Nine Key Mechanisms In Carbonyl Chemistry

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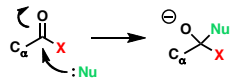
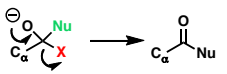
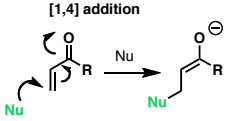
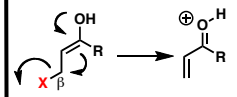
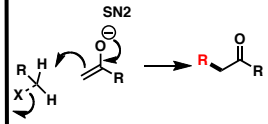
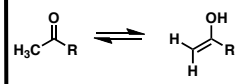
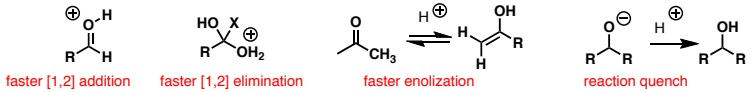
Mechanism	Description	Promoted by	Hindered by	Examples
Addition **[sometimes "[1,2] addition"]** 	Attack of a nucleophile at the carbonyl carbon, breaking the C–O π bond.	*Anything that makes the carbonyl carbon a better electrophile (more electron-poor)* Electron withdrawing groups on α carbon Electron-withdrawing X groups that are poor π-donors (e.g. Cl, Br, I, etc.) Addition of acid (protonates carbonyl oxygen, making carbonyl carbon more electrophilic. Note: acid must be compatible with nucleophile;alcohols are OK, strongly basic nucleophiles (e.g. Grignards) are not.	*1) Anything that makes the carbonyl carbon a poorer electrophile (more electron-rich)* *2) Sterically bulky substituents next to the carbonyl* X-groups that are strong π-donors (e.g. amino, hydroxy, alkoxy) Sterics: X=H (fastest) > 1° alkyl > 2° alkyl > 3° alkyl (most hindered, slowest) X=Cl (poorest π-donor, fastest addition) > OAc > OR > NH_2/NHR/NR_2 (best π donor, slowest rate)	Grignard reaction Imine formation Fischer esterification Aldol reaction Acetal formation Claisen condensation
Elimination **[sometimes "[1,2] elimination"]** 	Lone pair on carbonyl oxygen comes down to carbonyl carbon, forming new π-bond and displacing leaving group X.	The better the leaving group X, the faster the reaction will be. The rate follows pKa very well. Acid can turn poor leaving groups (NR_2, OH) into good leaving groups (HNR_2, H_2O) $I^- > Br^- > Cl^- > H_2O > OAc^- > SR^- > OR^- >> NR_2^-, O^{2-}$ H alkyl –9 –8 –7 –2 4 12 17 35 >40	X groups that are strong bases are poor leaving groups. Alkyl groups and hydrogens never leave. Amines and hydroxy are poor leaving groups under basic conditions, but are much better leaving groups under acidic conditions.	Fischer esterification Formation of amides by treatment of acid halides with amines. Claisen condensation
[1,4] addition 	Nucleophile attacks alkene polarized by electron withdrawing group, leading to formation of enolate.	So-called "soft" nucleophiles such as Gilman reagents (organocuprates) will add [1,4], as will amines, enolates etc. The more stable the conjugate base (enolate) of the carbonyl, the faster the reaction. Extra electron withdrawing groups on the α-carbon will promote the reaction.	[1,2]-addition can compete in the example of Grignard reagents. The more electron rich the carbonyl, the slower will be the rate of reaction (less able to stabilize negative charge). So addition to α,β-ketones > α,β–esters > α,β-amides.	MIchael reaction Addition of Gilman reagents (organocuprates)
[1,4] elimination 	Lone pair on oxygen comes down to form carbonyl, enol double bond displaces leaving group on the β-carbon	Facilitated if X is a good leaving group (just like [1,2]-elimination) In the aldol condensation, addition of acid helps OH group leave as H_2O. Note that in the Aldol reaction run under basic conditions, the enolate is a stronger base than OH(–), so in the base-promoted Aldol reaction, the [1,4]-elimination is favorable.	As with [1,2]elimination, X groups that are strong bases are poor leaving groups. Addition of acid will promote elimination of groups such as NR_2 and OH/OR.	Aldol condensation Knovenagel condensation
SN2 	Backside attack of nucleophile onto electrophile (alkyl halide or equivalent)	Facilitated by good leaving group on electrophile (alkyl halide or tosylate). Polar aprotic solvent is ideal. Enolate α-carbon is excellent nucleophile for S_N2 The higher the pKa of the carbonyl compound, the more reactive the conjugate base will be in the S_N2.	Rate of reaction will go primary alkyl halide > secondary alkyl halide Tertiary alkyl halides unreactive in S_N2.	Enolate alkylation Carboxylate alkylation
Keto-Enol Tautomerization 	Internal oxygen ↔ proton transfer with change in hybridization of oxygen and carbon.	Facilitated by acid The enol form is stabilized by internal hydrogen bonding if there is a carbonyl present at the β position.	Tautomerism under acidic conditions only significant for ketones, aldehydes, and acid halides (the latter under the conditions of the Hell-Vollhard-Zolinski reaction).	Acid-catalyzed aldol Acid-catalyzed bromination of ketones

Acid Base Reactions

Deprotonation	The conjugate base is always a better nucleophile than the conjugate acid. Deprotonation increases nucleophilicity. E.g. enolate > enol, alkoxide > alcohol, $NH_2(-) > NH_3$ Conjugate base can perform reactions the conjugate acid cannot. Deprotonation is also the last step in acid-catalyzed reactions, in order to generate the final (neutral) product	 *forms alkoxide* (more nucleophilic) deprotonation at end of acid-catalyzed acetal formation provides neutral product
Protonation	1) catalyzes [1,2] addition to carbonyls 2) promotes [1,2] elimination 3) to promote tautomerization. 4) quench (e.g. enolate from 1,4.	 faster [1,2] addition faster [1,2] elimination faster enolization reaction quench
Proton Transfer	An internal acid-base reaction. Not mechanistically distinct from the above, but often drawn as one step. Can proceed either intramolecularly or intermolecularly (both pathways operate) hence distinct arrow pushing steps often not drawn, and we just say "proton transfer"