CHEMISTRY 144
M. E. Jung Fall 2008
Tu/Th 11am 1044 Young Hall

Practical and Theoretical Introductory Organic Synthesis

This course is divided into two parts: an 8-hour/week laboratory and a 2-hour/week lecture. The grading of the course will be evenly divided between the two sections of the course. The laboratory grade will be derived from a final report at quarter's end (written in the style of a research publication) on the projects investigated during the quarter, the amount and type of research accomplished, and the evaluation of your laboratory proficiency by the Teaching Assistant.

The lecture grade will be derived from a mid-term examination on Tuesday, November 4th, and the final examination on Thursday, December 11th (3-6 pm). Problem sets will be assigned at various intervals during the quarter to help you determine your progress. On exams, students will be required to propose syntheses of many compounds, including complex natural products, and will be graded on the soundness, originality, and probable success of these proposals.

REQUIRED TEXT: None

OTHER BOOKS ON SYNTHESIS

1) "Organic Synthesis" by Smith
2) "Modern Organic Synthesis: Lecture Notes" by Boger
2) "Organic Synthesis: The Disconnection Approach" by Warren
3) "Modern Synthetic Reactions" by House
4) "The Logic of Chemical Synthesis" by Corey and Cheng
5) "Stereoselective Synthesis" (2nd Ed.) by Nógrádi
6) "Organic Synthesis" (2nd Ed.) by Fuhrhop and Penzlin
7) "Synthetic Approaches in Organic Chemistry" by Bansal
8) "Strategies and Tactics in Organic Synthesis" by Lindberg (ed.) (3 volumes)
9) "Total Synthesis of Natural Products: The Chiron Approach," by Hanessian
10) "Protective Groups in Organic Synthesis" (3nd Ed.) by Wuts and Greene
11) "Organic Synthesis" by Ireland
12) "Stereoelectronic Effects in Organic Chemistry" by Deslongchamps
13) "The Total Synthesis of Natural Products" by ApSimon (ed.) (9 volumes)
14) "Some Modern Methods of Organic Synthesis" (3rd Ed.) by Carruthers
15) "Reactions of Organic Compounds" by Hickinbottom
16) "Organic Chemistry of Drug Synthesis" by Lednicer and Mitscher (6 volumes)
17) "Selected Organic Syntheses" by Fleming
18) "Carbanions in Organic Synthesis" by Stowell
19) "Stereoselectivity in Organic Synthesis" by Procter
20) "Organic Synthesis: Theory and Applications" (Vol. 5) by Hudlicky
21) "Classics in Total Synthesis," Nicoloau and Sorenson, Eds.
22) "Advanced Organic Chemistry" by Carey and Sundberg

OTHER REFERENCE TEXTS

1) "Comprehensive Organic Transformations" by Larock (2nd Ed.)
2) "Comprehensive Organic Synthesis," (9 volumes) many authors (Pergamon Press)
3) "Compendium of Organic Synthetic Methods" various authors (7 volumes)
4) "Reagents for Organic Synthesis" by Fieser and Fieser (17 volumes and counting)
5) "Organic Reactions" and "Organic Syntheses"
6) "Asymmetric Synthesis" by Morrison (5 volumes)
7) "Advanced Organic Chemistry" (4th edition) by March
8) "Survey of Organic Syntheses" by Buehler and Pearson (2 volumes)
9) "Synthetic Methods of Organic Chemistry" by Theilheimer
10) "Name Reactions & Reagents in Organic Synthesis" by Mundy and Ellerd
11) "Annual Reports in Organic Synthesis" by various authors and others (annual)
12) "Stereochemistry of Organic Compounds," by Eliel
13) "Encyclopedia of Reagents for Organic Synthesis," by Paquette (ed.) (8 volumes)

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The following schedule for covering material in the course will be followed - more or less - throughout the quarter.

WEEK	DATES		SUBJECT
1		9/25	General & Reduction
2	9/30	10/2	Reduction & Oxidation
3	10/7	10/9	Oxidation
4	10/14	10/16	C-C Bond Formation: Alkylation
5	10/21	10/23	Alkylation & Condensation
6	10/28	10/30	Condensation & Alkenylation
7	11/4	11/6	HOUR EXAM & Cycloadditions
8	**11/11**	11/13	**Veterans Day Holiday** - Cycloadditions
9	11/18	11/20	Organometallics & Protecting Groups
10	11/25	**11/27**	Rearrangements - **Thanksgiving**
11	12/2	12/4	Rearrangements & Catch-up

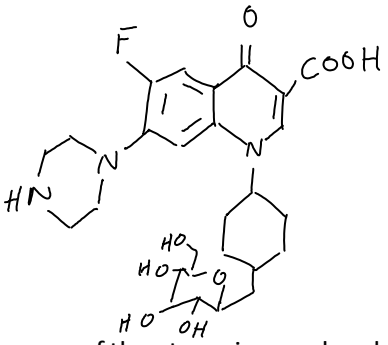
Final Exam Thursday, December 11th: 3:00 - 6:00 pm

Notes 09/25

Thursday, September 25, 2008
11:15 AM

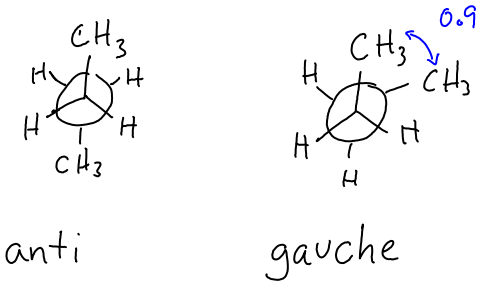
Organic Synthesis

1. Carbon framework
2. Stereochemistry
3. Functionality (ie oxidation state)

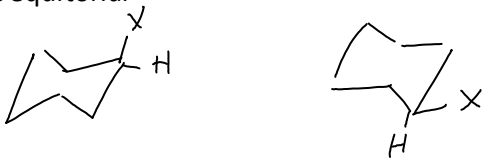


Definitions

1. **Conformation** - any non-identical arrangement in space of the atoms in a molecule obtainable by rotation about one or more single binds
   a. Anti vs gauche

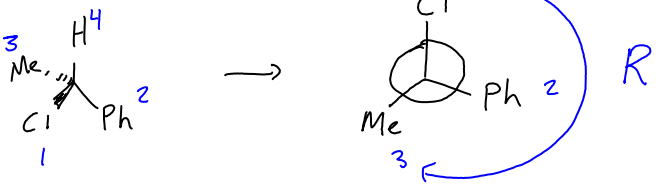


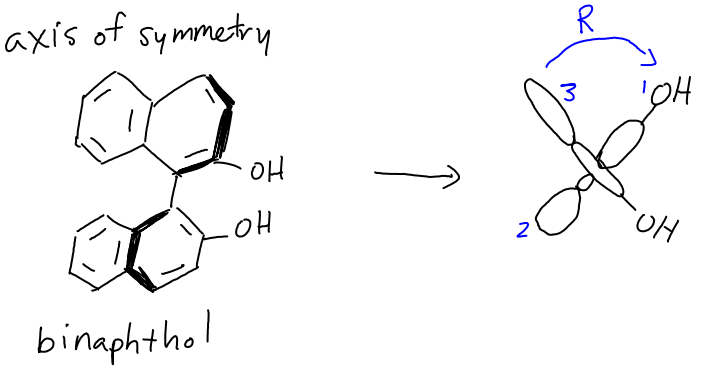
   b. Axial vs equitorial



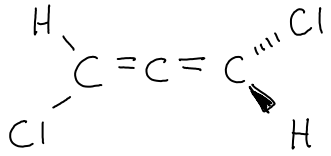
2. **Stereospecific** - reaction inwhich stereoisomerically different starting materials give rise to stereoisomerically different products
3. **Stereoselective reaction** - reaction in which two (or more) possible products, one is formed in preference (often in great preference) to all others
4. Steric Effects
   a. Steric Hinderance - steric crowding is more severe in the transition state than in the ground state
      - Axial vs equatorial energy difference
        - Linear $\Delta G^0 = 0.2 - 0.5$
        - Divalent $\Delta G^0 = 0.5 - 1.0$
        - Tetravalent $\Delta G^0 = 1.1 - 2.0$
        - Tetravalent 1.74
        - Never see tBu in axial (only equatorial)
   b. Acceleration - steric crowding is more severe in the groud state than in the transition state
5. Steric Hinderence
   a. Cahn-Ingold-Prelog (RS)

a. Cahn-Ingold-Prelog (RS)





HOMEWORK: assign R/S



- Reductions -> addition of H_2
  1. Catalytic Hydrogination

     $H\cdot + H\cdot$

  2. Metal hydride

     $H^{\ominus} + H^{\oplus}$

  3. Dissolving metal reduction

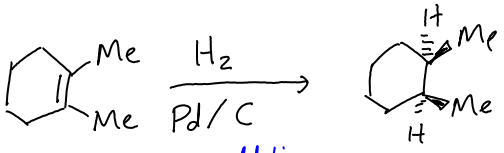
     $2e^- + 2H^+$

  4. Silane/string acid reduction

     $H^{\oplus}$ then $H^{\ominus}$

1. Catalytic Hydrogen
   a. Heterogeneous catalysis

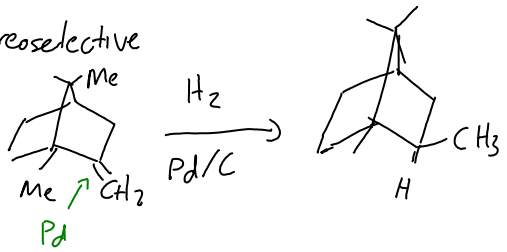
      Pd/Pt => Ru/Rh/Ir/Ni



syn addition

stereoselective → less hindered

eg stereoselective



Chemistry 144
Organic Synthesis
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Definitions

Conformation: Any non-identical arrangement in space of the atoms in a molecule obtainable by rotation about one or more single bonds.

Conformational Analysis: An analysis of the physical and chemical properties of a compound in terms of the conformation (or conformations) of the pertinent ground states, transition states, and (in the case of spectra and photochemical reactions) excited states.

Stereospecific Reaction: Reaction in which stereoisomerically different starting materials give rise to stereoisomerically different products.

Stereoselective Reaction: Reaction in which of two (or more) possible products, one is formed in preference (often in great preference) to all others.

Stereoelectronic Factor: Any factor concerned with the position in space of the electrons involved in bonding in the transition state of a given reaction.

Steric Effects:

Steric Hindrance: Steric crowding is more severe in the transition state than in the ground state.

Steric Acceleration: Steric crowding is more severe in the ground state than in the transition state.

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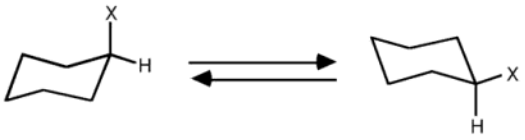
Organic Synthesis

A Values or Standard Free Energy Differences



A value = - ΔG° = standard free energy difference

Table: Free-energy differences between equatorial and axial substituents on a cyclohexane ring

Group (X)	Approx. - ΔG° (kcal/mol)	Group (X)	Approx. - ΔG° (kcal/mol)
HgCl	-0.25	**CHO**	0.56-0.8
HgBr	0	**COMe**	1.02-1.21
HgOAc	-0.3-0	**COOEt**	1.1-1.2
CN	0.20	**COOMe**	1.2-1.3
F	0.25-0.42	**COOH**	1.4
Cl	0.53-0.64	**COO^-**	2.0
Br	0.48-0.67	**NH_2**	1.23-1.7
I	0.47-0.61	**NH_3^+**	1.7-2.0
C≡CH	0.41-0.52	**NHCOPh**	1.6
N_3	0.45-0.62	**NMe_2**	1.53-2.1
NC	0.20	**$NHMe_2^+$**	2.4
NCO	0.44-0.51	**PPh_2**	1.8
OH	0.60-1.04	**$CH{=}CH_2$**	1.49-1.68
OTs	0.50	**CH_3**	1.74
OAc	0.68-0.87	**CH_2CH_3**	1.79
OMe	0.55-0.75	**$CH_2CH_2CH_3$**	2.1
OBz	0.50	**$CH_2C(CH_3)_3$**	2.0
$OCO(pNO_2)Ph$	0.62	**$CH(CH_3)_2$**	2.21
OtBu	0.75	**$CH_2C_6H_5$**	1.68
$OSiMe_3$	0.74	**CH_2X (X = OH, Br, CN)**	1.76-1.79
SH	1.21	**C_6H_{11}**	2.2
SPh	1.10-1.24	**C_6H_5**	2.8
SePh	1.0-1.2	**CF_3**	2.4-2.5
SOMe	1.2	**$C(CH_3)_3$**	4.7-4.9
SO_2Me	2.5	**$SiMe_3$**	2.5
NO_2	1.1	**$SiCl_3$**	0.61
$N{=}CHCHMe_2$	0.75	**$SnMe_3$**	1.0

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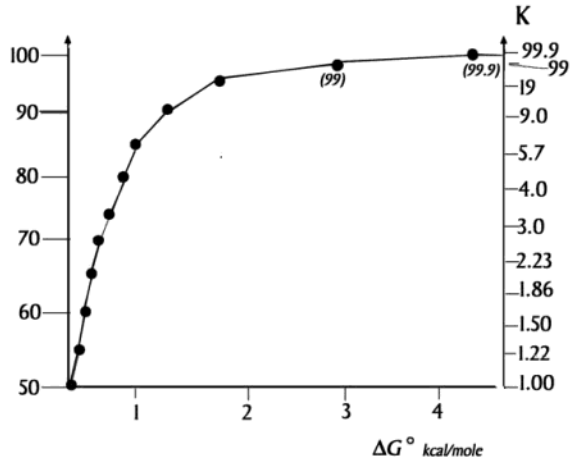
Equilibria and Free Energy Difference

Relationship between Percentage of More Stable Isomer at Equilibrium, Equilibrium Constant K, and Standard Free-Energy Difference ΔG° at 25 °C and 80 °C for an Equilibrium of Isomers: A ⇆ B

% More Stable Isomer	K	ΔG°_{25} kcal/mole	ΔG°_{80} kcal/mole
50	1.00	0	0
55	1.22	0.119	0.141
60	1.50	0.240	0.285
65	1.86	0.367	0.434
70	2.33	0.502	0.595
75	3.00	0.651	0.771
80	4.00	0.821	0.973
85	5.67	1.028	1.217
90	9.00	1.302	1.542
95	19.00	1.744	2.066
98	49.00	2.306	2.731
99	99.99	2.722	3.224
99.9	999.9	4.092	4.846
99.99	9999	5.456	6.463



Correlation between the free energy difference (ΔG°) and the equilibrium constant (K) for two equilibrating species (conformers), also expressed as the percentage of the component in excess.

Handout: Catalytic Dehydrogenation: Rate of Reduction

Thursday, September 25, 2008
7:26 PM

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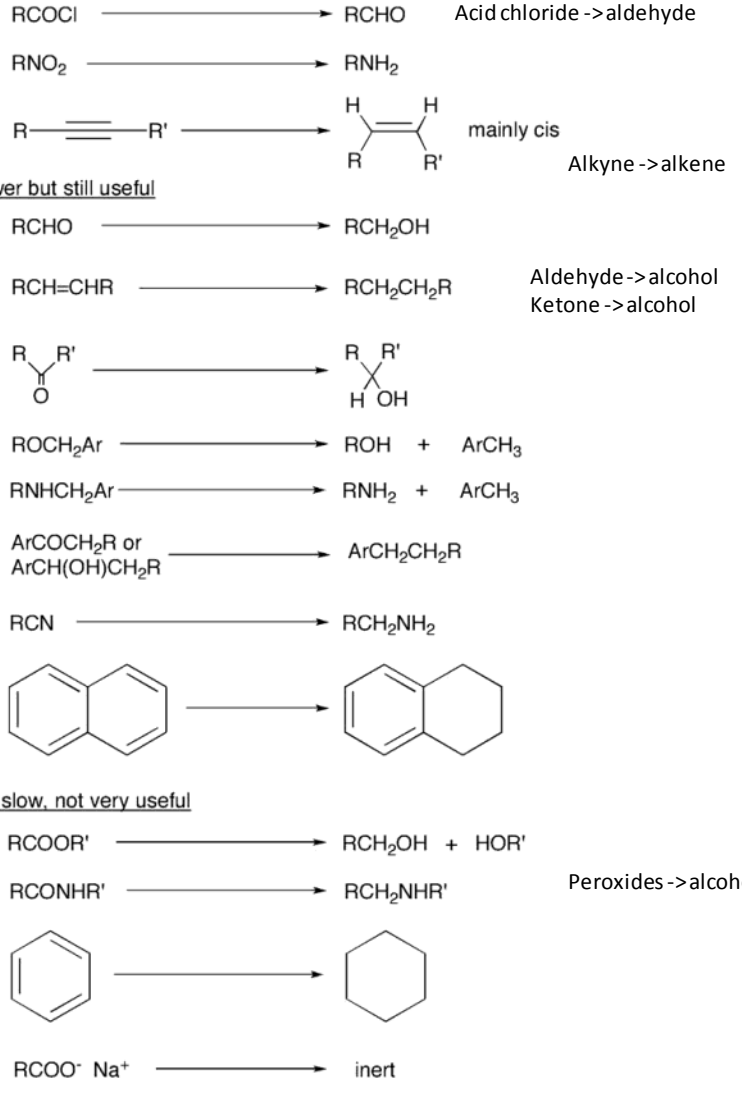
Organic Synthesis

Approximate Decreasing Rate of Reduction in Catalytic Hydrogenation

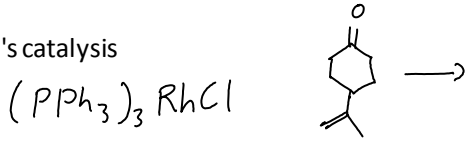
Fast, selective



Notes 09/30

Tuesday, September 30, 2008
6:06 PM

1. Heterogeneous cat
   I. PD/C + H_2
   II. Hydrogenolysis
   III. Alkyne -> alkene
      1. Cram's H_2, Pd/ $BaSO_4$ 
      2. Lindlar
         Pd/ $PbO/CeCO_3$, H_2
      3. Wilkinson's catalysis

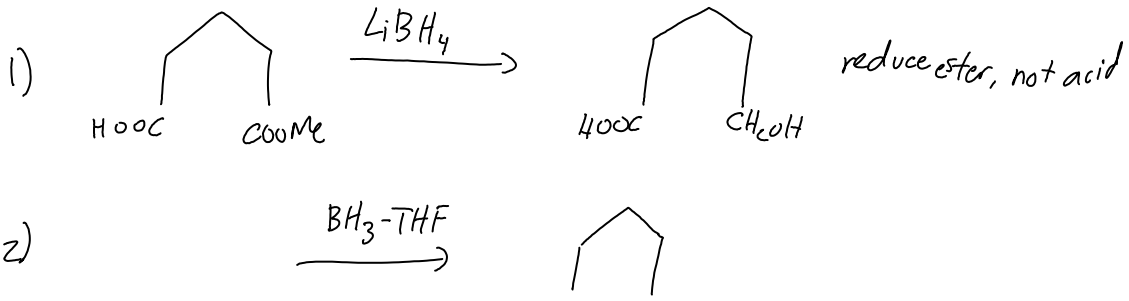


Hydride

a) $NaBH_4$ - weak. Aldehyde/ket only ->alcohol
b) LiAlH4 - strong. Everything except olefin
c) DIBAL - ester (-78^{0}C), CN, amide -> aldehyde.
d) $LiBH_4$ - ester, not acid to alcohol (BH_3-THF +$LiBH_4$)
e) REDAL - strong, ex CN and olefin
f) $NaNCBH_3$ or $NaBH(OH_2)_3$ weak, ald -> alchol (not ketone to alcohol)
g) $LiHB^-Et_3$ - superhydride. Reduce ester but not acid
h) $KHB^-(sBu)_3$ - K selectride or L selectride.

Reducing Power

LAH > $LiBH_4$, superhydride, selectride > $NaBH_4$ > $NaNCBH_3$



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Hydride Reagent Selectivity

Brown, *Aldrichimica Acta* **1979**, *12*, 9.

Table II. Summary of behavior of various functional groups toward the hydride reagents

	$NaBH_4$ in ethanol	$Li(O\text{-}t\text{-}Bu)_3AlH$	$NaBH_4 + LiCl$ in diglyme	$NaBH_4 + AlCl_3$ in diglyme	BH_3 in THF	Sia_2BH in THF	9-BBN in THF	AlH_3 in THF	$LiAl(OMe)_3H$ in THF	$LiAlH_4$ in THF	$LiEt_3BH$ in THF
Aldehyde	+	+	+	+	+	+	+	+	+	+	+
Ketone	+	+	+	+	+	+	+	+	+	+	+
Acid chloride	R	+	+	+	–	–	+	+	+	+	+
Lactone	–	±	+	+	+	+	+	+	+	+	+
Epoxide	–	±	+	+	+	±	±	+	+	+	+
Ester	–	±	+	+	±	–	±	+	+	+	+
Acid	–	–	–	+	+	–	±	+	+	+	–
Acid salt	–	–	–	–	–	–	–	+	+	+	–
tert-Amide	–	–	–	–	+	+	+	+	+	+	+
Nitrile	–	–	–	–	+	–	±	+	+	+	+
Nitro	–	–	–	–	–	–	–	–	+	+	+
Olefin	–	–	–	–	+	+	+	–	–	–	–

R = Reacts with solvent; reduced in nonhydroxylic solvent

Walker, *Chem. Soc. Rev.* **1976**, *5*, 23.

Group affected / *Reducing agent*	$NaBH_4$	$LiBH_4$	$Zn(BH_4)_2$	$LiEt_3BH$	$LiBu^s_3BH$	$NaBH_3CN$	$NaBH_2S_3$	$Li(Bu^tO)_3AlH$	RED-AL	$LiAlH_4$	B_2H_6	BH_3NR_3		AlH_3	
RCHO	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
RCOCl	✓	✓	✓	✓	✓		×	RCHO	✓	✓	×	✓	×	✓	
Lactone	V. slow	✓	×	✓	✓	×	✓	×	✓	✓	×		Lactol	✓	Lactol
	V. slow	✓	×	✓	✓	×	✓	×	✓	✓	✓		×	✓	
$R^1CO_2R^2$	V. slow	✓	×	✓	✓	×	×	R^2=Ph, →R^1CHO	✓	✓	×	×	×	✓	RCHO
RCO_2H	×	×	×			×	×	×	✓	✓	✓	×	×	✓	×
RCO_2M	×	×				×	×	×	✓	✓	×		×	✓	×
RCON<	×	×				×	✓	×		✓	✓		RCHO	✓	RCHO
RCN	×	×				×	✓	×	×	✓	✓	×	×	✓	RCHO
RNO_2	×	×				×	✓	×		✓	×		×	×	×
	×	×	×			×	×	×	×	×	✓	✓	✓	×	×
RHal	×	×		alkyl: ✓ aryl : ×		✓			✓	✓	×	×		×	×

* ✓ indicates that the functional group is reduced, while × indicates that it is resistant to reduction. Where appropriate the structure of the reduction product obtained is indicated in the Table.

Handout: Acyclic Stereocontrol pt 1

Tuesday, September 30, 2008
7:27 PM

Chemistry 144

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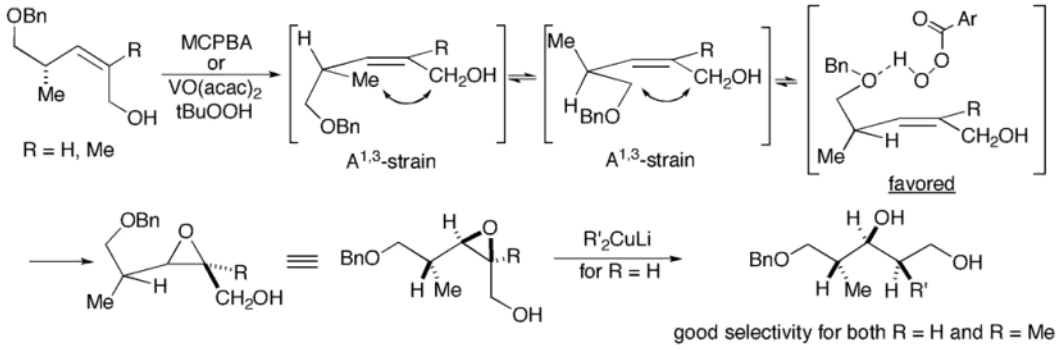
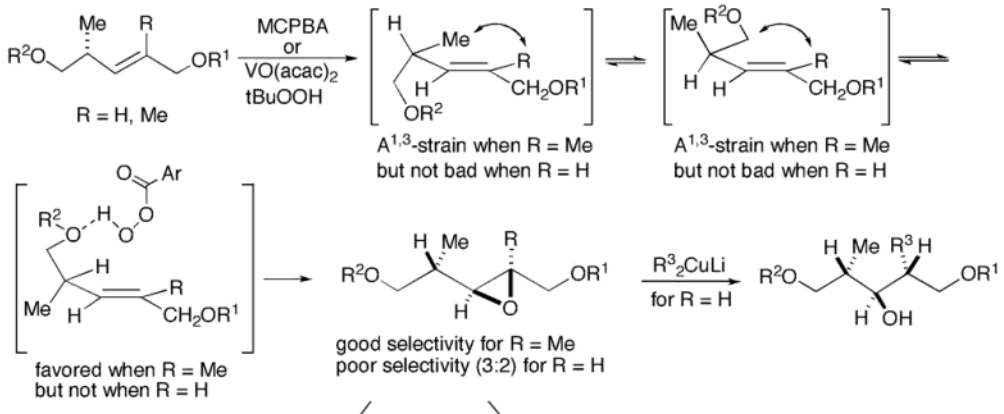
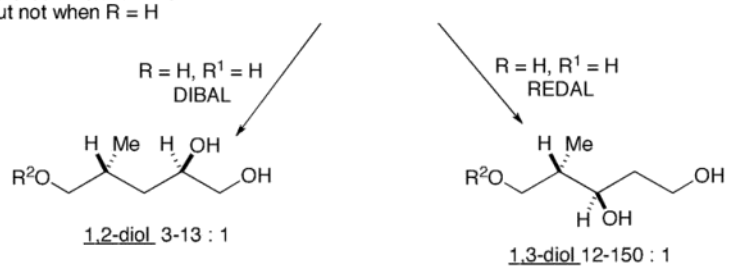
Organic Synthesis

Acyclic Stereocontrol

Kishi Epoxidation (*Tetrahedron Lett.* **1979**, 4343, 4347; **1982**, *23*, 2719)







Chemistry 144

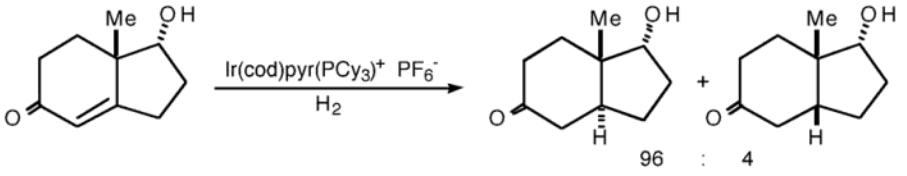
M. E. Jung
Organic Synthesis

Cyclic and Acyclic Stereocontrol

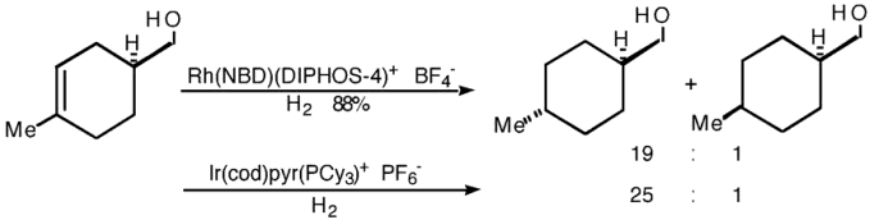
Hydroxyl-Directed Hydrogenation

Stork, G.; *et al. J. Am. Chem. Soc.* **1983**, *105*, 1072.
Evans, D. A.; *et al. J. Am. Chem. Soc.* **1984**, *106*, 3866; *Tetrahedron Lett.* **1985**, *26*, 6005; *Tetrahedron Lett.* **1984**, *25*, 4637.
Crabtree, R.; *et al. J. Organomet. Chem.* **1979**, *168*, 183; *Organometallics* **1983**, *2*, 681.
Schultz, A. G.; *et al.*, *J. Org. Chem.* **1985**, *50*, 5905.
Review: Brown, J. M. *Angew. Chem. Int. Ed. Eng.* **1987**, *26*, 190.

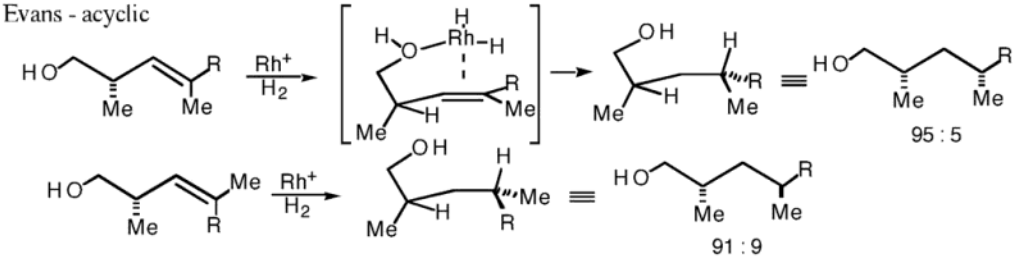
Stork - cyclic



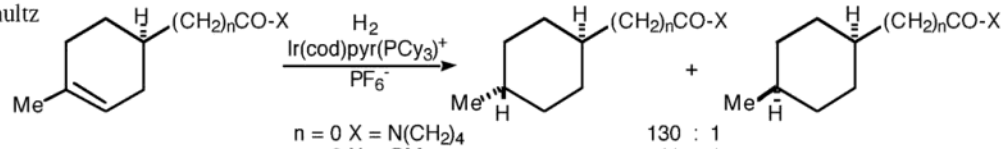
Evans - cyclic



Evans - acyclic



Schultz



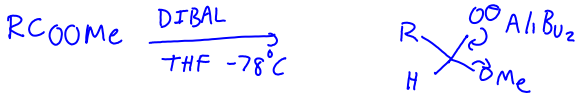
n = 0 X = $N(CH_2)_4$	130 : 1
n = 0 X = OMe	41 : 1
n = 1 X = $N(CH_2)_4$	>100 : 1
but n = 1 X = OMe	1.2 : 1

Notes 10/02

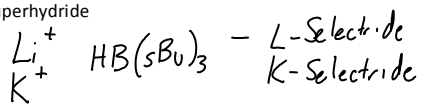
Thursday, October 02, 2008
11:02 AM

Reduction

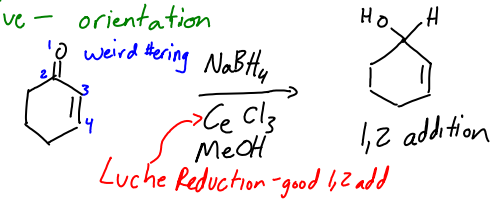
2) Hydride agents
   a) $NaBH_4$ - weak selective
   b) $LiAlH_4$ - strong nonselective
   c) DIBAL iBu_2AlH - useful
   d) $LiBH_4$
   e) REDAL $Na^+H_2Al(OCh2Ch2Ch4)_2$
   f) Na^+NCBH_3 or $Na^+ HB(OH_2)_3$ - very mild.. Reductive amination

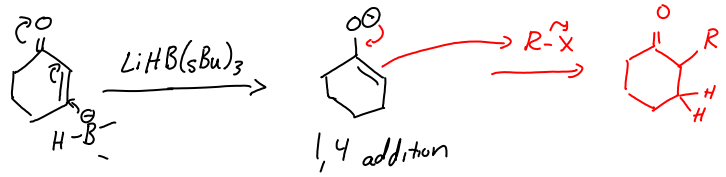


   g) Li^+HBEt_3 - superhydride



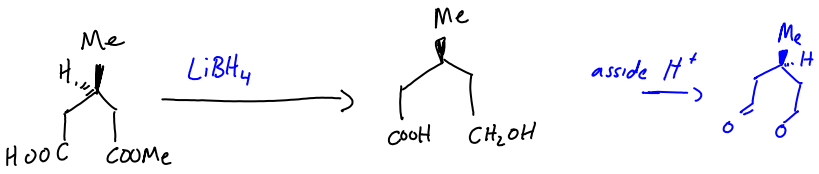
Regioselective – orientation

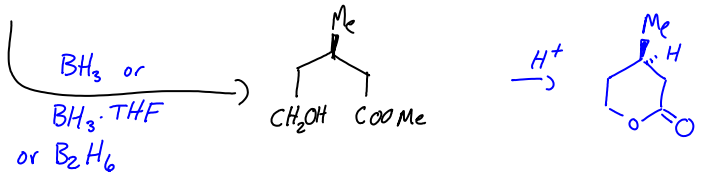




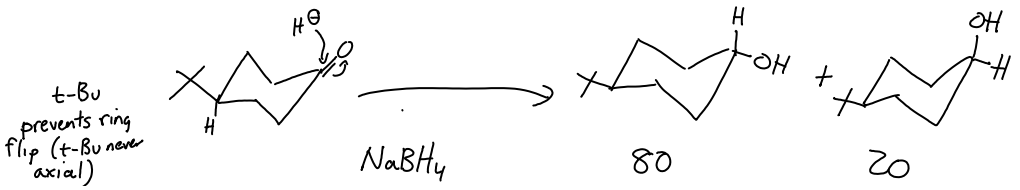
★ $LiAlH_3$ also 1,4 add

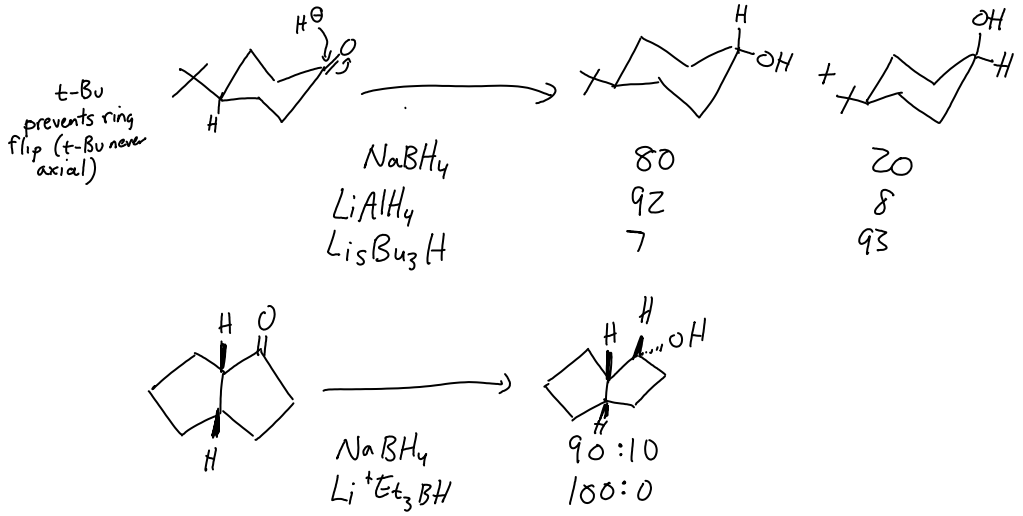
Chemoselectivity





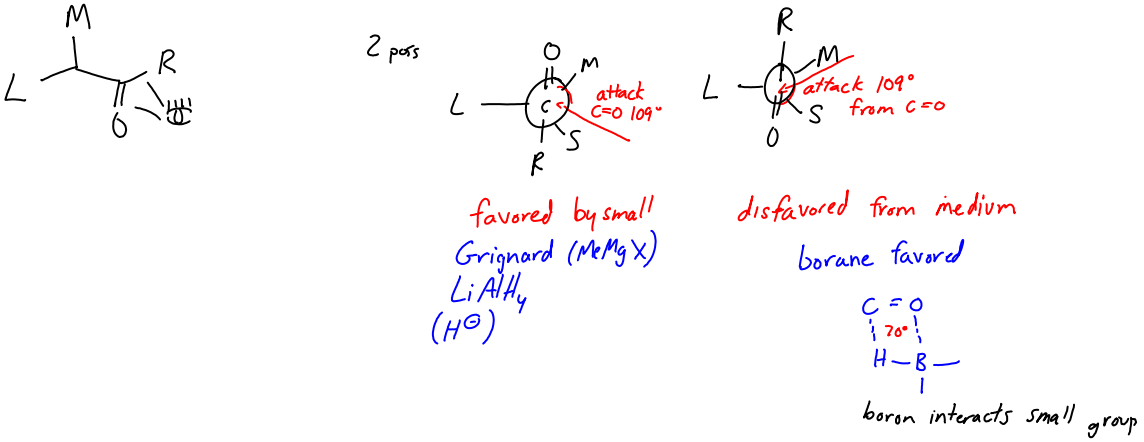
Diastereoselectivity





Cram's-Felkin-Anh-Hawk (see handout)

Look at stereocenter alpha to ketone



Enantioselective

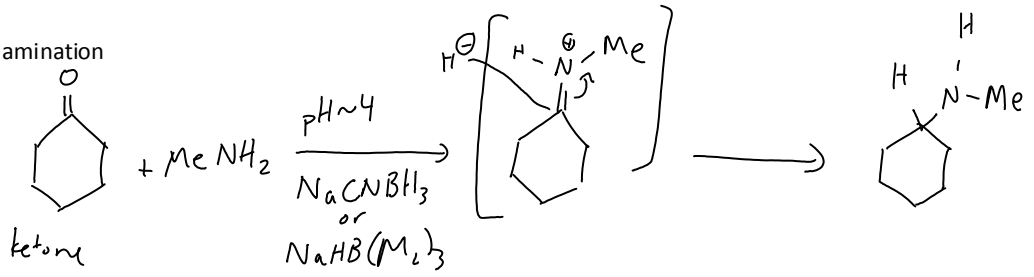
Look at 2 reagents (see handout)

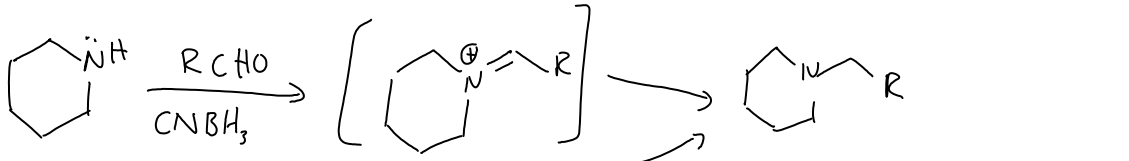
1) Alpine borane – R group must be different than acetylide

10/02

Thursday, October 02, 2008
11:07 AM

Reductive amination

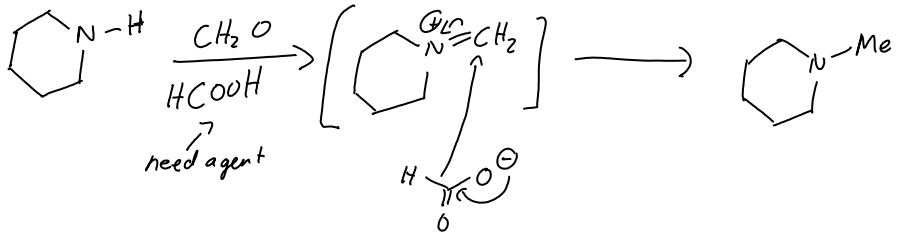




but problem 3° amine more reactive than starting (MeI in 30%)

Eschweiler Clarke:

React 2^0 amine



Notes 10/07

Tuesday, October 07, 2008
10:58 AM

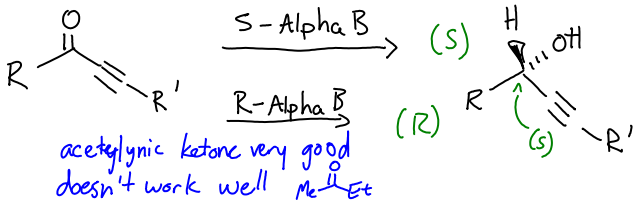
Notes 1007

Reductions

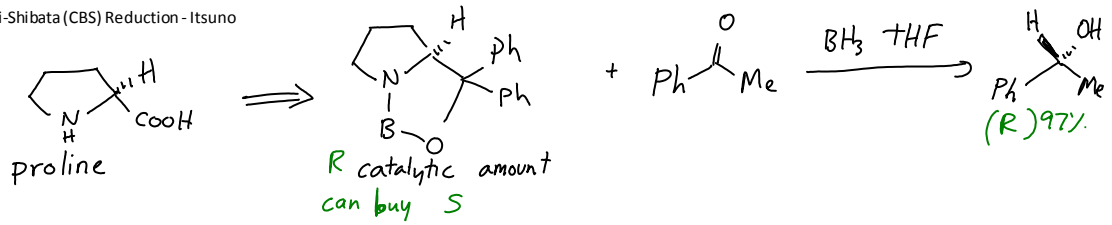
Audio recording started: 10:59 AM Tuesday, October 07, 2008

Enantioselectivity

1) Alpha borane (will be on test for sure)



2. Corey-Bakshi-Shibata (CBS) Reduction - Itsuno



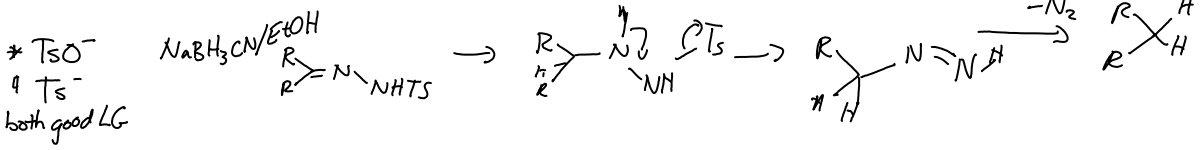
* chiral borohydride

Deoxygenation

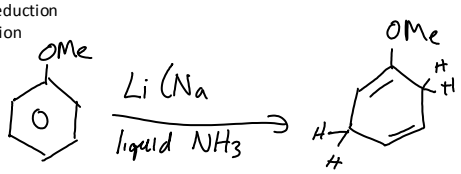
1) Wolff-Kishner
NH_2NH_2 / KOH / $HO\sim\sim O\sim\sim OH$ / ~200°C
* very basic so can't have base sensitive

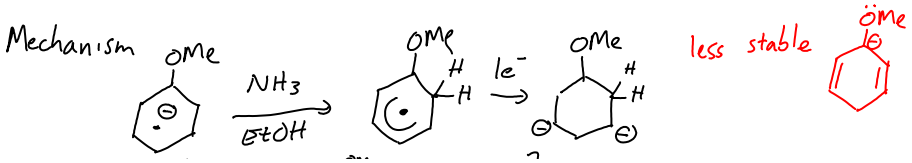
2) Clemmenser
Zn / Hg – HCl / Δ
* very acidic (ketal will be sensitive to acid and not work)

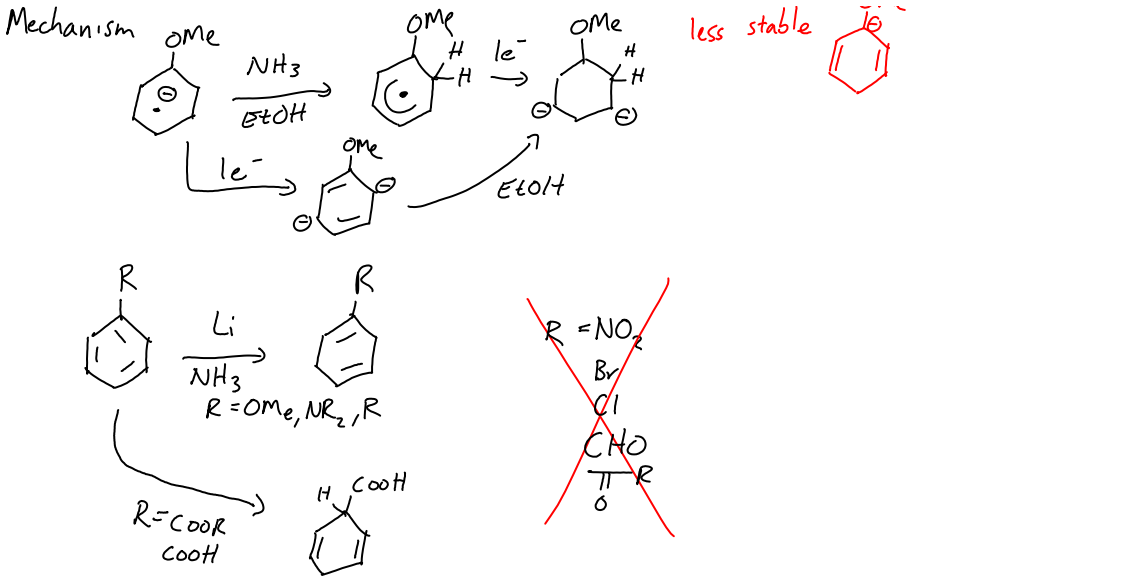
3) NH_2NHTs / EtOH

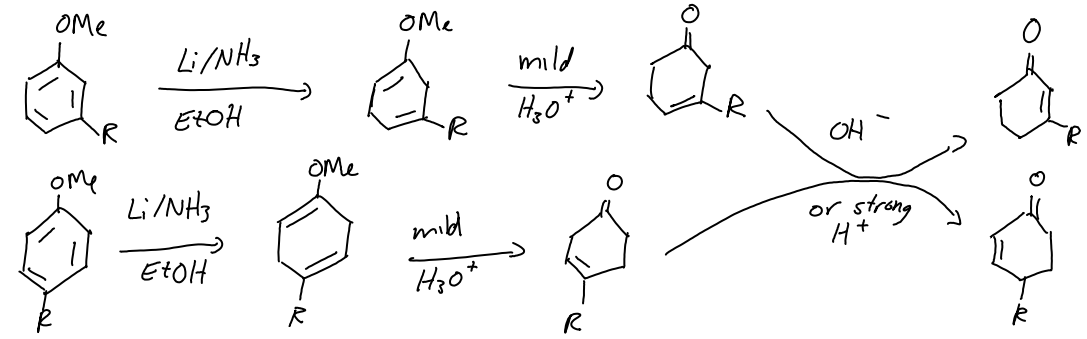


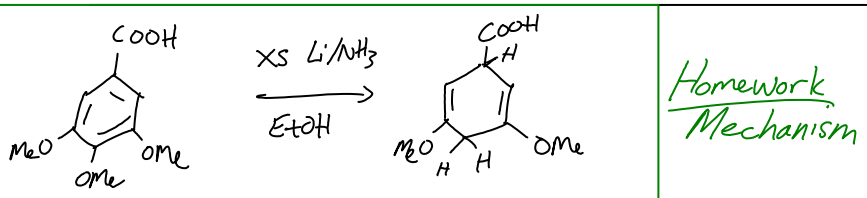
3. Dissolving metal reduction
Birch Reduction





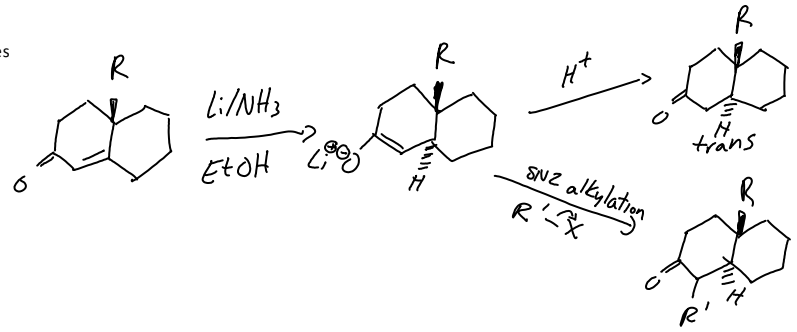




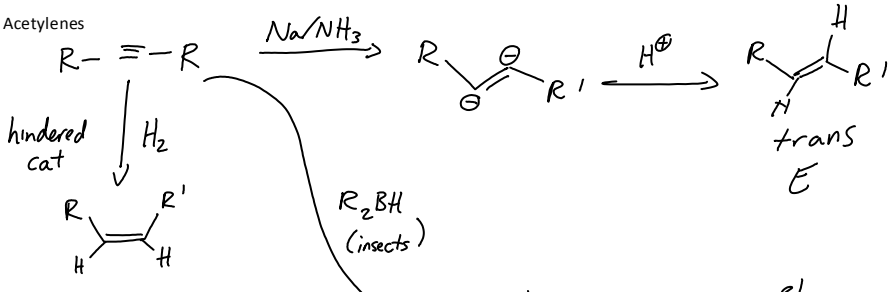


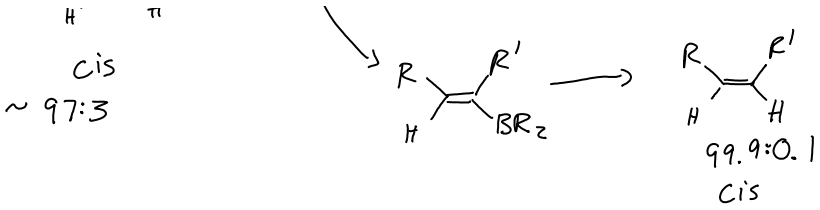
Homework
Mechanism

Enones



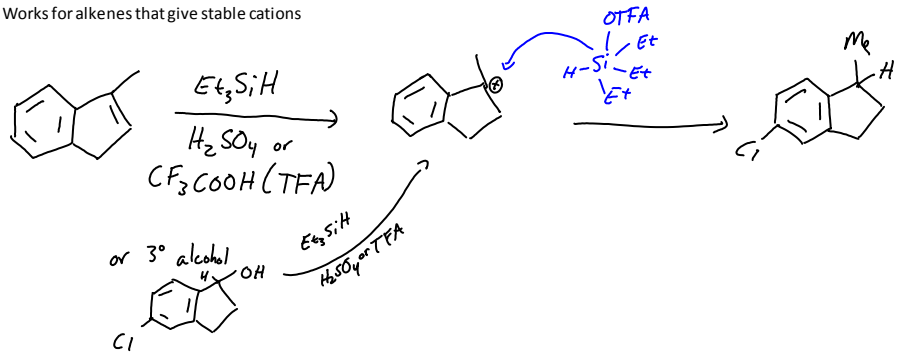
Acetylenes





4. Silane Acid

Works for alkenes that give stable cations

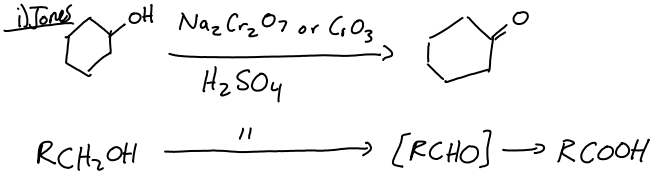


OXIDATIONS

Looking by class of compounds

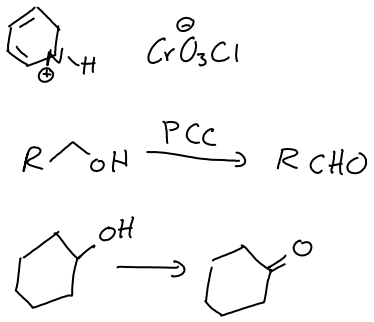
1) Alcohols

A) Cr^{+6}

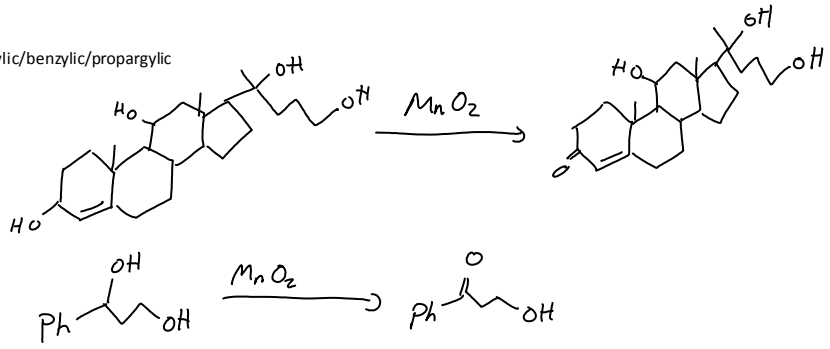


Ii) Collins CrO_3 x 2 pyr

III)PCC pyridinium dichlromate

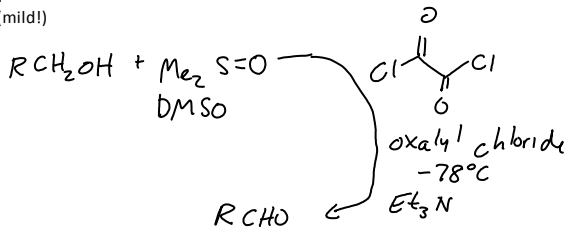


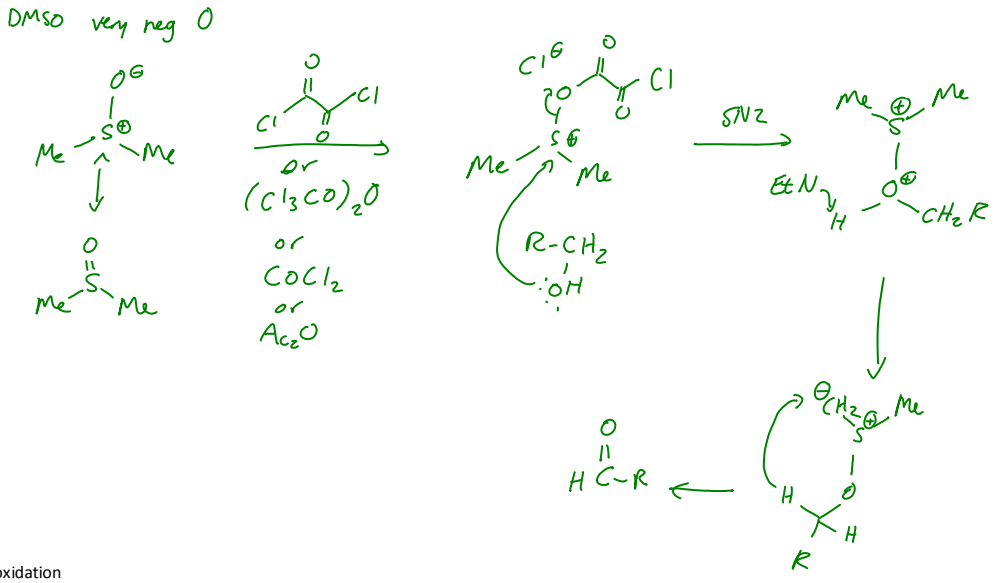
B) Mn^{+4} => only allylic/benzylic/propargylic



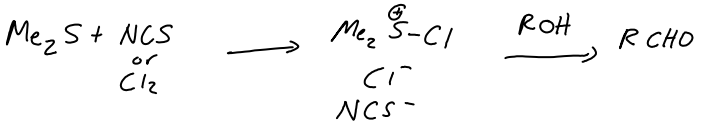
C) DMSO-based

i) Swern (mild!)

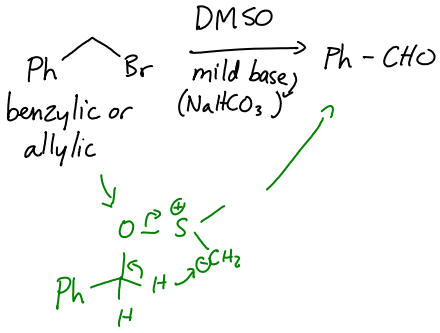




ii) Corey-Kim oxidation

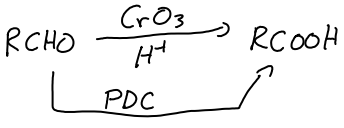


iii) kornblum oxidation

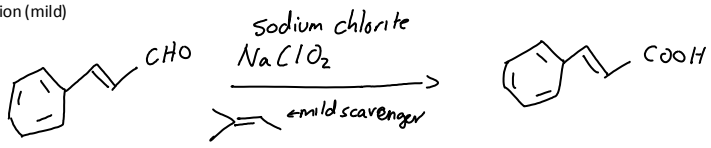


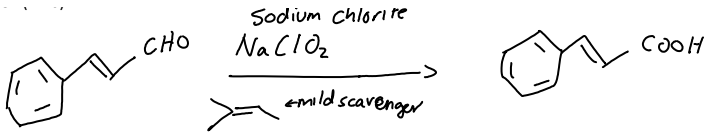
2) Aldehydes

A) Cr^{+6}



B) Chlorite oxidation (mild)




CHO
Sodium chlorite
$NaClO_2$
mild scavenger
COOH

3) Ketones


R
R'
MCPBA
R
R'-O

Notes 10/09

Thursday, October 09, 2008
11:01 AM

Notes 1009

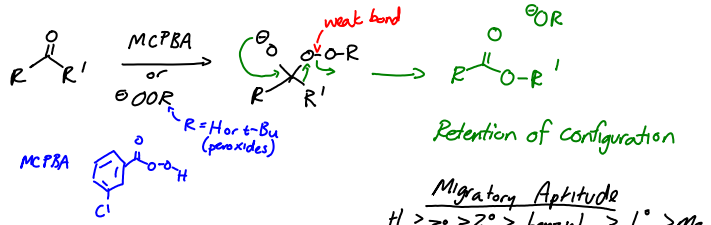
Audio recording started: 11:01 AM Thursday, October 09, 2008

1st lab report
Due thurs 10/16/08
Homework due tues 10/14

Oxidations

3) Ketones

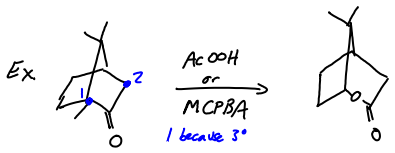
A) Baeyer-Villiger

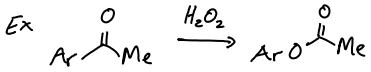


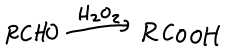
Retention of configuration

Migratory Aptitude

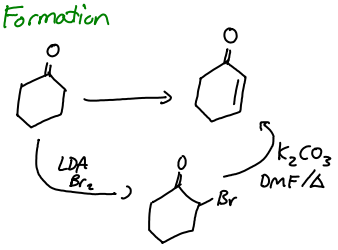
H > 3° > 2° > benzyl > 1° > Me
Allyl
phenyl

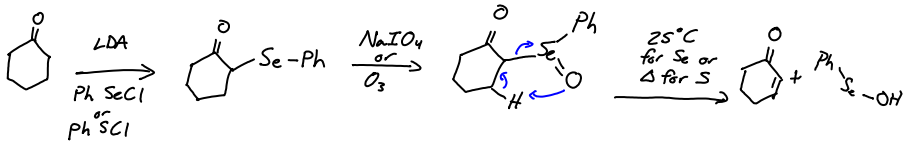






B) Enone Formation





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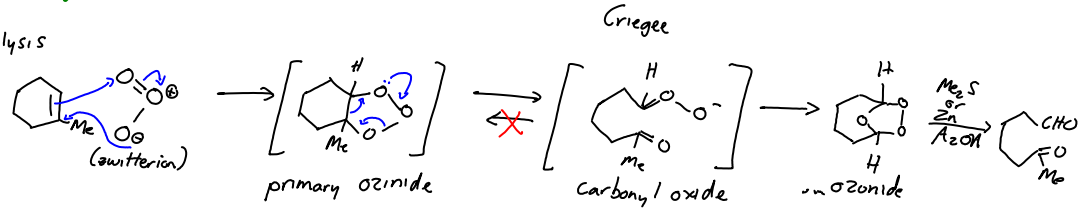
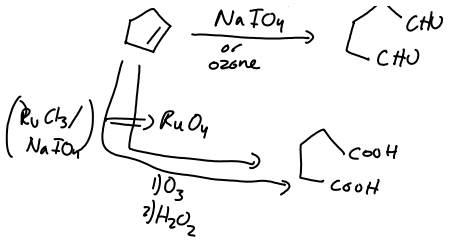
4) Alkenes

A) Oxidative Cleavage

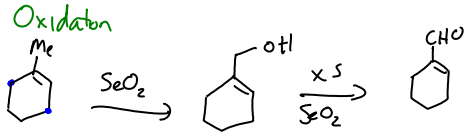
Ozonolysis



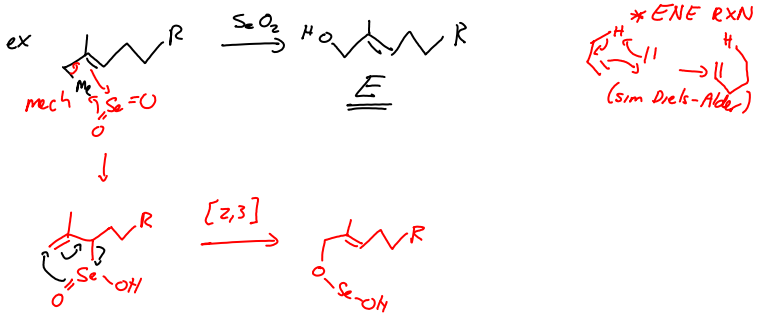
cat OsO_4

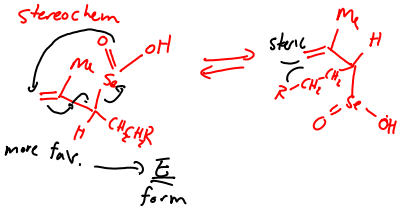


B) Allylic Oxidation



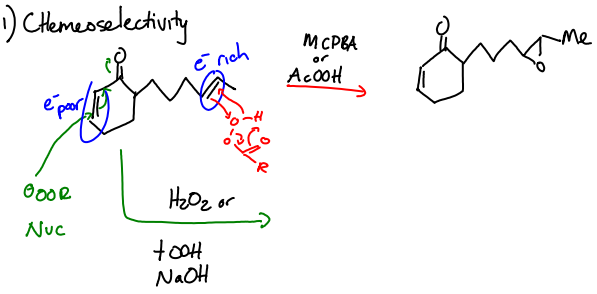
1) monosub end of ~~ oxidized
2) $CH_3 > CH_2 > CH$



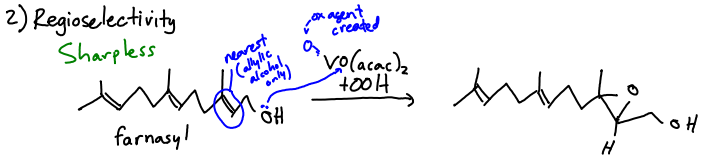


C) Epoxidation - Nuc, Elect

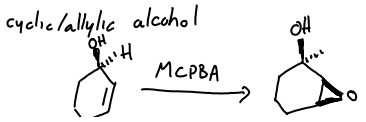
1) Chemoselectivity

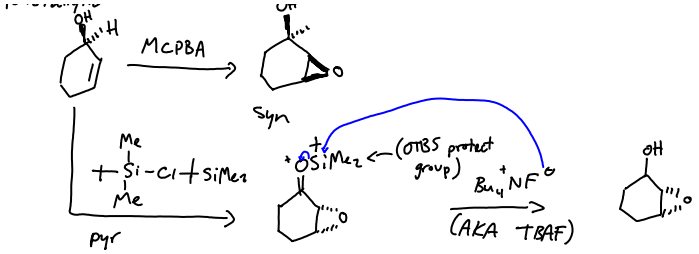


2) Regioselectivity



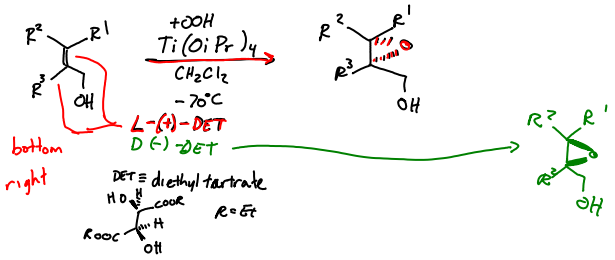
3) Stereoselectivity



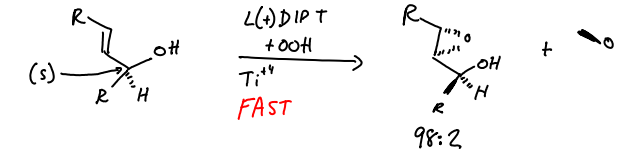


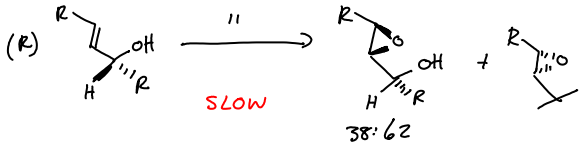
4) Enantioselectivity

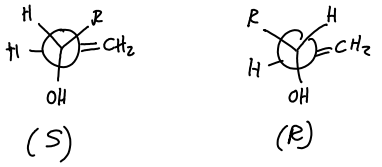
Kishi Epox *will be on tests

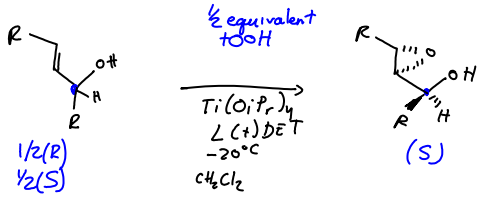


Ex



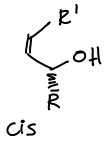






KINETIC RESOLUTION

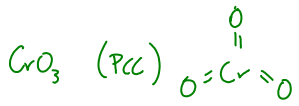
sharpless fails kinetic res



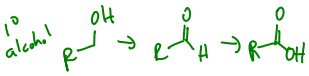
Homework due Tues
Report due Thurs

discussion

Tuesday, October 14, 2008
10:00 AM

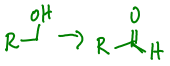


harsh
Jones CrO_3, H_2SO_4

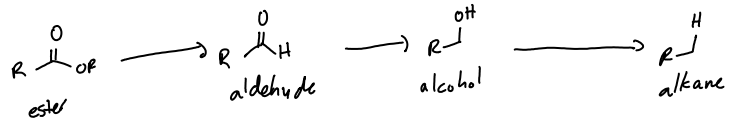


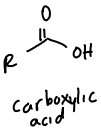
2° alcohol → ketone

mild
Collins reagent



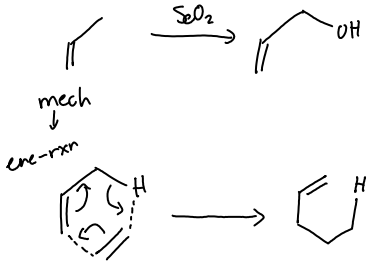
2° alcohol → ketone

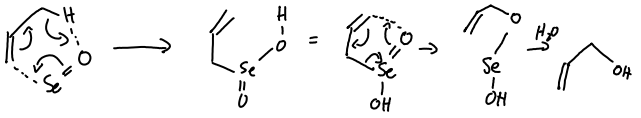




ester → aldehyde (DIBAL, low temp)
aldehyde → alcohol (lots: $NaBH_4$ if stronger)
alcohol → alkane (silane acid)
ester → alcohol (LiAlH$_4$)
carboxylic acid → alcohol (borane BH_3)
aldehyde → alkane (reductive deoxygenation, mild ≡ H_2N-NHTs, $NaCNBH_3$ (tosyl hydrazine)
harsh ≡ Wolff-Kishner NH_2NH_2, KOH, Δ & Clemmensen Hg/Zn HCl

alcohol → aldehyde "mild" PCC or Collin's or Swern
alcohol → ester/acid Jones = CrO_3, H_2SO_4
alkane → alcohol // SeO_2 allylic oxidation





Notes 10/14

Tuesday, October 14, 2008
10:58 AM

Notes 1014

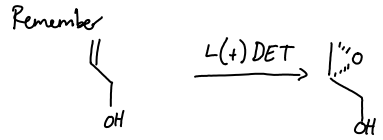
Audio recording started: 11:00 AM Tuesday, October 14, 2008

Oxidations

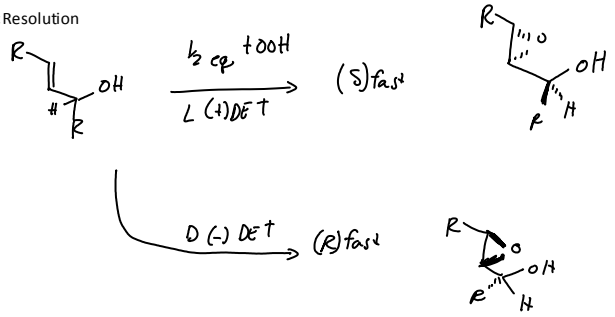
Sharpless (allyic alcohols only) (guaranteed on exam)

1. Asymmetric epoxidation

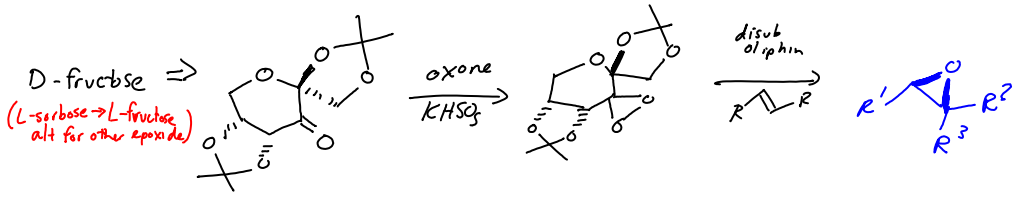
   Draw alcohol bottom and and tartrate comes from bottom

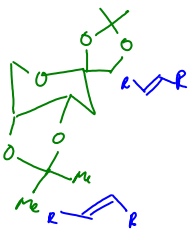


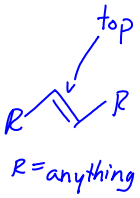
2. Kinetic Resolution

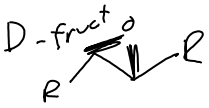


Y. Shi-Col

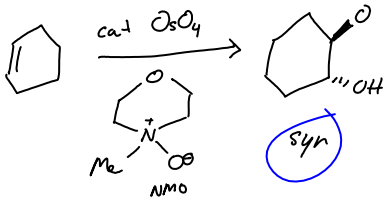


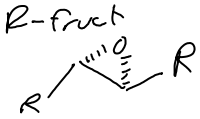






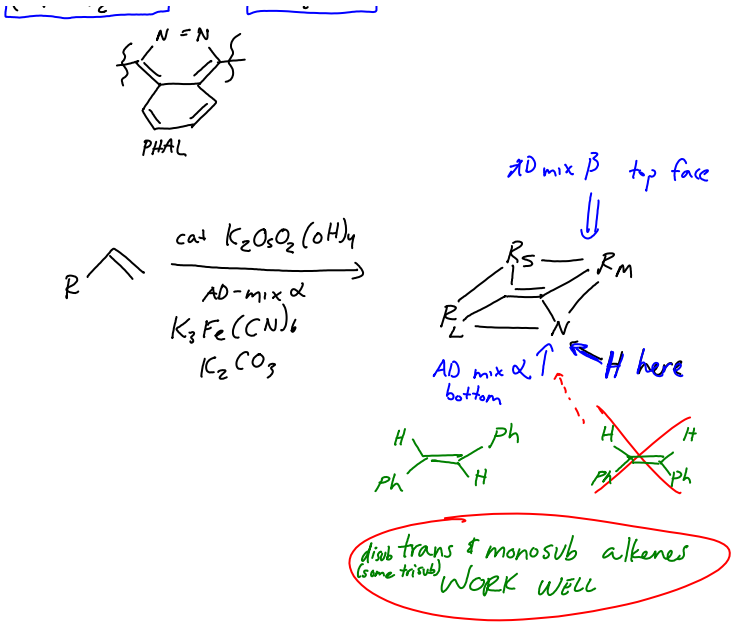
Dihydroxylation



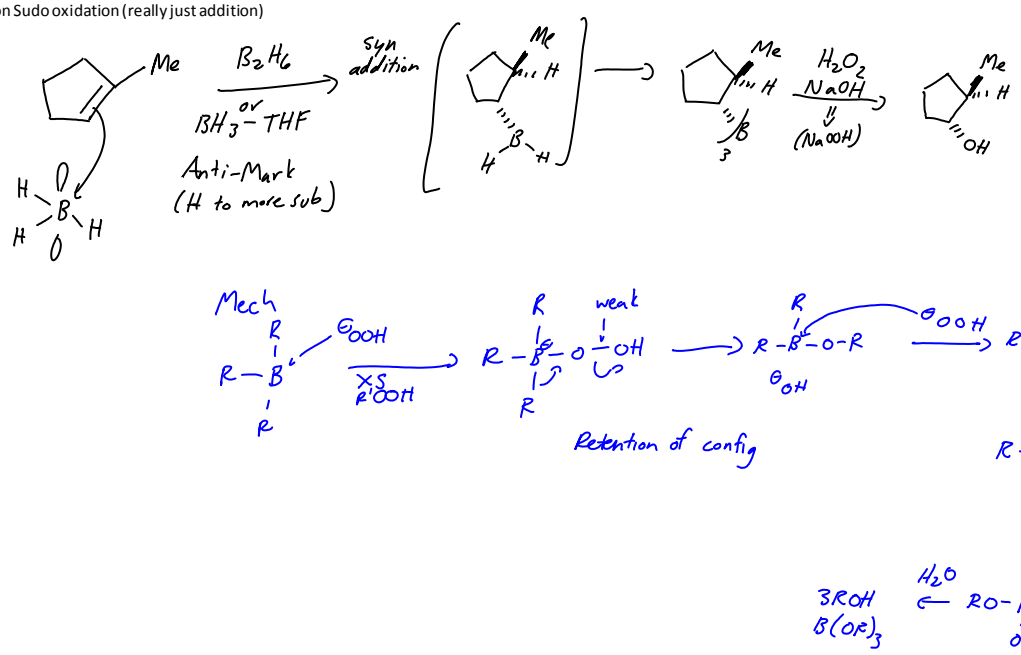


anti epoxidation of acid

Sharpless AD, AD mix B (DHQD)2-PHAL or AD mix α (DHQ)2-PHAL — must on give test — neumonic

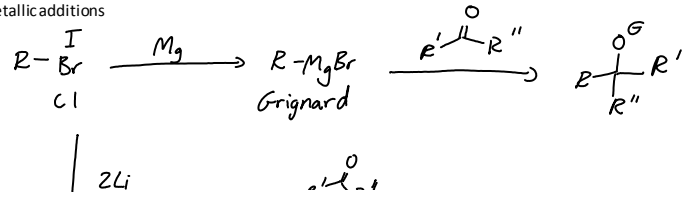


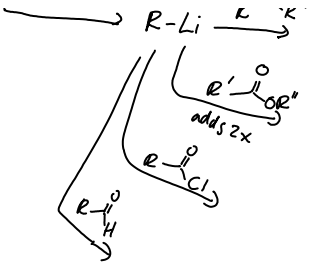
Hydroboration Sudo oxidation (really just addition)



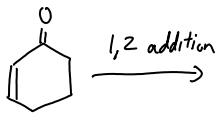
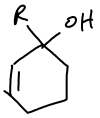
C-C bond formation

1. Organometallic additions





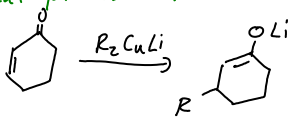
enones → 1,2 addition

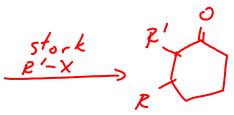
RLi or RMgX +  1,2 addition 

Gilman → lithium dialkyl cuprate

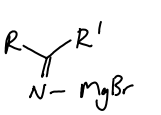
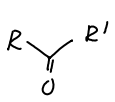
$2\,RLi \xrightarrow{CuI} R_2CuLi$

Radical process → 1,4 addition

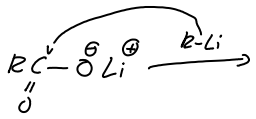
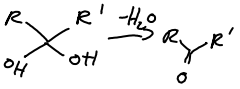




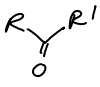
How to make KETONES?

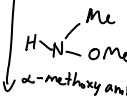
a) $RCN \xrightarrow{R'MgBr}$  $\xrightarrow{H_3O^+}$ 

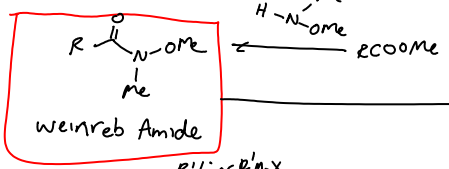
* C≡N in H_2O hydrolize

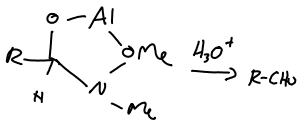
b) $RCOOH + 2R'Li \longrightarrow$  $\xrightarrow{H_3O^+}$ 

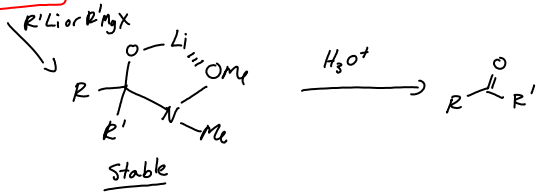
NaH → $R\text{-}COO^{\ominus}Na^{\oplus}$ $\xrightarrow{1\,R'Li}$ ~~$R'MgX$~~ doesn't work

c) $RCOOH \xrightarrow{SOCl_2}$  $\xrightarrow{R'_2CuLi}$  $\xrightarrow{R_2CuLi}$ N.R.

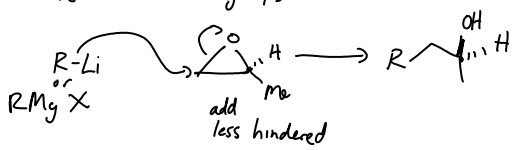


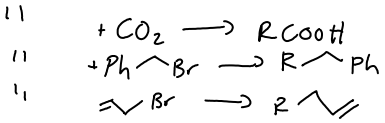


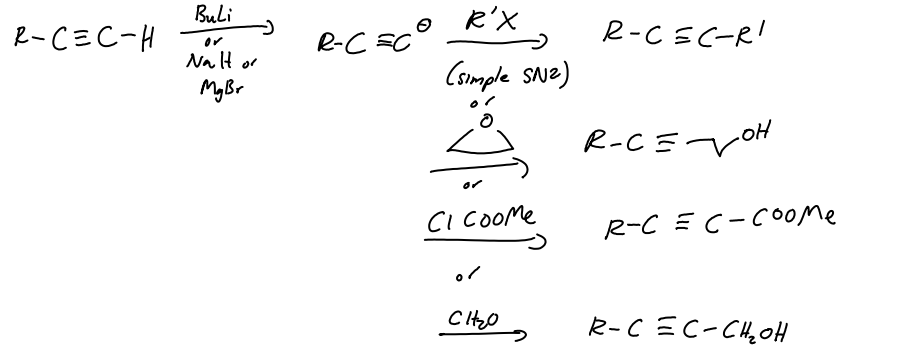


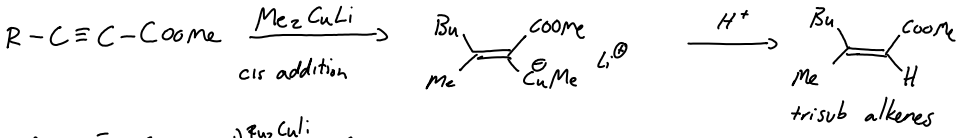


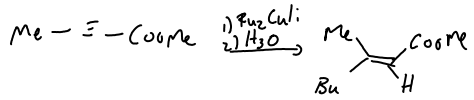
2) Addition to other groups



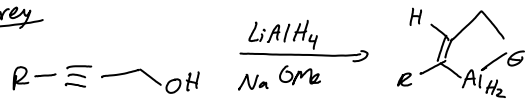


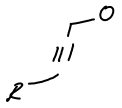






E.J Corey





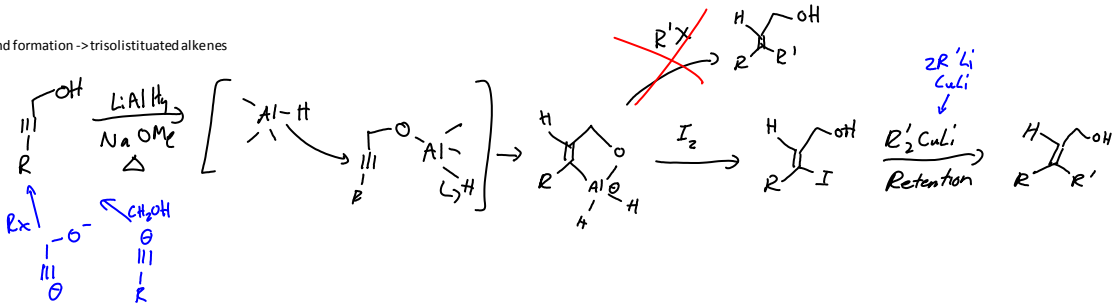
Notes 10/16

Thursday, October 16, 2008
11:05 AM

Notes 1016

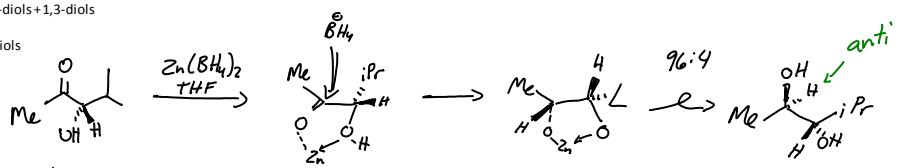
Audio recording started: 11:05 AM Thursday, October 16, 2008

C-C Bond formation -> trisolistituated alkenes

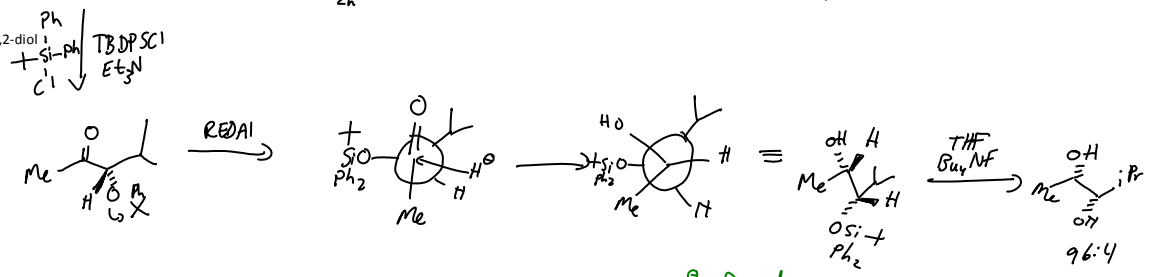


Reduction -> 1,2-diols + 1,3-diols

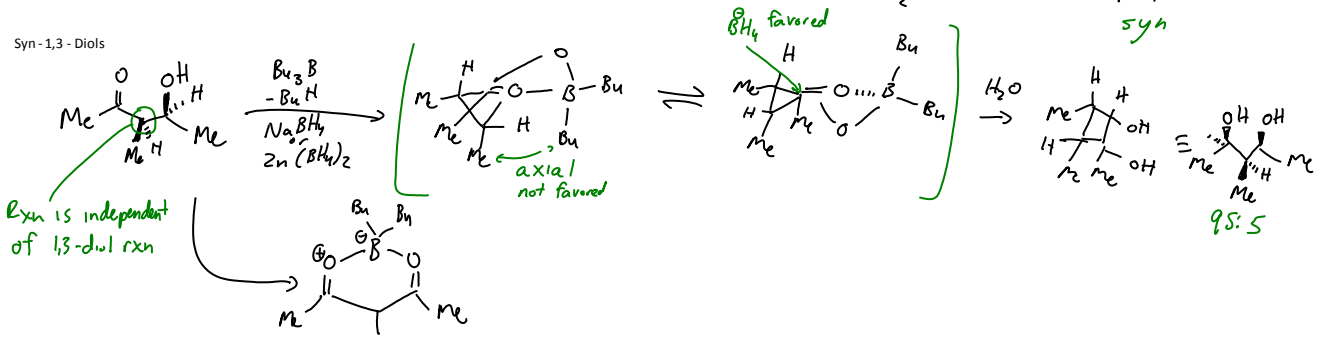
ANTI 1,2-diols



Syn 1,2-diol

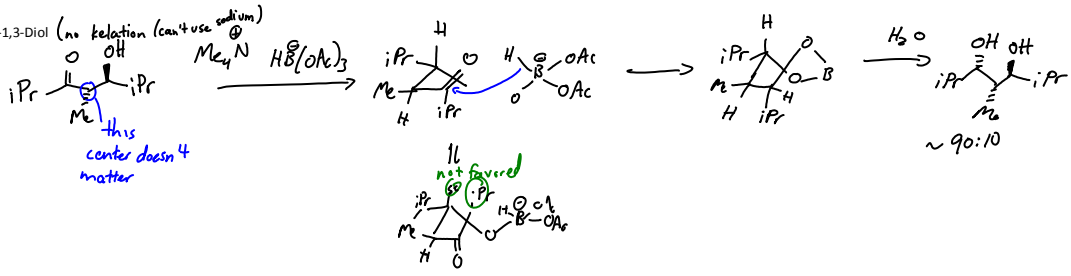


Syn - 1,3 - Diols

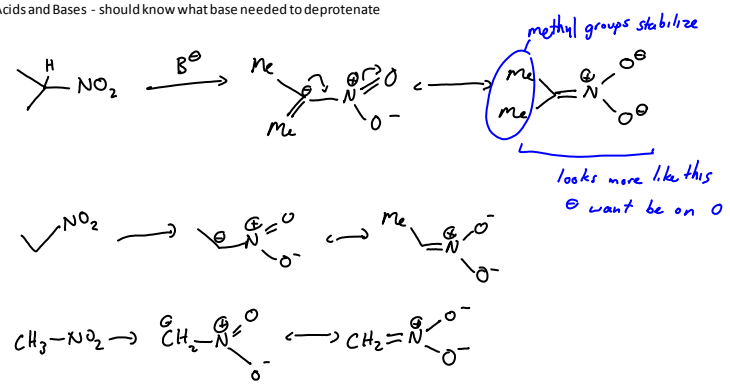


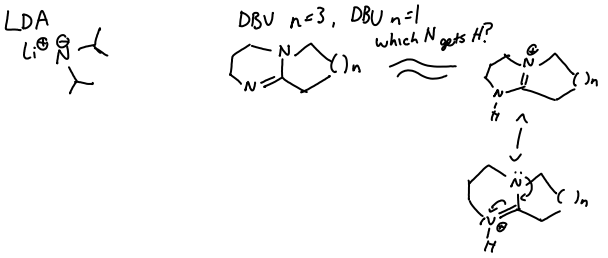
2) BH_3 / $(Ph_3P)_3RhCl$

Anti-1,3-Diol (no kelation (can't use sodium) Me_4N $HB(OAc)_3$



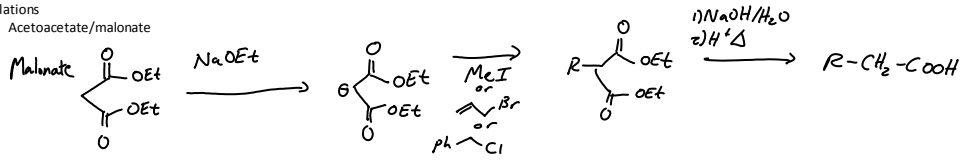
HANDOUT Organic Acids and Bases - should know what base needed to deprotenate

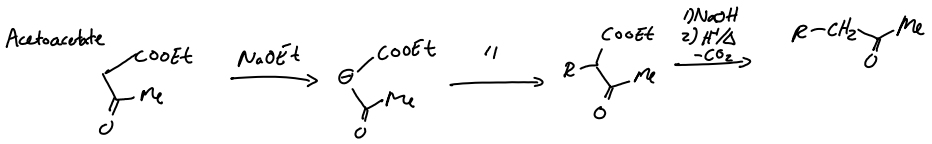


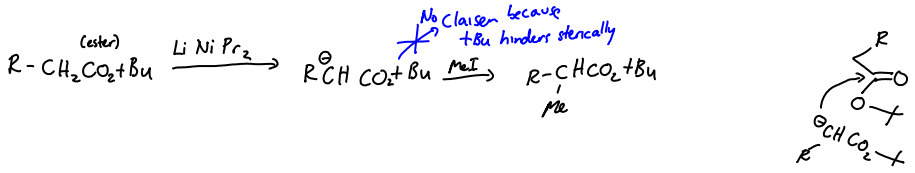


Alkylations

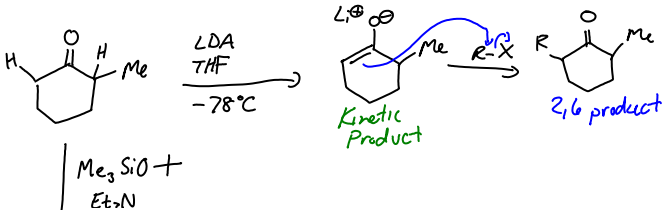
Acetoacetate/malonate

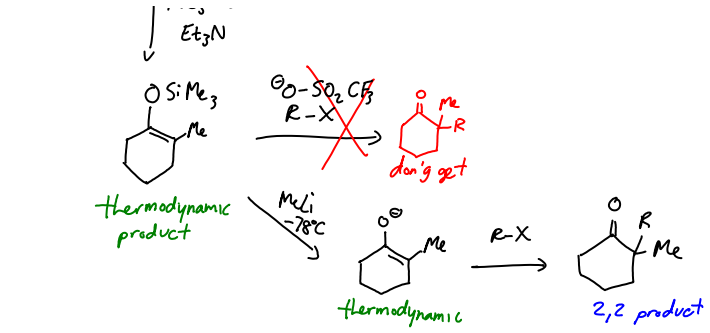


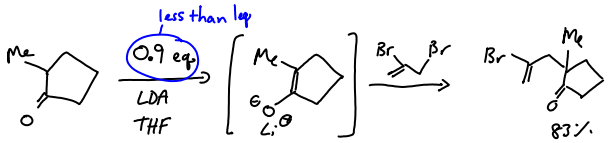




Regiochem -> Kinetic vs Thermodynamic




Et3N
OSiMe3
Me
Thermodynamic product
R-X
don't get
MeLi
-78°C
Thermodynamic
R-X
2,2 product


less than 1eq
0.9 eq.
LDA
THF
Br
Br
Br
83%

Chemistry 144
M. E. Jung

Oxidations

I) Metal-Based

1) Cr
2) Mn
3) DMSO
4) Pb
5) Hg

II) Peracids/Peroxides

1) MCPBA
2) tBuOOH

III) Other Oxidants

1) OsO_4
2) $NaIO_4$
3) SeO_2
4) $NaClO_2$
5) RuO_4/TPAP
6) Dess-Martin Periodinane
7) H_2O_2
8) O_3
9) Wacker
10) Dioxirane/Oxaziridine

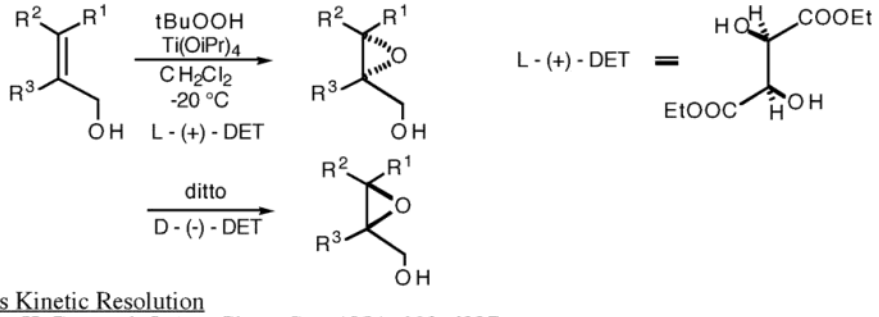
Handout: Acyclic Enantiocontrol pt 2

Monday, October 20, 2008
3:46 PM

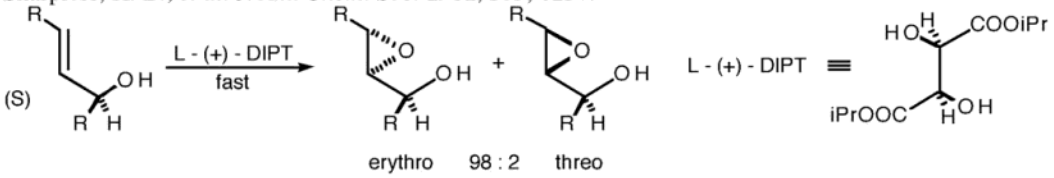
Chemistry 144
M. E. Jung
Organic Synthesis

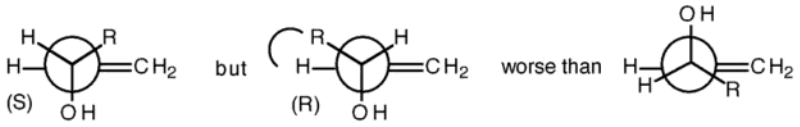
Acyclic Enantiocontrol

Sharpless Asymmetric Epoxidation and Kinetic Resolution
Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974; Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464.

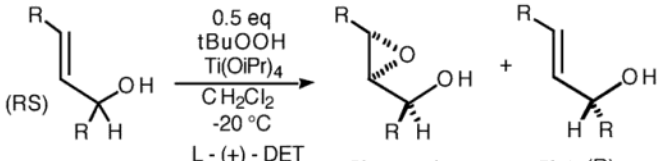


Sharpless Kinetic Resolution
Sharpless, K. B.; *et al. J. Am. Chem. Soc.* **1981**, *103*, 6237.

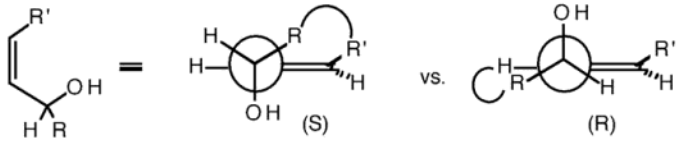




Therefore, when you epoxidize a racemic mixture of the secondary allylic alcohol at -20 °C using only 0.5 equivalent of tBuOOH, all of the (S) enantiomer is epoxidized to give the erythro epoxy alcohol while the (R) enantiomer remains unreacted. These two compounds can be easily separated by simple chromatography. Therefore in this process you have kinetically resolved the racemic allylic alcohol (resolved by a difference in the rates of reaction of the enantiomers)!



but cis-substituted has steric problems and gives low ee's in kinetic resolution



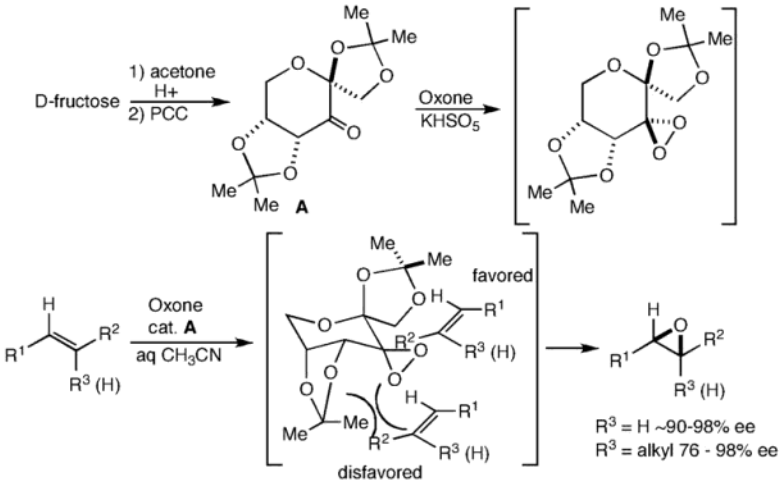
Chemistry 144

M. E. Jung
Organic Synthesis

Acyclic Enantiocontrol

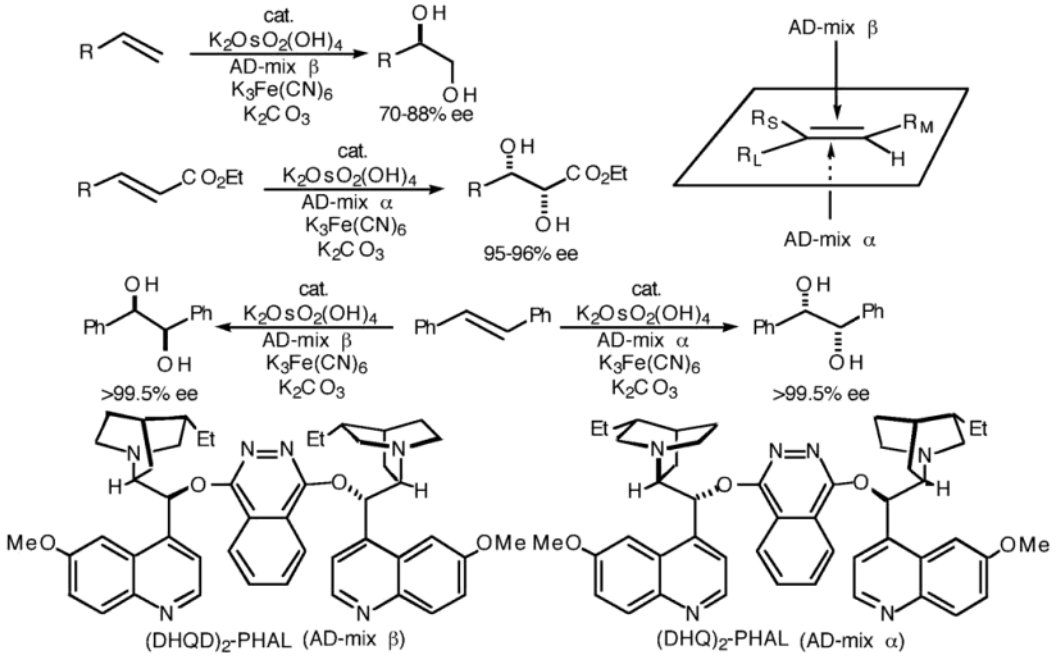
Shi Asymmetric Epoxidation

Shi, Y.; *et al. J. Am. Chem. Soc.* **1997**, *119*, 11224; **2000**, *122*, 11551; *Org. Lett.* **2001**, *3*, 1929; *Synthesis* **2000**, 1979 (Review).



Sharpless Asymmetric Dihydroxylation

Sharpless, K. B.; *et al. J. Org. Chem.* **1992**, *57*, 2768; **1993**, *58*, 844. Corey, E. J. *et al. J. Am. Chem. Soc.* **1993**, *115*, 3828.



Notes 10/21

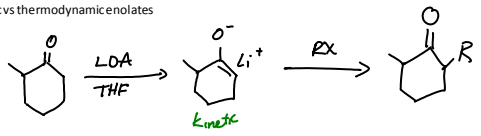
Tuesday, October 21, 2008
11:04 AM

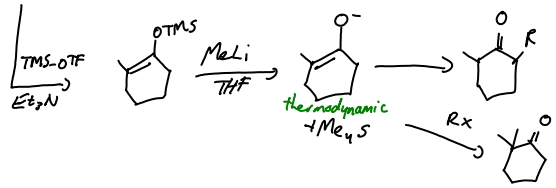
Notes 10...

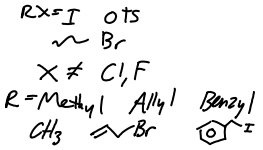
Audio recording started: 11:05 AM Tuesday, October 21, 2008

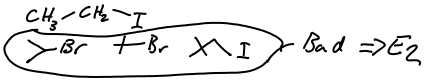
Carbon-carbon bond formation

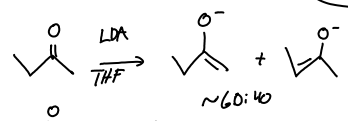
Kinetic vs thermodynamic enolates

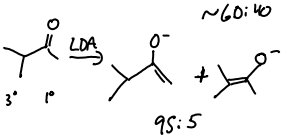


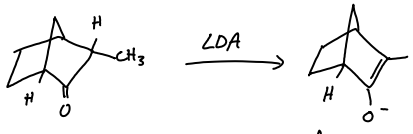


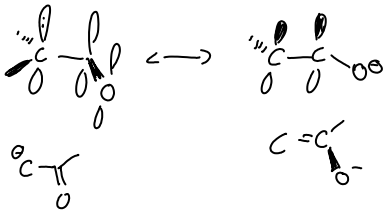


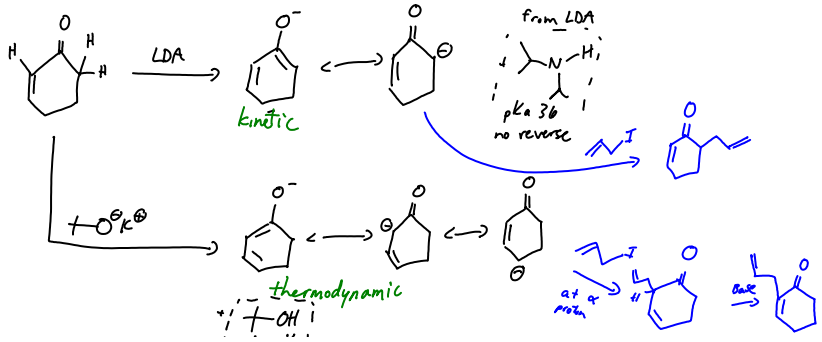








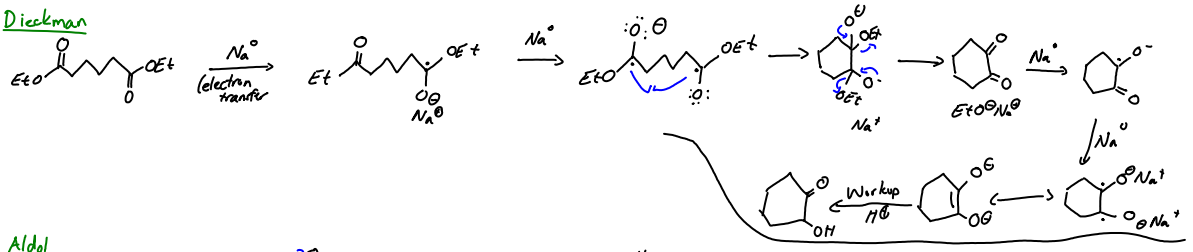




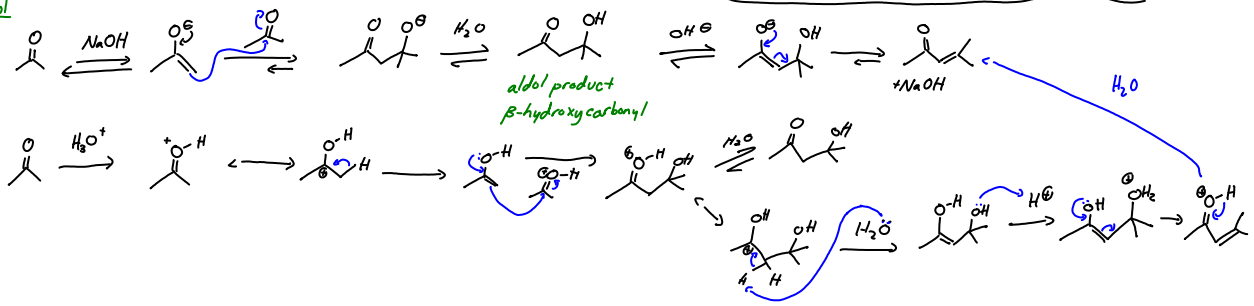
pKa ~ 16
reverse rxn

C-C bond formation - Condensations (see handout)

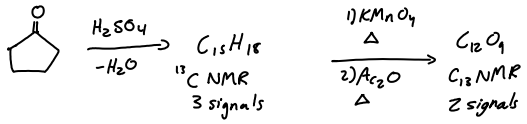
Dieckman



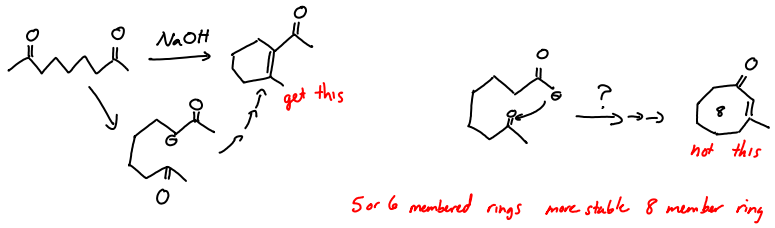
Aldol



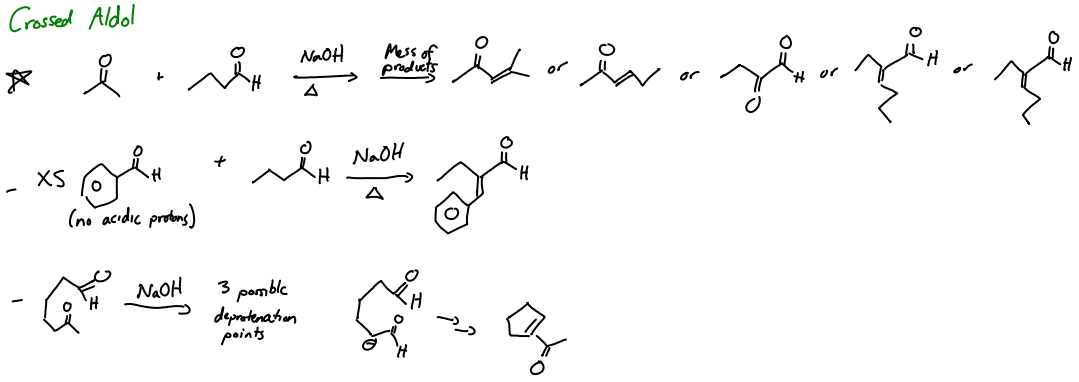
Fun Problem



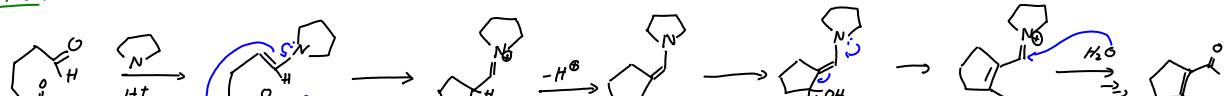
Intramolecular aldol



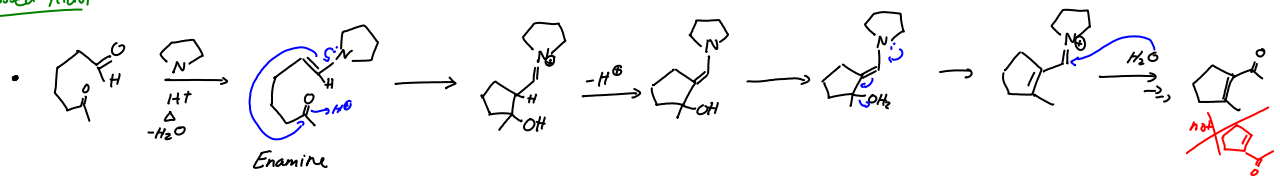
Crossed Aldol



Crossed Aldol



Crossed Aldol



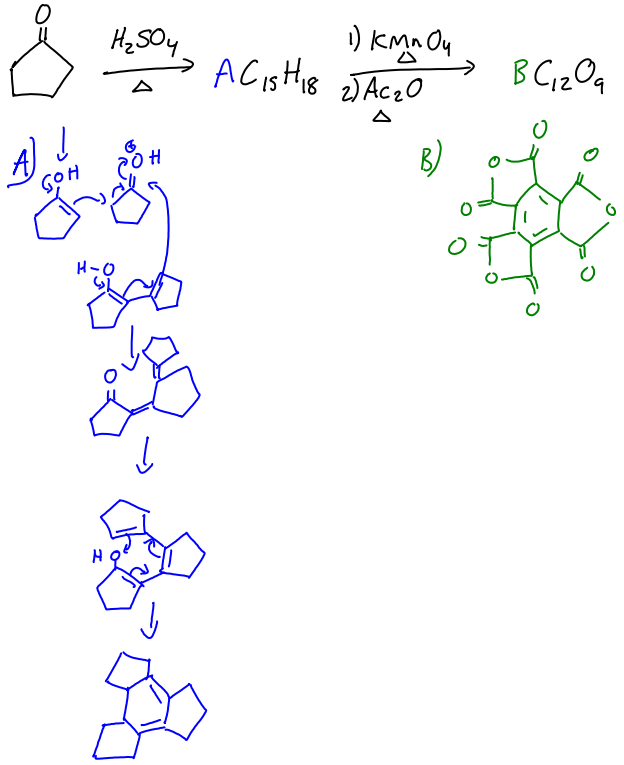
Notes 10/23

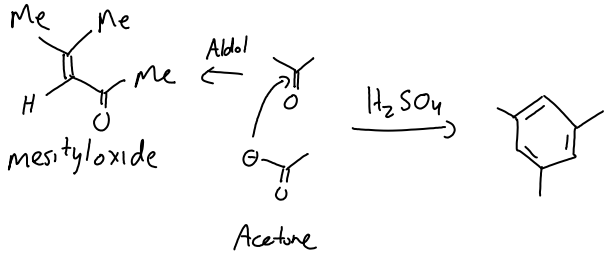
Thursday, October 23, 2008
10:55 AM

Notes 1023

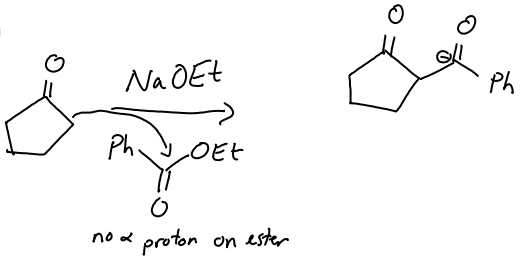
For Fun

Audio recording started: 10:56 AM Thursday, October 23, 2008

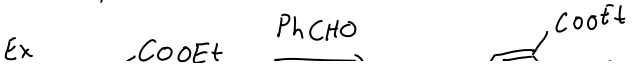


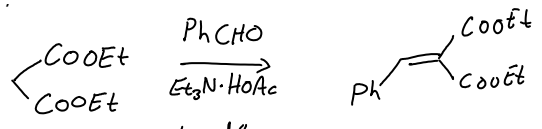


Crossed Claisen



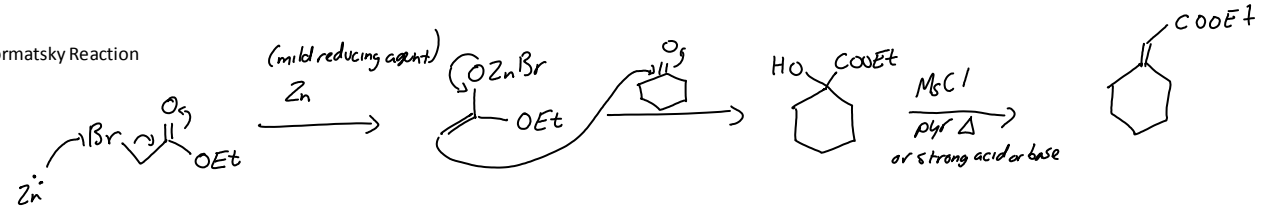
Knoevenagel Condensation
Has diactivated methylene



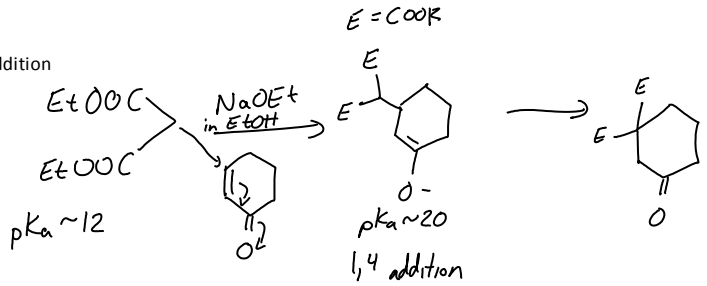
Ex 

only acid/base catalyzed
very mild, works because diethyl malonate has pKa ~12 which is doubly activated

Reformatsky Reaction

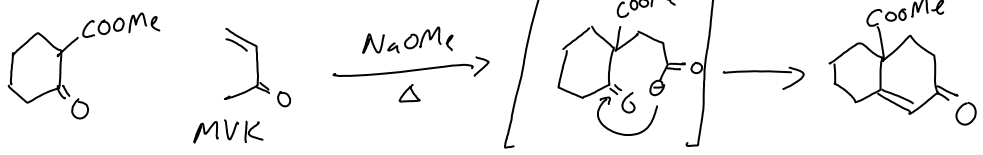


Michael Addition

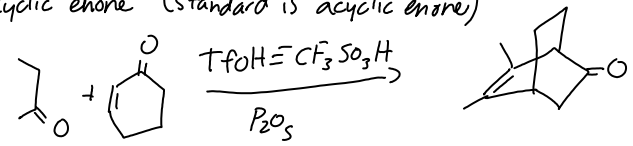


π C=C ~ 60kcal
C-C 80 kcal
this energy drives rxn even though pKa is higher (less favorable)

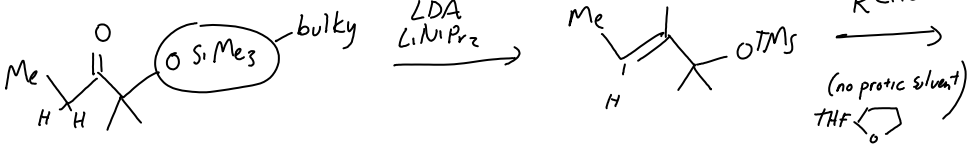
Robinson Amulation (michael-aldol reaction)



Jung Bridged Robinson amulation
1) strong acid
2) cyclic enone (standard is acyclic enone)

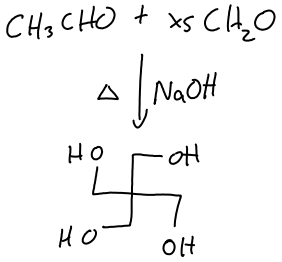


Aldol Reactions (stereochemistry of aldols) See handout



See handouts

For Fun



Review Discussion

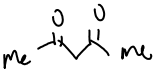
Tuesday, October 28, 2008
9:36 AM

Ranking acidity

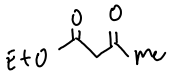
Lower pka, the more acidic.

pKa

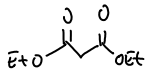
Most acidic



9

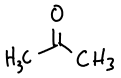


11

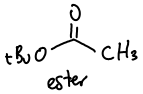


13

least acidic

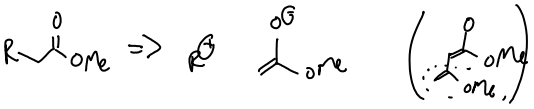


ketone
20

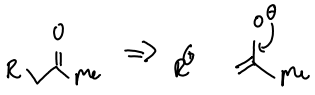


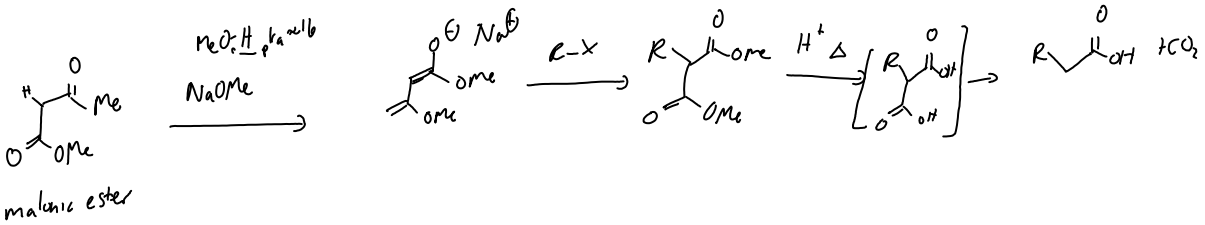
ester
25

CH_4 40



or





Notes 10/28

Tuesday, October 28, 2008
11:00 AM

Notes 1028

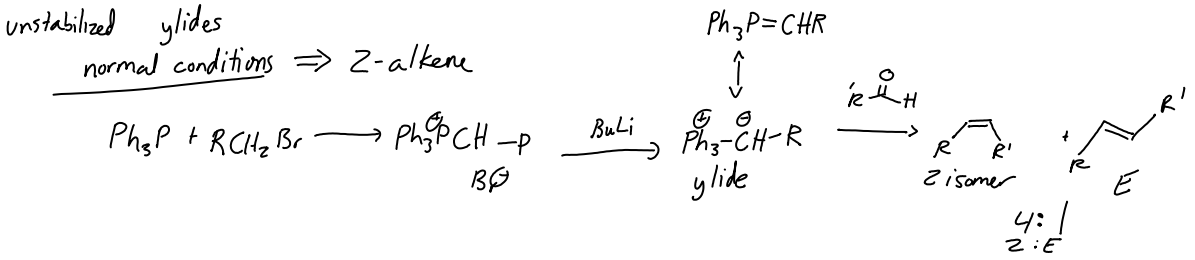
Audio recording started: 11:00 AM Tuesday, October 28, 2008

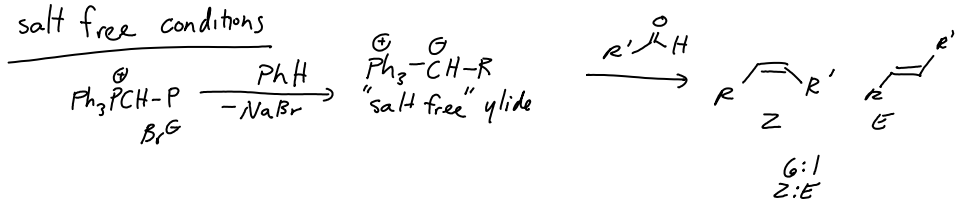
1) Hour exam tues 11/4
2) Practice exam posted on Voh
3) Today - 2nd homework due thurs
4) Merlick subs on thurs
5) 2nd lab report due mon 11/10
6) Review mon 11/3 2pm in 3515 mol sci

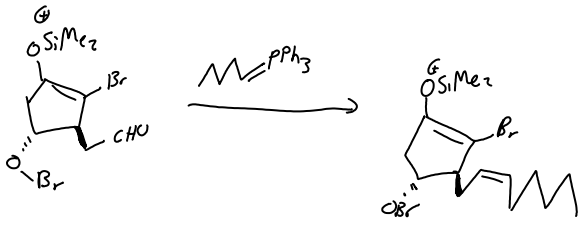
Evans see handoutevans and corey

See handout jung non-aldol aldol process

Olefination
1) Wittig + Wittig-like







Zimmerman-Traxler Aldol Condensation

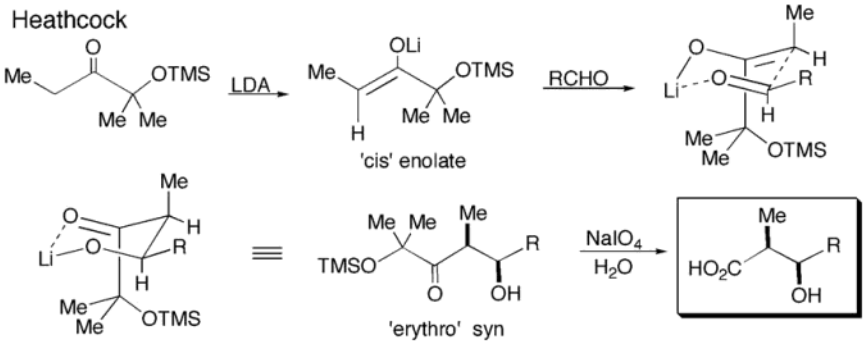
Wednesday, October 29, 2008
6:41 PM

Chemistry 144
Organic Synthesis
M. E. Jung

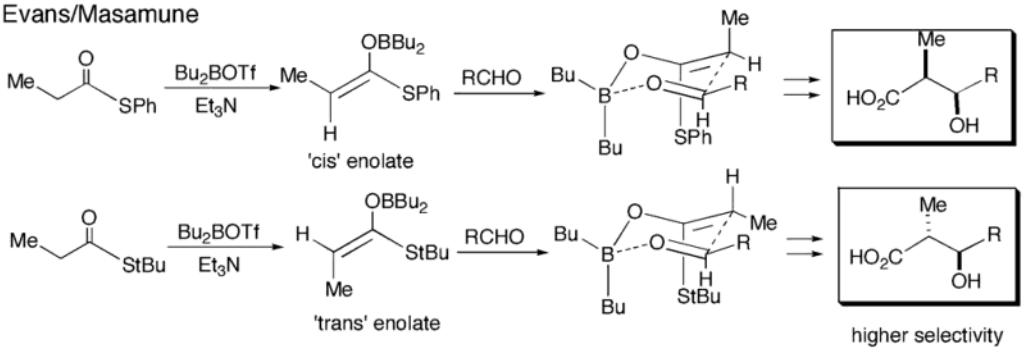
Zimmerman-Traxler Transition State for Aldol Condensation
Heathcock, C. H. *Science* **1981**, *214*, 395.

Relative Stereochemistry

Heathcock

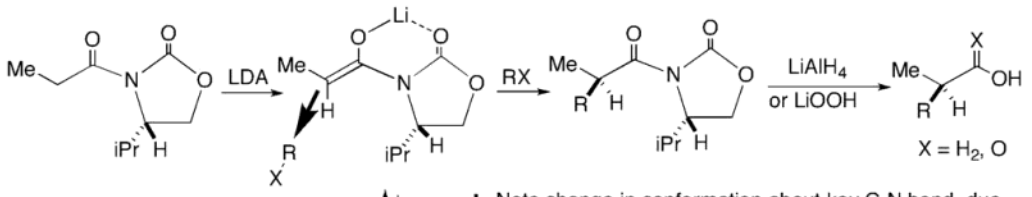


Evans/Masamune

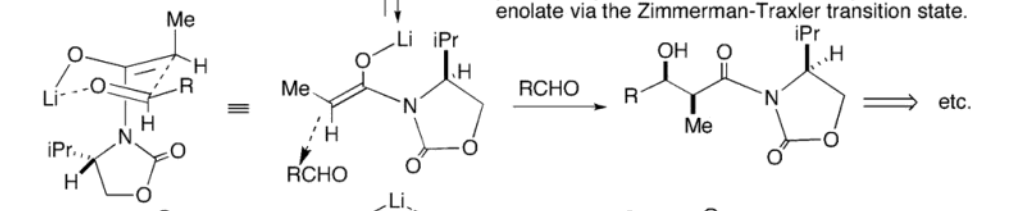


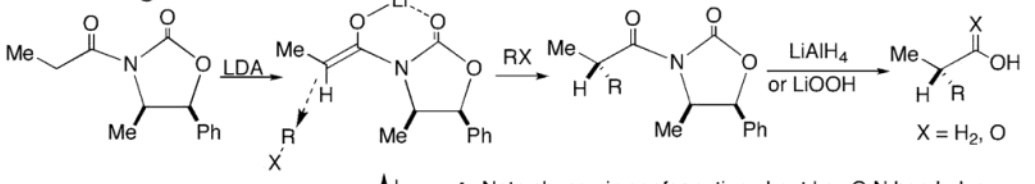
Chemistry 144
Organic Synthesis
M. E. Jung

Evans Chiral *N*-Acyl Oxazolidinone Methodology
Aldrichimica Acta **1982**, *15*, 23.

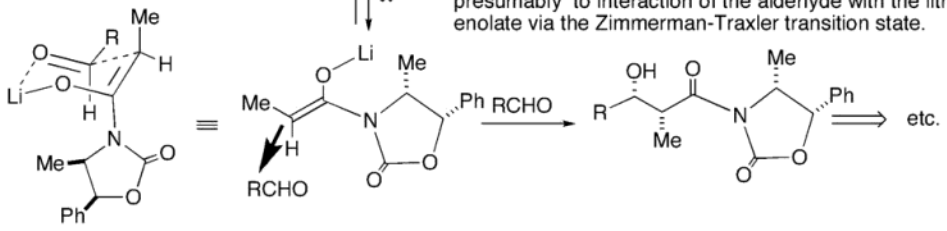


* Note change in conformation about key C-N bond, due presumably to interaction of the aldehyde with the lithium enolate via the Zimmerman-Traxler transition state.

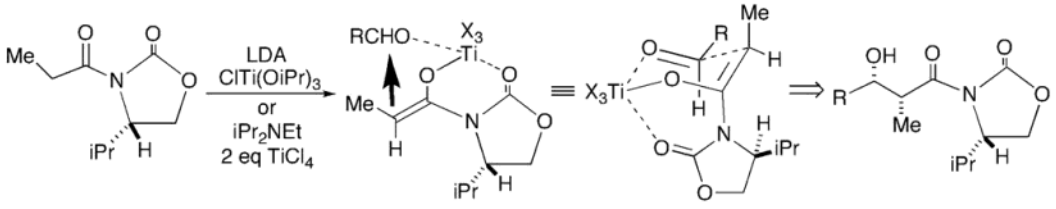




* Note change in conformation about key C-N bond, due presumably to interaction of the aldehyde with the lithium enolate via the Zimmerman-Traxler transition state.



However, Thornton and Crimmins both reported that then use of titanium salts reverses the 'normal' facial selectivity for the aldol and provides the opposite diastereomeric *syn* isomers, presumably via the more complexed chelated titanium transition state shown [*Tet. Letts.* **1986**, *27*, 897; *JACS*, **1997**, *119*, 7883].

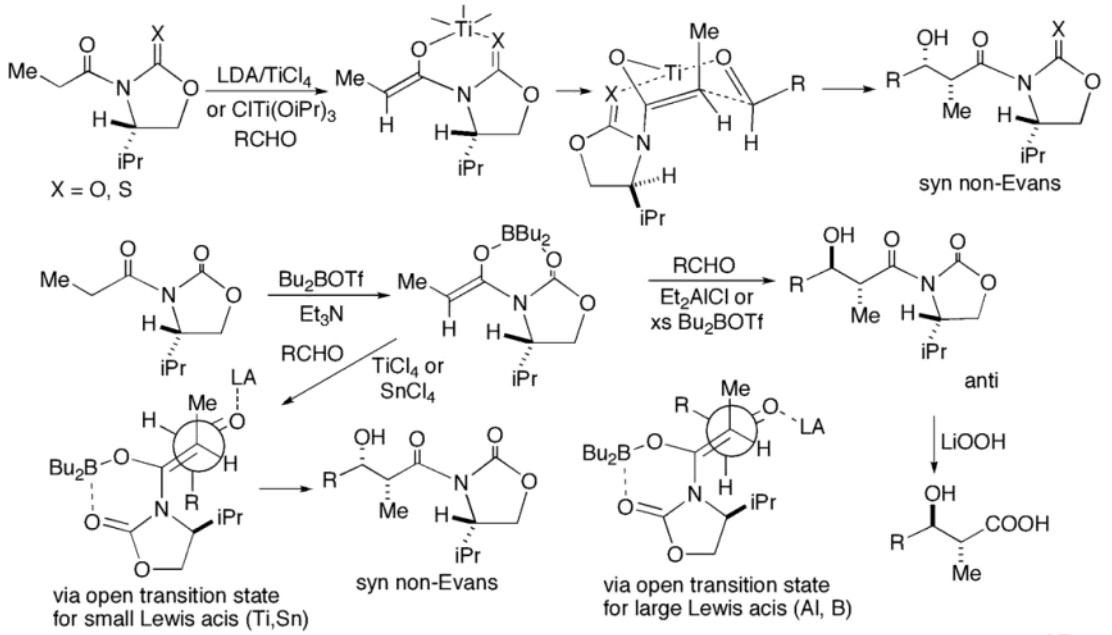


Crimmins/Thorton and Heathcock variations of Evans

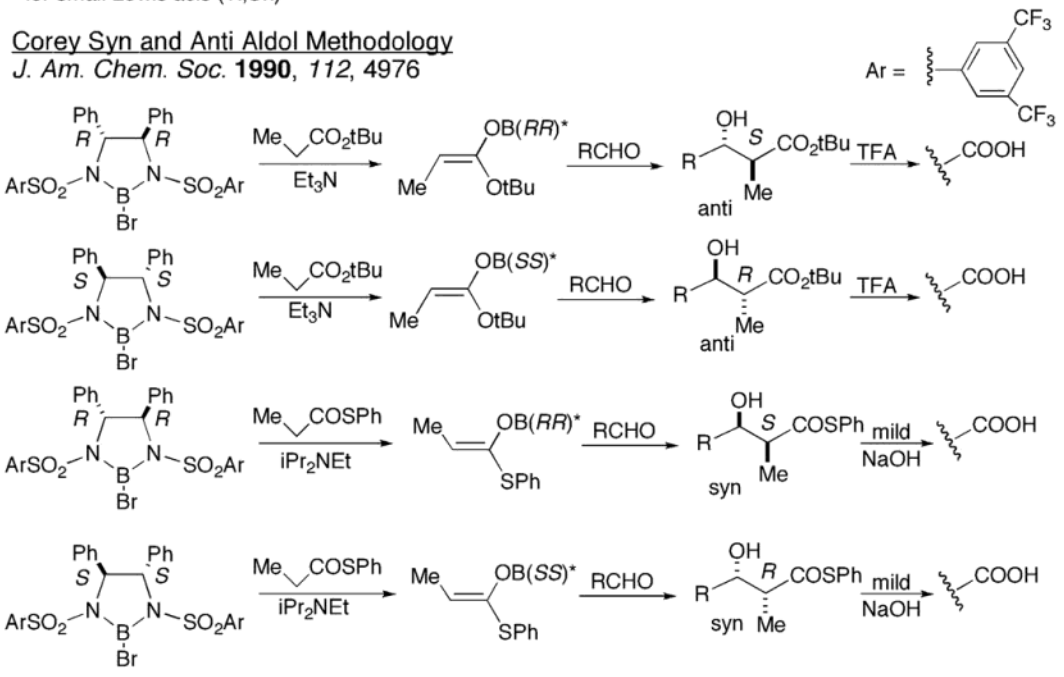
Wednesday, October 29, 2008
6:41 PM

Chemistry 144
Organic Synthesis
M. E. Jung

Crimmins/Thornton and Heathcock Variations of Evans Chiral *N*-Acyl Oxazolidinone Methodology
Tet. Lett. **1986**, *27*, 897; *JACS*, **1997**, *119*, 7883; *Synlett* **1995**, 1213; *JOC* **1991**, *56*, 5747



Corey Syn and Anti Aldol Methodology
J. Am. Chem. Soc. **1990**, *112*, 4976



Jung non-Aldol Aldol Process

Wednesday, October 29, 2008
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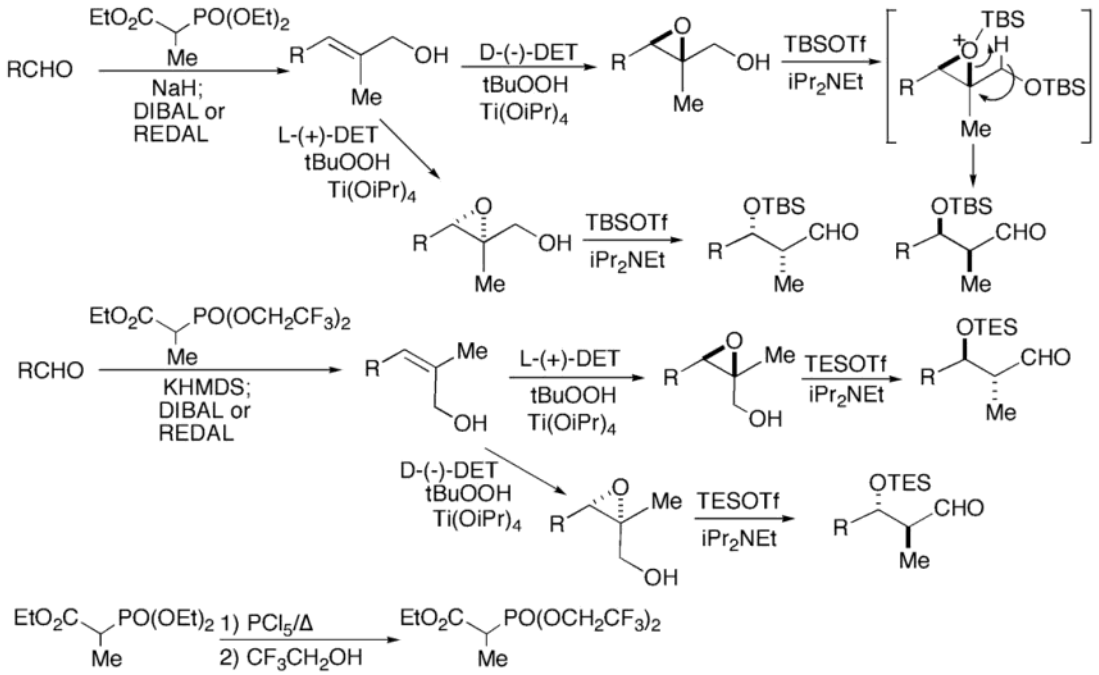
Chemistry 144
Organic Synthesis
M. E. Jung

Jung non-Aldol Aldol Process
J. Am. Chem. Soc. **1993**, *115*, 12208



TESOTf = $Et_3Si\text{-}OSO_2CF_3$

TBSOTf = $tBuMe_2Si\text{-}OSO_2CF_3$

Chemistry 144
Organic Synthesis
M. E. Jung

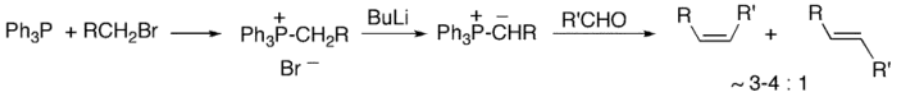
Olefination Reactions - Stereoselectivity

1) Wittig and Wittig-Like reactions

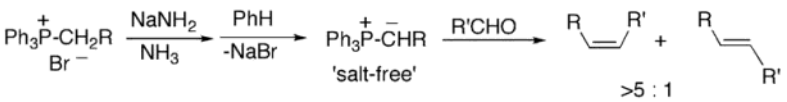
Review: *Topics Stereochem.* **1994**, *21*, 1

1) Unstabilized Ylides

Normal Conditions give Z Disubsituted Alkenes

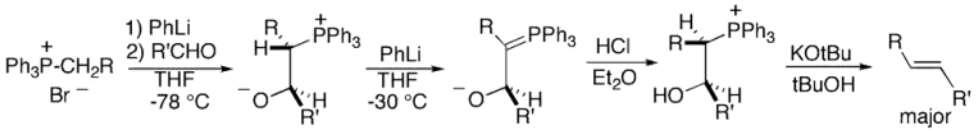


Better Selectivity of Z Disubsituted Alkenes withSalt-Free Conditions (*JACS* **1982**, *104*, 5821)

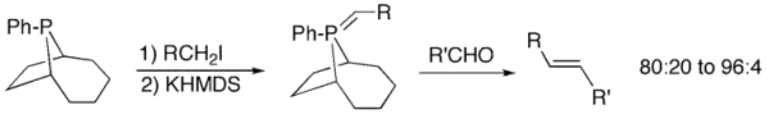


For *E*-Selective Wittigs:

a) Schlosser Modification (*Annalen* **1967**, *708*, 1; *JACS* **1970**, *92*, 226)

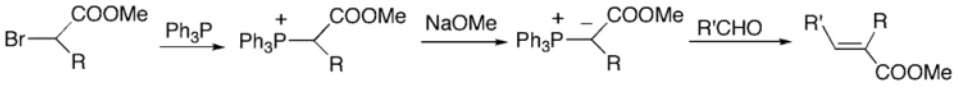


b) Cyclic Phosphines (Vedejs *J. Org. Chem.* **1993**, *58*, 1985, 6509)

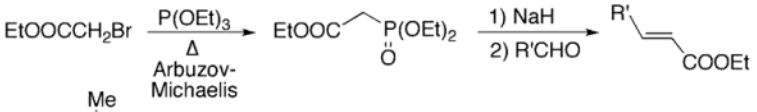


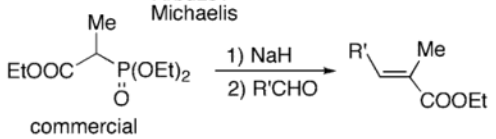
2) Stabilized Ylides

Normal Conditions give E Di- and Trisubsituted Alkenes



Wadsworth-Horner-Emmons



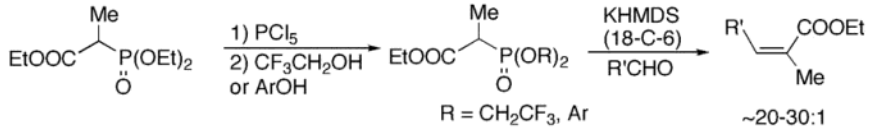


Chemistry 144
Organic Synthesis
M. E. Jung

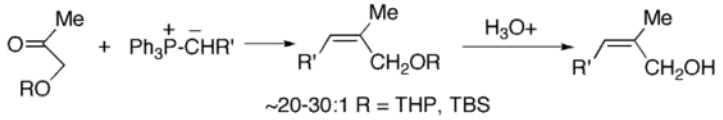
Olefination Reactions - Stereoselectivity

For Z-Selective Wittigs

a) Still/Ando Process (*Tet. Lett.* **1983**, 4405; *JOC* **2000**, *65*, 4745)

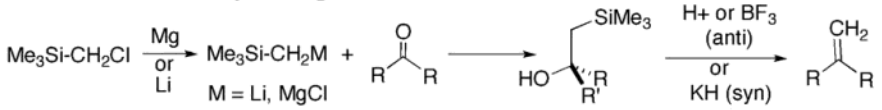


b) "Backwards" Wittig (*JOC* **1980**, *45*, 4260)

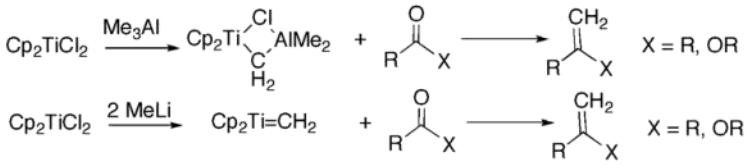


2) Other Olefinations

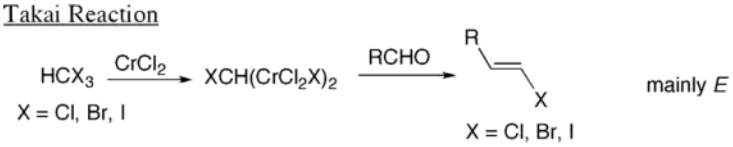
1) Peterson Reaction (Silyl-Wittig)



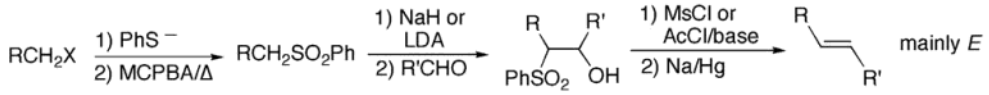
2) Tebbe/Petasis Olefination



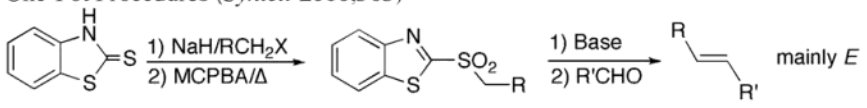
3) Takai Reaction



4) Julia Olefination



One-Pot Procedures (*Synlett* **2000**,365)



Practice Midterm Exam

Wednesday, October 29, 2008
6:44 PM

Mcba = electrophilic

Peroxide = nucleophilic

Chemistry 144

Fall 2007

Hour Exam

November 6, 2007

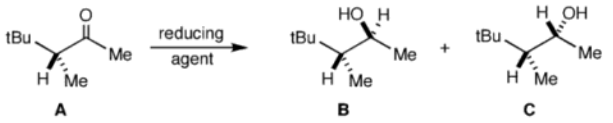
M. E. Jung

Name_____

Problem	Points	Score
1	10	
2	36	
3	36	
4	18	
Total	100	

Note: Place all of your answers on this exam. Scratch paper will be provided, but must not be used for final answers. Use the backs of these pages as necessary.

1. (10 points) Explain briefly but fully (using three-dimensional structural drawings whenever possible) why reduction of the ketone **A** with sodium borohydride affords the alcohols, **B** and **C**, in a 5 : 1 ratio whereas reduction with di(cyclohexyl)borane (Cy_2BH) gives a 1 : 8 ratio of **B** and **C**.



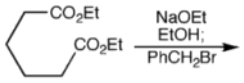
A **B** **C**

$NaBH_4$	5	1
$(C_6H_{11})_2BH$	1	8

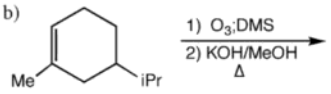
Remember to explain the formation of **both** products!

2. (36 points, 4 pts each) Predict the major product(s) of each of the following reactions, showing stereochemistry whenever appropriate. If no reaction is expected, state No Reaction. Assume normal aqueous workup after all reactions.

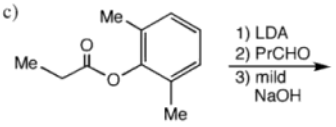
a)



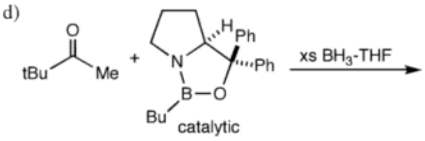
b)



c)

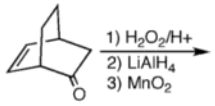


d)

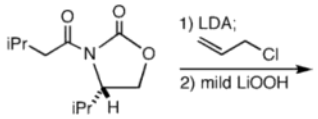


2. (continued) Predict . . .

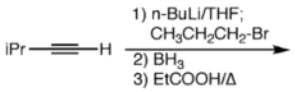
e)



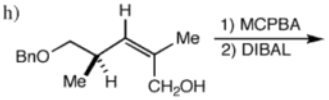
f)



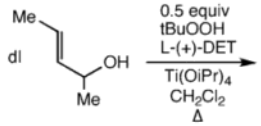
(g)



h)



i)



3. (36 points, as indicated) Transform each of the given starting materials into the desired products by a reasonable route, using any other readily available reagents.

(4) a)

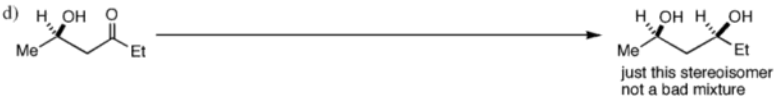
just this stereoisomer
not a bad mixture

(5) b)

(4) c)

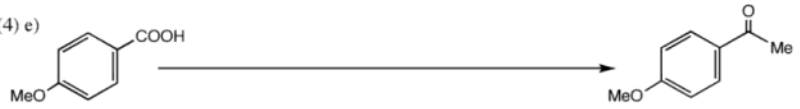
3. (continued) Transform . . .

(4) d)



just this stereoisomer
not a bad mixture

(4) e)

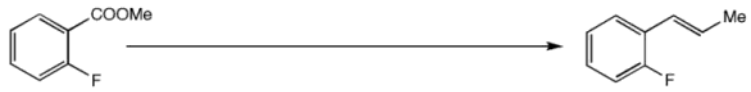


(4) f)

3. (continued) Transform . . .

(5) g)

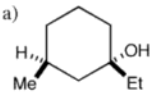
(6) h)



just this stereoisomer
not a bad mixture of
E and *Z* isomers

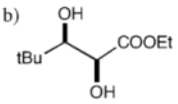
4. (18 points, as indicated) Synthesize each of the following molecules by a reasonable route beginning with readily available starting materials (i.e., commercially available or *Org. Synth.* preps).

(5) a)



dl, but just this stereoisomer

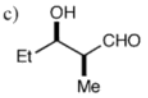
(6) b)



optically active, i.e., only this enantiomer

4. (continued) Synthesize . . .

(7) c)



optically active, i.e.,
only this enantiomer

Old practice exam

Wednesday, October 29, 2008
6:45 PM

Chemistry 144

Fall 2006

Hour Exam

November 7, 2006

M. E. Jung

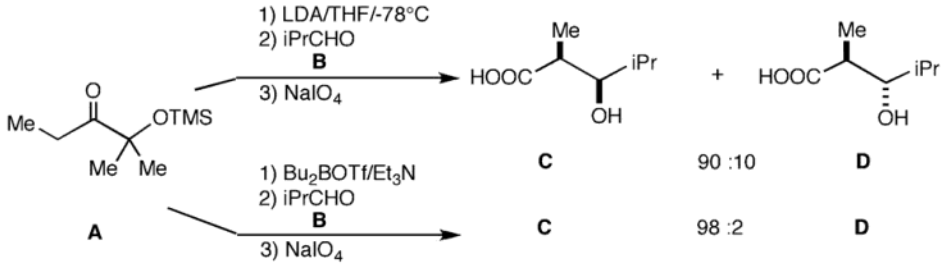
Name_____

Problem	Points	Score
1	10	
2	36	
3	34	
4	20	
Total	100	

Note: Place all of your answers on this exam. Scratch paper will be provided, but must not be used for final answers. Use the backs of these pages as necessary.

1. (10 points) Explain briefly but fully (using three-dimensional structural drawings whenever possible)
   i) Why the reaction of the ketone **A** with LDA in THF at -78 °C followed by addition of 2-methylpropanal **B** gives, after treatment with sodium periodate, mainly the syn product **C** rather than the anti product **D** (note that the products are racemic); and

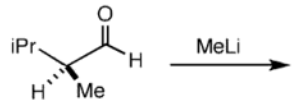
   ii) Why the ratio of **C:D** is higher for the reaction of the ketone **A** with dibutylboron triflate and triethylamine followed by addition of 2-methylpropanal **B** and oxidative workup.



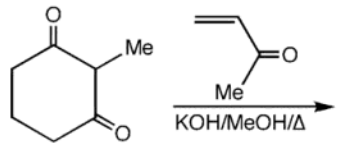
Remember to explain the formation of **both** products!

2. (36 points, 4 pts each) Predict the major product(s) of each of the following reactions, showing stereochemistry whenever appropriate. If no reaction is expected, state No Reaction. Assume normal aqueous workup after all reactions.

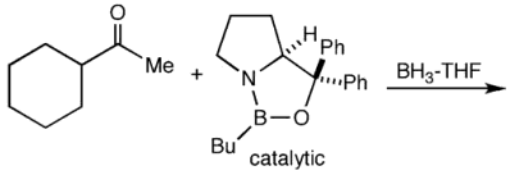
a)



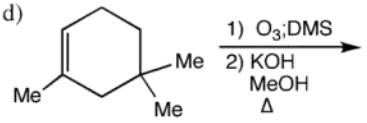
b)



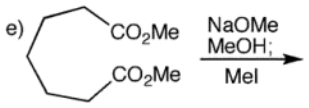
c)

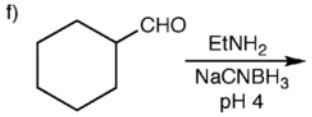


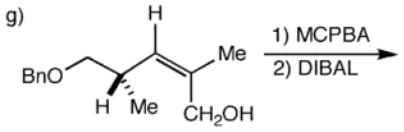
d)

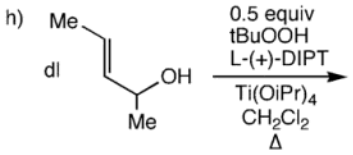


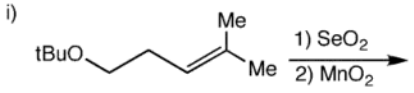
2. (continued) Predict . . .

e) 

f) 

g) 

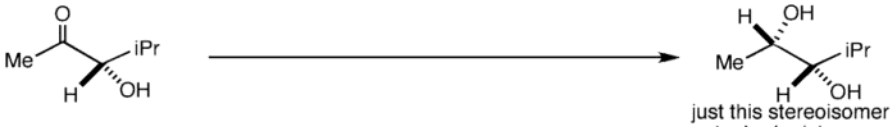
h) 

i) 

3. (34 points, as indicated) Transform each of the given starting materials into the desired products by a reasonable route, using any other readily available reagents.

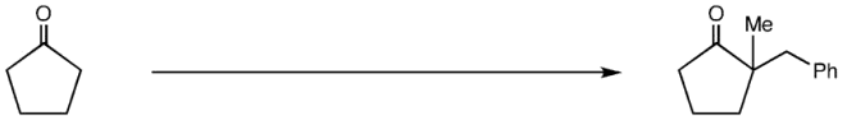
(4) a)

(4) b)



just this stereoisomer
not a bad mixture

(4) c)

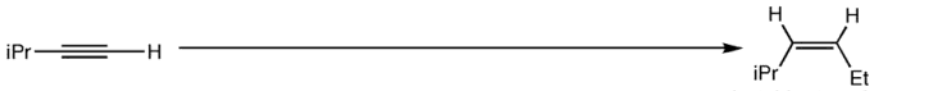


3. (continued) Transform . . .

(4) d)

just this stereoisomer
not a bad mixture

(4) e)

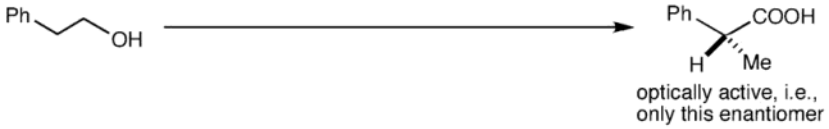


just this stereoisomer
not a bad mixture

(4) f)

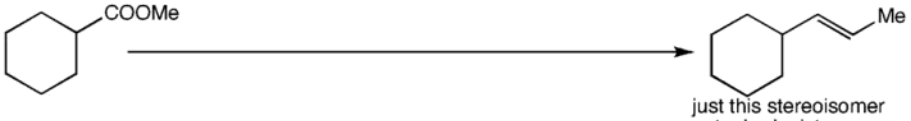
3. (continued) Transform . . .

(5) g)



optically active, i.e.,
only this enantiomer

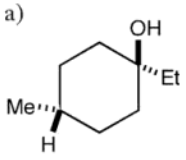
(5) h)



just this stereoisomer
not a bad mixture

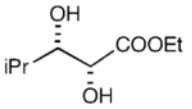
4. (20 points, as indicated) Synthesize each of the following molecules by a reasonable route beginning with readily available starting materials (i.e., commercially available or *Org. Synth.* preps).

(5) a)



dl, but just this stereoisomer

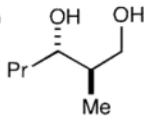
(7) b)



optically active, i.e., only this enantiomer

4. (continued) Synthesize . . .

(8) c)



optically active, i.e.,
only this enantiomer

Old practice key

Wednesday, October 29, 2008
6:49 PM

Chemistry 144

Fall 2006

Hour Exam

November 7, 2006

M. E. Jung

Name ANSWER KEY

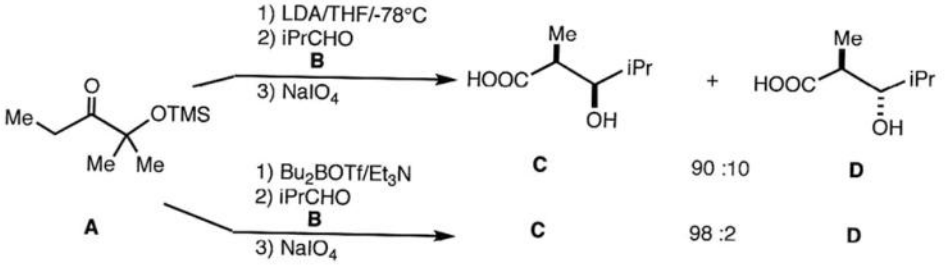
Problem	Points	Score
1	10	
2	36	
3	34	
4	20	
Total	100	

AVERAGE 51.5
HIGH 99.5
LOW 12.5

Note: Place all of your answers on this exam. Scratch paper will be provided, but must not be used for final answers. Use the backs of these pages as necessary.

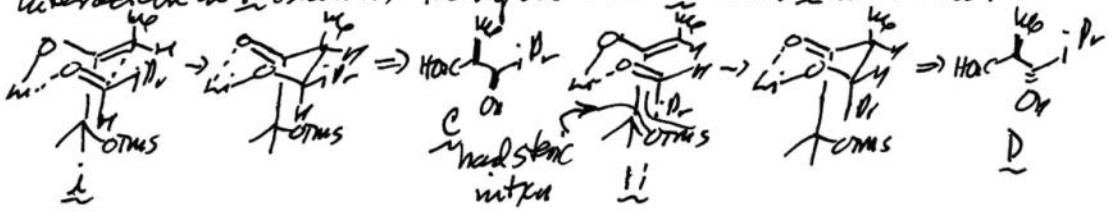
1. (10 points) Explain briefly but fully (using three-dimensional structural drawings whenever possible)
   i) Why the reaction of the ketone **A** with LDA in THF at -78 °C followed by addition of 2-methylpropanal **B** gives, after treatment with sodium periodate, mainly the syn product **C** rather than the anti product **D** (note that the products are racemic); and

   ii) Why the ratio of **C:D** is higher for the reaction of the ketone **A** with dibutylboron triflate and triethylamine followed by addition of 2-methylpropanal **B** and oxidative workup.

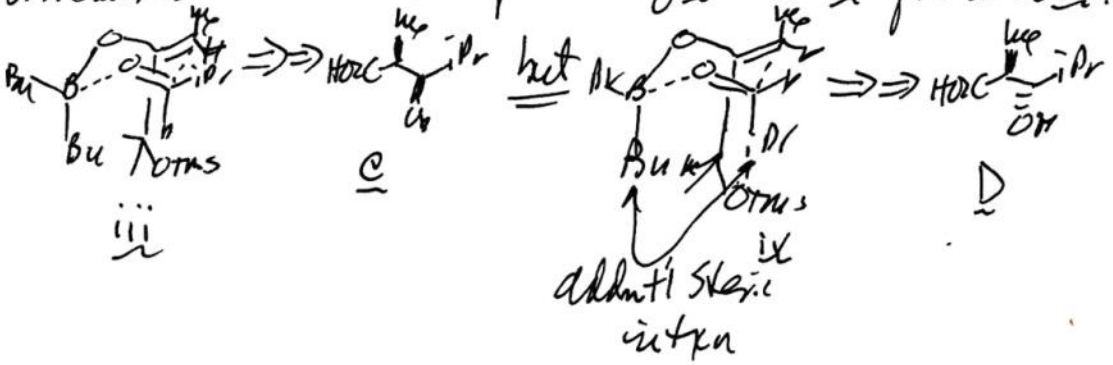


Remember to explain the formation of **both** products!

i) The reaction proceeds via the "cis" enolate and the Zimmerman-Traxler transition state - of the 2 possible TS's, i is more stable than ii because of the bad steric interaction in ii (shown) - therefore more C than D is formed!

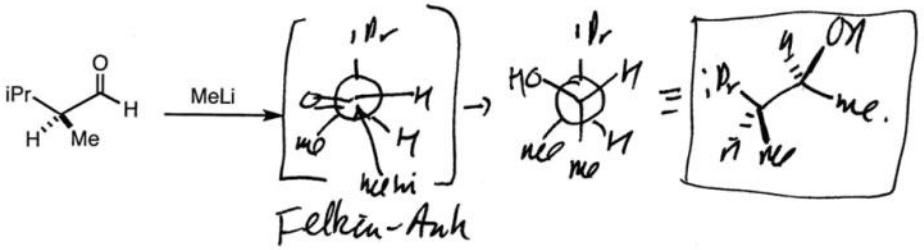


ii) In the second case using Bu_2BOTf there is an additional large group on the oxygen of the enolate (the butyl on Boron) in iv and this causes additional steric interaction which disfavors the formation of D so more C is formed via iii.

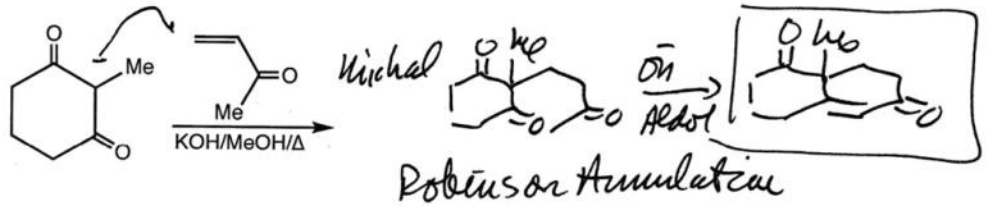


2. (36 points, 4 pts each) Predict the major product(s) of each of the following reactions, showing stereochemistry whenever appropriate. If no reaction is expected, state No Reaction. Assume normal aqueous workup after all reactions.

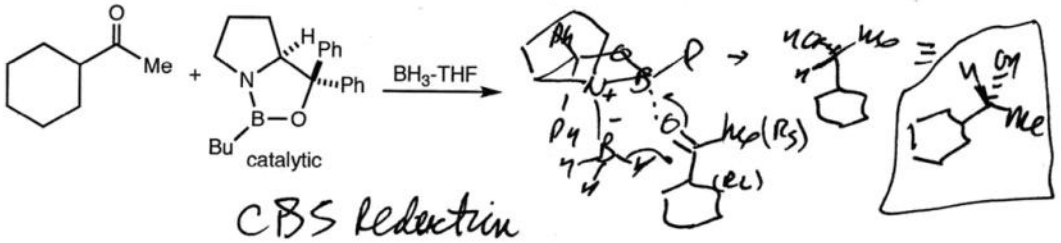
a)



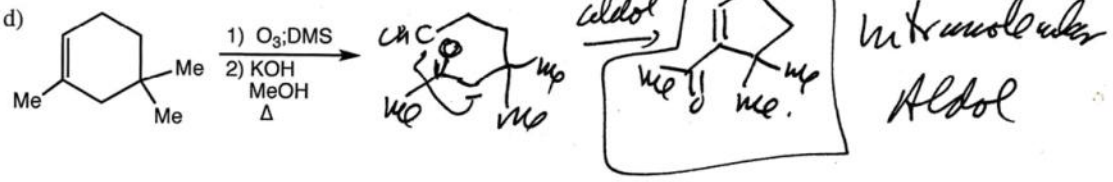
b)



c)

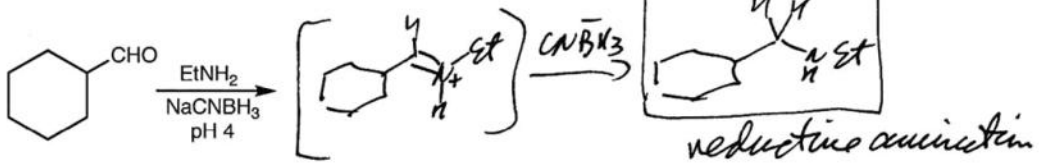


d)

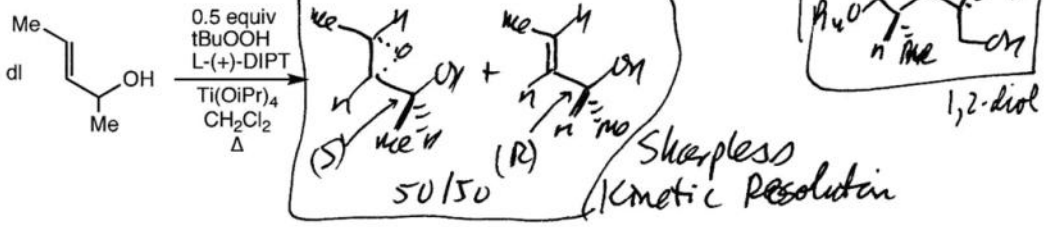


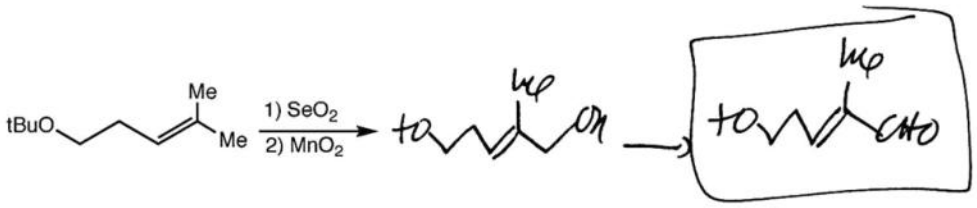
2. (continued) Predict . . .

e) 

f) 

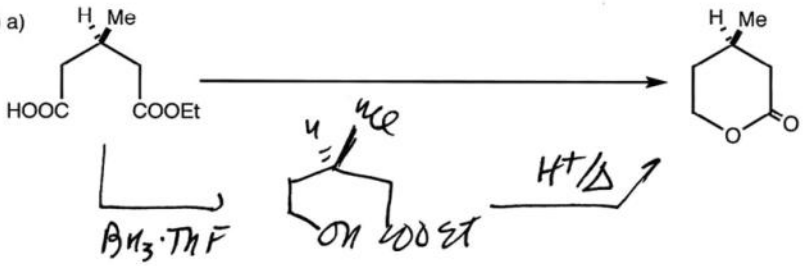
g) 

h) 

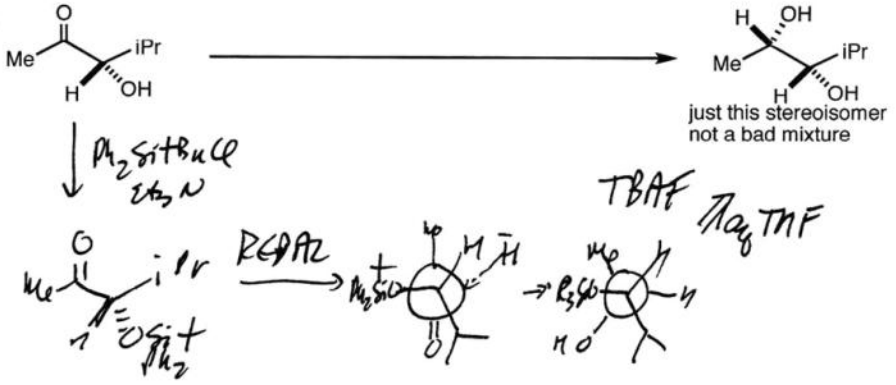
i) 

3. (34 points, as indicated) Transform each of the given starting materials into the desired products by a reasonable route, using any other readily available reagents.

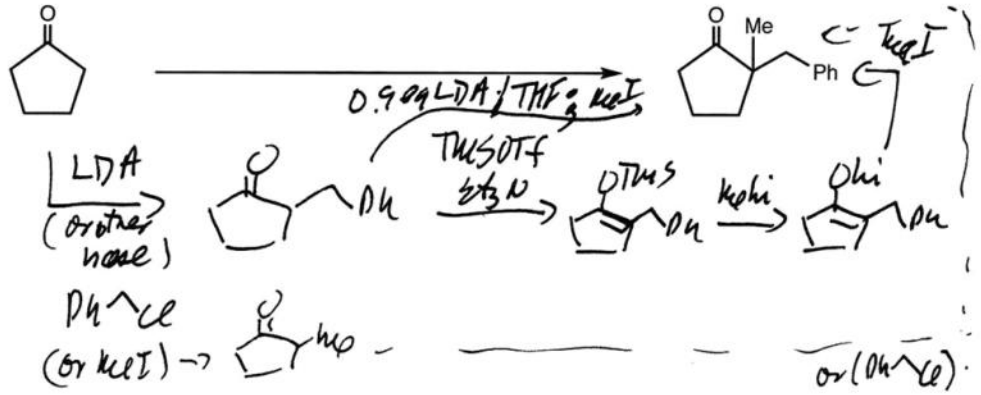
(4) a)



(4) b)

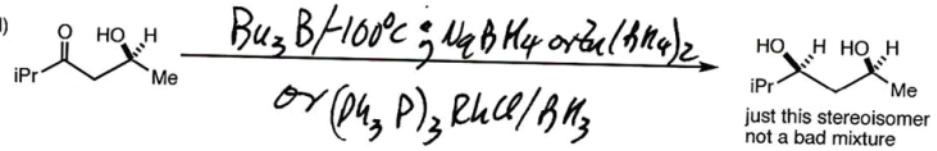


(4) c)

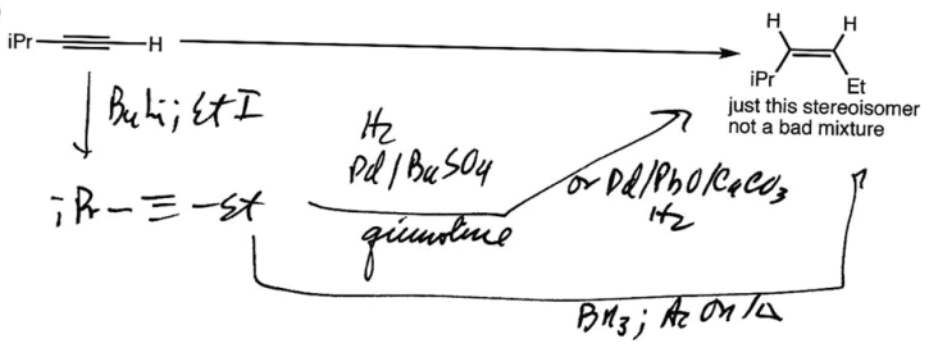


3. (continued) Transform . . .

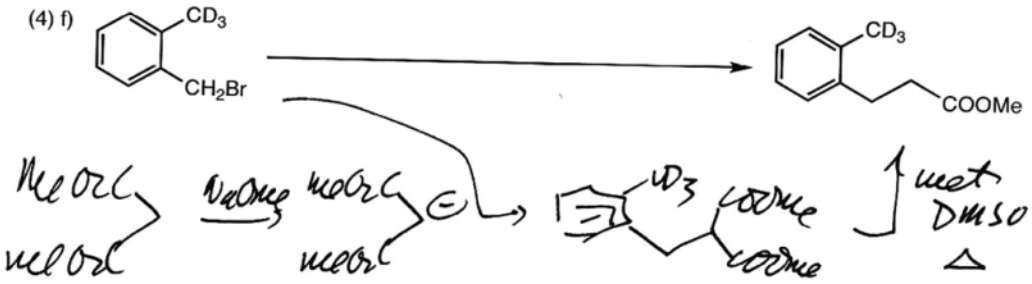
(4) d)



(4) e)

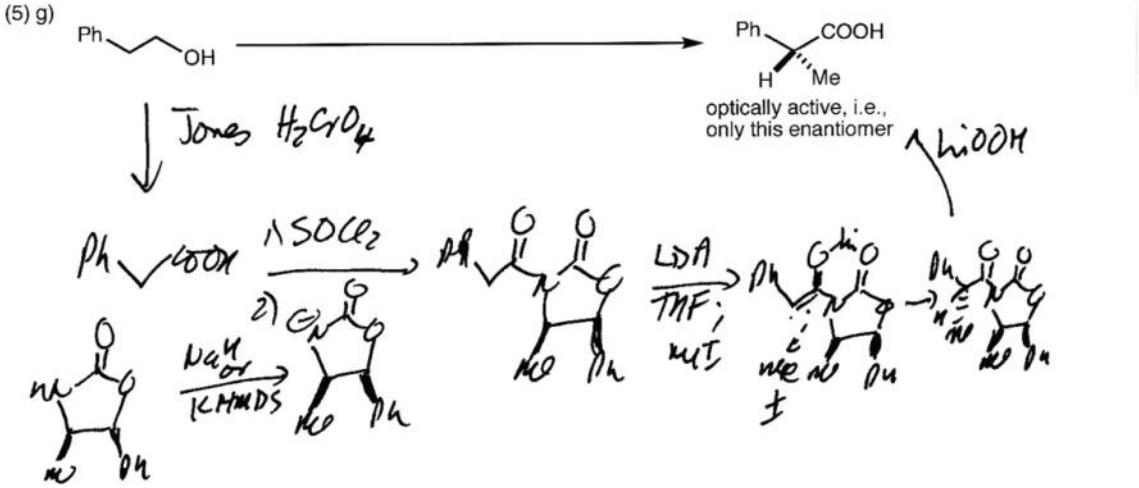


(4) f)

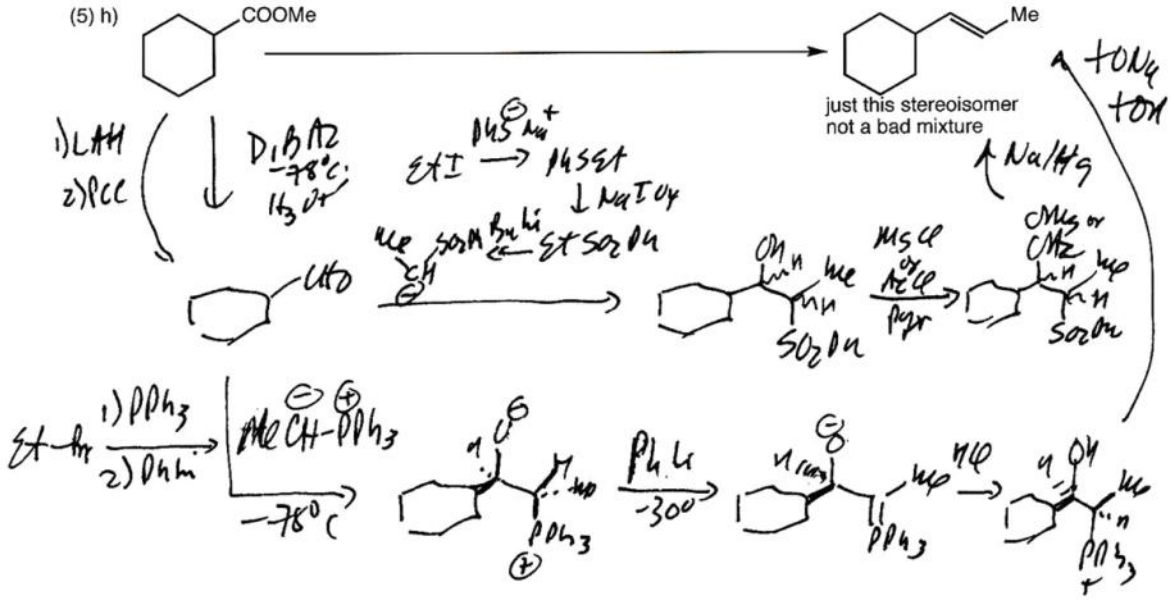


3. (continued) Transform . . .

(5) g)

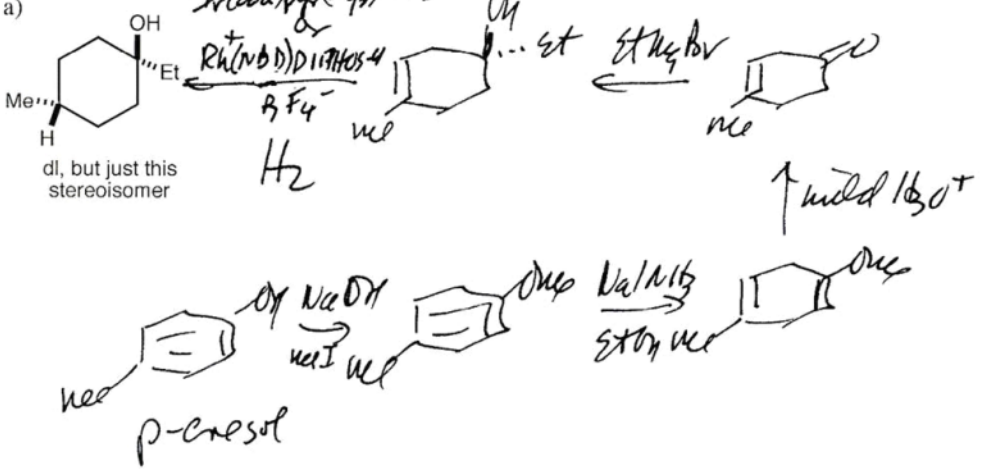


(5) h)

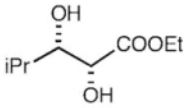


4. (20 points, as indicated) Synthesize each of the following molecules by a reasonable route beginning with readily available starting materials (i.e., commercially available or *Org. Synth.* preps).

(5) a)



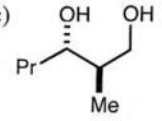
(7) b)



optically active, i.e., only this enantiomer

4. (continued) Synthesize . . .

(8) c)



optically active, i.e., only this enantiomer

Older practice key

Wednesday, October 29, 2008
6:50 PM

Chemistry 144

Fall 2005

Hour Exam

November 10, 2005

M. E. Jung

Name ANSWER KEY

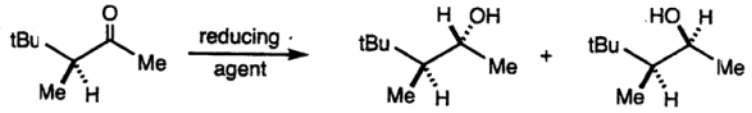
Problem	Points	Score
1	10	
2	36	
3	33	
4	21	
Total	100	

AVERAGE 47.1
HIGH 99
LOW 9

Note: Place all of your answers on this exam. Scratch paper will be provided, but must not be used for final answers. Use the backs of these pages as necessary.

1. (10 points) Explain briefly but fully (using three-dimensional structural drawings whenever possible) why reduction of the ketone **1** with sodium borohydride affords the alcohols **2** and **3** in a 5 : 1 ratio whereas reduction with di(cyclohexyl)borane [$(C_6H_{11})_2BH$] gives a 1 : 8 ratio of **2** and **3**.

Remember to explain the formation of both products.

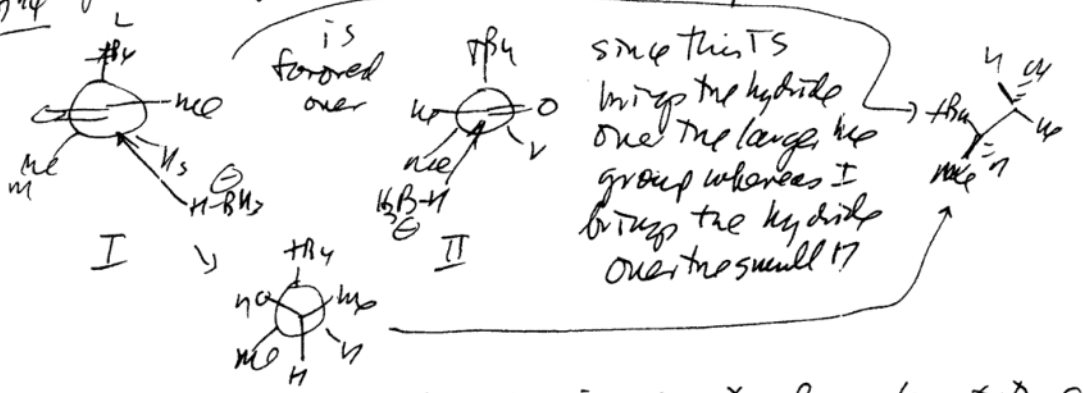


$NaBH_4$ 5 : 1

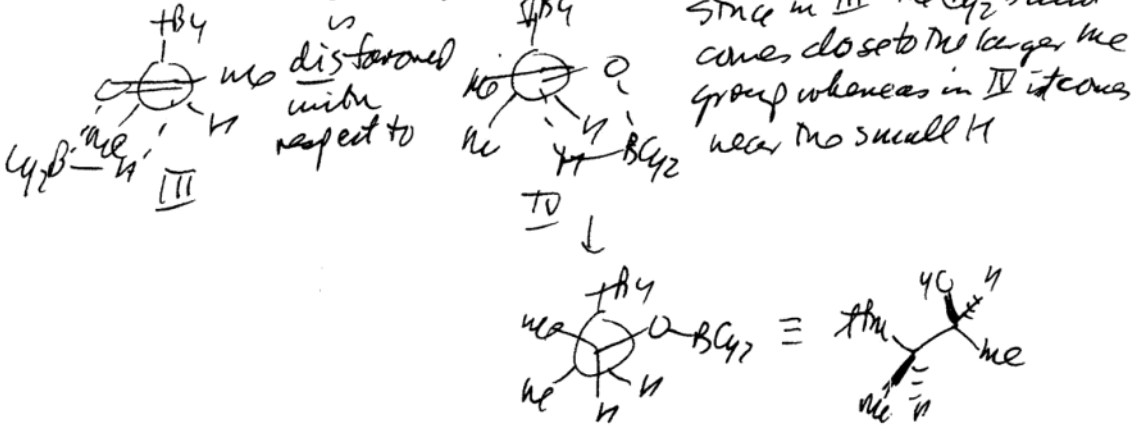
$(C_6H_{11})_2BH$ 1 : 8

Two different conformations lead to the two different favored products;

NaBH4

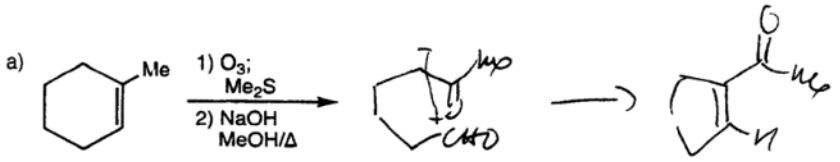


but with Cy_2BH, there is a diff. mechanism since the B complexes to the O.

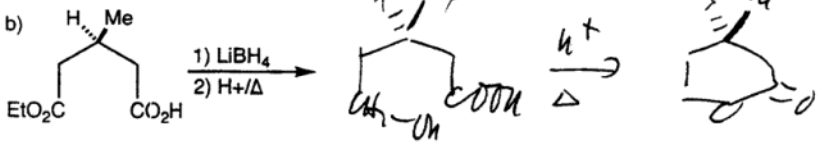


2. (36 points, 4 pts each) Predict the major product(s) of each of the following reactions, showing stereochemistry whenever appropriate. If no reaction is expected, state No Reaction. Assume normal aqueous workup after all reactions.

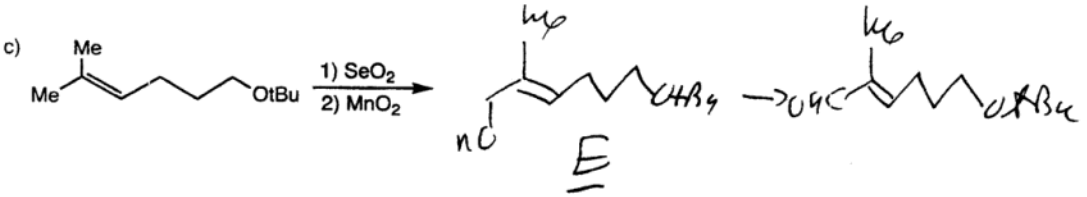
a)



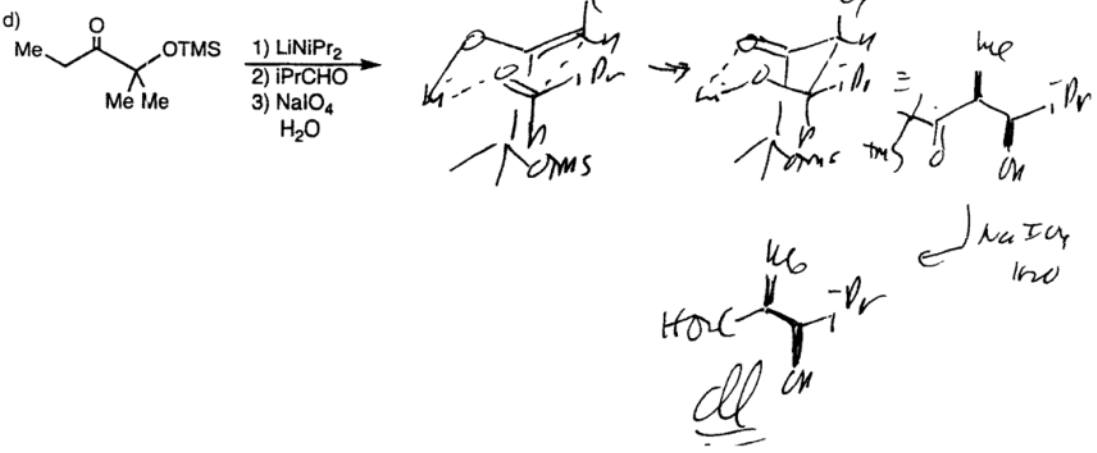
b)



c)

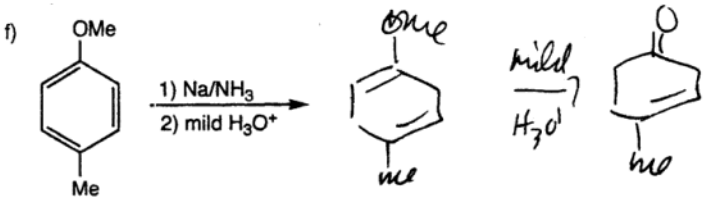


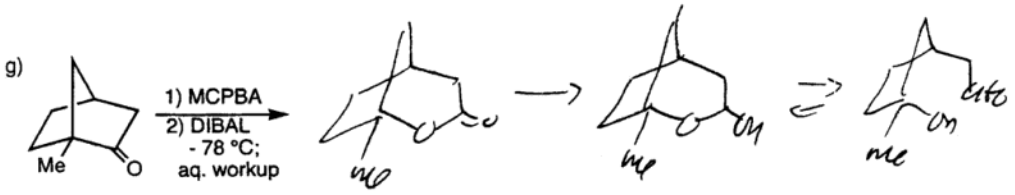
d)

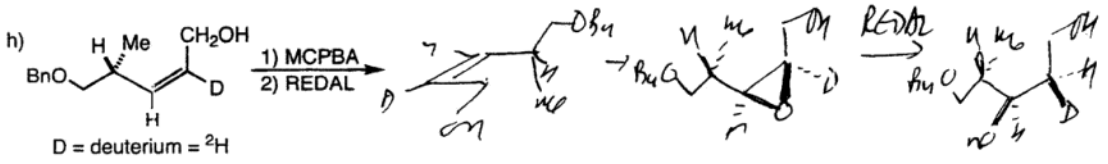


2. (continued) Predict . . .

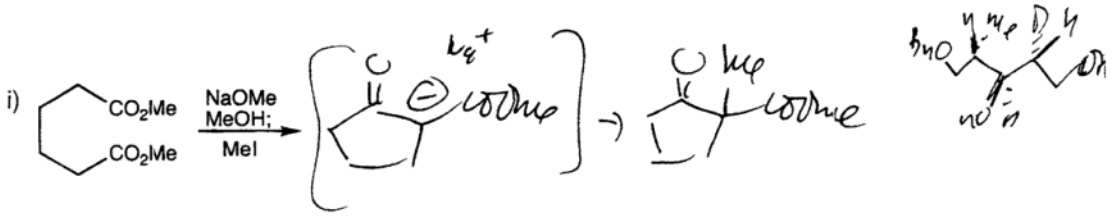
e) 

f) 

g) 

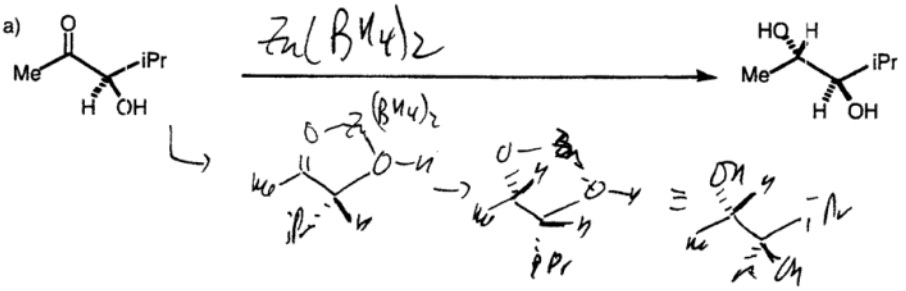
h) 

14

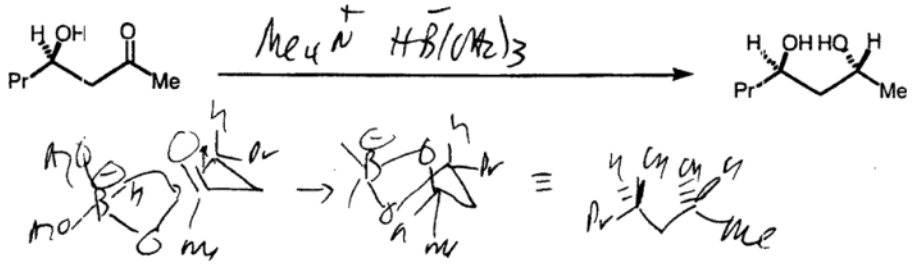
i) 

3. (33 points, as indicated) Transform each of the given starting materials into the desired products by a reasonable route, using any other readily available reagents.

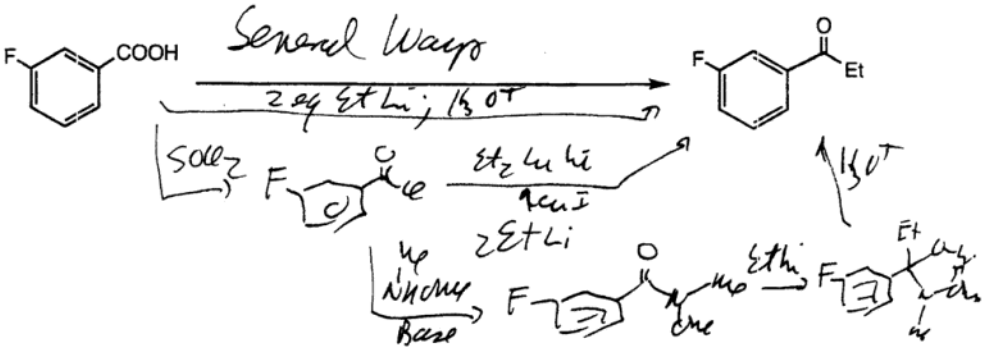
(4) a)



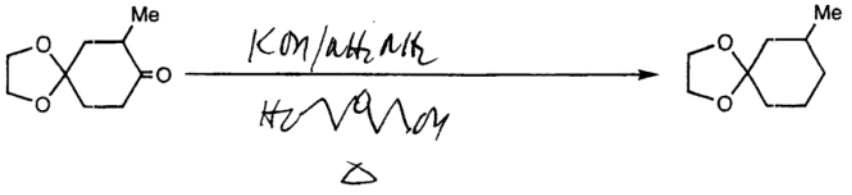
(4) b)



(4) c)



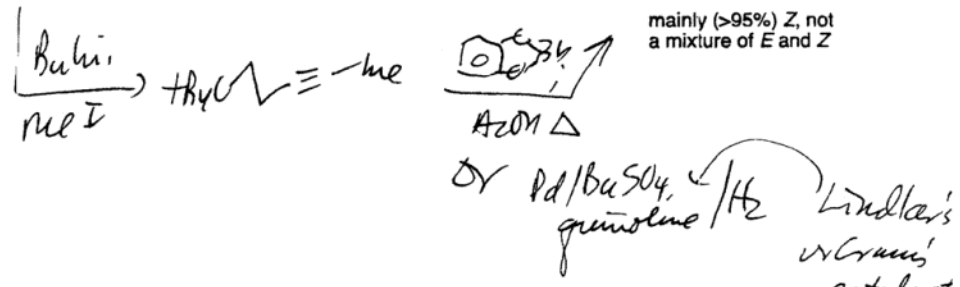
(4) d)



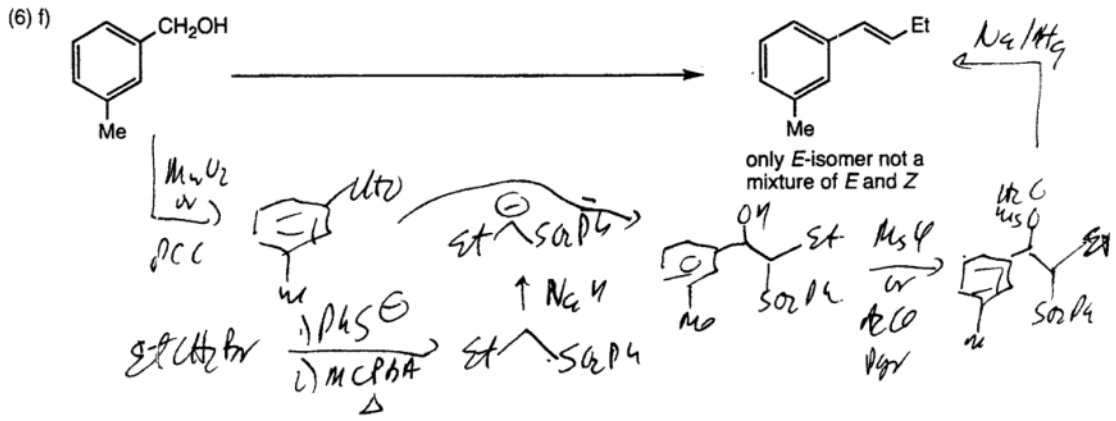
3. (continued) Transform . . .

(4) e) $tBuOCH_2CH_2-C\equiv C-H$ ⟶ $tBuOCH_2CH_2$, Me, H, H

mainly (>95%) Z, not a mixture of E and Z

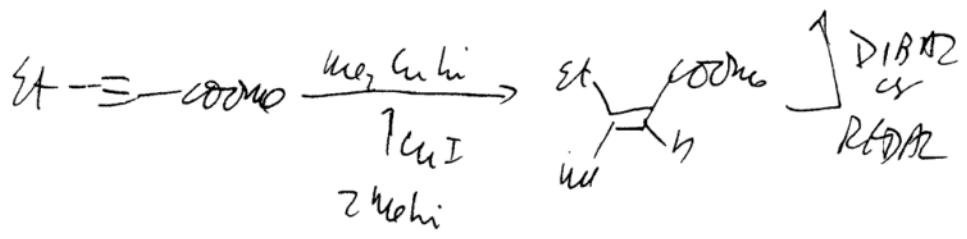


(6) f)



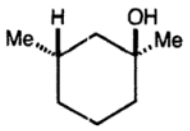
(7) g) $Et-C\equiv C-H$ ⟶ Et, CH_2OH, Me, H

mainly (>95%) Z, not a mixture of E and Z

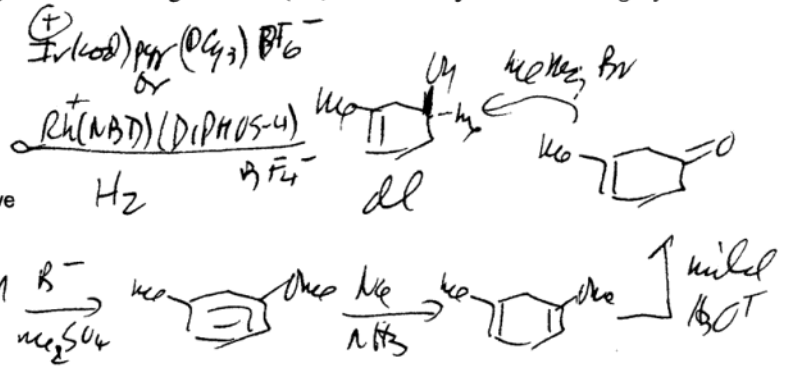


4. (21 points, as indicated) Synthesize each of the following molecules by a reasonable route beginning with readily available starting materials (i.e., commercially available or *Org. Synth.* preps).

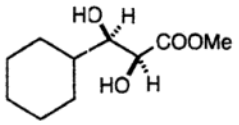
(6) a)



dl, not optically active



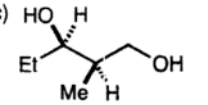
(7) b)



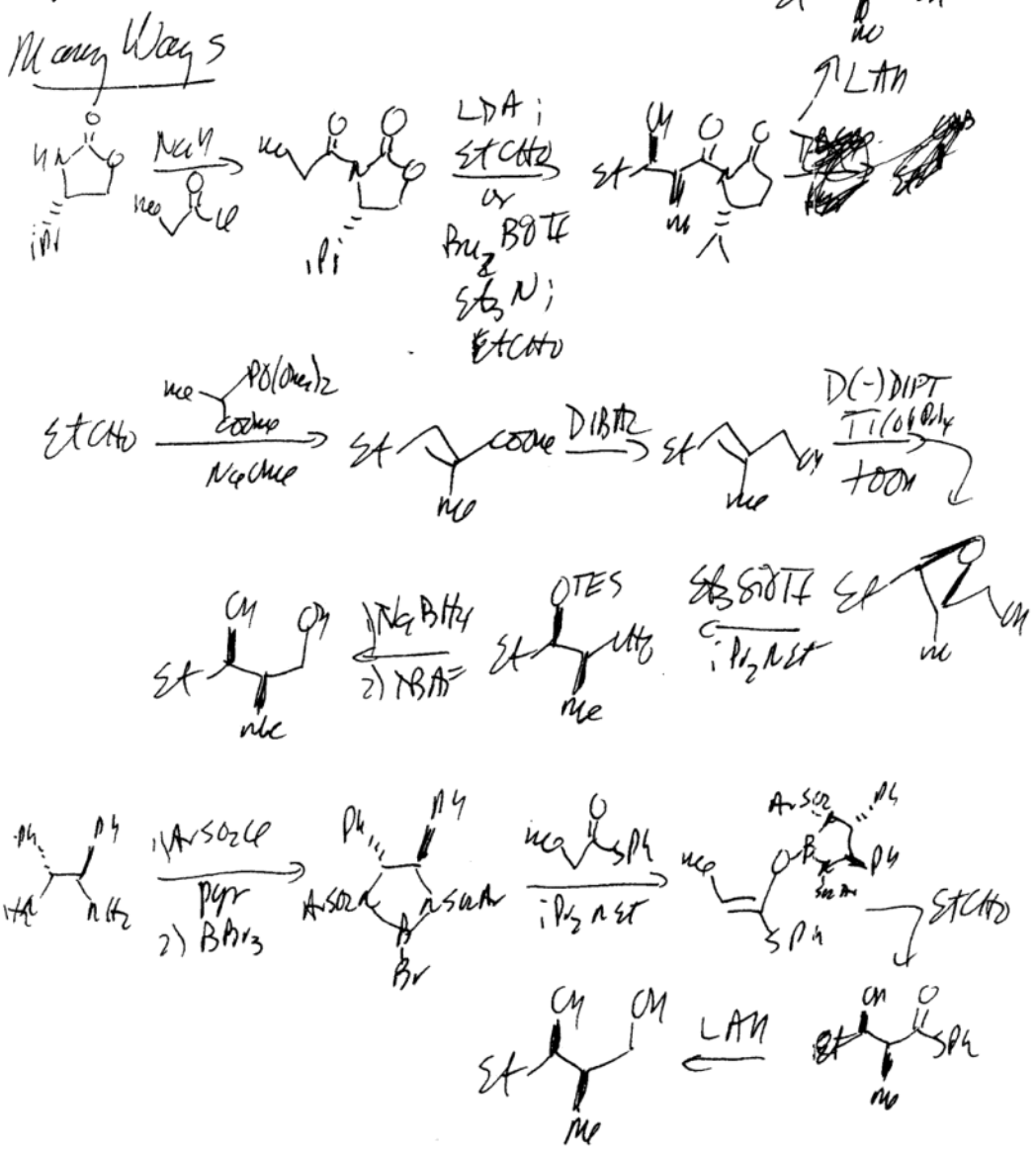
optically active, i.e., just this enantiomer

4. (continued) Synthesize . . .

(8) c)



optically active, i.e., just this enantiomer



Notes 10/30

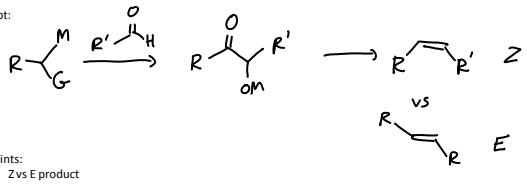
Thursday, October 30, 2008
11:00 AM

Notes1030

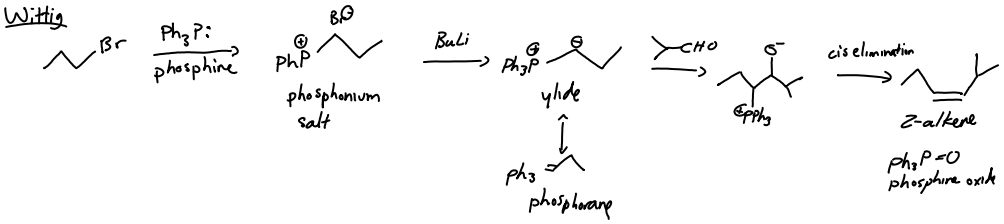
Audio recording started: 11:01 AM Thursday, October 30, 2008

Alkene Synthesis - Olefination

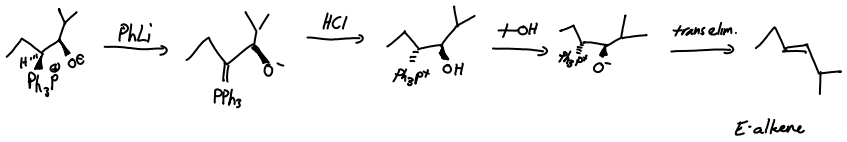
Concept:



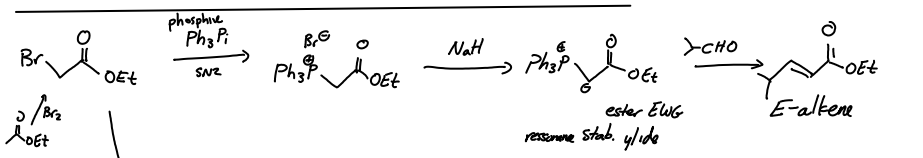
2 points:
1. Z vs E product
2. Functional groups



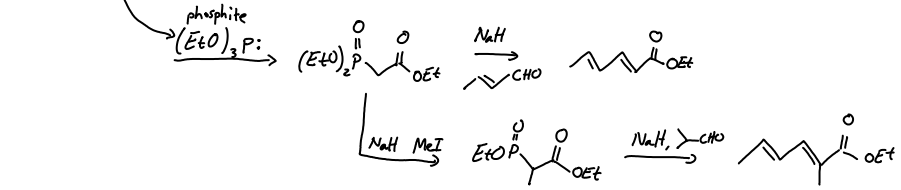
If you want E form. Schlosser Modification. Protenate the intermediate



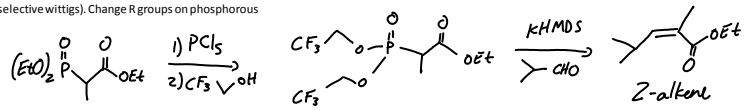
Vedejs used cyclic phosphines



Group that stabilizes ylide negative charge through resonance favors E alkene

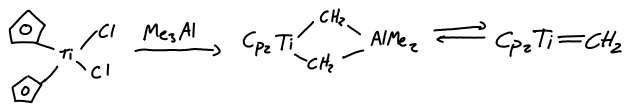


- Wittig is usually Z selective, resonance stabilizing groups make it E selective
- Still/Ando (Z selective wittigs). Change R groups on phosphorous

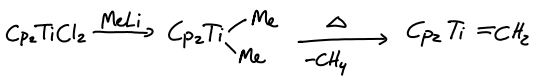


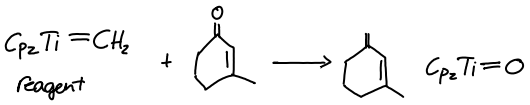
- Other Olefinations
  1) Peterson Reaction (silyl-wittig)

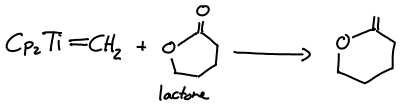
  2) Tebbe/Petasis
     - Tebbe:

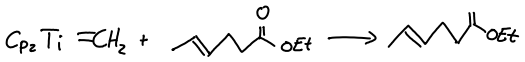


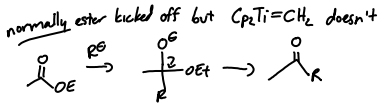
- Petasis



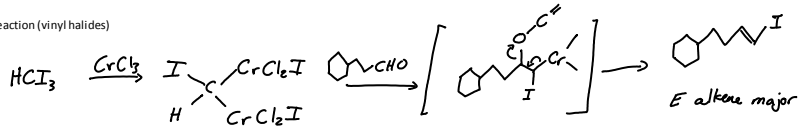




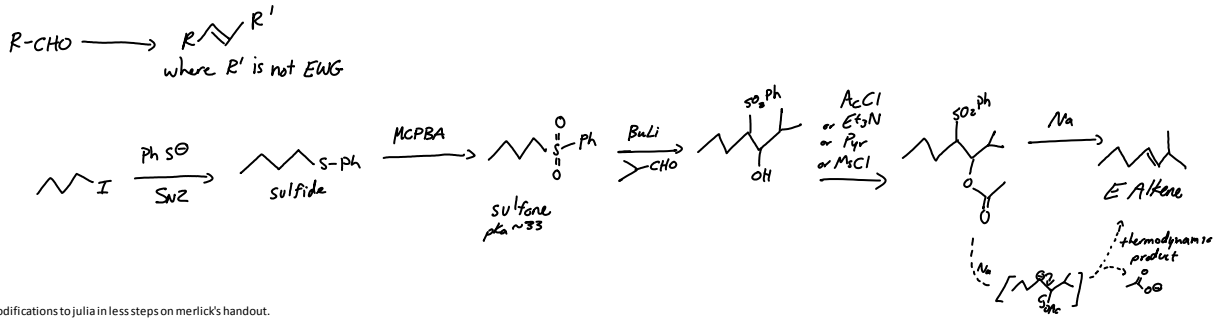




- Takai Reaction (vinyl halides)



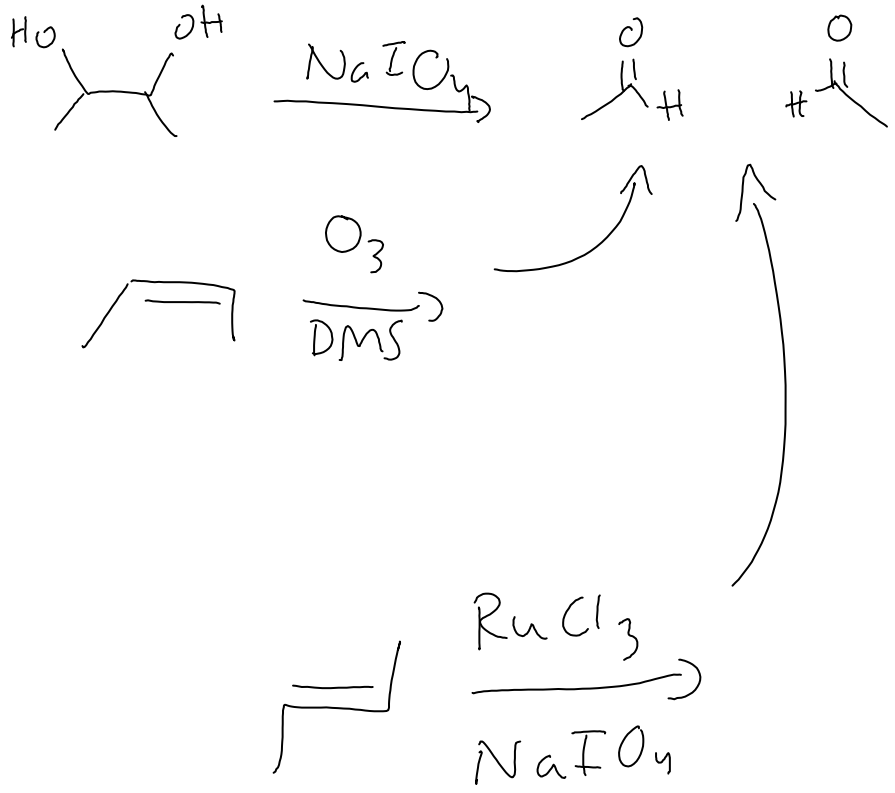
- Julia - important. Same outcome as Schlosser but doesn't need EWG. Used more often than Schlosser.



Modifications to julia in less steps on merlick's handout.

Notes

Thursday, October 30, 2008
6:23 PM



Notes 11/06

Thursday, November 06, 2008
10:55 AM

Notes 1106

Audio recording started: 11:00 AM Thursday, November 06, 2008

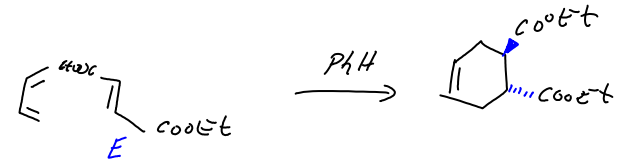
Exam
Average 58
High 90
Low 13

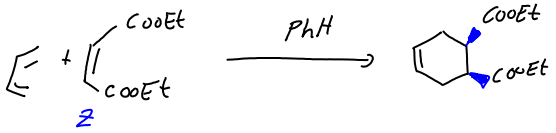
2nd lab report due mon 11/10 1pm in mol sci 3221

Cycloadditions:

- Diels Alder Reaction

1. Retain stereochemistry of the dienophile and diene

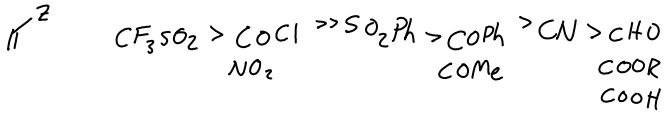


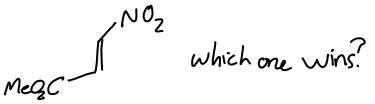


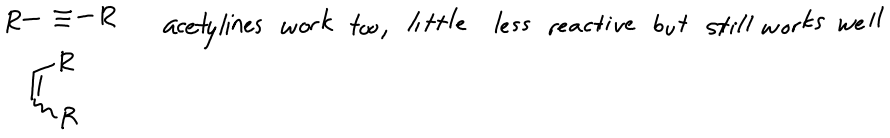
Reaction is concerted

4 handouts.
1 with rates of reaction. Reference only and won't really be quizzed on

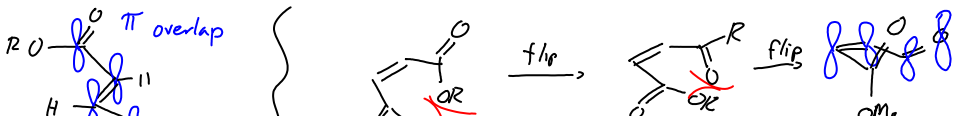
2. Rules for Dienophile (see handout)
   - Electron withdrawing groups makes better dienophile

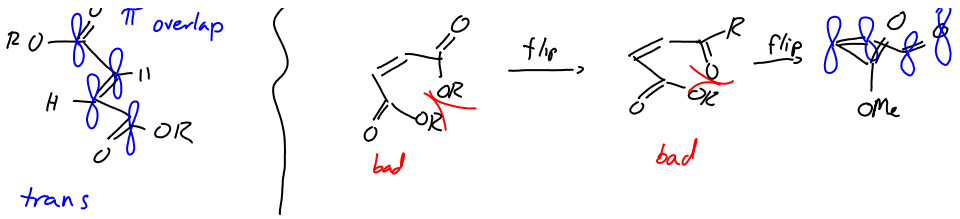






   - Trans vs cis
     - Trans always more reactive in alkenes, cis/trans have identical reactivity with acetylines

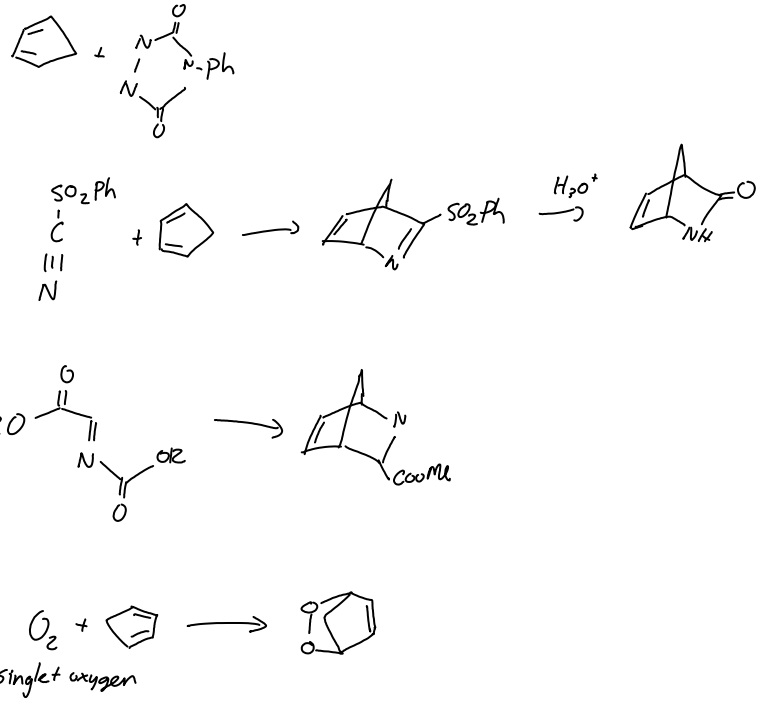




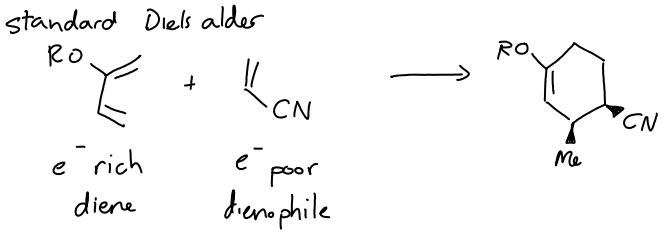
- Must be coplanar, trans allows this in alkenes. Can be coplanar

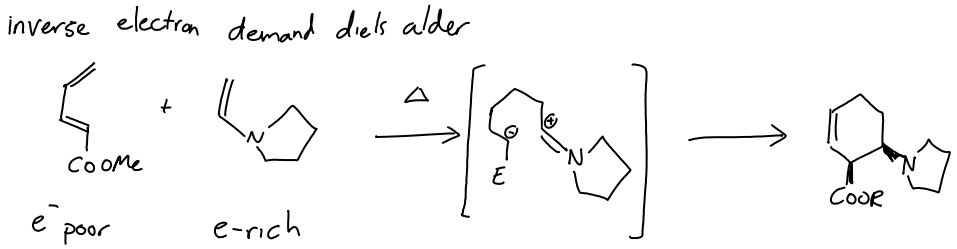
- Alkyl substitution on the dienophile retards the reaction
  - How to make good good dienophile (jung's rule)
    - For every one modest e donor (alkyl) need a good acceptor substituent

- Other bonds can be used as dienophiles

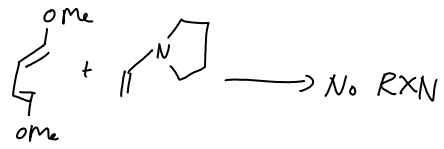


- Rules for Dienes in Diels-Alder (see handout)
  - More electron rich, the better

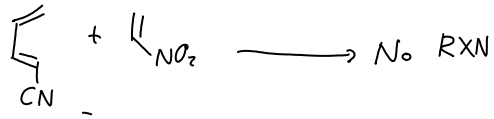




won't work with both rich or poor

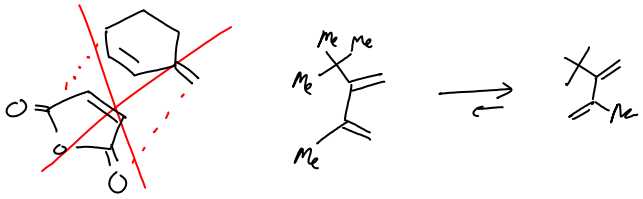


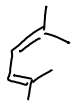
e⁻ rich

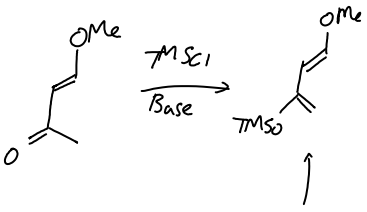


e⁻ poor

- Must be cis and coplanar

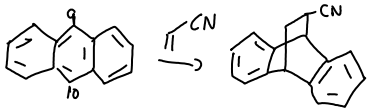




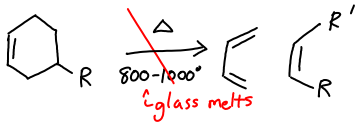


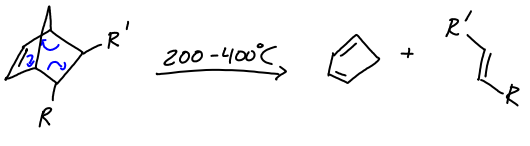
Danishefsky's diene works very well

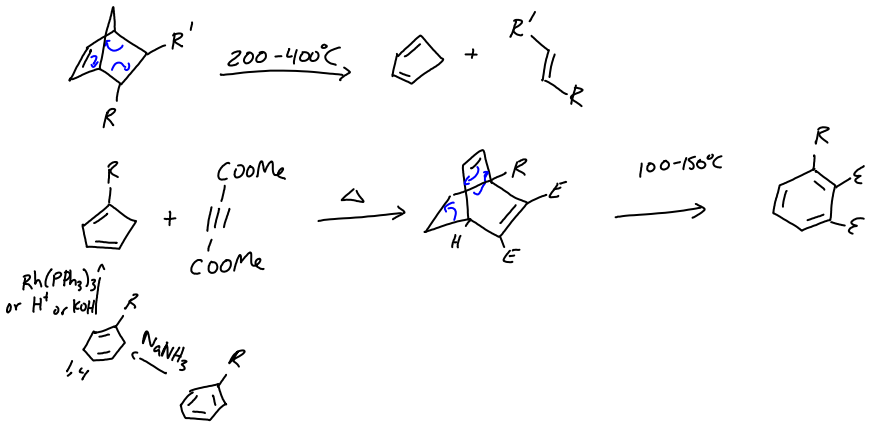
- Aromatic dienes are generally not very good
  - None on benzene, pyridine, thiophene
  - Furan works okay. Pyrole (with specific R groups such as ester).
  - Anthracene, center ring ressonance not too strong:



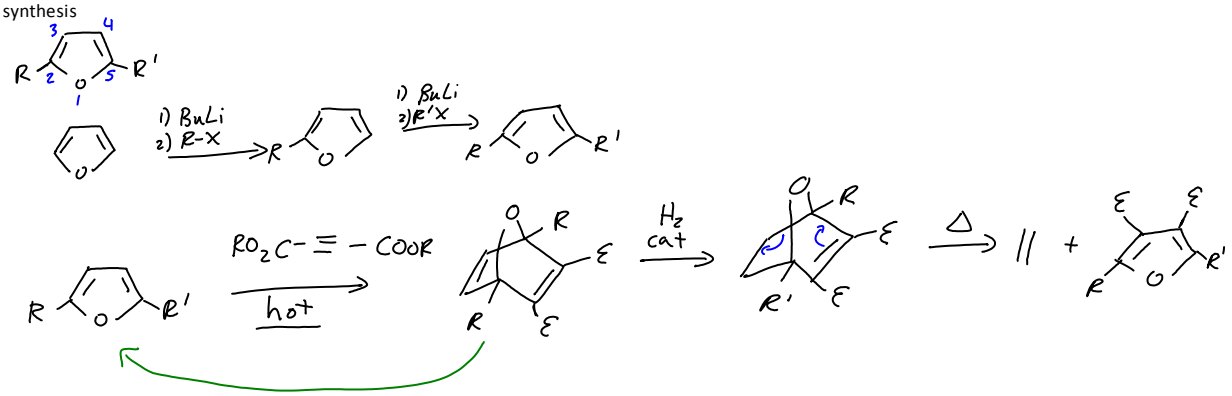
- Diels Alder is Reversible (not in handout but need to know). Alder-Ricket Reaction







Furan synthesis



Notes 11/13

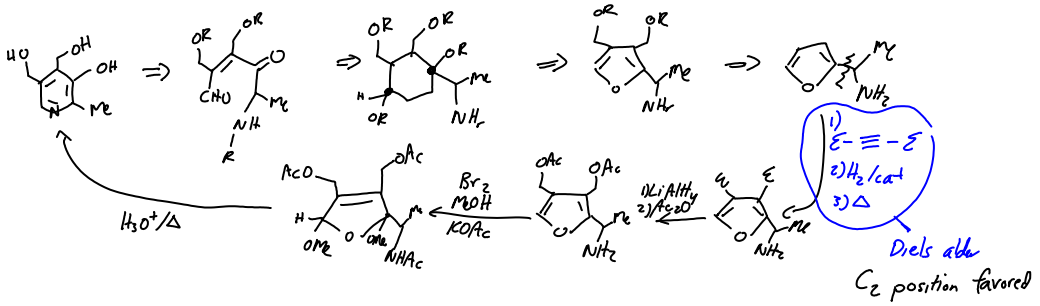
Thursday, November 13, 2008
11:03 AM

Notes 1113

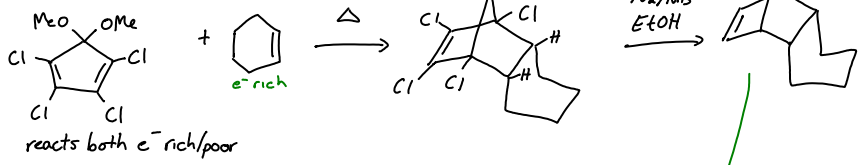
Audio recording started: 11:03 AM Thursday, November 13, 2008

Diels-Alder Reaction

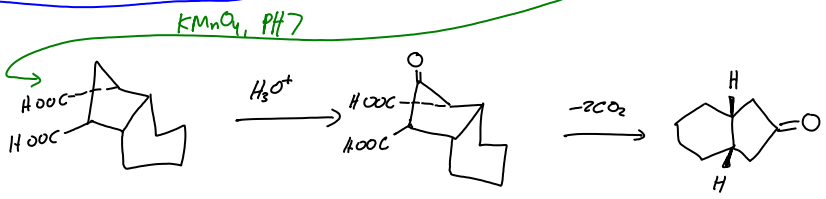
1) Stereochemistry of dienophile + diene retained
2) Rules for diene
3) Rules for dienophile
4) Reversible -> furans



c) Inverse - electron demand diels alder



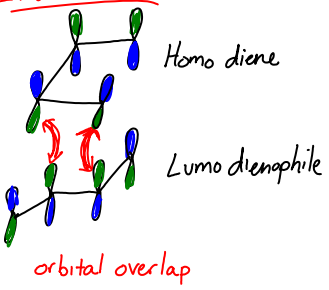
* 3 - carbo nannulation

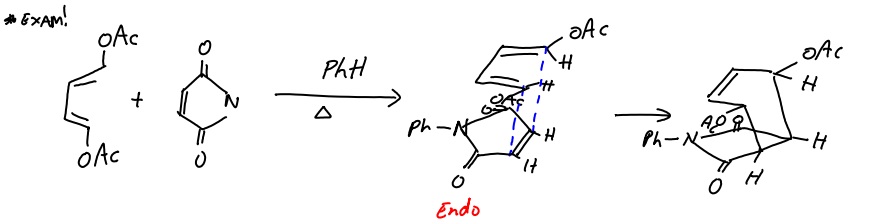


6) Stereochemistry
   i. Alder endo TS rules (see stereochemistry of diels-alder reaction andout)

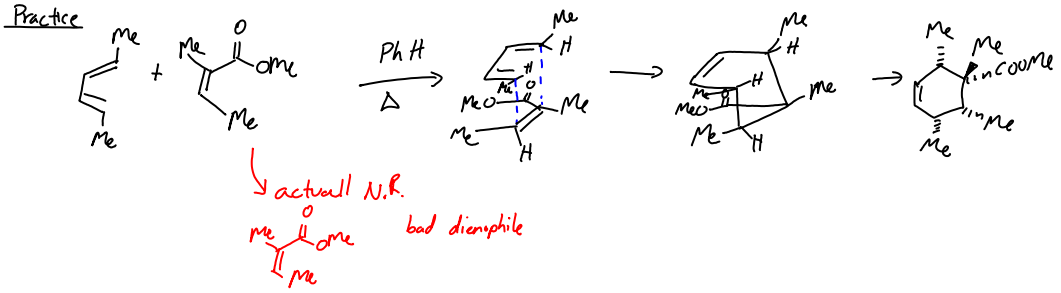
Endo TS

Exo TS





Draw diene in flat plane, draw dienophile under it. Most activating group goes underneath as endo



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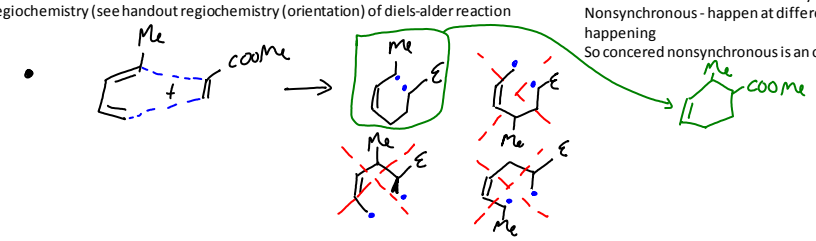
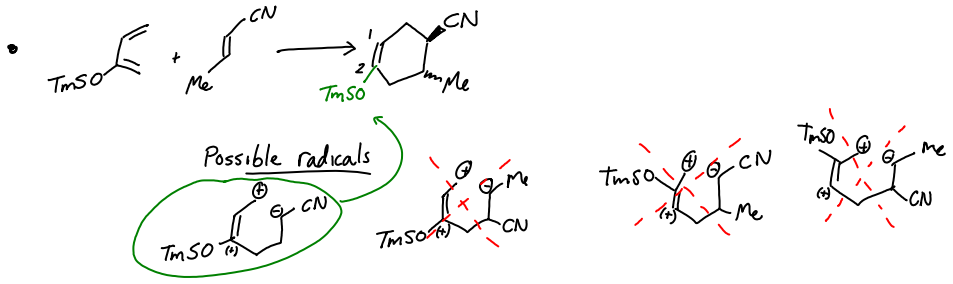
7) Regiochemistry (see handout regiochemistry (orientation) of diels-alder reaction

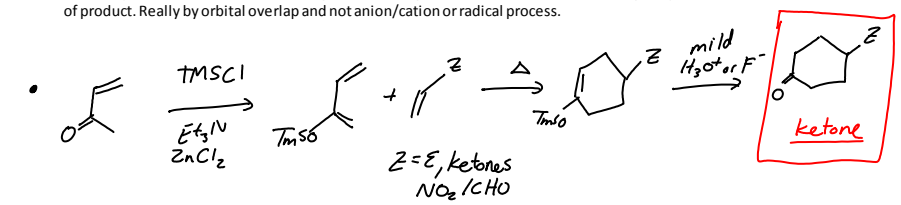
Concerted - when bonds form they form at exactly the same time
Nonsynchronous - happen at different times (though very close time interval) and no chance of 2nd not happening
So concered nonsynchronous is an oxymoron but is used to describe this

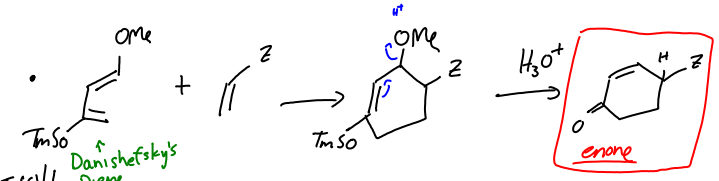


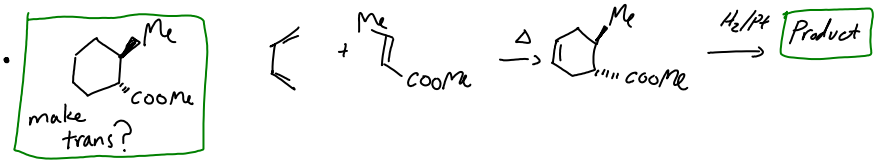
The most stable diradical predicts major product. The unstable ones have H substituents which is least stable for radicals.



* Not really radical or cation/anions being formed though this nmeunic device allows for good prediction of product. Really by orbital overlap and not anion/cation or radical process.



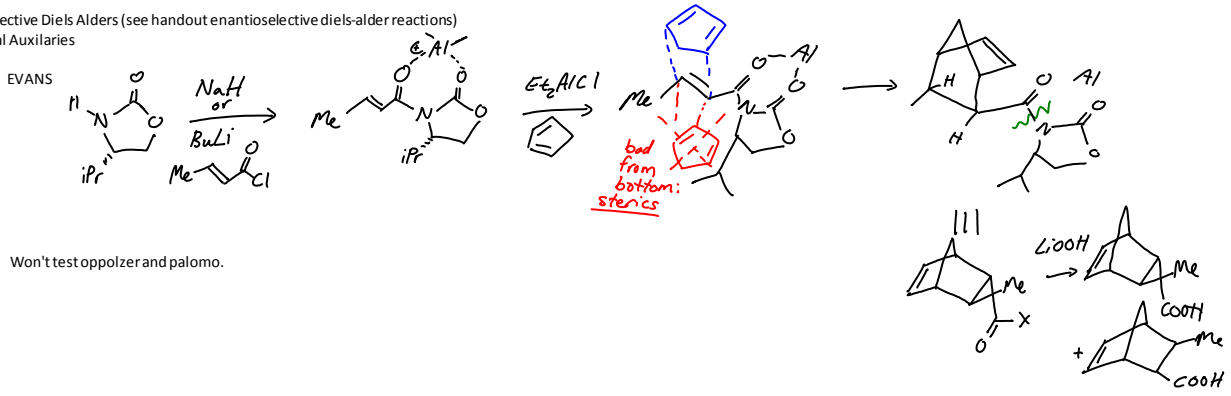




- How about cis? HW → think about

8) Enantioselective Diels Alders (see handout enantioselective diels-alder reactions)
   1) Chiral Auxilaries

EVANS



Won't test oppolzer and palomo.

Notes 11/18

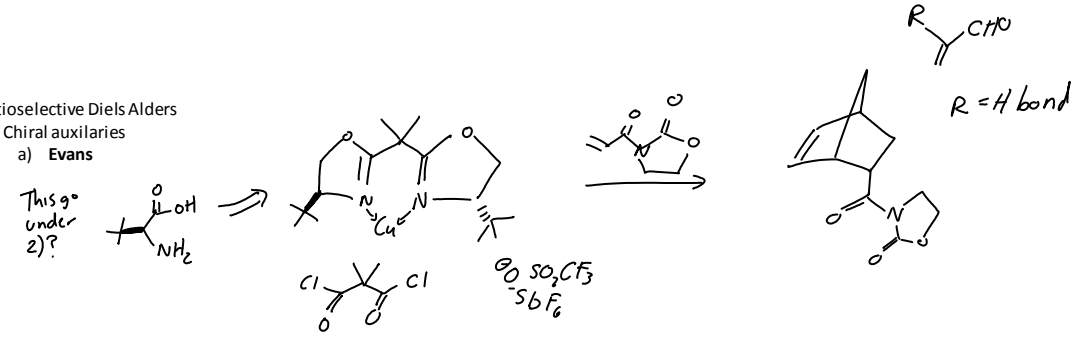
Tuesday, November 18, 2008
11:04 AM

Notes 1118

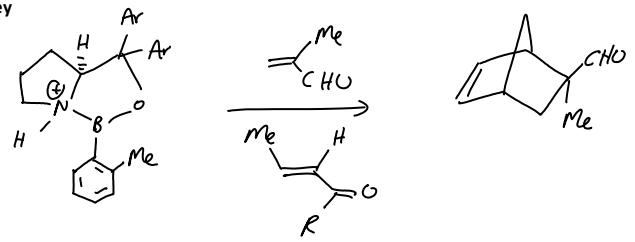
Audio recording started: 11:04 AM Tuesday, November 18, 2008

Enantioselective Diels Alders

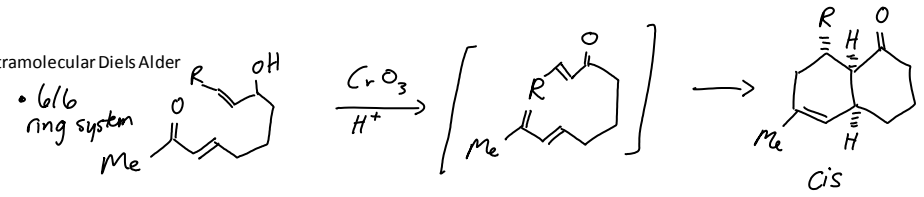
1) Chiral auxilaries
   a) **Evans**

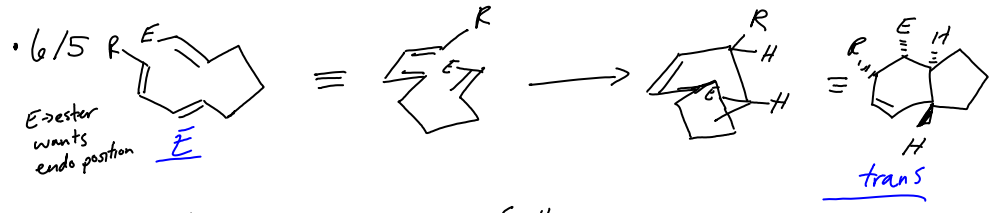


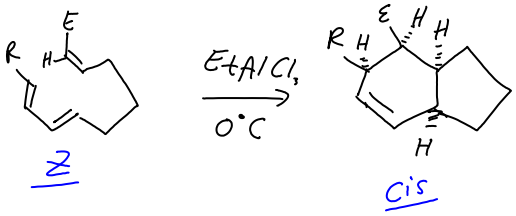
   a) Oppolzer
   b) Helchman
2) Enantioselective Catalysis
   a) **Corey**



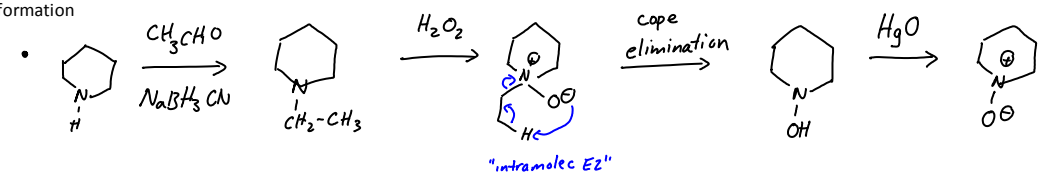
Intramolecular Diels Alder

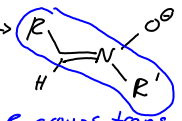






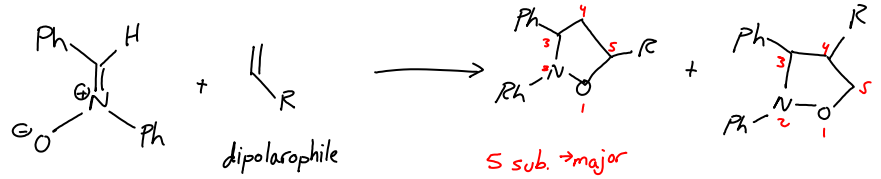
- 1,3-diPolarcycloaddition
  1) Nitrones
     a) formation



- $RCHO + R'NHOH \rightarrow$ 

R groups trans

b) Regiochemiistry

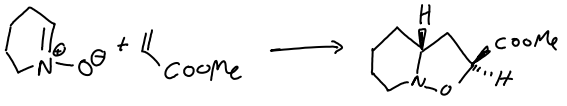


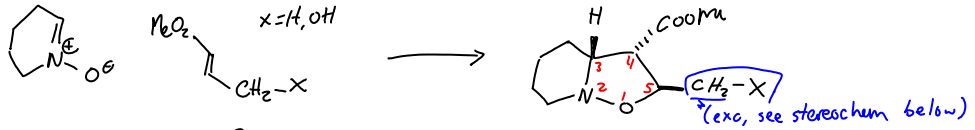
dipolarophile

5 sub. → major

R-group interacts by sterics, bulky then more 5 sub.

ex

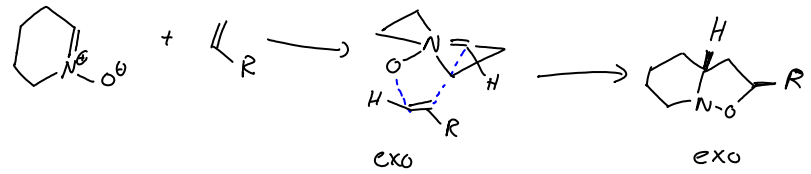
- 

- 

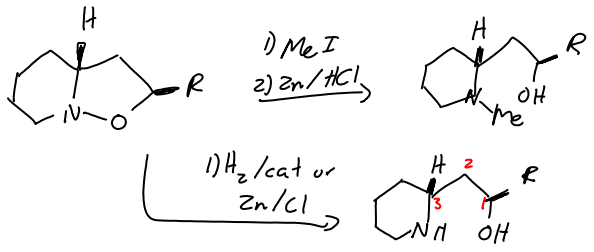
disub with $e^{\ominus}$ donating group → 5 pos
and $e^{\ominus}$ withdrawing group → 4 pos

* 5 pos EDG
* 4 pos EWG

3) Stereochemistry -> Exo TS favored

- 

exo exo

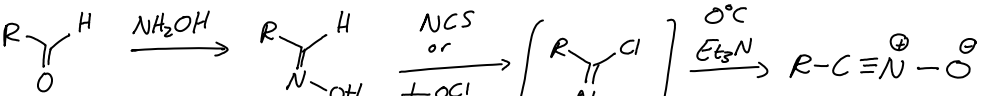
- Uses 

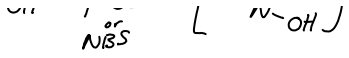
1,3-aminoalcohol

2) Nitrile Oxide

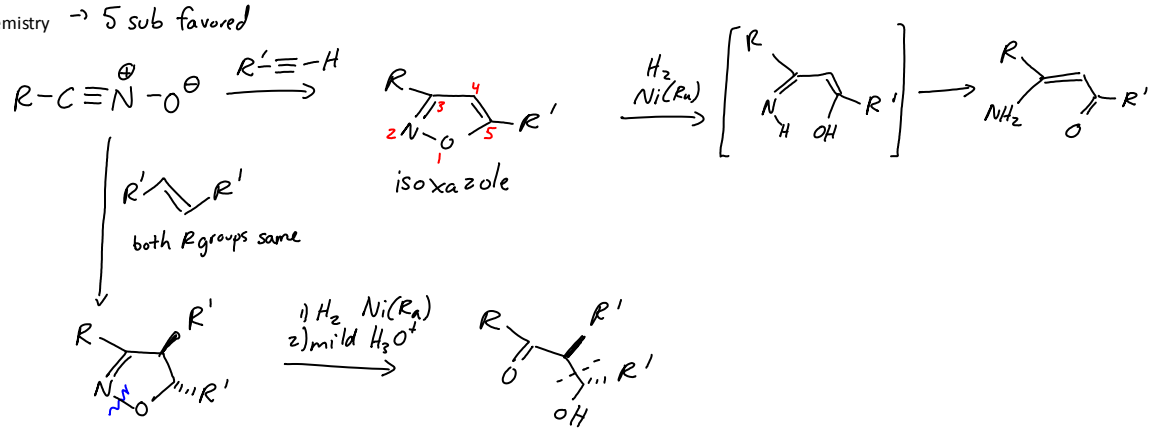
a) Formation

- $R-CH_2-NO_2 \xrightarrow[Et_3N]{2\,PhN=C=O} R-C\equiv\overset{\oplus}{N}-\overset{\ominus}{O}$

- 

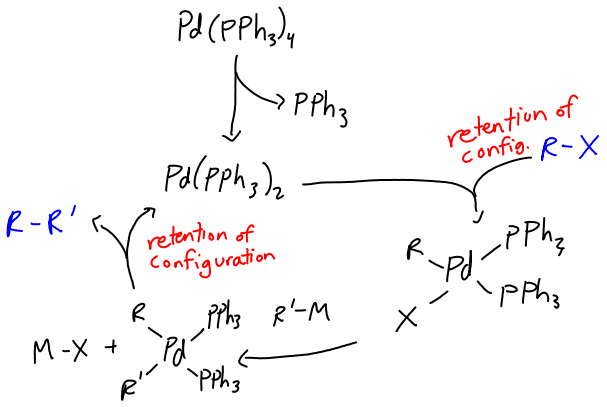


b) regiochemistry → 5 sub favored



c) Stereochemistry
- No stereochemistry. No endo or exo

- Special Organometallic Chemistry (see palladium cat cross coupling reactions handout)
  - Pd-cat Crossed Coupling Reactions



X=I, Br, Otf
X cannot be F, usually not Cl

R = sp2 character (alkenyl, aryl, allyl)
R cannot be alkyl

R'-M
R= = alkenyl,allyl, aryl, alkynyl, (alkyl)
M = ZnX, SnR_3, $B(OH)_2$, Cu, SiR_3, MgX

Notes 11/20

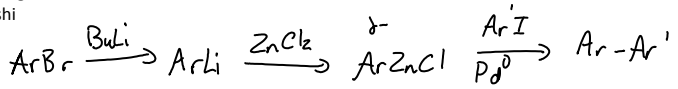
Thursday, November 20, 2008
11:07 AM

Notes 1120

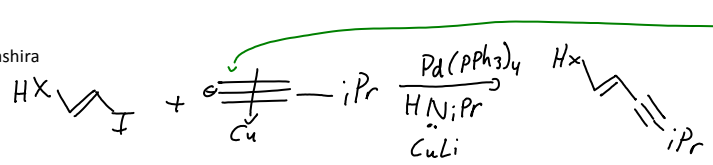
Audio recording started: 11:07 AM Thursday, November 20, 2008

Cross-coupling reactions

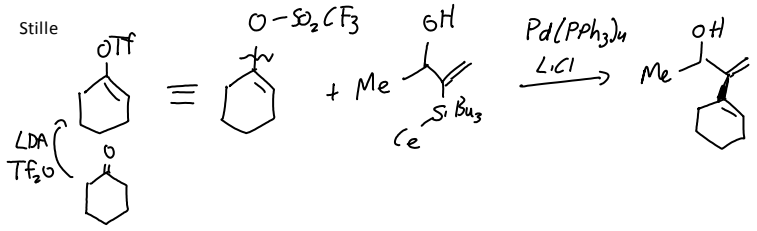
Negishi



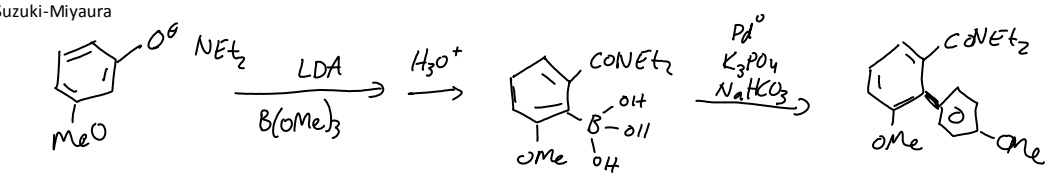
Sonogashira

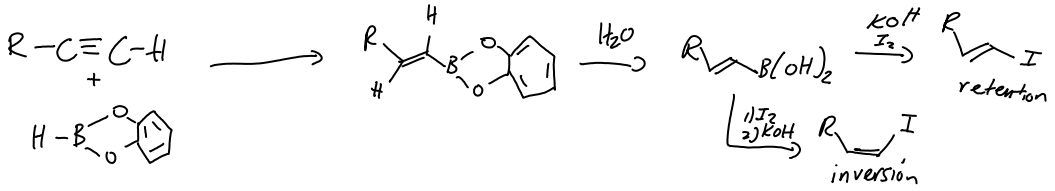


Stille

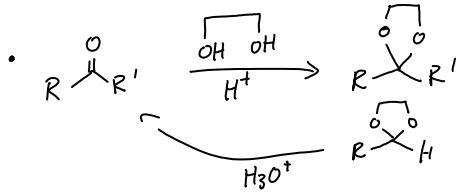


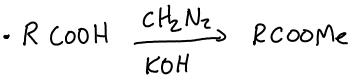
Suzuki-Miyaura



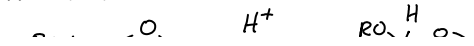


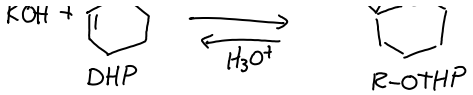
Protecting groups (see handout)



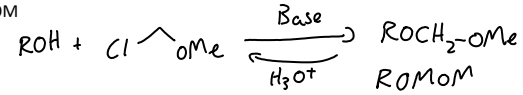


1. Acetals
   a) Tetrahydropyranal (THP)

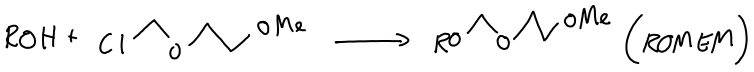




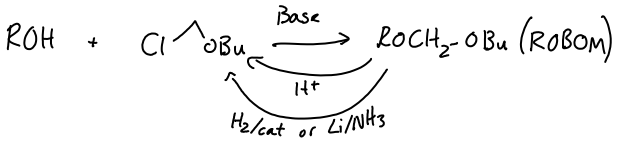
b) MOM



c) Methoxyethoxymethyl (MEM)

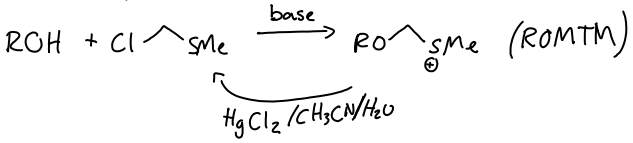


d) BOM (even though acid unstable, can remove by H_2/cat or Li/NH_3

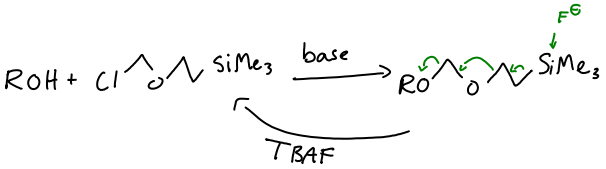


e) MTM

RSH = mercaptans



f) SEM



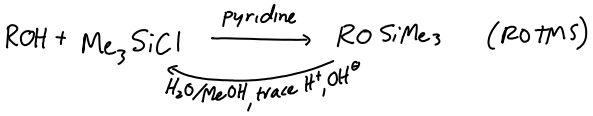
g) Ethoxyethyl (EE)

THP's older brother and used very little

2. Silyl Ethers

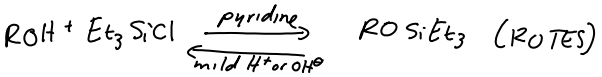
a) Trimethylsilys (TMS)

- Stable to cat hydrogenation and heat, everything else takes off



b) Triethylsilyl (TES)

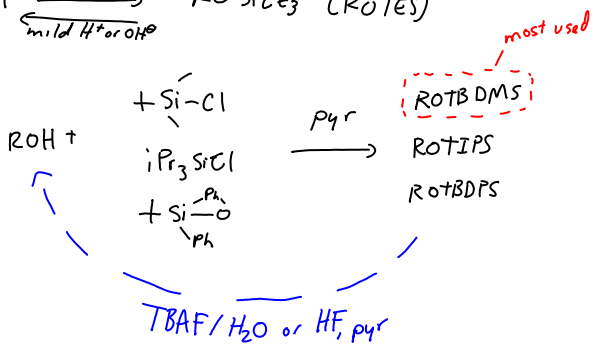
- More stable than TMS because sterics



c) TBDMS (TBS)

d) TIPS

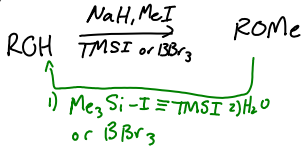
e) TBS

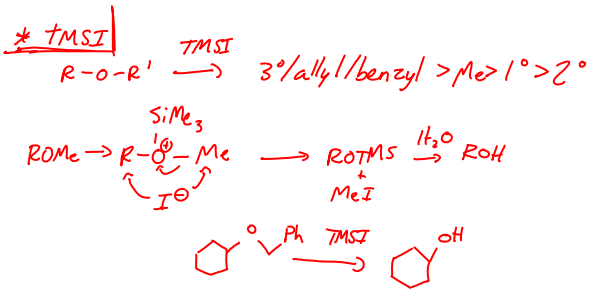


More hindered, the slower.

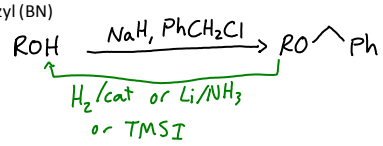
3. Ethers

a) methyl



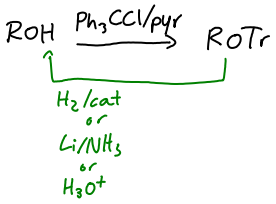


b) Benzyl (BN)

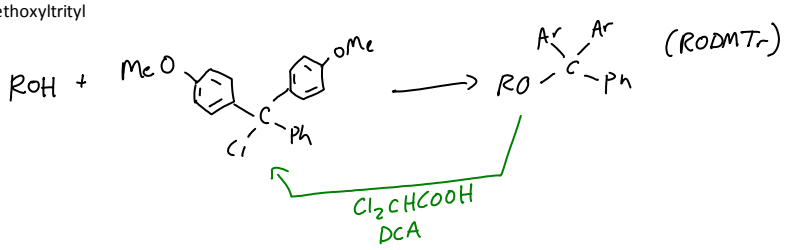


c) Trityl (Tr)

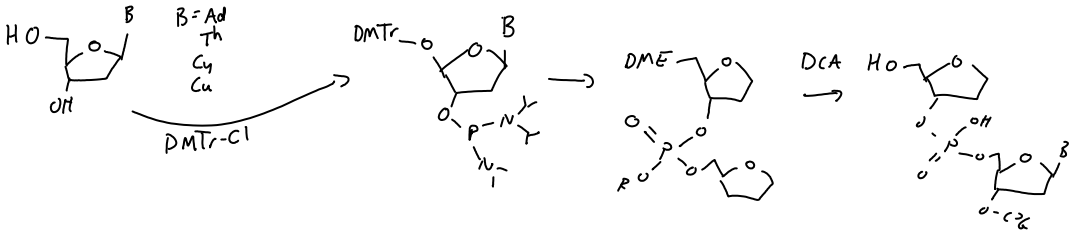
Big brother of benzyl, don't need NaH because cation is so stable



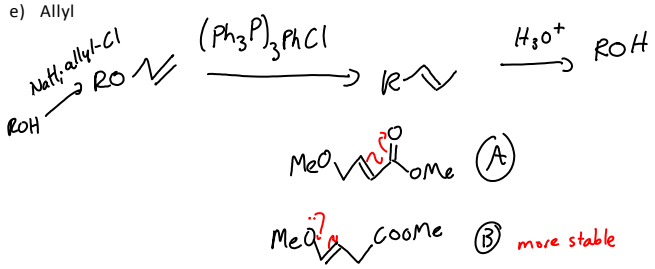
d) Dimethoxyltrityl



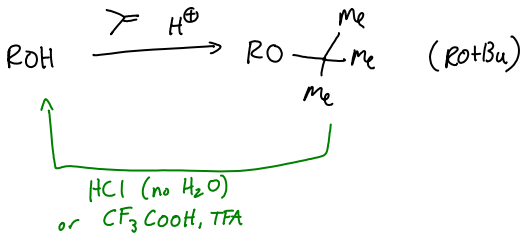
*Aside DNA synthesis using Dimethoxyltrityl:



e) Allyl



f) t-butyl



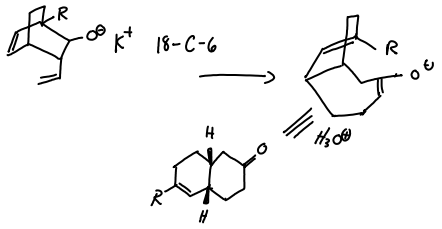
Notes 12/02

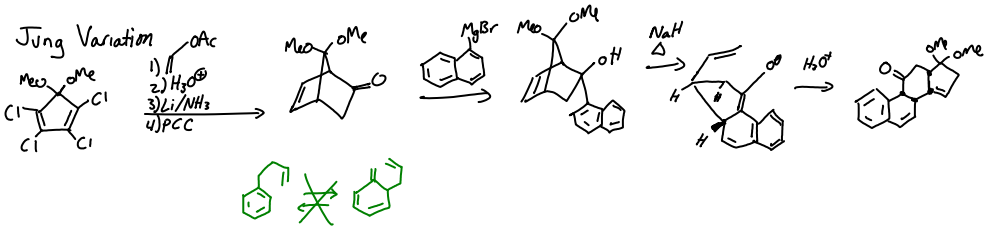
Tuesday, December 02, 2008
11:00 AM

1. Thurs 12/11/08 3-6pm FINAL
2. Wed 12/10/08 Review Session 3440 Mol Sci 1pm
3. Final labs due Mon 12/15/08 10AM to TA

Rearrangements:

1) Cope
2) Oxy-cope





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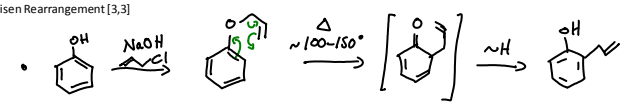
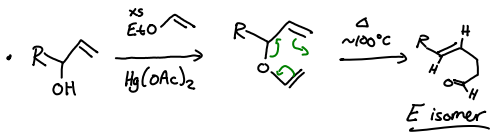
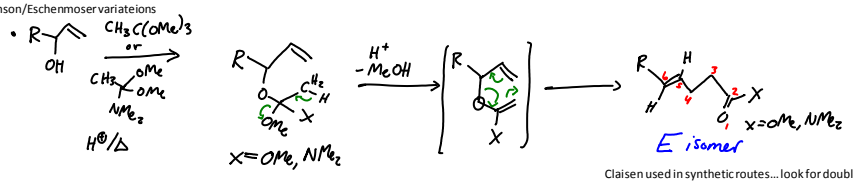
4) Claisen Rearrangement [3,3]



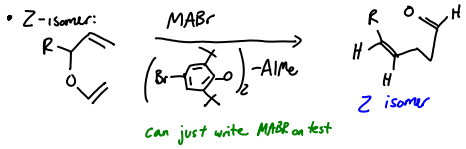


Johnson/Eschenmoser variateions



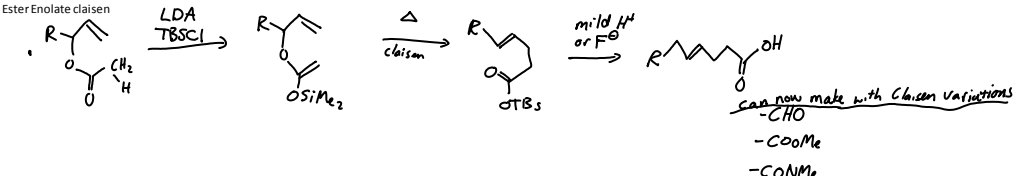
Claisen used in synthetic routes... look for double bond 5-6 pos from carbonyl

Yamamoto

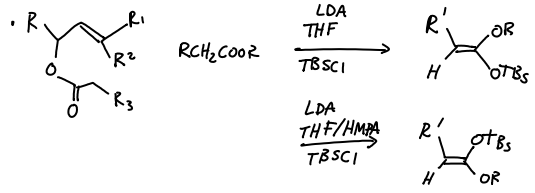


can just write MABR on test

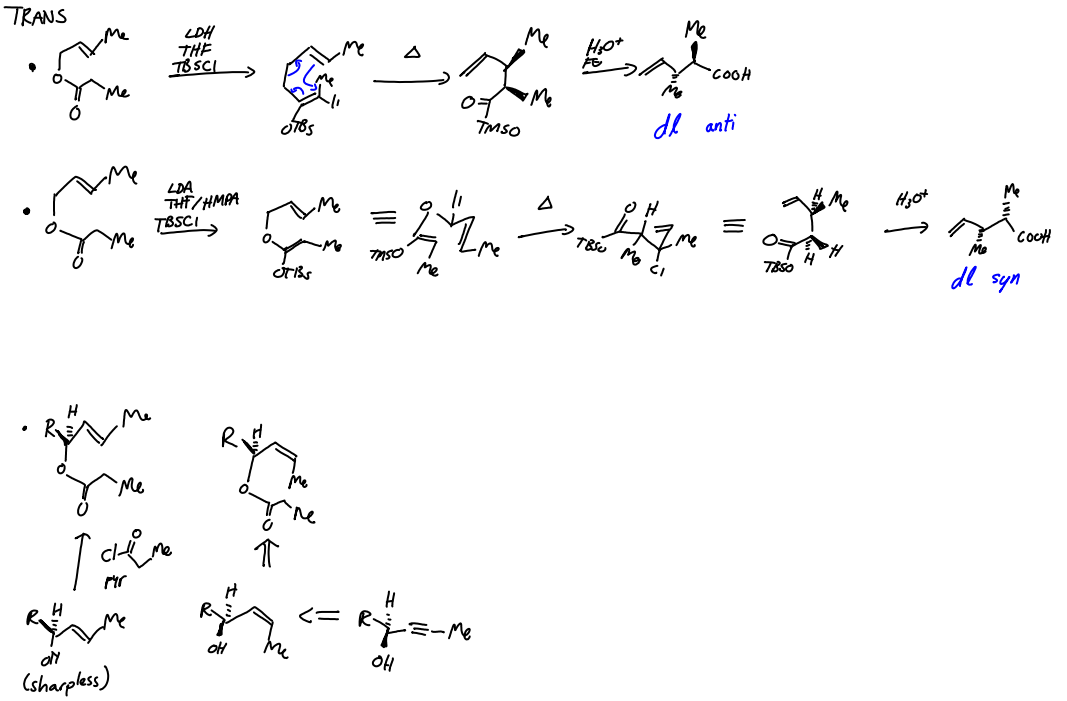
Ester Enolate claisen



can now make with Claisen variations

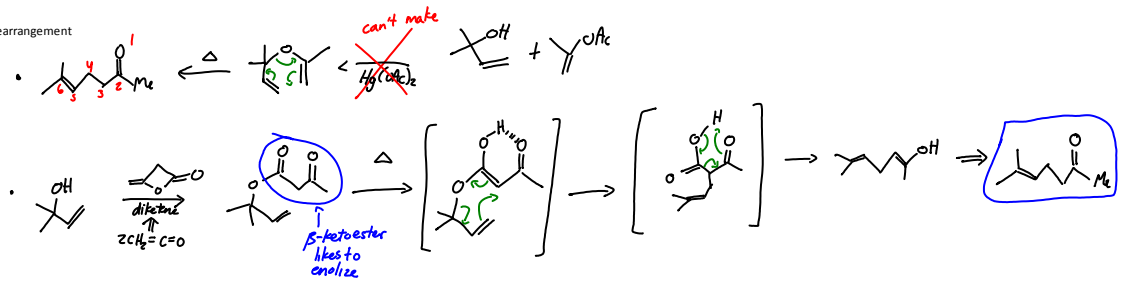


HMPA dissolves up ions and breaks ion pairs - breaks Li-O bond interaction.
TS is eclipsed with Li-O bond so when HMPA is employed there is no Li-O and so chair transition state rearranges to eliminate the eclipsing to steric model on handout.

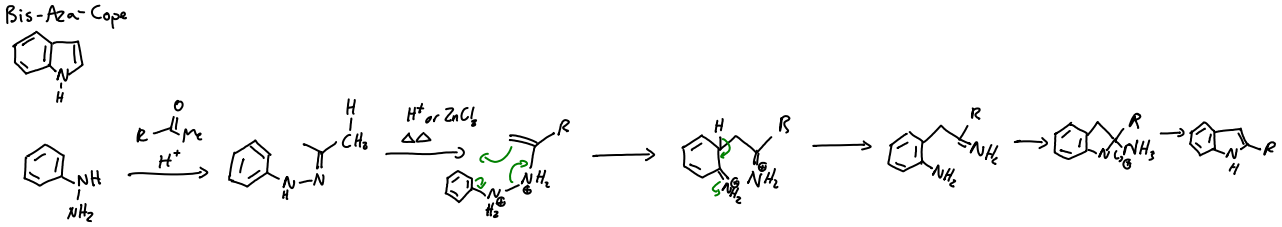


Know how to make 2 compounds on bottom of handout.

Caroll Rearrangement



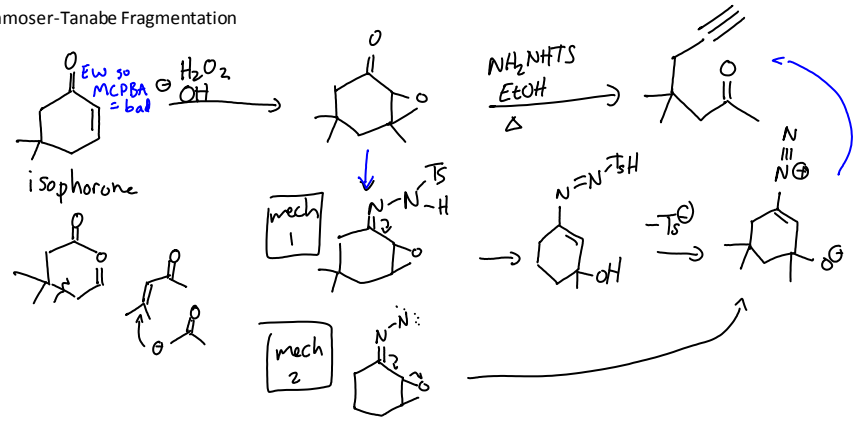
Fischer Indole Synthesis



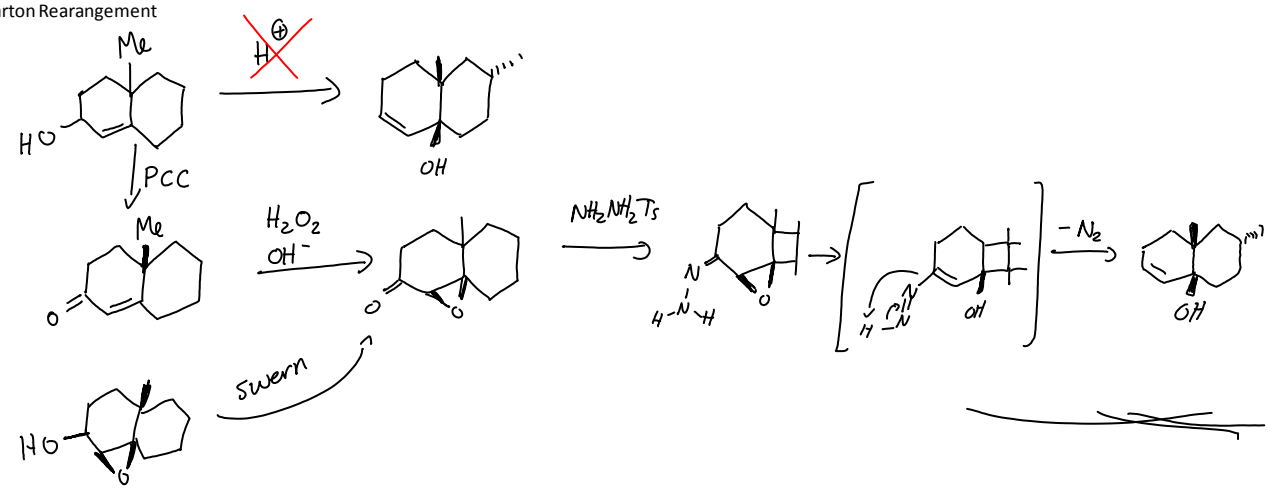
Notes 12/04

Thursday, December 04, 2008
11:05 AM

Eschenmoser-Tanabe Fragmentation



Wharton Rearangement



Final Exam

Thursday, December 04, 2008
11:35 AM

1) Explain: 2-3 probs
2) Predict: A $\xrightarrow{B}$?
3) Transform Lots: A $\xrightarrow{?}$ C
4) Synthesize Lots ? $\xrightarrow{?}$ C
5) Bonus: ~10 pts ... Hard