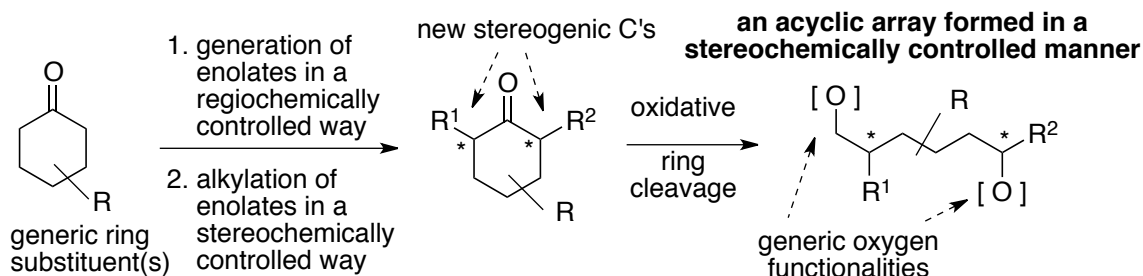


CHEM 330

Topics Discussed on Oct 19

Principle: the alkylation of cyclohexanone enolates is of special importance in the synthesis of compounds of current biomedical interest. This is because many such compounds incorporate:

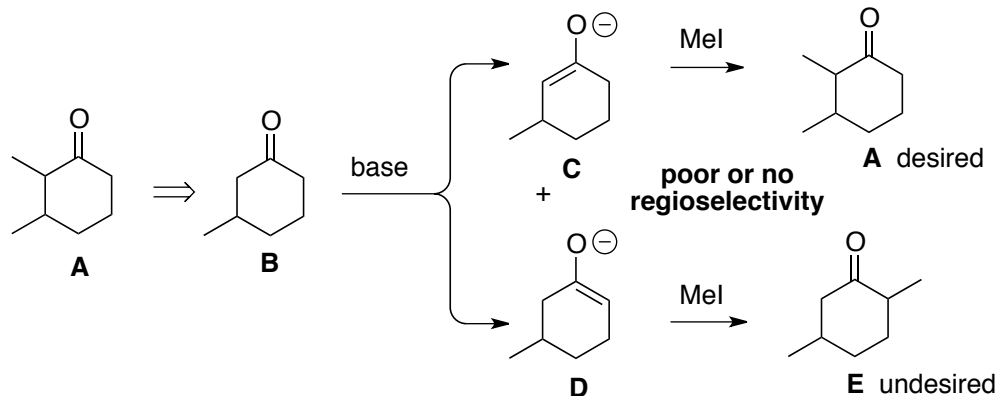
- (i) substituted six-membered rings that could be created by alkylation of a cyclohexanone in a regio- and stereocontrolled manner, and/or
- (ii) acyclic segments that contain multiple stereogenic carbons, and that may be created by alkylation of a cyclohexanone in a regio- and stereocontrolled manner, followed by oxidative cleavage of the ring:



Therefore, we need to explore additional regiochemical and stereochemical aspects of cyclohexanone enolate generation/alkylation in detail.

Difficulties encountered in the regioselective deprotonation of ketones such as 3-substituted cyclohexanones, e.g.:

Suppose that one needed to prepare compound **A**. In principle, one could make **A** by alkylation of the appropriate regioisomer of the enolate of 3-methylcyclohexanone **B** (enolate **C**). However, deprotonation of **B** would afford a mixture of enolates **C** and **D** with virtually no selectivity. The result would be a wasteful formation of desired **A** and undesired **E**, which then would have to be separated.

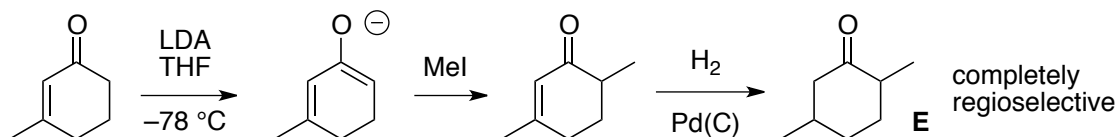


Is there any way to create enolates C and D regioselectively?

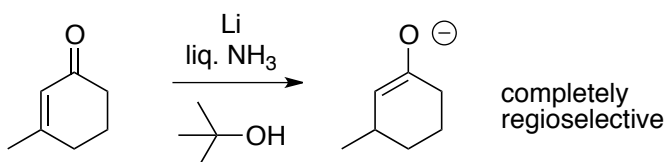
Use of an unsaturated variant of the above ketone (= an enone, i.e., an alkene-ketone) to control the regioselectivity of enolate formation:



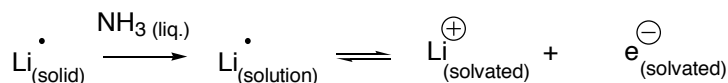
Regioselective kinetic deprotonation of the above enone with LDA (THF, $-78\text{ }^{\circ}\text{C}$), e.g. in the preparation of compound **E** in a selective manner:



Regioselective formation of enolates through dissolving metal (mostly Li, sometimes Na, or K) reduction of enones ($=\alpha,\beta$ -unsaturated ketones) in liquid NH_3 in the presence of *tert*-butanol:



Nature of a solution of Li (or Na, or K) in liquid NH_3 : dissociation of the metal into a metal ion and an electron (both solvated), e.g.:

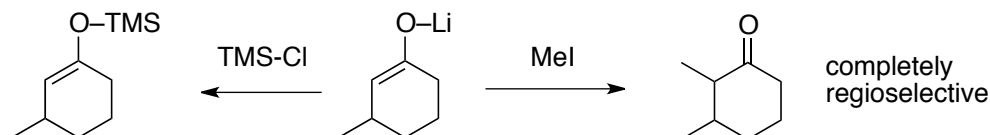


Powerful reducing properties of a solution of Li (or Na, or K) in liquid NH_3 (\approx a solution of electrons)

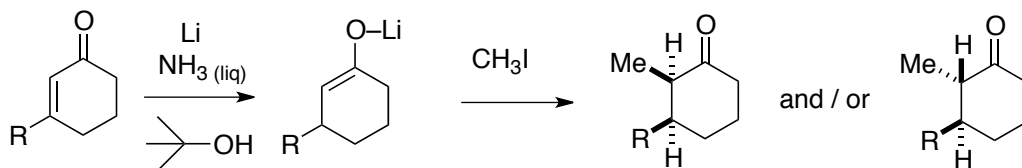
Mechanistic aspects of the dissolving metal reduction of enones

- Radical anions and dianions
- Use of a proton donor such as *t*BuOH to accelerate the protonation of a (presumed) dianion intermediate formed during dissolving metal reductions of enones

C- and O- reactivity of the enolates thus obtained:



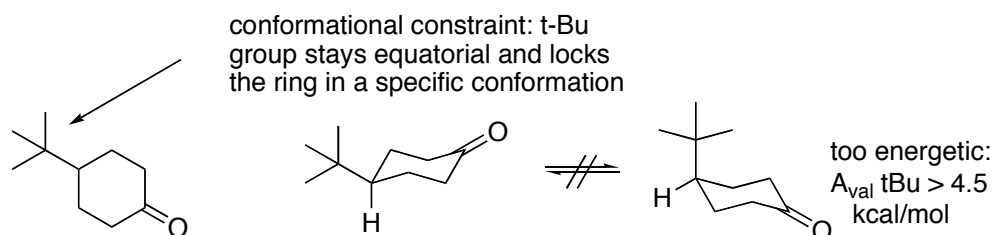
Stereochemical aspects of the alkylation of the above enolates, e.g.:



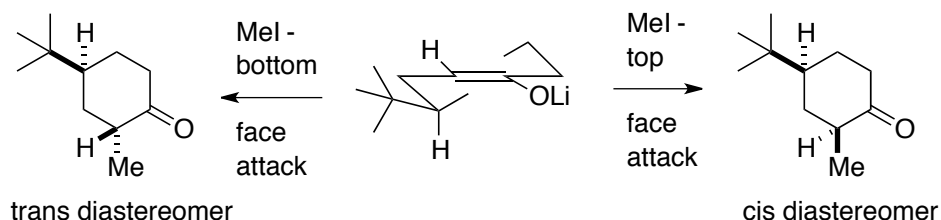
Problem: is the alkylation step going to be diastereoselective? If so, which isomer will be the major product of the reaction?

