Advanced Organic Chemistry: Synthesis Name:__Dr. Rick Marshall_____
CHEM 311/511
Final Exam
Monday, December 14, 2009
Wednesday, December 16, 2009

Review each question carefully before answering and be certain you understand everything the question is requesting. Do the easy questions first. If questions appear confusing or exceedingly complex, then you may need to rethink the question. Keep in mind the intended examination topics.

In organic chemistry, hand-drawn pictures convey specific information. Be sure the drawing you have made conveys the essential information required to answer the question. Make certain that three-dimensional pictures display the correct atom arrangements. Maximum credit will be given for answers that correctly address stereochemical considerations in a particular reaction. Don't forget to include formal charges when appropriate.

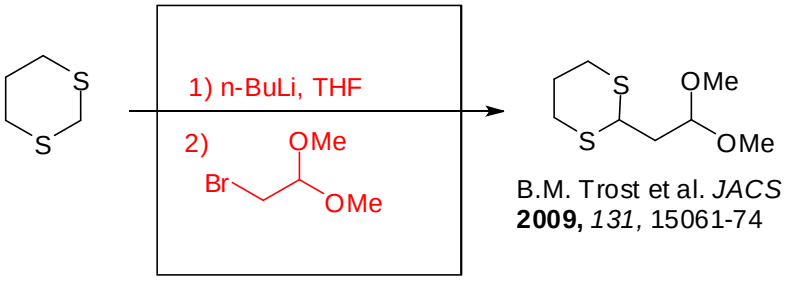
You may use models to assist in determining answers. You should use scrap paper to work out problems before entering your final answer on the exam sheets. In addition, feel free to use the back side of the exam sheets for scrap. If necessary, you may enter exam answers on the back side of the exam sheets, however you must clearly indicate which problems are located on the back of the exam pages.

Graduate students:
Complete 10 of 12 boxes in question 1 (40 pts.)
Complete six of eight parts in questions 2 and 3. (60 pts.)
Complete two retrosynthetic examples in question 4. (20 pts.)
Offer two examples for each part of question 5. (30 pts.)

Undergraduate students:
Complete 8 of 12 boxes in question 1 (40 pts.)
Complete five of eight parts in questions 2 and 3. (60 pts.)
Complete one retrosynthetic example in question 4. (20 pts.)
Offer one example for each part of question 5. (30 pts.)

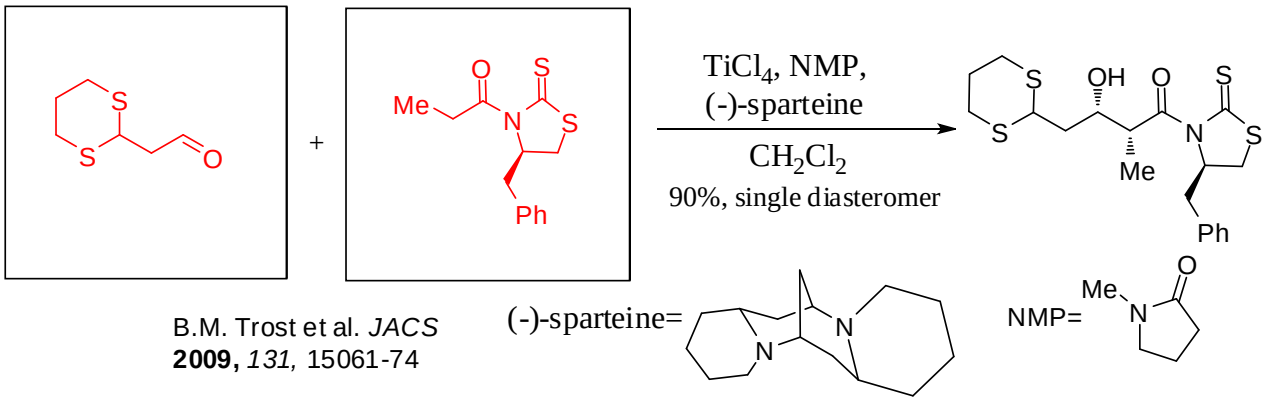
1. Box questions. Provide the necessary information, products or reagents, to complete the following reactions. Undergraduates complete eight of the twelve boxes and graduate students complete ten of twelve. (40 pts.)

a)



B.M. Trost et al. *JACS* **2009,** *131,* 15061-74

b)

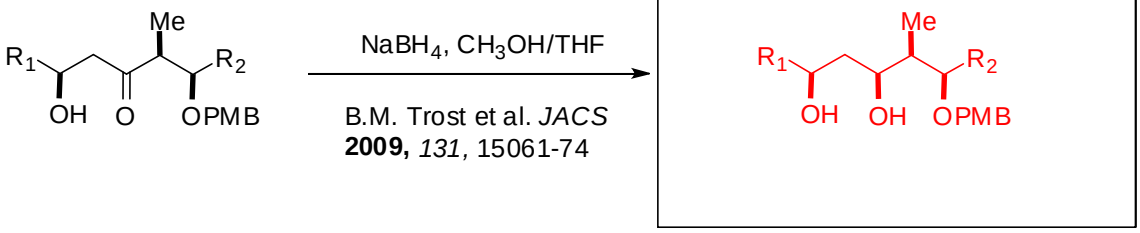


B.M. Trost et al. *JACS* **2009,** *131,* 15061-74

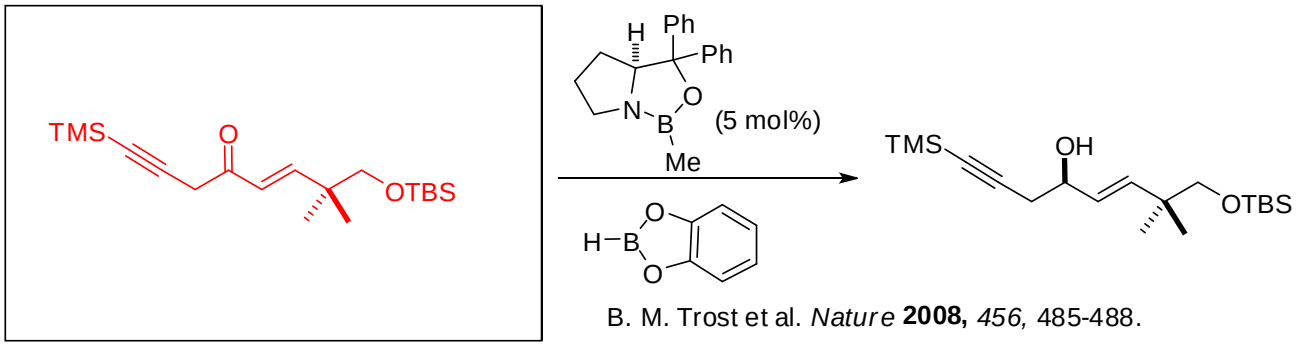
(-)-sparteine=

NMP=

c)

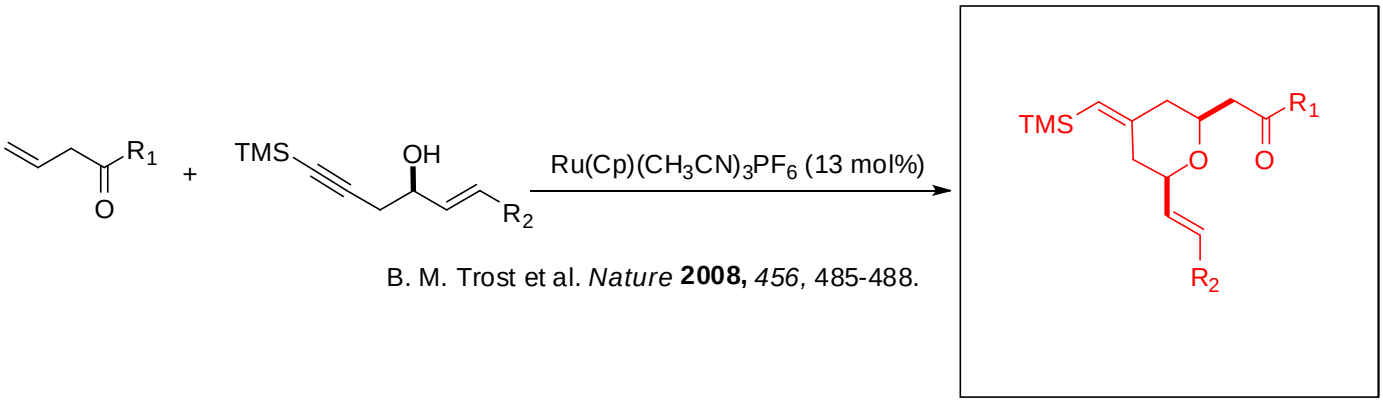


d)



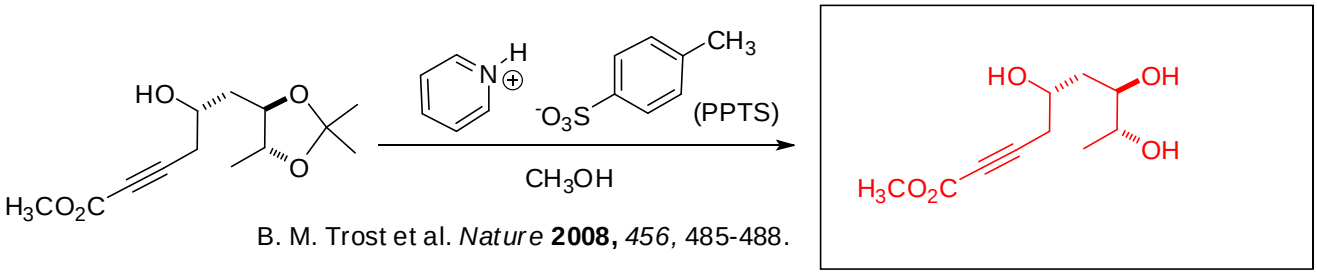
B. M. Trost et al. *Nature* **2008,** *456,* 485-488.

e)



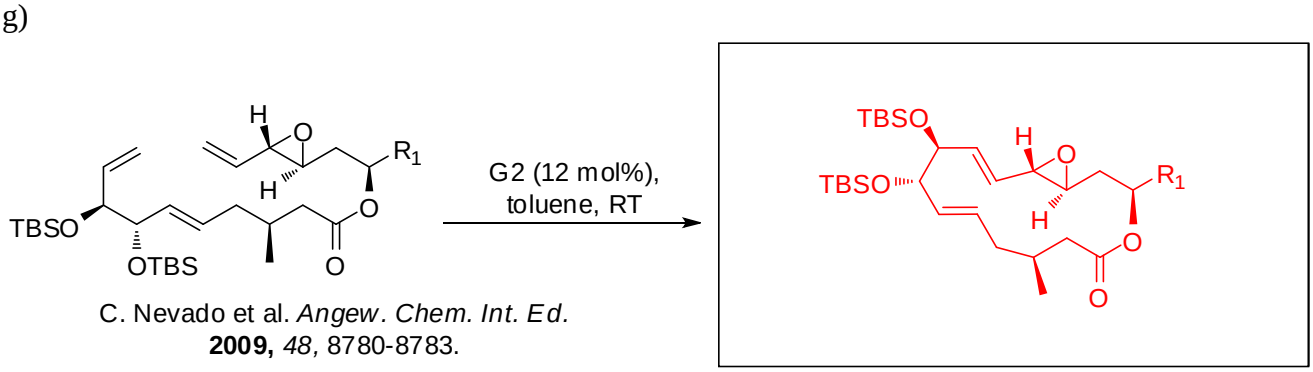
B. M. Trost et al. *Nature* **2008,** *456,* 485-488.

f)



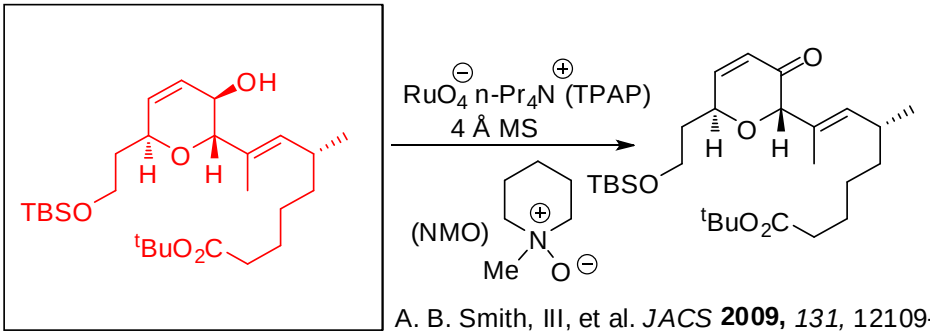
B. M. Trost et al. *Nature* **2008,** *456,* 485-488.

g)



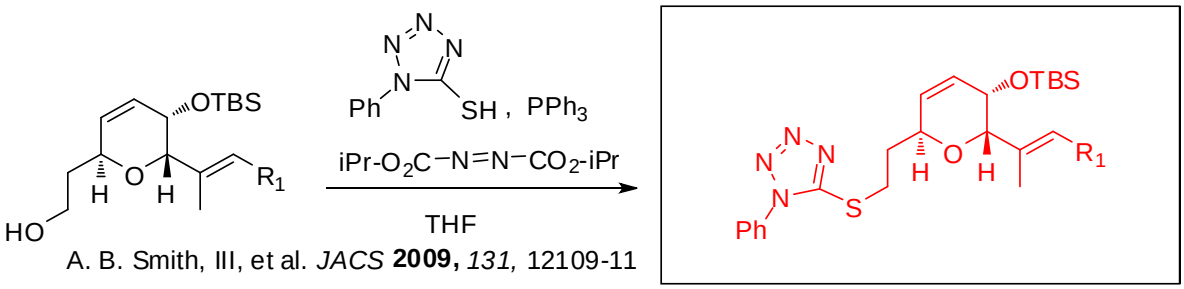
C. Nevado et al. *Angew. Chem. Int. Ed.* **2009,** *48,* 8780-8783.

h)



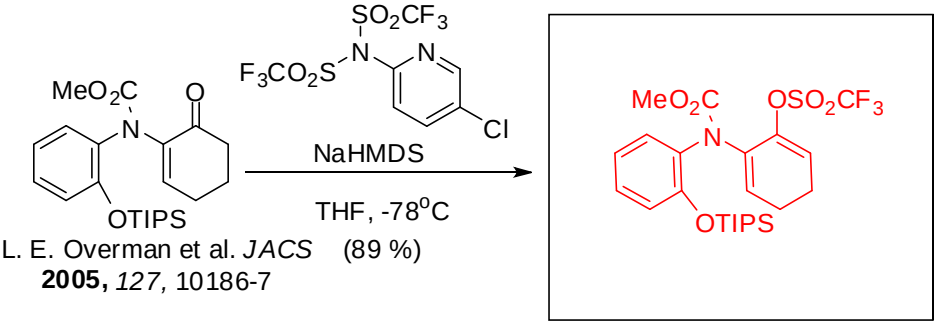
A. B. Smith, III, et al. *JACS* **2009,** *131,* 12109-11

i)



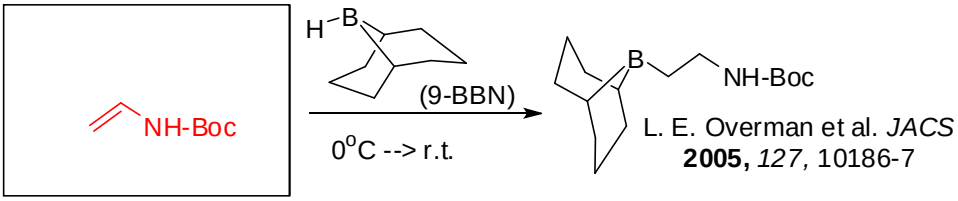
A. B. Smith, III, et al. *JACS* **2009,** *131,* 12109-11

j)



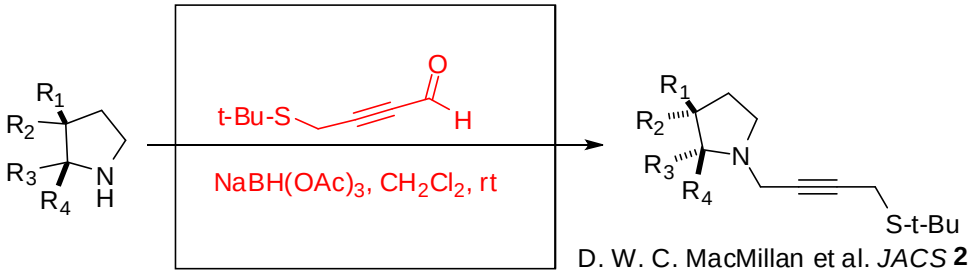
L. E. Overman et al. *JACS* (89 %)
2005, *127,* 10186-7

k)



L. E. Overman et al. *JACS*
2005, *127,* 10186-7

l)

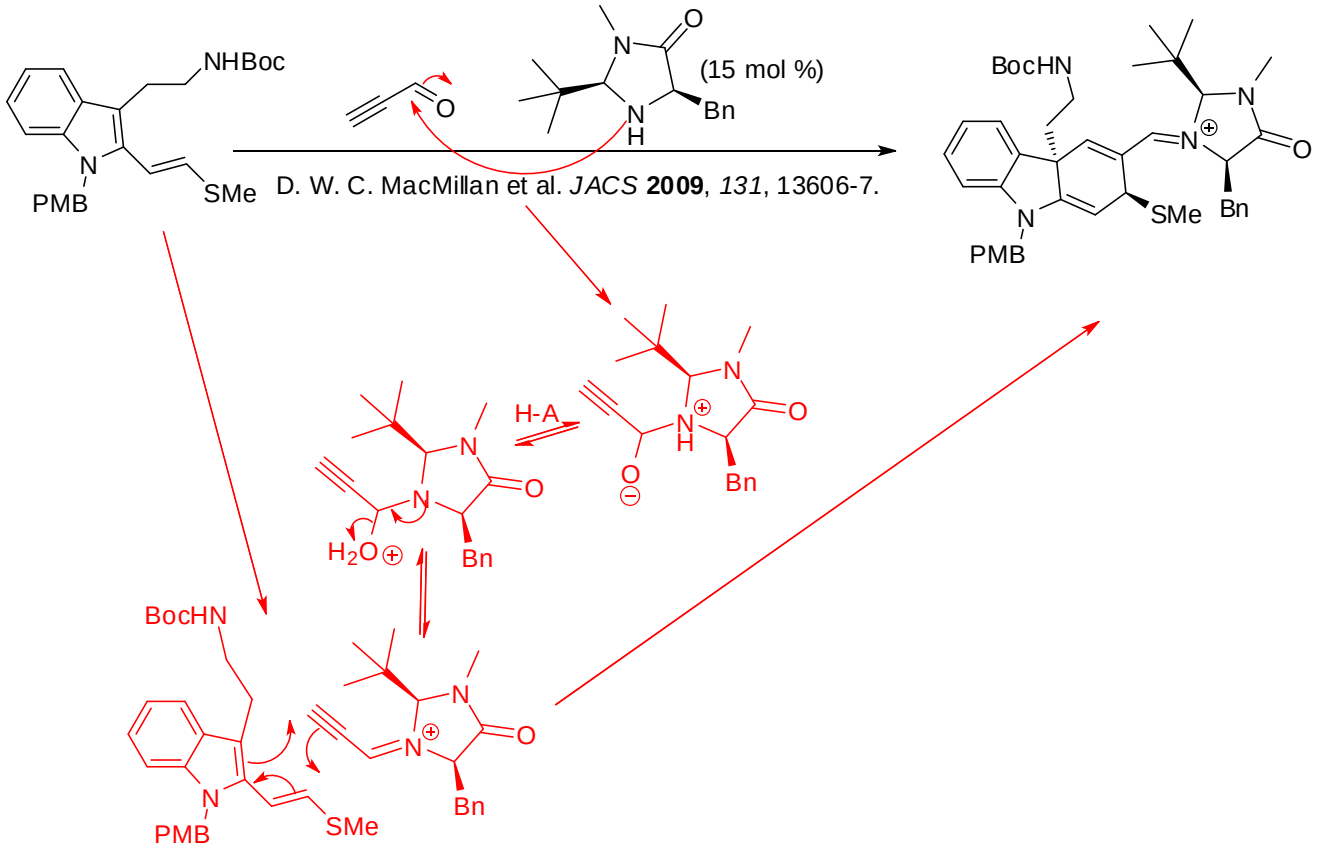


D. W. C. MacMillan et al. *JACS* **2009**, *131*, 13606-7.

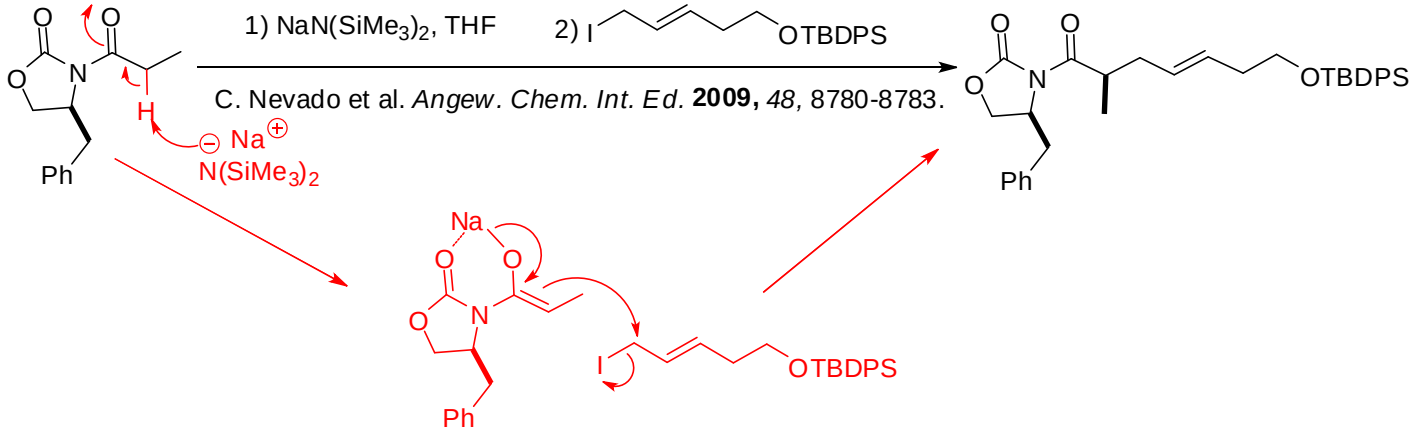
Questions 2 and 3: Undergraduate students must answer five of eight parts and at least two from each section. Graduates students must answer six of eight parts. (60 pts. total)

2. Mechanism questions. Provide the mechanism of the reactions shown. Use curved arrow electron flow conventions and show all key intermediates.

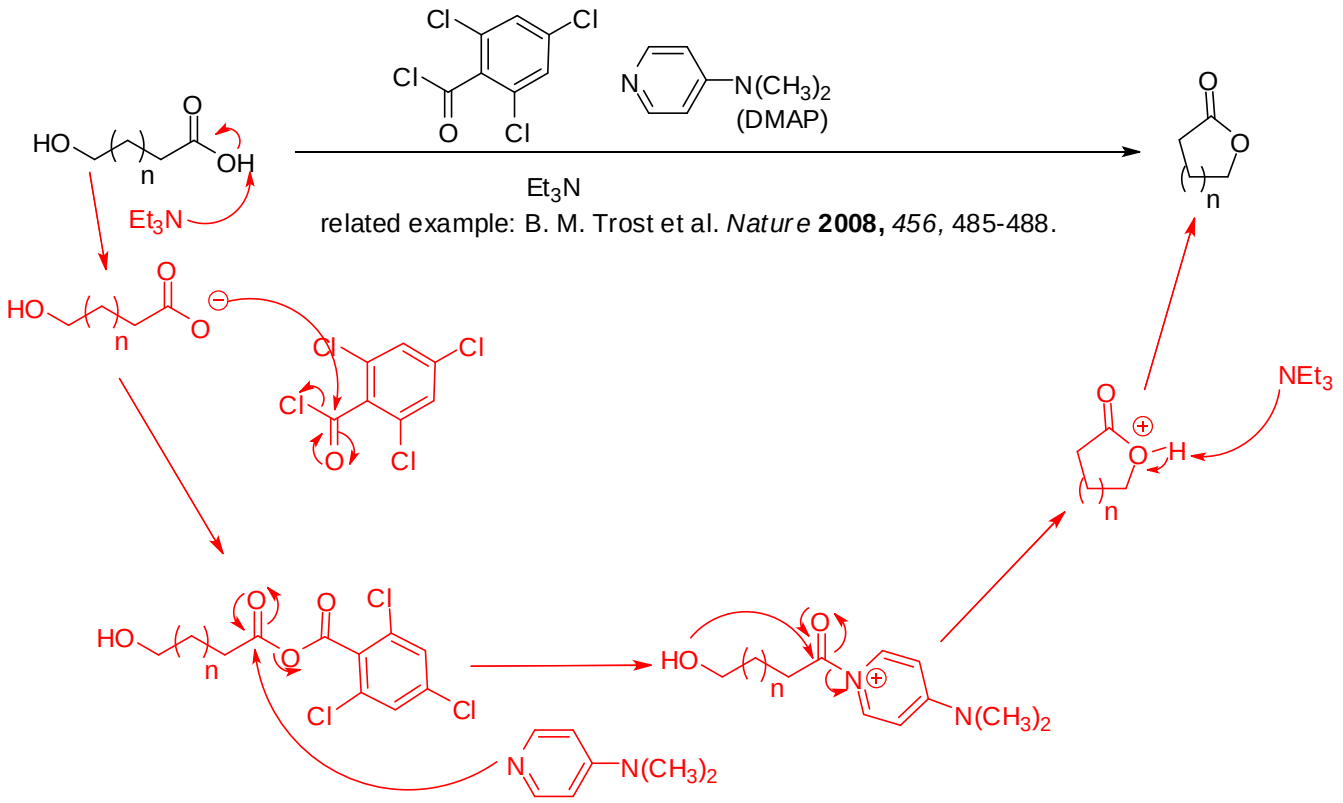
a)



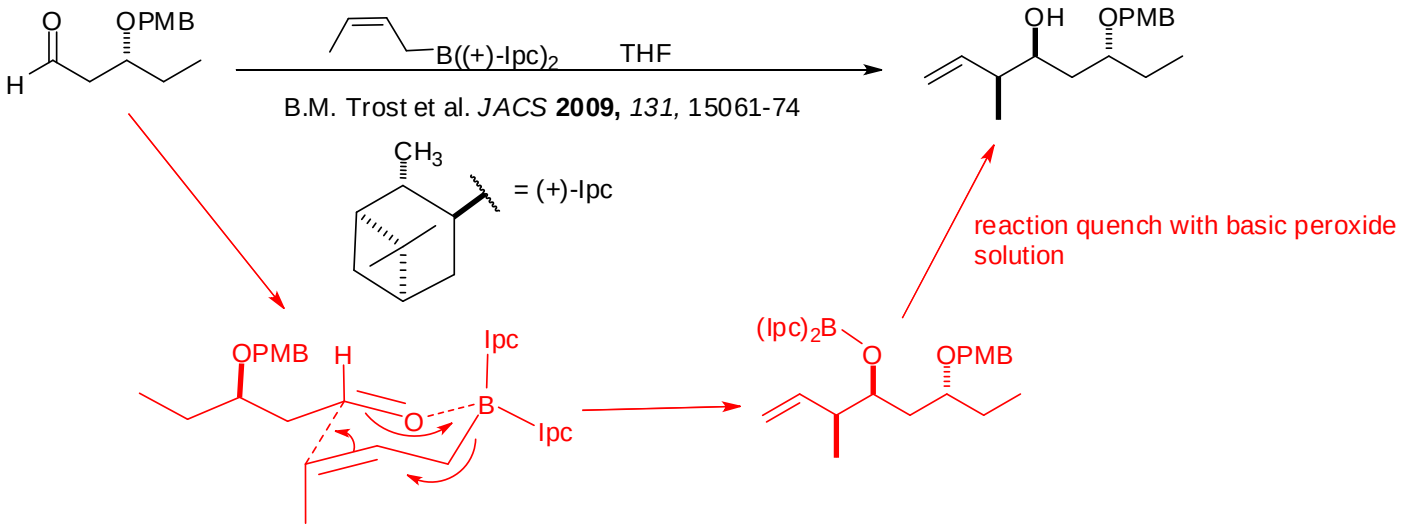
b) Show the mechanism of the following alkylation reaction.



c) Draw the mechanism of the macrolactonization process shown below.

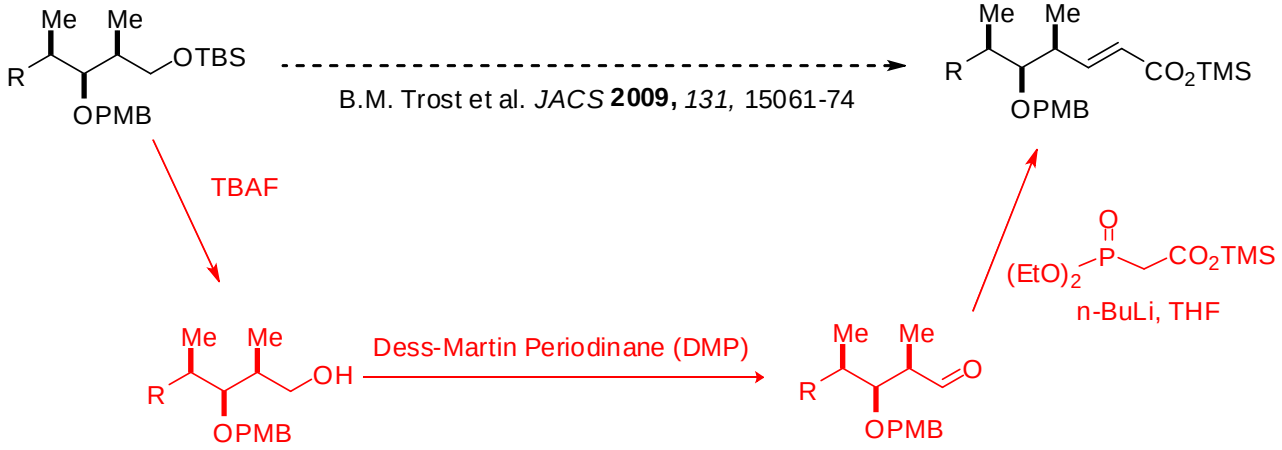


d) Draw the mechanism and transition state of the following reaction. Do not be concerned with explaining the stereochemistry. Hint: the transition state is the same as the boron enolate aldol reactions discussed earlier in the semester.

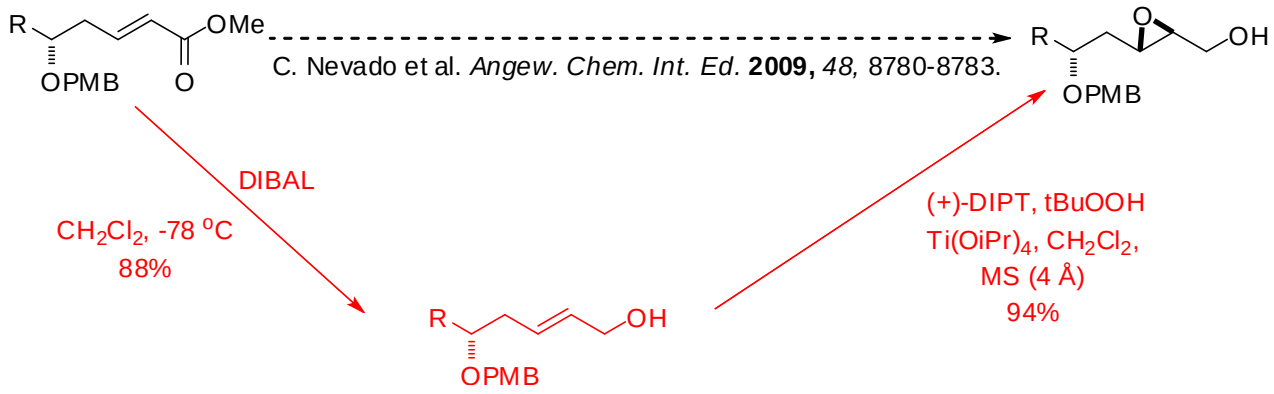


3. Synthesis questions. Provide a series of synthetic reactions to transform the starting material to the product shown. All syntheses can be completed in three or fewer steps.

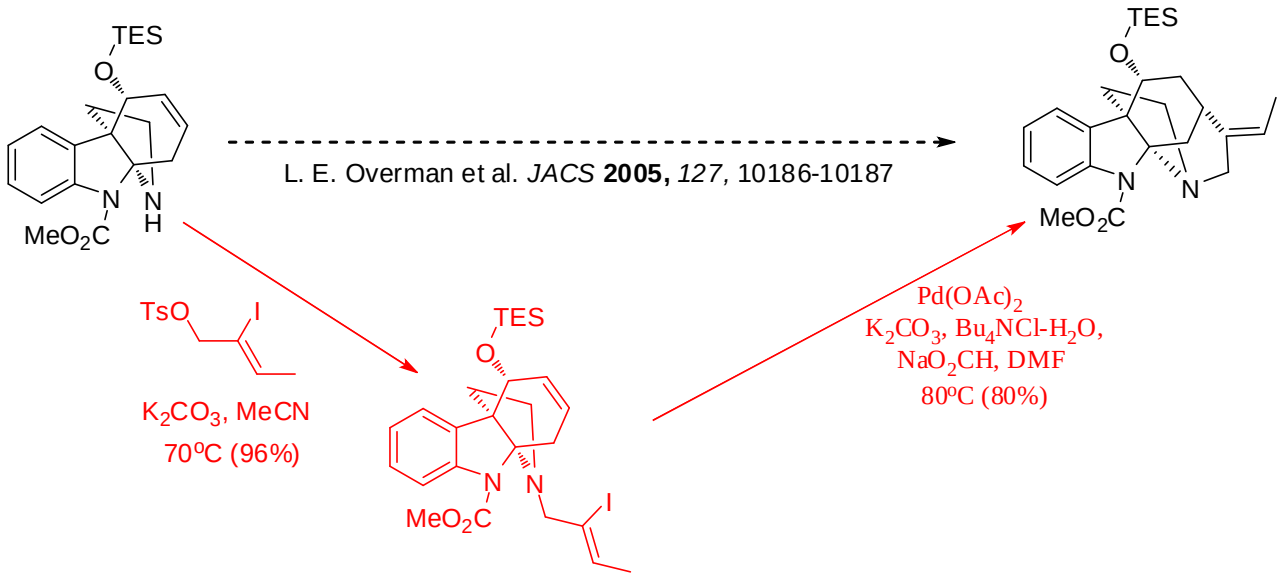
a)


Me
Me
R
OTBS
OPMB
B.M. Trost et al. JACS 2009, 131, 15061-74
Me
Me
R
CO2TMS
OPMB
TBAF
(EtO)2
P
O
CO2TMS
n-BuLi, THF
Me
Me
R
OH
OPMB
Dess-Martin Periodinane (DMP)
Me
Me
R
O
OPMB

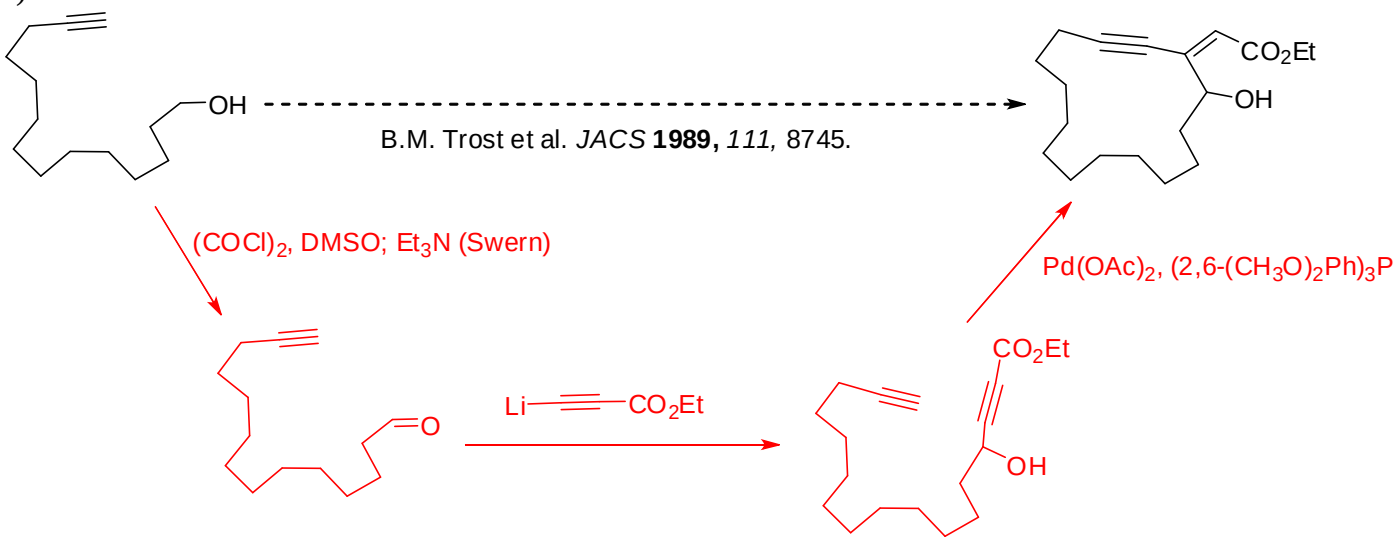
b)


R
OMe
OPMB
O
C. Nevado et al. Angew. Chem. Int. Ed. 2009, 48, 8780-8783.
R
O
OH
OPMB
DIBAL
CH2Cl2, -78 °C
88%
R
OH
OPMB
(+)-DIPT, tBuOOH
Ti(OiPr)4, CH2Cl2,
MS (4 Å)
94%

c)

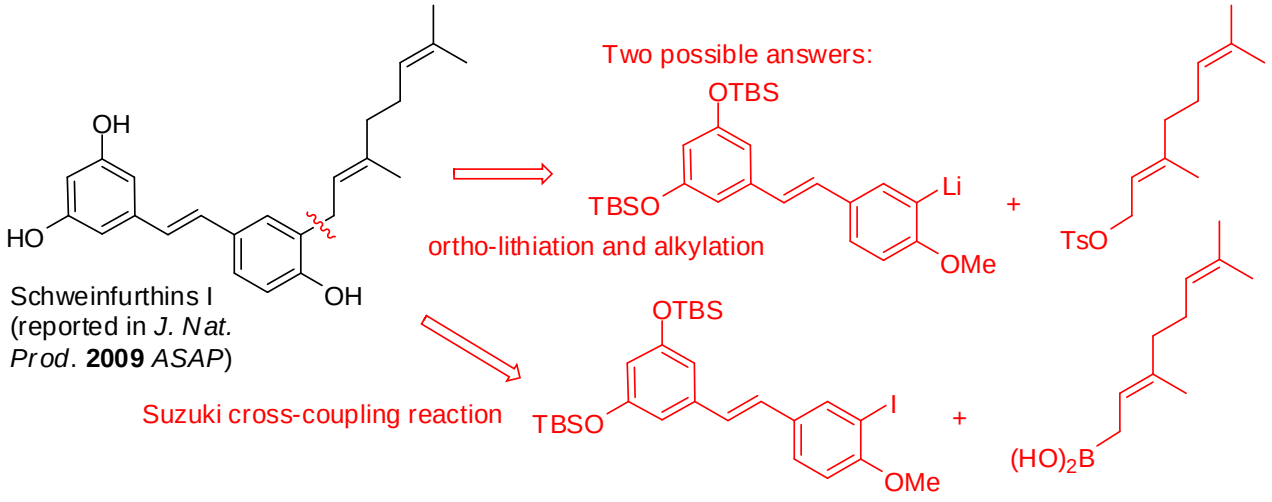

TES
O
N
N
H
MeO2C
L. E. Overman et al. JACS 2005, 127, 10186-10187
TES
O
N
N
MeO2C
TsO
I
K2CO3, MeCN
70°C (96%)
TES
O
N
N
MeO2C
I
Pd(OAc)2
K2CO3, Bu4NCl-H2O,
NaO2CH, DMF
80°C (80%)

d)



4. <u>Retrosynthetic analysis.</u> Provide a brief retrosynthetic plan for the following molecules. You should suggest one or two key bonds that might be central to the construction of these molecules. Include the structures of key intermediates. You should provide key reagents or name the reactions that will be used. Use protecting groups on your intermediates if one is required. Undergraduates must complete one retrosynthesis and graduate students must complete two. (20 pts.)

a)



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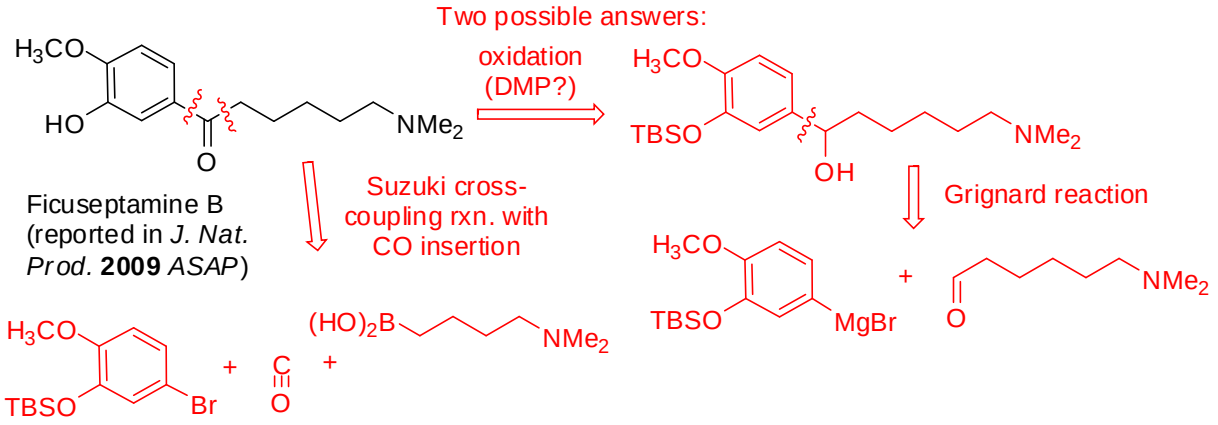
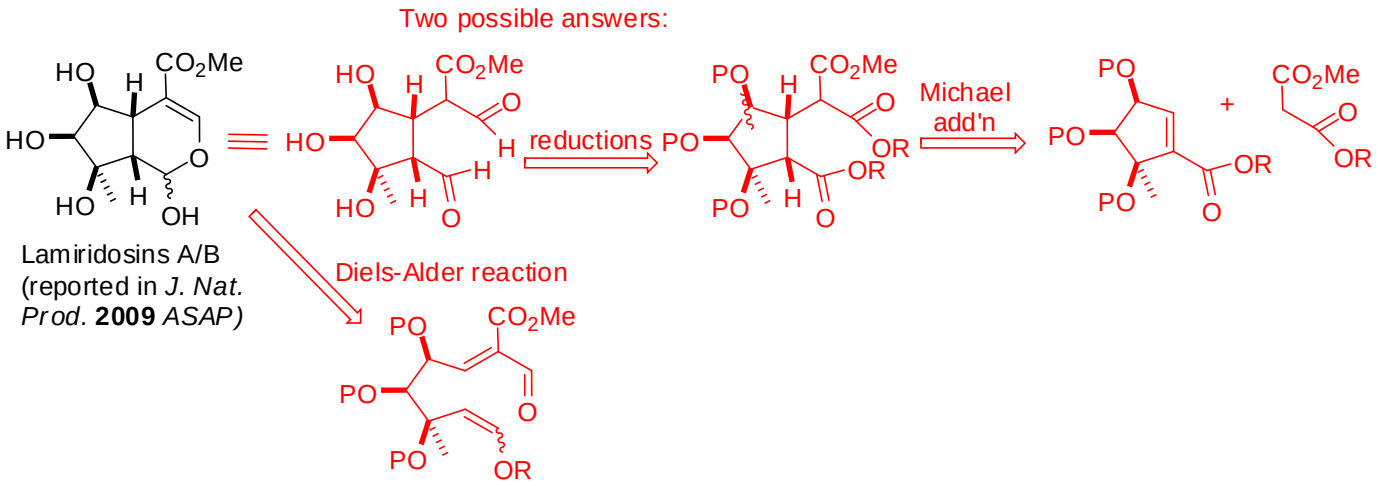


c)



5. Selectivity in synthetic chemistry. Complex molecule synthesis requires useful reactions to demonstrate selectivity, either chemo-, regio- or stereoselectivity. Undergraduate students show one example of each form of selectivity or site an example of each form used on this exam. Graduate students must show two examples of each form of selectivity. Both students must briefly explain the chemical basis of the selectivity if it is known. (30 pts.)

a) chemoselectivity example:

Question 1e:
Chemoselective Ru-catalyzed alkene-alkyne coupling between a beta,gamma-unsaturated ketone and an alkyne in the presence of another disubstituted alkene.

Question 1k:
Hydroboration of alkene in the presence of a carbamate group (NH-Boc). The alkene is most nucleophilic site.

Question 2c:
Chemoselective reaction between the best nucleophile, the carboxylate anion, and the best electrophile, the acid chloride. Note that the alcohol does not react. DMAP reacts to further activate the acid chloride.

Question 3a:

Chemoselective deprotection in first step due to TBS (tert-butyldimethylsilyl) ether group susceptibility to fluoride reagent (TBAF) versus p-methoxybenzyl ether protecting group. Fluoride atom forms a very strong bond with Si atoms.

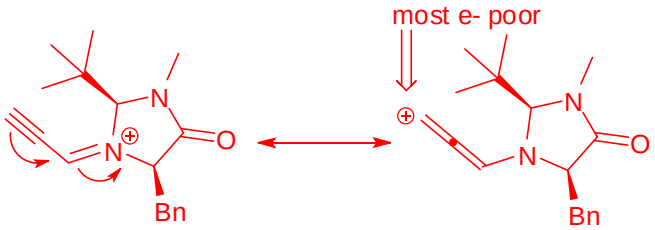
b) regioselectivity example:

Question 1g:
Regioselective (chemoselective also) reaction of Grubbs 2nd generation catalyst with least substituted, most sterically accessible monosubstituted alkenes in the presence of two monosubstituted and one disubstituted alkene.

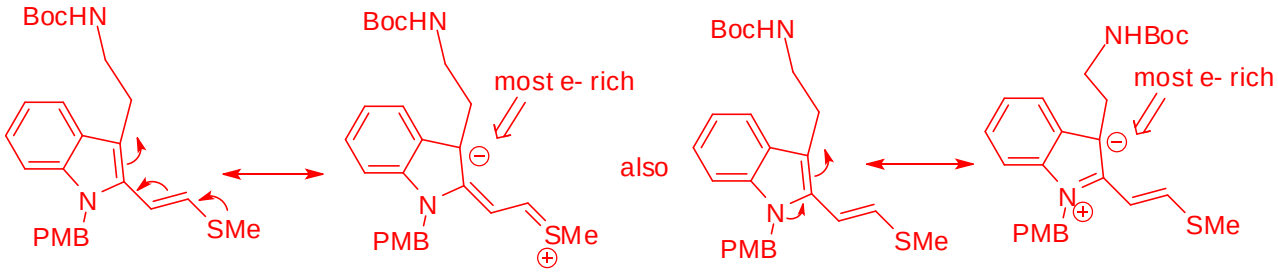
Question 1j:
Regioselective deprotonation of ketone at the most sterically accessible and most acidic alpha position with NaHMDS instead of at gamma position of enone system. This occurs because NaHMDS is a strong and bulky base.

Question 1k:
Hydroboration affords the anti-Markovnikov product, i.e. boron attached to least substituted end of alkene. The 9-BBN is a particularly bulky form of hydroborating agent which contributes to the regioselective preference for the least substituted side of the alkene.

Question 2a:
Regioselective due to electronics which aligns the most electron rich position of diene with the most electron poor position of alkyne (dienophile):
dienophile polarization:

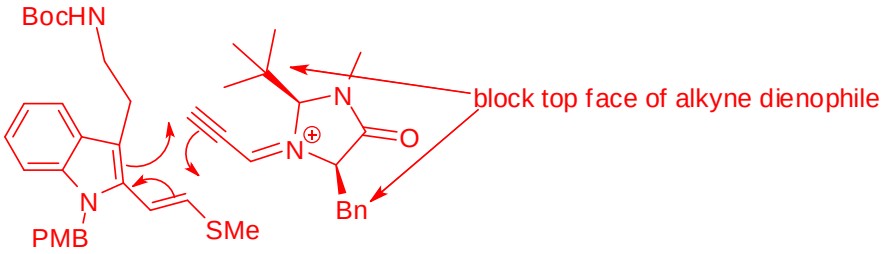


diene polarization:

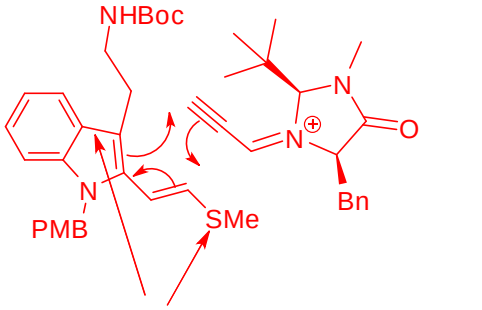


c) stereoselectivity example:

Question 2a:
Stereoselective (enantioselective) due to imidazolidinone ring which forms an iminium ion with propynal and blocks one face of pi system with t-Bu and Bn groups.



Stereoselective (diastereoselective) due to concerted, pericyclic reaction (cis principle).



Ph and SMe are cis in product because both groups are pointing 'out' or are Z relative to diene geometry.

Question 2b:

Stereoselective (enantioselective) due to Z enolate formation and facial bias due to Bn group blocking top (re) face of enolate.

Question 2d:
Stereoselective (enantioselective) reactin due to cyclic transition state and chiral/steric influence of (+)-isopinocamphyl (Ipc) groups on boron.

Question 3a:
Stereoselective reaction due to Horner-Wadsworth-Emmons reagent equilibrating during reaction (as oxaphosphetane intermediate) to form more stable E alkene.

Question 3b:
Stereoselective (enantioselective) reaction due to Sharpless asymmetric epoxidation using chiral ligand, (+)-DIPT, on Ti epoxidation catalyst.