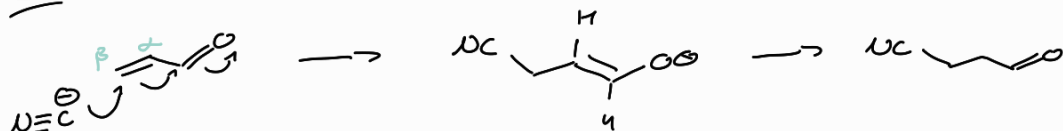


Conjugate additions

Alkenes with e^- withdrawing group = electrophile

ex

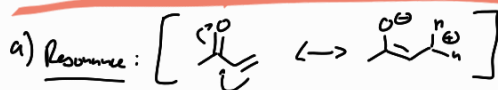


Most Nucleophiles react well in conjugate additions

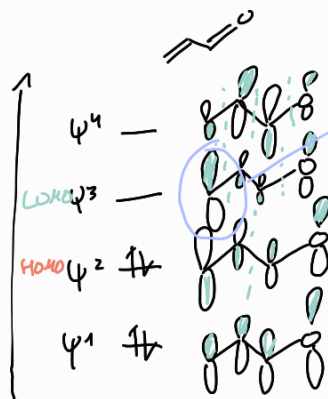
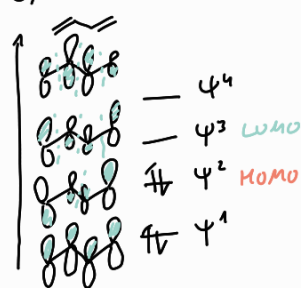
ex

Grignards	$EtMgBr$	very good
Alkyls	$Et-SH$	very good
Amines	Et_2NH	
Alcohols	$MeOH$	=
Halides	HBr, HCl	
Quaternaries	$\text{Cyclohexyl}^+/AlCl_3$	
Enolates	Enolate^-	good

Reactivity of Michael acceptors

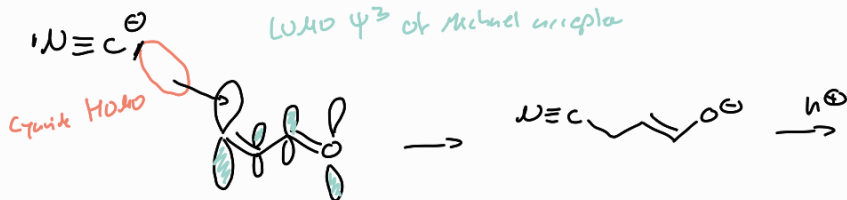


b) Orbitals

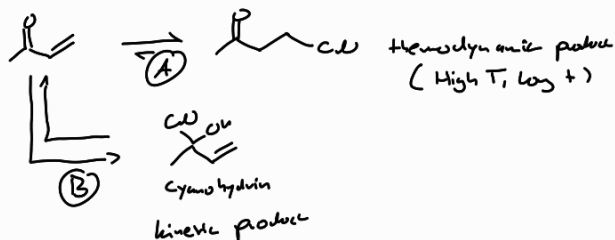


Michael acceptor LUMO has biggest p-orbital \Rightarrow biggest overlap when attack here

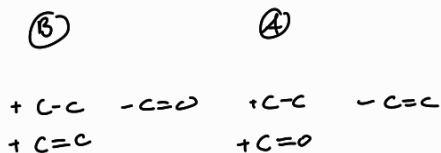
ex



Regiochemistry?

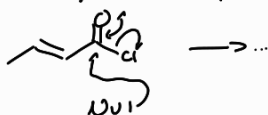


Bonds:



$\Rightarrow C=O$ more stable than $C=C$, Δ = thermodynamic

EWG favors 1,2 addition



Hard - soft Nu

Hard	In between	Soft
$F^{\ominus}, OH^{\ominus}, ROO^{\ominus}, Cl^{\ominus}$	Cu^{\ominus}	$RS^{\ominus}, I^{\ominus}$
H_2O, ROH	N_3^{\ominus}	RSn
NaN_3	Br^{\ominus}	RSn^{\ominus}, R_3P
$R-MgBr, R-Li$	RNH_2	Alkenes, aromatics
	R_2Sn	

\Rightarrow Hard Nu are dominated by electrostatics

\Rightarrow Soft Nu dominated by orbital interactions

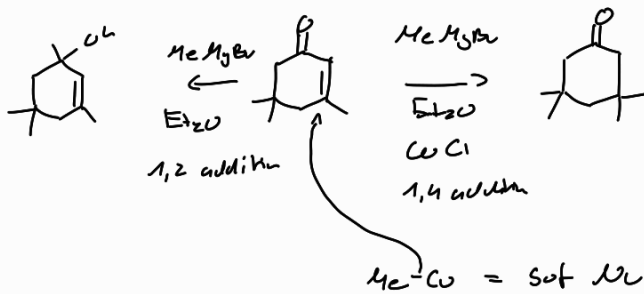
\Rightarrow various conj. addition



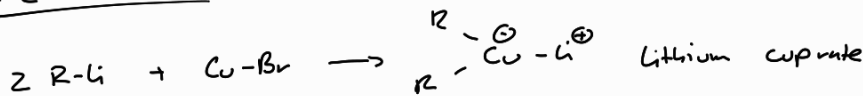
\rightarrow In between react on both sides but equilibrate to the thermodynamic product

How to make hard Nu ($R-MgBr$) undergo conjugate addition?

