CHEM – 750

Advanced Organic synthesis

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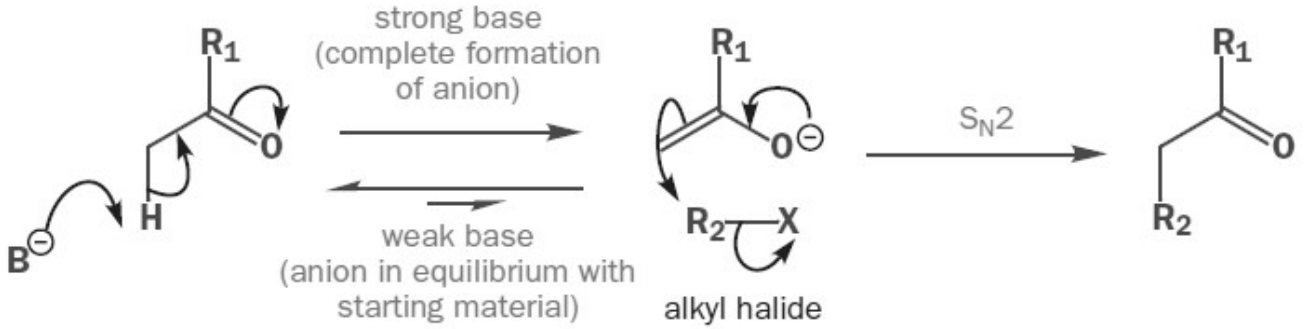
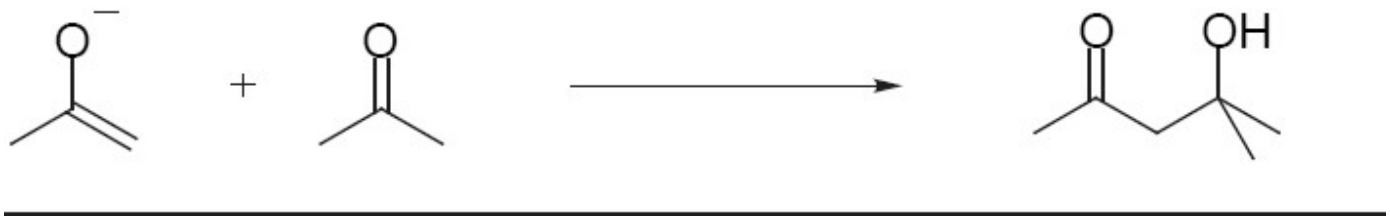
C-C BOND FORMATION

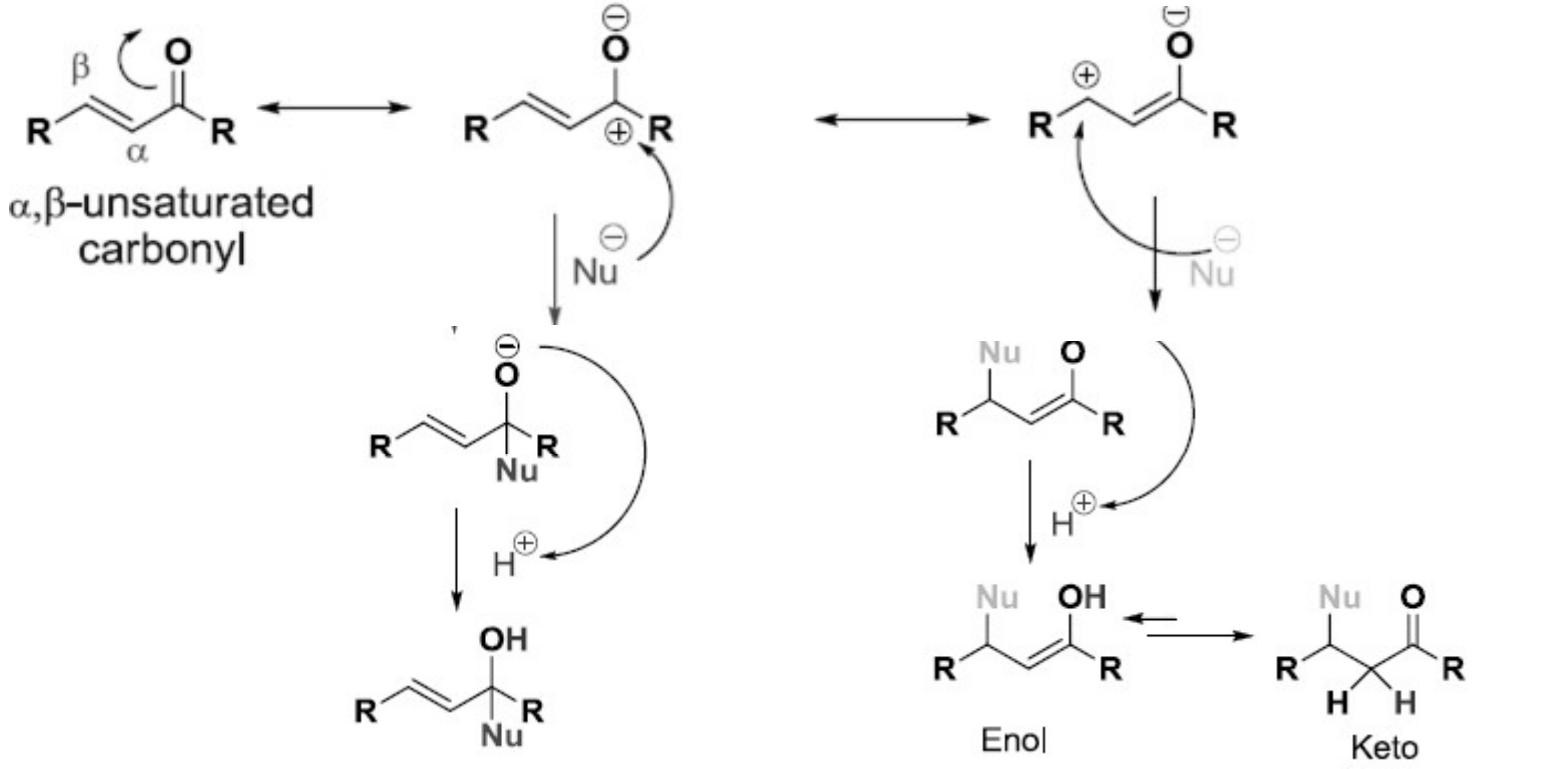
C-alkylation



Aldol type condensations



Nucleophilic addition to α,β-unsaturated systems



Direct Nucleophilic Addition

1,2-Addition

Kinetically controlled

Hard

Conjugate Addition

1,4-Addition or Michael Addition

Thermodynamically controlled

Soft

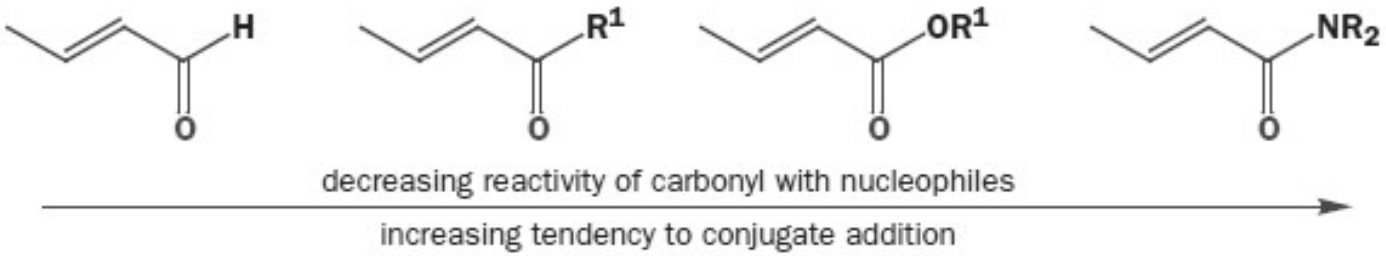
Direct Addition vs Conjugate Addition

SELECTIVITY

- **Reaction conditions**
- **Nature of nucleophile**
- **Nature of carbonyl**

Hard and soft nucleophiles

Hard nucleophiles	**Borderline**	**Soft nucleophiles**
F^-, **OH^-**, **RO^-**, SO_4^{2-}, Cl^-,	N_3^-, **CN^-**	**I^-**, **RS^-**, RSe^-, S^{2-}
H_2O, **ROH**, ROR′, RCOR′,	**RNH_2**, **RR′NH**,	**RSH**, RSR′, R_3P
NH_3, **RMgBr**, **RLi**	**Br^-**	alkenes, aromatic rings



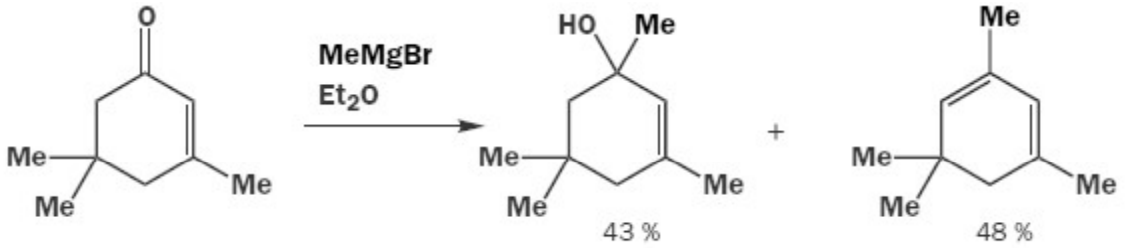
Direct Addition vs Conjugate Addition

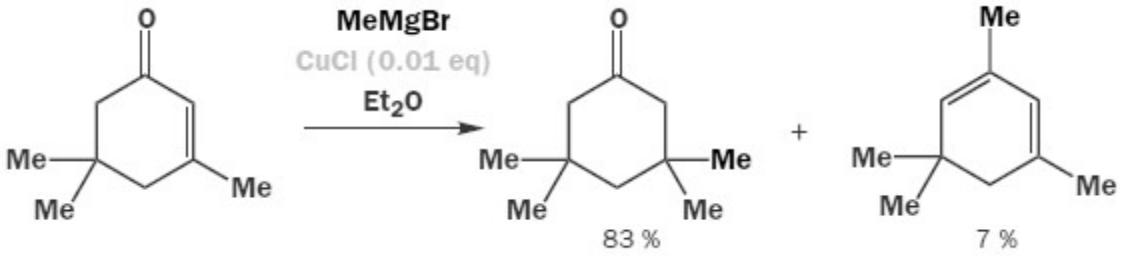
The Nature of the Nucleophile

Attribute	Direct Addition	Conjugate Addition
Base strength of nucleophile	Nucleophiles that are stronger bases	Nucleophiles that are weaker bases
Carbanion nucleophiles	Organolithium (RLi) and Grignard reagents (RMgBr)	**Organocopper reagents (R_2CuLi) Cyanide (NaCN) Enolates**
Hetero nucleophiles	Amines (RNH_2)	Thiols (RSH)
Hydride Nucleophiles	Lithium aluminium hydride ($LiAlH_4$)	Copper hydride (CuH)

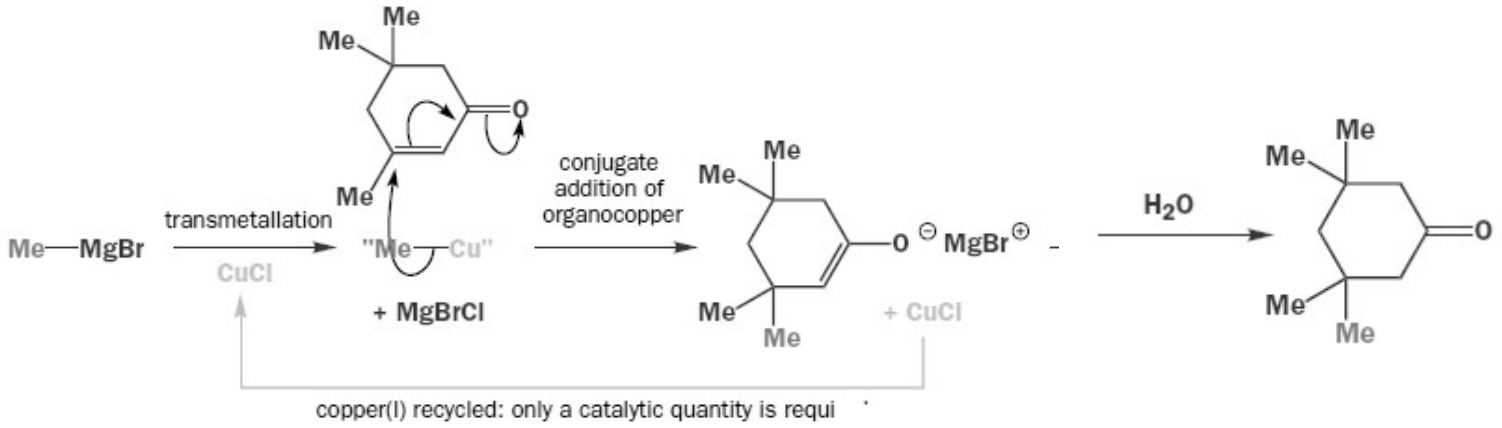
Direct Addition vs Conjugate Addition

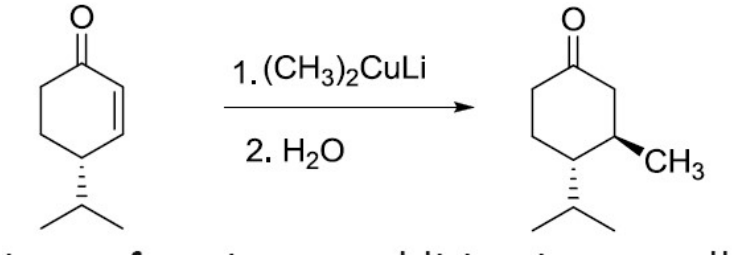
Organocuprates are weaker nucleophiles compared to Grignard and organolithium reagents.

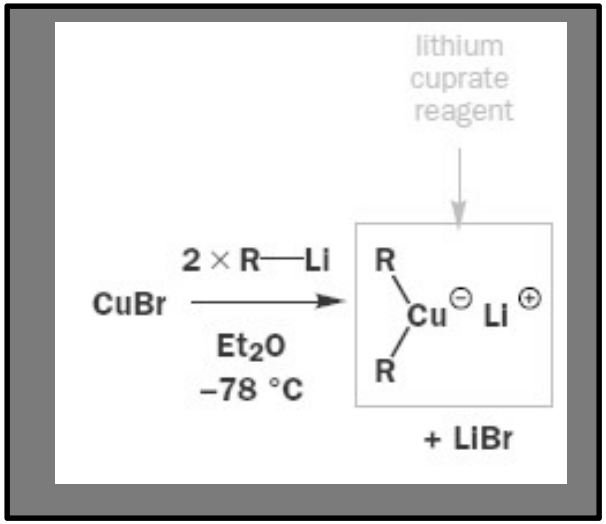




Direct Addition vs Conjugate Addition

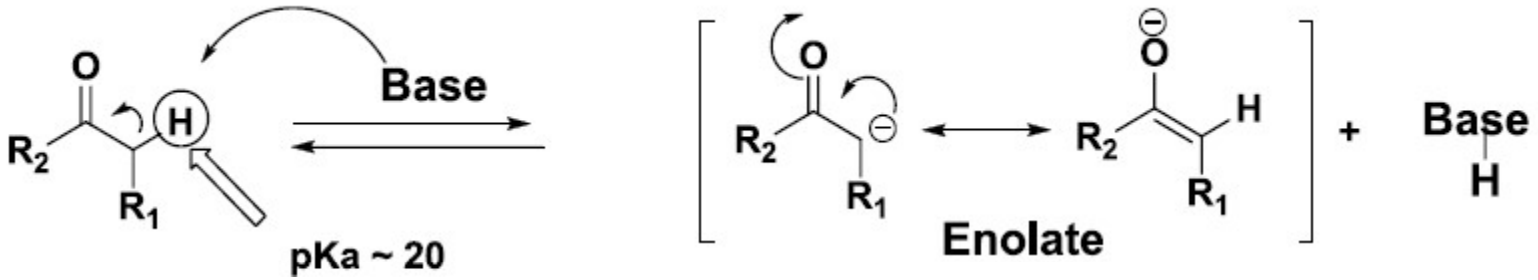




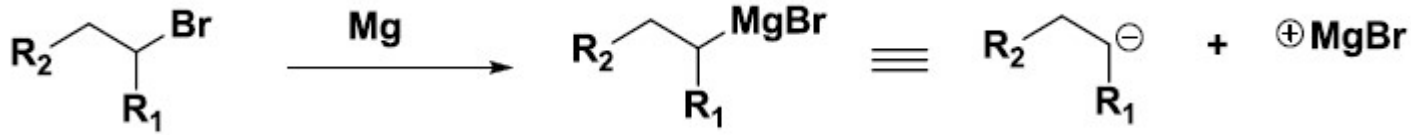


Direct Addition vs Conjugate Addition

Reactions of Enolates



Enolate nucleophile is resonance stabilized; consequently a weaker nucleophile

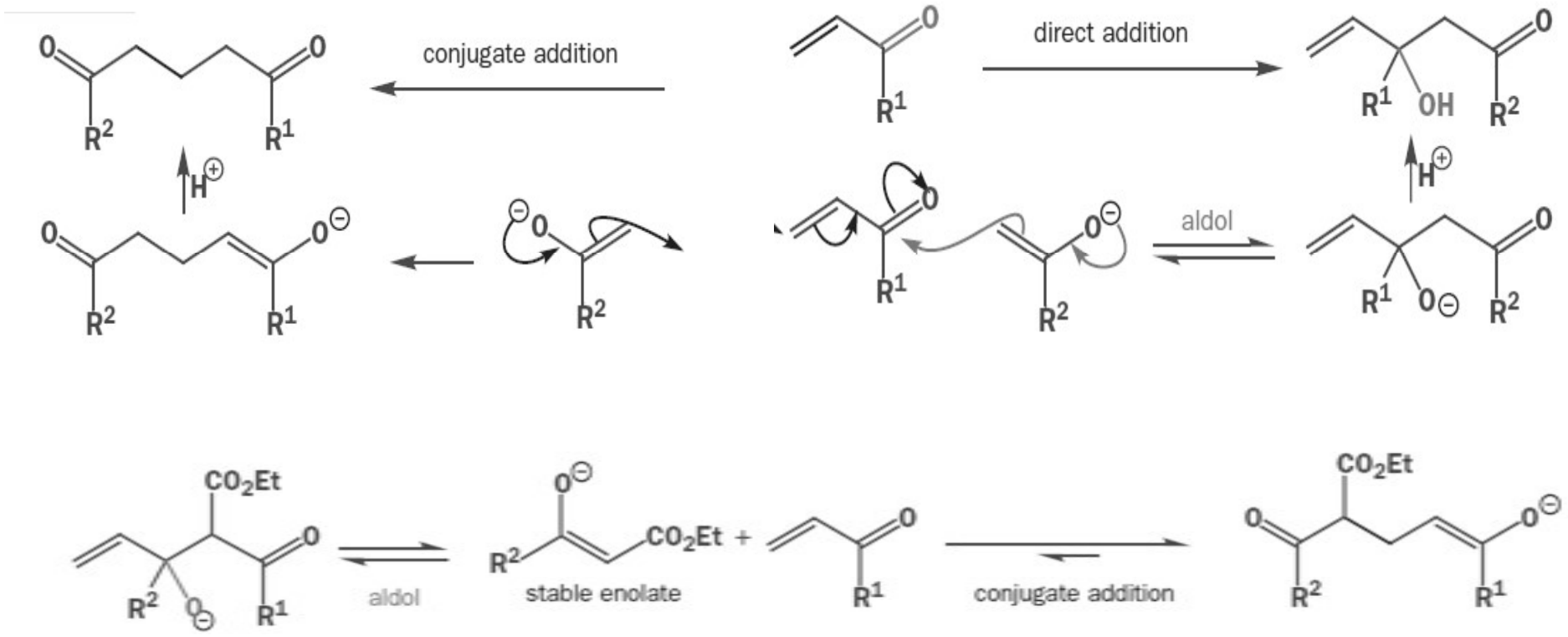


Grignard reagent **Carbanion**

No resonance stabilization of nucleophile; Consequently a very reactive nucleophile

Direct Addition vs Conjugate Addition

Reactions of Enolates



B

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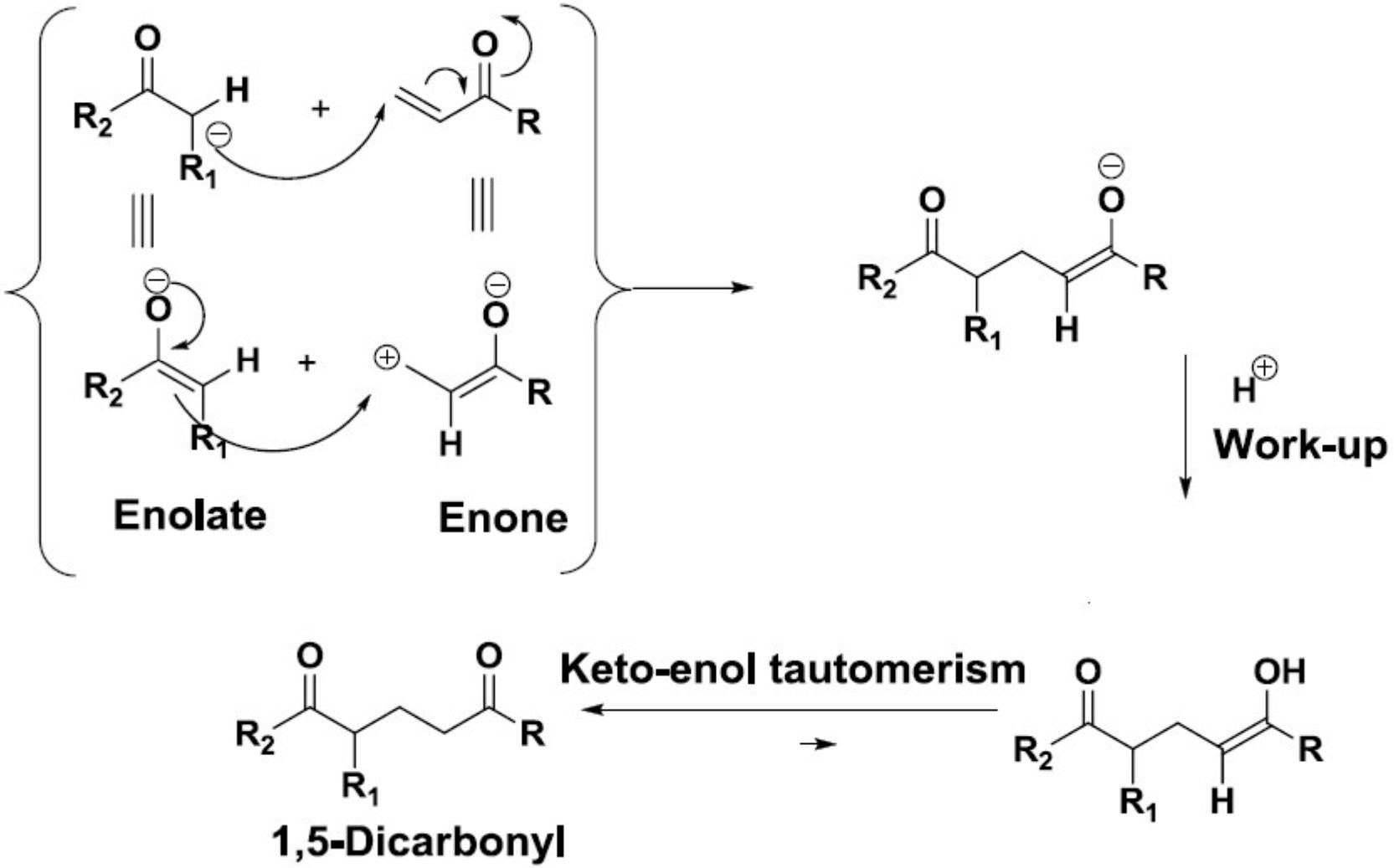
A

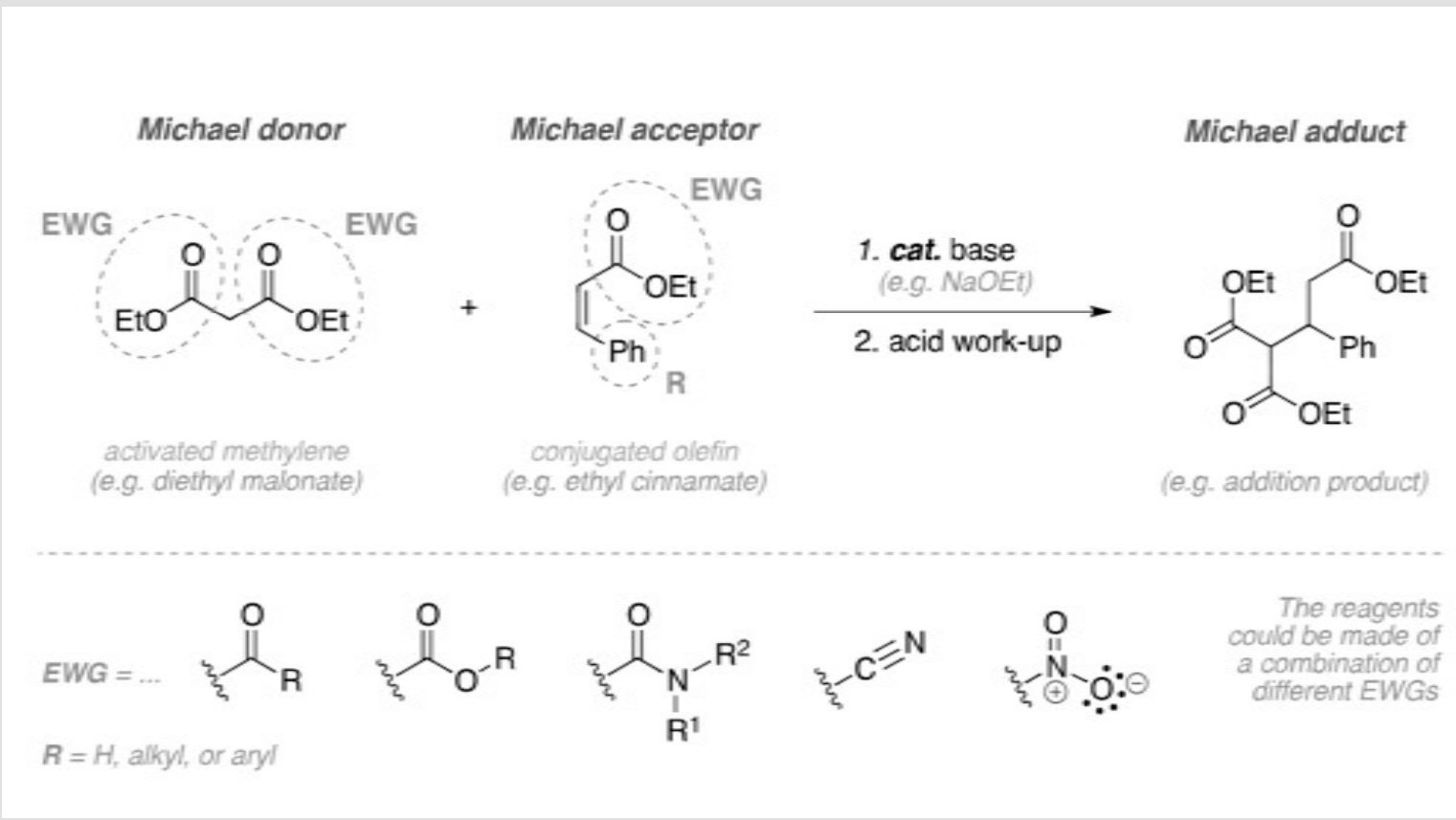
Reactions of Enolates

1,4-Addition (Conjugate Addition or Michael Addition)



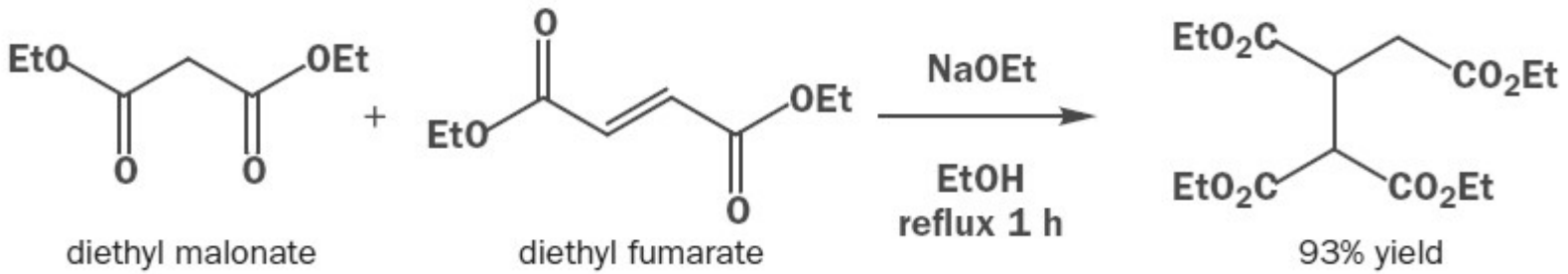
Reactions of Enolates

1,4-Addition (Conjugate Addition or Michael Addition)



1,4-Addition (Conjugate Addition or Michael Addition)

Esters are excellent Michael acceptors



diethyl malonate diethyl fumarate 93% yield