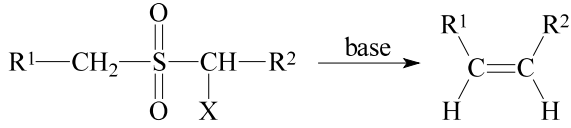
R

Ramberg–Bäcklund Reaction

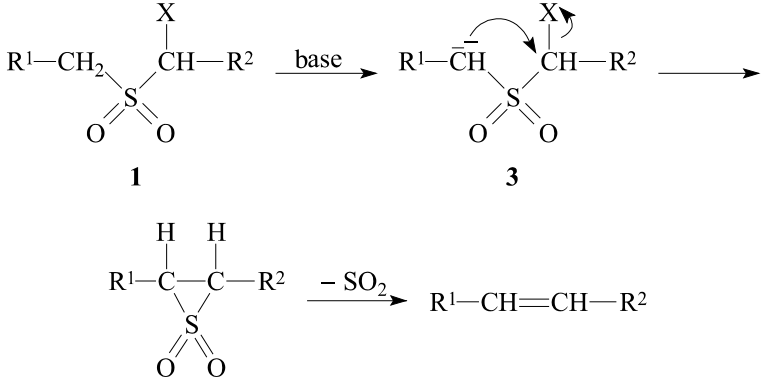
Conversion of α-halosulfones to alkenes



1 **2**

Treatment of an α-halosulfone **1** with base leads to extrusion of sulfur dioxide and formation of an alkene **2**. This reaction is referred to as the *Ramberg–Bäcklund reaction*;[1,2] it usually yields a mixture of *E*- and *Z*-isomers of the alkene.

An α-halosulfone **1** reacts with a base by deprotonation at the α'-position to give a carbanionic species **3**. An intramolecular nucleophilic substitution reaction, with the halogen substituent taking the part of the leaving group, then leads to formation of an intermediate episulfone **4** and the halide anion. This mechanism is supported by the fact that the episulfone **4** could be isolated.[3] Subsequent extrusion of sulfur dioxide from **4** yields the alkene **2**:



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

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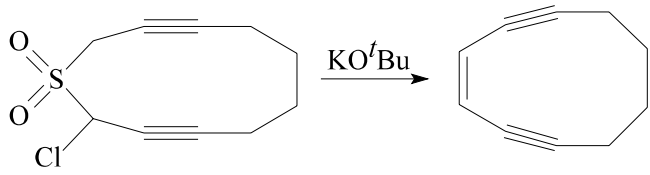
The Ramberg–Bäcklund reaction has been used for the preparation of strained unsaturated ring compounds that are difficult to obtain by other methods. A recent example is the synthesis of ene-diyne **5**[4] that has been used as starting material for a *Bergman cyclization*:



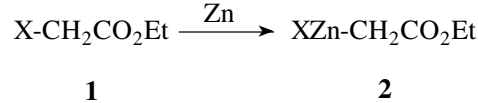
5

The α-halosulfone, required for the Ramberg–Bäcklund reaction, can for example be prepared from a sulfide by reaction with thionyl chloride (or with *N*-chlorosuccinimide) to give an α-chlorosulfide, followed by oxidation to the sulfone—e.g. using *m*-chloroperbenzoic acid. As base for the Ramberg–Bäcklund reaction have been used: alkoxides—e.g. potassium *t*-butoxide in an etheral solvent, as well as aqueous alkali hydroxide. In the latter case the use of a phase-transfer catalyst may be of advantage.[5]

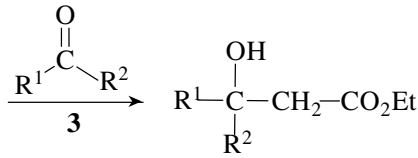
1. L. A. Paquette, *Org. React.* **1977**. *25*, 1–71.
2. F. G. Bordwell, E. Doomes, *J. Org. Chem.* **1974**, *39*, 2526–2531.
3. A. G. Sutherland, R. J. K. Taylor, *Tetrahedron Lett.* **1989**, *30*, 3267–3270.
4. K. C. Nicolaou, W.-M. Dai, *Angew. Chem.* **1991**, *103*, 1453–1481; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387.
5. G. D. Hartman, R. D. Hartman, *Synthesis* **1982**, 504–506.

Reformatsky Reaction

Synthesis of β-hydroxy esters



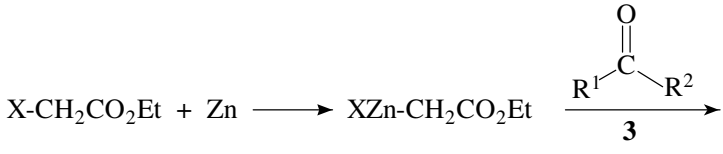
1 **2**



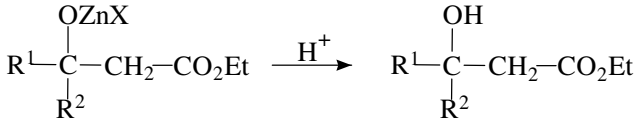
3 **4**

The classical *Reformatsky reaction*[1–4] consists of the treatment of an α-halo ester **1** with zinc metal and subsequent reaction with an aldehyde or ketone **3**. Nowadays the name is used generally for reactions that involve insertion of a metal into a carbon–halogen bond and subsequent reaction with an electrophile. Formally the Reformatsky reaction is similar to the *Grignard reaction*.

By reaction of an α-halo ester **1** with zinc metal in an inert solvent such as diethyl ether, tetrahydrofuran or dioxane, an organozinc compound **2** is formed (a Grignard reagent-like species). Some of these organozinc compounds are quite stable; even a structure elucidation by x-ray analysis is possible in certain cases:



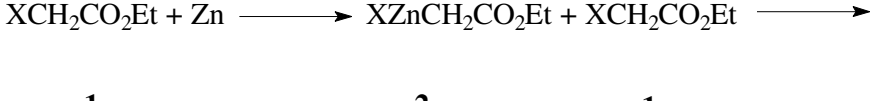
1 **2** **3**



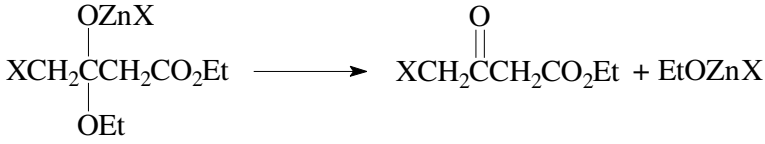
4

The reaction with a carbonyl substrate **3** is similar to a Grignard reaction. Hydrolytic workup then yields the β-hydroxy ester **4**. Sometimes product **4** easily eliminates water to yield directly an α,β-unsaturated ester.

The organozinc compound **2** is less reactive than an organomagnesium compound; the addition to an ester carbonyl group is much slower than the addition to an aldehyde or ketone. Nevertheless the addition of **2** to the carbonyl group of unreacted α-halo ester **1** is the most frequently observed side-reaction:



1 **2** **1**



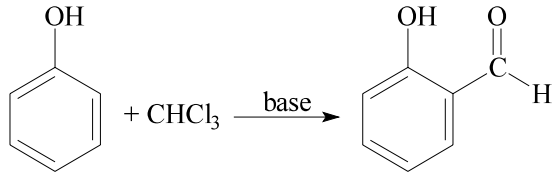
The carbonyl substrate **3** to be reacted with the organozinc compound **2** can be an aldehyde or ketone that may contain additional functional groups. With a vinylogous halo ester—i.e. a γ-halocrotyl ester—the corresponding γ-crotylzinc derivative is formed.

With special techniques for the activation of the metal—e.g. for removal of the oxide layer, and the preparation of finely dispersed metal—the scope of the Reformatsky reaction has been broadened, and yields have been markedly improved.[4,5] The attempted activation of zinc by treatment with iodine or dibromomethane, or washing with dilute hydrochloric acid prior to use, often is only moderately successful. Much more effective is the use of special alloys—e.g. zinc-copper couple, or the reduction of zinc halides using potassium (the so-called *Rieke procedure*[6]) or potassium graphite.[5] The application of ultrasound has also been reported.[7]

1. S. Reformatsky, *Ber. Dtsch. Chem. Ges*. **1887**, *20*, 1210–1211.
2. R. L. Shriner, *Org. React*. **1946**, *1*, 423–460.
3. M. W. Rathke, *Org. React*. **1975**, *22*, 423–460.
4. A. Fürstner, *Synthesis* **1989**, 571–590.
5. A. Fürstner, *Angew. Chem*. **1993**, *105*, 171–197; *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 164.
6. R. D. Rieke, S. J. Uhm, *Synthesis* **1975**, 452–453.
7. B. H. Han, P. Boudjouk, *J. Org. Chem*. **1982**, *47*, 5030–5032.

Reimer–Tiemann Reaction

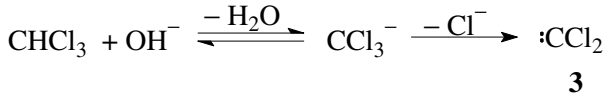
Formylation of aromatic substrates with chloroform



1 **2**

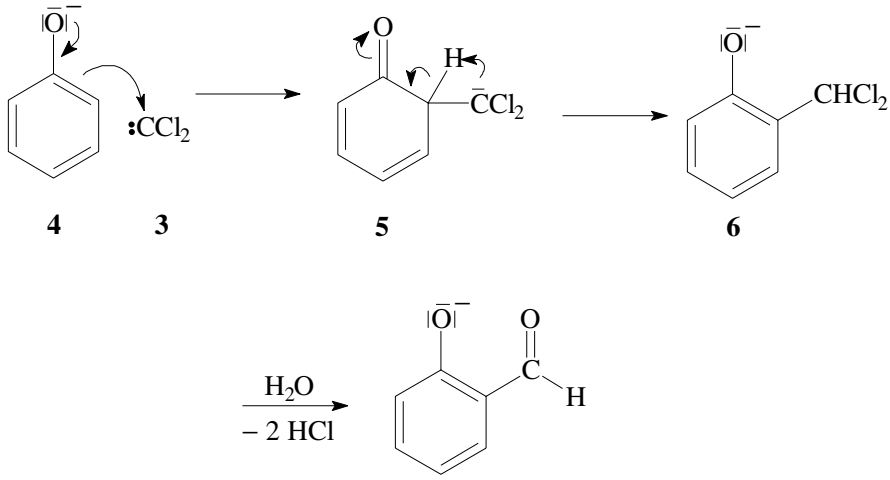
The formylation of a phenol **1** with chloroform in alkaline solution is called the *Reimer–Tiemann reaction*.[1–3] It leads preferentially to formation of an *ortho*-formylated phenol—e.g. salicylic aldehyde **2** —while with other formylation reactions, e.g. the *Gattermann reaction*, the corresponding *para*-formyl derivative is obtained as a major product. The Reimer–Tiemann reaction is mainly used for the synthesis of *o*-hydroxy aromatic aldehydes.

The actual formylation process is preceded by the formation of dichlorocarbene **3** as the reactive species. In strongly alkaline solution, the chloroform is deprotonated; the resulting trichloromethide anion decomposes into dichlorocarbene and a chloride anion:



3

In alkaline solution, the phenol **1** is deprotonated to the phenolate **4**, which reacts at the *ortho*-position with dichlorocarbene **3**. The initial addition reaction product **5** isomerizes to the aromatic *o*-dichloromethyl phenolate **6**, which under the reaction conditions is hydrolyzed to the *o*-formyl phenolate.[4]



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

The applicability of the Reimer–Tiemann reaction is limited to the formylation of phenols and certain reactive heterocycles like pyrroles and indoles. Yields are usually below 50%. In contrast to other formylation procedures, the Reimer–Tiemann reaction is *ortho*-selective; it is therefore related to the *Kolbe–Schmitt reaction*.

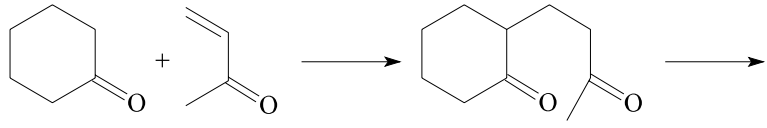
By a modified procedure using polyethyleneglycol as complexing agent a *para*-selective reaction can be achieved.[5]

As with other two-phase reactions, the application of ultrasound may lead to shorter reaction times and improved yields.[6]

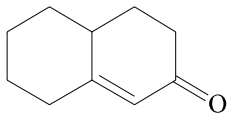
1. K. Reimer, *Ber. Dtsch. Chem. Ges*. **1876**, *9*, 423–424.
2. H. Wynberg, E. W. Meijer, *Org. React*. **1982**, *28*, 1–36.
3. G. Simchen, *Methoden Org. Chem (Houben-Weyl)*, **1983**, Vol. E3, p. 16–19.
4. E. A. Robinson, *J. Chem. Soc*. **1961**, 1663–1671.
5. R. Neumann, Y. Sasson, *Synthesis* **1986**, 569–570.
6. J. C. Cochran, M. G. Melville, *Synth. Commun*. **1990**, *20*, 609–616.

Robinson Annulation

Annulation of a cyclohexenone ring

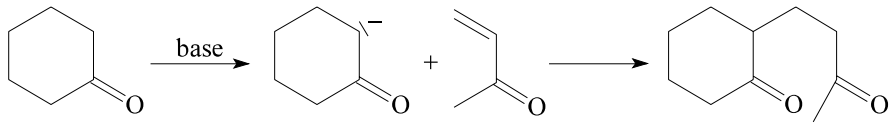


1 **2** **3**



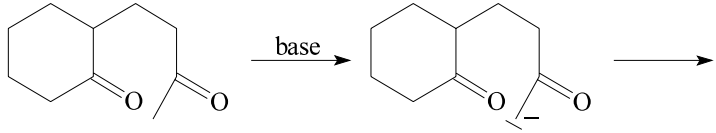
4

The reaction of a cyclic ketone—e.g. cyclohexanone **1**—with methyl vinyl ketone **2** resulting in a ring closure to yield a bicyclic α,β-unsaturated ketone **4**, is called the *Robinson annulation*.[1–3] This reaction has found wide application in the synthesis of terpenes, and especially of steroids. Mechanistically the Robinson annulation consists of two consecutive reactions, a *Michael addition* followed by an *Aldol reaction*. Initially, upon treatment with a base, the cyclic ketone **1** is deprotonated to give an enolate, which undergoes a conjugate addition to the methyl vinyl ketone, i.e. a Michael addition, to give a 1,5-diketone **3**:

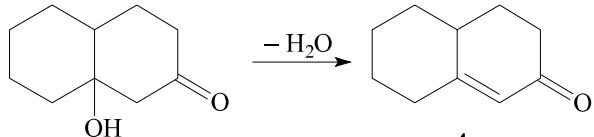


1 **2** **3**

The next step is an intramolecular aldol reaction leading to closure of a six-membered ring. Subsequent dehydration yields the bicyclic enone **4**:

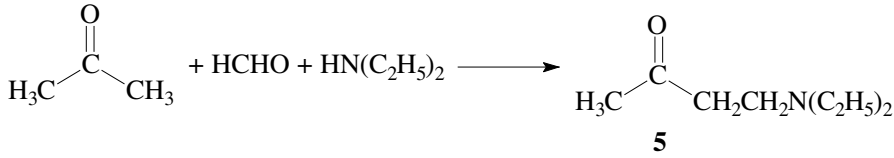


3



4

Methyl vinyl ketone **2** tends to polymerize, especially in the presence of a strong base; the yield of annulation product is therefore often low. A methyl vinyl ketone precursor, e.g. **6**, is often employed, from which the Michael acceptor **2** is generated *in situ*, upon treatment with a base. The quaternary ammonium salt **6** can be obtained by reaction of the tertiary amine **5**, which in turn is prepared from acetone, formaldehyde and diethylamine in a *Mannich reaction*.



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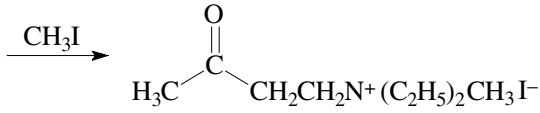
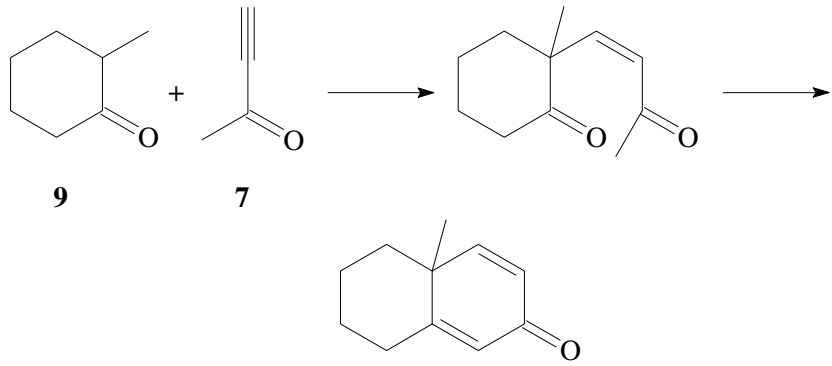


6

Besides a polymerization of the Michael acceptor, a double alkylation of the starting ketone, by reaction with a second Michael acceptor molecule, may take place as a side reaction, and thus further reduce the yield. The polymerization of the enone **2** as well as the double alkylation of the starting ketone can be avoided by application of a modern procedure for the Robinson annulation that uses an organotin triflate as catalyst.[4]

When 3-butyne-2-one **7** is used as a Michael acceptor component, a 2,5-cyclohexadienone, e.g. **8**, is obtained as the annulation product:[5]

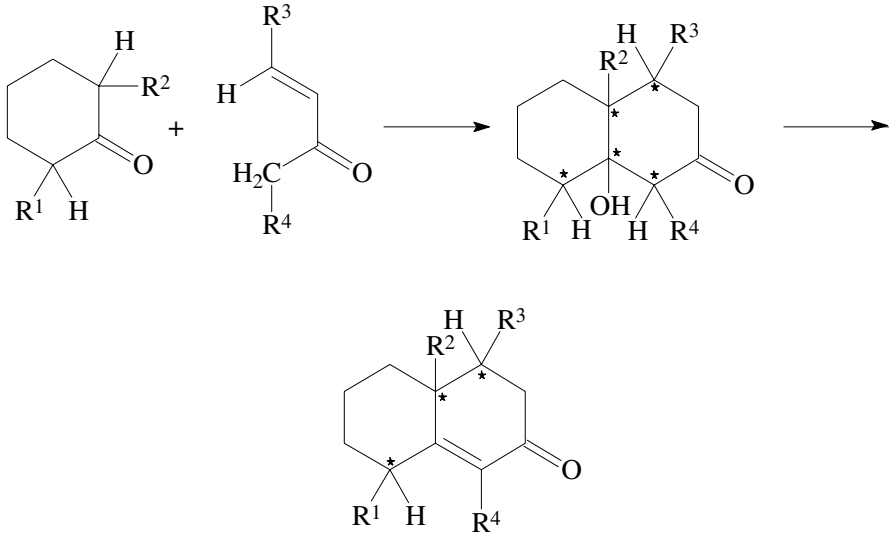


9 **7**

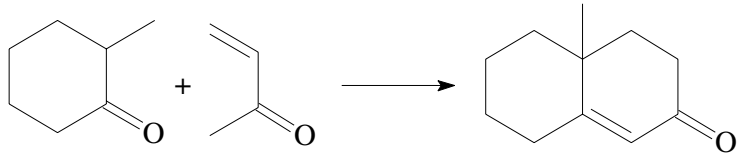
8

From a stereochemical point of view the Robinson annulation can be a highly complex reaction, since the configuration at five stereogenic sp^3-carbon centers

is influenced during formation of the initial annulation product; the subsequent dehydration however, that usually takes place, reduces the number of stereogenic centers to three.

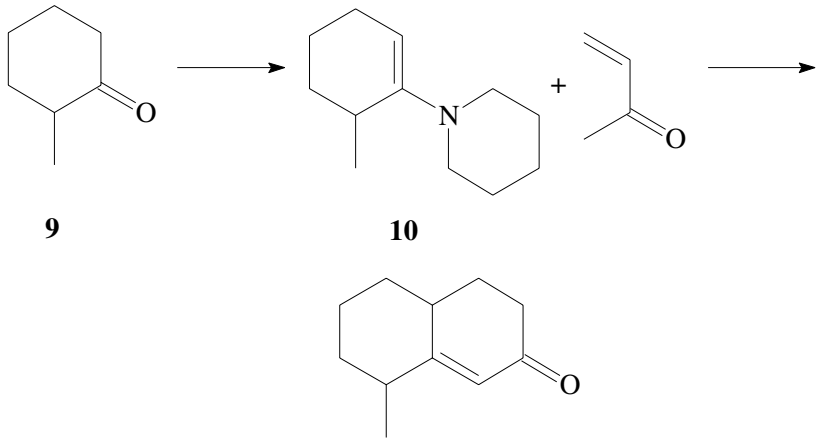


Since most often the selective formation of just one stereoisomer is desired, it is of great importance to develop highly selective methods. For example the second step, the aldol reaction, can be carried out in the presence of a chiral auxiliary—e.g. a chiral base—to yield a product with high enantiomeric excess. This has been demonstrated for example for the reaction of 2-methylcyclopenta-1,3-dione with methyl vinyl ketone in the presence of a chiral amine or α-amino acid. By using either enantiomer of the amino acid proline—i.e. (*S*)-(−)-proline or (*R*)-(+)-proline—as chiral auxiliary, either enantiomer of the annulation product 7a-methyl-5,6,7,7a-tetrahydroindan-1,5-dione could be obtained with high enantiomeric excess.[6] α-Substituted ketones, e.g. 2-methylcyclohexanone **9**, usually add with the higher substituted α-carbon to the Michael acceptor:



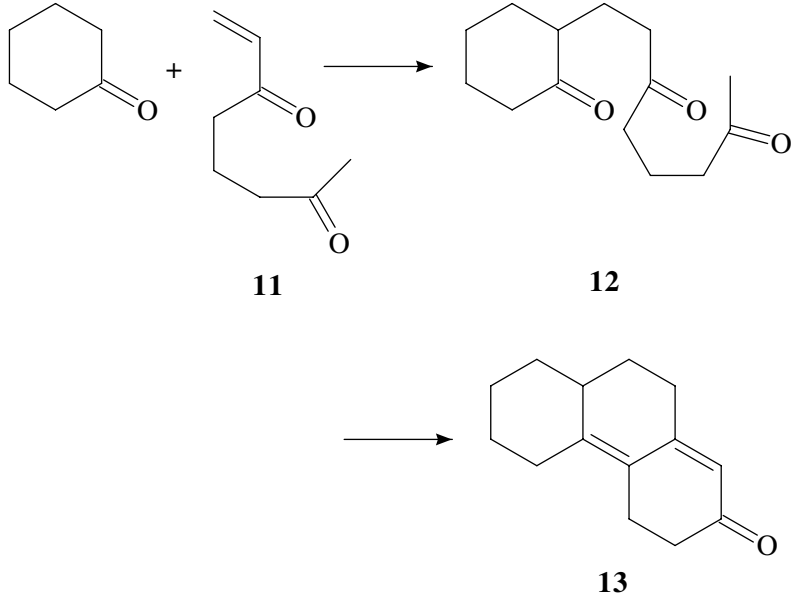
9

Exceptions to this rule may be a result of steric hindrance. However when the *Stork enamine method* is applied, for example with enamine **10**, the less substituted α-carbon becomes connected to the Michael acceptor:



9 **10**

The best method to achieve a high regioselectivity is the use of preformed enolates. A double annulation reaction is possible if, for example, a diketone such as **11** is used as starting material. The product of the Michael addition **12** can undergo two subsequent aldol condensation reactions to yield the tricyclic dienone **13**:[2]



11 **12**

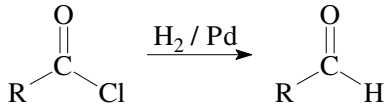
13

Since an annulated six-membered carbocycle is a common structural element of natural products, the Robinson annulation is an important reaction in organic synthesis.

1. W. S. Rapson, R. Robinson, *J. Chem. Soc.* **1935**, 1285–1291.
2. R. E. Gawley, *Synthesis* **1976**, 777–794.
3. M. E. Jung, *Tetrahedron* **1976**, *32*, 3–31.
4. T. Sato, Y. Wakahara, J. Otera, H. Nozaki, *Tetrahedron Lett.* **1990**, *31*, 1581–1584.
5. R. B. Woodward, G. Singh, *J. Am. Chem. Soc.* **1950**, *72*, 494–500.
6. U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493;
   Angew. Chem. Int. Ed. Engl. **1971**, *10*, 496.
   Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615.
   C. Agami, *Bull. Soc. Chim. Fr.* **1988**, 499–507.

Rosenmund Reduction

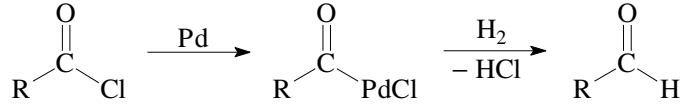
Aldehydes by reduction of acyl chlorides



1 **2**

The name *Rosenmund reduction*[1–3] is used for the catalytic hydrogenation of an acyl chloride **1** to yield an aldehyde **2**.

The reaction mechanism differs from that of other catalytic hydrogenations that also are carried out in the presence of palladium as catalyst, e.g. that of olefins. Presumably an organopalladium species is formed as an intermediate, which then reacts with the hydrogen:[6]



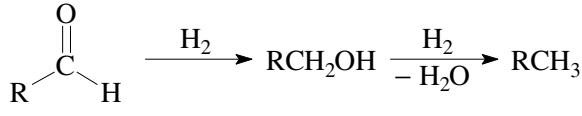
1 **3** **2**

By continuously passing hydrogen gas through the reaction mixture, the hydrogen chloride that is formed in the reaction can be removed. Better yields (around 90%) may be obtained by adding a base to the reaction mixture in order to remove the hydrogen chloride.[7]

As catalyst for the Rosenmund reaction palladium on a support, e.g. palladium on barium sulfate, is most often used. The palladium has to be made less active in order to avoid further reduction of the aldehyde to the corresponding alcohol. Such a poisoned catalyst is obtained for example by the addition of quinoline and sulfur. Recent reports state that the reactivity of the catalyst is determined by the morphology of the palladium surface.[4,5]

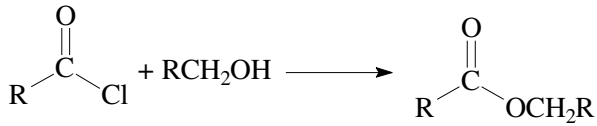
A number of side-reactions may be observed with the Rosenmund reduction, which however can be avoided by proper reaction conditions. A poorly deactivated catalyst will lead to reduction of aldehyde **2** to the alcohol **4**, or even to

the corresponding hydrocarbon **5**:



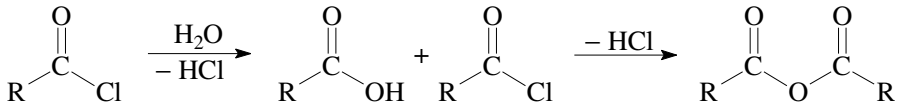
2 **4** **5**

Reaction of the acyl chloride **1** with alcohol **4** thus formed leads to formation of an ester **6**:



1 **4** **6**

Small amounts of water present will lead to partial hydrolysis of the acyl chloride to give the carboxylic acid **7**, which then may further react with the acyl chloride to give a carboxylic anhydride **8**:



1 **7** **1** **8**

The Rosenmund reduction is usually applied for the conversion of a carboxylic acid into the corresponding aldehyde *via* the acyl chloride. Alternatively a carboxylic acid may be reduced with lithium aluminum hydride to the alcohol, which in turn may then be oxidized to the aldehyde. Both routes require the preparation of an intermediate product; and each route may have its advantages over the other, depending on substrate structure.

1. M. Saytzeff, *J. Prakt. Chem*. **1873**, *6*, 128–135.
2. K. W. Rosenmund, *Ber. Dtsch. Chem. Ges*. **1918**, *51*, 585–593.
3. E. Mosettig, R. Mozingo, *Org. React*. **1948**, *4*, 362–377.
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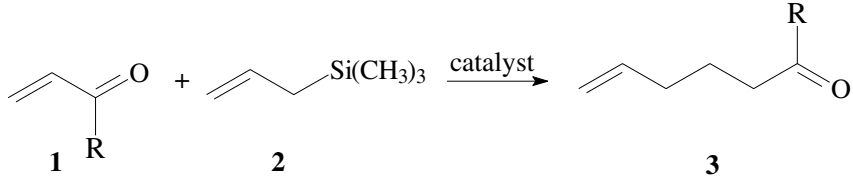
S

Sakurai Reaction

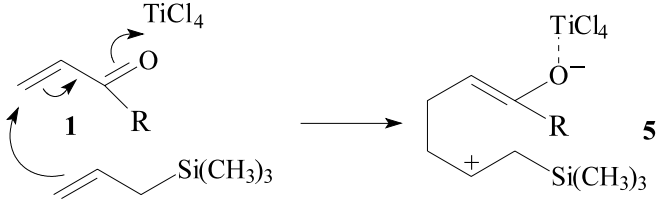
Conjugate addition of an allylsilane to an α,β-unsaturated ketone



1 **2** **3**

An allylsilane—e.g. allyltrimethylsilane **2**—can upon treatment with fluoride or in the presence of catalytic amounts of a Lewis acid undergo a nucleophilic conjugate addition to an α,β-unsaturated ketone **1**; as reaction product a δ,ε-unsaturated ketone **3** is obtained. This conjugate addition reaction is called the *Sakurai reaction*;[1,2] of particular interest from a synthetic point of view is the intramolecular variant.[3]

When a Lewis acid, e.g. titanium tetrachloride, coordinates to the carbonyl oxygen of an α,β-unsaturated carbonyl compound, the β-carbon center becomes more positively polarized. The allylsilane adds as a nucleophile with its γ-carbon to the β-carbon of the α,β-unsaturated carbonyl substrate.[4,5] This carbon–carbon single-bond forming step is the rate determining step. Cleavage of the trimethylsilyl group from the intermediate carbenium ion **5** leads to formation of a new carbon–carbon double bond. After hydrolytic workup the δ,ε-unsaturated ketone **3** is obtained:



1 **2**

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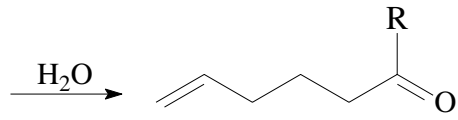
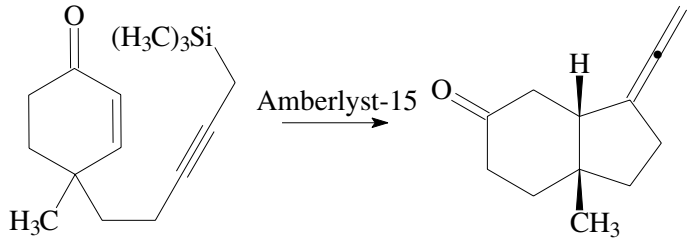


3

The intramolecular Sakurai reaction allows for the synthesis of functionalized bicyclic systems.[3] By proper choice of the reaction conditions, especially of the Lewis acid or fluoride reagent used, high stereoselectivity can be achieved, which is an important aspect for its applicability in natural products synthesis.

Propargylsilanes can also be employed in the Sakurai reaction. For example the enone **6**, containing a propargylsilane side chain, undergoes an intramolecular Sakurai reaction, catalyzed by an acidic ion-exchange resin—e.g. Amberlyst-15—to give stereoselectively the bicyclic product **7** in good yield:[6]



6 **7**

As Lewis acid, titanium tetrachloride, boron trifluoride or ethylaluminum dichloride is often used. The stereochemical outcome of the reaction strongly depends on the Lewis acid used. The Sakurai reaction is a relatively new carbon–carbon forming reaction, that has been developed into a useful tool for organic synthesis.[2,3,6]

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   A. Hosomi, *Acc. Chem. Res*. **1988**, *21*, 200–206.
   H. Sakurai, *Synlett* **1989**, 1.
2. I. Fleming, J. Dunogues, R. Smithers, *Org. React*. **1989**, *37*, 57–575; for competitive reaction pathways, and reactions with allyltriisopropylsilane *see*: H.-J. Knölker, *J. Prakt. Chem*. **1997**, *339*, 304–314.
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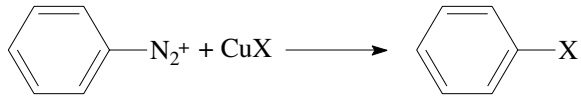
6. D. Schinzer, J. Kabbara, K. Ringe, *Tetrahedron Lett*. **1992**, *33*, 8017–8018.

Sandmeyer Reaction

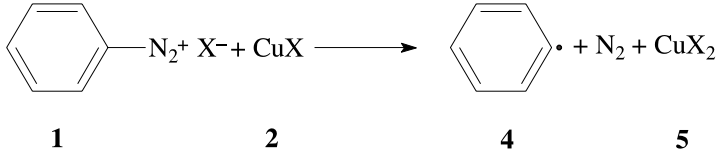
Conversion of arenediazonium salts into aryl halides



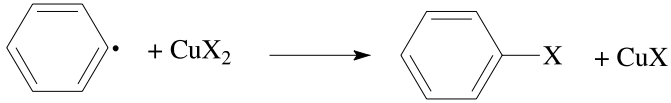
1 **2** **3**

The name *Sandmeyer reaction*[1,2] is used for the replacement of the diazonium group in an arenediazonium compound by halide or pseudohalide, taking place in the presence of a metal salt.[3] However this is not a strict definition, since the replacement of the diazonium group by iodide, which is possible without a metal catalyst, is also called a Sandmeyer reaction.

The reaction mechanism is not rigorously known, but is likely to involve the following steps.[4–6] First the arenediazonium ion species **1** is reduced by a reaction with copper-(I) salt **2** to give an aryl radical species **4**. In a second step the aryl radical abstracts a halogen atom from the CuX_2 compound **5**, which is thus reduced to the copper-I salt **2**. Since the copper-(I) species is regenerated in the second step, it serves as a catalyst in the overall process.



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

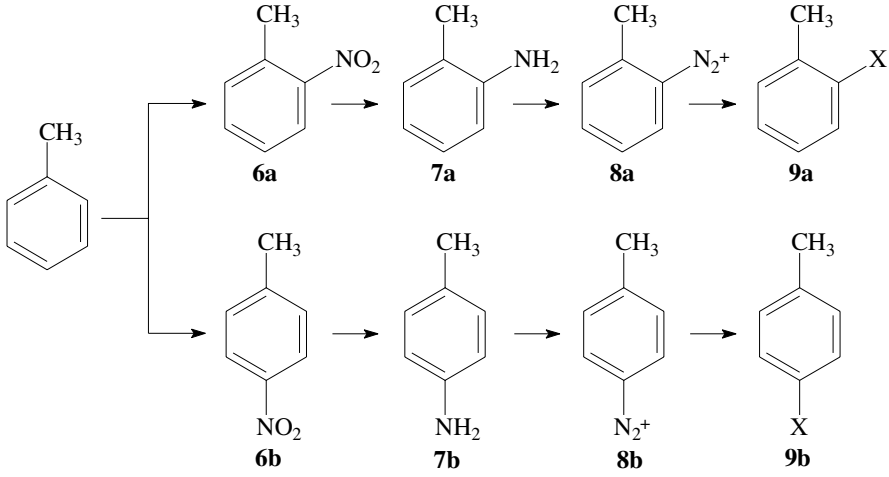


4 **5** **3** **2**

For the *in situ* preparation of the required arenediazonium salt from an aryl amine by application of the *diazotization reaction*, an acid HX is used, that corresponds to the halo substituent X to be introduced onto the aromatic ring. Otherwise—e.g. when using HCl/CuBr—a mixture of aryl chloride and aryl bromide will be obtained. The copper-(I) salt **2** (chloride or bromide) is usually prepared by dissolving the appropriate sodium halide in an aqueous solution of copper-(II) sulfate and then adding sodium hydrogensulfite to reduce copper-(II) to copper-(I). Copper-(I) cyanide CuCN can be obtained by treatment of copper-(I) chloride with sodium cyanide.

The Sandmeyer reaction generally permits the introduction of electron-withdrawing substituents onto an aromatic ring. Arenediazonium salts, as well as the Sandmeyer products derived thereof, are useful intermediates for the synthesis

of substituted aromatic compounds. For example an aromatic nitrile, that is accessible by reaction of an arenediazonium salt with copper-(I) cyanide, can be further converted into a carboxylic acid through hydrolysis, or reduced to give a benzylic amine, or reacted with an organometallic reagent to yield a ketone on hydrolytic workup. The Sandmeyer reaction may also be used to synthesize regioisomerically pure halotoluenes **9**:



While the direct halogenation of toluene gives a mixture of isomers that is difficult to separate into the pure isomers, the isomeric *o*- and *p*-nitrotoluenes **6a** and **6b**, formed by nitration, are easy to separate from each other. Thus reduction of the single *o*- or *p*-nitrotoluene **6** to the *o*- or *p*-toluidine **7a** or **7b** respectively, followed by conversion into the corresponding diazonium salt **8** and a subsequent Sandmeyer reaction leads to the pure *o*- or *p*-halotoluene **9**.

1. T. Sandmeyer, *Ber. Dtsch. Chem. Ges*. **1884**, *17*, 1633–1635.
2. H. H. Hodgson, *Chem. Rev*. **1947**, *40*, 251–277.
3. E. Pfeil, *Angew. Chem*. **1953**, *65*, 155–158.
4. J. K. Kochi, *J. Am. Chem. Soc*. **1957**, *79*, 2942–2948.
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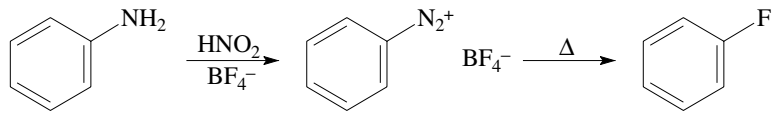
6. C. Galli, *J. Chem. Soc., Perkin Trans. 2*, **1982**, 1139–1142.

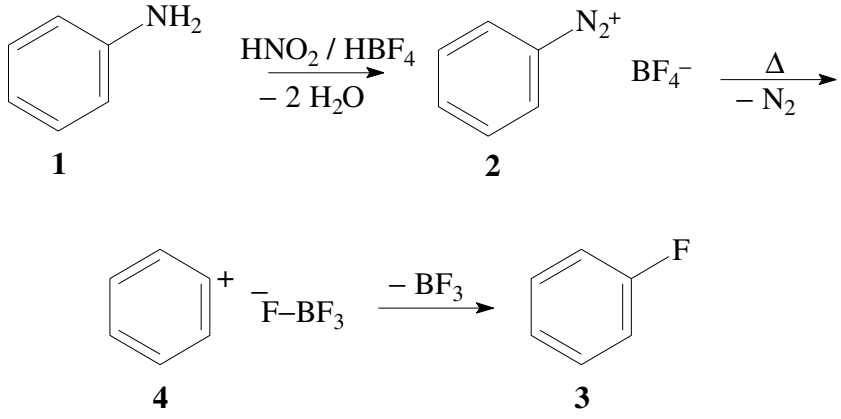
Schiemann Reaction

Aryl fluorides from arenediazonium fluoroborates



The preparation of an aryl fluoride—e.g. fluorobenzene **3**—starting from an aryl amine—e.g. aniline **1**—*via* an intermediate arenediazonium tetrafluoroborate **2**, is called the *Schiemann reaction* (also called the *Balz–Schiemann reaction*).[1,2] The *diazotization* of aniline **1** in the presence of tetrafluoroborate leads to formation of a benzenediazonium tetrafluoroborate **2** that can be converted into fluorobenzene **3** by thermolysis.

Treatment of aniline **1** with nitric acid in the presence of tetrafluoroboric acid leads to a relatively stable benzenediazonium tetrafluoroborate **2** by the usual diazotization mechanism. There are several variants for the experimental procedure.[3] Subsequent thermal decomposition generates an aryl cation species **4**, which reacts with fluoroborate anion to yield fluorobenzene **3**:[4]



In a general procedure the arenediazonium fluoroborate is isolated, and then heated without solvent. A modern variant permits the photochemical decomposition without initial isolation of the diazonium fluoroborate.[5]

The Schiemann reaction seems to be the best method for the selective introduction of a fluorine substituent onto an aromatic ring.[5] The reaction works with many aromatic amines, including condensed aromatic amines. It is however of limited synthetic importance, since the yield usually decreases with additional substituents present at the aromatic ring.

1. G. Balz, G. Schiemann, *Ber. Dtsch. Chem. Ges*. **1927**, *60*, 1186–1190.
2. A. Roe, *Org. React*. **1949**, *5*, 193–228.
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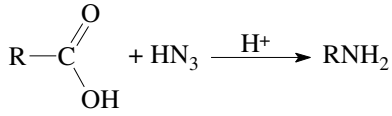
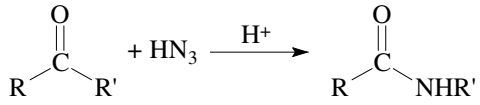
Schmidt Reaction

Reaction of carboxylic acids, aldehydes or ketones with hydrazoic acid



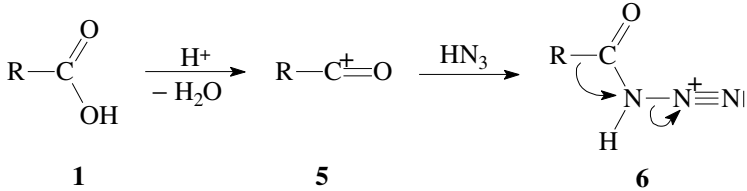
1 **2**



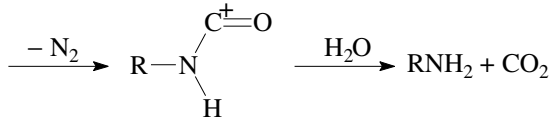
3 **4**

The reaction of carboxylic acids, aldehydes or ketones with hydrazoic acid in the presence of a strong acid is known as the *Schmidt reaction*.[1,2] A common application is the conversion of a carboxylic acid **1** into an amine **2** with concomitant chain degradation by one carbon atom. The reaction of hydrazoic acid with a ketone **3** does not lead to chain degradation, but rather to formation of an amide **4** by formal insertion of an NH-group.

For the different types of substrates, different reaction mechanisms are formulated.[3] For a carboxylic acid **1** as starting material the initial step is the protonation by a strong acid (most often sulfuric acid) and subsequent loss of water leading to formation of an acylium ion species **5**. Nucleophilic addition of hydrazoic acid to the acylium ion **5** gives an intermediate species **6** that further reacts by migration of the group R and concomitant loss of N_2 to the rearranged intermediate **7**. The latter reacts with water to give an unstable carbaminic acid that decomposes to the primary amine **2** and carbon dioxide:

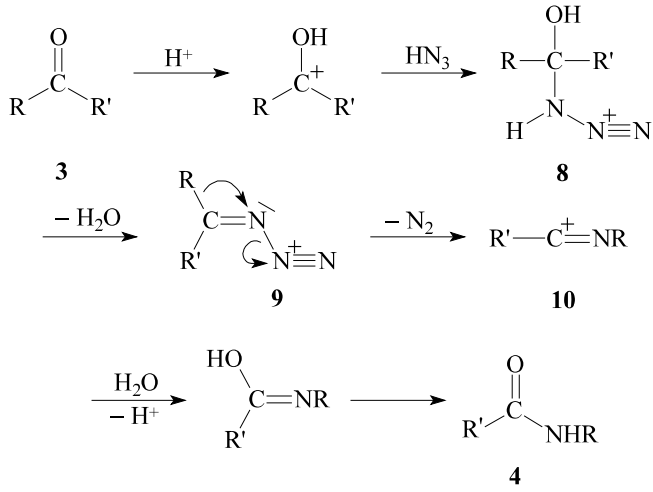


1 **5** **6**



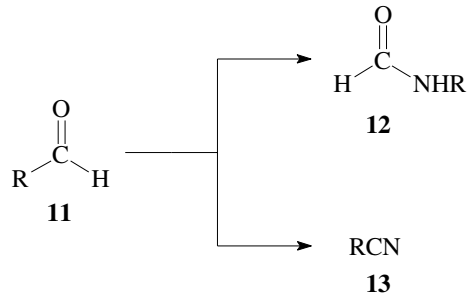
7 **2**

The nucleophilic addition of hydrazoic acid to a ketone **3** to give **8** is promoted by the protonation of the carbonyl oxygen. Elimination of water from **8** leads to an intermediate **9**, from which a nitrilium ion intermediate **10** is formed by migration of group R and loss of N_2. Migration of R and cleavage of N_2 from **9** is likely to be a concerted process, since nitrenium ions have so far not been identified as intermediates with such a reaction. At this point of the reaction pathway there is a strong similarity with the *Beckmann rearrangement*, which proceeds by a similar rearrangement to give an intermediate nitrilium ion species **10**. Reaction of **10** with water, followed by a tautomerization, yields the stable amide **4**:

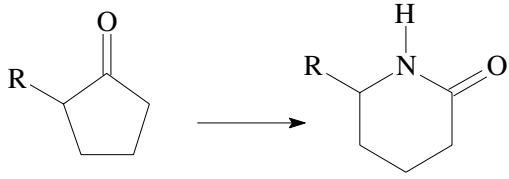


The cleavage of water from **8** usually leads to the isomer with the more voluminous substituent R *trans* to the diazonium group. It is that *trans*-substituent that will then migrate to the nitrogen-center in the rearrangement step; in case of an alkyl-aryl ketone as starting material, the aryl group usually will migrate.[4]

Aldehydes **11** react with hydrazoic acid to yield formamides **12**. The reaction pathway is similar to that formulated above for ketones. An important side-reaction however is the formation of nitriles **13**, resulting in a significant lower yield of amides, as compared to the reaction of ketones. Sometimes the nitrile **13** even is the major product formed:

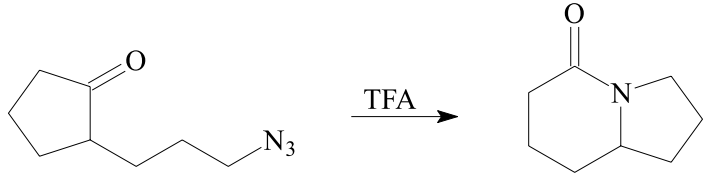


When applied to a cycloketone, the Schmidt reaction leads to formation of a ring-expanded lactam—e.g. **14** → **15**:[5]



14 **15**

In recent years the applicability of the Schmidt reaction for the synthesis of more complex molecules—especially the variant employing alkyl azides—has been further investigated. Cycloketones bearing an *azidoalkyl side-chain* at the α-carbon center have been shown to undergo, upon treatment with trifluoroacetic acid or titanium tetrachloride, an *intramolecular Schmidt reaction* to yield bicyclic lactams. e.g. **16** → **17**.[6]



16 **17**

Intermolecular Schmidt reactions of *alkyl azides* and *hydroxyalkyl azides* with cycloketones in the presence of a Lewis acid, lead to formation of *N*-alkyl lactams and *N*-hydroxyalkyl lactams respectively in good yield.[7] The synthesis of chiral lactams by an *asymmetric Schmidt reaction* has also been reported.[8]

By application of the Schmidt reaction, the conversion of a carboxylic acid into an amine that has one carbon atom less than the carboxylic acid, can be achieved in one step. This may be of advantage when compared to the *Curtius reaction* or the *Hofmann rearrangement*; however the reaction conditions are more drastic. With long-chain, aliphatic carboxylic acids yields are generally good, while with aryl derivatives yields are often low.

The Schmidt reaction of ketones works best with aliphatic and alicyclic ketones; alkyl aryl ketones and diaryl ketones are considerably less reactive. The reaction is only seldom applied to aldehydes as starting materials. The hydrazoic acid used as reagent is usually prepared *in situ* by treatment of sodium azide with sulfuric acid. Hydrazoic acid is highly toxic, and can detonate upon contact with hot laboratory equipment.

1. K. F. Schmidt, *Angew. Chem.* **1923**, *36*, 511.
2. H. Wolff, *Org. React.* **1946**, *3*, 307–336.

3. G. I. Koldobskii, V. A. Ostrovskii, B. V. Gidaspov, *Russ. Chem. Rev.* **1978**, *47*, 1084–1094.
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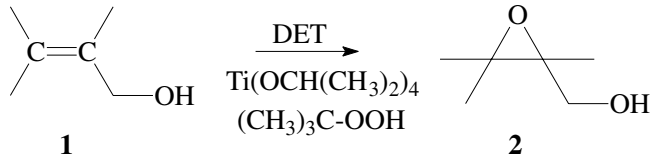
6. J. Aubé, G. L. Milligan, *J. Am Chem. Soc.* **1991**, *113*, 8965–8966.
   G. L. Milligan, C. J. Mossman, J. Aubé, *J. Am. Chem. Soc.* **1995**, *117*, 10449–10459;
7. J. Aubé, G. L. Milligan, C. J. Mossman, *J. Org. Chem.* **1992**, *57*, 1635–1637.
8. V. Gracias, G. L. Milligan, J. Aubé, *J. Am. Chem. Soc.* **1995**, *117*, 8047–8048.
   V. Gracias, G. L. Milligan, J. Aubé, *J. Org. Chem.* **1996**, *61*, 10–11.

Sharpless Epoxidation

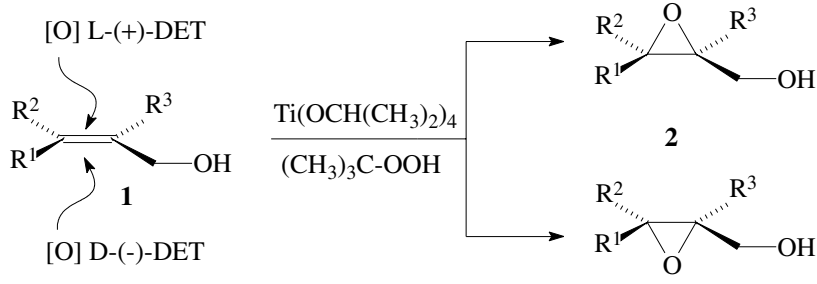
Asymmetric epoxidation of allylic alcohols



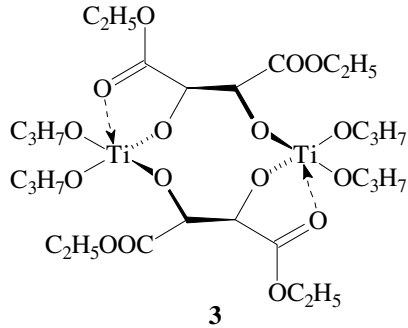
1 **2**

The asymmetric epoxidation of an allylic alcohol **1** to yield a 2,3-epoxy alcohol **2** with high enantiomeric excess, has been developed by *Sharpless* and *Katsuki*.[1] This enantioselective reaction is carried out in the presence of tetraisopropoxytitanium and an enantiomerically pure dialkyl tartrate—e.g. (+)- or (−)-diethyl tartrate (DET)—using *tert*-butyl hydroperoxide as the oxidizing agent.

With this epoxidation procedure it is possible to convert the achiral starting material—i.e. the allylic alcohol—with the aim of a chiral reagent, into a chiral, non-racemic product; in many cases an enantiomerically highly-enriched product is obtained. The desired enantiomer of the product epoxy alcohol can be obtained by using either the (+)- or (−)- enantiomer of diethyl tartrate as chiral auxiliary:[2–4]

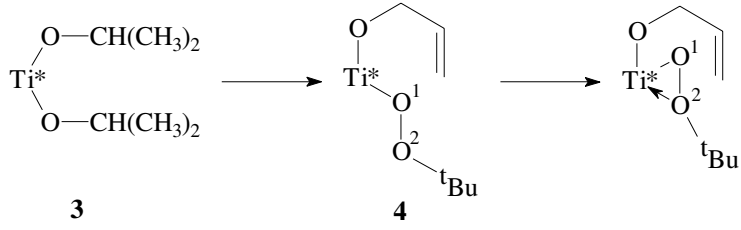


A model for the catalytically active species in the Sharpless epoxidation reaction is formulated as a dimer **3**, where two titanium centers are linked by two chiral tartrate bridges. At each titanium center two isopropoxide groups of the original tetraisopropoxytitanium-(IV) have been replaced by the chiral tartrate ligand:

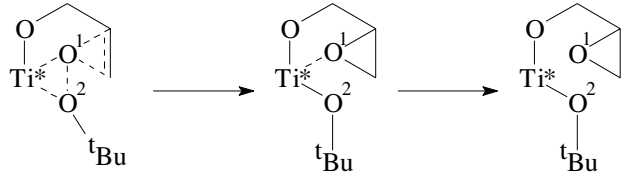


3

As the reaction proceeds, the two remaining isopropoxide groups at one titanium center are replaced by the allylic alcohol (the substrate) and *tert*-butyl hydroperoxide (the oxidizing agent) to give the complex **4**. Titanium-(IV) is suitable for such a reaction since it can form four covalent, but still reactive bonds, two bonds to bind the ends of two chiral bidentate tartrate ligands, one bond to the oxidizing agent, and one to the allylic alcohol substrate. The titanium thus serves as a template for the reactants; with the aim of the chiral ligands it has become a chiral template. The reactants are arranged geometrically in such a way to permit a facial selection, resulting in an enantioselective epoxidation step. Furthermore the tetraisopropoxytitanium-(IV) acts as a Lewis acid by coordinating to the other oxygen center—i.e. O-2 in the scheme below—of the *t*-butyl peroxy-ligand; as a result the oxygen center O-1 becomes more electrophilic. For the benefit of clarity the *bi*-centered titanium-tartrate moiety of the complex is shown simplified as Ti* in the following scheme:



3 **4**



5

The oxygen atom O-1 adds to the carbon–carbon double bond, while the oxygen O-2 forms a covalent bond to the titanium center. As a result complex **5** is

formed, from which upon hydrolytic workup the epoxy alcohol and *t*-butanol are liberated.

The reaction is limited to allylic alcohols; other types of alkenes do not or not efficiently enough bind to the titanium. The catalytically active chiral species can be regenerated by reaction with excess allylic alcohol and oxidant; however the titanium reagent is often employed in equimolar amount.

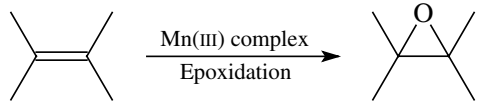
In order to obtain good yields, it is important to use dry solvent and reagents. The commercially available *t*-butyl hydroperoxide contains about 30% water for stabilization. For the use in a Sharpless epoxidation reaction the water has to be removed first. The effect of water present in the reaction mixture has for example been investigated by *Sharpless et al.*[5] for the epoxidation of (*E*)-α-phenylcinnamyl alcohol, the addition of one equivalent of water led to a decrease in enantioselectivity from 99% e.e. to 48% e.e.

Titanium-IV compounds with their Lewis acid activity may catalyze an interfering rearrangement of the starting allylic alcohol or the epoxy alcohol formed. In order to avoid such side-reactions, the epoxidation is usually carried out at room temperature or below.

The Sharpless epoxidation is one of the most important of the newer organic reactions. Although limited to allylic alcohols, it has found wide application in natural product synthesis.

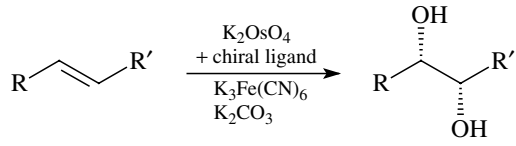
The 2,3-epoxy alcohols are often obtained in high optical purity (90% enantiomeric excess or higher), and are useful intermediates for further transformations. For example by nucleophilic ring opening the epoxide unit may be converted into an alcohol, a β-hydroxy ether or a vicinal diol.

Non-functionalized alkenes **6**, with an 'isolated' carbon–carbon double bond lacking an additional coordination site, can be epoxidized with high enantiomeric excess by applying the *Jacobsen–Katsuki epoxidation* procedure[6] using optically active manganese(III) complexes:



The Best results are obtained with *cis*-alkenes; however, the epoxidation of tri- and tetra-substituted double bonds is also possible. Because of its versatility, the Jacobsen–Katsuki epoxidation is an important method in asymmetric synthesis.

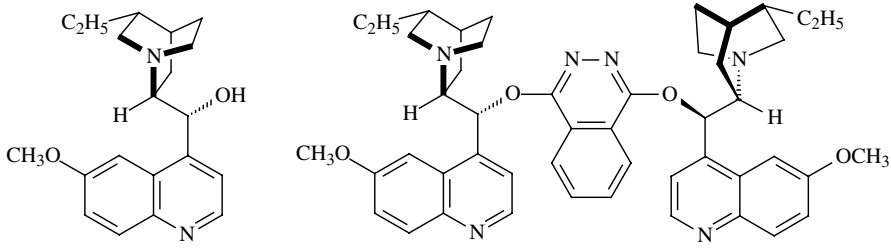
Another important reaction associated with the name of Sharpless is the so-called *Sharpless dihydroxylation*,[7] i.e. the asymmetric dihydroxylation of alkenes upon treatment with osmium tetroxide in the presence of a cinchona alkaloid, such as dihydroquinine, dihydroquinidine or derivatives thereof, as the chiral ligand. This reaction is of wide applicability for the enantioselective dihydroxylation of alkenes, since it does not require additional functional groups in the substrate molecule:[8]



7 **8**

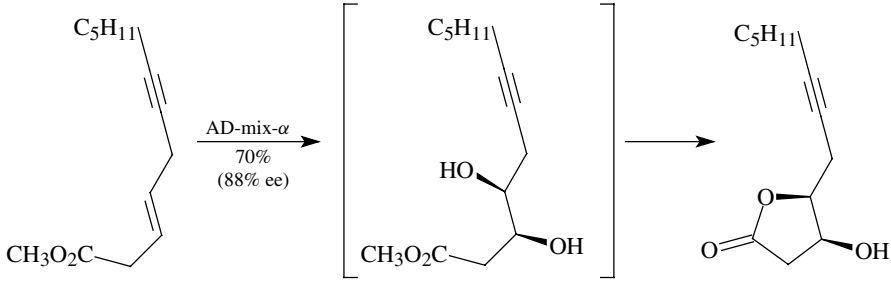
With this reaction, two new asymmetric centers can be generated in one step from an achiral precursor in moderate to good enantiomeric purity by using a chiral catalyst for oxidation. The Sharpless dihydroxylation has been developed from the earlier *syn*-dihydroxylation of alkenes with osmium tetroxide, which usually led to a racemic mixture.

The actual catalyst is a complex formed from osmium tetroxide and a chiral ligand, e.g. dihydroquinine (DHQ) **9**, dihydroquinidine (DHQD), *bis*-dihydroquinine-phthalazine **10** or the respective dihydroquinidine derivative. The expensive and toxic osmium tetroxide is employed in small amounts only, together with a less expensive co-oxidant, e.g. potassium hexacyanoferrate(III), which is used in stoichiometric quantities. The chiral ligand is also required in small amounts only. For the bench chemist, the procedure for the *a*symmetric *d*ihydroxylation has been simplified with commercially available mixtures of reagents, e.g. AD-mix-α or AD-mix-β,[10] containing the appropriate cinchona alkaloid derivative:



9 **10**

For the dihydroxylation of the achiral enyne **11**, *Corey* and co-workers[11] have used the AD-mix-α, and without isolation of the intermediate diol **12**, obtained the hydroxylactone **13** which is formed through an intramolecular transesterification:



11 **12** **13**

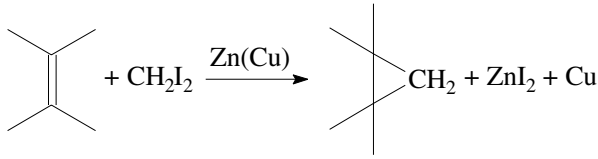
The Sharpless dihydroxylation reaction has great potential for the enantioselective synthesis of natural products. Which of the possible enantiomers/diastereomers is formed, is determined by the actual structure of the chiral catalyst complex formed from osmium tetroxide and the enantiomerically pure dihydroquinine or dihydroquinidine-type ligand. By switching to the respective other alkaloid ligand, the opposite enantiomer/diastereomer can be obtained as the major or even single product. *Trans*-alkenes are better substrates and react with higher enantioselectivity than *cis*-alkenes. The latter alkene geometry is less favourable for the binding site of the chiral catalyst complex. Many types of functional groups are tolerated as substituents at the double bond or in its vicinity, e.g. ketones, esters, amides, carbamates, halogenes, ethers and silyls.[8] The reaction conditions are mild and the yields are generally good.

For his work on chirally catalyzed oxidation reactions, representing a major contribution to the development of catalytic asymmetric synthesis, K. B. Sharpless was awarded the Nobel Prize for chemistry in 2001.[12]

1. T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976.
2. A. Pfenninger, *Synthesis* **1986**, 89–116.
3. K. B. Sharpless, *Chemtech* **1985**, *15*, 692–700.
4. D. Schinzer in *Organic Synthesis Highlights II* (Ed.: H. Waldmann), VCH, Weinheim, Germany, **1995**, p. 3–9.
5. J. G. Hill, B. E. Rossiter, K. B. Sharpless, *J. Org. Chem.* **1983**, *48*, 3607–3608.
6. T. Linher, *Angew. Chem.* **1997**, *109*, 2150–2152; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2060.
7. H. C. Kolb, M. S. VanNieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
8. E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415, *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 388.
9. C. M. G. Philippo, P. Mougenot, A. Braun, G. Defosse, S. Auboussier, P. R. Bovy, *Synthesis* **2000**, 127–134.
10. Aldrich, *Handbook of Fine Chemicals and Laboratory Equipment*, **2003–2004**.
11. X. Han, S. N. Crane, E. J. Corey, *Org. Lett.* **2000**, *2*, 3437–3438.
12. K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 2126–2135; *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 2024.

Simmons–Smith Reaction

Cyclopropanes from alkenes

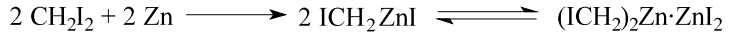


1 **2** **3**

By application of the *Simmons–Smith reaction*[1–4] it is possible to synthesize a cyclopropane from an alkene by formal addition of carbene to the carbon–carbon double bond, without a free carbene being present in the reaction mixture; the

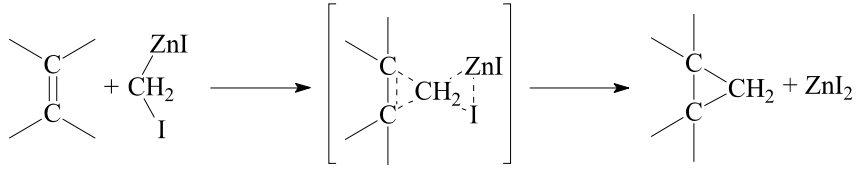
usual side-reactions of free carbenes can thus be avoided. The cyclopropanation is carried out by treating the olefinic substrate **1** with diiodomethane **2** and zinc-copper couple.

By reaction of zinc–copper couple with diiodomethane **2** an organozinc species **4** is formed, similar to a Grignard reagent. Its structure cannot be fully described by a single structural formula. The actual structure depends on the reaction conditions—e.g. the solvent used; this corresponds to the *Schlenk equilibrium* as it is observed with the *Grignard reaction*:



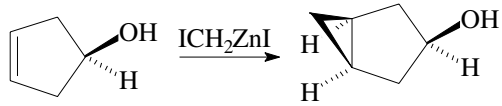
2 **4**

The addition reaction of the methylene to the carbon–carbon double bond is formulated as a one-step mechanism, where both new carbon-carbon bonds are formed simultaneously in a transition state of a structure like **5**:



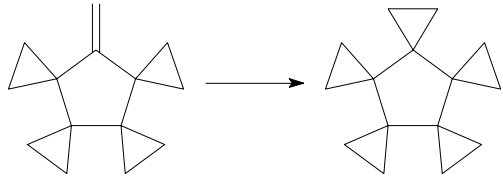
1 **4** **5** **3**

The addition usually takes place from the sterically less hindered side of the alkene. The stereochemical course of the addition can be controlled by suitably positioned oxygen center that can coordinate to the organozinc reagent. For example the reaction with 4-hydroxycyclopentene **6** as substrate exclusively yields the *cis*-3-hydroxybicyclo [3.1.0] hexane **7**:



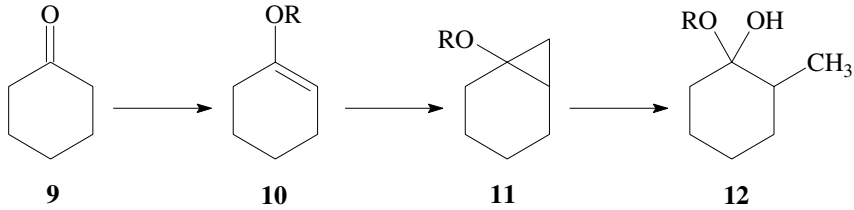
6 **7**

The Simmons–Smith reaction is well suited for the synthesis of spirocyclic compounds. It has for example been applied for the construction of the fifth cyclopropane ring in the last step of a synthesis of the rotane **8**:

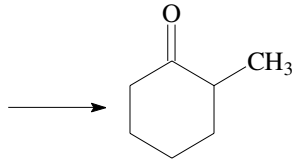


8

The Simmons–Smith cyclopropanation method has also found application for the α-methylation of ketones *via* an intermediate cyclopropane. The starting ketone—e.g. cyclohexanone **9**—is first converted into an enol ether **10**. Cyclopropanation of **10** leads to an alkoxynorcarane **11**, which on regioselective hydrolytic cleavage of the three-membered ring leads to the semiketal **12** as intermediate, and finally yields the α-methylated ketone **13**:



9 **10** **11** **12**



13

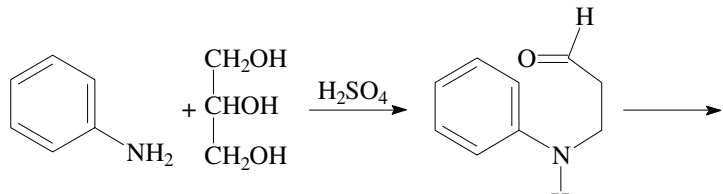
The zinc iodide formed in a Simmons–Smith reaction can act as Lewis acid, and thereby may catalyze rearrangement reactions; however interfering side-reactions are generally rare.

Yields are moderate to good. In addition to alkenes, the cyclopropanation also works with certain aromatic substrates.

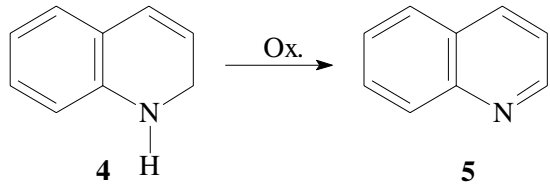
1. H. E. Simmons, R. D. Smith, *J. Am. Chem. Soc*. **1959**, *81*, 4256–4264.
2. H. E. Simmons, T. L. Cairns, S. A. Vladuchick, C. M. Hoiness, *Org. React*. **1973**, *20*, 1–131.
3. J. Furukava, N. Kawabata, *Adv. Organomet. Chem*. **1974**, *12*, 83–134.
4. H. E. Simmons, E. P. Blanchard, R. D. Smith, *J. Am. Chem. Soc*. **1964**, *86*, 1347–1356.
5. J. L. Ripoll, J. M. Conia, *Tetrahedron Lett*. **1969**, 979–984.

Skraup Quinoline Synthesis

Quinolines by reaction of anilines with glycerol



1 **2** **3**

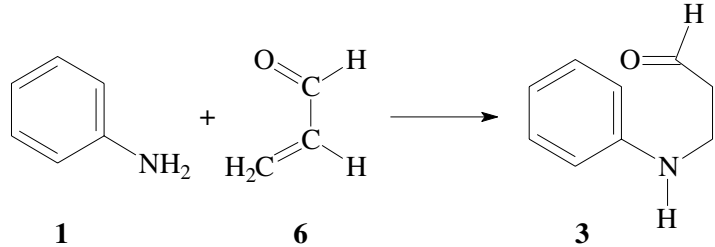


4 **5**

By reaction of a primary aromatic amine—e.g. aniline **1**—with glycerol **2**, and a subsequent oxidation of the intermediate product **4**, quinoline **5** or a quinoline derivative can be obtained.[1,2] As in the case of the related *Friedländer quinoline synthesis*, there are also some variants known for the *Skraup synthesis*, where the quinoline skeleton is constructed in similar ways using different starting materials.[3]

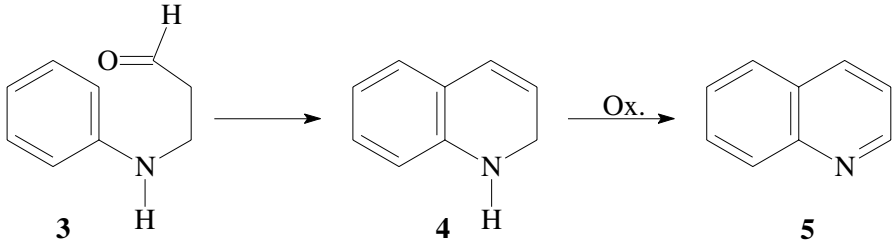
For the Skraup synthesis, glycerol **2** is used as starting material; in the presence of concentrated sulfuric acid (see scheme above) it is dehydrated to acrolein **6**. Although it is assumed that the reactive carbonyl component in the Skraup reaction actually is acrolein, attempts to use acrolein directly, instead of glycerol, proved to be unsuccessful.[4]

The formation of the quinoline is formulated to involve a conjugate addition of the primary aromatic amine to the acrolein **6**, to give a β-arylaminoaldehyde **3** as an intermediate:



1 **6** **3**

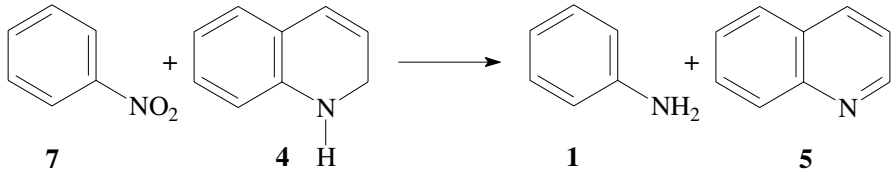
The β-arylaminoaldehyde **3** undergoes a ring-closure reaction with subsequent loss of water to give a dihydroquinoline **4**:



3 **4** **5**

The final product—quinoline **5**—is formed by an oxidation of the dihydroquinoline **4**. As oxidant the aromatic nitro compound **7**, that corresponds to the aromatic

amine **1**, can be employed. The aromatic nitro compound dehydrogenates the dihydroquinoline **4** to quinoline **5**, and in turn is reduced to the primary aromatic amine, which is then available as additional starting amine for reaction with excess glycerol:



7 **4** **1** **5**

Since the corresponding nitro derivative is not always available, other oxidants have also found application—e.g. arsenic pentoxide.

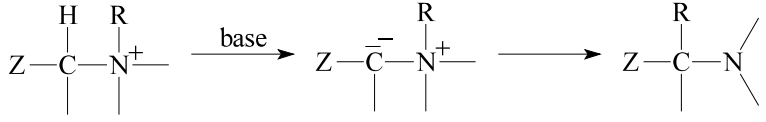
The Skraup reaction is of wide scope for the synthesis of substituted quinolines.[3] Certain primary amines, bearing a cyano, acetyl or methyl group, may however be subject to decomposition under the usual reaction conditions.

Quinolines substituted at the pyridine ring may be obtained by using a substituted α,β-unsaturated aldehyde or ketone instead of the glycerol as starting material. However often a large amount of the carbonyl component polymerizes under the reaction conditions.

1. Z. H. Skraup, *Ber. Dtsch. Chem. Ges*. **1880**, *13*, 2086–2087.
2. G. Jones, *Chem. Heterocycl. Compd* **1977**, *32(1)*, 100–117.
3. R. H. F. Manske, M. Kulka, *Org. React*. **1953**, *7*, 59–98.
4. B. C. Uff in *Comprehensive Heterocyclic Chemistry Vol. 2* (Eds. A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, p. 465–470.

Stevens Rearrangement

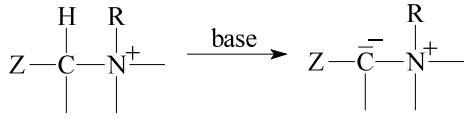
Tertiary amines from quaternary ammonium salts by migration of an alkyl group



1 **2** **3**

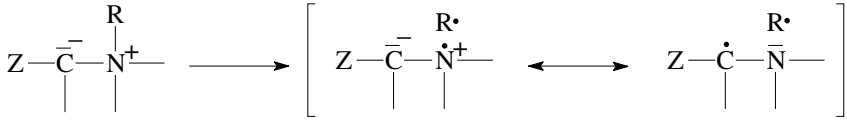
A quaternary ammonium species **1**, bearing an electron-withdrawing group Z α to the nitrogen center, can rearrange to a tertiary amine **3**, when treated with a strong base. This reaction is known as the *Stevens rearrangement*.[1,2]

Mechanistically the rearrangement is formulated to proceed *via* an intermediate radical-pair or ion-pair.[3] In either case the initial step is the formation of a nitrogen-ylide **2** by deprotonation of the ammonium species with a strong base. The abstraction of a proton from the α-carbon is facilitated by an electron-withdrawing group Z—e.g. an ester, keto or phenyl group:

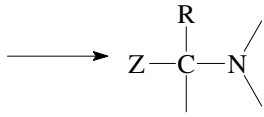


1 **2**

Following the radical pathway[4,5] the next step is a homolytical cleavage of the N−R bond. The rearrangement to yield the tertiary amine **3** then proceeds *via* an intermediate radical-pair **4a**. The order of migration is propargyl > allyl > benzyl > alkyl:[2]



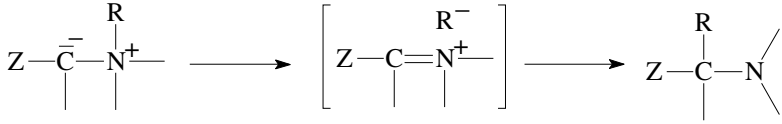
2 **4a**



3

Although the radical-pair is largely held together by the solvent cage, small amounts of the intermolecular coupling product R−R can be isolated sometimes.[5,6]

In certain cases,[7] e.g. with Z = *tert*-butyl, the experimental findings may better be rationalized by an ion-pair mechanism rather than a radical-pair mechanism. A heterolytic cleavage of the N−R bond will lead to the ion-pair **4b**, held together in a solvent cage:



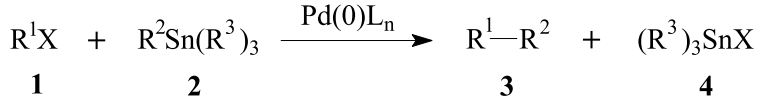
2 **4b** **3**

From a synthetic point of view the Stevens rearrangement is of minor importance. With Z being an ester or acyl group, an alkoxide will suffice as base. Usually a stronger base, such as sodium amide or an organolithium compound, is employed. In the latter case the use of a two-phase system may be necessary, since the quaternary ammonium salt may not be soluble in the solvent used for the organolithium reagent. The ammonium salts are for example soluble in liquid ammonia, dimethyl sulfoxide or hexamethylphosphoric triamide; however the use of those solvents may also give rise to side-reactions.

1. T. S. Stevens, E. M. Creighton, A. B. Gordon, M. Mac Nicol, *J. Chem. Soc.* **1928**, 3193–3197.
2. S. H. Pine, *Org. React.* **1970**, *18*, 403–464.
3. S. H. Pine, *J. Chem. Educ.* **1971**, *48*, 99–102.
4. U. Schöllkopf, U. Ludwig, *Chem. Ber.* **1968**, *101*, 2224–2230.
5. U. Schöllkopf, U. Ludwig, G. Ostermann, M. Patsch, *Tetrahedron Lett.* **1969**, 3415–3418.
6. G. F. Hennion, M. J. Shoemaker, *J. Am. Chem. Soc.* **1970**, *92*, 1769–1770.
7. S. H. Pine, B. A. Catto, F. G. Yamagishi, *J. Org. Chem.* **1970**, *35*, 3663.

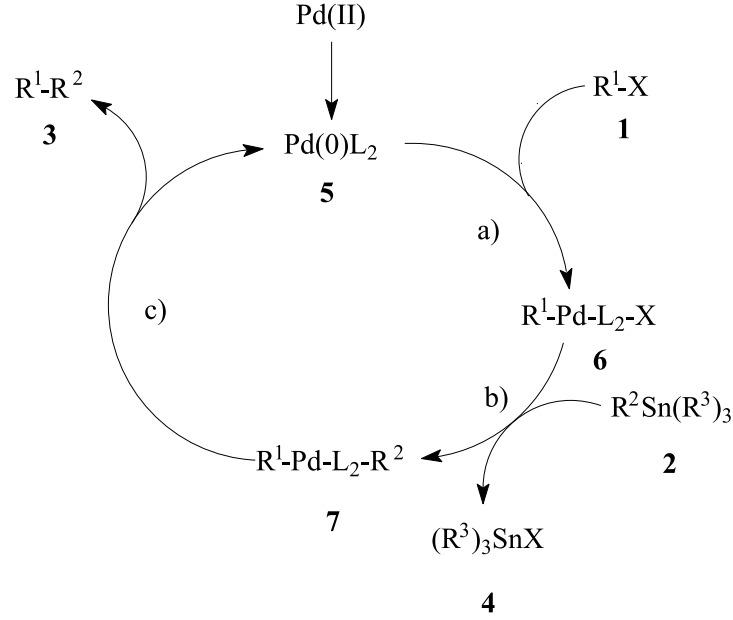
Stille Coupling Reaction

Coupling reaction of organotin compounds with carbon electrophiles



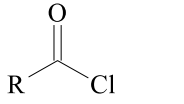
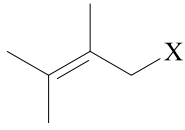
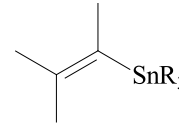
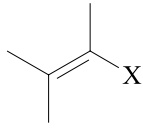
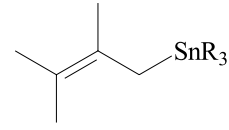
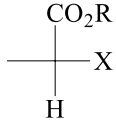
Together with reactions named after → *Heck* and → *Suzuki*, the *Stille reaction*[1–3] belongs to a class of modern, palladium-catalyzed carbon–carbon bond forming reactions. The palladium-catalyzed reaction of an organotin compound **2** with a carbon electrophile **1** is called *Stille coupling*.

As in case of other palladium-catalyzed reactions, the general mechanism of the Stille reaction is best described by a catalytic cycle—e.g. steps a) to c):



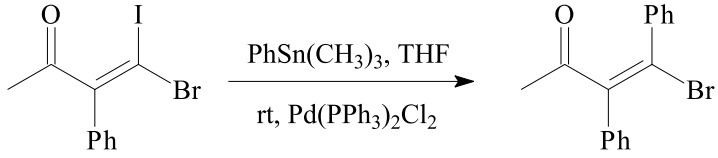
a) *Oxidative addition*—Reaction of the carbon electrophile with palladium-(0) complex **5** to give a palladium-(II) complex **6**.
b) *Transmetallation*—Transfer of substituent R^2 from tin to the palladium center thus generating a palladium species **7** that contains both the fragments R^1 and R^2 that are to be coupled.
c) *Reductive elimination*—to yield the coupling product **3** and regeneration of the catalytically active palladium-(0) complex **5**.

The palladium component may be added to the reaction mixture as Pd(0)- as well as Pd(II)- compound; in the latter case the Pd(II)- first has to be reduced to Pd(0)- by excess stannane. Since the first publication on this coupling method by Stille[1] in 1978, this reaction has gained increased importance in synthetic organic chemistry.[2–4] This is due to the fact that many different types of substrates can be used in this reaction. The following table lists possible carbon electrophiles and stannanes that can be coupled in any combination.

electrophile R^1X		organotin reagent $R^2Sn(R^3)_3$
		$H—SnR_3$
		$R'C{\equiv}C—SnR_3$
	(X = Cl, Br)	
	(X = I, OTf)	$Aryl—SnR_3$
$Aryl—CH_2—X$	(X = Cl, Br)	
Aryl—X	(X = Br, I)	
		$Aryl—CH_2—SnR_3$
	(X = Br, I)	$R'—SnR_3$

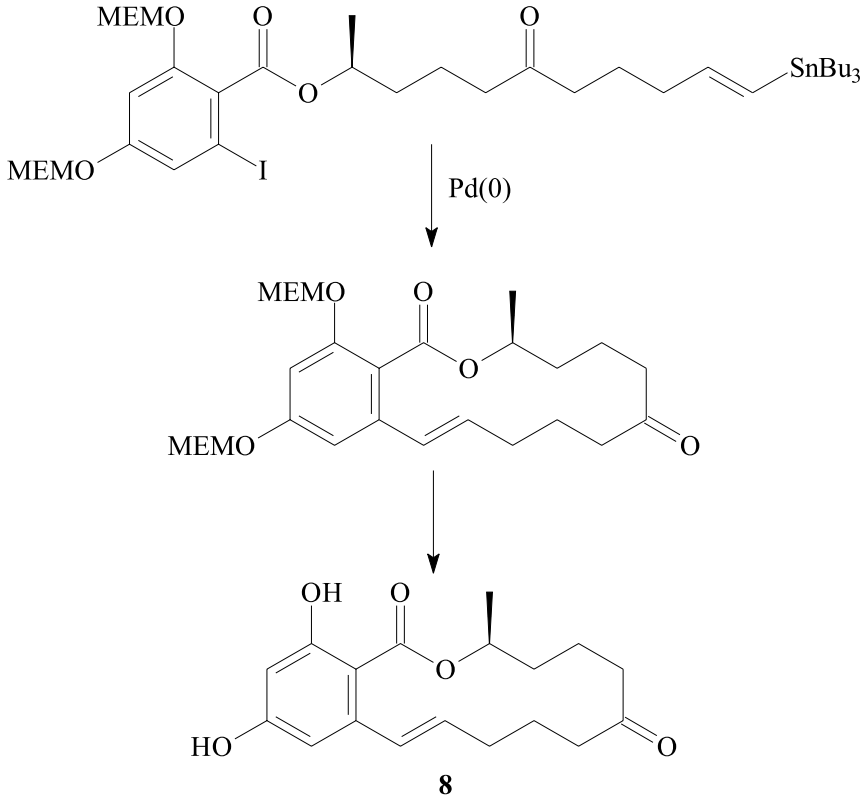
The transfer of simple alkyl groups (R^3 in the table—mostly *n*-Bu or Me), from tin to palladium complex **6** is a very slow process, and the substituent R^2 (see table) is transferred selectively. The leaving group X on the coupling component

can be halide or sulfonate—in many cases triflate is used. Iodide is a better leaving group than bromide; this can be used for a regioselective coupling reaction:



In the coupling with vinyl groups, the olefin geometry is usually retained; E/Z-isomerization is only rarely observed.

An intramolecular variant of the Stille coupling is suitable for the construction of macrocycles. An example is the ring-closing step to form a 14-membered lactone ring **8** in a synthesis of *zearalenone* as reported by Stille *et al.*[5]:



8

From the intramolecular coupling product, just the two MEM-groups protecting the phenol functions (MEM = 2-methoxyethoxymethyl) have to be removed, in order to obtain the target molecule.

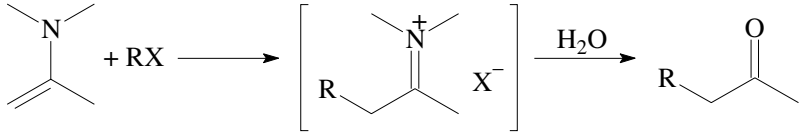
The organotin compounds required for the Stille reaction are easy to prepare for a wide range of substituents, and are easy to handle.[3] Many functional groups

are tolerated in the coupling step, which makes the Stille reaction suitable for the synthesis of complex target molecules.

1. D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638.
2. V. Farina, V. Krishnamurthy, W. J. Scott, *Org. React.* **1997**, *50*, pp. 1–652.
3. J. K. Stille, *Angew. Chem.* **1986**, *98*, 504–519; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 508; L. A. Agrofoglio, I. Gillaizeau, Y. Saito, *Chem. Rev.* **2003**, *103*, 1875–1916.
4. J. E. Baldwin, R. M. Adlington, S. H. Ramcharitar, *Tetrahedron* **1992**, *48*, 2957–2976.
5. A. Kalivretenos, J. K. Stille, L. S. Hegedus, *J. Org. Chem.* **1991**, *56*, 2883–2894.

Stork Enamine Reaction

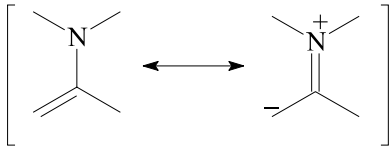
Alkylation and acylation of enamines



1 **2** **3**

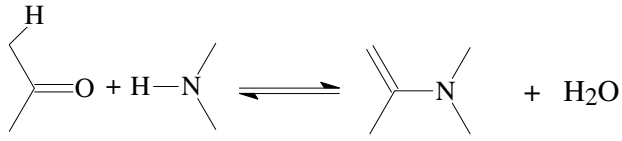
Enamines **1** are useful intermediates in organic synthesis. Their use for the synthesis of α-substituted aldehydes or ketones **3** by reaction with an electrophilic reactant—e.g. an alkyl halide **2**, an acyl halide or an acceptor-substituted alkene—is named after *Gilbert Stork*.[1–3]

The typical reactivity of an enamine **1** results from the nucleophilic character of the β-carbon center, as indicated by a resonance structure:



1

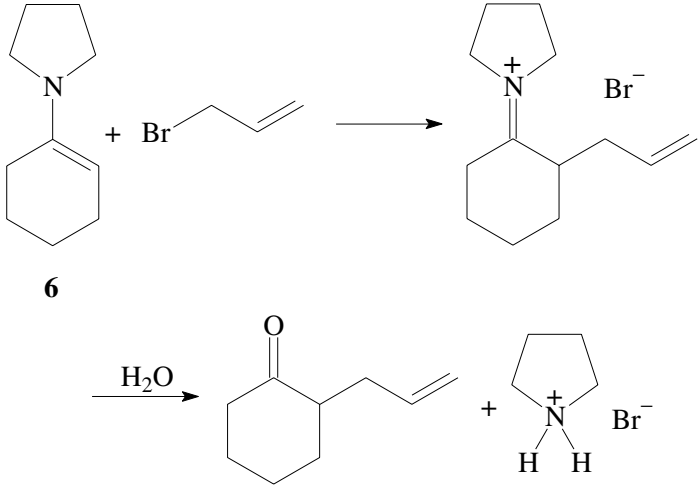
An enamine is easily prepared by reaction of the corresponding aldehyde or ketone **4** and a secondary amine **5**. A cyclic secondary amine like pyrrolidine, piperidine or morpholine is most often used. A general procedure has been reported by *Mannich* and *Davidsen*[4] in 1936:



4 **5** **1**

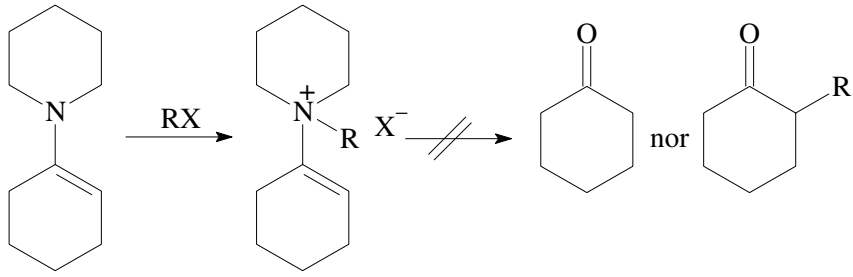
In order to shift the equilibrium, the water formed in that reaction is usually removed by azeotropic distillation with benzene or toluene.

In general the *Stork reaction* gives moderate yields with simple alkyl halides; better yields of alkylated product are obtained with more electrophilic reactants such like allylic, benzylic or propargylic halides or an α-halo ether, α-halo ester or α-halo ketone. An example is the reaction of 1-pyrrolidino-1-cyclohexene **6** with allyl bromide, followed by aqueous acidic workup, to yield 2-allylcyclohexanone:



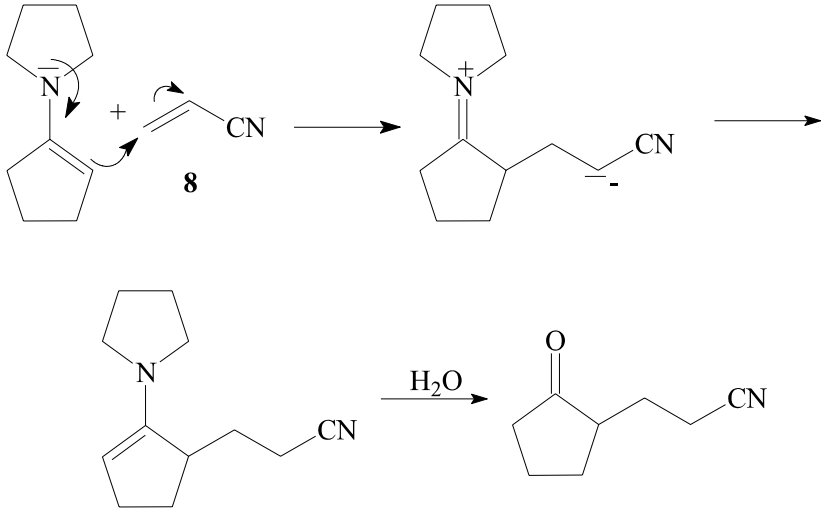
6

Generally the desired substituted carbonyl compound **3** is obtained after hydrolytic workup under acidic conditions. With simple alkyl halides an irreversible *N*-alkylation may take place as a side-reaction to give a quaternary ammonium salt **7**:

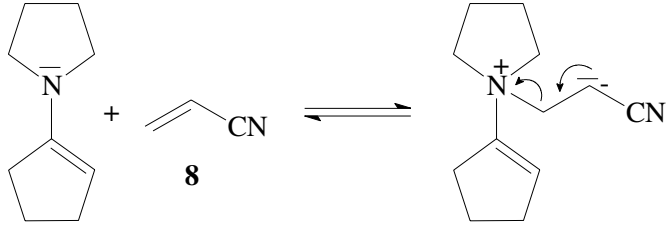


7

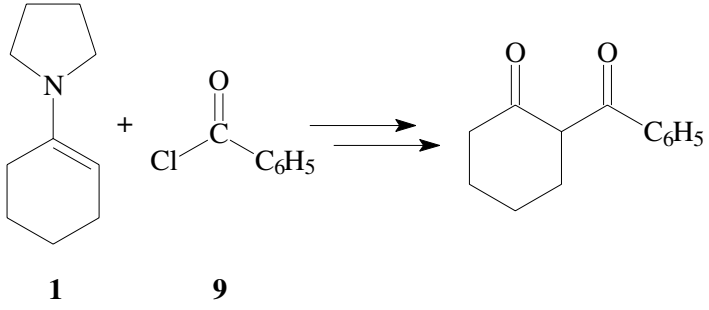
Enamines react with acceptor-substituted alkenes (Michael acceptors) in a conjugate addition reaction; for example with α,β-unsaturated carbonyl compounds or nitriles such as acrylonitrile **8**. With respect to the acceptor-substituted alkene the reaction is similar to a *Michael addition*:



This type of reaction usually gives good yields; here the possible *N*-alkylation is reversible—through a *retro-Michael-type reaction*:



Another important application is the acylation of enamines **1** with an acyl chloride **9** to give a 1,3-dicarbonyl compound as final product:



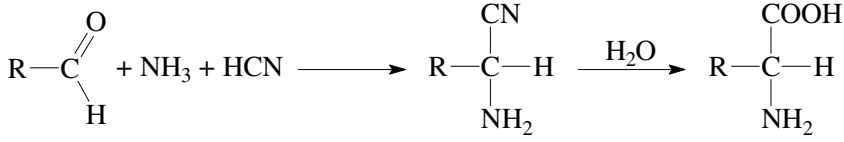
The Stork enamine reaction is an important and versatile method for the synthesis of α-substituted aldehydes and ketones. Such products should in principle also be

available by reaction of the aldehyde or ketone with the electrophilic reactant in the presence of a base that is strong enough to convert the carbonyl substrate to the corresponding enolate. However this direct method often leads to formation of undesired products from various side-reactions. For example polysubstituted products are often obtained, as well as products from self-condensation of the starting aldehyde or ketone (see *Aldol reaction*). The latter is especially the case with cyclopentanone. Furthermore Michael-acceptor substrates often polymerize in the presence of base. In general the regiochemical outcome of the alkylation reaction is easier to control by using the enamine method.

1. G. Stork, R. Terrell, J. Szmuszkovicz, *J. Am. Chem. Soc*. **1954**, *76*, 2029–2030.
2. G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, R. Trebell, *J. Am. Chem. Soc*. **1963**, *85*, 207–222.
3. J. K. Whitesell, M. A. Whitesell, *Synthesis* **1983**, 510–536.
4. C. Mannich, H. Davidsen, *Ber. Dtsch. Chem. Ges*. **1936**, *69*, 2106–2112.

Strecker Synthesis

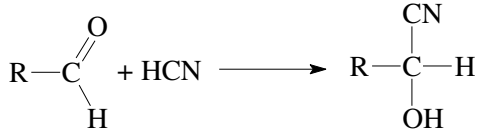
α-Amino acids from aldehydes or ketones



1 **2** **3**

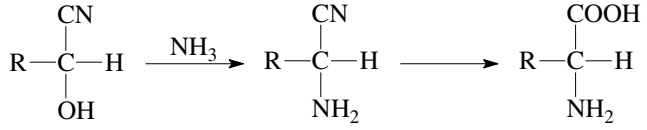
An α-amino acid **3** can be prepared by treating aldehyde **1** with ammonia and hydrogen cyanide and a subsequent hydrolysis of the intermediate α-amino nitrile **2**. This so-called *Strecker synthesis*[1,2] is a special case of the *Mannich reaction*; it has found application for the synthesis of α-amino acids on an industrial scale. The reaction also works with ketones to yield α,α-disubstituted α-amino acids.

The formation of α-amino nitrile **2** is likely to proceed *via* a cyanohydrin **4** (an α-hydroxy nitrile) as intermediate, which is formed by the addition of hydrogen cyanide to the aldehyde **1**:



1 **4**

Reaction of cyanohydrin **4** with ammonia leads to formation of α-amino nitrile **2**, which can easily be hydrolyzed to give the corresponding α-amino acid **3**:

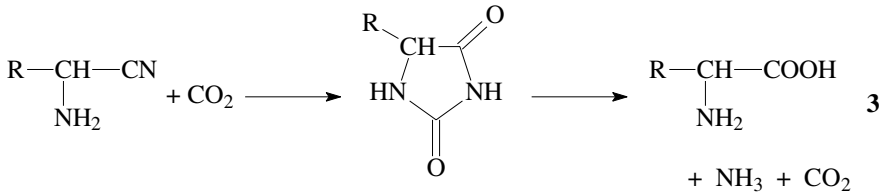


4 **2** **3**

Alternatively a Mannich-like pathway may be followed (see *Mannich reaction*), where ammonia reacts with the aldehyde **1** to give an intermediate iminium species, that adds hydrogen cyanide to give the α-amino nitrile **2**. The actual mechanistic pathway followed depends on substrate structure and reaction conditions.

The scope of the reaction depends on the availability of the starting aldehyde (or ketone). A drawback is the toxicity of the hydrogen cyanide used as reactant.[2]

A variant of the Strecker synthesis is the *Bucherer–Bergs reaction*;[2] it gives better yields, and proceeds *via* formation of an intermediate hydantoin **5**:



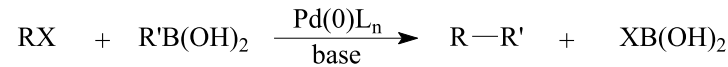
2 **5** **3**

The importance of chemical syntheses of α-amino acids on industrial scale is limited by the fact that the standard procedure always yields the racemic mixture (except for the achiral glycine H_2N-CH_2-COOH and the corresponding amino acid from symmetrical ketones R−CO−R). A subsequent separation of the enantiomers then is a major cost factor. Various methods for the asymmetric synthesis of α-amino acids on laboratory scale have been developed, and among these are asymmetric Strecker syntheses as well.[3]

1. A. Strecker, *Justus Liebigs Ann. Chem.* **1850**, *75*, 27–45.
2. Th. Wieland, R. Müller, E. Niemann, L. Birkhofer, A. Schöberl, A. Wagner, H. Söll, *Methoden Org. Chem. (Houben-Weyl)*, **1959**, Vol. XI/2, p. 305–306.
3. H.-J-Altenbach In: J. Mulzer, H.-J. Altenbach, M. Braun, K. Krohn, H.-U. Reissig, *Organic Synthesis Highlights*, VCH, Weinheim, **1991**, p. 300–305.

Suzuki Reaction

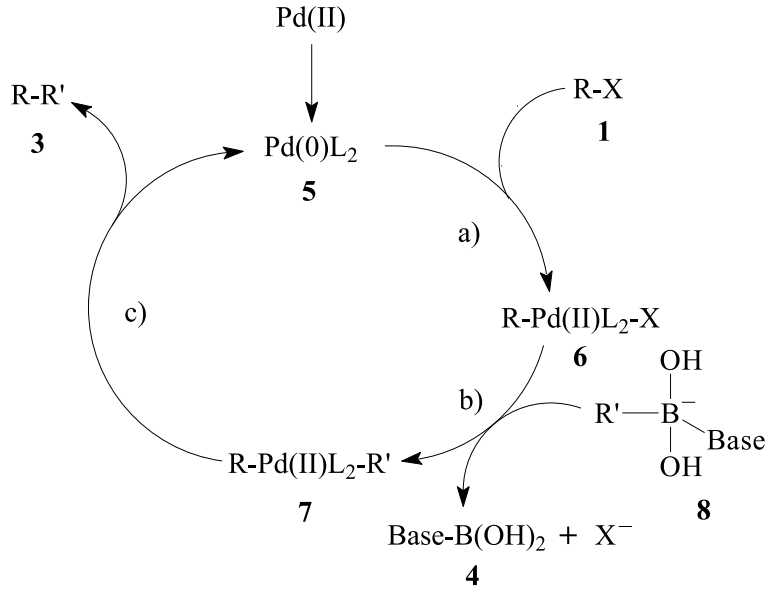
Palladium-catalyzed cross-coupling with organoboron compounds



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

Palladium-catalyzed carbon–carbon bond forming reactions like the *Suzuki reaction*[1–6] as well as the → *Heck reaction* and the → *Stille reaction*, have in recent years gained increased importance in synthetic organic chemistry. In case of the Suzuki reaction, an organoboron compound—usually a boronic acid—is reacted with an aryl (or alkenyl, or alkynyl) halide in the presence of a palladium catalyst.

The mechanism[2–7] of the Suzuki reaction is closely related to that of the Stille coupling reaction, and is also best described by a catalytic cycle:



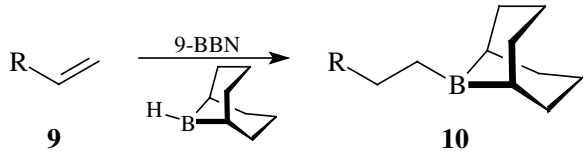
a) *Oxidative addition*—Reaction of the halide component with a palladium-(0) complex **5** to give a palladium-(II) species **6**.
b) *Transmetallation*—Transfer of substituent R′ from boron to the palladium center, thus generating a palladium-(II) species that contains both the substituent R and R′ that are to be coupled.
c) *Reductive elimination*—to yield the coupling product **3** and the regenerated catalytically active palladium-(0) complex **5**.

The boronic acid **2** is first converted to an activated species **8** containing a tetravalent boron center by reaction with a base. Halides or triflates (OTf = trifluoromethanesulfonate) are used as coupling partners R−X for the boronic acids. In many cases the rate-limiting step is the oxidative addition. With respect to the leaving group X, the rate decreases in the order:

$$\mathrm{I} > \mathrm{OTf} > \mathrm{Br} \gg \mathrm{Cl}$$

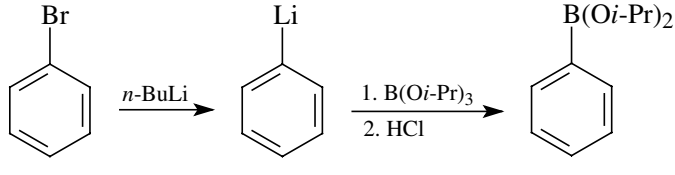
An alkyl- or alkenylboron compound, as a suitable organoboron component (a borane, boronic acid or ester) can be prepared through hydroboration of an

appropriate alkene or alkyne with a reagent such as 9-borabicyclo[3.3.1]nonane (9-BBN), e.g. the alkylborane derivative **10** from alkene **9**:[4]



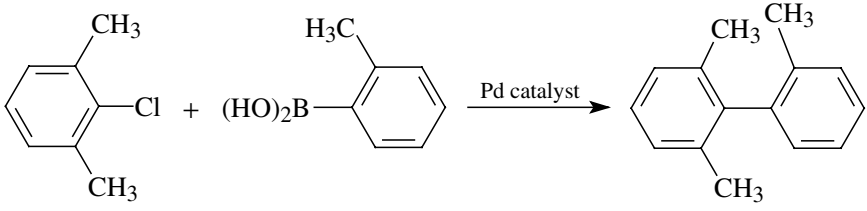
9 **10**

For the synthesis of a suitable arylboron compound, usually an aryl halide is converted to an aryllithium or aryl Grignard derivative, and then reacted with a trialkoxyborane to yield an arylboronic ester, e.g. the phenylboronic acid diisopropyl ester **13** from bromobenzene **11**:[5]



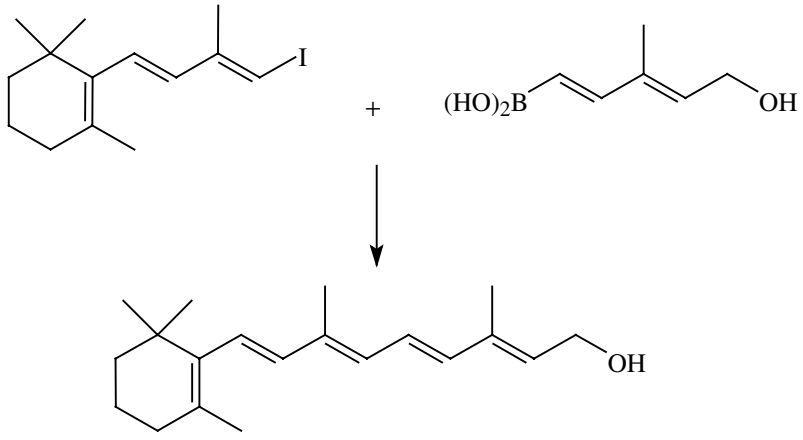
11 **12** **13**

Of particular synthetic importance is the coupling of aryl- and hetarylboronic acids to aryl- and hetaryl halides (or triflates), allowing for a convenient synthesis of biphenyls, even sterically demanding derivatives such as **14**, hetaryl phenyls and *bis*-hetaryls.[8] With appropriately disubstituted aromatic substrates, the Suzuki coupling reaction can be applied in the synthesis of polyphenylene materials.



14

The coupling of alkenylboronic acids with alkenyl halides is a good method for the *E*/*Z*-selective synthesis of conjugated dienes. An example is the Suzuki coupling step from a synthesis of retinol (vitamin A) **15**; this coupling occurs with retention of configuration at the sp^2-carbon centers, so leading to the *E*,*E*-configurated product only:[9]



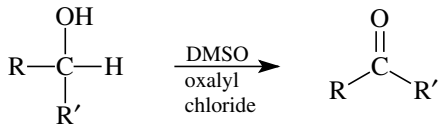
15

Many types of functional groups are tolerated in a Suzuki reaction, and the yields are often good to very good. The presence of a base, e.g. sodium hydroxide or sodium/potassium carbonate, is essential for this reaction. The base is likely to be involved in more than one step of the catalytic cycle, at least in the transmetallation step. Proper choice of the base is important in order to obtain good results.[4] In contrast to the Heck reaction and the Stille reaction, the Suzuki reaction does not work under neutral conditions.

1. A. Suzuki, N. Miyaura, *J. Chem. Soc., Chem. Commun*. **1979**, 866–867.
2. A. Suzuki, N. Miyaura, *Chem. Rev.* **1995**, *95*, 2457–2483.
3. L. A. Agrofoglio, I. Gillaizeau, Y. Saito, *Chem. Rev.* **2003**, *103*, 1875–1916.
4. S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676–4701; *Angew. Chem. Int. Ed. Engl.* **2001**, 40, 4544.
5. V. Wittmann, *Nachrichten Chem*. **2002**, *50*, 1122–1127.
6. A. R. Martin, Y. Yang, *Acta Chem. Scand.* **1993**, *47*, 221–230.
7. A. O. Aliprantis, J. W. Canary, *J. Am. Chem. Soc*. **1994**, *116*, 6985–6986.
8. H. Gröger, *J. Prakt. Chem.* **2000**, *342*, 334–339.
9. A. Torrado, B. Iglesias, S. López, A. R. de Lera, *Tetrahedron* **1995**, *51*, 2435–2454.

Swern Oxidation

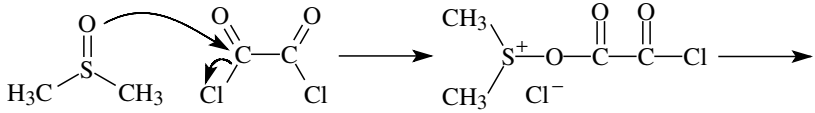
Oxidation of alcohols by activated dimethyl sulfoxide



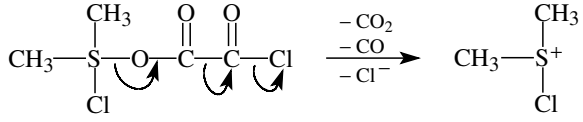
1 **2**

The *Swern oxidation* is a preparatively important reaction which allows for the oxidation of primary and secondary alcohols **1** to aldehydes and ketones **2**, respectively, under mild conditions, using activated dimethyl sulfoxide (DMSO) as the oxidizing agent.[1–3]

In order to enable the dimethyl sulfoxide **3** to oxidize the alcohol substrate effectively, it has to be converted into an reactive agent. This is carried out by treatment with oxalyl chloride **4**, hence leading to sulfonium ions **5** or **6** as the active species:

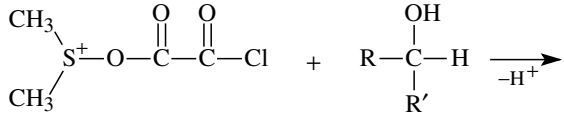


3 **4** **5**

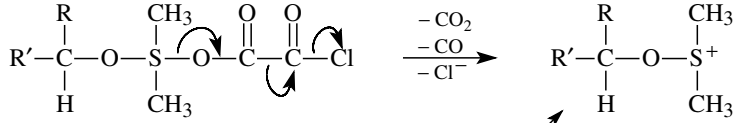


6

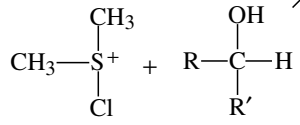
The ionic species **5**, as well as **6**, represent the so-called 'activated' dimethyl sulfoxide. Variants using reagents other than oxalyl chloride for the activation of DMSO are known.[3] In the reaction with an alcohol **1**, species **5**, as well as **6**, leads to the formation of a sulfonium salt **7**:



5 **1**

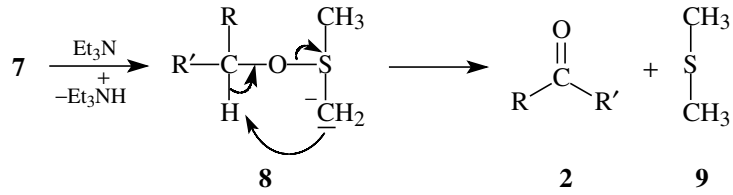


7



6 **1**

Upon addition of a base—triethylamine is often used—the sulfonium salt **7** is deprotonated to give a sulfonium ylide **8**. The latter decomposes into the carbonyl compound **2** and dimethyl sulfide **9** through β-elimination *via* a cyclic transition state.



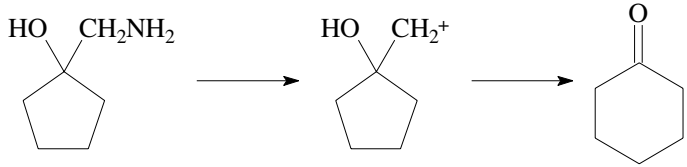
Further oxidation of an aldehyde product to the corresponding carboxylic acid does not take place. Moreover, the *Swern oxidation* reaction does not require the use of toxic and pollutant chromium reagents. The activated DMSO species, however, are stable only at low temperature, which might in some cases be a drawback of this method.

1 K. Omura, D. Swern, *Tetrahedron* **1978**, *34*, 1651–1659.
2 A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165–185.
3 T. T. Tidwell, *Org. React.* **1990**, *39*, 297–572.

T

Tiffeneau–Demjanov Reaction

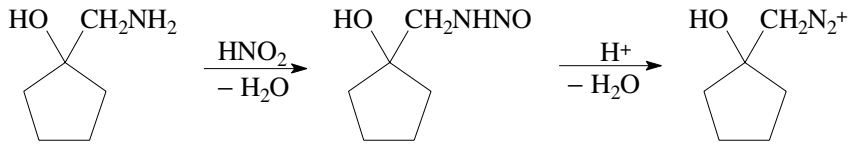
Ring enlargement of cyclic β-amino alcohols



1 **2** **3**

When a cyclic β-amino alcohol—e.g. **1**—is treated with nitrous acid, a deamination reaction can take place, to give a carbenium ion species **2**, which in turn can undergo a rearrangement and subsequent loss of a proton to yield a ring-enlarged cyclic ketone **3**. This reaction is called the *Tiffeneau–Demjanov reaction*;[1–3] it is of wider scope than the original *Demjanov reaction*.[2]

The reaction of nitrous acid with the amino group of the β-amino alcohol—e.g. 1-aminomethyl-cyclopentanol **1**—leads to formation of the nitrosamine **4**, from which, through protonation and subsequent loss of water, a diazonium ion species **5** is formed[2,4]—similar to a *diazotization reaction*:



1 **4** **5**

With diazonium species like **5**, dinitrogen (N_2) functions as a good leaving group. Loss of N_2 from **5** generates a carbenium ion species **2**, which rearranges by a

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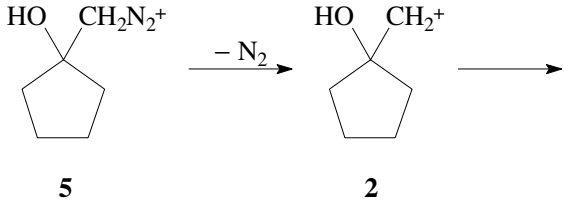
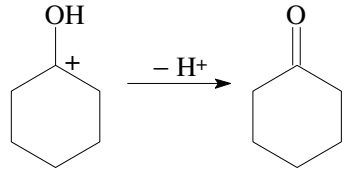
1,2-migration of a ring-CH_2 group to give the more stable hydroxy-substituted carbenium ion **6**. Loss of a proton from **6** yields a ring-enlarged ketone—e.g. cyclohexanone **3**—as the final product:

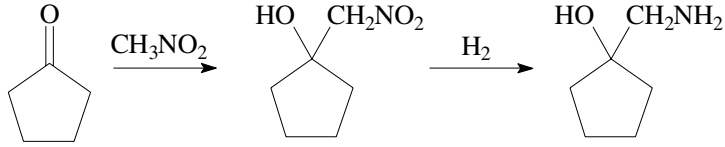


5 **2**



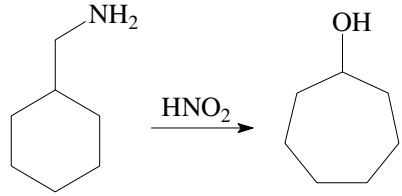
6 **3**

The starting material for the Tiffeneau–Demjanov reaction is available by various methods.[3] A common route is the addition of nitromethane to a cyclic ketone—e.g. cyclopentanone **7**—followed by a hydrogenation of the nitro group to give the β-amino alcohol, e.g. **1**:



7 **1**

The original *Demjanov reaction* is the conversion of an aminomethyl-cycloalkane into a cycloalkanol consisting of a carbocyclic ring that is expanded by one carbon center; e.g. the reaction of aminomethylcyclohexane **8** with nitrous acid leads to formation of cycloheptanol **9**:



8 **9**

Various side-reactions may be observed with the Demjanov reaction; the Tiffeneau–Demjanov reaction usually gives better yields of the ring-enlarged product.

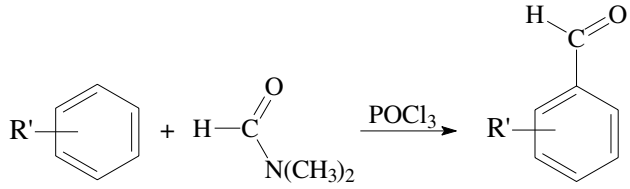
The Tiffeneau–Demjanov reaction has found application for the construction of four- to nine-membered rings by a ring-enlargement route.[2,5] The presence of a heteroatom such as nitrogen or sulfur within the ring usually does not interfere with the reaction.[2] If the carbon center α to the amino group bears an additional substituent, yields may be low. A ring-enlargement may then even not take place at all, since the carbenium ion species is stabilized by that additional substituent. With starting materials bearing a substituent on the ring, mixtures of isomeric rearrangement products may be obtained; the synthetic importance is rather limited in those cases.

1. M. Tiffeneau, P. Weill, B. Tchoubar, *C. R. Acad. Sci*. **1937**, *205*, 144–146.
2. P. A. S. Smith, D. R. Baer, *Org. React*. **1960**, *11*, 157–188.
3. M. Hesse, *Ring Enlargement in Organic Chemistry*, VCH, Weinheim, **1991**, p. 9–10.
4. H. Stach, M. Hesse, *Tetrahedron* **1988**, *44*, 1573–1590.
5. H. N. C. Wong, M.-Y. Hon, C.-W. Tse, Y.-C. Yip, *Chem. Rev*. **1989**, *89*, 165–198.
6. M. A. McKinney, P. P. Patel, *J. Org. Chem*. **1973**, *38*, 4059–4067.

V

Vilsmeier Reaction

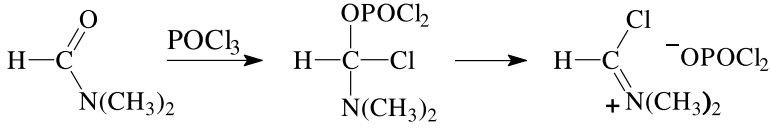
Formylation of aromatic compounds and of alkenes



1 **2** **3**

The reaction of electron-rich aromatic compounds with *N*,*N*-dimethylformamide **2** and phosphorus oxychloride to yield an aromatic aldehyde—e.g. **3** from the substituted benzene **1**—is called the *Vilsmeier reaction*[1–3] or sometimes the *Vilsmeier–Haack reaction*. It belongs to a class of formylation reactions that are each of limited scope (see also *Gattermann reaction*).

In an initial step the reactive formylating agent is formed from *N*,*N*-dimethylformamide (DMF) **2** and phosphorus oxychloride. Other *N*,*N*-disubstituted formamides have also found application; for example *N*-methyl-*N*-phenylformamide is often used. The formylating agent is likely to be a chloromethyl iminium salt **4**—also called the *Vilsmeier complex*[4] (however its actual structure is not rigorously known)—that acts as the electrophile in an electrophilic substitution reaction with the aromatic substrate[5] **1** (see also *Friedel–Crafts acylation reaction*):



2 **4**

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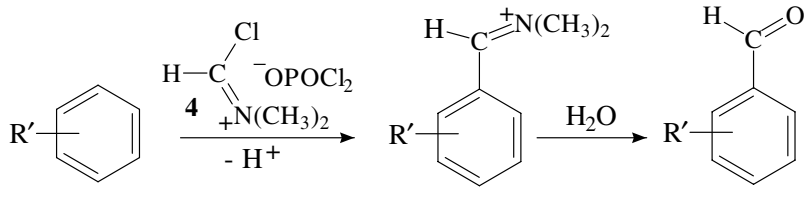
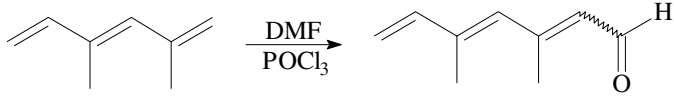


1 **5** **3**

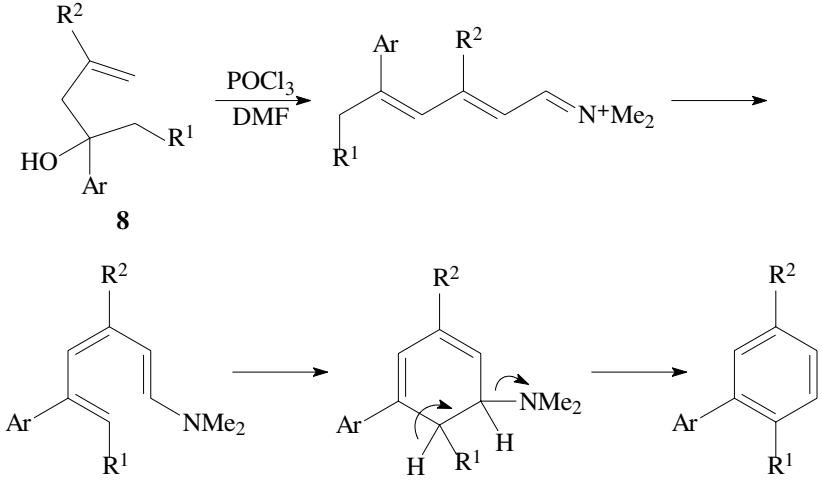
The initial product **5** of the electrophilic aromatic substitution step is unstable and easily hydrolyzes to yield the aromatic aldehyde **3** as the final reaction product. With *mono*-substituted aromatic substrates the *para*-substituted aldehyde is formed preferentially.

With respect to aromatic substrates, the Vilsmeier formylation reaction works well with electron-rich derivatives like phenols, aromatic amines and aromatic heterocycles like furans, pyrroles and indoles. However various alkenes are also formylated under Vilsmeier conditions.[9] For example the substituted hexatriene **6** is converted to the terminal hexatrienyl aldehyde **7** in 70% yield:[6]



6 **7**

An elegant application of the Vilsmeier reaction is the synthesis of substituted biphenyls as reported by *Rao* and *Rao*.[7] Starting with homoallylic alcohol **8**, the biphenyl derivative **9** was obtained from a one-pot reaction in 80% yield:



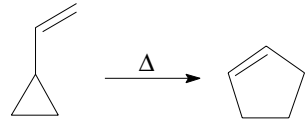
8 **9**

Although limited to electron-rich aromatic compounds and alkenes, the Vilsmeier reaction is an important formylation method. When *N*,*N*-dimethylformamide is used in excess, the use of an additional solvent is not necessary. In other cases toluene, dichlorobenzene or a chlorinated aliphatic hydrocarbon is used as solvent.[8]

1. A. Vilsmeier, A. Haack, *Ber. Dtsch. Chem. Ges*. **1927**, *60*, 119–122.
2. C. Jutz, *Adv. Org. Chem*. **1976**, *9*, *Vol. 1*, 225–342.
3. S. S. Pizey, *Synthetic Reagents* **1974**, *Vol. 1*, p. 54–71.
4. J. C. Tebby, S. E. Willetts, *Phosphorus Sulfur* **1987**, *30*, 293–296.
5. G. Jugie, J. A. S. Smith, G. J. Martin, *J. Chem. Soc., Perkin Trans. 2*, **1975**, 925–927.
6. P. C. Traas, H. J. Takken, H. Boelens, *Tetrahedron Lett*. **1977**, 2129–2132.
7. M. S. C. Rao, G. S. K. Rao, *Synthesis* **1987**, 231–233.
8. G. Simchen, *Methoden Org. Chem. (Houben-Weyl)*, **1983**, *Vol. E3*, p. 36–85.
9. C. Reichardt, *J. Prakt. Chem.* **1999**, *341*, 609–615.

Vinylcyclopropane Rearrangement

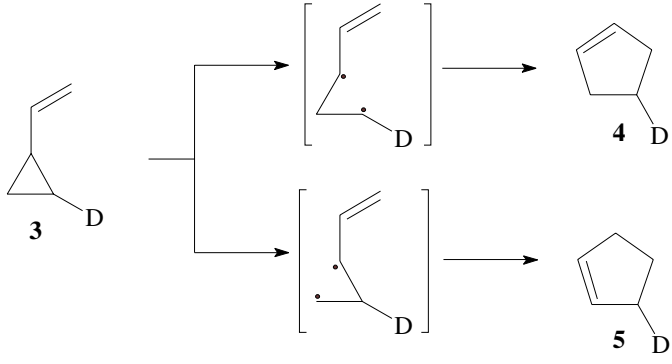
Cyclopentenes by rearrangement of vinylcyclopropanes



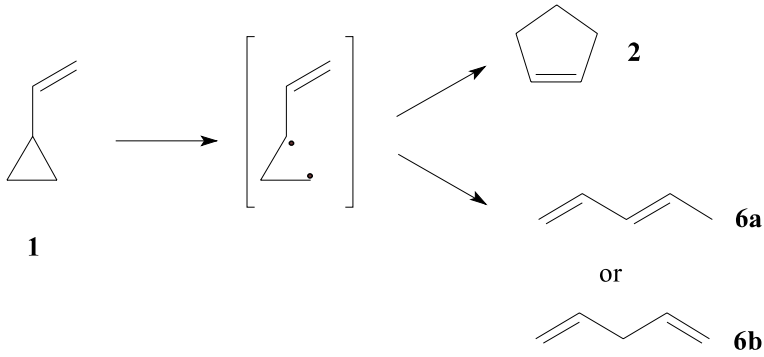
The thermal rearrangement of vinylcyclopropanes **1** to yield cyclopentenes **2** is called the *vinylcyclopropane rearrangement*.[1–3]

For the mechanistic course of that reaction two pathways are discussed:[2,4] a concerted [1,3]-sigmatropic rearrangement, and a pathway *via* an intermediate diradical species.[5] Experimental findings suggest that both pathways are possible. The actual pathway followed strongly depends on substrate structure; the diradical pathway appears to be the more important.

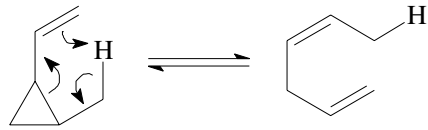
The direction of ring opening by homolytic cleavage of a cyclopropane bond is controlled by the stability of the diradical species formed. Upon heating of the mono-deuterated vinylcyclopropane **3**, a mixture of the two isomeric mono-deuterated cyclopentenes **4** and **5** is formed:



In addition to cyclopentenes, other types of compounds may be formed upon heating of vinylcyclopropanes. For example pentadienes **6a/b** may be formed by a competitive route from a diradical intermediate.

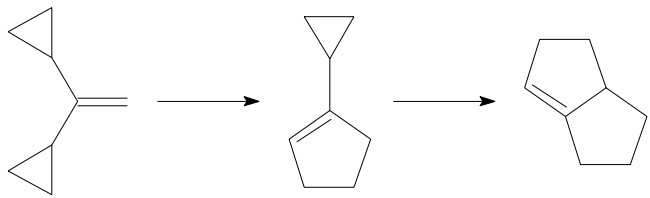


With a substitution pattern as found in 1-vinyl-2-methylcyclopropane **7**, a retro-ene reaction (see *Ene reaction*) may take place to yield hexa-1,4-diene **8**:



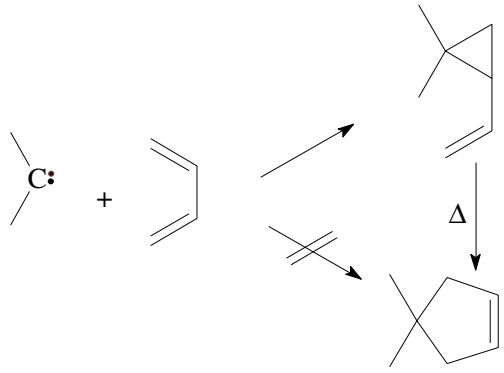
7 **8**

An illustrative example for the generation of cyclopentenes from vinylcyclopropanes is the formation of bicyclo[3.3.0]oct-1-ene **10** from 1,1-dicyclopropylethene **9** by two consecutive vinylcyclopropane → cyclopentene rearrangements.[6]



9 **10**

The vinylcyclopropane rearrangement is an important method for the construction of cyclopentenes. The direct 1,4-addition of a carbene to a 1,3-diene to give a cyclopentene works only in a few special cases and with poor yield.[7] The desired product may instead be obtained by a sequence involving the 1,2-addition of a carbene to one carbon–carbon double bond of a 1,3-diene to give a vinylcyclopropane, and a subsequent rearrangement to yield a cyclopentene:



Apart from the carbene-1,2-addition route starting from 1,3-dienes, vinylcyclopropanes may be obtained from 1,4-dienes through a *di-π-methane rearrangement*.

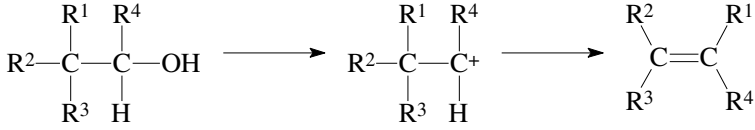
The vinylcyclopropane rearrangement is of synthetic importance, as well as of mechanistic interest—i.e. the concerted vs. the radical mechanism. A reaction temperature of 200 to 400 °C is usually required for the rearrangement; however, depending on substrate structure, the required reaction temperature may range from 50 to 600 °C. Photochemical[8] and transition metal catalyzed[2] variants are known that do not require high temperatures.

1. N. P. Neureiter, *J. Org. Chem*. **1959**, *24*, 2044–2046.
2. T. Hudlicky, T. M. Kutchan, S. Naqvi, *Org. React*. **1985**, *33*, 247–335.
3. H. M. Frey, *R. Walsh, Chem. Rev*. **1969**, *69*, 103–124.
4. E. M. Mil′vitskaya, A. V. Tarakanova, A. F. Plate, *Russ. Chem. Rev*. **1976**, *45*, 469–478.
5. G. McGaffin, A. de Meijere, R. Walsh, *Chem. Ber*. **1991**, *124*, 939–945.
6. G. R. Branton, H. M. Frey, *J. Chem. Soc. A* **1966**, *31*, 1342–1343.
7. C. J. Moody, G. H. Whitham, *Reactive Intermediates*, Oxford Science Publications, Oxford, **1992**, p. 38–39.
8. H. E. Zimmerman, S. A. Fleming, *J. Am. Chem. Soc*. **1983**, *105*, 622–625.

W

Wagner–Meerwein Rearrangement

Rearrangement of the carbon skeleton *via* carbenium ions

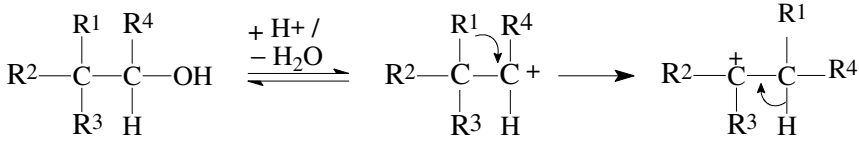


1 **2** **3**

Skeletal rearrangements of carbenium ion species **2**, that involve nucleophilic 1,2-migrations of alkyl groups, are called *Wagner–Meerwein rearrangements*.[1–3]

In an initial step the carbenium ion species **2** has to be generated, for example by protonation of an alcohol **1** at the hydroxyl oxygen under acidic conditions and subsequent loss of water. The carbenium ion **2** can further react in various ways to give a more stable product—e.g. by addition of a nucleophile, or by loss of a proton from an adjacent carbon center; the latter pathway results in the formation of an alkene **3**.

In the case of an appropriate substrate structure, the carbenium ion species can undergo a 1,2-alkyl shift, thus generating a different carbenium ion—e.g. **4**. The driving force for such an alkyl migration is the formation of a more stable carbenium ion, which in turn may undergo further rearrangement or react to a final product by one of the pathways mentioned above—e.g. by loss of a proton to yield an alkene **3**:



1 **2** **4**

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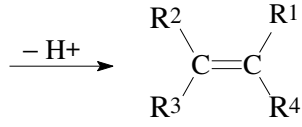
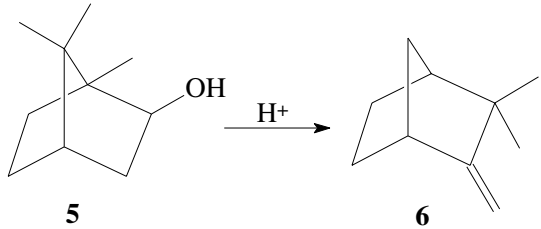


3

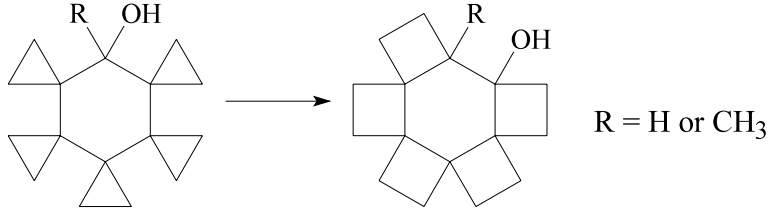
A carbenium ion center can be stabilized by an alkyl substituent through hyperconjugation, or by an aryl substituent through resonance. A tertiary carbenium ion is more stable than a secondary or a primary one. The order of migration for a few selected groups R is: phenyl > *tert*-butyl > ethyl > methyl. The migrating group R generally does not fully dissociate from the rest of the molecule, but is rather bound in a π-complex or a S_N2-like transition state or a tight ion pair.

Of synthetic importance is the Wagner–Meerwein rearrangement especially in the chemistry of terpenes and related compounds.[4,5] For example isoborneol **5** can be dehydrated and rearranged under acidic conditions to yield camphene **6**:



5 **6**

With appropriate substrates, two or more consecutive rearrangements may take place.[6,7] The carbon skeleton of the starting material may then suffer a major structural reorganization:



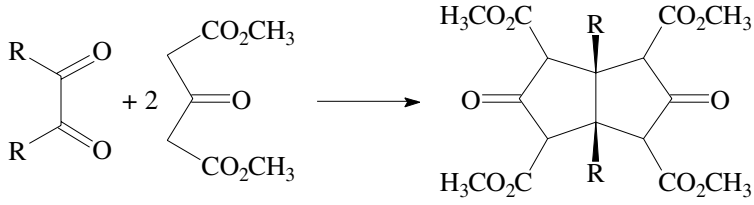
The leaving group doesn't have to be a water molecule; any group or substituent which upon cleavage from the carbon skeleton under appropriate reaction conditions leaves behind a carbenium ion—e.g. a halogen substituent—will suffice. The other substituents can be hydrogen, alkyl or aryl.[3]

Except for terpene chemistry, the Wagner–Meerwein rearrangement is of limited synthetic importance. It is rather found as an undesired side-reaction with other reactions, for example in the synthesis of alkenes by elimination reactions.

1. H. Meerwein, W. Unkel, *Justus Liebigs Ann. Chem.* **1910**, *376*, 152–163.
2. A. Streitwieser, Jr., *Chem. Rev.* **1956**, *56*, 698–713.
3. H. Hogeveen, E. M. G. A. v. Kruchten, *Top. Curr. Chem.* **1979**, *80*, 89–124.
4. T. S. Sorensen, *Acc. Chem. Res.* **1976**, *9*, 257–265.
5. L. A. Paquette, L. Waykole, H. Jendralla, C. E. Cottrell, *J. Am. Chem. Soc.* **1986**, *108*, 3739–3744.
6. L. Fitjer, D. Wehle, M. Noltemeyer, E. Egert, G. M. Sheldrick, *Chem. Ber.* **1984**, *117*, 203–221.
7. M. Hesse, *Ring Enlargement in Organic Chemistry*, VCH, Weinheim, **1991**, p. 8–9.

Weiss Reaction

A synthesis of the bicyclo[3.3.0]octane skeleton

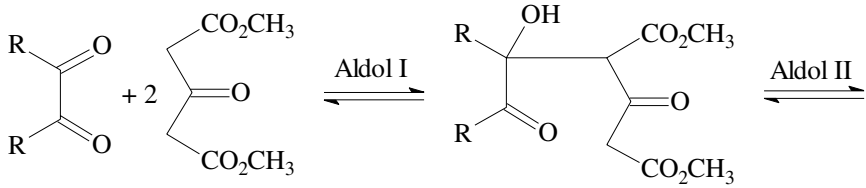


1 **2** **3**

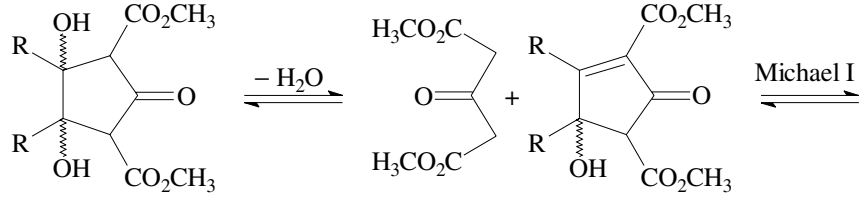
The formation of bicyclo[3.3.0]octane-3,7-diones **3** by reaction of an α-diketone **1** with a 3-oxoglutaric diester **2** is called the *Weiss reaction*.[1–3]

Four carbon–carbon bonds are formed in a one-pot reaction that involves two *aldol reactions* and two *Michael addition reactions*.

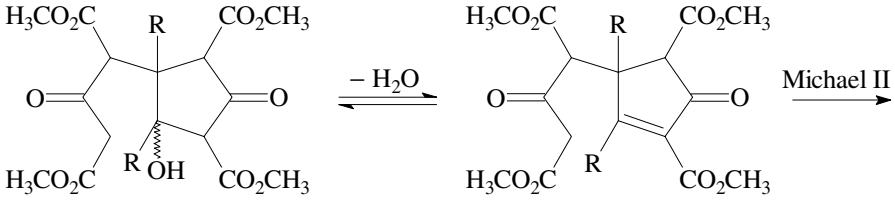
The initial step is an intermolecular aldol addition of 3-oxoglutaric diester **2** to the α-diketone **1**. A second—now intramolecular—aldol reaction leads to formation of the five-membered ring intermediate **4**. Elimination of water from **4** leads to a cyclopentenone derivative **5**, which then reacts with a second 3-oxoglutaric diester molecule in an intermolecular Michael addition. A second dehydration step then again generates a cyclopentenone derivative, which undergoes a second—now intramolecular—Michael addition reaction to yield the *cis*-bicyclo[3.3.0]octan-3,7-dione **3** as the final reaction product:[1,2]

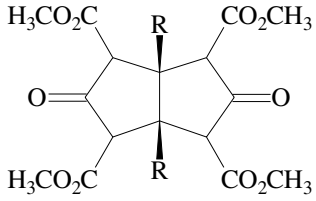


1 **2**



4 **1** **5**

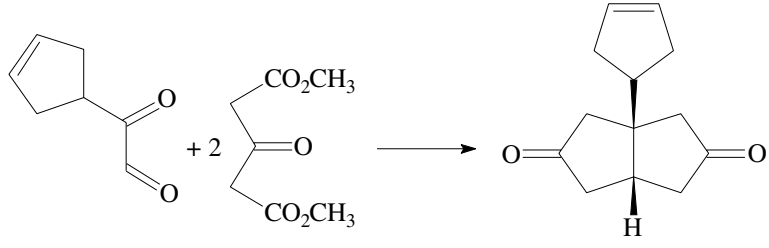




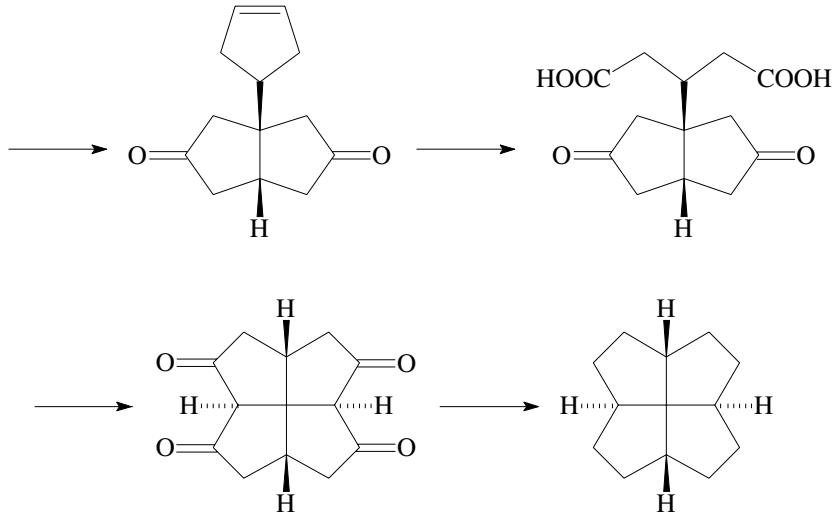
3

The reasonable mechanism outlined above has not yet been rigorously proven in every detail, but is supported by the fact that a 1 : 1-intermediate **5** has been isolated.[4] The ester groups are essential for the Weiss reaction; because of the β-keto ester functionalities however, the ester groups can be easily removed from the final product by ester hydrolysis and subsequent decarboxylation.

An illustrative example for the usefulness of the Weiss reaction for the construction of complex cyclopentanoid carbon skeletons is the synthesis of the all-*cis* [5.5.5.5]fenestrane **7** after *Cook et al.*,[5] starting from the α-diketone[6]:



6



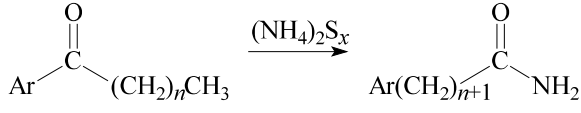
7

In order to obtain good yields from a Weiss reaction sequence, the H^+-concentration has to be adjusted properly in the reaction mixture. The reaction is usually carried out in a buffered, weakly acidic or weakly basic solution. By the Weiss reaction simple starting materials are converted into a complex product of defined stereochemistry. There is no simpler procedure for the synthesis of the 1,5-*cis*-disubstituted bicyclo[3.3.0]octane skeleton; it has for example found application in the synthesis of polyquinanes.[6]

1. U. Weiss, J. M. Edwards, *Tetrahedron Lett*. **1968**, 4885–4887.
2. J. Mulzer, H.-J. Altenbach, M. Braun, K. Krohn, H.-U. Reissig, *Organic Synthesis Highlights*, VCH, Weinheim, **1991**, p. 121–125.
3. X. Fu, J. M. Cook, *Aldrichimica Acta* **1992**, *25*, 43–54.
4. G. Kubiak, J. M. Cook, *Tetrahedron Lett*. **1985**, *26*, 2163–2166.
5. G. Kubiak, X. Fu, A. Gupta, J. M. Cook. *Tetrahedron Lett*. **1990**, *31*, 4285–4288.
6. A. Gupta, X. Fu, J. P. Snyder, J. M. Cook, *Tetrahedron* **1991**, *47*, 3665–3710.

Willgerodt Reaction

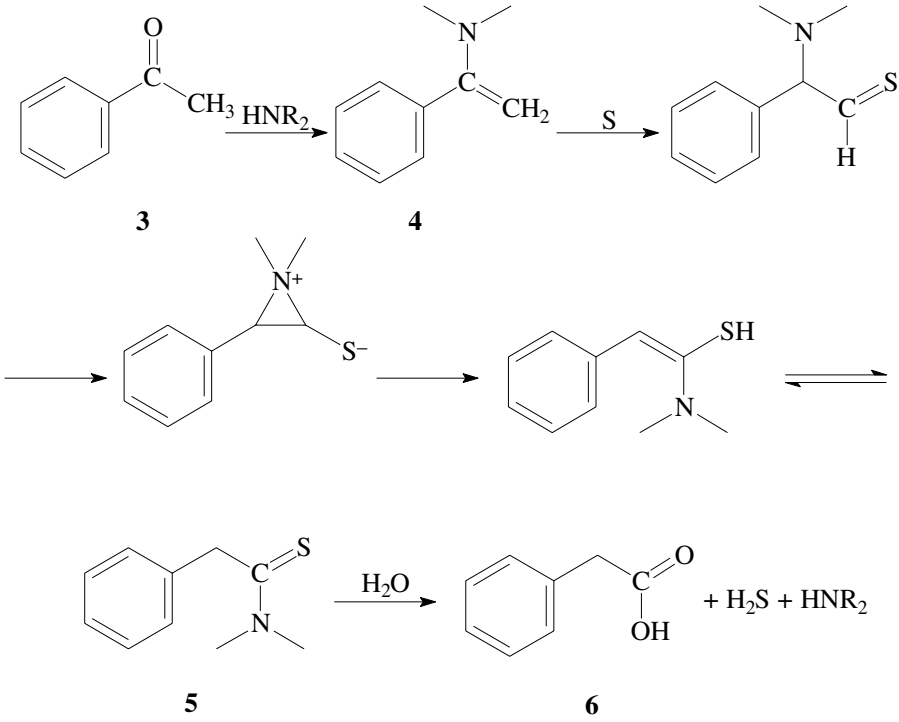
ω-Arylalkane carboxylic amides from aryl alkyl ketones



1 **2**

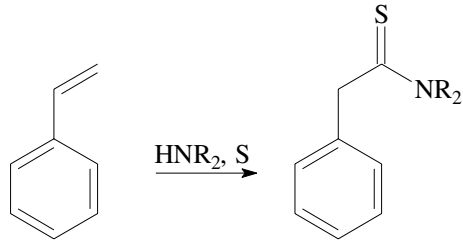
An aryl alkyl ketone **1** can be converted into an ω-arylalkane carboxylic amide **2** by employing the *Willgerodt reaction*.[1–3] The number of carbon centers is retained. The reaction is carried out by treating the ketone with an aqueous solution of ammonium polysulfide. A variant that has been developed by *Kindler*,[4] and which is called the *Willgerodt–Kindler reaction*, uses a mixture of sulfur and a secondary amine instead of the ammonium polysulfide.

The Willgerodt reaction starts with the formation of an enamine **4** from the ketone, e.g. from acetophenone **3**. The further course of the reaction cannot be described by a single mechanism that would apply to all examples known.[2,3,5] For aryl methyl ketones **3** the mechanism for the *Kindler variant* is formulated as follows:



The Willgerodt reaction yields amides **2** as products, while the Willgerodt–Kindler reaction yields N,N-disubstituted thioamides **5**. Both types of products can be converted to the corresponding carboxylic acid **6** by alkaline hydrolysis.

The Willgerodt reaction is usually carried out under high pressure, thus requiring special laboratory equipment, while with the Kindler variant this is not necessary. The Kindler variant is of wider scope, and yields are generally better. In addition aromatic compounds with vinyl substituents may be employed as substrates instead of the ketone, e.g. styrene **7**:[2]



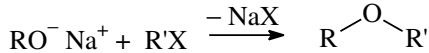
7

The Willgerodt reaction also works with hetaryl alkyl ketones, but often gives unsatisfactory yields. Yields generally decrease with increasing chain length of the alkyl group.

1. C. Willgerodt, *Ber. Dtsch. Chem. Ges*. **1888**, *21*, 534–536.
2. E. V. Brown, *Synthesis* **1975**, 358–375.
3. M. Carmack, M. A. Spielman, *Org. React*. **1946**, *3*, 83–107.
4. K. Kindler, *Justus Liebigs Ann. Chem*. **1923**, *431*, 187–207.
5. F. Asinger, W. Schäfer, K. Halcour, A. Saus, H. Triem, *Angew. Chem*. **1963**, *75*, 1050–1059; *Angew. Chem. Int. Ed. Engl*. **1964**, *3*, 19.

Williamson Ether Synthesis

Ethers by reaction of alkyl halides with alkoxides

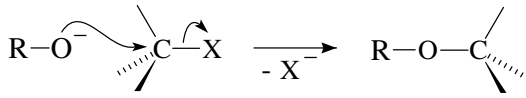


1 **2** **3**

This reaction, which is named after *W. Williamson*,[1,2] is the most important method for the synthesis of unsymmetrical ethers **3**. For this purpose an alkoxide or phenoxide **1** is reacted with an alkyl halide **2** (with R′ = alkyl, allyl or benzyl). Symmetrical ethers can of course also be prepared by this route, but are accessible by other routes as well.

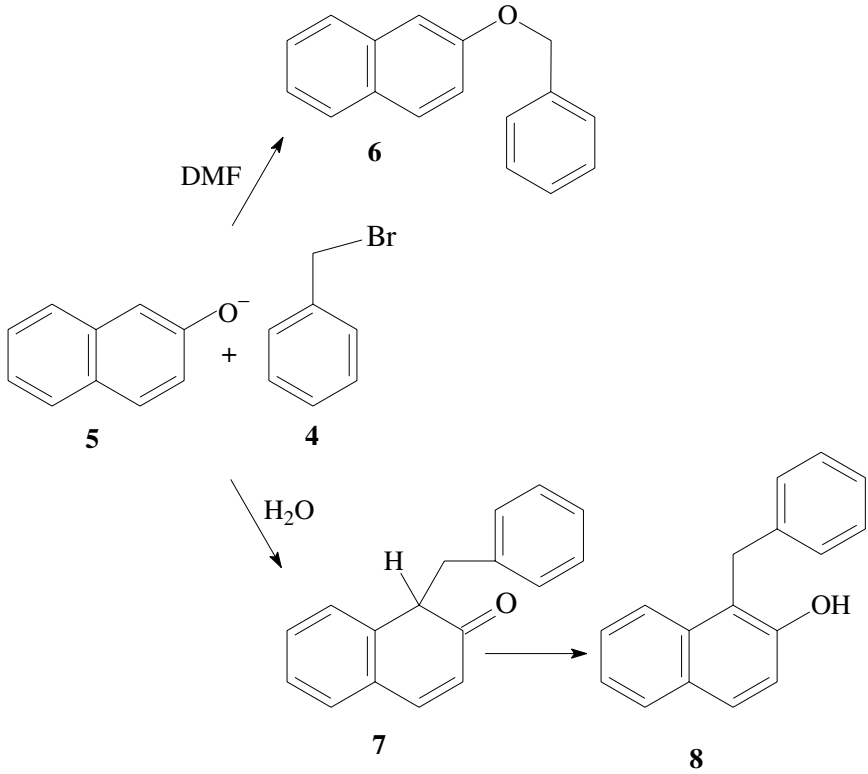
For the classical Williamson synthesis an alcohol is initially reacted with sodium or potassium to give an alkoxide, e.g. **1**. Alternatively an alkali hydroxide or amide may be used to deprotonate the alcohol. Phenols are more acidic, and can be converted to phenoxides by treatment with an alkali hydroxide or with potassium carbonate in acetone.[2]

In most cases the alkoxide or phenoxide **1** reacts with the alkyl halide **2** by a bimolecular nucleophilic substitution mechanism:



1 **2** **3**

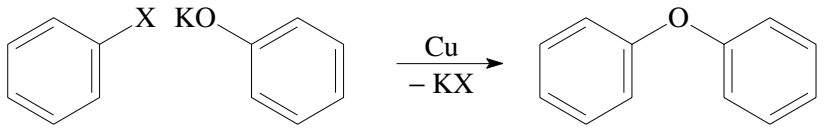
With secondary and tertiary alkyl halides an E_2-elimination is often observed as a side-reaction. As the alkyl halide reactant an iodide is most often employed, since alkyl iodides are more reactive than the corresponding bromides or chlorides. With phenoxides as nucleophiles a *C*-alkylation can take place as a competing reaction. The ratio of *O*-alkylation versus *C*-alkylation strongly depends on the solvent used. For example reaction of benzylbromide **4** with β-naphth-oxide **5** in *N*,*N*-dimethylformamide (DMF) as solvent yields almost exclusively the β-naphthyl benzylether **6**, while the reaction in water as solvent leads *via* intermediate **7** to formation of the *C*-benzylated product—1-benzyl-2-naphthol **8**—as the major product:[3]



An inert solvent such as benzene, toluene or xylene, or an excess of the alcohol corresponding to the alkoxide is often used as solvent. When a dipolar aprotic solvent such as *N*,*N*-dimethylformamide (DMF) or dimethylsulfoxide (DMSO) is used, the reaction often proceeds at higher rate.

As alkylating agent an alkyl halide, alkyl tosylate or dialkyl sulfate is used in most cases; the latter type of reagent is often used in the preparation of methyl and ethyl ethers by employing dimethyl sulfate and diethyl sulfate respectively. Dimethyl sulfate is an excellent methylating agent, but is acutely toxic as well as carcinogenic.[4]

A variant of the Williamson ether synthesis uses thallium alkoxides.[5] The higher reactivity of these can be of advantage in the synthesis of ethers from diols, triols and hydroxy carboxylic acids, as well as from secondary and tertiary alcohols; on the other hand however thallium compounds are highly toxic.



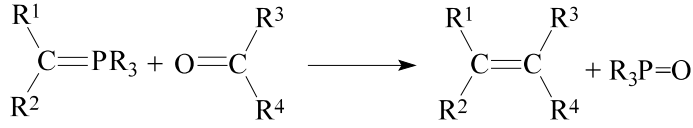
9

A variant for the synthesis of diaryl ethers—e.g. diphenyl ether **9**, where an aryl halide and a phenoxide are reacted in the presence of copper or a copper-(I) salt, is called the *Ullmann ether synthesis*.[6,7]

1. W. Williamson, *Justus Liebigs Ann. Chem*. **1851**, *77*, 37–49.
2. H. Feuer, J. Hooz in *The Chemistry of the Ether Linkage* (Ed.: S. Patai), Wiley, New York, **1967**, p. 445–498.
3. N. Kornblum, R. Seltzer, P. Haberfield, *J. Am. Chem. Soc*. **1963**, *85*, 1148–1154.
4. L. Roth, *Krebserzeugende Stoffe*, Wissenschaftliche Verlagsgesellschaft, Stuttgart, **1983**, pp. 49,54.
5. H.-O. Kalinowski, G. Grass, D. Seebach, *Chem. Ber*. **1981**, *114*, 477–487.
6. F. Ullmann, P. Sponagel, *Ber. Dtsch. Chem. Ges*. **1905**, *38*, 2211–2212.
7. A. A. Moroz, M. S. Shvartsberg, *Russ. Chem. Rev*. **1974**, *43*, 679–689.

Wittig Reaction

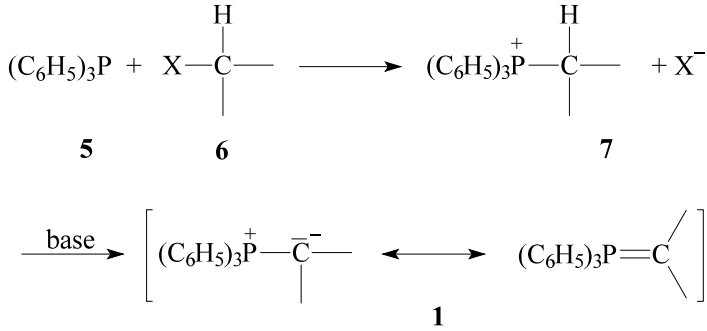
Alkenes (olefins) from reaction of phosphonium ylides with aldehydes or ketones



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

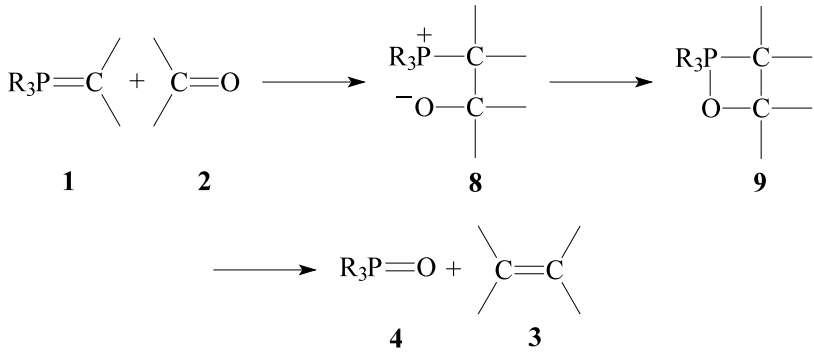
The reaction of an alkylidene phosphorane **1** (i.e. a phosphorus ylide) with an aldehyde or ketone **2** to yield an alkene **3** (i.e. an olefin) and a phosphine oxide **4**, is called the *Wittig reaction* or *Wittig olefination reaction*.[1–5]

Phosphorus ylides like **1** can be prepared by various routes. The most common route is the reaction of triphenylphosphine **5** with an alkyl halide **6** to give a triphenylphosphonium salt **7**, and treatment of that salt with a base to give the corresponding ylide **1**:



The phosphonium salt **7** is usually isolated, and in most cases is a crystalline material, while the ylide **1** is usually prepared in solution and used directly for reaction with the carbonyl substrate.

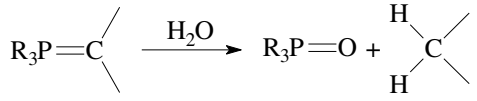
The initial step of olefin formation is a nucleophilic addition of the negatively polarized ylide carbon center (see the resonance structure **1** above) to the carbonyl carbon center of an aldehyde or ketone. A betain **8** is thus formed, which can cyclize to give the oxaphosphetane **9** as an intermediate. The latter decomposes to yield a trisubstituted phosphine oxide **4**—e.g. triphenylphosphine oxide (with R = Ph) and an alkene **3**. The driving force for that reaction is the formation of the strong double bond between phosphorus and oxygen:



Evidence for the four-membered ring intermediate—the oxaphosphetane **9**—comes from ^{31}P-NMR experiments;[6] betaines of type **8** have in some cases been isolated.

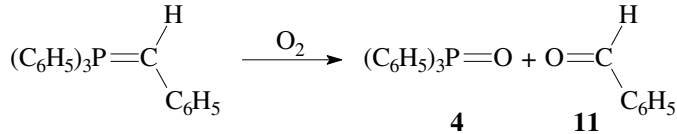
The reactivity of the phosphorus ylide **1** strongly depends on substituents R^1, R^2. For preparative use R often is a phenyl group. When R^1 or R^2 is an electron-withdrawing group, the negative charge can be delocalized over several centers, and the reactivity at the ylide carbon is reduced. The reactivity of the carbonyl compound towards addition of the ylide increases with the electrophilic character of the C=O group. R^1, R^2 are often both alkyl, or alkyl and aryl.

Simple ylides are sensitive towards water as well as oxygen. By reaction with water, the ylide is hydrolyzed to give the trisubstituted phosphine oxide **4** and the hydrocarbon **10**:

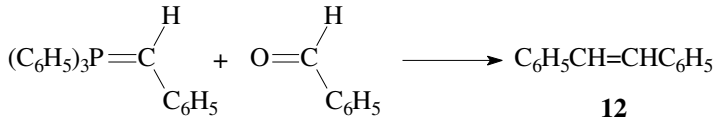


1 **4** **10**

By reaction with oxygen the ylide is cleaved to the trisubstituted phosphine oxide **4** and a carbonyl compound. The latter can undergo a Wittig reaction with excess ylide to give an alkene. This route can be used to prepare symmetrical alkenes by passing oxygen through a solution of excess phosphorus ylide; oxidants other than molecular oxygen may be used instead.[7] In the following scheme this route is outlined for the oxidative cleavage of benzylidene triphenylphosphorane to give triphenylphosphine oxide **4** and benzaldehyde **11**, and subsequent Wittig reaction of the latter with excess benzylidene phosphorane to yield stilbene **12**:

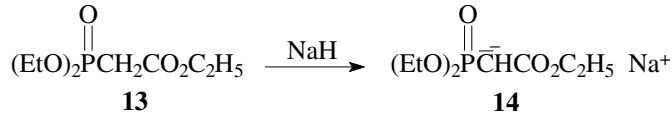


4 **11**

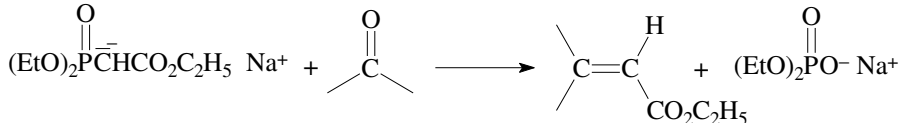


12

Important and widely used variants of the Wittig reaction are based on carbanionic organophosphorus reagents, and are known as the *Wadsworth–Emmons reaction*, *Wittig–Horner reaction* or *Horner–Wadsworth–Emmons reaction*.[8,9] As first reported by Horner,[10] carbanionic phosphine oxides can be used; today carbanions from alkyl phosphonates **13** are most often used. The latter are easily prepared by application of the *Arbuzov reaction*. The reactive carbanionic species—e.g. **14**—is generated by treatment of the appropriate phosphonate with base, e.g. with sodium hydride:



13 **14**



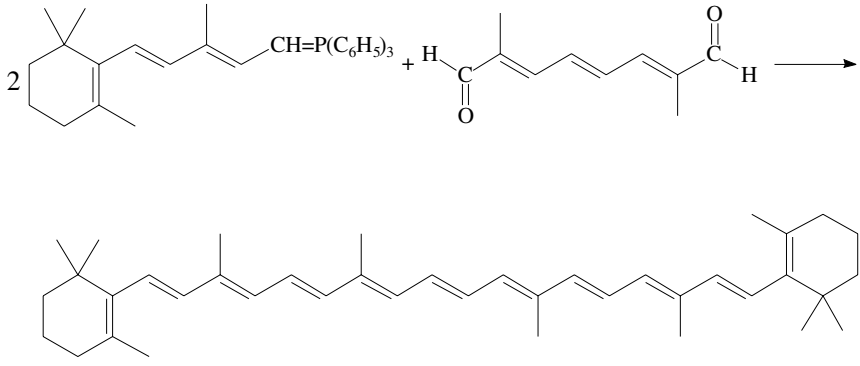
14 **2** **15** **16**

The carbanionic deprotonated phosphonate thus obtained—e.g. **14**—can be reacted with a carbonyl substrate **2** just like a phosphorus ylide. However

such carbanions are stronger nucleophiles then the corresponding ylides. As reaction products an alkene and a dialkyl phosphate salt are obtained—e.g. α,β-unsaturated ester **15** and sodium diethyl phosphate **16**. The dialkyl phosphate salt is soluble in water, and therefore can in most cases be easily removed from the desired olefination product, which is usually much less soluble in water.

The (Horner–)Wadsworth–Emmons reaction generally is superior to the Wittig reaction, and has found application in many cases for the synthesis of α,β-unsaturated esters, α,β-unsaturated ketones and other conjugated systems. Yields are often better then with the original Wittig procedure. However the Wadsworth–Emmons method is not suitable for the preparation of alkenes with simple, non-stabilizing alkyl substituents.

The Wittig reaction is one of the most important reactions in organic synthesis. The synthetic importance of the Wittig reaction and its variants and related reactions is based on the fact that the new carbon–carbon double bond in the product molecule is generated at a fixed position. Other methods for the formation of carbon–carbon double bonds, e.g. elimination of water or HX, or pyrolytic procedures often lead to mixtures of isomers. The Wittig and related reactions have found application in the synthesis of many organic target molecules, for example in natural product synthesis. As an illustrating example a step from a synthesis of β-carotene **17** is outlined:[11]



17

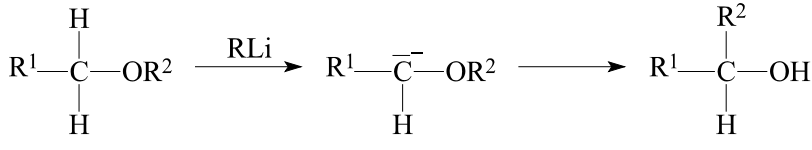
With respect to the carbonyl substrate, a variety of additional functional groups is tolerated, e.g. ester, ether, halogen. With compounds that contain an ester as well as a keto or aldehyde function, the latter usually reacts preferentially. Due to its mild reaction conditions the Wittig reaction is an important method for the synthesis of sensitive alkenes, as for example highly unsaturated compounds like the carotinoid **17** shown above.

1. G. Wittig, G. Geissler, *Justus Liebigs Ann. Chem.* **1953**, *580*, 44–57.
2. A. W. Johnson, *Ylid Chemistry*, Academic Press, New York, **1979**.
3. A. Maercker, *Org. React.* **1965**, *14*, 270–490.

4. H. Pommer, *Angew. Chem.* **1977**, *89*, 437–443; *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 423.
5. B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, *89*, 863–927.
6. B. E. Maryanoff, A. B. Reitz, M. S. Mutter, R. R. Inners, H. R. Almond, R. R. Whittle, R. A. Olofson, *J. Am. Chem. Soc.* **1986**, *108*, 7664–7678.
7. H. J. Bestmann, R. Armsen, H. Wagner, *Chem. Ber.* **1969**, *102*, 2259–2269.
8. W. S. Wadsworth, Jr, W. D. Emmons, *J. Am. Chem. Soc.* **1961**, *83*, 1733–1738.
9. W. S. Wadsworth, Jr, *Org. React.* **1977**, *25*, 73–253.
J. Clayden, S. Warren, *Angew. Chem.* **1996**, *108*, 261–291; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 241.
10. L. Horner, H. Hoffmann, H. G. Wippel, G. Klahre, *Chem. Ber.* **1959**, *92*, 2499–2505.
11. G. Wittig, H. Pommer, DBP 954 247, **1956**; *Chem. Abstr.* **1959**, *53*, 2279.

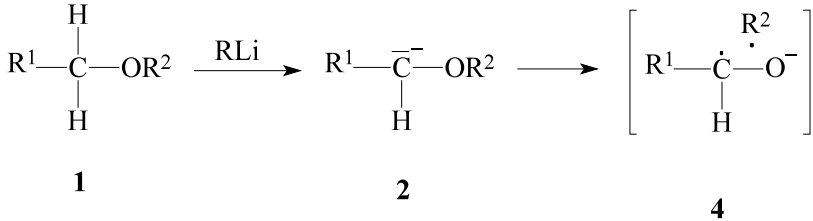
Wittig Rearrangement

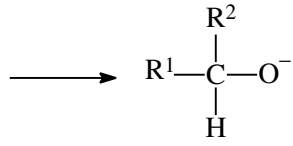
Rearrangement of ethers to yield alcohols



The rearrangement of an ether **1** when treated with a strong base, e.g. an organolithium compound RLi, to give an alcohol **3** *via* the intermediate α-metallated ether **2**, is called the *Wittig rearrangement*.[1,2] The product obtained is a secondary or tertiary alcohol. R^1, R^2 can be alkyl, aryl and vinyl. Especially suitable substrates are ethers where the intermediate carbanion can be stabilized by one of the substituents R^1, R^2; e.g. benzyl or allyl ethers.

In contrast to the related *Stevens rearrangement*, experimental findings suggest a radical or a concerted reaction pathway. The mechanism of the radical [1,2]-Wittig rearrangement is formulated as follows. In the initial step the ether **1** is deprotonated α to the oxygen by a strong base, e.g. an organolithium compound or sodium amide, to give a carbanion **2**. Homolytic cleavage of the α-carbon–oxygen bond leads to formation of a radical-pair **4**,[3] which then recombines to the rearranged alkoxide **5**. Aqueous workup finally yields the alcohol **3**.

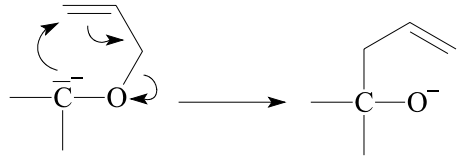




5

Driving force for the Wittig rearrangement is the transfer of the negative charge from carbon to the more electronegative oxygen. An analogous reaction with amines is known as the aza-witting rearrangement.[8]

In certain cases the reaction may proceed by a concerted mechanism. With allyl ethers a concerted [2,3]-sigmatropic rearrangement *via* a five-membered six-electron transition state is possible:[4,5]



Recently this [2,3]-Wittig rearrangement has received much attention and has been developed into a useful method for the stereoselective synthesis of homoallylic alcohols.[4–7]

1. G. Wittig, L. Löhmann, *Justus Liebigs Ann. Chem*. **1942**, *550*, 260–268.
2. D. L. Dalrymple, T. L. Kruger, W. N. White, in *The Chemistry of the Etherlinkage* (Ed.: S. Patai), Wiley, New York, **1967**, p. 617–628.
3. U. Schöllkopf, *Angew. Chem*. **1970**, *82*, 795–805;
   Angew. Chem. Int. Ed. Engl. **1970**, *9*, 763.
4. T. Nakai, K. Mikami, *Chem. Rev*. **1986**, *86*, 885–902.
   T. Nakai, K. Mikami, in *Organic Reactions*, *Vol. 46* (Ed.: L. Paquette), Wiley, New York, **1994**, p. 105–209.
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   R. Brückner, In *Comprehensive Organic Synthesis*, *Vol. 4* (Eds.: B.M. Trost, I. Fleming), Pergamon, Oxford, **1991**, ch. 4.6, p. 873–892.
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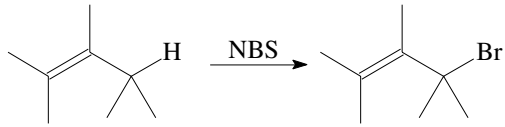
   J. Kallmerten, in *Houben-Weyl*, 4th Ed, *Vol. E21d* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1995**, p. 3758 and 3821.
7. For recent examples, *see* D. Enders, D. Backhaus, J. Runsink, *Tetrahedron* **1996**, *52*, 1503–1528, and references therein.
8. C. Vogel, *Synthesis* **1997**, 497–505.

Wohl–Ziegler Bromination

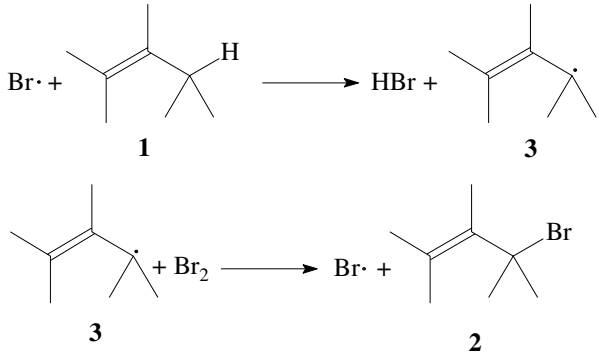
Allylic bromination with *N*-bromosuccinimide



1 **2**

Olefins react with bromine by addition of the latter to the carbon–carbon double bond. In contrast the *Wohl–Ziegler bromination reaction*[1–4] using *N*-bromosuccinimide (NBS) permits the selective substitution of an allylic hydrogen of an olefinic substrate **1** by a bromine atom to yield an allylic bromide **2**.

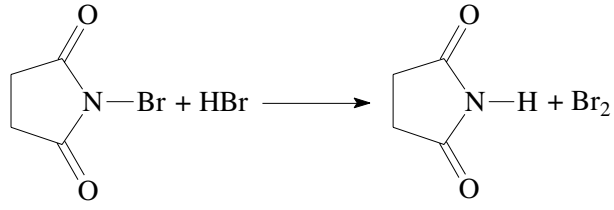
The allylic bromination of an olefin with NBS proceeds by a free-radical chain mechanism.[5,6] The chain reaction initiated by thermal decomposition of a free-radical initiator substance that is added to the reaction mixture in small amounts. The decomposing free-radical initiator generates reactive bromine radicals by reaction with the *N*-bromosuccinimide. A bromine radical abstracts an allylic hydrogen atom from the olefinic substrate to give hydrogen bromide and an allylic radical **3**:



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

The chain propagation step consists of a reaction of allylic radical **3** with a bromine molecule to give the allylic bromide **2** and a bromine radical. The intermediate allylic radical **3** is stabilized by delocalization of the unpaired electron due to resonance (see below). A similar stabilizing effect due to resonance is also possible for benzylic radicals; a benzylic bromination of appropriately substituted aromatic substrates is therefore possible, and proceeds in good yields.

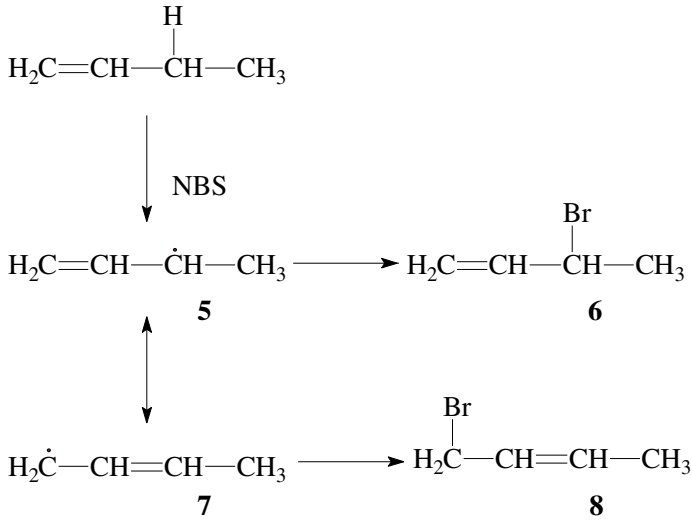
The low concentration of elemental bromine required for the chain propagation step is generated from NBS **4** by reaction with the hydrogen bromide that has been formed in the first step:



4

By this reaction a constantly low concentration of elemental bromine is supplied. With higher concentrations of free bromine, an addition to the carbon–carbon double bond is to be expected.

The allylic resonance may give rise to formation of a mixture of isomeric allylic bromides, e.g. **6** and **8** from but-1-ene. The product ratio depends on the relative stability of the two possible allylic radical species **5** and **7**:



With two competing allylic species, a secondary center $-CH_2-$ is brominated preferentially over a primary center $-CH_3$.

The free-radical chain reaction may also be terminated by coupling of two carbon-radical species. As solvent carbon tetrachloride is commonly used, where the *N*-bromosuccinimide is badly soluble. Progress of reaction is then indicated by the decrease of the amount of precipitated NBS and the formation of the succinimide that floats on the surface of the organic liquid layer.

In order to induce the free-radical chain reaction, a starter compound such as dibenzoyl diperoxide, azo-*bis*-(isobutyronitrile) or *tert*-butyl hydroperoxide or UV-light is used. The commercially available, technical grade *N*-bromosuccinimide contains traces of bromine, and therefore is of slight red-brown color. Since a small amount of elemental bromine is necessary for the radical

chain-propagation step, the usual slightly colored NBS needs not to be purified by recrystallization.

1. A. Wohl, *Ber. Dtsch. Chem. Ges*. **1919**, *52*, 51–63.
2. K. Ziegler, A. Späth, E. Schaaf, W. Schumann, E. Winkelmann, *Justus Liebigs Ann. Chem*. **1942**, *551*, 80–119.
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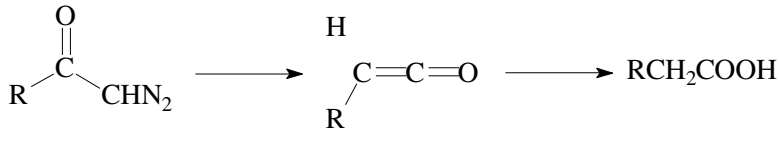
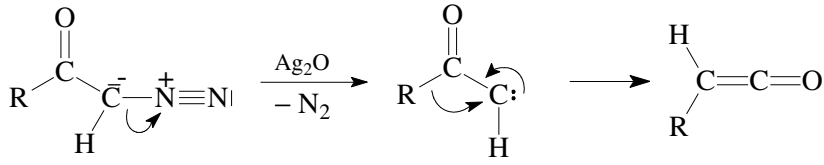
Wolff Rearrangement

Ketenes from α-diazo ketones



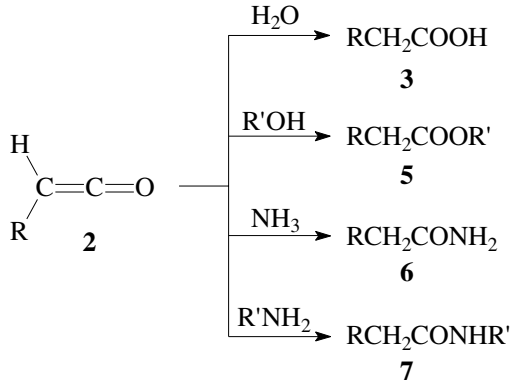
1 **2** **3**

An α-diazo ketone **1** can decompose to give a ketocarbene, which further reacts by migration of a group R to yield a ketene **2**. Reaction of ketene **2** with water results in formation of a carboxylic acid **3**. The *Wolff rearrangement*[1,2,6] is one step of the *Arndt–Eistert reaction*. Decomposition of diazo ketone **1** can be accomplished thermally, photochemically or catalytically; as catalyst amorphous silver oxide is commonly used:

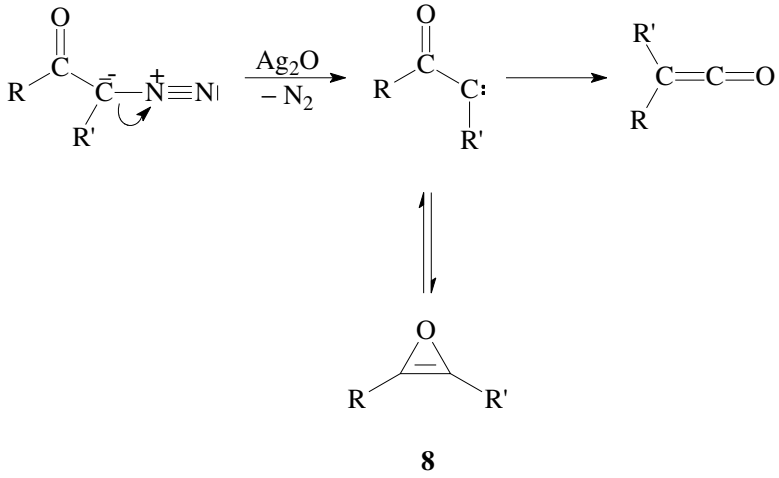


1 **4** **2**

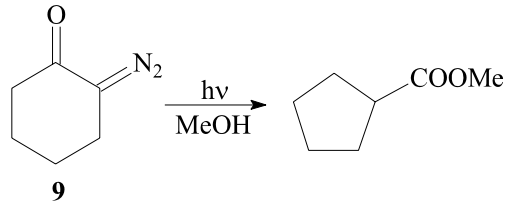
The ketocarbene **4** that is generated by loss of N_2 from the α-diazo ketone, and that has an electron-sextet, rearranges to the more stable ketene **2** by a nucleophilic 1,2-shift of substituent R. The ketene thus formed corresponds to the isocyanate product of the related *Curtius reaction*. The ketene can further react with nucleophilic agents, that add to the C=O-double bond. For example by reaction with water a carboxylic acid **3** is formed, while from reaction with an alcohol R′−OH an ester **5** is obtained directly. The reaction with ammonia or an amine R′−NH_2 leads to formation of a carboxylic amide **6** or **7**:



The intermediacy of a ketocarbene species **4** is generally accepted for the thermal or photochemical Wolff rearrangement;[3] oxirenes **8** that are in equilibrium with ketocarbenes, have been identified as intermediates:



With cyclic α-diazo ketones, e.g. α-diazo cyclohexanone **9**, the rearrangement results in a ring contraction by one carbon:[4,5]



The Wolff rearrangement is a versatile reaction: R can be alkyl as well as aryl; most functional groups do not interfere. The generally mild reaction conditions permit an application to sensitive substrates.

1. L. Wolff, *Justus Liebigs Ann. Chem*. **1912**, *394*, 23–59.
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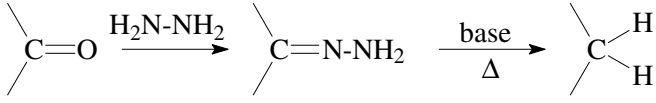
6. S. Motallebi, P. Müller, *Chimia* **1992**, *46*, 119–122.

Wolff–Kishner Reduction

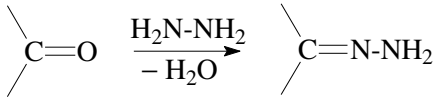
Hydrocarbons by reduction of aldehydes or ketones



1 **2** **3**

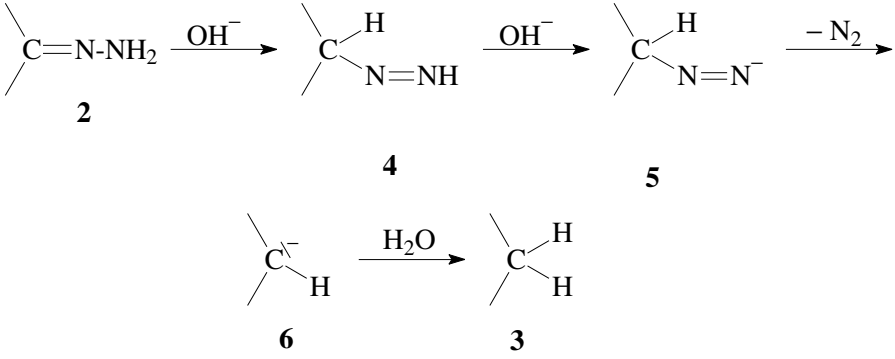
An aldehyde or ketone **1** can react with hydrazine to give a hydrazone **2**. The latter can be converted to a hydrocarbon—the methylene derivative **3**—by loss of N_2 upon heating in the presence of base. This deoxygenation method is called the *Wolff–Kishner reduction*.[1–3]

The initial step is the formation of hydrazone **2** by reaction of hydrazine with aldehyde or ketone **1**:



1 **2**

The subsequent steps are a sequence of base-induced H-shifts to give the anionic species **5**, from which loss of nitrogen (N_2) leads to a carbanionic species **6**. The latter is then protonated by the solvent to yield hydrocarbon **3** as the final product:



2 **4** **5** **6** **3**

The classical procedure for the Wolff–Kishner reduction—i.e. the decomposition of the hydrazone in an autoclave at 200 °C—has been replaced almost completely by the modified procedure after *Huang-Minlon*.[4] The isolation of the intermediate is not necessary with this variant; instead the aldehyde or ketone is heated with excess hydrazine hydrate in diethyleneglycol as solvent and in the presence of alkali hydroxide for several hours under reflux. A further improvement of the reaction conditions is the use of potassium *tert*-butoxide as base and dimethyl sulfoxide (DMSO) as solvent; the reaction can then proceed already at room temperature.[5]

The Wolff–Kishner reduction is an important alternative method to the *Clemmensen reduction*, and is especially useful for the reduction of acid-labile or high-molecular substrates.[3] Yields are often below 70%, due to various side-reactions such as elimination or isomerization reactions.[2]

1. L. Wolff, *Justus Liebigs Ann. Chem.* **1912**, *394*, 86–108.
2. H. H. Szmant, *Angew. Chem.* **1968**, *80*, 141–149; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 120.
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Wurtz Reaction

Hydrocarbons by coupling of alkyl halides

$$\underset{\mathbf{1}}{2\ RX} + 2\ Na \longrightarrow \underset{\mathbf{2}}{R{-}R} + 2\ NaX$$

The coupling of alkyl halides **1** upon treatment with a metal, e.g. elemental sodium, to yield symmetrical alkanes **2**, is called the *Wurtz reaction*.[1–4] Aryl alkanes can be prepared by the *Wurtz–Fittig reaction*, i.e. the coupling of aryl halides with alkyl halides.

Mechanistically the reaction can be divided into two steps.[5] Initially the alkyl halide **1** reacts with sodium to give an organometallic species **3**, that can be isolated in many cases. In a second step the carbanionic R^- of the organometallic compound **3** acts as nucleophile in a substitution reaction with alkyl halide **1** to replace the halide:

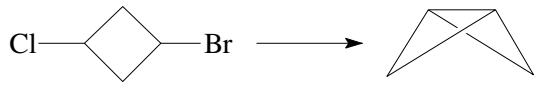
$$\underset{\mathbf{1}}{RX} + 2\ Na \longrightarrow \underset{\mathbf{3}}{R^-\ Na^+} + NaX$$

$$\underset{\mathbf{3}}{R^-\ Na^+} + \underset{\mathbf{1}}{X{-}R} \longrightarrow \underset{\mathbf{2}}{R{-}R} + Na$$

Alternatively a radical mechanism is discussed. There is no uniform mechanism that would apply to all kinds of substrates and the various reaction conditions.

The synthetic applicability is rather limited, due to the various side-reactions observed, such as eliminations and rearrangement reactions. The attempted coupling of two different alkyl halides in order to obtain an unsymmetrical hydrocarbon, usually gives the desired product in only low yield. However the coupling reaction of an aryl halide with an alkyl halide upon treatment with a metal (the *Wurtz–Fittig reaction*) often proceeds with high yield. The coupling of two aryl halides usually does not occur under those conditions (see however below!) since the aryl halides are less reactive.

In the case of an intramolecular Wurtz reaction less side-reactions are observed; this variant is especially useful for the construction of strained carbon skeletons.[6] For example bicyclobutane **5** has been prepared from 1-bromo-3-chlorocyclobutane **4** in a yield of > 90%:[7]



4 **5**

In addition to sodium, other metals have found application for the Wurtz coupling reaction, e.g. zinc, iron, copper, lithium, magnesium. The use of ultrasound can have positive effect on reactivity as well as rate and yield of this two-phase reaction;[8] aryl halides can then even undergo an aryl–aryl coupling reaction to yield biaryls.[9]

1. A. Wurtz, *Justus Liebigs Ann. Chem.* **1855**, *96*, 364–375.
2. B. Tollens, R. Fittig, *Justus Liebigs Ann. Chem.* **1864**, *131*, 303–323.
3. H. F. Ebel, A. Lüttringhaus, *Methoden Org. Chem. (Houben-Weyl)* **1970**, Vol. 13/1, p. 486–502.
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