Massachusetts Institute of Technology
Organic Chemistry 5.512

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Problem Set 3
Study Guide on Enolate Alkylation and Related Chemistry

The aim of these questions is to assist you in reviewing the basic enolate (and related) chemistry that will be involved in the reactions we will be discussing in Unit 2. Discussion of these questions can be found in Chapter 1 of Carey & Sundberg B and Chapter 26 of Clayden, et al., as well as your notes from 5.511.

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?

2. What are the approximate pKa values for the conjugate acids of the following bases: LDA, KOH, Et_3N, DBU, *n*-BuLi, KO*t*-Bu, NaHMDS, and dimsyl sodium?

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?

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

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.

7. Attempted alkylation of most aldehydes and simple ketones (e.g., acetone) under "standard condtions" (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.

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

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 ($BnEt_3NCl$) 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.

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