Houben-Weyl

Methods of Organic Chemistry

Additional and Supplementary Volumes to the 4th Edition

Vol. E 21 d

Stereoselective Synthesis:

C—C Bond Formation by Sigmatropic Rearrangements, Electrocyclic Reactions, C—H, C—Hal Bond Formation

Publication Year
1995

ISBN (Print)
978-3-13-100114-6

Thieme

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Volume E 21 d

METHODS OF
ORGANIC CHEMISTRY

METHODS OF ORGANIC CHEMISTRY

(HOUBEN-WEYL)

ADDITIONAL AND SUPPLEMENTARY VOLUMES TO THE 4TH EDITION

GEORG THIEME VERLAG STUTTGART · NEW YORK

VOLUME E 21 d

STEREOSELECTIVE SYNTHESIS

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Die Deutsche Bibliothek – CIP-Einheitsaufnahme

Methoden der organischen Chemie / (Houben-Weyl). –
Stuttgart ; New York : Thieme
Teilw. begr. von Eugen Müller und Otto Bayer. – Teilw. begr. von Eugen Müller ... Fortgef. von Heinz Kropf. – Erw.- und Folgebd. zur 4. Aufl. hrsg. von K. H. Büchel ... – Teilw. u.d.T.: Methods of organic chemistry
NE: Müller, Eugen [Hrsg.]; Houben, Josef [Hrsg.]; Kropf, Heinz [Hrsg.]; Büchel, Karl H. [Hrsg.]; Methods of organic chemistry

Additional and suppl. vol. of the 4. ed.
Vol. E 21 d. Stereoselective synthesis / ed. Günter Helmchen ... Authors H. Ahlbrecht ... – 1995
NE: Helmchen, Günter [Hrsg.]; Bohlmann, Rolf

Library of Congress Card No.: applied for

Date of publication 30.11.1995

Typesetting: Konrad Triltsch, Druck- und Verlagsanstalt GmbH, D-97070 Würzburg

Printing: Tutte Druckerei GmbH, D-94119 Salzweg-Passau

ISBN 3-13-100114-3

Preface

There was a time when stereoselectivity of a reaction was mostly of mechanistic interest and reactions that could result in the formation of stereoisomers were considered a nuisance and had to be avoided at best. However, this situation has changed over the past two decades, during which stereoselective synthesis has grown into a reliable methodology. This development began with the remodelling of readily available chiral compounds from nature. More recently, these "ex-chiral-pool" synthetic strategies have been complemented and, in many cases, surpassed by the powerful techniques of asymmetric synthesis.

Originally, only a few laboratories were concerned with the design of routes to enantiomerically pure compounds. Since the demand for nonracemic chiral drugs and pesticides has enormously increased, methods of asymmetric synthesis are now bound to be applied by almost every practising chemist. However, newcomers to the field soon find themselves confronted with a confusing vocabulary, with no guidance as to the appropriate method to solve their problem, and with lack of well-documented procedures. This situation frequently leads to frustration or at least to unnecessary work.

This called for the present volume set of the HOUBEN-WEYL series *Methods of Organic Chemistry*. Since the 1950s HOUBEN-WEYL has served the synthetic community by giving comprehensive critical reviews of the existing synthetic methods in a consistent style and with high reliability. The editors, authors and publisher of HOUBEN-WEYL "Stereoselective Synthesis" have worked together to confer this philosophy to the field of asymmetric synthesis. Thus, we hope to supply a treatise which should become the standard reference in the field.

"Stereoselective Synthesis" gives a comprehensive treatment of chemical transformations in which a new stereocenter is created, i.e., all enantio- and those diastereodifferentiating reactions which allow the absolute and relative configuration of a new stereogenic unit to be controlled. Consequently, mechanism-controlled reactions (e.g. S_N2 displacements), "ex-chiral-pool" syntheses which do not lead to new stereogenic units, and *E*/*Z* selective formation of alkenes are not covered.

Following the general introductory chapters covering principles, nomenclature, separation and analysis, the chapters on individual synthetic methods are organized by the type of bond that is broken or formed. Only starting material and products are considered as a basis for the classification, not the reaction mechanism. In the typical HOUBEN-WEYL style, the scope of the most important methods is illustrated with tables of selected examples. Insight into the practical application of the methods can be obtained from the experimental procedures provided.

The wealth of material forced us to break up the work into five volumes (E21a through f). Access to and properties of the common chiral auxiliaries, solvents, reagents and catalysts which are used in various different reactions is covered comprehensively in Volume E 21e avoiding duplication of information in the individual chapters.

The transition of HOUBEN-WEYL from German to English brought about changes in the layout and in the style of presentation without, however, sacrificing the high standard of quality and reliability that is the hallmark of HOUBEN-WEYL.

Special thanks go to our 101 authors who have spent a great deal of time and effort to achieve the goals we have set. We are also indebted to the editorial staff in Stuttgart, who had to cope with the special challenges of editing and publishing a gigantic amount of complex material.

May 1995

Günter Helmchen
Reinhard W. Hoffmann
Johann Mulzer
Ernst Schaumann

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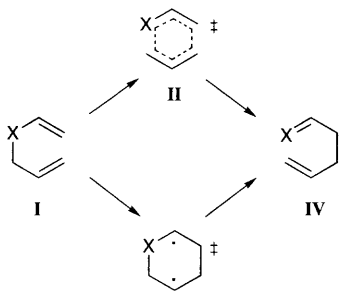
1.6.3. Formation of C–C Bonds by Sigmatropic Rearrangements and Electrocyclic Reactions

1.6.3.1. Formation of C–C Bonds by [3,3] Sigmatropic Rearrangements

H. FRAUENRATH

Introduction

Sigmatropic rearrangements have received much attention for stereoselective organic synthesis during the last decades. Among these rearrangements, [3,3] sigmatropic rearrangements, such as the Claisen (**I**, X = O), hetero-Claisen (**I**, X = S, N and related systems in which other positions in **I** are occupied by heteroatoms) or Cope (**I**, X = C) rearrangement, belong to the most powerful methods for stereoselective C–C bond formation[1–16].



As electron reorganizing processes, thermal [3,3] sigmatropic rearrangements have been referred to as concerted, but many other mechanisms may be operative, e.g., for the Claisen or Cope rearrangement, ranging in the transition-state structures from **II** to the biradical **III**. Though the definition of [i,j] sigmatropic reactions was originally restricted to uncatalyzed intramolecular reactions[17,18], catalyzed Claisen, hetero-Claisen and Cope rearrangements have also been defined as [3,3] sigmatropic rearrangements[10].

Because [3,3] sigmatropic rearrangements take place through highly ordered transition states, the stereochemical course of these reactions can be predicted from principles of conformational analysis and effectively controlled.

This section is limited to the stereochemical principles that govern [3,3] sigmatropic rearrangements and methods which allow the stereochemical outcome of these reactions to be controlled.

The formation of C–O and C–N bonds by sigmatropic rearrangements is referred to in this section only for the sake of completeness. For more detailed discussion on these subjects see Section D.4.11. (C–O bond formation) and Section D.7.6. (C–N bond formation).

1.6.3.1.1. (Hetero-, Polyhetero-)Claisen Rearrangements

1.6.3.1.1.1. General Aspects

1.6.3.1.1.1.1. Introduction, Definitions and Mechanisms

Even though Claisen first reported the rearrangement of allyl phenyl ether and ethyl β-allyloxycrotonate in 1912[19], it was not until the mid 1960s that this type of rearrangement became increasingly important for C–C bond formation. The widespread use of the Claisen rearrangement was mainly a result of the discovery of new reagents, which allowed the difficulties inherent in the synthesis of allyl vinyl ethers to be circumvented, and the development of highly stereoselective variants. For a historical overview see refs 20 and 21.

for references see p 3736

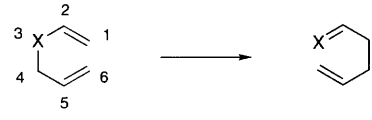
Nowadays, the Claisen rearrangement, particularly the aliphatic Claisen rearrangement, is without doubt the most synthetically useful [3,3] sigmatropic rearrangement. The popularity of the Claisen rearrangement in organic synthesis can be attributed to the following factors:

(1) the variety of products, which can be obtained by several variants (e.g., aldehydes, ketones, acids, esters, amides, etc.),
(2) the possibility of obtaining differentially functionalized intermediates (γ,δ-unsaturated carbonyl compounds), which can easily be transformed,
(3) readily accessible precursors, operational ease and high yields,
(4) high stereoselectivity in the formation of double bonds and stereocenters.

For specific introductions to the Claisen rearrangement see refs 1–16 and 21–41.

Conventionally, the term Claisen rearrangement is used for [3,3] sigmatropic rearrangements of type **I** → **IV** (X = O). For another notation, especially for polyhetero-Claisen systems, see ref 42.

The positions within the pericyclic system are generally marked as indicated in formula **I**.

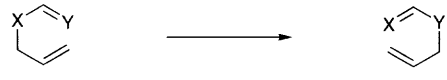


I **IV**

X = O Claisen rearrangement
X = N aza-Claisen rearrangement
X = S thia-Claisen rearrangement

If the carbons at positions 1 and 2 are part of an aromatic ring, the rearrangement is defined as an "aromatic Claisen rearrangement" (ortho-Claisen rearrangement: the rearrangement of an allyl aryl ether to an *o*-dienone, which immediately enolizes to an *o*-allylphenol; para-Claisen rearrangement: if the ortho position is substituted, a second [3,3] sigmatropic shift followed by enolization gives a *p*-allylphenol. If all the ortho and the para positions are substituted, no reaction occurs).

Rearrangements with other heteroatoms X, e.g., X = N, S, are called hetero-Claisen rearrangements. Sometimes, the rearrangement of **I**, X = S or N, is also called a 3-thia- or 3-aza-Cope rearrangement, respectively. In polyhetero-Claisen rearrangements other positions in **I** are occupied by heteroatoms, e.g., **V**.



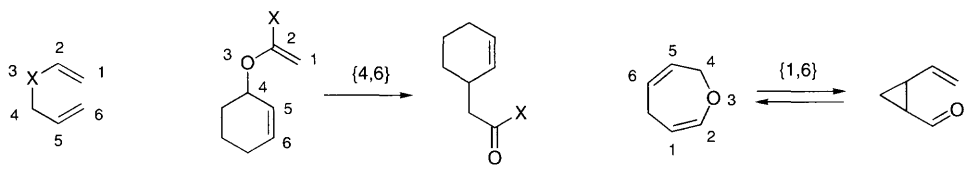
V **VI**

X = O, Y = O allyl esters, propargyl and allenyl esters, allyl *N,N*-dialkylcarbamates
X = N, Y = O *N*-allyl amides
X = O, Y = S allyl thionocarbamates
X = S, Y = S *S*-allyl dithioesters

A mnemonic method has been proposed which describes various ring systems[21]. This method can also be used in this context:

"The carbons of the pericyclic system according to formula **I** to which the chain is attached are expressed in the form {m,n;o,p}"[21].

For example, the following rearrangements are defined as:



I

The rearrangement of acyclic systems would be defined as {0,0}.

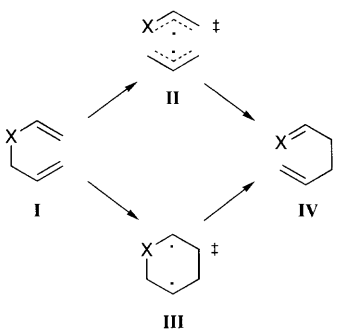
Mechanisms, Substituent Effects

The Claisen rearrangement can be formally considered as an intramolecular S_N2' addition of a carbonyl enol to an allylic alcohol. In contrast to the Cope rearrangement (see Section D.1.6.3.1.2.), it is an irreversible, highly exothermic reaction with the exception of some special substrates, such as cyclopropane derivatives[43,44] or some bicyclic compounds[45–47].

For other facile retro-Claisen rearrangements see refs 48–51, for an example in the thia-Claisen rearrangement series, cf. ref 52. However, it has been pointed out that the irreversibility of the Claisen rearrangement in the oxygen series is only attributed to the large stability difference between reactant and product which drives the equilibrium to the right[52].

Mechanistic details have been thoroughly investigated by experimental[53–63] as well as by theoretical methods[64–71]. First-order kinetics[54,72–74] and the lack of crossover products[73] support an intramolecular, cyclic mechanism with a negative entropy[54,72,74] and volume[75,76] of activation both indicating a constrained transition state relative to the ground state. From secondary deuterium isotope effects it has been concluded[18,58] that bond breaking is more advanced than bond making. For heavy-atom kinetic isotope effects see ref 77.

Despite some disagreements[68] an early reactant-like transition state[18,58,78], which resembles more closely the diradical **II** than the diyl **III** (see the More O'Ferrall–Jencks diagram in ref 21), is now generally accepted.



Substituents also influence the nature of the transition state[62].

π-Donor[67,79–85], as well as π-acceptor[67,86], groups in the C-1, C-2 and C-4 positions result in rate enhancements with respect to hydrogen[67]. Thus, 2-trialkylsilyloxy-substituted allyl vinyl ethers rearrange at almost ambient temperature[63,87,88], whereas the corresponding unsubstituted congeners require high temperatures for rapid rearrangement[89]. As an example, 4-alkyl-2-(trimethylsilyloxy)allyl vinyl ethers rearrange more rapidly than their 4-unsubstituted counterparts[87,88]. The rate enhancement in the case of the Ireland variation has been attributed to the greater stability of the 2-(trimethylsilyloxy)-1-oxaallyl moiety over the oxaallyl moiety[61].

for references see p 3736

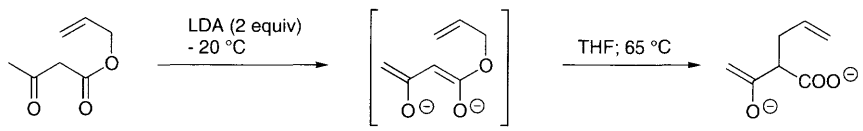
For substituents in position 5 and 6, an acceleration is observed with acceptor substituents in position 5 and donor substituents in position 6. Interchange of the substituents in these positions leads to deceleration. For example, a rate acceleration was observed with methoxy-substituted allyl vinyl ethers in the C-4 and C-6 position in benzene at 80 °C[89]. In contrast to other predictions[68], a C-5 methoxy group only results in a deceleration[89]. It has been suggested that a transition state with dipolar character (enolate–oxonium ion pair) is operating in this case[89]. This is further supported by a rate increase when the solvent is changed from benzene to methanol.

For kinetic parameters and relative rates for the rearrangement of cyano-substituted allyl vinyl ethers see refs 67 and 90.

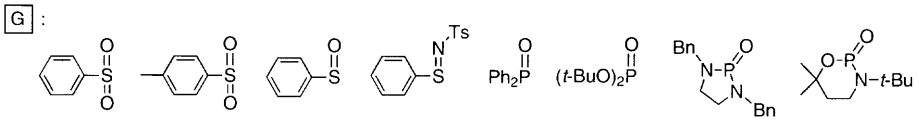
Charge Acceleration

Rate enhancements of Claisen rearrangements can be achieved by the formation of anions α to C-2 (which can formally be considered as strong π-donors in position 2). Ester enolates of lithium[87,88,91], sodium[92–95], magnesium[96–98] and zinc[99] have been widely used to effect charge-accelerated rearrangements.

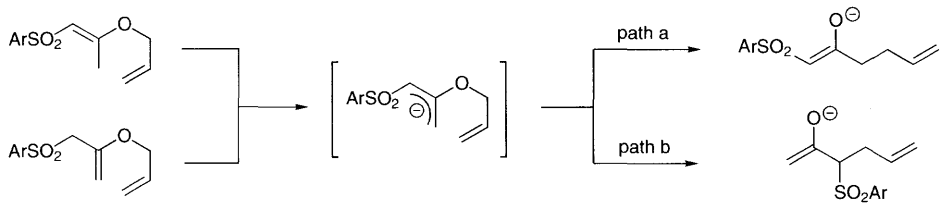
The rate of the Carroll rearrangement has been increased by formation of a dianion on treatment of allylic acetoacetates with two equivalents of lithium diisopropylamide in tetrahydrofuran at −78 °C followed by heating to reflux[100]. With one equivalent of base no reaction occurs.



High rate accelerations have been observed with carbanionic p-donors at position 2. Several sulfur and phosphorous anion stabilizing groups (G) have been used to perform carbanion-accelerated Claisen rearrangements[101–104].

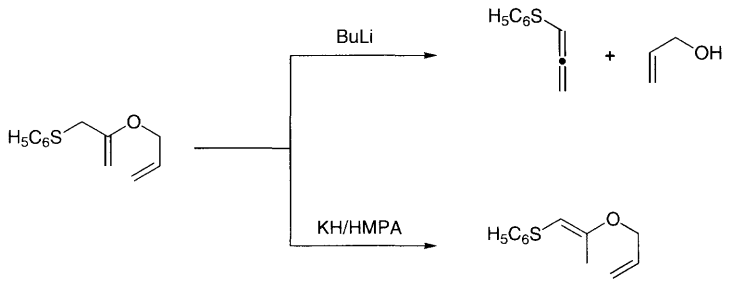


The best results are obtained with arylsulfonylmethylene groups at position 2, which rearrange in high yield and with high stereoselectivity (see Section 1.6.3.1.1.4.1.4.; p 3439) on treatment with 1.5 equivalents of potassium hydride in hexamethylphosphoric triamide/tetrahydrofuran (3:1, 50 °C). Deprotonation with 1.5 equivalents of potassium hydride in the presence of 1.5 equivalents of 18-crown-6 in refluxing tetrahydrofuran gives lower yields and requires higher temperatures for rearrangement[104].



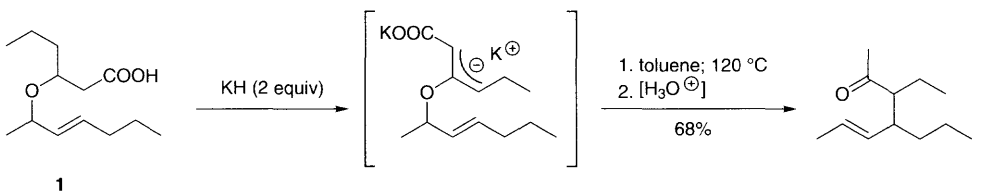
One of the most striking features of the base-induced rearrangement of unsaturated sulfones is the high regioselectivity. Both α,β- and γ,δ-unsaturated substrates yield the same product via path a. The observed regioselectivity has been explained by the greater stability of a β-oxo sulfone anion compared to a ketone enolate[104].

Allyl sulfides give only β-elimination products on treatment with butyllithium, and isomerization to the α,β-tautomers on treatment with potassium hydride:



Optically active phosphonamidates have been used for chiral auxiliary based Claisen rearrangements (see Section 1.6.3.1.1.5.2.2.; p 3508)[105, 106].

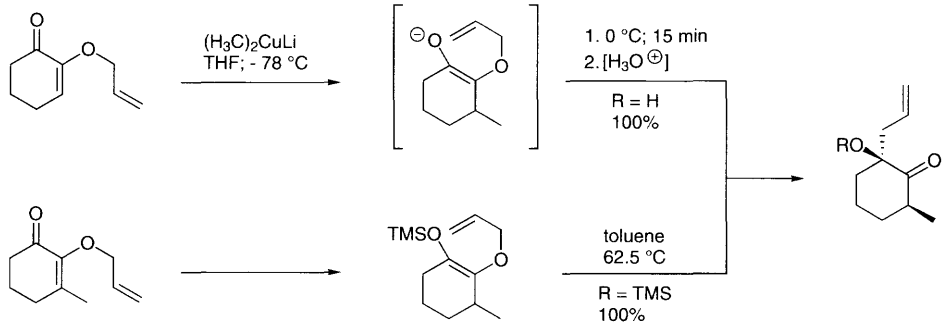
In a similar fashion, treatment of the 2-hexenoic acid derivative **1** with two equivalents of potassium hydride in refluxing toluene produces the rearranged ketone in 68% yield (see also p 3310). Under the same reaction conditions, use of one equivalent of potassium hydride does not effect the rearrangement[107].



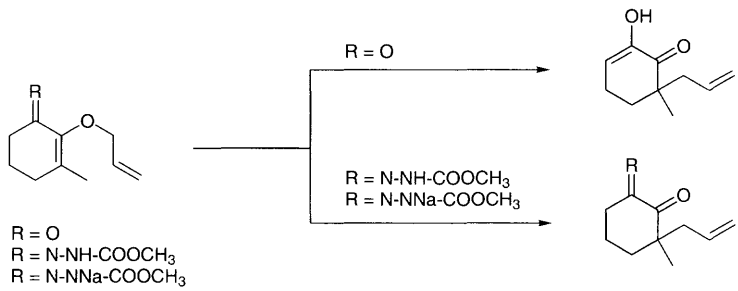
1

Charge acceleration has also been observed in the rearrangement of 2-allyloxy-2-cyclohexenones. In comparison to the silyl enol ether derivative of 2-allyloxy-3-methyl-2-cyclohexenone, the lithium cuprate derivative obtained by conjugate addition of lithium dimethylcuprate rearranges much faster. This effect has been explained by the intermediacy of an allyl radical/oxyoxaallyl radical anion (semi-dione) pair[84].

for references see p 3736

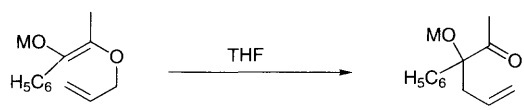


For a more complex example of this type of rearrangement (anionic Claisen rearrangement of a tricyclic α-allyloxy ketone) see ref 108. 2-Allyloxy-3-methyl-2-cyclohexenones[109–111] and nitrogen derivatives thereof[112] rearrange in a different way.



