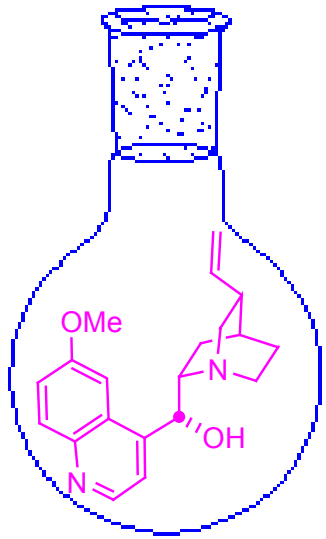
Synthetic Studies on Quinine: Quinuclidine Construction via a Ketone Enolate Regio- and Diastereoselective Pd-Mediated Allylic Alkylation



Deidre M. Johns, Makoto Mori, and Robert M. Williams
Department of Chemistry, Colorado State University
Organic Letters **2006**, *ASAP*

Current Literature, August 12, 2006

Timeline-Quinine

1820/Pelletier and Caventou

Two French chemists isolated quinine from the bark of cinchona tree which are found in the eastern slopes of the Andes mountains from Venezuela to Bolivia, and the natives called the cinchona tree “quina-quina” (“bark of barks’, known as “fever stick”).

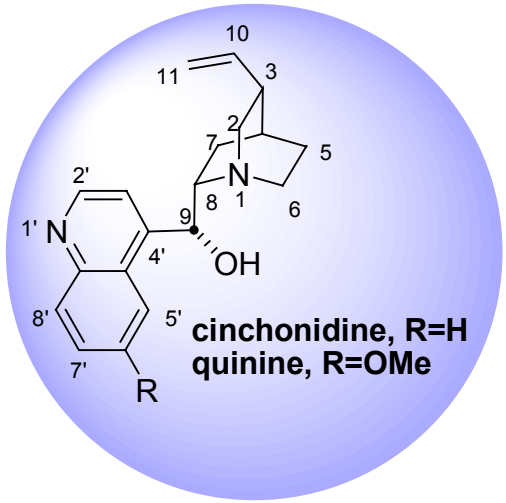
Natives

Bark was dried, ground to a fine powder and mixed into a liquid (usually wine) before being served.

Effective muscle relaxant and antipyretic agents.

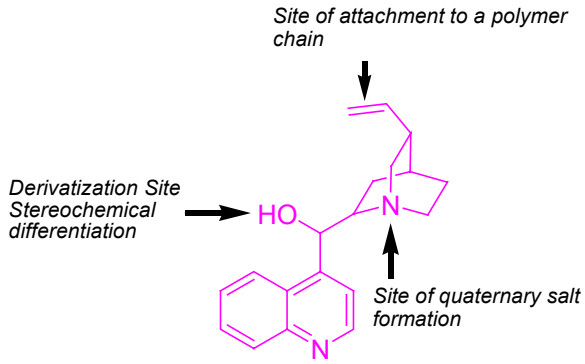
1600s/Europe

Quinine was first used to treat malaria in Rome in 1631, where malaria was epidemic and caused countless deaths in Europe.



cinchonidine, R=H
quinine, R=OMe

1900s-present/Versatile Catalysts and Ligands in Asymmetric Synthesis



1940s-present/Total Syntheses

Woodward and Doering

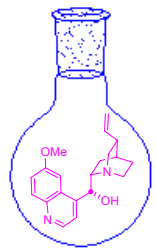
Uskokovic

Stork

Jacobsen

Kobayashi

Williams



1820-1930s/Searching for Alternative Methods

Pelletier and Caventou, Hofmann, Rabe

Streaker (1854 Emperical formula $C_{20}H_{24}N_2O_2$)

Perkins, Prostenik and Prelog

D. A. Casteel in Burgers Medicinal Chemistry and Drug Discovery, 5th Ed., Vol. 5 (Ed.: M. E. Wolff), Wiley, NewYork, 1997, Chap. 59, p. 16.

Treatments

Cinchona has been used for a number of medical reasons such as:

- Treats malaria
- Kills parasites
- Reduces fever
- Regulates heartbeat
- Calms nerves
- Stimulates digestion
- Kills germs
- Reduces spasms
- Kills insects
- Relieves pain
- Kills bacteria and fungi
- Dries secretions

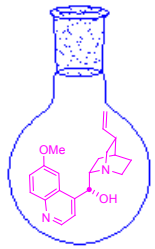
Malaria has been designated as "*the most significant disease for world civilization over the past three millennia".*

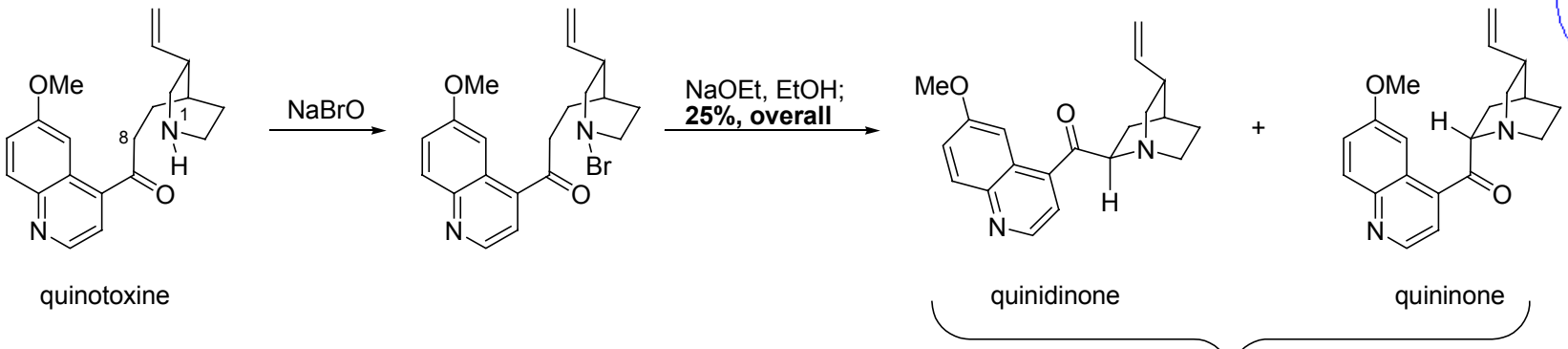
… and the quinine, the most celebrated cinchona alkaloid that was claimed as "*the drug to have relieved more human suffering than any other in history'.*

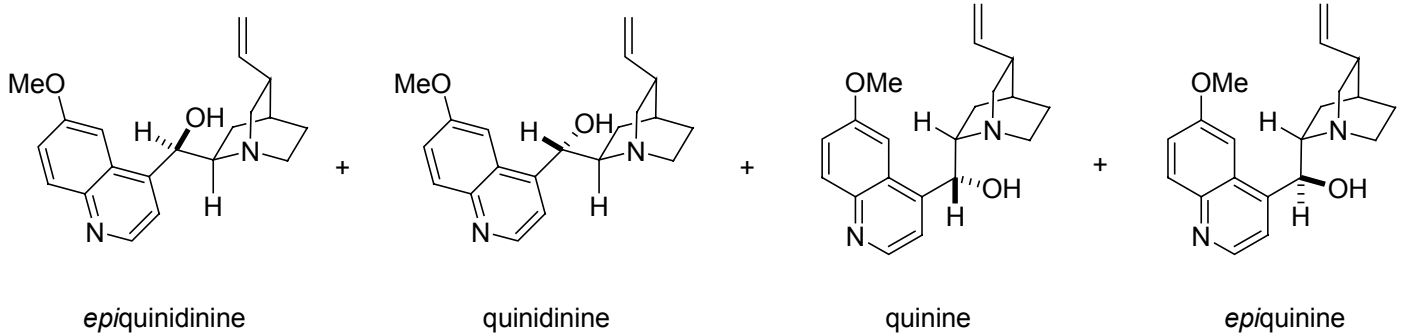
D. A. Casteel in Burgers Medicinal Chemistry and Drug Discovery, 5th Ed., Vol. 5 (Ed.: M. E. Wolff), Wiley, NewYork, 1997, Chap. 59, p. 16.

1918/Rabe and Kindlers' Synthetic Development of Quinine

"Uber die Partialle Synthesedes Chinins" /C8-N1 Bond Disconnection





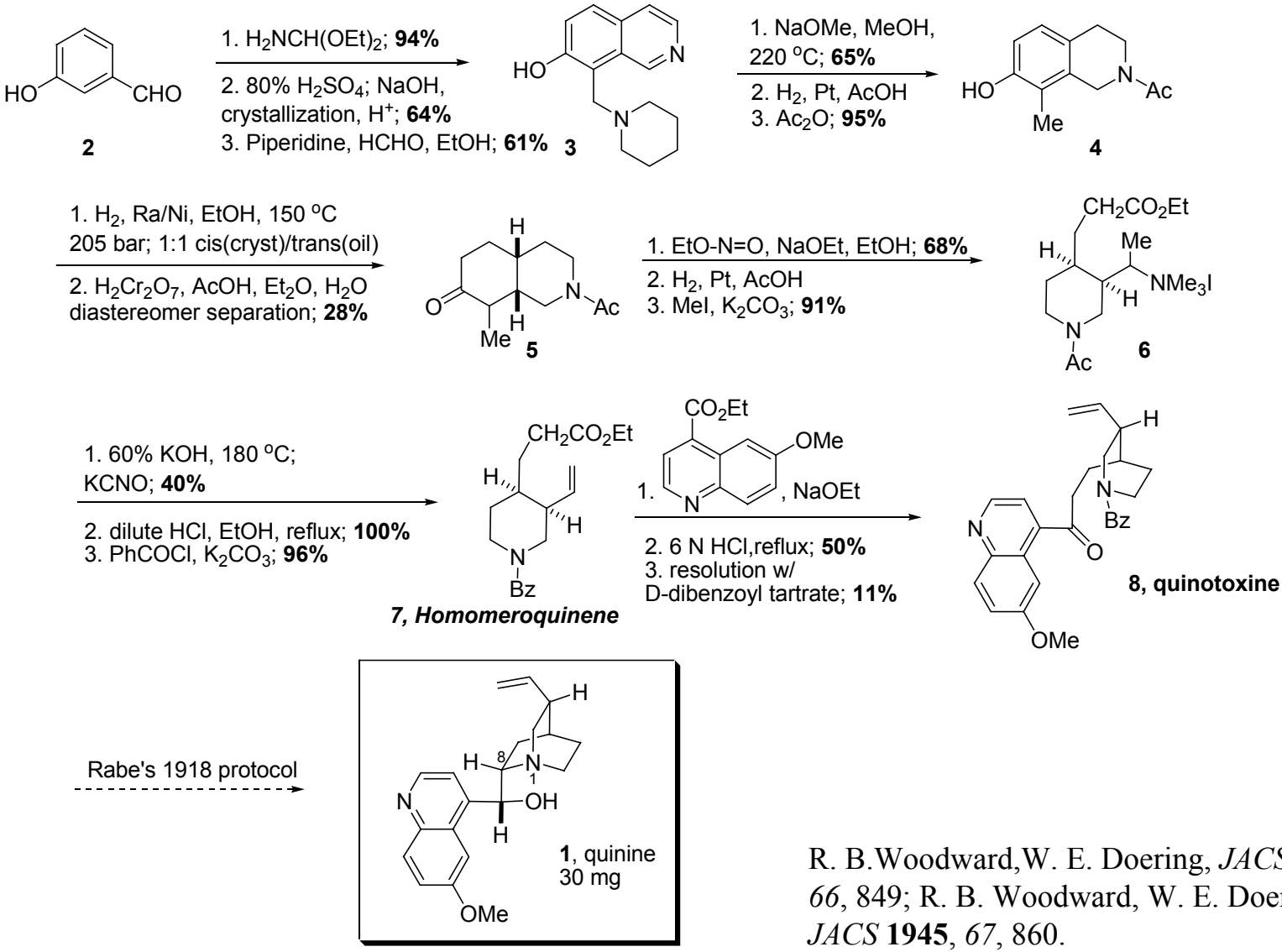


The first major step towards the synthesis of quinine!

