

CHEM 231A: METHODS OF ORGANIC SYNTHESIS



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Text

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Licensing

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0: Readings

All of the reading assignments from journals can be found here.

Week 1

- Misassigned Structures: *Angew. Chem. Int. Ed.*, 2005, 44, 1012-1044.
- History of ChemDraw: *Angew. Chem. Int. Ed.*, 2014, 53, 11140-11145.
- Diversity Oriented Synthesis: *Angew. Chem. Int. Ed.*, 2004, 43, 46-58.
- Green Chemistry: *Acc. Chem. Res.*, 2002, 35, 686-694.
- Redox Economy: *Angew. Chem. Int. Ed.*, 2009, 48, 2854-2867.
- Ideal Synthesis: *J. Org. Chem.*, 2010, 75, 4657-4673.
- Scalable Synthesis: *Nat. Prod. Rep.*, 2014, 31, 419-432.
- Umpolung Chemistry: *Angew. Chem. Int. Ed.*, 1979, 18, 239-336.
- Chiral Pool Retrosynthesis - Quinic Acid: *Tetrahedron Lett.*, 1986, 27, 5071-5074.
- Zaragasic Acid C: *J. Am. Chem. Soc.*, 2008, 130, 17281-17283.
- Asymmetric Ammonia Synthon: *J. Org. Chem.*, 1986, 51, 2820-2822.; *J. Org. Chem.*, 1992, 57, 2114-2121.
- Oxidative Kinetic Resolution Example: *Angew. Chem. Int. Ed.*, 2008, 47, 3755-3758.

Quinine

- Stork's Synthesis: *J. Am. Chem. Soc.*, **2001**, 123, 3239-3242.
- Historical Overview: *Angew. Chem. Int. Ed.*, **2007**, 46, 1378-1413.
- Proof of Woodward's Formal Synthesis: *Angew. Chem. Int. Ed.*, **2008**, 47, 1736-1740.

Longifolene

- Corey: *J. Am. Chem. Soc.*, 1961, 83, 1251-1253.
- McMurry: *J. Am. Chem. Soc.*, 1972, 94, 7132-7137.

Atom Economy

- Science, 1991, 254, 1471-1477.
- Angew. Chem. Int. Ed.*, 1995, 34, 259-281.

Week 2

- A(1,3)-Strain Review: *Chem. Rev.*, **1989**, 89, 1841-1860.
- Substrate Directed Reactions Review: *Chem. Rev.*, **1993**, 93, 1307-1370.
- Fürst-Plattner Example 1: *Tetrahedron Lett.*, **1998**, 39, 6811-6814.
- Fürst-Plattner Example 2: *J. Chem. Soc., Perkin Trans. 2*, **1978**, 627-632.
- Fürst-Plattner Example 3: *J. Am. Chem. Soc.*, **1983**, 105, 2354-2358.
- Fürst-Plattner Electronic Exceptions: *J. Am. Chem. Soc.*, **2000**, 122, 168-169.
- Dermostatin A: *Angew. Chem. Int. Ed.*, **2001**, 40, 3224-3227.

Week 3

- Protecting Groups Review: *Angew. Chem. Int. Ed. Engl.*, **1996**, 35, 2056-2083.

Week 4

Organometallic Reagents

- Grignard Reagents in Synthesis: *Angew. Chem. Int. Ed.*, **2003**, 42, 4302-4320.
- Lithium Reagent Review: *Acc. Chem. Res.*, **1996**, 29, 552-560.
- Lithioamine equivalents: *J. Org. Chem.*, **1990**, 55, 2578-2580.
- Seminal Cerium Chloride Paper: *J. Am. Chem. Soc.*, **1989**, 111, 4392-4398.
- Cerium Reagents: *J. Org. Chem.*, **1984**, 49, 3904-3912.
- 2-Oxazoline Synthesis: *Angew. Chem. Int. Ed. Engl.*, **1976**, 15, 270-281.

- Oxazoline Metalation: *J. Org. Chem.*, **1975**, 40, 3158-3159.

Weinreb Amides

- Original Publication: *Tetrahedron Lett.* 1981, 39, 3815-3818.
- Review: *J. Prakt. Chem.*, 1997, 339, 517-524.
- Review: *Synthesis*, 2008, 3707-3738.
- Formation: *J. Org. Chem.*, 2004, 69, 8984-8986.
- Formation: *Tetrahedron Lett.*, 1995, 36, 5461-5464.

Higher Order Cuprates

- Where is the Cyano Ligand?: *J. Org. Chem.*, 1994, 59, 7578-7587.
- On Lithium!/: *Chem. Commun.*, 1996, 815-816.

Week 5

- Chelate Review: *Acc. Chem. Res.*, **1993**, 26, 462-468.
- Cram's Rule: *J. Am. Chem. Soc.*, **1952**, 74, 5828-5835.
- Cram Chelate: *J. Am. Chem. Soc.*, **1959**, 81, 2748-2755.
- Keck's Lewis Acid study: *Tetrahedron Lett.*, **1984**, 25, 265-268.

Week 6

- Redox Economy: *Angew. Chem. Int. Ed.*, **2009**, 48, 2854-2867.
- Asymmetric Borane Reductions: *Acc. Chem. Res.*, **1992**, 25, 16-24.
- Modified Wolff-Kishner: *J. Am. Chem. Soc.*, **2004**, 126, 5436-5445.
- Luche Reduction: *J. Am. Chem. Soc.*, **1981**, 103, 5454-5459.
- Stryker Reduction: *J. Am. Chem. Soc.*, **1988**, 110, 291-293.
- Directed Borohydride: *J. Am. Chem. Soc.*, **1988**, 110, 3560-3578.
- Stereochemical Models of Reduction: *J. Org. Chem.*, **1984**, 49, 778-788.
- Organoborane Reductions: *J. Org. Chem.*, **1988**, 53, 2916-2920.
- CBS reagent prep: *J. Org. Chem.*, **1993**, 58, 2880-2888.
- CBS Transition State: *Tetrahedron Lett.*, **2009**, 50, 1324-1327.
- Chemoselective Aldehyde Reduction: *Tetrahedron Lett.*, **1983**, 24, 4287-4290.
- Alkoxydialkylborane reductions: *Tetrahedron Lett.*, **1987**, 28, 155-158.
- Chelate Control: *Tetrahedron Lett.*, **1985**, 26, 5139-5142.

Tar-BH

- Enantioselective Reductions with Boronic Esters: *Tetrahedron Lett.*, **2007**, 48, 9025-9029.
- Boronic Ester 2: *Synthesis*, **2008**, 23, 3874-3876.
- Boronic Ester 3: *Org. Lett.*, **2009**, 11, 4358-4361.

Week 7

- IBX Prep: *J. Org. Chem.*, **1999**, 64, 4537-4538.
- IBX oxidation procedure: *Org. Lett.*, **2002**, 4, 3001-3003.
- NHC catalyzed oxidation of allylic or benzylic alcohols to esters: *Org. Lett.*, **2007**, 9, 371-374.
- NHC catalyzed oxidation of aldehydes to esters: *Org. Lett.*, **2008**, 10, 4331-4334.
- Fetizon's reagent: *J. Chem. Soc. D*, **1969**, 1102-1102.

Tempo

- With Cupric Ions and Oxygen: *J. Am. Chem. Soc.*, **1984**, 106, 3374-3376.
- Primary Selective: *Org. Lett.*, **2001**, 3, 3041-3043.
- Use in Total Synthesis: *Org. Lett.*, **2004**, 6, 3985-3988.
- Review: *Synthesis*, **1996**, 10, 1153-1176.
- Synthesis of alpha-heteroatom substituted aldehydes: *Tetrahedron Lett.*, **1992**, 33, 5029-5032.

Week 8

- Cyclohexanone alkylation example: *Org. Lett.*, **2007**, 9, 2839-2842.
- Elemanolides: *Tetrahedron*, **1988**, 44, 1369-1392.
- beta-vetivone synthesis: *J. Am. Chem. Soc.*, **1973**, 95, 3414-3415.
- Evans Auxiliary: *J. Am. Chem. Soc.*, **1982**, 104, 1737-1739.

Myers Auxiliary

- *J. Am. Chem. Soc.*, **1994**, 116, 9361-9362.
- *J. Am. Chem. Soc.*, **1997**, 119, 6496-6511.

Week 9

- Review: *Chem. Soc. Rev.*, **2004**, 33, 65-75.
- Boron Enolates: *Chem. Letters*, **1976**, 5, 559-562.
- Boron Enolates 2: *J. Am. Chem. Soc.*, **1979**, 101, 6120-6123.
- Controlling Enolate Geometry: *J. Am. Chem. Soc.*, **1989**, 111, 3441-3442.
- E-selective enolate formation: *J. Am. Chem. Soc.*, **1991**, 113, 9571-9574.
- Evans Asymmetric Alkylation: *J. Am. Chem. Soc.*, **1982**, 104, 1737-1739.
- Evans Asymmetric Aldol Reaction: *J. Am. Chem. Soc.*, **1981**, 103, 2127-2129.
- Crimmins Auxilliary "Anti-Evans" product: *J. Org. Chem.*, **2001**, 66, 894-902.
- Magnesium catalyzed anti-Aldol: *J. Am. Chem. Soc.*, **2002**, 124, 392-393.
- Anti-selective Boron Aldol: *J. Am. Chem. Soc.*, **1997**, 119, 2586-2587.
- Ghosh anti-Aldol: *J. Am. Chem. Soc.*, **1996**, 118, 2527-2528.
- Prelog-Djerassi Lactone Synthesis: *Tetrahedron Lett.*, **1982**, 23, 807-810.

Acetate Aldol

- Sammakia Auxiliary: *Org. Lett.*, **2004**, 6, 23-25.
- Sammakia Auxiliary 2: *J. Org. Chem.*, **2006**, 71, 6262-6265.
- Sammakia Auxiliary 3: *Org. Lett.*, **2004**, 6, 3139-3141.
- Crimmins Auxiliary: *Org. Lett.*, **2007**, 9, 149-152.
- Olivio Auxiliary: *Tetrahedron*, **2004**, 60, 9397-9403.

Mukaiyama Aldol

- Yamamoto Lewis-acid catalyst: *J. Am. Chem. Soc.*, **1991**, 113, 1041-1042.
- Carreira Lewis-acid catalyst: *J. Am. Chem. Soc.*, **1994**, 116, 8837-8838.

Week 10

Diels-Alder

- Diels-Alder in Total Synthesis: *Angew. Chem., Int. Ed.* **2002**, 41, 1668-1698.
- Intramolecular DA: *Angew. Chem., Int. Ed.* **2001**, 40, 820-849.
- Intramolecular DA: *Synthesis* **2002**, 2457-2463.
- Catalytic Enantioselective DA: *Angew. Chem., Int. Ed.* **2002**, 41, 1650-1667.
- Asymmetric DA: *J. Am. Chem. Soc.* **1988**, 110, 1238-1256.
- Asymmetric DA: *J. Am. Chem. Soc.* **1984**, 106, 4261-4263.
- Diastereoselectivity of DA: *Angew. Chem., Int. Ed.* **1987**, 26, 1184-1186.
- Chiral Catalyst DA: *J. Am. Chem. Soc.* **1993**, 115, 6460-6461.
- Chiral Organocatalyst DA: *J. Am. Chem. Soc.* **2000**, 122, 4243-4244.
- Pumiliotoxin C: *Tetrahedron Lett.* **1977**, 18, 1253-1256.
- Pumiliotoxin C: *J. Am. Chem. Soc.* **1978**, 100, 5179-5185.
- Estrone: *J. Am. Chem. Soc.* **1980**, 102, 5253-5261.

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CHAPTER OVERVIEW

1: Retrosynthetic Analysis

Retrosynthetic analysis is a technique for solving problems in the planning of organic syntheses by transforming a target molecule into simpler precursor structures without assumptions regarding starting materials. Each precursor material is examined using the same method; this procedure is repeated until simple or commercially available structures are eventually reached.

[1.1: Chiral Pool Molecules](#)

[1.2: Common Synthetic Equivalents](#)

[1.3: Examples](#)

[1.4: Guidelines](#)

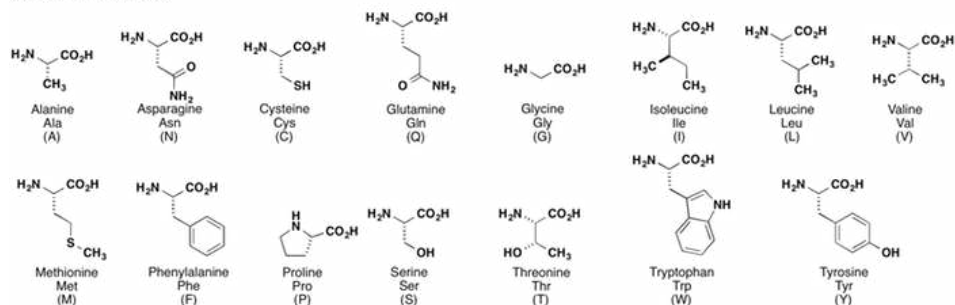
[1.5: Terminology](#)

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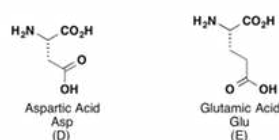
1.1: Chiral Pool Molecules

Amino Acids

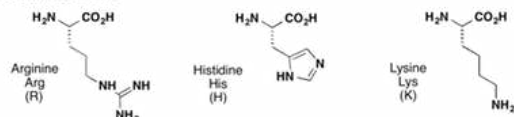
Neutral Amino Acids



Acidic Amino Acids



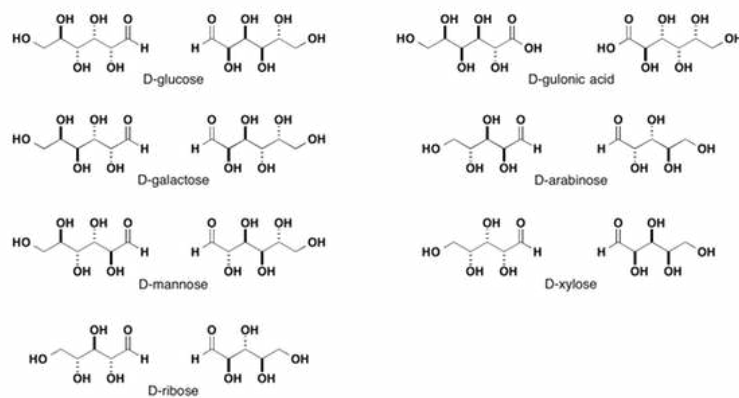
Basic Amino Acids



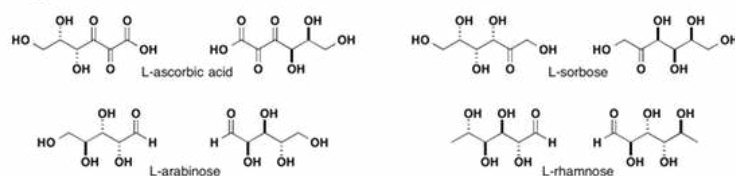
For a review of the use of amino acid derivatives in organic synthesis see: [Chem. Rev., 1989, 89, 149-164.](#)

Sugars

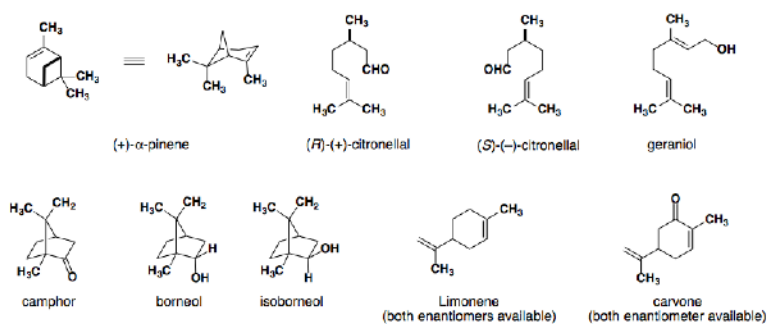
D-Sugars



L-Sugars



Terpenes



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1.2: Common Synthetic Equivalents

Carbon Synthetic Equivalents

Oxygen Synthetic Equivalents

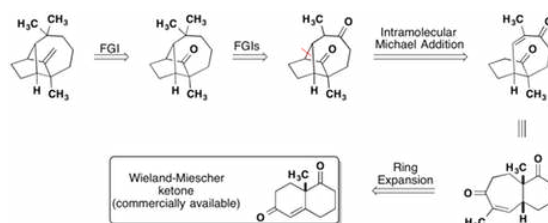
Nitrogen Synthetic Equivalents

Sulfur Synthetic Equivalents

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1.3: Examples

Longifolene - Corey



For the full forward Synthesis see: *J. Am. Chem. Soc.*, **1961**, *83*, pp 1251–1253.

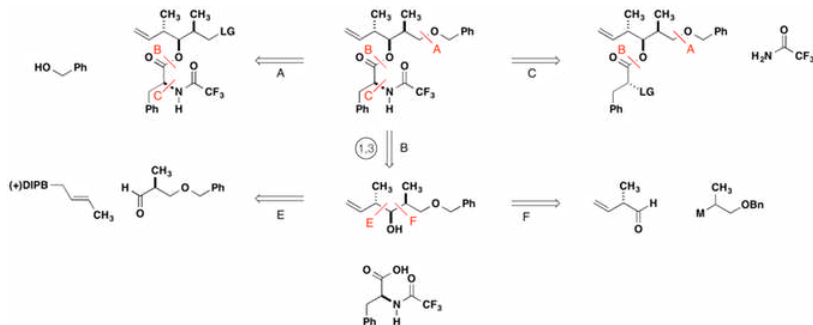
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1.4: Guidelines

1. Disconnect to intermediates of equal size and/or complexity. (Convergence)
2. Disconnect at branch points (stereochemistry)
3. Use functional groups present
4. Disconnect at heteroatom-C-bonds
5. Disconnect to the simplest material possible (commercially available)
6. Reduce ring complexity

Example

The molecule below provides an excellent example for the application of these guidelines.



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1.5: Terminology

Forward Synthesis

Retrosynthesis

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CHAPTER OVERVIEW

2: Conformational Analysis

Conformational analysis is the study of the energetics between different rotamers and is useful for understanding the stability of different isomers by taking into account the spatial orientation and through-space interactions of substituents. Conformational analysis can be used to predict and explain product(s) selectivity, mechanisms, and rates of reactions.

Topic hierarchy

[2.1: Acyclic Conformations](#)

[2.2: Cyclic Conformations](#)

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2.1: Acyclic Conformations

An understanding of the factors that go into determining the lowest energy conformation of acyclic molecules is required to understand the stereochemical outcomes of many reactions. Here we will discuss how steric, electronic, and stereoelectronic effects influence the conformation of acyclic organic molecules.

Contributors and Attributions

- Michael Di Maso (UC Davis)
- [Jared Shaw](#) (UC Davis)

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2.2: Cyclic Conformations

Types of Strain

There are three types of strain associated with cyclic conformations:

- Prelog Strain: Van der Waals interactions
- Baeyer Strain: Bond angle distortion away from the ideal
- Pitzer Strain: Torsional rotation about a sigma bond

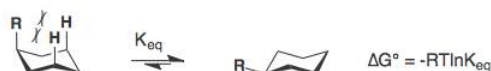
Baeyer Strain

Size of Ring	Heat of Combustion (kcal/mol)	Total Strain (kcal/mol)	Strain per "CH ₂ " (kcal/mol)	"Angle Strain" deviation from 109°28'
3	499.8	27.5	9.17	24°44'
4	656.1	26.3	6.58	9°44'
5	793.5	6.2	1.24	0°44'
6	944.8	0.1	0.02	-5°16'
7	1108.3	6.2	0.89	--
8	1269.2	9.7	1.21	--
9	1429.6	12.6	1.40	--
10	1586.8	12.4	1.24	--
11	1743.1	11.3	1.02	--
12	1893.4	4.1	0.34	--
13	2051.9	5.2	0.40	--
14	2206.1	1.9	0.14	--
15	2363.5	1.9	0.13	--

Substituted Cyclohexanes

A Values

Substituents on a cyclohexane prefer to be in the equatorial position. When a substituent is in the axial position, there are two gauche butane interactions more than when a substituent is in the equatorial position. We quantify the energy difference between the axial and equatorial conformations as the A-value, which is equivalent to the negative of the ΔG° , for the equilibrium shown below. Therefore the A-value, or $-\Delta G^\circ$, is the preference for the substituent to sit in the equatorial position.



Recall that the [equilibrium constant is related to the change in Gibbs Energies](#) for the reaction:

$$\Delta G^\circ = -RT \ln K_{eq} \quad (2.2.1)$$

The balance between reactants and products in a reaction will be determined by the free energy difference between the two sides of the reaction. The greater the free energy difference, the more the reaction will favor one side or the other.

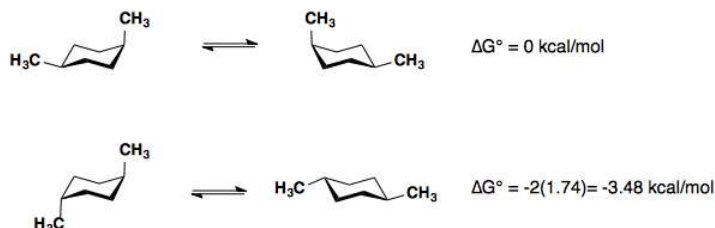
Table: Below is a table of A-values for some common substituents.

Substituent	ΔG° (kcal/mol)	A-value
-F	-0.28-0.24	0.24-0.28
-Cl	-0.53	0.53
-Br	-0.48	0.48
-I	-0.47	0.47
-CH ₃ (-Me)	-1.8	1.8
-CH ₂ CH ₃ (-Et)	-1.8	1.8
-CH(CH ₃) ₂ (-i-Pr)	-2.1	2.1
-C(CH ₃) ₃ (-t-Bu)	<-4.5	>4.5
-CHCH ₂	-1.7	1.7
-CCH	-0.5	0.5
-CN	-0.25-0.15	0.15-0.25
-C ₆ H ₅ (-Ph)	-2.9	2.9

Polysubstituted Cyclohexanes

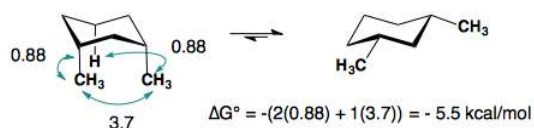
1,4-disubstitution

The A-values of the substituents are roughly additive in either the *cis*- or *trans*-diastereomers.



1,3-disubstitution

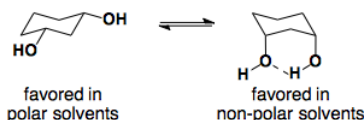
A-values are only additive in the *trans*-diastereomer:



When there are *cis*-substituents on the chair, there is a new interaction in the di-axial conformation:

In the above example, each methyl group has one 1,3-diaxial interaction with a hydrogen. The methyl groups also interact with each other. This new diaxial interaction is extremely unfavorable based on their steric interaction (see: double-gauche pentane conformation).

Solvent Effects



Substituted Cyclohexanones

Solvent Effects

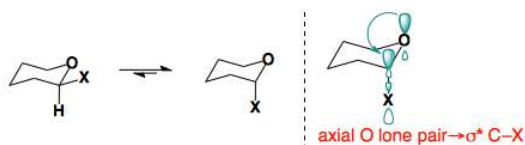


See: *J. Org. Chem.*, **1993**, *58*, 7865-7869.

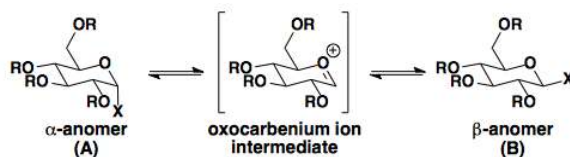
Saturated Heterocyclic 6-member Rings

Anomeric Effect

In 2-substituted pyranose rings, some substituents prefer to sit in the axial conformation.



This preference arises from orbital interactions between the oxygen lone pair and the low-lying σ^* of the C-X bond. This effect which provides the stabilization of the axial conformer, which overrides the inherent steric bias of the substituents, is referred to as the anomeric effect.

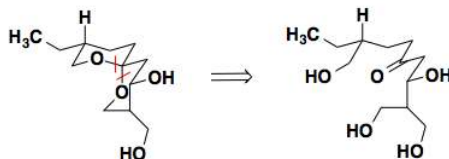


X	R	% A	% B	Solvent (25 °C)
OH	H	36	64	H ₂ O
OCH ₃	H	67	44	CH ₃ OH
OAce	Ac	86	14	AcOH
Cl	Ac	94	6	CH ₃ CN

As seen in the table, X groups with better σ^* -accepting capabilities are most affected by the anomeric effect.

Talaromycin B

In the synthesis of Talaromycin B, Schreiber noticed the lowest energy conformation of the molecule sits with all of the substituents in equatorial positions. In this conformation, the spirocyclic center also prefers a conformation stabilized by two anomeric effects. Understanding the thermodynamic preference for this conformation, Schreiber could disconnect at the spirocenter and concentrate on the synthesis of a linear precursor.

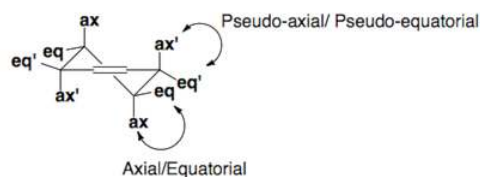


For the full synthetic sequence see: *Tetrahedron Lett.*, **1983**, *24*, 4781-4784.

Unsaturated Ring Systems

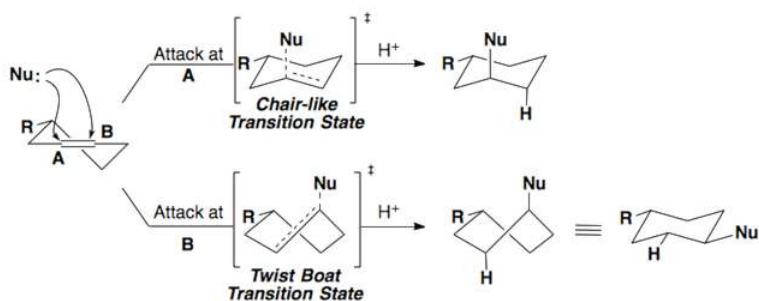
Cyclohexenes

Cyclohexenes adopt half-chair conformations which are pictured below. Substituents prefer to sit in the pseudo-equatorial or equatorial positions of the ring.

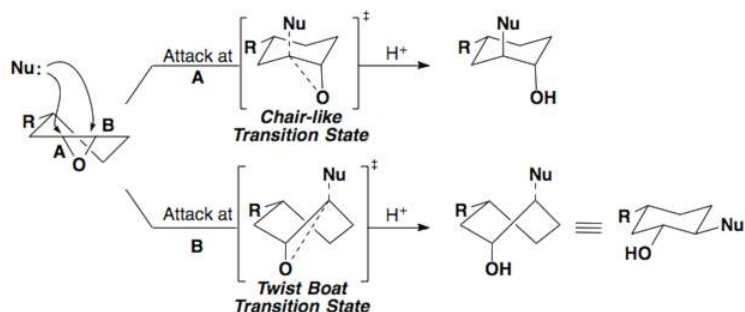


Fürst-Plattner Rule

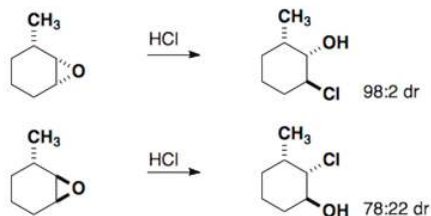
The Fürst-Plattner rule accounts for the observed stereochemical outcome from the nucleophilic addition to cyclohexenes and cyclohexene-like systems (ex: bicyclic epoxides, oxonium ions, etc.). Nucleophiles will react with these systems to yield the trans-diaxial addition product. This selectivity arises from torsional strain which builds in the transition state of the reaction.



These same rules can be applied to epoxides.



Here are a few examples of the **Fürst-Plattner** rule. Attempt to draw out the correct half-chair that leads to the product for each of these cases.

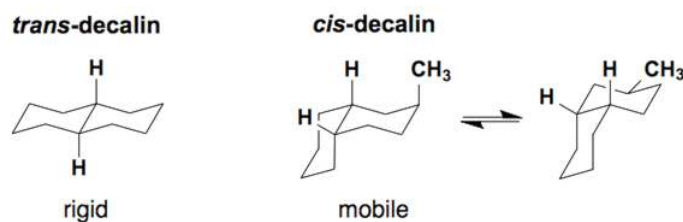


ref: *J. Chem Soc., Perkin Trans. 2*, **1978**, 627-632.

Bicyclic Ring Systems

Decalin ring system (6/6)

Decalins can come in two diastereomers, the *trans*- or *cis*- diastereomer. The *trans*-diastereomer is a rigid structure which cannot undergo a ring flip. The *cis*-diastereomer is mobile and can ring flip to allow substituents to sit in the equatorial position.



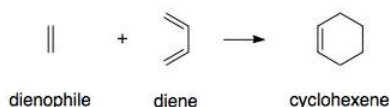
Hydrindane ring system (6/5)

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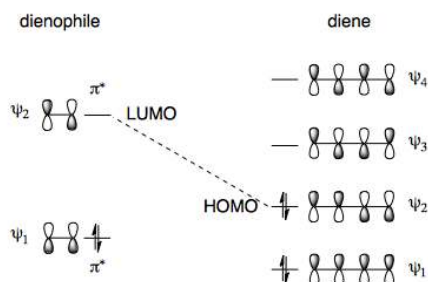
3: Diels-Alder Reaction

Basics

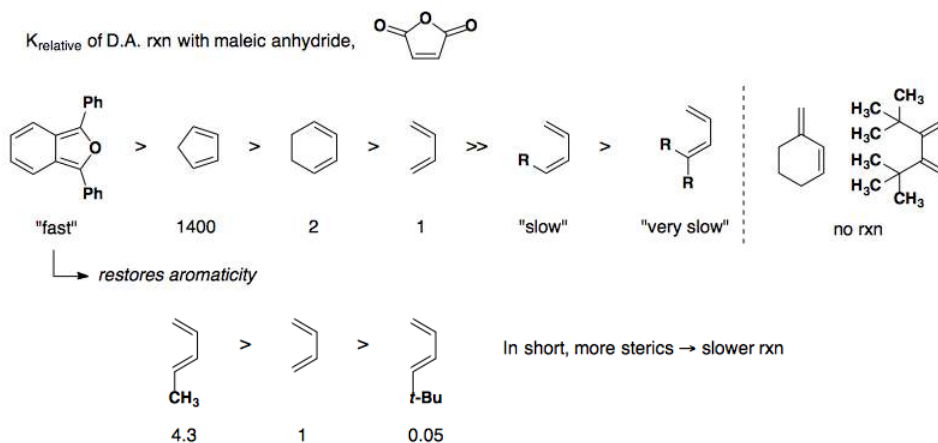
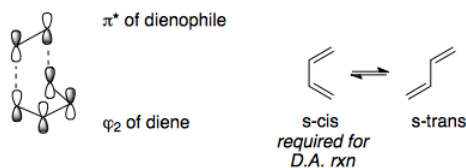
Discovered by Otto Paul Hermann Diels and Kurt Alder in 1928; awarded the Nobel prize in chemistry in 1950.



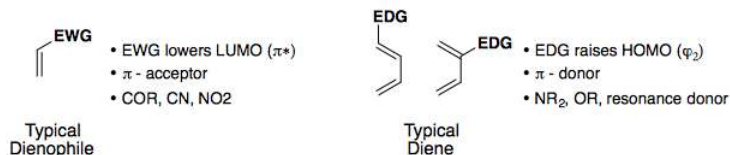
The LUMO of the dienophile reacts with the HOMO of the diene in a [4+2] cycloaddition. For more information, see Z/N p 421-432.



Steric Effects

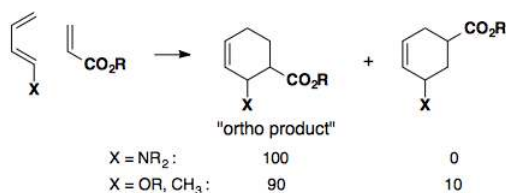


Electronic Effects

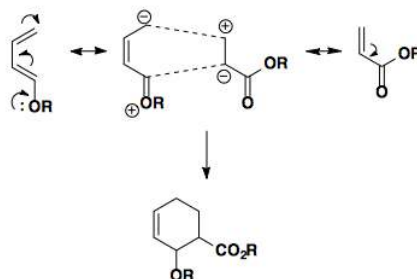


Regioselectivity

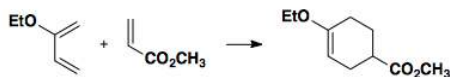
Electron-rich dienes paired with electron-poor dienophiles result in high selectivity for the "ortho products."



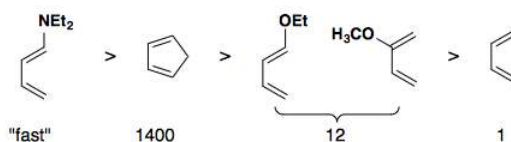
One way to think about pairing the diene/dienophile is to consider resonance structures in which the alkenes have charge separation. Note: there is no actual charge separation, but it can help explain the regiochemistry.



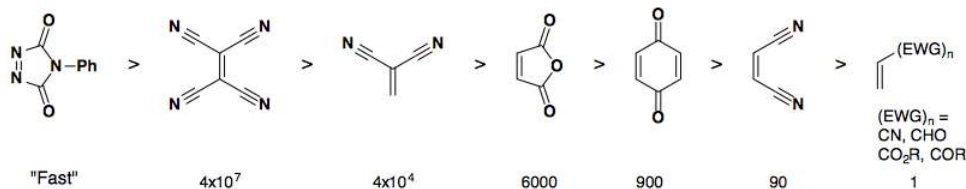
For practice, convince yourself the the following reaction yields the product shown.



Rate of reactivity: diene



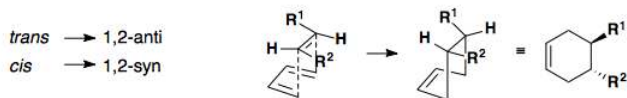
Rate of reactivity: dienophile



Stereochemistry

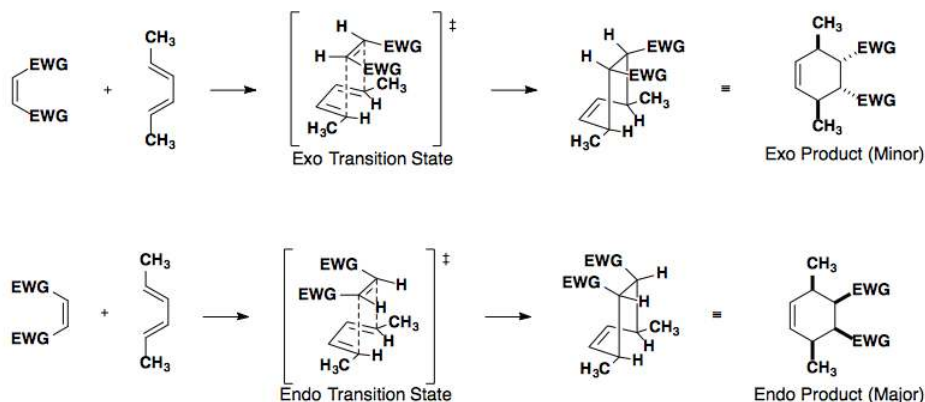
The stereochemistry of the diene and dienophile is translated to the cyclohexene product. In short, the geometry of the alkenes (cis/trans) is directly related to the syn/anti relationship observed in the product.

Dienophile

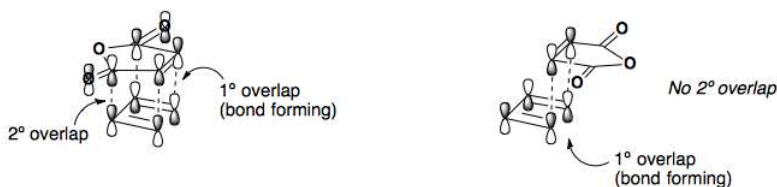


Diene

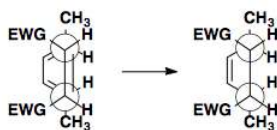
In this example, the diene can react with the dienophile in two ways: the exo or endo approach.



Endo approach is preferred due to the secondary overlap of pi-orbitals.

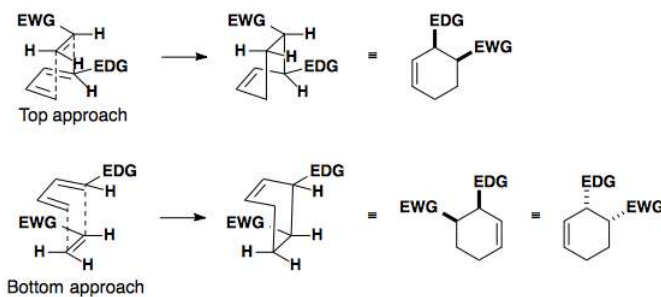


Another way to look at the transition state is to draw a double Newman projection.



Top/Bottom Approach

If the dienophile can approach the diene from the top or bottom face, enantiomers are formed.

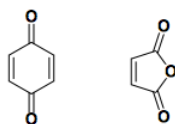


High Endo Selectivity

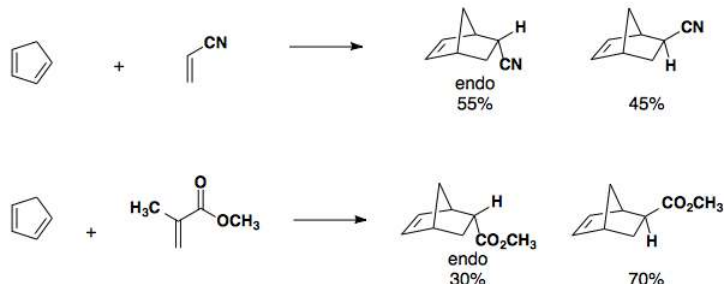
Controlling the Diels-Alder reaction to select for the endo product relies on changing the HOMO and/or LUMO of the system.

Cyclic dienophiles

Common examples are quinone and maleic anhydride.

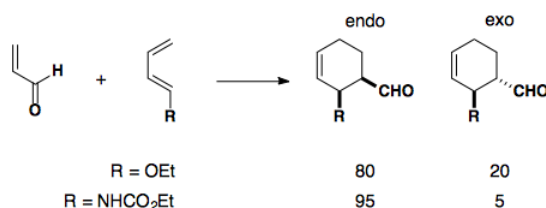


Electron-neutral cyclopentadiene paired with electron-poor dienophiles gives a mix of endo and exo products.



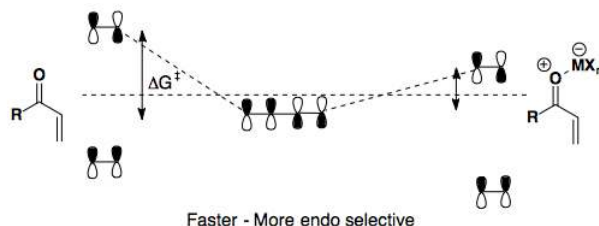
Electron-rich Dienes

If an electron-rich diene is paired with an electron-poor dienophile, the reaction undergoes cycloaddition with excellent endo selectivity. Adding electron density into the diene's molecular orbitals raises the HOMO.

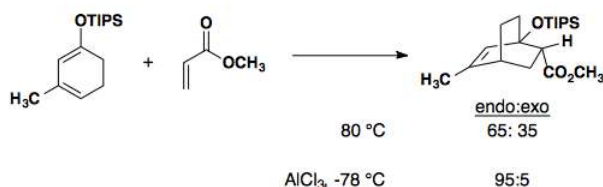


Electron-poor Dienophiles

Adding a Lewis acid further depletes the dienophile of its electron density, thereby lowering the LUMO.



Here, we see an electron-rich, cyclic diene paired with an electron-poor dienophile. Heating the reaction gives poor endo/exo selectivity. However, upon addition of a Lewis acid (AlCl₃), the reaction can proceed at low temperature and the endo product is highly favored.



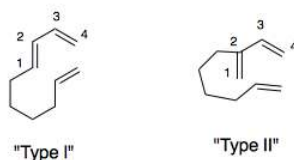
Intramolecular Diels-Alder: the rules are breakable

Two types of connectivity for intramolecular Diels-Alder reactions exist:

- Type I - a linear connection where the dienophile is attached (at length) at position 1 of the diene; or

- Type II - a branched connection where the dienophile is attached (at length) at position 2 of the diene.

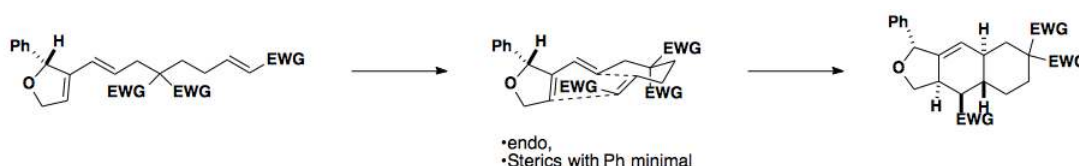
Type I results in a fused bicyclic ring system. Type II results in a bridged bicyclic ring system.



Intramolecular Diels-Alder reactions can be found in a number of total syntheses (*Angew. Chem., Int. Ed.* **2002**, *41*, 1668-1698). For an example of a Type II Diels-Alder reaction in practice, see *Angew. Chem., Int. Ed.* **2001**, *40*, 820-849.

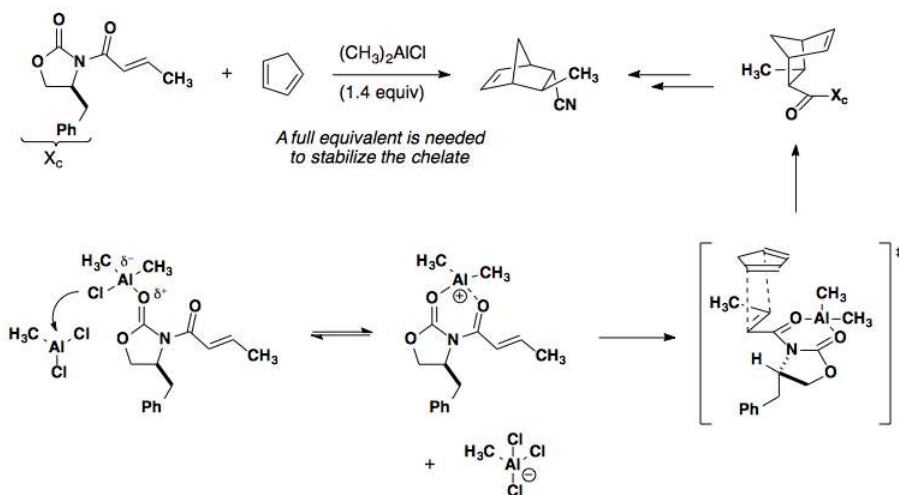
Asymmetric Diels-Alder

Substrates with bulky substituents will affect the diastereoselectivity of a Diels-Alder reaction by limiting the approach of the diene/dienophile pair. Here, we see the preferred endo product that minimizes steric interactions with the phenyl substituent (*Synthesis* **2002**, 2457-2463).



Chiral Auxiliaries

Incorporating a chiral auxiliary and Lewis acid can lead to facial control of the cycloaddition by blocking one face of the dienophile. Examples of oxazolidinones with $R_2\text{AlCl}$ can be found here: *J. Am. Chem. Soc.* **1988**, *110*, 1238-1256 (shown below); *J. Am. Chem. Soc.* **1987**, *109*, 1186-1194 (IMDA, Type I); *J. Am. Chem. Soc.* **1984**, *106*, 4261-4263 (IMDA, Type I); *Angew. Chem., Int. Ed.* **2002**, *41*, 1650-1667 (review); CAC '99 1177.

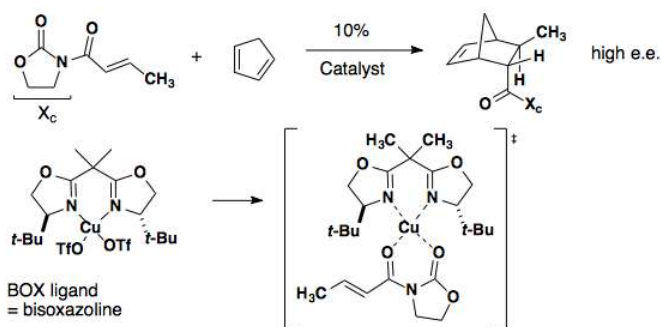


Chiral Catalysis

Chiral catalysts have also been shown to control the enantioselectivity of a Diels-Alder reaction.

Oxazolidinone/oxazoline

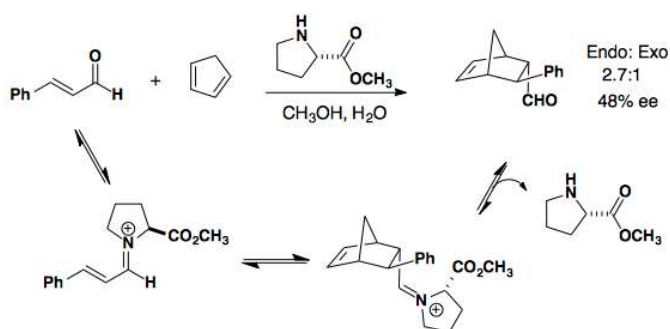
The achiral oxazolidinone below relies on a chiral BOX ligand and coordination of a copper catalyst (*J. Am. Chem. Soc.* **1993**, *115*, 6460-6461).



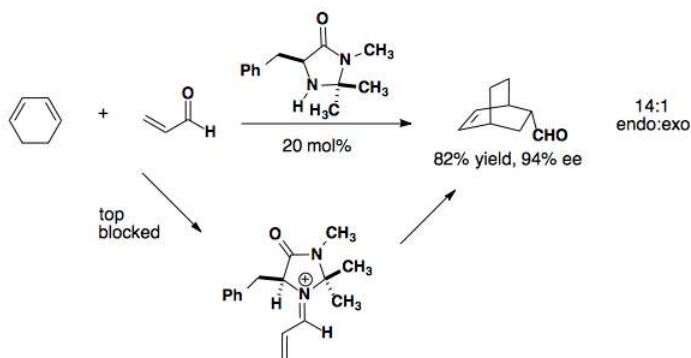
Iminium Catalyzed

Iminium formation blocks one face of the dienophile so that approach of the diene results in endo selectivity and good to high enantioselectivity (*J. Am. Chem. Soc.* **2000**, *122*, 4243-4244).

Proline derived

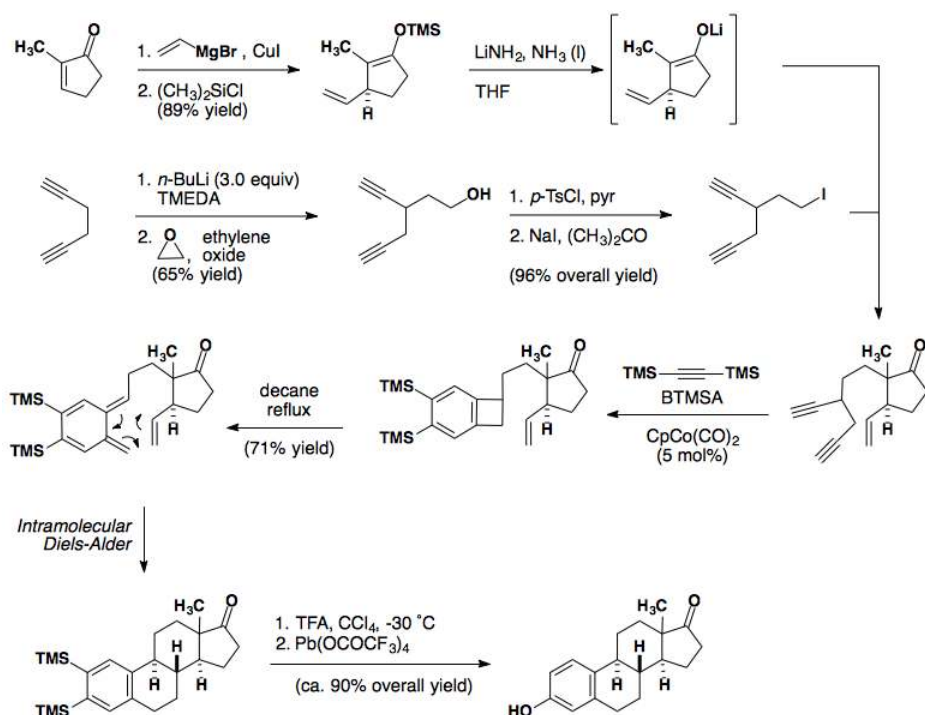


Imidazolidinone derived



Application to a Total Synthesis of *dl*-Estrone

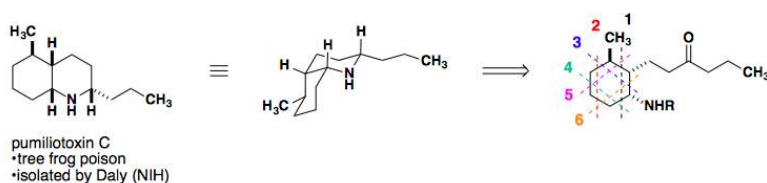
A cobalt-mediated alkyne cyclization undergoes a ring closing and re-opening to set up a Type I Diels-Alder reaction (*J. Am. Chem. Soc.* **1980**, *102*, 5253-5261).



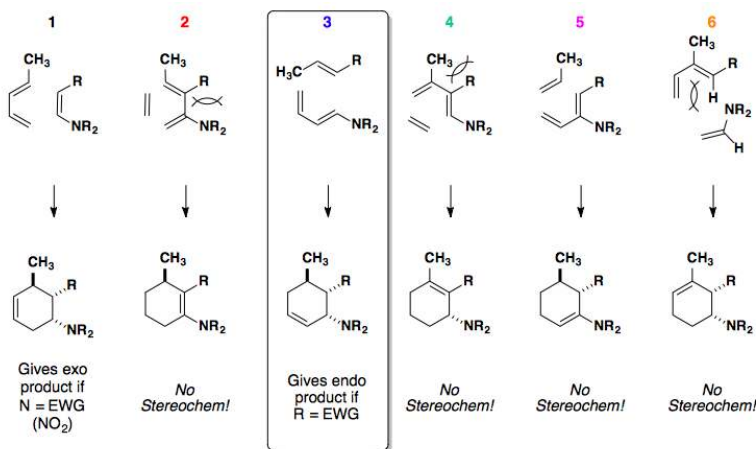
Application to a Total Synthesis of *d,l*-Pumiliotoxin C

L. E. Overman published a stereospecific synthesis of pumiliotoxin in 1977 as a racemic mixture. The following year, his group published a second iteration of the same core, but with a much shorter overall synthesis (*Tetrahedron Lett.* **1977**, *18*, 1253-1256; *J. Am. Chem. Soc.* **1978**, *100*, 5179-5185).

Retrosynthetic analysis of the *cis*-decalin core suggests six possible disconnections.

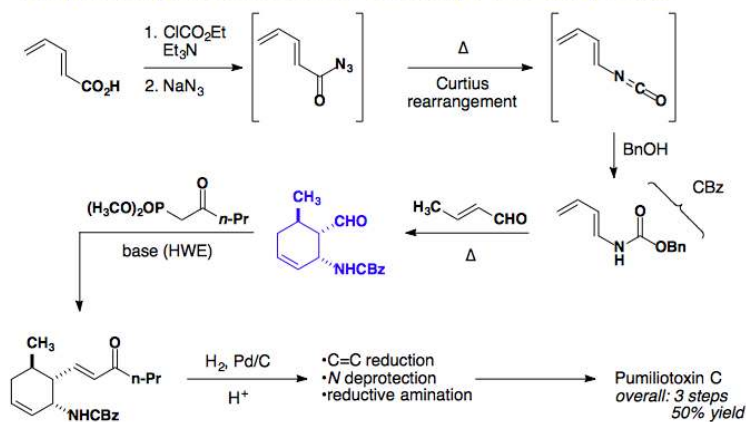


Considering all possible diene/dienophile pairs, disconnection #3 displays all favorable attributes: electron-rich diene, electron-poor dienophile, and endo selectivity to provide the desired stereochemistry of the product.



The forward synthesis showcases a Curtius rearrangement to build the requisite carbamate protected diene. Subsequent addition of crotonaldehyde and heat results in the cyclohexene core, which can undergo a Horner-Wadsworth-Emmons reaction and reduction to give an advanced intermediate. Deprotection and reductive amination provides the natural product in 3 steps and 50% overall yield.

One synthetic step to build core structure from commercially available starting materials!



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CHAPTER OVERVIEW

4: Enolates

Topic hierarchy

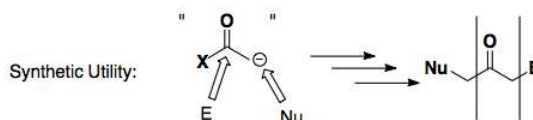
- [4.1: Acid Derivative Enolates](#)
- [4.2: Dicarbonyl Chemistry](#)
- [4.3: Ketone Enolates](#)
- [4.4: The aldol reaction](#)

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4.1: Acid Derivative Enolates

	<chem>CC(=O)C</chem>	<chem>CC(=O)OC(C)(C)C</chem>	<chem>CC(=O)NC</chem>
pK_a (DMSO)	26.5	30.3	[~33]
Stability	←		
Reactivity	→		

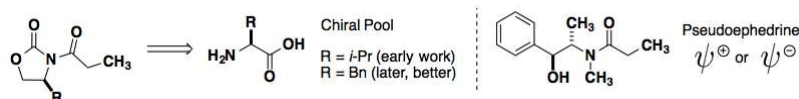
These enolates provide the following synthetic utility.



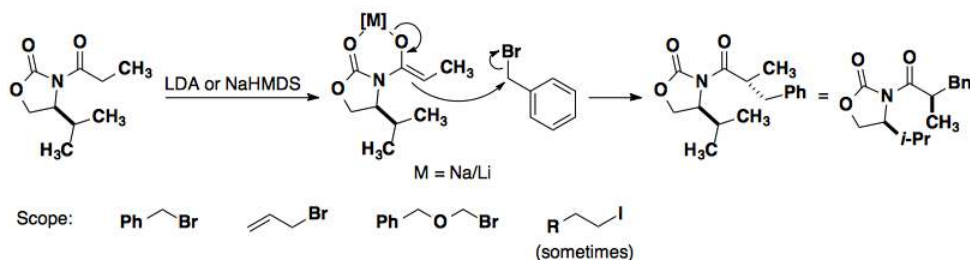
What should X be?

1. Should confer high reactivity
2. Should be cleavable under specific conditions
3. Should induce asymmetry. (Malonates are more convenient for systems that do not require asymmetry).

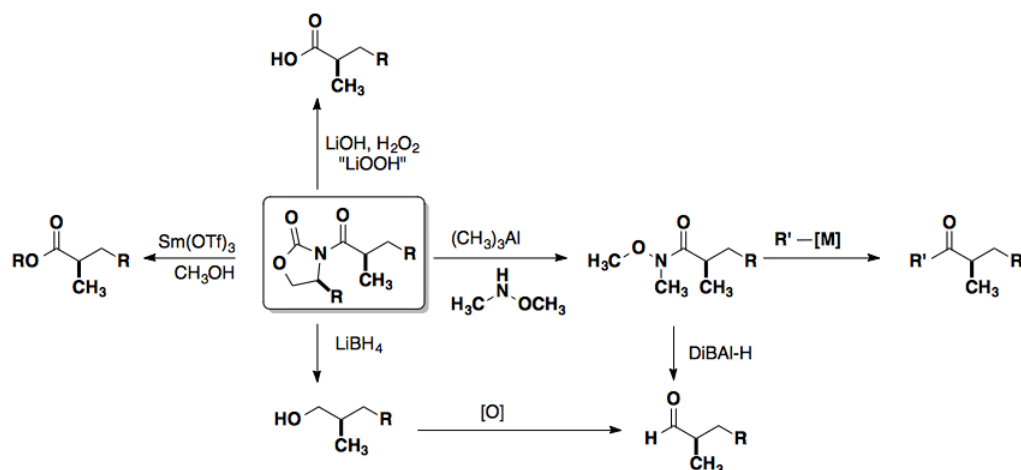
Two of the most widely used are the *Evans Oxazolidinone* and the *Myer's auxiliary*.



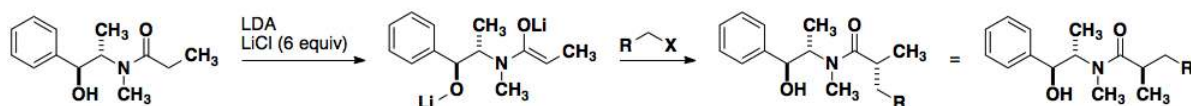
The Evans oxazolidinone is useful for asymmetric alkylations



The oxazolidinone can be removed in several ways to provide different functionality.

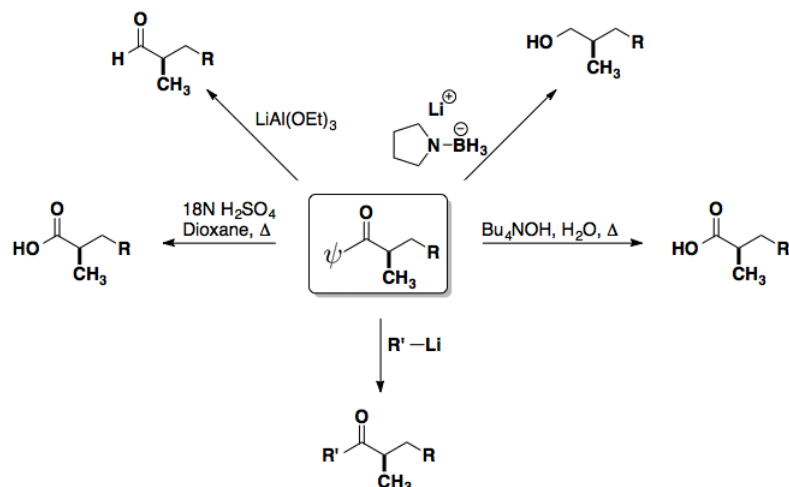


The Myers Auxiliary provides a more reactive enolate that can react with electrophiles that do not react with the imide auxiliary.



J. Am. Chem. Soc., **1994**, *116*, 9361–9362.

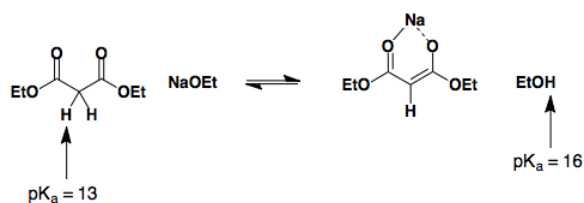
The Myers Auxiliary can also be cleaved by a variety of conditions.



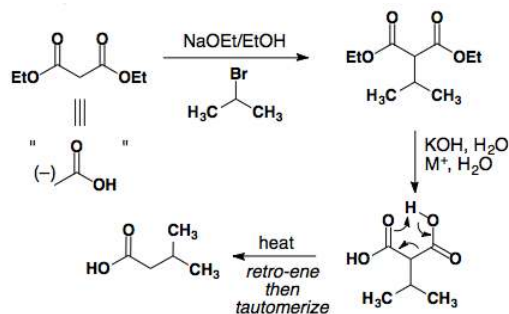
4.1: Acid Derivative Enolates is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

4.2: Dicarbonyl Chemistry

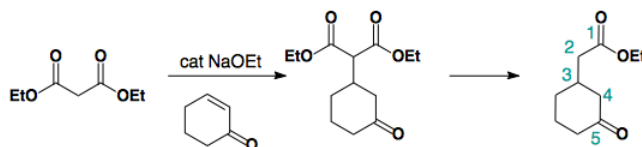
Malonates



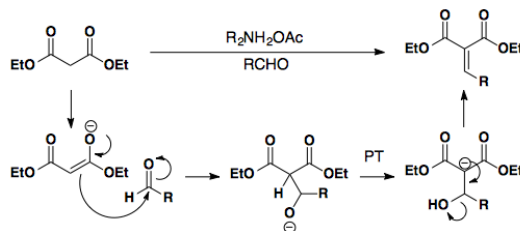
Alkylation



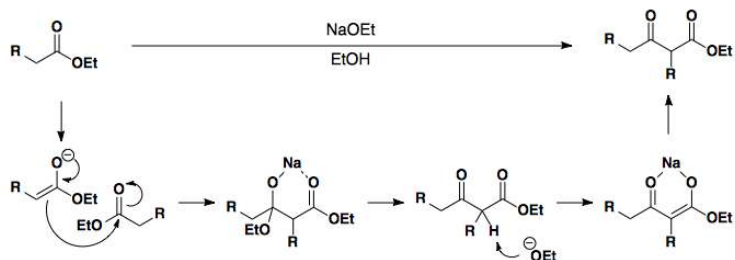
Michael



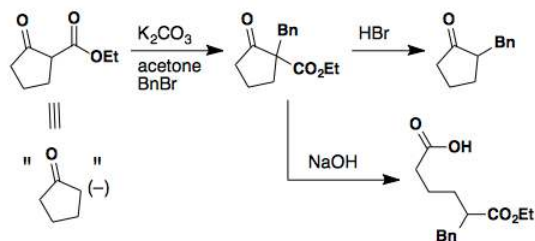
Knoevenagel



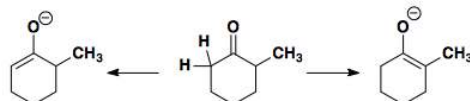
Beta-Keto Esters



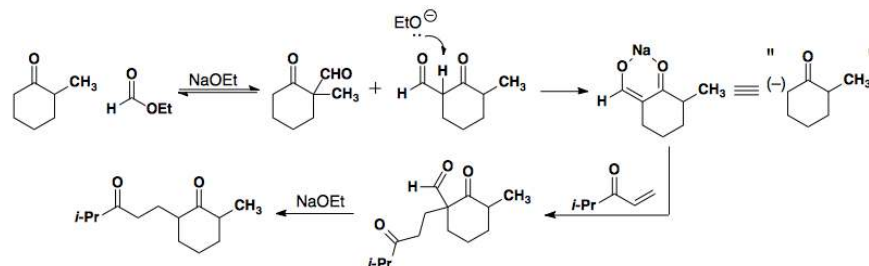
Alkylation



Asymmetric ketones can provide two separate enolate regioisomers.



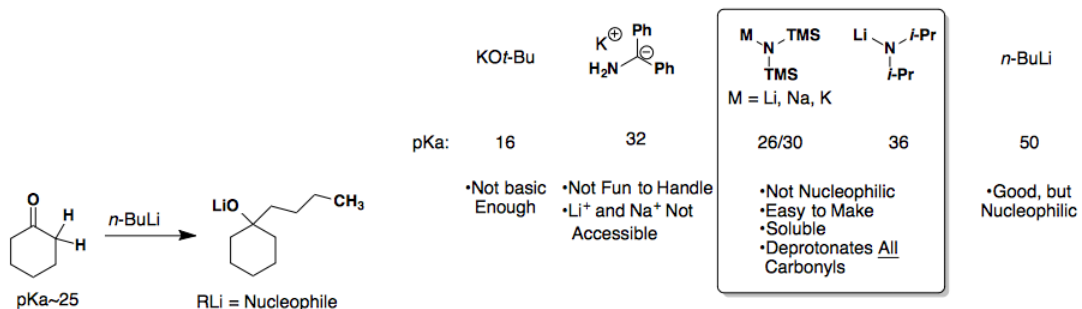
Selective substitution at the less substituted side can be achieved by reaction with ethyl formate. The initial addition of formate is reversible. This reversible addition allows for the formation of enolate on the less hindered side by drastically reducing the pK_a . The subsequent reaction (in this case a Michael addition) occurs and the formate is removed, thus providing a traceless directing group.



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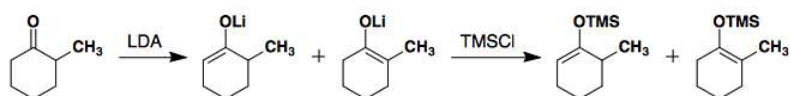
4.3: Ketone Enolates

Bases

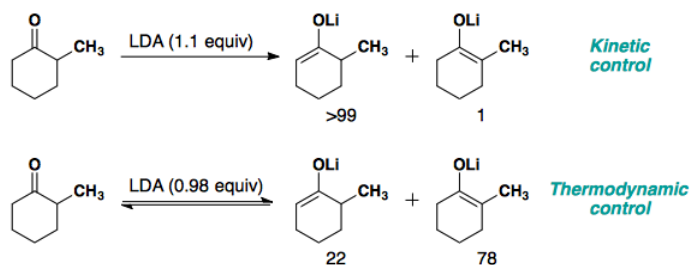
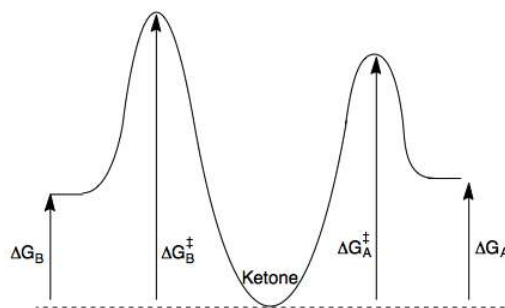


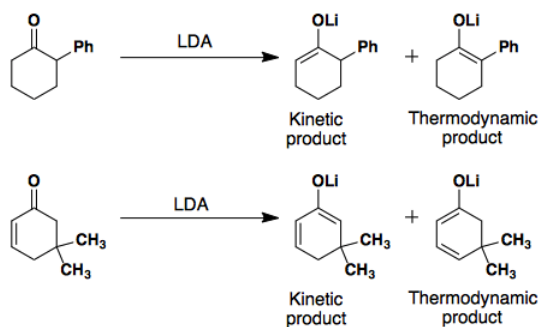
Kinetic vs. Thermodynamic Enolate

Enolate Regiochemistry must also be considered...



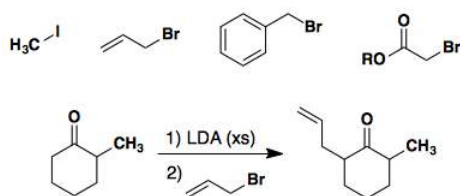
If we consider the energetics of the reaction, we can selectively produce one enolate.



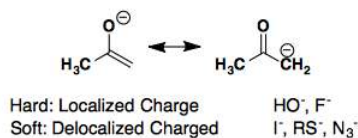


Carbon vs. Oxygen Nucleophilicity

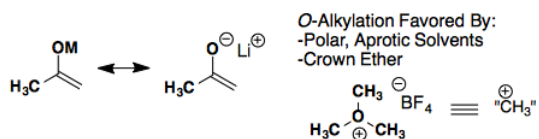
Ketones can be alkylated by very reactive electrophiles:



Enolates can act as nucleophiles at either the carbon or oxygen termini. The oxygen center acts as a hard nucleophile while the carbon center acts as a soft nucleophile.

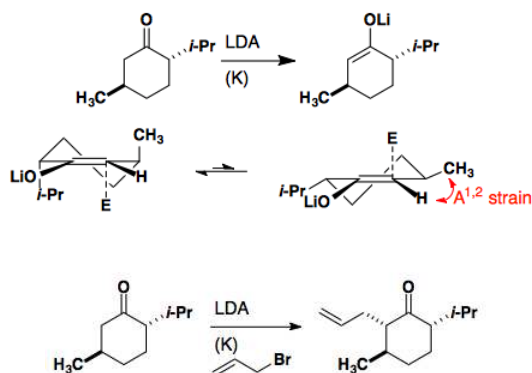


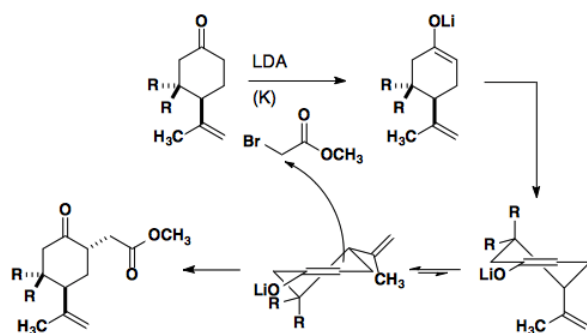
O alkylation can be favored by several methods



Stereochemistry

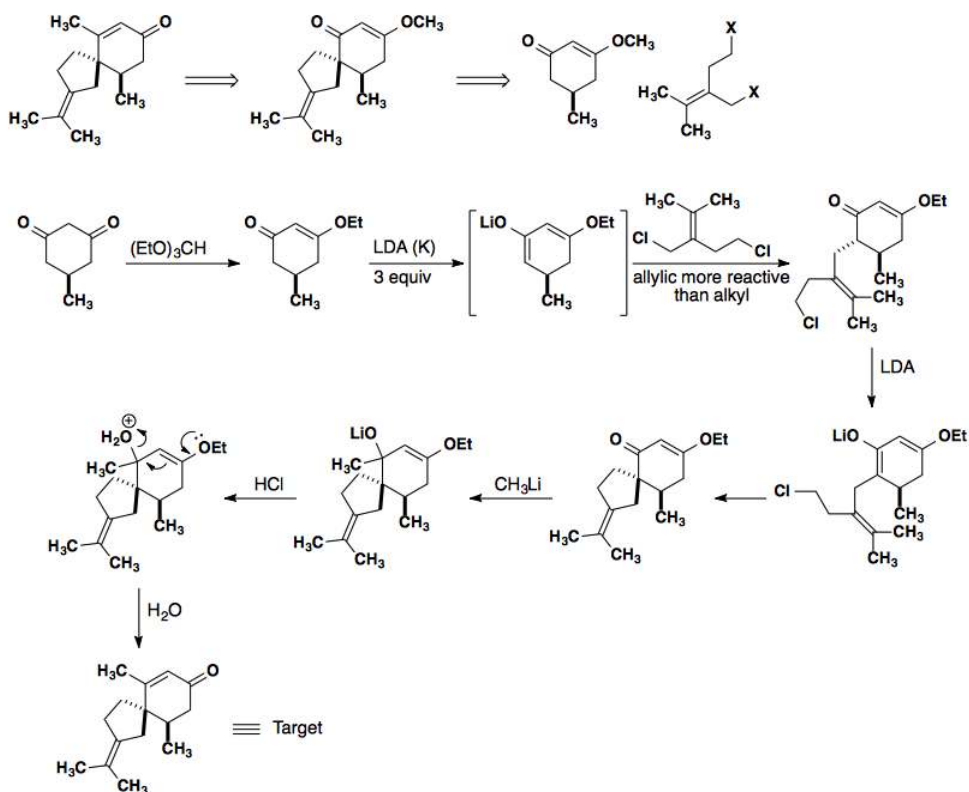
Cyclohexanones





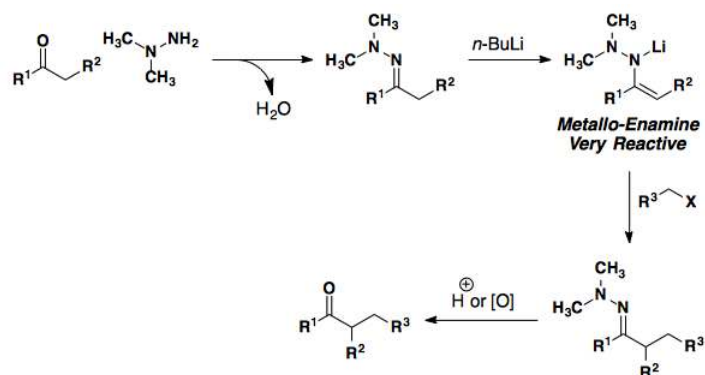
β -vetivone

The Stork synthesis of β -vetivone provides an elegant use of this selectivity.

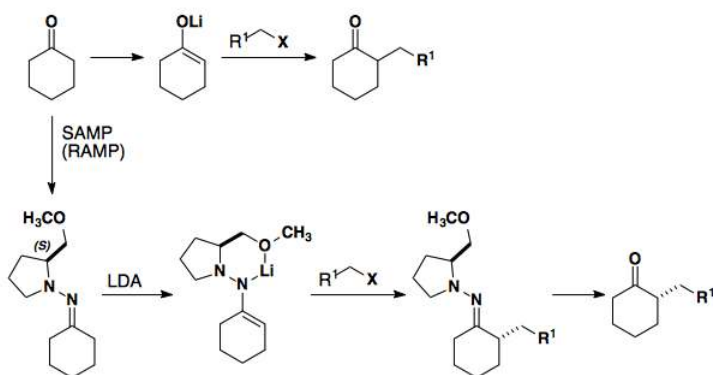


SAMP/RAMP

For unreactive enolates, the hydrazone can be formed and deprotonated with *n*-BuLi. This provides a metallo-enamine which is very reactive. Metallo-enamines will even react with poor electrophiles.



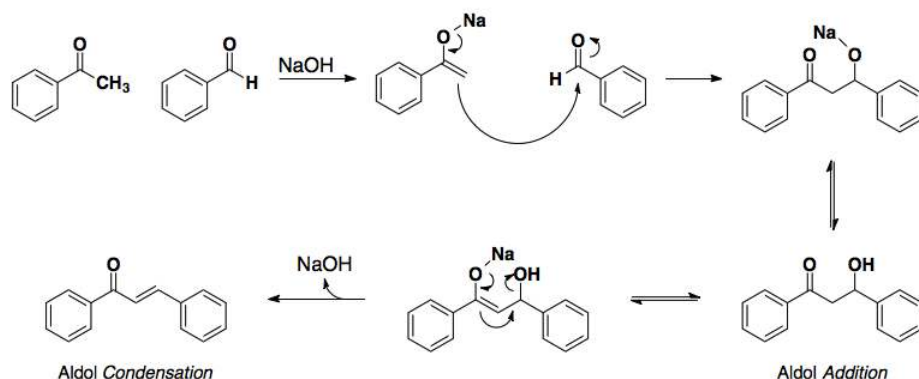
This alkylation can be rendered enantioselective by use of SAMP or RAMP



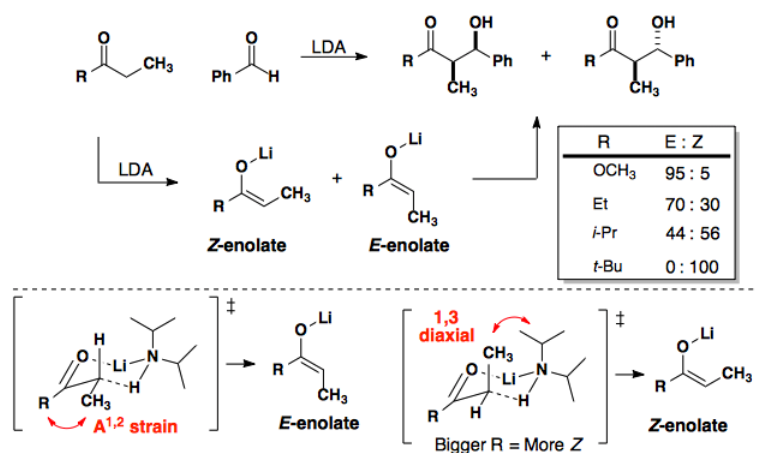
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4.4: The aldol reaction

Condensation vs. Addition

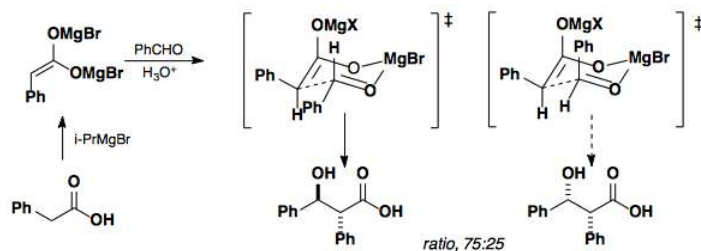


Enolate Geometry in Aldol Additions



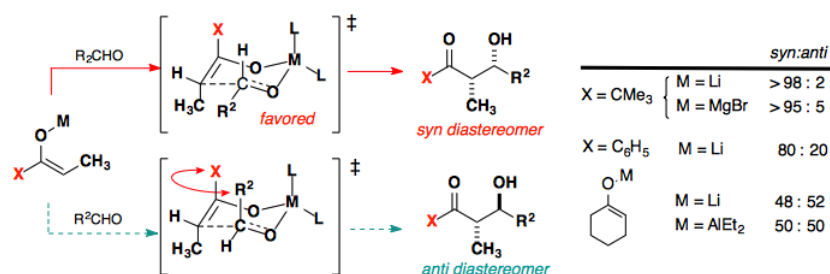
Zimmerman-Traxler Model

Zimmerman proposed a chair-like geometry for the Ivanov Reaction (a variant of the aldol reaction).



J. Am. Chem. Soc., **1956**, *79*, 1920-1923.

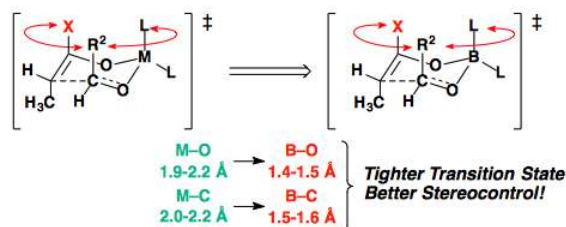
This model has since been generalized to the aldol reaction and is now known as the Zimmerman-Traxler Model.



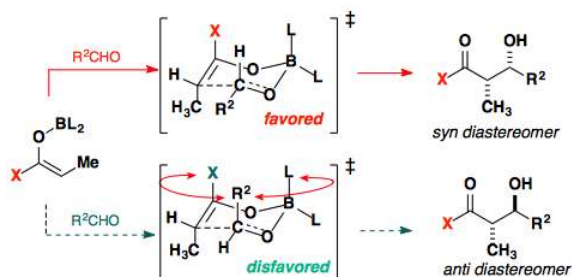
As can be seen from the above data, the model does not translate well to all enolates and works best when X is a large group; however, optimizations of the metal center have allowed for the development of a general model.

Boron aldol reaction

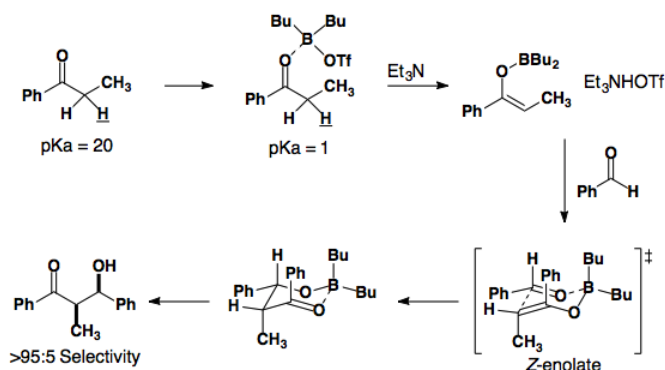
Switching to a Boron Lewis acid provides several advantages over other Lewis acids.



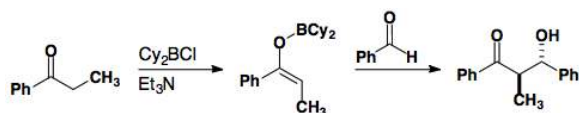
The shorter B–O bonds create a tighter transition state thus destabilizing the disfavored transition state.



Boron Lewis acids have been developed to provide either *Z* or *E* enolates in high selectivity.

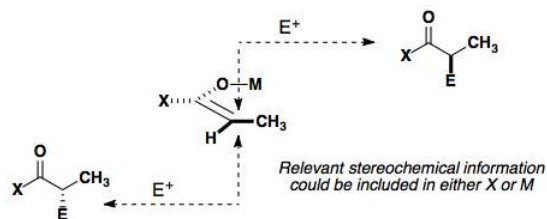


Ten years later, conditions were developed to provide the *E*-enolate in high selectivity.

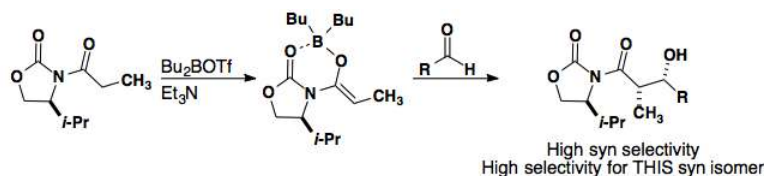


Absolute stereochemistry

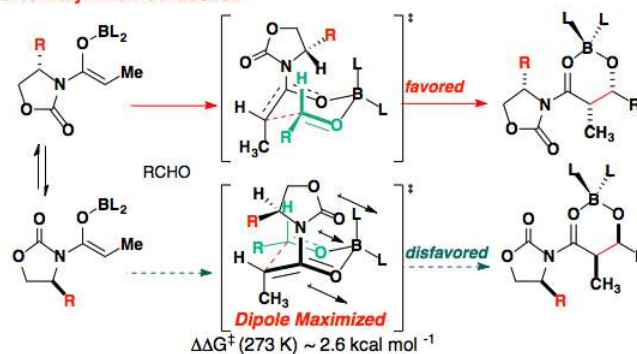
With good methods to reliably control the diastereoselectivity, we will now look at methods to control the facial selectivity of the reaction in order to control the absolute stereochemistry of the reaction.



Control of the reaction can original from a Chiral X group, such as the Evans auxiliary, or from a chiral ligand attached to the metal center.

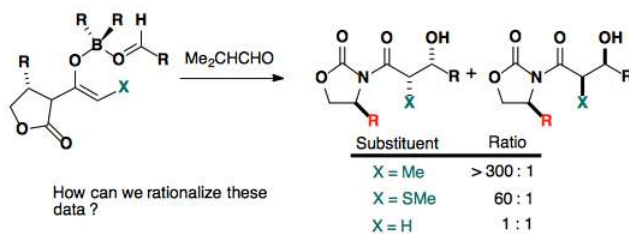


Model for Asymmetric Induction

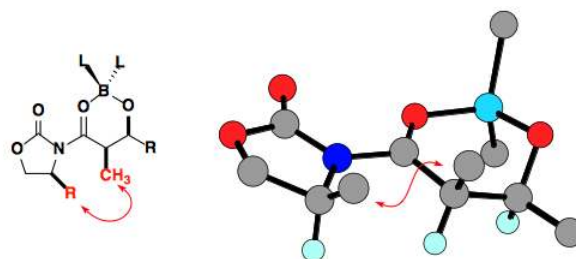


J. Am. Chem. Soc., **1981**, *103*, 2127-2129.

The enolate substituent also plays a large role in the selectivity.



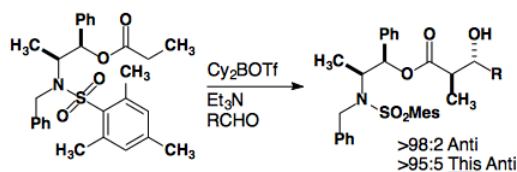
This is believed to arise from a destabilizing interaction in the product.



disfavoured product diastereomer: The destabilizing interaction?

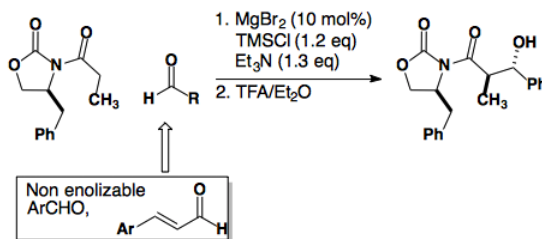
Anti-selectivity

Anti-selectivity can be achieved in several ways. Switching to a different auxiliary allows for the formation of the *E*-enolate.



J. Am. Chem. Soc., **1997**, *119*, 2586-2587.

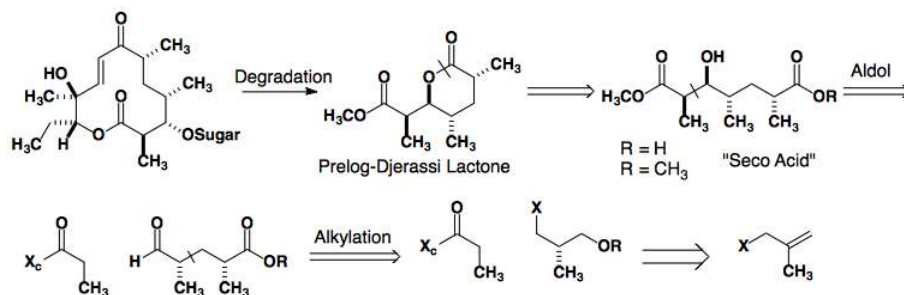
Alternatively, the Evans Auxiliary can generate the *anti*-product by switching to a magnesium lewis acid. This reaction is believed to proceed through a boat transition state to provide the *anti*-diastereomer.

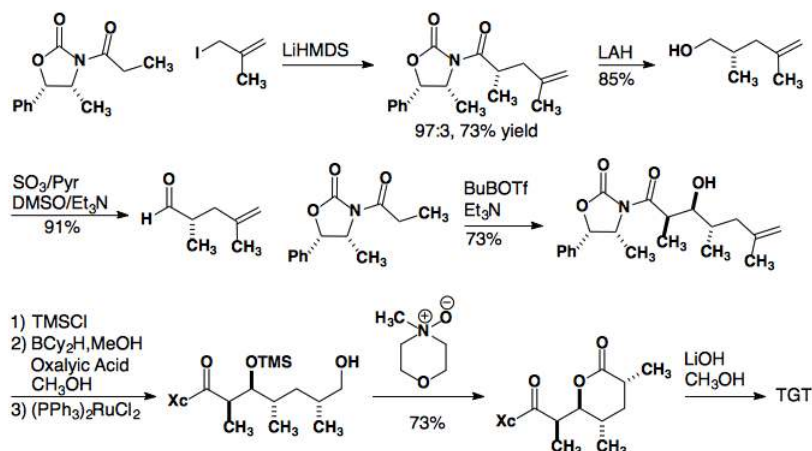


J. Am. Chem. Soc., **2002**, *124*, 392-393.

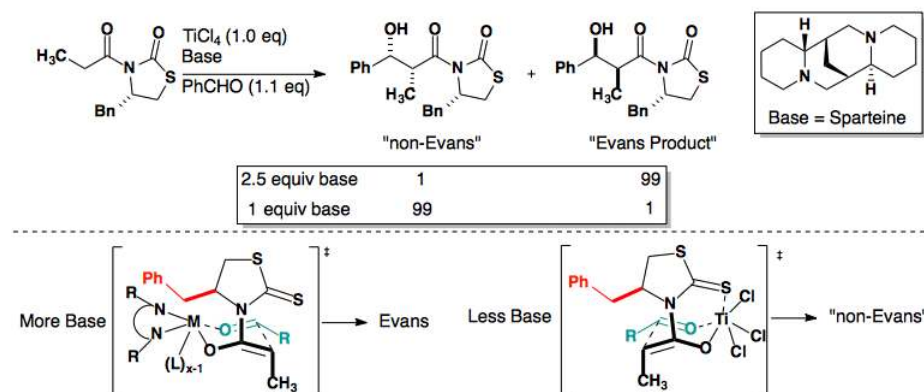
Examples

Prelog-Djerassi Lactone





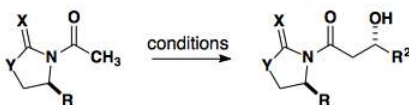
Thiazolidinethione Auxiliary



J. Org. Chem., **2001**, 66, 894-902.

Acetate Aldol

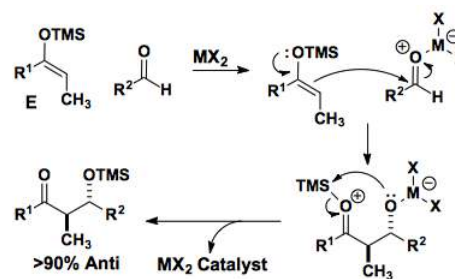
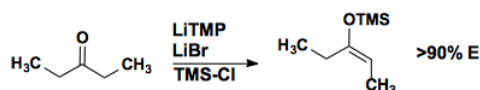
Several oxazolidinone derived auxiliaries have been shown to be useful in the acetate aldol reaction. The use of the parent Evans auxiliary with acetate substrates shows no diastereoselectivity.



