Week 7

Enolate and enamine chemistry

Enolate chemistry: Regiochemistry in enolate formation (kinetic and thermodynamic control; enolate structure; aldol and related reactions, Bredt's rule

Enamines: Stork enamine reaction; thermodynamic control

Organometallic chemistry

Grignard reagents and organolithiums: Formation and structure; reactions with carbon electrophiles (aldehydes and ketones, strained ethers, nitriles, carbon dioxide, 1,2-addition to α,β-unsaturated carbonyls, esters)

Organocuprates: Synthesis and structure; reactions; hard-soft acid-base principle

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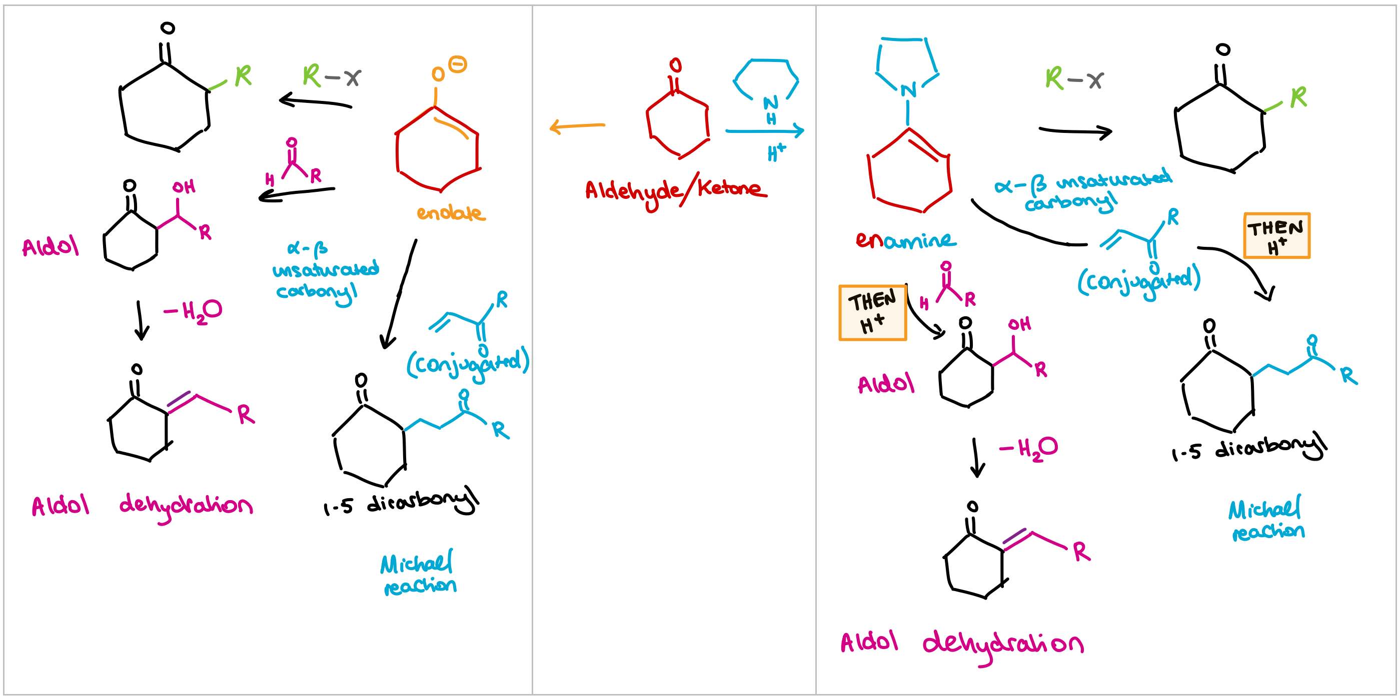
C–C BOND FORMATION

Enolate and Enamine Chemistry

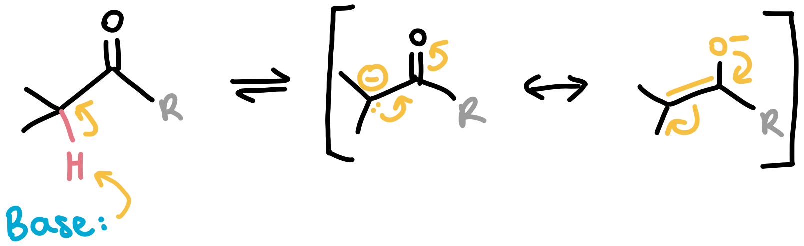


Enolates:

→ Anions stabilised by resonance structures

→ Nucleophilic carbanions and can react with electrophilic alkylating reagents.

Enolate formation: Base-catalysed

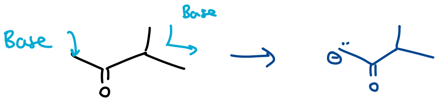
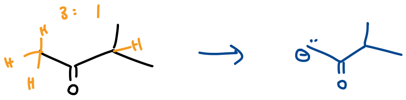


Enolates with alkyl halides → alkyl bond (C–C)

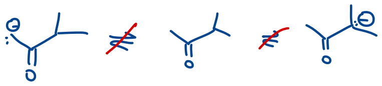
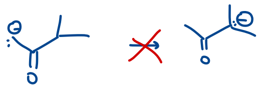
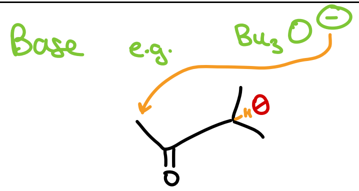
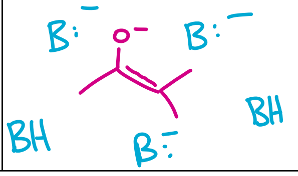
Thermodynamic control of enolate formation - *the more substituted enolate is rapidly formed by rapid equilibrium. Factors such as resonance stabilization can be helpful.*

Kinetic Control of Enolate formation:

Kinetically favourable products form the fastest.

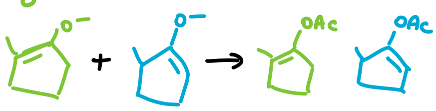
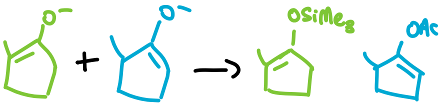
The less substituted carbon is faster to deprotonate for steric reasons	 however, less thermodynamically stable
The less substituted carbon has more hydrogens and is statistically more likely to deprotonate	 however, less thermodynamically stable

Forcing a kinetic enolate to form can occur under the following conditions:

Low temperature	lower the rate of equilibration	
Short reaction times	lower the extent of equilibration	
Hindered base	preferentially deprotonates the less substituted carbon	 Base e.g. $Bu_3O^{\ominus}$
excess of strong base	Deprotonates ketone (no equilibrium)  α-protons act as acid	 no available hydrogen for ketone intermediate

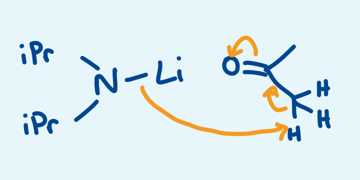
Determing the ratio of thermodynamic:kinetic product can be done by:

1. ‘trapping’ the enolates with acetic anhydride (Ac_2O) or trimethylsilyl chloride (Me_3SiCl).
2. Produces chemically stable enol acetates or trimethylsilyl enol ethers

Me_3SiCl	→ Trimethylsilyl enol ethers 	e.g. 
Ac_2O	→ Enole acetates 	

LDA formation of enolates:

Temp range	Enolate
~ –78ºC	kinetic enolate favoured (72% : 28%)
0ºC and above	thermodynamic enolate favoured (94% : 6%)



★ Once H⁺ removed, it cannot "rejoin" and form an equilibrium.

★ Bulky; will attack less sterically-hindered site

★ Low nucleophilicity → does not undergo nucleophillic addition.

relatively stable formed quickly and thus doesn't react with the ketone.

Sodium/Potassium Enolates:

↳ not long-lived; very reactive

- The larger the alkali metal, the more unstable the enolate. This is because the cation radius is larger and separates it further from the enolate.
- Deprotonation and alkylation occur in the same step due to the instability of enolates formed through the sodium/potassium.

e.g.