

Chapter 7. Reactions of Carbonyl Compounds

□ Reaction types: fate of tetrahedral intermediates

◆ addition, condensation & substitution: [📖 630 top](#)

□ Addition mechanisms: [📖 630 bot](#) & [📖 631 Fig. 7.1](#)

◆ mechanism A: weak Nu & acidic conditions

◆ mechanism B: strong Nu & basic conditions

◆ mechanism C: less basic Nu & concerted protonation

◆ metal cations/Lewis acids for activation: [📖 631 bottom](#)

Reactivity of Carbonyl Compounds

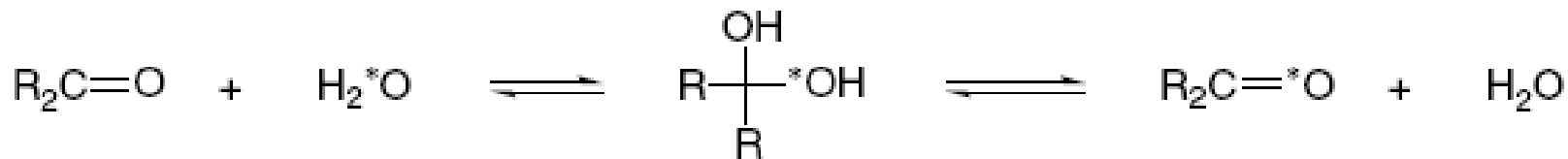
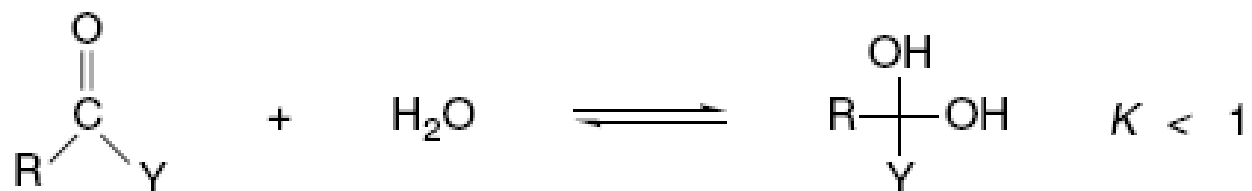
- Structural features: steric & electronic effects
 - ◆ irreversible reduction with NaBH_4 : H^- ; [📖 633 top](#)
 - ◆ ketones < aldehydes: bulkier & e⁻-donor; [📖 633 Table 7.1](#)
 - ◆ cyclic ketones: less strained when reduced; [📖 634 top](#)
 - other cyclic ketones: [📖 634 Table 7.2](#)
 - ◆ reversible addition to carbonyls: CN^- ; [📖 635 Table 7.3](#)
 - ◆ carboxylic acid derivatives: electronic; [📖 636 top](#)
 - resonance: decreasing vs inductive: increasing
 - ◆ activation by H^+ /Lewis acids: bond length & affinity; [📖 636 bot](#)
 - lowering the LUMO of the carbonyls: [📖 637 Fig. 7.2](#)

Addition of H₂O & Alcohols to RCHO & RCOR'

- Unfavorable equilibrium for hydration: [📖 638 top](#)
 - ◆ exceptions: HCHO, Cl₃CCHO, (CF₃)₂CO; [📖 638 Table 7.4](#)
 - ◆ rapid equilibrium: isotopic exchange, H₂O¹⁷; [📖 639 top](#)
 - ◆ acid catalysis: both specific & general catalysis: [📖 639 mid](#)
 - ◆ basic catalysis: HO⁻, specific & general; [📖 639 bottom](#)

- Addition of alcohols: hemiacetals & acetals (ketals)
 - ◆ acid-catalyzed equilibration in the 2nd addition: [📖 640 top](#)
 - stable to basic conditions but labile under acidic conditions
 - ◆ less favorable equilibrium: similar to the hydration reactions
 - bulky alcohols and alcohols with EWGs (less $n \rightarrow \pi^*$ overlap)
 - equilibrium control: removal of water or excess alcohol

❖ Equilibrium for Hydration

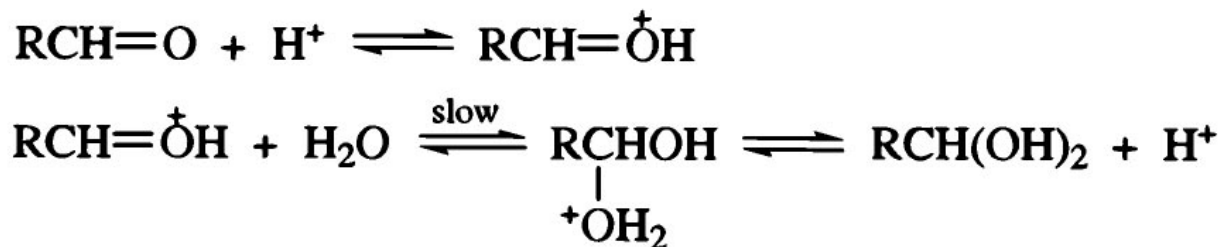


$$t_{1/2} \approx 1 \text{ min}; \quad k_{\text{CH}_3\text{CHO}} = 500 \text{ M}^{-1}\text{sec}^{-1}$$

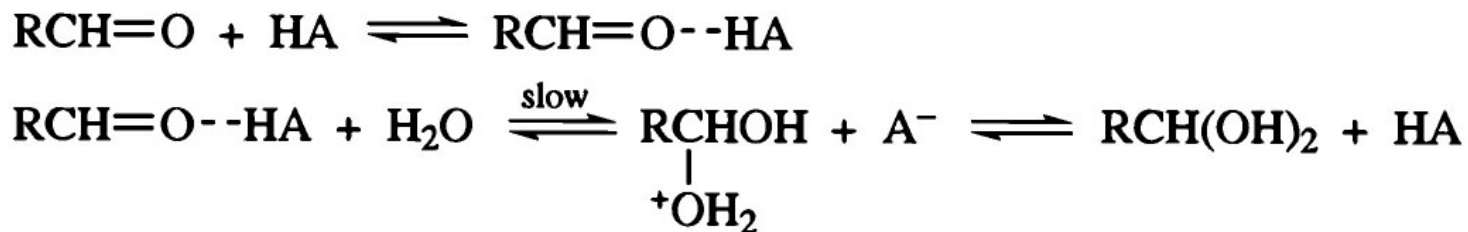


❖ Acid Catalysis of Hydration

Specific acid-catalyzed hydration




General acid-catalyzed hydration



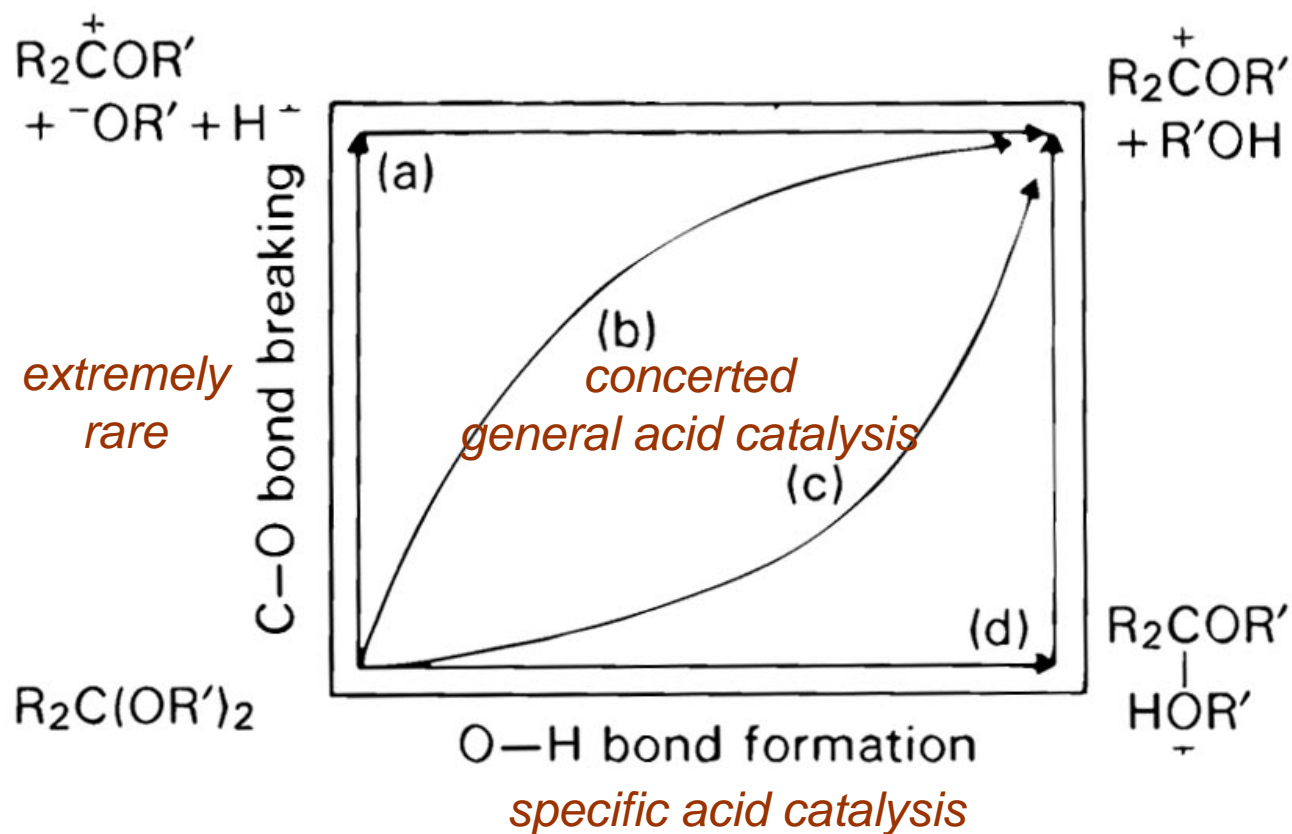
❖ Mechanism of Hydrolysis of Acetals (I)

- The reverse of acetal formation: [📖 641 top](#)
 - ◆ the 1st step of hydrolysis: base-stable & only acid hydrolysis
 - ◆ rupture of the C-O bond of the carbonyl carbon and oxygen: no substitution at the alcohol C-O bond; **isotopic labeling**
 - ◆ specific acid catalysis: preequilibrium for protonation
 - $k_{\text{D}_2\text{O}}/k_{\text{H}_2\text{O}} = 2-3$: fast equilibrium of initial protonation
 - ◆ S_N1 reaction at RDS: large negative ρ at the carbonyl carbon
 - ◆ but, general acid-catalyzed examples: [📖 642 Scheme 7.1](#)
 - facile cleavage of the C-O bonds

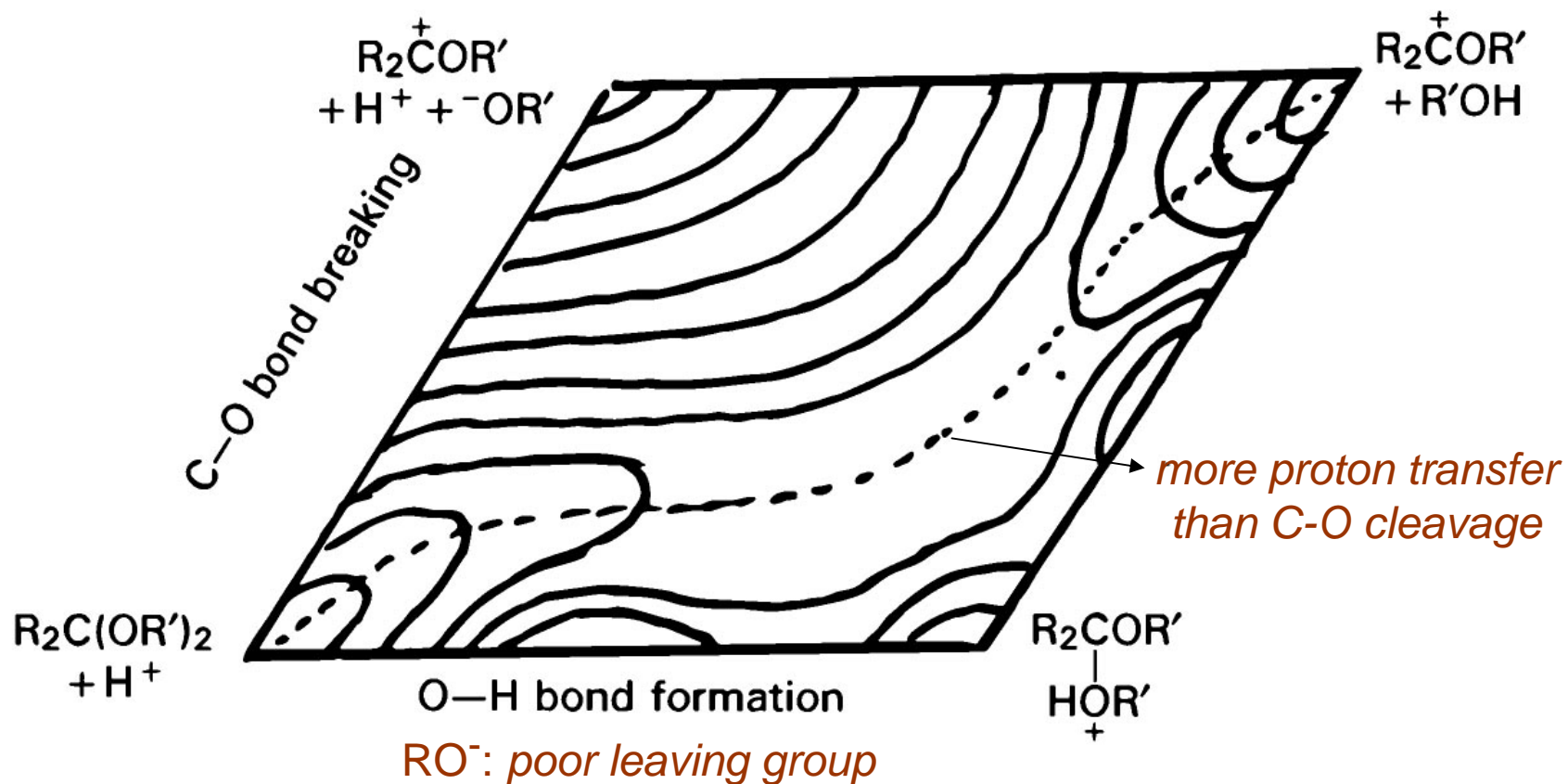
❖ Mechanism of Hydrolysis of Acetals (II)

- Mechanisms for the 1st stage:  643-4 [Fig. 7.3 & 7.4](#)
 - ◆ poor leaving RO group: complete proton transfer
 - ◆ good leaving RO⁻: concerted C-O cleavage with proton transfer but not always synchronous
- The 2nd step: similar to the 1st step mechanism
 - ◆ acid catalysis: faster than the 1st step of hydrolysis
 - concerted mechanism: less cationic TS, [644 bottom](#)
 - charge dispersion: $\rho = -1.9$ ($\rho = -3.25$ for the 1st step)
 - ◆ base catalysis: deprotonation & elimination; [645 top](#)
 - EWG favors the deprotonation step but disfavors the elimination step: small σ and some with the nonlinear Hammett plot






❖ The First Hydrolysis of Acetals: Pathways



❖ The First Hydrolysis of Acetals: Energy



❖ Addition-Elimination Reactions of Carbonyls

- RNH_2 with carbonyls: various imines;  646 [Sch. 7.2](#)
- ◆ favored equilibrium for imines:  [646 middle](#)
- Mechanism of hydrolysis of imines:  [646 top](#)
 - ◆ acidic/basic hydrolysis: addition of OH & elimination of RNH_2
 - ◆ RDS in basic solution (3): attack of HO^- on the $\text{C}=\text{NH}^+$ bond
 - ◆ RDS in acidic solution (5): breakdown of the sp^3 intermediate
 - ◆ pH-rate profile: aldimines of $^t\text{BuNH}_2$ & ArCHO ;  [649 Fig. 7.5](#)
 - aldimine of MeNH_2 & isobutyraldehyde:  [648](#) & [649 Fig. 7.5](#)
 - ◆ formation: reverse of the hydrolysis; removal of water needed, azeotropic distillation or use of dehydrating agents

❖ Characteristics of Other Imines

- $\text{H}_2\text{N-X}$: high K_{eq} for formation; [📖 651 top](#)
 - ◆ more stable: resonance & reduction of lone pair repulsion
 - ◆ pH-rate profile of oximes: [📖 652 Fig. 7.8](#)
- Imine formation catalyzed by amines: [📖 652 bot](#)
 - ◆ protonated imine: more reactive; [📖 653 top & middle](#)
- Enamines: with 2° amines; [📖 653 middle](#)
 - ◆ dehydration required for driving the equilibrium to product
 - ◆ RDS in the alkaline range: [C-protonation for \$\text{C}=\text{N}^+\$ bond](#)
 - ◆ RDS in acidic solution: breakdown of the sp^3 intermediate

❖ Ester Hydrolysis

- Acid catalysis: $A_{AC}2$, reversible; [📖 655 top](#)
 - ◆ cleavage of O=C-O bond: isotopic labeling; [📖 655 middle](#)
 - ◆ base catalysis with $B_{AC}2$: irreversible; [📖 656 top](#)
 - substituent effects in $B_{AC}2$: [📖 656 middle](#)
 - much less exchange with solvent: faster hydrolysis
 - ◆ acid catalysis with $A_{AL}1$: *tert*-butyl esters; [📖 656 bottom](#)
 - orthogonal deprotection & byproducts: alkene/alcohol
 - ◆ general base catalysis: EWG-acyl group; [📖 657 top](#)
 - ◆ nucleophilic catalysis: better Nu than $^-OH/H_2O$; [📖 657 mid](#)
 - imidazole: more reactive leaving group; [📖 657 middle](#)
 - carboxylate anions: similar basicity to ^-OR ; [📖 657 bottom](#)
 - ◆ alcoholysis: reversible in acid/base; [📖 658](#)

❖ Aminolysis of Esters

- Formation of amides: amine Nu; [📖 659 middle](#)
 - ◆ RDS depends on the leaving-group ability of R'
 - ◆ general base catalysis: [📖 659 bottom](#)
 - ◆ several forms of the tetrahedral intermediates: [📖 660 top](#)
 - leaving group in TI^{\ominus} & $\text{TI}^{\ominus-}$: $\text{R}''\text{O}^-$ with alkyl esters; [📖 660 mid](#)
 - leaving group in $\text{TI}^{+/-}$ & $\text{TI}^{\text{NH}+}$: RNH_2 / in $\text{TI}^{+/-}$, $\text{R}''\text{O}^-$ when $\text{R}''=\text{Ph}$
 - ◆ hydrolysis of amide acetals: [📖 660 bottom](#)
 - in basic solution: amide with alkoxide elimination; [📖 660 bot](#)
 - in acidic solution: ester via amine elimination; [📖 661 top](#)
 - ◆ direct substitution mechanism: [📖 661 middle](#)
 - 2-pyridone-catalyzed aminolysis: [📖 662 bottom](#)

❖ Amide Hydrolysis

□ More vigorous conditions than ester hydrolysis

- ◆ ground-state stabilization by resonance: [📖 663 top](#)
- ◆ in basic solution: $B_{AC}2$ mechanism; [📖 663 top](#)
 - poorer leaving group: RNH^- ; protonation
 - extensive oxygen exchange with water: slow hydrolysis
 - dianion intermediate: solvent-isotope & kinetic; [📖 663 middle](#)
- ◆ in acid: via the O-protonated amide; [📖 664 top](#)
 - no N-protonated form possible: resonance; [📖 663 bottom](#)
 - no oxygen exchange with water: exclusive N-elimination
- ◆ acylimidazole (imidazolide): facile hydrolysis; [📖 664 mid](#)
 - decreased resonance stabilization by the nitrogen lone pair
 - faster hydrolysis by protonation at N-3 in acid

❖ Acylation of Oxygen & Nitrogen Groups (I)

- Reverse of ester hydrolysis & aminolysis: [📖 664-5](#)
 - ◆ equilibrium control required & favorable K but rather slow
- Useful acylating agents: RCOX; [📖 665 top](#)
 - ◆ inductive effect and better leaving group: [📖 665 middle](#)
 - ◆ use of pyridine: nucleophilic catalyst & base; [📖 665 bottom](#)
 - DMAP: more effective catalyst due to the ERG, $-\text{NMe}_2$
 - NR_3 : via a ketene intermediate; [📖 666 top](#)
 - ◆ without base: rate $\propto k_1[\text{ROH}] + k_2[\text{ROH}]^2$; [📖 666 bottom](#)

❖ Acylation of Oxygen & Nitrogen Groups (II)

- S_N1-like mechanism: acylium ion; [📖 667 top](#)
 - ◆ acyl halides with an EDG: rather stable acylium ions
 - other acyl halides: mixed or borderline mechanisms
- Use of activating agents of the -OH group
 - ◆ carbodiimides: more stable C=O bond; [📖 667 middle](#)
 - no base necessary & anhydride formation without amines
 - ◆ via mixed anhydrides: [TFAA](#)
 - useful for hindered alcohols & phenols
 - active species: protonated form/acylium ion
 - ◆ enol esters: isopropenyl acetate; [📖 667 bottom](#)
 - in acid catalyst: via the C-protonated form or acylium ion

❖ Intramolecular Catalysis (I)

- key mechanisms in biological systems: enzymes
 - ◆ general acid catalysis: postulated for [lysozyme](#)
 - hydrolysis of the acetal linkage in certain polysaccharides
 - ◆ a model system: benzaldehyde acetals of salicylic acid
 - fastest hydrolysis in the intermediate pH: [📖 669 Fig. 7.10](#)
 - the most reactive: monoanion of the acetal; [📖 668 bottom](#)
 - ◆ intramolecular ester hydrolysis: [mechanism II](#); [📖 670 mid](#)
 - faster hydrolysis of the carboxylate: 3 mechanisms possible
 - no nucleophilic catalysis: no isotopic exchange; [📖 670 bottom](#)
 - no general acid catalysis (Mechanism III) by other Nu

❖ Intramolecular Catalysis (II)

□ Intramolecular nucleophilic catalysis: examples

- ◆ phthalic acid monoesters: good leaving RO⁻; [📖 671 middle](#)
 - pKa of ROH ≤ 13: R=Ph, CF₃CH₂ but not with R=Me, CCl₃CH₂
- ◆ acetylsalicylates with EWG: better L; [📖 671 bottom](#)

□ Ester hydrolysis by imidazole: [📖 672 top](#)

- ◆ histidine imidazole in the enzyme-catalyzed hydrolysis
- ◆ several functions in catalysis: pH-dependent; [Fig. 7.12](#)
 - pH < 2 & pH > 9: proportional & specific acid/base catalysis
 - pH 2-4: general acid catalysis; 25-100 fold rate enhancement
 - pH 6-8: general base catalysis; ca. 10⁴ increase
 - the nucleophilic catalysis occurs in substituted derivatives

❖ Intramolecular Catalysis (III)

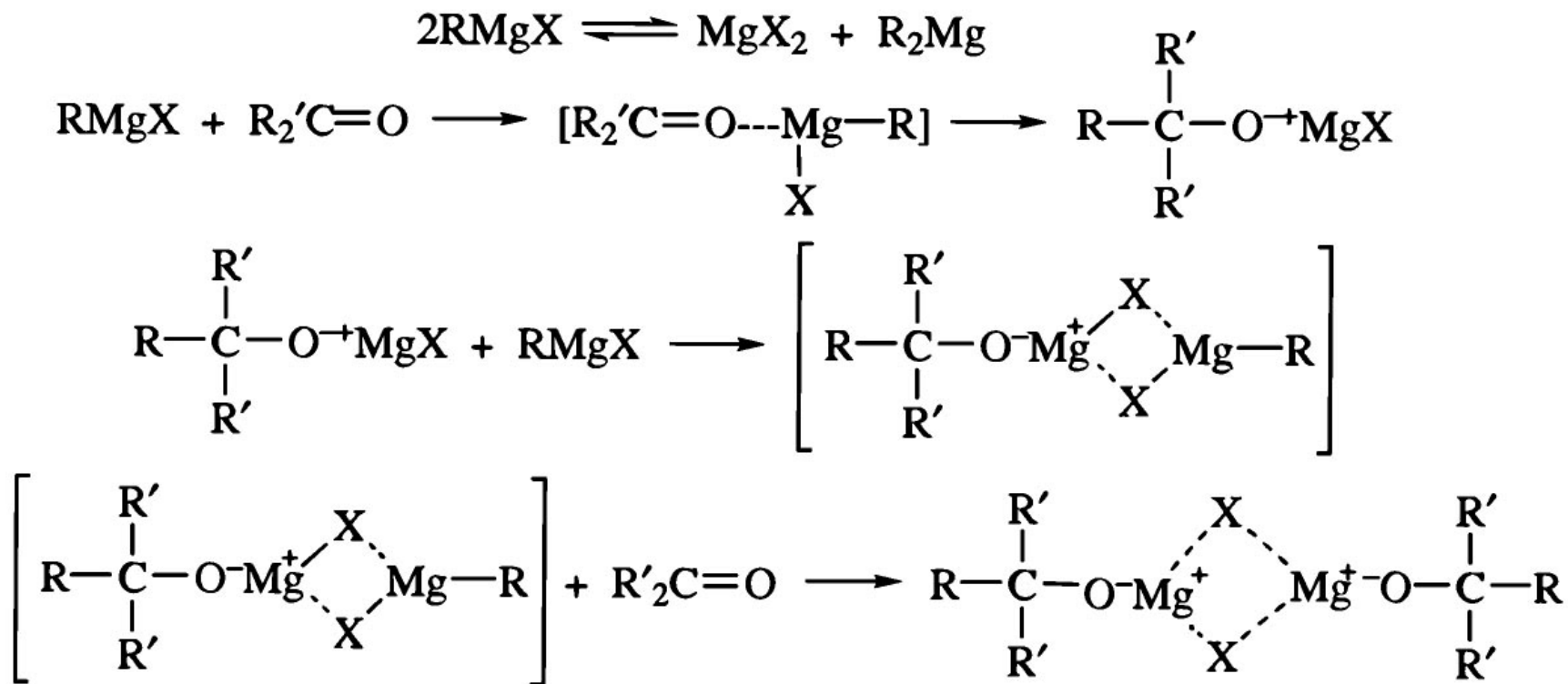
- Aminolysis of esters with an *o*-OH group: [📖 673 top](#)
 - ◆ intermolecular general base catalysis: rate $\propto [\text{RNH}_2]^2$
 - ◆ intermolecular general acid catalysis: [OH] group
 - ◆ faster aminolysis with concerted proton transfer: [📖 674 mid](#)
 - BuNH₂ & 2-pyridone (tautomeric/bifunctional catalyst, $\text{p}K_{\text{a}}$ 11.6 & $\text{p}K_{\text{aH}^+}$ 0.75) **vs** 2 eq. BuNH₂: 500 times greater
 - epimerization by 2-pyridone: 2 double transfers; [📖 674 bottom](#)
 - ◆ bifunctional catalysis for imine formation: [📖 675 top](#)
 - H₂N(CH₂)_{*n*}NMe₂: *n*=2, 1000; *n*=3, 10; *n*=4/5, ≈0; [📖 675 top](#)
 - ◆ “catalytic triads” in hydrolytic enzymes: [📖 676 top](#)
 - alignment of 3 groups at an active site for proton transfer: -OH (serine), -CO₂⁻ (glutamic/aspartic acid), imidazole (histidine)

❖ Addition of Unstabilized Carbanions

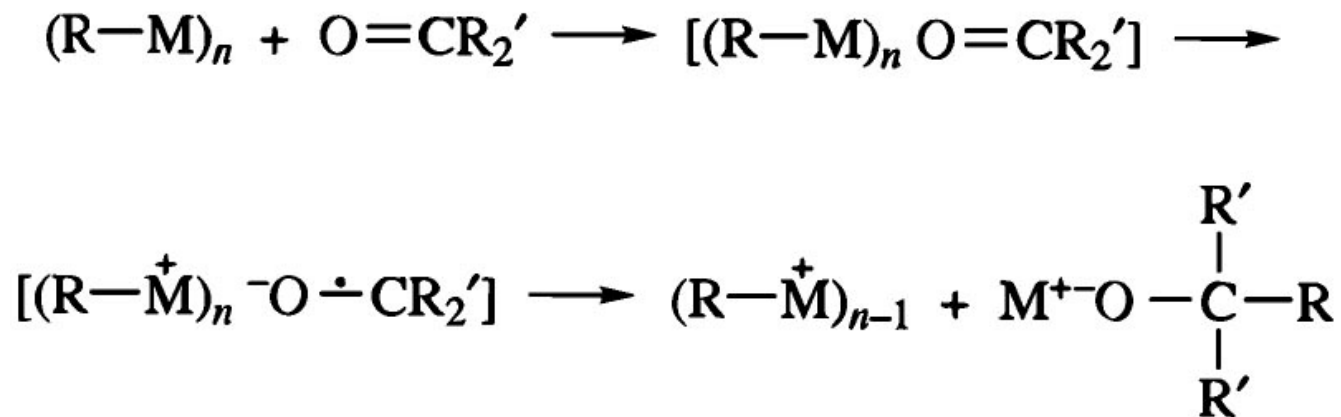
□ RLi & RMgX: highly reactive addition to carbonyls

- ◆ products & **reactivity** depend on the Y group: [📖 677 top](#)
- ◆ BuLi with PhCHO: 50-300 milisec at -85 °C (NMR)
 - dimer ([BuLi]₂): 10 times more reactive than tetramer ([BuLi]₄)
 - initial complexation & incorporation into aggregates: [📖 678 mid](#)
 - acceleration by chelating agents: TMEDA; [📖 678 bottom](#)
- ◆ addition RMgX: similar to RLi; [📖 679 top](#)
 - electron-transfer mechanism: radical anions; [📖 679 middle](#)
 - aryl ketone/diones: stabilized radical anions
- ◆ stereoselectivity: bulky Nu with steric factors; [📖 680 top](#)
 - Cram's rule & Felkin TS: [📖 680 middle](#) & [📖 681 Table 7.5](#)
 - chelation TS: rate increase ($\alpha \gg \beta$); [📖 680 bottom](#)

❖ Addition Model of RMgX with Carbonyls



❖ Single Electron-Transfer Mechanism



❖ Addition of Stabilized Carbanions (I)

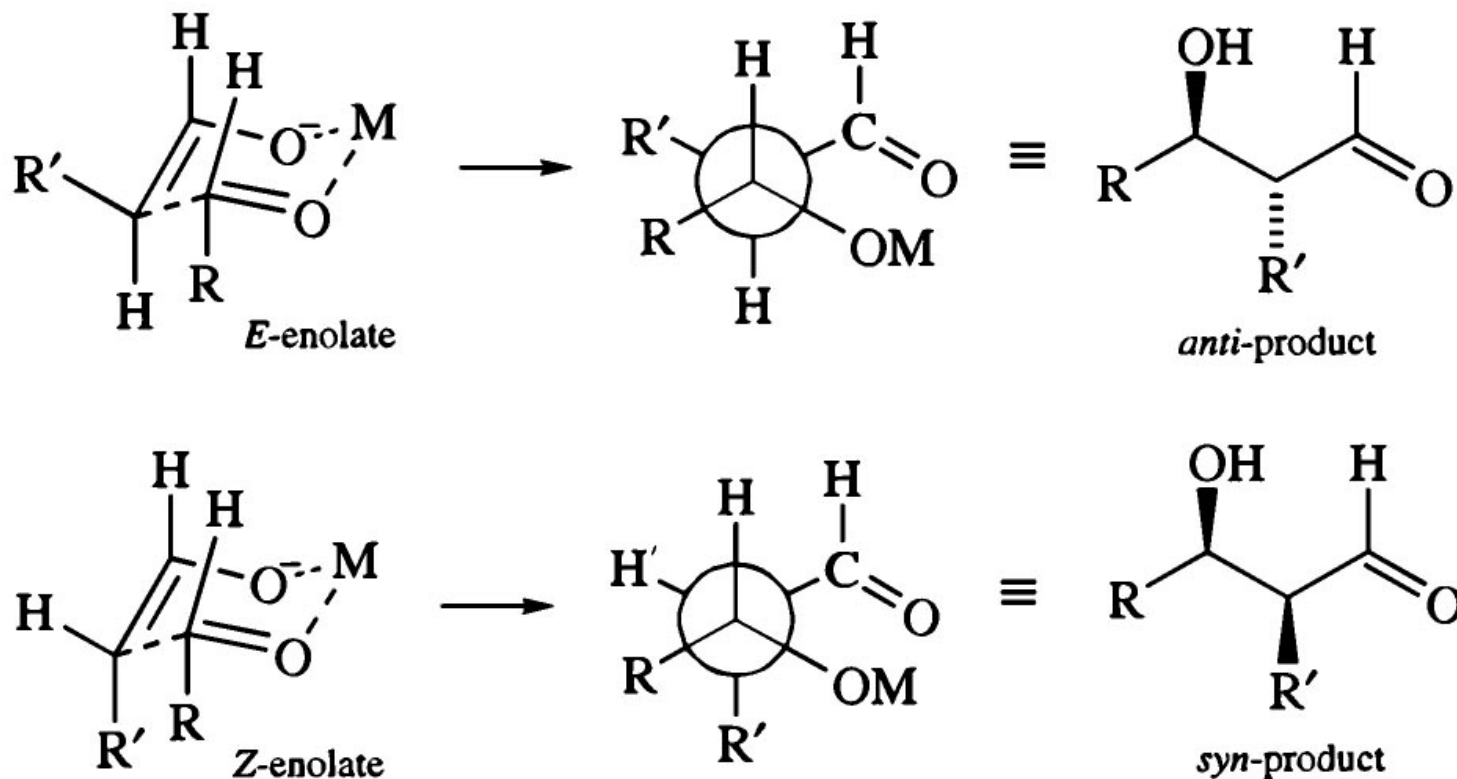
- Aldol addition & condensation: [📖 683 top](#)
 - ◆ base-catalyzed mechanism: enolate; [📖 683 middle](#)
 - ◆ acid-catalyzed mechanism: enol; [📖 683 bottom](#)
 - products depend on the conditions: [📖 684 Scheme 7.3](#)
 - ◆ mixed aldol condensations: [📖 685 top](#)
 - aromatic aldehydes + alkyl ketones: Claisen-Schmidt; [E-alkenes](#)
 - dehydration step: larger K but smaller k : [📖 685 bottom](#)
 - unsymmetrical ketones: CH_2 with base vs CH_3 with acid: [📖 686 top](#); decomposition study: [📖 686 middle](#)
 - C-S reactions with unsymmetrical ketones: [📖 687 Scheme 7.4](#)

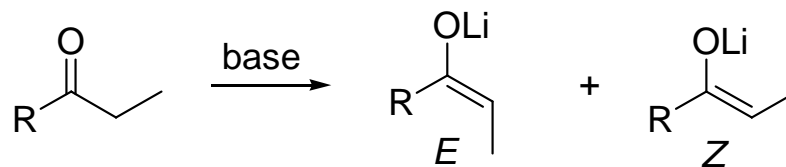
❖ Addition of Stabilized Carbanions (II)

□ Directed aldol addition: control of aldol products

- ◆ kinetic control: stoichiometric enolates (no equilibration), usually Li^+ , then addition of E^+ ; [📖 688 \(cyclic chair-type TS\)](#)
 - *E* enolates → *anti* vs *Z* enolates → *syn*: [📖 689 top](#)
 - stereochemistry of enolates: [📖 689 bottom](#)
- ◆ thermodynamic control: more stable enolates (equilibration): excess ketone, protic solvents, higher temp., less chelating cations; [📖 690 middle](#)
 - not as highly selective as kinetic control & relative stability of the adduct determines the product ratio

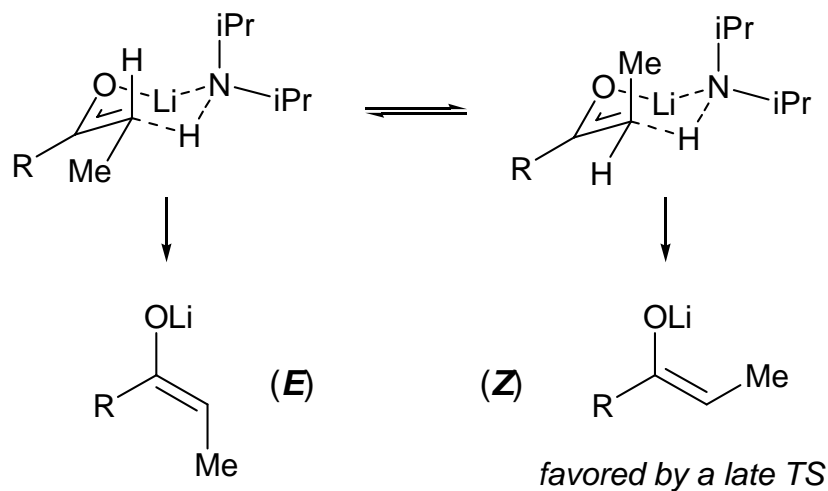
Directed Aldol Reactions: Stereoselectivity





E : *Z* Stereoselectivity


R	LDA	LiHMDS	LiTMP	LiTMP-LiBr	LiTMSN <i>t</i> Bu	LiNHAr
Ethyl	77:33	34:66	83:17	98:2	92:8	11:89
Isopropyl	63:37	2:98	66:34	95:5	94:6	2:98
<i>t</i> -Butyl	1:99	>2:98	<5:>95	<5:95	11:89	0:100



❖ Addition of Stabilized Carbanions (III)