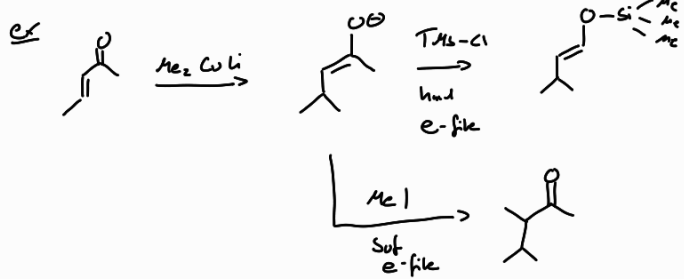
\Rightarrow Solution: Transmetalate with Cu^{\oplus} (e.g. $CuCl$ at 0.01%)



Same with $R-Li$



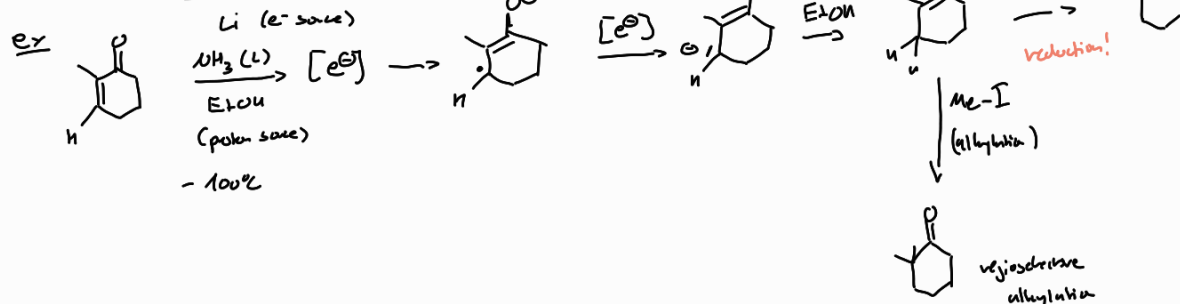
Works well with electrophiles trapping the intermediate enolate



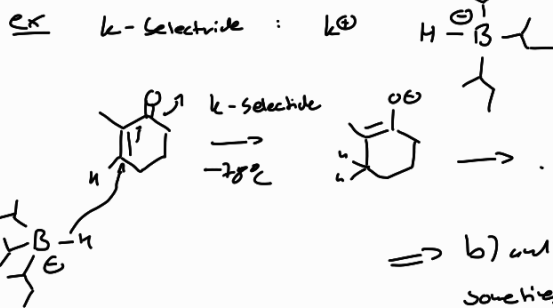
Regioselective enolates from Michael addition

a) Cuprate addition

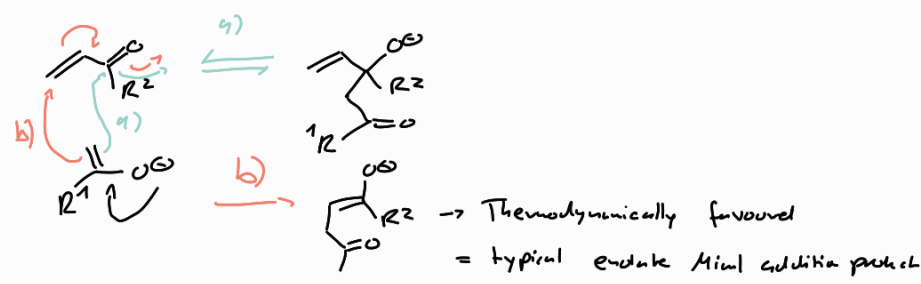
b) Dissolving metal reduction:



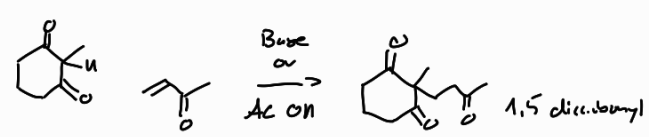
c) Regioselective enolate for Hydrate conjugate addition with alkyl borates



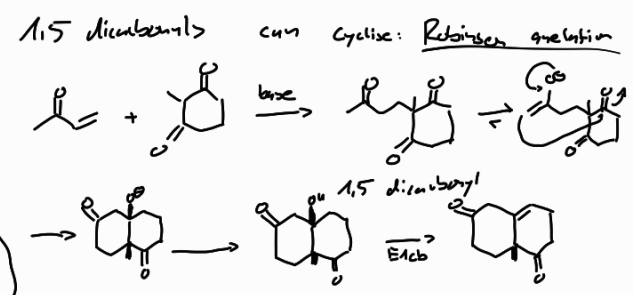
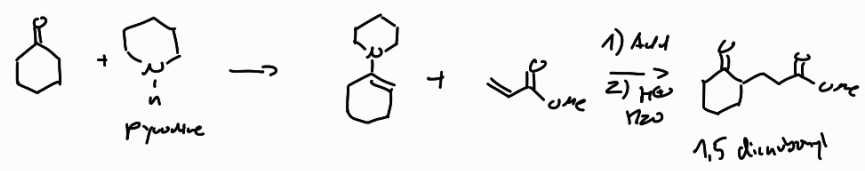
Enolates as Nu