The sodium salt of the *N*-methoxycarbonyl hydrazone rearranges faster than the hydrazone itself or the parent ketone. This method has been used for the construction of vicinal quaternary centers, since the accelerating functionality can simply be removed by Wolff–Kischner reduction. For charge-accelerated Claisen rearrangements of related systems see refs 85 and 113–118.

A correlation between rate acceleration and the electron-donating ability of the MO group of enolates **2** shows the potassium enolate to be superior to the lithium, sodium or trimethylsilyl derivative[84]. The rate enhancement, in this case, has been attributed to a vinylogous weakening effect of the oxyanion on the O-3–C-4, oxygen–carbon bond, similar to effects that have been encountered in anionic oxy-Cope rearrangements[119].



2
M = Li, Na, K, TMS

For fluoride-accelerated rearrangements see refs 86, 120 and 121.

Catalysis

The catalytic influence of ammonium chloride on the rate of the reaction was discussed by Claisen in his first report[19]. Since then, numerous catalysts have been introduced to affect rate enhancements of Claisen rearrangements, e.g., Brønsted and Lewis acids, bases or transition metal complexes. The literature concerning catalytic effects in the Claisen rearrangement has been thoroughly covered until 1984[10, 122].

New developments concentrate on organoaluminum catalysts[123-131] and transition metal complexes (palladium complexes[132-135], ruthenium complexes[136]) as a means of achieving a change in the normal stereoselectivity observed in thermal rearrangements (e.g., of the double-bond configuration, Section 1.6.3.1.1.2.2., p 3347; internal asymmetric induction, Section 1.6.3.1.1.4., p 3403). Moreover, chiral organoaluminum reagents have been used for asymmetric catalysis (Section 1.6.3.1.1.6., p 3533)[137-139]. For the use of organoaluminum catalysts in the aromatic Claisen rearrangement cf. ref 140.

Solvent Effects

Due to the low significance of Coulomb interactions, solvents generally have little effect on pericyclic reactions[141]. On the other hand, it has been observed that the rate of ortho-Claisen rearrangements is increased by the use of polar solvents[142]. Moreover, aliphatic Claisen rearrangements can be accelerated by polar solvents[143] (e.g., from benzene to methanol in the rearrangement of methoxy-substituted allyl vinyl ethers[89]). From the latter results, a more dipolar character or a tight ion pair in the transition state has been proposed[89, 144]. For a discussion of polar solvent effects in the Claisen rearrangement see also ref 145.

Water as the solvent has been shown to give high rate accelerations[146-149]. This effect has also been explained by the polarity of the solvent[146, 149]; however, due to the high degree of rate acceleration (e.g., the nonenzymatic Claisen rearrangement of chorismate to prephenate is 100 times faster in water than in methanol[144]) it has been argued[147, 148] that the polarity of the solvent cannot be the only explanation. Therefore, a hydrophobic effect (kinetically controlled reactions between two hydrophobic molecules, for which the volume of activation is negative, are accelerated in water) has been postulated as promoting the Claisen rearrangement in water[147, 148]. This effect is also believed to be operating in the aqueous Diels–Alder and Mukaiyama reactions[148].

1.6.3.1.1.1.2. Variants of the Claisen Rearrangement

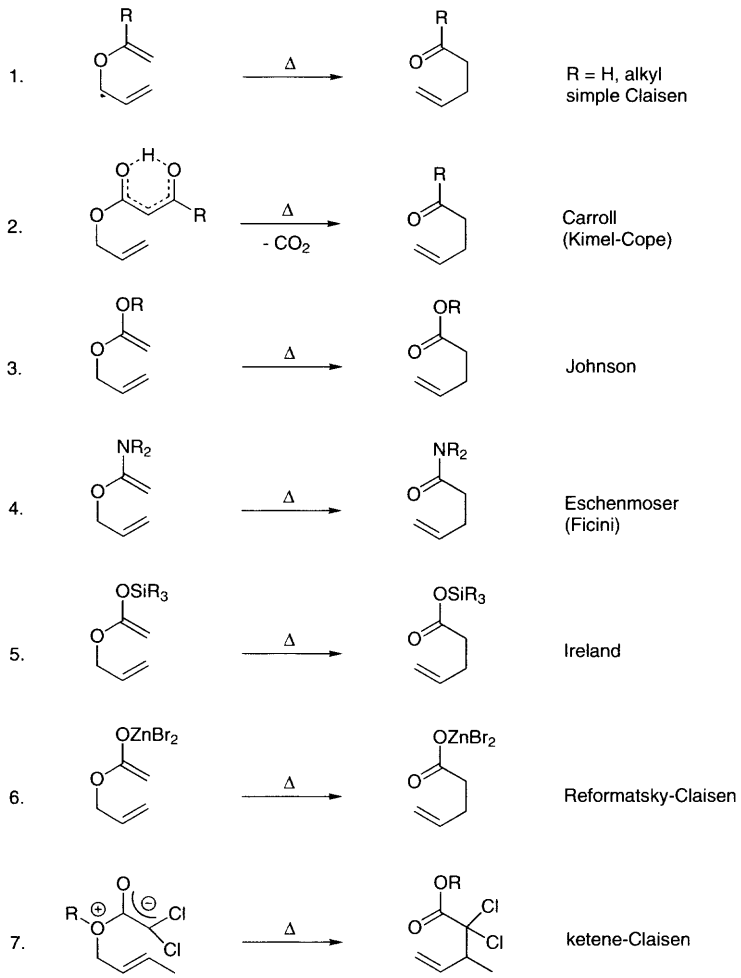
In addition to the classical allyl vinyl ether rearrangement, several variations have been developed which improve the synthetic value of the Claisen rearrangement with respect to the preparation of the parent compounds, reaction conditions and stereoselectivity.

The most popular variants are depicted below. Depending on the oxidation level of the products, they can be classified as two types:

(1) rearrangements which afford aldehydes and ketones (1 and 2),

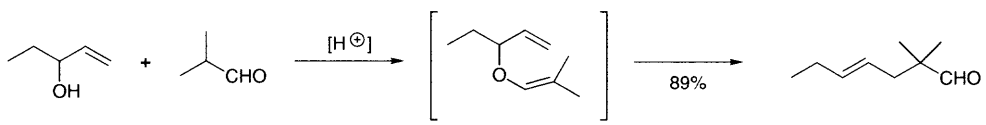
(2) rearrangements which afford acid derivatives (3–7).

for references see p 3736

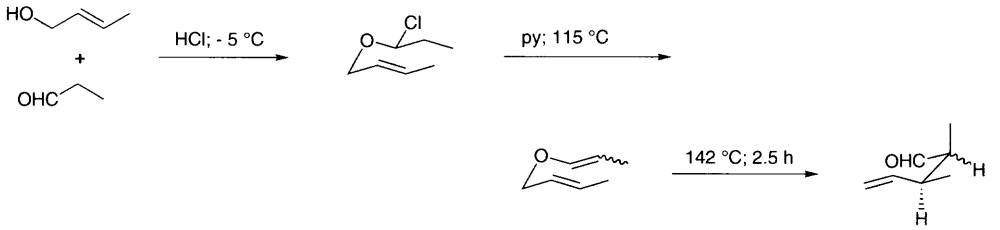


Claisen Rearrangement of Allyl Vinyl Ethers

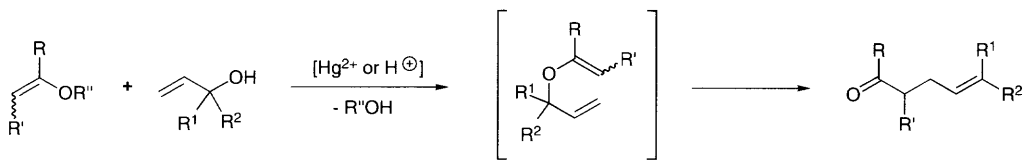
Allyl vinyl ethers have been prepared by acid-catalyzed exposure of an aldehyde to an allylic alcohol followed by thermolysis of the bis-allyl acetal[150].



If the reaction is carried out at low temperature in the presence of hydrogen chloride, the chlorohydrin can be isolated and dehydrohalogenated in a separate step[151].

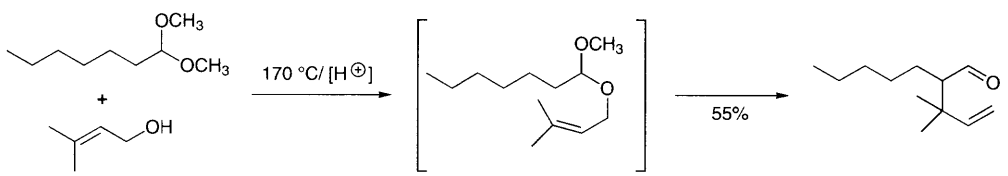


A frequently used route is the mercury- or acid-catalyzed transvinylation of vinyl ethers with allylic alcohols (Saucy–Marbet reaction)[152–154].



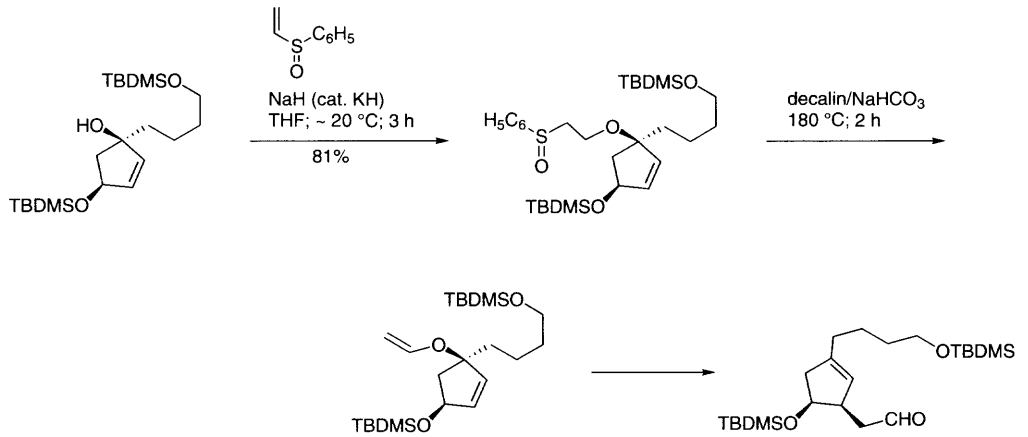
The allyl vinyl ethers are usually prepared in situ, but it is also possible to isolate the primarily formed mixed acetals or allyl vinyl ethers[155–157]. With low-boiling vinyl ethers the reaction is carried out in a sealed tube with an excess of the vinyl ether. For a tandem Claisen-rearrangement–ene cyclization involving the Saucy–Marbet reaction cf. ref 158. The generation of isopropenyl ethers from esters is described in ref 159. For a related Claisen rearrangement by the reaction of 2-methoxybutadiene with enols and phenols see ref 160.

Acetals can be used as chemical equivalents for vinyl ethers[161–163]. With high-boiling acetals the reaction can be carried out under atmospheric pressure.



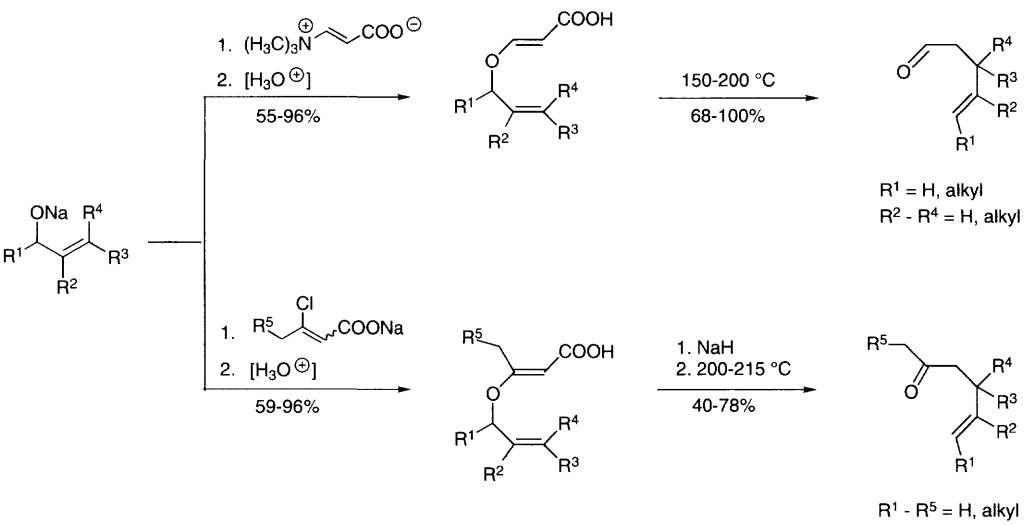
Allyl vinyl ethers have also been obtained by elimination reactions, e.g., intramolecular bromoetherification/base-catalyzed hydrogen bromide elimination[164–166], or the phenylseleno etherification/selenoxide elimination reaction[158, 167]. Tertiary allylic alcohols have been vinylated by a Michael-type addition to a vinyl sulfoxide followed by elimination of benzenesulfenic acid[168].

for references see p 3736

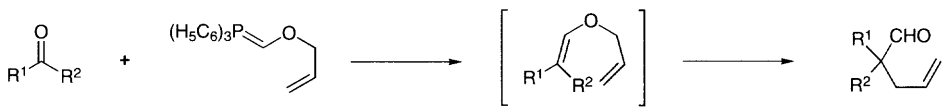


Furthermore, base-catalyzed intramolecular additions of allylic alcohols[169] or allyloxy radicals[170] to alkynes, or dehydration[171,172], have been employed for the synthesis of allyl vinyl ethers.

An alternative route to allyl vinyl ethers is the addition of allylic alcoholates to acrylic acid derivatives (cf. p 3305)[107,173]. This method is limited to primary and secondary allylic alcohols.

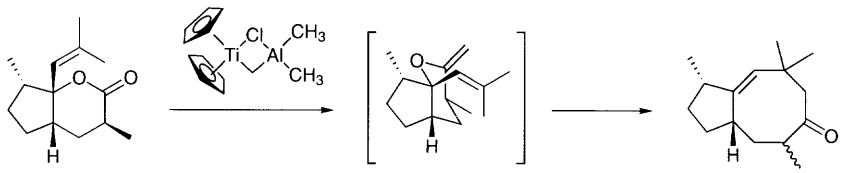


Carbonyl precursors can easily be transformed to allyl vinyl ethers by olefination reactions[174,175]. For example, the vinyl ether double bond of allyl vinyl ethers has been constructed with allyloxymethyltriphenylphosphonium ylides[175].



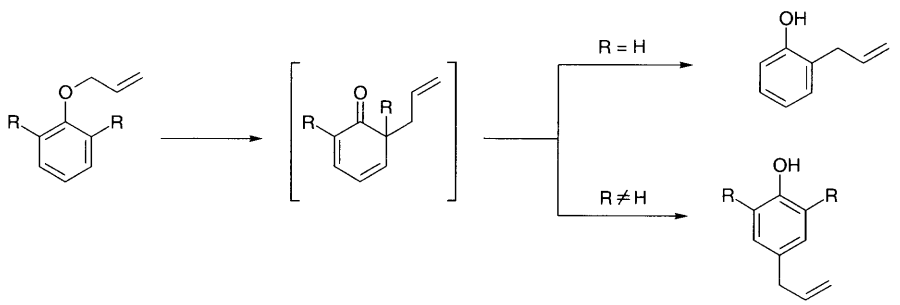
The construction of the allyl ether double bond can be achieved with normal Wittig-type olefinations[176,177].

The Tebbe reagent, prepared from cyclopentadienyltitanium dichloride and trimethylaluminum, is an extremely useful reagent for the methylenylation of lactones[178-180].



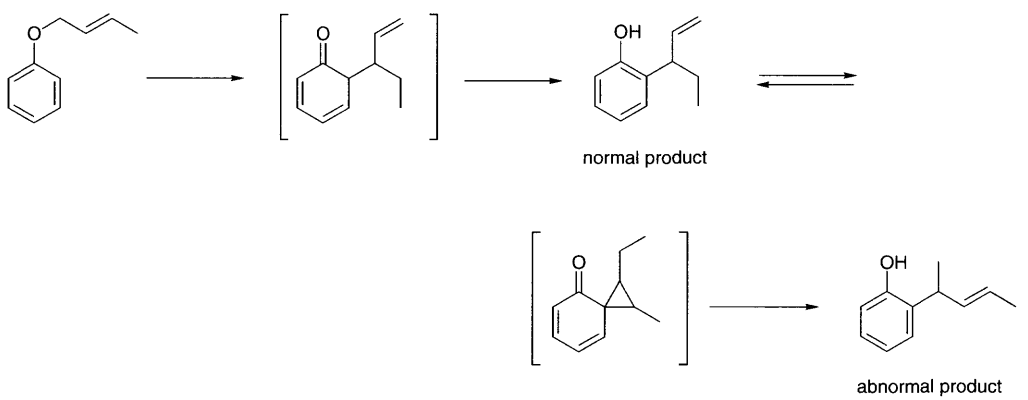
For new developments in the synthesis of vinyl ethers (and allyl vinyl ethers), particularly for stereoselective methods, see ref 181.

The aromatic Claisen rearrangement of substrates, which are unsubstituted in the ortho position, produces ortho-substituted phenols via intermediate *ortho*-dienones[182-184]. If the ortho positions are substituted, a tandem Claisen–Cope rearrangement (also termed as para-Claisen rearrangement) occurs to give a para-substituted allylphenol[185,186] (cf. Section 1.6.3.1.3.1.). These rearrangements are usually regarded as concerted[57].



Sometimes, the *para*-product is obtained, even if both ortho positions are unsubstituted[187,188], particularly, when the rearrangement is catalyzed by organoaluminum reagents[140,189].

In the "abnormal" Claisen rearrangement[29], a subsequent homodienyl [1,5] sigmatropic H-shift leads to the formation of isomeric allylphenols[190-194].



The aromatic Claisen rearrangement has found wide application, e.g., in the syntheses of flavenes[195], dideoxydaunomycinone[196], dihydrocoumarins[197], (±)-herbertene[198], cyclotri-

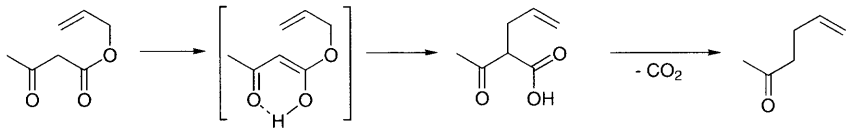
for references see p 3736

guaiacylene[199], indoles[200], 2*H*-benzopyrans[201], *p*-benzochinones[202], tetrahydrobenzochinolines[203], calix[4]arenes[204], and mycophenolic acid[205].

For a consecutive electrocyclic ring closure–Claisen rearrangement–intramolecular amination process see refs 206 and 207. For studies on the sequential Claisen rearrangement of methyl-3-aryloxy-2-(aryloxymethyl)prop-2-enoates see ref 208 and for the base-catalyzed aromatic Claisen rearrangement of 3-hydroxyphenyl allyl ethers, cf. ref 209.

Carroll Rearrangement

The Carroll rearrangement, first reported in 1940[210–212], is an old and well-established versatile yet complementary variant of the Claisen rearrangement. The mechanism of this reaction was proposed in 1943 by Kimel and Cope[213]. With respect to the stereoselectivity, the most favorable feature of the Carroll rearrangement is the defined configuration of the double bond generated in the intermediate hydrogen-bonded enol.



The substrates can easily be prepared by the condensation of an allylic alcohol with acetoacetic ester. Another approach is the reaction of 5-acyl Meldrum's acid with allylic alcohols[214]. Treatment of diketene with an allylic alcohol in the presence of catalytic amounts of 4-(dimethylamino)pyridine[215] at −20 °C followed by stirring at ~20 °C makes the generation of the substrates routine (80–93%[100]).

Uncatalyzed thermal Carroll rearrangements normally require harsh conditions [heating to 130–220 °C; neat or in a high-boiling solvent (xylene, diphenyl ether)]. Occasionally, under these conditions, allylic regiomers are obtained as byproducts. These probably result from an allylic rearrangement of the β-oxo esters followed by normal [3,3] sigmatropic rearrangement[100,216].

Rate enhancements with bases have been observed (triisopropoxyaluminum[217,218], *s*-collidine[219], sodium acetate[220], sodium hydride[221]).

A further improvement is the ester enolate Carroll rearrangement of the dianion of allylic acetoacetates, generated by treatment with two equivalents of lithium diisopropylamide at −78 °C in tetrahydrofuran[100]. The dianions rearrange at ~20 °C to 65 °C in 40–80% yield. For an example, see p 3320.

Another modification is the rearrangement of silyl ketene acetals[222].

A low temperature Carroll rearrangement catalyzed by palladium(0) has also been reported[223].

Johnson Rearrangement

The Johnson ortho ester method is closely related to the acetal method[224,225]. The rearrangement proceeds via a ketene acetal intermediate derived from an allylic alcohol and an ortho ester in the presence of an acid[226,227].