Principle: stereochemical aspects of the alkylation of cyclohexanone enolates may be understood starting with an analysis of the stereochemical preferences of simpler, conformationally constrained cyclohexanones.

4-*tert*-Bu-cyclohexanone as a simple, conformationally constrained cyclohexanone:



Possible stereochemical outcome of the alkylation of the enolate of 4-*tert*-Bu-cyclohexanone with, e.g., MeI: diastereomeric products will result depending on whether the enolate reacts with the electrophile from the top – or from the bottom face of the enolate:

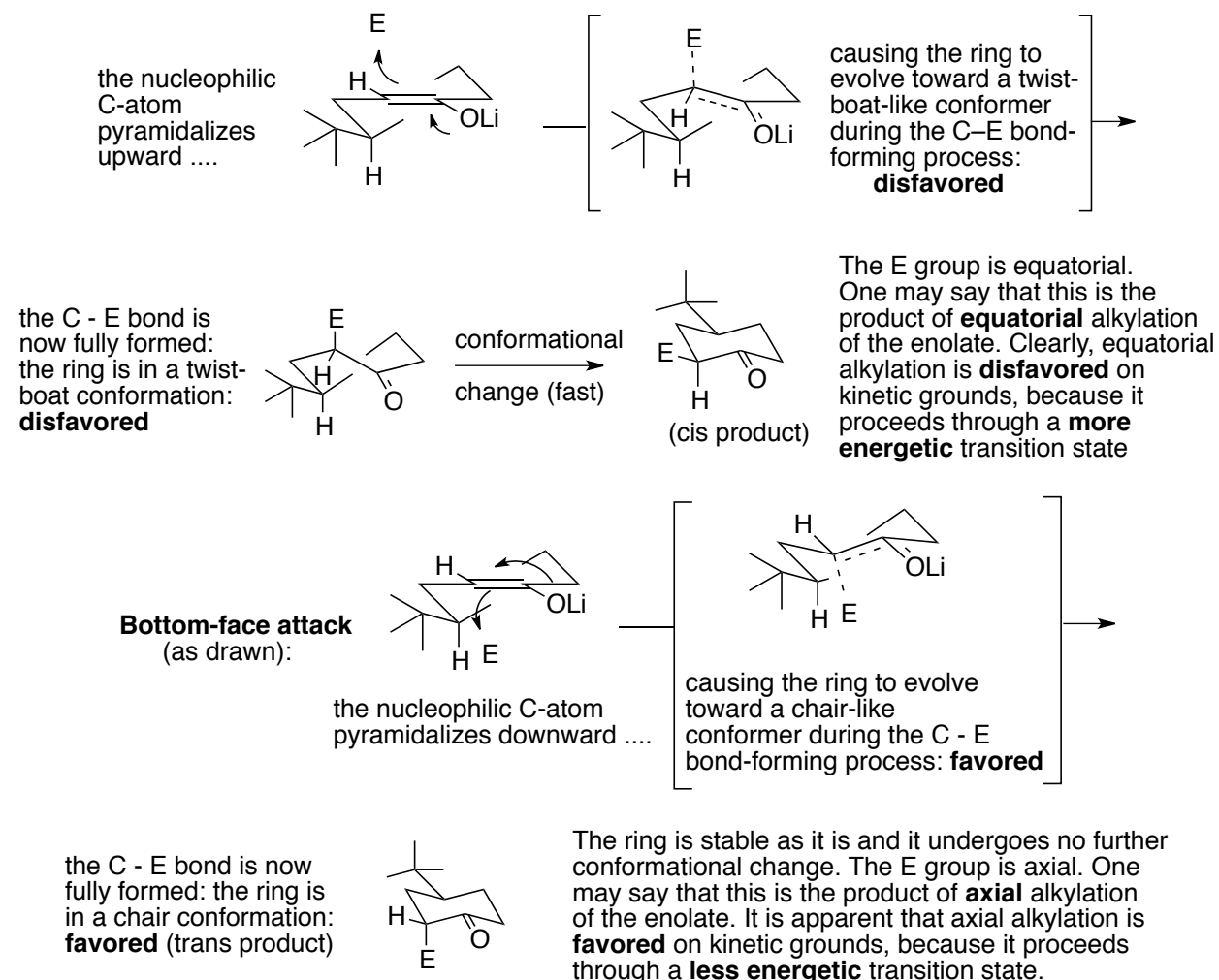


will there be any preference for one particular mode of reactivity?

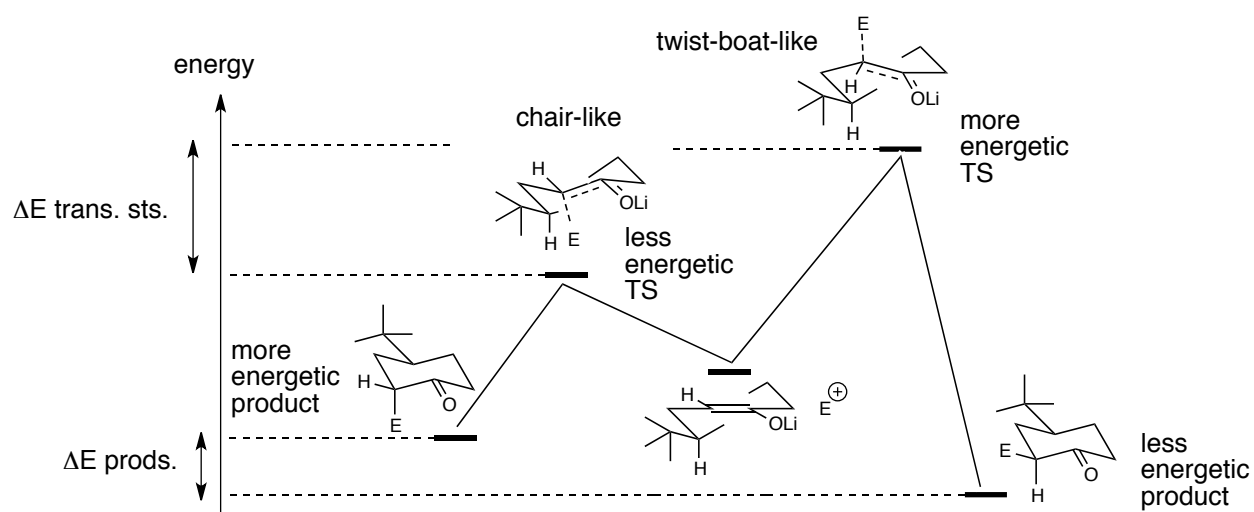
Principle: the alkylation of an enolate with an alkyl halide is **irreversible**, therefore, the reaction occurs under kinetic control. This means that the major product of the reaction will be the one obtained through the *least energetic transition state*.

Pyramidalization of the nucleophilic sp^2 C atom of an enolate as it rehybridizes to an sp^3 state during alkylation

Approximate transition states for the alkylation of the enolate of 4-*tert*-Bu-cyclohexanone from the top or the bottom face of the π system:



Reaction diagram for the alkylation of a conformationally rigid cyclohexanone enolate:



Because the reaction is irreversible, the product distribution will be determined **solely** by the relative energies of the transition states; i.e., the major product will be the one

that forms through the least energetic transition state. The reaction is said to proceed under **kinetic control**

Principle: the alkylation of conformationally rigid cyclohexanone enolates tends to occur so that the pyramidalization of the nucleophilic C atom of the enolate (i.e., the transition from a planar sp^2 hybrid to a tetrahedral sp^3 hybrid) causes the ring to evolve toward a **chair** conformer. This is the same as saying that alkylation of cyclohexanone enolates tends to occur in the **axial mode**.

Isomerization of the kinetic (axial) product of C-alkylation of an enolate to the thermodynamic (equatorial) isomer upon treatment with a catalytic amount of weak base that induces reversible enolate formation, e.g., MeONa / MeOH:

