Claisen Rearrangement over the Past Nine Decades

Ana M. Martín Castro*

Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, 28049 Madrid, Spain

Received February 18, 2003

Contents

1. Introduction 2939
2. Definition and Historic Overview of the Claisen Rearrangement 2940
3. Related [3,3] Sigmatropic Rearrangements 2941
   3.1. Carroll Rearrangement 2941
   3.2. Eschenmoser Rearrangement 2941
   3.3. Johnson Rearrangement 2942
   3.4. Ireland–Claisen Rearrangement 2942
   3.5. Reformatsky–Claisen Rearrangement 2942
   3.6. Thio–Claisen Rearrangement 2943
   3.7. Aza–Claisen Rearrangement 2943
   3.8. Chelate Claisen Rearrangement 2943
   3.9. Diosphenol–Claisen Rearrangement 2944
   3.10. Metallo–Claisen Rearrangement 2944
   3.11. Retro-Claisen Rearrangement 2944
4. Mechanistic and Kinetic Aspects 2945
   4.1. General Remarks 2945
   4.2. Factors Affecting the Reaction Rate 2945
      4.2.1. Influence of the Substituents 2945
      4.2.2. Influence of Charged Intermediates 2947
      4.2.3. Catalyzed Claisen Rearrangements 2949
      4.2.4. Other Parameters 2954
5. Enzymatic Claisen Rearrangement 2956
6. Stereoselective Claisen Rearrangement 2956
   6.1. General Aspects 2956
   6.2. Intraannular Diastereoselectivity 2956
      6.2.1. Transition-State Geometry 2956
      6.2.2. Vinyl Double-Bond Geometry 2958
      6.2.3. Allyl Double-Bond Geometry 2960
      6.2.4. Configuration at C-4 2961
   6.3. Diastereoselective Synthesis of Achiral Products 2963
      6.3.1. Diastereoselective Synthesis of Cycloalkane Derivatives 2963
      6.3.2. *E/Z* Selectivity 2963
   6.4. Diastereoselective Synthesis of Chiral Products 2963
      6.4.1. Chiral Auxiliary at the Allyl Fragment 2964
      6.4.2. Chiral Auxiliary at the Vinyl Fragment 2965
   6.5. Enantioselective Claisen Rearrangement 2968
      6.5.1. Chiral Catalysts 2968
      6.5.2. Chiral Solvents 2972
7. Application of Claisen Rearrangement Products to the Synthesis of Organic Building Blocks 2973
   7.1. Heterocyclic Compounds 2973
   7.2. Carbocyclic Skeletons 2980
   7.3. Dienes 2982
   7.4. Condensed Aromatic Structures 2984
   7.5. Carboxylic Acid Derivatives 2984
   7.6. Quaternary Carbons 2988
   7.7. Polysubstituted Alkenes 2989
   7.8. Sugar Derivatives 2989
8. Application of Claisen Rearrangement to the Synthesis of Natural Products 2990
9. Other Applications 2998
10. Conclusion 2998
11. Acknowledgments 2999
12. References 2999

* E-mail: martin.castro@uam.es.

1. Introduction

The discovery of the Claisen rearrangement almost a century ago[1] offered a potentially useful synthetic tool to the organic chemist. Over the decades this usefulness has been realized and the reaction has drawn the attention of numerous research groups, which has been reflected in the number of papers on the topic published in the literature.[2] In the 1970s and 1980s several general reviews appeared on the title reaction or related processes.[2a−g] However, in recent years only specific issues related to this type of rearrangement have been addressed,[2k−m] the studies on the stereochemical aspects of the reaction deserving special mention. This review provides a general overview covering the most relevant topics related to the Claisen rearrangement, starting from its first publication by Ludwig Claisen in 1912 as a new [3,3] reorganization of allyl aryl (or vinyl) ethers up to its most recent applications in different organic chemistry fields. First, a brief description of the reaction along with its historic profile are given. This leads to the presentation of other [3,3] rearrangements closely related to the title reaction, which are of relevant interest for having been largely exploited as synthetic methods. Next, mechanistic and kinetic aspects are discussed with attention focused on the main factors affecting the reaction rate, basically the presence of different substituents at the 1,5-heterodiene skeleton, the use of catalysts, and changes in the physical parameters affecting the reaction. The following section in the review briefly deals with the enzymatic version of the Claisen rearrangement, which is of relevant interest in metabolic routes.

A significant section of the review is constituted by the study of the stereoselective version of the rearrangement. After a presentation of some general

10.1021/cr020703u CCC: $48.50
Published on Web 04/23/2004

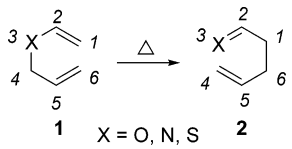
Ana M. Martin Castro was born in Madrid, Spain, in 1964. She received her B.S. (1988) and Ph.D. (1994) degrees under the supervision of Professors J. L. Garcia Ruano and J. H. Rodriguez Ramos at the Universidad Autónoma of Madrid. As a postdoctoral fellow she joined the groups of Professor P. R. Raithby at the University of Cambridge (U.K., 1997) and Professor V. K. Aggarwal at the University of Sheffield (U.K., 1998–2000). She retuned to Professor Garcia Ruano's group as an Assistant Professor. Her present research interests include the development of novel asymmetric methodologies assisted by a chiral sulfinyl group, particularly hydrocyanation processes and Diels–Alder and 1,3-dipolar cycloadditions.

aspects regarding chirality transfer in these processes, different strategies to control intraannular diastereoselectivity as well as methods to perform diastereoselective synthesis of both achiral and chiral compounds are examined. The enantioselective Claisen rearrangement is also thoroughly considered. Finally, in the last sections of the review a selection of the most outstanding applications of the reaction is presented. A number of examples illustrating the use of the Claisen rearrangement in the preparation of a wide range of synthetically interesting building blocks and natural or biologically active compounds are considered. Some other potentially interesting applications of the rearrangement in further fields of organic chemistry are also presented.

2. Definition and Historic Overview of the Claisen Rearrangement

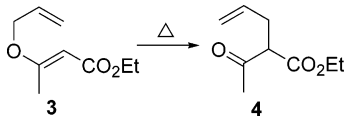
The [3,3] sigmatropic rearrangement of allyl vinyl ethers, which allows the preparation of γ,δ-unsaturated carbonyl compounds, is worthy of study due to its special synthetic relevance as well as the large number of theoretical studies generated. This reaction, first reported by Ludwig Claisen in 1912,[1] was originally described as "the thermal isomerization of an allyl vinyl ether **1**—or of its nitrogen or sulfur containing analogue derivatives—to afford a bifunctionalized molecule **2**" (Scheme 1) in a [π^2s + σ^2s + π^2s] process.

Scheme 1



This first paper essentially described the transformation of allyl phenyl ether into *C*-allyl phenol. However, it also dealt with the formation, starting from *O*-allylated ethyl acetoacetate (**3**), of its *C*-allyl isomer **4** after distillation in the presence of NH_4Cl (Scheme 2) in a process which adopted the general

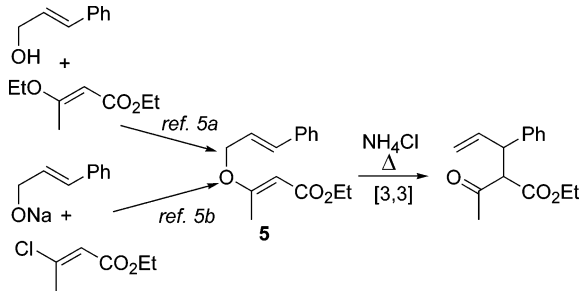
Scheme 2



denomination of *Claisen rearrangement*. As we shall see, this is a reaction exhibiting all the essential properties required by a synthetic procedure to be considered as efficient: it can be chemo-, regio-, diastereo-, and enantioselective,[3] can be performed under mild conditions, and affords potentially useful polyfunctionalized molecules.

The synthetic potential of the process encouraged, in the following years after its first publication, a number of research groups to make significant efforts to find the experimental conditions which would allow the generalization of the reaction to a wide variety of substrates. To verify that the conditions initially reported by Claisen to perform the rearrangement on aromatic substrates[4] could be successfully applied to aliphatic skeletons, independently Bergman and Corte in 1935[5a] and Lauer and Kilburn in 1937[5b] studied the rearrangement in the presence of NH_4Cl of ethyl cinnamyl oxycrotonate (**5**). This substrate was generated either by reaction of cinnamyl alcohol and ethyl 3-ethoxy-2-crotonate[5a] or from sodium cinnamylate and ethyl β-chlorocrotonate[5b] (Scheme 3). The formation of the rearranged product

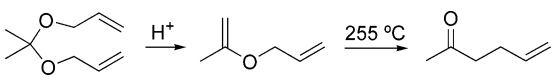
Scheme 3



afforded a formal way of S_N2' *C*-alkylation of cinnamyl halides with the anion derived from acetoacetates.

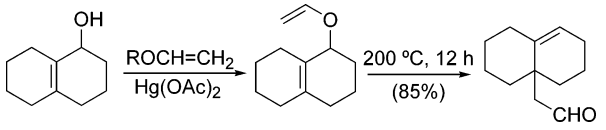
The interest of this new rearrangement prompted the development of different methods for the preparation of the starting materials. Hurd and Pollack[6] described the synthesis of allyl vinyl ethers by acidic or basic elimination as well as the rearrangement of such compounds into the corresponding γ,δ-unsaturated carbonyl compounds (Scheme 4). However, this method did not provide general access to allyl vinyl ethers.

Scheme 4



Several years later this procedure for the synthesis of allyl vinyl ethers was improved by the interchange of alcohols with alkyl vinyl ethers catalyzed by $Hg(OAc)_2$.[7] Those compounds once again proved to be excellent substrates to undergo a [3,3] rearrangement (Scheme 5). This mercury-catalyzed reaction

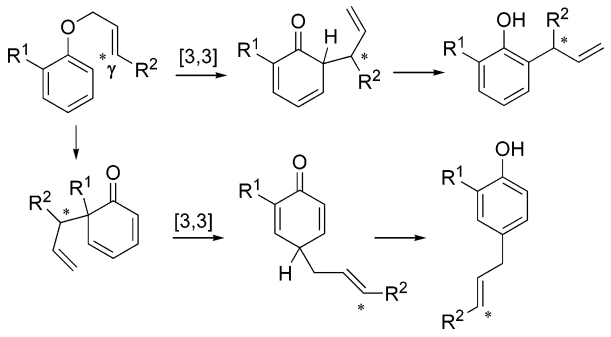
Scheme 5



has become one of the typical methods of preparation of allyl vinyl ethers despite that the yields of these reactions are often low.

The development of the aliphatic Claisen rearrangement was simultaneous with the study of the aromatic version of the reaction.[2a,b,8] Thus, in the Claisen rearrangement of an allyl aryl ether, the first [3,3] step affords an *ortho* dienone which usually enolizes into an *o*-allylphenol. It is the reaction known as the *ortho Claisen rearrangement* (Scheme 6). When the rearrangement takes place on an *ortho*

Scheme 6



position bearing a substituent, a second [3,3] rearrangement (Cope rearrangement) takes place followed by enolization. This reaction, usually called the *para Claisen rearrangement*, leads to the corresponding *p*-allylphenol.

The product resulting from the *ortho* Claisen rearrangement is usually obtained from the reaction, although the *para* process can compete even when both *ortho* positions are unoccupied.[2b] The proposed mechanism for the aromatic Claisen rearrangement has been corroborated by the product resulting from the rearrangements of allyl phenyl ether and allyl 2,6-dimethylphenyl ether, both compounds ^{14}C-labeled on the γ carbon of the allyl chain[8a] (see Scheme 6). The result of the *ortho* rearrangement shows that the rearrangement with inversion at the allyl group is the only reaction taking place. In the case of the *para* rearrangement, the migration only proceeds without inversion of the allyl group. This means that during the course of the reaction such a group is never free enough to undergo resonance.[8b]

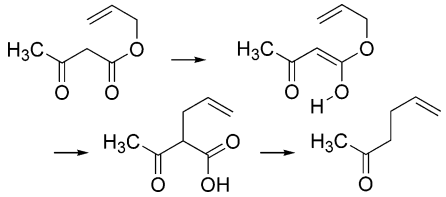
3. Related [3,3] Sigmatropic Rearrangements

The interest generated by the Claisen rearrangement prompted the development of a considerable number of different versions of [3,3] sigmatropic rearrangement. Some of the most noteworthy ones will be considered next.

3.1. Carroll Rearrangement

The Carroll reaction, initially described in 1940,[9] is a thermal rearrangement of allylic β-ketoesters followed by decarboxylation[10] to yield γ,δ-unsaturated ketones (Scheme 7). This reaction has not been

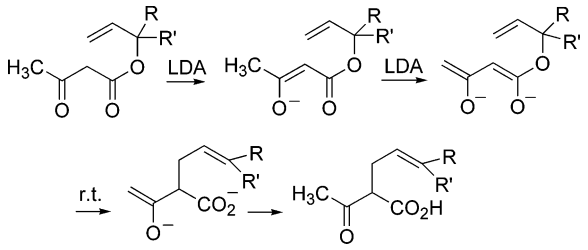
Scheme 7



widely developed due to the drastic conditions (temperatures of 130−220 °C after in situ preparation of the β-ketoester) which are required to perform the transformation.

After the publication of these results, it was reported that dianions derived from allylic acetoacetates, prepared by treatment of acetoacetates with 2 equiv of LDA, rearranged under milder thermal conditions to give easily isolated β-keto acids (Scheme 8).[11]

Scheme 8

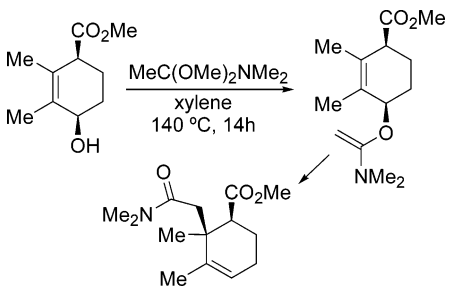


A dependence of the reaction rate on the substitution pattern on the allylic fragment (R, R′ = H, alkyl, aryl) has also been detected. Thus, acetoacetates derived from primary alcohols rearrange more slowly than those derived from secondary and tertiary alcohols.

3.2. Eschenmoser Rearrangement

In 1964 Eschenmoser,[12] based on observations previously reported by Meerwein[13] on the interchange of amide acetals with allylic alcohols, described the [3,3] rearrangement of *N*,*O*-ketene acetals to yield γ,δ-unsaturated amides (Scheme 9).

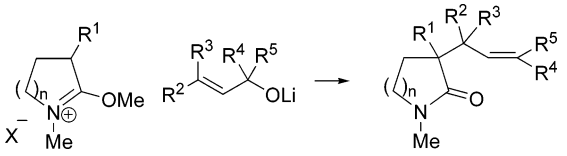
Scheme 9



This reaction allows the formation of a carbon−carbon bond at the β position to a nitrogen atom, which is of great applicability in alkaloid synthesis, although it has the inconvenience of the difficulty inherent to the preparation of more elaborated *N*,*O*-ketene acetals, which usually requires elevated temperatures leading, in some cases, to decomposition of the resulting amides.

Several years later an Eschenmoser rearrangement by reaction of lithium allyl alkoxides with acyclic[14] and cyclic[15] salts of *N*,*N*-dialkylalkoxymethyleneiminium was reported to proceed in excellent yields (Scheme 10). The high temperatures reported for the

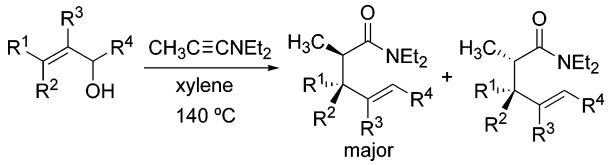
Scheme 10



Eschenmoser rearrangement are usually required for the alcohol exchange reaction, not for the actual rearrangement. Therefore, the mild conditions employed for the preparation of *N*,*O*-ketene acetals such as those depicted in Scheme 10 increased the synthetic interest of the method.

Similar results are obtained by the ynamine−Claisen rearrangement,[16] also known as Ficini−Claisen rearrangement, by reaction of an allylic alcohol with 1-(diethylamino)propyne (Scheme 11). This

Scheme 11

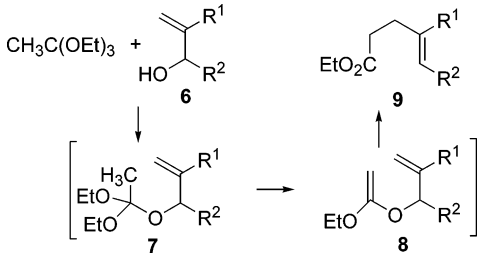


is a process whose stereochemical course may be modified by the reaction conditions, as discussed in section 6.2.2. When the *N*,*O*-ketene acetal is obtained by adding the alcohol slowly to a refluxing solution of the ynamine in xylene, the rearrangement takes place via the kinetically formed (*E*)-isomer. In the presence of a Lewis acid, equilibration to the thermodynamically favored (*Z*)-stereoisomer occurs before rearrangement. Transformation of the kinetically favored (*E*)-*N*,*O*-ketene acetal to the *threo* γ,δ-unsaturated amide can be considered as complementary to the Eschenmoser rearrangement, which evolves through the (*Z*)-isomer affording the *erythro* product.

3.3. Johnson Rearrangement

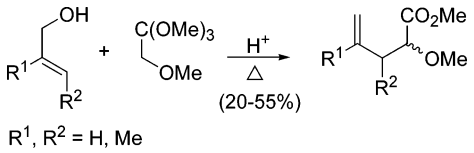
First reported in 1970,[17] the Johnson rearrangement, which may afford *trans*-trisubstituted alkenes, was originally described as the process consisting of the heating of an allylic alcohol (**6**) with an excess of ethyl orthoacetate in the presence of trace amounts of a weak acid (typically propionic acid). The initially formed mixed ortho ester (**7**) loses ethanol to generate the ketene acetal **8**, which undergoes rearrangement leading to a γ,δ-unsaturated ester (**9**) (Scheme 12).

Scheme 12



Subsequently the Claisen rearrangement of ortho esters was shown to be compatible with the presence of a heteroatomic substituent directly bonded to the allyl vinyl ether moiety. One of the few reported examples of Johnson rearrangement with heteroatomic substitution (OCH_3) is the reaction of allylic alcohols with methyl methoxyorthoacetate that gives methyl α-methoxy-γ,δ-unsaturated esters in a process that occurs under acidic conditions (Scheme 13).[18]

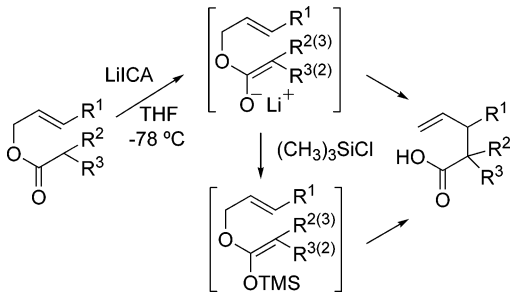
Scheme 13



3.4. Ireland−Claisen Rearrangement

In 1972 Ireland reported the rearrangement of allyl trimethylsilyl ketene acetals,[19] prepared by reaction of allylic ester enolates with trimethylsilyl chloride, to yield γ,δ-unsaturated carboxylic acids (Scheme 14).

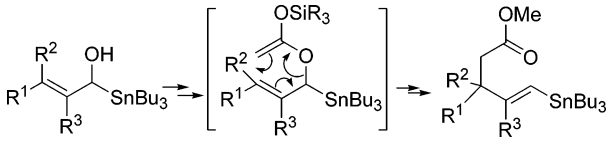
Scheme 14



As compared with other reported rearrangements, this reaction proceeds under mild basic or neutral conditions.

These conditions have allowed the preparation of polyfunctionalized structures, such as the vinylstannanes represented in Scheme 15.[20] This example

Scheme 15



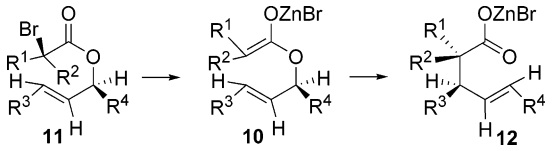
provides a method of functionalizing the newly formed double bond due to the high synthetic versatility of organotin compounds.

3.5. Reformatsky−Claisen Rearrangement

We have so far seen that allylic ester enolates rearrange quite easily. [3,3] Sigmatropic rearrange-

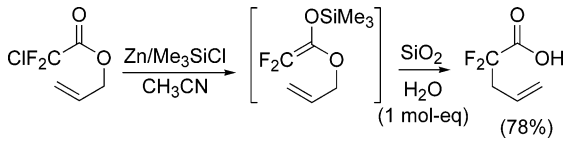
ment of zinc enolates, known as the Reformatsky–Claisen rearrangement, has also been reported.[21] These zinc enolates (**10**), generated by Reformatsky reaction of α-haloesters (**11**) with zinc dust, lead to the corresponding γ,δ-unsaturated zinc carboxylates (**12**) (Scheme 16) in good yields under neither acidic nor basic conditions.

Scheme 16



Similar reaction conditions, in the presence of trimethylsilyl chloride, allowed the synthesis of 2,2-difluoro-4-pentenoic acid starting from allyl chlorodifluoroacetate[22] (Scheme 17). This silicon-induced

Scheme 17

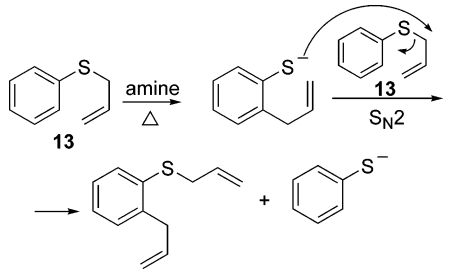


Reformatsky–Claisen reaction did not occur in the absence of chlorotrimethylsilane. This indicates that the ketene acetal depicted in Scheme 17 is most likely a reaction intermediate.

3.6. Thio–Claisen Rearrangement

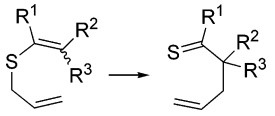
Thermolysis of allyl phenyl sulfides (**13**)[23] leading to a [3,3] sigmatropic rearrangement contrasts with the classic Claisen rearrangement: it requires higher temperature to produce the corresponding thiols, intermediates which are not easily isolated and usually evolve into the corresponding diallyl derivatives due to a S_N2 displacement by the intermediate thiolate on the starting sulfide (Scheme 18).[24]

Scheme 18



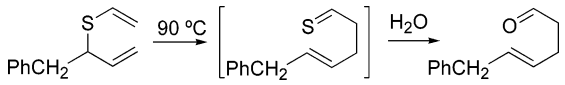
In contrast, the aliphatic version of the thio–Claisen rearrangement may proceed under milder conditions than those reported for oxygenated substrates (Scheme 19).[25]

Scheme 19



Nevertheless, the low applicability of this methodology is a consequence of the instability of the products. This prompted the development of conditions to trap and transform them into more stable compounds such as, for example, the hydrolysis of the intermediate thioaldehyde into the corresponding aldehyde (Scheme 20).[26]

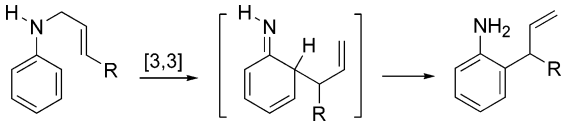
Scheme 20



3.7. Aza–Claisen Rearrangement

The [3,3] sigmatropic rearrangement of *N*-allyl-*N*-arylamines, known as the aza–Claisen rearrangement (Scheme 21),[27] usually requires more drastic

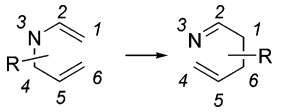
Scheme 21



conditions than those required for the classic Claisen rearrangement of oxygenated substrates (this rearrangement occurs at 200–350 °C). In addition, it affords the corresponding anilines along with undesired byproducts.

Similar energetic conditions are needed for the aliphatic aza–Claisen rearrangement to take place (Scheme 22).[2a] The thermal process requires higher

Scheme 22

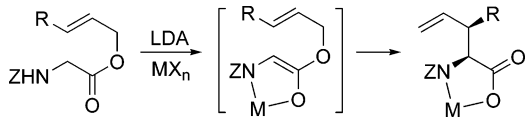


temperatures than those needed for oxygen substrates. In a number of cases the reaction only evolves under Lewis-acid catalysis.

3.8. Chelate Claisen Rearrangement

Chelated enolates derived from amino acid esters undergo Claisen rearrangement upon standing at room temperature to produce γ,δ-unsaturated amino acids (Scheme 23).[28] Starting from *E*-allylic esters,

Scheme 23



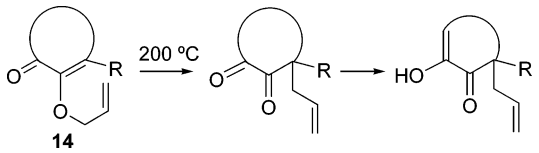
syn products are obtained in a diastereoselective fashion. These reaction conditions are based on the fact that, in general, chelation sharply increases the thermal stability with no negative influence on the reactivity of those enolates. As a consequence of the rigid geometry of the enolate and the predictable geometry of the transition state, any transformation

will tend to take place with a very high stereoselectivity (see section 6.2.2).

3.9. Diosphenol–Claisen Rearrangement

This variety of Claisen rearrangement uses allyl ethers (**14**) derived from diosphenol, with an endocyclic vinyl double bond, to give rise to a bond between a functionalized carbon moiety and a sterically hindered carbon which is part of a cyclic structure (Scheme 24).[29] The resulting bisketone usually tautomerizes into the ketoenol derivative.

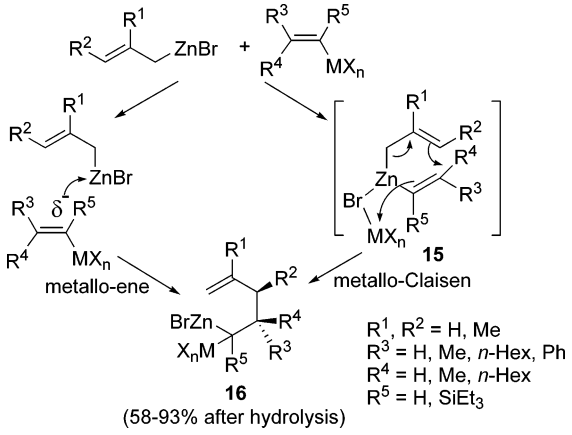
Scheme 24



3.10. Metallo–Claisen Rearrangement

Several studies focused on the development of synthetic applications of *gem*-dimetallic compounds,[30] which were prepared by carbometalation of an alkenyl organometallic magnesium, lithium, or aluminum derivative with an allyl zinc bromide. The initially accepted pathway for the carbometalation consists first in the formation of an allyl vinyl zinc compound (**15**) (Scheme 25), which next undergoes a

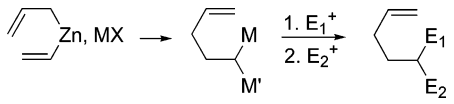
Scheme 25



[3,3] rearrangement—a process known as the metallo–Claisen rearrangement[30a]—to afford the 1,1-bimetallic species **16**. However, two mechanistic rationales, a metallo–ene reaction and a metallo–Claisen rearrangement, account for the resulting products as shown in Scheme 25. Density functional (B3LYP) studies on this reaction have demonstrated that the process is an endothermic Lewis-acid-assisted metallo–Claisen rearrangement with some character of metallo–ene reaction of the vinylmagnesium species (MX_n = MgCl in Scheme 25).[31] The high diastereoselectivity of the reaction has been explained by the short length of the forming C–C bond in the late transition state of the metallo–Claisen process.

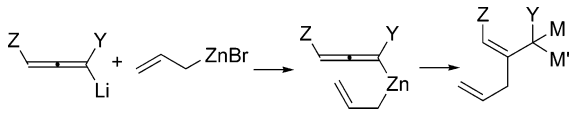
These organic *gem*-dimetallic compounds are able to react successively with two different electrophiles to produce various *gem*-difunctionalized structures[30b–d] (Scheme 26).

Scheme 26



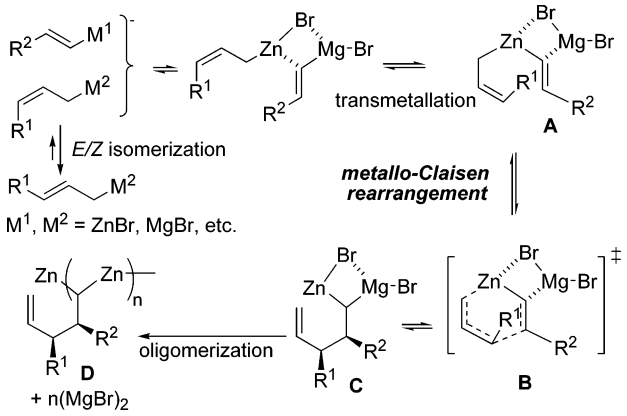
Several years later this methodology was expanded to the rearrangement of allyl allenyl derivatives to give access to *gem*-dimetalated dienes[30e,f] (Scheme 27).

Scheme 27



As mentioned, recently a series of theoretical calculations has supported a mechanism in which the reaction of an allyl zinc bromide with a vinylmagnesium bromide initially proceeds through a fast transmetalation process to generate an allyl vinyl zinc intermediate **A**, which undergoes a $MgBr_2$-assisted metallo–Claisen rearrangement through transition state **B**, which generates the 1,1-dimetallic species **C**. The reaction product **D** results from a final oligomerization step[31] (Scheme 28). An equilibrium

Scheme 28

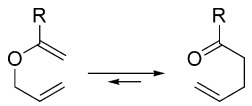


mixture of (*E*/*Z*)-allyl zinc bromide affords a single diastereomer resulting from reaction of the minor (*Z*)-allyl isomer. This result is explained by comparison of the relative energies of the diastereomeric transition states since the pathway through the (*Z*)-isomer is favored over that evolving through the (*E*) reagent.

3.11. Retro-Claisen Rearrangement

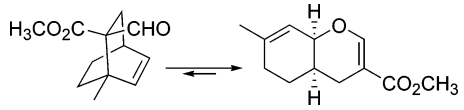
The Claisen rearrangement, as in any other [3,3] sigmatropic rearrangement, takes place under thermodynamic control. This reaction is irreversible toward the formation of the carbonyl compounds (Scheme 29) due to their higher thermodynamic stability.

Scheme 29



However, some structural features have been identified as being responsible for inversion of the normal situation, favoring the transformation of the carbonyl compound into the vinyl ether. In this sense, both the presence of any substituent at a bridgehead position and vicinal quaternary carbons in the carbonyl compound shifts the equilibrium toward the retro-Claisen isomer as a result of a relief in torsional strain (Scheme 30).[32] This effect is particularly

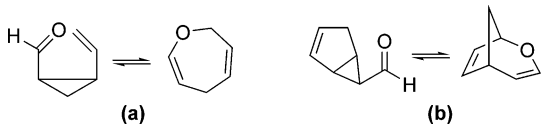
Scheme 30



marked in the presence of a catalytic amount of Lewis acid ($BF_3.OEt_2$). This retro-Claisen process is general for a number of substrates containing contiguous quaternary centers whenever the α-carbonyl substituent is not an electron-releasing group.

A similar thermolability has been detected for vinylcyclopropane carboxaldehydes, which evolve into 2,5-dihydrooxepines by retro-Claisen rearrangement, as indicated in Scheme 31a. In this example the

Scheme 31



thermodynamic stability of the carbonyl group, which is favored at equilibrium, compensates for the unstabilizing strain of the cyclopropane ring.[33a] The ready retro-Claisen reaction of this type of vinylcyclopropanes is evidenced by a number of examples reported in the literature (see, for example, Scheme 31b[33b]).

4. Mechanistic and Kinetic Aspects

4.1. General Remarks

The term "Claisen rearrangement" was originally applied to rearrangements of allyl aryl ethers to afford *ortho*- and occasionally *para*-substituted phenols. Afterward it expanded to analogue rearrangements of allyl vinyl ethers into unsaturated carbonyl compounds, which were classified as [3,3] sigmatropic rearrangements.[34] Initially a synchronic evolution for these reactions through aromatic transition states was accepted,[35,36] formed by a combination of σ and π overlap of 2p atomic orbitals of the carbon atoms of both allyl fragments. It was concluded that, out of the two feasible geometries for the transition state, the reaction proceeded through chairlike intermediates (**17**) instead of boatlike intermediates (**18**) (Figure 1).[37] Both transition states (**17** and **18**) are

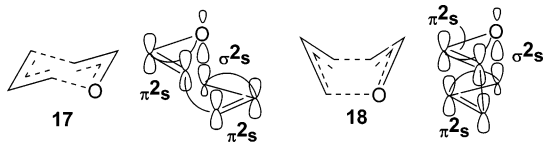


Figure 1.

the only ones corresponding to *supra-supra* processes and, therefore, allowed by Woodward−Hoffmann rules.[34]

The intramolecular cyclic character of the rearrangement is generally accepted. However, the research to understand the precise nature and the geometry of the transition state continues. A large number of theoretical calculations aiming to predict the structures of the transition states involved in the Claisen rearrangement have been reported.[38−41] Most of them accept a concerted rearrangement through a chairlike transition state. However, recently Houk used quantum mechanical calculations to rationalize the stereoselectivity of the Ireland−Claisen rearrangement of cyclohexenyl silyl enol ethers from the chair or boat preferences in the transition state which derived from the substituents on the cyclohexenyl ring.[38c] In addition, there is no general agreement about the structure of this transition state (Figure 2).[42]

Figure 2.

Over the decades several experimental studies based on kinetic isotopic effects have been reported in order to determine the geometry of the transition state of aliphatic and aromatic Claisen rearrangements.[42−44] However, this has not proved to be an easy task, and despite the numerous papers dealing with the Claisen rearrangement in different fields related to organic chemistry, there is no general agreement about such a geometry from theoretical predictions. The difficulty of describing such a geometry still persists.

4.2. Factors Affecting the Reaction Rate

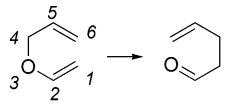
The most frequently reported Claisen rearrangement—thermal isomerization of allyl vinyl ethers—is a process that requires high temperatures and proceeds quite slowly at atmospheric pressure. To transform this reaction into a synthetically useful procedure, numerous attempts to find milder experimental conditions have been reported. The introduction of different substituents in the carbon skeleton of the substrate as well as variations of the catalyst are worth mentioning.

4.2.1. Influence of the Substituents

In the last 20 years a considerable number of studies to determine the inductive or mesomeric effects of electron-withdrawing or electron-donating substituents located at different positions of the carbon skeleton have been mentioned. These effects are qualitatively described in Scheme 32.

Carpenter studied the effect of the cyano group at different positions of allyl vinyl ethers. Such an effect was interpreted as basically electronic.[45] In the case of substrates substituted at positions C-2 (k_{rel} 111), C-4 (k_{rel} 270), and C-5 (k_{rel} 15.6), an acceleration of the rearrangement was detected, whereas substitu-

Scheme 32



ELECTRON DONATING GROUP ACCELERATION

Position	Group
1	-O,-NH_2, -F, -CH_3
2	-$OSi(CH_3)_3$, -CH_3, -CH^-SO_2Ph, -F
4	-CH_3, -OCH_3
6	-CH_3, -OCH_3

ELECTRON DONATING GROUP DECELERATION

Position	Group
5	-CH_3, -OCH_3

ELECTRON WITHDRAWING GROUP ACCELERATION

Position	Group
2	-CN, -CO_2^-, -CO_2CH_3, -CF_3
4	-CN, -CF_3
5	-CN

ELECTRON WITHDRAWING GROUP DECELERATION

Position	Group
1	-CN, -CO_2CF_3
6	-CN

tion at C-1 and C-6 resulted in a decrease in the reaction rate. These observations were rationalized from Hückel molecular orbital (HMO) theory, which allowed evaluation of the effect of a substituent in the transition state and in the ground state.[45b] The comparison of the difference of π energy of HMO (ΔE_π) between the ground state and the transition state with the value of ΔE_π for the unsubstituted analogue compound allowed them to predict the sign and magnitude of the effect of the substituent in the activation enthalpy of the reaction. In this model the electron-withdrawing and -donating substituents are represented as carbocations and carbanions, respectively. From the delocalized model of the transition state, some qualitative predictions about the effects of the substituents in the Claisen rearrangement could be made. The main inconvenience of this model is that the cyano group is not only an electron-withdrawing group, but also a radical-stabilizing group, so that the acceleration resulting from the presence of a cyano group at C-2 and C-4 may not be a consequence of its electron-withdrawing character.

To differentiate the inductive electron-withdrawing character and the result of a combination of inductive and mesomeric electron-withdrawing effects, the behavior of allyl vinyl ethers bearing a trifluoromethyl group at C-2 and C-4 was studied.[46] A CF_3 group is an electron-withdrawing substituent with an inductive character but with no mesomeric one; it is not able to stabilize radicals. Hence, the Claisen rearrangement of allyl vinyl ethers bearing a CF_3 group at C-2 suffered an accelerating factor of 73 in relation with the unsubstituted substrate, in comparison with the value of k_{rel} 111 observed for cyano derivatives at C-2.[45a] In its turn, a CF_3 group at C-4 exerted no influence in the reaction rate. These results allowed Gajewski[46] to suggest that the electron-withdrawing character of the substituent at C-4 is not that responsible for the increase in the rate but its ability to stabilize radicals, which is reflected in the stabilization of the transition state. Similarly, quite recently it has been reported that a CF_3 group at C-1 does not modify the reaction rate, whereas the effect of a fluorine atom at the same position will depend on the influence of an alkyl substituent R at C-2 (Figure 3).[47]

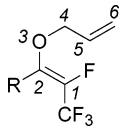
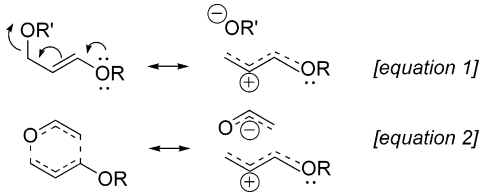


Figure 3.

Different theoretical models predicting the effects of several substituents in the Claisen rearrangement rate have been proposed. The model suggested by Gajewski[48] assumes that the structure of the transition state adopts the features of the substrate or product depending on the exothermic properties of the reaction. In addition, it will have an associative or dissociative character according to the way that the substituents can stabilize such a character. Also, recently some theoretical calculations on the effects of cyano, amino, and trifluoromethyl substituents on the rate, whose results are coincident with those attained from experimental studies, have been reported.[49]

The effect of alkoxy groups has been largely studied by Curran.[50,51] An electron-donating substituent (alkoxy group) at C-6 sharply accelerates the Claisen rearrangement.[50] This effect seems to contradict Carpenter's model,[45] which predicts a deceleration in the presence of a donating substituent at C-6, despite the loss of resonance energy from the ground state to the transition state. To compensate for this effect, the model proposes a $\pi \rightarrow \sigma^*$ stabilization by a "vinylogous anomeric effect" of the O_3-C_4 bond of the vinyl ether as responsible for the Claisen rearrangement acceleration by donating substituents at C-6. The transition state of the Claisen rearrangement (eq 2 in Scheme 33) can be understood in a similar way

Scheme 33

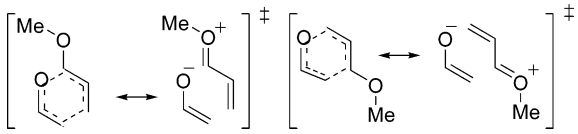


to the "double bond−no bond" resonance explaining the vinylogous anomeric effect (eq 1 in Scheme 33). The process goes through an early transition state where the bond breaking is more advanced than the bond formation.[45] As can be seen, an oxygenated substituent at C-6 must decrease the energy of the transition state—and, therefore, accelerate the reaction—as it makes the breaking of the weakened O_3–C_4 bond easier.

A similar acceleration was detected with the presence of an alkoxy group at C-4. In addition, the rates of the rearrangements of 4- and 6-alkoxyallyl enol ethers were quite sensitive to the solvent polarity and considerably increased in hydrogen bonding solvents[51]—it could not be detected from unsubstituted substrates. These results were attributed to an

enhanced dipolar character of the transition state of the Claisen rearrangement. In other words, the partial delocalization of a nonbonding electron pair at the donating substituent generates a significant degree of enolate−oxonium ion pair, which stabilizes the transition state (Scheme 34).

Scheme 34



A trimethylsilyloxy group at C-2 of the allyl vinyl ether (Ireland−Claisen rearrangement[19]) causes a decrease in the activation free energy of about 9 kcal·mol^{-1} in relation with the unsubstituted substrate.[19b] As the rearrangement rate is independent of the solvent polarity, in this case the mechanistic interpretation must be based upon a neutral transition state.[52] However, it has been admitted that a Me_3SiO group at C-2 generates a transition state where the degree of bond breaking is much higher than that in an unsubstituted substrate. Therefore, to account for the easier Ireland−Claisen rearrangement as compared with the classic Claisen rearrangement, one must invoke the higher stability of the 2-(trimethylsilyloxy)-1-oxallyl moiety. This different stability influences the structure of the transition state.

The results reported by Wilcox[53] on rearrangements of *O*-allyl silyl ketene acetals are worth mentioning. Accordingly, an increase in the steric volume of the substituent at C-5 produces an acceleration of the reaction, whereas the electron-donating character of a substituent at the same position decreases the rate. The study of the influence of alkyl groups was proposed taking into account that these substituents should not substantially affect the geometry and the electronic structure of the transition state. From these effects the influence of more polar substituents in the rearrangement rate could be evaluated. In fact, the different transition states (synchronic, fragmented, or 1,4-diyl) which have been proposed for the Claisen rearrangement can be more or less stabilized according to the nature of the substituents (Figure 4).

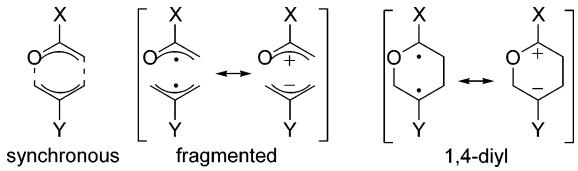


Figure 4.

Therefore, it can be concluded that donor and acceptor substituents at positions 1, 2, and 4 increase the rate in comparison with a hydrogen atom. At positions 5 and 6 the effects are complementary. A rate acceleration is observed with donor groups at position 6 and acceptor groups at position 5, whereas the reaction is decelerated when the donor and acceptor groups are interchanged at those positions. The decelerating effect of a methoxy group has been accepted as evidence against a 1,4-diyl transition state.

Finally, in the case of the *ortho*-Claisen rearrangement, changes in the reaction rate for differently substituted aromatic substrates have been observed. Schmid[54] explained this behavior as a consequence of a different 1,2-bond order of the aromatic fragment of the allyl aryl ether, whereas Tarbell and Wilson[55] proposed a directional electron flow during the rearrangement both for substituted and unsubstituted substrates (Figure 5).

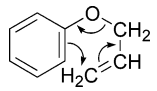


Figure 5.

The polar nature of the reaction was reinforced by the fact that the rate of the rearrangement of allyl *p*-tolyl ether gradually increased as the polarity of the solvent was higher (reactions were faster when the solvent was phenol instead of diethyl ether).[56] There are several possible explanations accounting for the effect of the substituents in the rearrangement rate.[57] If concerted, the reaction could be rationalized as taking place almost as simultaneously at both the *para* and *meta* positions relative to the substituents; bond formation and rupture will exhibit a polar nature and should not be equally important in the activated complex. White proposed that the overall electronic change could be summarized as indicated in Figure 6.[58]

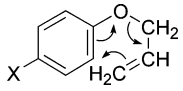


Figure 6.

Another plausible mechanism implies the formation of "ionic pairs" (with a markedly oriented character) as an intermediate step between the allyl aryl ether and the dienone, so that the allyl group will ionize as an anion and the aromatic moiety as a cation (Figure 7).

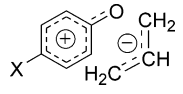


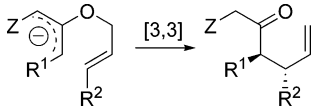
Figure 7.

Undoubtedly, the mechanism for the Claisen rearrangement lies, for a number of substrates, somewhere between these two extremes (Figures 6 and 7).

4.2.2. Influence of Charged Intermediates

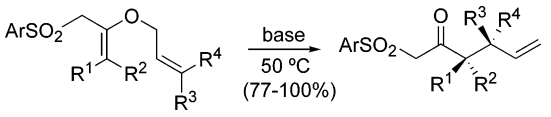
On the basis of the empirical observations that π-electron-donating groups at the C-2 position of an allyl vinyl ether accelerate the Claisen rearrangement, Denmark studied the effect of the strongest π-donating group, a carbanion (Scheme 35).

Scheme 35



Carbanions stabilized by cyano or alkoxycarbonyl groups (Z = CN or CO_2Et) exerted no positive influence in the reaction rate, maybe due to the extensive charge delocalization and the covalent nature of the anions. However, a carbanion on an arylsulfonylmethyl group at the C-2 position of an allyl vinyl ether accelerates the Claisen rearrangement about 300 times (Scheme 36);[59] this has been

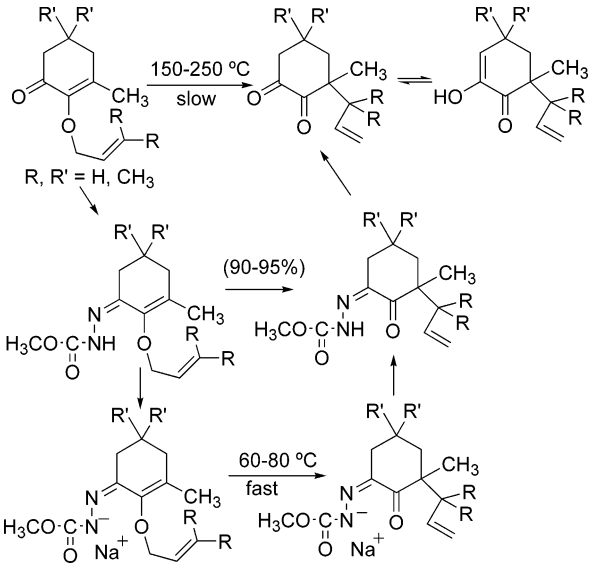
Scheme 36



attributed to the inductive charge-stabilizing effect of the sulfonyl group. This acceleration has not been observed in the presence of other sulfur functional groups.[59c] The reaction can be considered as a regio- and stereoselective procedure capable of creating vicinal quaternary centers in high yields.

The above-mentioned diosphenol−Claisen rearrangement[29] was considerably accelerated by the transformation of the substrates into carbomethoxyhydrazones, whose sodium salts rearranged more than 200 times faster than the corresponding carbonyl derivatives[60] (Scheme 37). This reaction pro-

Scheme 37

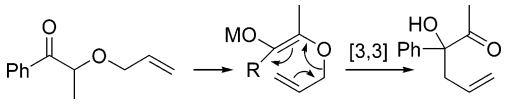


ceeded in high yields and allowed the creation of sterically hindered bonds such as the bond between two quaternary carbons.

Similarly, the so-called anionic oxy−Claisen rearrangement of enolates derived from α-allyloxyketones has been reported.[61] This reaction, which took place at unexpectedly low temperatures, was influenced by the counterion and solvent (Table 1).

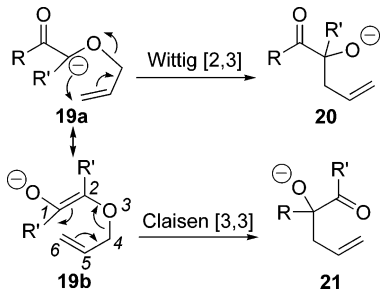
The enolates derived from α-allyloxyketones are able to evolve through two possible sigmatropic rearrangements (Scheme 38). Resonance form **19a** (α-allyloxy-α-carbanion) illustrates how it is able to undergo a [2,3] rearrangement (Wittig rearrangement) to yield the α-alkoxyketone **20**. In its turn, **19b**

Table 1. Oxy−Claisen Rearrangement under Different Experimental Conditions



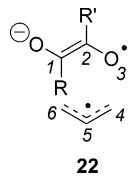
entry	solvent	M	temp (°C)	$t_{1/2}$ (h)
1	toluene	K	−23	3.3
2	toluene	Na	0	2.6
3	toluene	Li	+96.5	1.1
4	toluene	Me_3Si	+71	0.5
5	THF	K	−42	6.2
6	THF	K	−23	<0.1
7	THF	Na	−23	2.4
8	THF	Li	+67	1.3

Scheme 38



can be considered as a 1-oxy-3-oxa-1,5-hexadiene able to evolve through a [3,3] sigmatropic rearrangement resulting in the isomeric alkoxyketone **21**.

As can be deduced from the data collected in Table 1, there are some conditions favoring the [3,3] process. A considerable acceleration was indeed observed as a function of the electron-donating ability of the group OM at C-1. Thus, whereas the rearrangement evolved at −23 °C with potassium hydride in toluene, there was practically no reaction with sodium hydride under the same conditions. This acceleration of the Claisen rearrangement evidences the effect of the alkoxy anion in the transition state. As we have already seen, the rearrangement proceeds through an early transition state quite close to a radical pair resulting from the homolytic fragmentation of the O_3-C_4 bond. In the case of the anionic oxy−Claisen rearrangement, this fragmentation will generate a pair formed by an allyl radical and a stable oxy−oxallyl radical **22** (Figure 8). Therefore,



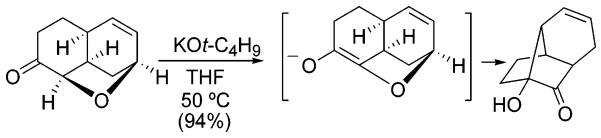
22

Figure 8.

the rate-accelerating effect can be attributed, to a large extent, to the contribution of the extraordinarily stable radical anion **22** to the transition state of the reaction.

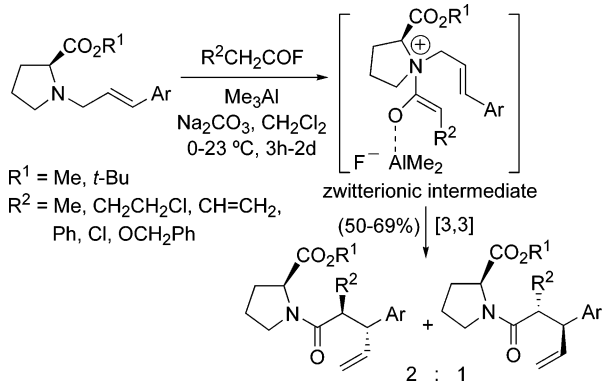
An anionic oxy−Claisen rearrangement has been reported as the key step in the synthesis of the skeleton existing in a family of natural sesquiterpenes derived from campherenone (Scheme 39).[62]

Scheme 39



The rate of the aza−Claisen rearrangement of *N*-allylamines has been considerably increased by treatment of allylamines with acid fluorides in the presence of Me_3Al.[63] The zwitterionic rearrangement implies either the formation of a complex of the acylammonium salt with the Lewis acid or the direct formation of the zwitterionic intermediate as a result of a nucleophilic attack of the amine to the ketene−Lewis-acid complex (Scheme 40). In any case, the

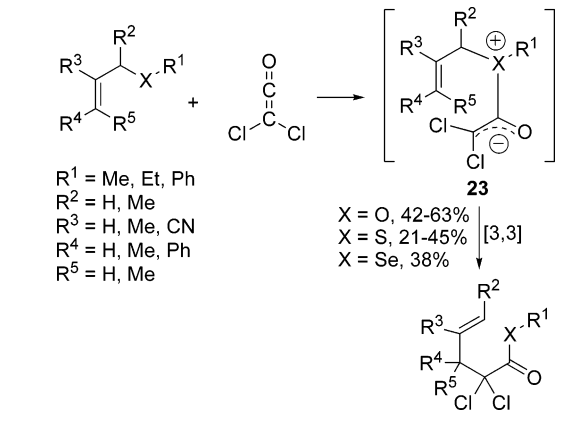
Scheme 40



reaction took place in high yields for a wide range of substrates under milder conditions than those reported for the aza−Claisen rearrangement.

This reaction exemplifies how a positively charged heteroatom decreases the activation energy of the rearrangement. This result prompted the study of 1,3-dipolar intermediates in the reaction (Scheme 41),

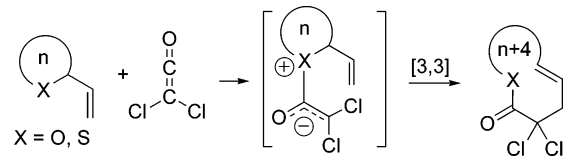
Scheme 41



which were easily formed by reaction of allyl ethers, sulfides, or selenides with haloketenes.[64]

It is generally admitted that the reaction products are obtained by [3,3] rearrangement of a dipolar oxonium intermediate **23**. Although intermediate **23** is supposed to be less stable than the corresponding sulfur derivative (due to stabilization of the latter through d orbitals), the yields of *O*-esters are higher than those of the *S* esters. The results from open chain allylic esters prompted the study of the reaction of vinyl-substituted heterocyclic systems with electrophilic haloketenes, which afforded medium-sized lactones, although in moderate to low yields (Scheme 42). Subsequent metal (Zn, Fe) reduction allowed the elimination of the chlorine atoms of the molecule.

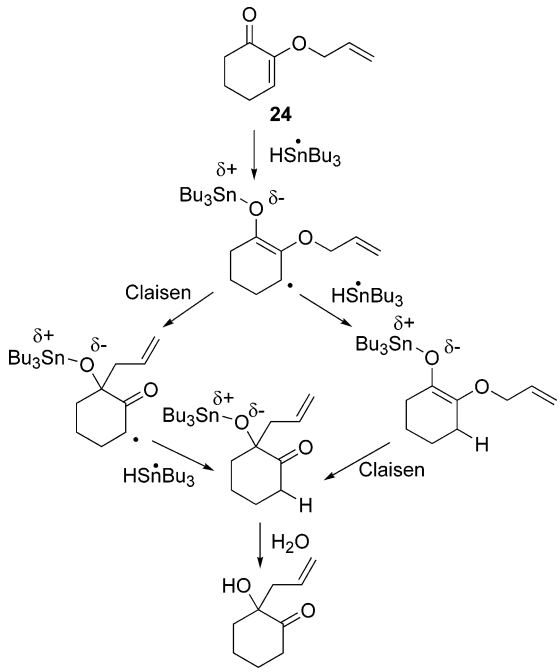
Scheme 42



This ketene−Claisen variant could be recognized as an important Claisen rearrangement class on the basis of the number of syntheses that have used this chemistry and the enantioselective and Lewis-acid-catalyzed examples reported on this methodology (see later).

Finally, another type of Claisen rearrangement accelerated by charged substrates is the [3,3] rearrangement of the intermediates obtained by treatment of dienones **24** with tri-*n*-butyltin hydride (Scheme 43).[65] These reactions, which provided a

Scheme 43



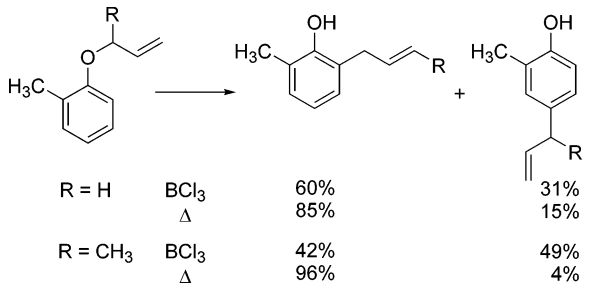
considerable increase in rate, proceeded under neutral conditions. The rearrangement mechanism has been studied independently by Enholm[65a] and Curran,[65b] resulting in two different mechanistic proposals. Enholm's hypothesis supports the so-called "anion-radical mechanism", whereas isotopic-labeling experiments with *n*-Bu_3SnD led Curran to defend the mechanism reported as a "stannyloxy−Claisen mechanism" or an "anionic mechanism" (Scheme 43).

4.2.3. Catalyzed Claisen Rearrangements

Allyl aryl ethers with no electron-withdrawing substituents undergo [3,3] sigmatropic rearrangement

in the presence of boron trichloride at low temperature to afford the corresponding *o*-allyl phenols in good yields.[66,67] The charge induced at the reaction site by the catalyst generates a rate increase of ca. 10^{10} relative to the thermal Claisen rearrangement. The rearrangement of allyl aryl ethers bearing an *ortho* alkyl group, in the presence of boron trichloride, produced a mixture of *o*- and *p*-allyl phenols, the ratio of the *para* product being higher than that resulting from the thermal reaction (Scheme 44).[67] This "*para*

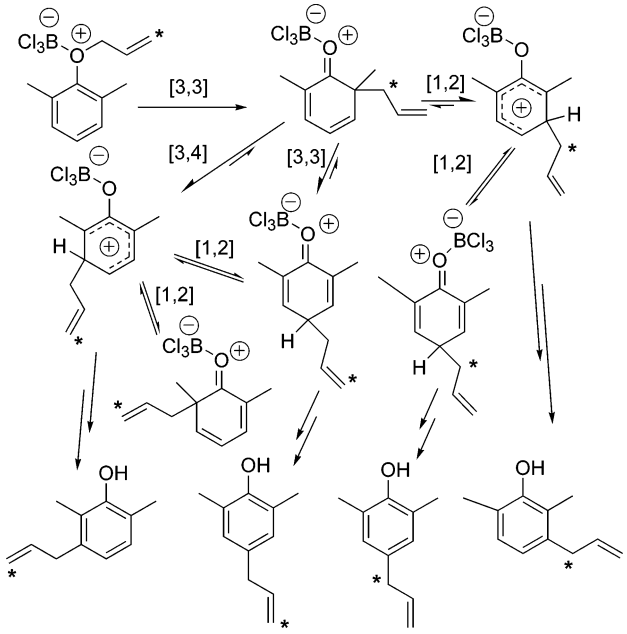
Scheme 44



effect" was especially marked for *o*-alkyl α-methylallyl aryl ethers.

In the presence of boron trichloride, 2,6-dialkyl allyl aryl ethers gave products resulting from a sequence of *ortho*-Claisen rearrangement followed by a [1,2], [3,3], or [3,4] rearrangement of the allyl moiety. These rearrangements, which were studied with deuterium- or ^{14}C isotopically-labeled substrates, are represented in Scheme 45. In the presence of protic

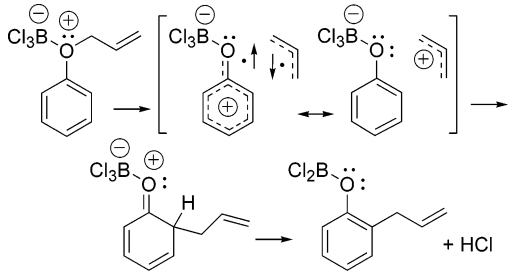
Scheme 45



acids there was always a [3,3] rearrangement of the allyl group of 2,6-disubstituted 6-allylcyclohexa-2,4-dien-1-ones, whereas the use of boron trichloride produced the [3,3] rearrangement product along with those compounds resulting from the [1,2] and [3,4] processes, although the latter ones were obtained as the minor reaction products.

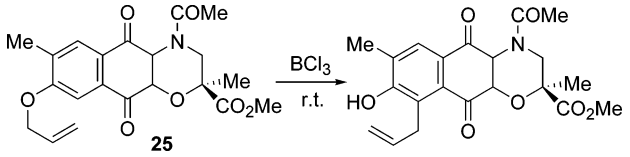
The mechanism which was proposed to explain the behavior of allyl aryl ethers under boron chloride catalysis[67] implies a fragmented transition state, similar to the one proposed under thermal conditions, as depicted in Scheme 46.

Scheme 46



From the above results it should be deduced that use of BCl_3 as the catalyst of the aromatic Claisen rearrangement has a restricted synthetic applicability since it provokes undesired side reactions. However, in the case of complex systems such as **25** (Scheme 47), BCl_3 catalysis afforded the Claisen

Scheme 47

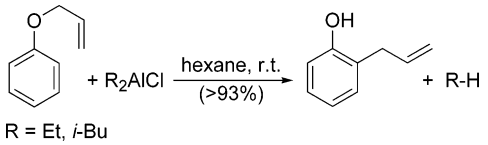


25

rearrangement product, while under thermal conditions the starting material only evolved with decomposition.[68]

The aromatic Claisen rearrangement of allyl phenyl ether was reported in the presence of alkylaluminum halides under mild conditions.[69] Treatment of allyl phenyl ether in hexane with an excess of diethylaluminum chloride at room temperature produced *o*-allylphenol almost quantitatively (Scheme 48). Similar results were attained in the presence of ethylaluminum dichloride.

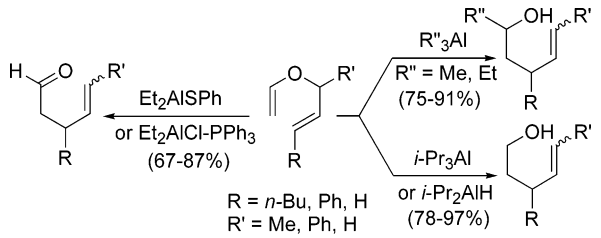
Scheme 48



In contrast with the catalyst boron trichloride, these alkylaluminum derivatives are able to catalyze [3,3] rearrangement of allyl aryl ethers bearing electron-withdrawing groups on the aromatic ring. Thus, allyl *o*-, *m*-, and *p*-chlorophenyl ethers rearranged in high yields into the corresponding allylchlorophenols bearing the allyl group in *ortho* position relative to the hydroxy group.[69]

Despite the large number of reported examples of catalysis of the aromatic Claisen rearrangement,[66] the number of published results on the influence of aluminum Lewis acids in the aliphatic Claisen rearrangement is quite low. Nevertheless, it was reported that in the presence of organoaluminum compounds of the type R_3Al or R_2AlX, or Et_2AlSPh or $Et_2AlCl-PPh_3$, a series of allyl vinyl ethers rearranged under mild conditions, although the overall results were

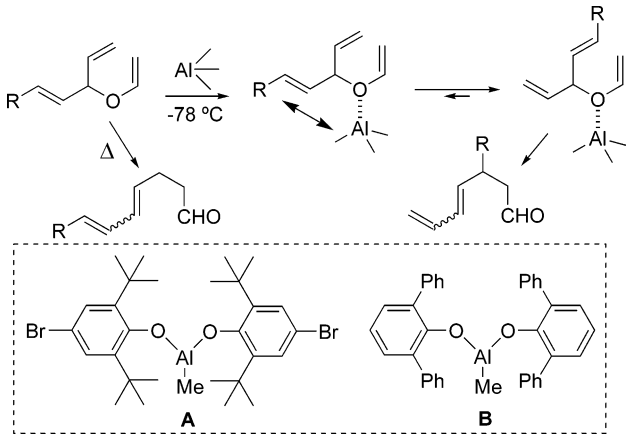
Scheme 49



closely dependent on the catalyst nature (Scheme 49).[70] Thus, in the presence of trialkylalanes, the rearrangement product underwent nucleophile attack, either by the alkyl group or by a hydride. In contrast, use of Et_2AlSPh or $Et_2AlCl-PPh_3$ produced the aldehydes or ketones derived from the rearrangement with no nucleophilic attack.

The use of especially bulky aluminum reagents allowed control of the regiochemistry of the Claisen rearrangement in compounds bearing two allyl fragments.[71] Under thermal conditions the rearrangement evolved through the less hindered allyl group. In contrast, in the presence of aluminum reagents such as **A** or **B** (Scheme 50), the minimization of

Scheme 50



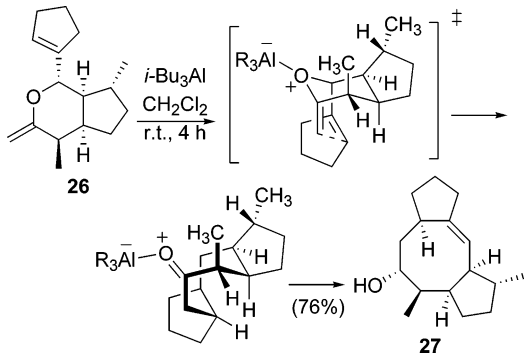
steric repulsions between the more substituted allyl group and the Lewis acid afforded the opposite regioselectivity.

Triisobutylaluminum-catalyzed Claisen rearrangements with concomitant reduction of the resulting carbonyl group allowed ring enlargement processes.[72] From the above-mentioned results on the rearrangement acceleration in the presence of charged intermediates, alkylaluminum-catalyzed rearrangements may be considered as the cationic analogues of the anionic oxy−Claisen rearrangements. The transformation of **26** into **27** may be understood considering that the rearrangement takes place through a chairlike transition state such as that depicted in Scheme 51.

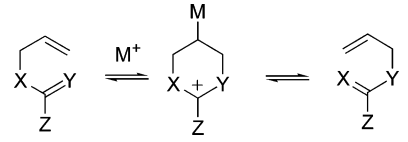
Many [3,3] sigmatropic rearrangements of allylic esters, allyl imidates, and *S*-allyl thioimidates in the presence of Hg(II) or Pd(II) salts have been reported. These reactions proceeded by a "cyclization induced rearrangement", which explains the effect of the metal catalysts (Scheme 52).

Nevertheless, the number of reported examples of Hg(II)- or Pd(II)-catalyzed Claisen rearrangements

Scheme 51

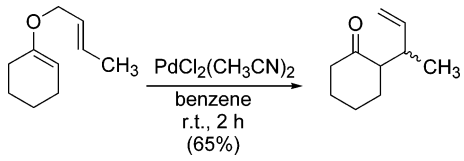


Scheme 52



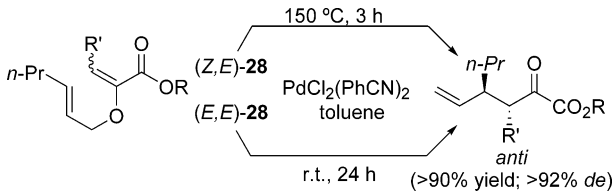
of 3-hetero-1,5-dienes, such as allyl vinyl ethers (X = O, Y = CR_2, Z = H, alkyl, aryl), is quite low. This fact was explained as a consequence of the irreversible binding of the electrophilic metal catalyst at the strongly nucleophilic vinyl ether, which prevented its binding at the allylic double bond.[74] In contrast, those substrates bearing a vinyl moiety protected by alkyl substitution from the attack of the metal catalyst are able to rearrange in the presence of $PdCl_2(CH_3CN)_2$,[75] whereas they are unstable under thermal conditions (Scheme 53).

Scheme 53



The Pd(II)-catalyzed Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers (**28**) was reported.[76] Whereas under thermal conditions the reaction required heating at 150 °C in a sealed tube, in the presence of $PdCl_2(PhCN)_2$, 2-alkoxycarbonyl-substituted *Z,E*- and *E,E*-allyl vinyl ethers exhibited markedly different reactivities. Thus, (*E,E*)-**28** rearranged through a boatlike transition state to afford *anti*-β,γ-alkyl-substituted α-ketoesters, while (*Z,E*)-**28** did not rearrange at room temperature. However, the latter rearranged at higher temperatures through a chairlike transition state to produce the same anti product (Scheme 54).

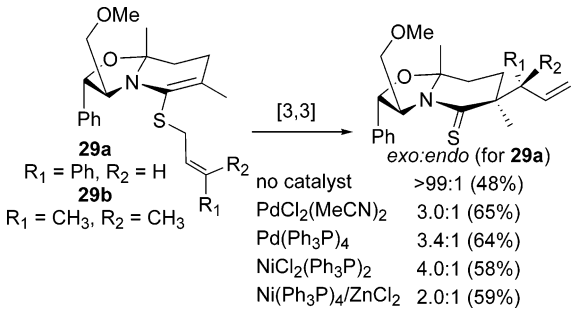
Scheme 54



Similarly, some thio−Claisen rearrangements catalyzed by transition metals [Pd(II), Ni(II)] under mild

conditions are known.[77] Ketene *N,S*-acetals **29a** and **29b** underwent transition-metal-promoted [3,3] sigmatropic rearrangements, under smooth conditions, to yield the corresponding thiolactams (Scheme 55),

Scheme 55



whereas the thermal rearrangement required heating at 140 °C. Although in the presence of a catalyst the *exo* diastereoselectivity dramatically decreased as compared with the thermal process, the isolated yield of the major *exo* diastereomer was higher than under thermal conditions.

$PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$, and $Pd(OAc)_2$ were Pd(II) derivatives able to catalyze the rearrangement at 25 °C. $Pd(PPh_3)_4$ was used at 25 °C as a Pd(0) catalyst. The results with $NiCl_2(PPh_3)_2$ should also be considered. Coordination of the metal with the double bond (**E** in Scheme 56) was proposed to explain the stereochemical results obtained from **29a** in the presence of Pd(II). Nucleophilic attack of the thioenol ether generated an intermediate six-membered palladate (**F**), which underwent Pd(II) elimination to afford the [3,3] product. The Pd(0) reaction was proposed to proceed via the formation of a π-allylpalladium complex (**I**) (Scheme 56).

The catalytic effect of other Lewis acids ($ZnCl_2$, $TiCl_4$, $AgBF_4$) in the Claisen rearrangement rate has been studied. However, only moderate rate accelerations and/or poor yields have been observed. This is probably due to the formation of byproducts or to the decomposition of the rearranged products under the reaction conditions.[66] On the other hand, it has been reported that ytterbium triflate catalyzes the Claisen rearrangement of aromatic allyl and crotyl ethers to give the corresponding *C*-allyl phenols with an increase in the rate relative to the uncatalyzed reaction (Scheme 57).[78] The increase in the rate was evident from the results obtained on increasing the substitution at the olefinic position. α-Naphthol was also obtained as a byproduct (15−30% yield).

Eu(III) was also reported as a catalyst of the Claisen rearrangement of the prenyl ether **30** to afford the phenols resulting from the migrations to *ortho* and *para* positions (Scheme 58).[79] These compounds, after basic treatment, gave rise to flavonoids 6-(1,1-dimethylallyl)naringenin (**31**) and 8-prenylnaringenin (**32**), respectively.

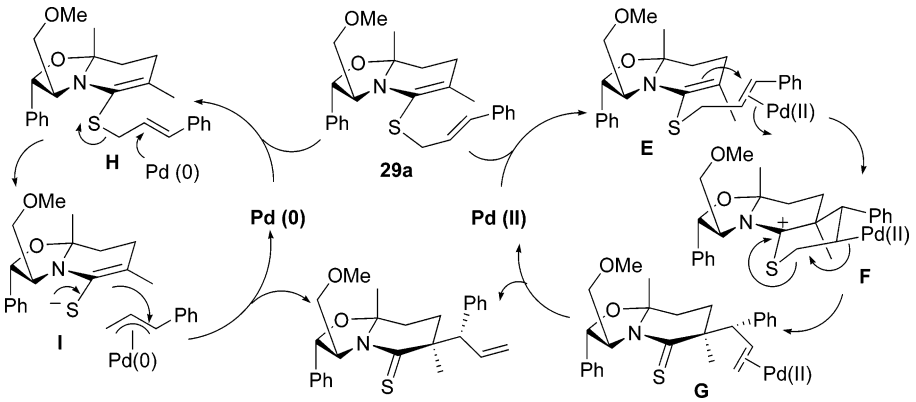
Zwitterionic aza−Claisen rearrangements were also studied in the presence of a number of Lewis acids, and a remarkable catalytic effect was determined.[80] Allyl vinylammonium complexes, generated by the reaction of ketenes with tertiary allylamines in the presence of a Lewis acid, rearranged to give 2,3-disubstituted Claisen products in good yields (>75%) and excellent stereocontrol (>99:1 *anti*:*syn* ratio), the best results having been obtained with $Yb(OTf)_3$, $AlCl_3$, $Ti(O\textit{i}\text{-}Pr)_2Cl_2$, and $TiCl_4$·THF (Scheme 59).

Similarly, the Ireland−Claisen rearrangement of allylic aryl acetates has been reported to proceed in high yields and diastereoselectivities by addition of catalytic amounts of Lewis acids such as $TiCl_4$ or $SnCl_4$.[81] However, the nature of this Lewis-acid effect could not be satisfactorily explained by spectroscopic methods.

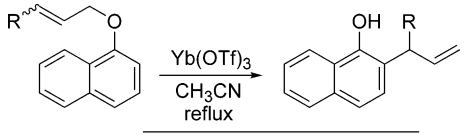
Claisen rearrangements promoted by rhodium carbenoids have recently been shown to be a general stereoselective method for the synthesis of tertiary alcohols.[82] The reaction occurs when the diazosubstrates are combined with allylic alcohols in the presence of a Rh(II) catalyst. The process takes place through a mechanistic pathway where the insertion in the O−H bond generates a reactive enol intermediate which will undergo rearrangement (Scheme 60). This reaction proceeds with a highly efficient stereochemical transfer from enantiomerically enriched allylic alcohols to the resulting α-hydroxy carbonyl compounds. This stereochemical outcome of the rearrangement is rationalized by a chairlike transition state with a (*Z*)-enol fragment and an equatorial methyl substituent.

In the context of the use of Lewis acids as catalysts of the Claisen rearrangement, in the last few months the allenoate−Claisen rearrangement has been reported as a general method for the diastereoselective preparation of 4,5-disubstituted-β-enamino esters.[83] As depicted in Scheme 61, the reaction of a Lewis-

Scheme 56

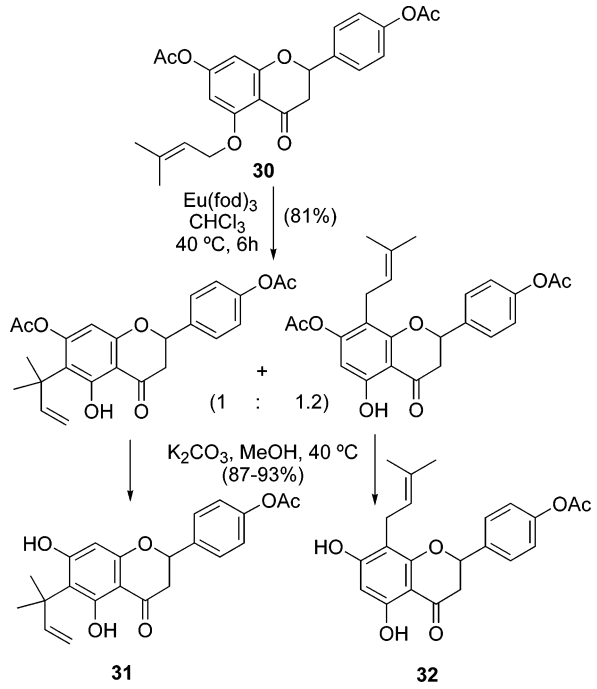


Scheme 57

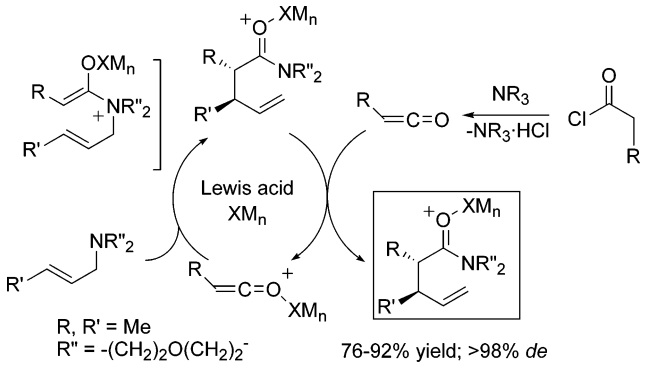


R	t (h)	Yield (%)
H	72	65
CH_3	3	60

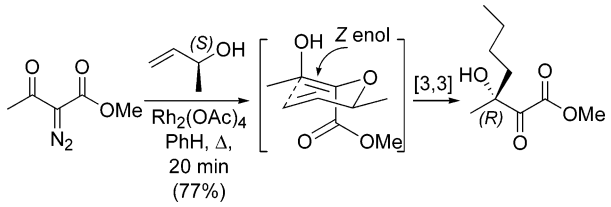
Scheme 58



Scheme 59

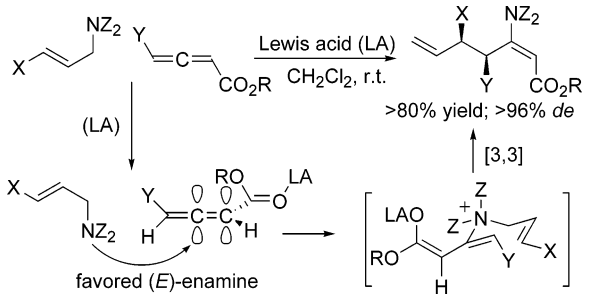


Scheme 60



acid-activated allenic ester with a tertiary allylamine proceeded with a high π-facial discrimination to give an allyl vinylammonium complex exhibiting (*E*)-stereochemistry at the enamine double bond. This complex evolved through a chairlike transition state to afford the [3,3] rearranged product. Excellent

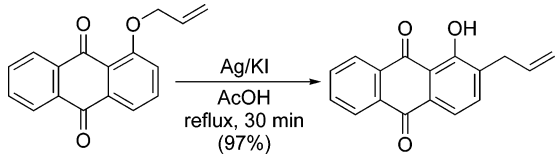
Scheme 61



yields and stereoselectivities were obtained in the presence of $Yb(OTf)_3$, $Sn(OTf)_2$, $Cu(OTf)_2$, or $Zn(OTf)_2$.

Recently, a new catalytic system able to accelerate a type of aromatic Claisen rearrangement was reported. Thus, the Ag−KI/HOAc system promoted the reductive rearrangement of allyloxyanthraquinones (Scheme 62).[84] The reduction of the anthraquinone

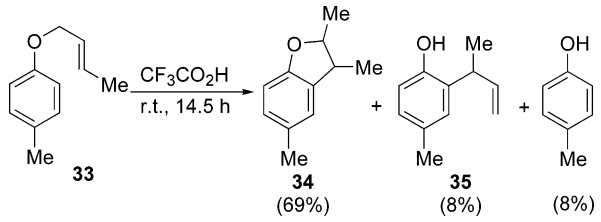
Scheme 62



moiety to its hydroquinone state by Ag/KI was proposed as being responsible for the acceleration of the rearrangement.

Trifluoroacetic acid considerably increases the allyl aryl ether Claisen rearrangement rate, although the resulting allylphenols generally undergo further transformations under the acidic reaction conditions.[66] Thus, the reaction of crotyl tolyl ether (**33**) in trifluoroacetic acid afforded, as the major product, cumarane **34**, resulting from the cyclization of the [3,3] rearranged product **35** (Scheme 63).[85] Similar

Scheme 63

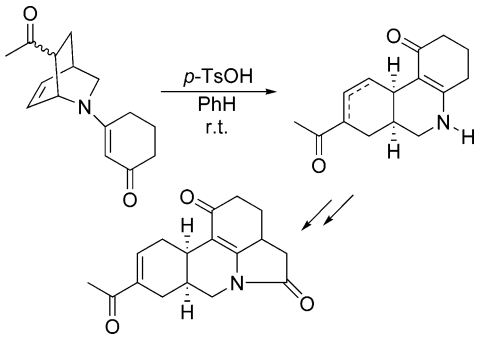


mixtures were obtained by using sulfuric acid as the catalyst.

Aza−Claisen rearrangements of *N*-(*β*-ketovinyl)-isoquinuclidines have also been described under protic acid (*p*-toluenesulfonic acid) catalysis to give structures which afforded polycyclic skeletons bearing the hydroisoquinoline core (Scheme 64).[86]

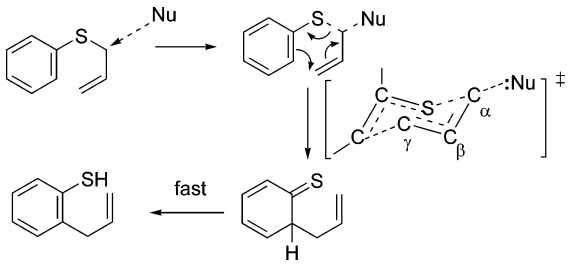
The thio−Claisen rearrangement was considerably accelerated in the presence of neutral or anionic nucleophiles (amines, PhS−, PhO−, MeCOO−).[87a] The proposed mechanism for this transformation, tested by the secondary kinetic deuterium isotope effect and the substituent rate effect,[87b] implies a concerted bimolecular process where the nucleophile approaches the substrate to reach a chairlike [3,3] transition state, where the nucleophile is weakly

Scheme 64



bonded to the substrate. As the reaction advances, the nucleophile detaches, as depicted in Scheme 65.

Scheme 65



The rate of the Claisen rearrangement of allyl phenyl ether into 2-allylphenol is enhanced (ca. 15%) by an increase in the solvent viscosity. A considerable acceleration was reported by addition of small amounts of low molecular weight polyethylene into the reaction solvent.[88] The viscous but amorphous nature of the polyethylene catalytic fragment was of high importance. It was concluded that in the case of enzymes, regardless of the traditionally accepted role played by the transition-state binding, the higher viscosity of the active center also contributes significantly to the enzymatic catalysis.

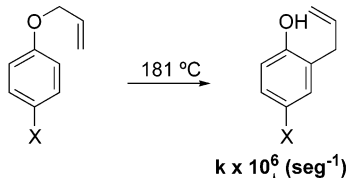
4.2.4. Other Parameters

To increase the Claisen rearrangement rate, several physical parameters affecting the reaction have been investigated with successful results in many cases. Next some of the most noteworthy examples will be described.

The empirical reaction acceleration observed on increasing the pressure means that the transition state, which includes not only the reacting atoms but also the solvent molecules surrounding them, occupies a smaller volume than the reactants. Bond-forming reactions are prone to undergo an increase in their rates on increasing the pressure. The volume of activation ($\Delta V^{\ddagger}$) is generally assumed as merely a volume term. However, it has been suggested that $\Delta V^{\ddagger}$ derives only partially from the volume, since a pressure increase may induce kinetic effects which are not a result of changes in the volume. The term "phantom activation volume" has been coined to denote any change in the rate induced by pressure which, although defined as $\Delta V^{\ddagger}$, actually is not related to the volume.[89] One example is the Claisen rearrangement, which is accelerated by pressure,[90] although there is no significant decrease in the volume along the reaction coordinate. One example may be illustrative. The molar volume of allylacetaldehyde is only 6 mL/mol (5.4%) smaller than that of allyl vinyl ether. This fact is not surprising since the numbers of bonds and rings are not modified, which means that the Claisen rearrangement products get no thermodynamic advantage over the reactants from an increase in the pressure. Therefore, only one kinetic factor related to the volume will be considered: the fact that the cyclic transition state has one more ring than the substrate. Hence, the ensemble [transition state + solvent] is smaller than [reactant + solvent], and the activation volume will be negative. For example, [3,3] rearrangements of allyl phenyl ether at 160 °C and ethyl (1-ethylpropenyl)-allylcyanoacetate at 119 °C have been reported to be pressure-accelerated.[90b]

Polar solvents increase the rearrangement rate. The contribution of the polar effects to the increase in the reaction rate was first observed in the *ortho* Claisen rearrangement of allyl *p*-X-phenyl ethers (Scheme 66).[91]

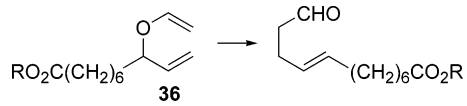
Scheme 66



Solvent	NO_2	Br	CH_3	OCH_3
tetradecane	2.34	5.98	7.94	28.3
carbitol	10.3	27.7	44.2	91.6
EtOH-H_2O (28.5%)	90.0	134	233	621

The accelerating influence of water as the solvent of the reaction of aliphatic substrates has been demonstrated by measuring the first-order rate constants of the rearrangement of the allyl vinyl ether **36** (R = Na, Me) in solvents of increasing polarity (Scheme 67).[92] The relative rate decreases in the

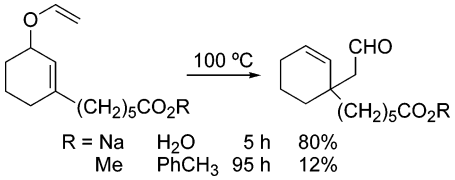
Scheme 67



order water > trifluoroacetic acid > methanol > ethanol > 2-propanol > acetonitrile > acetone ≈ benzene > cyclohexane, which reinforces the polar character of the transition state.

A similar accelerating effect has been observed with other substrates (Scheme 68).[93]

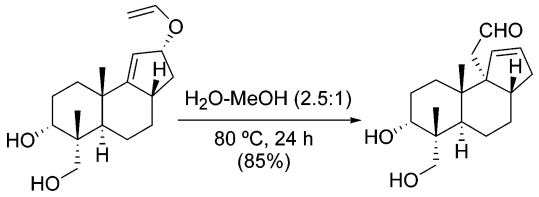
Scheme 68



The use of polar solvents under mild conditions has given rise to rearrangement products unable to be

obtained under classical conditions due to thermal decomposition (Scheme 69).[93]

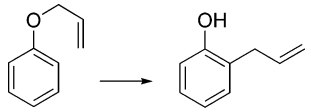
Scheme 69



Theoretical calculations have corroborated the role of polar solvents.[94] The incorporation of two molecules of water leads to the conclusion that hydrogen bonding with the oxygen atom of the solute is stronger in the transition states than in the substrates. In addition, the presence of two molecules of water affords more dissociative and polarized transition states.

Microwave irradiation strongly accelerates the Claisen rearrangement. This fact contributes to solve the problem of the long thermal treatments implied by the classical conditions reported for the reaction. In this sense, the first reported studies pointed out a combined effect of microwave irradiation and temperature, the latter directly dependent on the solvent, that allowed a considerable decrease in the reaction time, as deduced from the results collected in Table 2.[95]

Table 2. Aromatic Claisen Rearrangement Accelerated by Microwave Irradiation[a]

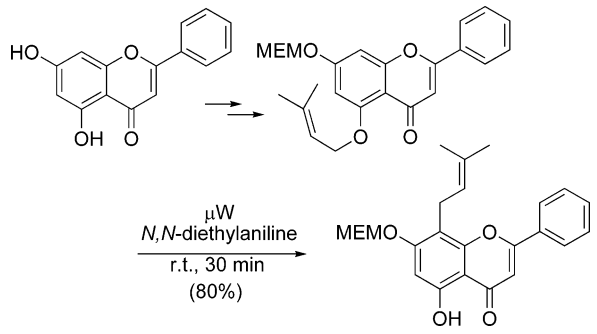


entry	irradiation	time	temp (°C)	solvent	yield (%)
1		6 h	220		85
2	μW	10 min	325−361		21
3	μW	6 min	300−315	DMF	92

[a] Adapted with permission from ref 95. Copyright 1986 Elsevier.

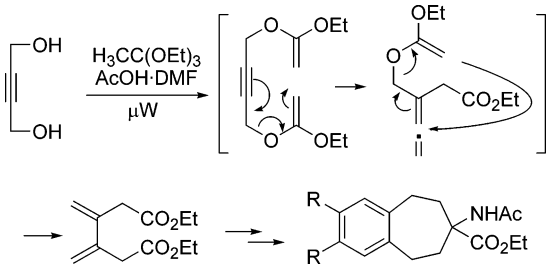
However, what is synthetically more interesting is the fact that compounds which decompose or are inert under thermal conditions react with excellent regiocontrol upon microwave irradiation. Such is the case, for example, of the aromatic Claisen rearrangement that, with microwave irradiation, allows the regioselective isoprenylation at the *para* position of flavonoids (Scheme 70).[96]

Scheme 70



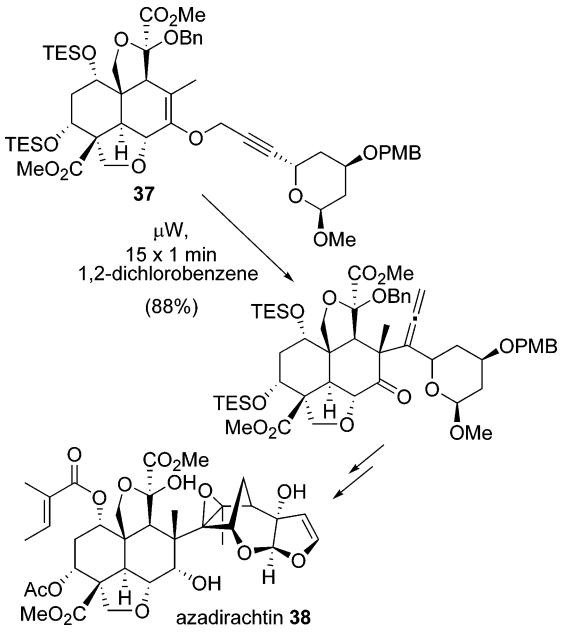
Similarly, microwave irradiation successfully afforded the key step of the synthesis of α,α-dialkyl amino acids derived from benzocycloheptene. The transformation, which had been unsuccessful under thermal conditions, implied a double Johnson rearrangement from 2-butyne-1,4-diol (Scheme 71).[97]

Scheme 71



A microwave-induced Claisen rearrangement of the propargylic enol ether **37** was also the key step in the synthesis of the skeleton present in the triterpenoid azadirachtin **38** (Scheme 72).[98] Once again, this

Scheme 72

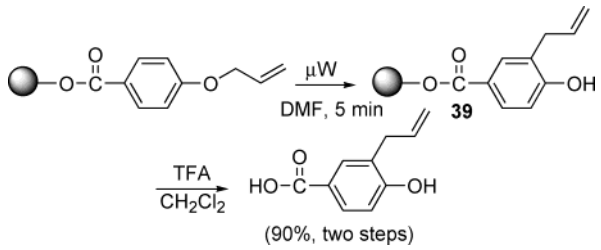


transformation under thermal or catalytic conditions did not take place at all.

In recent years the main feature of the evolution of combinatorial chemistry has been the building of polyfunctionalized libraries of small organic molecules on solid supports.[99] Some parameters such as time and temperature of solid-phase organic reactions may be critical. Recently, microwave irradiation has been used to perform the Claisen rearrangement in the solid phase of *O*-allyl aryl ethers derived from salicylic acids anchored to a Merrifield resin, affording the corresponding trisubstituted aromatic systems (**39**) in 4−6 min (in contrast with the 10−16 h required under thermal conditions) in high yields (Scheme 73).[100]

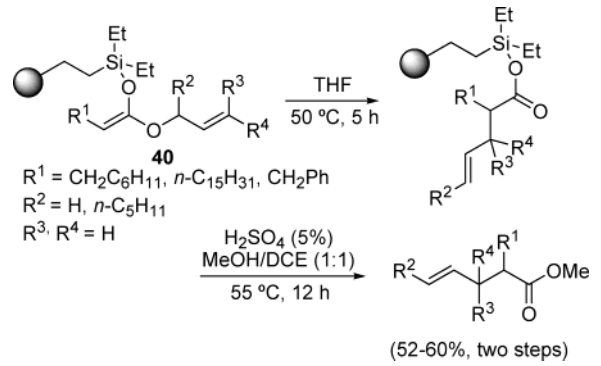
An Ireland−Claisen rearrangement of silyl ketene acetals anchored to a polystyrene−diethylsilane (**40**) was also reported.[101] This reaction proceeded under

Scheme 73



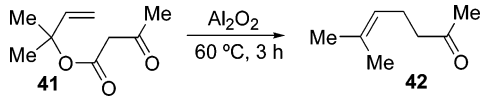
mild conditions (50 °C, 5 h) to produce the corresponding silyl esters in high yields (Scheme 74).

Scheme 74



The results of the Carroll rearrangement of **41** on the surface of an adsorbent such as alumina should be considered. The corresponding γ,δ-unsaturated ketone **42** was obtained in good yield (Scheme 75).[102]

Scheme 75

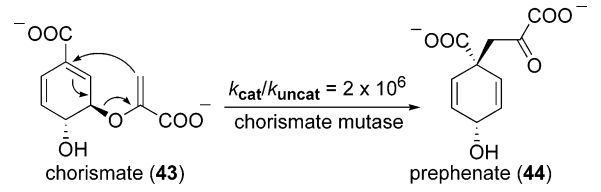


The rate enhancement as compared with that reported in solution has been attributed to restrictions of the conformational mobility imposed by the interaction with the surface adsorption centers.

5. Enzymatic Claisen Rearrangement

Chorismic acid is a key intermediate in the shikimate biosynthetic pathway. Sigmatropic rearrangement of chorismate (**43**) into prephenate (**44**) (Scheme 76) represents the first step in the transformation of

Scheme 76



chorismate into phenylalanine and tyrosine. This process is a Claisen rearrangement, in vivo catalyzed by the enzyme chorismate mutase, which generates a rate increase of 2×10^6 at 37 °C.[103] It is the only known formal enzyme-catalyzed pericyclic reaction and is widely reported in the literature.[104] Although the comprehensive scope of the present review justifies a brief mention of the reported examples of enzyme-catalyzed Claisen rearrangements, the peculiar features of these processes as well as their special relevance in metabolic routes make advisory their detailed study elsewhere.

6. Stereoselective Claisen Rearrangement

6.1. General Aspects

The highly ordered cyclic transition states involved in the Claisen rearrangement, along with the restrictions imposed by the orbital symmetry rules, allow one to predict excellent stereochemical results. Two strategies have been developed to control the stereoselectivity of the reaction: either the stereogenic elements accounting for the selectivity are "intraannular" (i.e., they are incorporated into the cyclic structure of the transition state) or they are "extraannular" (therefore, lacking any cyclic restriction).

The strategy of intraannular stereoselection considers the use of an achiral auxiliary inherent to the stereochemistry of the allyl or vinyl double bond or else a chiral auxiliary, derived from the presence of a stereocenter directly bonded to the heteroatom. This stereocenter disappears as a consequence of the change in the hybridization. The extraannular control is represented by the presence of a chiral element in the allyl or vinyl fragment of the starting structure. In any of the above situations, the diastereoselectivity of the Claisen rearrangements is considered. The use of chiral catalysts or solvents determines the enantioselectivity of these processes.

It is also possible to find conditions making the Claisen rearrangement a stereoselective process regardless of the optical purity of the newly created chiral center. In these cases, the E/Z selectivity of the new double bond is considered.

6.2. Intraannular Diastereoselectivity

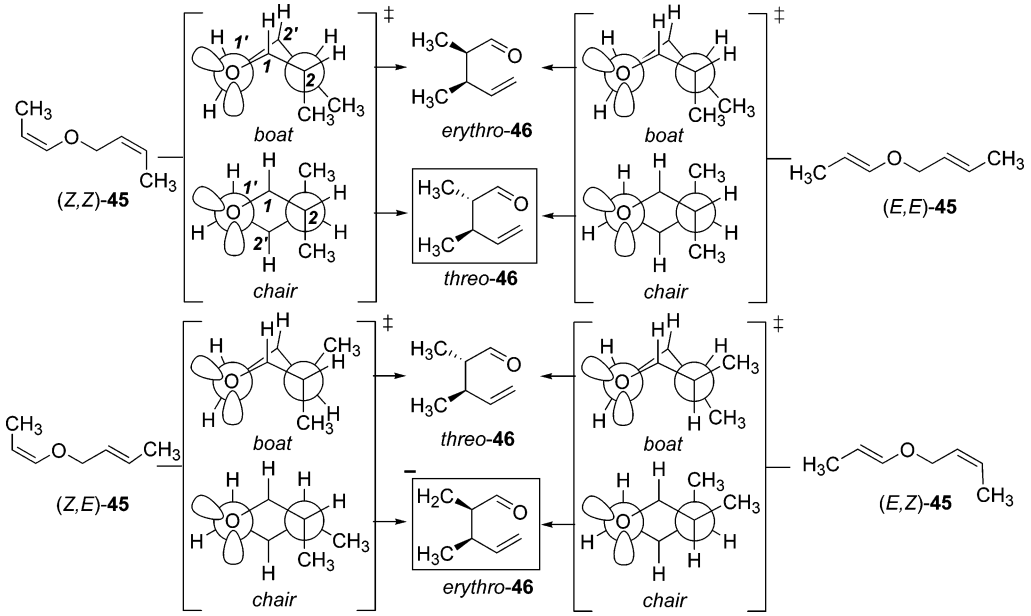
6.2.1. Transition-State Geometry

The generally accepted geometry for the transition state of the Claisen rearrangement is a chair conformation, controlled by the steric[105] and electronic[106] features of the system. The gas-phase rearrangement of (1*Z*,2′*E*)-, (1*Z*,2′*Z*)-, (1*E*,2′*E*)-, and (1*E*,2′*Z*)-propenyl but-2′-enyl ether [(*Z*,*E*)-, (*Z*,*Z*)-, (*E*,*E*)-, and (*E*,*Z*)-**45**] into *erythro* and *threo*-2,3-dimethylpent-4-enal (*erythro*- and *threo*-**46**) proceeds preferentially through chairlike transition states in order to minimize repulsive steric interactions, as depicted in the Newman projections represented in Scheme 77.

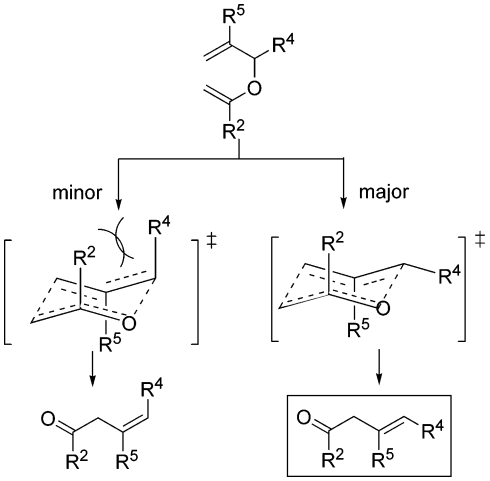
Therefore, the chairlike transition state determines that the relative stereochemistry (*erythro*/*threo*) at the newly generated vicinal stereocenters is controlled by the relative geometry of the double bonds at the starting material. Hence, (*Z*,*Z*) and (*E*,*E*) substrates afford *threo* products, whereas (*E*,*Z*) and (*Z*,*E*) substrates yield *erythro* products.[107]

In the presence of a substituent $R^4 \neq H$ at C-4, the different stability of both chair conformations for the transition state determines a clear predominance of *E* alkenes as the reaction products (Scheme 78).

Scheme 77



Scheme 78



Diastereofacial selectivity of the Claisen rearrangement has also been explained by considering electrostatic interactions.[106] The chairlike structure proposed for the transition state of the Claisen rearrangement, especially the Ireland−Claisen rearrangement, could be conceptually divided into a nucleophilic "ester enolate" allylic fragment and an electrophilic "hydrocarbon" allylic fragment (Figure 9).

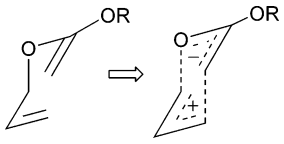


Figure 9.

As a consequence of the latent "dipolar" nature of these rearrangements, their stereochemical pathway derives from the electrostatic requirements of both allyl components, so that the most electrophilic face of the relatively electronically poor component combines with the electronically rich "nucleophilic" fragment (Figure 10). In the presence of allyl alcohols or ethers on the "electrophilic" fragment, the addition

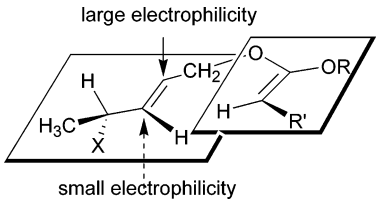


Figure 10.

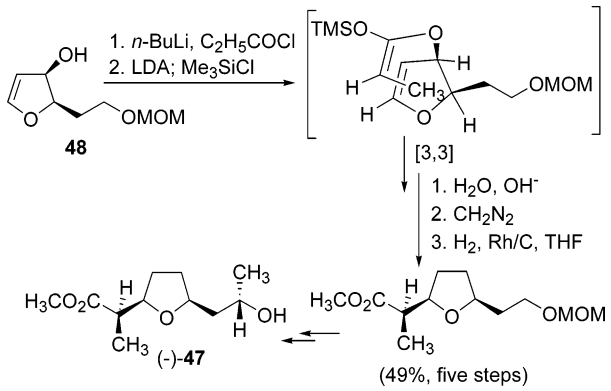
of the nucleophilic "ester enolate" takes place in the anti position with respect to the electronically rich allyl oxygen of the most reactive (more electrophilic) conformer where the allyl C−H bond eclipses the C=C double bond.

Despite the clear predominance of the chair conformation in the cyclic transition state of the Claisen rearrangement, some examples have been reported to produce the isomers resulting from a boat conformation in the transition state, as a consequence of either the structural features of the substrate or the reaction conditions. In the context of the stereoselective synthesis of nonactic acids (**47**), the Claisen rearrangement of the involved heterocyclic systems takes place through a boatlike transition state from the silyl ketene acetal derived from the glycal **48** (Scheme 79).[108]

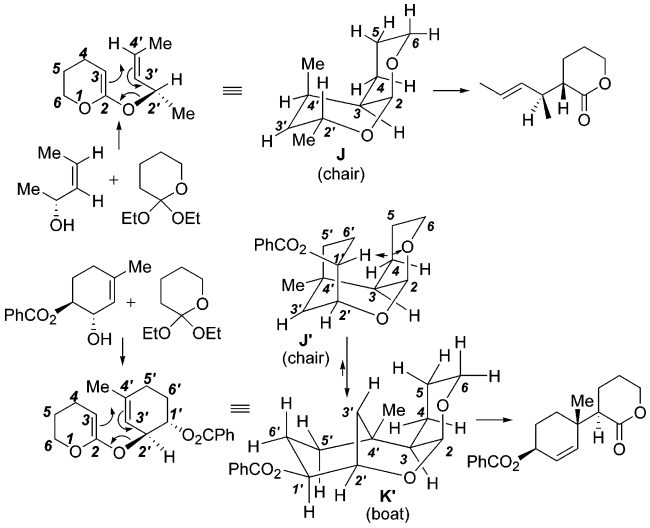
A similar explanation has been proposed for the [3,3] rearrangement of carbocyclic systems where the steric interactions may destabilize a chairlike transition state, thus shifting the Johnson rearrangement of cyclic ortho esters toward a boat conformation for the transition state (Scheme 80).[109a] Thus, whereas acyclic allyl alcohols evolve through a chairlike transition state (**J**), destabilizing 1,3-syndiaxial interactions present in the chair conformation **J′** derived from cyclohexenols determine that the Johnson rearrangement proceeds through a boatlike transition state (**K′**).

It is even possible to invert the conformation of the transition state of an Ireland−Claisen rearrangement through inversion of the stereochemistry of the

Scheme 79

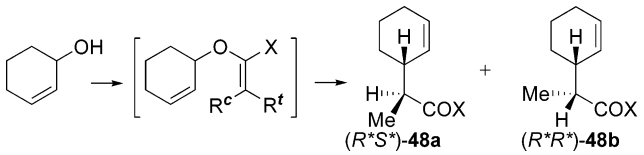


Scheme 80



enol double bond,[110] as deduced from the results collected in Table 3.

Table 3. Ireland−Claisen Rearrangement of 2-Cyclohexenols



entry	conditions	favored intermediate X	R^c	R^t	48a:48b	transition state	yield (%)
1	LDA, THF; *t*-BuMe$_2$SiCl; Δ	$OSiR_3$	Me	H	85:15	chair	47
2	LDA, HMPA/THF; *t*-BuMe$_2$SiCl; Δ	$OSiR_3$	H	Me	75:25	boat	36

To explain the operativity of the chair and boat transition states in these rearrangements, bicyclic structures **L** and **M** depicted in Figure 11, with different steric interactions in each, should be considered. In the chair conformation **L**, there is an unfavorable interaction between the substituent X and the cyclohexenyl ring, which leads to a preference for the boat conformation **M** (see Table 3, entry 2). On the other hand, when R^c = methyl, the boat conformation is unstabilized because this methyl group and an allyl methylene are eclipsed (entry 1).

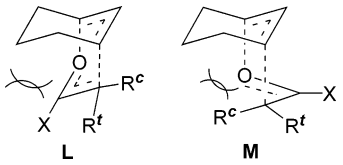
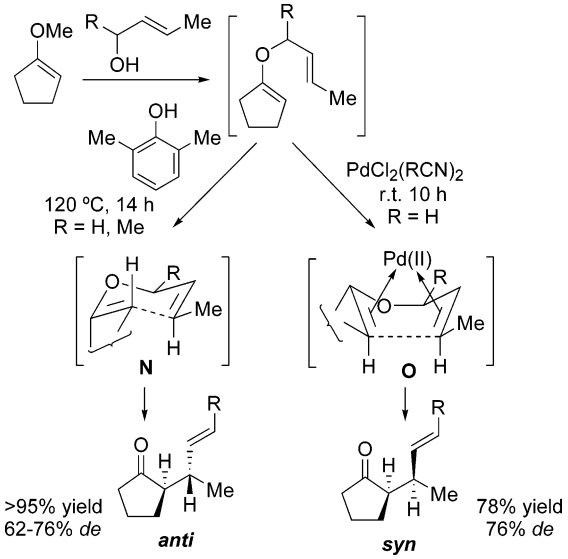


Figure 11.

From cyclic enol ethers—and, therefore, with a defined *E* stereochemistry—it is possible to direct the Claisen rearrangement toward the diastereoselective formation of syn or anti (*erythro* or *threo*) products by the suitable choice of catalyst (Scheme 81).[111] The

Scheme 81



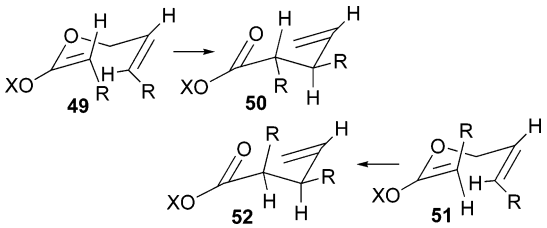
E → anti diastereoselectivity of the rearrangement in the presence of a catalytic amount of 2,6-dimethylphenol is explained by a chairlike transition state (**N**), whereas the *E* → syn selectivity of the Pd(II)-catalyzed rearrangement can be understood by assuming a boatlike transition state (**O**) where the diene acts as a bidentate ligand.

6.2.2. Vinyl Double-Bond Geometry

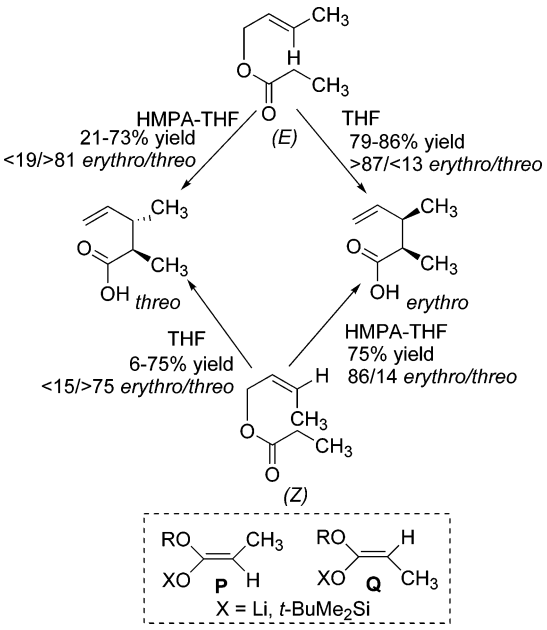
As a consequence of the chairlike transition state of the rearrangement, the relative configuration of the stereogenic center at the new C−C single bond can be predicted from the geometry of the vinyl double bond of the starting 1,5-diene system. In this context the studies on the Ireland−Claisen rearrangement are particularly interesting.[112] It was demonstrated that the silyl ketene acetal **49** (X = *t*-BuMe$_2$Si, R = alkyl) afforded acid **50**, whereas starting from **51** the major reaction product was acid **52** (Scheme 82).

The rearrangement of (*E*)- and (*Z*)-crotyl propionates proved the stereochemical outcome of the enolization, where a marked influence of the solvent polarity was observed (Scheme 83).[112] When (*E*)-crotyl propionate was enolized in THF and then treated under rearrangement conditions for the enolate or the corresponding silyl ketene acetal, the *erythro* acid was diastereoselectively formed. In a more coordinative solvent (HMPA−THF), the enolization followed a different pathway and the *threo* acid was obtained.

Scheme 82



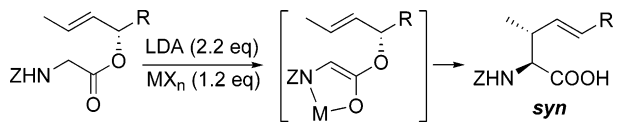
Scheme 83



The rearrangement of (*Z*)-crotyl propionate proceeded with the opposite diastereoselectivity, which led to the conclusion that the selectivity determining step is the enolization. In fact, *Z* enolates (**P**) are preferentially formed in THF, while the isomeric *E* enolates (**Q**) are obtained in HMPA−THF.

Among the methods allowing the synthesis of γ,δ-unsaturated amino acids, the above-mentioned Claisen rearrangement modification evolving through chelated enolates derived from amino acid esters should be considered.[28] As the enolate geometry is determined by the chelation and the chairlike transition state is preferred, compounds exhibiting a syn relative configuration are formed diastereoselectively (Scheme 84).[113] When esters derived from optically

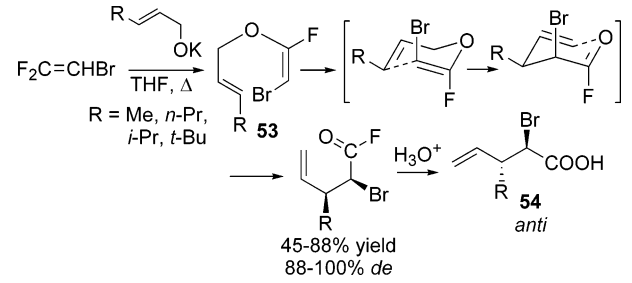
Scheme 84



pure allyl alcohols were used, enantiomerically pure amino acids were obtained (vide infra).

The effect of a halogen on the vinyl fragment of the starting material for the Claisen rearrangement was also investigated to check the influence of such a substituent in the geometry of the transition state.[114] The rearrangement of allyl *trans*-bromofluorovinyl ethers **53** took place at low temperature with high diastereoselectivity to produce γ,δ-unsaturated β-substituted α-bromoacids **54** in a process with a

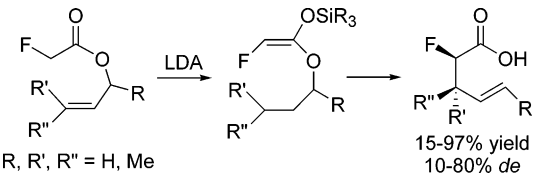
Scheme 85



marked internal stereocontrol (Scheme 85). The influence of a halogen in the geometry of the vinyl group of the ethers **53**, and therefore the selectivity of the acids **54,** could also be investigated. The *trans*-bromofluorinated ether **53** led to the anti acid **54** through a chairlike transition state.

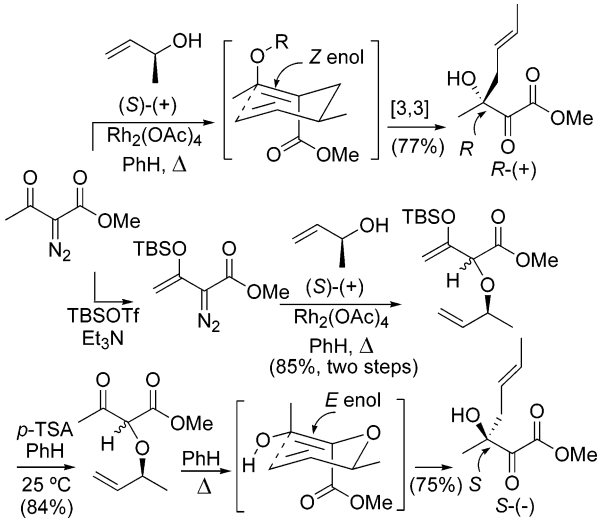
Similarly, *E* enolates, prepared by stereoselective deprotonation of allyl fluoroacetates, underwent a diastereoselective Claisen rearrangement (Scheme 86).[115]

Scheme 86



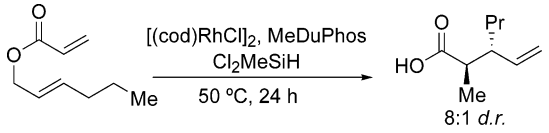
The Claisen rearrangement promoted by rhodium carbenoids has already been considered as a general stereoselective method for the synthesis of enantiomerically pure tertiary alcohols, whose configuration is a consequence of the stereochemistry of the rearranged enol (Scheme 87).[82]

Scheme 87



Closely related to these results, it has been recently demonstrated that (*E*)-silyl ketene acetals, diastereoselectively generated by treatment of allyl acrylates with $[(cod)RhCl]_2$ and 1,2-bis(dimethylphospholano)benzene (Me-DuPhos) in the presence of a silane, underwent reductive Ireland−Claisen rearrangement with good diastereocontrol to give γ,δ-unsaturated carboxylic acids (Scheme 88).[116] The control of the

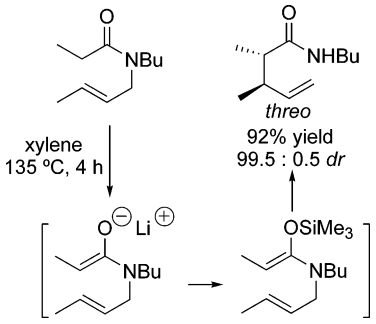
Scheme 88



silyl ketene acetal geometry was crucial for the control of the overall stereoselectivity.

The aza−Claisen rearrangement of enolates derived from *N*-2-butenyl-*N*-butylpropanamides proceeded with high diastereoselectivity to generate *N*-butyl-2,3-dimethyl-4-pentenamides (Scheme 89).[117]

Scheme 89



This excellent diastereoselectivity shows both the exclusive formation of *Z* enolates and the participation of a chair conformation for the transition state of the aza−Claisen rearrangement. The formation of the *Z* enolate was rationalized by assuming that the steric repulsion between methyl and dialkylamino groups in the *E* enolate was stronger than the interaction of the methyl group with the negatively charged oxygen atom in the *Z* enolate (Figure 12).

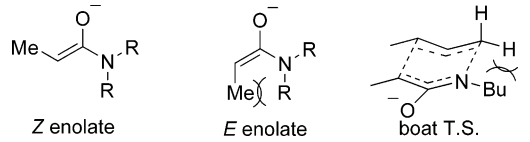


Figure 12. Reprinted with permission from ref 117. Copyright 1990 Elsevier Science.

The repulsion of the butyl group when eclipsed by one of the allyl hydrogen atoms in the boat conformation may account for the preferred chairlike transition state. This interaction does not exist in the reaction of ester enolates.

The salts derived from alkylation of propionamides reacted with the lithium alkoxide of (*E*) or (*Z*)-2-butenol to afford the product of Eschenmoser rearrangement of the corresponding *N*,*O*-ketene acetals (Scheme 90).[118]

The diastereoselectivity of the rearrangement was explained by unfavorable steric interactions, inherent to the vinyl double-bond geometry, between the nitrogen substituents and the enamine substituent at the β position (Figure 13). This shows that the most stable (*Z*)-enolate reacts faster than the (*E*)-

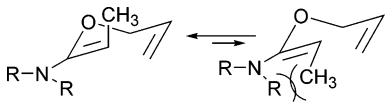
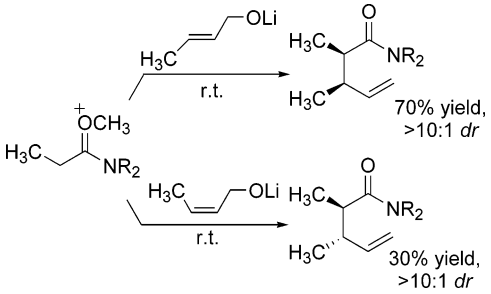


Figure 13.

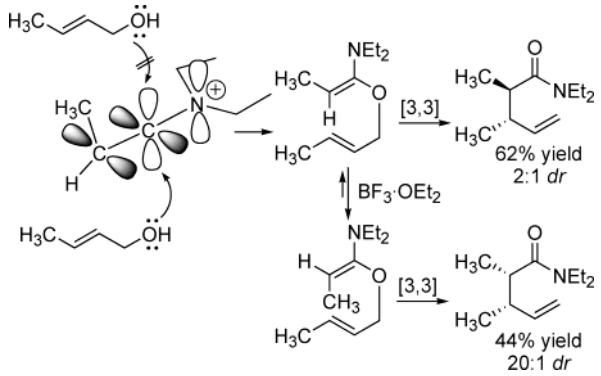
Scheme 90



enolate. However, in this reaction it is actually the geometry about the allylic alkoxide that leads to the selectivity, as discussed in section 6.2.3.

The ynamine−Claisen rearrangement can be considered to be complementary to the Eschenmoser−Claisen rearrangement due to its stereochemical outcome. Ynamine−Claisen rearrangements begin with the addition of an alcohol (or alkoxide) to a keteniminium intermediate (Scheme 91).[119] As the

Scheme 91



alcohol must approach this intermediate onto the plane of the C=C double bond, the steric interaction with the methyl group will favor the formation of the (*E*)-*N*,*O*-ketene acetal. The rearrangement of the *E* isomer, formed under kinetic control conditions, yielded the *threo* product. In the presence of a Lewis acid, the initially formed adduct equilibrated to the thermodynamically favored *Z* stereoisomer to generate, upon rearrangement, the same isomer—*erythro*—that would result from the classical Eschenmoser rearrangement.

6.2.3. Allyl Double-Bond Geometry

The highly ordered cyclic transition state of the Claisen rearrangement results in the high observed stereoselectivity. Within the context of the stereospecific control of the C-20 configuration of cholesterol (Figure 14), from the analysis of the respective transition states of the rearrangement of both possible allyl alcohols (**55** and **56**) it can be deduced that

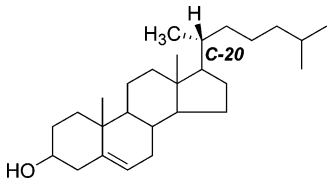
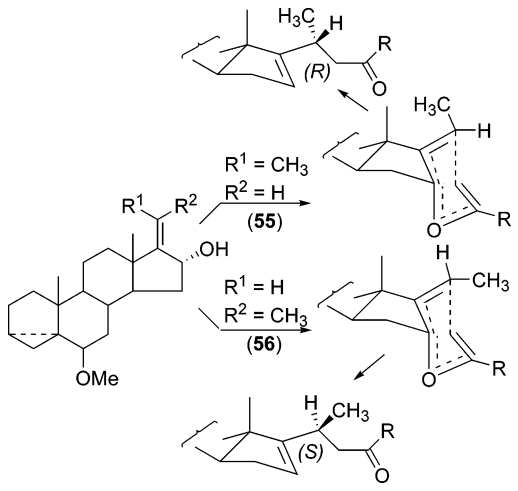


Figure 14.

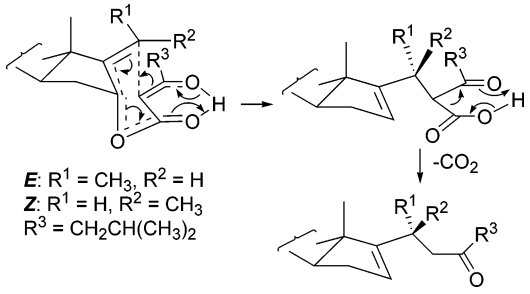
the *E* isomer (**55**) will produce the natural configuration (20*R*) at C-20, whereas from the *Z* isomer (**56**) the unnatural isomer at C-20 will be obtained (Scheme 92).[120]

Scheme 92



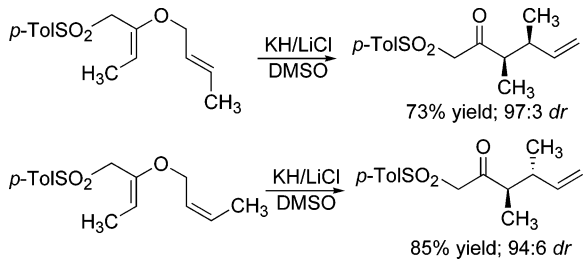
The use of the Carroll version of the Claisen rearrangement of the corresponding allyl ketoacetates led to complete diastereocontrol in the process (Scheme 93).[120]

Scheme 93



Carbanionic Claisen rearrangement can also exhibit high diastereoselectivity. This is directly controlled by the most favored chairlike geometry of the transition state, which is dependent on the geometry of the allyl double bond (Scheme 94).[121]

Scheme 94



The high diastereoselectivity observed in these reactions, as well as their stereochemical results, similar to those obtained under thermal conditions, suggested a chairlike transition state. Under thermal conditions the isomer **T** rearranged twice as fast as **U**, whereas under anionic conditions (Na^+ salt) the reaction of **T** was 12 times faster than that of **U** (Figure 15). This suggests an increase in the steric

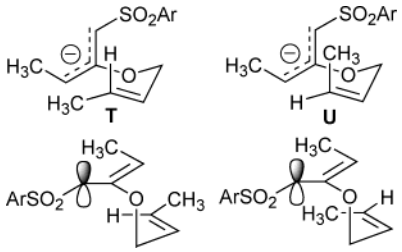


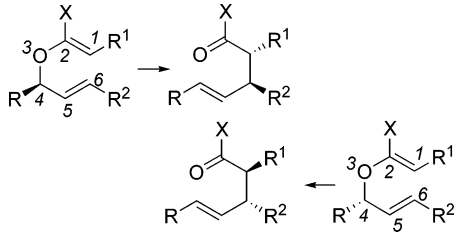
Figure 15.

volume of the sulfonylmethyl group due to its association with the cation and the solvent.[121b]

6.2.4. Configuration at C-4

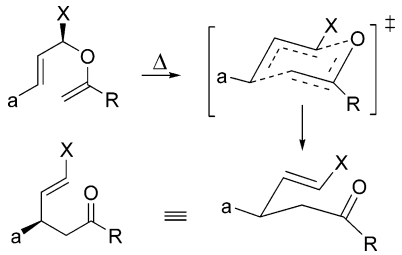
In the Claisen rearrangement, if the substrate is a chiral molecule due to the presence of a substituent at C-4 of the allyl vinyl ether, particularly in the case of acyclic molecules, this chirality can be transferred to the 1 and/or 6 positions through a cyclic transition state (Scheme 95).[122]

Scheme 95



These chiral substrates usually undergo rearrangement through a chairlike transition state where the bulkiest group bonded to the stereogenic carbon adopts an equatorial arrangement (Scheme 96).

Scheme 96

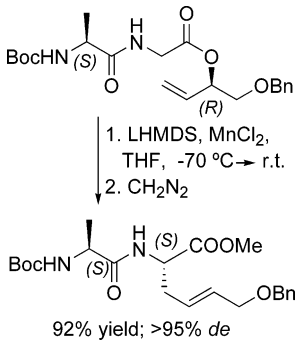


Similarly, the substituent at the double bond also arranges in an equatorial position. The absolute stereochemistry and the double-bond geometry of the product must be those depicted in Scheme 96.

Magnesium enolates are extraordinarily useful for peptide transformations through Claisen rearrangements of chelated enolates.[123] This methodology is especially interesting for esters derived from chiral alcohols. As the vicinal amino acids had no significant influence on the rearrangement, the use of chiral esters, in the presence of LiHMDS as the base, afforded diastereomerically pure peptides (Scheme 97). This rearrangement also allowed the generation of *S* or *R* amino acids through an intramolecular chirality transfer.

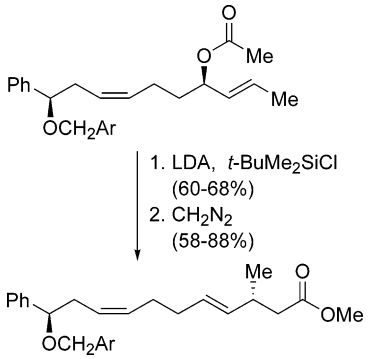
A chirality 1,3-migration through a chairlike transition state was also reported from acetates derived from chiral allyl alcohols under Ireland−Claisen rear-

Scheme 97



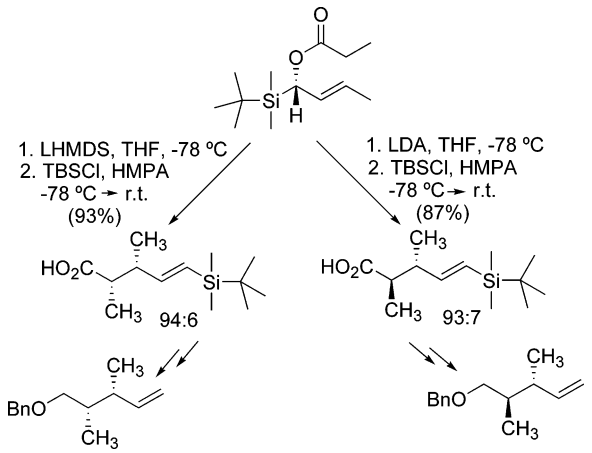
rangement conditions (Scheme 98).[124] This strategy is useful for controlling the relative configuration of really remote chiral centers.

Scheme 98



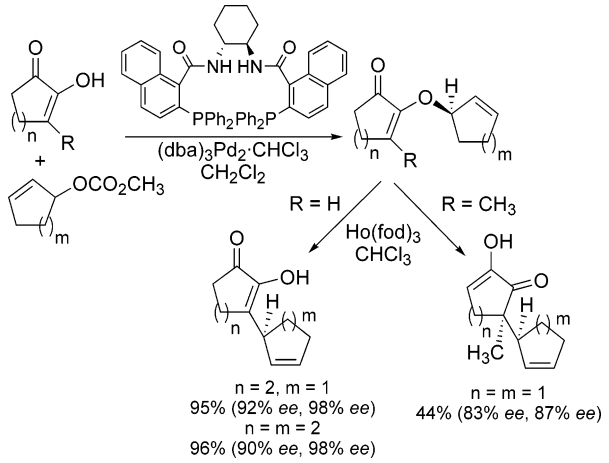
The use of a temporary chiral secondary allyl alcohol was also investigated, since the corresponding rearranged product could eventually be transformed into the product resulting from the rearrangement of the corresponding achiral primary allyl alcohol. One example of this type of chiral equivalents of primary alcohols, developed by Ireland−Claisen,[125] was the enantiomerically pure α-silylcrotyl alcohol, whose propionate was able to transfer its chirality in a [3,3] rearrangement to the corresponding enantiomerically enriched carboxylic acids (Scheme 99). The strategy was completed by cleavage of the silicon function.

Scheme 99



An excellent chirality transfer was also reported in the Claisen rearrangement, performed in the presence of a holmium catalyst, of chiral allyl vinyl ethers derived from cyclic 1,2-diketones (Scheme 100).[126] The starting materials for these reactions

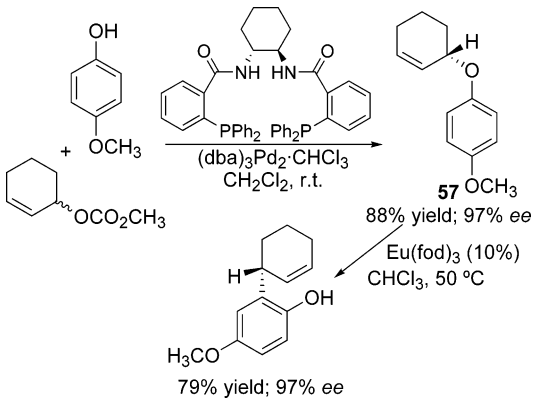
Scheme 100



were prepared by enantioselective *O*-alkylation in the presence of a chiral palladium catalyst.

In general, an important drawback for the development of the stereoselective version of the aromatic Claisen rearrangement is the problem of *ortho*/*para* selectivity. In addition, the rearrangement mechanism implies an allyl cation with the subsequent loss of regioselectivity and stereospecificity with respect to the geometry of the allyl fragment at the substrate. For these reasons the results described by Trost on a diastereospecific aromatic Claisen rearrangement with intramolecular chirality transfer starting from *para*-protected chiral substrates (**57**) are particularly interesting (Scheme 101).[127] Chiral allyl aryl ethers

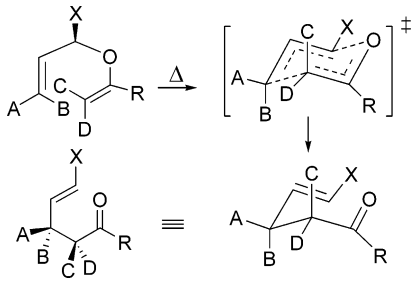
Scheme 101



were prepared following a methodology similar to that depicted in Scheme 100 by enantioselective *O*-alkylation of hydroquinone monomethyl ether in the presence of a chiral palladium catalyst. The substrate **57** evolved with an excellent intraannular diastereoselectivity in the presence of a catalytic amount of $Eu(fod)_3$ as the Lewis acid.

All the above-mentioned results regarding the strategies used to achieve a high intraannular diastereoselectivity in the Claisen rearrangement are summarized in Scheme 102. As shown, the product stereochemistry is defined by the chirality of the

Scheme 102



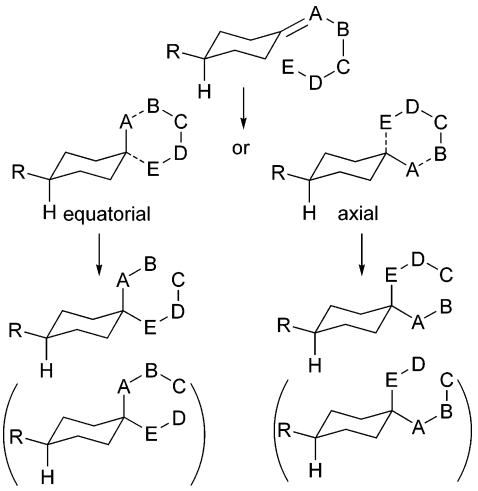
original stereocenter as well as the geometry of both double bonds.

6.3. Diastereoselective Synthesis of Achiral Products

6.3.1. Diastereoselective Synthesis of Cycloalkane Derivatives

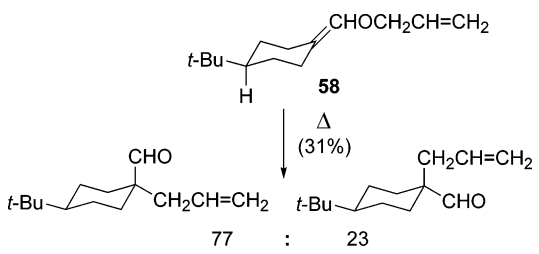
Although diastereoisomerism is often associated with chiral molecules, chirality is not an essential previous condition. Both π faces of a double bond can be considered diastereotopic in cyclic systems, as a consequence of the conformational preferences, especially in six-membered rings. The Claisen rearrangement of allyl vinyl ethers bearing an exocyclic double bond on a cyclohexane ring provides an example of the axial−equatorial diastereoselectivity of a process evolving through a six-membered transition state, as depicted in Scheme 103.

Scheme 103



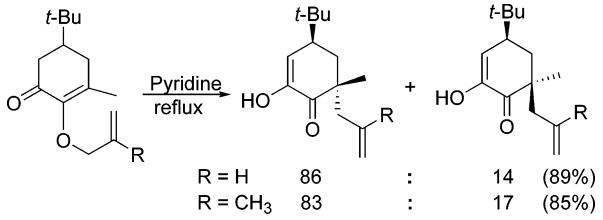
In this sense, the thermal rearrangement of **58** produces a mixture of aldehydes in a 77:23 axial−equatorial ratio (Scheme 104),[128] with a clear predominance of the sterically favored equatorial attack.

Scheme 104



In contrast, the diastereocontrol observed in the diosphenol−Claisen reaction derives from the preferred formation of an axial bond in the rearrangement of allyl vinyl ethers contained in conformationally rigid cyclohexane systems (Scheme 105).[129]

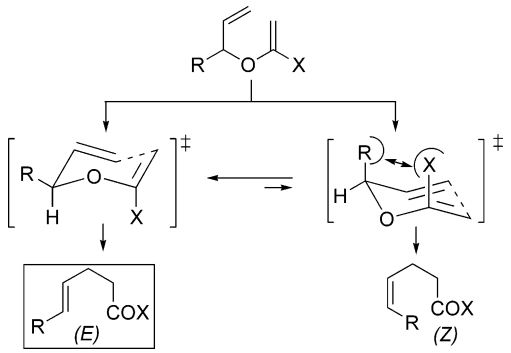
Scheme 105



6.3.2. E/Z Selectivity

The *E*/*Z* stereoselectivity of the Claisen rearrangement is very high, especially when the substituent X at the allyl vinyl ether is not a hydrogen atom. Thus, the newly created double bond usually exhibits the *E* configuration, which can be rationalized from the two plausible conformations for the transition state. The conformation exhibiting the R group in an equatorial arrangement gives rise to the *E* alkene, whereas the lower energy conformation, with R in an axial arrangement, would lead to the *Z* alkene (Scheme 106). In fact, the *Z* selectivity is difficult to be attained under the reported classical conditions.

Scheme 106



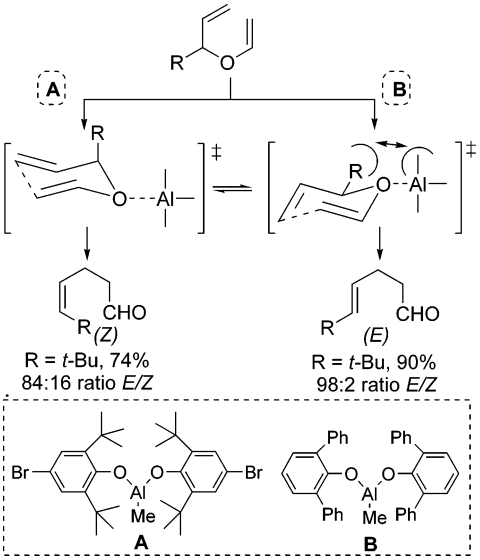
In this context, a variety of Claisen rearrangements have been developed in the presence of bulky aluminum Lewis acids, capable of modifying the transition-state structure and, therefore, generating the *Z* product (Scheme 107).[130] The *E* selectivity was even improved in comparison with that obtained under thermal conditions by incorporation of steric modifications to the ligands of the aluminum catalyst.

Similarly, a marked *E* selectivity was reported for the aromatic Claisen rearrangement of allyl aryl ethers where the allyl fragment was part of an acyclic system.[127] The 6:1 mixture of *E* and *Z* alkenes obtained in the presence of $Eu(fod)_3$ resulted from a chair or boat transition state, respectively (Scheme 108).

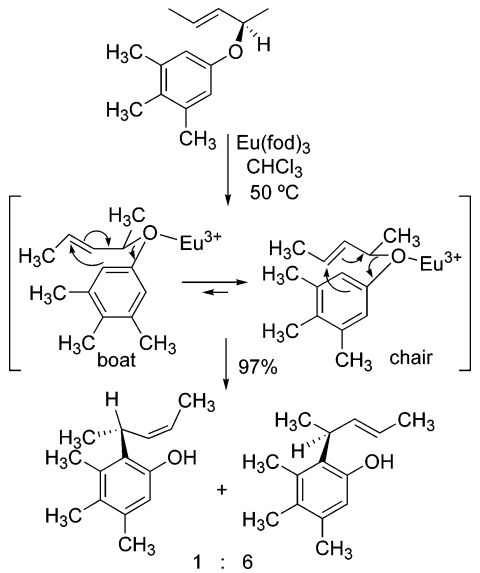
6.4. Diastereoselective Synthesis of Chiral Products

The presence of a chiral element at the vinyl or allyl fragment of the starting material may generate more than one diastereomer in the process. Next, the

Scheme 107



Scheme 108



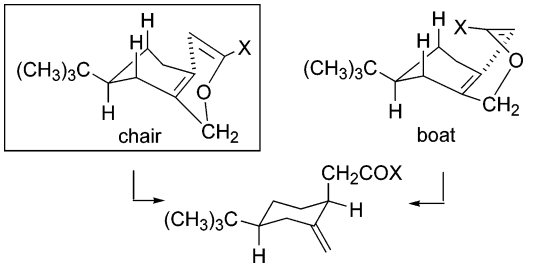
influence of the incorporation of a chiral auxiliary at different positions of the substrate in the stereochemical course of the Claisen rearrangement from both a steric and a stereoelectronic point of view will be considered.

6.4.1. Chiral Auxiliary at the Allyl Fragment

Most of the reported examples of ethers derived from allyl alcohols bearing a chiral element as a strategy to achieve a diastereocontrol of the rearrangement are based on the use of structures derived from cycloalkenyl skeletons. The conformational preferences of these cycles dictate the stereochemical course of the reaction, mainly in the presence of an additional stereocenter in their structures. For example, in the Claisen rearrangement of 5-*tert*-butyl-1-(hydroxymethyl)-1-cyclohexene derivatives, the favored axial approach must take place preferentially through a chairlike transition state, wherein the steric interactions with the ring are minimized (Scheme 109).[131]

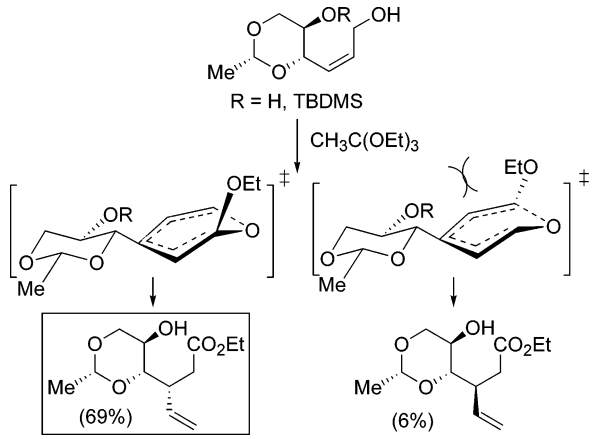
In a similar way, the favored conformation of γ-(1,3-dioxan-4-yl)allyl alcohols accounts for the high

Scheme 109



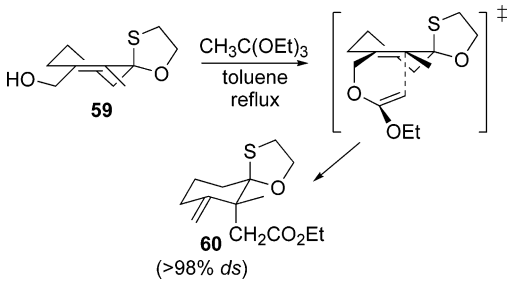
diastereoselectivity of the Johnson rearrangement from the chairlike transition state where the nonbonding interactions between the ketene acetal and the substituent at C-5 will be minimized (Scheme 110).[132]

Scheme 110



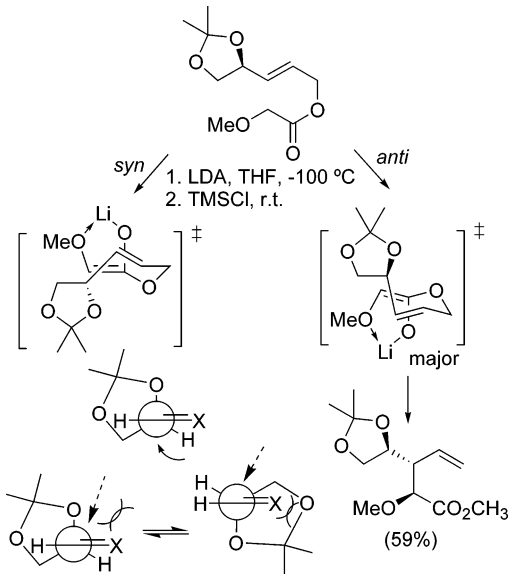
Stereoelectronic effects can be important in Johnson rearrangements with heteroatom-containing auxiliaries. The transformation of **59** into **60** with the formation of the axial C−C bond antiperiplanar to the electron-donor C−S bond in an axial arrangement is consistent with the Cieplak mode of diastereoselection, which assumes an electronic donation to the incipient σ* orbital from a σ bond on a neighbor carbon (Scheme 111).[133]

Scheme 111



In the case of acyclic substrates, the diastereoselectivity control is not so easily foreseeable. However, significant diastereomeric excesses were attained in the "chelation controlled" Ireland−Claisen rearrangement of compounds bearing an enantiomerically pure acetonide moiety as a chiral auxiliary on the allyl fragment.[134] The relative stereochemistry of the neighbor alkoxy group and the new C−C bond at the major rearranged product was anti (*erythro*) in all the considered cases, which led to the development

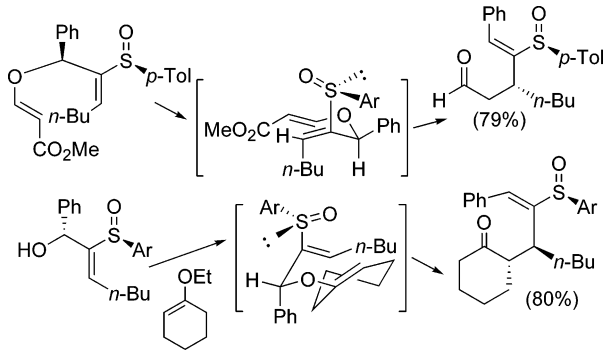
Scheme 112



of a method for the synthesis of α-hydroxy and α-alkoxy acids (Scheme 112).

The first example of a sulfinyl group directly bonded to the allyl fragment of an allyl vinyl ether as a chiral auxiliary of the Claisen rearrangement has been recently reported.[135] The reaction proceeded in a highly diastereoselective way, allowing the regeneration of a vinyl sulfoxide moiety (Scheme 113).

Scheme 113

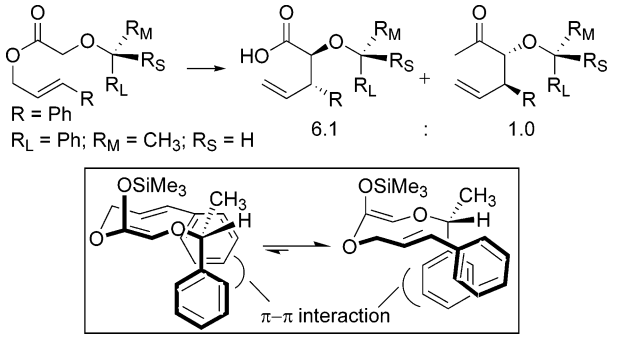


The stereochemical outcome was rationalized by a mechanism through the most favored chairlike transition state with an *s-cis* conformation around the C−S bond. The sulfinyl stereocenter controls the approach of the vinyl fragment to the less hindered face of the allyl double bond.

6.4.2. Chiral Auxiliary at the Vinyl Fragment

In comparison with the reported examples of substrates bearing a chiral auxiliary in the allyl fragment, the number of diastereoselective Claisen rearrangements from ethers supporting a chiral auxiliary in the vinyl moiety is considerably larger. High diastereoselection levels were observed in the Ireland−Claisen rearrangement of acyclic α-alkoxy esters. Thus, the stereochemical pathway of the [3,3] rearrangement of allyl glycolates could be controlled by a chiral substituent bonded to the glycolate hydroxy group (Scheme 113).[136] An essential requirement to achieve a high asymmetric induction in the rearrangement of this type of systems is the possibility of adopting a favored conformation in the transition state where the chiral auxiliary is able to direct the facial selectivity of the addition to the enolate π system. In this sense, the best results regarding diastereoselectivity were achieved with cinnamyl glycolates, where a favored interaction by π-stacking between the vinylic aryl group and the aromatic group on the auxiliary was proposed as being responsible for a shift of the conformational equilibrium, as depicted in Scheme 114. The enhanced auxiliary-

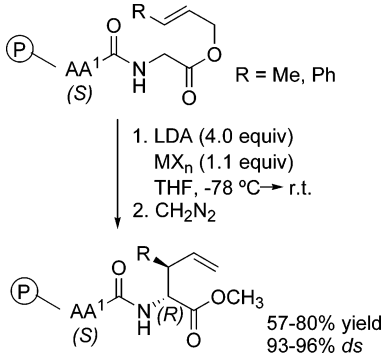
Scheme 114



directed selectivity exhibited by cinnamyl glycolates as compared with that exhibited by other substituted glycolates, supports such a hypothesis.

From the strategy based upon the chelation control of the Ireland−Claisen rearrangement, the chiral information of a peptidic chain was used as a stereodifferentiating element in the diastereoselective synthesis of amino esters.[137] A multiple coordination of the deprotonated peptidic chain with the chelating metal—the best results were achieved in the presence of $Ti(O\textit{i}\text{-}Pr)_4$ and $NiCl_2$—generated metallic complexes where one of the enolate faces was hindered (Scheme 115).

Scheme 115



As observed, when the peptidic chain contains an *S* amino acid, the Claisen rearrangement will afford an *R* amino acid. In the presence of $NiCl_2$, this stereochemical result was understood in terms of the formation of a square planar chelated complex (Figure 16) where one of the enolate faces was hindered by the side chain of the *S* amino acid. Therefore, the rearrangement took place through the sterically less hindered face of the enolate to produce the *R* amino acid.

As already observed, anions derived from allyl vinyl ethers may undergo anionic Claisen rearrangement

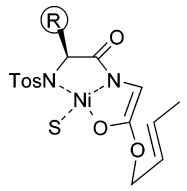
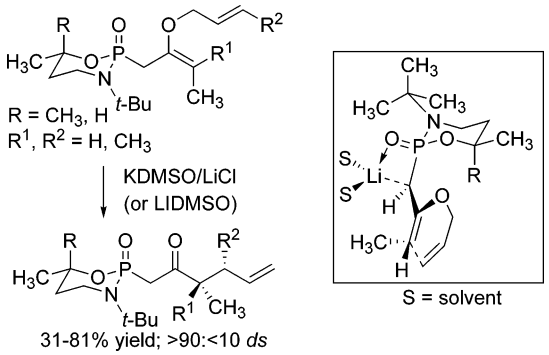


Figure 16.

under mild conditions. The incorporation of carbanion-stabilizing groups able to act as chiral auxiliaries to the substrate skeleton enhanced the synthetic potential interest of this reaction in its diastereoselective version. The diastereofacial stereoselectivity achieved with 1,3,2-oxazaphosphorinanes is outstanding.[138] A series of cyclic phosphoramidates rearranged anionically under mild conditions in a process which took place with a high asymmetric induction in the presence of Li^+ salts (Scheme 116).[138a] Some studies

Scheme 116

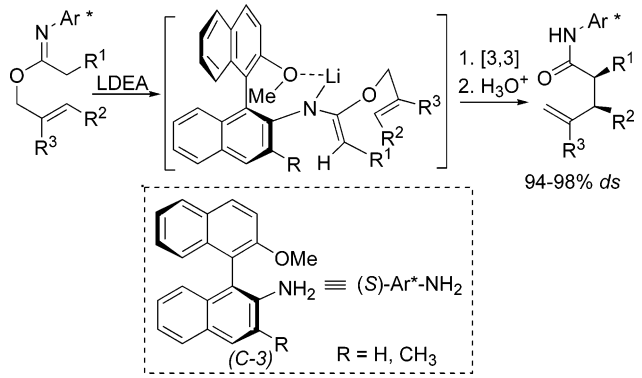


performed on different substrates showed not only the crucial role of Li^+ in the diastereocontrol, but also the importance of the steric volume of the nitrogen substituent, which led to the structure proposed in Scheme 116 for the rearranging anion.[138b]

Several studies have also been reported on the use of a chiral auxiliary bonded to the nitrogen atom at imidates undergoing Eschenmoser rearrangements. Excellent diastereoselectivities were attained starting from binaphthylamine-derived allyl imidates exhibiting axial chirality. The azaenolates obtained by deprotonation of these compounds with lithium diethylamide rearranged to γ,δ-unsaturated amides with a high 2,3-anti selectivity (98:2 *anti*/*syn*) and an excellent asymmetric induction (94% de for the anti isomer).[139a] To explain the stereochemical outcome, a $(Z)_{CC}/(E)_{CN}$ configuration was proposed for the intermediate azaenolate as well as a chelated model incorporating the lithium and methoxy group (Scheme 117). The lower face of the azaenolate will be sterically hindered by the hydrogen atom of the naphthyl group at the *ortho* position relative to the nitrogen, and therefore, the new C−C bond will be formed preferentially along the *re* face of the azaenolate. Supporting this hypothesis, when the hydrogen at C-3 of the auxiliary was substituted by a bulkier alkyl group, the diastereoselectivity of the rearrangement increased.[139b] Thus, diastereoselectivities greater than 98% were achieved with a methyl group at C-3 of the chiral auxiliary.

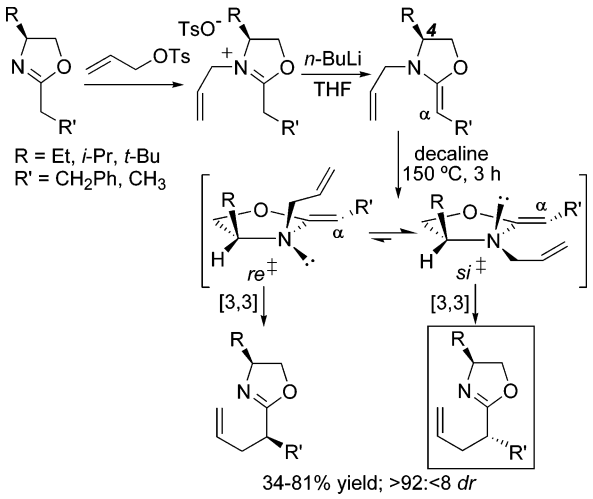
The effect of a chiral auxiliary covalently bound to the nitrogen of *N*-allylketene *N*,*O*-acetals in the aza−

Scheme 117



Claisen rearrangement was analyzed.[140] To maximize the topological effect of the chiral auxiliary, the influence of incorporating such an auxiliary, the nitrogen atom, and the vinyl C-1 carbon into a five-membered ring was considered.[140a] The size of the substituent at C-4 of *N*-allylketene *N*,*O*-acetal was crucial for the rearrangement diastereoselectivity, as depicted in Scheme 118. Out of the two diastereo-

Scheme 118

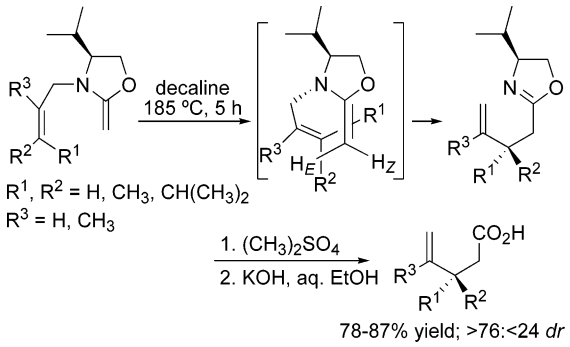


meric transition states, the Cα−*si* is more stable than the Cα−*re* transition state, which is sterically more congested. A fast inversion at the nitrogen ($re^{\ddagger} \leftrightarrows si^{\ddagger}$) prior to the rearrangement rate-determining step accounts for the Cα−*si* selectivity. As would be predicted from such an analysis, the diastereoselectivity increased as the steric volume of the substituent at C-4 was larger.[140b,d]

This methodology afforded the preparation of enantiomerically enriched 3-substituted 4-pentenoic acids with the concomitant recovery of the chiral auxiliary (Scheme 119).[140c]

More recently, 1,4-chirality transfer has been reported in zwitterionic aza−Claisen rearrangements starting from *trans*-4-silyloxy-2-vinylpyrrolidines and carboxylic acid fluorides to generate nine-membered lactams in high yields.[141] In this reaction, the formation of an *E* double bond in medium-sized rings afforded compounds bearing a chiral plane (Scheme 120). The chirality of the stereocenters of the substrate accounted for the stereocontrol of the process. Initially the attack of the activated acid fluoride to

Scheme 119



the 2-vinylpyrrolidine took place anti to the bulky TBSO substituent and gave the zwitterion exhibiting 1,2-syn configuration with a *Z* enolate (the usual geometry for amide enolates). The rearrangement took place through a boatlike transition state to produce the 3,8-*trans*-lactam; the corresponding chairlike transition state would exhibit strong repulsive interactions (1,3 strain). The combination of the defined enolate geometry and a defined transition-state geometry accounted for the successful 1,4-chirality transfer of the rearrangement.

In the last few months the first diastereoselective ynamine−Claisen rearrangement from chiral ynamides has been reported.[142] Reactions of ynamides containing the Sibi auxiliary[143] with an allyl alcohol took place in good yields in the presence of 0.1−0.2 equiv of *p*-nitrobenzenesulfonic acid (PNBSA) to give rise to the corresponding rearrangement products with high diastereoselectivities (Scheme 121). Initially, ynamide protonation led to the corresponding ketene imminium salt; the subsequent addition of the allyl alcohol on the same side as the hydrogen atom afforded the *E* ketene aminal. The diastereoselectivity of the Claisen rearrangement is understood from a chairlike transition state exhibiting the conformation where the polar interactions between the urethane C═O and vinyl C−O bonds are minimized and, therefore, is able to differentiate the π faces of the ketene aminal.

In recent years the literature has shown an increasing interest in the chiral induction in the thio−Claisen rearrangement, several examples having been described where the chirality resides in the amino moiety of the starting thioamide. A long-distance steric effect was reported as being responsible for the stereochemical results of the thio−Claisen rearrangement of bicyclic oxazolidine-fused thiolactams.[144] The substitution at the oxazolidine ring of the bicyclic lactam played an essential role in the *exo-endo* diastereoselectivity in the course of the sigmatropic rearrangement, even when these substituents were far from the reaction center. For example, starting from the norephedrine-derived lactam **61**, with cis substitution, thio−Claisen rearrangement proceeded with a high diastereoselectivity as a consequence of a marked steric effect (Scheme 122).[144b] Perhaps it is one of the few reported examples where the rigid structure of the bicyclic thiolactam hinders the rotation around the C−N bond of the intermediate *N,S*-ketene acetal to afford a high diastereofacial selectivity.

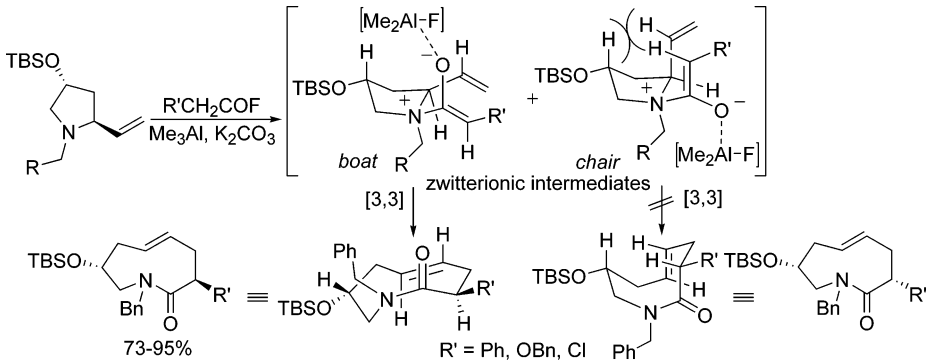
In the case of acyclic *N,S*-ketene acetals, the rearrangement of a system bearing a C_2-symmetric amide as the chiral auxiliary proceeded with exceptionally high diastereoselectivity.[145] This reaction, which took place from the *Z*-thioenolate, proceeded through the chairlike transition state that would be favored on steric grounds (Scheme 123).

A Claisen rearrangement of *S,S*-ketene acetals was also reported to proceed with a high 1,2-asymmetric induction controlled by a neighbor sulfinyl group as the chiral auxiliary (Scheme 124).[146]

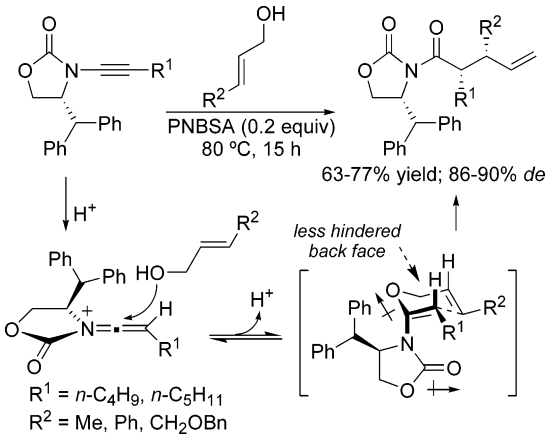
This reaction is generally thought to proceed under orbital control with sterics playing a less significant role. From a pseudo-cyclic chairlike transition state, the electronic transfer will be favored when the most electronic donating sulfinyl group, the lone electron pair, is in an anti arrangement with respect to the direction of the electrophilic attack by the allyl chain. The two possible transition states meeting such a requirement, depicted in Scheme 123, differed in the orientation of the oxygen atom and the alkyl group at sulfur, so that the species having the bulky isopropyl substituent oriented on the inside was sterically unfavored as compared with the species having the isopropyl oriented on the outside. A similar stereochemical model has recently been used to account for the excellent diastereoselectivities of the rearrangements of *N,S*-ketene acetals bearing a cyclohexylsulfinyl group as the chiral auxiliary (Scheme 125).[147]

The thio−Claisen rearrangement has also been reported from atropoisomeric thioamides where the substrate structure itself determined the observed diastereoselectivity.[148] This methodology allows the stereocontrolled allylation of amide enolates. The *tert*-

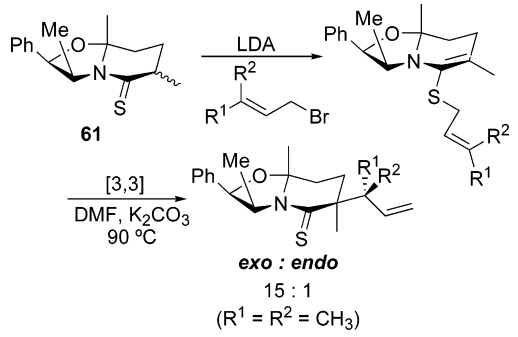
Scheme 120



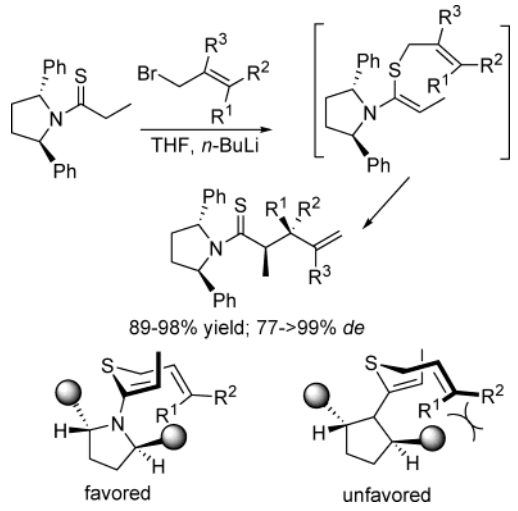
Scheme 121



Scheme 122



Scheme 123

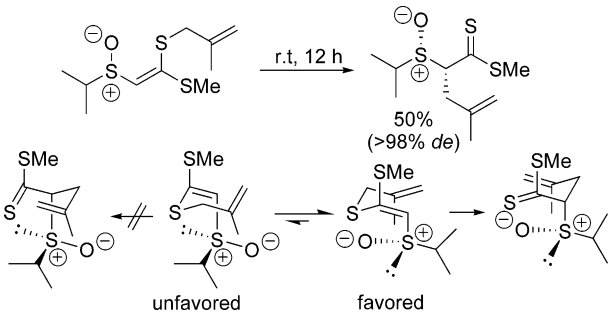


butyl substituent at the *ortho* position of the aromatic ring hinders the approach of the *S*-allyl fragment to the *si* face, which rationalizes the high diastereoselectivity on the *re* face (Scheme 126).

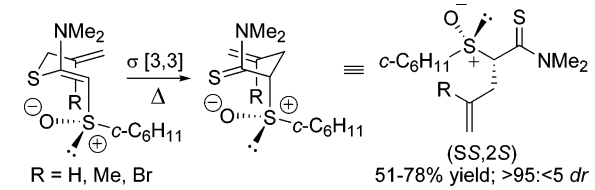
6.5. Enantioselective Claisen Rearrangement

The reported attempts to achieve remarkable enantiomeric excesses in the Claisen rearrangement use chiral enantiopure catalysts, cocatalysts, or solvents capable of creating an asymmetric environment in the transition state. Most of the papers in this field are devoted to the use of chiral Lewis acids as the reaction catalysts.

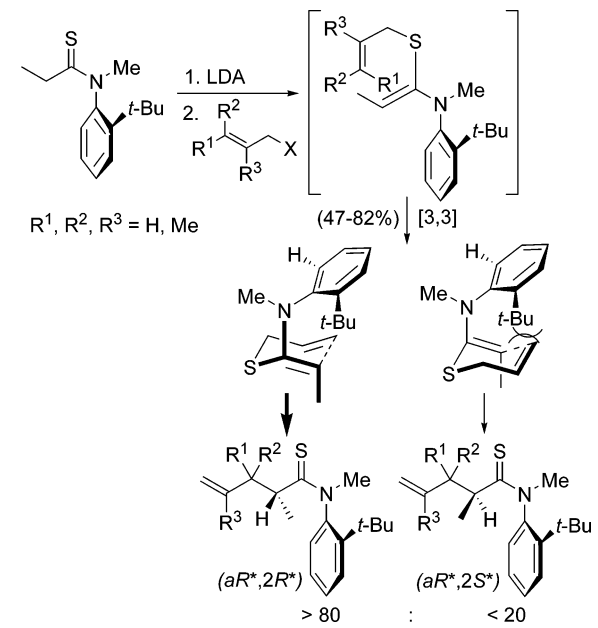
Scheme 124



Scheme 125



Scheme 126



6.5.1. Chiral Catalysts

As already discussed, a number of papers describe the accelerating rate effect for the Claisen rearrangement in the presence of Lewis-acid catalysts. These results determined the study of the influence of chiral Lewis acids in the enantioselectivity of the reaction, a series of studies having been developed in order to discover ligands capable of accelerating the process to achieve good chirality transfer.

In 1990 Yamamoto described the first example of an enantioselective Claisen rearrangement catalyzed by a chiral Lewis acid.[149] It is a modified chiral aluminum−binaphthol (**62**) which discriminates the two possible chairlike transition states of the Claisen rearrangement of trimethylsilyl derivatives **63** to generate the corresponding acylsilanes with high optical purities (80−90% ee) (Scheme 127).

Similarly, C_3-symmetric aluminum complexes, such as those depicted in Figure 17, have been developed. These complexes act as chiral Lewis receptors ca-

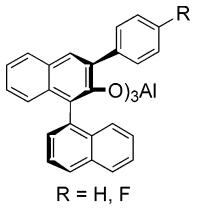
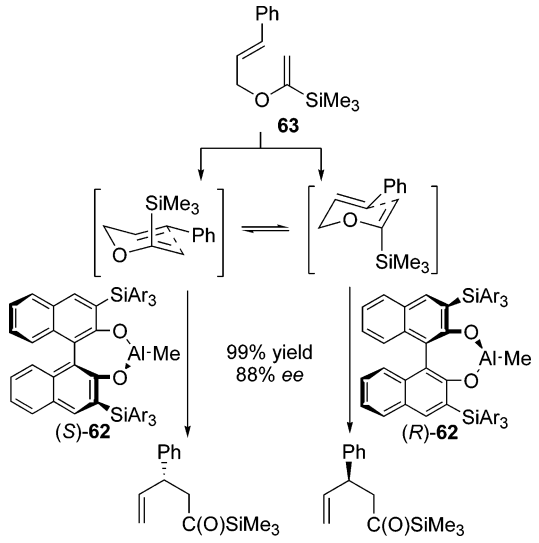


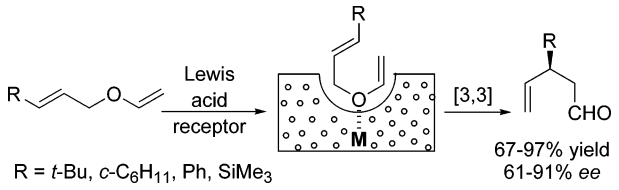
Figure 17.

Scheme 127



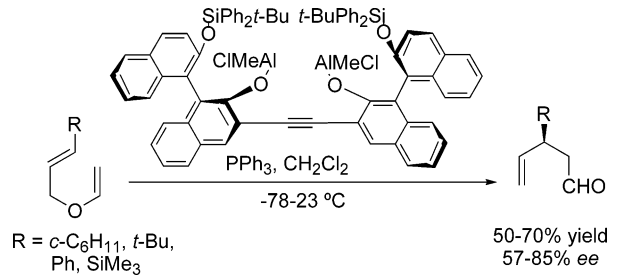
pable of facilitating, through a molecular recognition process, the formation of a transition state for a Claisen rearrangement of an allyl vinyl ether, as depicted in the Scheme 128 for a general case.[150]

Scheme 128



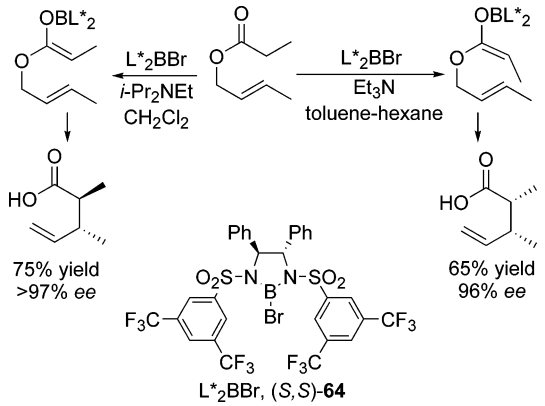
Moderate to good enantioselectivities were also recently reported for the Claisen rearrangement of allyl vinyl ethers activated by chiral bis(organoaluminum) Lewis acids synthesized from (*S*)-binaphthol, although the chemical yields of these reactions turned out to be moderate (Scheme 129).[151]

Scheme 129



In 1991 Corey reported the first enantioselective Ireland−Claisen rearrangement of achiral allylic esters in the presence of catalytic amounts of a chiral C_2-symmetric bisulfonamide-derived boron reagent

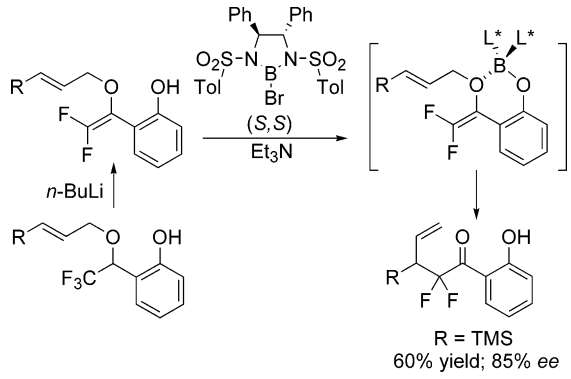
Scheme 130



(**64**).[152] These conditions generated a boron enolate exhibiting a chiral environment (Scheme 130), the boron enolate geometry being controlled by the tertiary amine and the solvent. Thus, the use of triethylamine in toluene−hexane in the presence of the boron reagent **64** led selectively to the *E* enolate from (*E*)-crotyl propionate. The diastereoselective rearrangement of this enolate afforded the anti isomer with excellent enantioselectivity (96% ee). In its turn, the *Z* enolate was selectively formed with diisopropylamine in dichloromethane and rearranged into the syn isomer (>97% ee).

In the presence of a closely related boron reagent, the Claisen rearrangement of allyl difluorovinyl ethers bearing a phenolic ring produced the corresponding β-substituted α,α-difluoroketones with good enantioselectivities (Scheme 131).[153] A covalent bond

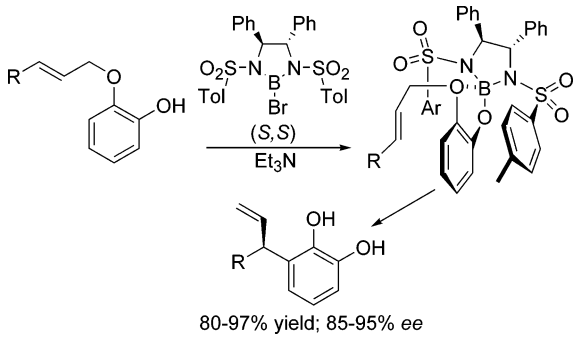
Scheme 131



formed between the chiral boron reagent and the hydroxy group, and further coordination of the ether oxygen to the boron atom accounted for the chiral environment responsible for the evolution of the process with remarkable levels of stereoselectivity.

The same chiral catalyst allowed the development of the first enantioselective aromatic Claisen rearrangement of an achiral substrate with complete regioselectivity (*ortho* selectivity).[154] The observed asymmetric induction was interpreted in terms of a five-membered cyclic intermediate also formed from a covalent bond between the boron atom and the phenolic hydroxy group, followed by coordination of the ether oxygen to the boron atom (Scheme 132). In this cyclic intermediate one of the arenesulfonyl groups will shield the *re* face of the benzene ring, so

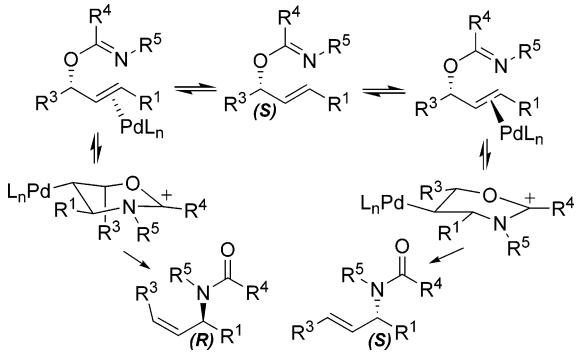
Scheme 132



that the allyl fragment will approach the *si* face, resulting in an enantiotopic facial selectivity of the allyl double bond.

As mentioned previously, $PdCl_2$ complexes have proved to be optimal catalysts for the [3,3] rearrangement of allyl imidates. The development of chiral Pd(II) catalysts of the rearrangement of these substrates offers new opportunities for the synthesis of enantiomerically enriched nitrogen compounds (Scheme 133).

Scheme 133



Special mention should be made of the use of bidentate cationic Pd(II) catalysts. Rearrangements in the presence of catalysts derived from 2-(isoindolinylmethyl)-*N*-methylpyrrolidine (**65**)[155] and 2-(2-diphenylphosphine)phenyl-4-alkyloxazoline (**66**),[156] both of them in the presence of silver salts, as well as palladacyclic ferrocenylamines (**67**) and imines (**68**)[157] have been reported. However, the enantiomeric excesses achieved with these catalysts, shown in Figure 18, were lower than 80% and the chemical yields were quite low.

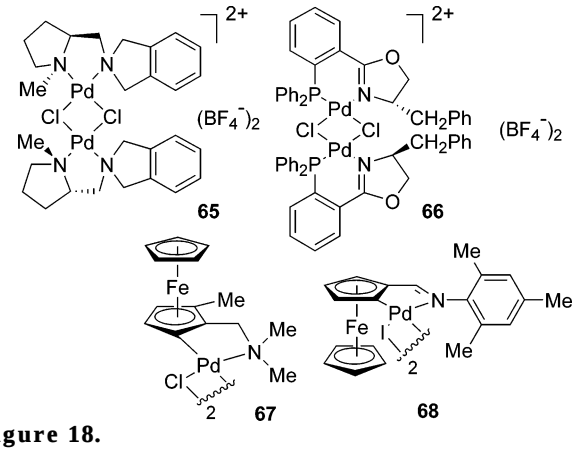
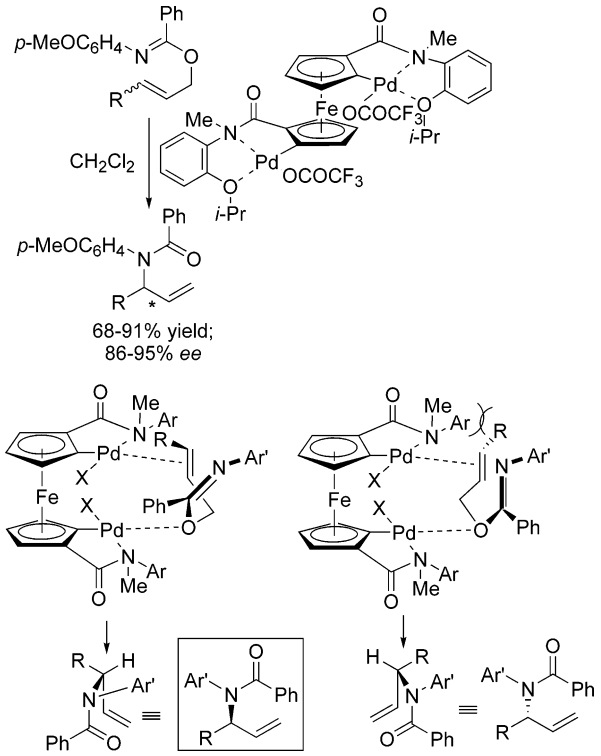


Figure 18.

Nevertheless, a member of the family of chiral ferrocene-derived bis[palladacycles] has recently proved to be an excellent catalyst of the asymmetric rearrangement of allyl imidates,[158] presumably due to a double coordination of both Pd atoms in the catalyst to the alkene moiety and the oxygen atom in the imidate, respectively, as depicted in Scheme 134. This would lead to two possible transition states,

Scheme 134



one of them sterically more favored to yield the *R* rearranged product.

Chiral Pd(II) complexes with tridentate ligands (Figure 19) were also studied as catalysts of the

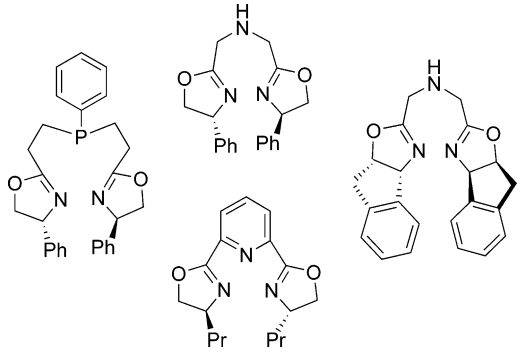
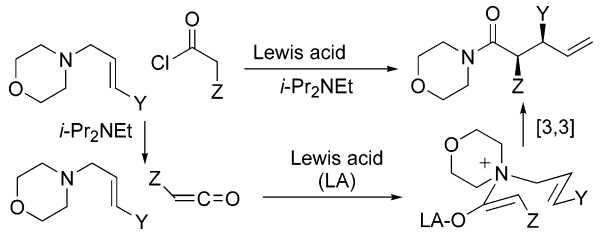


Figure 19. Reprinted with permission from ref 159. Copyright 1999 Elsevier Science.

enantioselective aza−Claisen rearrangement, although neither yields nor enantioselectivities were substantially improved.[159]

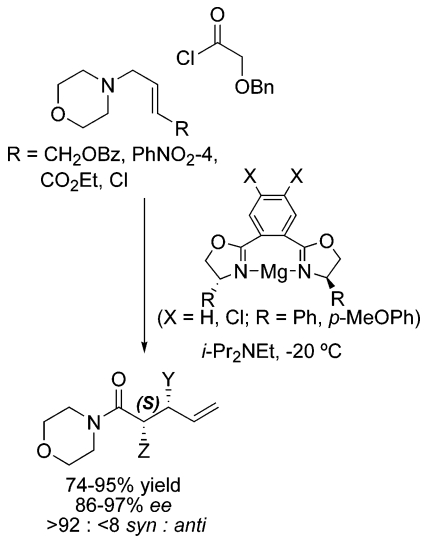
The Lewis-acid complex geometry has been shown to play a significant role in the design of the enantioselective version of the acyl−Claisen rearrangement (Scheme 135).

Scheme 135



For example, Lewis-acid complexes derived from MgI_2 and bis(oxazolinyl)aryl ligands generated an efficient asymmetric environment for the acyl−Claisen rearrangement of compounds capable of chelation. In fact, the addition−rearrangement sequence of benzyloxyacetyl chloride and *N*-allylmorpholine in the presence of this kind of chiral Lewis acids proceeded with excellent stereoselectivity (Scheme 136)[160] as a consequence of a bidentate

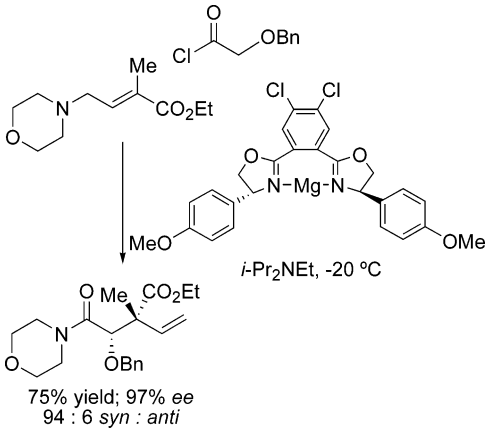
Scheme 136



coordination of the chiral complex to the α-heterosubstituted allyl vinylammonium salts.

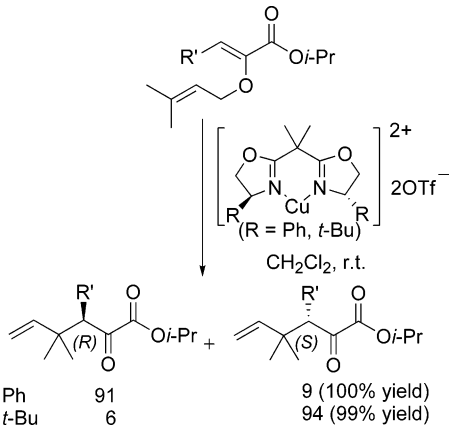
This protocol has been used to generate quaternary carbons of acyclic structures with high enantiocontrol (Scheme 137).

Scheme 137



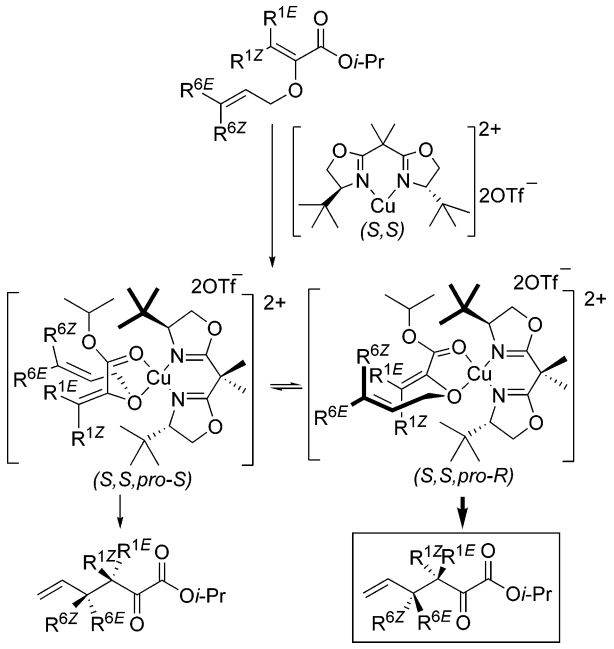
Bis(oxazoline)copper(II) complexes were reported as chiral catalysts of the enantioselective Claisen rearrangement.[161] The reactions of 6,6-dimethyl-substituted allyl vinyl ethers proceeded with high enantioselectivities (Scheme 138).

Scheme 138



Coordination of the allyl vinyl ether with the bis(oxazoline)copper complex exhibiting a square planar geometry around the Cu(II) cation was proposed to account for the enantioselectivity of the rearrangement (Scheme 139). If a chairlike transition state is

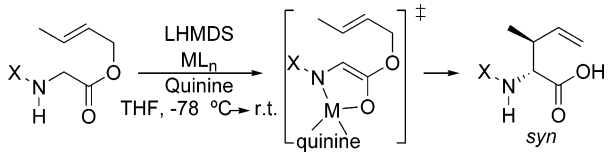
Scheme 139



assumed for the Claisen rearrangement, the allyl fragment must approach the vinyl moiety opposite the *tert*-butyl substituent at the bisoxazoline. In this model the catalyst differentiated the enantiomeric chair conformations by distinguishing between the enantiotopic electron pair [(*pro-R*) and (*pro-S*)] at the ether oxygen atom. From the results shown in Scheme 138, it can be inferred that the phenyl-substituted catalyst preferentially coordinated with the *pro-R* pair, whereas the catalyst bearing a *tert*-butyl group preferred to coordinate with the *pro-S* pair. From this stereochemical relation and the configuration of the double bond of the allyl vinyl ether, the absolute configuration of the major isomer of the rearrangement could be explained.

Within the past few years the enantioselectivity induced in the Claisen rearrangement by metallic complexes bearing different chiral ligands has been widely studied. The rearrangement of enolates derived from chelated allylic esters proceed with high syn selectivity, as a consequence of the fixed enolate geometry derived from the chelate formation (see above). When the reaction was performed in the presence of chiral bidentate ligands, such as quinine, chiral γ,δ-unsaturated amino acids were obtained in good yields with high stereocontrol (Scheme 140).[162]

Scheme 140



The amino alcohols whose behavior as chiral ligands was studied are depicted in Figure 20. As the steric volume of the substituents at the amino alcohol increased, the yield and enantioselectivity became higher. The best results were attained with cinchona alcohols as ligands, and both enantiomers of γ,δ-unsaturated amino acids could be formed (L-amino acids were prepared with quinidine, whereas D-amino acids were synthesized with quinine).

The stereoselectivity of these reactions, where the best enantiomeric excesses were achieved with aluminum or magnesium alkoxides (>83% ee), was explained by a bidentate chelation of the amino alcohols. In fact, methylation of the hydroxy group at quinine furnished, with good diastereoselectivity, a racemic mixture of the rearranged product (Figure 20).[162c] The chiral ligand stabilized the lithium enolate, which was assumed to undergo rearrangement. Formation of a bimetallic complex by coordination of the bidentate ligand (quinine or quinidine) to the lithium enolate was proposed (Figure 21). Incorporation of a second metallic ion M (Li^+, Al^{3+}, Mg^{2+}) would stabilize the complex by the generation of a rigid structure where one of the enolate faces would be hindered by the bicyclic quinine substructure. This model accounted for the high enantioselectivities obtained with this catalytic system.

6.5.2. Chiral Solvents

The influence of a chiral solvent on the enantioselectivity of the Claisen rearrangement could be studied. Nevertheless, the results in this field are practically nonexistent. There is an example of Claisen rearrangement were the anisotropic arrangement of the solutes in liquid crystalline mesophases directed the evolution of the reaction in a way which cannot be usually achieved in an isotropic environment.[163] In a cholesteric mesophase there is a helicoidal macroscopic structure formed by the chiral organization of "nematic" layers with a uniaxial molecular arrangement within the layers. This mesophase can be considered as a suprachiral environment where linear solute molecules can organize readily within nematic layers. Thus, in a cholesteric crystalline solvent, γ-methylallyl *p*-tolyl ether underwent a stereospecific *ortho*-Claisen rearrangement to give rise to enantiomerically enriched 2-(α-methylallyl)-4-methylphenol (Scheme 141). The optical purity of the product was demonstrated by its circular dichroism values. However, no enantiomeric excess was determined.

Optical polarization studies demonstrated that the molecules of the allyl aryl ether aligned in the "nematic" layers of the cholesteric mesophase with the long axis parallel to the long axis of the molecules of the liquid crystal. The turn of the allyl moiety needed for the Claisen rearrangement to take place will be more favored from one of the two possible directions according to the helicoidal chirality of the cholesteric mesophase. In the absence of an "asymmetric catalyst" there is no difference between the energies of the transition states affording either enantiomeric phenols ($\Delta E_a^R = \Delta E_a^S$), which will furnish the racemic product. However, the use of a cholesteric liquid crystal acting as an "asymmetric catalyst" as the solvent causes a diastereomeric relationship between the corresponding transition states ($\Delta E_a^R \neq \Delta E_a^S$), which will lead to an enantiomerically enriched product.

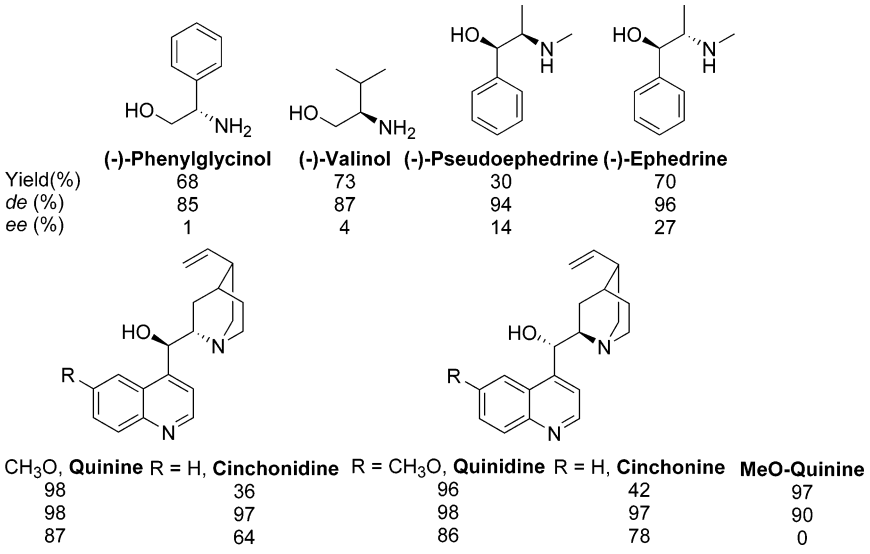


Figure 20. Reprinted with permission from ref 162c. Copyright 2002 Wiley-VCH.

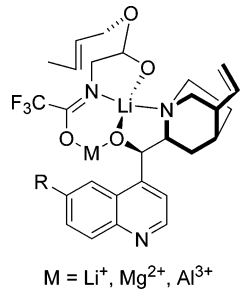
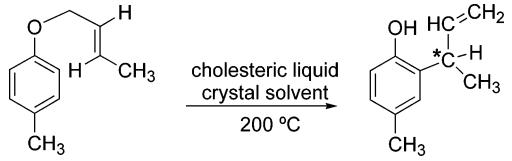


Figure 21. Reprinted with permission from ref 162c. Copyright 2002 Wiley-VCH.

Scheme 141



7. Application of Claisen Rearrangement Products to the Synthesis of Organic Building Blocks

Increasing interest in the Claisen rearrangement over the last few decades derives to a large extent from the functional versatility of the resulting products. These compounds bear two functional groups (a carbonyl group or a derivative and a double bond) as well as potentially two chiral centers. Therefore, they are compounds able to undergo regio- and stereoselectively controlled transformations to furnish synthetically useful structures. Some of the most important applications will be disclosed according to the nature of the products.

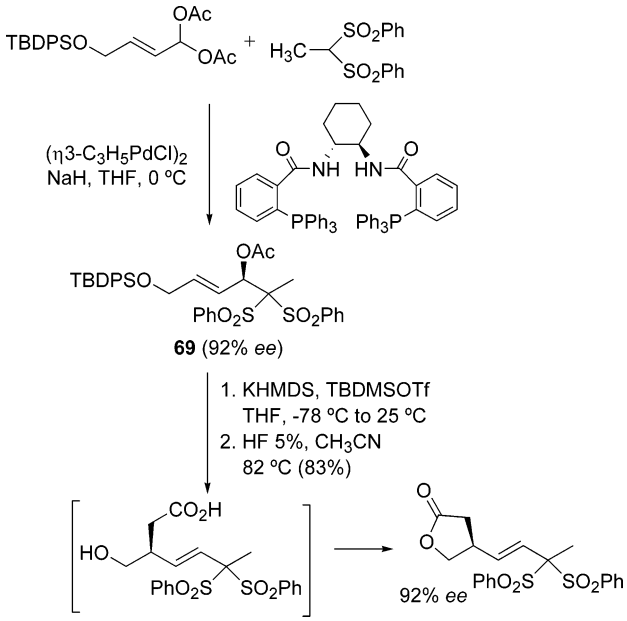
7.1. Heterocyclic Compounds

Claisen rearrangement products have been interestingly transformed into lactones. When the TBDPS-substituted compound **69**, formed by stereoselective alkylation of bis(phenylsulfonyl)ethane, was treated with KHMDS and TBDMSOTf in THF, a ketene silylacetal was obtained. This ketene silylacetal underwent Ireland−Claisen rearrangement and subsequent desilylation—presumably through the corresponding hydroxy acid—to provide the corresponding γ-lactone in good yield and in a completely stereoselective fashion (Scheme 142).[164]

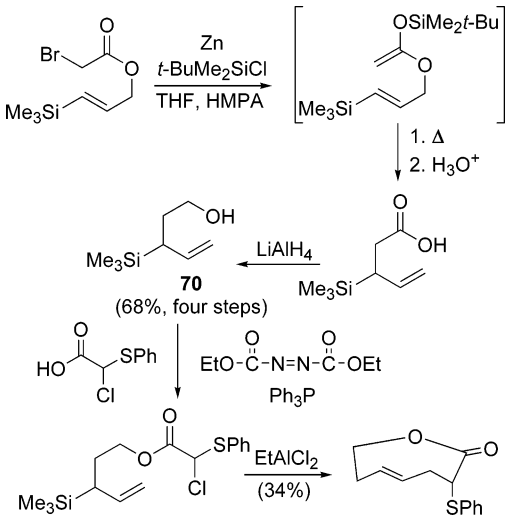
A procedure for the synthesis of medium-sized lactones was developed from 3-trimethylsilyl-4-penten-1-ol (**70**), prepared by a Reformatsky−Claisen rearrangement and reduction of the resulting carboxylic acid. The immediate precursor of the lactones was obtained from **70** under Mitsunobu conditions. Intramolecular allylation using $EtAlCl_2$ afforded the corresponding macrocycle (Scheme 143).[165]

Claisen rearrangement of alkenyl-substituted ketene acetals—prepared in situ by selenoxide elimination from phenylselenoacetaldehyde-derived acetals of enantiomerically pure 1,3-diols—produced unsaturated eight-membered lactones. This reaction, proceeding through a chairlike transition state, afforded complete stereocontrol at C-4, C-5, and C-7 (Scheme 144).[166] These lactones could be functionalized at

Scheme 142



Scheme 143



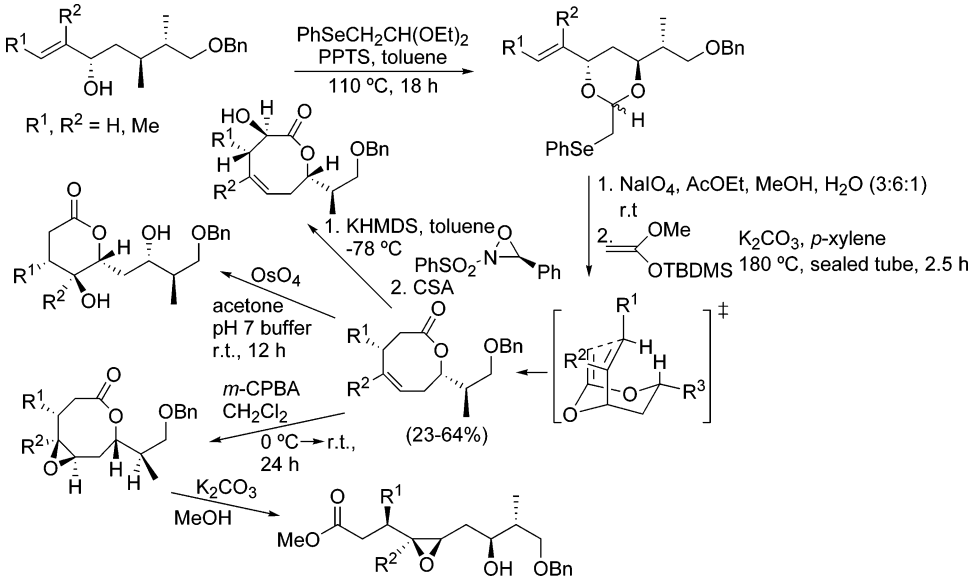
different carbons of the ring to generate synthetically interesting, enantiomerically pure compounds.[167]

Recently, a similar methodology was reported for the preparation of nine-membered lactones[168] from cyclic carbonates derived from 1,4-diols by reaction with triphosgene and pyridine. The corresponding lactones were obtained in good yields by a tandem sequence consisting of methylation with dimethyltitanocene followed by in situ Claisen rearrangement of the intermediate ketene acetals (Scheme 145).

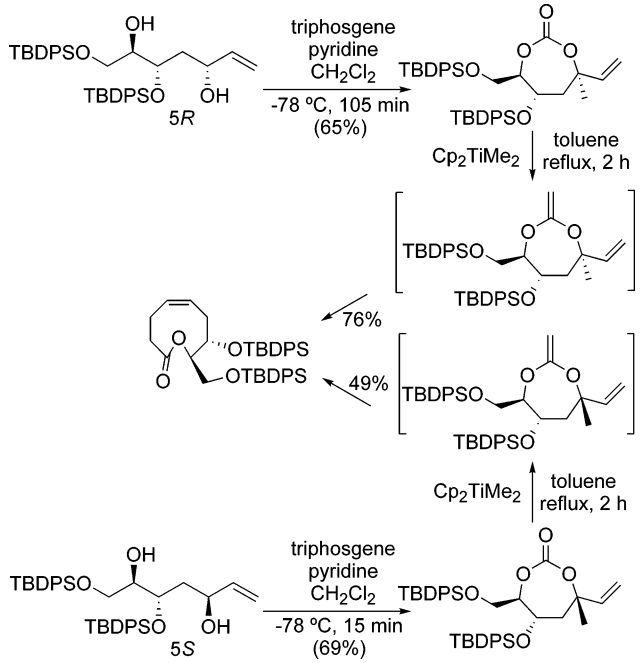
A tandem Claisen−Conia rearrangement was developed for the synthesis of dispirolactones by heating 5-spirotetronates in toluene in a sealed tube (Scheme 146).[169] The first step in the synthesis consisted of a Claisen rearrangement to produce the corresponding 3-allyltetronic acids, which suffered a fast Conia oxa−ene reaction leading to the 3-spirocyclopropyl ring closing, whose stereoselectivity could be understood in terms of the orbital interactions between the enol HOMO and the alkene LUMO.

Trifluoromethyl-substituted butenolides and their thioanalogues were prepared by a tandem nucleo-

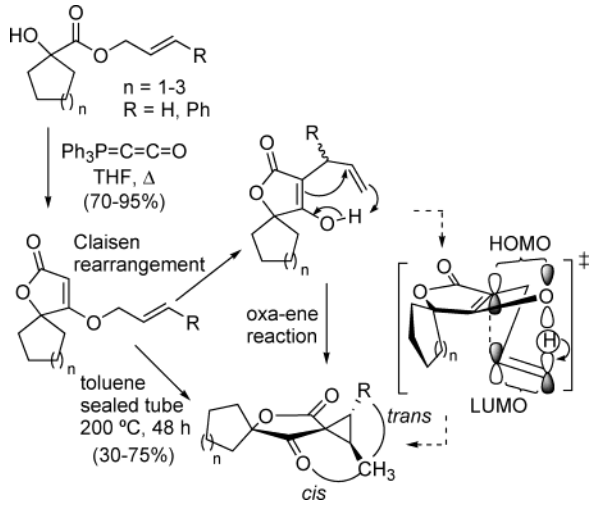
Scheme 144



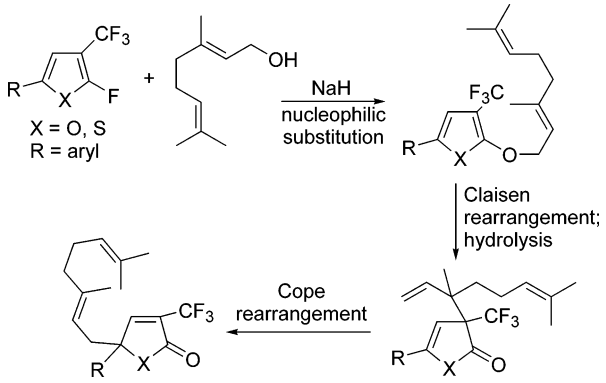
Scheme 145



Scheme 146



Scheme 147



philic substitution, Claisen rearrangement, and Cope rearrangement from 2-fluoro-3-trifluoromethylfurans and thiophenes, respectively (Scheme 147).[170]

The synthesis of coumarins isolated from *Harboria trachypleura* was developed by a tandem sequence of Claisen−Cope rearrangements of phenyl prenyl ethers in refluxing diethylaniline, followed by a Shi asymmetric epoxidation. Other related coumarins were accessible from the so-obtained coumarin (Scheme 148).[171] These coumarins have been shown to be capable of potentiating the action of anthraquinones as MDR (multidrug resistance) efflux pump inhibitors.

Recently, oxepin- and oxocin-annulated coumarins (Figure 22) were prepared by a combined sequence of Claisen rearrangement and ring-closing metathesis.[172]

In the literature there are several papers describing the application of Claisen rearrangements to the synthesis of lactams. An Eschenmoser [3,3] rearrangement starting from *N,N*-dialkylalkoxymethyleniminium salts and lithium alkoxides derived from allyl alcohols was used for the synthesis of 3-allyl-substituted five- to seven-membered lactams in good yields (Scheme 149).[173] Secondary and tertiary lithium alkoxides could also be used, stereoselectively affording quaternary chiral centers.

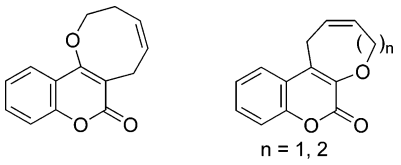
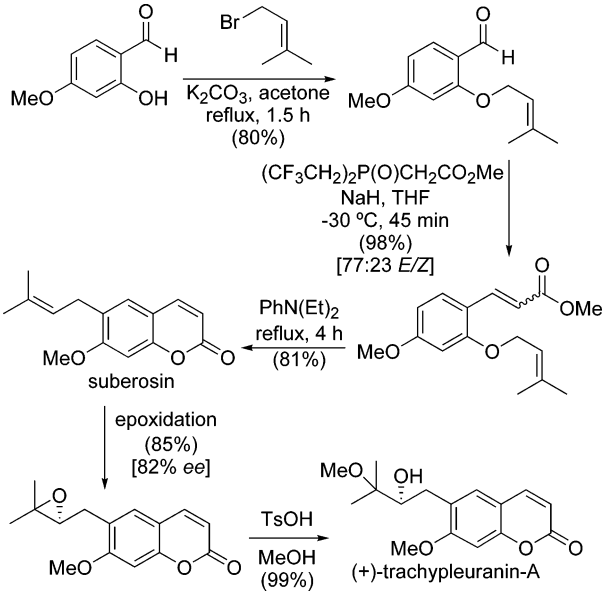
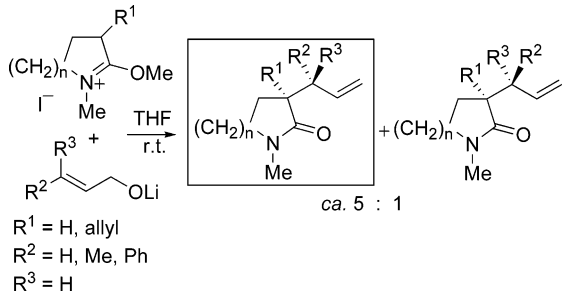


Figure 22.

Scheme 148

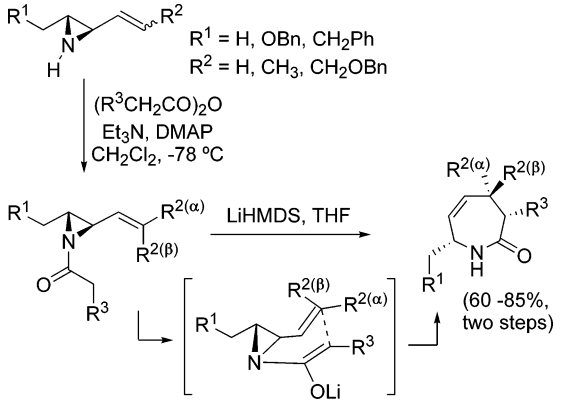


Scheme 149



N-Acyl vinyl aziridines are excellent substrates of the base-induced aza−Claisen rearrangement, providing mono-, di-, or trisubstituted seven-membered lactams with high stereoselectivity (Scheme 150).[174]

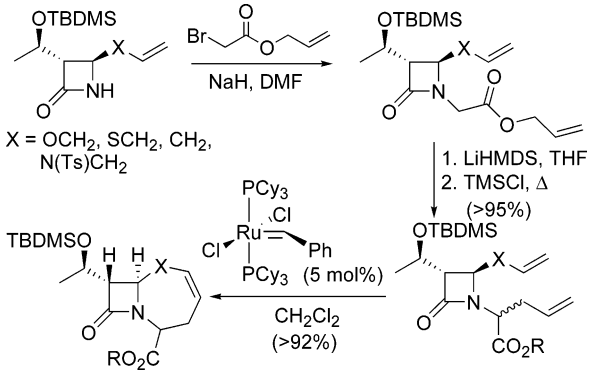
Scheme 150



A kinetically controlled concerted mechanism through a six-membered boatlike transition state accounted for retention of the alkene stereochemistry in the process.

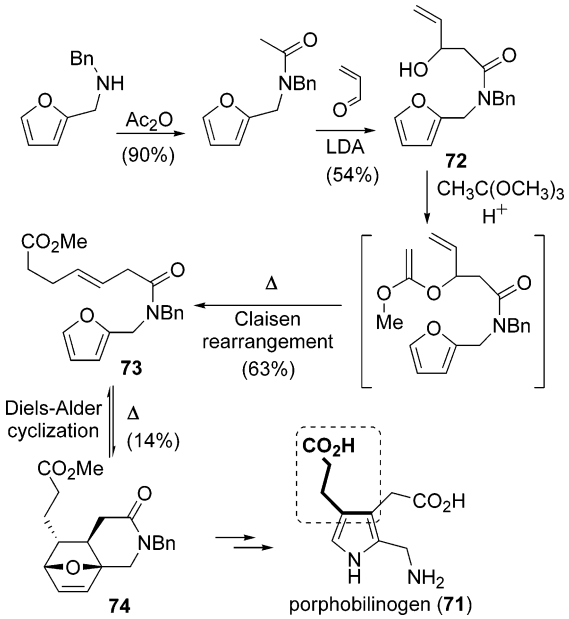
A sequence using the Ireland−Claisen rearrangement of ester enolates followed by ring-closing metathesis using Schrock {[$(CF_3)_2MeCO]_2Mo$(=CHCMe$_2$-Ph)(=NC_6H_3-2,6-*iso*-Pr_2)} or Grubbs carbenes [Cl_2-$(Cy_3P)_2$Ru=CHPh] easily afforded bicyclic β-lactams (Scheme 151).[175]

Scheme 151



A synthesis using a tandem Johnson rearrangement and Diels−Alder cycloaddition as the key step was developed for the preparation of lactam precursors of biologically interesting tetrapyrrols such as porphobilinogen (**71**).[176] The reaction of allyl alcohol **72** with methyl orthoacetate gave the rearranged furanamide **73**, which was not isolated and underwent a Diels−Alder cyclization to generate the 7-oxonorbornene **74**, precursor of porphobilinogen (**71**) (Scheme 152).

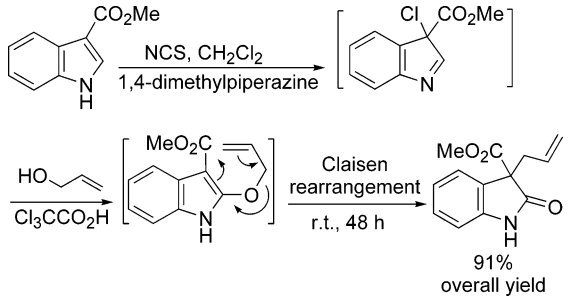
Scheme 152



3-Allyl-2-oxyindoles were synthesized in good yields by a tandem nucleophilic addition−Claisen rearrangement sequence.[177] Reaction of 3-methoxycarbonylindole with *N*-chlorosuccinimide in the presence of 1,4-dimethylpiperazine furnished the corresponding chloroindolenine. The latter reacted with an allyl alcohol under acid conditions to afford an allyl vinyl

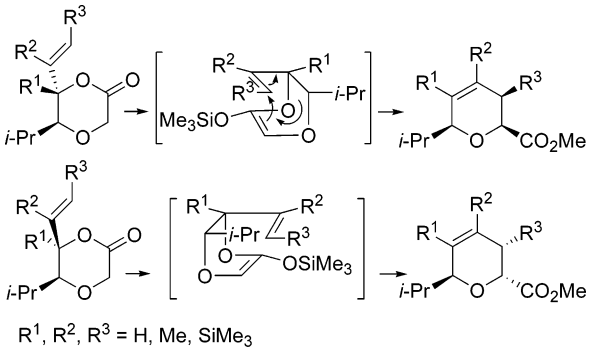
ether, which underwent a fast sigmatropic [3,3] rearrangement leading to the oxyindole (Scheme 153).

Scheme 153



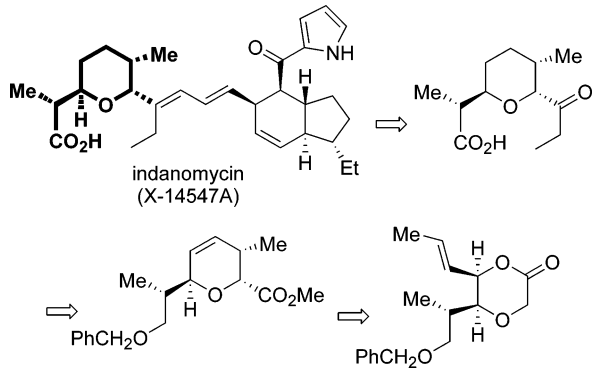
Different kinds of cyclic ethers could be synthesized starting from Claisen rearrangement products. For example, the stereoselective preparation of polysubstituted dihydropyrans was reported by a synthetic sequence involving a [3,3] sigmatropic rearrangement of ketene trimethylsilylacetals derived from 6-alkenyl-4-oxapyran-2-ones (Scheme 154).[178a]

Scheme 154



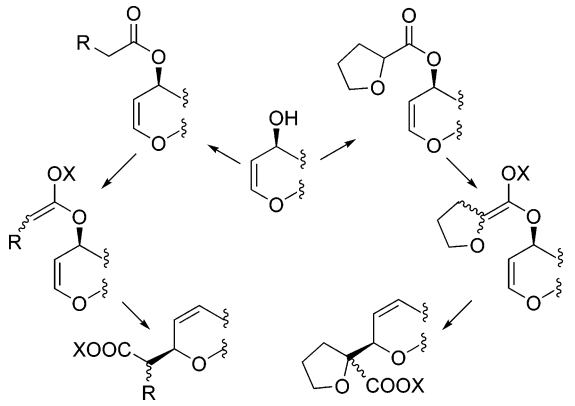
This methodology was applied to the enantioselective synthesis of the tetrahydropyran subunit of the ionophore antibiotic indanomycin (X-14547A) following the retrosynthetic sequence shown in Scheme 155, where an Ireland−Claisen rearrangement was the key step.[178b]

Scheme 155



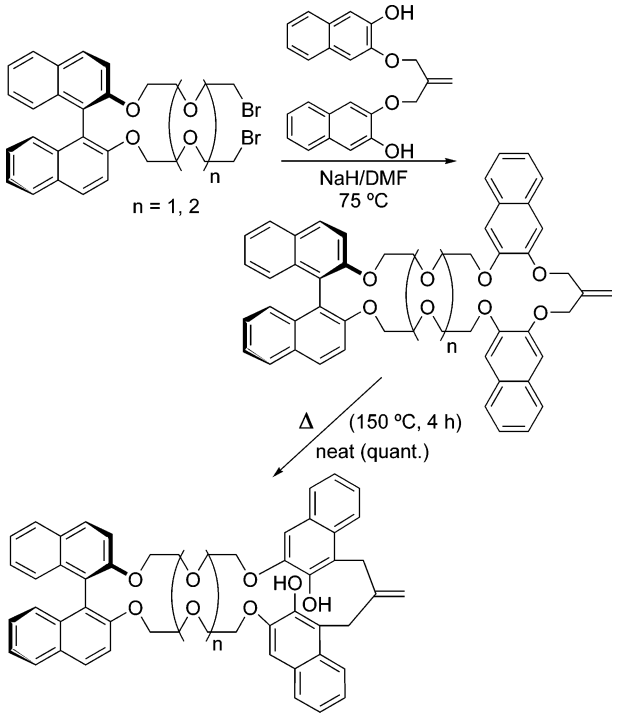
An Ireland−Claisen rearrangement was also the key carbon−carbon bond-forming step for the synthesis of furanoid and pyranoid glycals from glycal esters.[179] This methodology (depicted in Scheme 156, where the partial structures denote furan or pyran rings) made use of heterocyclic allyl alcohol to generate either an aliphatic ester or an α-alkoxy ester. These esters afforded aldol-type structures or glycolic diethers, respectively, by [3,3] sigmatropic rearrangement.

Scheme 156



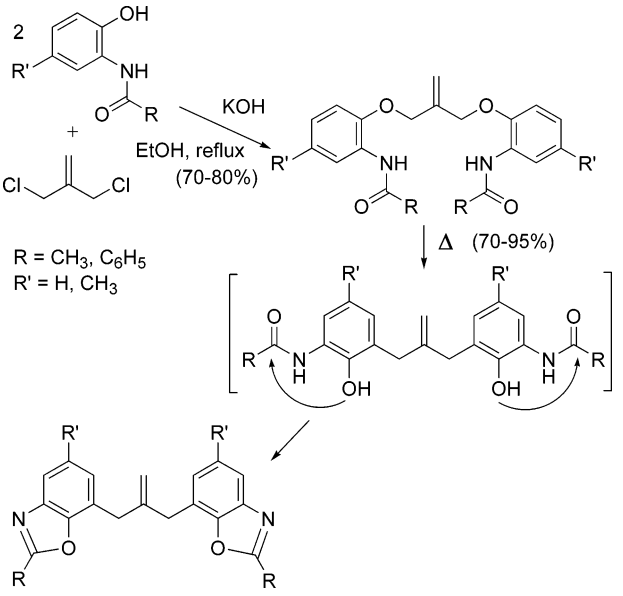
Crownophanes are macrocycles exerting excellent properties concerning molecular recognition as a consequence of the hybridization of both the rigid and flexible parts in the molecule. 1,1-Bis(aryloxymethyl)-ethylene derivatives were transformed thermally into bis(hydroxyaryl) derivatives in high yields by a tandem sequence consisting of two Claisen rearrangements. This reaction afforded crownophanes bearing phenolic units. Axially asymmetric crownophanes were synthesized through a tandem Claisen rearrangement (Scheme 157) from enantiomerically pure (*R*)-(+)-1,1′-bi-2,2′-naphthol.[180]

Scheme 157



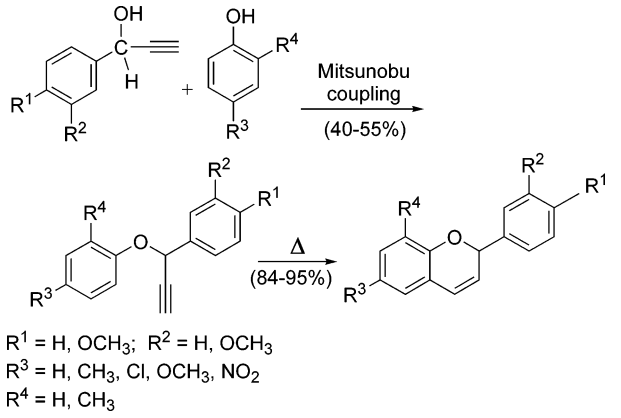
Similarly, a tandem Claisen rearrangement was used for the synthesis of photoluminescent bis-(benzoxazole) derivatives from 1,3-bis(*o*-acylamino phenyloxy)-2-methylene propane derivatives (Scheme 158).[181] This sequence proceeded in good yields when the reaction was run neat.

Scheme 158



The aromatic Claisen rearrangement of aryl propargyl ethers was described as a method for the synthesis of differently substituted aromatic cyclic ethers. A nice example was the [3,3] sigmatropic rearrangement of 1-arylprop-2-ynyl aryl ethers in *N*,*N*-diethylaniline/*o*-dichlorobenzene, which led to flav-3-enes,[182] intermediates in the synthesis of flavonoids, in high yields (Scheme 159).

Scheme 159

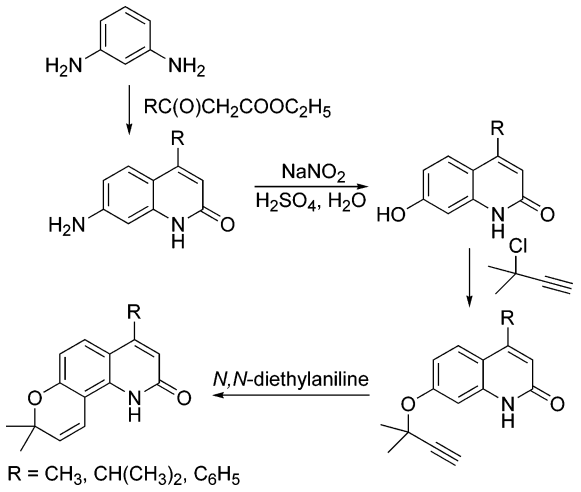


A similar reaction produced 8,8-dimethyl-2*H*,8*H*-pyrano[6,5-*h*]quinolin-2-ones, compounds with antithrombotic, antiallergic, and antitumor properties, in a four-step sequence involving the regiospecific aromatic Claisen rearrangement of an aryl propargyl ether (Scheme 160).[183]

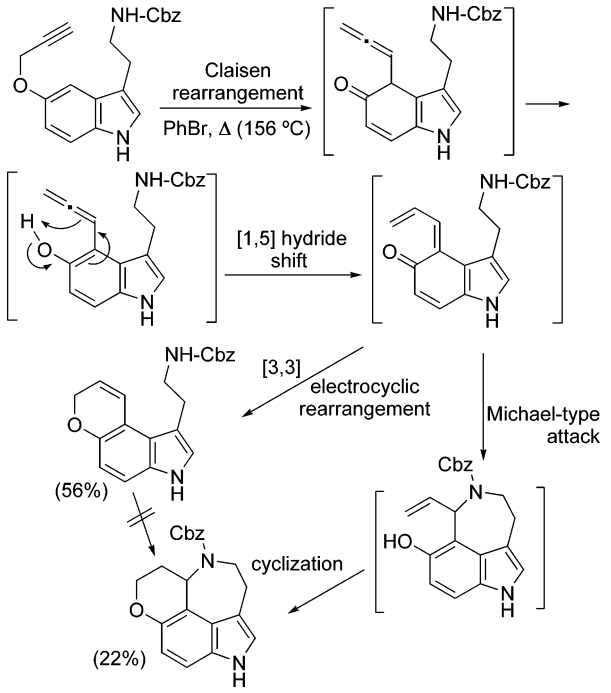
The Claisen rearrangement of 5-propargyloxyindoles was developed as a straightforward synthesis of the pyrano[3,2-*e*]indole framework.[184] As depicted in Scheme 161, the allene resulting from the rearrangement tautomerized and after [1,5] hydride shift afforded an intermediate for either pyrano[3,2-*e*]-indoles by [3,3] electrocyclic rearrangement or tetracyclic indoles by Michael addition.

Claisen rearrangement strategies have been used in the generation of a number of nitrogen-containing heterocycles. The Ireland−Claisen rearrangement of

Scheme 160



Scheme 161

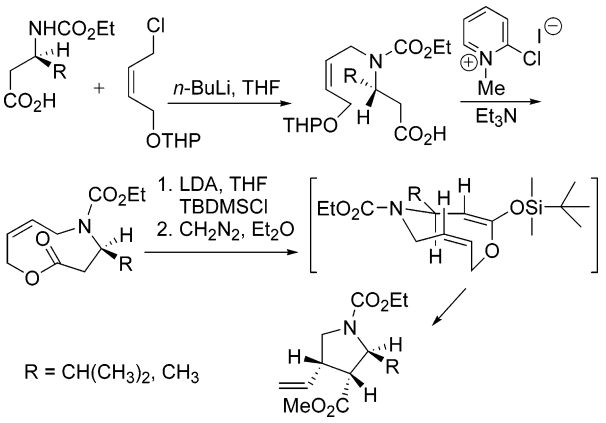


azalactones was used in the synthetic route for trisubstituted pyrrolidines.[185] When azalactones derived from amino acids bearing a chiral center were used, the method led to a direct access to optically active pyrrolidines. The boatlike nature of the transition state of the rearrangement determined the sole formation of *cis*-1,2-disubstituted heterocycles (Scheme 162).

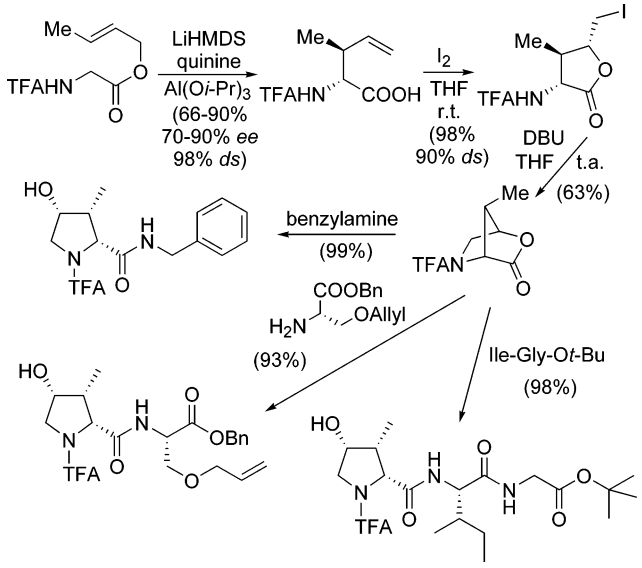
As discussed earlier, rearrangement of chelated allylic ester enolates in the presence of chiral ligands such as quinine afforded chiral γ,δ-unsaturated amino acids.[162] This reaction was successfully applied to the preparation of *cis*-hydroxyprolines directly incorporated into peptides by a sequence consisting of iodolactonization, bicyclization, and nucleophilic lactone ring opening with amino acids and peptides (Scheme 163).[186]

A synthetic sequence involving an enantioselective aza−Claisen rearrangement was developed for the synthesis of optically active *cis*-3-arylproline deriva-

Scheme 162



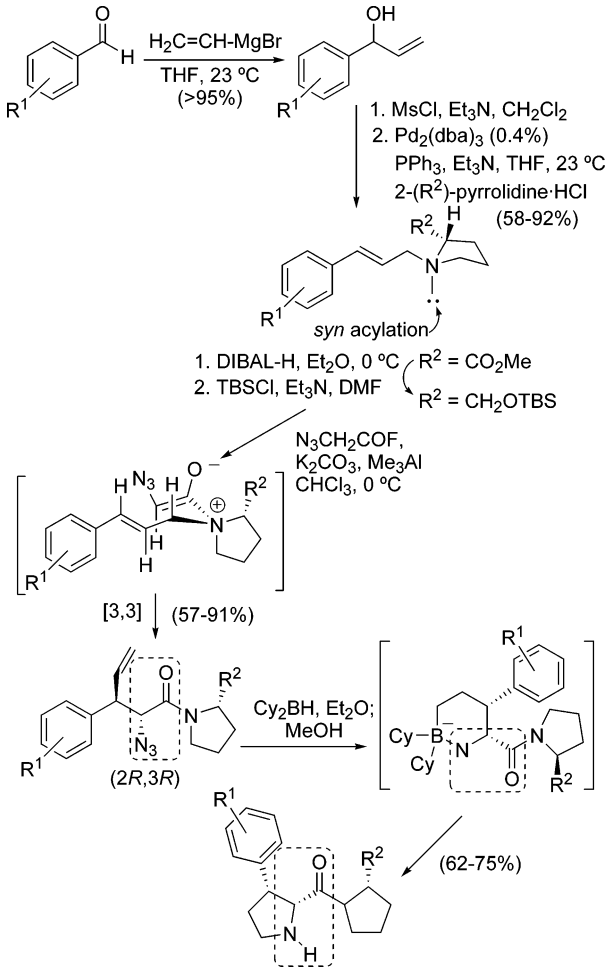
Scheme 163



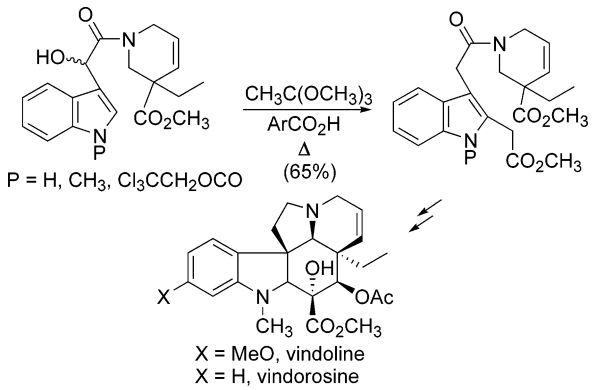
tives,[187] interesting building blocks in the preparation of biologically active cyclopeptides. The synthesis of the starting materials was performed by Pd(0)-catalyzed amination of the corresponding *N*-allyl mesylates with optically active proline derivatives acting as the chiral auxiliaries (Scheme 164). Zwitterionic aza−Claisen rearrangement incorporated the stereocenters in a process whose stereochemical course was ruled by both intraannular asymmetric induction and diastereoselectivity induced by a chiral auxiliary to afford *anti*-γ,δ-unsaturated amides. The stereochemical outcome was rationalized by diastereoselective syn acylation of allylamines and subsequent [3,3] sigmatropic rearrangement through a chairlike transition state where repulsive interactions were minimized (1,3-chirality transfer through a vinyl system). Reductive cyclization affording the desired 3-arylproline amides was performed under Sabol cycloalkylation conditions[188] consisting of a hydroboration−azide insertion−rearrangement sequence leading to 2,3-syn products exclusively.[187]

Claisen rearrangement of indole-3-glycolamide-derived ortho esters gave 2,3-disubstituted indoles, intermediates in the synthesis of alkaloids vindoline and vindorosine (Scheme 165).[189]

Scheme 164



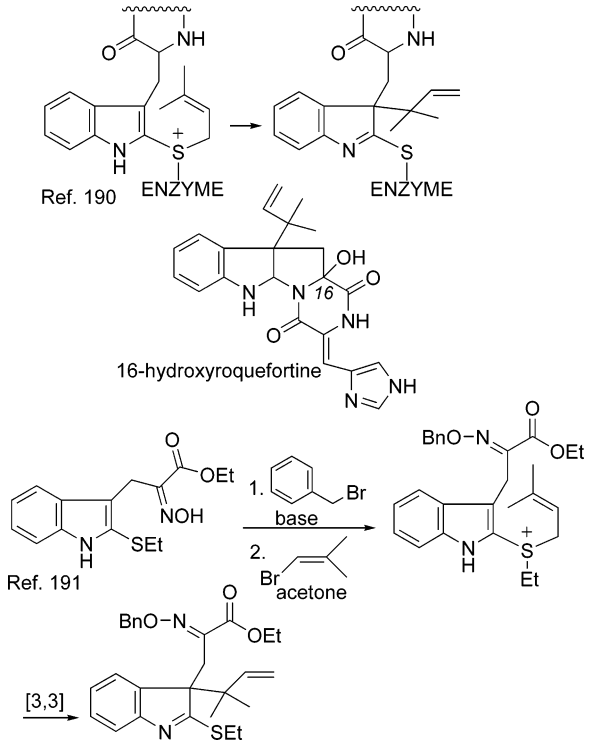
Scheme 165



Sulfonium salts derived from enzyme-bonded tryptophans are intermediates via Claisen rearrangement in the biosynthesis of marine products bearing a 3-(1,1-dimethyl-2-propenyl)indolenine subunit,[190] such as 16-hydroxyroquefortine (Scheme 166). Thio−Claisen rearrangement of ethylsulfonium salts prepared from a 2-(ethylthio)tryptophan derivative[191] confirmed this proposal and was considered as a chemical analogue of the enzymatic incorporation of a dimethylallyl moiety to indole alkaloids.

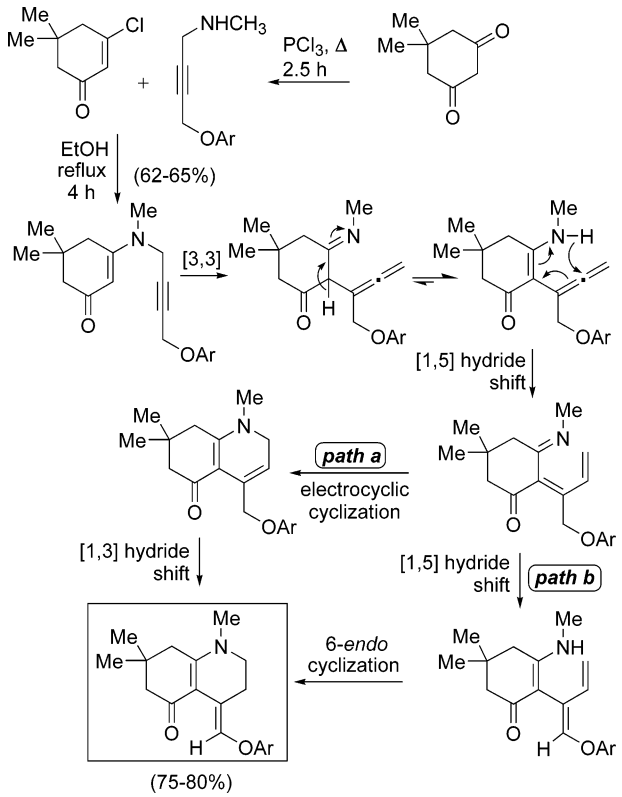
The aza−Claisen rearrangement was also applied to the synthesis of fused nitrogen heterocycles such as quinolinones.[192] The substrates are particularly interesting structures exhibiting two subunits—the

Scheme 166



propargyl vinylamine and the aryl propargyl ether fragments—able to undergo [3,3] sigmatropic rearrangement. In all the studied substrates, the rearrangement took place through the amine fragment (Scheme 167). The formation of the exocyclic products

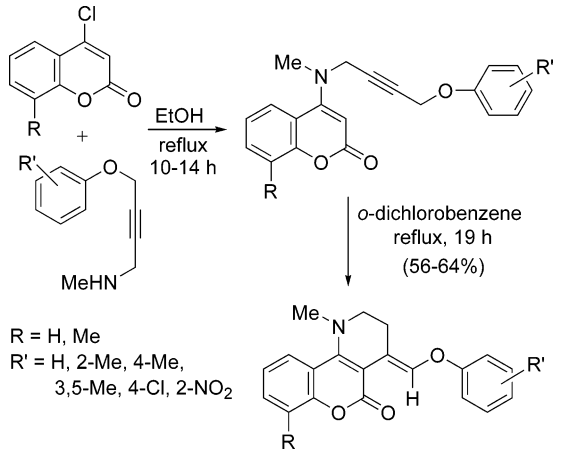
Scheme 167



could be rationalized by an initial [3,3] sigmatropic rearrangement of the propargyl vinylamine fragment to generate an intermediate allene and further tautomerization, [1,5] hydride shift, and electrocyclic cyclization to afford an endocyclic intermediate which yields the final product by prototropic [1,3] rearrangement (path a). A hydride [1,5] shift followed by a 6-*endo* cyclization (path b) was also possible.

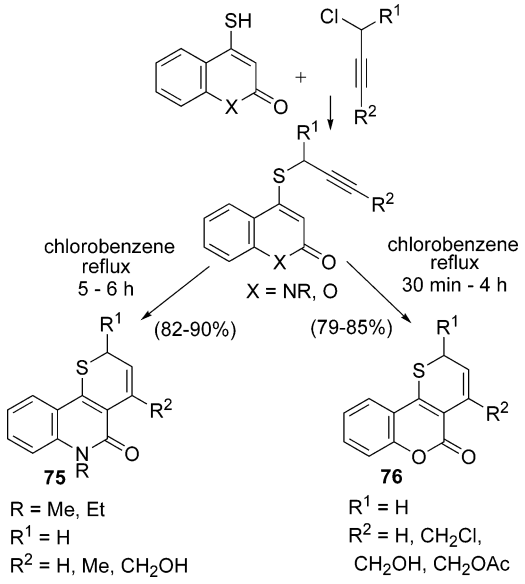
A similar methodology consisting of an aza–Claisen rearrangement of 4-*N*-(4-aryloxy-but-2-ynyl)-*N*-methylaminocoumarins furnished tricyclic skeletons containing an exocyclic double bond (Scheme 168).[193]

Scheme 168



The analogous thio–Claisen rearrangement of suitably substituted aryl propargyl sulfides led to thiopyranoquinolinones (**75**)[194] and thiopyranobenzopyranones (**76**),[195] as depicted in Scheme 169. The

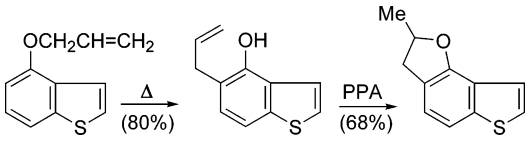
Scheme 169



mechanism proposed for these reactions was quite similar to that of the aza–Claisen reaction.

A thermal Claisen rearrangement of allyl or propargyl ethers derived from 7-hydroxy-1-benzothiophene followed by cyclization of the resulting *ortho*-alkenyl or *ortho*-alkynyl phenols generated tricyclic molecules bearing a fused thiophene ring (Scheme 170).[196]

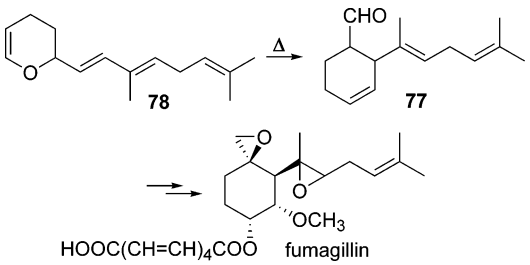
Scheme 170



7.2. Carbocyclic Skeletons

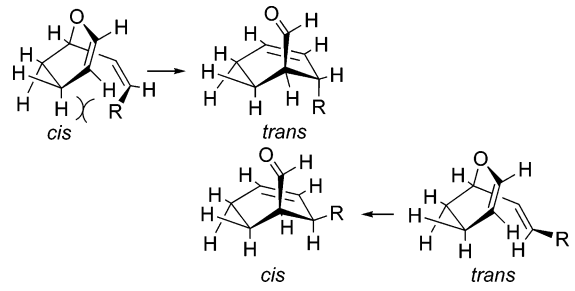
Several syntheses of carbocyclic structures have been described from Claisen rearrangement products. For example, the Claisen rearrangement of 3,4-dihydro-2*H*-pyranylethylenes represents a method for the synthesis of substituted cyclohexenes.[197] To a certain extent this is a complementary method to the Diels−Alder reaction since it affords specific cyclohexenes not easily synthesized by cycloaddition. The feasibility of the rearrangement depends on the geometry of the bulky substituents at the terminal carbon of the aliphatic double bond. One example of thus synthesized cyclohexenes is the aldehyde **77**, which was obtained from the tetraene **78** and an intermediate in the synthesis of the antibiotic fumagillin (Scheme 171).

Scheme 171



Despite the generally admitted chairlike transition state for the aliphatic Claisen rearrangement, a boatlike transition state was suggested to account for the results of the rearrangement of dihydropyranylethylenes (Scheme 172). The rearrangement of a

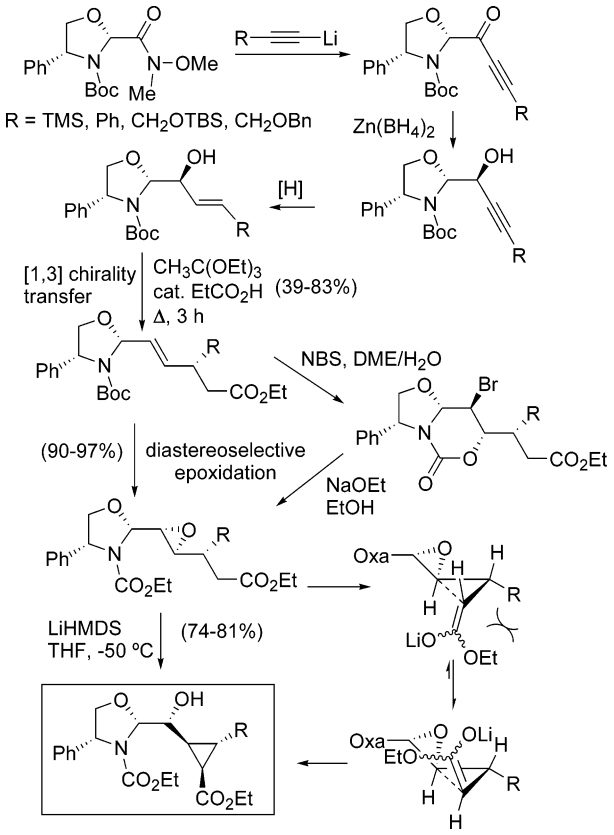
Scheme 172



trans-alkene through a boatlike transition state stereospecifically generated a 1,2-*cis*-disubstituted cyclohexene, whereas the corresponding *cis*-alkene gave the *trans*-epimer. A substituent on the alkene in the cis arrangement decelerated the rearrangement due to steric interactions with the hydrogen atoms of the dihydropyran ring.

The stereoselective Claisen rearrangement of alkenols prepared from the Weinreb amide derived from (*R*)-phenylglycinol was described.[198] This methodology was applied to the synthesis of trisubstituted cyclopropanes.[198b] The 1,3-chirality transfer was controlled by Zimmerman−Traxler transition states, and the double-bond configuration at the starting alkenol determined the configuration at the new stereocenter. The epoxidation step consisted of an intramolecular formation of a bromocarbamate and further treatment of the resulting bicyclic urethane with sodium ethoxide. The stereochemical course of this transformation was not influenced by the stereocenter formed during the rearrangement. Finally, the reaction of the intermediate epoxy esters with LiHMDS gave trisubstituted cyclopropanes by a stereoselective 3-*exo*-trig cyclization. In fact, the configuration of the stereocenter generated in the Claisen rearrangement controlled the stereochemical evolution of the intramolecular cyclopropanation: ethoxycarbonyl and R groups adopted a trans relative arrangement in the product as a consequence of the minimization of the $A^{(1,3)}$ allylic strain in the transition state, as shown in Scheme 173.

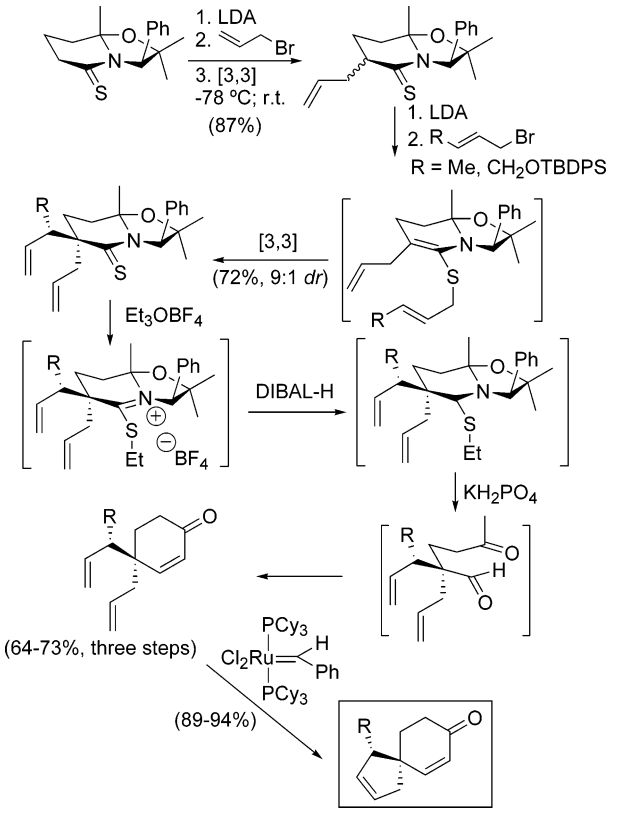
Scheme 173



We have already seen (Scheme 121)[143] that [3,3] sigmatropic rearrangement of *N*,*S*-ketene acetals yielded compounds bearing quaternary chiral centers on vicinal centers. This methodology was successfully applied to the synthesis of chiral spiro[4,5]decane skeletons.[199] A sequential thio−Claisen rearrangement diastereoselectively incorporated two different allyl moieties to thiolactam molecules. The *S*-iminium salt derived from the rearranged product was converted into the corresponding keto aldehyde (or diketone) and then, via a tandem aldol condensation and ring-closing metathesis reaction, the above-mentioned chiral spiroskeletons (Scheme 174).

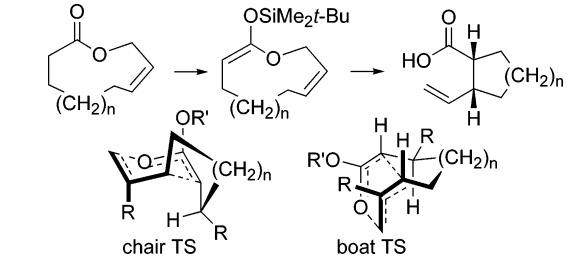
The Ireland−Claisen rearrangement of suitably modified substrates where both terminal carbons

Scheme 174



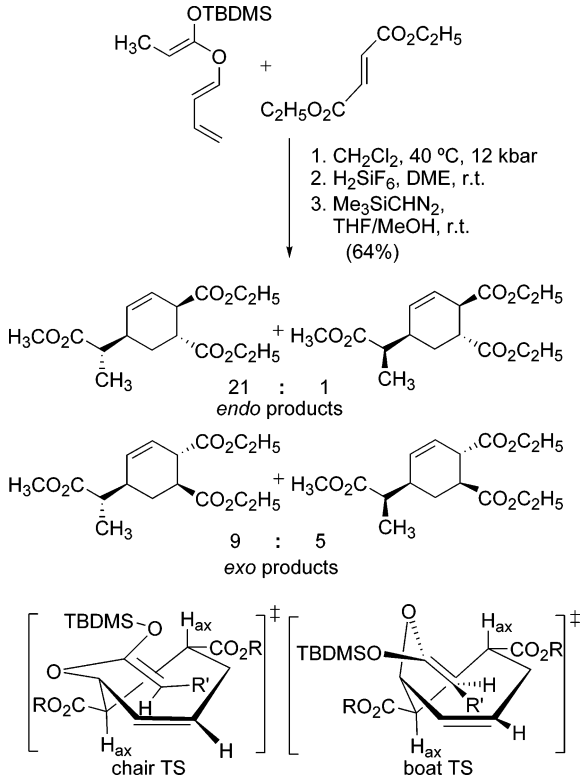
were connected by a carbon chain produced polysubstituted cycloalkanes in a stereocontrolled fashion.[200] In this reaction, all six atoms participating in the sigmatropic rearrangement were incorporated in the ring, which justifies the term of alicyclic Claisen rearrangement. The transformation of medium- or large-ring lactones, via cyclic ketene acetals, into the corresponding carbocycles resulted from a four-membered ring contraction (Scheme 175).

Scheme 175



The synthesis of substituted cyclohexenes from a tandem Diels−Alder cyclization, Ireland−Claisen rearrangement sequence led to the formation of three C−C bonds with high levels of stereocontrol not only of the chiral centers at the cyclohexene ring but also of the relative configuration of the exocyclic center.[201] The Ireland−Claisen rearrangement was a stereoselective process evolving through a boatlike transition state for the cyclohexene rings formed by *endo* Diels−Alder reaction (Scheme 176). In contrast, the selectivity of the rearrangement of the cyclohexenes resulting from *exo* Diels−Alder cyclization was considerably lower. In fact, the conformation of the cyclohexene ring for *exo* adducts minimized the steric

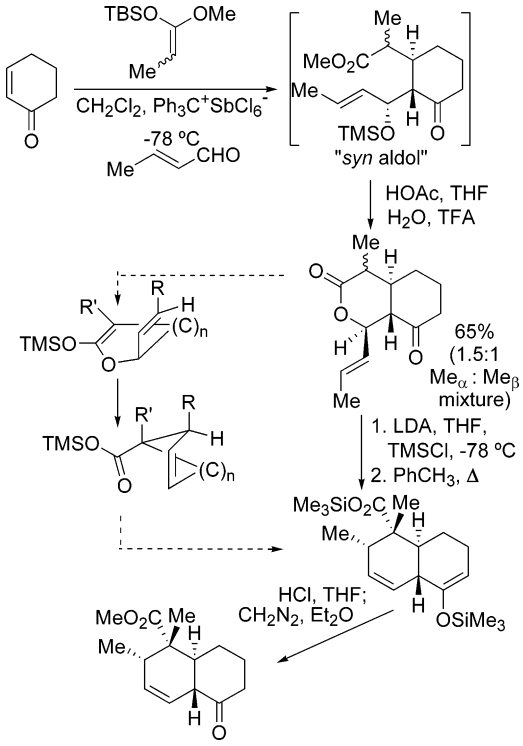
Scheme 176



interactions existing in the *endo* adducts, which resulted in a decrease in the selectivity.

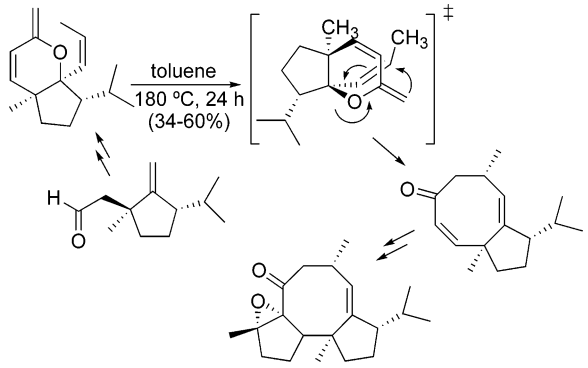
Starting from cyclohexanone, a sequence consisting of a Michael addition, aldol condensation/lactonization, and stereospecific Ireland−Claisen rearrangement gave access to fused carbocyclic systems (Scheme 177).[202]

Scheme 177



A Claisen rearrangement was also used as the key step of a stereocontrolled synthetic sequence leading

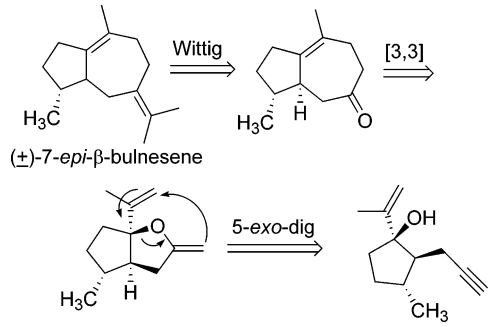
Scheme 178



to fused 2,5-cyclooctadienones bearing several chiral centers, which were intermediates in the synthesis of basmane diterpenes (Scheme 178).[203]

A strategy for the preparation of bicyclo[5.3.0]-decane skeletons was developed using an oxy-anion-catalyzed tandem 5-*exo*-dig cyclization/Claisen rearrangement sequence as the key step.[204] The synthesis of these structures was accomplished from suitably substituted acetylenic alcohols, as depicted in the retrosynthetic Scheme 179. The incorporation of an

Scheme 179

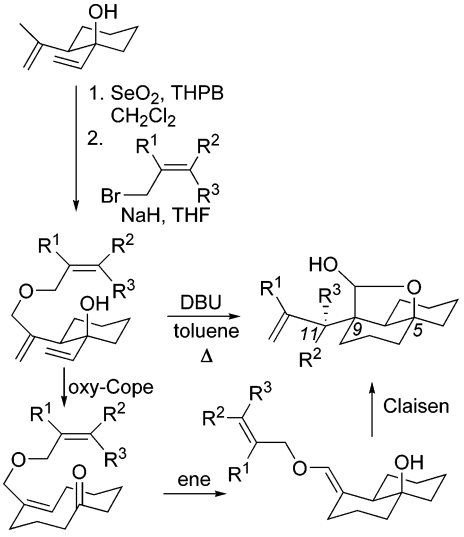


isopropylidene group into the B ring through the use of a Wittig reaction completed the synthesis of (±)-7-*epi*-*β*-bulnesene.

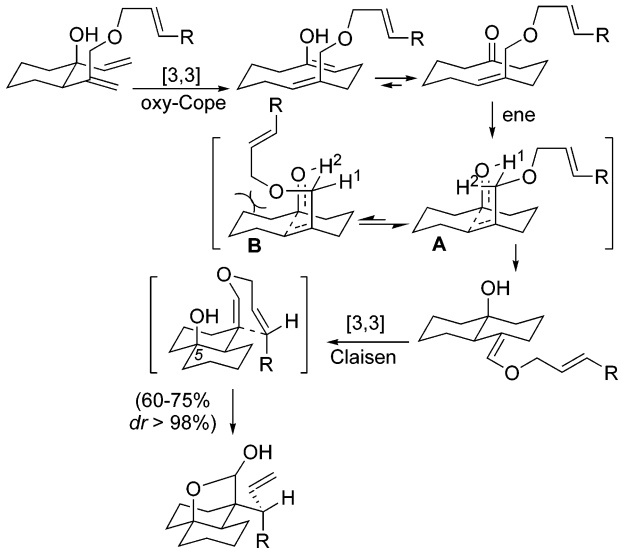
A diastereoselective thermal tandem sequence of three consecutive pericyclic reactions from allyl and propargyl ethers derived from 1,2-divinylcyclohexanol was recently reported for the synthesis of Decaline skeletons bearing quaternary carbons.[205] The method was based on a tandem sequence consisting of oxy-Cope/transannular ene/Claisen reactions capable of generating up to four vicinal stereocenters, including two quaternary carbons at C-5 and C-9 (Scheme 180). The allyl vinyl ether in-situ-generated by the oxy-Cope/ene sequence underwent a Claisen rearrangement affording a bicyclic lactol, which was the structural unit of sesquiterpene and diterpene skeletons.

The mechanism depicted in Scheme 181 explains the high diastereoselectivity of this triple tandem reaction. The oxy−Cope rearrangement provided an enol, which tautomerized into the corresponding ketone. This ketone could adopt two chair conformations **A** and **B** in the transition state. The pseudo-1,3-diaxial interaction existing in **B** between the allylic oxygen and a methylene group of the ring determined that the ene reaction took place through

Scheme 180



Scheme 181

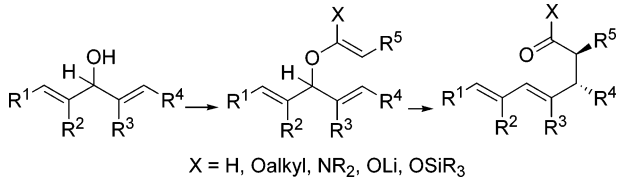


A to generate the enol, which was the substrate of the Claisen rearrangement. During the last step the rearrangement must proceed anti to the bridgehead alcohol at C-5, with the subsequent formation of the polycyclic product.

7.3. Dienes

The first synthesis of 1,3-dienes by Claisen rearrangement of bis-allyl vinyl ethers was reported in 1965 (Scheme 182).[206] Johnson, Ireland, and Eschen-

Scheme 182

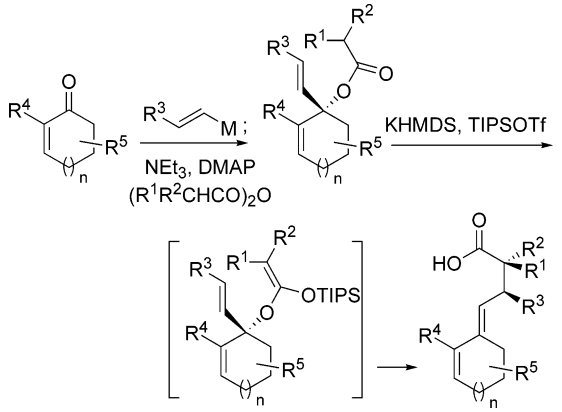


moser rearrangements of asymmetric bis-allyl vinyl ethers also proved to be highly stereoselective.[207]

A closely related Ireland−Claisen rearrangement of bis-allylic esters, where the carbinolic center

belonged to a cycloalkene, was recently developed (Scheme 183).[208] These substrates were prepared by

Scheme 183



vinylmetal addition to cycloalkenones followed by esterification. The products of the rearrangement were alkylidenecycloalkenes.

The regioselectivity and stereochemistry of the alkene as well as the chirality transfer detected in the rearrangement were explained from the possible transition states for the reaction (Scheme 184). The exocyclic rearrangement was favored, since the transition states **a** and **b** affording alkylidenecycloalkenes exhibited smaller eclipsing and/or transannular interactions than the transition states **c** and **d**, which would lead to the endocyclic products. The exocyclic transition state was also dependent on the substitution at C-2 and/or C-6 of the cyclohexene ring of the bis-allylic ester. The carbon of the ring bearing the bulkiest group will adopt a pseudoequatorial arrangement in the chairlike transition state. Therefore, C-2 substituted ketene acetals preferentially rearranged through transition-state **b** to afford the *E* alkene, whereas C-6-substituted ketene acetals evolved through transition-state **a**, with the subsequent formation of the *Z* alkene. The chirality transfer from the carbinolic center at C-1 to the new stereocenters derived from the evolution through chairlike transition states.

The preparation of 1,3-dienes was also described by a Johnson rearrangement from allyl alcohols using a sulfinylortho ester and further 1,2-pyrolytic elimination of the sulfinyl group (Scheme 185).[209] This new ortho ester completed the sequence without isolation of the intermediate, in yields which were much higher than those obtained in the two-step sequence.

A general synthesis of 1,3-dienes resulted from a ruthenium [CpRu(CO)Cl or $CpRu(CH_3CN)_3PF_6$] catalyzed coupling of an allene and an enone through a mechanism involving a ruthenocycle (Scheme 186).[210] Considering that the most versatile reported method for the preparation of β-allenic ester derivatives involves a Claisen rearrangement, the combination of this reaction and the above-mentioned coupling can be considered as a generally useful method to prepare such dienes.

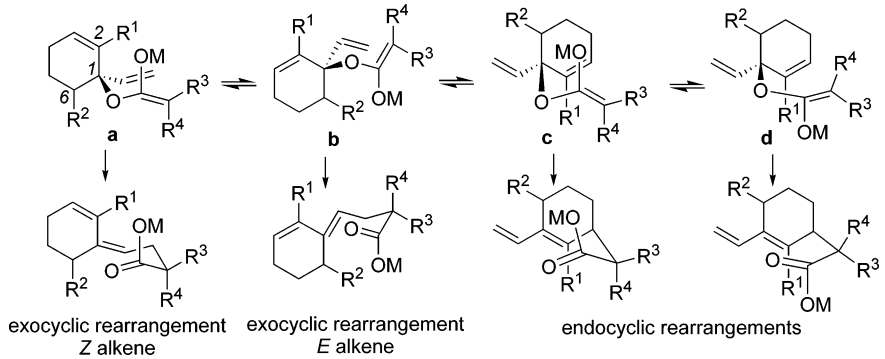
A wide range of aryl and heteroaryl phenols reacted with 2 equiv of an allene to generate phenoxymethyl-1,3-dienyl ethers in a Pd(0)-catalyzed process evolving through a Pd(IV) intermediate (Scheme 187). The aromatic Claisen rearrangement of the obtained *O*-dienyl ethers afforded 1,3-dienes, which were used in the preparation of *exo*-methylenechromanes and dihydrobenzofurans by cyclization under acidic conditions.[211]

The synthesis of 1,4-dienes incorporated into the steroid side chain bearing a substituent with a defined configuration at C-3 must also be considered.[212] That was the case of $\Delta^{22,25}$-24-alkyl steroids, isolated from marine organisms. The method was based on the Ireland−Claisen rearrangement of steroidal Δ^{23}-22-alcohols. C-25 Silylation of the obtained ester and Peterson olefination completed the sequence (Scheme 188).

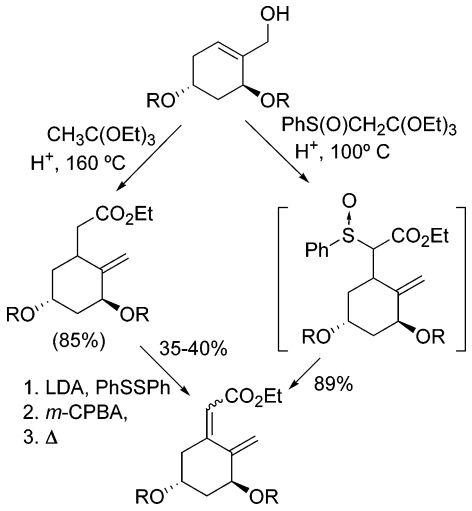
The synthesis of 1,5-dienes was also reported from the products resulting from a Claisen rearrangement. 1,5-Dienes were prepared by a sequence involving methylenation of allylic esters with Tebbe's reagent, followed by Claisen rearrangement, and eventually a second methylenation reaction. The allylic ester → 1,5-diene transformation was carried out without isolation of the intermediates by treatment of the substrates with an excess of the methylenation reagent (Scheme 189)[213] in a tandem sequence where the [3,3] rearrangement was catalyzed by the Al-$(CH_3)_2Cl$ present in the reaction.

An additional example describing the synthesis of 1,5-dienes using a [3,3] sigmatropic rearrangement is depicted in Scheme 190. The terpenoid derivative (2*Z*,6*E*)-3,6-dimethylocta-2,6-dien-1-ol (**79**) is a constitutional isomer of nerol with interesting odor properties. Compound **79** was synthesized starting with Steglich esterification of 3-methylbut-2-en-1-oic acid (senecioic acid) with (2*E*)-2-methylbut-2-en-1-ol (tiglic alcohol). Stereoselective Ireland−Claisen rearrangement of the resulting ester at 0 °C and Cope

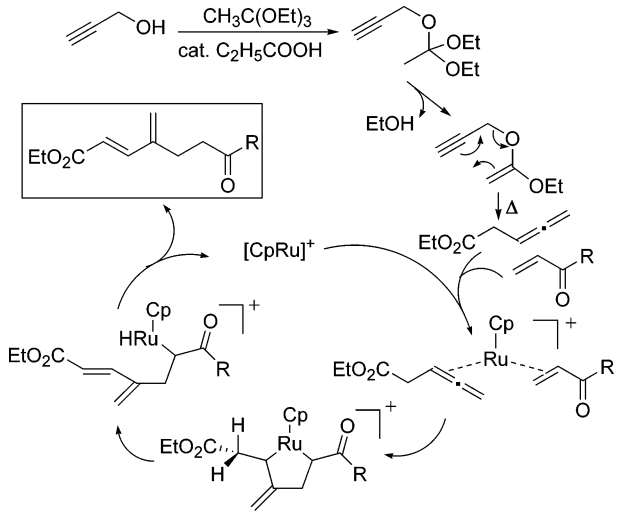
Scheme 184



Scheme 185



Scheme 186



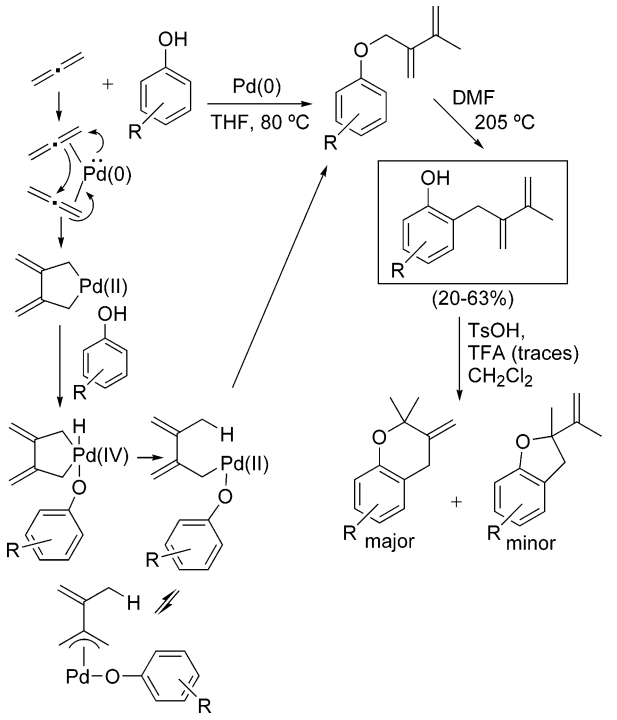
rearrangement of the intermediate at 140 °C completed the synthesis.[214] Both rearrangements proceeded through chairlike transition states. The synthetic sequence was completed by reduction of the α,*β*-unsaturated carboxylic acid into the corresponding alcohol.

7.4. Condensed Aromatic Structures

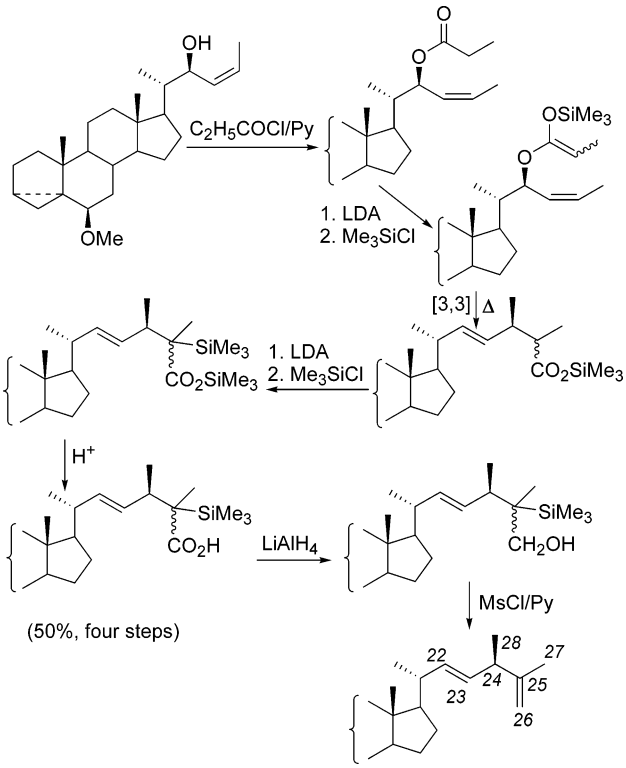
Natural products containing a naphthalene unit are often biologically active, which makes them attractive synthetic targets. Aromatic Claisen rearrangement of isovanillin-derived allyl aryl ethers produced the corresponding phenols that, after being protected as isopropyl ethers, furnished suitable substrates for the synthesis of naphthalenes (Scheme 191).[215] The last step of the sequence consisted of treatment with potassium *tert*-butoxide in DMF under ultraviolet irradiation. The proposed mechanism involved the photoenolization of *o*-allylbenzaldehydes (or their anion derivatives) to give the corresponding diene, which, through a 6*π* electrocyclic process, led to an alcohol that afforded the desired naphthalenes after dehydration.

Several naphthalene syntheses involving a Claisen rearrangement have been reported. Starting again

Scheme 187



Scheme 188

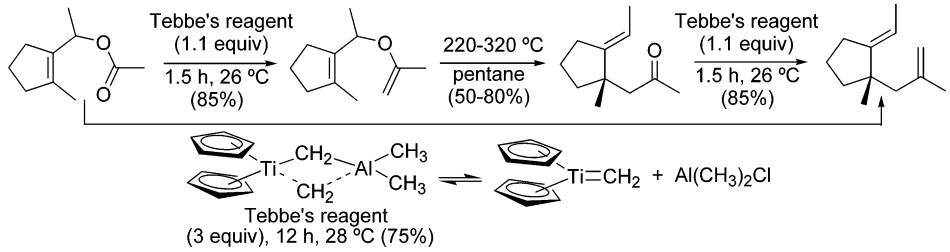


from isovanillin, preparation of 1-alkoxy-2-methoxynaphthalenes was recently reported as a synthetic sequence based on a Claisen rearrangement and further ring-closing metathesis in the presence of the Grubbs catalyst (Scheme 192).[216]

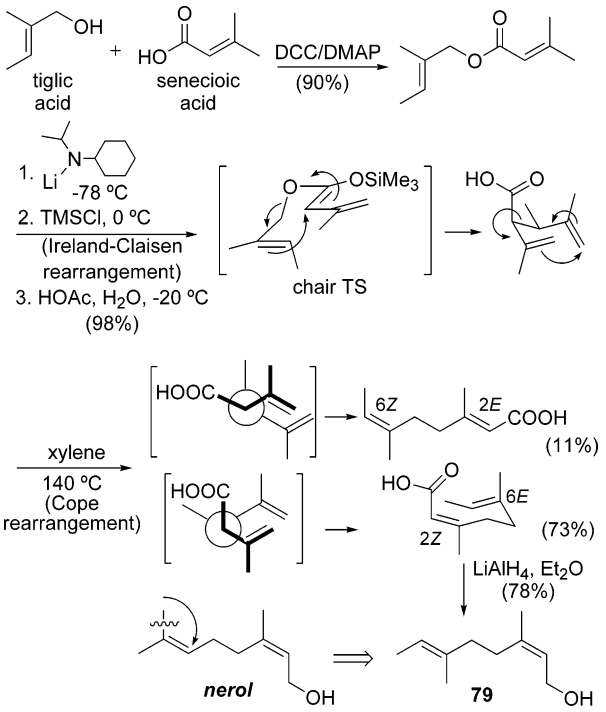
7.5. Carboxylic Acid Derivatives

Ireland and Johnson rearrangements have been the most widely reported [3,3] sigmatropic rearrangements for the synthesis of functionalized car-

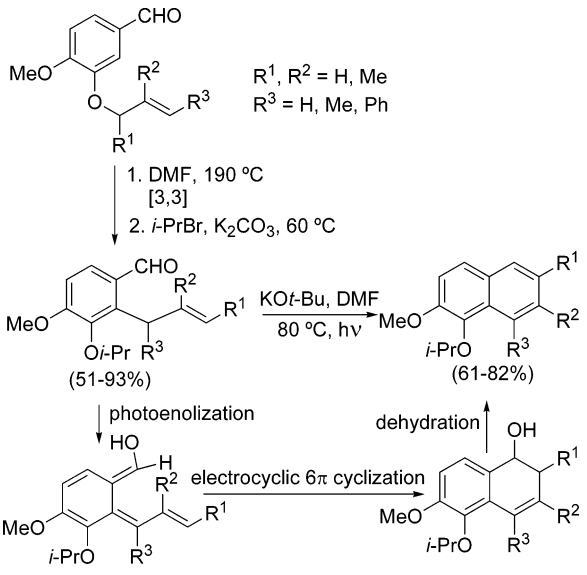
Scheme 189



Scheme 190

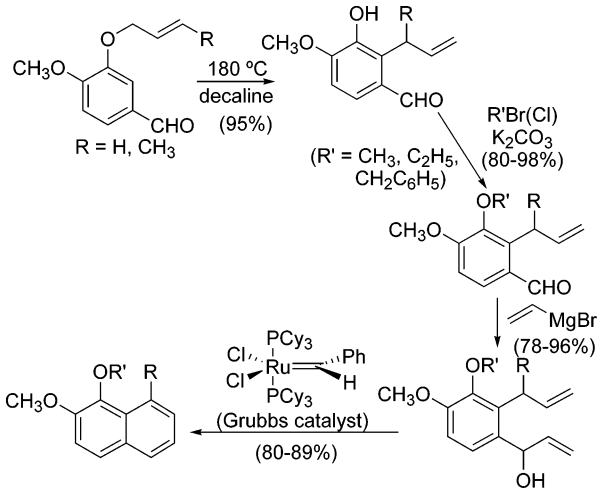


Scheme 191

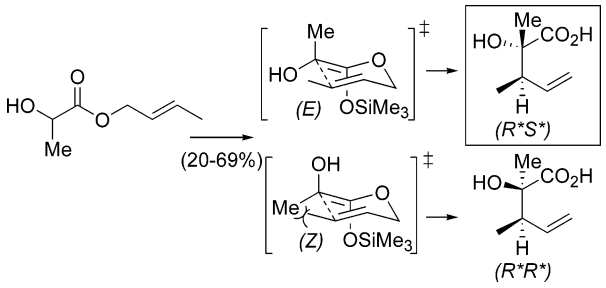


boxylic acids. The Ireland−Claisen rearrangement readily provides α- and *β*-hydroxy acids. The synthesis of α-hydroxy acids was reported by rearrangement of lactic acid derivatives.[217] For example, crotyl lactate was transformed into the corresponding enediolate; silylation and further rearrangement afforded a 4:1 mixture of *R*S** and *R*R** diastereomers. As the rearrangement likely proceeded through a chairlike transition state, the major isomer derived from *E* enediolates, where the oxygenated substituent at α position occupied a cis arrangement with respect to the enolate oxygen (Scheme 193).

Scheme 192



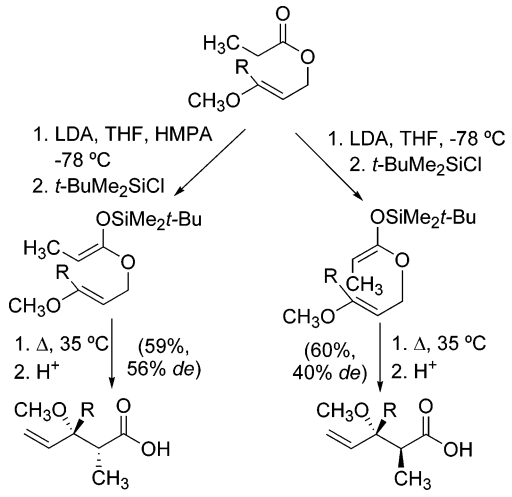
Scheme 193



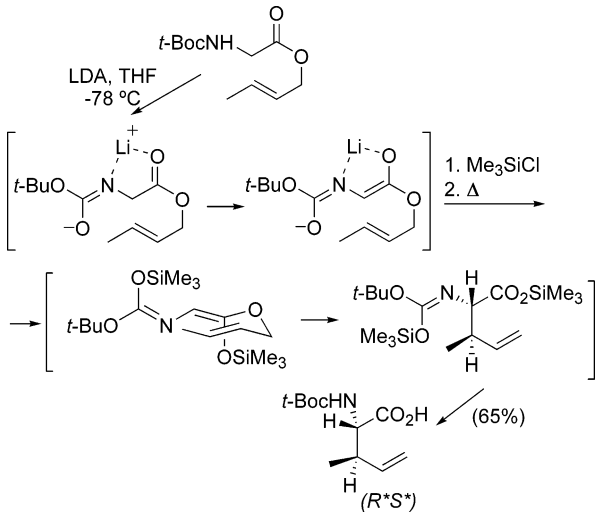
Aldol-type *β*-alkoxy acids were synthesized from substrates having an oxygen functionality on the allylic double bond.[218] The configuration at C-α of the product was dependent on the double-bond geometry of the enolate generated in the reaction (Scheme 194).

The synthesis of biologically active *γ*,*δ*-unsaturated amino acids was also developed by using an Ireland−Claisen rearrangement.[219] Deprotonation of *trans*-crotyl *N*-(*tert*-butoxycarbonyl)glycinate with LDA followed by silylation and heating furnished the rearranged product as a 9:1 mixture of *R*S** and *R*R** diastereomers.[219b] Once again, the major diastereomer derived from the *E* dianion through a chairlike transition state, as depicted in Scheme 195, where the coordination of the counterion with the carbonyl oxygen and the anionic nitrogen were thought to be important.

Scheme 194

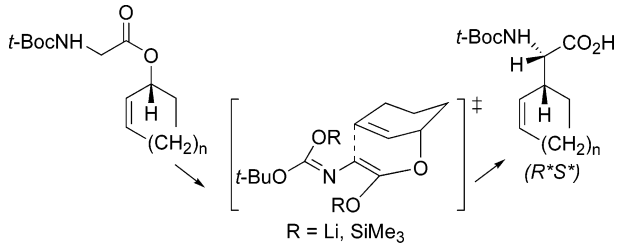


Scheme 195



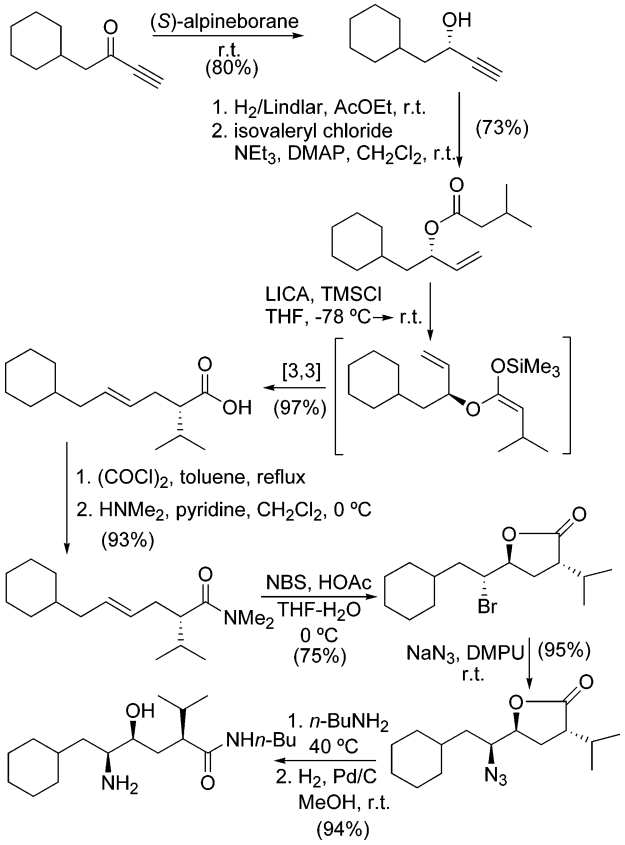
This methodology also afforded α-(2-cycloalkenyl) α-amino acids, bacterial growth inhibitors, by rearrangement of glycine derivatives.[219a] In this case, the *R*S** selectivity derived from the preference for a boatlike transition state in the rearrangement of enol ethers derived from *E* enolates (Scheme 196).

Scheme 196



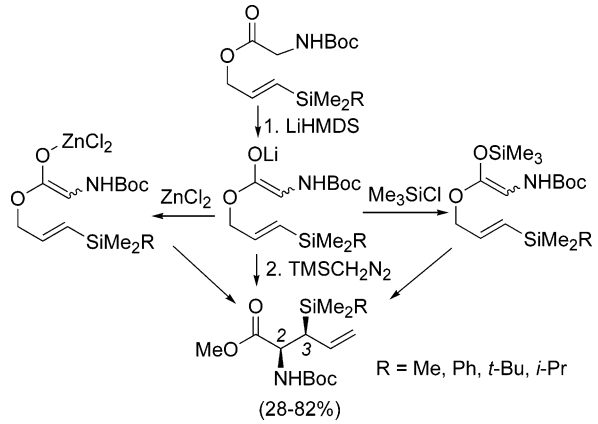
In pursuit of the synthesis of dipeptidomimetics, the stereoselective preparation of 2,5-disubstituted 5-amino-4-hydroxypentanoic acid derivatives was reported. In this process the desired chirality at C-2 was introduced by asymmetric reduction of the corresponding alkynones followed by a stereocontrolled Ireland−Claisen rearrangement. In its turn, the correct configuration at C-4 and C-5 was introduced by diastereoselective bromolactonization followed by azide displacement (Scheme 197).[220]

Scheme 197



Similarly, the Ireland−Claisen rearrangement of 3-silylpropen-1-ol glycinates allowed the generation of α-allylsilyl amino acids.[221] It is a reaction which proceeded with a high diastereoselectivity through a chairlike transition state to preferentially give the syn isomer (Scheme 198).

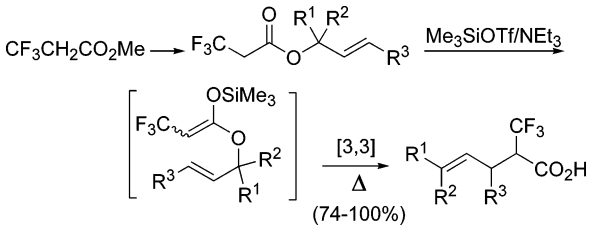
Scheme 198



When 2-alkenyl trifluoropropionates were used as substrates in the rearrangement, α-trifluoromethyl *γ*,*δ*-unsaturated carboxylic acids were obtained in good yields (Scheme 199).[222]

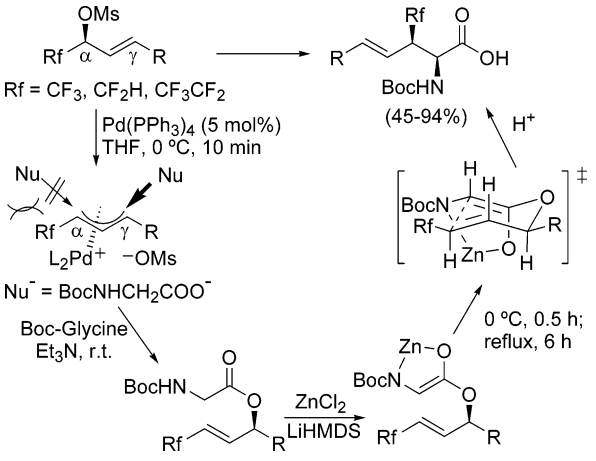
The preparation of *β*-fluoroalkyl *γ*,*δ*-unsaturated α-amino acids, used as enzymatic inhibitors, was described by a combination of a palladium-catalyzed allylic substitution and an Ireland−Claisen rearrangement.[223] Thus, the allylic substitution reactions of chiral α-fluoroalkyl mesylates with carboxylic acids

Scheme 199



in the presence of a palladium catalyst produced γ-fluoroalkyl allylic esters, which evolved through a [3,3] rearrangement (Scheme 200) to generate the

Scheme 200



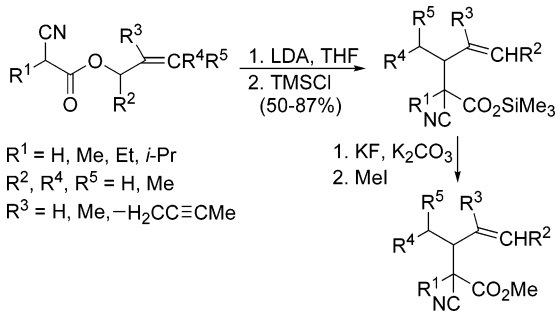
syn-2*S*,3*R* isomer. When the palladium complex coordinates to the alkene face distal to the mesyloxy group, the palladium species displaces the mesylate group with inversion of the configuration to furnish a π-allyl palladium complex. The nucleophilic carboxylate attacks the opposite face to that occupied by the palladium, thus resulting in the formation of products coming from an overall double inversion. The Pd is nearer the Rf group than the R group, due to the electron-withdrawing character of the Rf group. Therefore, the nucleophile preferentially attacks the less hindered γ carbon to produce the γ-fluoroalkyl allylic ester. The reaction of the latter with $ZnCl_2$−LiHMDS stereoselectively leads to the *Z* enolate, which undergoes Ireland−Claisen rearrangement through a chairlike transition state with the R group in an equatorial arrangement, eventually leading to the 2*S*,3*R*-amino acid.

The Ireland−Claisen rearrangement of allyl α-isocyanocarboxylates regioselectively afforded a C−C bond between the C-α of the α-isocyanoester and the C-3 of the allylic fragment, resulting in the α-allylation of isocyanoesters (Scheme 201).[224]

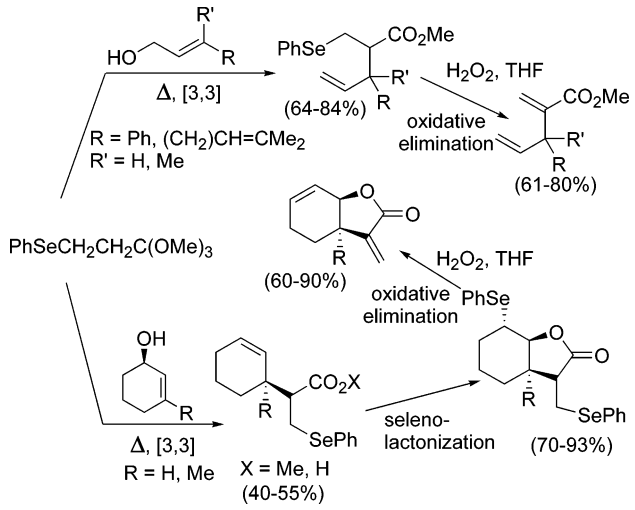
The Johnson rearrangement was also reported as a method for the preparation of a range of functionalized carboxylic acid derivatives. Thus, the syntheses of 2-substituted acrylates and α-methylene-γ-butyrolactones were described starting from methyl 3-(phenylseleno)orthopropionate via ortho ester−Claisen rearrangement followed by oxidative elimination of PhSeOH (Scheme 202).[225]

The use of functionalized ortho esters furnished α-heterosubstituted unsaturated esters.[226] Some ex-

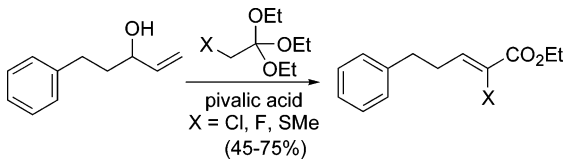
Scheme 201



Scheme 202



Scheme 203



amples are collected in Scheme 203, although this procedure was limited by low levels of diastereoselectivity.

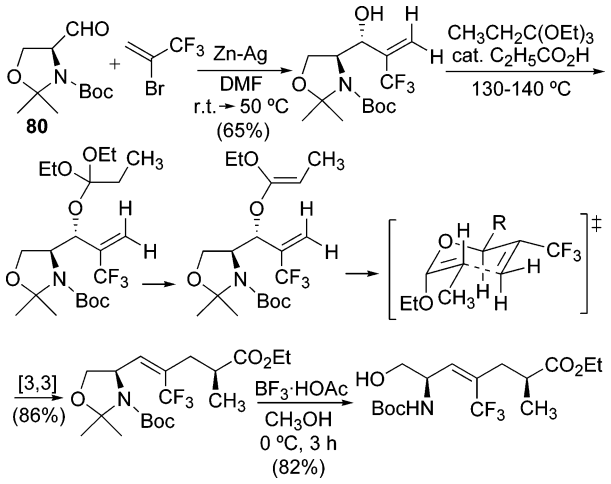
The ortho ester−Claisen rearrangement of optically active fluorinated allyl alcohols, obtained with high diastereomeric excesses from the Garner aldehyde (**80**), yielded aliphatic esters bearing hydroxy, amino, and fluoroalkyl groups in a stereocontrolled fashion (Scheme 204).[227]

Allyl alcohols bearing an alkoxy group at C-2 were attained by reaction of 1-ethoxyvinyllithium with aldehydes. These alcohols produced 4-oxoesters via Johnson rearrangement followed by acid treatment.[228] As depicted in Scheme 205, the sequence resulted in the homologation of the starting aldehyde with a four-carbon chain.

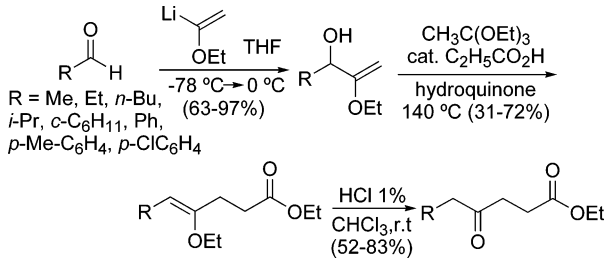
An ortho ester−Claisen rearrangement was also used for the preparation of 4-oxoesters and 3-cyanoesters starting from γ-hydroxy ketones and γ-hydroxy nitriles, respectively.[229] The carbonyl and the cyano groups of the rearranged products were suitably transformed into the corresponding lactones and pyrrolidinones (Scheme 206).

On the basis of the above-mentioned ketene−Claisen rearrangement reported by Belluš, Mac-

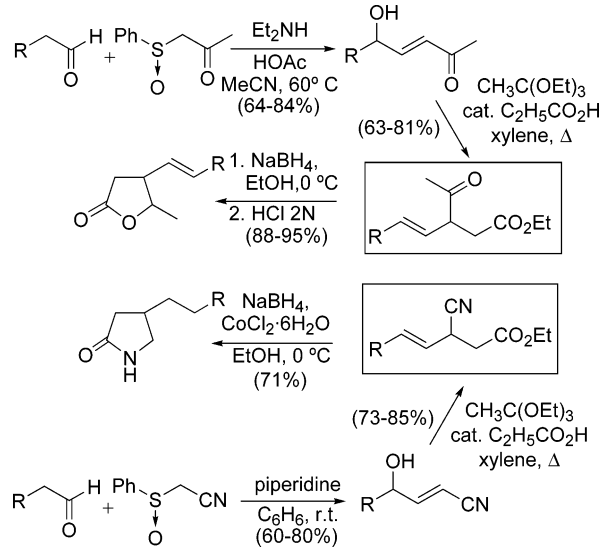
Scheme 204



Scheme 205

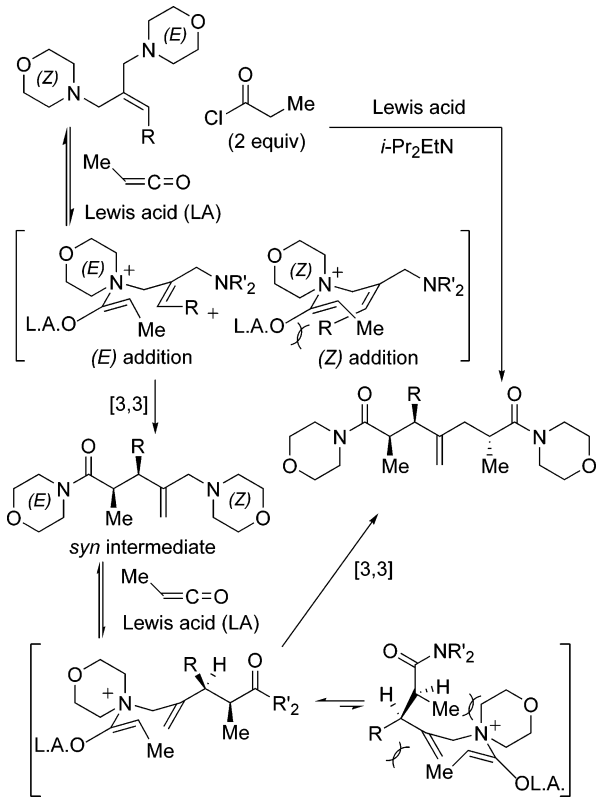


Scheme 206



Millan developed the acyl−Claisen rearrangement of a ketene with an allylamine in the presence of a Lewis acid to stereoselectively generate α,*β*-disubstituted *γ*,*δ*-unsaturated carbonyl compounds.[230a] The use of a tandem sequence of two consecutive acyl−Claisen rearrangements stereoselectively led to 2,3,6-trisubstituted 1,7-heptanedioic acids,[230b] as represented in Scheme 207. Initially the Lewis-acid-catalyzed ketene addition took place preferentially onto the *E* amine of the allyl diamine in order to minimize 1,3-diaxial interactions. The *syn*-2,3-disubstituted intermediate underwent a second [3,3] rearrangement on the intermediate ammonium ion in the conformation, minimizing the $A^{(1,2)}$ allyl strain and exhibiting smaller destabilizing transannular interactions. The experimental results are satisfactorily explained. However, the importance of the destabilizing interactions present in the productive conformer remains unclear.

Scheme 207



The synthetic applicability of this methodology was explored through the preparation (starting from substrates with R = OBz) of chiral subunits present in macrolide antibiotics having 2-*syn*-3,6-*anti*-2,6-dimethyl-1,7-dioxo-3-hydroxyheptane. The additional double bond at C-4 allowed, by oxidative or reductive transformations, the synthesis of the C(1)−C(7) fragment of erythronolide B or neomethynolide (Figure 23).

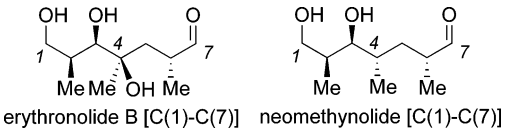


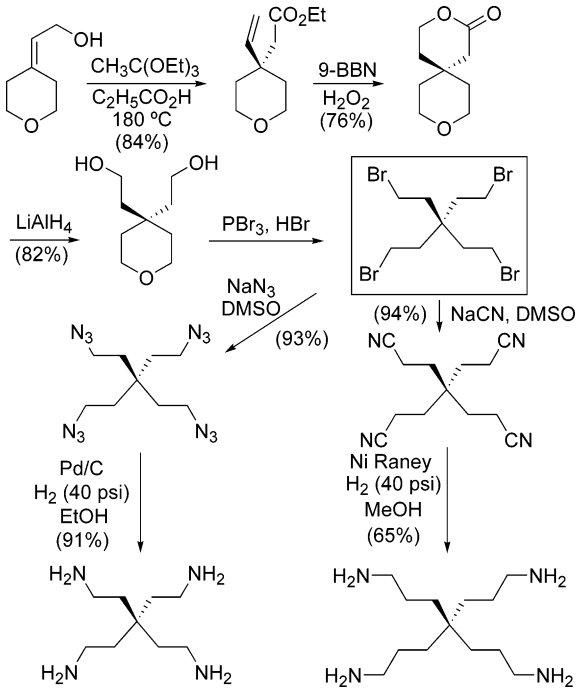
Figure 23.

7.6. Quaternary Carbons

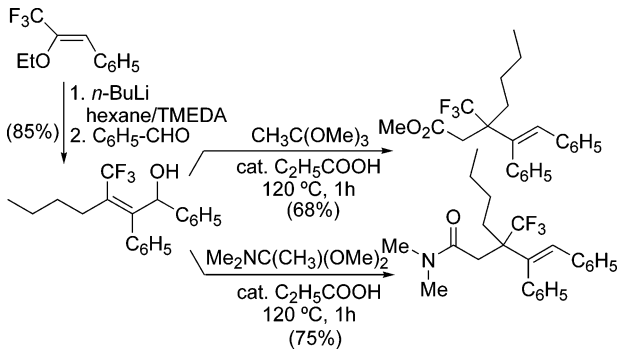
A sequence using a Johnson rearrangement as the first synthetic step was used in the preparation of the central tetrasubstituted core of tetradirectional dendrimeric molecules (Scheme 208).[231]

The preparation of molecules bearing trifluoromethyl-substituted quaternary carbons was also reported using an Eschenmoser or Johnson rearrangement, starting from *γ*-trifluoromethyl *γ*-alkyl allyl alcohols, with the concomitant generation of a double bond in a stereoselective manner.[232] The synthesis of the starting allyl alcohols was reported in two steps from CF_3-substituted enol ethers, as depicted in Scheme 209.

Scheme 208



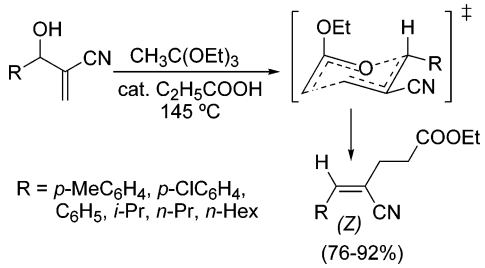
Scheme 209



7.7. Polysubstituted Alkenes

The Johnson rearrangement of 3-hydroxy-2-methylenealkanenitriles, prepared through a Baylis−Hillman reaction, stereoselectively afforded ethyl (*Z*)-4-cyano-4-alkenoates (Scheme 210).[233] The most

Scheme 210

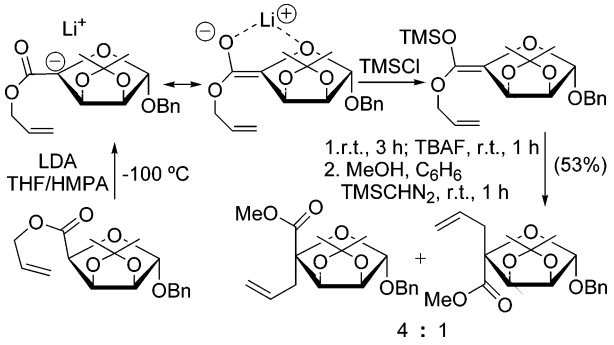


favored chairlike transition state of the rearrangement accounts for the geometry of the resulting trisubstituted alkenes.

7.8. Sugar Derivatives

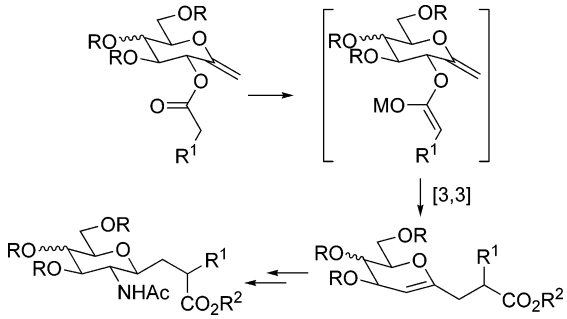
Several research groups have developed different experimental procedures to perform the Claisen rearrangement of allylic ketene acetals derived from furanoside-related uronic acids. However, in all the reported examples, diastereomeric mixtures were obtained and the described conditions were not easily reproduced (Scheme 211).[234]

Scheme 211



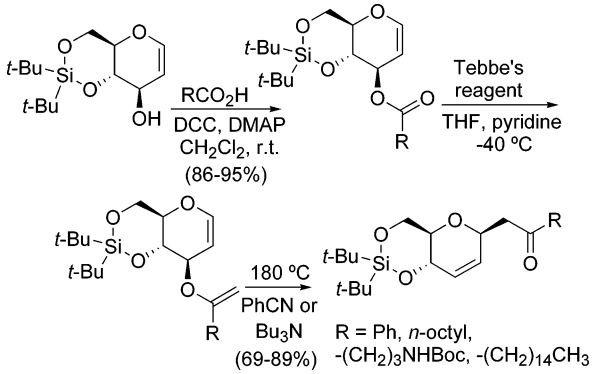
In the past few years several methods for the synthesis of *C*-glycosides using a Claisen or Claisen-related rearrangement as the key step have been reported. Starting from 1-*exo*-methylenemonosaccharides bearing an ester moiety at C-3, glycal intermediates were obtained via an Ireland−Claisen rearrangement. These compounds afforded *β*-*C*-glucosamine and *β*-*C*-galactosamine derivatives by azidonitration of the double bond of the enol ether followed by reduction of both the azido group and the anomeric carbon (Scheme 212).[235]

Scheme 212



β-*C*-Glycosides were also stereoselectively prepared from esters derived from selectively protected 3-hydroxyglycals by Tebbe methylenation followed by a thermal Claisen rearrangement.[236] This created a new C−C bond at the anomeric carbon with complete stereochemical control (Scheme 213).

Scheme 213



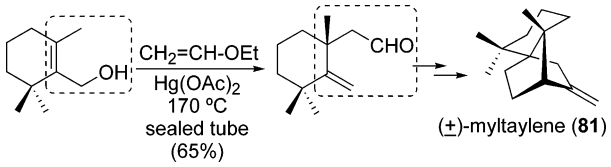
The incorporation of protected amino acids to this sequence can also be considered as a way to *C*-glycosyl amino acids, interesting intermediates in the synthesis of *C*-glycopeptides.

8. Application of Claisen Rearrangement to the Synthesis of Natural Products

This section will deal with the large number of natural products whose syntheses include some step closely related to any of the different [3,3] sigmatropic rearrangements related to the Claisen rearrangement. Several illustrative compounds prepared via some of the above-mentioned rearrangements will be presented.

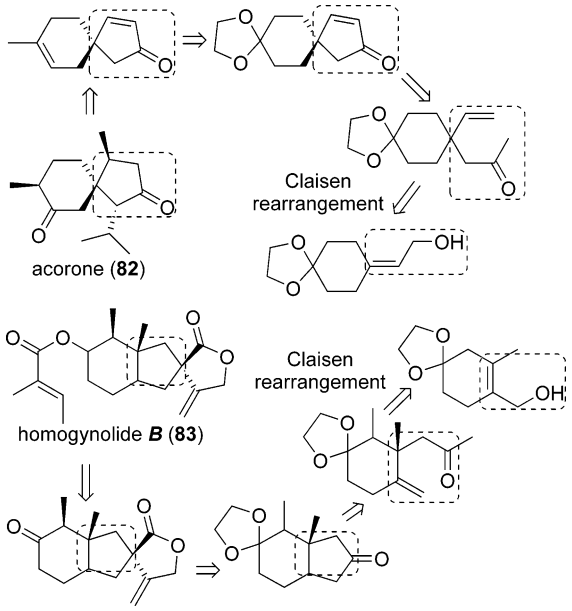
A thermal aliphatic Claisen rearrangement has been used as the key step in the synthesis of sesquiterpenes bearing quaternary carbons starting from suitably substituted allyl alcohols by reaction with alkyl vinyl ethers in the presence of mercuric acetate. Starting from cyclogeraniol, the synthesis of (±)-myltaylene (**81**) was accomplished via Claisen rearrangement (Scheme 214).[237]

Scheme 214



Similarly, this reaction was applied to the preparation of spirocyclic sesquiterpenes such as (±)-acorone (**82**),[238] a compound extracted from the oil of *Acorus calamus*, and (±)-homogynolide B (**83**),[239] which was isolated from *Homogyne alpina* and used for the extermination of beetle larvae. In Scheme 215 are

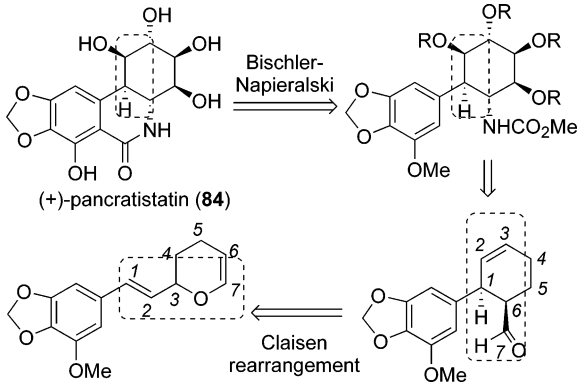
Scheme 215



depicted both shortened retrosynthetic sequences identifying the fragments generated by Claisen rearrangement.

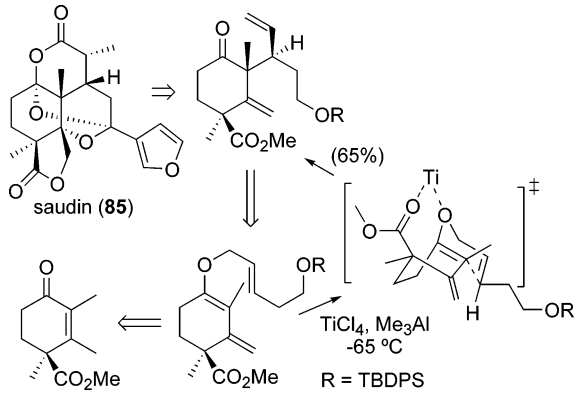
As we have already seen, Claisen rearrangement of 3,4-dihydro-2*H*-pyranylethylenes provides substituted cyclohexenes.[197] This methodology was applied to the total synthesis of (+)-pancratistatin (**84**),[240] an alkaloid with a phenanthridone skeleton exhibiting a tumor growth inhibiting activity. From its retrosynthetic analysis, the synthesis of the intermediate bearing a γ,δ-unsaturated carbonyl moiety was proposed via such a rearrangement (Scheme 216).

Scheme 216



In the presence of a Lewis acid ($TiCl_4/Me_3Al$), a stereoselective Claisen rearrangement furnished the key intermediate in the synthesis of the diterpene saudin (**85**),[241] having potent hypoglycemic activity. The bidentate coordination of Ti(IV) with the oxygens of both the vinyl ether and the ester forced a boat conformation for the cyclohexene ring which underwent rearrangement through a chairlike transition state by axial approach to the less hindered face of the molecule (Scheme 217).

Scheme 217

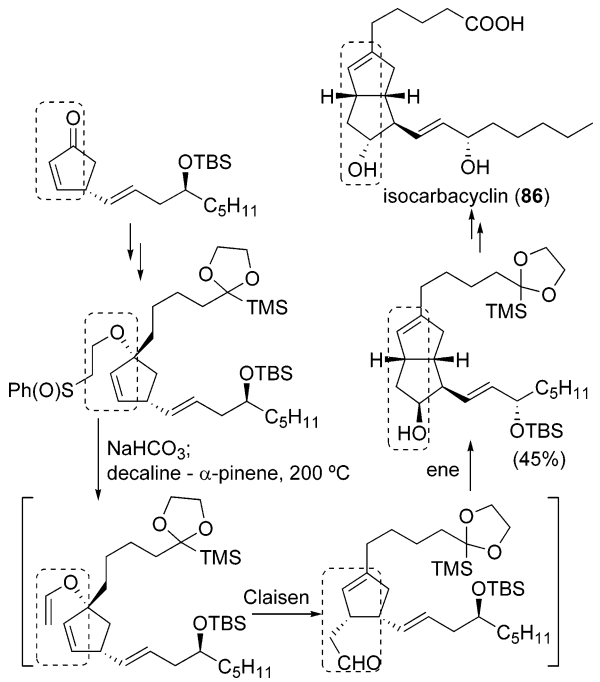


Biologically active compounds were also synthesized by a stereoselective tandem Claisen rearrangement−ene sequence. This was the case of the synthesis of isocarbacyclin (**86**),[242] a structural analogue of prostacyclin used in the treatment of vascular diseases (Scheme 218).

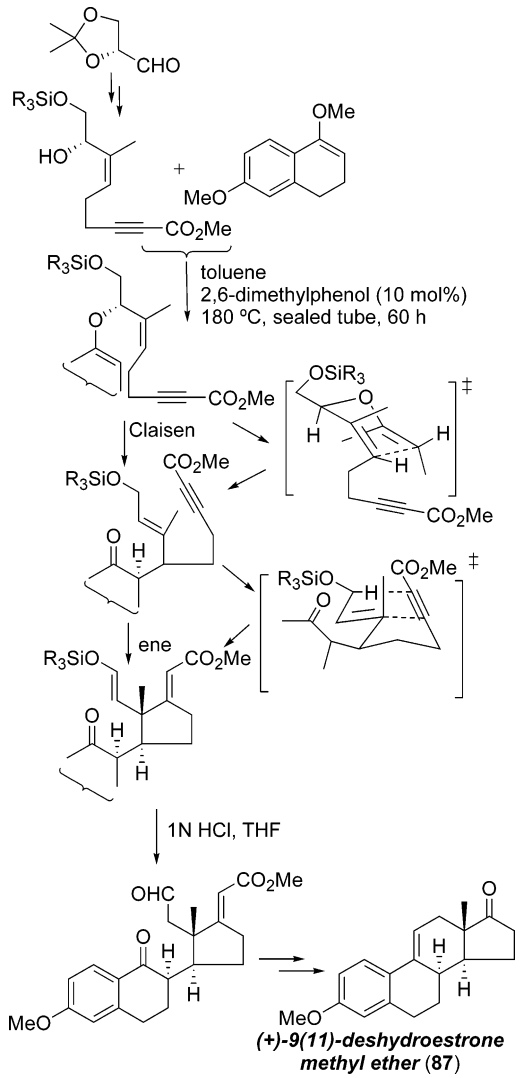
A tandem Claisen−ene sequence also afforded the (+)-9(11)-dehydroestrone methyl ether (**87**), a key intermediate in the synthesis of estrogens. The main steps involved in the sequence are depicted in Scheme 219.[243]

The synthetic potential of the aromatic Claisen rearrangement is represented by the number of total

Scheme 218

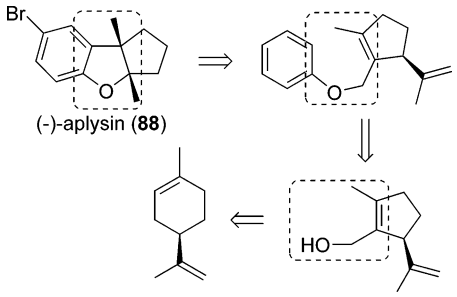


Scheme 219



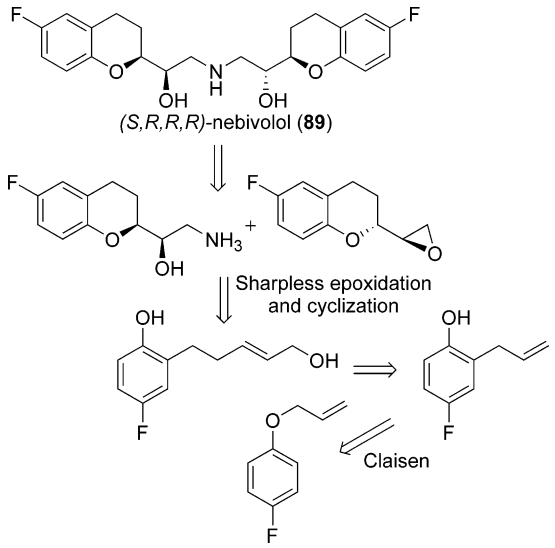
syntheses of natural products which include this reaction in their strategies, those reported in the past few years being of special interest. The enantioselective synthesis of the marine sesquiterpene (−)-aplysin (**88**) began with (*R*)-limonene and used an *ortho* Claisen rearrangement as the key step (Scheme 220).[244]

Scheme 220



The aromatic Claisen rearrangement is also one of the first steps in the enantioselective synthesis of the antihypertensive reagent (*S*,*R*,*R*,*R*)-nebivolol (**89**) (Scheme 221).[245]

Scheme 221



The structures of heliquinomycin (**90**),[246] an isocoumarin acting as a DNA-helicase inhibitor, and tricyclollicinone (**91**),[247] a polycycle used for its ability to enhance the acetylcolinetransferase activity in the treatment of the Alzheimer disease, are depicted in Figure 24. The key step in each synthesis consisted of an aromatic Claisen rearrangement. The high-

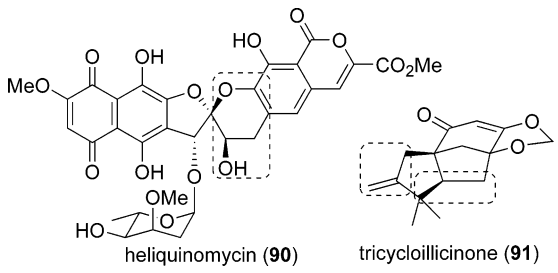
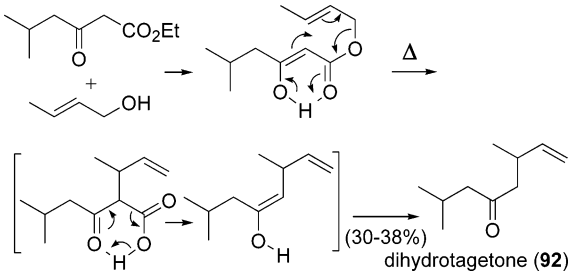


Figure 24.

lighted fragments in the molecules were prepared by this reaction.

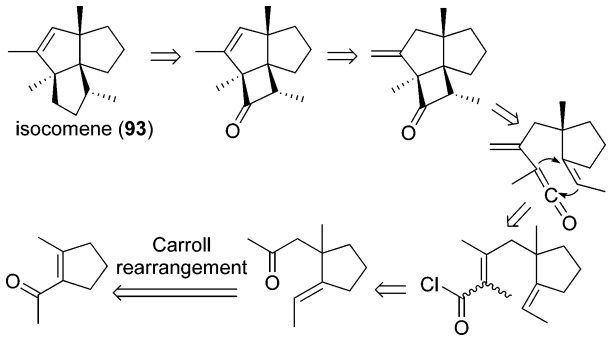
The ready access to γ,δ-unsaturated ketones via a Carroll rearrangement led to the development of the synthesis of acyclic monoterpenes such as dihydrotagetone (**92**) involving this reaction (Scheme 222).[248]

Scheme 222



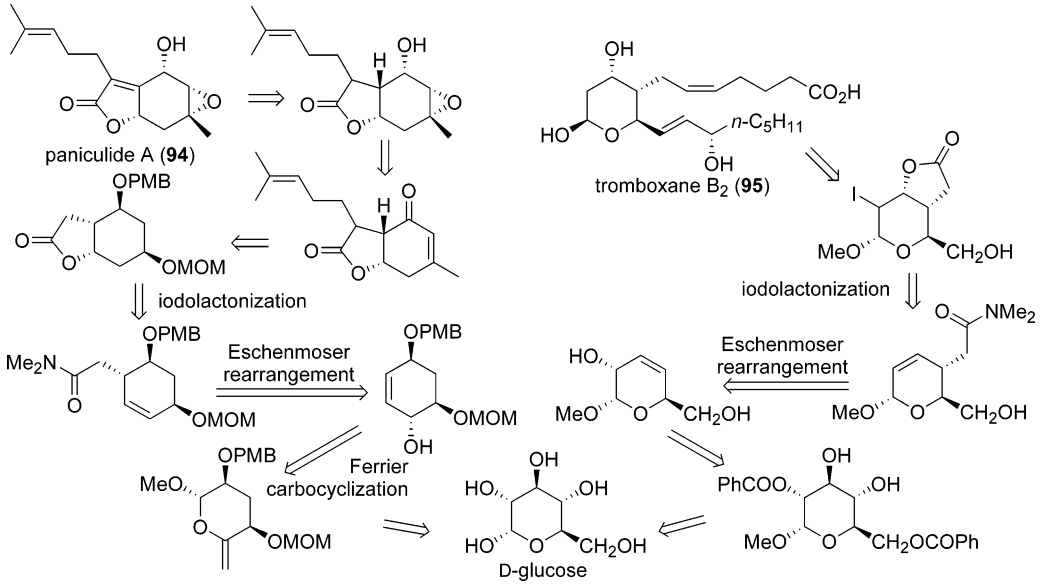
The anionic Carroll rearrangement was also used as the key step in the synthesis of the sesquiterpene isocomene (**93**), in combination with a stereospecific intramolecular cycloaddition of a ketene and an alkene (Scheme 223).[249]

Scheme 223



The amide acetal rearrangement, the Eschenmoser rearrangement, yields γ,δ-unsaturated lactams. This reaction has been applied to the synthesis of the sesquiterpene paniculide A (**94**)[250] and tromboxane B_2 (**95**)[251] starting from D-glucose derivatives (Scheme 224).

Scheme 224



Similarly, the Eschenmoser rearrangement of a D-mannitol-derived C_2-symmetric enediol afforded both enantiomers of a series of paraconic acids (Scheme 225).[252]

In 1976 Stork reported the first total synthesis of the natural prostaglandin PGA_2 (**96**) starting from a simple sugar by using the Johnson ortho ester rearrangement as the key step of the strategy.[253] As seen in Scheme 226, this reaction was used to both generate the trans geometry of the double bond and transfer the chirality from a C−O bond to a distant C−C bond.

A total synthesis based on the Johnson rearrangement was developed for the antitumor agent halomon (**97**), a natural product isolated from the red algae *Portieria hornemanii* with a high cytotoxicity toward a wide range of tumor cells. Thus, the incorporation of a tertiary chlorinated atom into the molecule was achieved from the corresponding chlorinated alkene (Scheme 227).[254]

The presence of several vicinal quaternary carbons in a number of sesquiterpene families has encouraged the development of a synthetic sequence combining a Johnson rearrangement and an intramolecular cyclopropanation to their synthesis. This strategy allowed for completion of the synthesis of the pinguisanes, containing a carbocyclic unit of *cis*-bicyclo-[4.3.0]nonane with two consecutive quaternary carbons and four methyl groups in a relative cis arrangement, and the thapsanes, with a *cis*-1,2,2,6,8,9-hexamethylbicyclo[4.3.0]nonane skeleton incorporating three vicinal quaternary carbons (Figure 25).

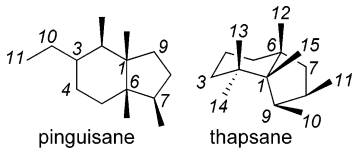
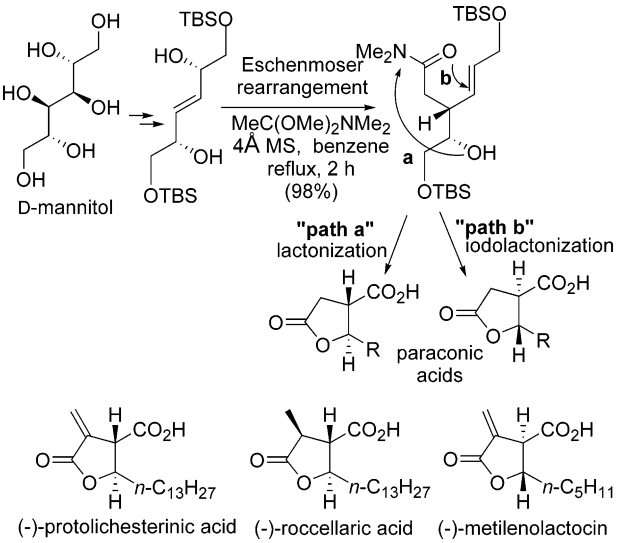


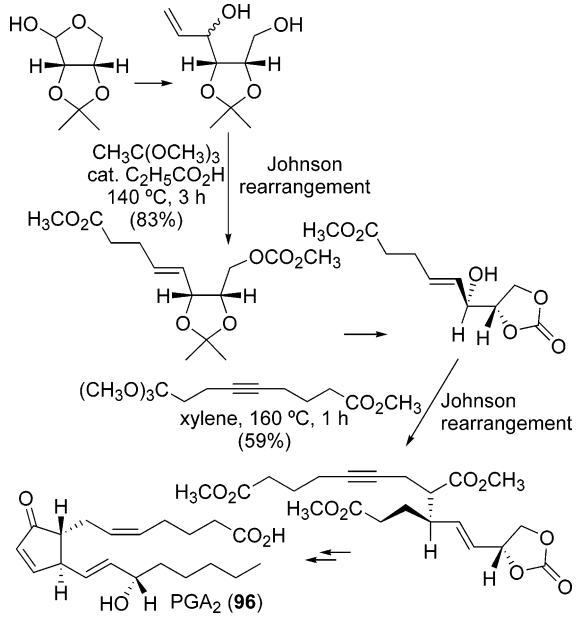
Figure 25.

Thus, (±)-3-methoxythaps-8-ene (**98**),[255] a thapsane bearing an oxygen functionality at C-3 isolated from the root of *Thapsia villosa*, and α-pinguisene (**99**) and

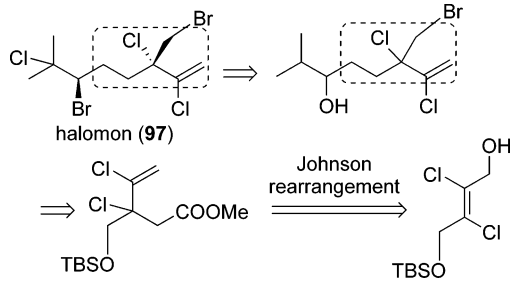
Scheme 225



Scheme 226



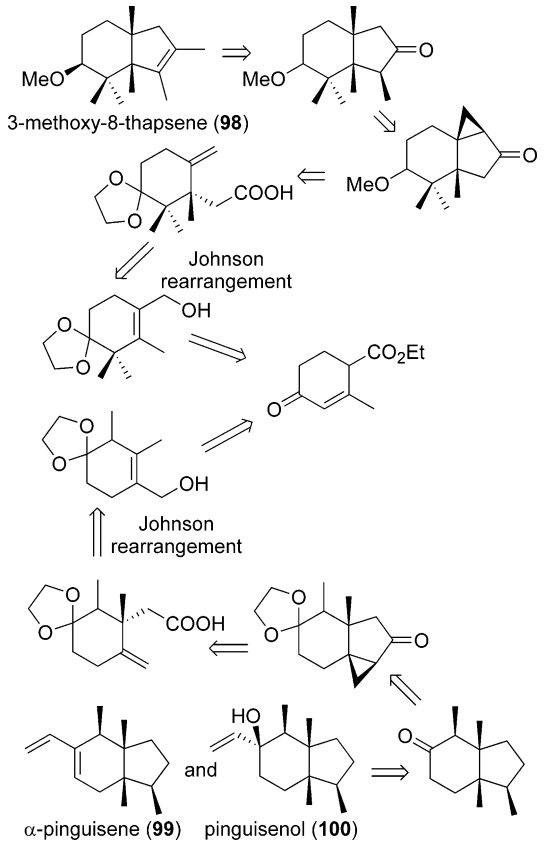
Scheme 227



pinguisenol (**100**),[256] pinguisanes isolated from the hepatic plants *Porella vernicosa* and *Porella elaguntala*, respectively, were constructed employing a Johnson rearrangement/intramolecular cyclopropanation sequence. The main steps of the retrosynthetic analysis of both sesquiterpene families are depicted in Scheme 228.

Another application of the Johnson rearrangement can be found in the total synthesis of the sesquiterpenes AM6898A (**101**) and AM6898D (**102**), inhibitors of the biosynthesis of inmunoglobulin IgE. The preparation of these compounds involved a sequence consisting of a Johnson rearrangement, stereoselective epimerization, and incorporation of an isoprene subunit via umpolung chemistry (Scheme 229).[257] The preparation of AM6898A (**101**) required an additional intramolecular aldol condensation from a common intermediate.

Scheme 228



A number of other natural products have also been synthesized using a Johnson rearrangement. Three examples are depicted in Figure 26 with that portion coming from the rearrangement highlighted.

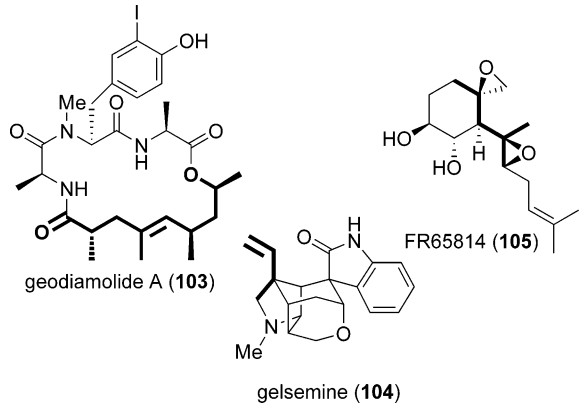
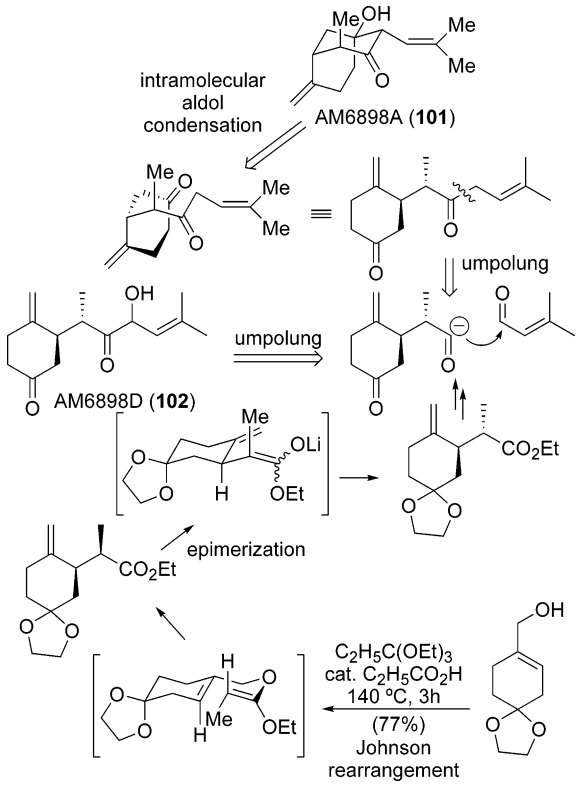


Figure 26.

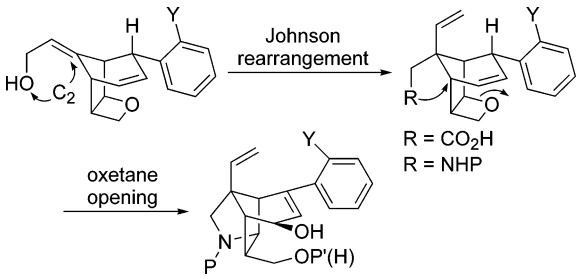
The insecticide cyclodepsipeptide geodiamolide A (**103**), isolated from the sponge *Geodia sp.*, contains a hydroxy acid moiety [(2*S*,6*R*,8*S*)-8-hydroxy-2,4,6-trimethyl-(4*E*)-nonenoic acid] that was introduced via

Scheme 229



orthopropionate sigmatropic rearrangement.[258] In its turn, one of the reported approaches to the synthesis of the alkaloid gelsemine (**104**) was based on an ortho ester−Claisen rearrangement followed by oxetane ring opening in the presence of a Lewis acid (Scheme 230).[259]

Scheme 230



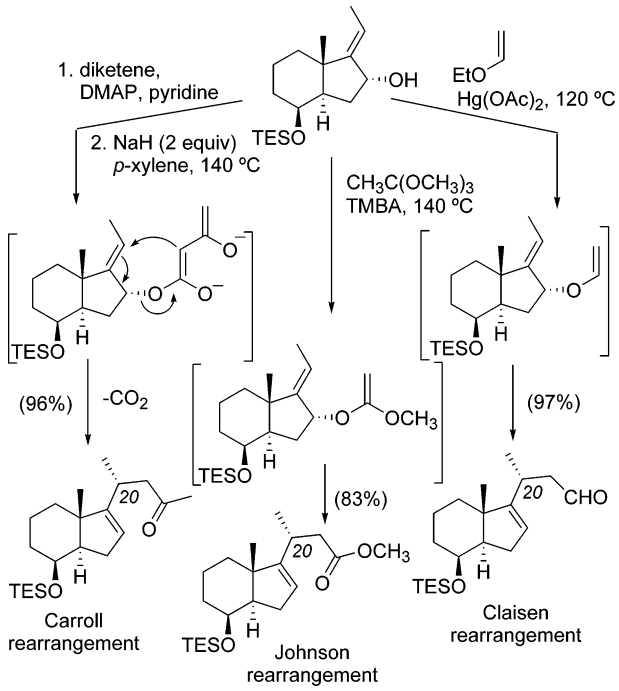
The stereoselective synthesis of the inmunosupressant sesquiterpene FR65814 (**105**), isolated from a *Penicillium jensenii* culture, incorporated the side carbon chain with chirality transfer by a Johnson rearrangement of a cyclohexenol derivative.[260]

Recently, Hatcher and Posner reported efficient, stereocontrolled access to differently functionalized 16-ene vitamin D_3 side-chain units with the natural C-20(*S*) stereochemistry present in analogues of calcitriol. The method was based on Claisen, Johnson, or Carroll rearrangements starting from an enantiomerically pure allylic alcohol (Scheme 231).[261]

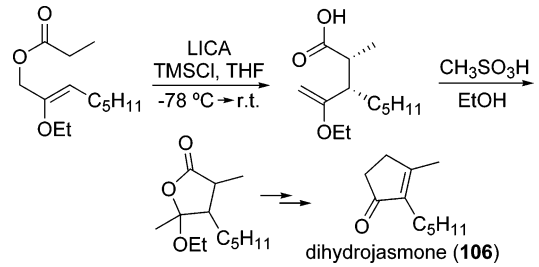
When Ireland and Mueller first described the [3,3] sigmatropic rearrangement of silyl ketene acetals in 1972,[19] this methodology was applied to the synthesis of dihydrojasmone (**106**) (Scheme 232).

Several years before, in 1964, Julia reported the first application of an ester enolate Claisen rearrangement to the synthesis of a natural product in the course of the preparation of (±)-chrysanthemic acid (**107a**) (Scheme 233).[262]

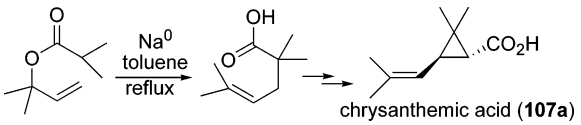
Scheme 231



Scheme 232



Scheme 233

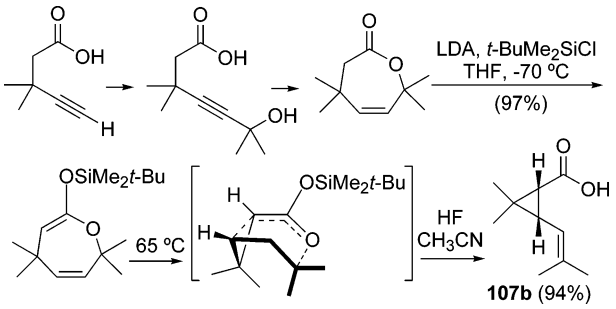


Many applications of the Ireland−Claisen rearrangement in the preparation of natural products have appeared in the literature. Diverse remarkable examples will be considered. Several decades after the first reported applications, the stereoselective synthesis of the unnatural *cis*-chrysanthemic acid (**107b**) was described via an Ireland−Claisen rearrangement of a silyl ketene acetal through a boatlike transition state (Scheme 234).[263]

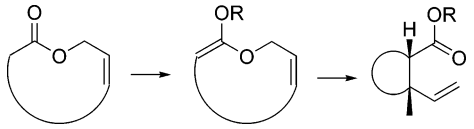
This transformation represents an application of the methodology known as "alicyclic Claisen rearrangement", which means the stereospecific formation of *cis*-2-alkenylcycloalkanecarboxylic acids by Claisen rearrangements through ring contraction of macrocyclic ketene acetals (Scheme 235).[264]

The same type of transformation was successfully applied to the preparation of bridged bicycloalkanes

Scheme 234

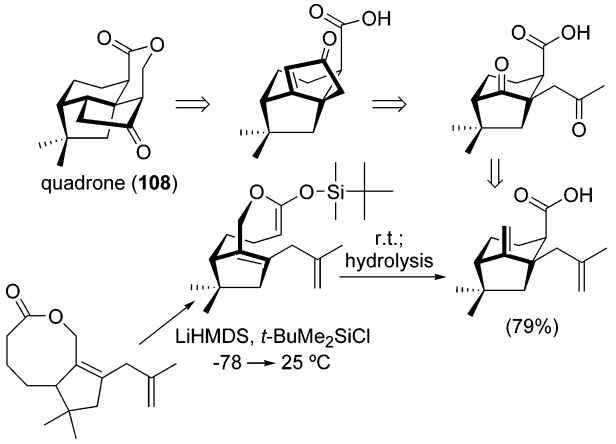


Scheme 235



within the context of the synthesis of (±)-quadrone (**108**) (Scheme 236).[265]

Scheme 236



A synthetic strategy coupling an aldol condensation and an Ireland−Claisen rearrangement of ester enolates was applied to the preparation of (±)-ebelactone A (**109**),[266] an enzymatic inhibitor capable of enhancing the mammalian inmunological response. Aldol condensations were used to control the stereochemistry at C-2, C-3, C-8, C-10, and C-11, whereas the configuration of the stereocenter at C-4 and the *E* geometry of the double bond resulted from an Ireland−Claisen rearrangement (Scheme 237).

