


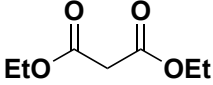

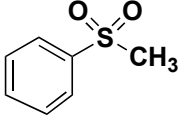

**Massachusetts Institute of Technology
Organic Chemistry 5.512**

9 March 2007
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Jennie Fong

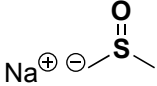
Problem Set 3

Study Guide on Enolate Alkylation and Related Chemistry

1. What are the approximate pKa values for the following carbon acids: acetone, nitromethane, DMSO, methane, diethyl malonate, dithiane, ethylene, cyclopentadiene, TMS-acetylene, acetonitrile, ethyl acetate, methyl phenyl sulfone, and the dimethylhydrazone derivative of cyclohexanone?

acetone	20		15
CH ₃ NO ₂	10		
DMSO	35	Me ₃ Si—≡	24
CH ₄	55	CH ₃ CN	25
	13	EtOAc	25
	31		29 (in DMSO)
H ₂ C=CH ₂	44	Me ₂ N—N=C 	26

2. What are the approximate pKa values for the conjugate acids of the following bases: LDA, KOH, Et₃N, DBU, *n*-BuLi, KO*t*-Bu, NaHMDS, and dimethyl sodium?

LDA	35	<i>n</i> -BuLi	50
KOH	16	KO <i>t</i> -Bu	17
Et ₃ N	11	NaHMDS	26
DBU	12		35

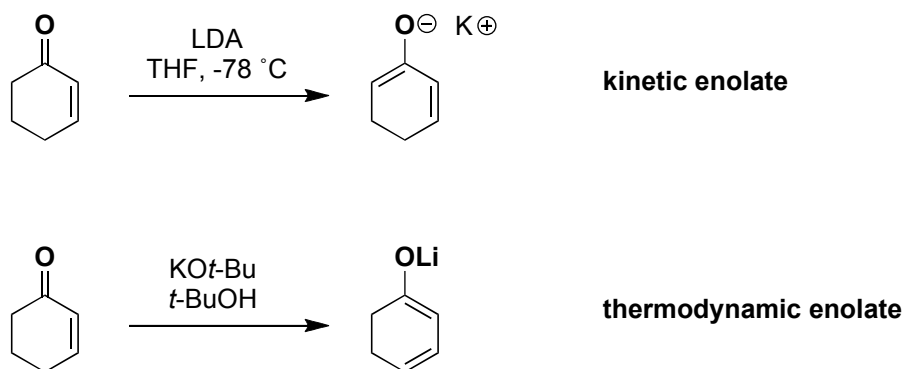
3. Define the terms "thermodynamic enolate" and "kinetic enolate" and illustrate by drawing the thermodynamic and kinetic enolates that would be obtained from 2-cyclohexenone. What conditions are most commonly used to generate each enolate?

Deprotonation of a carbonyl compound to form an enolate may proceed under thermodynamic conditions such that the enolate products are in equilibrium. The ratio of the products is determined by the equilibrium which favors the most stable enolate. The resulting product is the thermodynamic product.

Thermodynamic control is established when the two possible enolate products can rapidly interconvert (via the starting ketone) upon protonation followed by deprotonation.

Deprotonation may also occur under kinetic conditions in which deprotonation is irreversible and which result in a distribution of products that depend on the rate of deprotonation. Under these conditions the resulting product is considered to be the kinetic product.

Kinetic control, which is operative when the rate-determining step is proton abstraction, occurs when reaction conditions favor rapid, quantitative, and irreversible deprotonation. This is favored when using strong bases such that the pKa of the conjugate acid is 3 or 4 units higher than the pKa of the carbonyl compound.