X	Y	R	reference
S	S	<i>t</i> -Bu	<i>Org. Lett.</i> , 2004 , 6, 23-25.
S	S	C(CH ₃) ₂ OTES	<i>Org. Lett.</i> , 2004 , 6, 3139-3141.
S	S or O	mesityl	<i>Org. Lett.</i> , 2007 , 9, 149-152.

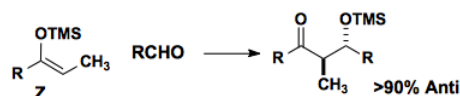
Mukaiyama Aldol

Enol silanes can be generated with high levels of enolate selectivity.

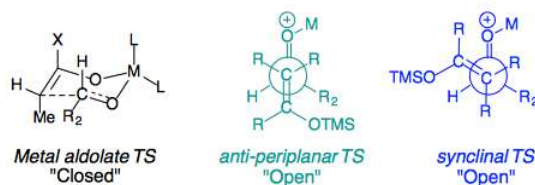


In the presence of a Lewis acid, these enol silanes will add to aldehydes.

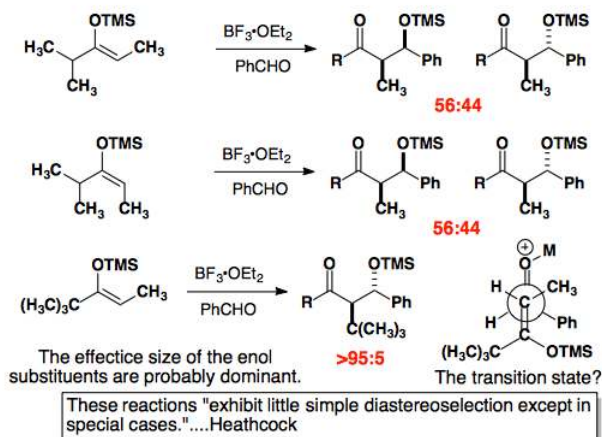
The Z-enol silane also reacts, albeit with similar *anti*-selectivity.



The Mukaiyama aldol reaction proceeds through an open transition state, which can be represented in a Newman projection. The two illustrated transition states do not differ significantly in energy, but there is a prevalent view that the anti-periplanar transition state is favored based on electrostatic effects.



Studies from the Heathcock group cast doubt on an inherent preference.

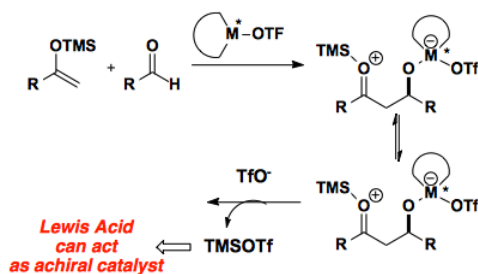


J. Org. Chem. **1986**, *51*, 3027-3037.

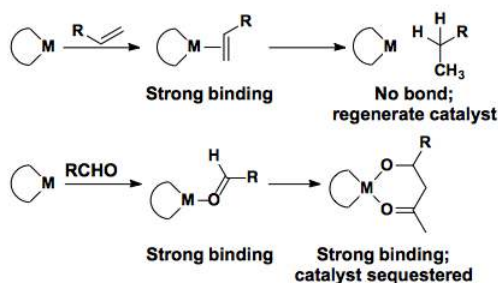
Asymmetric Catalysis

Despite the low inherent levels of diastereoselectivity in the Mukaiyama aldol reaction, several asymmetric, catalytic systems have been developed which rely on the catalyst to provide high levels of diastereoselectivity as well as enantioselectivity. The transition states of these reactions are believed to proceed through a closed transition state.

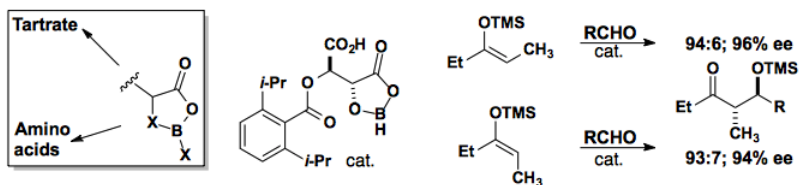
One of the major problems associated with catalyzing the Mukaiyama aldol is the possible generation of TMSOTf through the course of the reaction. This Lewis acid can then act as an achiral catalyst and erode the enantioselectivity of the reaction.



Additionally, Lewis acid catalyzed processes suffer from product inhibition of the active catalyst.

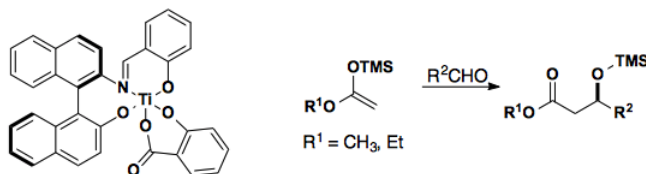


Yashimoto developed boron-based lewis acid catalysts that are readily available from tartrate or amino acids. These have been shown to convert the *E*- or *Z*-enolate to the anti-product in high diastereoselectivity and enantioselectivity.



J. Am. Chem. Soc., **1991**, *113*, 1041-1042.

The Carreira group developed a titanium based lewis acid that allows for enantioselective acetate Mukaiyama aldol reactions.



J. Am. Chem. Soc., **1994**, *116*, 8837-8838.

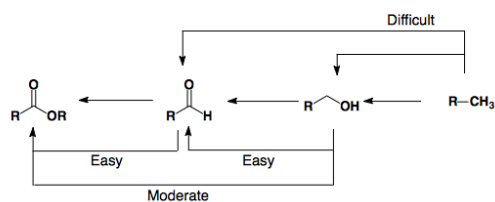
Aldol Alternatives

Access to the aldol retron (a beta-hydroxy carbonyl) can also be achieved by the [Noyori reduction](#) which will reduce a beta-keto ester to a beta-hydroxy ester.

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CHAPTER OVERVIEW

5: Oxidations



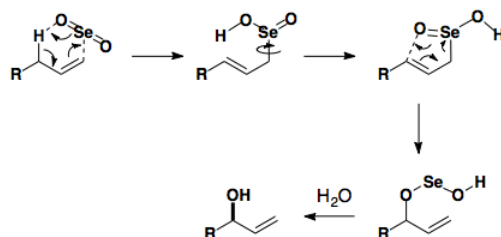
Topic hierarchy

- 5.1: Oxidation of activated C–H bonds
- 5.2: Oxidation of Alcohols
- 5.3: Oxidation of Aldehydes

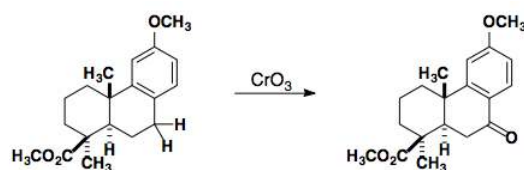
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5.1: Oxidation of activated C–H bonds

Allylic C–H bonds



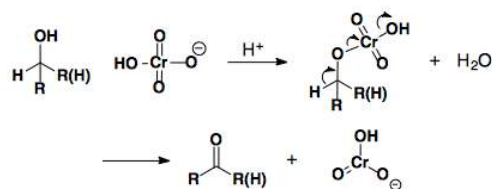
Benzylic C–H bonds



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5.2: Oxidation of Alcohols

Chromium based oxidations

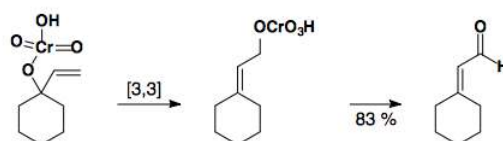


Typical Oxidants:

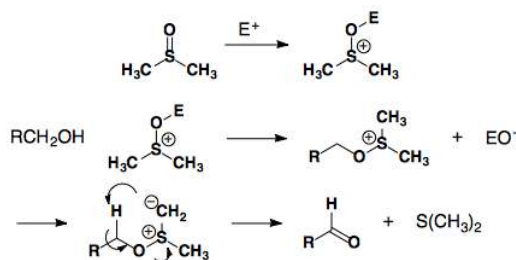
- Jones's Reagent
- Pyridinium Chlorochromate (PCC)
- Pyridinium Dichromate (PDC)
- Collins Reagent

Chromium oxidants in aqueous media will oxidize primary alcohols to the corresponding carboxylic acid. The use of PCC, PDC, and Collins Reagent in methylene chloride allows for selective oxidation to the aldehyde.

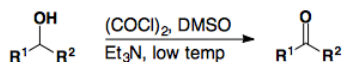
Tertiary, vinylic alcohols are known to undergo 3,3-sigmatropic rearrangements.



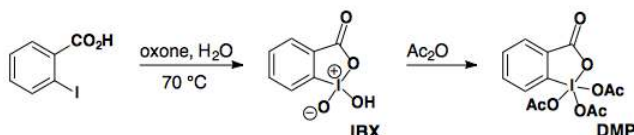
DMSO based oxidations



Swern Oxidation



IBX/DMP



IBX can be used to oxidize 1,2-diols without C-C bond cleavage.



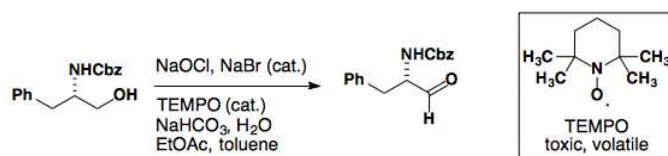
Tetrahedron Lett., **1994**, 35, 8019-8022.

Selective Oxidations

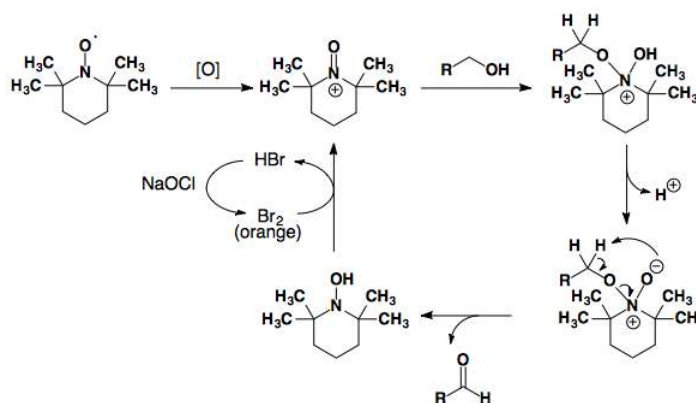
1° Selective

TEMPO

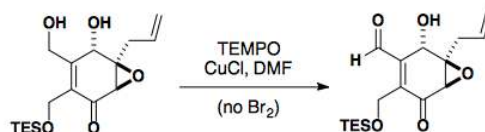
Tempo can be used to oxidize primary alcohols to aldehydes.



Tetrahedron Lett., **1992**, 33, 5029-5033.



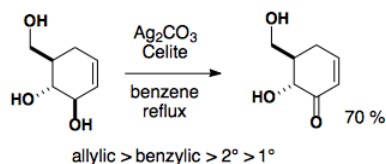
TEMPO can be used to selectively oxidize primary alcohols in the presence of secondary alcohols.

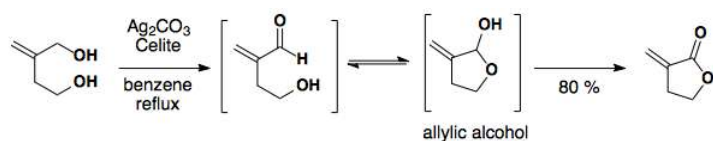


Org. Lett., **2004**, 6, 3985-3988.

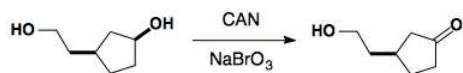
2° Selective

Fetizen's Reagent: Ag₂CO₃ on celite

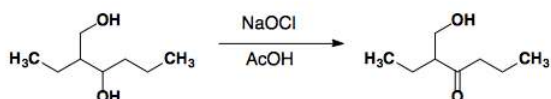




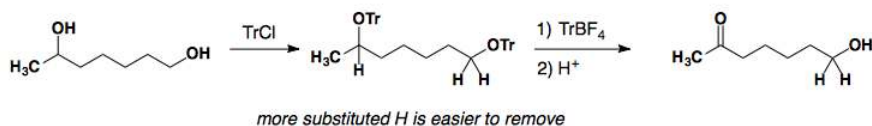
Ceric ammonium Nitrate (CAN)



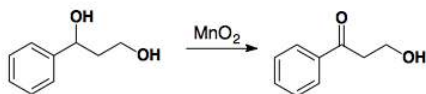
NaOCl (Bleach)



Triphenylcarbenium tetrafluoroborate (TrBF_4)



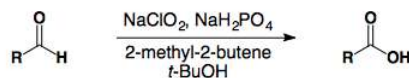
Allylic/Benzylic Selective



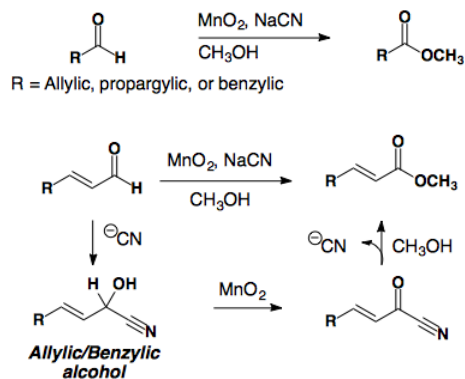
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5.3: Oxidation of Aldehydes

Pinnick Oxidation

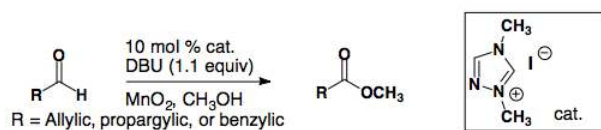


Corey-Gilman-Ganem Oxidation

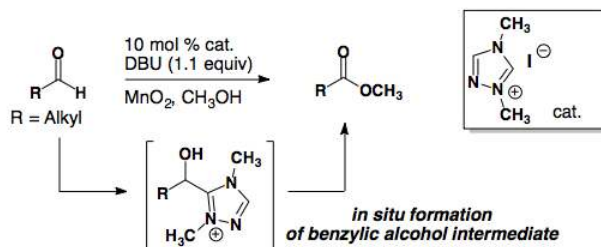


Cyanide-Free Modification

The Scheidt group developed a modified Corey-Gilman-Ganem using N-heterocyclic Carbenes (NHCs) as catalysts instead of cyanide.



The Scheidt group was also able to expand the scope of the reaction to use non-benzylic or allylic substrates.

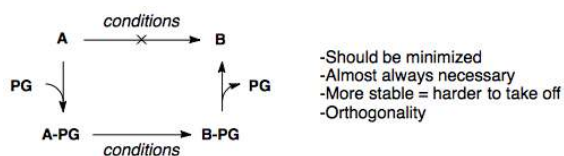


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CHAPTER OVERVIEW

6: Protecting Groups

A protecting group is introduced into a molecule by chemical modification of a functional group to obtain chemoselectivity in a subsequent chemical reaction and is an important role in organic synthesis.



[6.1: Alcohol Protecting Groups](#)

[6.2: Amine Protecting Groups](#)

[6.3: Carbonyl Protecting Groups](#)

[6.4: Diol Protecting Groups](#)

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6.1: Alcohol Protecting Groups

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6.2: Amine Protecting Groups

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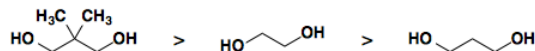
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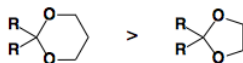
6.3: Carbonyl Protecting Groups

Acetals and Ketals

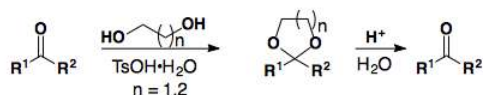
Cyclic acetals and ketals are the most useful carbonyl (aldehyde or ketone) protecting groups. Common diols used to form ketals are shown below in order of their relative rate of formation.



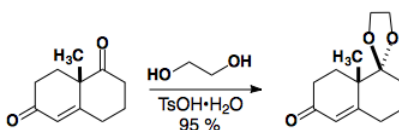
1,3-dioxanes cleave faster than 1,3-dioxolanes.



Acetals and ketals are easily formed and cleaved.

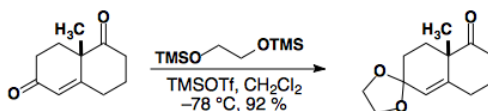


In general, saturated ketones can be selectively protected in the presence of α,β -unsaturated ketones



See: *J. Org. Chem.*, **1986**, *51*, 773-784.

Conditions have also been developed to reverse this selectivity:



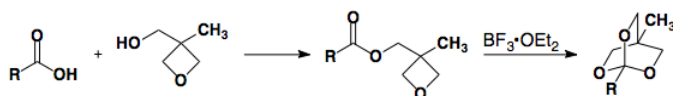
See: *Tetrahedron Lett.*, **1980**, *21*, 1357-1358.

Carboxylic Acid Protecting Groups

Esters

Ester protecting groups are [analogous to the carbamate protecting groups](#) used to protect amines.

Orthoesters



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6.4: Diol Protecting Groups

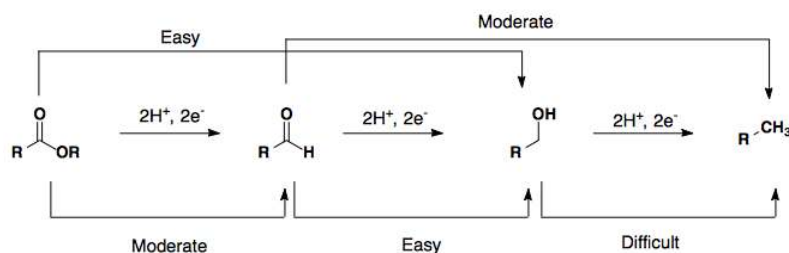
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CHAPTER OVERVIEW

7: Reductions



General Guidelines for Various Reducing Agents

Hydride Donor	Iminium Ion	Acid Halide	Aldehyde	Ester	Amide	Carboxylic Salt
LiAlH_4	Amine	Alcohol	Alcohol	Alcohol	Amine	Alcohol
DIBAL-H	–	Alcohol	Alcohol	Alcohol Aldehyde	Amine Aldehyde	Alcohol
$\text{NaAlH}(\text{O}t\text{-Bu})_3$ (Red-Al)	–	Aldehyde	Alcohol	Alcohol (slow)	Amine (slow)	–
AlH_3	–	Alcohol	Alcohol	Alcohol	Amine	Alcohol
NaBH_4	Amine	–	Alcohol	–*	–	–
NaCNBH_3	Amine	–	Alcohol (slow)	–	–	–
$\text{Na}(\text{OAc})_3\text{BH}$	Amine	–	Alcohol (slow)	Alcohol (slow)	Amine (slow)	–
B_2H_6	–	Alcohol	Alcohol	Alcohol (slow)	Amine (slow)	Alcohol
$\text{Li}(\text{Et})_3\text{BH}$ (Super Hydride)	–	Alcohol	Alcohol	Alcohol	Amine	–

* α -alkoxy esters are reduced to the corresponding alcohol

Topic hierarchy

- 7.1: Reduction of Acid Derivatives
- 7.2: Reduction of Alcohols
- 7.3: Reduction of Aldehydes and Ketones

7.1: Reduction of Acid Derivatives

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7.2: Reduction of Alcohols

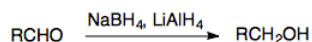
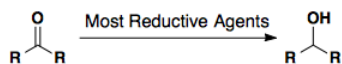
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- [Jared Shaw](#) (UC Davis)

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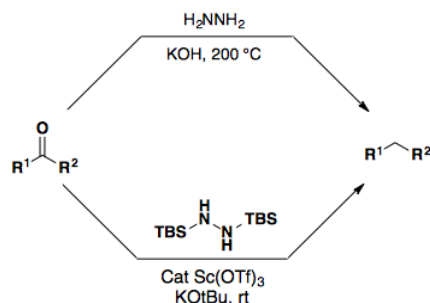
7.3: Reduction of Aldehydes and Ketones

Aldehydes and Ketones are reduced by most reducing agents. Sodium borohydride and lithium aluminumhydride are very common

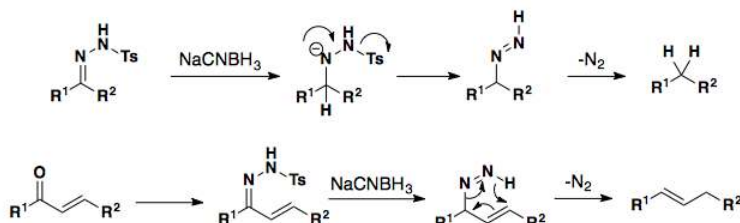


reducing agents.

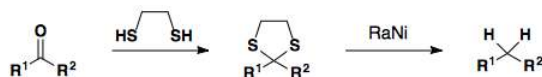
Ketones and Aldehydes can also be reduced to the respective alkanes. The Wolff-Kischner Reduction proceeds through a hydrazone intermediate under very harsh conditions. Myers developed a variation on the Wolff-Kischner reaction using a TBS-protected hydrazone which proceeds under mild conditions.



Tosyl-hydrazones can also be reduced with sodium cyanoborohydrides to yield the alkane. Additionally, α,β -unsaturated tosyl-hydrazones can be used to provide the regioisomeric alkene after a retro-ene elimination of nitrogen. This process is referred to as the alkene walk.



Alternatively, the carbonyl can be converted to the dithiane and reduced with Raney nickel to give the alkane product.



Chemoselective Reductions

Enones present unique challenges as reducing agents can also attack the alkene giving a mixture of products. Methods to selectively reduce the ketone (Luche Reduction) and the alkene (Stryker Reduction) have been developed.

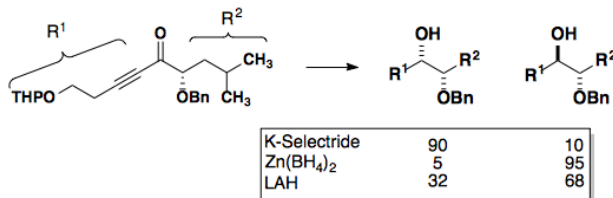
reducing agent				
NaBH_4	51	-	49	
$\text{NaBH}_4 + \text{CeCl}_3$	>99	-	>1	
$[\text{Ph}_3\text{P}(\text{CuH})]_6 + \text{Et}_3\text{SiH}$	-	94	-	

will not reduce isolated alkene

Diastereoselective Reductions

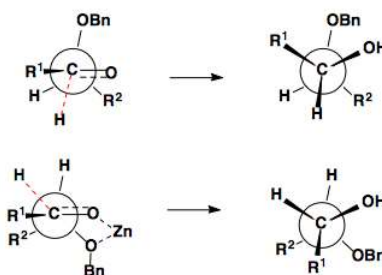
Acyclic Compounds

Reductions of aldehydes and ketones follow the same selectivity models as the addition of unstabilized carbon nucleophiles to these functional groups. Non-chelating reducing agents (NaBH_4 , LiAlH_4 , etc.) show [Felkin-Anh selectivity](#) while reducing agents which can chelate ($\text{Zn}(\text{BH}_4)_2$) show [Cram Chelate selectivity](#).



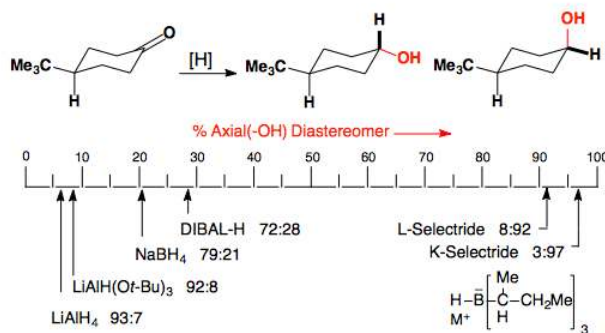
Tetrahedron Lett., **1985**, 26,5139-5142.

As seen in the example above, lithium will sometimes chelate.

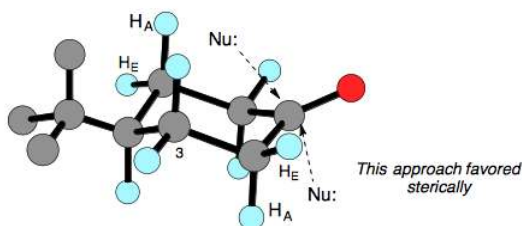


Cyclohexanones

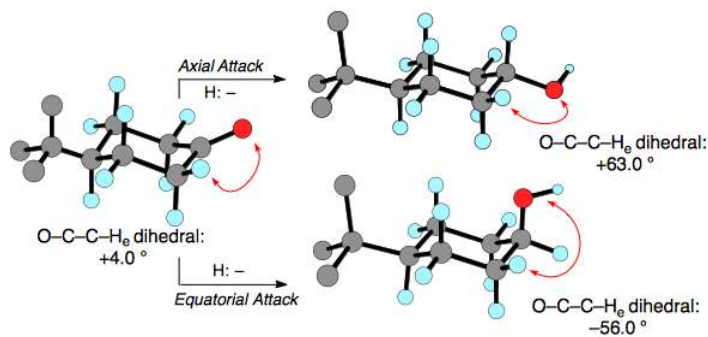
Hydrides can approach cyclohexanones from the axial or equatorial face of the ketone.



It has been observed that increasingly bulky hydride reagents prefer to attack from the equatorial face of the carbonyl. This is rationalized by the increased steric demand of a nucleophile approaching from the axial face of the carbonyl as it encounters the axial substituents (H in this case) at the 3 and 5 positions.

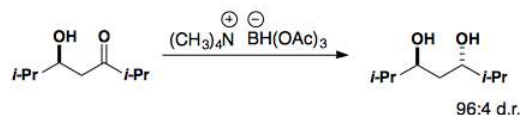


This argument would thus seem to always argue for attack from the equatorial face, but we must also take into consideration any developing torsional strain through the transition state. Attack from the axial face avoids developing eclipsing interactions between the C–O bond and the C–H_E bonds at the 2 and 6 positions. Attack from the equatorial face forces the C–O bond to travel past the C–H_E bonds to sit in the chair conformation. We can see this below as the dihedral angle in the starting cyclohexanone starts as a positive number and ends up as a negative number which shows that the C–O bond must have gone through an eclipsing conformation to reach its final position. Axial attack does not cause a change in sign of the dihedral angle, thus avoiding any eclipsing interactions in the transition state.

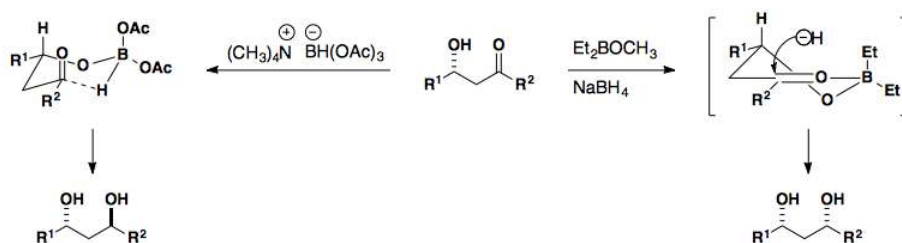
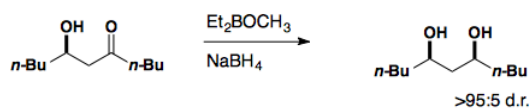


We can thus predict that small hydride reagents, such as LiAlH₄, will prefer to attack from the axial face as the torsional strain in the transition state is the dominant interaction while large hydride reagents, such as H–BR₄, will attack from the equatorial face as the steric interactions from the reagent's approach are now the dominant interaction.

Substrate Directed Reductions



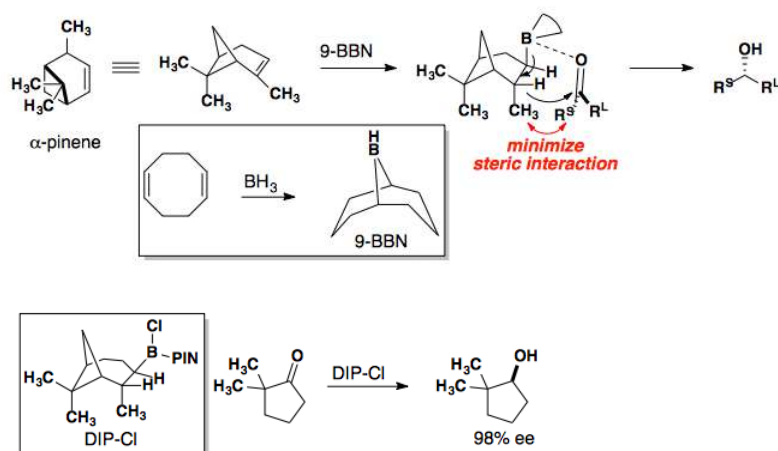
J. Am. Chem. Soc., **1988**, *110*, 3560-3578.



Tetrahedron Lett., **1987**, *28*, 155-158.

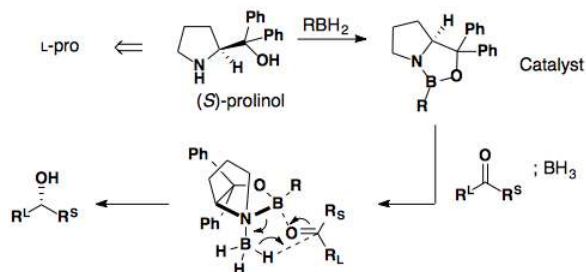
Enantioselective Reductions

Chiral Boronates

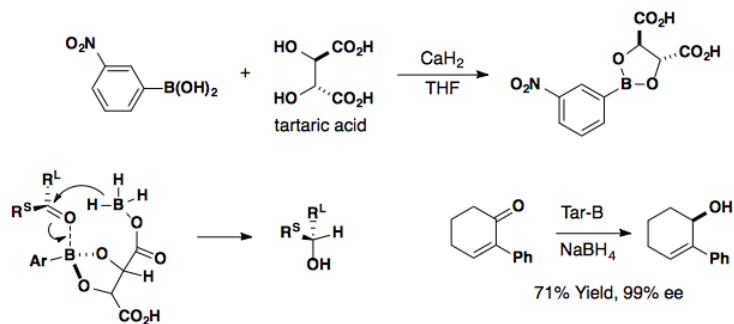


If the selectivity from these reactions is the opposite of your desired product, you can use a Mitsunobu Reaction to invert the stereocenter.

Corey-Bakshi-Shibata (CBS) Reductions



Tar-B



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8: Synthetic Efficiency

Linear Synthesis

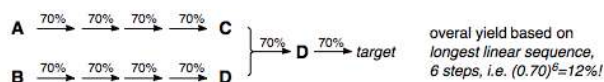
We can determine the overall yield of a linear synthetic sequence by multiplying the yields of each individual step. For example...

Steps	Yield/Step (%)	Overall yield (%)
10	70	2.8
15	70	0.5
10	90	35
10	95	60
100	95	0.0059

As you can see, the overall yield of a linear sequence of steps quickly drops off especially when the yields of individual steps are below 90%. Even when all of the yields of a series of reactions are above 90%, the overall yield still drops, albeit at a slower rate.

Convergent Synthesis

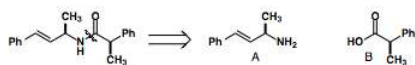
To increase the efficiency of a synthetic route, we can try to break target molecules into precursors of roughly the same size and complexity. In this way we can cut down the longest linear sequence and increase our overall yield of the process.



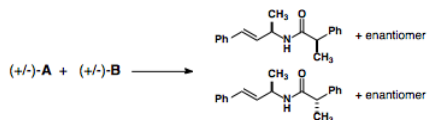
In the route above, there are still 10 overall steps in the synthesis, but our longest linear sequence (LLS) is only 6 steps. We have increased our yield to 12 %, significantly higher than the 2.8 % we would have recovered from a linear synthesis of the target.

Stipulations to Convergent Synthesis

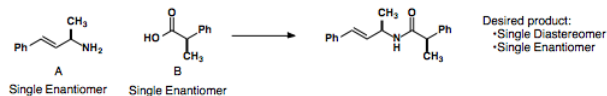
If we are targeting the Amide seen below, we would disconnect the amide bond to form intermediates A and B.



If we combine a racemic mixture of these intermediates, we end up with a statistical distribution of the four possible stereoisomers.



So while convergent routes are the most efficient, they require that each intermediate in the synthetic pathway be either achiral or a optically pure.



Atom Efficiency

Redox Efficiency

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CHAPTER OVERVIEW

9: Unstabilized Carbon Nucleophiles

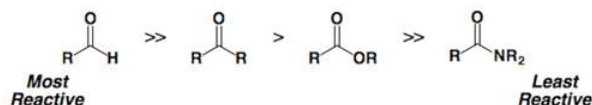
Topic hierarchy

- 9.1: Addition to Carbonyl Compounds
- 9.2: Alkylations
- 9.3: Cuprates
- 9.4: Diastereoselective Addition to Aldehydes and Ketones
- 9.5: Ketone Synthesis
- 9.6: Preparation of Organometallic Reagents

9: Unstabilized Carbon Nucleophiles is shared under a [CC BY-NC-SA 4.0](#) license and was authored, remixed, and/or curated by LibreTexts.

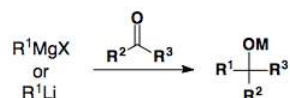
9.1: Addition to Carbonyl Compounds

Addition to carbonyl groups varies depending on the type of carbonyl. The following trend is observed:



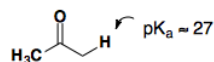
Some important topics related to carbonyl addition reactions are listed below. Reactions of enolates with other carbonyl compounds can be found in the [Enolates](#) section.

Aldehydes and Ketones

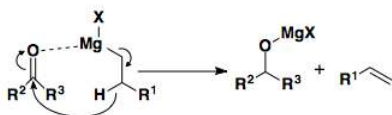


Problems

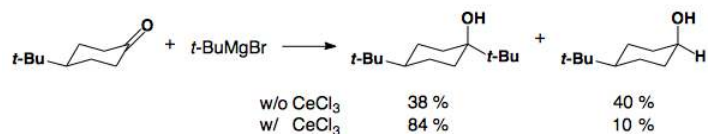
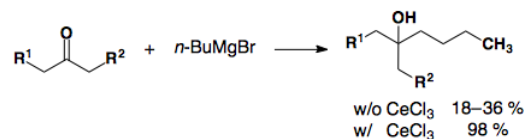
Deprotonation:



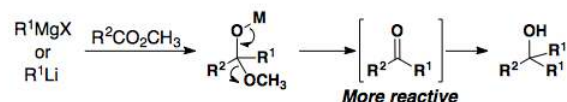
Reduction:



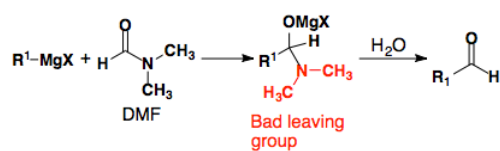
Reduction can be avoided by the addition of Cerium(III) Chloride:



Esters



Amides



The [Weinreb amide](#) is a useful functional group to synthesize ketones.

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9.2: Alkylations

Epoxide Opening

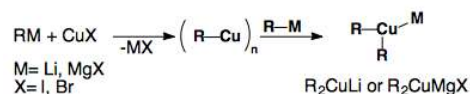
Corey-House Reaction

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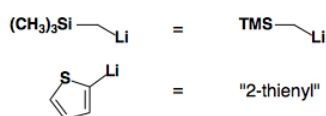
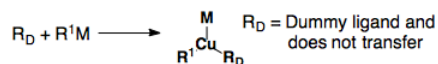
9.3: Cuprates

Preparation

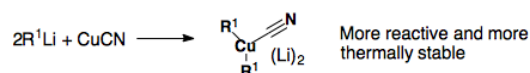
Homocuprates



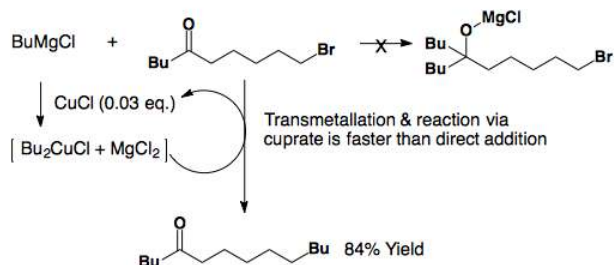
Heterocuprates



Higher Order Cuprates

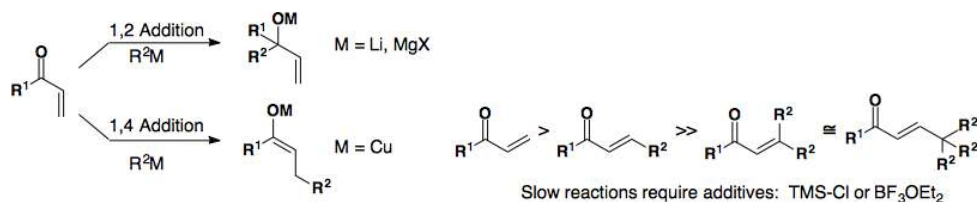


Catalysis via Cuprate



Reactions

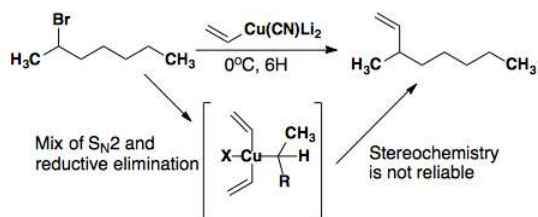
1,4-Addition (Conjugate Addition)



Ketone Synthesis

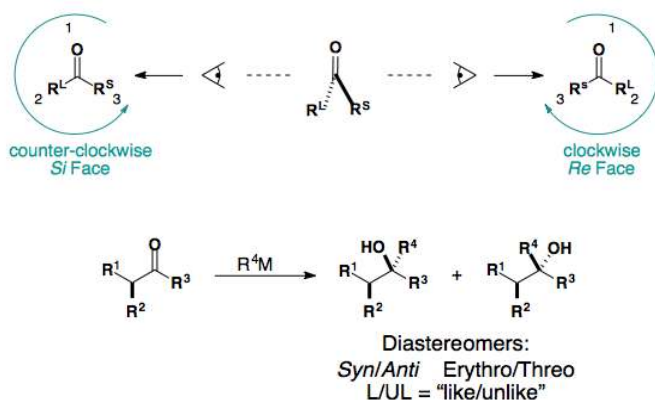
Cuprates will react with acid chlorides to form ketones.

Alkylation

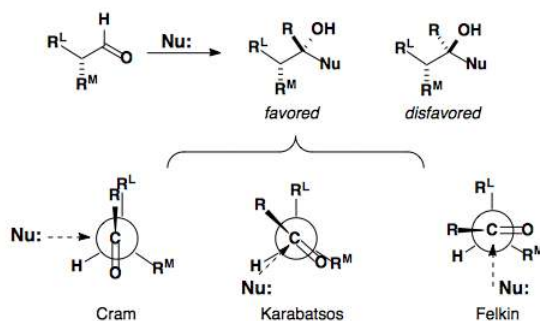


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9.4: Diastereoselective Addition to Aldehydes and Ketones



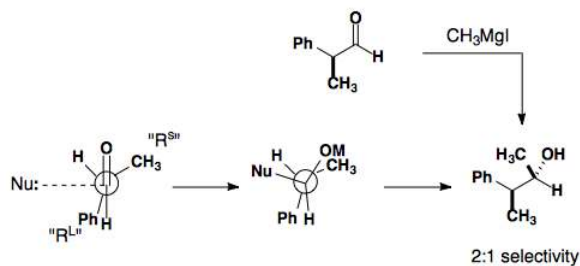
Advancements in Acyclic Stereochemical Models



- Cram's Model: *J. Am. Chem. Soc.*, **1952**, 74, 5828-5835.
- Karabatsos Model: *J. Am. Chem. Soc.*, **1967**, 89, 1367-1371.
- Felkin Model: *Tetrahedron Lett.*, **1968**, 2199-2204.

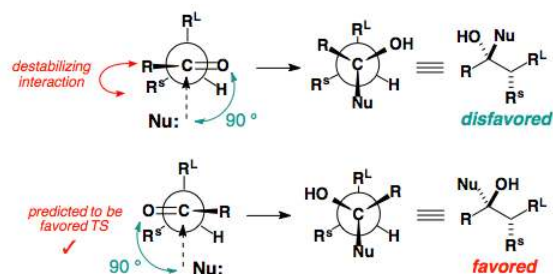
Cram Model (Cram's Rule)

Cram's rule suggests that we should place the largest substituent of the adjacent stereocenter eclipsed with the R group (H in below depiction) of the carbonyl. The Nucleophile then attacks from the less hindered face of the carbonyl to provide the major product.

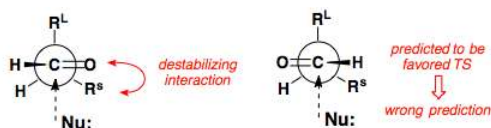


While Cram's Rule correctly predicts many reactions, it has its limitations. The conformation of the starting material leads to an eclipsed product after the initial addition which is unfavorable due to increasing torsional strain through the reaction coordinate, and the model works best when the R^L is phenyl.

Felkin Model

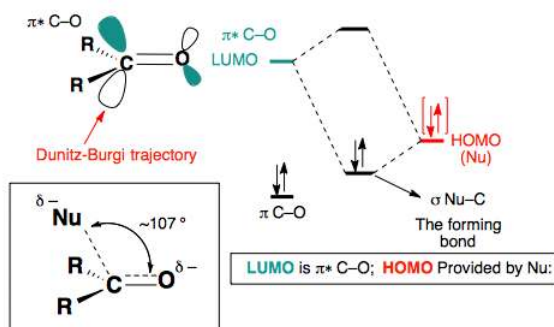


One flaw with the Felkin model is that it predicts the wrong transition state for reactions with aldehydes:

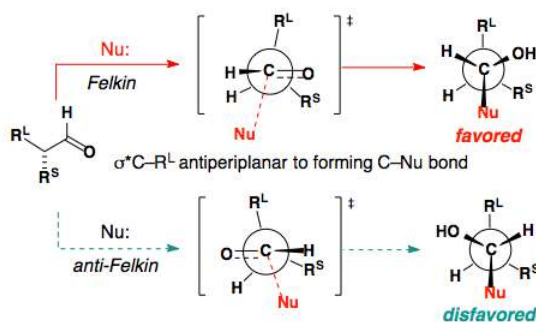


Felkin-Anh Model

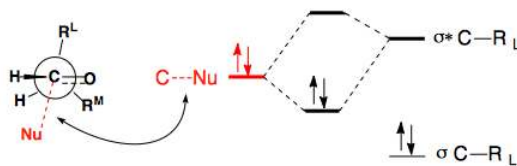
Anh and Eisenstein provided key advancements to Felkin's model. First, they suggested that the nucleophile attacked the Carbonyl at a larger bond angle than 90° . The HOMO-LUMO interaction between the NU and Carbonyl requires a larger bond angle, estimated between $100-110^\circ$. This angle is now referred to as the Burgi-Dunitz angle, after the two crystallographers who proposed it (*Acc. Chem. Res.*, **1983**, *16*, 153-161.).



Anh and Eisenstein also hypothesized that there was favorable overlap between the forming C–Nu bond with the antibonding orbital of C–R^L. This would allow for two possible conformers during the addition. One conformer requires the nucleophile to approach over the R^S substituent, whereas the other conformer allows the nucleophile to approach over the smallest substituent, in this case hydrogen. The least hindered trajectory (red arrows) is less sterically demanding in the transition state and leads to the favored product.



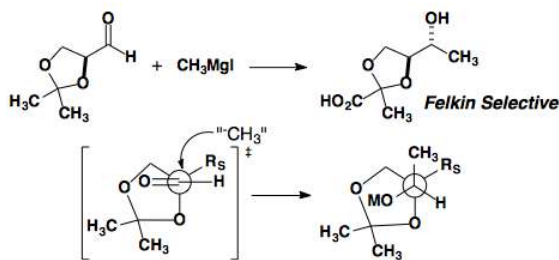
This model suggests that the substituent with the best acceptor antibonding orbital will be oriented antiperiplanar to the forming C–Nu bond.



Houk has provided theoretical support for staggered transition states: *J. Am. Chem. Soc.*, **1982**, *104*, 7162-7166. and *Science*, **1986**, *231*, 1108-1117.

Padden-Row provides theoretical support for the Felkin-Anh-Eisenstein Model: *J. Chem. Soc., Chem. Commun.* **1990**, 456-458.

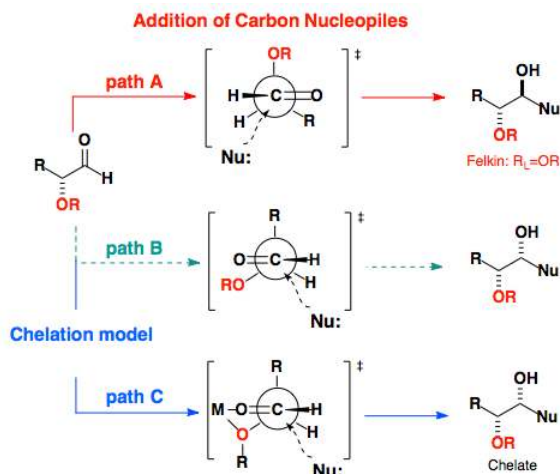
This model applies to many alpha-chiral carbonyls and many nucleophiles, including hydrides.



Borane reducing agents do not follow this trend. In general, non-spherical nucleophiles are unreliable in the Felkin-Anh analysis.

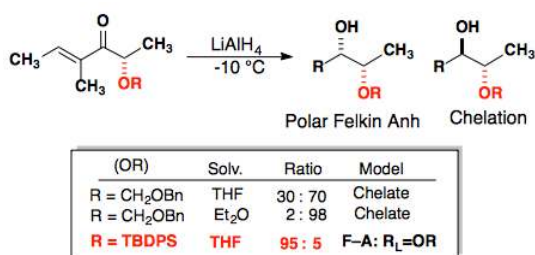
Cram Chelate

alpha-substituents that can chelate a metal allow cause a reversal in selectivity:



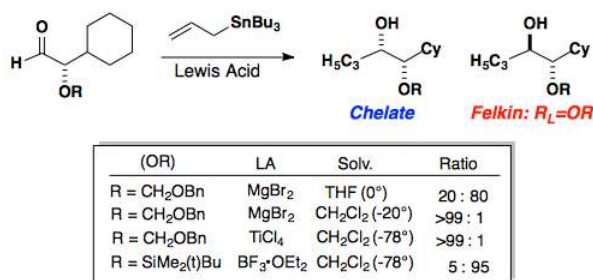
Path A shows our typical Felkin-Anh selective model while Path B shows the transition state leading to the minor diastereomer in a Felkin-Anh analysis. Depending on the metal and the R^L ($R^L = OR$ in figure), a reversal of selectivity can occur due to chelation of the metal between the carbonyl oxygen and R^L . Chelation controls the conformation of the transition state and causes the nucleophile to attack from the opposite face.

In the below table, BOM-protected alcohols show high preference for the chelate product while the TBDPS-protected alcohol almost exclusively forms the Felkin-Anh product. Thus, we can control the product distribution based on the protecting group or solvent.



Tetrahedron Lett., **1982**, 23, 2355-2358.

Work from the Keck lab has also shown that, while solvent and R-groups affect the selectivity, the choice of Lewis Acid can also drastically change the selectivity. In general, the lewis acid must be good at chelation in order to form the Cram Chelate product. A few examples of good lewis acids for chelation are MgBr₂, ZnBr₂, TiCl₄, and SnCl₄. As seen in the table below, BF₃•OEt₂ does not chelate and provides the Felkin-Anh product.



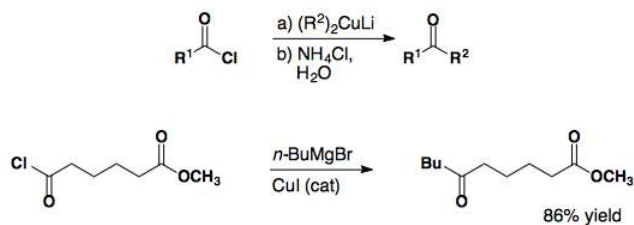
Tetrahedron Lett., **1984**, 25, 265-268.

Padden-Row provides theoretical support for the Cram Chelate model: *J. Chem. Soc., Chem. Commun.*, **1991**, 327-330.

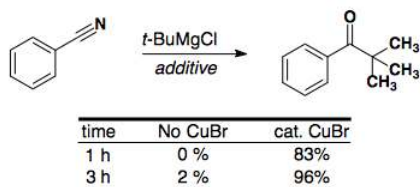
9.4: Diastereoselective Addition to Aldehydes and Ketones is shared under a CC BY-NC-SA 4.0 license and was authored, remixed, and/or curated by LibreTexts.

9.5: Ketone Synthesis

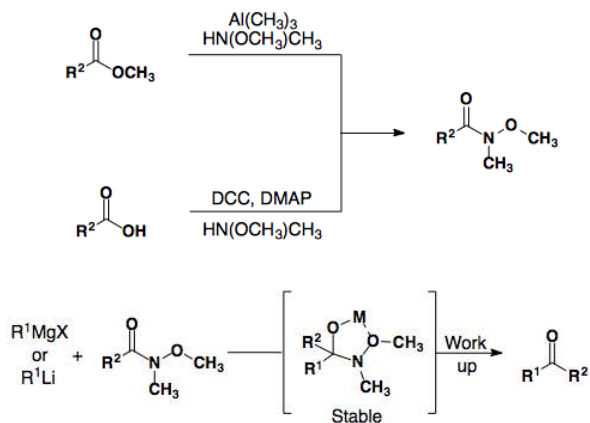
From Acid Chlorides



From Nitriles



Weinreb Amide



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Reduction


$$\text{C}_6\text{H}_5\text{X} \xrightarrow[\text{X} = \text{Br, I}]{n\text{-BuLi}} \text{C}_6\text{H}_5\text{Li} + n\text{-Bu-X}$$
$$\text{R}-\text{CH}=\text{CH}-\text{Br} \xrightarrow{n\text{-BuLi}} \text{R}-\text{CH}=\text{CH}-\text{Li} + n\text{-Bu-X} \longrightarrow \text{R}-\text{CH}=\text{CH}-\text{C}_4\text{H}_9$$
[illegible]CC1(C)N(C2=CC=CC=C2)OC1>[n-BuLi, -45 °C]>CC1(C)N(C2=CC=CC=C2)OC1Br
$$\text{H}_3\text{C}-\text{C}(\text{CH}_3)_2-\text{O}-\text{C}(=\text{O})-\text{N}(\text{CH}_2)_5 \xrightarrow[-20^\circ\text{C}]{\text{sec-BuLi}} \text{H}_3\text{C}-\text{C}(\text{CH}_3)_2-\text{O}-\text{C}(=\text{O})-\text{N}(\text{CH}_2)_5\text{L}$$

For an in depth review of directed ortho-metalation reactions see: *Chem. Rev.*, **1990**, *90*, 879-933.

Reduction


$$\text{R}^1\text{-X} \xrightarrow{i\text{-PrMgX}} \text{R}^1\text{-MgX} + i\text{-PrX}$$

$\text{R}^1 = \text{aryl, vinyl}$

For a review of organomagnesium reagents prepared through exchange reactions see: [Angew. Chem. Int. Ed.](#), **2003**, 36, 4302.-4320.

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C

Carbonyl Protecting Groups

[6.3: Carbonyl Protecting Groups](#)

P

Protecting Groups

[6: Protecting Groups](#)

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