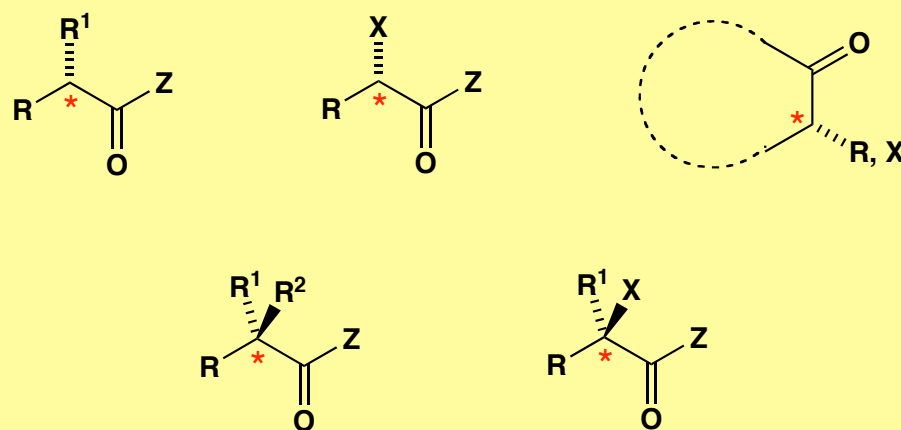


Massachusetts Institute of Technology
Organic Chemistry 5.512

March 7, 2007
Prof. Rick L. Danheiser

Unit 2
Stereocontrolled Alkylation
and Related Electrophilic Substitution Strategies

Key Retrons



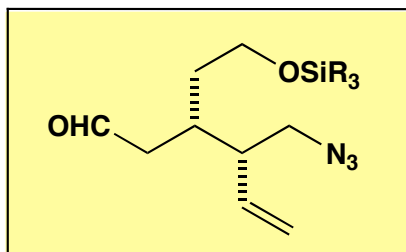
Outline of Unit

- I. Intrinsic Stereochemistry*
- II. Substrate Control: Asymmetric Induction by Molecular Framework*
- III. Substrate Control: Asymmetric Induction by Chiral Auxiliaries*
- IV. Reagent Control Strategies: Chiral Electrophiles*
- V. Catalytic Methods*

Background Topics for Review: Conditions for generating enolates, "azaenolates", and related species; pK_A of relevant substrates and bases, kinetic vs. thermodynamic conditions for enolate generation, enolate stereochemistry, relative reactivity of alkylating agents, conditions for imine and hydrazone formation and cleavage, synthetically useful transformations of carbonyl compounds.

Case Study

"The First Stereoselective Synthesis of Quinine"
G. Stork et al. *J. Am. Chem. Soc.* **2001**, 123, 3239



Case study target

Reviews

T. S. Kaufman and E. A. Rúveda

Natural Products Synthesis

The Quest for Quinine: Those Who Won the Battles and Those Who Won the War

Teodoro S. Kaufman* and Edmundo A. Rúveda

Keywords:
alkaloids · asymmetric synthesis ·
history of chemistry · quinine ·
structural determination



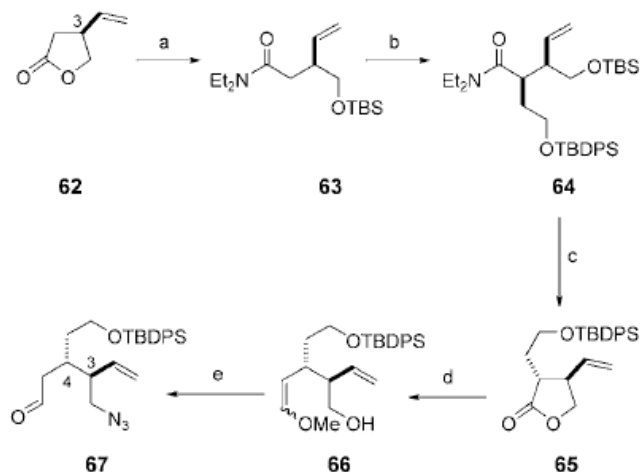
Angewandte
Chemie

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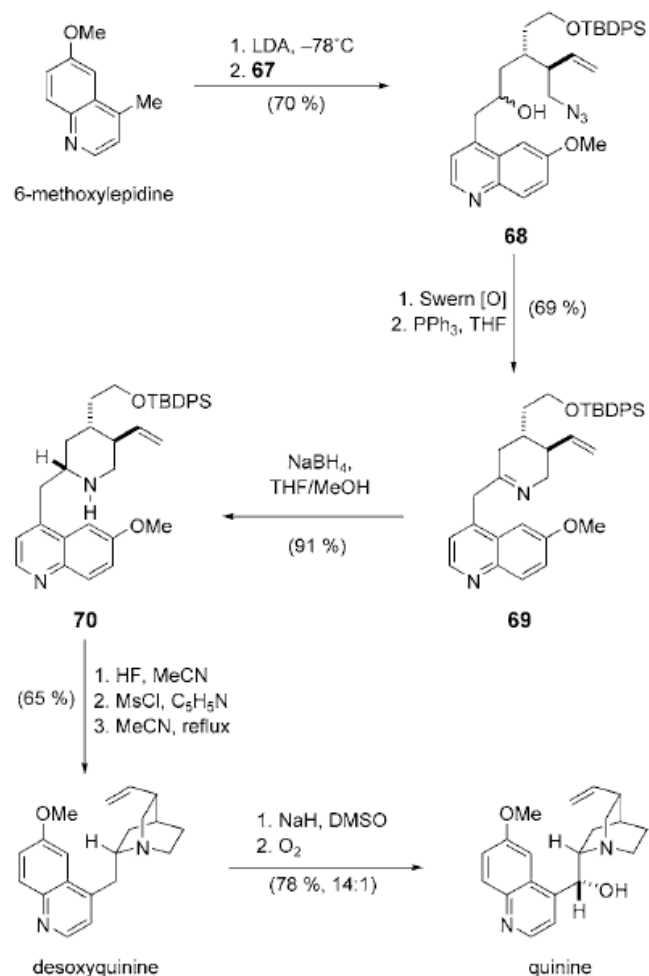
DOI: 10.1002/ange.200400663

Angew. Chem. Int. Ed. 2005, 44, 854–885

Kaufman, T. S.; Rúveda, E. A.
Angew. Chem. Int. Ed. **2005**, 44, 854



Scheme 20. Synthesis of quinine by Stork et al. by chemical manipulation of Taniguchi's lactone. Reagents and conditions: a) 1. $\text{Et}_2\text{NAlMe}_2$; 2. TBSCl, imidazole (79%); b) 1. LDA, -78°C ; 2. $\text{ICH}_2\text{CH}_2\text{OTBDPS}$ (79%, 20:1); c) 1. PPTS, EtOH; 2. xylene (93%); d) 1. DIBAL-H; 2. $\text{Ph}_3\text{PCH}(\text{OMe})$ (93%); e) 1. $(\text{PhO})_2\text{P}(\text{O})\text{N}_3$; PPh_3 , DEAD; 2. 5 N HCl (74%). DEAD = diethylazodicarboxylate, PPTS = pyridinium *p*-toluenesulfonate, TBS = *tert*-butyldimethylsilyl, TBDPS = *tert*-butyldiphenylsilyl.



Scheme 21. Synthesis of quinine by Stork et al.: The final steps.