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The steering pathway: Ketene-Claisen rearrangement (KCR)-1978−2016

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ABSTRACT

From what began as a casual discovery of the ketene-Claisen rearrangement (the Malherbe-Belluš rearrangement) over 3 decades ago has flourished a reaction of substantial significance. The noticeable qualities of the ketene-Claisen rearrangement is accomplished in terms of experimental simplicity, forming new C−C bonds, high levels of chemo- and stereocontrol, ring enlargements and constructing new stereocenters. This survey of the ketene-Claisen rearrangement with some applications in organic synthesis will not only recapitulate the prospective of this reaction so far but also illustrate the achievable future significant prospective.

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Contents

1. Introduction

Ludwig Claisen[1] reported in 1912, the Claisen rearrangement, which involved the [3,3]-sigmatropic rearrangement of an allyl-vinyl ether to give a γ,δ-unsaturated carbonyl scaffold (Scheme 1). Simply the Claisen rearrangement to construct a C−C σ-bond can be considered as the intramolecular nucleophilic substitution addition of a carbonyl enol (Claisen rearrangement), thiocarbonyl enol (thia-Claisen rearrangement) or enamine (aza-Calisen

rearrangement) to an allylic ether, sulfide or amine, respectively. The process involves π-bond migration and falls under the classification [3,3]-sigmatropic shift.[2]

In addition, the esteemed growth of this reaction can be seen from different variants such as the Carroll (1940),[3] Eschenmoser (1964),[4] Saucy-Marbet (1967),[5] Johnson (1970),[6] Ireland (1972),[7] Reformatsky-Claisen rearrangement (1973),[8] Malherbe and Belluš (1978)[9] and Denmark (1982).[10]
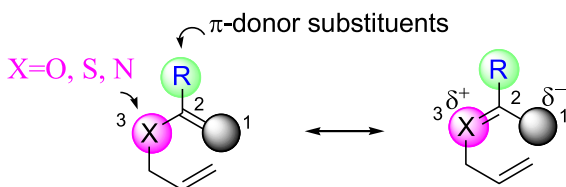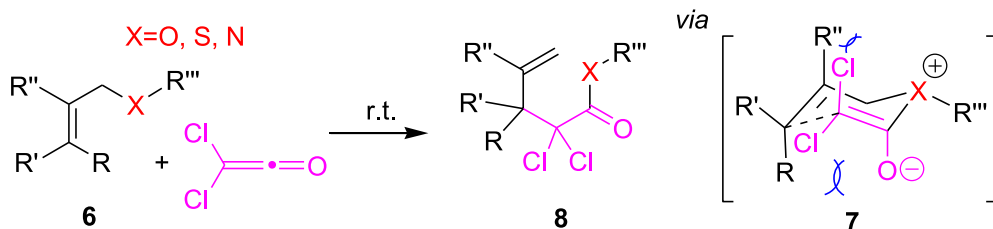
The ketene-Claisen reaction (the Malherbe-Belluš rearrangement or ketene-[3,3]-sigmatropic rearrangement) was first described by Belluš and Malherbe in 1978.[9] Treatment of allylic ethers with *in situ* prepared dichloroketene (a solo subunit) afford

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X=O　Claisen rearrangement
X=S　thia-Claisen rearrangement
X=N　aza-Claisen rearrangement
X=C　Cope rearrangement
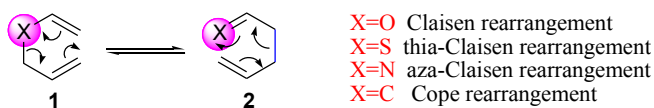
Scheme 1. The [3,3]-sigmatropic rearrangement.[1]
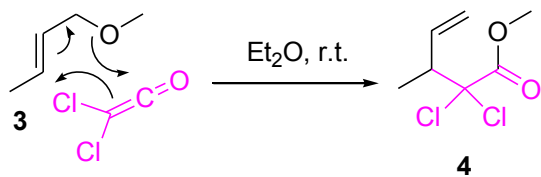
Scheme 2. The general ketene-Claisen rearrangement.[11]
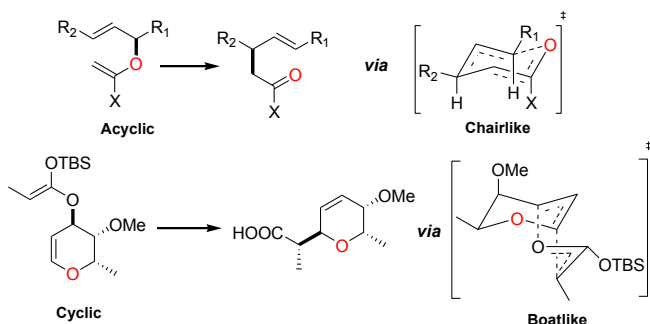
Scheme 3. The Stereocontrol of the [3,3]-sigmatropic rearrangement.[9]

rearrangement adducts in good yield[11] (Scheme 2). This protocol works as well with allylic sulfides[12,13] and tertiary allylic amines.[14,15] The ketene-Claisen reaction can be quite efficient and usually takings with high levels of stereocontrol. Accordingly, it has been used in making natural products and medicinal agents.[16]

All the reports published in this area between 1978 (the year of its discovery) and 2016 have been summarized in this review article, in order to provide detailed information about this smart and useful reaction.

Fig. 1. The ideal 1,3-dipolar intermediates in the [3,3]-sigmatropic rearrangement. [9]

1.1. Sterochemical aspects for the ketene-Claisen reaction

The high level of stereocontrol of the [3,3]-sigmatropic rearrangements in the acyclic systems can be achieved through the chair-like transition states depending on the temperature (Scheme 3).

Consequently, a high stereo-control can be attained of usually well-ordered transition states. However such desired conversion frequently involves in elevated temperatures in order to the survival of different functional moieties. Accordingly this issue has been determined through the fixing of a π-donor substituent at position 2 or a negative charge at position 1 in the enolate coordination and a heteroatom with a positive charge at position 3 (Fig. 1).[9]

A facile synthesis of compound **8** (Scheme 4) via [3,3]-sigmatropic rearrangement, can be depicted as a two-step reaction commenced by a nucleophilic addition reaction of the allylic heteroatom (O, S, N) at the ketene's sp carbon atom to generate the 1,3- dipolar intermediate **7** (preferred chair-like transition state with least 1,3 diaxial steric hindrances).[11]

The structure-function relation study on the chemo- and stereoselectivity of the ketene-Claisen reaction was initially recognized by Belluš et al.[12,17] that depicted the full chirality shift from C−S to C−C bond. For instance, chiral cyclic allyl thioethers **9** as a precursor, gave almost a complete chirality transfer (99% ee) (Scheme 5), whilst, a chirality transfer of 96–98% was observed when chiral acyclic allyl thioethers **12, 13** were employed as starting precursors (Scheme 6). Here the more favoured nucleophilic sulphur showed the complete chemoselection due to compete for dichloroketene. Likewise, Aggarwal et al.[31] depicted a stereospecifically complete chirality transfer of tertiary and quaternary stereocenters via the reaction of dichloroketene with camphor-derived 1,3-oxathianes of α,β-unsaturated aldehydes **18** to give macrocyclic thiolactones **20**.

A novel 1,2-asymmetric induction in the ketene-Claisen rearrangement was also described by Belluš and co-workers,[17a] where the optically active allyl thioethers **21** (a moiety for the rearrangement) showed the excellent chemo-selectivity (syn-selectively ca 20:1). Only the sulphur migration was observed in the rearranged thio-esters **23** that subsequently gives the cyclization products **24** and **25** (Scheme 7).

Two decades later, after the discovery of reversal of diastereoselectivity, Porter et al.[13a] has attempted to produce reversal of facial selectivity in a thia-Claisen rearrangement via the reaction of N-benzylpyrrolidine-2-thione and D-mannitol derived chiral allylic bromides. The presence of a bromine atom on the allylic bromide double bond turns around the logic of diastereoselectivity in the [3,3]-sigmatropic rearrangement. A research on the stereochemical reaction pathway demonstrates a quality for reaction through the facial selectivity; N,S-ketene acetal proceeds through Re-face selectivity (conformation **I**) whereas vinyl bromide reacts mostly through Si-face selectivity (conformation **II**) Scheme 8.[13]

In contrast to the Bellus's study of high 1,2-stereoinduction, Gonda obtained, under the similar conditions, only 60% and 80% of

Scheme 4. Reactions of haloketenes with allylethers and thioethers.[11]
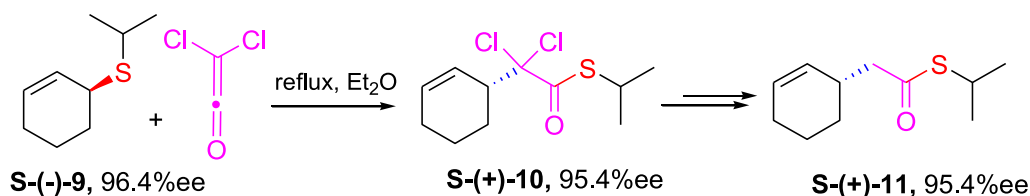
Scheme 5. Chirality transfer in ketene-Claisen rearrangement.[17]
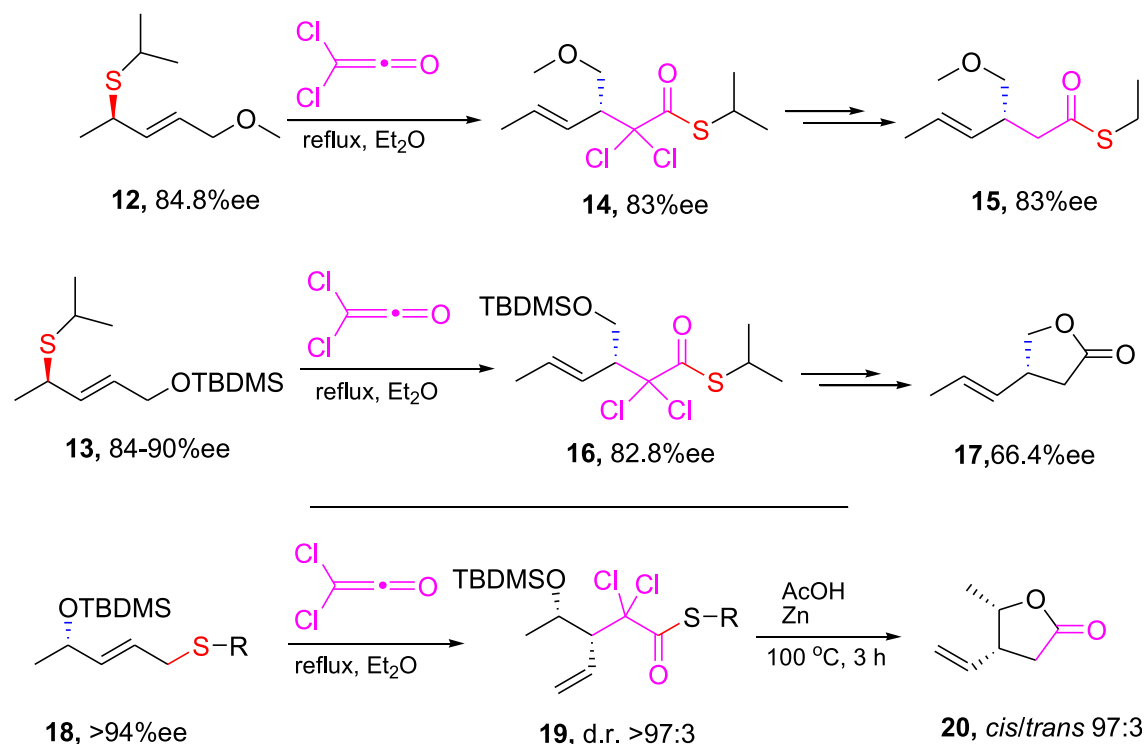
Scheme 6. Chemo- and Stereoselective ketene-Claisen rearrangement of chiral allyltioethers.[12,31]

1,2-stereo-induction originating from protected chiral (2S,3E)-5-(iso-propylsulfonyl)-3-penten-2-amines **26** with Boc and Tos respectively (Scheme 9).[17d] To support this fact, Gonda has performed theoretical calculations subsequently and has established the mechanism and stereoselectivity in the ketene-Claisen rearrangement relating to the models for the steric and electronic
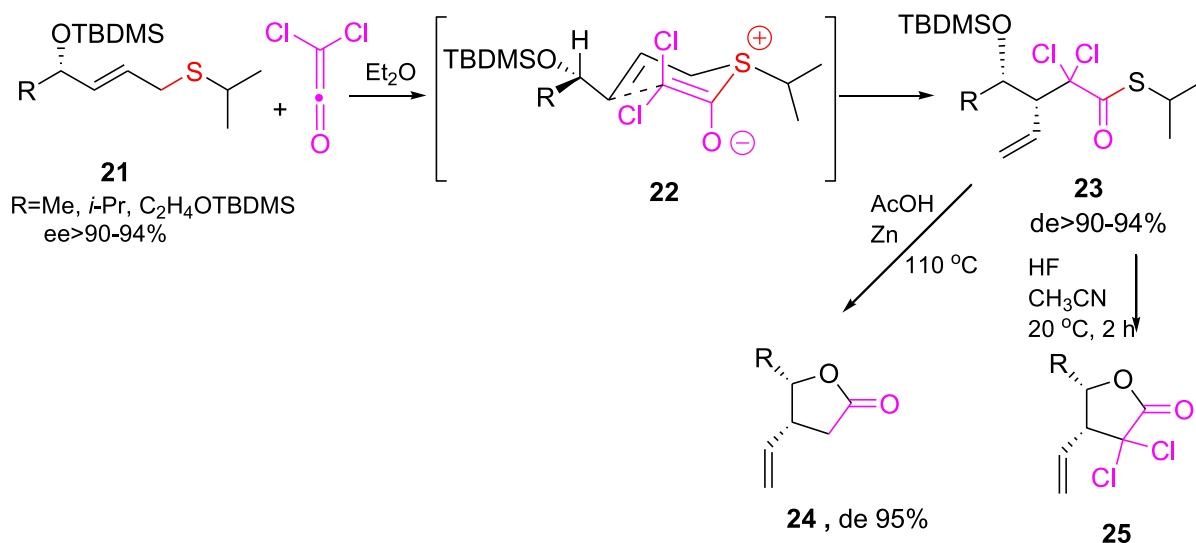
Scheme 7. A 1,2-asymmetric induction in the ketene-Claisen rearrangement.[17a]
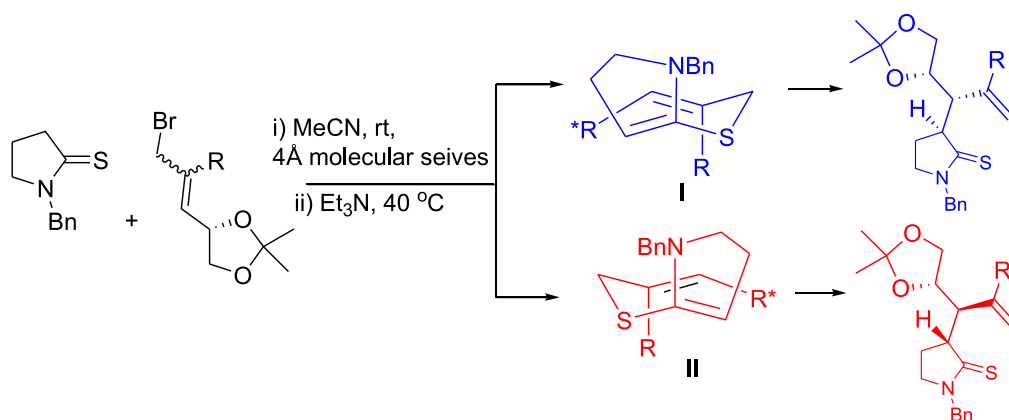
Scheme 8. The reversal of facial selectivity in thia-Claisen rearrangement.[13]
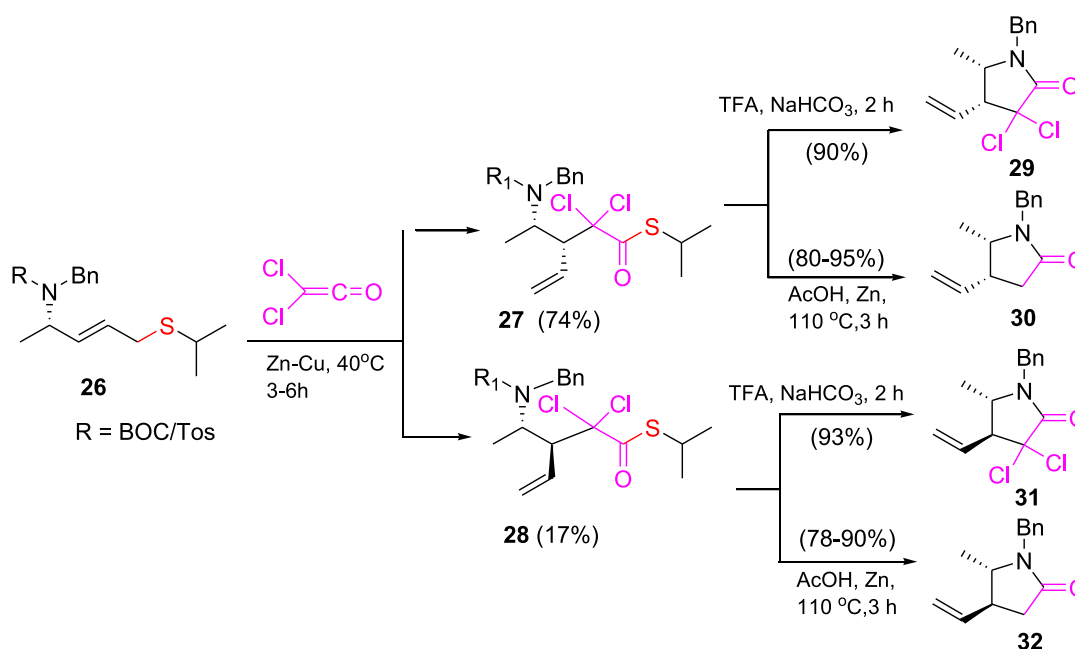
Scheme 9. The ketene Claisen rearrangement of chiral (2S,3E)-5-(isopropylsulfanyl)-3-penten-2-amines **26**.[17d]

course of [3,3]-sigmatropic reactions previously investigated by many research groups.[19–21] Whilst the initial steps towards an enantioselective catalytic ketene-Claisen process were reported by MacMillan and co-workers.[16]

Hence because of the development of the Claisen reaction, opposite stereochemistry in any reaction can be accounted through the suitable selection of olefinic double bond geometry in the substrate.

1.2. The scope of ketenes

Dihaloketene *i.e.* dichloroketene is the most reactive, high electrophilic and commonly used precursor in the ketene-Claisen rearrangement. The chlorines in the rearranged gem-dichloro substrates can be conveniently separated by metal (Zn, Fe) reduction, making this reagent very handy for further transformations.[22]

Due to less stability and quick polymerization of dichloroketene, it is furnished *in situ* in presence of the allylic olefin by (**a**) the dehydrohalogenation of a dichloroacetyl halide **33** with triethylamine or (**b**) the dehalogenation of a trichloroacetyl halide **34** with

activated zinc (Scheme 10). Although, there are certain drawbacks like ammonium salts catalyse the decomposition of dichloroketene in (**a**) and certain olefins are polymerised by zinc salts in (**b**).[23]

Furthermore, the ketenes for the acylation process of an allyl ether, allyl thio-ether or allyl amine involved in the ketene-Claisen rearrangement, have been generally formed *via* one of the two methods showed above (Scheme 10).[15,24]

In addition, the reactions of ketenes with electrophilic and
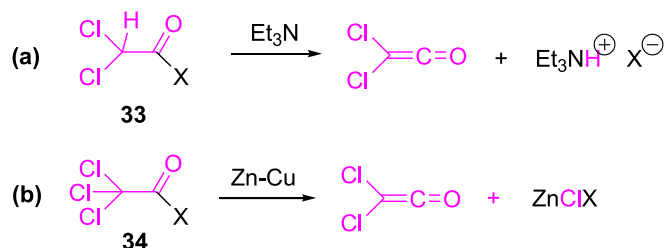
Scheme 10. The cycloaddition of halogenated ketenes.[23]
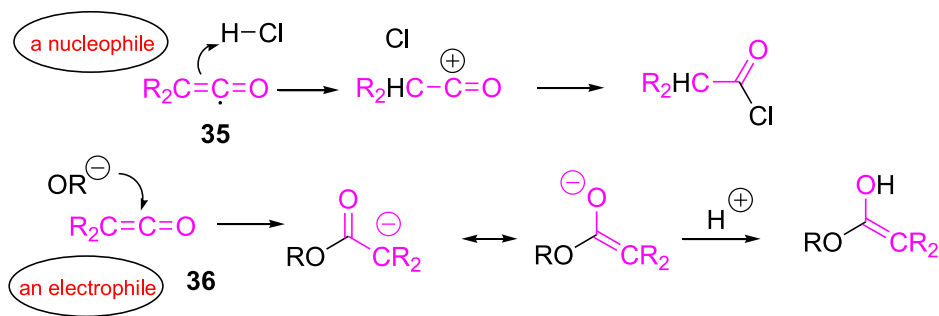
Scheme 11. Reactions of ketenes with electrophilic and nucleophilic reagents.[25]

nucleophilic reagents by concerning the dipole moment, make them more prominent (Scheme 11).[25]

Most interestingly, the cyclic four membered transition states having the polarized electron density at the olefin linkage in most of the ketene addition reactions were reported to give products **37** and **38** (Scheme 12). Likewise the ketene dimerizes *via* addition reactions to generate **39** and **40**.[25] Whereas the reaction of ketenes with alkenes go through concerted [2+2] cycloaddition process to give cyclobutanones **42**.[26,27] However, alkenes having heteroatoms at the allylic position can experience competitive reaction at the heteroatom to form zwitterionic intermediates **43** which instigate the Malherbe-Bellus variant of the Claisen rearrangement particularly in presence of Lewis acids.[28]

The selection of the ketene-Claisen reaction appears to be inadequate to highly electrophilic ketenes,[9,11] while dichloroketene, chloroalkylketenes and diphenylketene[15] have shown to be well-organized in providing the rearrangement. The application of Lewis acid-activated ketenes as alkylketenes and ketenes bearing oxygen, sulphur and nitrogen substituents have been described initially by MacMillan and co-workers.[16]

Many others haloketenes were employed by Malherbe and

Bellus[11] in order to substantiate the reactivity of dichloroketene. None of them were capable for the ketene-Claisen rearrangement. Accordingly, dibromoketene, prepared *in situ* from tribromoacetyl bromide and an amine, could not react with starting allyl ethers and thio-ethers (possibly due to less electrophilic affinity and the presence of bulky bromo-substituents near the reaction centers); difluoroketene (prepared by dehalogenation of bromodifluoroacetyl fluoride) was too unstable and readily decomposed into carbon monoxide and fluorocarbene; whilst monochloroketene (prepared from zinc wool and dichloroacetyl chloride) and chlorocyanoketene (prepared by thermolysis of 4-azido-3-chlor-5-methoxy-2-chloride-2-(5H)-furanone) afforded poor yields.
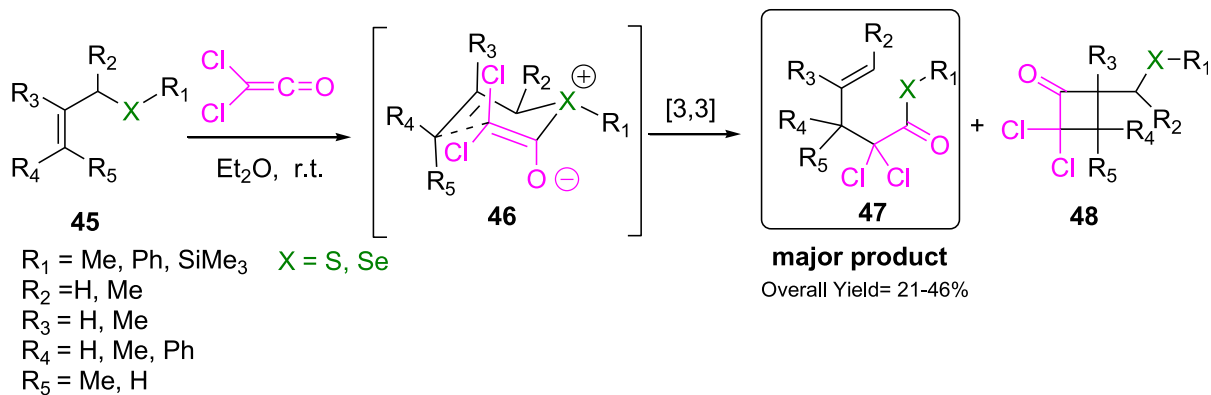
1.3. The Malherbe-Belluš rearrangement's role in synthetic chemistry
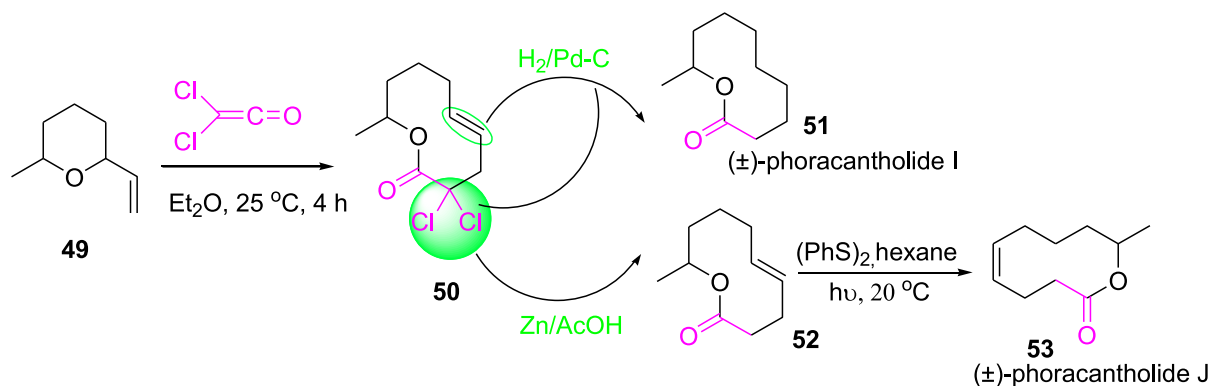
1.3.1. Ketene-Claisen reactions

Conceptually, the initial novel ketene-Claisen rearrangement was investigated by Malherbe and Belluš in 1978.[9,11] In attempt to achieve a [2+2]-cycloaddition, the authors demonstrated that
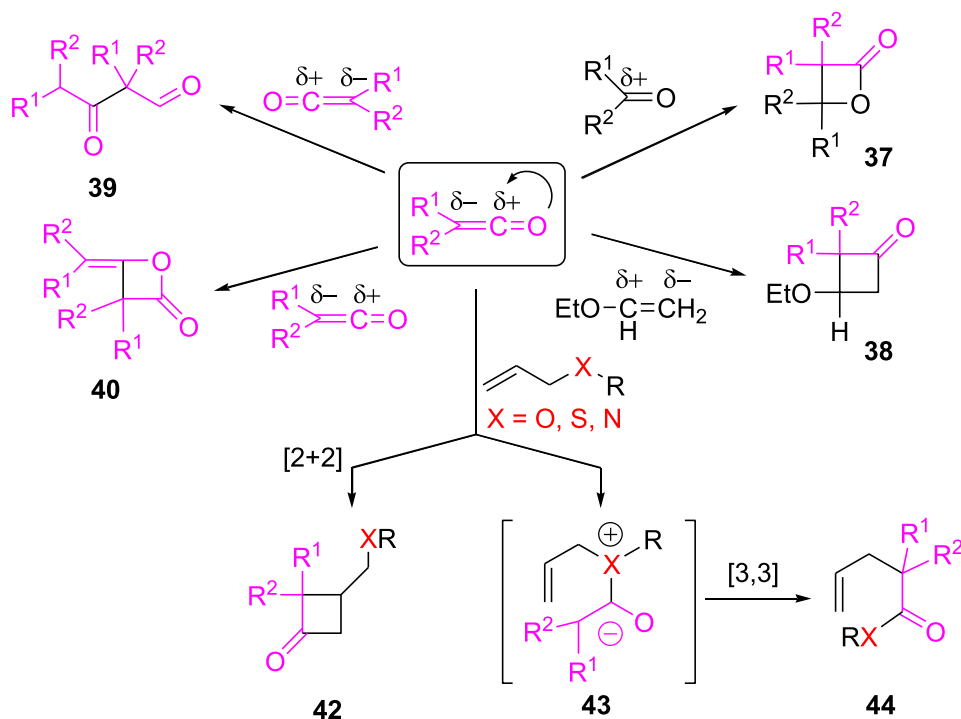
Scheme 12. The reactivity of ketenes in ketene-Claisen rearrangement.[25–28]

**Scheme 13.** The reaction of allylether **45** with dichloroketene.[11]

Scheme 14. The synthesis of (±)-phoracantholide I **51**, and (±)-phoracantholide J **53**.[9]

treatment of an allyl ether **45** (Scheme 13) with dichloroketene resulted instead in the formation of a 1,3-dipolar allyl vinyl ether **46**, which subsequently underwent [3,3]-bond reorganization to give **47** as a major product. This work initially shown the ability of

zwitterionic 1,5-dienes to readily involve in charge accelerated sigmatropic isomerization.

The very simple synthesis of the naturally occurring 10-membered ring macrolides (±)-phoracantholide I **51**, and
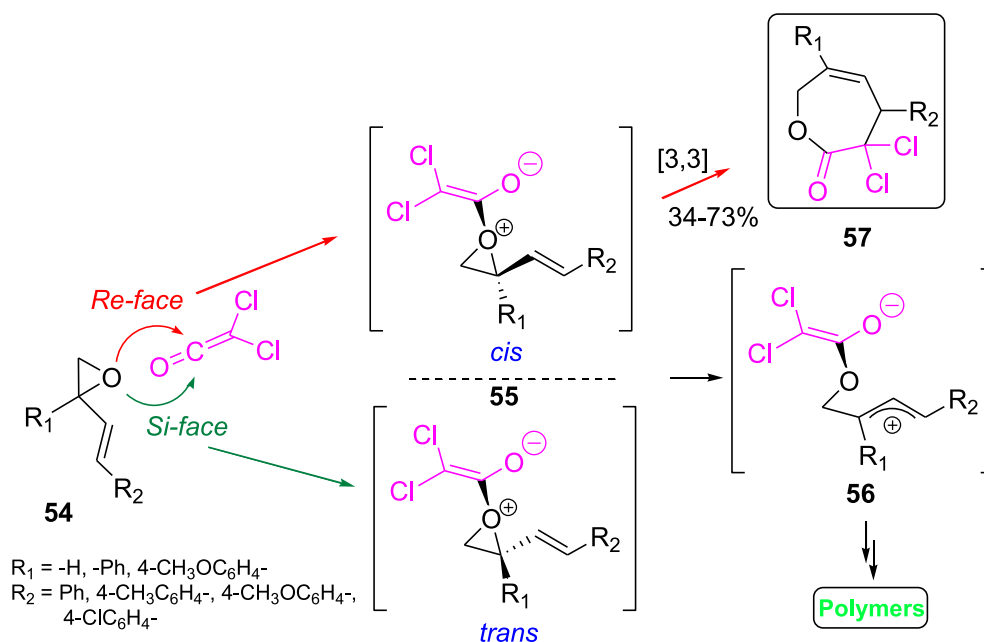
Scheme 15. The cycloaddition reaction of 2-vinyloxiranes **54** and dichloroketene.[29]
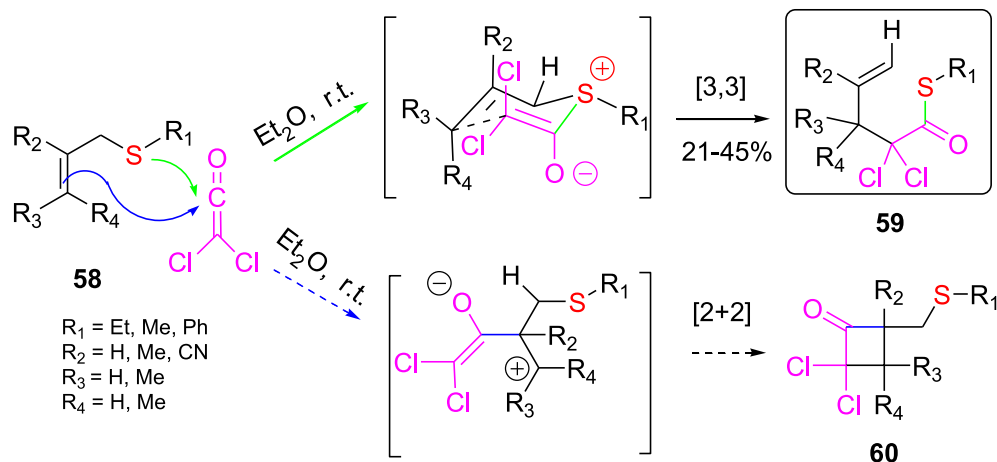
Scheme 16. The reaction of allyl sulfides **58** with *in situ* prepared dichloroketene.[11]

(±)-phoracantholide J **53** demonstrates the felicity of this versatile rearrangement to convert cyclic n-membered, α-vinylsubstituted ethers **50** into unsaturated (n+4)-membered lactones **52**[9] (Scheme 14).

Another convenient and regioselective synthesis of 4,6-diaryl-2,3,4,7-tetrahydrooxepin-2-ones **55** from the cycloaddition reaction between easily available 2-vinyloxiranes **54** and dichloroketene (Scheme 15) have been demonstrated by Ishida et al.[29] Where the synthesis of lactone derivatives such as **57** is proved to be one of the most demanding targets in organic chemistry due to its occurrence in natural products and synthetic utilities as acylating reagents.

1.3.2. Thia ketene-Claisen reaction

Malherbe and Belluš[9,11] also reported the reaction of allyl sulfides (thia-ketene reaction) **58** (Scheme 16) with *in situ* prepared dichloroketene, two competing pathways were observed. Moreover instead of [2+2]-cycloaddition, a [3,3]-sigmatropic rearrangement took place predominantly.

Similarly when an allyl cyclothioether **61** was used as starting unit, a cycloenlargement of the cycle **62** by four carbon atoms was obtained due to [3,3]-rearrangement (Scheme 17).[13a] In addition, the merging of vinylic bromide substituent **63** has also been

reported to establish high facial selectivity, where a thia-Claisen rearrangement of *S*-allylic ketene *N*, *S*-acetals were carried out using substrate with an external allylic stereogenic centre[13b] (Scheme 17).

Rosini and Spineti[18] adopted quite similar approach in order to synthesize multifunctional *di*-thia-macrocyclic systems. Starting from the reaction of dichloroketene with the cyclic thioketals (precursors of α,β-cycloalkenones **66**) to give ring enlargement 1,7-dithiacycloalk-5-en-2-one derivatives **67** even at room temperature and in high yield (Scheme 18).

As mentioned above in Scheme 7, Belluš and co-workers[12,17] had described a route to optically active γ-butyrolactones through a reaction of appropriate substituted precursors **21** and dichloroketene. Furthermore the major advantage is that the less reactive dichloromethylketene also reacts with thioether **21**. The significant thioester **68**, which holds a further stereocenter in the α-position to the carbonyl group was acquired as an inseparable mixture of diastereomers (de ≈ 50%)[30] (Scheme 19). Subsequently, desilylation through the chromatography provided the separable lactones **69** and **70** in ratio 3:1. Reduction of ester **68** furnished the chlorine free lactones **71** and **72** (ratio 3:1). Moreover, the radical dechlorination of **69** and **70** directed the same ratio of dechlorinated lactones.

Aggarwal and co-workers[31] have investigated the in control reactivity of camphor-derived 1,3 oxothianes **73** (previously available from commercial (+)-(10)-camphorsulfonyl chloride) with dichloroketene. They have described that the nucleophilic sulphur atom of the oxathiane moiety **66** attacks stereoselectively to the haloketene to form a macrocylic product **74** (Scheme 20). As an outcome of the high level of stereo-control of tertiary and quaternary chiral centers *via* the tightly ordered transition state ([3,3]-sigmatropic rearrangement), diastereomerically pure oxathianes **67** furnish the final diastereoisomerically pure products **74** in high yield and with complete transfer of chirality. They have noticed that the elimination conditions (Et$_3$N and Cl$_2$CHCOCl) for the formation of the dichloroketene were found to be superior to the reductive conditions (Zn-Cu and Cl$_3$CCOCl) so far as yields and side products were concerned.

1.3.3. Aza-ketene Claisen reaction

Early studies on the aza-ketene Claisen reaction relied on the use of long-lived, electron poor ketenes (Scheme 21) that were either isolated before use,[32] or generated in *situ*.[33] Many researchers have introduced modifications to the aza-ketene-Claisen rearrangement with a view to removing the need for electron-poor ketenes.[34]
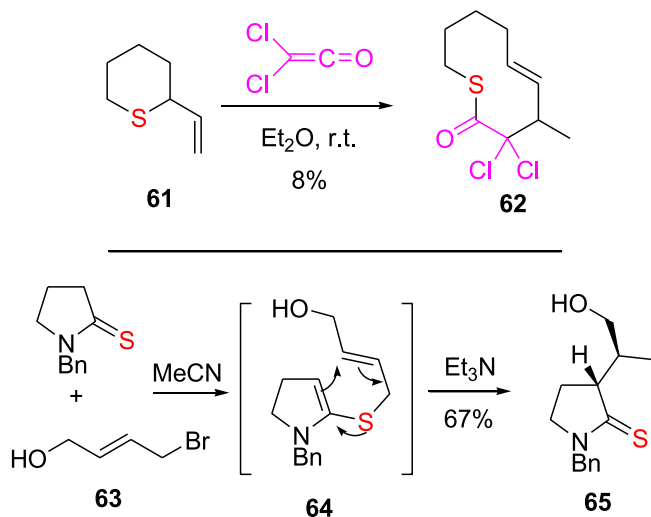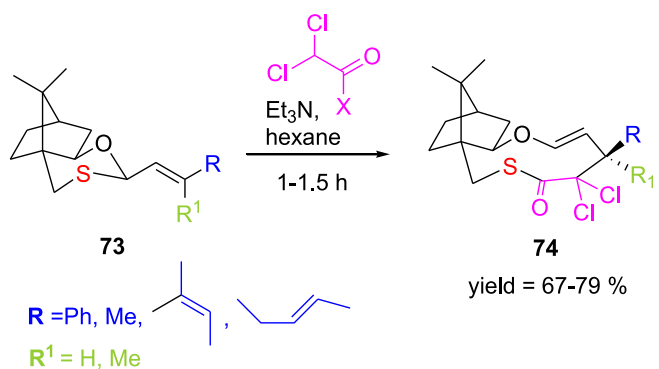

**Scheme 17.** The [3,3]-rearrangement of allyl cyclothioether and *S*-allylic ketene.[13]
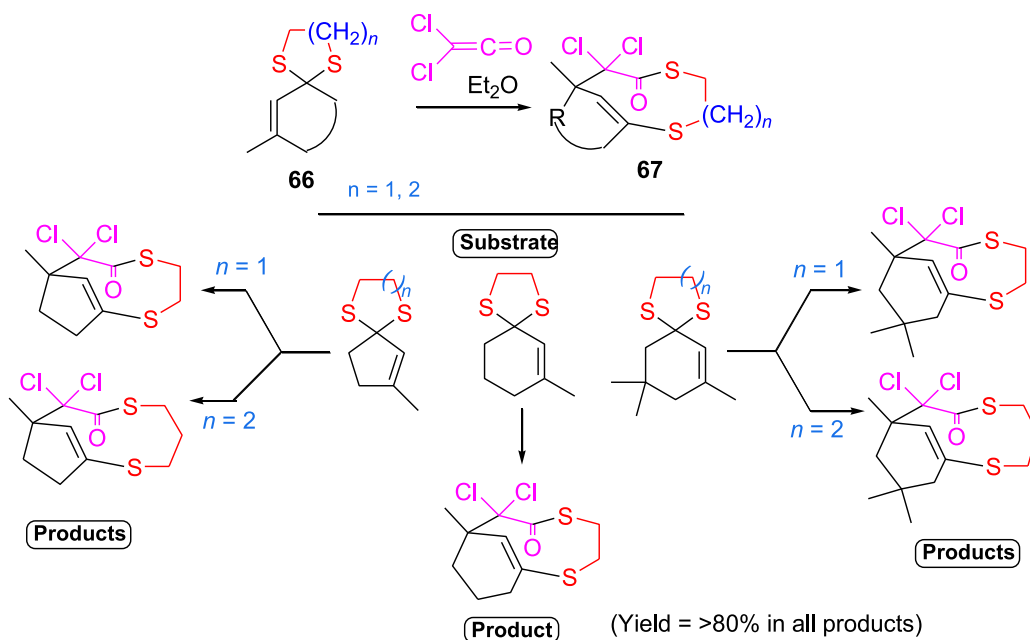
Scheme 18. Rosini and Spineti's synthetic approach of dichloroketene with the cyclic thioketals.[18]
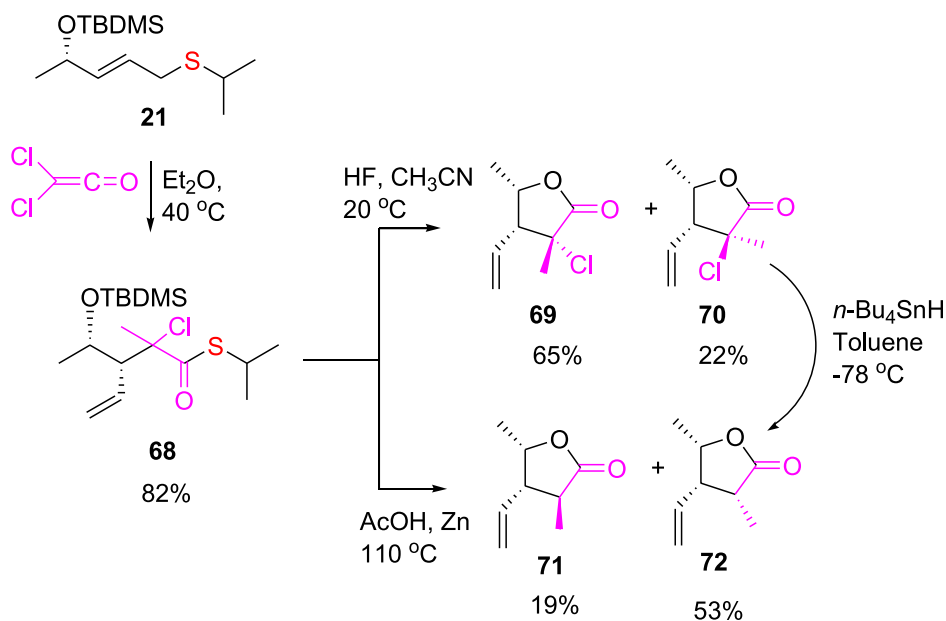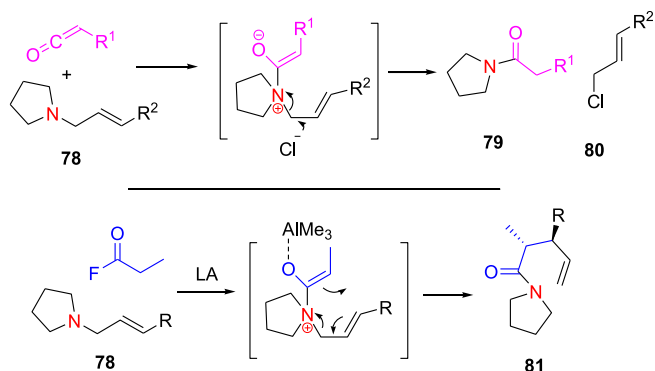
Scheme 19. The Belluš's route to optically active γ-butyrolactones via substituted thioether **21** and dichloroketene.[30]

Scheme 20. The Aggarwal's stereocontrolled approach to form a macrocyclic product **74** from the camphor-derived 1,3 oxothianes **73** with dichloroketene.[31]
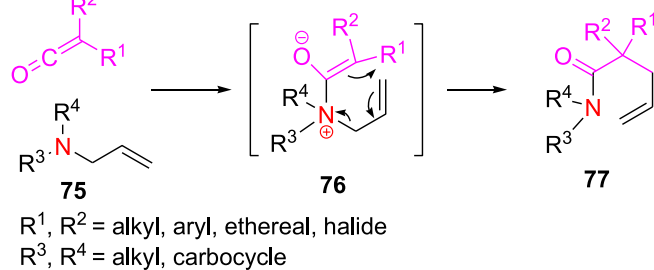
Scheme 21. The general aza-ketene-Claisen rearrangement.[32–34]

Scheme 22. The Nubbemeyer's approach towards the reaction of *N*-allyl pyrrolidines **78** with ketenes.[34b–34c]

Nubbemeyer and co-workers further depicted the reaction of *N*-allyl pyrrolidines **78** with ketenes, generated *in situ via* dehalogenation of α-halogenated acyl chlorides or *via* dehydrohalogenation of acyl chlorides, with no success.[34b] Only 'von Braun' type side products **79** and **80** were recovered (Scheme 22). While a modified approach using two phase systems was successful — a sequential addition of K₂CO₃ of allyl-pyrrolidine, acetyl chloride and trimethyl aluminium furnished the desired rearranged product **81**.[34c] In an attempt to eliminate the competing 'von Braun' process, acyl fluorides were brought in to contact with Lewis acid. The observed stereochemistry in this research was not as simple as in other Claisen rearrangements as the allylic amines were chiral non-racemic compounds and therefore the authors anticipated for a diastereoselective rearrangement by using allyl amines.

Moreover Craig and co-workers prescribed a ketene-Ireland-Claisen hybrid rearrangement utilising stoichiometric amount of trimethylsilyl trifluoromethane sulfonate (TMSOTf) as a Lewis acid to trap the enolate during rearrangement to an imine followed by expulsion of the silyl group to yield an amide (Scheme 23).[34d] A wide variety of allylic amines **82** were examined using ketenes generated in *situ* from propionyl chloride or phenyl acetyl chloride, giving predominantly *syn*-susbstituted products **85**.

In 1989, Ishida and co-workers[29] reported for the first time the reaction of *N*-phenyl-2-(2-phenylvinyl)-aziridine **86** with ketene done in situ by dechlorination of dichloroacetyl chloride led to the synthesis of unsaturated lactam precursors, 3,3-dichloro-1,4-diphenyl-2,3,4,7-tetrahydro-1*H*-azepin-2-one **87** (Scheme 24).

While in 1990, Roberts and co-workers[32] reported a further extension of the aza-ketene-Claisen rearrangement of racemic 2-azabicyclo [2.2.1] heptanes **88** with appropriate functionality (Scheme 25). This approach affords an immediate access to the azabicyclo [4.3.0] nonane skeleton **90** that is a general part of a series of alkaloids possessing diverse biological activities.[35]
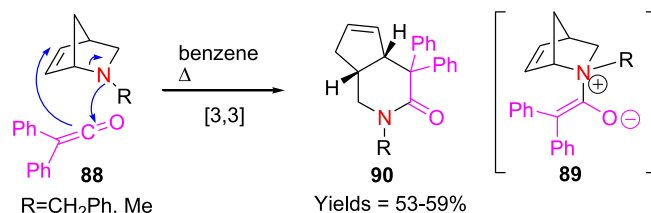
Likewise, Pombo-Villar et al.[36] described the enantioselective synthesis of an alkaloid (−)-δ-*N*-normethylskytantine **94** using an
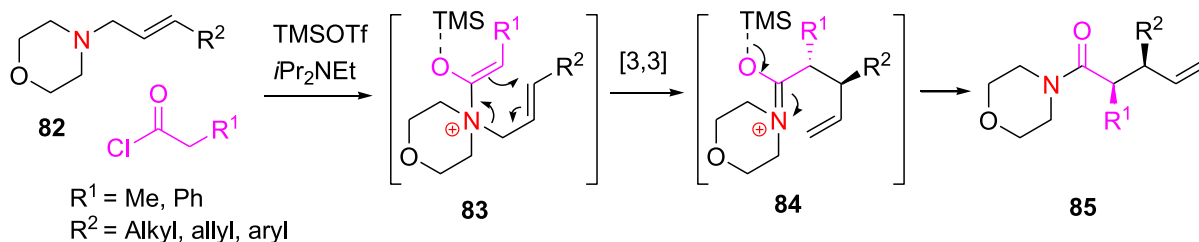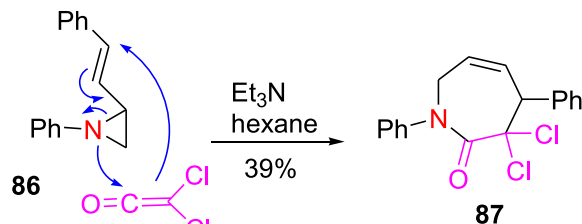
Scheme 24. The Ishida's strategy of reacting *N*-phenyl-2-(2-phenylvinyl)-aziridine **86** with ketene.[29]
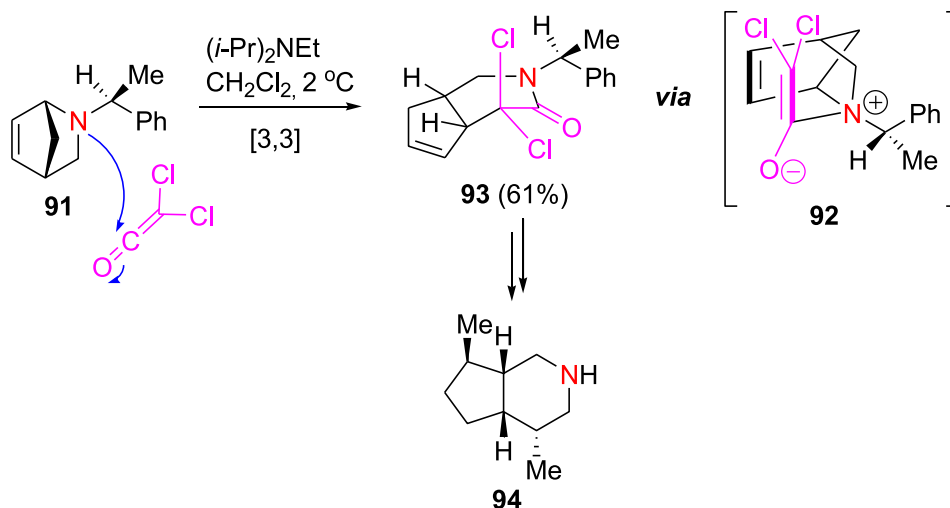

Scheme 25. The Roberts's extension of the aza-ketene-Claisen rearrangement.[32]

aza-ketene- Claisen rearrangement. The lactam **93**, was obtained from the direct reaction of (*S*)-phenylethylamine, optically pure (1*R*,4*R*,1′*S*)-2-(phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene **91** with ketenes through an intermediate **92** ((Scheme 26).

Accordingly, Edstrom[37] had got idea to develop a new approach for the building of structural subunits; indolizidine **97a**, **97b** and quinolizidine **100a**, **100b** across many families of alkaloids[14] possessing promising biological profiles (Scheme 27). Their strategy involves an aza-ketene-Claisen rearrangement starting from simple monocyclic precursors **95a**, **95b**. This approach affords a novel region-controlled mode for the synthesis of nine- and ten-membered unsaturated lactams (**96a, 96b** and **99a, 99b**, Scheme 27).

The zwitterionic aza-Claisen ketene rearrangement, another synthetic common approach analogous to aza-Claisen ketene reaction to synthesize hydroisoquinoline subunits has been initially depicted by Mariano in 1983.[24a] The zwitterionic intermediate **103**, produced by reversible addition reaction of tertiary iso-quinuclidines **101** to acetylenic esters **102**, experiences [3,3] sigmatropic rearrangement to furnish corresponding *cis*-fused hydroisoquinoline **104** (Scheme 28). The reaction involves the formation of the very stable intermediate (vinylogous urethane **103**, an attractive precursor of yohimbane derivatives.[24c]

Similarly, Hedegus et al.[24b] has reported a versatile approach to form unsaturated lactams (as an intermediate **106**) *via* a zwitterion aza-Cope rearrangement subsequently furnish indolizidine and quinolizidine ring structures **107** (Scheme 29). In the presence of a Lewis acid, the ketenes were formed by photolysis of chromium carbene complexes. The importance of chromium carbene

Scheme 23. The Craig's approach involving a ketene-Ireland-Claisen hybrid rearrangement of allylic amines **82**.[34d]

Scheme 26. The Pombo-Villar's route towards the enantioselective synthesis of (-)-δ-*N*-normethylskytantine **94**.[36]
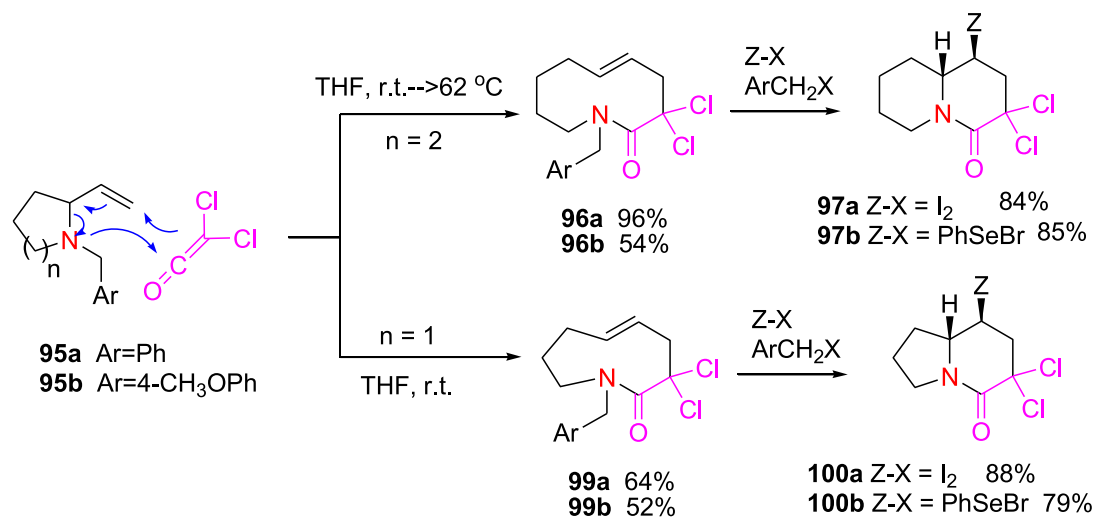
Scheme 27. The Edstrom's region-selective synthesis of nine- and ten-membered unsaturated lactams.[37]
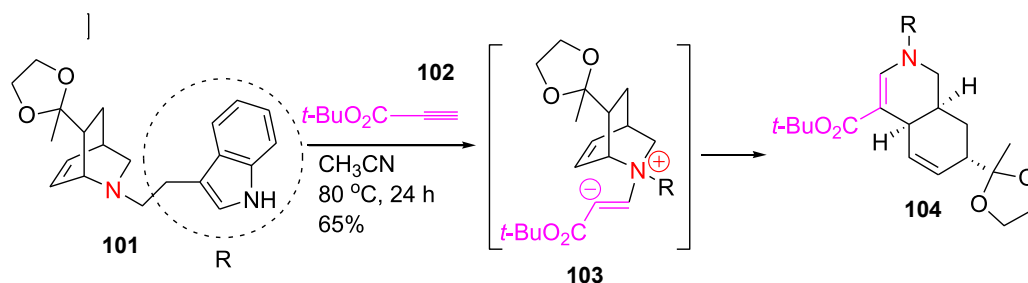

Scheme 28. The Mariano's zwitterionic aza-Claisen ketene rearrangement of tertiary isoquinuclidenes **101**.[24a]

complexes is to fit substituents α-to the carbonyl carbon despite the dichlorosubstituents resulting from the dichloroketene.

As depicted earlier that McMillan and co-workers have provided an attractive platform for the development of an enantioselective catalytic ketene-Claisen method.[16] The process was involve an acid–catalyzed ketene [3,3]-sigmatropic rearrangement using allyl morpholines **109** (Scheme 30).[16a] Moreover, this flourishing rearrangement has capability to form a reaction with a series of Lewis

acids to furnish a high yield and good stereocontrol 1,2-disubstituted Claisen adduct **113** (Table 1).

Besides above, the proper geometry of olefinic double bond on the allyl component in the substrate also gives the respective stereocontrol. For instance, with *trans* allylic morpholines, the *syn* product with excellent levels of stereoselection were observed while the *cis* double bond isomer introduced the *anti* Claisen adduct (Scheme 31). The ability of this protocol was further
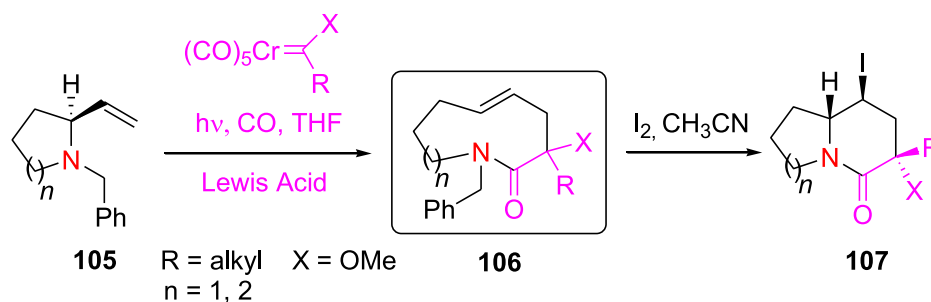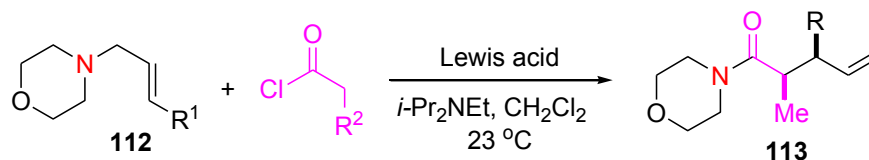
Scheme 29. The Hedegus's approach to form unsaturated lactams *via* a zwitterion aza-Cope rearrangement.[24b]
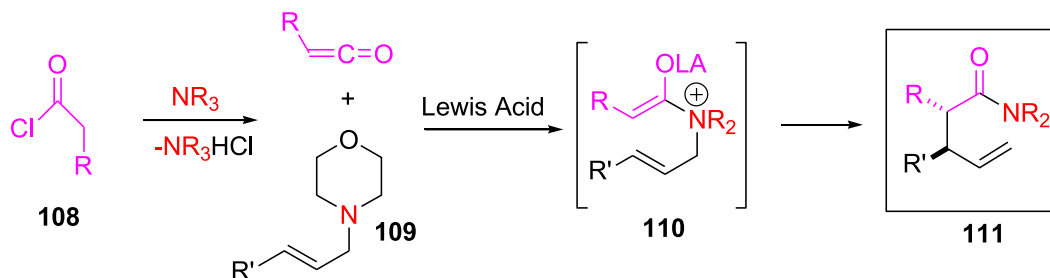
Scheme 30. The McMillan's strategy for the development of an enantioselective catalytic ketene-Claisen method.[16a]

Table 1
The formation of a 1,2–disubstituted Claisen adduct using a range of Lewis acids. [16c]

Entry	R^1	R^2	Yield	*syn:anti*
1	Me	Me	92	>99:1
2	Me	Npht	77	>99:1
3	Me	SPh	81	92:8
4	Me	OBn	91	86:14
5	Ph	Me	76	>99:1
6	Cl	Me	95	>99:1
7	H	Me	95	−

enhanced on cyclic and acyclic architectures in which the transition state-controlled π-facial bigotry to prefer quaternary carbon stereocenters on both.

Another major development in the ketene-Claisen rearrangement is a tandem ketene-Claisen reaction. This is based on the highly stereoselective three-component coupling reaction which facilitates the formation of versatile acyclic systems *e.g.* acyclic 2,3,6-trisubstituted-1,7-dioxoheptane structure **117** (previously formed from allyl diamine **115** and propionyl chloride **114** (Scheme 32).[16b] Here the depicted tandem sequence was thriving with a range of Lewis acids furnishing the tandem adduct **117** in excellent yield and stereoselectivity. This sort of reaction is quite simple with respect to the nature of the tertiary amine component, the structure of the acyl chloride and the olefin substituent (see Scheme 33).

Moreover, the tandem ketene-Claisen rearrangement proves itself a powerful significant tool in the natural product synthesis.[16b] Compound **119** is a stereochemical model commonly originated throughout the building blocks of macrolide antibiotics.[38] This sort

of protocol in acyclic stereochemical arrangement can be employed conveniently from allyl diamine **118** and propionyl chloride to furnish product in excellent yield (72%) and high stereoselectivity (91:9 *syn-anti:syn-syn*).

Correspondingly, MacMillan and Yoon[16c] have developed the first enantioselective ketene-Claisen reaction that involves the vital use of a Lewis acid. Specially, the optically active Lewis acid metal-chelating complex **121** (Scheme 34), MgI$_2$ derivative and bis(oxazolinyl)aryl (Arbox) ligand, provide a very effectual chiral space for a wide variety of ketene-Claisen rearrangements that utilize chelating substrates.

In addition, It was also observed that the structure of both the acid chloride and the tertiary allylic amine **123** have an influence on enantioselectivity. Their ability to contribute in metal chelation is related to the enantiofacial favouritism of the [3,3] isomerization process.[16c] The appended Scheme 35 shows the importance of chelation as an organisational control element in asymmetric catalysis to afford enantioselective access to subtle acyclic
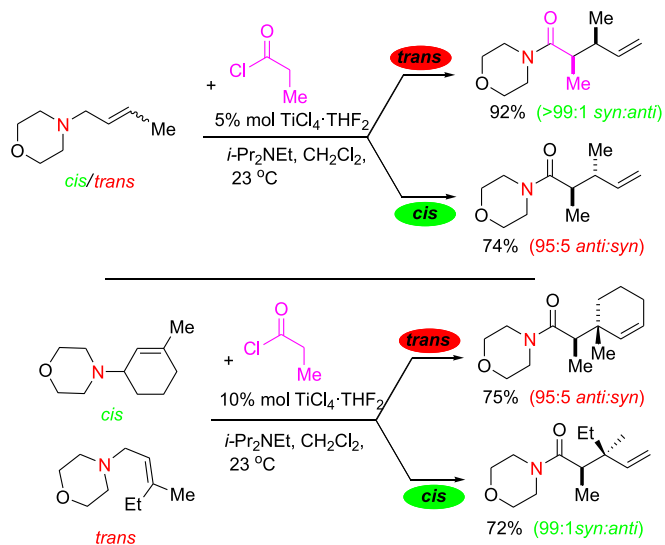
Scheme 31. The stereocontrolled reactions of *cis/trans* allylic morpholines.[16a]

structural precursors. The outcome of this asymmetric reaction is to align quaternary carbon centers on an allylic framework that is controlled by the Lewis acid.

Moreover, the high level of asymmetric induction and the good yields in the convergent stereoselective synthesis of the α-amino acids encouraged Nubbemeyer and co-workers[39] to test the scope and limitation of the zwitterionic ketene aza-Claisen rearrangement. This has been reported as a persistent makeover for the synthesis of an optically active α, β-disubstituted and γ, δ-unsaturated amino acid derivatives of type **128** using chiral pyrollidine precursors as auxiliaries **126** (Scheme 36). The activated ketenes **125** could form through the action of trimethylaluminium on acid flourides which subsequently add to substituted pyrrolidines **126** to give intermdediate **127** with preffered *Z*-enolate geometry. The *anti*-amides **128** could form through [3,3]-open chain Claisen rearrangement of *syn* adduct.

More recently, Shen and Xu[40a] has introduced the methodology for the stereoselective synthesis of α-allyl-α-cyano-lactams **131** from *N*-allyl amino ketene **130**. In which an electron withdrawing group (-CN) at α-position favours the intramolecular zwitterionic ketene-aza-Claisen rearrangement (Scheme 37). The most
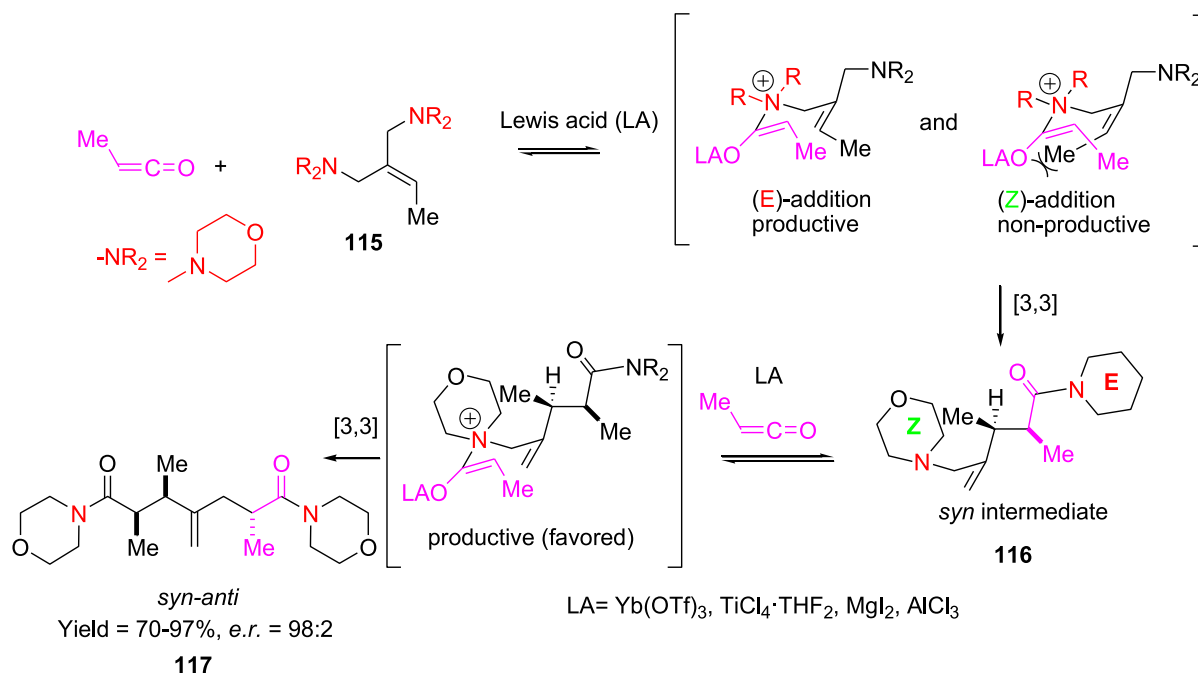
Scheme 32. Multicomponent tandem ketene-Claisen reaction.[16b]
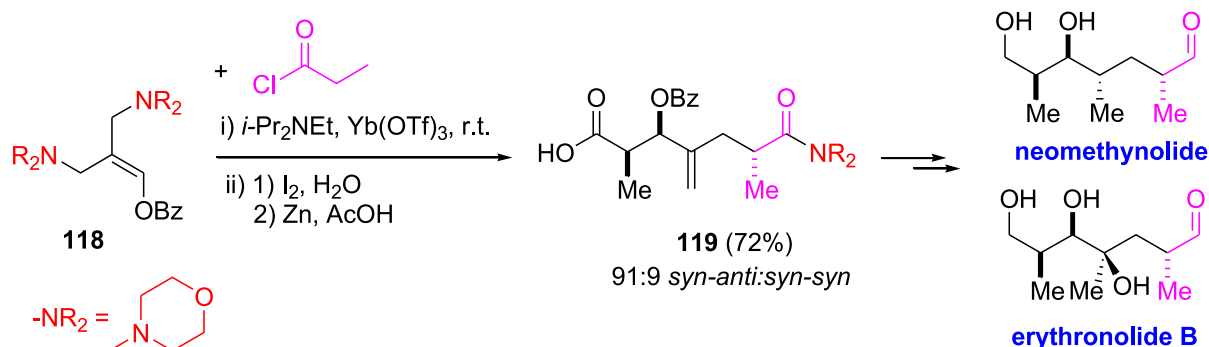
Scheme 33. The tandem ketene-Claisen rearrangement employed allyl diamine **118** and propionyl chloride.[16b]
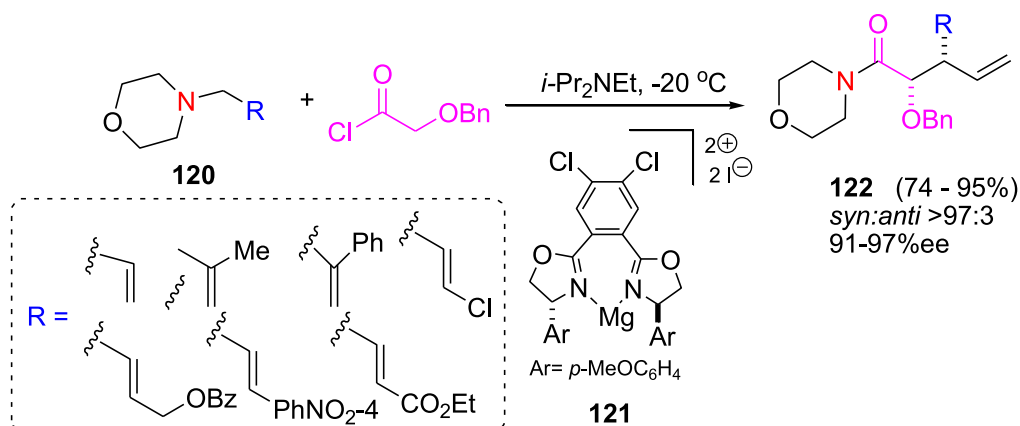
Scheme 34. MacMillan and Yoon's first enantioselective ketene-Claisen reaction.[16c]
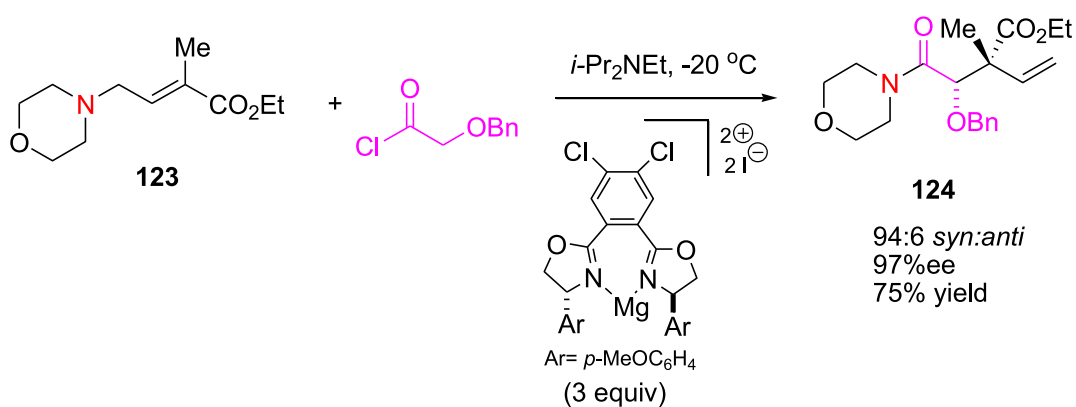
Scheme 35. The effect of chelation on the enantioselective ketene-Claisen reaction.[16c]

R = CO₂Me, CO₂tBu, CH₂OBn, CH₂OTBS, CH₂OTPS
R' = H, Ar, Alkyl,
R" = H, OME, OCH₂O
X = OH, OR, NR₂
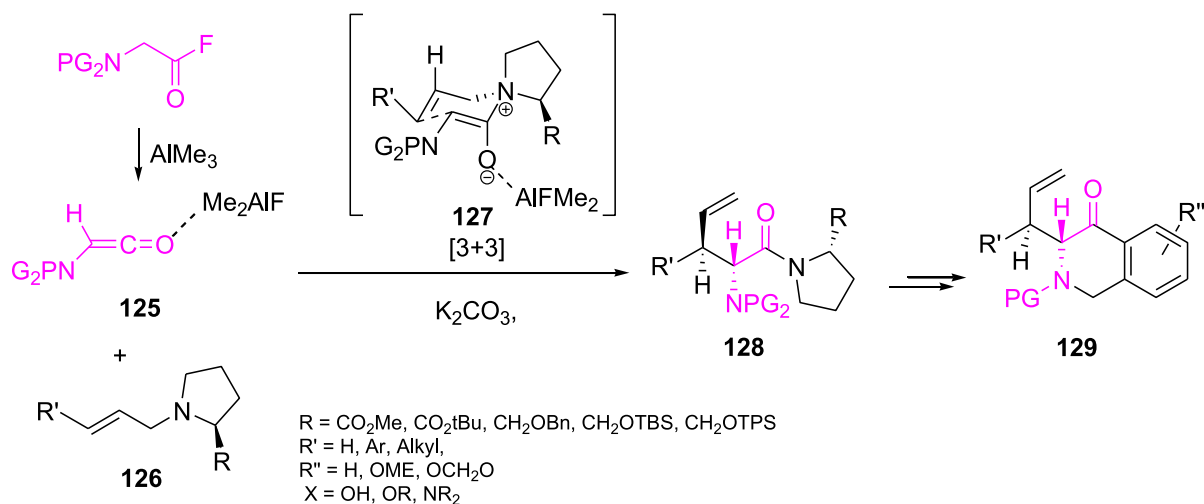
Scheme 36. The Nubbemeyer's convergent stereoselective synthesis of the α-amino acids.[39]
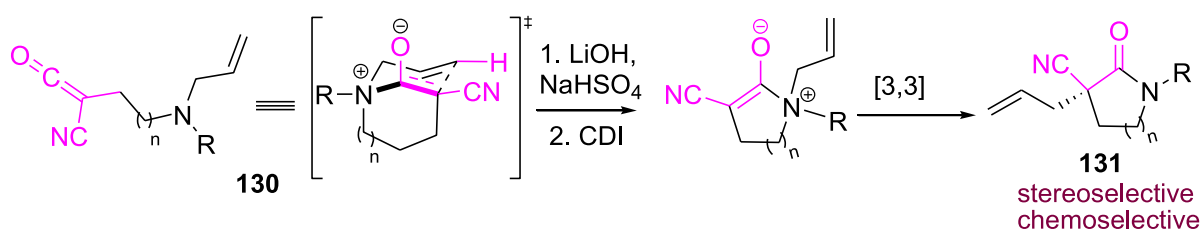
Scheme 37. Shen and Xu's stereoselective synthesis of α-allyl-α-cyano-lactams **131** from N-allyl amino ketene **130**.[40]
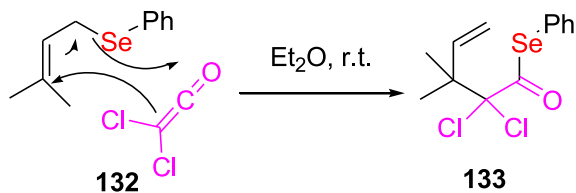
Scheme 38. The Bellus's ketene-Claisen reaction involving allyl *Se*-esters.[11]

importantly, an unsymmetrical bis-*N*-allyl moiety in the reactant displays significant chemoselectivity.

1.3.4. Diversity in ketene-Claisen reaction

The ketene-Claisen reaction is not only limited to allyl ethers, allyl thio-ethers and tertiary allyl amines but also involve allyl *Se*-esters. This study was carried out by Bellus and co-workers in which they described the combination of allyl *Se*-ethers **132** with dichloroketene to form *Se*-esters of γ-δ-unsaturated acids **133** smoothly at room temperature (Scheme 38).[11]

Recently a convenient method of the use of ketene-acetal variation or ester-enolate variation was demonstrated by Bravo et al.[40b] This protocol involves in the stereoselective synthesis of a natural monoterpene, γ-δ-unsaturated amino acids precursors and vinyl lactones (Scheme 39).

Another important type of Pummerer rearrangement to construct a variety of enantiopure substituted lactone precursors **144** has been developed by Marino and co-workers.[41] Here the [3,3] sigmatropic rearrangement of intermediate vinylic oxosulfonium enolates **143**, is represented by the reaction of cyclopentene sulfoxide **142** with dichloroketene (Scheme 40).

An asymmetric, cationic 3-aza-Cope rearrangement has also been described by Vedejs and Gingras.[42] As depicted in Scheme 41, the asymmetric tertiary allylic amine **145** after Michael addition with dimethyl acetylenedicarboxylate (DMAD) gave the allylic

enamine system **146**, which subsequently undergo [3,3]-sigmatropic rearrangement that isomerised to enaminoester **147**. Then ketoester **148** after hydrolysis undergo cleavage and decarboxylation reaction to furnish the amide **149** after amidation of mixed anhydride with (*S*)-phenylethylamine.

Nubbemeyer and Diedrich have illustrated the zwitterionic aza-Claisen rearrangement in chiral allylamines **150** to produce optically active hexahydroazoninones *via* with complete 1,3-chirality transfer Scheme 42.[43] This protocol permits the formation of optically active nine-membered ring lactams **154** in high yields. Regarding the mechanism, it looks rational to suppose that the acyl ammonium salt **151** forms at first. This intermediary compound then undergo the addition reactions by a base (*e.g.* the chloride ion) and ultimately it forms the zwitterionic intermediate **152** *via* lithiation on the α-position of the activated carbonyl and subsequently undergoes the [3,3]-sigmatropic rearrangement to give azoninones **153**. Which upon selective reduction furnishes **154**[44]

An application of the ketene-acetal Claisen reaction was illustrated by Werchkun and Thiem[45] that C–C bond formation in novel divalent saccharide structures **156** can be achieved conveniently In this protocol, *C*-allyl branched urinate **156** could be achieved by the enolization of the allyl ester prepared from the analogous uronic acid **155** (Scheme 43).

Ryan and co-workers[46] described the in-*situ* formation of a potentially advanced precursor (hydroxylated vinyl-appended nine-membered lactones (+)-**158**) for many natural products, from tartaric acid **157** *via* the ketene acetal that undergoes spontaneous Claisen rearrangement (Scheme 44).

It was described[47] that γ,δ-unsaturated functionalized α,α-dibromo esters **161** were synthesized through the Claisen rearrangements of dibromo-ketene acetals **160** by allylic alcohols **159**. Besides, the α,α-dibromo esters **163** have capability to undergo various important carbon–carbon bond-forming reactions, oxidations, and lactonizations (Scheme 45).

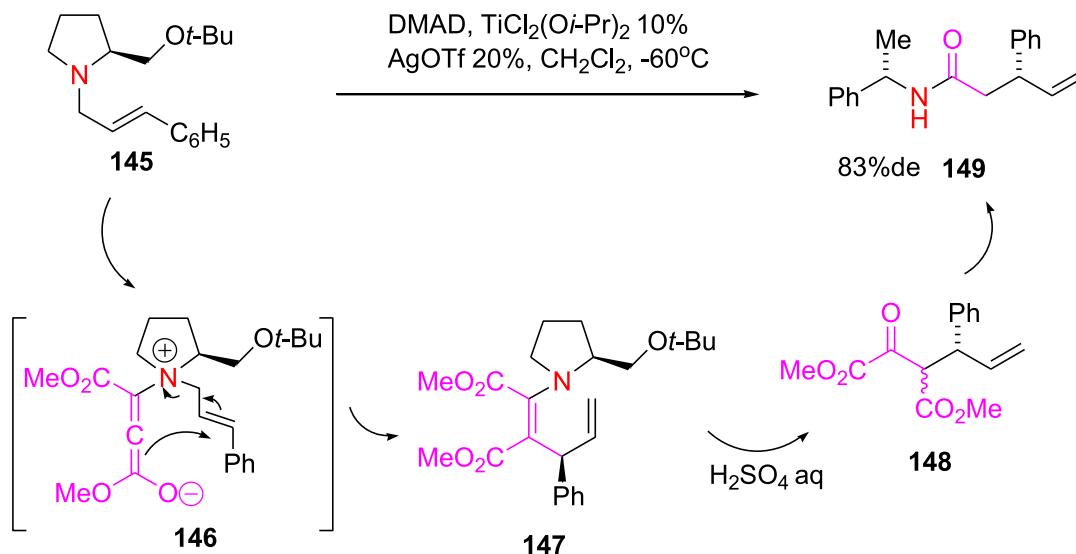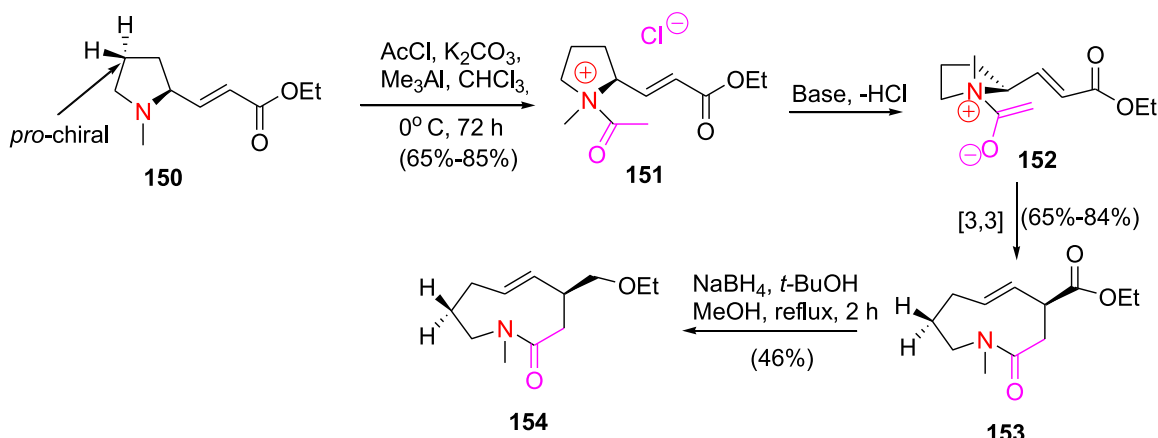Barcan and co-workers[48] have further showed a novel low-
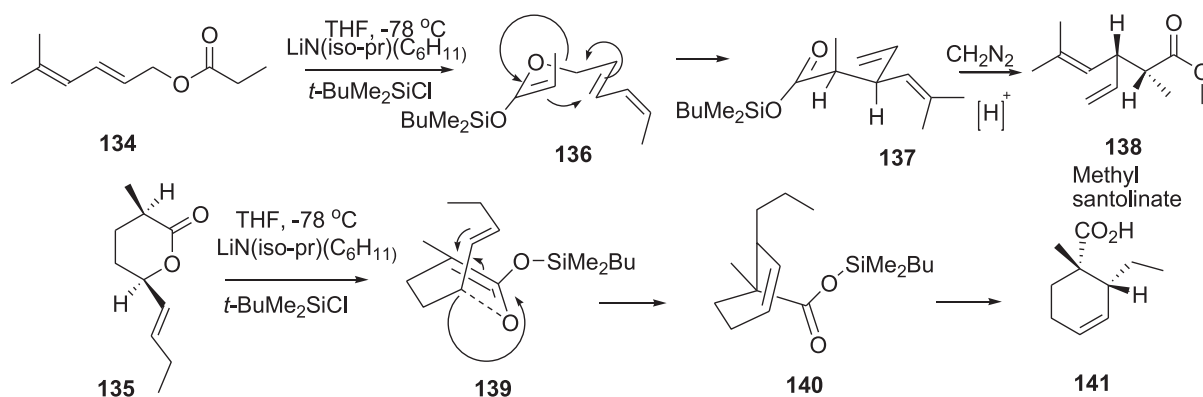
**Scheme 39.** The Bravo's approach of ketene-acetal variation.[40b]
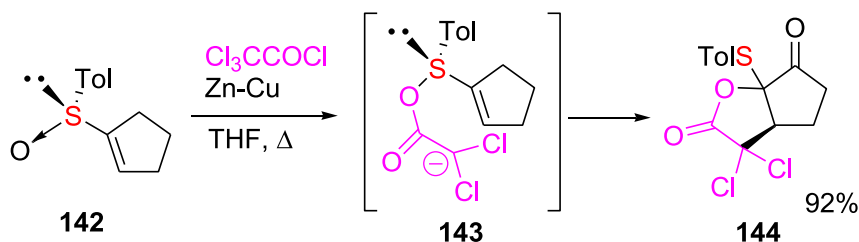
Scheme 40. The Marino's Pummerer rearrangement towards the enantiopure substituted lactone precursors **144**.[41]

Scheme 41. The cationic 3-aza-Cope rearrangement.[42]

Scheme 42. Nubbemeyer and Diedrich's approach towards the zwitterionic aza-Claisen rearrangement in chiral allylamines **150**.[43]
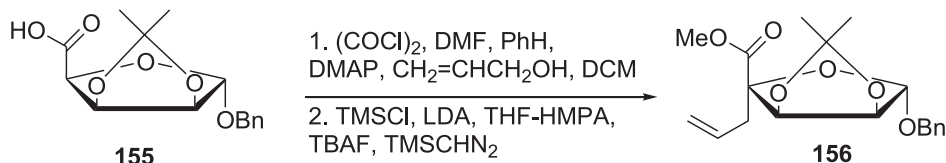
Scheme 43. Werchkun and Thiem's protocol in the C—C bond formation *via* ketene-acetal Claisen reaction.[45]
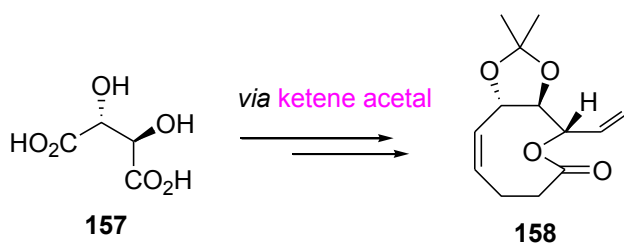
Scheme 44. The Ryan's approach involving tartaric acid **157** *via* the ketene acetal.[46]

temperature dibromo-ketene acetal Claisen rearrangement in exocyclic dienylbromide precursor which involved a palladium-catalyzed cross-coupling reaction (Scheme 46). Furthermore, the relative stereochemistry at positions C-3 and C-18 in the adduct **165**, can be directed by an extremely torquoselective thermal triene 6π electrocyclization. The product **165** is an important framework of reserpine-type alkaloids.

Another novel discovery for the synthesis and Claisen rearrangement of bridged bicyclic enol ethers through ketene (S)-*cis*-diene cycloaddition has been investigated *via* a non-dissociative pathway for the rearrangement (Scheme 47).[49] In which the bicyclic cyclobutanones **167** synthesis is described through the Claisen
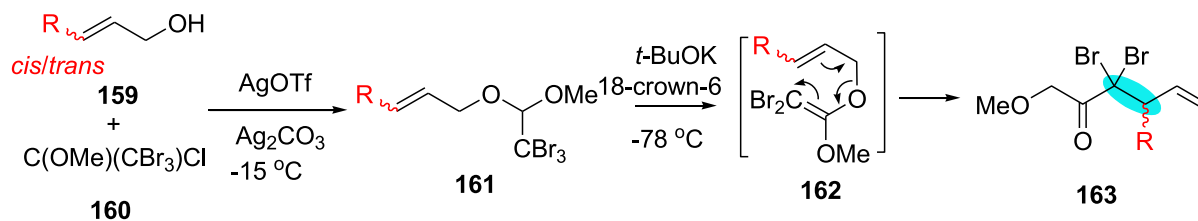
Scheme 45. Dupper and Kwon's strategy involving dibromo-ketene acetals **160**. [47]
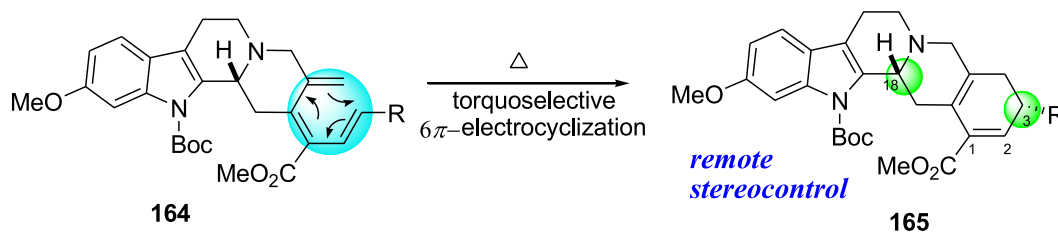
Scheme 46. The Barcan's protocol of low-temperature dibromo-ketene acetal Claisen rearrangement. [48]
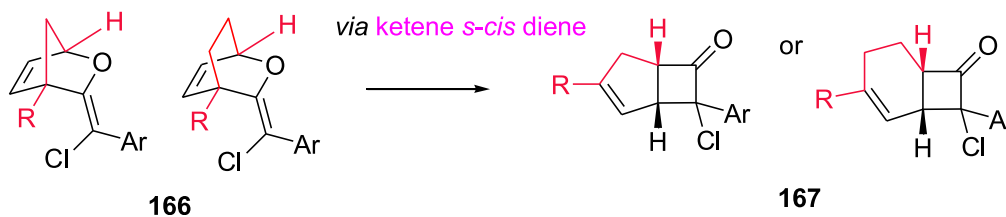
Scheme 47. The synthesis bridged bicyclic enol ethers through ketene (*S*)-*cis*-diene cycloaddition. [49]
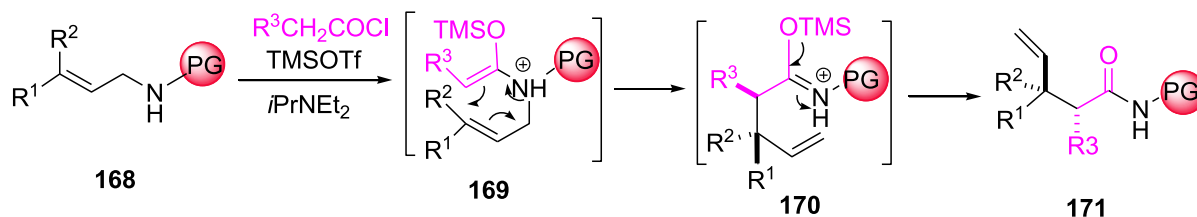
Scheme 48. The reactions of allylic amines and ketenes in the presence of the silyl- reagent. [50]
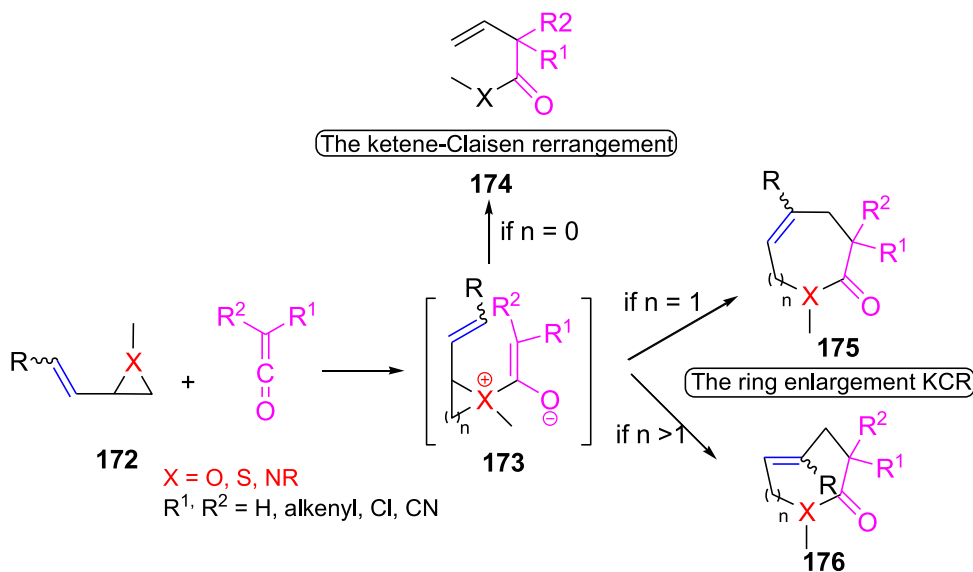
Scheme 49. Ring enlargement through the ketene-Claisen rearrangement. [51]
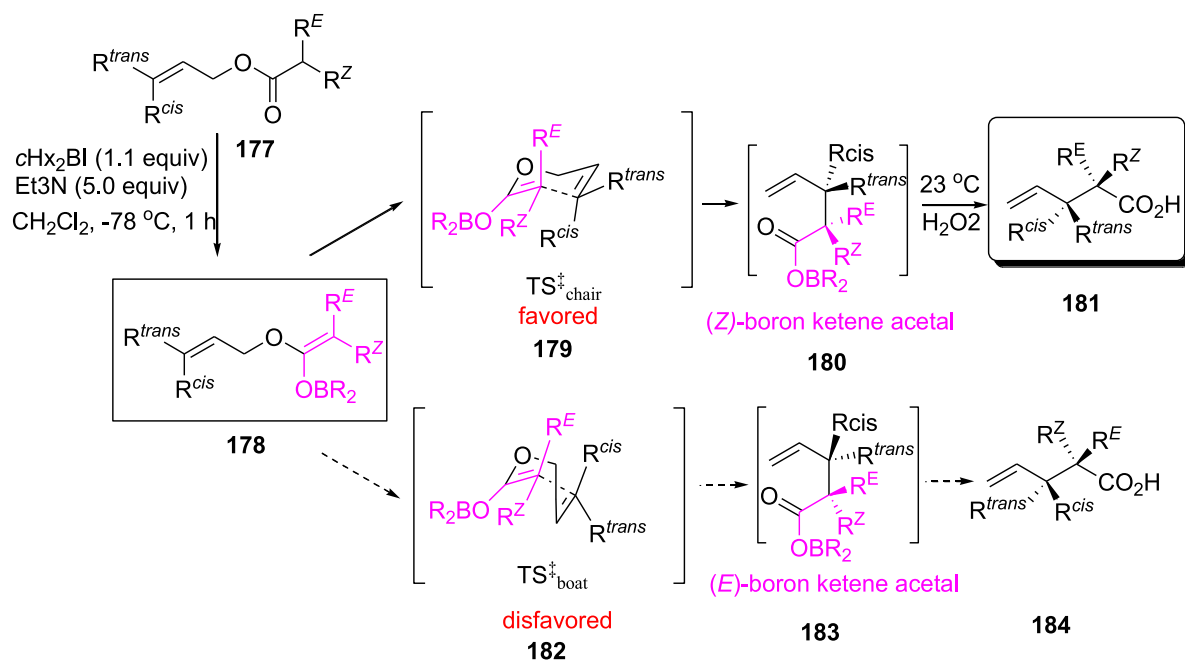
Scheme 50. Ferreira and Seizert's approach for the promoting boron-ketene acetal formation. [52]

rearrangement by a variety of 3-alkylidene-2-oxabicyclo[2.2.1]hept/oct-5-ene precursors thermally or in the presence of a Lewis acid.

Also a silyl-modified alternative of the ketene–Claisen rearrangement has been demonstrated with a range of allylic amines and ketenes (Scheme 48).[50]

Ring enlargement through ketene-Claisen rearrangement is a very significant synthetic tool and could be carried out easily in a single step (Scheme 49).[51] Unsaturated nine-member lactones **175, 176** have been formed by ketene-Claisen reaction for the total synthesis of different bioactive metabolites. Based on this versatile methodology, one can synthesize any ring core of slective configuration by the choice of starting heterocyclic precursors, for example, six-member tetrahydropyrans as a precursors give the ten member ring with E configurated double bond, similarly the five-member tetrahydrofuran rings produce expected unsaturated nine-member rings with E configuration. Whilst the use of the a potential starting material e.g. four-member oxygen containing rings give the product with E configuration due to the more ring strain and even three-member oxiranes has been reported of which a double bond with Z configuration **174**.

An examination for the promoting boron-ketene acetal formation and its scope and stereochemistry in the Irland-Claisen rearrangement has been described by Ferreira and Seizert (Scheme 50).[52] It was observed that the relative stereochemistry originates through a competing chair-like and boat-like transition states, where the major diastereomer is most reliable with (Z)-boron ketene acetal **180** proceeding through a favoured chair-like conformation **179** to furnish desired product **181**. Alternatively, severe non-bonded interactions in the E-isomer **183** could lead to disfavoured path and it unlikely proceed via boat like transition state **182**.

References

1. Claisen L. *Ber Dtsch Chem Ges.* 1912;45:3157–3166.
2. a) Woodward RB, Hoffmann R. *The Conservation of Orbital Simmetry*. New York: Verlag Chemie/Academic Press; 1970;
   b) Hiersemann M, Nubbemeyer U. *The Claisen Rearrangement*. Weinheim, Germany: Wiley-VCH; 2007;
   c) Chen Chi-Li, Namba K, Kishi K. *Org Lett.* 2009;11(2):409–412.
3. Carroll MF. *J Chem Soc.* 1940;704(706):1266–1268.
4. Wick AE, Felix D, Steen K, Eschenmoser A. *Helv Chem Acta.* 1964;47:2425–2429.
5. Marbet R, Saucy G. *Helv Chem Acta.* 1967;50:2091–2100.
6. Johnson WS, Wethermann L, Barlett WR. *J Am Chem Soc.* 1970;92:741–743.
7. Ireland RE, Mueller RH. *J Am Chem Soc.* 1972;94:5897–5898.
8. Baldwin JE, Walker JA. *J Chem Soc Chem Commun.* 1973:117–118.
9. Malherbe R, Belluš D. *Helv Chim Acta.* 1978;61(8):3096–3099.
10. Denmark SE, Harmata MA. *J Am Chem Soc.* 1982;104:4972–4974.
11. Malherbe R, Rist G, Belluš D. *J Org Chem.* 1983;48(6):860–869.
12. Oehrlein R, Jeschke J, Ernst B, Belluš D. *Tetrahedron Lett.* 1989;30:3517–3520.
13. a) Ellwood A, Price Mortimer AJ, Goodman GM, Porter M j. *Org Biomol Chem.* 2013;11:7530–7539;
    b) Ellwood A, Price Mortimer AJ, Tocher DA, Porter MJ. *Synlett.* 2008;14:2199–2209.
14. Howard AS, Michael JP. *Alkaloids.* 1986;28:183.
15. Roberts SM, Rakesh M, Pittol CA. *J Chem Soc Perkin Trans I.* 1992:1617.
16. a) Yoon TP, Dong YM, MacMillan DWC. *J Am Chem Soc.* 1999;121(41):9726–9727;
    b) Dong YM, MacMillan DWC. *J Am Chem Soc.* 2001;123(10):2448–2449;
    c) Yoon TP, MacMillan DWC. *J Am Chem Soc.* 2001;123(12):2911–2912.
17. a) Belluš D, Gonda J, Jeschke R, Ernst B, Nubbemeyer U. *Helv Chim Acta.* 1997;80:876–891;
    b) Ireland RE, Wipf P, Xiang JJ. *Org Chem.* 1991;56:3572;
    c) Nubbemeyer U, Gonda J, Ernst B, Belluš D. *Angew Chem Int Ed Engl.* 1991;30:1465–1467;
    d) Gonda J, Miroslava M, Ernst B, Belluš D. *Tetrahedron.* 2001;57:5607–5613;
    e) Gonda J. *Angew Chem Int Ed.* 2004;43:3516–3524.
18. Rosini G, Spineti EG, Pradella G. *J Org Chem.* 1981;46(11):2228–2230.
19. Cherest M, Felkin H, Prudent N. *Tetrahedron Lett.* 1968:2199.
20. Houk KN, Moses SR, Rondan NG, Schohe R, Fronczek FR. *J Am Chem Soc.* 1984;106(13):3880–3882.
21. Kahn SD, Hehre WJ. *J Org Chem.* 1988;53(2):301–305.
22. Krepski LR, Hassner A. *J Org Chem.* 1978;43:2879–2882.
23. Brady WT, Waters OH. *J Org Chem.* 1967;32(11):3703–3705.
24. a) Kunng FA, Gu J-M, Chao S, Chen Y, Mariano P. *J Org Chem.* 1983;48(23):4262–4266;
    b) Deur CJ, Miller MW, Hedegus LS. *J Org Chem.* 1996;61(8):2871–2876;
    c) Blasko G, Szantay P, Honty K, Dornyei G. *Alkaloids.* 1986;27:131.
25. Patai S. *The Chemistry of Allenes, Ketenes and Realated Compounds*. New York:

Wiley; 1980. ISBN 10: 0471276715 ISBN 13: 9780471276715.

26. Snider BB. *Chem Rev.* 1988;88:793—811.
27. Valenti E, Pericas MA, Moyano A. *J Org Chem.* 1990;55(11):3582—3593.
28. Johnston BP, Czyzewska E, Oehlschlager AC. *J Org Chem.* 1987;52(16): 3693—3697.
29. Ishida M, Muramaru H, Kato S. *Synthesis.* 1989:562—564. For review; Nubbe-meyer, U., Top. Curr. Chem., 2005, 244, 149—213.
30. Koseki K, Ebata T, Kawakami H, Matsushita H, Naoi Y, Itoh K. *Heterocycles.* 1990;31:423—426.
31. Aggarwal VK, Lattanzi A, Fuentes D. *Chem Commun.* 2002:2534—2535.
32. Roberts SM, Smith C, Thomas RJ. *J Chem Soc, Perkin Trans.* 1990;1:1493—1495; b) Maurya R, Pittol CA, Pryce RJ, Roberts SM, Thomas RJ, Williams JO. *J Chem Soc, Perkin Trans.* 1992;1:1617—1621.
33. a) Deur CJ, Miller MW, Hegedus LSJ. *Org Chem.* 1996;61:2871; b) Ishida M, Muramaru H, Kato S. *Synthesis.* 1989;07:562.
34. a) Yoon TP. *The Acyl-Claisen Rearrangement. Development of a Novel Metal-Catalyzed Claisen Rearrangement and Enantioselective Variants of the Acyl-Claisen Rearrangement.* California Institute of Technology; 2002; b) Nubbemeyer UJ. *Org Chem.* 1995;60(12):3773—3780; c) Nubbemeyer UJ. *Org Chem.* 1996;61(11):3677—3686; d) Craig D, King NP, Mountford DM. *Chem Commun.* 2007:1077—1079.
35. Takahashi A, Nagakawa H, Ikeda D, Okami Y. *Tetrahedron.* 1991;47: 3621—3632.
36. Cid MM, Eggnauer U, Weber HP, Pombo-Villar E. *Tetrahedron Lett.* 1991;32: 7233—7236.
37. Edstrom ED. *J Am Chem Soc.* 1991;113:6690—6692.
38. Omura S. *Macrolide Antibiotics. Chemistry, Biology and Practice.* Orlando FL: Academic Press; 1984.
39. Friedemann NM, Härter A, Brandes S, et al. *Eur J Org Chem.* 2012:2346—2358.
40. a) Shen MH, Han M, Xu HD. *Org Lett.* 2016;18(5):889—891; b) Bravo JA, Vial JL. *Rev Bol Quim.* 2016;33(3):127—133.
41. a) Marino JP, De la Pradella RF. *Tetrahedron Lett.* 1985;26:5381—5384; b) Marino JP, Perez AZ. *J Am Chem Soc.* 1984;106:7643—7644.
42. a) Vedejs E, Gingras M. *J Am Chem Soc.* 1994;116:579—588; b) Anders D, Knopp M, Schiffers R. *Tetrahedron Asymmetry.* 1996;7:1847—1882.
43. Nubbemeyer U, Diedrich M. *Angew Chem Int Ed.* 1995;34:1026—1028.
44. Hagemann HA. *Org React.* 1953;7:158.
45. Werschkun B, Thiem J. *Tetrahedron Asymmetry.* 2005;16:569—576.
46. Wong LS—M, Turner KA, White JM, Holmes AB, Ryan j H. *Aust J Chem.* 2010;63: 529.
47. Dupper NJ, Kwon O. *Org Lett.* 2015;17:1054—1057.
48. Barcan GA, Patel A, Houk KN, Kwon O. *Org Lett.* 2012;14:5388—5391.
49. Robertson J, Fowler TG. *Org Biomol Chem.* 2006;4:4307—4318.
50. Donald C, Paul KN, David MM. *Chem Commun.* 2007;10:1077—1079.
51. Ghadari R, Arabieh M, Zahedi M, Shaaban A. *Comput Theor Chem.* 2012;981: 25—30.
52. Seizert CA, Ferreira EM. *Chem Eur J.* 2014;20:4460—4468.

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