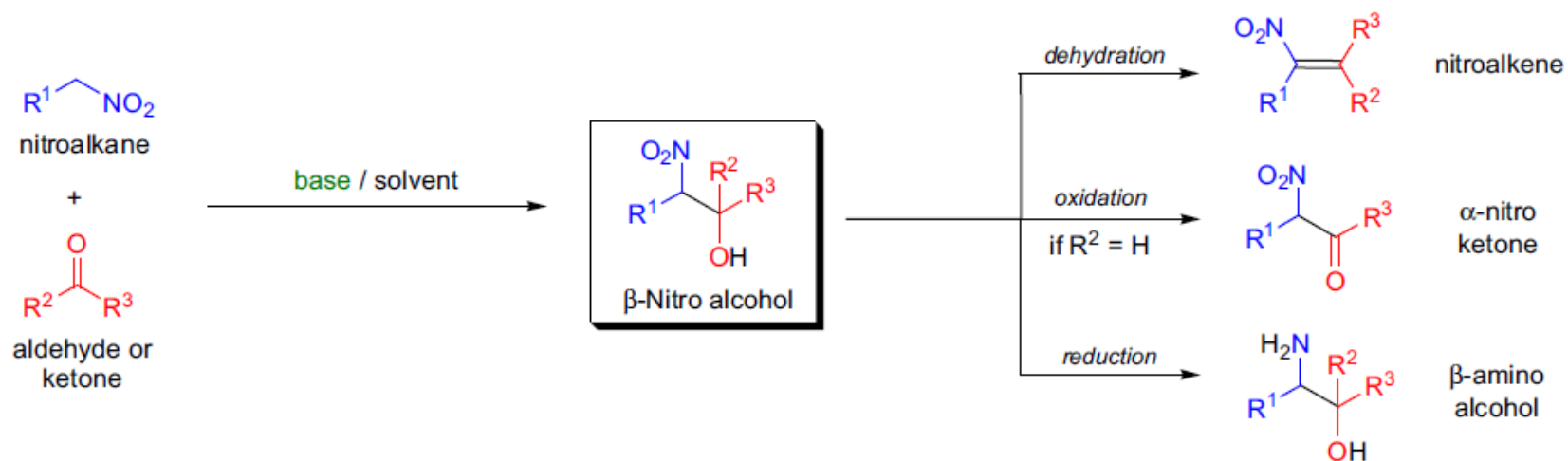


# Henry Reaction

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2015.9.1

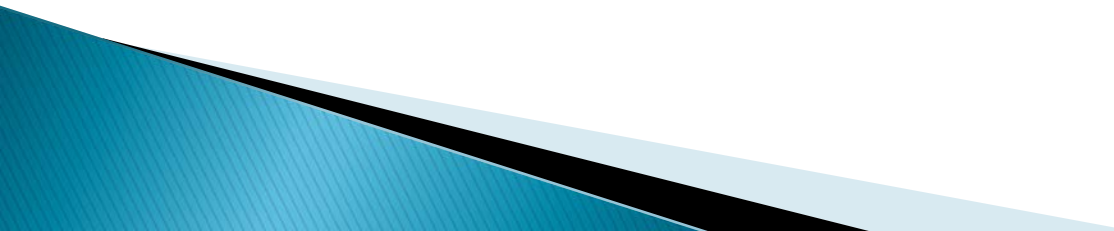
# Discovery

- ▶ In 1895, L. Henry discovered that nitroalkanes were easily combined with aldehydes and ketones to give  $\beta$ -nitro alcohols in the presence of a base. Since its discovery, the aldol condensation between nitroalkanes and carbonyl compounds (nitro-aldol reaction) has become a significant tool in the formation of C-C bonds and is referred to as the Henry reaction.



$\text{R}^1$  = alkyl, aryl,  $\text{CO}_2\text{R}$ , alkenyl;  $\text{R}^2, \text{R}^3$  = alkyl, aryl, H; base =  $\text{NR}_3$ , DBU, DBN, PAP, TMG, KF, TBAF,  $\text{Al}_2\text{O}_3$ ,  $\text{La}_3(\text{OR})_9$ , NaOH, NaOR, amberlyst A-21, etc.

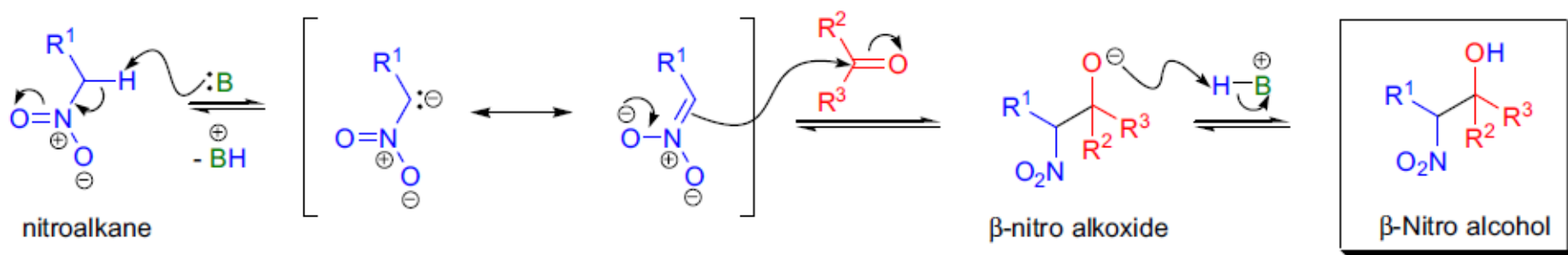
# Features

- ▶ Only a catalytic amount of base is necessary;
  - ▶ Both ionic and nonionic bases may be used;
  - ▶ The solvents and bases do not have significant influence on the outcome of the reaction;
  - ▶ The steric properties of the reactants play an important role: hindered substrates (usually ketones) react slowly and side reactions often occur;
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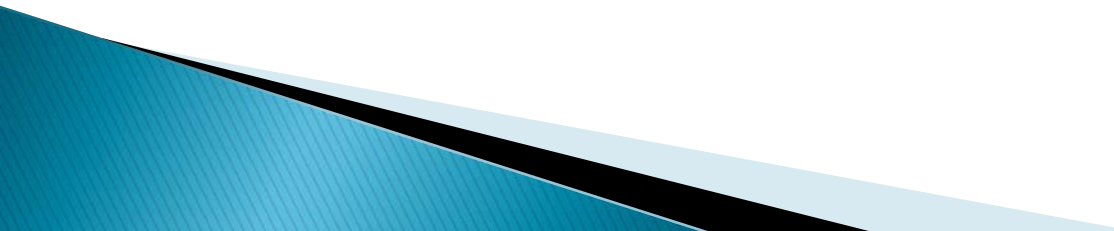
# Features

- ▶ Usually the  $\beta$ -nitro alcohols are formed as a mixture of diastereomers (*syn* and *anti*) but by modification of the reaction conditions high levels of diastereoselectivity can be achieved;
- ▶ The stereocenter to which the nitro group is attached to is easy to epimerize.

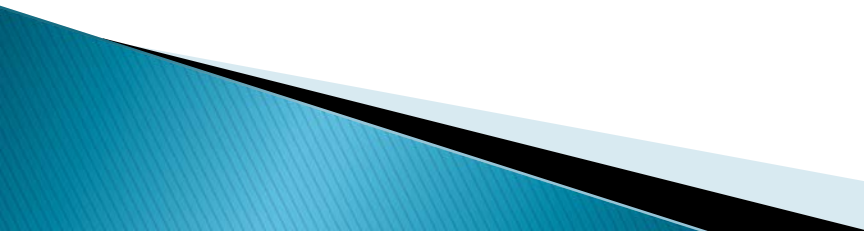
# Mechanism



# Side reactions

- ▶ The  $\beta$ -nitro alcohols undergo dehydration, especially when aromatic aldehydes are used as substrates; however, by carefully chosen conditions this can be suppressed;
  - ▶ With sterically hindered carbonyl compounds, a base-catalyzed self-condensation or *Cannizzaro reaction* may take place;
  - ▶ The *retro-Henry reaction* may prevent the reaction from going to completion.
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# Modifications

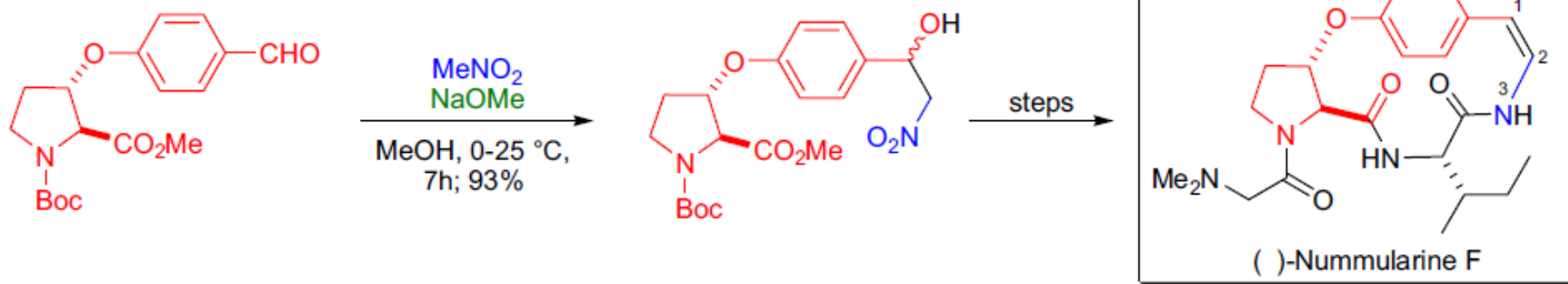
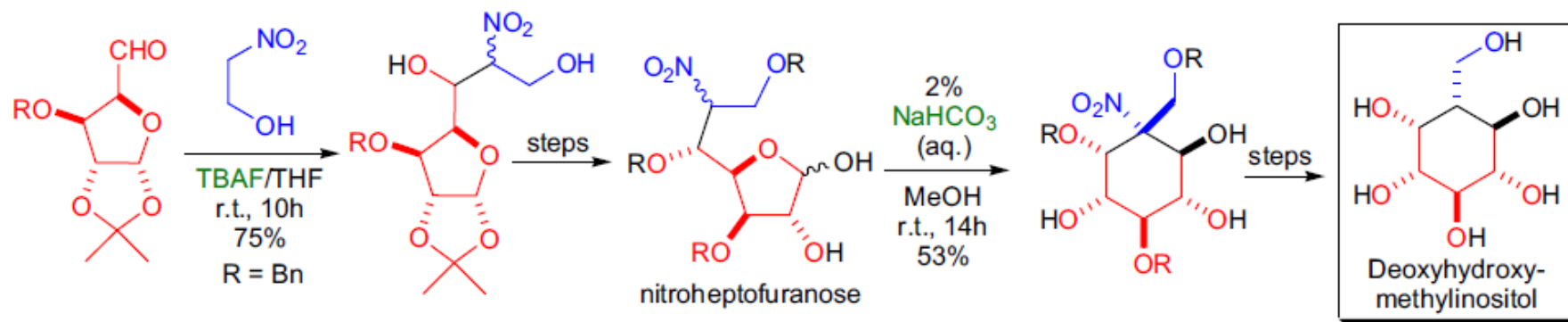
- ▶ Unreactive alkyl nitro compounds are converted to their corresponding dianions which react faster with carbonyl compounds;
  - ▶ Reactions of ketones are accelerated by using PAP as the base;
  - ▶ When imines are used instead of carbonyl compounds as substrates, the aza-Henry reaction takes place to afford nitroamines; upon the reduction of nitroamines, vicinal diamines are obtained;
  - ▶ In the presence of chiral catalysts the asymmetric Henry reaction can be realized;
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# Modifications

- ▶ Aldehydes react with  $\alpha,\alpha$ -doubly deprotonated nitroalkanes to give nitronate alkoxides that afford mainly syn-nitro alcohols upon kinetic protonation;
- ▶ Nitronate anions on which the alcohol oxygen atom is silylprotected give predominantly anti- $\beta$ -nitro alcohols upon kinetic protonation;
- ▶ Nitronate anions in which one oxygen atom of the nitro group is silyl-protected give mainly anti- $\beta$ -nitro alcohols when reacted with aldehydes in the presence of catalytic amounts of fluoride ion.

# Synthetic applications



# Synthetic applications

