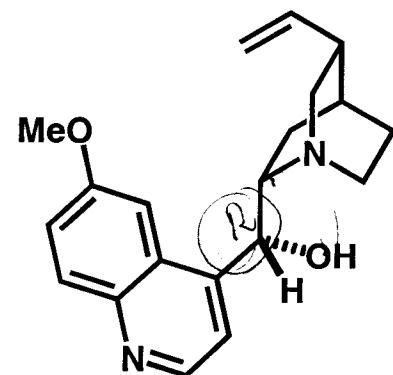


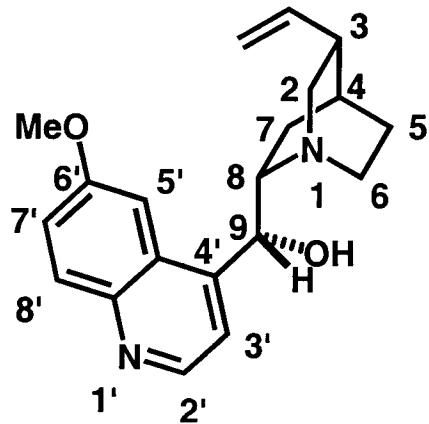
Synthetic Approaches to Quinine



John Baird

June 7, 2005

Properties



Isolated from the bark of cinchona and Remijia species of evergreens originally found in the eastern slopes of the Andes mountains

MF: C₂₀H₂₄N₂O₂

mp: 211.0-212.5 °C, [α]²⁵_D -156.4 (c 0.97, methanol)

Contains 4 stereogenic centers

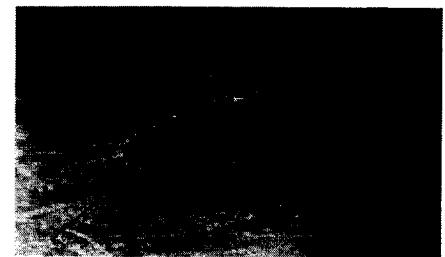
Structure elucidation was performed by chemical degradation

One of the most important drugs in history used in the treatment of Malaria

The Wonder drug for the treatment of Malaria

“the drug to have relieved more human suffering than any other in history”

Malaria is caused by parasites of the species *plasmodium*, who reside in the salivary gland of mosquitoes

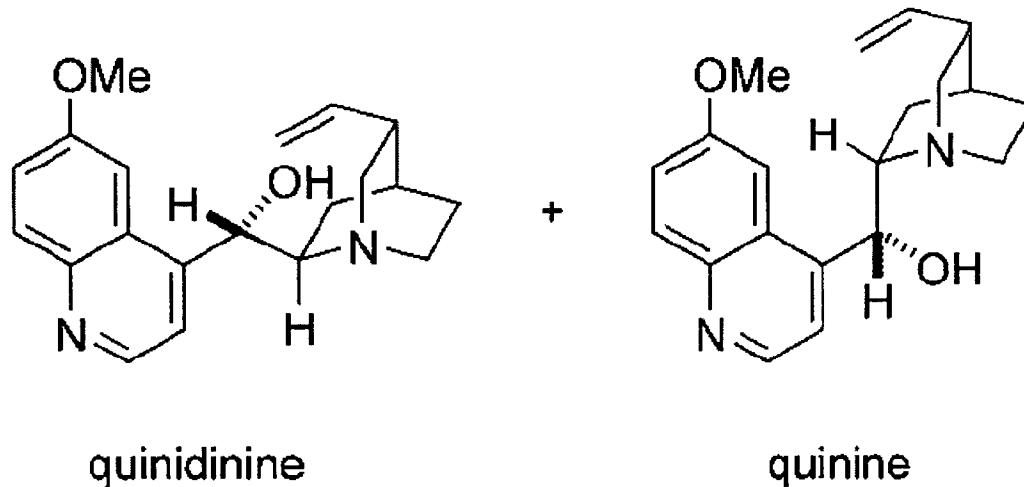


Parasites enter red blood cells, feed upon the protein within before destroying the cell

Symptoms of Malaria include fever and weakness

Each year, the disease claims between 1.5 and 2.7 million lives

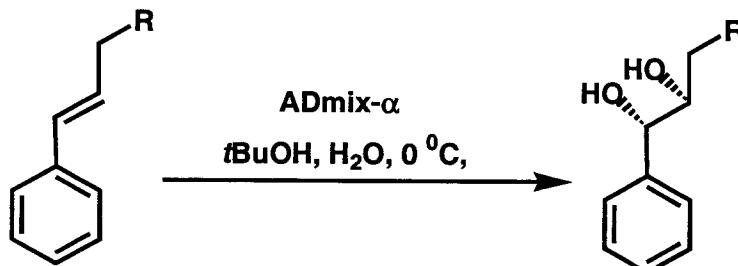
Cinchona Alkaloids



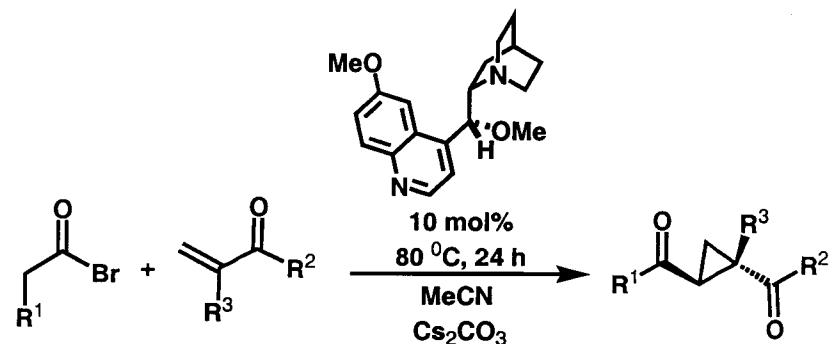
Quinine was first brought to Europe around 1640, where according to legend, bark containing quinine saved the Countess of Chinchon from Malaria, and these compounds are called cinchona alkaloids

Select reactions using quinine

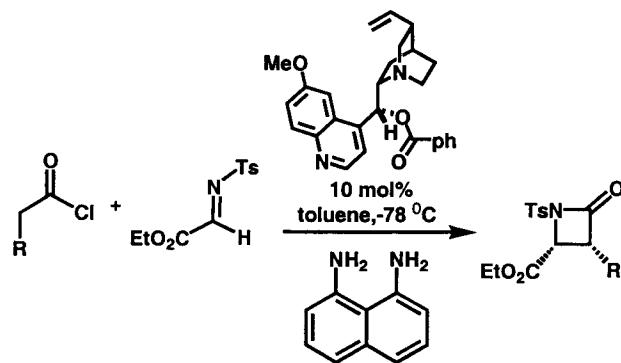
Sharpless Asymmetric Dihydroxylation



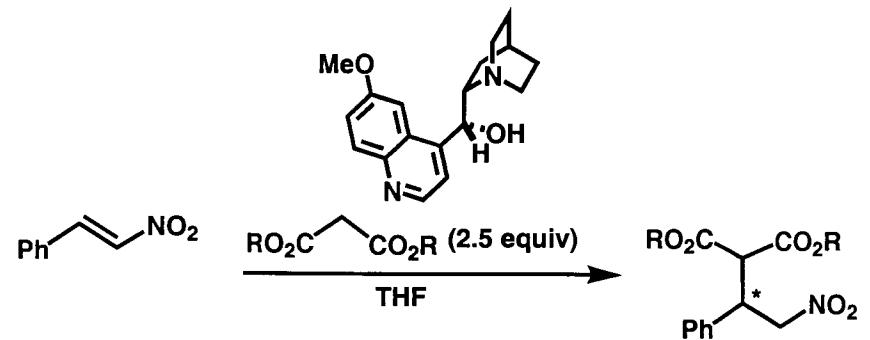
Enantioselective cyclopropanation



Catalytic asymmetric [2+2] cycloaddition

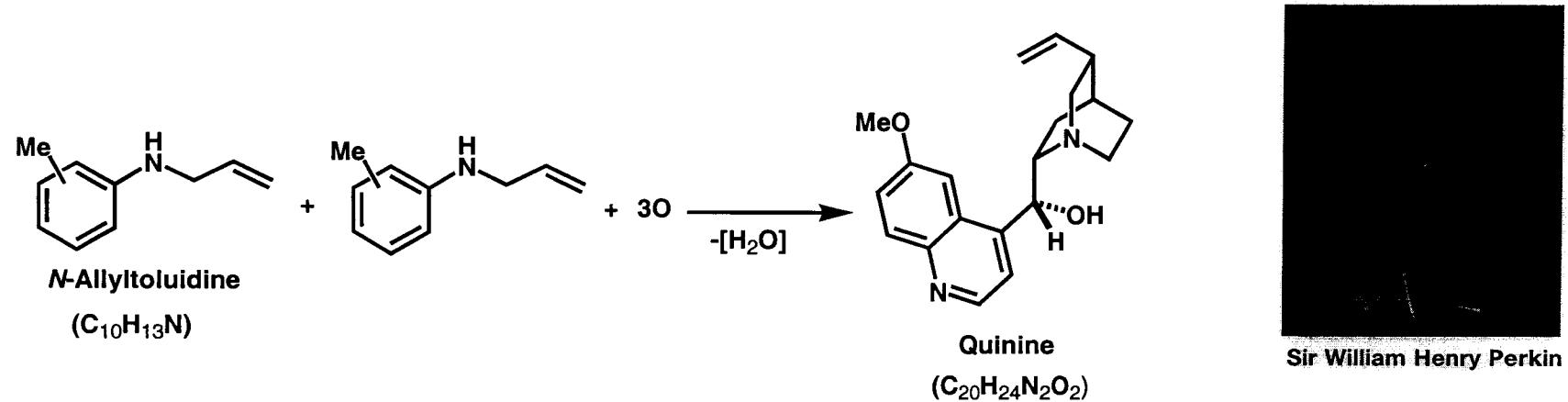


Conjugate Additions

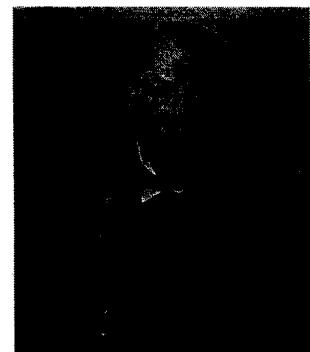


Quinine-Early Attempts

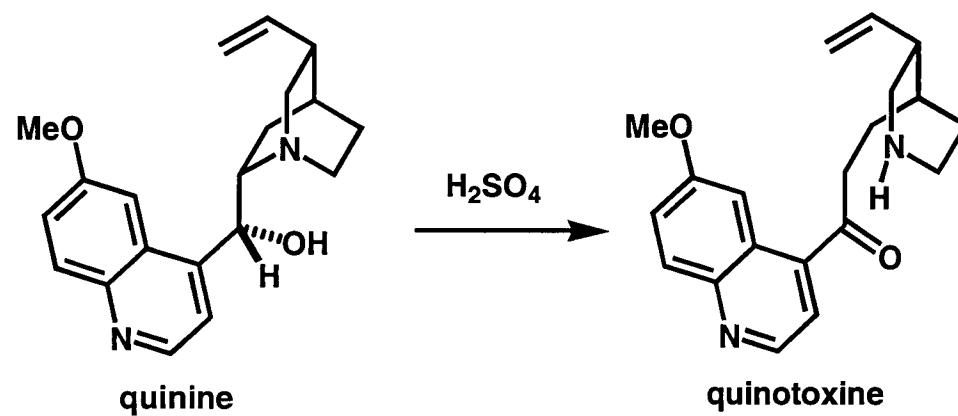
“Mathematical Approach” by Sir William Henry Perkin in 1856



