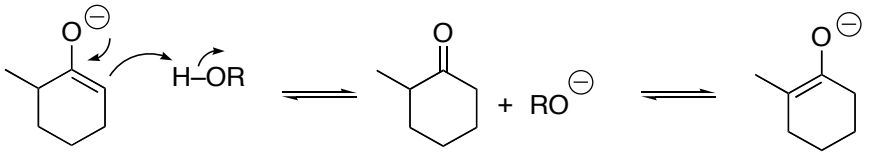
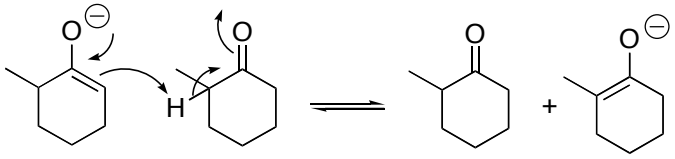
CHEM 330

Topics Discussed on Oct 14

Principle: equilibration of the enolates occurs through proton exchange mediated by a suitable "proton shuttle." For instance, in the deprotonation of ketones with *tert*-BuOK, this may be a molecule of alcohol *or one of intact ketone*:



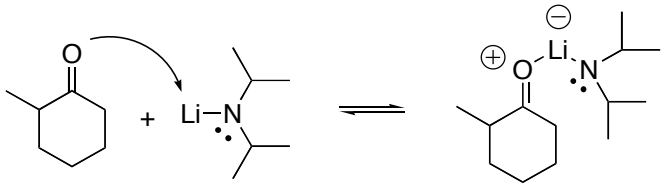
or



Mechanistic model (**NOT** "mechanism") for the deprotonation of ketones with, e.g., LDA (–78 °C, THF), resulting in formation of the thermodynamically less favorable enolate

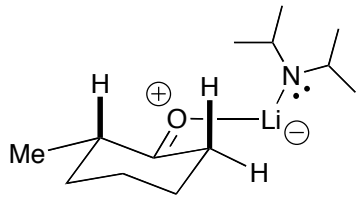
Lewis acidic, oxophilic character of Li^+

Probable first interaction of LDA with the substrate, e.g., 2-methylcyclohexanone: complex formation:



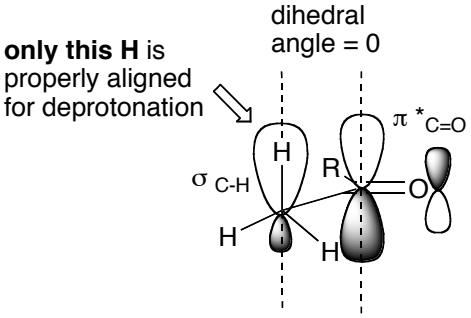
note: the formal (+) on the O atom enhances the acidity of adjacent protons by making the O more electron-attracting. Moreover, the formal (–) on the Li atom enhances the basicity of the N atom by increasing the extent of N–Li bond polarization, thus augmenting the electronic density on the N atom. The complex is therefore **doubly activated** toward proton transfer from C to N

Preferred conformation of the complex:



cyclohexane in a chair conformation
Me group (A-value = 1.8) equatorial:

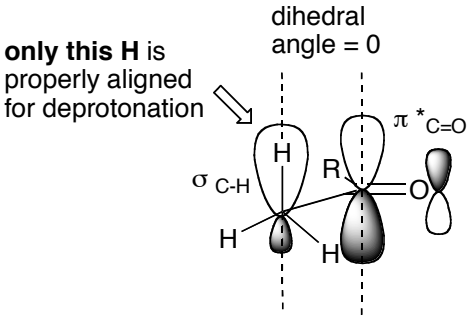
Principle: The σ_{C-H} orbital of the proton that is removed by the base must be aligned with the large lobe of the $\pi^*_{C=O}$ orbital to permit maximum electron delocalization during proton transfer



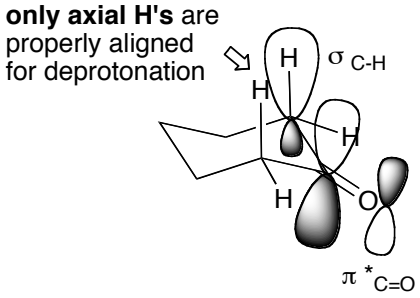
The σ_{C-H} orbital of the proton that is removed by the base must be aligned with the large lobe of the $\pi^*_{C=O}$ orbital to permit maximum electron delocalization during proton transfer.

Principle: in a cyclohexanone derivative, only the axial proton(s) satisfy the stereoelectronic requirements for deprotonation; i.e., a base can only abstract an axial H:

<u>case of an acyclic ketone:</u>



<u>case of a cyclohexanone:</u>

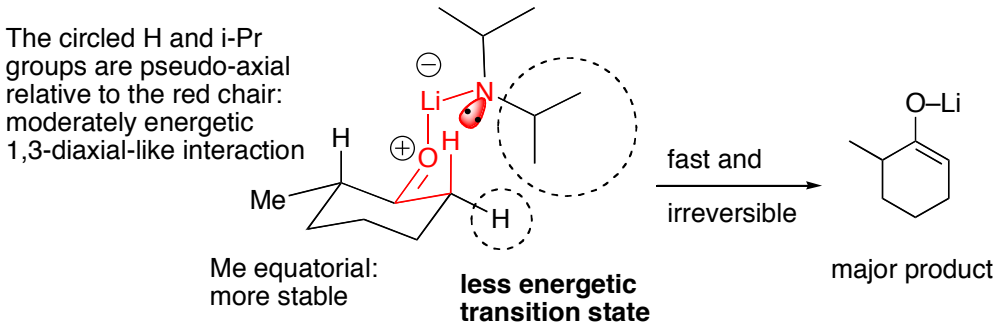


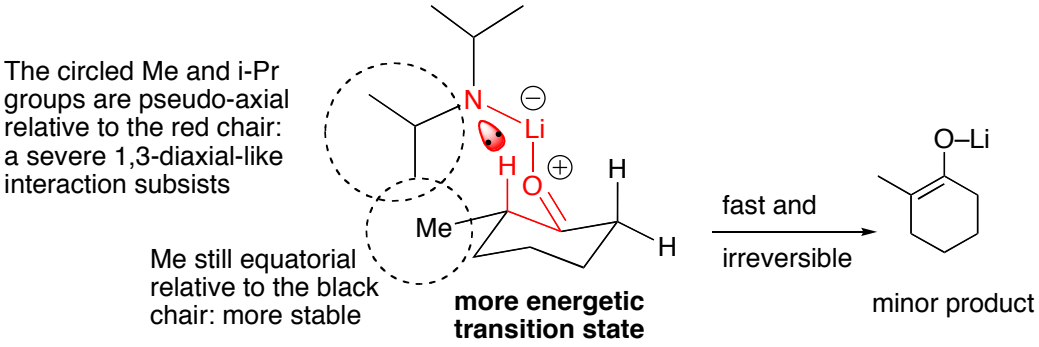
Greater likelihood of proton transfer in an intramolecular (=within the same molecule) sense than in a bimolecular one (= between two distinct molecules: e.g., one of the above complex and a second molecule of LDA)

Corollary: the above ketone-LDA complex must "fold back" onto itself in such a way that the N atom can abstract one of the axial protons

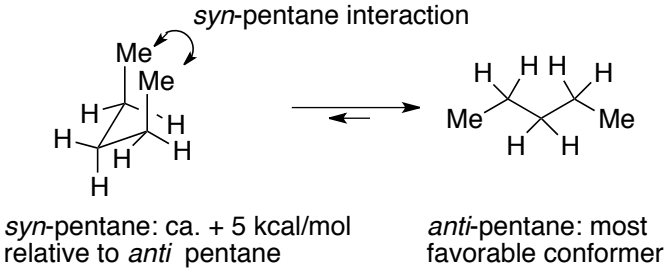
"Folding back" of the complex setting the stage for proton transfer through a chair-like 6-centered transition state

Possible evolution of the LDA-ketone complex toward two transitions states:



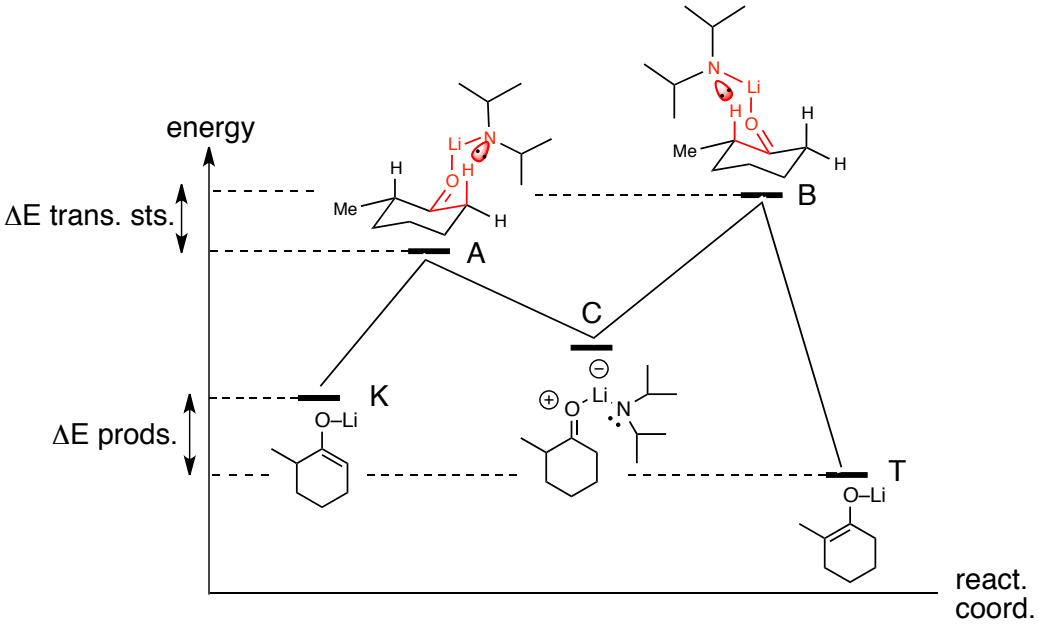


Syn-pentane interaction: a very energetic conformational interaction in a molecule of pentane that has acquired the following conformation:



Syn-pentane-type interaction between the isopropyl group and the Me group in the more energetic transition state above

Reaction diagram for the regioselective deprotonation of 2-methylcyclohexanone with LDA:



the ketone-LDA complex, C, may evolve toward two energetically different transition states: A (less energetic) and B (more energetic). If the reaction is irreversible, the product ratio will

be determined **solely** by the energy difference between transition states A and B, i.e, by the relative rates of formation of the products, regardless of the relative thermodynamic stability of these. In the present case, the majority of the molecular population of C will be channeled through transition state A (less energetic than B), to give enolate K as the major product.

A reaction that proceeds under these conditions is said to be **kinetically controlled**. Enolate K may be described as the **kinetic** product of the deprotonation reaction, i.e., the kinetic enolate (= the one that forms faster).

Note concerning the extent of selectivity in the deprotonation of an unsymmetrical ketone:

The extent of selectivity, **T** / **K** for a reaction that proceeds under ***thermodynamic*** conditions (equilibration of enolates through proton exchange) will be defined by the energy difference between **T** and **K** (i.e., ΔE prods.) through the Gibbs equation:

$$\Delta E \approx \Delta G^\circ = - nRT \ln k$$

where *k* is the ratio of products **T** and **K**

The extent of selectivity, **T** / **K** for a reaction that proceeds under ***kinetic*** conditions (irreversible deprotonation) will be defined by the energy difference between the transition states leading to **T** and **K** (i.e., ΔE trans. sts.), also through the Gibbs equation:

$$\Delta E \approx \Delta G^\circ = - nRT \ln k$$

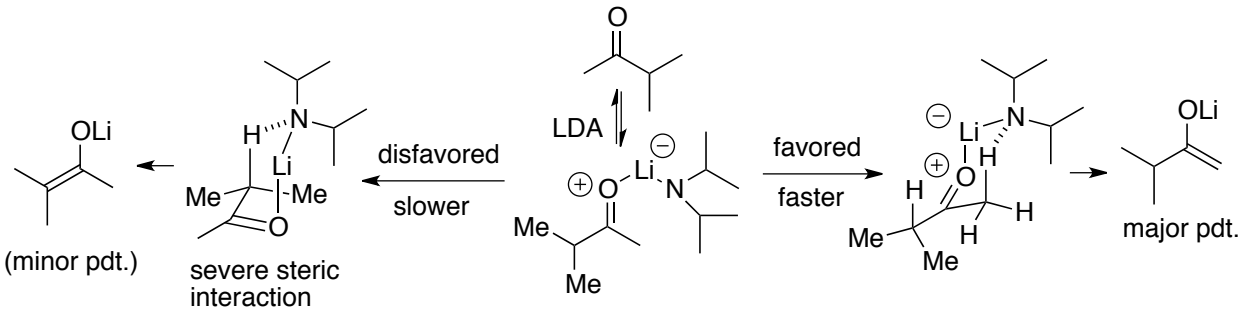
where *k* is the ratio of products **T** and **K**

Possible formation of a thermodynamic enolate upon reaction of an unsymmetrical ketone such as 2-methylcyclohexanone with a molar defect of LDA: leftover ketone can act as a proton shuttle and catalyzes isomerization of the kinetic enolate to the thermodynamic one (see above).

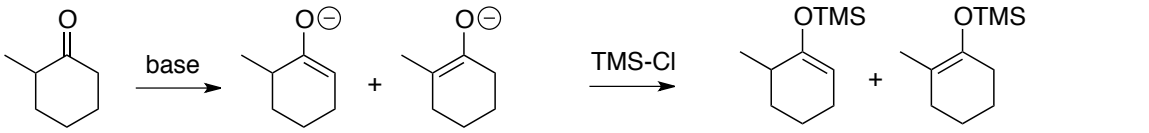
Use of a slight excess (1.1 equiv) of LDA at low temperature (–78 °C) in the deprotonation of ketones (and of carbonyl compounds in general) to minimize proton-transfer reactions and to preserve the positional integrity of the highly reactive enolates (which may decompose at or near room temperature)

Principle: the deprotonation chemistry of unsymmetrical, acyclic ketones parallels that of their cyclic analogs

Deprotonation of acyclic ketones under kinetically controlled (=irreversible) conditions: the same mechanistic model applies; e.g:

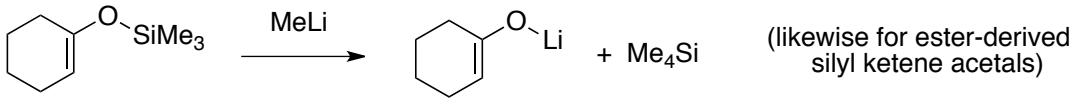


Determination of the selectivity of enolate formation through O-silylation of the enolate mixture and analysis (e.g., by NMR) of the resulting mixture of silyl enol ethers:

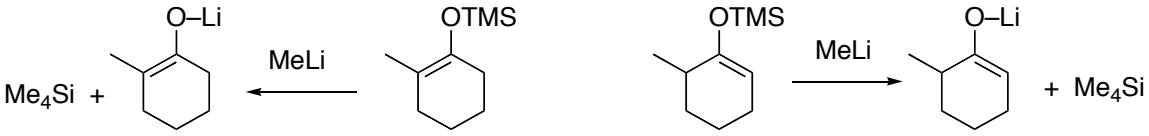


reactive, air- and moisture sensitive relatively stable, easily analyzed, e.g. by NMR

Conversion of silyl enol ethers (or silyl ketene acetals) back into Li enolates by reaction with MeLi:

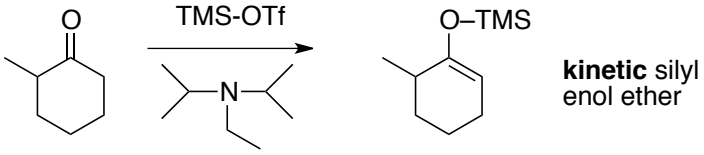


Principle: regiochemically defined enolates are sometimes prepared by MeLi cleavage of the corresponding silyl enol ethers, which may be purified to homogeneity by a number of methods:



"Soft enolization" methods: techniques for the direct regioselective preparation of silyl enol ethers without passing through metal enolates ("hard enolization")

Direct formation of the kinetic (=less highly substituted) silyl enol ether from an unsymmetrical ketone by reaction with a trialkylsilyl triflate in the presence of a hindered amine base such as diisopropyl ethylamine ("Hünig base")



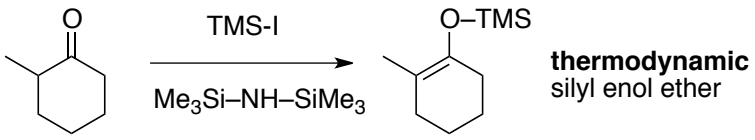
Trifluoromethane sulfonic acid (triflic acid, CF_3-SO_2-OH, TfOH; pKa ≈ –10) as a "superacid" (= a Bronsted acid stronger than H_2SO_4)

The trifluoromethanesulfonate (triflate, TfO^-) ion as an exceptionally good leaving group

Trialkylsilyl triflates, e.g., trimethylsilyl triflate, Me_3SiOTf, as powerful silicon electrophiles

Mechanistic aspects of the formation of kinetic silyl enol ethers of ketones through "soft enolization" technology

Direct formation of the thermodynamic (=more highly substituted) silyl enol ether from an unsymmetrical ketone by the **Miller reaction**: treatment of the substrate with trimethylsilyl iodide in the presence of hexamethyldisilazane, a compound of formula $Me_3Si–NH–SiMe_3$):



Mechanistic aspects of the formation of thermodynamic silyl enol ethers of ketones through "soft enolization" technology: probable proton-catalyzed equilibration of kinetic silyl enol ethers with their thermodynamic isomers during the Miller reaction

Soft enolization of acyclic ketones: the principles developed above for the case of 2-methylcyclohexanone apply to the acyclic case as well; e.g.: