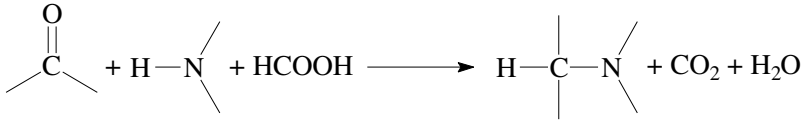
L

Leuckart–Wallach Reaction

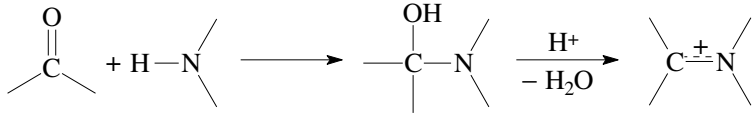
Reductive alkylation of amines



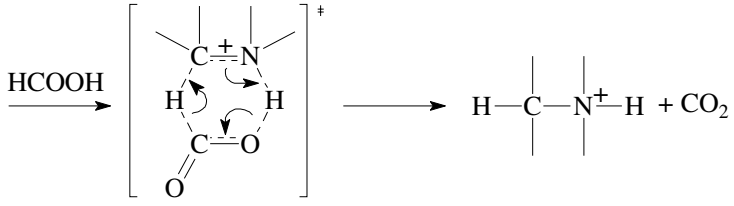
1 **2** **3** **4**

By application of the *Leuckart–Wallach reaction*,[1–3] amines **2** can be alkylated with a carbonyl compound **1**; formic acid is used as reductive agent, and is in turn oxidized to give carbon dioxide.

The carbonyl compound **1** is assumed to react first with amine **2** to give the unstable α-aminoalcohol **5** as intermediate,[3] from which an iminium species **6** is



1 **2** **5** **6**



7

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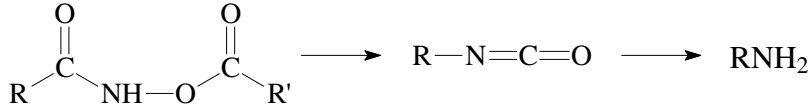
formed. The latter is reduced by reaction with formic acid *via* cyclic transition state **7** to yield the alkylated amine:
A primary or secondary amine can be used, as well as ammonia. With respect to the carbonyl component used, the best results have been obtained with aromatic aldehydes and with high boiling ketones.

The usual procedure is to simply heat a mixture of the starting materials. A common side-reaction is the polyalkylation; it can be suppressed by employing an excess of amine. In addition carbonyl substrates with α-hydrogens may undergo competitive *aldol reactions*; the corresponding reaction products may then undergo a subsequent Leuckart–Wallach reaction.

1. R. Leuckart, *Ber. Dtsch. Chem. Ges*. **1885**, *18*, 2341–2344.
2. M. L. Moore, *Org. React*. **1949**, *5*, 301–330.
3. A. Lukasiewicz, *Tetrahedron* **1963**, *19*, 1789–1799.

Lossen Reaction

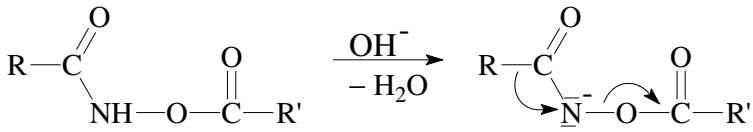
Isocyanates from hydroxamic acids



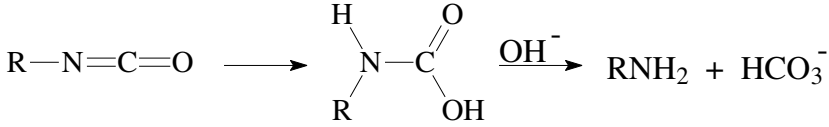
1 **2** **3**

In the *Lossen reaction*[1,2] a hydroxamic acid derivative (usually an O-acyl derivative) is deprotonated by base, and rearranges *via* migration of the group R to give an isocyanate **2**. Under the usual reaction conditions—i.e. aqueous alkaline solution—the isocyanate reacts further to yield the amine **3**. The Lossen reaction is closely related to the *Hofmann rearrangement* and the *Curtius reaction*.

By reaction of the hydroxamic acid derivative **1** with a base, the anionic species **4** is formed. Cleavage of the leaving group from the nitrogen and migration of the group R from the carbon center to the developing electron-deficient nitrogen center are concerted—just like in the Hofmann rearrangement. The isocyanate formally is the final product of the Lossen reaction:



1 **4**



2 **5** **3**

In aqueous alkaline solution, the isocyanate is unstable; it reacts by addition of water to give the intermediate carbaminic acid **5**, which subsequently decarboxylates to yield the amine **3**.

Unsubstituted hydroxamic acids do not undergo the Lossen reaction.[3] An activation by an electron-acceptor substituent is necessary—e.g. by an acyl group. Furthermore a carboxylate anion is a much better leaving group as is the hydroxide anion. A substituent R with electro-donating properties can also facilitate the reaction. With substrates containing a chiral group R, the configuration of R is usually retained.

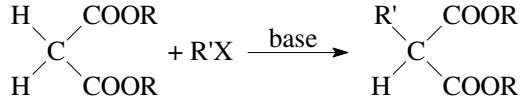
The Lossen reaction is of limited importance in synthetic organic chemistry; one reason for that is the poor availability of the required hydroxamic acid derivatives. Some hydroxamic acids are even unreactive.[4]

1. W. Lossen, *Justus Liebigs Ann. Chem.* **1872**, *161*, 347–362.
2. H. L. Yale, *Chem. Rev.* **1943**, *33*, 209–256.
3. L. Bauer, O. Exner, *Angew. Chem.* **1974**, *86*, 419–428; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 376.
4. G. B. Bachmann, J. E. Goldmacher, *J. Org. Chem.* **1964**, *29*, 2576–2579.

M

Malonic Ester Synthesis

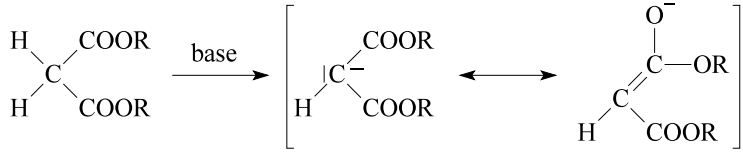
Alkylation of malonic esters



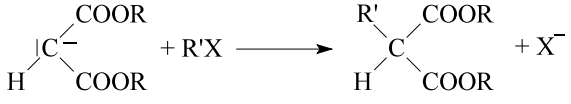
1 **2** **3**

Compounds bearing two strongly electron-withdrawing groups at a methylene or methine group can be deprotonated and subsequently alkylated at that position;[1,2] as alkylating agent an alkyl halide **2** is often used. The most important reaction of this type is known as the *malonic ester synthesis*, where both electron-withdrawing substituents are ester groups; see scheme above **1** → **3**.

The reactive species is the corresponding enolate-anion **4** of malonic ester **1**. The anion can be obtained by deprotonation with a base; it is stabilized by resonance. The alkylation step with an alkyl halide **2** proceeds by a S_N2 reaction:



1 **4**



4 **2** **3**

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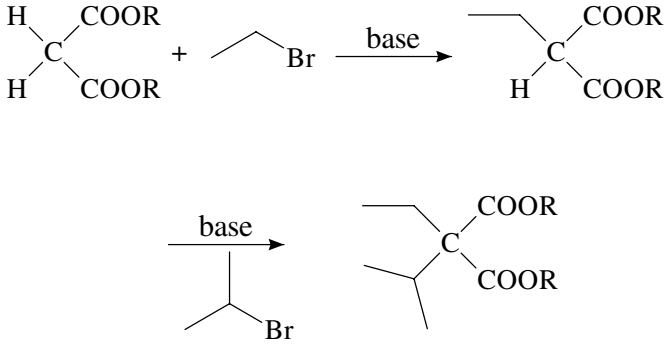
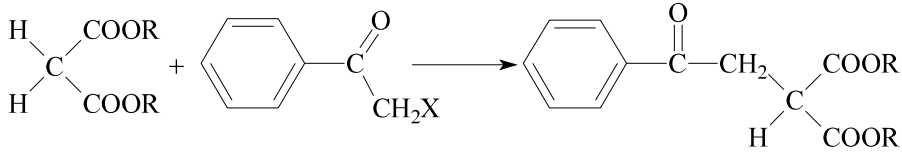
In order to generate a sufficient amount of malonic ester-enolate **4** in the reaction mixture, the corresponding acid BH^+ of the base and the solvent used, have to be less acidic than malonic ester **1**. A metal alkoxide is often used as base—e.g. sodium ethoxide or potassium *t*-butoxide. Usually that alkoxide is employed that corresponds to the ester alkyl, in order to avoid the formation of a product mixture through exchange of the alkoxy groups at the carbonyl center. For the same reason, the corresponding alcohol is used as solvent. Inert solvents are often less suitable, since the starting materials may not be sufficiently soluble, and the strength of the base will usually differ from that in the system RO^-/ROH.

The rate of the alkylation reaction depends on the enolate concentration, since it proceeds by a S_N2-mechanism. If the concentration of the enolate is low, various competitive side-reactions may take place. As expected, among those are E2-eliminations by reaction of the alkyl halide **2** with base. A second alkylation may take place with *mono*-alkylated product already formed, to yield a *bis*-alkylated malonic ester; however such a reaction is generally slower than the alkylation of unsubstituted starting material by a factor of about 10^2. The monoalkylation is in most cases easy to control. Dialkylated malonic esters with different alkyl substituents—e.g. ethyl and isopropyl—can be prepared by a step by step reaction sequence:

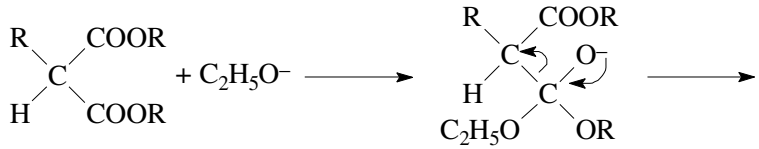


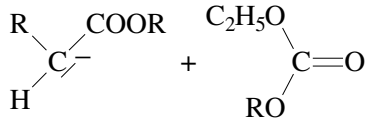
With highly reactive alkyl halides, like allylic, benzylic or phenacyl halides, the *bis*-alkylation can be a serious side-reaction. Because of a S_N1-like mechanism in those cases, the effect of enolate concentration on the reaction rate is low, and the resulting monoalkylester **5** may be more acidic than the unsubstituted starting material:



5

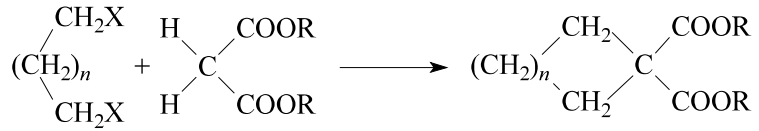
In general the *bis*-alkylation can be suppressed by using excess malonic ester **1**. Another side-reaction is the decarbalkoxylation, whereby dialkyl carbonates **6** are formed:





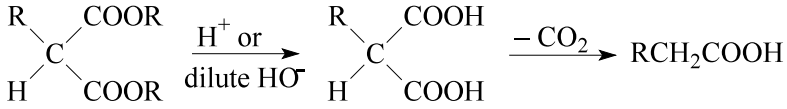
6

An important application of the potential for bis-alkylation is the use of a dihalide **7** as alkylating agent. This variant allows for the synthesis of cyclic compounds **8**; by this route, mainly five- to seven-membered ring compounds have been prepared:[3]



7 **1** **8**

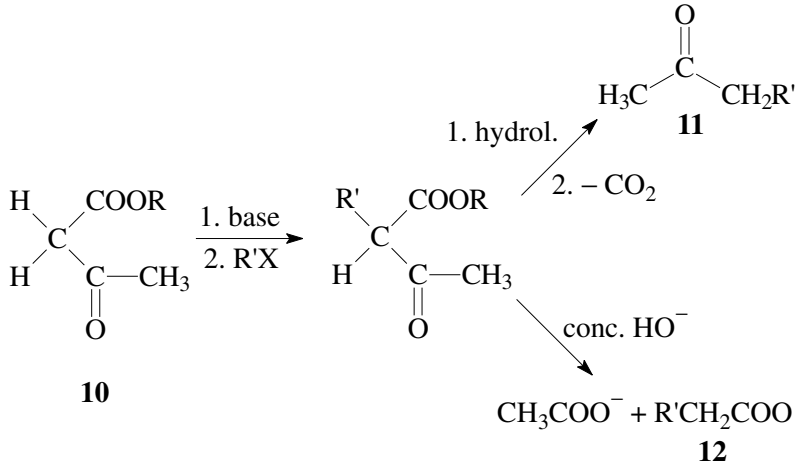
The synthetic importance of the malonic ester synthesis follows from the fact that the substituted malonic ester can easily be hydrolyzed, and subsequently decarboxylates to yield a substituted acetic acid **9**. This route to substituted acetic acids is an important method in organic synthesis:

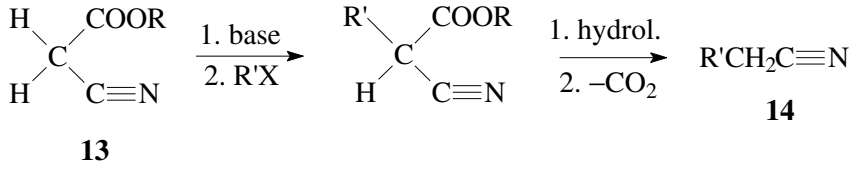


3 **9**

As alkylating agents may for example be used: alkyl halides, dialkyl sulfates, alkyl sulfonates and epoxides. Aryl halides and vinylic halides do not react.

Related and equally important reactions are the *acetoacetic ester synthesis* and the *cyanoacetic ester synthesis*.[2] Here too the initial substituted product can be hydrolyzed and decarboxylated, to yield a ketone **11** (i.e. a substituted acetone) from acetoacetic ester **10**, and a substituted acetonitrile **14** from cyanoacetic ester **13** respectively. Furthermore a substituted acetoacetic ester can be cleaved into a substituted acetic ester **12** and acetate by treatment with strong alkali:



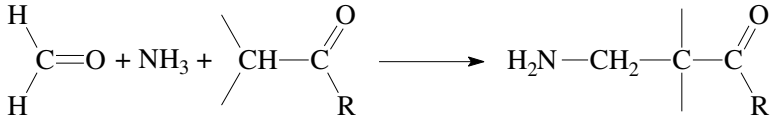


With two acidic CH-centers present in the starting material, the deprotonation and subsequent substitution (e.g. alkylation) takes place at the more acidic position; as shown above, acetoacetic ester will be alkylated at the methylene group rather than the methyl group. A substitution at the less acidic methyl group can be achieved by first converting the acetoacetic ester into its dianion; the reaction with an alkylating agent will then first take place at the more reactive, less acidic (i.e. stronger basic) position.

1. J. Wislicenus, *Justus Liebigs Ann. Chem.* **1877**, *186*, 161–228.
2. A. C. Cope, H. L. Holmes, H. O. House, *Org. React.* **1957**, *9*, 107–331.
3. N. S. Zefirov, T. S. Kuznetsova, S. I. Kozhushkov, L. S. Surmina, Z. A. Rashchupkina, *J. Org. Chem. USSR* **1983**, *19*, 474–480.

Mannich Reaction

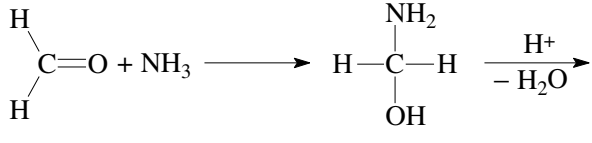
Aminomethylation of CH-acidic compounds



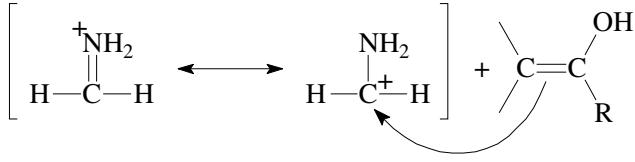
1 **2** **3** **4**

The condensation reaction of a CH-acidic compound—e.g. a ketone **3**—with formaldehyde **1** and ammonia **2** is called the *Mannich reaction*;[1–5] the reaction products **4** are called *Mannich bases*. The latter are versatile building blocks in organic synthesis, and of particular importance in natural products synthesis.

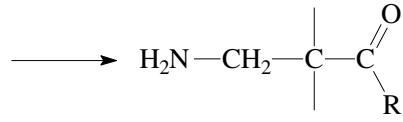
There have been extensive investigations on the reaction mechanism.[6,7] In most cases the reaction proceeds *via* initial nucleophilic addition of ammonia **2** to formaldehyde **1** to give adduct **5**, which is converted into an iminium ion species **6** (note that a resonance structure—an aminocarbenium ion can be formulated) through protonation and subsequent loss of water. The iminium ion species **6** then reacts with the enol **7** of the CH-acidic substrate by overall loss of a proton:



1 **2** **5**



6 **7**



4

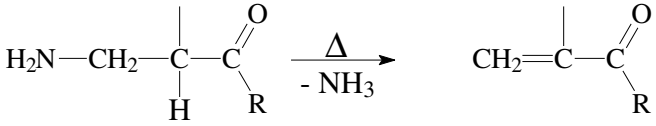
Instead of formaldehyde, other aldehydes or ketones may be used—aliphatic as well as aromatic; recently methylene dihalides have been employed with success. The amine component is often employed as hydrochloride; in addition to

ammonia, aliphatic amines, hydroxylamine or hydrazine can be used. Aromatic amines usually do not undergo the reaction.

As solvent an alcohol—often ethanol—as well as water or acetic acid can be used. The reaction conditions vary with the substrate; various CH-acidic compounds can be employed as starting materials. The Mannich bases formed in the reaction often crystallize from the reaction mixture, or can be isolated by extraction with aqueous hydrochloric acid.

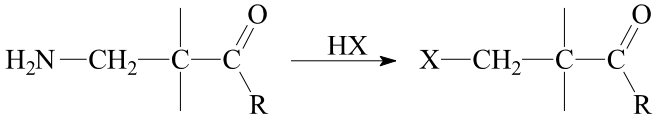
With an unsymmetrical ketone as CH-acidic substrate, two regioisomeric products can be formed. A regioselective reaction may in such cases be achieved by employing a preformed iminium salt instead of formaldehyde and ammonia. An iminium salt reagent—the *Eschenmoser salt*—has also found application in Mannich reactions.[8,9]

Because of their manifold reactivity, Mannich bases **4** are useful intermediates in organic synthesis. For example the elimination of amine leads to formation of an α,β-unsaturated carbonyl compound **8**:



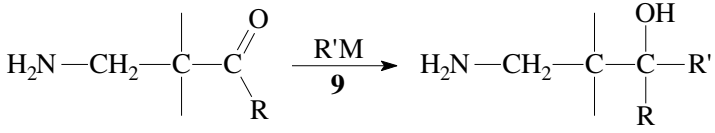
4 **8**

Furthermore, a substitution of the amino group is possible. An important application of Mannich bases **4** is their use as alkylating agents:[3]



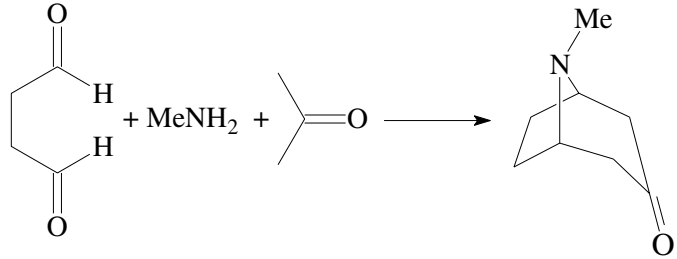
4

The reaction with organolithium or organomagnesium reagents **9** leads to formation of β-aminoalcohols **10**:



4 **10**

The Mannich reactions plays an important role in pharmaceutical chemistry. Many β-aminoalcohols show pharmacological activity. The Mannich reaction can take place under physiological conditions (with respect to pH, temperature, aqueous solution), and therefore can be used in a biomimetic synthesis; e.g. in the synthesis of alkaloids.



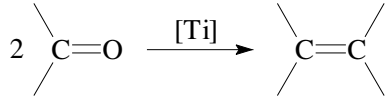
11 **12** **13** **14**

The synthesis of tropinone **14**, a precursor of atropine and related compounds, is a classical example. In 1917 *Robinson*[10] has prepared tropinone **14** by a Mannich reaction of succindialdehyde **11** and methylamine **12** with acetone **13**; better yields of tropinone were obtained when he used the calcium salt of acetonedicarboxylic acid instead of acetone. Modern variants are aimed at control of regio- and stereoselectivity of the Mannich reaction.[11]

1. C. Mannich, *Arch. Pharm*. **1917**, *255*, 261–276.
2. F. F. Blicke, *Org. React*. **1942**, *1*, 303–341.
3. M. Tramontini, *Synthesis* **1973**, 703–775.
4. G. A. Gevorgyan, A. G. Agababyan, O. L. Mndzhoyan, *Russ. Chem. Rev*. **1984**, *53*, 561–581.
5. M. Tramontini, L. Angiolini, *Tetrahedron* **1990**, *46*, 1791–1837.
   L. Overman, *Acc. Chem Res*. **1992**, *25*, 352–359;
   L. Overman, *Aldrichim. Acta* **1995**, *28*, 107–119.
6. B. Thompson, *J. Pharm. Sci*. **1968**, *57*, 715–733.
7. T. F. Cummings, J. R. Shelton, *J. Org. Chem*. **1960**, *25*, 419–423.
8. J. Schreiber, H. Maag, N. Hashimoto, A. Eschenmoser, *Angew.Chem*. **1971**, *83*, 355–357; *Angew. Chem. Int. Ed. Engl*. **1971**, *10*, 330.
9. N. Holy, R. Fowler, E. Burnett, R. Lorenz *Tetrahedron* **1979**, *35*, 613–618.
10. R. Robinson, *J. Chem. Soc*. **1917**, *111*, 762–768.
11. M. Arend, B. Westermann, N. Risch, *Angew. Chem.* **1998**, *110*, 1096–1122; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1044.

McMurry Reaction

Reductive coupling of aldehydes or ketones

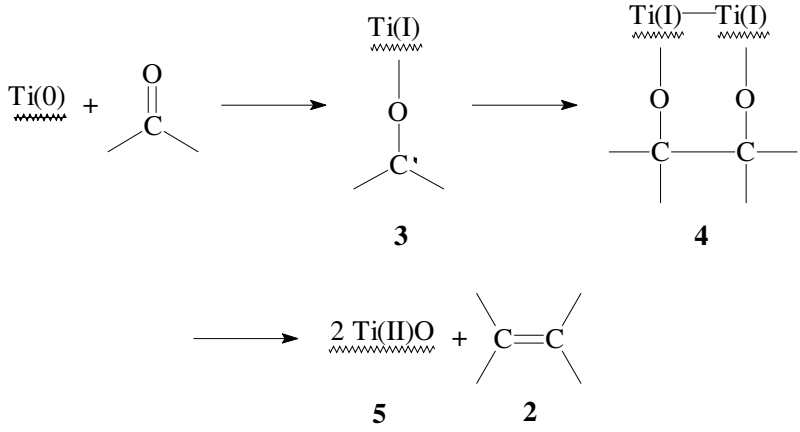


1 **2**

Among the more recent name reactions in organic chemistry, the *McMurry reaction*[1–3] is of particular importance as a synthetic method. It permits the

reductive dimerization of aldehydes or ketones **1** to yield alkenes **2** by reaction with low-valent titanium as reducing agent.

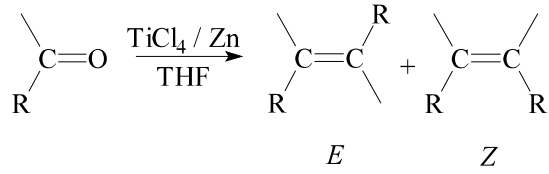
The initial step of the coupling reaction is the binding of the carbonyl substrate to the titanium surface, and the transfer of an electron to the carbonyl group.[3] The carbonyl group is reduced to a radical species **3**, and the titanium is oxidized. Two such ketyl radicals can dimerize to form a pinacolate-like intermediate **4**, that is coordinated to titanium. Cleavage of the C−O bonds leads to formation of an alkene **2** and a titanium oxide **5**:



Under appropriate reaction conditions—e.g. at low temperatures—the cleavage of the C−O bonds does not take place, and a vicinal diol can be isolated as product.[4]

The low-valent titanium reagents used are not soluble under the reaction conditions; the McMurry coupling is thus a heterogenous reaction. Low-valent titanium can be prepared from $TiCl_4$ or $TiCl_3$ by reaction with, e.g., lithium aluminum hydride, an alkali metal (Li, Na or K), magnesium or zinc-copper couple. The low-valent titanium reagent has to be prepared freshly prior to reaction. Depending on molar ratio and the reductive agent used, a reagent is obtained that contains titanium of different oxidation states; however Ti(0) appears to be the active species.

The coupling of unsymmetrical ketones leads to formation of stereoisomeric alkenes; the ratio depending on steric demand of substituents R:[2]

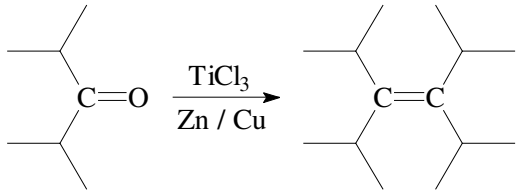


R = *n*-Propyl $E/Z = 3 : 1$

R = *tert*-Butyl $E/Z = 200 : 1$

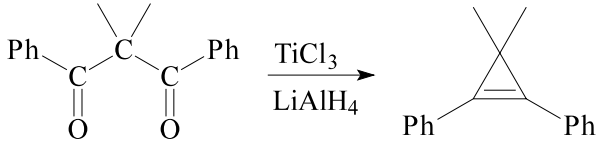
The intermolecular McMurry reaction is first of all a suitable method for the synthesis of symmetrical alkenes. With a mixture of carbonyl compounds as starting material, the yield is often poor. An exception to this being the coupling of diaryl ketones with other carbonyl compounds, where the mixed coupling product can be obtained in good yield. For example benzophenone and acetone (stoichiometric ratio 1 : 4) are coupled in 94% yield.[5]

The McMurry procedure is a valuable method for the synthesis of highly substituted, strained alkenes; such compounds are difficult to prepare by other methods. Diisopropyl ketone **6** can be coupled to give tetraisopropylethene **7** in 87% yield; attempts to prepare tetra-*t*-butylethene however were not successful.[3,6]



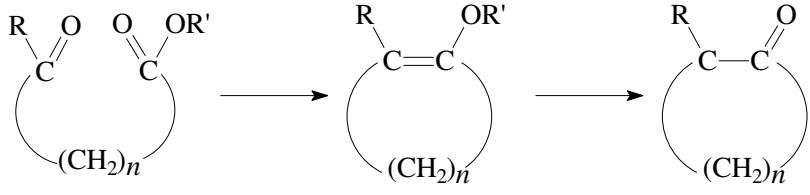
6 **7**

Highly strained cyclic compounds are accessible by an intramolecular variant. An instructive example for the synthetic potential of the McMurry coupling reaction is the synthesis of 3,3-dimethyl-1,2-diphenylcyclopropene **8**:[7]



8

Ketoesters **9** can be coupled to give enol ethers **10**, which may for example be converted to cycloalkanones by hydrolysis.



9 **10** **11**

The McMurry reaction is a valuable tool in organic synthesis. Yields are generally good, even for sterically demanding targets. The optimal ratio of titanium precursor and reducing agent has to be adjusted for a particular reaction. Functional groups that can be reduced by low-valent titanium usually will interfere with the attempted coupling reaction.

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   A. Fürstner, *Angew. Chem.* **1993**, *105*, 171; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 164.
   A. Fürstner, B. Bogdanovic, *Angew. Chem.* **1996**, *108*, 2582–2609; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2442.
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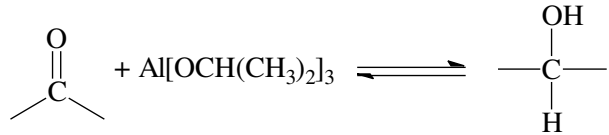
Meerwein–Ponndorf–Verley Reduction

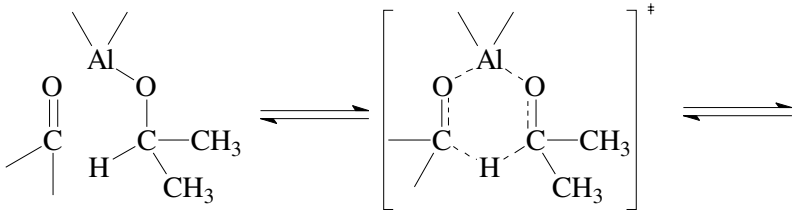
Reduction of aldehydes and ketones with aluminum isopropoxide



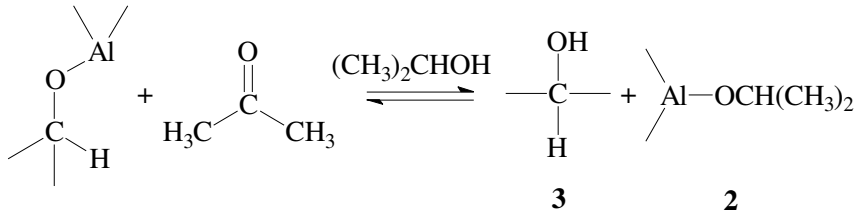
1 **2** **3**

The reduction of ketones to secondary alcohols and of aldehydes to primary alcohols using aluminum alkoxides is called the *Meerwein–Ponndorf–Verley reduction*.[1–4] The reverse reaction also is of synthetic value, and is called the *Oppenauer oxidation*.[5,6]

The aldehyde or ketone, when treated with aluminum triisopropoxide in isopropanol as solvent, reacts *via* a six-membered cyclic transition state **4**. The aluminum center of the Lewis-acidic reagent coordinates to the carbonyl oxygen, enhancing the polar character of the carbonyl group, and thus facilitating the hydride transfer from the isopropyl group to the carbonyl carbon center. The intermediate mixed aluminum alkoxide **5** presumably reacts with the solvent isopropanol to yield the product alcohol **3** and regenerated aluminum triisopropoxide **2**; the latter thus acts as a catalyst in the overall process:



1 **2** **4**



3 **2**

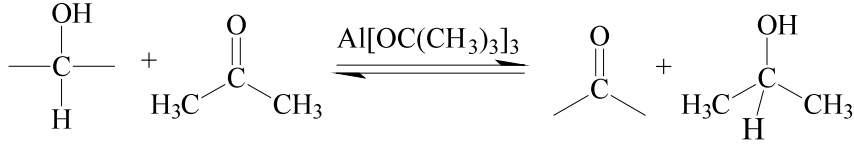
Thus one of the transferred hydrogens comes from the aluminum reagent, and the other one from the solvent. In addition to the mechanism *via* a six-membered cyclic transition state, a radical mechanism is discussed for certain substrates.[7]

In order to shift the equilibrium of the reaction, the low boiling reaction product acetone is continuously removed from the reaction mixture by distillation. By keeping the reaction mixture at a temperature slightly above the boiling point of acetone, the reaction can then be driven to completion.

Other Lewis-acidic alkoxides might also be employed; however aluminum isopropoxide has the advantage to be sufficiently soluble in organic solvents, and acetone as oxidation product can be easily removed for its low boiling point. Recently lanthan isopropoxide[8] has been used with success, and showed good catalytic activity.

The Meerwein–Ponndorf–Verley procedure has largely been replaced by reduction procedures that use lithium aluminum hydride, sodium borohydride or derivatives thereof. The Meerwein–Ponndorf–Verley reduction however has the advantage to be a mild and selective method, that does not affect carbon–carbon double or triple bonds present in the substrate molecule.

The reverse reaction, the so-called *Oppenauer oxidation*, is carried out by treating a substrate alcohol with aluminum tri-*t*-butoxide in the presence of acetone. By using an excess of acetone, the equilibrium can be shifted to the right, yielding the ketone **1** and isopropanol:



1

As a synthetic method however the Oppenauer oxidation is of limited importance.

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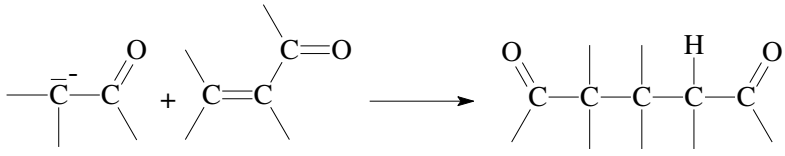
Michael Reaction

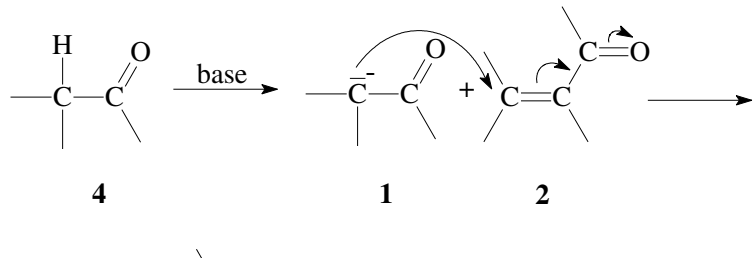
1,4-Addition to α,β-unsaturated carbonyl compounds



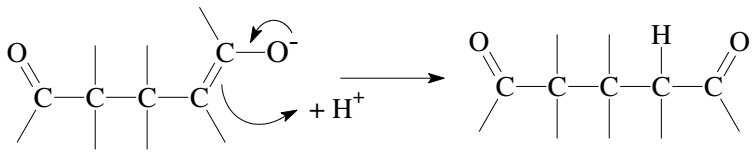
1 **2** **3**

The 1,4-addition of an enolate anion **1** to an α,β-unsaturated carbonyl compound **2**, to yield a 1,5-dicarbonyl compound **3**, is a powerful method for the formation of carbon–carbon bonds, and is called the *Michael reaction* or *Michael addition*.[1,2] The 1,4-addition to an α,β-unsaturated carbonyl substrate is also called a *conjugate addition*. Various other 1,4-additions are known, and sometimes referred to as *Michael-like additions*.

The enolate anion **1** may in principle be generated from any enolizable carbonyl compound **4** by treatment with base; the reaction works especially well with β-dicarbonyl compounds. The enolate **1** adds to the α,β-unsaturated compound **2** to give an intermediate new enolate **5**, which yields the 1,5-dicarbonyl compound **3** upon hydrolytic workup:



4 **1** **2**



5 **3**

As enolate precursors can be used CH-acidic carbonyl compounds such as malonic esters, cyanoacetic esters, acetoacetic esters and other β-ketoesters, as well as aldehydes and ketones. Even CH-acidic hydrocarbons such as indene and fluorene can be converted into suitable carbon nucleophiles.

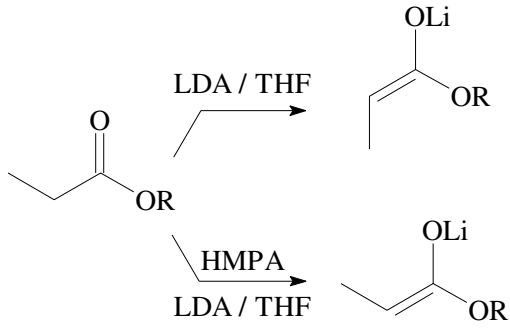
The classical Michael reaction is carried out in a protic organic solvent—e.g. an alcohol—by use of an alkoxide as base—e.g. potassium *t*-butoxide or sodium ethoxide.

The overall process is the addition of a CH-acidic compound to the carbon–carbon double bond of an α,β-unsaturated carbonyl compound. The Michael reaction is of particular importance in organic synthesis for the construction of the carbon skeleton. The above CH-acidic compounds usually do not add to ordinary carbon-carbon double bonds. Another and even more versatile method for carbon–carbon bond formation that employs enolates as reactive species is the *aldol reaction*.

Various competitive reactions can reduce the yield of the desired Michael-addition product. An important side-reaction is the 1,2-addition of the enolate to the C=O double bond (see *aldol reaction*, *Knoevenagel reaction*); especially with α,β-unsaturated aldehydes, the 1,2-addition product may be formed preferentially, rather than the 1,4-addition product. Generally the 1,2-addition is a kinetically favored and reversible process. At higher temperatures, the thermodynamically favored 1,4-addition products are obtained.

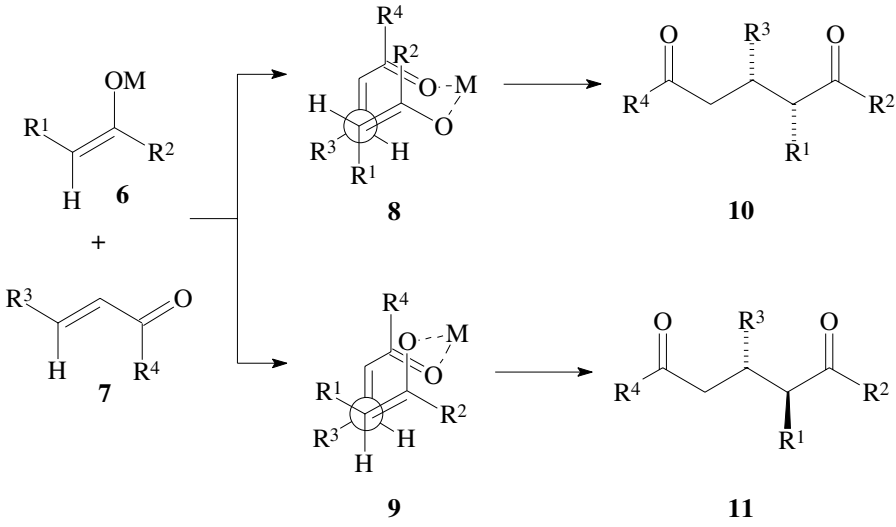
Certain starting materials may give rise to the non-selective formation of regioisomeric enolates, leading to a mixture of isomeric products. Furthermore α,β-unsaturated carbonyl compounds tend to polymerize. The classical Michael procedure (i.e. polar solvent, catalytic amount of base) thus has some disadvantages, some of which can be avoided by use of preformed enolates. The CH-acidic carbonyl compound is converted to the corresponding enolate by treatment with an equimolar amount of a strong base, and in a second step the α,β-unsaturated carbonyl compound is added—often at low temperature. A similar procedure is applied for variants of the *aldol reaction*.

Substituted enolates are usually obtained as a mixture of *E*- and *Z*-isomers; under suitable reaction conditions, one particular isomer may be obtained preferentially:[4]



The stereochemical outcome of the Michael addition reaction with substituted starting materials depends on the geometry of the α,β-unsaturated carbonyl compound as well as the enolate geometry; a stereoselective synthesis is possible.[3,4] Diastereoselectivity can be achieved if both reactants contain a stereogenic center. The relations are similar to the aldol reaction, and for

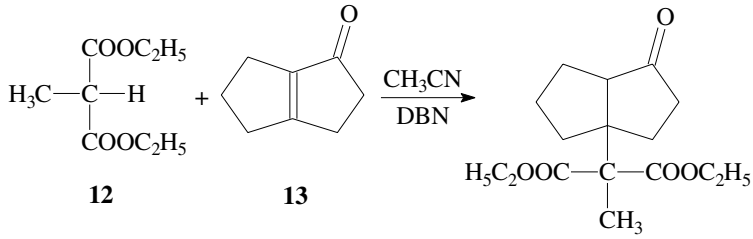
kinetically controlled Michael reactions, the observed selectivities can be rationalized by taking into account the diastereomeric transition states. For diastereoselective reactions, four cases have to be considered, since enolate **1** and acceptor **2** can each exist as *E*- as well as *Z*-isomer. If for example a *Z*-enolate **6** reacts with an *E*-configurated acceptor **7**, two staggered transition states **8** and **9** can be written, where the reactants are brought together through coordination to the metal center (chelation control):



Transition state **8**, which would lead to the *syn*-addition product **10**, is energetically disfavored because of mutual steric hindrance of groups R^2 and R^4. The predominant formation of *anti*-products **11** is generally observed, and is believed to proceed via the favored transition state **9**. The actual diastereoselectivity strongly depends on the steric demand of R^2 and R^4. Analogous considerations apply to the other combinations, and can be summarized as follows. An *E*-configured enolate reacts with an *E*-configured acceptor to give the *syn*-product; *Z*-enolate and *E*-acceptor react to yield preferentially the *anti*-product. For reactions with a *Z*-configured acceptor the opposite diastereoselectivities are observed.

With the use of chiral reagents a differentiation of enantiotopic faces is possible, leading to an enantioselective reaction. The stereoselective version of the Michael addition reaction can be a useful tool in organic synthesis, for instance in the synthesis of natural products.

An interesting feature is the sometimes observed pressure dependence of the reaction.[5] The Michael addition of dimethyl methylmalonate **12** to the bicyclic ketone **13** does not occur under atmospheric pressure, but can be achieved at 15 Kbar in 77% yield:



12 **13**

The Michael reaction is of great importance in organic synthesis.

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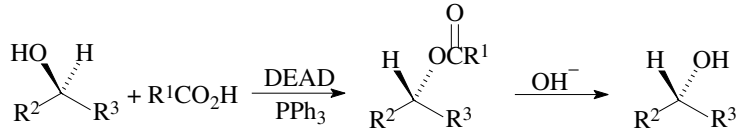
   For intramolecular variants see: M. Ihara, K. Fukumoto, *Angew. Chem.* **1993**, *105*, 1059–1071; *Angew. Chem. Int. Ed. Engl.* **1993**, 1010.
   R. D. Little, M. R. Masjedizadeh, O. Wallquist, J. I. McLoughliu, *Org. React.* **1995**, *47*, 315–552.

Mitsunobu Reaction

Esterification of an alcohol with carboxylic acid in the presence of dialkyl azodicarboxylate and triphenylphosphine

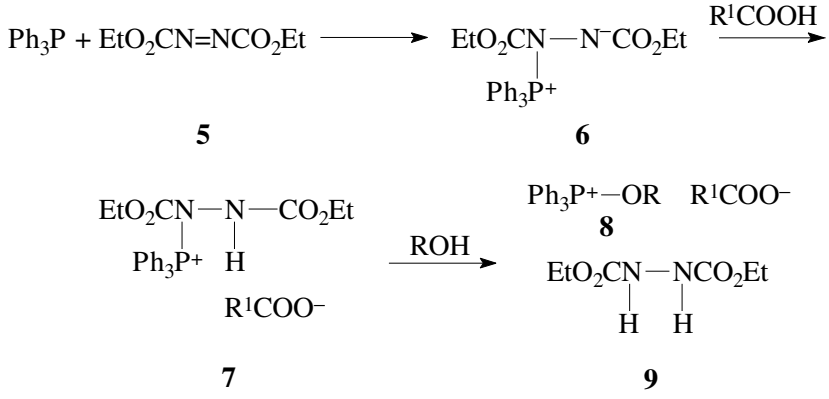


1 **2** **3** **4**

The major application of the *Mitsunobu reaction*[1–3] is the conversion of a chiral secondary alcohol **1** into an ester **3** with concomitant inversion of configuration at the secondary carbon center. In a second step the ester can be hydrolyzed to yield the inverted alcohol **4**, which is enantiomeric to **1**. By using appropriate nucleophiles, alcohols can be converted to other classes of compounds—e.g. azides, amines or ethers.

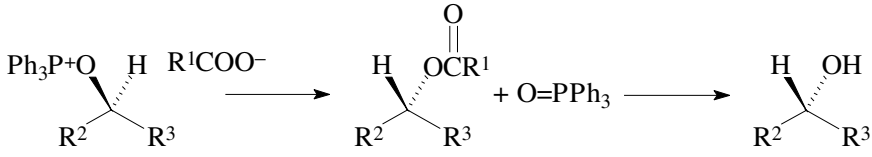
The mechanistic pathway[4–6] can be divided into three steps: 1. formation of the activating agent from triphenylphosphine and diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD); 2. activation of the substrate alcohol **1**; 3. a bimolecular nucleophilic substitution (S_N2) at the activated carbon center.

In an initial step triphenylphosphine adds to diethyl azodicarboxylate **5** to give the zwitterionic adduct **6**, which is protonated by the carboxylic acid **2** to give intermediate salt **7**. The alcohol reacts with **7** to the alkoxyphosphonium salt **8** and the hydrazine derivative **9**, and is thus activated for a S_N2-reaction:



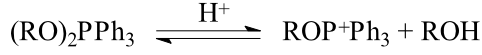
5 **6** **7** **9**

The final step is the nucleophilic displacement of the oxyphosphonium group by the carboxylate anion *via* a S_N2-mechanism, yielding ester **3** with inverted configuration at the stereogenic center, and triphenylphosphine oxide. A hydrolysis of the ester **3** will leave the new configuration unchanged, and yield the inverted alcohol **4**:



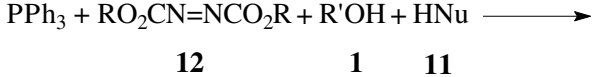
8 **3** **4**

Recent mechanistic studies have shown that the many combinations of alcohols, carboxylic acids and solvents cannot be correctly described by a uniform mechanism. In certain cases the reaction appears to involve a pentavalent dialkoxyphosphorane **10** as an intermediate, which is in equilibrium with oxyphosphonium salt **8**:[4,6]

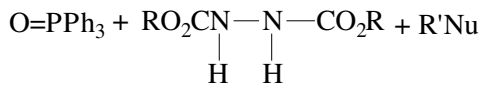


10 **8**

In summary the Mitsunobu reaction can be described as a condensation of an alcohol **1** and a nucleophile—NuH—**11**, where the reagent triphenylphosphine is oxidized to triphenylphosphine oxide and the azodicarboxylate reagent **12** is reduced to a hydrazine derivative **13**:

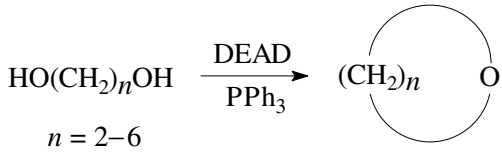


12 **1** **11**

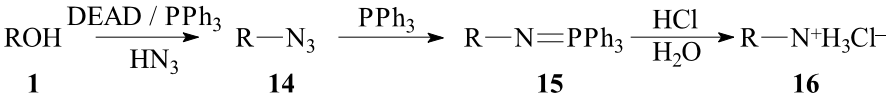


13

Alkyl aryl ethers and enol ethers are also accessible by the Mitsunobu method.[2] Cyclic ethers can be obtained by an intramolecular variant, which is especially suitable for the synthesis of three- to seven-membered rings:



The conversion of an alcohol to an amine can be achieved in a one-pot reaction;[2] the alcohol **1** is treated with hydrazoic azid (HN_3), excess triphenylphosphine and diethyl azodicarboxylate (DEAD). The initial Mitsunobu product, the azide **14**, further reacts with excess triphenylphosphine to give an iminophosphorane **15**. Subsequent hydrolytic cleavage of **15** yields the amine—e.g. as hydrochloride **16**:



Suitable starting materials for the Mitsunobu reaction are primary and secondary alcohols. Tertiary alcohols are less suitable since these are bad substrates for a S_N2-mechanism.

A variety of nucleophiles can be employed—e.g. carboxylic acids, phenols, imides, thiols, thioamides, and even β-ketoesters as carbon nucleophiles. Of major importance however is the esterification as outlined above, and its use for the clean inversion of configuration of a chiral alcohol.

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   J. McNulty, A. Capretta, V. Laritchev, J. Dyck, A. J. Robertson, *Angew. Chem.* **2003**, *115*, 4185–4188; *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 4051.
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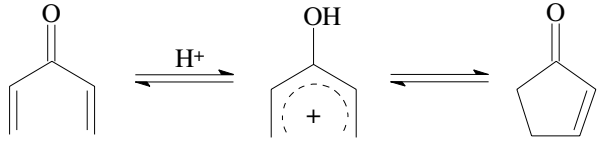
N

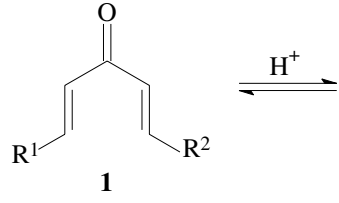
Nazarov Cyclization

Cyclization of divinyl ketones to yield cyclopentenones



1 **2** **3**

Upon treatment of a divinyl ketone **1** with a protic acid or a Lewis acid, an electrocyclic ring closure can take place to yield a cyclopentenone **3**. This reaction is called the *Nazarov cyclization*.[1,2] Protonation at the carbonyl oxygen of the divinyl ketone **1** leads to formation of a hydroxypentadienyl cation **2**, which can undergo a thermally allowed, conrotatory electrocyclic ring closure reaction to give a cyclopentenyl cation **4**. Through subsequent loss of a proton a mixture of isomeric cyclopentenones **5** and **6** is obtained:



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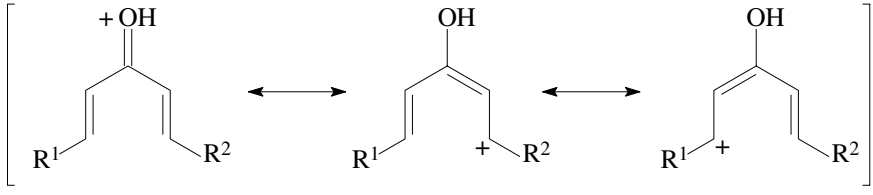

2

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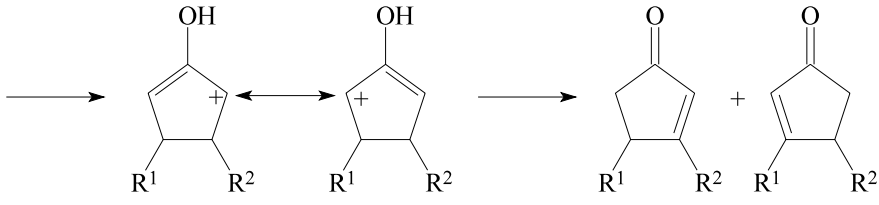
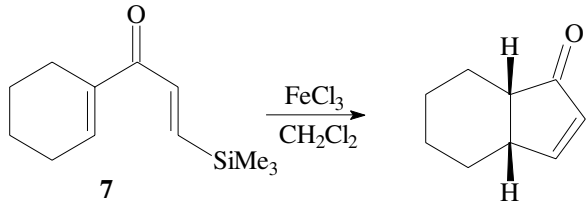


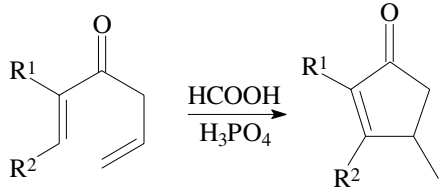
4 **5** **6**

With the use of trimethylsilyl-substituted starting materials after *Denmark et al.*,[4] the disadvantageous formation of a mixture of isomers can be avoided. The vinyl silane derivatives react by loss of the TMS group in the last step:



7

A variant of the Nazarov reaction is the cyclization of allyl vinyl ketones **8**. These will first react by double bond isomerization to give divinyl ketones, and then cyclize to yield a cyclopentenone **9** bearing an additional methyl substituent:[2]



8 **9**

For the preparation of divinyl ketones, as required for the Nazarov reaction, various synthetic routes have been developed.[3,5] A large variety of substituted divinyl ketones, including vinylsilane derivatives, can thus be prepared. The Nazarov cyclization, and especially the vinylsilane variant, has found application for the synthesis of complex cyclopentanoids.

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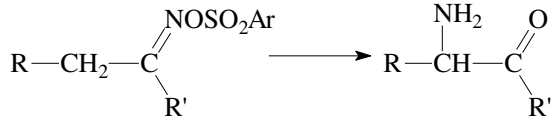
Neber Rearrangement

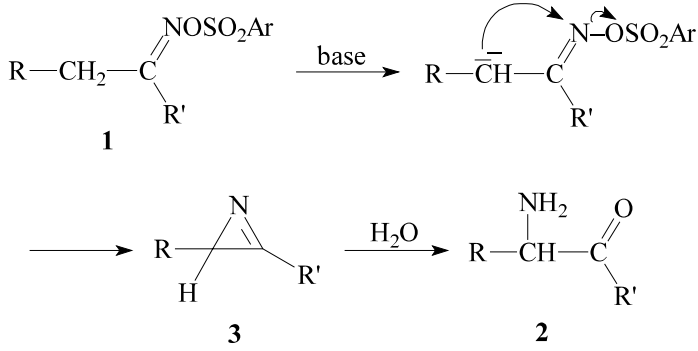
α-Amino ketones from ketoxime tosylates



1 **2**

A ketoxime tosylate **1** can be converted into an α-amino ketone **2** *via* the *Neber rearrangement*[1,2] by treatment with a base—e.g. using an ethoxide or pyridine. Substituent R is usually aryl, but may as well be alkyl or H; substituent R′ can be alkyl or aryl, but not H.

The following mechanism is generally accepted, since azirine **3**, that has been identified as intermediate, can be isolated:[3,4]



1 **3** **2**

The ketoxime derivatives, required as starting materials, can be prepared from the appropriate aromatic, aliphatic or heterocyclic ketone. Aldoximes (where R′ is H) do not undergo the rearrangement reaction, but rather an elimination of toluenesulfonic acid to yield a nitrile. With ketoxime tosylates a *Beckmann rearrangement* may be observed as a side-reaction.

Unlike the Beckmann rearrangement, the outcome of the Neber rearrangement does not depend on the configuration of the starting oxime derivative: *E*- as well as *Z*-oxime yield the same product. If the starting oxime derivative contains two different α-methylene groups, the reaction pathway is not determined by the configuration of the oxime, but rather by the relative acidity of the α-methylene protons; the more acidic proton is abstracted preferentially.[2]

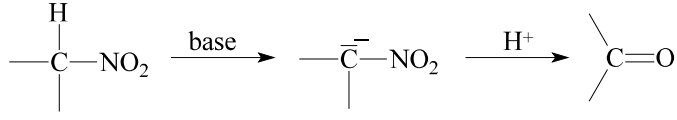
An α-amino ketone, obtained by the Neber rearrangement, can be further converted into an oxime tosylate, and then subjected to the Neber conditions; α,α'-diamino ketones can be prepared by this route.

The Neber rearrangement has for example found application in natural product synthesis.

1. P. W. Neber, A. Burgard, *Justus Liebigs Ann. Chem.* **1932**, *493*, 281–285.
2. C. O'Brien, *Chem. Rev.* **1964**, *64*, 81–89.
3. D. J. Cram, M. J. Hatch, *J. Am. Chem. Soc.* **1953**, *75*, 33–38.
4. M. J. Hatch, D. J. Cram, *J. Am. Chem. Soc.* **1953**, *75*, 38–44.

Nef Reaction

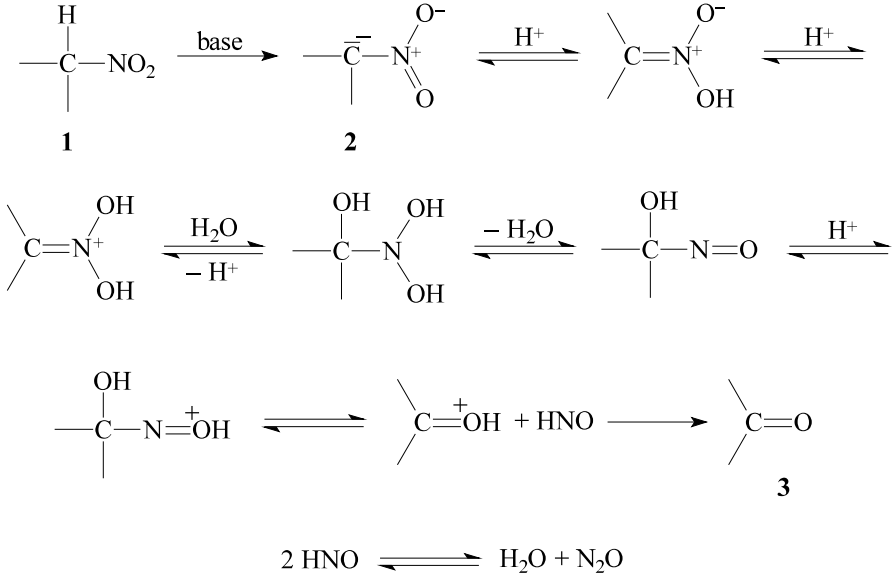
Carbonyl compounds from nitro alkanes



1 **2** **3**

The conversion of a primary or secondary nitro alkane **1** to a carbonyl compound **3** *via* an intermediate nitronate **2** is called the *Nef reaction*.[1,2] Since carbonyl compounds are of great importance in organic synthesis, and nitro alkanes can on the other hand be easily prepared, the Nef reaction is an important tool in organic chemistry.

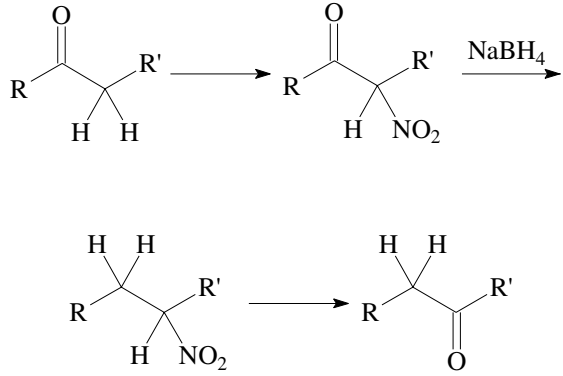
The mechanism of the Nef reaction has been thoroughly investigated.[2] Initial step is the abstraction of a proton from the α-carbon of the nitro alkane **1**, leading to nitronate anion **2**, which is then stepwise protonated at both negatively charged oxygens. Subsequent hydrolytic cleavage yields the carbonyl compound **3** together with dinitrogen oxide and water:



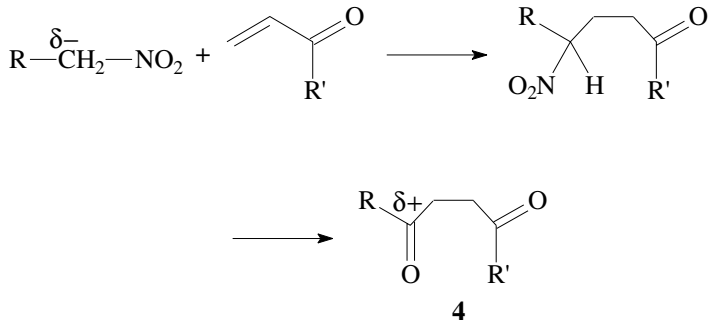
Various side-reactions may complicate the course of the Nef reaction. Because of the delocalized negative charge, the nitronate anion **2** can react at various positions with an electrophile; addition of a proton at the α-carbon reconstitutes the starting nitro alkane. **1**. The nitrite anion can act as leaving group, thus leading to elimination products.

The required nitro compounds are easy to prepare, and are useful building blocks for synthesis. Treatment with an appropriate base—e.g. aqueous alkali—leads to formation of nitronates **2**. Various substituted nitro compounds, such as nitro-ketones, -alcohols, -esters and -nitriles are suitable starting materials.

The Nef reaction has for example been applied for the 1,2-transposition of carbonyl groups:[3]



Another important feature of the Nef reaction is the possible use of a $CH-NO_2$ function as an *umpoled* carbonyl function. A proton at a carbon α to a nitro group is acidic, and can be abstracted by base. The resulting anionic species has a nucleophilic carbon, and can react at that position with electrophiles. In contrast the carbon center of a carbonyl group is electrophilic, and thus reactive towards nucleophiles. 1,4-Diketones **4** can for example be prepared from α-acidic nitro compounds by a *Michael addition*/Nef reaction sequence:[4]



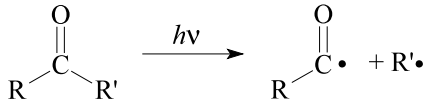
4

For starting materials containing base- and/or acid-sensitive functional groups, modified procedures have been developed—e.g. using oxidizing agents.[2]

1. J. U. Nef, *Justus Liebigs Ann. Chem.* **1894**, *280*, 263–291.
2. H. W. Pinnick, *Org. React.* **1990**, *38*, 655–792.
3. A. Hassner, J. M. Larkin, J. E. Dowd, *J. Org. Chem.* **1968**, *33*, 1733–1739.
4. O. W. Lever Jr., *Tetrahedron.* **1976**, *32*, 1943–1971.

Norrish Type I Reaction

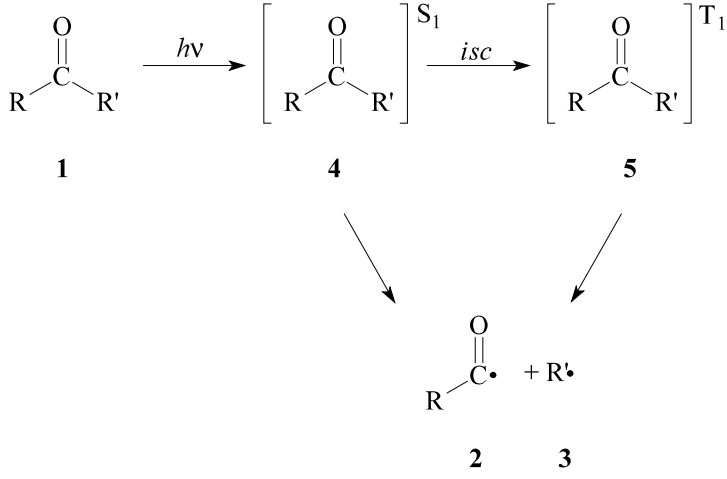
Photochemical cleavage of aldehydes and ketones



1 **2** **3**

Carbonyl compounds can undergo various photochemical reactions; among the most important are two types of reactions that are named after *Norrish*.[1] The term *Norrish type I fragmentation*[1–4] refers to a photochemical reaction of a carbonyl compound **1** where a bond between carbonyl group and an α-carbon is cleaved homolytically. The resulting radical species **2** and **3** can further react by decarbonylation, disproportionation or recombination, to yield a variety of products.

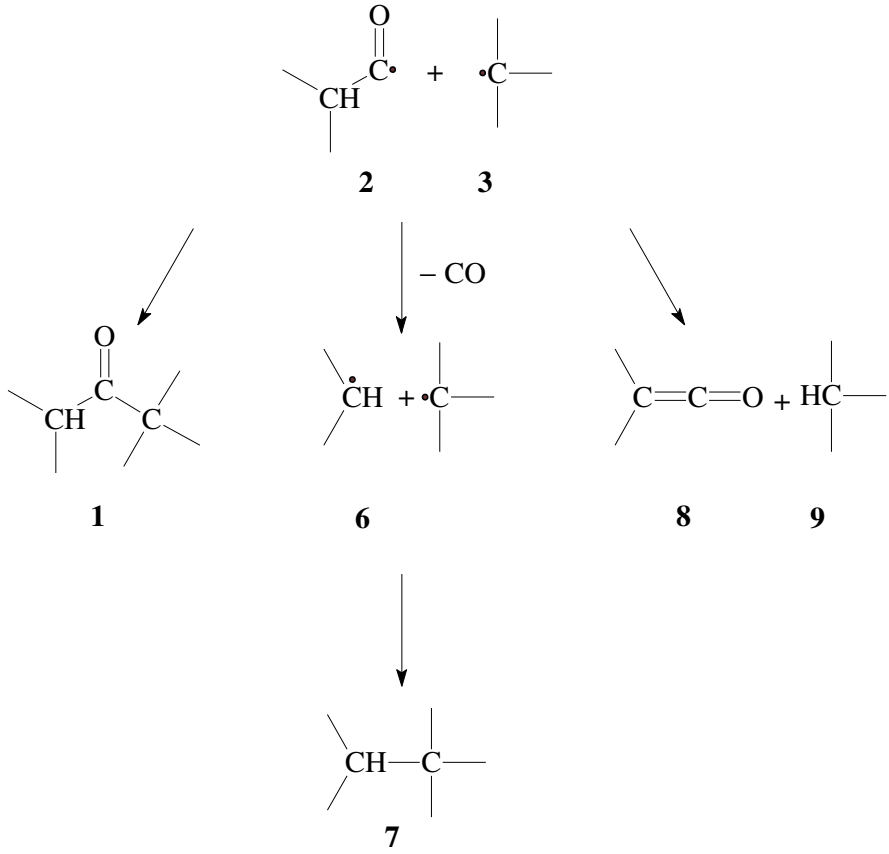
By absorption of a photon of light, a ketone or aldehyde molecule **1** can be converted into a photoactivated species; it is promoted to the singlet excited (S_1)-state **4**, from which it can reach the triplet excited (T_1)-state **5** by *intersystem crossing*. The homolytic Norrish type I cleavage may occur from either or both states, and leads to formation of an acyl radical **2** and an allyl radical **3**. Aromatic ketones generally undergo the photolytic cleavage from the triplet excited state, since the intersystem crossing is usually fast in those cases.



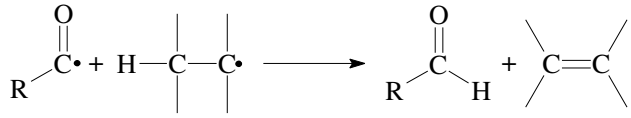
1 **4** **5** **2** **3**

With unsymmetrical ketones two different bonds are available for photolytic cleavage; the actual cleavage pathway depends on the relative stability of the possible radical species R• and R′•.

The radical pair **2/3** can undergo various subsequent reactions: the most obvious is the recombination to the starting carbonyl compound **1**. The acyl radical **2** can undergo a fragmentation by loss of CO to the radical **6**, which can further react with radical **3** to yield the hydrocarbon **7** (i.e. R-R′). Cleavage of CO from **2** and subsequent combination of **6** and **3** usually is a fast process taking place in a solvent cage, which largely prevents formation of symmetrical hydrocarbons (R-R or R′-R′). If the acyl radical **2** bears an α-hydrogen, this hydrogen can be abstracted by radical **3**, resulting in formation of a ketene **8** and hydrocarbon **9**:

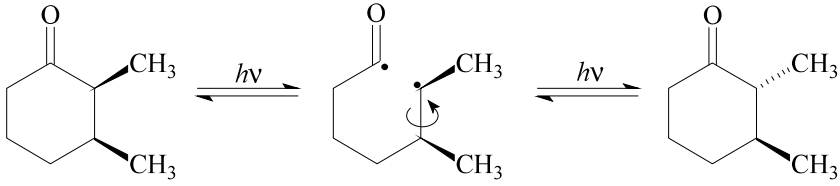


The acyl radical **2** can abstract a β-hydrogen from the radical **3**, to give an aldehyde **10** and an alkene **11**:



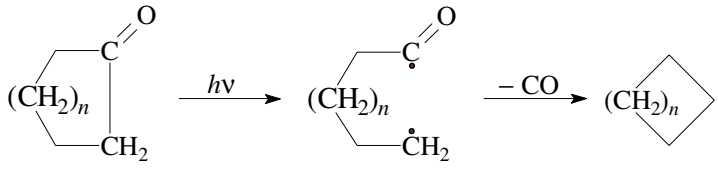
3 **10** **11**

Since the quantum yield of the Norrish type I reaction is generally low, it has been assumed that the initial homolytic cleavage is a reversible process. Evidence came from an investigation by *Barltrop et al.*[5] which has shown that *erythro*-2,3-dimethylcyclohexanone **12** isomerizes to *threo*-2,3-dimethylcyclohexanone **13** upon irradiation:



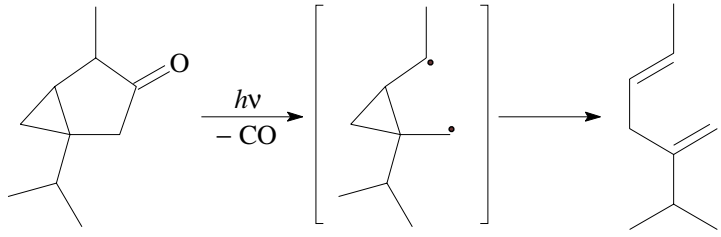
12 **13**

The photolytic cleavage of cyclic ketones **14** leads to formation of a diradical species, that can undergo analogously the various reactions outlined above. The decarbonylation followed by intramolecular recombination yields a ring-contracted cycloalkane **15**:



14 **15**

With strained cycloketones the type I-cleavage gives better yields, and can be used as a preparative method. For example photolysis of the bicyclic ketone **16** gives diene **17** in good yield:[6]



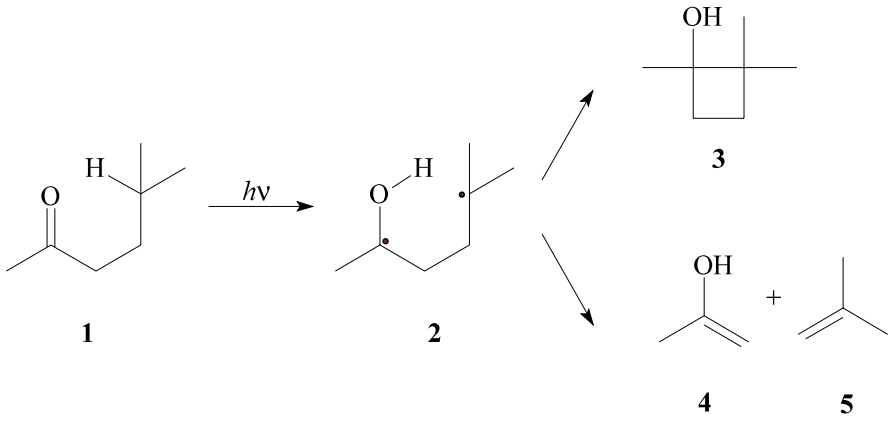
16 **17**

In general however the various possible reaction pathways give rise to formation of a mixture of products. The type I-cleavage reaction is only of limited synthetic importance, but rather an interfering side-reaction—e.g. with an attempted *Paterno–Büchi reaction*, or when an aldehyde or ketone is used as sensitizer in a [2 + 2]-*cycloaddition reaction*.

1. R. G. W. Norrish, *Trans. Faraday Soc*. **1937**, *33*, 1521–1528.
2. J. N. Pitts, Jr., J. K. S. Wan in *The Chemistry of the Carbonyl Group* (Ed.: S. Patai), Wiley, New York, **1966**, p. 823–916.
3. J. S. Swenton, *J. Chem. Educ*. **1969**, *46*, 217–226.
4. J. M. Coxon, B. Halton, *Organic Photochemistry*, Cambridge University Press, London, **1974**, p. 58–78.
5. J. A. Barltrop, J. D. Coyle, *J. Chem. Soc. Chem. Commun*. **1969**, 1081–1082.
6. J. Kopecky, *Organic Photochemistry*, VCH, Weinheim, **1991**, p. 119–122.

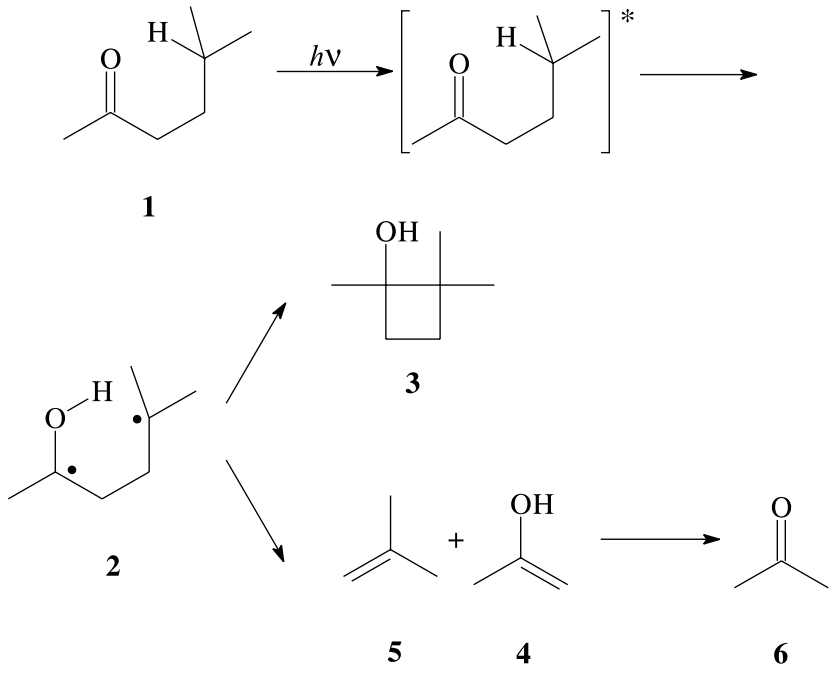
Norrish Type II Reaction

Photochemical reaction of aldehydes or ketones bearing γ-hydrogens

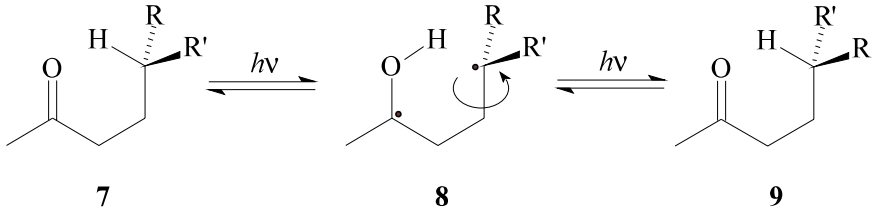


An aldehyde or ketone **1** bearing a γ-hydrogen atom can upon irradiation undergo an intramolecular hydrogen shift by the so-called *Norrish type II reaction*.[1–4] The resulting diradical species **2** can undergo a subsequent ring closure reaction to yield a cyclobutanol **3**, or suffer fragmentation to yield an enol **4** and an alkene **5**.

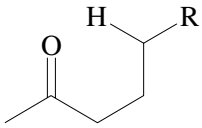
Photoactivated aldehyde or ketone molecules with γ-hydrogens can undergo the intramolecular hydrogen abstraction from the singlet excited (S_1)-state as well as the triplet excited (T_1)-state. This reaction proceeds via a cyclic six-membered transition state. The resulting 1,4-diradical species **2** can further react either by ring closure to give a cyclobutanol **3** or by carbon–carbon bond cleavage to give an enol **4** and an alkene **5**; enol **4** will subsequently tautomerize to carbonyl compound **6**:



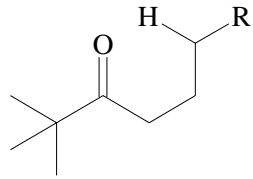
The fragmentation/cyclization ratio is determined by the relative orientation of the respective molecular orbitals, and thus by the conformation of diradical species **2**.[5] The quantum yield with respect to formation of the above products is generally low; the photochemically initiated 1,5-hydrogen shift from the γ-carbon to the carbonyl oxygen is a reversible process, and may as well proceed back to the starting material. This has been shown to be the case with optically active ketones **7**, containing a chiral γ-carbon center; an optically active ketone **7** racemizes upon irradiation to a mixture of **7** and **9**:



As a side reaction, the *Norrish type I reaction* is often observed. The stability of the radical species formed by α-cleavage determines the Norrish type I/Norrish type II ratio. For example aliphatic methyl ketones **10** react by a Norrish type II-mechanism, while aliphatic *tert*-butyl ketones **11** react preferentially by a Norrish type I-mechanism.



10



11

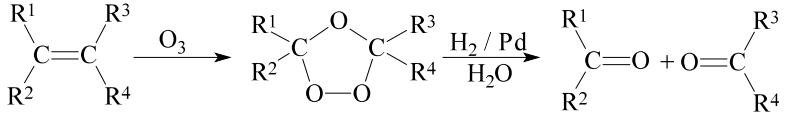
There are only a few examples for a preparative use of this reaction;[5] of more importance have so far been mechanistic aspects.[6]

1. R. G. W. Norrish, *Trans. Faraday Soc*. **1937**, *33*, 1521–1528.
2. J. N. Pitts, Jr., J. K. S. Wan in *The Chemistry of the Carbonyl Group* (Ed.: S. Patai), Wiley, New York, **1966**, p. 823–916.
3. P. J. Wagner, *Acc. Chem. Res*. **1971**, *4*, 168–177.
4. J. M. Coxon, B. Halton, *Organic Photochemistry*, Cambridge University Press, London, **1974**, p. 58–78.
5. J. Kopecky, *Organic Photochemistry*, VCH, Weinheim, **1991**, p. 123–125.
6. S. D. Feyter, E. W.-G. Diau, A. H. Zewail, *Angew. Chem.* **2000**, *112*, 266–269; *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 260.

O

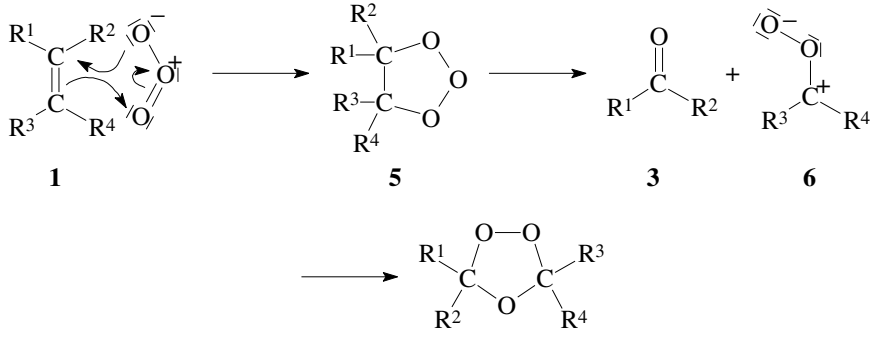
Ozonolysis

Cleavage of a carbon–carbon double bond by reaction with ozone



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

Harries[1] has introduced at the beginning of this century *ozonolysis*[2,3,4] as a method for the cleavage of carbon–carbon double bonds. The reaction proceeds *via* several intermediates to yield carbonyl compounds **3** and **4**. The following mechanism, which has been proposed by *Criegee*[2] and which is named after him, is generally accepted. Initial step is a *1,3-dipolar cycloaddition* reaction of ozone and alkene **1**, to give the *primary ozonide* **5** (also called *molozonide*). The initial ozonide **5** is unstable under the reaction conditions, and decomposes by a cycloreversion to give a carbonyl oxide **6** together with carbonyl compound **3**. Carbonyl oxide **6** again is a 1,3-dipolar species—isoelectronic to ozone—and rapidly undergoes a cycloaddition to the C=O double bond of **3**, to give the *secondary ozonide* **2**. The actual reaction sequence leading from **1** to **2** thus is: cycloaddition–cycloreversion–cycloaddition:



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

2

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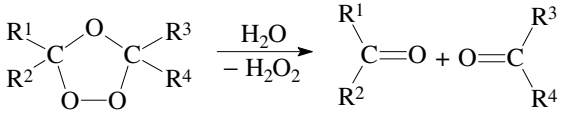
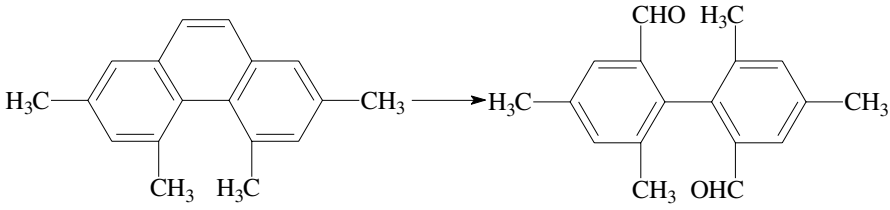
The ozonides **2** are reactive compounds that decompose violently upon heating. Nevertheless numerous ozonides have been isolated and studied by spectroscopic methods. With polar solvents, trapping products of carbonyl oxide **6** can be obtained. An external aldehyde, when added to the reaction mixture, will react with **6** to give a new secondary ozonide. Upon subsequent hydrolysis of ozonide **2**, different products may be obtained, depending on the particular reaction conditions. Under oxidative conditions an initially formed aldehyde will be oxidized to yield a carboxylic acid. In most cases however a reducing agent is added during hydrolytic workup, in order to avoid subsequent reactions with hydrogen peroxide. When the ozonide **2** is treated with lithium aluminum hydride, alcohols are obtained as products.



2

The reaction of ozone with an aromatic compound is considerably slower than the reaction with an alkene. Complete ozonolysis of one mole of benzene with workup under non-oxidative conditions will yield three moles of glyoxal. The selective ozonolysis of particular bonds in appropriate aromatic compounds is used in organic synthesis, for example in the synthesis of a substituted biphenyl **8** from phenanthrene **7**:[5]



7 **8**

In general however, ozonolysis is of limited synthetic importance. For quite some time ozonolysis has been an important tool for structure elucidation in organic chemistry, but has lost its importance when spectroscopic methods were fully developed for that purpose. The identification of the aldehydes and/or ketones obtained by ozonolysis of unsaturated compounds allowed for conclusions about the structure of the starting material, but has practically lost its importance since then.

Ozone has received increased attention for its occurrence and function in the Earth's atmosphere.[6,7] For example the decreasing ozone concentration in the stratospheric ozone layer, becoming most obvious with the Antarctic ozone hole,

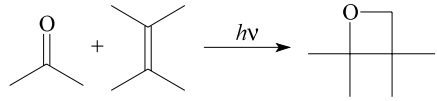
and on the other hand the increasing ozone concentration in the ground level layer of the atmosphere during summer that is related to air pollution.[6] In the latter case ozone has manifold effects on man, animals and plants; for example it contributes to the dying of forests, but also to the degradation of organic environmental chemicals.[7]

1. C. Harries, *Justus Liebigs Ann. Chem*. **1905**, *343*, 311–374.
2. R. Criegee, *Angew. Chem*. **1975**, *87*, 765–771; *Angew. Chem. Int. Ed. Engl*. **1975**, *14*, 745.
3. R. L. Kuczkowski, *Chem. Soc. Rev*. **1992**, *21*, 79–83.
4. W. Sander, *Angew. Chem*. **1990**, *102*, 362–372; *Angew. Chem. Int. Ed. Engl*. **1990**, *29*, 344.
   O. Horie, G. K. Moorgat, *Acc. Chem. Res.* **1998**, *31*, 387–396.
5. T.-J. Ho, C.-S. Shu, M.-K. Yeh, F.-C. Chen, *Synthesis* **1987**, 795–797.
6. F. Zabel, *Chem. Unserer Zeit* **1987**, *21*, 141–150.
7. H. K. Lichtenthaler, *Naturwiss. Rundsch*. **1984**, *37*, 271–277.

P

Paterno–Büchi Reaction

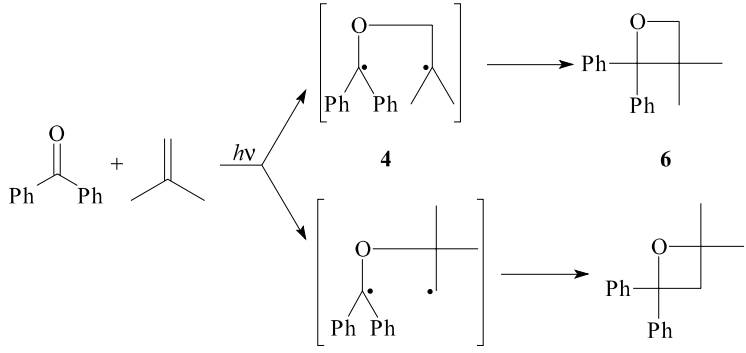
Cycloaddition of a carbonyl compound to an alkene



1 **2** **3**

The photochemical cycloaddition of a carbonyl compound **1** to an alkene **2** to yield an oxetane **3**, is called the *Paterno–Büchi reaction*.[1,2] This reaction belongs to the more general class of photochemical [2 + 2]-cycloadditions, and is just as these, according to the Woodward–Hofmann rules,[3] photochemically a symmetry-allowed process, and thermally a symmetry-forbidden process.

The irradiation is usually carried out with light of the near UV region, in order to activate only the $n \rightarrow \pi^*$ transition of the carbonyl function,[4] thus generating excited carbonyl species. Depending on the substrate, it can be a singlet or triplet excited state. With aromatic carbonyl compounds, the reactive species are usually in a T_1-state, while with aliphatic carbonyl compounds the reactive species are in a S_1-state. An excited carbonyl species reacts with a ground state alkene molecule to form an *exciplex*, from which in turn diradical species can be formed—e.g. **4** and **5** in the following example:



4 **6**

5 **7**

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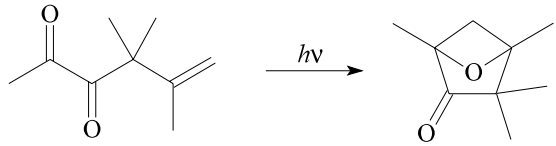
Diradical species **4** is more stable than diradical **5**, and the oxetane **6** is thus formed preferentially; oxetane **7** is obtained as minor product only. Evidence for diradical intermediates came from trapping experiments,[5] as well as spectroscopic investigations.[6]

In addition to the intermolecular Paterno–Büchi reaction, the intramolecular variant has also been studied;[2] the latter allows for the construction of bicyclic structures in one step. For example the diketone **8** reacts quantitatively to the bicyclic ketone **9**:



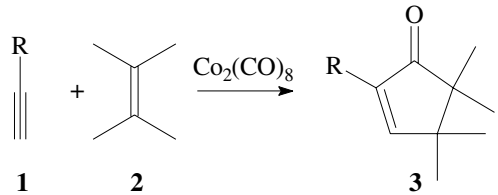
8 **9**

Although the Paterno–Büchi reaction is of high synthetic potential, its use in organic synthesis is still not far developed.[2] In recent years some promising applications in the synthesis of natural products have been reported.[8] The scarce application in synthesis may be due to the non-selective formation of isomeric products that can be difficult to separate—e.g. **6** and **7**—as well as to the formation of products by competitive side-reactions such as *Norrish type-I-* and *type-II fragmentations*.

1. G. Büchi, C. G. Inman, E. S. Lipinsky, *J. Am. Chem. Soc*. **1954**, *76*, 4327–4331.
2. I. Ninomiya, T. Naito, *Photochemical Synthesis*, Academic Press, New York, **1989**, p. 138–151.
3. R. B. Woodward, R. Hoffmann, *The Conservation of Orbital Symmetry*, Academic Press, New York, **1970**.
4. M. Demuth, G. Mikhail, *Synthesis* **1989**, 145–162.
5. W. Adam, U. Kliem, V. Lucchini, *Tetrahedron Lett*. **1986**, *27*, 2953–2956.
6. S. C. Freilich, K. S. Peters, *J. Am. Chem. Soc*. **1985**, *107*, 3819–3822.
7. R. Bishop, N. K. Hamer, *J. Chem. Soc. Chem. Commun*. **1969**, 804.
8. J. Mulzer, H.-J. Altenbach, M. Braun, K. Krohn, H.-U. Reissig, *Organic Synthesis Highlights*, VCH, Weinheim, **1991**, p. 105–110.

Pauson–Khand Reaction

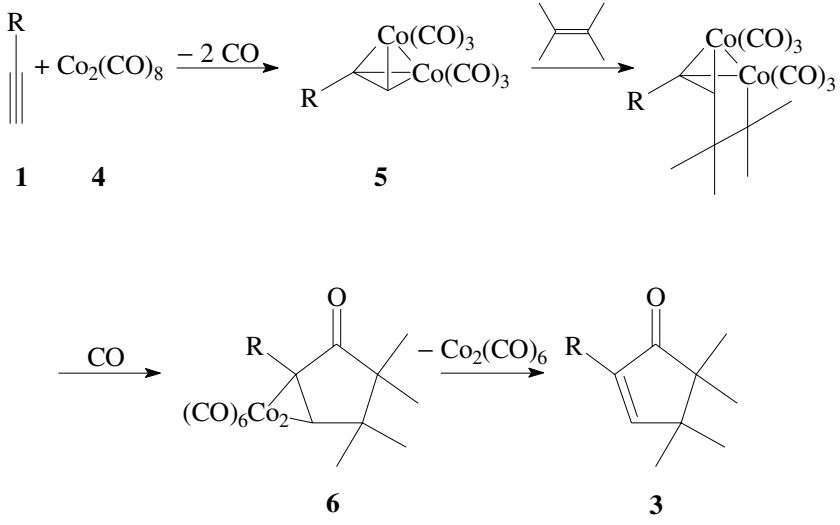
Synthesis of cyclopentenones by a formal [2 + 2 + 1]-cycloaddition



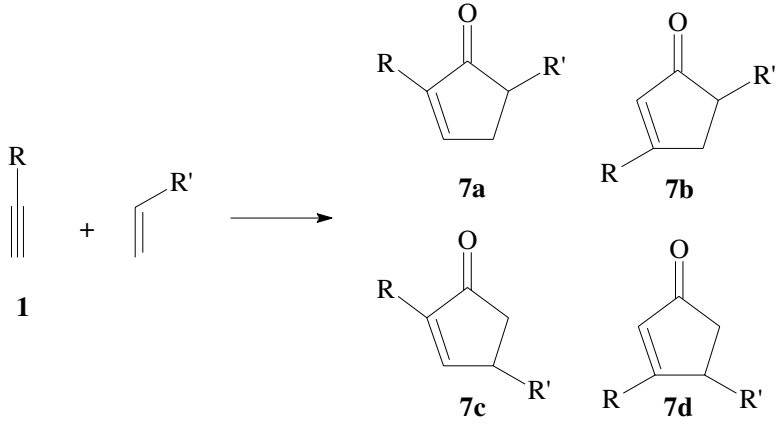
1 **2** **3**

The reaction of an alkyne **1** and an alkene **2** in the presence of dicobaltoctacarbonyl to yield a cyclopentenone **3** is referred to as the *Pauson–Khand reaction*.[1–4] Formally it is a [2 + 2 + 1]-cycloaddition reaction. The dicobaltoctacarbonyl acts as coordinating agent as well as a source of carbon monoxide.

Initial step is the formation of a dicobalthexacarbonyl-alkyne complex **5** by reaction of alkyne **1** with dicobaltoctacarbonyl **4** with concomitant loss of two molecules of CO. Complex **5** has been shown to be an intermediate by independent synthesis. It is likely that complex **5** coordinates to the alkene **2**. Insertion of carbon monoxide then leads to formation of a cyclopentenone complex **6**, which decomposes into dicobalthexacarbonyl and cyclopentenone **3**:[2]

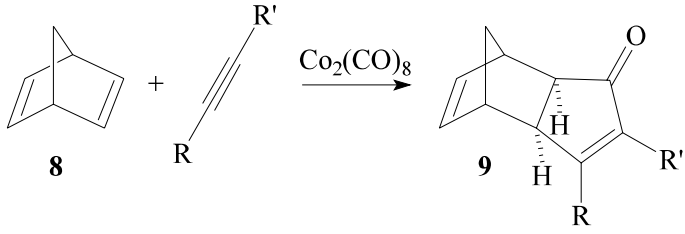


From reaction of simple alkynes and alkenes four regioisomeric products **7a–d** may be formed:



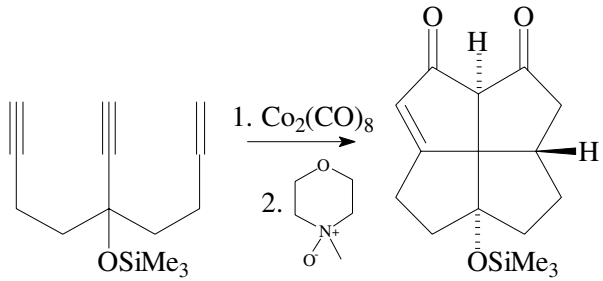
Products **7a** and **7c**, with the substituent R α to the carbonyl group, are by far predominantly formed.[5,6] This regioselectivity is a result of the preferential approach of the alkene **2** to the dicobalthexacarbonyl-alkyne complex **5** from the side opposite to the substituent R of the original alkyne. The actual incorporation of the alkene however is less selective with respect to the orientation of the olefinic substituent R′, thus leading to a mixture of isomers **7a** and **7c**.

The reaction with bicyclic alkenes—e.g. norbornadiene **8**—preferentially yields the *exo*-product **9**:



8 **9**

An example for the synthetic potential is the formation of a fenestrane skeleton **11** from the open-chain compound **10** by a cascade of two consecutive *intramolecular Pauson–Khand reactions*; the yield in this case is however only 9%:[7]



10 **11**

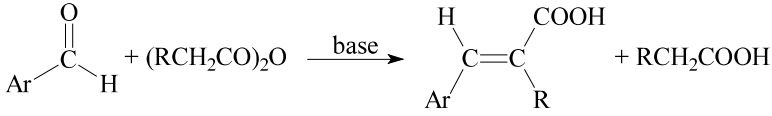
The Pauson–Khand reaction was originally developed using strained cyclic alkenes, and gives good yields with such substrates. Alkenes with sterically demanding substituents and acyclic as well as unstrained cyclic alkenes often are less suitable substrates. An exception to this is ethylene, which reacts well. Acetylene as well as simple terminal alkynes and aryl acetylenes can be used as triple-bond component.

1. I. U. Khand, G. R. Knox, P. L. Pauson, W. E. Watts, M. I. Forman, *J. Chem. Soc., Perkin Trans. 1*, **1973**, 977–981.
2. N. E. Schore, *Org. React*. **1991**, *40*, 1–90.
3. P. L. Pauson, *Tetrahedron* **1985**, *41*, 5855–5860.
4. J. Mulzer, H.-J. Altenbach, M. Braun, K. Krohn, H.-U. Reissig, *Organic Synthesis Highlights*, VCH, Weinheim, **1991**, p. 140–144.

5. S. E. MacWhorter, V. Sampath, M. M. Olmstead, N. E. Schore, *J. Org. Chem.* **1988**, *53*, 203–205.
6. M. E. Krafft, *J. Am. Chem. Soc.* **1988**, *110*, 968–970.
7. L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131.

Perkin Reaction

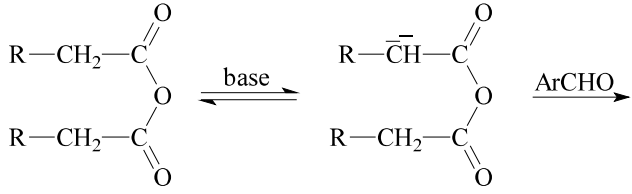
Condensation of aromatic aldehydes with carboxylic anhydrides



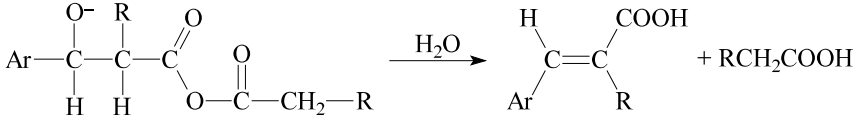
1 **2** **3**

The aldol-like reaction of an aromatic aldehyde **1** with a carboxylic anhydride **2** is referred to as the *Perkin reaction*.[1,2] As with the related *Knoevenagel reaction*, an α,β-unsaturated carboxylic acid is obtained as product; the β-aryl derivatives **3** are also known as cinnamic acids.

The reaction mechanism involves deprotonation of the carboxylic anhydride **2** to give anion **4**, which then adds to aldehyde **1**. If the anhydride used bears two α-hydrogens, a dehydration takes place already during workup; a β-hydroxy carboxylic acid will then not be isolated as product:



2 **4** **1**



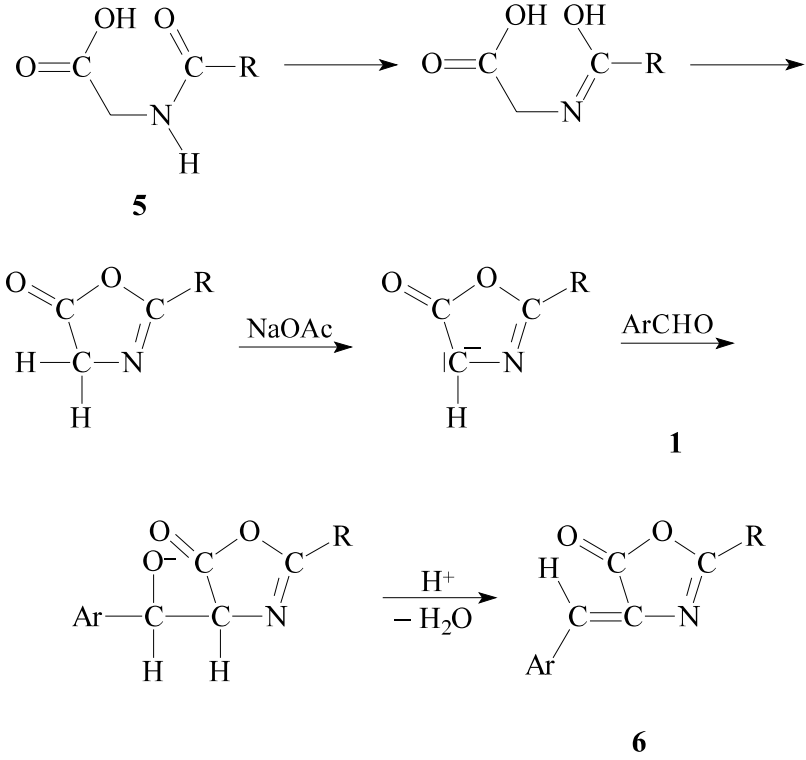
3

If the starting anhydride bears only one α-hydrogen, the dehydration step cannot take place, and a β-hydroxy carboxylic acid is obtained as the reaction product.

In principle the formation of a mixture of *E*- and *Z*-isomers is possible; however the preferential formation of the *E*-isomer is generally observed.

The general procedure is to heat a mixture of aldehyde **1** and carboxylic anhydride **2** together with a base to a temperature of 170–200 °C for several hours. As base the sodium salt of the carboxylic acid corresponding to the anhydride is most often used.

A variant of the Perkin reaction is the *Erlenmeyer–Plöchl–azlactone synthesis*.[3–5] By condensation of an aromatic aldehyde **1** with an N-acyl glycine **5** in the presence of sodium acetate and acetic anhydride, an azlactone **6** is obtained *via* the following mechanism:



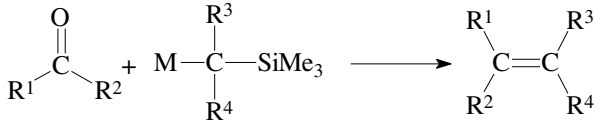
Azlactones like **6** are mainly used as intermediates in the synthesis of α-amino acids and α-keto acids. The Erlenmeyer–Plöchl reaction takes place under milder conditions than the Perkin reaction.

1. W. H. Perkin, *J. Chem. Soc*. **1877**, *31*, 388–427.
2. J. R. Johnson, *Org. React*. **1942**, *1*, 210–266.
3. E. Erlenmeyer, *Justus Liebigs Ann. Chem*. **1893**, *275*, 1–3.

4. J. Plöchl, *Ber. Dtsch. Chem. Ges*. **1883**, *16*, 2815–2825.
5. H. E. Carter, *Org. React*. **1946**, *3*, 198–239.

Peterson Olefination

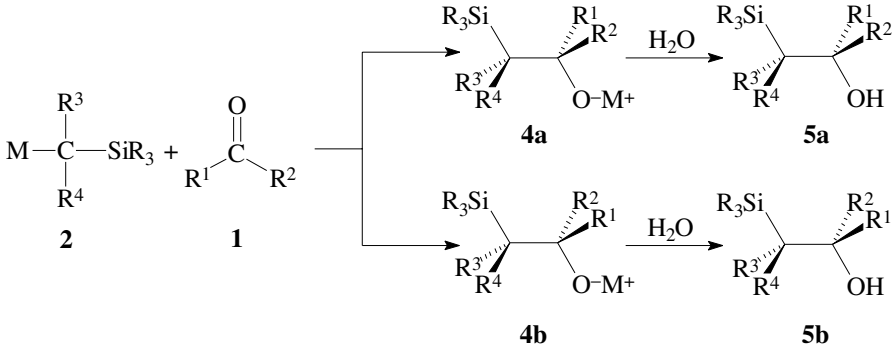
Synthesis of alkenes from ketones or aldehydes



1 **2** **3**

The *Peterson olefination*[1–3] can be viewed as a silicon variant of the *Wittig reaction*, the well-known method for the formation of carbon–carbon double bonds. A ketone or aldehyde **1** can react with an α-silyl organometallic compound **2**—e.g. with M = Li or Mg—to yield an alkene **3**.

The Peterson olefination is a quite modern method in organic synthesis; its mechanism is still not completely understood.[2,4,5] The α-silyl organometallic reagent **2** reacts with the carbonyl substrate **1** by formation of a carbon–carbon single bond to give the diastereomeric alkoxides **4a** and **4b**; upon hydrolysis the latter are converted into β-hydroxysilanes **5a** and **5b**:

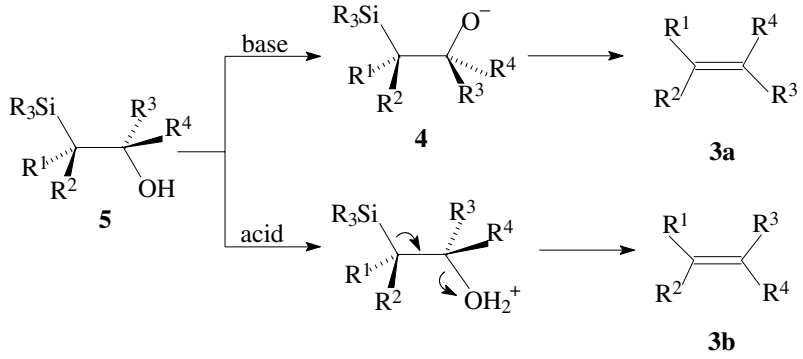


2 **1** **4a** **5a** **4b** **5b**

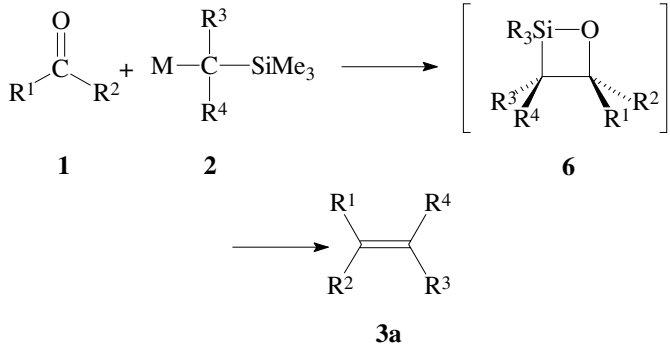
By application of the most common procedure—i.e by using an α-silylated organolithium or magnesium reagent—the β-hydroxysilane **5a/5b** can be isolated. However in the case of M = Na or K, the alkoxide oxygen in **4a/4b** is of strong ionic character, and a spontaneous elimination step follows to yield directly the alkene **3**.

The next step of the Peterson olefination allows for the control of the *E*/*Z*-ratio of the alkene to be formed by proper choice of the reaction conditions. Treatment of β-hydroxysilanes **5** with a base such as sodium hydride or potassium hydride leads to preferential *syn*-elimination to give alkene **3a** as major

product. In contrast treatment with acid leads to preferential *anti*-elimination by an E_2-mechanism, then yielding alkene **3b** as major product:



Whether the formation of alkene **3** proceeds directly from alkoxide **4** or *via* a penta-coordinated silicon-species **6**, is not rigorously known. In certain cases—e.g. for β-hydroxydisilanes ($R^3 = SiMe_3$) that were investigated by *Hrudlik et al.*[4]—the experimental findings suggest that formation of the carbon–carbon bond is synchronous to formation of the silicon–oxygen bond:



For the purpose of stereoselective synthesis the selective elimination at the stage of the β-hydroxysilane **5** is not a problem; the diastereoselective preparation of the desired β-hydroxysilane however is generally not possible. This drawback can be circumvented by application of alternative reactions to prepare the β-hydroxysilane;[2] however these methods do not fall into the category of the Peterson reaction.

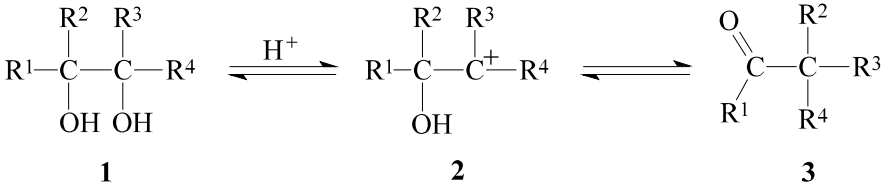
The Peterson olefination presents a valuable alternative to the Wittig reaction. It has the advantage to allow for a simple control of the alkene geometry. Its applicability in synthesis depends on the availability of the required silanes.[2]

1. D. J. Peterson, *J. Org. Chem.* **1968**, *33*, 780–784.
2. D. J. Ager, *Org. React.* **1990**, *38*, 1–223.
3. D. J. Ager, *Synthesis* **1984**, 384–398.

4. P. F. Hudrlik, E. L. O. Agwaramgbo, A. M. Hudrlik, *J. Org. Chem.* **1989**, *54*, 5613–5618.
5. A. R. Bassindale, R. J. Ellis, J. C.-Y. Lau, P. G. Taylor, *J. Chem. Soc., Perkin Trans. 2*, **1986**, 593–597.

Pinacol Rearrangement

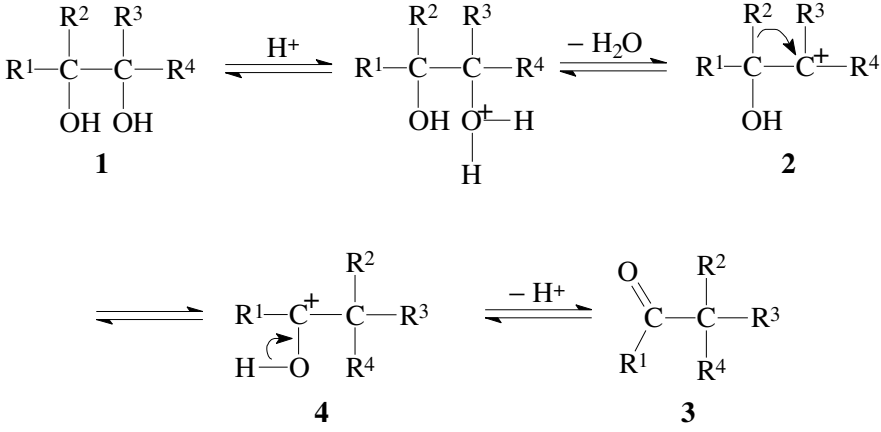
Rearrangement of vicinal diols



1 **2** **3**

A vicinal diol **1**, when treated with a catalytic amount of acid, can rearrange to give an aldehyde or ketone **3** by migration of an alkyl or aryl group. The prototype of this reaction is the rearrangement of pinacol ($R^1 = R^2 = R^3 = R^4 = CH_3$) to yield pinacolone. The *pinacol rearrangement reaction*[1,2] can be viewed as a special case of the *Wagner–Meerwein rearrangement*.

In the initial step one hydroxy group is protonated, and thus converted into a good leaving group—i.e. water.[3] Subsequent loss of water from the molecule proceeds in such a way that the more stable carbenium ion species **2** is formed. The next step is a 1,2-shift of a group R to the tertiary carbenium center to give a hydroxycarbenium ion species **4**:

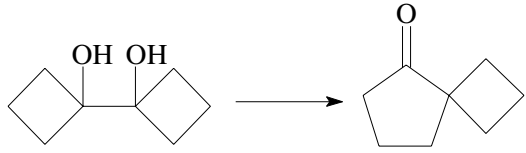


1 **2** **4** **3**

The reaction is strictly intramolecular; the migrating group R is never completely released from the substrate. The driving force is the formation of the more stable rearranged carbenium ion **4**, that is stabilized by the hydroxy substituent. The

electron-deficiency of the carbenium ion center in **4** is to some extent compensated by an electron pair from the adjacent oxygen center—a resonance structure—a protonated carbonyl group $C{=}OH^+$—can be written. Loss of a proton yields the stable carbonyl compound **3**. The elimination of water to give an alkene may be observed as a side-reaction. Substituents R^1, R^2, R^3, R^4 can be alkyl or aryl; single substituents can even be hydrogen. Reaction with an unsymmetrical diol as starting material may give rise to formation of a mixture of products. The order of migration is $R_3C > R_2CH > RCH_2 > CH_3 > H$. The product ratio may also depend on the acid used.

The pinacol rearrangement reaction is of limited synthetic importance; although it can be a useful alternative to the standard methods for synthesis of aldehydes and ketones.[4] Especially in the synthesis of ketones with special substitution pattern—e.g. a spiro ketone like **5**—the pinacol rearrangement demonstrates its synthetic potential:[5]



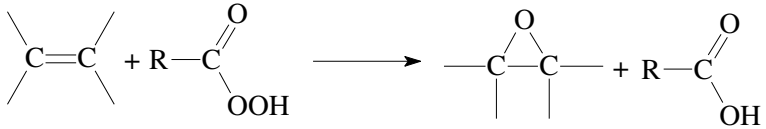
5

The required vicinal diols are in general accessible by standard methods.[6] Pinacol itself can be obtained by dimerization of acetone. For the rearrangement reaction concentrated or dilute sulfuric acid is often used as catalyst.

1. R. Fittig, *Justus Liebigs. Ann. Chem.* **1859**, *110*, 17–23.
2. C. J. Collins, J. F. Eastham in *The Chemistry of the Carbonyl Group* (Ed.: S. Patai), Wiley, New York, **1966**, p. 762–767.
3. C. J. Collins, *J. Am. Chem. Soc.* **1955**, *77*, 5517–5523.
4. D. Dietrich, *Methoden Org. Chem. (Houben-Weyl)*, **1973**, Vol. 7/2a, p. 1016–1034.
5. E. Vogel, *Chem. Ber.* **1952**, *85*, 25–29.
6. Th. Wirth, *Angew. Chem.* **1996**, *108*, 65–67;
   Angew. Chem. Int. Ed. Engl. **1996**, *35*, 61.

Prilezhaev Reaction

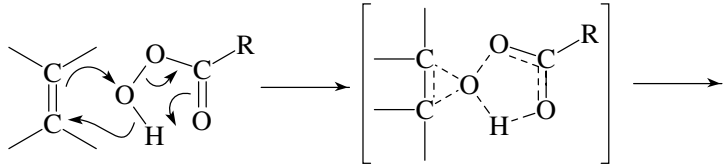
Epoxidation of alkenes



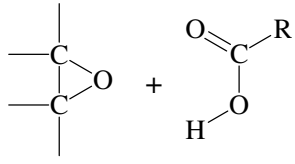
1 **2** **3** **4**

The *Prilezhaev reaction*[1–4] is a rarely used name for the epoxidation of an alkene **1** by reaction with a peracid **2** to yield an oxirane **3**. The epoxidation of alkenes has been further developed into an enantioselective method, that is named after *Sharpless*.

The hydroxy oxygen of a peracid has a higher electrophilicity as compared to a carboxylic acid. A peracid **2** can react with an alkene **1** by transfer of that particular oxygen atom to yield an oxirane (an epoxide) **3** and a carboxylic acid **4**. The reaction is likely to proceed *via* a transition state as shown in **5** (butterfly mechanism),[5] where the electrophilic oxygen adds to the carbon-carbon π-bond and the proton simultaneously migrates to the carbonyl oxygen of the acid:[3,6]

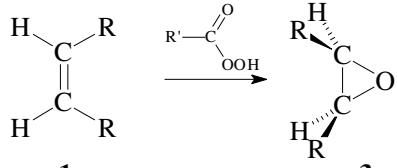


1 **2** **5**



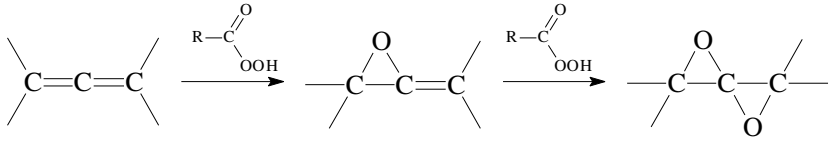
3 **4**

The mechanism formulated above is in agreement with the experimental findings, that stereospecifically a *syn*-addition takes place; the stereochemical relation between substituents in the alkene **1** is retained in the oxirane **3**.



1 **3**

Allenes **6** also react with peracids; allene oxides **7** are formed, or even a spiro dioxide **8** can be obtained by reaction with a second equivalent of peracid:



6 **7** **8**

Oxiranes **3** are versatile intermediates in organic synthesis. The ring-opening reaction with a nucleophile is of wide scope. By this route alcohols, vicinal diols, ethers and many other classes of compounds can be prepared. With Grignard reagents (see *Grignard reaction*) the ring-opening proceeds with concomitant formation of a carbon–carbon bond.

m-Chloroperbenzoic acid is often used as epoxidation reagent; it is commercially available, quite stable and easy to handle. Various other peracids are unstable, and have to be prepared immediately prior to use.

The separation of the reaction products—i.e. the oxidation product and the carboxylic acid—can usually be achieved by extraction with mild aqueous base.

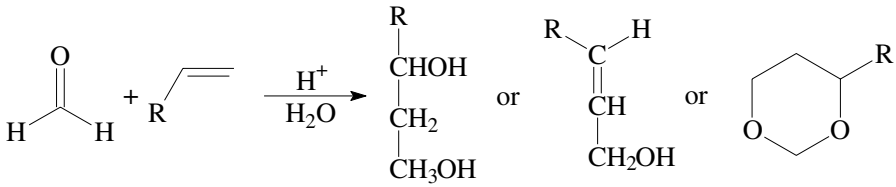
A modern reagent, that has found increased application, is *dimethyldioxirane*; it is prepared *in situ* by oxidation of acetone with potassium peroxomonosulfate $KHSO_5$.[7]

The epoxidation reaction usually takes place under mild conditions and with good to very good yield. Functional groups that are sensitive to oxidation should not be present in the starting material; with carbonyl groups a *Baeyer–Villiger reaction* may take place.

1. N. Prilezhaev, *Ber. Dtsch. Chem. Ges*. **1909**, *42*, 4811–4815.
2. B. Plesnicar in *The Chemistry of Peroxides* (Ed.: S. Patai), Wiley, New York, **1983**, p. 521–584.
3. C. Berti, *Top. Stereochem*. **1973**, *7*, 93–251.
4. B. Plesnicar in *Oxidation in Organic Chemistry, Vol. C* (Ed.: W. S. Trahanovsky), Academic Press, New York, **1978**, p. 211–252.
5. K. W. Woods, P. Beak, *J. Am. Chem. Soc*. **1991**, *113*, 6281–6283.
6. V. G. Dryuk, *Russ. Chem. Rev*. **1985**, *54*, 986–1005.
7. W. Adam, R. Curci, J. O. Edwards, *Acc. Chem. Res*. **1989**, *22*, 205–211.

Prins Reaction

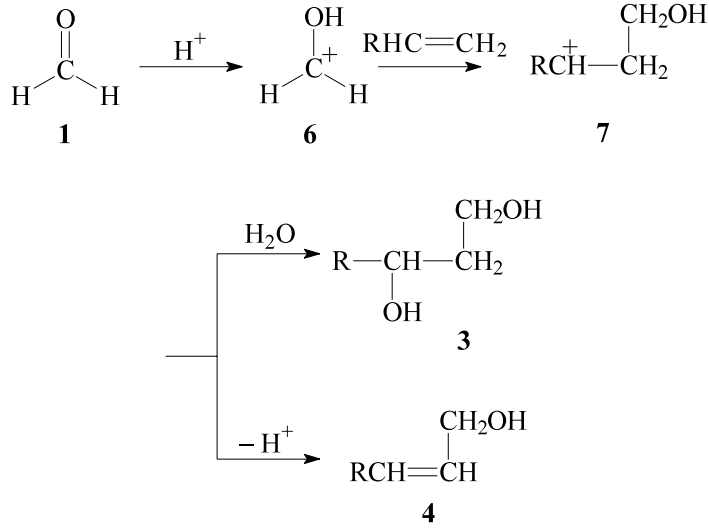
Addition of formaldehyde to alkenes



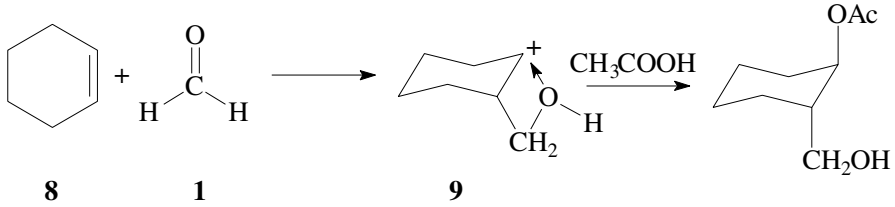
1 **2** **3** **4** **5**

The acid-catalyzed addition of an aldehyde—often formaldehyde **1**—to a carbon–carbon double bond can lead to formation of a variety of products. Depending on substrate structure and reaction conditions, a 1,3-diol **3**, allylic alcohol **4** or a 1,3-dioxane **5** may be formed. This so-called *Prins reaction*[1–4] often leads to a mixture of products.

The initial step is the protonation of the aldehyde—e.g. formaldehyde—at the carbonyl oxygen. The hydroxycarbenium ion **6** is thus formed as reactive species, which reacts as electrophile with the carbon–carbon double bond of the olefinic substrate by formation of a carbenium ion species **7**. A subsequent loss of a proton from **7** leads to formation of an allylic alcohol **4**, while reaction with water, followed by loss of a proton, leads to formation of a 1,3-diol **3**:[3,4]

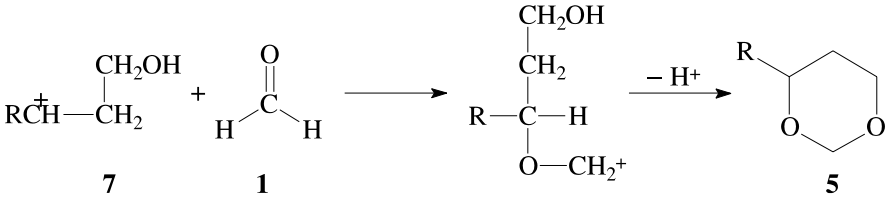


The Prins reaction often yields stereospecifically the *anti*-addition product; this observation is not rationalized by the above mechanism. Investigations of the sulfuric acid-catalyzed reaction of cyclohexene **8** with formaldehyde in acetic acid as solvent suggest that the carbenium ion species **7** is stabilized by a neighboring-group effect as shown in **9**. The further reaction then proceeds from the face opposite to the coordinating OH-group:[3,4]



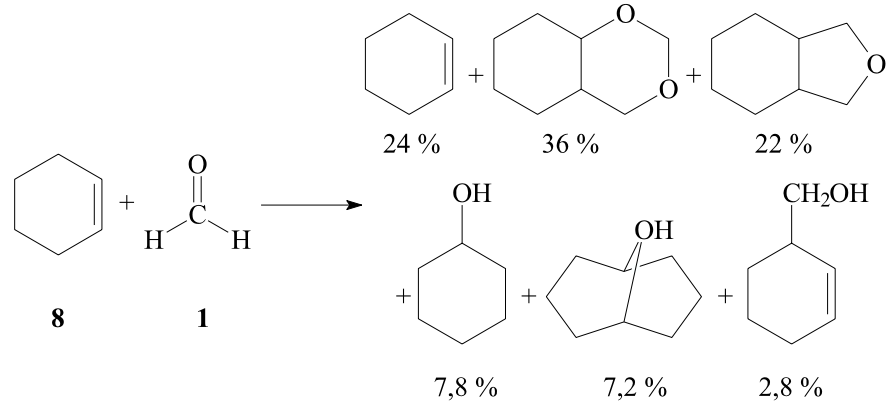
The *anti*-selective addition is not always observed; in some cases the *syn*-addition product predominates, and sometimes there is no selectivity observed at all. Obviously not all substrates are likely to react *via* a four-membered ring intermediate like **9**.

In the presence of excess formaldehyde, the carbenium ion species **7** can further react to give a 1,3-dioxane **5**. If only one equivalent of formaldehyde is used however, 1,3-diol **3** is formed as the major product:



7 **1** **5**

The formation of complex mixtures of products by a Prins reaction can be a problem. An example is the reaction of aqueous formaldehyde with cyclohexene **8** under acid catalysis:



8 **1**

Under appropriate conditions 1,3-dioxanes can be obtained in moderate to good yields. Below 70 °C the acid-catalyzed condensation of alkenes with aldehydes yields 1,3-dioxanes as major products, while at higher temperatures the hydrolysis of dioxanes to diols is observed.

As a catalyst sulfuric acid is most often used; phosphoric acid, boron trifluoride or an acidic ion exchange resin have also found application. 1,1-disubstituted alkenes are especially suitable substrates, since these are converted to relatively stable tertiary carbenium ion species upon protonation. α,β-unsaturated carbonyl compounds do not react as olefinic component.

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