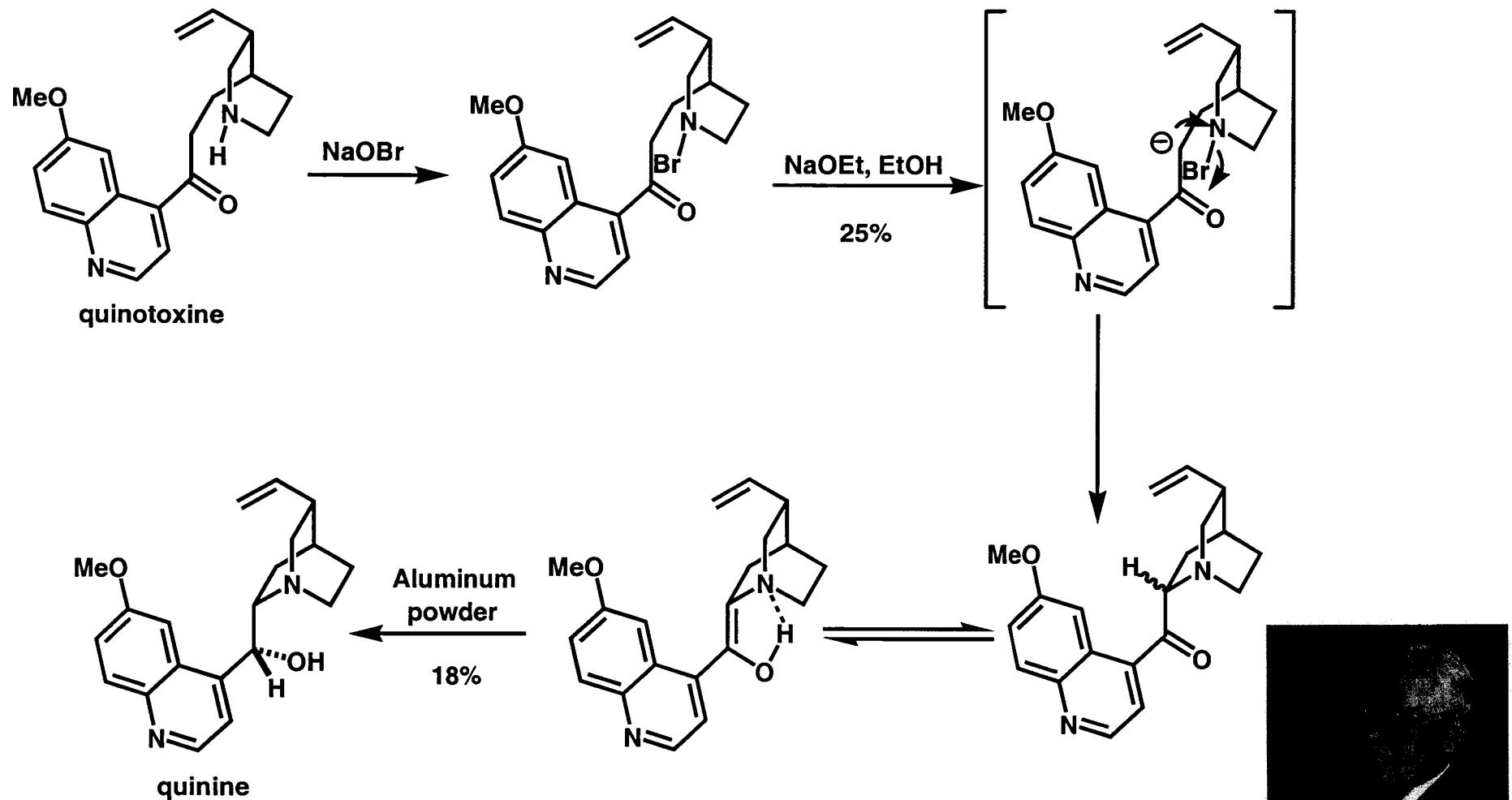
Pasteur’s acid catalyzed rearrangement of quinine to quinotoxine



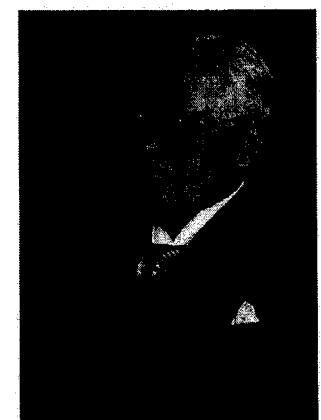
Louis Pasteur



Rabe's Reconstitution of Quinine-1918



Rabe suggested the correct connectivity of quinine in 1908



Paul Rabe

Woodward's Synthesis-Background

During World War II Quinine supplies became scarce

Thousands of soldiers died during campaigns in Africa and the Pacific

The Polaroid Company



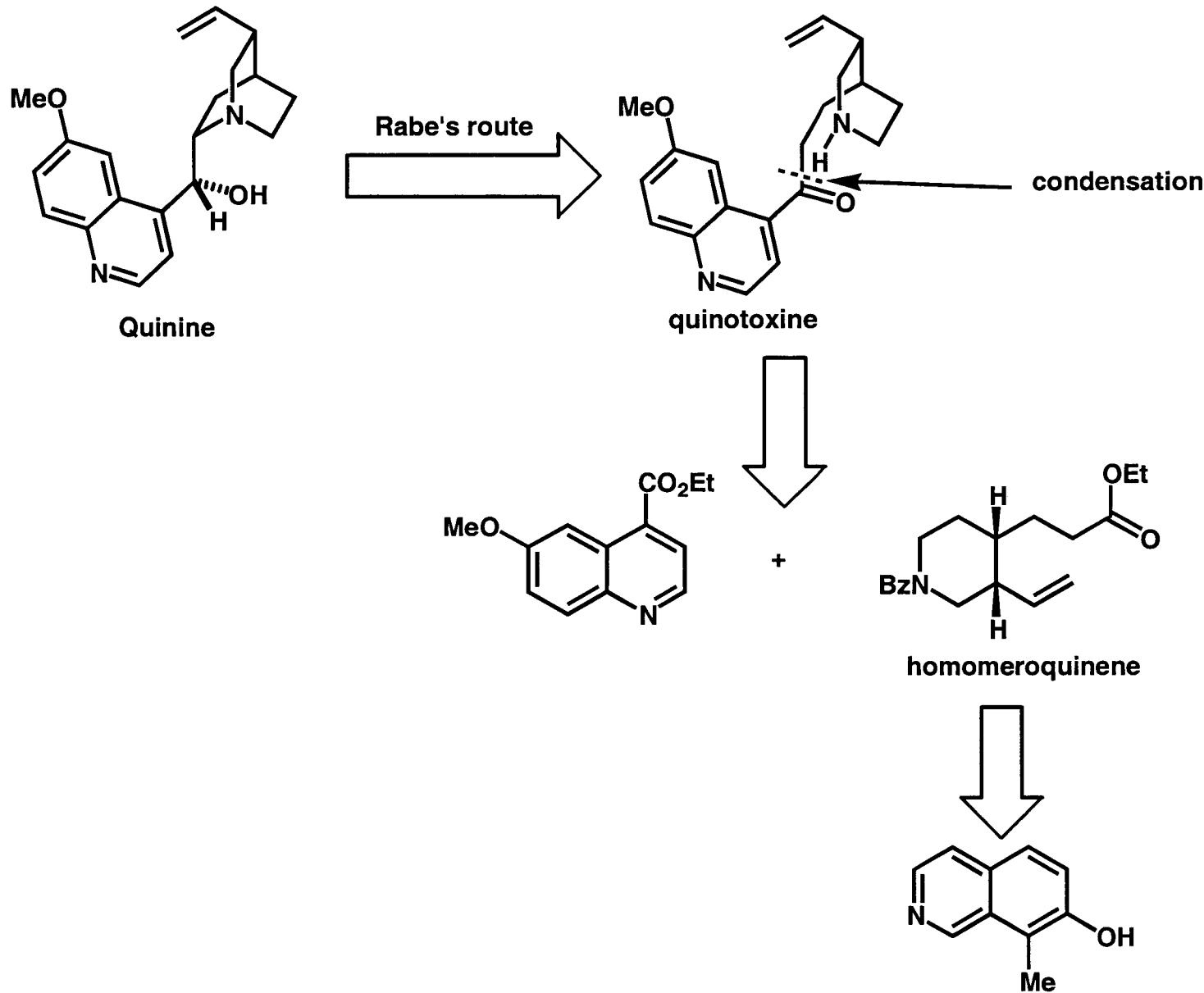
Synthetic chemistry as wartime savior, coping with the losses of rubber, oil, and quinine.
Cartoon in the *Oregon Journal*, Portland, 28 May 1944. Courtesy Library of Congress.

Polaroid relied on quinine as a light polarizer

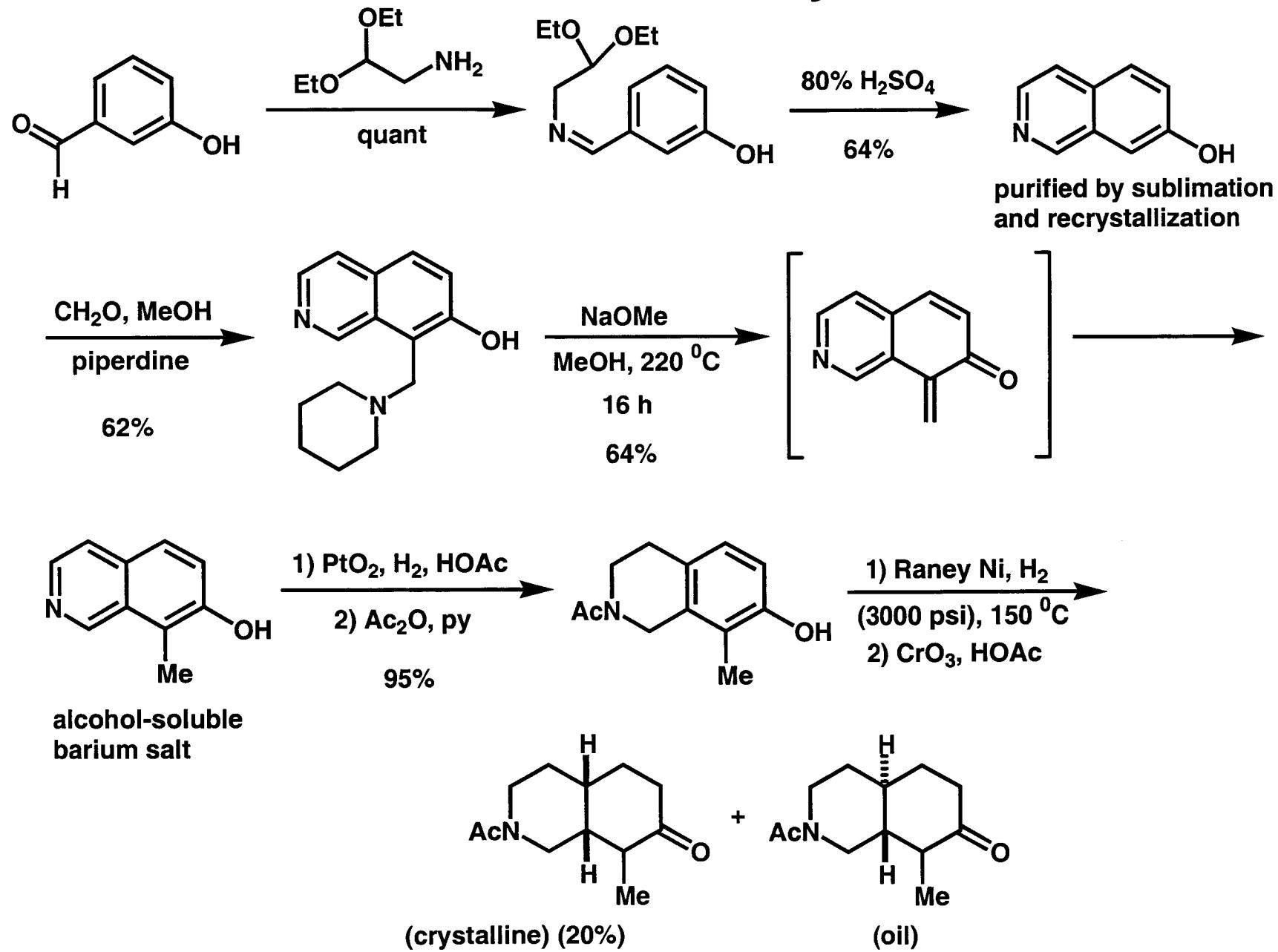
Woodward was a consultant to Polaroid and proposed a quinine substitute (1942)

The founder of Polaroid agreed to finance Woodward's synthetic project on quinine

