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 °C), e.g. in the preparation of compound E in a selective manner:

\[
\text{ketone} \xrightarrow{\text{LDA, THF, –78 °C}} \text{enolate} \xrightarrow{\text{MeI}} \text{enone} \xrightarrow{\text{H}_2, \text{Pd(C)}} \text{E}
\]

Regioselective formation of enolates through dissolving metal (mostly Li, sometimes Na, or K) reduction of enones (= α,β-unsaturated ketones) in liquid NH\(_3\) in the presence of tert-butanol:

\[
\text{enone} \xrightarrow{\text{Li, liq. NH}_3} \text{enolate}
\]

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.:

\[
\text{Li}^{\text{solid}} \rightarrow \text{Li}^{\text{solution}} \rightleftharpoons \text{Li}^{\text{solvent}}^+ + \text{e}^-^{\text{solvent}}
\]

Powerful reducing properties of a solution of Li (or Na, or K) in liquid NH\(_3\) (≈ a solution of electrons)

Mechanistic aspects of the dissolving metal reduction of enones

- Radical anions and dianions
- Use of a proton donor such as tBuOH 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.:
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:

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

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 sp² C atom of an enolate as it rehybridizes to an sp³ 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

The E group is equatorial. One may say that this is the product of equatorial alkylation of the enolate. Clearly, equatorial alkylation is disfavored on kinetic grounds, because it proceeds through a more energetic transition state.

The ring is stable as it is and it undergoes no further conformational change. The E group is axial. One may say that this is the product of axial alkylation of the enolate. It is apparent that axial alkylation is favored on kinetic grounds, because it proceeds through a less energetic transition state.

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: