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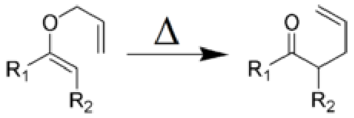
Claisen rearrangement

The **Claisen rearrangement** is a powerful carbon–carbon bond-forming chemical reaction discovered by Rainer Ludwig Claisen.[1] The heating of an allyl vinyl ether will initiate a [3,3]-sigmatropic rearrangement to give a γ,δ-unsaturated carbonyl.[2][3][4][5]

Claisen rearrangement	
Named after	Rainer Ludwig Claisen
Reaction type	Rearrangement reaction
Identifiers	
Organic Chemistry Portal	claisen-rearrangement
RSC ontology ID	RXNO:0000148



Contents

Mechanism

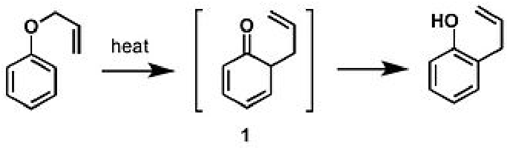
The Claisen rearrangement is an exothermic, concerted (bond cleavage and recombination) pericyclic reaction. Woodward–Hoffmann rules show a suprafacial, stereospecific reaction pathway. The kinetics are of the first order and the whole transformation proceeds through a highly ordered cyclic transition state and is intramolecular. Crossover experiments eliminate the possibility of the rearrangement occurring via an intermolecular reaction mechanism and are consistent with an intramolecular process.[6][7]

There are substantial solvent effects observed in the Claisen rearrangement, where polar solvents tend to accelerate the reaction to a greater extent. Hydrogen-bonding solvents gave the highest rate constants. For example, ethanol/water solvent mixtures give rate constants 10-fold higher than sulfolane.[8][9] Trivalent organoaluminium reagents, such as trimethylaluminium, have been shown to accelerate this reaction.[10][11]

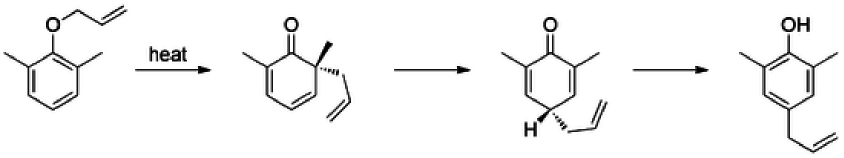
Variations

Aromatic Claisen rearrangement

The first reported Claisen rearrangement is the [3,3]-sigmatropic rearrangement of an allyl phenyl ether to intermediate 1, which quickly tautomerizes to a 2-allylphenol.



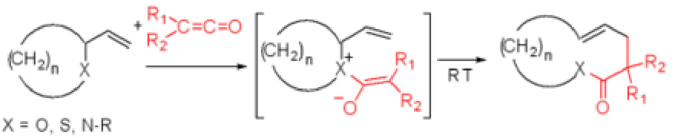
Meta-substitution affects the regioselectivity of this rearrangement.[12][13] For example, electron withdrawing groups (such as bromide) at the *meta*-position direct the rearrangement to the *ortho*-position (71% *ortho* product), while electron donating groups (such as methoxy), direct rearrangement to the *para*-position (69% *para* product). Additionally, presence of *ortho* substituents exclusively leads to para-substituted rearrangement products (tandem Claisen and Cope rearrangement).[14]



If an aldehyde or carboxylic acid occupies the *ortho* or *para* positions, the allyl side-chain displaces the group, releasing it as carbon monoxide or carbon dioxide, respectively.[15][16]

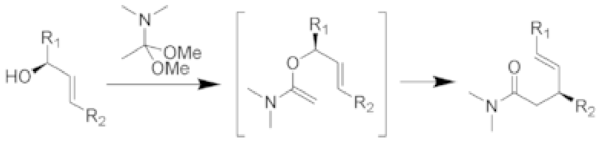
Bellus–Claisen rearrangement

The Bellus–Claisen rearrangement is the reaction of allylic ethers, amines, and thioethers with ketenes to give γ,δ-unsaturated esters, amides, and thioesters.[17][18][19] This transformation was serendipitously observed by Bellus in 1979 through their synthesis of an intermediate to an insecticide, pyrethroid. Halogen substituted ketenes (R_1, R_2) are often used in this reaction for their high electrophilicity. Numerous reductive methods for the removal of the resulting α-haloesters, amides and thioesters have been developed.[20][21] The Bellus-Claisen offers synthetic chemists a unique opportunity for ring expansion strategies.

