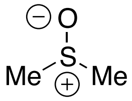
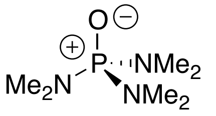
CHEM 330

Topics Discussed on Oct 2

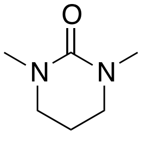
Effect of solvent: C-reactivity is more pronounced in enolates prepared in mildly Lewis basic (=weakly coordinating) solvents, such as tetrahydrofuran (THF). O-reactivity is more pronounced in enolates prepared in strongly Lewis basic solvents (=strongly coordinating), e.g., DMSO, HMPA, DMPU and the like.



dimethyl sulfoxide
DMSO



hexamethyl phosphoramide
HMPA



dimethyl propylene urea
DMPU

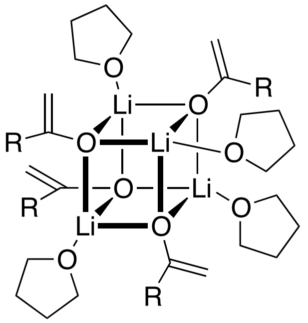
HMPA (hexamethylphosphoric triamide) as a very polar, strongly Lewis basic solvent

Toxic and carcinogenic properties of HMPA and use of dimethyl propylene urea (DMPU) as a safer alternative

Urea: a compound of formula $H_2N–CO–NH_2$, and by extension, a functional group containing the N–CO–N arrangement of atoms

Influence of the solvent on the **degree of aggregation** of enolates:

enolates prepared in weakly coordinating solvents, such as THF, exist in solution as aggregates. Thus, many carbonyl enolates prepared by deprotonation with LDA in THF (–78°C) are tetrameric. The tetramer displays a cubic core of alternating Li and O atoms:



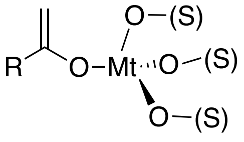
- C more exposed
- O less exposed & strongly bound to 3 Li^+ ions, so weak e^- density around O

greater C-reactivity

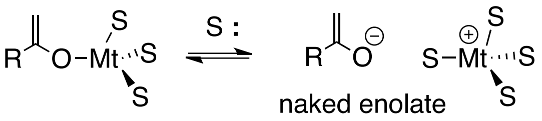
enolates prepared in strongly coordinating solvents, such as DMSO, HMPA, DMPU... exist in solution as monomers:

- O more exposed & bound to only 1 Mt^+, so greater e^- density around O

greater O-reactivity



"Naked" enolates: essentially free enolate anions existing in equilibrium with the monomeric form of the enolate in a strongly coordinating solvent:

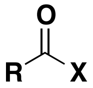
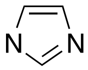
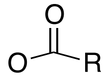


S : = strongly coordinating solvent

Methods to study the state of aggregation of enolates: colligative measurements and / or NMR spectrometry of enolate solutions

> **Reminder**: colligative properties of solutions are those that depend on the total number of *particles* (**not** concentration) of a solute present in the medium, and include: lowering of the vapor pressure and of the freezing point of the solution relative to pure solvent, increase in osmotic pressure, elevation of the boiling point, etc.

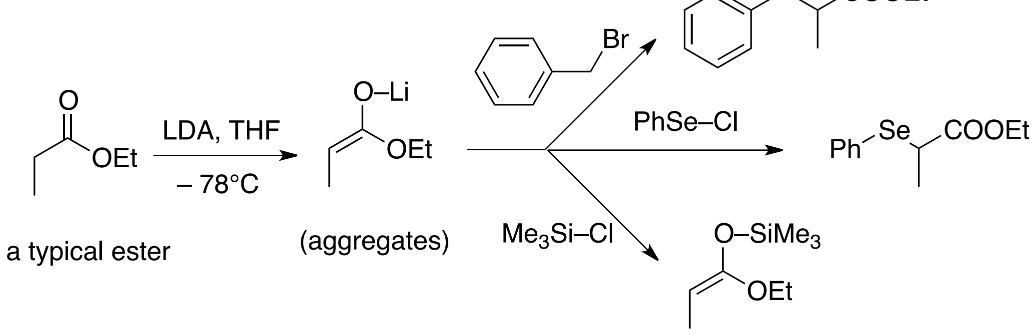
Nature of the electrophile: this is by far the most significant factor that determines C- vs. O-reactivity. The table below lists the C- vs. O-reactivity of enolates toward a range of common electrophiles of interest in CHEM 330 and in modern synthetic chemistry.

type of electrophile	**C-reactivity**	**(intermediate - of no interest to us)**	**O-reactivity**
alkyl halides and congeners **R-CH$_2$–X** (mostly primary)	X = I, Br	(X = Cl, OTs)	X = OSO$_2$OR
epoxides			
acyl derivatives 	X = OR', CN, 		X = halogen X = 
sulfenyl & selenenyl halides	R-S–Cl R-Se–Br		
trialkylsilyl halides (very important)			R$_3$Si–Cl

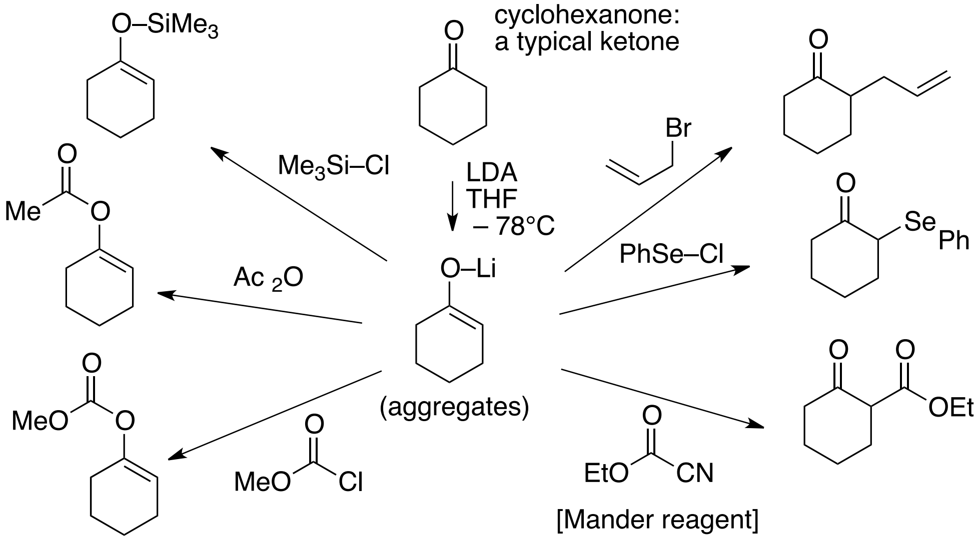
> **Note**: the reasons why particular electrophiles prefer to react at the C terminus of an enolate, while others favor reaction at O, are manifold, complex, and not fully understood.
>
> Interpretations based of **H**ard / **S**oft **A**cid – **B**ase (HSAB) theory have been advanced, but are not fully satisfactory. In CHEM 330 we are not concerned about the rationale for the C- vs. O-preference of such electrophiles. We simply accept the data in the table as fact.

Examples of C– and O–derivatization of enolates:

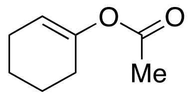
- esters



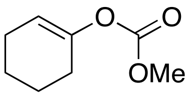
- ketones



Enol esters and enol carbonates: structures obtained upon O-acylation of a carbonyl enolate:



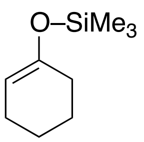
an enol ester (enol acetate in this case)

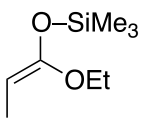


an enol carbonate

Silyl ketone ethers and silyl ketene acetals: compounds obtained upon O-silylation of the enolate of a ketone and of an ester, respectively:

silyl enol ether derivative of cyclohexanone





silyl ketene acetal derivative of ethyl propionate

Irreversible nature of the reaction of a carbonyl enolate with the electrophiles shown in the table above