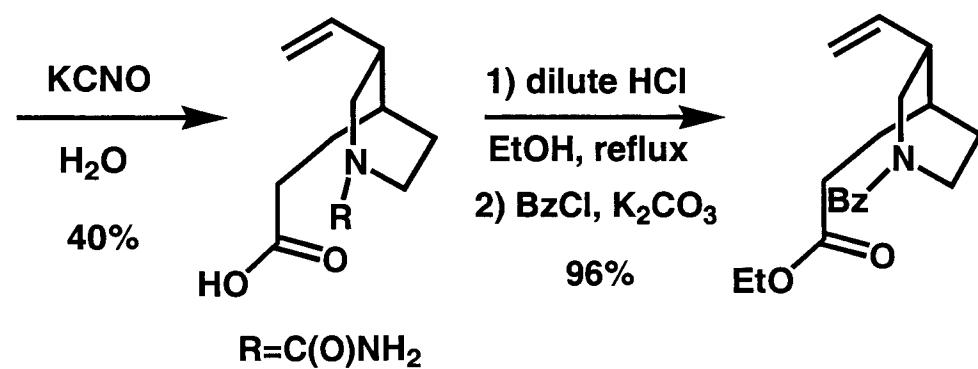
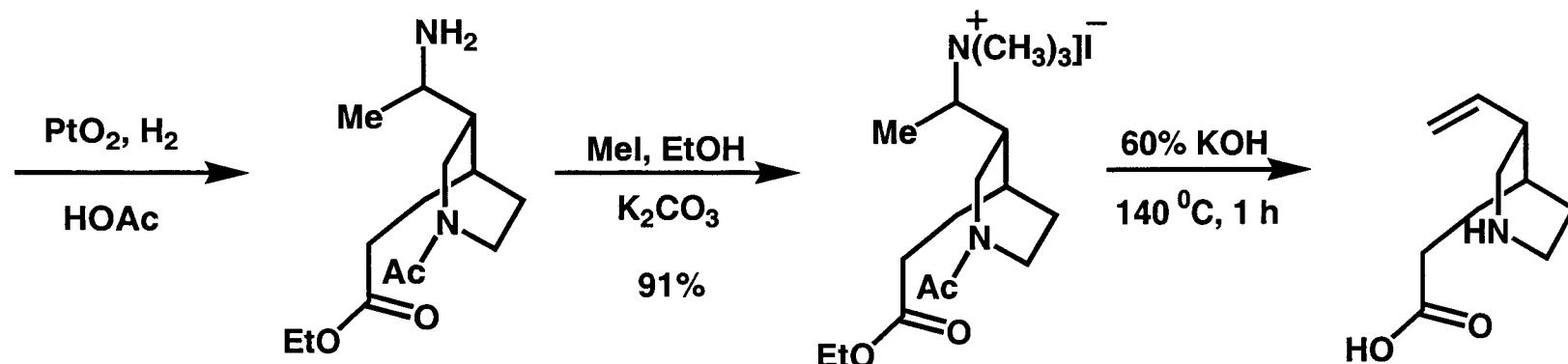
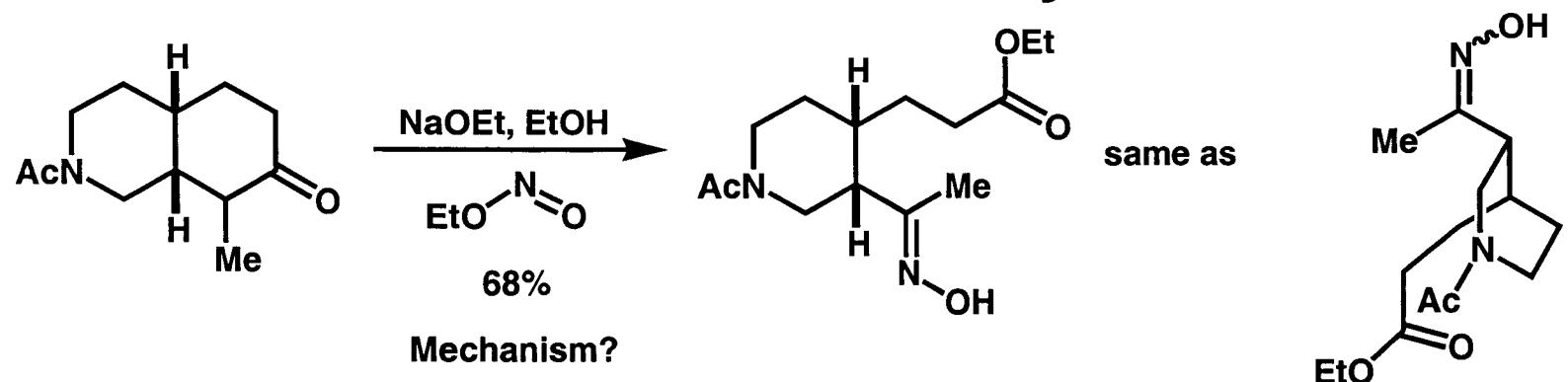
Woodward Retrosynthetic Analysis



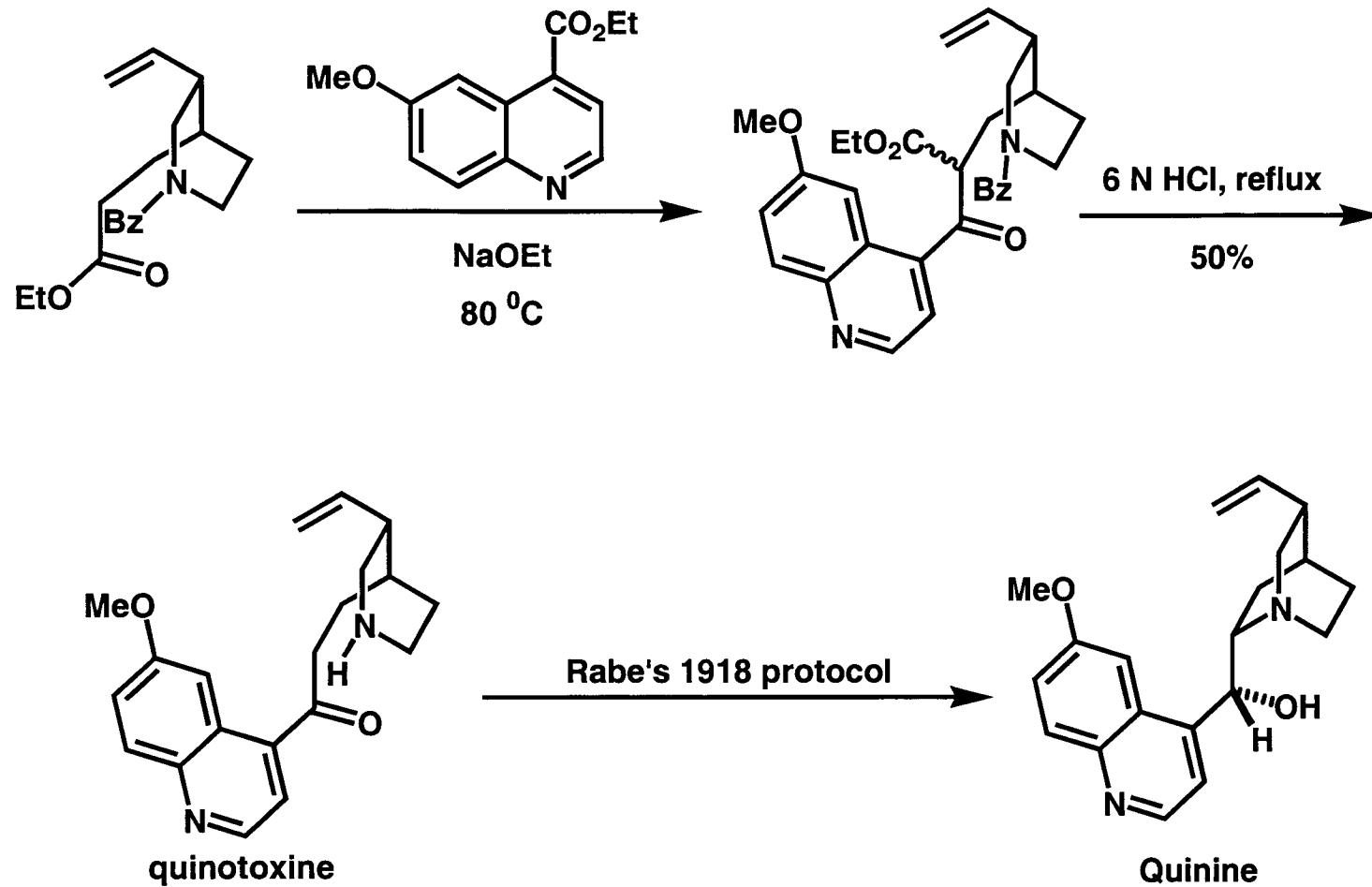
Woodward Forward Synthesis 1



Woodward Forward Synthesis 2



“Completion” of the Formal Synthesis



18 steps, 0.57% overall

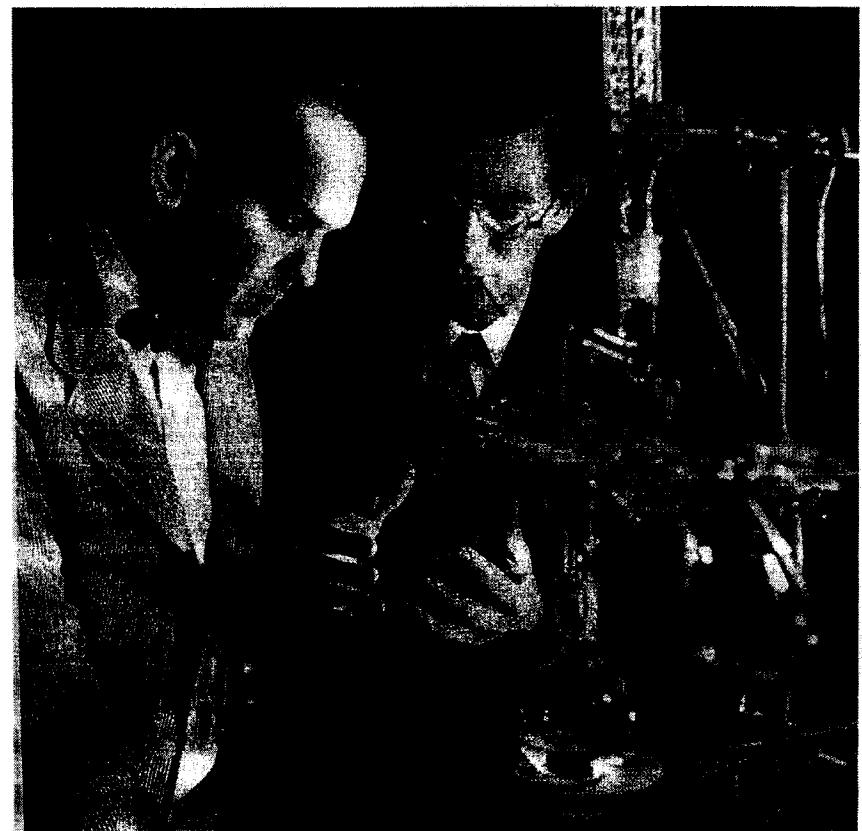
Quinine Synthesis- The subject of Great Fanfare

Landmark Synthesis celebrated in
The New York Times
*“Synthetic Quinine Produced,
Ending Century Search”*

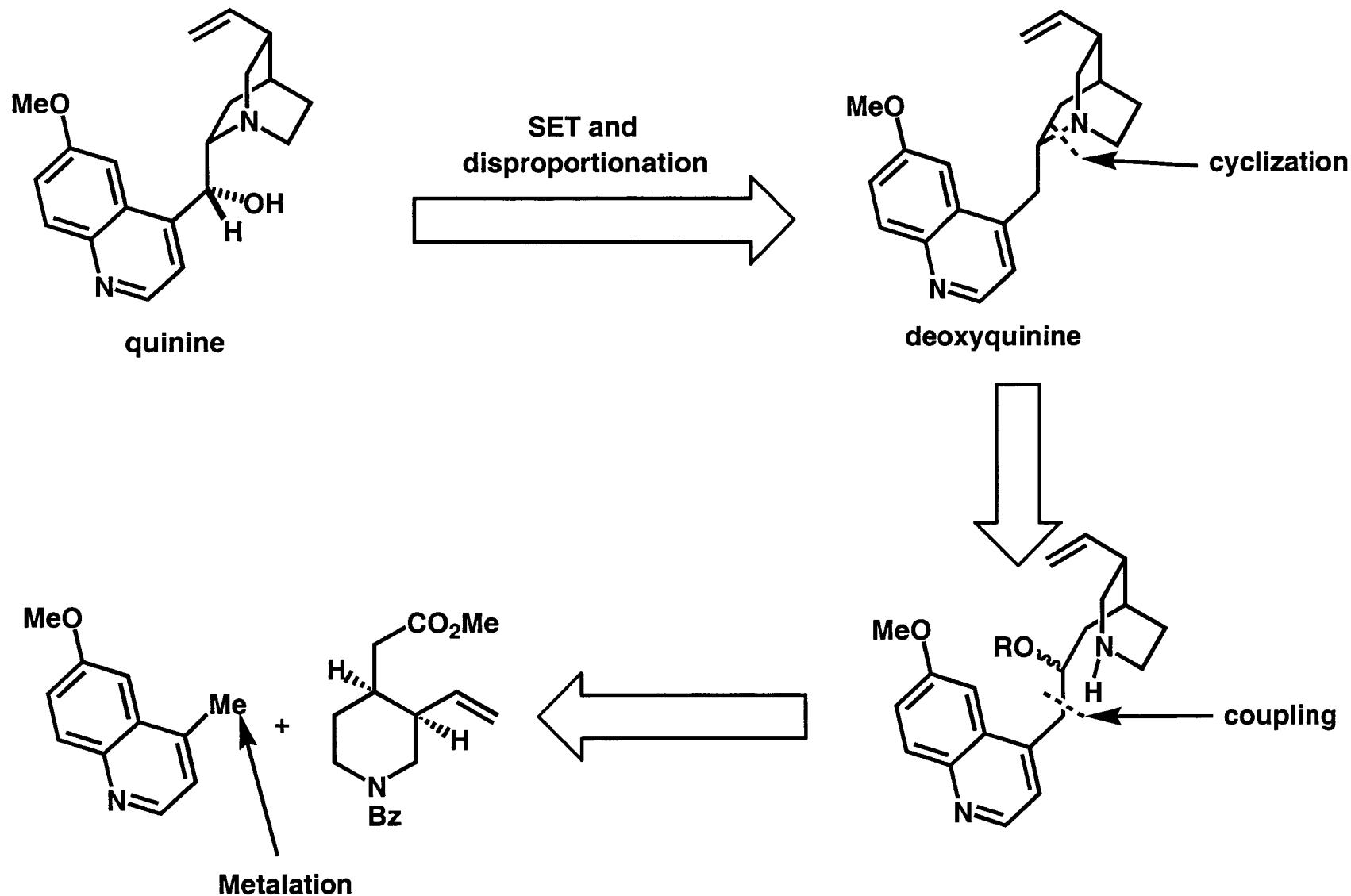
Woodward's first total synthesis

Cost was still a prohibitive factor;
would have cost 200 times more than
its natural equivalent if it was feasible

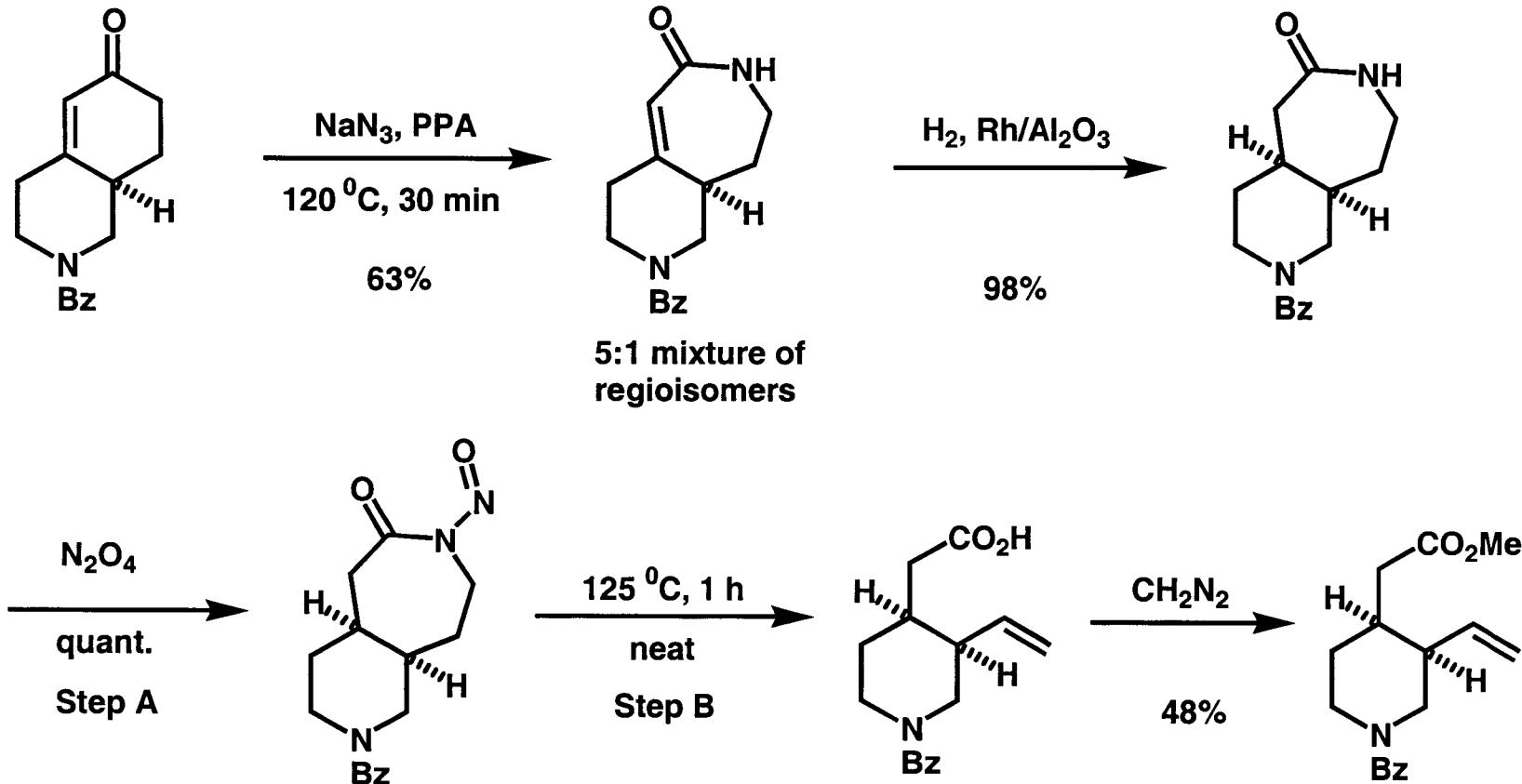
However, Rabe's work was not reproducible



Uskokovic Retrosynthesis

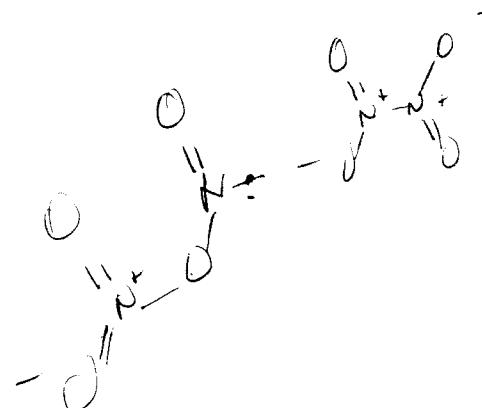


Preparation of piperidine methyl ester

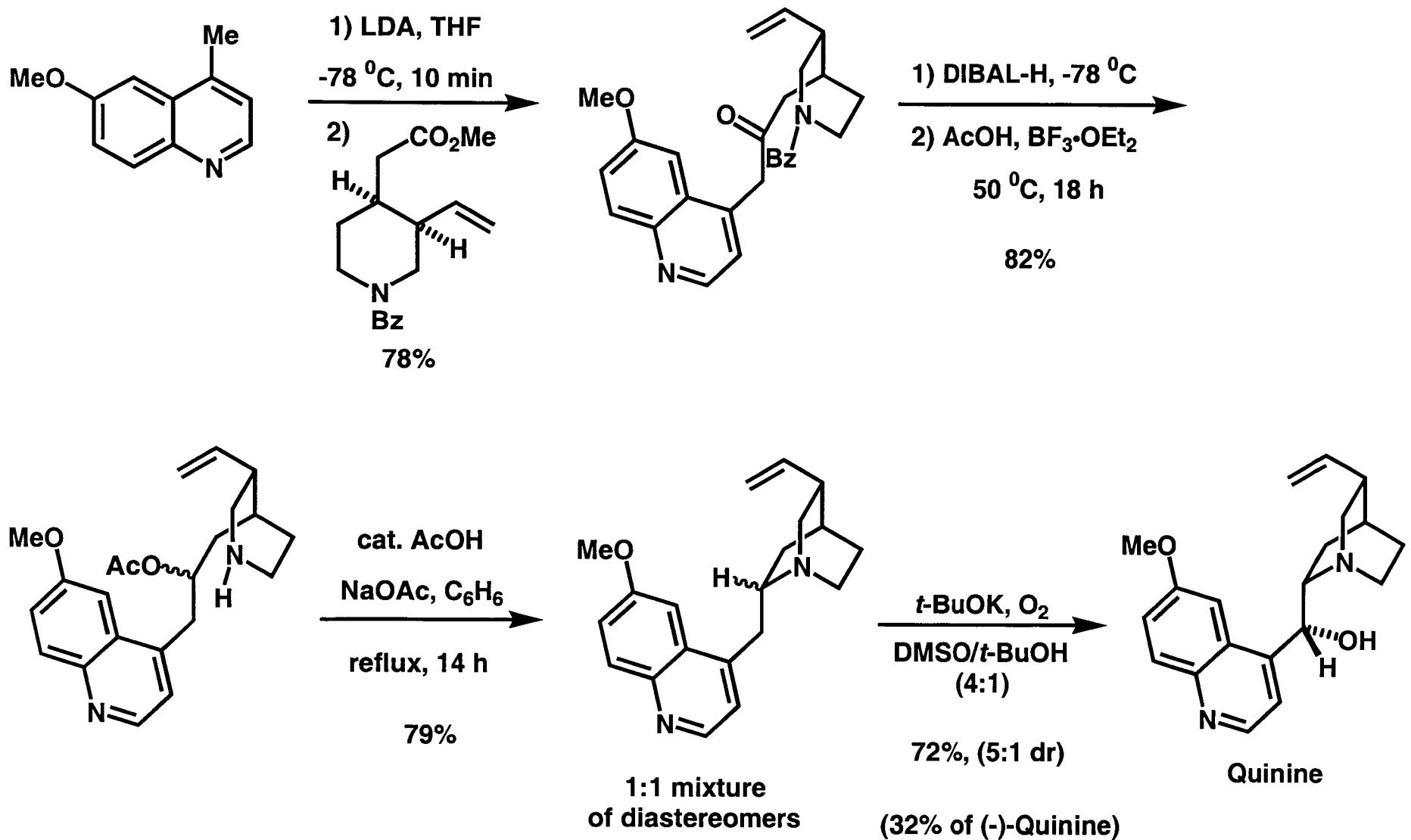


Question?

Draw a mechanism for steps A and B

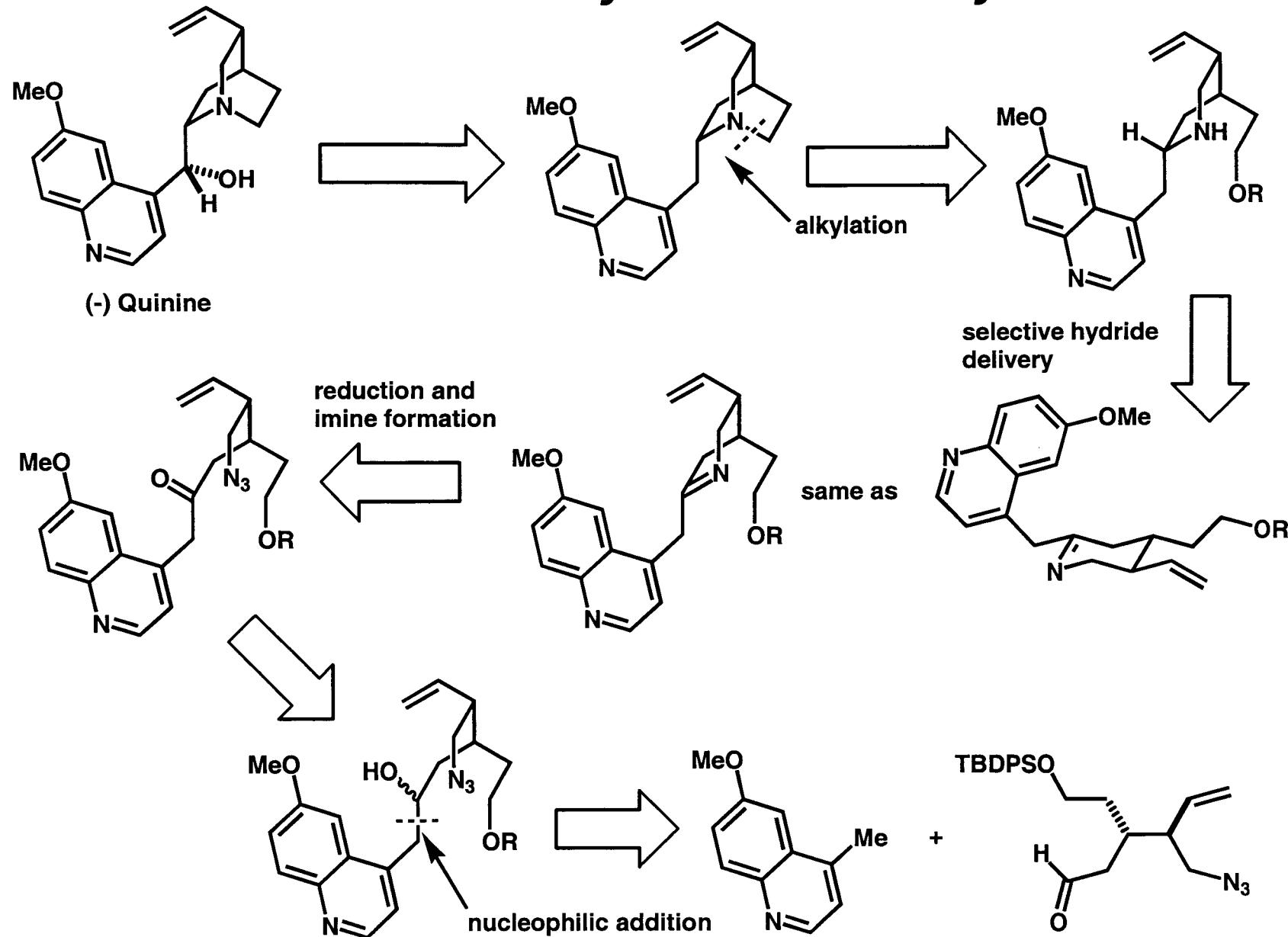


Completion of the Uskokovic Synthesis

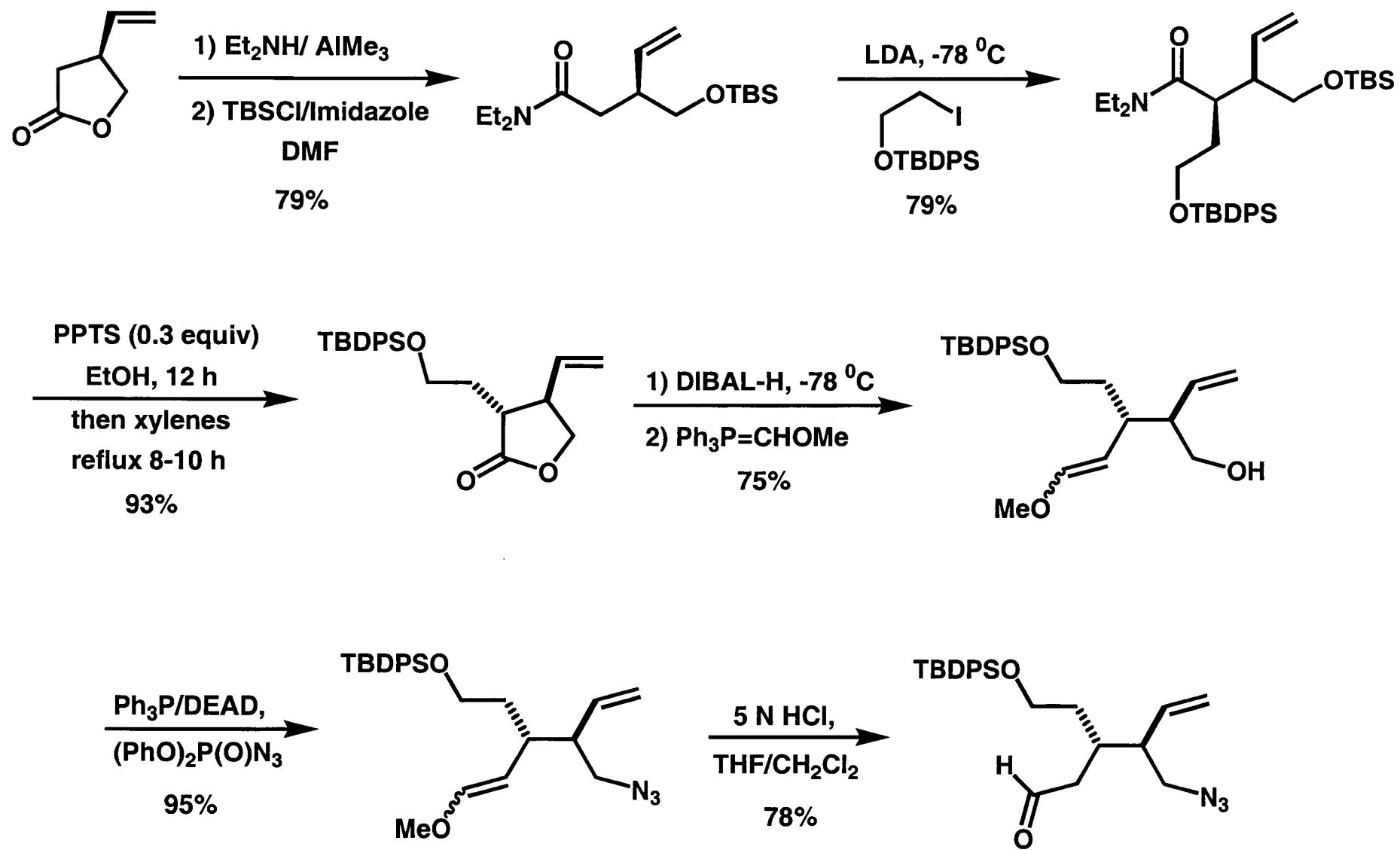


11 steps, 4.8% overall

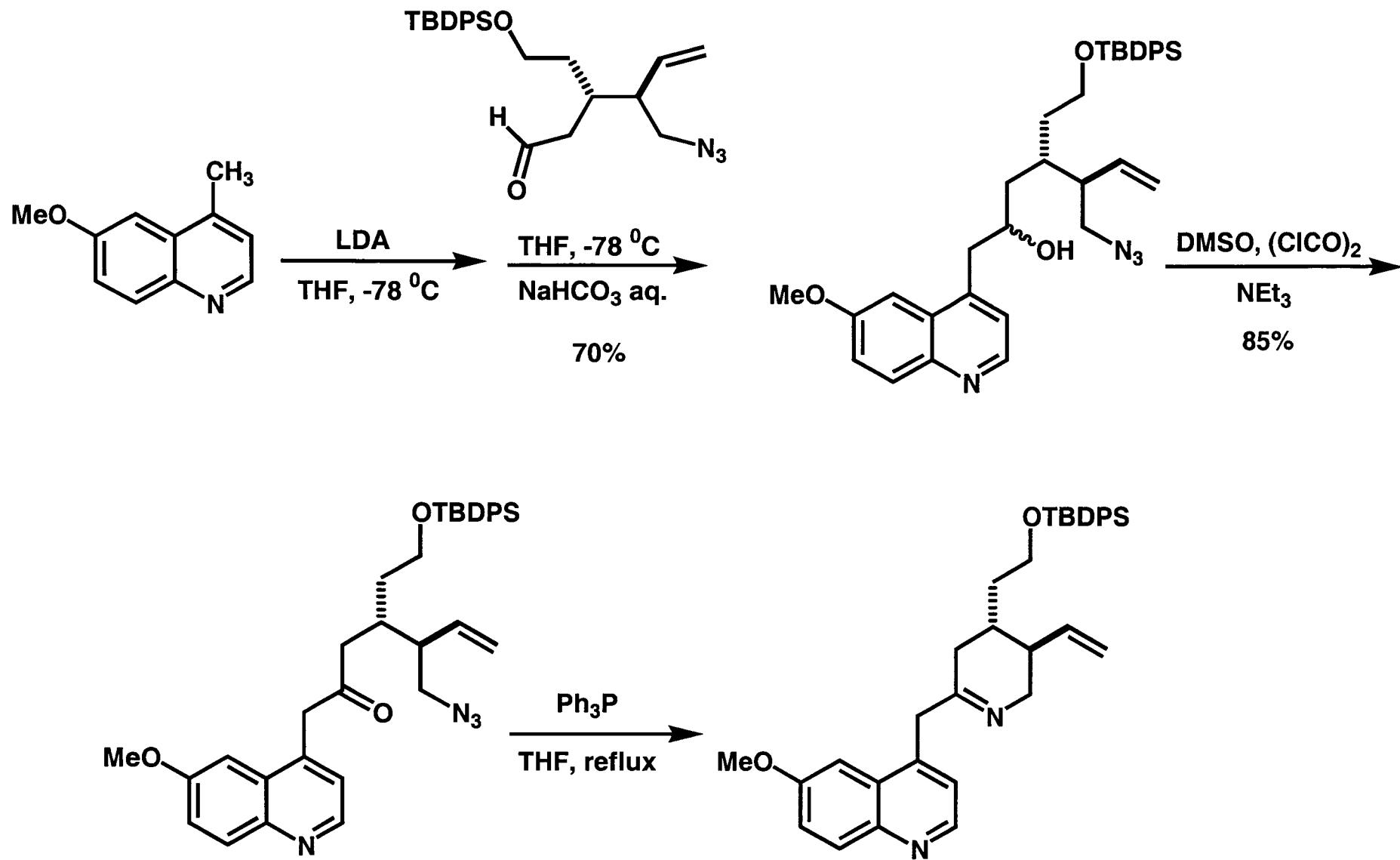
Stork Retrosynthetic Analysis



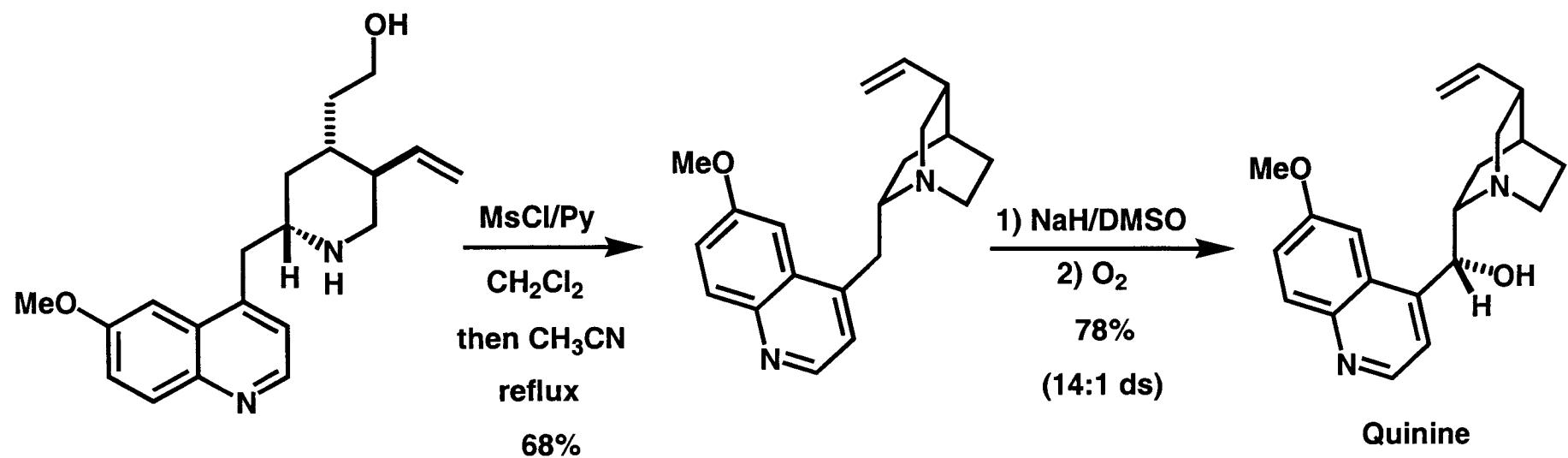
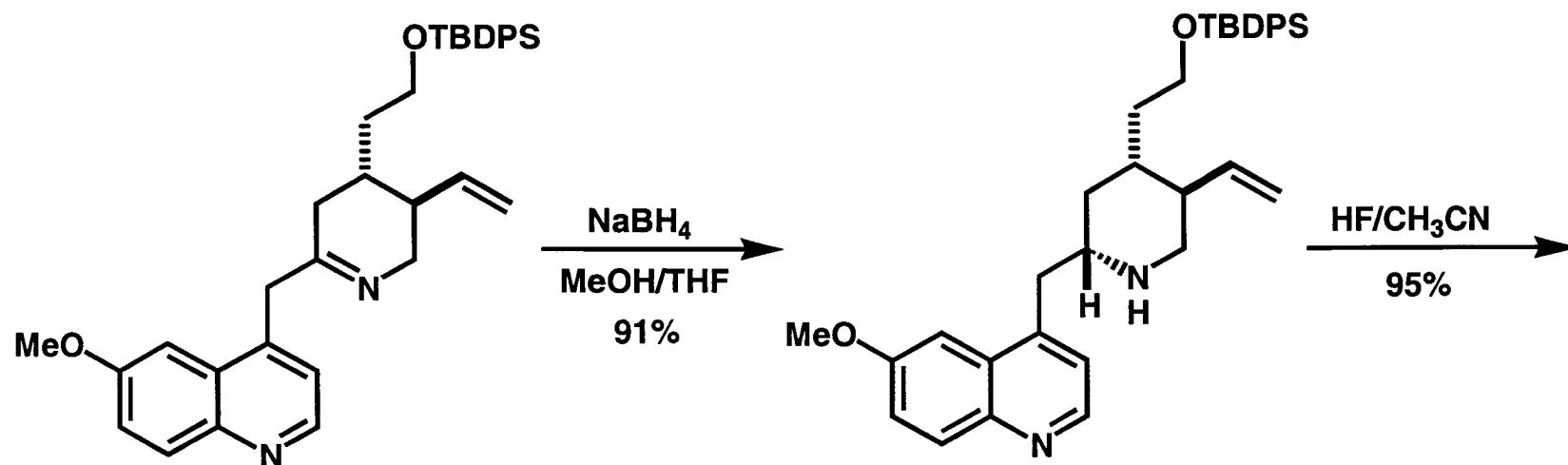
Stork Forward Synthesis 1



Stork Forward Synthesis 2

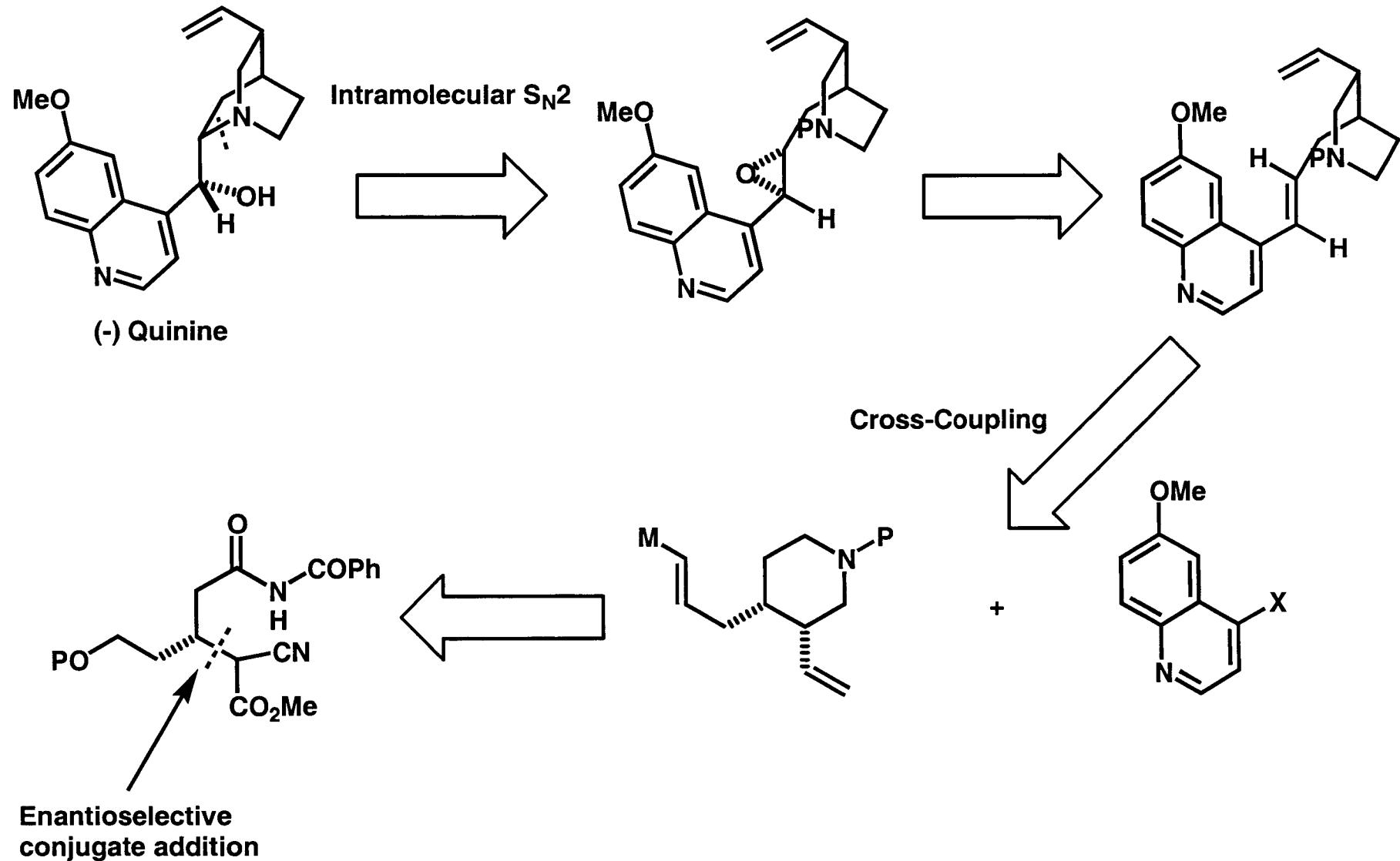


Completion of the First Stereoselective Synthesis



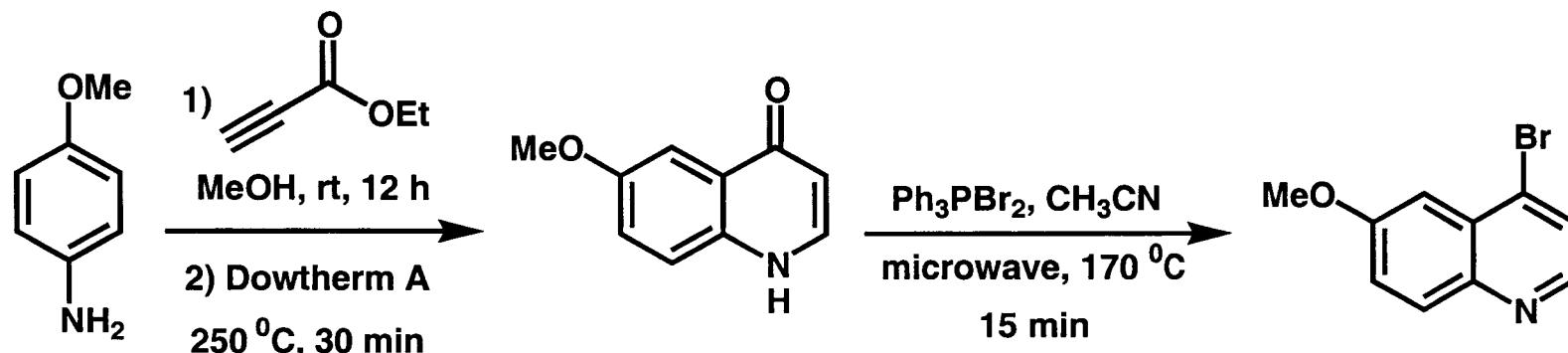
13 steps, 15% overall

Jacobsen Approach

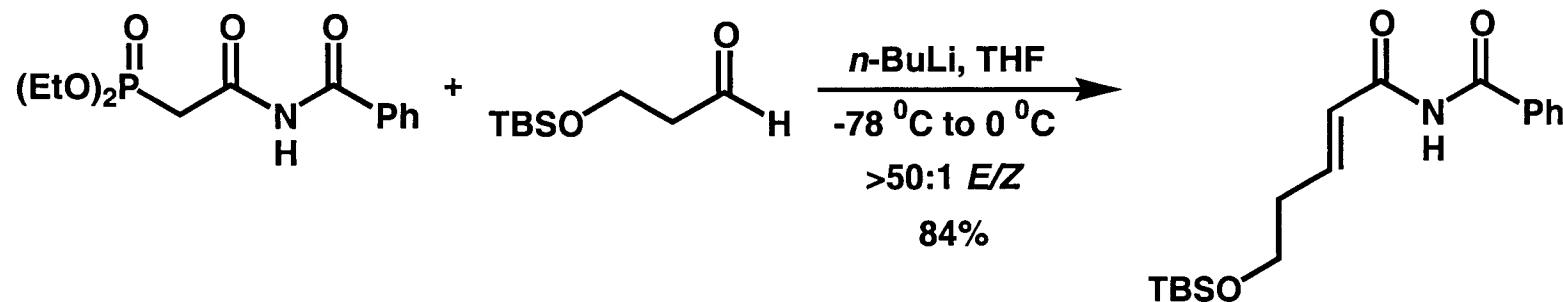


Jacobsen Forward Synthesis

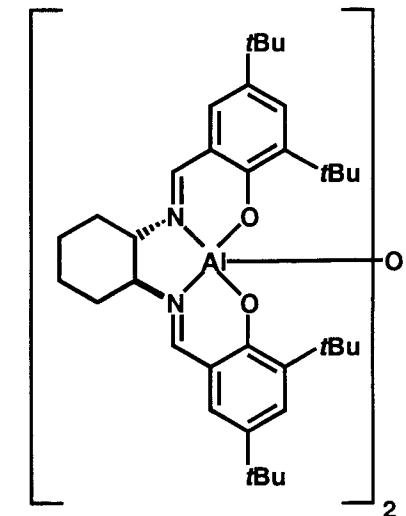
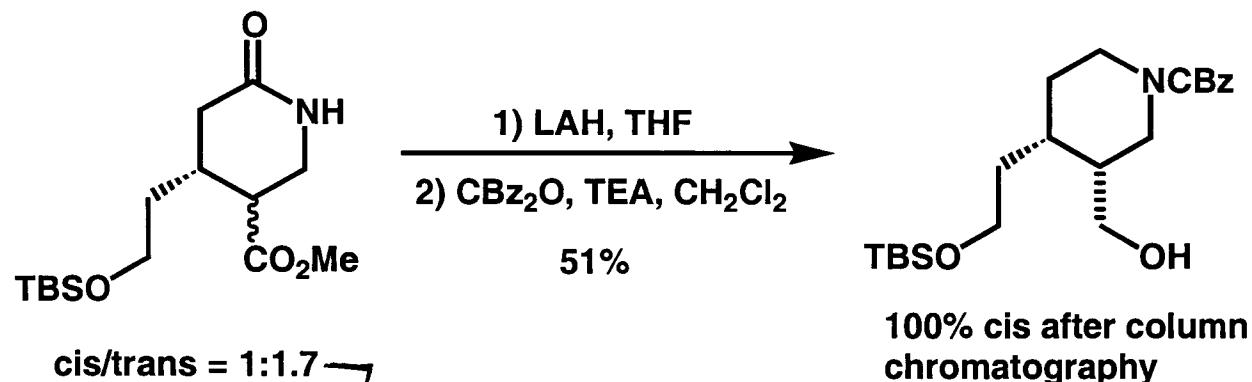
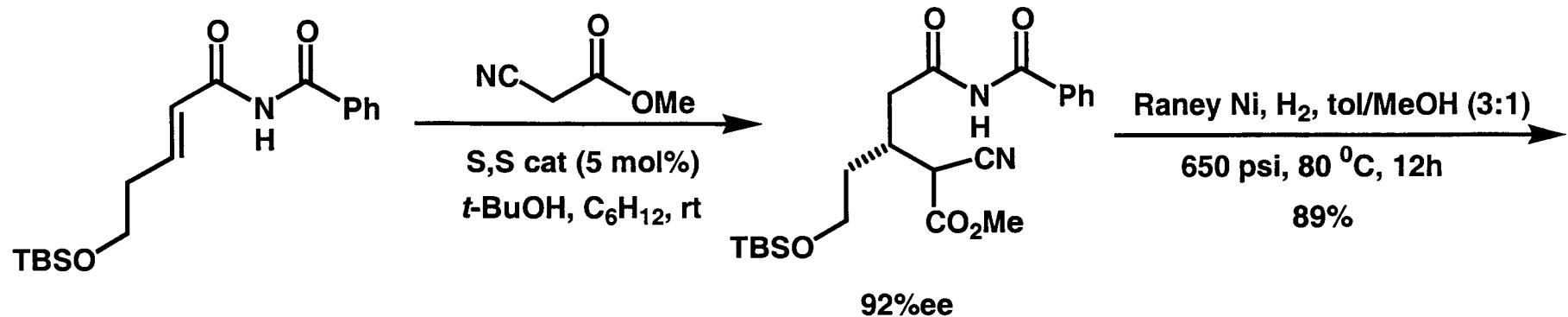
Preparation of bromo quinoline



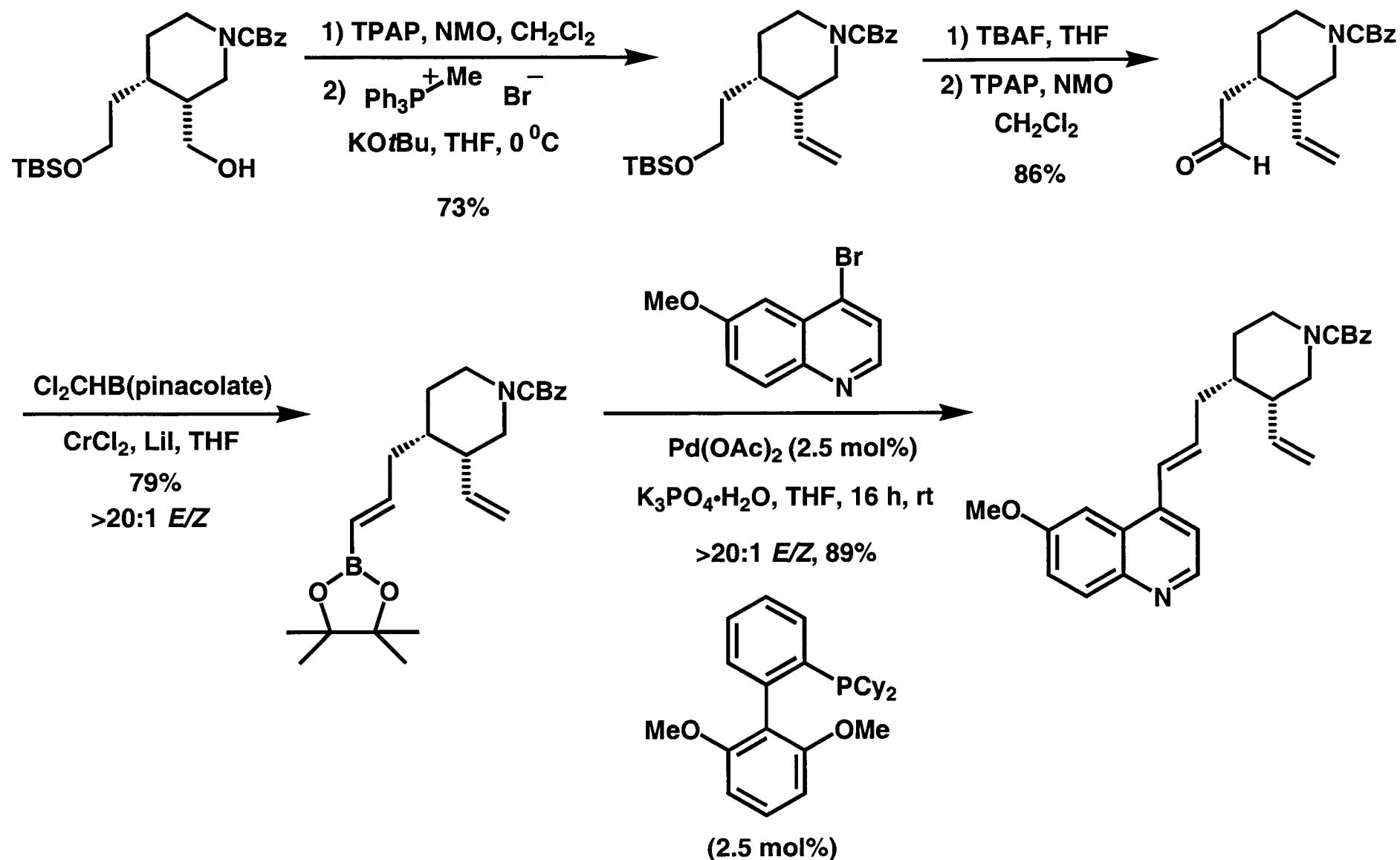
Preparation of quinuclidine portion



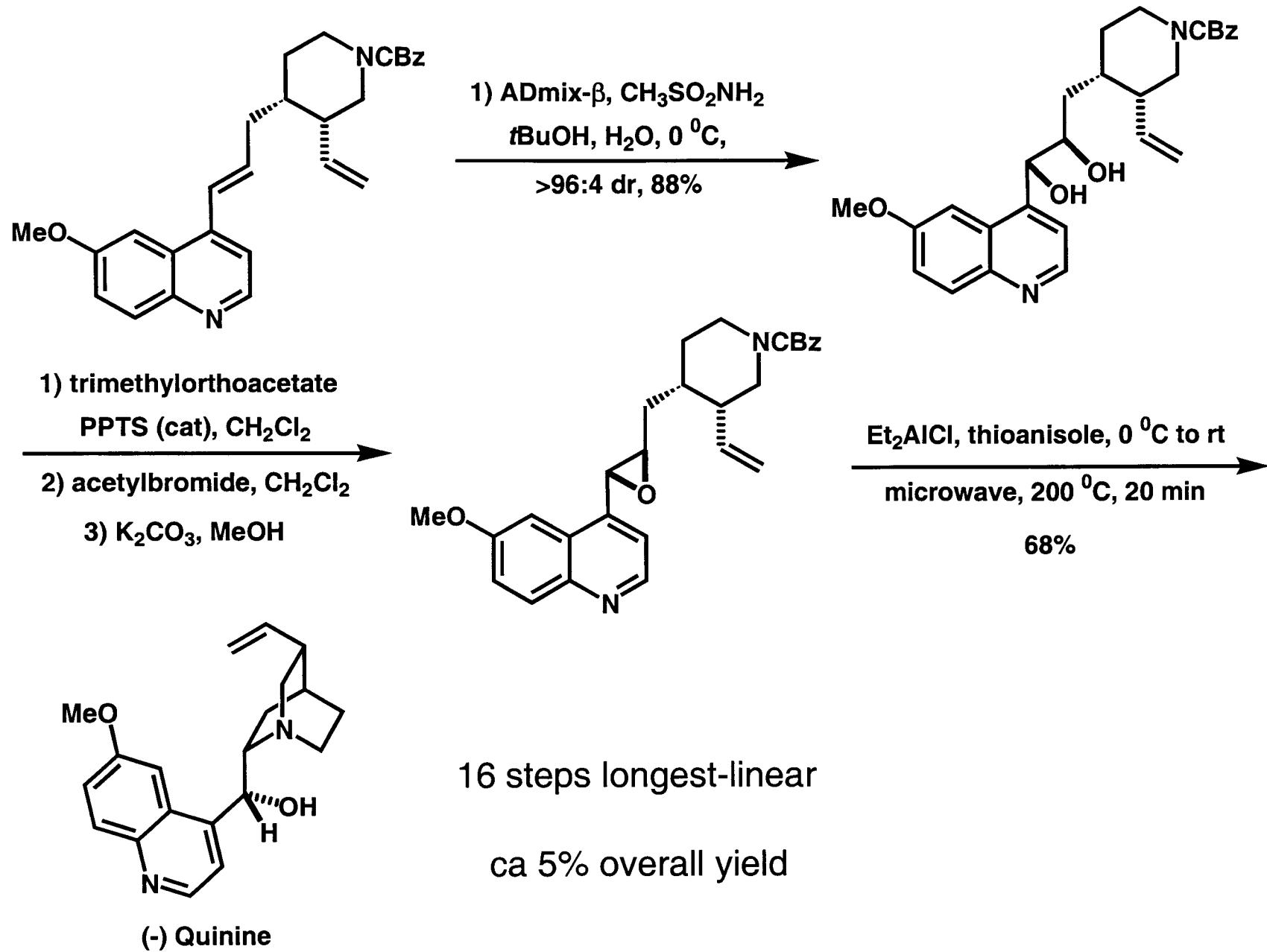
Forward Synthesis 2



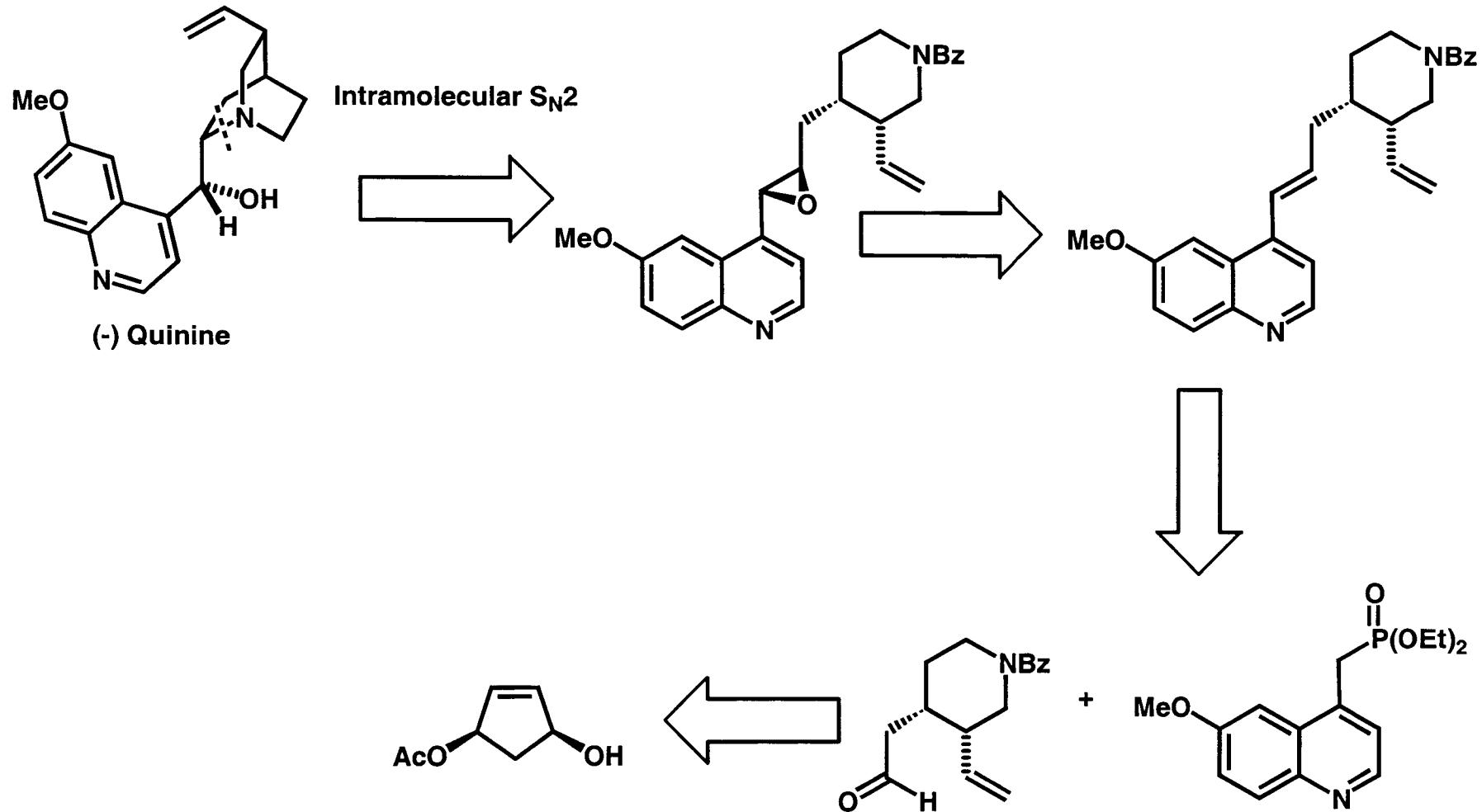
Jacobsen Forward Synthesis 3



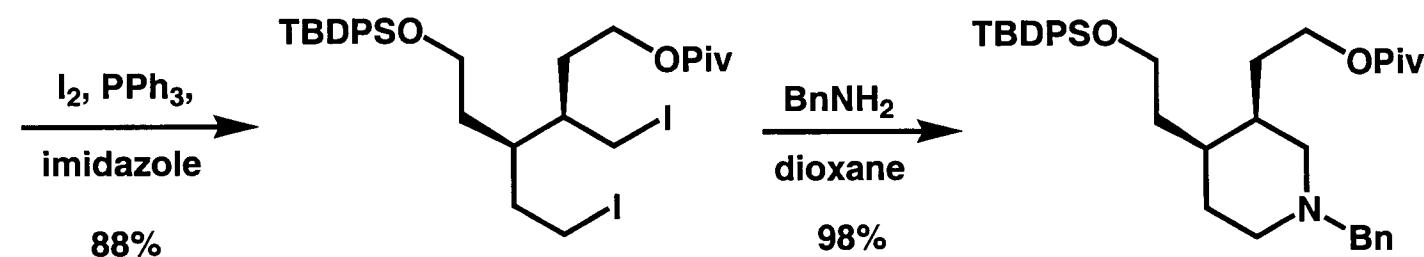
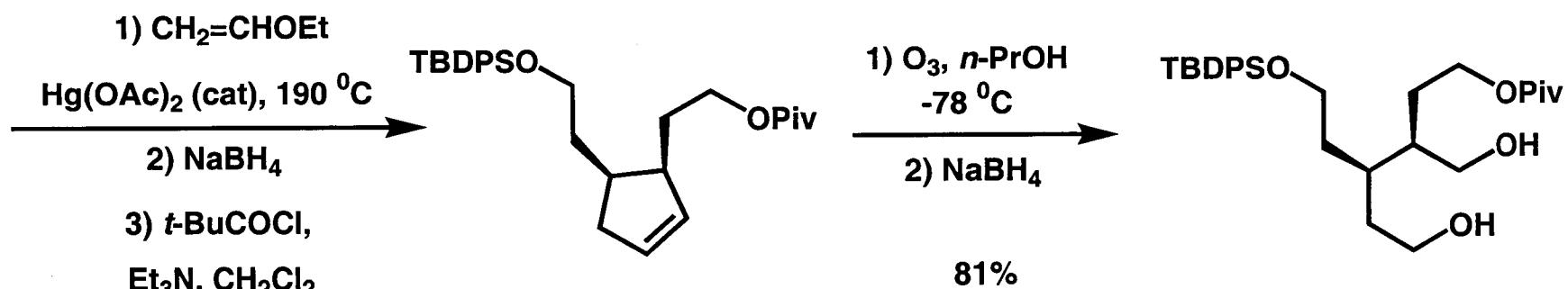
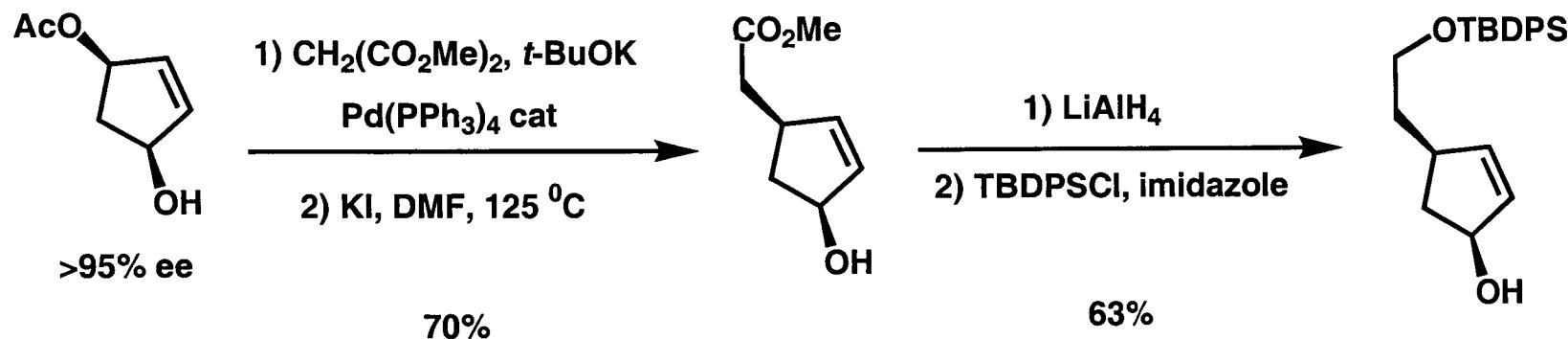
Completion of the Jacobsen Synthesis



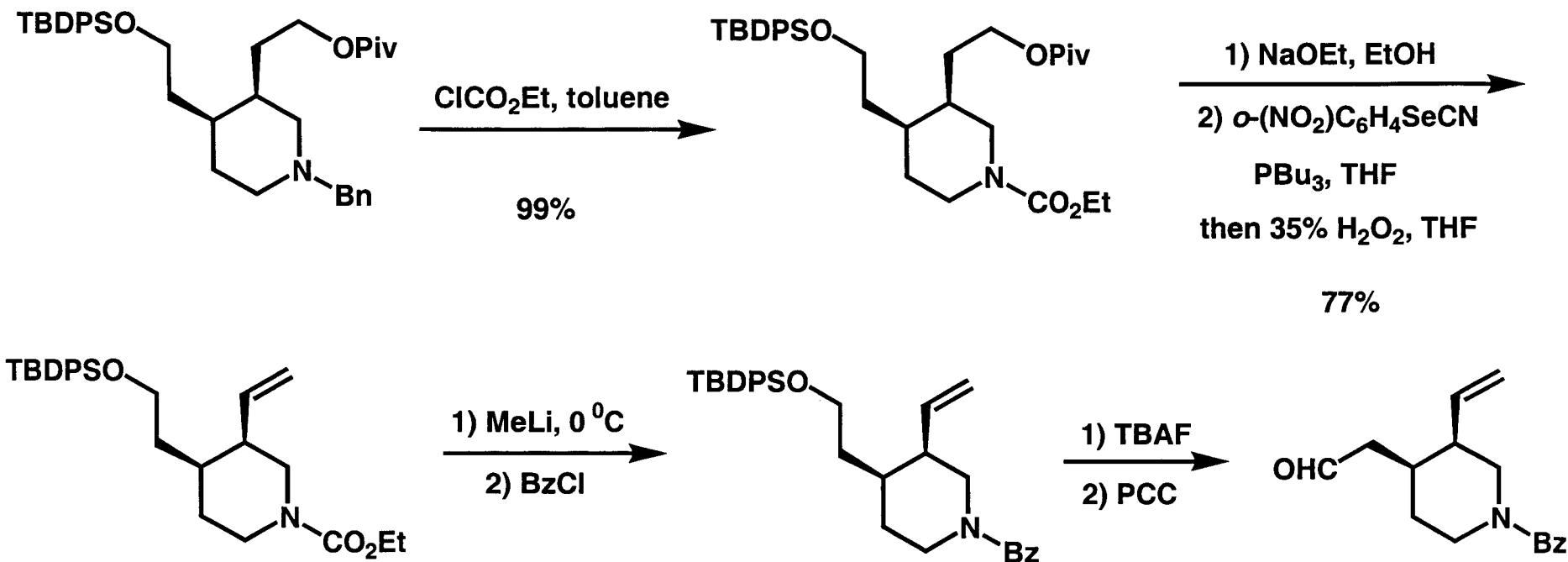
Kobayashi Retrosynthesis



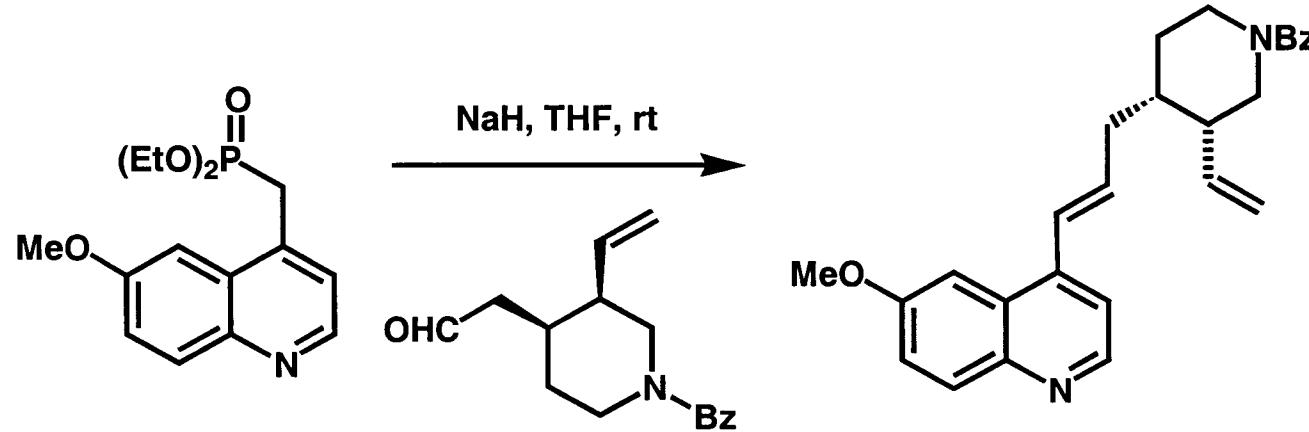
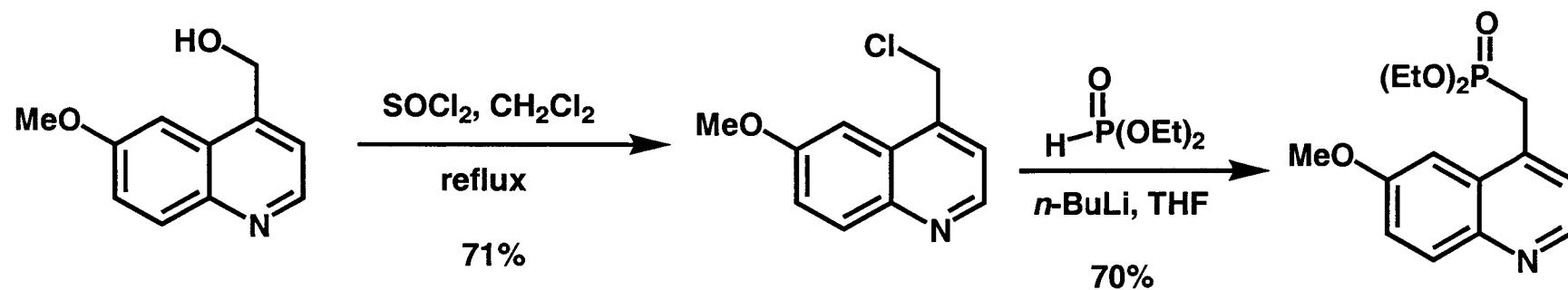
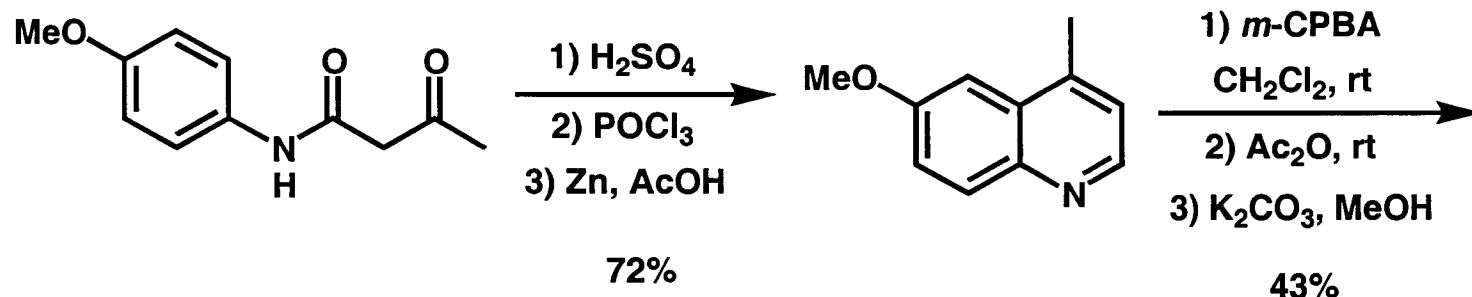
Kobayashi Forward Synthesis 1



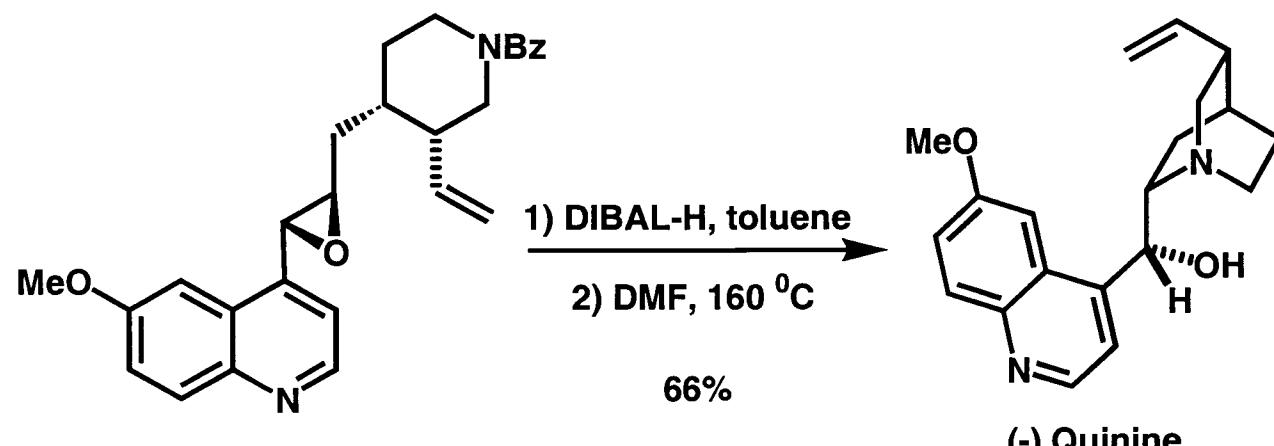
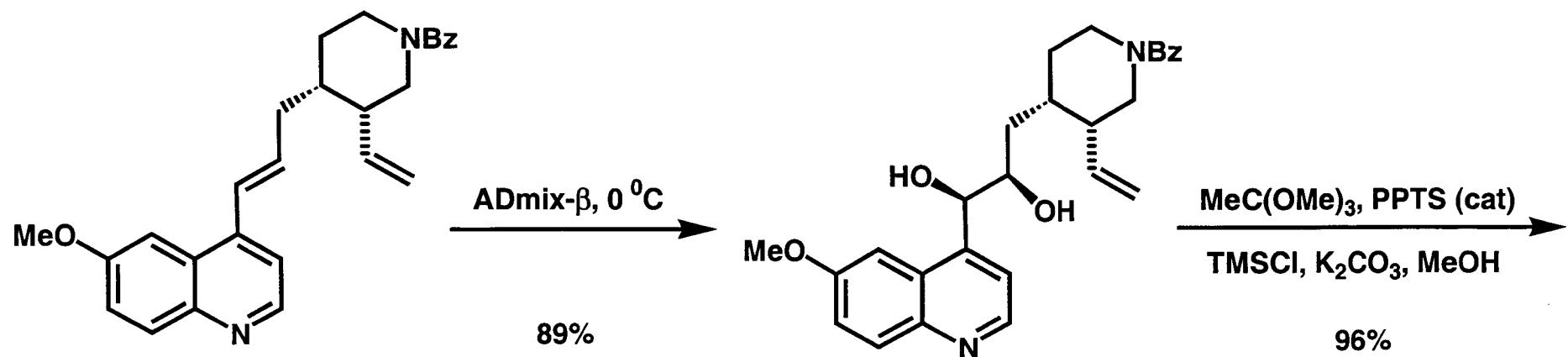
Completion of the Piperidine aldehyde



Preparation of the Quinoline Phosphonate



Completion of the Synthesis



3.5% overall
23 steps longest-linear

Conclusions

Woodward Synthesis (1944):

Used isoquinoline skeleton for quinuclidene ring; 18 steps to quinotoxine, 0.6% yield in a time before NMR and column chromatography,

Uskokovic Synthesis (1978):

Prepared quinine in 11 steps, 5% yield, but suffered from poor stereocontrol

Stork Synthesis (2001):

First stereoselective synthesis of (-) quinine. Quinuclidine ring formation through N1-C6 displacement reaction. Synthesis proceeded in 15% yield (13 steps)

Jacobsen (2004):

First catalytic, enantioselective synthesis of quinine. Synthesis also allowed for the preparation of quinidine. 16 steps; 5% overall yield

Kobayashi (2004):

Catalytic, enantioselective synthesis proceeded in 23 steps, 3.5% yield