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, ee)
   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

Stereochemistry of Organic Reactions
↳ determined by Rxn Mechanism!

Stereospecific a rxn that proceeds w/a definite stereoch
stereoisomer starting materials(SM) → different produc
(eg, cis or trans)

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

Possible stereochemistries:

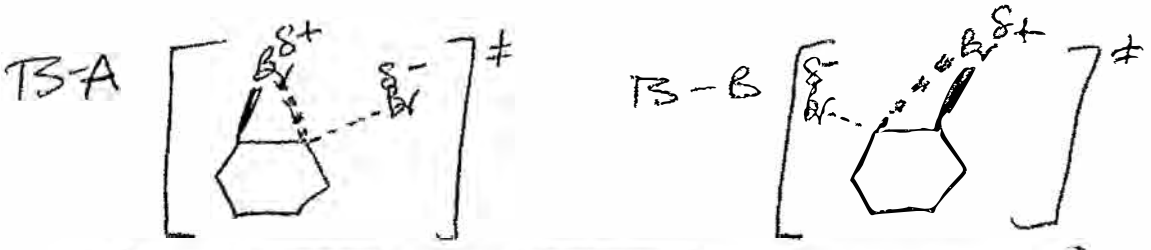
Substitution Rxns

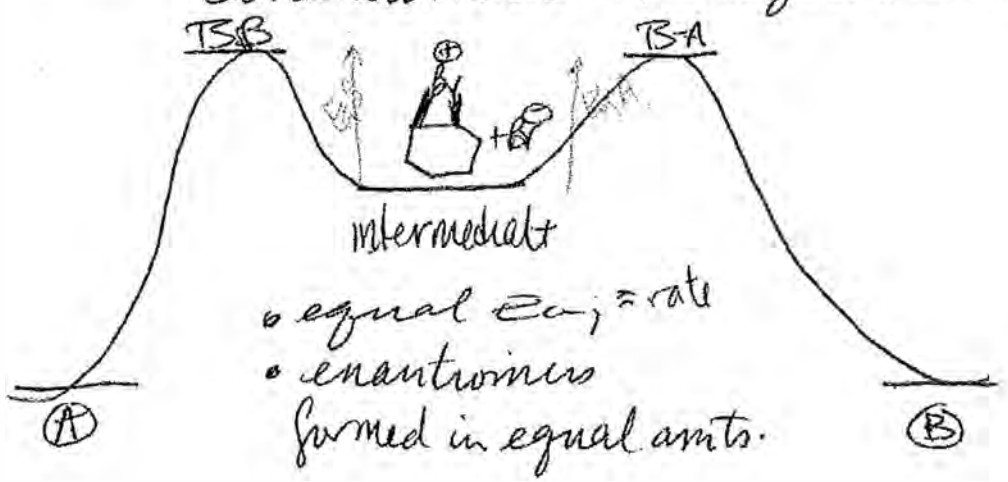
retention of configuration: same spatial arrangement of SM
inversion of config: stereochem of product is mirror image of
racemization (complete or partial)
single enantiomer SM → both possible enant produc
(if only one of multiple chiral centers is involved: epimeriza

b) anti addition (via cyclic intermediate)

i) bromination/chlorination

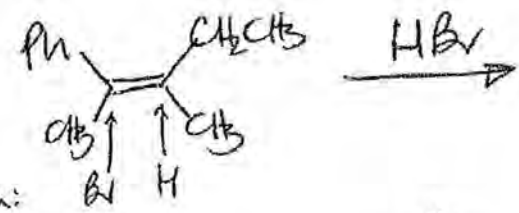
bromonium ion





- equal Ea, ∴ rate
- enantiomers formed in equal amts.

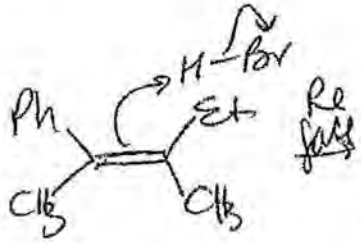
c) mixed stereochemistry



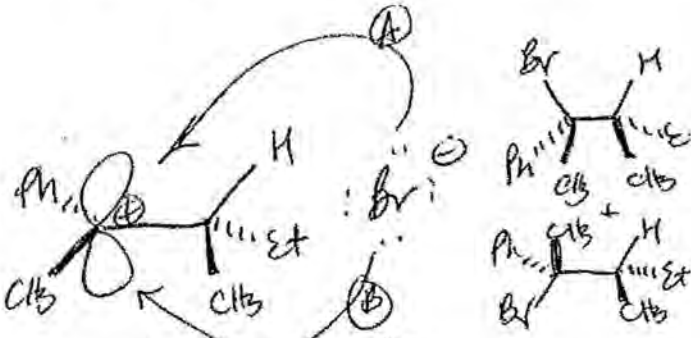
stereochem: all possibilities → 4 products

regiochem: (fixed)

Mech



Re face



Si face

both

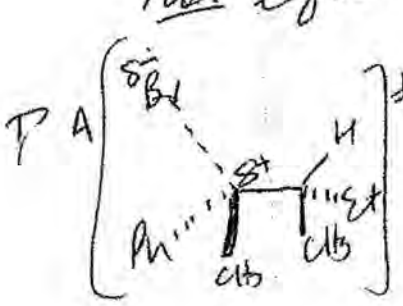
- syn + anti addn
- A/D + B/C B:C 1:1
- A/D: dl pair; B/C: dl pair
- A:D 1:1

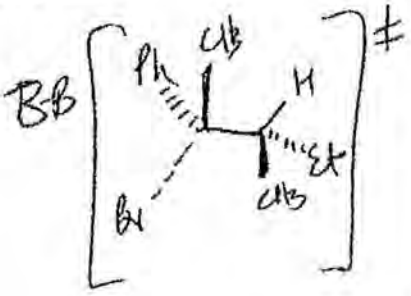
diastereomers: not formed in equal amounts

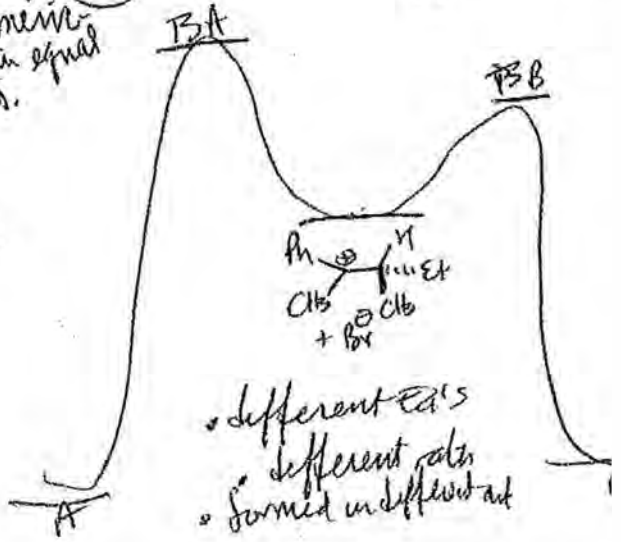
A:B ≠ 1:1

enantiomeric formed in equal amts.

why? Diastereomeric T.S. not equal in E







↑ E difference, ↑ stereoselectivity
(larger difference in product mixture)

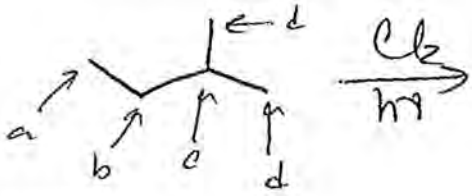
diastereomeric excess

% de = (% major diastereomer) - (% minor diast.)

100% de → single diastereomer is produced

0% de → diastereomers produced in equal am

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



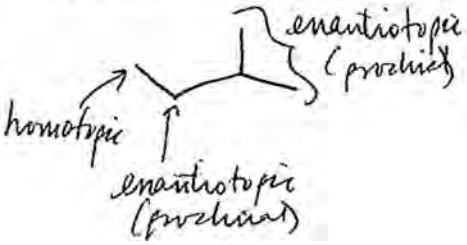
a achiral

b 1:1

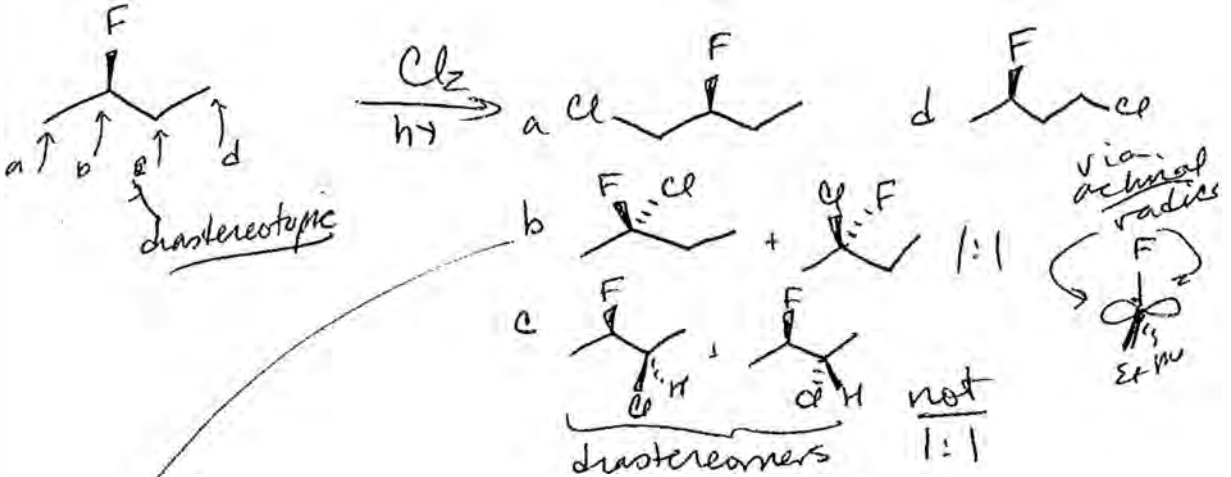
c achiral

d 1:1

stereochem:

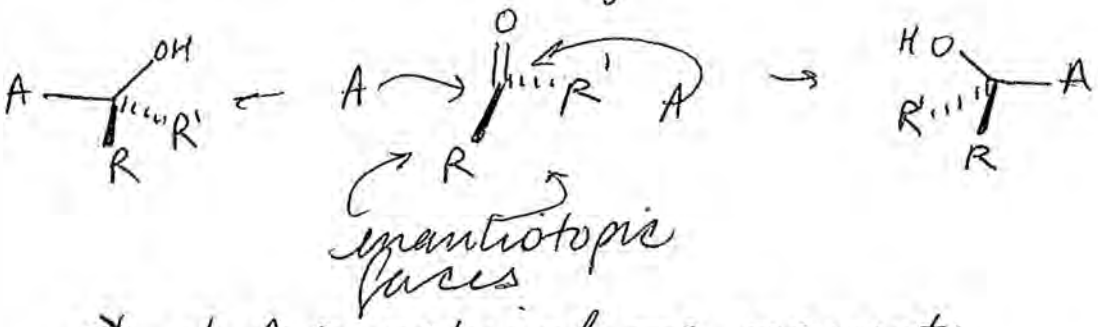


enantiomers!

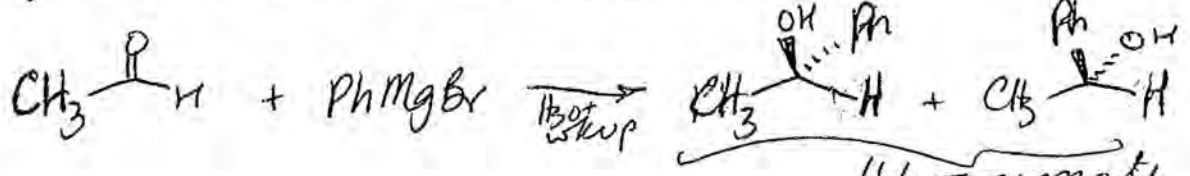


Loss of a group from a chiral carbon → racemize

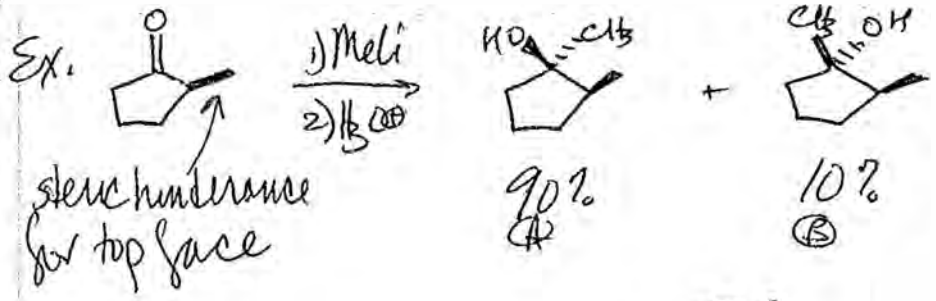
④ Addn to carbonyls

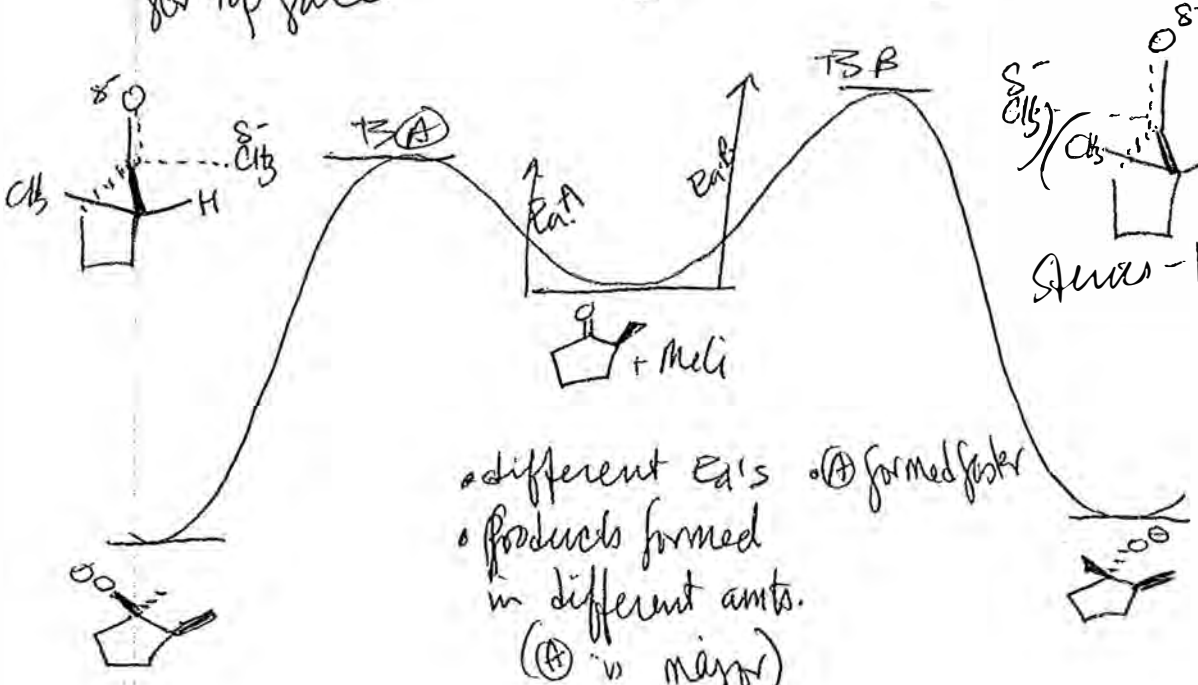


→ if A is achiral → racemate



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

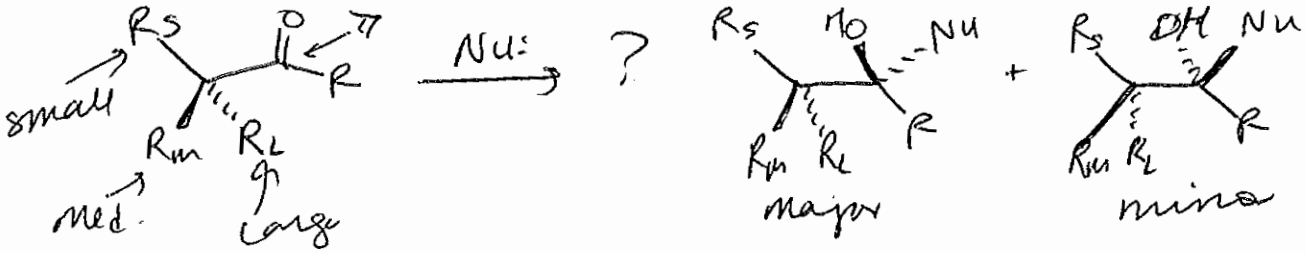




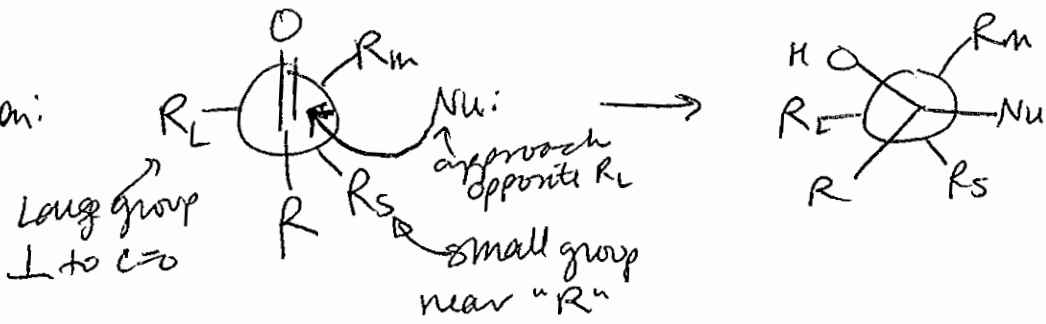
- different Ea's
- (A) formed faster
- Products formed in different amts. ((A) is major)

To predict product of a chiral carbon:

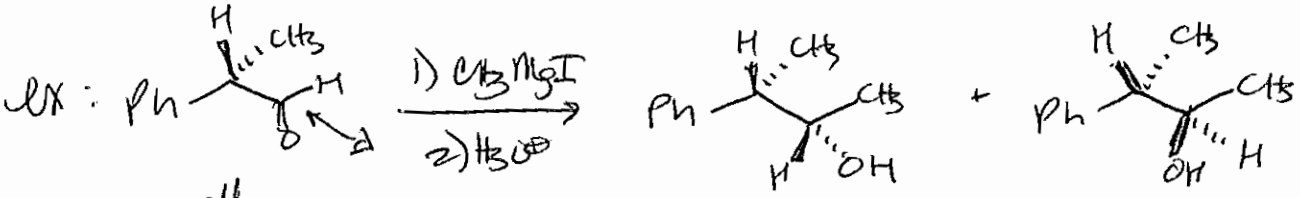
Cram's Rule JACS (1952) 74 5828, 5835, 5846

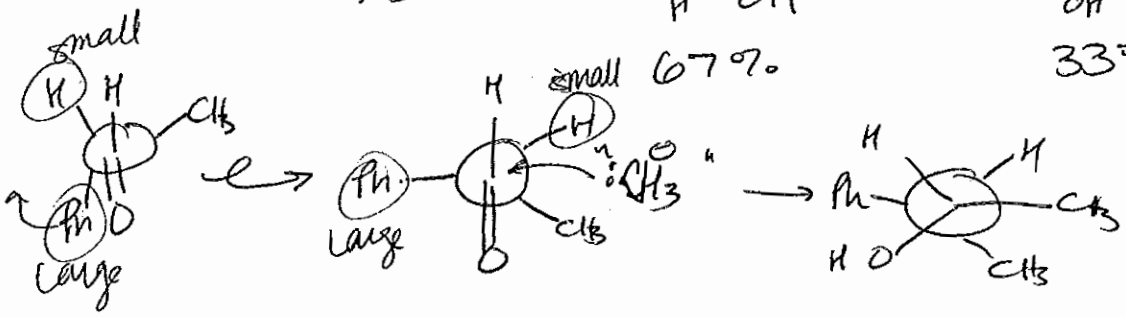


proper orientation:

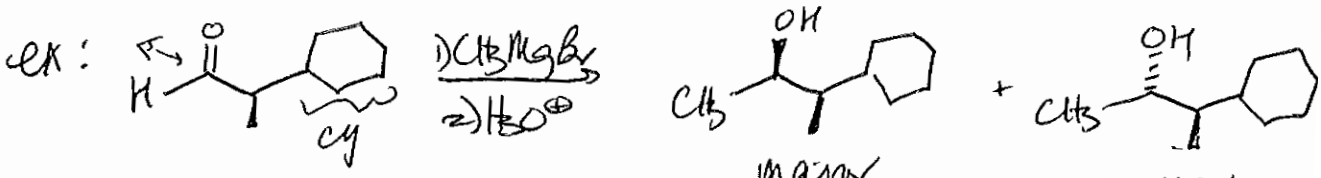


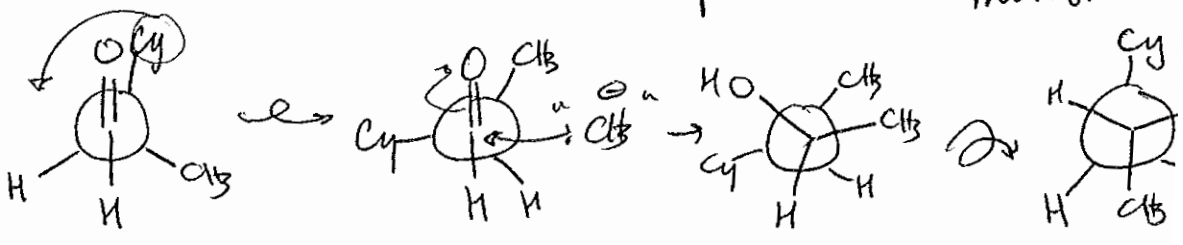
ex:



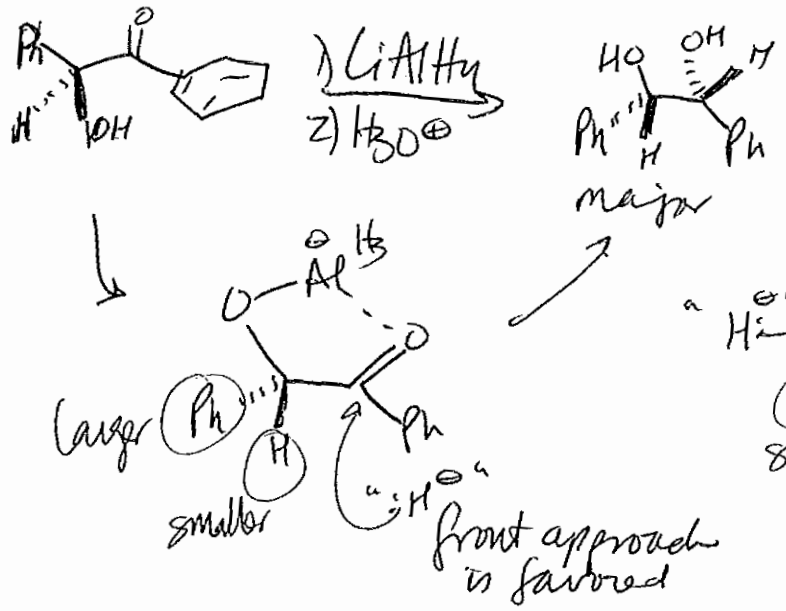


ex:





If a OH group, stereochem. controlled by chelatio



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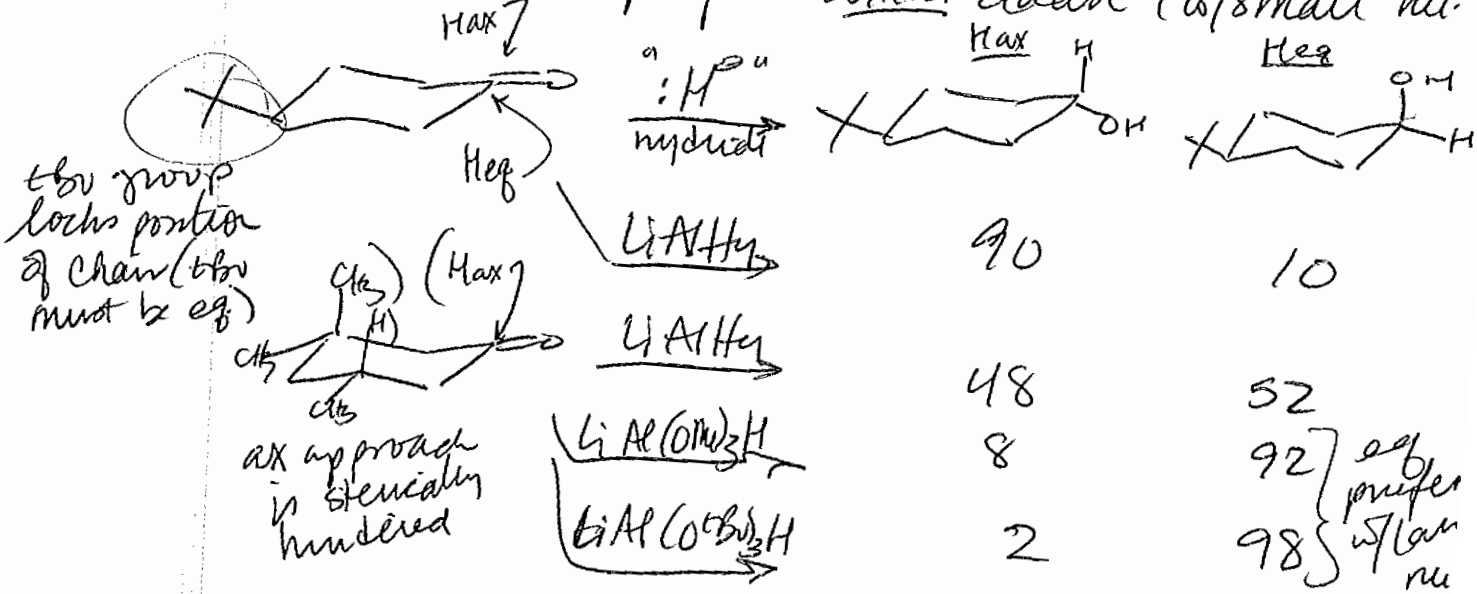
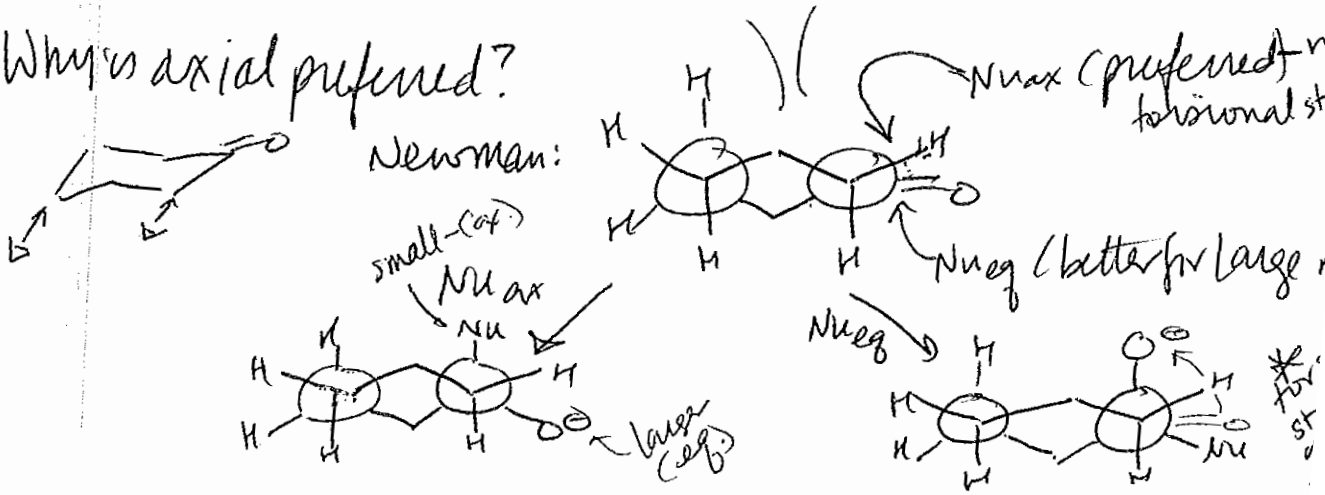
cyclohexanone prefers axial addn (w/small nu:

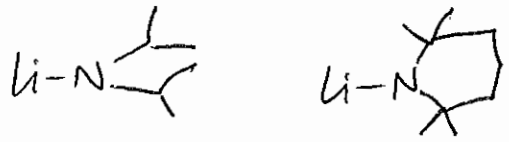


Why is axial preferred?

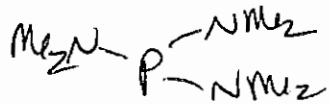


More on enolates:

bases LDA LTMP - tetramethyl piperidide (bulkier)



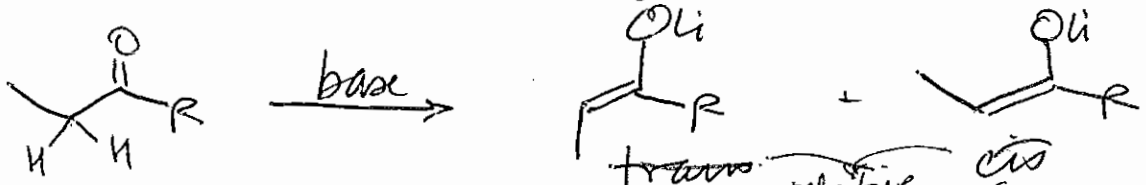
additives HMPT HMPA



$(Me_2N)_3P=O$

↳ complex w/ Li so Li-O bond still as strong can break + reform (can equilibrate)

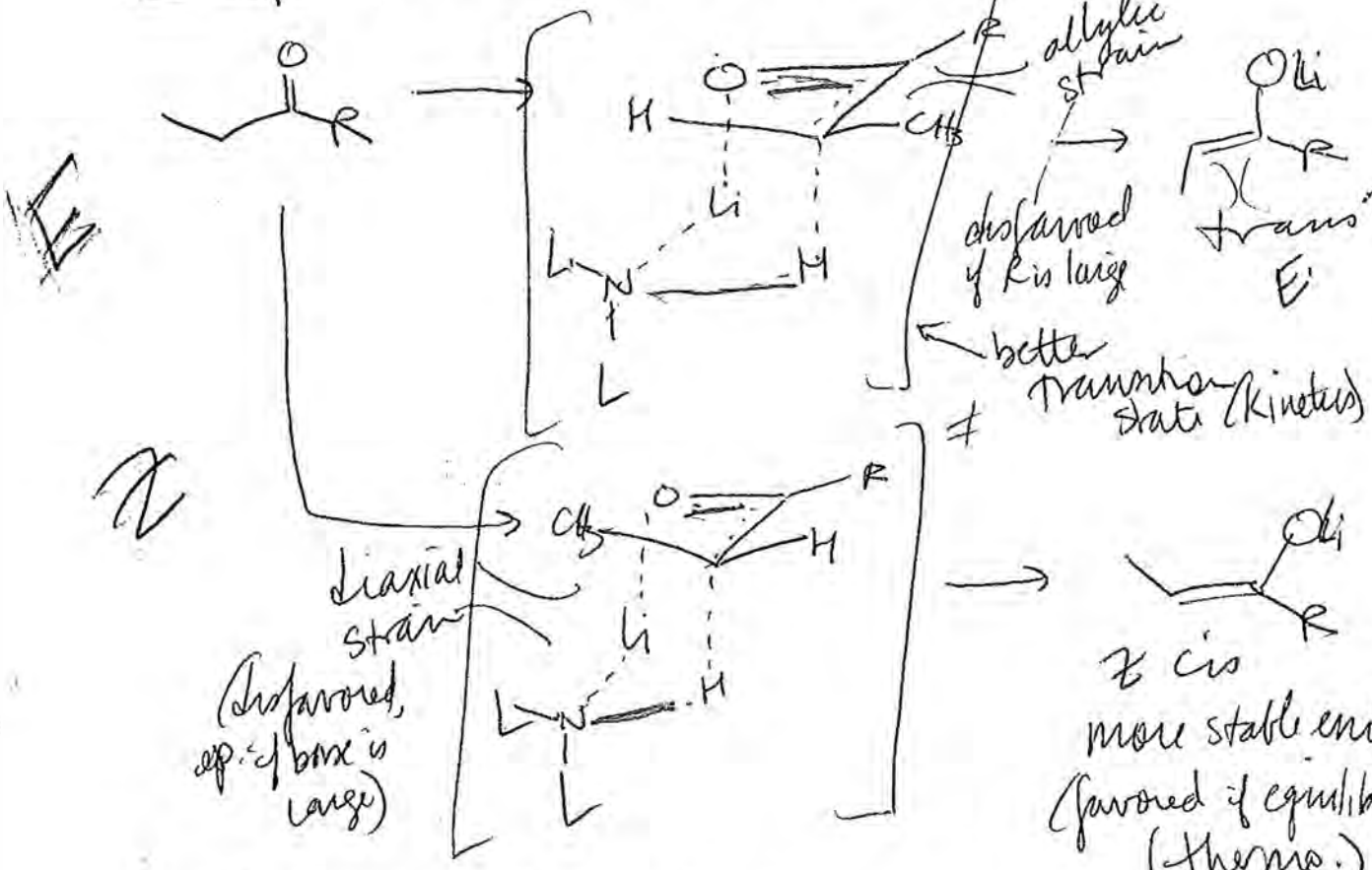
Stereochem. of enolate formation



R	base	% trans (E)	% cis (Z)	
-Et	LDA	77	23	
-Et	LTMP	86	14	← bulkier base favors Z
-Et	LTMP (HMPT)	8	92	← additive favors Z
-OCH3	LDA	95	5	
-O^{t}Bu	LDA	95	5	
-NEt2	LDA	3	97	bulky R favors cis
-^{t}Bu	LDA	2	98	
-Ph	LDA	2	98	
		(kinetic)	(thermo)	

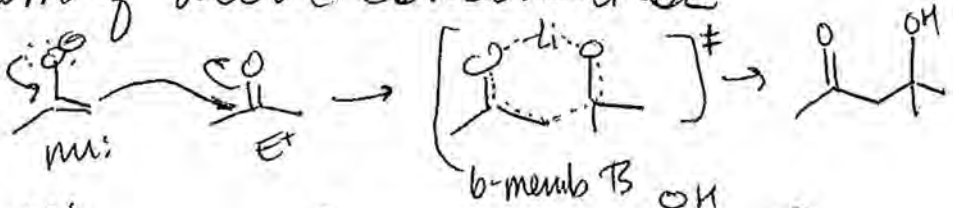
Conclusion: Trans (E) enolate preferred unless additive is used, or R is bulky

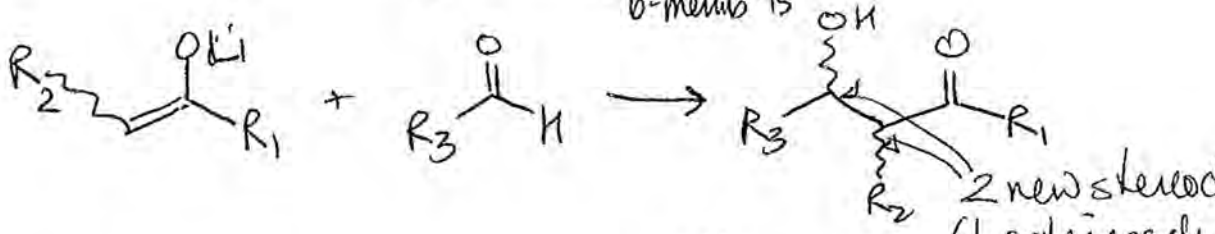
Why? possible transition states

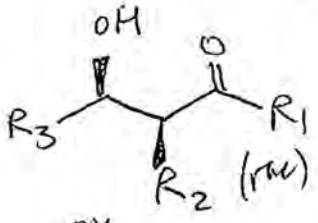


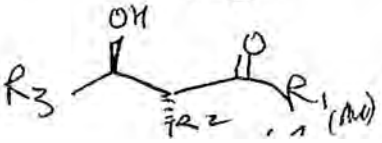
Ireland et al. (1976) JACS 98 2868.

Stereochem of aldol condensation

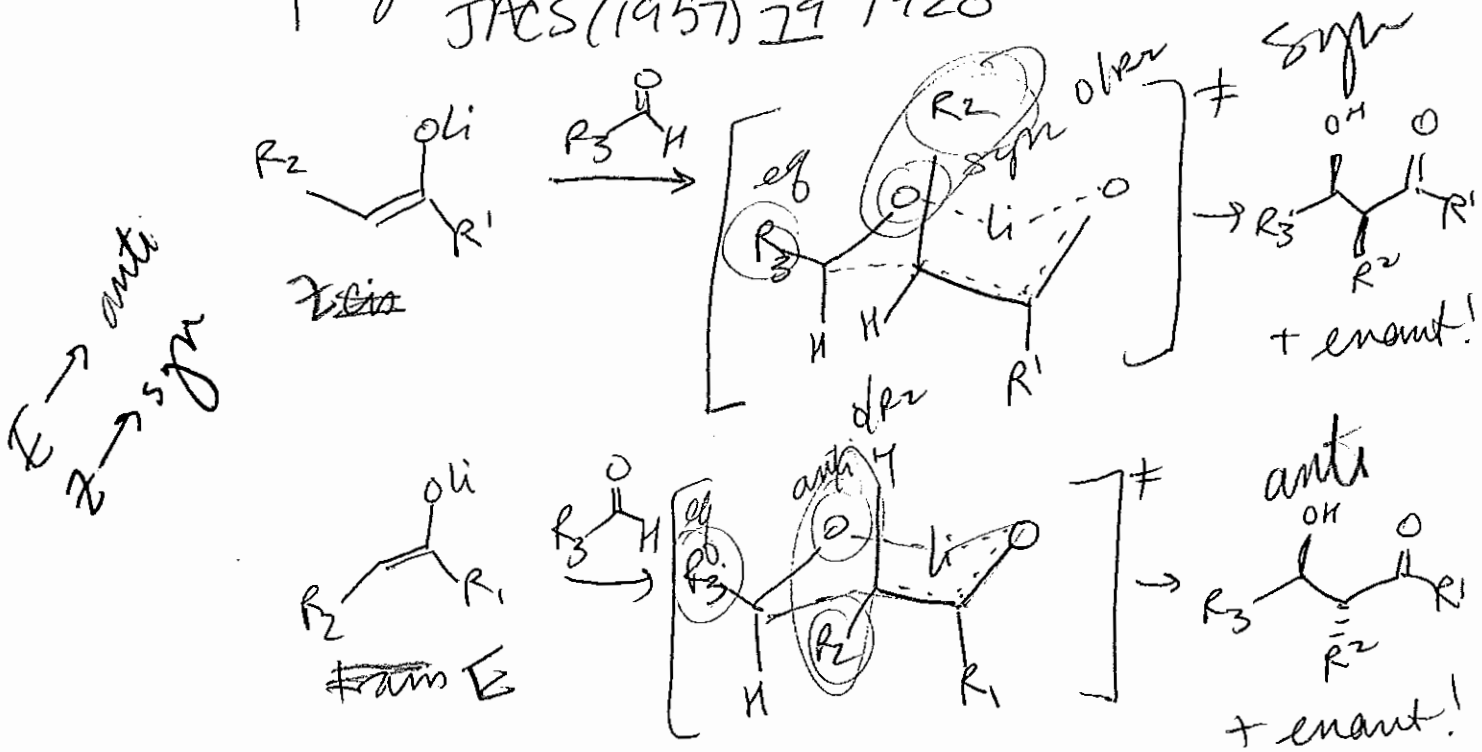




Z ~~cis~~ enolate →  syn product major

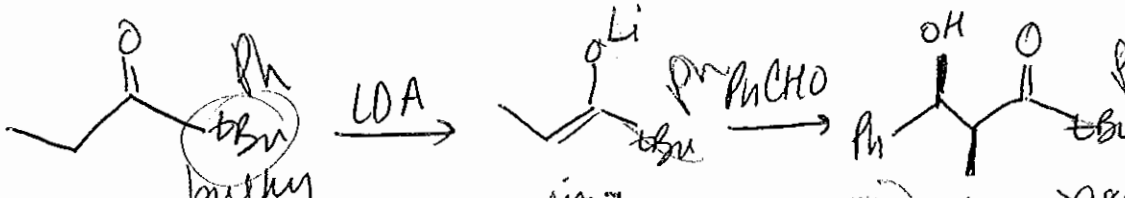
E ~~trans~~ enolate →  anti product

Why? Zimmerman-Traxler TS.
JACS (1957) 79 1920

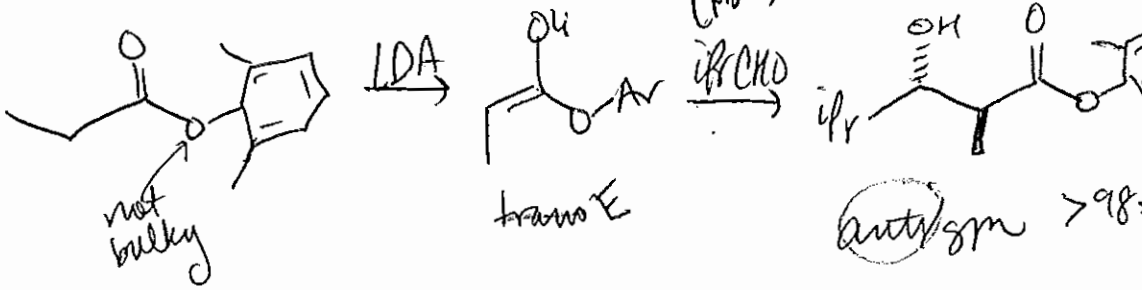


R_3 axial disfavored: always

ex:



ex



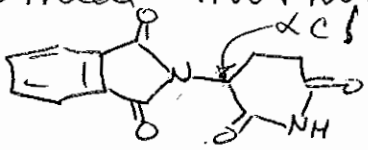
Chiral Drugs

→ most are patented/sold as racemates
→ each enantiomer has <u>different</u> activity

active	+	inactive	single enantiomer version is better!
active	+	bad side effects	
active	+	lowers activity	
active	+	enhances activity	racemate better
active	+	counteracts bad side effects (may offer protection-synergy)	

ex (±) ibuprofen takes 30 min for full effect
(S)-(+) ibuprofen takes 12 min

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



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

<u>Racemic switch</u> - redevelop single enantiomer of already approved racemate drug (may be done by different co-sponsor)

<u>goals</u>: → 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?

Ⓐ use a chiral starting material

"chiral pool" → natural (amino acids) (carbohydrates)

→ synthetic (specialty chemicals)

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

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)

Ⓑ use asymmetric (enantioselective) synthesis

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

how most chiral drugs are made

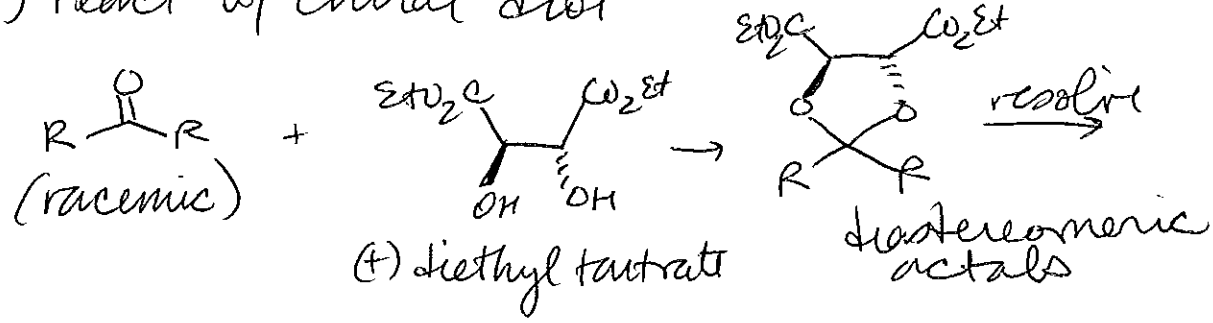
* Ⓒ make racemate + separate enantiomers (resolution)

advantages: • economical • both enantiomers can be studied

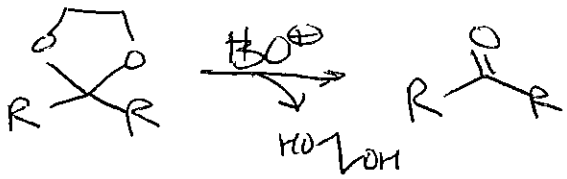
disadvant.: • throw away ½ of material! (try to do resolution early in synthesis)

d) to resolve aldehydes/ketones

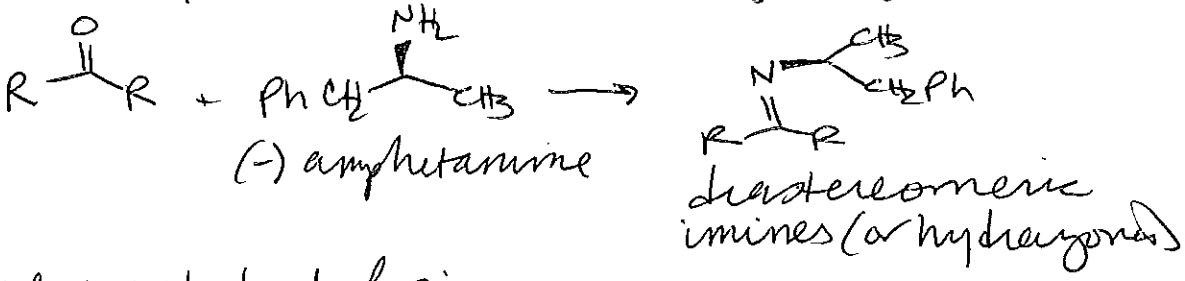
i) react w/ chiral diol



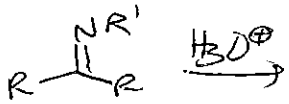
recover by hydrolysis:



ii) react w/ chiral amines or hydrazines



recover by hydrolysis



③ chiral chromatography - handout

⑤ Enzymatic methods - handout

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

ex: S + R (racemate) —chiral reagent (incomplete rxn, ½ equiv)→ 50% unreacted starting material (enriched in R enantiomer)

50% product (enriched in S)

(50% yield is max)

if reacts faster

California State Polytechnic University, Pomona

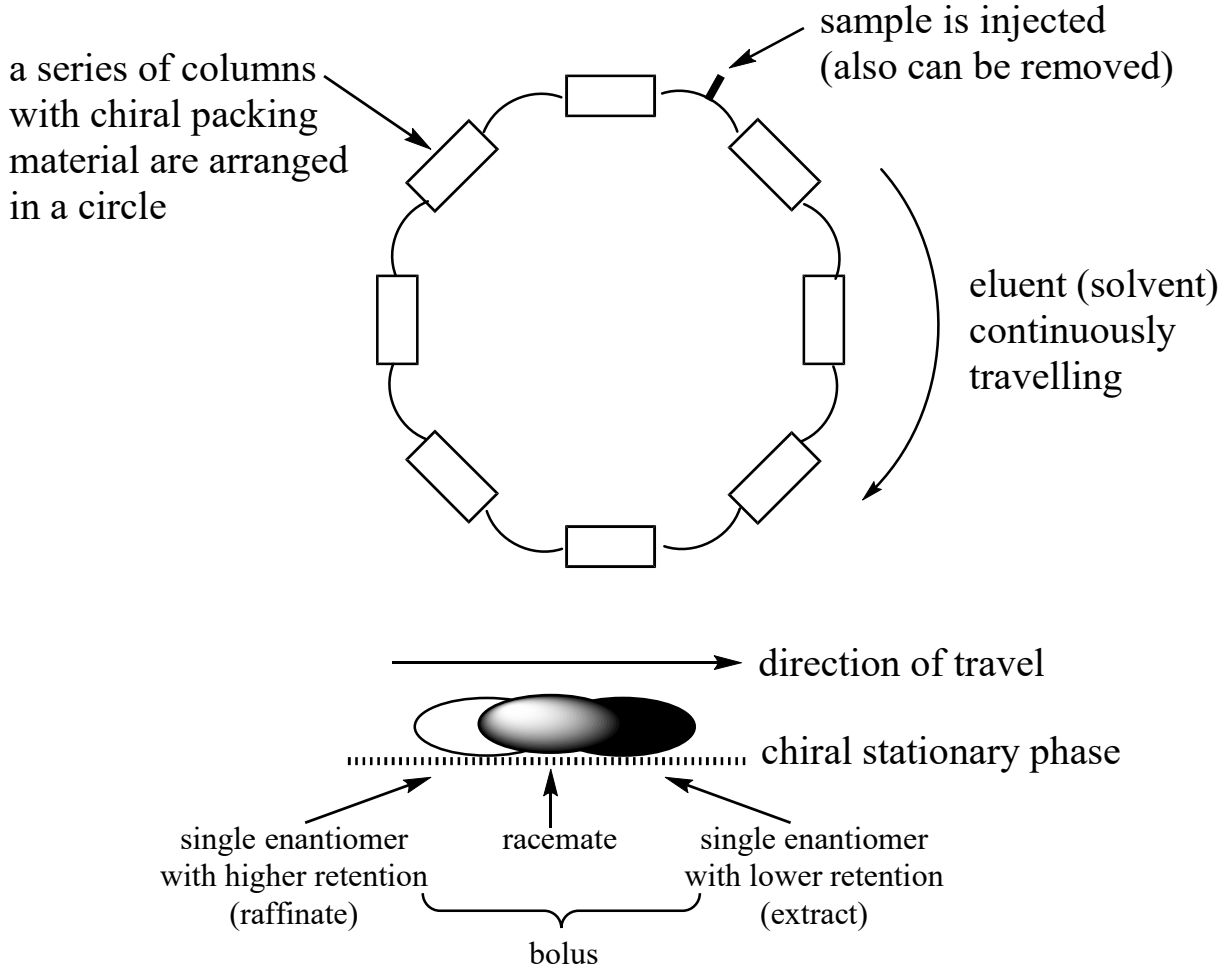
Laurie S. Starkey, CHM 543, Topics in Stereochemistry

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

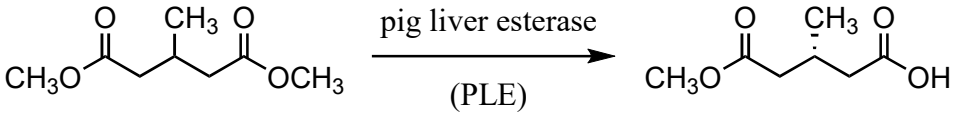
Enzymes can be used to separate enantiomers by preferentially reacting with only one enantiomer (called a **kinetic resolution**). Also, enzymes can sometimes differentiate between enantiotopic groups. Following are some general features of enzymatic reactions:

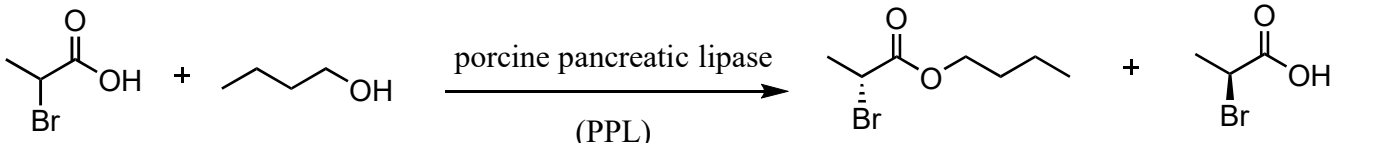
advantages:

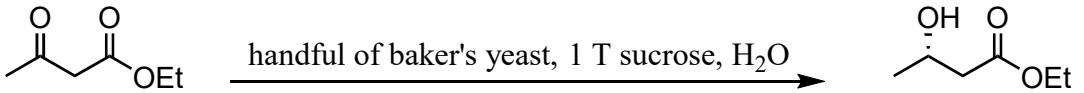
economical (PLE ~$0.006/u, where u=amount of enzyme required to transform 1 μmol/min
very stereoselective (100% ee)
water buffers as solvents (no organic solvents or chemical wastes; environmentally benign)

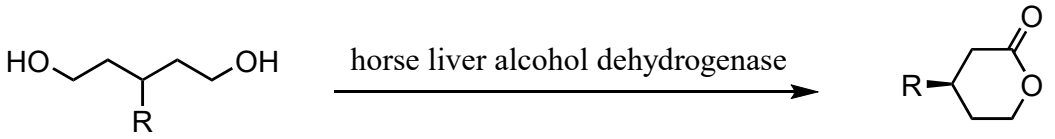
disadvantages:

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)

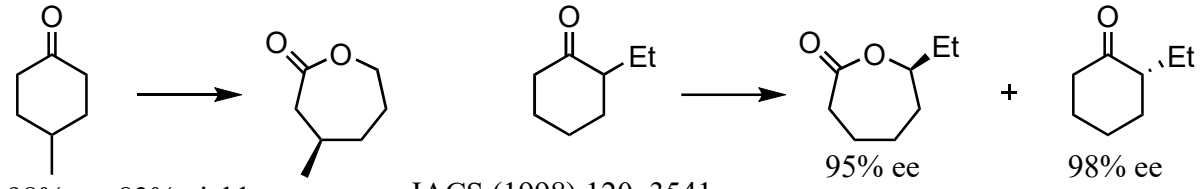




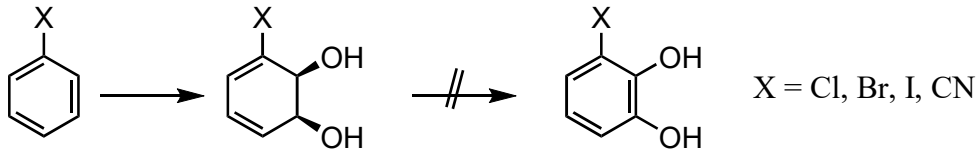




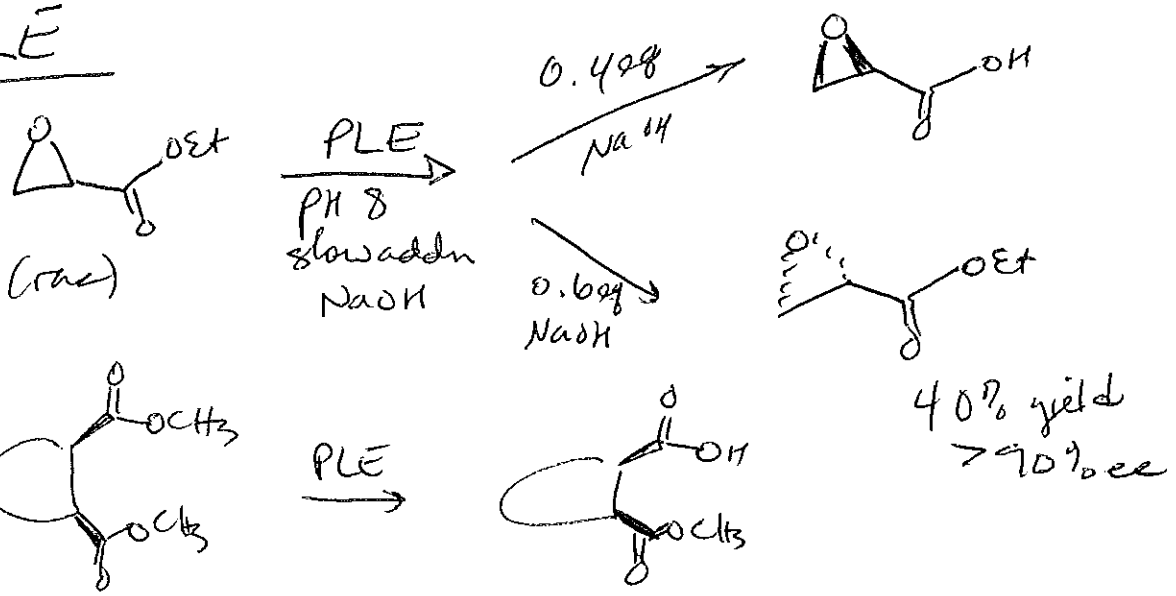
*Baeyer-Villiger designer enzyme (cyclohexanone monooxygenase spliced into brewer's yeast)



*arene dioxygenase (makes catechols) with the dehydrogenase gene disabled (knocked out)

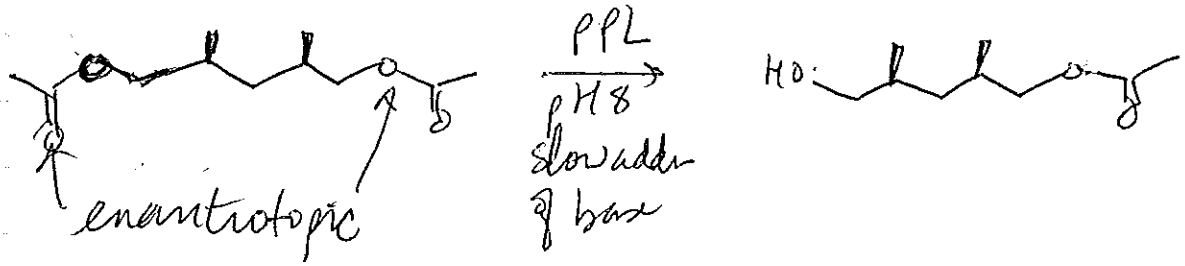


PLE

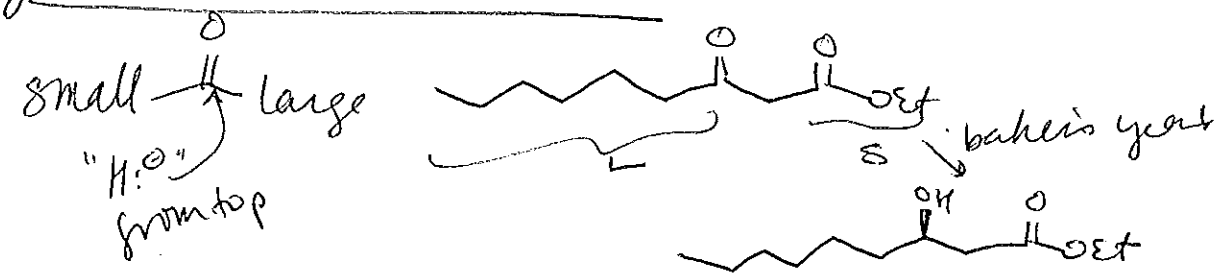


selectivity depends on ring size

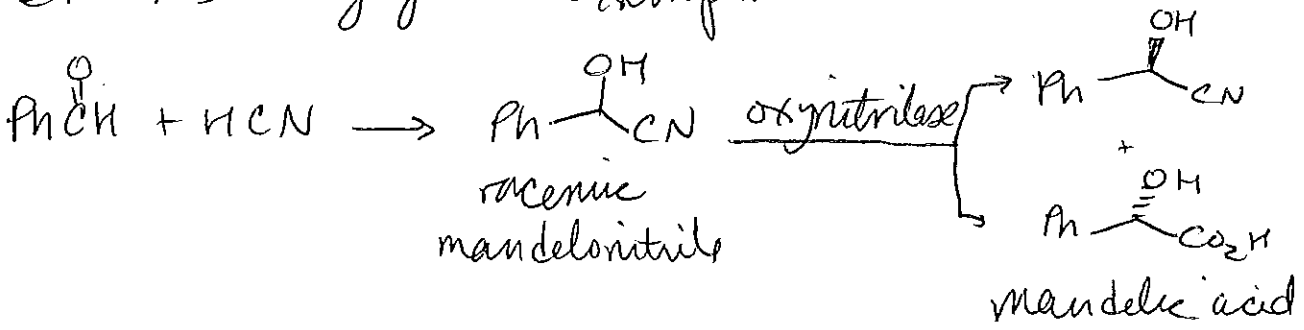
PPL - very cheap $0.000002/U (use excess)

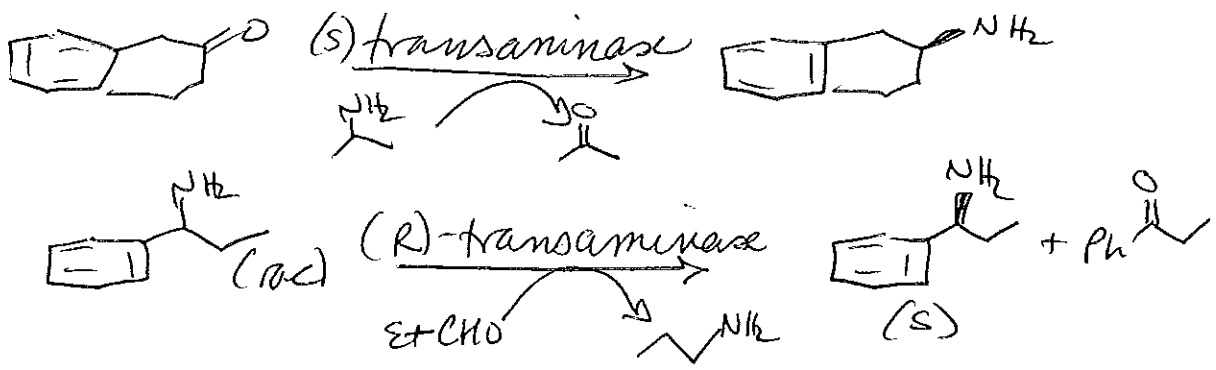


Yeast Reductions (1918)



Other enzyme examples:

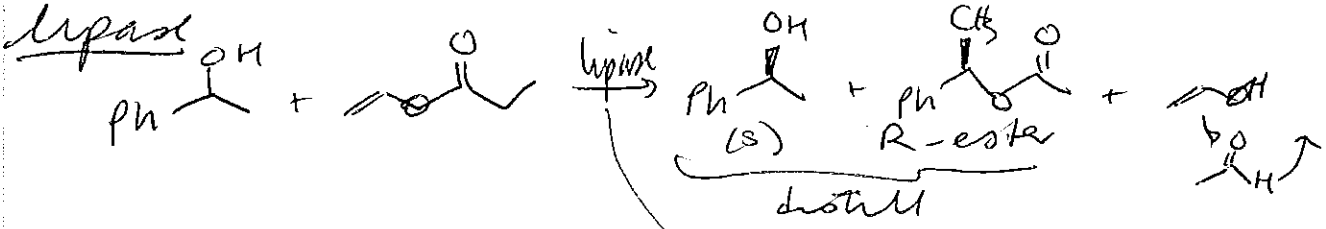




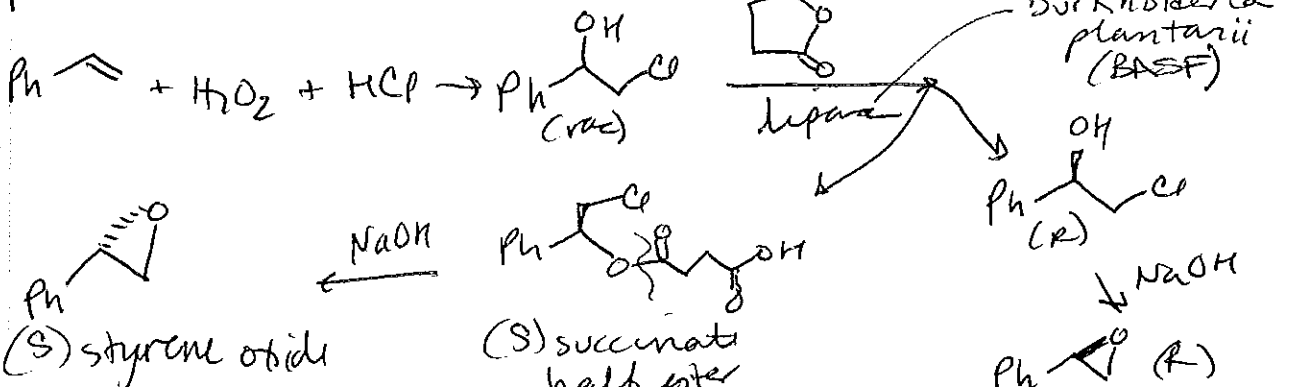
Pyruvate aldolase

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

Lipase

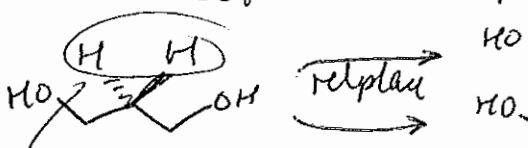


prep. of styrene oxide:

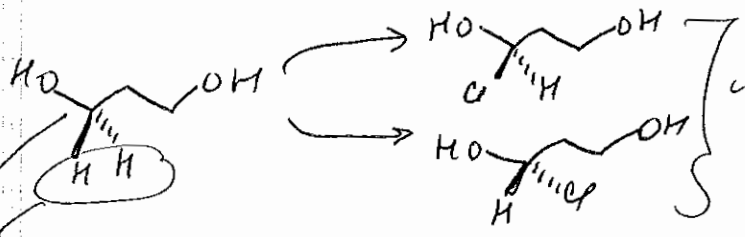


Prochiral Relationships

Replace each ligand w/a test group (D, Cl, Z, ☺) and determine resulting relationship



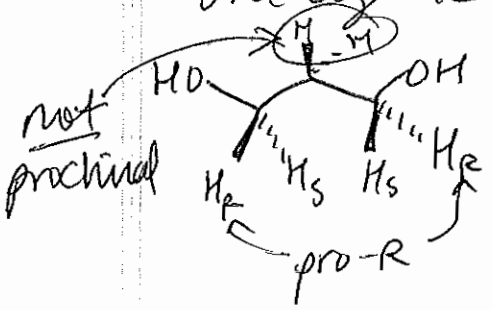
↳ called "homotopic", these are chemically equivalent
↳ general form: 

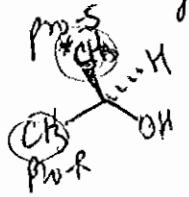


↳ called "enantiotopic", these are nonequivalent
↳ general form X—C(H)(H)—Y (if X+Y are achir

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

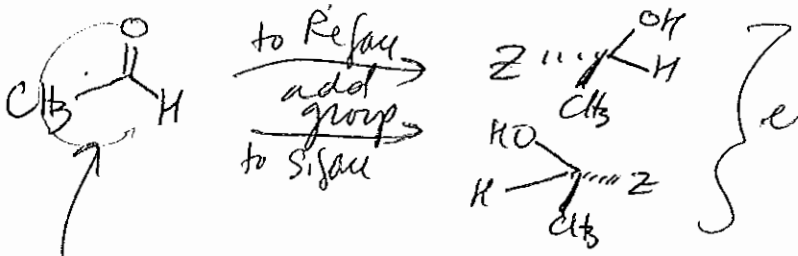
one ligand is pro-R, the other is pro-S
↳ replacement of this ligand w/a heavier isotope (D) gives R config.





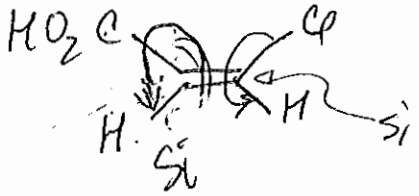
* enantiotopic atoms or groups are equivalent in all ways (chemical + physical, NMR) except for rxn w/chiral reagents

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



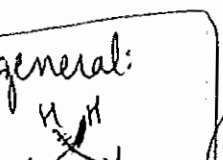
enantiotopic faces (viewing Si face)

alkene faces - give separate re+si designation for each

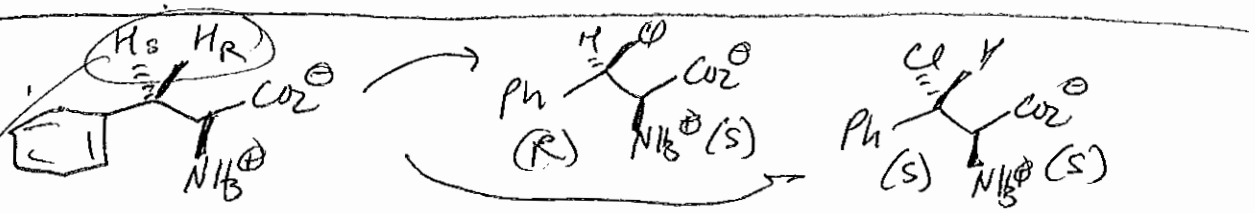


Si - si face shown

general:



if X or Y is chiral → called "diastereotopic" Hs



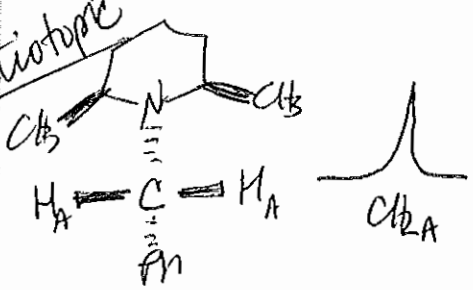
diastereomers.

↳ behave differently in any environment, chiral or achiral

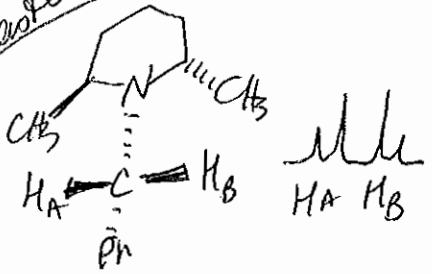
* returns to original relationships of stereochem *

different by NMR: (if close to chiral center!)

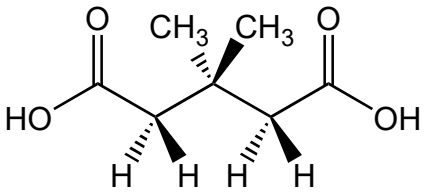
enantiotopic

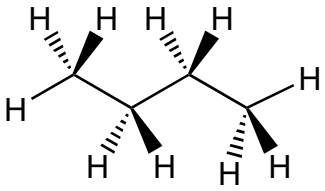


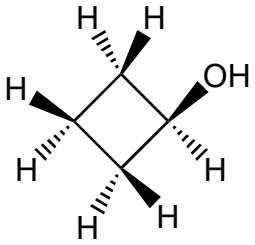
diastereotopic

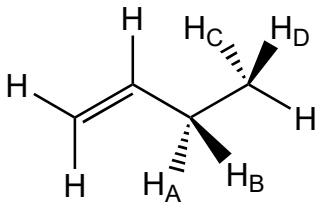


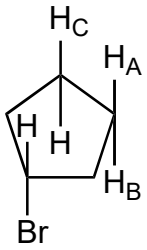
* both appear as doublets b/c split by the nonequivalent neighbor!

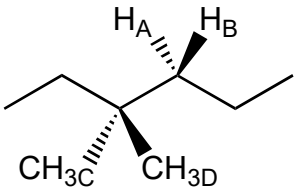






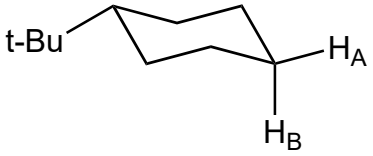


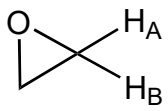


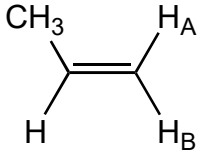


H_A & H_B _____ H_A & H_B _____ H_A & H_B _____

H_C & H_D _____ H_A & H_C _____ Me_C & Me_D _____







H_A & H_B _____ H_A & H_B _____ H_A & H_B _____