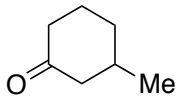
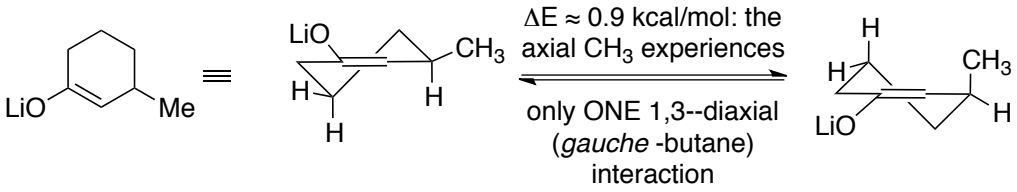
CHEM 330

Topics Discussed on Oct 21

Conformationally mobile (flexible) cyclohexanones: those carrying substituents characterized by a small A-value; for instance, small alkyls like Me, Et, ..., e.g.:



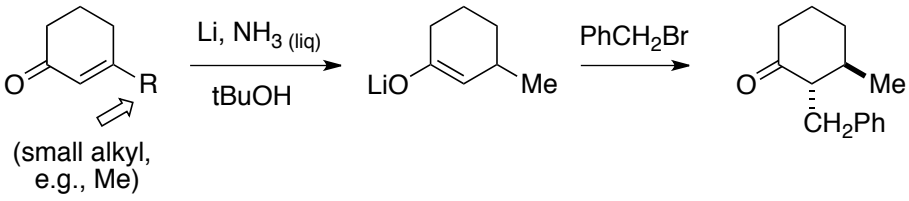
Principle: the 6-membered ring in the enolate of a conformationally mobile cyclohexanone may readily access either half-chair conformer, because the energy difference between the two is small. For instance:



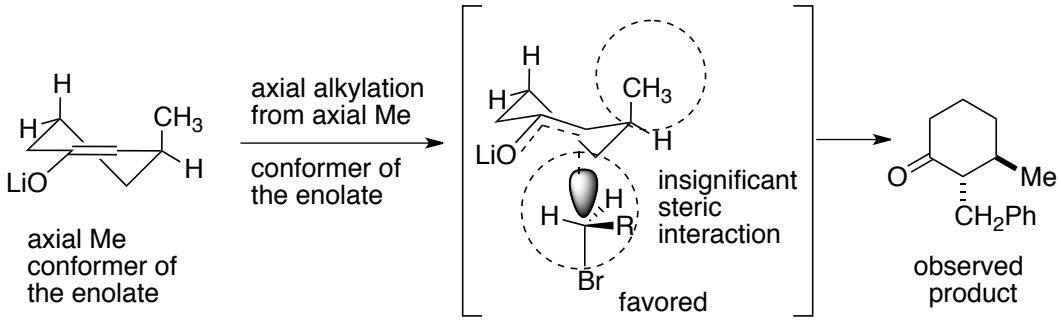
Consequence: the inherent preference for the axial mode of alkylation may manifest itself from either conformer, complicating the prediction of the stereochemical outcome of alkylation reactions.

> The 6-membered ring will generally tend to evolve from a half-chair to a chair-like conformer during the alkylation reaction. However, a multitude of interactions (steric, conformational, etc.) will determine which half-chair conformer of the enolate is more likely to participate in the alkylation event

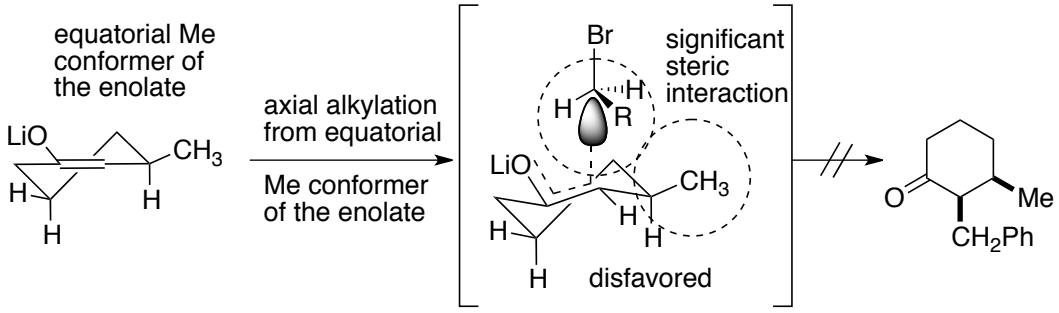
Alkylation of enolates of simple 3-substituted cyclohexanones leading selectively to *trans* products, e.g.:



because:



whereas:



Conclusion: refining what was stated earlier regarding conformationally fixed cyclohexanone enolates, the stereochemical outcome of the C-alkylation of a generic cyclohexanone enolate is controlled by:

(i) the innate preference for axial alkylation through a chair-like transition state;

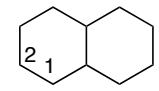
(ii) the steric interactions between the incoming electrophile and various molecular subunits;

(iii) conformational factors.

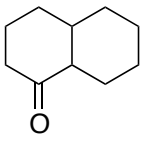
All such factors contribute to determining the overall energy of the transition states leading to the various possible products. The major product of the reaction (at least initially) will always be the one obtained through the least energetic transition state — so long as the reaction is strictly kinetically controlled.

The interplay of the above factors in the stereochemical course of the alkylation of enolates of more complex cyclohexanones: the case of **decalones**

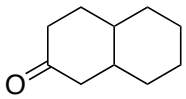
Decalone: a ketone based on the decalin framework, e.g.:



decalin
(cis or trans)

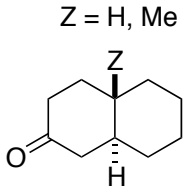


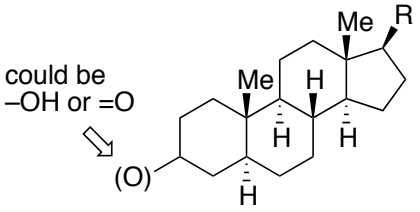
1-decalone



2-decalone

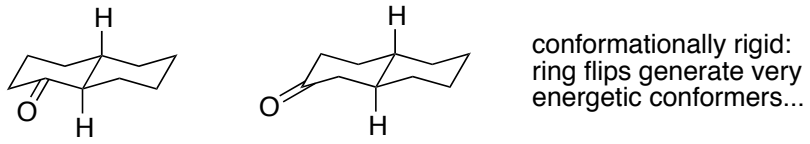
Similarity between *trans*-2-decalone and the A-B ring system of most steroids





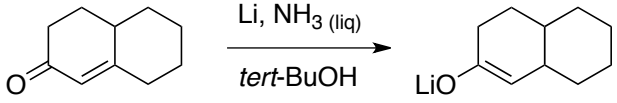
Alkylation of enolates of *trans*-2-decalones as an issue of special relevance in the synthesis of steroids and other bioactive substances of current interest

Trans-decalones as conformationally fixed cyclohexanones

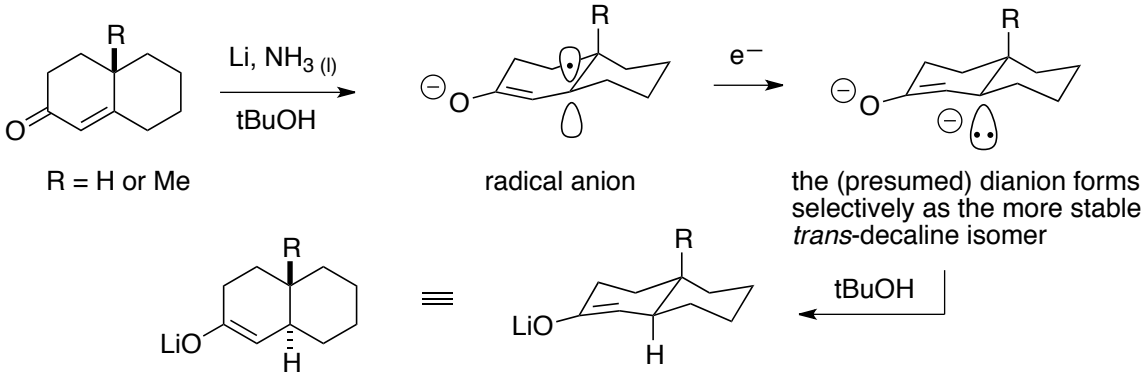


Analogy between 2-decalones and 3-alkylcyclohexanones and potential difficulties encountered during their attempted conversion into regiochemically defined enolates by direct deprotonation

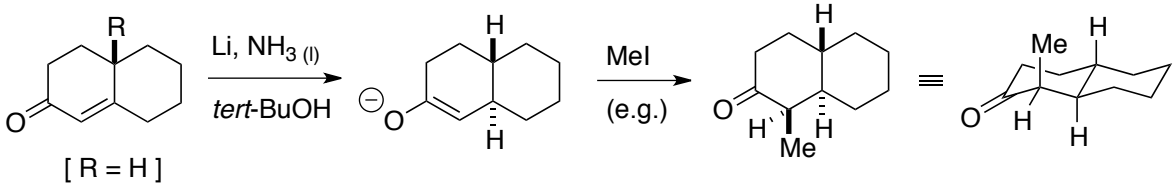
Dissolving metal reduction of conjugated 2-decalones as a means to access regiochemically defined enolates; e.g.:



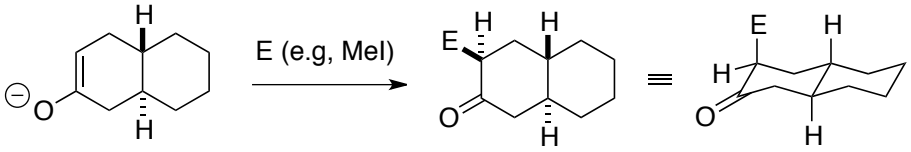
Selective formation of a *trans*-decalin framework during protonation of the (presumed) dianion intermediate in the dissolving metal reduction of unsaturated decalones:



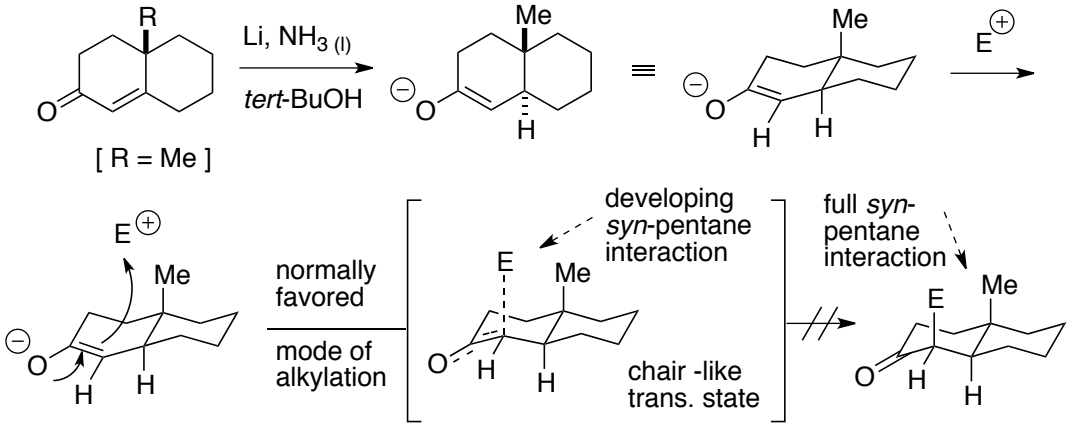
Axial alkylation preference in the reaction of enolates of *trans*-decalones in which the substituent Z at the ring junction is an H atom; e.g.:



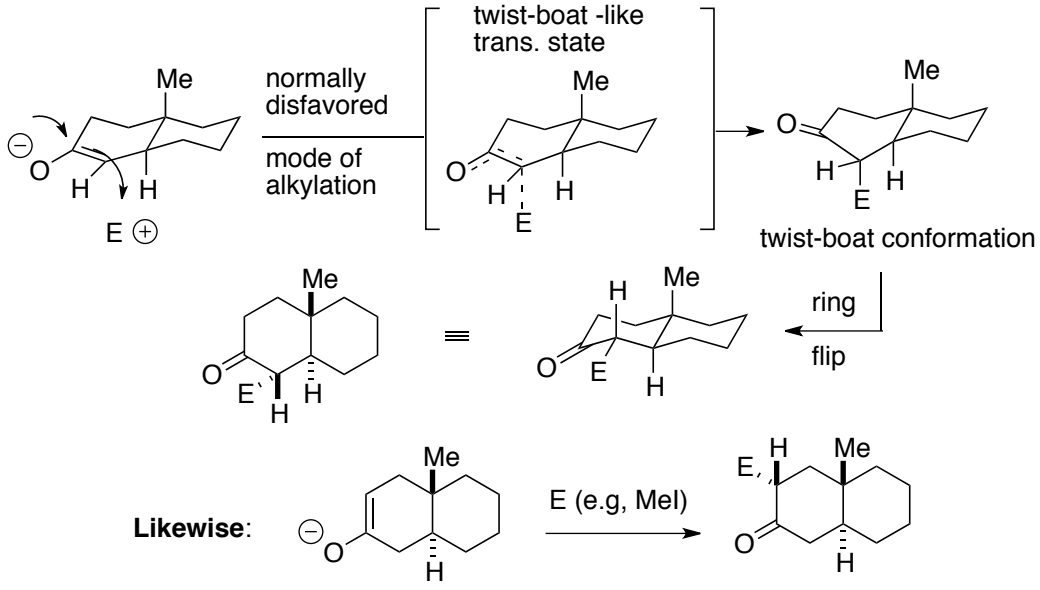
likewise:



Problems with the axial alkylation of enolates of *trans*-decalones in which group Z at the ring junction is alkyl: a developing *syn*-pentane interaction (notes of Oct. 14) between the incoming electrophile and the alkyl substituent promotes equatorial alkylation:



the energy required to overcome the developing *syn*-pentane interaction is greater than the energy required to cause alkylation through a twist-boat conformation !!
Therefore, the alkylation occurs via:



Enolates of decalones in which an alkyl (e.g., a methyl) group is present at the ring junction: preferential alkylation of via an energetic twist-boat transition state to avoid an even more energetic *syn*-pentane interaction.

Kinases (phosphokinases): enzymes that are involved in cell signaling, and that act by transferring a phosphoryl unit from ATP to the OH group (or other nucleophilic heteroatoms) of particular aminoacid residues in certain proteins

Kinase inhibitors: drugs that block the activity of kinases (treatment of cancer & other diseases)