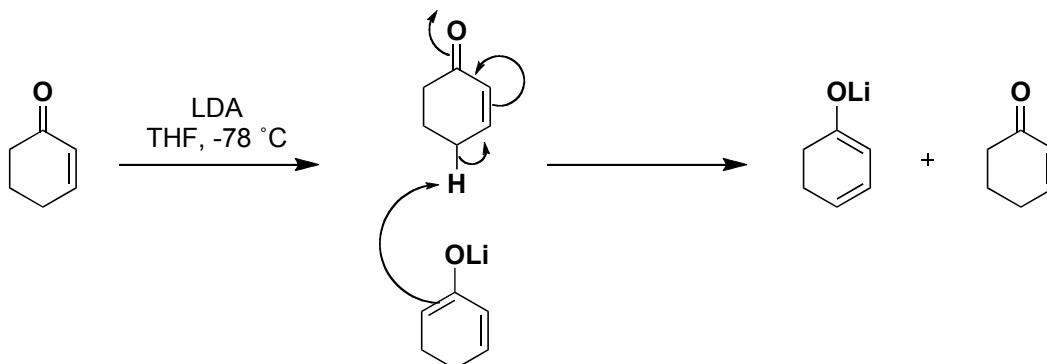


Deprotonation of α,β -unsaturated ketones is favored at the α' -carbon under kinetic conditions for two reasons. First, the inductive effects of the carbonyl render the α' -protons more acidic. Second, coordination of the counterion (e.g., lithium) by the carbonyl oxygen orients the base into a 6-membered transition state for deprotonation at the α' position.

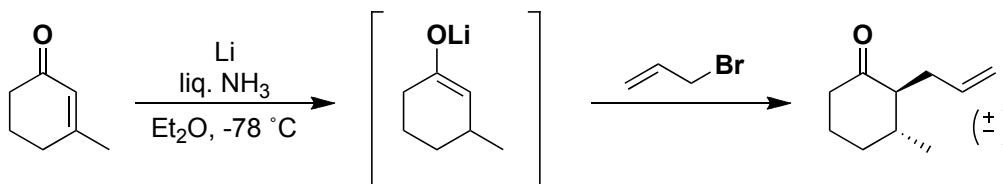
Under thermodynamic conditions, deprotonation is favored at the γ -carbon which results in the enolate product that is lower in energy compared to the kinetic enolate. The thermodynamic enolate in this case is lower energy due to a greater delocalization of electron density throughout the conjugated system.

4. Treatment of ketones with 0.9 equiv of LDA leads to the thermodynamic enolate. Explain.

The thermodynamic enolate will be the dominant product because the use of a substoichiometric amount of base (relative to the ketone) allows for reversible enolate formation via protonation of the enolate by the remaining small amount of ketone starting material. This generally requires extended reaction time to allow for complete equilibration since proton transfer in lithium enolates is relatively slow.

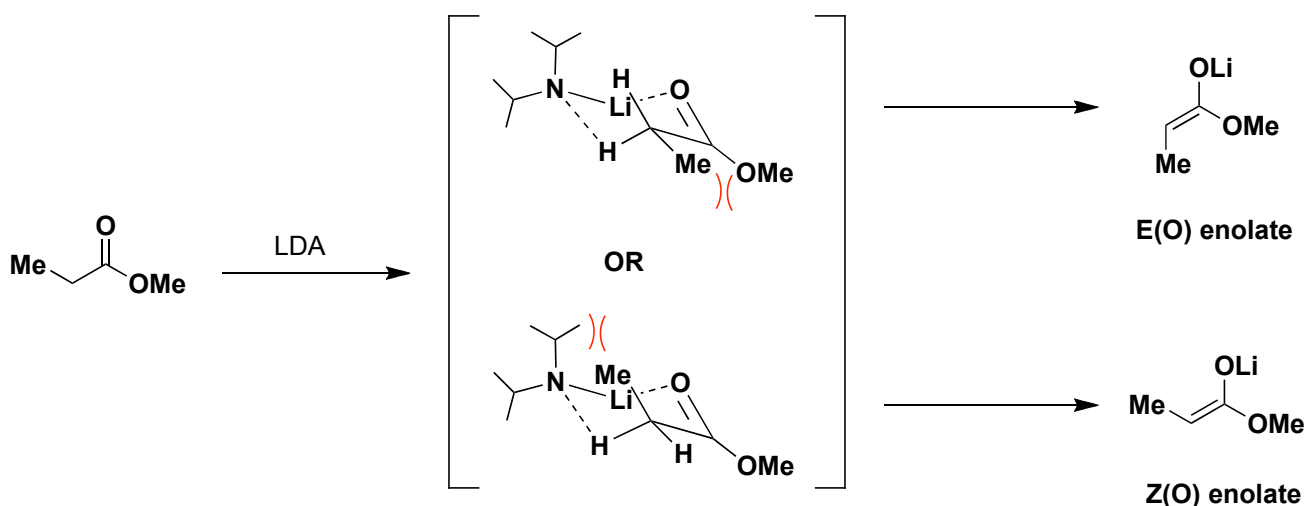


5. Provide an example to illustrate the "reductive alkylation" strategy for the regioselective generation and alkylation of ketone enolates (beginning with α,β -unsaturated ketones).

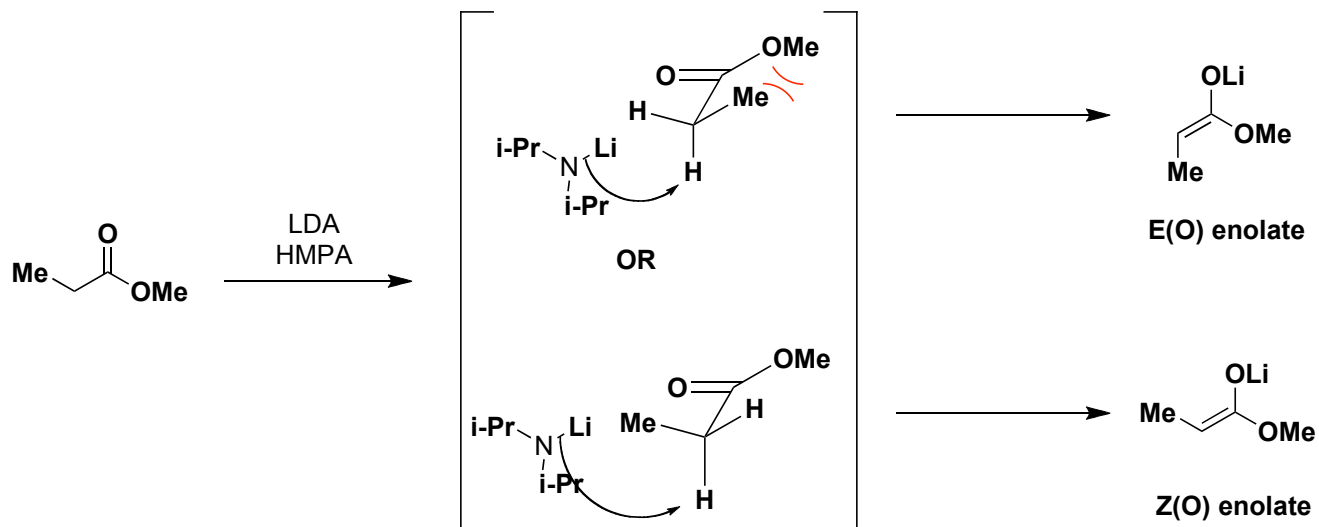


6. Esters are converted to mainly the E(O) enolates with LDA and to the Z(O) enolates using LDA-HMPA. Provide transition state models to rationalize these results.

Deprotonation at the α -carbon of an ester by LDA proceeds through a closed transition state in which the ester is in a conformation to minimize 1,3-diaxial interactions. Deprotonation of the ester in this conformation results in the formation of an E(O) enolate.



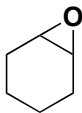
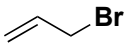
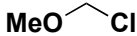
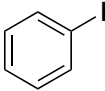
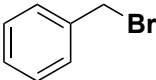
The reaction of HMPA and LDA with an ester results in deprotonation of the α -protons via an open transition state since the carbonyl oxygen is not as strongly coordinated to the lithium due to the solvating effects of HMPA. Furthermore, the ester enolate will prefer to react in the lower energy conformation that minimizes the $A^{1,2}$ strain between the alkoxy group and the neighboring α -substituent since the 1,3-diaxial interaction is absent in the open transition state.



7. Attempted alkylation of most aldehydes and simple ketones (e.g., acetone) under "standard conditions" (i.e., treatment with 1 equiv of LDA in THF at -78 °C followed by addition of the alkyl halide) fails to give the desired alkylated product in good yield. Explain.

The rate of self-condensation is competitive with the rate of deprotonation because of the high reactivity of the carbonyl group toward addition of nucleophiles. Therefore, the enolate formed from these highly reactive carbonyl compounds will quickly add to the carbonyl of an unenolized molecule of starting material.

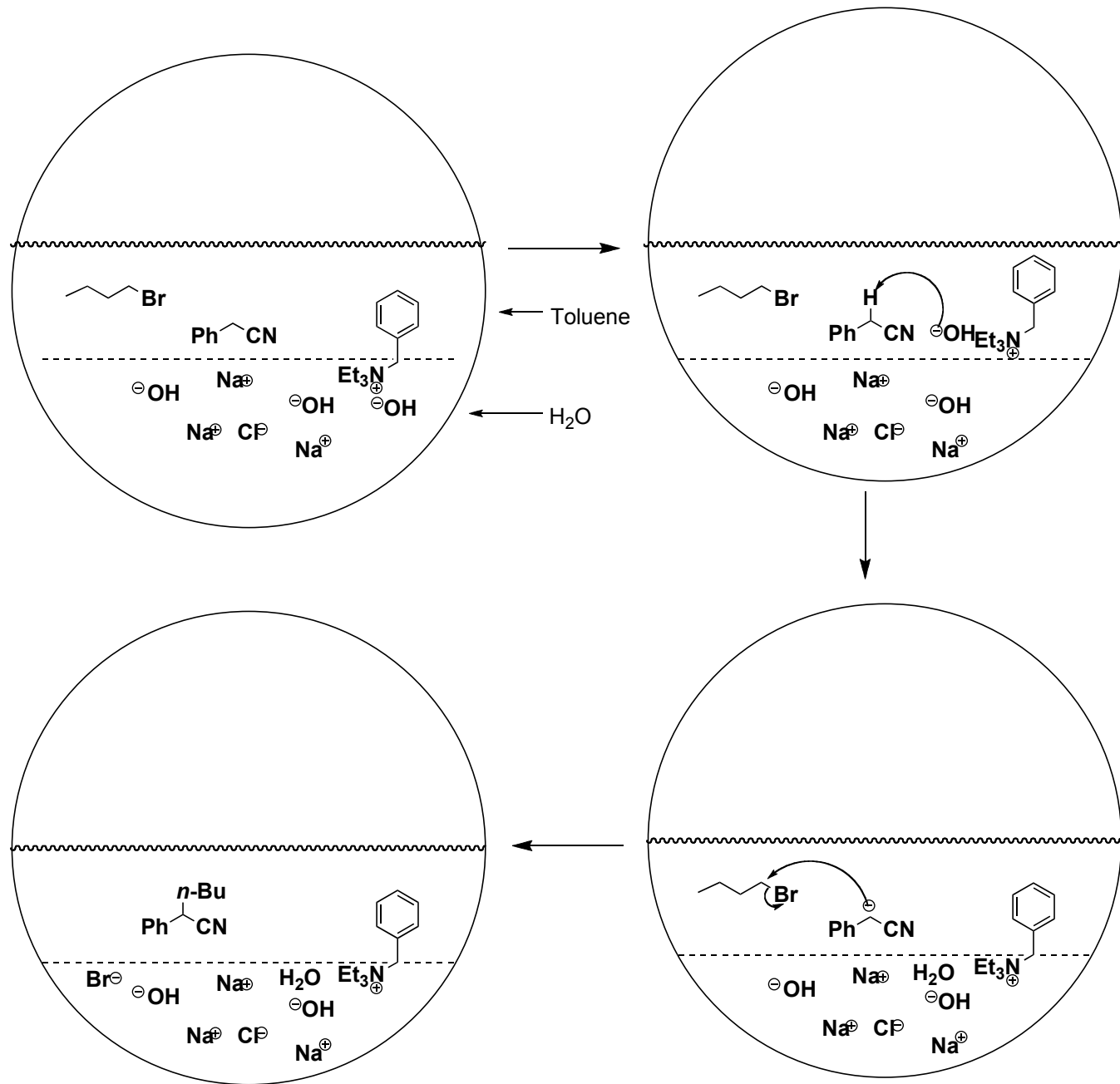
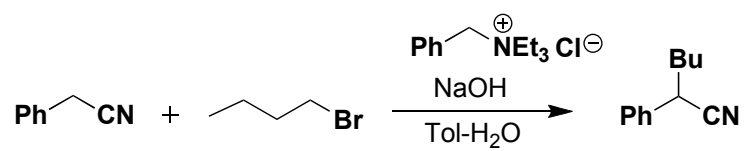
8. Classify the following electrophiles as "highly reactive" (H), "moderately reactive" (M), or "dead as a doornail" (D) in reactions with enolates: cyclohexene oxide, methyl iodide, TMS chloride, *n*-butyl bromide, pivaldehyde, allyl bromide, MOM chloride, iodobenzene, and benzyl bromide.

	M		H
MeI	H		H
Me ₃ SiCl	H		D
<i>n</i> -BuBr	M		H
<i>t</i> -BuCHO	H		

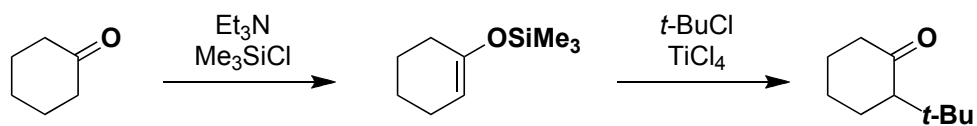
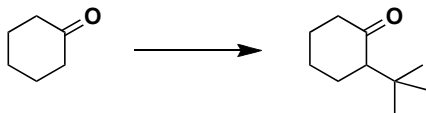
9. Define phase transfer catalysis. No reaction occurs if phenylacetonitrile is treated with NaOH and *n*-butyl bromide in a two-phase mixture of water and toluene. However, if a catalytic amount of TEBA (BnEt₃NCl) is added, the desired alkylation occurs in good yield. Provide a detailed mechanism to explain these results, indicating what species are present in each phase of the reaction mixture

Phase transfer catalysis is a method used to catalyze a biphasic reaction. A phase transfer catalyst transfers ions (e.g. OH⁻) in the aqueous phase to the organic phase where the reaction takes place. For example, NaOH is soluble in water but not in toluene. Since PhCH₂CN is all in the toluene phase, negligible deprotonation can take place. However, BnEt₃N⁺OH⁻ is soluble in both phases, and deprotonation (and alkylation) can thus occur smoothly. Only a catalytic amount of the TEBA is needed since after alkylation the resulting BnEt₃NBr is soluble in both phases and can serve to "carry" another hydroxide from the aqueous to the organic phase.

See next page for a schematic of the described phase transfer catalyzed reaction.



10. How would you effect the following transformation (more than one step may be necessary)?



Alkylation of the silyl enol ether occurs via the following mechanism:

