzwiller in 1978[6]
- First stereoselective synthesis of quinine by Stork et. al. in 2001[7]
- Synthesis of quinine and quinidine by Jacobsen et. al. in 2004[8]

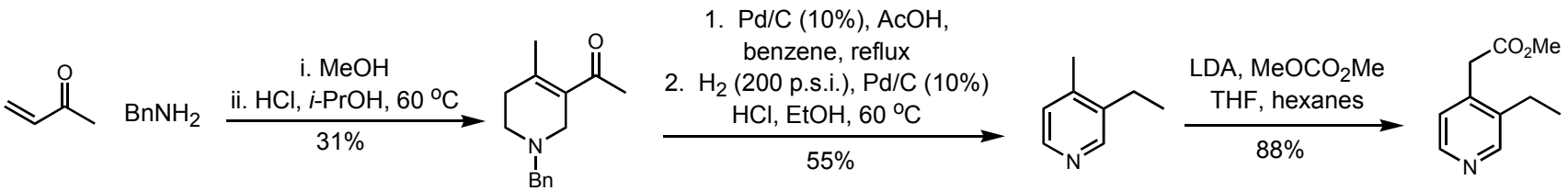
1. Rabe, P.; Ackerman, E.; Schneider, W. *Chem. Ber.* **1907**, *40*, 3655. 2. Kacprzak, K.; Gawronski, J.. *Synthesis* **2001**, 961-998. 3. Rabe, P.; Kindler, K. *Chem. Ber.* **1918**, *51*, 466. 4. Prostenik, M.; Prelog, V. *Helv. Chim. Acta* **1943**, *26*, 1965. 5. Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1944**, *66*, 849. 6. Gutzwiller, J; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 576-581. 7. Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R., Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239-3242. 8. Raheem, I. T.; Goodman, S. N., Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706-707.

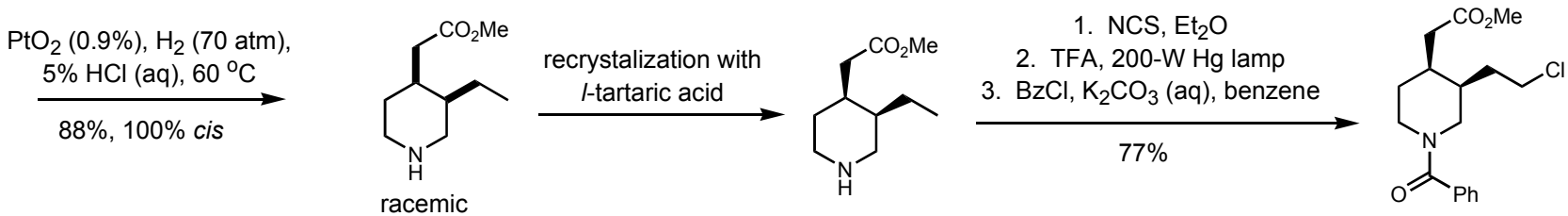
Uskokovic Approach



1. Uskokovic, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571-576.
2. Gutzwiller, J; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 576-581.

Preparation of the *cis*-Disubstituted Piperidine

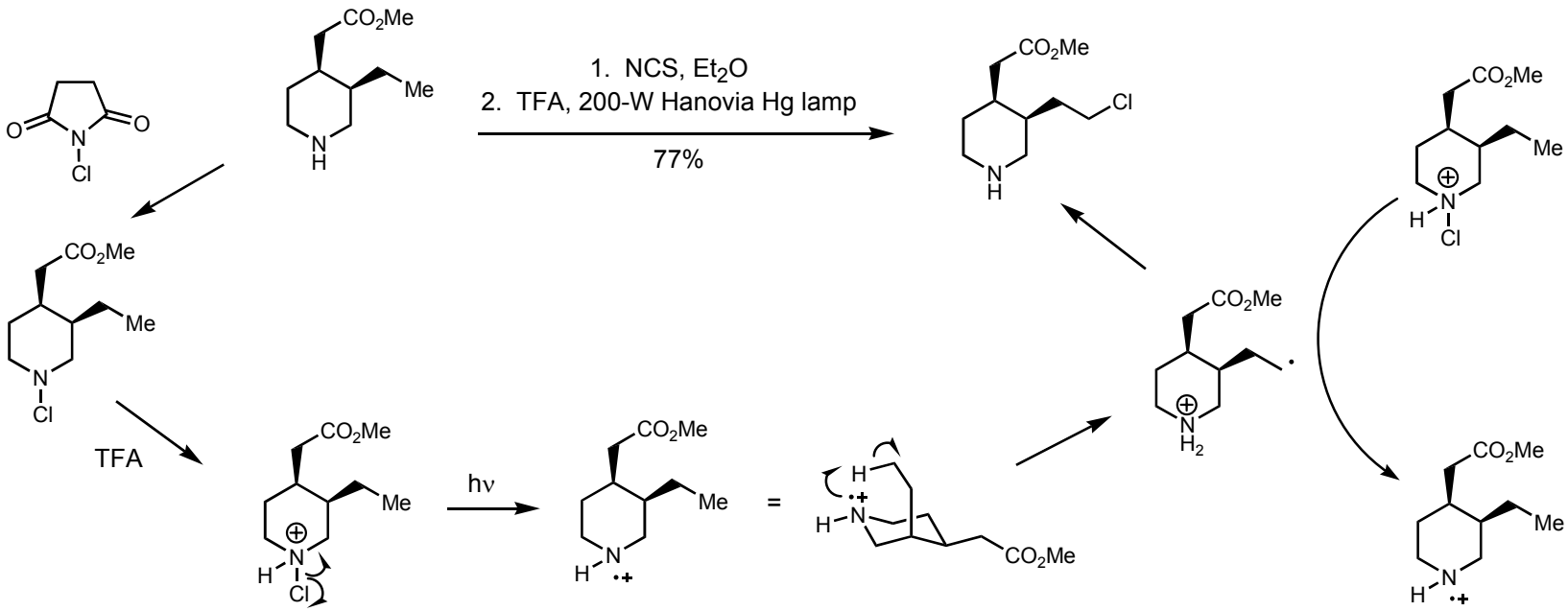




1. Gutzwiller, J; Uskokovic, M. R. U.S. Patent 3,663,554 1972.
2. Uskokovic, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571-576.

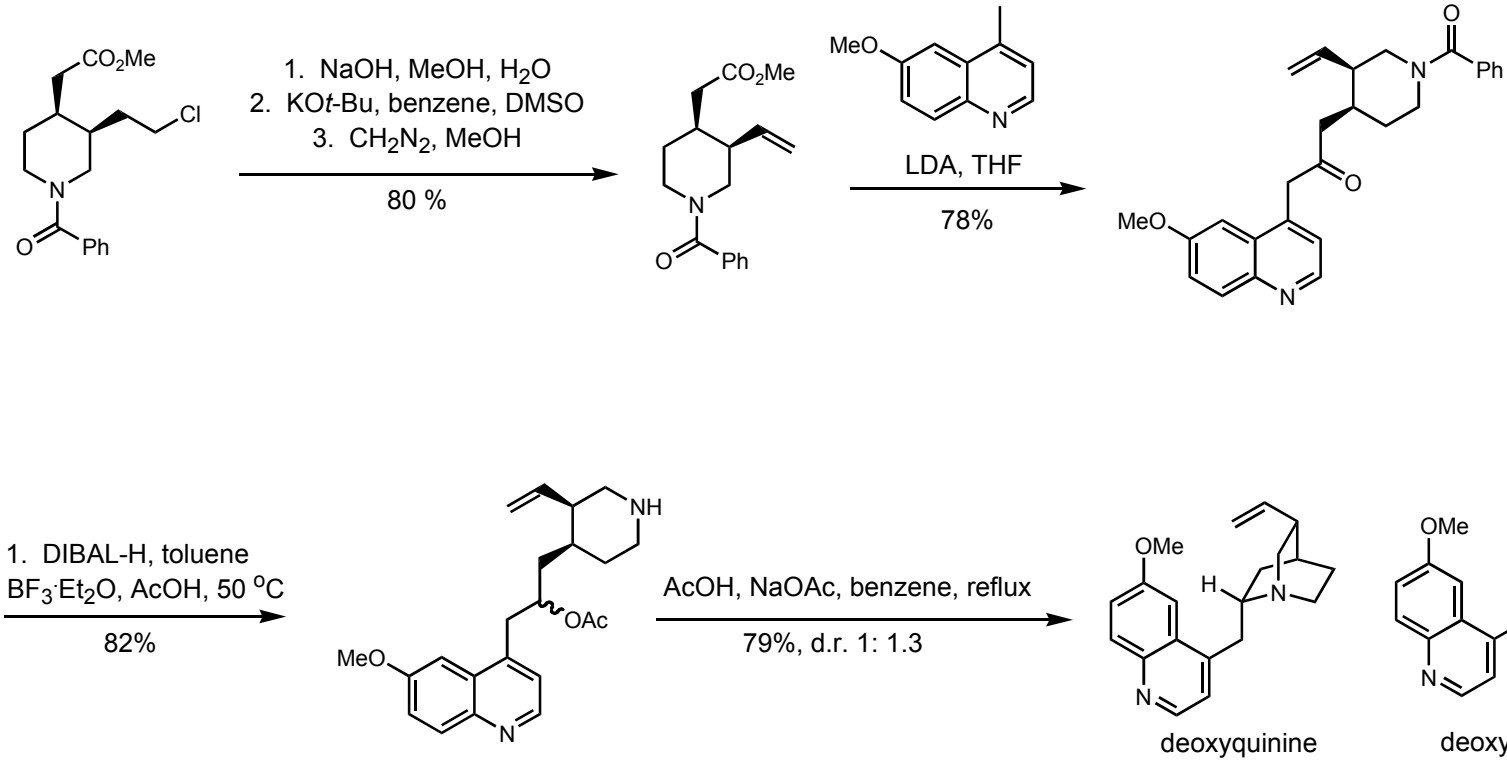
Problem #1

Provide a mechanism for the following transformation, including a 3-D structure that accounts for the selectivity of the chlorination.



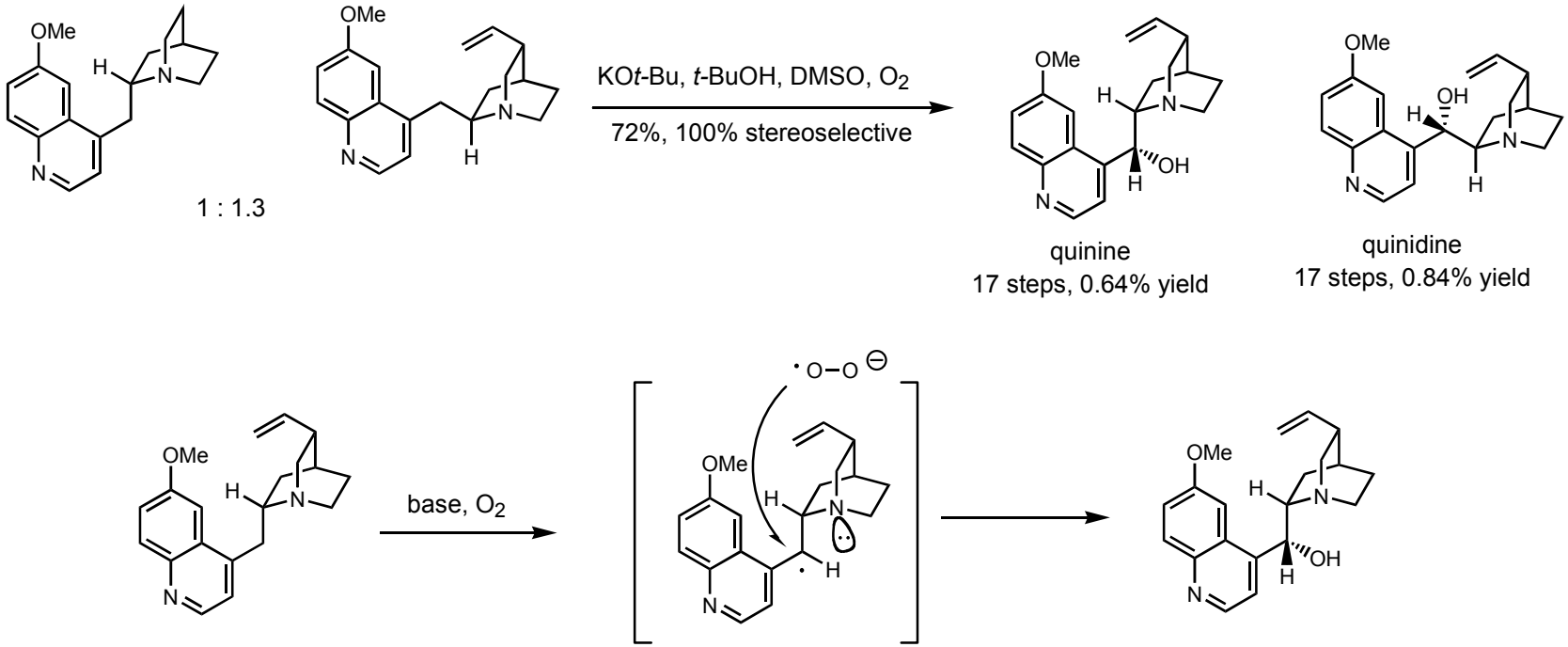
1. Uskokovic, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571-576.

Fragment Coupling and Quinuclidine Synthesis



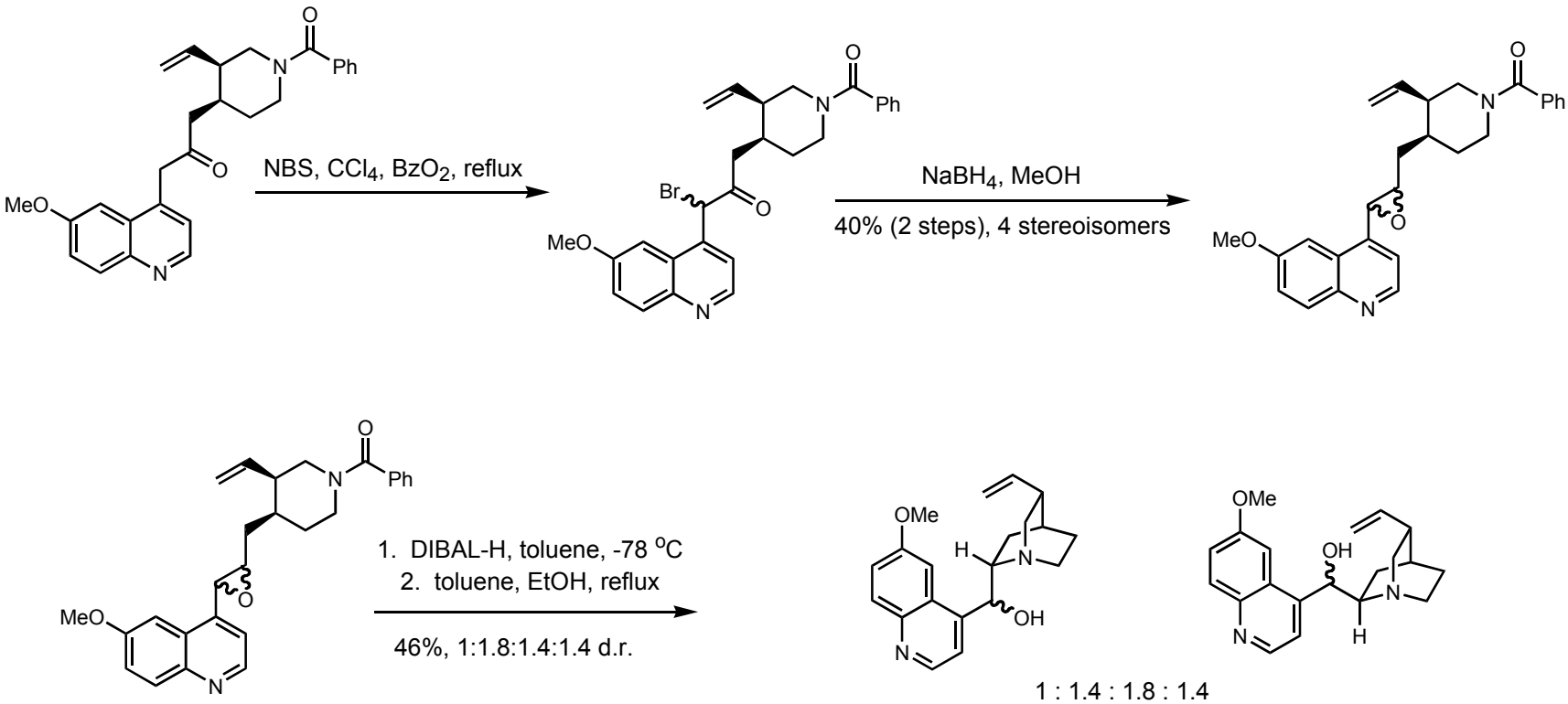
1. Uskokovic, M. R.; Henderson, T.; Reese, C.; Lee, H. L.; Grethe, G.; Gutzwiller, J. *J. Am. Chem. Soc.* **1978**, *100*, 571-576.
2. Gutzwiller, J; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 576-581.

Stereoselective Oxidations of Deoxyquinine and Deoxyquinidine



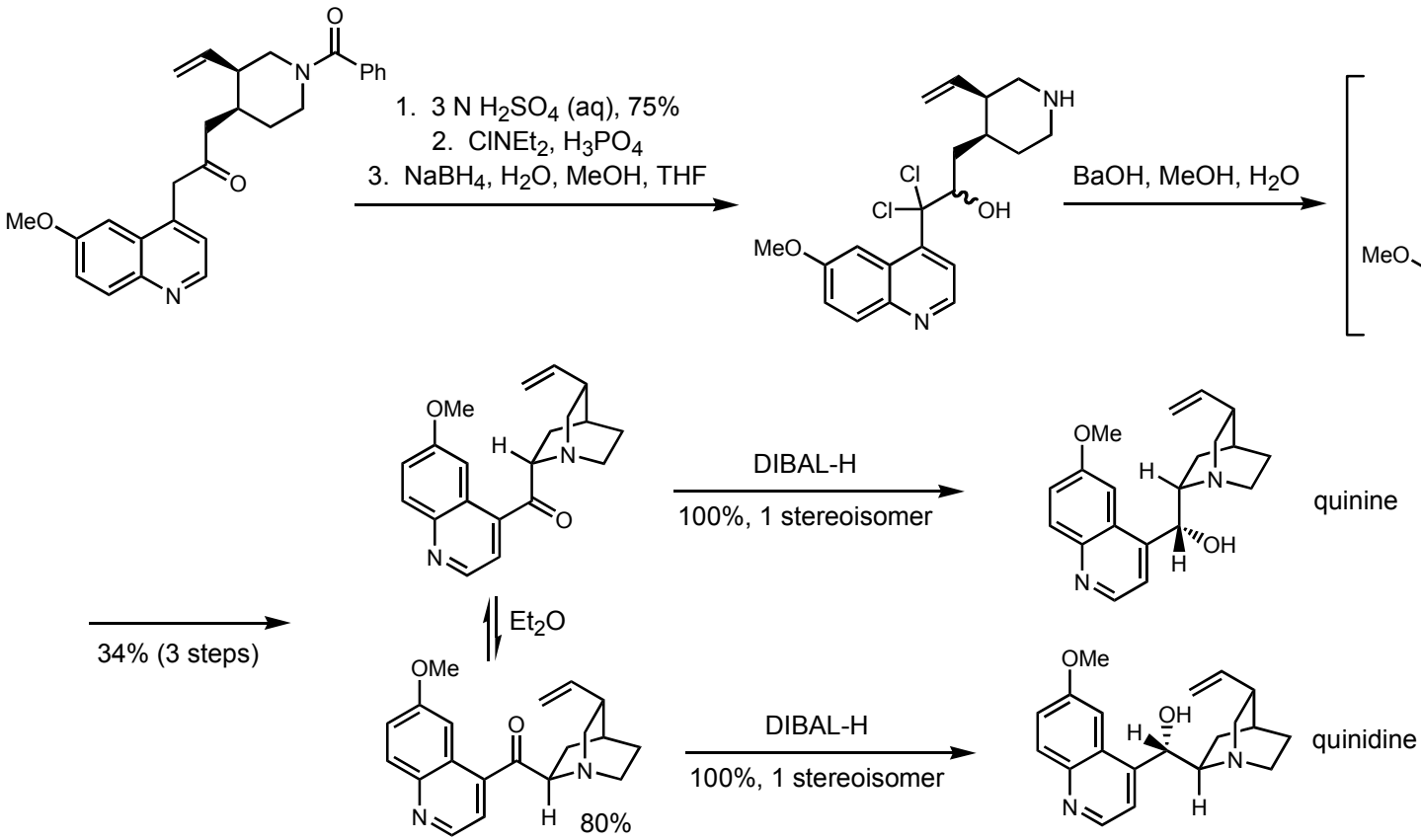
1. Gutzwiller, J; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 576-581.

Nonselective Epoxide Approach



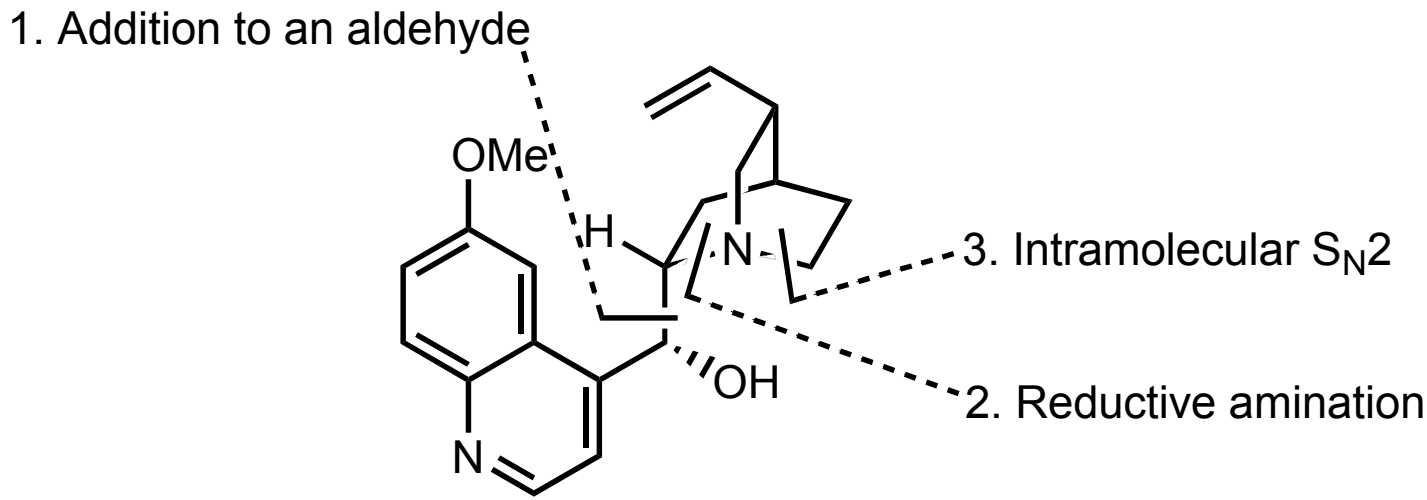
1. Gutzwiller, J; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 576-581.

First Stereoselective Synthesis of Quinidine



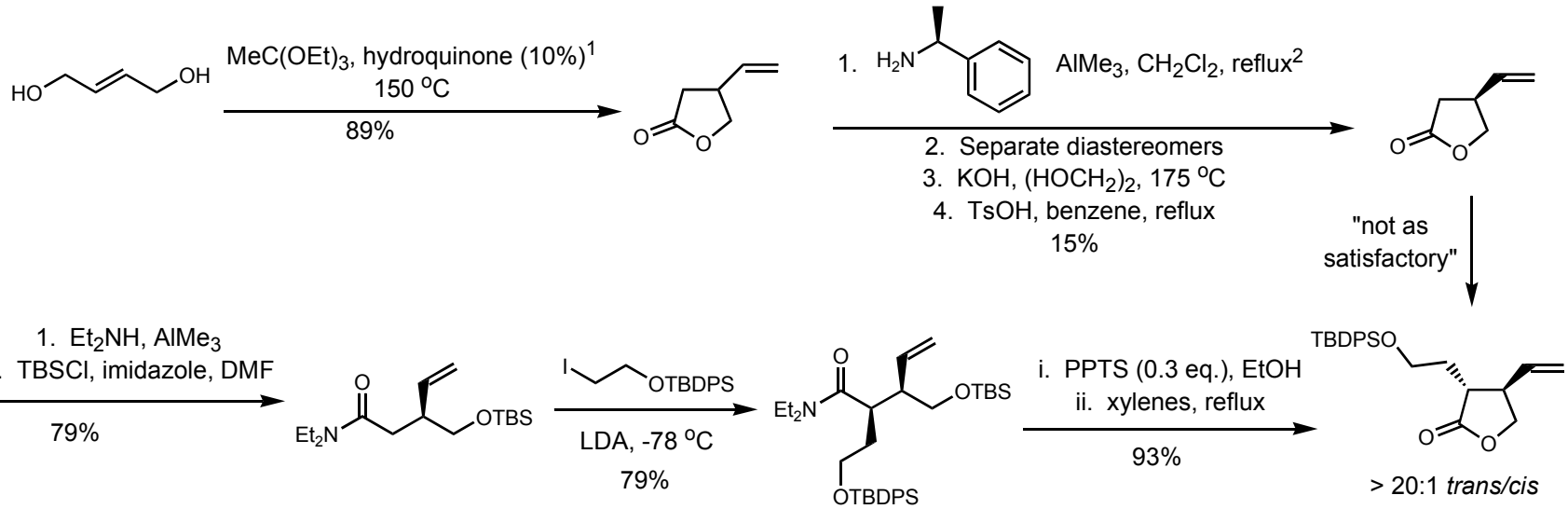
1. Gutzwiller, J; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 576-581.

Stork's Stereoselective Approach to Quinine



1. Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R., Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239-3242.

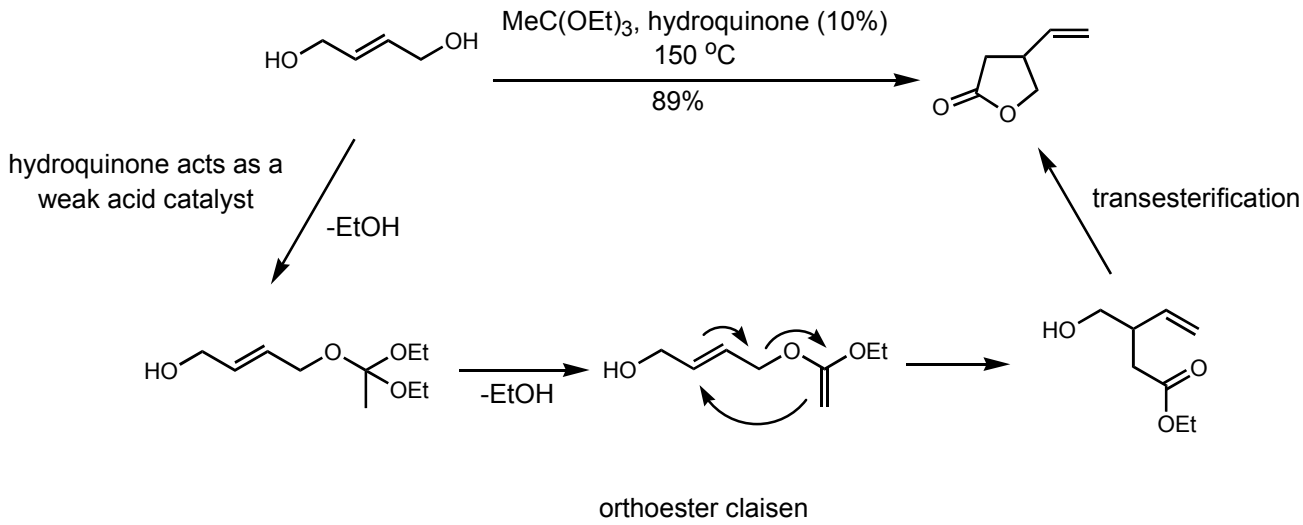
Installation of the C-4 Stereocenter



1. Kondo, K.; Mori, F. *Chem. Lett.* **1974**, 741.
2. Ishibashi, F.; Taniguchi, E. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4361.
3. Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R., Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239-3242.

Problem #2

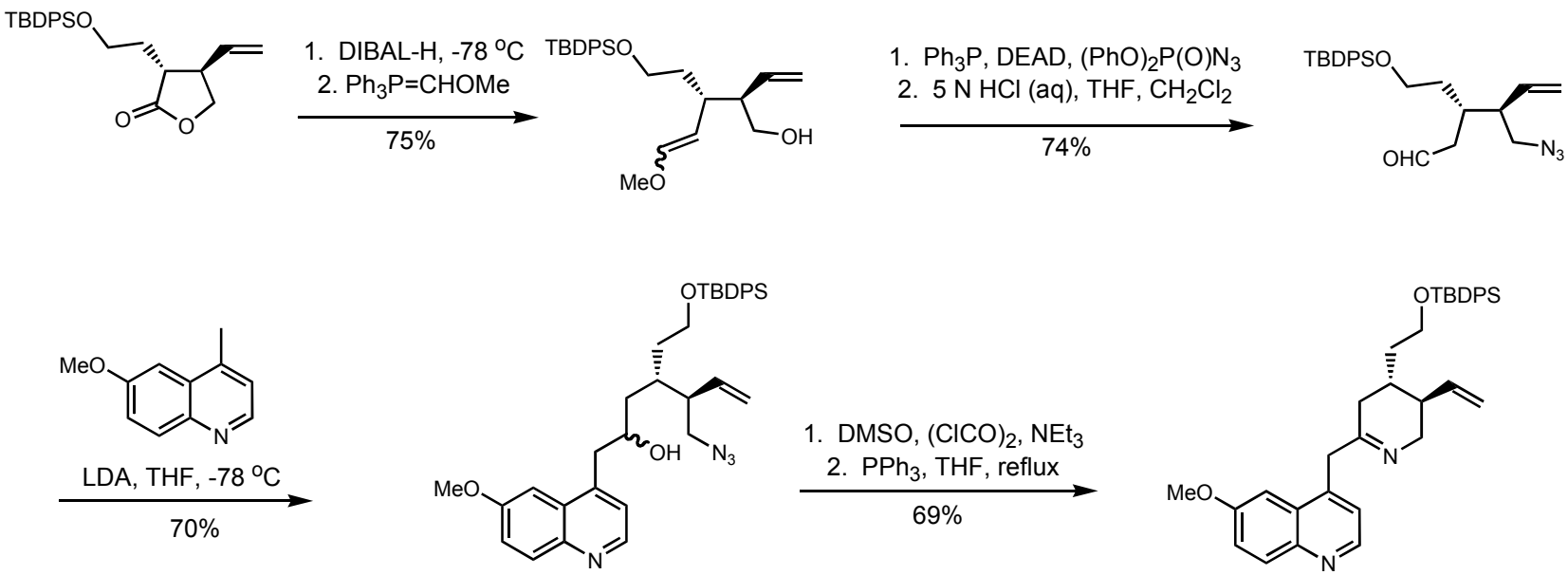
Provide a mechanism for the following reaction.



orthoester claisen

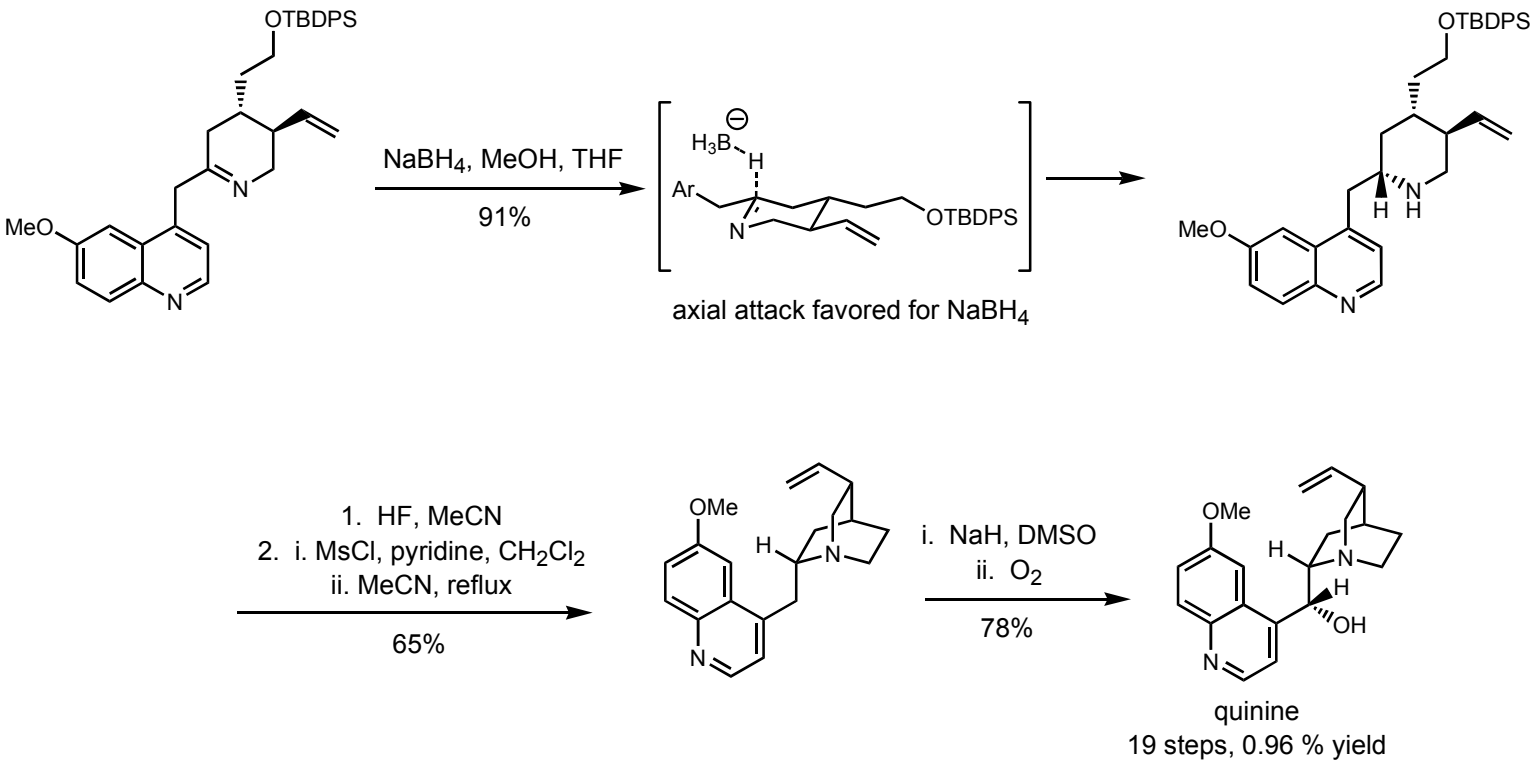
1. Kondo, K.; Mori, F. *Chem. Lett.* **1974**, 741.

