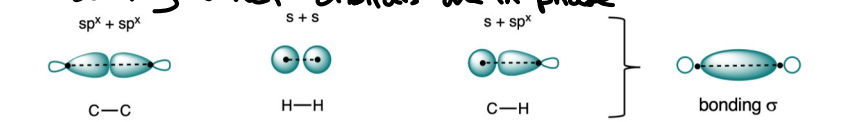
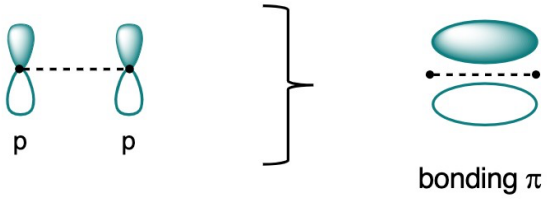
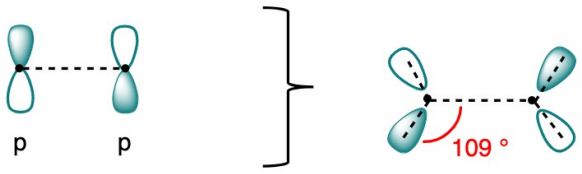
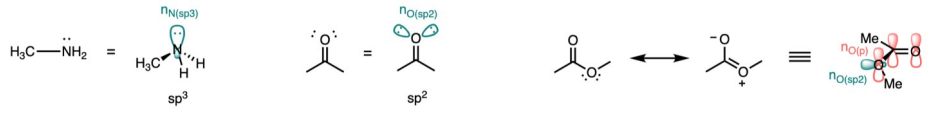
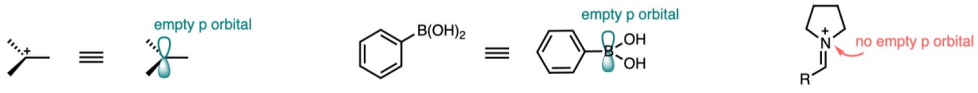
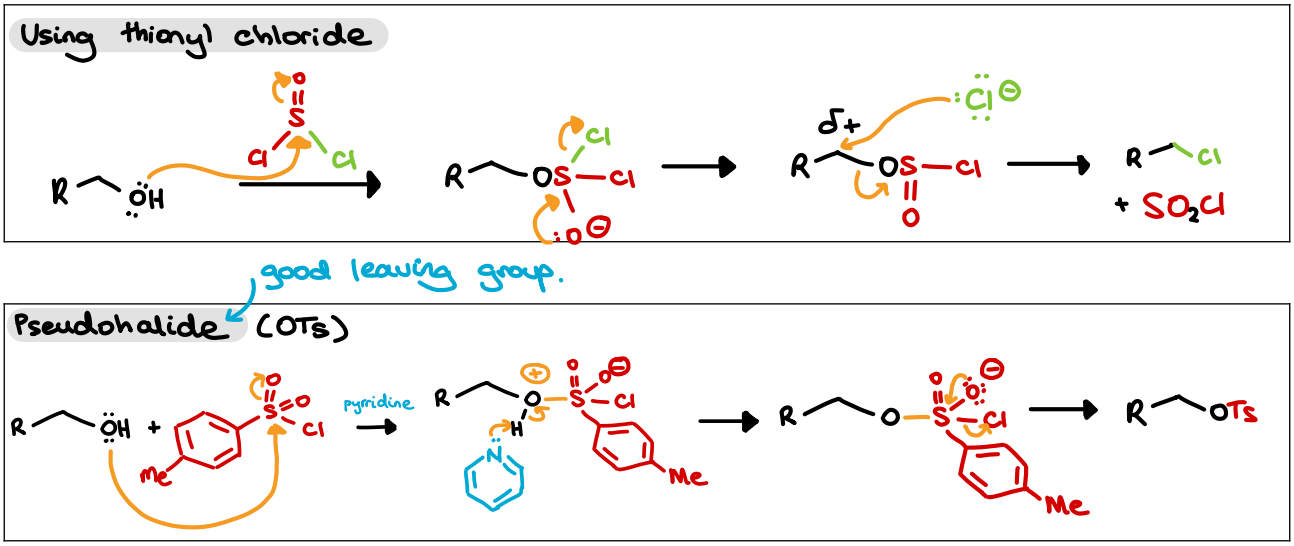
FMO Theory:

Atomic Orbitals	s, p, d and f. **electronegativity decreases bond energy**
Hybrid Orbitals	sp, sp^2 and sp^3
Molecular Orbitals	**σ orbitals** bonding when orbitals are in phase   antibonding when orbitals are out of phase **π orbitals**   **N-orbitals**  non-bonding orbitals; lone pairs. can be sp^3, sp^2, sp or p-type orbitals. **P-orbitals**  empty p orbitals. Present on both charged and neutral species.

Converting hydroxide to good leaving groups:



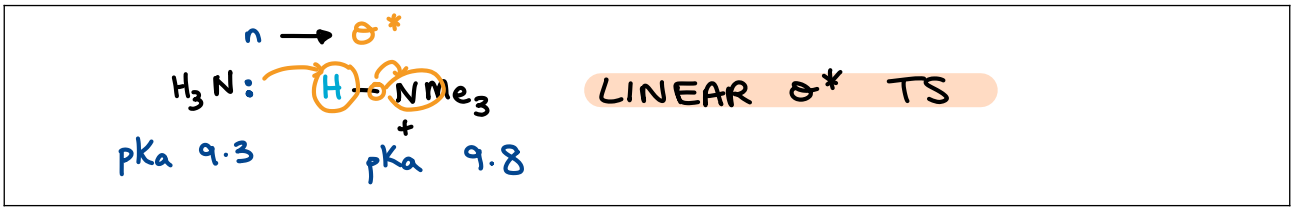
Nucleophilicity and Basicity:

Deprotonation to generate an anionic intermediate raises energy of the HOMO and is often a key step in S_N2 reactions

Proton transfer:

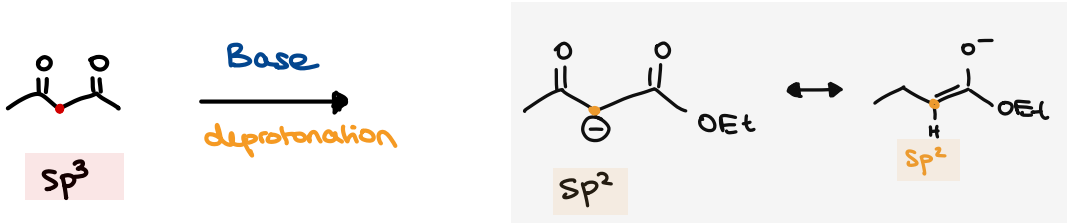
Proton transfer steps involve addition to σ* orbital of H-X bond. The consequence is that the transition state of proton transfer is **linear**, not bent.

That's why proton transfer through a 4-membered transition state is geometrically impossible.



Proton transfers to and from carbon are usually **slow**. The more nuclei that need to be reorganised, the slower the reaction because it comes at an energy cost.

→ hybridisation changes from sp3 to sp2 and therefore shape changes from tetrahedral to trigonal planar



pKa plays a major role in deprotonation reactions!

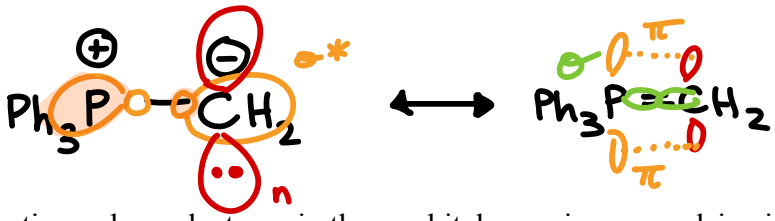
Diffusion-controlled proton transfers including heteroatoms are extremely fast when $\Delta pK_a > 3$

$\Delta pK_a = 6.7$ ⇒ diffusion-controlled rates 	$\Delta pK_a = 0.5$ ⇒ slow 

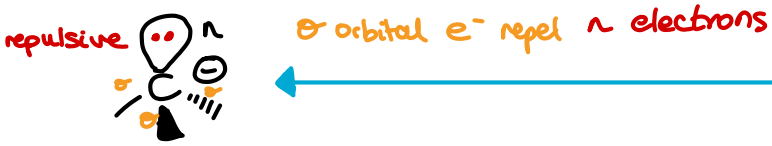
Carbanions:

Don't really exist in solution; they're masked by compounds such as enolates or ylids. Naked carbanions don't exist as they're too reactive.

In enolates/ylids etc, phosphorous and sulphur stabilise the carbanions via **n→σ*** bonding.



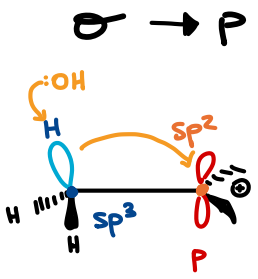
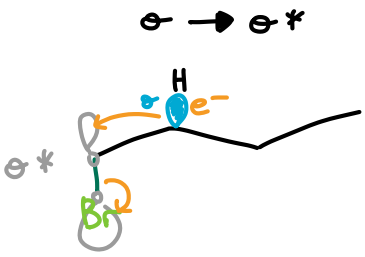
Destabilising σ conjugation, where electrons in the n orbital experience repulsive interaction with electrons in the σ orbitals.



Nucleophilic σ bonds:

Carbanion equivalents (i.e., C-Mg or C-Li bonds). They're typically so basic that they promote elimination over S_N2 reactions, so enolates are the only useful carbanion for S_N2 reactions.

e.g., FMO descriptions 

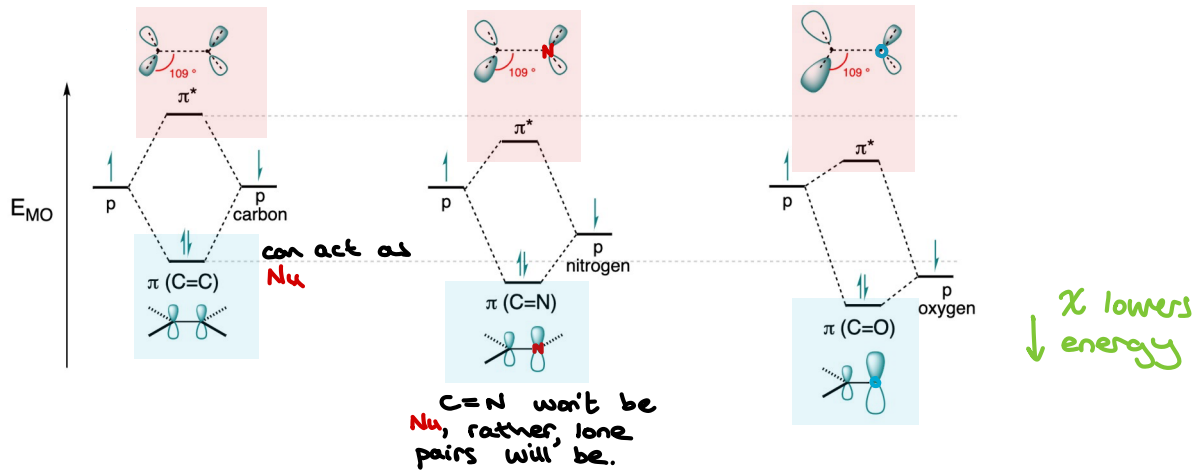
E1 	E2 

This is why 3°, 2° and 1° amines are more reactive than ammonia. σ bonds and filled p orbital have repulsive interactions.

Synthesis of Carbon-Heteroatom Bonds

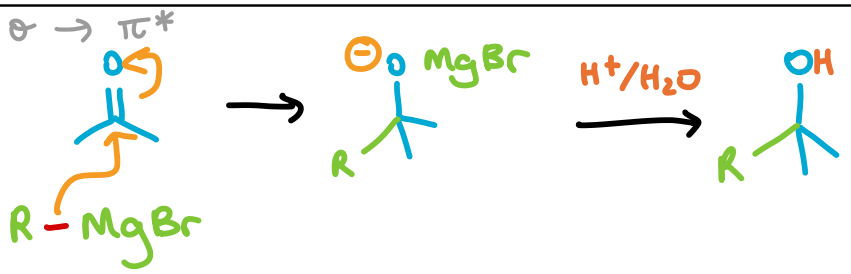
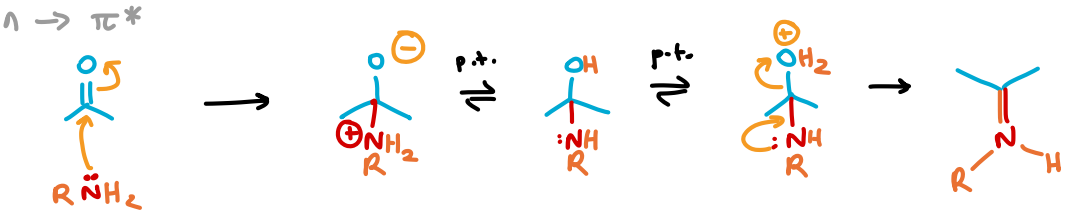
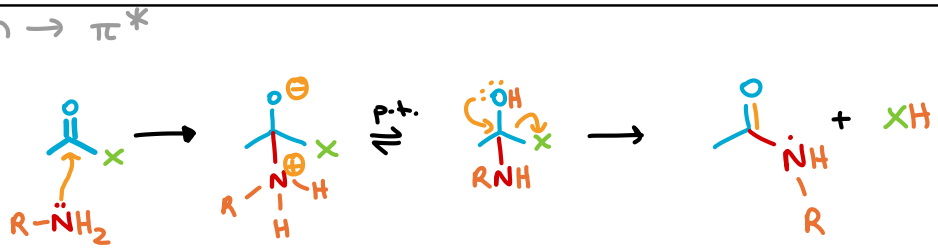
Substitution at the Carbonyl Carbon

FMO description of double bonds

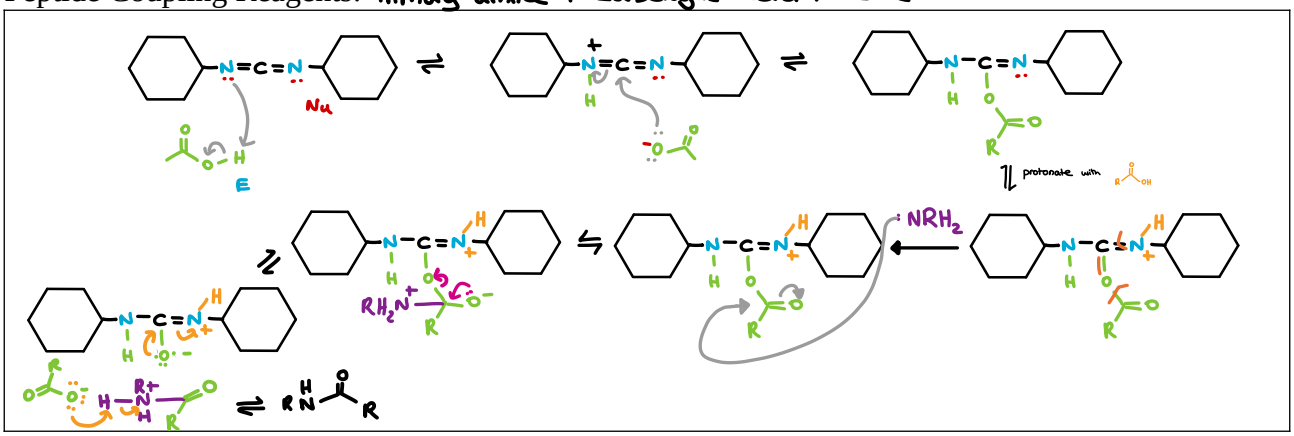


Electronegativity lowers energy of HOMO and LUMO

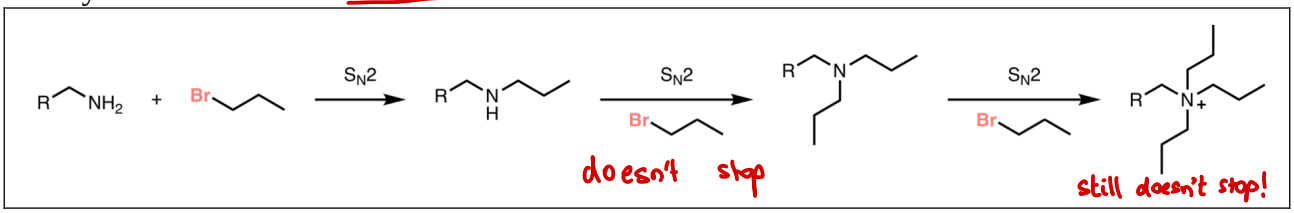
Thus the lowest energy is the C=O bond, making the LUMO more accepting of the Nu attack. Contrastingly, the C=C bond won't accept from a Nu, but will donate to an E.

Nucleophilic Addition	
Substitution Reaction: Condensation	
Substitution Reaction: Acyl Transfer	

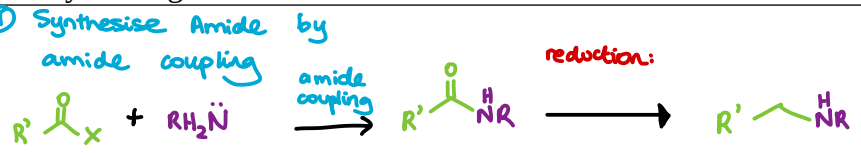
Peptide Coupling Reagents: Primary amine + carboxylic acid + DCC.



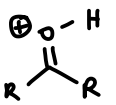
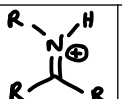
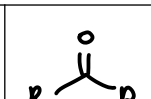
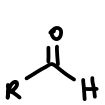
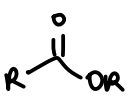
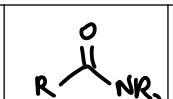
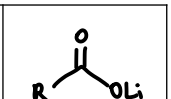
SN2 synthesis of 2° and 3° amines is often uncontrollable:



So, instead, we can use carbonyl strategies:

Reduction of Amides	① Synthesise Amide by amide coupling 
Reductive Amination	aldehyde + amine → amide  condensation

Reactivity of Metal Hydride reductants:

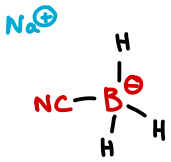
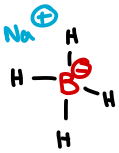
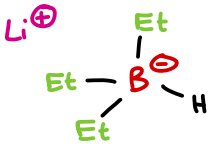
							
$LiAlH_4$/THF	✓	✓	✓	✓	✓	✓	✓
NaBH4/MeOH	✓	✓	✓	✓	×	×	×
$NaBH_3CN$	✓	✓	×	×	×	×	×

Note: Mechanism of amine + aldehyde condensation

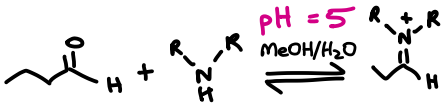
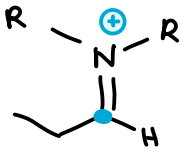
Dependant on substituent functionality:

Electron-poor boron substituents are more selective in their reductions.

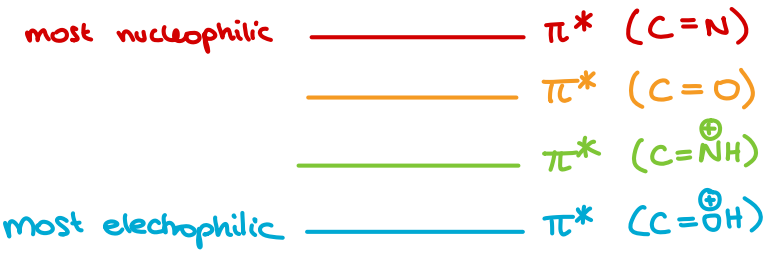
Electron-rich boron substituents are stronger reducing agents.

Electron-poor substituent		Electron-rich substituent
		

Reductive Amination:

Condensation	 Mildly acidic conditions Too acidic and the 3º N amide will be protonated Too basic and the alcohol won't be protonate to afford the H_2O leaving group.	Forms charged iminium intermediate which is more electrophilic than carbonyls.  Selective reduction of iminium → amine
Reduction		Use sodium cyanoborohydride $NaBH_3CN$

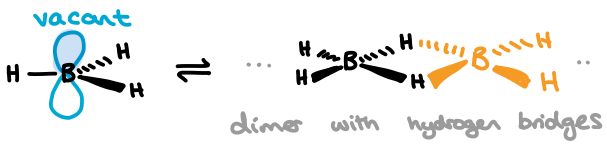
Orbitals:



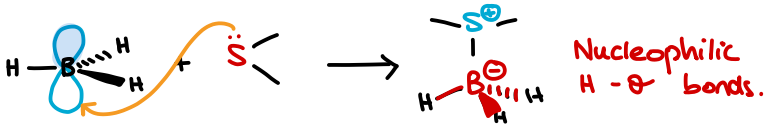
C=N bond is higher energy (more nucleophilic) than the C=O bond

Boranes:

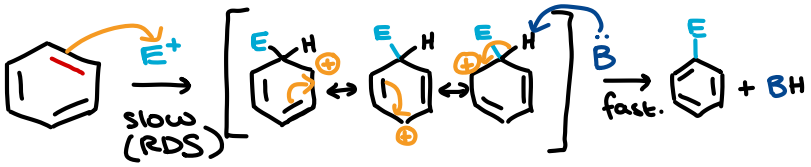
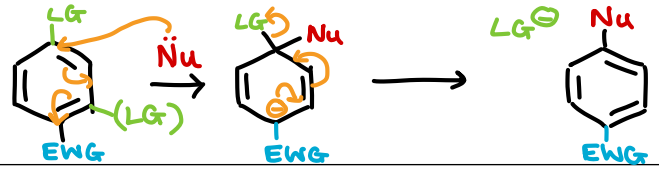
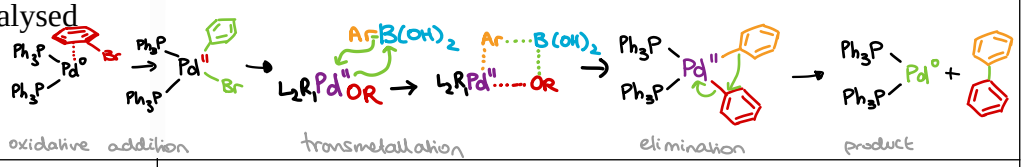
Vacant p-orbital exists as a dimer with hydrogen bridges.



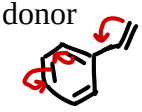
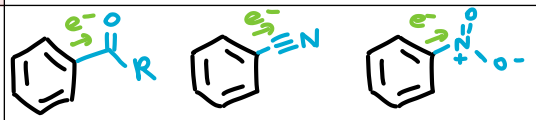
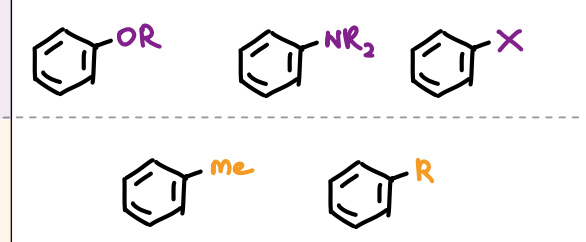
Neutral borane + nucleophile → negatively charged borate



Week 6 – Aromatic Chemistry:

Electrophilic aromatic substitution	
Nucleophilic aromatic substitution	
Substitution via S_N1 Mechanism observed in benzene diazonium compounds	
Transition metal catalysed cross-coupling	
Photoredox chemistry	See <Green chemistry>
Combination of transition metals and photoredox catalysis	See <Green chemistry>

Substituent Classes:

Simple conjugated systems (C-type)	Resonance donor 	π donors π acceptors σ neutral	
π bonded systems, *Electron withdrawing* (Z-type)	Resonance acceptor	π acceptors σ acceptors	
Heteroatoms which carry a lone pair (X-type)	Resonance donor 	π donors σ acceptors *or* π donors σ neutral	

Note: resonance effects are also called mesomeric effects

Resonance: $\pi \rightarrow \pi^*$ $n \rightarrow \pi^*$ $\sigma \rightarrow \pi^*$