

Massachusetts Institute of Technology

Organic Chemistry 5.512

March 3, 2006
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Introduction: Strategies for Stereocontrolled Synthesis

★ Thermodynamic Control

Relative energy of diastereomers determines outcome of reaction

I. What determines the relative energy of stereoisomers?

- ☆ De-stabilizing Non-bonded Repulsion
- ☆ Stabilizing Non-covalent Interactions
- ☆ Stereoelectronic Effects

II. Tactics for establishing thermodynamic control

★ Kinetic Control

Relative energy of diastereomeric transition states determines outcome

☆ Substrate Control

- * Steric Approach Control
- * Stereoelectronic Control
- * Internal Stereodirection

☆ Reagent Control

- * Achiral Substrate: enantiotopic face selectivity
- * Achiral Substrate: enantiotopic group selectivity
- * Chiral Substrate: double asymmetric synthesis

☆ Dynamic Kinetic Resolution

Cyclohexane A Values (kcal/mol)

F	0.25-0.42
C	0.53-0.64
Br	0.48-0.67
I	0.47-0.61

OMe	0.55-0.75
OAc	0.68-0.87
OSiMe ₃	0.74

NH ₂	1.23-1.7
NMe ₂	1.5-2.1

CH ₃	1.74
Et	1.70
<i>i</i> -Pr	2.21
<i>t</i> -Bu	4.7-4.9
Vinyl	1.5-1.7
Ethynyl	0.41-0.52
Ph	2.8

CN	0.2
CHO	0.56-0.8
CH ₂ OH	1.76
COMe	1.0-1.5
CO ₂ Me	1.2-1.3

SiMe ₃	2.5
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From Eliel, E. L.; Wilen, S. H.; Mander, L. N.
Stereochemistry of Organic Compounds, Wiley: New York,
 1994, pp 696-697.