Special case: 1,3-dicarbonyl - good Nu in Michael addition



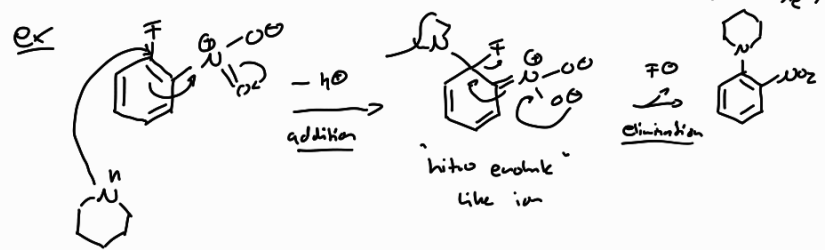
Another one: Enamines = good Nu



Nucleophilic aromatic substitution

- 1) S_NAr via addition-elimination
- 2) S_NAr via S_N1 like
- 3) S_NAr via benzyne

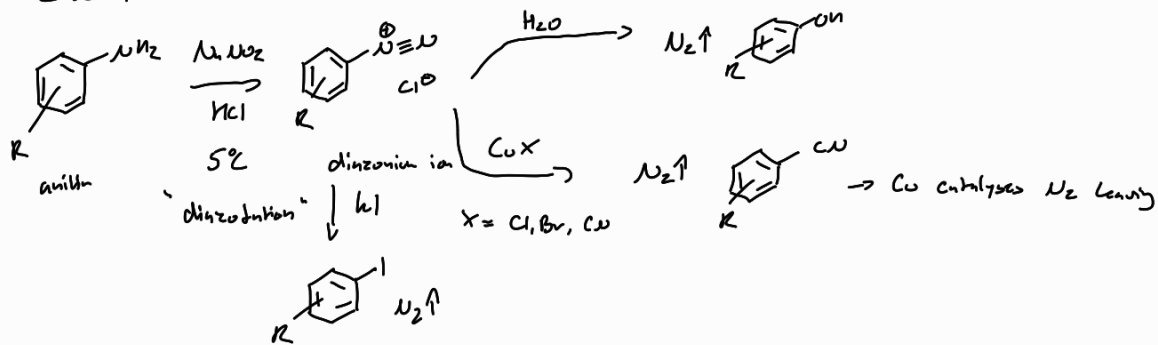
1) Aromatic with EWG: $-NO_2$, $-C\equiv N$ (CF_3 , $-SO_2R$)



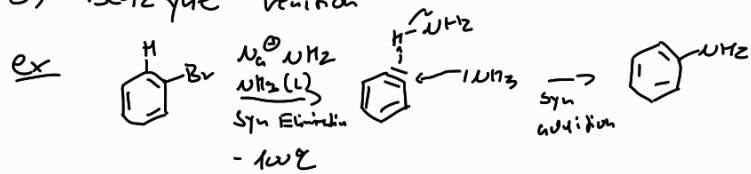
CF_3 bond 1.3 eV, but the rate limiting step is the addition (breaks aromaticity), this is accelerated by F

\Rightarrow Nucleophilic aromatic substitution S_NAr

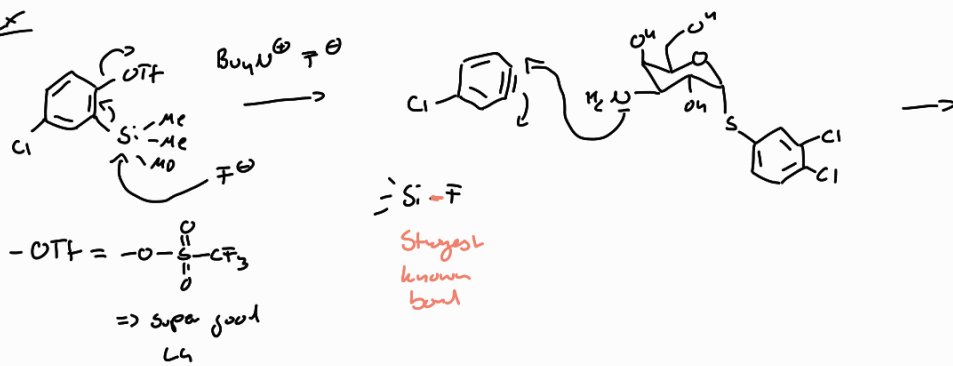
2) "S_N1" like S_NAR: Super good LG needed



3) Benzyne reaction



ex



⇒ Inhibits a protein controlling T-cell immunity in tumors
→ Checkpoint inhibition (Biomimicry)