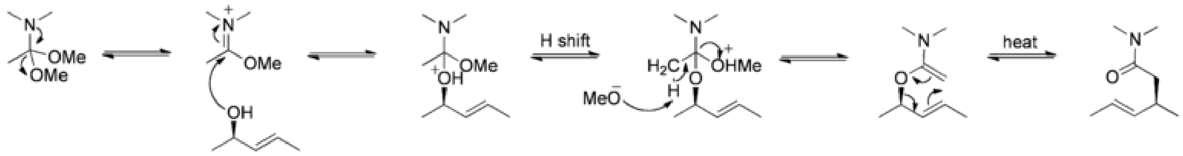


Eschenmoser–Claisen rearrangement

The Eschenmoser–Claisen rearrangement proceeds by heating allylic alcohols in the presence of *N*,*N*-dimethylacetamide dimethyl acetal to form a γ,δ-unsaturated amide. This was developed by Albert Eschenmoser in 1964.[22][23] Eschenmoser-Claisen rearrangement was used as a key step in the total synthesis of morphine.[24]

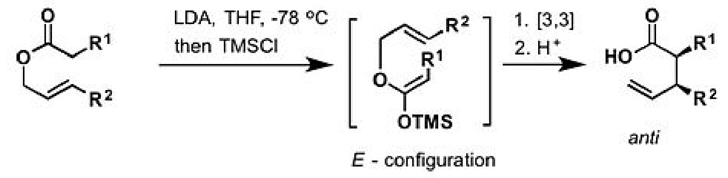


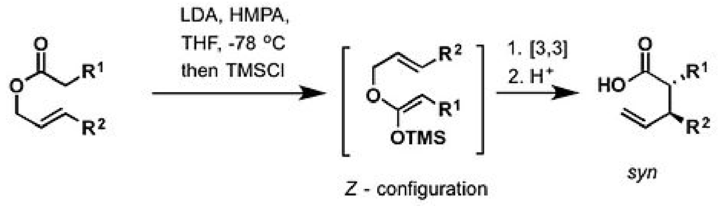
Mechanism:[14]



Ireland–Claisen rearrangement

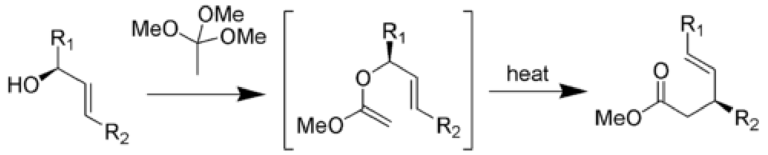
The Ireland–Claisen rearrangement is the reaction of an allylic carboxylate with a strong base (such as lithium diisopropylamide) to give a γ,δ-unsaturated carboxylic acid.[25][26][27] The rearrangement proceeds via silylketene acetal, which is formed by trapping the lithium enolate with chlorotrimethylsilane. Like the Bellus-Claisen (above), Ireland-Claisen rearrangement can take place at room temperature and above. The *E*- and *Z*-configured silylketene acetals lead to anti and syn rearranged products, respectively.[28] There are numerous examples of enantioselective Ireland-Claisen rearrangements found in literature to include chiral boron reagents and the use of chiral auxiliaries.[29][30]



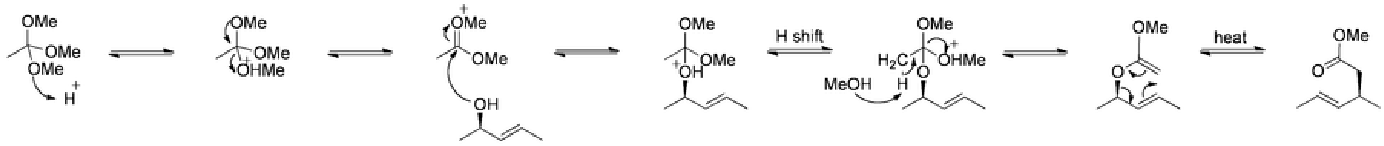


Johnson–Claisen rearrangement

The Johnson–Claisen rearrangement is the reaction of an allylic alcohol with an orthoester to yield a γ,δ-unsaturated ester.[31] Weak acids, such as propionic acid, have been used to catalyze this reaction. This rearrangement often requires high temperatures (100–200 °C) and can take anywhere from 10 to 120 hours to complete.[32] However, microwave assisted heating in the presence of KSF-clay or propionic acid have demonstrated dramatic increases in reaction rate and yields.[33][34]



Mechanism:[14]



Kazmaier–Claisen rearrangement

The Kazmaier-Claisen rearrangement is the reaction of an unsaturated amino acid ester with a strong base (such as lithium diisopropylamide) and a metal salt at –78 °C to give a chelated enolate as intermediate.[35][36] While different metal salts can be used to form the enolate, the use of zinc chloride results in the highest yield and gives the best stereospecificity.[37] The enolate species rearranges at –20 °C to form an amino acid with an allylic side chain in α-position. This method was described by Uli Kazmaier in 1993.[38]

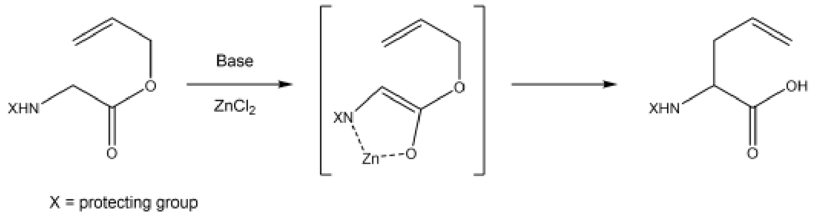


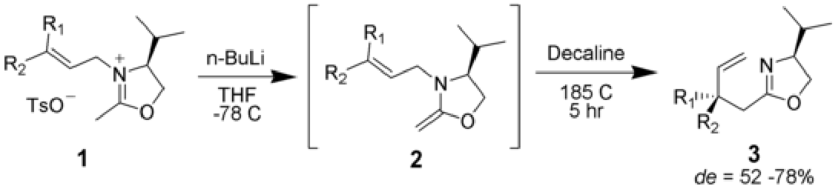
Photo-Claisen rearrangement

The Claisen rearrangement of aryl ethers can also be performed as a photochemical reaction. In addition to the traditional *ortho* product obtained under thermal conditions (the [3,3] rearrangement product), the photochemical variation also gives the *para* product ([3,5] product), alternate isomers of the allyl group (for example, [1,3] and [1,5] products), and simple loss of the ether group, and even can rearrange alkyl ethers in addition to allyl ethers. The photochemical reaction occurs via a stepwise process of radical-cleavage followed by bond-formation rather than as a concerted pericyclic reaction, which therefore allows the opportunity for the greater variety of possible substrates and product isomers.[39] The [1,3] and [1,5] results of the photo-Claisen rearrangement are analogous to the photo-Fries rearrangement of aryl esters and related acyl compounds.[40]

Hetero-Claisens

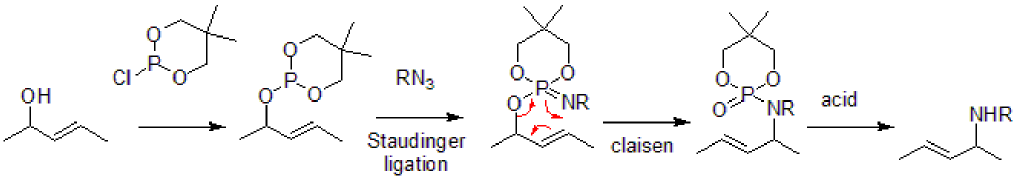
Aza–Claisen

An iminium can serve as one of the pi-bonded moieties in the rearrangement.[41]



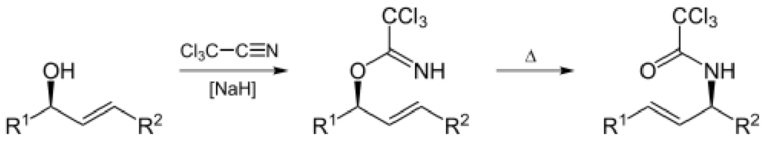
Chen–Mapp reaction

The Chen–Mapp reaction, also known as the [3,3]-phosphorimidate rearrangement or Staudinger–Claisen reaction, installs a phosphite in the place of an alcohol and takes advantage of the Staudinger reduction to convert this to an imine. The subsequent Claisen is driven by the fact that a P=O double bond is more energetically favorable than a P=N double bond.[42]



Overman rearrangement

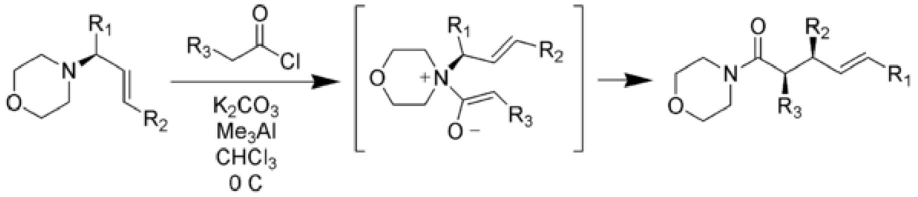
The Overman rearrangement (named after Larry Overman) is a Claisen rearrangement of allylic trichloroacetimidates to allylic trichloroacetamides.[43][44][45]



The Overman rearrangement is applicable to the synthesis of vicinol diamino compounds from 1,2-vicinal allylic diols.

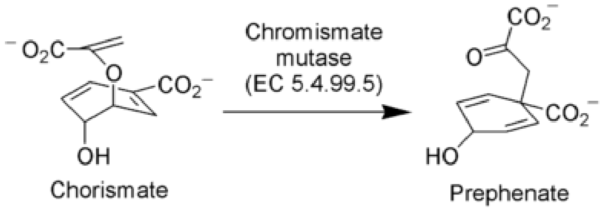
Zwitterionic Claisen rearrangement

Unlike typical Claisen rearrangements which require heating, zwitterionic Claisen rearrangements take place at or below room temperature. The acyl ammonium ions are highly selective for *Z*-enolates under mild conditions.[46][47]



In nature

The enzyme chorismate mutase (EC 5.4.99.5) catalyzes the Claisen rearrangement of chorismate to prephenate, an intermediate in the biosynthetic pathway towards the synthesis of phenylalanine and tyrosine.[48]



History

Discovered in 1912, the Claisen rearrangement is the first recorded example of a [3,3]-sigmatropic rearrangement.[1][49][50]

See also

- Carroll rearrangement
- Cope rearrangement

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