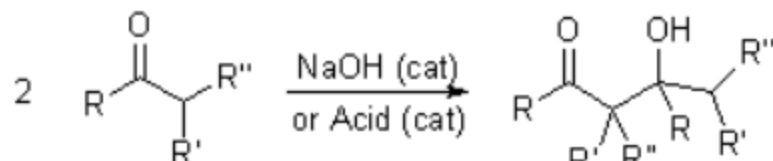


Aldol Addition

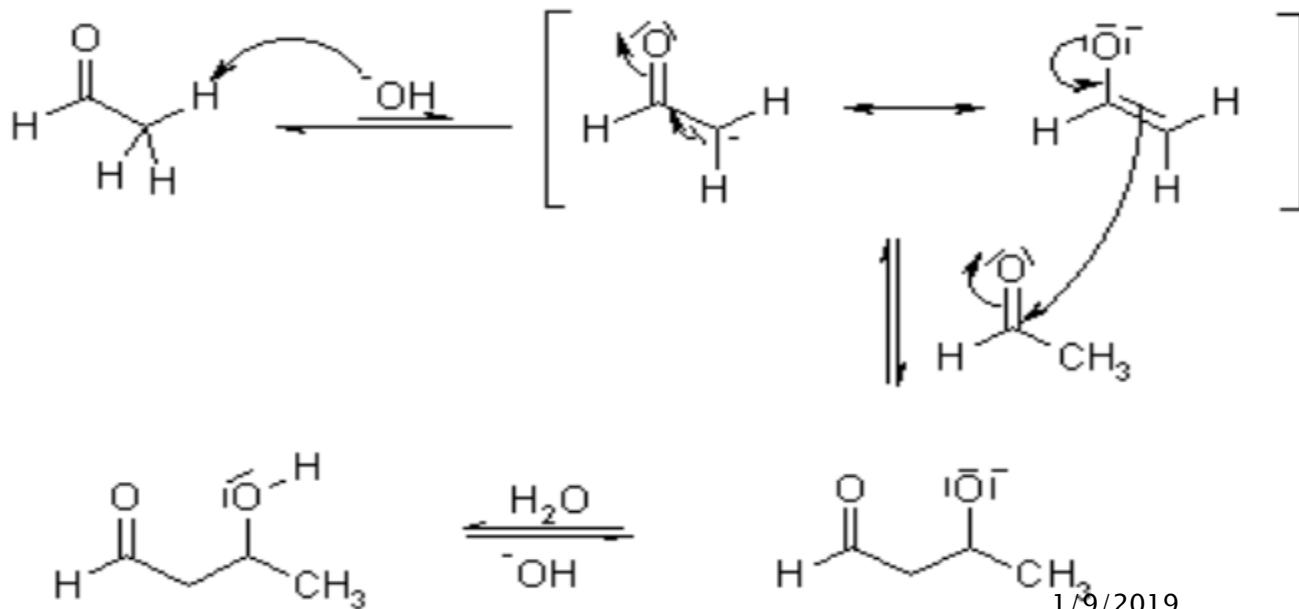
Aldol Reaction



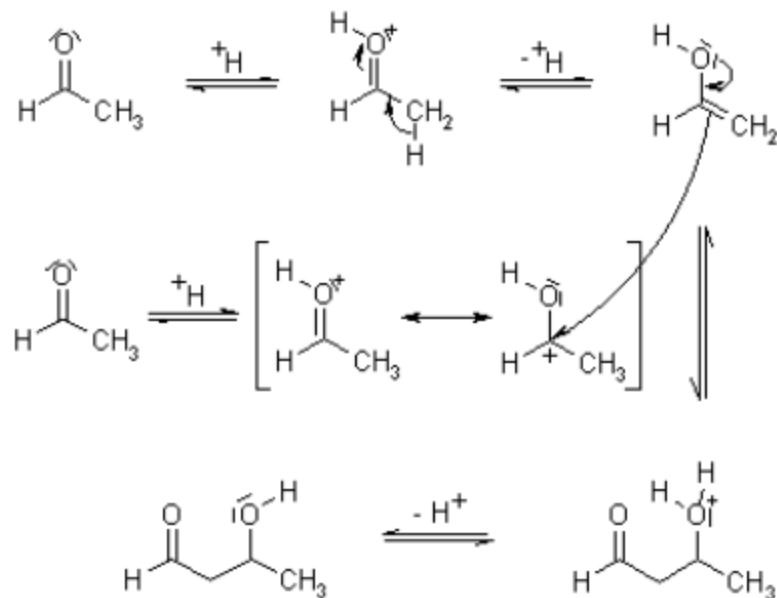
'Aldol' is an abbreviation of **aldehyde** and **alcohol**. When the enolate of an aldehyde or a ketone reacts at the α -carbon with the carbonyl of another molecule under basic or acidic conditions to obtain β -hydroxy aldehyde or ketone, this reaction is called Aldol Reaction.

Mechanism

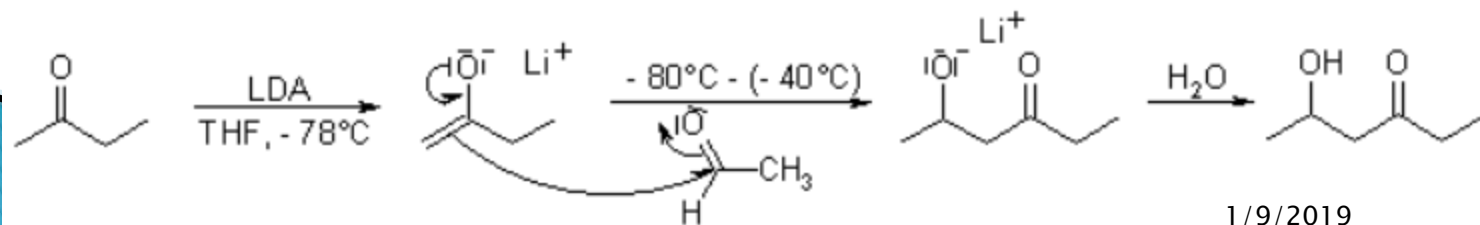
Base catalyzed:



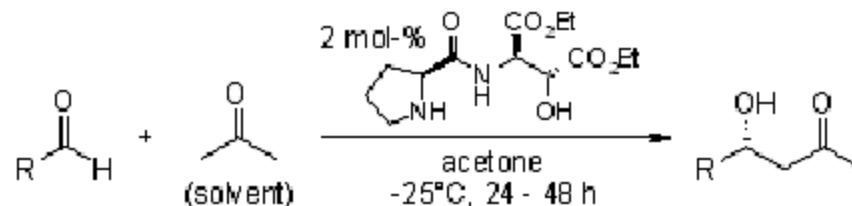
Acid catalyzed:



Under conditions of kinetic control, the mixed Aldol Addition can be used to prepare adducts that are otherwise difficult to obtain selectively. This process begins with the irreversible generation of the kinetic enolate, e.g. by employing a sterically hindered lithium amide base such as LDA (lithium diisopropylamide). With an unsymmetrically substituted ketone, such a non-nucleophilic, sterically-demanding, strong base will abstract a proton from the least hindered side. Proton transfer is avoided with lithium enolates at low temperatures in ethereal solvents, so that addition of a second carbonyl partner (ketone or aldehyde) will produce the desired aldol product.

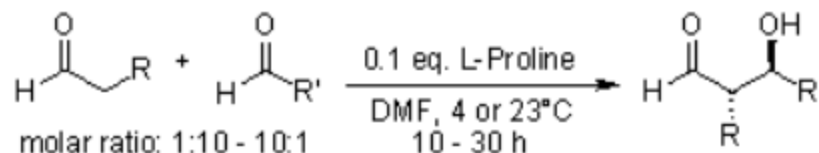


Recent Literature



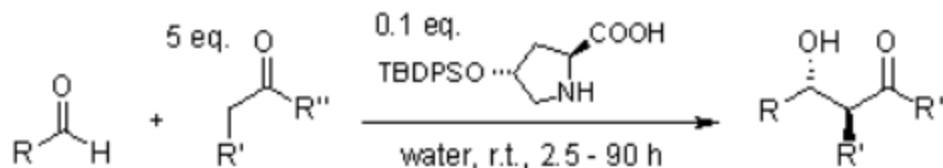
A Highly Efficient Organocatalyst for Direct Aldol Reactions of Ketones with Aldehydes

Z. Tang, Z.-H. Yang, X.-H. Chen, L.-F. Cun, A.-Q. Mi, Y.-Z. Jiang, L.-Z. Gong, *J. Am. Chem. Soc.*, **2005**, *127*, 9285-9289.



The First Direct and Enantioselective Cross-Aldol Reaction of Aldehydes

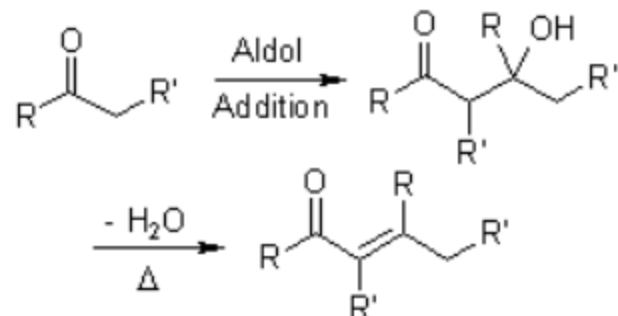
A. B. Northrup, D. W. C. MacMillan, *J. Am. Chem. Soc.*, **2002**, *124*, 6798-6799.



Highly Diastereo- and Enantioselective Direct Aldol Reactions in Water

Y. Hayashi, T. Sumiya, J. Takahashi, H. Gotoh, T. Urushima, M. Shoji, *Angew. Chem. Int. Ed.*, **2006**, *45*, 958-961.

Aldol Condensation



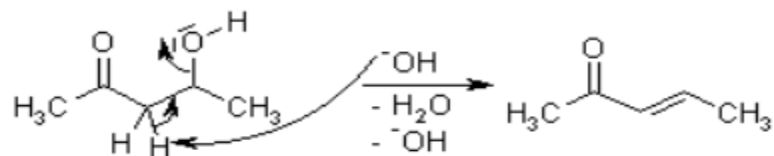
In some cases, the adducts obtained from the Aldol Addition can easily be converted (in situ) to α,β -unsaturated carbonyl compounds, either thermally or under acidic or basic catalysis. The formation of the conjugated system is the driving force for this spontaneous dehydration. Under a variety of protocols, the condensation product can be obtained directly without isolation of the aldol.

The aldol condensation is the second step of the [Robinson Annulation](#).

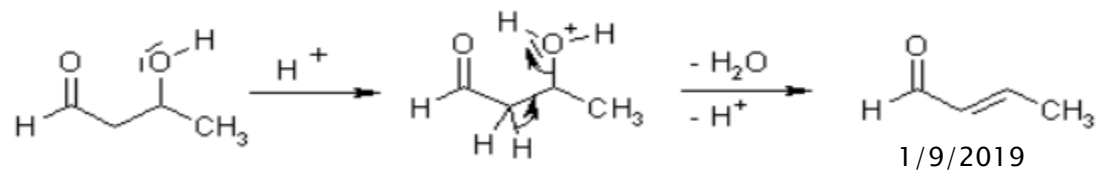
Mechanism

For the addition step see [Aldol Addition](#)

Base catalyzed condensation :



Acid catalyzed condensation :

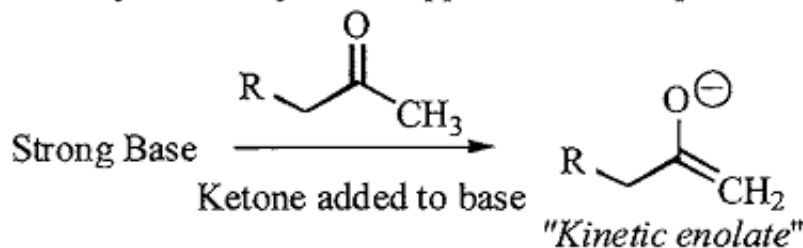


Aldol Type Reactions

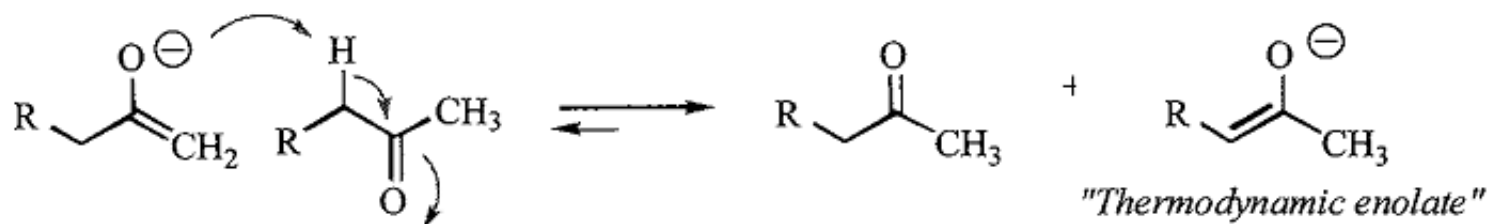
The Reaction:

This reaction has become an extremely important tool in the reaction toolbox of organic chemists. Because of the variety of approaches to the aldol products, this summary section is prepared.

Most synthetically useful approaches use a preformed enolate as one of the reactants.



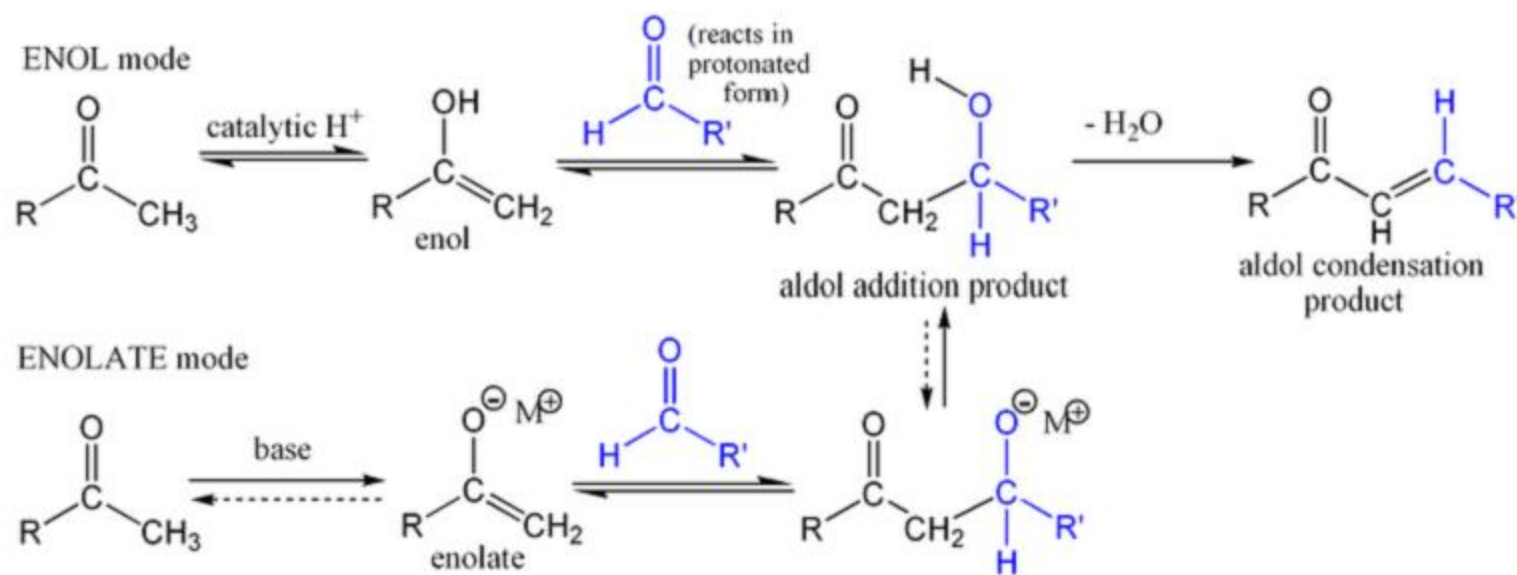
With a weaker base and / or slow addition of base to the ketone, an equilibrium will be established and a "thermodynamic enolate" will predominate.



The most useful approach is when the enolate can be trapped and used in a configurationally stable form.

An **aldol condensation** is an organic reaction in which an enol or an enolate ion reacts with a carbonyl compound to form a β -hydroxyaldehyde or β -hydroxyketone, followed by a dehydration to give a conjugated enone.

Aldol condensations are important in organic synthesis, providing a good way to form carbon-carbon bonds. The Robinson annulation reaction sequence features an aldol condensation; the Wieland-Miescher ketone product is an important starting material for many organic syntheses. Aldol condensations are also commonly discussed in university level organic chemistry classes as a good bond-forming reaction that demonstrates important reaction mechanisms.^{[1] [2] [3]} In its usual form, it involves the nucleophilic addition of a ketone enolate to an aldehyde to form a β -hydroxy ketone, or "**aldol**" (**aldehyde** + **alcohol**), a structural unit found in many naturally occurring molecules and pharmaceuticals.^{[4] [5] [6]}



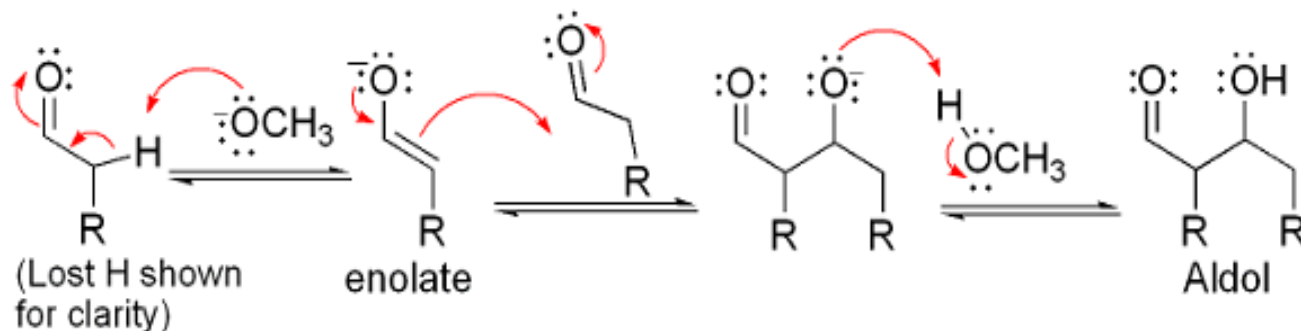
The name **aldol condensation** is also commonly used, especially in biochemistry, to refer to the aldol reaction itself, as catalyzed by aldolases. However, the aldol reaction is not formally a condensation reaction because it does not involve the loss of a small molecule.

The reactions between a ketone and an aldehyde (crossed aldol condensation) or between two aldehydes also go by the name **Claisen-Schmidt condensation**. These reactions are named after two of its pioneering investigators Rainer Ludwig Claisen and J. G. Schmidt, who independently published on this topic in 1880 and 1881.^{[7] [8] [9]} An example is the synthesis of dibenzylideneacetone.

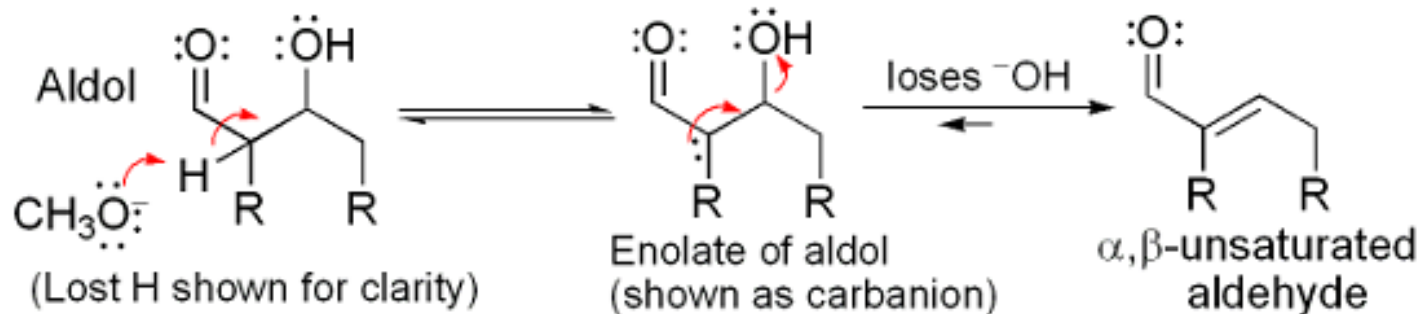
Mechanism

The first part of this reaction is an aldol reaction, the second part a dehydration—an elimination reaction. Dehydration may be accompanied by decarboxylation when an activated carboxyl group is present. The aldol addition product can be dehydrated via two mechanisms; a strong base like potassium *t*-butoxide, potassium hydroxide or sodium hydride in an enolate mechanism,^[10] or in an acid-catalyzed enol mechanism.

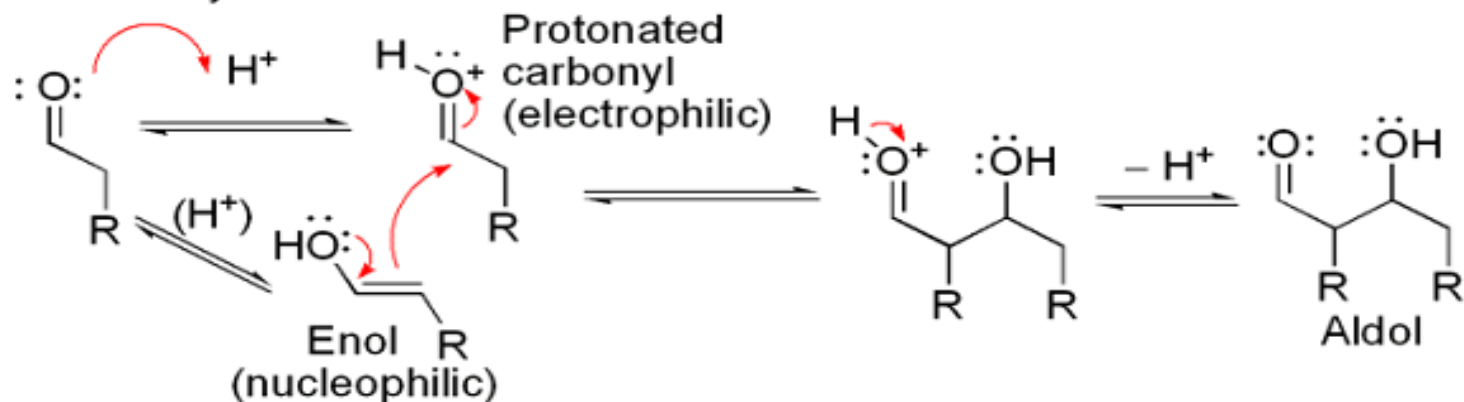
Base catalyzed aldol reaction (shown using $^-OCH_3$ as base)



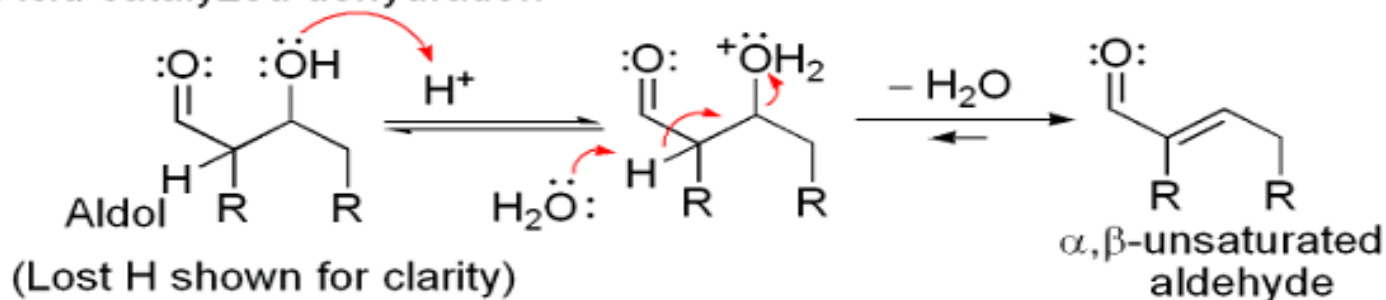
Base catalyzed dehydration (sometimes written as a single step)



Acid catalyzed aldol reaction

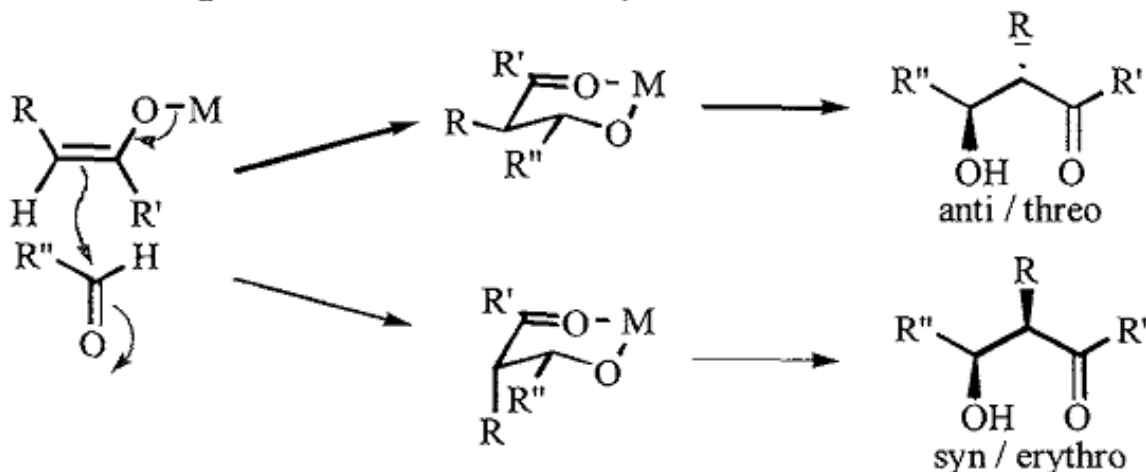


Acid catalyzed dehydration



Notes:

If the starting materials are not the same, the reaction is known as a "*mixed*" aldol condensation.



M. B. Smith, J. March in *March's Advanced Organic Chemistry*, 5th ed., John Wiley and Sons, Inc. New York, 2001, pp 1218-1213; T. Laue, A. Plagens, *Named Organic Reactions*, John Wiley and Sons, Inc., New York, 1998, pp. 4-10; A. T. Nielsen, W. J. Houlihan, *Organic Reactions* **16** (full volume); T. Mukaiyama, *Organic Reactions*, **28**, 3; C. J. Cowden, I. Patterson, *Organic Reactions* **51**, 1.

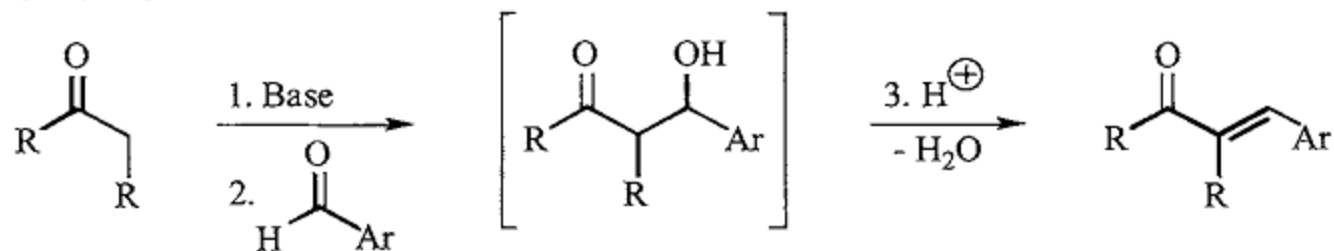
Condensation types

It is important to distinguish the aldol condensation from other addition reactions to carbonyl compounds.

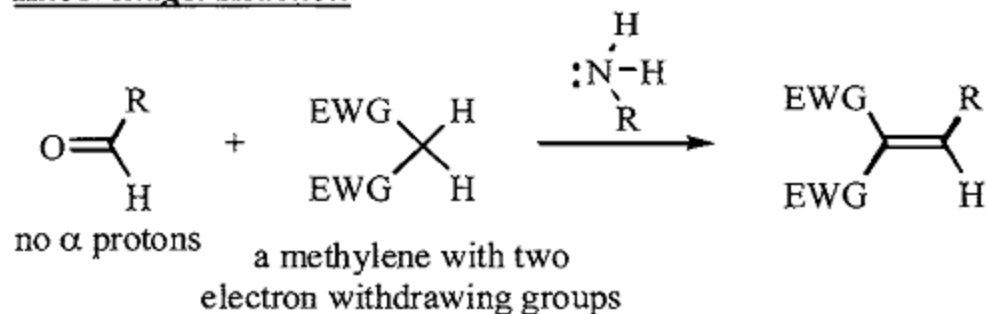
- When the base is an amine and the active hydrogen compound is sufficiently activated the reaction is called a Knoevenagel condensation.
- In a Perkin reaction the aldehyde is aromatic and the enolate generated from an anhydride.
- A Claisen condensation involves two ester compounds.
- A Dieckmann condensation involves two ester groups in the *same molecule* and yields a cyclic molecule
- A Henry reaction involves an aldehyde and an aliphatic nitro compound.
- A Robinson annulation involves a α,β -unsaturated ketone and a carbonyl group, which first engage in a Michael reaction prior to the aldol condensation.
- In the Guerbet reaction, an aldehyde, formed *in situ* from an alcohol, self-condenses to the dimerized alcohol.
- In the Japp-Maitland condensation water is removed not by an elimination reaction but by a nucleophilic displacement

Reactions based on the Aldol Reaction:

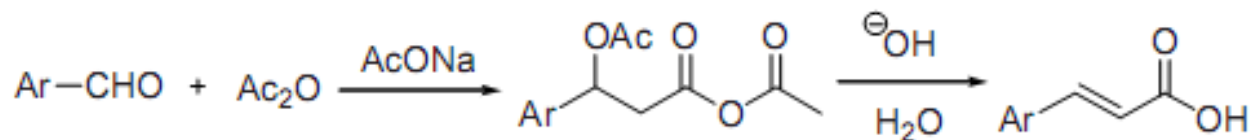
Claisen-Schmidt:



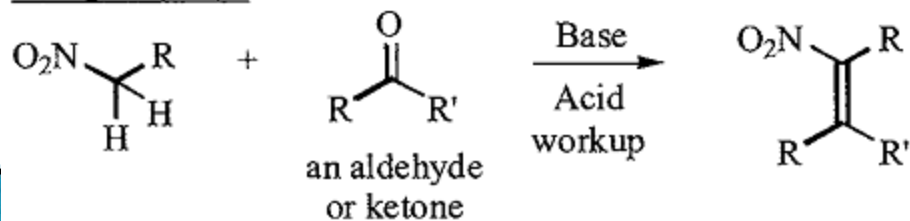
Knoevenagel Reaction



Perkin reaction



Henry Reaction

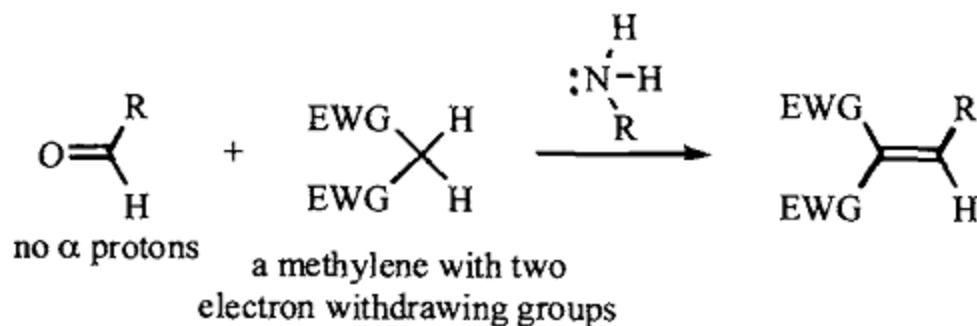


Knoevenagel Condensation (Reaction)

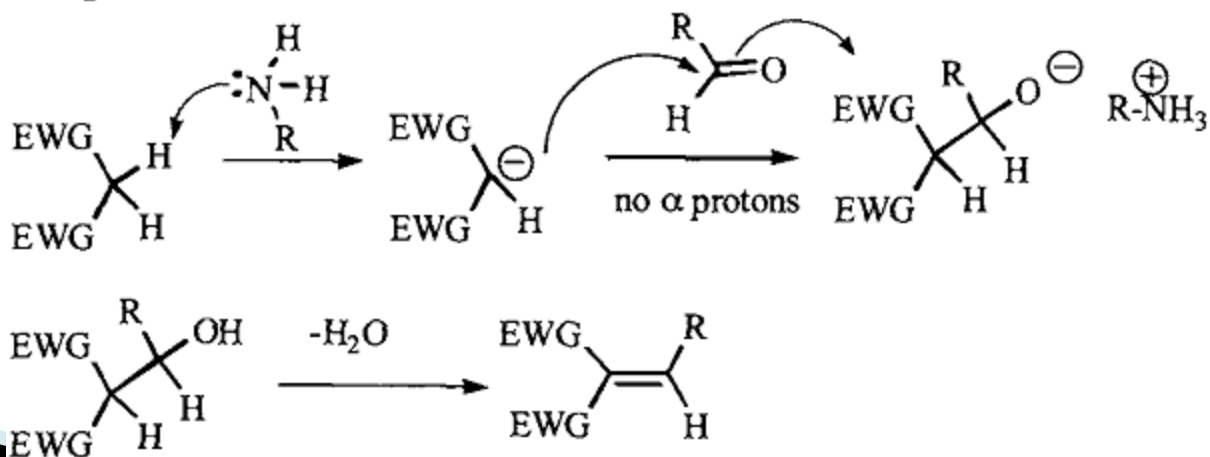
The **Knoevenagel condensation** reaction is an organic reaction named after Emil Knoevenagel. It is a modification of the Aldol condensation^{[1][2]}.

A Knoevenagel condensation is a nucleophilic addition of an active hydrogen compound to a carbonyl group followed by a dehydration reaction in which a molecule of water is eliminated (hence *condensation*). The product is often an alpha, beta conjugated enone.

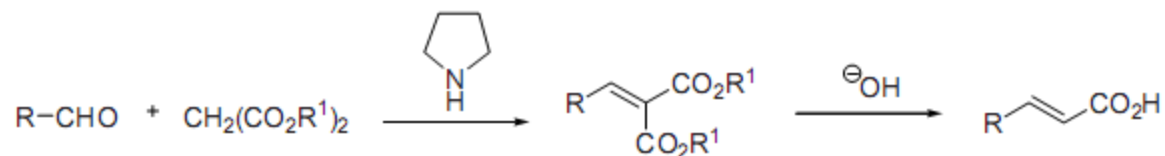
The Reaction:



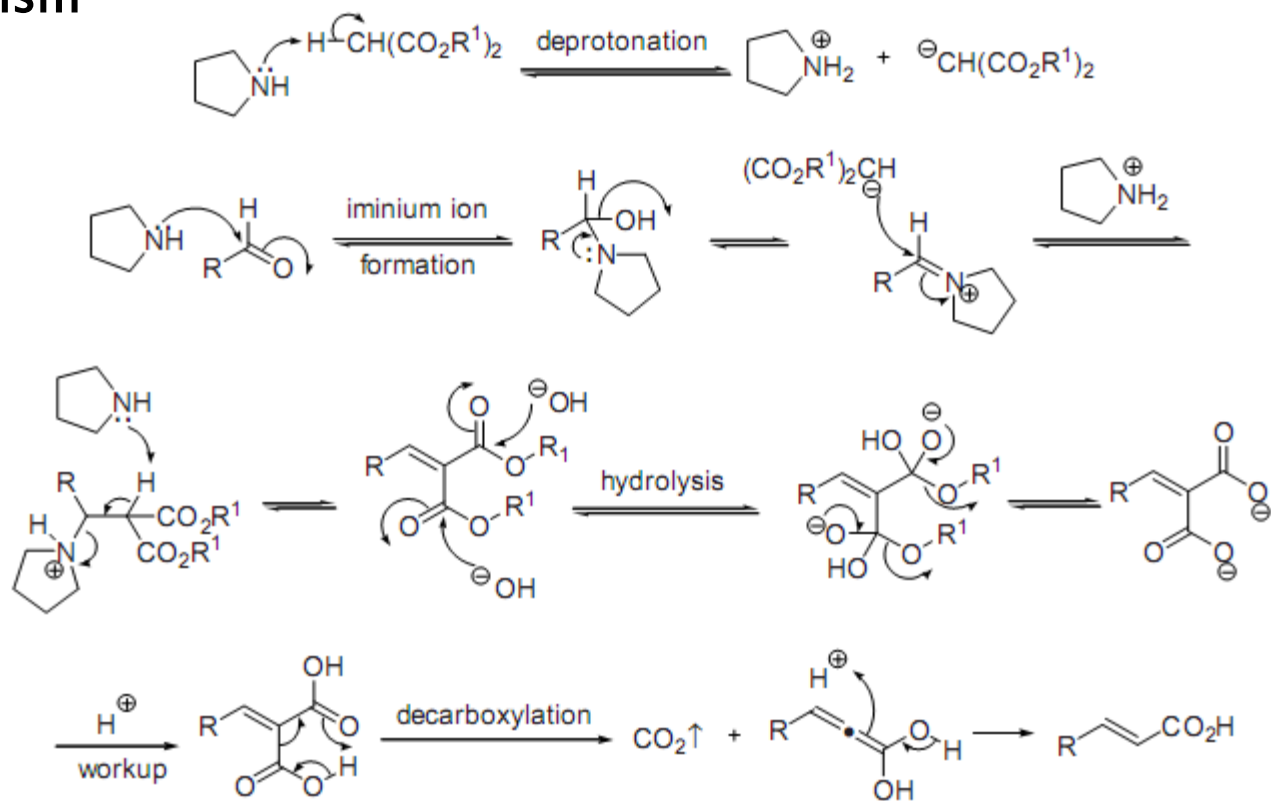
Proposed Mechanism:



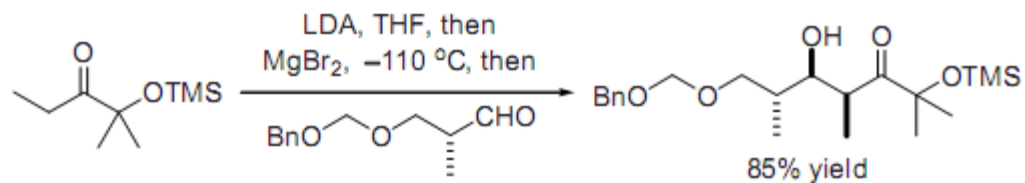
Knoevenagel condensation



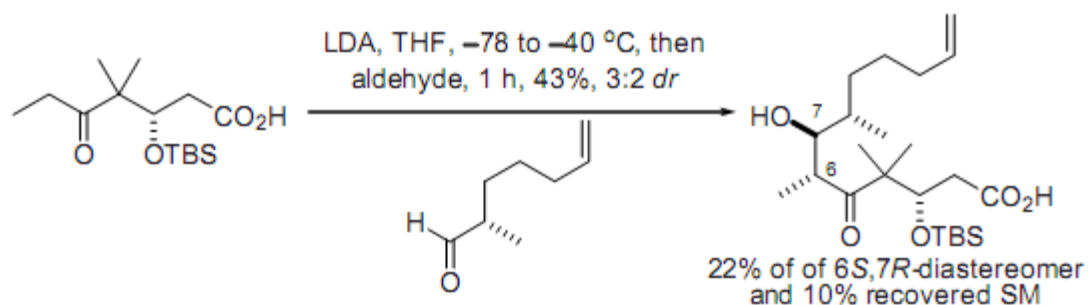
Other Mechanism



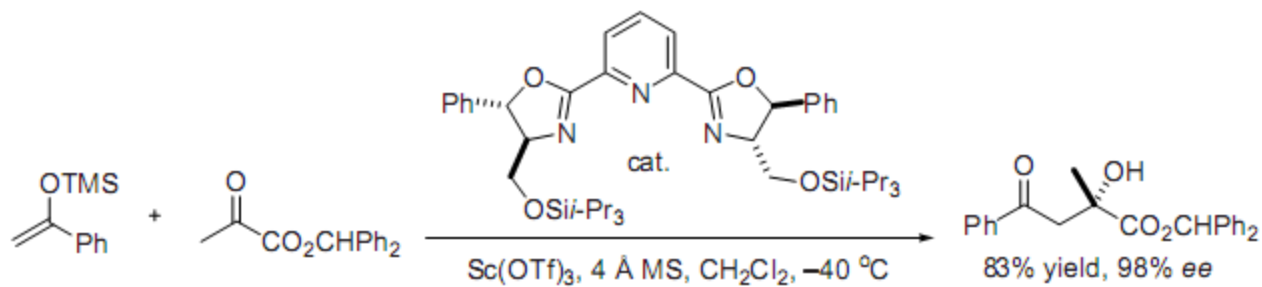
Example 1³



Example 2⁸

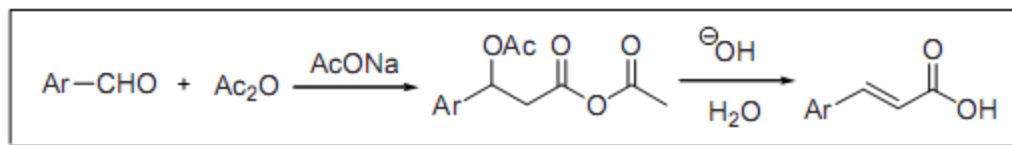


Example 3, Enantioselective Mukaiyama-aldol reaction¹⁰

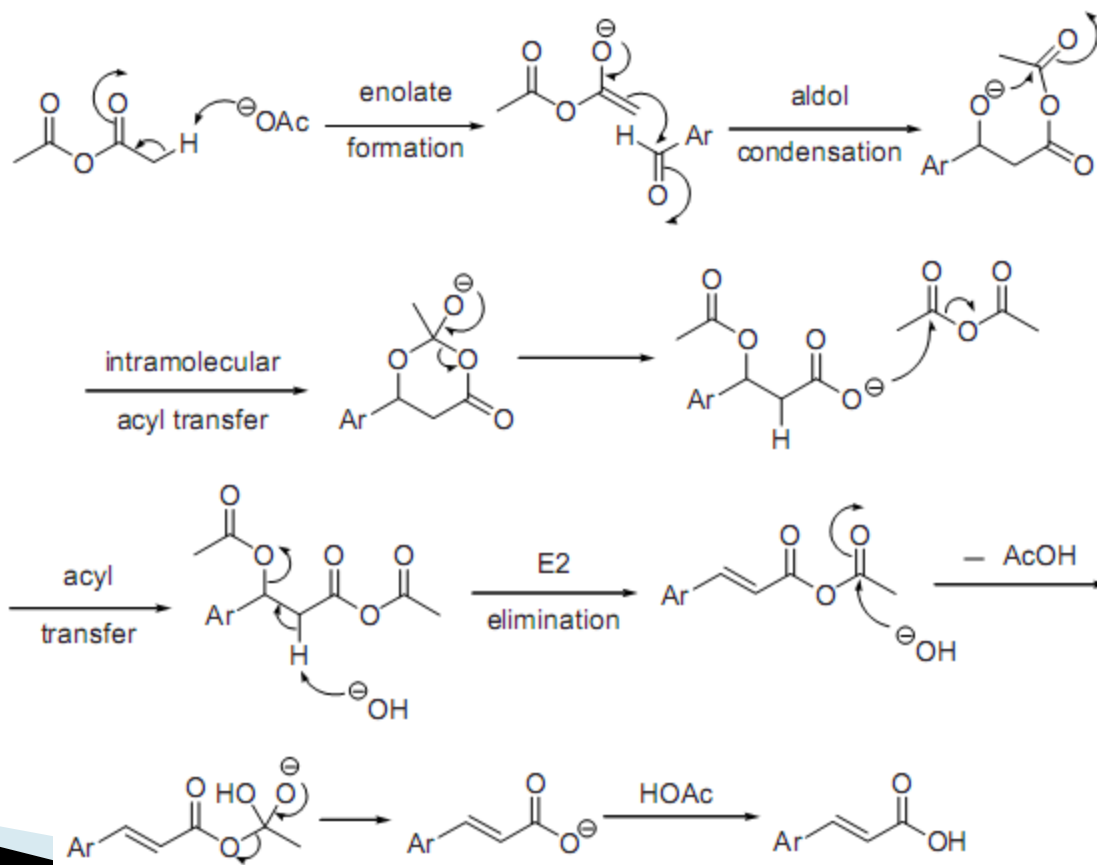


Perkin reaction

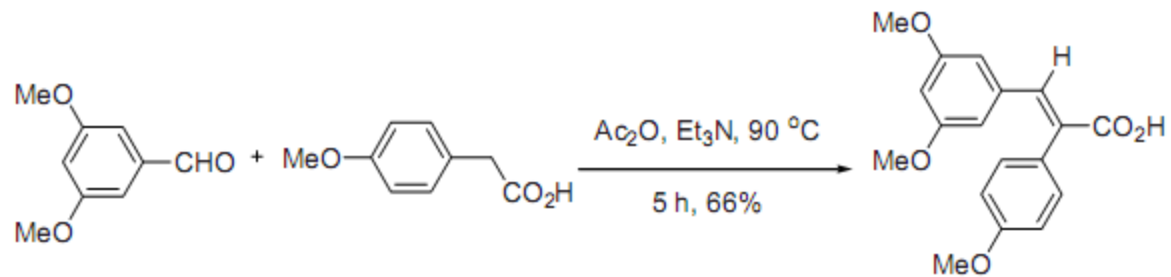
Cinnamic acid synthesis from aryl aldehyde and acetic anhydride.



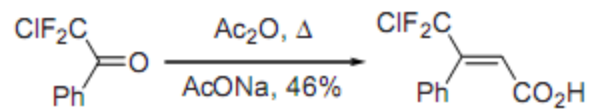
cinnamic acid



Example 1⁷

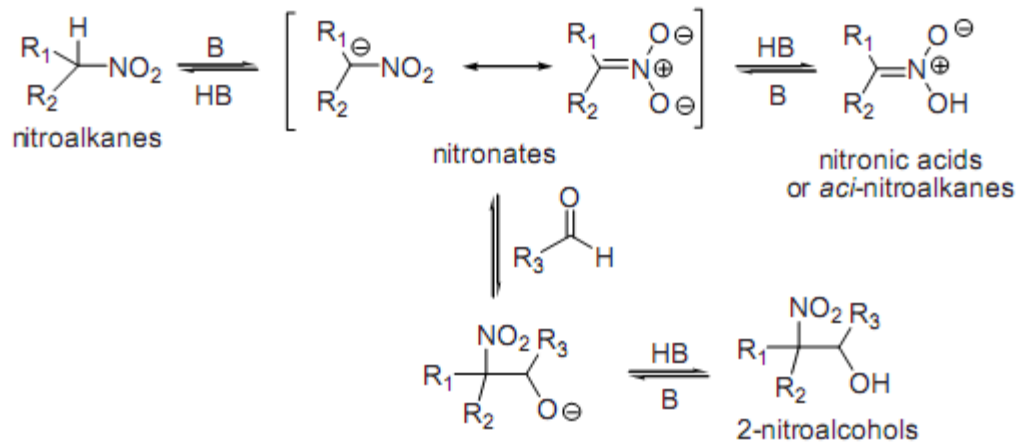
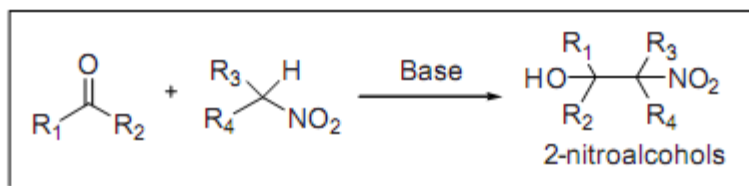


Example 2⁹

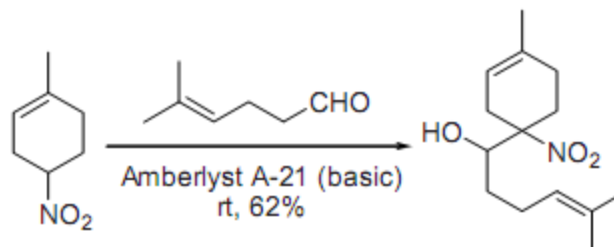


Henry nitroaldol reaction

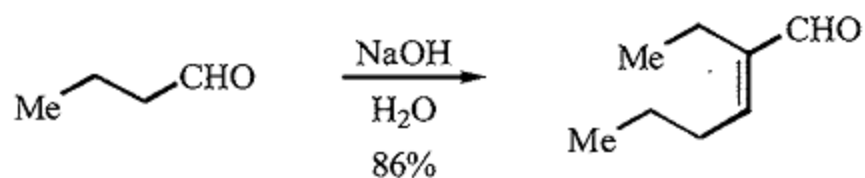
The nitroaldol condensation reaction involving aldehydes and nitronates, derived from deprotonation of nitroalkanes by bases.



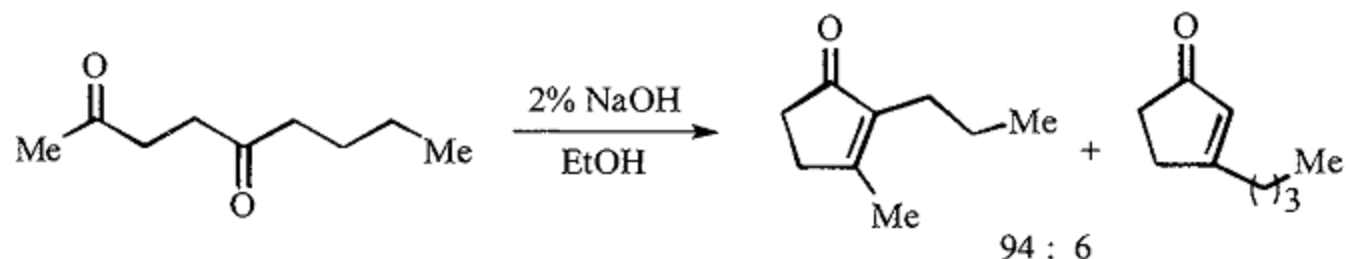
Example 1⁴



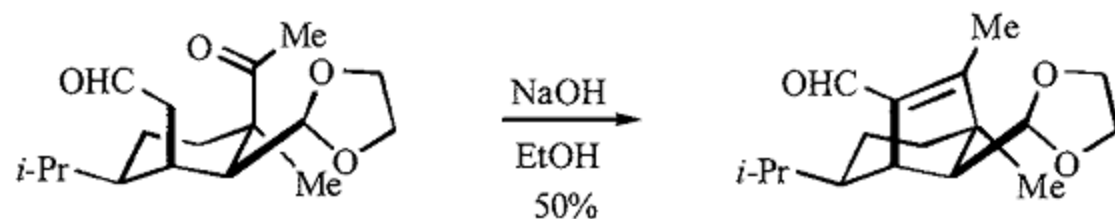
Examples:



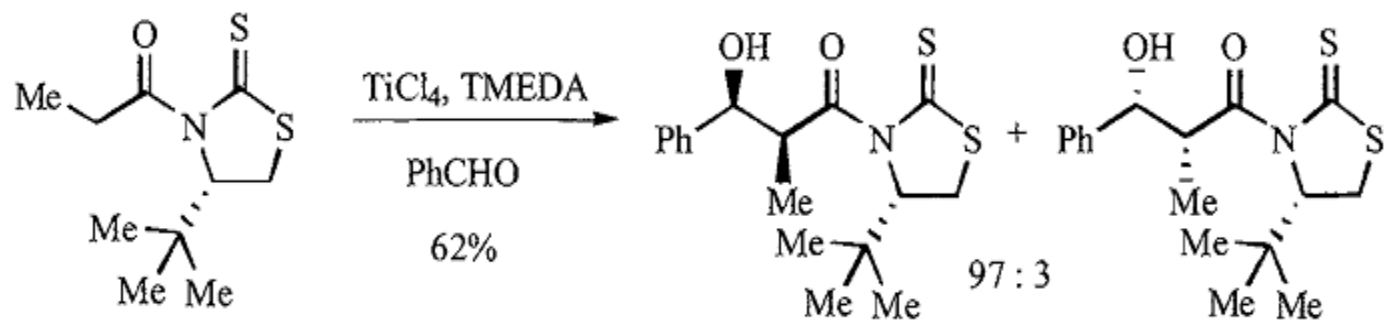
M. Haussermann, *Helvetica Chimica Acta* **1951**, 34, 1482 (Reported in A. T. Nielsen, W. J. Houlihan, *Organic Reactions* **16**, page 8).



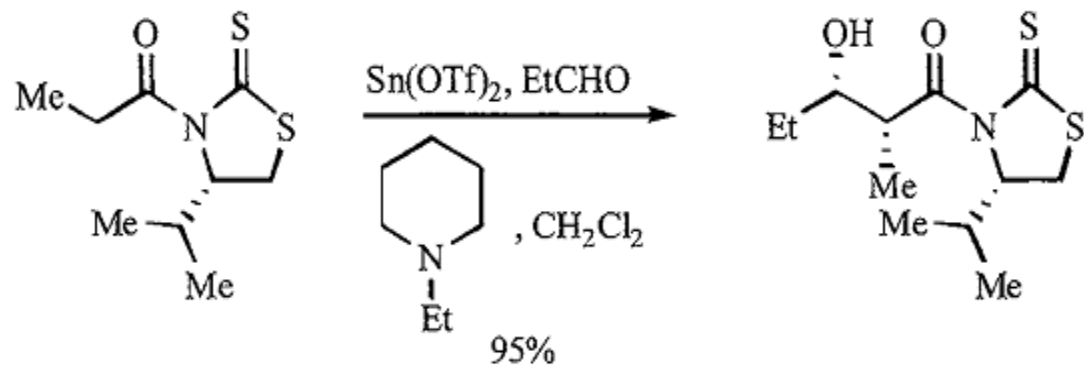
P. M. McCurry, Jr., R. K. Singh, *Journal of Organic Chemistry* **1974**, 39, 2316



E. J. Corey, S. Nozoe, *Journal of the American Chemical Society* **1965**, 87, 5728



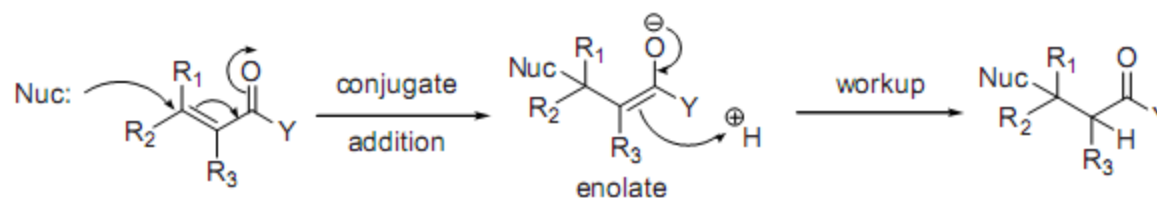
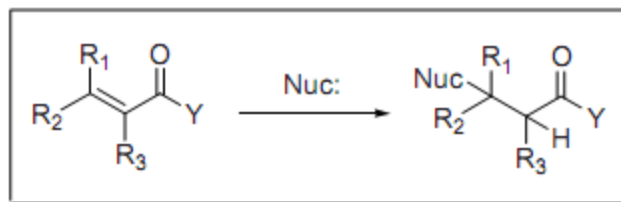
M. T. Crimmins, K. Chaudhary, *Organic Letters* **2000**, 2, 775



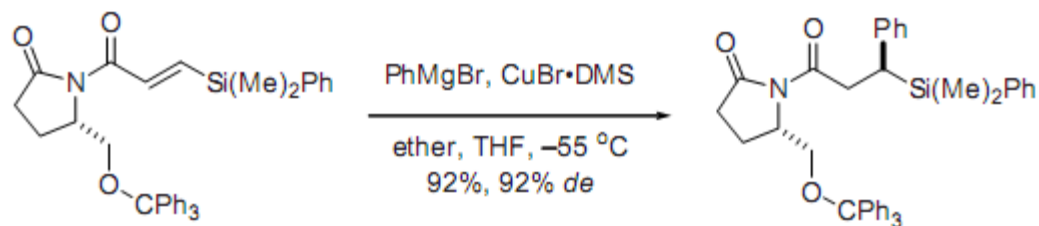
D. Zuev, L. A. Paquette, *Organic Letters* **2000**, 2, 679

Michael addition

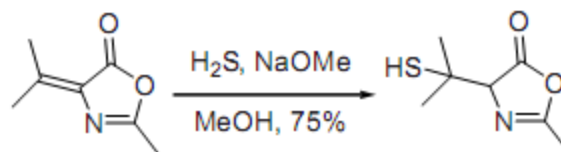
Also known as conjugate addition, Michael addition is the 1,4-addition of a nucleophile to an α,β -unsaturated system.



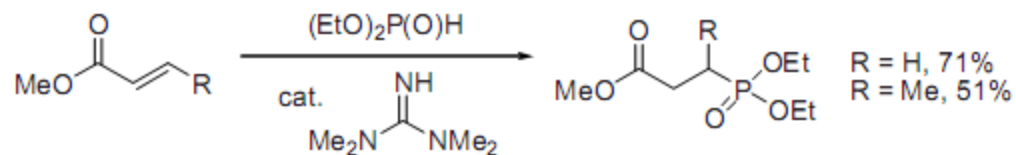
Example 1, Asymmetric Michael addition²



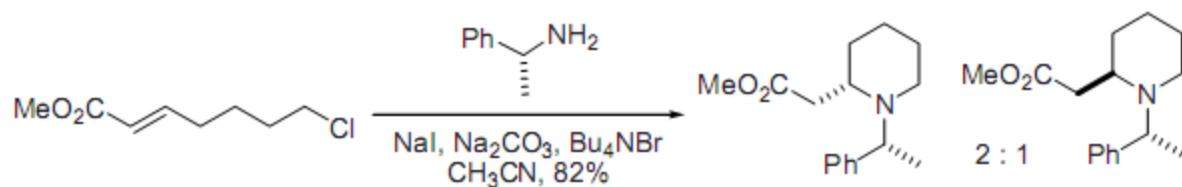
Example 2, Thia-Michael addition³



Example 3, Phospha-Michael addition⁷



Example 4, Asymmetric aza-Michael addition⁹



Example 5, Intramolecular Michael addition¹⁰

