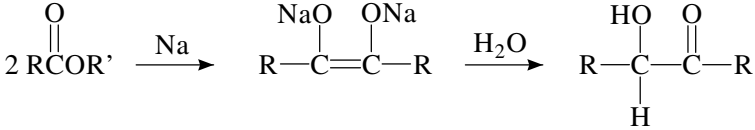
A

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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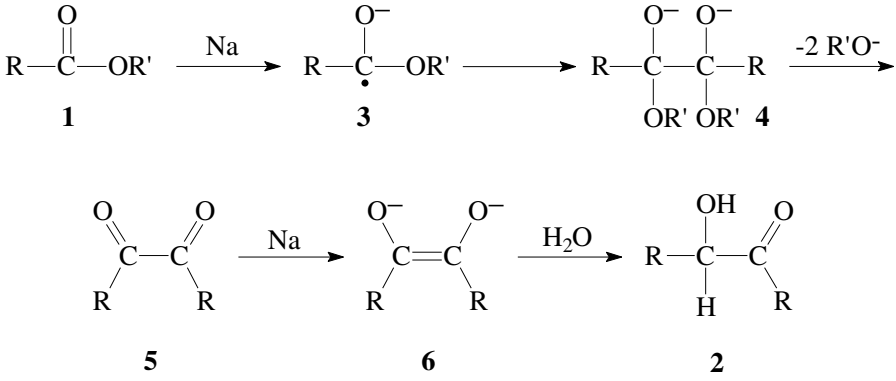
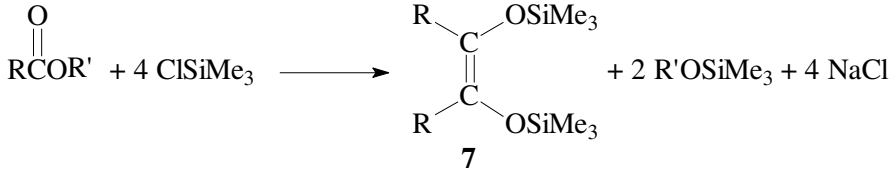


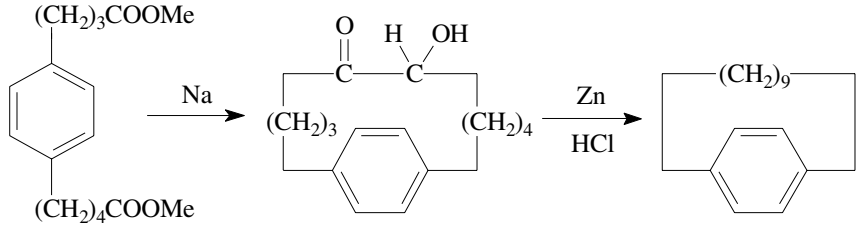
An intramolecular reaction is possible with appropriate substrates containing two ester groups, leading to the formation of a carbocyclic ring. This reaction is especially useful for the formation of rings with ten to twenty carbon atoms, the yield depending on ring size.[4] The presence of carbon–carbon 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**:



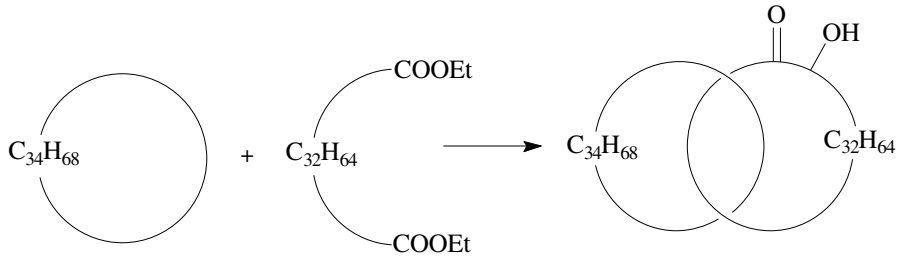
This modification has become the standard procedure for the acyloin ester condensation. By doing so, the formation of products from the otherwise competitive *Dieckmann condensation* (*Claisen ester condensation*) can be avoided. A product formed by ring closure through a Dieckmann condensation consists 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:



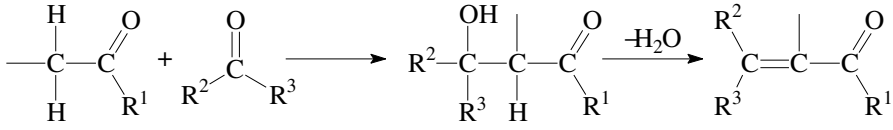
9 **10** **11**

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.
5. K. Rühlmann, *Synthesis* **1971**, 236–253.
6. D. J. Cram, M. F. Antar, *J. Am. Chem. Soc.* **1958**, *80*, 3109–3114.
7. E. Wasserman, *J. Am. Chem. Soc.* **1960**, *82*, 4433–4434.
8. J.-P. Sauvage, *Acc. Chem. Res.* **1990**, *23*, 319–327.

Aldol Reaction

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

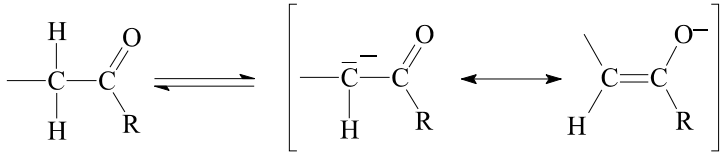


1 **2** **3** **4**

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*.

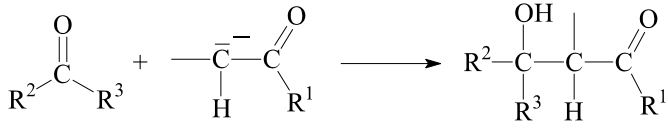
The aldol reaction as well as the dehydration are reversible. In order to obtain the desired product, the equilibrium might have to be shifted by appropriate reaction conditions (see below).

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:



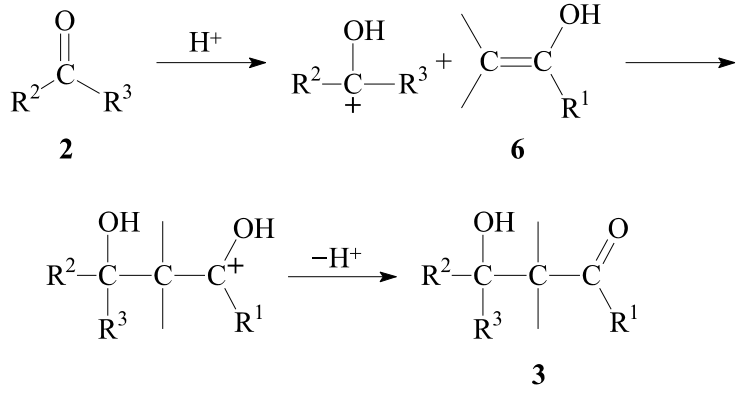
1 **5**

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**:

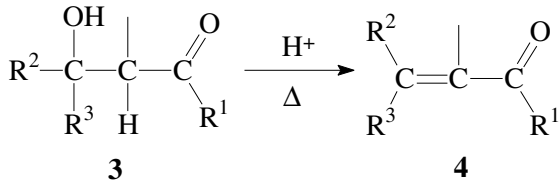


2 **5** **3**

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).

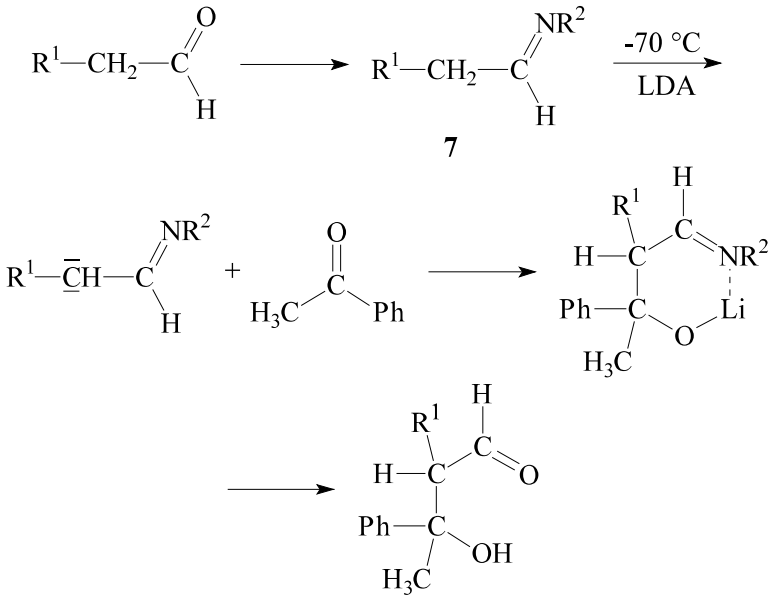
With unsymmetrical ketones, having hydrogens at both α-carbons, a mixture of products can be formed. In general such ketones react preferentially at the less substituted side, to give the less sterically hindered product.

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.

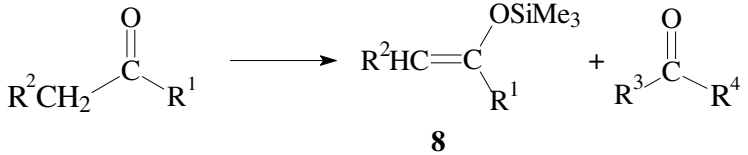
From a mixture of two different aldehydes, each with α-hydrogens, four different aldols can be formed—two aldols from reaction of molecules of the same aldehyde + two crossed aldol products; not even considering possible stereoisomers (see below). By taking into account the unsaturated carbonyl compounds 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.

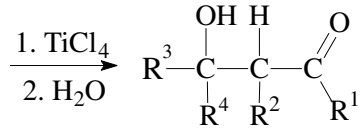
If only one of the two aldehydes has an α-hydrogen, only two aldols can be formed; and numerous examples have been reported, where the crossed aldol reaction is the major pathway.[2] For two different ketones, similar considerations do apply in addition to the unfavorable equilibrium mentioned above,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

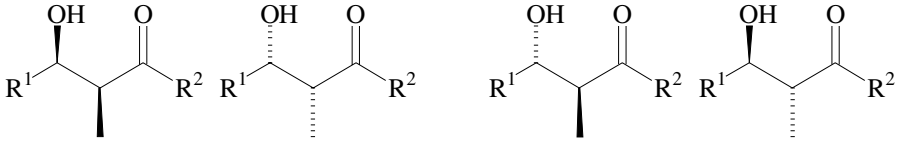


By using the directed aldol reaction, unsymmetrical ketones can be made to react regioselectively. After conversion into an appropriate enol derivative (e.g. trimethylsilyl enol ether **8**) the ketone reacts at the desired α-carbon.



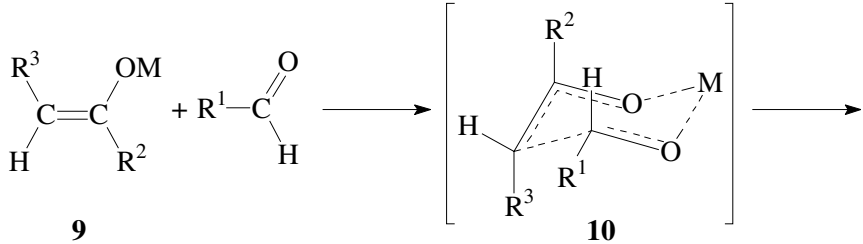


An important aspect is the control of the stereochemical outcome.[5–7] During the course of the reaction two new chiral centers can be created and thus two diastereomeric pairs of enantiomers (*syn/anti* resp. *erythro/threo* pairs) may be obtained.

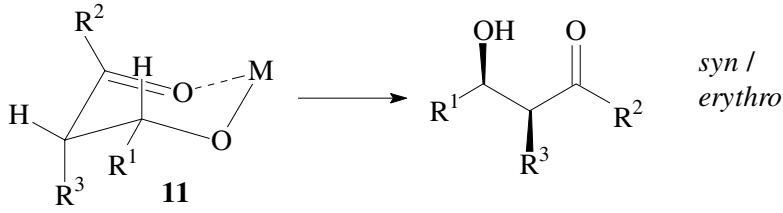


syn / erythro *anti / threo*

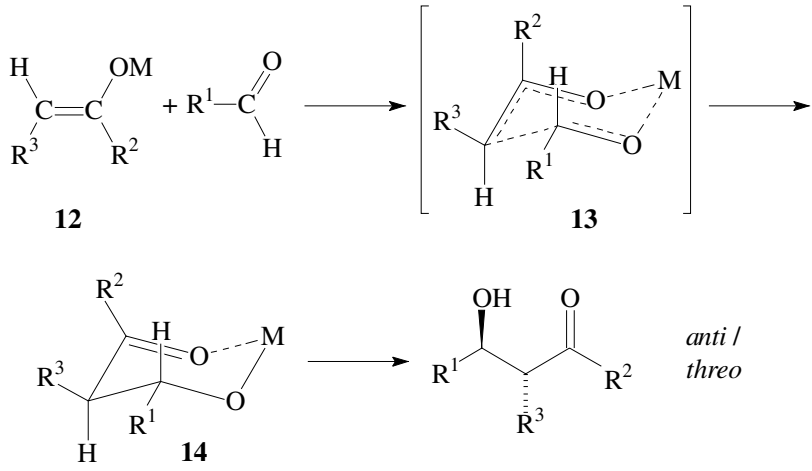
The enantiomers are obtained as a racemic mixture if no asymmetric induction becomes effective. The ratio of diastereomers depends on structural features of the reactants as well as the reaction conditions as outlined in the following. By using properly substituted preformed enolates, the diastereoselectivity 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:



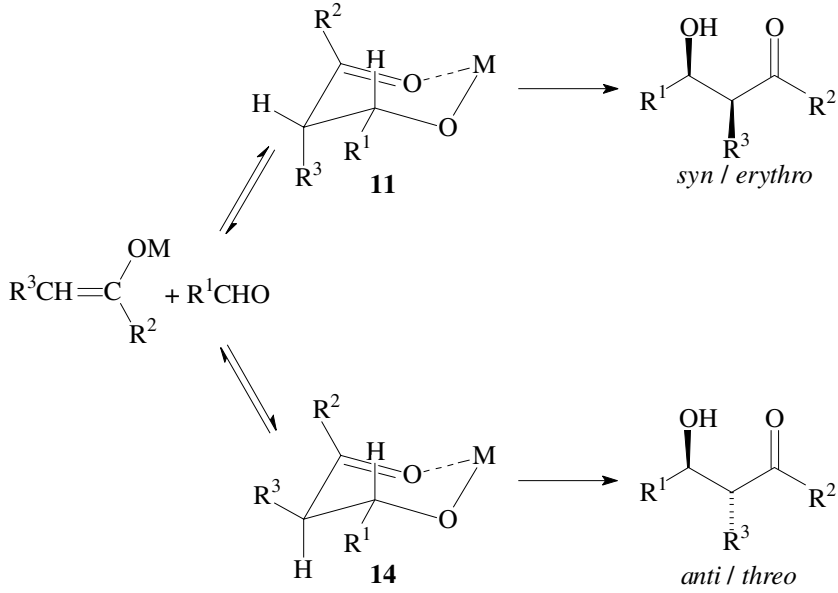
9 **10**



11 *syn / erythro*

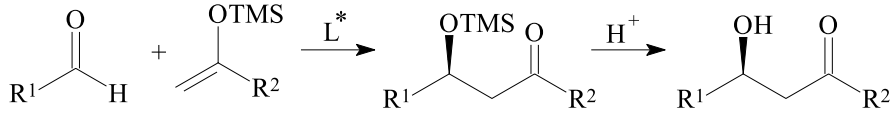


Under conditions which allow for equilibration (thermodynamic control) however, the *anti*-product is obtained, since the metal-chelate **14** is the more stable. As compared to **11** it has more substituents in the favorable equatorial position:



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]



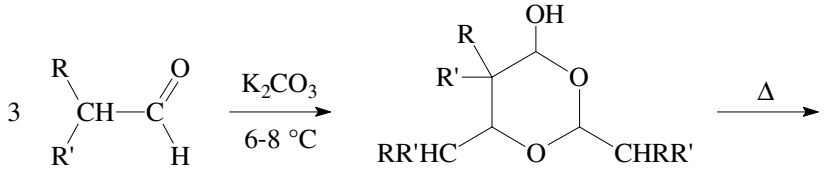
8

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.

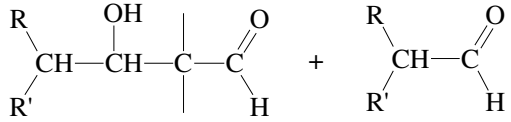
Especially with the ordinary aldol reaction a number of side reactions can be observed, as a result of the high reactivity of starting materials and products. For instance, the α,β-unsaturated carbonyl compounds **4** can undergo further aldol reactions by reacting as vinylogous components. In addition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

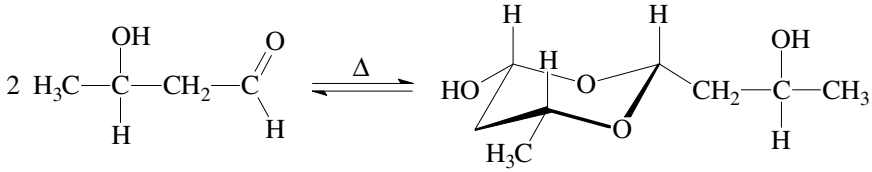


15



3 **1**

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



16 **17**

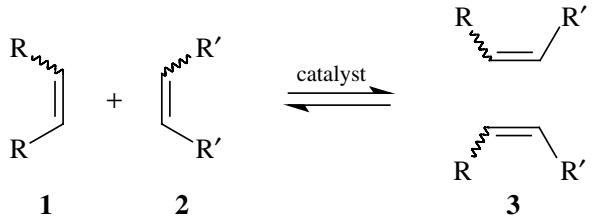
Because of the many possible reactions of aldols, it is generally recommended to use a freshly distilled product for further synthetic steps.

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.
7. C. H. Heathcock in *Modern Synthetic Methods 1992* (Ed.: R. Scheffold), VHCA, Basel, **1992**, p. 1–102.
8. D. Enders, R. W. Hoffmann, *Chem. Unserer Zeit* **1985**, *19*, 177–190.
9. U. Koert, *Nachr. Chem. Techn. Lab.* **1995**, *43*, 1068–1074.
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.

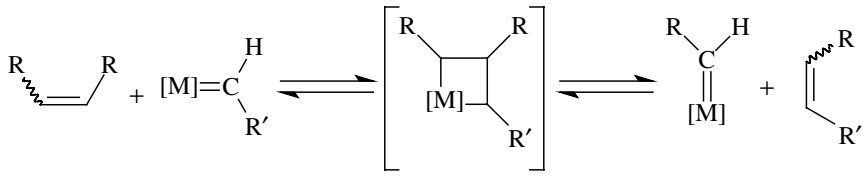
Alkene Metathesis

Exchange of alkylidene groups of alkenes—metathesis of olefins



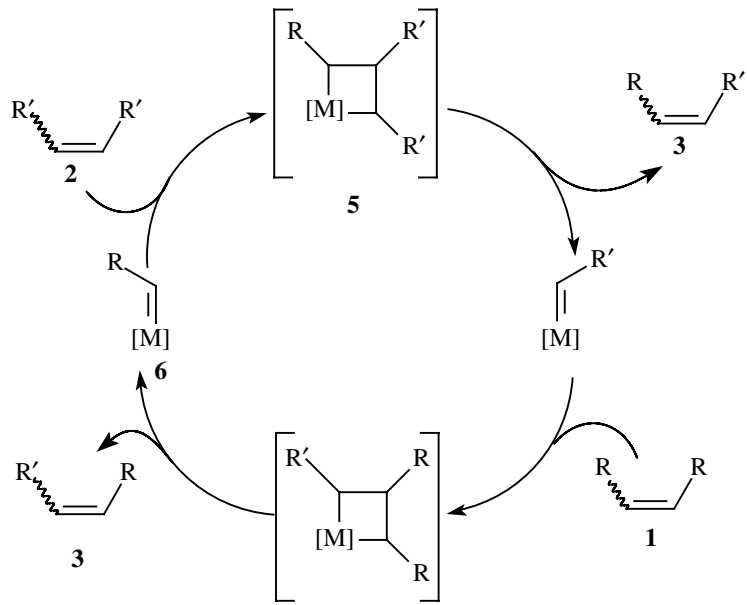
When a mixture of alkenes **1** and **2** or an unsymmetrically substituted alkene **3** is treated with an appropriate transition-metal catalyst, a mixture of products (including *E*/*Z*-isomers) from apparent interchange of alkylidene moieties is obtained by a process called *alkene metathesis*.[1–5] 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**:

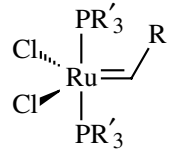


1 **4** **5** **6** **3**

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

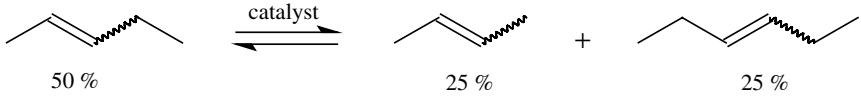


As catalysts, ruthenium- or molybdenum-alkylidene complexes are often employed, e.g. commercially available compounds of type **7**. Various catalysts have been developed for special applications.[2,4]



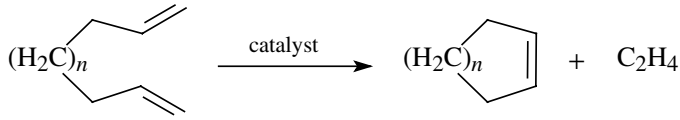
7

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]



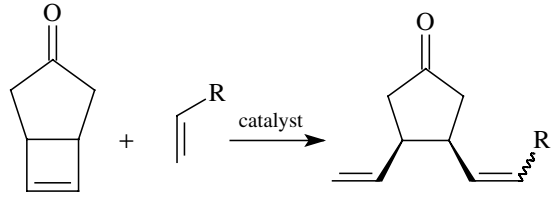
8

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.



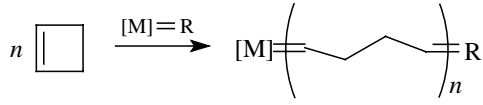
9 **10** **11**

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**:



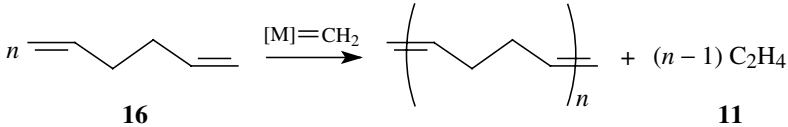
12 **13**

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.



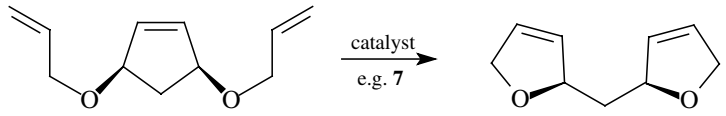
14 **15**

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.

1. R. L. Blanks, C. G. Bailey, *Ind. Eng. Chem. Prod. Res. Dev.* **1964**, *3*, 170–173.
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   N. Calderon, E. A. Ofstead, W. A. Judy, *Angew. Chem.* **1976**, *88*, 433–442; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 401.
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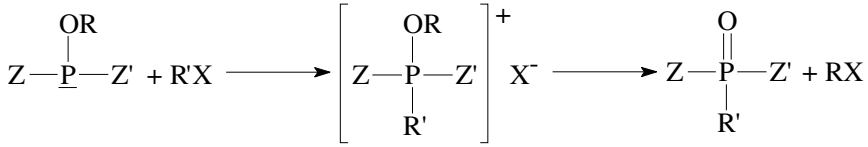
Arbuzov Reaction

Alkyl phosphonates from phosphites

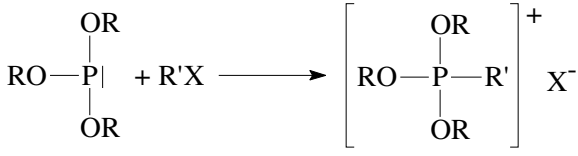


1 **2** **3** **4** **5**

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**.

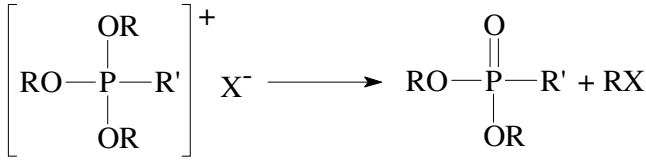
Most common is the preparation of alkyl phosphonic acid esters (phosphonates) **4** (Z,Z′ = OR) from phosphorous acid esters (phosphites) **1** (Z,Z = OR). The preparation of phosphinic acid esters (Z = R, Z′ = OR) from phosphonous acid esters, as well as phosphine oxides (Z,Z′ = R) from phosphinous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

1. A. Michaelis, R. Kaehne, *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 1048–1055.
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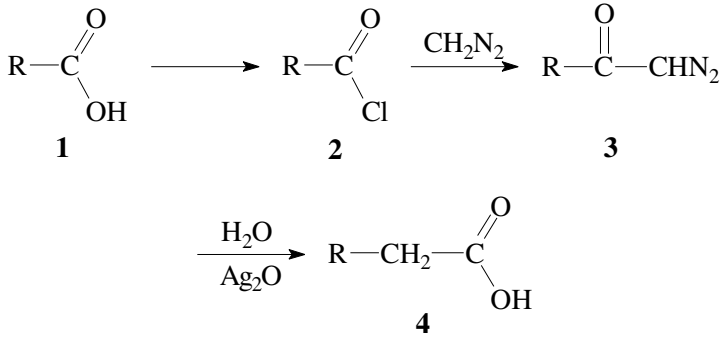
4. H. Pommer, *Angew. Chem.* **1960**, *72*, 811–819 and 911–915.

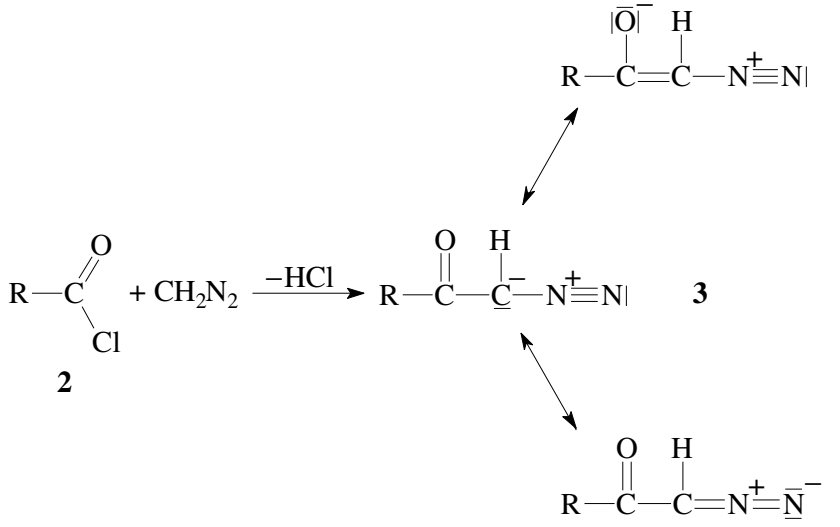
Arndt–Eistert Synthesis

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.

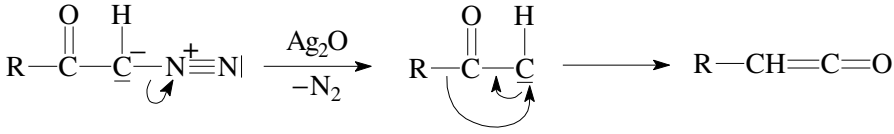
In a first step, the carboxylic acid **1** is converted into the corresponding acyl chloride **2** by treatment with thionyl chloride or phosphorous trichloride. The acyl chloride is then treated with diazomethane to give the diazo ketone **3**, which is stabilized by resonance, and hydrogen chloride:



2 **3**

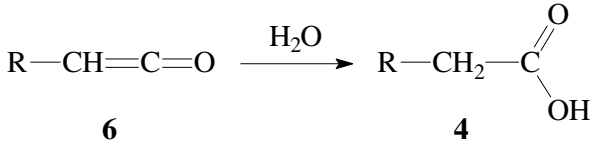
The hydrogen chloride thus produced can in turn react with the diazoketone to yield a α-chloro ketone. In order to avoid this side reaction, two equivalents of diazomethane are used. The second equivalent reacts with HCl to give methyl chloride.[2]

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**:



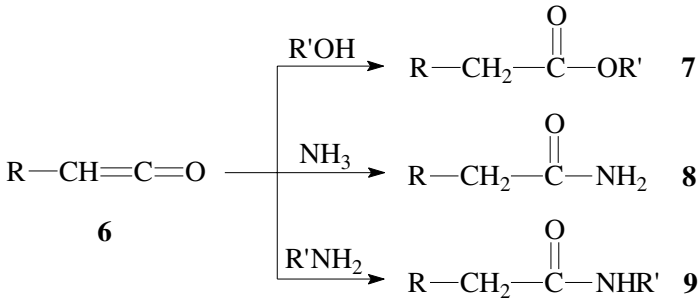
3 **5** **6**

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]

1. F. Arndt, B. Eistert, *Ber. Dtsch. Chem. Ges*. **1935**, *68*, 200–208.
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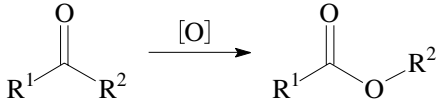
3. T. Hudlicky, J. P. Sheth, *Tetrahedron Lett*. **1979**, *20*, 2667–2670.

B

Baeyer–Villiger Oxidation

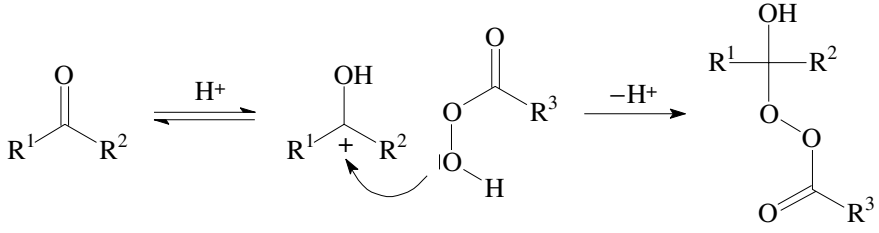
Oxidation of ketones to carboxylic esters



1 **2**

When a ketone **1** is treated with hydrogen peroxyde or a peracid, a formal insertion of oxygen can take place to yield a carboxylic ester **2**. This process is called the *Baeyer–Villiger oxidation*.[1–3]

In a first step the reactivity of the carbonyl group is increased by protonation at the carbonyl oxygen. The peracid then adds to the cationic species **3** leading to the so-called *Criegee intermediate* **4**:



1 **3** **4**

Cleavage of the carboxylic acid R^3COOH from that intermediate leads to an electron-deficient oxygen substituent with an electron sextet configuration. This deficiency can be compensated through migration of the substituent R^1 or R^2; experimental findings suggest that cleavage and migration are a concerted process. The cationic species **5** which can be thus formed (e.g. by migration of R^2), loses a proton to yield the stable carboxylic ester **2**:

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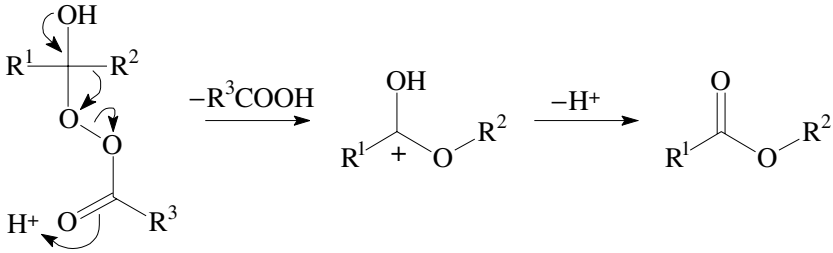
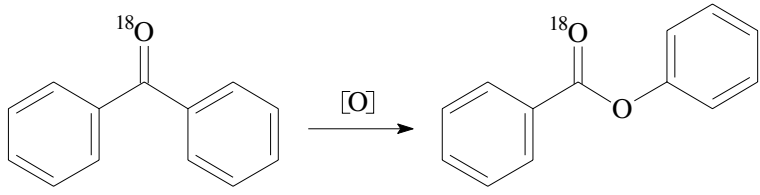


4 **5** **2**

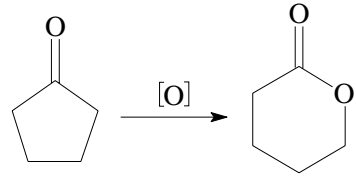
The ease of migration of substituents R^1, R^2 depends on their ability to stabilize a positive charge in the transition state. An approximate order of migration[2] has been drawn: $R_3C > R_2CH > Ar > RCH_2 > CH_3$. Thus the Baeyer–Villiger oxidation of unsymmetrical ketones is regioselective. On the other hand aldehydes usually react with migration of the hydrogen to yield the carboxylic acid.

The reaction mechanism is supported by findings from experiments with ^{18}O-labeled benzophenone **6**; after rearrangement, the labeled oxygen is found in the carbonyl group only:



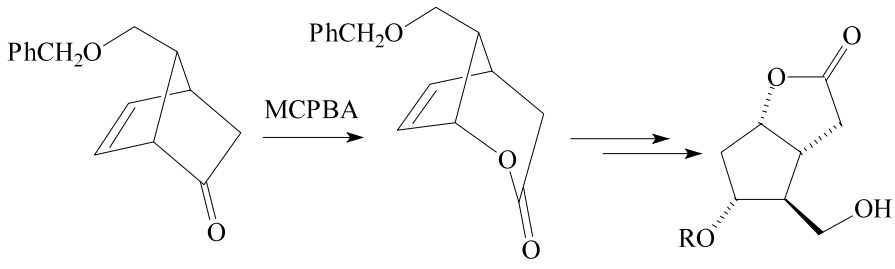
6

Cyclic ketones react through ring expansion to yield lactones (cyclic esters). For example cyclopentanone **7** can be converted to *δ*-valerolactone **8**:



7 **8**

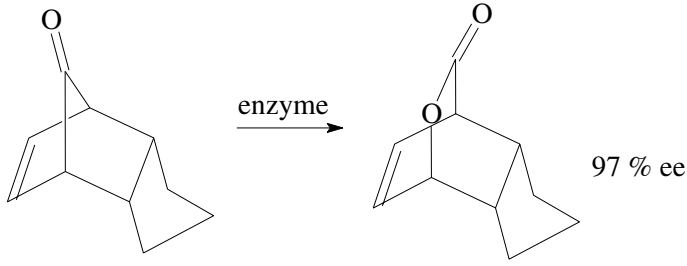
The Baeyer–Villiger oxidation is a synthetically very useful reaction; it is for example often used in the synthesis of natural products. The *Corey lactone* **11** is a key intermediate in the total synthesis of the physiologically active prostaglandins. It can be prepared from the lactone **10**, which in turn is obtained from the bicyclic ketone **9** by reaction with *m*-chloroperbenzoic acid (MCPBA):[4]



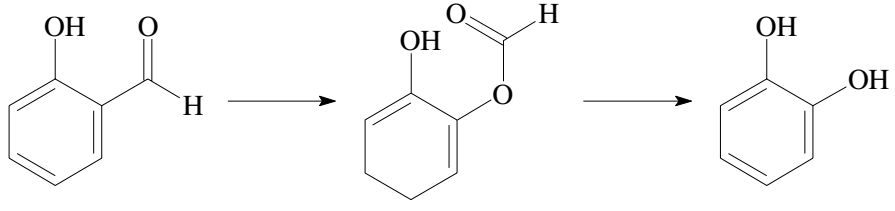
9 **10** **11**

As peracids are used peracetic acid, peroxytrifluoroacetic acid, *m*-chloroperbenzoic acid and others. Hydrogen peroxide or a peracid in combination with trifluoroacetic acid[5] or certain organoselenium compounds[6] have been successfully employed.

Modern variants are the enzyme-catalyzed[7,8] and the transition-metal-catalyzed[9] Baeyer–Villiger reaction, allowing for an oxidation under mild conditions in good yields, with one stereoisomer being formed predominantly in the enzymatic reaction:



The *Dakin reaction*[2,10] proceeds by a mechanism analogous to that of the Baeyer–Villiger reaction. An aromatic aldehyde or ketone that is activated by a hydroxy group in the *ortho* or *para* position, e.g. salicylic aldehyde **12** (2-hydroxybenzaldehyde), reacts with hydroperoxides or alkaline hydrogen peroxide. Upon hydrolysis of the rearrangement product **13** a dihydroxybenzene, e.g. catechol **14**, is obtained:



12 **13** **14**

The electron-donating hydroxy substituent is necessary in order to facilitate the migration of the aryl group; otherwise a substituted benzoic acid would be obtained as reaction product.

1. A. v. Baeyer, V. Villiger, *Ber. Dtsch. Chem. Ges*. **1899**, *32*, 3625–3633.
2. C. H. Hassall, *Org. React*. **1957**, *9*, 73–106;
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4. E. J. Corey, N. M. Weinshenker, T. K. Schaaf, W. Huber, *J. Am. Chem. Soc*. **1969**, *91*, 5675–5677.
5. A. R. Chamberlin, S. S. C. Koch, *Synth. Commun*. **1989**, *19*, 829–833.
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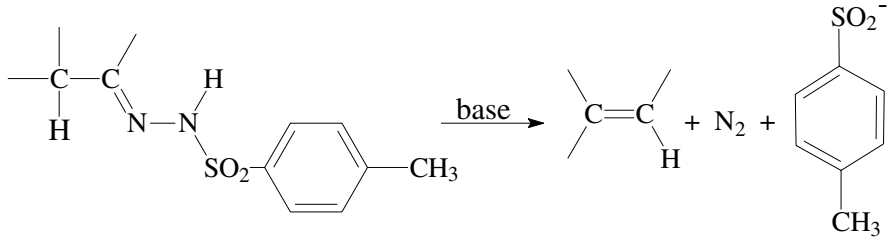
Bamford–Stevens Reaction

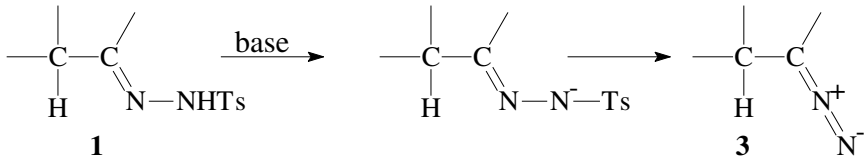
Alkenes from tosylhydrazones



1 **2**

p-Toluenesulfonyl hydrazones **1** (in short tosyl hydrazones) of aliphatic aldehydes or ketones furnish alkenes **2** when treated with a strong base. This reaction is called the *Bamford–Stevens reaction*.[1–3]

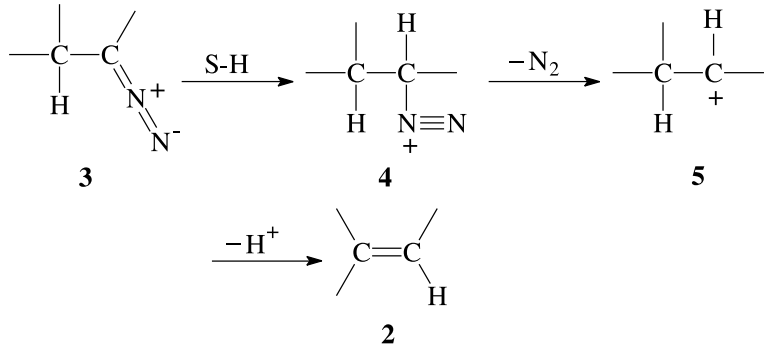
Reaction of tosyl hydrazone **1** with a strong base initially leads to a diazo compound **3**, which in some cases can be isolated:



1 **3**

Depending on the reaction conditions, the further reaction can follow either one of two pathways which lead to different products.

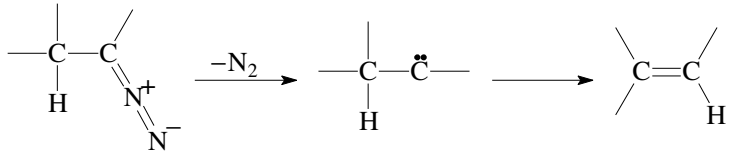
In a protic solvent—glycols are often used, with the base being the corresponding sodium glycolate—the reaction proceeds *via* formation of a carbenium ion **5**. The diazo compound **3** can be converted into the diazonium ion **4** through transfer of a proton from the solvent (S−H). Subsequent loss of nitrogen then leads to the carbenium ion **5**:



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

From **5** the formation of alkene **2** is possible through loss of a proton. However, carbenium ions can easily undergo a *Wagner–Meerwein rearrangement*, and the corresponding rearrangement products may be thus obtained. In case of the Bamford–Stevens reaction under protic conditions, the yield of non-rearranged olefins may be low, which is why this reaction is applied only if other methods (e.g. dehydration of alcohols under acidic conditions) are not practicable.

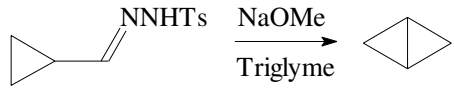
When an aprotic solvent is used, the reaction proceeds *via* an intermediate carbene **6**. In the absence of a proton donor, a diazonium ion cannot be formed and the diazo compound **3** loses nitrogen to give the carbene **6**:



3 **6** **2**

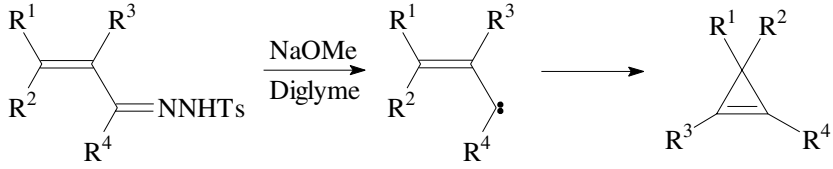
High boiling ethers such as ethylene glycol dimethyl ether or higher homologs are often used as solvents, and a sodium alkoxide is often used as base. The olefin **2** can be formed by migration of hydrogen. Products from insertion reactions typical for carbenes may be obtained. The 1,2-hydrogen shift generally is the faster process, which is why the aprotic Bamford–Stevens reaction often gives high yields of the desired alkene. Consequently numerous examples have been reported.

A special case is the reaction of the tosylhydrazone **7** of cyclopropane carbaldehyde. It conveniently gives access to bicyclobutane[4] **8**:



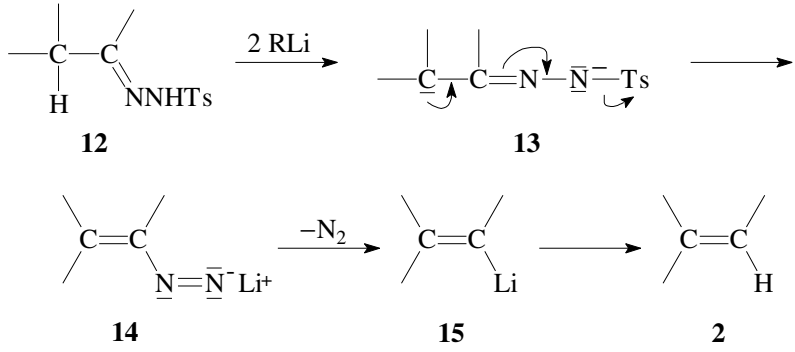
7 **8**

Tosylhydrazones **9** derived from α,β-unsaturated ketones can react *via* vinylcarbenes **10** to yield cyclopropenes[5] **11**:



9 **10** **11**

A more promising procedure for the formation of alkenes from tosylhydrazones is represented by the *Shapiro reaction*.[3,6] It differs from the Bamford–Stevens reaction by the use of an organolithium compound (e.g. methyl lithium) as a strongly basic reagent:



12 **13**

14 **15** **2**

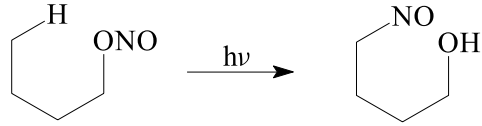
The reaction mechanism has been confirmed by trapping of intermediates **13**, **14** and **15**. Because of the fact that neither a carbene nor a carbenium ion species is involved, generally good yields of non-rearranged alkenes **2** are obtained. Together with the easy preparation and use of tosylhydrazones, this explains well the importance of the Shapiro reaction as a synthetic method.

1. W. R. Bamford, T. S. Stevens, *J. Chem. Soc*. **1952**, 4735–4740.
2. W. Kirmse, *Carbene Chemistry*, Academic Press, New York, 2nd ed., **1971**, p. 29–34.
3. R. H. Shapiro, *Org. React*. **1976**, *23*, 405–507;
   A. R. Chamberlin, S. H. Bloom, *Org. React*. **1990**, *39*, 1–83.

4. H. M. Frey, I. D. R. Stevens, *Proc. Chem. Soc*. **1964**, 144.
5. U. Misslitz, A. de Meijere, *Methoden Org. Chem. (Houben-Weyl)*, **1990**, *Vol. E19b*, p. 675–680.
6. R. M. Adlington, A. G. M. Barrett, *Acc. Chem. Res*. **1983**, *16*, 55–59.

Barton Reaction

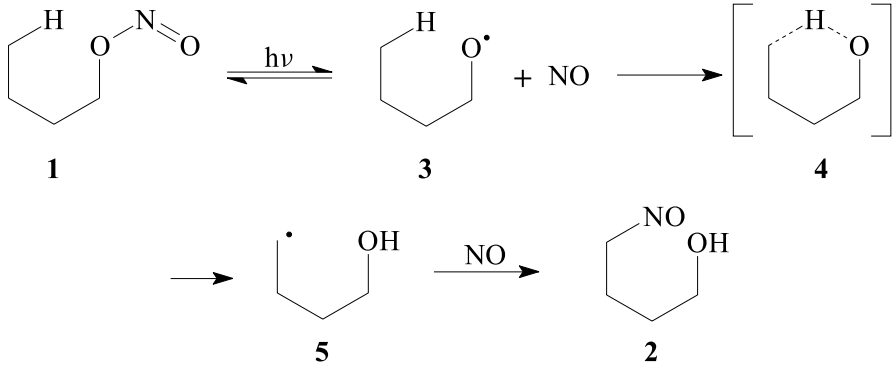
Photolysis of nitrite esters



1 **2**

Nitrous acid esters **1** can be converted to δ-nitroso alcohols **2** by irradiation with ultraviolet light. This conversion is called the *Barton reaction*.[1–3]

Upon the irradiation the nitrous acid ester **1** decomposes to give nitrous oxide (NO) and an alkoxy radical species **3**. The latter further reacts by an intramolecular hydrogen abstraction via a cyclic, six-membered transition state **4** to give an intermediate carbon radical species **5**, which then reacts with the nitrous oxide to yield the δ-nitroso alcohol **2**:

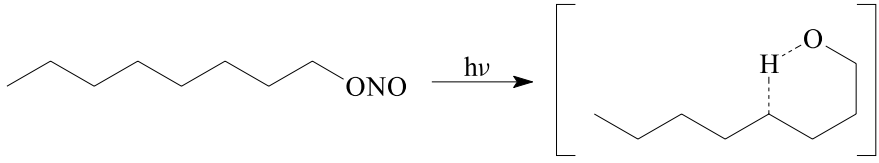


1 **3** **4**

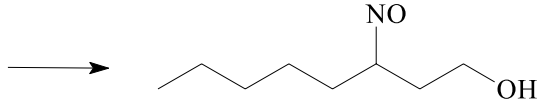
5 **2**

There is quite some evidence for a mechanism as formulated above,[2,3] especially for the six-membered transition state—the Barton reaction is observed only with starting materials of appropriate structure and geometry, while the photolysis of nitrite esters in general seldom leads to useful products formed by fragmentation, disproportionation or unselective intermolecular hydrogen abstraction.

The photolysis of 1-octyl nitrite **6** yields 4-nitroso-1-octanol **8** in 45% yield, via cyclic transition state **7**—the formation of regioisomeric nitroso alcohols is not observed:



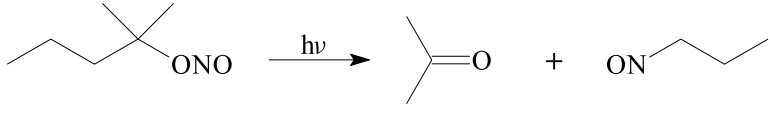
6 **7**



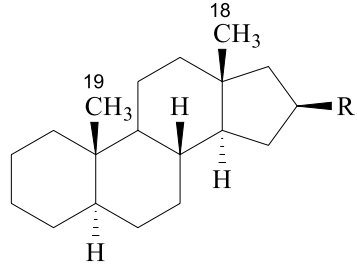
8

With a radical-scavenging compound present in the reaction mixture, an alkyl radical species like **5** can be trapped, thus suggesting a fast conversion of the alkoxy radical **3** by intramolecular hydrogen abstraction, followed by a slow intermolecular reaction with nitrous oxide.

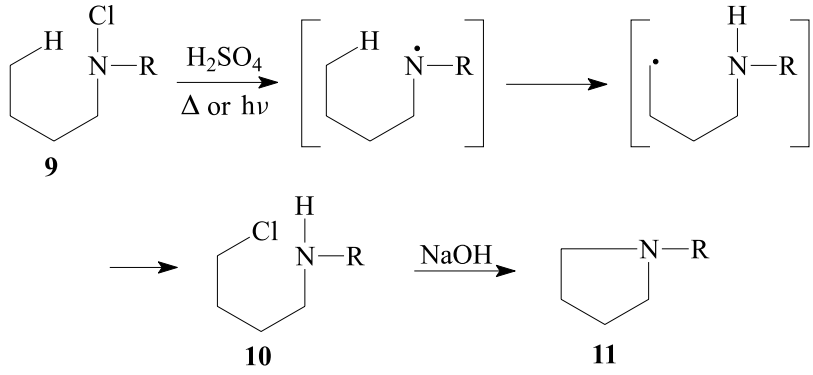
The Barton reaction is usually carried out by irradiation of a nitrite ester **1** dissolved in a hydroxyl-free solvent under nitrogen atmosphere. Possible side-reactions can be decomposition reactions and intermolecular reactions; sometimes the disproportionation may even predominate:



The required nitrite esters **1** can easily be obtained by reaction of an appropriate alcohol with nitrosyl chloride (NOCl). The δ-nitroso alcohols **2** formed by the Barton reaction are useful intermediates for further synthetic transformations, and might for example be converted into carbonyl compounds or amines. The most important application for the Barton reaction is its use for the transformation of a non-activated C−H group into a functional group. This has for example been applied for the functionalisation of the non-activated methyl groups C-18 and C-19 in the synthesis of certain steroids.[2]



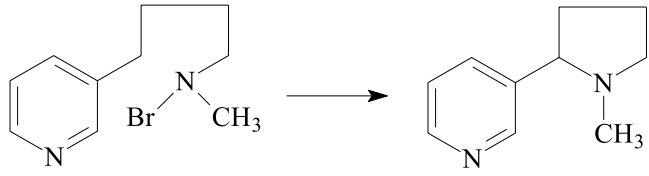
The so-called *Hofmann–Loeffler–Freytag* reaction[4–8] of *N*-chloroamines **9** proceeds by a similar mechanism, and is for example used for the synthesis of pyrrolidines **11**:



Upon heating or irradiation with uv-light of a solution of an *N*-chloroamine **9** in strong acid (concentrated sulfuric acid or trifluoroacetic acid) a *δ*-chloroamine **10** is formed, which however is usually not isolated, but rather reacts during workup with aqueous sodium hydroxide to yield a pyrrolidine **11**. A radical mechanism is presumed, since the transformation of the *N*-chloroamine does not take place in the dark and not at room temperature, but rather requires light, heat or the presence of Fe-(II) ions, while on the other hand the presence of oxygen inhibits the reaction. The highly specific hydrogen abstraction from the *δ*-carbon further suggests an intramolecular reaction via a cyclic, six-membered transition state. A mechanism as formulated above is supported by the fact, that in certain cases the intermediate *δ*-chloroamines **10** can be isolated.

The required *N*-chloroamines **9** can be prepared from the corresponding amine by treatment with sodium hypochlorite or *N*-chlorosuccinimide.

The *Hofmann–Loeffler–Freytag* reaction has been described with *N*-chloro- as well as *N*-bromoamines—the former however usually give better yields. *N*-chlorinated primary amines react well in the presence of Fe-(II) ions. Just like the Barton reaction, the Hofmann–Loeffler–Freytag reaction has been applied mainly in steroid chemistry. An interesting example from alkaloid chemistry is the synthesis of nicotine **12** by Loeffler:[6]



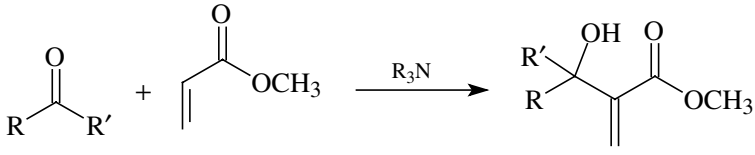
12

Many synthetically useful reactions are based on the presence of double or triple bonds, a good leaving group or a C−H bond that is activated by an adjacent functional group; radical reactions often are unselective and give products from side-reactions. In contrast the Barton reaction as well as the Hofmann–Loeffler–Freytag reaction and related intramolecular radical reactions are well suited for the introduction of a functional group by reaction with a specific, non-activated carbon–hydrogen bond.

1. D. H. R. Barton, J. M. Beaton, L. E. Geller, M. M. Pechet, *J. Am. Chem. Soc.* **1960**, *82*, 2640–2641.
2. D. H. R. Barton, *Pure Appl. Chem.* **1968**, *16*, 1–15.
3. H. I. Hansen, J. Kehler, *Synthesis* **1999**, 1925–1930.
4. W. Carruthers, *Some Modern Methods of Organic Synthesis*, Cambridge University Press, Cambridge, **1986**, p. 263–279.
5. A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558–560.
6. K. Loeffler, C. Freytag, *Ber. Dtsch. Chem. Ges.* **1909**, *42*, 3427–3431.
7. M. E. Wolff, *Chem. Rev.* **1963**, *63*, 55–64.
8. L. Stella, *Angew. Chem.* **1983**, *95*, 368–380; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 337.

Baylis–Hillman Reaction

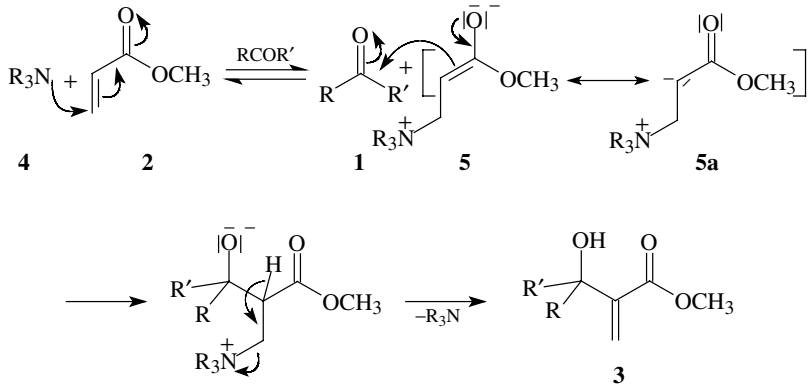
Hydroxyalkylation of activated alkenes



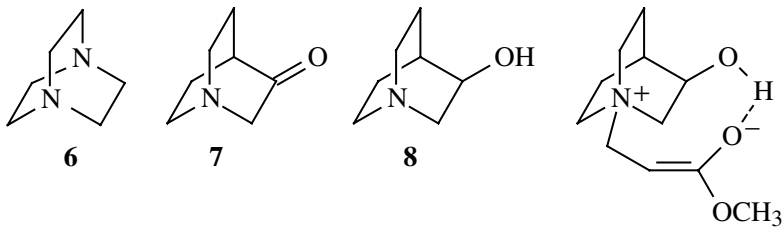
1 **2** **3**

An alkene activated by an electron-withdrawing group—often an acrylic ester **2** is used—can react with an aldehyde or ketone **1** in the presence of catalytic amounts of a tertiary amine, to yield an α-hydroxyalkylated product. This reaction, known as the *Baylis–Hillman reaction*,[1–3] leads to the formation of useful multifunctional products, e.g. α-methylene-β-hydroxy carbonyl compounds **3** with a chiral carbon center and various options for consecutive reactions.

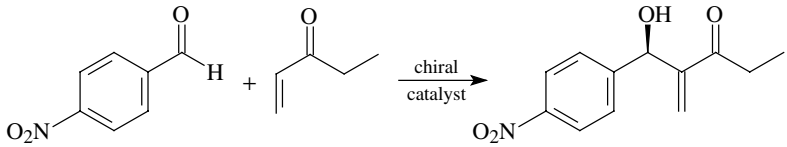
The reaction starts with the nucleophilic addition of a tertiary amine **4** to the alkene **2** bearing an electron-withdrawing group. The zwitterionic intermediate **5** thus formed, has an activated carbon center α to the carbonyl group, as represented by the resonance structure **5a**. The activated α-carbon acts as a nucleophilic center in a reaction with the electrophilic carbonyl carbon of the aldehyde or ketone **1**:[3]



Together with a shift of the proton from the α-carbon to the alkoxide oxygen, the tertiary amine is eliminated from the addition product to yield the unsaturated product **3**. Early examples of the Baylis–Hillman reaction posed the problem of low conversions and slow reaction kinetics, which could not be improved with the use of simple tertiary amines. The search for catalytically active substances led to more properly adjusted, often highly specific compounds, with shorter reaction times.[4] Suitable catalysts are, for example, the nucleophilic, sterically less hindered bases diazabicyclo[2.2.2]octane (DABCO) **6**, quinuclidin-3-one **7** and quinuclidin-3-ol (3-QDL) **8**. The latter compound can stabilize the zwitterionic intermediate through hydrogen bonding.[5]

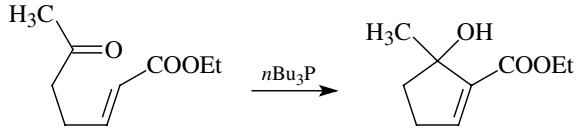


Apart from tertiary amines, the reaction may be catalyzed by phosphines, e.g. tri-*n*-butylphosphine[1] or by diethylaluminium iodide.[4] When a chiral catalyst, such as quinuclidin-3-ol **8** is used in enantiomerically enriched form, an asymmetric Baylis–Hillman reaction is possible. In the reaction of ethyl vinyl ketone with an aromatic aldehyde in the presence of one enantiomer of a chiral 3-(hydroxybenzyl)-pyrrolizidine as base, the coupling product has been obtained in enantiomeric excess of up to 70%, e.g. **11** from **9** + **10**:[5]



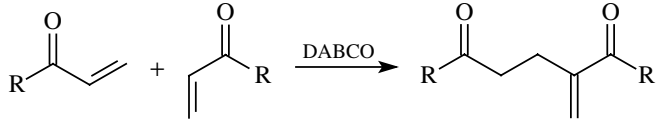
9 **10** **11**

An intramolecular variant of the Baylis–Hillman reaction is also possible, and may be used for the construction of functionalized ring systems, e.g. a cyclopentene derivative such as **12**. However, good yields have been achieved in only a few cases:[1]



12

The Baylis–Hillman reaction is usually carried out under mild conditions (0 °C or room temperature). The reaction time varies from a few minutes to even days. With the proper catalyst, good yields are possible. In the absence of an aldehyde or ketone as the electrophilic component, a dimerization of the activated alkene can take place under the influence of the catalyst, as also observed as a side reaction under the usual reaction conditions:[1]



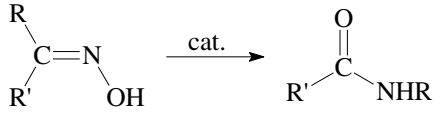
Apart from the acrylates discussed above, various other types of acceptor-substituted alkenes can serve as substrates. As electron-withdrawing substituents, aldehyde, keto or nitrile groups, as well as sulfur- and phosphor-based substituents such as $-SOPh$, $-SO_2Ph$ and $-PO(OEt)_2$, have found application. As the electrophilic component **1**, some substrates containing appropriately substituted nitrogen instead of the carbonyl oxygen (e.g. $=N-COOR$, $=N-SO_2Ph$ and =N-*p*-Tosyl) have been used successfully. Because of the large variety of possible starting materials and the many possible subsequent reactions, the Baylis–Hillman reaction has become an important method for the construction of carbon–carbon bonds.[3]

1. D. Basavaiah, P. D. Rao, R. S. Hyma, *Tetrahedron* **1996**, *52*, 8001–8062.
2. E. Ciganek, *Org. React.* **1997**, *51*, 201–350.

3. D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811–891.
4. W. Pei, H.-X. Wie, G. Li, *Chem. Commun.* **2002**, 2412–2413.
5. A. G. M. Barrett, A. S. Cook, A. Kamimura, *J. Chem. Soc., Chem. Commun.* **1998**, 2533–2534.
P. Langer, *Angew. Chem.* **2000**, *112*, 3177–3180; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3049.

Beckmann Rearrangement

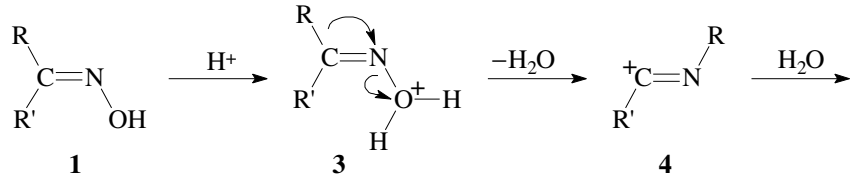
Rearrangement of oximes to give *N*-substituted carboxylic amides



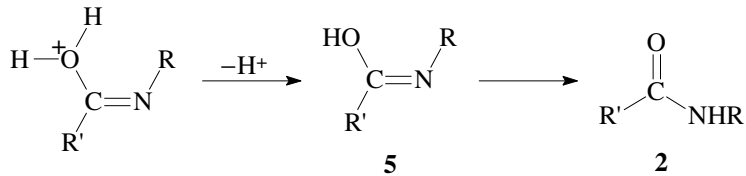
1 **2**

The rearrangement of oximes **1** under the influence of acidic reagents to yield *N*-substituted carboxylic amides **2**, is called the *Beckmann rearrangement*.[1,2] The reaction is usually applied to ketoximes; aldoximes often are less reactive.

Upon treatment with a protic acid, the hydroxy group of the oxime **1** initially is protonated to give an oxonium derivative **3** which can easily lose a water molecule. The migration of the substituent R (together with the bonding electrons) and loss of water proceed simultaneously:[3]



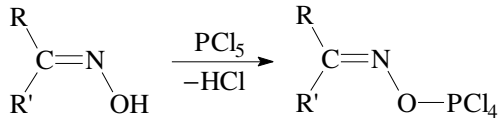
1 **3** **4**



5 **2**

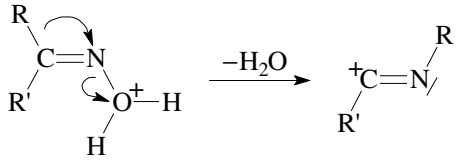
The cationic species **4** thus formed reacts with water to give the iminol **5**, which tautomerizes to a more stable amide tautomer, the *N*-substituted carboxylic amide **2**. Those steps correspond to the formation of amides by the *Schmidt reaction*. A side reaction can give rise to the formation of nitriles.

As reagents concentrated sulfuric acid, hydrochloric acid, liquid sulfur dioxide, thionyl chloride, phosphorus pentachloride, zinc oxide[4] and even silica gel[5] can be used. Reagents like phosphorus pentachloride (as well as thionyl chloride and others) first convert the hydroxy group of the oxime **1** into a good leaving group:



1

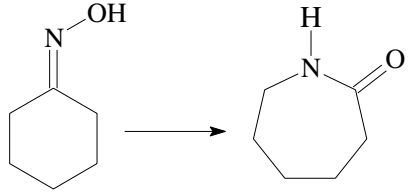
The stereochemical course of the Beckmann rearrangement often allows for the prediction of the reaction product to be obtained; in general the substituent R *anti* to either the hydroxy or the leaving group will migrate:



In some cases a mixture of the two possible amides may be obtained. This has been rationalized to be a result of partial isomerization of the oxime under the reaction conditions, prior to rearrangement.

With aldoximes (R = H) a migration of hydrogen is seldom found. The Beckmann rearrangement therefore does not give access to *N*-unsubstituted amides.

The reaction with oximes of cyclic ketones leads to formation of lactams (e.g. **6** → **7**) by ring enlargement:



6 **7**

This particular reaction is performed on an industrial scale; ε-caprolactam **7** is used as monomer for polymerization to a polyamide for the production of synthetic fibers.

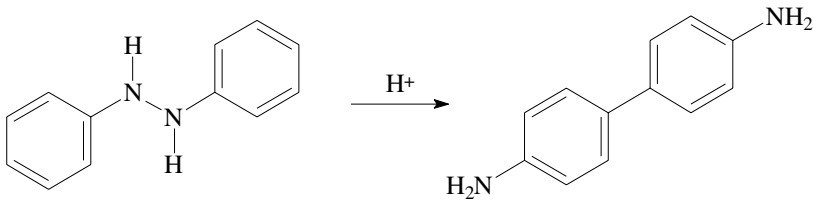
Substituents R, R′ at the starting oxime **1** can be H, alkyl, or aryl.[2,3] The reaction conditions for the Beckmann rearrangement often are quite drastic (e.g. concentrated sulfuric acid at 120 °C), which generally limits the scope to less sensitive substrates. The required oxime can be easily prepared from the respective aldehyde or ketone and hydroxylamine.

1. E. Beckmann, *Ber. Dtsch. Chem. Ges*. **1886**, *19*, 988–993.
2. L. G. Donaruma, W. Z. Heldt, *Org. React*. **1960**, *11*, 1–156.
   R. E. Gawley, *Org. React*. **1988**, *35*, 1–420.

D. Schinzer, Y. Bo, *Angew. Chem.* **1991**, *103*, 727; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 687. D. Schinzer, E. Langkopf, *Synlett* **1994**, 375.
3. M. I. Vinnik, N. G. Zarakhani, *Russ. Chem. Rev.* **1967**, *36*, 51–64.
4. H. Shargie, M. Hosseini, *Synthesis* **2002**, 1057–1060.
5. A. Costa, R. Mestres, J. M. Riego, *Synth. Commun.* **1982**, *12*, 1003–1006.

Benzidine Rearrangement

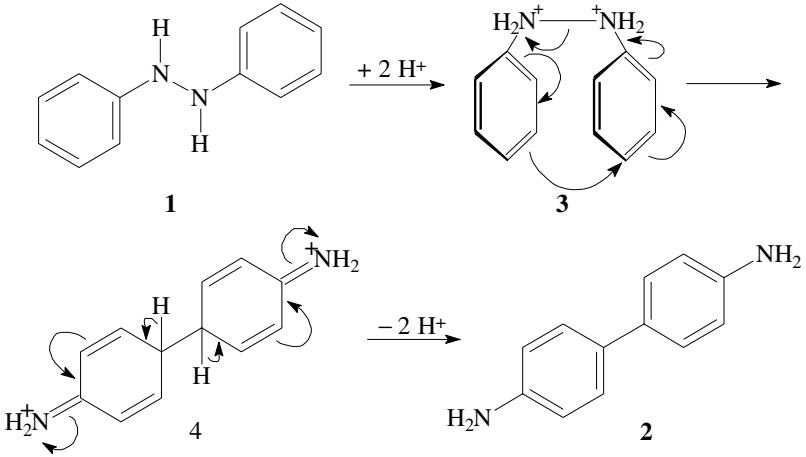
Rearrangement of hydrazobenzene to yield benzidine



1 **2**

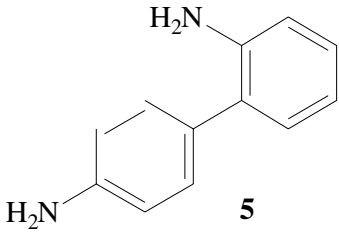
Hydrazobenzene **1** (1,2-diphenyl hydrazine) is converted to benzidine **2** (4,4′-diaminobiphenyl) under acidic conditions.[1,2] This unusual reaction is called the *benzidine rearrangement*,[3,4] and can be observed with substituted diphenyl hydrazines as well.

In accord with the experimental findings a mechanism *via* a [5,5]-sigmatropic rearrangement has been formulated.[5,6] In a first step the hydrazobenzene is protonated to the dicationic species **3**, in which the phenyl groups can arrange in such a way to allow for rearrangement:

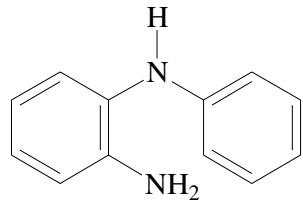


The reaction can be first or second order with respect to the H^+ concentration. In weakly acidic solution it is first order in $[H^+]$, but second order in strongly acidic solution. This indicates that the monoprotonated as well as the diprotonated hydrazobenzene can undergo rearrangement.

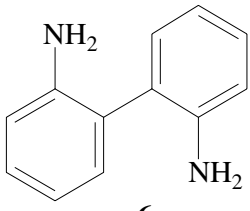
The rearranged dicationic species **4**, which has been shown to be an intermediate,[7] leads to the stable benzidine **2** upon deprotonation. It has been demonstrated by crossover experiments that the rearrangement does not proceed *via* a dissociation/recombination process. From the reaction of hydrazobenzene the benzidine is obtained as the major product (up to 70% yield), together with products from side reactions—2,4′-diaminobiphenyl **5** (up to 30% yield) and small amounts of 2,2′-diaminobiphenyl **6** as well as *o*- and *p*-semidine **7** and **8**:



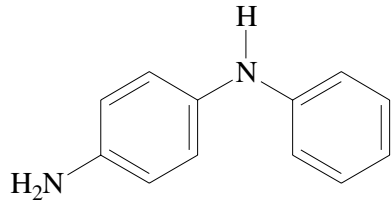
5



7



6



8

The rearrangement takes place in the presence of strong mineral acids (e.g. hydrochloric or sulfuric acid) in aqueous solution or water–alcohol mixtures at room temperature; in some cases slight warming may be necessary.[3]

The benzidine rearrangement is of interest for mechanistic considerations. The preparative applicability may be limited because of the many side products, together with low yields. Furthermore benzidine is a carcinogenic compound.[8]

1. N. Zinin, *J. Prakt. Chem.* **1845**, *36*, 93–107.
2. P. Jacobsen, *Justus Liebigs Ann. Chem.* **1922**, *428*, 76–121.
3. F. Möller, *Methoden Org. Chem. (Houben-Weyl)* **1957**, *Vol. 11/1*, p. 839–848.
4. R. A. Cox, E. Buncel in *The Chemistry of the Hydrazo, Azo, and Azoxy Groups* (Ed.: S. Patai), Wiley, New York, **1975**, *Vol. 2*, p. 775–807.
5. H. J. Shine, H. Zmuda, K, H, Kwart, A. G. Horgan, C. Collins, B. E. Maxwell, *J. Am. Chem. Soc.* **1981**, *103*, 955–956.
6. H. J. Shine, H. Zmuda, K, H, Kwart, A. G. Horgan, M. Brechbiel, *J. Am. Chem. Soc.* **1982**, *104*, 2501–2509.
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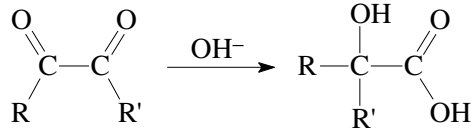
8. Deutsche Forschungsgemeinschaft, *Maximale Arbeitsplatzkonzentration und biologische Arbeitsstofftoleranzwerte*, VCH, Weinheim, **1981**, p. 21.

Benzilic Acid Rearrangement

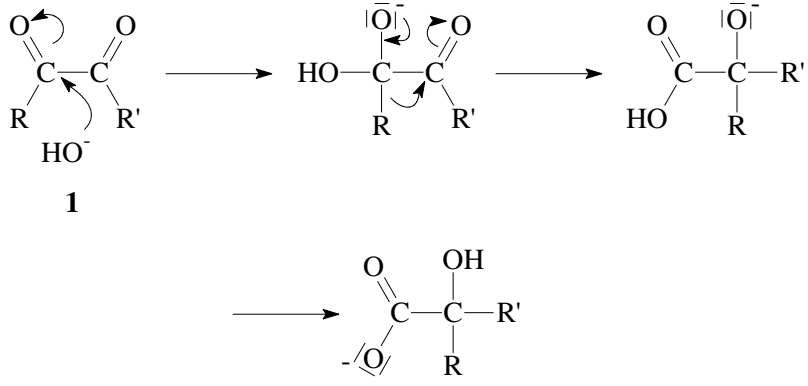
Rearrangement of 1,2-diketones to give α-hydroxy carboxylic acids



1 **2**

1,2-Diketones **1** can be converted into the salt of an α-hydroxy carboxylic acid upon treatment with alkali hydroxide;[1–3] after acidic workup the free α-hydroxy carboxylic acid **2** is obtained. A well-known example is the rearrangement of benzil (R, R′ = phenyl) into benzilic acid (2-hydroxy-2,2-diphenyl acetic acid). The substituents should not bear hydrogens α to the carbonyl group, in order to avoid competitive reactions, e.g. the *aldol reaction*.

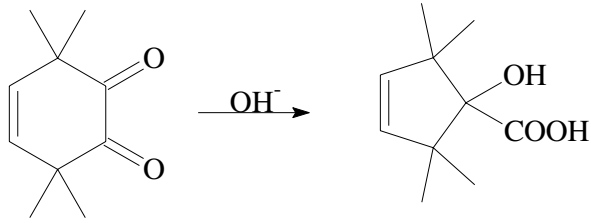
The reaction is induced by nucleophilic addition of the hydroxide anion to one of the two carbonyl groups. Then the respective substituent R migrates with the bonding electrons to the adjacent carbon atom (a 1,2-shift). Electron excess at that center is avoided by release of a pair of π-electrons from the carbonyl group to the oxygen:



1 **3**

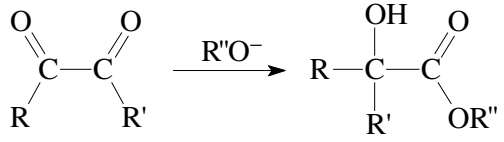
Finally a proton transfer leads to formation of carboxylate anion **3**. Of particular interest is the benzilic acid rearrangement of cyclic diketones such as **4**, since it

leads to a ring contraction:[4]



4

A variant is represented by the *benzilic ester rearrangement*,[2,3] where an alkoxide is used as nucleophile. The alkoxide should not be sensitive towards oxidation. The reaction product is the corresponding benzilic acid ester **5**:



1 **5**

Substrates can be 1,2-diketones with aryl groups as well as some aliphatic substituents, cyclic and heterocyclic diketones. However the benzilic acid rearrangement is of limited preparative importance.

1. N. Zinin, *Justus Liebigs Ann. Chem.* **1839**, *31*, 329–332.
2. S. Selman, J. F. Eastham, *Q. Rev. Chem. Soc.* **1960**, *14*, 221–235.
3. C. J. Collins, J. F. Eastham in *The Chemistry of the Carbonyl Group* (Ed.: S. Patai), Wiley, New York, **1966**, p. 783–787.
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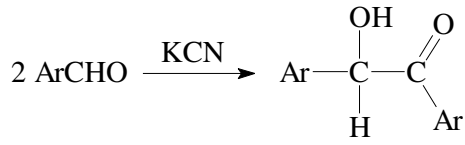
Benzoin Condensation

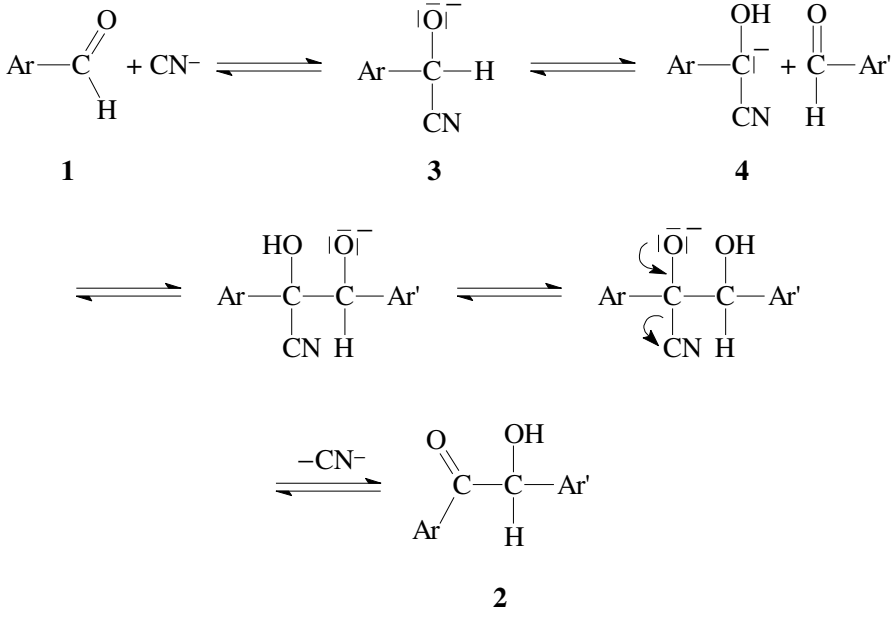
Benzoins from aromatic aldehydes



1 **2**

Aromatic aldehydes **1** can undergo a condensation reaction to form α-hydroxy ketones **2** (also called *benzoins*) upon treatment with cyanide anions.[1,2] This reaction, which is called *benzoin condensation*, works by that particular procedure with certain aromatic aldehydes and with glyoxals (RCOCHO).

A cyanide anion as a nucleophile adds to an aldehyde molecule **1**, leading to the anionic species **3**. The acidity of the aldehydic proton is increased by the adjacent cyano group; therefore the tautomeric carbanion species **4** can be formed and then add to another aldehyde molecule. In subsequent steps the product molecule becomes stabilized through loss of the cyanide ion, thus yielding the benzoin **2**:



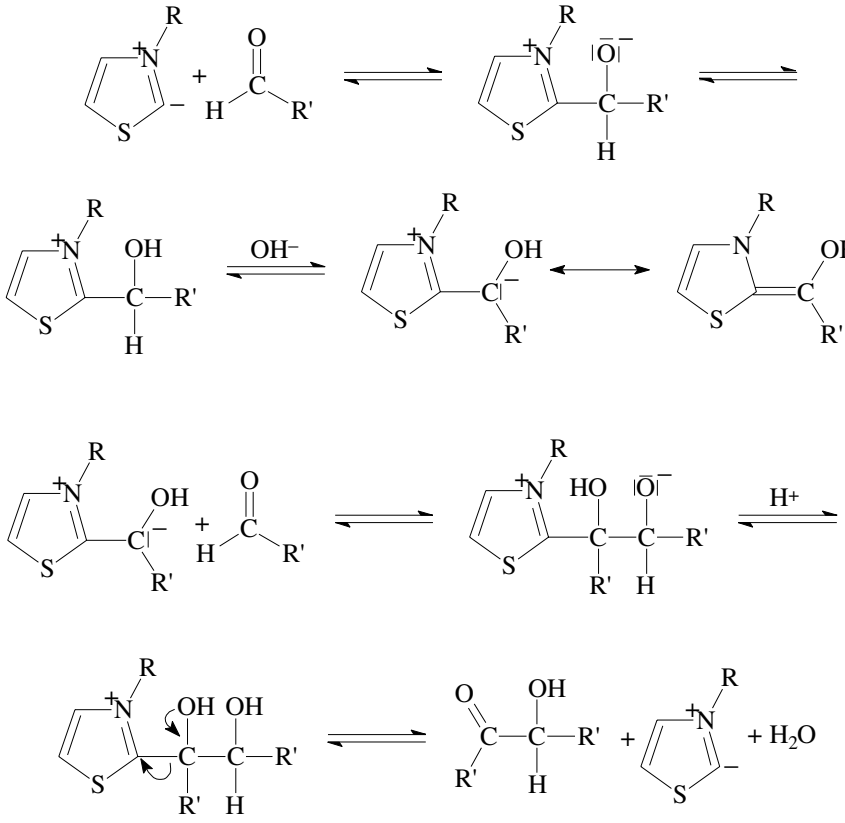
1 **3** **4**

2

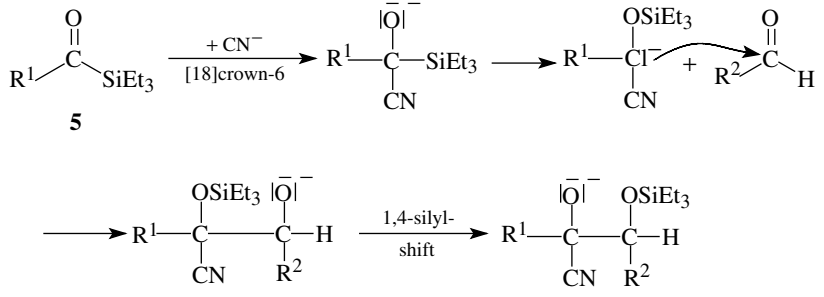
One aldehyde molecule has transferred its aldehyde hydrogen during course of the reaction onto another aldehyde molecule, which is why the reactants are called donor and acceptor (see below).

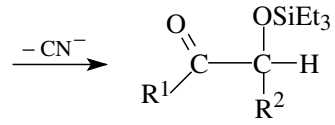
The cyanide ion plays an important role in this reaction, for it has three functions: in addition to being a good nucleophile, its electron-withdrawing effect allows for the formation of the carbanion species by proton transfer, and it is a good leaving group. These features make the cyanide ion a specific catalyst for the benzoin condensation.

The reaction can also be catalyzed by certain thiazolium ylides[3], in which case it also works with aliphatic substrates. For this modified procedure the following mechanism has been formulated:



In a *cross-coupling benzoin condensation* of two different aldehydes, usually a mixture of products is obtained, with the ratio being determined by the relative stabilities of the four possible coupling products under thermodynamic control. If, however, an acyl silane, e.g. **5**, is used as the donor component, the α-silyloxyketone **6** is obtained as a single product:[4]





6

Highly selective cross-coupling benzoin condensations have been achieved via the use of enzymatic methods.[5]

1. H. Staudinger, *Ber. Dtsch. Chem. Ges*. **1913**, *46*, 3535–3538.
2. W. S. Ide, J. S. Buck, *Org. React*. **1948**, *4*, 269–304;
   H. Stetter, H. Kuhlmann, *Org. React*. **1991**, *40*, 407–496.
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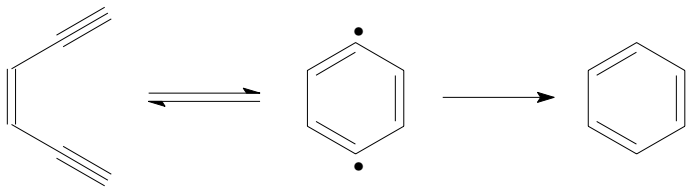
Bergman Cyclization

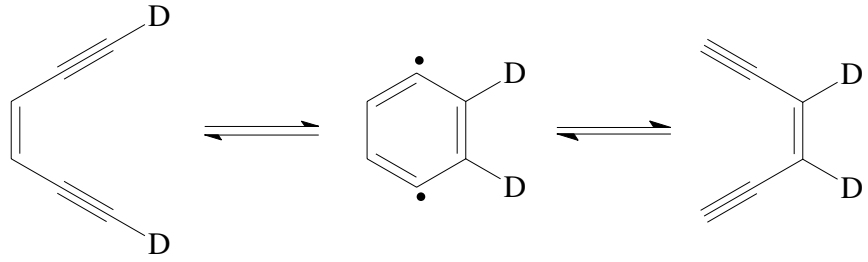
Cyclization of enediynes



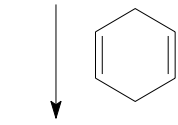
1 **2** **3**

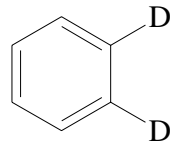
The cycloaromatization of enediynes, having a structure like **1**, proceeds *via* formation of a benzenoid 1,4-diradical **2**, and is commonly called the *Bergman cyclization*.[1,2] It is a relatively recent reaction that has gained importance especially during the last decade. The unusual structural element of enediynes as **1** has been found in natural products (such as calicheamicine and esperamicine)[3] which show a remarkable biological activity.[4,5]

Upon heating the enediyne **1a** rearranges reversibly to the 1,4-benzenediyl diradical **2a**, which in its turn can rearrange to the enediyne **1b** or—in the presence of a hydrogen donor (e.g. cyclohexa-1,4-diene)—react to the aromatic compound[2,8,9] **3a**.



1a **2a** **1b**



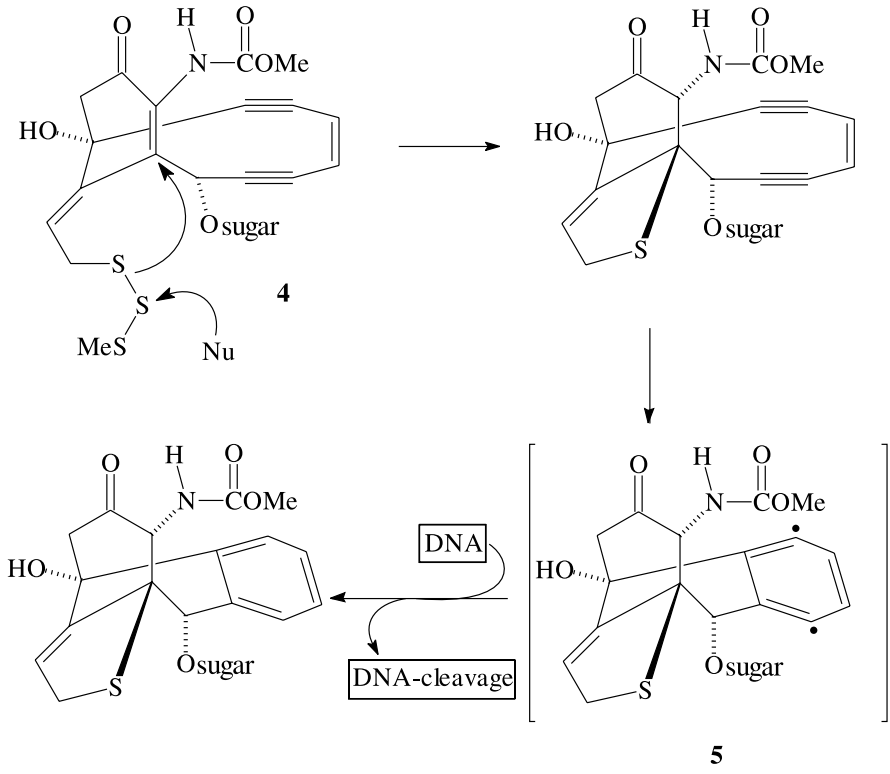


3a

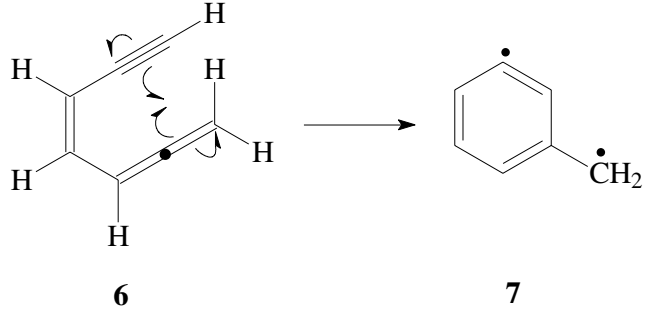
Of great importance for the Bergman cyclization is the distance between the triple bonds. The reaction cannot occur at moderate temperatures if the distance is too large. Optimal reactivity at physiological temperatures is obtained by fitting the enediyne element into a ten-membered ring.[4]

The biological activity of *calicheamicin* **4** (simplified structure) is based on the ability to damage DNA. At the reaction site, initially the distance between the triple bonds is diminished by an addition reaction of a sulfur nucleophile to the enone carbon–carbon double bond, whereupon the Bergman cyclization takes place leading to the benzenoid diradical **5**, which is capable of cleaving double-stranded DNA.[4,5]

Myers has discovered[6,7] a related reaction of the natural product *neocarzinostatine* **8** (simplified structure). As in the case of the Bergman cyclization a diradical intermediate is generated by a chemical activation step taking place at the reaction site, where it then can cleave DNA. Because of this feature, together with its discriminating affinity towards different DNA strands, neocarzinostatine is regarded as a potential antitumor agent.

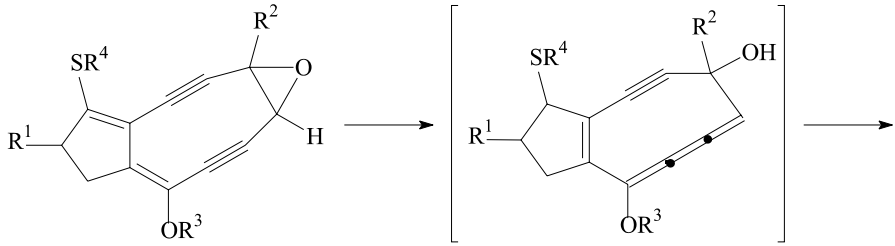


The reactive structural element for the *Myers cyclization* is an enyne allene, the heptatrienyne **6**, which reacts to form a diradical species **7**:

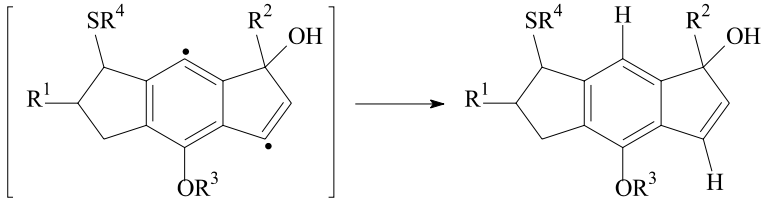


In the initial step, neocarzinostatine **8** (simplified structure) is converted to the cyclization precursor **9**, which contains a cumulated triene unit.[9] The reaction

then proceeds *via* the cyclized diradical species **10**, which abstracts hydrogen from a suitable donor to give **11**.



8 **9**



10 **11**

At present the synthetic importance of both the Bergman cyclization and the Myers reaction remains rather small. However, because of the considerable biological activity[4] of the natural products mentioned above, there is great mechanistic interest in these reactions[8,9] in connection with the mode of action of DNA cleavage.

1. R. G. Bergman, R. R. Jones, *J. Am. Chem. Soc*. **1972**, *94*, 660–661.
2. R. G. Bergman, *Acc. Chem. Res*. **1973**, *6*, 25–31.
3. R. Gleiter, D. Kratz, *Angew. Chem.* **1993**, *105*, 884–887;
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   A. Basak, S. Mandal, S. S. Bag, *Chem. Rev.* **2003**, *103*, 4077–4094.
4. K. C. Nicolaou, W.-M. Dai, *Angew. Chem*. **1991**, *103*, 1453–1481;
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5. K. C. Nicolaou, G. Zuccarello, C. Riemer, V. A. Estevez, W.-M. Dai, *J. Am. Chem. Soc*. **1992**, *114*, 7360–7371.
   K. C. Nicolaou, *Angew. Chem*. **1993**, *105*, 1462–1471; *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 1377.
   S. A. Hitchcock, S. H. Boyer, M. Y. Chu-Moyer, S. H. Olson, S. J. Danishefsky, *Angew. Chem. 1994*, *106*, 928–931; *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 858.
6. A. G. Myers, P. J. Proteau, T. M. Handel, *J. Am. Chem. Soc*. **1988**, *110*, 7212–7214.

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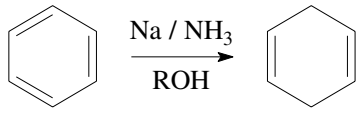
8. M. E. Maier, *Synlett* **1995**, 13–26.
   H. Lhermitte, D. S. Grierson, *Contemp. Org. Synth*. **1996**, *3*, 41–64.
9. The chemistry of enediynes, enyne allenes and related compounds:
   J. W. Grissom, G. U. Gunawardena, D. Klingberg, D. Huang, *Tetrahedron* **1996**, *52*, 6453–6518.

Birch Reduction

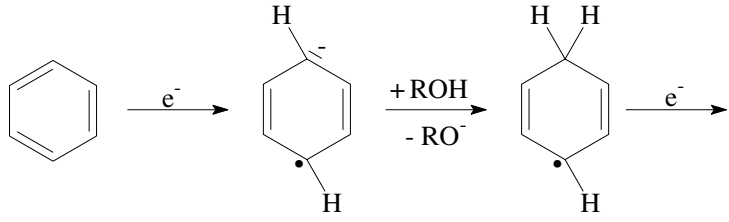
Partial reduction of aromatic compounds



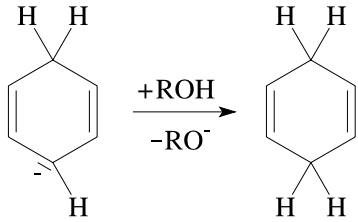
1 **2**

The reduction of aromatic compounds **1** by alkali metals in liquid ammonia in the presence of an alcohol is called the *Birch reduction*, and yields selectively the 1,4-hydrogenated product[1–3] **2**.

Alkali metals in liquid ammonia can transfer an electron to the solvent, leading to so-called solvated electrons. These can add to the aromatic substrate **1** to give a reduced species, the radical anion **3**:



1 **3** **4**

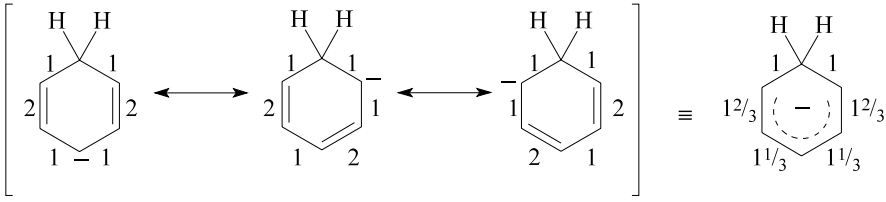


5 **2**

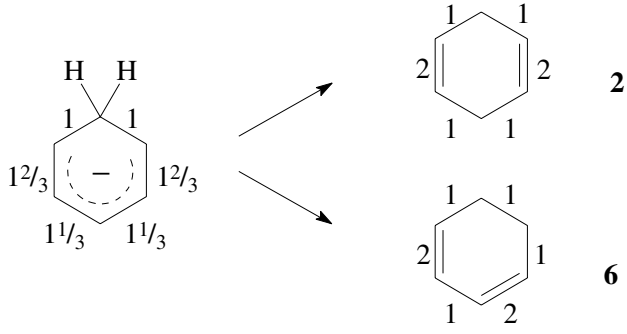
Evidence for the radical anion **3** came from esr spectroscopic experiments, thus supporting this mechanism. The radical anion is protonated by the alcohol to give

the radical species **4**, which is further reduced by a solvated electron to give the carbanion **5**. This anion is protonated by the alcohol leading to the 1,4-dihydro product **2**. Thus the alkali metal serves as a source of electrons, while the alcohol serves as a source of protons.

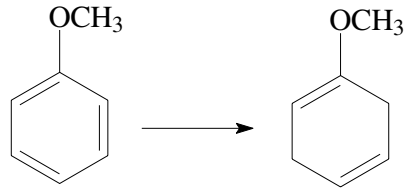
The negative charge of the cyclohexadienyl anion **5** is delocalized over several carbon centers, as is illustrated by the following resonance structures:



At first glance it may be surprising that the 1,4-diene is formed instead of the thermodynamically more stable, conjugated 1,3-diene derivative. An explanation is offered by the *principle of least motion*,[4] which favors those reaction pathways that involve the least change in atomic position and electronic configuration. A description of the bond orders for the carbon–carbon bonds of the carbanionic species **5** and the possible products **2** and **6** by a simplified valence-bond method (1 for a single bond, 2 for a double bond), shows the smaller change when going from **5** to the 1,4-diene **2** ($\Delta = 4/3$) compared to the greater change when going from **5** to the 1,3-diene **2** ($\Delta = 2$).

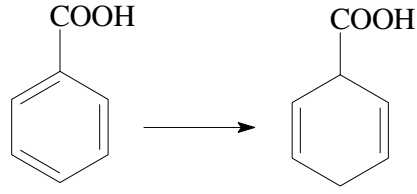


For the Birch reduction of mono-substituted aromatic substrates the substituents generally influence the course of the reduction process.[5] Electron-donating substituents (e.g. alkyl or alkoxyl groups) lead to products with the substituent located at a double bond carbon center. The reduction of methoxybenzene (anisole) **7** yields 1-methoxycyclohexa-1,4-diene **8**:[6]



7 **8**

An electron-withdrawing substituent leads to a product where it is bound to a saturated carbon center. Benzoic acid **9** is reduced to the cyclohexa-2,5-diene carboxylic acid **10**:



9 **10**

The Birch reduction is the method of choice for the partial reduction of aromatic compounds. The catalytic hydrogenation would lead to fully hydrogenated products. Ordinary olefins are not reduced under Birch conditions, while conjugated olefins will react. Halogen substituents, nitro, aldehyde and keto groups can suffer reduction. In some cases the insufficient solubility of the aromatic substrate in liquid ammonia may cause problems, which can be avoided by use of a co-solvent. The yields are generally good or even high. With polycyclic benzenoid substrates mixtures of isomers may be obtained.

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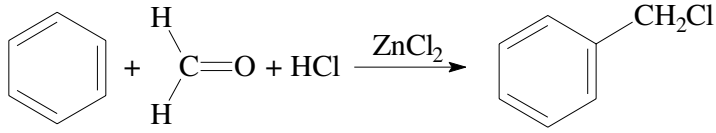
Blanc Reaction

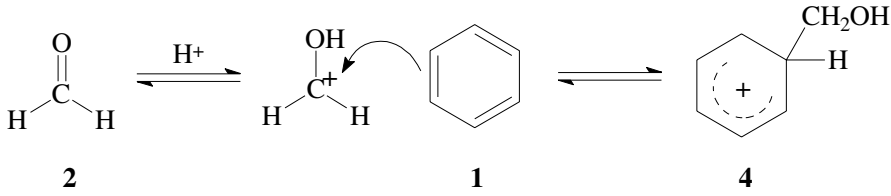
Chloromethylation of aromatic compounds



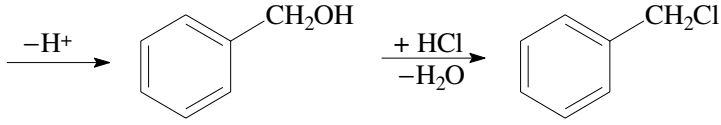
1 **2** **3**

The introduction of a chloromethyl group on aromatic compounds (e.g. benzene **1**) by reaction with formaldehyde **2** and gaseous hydrogen chloride in the presence of a catalyst is called the *Blanc reaction*.[1,2]

In a first reaction step the formaldehyde **2** is protonated, which increases its reactivity for the subsequent electrophilic aromatic substitution at the benzene ring. The cationic species **4** thus formed loses a proton to give the aromatic hydroxymethyl derivative **5**, which further reacts with hydrogen chloride to yield the chloromethylated product[3] **3**:



2 **1** **4**



5 **3**

The rate-determining step is the electrophilic aromatic substitution as in the closely related *Friedel–Crafts reaction*. Both reactions have in common that a Lewis acid catalyst is used. For the Blanc reaction zinc chloride is generally employed,[2] and the formation of the electrophilic species can be formulated as follows:[3]

$$CH_2O + HCl + ZnCl_2 \longrightarrow CH_2OH^+ZnCl_3^-$$

Electron-rich aromatic substrates can react without a catalyst present. Modern variants of the Blanc reaction use chloromethyl ether[4] (e.g. $(ClCH_2)_2O$, $ClCH_2OMe$) or methoxyacetyl chloride,[5] since those reagents are more reactive and give higher yields.

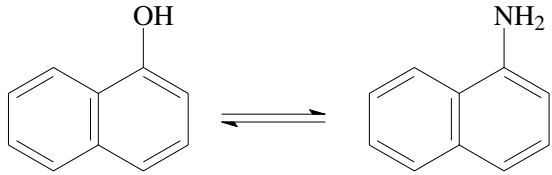
The chloromethylation can be generally employed in aromatic chemistry; benzene, naphthaline, anthracene, phenanthrene, biphenyls and many derivatives thereof are appropriate substrates. The benzylic chlorides thus obtained can be further transformed, for example to aromatic aldehydes. Ketones like benzophenone are not reactive enough. In contrast phenols are so reactive that polymeric products are obtained.[2]

An important side reaction is the formation of diaryl methane derivatives $ArCH_2Ar$. Moreover polysubstituted products may be obtained as minor products. Aromatic compounds have been treated with formaldehyde and hydrogen bromide or hydrogen iodide instead of hydrogen chloride. The formaldehyde may be replaced by another aldehyde; the term 'Blanc reaction' however stands for the chloromethylation only.

1. M. G. Blanc, *Bull. Soc. Chim. Fr*. **1923**, *33*, 313–319.
2. R. C. Fuson, C. H. McKeever, *Org. React*. **1942**, *1*, 63–90.
3. L. I. Belenkii, Yu. B. Volkenshtein, I. B. Karmanova, *Russ. Chem. Rev*. 1977, *46*, 891–903.
4. G. A. Olah, D. A. Beal, J. A. Olah, *J. Org. Chem*. **1976**, *41*, 1627–1631.
5. A. McKilloq, F. A. Madjdabadi, D. A. Long, *Tetrahedron Lett*. **1983**, *24*, 1933–1936.

Bucherer Reaction

Interconversion of naphtholes and naphthylamines

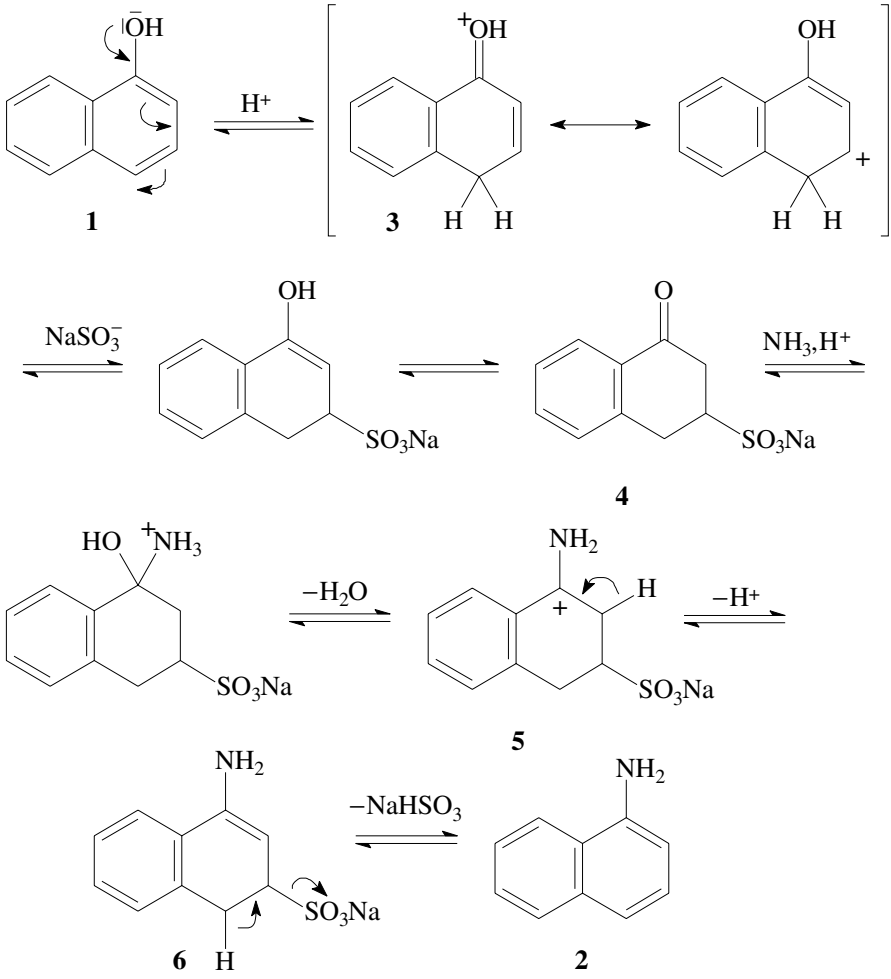


1 **2**

An important reaction in the chemistry of naphthalenes is the *Bucherer reaction*,[1–3] i.e. the conversion of naphthols **1** to naphthylamines **2** as well as the reverse reaction. The reaction is carried out in aqueous medium in the presence of catalytic amounts of a sulfite or bisulfite. Apart from very few exceptions it does not apply to benzene derivatives, which limits the scope of that reaction.

Naphthol **1** is initially protonated at a carbon center of high electron density (C-2 or C-4). The cationic species **3** thus formed is stabilized by resonance; it can add a bisulfite anion at C-3. The addition product can tautomerize to give the more stable tetralone sulfonate **4**; the tetralone carbonyl group is then attacked by a nucleophilic amine (e.g. ammonia). Subsequent dehydration leads to the cation

5 which again is stabilized by resonance. Loss of a proton leads to the enamine **6**, which upon loss of the bisulfite leads to the aromatic naphthylamine[4] **2**:



Every step of the Bucherer reaction is reversible, and the reverse sequence is also of synthetic value. The equilibrium can be shifted by varying the concentration of free ammonia.[3]

As mentioned above, the scope of the Bucherer reaction is limited. It works with anthracenes and phenanthrenes, but only very few examples with substituted benzenes are known. Naphthylamines can be converted into the corresponding naphthols, and these can then be further converted into primary, secondary or tertiary naphthylamines (*transamination*). Naphthylamines are of importance for

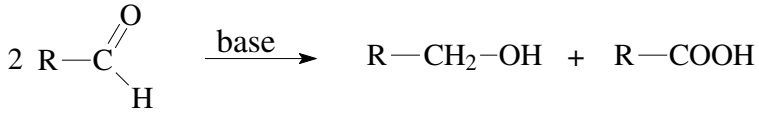
the synthesis of dyes, and derivatives of tetralone sulfonic acid, which are accessible through the Bucherer reaction, are of synthetic value as well.[4]

1. H. T. Bucherer, *J. Prakt. Chem.* **1904**, *69*, 49–91.
2. N. L. Drake, *Org. React.* **1942**, *1*, 105–128.
3. R. Schröter, *Methoden Org. Chem. (Houben-Weyl)* **1957**, *Vol. 11/1*, p. 143–159.
4. H. Seeboth, *Angew. Chem.* **1967**, *79*, 329–340; *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 307.

C

Cannizzaro Reaction

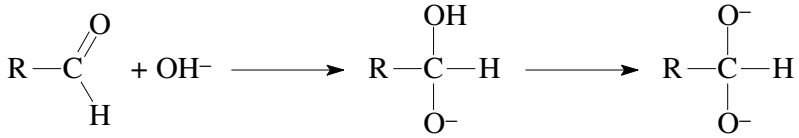
Disproportionation of aldehydes



1 **2** **3**

Aldehydes **1** that have no α-hydrogen give the *Cannizzaro reaction* upon treatment with a strong base, e.g. an alkali hydroxide.[1,2] In this disproportionation reaction one molecule is reduced to the corresponding alcohol **2**, while a second one is oxidized to the carboxylic acid **3**. With aldehydes that do have α-hydrogens, the *aldol reaction* takes place preferentially.

The key step of the Cannizzaro reaction is a hydride transfer. The reaction is initiated by the nucleophilic addition of a hydroxide anion to the carbonyl group of an aldehyde molecule **1** to give the anion **4**. In a strongly basic medium, the anion **4** can be deprotonated to give the dianionic species **5**:



1 **4** **5**

The reaction can proceed from both species **4** or **5** respectively. The strong electron-donating effect of one or even two O^--substituents allows for the transfer of a hydride ion H^- onto another aldehyde molecule:

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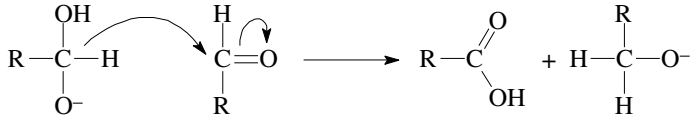
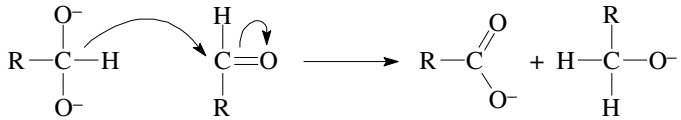


4 **1**

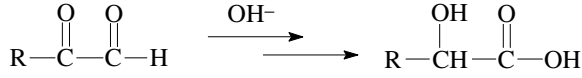


5 **1**

This mechanism is supported by the outcome of experiments with D_2O as solvent. The resulting alcohol **2** does not contain carbon-bonded deuterium, indicating that the transferred hydrogen comes from a second substrate molecule, and not from the solvent.

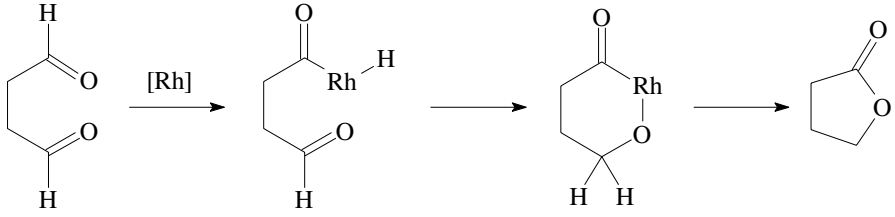
The synthetic importance of the reaction is limited, because as a consequence of the disproportionation, the yield of the alcohol as well as the carboxylic acid is restricted to 50%. However good yields of alcohols can often be obtained when the reaction is carried out in the presence of equimolar amounts of formaldehyde. The formaldehyde is oxidized to formic acid and concomitantly reduces the other aldehyde to the desired alcohol. This variant is called the *crossed Cannizzaro reaction*.

α-Keto aldehydes **6** can be converted to α-hydroxy carboxylic acids **7** by an intramolecular Cannizzaro reaction:



6 **7**

1,4-Dialdehydes **8** have been converted to γ-lactones **9** in the presence of a rhodium phosphine complex as catalyst.[3] The example shown below demonstrates that this reaction works also with aldehydes that contain α-hydrogen atoms.



8 **9**

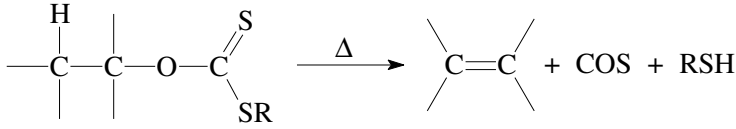
The applicability of the Cannizzaro reaction may be limited, if the substrate aldehyde can undergo other reactions in the strongly basic medium. For instance an α,α,α-trihalo acetaldehyde reacts according to the *haloform reaction*.

Mechanistically closely related is the *benzilic acid rearrangement*, where an alkyl or aryl group migrates instead of the hydrogen.

1. S. Cannizzaro, *Justus Liebigs Ann. Chem.* **1853**, *88*, 129–130.
2. T. A. Geissman, *Org. React.* **1944**, *2*, 94–113.
3. S. H. Bergens, D. P. Fairlie, B. Bosnich, *Organometallics* **1990**, *9*, 566–571.

Chugaev Reaction

Formation of olefins from xanthates



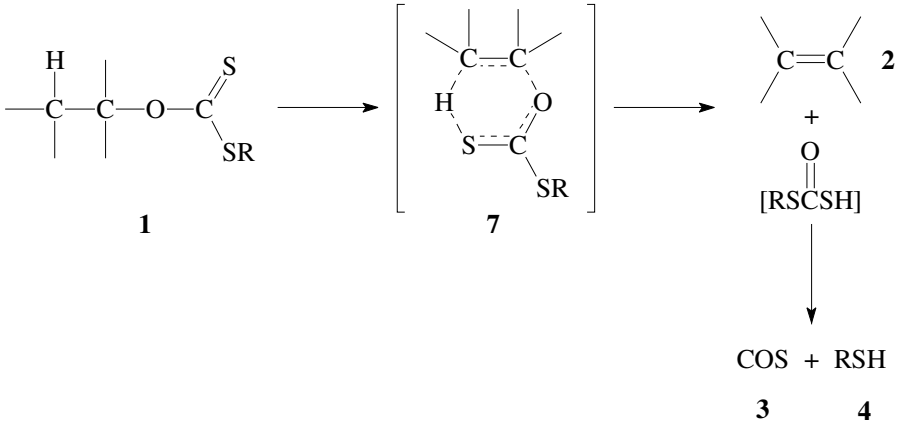
1 **2** **3** **4**

Upon thermolysis of xanthates (xanthogenates) **1** olefins **2** can be obtained, together with gaseous carbon oxysulfide COS **3** and a thiol RSH **4**. This decomposition process is called the *Chugaev reaction*;[1–3] another common transcription for the name of its discoverer is *Tschugaeff*.

The required xanthates **1** can be prepared from alcohols **5** by reaction with carbon disulfide in the presence of sodium hydroxide and subsequent alkylation of the intermediate sodium xanthate **6**. Often methyl iodide is used as the alkylating agent:

5 **6** **1**

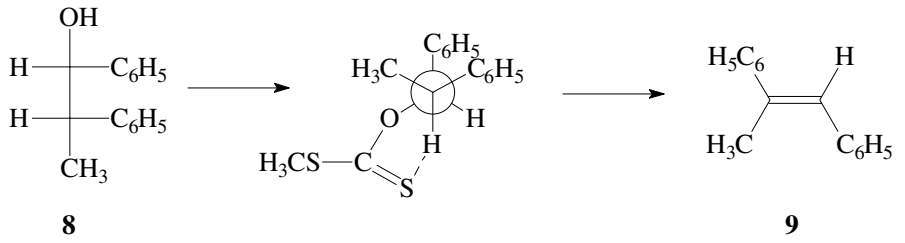
The thermolysis (pyrolysis) is generally carried out at temperatures ranging from 100–250 °C. Similar to the closely related *ester pyrolysis* the reaction mechanism is of the E_i-type, which involves a six-membered cyclic transition state **7**:

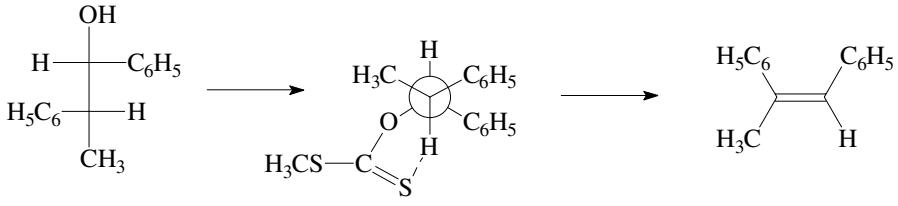


This mechanism of a *syn*-elimination reaction is supported by experimental findings with ^{34}S- and ^{13}C-labeled starting materials.[4] The Chugaev reaction is analogous to the ester pyrolysis, but allows for milder reaction conditions—i.e. it occurs at lower temperatures. It is less prone to side reactions, e.g. the formation of rearranged products, and is therefore the preferred method.

The thermolysis of xanthates derived from primary alcohols yields one olefin only. With xanthates from secondary alcohols (acyclic or alicyclic) regioisomeric products as well as *E*/*Z*-isomers may be obtained; see below. While acyclic substrates may give rise to a mixture of olefins, the formation of products from alicyclic substrates often is determined by the stereochemical requirements; the β-hydrogen and the xanthate moiety must be *syn* to each other in order to eliminate *via* a cyclic transition state.

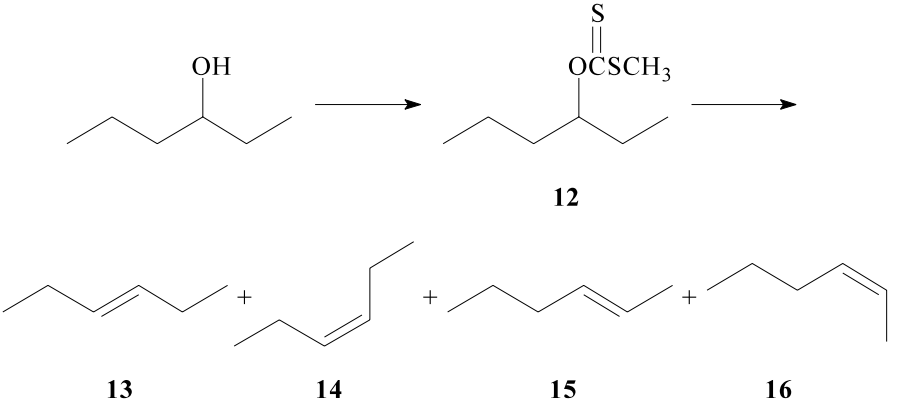
An instructive example on how stereochemical features influence the stereochemical outcome of the elimination is the pyrolysis of xanthates from *erythro*- and *threo*-1,2-diphenyl-1-propanol. The *erythro*-alcohol **8** is converted into *E*-methylstilbene **9** only, and the *threo*-alcohol **10** is converted into the corresponding *Z*-isomer **11** only. These results support the assumption of a *syn*-elimination process through a cyclic transition state:[5]





10 **11**

The Chugaev elimination is of synthetic value, because it proceeds without rearrangement of the carbon skeleton.[2] Other non-thermolytic elimination procedures often lead to rearranged products, when applied to the same substrates. However applicability of the Chugaev reaction is limited if the elimination is possible in more than one direction, and if a β-carbon has more than one hydrogen. Complex mixtures of isomeric olefins may then be obtained. For example the thermolysis of xanthate **12**, derived from 3-hexanol yields 28% *E*-hex-3-ene **13**, 13% *Z*-hex-3-ene **14**, 29% *E*-hex-2-ene **15** and 13% *Z*-hex-2-ene[6] **16**:



12

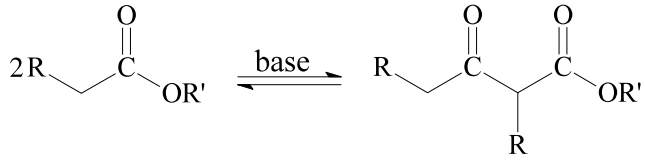
13 **14** **15** **16**

The applicability to alicyclic alcohols may be limited, since the mechanistic course *via* a cyclic transition state requires a suitably positioned hydrogen in order to afford the desired product.

1. L. Tschugaeff, *Ber. Dtsch. Chem. Ges*. **1899**, *32*, 3332–3335.
2. H. R. Nace, *Org. React*. **1962**, *12*, 57–100.
3. C. H. DePuy, R. W. King, *Chem. Rev*. **1960**, *60*, 431–457.
4. R. F. W. Bader, A. N. Bourns, *Can. J. Chem*. **1961**, *39*, 346–358.
5. D. J. Cram, F. A. A. Elhafez, *J. Am. Chem. Soc*. **1952**, *74*, 5828–5835.
6. R. A. Benkeser, J. J. Hazdra, M. L. Burrous, *J. Am. Chem. Soc*. **1959**, *81*, 5374–5379.

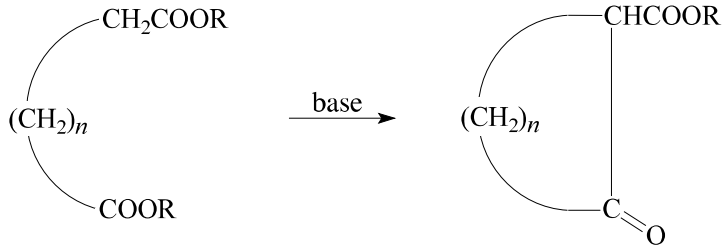
Claisen Ester Condensation

Formation of β-keto esters from carboxylic esters

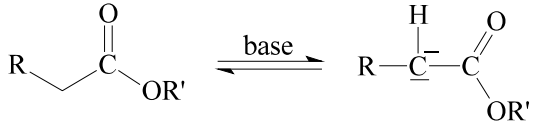


1 **2**

Carboxylic esters **1** that have an α-hydrogen can undergo a condensation reaction upon treatment with a strong base to yield a β-keto ester **2**. This reaction is called the *Claisen ester condensation*[1,2] or *acetoacetic ester condensation*; the corresponding intramolecular reaction is called the *Dieckmann condensation*:[3,4]

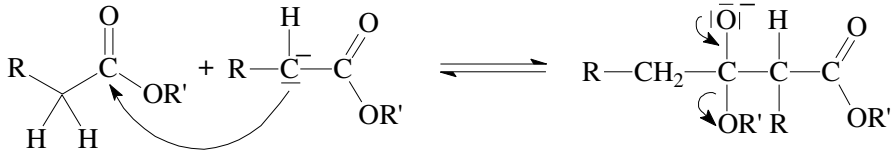


The mechanism involves the formation of anion **3** from ester **1** by reaction with base:

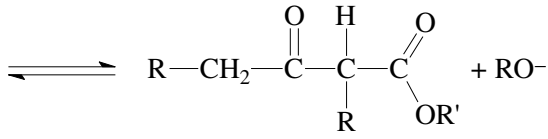


1 **3**

Anion **3** can add to another ester **1**. The resulting anionic species **4** reacts to the stable β-keto ester by loss of an alkoxide anion $R'O^-$ **5**:

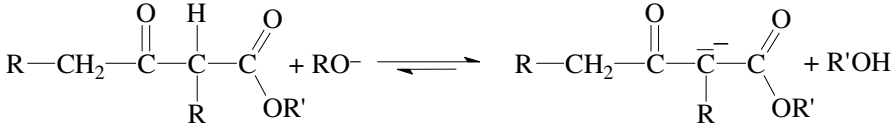


1 **3** **4**



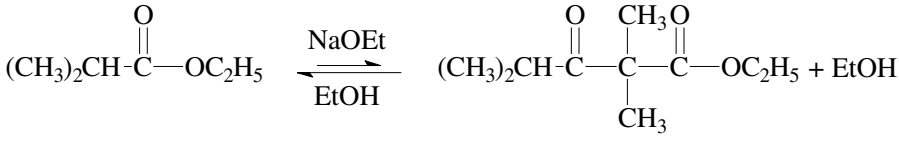
2 **5**

Those steps are reversible reactions, with the equilibrium shifted to the left. However the overall reaction can be carried out in good yield since the β-ketoester **2** is converted into the conjugate base **6** by the lost alkoxide **5**; the ester is more acidic than the alcohol R′OH **7**:



2 **5** **6** **7**

This mechanism is supported by the finding, that esters containing just one α-hydrogen do not undergo that reaction, unless much stronger bases are used, since the condensation product **9** cannot be stabilized under the usual reaction conditions and the equilibrium lies to the left:



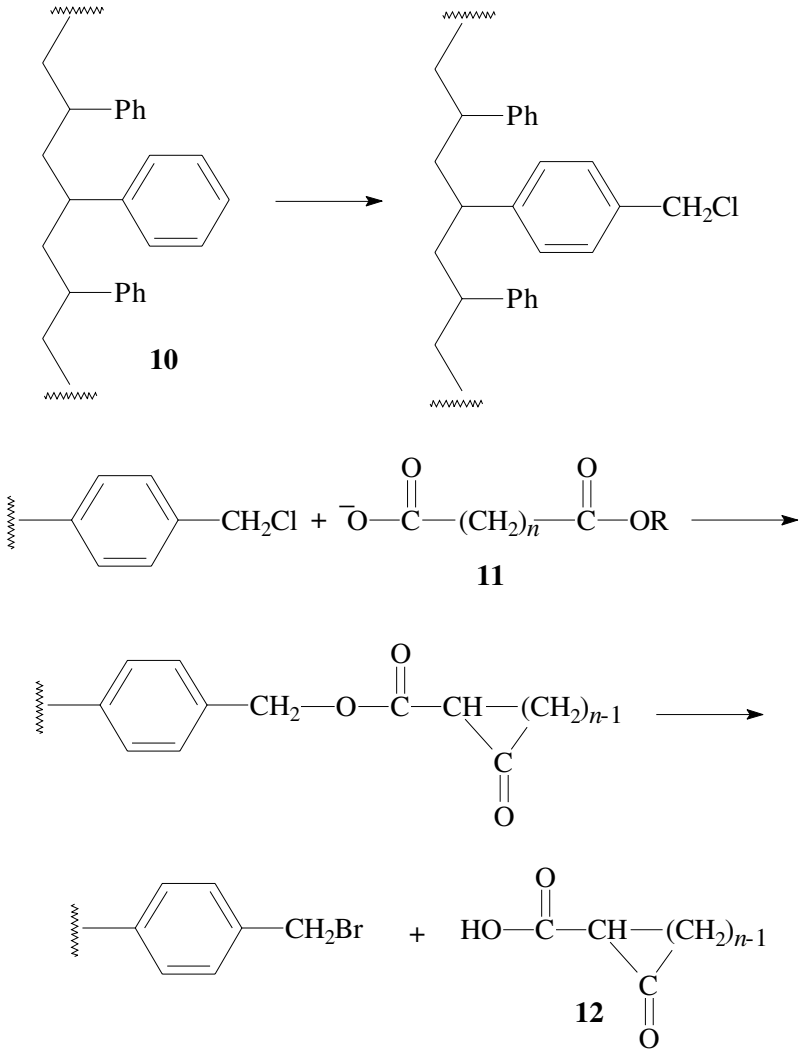
8 **9**

α,α-disubstituted β-ketoesters like **9**, when treated with an alkoxide, can be cleaved into ordinary esters by the reverse of the condensation reaction, the *retro-Claisen reaction*. However the condensation of esters with only one α-hydrogen is possible in moderate yields by using a strong base, e.g lithium diisopropyl amide (LDA).[5]

The most common base used for the Claisen condensation is sodium ethoxide, although for some substrates stronger bases such as sodium amide or sodium hydride may be necessary.

The application to a mixture of two different esters, each with α-hydrogens, is seldom of preparative value, since a mixture of the four possible condensation products will be obtained. If however only one of the starting esters contains α-hydrogens, the *crossed Claisen condensation* often proceeds in moderate to good yields.

The intramolecular condensation reaction of diesters, the *Dieckmann condensation*,[3,4] works best for the formation of 5- to 7-membered rings; larger rings are formed with low yields, and the *acyloin condensation* may then be a faster competitive reaction. With non-symmetric diesters two different products can be formed. The desired product may be obtained regioselectively by a modified procedure using a solid support—e.g with a polystyrene[6] **10**:



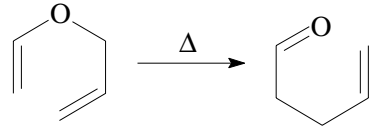
A functional group is introduced to the polystyrene **10** by chloromethylation (*Blanc reaction*) in order to allow for reaction with the substrate **11**. The polymer-bound diester is then treated with base to initiate the Dieckmann condensation.

Finally treatment with HBr leads to cleavage of product **12** from the polymer.

1. L. Claisen, O. Lowman, *Ber. Dtsch. Chem. Ges*. **1887**, *20*, 651–657.
2. C. R. Hauser, B. E. Hudson, *Org. React*. **1942**, *1*, 266–302.
3. W. Dieckmann, *Ber. Dtsch. Chem. Ges*. **1900**, *33*, 2670–2684.
4. J. P. Schaefer, J. J. Bloomfield, *Org. React*. **1967**, *15*, 1–203.
5. M. Hamell, R. Levine, *J. Org. Chem*. **1950**, *15*, 162–168.
6. J. I. Crowley, H. Rapoport, *J. Org. Chem*. **1980**, *45*, 3215–3227.

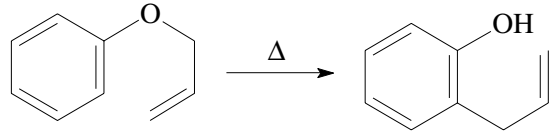
Claisen Rearrangement

Rearrangement of allyl vinyl ethers or allyl aryl ethers



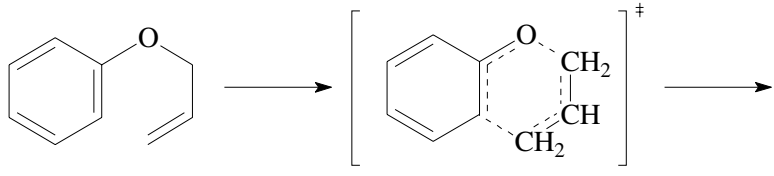
1

The *Claisen rearrangement*[1–3] is a thermal rearrangement of allyl aryl ethers and allyl vinyl ethers respectively. It may be regarded as the *oxa*-version of the closely related *Cope rearrangement*. Claisen has discovered this reaction first on allyl vinyl ethers **1**, and then extended to the rearrangement of allyl aryl ethers[1] **2** to yield *o*-allylphenols **3**:



2 **3**

Mechanistically this reaction is described as a concerted pericyclic [3,3] sigmatropic rearrangement. A carbon–oxygen bond is cleaved and a carbon–carbon bond is formed. In a subsequent step the initial product **4** tautomerizes to the stable aromatic allylphenol **3**:



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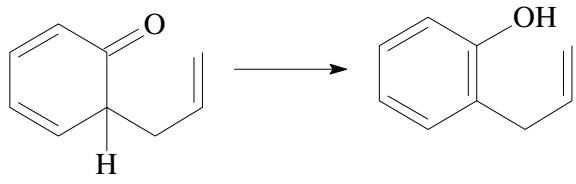
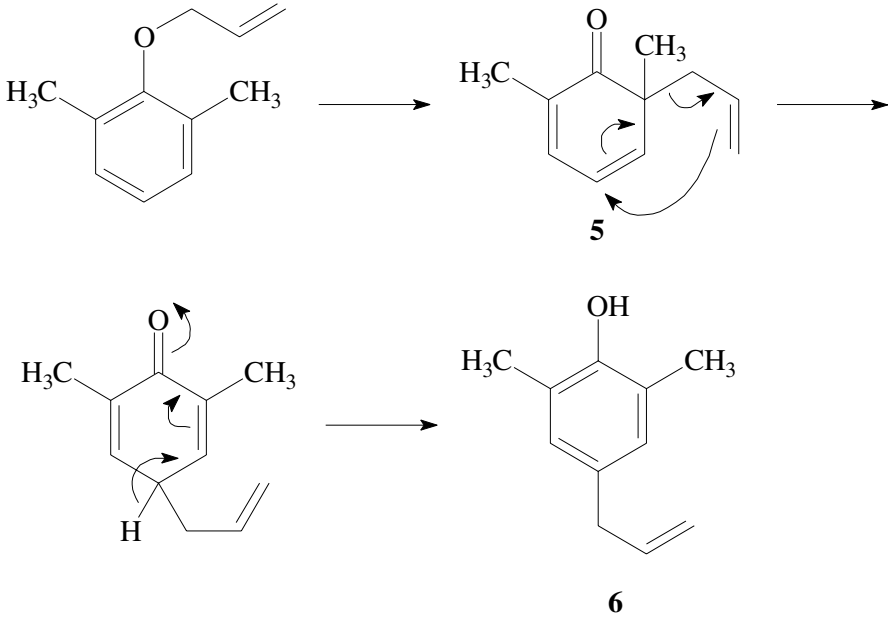


4 **3**

If both *ortho* positions bear substituents other than hydrogen, the allyl group will further migrate to the *para* position. This reaction is called the *para-Claisen rearrangement*. The formation of the *para*-substituted phenol can be explained by an initial Claisen rearrangement to an *ortho*-allyl intermediate which cannot tautomerize to an aromatic *o*-allylphenol, followed by a *Cope rearrangement* to the *p*-allyl intermediate which can tautomerize to the *p*-allylphenol; e.g. **6**:

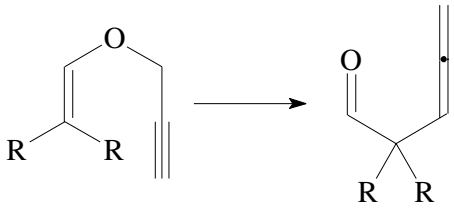


Compound **5** can be trapped through a *Diels–Alder reaction* with maleic anhydride and thus be shown to be an intermediate. Further evidence for a mechanism involving two subsequent allyl conversions has been provided by experiments with ^{14}C-labeled substrates.

If both *ortho*-positions as well as the *para*-position bear substituents other than hydrogen, no Claisen rearrangement product is obtained.

The stereochemical outcome of the reaction is determined by the geometry of the transition state; for the Claisen rearrangement a chairlike conformation is preferred,[3,4] and it proceeds strictly by an intramolecular pathway. It is therefore possible to predict the stereochemical course of the reaction, and thus the configuration of the stereogenic centers to be generated. This potential can be used for the planning of stereoselective syntheses; e.g the synthesis of natural products.[4–6]

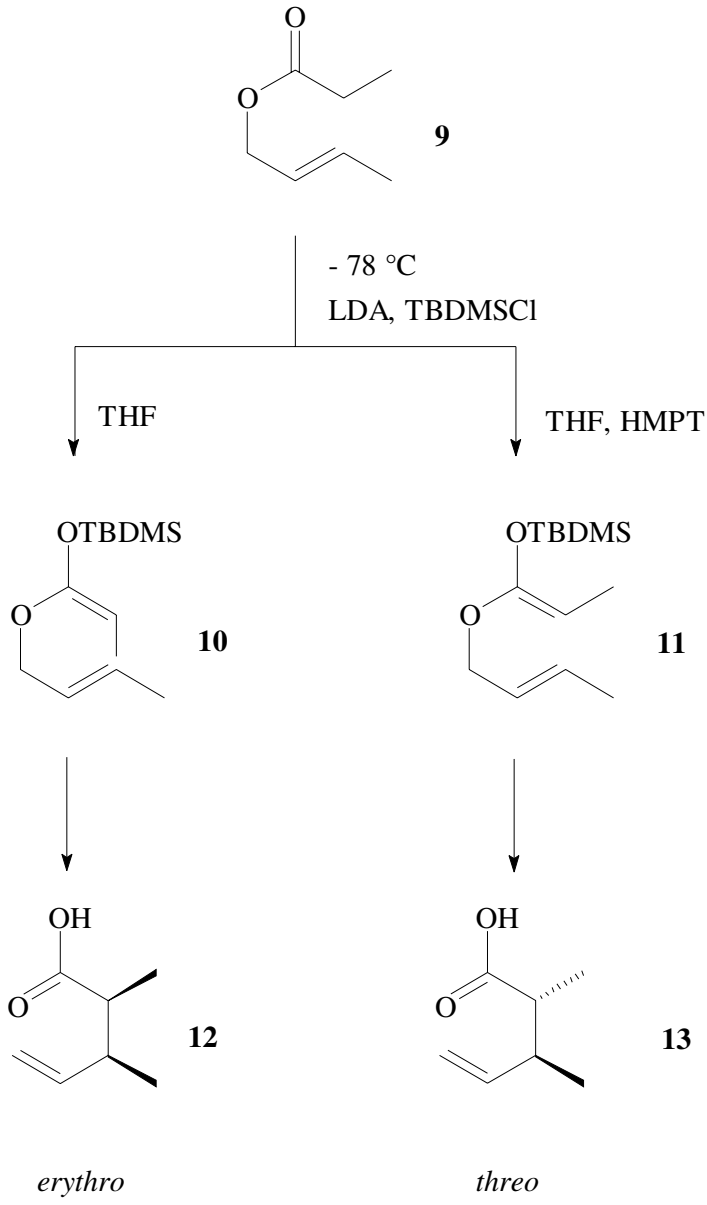
In order to broaden the scope of the Claisen rearrangement, various analogous reactions have been developed. For instance, the *Aza-* or *Amino–Claisen rearrangement*,[2,7] where the oxygen is replaced by a NR group, and the rearrangement of propargyl ethers **7** gives access to penta-3,4-dienals[8] **8**:



7 **8**

An important variant is the rearrangement of silylketene acetals like **10** and **11** which are easily accessible from allyl esters **9**. This so-called *Ireland–Claisen rearrangement*[9–11] is a valuable carbon–carbon bond forming reaction that takes advantage of the fact that the reactants are first connected to each other by an ester linkage as in allyl esters **9**, that are easy prepare.

By proper choice of the reaction conditions, the configuration of the enolate and the silylketene acetal derived thereof can be controlled to a great extent. The stereochemical course of the rearrangement then leads to the conversion of two stereogenic sp^2 centers of specific geometry into stereogenic sp^3 centers with the desired relative configuration predominating. Upon deprotonation of the allyl ester **9** by lithium diisopropylamide (LDA) in tetrahydrofuran solution the *E*-enolate is formed predominantly, and can be silylated (e.g. with *tert*-butyldimethylsilyl chloride TBDMSCl) to give the *E*-configured silylketene acetal **10**. On the other hand in tetrahydrofuran solution containing 23% hexamethylphosphoric triamide (HMPA) the *Z*-configured derivative **11** is formed predominantly. The *E*-derivative **10** upon rearrangement and hydrolytic cleavage of the silyl ester yields the *erythro*-γ,δ-unsaturated carboxylic acid **12**, while the *Z*-derivative **11** yields the corresponding *threo* product **13**:

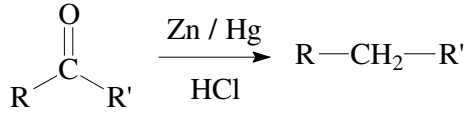


By employing optically active enol borinates instead of silylketene acetals, the Ireland–Claisen rearrangement has been further developed to an enantioselective reaction.[12]

1. L. Claisen, *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157–3166.
2. D. S. Tarbell, *Org. React.* **1944**, *2*, 1–48;
   S. J. Rhoads, N. R. Raulins, *Org. React.* **1975**, *22*, 1–252.
3. B. Ganem, *Angew. Chem.* **1996**, *108*, 1014–1023; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 936.
   J. J. Gajewski, *Acc. Chem. Res.* **1997**, *30*, 219–225.
4. F. E. Ziegler, *Chem. Rev.* **1988**, *88*, 1423–1452.
5. Y. Hirano, C. Djerassi, *J. Org. Chem.* **1982**, *47*, 2420–2426.
6. S. D. Burke, G. J. Pacofsky, *Tetrahedron Lett.* **1986**, *27*, 445–448.
7. U. Nubbemeyer, *Synthesis* **2003**, 961–1008.
8. A. Viola, J. J. Collins, N. Filipp, *Tetrahedron* **1981**, *37*, 3785–3791.
9. R. E. Ireland, R. H. Mueller, *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.
10. R. E. Ireland, R. H. Mueller, A. K. Willard, *J. Am. Chem. Soc.* **1976**, *98*, 2868–2877.
11. A. G. Cameron, D. W. Knight, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 161–167.
12. E. J. Corey, D.-H. Lee, *J. Am. Chem. Soc.* **1991**, *113*, 4026–4028.

Clemmensen Reduction

Reduction of aldehydes and ketones to methylene compounds

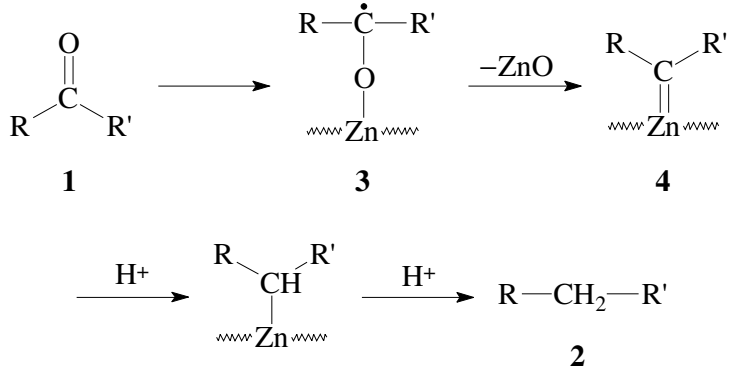


1 **2**

By application of the *Clemmensen reduction*,[1,2] aldehydes and ketones **1** can be converted into the corresponding hydrocarbons **2**. As the reducing agent zinc amalgam, together with concentrated hydrochloric acid or gaseous hydrogen chloride, is used.

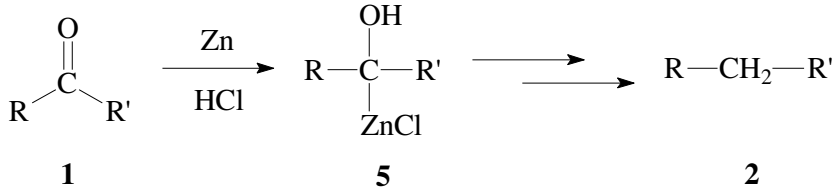
The reactions of various substrates under various reaction conditions cannot be rationalized by one general mechanism. Alcohols are not considered to be intermediates, since these generally are not reduced under Clemmensen conditions, as has been demonstrated with independently prepared alcohols corresponding to the carbonyl substrates.[3]

The Clemmensen reduction can be formulated to proceed by a sequence of one-electron and proton transfer reactions. It is a heterogenous reaction, taking place at the zinc surface. Initially an electron is transferred from zinc to the carbonyl group of ketone **1**, leading to a radical species **3**, which is presumed to react further to a zinc-carbenoid species[3] **4**:



Upon subsequent addition of protons the methylene product **2** is formed.

Alternatively a mechanism involving a α-hydroxyalkylzinc chloride **5** has been formulated:[2]



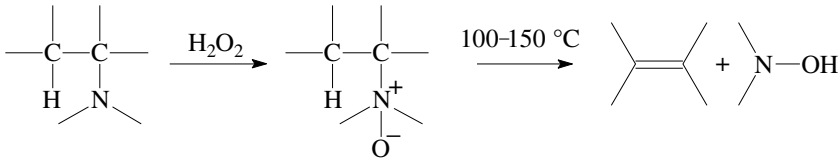
A modified procedure[4] uses activated zinc together with dry gaseous hydrogen chloride in an organic solvent, e.g. acetic acid, as reducing agent. Under those conditions the reaction occurs at lower temperatures as with the original procedure.

Another important synthetic method for the reduction of ketones and aldehydes to the corresponding methylene compounds is the *Wolff–Kishner reduction*. This reaction is carried out under basic conditions, and therefore can be applied for the reduction of acid-sensitive substrates; it can thus be regarded as a complementary method. The experimental procedure for the Clemmensen reduction is simpler: however for starting materials of high molecular weight the Wolff–Kishner reduction is more successful.

1. E. Clemmensen, *Ber. Dtsch. Chem. Ges*. **1913**, *46*, 1837–1843.
2. E. L. Martin, *Org. React*. **1942**, *1*, 155–209.
   E. Vedejs, *Org. React*. **1975**, *22*, 401–422.
3. J. Burdon, R. C. Price, *J. Chem. Soc., Chem. Commun*. **1986**, 893–894.
4. M. L. DiVona, V. Rosnati, *J. Org. Chem*. **1991**, *56*, 4269–4273.

Cope Elimination Reaction

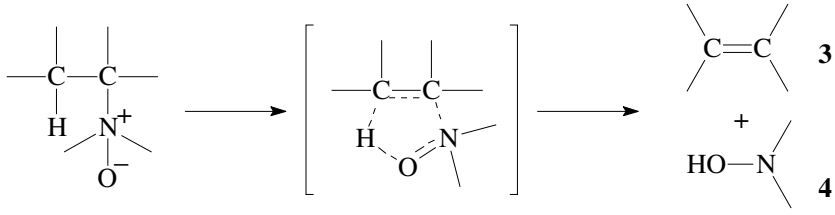
Olefins from amine oxides



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

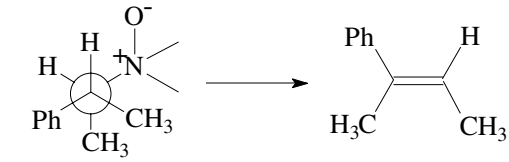
Amine oxides **2**, which can be prepared by oxidation of amines **1**, react upon heating to yield an olefin **3** and a hydroxylamine **4**. This reaction is called the *Cope elimination reaction*,[1–3] and as a synthetic method is a valuable alternative to the *Hofmann degradation reaction* of quaternary ammonium salts.

Similar to the *Ester pyrolysis* the mechanism is formulated to proceed by a E_i-mechanism; however in this case *via* a five-membered transition state **5**:

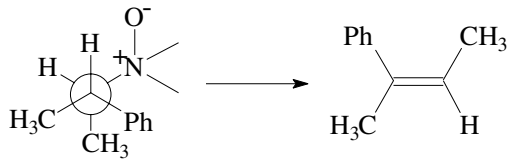


2 **5**

The mechanism is supported by findings from the decomposition reaction of the amine oxides derived from *threo*- and *erythro*-2-amino-3-phenylbutane. The *threo*-amine oxide **6** yields *E*-2-phenylbut-2-ene **7** with a selectivity of 400 : 1, and the *erythro*-derivative **8** yields the *Z*-olefin **9** with a selectivity of 20 : 1:



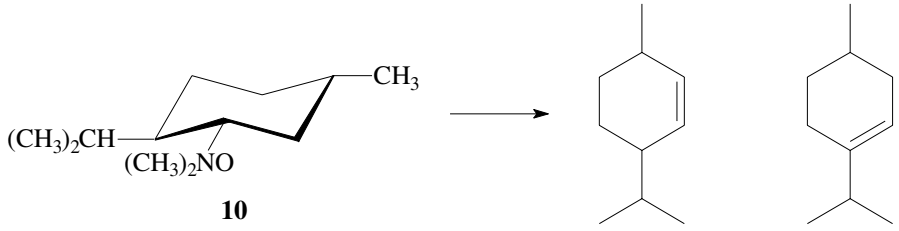
6 **7**



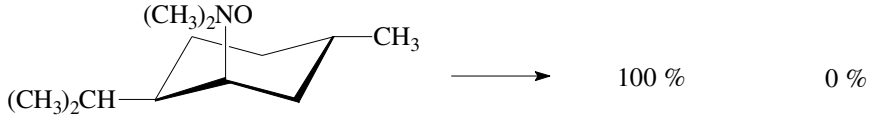
8 **9**

The higher selectivity observed with the *threo*-compound has been rationalized to arise from less steric hindrance in the five-membered transition state.

For the regioselectivity similar rules as for the ester pyrolysis do apply. With simple, alkylsubstituted amine oxides a statistical mixture of regioisomeric olefins is obtained. On the other hand with cycloalkyl amine oxides the regioselectivity is determined by the ability to pass through a planar, five-membered transition state. This has been demonstrated for the elimination reaction of menthyl dimethylamine oxide **10** and neomenthyl dimethylamine oxide **11**:



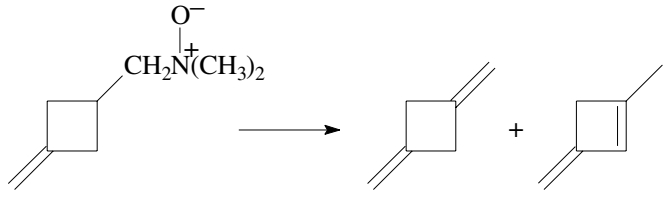
10



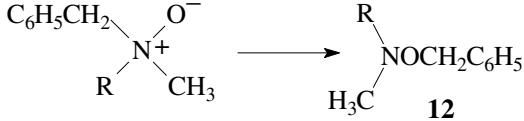
11

Certain amine oxides, especially those derived from six-membered heterocyclic amines e.g. N-methylpiperidine oxide, that cannot go through a planar, five-membered transition state, do not undergo the Cope elimination reaction.

In general side reactions are rare. In a few cases an isomerization by shift of the double bond favored by formation of a conjugated system can be observed:



Furthermore the formation of *O*-substituted hydroxylamines **12**, e.g. by migration of an allyl or benzyl substituent, is possible:



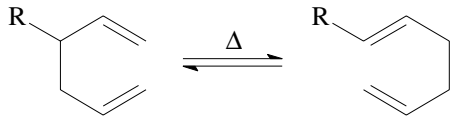
12

In addition to being a valuable method for the preparation of olefins, the Cope elimination reaction also gives access to *N*,*N*-disubstituted hydroxylamines.

1. A. C. Cope, T. T. Foster, P. H. Towle, *J. Am. Chem. Soc*. **1949**, *71*, 3929–3935.
2. A. C. Cope, E. R. Trumbull, *Org. React*. **1960**, *11*, 317–493.
3. C. H. DePuy, R. W. King, *Chem. Rev*. **1960**, *60*, 431–457.

Cope Rearrangement

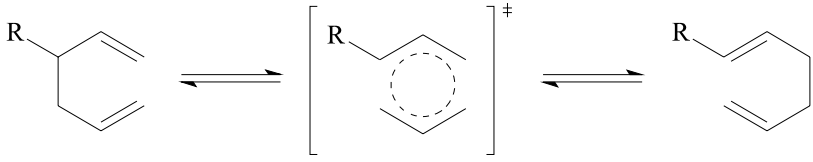
Isomerization of 1,5-dienes



1 **2**

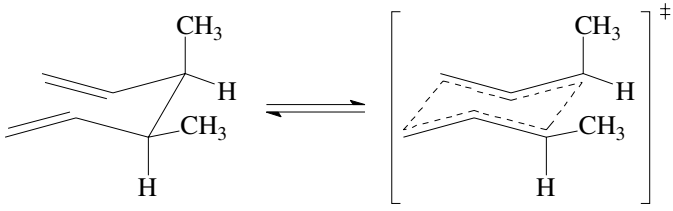
The thermal rearrangement of 1,5-dienes **1** to yield the isomeric 1,5-dienes **2**, is called the *Cope rearrangement*[1–3]—not to be confused with the thermolysis of amine oxides, which is also named after *Arthur C. Cope*.

This reaction proceeds by a concerted, [3,3] sigmatropic rearrangement (cf. the *Claisen rearrangement*) where one carbon–carbon single bond breaks, while the new one is formed. It is a reversible reaction; the thermodynamically more stable isomer is formed preferentially:

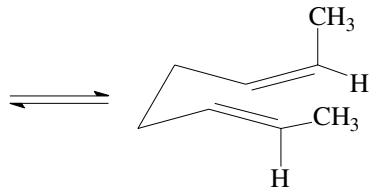


1 **3** **2**

The diene passes through a six-membered cyclic transition state **3**; preferentially of chair-like conformational geometry:



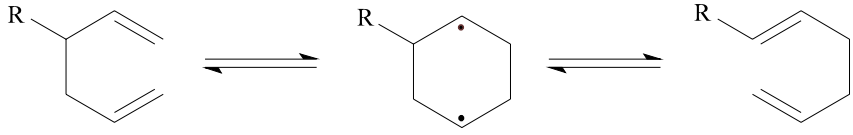
4



5

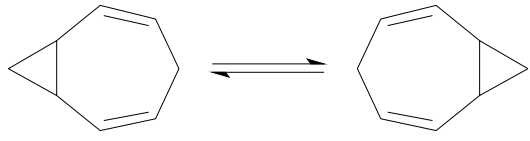
Evidence for that stereochemical course comes from the rearrangement of *meso*-3,4-dimethylhexa-1,5-diene **4**, which yields the *E*,*Z*-configured diene **5** almost quantitatively. With a transition state of boatlike geometry, a *Z*,*Z*- or *E*,*E*-configured product would be formed.[4]

With certain donor substituents at C-3 the experimental findings may be rationalized rather by a diradical mechanism,[5] where formation of the new carbon–carbon single bond leads to a diradical species **6**, which further reacts by bond cleavage to give the diene **2**:



1 **6** **2**

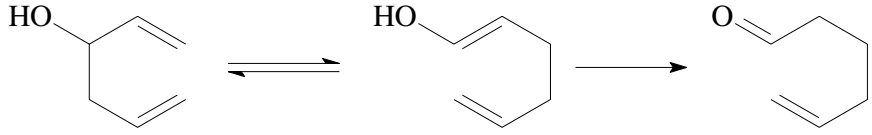
The Cope rearrangement of hexa-1,5-diene does not allow for differentiation of starting material and product; this is called a degenerate Cope rearrangement. Another example is the *automerization* of bicyclo[5,1,0]octa-2,5-diene **7**:



7 **7**

The required temperatures for the Cope rearrangement are generally lower, if the starting material contains a substituent at C-3 or C-4 which can form a conjugated system with one of the new double bonds.

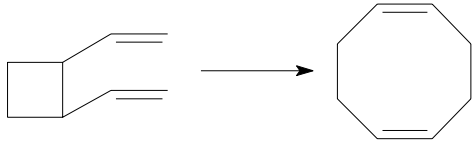
Starting from a 3-hydroxy-1,5-diene **8**, the rearrangement is not reversible, because the Cope product **9** tautomerizes to an aldehyde or ketone **10**, and is thereby removed from equilibrium:



8 **9** **10**

This variant is called the *oxy-Cope rearrangement*[6]. The rate of the Cope rearrangement is strongly accelerated with an oxy-anion substituent at C-3;[6] i.e. by use of the corresponding alkoxide instead of alcohol **8**. This *anionic oxy-Cope rearrangement* is especially fast with the potassium alkoxide derivative in the presence of the ionophor 18-crown-6. Appropriate starting materials containing nitrogen or sulfur can also undergo Cope rearrangements;[7] a clear definition as a Cope or Claisen rearrangement then may sometimes be difficult.

In some cases the rearrangement can be catalyzed by transition metal compounds,[7] and thus caused to take place at room temperature. The ordinary, uncatalyzed rearrangement requires temperatures in the range of 150–250 °C.



11 **12**

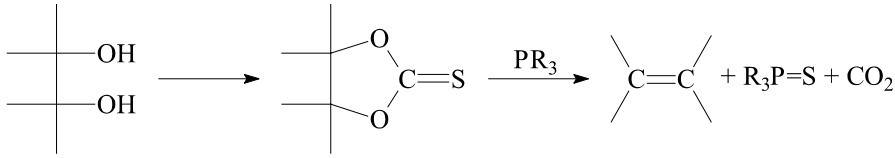
The Cope rearrangement is of great importance as a synthetic method;[6] e.g. for the construction of seven- and eight-membered carbocycles from 1,2-divinylcyclopropanes and 1,2-divinylcyclobutanes respectively (e.g. **11** → **12**), and has found wide application in the synthesis of natural products. The second step of the *para-Claisen rearrangement* is also a Cope rearrangement reaction.

1. A. C. Cope, E. M. Hardy, *J. Am. Chem. Soc*. **1940**, *62*, 441–444.
2. S. J. Rhoads, N. R. Raulins, *Org. React*. **1975**, *22*, 1–252.
3. U. Nubbemeyer, *Synthesis* **2003**, 961–1008.

4. W. v. E. Doering, W. R. Roth, *Tetrahedron* **1962**, *18*, 67–74.
5. M. Dollinger, W. Henning, W. Kirmse, *Chem. Ber.* **1982**, *115*, 2309–2325.
6. D. A. Evans, A. M. Golob, *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.
L. A. Paquette, *Angew. Chem.* **1990**, *102*, 642–660; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 609.
7. R. P. Lutz, *Chem. Rev.* **1984**, *84*, 205–247.
E. J. Corey, A. Guzman–Perez, *Angew. Chem.* **1998**, *110*, 405–415; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 388.

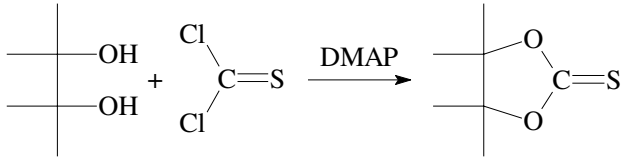
Corey–Winter Fragmentation

Olefins from vicinal diols



1 **2** **3**

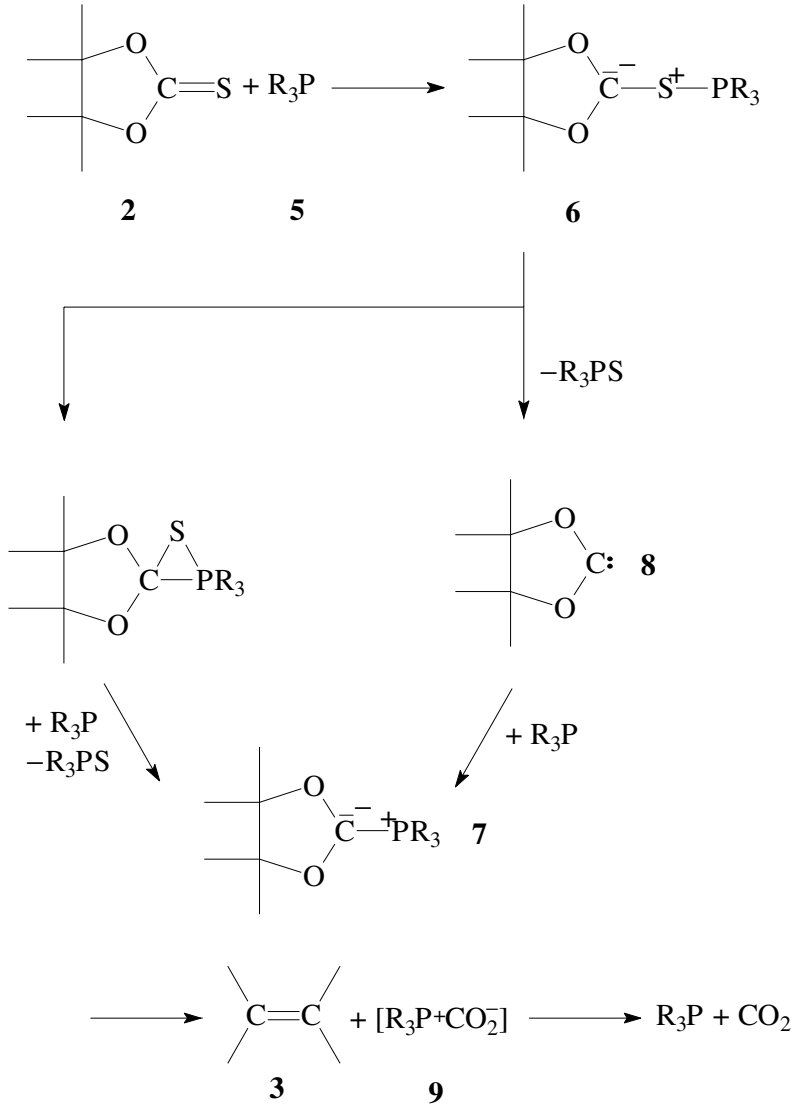
By application of the *Corey–Winter reaction*,[1,2] vicinal diols **1** can be converted into olefins **3**. The key step is the cleavage of cyclic thionocarbonates **2** (1,3-dioxolanyl-2-thiones) upon treatment with trivalent phosphorus compounds. The required cyclic thionocarbonate **2** can be prepared from a 1,2-diol **1** and thiophosgene **4** in the presence of 4-dimethylaminopyridine (DMAP):



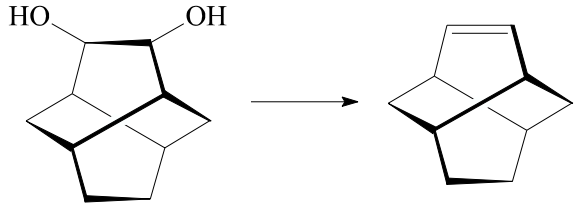
1 **4** **2**

In addition there are certain other methods for the preparation such compounds.[2]

Upon heating of the thionocarbonate **2** with a trivalent phosphorus compound e.g. trimethyl phosphite, a *syn*-elimination reaction takes place to yield the olefin **3**. A nucleophilic addition of the phosphorus to sulfur leads to the zwitterionic species **6**, which is likely to react to the phosphorus ylide **7** *via* cyclization and subsequent desulfurization. An alternative pathway for the formation of **7** *via* a 2-carbena-1,3-dioxolane **8** has been formulated. From the ylide **7** the olefin **3** is formed stereospecifically by a concerted 1,3-dipolar cycloreversion (see *1,3-dipolar cycloaddition*), together with the unstable phosphorus compound **9**, which decomposes into carbon dioxide and R_3P. The latter is finally obtained as R_3PS:

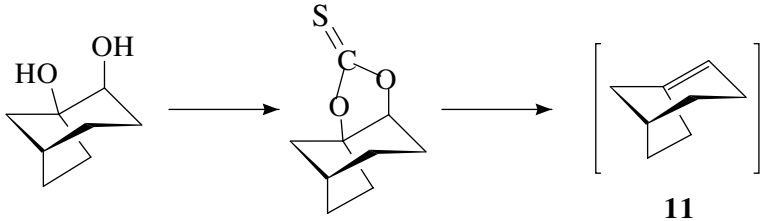


The Corey–Winter reaction provides a useful method for the preparation of olefins that are not accessible by other routes. For instance it may be used for the synthesis of sterically crowded targets, since the initial attack of phosphorus at the sulfur takes place quite distantly from sterically demanding groups that might be present in the substrate molecule. Moreover the required vicinal diols are easily accessible, e.g. by the carbon–carbon bond forming *acyloin ester condensation* followed by a reductive step. By such a route the twistene **10** has been synthesized:[3]



10

Furthermore highly strained compounds such as bicyclo[3.2.1]oct-1-ene **11**, containing a double bond to a bridgehead carbon atom, have been prepared; however this strained olefin could be identified only as its Diels–Alder product from subsequent reaction with an added diene.[4]



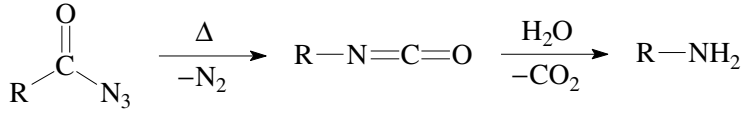
11

According to *Bredt's rule* such olefins of small ring size are unstable; ordinary elimination reactions usually yield an isomeric olefin where a bridgehead carbon does not participate in the double bond.

1. E. J. Corey, R. A. E. Winter, *J. Am. Chem. Soc*. **1963**, *85*, 2677–2678.
2. E. Block, *Org. React*. **1984**, *30*, 457–566.
3. M. Tichy, J. Sicher, *Tetrahedron Lett*. **1969**, 4609–4613.
4. J. A. Chong, J. R. Wiseman, *J. Am. Chem. Soc*. **1972**, *94*, 8627–8629.

Curtius Reaction

Isocyanates from acyl azides

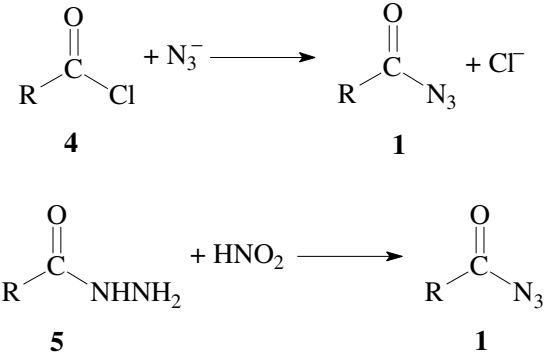


1 **2** **3**

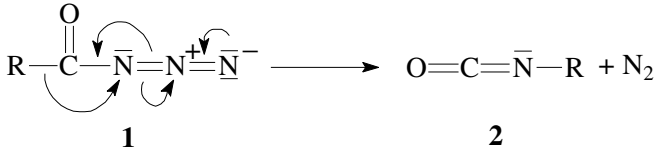
The thermal decomposition of an acyl azide **1** to yield an isocyanate **2** by loss of N_2, is called the *Curtius reaction*[1,2] or *Curtius rearrangement*. It is closely

related to the *Lossen reaction* as well as the *Hofmann rearrangement*, and like these allows for the preparation of amines **3** *via* intermediate formation of an isocyanate. The Curtius reaction can thus be applied to convert carboxylic acids into primary amines.

The required acyl azide **1** can be prepared from the corresponding acyl chloride **4** and azide ion (e.g. with sodium azide) or alternatively from an acylhydrazine **5** by treatment with nitrous acid:

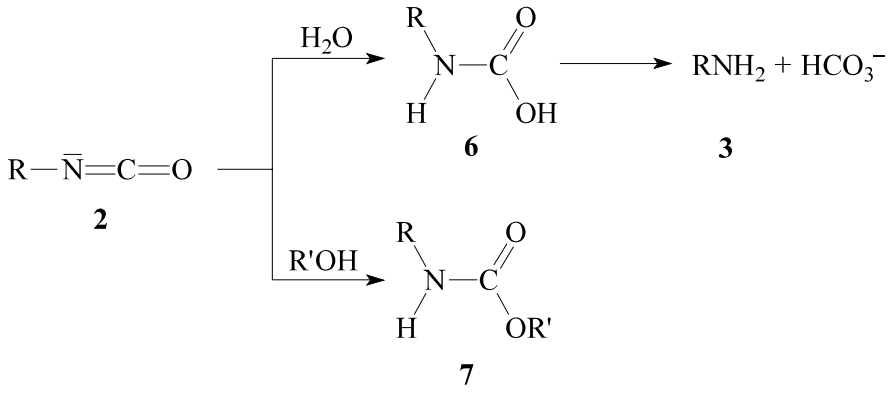


Loss of N_2 and migration of the group R is likely to be a concerted process,[3,4] since evidence for a free acyl nitrene RCON in the thermal reaction has not been found:[4]

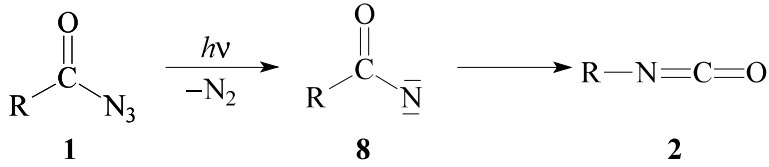


The Curtius rearrangement can be catalyzed by Lewis acids or protic acids, but good yields are often obtained also without a catalyst. From reaction in an inert solvent (e.g. benzene, chloroform) in the absence of water, the isocyanate can be isolated, while in aqueous solution the amine is formed. Highly reactive acyl azides may suffer loss of nitrogen and rearrange already during preparation in aqueous solution. The isocyanate then cannot be isolated because it immediately reacts with water to yield the corresponding amine.

An isocyanate **2** formed by a Curtius rearrangement can undergo various subsequent reactions, depending on the reaction conditions. In aqueous solution the isocyanate reacts with water to give a carbaminic acid **6**, which immediately decarboxylates to yield an amine **3**. When alcohol is used as solvent, the isocyanate reacts to a carbamate **7**:



Acyl azides can undergo photolytic cleavage and rearrangement upon irradiation at room temperature or below. In that case acyl nitrenes **8** have been identified by trapping reactions and might be reactive intermediates in the *photo Curtius rearrangement*. However there is also evidence that the formation of isocyanates upon irradiation proceeds by a concerted reaction as in the case of the thermal procedure, and that the acyl nitrenes are formed by an alternative and competing pathway:[3,4]

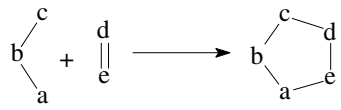


The Curtius rearrangement is a useful method for the preparation of isocyanates as well as of products derived thereof.[5] The substituent R can be alkyl, cycloalkyl, aryl, a heterocyclic or unsaturated group; most functional groups do not interfere.

1. T. Curtius, *Ber. Dtsch. Chem. Ges*. **1890**, *23*, 3023–3041.
2. P. A. S. Smith, *Org. React*. **1946**, *3*, 337–449.
3. A. Rauk, P. Alewood, *Can. J. Chem*. **1977**, *55*, 1498–1510.
4. W. Lwowski, *Angew. Chem*. **1967**, *79*, 922–931; *Angew. Chem. Int. Ed. Engl*. **1967**, *6*, 897.
   W. Lwowski in: *Azides and Nitrenes* (Ed.: E. F. V. Scriven), Academic Press, Orlando, **1984**, p. 205–246.
5. N. A. LeBel, R. M. Cherluck, E. A. Curtis, *Synthesis* **1973**, 678–679.

1,3-Dipolar Cycloaddition

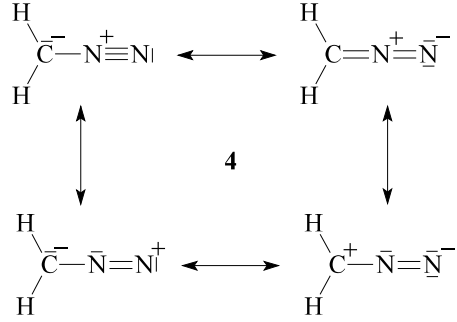
Five-membered heterocycles through a cycloaddition reaction



1 **2** **3**

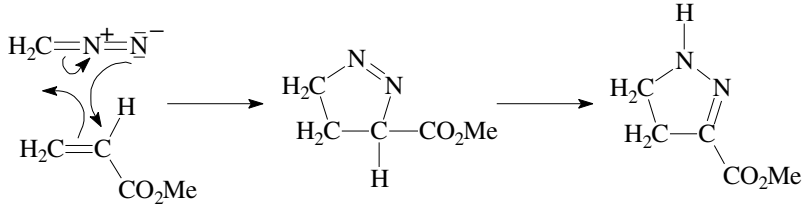
Huisgen[1,2] has reported in 1963 about a systematic treatment of the *1,3-dipolar cycloaddition reaction*[3–5] as a general principle for the construction of five-membered heterocycles. This reaction is the addition of a 1,3-dipolar species **1** to a multiple bond, e. g. a double bond **2**; the resulting product is a heterocyclic compound **3**. The 1,3-dipolar species can consist of carbon, nitrogen and oxygen atoms (seldom sulfur) in various combinations, and has four non-dienic π-electrons. The 1,3-dipolar cycloaddition is thus a $4\pi + 2\pi$ cycloaddition reaction, as is the *Diels–Alder reaction*.

Mechanistically the 1,3-dipolar cycloaddition reaction very likely is a concerted one-step process *via* a cyclic transition state. The transition state is less symmetric and more polar as for a Diels–Alder reaction; however the symmetry of the frontier orbitals is similar. In order to describe the bonding of the 1,3-dipolar compound, e.g. diazomethane **4**, several Lewis structures can be drawn that are resonance structures:



4

The cycloaddition reaction of diazomethane **4** and an olefin, e.g. methyl acrylate **5**, leads to a dihydropyrazole derivative **6**:



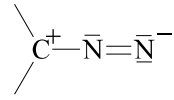
5 **6**

The shifting of electrons as shown in the scheme should be taken as a simplified depiction only. A more thorough understanding follows from consideration of the frontier orbitals and their coefficients;[6] this may then permit a prediction of the regiochemical course of the cycloaddition.

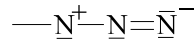
A well-known example for a 1,3-dipolar compound is ozone. The reaction of ozone with an olefin is a 1,3-dipolar cycloaddition (see *ozonolysis*).

Further examples of 1,3-dipolar compounds:[4]

Diazoalkanes

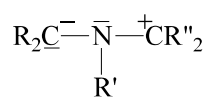


Azides

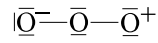


Nitriloxides

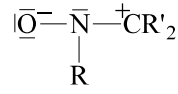
Azomethinylides



Ozone



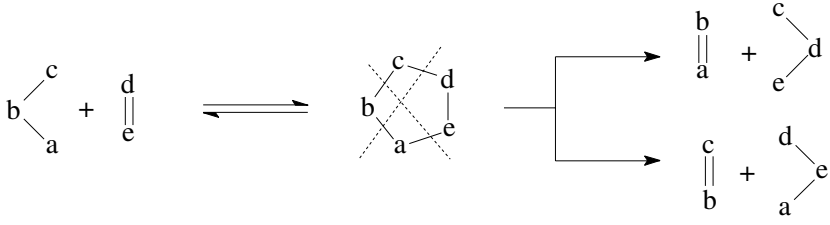
Nitrones



Dipolar compounds often are highly reactive, and therefore have to be generated *in situ*.

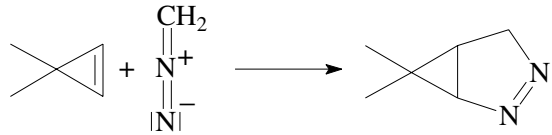
The 2π component **2**, the so-called *dipolarophile* (analogously to the dienophile of the Diels–Alder reaction) can be an alkene or alkyne or a heteroatom derivative thereof. Generally those substrates will be reactive as dipolarophiles, that also are good dienophiles.

An interesting perspective for synthesis is offered by the reaction sequence cycloaddition/cycloreversion.[7,8] It often does not lead to the initial reactants, but to a different pair of dipole and dipolarophile instead:



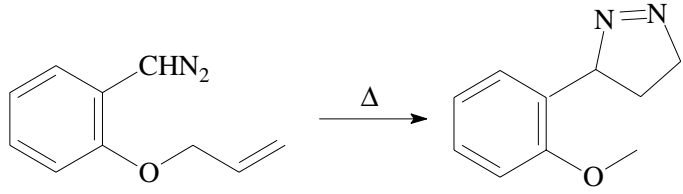
By analogy to the *alkene metathesis*, this reaction sequence is called *1,3-dipol metathesis*.

Strained bicyclic compounds can be obtained e.g. when cyclopropenes are used as dipolarophiles. Reaction of 3,3-dimethylcyclopropene **7** with diazomethane **4** gives the heterobicyclic cycloaddition product **8** in 85% yield:[9]



7 **4** **8**

The importance of the 1,3-dipolar cycloaddition reaction for the synthesis of five-membered heterocycles arises from the many possible dipole/dipolarophile combinations. Five-membered heterocycles are often found as structural subunits of natural products. Furthermore an intramolecular variant[10] makes possible the formation of more complex structures from relatively simple starting materials. For example the tricyclic compound **10** is formed from **9** by an intramolecular cycloaddition in 80% yield:[11]



9 **10**

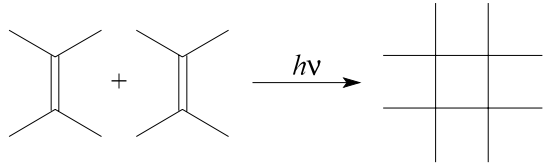
In many cases a change of the solvent has little effect on the 1,3-dipolar cycloaddition; but similar to the Diels–Alder reaction, the intermolecular 1,3-dipolar cycloaddition exhibits a large negative volume of activation, and therefore a rate enhancement is often observed on application of high pressure.[12] Inert solvents such as benzene, toluene or xylene are often used, or even no solvent at all. Depending on the reactivity of the starting materials the further reaction conditions can range from a few minutes at room temperature to several days at 100 °C or higher.

1. R. Huisgen, *Angew. Chem.* **1963**, *75*, 604–637; *Angew. Chem. Int. Ed. Engl.* **1963**, *14*, 565.
2. R. Huisgen, *Angew. Chem.* **1963**, *75*, 742–754; *Angew. Chem. Int. Ed. Engl.* **1963**, *14*, 633.
3. R. Huisgen in *1,3-Dipolar Cycloaddition Chemistry*, (Ed.: A. Padwa), Wiley, New York, **1984**, *Vol. 1*, p. 1–176.

4. W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **1990**, p. 269–331.
5. P. N. Confalone, E. M. Huie, *Org. React.* **1988**, *36*, 1–173.
6. I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, **1976**, p. 148–161.
7. B. Stanovnik, *Tetrahedron* **1991**, *47*, 2925–2945.
8. G. Bianchi, C. De Micheli, R. Gandolfi, *Angew. Chem.* **1979**, *91*, 781–798; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 673.
9. M. L. Deem, *Synthesis* **1982**, 701–716.
10. A. Padwa, *Angew. Chem.* **1976**, *88*, 131–144; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 123.
11. W. Kirmse, H. Dietrich, *Chem. Ber.* **1967**, *100*, 2710–2718.
12. K. Matsumoto, A. Sera, *Synthesis* **1985**, 999–1027.

[2 +2] Cycloaddition

Photochemical dimerization of alkenes

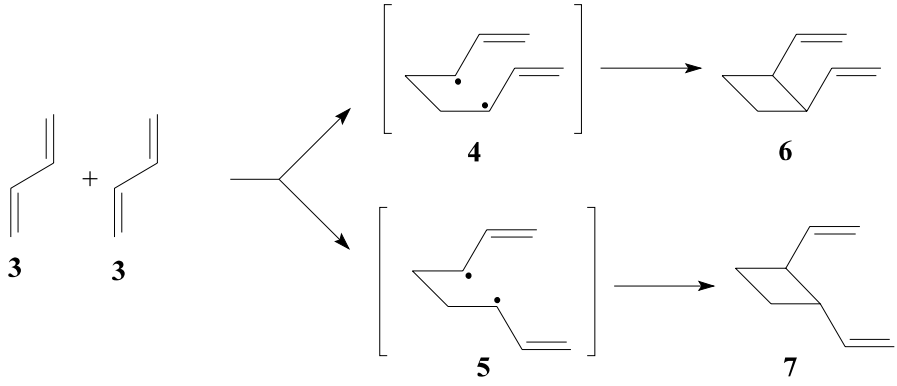


1 **1** **2**

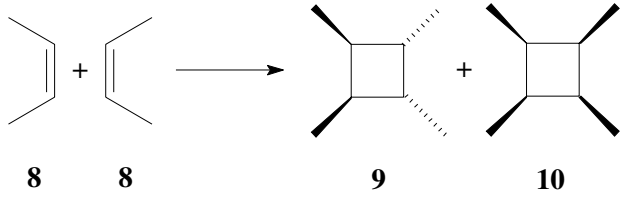
According to the *Woodward–Hofmann rules*[1] the concerted thermal $[2\pi + 2\pi]$ cycloaddition reaction of alkenes **1** in a suprafacial manner is symmetry-forbidden, and is observed in special cases only. In contrast the photochemical $[2\pi + 2\pi]$ cycloaddition is symmetry-allowed, and is a useful method for the synthesis of cyclobutane derivatives[2,3] **2**.

For the mechanistic course, two pathways have to be considered: the direct activation of an alkene through absorption of light upon irradiation and the activation mediated through a photosensitizer. For simple alkenes the former process can be difficult to realize experimentally, since these substrates absorb in the far UV (i.e. beyond 200 nm). A photosensitizer (e.g. an aldehyde or ketone) may then be added that absorbs light of higher (longer) wavelength than the alkene. A photosensitizer molecule in an excited state can transfer its excess energy to an alkene molecule which is thus brought to a triplet excited state—a diradical—while the sensitizer drops to its ground state. The excited alkene can react with a second alkene molecule by cycloaddition to yield the dimer.

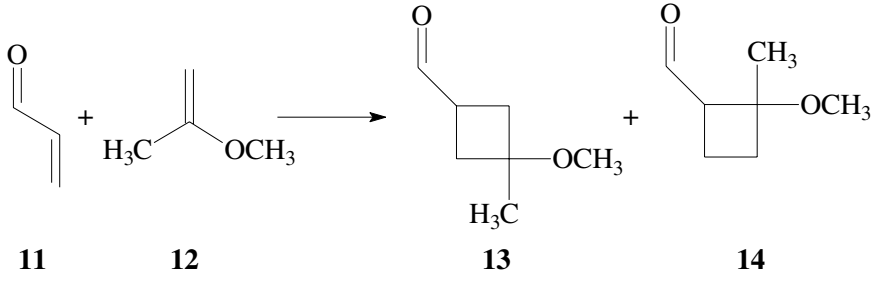
When buta-1,3-diene **3** is irradiated in the presence of a *photosensitizer*[2] (e.g. benzophenone), the isomeric divinylcyclobutanes **6** and **7** are formed *via* the intermediate diradical species **4** and **5** respectively; in addition the $[4 + 2]$ cycloaddition product 4-vinylcyclohexene (see *Diels–Alder reaction*) is obtained as a side product:



Irradiation of *Z*-but-2-ene **8** initiates a cyclodimerization reaction, even without a photosensitizer.[4] This cycloaddition proceeds from a singlet state and is likely to be a concerted, one-step reaction. Bond formation occurs suprafacial with respect to both reactants, whereupon only the tetramethylcyclobutanes **9** and **10** can be formed:

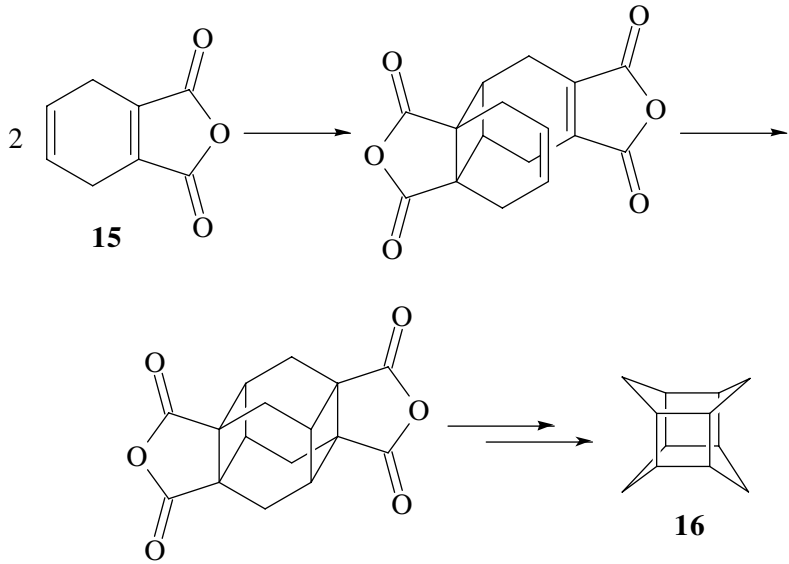


Two different alkenes can be brought to reaction to give a [2 + 2] cycloaddition product. If one of the reactants is an α,β-unsaturated ketone[5] **11**, this will be easier to bring to an excited state than an ordinary alkene or an enol ether e.g. **12**. Consequently the excited carbonyl compound reacts with the ground state enol ether. By a competing reaction pathway, the *Paterno–Büchi reaction* of the α,β-unsaturated ketone may lead to formation of an oxetane,[3] which however shall not be taken into account here:



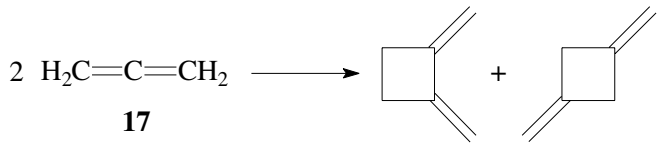
Regio- and stereoisomeric cycloaddition products might be formed in such reactions.[6] In this case the regioisomer **13** is formed as the major product in 98.5% yield.[5]

The intramolecular variant leads to formation of more than one ring; an interesting example is the formation of an intermediate in the synthesis of tetraasterane **16** by *Musso* and coworkers[8] from 3,6-dihydrophthalic anhydride **15** by two subsequent [2 + 2] cycloaddition reactions, an intermolecular step followed by an intramolecular one:



15 **16**

The thermal [2 + 2] cycloaddition[9] is limited to certain activated alkenes. For instance tetrafluoroethylene, tetrachloroethylene, allenes e.g. **17**, ketenes and enamines can form cyclic dimers or react with other alkenes:



17

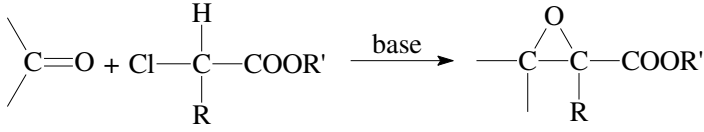
From a preparative point of view, the photochemical [2 + 2] cycloaddition is the most important of the photochemical reactions; especially the cycloaddition involving enones.[5] The [2 + 2] cycloaddition is the method of choice for the construction of cyclobutane derivatives as well as cyclobutane units within larger target molecules.

1. R. B. Woodward, R. Hoffmann, *Angew. Chem*. **1969**, *81*, 797–869; *Angew. Chem. Int. Ed. Engl*. **1969**, *8*, 781.
   R. B. Woodward, R. Hoffmann, *The Conservation of Orbital Symmetry*, Academic Press, New York, **1970**.
2. N. J. Turro, *Modern Molecular Photochemistry*, Benjamin/Cunnings Publishing Co., London, **1978**, p. 419–465.
3. J. Ninomiya, T. Naito, *Photochemical Synthesis*, Academic Press, New York, **1989**, p. 59–109.
4. Y. Yamazaki, R. J. Cvetanovic, *J. Am. Chem. Soc*. **1969**, *91*, 520–522.
5. M. Demuth, G. Mikhail, *Synthesis* **1989**, 145–162.
6. K. Y. Burstein, E. P. Serebryakov, *Tetrahedron* **1978**, *34*, 3233–3238.
7. M. T. Crimmins, *Chem. Rev*. **1988**, *88*, 1453–1473.
8. H.-G. Fritz, H.-M. Hutmacher, H. Musso, G. Ahlgren, B. Akermark, R. Karlsson, *Chem. Ber*. **1976**, *109*, 3781–3792.
9. J. D. Roberts, C. M. Shorts, *Org. React*. **1962**, *12*, 1–56.

D

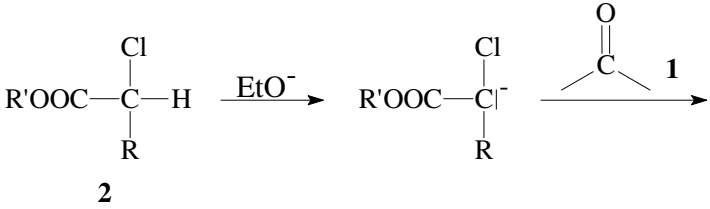
Darzens Glycidic Ester Condensation

α,β-Epoxycarboxylic esters from aldehydes or ketones and α-halo esters

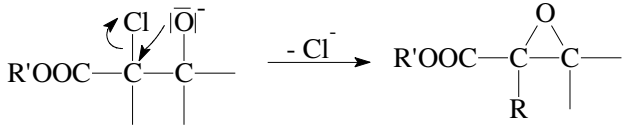


1 **2** **3**

An α,β-epoxycarboxylic ester (also called *glycidic ester*) **3** is formed upon reaction of a α-halo ester **2** with an aldehyde or ketone **1** in the presence of a base such as sodium ethoxide or sodium amide.[1–3] Mechanistically it is a Knoevenagel-type reaction of the aldehyde or ketone **1** with the deprotonated α-halo ester to the α-halo alkoxide **4**, followed by an intramolecular nucleophilic substitution reaction to give the epoxide **3**:



2



4 **3**

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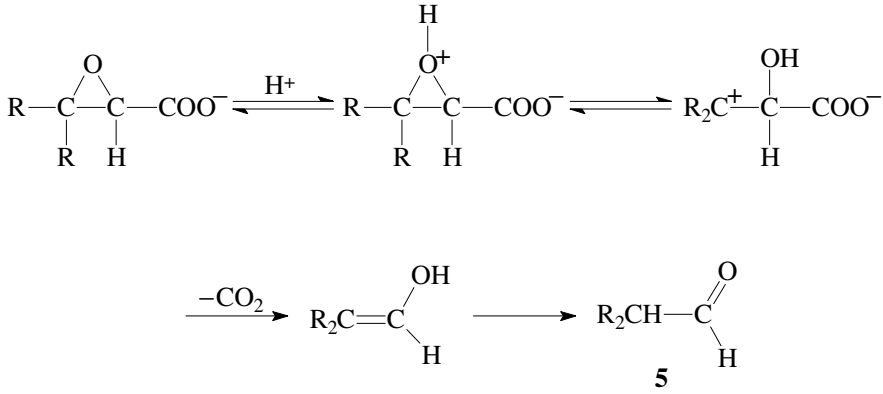
Generally the intermediate **4** is not isolated; however this can be done, thus supporting the formulated mechanism.

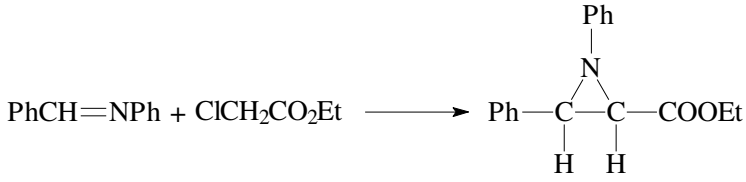
Good yields are usually obtained with aromatic aldehydes or ketones. Aliphatic aldehydes are poor substrates for the ordinary procedure, but react much better if the halo ester is first deprotonated with lithium diisopropylamide (LDA) in tetrahydrofuran at −78 °C, prior to addition of the aldehyde.

Instead of α-halo esters, related reactants can be used e.g. the α-halo derivatives of ketones, nitriles, sulfones and *N*,*N*-disubstituted amides. The Darzens condensation is also of some importance as a synthetic method because a glycidic acid can be converted into the next higher homolog of the original aldehyde, or into a branched aldehyde (e.g. **5**) if the original carbonyl substrate was a ketone:



5

By reaction of an imine **6** with a α-halo ester **2**, an aziridine derivative **7** can be obtained:[4]



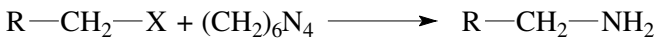
6 **2** **7**

Although this variant often gives yields of less than 50%, it is a general method for the preparation of aziridines, especially of aziridinecarboxylic esters such as **7**.

1. E. Erlenmeyer, *Justus Liebigs Ann. Chem.* **1892**, *271*, 137–163.
2. M. S. Newman, B. J. Magerlein, *Org. React.* **1949**, *5*, 413–440.
3. G. Berti, *Top. Stereochem.* **1973**, *7*, 210–218.
4. J. A. Deyrup, *J. Org. Chem.* **1969**, *34*, 2724–2727.

Delépine Reaction

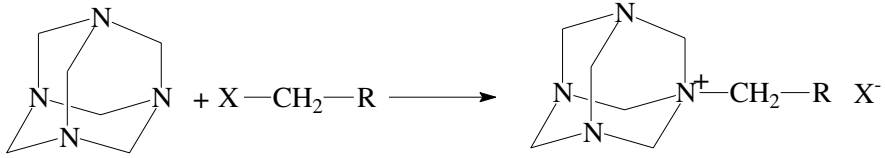
Primary amines through reaction of alkyl halides with hexamethylenetetramine



1 **2** **3**

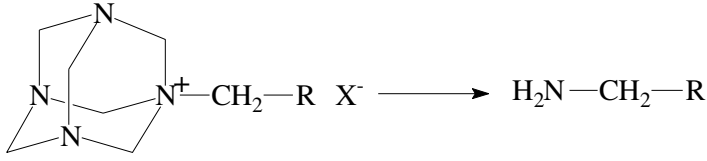
Reaction of alkyl halides **1** with hexamethylenetetramine **2** (trivial name: *urotropine*) followed by a hydrolysis step, leads to formation of primary amines **3** free of higher substituted amines. This method is called the *Delépine reaction*;[1,2] a comparable method is the *Gabriel synthesis*.

An alkyl halide **1** reacts with hexamethylenetetramine **2** to the quaternary ammonium salt **4**, which crystallizes from the reaction mixture:



2 **1** **4**

Upon heating with a mixture of concentrated hydrochloric acid and ethanol under reflux, the hexaminium salt **4** is cleaved into the primary amine and formaldehyde. The latter can further react with ethanol under the acidic conditions to give formaldehyde diethylacetal:



4

The Delépine reaction is a useful synthetic method, since it permits the selective preparation of primary amines from simple starting materials under simple reaction conditions and with short reaction time.

1. M. Delépine, *Bull. Soc. Chim. Fr.* **1895**, *13*, 352–361.
2. N. Blazevic, D. Kolbah, B. Belin, V. Sunjic, F. Kafjez, *Synthesis* **1979**, 161–176.

Diazo Coupling

Coupling reaction of diazonium ions with electron-rich aromatic compounds

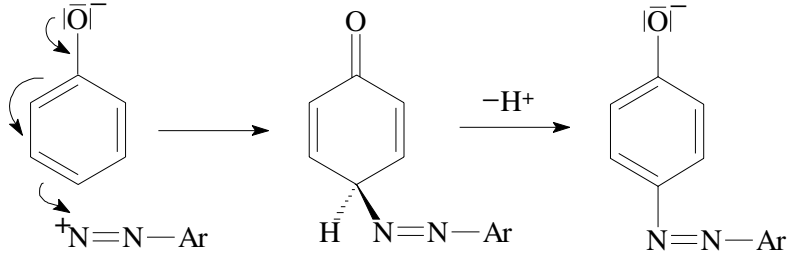
$$\underset{\mathbf{1}}{ArN_2^+} + \underset{\mathbf{2}}{Ar'H} \longrightarrow \underset{\mathbf{3}}{Ar{-}N{=}N{-}Ar'}$$

Arenediazonium ions **1** can undergo a coupling reaction with electron-rich aromatic compounds **2** like aryl amines and phenols to yield azo compounds[1,2] **3**. The substitution reaction at the aromatic system **2** usually takes place *para* to the activating group; probably for steric reasons. If the para position is already occupied by a substituent, the new substitution takes place *ortho* to the activating group.

Arenediazonium ions are stable in acidic or slightly alkaline solution; in moderate to strong alkaline medium they are converted into diazohydroxides **4**:

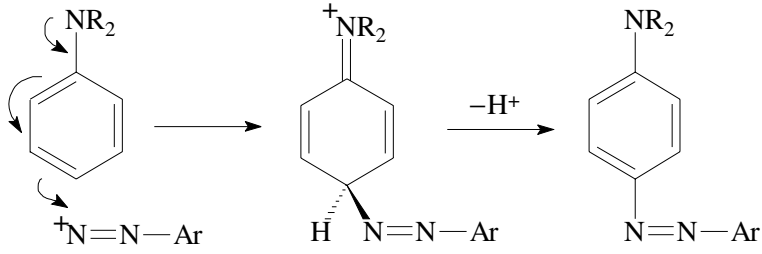
$$\underset{\mathbf{1}}{ArN_2^+} \xrightarrow{OH^-} \underset{\mathbf{4}}{Ar{-}N{=}N{-}OH}$$

The optimal pH-value for the coupling reaction depends on the reactant. Phenols are predominantly coupled in slightly alkaline solution, in order to first convert an otherwise unreactive phenol into the reactive phenoxide anion. The reaction mechanism can be formulated as electrophilic aromatic substitution taking place at the electron-rich aromatic substrate, with the arenediazonium ion being the electrophile:



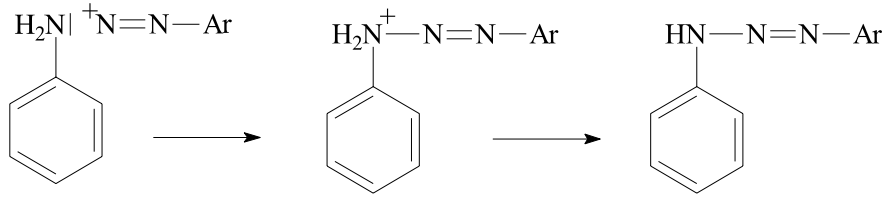
3a

For aryl amines the reaction mixture should be slightly acidic or neutral, in order to have a high concentration of free amine as well as arenediazonium ions. Aryl ammonium species—$ArNH_3^+$—are unreactive. The coupling of the diazonium species with aromatic amines proceeds by an analogous mechanism:



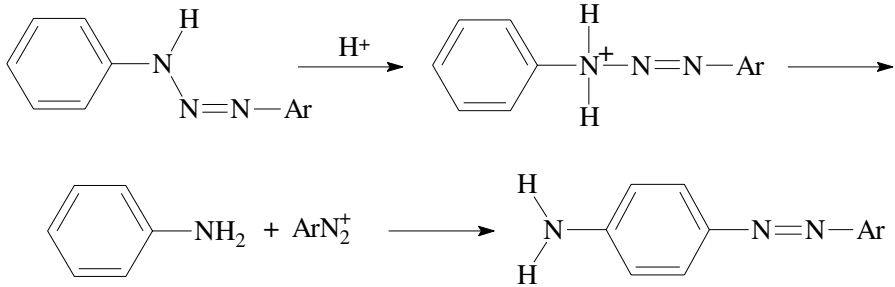
3b

With primary and secondary aryl amines a reaction at the amino nitrogen can occur, leading to formation of an aryl triazene **5**:



5

The N-azo compound **5** thus obtained can isomerize by an intermolecular process to give the C-azo derivative:[3–5]

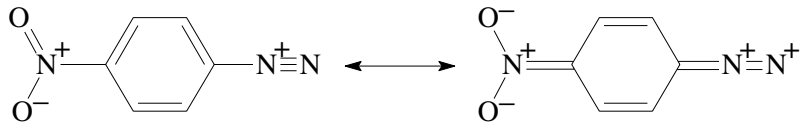


3b

If the para position is not already occupied, this isomerization generally leads to the para isomer. The desired C-azo product can be obtained in one laboratory step.[5]

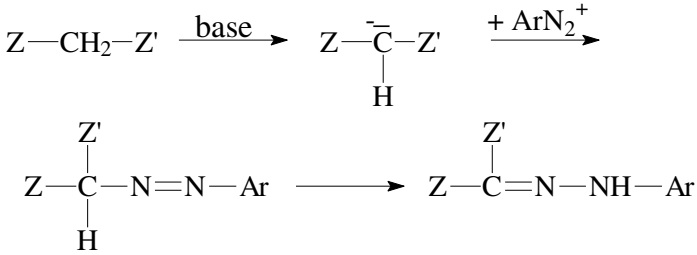
Arenediazonium ions are relatively weak electrophiles, and therefore react only with electron-rich aromatic substrates like aryl amines and phenols. Aromatic compounds like anisole, mesitylene, acylated anilines or phenolic esters are ordinarily not reactive enough to be suitable substrates; however they may be coupled

to activated arenediazonium ions. An electron-withdrawing substituent in the para position of the arenediazonium system increases the electrophilicity of the diazo group by concentrating the positive charge at the terminal nitrogen:



Certain aliphatic diazonium species such as bridgehead diazonium ions and cyclopropanediazonium ions, where the usual loss of N_2 would lead to very unstable carbocations, have been coupled to aromatic substrates.[1]

The opposite case—reaction of an arenediazonium species with an aliphatic substrate[6]—is possible if a sufficiently acidic C−H bond is present; e.g. with β-keto esters and malonic esters. The reaction mechanism is likely to be of the S_E1-type; an electrophilic substitution at aliphatic carbon:



(Z, Z′ = COOR, CHO, COR, $CONR_2$, COO−, CN, NO_2, SOR, SO_2R, SO_2OR, SO_2NR_2)

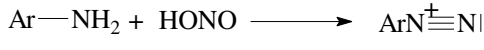
The diazo coupling with C−H acidic aliphatic substrates is a feature of the *Japp–Klingemann reaction*.

Suitably substituted azo compounds constitute an important class of dyes—the azo dyes. Some derivatives such as *p*-dimethylaminoazobenzene-*p*′-sulfonic acid Na-salt (trivial name: *methyl orange*) are used as pH-indicators.

1. I. Szele, H. Zollinger, *Top. Curr. Chem.* **1983**, *112*, 1–66.
2. A. F. Hegarty in *The Chemistry of the Diazonium and Diazo Groups, Vol. 2* (Ed.: S. Patai), Wiley, New York, **1978**, p. 545–551.
3. H. J. Shine, *Aromatic Rearrangements*, American Elsevier, New York, **1967**, p. 212–221.
4. J. R. Penton, H. Zollinger, *Helv. Chim. Acta* **1981**, *64*, 1717–1727 and 1728–1738.
5. R. P. Kelly, J. R. Penton, H. Zollinger, *Helv. Chim. Acta* **1982**, *65*, 122–132.
6. S. M. Parmerter, *Org. React.* **1959**, *10*, 1–142.

Diazotization

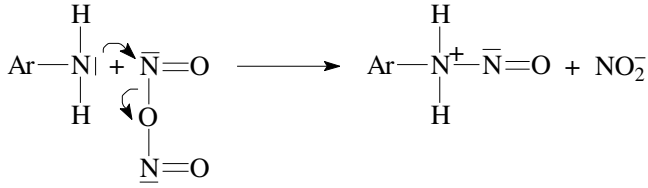
Diazonium salts from primary aromatic amines



1 **2** **3**

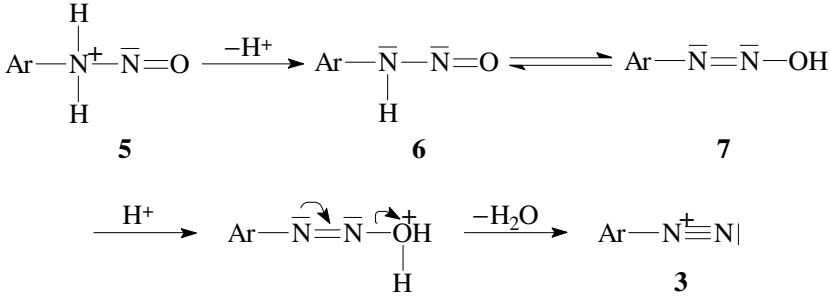
The nitrosation of primary aromatic amines **1** with nitrous acid **2** and a subsequent dehydration step lead to the formation of diazonium ions **3**.[1–3] The unstable nitrous acid can for example be prepared by reaction of sodium nitrite with aqueous hydrochloric acid.

The reactive species for the transfer of the nitrosyl cation NO^+ is not the nitrous acid **2** but rather N_2O_3 **4** which is formed in weakly acidic solution. Other possible nitrosating agents are NOCl or $H_2NO_2^+$, or even free NO^+ in strong acidic solution. The initially formed N_2O_3 **4** reacts with the free amine **1**:



1 **4** **5**

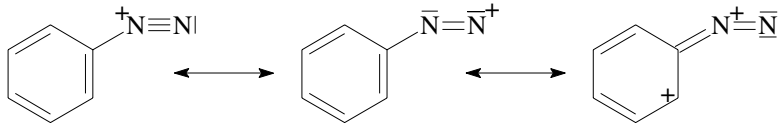
Although the diazotization reaction takes place in acidic solution, it is the free amine that reacts,[1] and not the ammonium salt $ArNH_3^+$ X^-. Even in acidic solution there is a small amount of free amine present, since aromatic amines are relatively weak bases.



5 **6** **7** **3**

The cation **5** loses a proton to give the more stable nitrosoamine **6**, which is in equilibrium with the tautomeric diazohydroxide **7**. Protonation of the hydroxy group in **7** and subsequent loss of H_2O leads to the diazonium ion **3**.

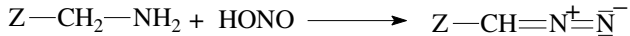
Aliphatic primary amines also undergo the diazotization reaction in weakly acidic solution; however the resulting aliphatic diazonium ions are generally unstable, and easily decompose into nitrogen and highly reactive carbenium ions. The arenediazonium ions are stabilized by resonance with the aromatic ring:



However even arenediazonium ions generally are stable only at temperatures below 5 °C; usually they are prepared prior to the desired transformation, and used as reactants without intermediate isolation[5]. They can be stabilized more effectively through complexation by crown ethers.[4,5]

Most functional groups do not interfere with the diazotization reaction. Since aliphatic amines are stronger bases and therefore completely protonated at a pH < 3, it is possible that an aromatic amino group is converted into a diazonium group, while an aliphatic amino group present in the same substrate molecule is protected as ammonium ion and does not react.[6]

Instead of a diazonium salt, a *diazo compound* is obtained from reaction of a primary aliphatic amine **8** that has an electron-withdrawing substituent at the α-carbon (e.g. Z = COOR, CN, CHO, COR) as well as an α-hydrogen:[7]



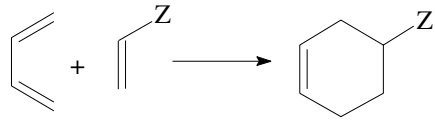
8 **2** **9**

Diazonium salts are important intermediates in organic synthesis, e.g. for the *Sandmeyer reaction*. The most important use is the coupling reaction with phenols or aromatic amines to yield azo dyes (see *Diazo coupling*).

1. B. C. Challis, A. R. Butler in *The Chemistry of the Amino Group* (Ed.: S. Patai), Wiley, New York, **1968**, p. 305–320.
2. K. Schank in *The Chemistry of the Diazonium and Diazo Groups* (Ed.: S. Patai), Wiley, New York, **1978**, *Vol. 2*, p. 645–657.
3. J. H. Ridd, *Q. Rev. Chem. Soc*. **1961**, *15*, 418–441.
4. S. H. Korzeniowski, A. Leopold, J. R. Beadle, M. F. Ahern, W. A. Sheppard, R. K. Khanna, G. W. Gokel, *J. Org. Chem*. **1981**, *46*, 2153–2159.
5. R. A. Bartsch in *The Chemistry of Functional Groups, Supp. C* (Eds.: S. Patai, Z. Rappoport), Wiley, New York, **1983**, *Vol. 1*, p. 889–915.
6. N. Kornblum, D. C. Iffland, *J. Am. Chem. Soc*., **1949**, *71*, 2137–2143.
7. M. Regitz in *The Chemistry of the Diazonium and Diazo Groups* (Ed.: S. Patai), Wiley, New York, **1978**, *Vol. 2*, p. 659–708.

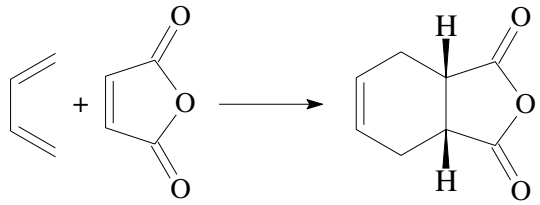
Diels–Alder Reaction

[4 + 2] Cycloaddition of diene and dienophile



1 **2** **3**

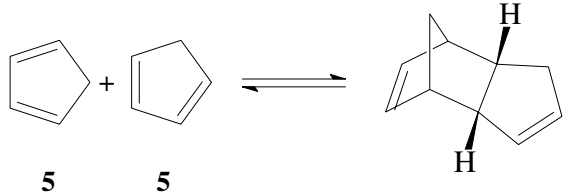
The *Diels–Alder reaction*,[1–4] is a cycloaddition reaction of a conjugated diene with a double or triple bond (the *dienophile*); it is one of the most important reactions in organic chemistry. For instance an electron-rich diene **1** reacts with an electron-poor dienophile **2** (e.g. an alkene bearing an electron-withdrawing substituent Z) to yield the unsaturated six-membered ring product **3**. An illustrative example is the reaction of butadiene **1** with maleic anhydride **4**:



1 **4**

The Diels–Alder reaction is of wide scope. Not all the atoms involved in ring formation have to be carbon atoms; the *hetero-Diels–Alder reaction* involving one or more heteroatom centers can be used for the synthesis of six-membered heterocycles.[5] The reverse of the Diels–Alder reaction—the *retro-Diels–Alder reaction*[6,7]—also is of interest as a synthetic method. Moreover and most importantly the usefulness of the Diels–Alder reaction is based on its *syn*-stereospecificity, with respect to the dienophile as well as the diene, and its predictable regio- and *endo*-selectivities.[8–10]

For a discussion of the mechanistic course of the reaction, many aspects have to be taken into account.[9,11] The *cisoid* conformation of the diene **1**, which is in equilibrium with the thermodynamically more favored *transoid* conformation, is a prerequisite for the cycloaddition step. Favored by a fixed cisoid geometry are those substrates where the diene is fitted into a ring, e.g. cyclopentadiene **5**. This particular compound is so reactive that it dimerizes easily at room temperature by undergoing a Diels–Alder reaction:

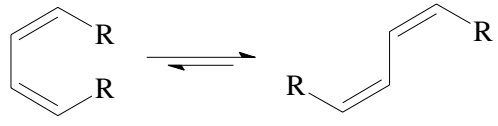


5 **5**

Since the equilibrium lies to the left at higher temperatures, cyclopentadiene can be obtained by thermolytic cleavage of the dimer and distilling the monomer prior to use (*cracking distillation*).

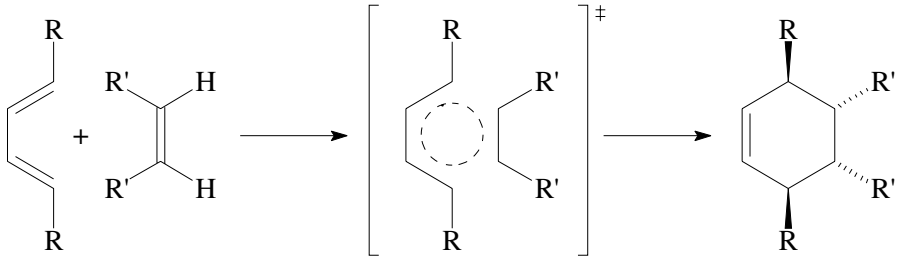
In case of a *Z*,*Z*-configurated diene **6**, the transoid conformation is favored, because of unfavorable steric interactions of substituents at C-1 and C-4 in the

cisoid conformation:



6

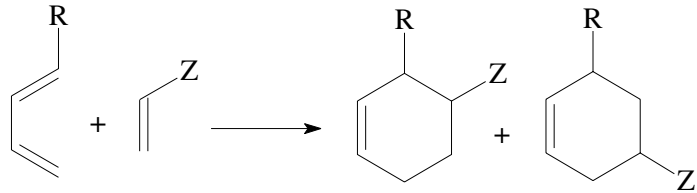
Mechanistically the observed stereospecificity can be rationalized by a concerted, pericyclic reaction. In a one-step cycloaddition reaction the dienophile **8** adds 1,4 to the diene **7** *via* a six-membered cyclic, aromatic transition state **9**, where three π-bonds are broken and one π- and two σ-bonds are formed. The arrangement of the substituents relative to each other at the stereogenic centers of the reactants is retained in the product **10**, as a result of the stereospecific *syn*-addition.



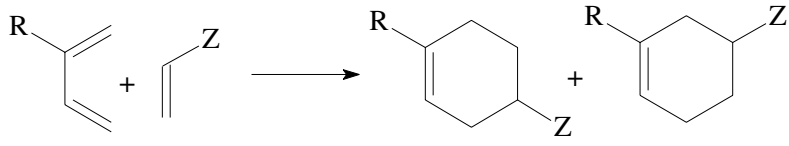
7 **8** **9** **10**

An explanation for the finding that concerted [4 + 2] cycloadditions take place thermally, while concerted *[2 + 2] cycloadditions* occur under photochemical conditions, is given through the *principle of conservation of orbital symmetry*[12]. According to the *Woodward–Hofmann rules*[12] derived thereof, a concerted, pericyclic [4 + 2] cycloaddition reaction from the ground state is symmetry-allowed.

From reaction of an unsymmetrically substituted diene **11a**, **b** and dienophile **12**, different regioisomeric products **13a**, **b** and **14a**, **b** can be formed. The so-called '*ortho*' and the '*para*' isomer **13a**, resp. **13b**, is formed preferentially.



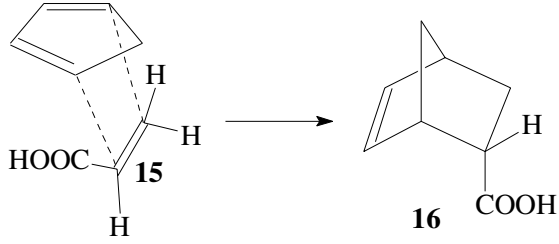
11a **12** **13a** **14a**

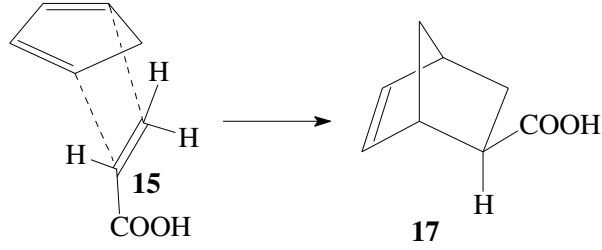


11b **12** **13b** **14b**

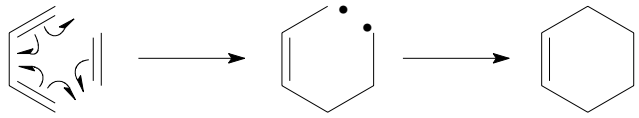
The observed regioselectivity[9] can be explained by taking into account the frontier orbital coefficients of the reactants.[13]

The Diels–Alder reaction of a diene with a substituted olefinic dienophile, e.g. **2**, **4**, **8**, or **12**, can go through two geometrically different transition states. With a diene that bears a substituent as a stereochemical marker (any substituent other than hydrogen; deuterium will suffice[27]) at C-1 (e.g. **11a**) or substituents at C-1 and C-4 (e.g. **5**, **6**, **7**), the two different transition states lead to diastereomeric products, which differ in the relative configuration at the stereogenic centers connected by the newly formed σ-bonds. The respective transition state as well as the resulting product is termed with the prefix *endo* or *exo*. For example, when cyclopentadiene **5** is treated with acrylic acid **15**, the *endo*-product **16** and the *exo*-product **17** can be formed. Formation of the *endo*-product **16** is kinetically favored by secondary orbital interactions (*endo rule* or *Alder rule*).[11,13] Under kinetically controlled conditions it is the major product, and the thermodynamically more stable *exo*-product **17** is formed in minor amounts only.





For most Diels–Alder reactions a concerted mechanism as described above, is generally accepted. In some cases, the kinetic data may suggest the intermediacy of a diradical intermediate[9] **18**:

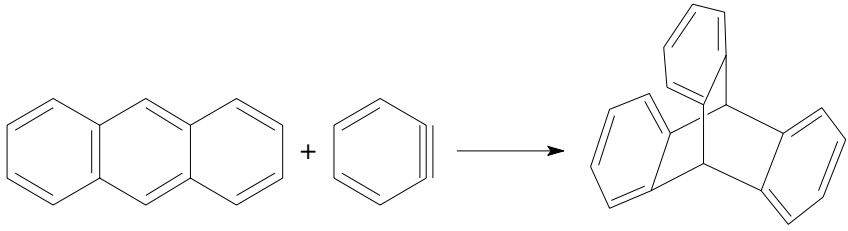


18

Furthermore in certain cases Diels–Alder reactions may proceed by an ionic mechanism.[14]

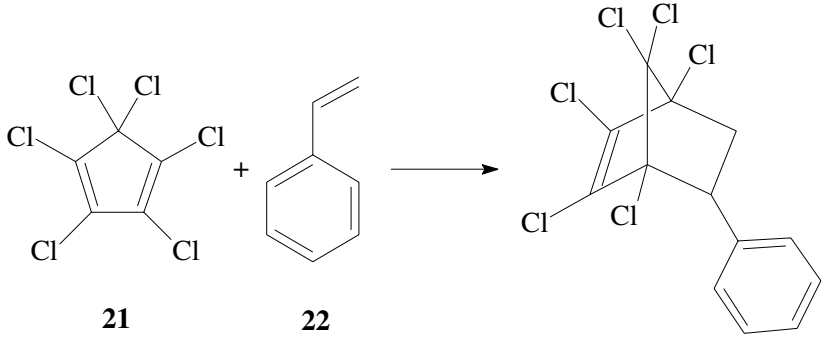
For the ordinary Diels–Alder reaction the dienophile preferentially is of the electron-poor type; electron-withdrawing substituents have a rate enhancing effect. Ethylene and simple alkenes are less reactive. Substituent Z in **2** can be e.g. CHO, COR, COOH, COOR, CN, Ar, NO_2, halogen, C=C. Good dienophiles are for example maleic anhydride, acrolein, acrylonitrile, dehydrobenzene, tetracyanoethylene (TCNE),[15] acetylene dicarboxylic esters. The diene preferentially is of the electron-rich type; thus it should not bear an electron-withdrawing substituent.

Because of their strong aromatic character, benzene and naphthalene are very unreactive as dienes; however anthracene **19** reacts with highly reactive dienophiles, such as dehydrobenzene (benzyne) **20**:



19 **20**

There are Diels–Alder reactions known where the electronic conditions outlined above are just reversed. Such reactions are called Diels–Alder reactions with *inverse electron demand*.[9] For example[16] the electron-poor diene hexachlorocyclopentadiene **21** reacts with the electron-rich styrene **22**:



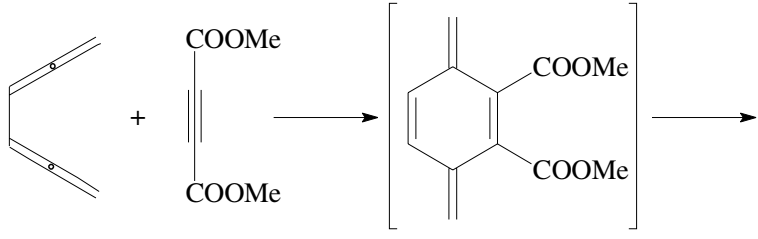
21 **22**

In many cases the solvent has little effect on the Diels–Alder reaction, which is an additional argument for a concerted mechanism. The intermolecular Diels–Alder reaction exhibits a large negative volume of activation, together with a large negative volume of reaction, and therefore the application of high pressure can lead to rate enhancement and improved *endo*-selectivity.[17,18] The strong acceleration of the Diels–Alder reaction and the enhanced *endo*-selectivity observed when using a special solvent system, consisting of a five-molar solution of lithium perchlorate in diethyl ether,[19] is attributed to an internal pressure effect, rather than to an ordinary solvent effect.

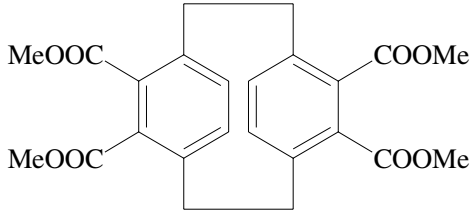
The use of catalysts for a Diels–Alder reaction is often not necessary, since in many cases the product is obtained in high yield in a reasonable reaction time. In order to increase the regioselectivity and stereoselectivity (e.g. to obtain a particular *endo*- or *exo*-product), Lewis acids as catalysts (e.g. $TiCl_4$, $AlCl_3$, BF_3-etherate) have been successfully employed.[4] The usefulness of strong Lewis acids as catalysts may however be limited, because they may also catalyze polymerization reactions of the reactants. Chiral Lewis acid catalysts are used for catalytic enantioselective Diels–Alder reactions.[20]

The Diels–Alder reaction with triple bond dienophiles gives access to cyclohexa-1,4-diene derivatives. Further reaction of a reactive intermediate thus produced or a subsequent oxidation step can then lead to a six-membered ring aromatic target molecule.

An example is the synthesis of substituted [2.2]paracyclophanes as reported by *Hopf et al*.[21] When hexa-1,2,4,5-tetraene **23** is treated with dimethyl acetylenedicarboxylate **24** (an electron-poor acetylenic dienophile), the initially formed reactive intermediate **25** dimerizes to yield the [2.2]paracyclophane **26**:



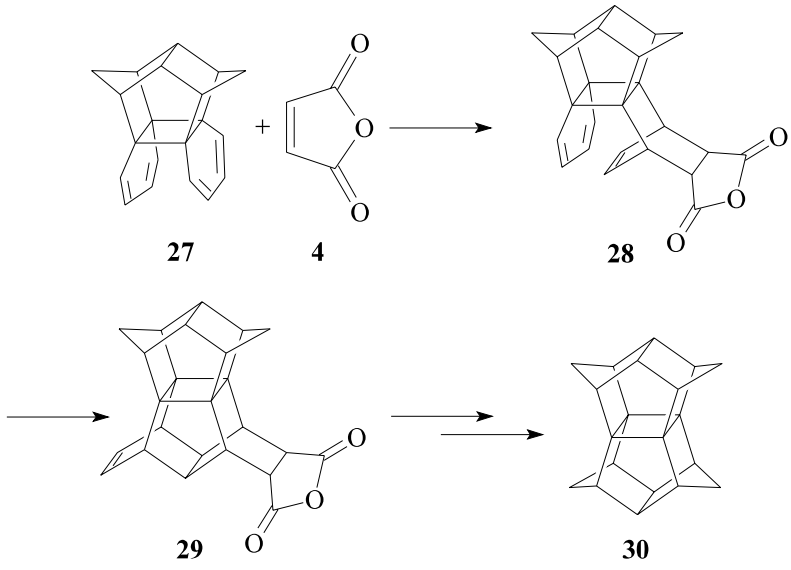
23 **24** **25**



26

Numerous examples of intramolecular Diels–Alder reactions have been reported;[22,23] especially from application in the synthesis of natural products, where stereoselectivity is of particular importance; e.g. syntheses of steroids.[24]

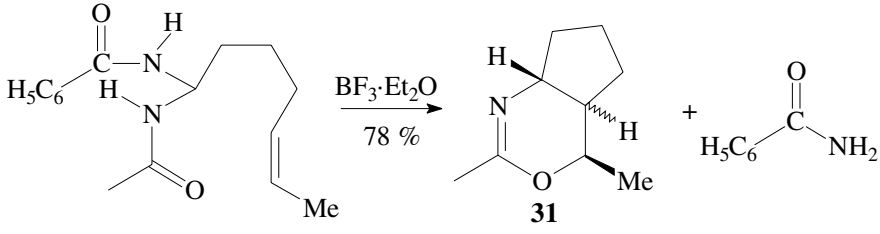
A *domino reaction*,[26] in this case consisting of an inter- and an intramolecular Diels–Alder reaction, is a key step in the synthesis of the hydrocarbon pagodane **30**, reported by *Prinzbach et al.*[25] When the *bis*-diene **27** is treated with maleic anhydride **4**, an initial intermolecular reaction leads to the intermediate product **28**, which cannot be isolated, but rather reacts intramolecularly to give the pagodane precursor **29**:



27 **4** **28**

29 **30**

The versatility of the Diels–Alder reaction becomes especially obvious, when considering the hetero-variants.[5] One or more of the carbon centers involved can be replaced by hetero atoms like nitrogen, oxygen and sulfur. An illustrating example is the formation of the bicyclic compound **31**, by an intramolecular *hetero-Diels–Alder reaction*:[5]



31

The Diels–Alder reaction is the most important method for the construction of six-membered rings. For example it can be used as a step in a benzo-anellation procedure. The experimental procedure is simple, and yields are generally good; side reactions play only a minor role.

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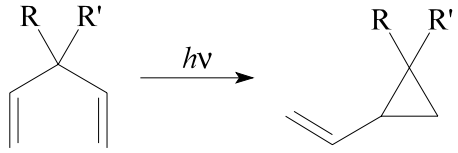
Di-π-Methane Rearrangement

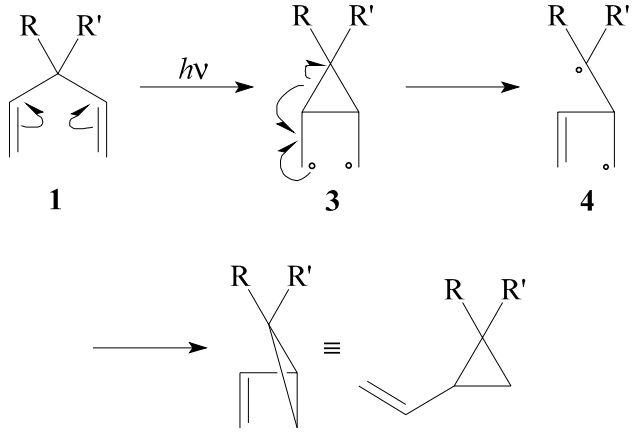
Photochemical rearrangement of 1,4-dienes to vinylcyclopropanes



1 **2**

The photochemical isomerization of 1,4-dienes **1**, bearing substituents at C-3, leads to vinyl-cyclopropanes **2**, and is called the *di-π-methane rearrangement*.[1,2,3] This reaction produces possible substrates for the *vinylcyclopropane rearrangement*.

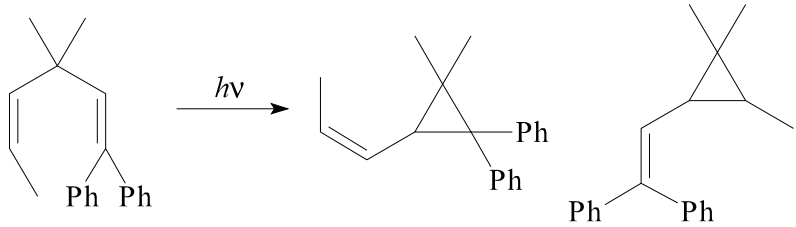
A mechanism has been formulated[2] that would involve formation of diradical species **3** and **4**, which however might not be real intermediates. At least one substituent at C-3 is required in order to stabilize the radical **4**, and thereby facilitate the cleavage of the C-2/C-3 bond:



1 **3** **4**

2

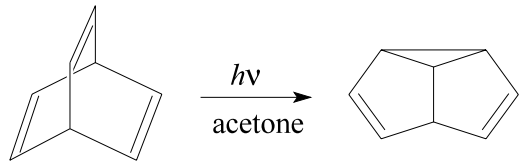
The rearrangement proceeds from the S_1-state of the 1,4-diene **1**. The T_1-state would allow for different reactions like double bond isomerization. Rigid systems like cyclic dienes, where *E*/*Z*-isomerization of a double bond is hindered for steric reasons, can react through the T_1-state. When the rearrangement proceeds from the S_1-state, it proves to be stereospecific at C-1 and C-5; no *E*/*Z*-isomerization is observed. *Z*-1,1-Diphenyl-3,3-dimethyl-1,4-hexadiene **5** rearranges to the *Z*-configured vinylcyclopropane **6**.[4] In this case the reaction also is regiospecific. Only the vinylcyclopropane **6** is formed, but not the alternative product **7**.[4]



5 **6** **7**

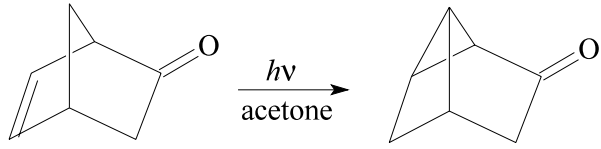
However, from substrates where the substituents at C-1 and C-5 are not that different in structure, a mixture of regioisomers may be obtained.

The di-π-methane rearrangement is a fairly recent reaction. One of the first examples has been reported in 1966 by Zimmerman and Grunewald[1] with the isomerization of barrelene **8** to semibullvalene **9**. This rearrangement reaction occurs in the presence of acetone as photosensitizer, and proceeds from the T_1-state.[5]



8 **9**

A related reaction is the *oxa-di-π-methane rearrangement*,[2,6] where one of the C=C double bonds is replaced by a C=O double bond. The substrates are thus β,γ-unsaturated ketones. The rearrangement proceeds from the triplet state. This *oxa*-variant gives access to highly strained molecules containing small rings, as has been demonstrated by irradiation of norborn-5-ene-2-one **10**:



10

Yields of the di-π-methane rearrangement reaction strongly depend on substrate structure, and are ranging from poor to nearly quantitative. Acetone and acetophenone have been used as photosensitizers.[4,5]

1. H. E. Zimmerman, G. L. Grunewald, *J. Am. Chem. Soc*. **1966**, *88*, 183–184.
2. S. S. Hixson, P. S. Mariano, H. E. Zimmerman, *Chem. Rev*. **1973**, *73*, 531–551.
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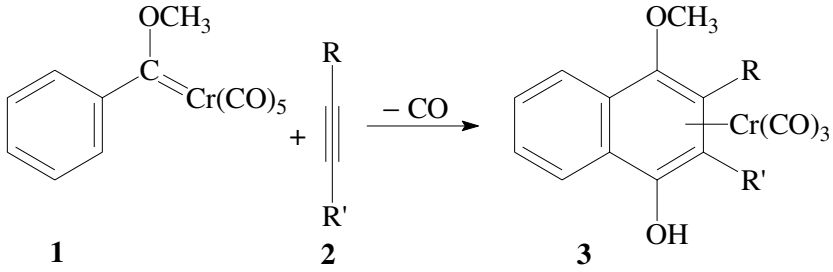
6. M. Demuth, G. Mikhail, *Synthesis* **1989**, 145–162.

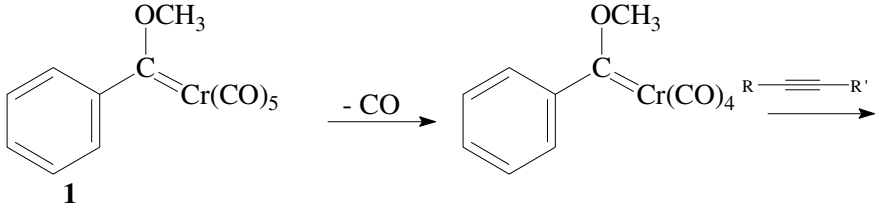
Dötz Reaction

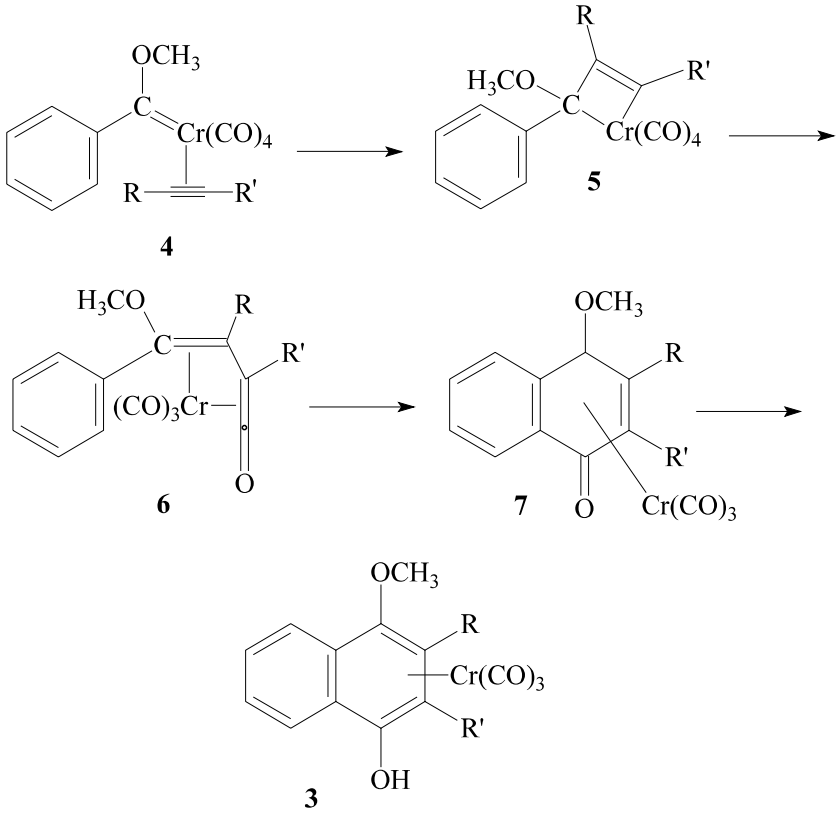
Benzo-anellation *via* chromium carbene complexes



The coupling reaction of an α,β-unsaturated chromium carbene complex, e.g. **1**, and an alkyne **2**, through coordination to the chromium center, is called the *Dötz reaction*.[1–3] The initial product is the chromium tricarbonyl complex of a hydroquinone derivative **3**, which can easily be converted to a free hydroquinone or quinone.

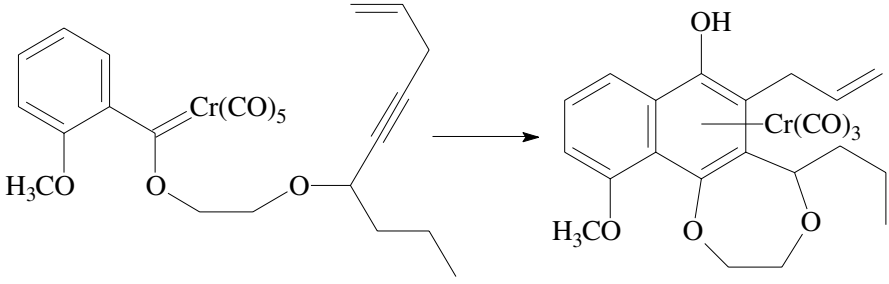
By a photochemically induced elimination of CO, a chromium carbene complex with a free coordination site is generated. That species can coordinate to an alkyne, to give the alkyne–chromium carbonyl complex **4**. The next step is likely to be a cycloaddition reaction leading to a four-membered ring compound **5**. A subsequent electrocyclic ring opening and the insertion of CO leads to the vinylketene complex **6**:[3–5]



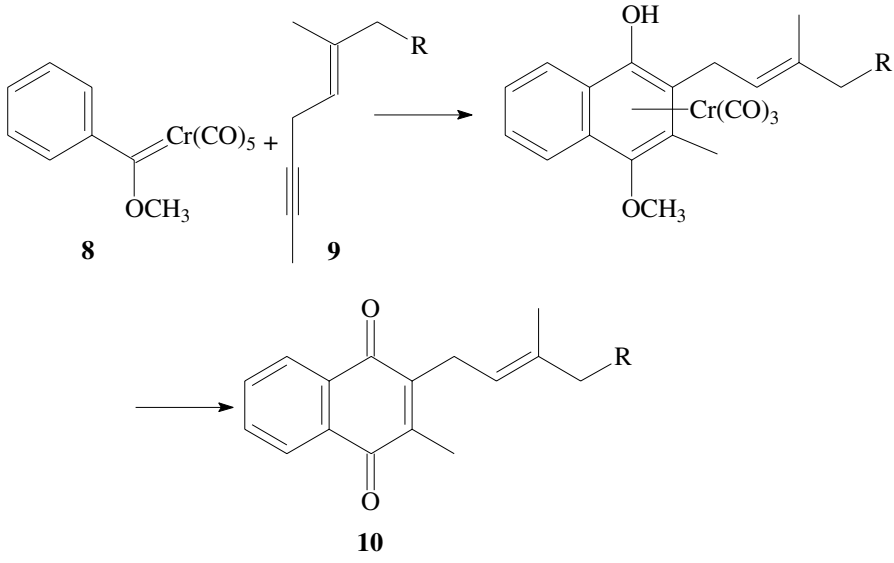


An electrocyclic ring closure then leads to a cyclohexadienone complex **7**, which upon migration of a proton, yields the chromium tricarbonyl-hydroquinone complex **3**.

The regioselectivity of the reaction with unsymmetrical alkynes is poor. Mixtures of isomers are obtained with alkyl substituted acetylenes, if the alkyl groups do not differ much in size. A solution to this problem has been reported by *Semmelhack et al.*[6] The reactants are connected by a $-OCH_2CH_2O$-tether, which can later be removed; the coupling step thus becomes intramolecular:

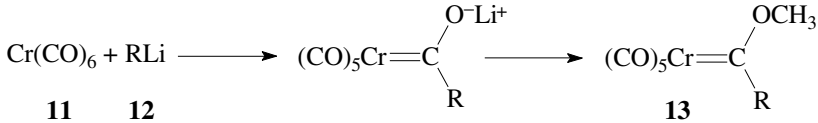


The synthetic value of the Dötz reaction has for example been demonstrated by the synthesis of vitamin $K_{1(20)}$ **10** (simplified structure). This natural product has been prepared synthetically from the chromium carbene complex **8** and the alkyne **9** in two steps; the second step being the oxidative decomplexation to yield the free product **10**:[7]



8 **9** **10**

Chromium carbene complexes like **13**, which are called *Fischer carbene complexes*,[3] can conveniently be prepared from chromium hexacarbonyl **11** and an organolithium compound **12**, followed by an O-alkylation step:



11 **12** **13**

The unsaturated substituent in the carbene complex **1** often is aromatic or heteroaromatic, but can also be olefinic. The reaction conditions of the Dötz procedure are mild; various functional groups are tolerated. Yields are often high. The use of chromium hexacarbonyl is disadvantageous, since this compound is considered to be carcinogenic;[8] however to date it cannot be replaced by a less toxic compound. Of particular interest is the benzo-anellation procedure for the synthesis of anthracyclinones, which are potentially cytostatic agents.[9]

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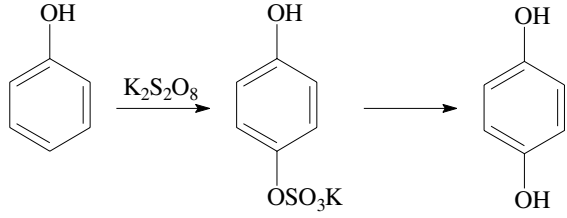
E

Elbs Reaction

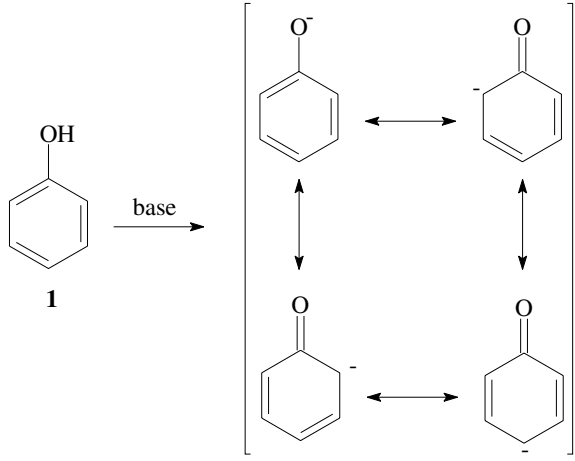
Oxidation of phenols by peroxodisulfate



1 **2** **3**

The hydroxylation of a phenol **1** upon treatment with a peroxodisulfate in alkaline solution, to yield a 1,2- or 1,4-dihydroxybenzene **3**, is called the *Elbs reaction*.[1,2]

The phenol is deprotonated by base to give a phenolate anion **4**, that is stabilized by resonance, and which is activated at the *ortho* or the *para* position towards reaction with an electrophilic agent:



1 **4**

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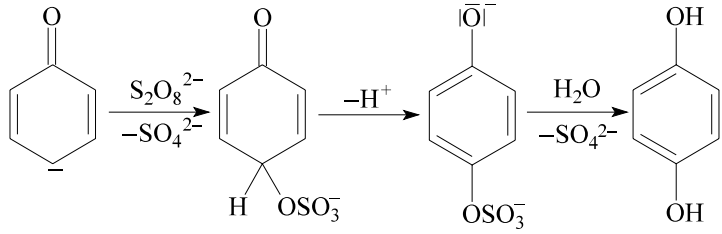
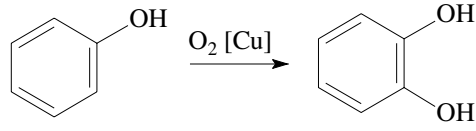
Reaction with the electrophilic peroxodisulfate occurs preferentially at the *para* position, leading to formation of a cyclohexadienone derivative **5**, which loses a proton to give the aromatic compound **6**. Subsequent hydrolysis of the sulfate **6** yields 1,4-dihydroxybenzene **3**:



5 **6** **3**

The main product of the Elbs reaction is the 1,4-dihydroxybenzene (hydroquinone). If the *para* position is already occupied by a substituent, the reaction occurs at an *ortho* position, leading to a catechol derivative; although the yields are not as good as for a hydroquinone. Better yields of catechols 7 can be obtained by a copper-catalyzed oxidation of phenols with molecular oxygen:[3]



1 **7**

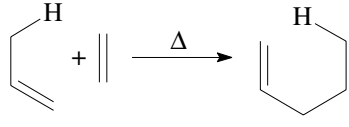
This reaction, that can be viewed as a modified Elbs reaction, often gives good yields, while the ordinary procedure often gives catechols in less then 50% yield.

Nevertheless the Elbs reaction is a valuable method for the preparation of dihydroxybenzenes. The experimental procedure is simple, and the reaction conditions are mild; a variety of functional groups is tolerated.

1. K. Elbs, *J. Prakt. Chem.* **1893**, 48, 179–185.
2. E. J. Behrman, *Org. React.* **1988**, *35*, 421–511.
3. P. Capdevielle, M. Maumy, *Tetrahedron Lett.* **1982**, *23*, 1573–1576 and 1577–1580.

Ene Reaction

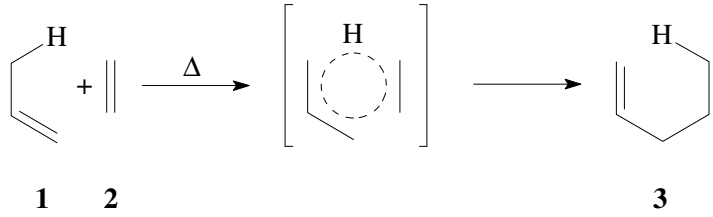
Addition of a double bond to an alkene with allylic hydrogen



1 **2** **3**

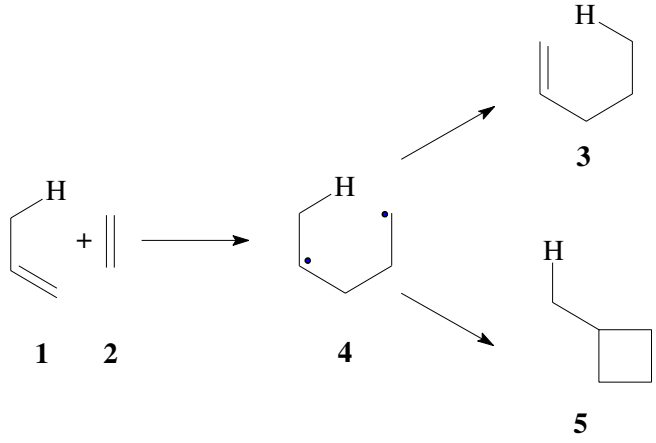
The *ene reaction* as a reaction principle has been first recognized and systematically investigated by *Alder*.[1] It is a thermal addition reaction of a double bond species **2**—the *enophile*—and an alkene **1**—the *ene*—that has at least one allylic hydrogen.[2] The intramolecular variant[3] is of greater synthetic importance than is the intermolecular reaction.

Just like the *Diels Alder reaction* or the 1,5-sigmatropic hydrogen shift, the ene reaction is believed to proceed *via* a six-membered aromatic transition state.



1 **2** **3**

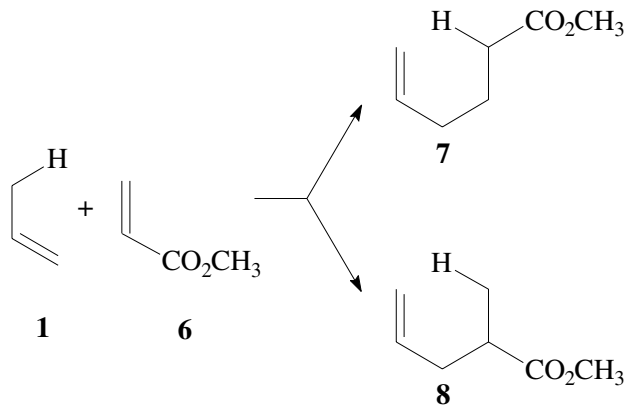
The overall reaction includes allylic transposition of a double bond, migration of the allylic hydrogen and formation of a bond between ene and enophile. Experimental findings suggest a concerted mechanism. Alternatively a diradical species **4** might be formed as intermediate; however such a species should also give rise to formation of a cyclobutane derivative **5** as a side-product. If such a by-product is not observed, one might exclude the diradical pathway:



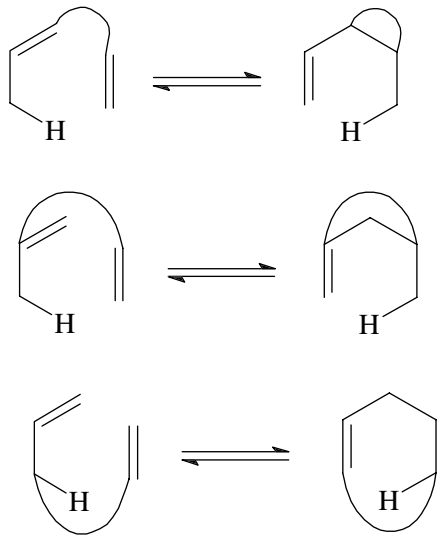
1 **2** **4**

A primary allylic hydrogen at the ene **1** is especially reactive; a secondary hydrogen migrates less facile, and a tertiary one is even less reactive. The enophile unit should be of an electron-poor nature; it can consist of a carbon–carbon double or triple bond, a carbonyl group or an azo group. Mixtures of regioisomeric products may be obtained with substituted enophiles. The acrylic ester **6** reacts with

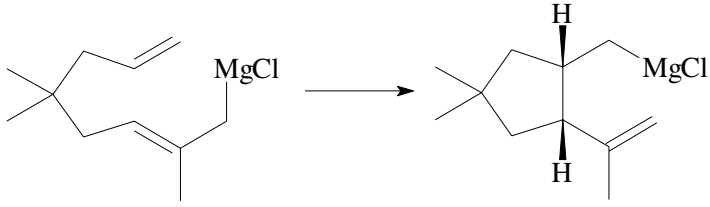
propene **1** to give the regioisomers **7** (88%) and **8** (12%):



For the intramolecular variant, synthetically valuable applications have been developed during the last decade.[4–6] Three types of intramolecular ene reactions are formulated—depending on the structure of the starting material:[3]

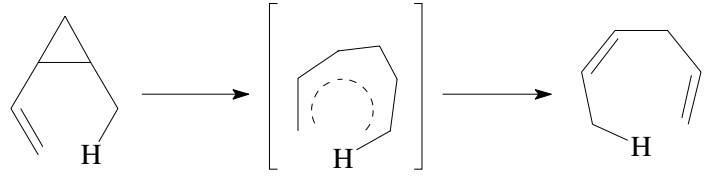


A modern variant is the intramolecular *magnesium-ene reaction*, e.g. the reaction of the alkene-allylic-Grignard compound **9** to give the five-membered ring product **10**. This reaction proceeds regio- and stereoselectively, and is a key step in a synthesis of the sesquiterpenoid 6-protoilludene:[6]



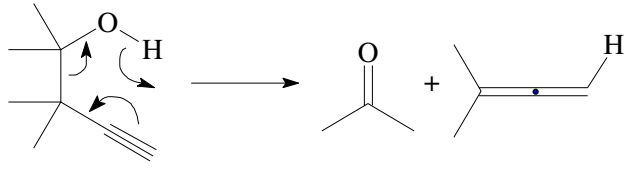
9 **10**

The *retro-ene reaction* also is of synthetic importance. While the application of high pressure facilitates the ene reaction, the retro-ene reaction is favored at higher temperatures.[2] Furthermore small-ring strain can shift the equilibrium towards the side of the dienes. The vinylcyclopropane **11** rearranges by a synchronous process to the open-chain diene **12**. Formally this process is the reverse of an intramolecular ene reaction:



11 **12**

β-Hydroxyalkenes are especially suitable starting materials for the retro-ene reaction; since a stable carbonyl compound is then released as product. The retro-ene reaction of β-hydroxyalkynes, e.g. **13** → **14**, can be used for the preparation of allenes:[7,8]



13 **14**

The reaction conditions for the ene reaction of simple starting materials are, for example, 220 °C for 20 h in an aromatic solvent like trichlorobenzene. Lewis acid-catalyzed intramolecular reactions have been described, e.g. with $FeCl_3$ in dichloromethane at −78 °C.[4] Yields strongly depend on substrate structure.

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2. H. M. R. Hoffmann, *Angew. Chem*. **1969**, *90*, 597–618; *Angew. Chem. Int. Ed. Engl*. **1969**, *8*, 556.
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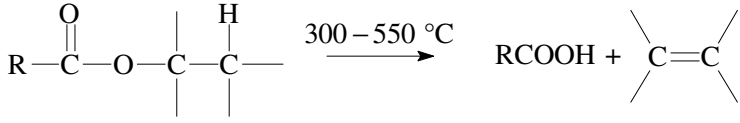
Ester Pyrolysis

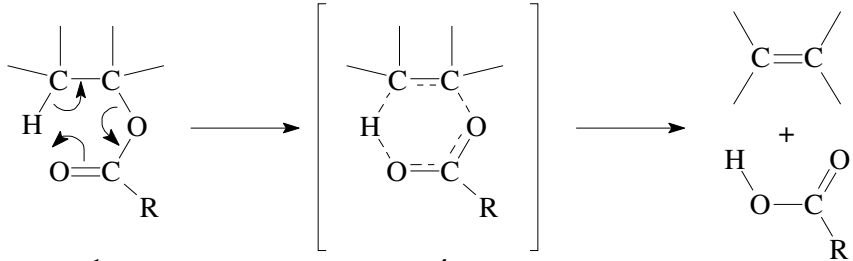
Alkenes by pyrolysis of carboxylic esters



1 **2** **3**

Carboxylic esters **1**, having an O-alkyl group with a β-hydrogen, can be cleaved thermally into the corresponding carboxylic acid **2** and an alkene **3**.[1,2] This reaction often is carried out in the gas phase; generally the use of a solvent is not necessary.

The reaction proceeds by an E_i-mechanism. The β-hydrogen and the carboxylate are cleaved synchronously from the substrate molecule, while forming a new bond. This elimination reaction belongs to the class of *syn*-eliminations; in the case of the ester pyrolysis, the substrate molecule passes through a six-membered cyclic transition state **4**:

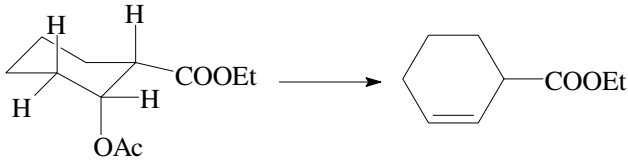


1 **4**

For the formation of the new double bond, the general rules for eliminations do apply. Following *Bredt's rule*, no double bond to a bridgehead carbon atom will be formed. If the elimination can lead to a conjugated system of unsaturated groups, this pathway will be favored. Otherwise the Hofmann rule will be followed, which favors an elimination towards the less substituted carbon center.

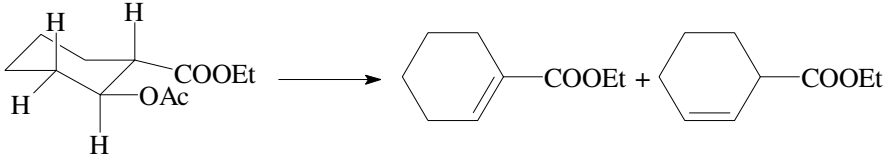
With cyclic substrates, the formation of the new double bond depends on the availability of a *cis*-β-hydrogen, which is required for the *syn*-elimination

mechanism. In the case of six-membered ring substrates this means that the β-hydrogen has to be equatorial for elimination with an axial acetate group (OAc), and axial for elimination with an equatorial acetate. The six-membered cyclic transition state **4** does not have to be completely coplanar. For example the pyrolysis of the cyclohexane derivative **5**, bearing an axial acetate group, yields the alkene **6** only,[3] by elimination of the axial acetate and the equatorial β-hydrogen:



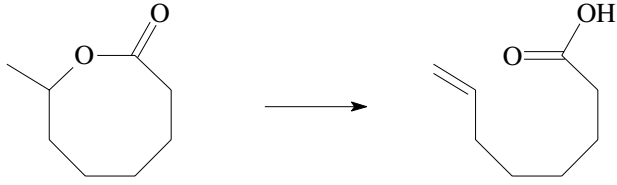
5 **6**

In the case of the cyclohexane derivative **7** however, that bears an equatorial acetate group, two axial cis-β-hydrogens are available, and elimination in both directions is possible. The pyrolysis of **7** yields the two elimination products **8** and **6**. Formation of product **8** is strongly favored, because the new double bond is in conjugation to the ester carbonyl group.[3]



7 **8** (97 %) **6** (3 %)

Rearrangements and other side-reactions are rare. The ester pyrolysis is therefore of some synthetic value, and is used instead of the dehydration of the corresponding alcohol. The experimental procedure is simple, and yields are generally high. Numerous alkenes have been prepared by this route for the first time. For the preparation of higher alkenes ($> C_{10}$), the pyrolysis of the corresponding alcohol in the presence of acetic anhydride may be the preferable method.[4] The pyrolysis of lactones **9** leads to unsaturated carboxylic acids **10**:[5]



9 **10**

Since the *syn*-elimination mechanism requires formation of a six-membered cyclic transition state, this reaction is not possible for five- or six-membered lactones, but may be applied to higher homologs.

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