□ Boron enolates: higher selectivity;  **690 bottom**

◆ more compact TS: shorter B-O distance

◆ $R_2BOTf/iPr_2NEt \rightarrow Z$ vs $R_2BCl/Et_3N \rightarrow E$:  691 middle

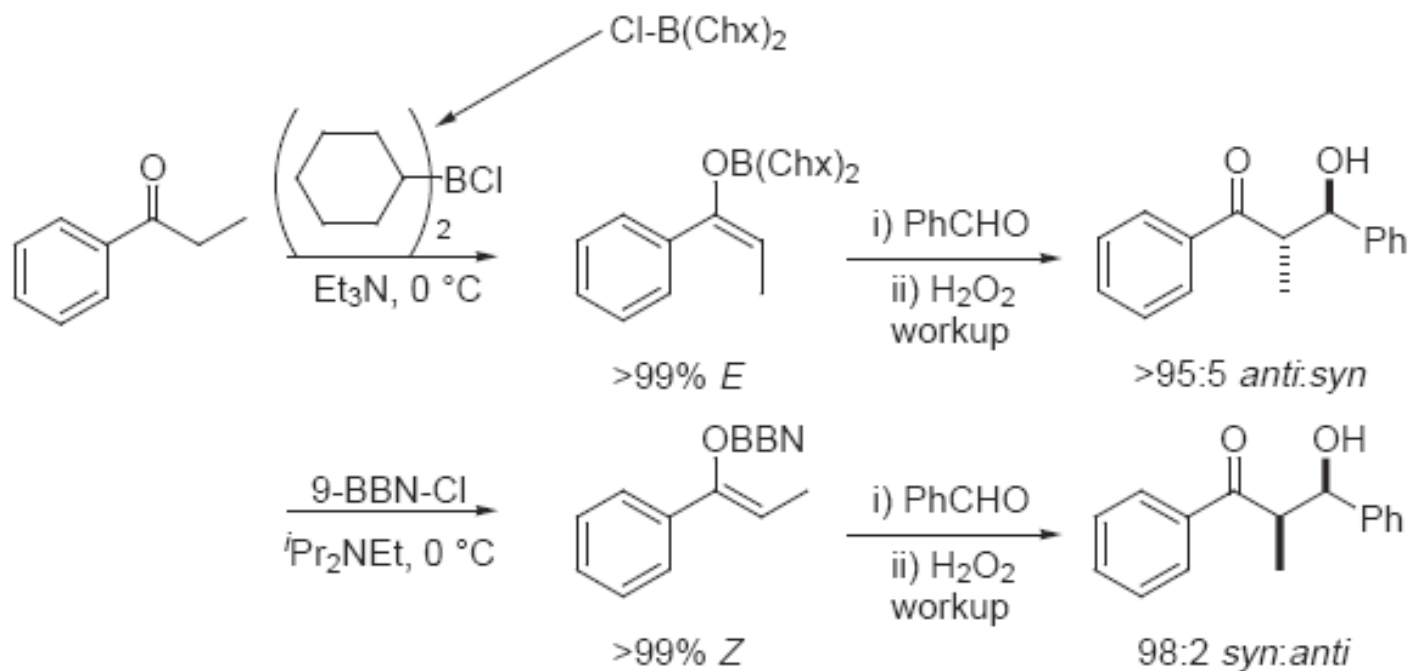
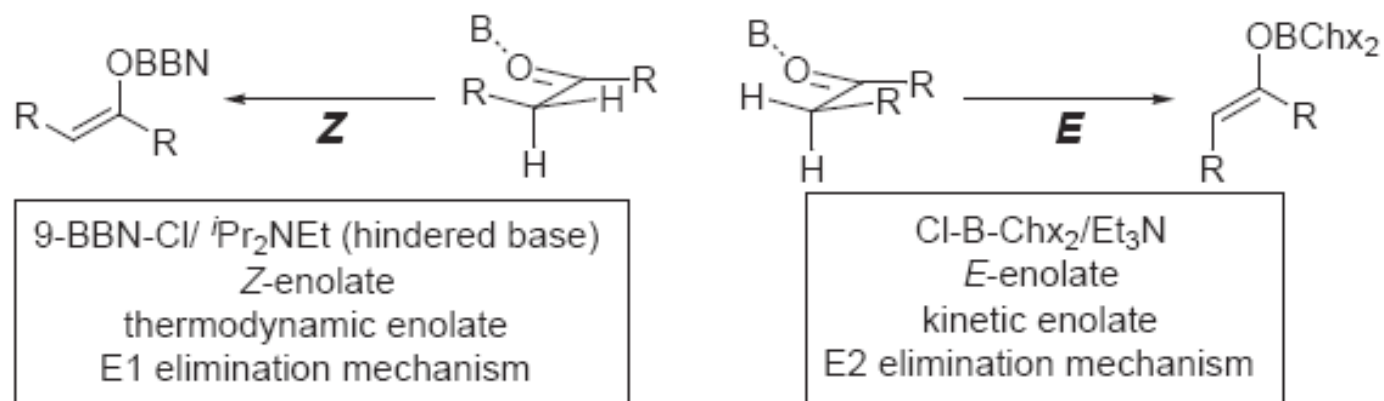
○ E1 (ion pair) vs E2: effect of a leaving group and base

□ Ti enolates: cyclic TS;  692 top

◆ formation: $(RO)_3TiCl/Li$ enolate, $TiCl_4/R_3N$ ( 691 bottom)

□ Sn enolates: from $Sn(OTf)_2/R_3N$;  692 middle

◆ *syn*-selective aldol: open TS



Brown *J. Am. Chem. Soc.* **1989**, *111*, 3441



❖ Addition of Stabilized Carbanions (IV)

- Ester enolates: higher *E* selectivity than [ketones](#)
 - ◆ Li enolates: cyclic (*E*) vs open TS (*Z*): [693 top](#)
 - ◆ B enolates: similar to [ketones](#): [693 bottom](#)
 - ◆ Ti enolates: -Ph/-SPh, *syn*; [694 top](#)

- Enantioselective enolates: chiral auxiliary/catalyst
 - ◆ Evans' oxazolidinones: *syn* aldol; [694 bot](#) & [695 middle](#)
 - ◆ oxaborazolidinone: catalyst for *re* attack; [696](#) & [Fig. 7.15](#)
 - ◆ Cu bis(oxazoline): catalyst for *si* attack; [697](#) & [Fig. 7.16](#)