P. Rabe, K. Kindler, *Ber. Dtsch. Chem. Ges*. **1918**, *51*, 466.

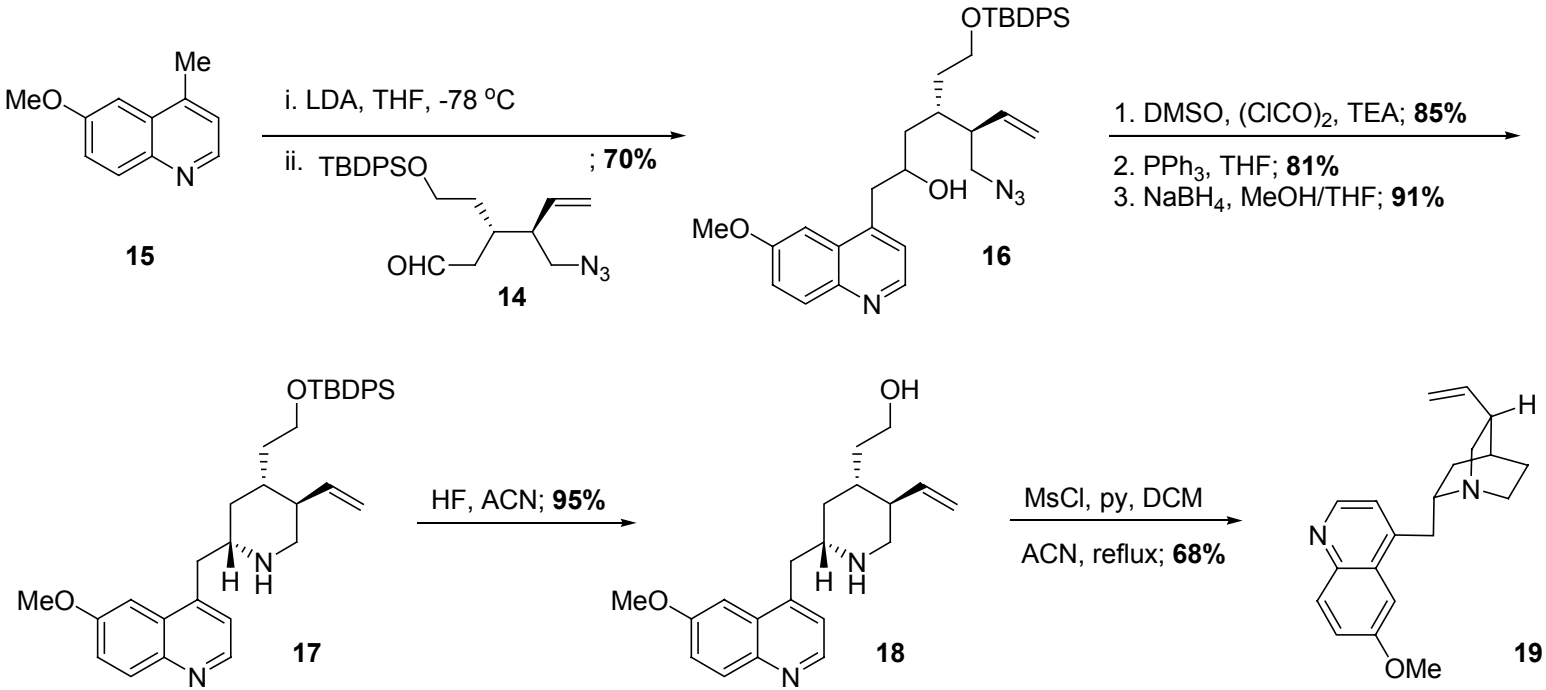
April 11, 1944/Woodward's Formal Total Synthesis of Quinine

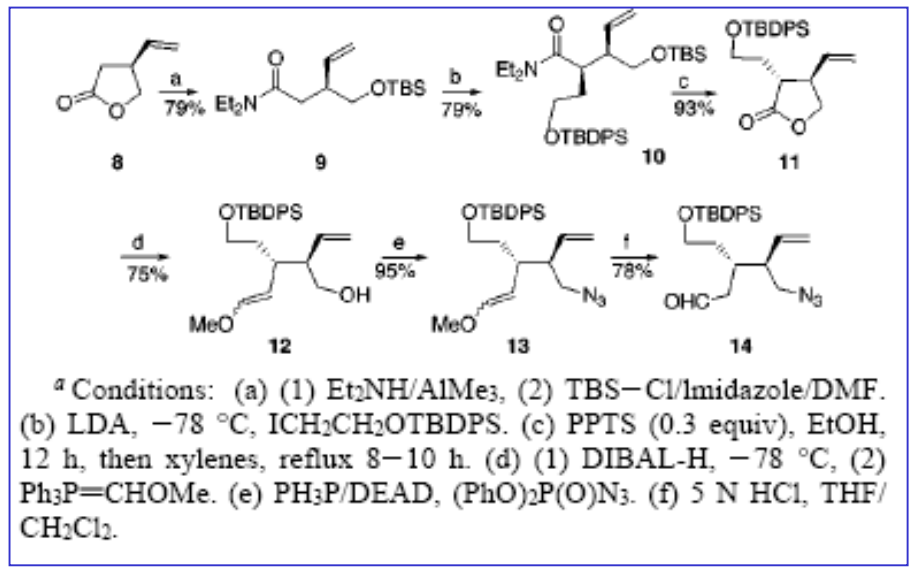
C8-N1 Bond Disconnection



R. B.Woodward,W. E. Doering, *JACS* **1944**, *66*, 849; R. B. Woodward, W. E. Doering, *JACS* **1945**, *67*, 860.

57 Years Later…2001/Stork's First Stereoselective Total Synthesis of Quinine-C6-N1 Bond Disconnection



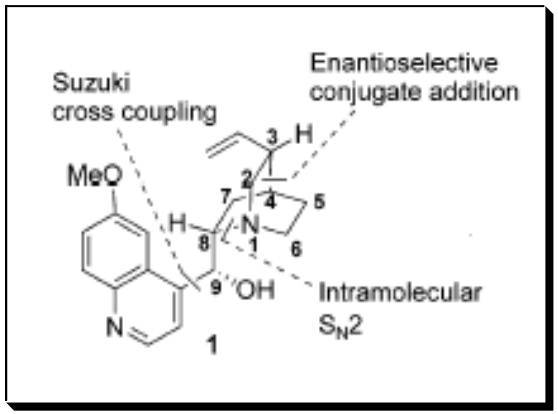


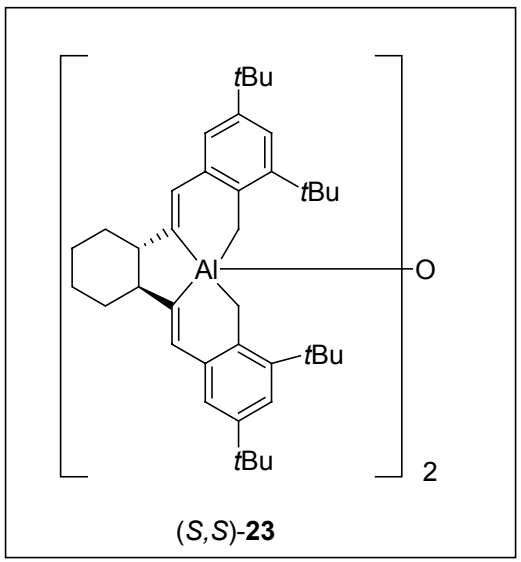
[a] Conditions: (a) (1) $Et_2NH/AlMe_3$, (2) TBS−Cl/Imidazole/DMF. (b) LDA, −78 °C, $ICH_2CH_2OTBDPS$. (c) PPTS (0.3 equiv), EtOH, 12 h, then xylenes, reflux 8−10 h. (d) (1) DIBAL-H, −78 °C, (2) $Ph_3P{=}CHOMe$. (e) PH_3P/DEAD, $(PhO)_2P(O)N_3$. (f) 5 N HCl, THF/CH_2Cl_2.

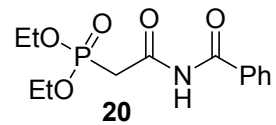
G. Stork, *et al JACS* **2001**, **123**, 3239.

2004/Jacobsen's First Catalytic Asymmetric Total Syntheses of Quinine and Quinidine

C8-N1 Bond Disconnection







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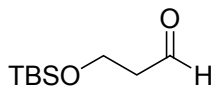
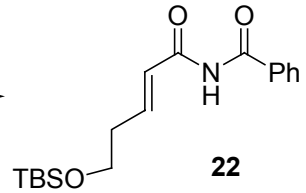


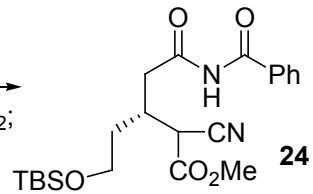
n-BuLi, THF

>50:1 E/Z; **84%**

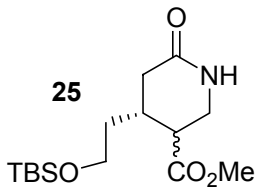


methylcyanoacetate,

(*S,S*)-**23**, *t*-BuOH, C_6H_{12};
91%, 92%ee



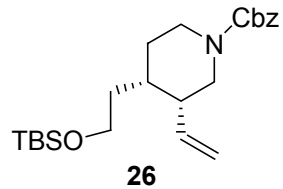
Ra/Ni, H_2, 650 psi;
89%



cis/trans=1:1.7
3:1] LDA

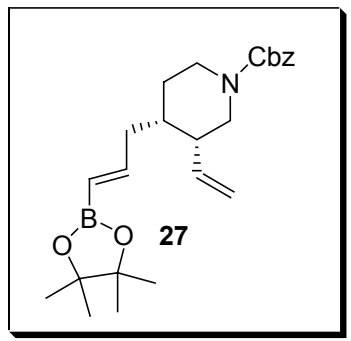
1. LAH, THF; CBz_2O,
TEA; **51%**

2. TPAP, NMO, DCM
3. methyltriphenylphosphonium
bromide, KO*t*Bu; **73%**



1. TBAF, THF
2. TPAP, NMO, DCM; **86%**

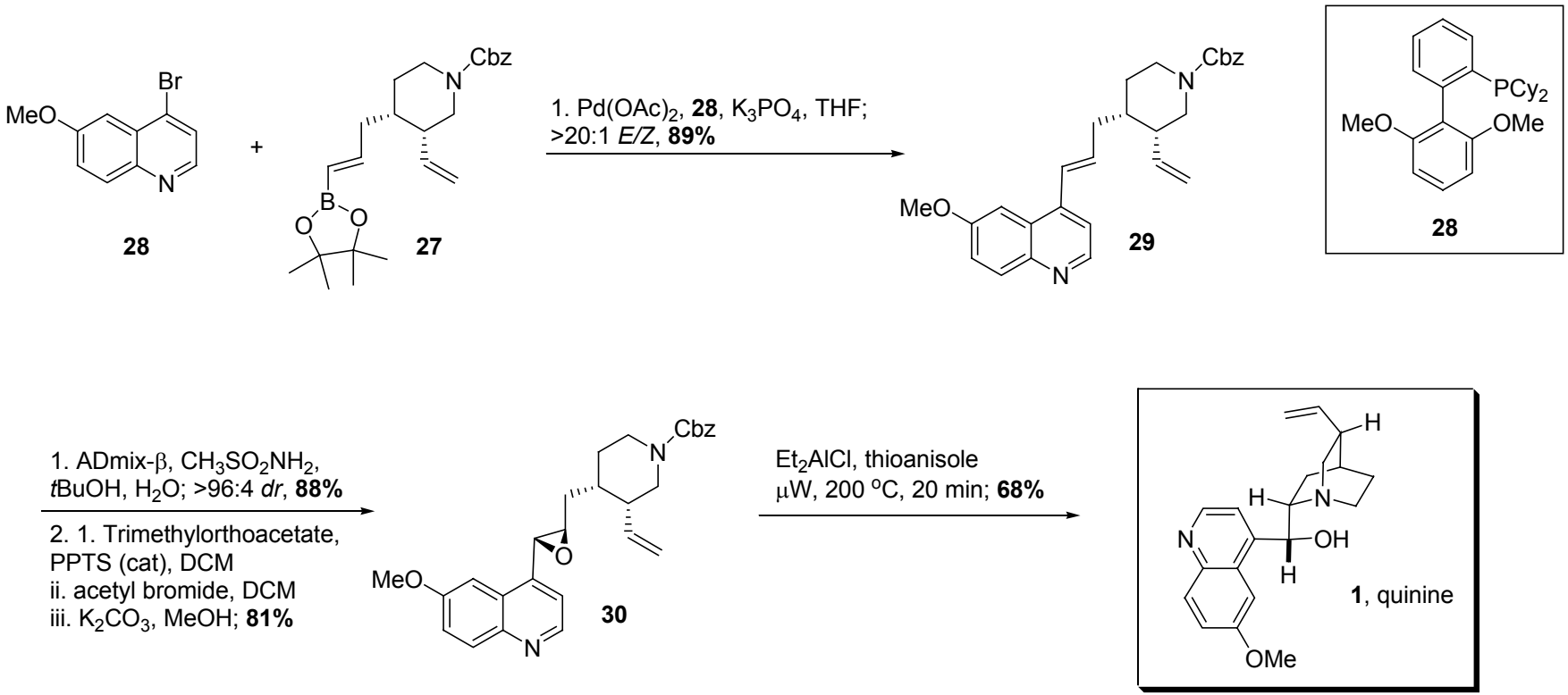
3. Cl_2CHB(pinacolate), $CrCl_2$,
LiI, THF; >20:1 E/Z, **79%**



I. T. Raheem, S. N. Goodman, E. N. Jacobsen, *JACS* **2004**, *126*, 706.

2004/Jacobsen's Catalytic Asymmetric Total Syntheses of Quinine and Quinidine

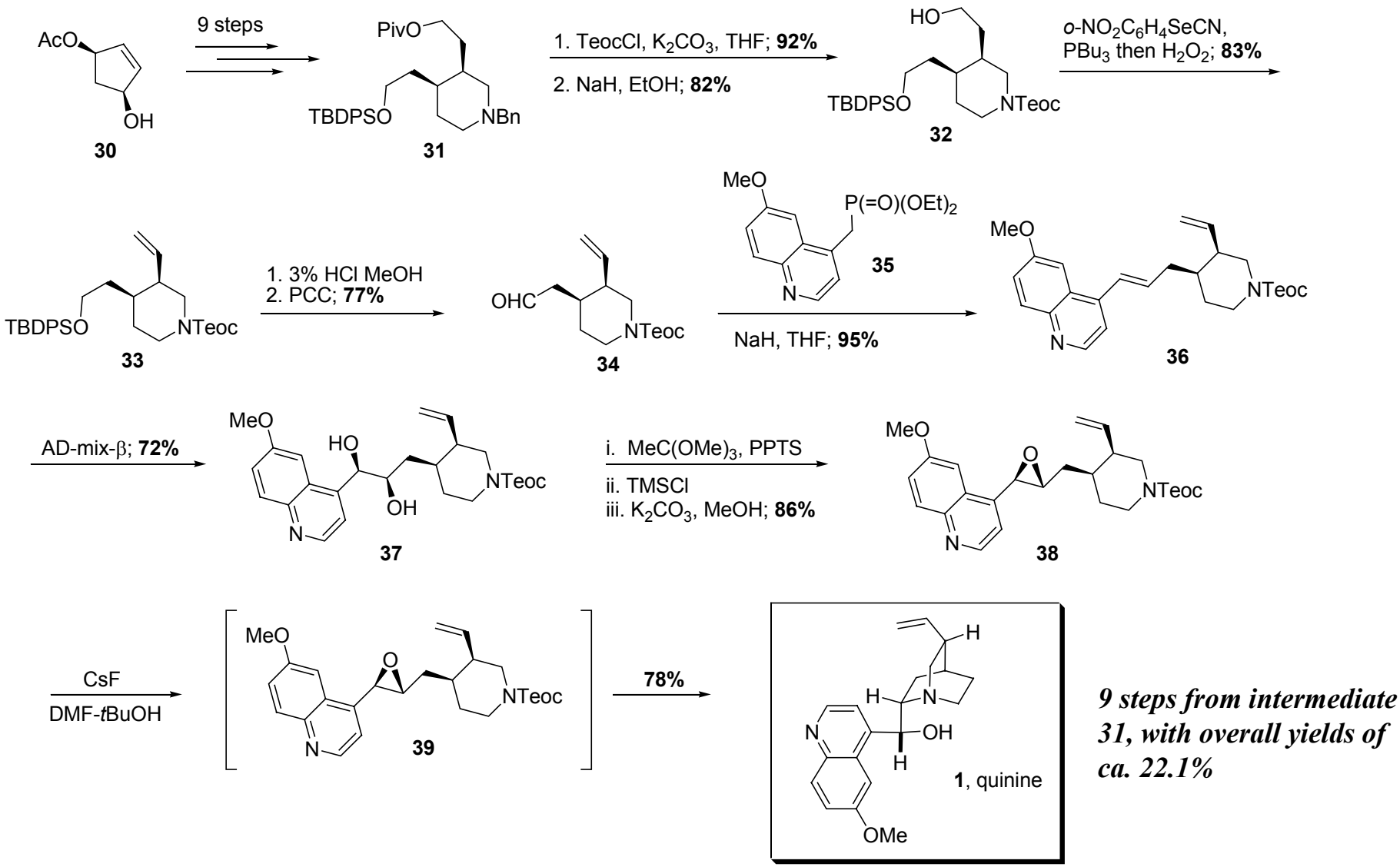
C8-N1 Bond Disconnection



16 longest linear steps with overall yields of ca. 5%

I. T. Raheem, S. N. Goodman, E. N. Jacobsen, *JACS* **2004**, *126*, 706.

2004-5/Kobayashi's Stereocontrolled Synthesis of Quinine and Quinidine C8-N1 Bond Disconnection

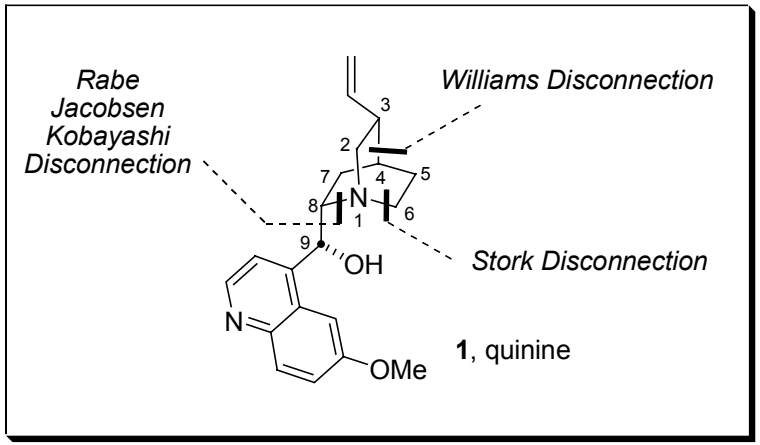


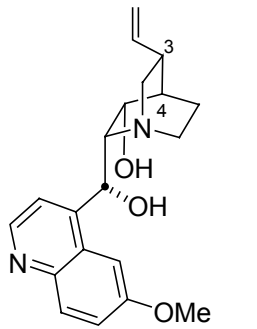
9 steps from intermediate 31, with overall yields of ca. 22.1%

J. Igarashi, M. Katsukawa, Y.-G. Wang, H. P. Acharya, Y. Kobayashi, *TL* **2004**, *45*, 3783; J. Igarashi, Y. Kobayashi, *TL* **2005**, *46*, 6381

2006/Williams' Synthetic Studies on Quinine

C3-C4 Bond Disconnection

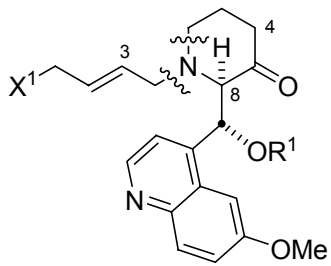




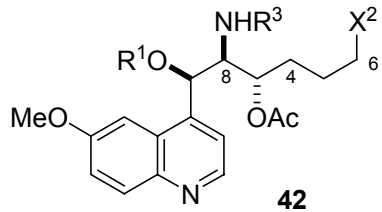
40, 7-hydroxyquinine

Pd(0)-mediated cyclization

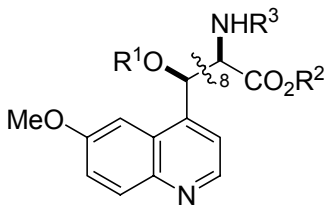
(C3-C4 ring closure)



41



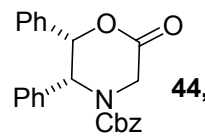
42



43

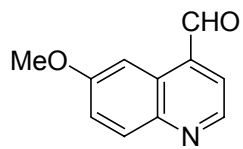
asymmetric aldol

(setting stereo-chemistries at C8/C9)



44, Willliam's lactone

+

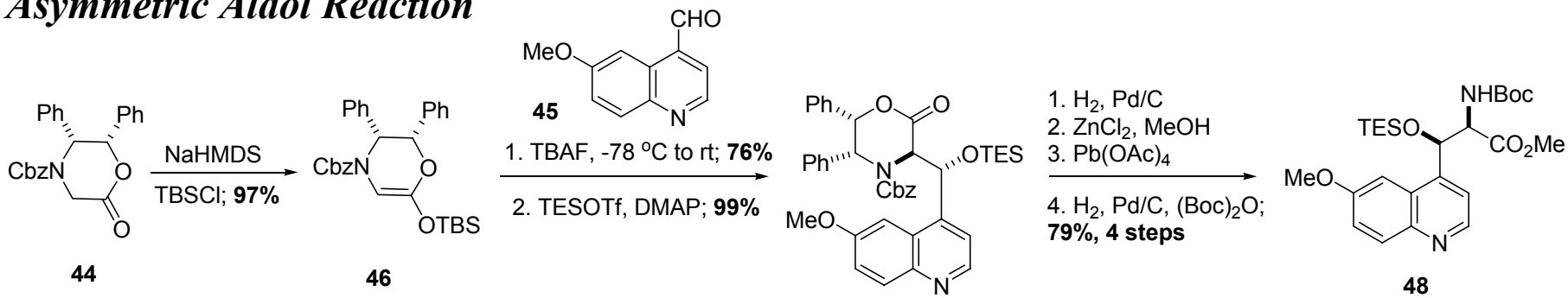


45

D. M. Johns, M. Mori, R. M. Williams, *OL* **2006**, *asap.*

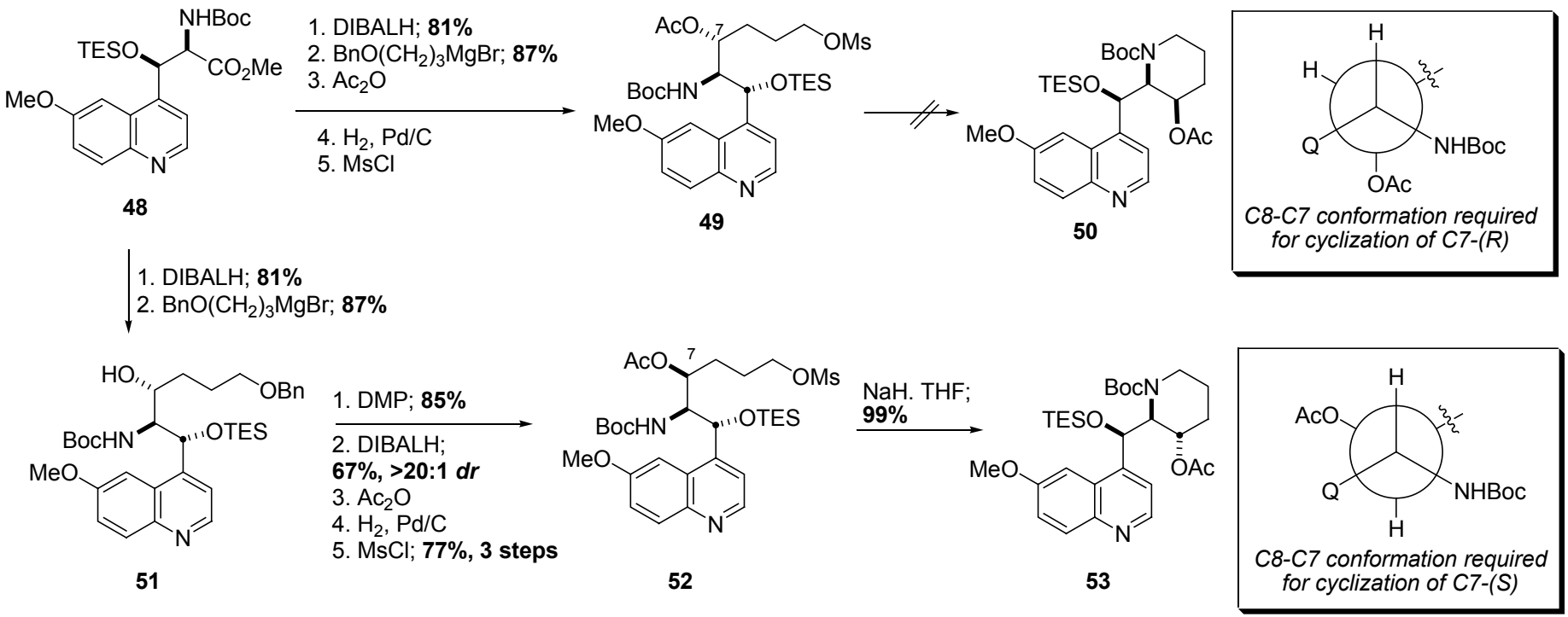
2006/Williams' Synthetic Studies on Quinine

Asymmetric Aldol Reaction



44 **46** **47**, >30:1 dr **48**

Preparation of Piperidine Derivative

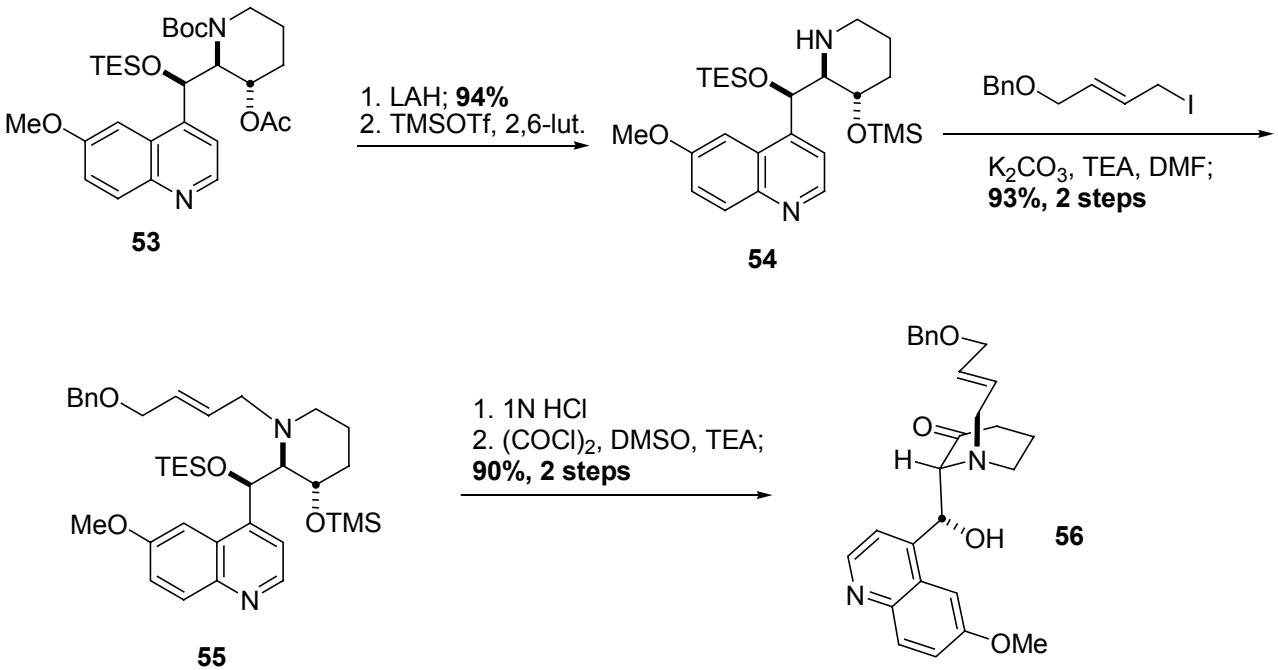


48 **49** **50** **51** **52** **53**

D. M. Johns, M. Mori, R. M. Williams, *OL* **2006**, *asap*.

2006/Williams' Synthetic Studies on Quinine

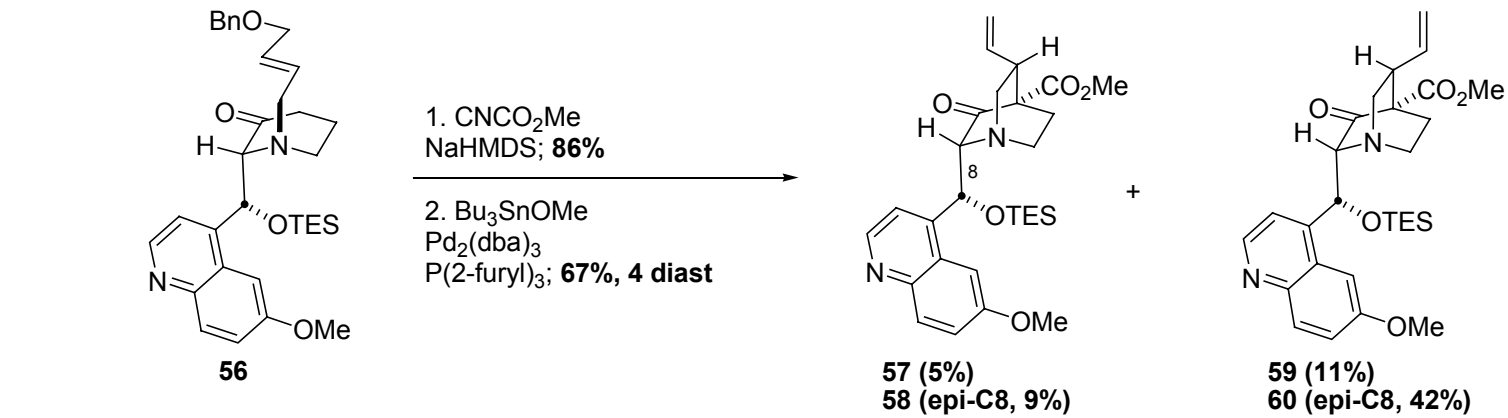
Completion of Allylic Alkylation Precursor



D. M. Johns, M. Mori, R. M. Williams, *OL* **2006**, *asap.*

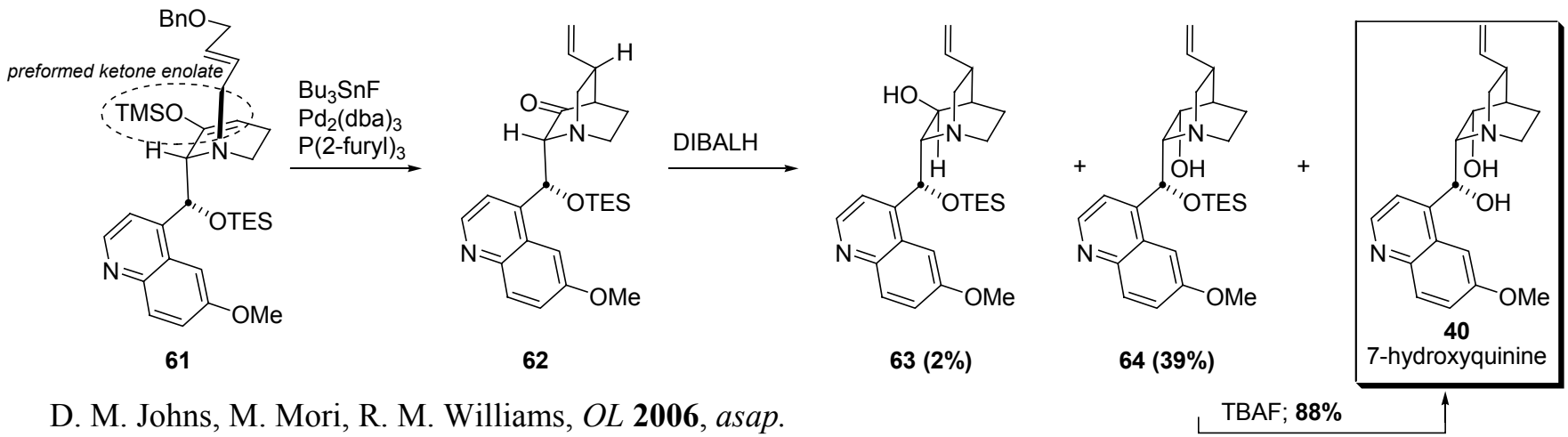
2006/Williams' Synthetic Studies on Quinine-Key Transformation
*Pd(O)-Mediated Allylic Alkylation-*C3-C4 Bond Formation

Allylic Alkylation of Malonic Ester Derivatives



TMSCl, LHMDS,
-78 °C; **59%**

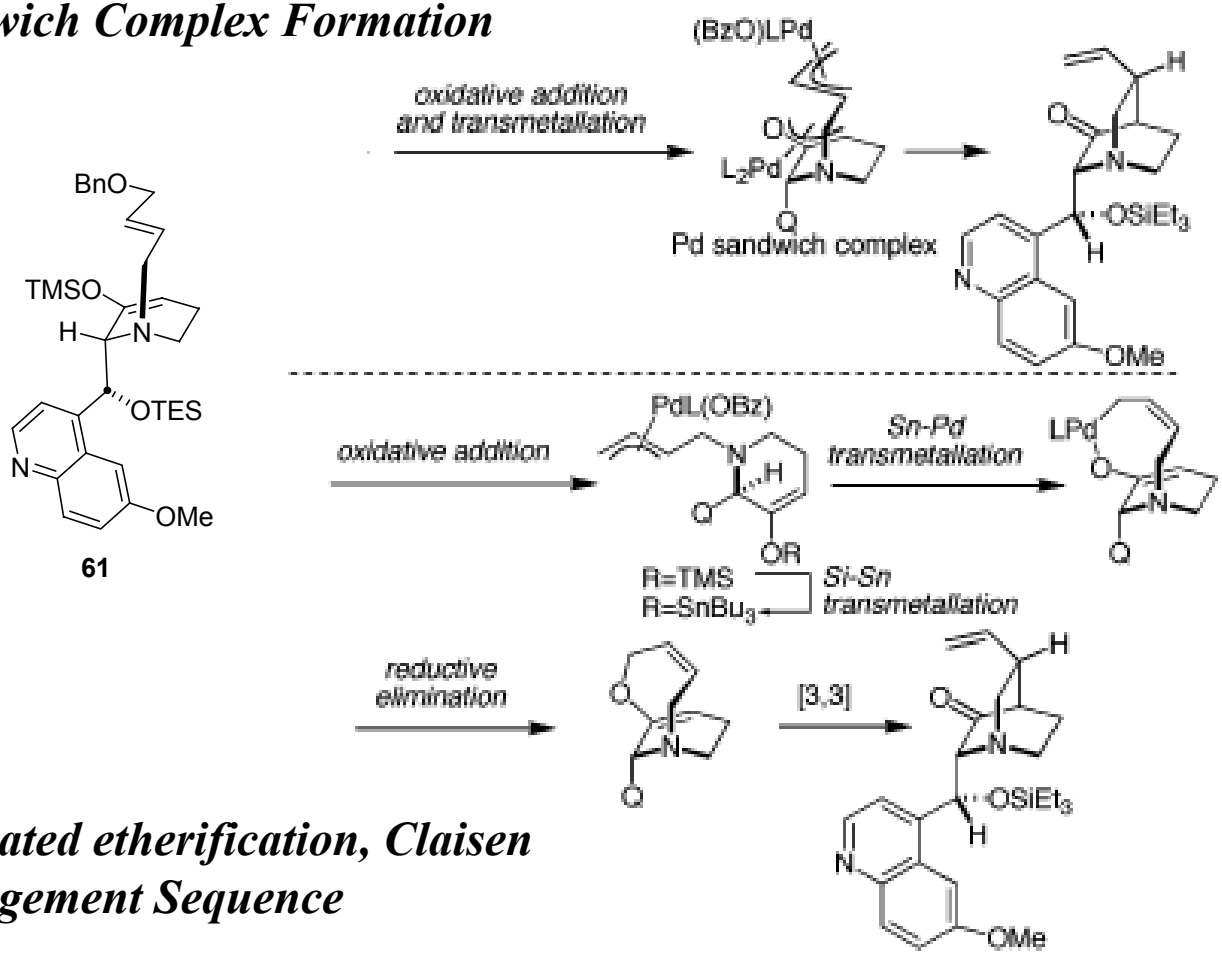
Regio- and Diastereoselective Allylic Alkylation of Ketone-Derived TMS Enol Ether



D. M. Johns, M. Mori, R. M. Williams, *OL* **2006**, *asap.*

2006/Williams' Synthetic Studies on Quinine
Plausible Mechanism for the Key Pd(O)-Mediated Allylic Alkylation

Pd-Sandwich Complex Formation

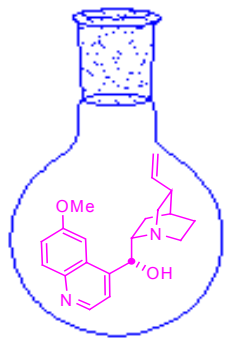


Pd-mediated etherification, Claisen Rearrangement Sequence

D. M. Johns, M. Mori, R. M. Williams, *OL* **2006**, *asap.*

Summary

- While the quinine has played an important historical role in organic chemistry, the first stereoselective total synthesis was accomplished by Stork et al, only five years ago.
- Since, the Stork's asymmetric synthesis of quinine, only a handful of alternative syntheses has been published, in which most of them following the classical Rabe's C8-N1 disconnection strategy to build the quinuclidine ring system.
- In Williams group, the synthesis of 7-hydroxyquinine was accomplished by featuring a C3-C4 Pd-mediated S_N2'-type cyclization reaction to construct the quinuclidine ring system.
- In addition, the establishment of the C8/C9 stereogenic centers were set by the asymmetric aldol reaction developed in Williams' group,
- While 7-hydroxyquinine was successfully synthesized in Williams' group, this quinine analogue was found to be inactive against two strains of *Plasmodium falciparum*, a parasite that causes malaria.
- The further application of this innovative approach to the total synthesis of the *Cinchona* alkaloids is currently being investigated in Williams' group.



Relevent Readings:

T.S. Kaufmann and E. A. Ruveda *ACIE* **2005***, 44*, 854.

K.K.J. Gawronski *Synthesis* **2001**, *7*, 961.