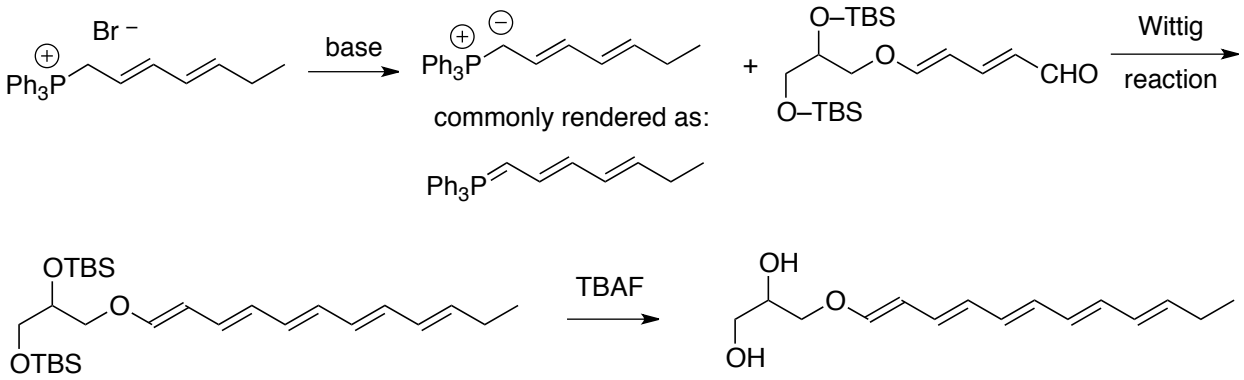
CHEM 330

Topics Discussed on Oct 9

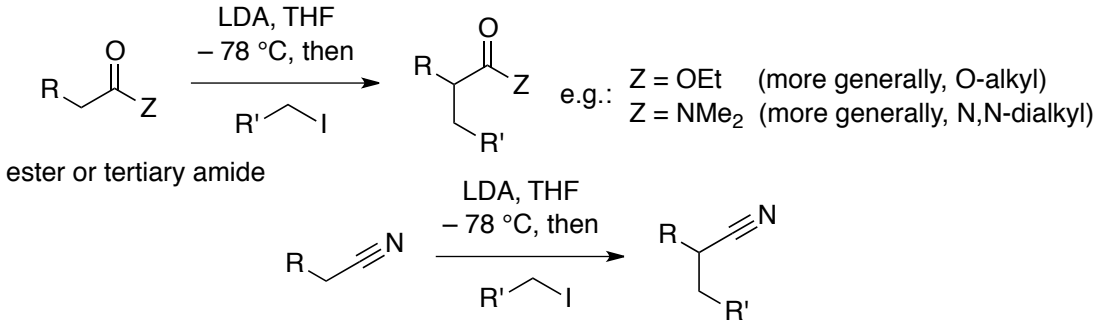
Completion of the synthesis of fecaene



Scope, mechanistic, and stereochemical aspects of the C-alkylation of carbonyl enolates: fundamental C-C bond forming processes in modern synthetic organic chemistry

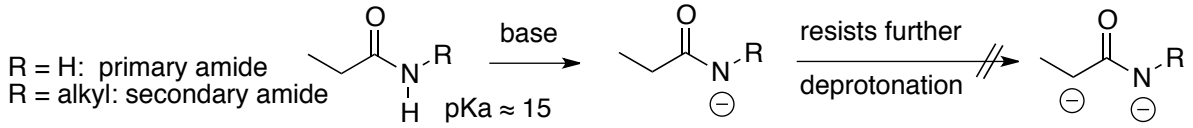
Preparation and C-alkylation of enolates of the major classes of carbonyl compounds

Preparation of enolates of esters, nitriles, and tertiary amides with LDA (or other appropriate strong bases) and their C-alkylation:

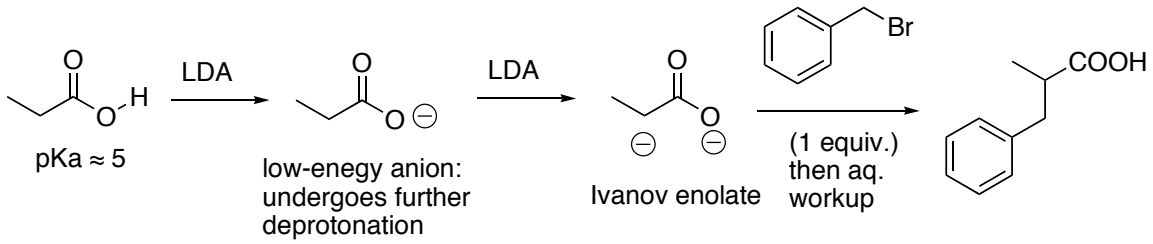


in all cases, the enolate is prepared by addition of the substrate to a solution of LDA (or alternative strong bases) in THF at low temperature (–78 °C) to prevent undesirable side reactions of the highly reactive, sensitive enolate

Inability of primary and secondary amides to form enolates due to initial deprotonation of the N–H group (pKa ≈ 15) and formation of a fairly energetic anion which resists further deprotonation:



Ivanov enolates of carboxylic acids:



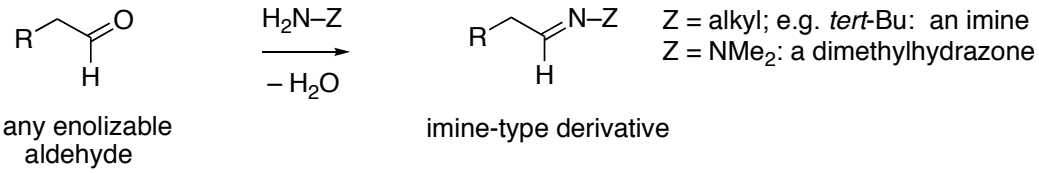
Difficulties encountered in the deprotonation of aldehydes with LDA:

> rate of deprotonation ≈ rate of aldol addition of the enolate to an intact aldehyde
> and consequent polymerization of the aldeyde under basic conditions

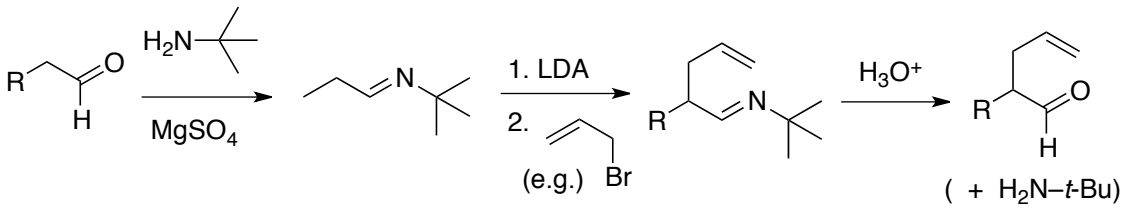
Principle: because of the above, it is NOT possible to convert an aldehyde completely and irreversibly into a well-behaved enolate with a strong base such as LDA

Significantly diminished electrophilicity of imines (=Schiff bases; N-analogs of C=O's) derived from aldehydes (or ketones) relative to the parent carbonyl compounds:

Temporary conversion of aldehydes into imine-type derivatives as way to suppress aldol-type reactions during deprotonation:

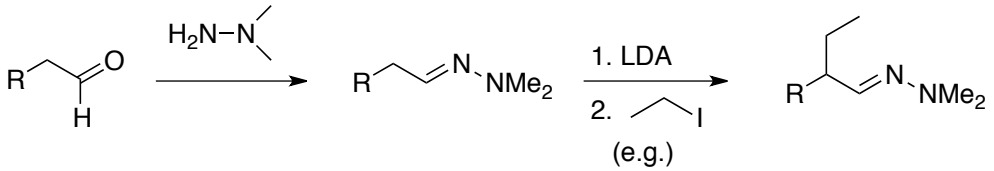


Formation, deprotonation, alkylation, and hydrolysis of *tert*-butylimine derivatives of aldehydes:

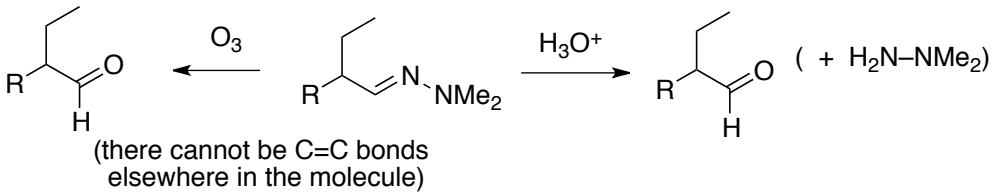


> the overall result is equivalent to the alkylation of the enolate of the starting aldehyde

Formation, deprotonation, and alkylation of N,N-dimethylhydrazones derivatives of aldehydes:



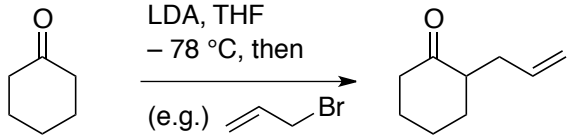
Post-alkylation hydrolysis or ozonolysis of hydrazones as a method to retrieve the corresponing aldehyde:



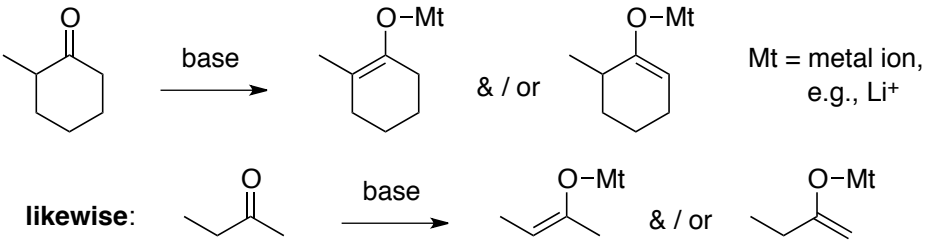
again, the overall result is equivalent to the alkylation of the enolate of the starting aldehyde

The α-alkylation of aldehydes by the above methodology as a process of considerably lesser significance than the α-alkylation of other carbonyl compounds

Deprotonation and alkylation of symmetrical ketones:



Deprotonation of unsymmetrical ketones: the issue of regioselectivity:

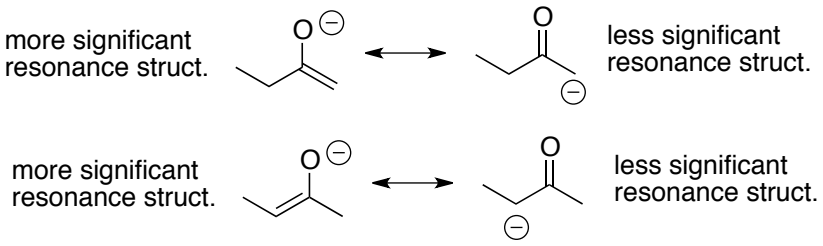


will there be any preference for one regioisomer?

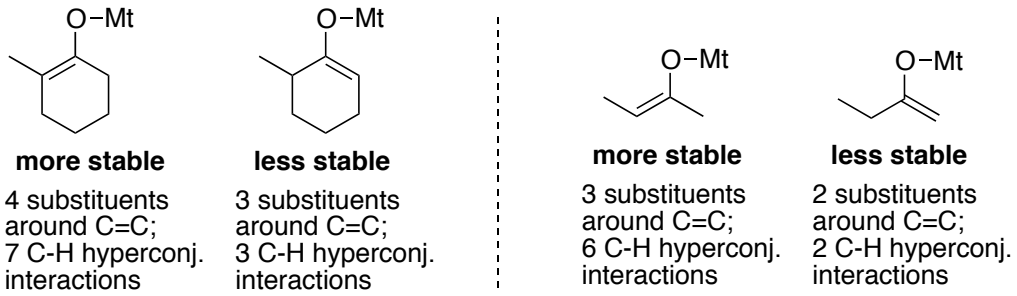
Olefin-like nature of enolates:

The metal ion that accompanies the enolate (especially a Lewis acidic, oxophilic one such as Li^+) is tightly bound to O. This "freezes out" the olefinic character of the enolate (see the above structures)

Even simple resonance considerations suggest that the olefinic structure must be favored over the "carbanionic" one, because the negative charge can accumulate on the more electronegative O atom:

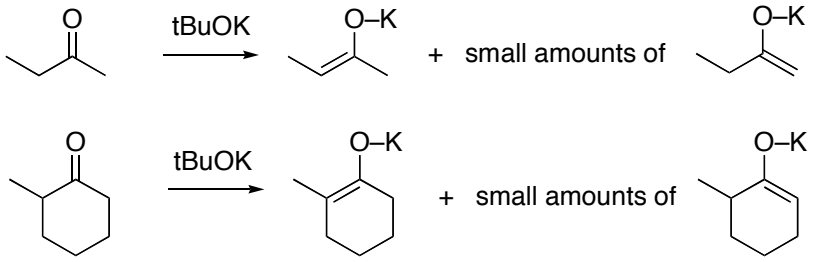


Principle: just as in the case of an olefin, the thermodynamic stability of an enolate increases with increasing substitution around the C=C bond, probably because this results in a greater number of hyperconjugative interactions between allylic C–H σ-electrons and the vacant C=C π-antibonding orbital (see notes from CHEM 203):



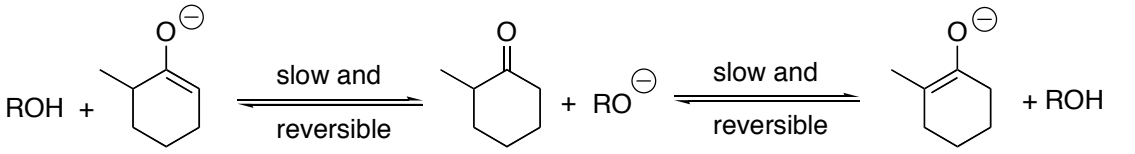
"Enormous complexity" of the mechanism(s) of deprotonation of ketones (D. Collum)

Principle: treatment of an usymmetrical ketone of the type shown above with a **weaker** base that deprotonates the substrate **incompletely**, **slowly** and **reversibly** (i.e., the conjugate base of an acid that has a pKa comparable to that of the ketone (≈ 20); such an alkoxide like EtONa (pKa EtOH ≈ 17) or *tert*-BuOK (pKa *tert*-BuOH ≈ 19), leads preferentially to the *more substituted, more thermodynamically favorable* enolate:



Mechanistic rationale for formation of the more thermodynamically favorable enolate upon deprotonation of, e.g., 2-methylcyclohexanone with tBuOK (or with EtONa):

> Alkoxides (pKa ≈ 17-19) are insufficiently basic to deprotonate the ketone (pKa ≈ 20) completely and irreversibly. Enolate formation will be reversible, resulting in accumulation of the thermodynamically favorable enolate, **T**, at the expense of its regioisomer **K**:

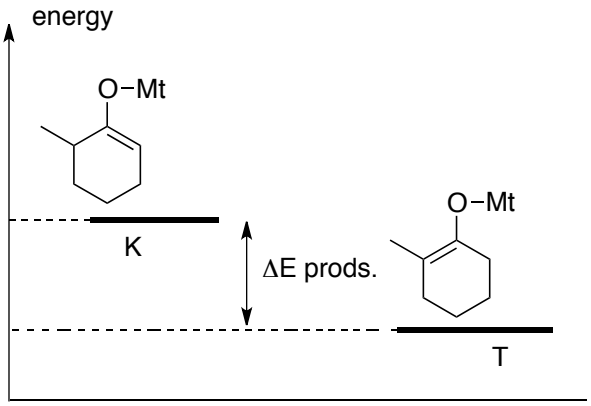


K - less stable:
minor enolate at equilibrium

C

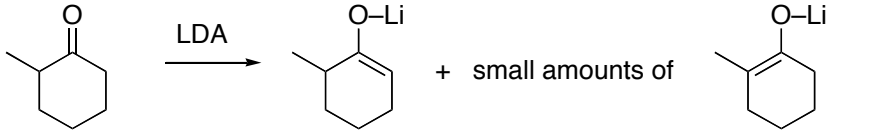
T - more stable:
major enolate at equilibrium

In such a reversible reaction, the product ratio is determined **solely** by the energy difference between products T and K. In the present case, the majority of the molecular population of starting ketone will be channeled through the reaction pathway leading to enolate **T**, which becomes the major product.



Recall, a reaction that proceeds under these conditions is said to be **thermodynamically controlled**. Enolate T may be described as the **thermodynamic** product of the deprotonation reaction (= thermodynamic enolate).

Principle: treatment of an unsymmetrical ketone, e.g., 2-methylcyclohexanone, with a **stronger**, **hindered** base that deprotonates the substrate **rapidly**, **completely** and **irreversibly** at **low temperature** (–78 °C), leads preferentially to the *less substituted, less thermodynamically favorable* enolate ("K" – enolate). This selectivity is especially pronounced if the base contains a **Lewis acidic, oxophilic** metal ion such as Li^+ (e.g., LDA):



K - less stable
major product

T - more stable
minor product

The K-type product above as the *kinetic enolate*: the one that forms faster under these conditions, even though it is less stable than the regioisomer T