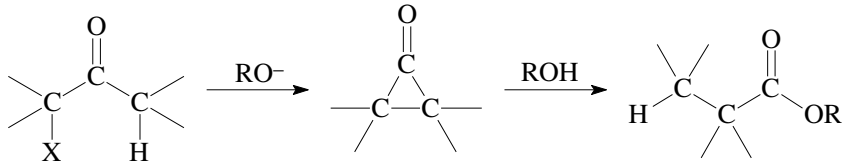
F

Favorskii Rearrangement

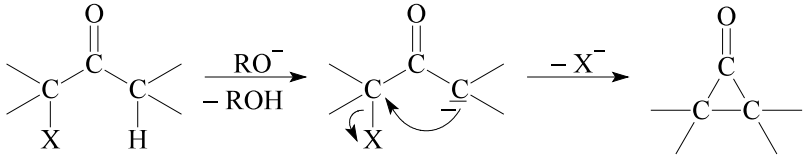
Carboxylic esters from α-haloketones



1 **2** **3**

α-Halo ketones **1**, when treated with a base, can undergo a rearrangement reaction to give a carboxylic acid or a carboxylic acid derivative **3**, e.g. an ester or amide, depending on the base used. This reaction is called the *Favorskii rearrangement*.[1,2] As base a hydroxide, alkoxide or amine is used; the halogen substituent can be a chlorine, bromine or iodine atom.

In the initial step[3,4] the α-halo ketone **1** is deprotonated by the base at the α'-carbon to give the carbanion **4**, which then undergoes a ring-closure reaction by an intramolecular substitution to give the cyclopropanone derivative **2**. The halogen substituent functions as the leaving group:



1 **4** **2**

Nucleophilic addition of the base to the intermediate **2** leads to ring opening. With a symmetrically substituted cyclopropanone, cleavage of either C_α–CO bond leads to the same product. With unsymmetrical cyclopropanones, that bond is broken preferentially that leads to the more stable carbanion **5**:

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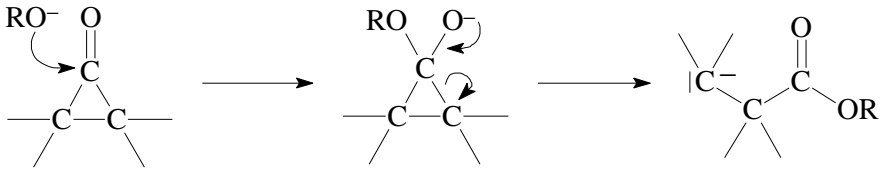
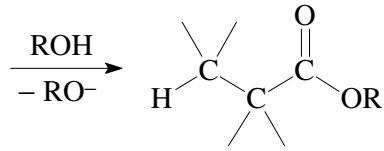
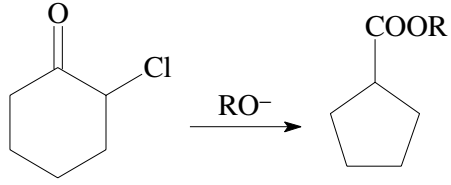


2 **5**



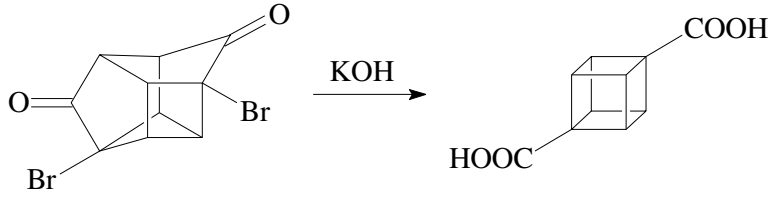
3

The carbanionic species thus formed is protonated to give the final product **3**. The use of an alkoxide as base leads to formation of a carboxylic ester as rearrangement product; use of a hydroxide will lead to formation of a carboxylic acid salt:

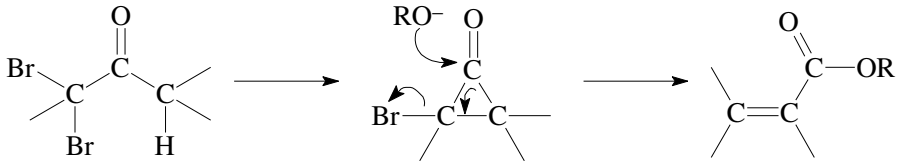


6

With cyclic α-halo ketones, e.g. 2-chloro cyclohexanone **6**, the Favorskii rearrangement leads to a ring contraction by one carbon atom. This type of reaction has for example found application as a key step in the synthesis of cubane by *Eaton* and *Cole*[5] for the construction of the cubic carbon skeleton:



Under Favorskii conditions α,α-dihalo ketones **7**, as well as α,α'-dihalo ketones, bearing one α'-hydrogen, rearrange to give α,β-unsaturated esters **8**:[6]



7 **8**

The rearrangement with ring contraction probably is the most important synthetic application of the Favorskii reaction; it is for example used in the synthesis of steroids. Yields can vary from good to moderate. As solvents diethyl ether or alcohols are often used. With acyclic α-halo ketones bearing voluminous substituents in α'-position, yields can be low; a *tert*-butyl substituent will prevent the rearrangement.

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4. H. H. Wasserman, G. M. Clark, P. C. Turley, *Top. Curr. Chem.* **1974**, *47*, 73–156.
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Finkelstein Reaction

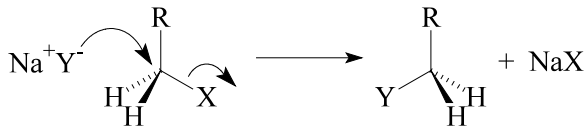
Exchange of the halogen in alkyl halides

$$R{-}X \underset{-X^-}{\overset{+Y^-}{\rightleftharpoons}} R{-}Y$$

The synthesis of alkyl halides from alkyl halides is called the *Finkelstein reaction*.[1–3]

For preparative use it is necessary to shift the equilibrium in favor of the desired product. This may for example be achieved by taking advantage of different solubilities of the reactants.

With primary alkyl halides **1** the Finkelstein reaction proceeds by a S_N2-mechanism. An alkali halide is used to deliver the nucleophilic halide anion:[3]



1

Of preparative importance is the substitution of chloride or bromide or iodide, since the more reactive alkyl iodides are better substrates for further transformations. Alkyl iodides often are difficult to prepare directly, which is why the conversion of readily accessible chlorides or bromides *via* a Finkelstein reaction is often preferred.

Differences in solubility of the reactants may for example be utilized as follows. Sodium iodide is much more soluble in acetone than are sodium chloride or sodium bromide. Upon treatment of an alkyl chloride or bromide with sodium iodide in acetone, the newly formed sodium chloride or bromide precipitates from the solution and is thus removed from equilibrium. Alkyl iodides can be conveniently prepared in good yields by this route. Alkyl bromides are more reactive as the corresponding chlorides. Of high reactivity are α-halogen ketones, α-halogen carboxylic acids and their derivatives, as well as allyl and benzyl halides.

Secondary or tertiary alkyl halides are much less reactive. For example an alkyl dichloride with a primary and a secondary chloride substituent reacts selectively by exchange of the primary chloride. The reactivity with respect to the Finkelstein reaction is thus opposite to the reactivity for the hydrolysis of alkyl chlorides. For the Finkelstein reaction on secondary and tertiary substrates Lewis acids may be used,[4] e.g. $ZnCl_2$, $FeCl_3$ or Me_3Al.

Alkyl fluorides can be prepared by the Finkelstein reaction.[5,6] The fluoride anion is a bad leaving group; the reverse reaction thus does not take place easily, and the equilibrium lies far to the right. As reagents potassium fluoride, silver fluoride or gaseous hydrogen fluoride may be used.

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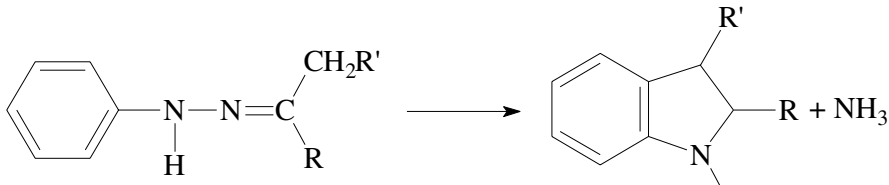
Fischer Indole Synthesis

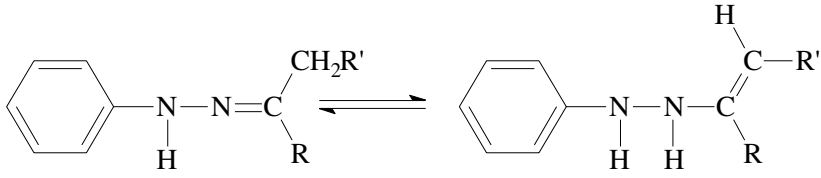
Indoles from aryl hydrazones



1 **2**

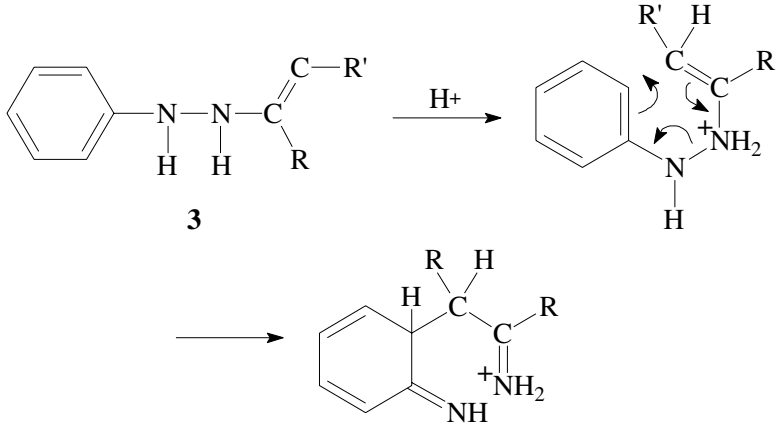
Heating of an aryl hydrazone **1** in the presence of a catalyst leads to elimination of ammonia and formation of an indole **2**. This reaction is known as the *Fischer indole synthesis*,[1–7] and is somewhat related to the *Benzidine rearrangement*.

A mechanism, that has been proposed by *G. M. Robinson* and *R. Robinson*,[8] consists of three steps. Initially the phenyl hydrazone **1** undergoes a reversible rearrangement to give the reactive ene-hydrazine **3**:



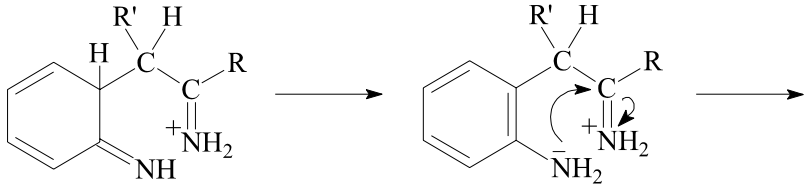
1 **3**

A [3.3]-sigmatropic rearrangement of **3** leads to formation of a new carbon–carbon bond and the cationic species **4**:

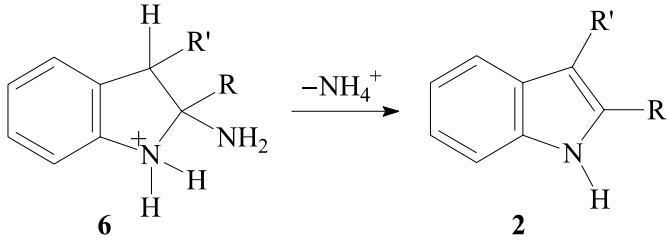


3 **4**

That electrocyclic reaction is related to the *Claisen rearrangement* of phenyl vinyl ether. In a final step a cyclization takes place with subsequent elimination of ammonia to yield the indole **2**:



4 **5**

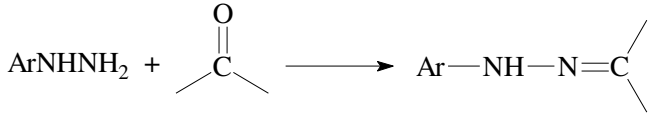


6 **2**

The mechanism outlined above is supported by experimental findings. An intermediate **5** has been isolated,[9–11] and has been identified by ^{13}C- and ^{15}N-nuclear magnetic resonance spectroscopy.[12] Side-products have been isolated, which are likely to be formed from intermediate **4**.[3] ^{15}N-isotope labeling experiments have shown that only the nitrogen remote from the phenyl group is eliminated as ammonia.[13]

Metal halides like zinc chloride are used as Lewis-acid catalysts. Other Lewis-acids or protic acids, as well as transition metals, have found application also. The major function of the catalyst seems to be the acceleration of the second step—the formation of the new carbon–carbon bond.

The hydrazones **1** used as starting materials are easily prepared by reaction of an aldehyde or ketone **8** with an aryl hydrazine **7**:

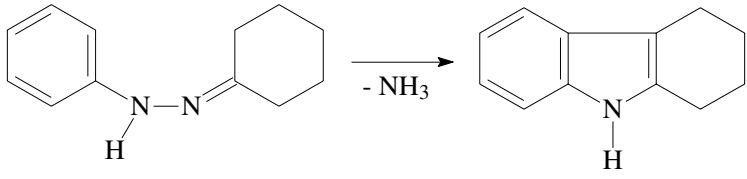


7 **8** **1**

In order to allow further transformation to an indole, the carbonyl compound **8** must contain an α-methylene group. The hydrazone **1** needs not to be isolated. An equimolar mixture of arylhydrazine **7** and aldehyde or ketone **8** may be treated directly under the reaction conditions for the Fischer indole synthesis.[3]

Another route to suitable arylhydrazones is offered by the *Japp–Klingemann reaction*.

The Fischer indole synthesis is of wide scope, and can be used for the preparation of substituted indoles and related systems. For example reaction of the phenylhydrazone **9**, derived from cyclohexanone, yields the tetrahydrocarbazole **10**:[5,6,7]



9 **10**

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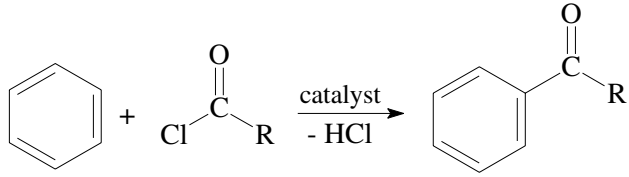
Friedel–Crafts Acylation

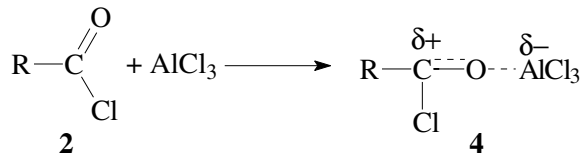
Acylation of aromatic compounds



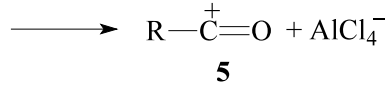
1 **2** **3**

The most important method for the synthesis of aromatic ketones **3** is the *Friedel–Crafts acylation*.[1–4] An aromatic substrate **1** is treated with an acyl chloride **2** in the presence of a Lewis-acid catalyst, to yield an acylated aromatic compound. Closely related reactions are methods for the formylation, as well as an alkylation procedure for aromatic compounds, which is also named after *Friedel* and *Crafts*.

The reaction is initiated by formation of a donor–acceptor complex **4** from acyl chloride **2**, which is thereby activated, and the Lewis acid, e.g. aluminum trichloride. Complex **4** can dissociate into the acylium ion **5** and the aluminum tetrachloride anion; **4** as well as **5** can act as an electrophile in a reaction with the aromatic substrate:

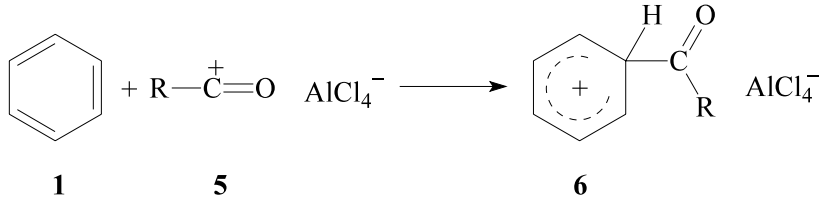


2 **4**

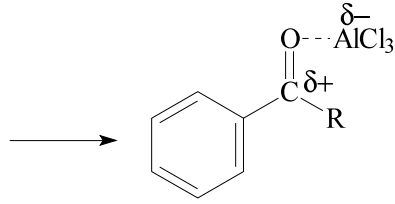


5

Depending on the specific reaction conditions, complex **4** as well as acylium ion **5** have been identified as intermediates; with a sterically demanding substituent R, and in polar solvents the acylium ion species **5** is formed preferentially.[5] The electrophilic agent **5** reacts with the aromatic substrate, e.g. benzene **1**, to give an intermediate σ-complex—the cyclohexadienyl cation **6**. By loss of a proton from intermediate **6** the aromatic system is restored, and an arylketone is formed that is coordinated with the carbonyl oxygen to the Lewis acid. Since a Lewis-acid molecule that is coordinated to a product molecule is no longer available to catalyze the acylation reaction, the catalyst has to be employed in equimolar quantity. The product-Lewis acid complex **7** has to be cleaved by a hydrolytic workup in order to isolate the pure aryl ketone **3**.



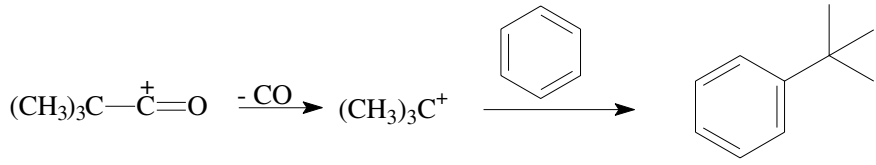
1 **5** **6**



7

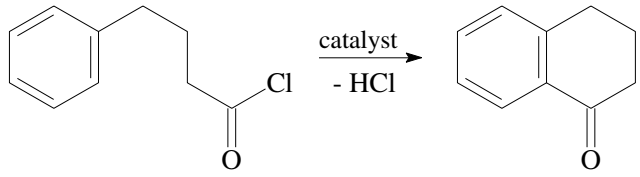
Product complex **7** as well as the free product **3** are much less reactive towards further electrophilic substitution as is the starting material; thus the formation of polyacylated products is not observed. If the starting material bears one or more non-deactivating substituents, the direction of acylation can be predicted by the general rules for aromatic substitution.

Drawbacks as known from the *Friedel–Crafts alkylation* are not found for the Friedel–Crafts acylation. In some cases a decarbonylation may be observed as a side-reaction, e.g. if loss of CO from the acylium ion will lead to a stable carbenium species **8**. The reaction product of the attempted acylation will then be rather an alkylated aromatic compound **9**:

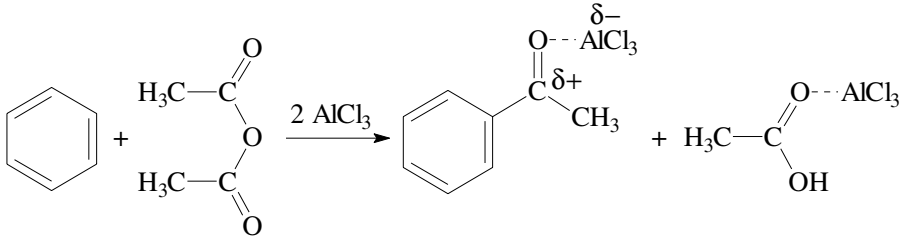


8 **9**

An important application of the Friedel–Crafts acylation is the intramolecular reaction, leading to ring closure. This variant is especially useful for the closure of six-membered rings, but five-membered ring products and larger rings, as well as heterocycles,[9] are also accessible:



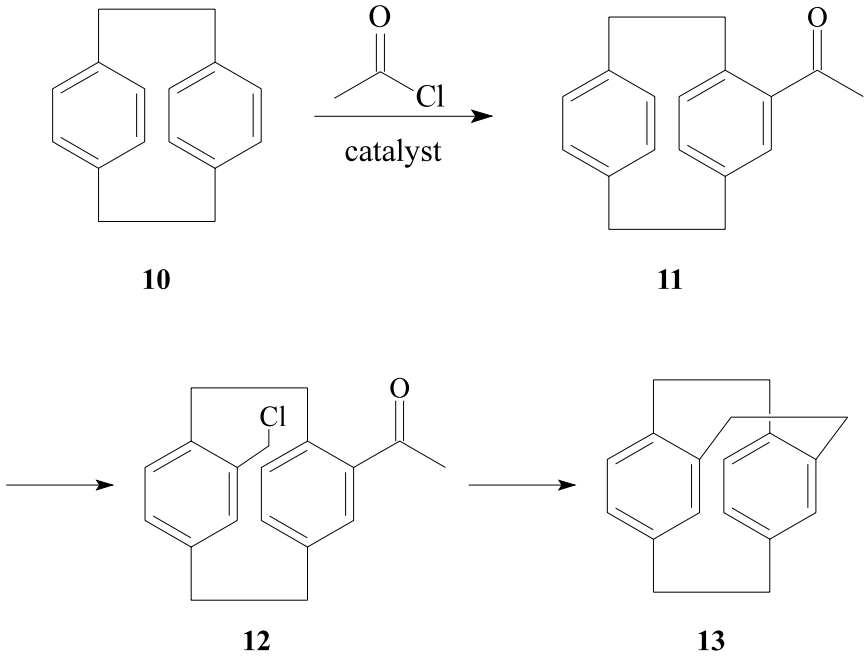
As acylating agent, a carboxylic anhydride may be used instead of the acyl halide. The reaction then yields the arylketone together with a carboxylic acid, each of which forms a complex with the Lewis acid used. The catalyst therefore has to be employed in at least twofold excess:



With a mixed anhydride two different arylketones may be formed. Reaction of a cyclic anhydride of a dicarboxylic acid, e.g. succinic anhydride, leads to formation of an arylketo acid.[2]

A carboxylic acid may also be employed directly as acylating agent, without being first converted into an acyl halide; in that case a protic acid is used as catalyst.

As an illustrating example for the application of the Friedel–Crafts acylation in the synthesis of complex molecules, its use in the synthesis of [2.2.2]cyclophane **13** by *Cram and Truesdale*[6] shall be outlined. The reaction of [2.2]paracyclophane **10** with acetyl chloride gives the acetyl-[2.2]paracyclophane **11**, which is converted into the pseudo-geminal disubstituted phane **12** by a *Blanc reaction*, and further to the triple bridge hydrocarbon **13**:



10 **11**

12 **13**

The Friedel–Crafts reaction is one of the most important reactions in organic chemistry. Nitrobenzene does not react; it may even be used as solvent. Phenols are acylated at oxygen; the phenyl ester thus obtained, can be converted into an *o*- or *p*-acylphenol by the *Fries reaction*. Many aromatic heterocycles do react; however pyridine as well as quinoline are unreactive. As catalyst a Lewis acid, e.g. $AlCl_3$, $ZnCl_2$, BF_3, SbF_5,[7] or a protic acid such as H_2SO_4, H_3PO_4 and $HClO_4$ is used. The necessity of large amounts of catalyst has been outlined above. In some cases, a Friedel–Crafts acylation can be carried out with small amounts or even without catalyst; however the application of higher temperatures is then generally required.[8]

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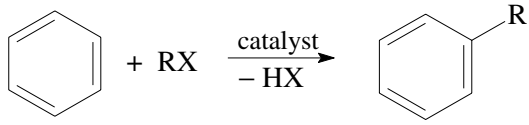
Friedel–Crafts Alkylation

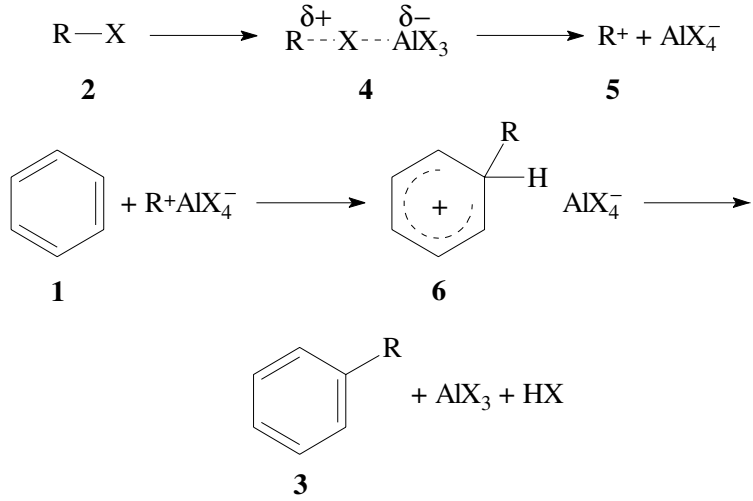
Alkylation of aromatic compounds



1 **2** **3**

The synthesis of an alkylated aromatic compound **3** by reaction of an aromatic substrate **1** with an alkyl halide **2**, catalyzed by a Lewis acid, is called the *Friedel–Crafts alkylation*.[1–4] This method is closely related to the *Friedel–Crafts acylation*. Instead of the alkyl halide, an alcohol or alkene can be used as reactant for the aromatic substrate under Friedel–Crafts conditions. The general principle is the intermediate formation of a carbenium ion species, which is capable of reacting as the electrophile in an electrophilic aromatic substitution reaction.

The initial step is the coordination of the alkyl halide **2** to the Lewis acid to give a complex **4**. The polar complex **4** can react as electrophilic agent. In cases where the group R can form a stable carbenium ion, e.g. a *tert*-butyl cation, this may then act as the electrophile instead. The extent of polarization or even cleavage of the R–X bond depends on the structure of R as well as the Lewis acid used. The addition of carbenium ion species to the aromatic reactant, e.g. benzene **1**, leads to formation of a σ-complex, e.g. the cyclohexadienyl cation **6**, from which the aromatic system is reconstituted by loss of a proton:

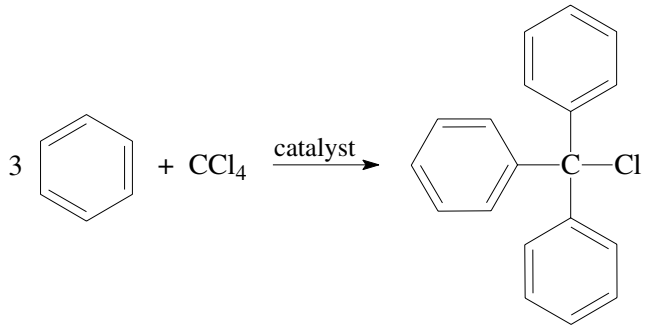


2 **4** **5**

1 **6** **3**

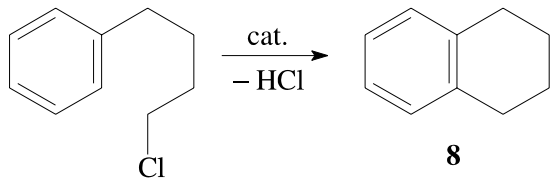
That mechanism is supported by the detection of such σ-complexes at low temperatures.[5,6] An analogous mechanism can be formulated with a polarized species **4** instead of the free carbenium ion **5**.

If the alkyl halide contains more than one, equally reactive C-halogen centers, these will generally react each with one aromatic substrate molecule. For example dichloromethane reacts with benzene to give diphenylmethane, and chloroform will give triphenylmethane. The reaction of tetrachloromethane with benzene however stops with the formation of triphenyl chloromethane **7** (trityl chloride), because further reaction is sterically hindered:



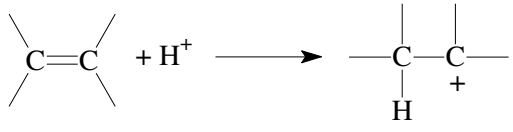
7

The intramolecular variant[3] of the Friedel–Crafts alkylation is also synthetically useful, especially for the closure of six-membered rings, e.g. the synthesis of tetraline **8**; but five- and seven-membered ring products are also accessible:

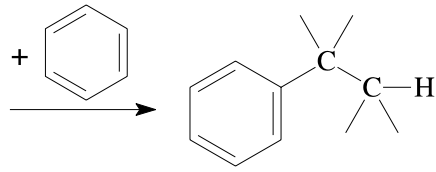


8

The alkylation with alkenes can be catalyzed by protons. The carbon–carbon double bond of the alkene is protonated according to *Markownikoff's rule*, to give a carbenium ion **10**, which then reacts by the above mechanism to yield the alkylated aromatic product **11**:



8 **10**



11

Alcohols can be converted into reactive species by reaction with a Lewis acid, e.g. $AlCl_3$, or by protonation and subsequent loss of H_2O to give a carbenium ion **12**.

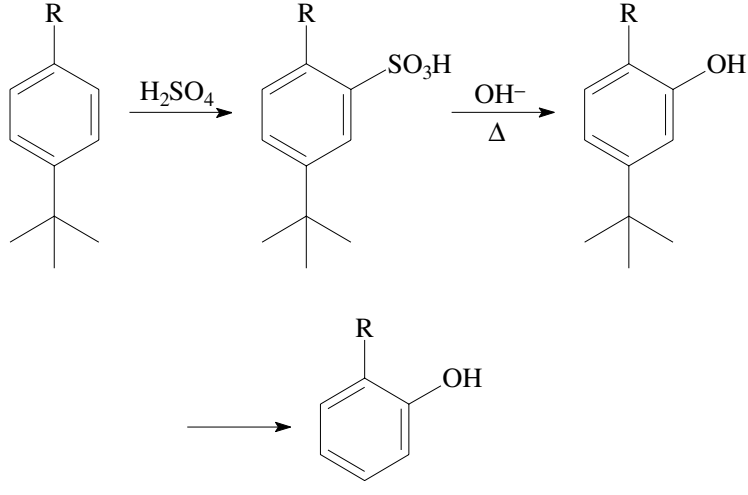
$$ROH + AlCl_3 \longrightarrow ROAlCl_2 \longrightarrow R^+ + OAlCl_2^-$$

12

$$ROH + H^+ \longrightarrow ROH_2^+ \longrightarrow R^+ + H_2O$$

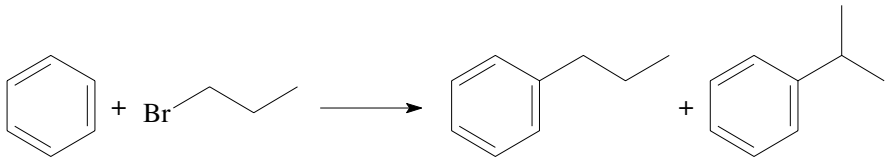
12

In contrast to the Friedel–Crafts acylation, the alkylation is a reversible reaction. That feature can be used for the regioselective synthesis of substituted aromatic derivatives.[6] The *t*-butyl group can be used as a bulky protecting group, that can be removed later. In the following example, an *ortho* substituted phenol is to be synthesized: without the *t*-butyl-group *para* to the substituent R, the usual reactivity with respect to an incoming second substituent would lead to a mixture or *ortho*- and *para*-substituted product. With the *t*-butyl group blocking the *para*-position, the sulfonation occurs *ortho* to R only. After conversion of the sulfonic acid to the phenol, and removal of the *t*-butyl group, the desired *ortho*-substituted phenol **13** is obtained:



13

The applicability of the Friedel–Crafts alkylation reaction in organic synthesis is somewhat limited for the following reasons. Due to the activating effect of an alkyl group connected to an aromatic ring, the monoalkylated reaction product is more reactive towards electrophilic substitution than the original starting material. This effect favors the formation of di- or even poly-substituted products. The scope of the reaction is limited by the reactivity of certain starting materials. Naphthalenes and related polycyclic aromatic substrates may undergo side reactions because of their high reactivity towards the catalyst, and give low yields of monoalkylated product. Many aromatic heterocycles are not suitable substrates for a Friedel–Crafts alkylation. Functional groups like $-OH$, $-NH_2$, $-OR$, that coordinate to the Lewis acid also should not be present on the aromatic ring. Another problem is the formation of rearranged products, either from reaction of rearranged carbenium ions or migration of the alkyl substituent at the aromatic ring. When benzene **1** is treated with 1-bromopropane under Friedel–Crafts conditions, the rearranged product *i*-propylbenzene (cumene) **15** is obtained as the major product, together with the expected *n*-propylbenzene **14**:



1 **14** **15**

Since the alkylation reaction is reversible, a rearrangement of the initial alkylation product can take place, resulting in a migration of the alkyl group on the aromatic ring. This can be used for the deliberate isomerization of alkylated products. Because of these complications it can be more effective to prepare an alkylated aromatic derivative by first conducting a Friedel–Crafts acylation, and then reduce the keto group to a methylene group in order to get the alkyl side chain. This route has one additional step, but avoids the drawbacks mentioned above.

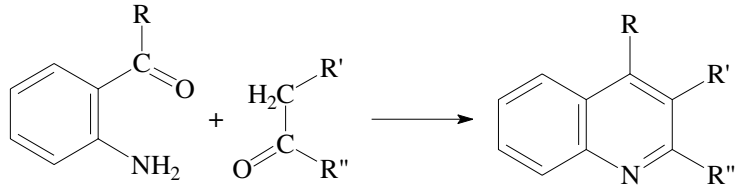
As catalysts Lewis acids such as $AlCl_3$, $TiCl_4$, SbF_5, BF_3, $ZnCl_2$ or $FeCl_3$ are used. Protic acids such as H_2SO_4 or HF are also used, especially for reaction with alkenes or alcohols. Recent developments include the use of acidic polymer resins, e.g. Nafion-H, as catalysts for Friedel–Crafts alkylations[8] and the use of asymmetric catalysts.[9]

1. C. Friedel, J. M. Crafts, *J. Chem. Soc.* **1877**, *32*, 725.
2. C. C. Price, *Org. React.* **1946**, *3*, 1–82.
3. G. A. Olah, *Friedel–Crafts and Related Reactions*, Wiley, New York, **1963–1964**, Vol. 1 and 2.
4. R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, New York, **1990**, p. 187–203.
5. G. A. Olah, S. J. Kuhn, *J. Am. Chem. Soc.* **1958**, *80*, 6541–6545.
6. F. Effenberger, *Chem. Unserer Zeit* **1979**, *13*, 87–94.
7. G. G. Yakobson, G. G. Furin, *Synthesis* **1980**, 345–364.

8. G. A. Olah, P. S. Iyer, G. K. S. Prakash, *Synthesis* **1986**, 513–531.
9. K. A. Jorgensen, *Synthesis* **2003**, 1117–1125.

Friedländer Quinoline Synthesis

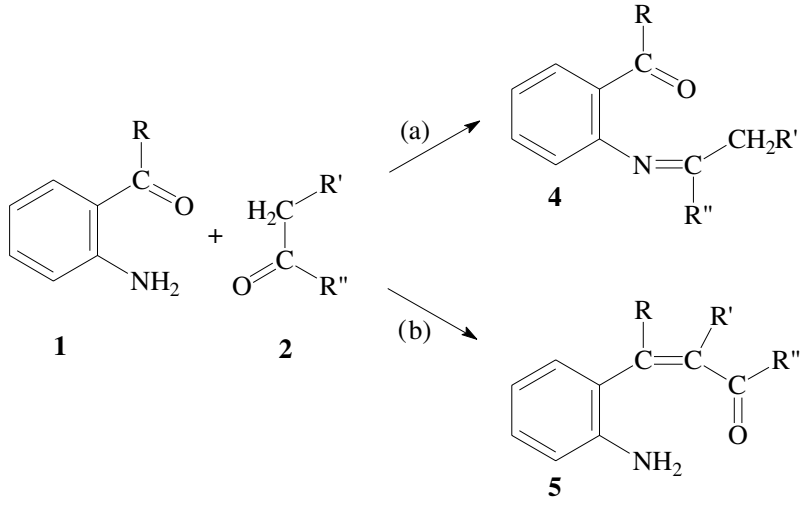
Condensation of *o*-aminobenzaldehydes with α-methylene carbonyl compounds



1 **2** **3**

Quinolines **3** can be obtained from reaction of *ortho*-aminobenzaldehydes or *o*-aminoarylketones **1** with α-methylene carbonyl compounds.[1–3] Various modified procedures are known; a related reaction is the *Skraup quinoline synthesis*.

The mechanistic pathway of the ordinary Friedländer synthesis is not rigorously known. Two steps are formulated. In a first step a condensation reaction, catalyzed by acid or base, takes place, that can lead to formation of two different types of products: (a) an imine (Schiff base) **4**, or (b) an α,β-unsaturated carbonyl compound **5**:

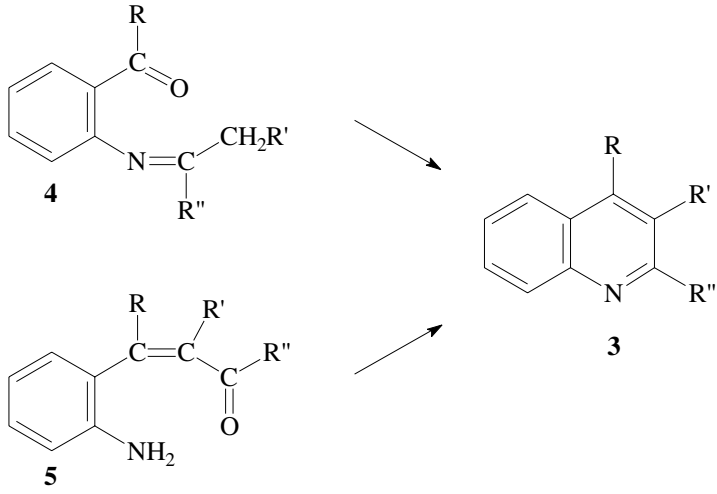


1 **2**

Although that reaction has been known for more than one hundred years, it is not clear whether the reaction proceeds *via* pathway (a) or (b) or both. Since the reaction works with a large number of different substrates and under various

reaction conditions, e.g. catalyzed by acid or base, or without a catalyst, it is likely that the actual mechanistic pathway varies with substrate and reaction conditions.[3]

The next step in both cases is a dehydrative cyclization to yield the quinoline **3**:



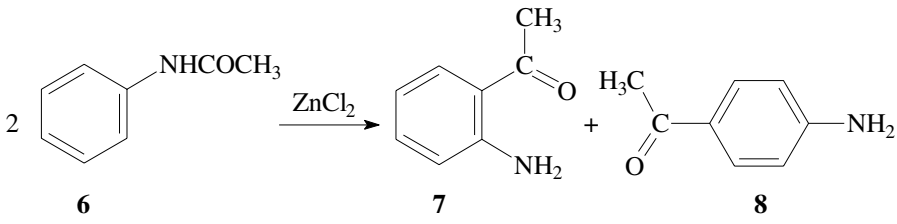
Since various substituents are tolerated, the Friedländer reaction is of preparative value for the synthesis of a large variety of quinoline derivatives. The benzene ring may bear for example alkyl, alkoxy, nitro or halogen substituents. Substituents R, R′ and R″ also are variable.[3] The reaction can be carried out with various carbonyl compounds, that contain an enolizable α-methylene group. The reactivity of that group is an important factor for a successful reaction.

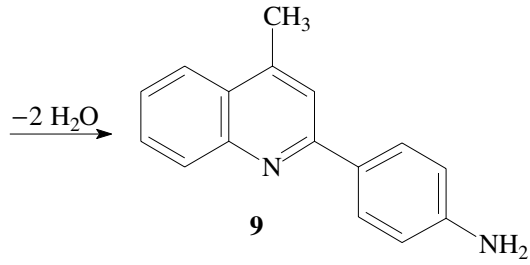
Usually the reaction is carried out in the presence of a basic catalyst, or simply by heating the reactants without solvent and catalyst.

As basic catalysts KOH, NaOH or piperidine are used. As acidic catalysts are used HCl, H_2SO_4, polyphosphoric acid or *p*-toluenesulfonic acid.

Although the uncatalyzed Friedländer reaction requires more drastic conditions, i.e. temperatures of 150–200 °C, it often gives better yields of quinolines.[3]

Certain quinolines can be prepared by heating a single suitable compound. For example acetanilide **6** rearranges upon heating in the presence of zinc chloride as catalyst, to give a mixture of *o*- and *p*-acetylaniline **7** and **8**. These two reactants then do undergo the condensation reaction to yield flavaniline **9** that has found application as a dyestuff:[4]





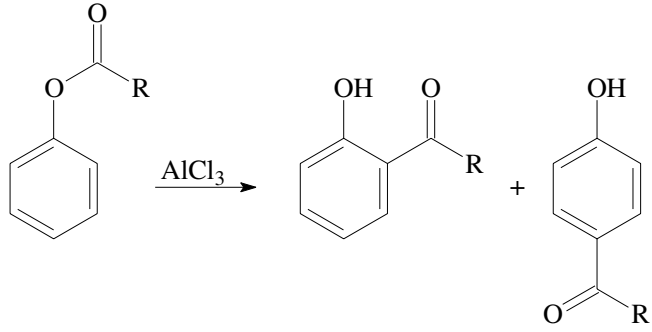
9

The Friedländer quinoline synthesis is particular useful for the preparation of 3-substituted quinolines, which are less accessible by other routes. A drawback however is the fact that the required *o*-aminobenzaldehydes or *o*-aminoarylketones are not as easy to prepare as, e.g., the anilines that are required for the Skraup synthesis.

1. P. Friedländer, *Ber. Dtsch. Chem. Ges*. **1883**, *16*, 1833–1839.
2. G. Jones, *Chem. Heterocycl. Compd*. **1977**, *32(1)*, 181–207.
3. C. Cheng, S. Yan, *Org. React*. **1982**, *28*, 37–201.
4. E. Besthorn, O. Fischer, *Ber. Dtsch. Chem. Ges*. **1883**, *16*, 68–75.

Fries Rearrangement

Acylphenols from phenyl esters



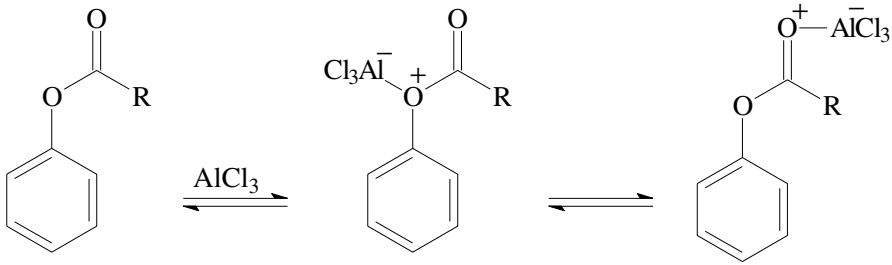
1 **2** **3**

Phenolic esters **(1)** of aliphatic and aromatic carboxylic acids, when treated with a Lewis acid as catalyst, do undergo a rearrangement reaction to yield *ortho*- and *para*-acylphenols **2** and **4** respectively. This *Fries rearrangement* reaction[1,2] is an important method for the synthesis of hydroxyaryl ketones.

The reaction mechanism[3–5] is not rigorously known. Evidence for an intramolecular pathway as well as an intermolecular pathway has been found;

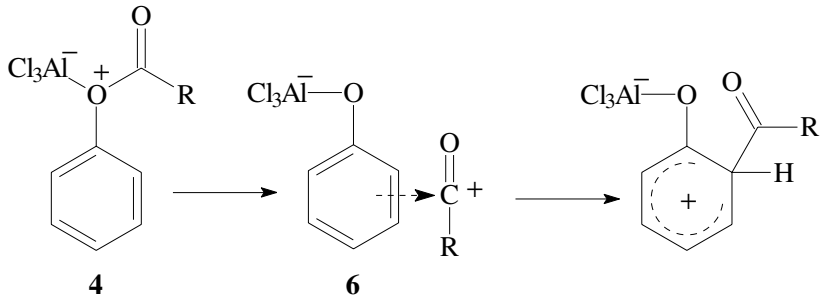
however crossover experiments did not lead to clear distinction. Results from extensive studies[3] suggest that a phenyl ester can rearrange by both pathways in the same reaction. The actual reactivity depends on substrate structure, reaction temperature, the solvent used, and the kind and concentration of Lewis acid used. Usually at least equimolar amounts of Lewis acid are employed.

The Lewis acid can coordinate to the substrate at either one of the oxygen centers, or even both when used in excess:[3]

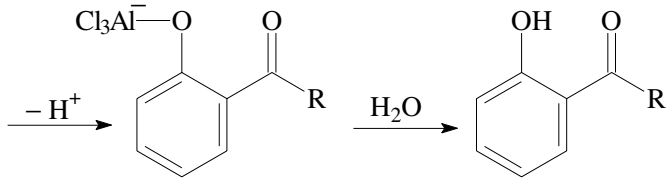


1 **4** **5**

The Lewis acid complex **4** can cleave into an ion-pair that is held together by the solvent cage, and that consists of an acylium ion and a Lewis acid-bound phenolate. A π-complex **6** is then formed, which further reacts *via* electrophilic aromatic substitution in the *ortho*- or *para*-position:



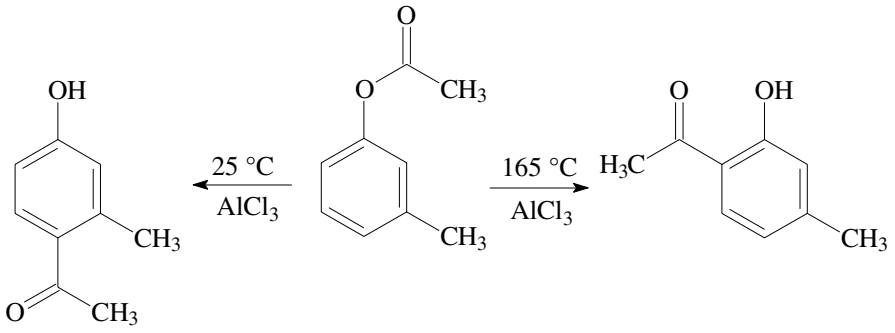
4 **6**



7 **2**

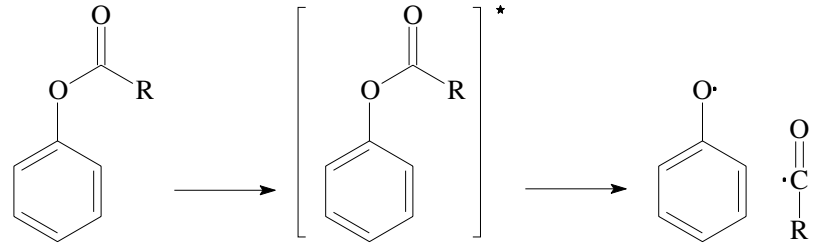
The mechanism for that step is closely related to that of the *Friedel–Crafts acylation*. Upon subsequent hydrolysis the *o*-substituted Lewis acid-coordinated phenolate **7** is converted to the free *o*-acylphenol **2**. By an analogous route, involving an electrophilic aromatic substitution *para* to the phenolate oxygen, the corresponding *para*-acylphenol is formed.

Since the Fries rearrangement is a equilibrium reaction, the reverse reaction may be used preparatively under appropriate experimental conditions.[2,6] An instructive example,[2] which shows how the regioselectivity depends on the reaction temperature, is the rearrangement of *m*-cresyl acetate **8**. At high temperatures the *ortho*-product **9** is formed, while below 100 °C the *para*-derivative **10** is formed:

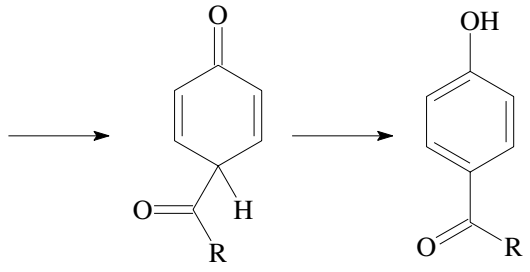


10 **8** **9**

A photochemical variant, the so-called *photo-Fries rearrangement*,[7] proceeds *via* intermediate formation of radical species. Upon irradiation the phenyl ester molecules **(1)** are promoted into an excited state **11**. By homolytic bond cleavage the radical-pair **12** is formed that reacts to the semiquinone **13**, which in turn tautomerizes to the *p*-acylphenol **3**. The corresponding *ortho*-derivative is formed in an analogous way:



1 **11** **12**



13 **3**

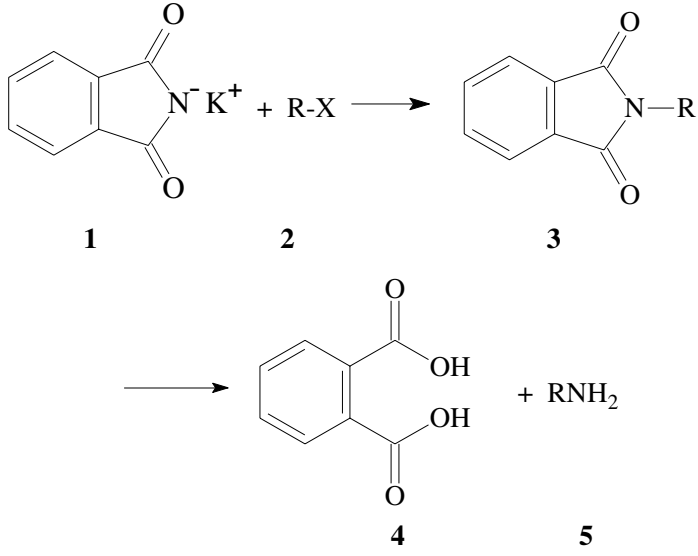
As catalysts for the Fries rearrangement reaction are for example used: aluminum halides,[3] zinc chloride, titanium tetrachloride,[8] boron trifluoride and trifluoromethanesulfonic acid.[7]

1. K. Fries, G. Finck, *Ber. Dtsch. Chem. Ges*. **1908**, *41*, 4271–4284.
2. A. H. Blatt, *Org. React*. **1942**, *1*, 342–369.
3. M. J. S. Dewar, L. S. Hart, *Tetrahedron* **1970**, *26*, 973–1000.
4. Y. Ogata, H. Tabuchi, *Tetrahedron* **1964**, *20*, 1661–1666.
5. A. Warshawsky, R. Kalir, A. Patchornik, *J. Am. Chem. Soc*. **1978**, *100*, 4544–4550.
6. F. Effenberger, R. Gutmann, *Chem. Ber*. **1982**, *115*, 1089–1102.
7. D. Bellus, P. Hrdlovic, *Chem. Rev*. **1967**, *67*, 599–609.
8. R. Martin, P. Demerseman, *Synthesis* **1989**, 25–28.

G

Gabriel Synthesis

Primary amines from *N*-substituted phthalimides



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

The reaction of potassium phthalimide **1** with an alkyl halide **2** leads to formation of a *N*-alkyl phthalimide **3**,[1,2] which can be cleaved hydrolytically or by reaction with hydrazine (*Ing–Manske* variant)[3] to yield a primary amine **5**. This route owes its importance as a synthetic method to the fact that primary amines are prepared selectively, not contaminated with secondary or tertiary amines.

The two-step procedure includes formation of a *N*-substituted phthalimide **3**, and its subsequent cleavage to the primary amine **5**. Phthalimide (which can be obtained from reaction of phthalic acid with ammonia) shows NH-acidity, since the negative charge of the phthalimide anion (the conjugated base) is stabilized

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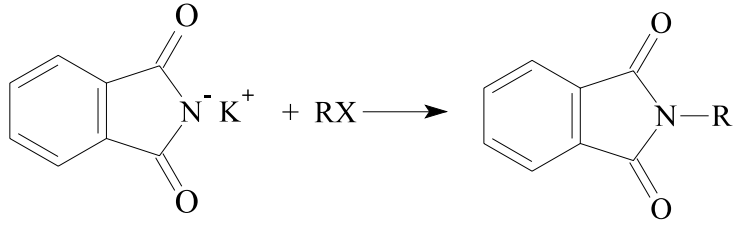
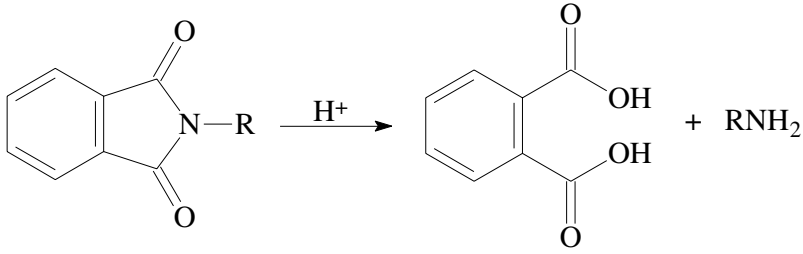
by resonance. Phthalimide is even more acidic than related 1,3-diketones, since the nitrogen center is more electronegative than carbon. The phthalimide anion acts as nucleophile in reaction with an alkyl halide; the substitution reaction is likely to proceed by a S_N2-mechanism:



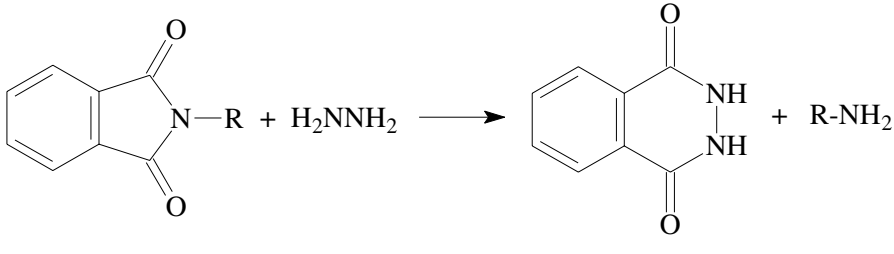
1 **2** **3**

A further alkylation of the nitrogen is not possible. In a second step the *N*-substituted phthalimide **3** is hydrolyzed to give the desired amine **5** and phthalic acid **4**:



3 **4** **5**

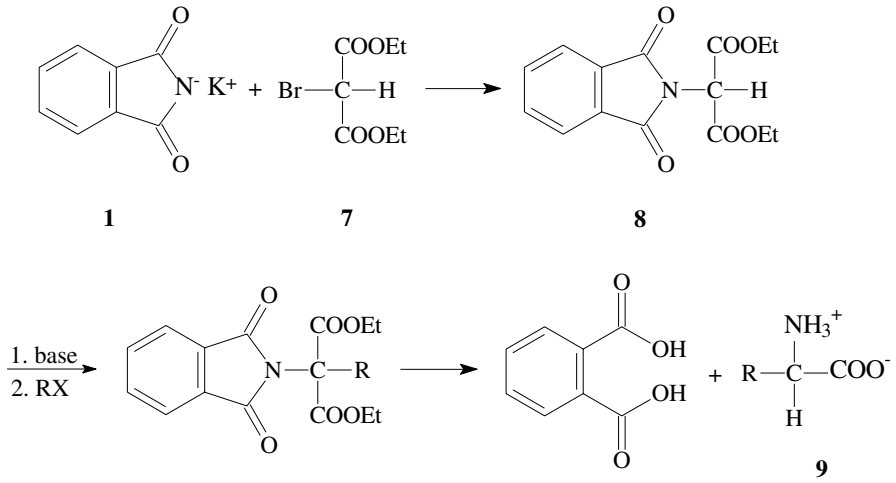
The hydrolytic cleavage is usually slow, and requires drastic reaction conditions. A more elegant method is presented by the *Ing–Manske* procedure,[3] where the *N*-alkylated imide is treated with hydrazine under milder conditions. In addition to the desired amine **5**, the cyclic phthalic hydrazide **6** is then formed:



3 **6** **5**

The Gabriel synthesis is often carried out by heating the starting materials without a solvent for several hours at a temperature of 150 °C or higher. The use of solvents like dimethylformamide can lead to better results. In a number of solvents—e.g. toluene—the phthalimide is insoluble; the reaction can however be conducted in the presence of a phase transfer catalyst.[4]

The hydrazinolysis is usually conducted in refluxing ethanol, and is a fast process in many cases. Functional groups, that would be affected under hydrolytic conditions, may be stable under hydrazinolysis conditions. The primary amine is often obtained in high yield. The Gabriel synthesis is for example recommended for the synthesis of isotopically labeled amines and amino acids.[2] α-Amino acids **9** can be prepared by the Gabriel route, if a halomalonic ester—e.g. diethyl bromomalonate **7**—is employed as the starting material instead of the alkyl halide:

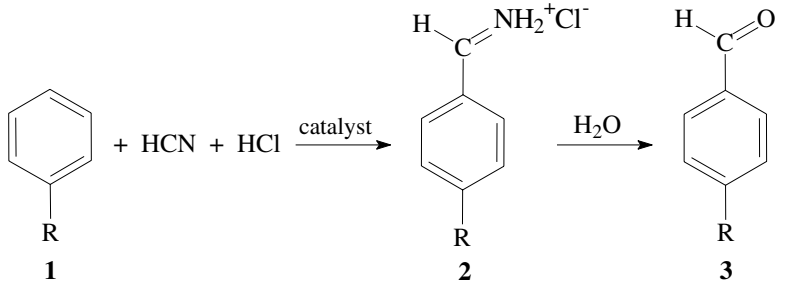


The *N*-phthalimidomalonic ester **8** can be further alkylated at the malonic carbon center with most alkyl halides, or with an α,β-unsaturated carbonyl compound; thus offering a general route to α-amino acids **9**.

1. S. Gabriel, *Ber. Dtsch. Chem. Ges*. **1887**, *20*, 2224–2236.
2. M. S. Gibson, R. W. Bradshaw, *Angew. Chem*. **1968**, *80*, 986–996; *Angew. Chem. Int. Ed. Engl*. **1968**, *7*, 919.
3. H. R. Ing, R. H. F. Manske, *J. Chem. Soc*. **1926**, 2348–2351.
4. D. Landini, F. Rolla, *Synthesis* **1976**, 389–391.

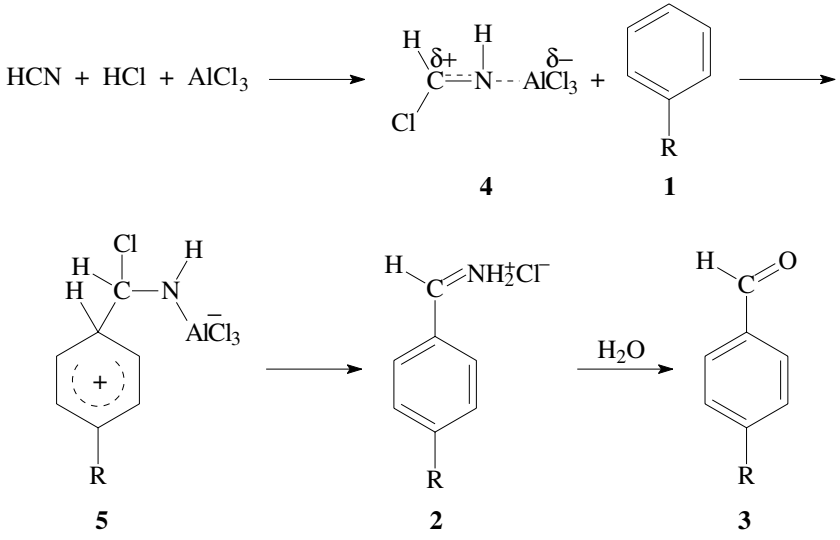
Gattermann Synthesis

Formylation of aromatic compounds



The preparation of a formyl-substituted aromatic derivative **3** from an aromatic substrate **1** by reaction with hydrogen cyanide and gaseous hydrogen chloride in the presence of a catalyst is called the *Gattermann synthesis*.[1,2] This reaction can be viewed as a special variant of the *Friedel–Crafts acylation* reaction.

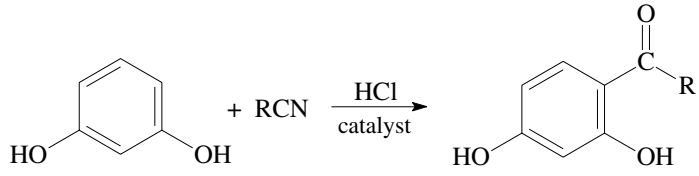
Mechanistically it is an electrophilic aromatic substitution reaction. The electrophilic species (**4**—its exact structure is not known) is generated in a reaction of hydrogen cyanide and hydrogen chloride (gas) and a Lewis acid:



The electrophile **4** adds to the aromatic ring to give a cationic intermediate **5**. Loss of a proton from **5** and concomitant rearomatization completes the substitution step. Subsequent hydrolysis of the iminium species **2** yields the formylated aromatic product **3**. Instead of the highly toxic hydrogen cyanide, zinc cyanide can be used.[3] The hydrogen cyanide is then generated *in situ* upon reaction with the hydrogen chloride. The zinc chloride, which is thereby formed, then acts as Lewis acid catalyst.

The applicability of the Gattermann synthesis is limited to electron-rich aromatic substrates, such as phenols and phenolic ethers. The introduction of the formyl group occurs preferentially *para* to the activating substituent (compare *Friedel–Crafts acylation*). If the *para*-position is already substituted, then the *ortho*-derivative will be formed.

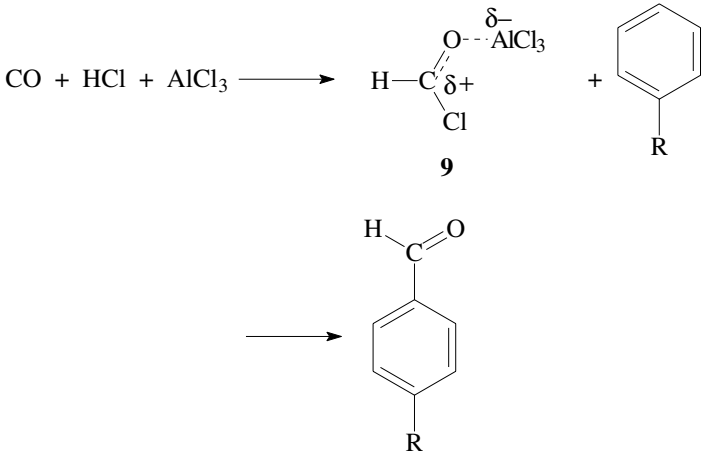
An analogous reaction is the *Houben–Hoesch reaction*,[4,5] (sometimes called the *Hoesch reaction*) using nitriles **7** to give aryl ketones **8**. This reaction also is catalyzed by Lewis acids; often zinc chloride or aluminum chloride is used. The Houben–Hoesch reaction is limited to phenols—e.g. resorcinol **6**—phenolic ethers and certain electron-rich aromatic heterocycles:[6,7]



6 **7** **8**

The synthetic importance of the Houben–Hoesch reaction is even more limited by the fact that aryl ketones are also available by application of the Friedel–Crafts acylation reaction.

Another formylation reaction, which is named after Gattermann, is the *Gattermann–Koch reaction*.[8] This is the reaction of an aromatic substrate with carbon monoxide and hydrogen chloride (gas) in the presence of a Lewis acid catalyst. Similar to the Gattermann reaction, the electrophilic agent **9** is generated, which then reacts with the aromatic substrate in an electrophilic aromatic substitution reaction to yield the formylated aromatic compound **10**:



9

10

In order to achieve high yields, the reaction usually is conducted by application of high pressure. For laboratory use, the need for high-pressure equipment, together with the toxicity of carbon monoxide, makes that reaction less practicable. The scope of that reaction is limited to benzene, alkyl substituted and certain other electron-rich aromatic compounds.[9] With mono-substituted benzenes, the *para*-formylated product is formed preferentially. Super-acidic catalysts have been developed[3], for example generated from trifluoromethanesulfonic acid, hydrogen fluoride and boron trifluoride; the application of elevated pressure is then not necessary.

While the Friedel–Crafts acylation is a general method for the preparation of aryl ketones, and of wide scope, there is no equivalently versatile reaction for the preparation of aryl aldehydes. There are various formylation procedures known, each of limited scope. In addition to the reactions outlined above, there is the *Vilsmeier reaction*, the *Reimer–Tiemann reaction*, and the *Rieche formylation reaction*.[10–12] The latter is the reaction of aromatic compounds with 1,1-dichloromethyl ether as formylating agent in the presence of a Lewis acid catalyst. This procedure has recently gained much importance.

1. L. Gattermann, *Ber. Dtsch. Chem. Ges*. **1898**, *31*, 1149–1152.
2. W. E. Truce, *Org. React*. **1957**, *9*, 37–72.
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8. L. Gattermann, J. A. Koch, *Ber. Dtsch. Chem. Ges*. **1897**, *30*, 1622–1624.
9. N. N. Cronnse, *Org. React*. **1949**, *5*, 290–300.
10. A. Rieche, H. Gross, E. Höft, *Chem. Ber*. **1960**, *93*, 88–94.
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12. G. Simchen, *Methoden Org. Chem. (Houben-Weyl)* **1983**, Vol. E3, p. 19–27.

Glaser Coupling Reaction

Coupling of terminal alkynes

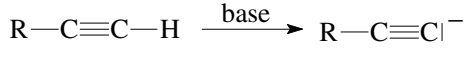
$$2\ \mathrm{R{-}C{\equiv}C{-}H} \xrightarrow[\text{base}]{\text{catalyst}} \mathrm{R{-}C{\equiv}C{-}C{\equiv}C{-}R}$$

1 **2**

The *Glaser reaction*[1,2] is an oxidative coupling of terminal alkynes **1** to yield a symmetrical *bis*-acetylene **2**; the coupling step is catalyzed by a copper salt. Closely related is the *Eglinton reaction*,[3] which differs from the Glaser reaction mainly by the use of stoichiometric amounts of copper salt as oxidizing agent.

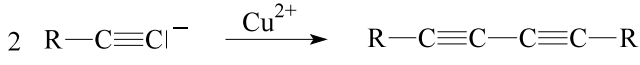
Acetylene and terminal alkynes are CH-acidic compounds; the proton at the carbon–carbon triple bond can be abstracted by a suitable base. Such a deprotonation is the initial step of the Glaser reaction as well as the Eglinton

reaction. Both reactions proceed by very similar mechanisms; therefore only one is outlined in the following:[4,5]



1 **3**

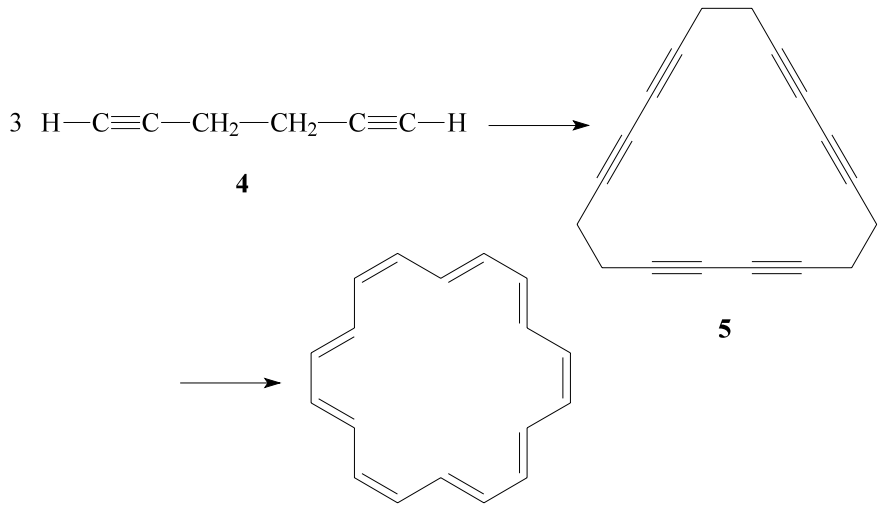
The acetylide anion **3** is likely to form an alkynyl-copper complex by reaction with the cupric salt. By electron transfer the copper-II ion is reduced, while the acetylenic ligands dimerize to yield the *bis*-acetylene **2**:



3 **2**

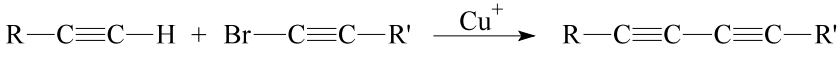
The Glaser coupling reaction is carried out in aqueous ammonia or an alcohol/ammonia solution in the presence of catalytic amounts of a copper-I salt. The required copper-II species for reaction with the acetylide anion $R-C\equiv C^-$ are generated by reaction with an oxidant—usually molecular oxygen. For the Eglinton procedure, equimolar amounts of a copper-II salt are used in the presence of pyridine as base.

The Glaser reaction and the Eglinton reaction are well suited for the preparation of cyclic oligo-ynes.[6] This has been used by Sondheimer and coworkers in the synthesis of annulenes.[7] For example the 1,5-hexadiyne **5** under Glaser conditions gave a trimeric coupling product—the cyclic *hexa*-yne **6**—together with other oligomers. Product **6** was then converted to the [18]annulene **7**:



4 **5** **6**

The two reactions described above can be applied for the synthesis of symmetrical *bis*-acetylenes only. Unsymmetrical bis-acetylenes can be prepared by using the *Cadiot–Chodkiewicz reaction*.[8,9] For that method a terminal alkyne **1** is reacted with a bromoalkyne **8** in the presence of a copper catalyst, to yield an unsymmetrical coupling product **9**:



1 **7** **8**

All three coupling procedures are suitable to give high yields under mild reaction conditions. Many functional groups do not interfere. For the application in organic synthesis the Eglinton variant may be more convenient than the Glaser method; a drawback however is the need for stoichiometric amounts of copper salt.

1. C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422–424.
2. L. I. Simandi in *The Chemistry of Triple-Bonded Functional Groups, Supp. C* (Ed.: S. Patai, Z. Rappoport), Wiley, New York, **1983**, Vol. 1, p. 529–534.
3. L. G. Fedenok, V. M. Berdnikov, M. S. Shvartsberg, *J. Org. Chem. USSR* **1973**, **9**, 1806–1809.
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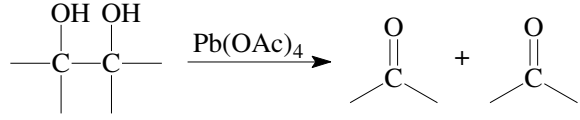
5. A. A. Clifford, W. A. Waters, *J. Chem. Soc.* **1963**, 3056–3062.
6. N. Nakagawa in *The Chemistry of the Carbon-Carbon Triple Bond* (Ed.: S. Patai), Wiley, New York, **1978**, Vol. 2, p. 654–656.
   F. Diederick, *J. Chem. Soc., Chem. Commun.* **2001**, 219–227.
7. F. Sondheimer, R. Wolovsky, *J. Am. Chem. Soc.* **1962**, *84*, 260–269.
8. W. Chodkiewicz, *Ann. Chim. (Paris)* **1957**, *13/2*, 819–869.
9. N. Ghose, D. R. M. Walton, *Synthesis* **1974**, 890–891.

Glycol Cleavage

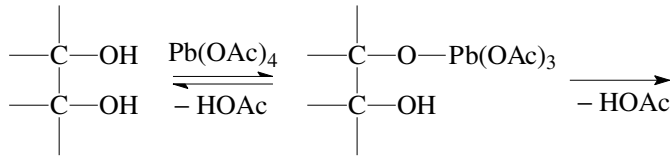
Oxidative cleavage of vicinal diols



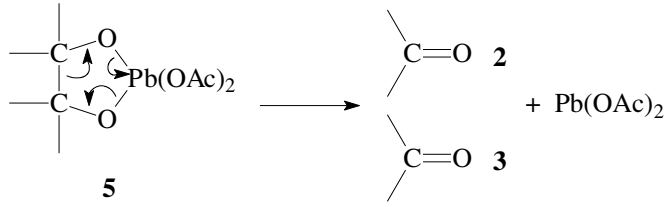
1 **2** **3**

The oxidative cleavage of the central carbon–carbon bond in a vicinal diol **1**, by reaction with lead tetraacetate or periodic acid, yields two carbonyl compounds **2** and **3** as products.

Lead tetraacetate $Pb(OAc)_4$ reacts with one of the hydroxyl groups to give an intermediate lead compound **4** and acetic acid. The rate determining step is the formation of a five-membered ring product **5** by further loss of acetic acid. Ring opening by carbon–carbon bond cleavage affords the carbonyl compounds **2** and **3**, together with lead-II-acetate:

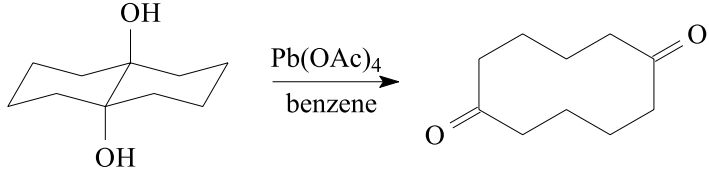


1 **4**



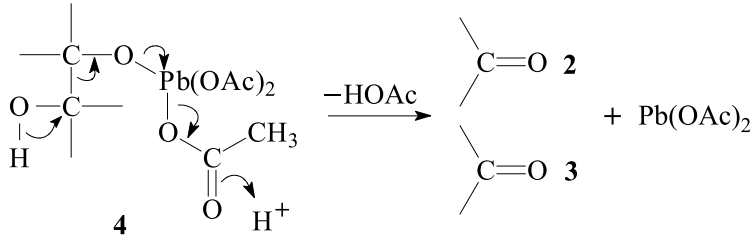
5

This mechanism applies to cis-1,2-diols and to open-chain 1,2-diols that can arrange in cisoid conformation. *Trans*-1,2-diols also do undergo the cleavage reaction, but at considerably lower rate, and by a different mechanism.



6

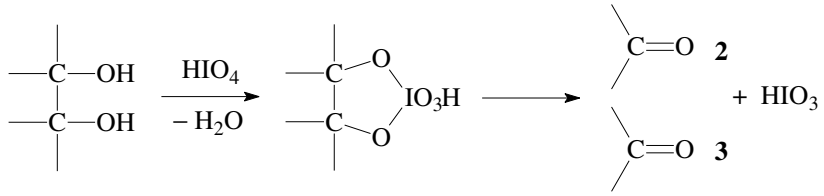
For the latter case an acid-catalyzed decomposition of intermediate **4** is assumed to give the carbonyl products **2** and **3**, or a diketone as shown above, without going through a cyclic intermediate:



4

Under basic conditions, the cleavage would be initiated by deprotonation of a free hydroxyl group, as shown in **4**.

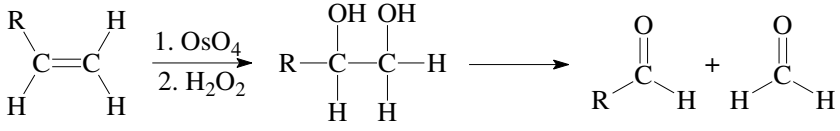
The cleavage of 1,2-diols **1** by periodic acid is associated with the name of the French chemist *Malaprade*.[4] The reaction mechanism[5,6] is related to that outlined above, and is likely to involve a five-membered ring periodate ester intermediate **7**:



1 **7**

Lead tetraacetate and periodic acid complement one another in their applicability as reagents for glycol cleavage. The water sensitive lead tetraacetate is used in organic solvents, while periodic acid can be used for cleavage of water-soluble diols in aqueous medium.

The carbon–carbon double bond of an alkene **8** can be cleaved oxidatively, by a dihydroxylation reaction-glycol cleavage sequence:



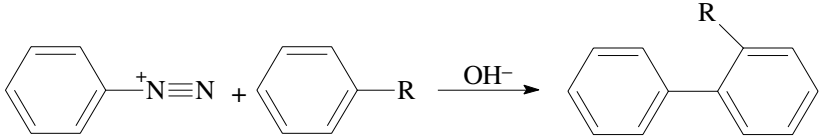
8

This two-step sequence is a valuable alternative to the direct double bond cleavage by *ozonolysis*.

1. R. Criegee, L. Kraft, B. Rank, *Justus Liebigs Ann. Chem.* **1933**, *507*, 159–197.
2. R. Criegee, E. Höger, G. Huber, P. Kruck, F. Marktscheffel, H. Schellenberger, *Justus Liebigs Ann. Chem.* **1956**, *599*, 81–125.
3. G. M. Rubottom in *Oxidation in Organic Chemistry* (Ed.: W. S. Trahanovsky), Academic Press, New York, **1982**, p. 27–37.
4. M. L. Malaprade, *Bull. Soc. Chim. France* **1928**, *43*, 683–696.
5. E. J. Jackson, *Org. React.* **1944**, *2*, 341–375.
6. B. Sklarz, *Q. Rev. Chem. Soc.* **1967**, *21*, 3–28.

Gomberg–Bachmann Reaction

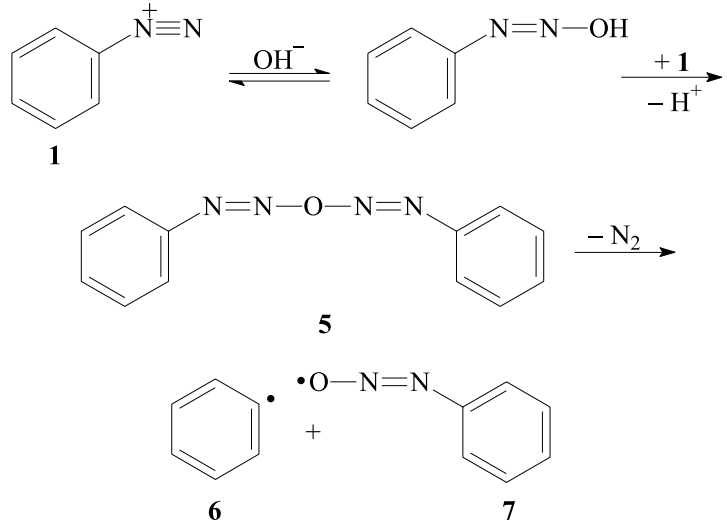
Synthesis of biaryls



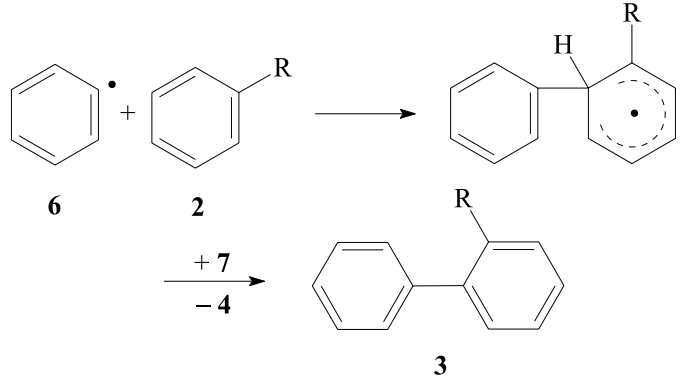
1 **2** **3**

Arenediazonium species **1** can be reacted with another aromatic substrate **2**, by the *Gomberg–Bachmann* procedure,[1,2] to yield biaryl compounds **3**. The intramolecular variant is called the *Pschorr reaction*.[3]

An arenediazonium ion **1** in aqueous alkaline solution is in equilibrium with the corresponding diazohydroxide **4**.[4] The latter can upon deprotonation react with diazonium ion **1**, to give the so-called 'anhydride' **5**. An intermediate product **5** can decompose to a phenyl radical **6** and the phenyldiazoxy radical **7**, and molecular nitrogen. Evidence for an intermediate diazoanhydride **5** came from crossover experiments:[4]



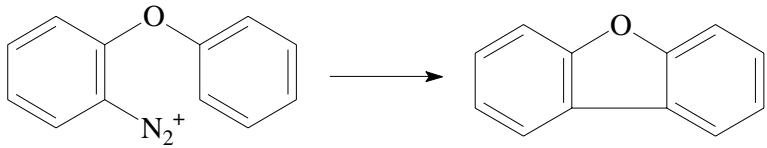
The very reactive phenyl radical reacts with the aromatic substrate **2**, present in the reaction mixture. Subsequent loss of a hydrogen radical, which then combines with **7** to give **4**, yields a biaryl coupling product; e.g. the unsymmetrical biphenyl derivative **3**:



With a substituted aromatic ring compound **2**, mixtures of isomeric coupling products may be formed; the *ortho*-product usually predominates. The rules for regiochemical preferences as known from electrophilic aromatic substitution reactions (see for example *Friedel–Crafts acylation*), do not apply here.

Symmetrical biphenyls are also accessible by that procedure, but can often be prepared more conveniently by other routes.

In contrast to the Gomberg–Bachmann reaction, the intramolecular variant, the Pschorr reaction,[5] is carried out in strongly acidic solution, and in the presence of copper powder. Diazonium biphenyl ethers are converted to dibenzofurans, e.g. **8** → **9**:[3]



8 **9**

The Pschorr reaction also works with substrates containing a bridge other than oxygen. Thus various tricyclic products containing a biaryl subunit are accessible, e.g. carbazoles and fluorenes.

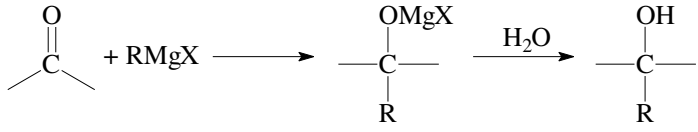
When the arenediazonium compound **1** is treated with sodium acetate, instead of alkali hydroxide, the reaction proceeds *via* an intermediate nitroso compound, and is called the *Hey reaction*.[6,7]

The Gomberg–Bachmann reaction is usually conducted in a two-phase system, an aqueous alkaline solution, that also contains the arenediazonium salt, and an organic layer containing the other aromatic reactant. Yields can be improved by use of a phase transfer catalyst.[8] Otherwise yields often are below 40%, due to various side reactions taking place. The Pschorr reaction generally gives better yields.

1. M. Gomberg, W. E. Bachmann, *J. Am. Chem. Soc*. **1924**, *46*, 2339–2343.
2. R. Bolton, G. Williams, *Chem. Soc. Rev*. **1986**, *15*, 261–289.
3. D. F. DeTar, *Org. React*. **1957**, *9*, 409–462.
4. C. Rüchardt, E. Merz, *Tetrahedron Lett*. **1964**, 2431–2436.
5. R. Pschorr, *Ber. Dtsch. Chem. Ges*. **1896**, *29*, 496–501.
6. J. Elks, J. W. Haworth, P. H. Hey, *J. Chem. Soc*. **1940**, 1284–1286.
7. D. R. Augood, G. H. Williams, *Chem. Rev*. **1957**, *57*, 123–190.
8. J. R. Beadle, S. H. Korzeniowski, D. E. Rosenberg, B. J. Garcia-Slanga, G. W. Gokel, *J. Org. Chem*. **1984**, *49*, 1594–1603.

Grignard Reaction

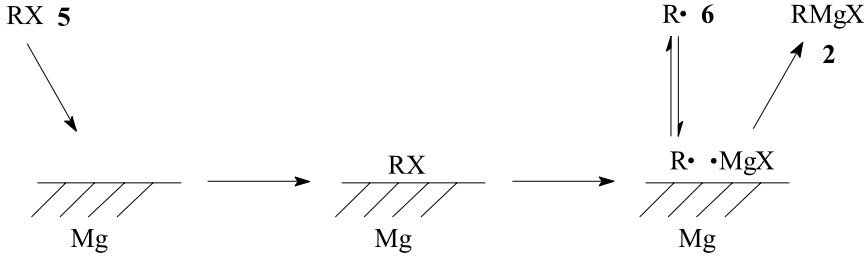
Addition of organomagnesium compounds to polarized multiple bonds



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

Organomagnesium compounds of the general structure RMgX **(2)** can be prepared by reaction of an alkyl or aryl halide RX with magnesium metal, and are called Grignard reagents. Such a reagent can add to a polarized double or triple bond in the so-called *Grignard reaction*.[1,2] Suitable reactants for this versatile reaction are for example aldehydes, ketones, esters, nitriles, carbon dioxide and other substrates containing polar functional groups such as C=N−, C=S, S=O, N=O. Most common and of synthetic importance is the reaction of a carbonyl compound **1**, to give a magnesium alkoxide **3**, which yields an alcohol **4** upon hydrolytic workup.

Grignard reagents are a very important class of organometallic compounds. For their preparation an alkyl halide or aryl halide **5** is reacted with magnesium metal. The formation of the organometallic species takes place at the metal surface; by transfer of an electron from magnesium to a halide molecule, an alkyl or aryl radical species **6** respectively is formed. Whether the intermediate radical species stays adsorbed at the metal surface (the *A-model*)[3], or desorbs into solution (the *D-model*)[4], still is in debate:

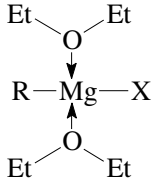


At the metal surface, the radical species R• and •MgX combine to form the Grignard reagent **2**, which subsequently desorbs from the surface into solution. Macroscopically, the overall process is observed as a continuous decrease of the amount of magnesium metal.

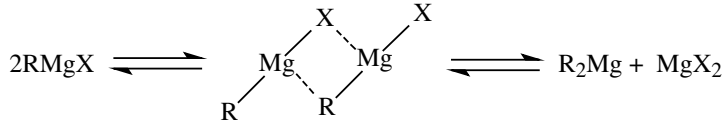
In the alkyl halide **5**, the carbon–halogen bond is polarized, because of the higher electronegativity of the halogen. The carbon center next to the halogen has a formal $\delta+$ charge, and is electrophilic in its reactivity. In the Grignard reagent **2** however, the polarization is reversed; the carbon center next to the magnesium is carbanionic in nature; it has a formal $\delta-$ charge, and reacts as a nucleophile. This reversal of reactivity is called *Umpolung*.[12]

Since the formation of the Grignard compound takes place at the metal surface, a metal oxide layer deactivates the metal, and prevents the reaction from starting. Such an unreactive metal surface can be activated for instance by the addition of small amounts of iodine or bromine.

The solvent used plays an important role, since it can stabilize the organomagnesium species through complexation. Nucleophilic solvents such as ethers—e.g. diethyl ether or tetrahydrofuran—are especially useful. The magnesium center gets coordinated by two ether molecules as ligands.



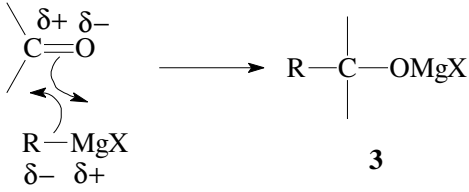
In a nucleophilic solvent, the organomagnesium species not only exists as RMgX, but is rather described by the *Schlenk equilibrium*:



2

In addition dimeric species are formed, being in equilibrium with the monomeric RMgX. The Schlenk equilibrium is influenced by substrate structure, the nature of the solvent, concentration and temperature.

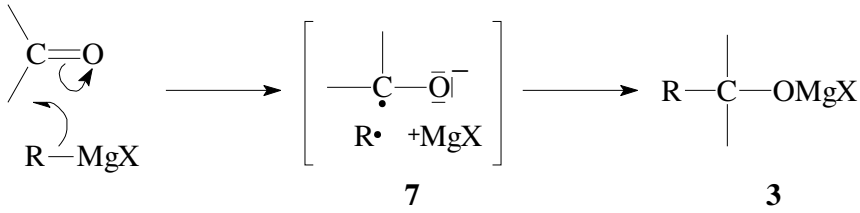
The many diverse Grignard reactions, resulting from possible substrates and reaction conditions, cannot be described by a uniform reaction mechanism. The reaction of a ketone **1** with a Grignard reagent can be rationalized by a polar mechanism, as well as a *radical* mechanism.[5,6] The polar mechanism is formulated as the transfer of the group R together with the binding electron pair onto the carbonyl carbon center, and the formation of a magnesium–oxygen bond. The overall result is the formation of the magnesium alkoxide **3** of a tertiary alcohol:



3

An alternative radical mechanism is formulated as the transfer of a single electron from the Grignard reagent **2** onto the carbonyl group (single electron transfer

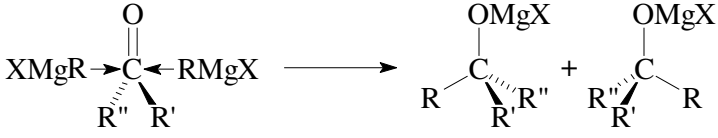
mechanism —*SET mechanism*). The intermediate pair of radicals **7** then combines to form product **3**:



7 **3**

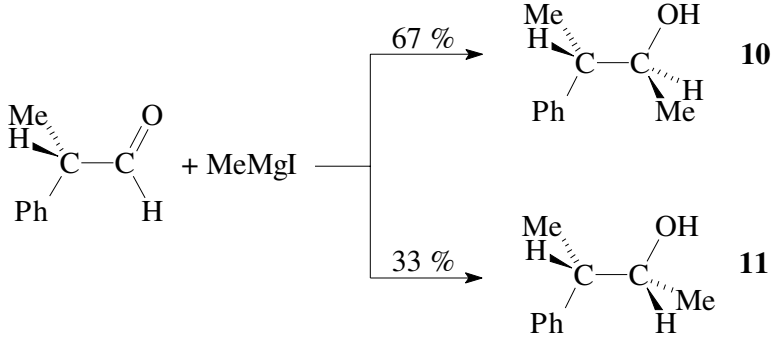
The actual mechanism by which a particular reaction proceeds strongly depends on the nature of the organomagnesium reagent. For instance benzophenone reacts with methylmagnesium bromide by a polar mechanism, while the reaction with *t*-butylmagnesium chloride proceeds for steric reasons by a SET-mechanism.

The carbonyl carbon of an unsymmetrical ketone is a prochiral center; reaction with a Grignard reagent **2** ($R \neq R', R''$) can take place on either face of the carbonyl group with equal chance. The products **8a** and **8b** are consequently formed in equal amounts as racemic mixture, as long as no asymmetric induction becomes effective:[7]



1 **8a** **8b**

By treatment of a racemic mixture of an aldehyde or ketone that contains a chiral center—e.g. 2-phenylpropanal **9**—with an achiral Grignard reagent, four stereoisomeric products can be obtained; the diastereomers **10** and **11** and the respective enantiomer of each.



By application of *Cram's rule* or a more recent model on the reactivity of α-chiral aldehydes or ketones,[8] a prediction can be made, which stereoisomer will be formed predominantly, if the reaction generates an additional chiral center.

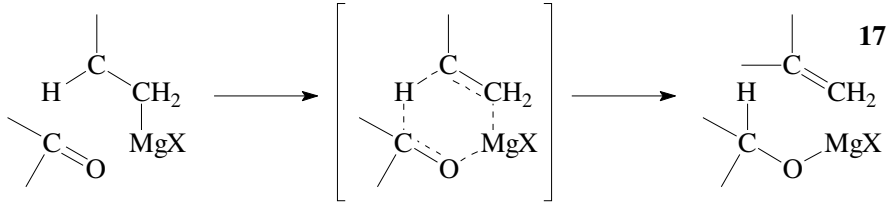
With compounds that contain acidic hydrogens—e.g. water, alcohols, phenols, enols, carboxylic acids, primary or secondary amines—the Grignard reagent RMgX reacts to give the corresponding hydrocarbon RH. For that reason, a Grignard reaction must be run in dry solvent, and by strictly excluding moisture. Grignard reagents also react with molecular oxygen present in the reaction mixture, resulting in a lower yield of the desired product. Solvolysis with D_2O can be used to introduce a deuterium atom selectively at a particular carbon center.

$$\mathrm{RMgX} \xrightarrow{\mathrm{D_2O}} \mathrm{RD}$$

The acidity of certain reactants can be used for an exchange of the group R in a Grignard reagent RMgX. For example the alkyne **12** reacts with a Grignard compound **2** to give the alkynylmagnesium derivative **13** and the less acidic hydrocarbon **14**:

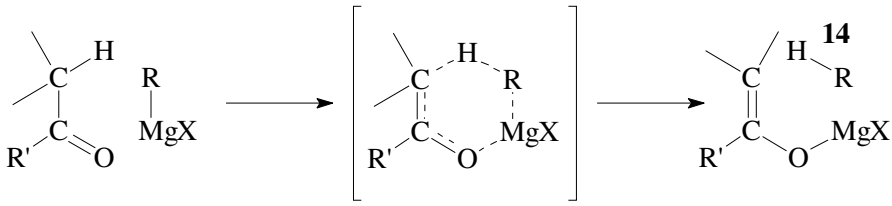
$$\underset{\mathbf{12}}{\mathrm{R'{-}C{\equiv}C{-}H}} + \underset{\mathbf{2}}{\mathrm{RMgX}} \longrightarrow \underset{\mathbf{13}}{\mathrm{R'{-}C{\equiv}C{-}MgX}} + \underset{\mathbf{14}}{\mathrm{RH}}$$

Grignard reagents that contain a β-hydrogen—e.g. **15**—can reduce a carbonyl substrate by transfer of that hydrogen as a side-reaction. The so-called *Grignard reduction* is likely to proceed *via* a six-membered cyclic transition state **16**; the alkyl group of alkylmagnesium compound **15** is thereby converted into an alkene **17**.



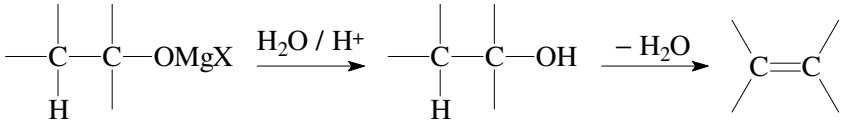
1 **15** **16**

Another side-reaction can be observed with sterically hindered ketones that contain an α-hydrogen—e.g. **18**. By transfer of that hydrogen onto the group R of RMgX **2**, the ketone **18** is converted into the corresponding magnesium enolate **19**, and the hydrocarbon RH **14** is liberated:



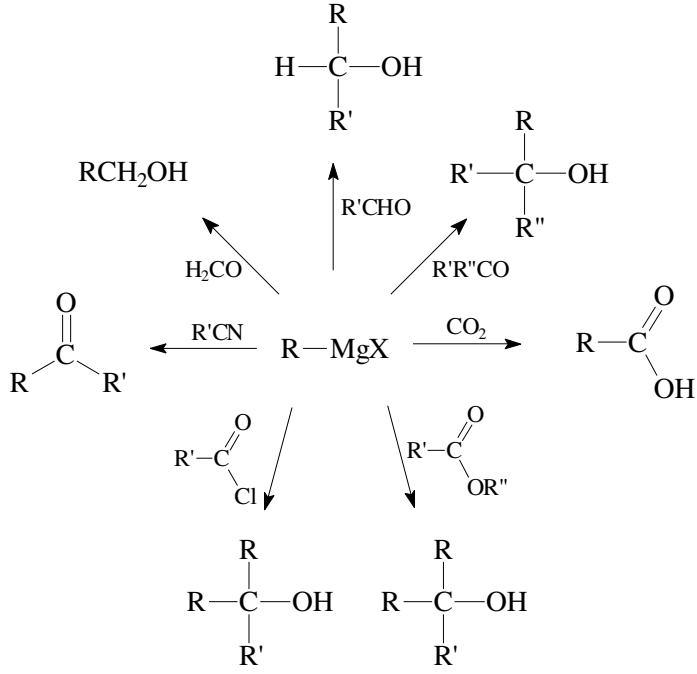
18 **2** **19**

Tertiary magnesium alkoxides **20**, bearing a β-hydrogen, may undergo a dehydration reaction upon acidic workup, and thus yield an alkene **21**:

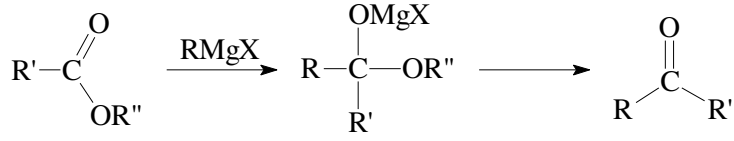


20 **21**

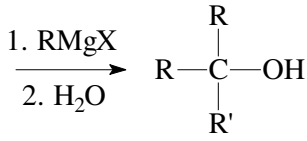
Grignard reagents can react as nucleophiles with a large variety of carbonyl substrates; in the following scheme the products obtained after a hydrolytic workup are shown. The scheme gives an impression of the versatility of the Grignard reaction:



The conversion of a nitrile R′−CN into a ketone R′−CO−R demonstrates that polarized multiple bonds other than C=O also react with Grignard reagents, and that such reactions are synthetically useful. Esters **22** and acid chlorides can react subsequently with two equivalents of RMgX: the initially formed tetravalent product from the first addition reaction can decompose to a ketone that is still reactive, and reacts with a second RMgX. The final product **23** then contains two substituents R, coming from the Grignard reagent:

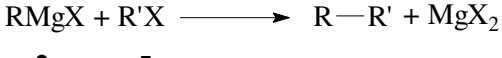


22



23

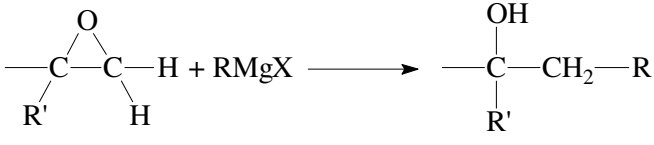
Another type of Grignard reaction is the alkylation with alkyl halides.[9] Upon treatment of a Grignard reagent RMgX with an alkyl halide **5**, a *Wurtz*-like coupling reaction takes place.



2 **5**

This reaction can be used for the synthesis of hydrocarbons; but it may also take place as a side-reaction during generation of a Grignard reagent from an alkyl halide and magnesium, then leading to formation of undesired side-products.

Grignard reagents do react with epoxides **24** by an S_N2-mechanism, resulting in a ring-opening reaction. An epoxide carbon bearing no additional substituent—i.e. a methylene group—is more reactive towards nucleophilic attack than a substituted one:



24

The Grignard reaction is one of the most important reactions in organic chemistry, because of its versatility in carbon–carbon bond formation. For some of the Grignard reactions mentioned above, alternative procedures using organolithium compounds have been developed, and may give better results. The formation of Grignard reagents from slow reacting alkyl or aryl halides has been made possible by recently developed modified procedures like the application of ultrasound,[10] or variants using activated magnesium.[11]

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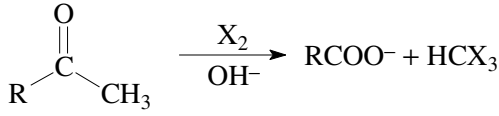
H

Haloform Reaction

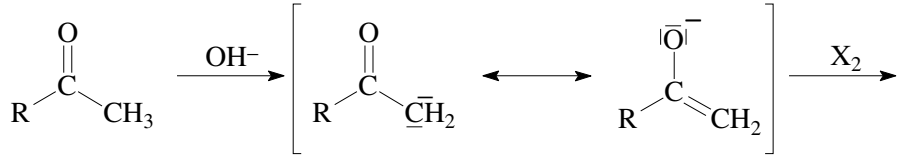
Oxidative cleavage of methyl ketones



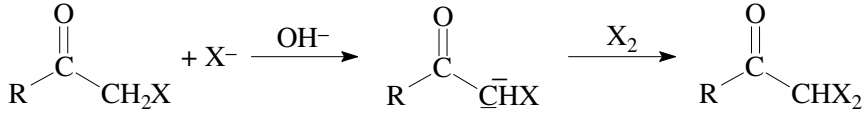
1 **2** **3**

Methyl ketones **1**, as well as acetaldehyde, are cleaved into a carboxylate anion **2** and a trihalomethane **3** (a haloform) by the *Haloform reaction*.[1,2] The respective halogen can be chlorine, bromine or iodine.

The methyl group of a methyl ketone is converted into an α,α,α-trihalomethyl group by three subsequent analogous halogenation steps, that involve formation of an intermediate enolate anion **(4–6)** by deprotonation in alkaline solution, and introduction of one halogen atom in each step by reaction with the halogen. A



1 **4**



5

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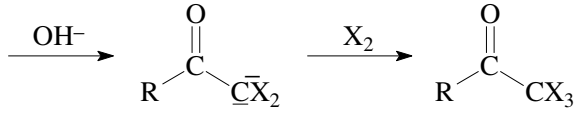
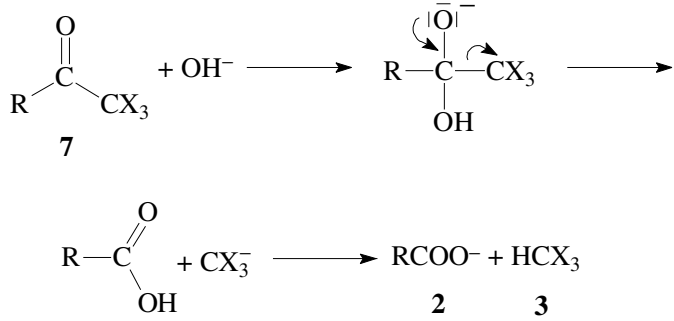
halogen substituent α to the carbonyl group makes an adjacent hydrogen more acidic, and further halogenation will take place at the same carbon center:



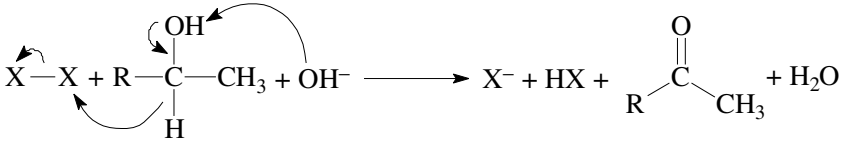
6 **7**

The α,α,α-trihaloketone **7** can further react with the hydroxide present in the reaction mixture. The hydroxide anion adds as a nucleophile to the carbonyl carbon; the tetravalent intermediate suffers a carbon–carbon bond cleavage:[3]



7 **2** **3**

The reaction also works with primary and secondary methyl carbinols **8**. Those starting materials are first oxidized under the reaction conditions to the corresponding carbonyl compound **1**:



8 **1**

With ketones bearing α'-hydrogens, a halogenation at that position is a possible side-reaction, and may lead to cleavage of the substrate.[2]

Fluorine cannot be used, although trifluoroketones can be cleaved into carboxylate and trifluoromethane. The haloform reaction can be conducted under mild conditions—at temperatures ranging from 0–10 °C—in good yields; even a sensitive starting material like methylvinylketone can be converted into acrylic acid in good yield.

Besides its synthetic importance, the haloform reaction is also used to test for the presence of a methylketone function or a methylcarbinol function in a molecule. Such compounds will upon treatment with iodine and an alkali

hydroxide lead to formation of iodoform (*iodoform test*). The iodoform is easily identified by its yellow colour, its characteristic odour and the melting point.

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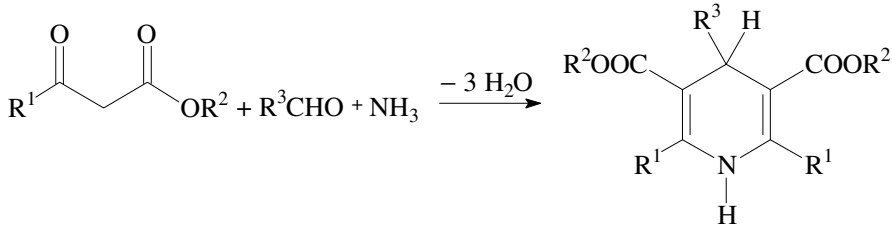
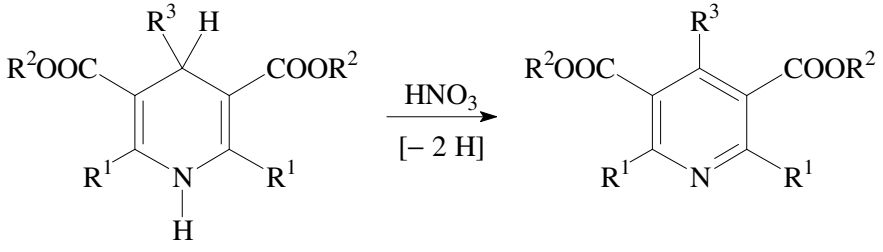
Hantzsch Pyridine Synthesis

1,4-Dihydropyridines from condensation of β-ketoesters with aldehydes and ammonia



1 **2** **3**

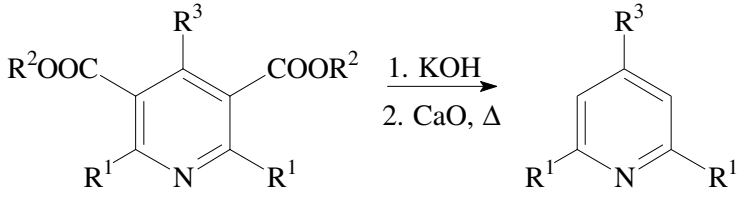
A general method for the construction of a pyridine ring is the *Hantzsch synthesis*.[1–4] A condensation reaction of two equivalents of a β-ketoester **1** with an aldehyde **2** and ammonia leads to a 1,4-dihydropyridine **3**, which can be oxidized to the corresponding pyridine **4**—for example by nitric acid:



3 **4**

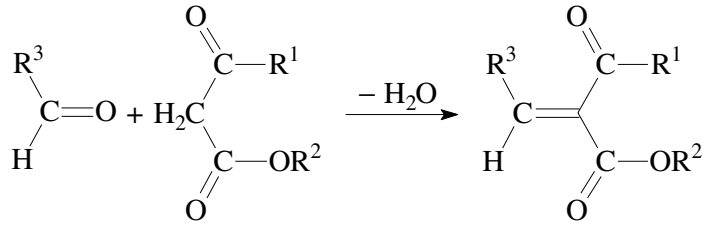
In general the oxidation does not affect the substituent R^3 at C-4; however if R^3 is a benzyl group $PhCh_2-$, this will be cleaved from C-4, and a hydrogen is retained in that position (unusual oxidation to yield pyridine).

The classical synthesis started from acetoacetic ester (**1**, $R^1 = CH_3$, $R^2 = C_2H_5$) and acetaldehyde (**2**, $R^3 = CH_3$). By subsequent cleavage of the substituents from C-3 and C-5, the collidine **5** was obtained ($R^1 = R^3 = CH_3$):[1]



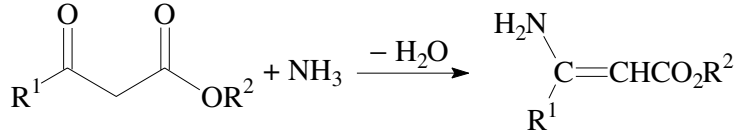
4 **5**

The initial step of the Hantzsch synthesis is likely to be a *Knoevenagel condensation* reaction of aldehyde **2** and β-ketoester **1** to give the α,β-unsaturated ketoester **6**:



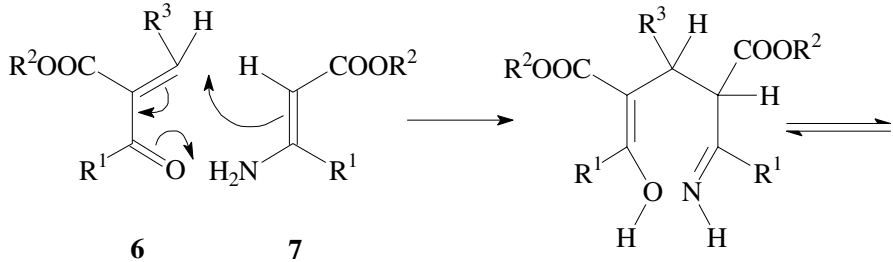
2 **1** **6**

From β-ketoester **1** and ammonia the enamine **7** and water is formed:

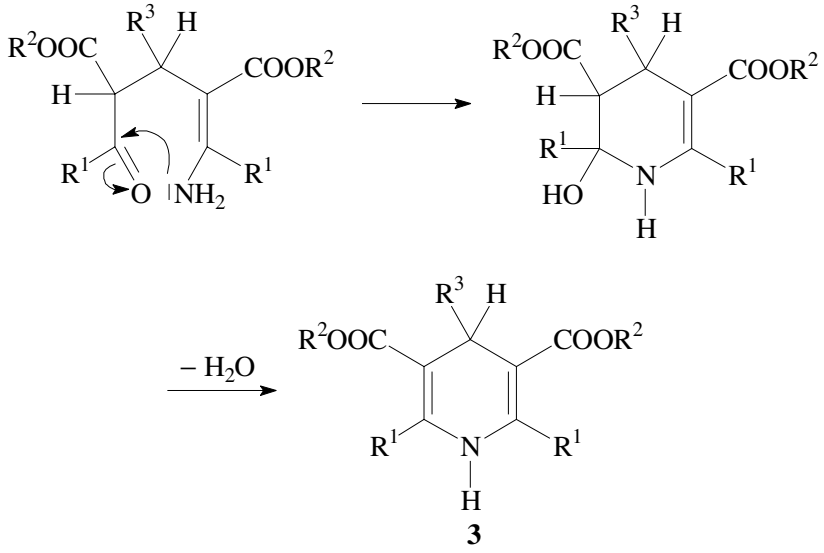


1 **7**

The ring synthesis then proceeds in subsequent steps by condensation of the unsaturated ketoester **6** and enamine **7** to yield a 1,4-dihydropyridine **3**:



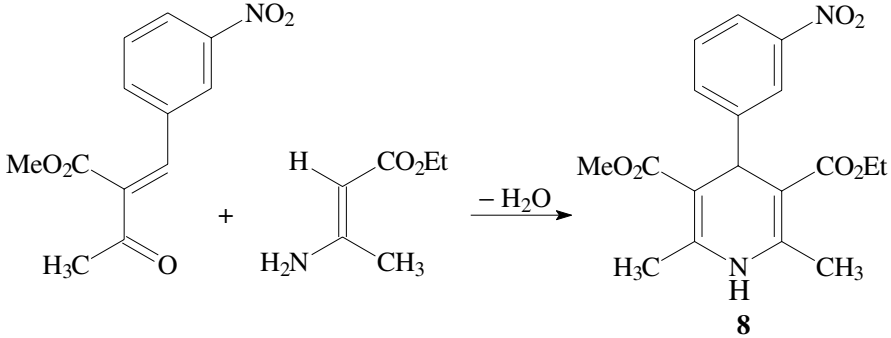
6 **7**



3

1,4-Dihydropyridines not only are intermediates for the synthesis of pyridines, but also are themselves an important class of N-heterocycles;[5,6] an example is the coenzyme NADH. Studies on the function of NADH led to increased interest in the synthesis of dihydropyridines as model compounds. Aryl-substituted dihydropyridines have been shown to be physiologically active as calcium antagonists. Some derivatives have found application in the therapy of high blood pressure and angina pectoris.[7] For that reason the synthesis of 1,4-dihydropyridines has been the subject of intensive research and industrial use. The Hantzsch synthesis has thus become an important reaction.

Many dihydropyridines that are of therapeutic interest are unsymmetrically substituted at C-3 and C-5. The synthesis of such compounds is possible from separately prepared Knoevenagel condensation products **6**, as is outlined in the following scheme for nitrendipine **8**, which is used in the medical treatment of high blood pressure.[4]



8

The reaction is of wide scope. Instead of ester groups as substituents at C-3 and C-5, other acceptor substituents—e.g. oxo, cyano, sulfonyl or nitro groups—can be employed in order to stabilize the 1,4-dihydropyridine system.

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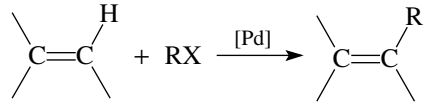
Heck Reaction

Arylation or vinylation of alkenes

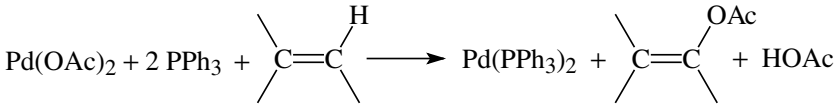


1

A modern and very important reaction in organic chemistry is the *Heck reaction*,[1–6] i.e. the palladium-catalyzed carbon–carbon bond coupling of an alkyl, aryl or vinyl group to an alkene **1**. The actual reactive coupling species is a palladium complex, generated from a halide RX (X = Br or I), which adds to the olefinic substrate. The Heck reaction, just like the *Suzuki reaction*, the *Stille coupling reaction* and the *Sonogashira reaction*, belongs to a family of palladium-catalyzed carbon–carbon coupling reactions of related mechanism.[7]

In the following, the reaction mechanism is formulated for aryl halides; analogous mechanisms can also be written for vinyl and alkyl halides. Arylpalladium complexes can be prepared by various methods. Aryl halides, arylmercury compounds or other aryl derivatives can be reacted with various palladium compounds. As a stabilizing ligand, triphenylphosphine is often employed. A typical reagent for the coupling of an aryl derivative ArX to an alkene, consists of palladium acetate **2** (1%), triphenylphosphine (2%) and a stoichiometric amount of triethylamine. The latter is necessary for the regeneration of the catalyst during reaction.

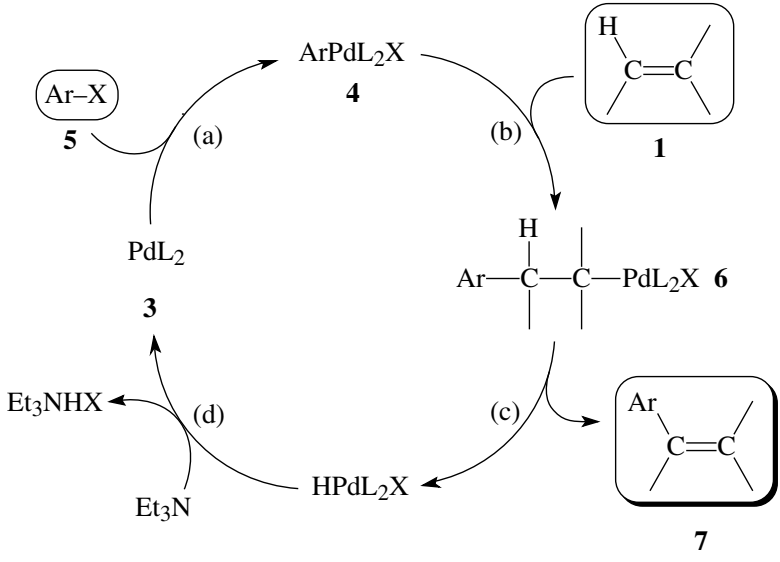
A catalytic amount of a reactive palladium(0)-complex **3** (i.e. PdL_2 in the catalytic cycle scheme shown below) is likely to be formed when the palladium(II) acetate **2** oxidizes a small amount of the alkene:[2]



2 **1** **3**

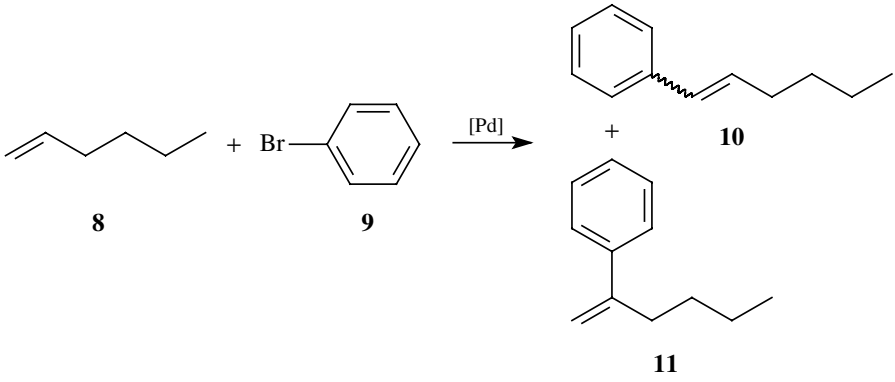
The catalytic cycle of the Heck reaction can be formulated with four steps as follows:[2,8,9]

(a) Formation of an arylpalladium complex **4** from the palladium(0) complex **3** and the aryl derivative **5** by oxidative addition.
(b) Addition of complex **4** to the alkene (olefin insertion).
(c) A β-elimination reaction from complex **6**, releasing the substituted alkene **7**.
(d) Regeneration of the palladium(0) complex **3** by reaction with a base, e.g. triethylamine.



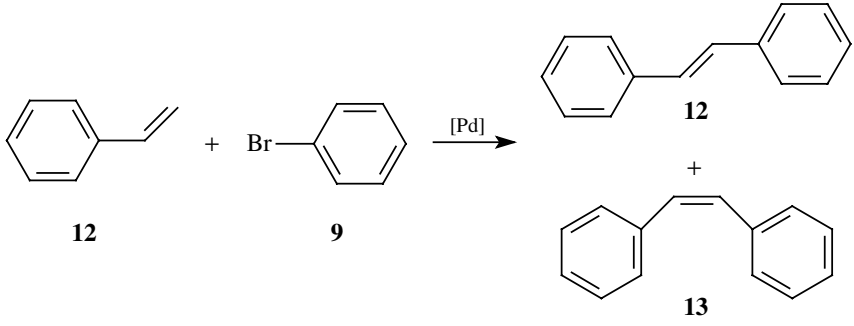
The regioselectivity of the addition of complex **4** to a substituted alkene is mainly influenced by steric factors. The substitution of hydrogen occurs preferentially at the carbon center which has the larger number of hydrogens. The Heck reaction

of hex-1-ene **8** with bromobenzene **9** leads to a 4:1 mixture of phenylhexenes **10** and **11**, where **10** is obtained as a mixture of E/Z-isomers:



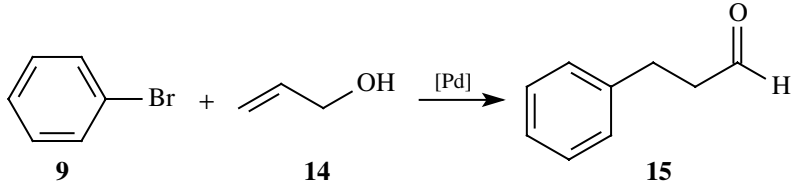
8 **9** **10** **11**

The coupling of bromo- or iodobenzene to styrene yields regioselectively a mixture of *E*- and *Z*-stilbenes **12** and **13**. An electron-withdrawing substituent at the olefinic double bond often improves the regioselectivity, while an electron-donor-substituted alkene gives rise to the formation of regioisomers.



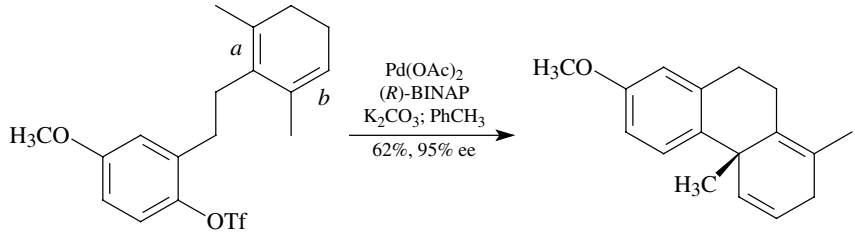
12 **9** **12** **13**

With respect to the olefinic substrate, various functional groups are tolerated, e.g. ester, ether, carboxy or cyano groups. Primary and secondary allylic alcohols, e.g. **14**, react with concomitant migration of the double bond, to give an enol derivative, which then tautomerizes to the corresponding aldehyde (e.g. **15**) or ketone:



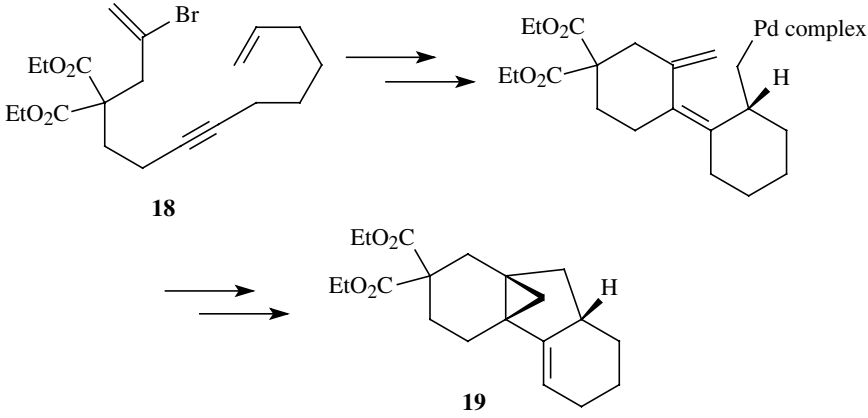
9 **14** **15**

For the performance of an enantioselective synthesis, it is of advantage when an asymmetric catalyst can be employed instead of a chiral reagent or auxiliary in stoichiometric amounts. The valuable enantiomerically pure substance is then required in small amounts only. For the Heck reaction, catalytically active asymmetric substances have been developed. An illustrative example is the synthesis of the tricyclic compound **17**, which represents a versatile synthetic intermediate for the synthesis of diterpenes. Instead of an aryl halide, a trifluoromethanesulfonic acid arylester (ArOTf) **16** is used as the starting material. With the use of the *R*-enantiomer of 2,2′-*bis*-(diphenylphosphino)-1,1′-binaphthyl ((R)-BINAP) as catalyst, the Heck reaction becomes regio- and face-selective. The reaction occurs preferentially at the trisubstituted double bond *b*, leading to the tricyclic product **17** with 95% ee.[10]



16 **17**

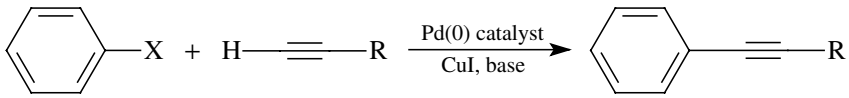
This reaction also represents an example of the *intramolecular Heck reaction*, a variant that has gained some importance in recent years. Another instructive example of the potential of this reaction for the construction of ring systems has been reported by de Meijere and coworkers,[11] taking advantage of a sequence of four consecutive intramolecular Heck reactions. The bromodiene-yne **18** reacts in a sequence of *domino reactions* within 3 d at 80 °C under Heck conditions to give the tetracyclic product **19** in 74% yield:



18 **19**

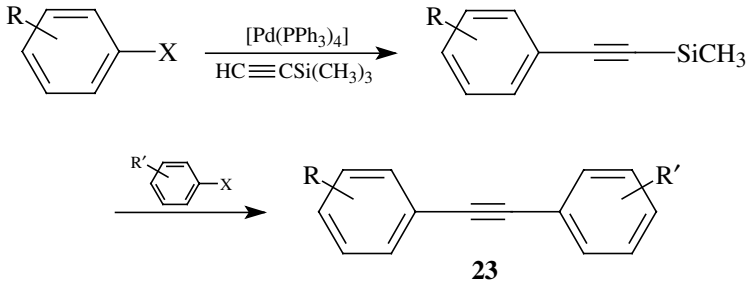
The Heck reaction is considered to be the best method for carbon–carbon bond formation by substitution of an olefinic proton. In general, yields are good to very good. Sterically demanding substituents, however, may reduce the reactivity of the alkene. Polar solvents, such as methanol, acetonitrile, *N*,*N*-dimethylformamide or hexamethylphosphoric triamide, are often used. Reaction temperatures range from 50 to 160 °C. There are various other important palladium-catalyzed reactions known where organopalladium complexes are employed; however, these reactions must not be confused with the Heck reaction.

Closely related to the Heck reaction is the *Sonogashira reaction*,[7,12,13] i.e. the palladium-catalyzed cross-coupling of a vinyl or aryl halide **20** and a terminal alkyne **21**:



20 **21** **22**

The original Sonogashira reaction uses copper(I) iodide as a co-catalyst, which converts the alkyne *in situ* into a copper acetylide. In a subsequent transmetalation reaction, the copper is replaced by the palladium complex. The reaction mechanism, with respect to the catalytic cycle, largely corresponds to the Heck reaction.[12] Besides the usual aryl and vinyl halides, i.e. bromides and iodides, trifluoromethanesulfonates (triflates) may be employed. The Sonogashira reaction is well-suited for the synthesis of unsymmetrical *bis*-aryl ethynes, e.g. **23**, which can be prepared as outlined in the following scheme, in a one-pot reaction by applying the so-called *sila-Sonogashira reaction*:[13]



23

A variety of catalysts, solvents and amines as base can be employed for the Sonogashira reaction. Typical conditions are, e.g. tetrakis(triphenylphosphine)palladium(0)

plus copper(I) iodide plus tetrahydrofuran plus an amine such as triethylamine, diethylamine, morpholine, piperidine or pyrrolidine.[7]

1. R. F. Heck, H. A. Dieck, *J. Am. Chem. Soc*. **1974**, *96*, 1133–1136.
2. R. F. Heck, *Org. React.* **1982**, *27*, 345–390.
3. A. de Meijere, F. E. Meyer, *Angew. Chem.* **1994**, *106*, 2473–2506; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2379.
4. R. F. Heck, *Palladium Reagents in Organic Syntheses*, Academic Press, New York, **1985**.
5. J. T. Link, *Org. React.* **2002**, *60*, 157–534.
6. I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066.
7. L. A. Agrofoglio, I. Gillaizeau, Y. Saito, *Chem. Rev.* **2003**, *103*, 1875–1916.
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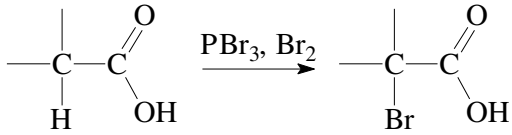
9. W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2–7.
10. K. Kondo, M. Sodeoka, M. Shibasaki, *Tetrahedron Asymm* **1995**, *6*, 2453–2464.
    E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 388.
11. S. Schweizer, Z.-Z. Song, F. E. Meyer, P. J. Parson, A. de Meijere, *Angew. Chem.* **1999**, *111*, 1550–1552; *Angew. Chem. Int. Ed. Engl.* **1999**, *38*, 1452.
12. K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *50*, 4467–4470.
13. R. R. Tykwinski, *Angew. Chem.* **2003**, *115*, 1604–1606; *Angew. Chem. Int. Ed. Engl.* **2003**, *42*, 1566.

Hell–Volhard–Zelinskii Reaction

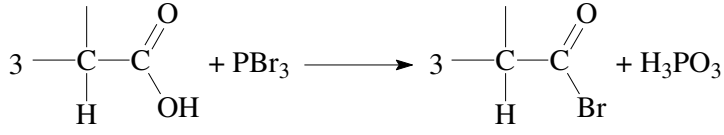
α-Halogenation of carboxylic acids



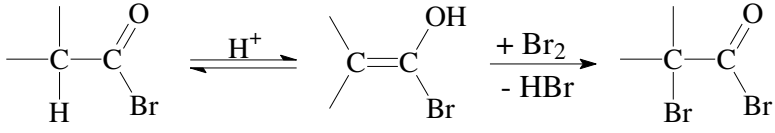
1 **2**

By application of the *Hell–Volhard–Zelinskii reaction*,[1,2] an α-hydrogen of a carboxylic acid **1** can be replaced by bromine or chlorine to give an α-bromo- or α-chlorocarboxylic acid **2** respectively.

In the following the reaction is outlined for an α-bromination. The reaction mechanism involves formation of the corresponding acyl bromide **3** by reaction of carboxylic acid **1** with phosphorus tribromide PBr_3. The acyl bromide **3** is in equilibrium with the enol derivative **4**, which further reacts with bromine to give the α-bromoacyl bromide **5**:

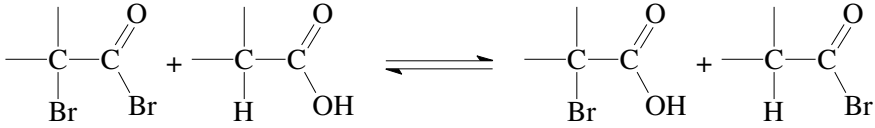


1 **3**



3 **4** **5**

The α-bromoacyl bromide **5** converts unreacted carboxylic acid **1** by an exchange reaction into the more reactive acyl bromide **3**, which subsequently becomes α-brominated as formulated above:



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

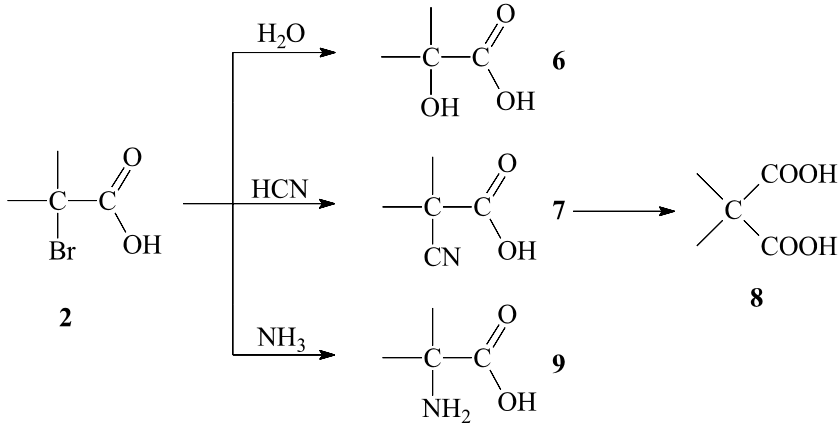
Instead of phosphorus tribromide, red phosphorus can be used as catalyst. The phosphorus tribromide is then formed *in situ*. Carboxylic acids that enolize easily will also react without a catalyst present.

The formulated mechanism is supported by the finding that no halogen from the phosphorus trihalide is transferred to the α-carbon of the carboxylic acid. For instance, the reaction of a carboxylic acid with phosphorus tribromide and chlorine yields exclusively an α-chlorinated carboxylic acid. In addition, carboxylic acid derivatives that enolize easily—e.g. acyl halides and anhydrides—do react without a catalyst present.

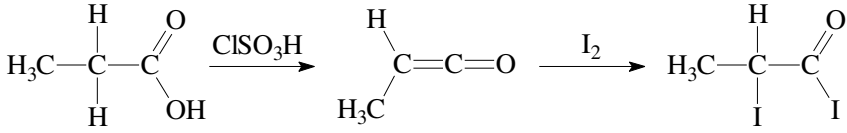
A second α-hydrogen may also be replaced by halogen. In some cases it may be difficult to obtain the *mono*-halogenated product. α-Fluorinated or α-iodinated carboxylic acids cannot be prepared by this method.

The α-bromo or α-chloro carboxylic acids **2** are versatile intermediates for further synthetic transformations. For example they can be converted into α-hydroxy carboxylic acids by reaction with water; by reaction with cyanide α-cyanocarboxylic acids **7** are obtained, which can be further converted to

1,3-dicarboxylic acids **8** by hydrolysis of the cyano group. Reaction of an α-halocarboxylic acid **2** with ammonia leads to formation of an α-amino acid **9**:



The preparation of α-iodocarboxylic acids is of particular interest, since iodide is a better leaving group as is chloride or bromide. A similar α-iodination with a phosphorus trihalide as catalyst is not known. However the iodination can be achieved in the presence of chlorosulfonic acid; mechanistically the intermediate formation of a ketene **10** by dehydration of the carboxylic acid is assumed:



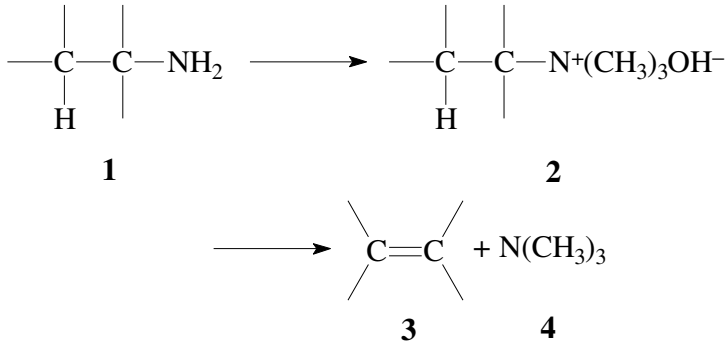
10

The ketene as a more reactive species is iodinated by reaction with iodine. Bromine or chlorine as substituents may also be introduced by this method.[3]

1. C. Hell, *Ber. Dtsch. Chem. Ges*. **1881**, *14*, 891–893.
2. H. J. Harwood, *Chem. Rev*. **1962**, *62*, 99–154.
3. Y. Ogata, K. Tomizawa, *J. Org. Chem*. **1979**, *44*, 2768–2770.

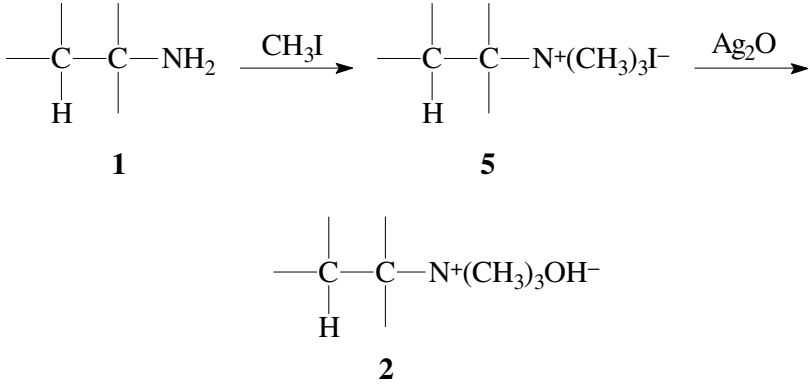
Hofmann Elimination Reaction

Alkenes from amines

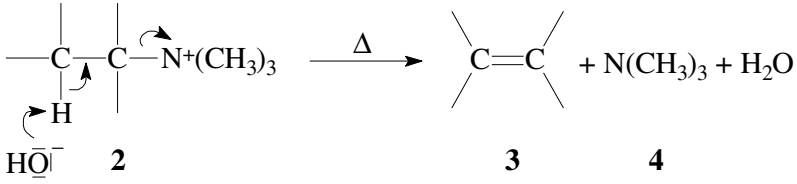


The preparation of an alkene **3** from an amine **1** by application of a β-elimination reaction is an important method in organic chemistry. A common procedure is the *Hofmann elimination*,[1,2] where the amine is first converted into a quaternary ammonium salt by exhaustive methylation. Another route for the conversion of amines to alkenes is offered by the *Cope elimination*.

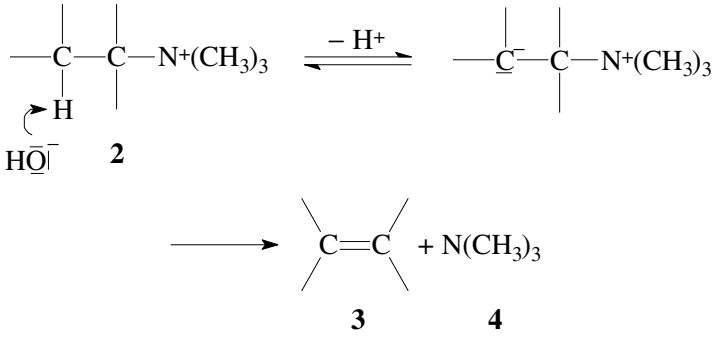
Primary, secondary and tertiary amines can serve as starting materials. The amine, e.g. **1**, is first treated with excess methyl iodide, to generate the quaternary ammonium iodide **5**. Subsequent treatment with silver oxide in water gives the corresponding ammonium hydroxide **2**:



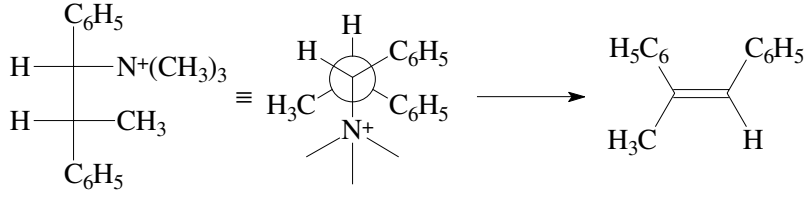
The elimination reaction takes place upon heating of the ammonium hydroxide to a temperature of 100–200 °C, often under reduced pressure:



In general the β-elimination proceeds by a E2-mechanism. It involves cleavage of trimethylamine and a β-hydrogen from the original substrate alkyl group; see scheme above—**2** → **3**. In some cases—depending on substrate structure and reaction conditions—evidence for a E1cB-mechanism has been found:

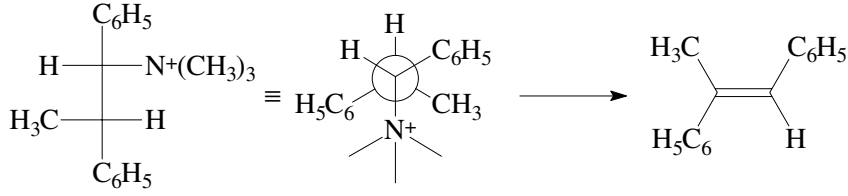


For the elimination of trimethylamine and water from the *erythro*- and *threo*-isomer of trimethyl-1,2-diphenylpropylammonium iodide **6** and **7** respectively, by treatment with sodium ethoxide, a stereospecific *trans*-elimination has been found to take place; thus supporting a E2-mechanism. From the *erythro*-isomer **6** the *Z*-alkene **8** was obtained, while the *threo*-isomer **7** yielded the *E*-alkene **9**:



6
erythro

8



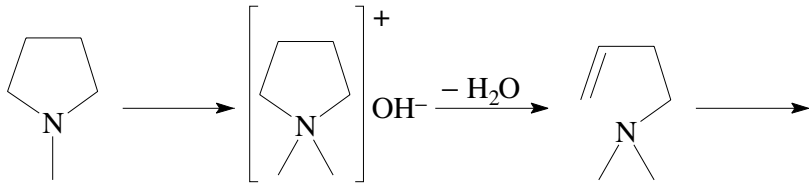
7
threo

9

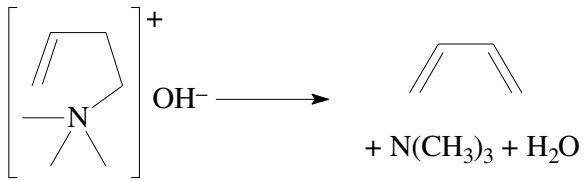
If however a *t*-butoxide was used as base, only the thermodynamically favored *E*-alkene **9** was formed, suggesting a E1cB-mechanism in that case. It has

been shown that a $Z \rightarrow E$-isomerization does not occur under these reaction conditions.

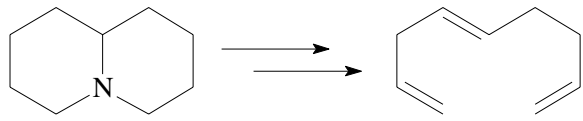
When the nitrogen is part of a ring, as for example in *N*-methylpyrolidine **10**, the olefinic product resulting from one elimination step still contains the nitrogen as a tertiary amino group. A second quaternization/elimination sequence is then necessary to eliminate the nitrogen function from the molecule; as final product a diene is then obtained:



10



With starting materials containing a bridgehead-nitrogen, e.g. quinolizidine **11**, a third quaternization/elimination sequence is necessary for complete elimination of the nitrogen; as final product a triene is then obtained:



11

The number of reaction sequences required for liberation of trimethylamine **4** indicates the degree of incorporation of a particular nitrogen into the molecular skeleton. Because of that feature, the Hofmann elimination has been used for the structural analysis of natural products, e.g. alkaloids.

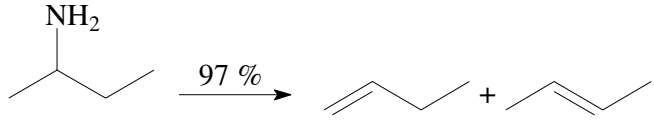
As a side-reaction, a nucleophilic substitution to give an alcohol **12** is often observed:

$$R{-}N^{+}(CH_3)_3 + OH^{-} \longrightarrow ROH + N(CH_3)_3$$

12

With substrates, where a β-hydrogen as well as a β'-hydrogen is available for elimination, product formation follows the so-called *Hofmann rule*, which states

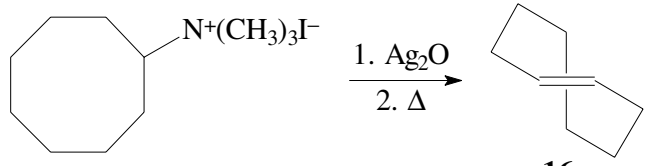
that the less substituted alkene will be formed preferentially. For example from 2-aminobutane **13**, but-1-ene **14** is formed preferentially, while but-2-ene **15** is formed in minor amounts only:



13 **14** **15**

95 % 5 %

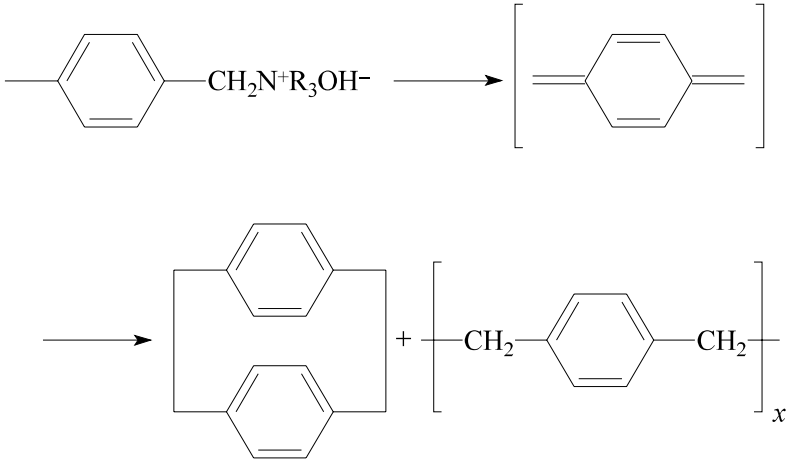
In addition to its application for structural analysis, the Hofmann elimination also is of synthetic importance. For instance the method has been used to prepare *E*-cyclooctene **16**, as well as higher homologs:[3]



16

Such reactions usually lead to formation of *E*- and *Z*-isomers, with the more strained *E*-isomer predominating.

A variant, the *1,6-Hofmann elimination*, has become a standard method for the synthesis of [2.2]paracyclophanes **17**; although it often gives low yields.



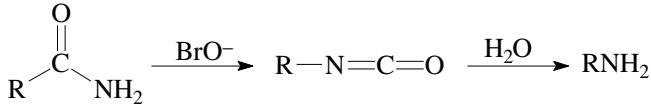
17

This method can also be used to synthesize multilayer phanes.[4]

1. A. W. Hofmann, *Justus Liebigs Ann. Chem.* **1851**, *78*, 253–286.
2. A. C. Cope, E. R. Trumbull, *Org. React.* **1960**, *11*, 317–493.
3. K. Ziegler, H. Wilms, *Justus Liebigs Ann. Chem.* **1950**, *567*, 1–43.
4. F. Vögtle, P. Neumann, *Synthesis* **1973**, 85–103.

Hofmann Rearrangement

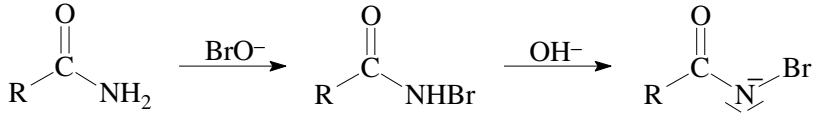
Primary amines from carboxylic amides



1 **2** **3**

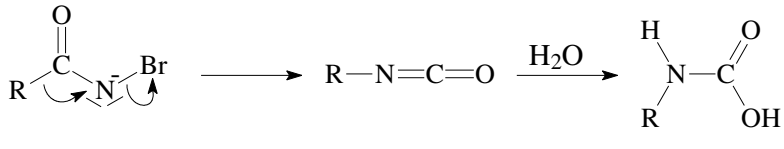
By application of the *Hofmann rearrangement* reaction,[1,2] a carboxylic amide is converted into an amine, with concomitant chain degradation by one carbon (*Hofmann degradation*). Formally this reaction can be considered as a removal of the carbonyl group from a carboxylic amide. The reaction is closely related to the *Curtius rearrangement* and the *Lossen rearrangement*. In each case the rearrangement is initiated by generating an electron-sextet configuration at nitrogen.

For the Hofmann rearrangement reaction, a carboxylic amide **1** is treated with hypobromite in aqueous alkaline solution. Initially an *N*-bromoamide **4** is formed. With two electron-withdrawing substituents at nitrogen the *N*-bromoamide shows NH-acidity, and can be deprotonated by hydroxide to give the anionic species **5**.



1 **4** **5**

The next step involves cleavage of bromide from the nitrogen center and migration of the group R, to give an isocyanate **2**. Here the question arises, whether the N−Br bond is cleaved first and the migration of R takes place afterwards, or both steps proceed in a concerted way? So far most findings suggest a concerted process.[3] In general the rearrangement of a chiral group R takes place without racemization. The isocyanate **2** under these reaction conditions reacts with water, to form the carbaminic acid **6**. This addition product is unstable, and decomposes to yield the amine **3** and carbon dioxide or rather carbonate in alkaline solution:



5 **2** **6**

3

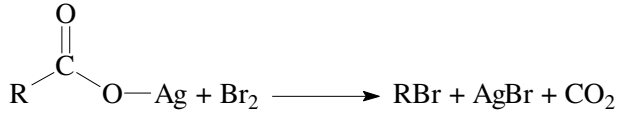
The *N*-bromoamide, its anion as well as the isocyanate have been identified as intermediates; thus supporting the reaction mechanism as formulated above.

Generally yields are good. R can be alkyl or aryl. Modern variants of the Hofmann rearrangement use lead tetraacetate[4] or iodosobenzene[5] instead of hypobromite.

1. A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1881**, *14*, 2725–2736.
2. E. S. Wallis, J. F. Lane, *Org. React.* **1946**, *3*, 267–306.
3. T. Imamoto, Y. Tsuno, Y. Yukawa, *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1632–1638.
4. H. E. Baumgarten, H. L. Smith, A. Staklis, *J. Org. Chem.* **1975**, *40*, 3554–3561.
5. A. S. Radhakrishna, C. G. Rao, R. K. Varma, B. B. Singh, S. P. Batnager, *Synthesis* **1983**, 538.

Hunsdiecker Reaction

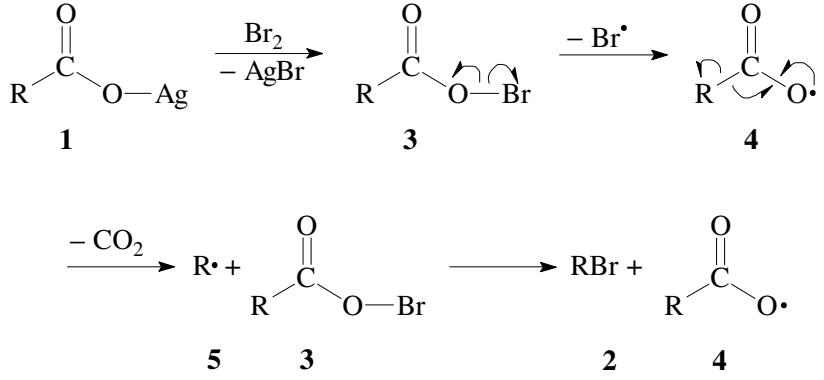
Alkyl bromides from carboxylates



1 **2**

Silver carboxylates **1** can be decarboxylated by treatment with bromine, to yield alkyl bromides **2** in the so-called *Hunsdiecker reaction*.[1,2]

The reaction is likely to proceed by a radical-chain mechanism, involving intermediate formation of carboxyl radicals, as in the related *Kolbe electrolytic synthesis*. Initially the bromine reacts with the silver carboxylate **1** to give an acyl hypobromite species **3** together with insoluble silver bromide, which precipitates from the reaction mixture. The unstable acyl hypobromite decomposes by homolytic cleavage of the O−Br bond, to give a bromo radical and the carboxyl radical **4**. The latter decomposes further to carbon dioxide and the alkyl radical **5**, which subsequently reacts with hypobromite **3** to yield the alkyl bromide **2** and the new carboxyl radical **4**:[3]

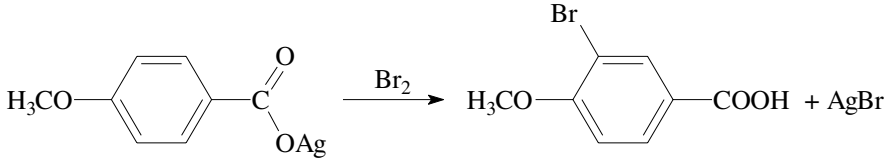


1 **3** **4**

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

By trapping experiments, the intermediate radical species have been identified, thus supporting the mechanism as formulated above.

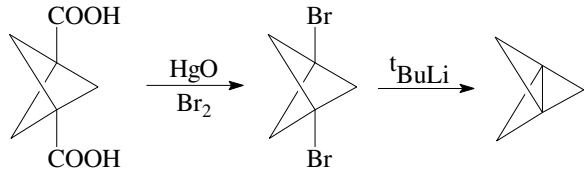
Suitable substrates for the Hunsdiecker reaction are first of all aliphatic carboxylates. Aromatic carboxylates do not react uniformly. Silver benzoates with electron-withdrawing substituents react to the corresponding bromobenzenes, while electron-donating substituents can give rise to formation of products where an aromatic hydrogen is replaced by bromine. For example the silver *p*-methoxybenzoate **6** is converted to 3-bromo-4-methoxybenzoic acid **7** in good yield:



6 **7**

The silver carboxylate employed as starting material can be prepared from the corresponding carboxylic acid and silver oxide. In order to achieve the conversion to an alkyl bromide through decarboxylation in good yield, the silver carboxylate must be sufficiently pure. Bromine is often used as reagent in the Hunsdiecker reaction, though chlorine or iodine may also be employed. As solvent, carbon tetrachloride is most often used. In general yields are moderate to good.

In a modified procedure the free carboxylic acid is treated with a mixture of mercuric oxide and bromine in carbon tetrachloride; the otherwise necessary purification of the silver salt is thereby avoided. This procedure has been used in the first synthesis of [1.1.1]propellane **10**. Bicyclo[1.1.1]pentane-1,3-dicarboxylic acid **8** has been converted to the dibromide **9** by the modified Hunsdiecker reaction. Treatment of **9** with *t*-butyllithium then resulted in a debromination and formation of the central carbon–carbon bond; thus generating the propellane **10**.[4]



8 **9** **10**

A complementary method is the *Kochi reaction*.[5,6] This reaction is especially useful for the generation of secondary and tertiary alkyl chlorides through decarboxylation of carboxylic acids, where the classical method may not work. As reagents, lead tetraacetate and lithium chloride are then employed:

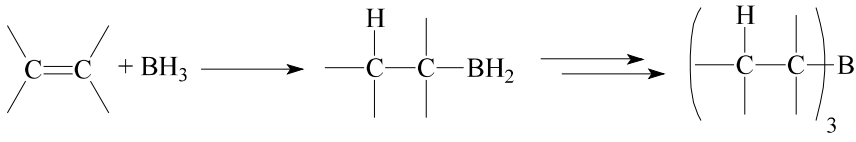
$$RCOOH + Pb(OAc)_4 + LiCl \longrightarrow RCl + CO_2 + LiPb(OAc)_3 + HOAc$$

Another decarboxylation reaction that employs lead tetraacetate under milder conditions, has been introduced by Grob *et al*.[7] In that case *N*-chlorosuccinimide is used as chlorinating agent and a mixture of *N*,*N*-dimethylformamide and acetic acid as solvent.

1. H. Hunsdiecker, C. Hunsdiecker, *Ber. Dtsch. Chem. Ges*. **1942**, *75*, 291–297.
2. C. V. Wilson, *Org. React*. **1957**, *9*, 332–387.
3. R. G. Johnson, R. K. Ingham, *Chem. Rev*. **1956**, *56*, 219–269.
4. K. B. Wiberg, *Acc. Chem. Res*. **1984**, *17*, 379–386.
5. J. K. Kochi, *J. Org. Chem*. **1965**, *30*, 3265–3271.
6. R. A. Sheldon, J. K. Kochi, *Org. React*. **1972**, *19*, 279–421.
7. K. B. Becher, M. Geisel, C. A. Grob, F. Kuhnen, *Synthesis* **1973**, 493–495.

Hydroboration

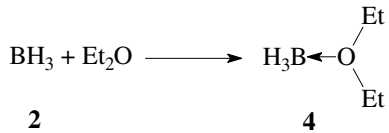
Addition of boranes to alkenes



1 **2** **3**

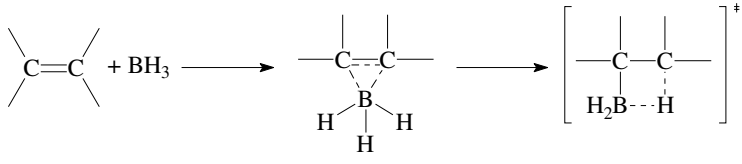
Borane **2** adds to carbon–carbon double bonds without the need of catalytic activation. This reaction has been discovered and thoroughly investigated by *H. C. Brown*,[1] and is called *hydroboration*.[2–5] It permits a regioselective and stereospecific conversion of alkenes to a variety of functionalized products.

Free borane **(2)** exists as gaseous dimer—the diborane B_2H_6. In addition Lewis acid/Lewis base-complexes, as for example formed in an ethereal solvent, e.g. **4**, are commercially available:

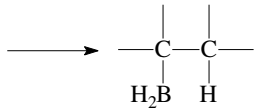


2 **4**

In reaction with an alkene, initially a three-membered ring Lewis acid/Lewis base-complex **5** is formed, where the carbon–carbon double bond donates π-electron density into the empty p-orbital of the boron center. This step resembles the formation of a bromonium ion in the electrophilic addition of bromine to an alkene:

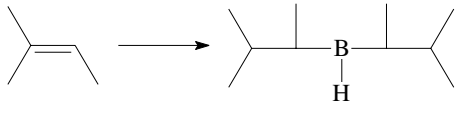


1 **2** **5** **6**

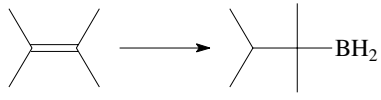


3

In the next step, one of the borane-hydrogens is transferred to a sp^2-carbon center of the alkene and a carbon–boron bond is formed, *via* a four-membered cyclic transition state **6**. A *mono*-alkylborane $R-BH_2$ molecule thus formed can react the same way with two other alkene molecules, to yield a trialkylborane R_3B. In case of *tri*- and *tetra*-substituted alkenes—e.g. 2-methylbut-2-ene **7** and 2,3-dimethylbut-2-ene **9**—which lead to sterically demanding alkyl-substituents at the boron center, borane will react with only two or even only one equivalent of alkene, to yield a *di*alkylborane or *mono*alkylborane respectively:

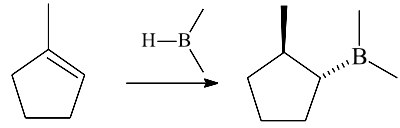


7 **8**



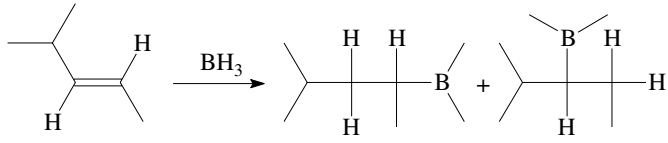
9 **10**

The hydroboration is a *syn*-stereospecific reaction. For example reaction with 1-methylcyclopentene **11** yields the 1,2-*trans*-disubstituted product **12** only:



11 **12**

The hydroboration is a regioselective reaction. In general the addition will lead to a product, where the boron is connected to the less substituted or less sterically hindered carbon center. If the olefinic carbons do not differ much in reactivity or their sterical environment, the regioselectivity may be low. It can be enhanced by use of a less reactive alkylborane—e.g. disiamylborane **8**:

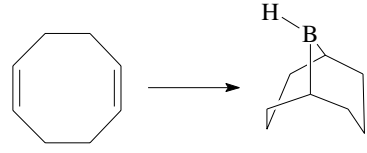


57 % 43 %

8

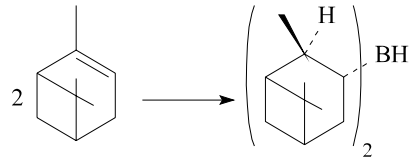
95 % 5 %

Since borane BH_3 reacts with only one or two equivalents of a sterically hindered alkene, it is possible to prepare less reactive and more selective borane reagents R_2BH and RBH_2 respectively. In addition to disiamylborane **8** and thexylborane **10**, the 9-borabicyclo[3.3.1]nonane (9-BBN) **14** is an important reagent for hydroboration, since it is stable to air; it is prepared by addition of borane **2** to cycloocta-1,5-diene **13**:



13 **14**

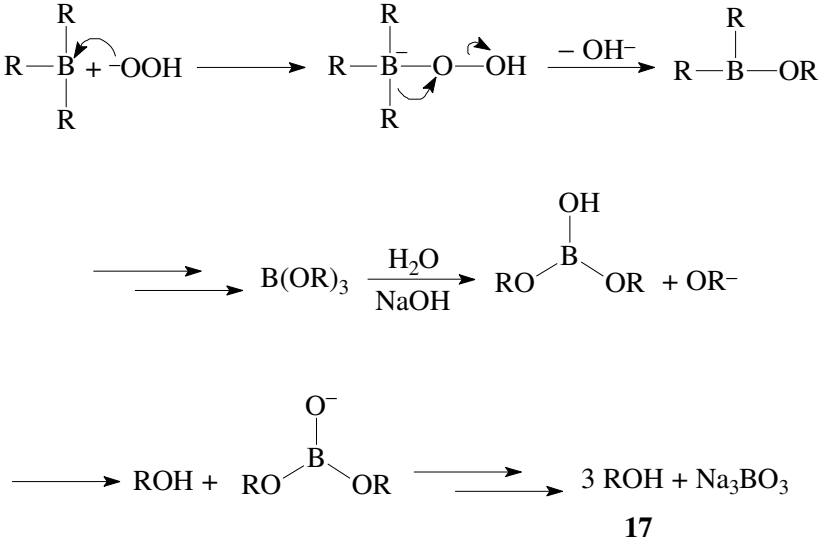
By reaction of borane with two equivalents of α-pinene **15**, the chiral hydroboration reagent diisopinocampheylborane **16** (Ipc_2BH) is formed:



15 **16**

This reagent can be used for the enantioselective hydroboration of *Z*-alkenes with enantiomeric excess of up to 98%. Other chiral hydroboration reagents have been developed.[6]

The alkylboranes obtained by the hydroboration reaction are versatile intermediates for further transformations. The most important transformation is the oxidation to yield alcohols **17**; it is usually carried out by treatment with hydroperoxide in alkaline solution. The group R migrates from boron to oxygen with retention of configuration:



17

The overall result of the sequence hydroboration + oxidation is a regioselective *anti*-Markownikoff-addition of water to an alkene. This reaction is an important method in organic synthesis, since it can be made stereoselective and even enantioselective.

Other important applications for organoboranes[4] include the Michael-like addition reaction to α,β-unsaturated carbonyl compounds, and the alkylation of α-halogenated carbonyl compounds.

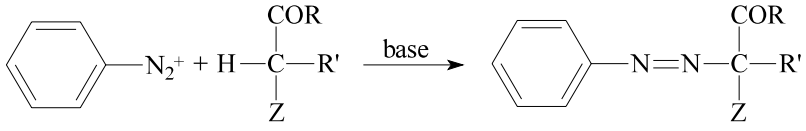
The reaction conditions are mild—e.g. reaction temperatures between 0 °C and room temperature. Side-reactions like for example rearrangements of the carbon skeleton are usually not observed.

1. H. C. Brown, B. C. Subba Rao, *J. Am. Chem. Soc.* **1956**, *78*, 5694–5695.
2. G. Zweifel, H. C. Brown, *Org. React.* **1963**, *13*, 1–54.
3. H. Hopf, *Chem. Unserer Zeit* **1970**, *4*, 95–98.
4. A. Suzuki, R. S. Dhillon, *Top. Curr. Chem.* **1986**, *130*, 23–88.
5. A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*, Academic Press, New York, **1988**.
6. H. C. Brown, B. Singaram, *Acc. Chem. Res.* **1988**, *21*, 287–293.

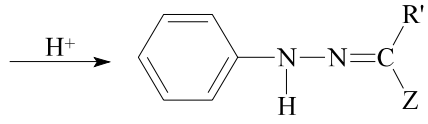
J

Japp-Klingemann Reaction

Arylhydrazones from reaction of β-dicarbonyl compounds with arenediazonium salts



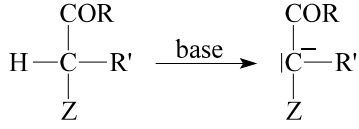
1 **2** **3**



4

The coupling of arenediazonium compounds **1** to 1,3-dicarbonyl substrates **2** (Z = COR) is known as the *Japp–Klingemann reaction*.[1,2] As suitable substrates, β-ketoacids (Z = COOH) and β-ketoesters (Z = COOR) can be employed. As reaction product an arylhydrazone **4** is obtained.

In general the reaction is conducted in aqueous solution under basic conditions—e.g. in the presence of KOH. The 1,3-dicarbonyl substrate is deprotonated to give the corresponding anion **5**, which then couples to the arenediazonium species **1**, to give the diazo compound **3**:



2 **5**

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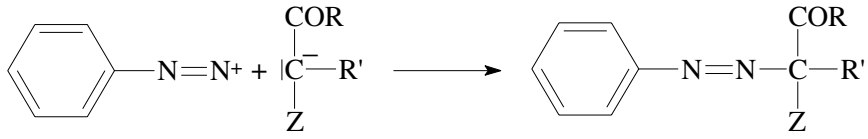
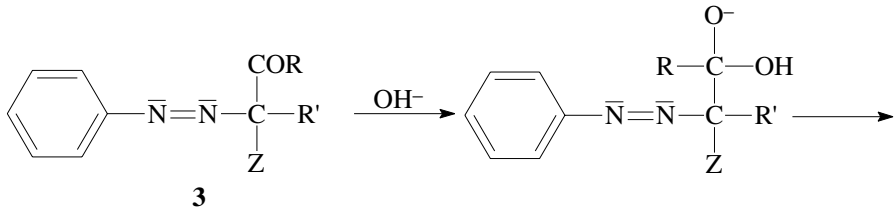
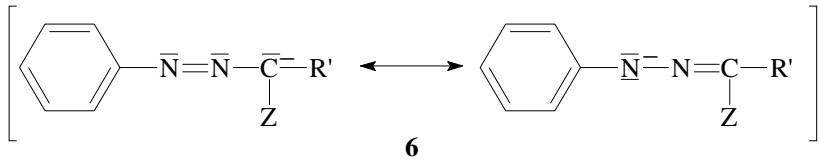


1 **5** **3**

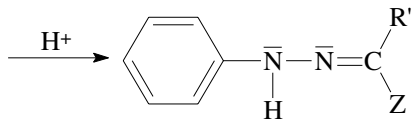
Such diazo compounds **3** however, that contain two electron-withdrawing substituents, are unstable under these reaction conditions. They further react by hydrolytic cleavage of one carbonyl substituent to give an anionic species **6**, that is stabilized by resonance, and which yields the hydrazone **4** upon acidic workup:



3



6



4

The mechanism outlined above is supported by the fact that various diazo intermediates **3** could be isolated.[3,4]

The Japp–Klingemann reaction is a special case of the aliphatic diazo coupling. For a successful reaction, the dicarbonyl substrate **2** should bear a sufficiently CH-acidic hydrogen.

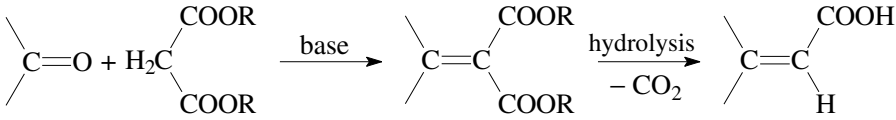
In addition to β-diketones, β-ketoacids and β-ketoesters, cyanoacetic ester and related compounds are suitable starting materials. The arylhydrazones **4** thus obtained are of great importance as starting materials for the *Fischer indole synthesis*, as well as for the preparation of other *N*-heterocycles.[5]

1. F. R. Japp, F. Klingemann, *Justus Liebigs Ann. Chem*. **1888**, *247*, 190–225.
2. R. R. Phillips, *Org. React*. **1959**, *10*, 143–178.
3. O. Dimroth, *Ber. Dtsch. Chem. Ges*. **1908**, *41*, 4012–4028.
4. L. Kalb, F. Schweizer, H. Zellner, E. Berthold, *Ber. Dtsch. Chem. Ges*. **1926**, *59*, 1860–1870.
5. M. Kocevar, D. Kolman, H. Krajnc, S. Polanc, B. Porovne, B. Stanovnik, M. Tisler, *Tetrahedron* **1976**, *32*, 725–729.

K

Knoevenagel Reaction

Condensation of an aldehyde or ketone with an active methylene compound

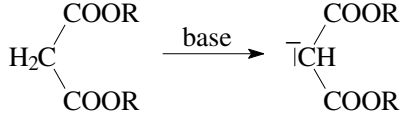


1 **2** **3** **4**

The prototype of a *Knoevenagel reaction*[1,2] shown in the scheme above is the condensation of an aldehyde or ketone **1** with a malonic ester **2**, to yield an α,β-unsaturated carboxylic ester **4**.

The term Knoevenagel reaction however is used also for analogous reactions of aldehydes and ketones with various types of CH-acidic methylene compounds. The reaction belongs to a class of carbonyl reactions, that are related to the *aldol reaction*. The mechanism[3] is formulated by analogy to the latter. The initial step is the deprotonation of the CH-acidic methylene compound **2**. Organic bases like amines can be used for this purpose; a catalytic amount of amine usually suffices. A common procedure, that uses pyridine as base as well as solvent, together with a catalytic amount of piperidine, is called the *Doebner modification*[4] of the Knoevenagel reaction.

The corresponding anion **5**, formed from **2** by deprotonation, subsequently adds to the carbonyl substrate to give the aldol-type intermediate **6**. Loss of water from intermediate **6** leads to a primary α,β-unsaturated condensation product **3**:



2 **5**

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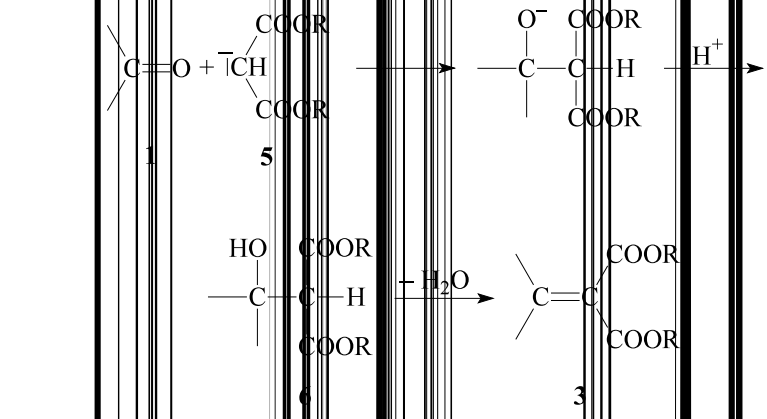
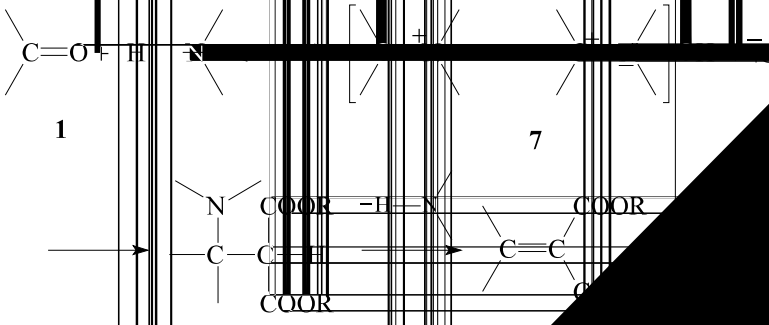


1 **5**

6 **3**

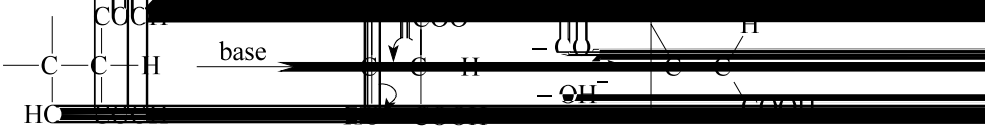
Another mechanism has been formulated, which is based on results
by Knoevenagel,[5] and which is supported by more recent investigati
involves the formation of an intermediate iminium species **7**:



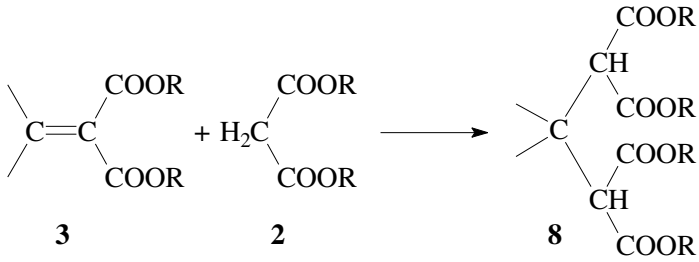
1 **7**

This reaction pathway explains well the appl
is evidence
scope of the reaction, there may be
all cases.

If a Knoevenagel condensati
pyridine, a subsequent decarb
decarboxylation of α,β-u
the decarboxylation of
follows:



The formation of *bis*-adducts—e.g. **8** by a consecutive *Michael addition reaction*, is observed in some cases. This reaction is formulated as a 1,4-addition of a second molecule of the CH-acidic starting material **2** to the initially formed α,β-unsaturated carbonyl compound **3**:



3 **2** **8**

Virtually any aldehyde or ketone and any CH-acidic methylene compound can be employed in the Knoevenagel reaction; however the reactivity may be limited due to steric effects. Some reactions may lead to unexpected products from side-reactions or from consecutive reactions of the initially formed Knoevenagel product.

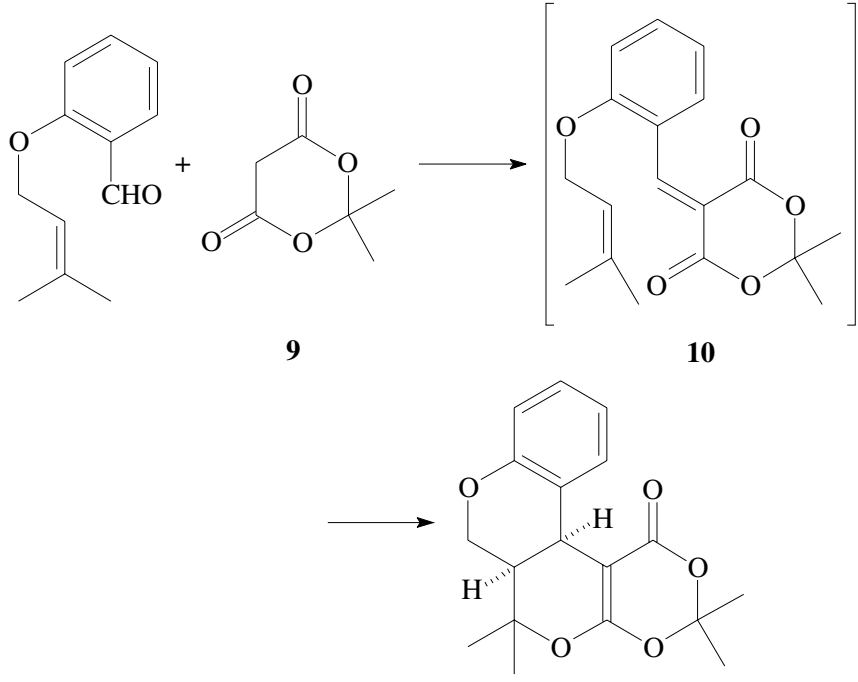
Suitable substituents X and Y that can activate the methylene group to become CH-acidic, are electron-withdrawing groups—e.g. carboxy, nitro, cyano and carbonyl groups. Malonic acid as well as cyano acetic acid and derivatives (ester, nitrile, amide) are often used. In general two activating groups X and Y are required to achieve sufficient reactivity; malononitrile $CH_2(CN)_2$ is considered to be the most reactive methylene compound with respect to the Knoevenagel reaction. As would be expected, ketones are less reactive than aldehydes. In addition yield and rate of the condensation reaction are influenced by steric factors.

Because of the mild reaction conditions, and its broad applicability, the Knoevenagel reaction is an important method for the synthesis of α,β-unsaturated carboxylic acids.[2] Comparable methods[8] are the *Reformatsky reaction*, the *Perkin reaction*, as well as the *Claisen ester condensation*. The Knoevenagel reaction is of greater versatility; however the Reformatsky reaction permits the preparation of α,β-unsaturated carboxylic acids that are branched in α-position.

A more recent application of the Knoevenagel reaction is its use in *domino reactions*. The term domino reaction is used for two or more subsequent transformations, where the next reaction step is based on the functionality generated in the preceding step.[9] Such reactions are also called *tandem reactions* or *cascade reactions*.

The following example is a sequence consisting of a Knoevenagel condensation and a subsequent *hetero-Diels–Alder reaction*.[10] An aromatic

aldehyde is condensed *in situ* with a β-dicarbonyl compound **9**—i.e. meldrum's acid—to give a 1-oxabuta-1,3-diene derivative **10**, which further undergoes an intramolecular [4 + 2]-cycloaddition reaction with the trisubstituted double bond acting as dienophile:



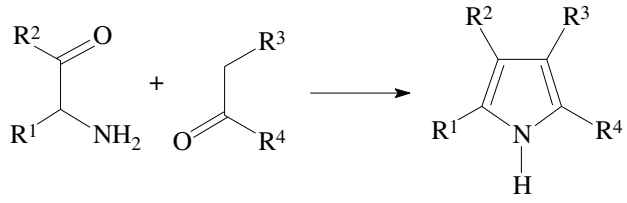
9 **10**

A large number of aldehydes and structurally different CH-acidic methylene compounds can be employed in such a *domino-Knoevenagel + hetero-Diels–Alder reaction*.

1. E. Knoevenagel, *Ber. Dtsch. Chem. Ges*. **1894**, *27*, 2345–2346.
2. G. Jones, *Org. React*. **1967**, *15*, 204–599.
3. A. C. O. Hann, A. Lapworth, *J. Chem. Soc*. **1904**, *85*, 46–56.
4. O. Doebner, *Ber. Dtsch. Chem. Ges*. **1900**, *33*, 2140–2142.
5. E. Knoevenagel, *Ber. Dtsch. Chem. Ges*. **1898**, *31*, 2596–2619.
6. G. Charles, *Bull. Soc. Chim. Fr*. **1963**, 1576–1583.
7. T. I. Crowell, D. W. Peck, *J. Am. Chem. Soc*. **1953**, *75*, 1075–1077.
8. R. L. Shriner, *Org. React*. **1942**, *1*, 1–37.
9. H. Waldmann, *Nachr. Chem. Tech. Lab*. **1992**, *40*, 1133–1140.
10. L. F. Tietze, U. Beifuss, *Angew. Chem*. **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 131.

Knorr Pyrrole Synthesis

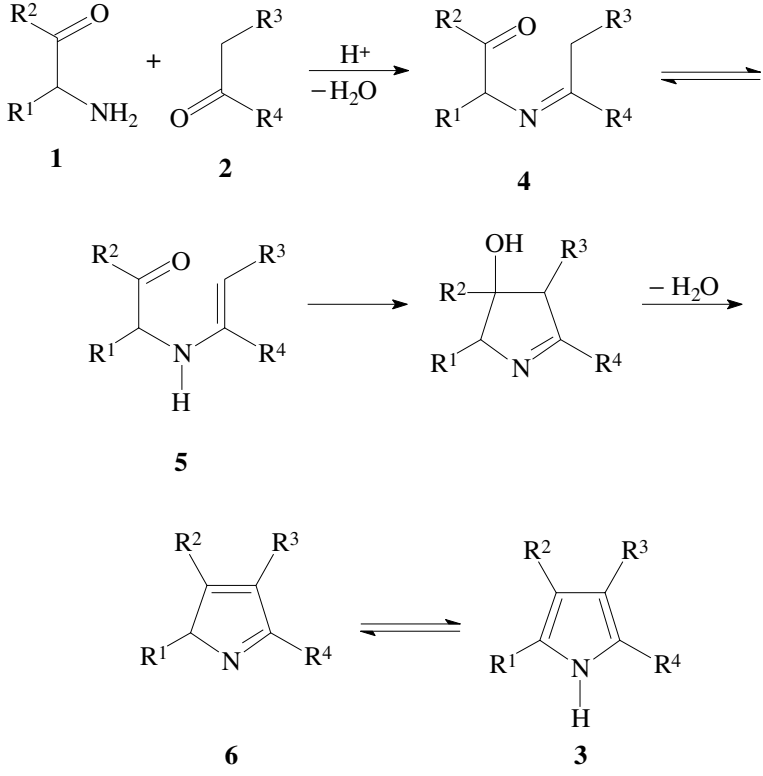
Formation of pyrroles by condensation of ketones with α-aminoketones



1 **2** **3**

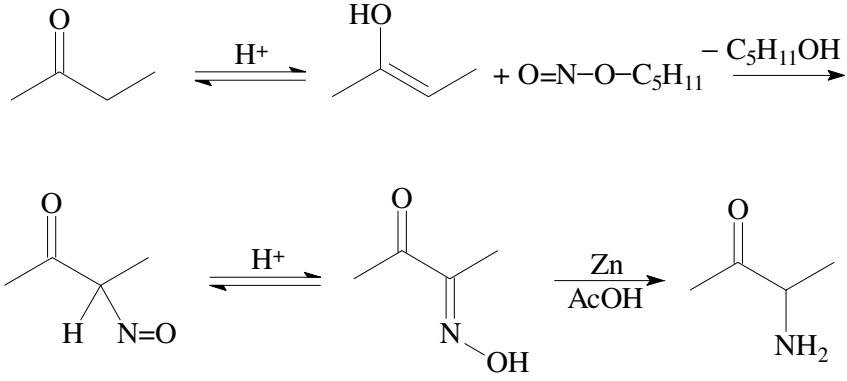
By a condensation reaction of an α-aminoketone **1** with a ketone **2**, a pyrrole **3** can be obtained. This reaction is known as the Knorr pyrrole synthesis.[1,2]

A mechanism has been formulated, starting with a condensation to give the imine **4**, that can tautomerize to the corresponding enamine **5**. The latter can be isolated in some cases, thus supporting the formulated mechanism. A cyclization and subsequent dehydration leads to the imine **6**, which tautomerizes to yield the aromatic pyrrole **3**:



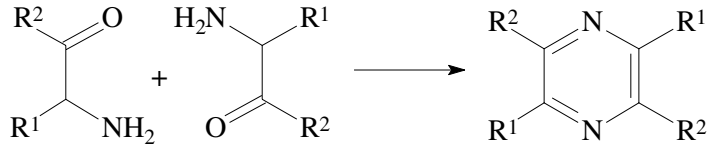
1 **2** **4** **5** **6** **3**

The aminoketone **1**, required as starting material, can be obtained by a *Neber rearrangement* from a *N*-tosylhydrazone. Another route to α-aminoketones starts with the nitrosation of an α-methylene carbonyl compound—often *in situ*—to give the more stable tautomeric oxime **7**, which is then reduced in a subsequent step to yield **1**:



7 **1**

With excess ketone, the preparation of the aminoketone and subsequent condensation to a pyrrole can be conducted in one pot. In a side-reaction α-aminoketones can undergo a self-condensation to give pyrazines **8**:



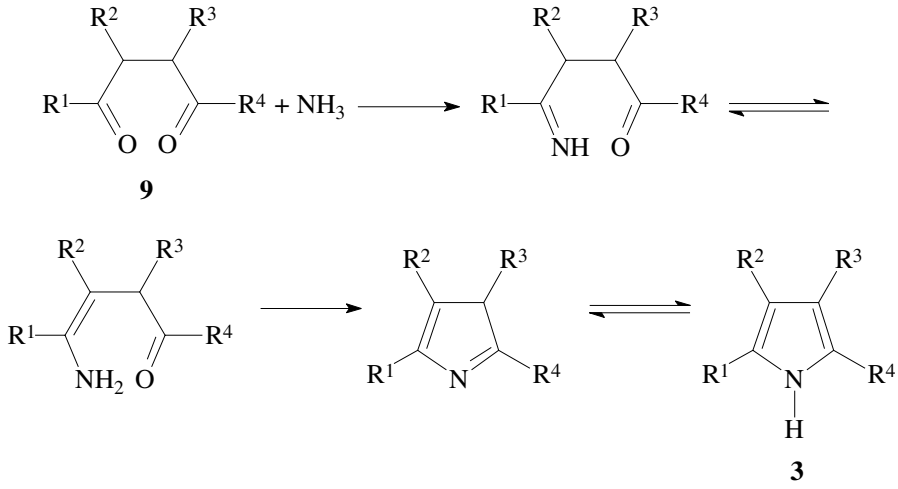
1 **1** **8**

The self-condensation is largely suppressed in reactions with those ketones **2**, that are activated by an electron-withdrawing substituent R^3 or R^4. The carbonyl activity is then increased, and the enamine-intermediate **5** is favored over the imine **4**, by conjugation with the electron-withdrawing group.[3]

Mainly C-substituted pyrroles have been synthesized by application of the Knorr pyrrole synthesis; however N-substituted pyrroles can also be prepared, when starting with secondary aminoketones, e.g. bearing an N-methyl or N-phenyl substituent.

Another important route to pyrroles is offered by the *Paal–Knorr reaction*;[4] where the pyrrole system is formed by condensation of a 1,4-diketone **9**

with ammonia:[5]



This reaction is of wide scope; it is limited only by the availability of the appropriate 1,4-diketone. 1,4-Diketones are easily accessible, e.g. by the *Nef reaction*.

Methods for the synthesis of pyrroles are of importance, since the pyrrole unit is found in natural products widespread in nature. For example a pyrrole unit is the building block of the porphyrin skeleton, which in turn is the essential structural subunit of chlorophyll and hemoglobin.

1. L. Knorr, *Ber. Dtsch. Chem. Ges*. **1884**, *17*, 1635–1642.
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3. A. H. Corwin, *Heterocyclic Compounds*, Wiley, New York, **1950**, *Vol. 1*, p. 287–290.
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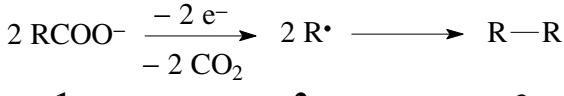
5. R. P. Bean in *The Chemistry of Pyrroles* (Ed.: R. A. Jones), Wiley, New York, **1990**, *Vol. 48/1*, p. 206–220.

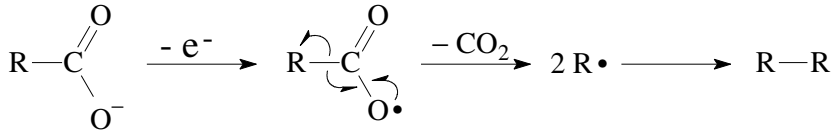
Kolbe Electrolytic Synthesis

Electrolysis of carboxylate salts



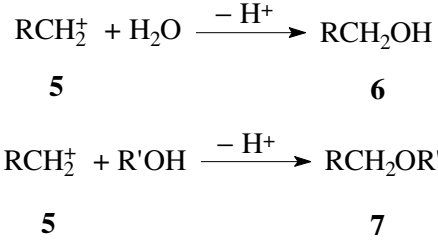
1 **2** **3**

The anodic oxidation of the carboxylate anion **1** of a carboxylate salt to yield an alkane **3** is known as the *Kolbe electrolytic synthesis*.[1–4] By decarboxylation alkyl radicals **2** are formed, which subsequently can dimerize to an alkane. The initial step is the transfer of an electron from the carboxylate anion **1** to the anode. The carboxyl radical species **4** thus formed decomposes by loss of carbon dioxide. The resulting alkyl radical **2** dimerizes to give the alkane **3**:[4]



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

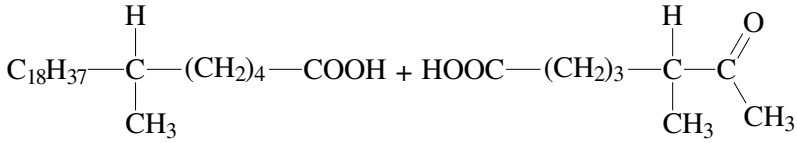
The radical mechanism is supported by a number of findings: for instance, when the electrolysis is carried out in the presence of an olefin, the radicals add to the olefinic double bond; styrene does polymerize under those conditions. Side products can be formed by further oxidation of the alkyl radical **2** to an intermediate carbenium ion **5**, which then can react with water to yield an alcohol **6**, or with an alcohol to yield an ether **7**:



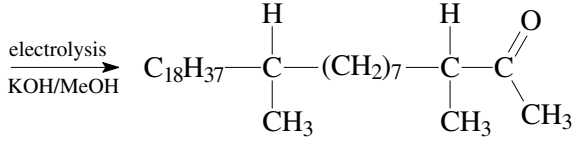
5 **6**

5 **7**

From the mechanism outlined above it follows that the Kolbe electrolytic synthesis is first of all applicable for the preparation of symmetrical target molecules with an even number of carbons. By electrolysis of a mixture of two carboxylates the formation of unsymmetrical products is possible. Generally a statistical mixture of symmetrical and unsymmetrical products is obtained; however if one carboxylic acid, e.g. the less expensive one, is used in large excess, the formation of the symmetrical product from the minor component can be largely suppressed. Such a mixed Kolbe electrolytic synthesis often gives unsatisfactory yields; however this variant leads to the more valuable products. An instructive example is the synthesis of 3,11-dimethyl-2-nonacosanone **10**, which serves as a sex pheromone for the German cockroach. As starting material the 6-methyltetracosanoic acid **8** together with three equivalents of 5-methyl-6-oxoheptanoic acid **9** is used; the product **10** is then obtained in 42% yield:[5]



8 **9**



10

Suitable starting materials for the Kolbe electrolytic synthesis are aliphatic carboxylic acids that are not branched in α-position. With aryl carboxylic acids the reaction is not successful. Many functional groups are tolerated. The generation of the desired radical species is favored by a high concentration of the carboxylate salt as well as a high current density. Product distribution is further dependend on the anodic material, platinum is often used, as well as the solvent, the temperature and the pH of the solution.[4]

1. H. Kolbe, *Justus Liebigs Ann. Chem.* **1849**, *69*, 257–294.
2. A. K. Vijh, B. E. Conway, *Chem. Rev.* **1967**, *67*, 623–664.
3. H. J. Schäfer, *Angew. Chem.* **1981**, *93*, 978–1000; *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 911.
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5. W. Seidel, H. J. Schäfer, *Chem. Ber.* **1981**, *113*, 451–456.

Kolbe Synthesis of Nitriles

Nitriles from alkyl halides

1 **2**

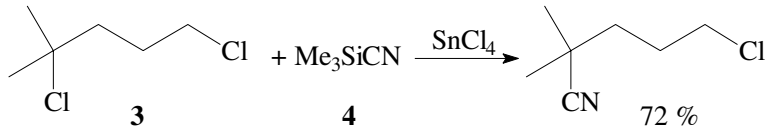
A common method for the preparation of alkyl cyanide **2** is the treatment of corresponding alkyl halides **1** with cyanide.[1–3] The corresponding reaction with aromatic substrates is called the *Rosenmund–von-Braun reaction*.

The *Kolbe synthesis of nitriles* is an important method for the elongation of an alkyl chain by one carbon center (see also the *Arndt–Eistert synthesis*). The nitrile **2** can for example easily be converted to the corresponding carboxylic acid by hydrolysis.

Since the cyanide anion is an ambident nucleophile, isonitriles R−NC may be obtained as by-products. The reaction pathway to either nitrile or isonitrile can be controlled by proper choice of the counter cation for the cyanide anion.

With alkali cyanides, a reaction *via* a S_N2-mechanism takes place; the alkyl halide is attacked by cyanide with the more nucleophilic carbon center rather than the nitrogen center, and the alkylnitrile is formed. In contrast, with silver cyanide the reaction proceeds by a S_N1-mechanism, and an isonitrile is formed, since the carbenium intermediate reacts preferentially with the more electronegative center of the cyanide—i.e. the nitrogen (*Kornblum's rule, HSAB concept*).[4,5]

The reaction works well with primary alkyl halides, especially with allylic and benzylic halides, as well as other alkyl derivatives with good leaving groups. Secondary alkyl halides give poor yields. Tertiary alkyl halides react under the usual reaction conditions by elimination of HX only. Nitriles from tertiary alkyl halides can however be obtained by reaction with trimethylsilyl cyanide **4**:[6]



This variant gives good to very good yields, and it is chemoselective; the primary alkyl halide function in **3** is left unaffected under these reaction conditions.

1. F. Wöhler, J. von Liebig, *Justus Liebigs Ann. Chem.* **1832**, *3*, 267–268.
2. K. Friedrich, K. Wallenfels in *The Chemistry of the Cyano Group* (Ed.: S. Patai), Wiley, New York, **1970**, p. 77–86.
3. K. Friedrich in *The Chemistry of Functional Groups, Supp. C* (Eds. S. Patai, Z. Rappoport), Wiley, New York, **1970**, *Vol. 2*, p. 1345–1390.
4. N. Kornblum, R. A. Smiley, R. K. Blackwood, D. C. Iffland, *J. Am. Chem. Soc* **1955**, *77*, 6269–6280.
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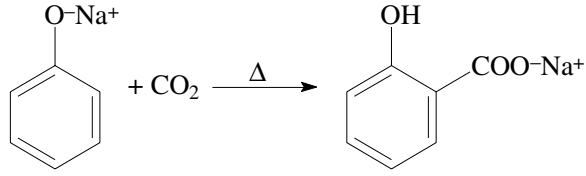
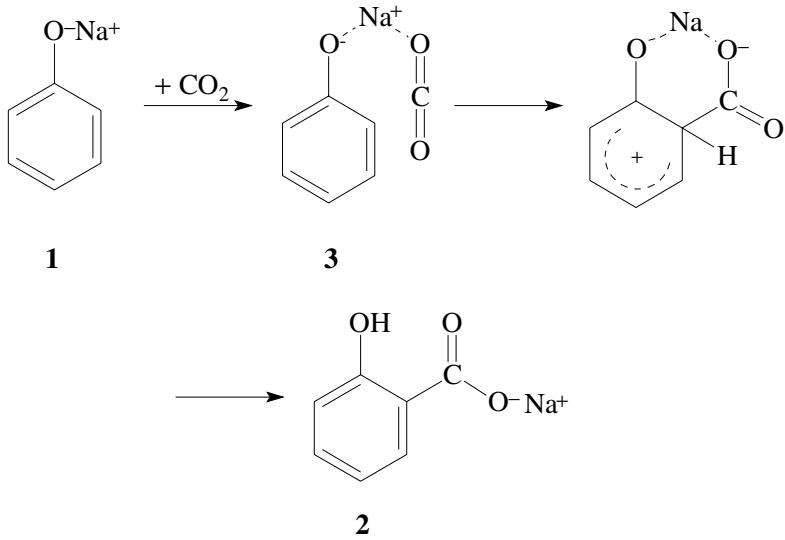
Kolbe–Schmitt Reaction

Carboxylation of phenolates/synthesis of salicylic acid



Carbon dioxide reacts with phenolates **1** to yield salicylate **2**; with less reactive mono-phenolates, the application of high pressure may be necessary in order to obtain high yields. This reaction, which is of importance for the large scale synthesis of salicylic acid, is called the *Kolbe–Schmitt reaction*.[1–3]

In order to rationalize the *ortho*-selectivity observed in the reaction of sodium phenoxide **1** with carbon dioxide, the formation of a complex **3** is assumed. By that complexation the carbon dioxide becomes polarized, and its electrophilic character is increased. Complex **3** is of suitable geometry for reaction with the activated *ortho*-carbon center:[4]



1 **3** **2**

The *para*-substituted product, which is not accessible from complex **3**, can however be obtained from reaction of potassium phenoxide with carbon dioxide.

The Kolbe–Schmitt reaction is limited to phenol, substituted phenols and certain heteroaromatics.[5] The classical procedure is carried out by application of high pressure using carbon dioxide without solvent; yields are often only moderate.[2] In contrast to the minor importance on laboratory scale, the large scale process for the synthesis of salicylic acid is of great importance in the pharmaceutical industry.

1. H. Kolbe, *Justus Liebigs Ann. Chem.* **1860**, *113*, 125–127.
2. A. S. Linsey, H. Jeskey, *Chem. Rev.* **1957**, *57*, 583–620.
3. H. J. Shine, *Aromatic Rearrangements*, Elsevier, New York, **1967**, p. 344–348.
4. I. Hirao, T. Kito, *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3470–3474.
5. H. Henecka, *Methoden Org. Chem. (Houben-Weyl)*, **1952**, *Vol. 8*, p. 372–377.