Fragment Coupling



1. Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R., Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239-3242.

Stereoselective Completion of the Synthesis

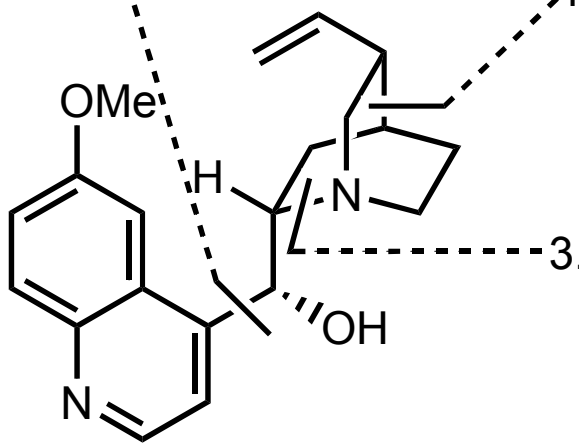


1. Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R., Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239-3242.

Jacobsen's Catalytic Asymmetric Approach

2. Suzuki cross coupling

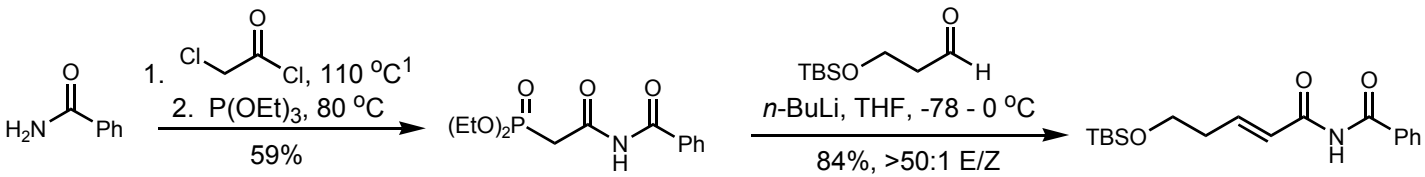
1. Enantioselective conjugate addition

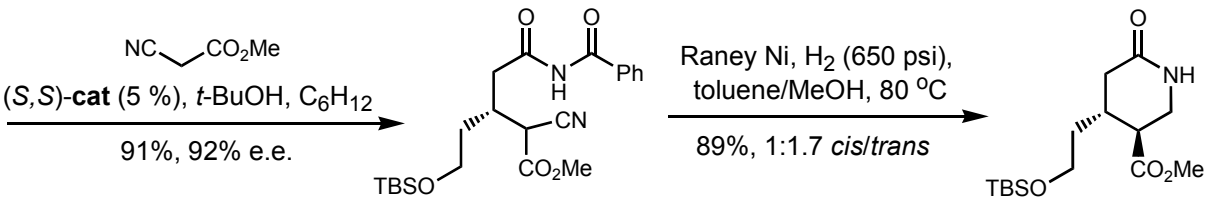


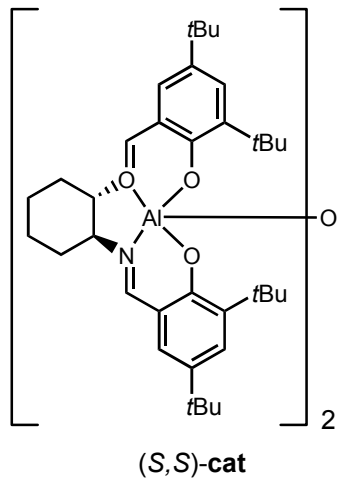
3. Intramolecular S_N2 epoxide opening

1. Raheem, I. T.; Goodman, S. N., Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706-707.

Asymmetric Catalytic Conjugate Addition



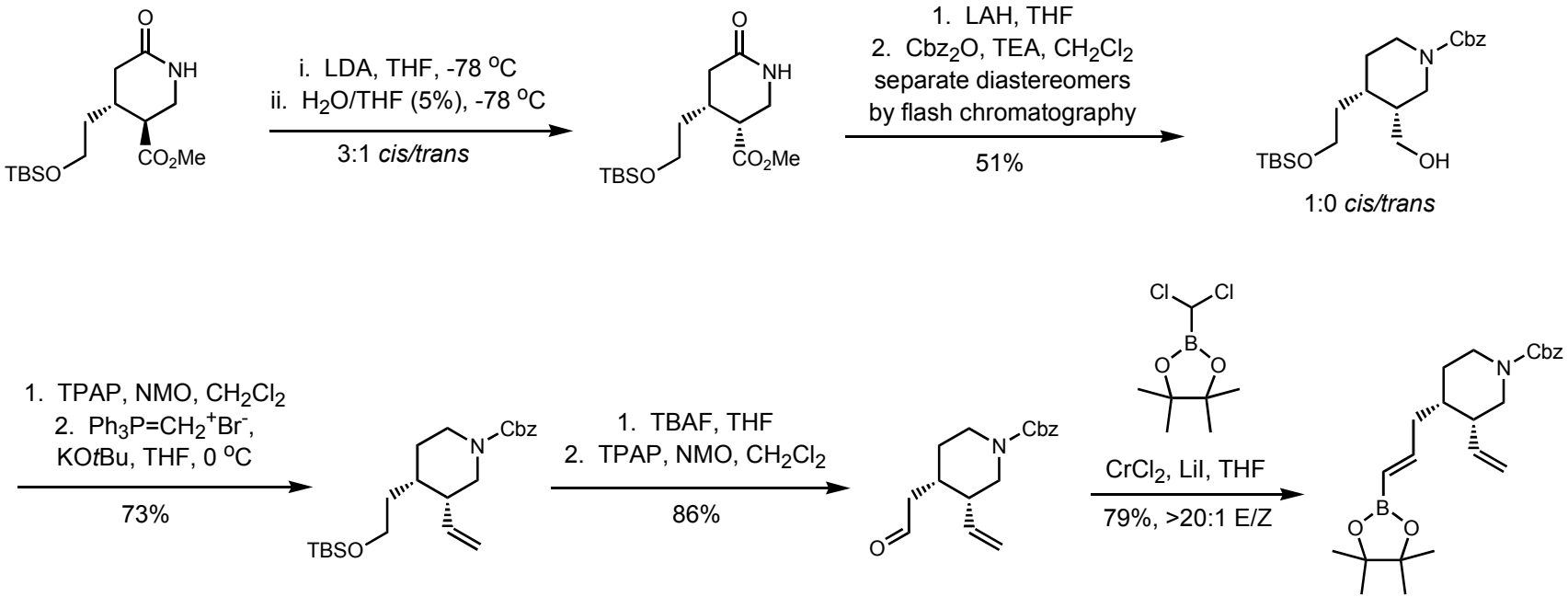




(*S,S*)-**cat**

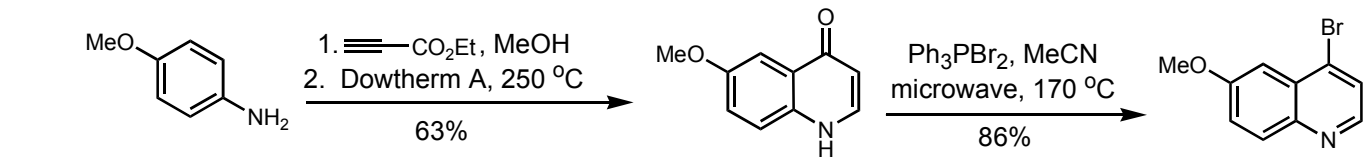
1. Goodman, S. N., Jacobsen, E. N. *Adv. Synth. Catal.* **2003**, *344*, 953-956.
2. Raheem, I. T.; Goodman, S. N., Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706-707.

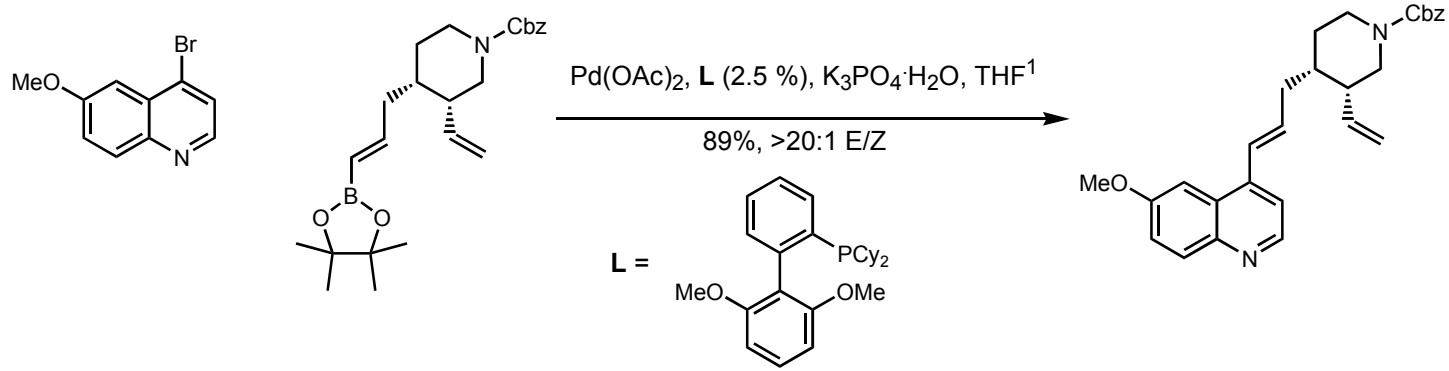
Fixing the C-3 Stereocenter, Elaboration of the Structure



1. Raheem, I. T.; Goodman, S. N., Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706-707.

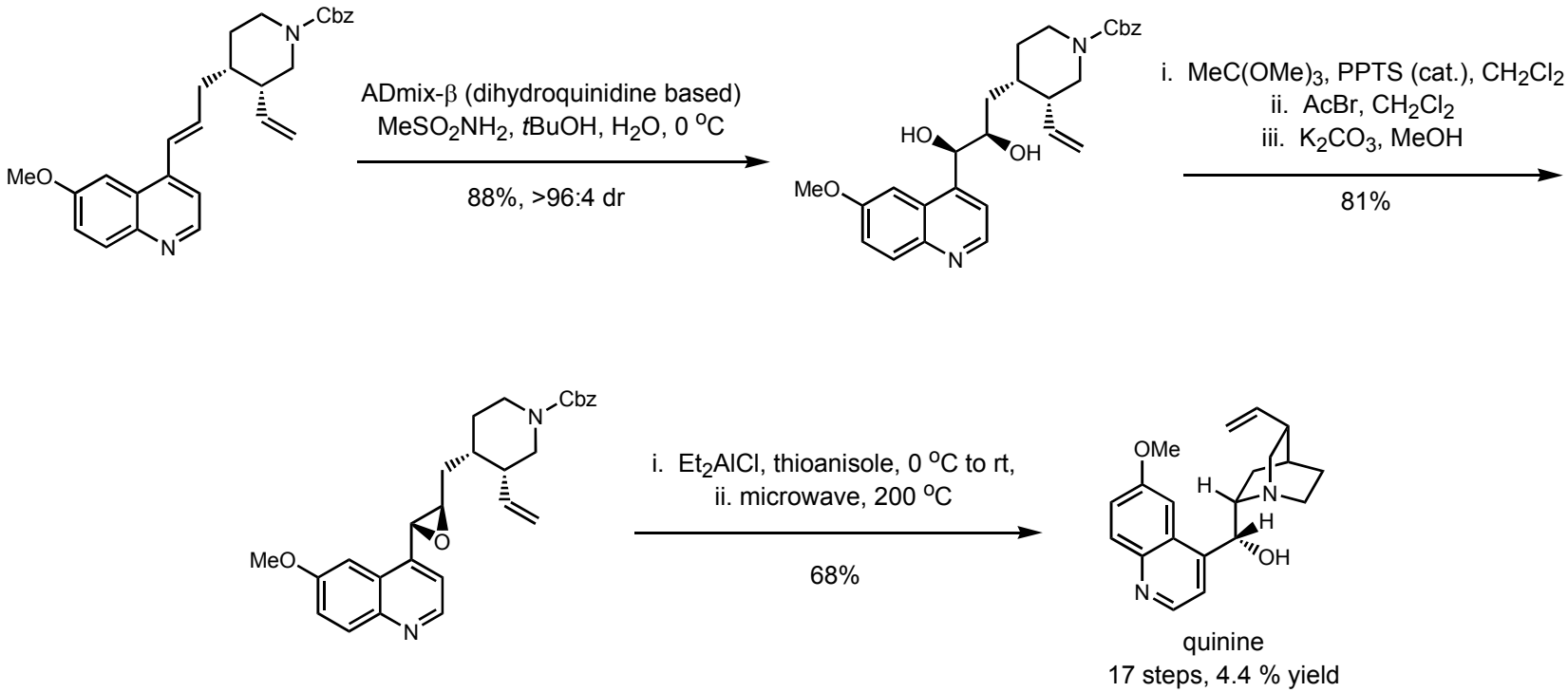
Suzuki Coupling





1. Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *A.C.I.E.E.* **2004**, *43*, 1871-1876.
2. Raheem, I. T.; Goodman, S. N., Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706-707.

