

Chapter 7 - Predicting & Controlling Stereochemistry

Graduate course "Topics in Stereochemistry" (10 weeks)

Goals of CHM 543: Students will explore the field of stereochemistry, including nomenclature, analytical techniques, asymmetric syntheses and "real-world" applications. Students will also gain experience searching the current literature by preparing and presenting a research report.

1. stereochemical nomenclature & terminology
 - a. discussion of chirality (chiral carbons, allenes, biphenyls, etc.)
 - b. 2-D representations (line drawings, Fischer, Haworth projections)
 - c. stereochemical terminology for sugars, amino acids
 - d. physical and chemical properties of stereoisomers
2. stereochemical analysis: determination of relative and absolute configuration
 - a. polarimetry (optical activity, specific rotation, $[\alpha]$)
 - b. chiral GC & HPLC
 - c. NMR techniques
3. stereochemistry of organic reactions
 - a. retention, inversion, racemization, epimerization
 - b. enantiotopic and diastereotopic environments
4. chiral techniques and syntheses
 - a. optical resolution
 - b. asymmetric oxidations & reductions
 - c. asymmetric C-C bond forming reactions
 - d. use of catalytic enzymes
5. real-world applications, including chiral drugs

Starkey textbook Chapter 7

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Stereochemistry of Organic Reactions

↳ determined by Rxn Mechanism!

Stereospecific a rxn that proceeds w/ a definite stereochemical outcome
stereoisomer starting material(s) → different products
(eg, cis or trans)

Stereoselective single reactant can give 2 or more stereoisomer products, but only one is preferred (is selected) + formed as major product

Possible stereochemistries:

Substitution Rxns

retention of configuration: same spatial arrangement of SM groups
inversion of config: stereochem of product is mirror image of SM
racemization (complete or partial)

single enantiomer SM → both possible enant products
(if only one of multiple chiral centers is involved: epimerization)

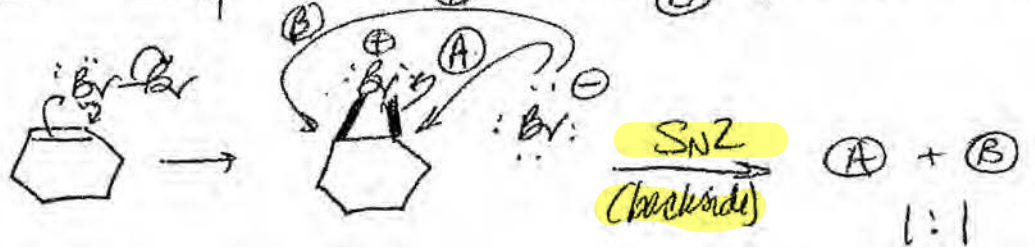
7.2-7.4

b) anti addition (via cyclic intermediate)

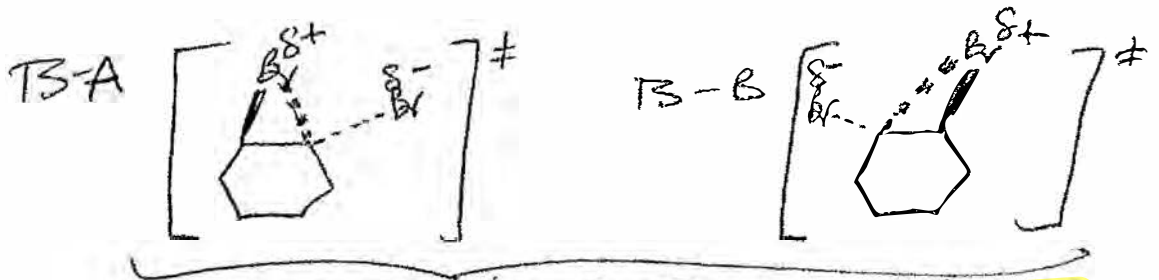


stereospecific

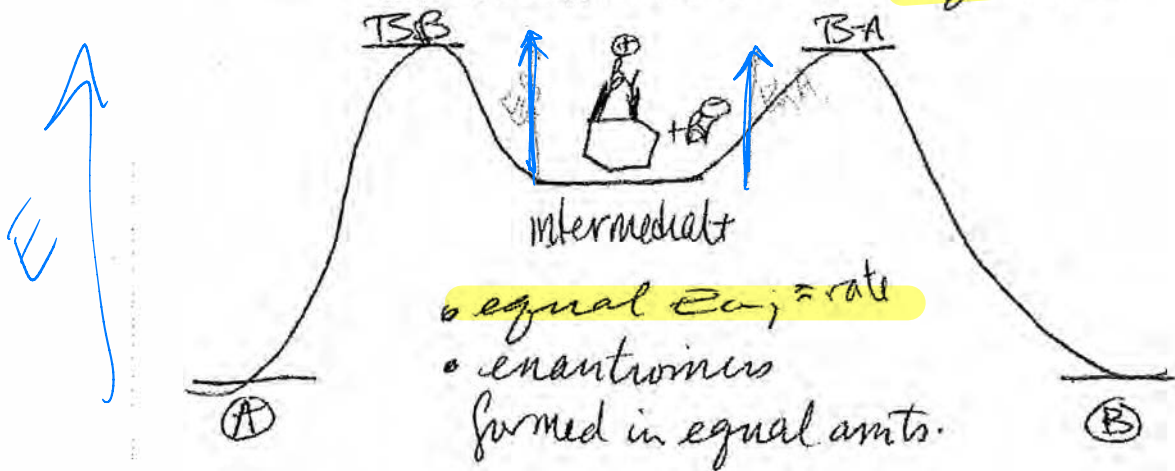
Mech



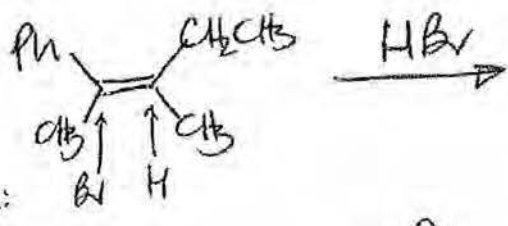
bromonium ion



enantiomeric TS $\rightarrow$ equal in E

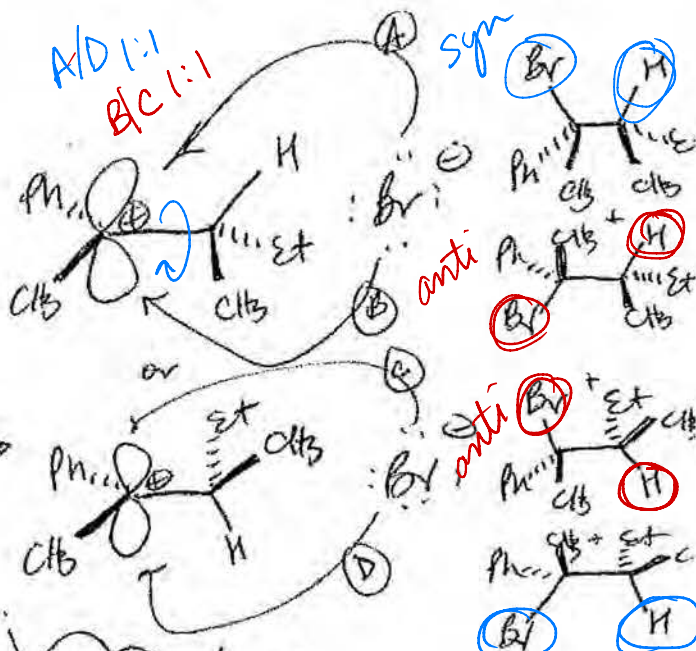
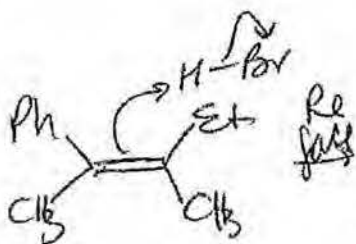


c) mixed stereochemistry



stereochem: all possibilities $\rightarrow$ 4 products

Mech



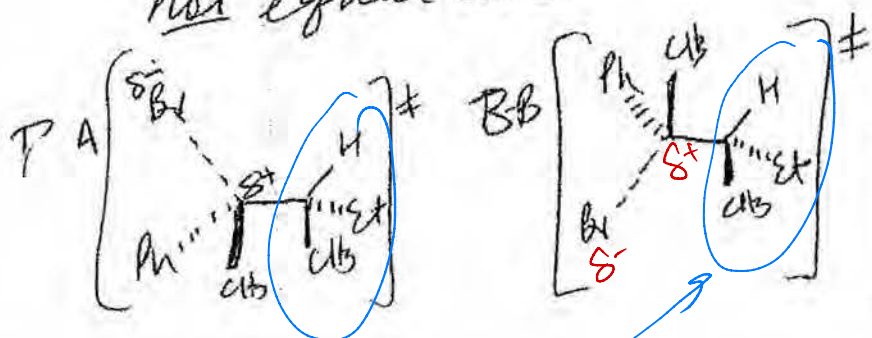
both

syn + anti addn

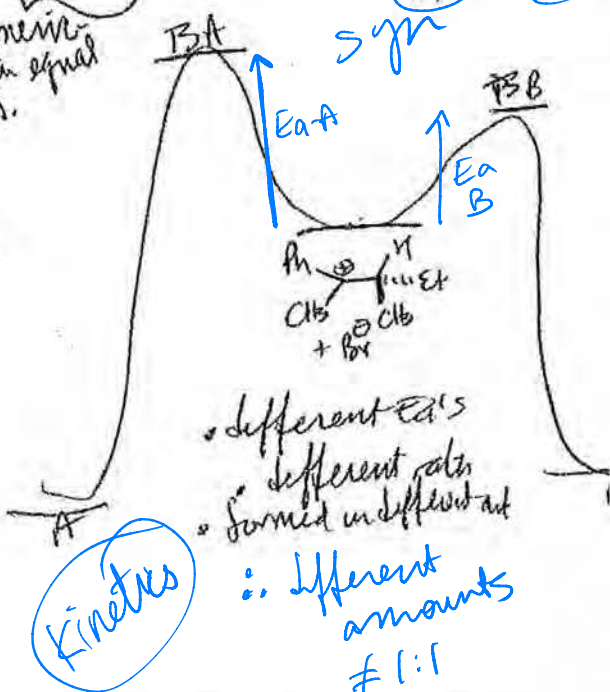
$\begin{matrix} A/D & B/C \\ 1:1 & 1:1 \end{matrix}$

diastereomers: not formed in equal amounts
 $A:B \neq 1:1$

why? **Diastereomeric T.S.**
 not equal in E



same



Kinetics

$\uparrow E$ difference, $\uparrow$ stereoselectivity
 (larger difference in product mixture)
 diastereomeric excess

$\%de = (\% \text{ major diastereomer}) - (\% \text{ minor diast.})$

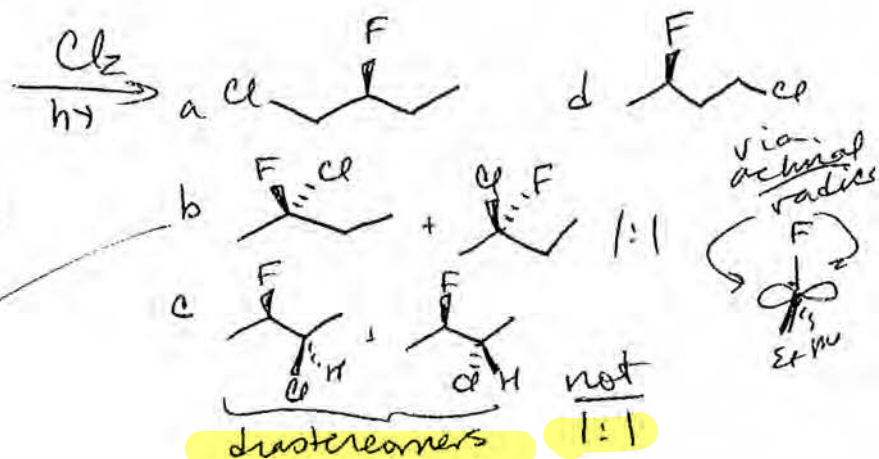
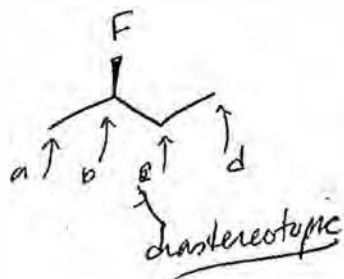
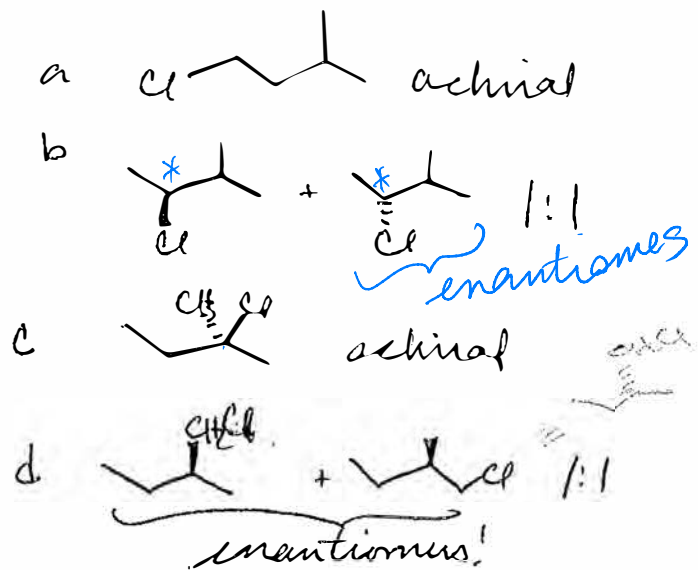
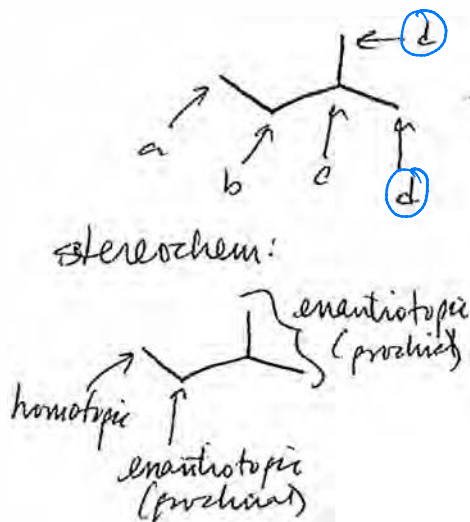
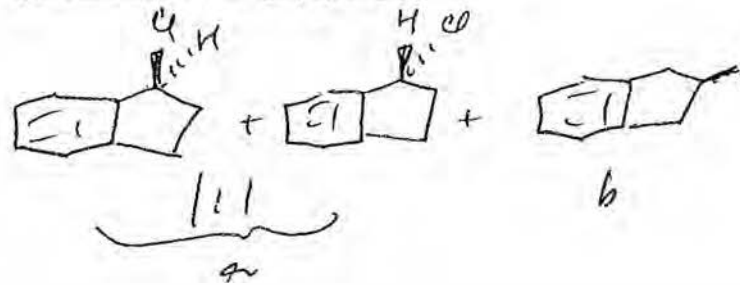
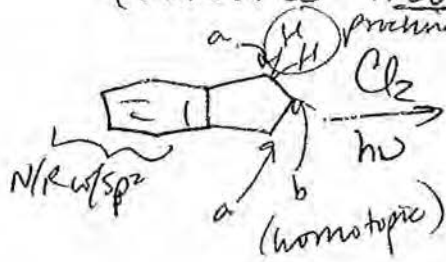
100% de $\rightarrow$ single diastereomer is produced

0% de $\rightarrow$ diastereomers produced in equal am

50:50

ee = enantiomeric excess

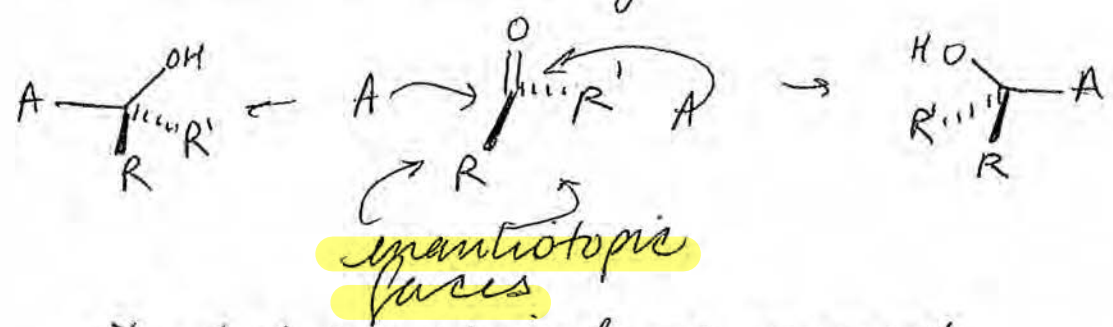
Predict products (including regio + stereoisomers)
(assume mono chlorination)



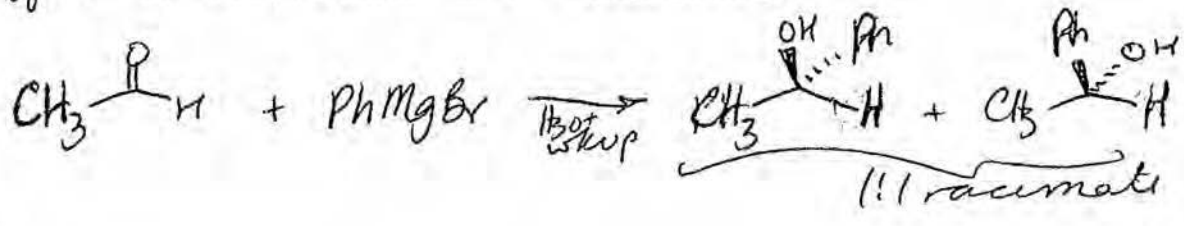
loss of a group from a chiral carbon $\rightarrow$ racemize

15

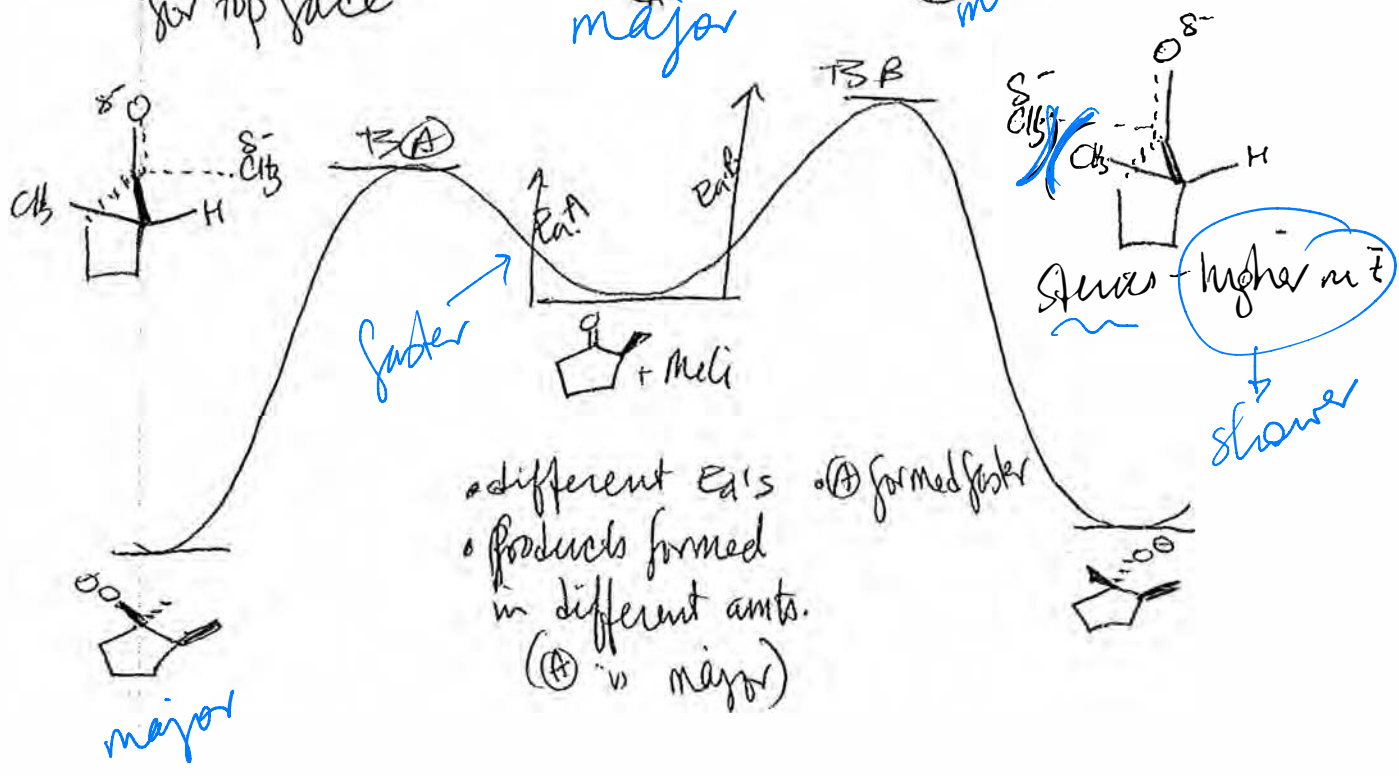
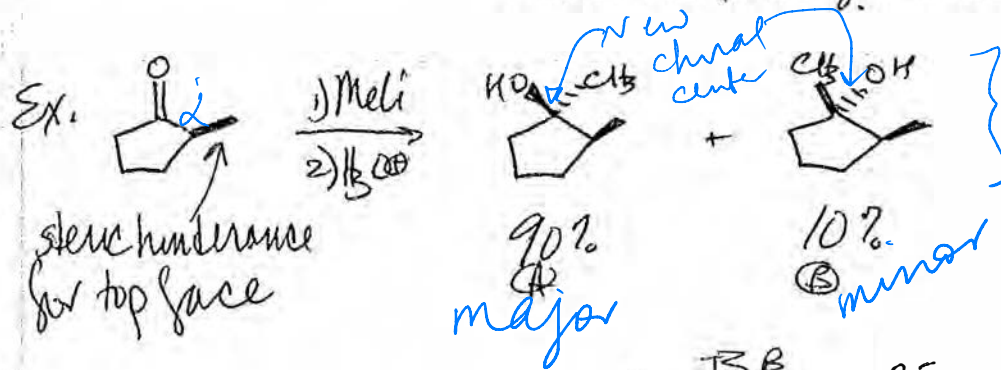
④ Addn to carbonyls



→ if A is achiral → racemate

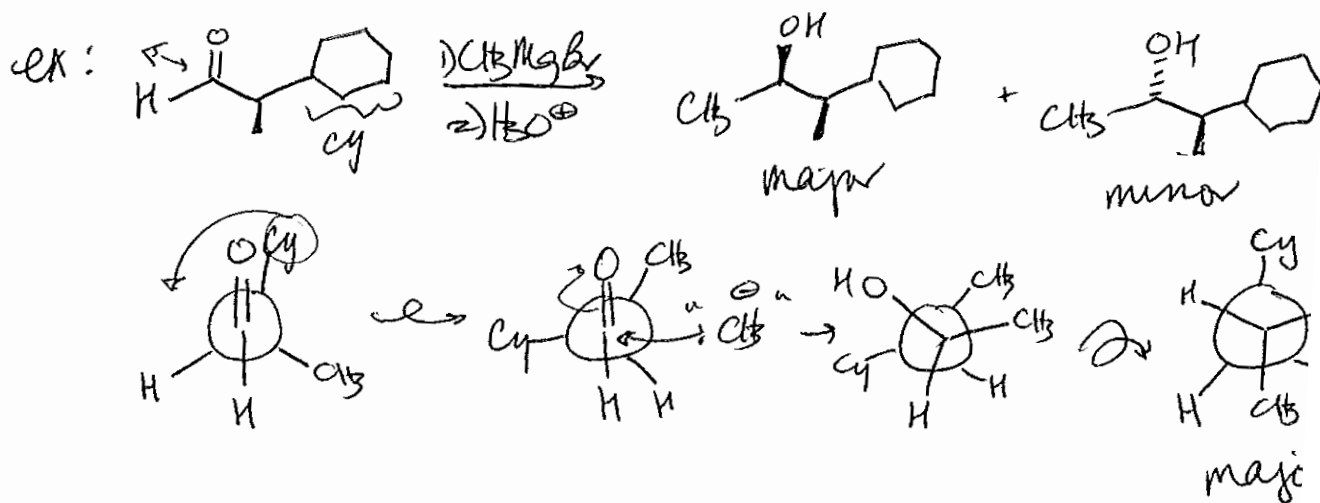
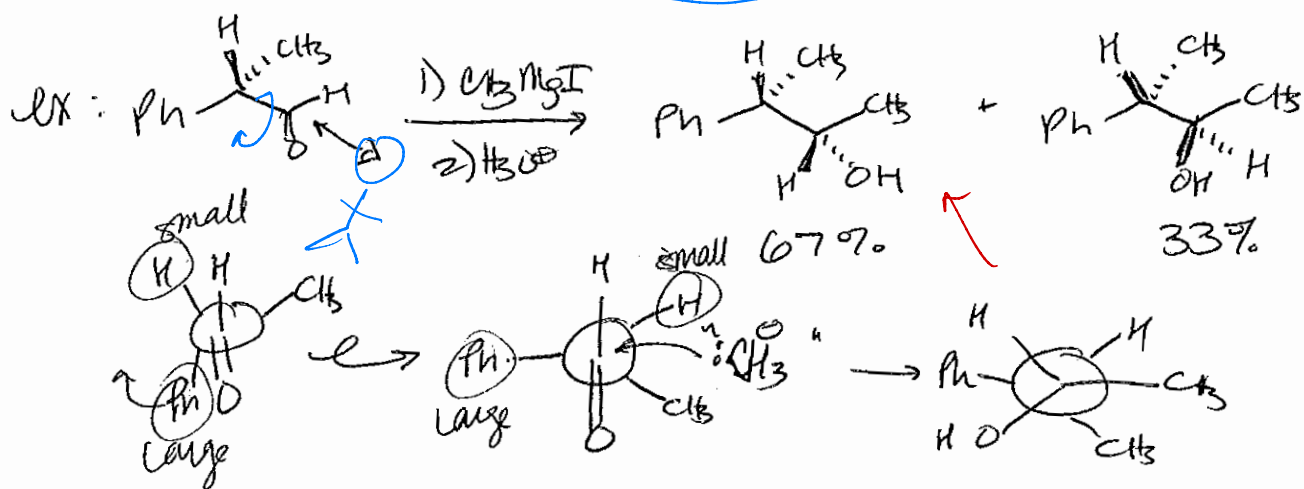
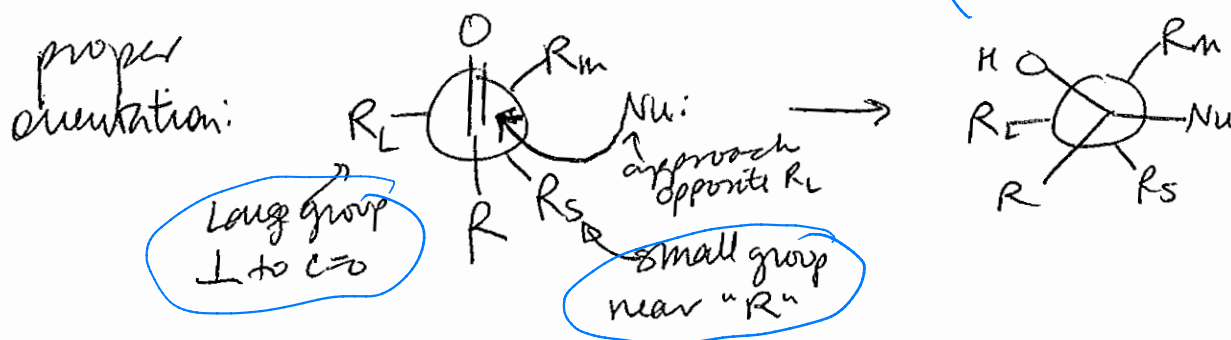
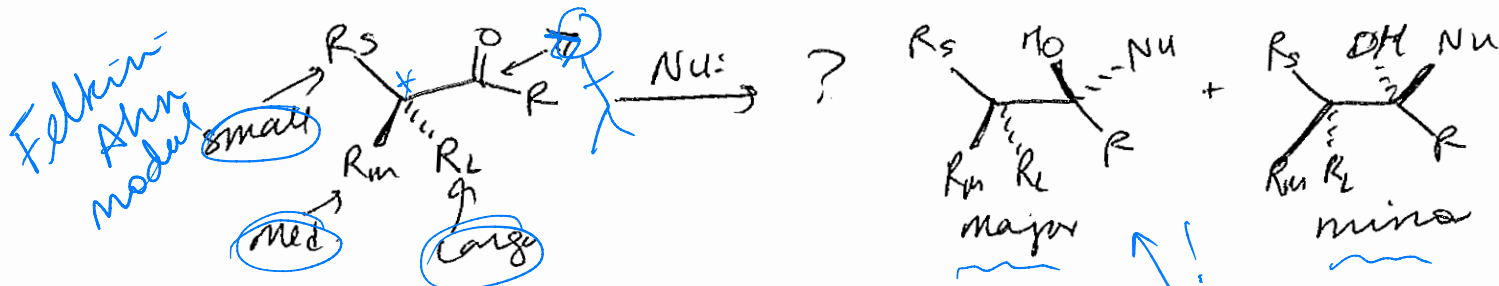


→ if A is chiral or carbonyl is chiral → diastereomeric TS
 products not formed in equal amt
 called asymmetric induction

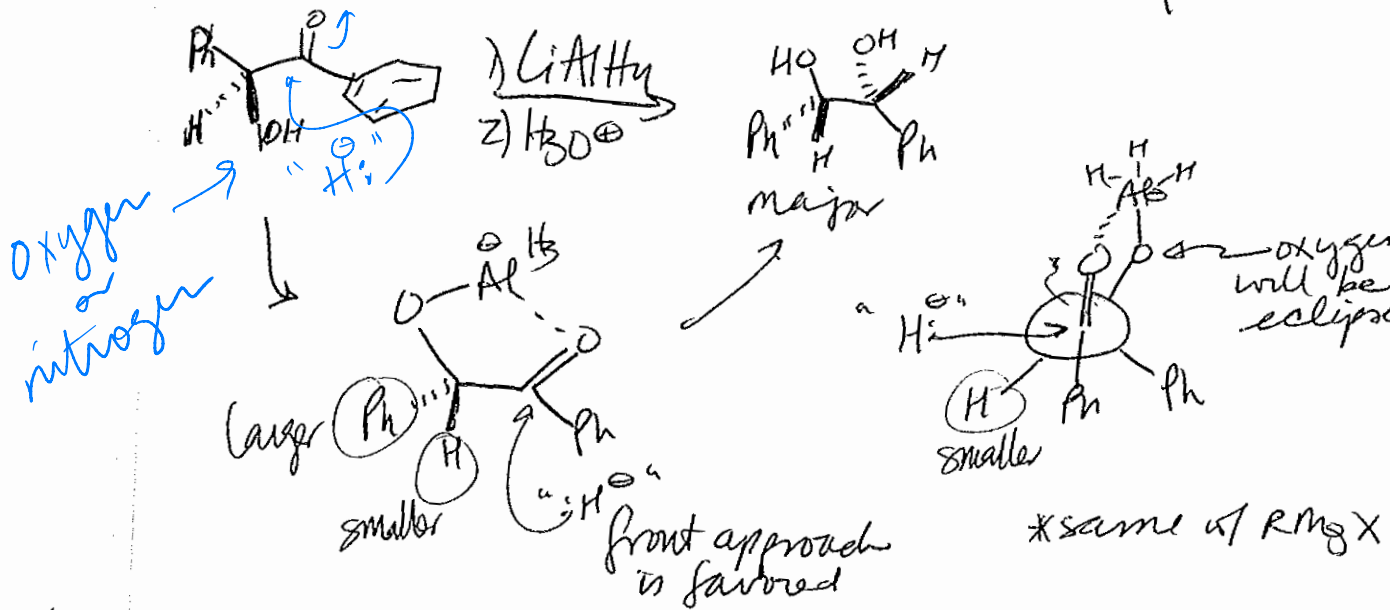


To predict product w/ a chiral carbon:

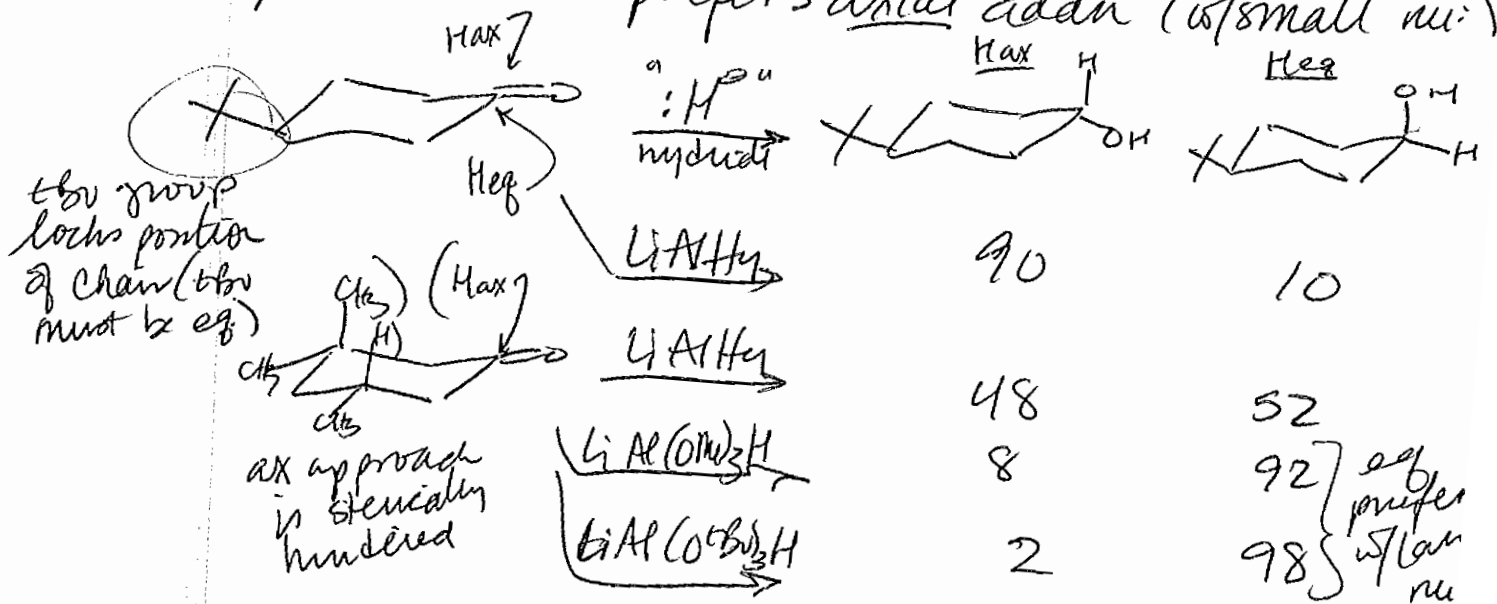
Cram's Rule JACS (1952) 74 5828, 5835, 5846



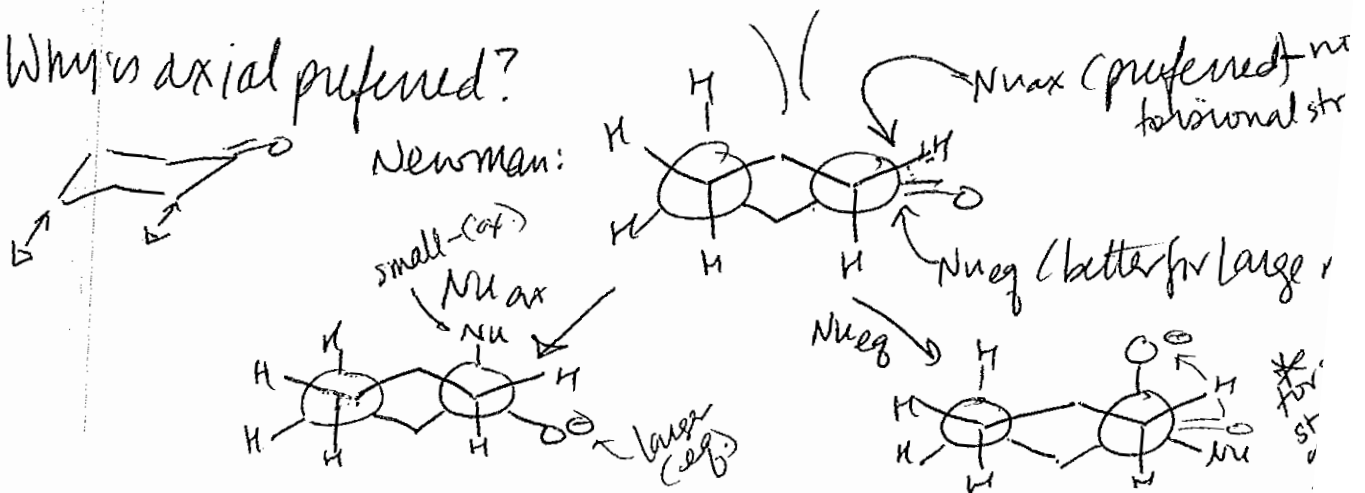
If a OH group, stereochem. controlled by chelation



cyclohexanone prefers axial addn (w/ small nu:)



Why is axial preferred?



7.6

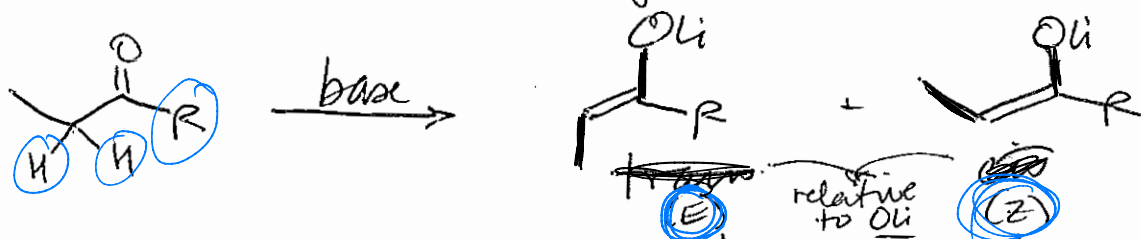
More on enolates:

bases LDA LTMP - tetramethylpiperidide (bulkier)

additives HMPT HMPA

Complex w/ Li so Li-O bond isn't as strong can break + reform (can equilibrate)

Stereochem. of enolate formation



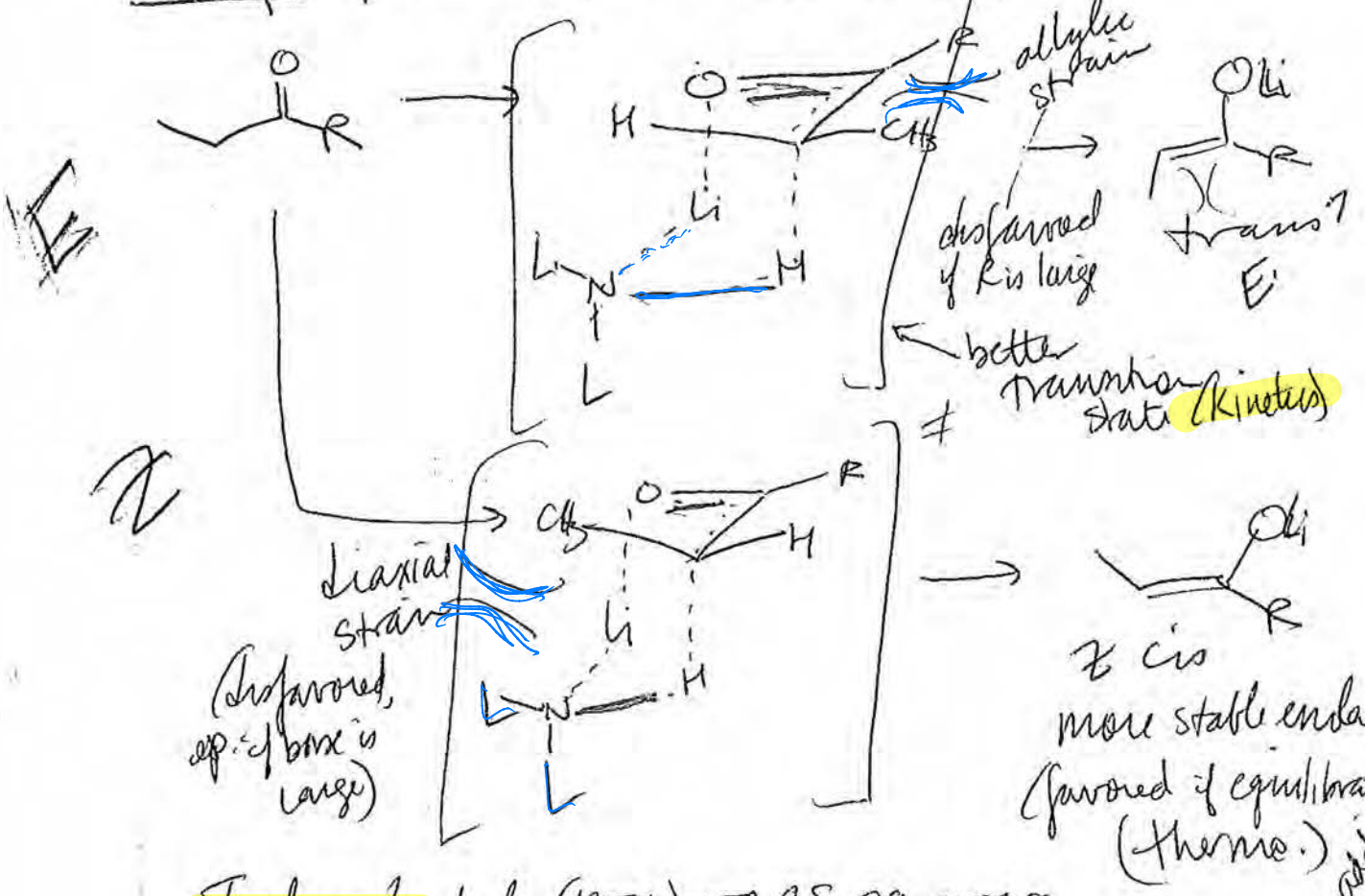
R	base	% E	% Z
-Et	LDA	77	23
-Et	LTMP	86	14
-Et	LTMP (HMPT)	8	92
-OCH ₃	LDA	95	5
-OBu	LDA	95	5
-NEt ₂	LDA	3	97
-tBu	LDA	2	98
-Ph	LDA	2	98

~~Controlled Enolate formation~~ ~~performed unless additives used~~ ~~or R is bulky~~

(kinetic) formed faster

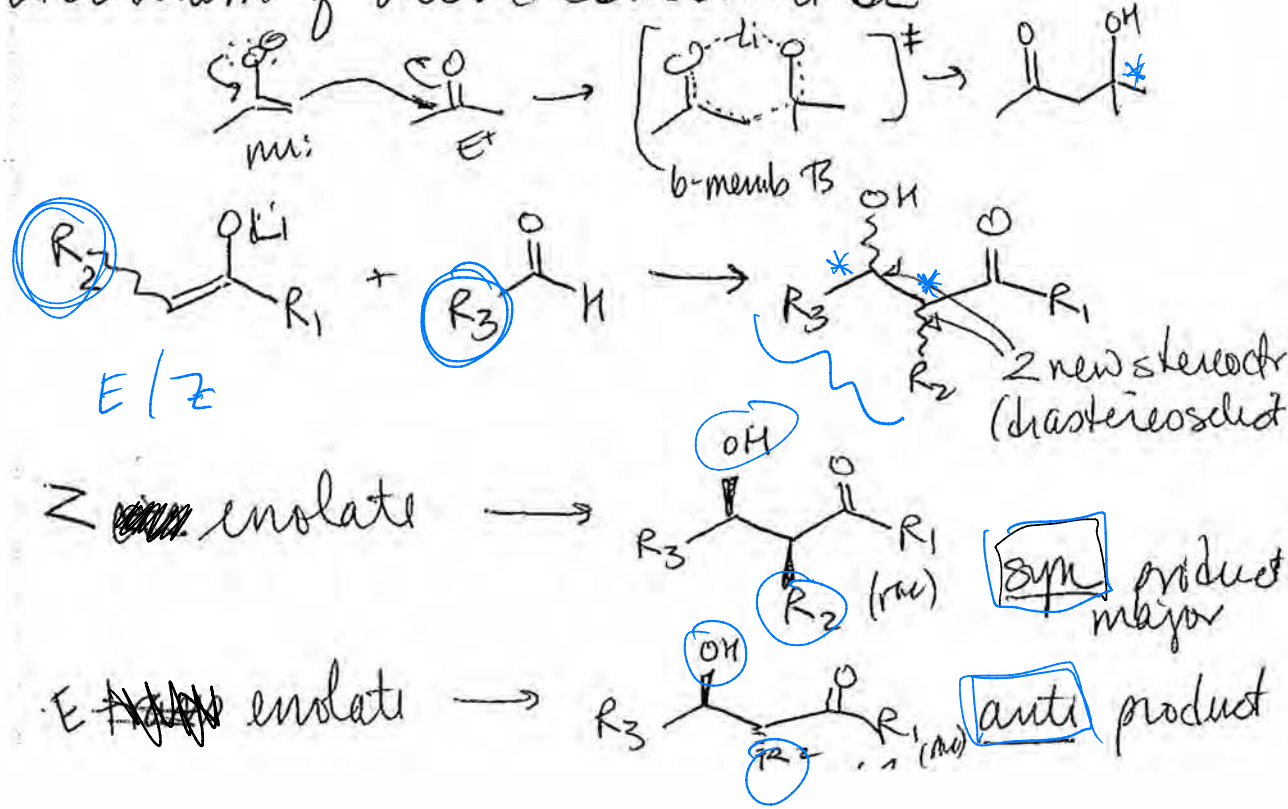
(thermo) more stable enolate

Why? possible transition states:



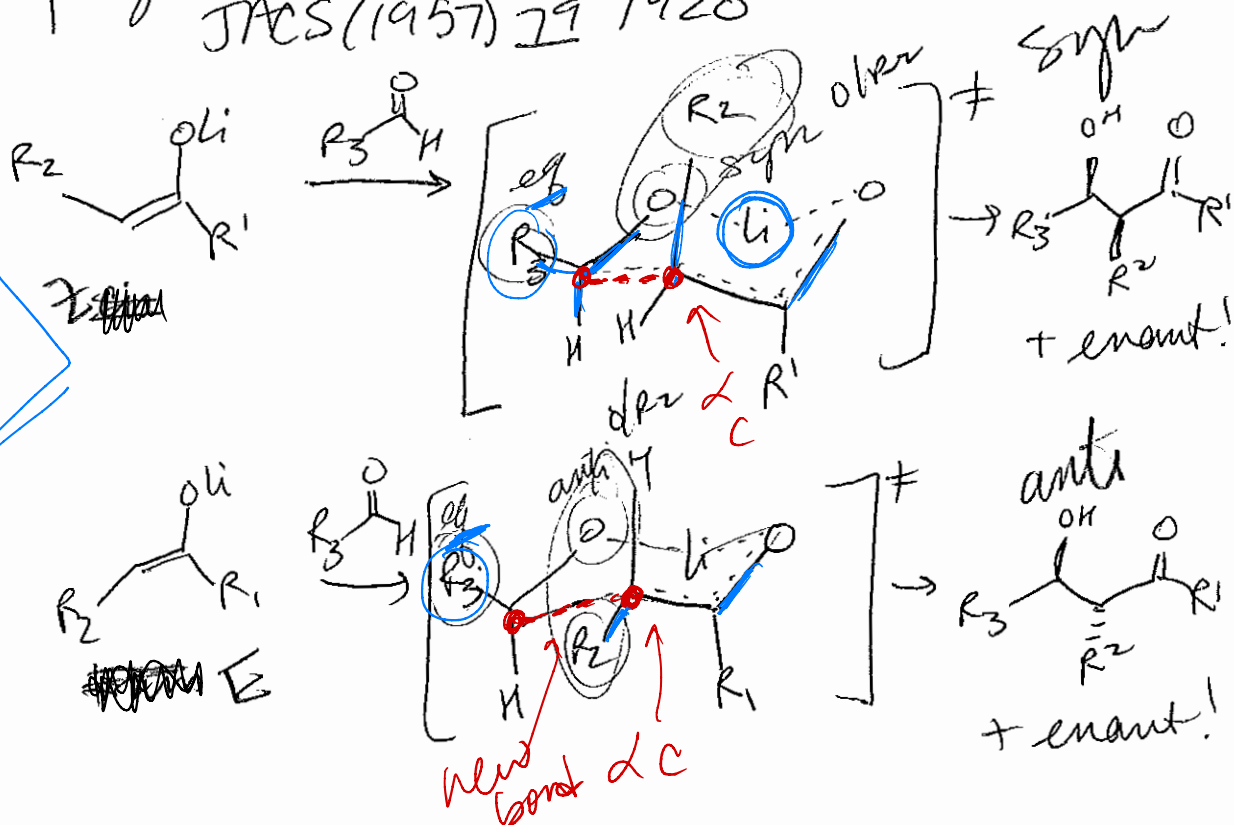
Ireland et al. (1976) JACS 98 2868.

Stereochem of aldol condensation

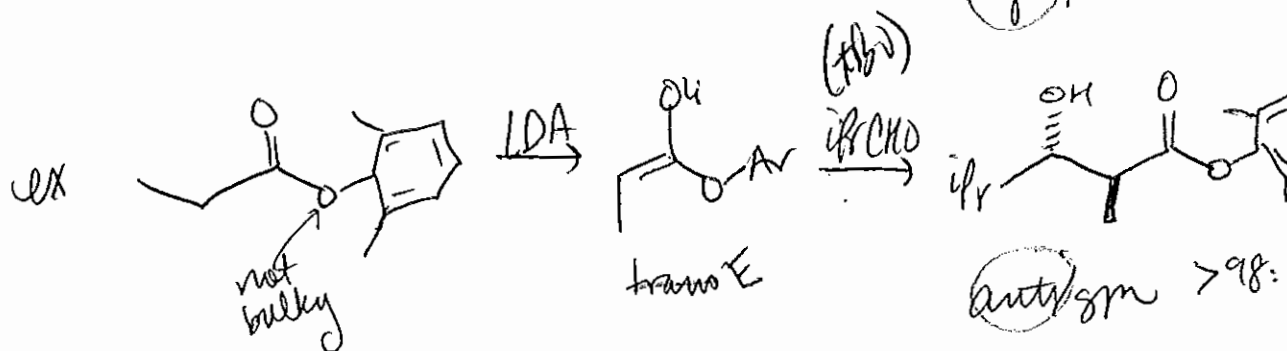
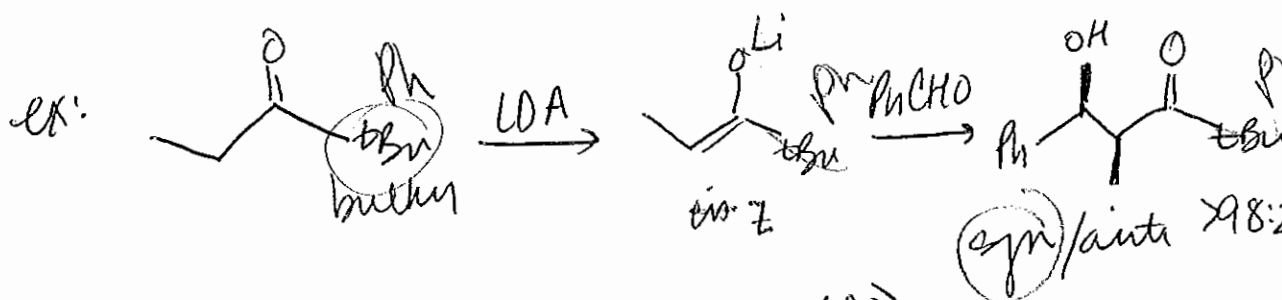


Why? Jimmerson-Traxler TIS.
JACS (1957) 79 1920

$E \rightarrow \text{anti}$
 $Z \rightarrow \text{syn}$



R_{ax} disfavored:
always



11

Chiral Drugs

→ most are patented/sold as racemates

→ each enantiomer has different activity

active + inactive

active + bad side effects

active + lowers activity

active + enhances activity

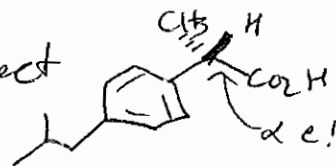
active + counteracts bad side effects
(may offer protection-synergy)

} single enantiomer version is better!

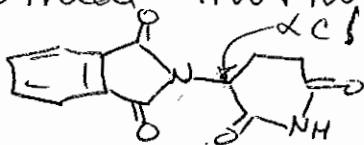
} racemate better

ex(±) ibuprofen takes 30 min for full effect

(S)-(+)-ibuprofen takes 12 min



(±) thalidomide - morning sickness; caused birth defects
one enant.



potential problem with single enantiomer drugs -
your body can racemize / epimerize!

Racemic switch - redevelop single enantiomer

of already approved racemate drug (may be done by different co-separator)

goals: → improve activity

→ extend patent life

→ compete w/ generics

(40 mg racemate = 20 mg single-enant.)

reduce price!

Single-enantiomer drug sales (billions)

1994	\$45	
1996	\$73	
1997	\$88	
1998	\$99	(30% of all drug sales)
1999	\$115	(32%)
2000	\$123	
project: 2003	\$143	

How do you make a single-enantiomer drug?

① use a chiral starting material

"Chiral pool" → natural (amino acids)
(carbohydrates)
→ synthetic (specialty chemicals)

advantages: • all chiral centers are in place OR
formation of new chiral centers is diastereoselective
(asymmetric induction) • some are very cheap*
disadvantages: • limited to chiral pool (growing!)
• most are expensive (D-amino acids)

② use asymmetric (enantioselective) synthesis

drawbacks: • expensive chiral reagents
• may add steps to synthesis

* ③ make racemate + separate enantiomers (resolution)

advantages: • economical

• both enantiomers can be studied

disadvant.: • throw away 1/2 of material!

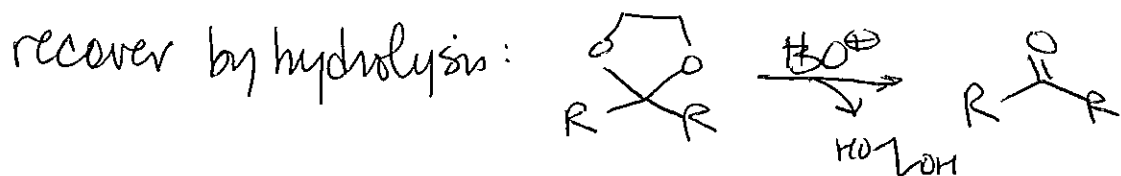
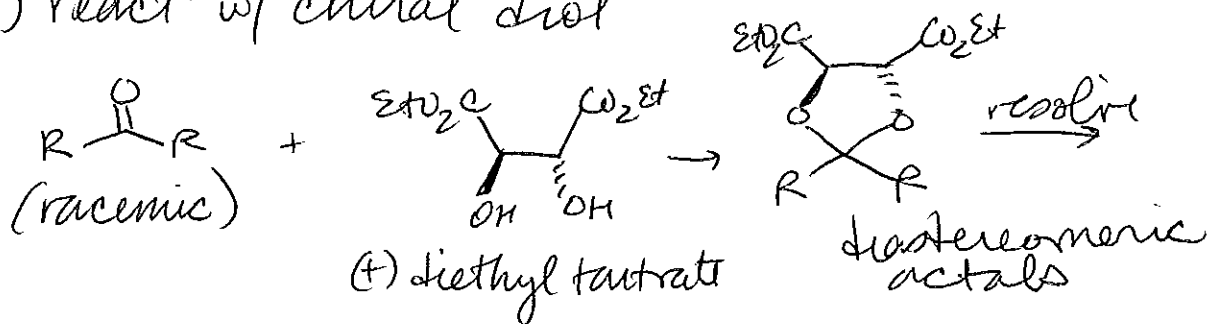
(try to do resolution early in synthesis)

* chiral products:
lactose (from making cheese)
L-ascorbic acid (from sugar beet processing)

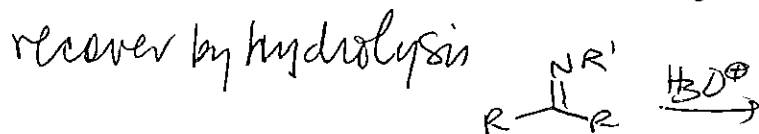
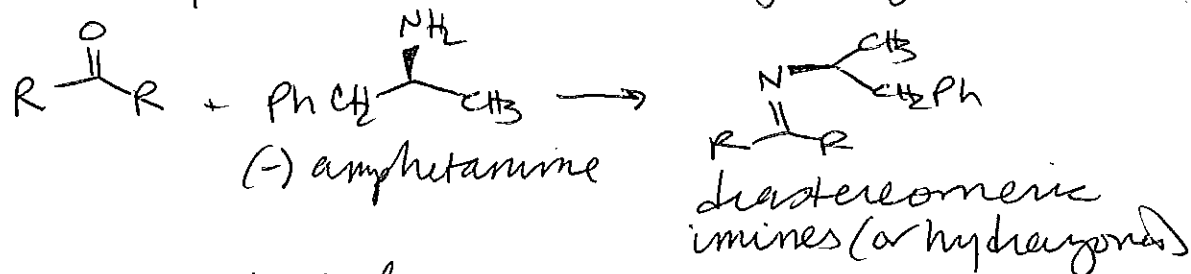
how most chiral drugs are made

d) to resolve aldehydes/ketones

i) react w/ chiral diol



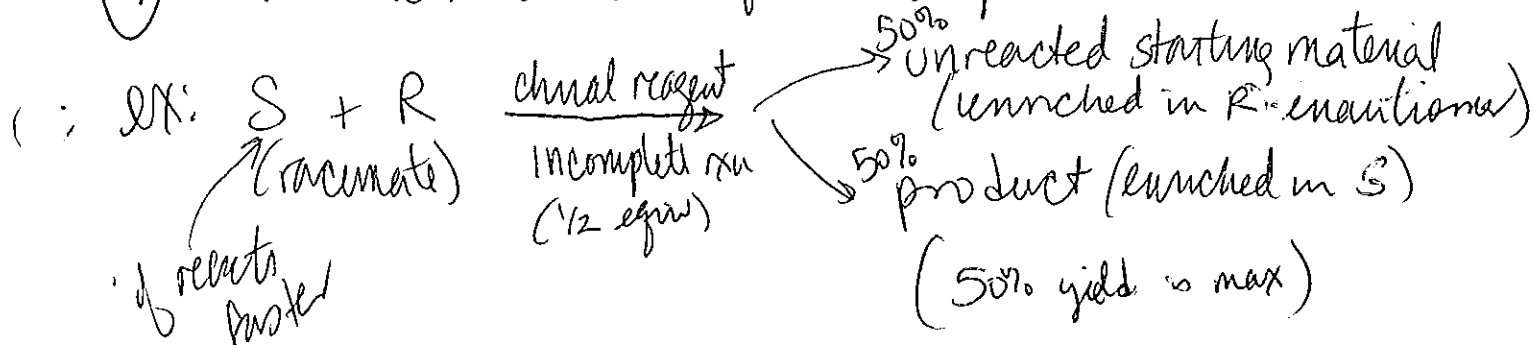
ii) react w/ chiral amines or hydrazines



③ chiral chromatography - handout

⑤ Enzymatic methods - handout

④ kinetic resolution - if (S) reacts faster than (R)



California State Polytechnic University, Pomona

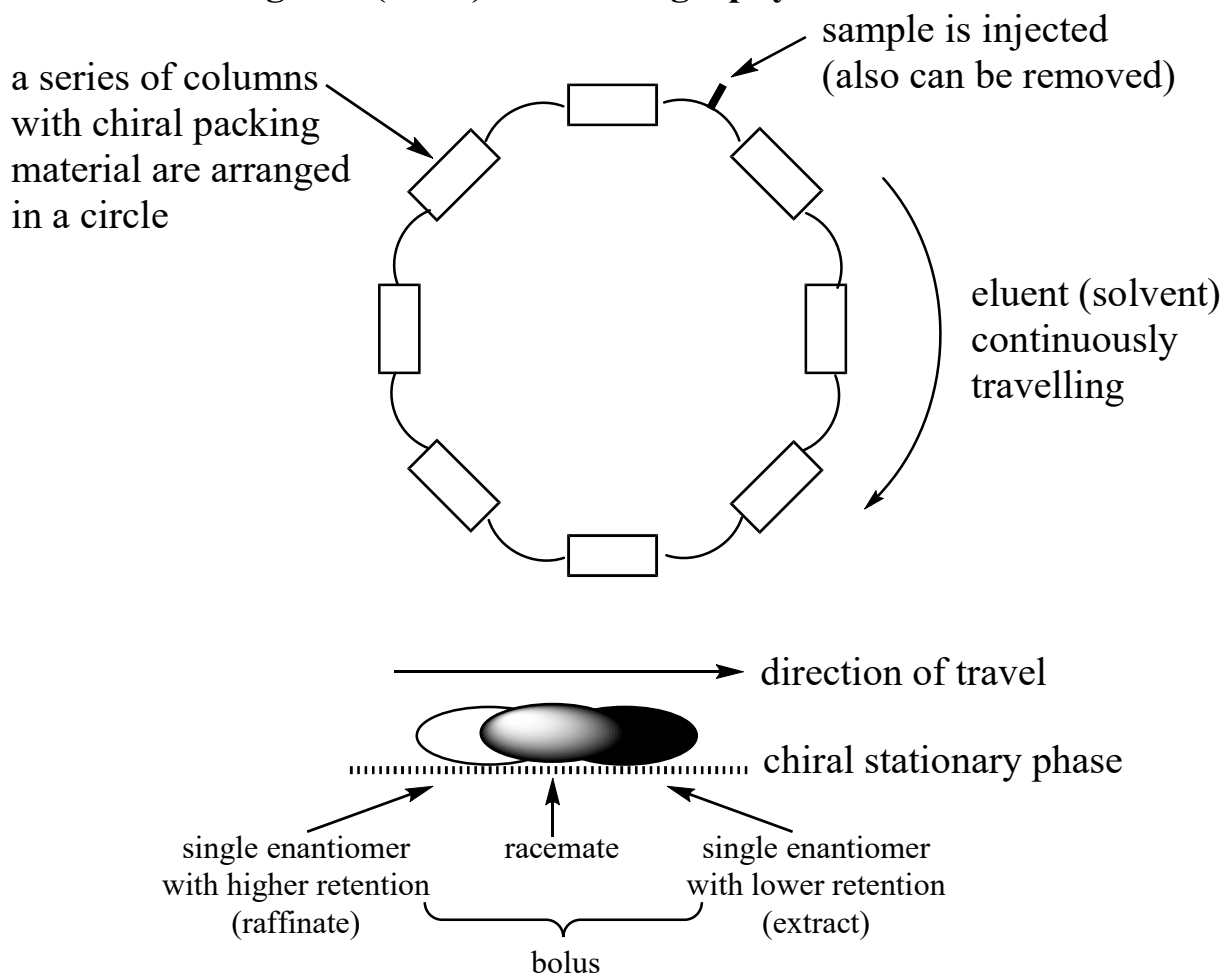
Laurie S. Starkey, CHM 543, Topics in Stereochemistry

Resolution by Chiral Chromatography

Chromatographic methods which utilize chiral packing materials have long been the preferred way to analyze optical purity (HPLC, GC, etc.). Rather than being limited to small, analytical samples, however, chiral chromatography can be extended to a large scale for purification purposes (called **preparative chromatography**). In this manner, enantiomers can be resolved in a commercial environment (gram to kilogram scales). An advantage to chromatographic resolution is being able to obtain BOTH enantiomers in high yields and high optical purity.

A promising, high-throughput technique is simulated moving bed (SMB), which utilizes a series of columns arranged in a circle. The packing material is very expensive (\$8,000/kg) but solvent is conserved compared to typical elution chromatography.

Simulated Moving Bed (SMB) Chromatography



The racemic sample is injected and separation of the enantiomers begins but the process is never complete. The location of the bolus is tracked by computer software. Purification is achieved when the operator removes a small amount of the leading enantiomer (extract) and the trailing enantiomer (raffinate), while injecting some more of the racemate into the center of the bolus. Such continuous purification can resolve up to several kilograms per day.

California State Polytechnic University, Pomona

Laurie S. Starkey, CHM 422, Organic Synthesis

Resolution by Enzymatic Methods

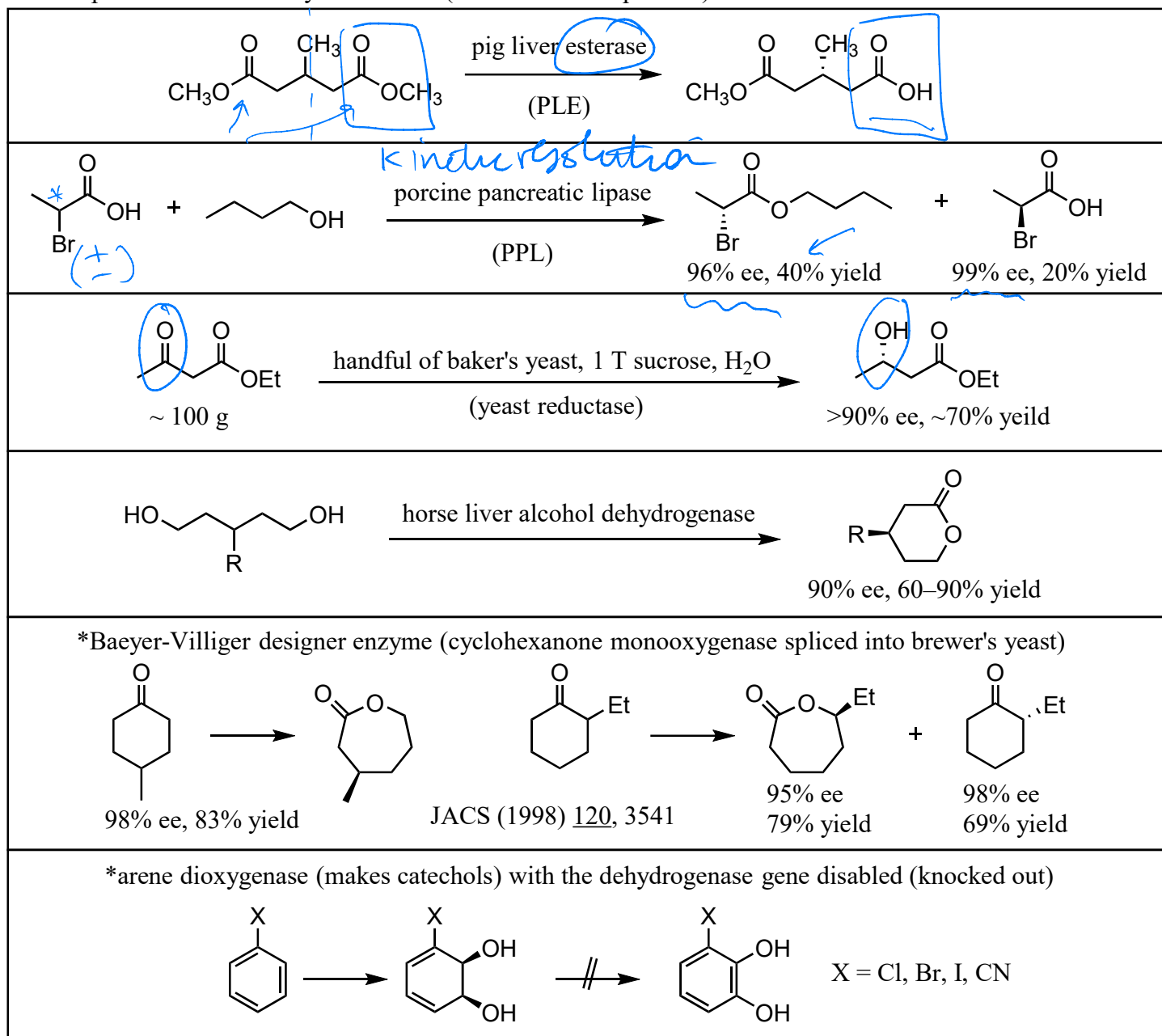
Enzymes can be used to separate enantiomers by preferentially reacting with only one enantiomer (called a **kinetic resolution**). Also, enzymes can sometimes differentiate between enantiotopic groups. Following are some general features of enzymatic reactions:

advantages:

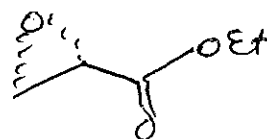
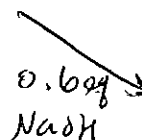
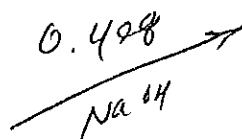
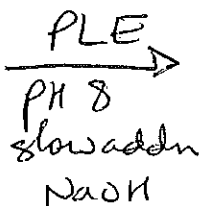
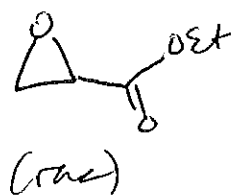
- ✗ economical (PLE ~\$0.006/u, where u=amount of enzyme required to transform 1 μ mol/min)
- very stereoselective (100% ee)
- water buffers as solvents (no organic solvents or chemical wastes; environmentally benign)

disadvantages:

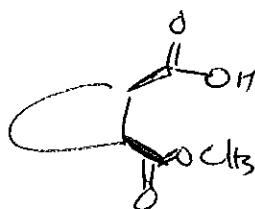
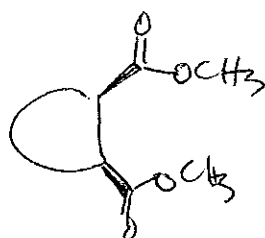
- ✗ only works on a limited number of substrates ("designer" enzymes can be developed*)
- may be very slow (2 hours – 2 days)
- dilute reaction conditions (need large reaction vessels)
- product isolation may be difficult (elaborate and expensive)



PLE

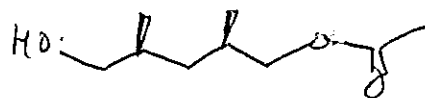
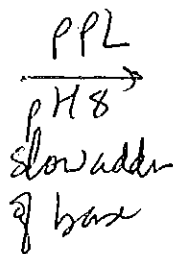
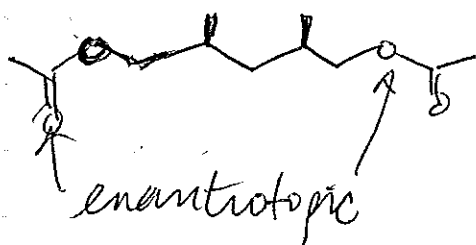


40% yield
 >90% ee



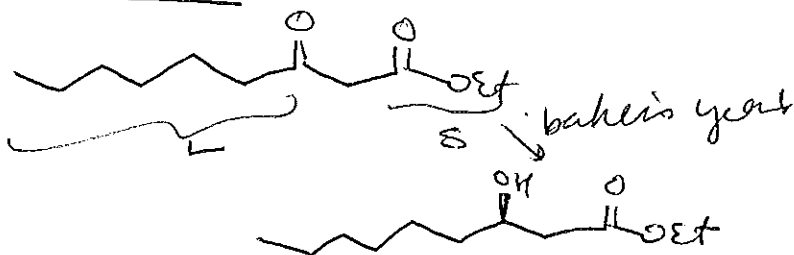
selectivity depends on ring size

PPL - very cheap \$0.000002/u (use excess)

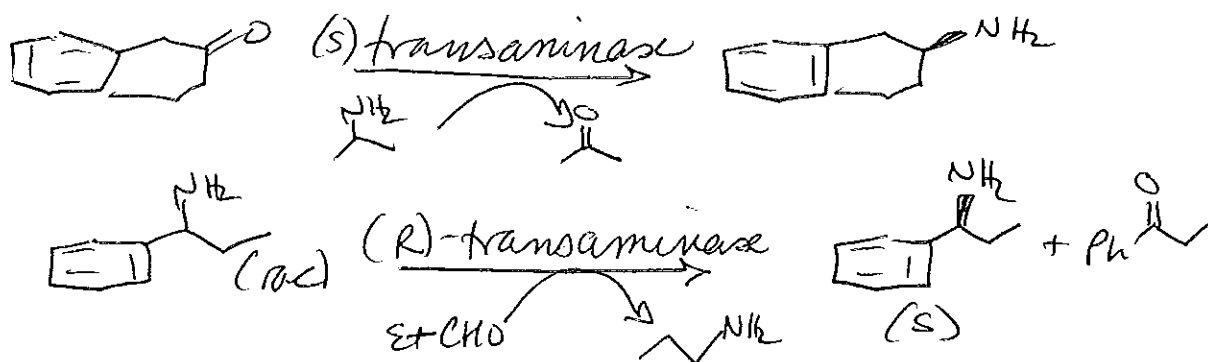
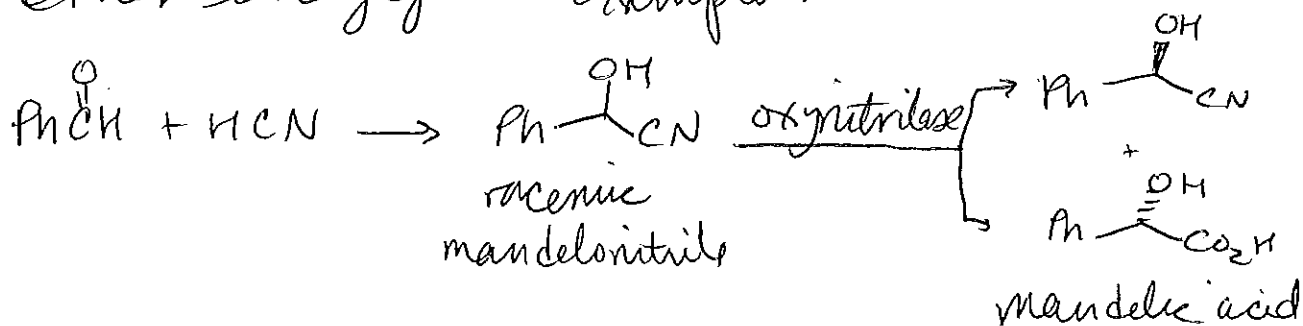


Yeast Reductions (1918)

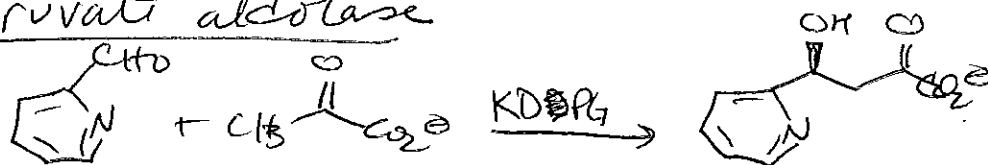
small — large
 "H₂O"
 from top



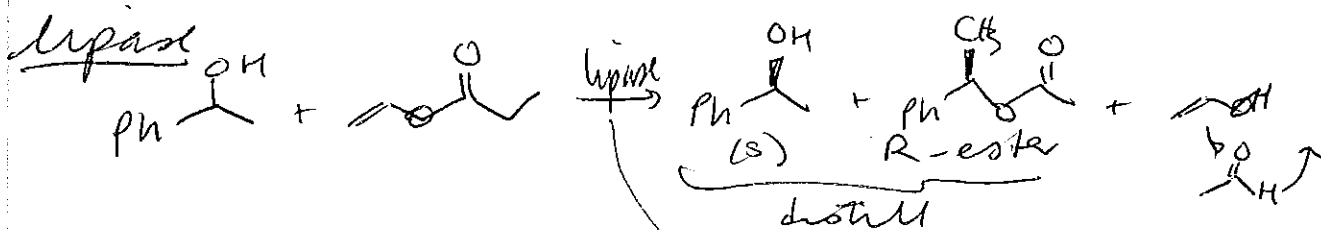
Other enzyme examples:



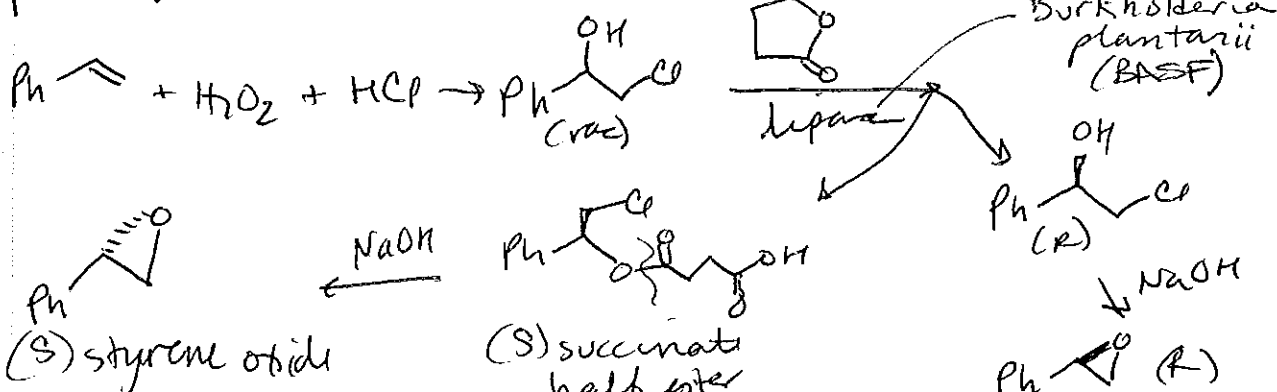
pyruvate aldolase



JDC(98)63 902 2-keto-3-deoxy-6-phosphogluconate



prep. of styrene oxide:

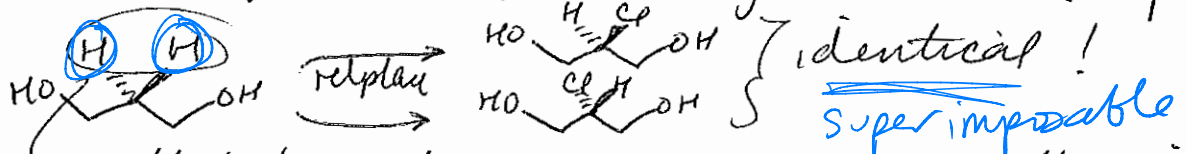


Prochiral Relationships

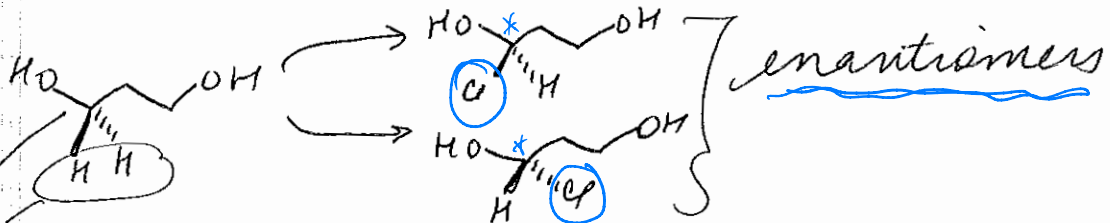
↳ can form a chiral center

Replace each ligand w/ a test group (D, Cl, Z, @)

and determine resulting relationship



↳ called "homotopic", these are chemically equivalent



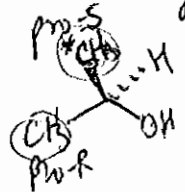
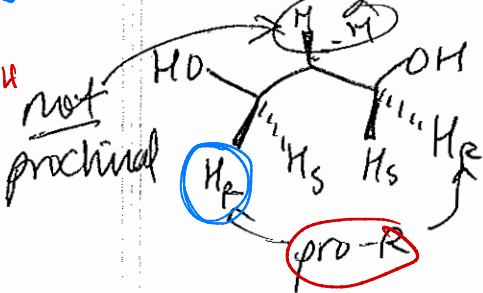
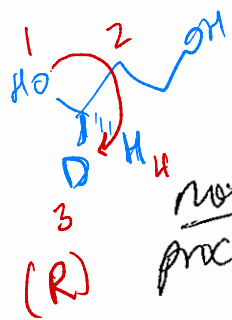
↳ called "enantiotopic", these are nonequivalent

↳ general form $X \begin{matrix} H & H \\ & \diagdown \diagup \\ & C \\ & \diagup \diagdown \\ Y & Y \end{matrix}$ (if X+Y are chiral)

a "prochiral center" since a chiral C is created if a ligand is replaced.

one ligand is pro-R, the other is pro-S

↳ replacement of this ligand w/ a heavier isotope (D) gives R config.

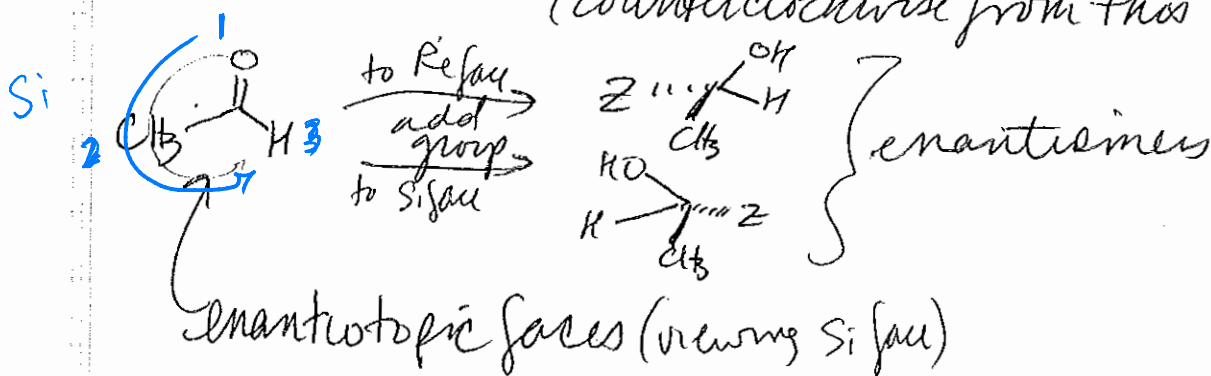


* enantiotopic atoms or groups are equivalent in all ways (chemical + physical, NMR) except for rxn w/ chiral reagents

Prochiral faces for trigonal planar C's
(would be chiral if 4th group is added)



Si face (sinister)
(counterclockwise from this POV)



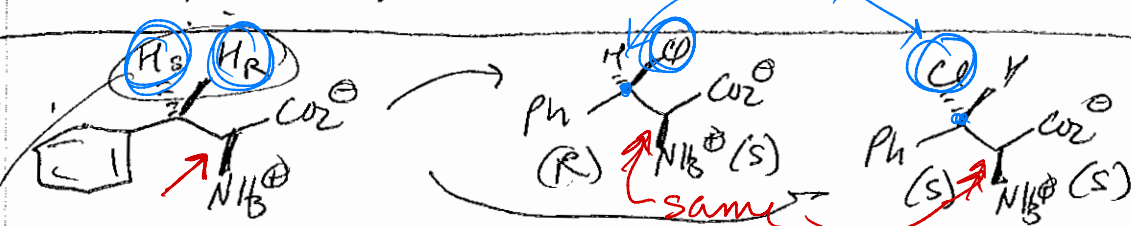
alkene faces - give separate re + si designation for each



Si-Si face shown

swapped / marked

general:

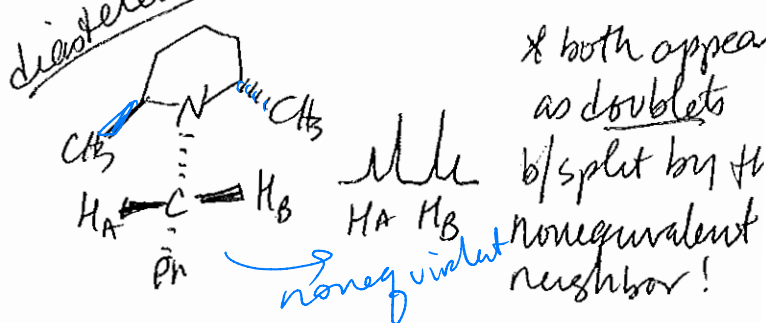
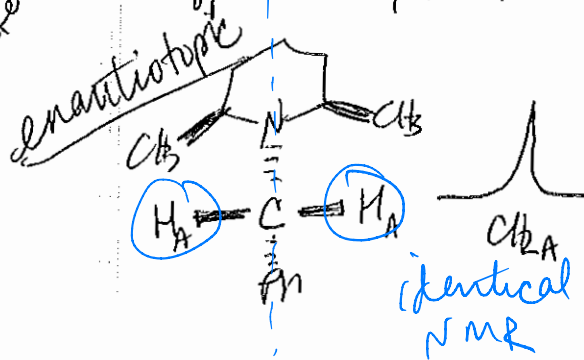


called "diastereotopic" H's

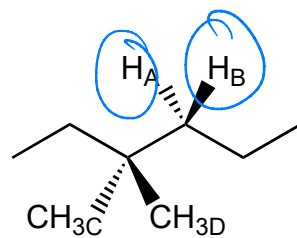
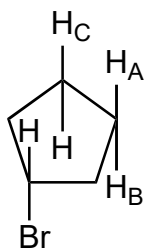
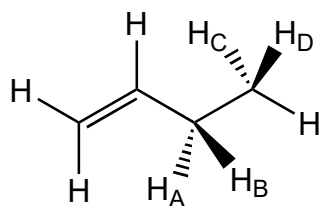
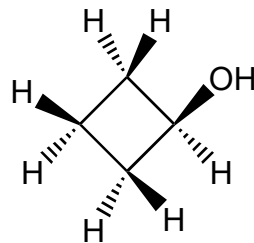
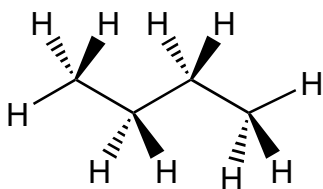
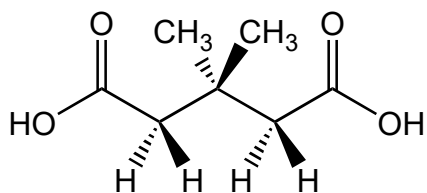
diastereomers

behave differently in any environment, chiral or achiral

different by NMR (if close to chiral center!)



* return to general relationships stereo-19 *



H_A & H_B _____

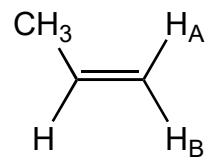
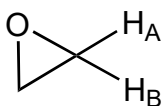
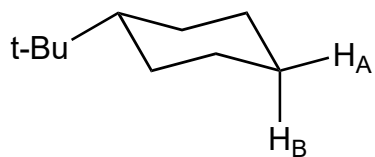
H_A & H_B _____

H_A & H_B _____

H_C & H_D _____

H_A & H_C _____

Me_C & Me_D _____



H_A & H_B _____

H_A & H_B _____

H_A & H_B _____