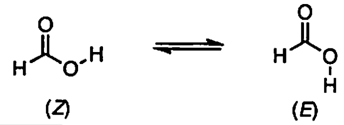
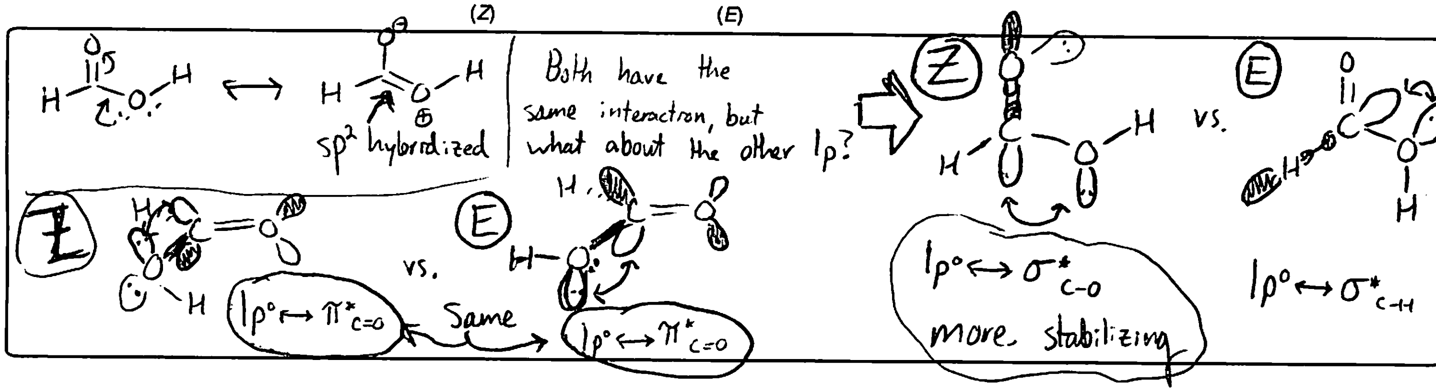
Name: Answer Key

CHEM 633: Advanced Organic Chem: Physical
Problem Set 2. Due 9/22/16. ***Do not look up references until after you have turned in the problem set!***

5 1. Using FMO arguments, please explain why the *Z* acid conformation is more stable than then *E* conformation.

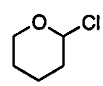


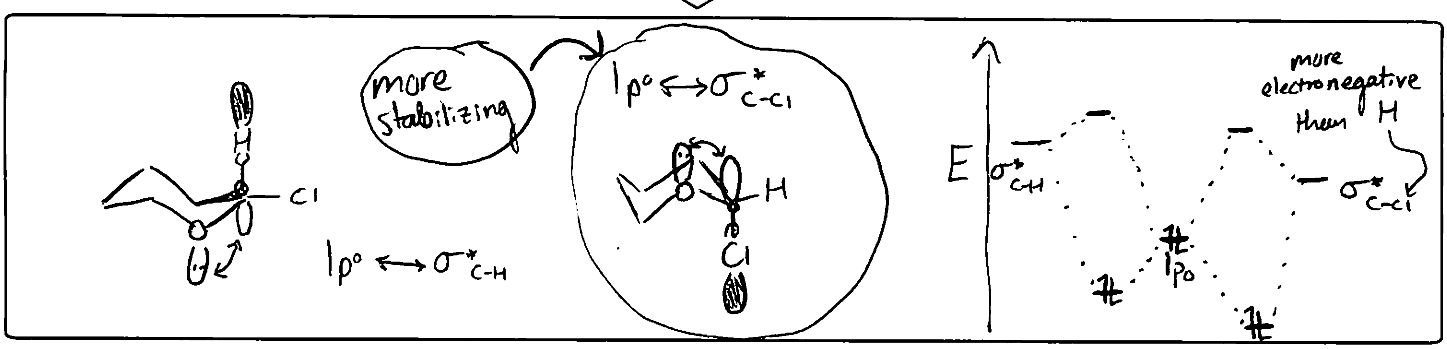
$\Delta G° = +2$ kcal/mol



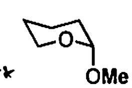
5 2. Please predict the lowest energy conformation of 2-chlorotetrahydropyran. Explain your answer using pictures and less than 10 words.

0, 3, 5

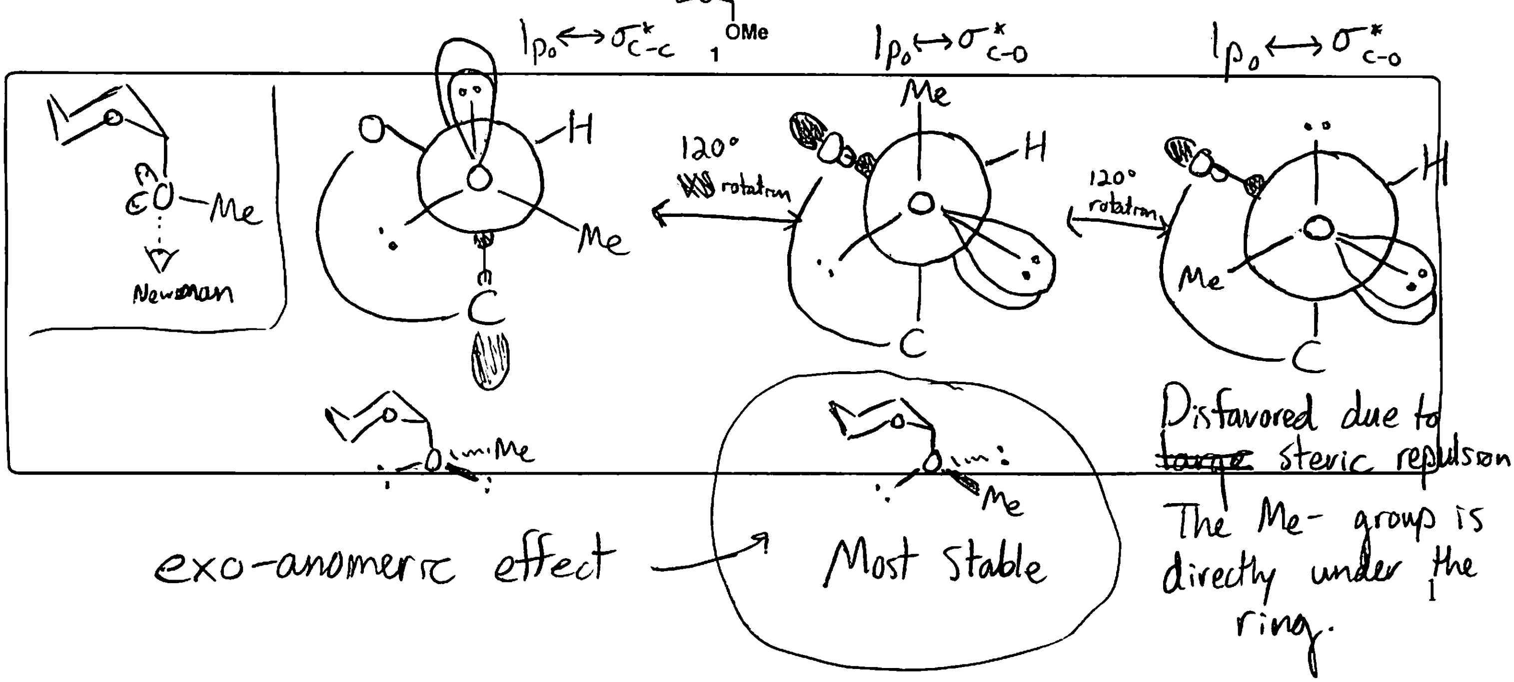




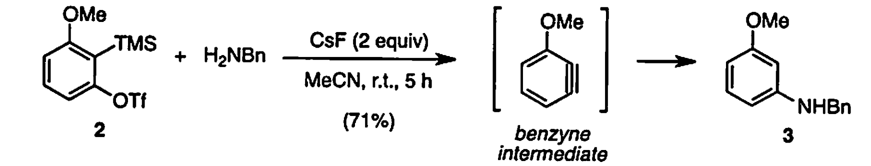
5 3. Where is the methyl group in the lowest energy conformation of ketal **1**? Please use Newman projections to clearly illustrate the position of the methyl group. Also, please explain your reasoning. You may use steric, electronic and/or stereoelectronic arguments.



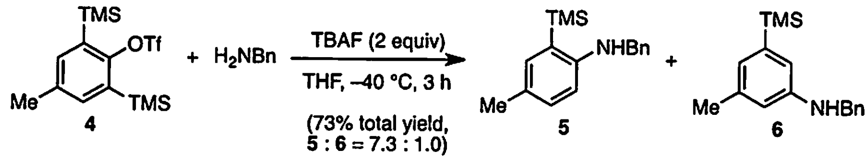
1



10 4. *ortho*-Silylaryl triflates, such as **2**, are useful substrates for generating benzyne intermediates. Larock et al. found that *meta*-substituted product **3** was the only observed product in the addition of benzyl amine to **2**. In contrast, Akai et al. observed that *ortho*-substituted aniline **5** was the major product in the reaction of **4**.

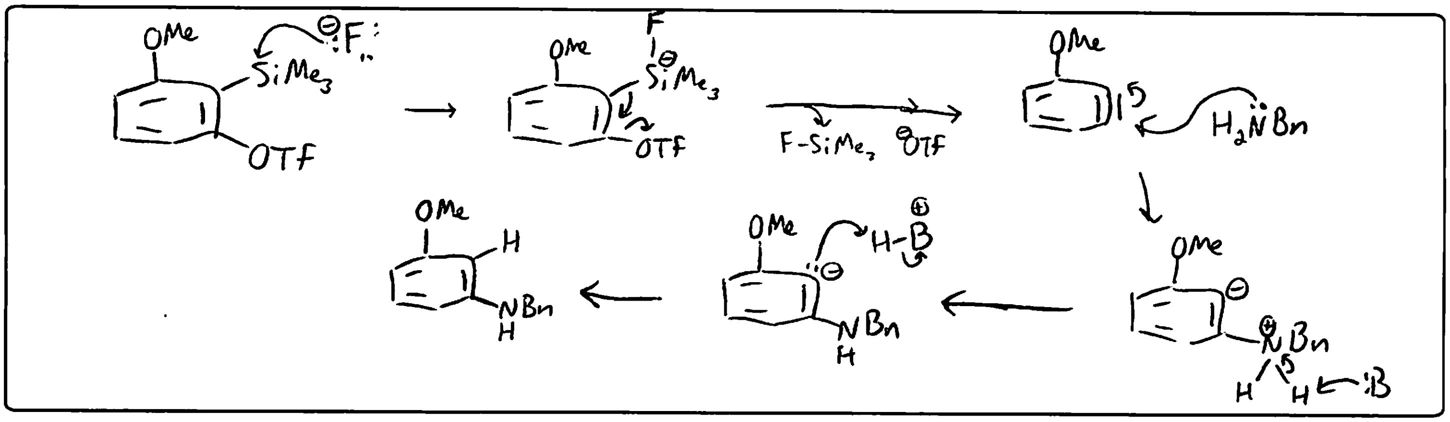


Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198.

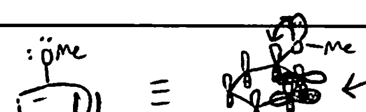


Ikawa, T.; Nishiyama, T.; Shigeta, T.; Mohri, S.; Morita, S.; Takayanagi, S.; Terauchi, Y.; Morikawa, Y.; Takagi, A.; Ishikawa, Y.; Fujii, S.; Kita, Y.; Akai, S. *Angew. Chem. Int. Ed.* **2011**, *50*, 5674.

(a) Please draw a reasonable arrow-pushing mechanism for the transformation of **2** to **3**.



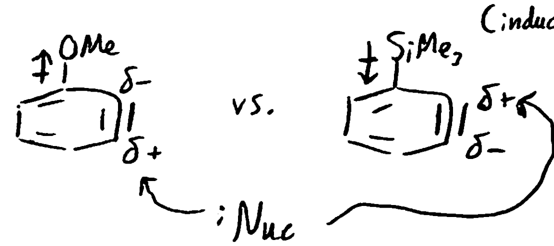
(b) Please rationalize the observed regiochemistry in both of these reactions. Specifically address why *meta* substitution is favored in one case and *ortho* in the other.



π + π* of benzyne (≡) is orthogonal (no geometric overlap) to π-system of benzene. Thus, no stereoelectronic effects.

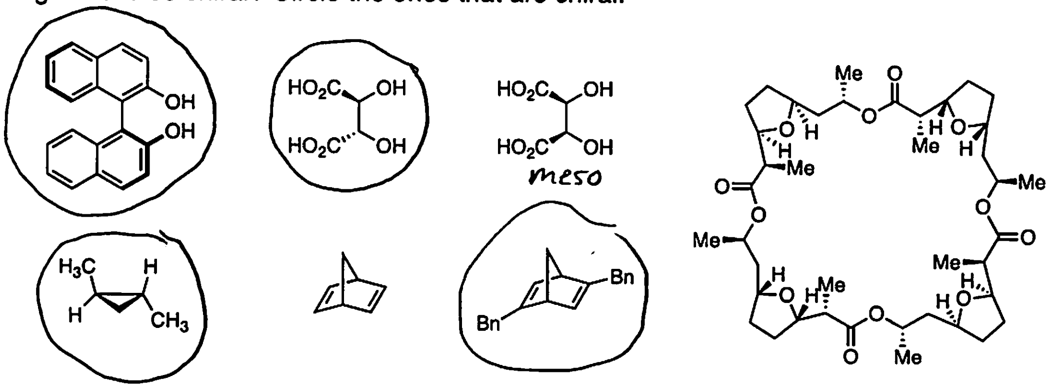
–SiMe3 is larger than –OMe; steric effects very unlikely.

Selectivity is governed by inductive electronic effects: –SiMe3 is donating (inductively)



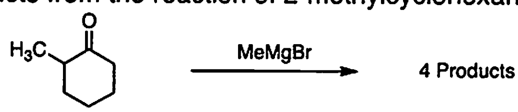
5

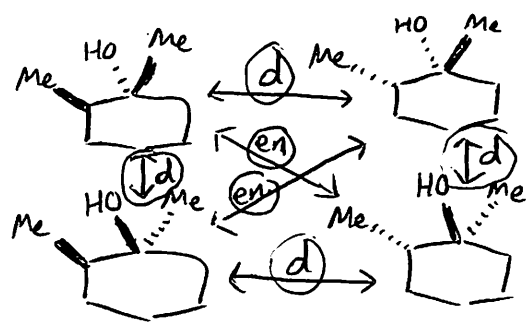
5. Are the following molecules chiral? Circle the ones that are chiral.



10

6. (a) Please draw the 4 possible products from the reaction of 2-methylcyclohexanone and methyl magnesium bromide.





d= diastereomers

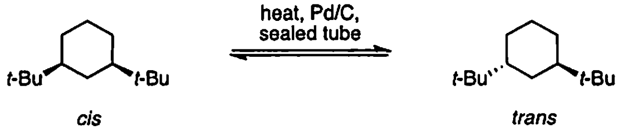
en. = enantiomers

(b) What are the stereochemical relationships between these products?

See above

10

7. The temperature-dependent ratio of isomers of 1,3-di-*tert*-butylcyclohexane has been examined at equilibrium (*J. Am. Chem. Soc.* **1960**, *82*, 2393).



Temperature (K)	% *trans*
492.6	2.69
522.0	3.61
555.0	5.09
580.0	6.42
613.0	8.23

(a) Are the *cis* and *trans* conformations enantiomers or diastereomers?

Diastereomers

(b) Determine ΔH° and ΔS° for this process in kcal/mol and eu, respectively. Please attach your Excel worksheet and graph to the end of your problem set.

$\Delta H° = 5.9$ kcal/mol

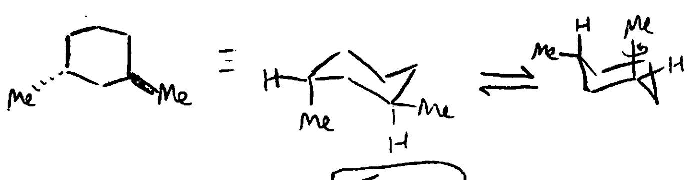
$\Delta S° = 4.9$ eu

See next page for graph

l)hexanoate

Compare the difference in entropy (amount of disorder) between the cis + trans isomers.

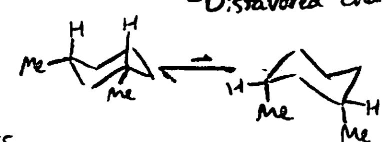
(c) Compare the measured value of ΔS° with those determined for other alkyl substituents by NMR spectroscopy (Me = −0.03 eu, Et = 0.64, *i*-Pr = 2.31), and provide an explanation for the sign and magnitude of the observed value in the *t*-Bu case.



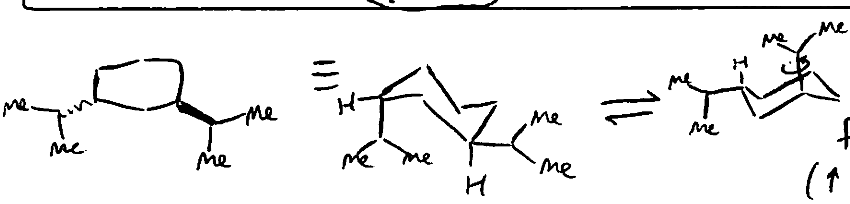
Trans

Favorable
- Chair flip ↑ΔS
- Free C-C bond rotation of methyls ↑ΔS
(Same for ethyl) ~~but less rotation~~

- Disfavored chair flip



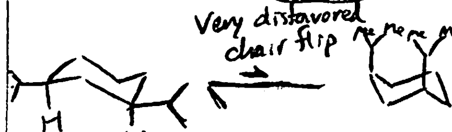
Cis



Poor rotational freedom (↑ in order)

Trans

Very disfavored chair flip

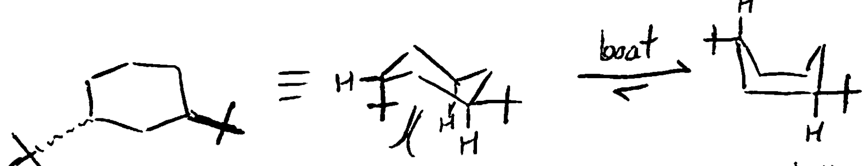


ΔS between cis + trans is thus larger than it is for methyl.

Cis

Trans

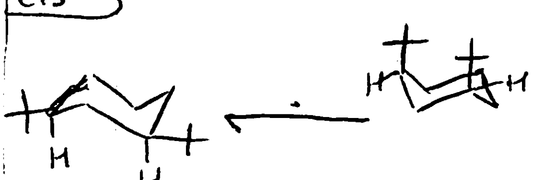
Cis



Massive 1,3 diaxial interaction (A value = 5 kcal/mol)

Now both ᵗBu's are equatorial

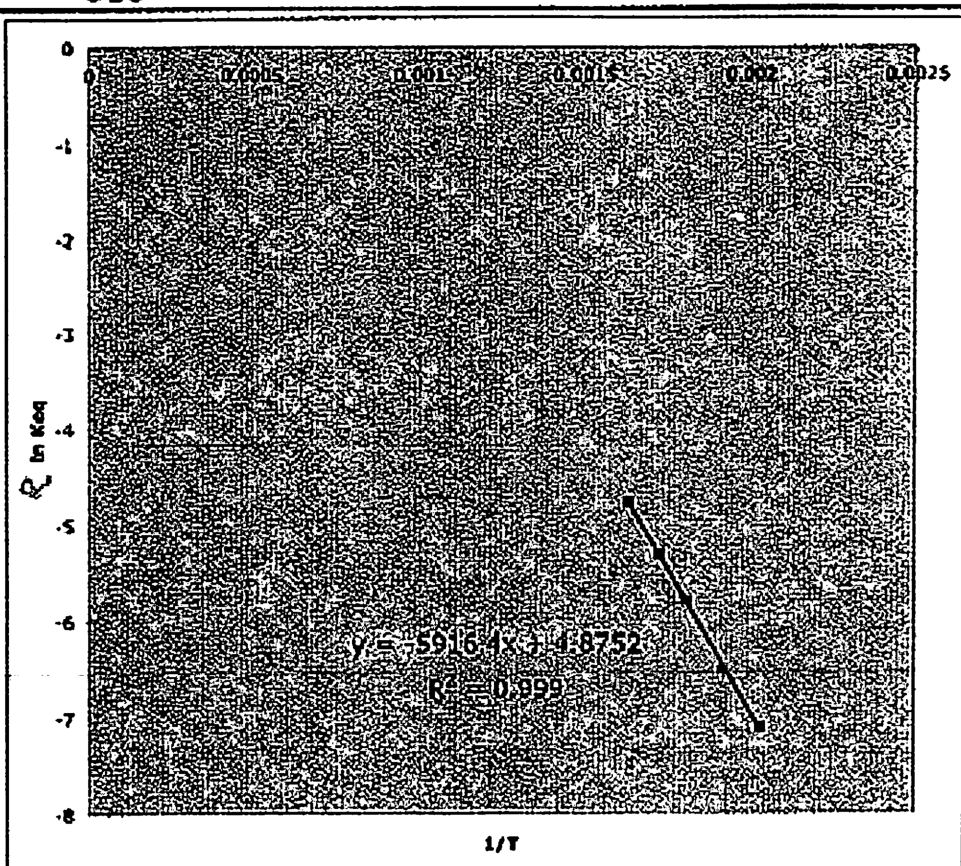
Huge ↑ in ~~ΔS~~ disorder



Very ordered, diaxial ᵗBu's extremely disfavored

(7) (b) Determine $\Delta H°$ and $\Delta S°$ for this process in kcal/mol and eu, respectively.

temperature (K)	1/T	% trans	% cis	Keq	RlnKeq
492.6	0.002030045	2.69	97.31	0.027643613	-7.104953919
522	0.001915709	3.61	96.39	0.037452018	-6.503695485
555	0.001801802	5.09	94.91	0.053629755	-5.792789462
580	0.001724138	6.42	93.58	0.068604403	-5.305209164
613	0.001631321	8.23	91.77	0.089680724	-4.774768876



$$\Delta G° = \Delta H° - T\Delta S°$$

$$-RT \ln K_{eq} = \Delta H° - T\Delta S°$$

$$R \ln K_{eq} = -\frac{1}{T}\Delta H° + \Delta S°$$

slope = $-\Delta H°$

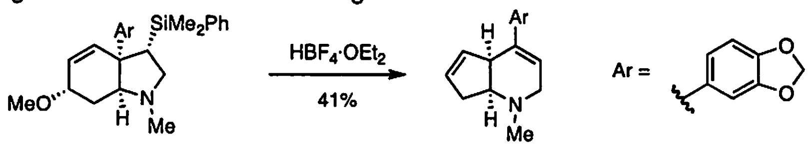
y-intercept = $\Delta S°$

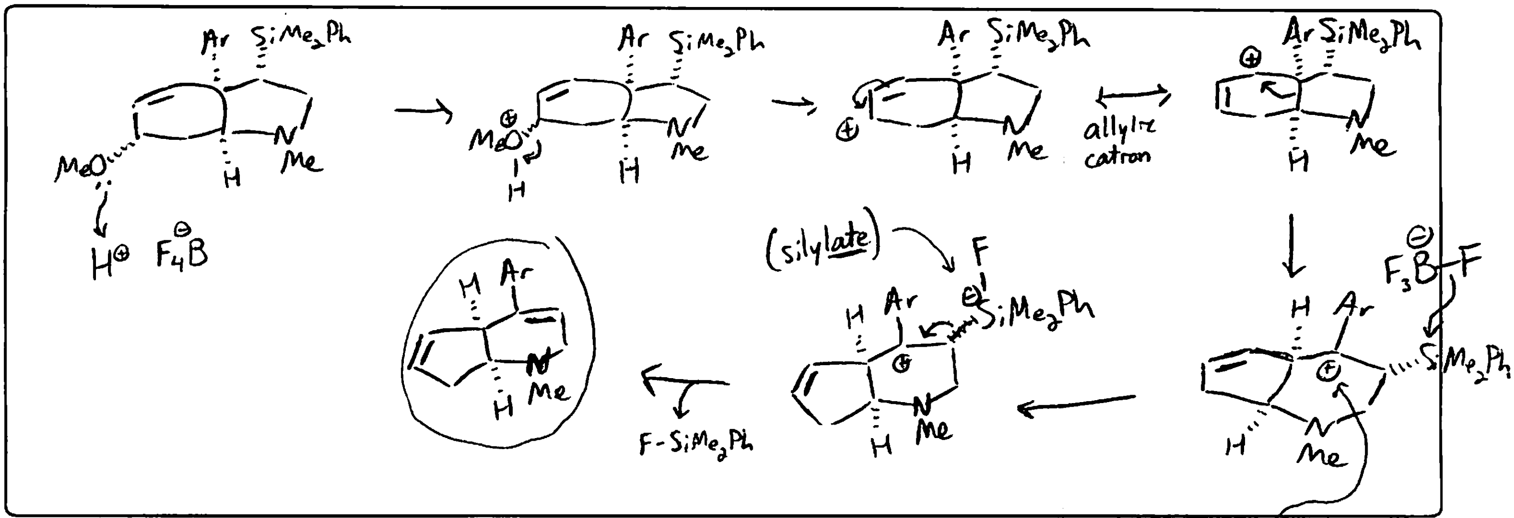
$\Delta H°$ = 5.9 kcal/mol

$\Delta S°$ = 4.9 eu

10

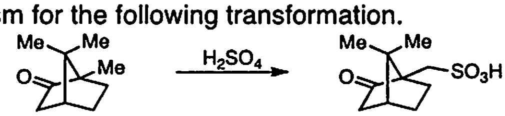
8. Propose an arrow-pushing mechanism for the following transformation.

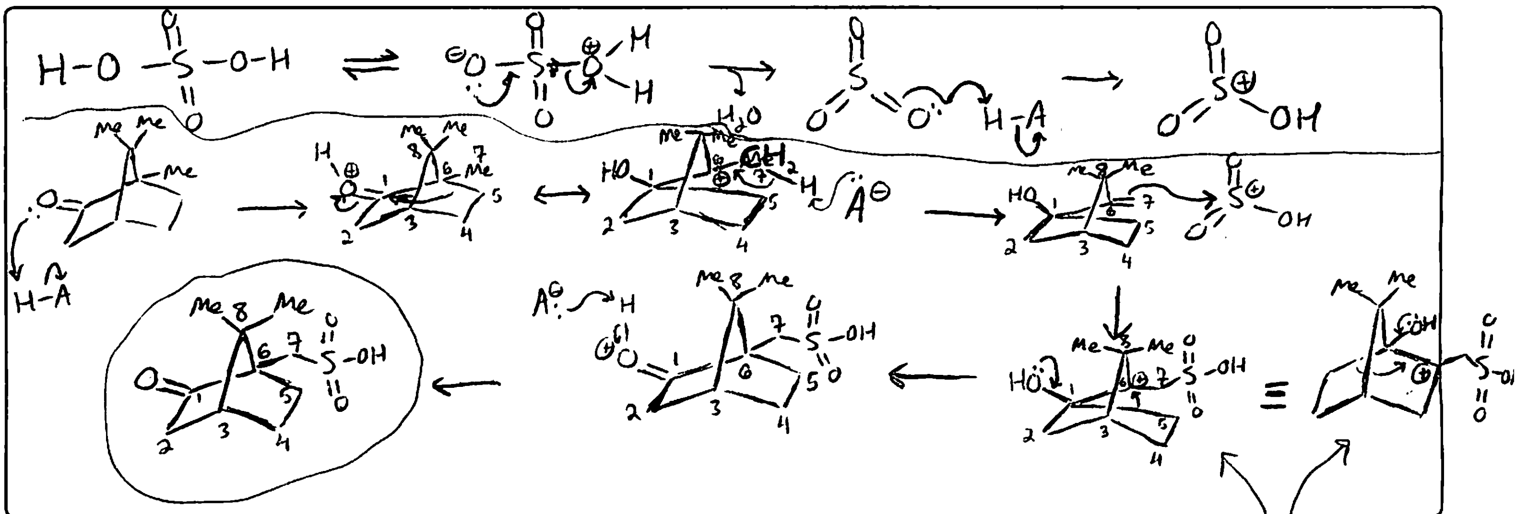




Stabilized by β-silicon effect; also 3° + benzylic

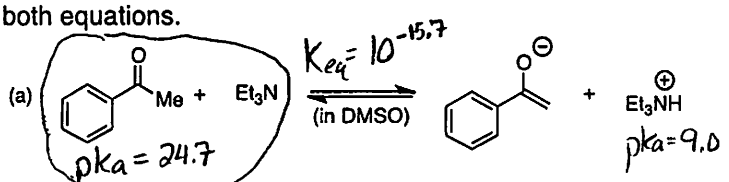
10 9. Propose an arrow-pushing mechanism for the following transformation.

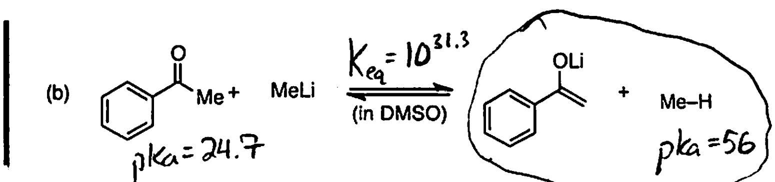




different drawing of the same thing

10 10. Please circle which side of the following equilibria will be favored. Please report the relevant pKa's and give K_{eq} for both equations.

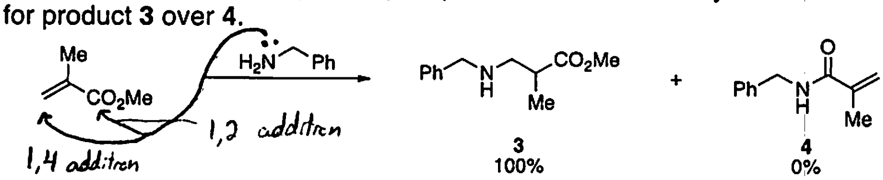




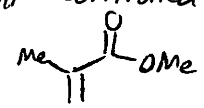
See above	See above

10

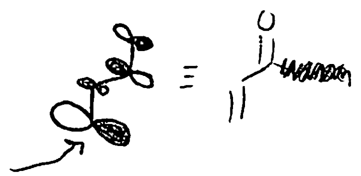
11. (a) The reaction of benzylamine and methyl methylacrylate results exclusively in the formation of product **3**. Please explain the selectively for product **3** over **4**.



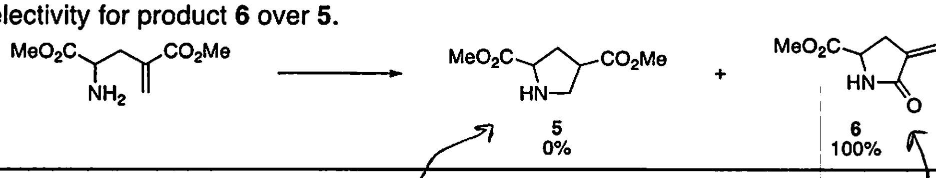
Coefficient controlled LUMO of



largest coefficient



(b) In contrast, product **6** is the exclusive product in the intramolecular addition of an amine to a similar electrophile (Baldwin, J.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. *J. Chem. Soc., Chem. Commun.* **1976**, 736). Please explain the selectivity for product **6** over **5**.

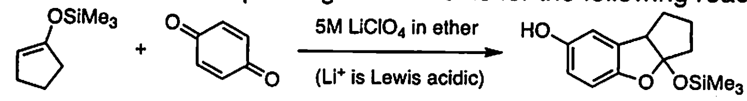


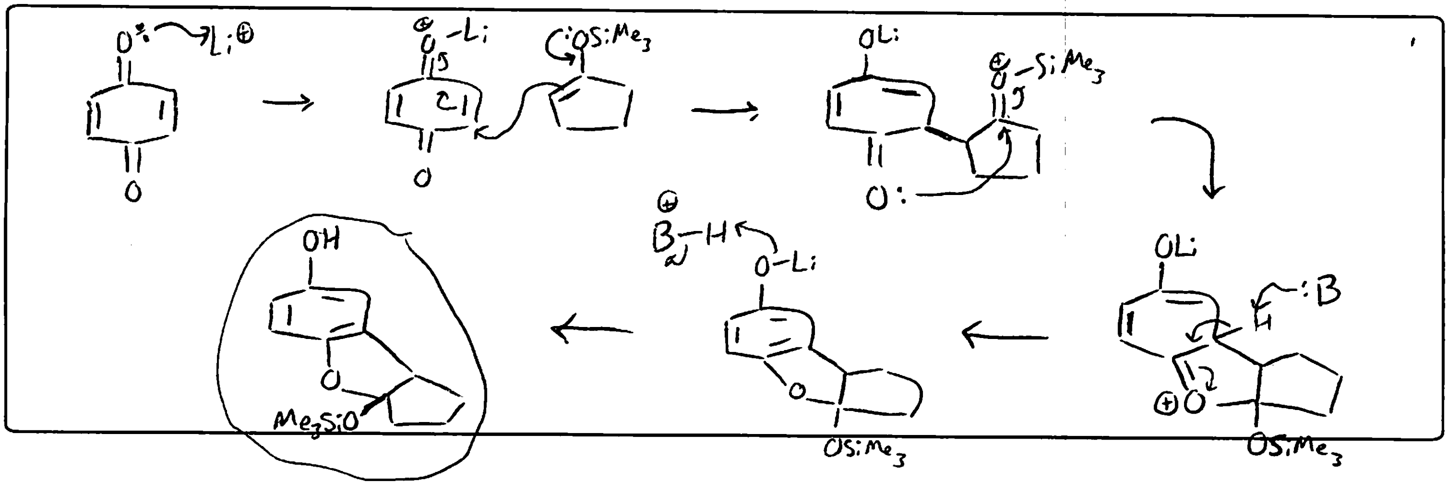
Baldwin's rules forbid 5-endo-trig; the ring is too small to allow the nucleophile to attack at the correct angle.

5-exo-trig

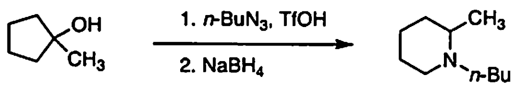
10 12. (Grossman, Ch 2, #4) Draw reasonable arrow-pushing mechanisms for the following reactions.

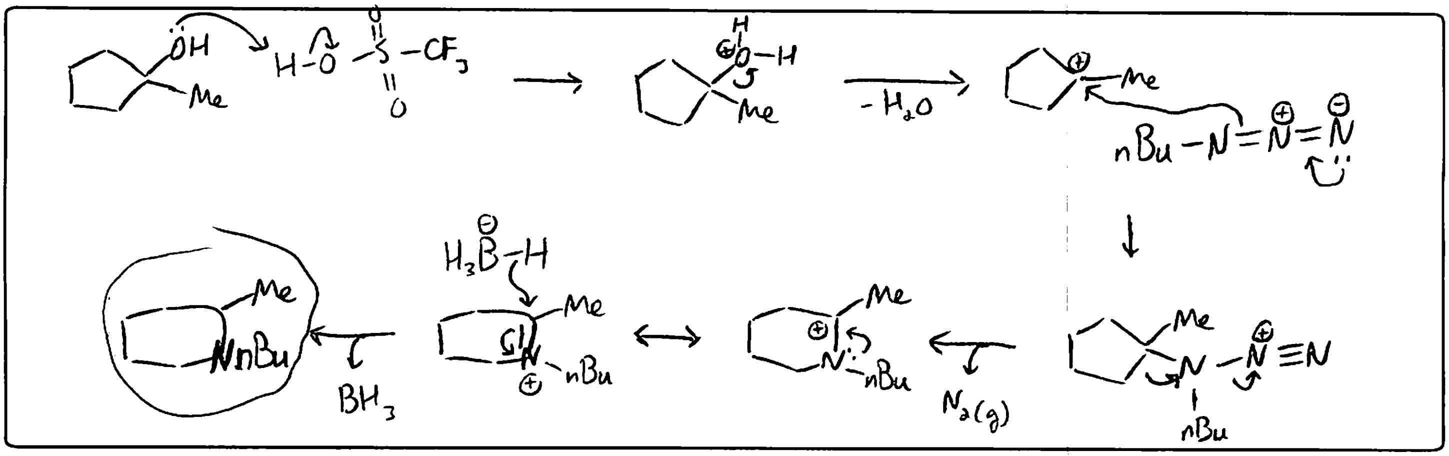
(a)



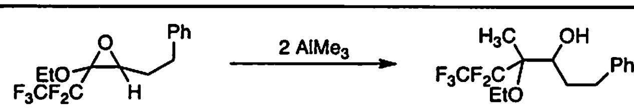


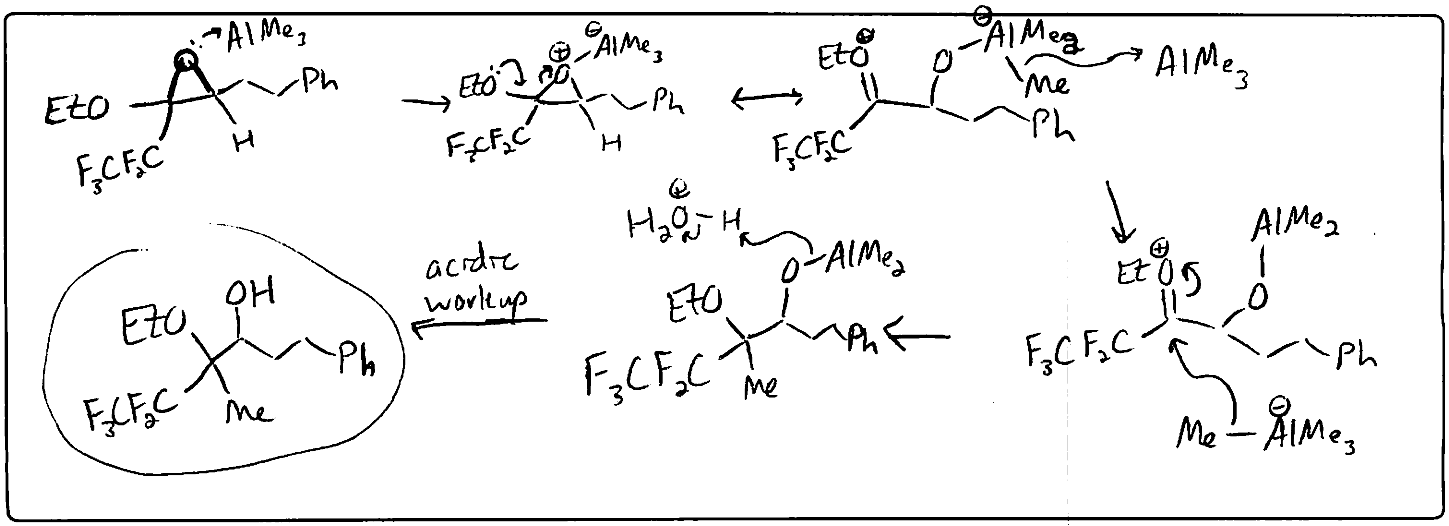
(b)

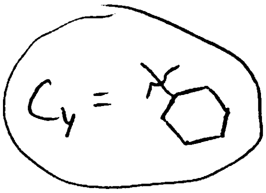




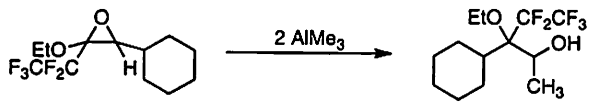
(c)

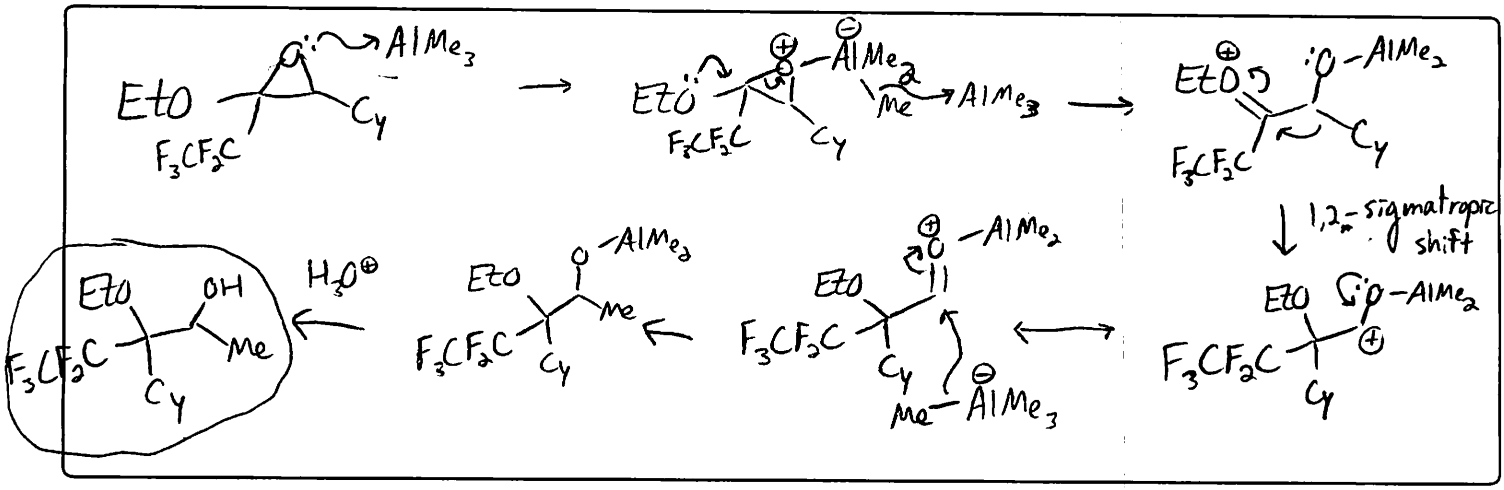




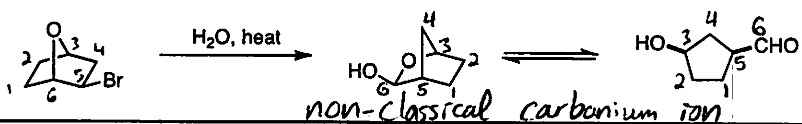

Cy =

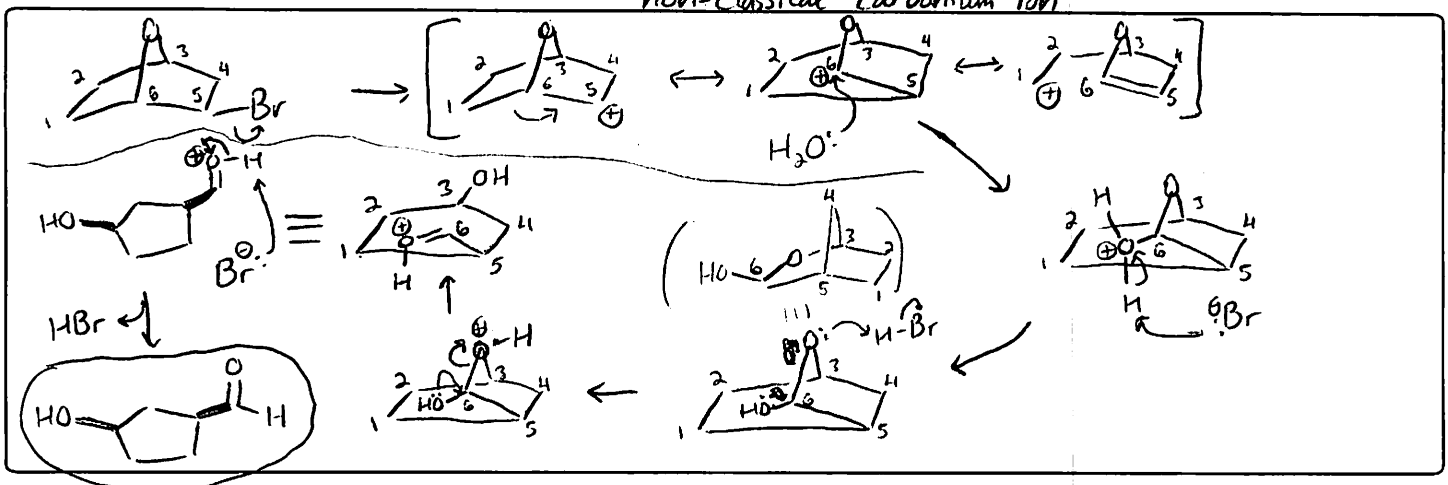
(d)


EtO
F3CF2C
O
H
2 AlMe3
EtO CF2CF3
OH
CH3

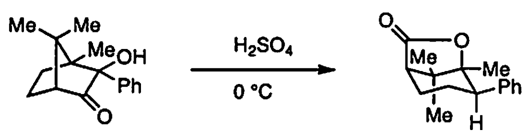

1,2-sigmatropic shift
H3O⊕

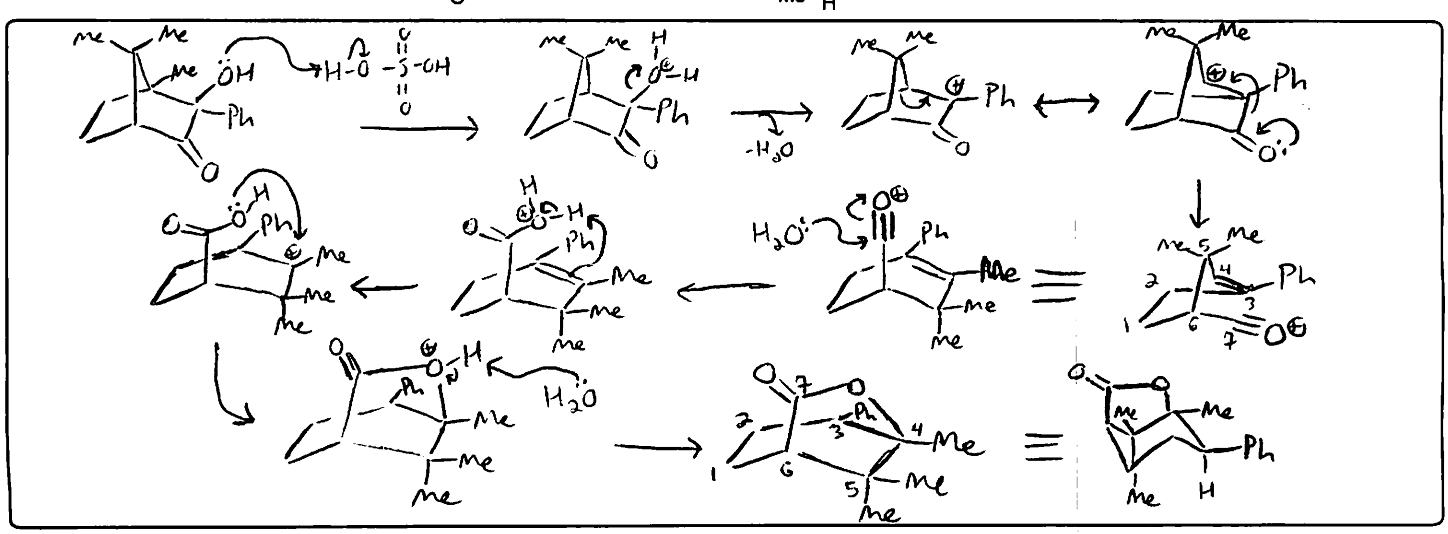
(e)


Br
H2O, heat
HO
CHO
non-classical carbonium ion


HBr

(f)


Me
Me
Me
OH
Ph
O
H2SO4
0 °C
Me
Me
Ph
Me
H


-H2O