Massachusetts Institute of Technology

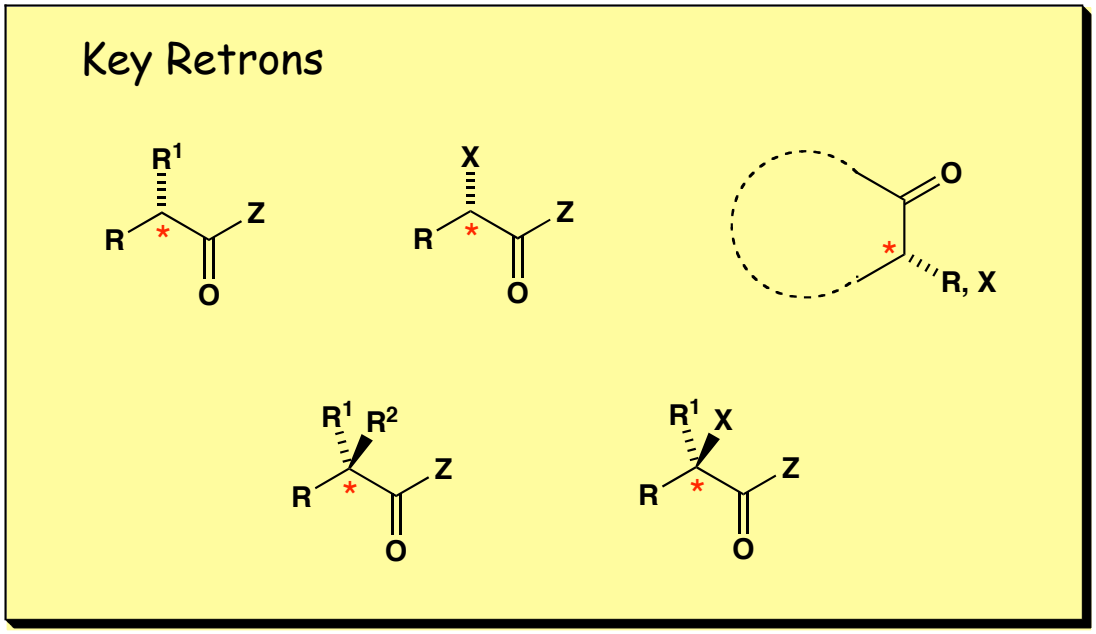
Organic Chemistry 5.512

March 7, 2007
Prof. Rick L. Danheiser

Unit 2

Stereocontrolled Alkylation

and Related Electrophilic Substitution Strategies



Outline of Unit

I. Intrinsic Stereochemistry

II. Substrate Control: Asymmetric Induction by Molecular Framework

III. Substrate Control: Asymmetric Induction by Chiral Auxiliaries

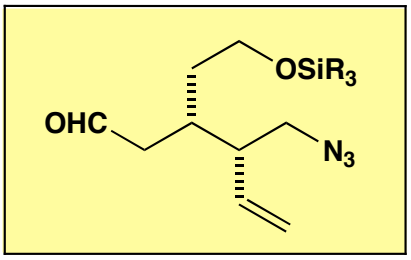
IV. Reagent Control Strategies: Chiral Electrophiles

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.

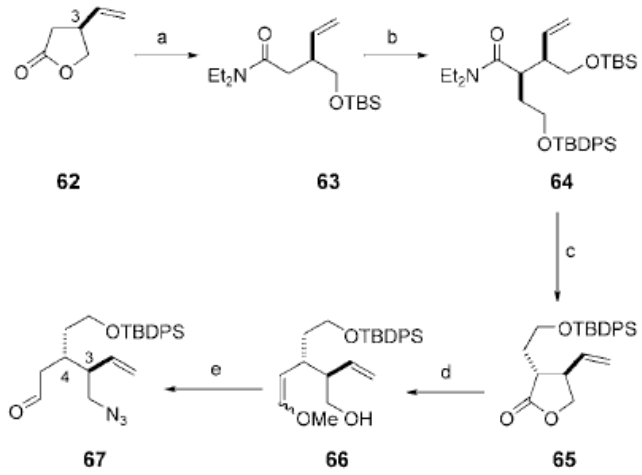
Case Study

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

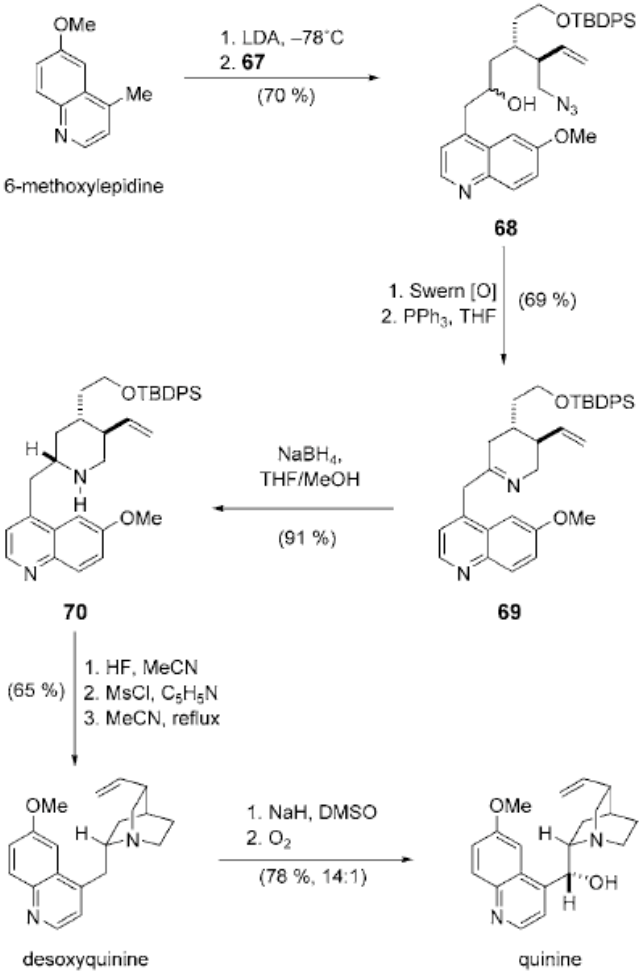


Case study target

Kaufman, T. S.; Ruveda, 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. Et_2NAlMe_2; 2. TBSCl, imidazole (79%); b) 1. LDA, −78 °C; 2. $ICH_2CH_2OTBDPS$ (79%, 20:1); c) 1. PPTS, EtOH; 2. xylene (93%), d) 1. DIBAL-H; 2. $Ph_3PCH(OMe)$ (93%); e) 1. $(PhO)_2P(O)N_3$; 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.