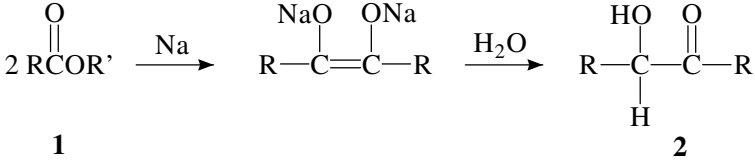
A

Acyloin Ester Condensation

α-Hydroxyketones from carboxylic esters



1 **2**

Upon heating of a carboxylic ester **1** with sodium in an inert solvent, a condensation reaction can take place to yield a α-hydroxy ketone **2** after hydrolytic workup.[1–3] This reaction is called *Acyloin condensation*, named after the products thus obtained. It works well with alkanoic acid esters. For the synthesis of the corresponding products with aryl substituents (R = aryl), the *Benzoin condensation* of aromatic aldehydes is usually applied.

For the mechanistic course of the reaction the diketone **5** is assumed to be an intermediate, since small amounts of **5** can sometimes be isolated as a minor product. It is likely that the sodium initially reacts with the ester **1** to give the radical anion species **3**, which can dimerize to the dianion **4**. By release of two alkoxides $R'O^-$ the diketone **5** is formed. Further reaction with sodium leads to the dianion **6**, which yields the α-hydroxy ketone **2** upon aqueous workup:

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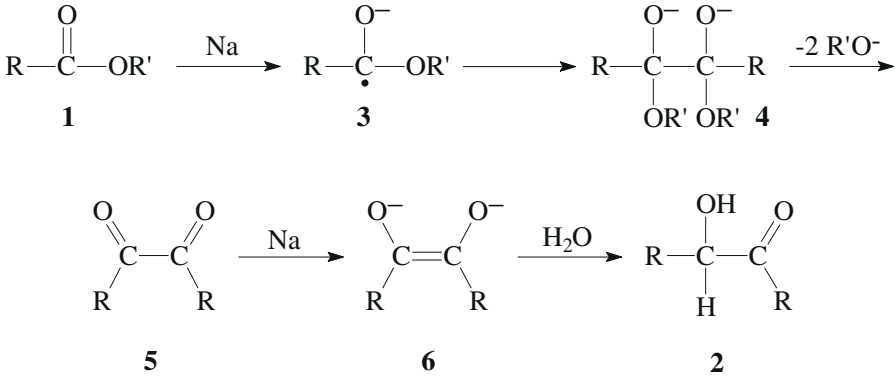
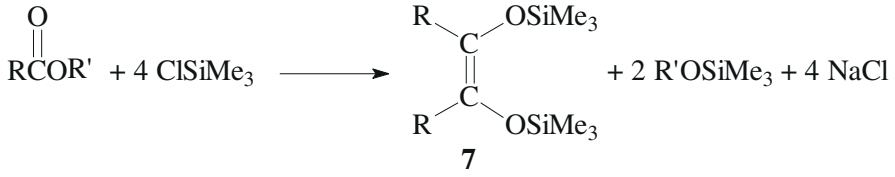


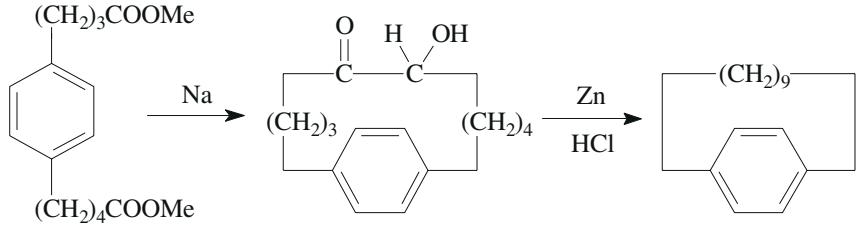
An intramolecular reaction is possible with appropriate substrates containing two ester groups, leading to the formation of a carbocyclic ring. This reaction is especially useful for the formation of rings with ten to twenty carbon atoms, the yield depending on ring size.[4] The presence of carbon–carbon double or triple bonds does not affect the reaction. The strong tendency for ring formation with appropriate diesters is assumed to arise from attachment of the chain ends to the sodium surface and thereby favoring ring closure.

A modified procedure, which uses trimethylsilyl chloride as an additional reagent, gives higher yields of acyloins and is named after Rühlmann.[5] In the presence of trimethylsilyl chloride, the *bis*-O-silylated endiol **7** is formed and can be isolated. Treatment of **7** with aqueous acid leads to the corresponding acyloin **2**:



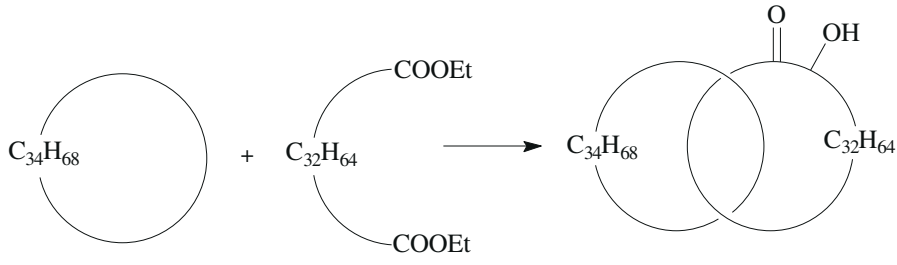
This modification has become the standard procedure for the acyloin ester condensation. By doing so, the formation of products from the otherwise competitive *Dieckmann condensation* (*Claisen ester condensation*) can be avoided. A product formed by ring closure through a Dieckmann condensation consists of a ring that is smaller by one carbon atom than the corresponding cyclic acyloin.

As an example of ring systems which are accessible through this reaction, the formation of [*n*]paracyclophanes[6] like **8** with $n \geq 9$ shall be outlined:



8

A spectacular application of the acyloin ester condensation was the preparation of catenanes like **11**.[7] These were prepared by a statistical synthesis; which means that an acyloin reaction of the diester **10** has been carried out in the presence of an excess of a large ring compound such as **9**, with the hope that some diester molecules would be threaded through a ring, and would then undergo ring closure to give the catena compound:



9 **10** **11**

As expected, the yields of catenanes by this approach are low, which is why improved methods for the preparation of such compounds have been developed.[8] The acyloins are often only intermediate products in a multistep synthesis. For example they can be further transformed into olefins by application of the *Corey–Winter fragmentation*.

1. A. Freund, *Justus Liebigs Ann. Chem.* **1861**, *118*, 33–43.
2. S. M. McElvain, *Org. React.* **1948**, *4*, 256–268.
3. J. J. Bloomfield, D. C. Owsley, J. M. Nelke, *Org. React.* **1976**, *23*, 259–403.
4. K. T. Finley, *Chem. Rev.* **1964**, *64*, 573–589.
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6. D. J. Cram, M. F. Antar, *J. Am. Chem. Soc.* **1958**, *80*, 3109–3114.
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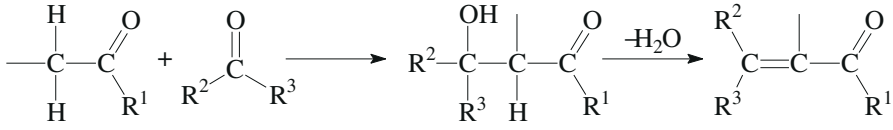
8. J.-P. Sauvage, *Acc. Chem. Res.* **1990**, *23*, 319–327.

Aldol Reaction

Reaction of aldehydes or ketones to give β-hydroxy carbonyl compounds

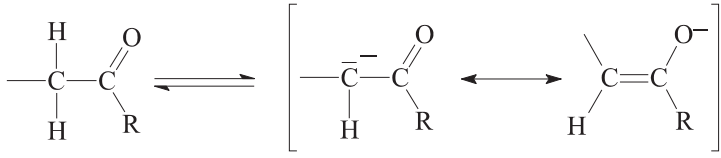


1 **2** **3** **4**

The addition of the α-carbon of an enolizable aldehyde or ketone **1** to the carbonyl group of a second aldehyde or ketone **2** is called the *aldol reaction*.[1,2] It is a versatile method for the formation of carbon–carbon bonds, and is frequently used in organic chemistry. The initial reaction product is a β-hydroxy aldehyde (aldol) or β-hydroxy ketone (ketol) **3**. A subsequent dehydration step can follow, to yield an α,β-unsaturated carbonyl compound **4**. In that case the entire process is also called *aldol condensation*.

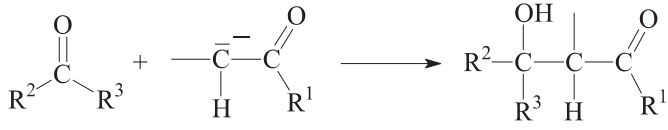
The aldol reaction as well as the dehydration are reversible. In order to obtain the desired product, the equilibrium might have to be shifted by appropriate reaction conditions (see below).

The reaction can be performed with base catalysis as well as acid catalysis. The former is more common; here the enolizable carbonyl compound **1** is deprotonated at the α-carbon by base (e.g. alkali hydroxide) to give the enolate anion **5**, which is stabilized by resonance:



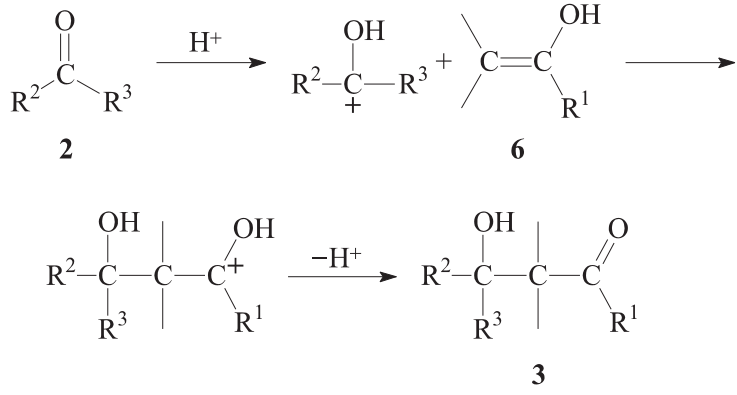
1 **5**

The next step is the nucleophilic addition of the enolate anion **5** to the carbonyl group of another, non-enolized, aldehyde molecule **2**. The product which is obtained after workup is a β-hydroxy aldehyde or ketone **3**:

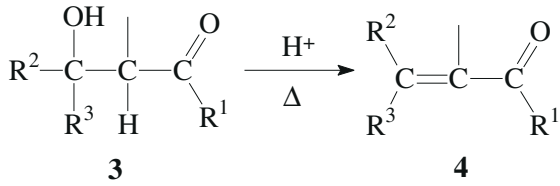


2 **5** **3**

In the acid-catalyzed process, the enol **6** reacts with the protonated carbonyl group of another aldehyde molecule **2**:



If the initially formed β-hydroxy carbonyl compound **3** still has an α-hydrogen, a subsequent elimination of water can take place, leading to an α,β-unsaturated aldehyde or ketone **4**. In some cases the dehydration occurs already under the aldol reaction conditions; in general it can be carried out by heating in the presence of acid:



Several pairs of reactants are possible. The aldol reaction between two molecules of the same aldehyde is generally quite successful, since the equilibrium lies far to the right. For the analogous reaction of ketones, the equilibrium lies to the left, and the reaction conditions have to be adjusted properly in order to achieve satisfactory yields (e.g. by using a Soxhlet extractor).

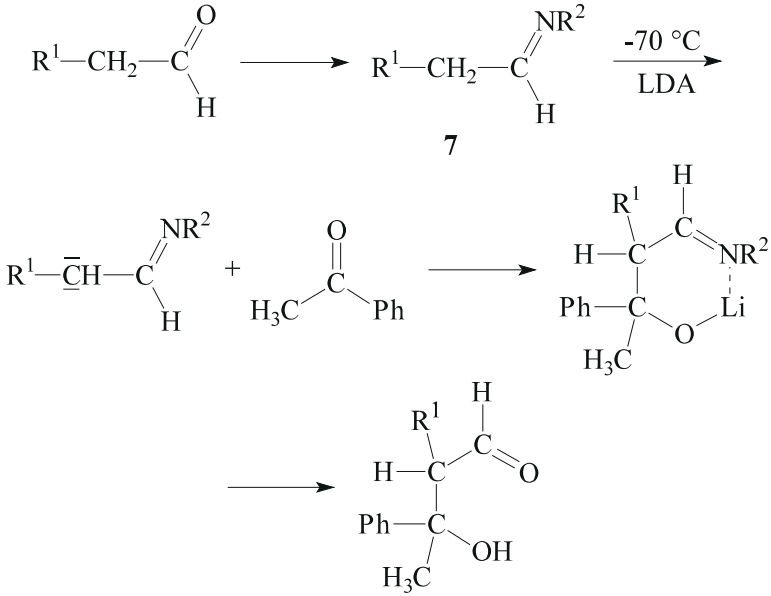
With unsymmetrical ketones, having hydrogens at both α-carbons, a mixture of products can be formed. In general such ketones react preferentially at the less substituted side, to give the less sterically hindered product.

A different situation is found in the case of *crossed aldol reactions*, which are also called *Claisen–Schmidt reactions*. Here the problem arises, that generally a mixture of products might be obtained.

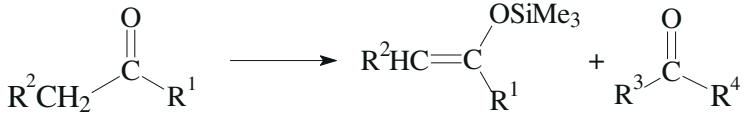
From a mixture of two different aldehydes, each with α-hydrogens, four different aldols can be formed—two aldols from reaction of molecules of the same aldehyde + two crossed aldol products; not even considering possible stereoisomers (see below). By taking into account the unsaturated carbonyl compounds which could be formed by dehydration from the aldols, eight different reaction products might be obtained, thus indicating that the aldol reaction may have preparative limitations.

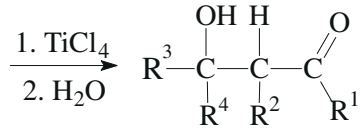
If only one of the two aldehydes has an α-hydrogen, only two aldols can be formed; and numerous examples have been reported, where the crossed aldol reaction is the major pathway.[2] For two different ketones, similar considerations do apply in addition to the unfavorable equilibrium mentioned above, which is why such reactions are seldom attempted.

In general the reaction of an aldehyde with a ketone is synthetically useful. Even if both reactants can form an enol, the α-carbon of the ketone usually adds to the carbonyl group of the aldehyde. The opposite case—the addition of the α-carbon of an aldehyde to the carbonyl group of a ketone—can be achieved by the *directed aldol reaction*.[3,4] The general procedure is to convert one reactant into a preformed enol derivative or a related species, prior to the intended aldol reaction. For instance, an aldehyde may be converted into an aldimine **7**, which can be deprotonated by lithium diisopropylamide (LDA) and then add to the carbonyl group of a ketone:

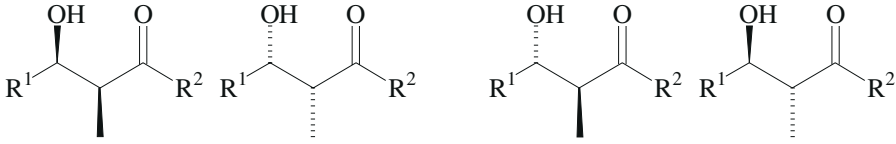


By using the directed aldol reaction, unsymmetrical ketones can be made to react regioselectively. After conversion into an appropriate enol derivative (e.g. trimethylsilyl enol ether **8**) the ketone reacts at the desired α-carbon.



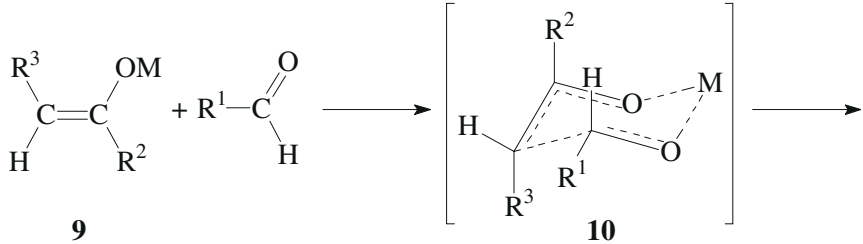


An important aspect is the control of the stereochemical outcome.[5–7] During the course of the reaction two new chiral centers can be created and thus two diastereomeric pairs of enantiomers (*syn/anti* resp. *erythro/threo* pairs) may be obtained.

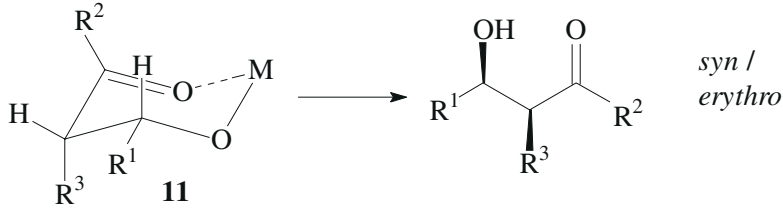


syn / erythro *anti / threo*

The enantiomers are obtained as a racemic mixture if no asymmetric induction becomes effective. The ratio of diastereomers depends on structural features of the reactants as well as the reaction conditions as outlined in the following. By using properly substituted preformed enolates, the diastereoselectivity of the aldol reaction can be controlled.[7] Such enolates can show *E*-or *Z*-configuration at the carbon–carbon double bond. With *Z*-enolates **9**, the *syn* products are formed preferentially, while *E*-enolates **12** lead mainly to *anti* products. This stereochemical outcome can be rationalized to arise from the more favored transition state **10** and **13** respectively:



9 **10**



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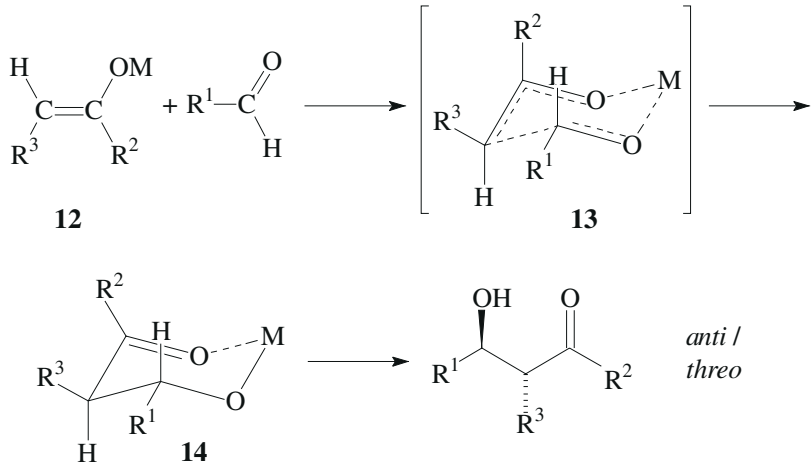
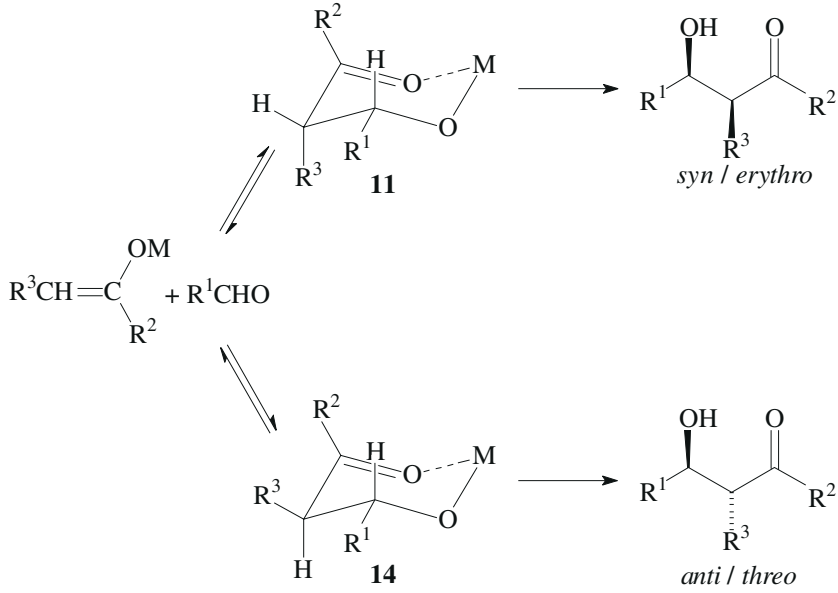
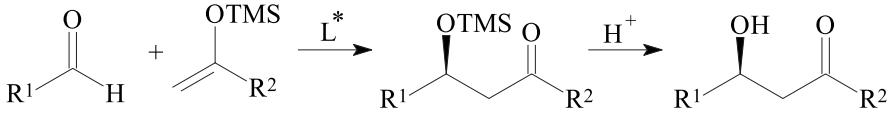


Under conditions which allow for equilibration (thermodynamic control) however, the *anti*-product is obtained, since the metal-chelate **14** is the more stable. As compared to **11** it has more substituents in the favorable equatorial position:



With an appropriate chiral reactant, high enantioselectivity can be achieved, as a result of *asymmetric induction*.[8] If both reactants are chiral, this procedure is called the *double asymmetric reaction*,[6] and the observed enantioselectivity can be even higher.

An enantioselective aldol reaction may also be achieved with non-chiral starting materials by employing an asymmetric Lewis acid as catalyst:[9]



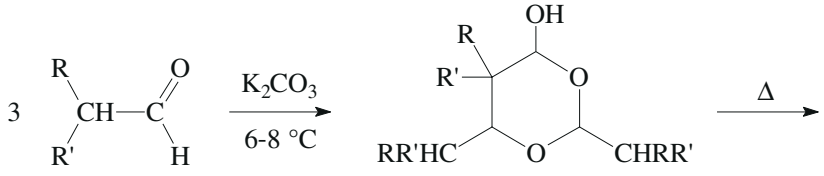
8

For example in the so-called *Mukaiyama aldol reaction*[4,10,11] of an aldehyde R^1-CHO and a trimethylsilyl enol ether **8**, which is catalyzed by Lewis acids, the required asymmetric environment in the carbon–carbon bond forming step can be created by employing an asymmetric Lewis acid L^* in catalytic amounts.

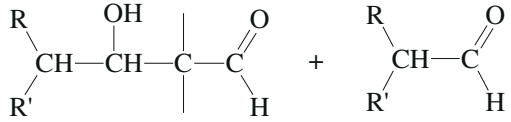
Especially with the ordinary aldol reaction a number of side reactions can be observed, as a result of the high reactivity of starting materials and products. For instance, the α,β-unsaturated carbonyl compounds **4** can undergo further aldol reactions by reacting as vinylogous components. In addition compounds **4** are potential substrates for the *Michael reaction*.

Aldehydes can react through a hydride transfer as in the *Cannizzaro reaction*.

Moreover aldoxanes **15** may be formed; although these decompose upon heating to give an aldol **3** and aldehyde **1**:

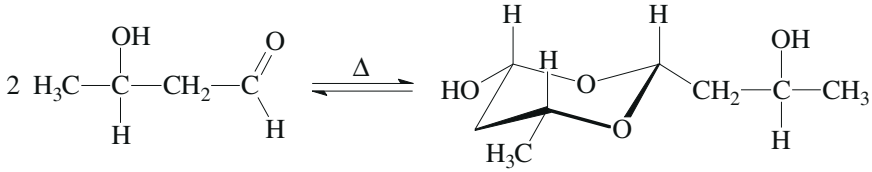


15



3 **1**

Aldols can form dimers; e.g. acetaldol **16** dimerizes to give paraldol **17**:



16 **17**

Because of the many possible reactions of aldols, it is generally recommended to use a freshly distilled product for further synthetic steps.

Besides the aldol reaction in the true sense, there are several other analogous reactions, where some enolate species adds to a carbonyl compound. Such reactions are often called *aldol-type reactions*; the term aldol reaction is reserved for the reaction of aldehydes and ketones.

1. M. A. Wurtz, *Bull. Soc. Chim. Fr.* **1872**, *17*, 436–442.
2. A. T. Nielsen, W. J. Houlihan, *Org. React.* **1968**, *16*, 1–438.
3. G. Wittig, H. Reiff, *Angew. Chem.* **1968**, *80*, 8–15; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 7.
4. T. Mukaiyama, *Org. React.* **1982**, *28*, 203–331;
   T. Mukaiyama, S. Kobayashi, *Org. React.* **1994**, *46*, 1–103.
5. C. H. Heathcock, *Science* **1981**, *214*, 395–400.
6. S. Masamune, W. Choy, J. S. Petersen, L. S. Sita, *Angew. Chem.* **1985**, *97*, 1–31; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1.
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8. D. Enders, R. W. Hoffmann, *Chem. Unserer Zeit* **1985**, *19*, 177–190.
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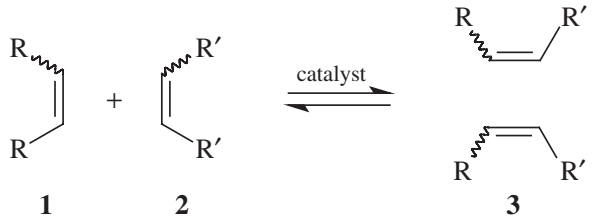
10. S. Kobayashi, H. Uchiro, I. Shiina, T. Mukaiyama, *Tetrahedron* **1993**, *49*, 1761–1772.
11. T. D. Machajewski, C. H. Wong, *Angew. Chem.* **2000**, *112*, 1406–1430; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 1376.

Alkene Metathesis

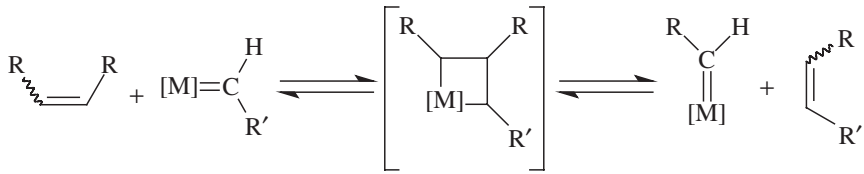
Exchange of alkylidene groups of alkenes—metathesis of olefins



1 **2** **3**

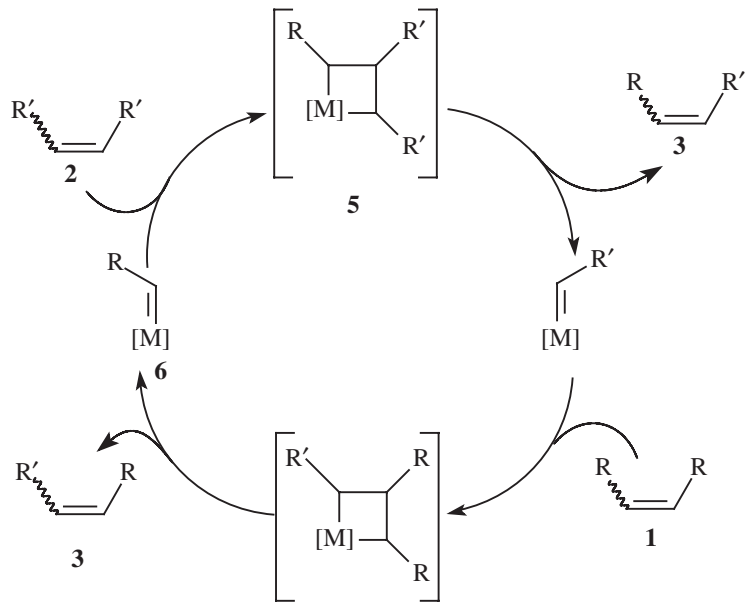
When a mixture of alkenes **1** and **2** or an unsymmetrically substituted alkene **3** is treated with an appropriate transition-metal catalyst, a mixture of products (including *E*/*Z*-isomers) from apparent interchange of alkylidene moieties is obtained by a process called *alkene metathesis*.[1–5] With the development of new catalysts in recent years, alkene metathesis has become a useful synthetic method. Special synthetic applications are, for example, *ring-closing metathesis* (RCM) and *ring-opening metathesis polymerization* (ROM) (see below).

The reaction proceeds by a catalytic cycle mechanism.[2–6] Evidence for the intermediacy of transition-metal alkylidene complexes (i.e. 16e-transition-metal carbene complexes) such as **6** led to the formulation of the *Chauvin mechanism*, which involves the formation of metallacyclobutanes such as **5** as intermediates. In an initial step, the catalytically active transition-metal alkylidene complex **6** is formed from the reaction of a small amount of an alkylidene complex **4** added to the starting alkene, e.g. **1**. The initial alkylidene complex **4** may also be formed from small amounts of the starting alkene and some transition-metal compound (see below). The exchange of alkylidene groups proceeds through the formation of a metallacyclobutane, e.g. **5**, from the addition of **4** to a carbon–carbon double bond. The four-membered ring intermediate decomposes to give the new alkene, e.g. **3**, together with the new transition-metal alkylidene complex **6**:

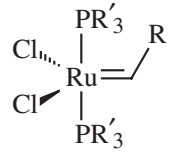


1 **4** **5** **6** **3**

The metathesis process can be illustrated by a catalytic cycle, as follows:

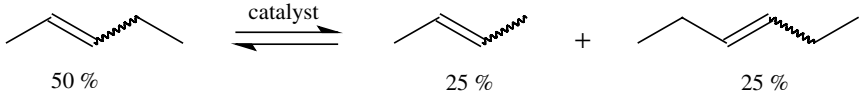


As catalysts, ruthenium- or molybdenum-alkylidene complexes are often employed, e.g. commercially available compounds of type **7**. Various catalysts have been developed for special applications.[2,4]



7

The synthetic utility of the alkene metathesis reaction may in some cases be limited because of the formation of a mixture of products.[2] The steps of the catalytic cycle are equilibrium processes, with the yields being determined by the thermodynamic equilibrium. The metathesis process generally tends to give complex mixtures of products. For example, pent-2-ene **8** 'disproportionates' to give, at equilibrium, a statistical mixture of but-2-enes, pent-2-enes and hex-3-enes:[2,6]

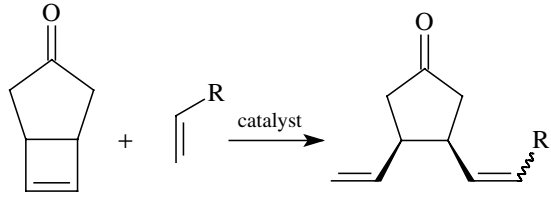


8

However, yields of the desired products can often be improved by choosing the appropriate catalyst, e.g. one which selectively activates terminal alkenes. Furthermore, the outcome of an equilibrium reaction can be influenced by removing one reaction product from the reaction mixture. An example is the formation of a cycloalkene (**10**), together with ethylene (**11**), from an alka-1, $n + 5$-diene (**9**) through catalytic *ring-closing metathesis*.[2] The gaseous product ethylene can be allowed to escape from the reaction mixture, thus driving the reaction to completion by preventing the reverse reaction, with the result of a higher yield of the cycloalkene.

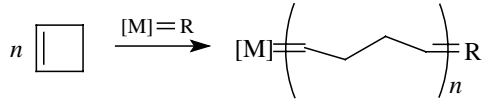
9 **10** **11**

The reversal of ring-closing metathesis, namely *ring-opening metathesis*, is also a synthetically useful reaction. With strained (small-ring) cycloalkenes, e.g. **12**, the equilibrium of the reaction lies on the side of the open-chain product **13**:



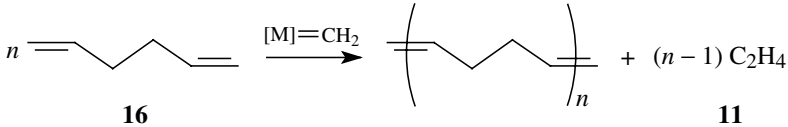
12 **13**

With no acyclic alkene present, strained cycloalkenes, e.g. **14**, polymerize under metathesis conditions. This reaction is known as *ring-opening metathesis polymerization* (ROMP),[7] with the starting transition-metal carbene complex added to the cycloalkene (the monomer) being the chain-initiating agent. The metal carbene complex may also be formed from reaction of a small amount of cycloalkene with some transition-metal compound. These polymerization reactions are often 'living polymerizations' which can be terminated under controlled conditions through addition of an aldehyde, yielding polymers of defined chain lengths. The reactive metal-alkylidene chain ends of intermediates **15** are terminated by coupling to the aldehyde and transfer of the aldehyde-oxygen to the metal.



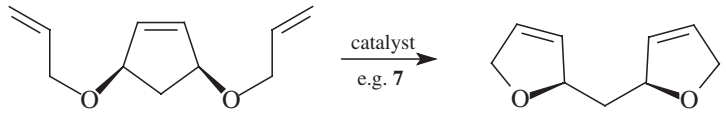
14 **15**

Another metathesis polymerization procedure uses terminal dienes such as hexa-1,5-diene (**16**) (*acyclic diene metathesis* (ADMET)). Here again, the escape of the gaseous reaction product, i.e. ethylene, ensures the irreversible progress of the reaction:



16 **11**

The basic mode of the reaction, as well as the stability of the intermediate metal-alkylidene complexes, suggest that alkene metathesis can be used for 'domino reactions'.[3,5] In the conversion of the 3,5-*bis*-allyloxy-cyclopentene **17** to product **18**, the metal-alkylidene complex formed through a ring-closing metathesis step, followed by a ring-opening metathesis step, becomes the 'proper' reactant for the second allyloxy side-chain, so enabling a further intramolecular ring-closing metathesis reaction. The driving force for this reaction is the thermodynamically favoured formation of a second five-membered ring:



17 **18**

In synthetic organic chemistry, alkene metathesis has become a valuable method for the construction of ring systems. This reaction has also gained industrial importance.[2] A major field is the production of key chemicals for polymer and petrochemistry, and the preparation of special polymers from cycloalkenes by ring-opening metathesis polymerization. As metathesis catalysts, various transition-metal compounds[2] are used; in particular, tungsten, molybdenum, rhenium and ruthenium compounds, e.g. $WCl_6/SnMe_4$, MoO_3, Re_2O_7 and $MeReO_3$[8], as well as carbene complexes of tungsten, molybdenum and ruthenium.

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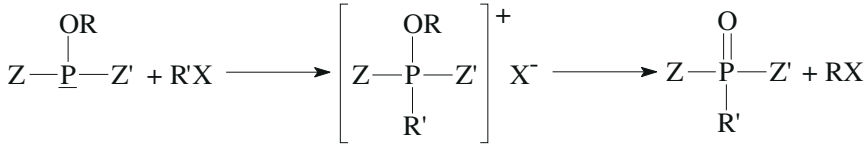
Arbuzov Reaction

Alkyl phosphonates from phosphites

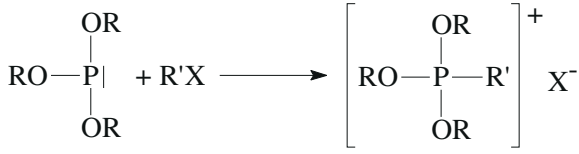


1 **2** **3** **4** **5**

The *Arbuzov reaction*,[1–3] also called the *Michaelis–Arbuzov reaction*, allows for the synthesis of pentavalent alkyl phosphoric acid esters **4** from trivalent phosphoric acid esters **1** (Z,Z′ = R,OR) by treatment with alkyl halides **2**.

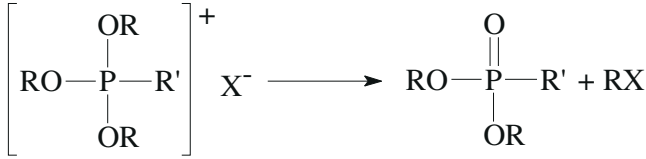
Most common is the preparation of alkyl phosphonic acid esters (phosphonates) **4** (Z,Z′ = OR) from phosphorous acid esters (phosphites) **1** (Z,Z = OR). The preparation of phosphinic acid esters (Z = R, Z′ = OR) from phosphonous acid esters, as well as phosphine oxides (Z,Z′ = R) from phosphinous acid esters is also possible.

The reaction mechanism outlined below for phosphorous acid esters analogously applies for the other two cases. The first step is the addition of the alkyl halide **2** to the phosphite **1** to give a phosphonium salt[2] **3**:



1 **2** **3**

This intermediate product is unstable under the reaction conditions, and reacts by cleavage of an O-alkyl bond to yield the alkyl halide **5** and the alkyl phosphonate **4**:



3 **4** **5**

It is a reaction of wide scope; both the phosphite **1** and the alkyl halide **2** can be varied.[3] Most often used are primary alkyl halides; iodides react better than chlorides or bromides. With secondary alkyl halides side reactions such as elimination of HX can be observed. Aryl halides are unreactive.

With acyl halides, the corresponding acyl phosphonates are obtained. Furthermore allylic and acetylenic halides, as well as α-halogenated carboxylic esters and dihalides, can be used as starting materials. If substituents R and R′ are different, a mixture of products may be obtained, because the reaction product RX **5** can further react with phosphite **1** that is still present:

1 **5**

However with appropriate reaction control, the desired product can be obtained in high yield.[3]

The phosphonates obtained by the Arbuzov reaction are starting materials for the *Wittig–Horner reaction* (*Wittig reaction*); for example, appropriate phosphonates have been used for the synthesis of vitamin A and its derivatives.[4]

Moreover organophosphoric acid esters have found application as insecticides (e.g. Parathion). Some derivatives are highly toxic to man (e.g. Sarin, Soman). The organophosphonates act as inhibitors of the enzyme cholinesterase by phosphorylating it. This enzyme is involved in the proper function of the parasympathetic nervous system. A concentration of 5×10^{-7} g/L in the air can already cause strong toxic effects to man.

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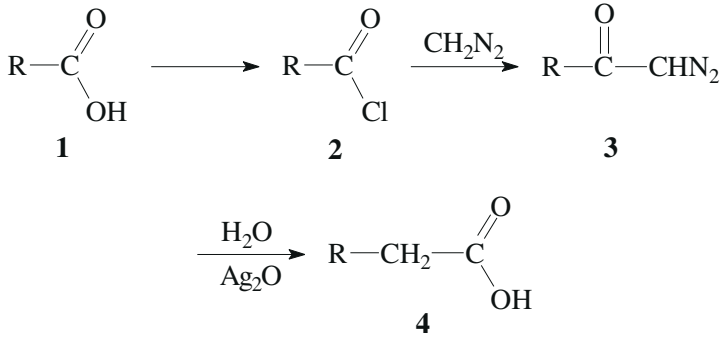
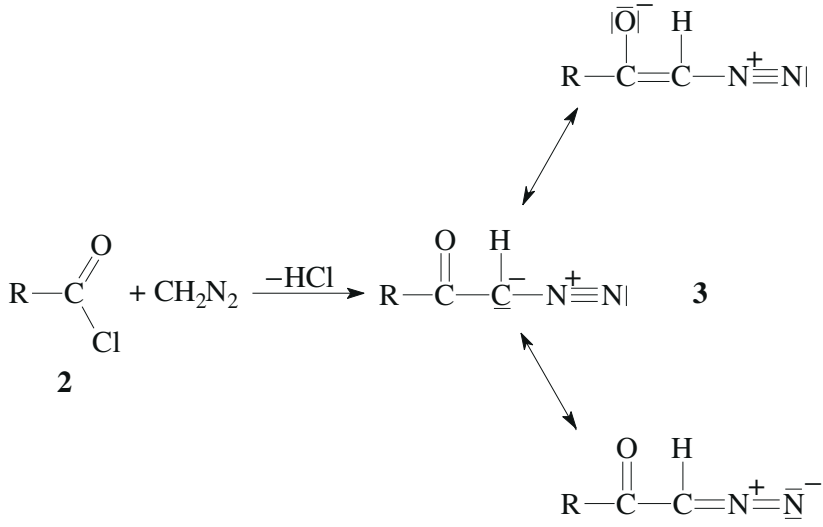
Arndt–Eistert Synthesis

Chain elongation of carboxylic acids by one methylene group



The Arndt–Eistert synthesis allows for the conversion of carboxylic acids **1** into the next higher homolog[1,2] **4**. This reaction sequence is considered to be the best method for the extension of a carbon chain by one carbon atom in cases where a carboxylic acid is available.

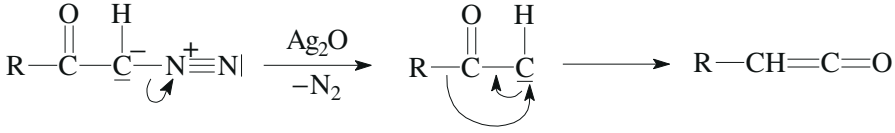
In a first step, the carboxylic acid **1** is converted into the corresponding acyl chloride **2** by treatment with thionyl chloride or phosphorous trichloride. The acyl chloride is then treated with diazomethane to give the diazo ketone **3**, which is stabilized by resonance, and hydrogen chloride:



2 **3**

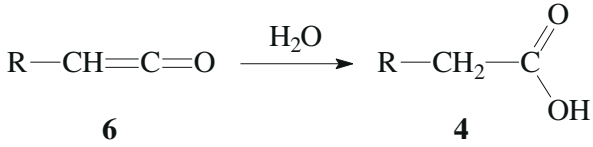
The hydrogen chloride thus produced can in turn react with the diazoketone to yield a α-chloro ketone. In order to avoid this side reaction, two equivalents of diazomethane are used. The second equivalent reacts with HCl to give methyl chloride.[2]

The diazo ketone **3**, when treated with silver oxide as catalyst, decomposes into ketocarbene **5** and dinitrogen N_2. This decomposition reaction can also be achieved by heating or by irradiation with uv-light. The ketocarbene undergoes a *Wolff rearrangement* to give a ketene **6**:



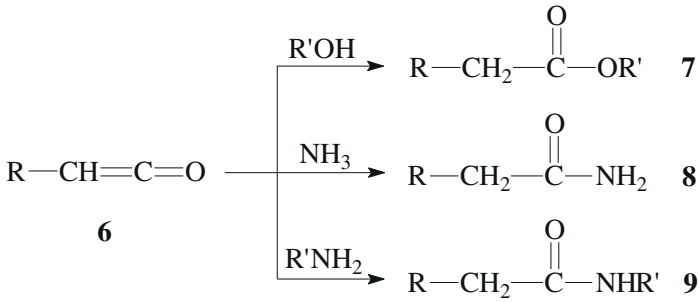
3 **5** **6**

The final step is the reaction of the ketene with the solvent; e.g. with water to yield the carboxylic acid **4**:



6 **4**

If an alcohol R′OH is used as solvent instead of water, the corresponding ester **7** can be obtained directly. In analogous reactions with ammonia or amines ($R'NH_2$) the amides **8** and **9** respectively are accessible.



The reaction is of wide scope (R = alkyl, aryl); however the substrate molecule should not contain other functional groups that can react with diazomethane. With unsaturated acyl halides the yield can be poor, but may be improved by modified reaction conditions.[3]

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