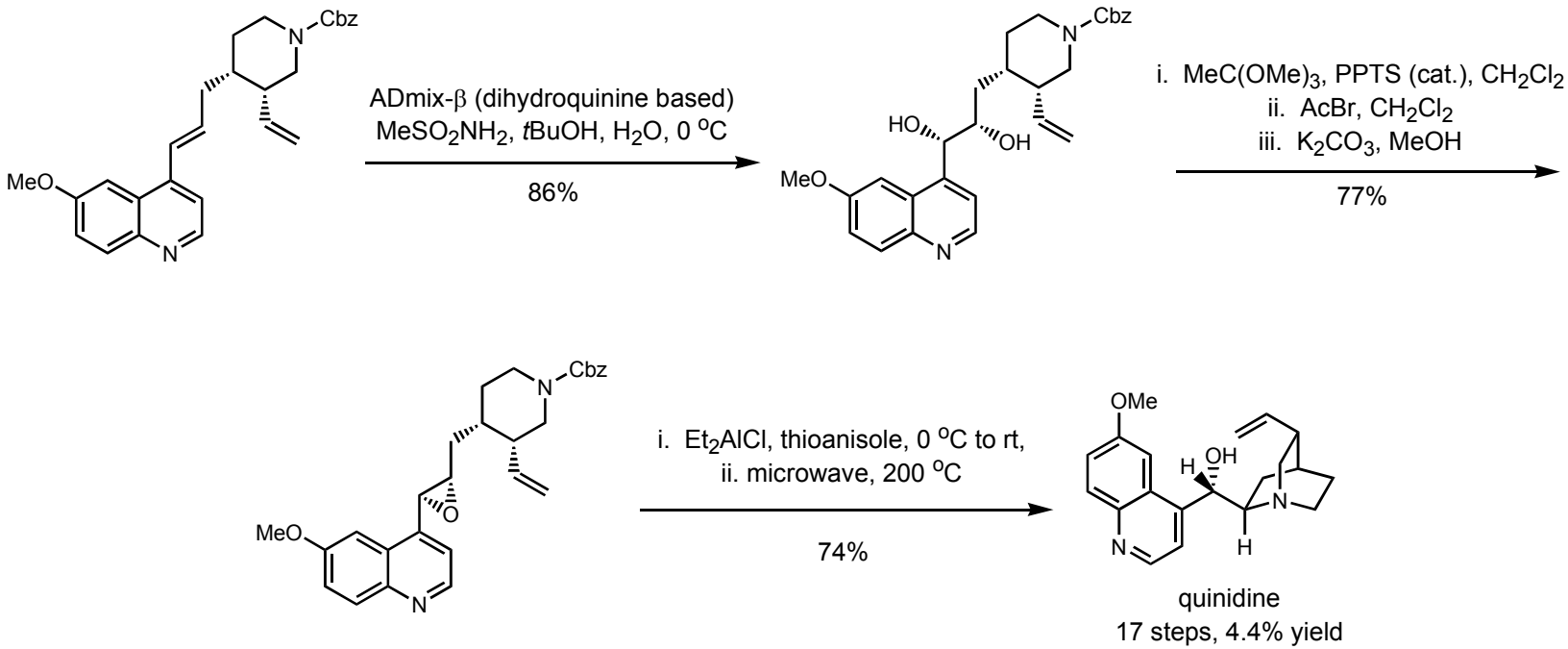
Catalytic Asymmetric Introduction of the C-8 and C-9 Stereochemistry



quinine
17 steps, 4.4 % yield

1. Raheem, I. T.; Goodman, S. N., Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706-707.

Stereoselective Synthesis of Quinidine by the Same Route

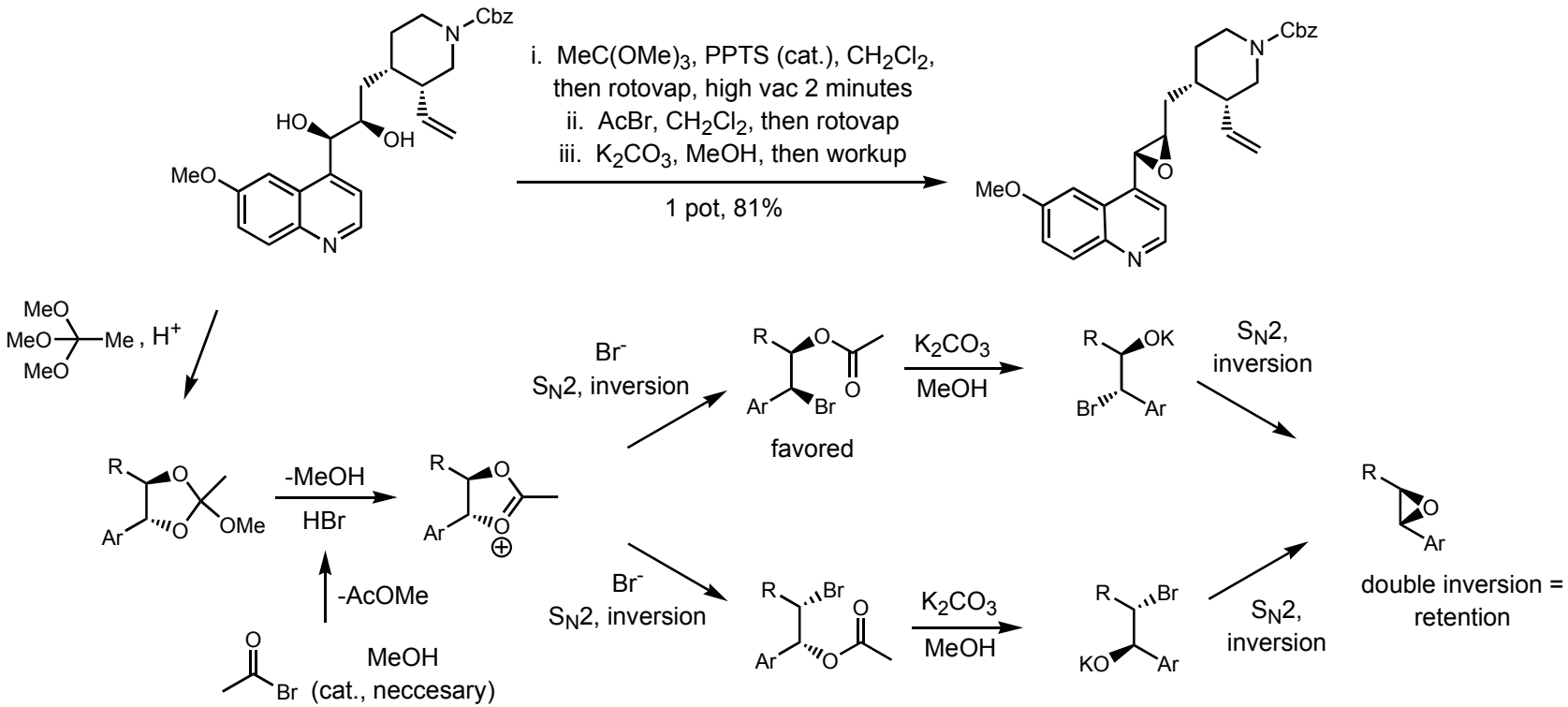


quinidine
17 steps, 4.4% yield

1. Raheem, I. T.; Goodman, S. N., Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706-707.

Problem #3

Provide a mechanism for the following transformation that accounts for the observed stereochemistry.



1. Kolb, H. C.; Sharpless, K. B. *Tetrahedron* **1992**, *48*, 10515-10530.
2. Raheem, I. T.; Goodman, S. N., Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706-707.