Some of the numerous natural products whose carbon skeletons were synthesized using an Ireland−Claisen rearrangement as the key step are depicted in Figure 27. Myxalamide A (**110**), a polyenic antibiotic isolated from *Myxococcus xanthus*, contains three stereogenic carbons in a relative 1,2,5-arrangement. Its synthesis was carried out using a sequence consisting of a stereocontrolled aldol reaction from an α,β-unsaturated β-alkylthio aldehyde followed by an Ireland−Claisen rearrangement and then an Evans−Mislow rearrangement of an allylic sulfoxide.[267] In the synthesis of aspidophitine (**111**), an alkaloid with insecticidal properties, the Ireland−Claisen rearrangement produced one of the quaternary chiral carbons contained in the molecule.[268] The applicability of the ester enolate rearrangement was

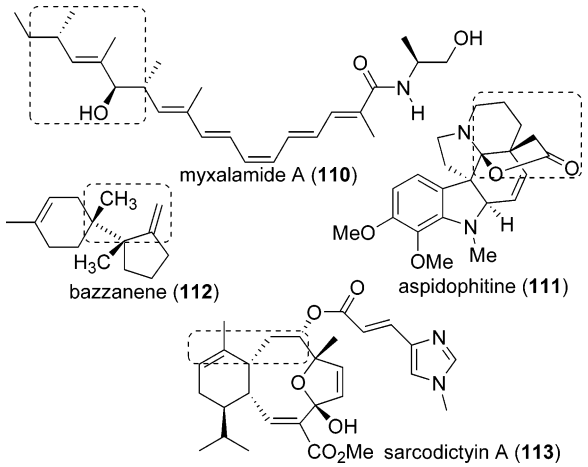
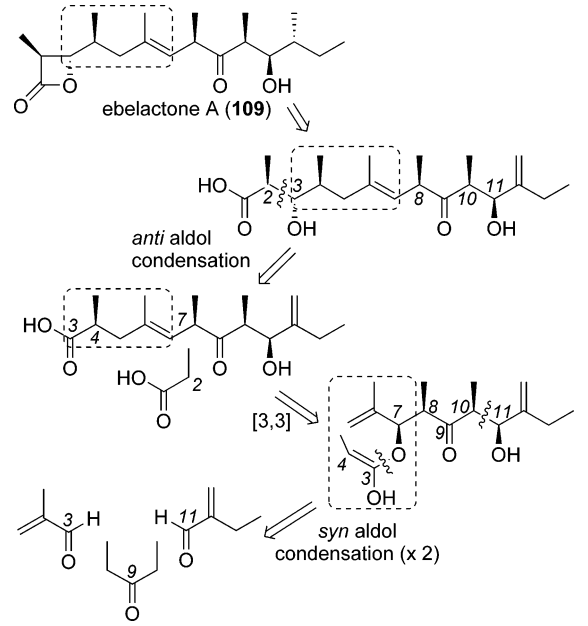


Figure 27.

Scheme 237



also demonstrated by the reaction which generated the two vicinal quaternary carbons in the skeleton of the fungal metabolite bazzanene (**112**),[269] which possesses insecticidal, antifungal, and cytotoxic activity. Similarly, an Ireland−Claisen rearrangement was involved in the creation of the carbon skeleton of the marine diterpenoid sarcodictyine A (**113**).[270]

Ireland applied his methodology to the development of synthetic strategies affording a number of natural products, such as tirandamycic acid (**114**)[271] and streptocolic acid (**115**),[272] antibiotics exhibiting the structure of 3-acyltetramic acid intermediates in the syntheses of tirandimycine and streptolidigine, respectively (Figure 28). Their syntheses involved the use of D-(+)-glucose as the absolute stereochemistry source as well as a chirality transfer via the ester enolate Ireland−Claisen rearrangement.

The Ireland−Claisen rearrangement was also used in the synthesis of polyether ionophore antibiotics to assemble tetrahydropyran and tetrahydrofuran rings. This approach is an intramolecular reaction that proceeds with a high stereocontrol in the formation of the C−C bond, after both fragments have been

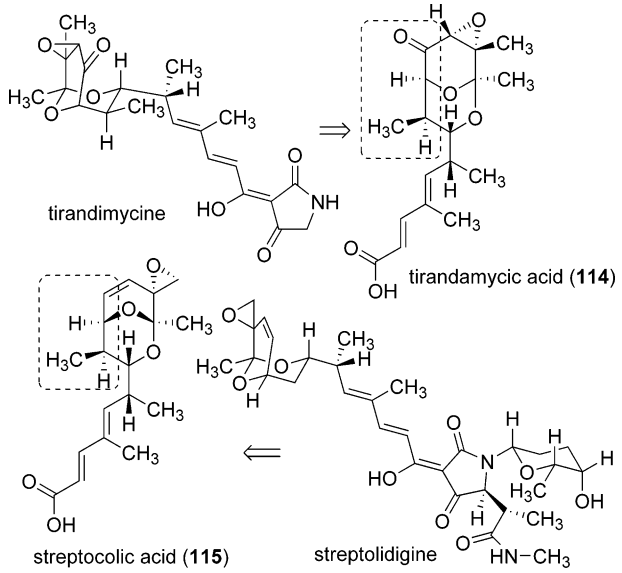
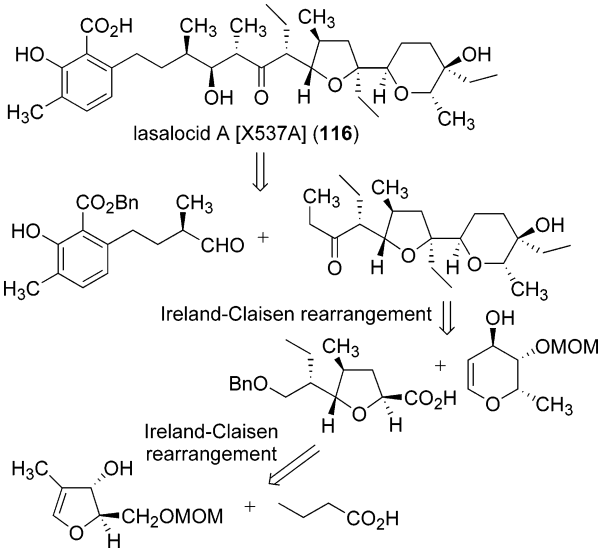


Figure 28.

joined in an intermolecular esterification. This strategy was used for the synthesis of the antibiotic lasalocid A (X537A) (116),[273] whose retrosynthetic analysis is shown in Scheme 238.

Scheme 238



A similar synthetic plan was applied to the synthesis of the antibiotics monensine (**117**)[274] and carbamonensine (**118**),[275] whose spiranic moieties were also prepared using an Ireland−Claisen rearrangement as one of the key steps (Figure 29).

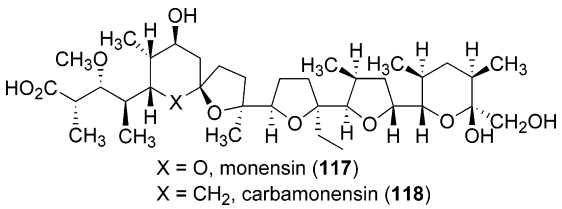
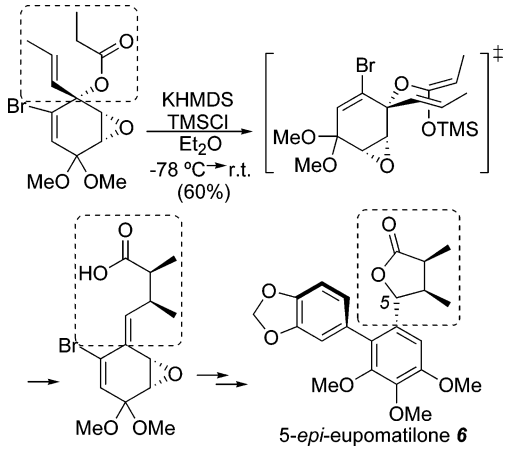


Figure 29.

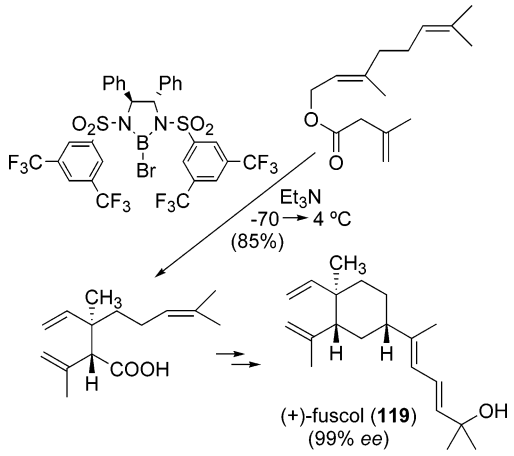
Recently, a regioselective intramolecular Ireland−Claisen rearrangement of a highly functionalized bisallylic ester was reported as the key step in the synthetic sequence affording compounds belonging to the eupomatilone family (Scheme 239).[276]

Scheme 239



The complete enantioselectivity detected in an Ireland−Claisen rearrangement in the presence of a chiral boron catalyst afforded the preparation of the antiinflammatory agent (+)-fuscol (**119**)[277] as depicted in Scheme 240.

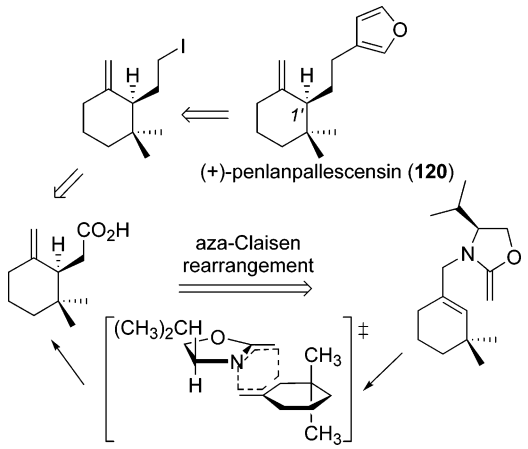
Scheme 240



Some reported examples also evidence the applicability of the aza−Claisen rearrangement to the synthesis of biologically active natural products. The above-described methodology on the use of *N*-allylketene *N*,*O*-acetals as chiral auxiliaries of the aza−Claisen rearrangement[139] was used in the stereoselective synthesis of the sesquiterpene (+)-penlanpallescensin (**120**), where the chiral auxiliary was able to control the formation of the *S* configuration at C-1′ as a consequence of the anti facial selectivity of the *N*,*O*-acetal approach to the less hindered face through a chairlike transition state (Scheme 241).[278]

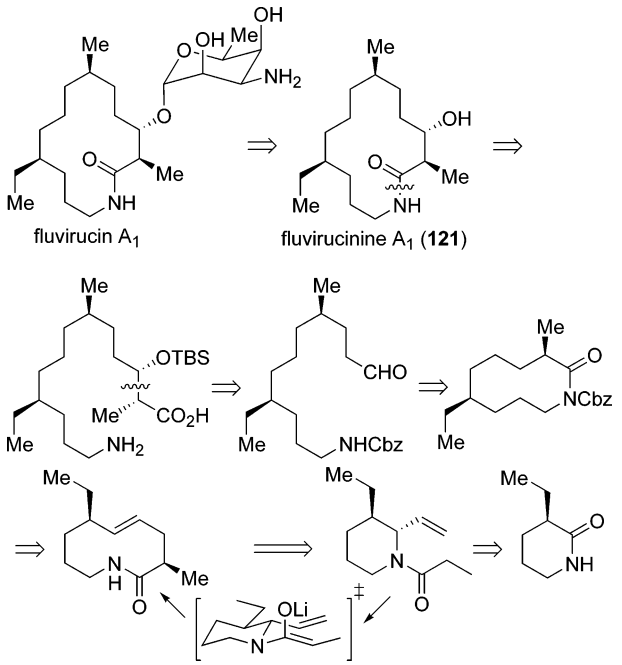
An aza−Claisen rearrangement induced by an amide enolate generated one of the stereocenters existing in the molecule fluvirucinine A_1 (**121**), the aglycon of the macrolactamic antibiotic fluvirucin A_1. This stereoselectivity was rationalized by assuming a chairlike transition state for the rearrangement from the chair conformation of the cyclic amine bearing the substituent in an equatorial arrangement

Scheme 241



as well as the preferred formation of the amide *Z* enolate (Scheme 242).[279]

Scheme 242



The stereoselective aza−Claisen rearrangement induced by an amide enolate was also described as the key step in the preparation of (−)-antimycin A_{3b} (**122**),[280] the enantiomer of the natural antibiotic antimycin A_{3b}, which is used as an inhibitor of the oxidoreductase electronic transfer in the ubiquinol−cytochrome *c* system. The application of this reaction to the synthesis of **122** is shown in Scheme 243.

A strategy involving zwitterionic aza−Claisen rearrangement and Wenkert cyclization[281] was developed for the synthesis of indole alkaloids bearing the yohimbane pentacyclic skeleton (Scheme 244).[282]

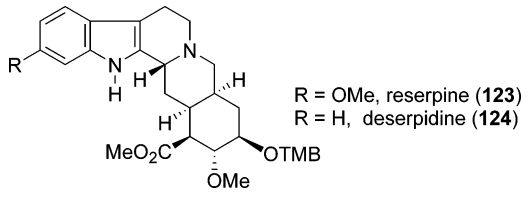
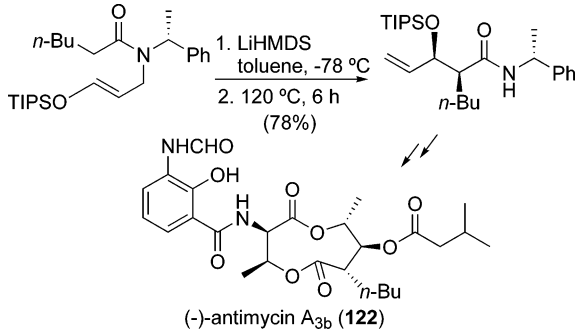
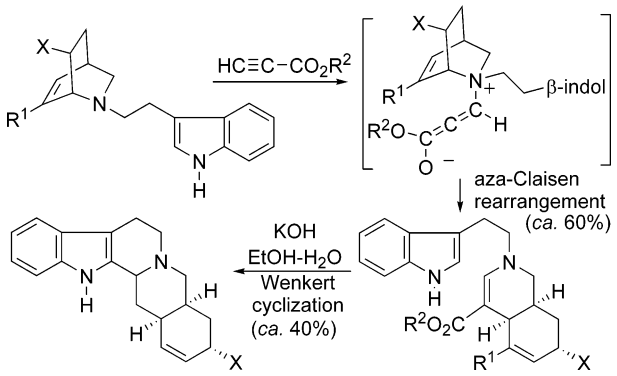


Figure 30.

Scheme 243



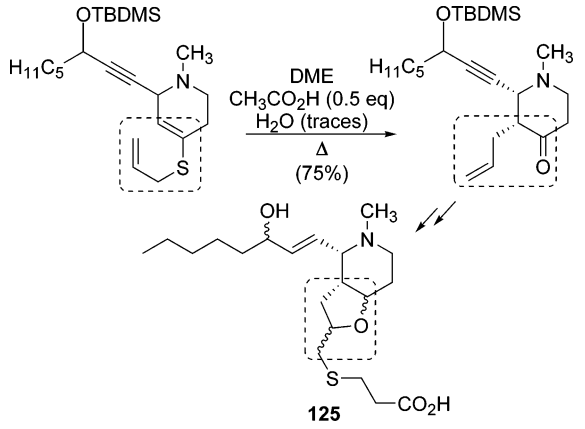
Scheme 244



This methodology afforded alkaloids such as reserpine (**123**) and deserpidine (**124**) (Figure 30).[282b]

A thio−Claisen rearrangement was successfully used for the synthesis of azaprostacyclins (**125**),[283] structural analogues of prostacyclin PGI_1, where the hydroxy-substituted cyclopentane ring was replaced by a piperidine ring. The axial arrangement of the acetylenic chain in the rearrangement product was attributed to a stabilizing anomeric effect (Scheme 245).

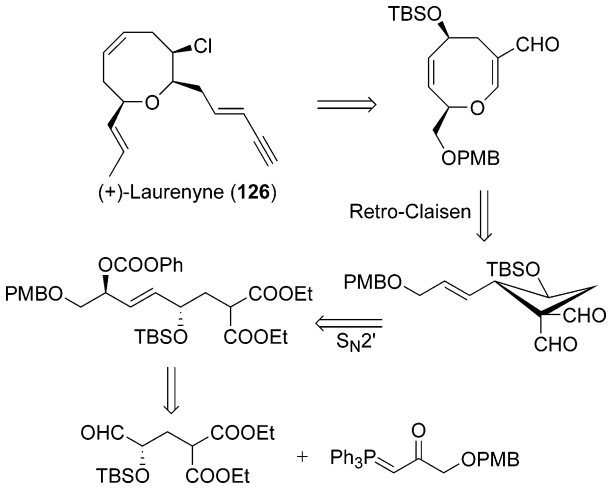
Scheme 245



Retro-Claisen rearrangement has also been used for the synthesis of natural products. A combination of S_N2' cyclization and retro-Claisen rearrangement was nicely applied as the key steps in the first total synthesis of the marine metabolite (+)-laurenyne

(**126**).[284] In this sequence the retro-Claisen reaction allowed the construction of the oxocene ring existing in the target molecule (Scheme 246).

Scheme 246



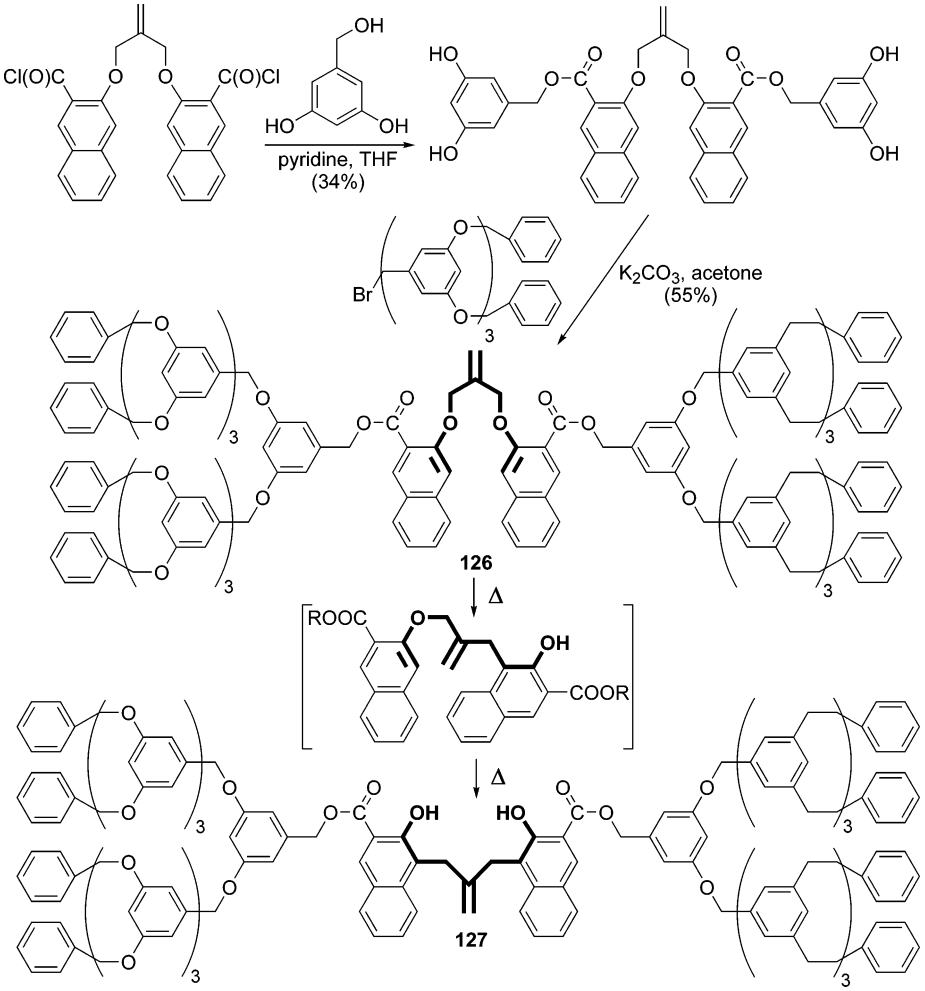
9. Other Applications

In the past few years the theoretical and applied interest for dendrimeric structures has considerably increased. The light-collecting role played by dendrimers led to the possibility of creating systems acting as photosynthetic biomimetics. In this sense, the control of the fluorescence emission by these molecules would provide new perspectives. Following this research, recently polybenzyl ether dendrimers containing a central core bearing an isobutenyl group and two naphthylformate units were synthesized.[285] These dendrimers exhibited fluorescence derived from both the core (ca. 400 nm) and their peripheral structure (308 nm). As shown in Scheme 247, dendrimer **127** has the suitable skeleton to undergo a tandem sequence involving two successive Claisen rearrangements. In the product **127** resulting from the double thermal rearrangement of **126,** the fluorescence at 400 nm was completely switched off whereas the fluorescence emission at 308 nm derived from the dendritic periphery was still on. This result points out that high-generation dendrimers may produce thermally induced high-contrast fluorescent images if their structures contain reactive groups able to act as molecular switchers.

10. Conclusion

It can be concluded that the understanding and applications of the Claisen and Claisen-related rearrangements have considerably advanced over the past nine decades. These reactions offer an enormous potential facing the 21st century as a tool for the chemist both from a synthetic point of view and in the field of materials science. The increasing number

Scheme 247



of papers on the reaction appearing in the literature clearly demonstrate its widespread utility.

11. Acknowledgments

Financial support from the Spanish *Dirección de Investigación Científica y Técnica* CAICYT (BQU-2000-0246) is gratefully acknowledged. The author thanks Professor José Luis García Ruano for valuable help and discussions during the elaboration of this manuscript and Carlos Alemparte for his constructive comments. I am also highly indebted to (the late) Professor Jesús H. Rodríguez Ramos for introducing me to sigmatropic rearrangements some years ago. I thank the following publishers for their permission to reproduce figures or data for which they hold the copyright: Elsevier Science B.V. (Table 2 and Figures 12 and 19) and Wiley-VCH (Figures 20 and 21). Thanks are also due to the referees for their careful reading of the manuscript.

12. References

(1) Claisen, L. *Chem. Ber.* **1912**, *45*, 3157.
(2) (a) Bennett, G. B. *Synthesis* **1977**, 589. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (c) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. (d) Hill, R. K. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, pp 503−572. (e) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (f) Blechert, S. *Synthesis* **1989**, 71. (g) Wipf, P. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, pp 827−873. (h) Tadano, K. *Studies in Natural Products Chemistry*; Rahman, A.-U., Ed.; Elsevier: Amsterdam, 1992; pp 405−455. (i) Pereira, S.; Srebnik, M. *Aldrichimica Acta* **1993**, *26*, 17. (j) Frauenrath, H. *Stereoselective Synthesis*; Helchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme: Stuttgart, 1995; Vol. E21d, pp 3301−3756. (k) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847. (l) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43. (m) Chai, Y.; Hong, S.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905. (n) When the revision of the present review was under way, another review appeared in the literature, see: Nubbemeyer, U. *Synthesis* **2003**, 961.
(3) Trost, B. M. *Science* **1983**, *219*, 245.
(4) Claisen, L. *Justus Liebigs Ann. Chem.* **1918**, *418*, 69.
(5) (a) Bergmann, E.; Corte, H. *J. Chem. Soc.* **1935**, 1363. (b) Lauer, W. M.; Kilburn, E. I. *J. Am. Chem. Soc.* **1937**, *59*, 2586.
(6) Hurd, C. D.; Pollack, M. A. *J. Am. Chem. Soc.* **1938**, *60*, 1905.
(7) Burgstahler, A. W.; Nordin, I. C. *J. Am. Chem. Soc.* **1961**, *83*, 198.
(8) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 1. (b) Ryan, J. P.; O'Connor, P. R. *J. Am. Chem. Soc.* **1952**, *74*, 5866.
(9) (a) Carroll, M. F. *J. Chem. Soc.* **1940**, 704. (b) Carroll, M. F. *J. Chem. Soc.* **1940**, 1266. (c) Carroll, M. F. *J. Chem. Soc.* **1941**, 507.
(10) Kimel, W.; Cope, A. C. *J. Am. Chem. Soc.* **1943**, *65*, 1992.
(11) Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722.
(12) (a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425. (b) Wick, A. E.; Felix, D.; Gschwend-Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.
(13) Meerwein, H.; Florian, W.; Schön, N.; Stopp, G. *Justus Liebigs Ann. Chem.* **1961**, *641*, 1.
(14) (a) Welsh, J. T.; Eswarakrishnan, S. *J. Org. Chem.* **1985**, *50*, 5909. (b) Welsh, J. T.; Eswarakrishnan, S. *J. Am. Chem. Soc.* **1987**, *109*, 6716.
(15) Coates, B.; Montgomery, D.; Stevenson, P. J. *Tetrahedron Lett.* **1991**, *32*, 4199.
(16) (a) Ficini, J.; Barbara, C. *Tetrahedron Lett.* **1966**, 6425. (b) Ficini, J. *Tetrahedron* **1976**, *32*, 1449. (c) Bartlett, P. A.; Hahne, W. F. *J. Org. Chem.* **1979**, *44*, 882.
(17) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brockson, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
(18) Daub, G. W.; Teramura, D. H.; Bryant, K. E.; Burch, M. T. *J. Org. Chem.* **1981**, *46*, 1485.
(19) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(20) Ritter, K. *Tetrahedron Lett.* **1990**, *31*, 869.
(21) Baldwin, J. E.; Walker, J. A. *J. Chem. Soc., Chem. Commun.* **1973**, 117.
(22) Greuter, H.; Lang, R. W.; Romann, A. J. *Tetrahedron Lett.* **1988**, *29*, 3291.
(23) Kwart, H.; Hackett, C. M. *J. Am. Chem. Soc.* **1962**, *84*, 1754.
(24) Kwart, H.; Schwartz, J. L. *J. Org. Chem.* **1974**, *39*, 1575.
(25) Takahashi, H.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 5803.
(26) Oshima, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2693.
(27) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978.
(28) Kazmaier, U. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 998.
(29) Ponaras, A. A. *Tetrahedron Lett.* **1980**, *21*, 4803.
(30) (a) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 1039. (b) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 1043. (c) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 4427. (d) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, *27*, 4431. (e) Normant, J. F.; Quirion, J. Ch.; Alexakis, A.; Masuda, Y. *Tetrahedron Lett.* **1989**, *30*, 3955. (f) Normant, J. F.; Quirion, J. Ch. *Tetrahedron Lett.* **1989**, *30*, 3959.
(31) Hirai, A.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 11791.
(32) Boeckman, R. K., Jr.; Flann, C. J.; Poss, K. M. *J. Am. Chem. Soc.* **1985**, *107*, 4359.
(33) (a) Rhoads, S. J.; Cockroft, R. D. *J. Am. Chem. Soc.* **1969**, *91*, 2815. (b) Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1965**, *48*, 1985.
(34) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.
(35) Evans, M. G. *Trans. Faraday Soc.* **1939**, *35*, 824.
(36) Dewar, M. J. S. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 761.
(37) (a) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 67. (b) Frater, G.; Habich, A.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1969**, *52*, 335.
(38) (a) Dewar, M. J. S.; Healy, E. F. *J. Am. Chem. Soc.* **1984**, *106*, 7127. (b) Vance, R. L.; Rondan, N. G.; Houk, K. N.; Jensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314. (c) Khaledy, M. M.; Kalani, M. Y. S.; Khuong, K. S.; Houk, K. N.; Aviyente, V.; Neier, R.; Soldermann, N.; Velker, J. *J. Org. Chem.* **2003**, *68*, 572.
(39) Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 10336.
(40) Dewar, M. J. S.; Jie, C. *J. Am. Chem. Soc.* **1989**, *111*, 511.
(41) Davidson, M. M.; Hillier, I. H.; Vincent, M. A. *Chem. Phys. Lett.* **1995**, *246*, 536.
(42) Meyer, M. P.; DelMonte, A. J.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 10865.
(43) (a) McMichael, K. D.; Korver, G. L. *J. Am. Chem. Soc.* **1979**, *101*, 2746. (b) Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 2747.
(44) Schuler, F. W.; Murphy, G. W. *J. Am. Chem. Soc.* **1950**, *72*, 3155.
(45) (a) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983. (b) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6984.
(46) Gajewski, J. J.; Gee, K. R.; Jurayj, J. *J. Org. Chem.* **1990**, *55*, 1813.
(47) Cooper, J. A.; Olivares, C. M.; Sandford, G. *J. Org. Chem.* **2001**, *66*, 4887.
(48) Gajewski, J. J.; Gilbert, K. E. *J. Org. Chem.* **1984**, *49*, 11.
(49) Aviyente, V.; Houk, K. N. *J. Phys. Chem. A* **2001**, *105*, 383.
(50) Curran, D. P.; Suh, Y.-G. *J. Am. Chem. Soc.* **1984**, *106*, 5002.
(51) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160.
(52) Gajewski, J. J.; Emrani, J. *J. Am. Chem. Soc.* **1984**, *106*, 5733.
(53) Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636.
(54) Schmid, H. *Helv. Chim. Acta* **1957**, *20*, 13.
(55) Tarbell, D. S.; Wilson, J. W. *J. Am. Chem. Soc.* **1940**, *62*, 607.
(56) Kincaid, J. F.; Tarbell, D. S. *J. Am. Chem. Soc.* **1939**, *61*, 3085.
(57) Hurd, C. D.; Pollack, M. A. *J. Org. Chem.* **1939**, *3*, 550.
(58) White, W. N.; Gwynn, D.; Schlitt, R.; Girard, C.; Fife, W. *J. Am. Chem. Soc.* **1958**, *80*, 3271.
(59) (a) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972. (b) Denmark, S. E.; Harmata, M. A. *Tetrahedron Lett.* **1984**, *25*, 1543. (c) Denmark, S. E.; Harmata, M. A.; White, K. S. *J. Am. Chem. Soc.* **1989**, *111*, 8878.
(60) Ponaras, A. A. *J. Org. Chem.* **1983**, *48*, 3866.
(61) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572.
(62) Kirchner, J. J.; Pratt, D. V.; Hopkins, P. B. *Tetrahedron Lett.* **1988**, *29*, 4229.
(63) Laabs, S.; Scherrmann, A.; Sudau, A.; Diederich, M.; Kierig, C.; Nubbemeyer, U. *Synlett* **1999**, 25.
(64) (a) Malherbe, R.; Belluš, D. *Helv. Chim. Acta* **1978**, *61*, 3096. (b) Malherbe, R.; Rist, G.; Belluš, D. *J. Org. Chem.* **1983**, *48*, 860. (c) Nubbemeyer, U.; Oehrlein, R.; Gonda, J.; Ernst, B.; Belluš, D. *Angew. Chem., Int. Ed.* **1991**, *30*, 1465. (d) Ernst, B.; Gonda, J.; Jeschke, R.; Nubbemeyer, U.; Oehrlein, R.; Belluš, D. *Helv. Chim. Acta* **1997**, *80*, 876.
(65) (a) Enholm, E. J.; Moran, K. M.; Whitley, P. E.; Battiste, M. A. *J. Am. Chem. Soc.* **1998**, *120*, 3807. (b) Curran, D. P.; Nishii, Y. *J. Am. Chem. Soc.* **1999**, *121*, 8955.
(66) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205.

(67) Borgulya, J.; Madeja, R.; Fahrni, P.; Hansen, H.-J.; Schmid, H.; Barner, R. *Helv. Chim. Acta* **1973**, *56*, 14.
(68) Kozikowski, A. L.; Sugiyama, K.; Huie, E. *Tetrahedron Lett.* **1981**, *22*, 3381.
(69) Sonnenberg, F. M. *J. Org. Chem.* **1970**, *35*, 3166.
(70) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 3985.
(71) Maruoka, K.; Banno, H.; Nonoshita, K.; Yamamoto, H. *Tetrahedron Lett.* **1989**, *30*, 1265.
(72) Paquette, L. A.; Friedrich, D.; Rogers, R. D. *J. Org. Chem.* **1991**, *56*, 3841.
(73) Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225.
(74) Overman, L. E. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579.
(75) Baan, J. L.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, *27*, 6267.
(76) Hiersemann, M. *Synlett* **1999**, 1823.
(77) Watson, D. J.; Devine, P. N.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 1363.
(78) Sharma, G. V. M.; Ilangovan, A.; Sreenivas, P.; Mahalingam, A. K. *Synlett* **2000**, 615.
(79) Gester, S.; Metz, P.; Zieran, O.; Vollmer, G. *Tetrahedron* **2001**, *57*, 1015.
(80) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 9726.
(81) Koch, G.; Janser, P.; Kottirsch, G.; Romero-Giron, E. *Tetrahedron Lett.* **2002**, *43*, 4837.
(82) Wood, J. L.; Moniz, G. A.; Pflum, D. A.; Stoltz, B. M.; Holubec, A. A.; Dietrich, H.-J. *J. Am. Chem. Soc.* **1999**, *121*, 1748.
(83) Lambert, T. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 13646.
(84) Sharghi, H.; Aghapour, G. *J. Org. Chem.* **2000**, *65*, 2813.
(85) Widmer, U.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1973**, *56*, 2644.
(86) Chen, Y.; Huesmann, P. L.; Mariano, P. S. *Tetrahedron Lett.* **1983**, *24*, 1021.
(87) (a) Kwart, H.; Schwartz, J. L. *J. Org. Chem. Soc.* **1974**, *39*, 1575. (b) Kwart, H.; Miles, W. H.; Horgan, A. G.; Kwart, L. D. *J. Am. Chem. Soc.* **1981**, *103*, 1757.
(88) Swiss, K. A.; Firestone, R. A. *J. Org. Chem.* **1999**, *64*, 2158.
(89) Swiss, K. A.; Firestone, R. A. *J. Phys. Chem. A* **2000**, *104*, 3057.
(90) (a) Brower, K. R. *J. Am. Chem. Soc.* **1961**, *83*, 4370. (b) Walling, C.; Naiman, M. *J. Am. Chem. Soc.* **1962**, *84*, 2628.
(91) White, W. N.; Wolfarth, E. F. *J. Org. Chem.* **1970**, *35*, 3585.
(92) Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515.
(93) Grieco, P. A.; Brandes, E. B.; McCann, S.; Clark, J. D. *J. Org. Chem.* **1989**, *54*, 5849.
(94) Hu, H.; Kobrak, M. N.; Xu, C.; Hammes-Schiffer, S. *J. Phys. Chem. A* **2000**, *104*, 8058.
(95) Gignere, R. J.; Bray, T. L.; Duncan, S. M.; Majetich, G. *Tetrahedron Lett.* **1986**, *27*, 4945.
(96) Daskiewicz, J.-B.; Bayet, C.; Barron, D. *Tetrahedron Lett.* **2001**, *42*, 7241.
(97) Kotha, S.; Sreenivasachary, N.; Brahmachary, E. *Tetrahedron* **2001**, *57*, 6261.
(98) Durand-Reville, T.; Gobbi, L. B.; Gray, B. L.; Ley, S. V.; Scott, J. S. *Org. Lett.* **2002**, *4*, 3847.
(99) Madden, D.; Krchnak, V.; Lebl, M. *Perspectives Drug Discov. Des.* **1995**, *51*, 8135.
(100) Sampath Kumar, H. M.; Anjaneyulu, S.; Subba Reddy, B. V.; Yadav, J. S. *Synlett* **2000**, 1129.
(101) Hu, Y.; Porco, J. A., Jr. *Tetrahedron Lett.* **1999**, *40*, 3289.
(102) Pogrebnoi, S. I.; Kalyan, Y. B.; Krimer, M. Z.; Smit, W. A. *Tetrahedron Lett.* **1987**, *28*, 4893.
(103) Andrews, P. R.; Smith, G. D.; Young, I. G. *Biochemistry* **1973**, *12*, 3492.
(104) (a) Grimshaw, C. E.; Sogo, S. G.; Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 2699. (b) Asano, Y.; Lee, J. J.; Shieh, T. L.; Spreafico, F.; Kowal, C.; Floss, H. G. *J. Am. Chem. Soc.* **1985**, *107*, 4314. (c) Addadi, L.; Jaffe, E.; Knowles, J. R. *Biochemistry* **1983**, *22*, 4494. (d) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170. (e) Bruce, G. *Angew. Chem., Int. Ed.* **1996**, *35*, 936. (f) Gustin, D. J.; Mattei, P.; Kast, P.; Wiest, O.; Lee, L.; Cleland, W. W.; Hilvert, D. *J. Am. Chem. Soc.* **1999**, *121*, 1756. (g) Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5008. (h) Guilford, W. J.; Copley, S. D.; Knowles, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 5013. (i) Khanjin, N. A.; Snyder, J. P.; Menger, F. M. *J. Am. Chem. Soc.* **1999**, *121*, 11831. (j) Worthington, S. E.; Roitberg, A. E.; Krauss, M. *J. Phys. Chem. B* **2001**, *105*, 7087. (k) Worthington, S. E.; Krauss, M. *J. Phys. Chem. B* **2001**, *105*, 7096. (l) Aemisseger, A.; Jaun, B.; Hilvert, D. *J. Org. Chem.* **2002**, *67*, 6725.
(105) Vittorelli, P.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1293.
(106) Kahn, S. D.; Hehre, W. J. *J. Org. Chem.* **1988**, *53*, 301.
(107) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847.
(108) Ireland, R. E.; Vevert, J.-P. *J. Org. Chem.* **1980**, *45*, 4260.
(109) Cave, R. J.; Lythgoe, B.; Metcalfe, D. A.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1218.
(110) Bartlett, P. A.; Pizzo, Ch. F. *J. Org. Chem.* **1981**, *46*, 3896.
(111) Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28*, 5879.
(112) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(113) (a) Kazmaier, U.; Schneider, C. *Synlett* **1996**, 975. (b) Kazmaier, U.; Schneider, C. *Synthesis* **1998**, 1321. (c) Kazmaier, U. *J. Org. Chem.* **1994**, *59*, 6667.
(114) Tellier, F.; Audouin, M.; Baudry, M.; Sauvêtre, R. *Eur. J. Org. Chem.* **2000**, 1933.
(115) Welch, J. T.; Samartino, J. S. *J. Org. Chem.* **1985**, *50*, 3663.
(116) Miller, S. P.; Morken, J. P. *Org. Lett.* **2002**, *4*, 2743.
(117) Tsunoda, T.; Sasaki, O.; Itô, S. *Tetrahedron Lett.* **1990**, *31*, 727.
(118) Welch, J. T.; Eswarakrishnan, S. *J. Org. Chem.* **1985**, *50*, 5909.
(119) Bartlett, P. A.; Hahne, W. F. *J. Org. Chem.* **1979**, *44*, 882.
(120) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862.
(121) (a) Denmark, S. E.; Harmata, M. A. *J. Org. Chem.* **1983**, *48*, 3369. (b) Denmark, S. E.; Harmata, M. A.; White, K. S. *J. Am. Chem. Soc.* **1989**, *111*, 8878.
(122) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43.
(123) Maier, S.; Kazmaier, U. *Eur. J. Org. Chem.* **2000**, 1241.
(124) Moffatt, E.-M.; Thomas, E. J. *Tetrahedron* **1999**, *55*, 3723.
(125) Ireland, R. E.; Varney, M. D. *J. Am. Chem. Soc.* **1984**, *106*, 3668.
(126) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **2000**, *122*, 3785.
(127) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1998**, *120*, 815.
(128) House, H. O.; Lubinkowski, J.; Good, J. J. *J. Org. Chem.* **1975**, *40*, 86.
(129) Ponaras, A. A. *Tetrahedron Lett.* **1983**, *24*, 3.
(130) (a) Maruoka, K.; Nonoshita, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 7922. (b) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316.
(131) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1983**, *48*, 1829.
(132) Tadano, K.; Minami, M.; Ogawa, S. *J. Org. Chem.* **1990**, *55*, 2108.
(133) Yadav, V. K.; Jeyaraj, D. A.; Parvez, M.; Yamdagni, R. *J. Org. Chem.* **1999**, *64*, 2928.
(134) Cha, J. K.; Lewis, S. C. *Tetrahedron Lett.* **1984**, *25*, 5263.
(135) Fernández de la Pradilla, R.; Montero, C.; Tortosa, M. *Org. Lett.* **2002**, *4*, 2373.
(136) Kallmerten, J.; Gould, T. J. *J. Org. Chem.* **1986**, *51*, 1155.
(137) Kazmaier, U.; Maier, S. *J. Org. Chem.* **1999**, *64*, 4574.
(138) (a) Denmark, S. E.; Marlin, J. E. *J. Org. Chem.* **1987**, *52*, 5742. (b) Denmark, S. E.; Rajendra, G.; Marlin, J. E. *Tetrahedron Lett.* **1989**, *30*, 2469.
(139) (a) Hungerhoff, B.; Metz, P. *J. Org. Chem.* **1997**, *62*, 4442. (b) Hungerhoff, B.; Metz, P. *Tetrahedron* **1999**, *55*, 14941.
(140) (a) Kurth, M. J.; Decker, O. H. W. *Tetrahedron Lett.* **1983**, *24*, 4535. (b) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443. (c) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1985**, *50*, 5769. (d) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1986**, *51*, 1377.
(141) Sudau, A.; Münch, W.; Nubbemeyer, U. *J. Org. Chem.* **2000**, *65*, 1710.
(142) Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zificsak, C. A. *Org. Lett.* **2002**, *4*, 1383.
(143) Sibi, M. P.; Ji, J. G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 190.
(144) (a) Devine, P. N.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 2633. (b) Watson, D. J.; Lawrence, C. M.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 815.
(145) He, S.; Kozmin, S. A.; Rawal, V. H. *J. Am. Chem. Soc.* **2000**, *122*, 190.
(146) Alayrac, C.; Fromont, C.; Metzner, P.; Anh, N. T. *Angew. Chem., Int. Ed.* **1997**, *36*, 371.
(147) Nowaczyk, S.; Alayrac, C.; Reboul, V.; Metzner, P.; Averbuch-Pouchot, M.-T. *J. Org. Chem.* **2001**, *66*, 7841.
(148) Dantale, S.; Reboul, V.; Metzner, P.; Philouze, C. *Chem. Eur. J.* **2002**, *8*, 632.
(149) Maruoka, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 7791.
(150) Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 1165.
(151) Tayama, E.; Saito, A.; Ooi, T.; Maruoka, K. *Tetrahedron* **2002**, *58*, 8307.
(152) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026.
(153) Ito, H.; Sato, A.; Kobayashi, T.; Taguchi, T. *Chem. Commun.* **1998**, 2441.
(154) Ito, H.; Sato, A.; Taguchi, T. *Tetrahedron Lett.* **1997**, *38*, 4815.
(155) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449.
(156) Uozumi, Y.; Kato, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1065.
(157) Cohen, F.; Overman, L. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3213.
(158) Kang, J.; Han Yew, K.; Hyung Kim, T.; Hyuk Choi, D. *Tetrahedron Lett.* **2002**, *43*, 9509.
(159) Jiang, Y.; Longmire, J. M.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 1449.

(160) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911.
(161) (a) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4700. (b) Hiersemann, M.; Abraham, L. *Eur. J. Org. Chem.* **2002**, 1461.
(162) (a) Krebs, A.; Kazmaier, U. *Tetrahedron Lett.* **1996**, *37*, 7945. (b) Kazmaier, U.; Krebs, A. *Tetrahedron Lett.* **1999**, *40*, 479. (c) Kazmaier, U.; Mues, H.; Krebs, A. *Chem. Eur. J.* **2002**, *8*, 1850.
(163) Saeva, F. D.; Sharpe, P. E.; Olin, G. R. *J. Am. Chem. Soc.* **1975**, *97*, 204.
(164) Trost, B. M.; Lee, Ch. B. *J. Am. Chem. Soc.* **2001**, *123*, 3687.
(165) Wada, M.; Shigehisa, T.; Akiba, K. *Tetrahedron Lett.* **1985**, *26*, 5191.
(166) Harrison, J. R.; Holmes, A. B.; Collins, I. *Synlett* **1999**, *51*, 972.
(167) Anderson, E. A.; Holmes, A. B.; Collins, I. *Tetrahedron Lett.* **2000**, *41*, 117.
(168) Anderson, E. A.; Davidson, J. E. P.; Harrison, J. R.; O'Sullivan, P. T.; Burton, J. W.; Collins, I.; Holmes, A. B. *Tetrahedron* **2002**, *58*, 1943.
(169) Schobert, R.; Siegfried, S.; Gordon, G.; Nieuwenhuyzen, M.; Allenmark, S. *Eur. J. Org. Chem.* **2001**, 1951.
(170) Burger, K.; Fuchs, A.; Hennig, L.; Helmreich, B. *Tetrahedron Lett.* **2001**, *42*, 6491.
(171) Guz, N. R.; Lorenz, P.; Stermitz, F. R. *Tetrahedron Lett.* **2001**, *42*, 6491.
(172) Chattopadhyay, S. K.; Maity, S.; Panja, S. *Tetrahedron Lett.* **2002**, *43*, 7781.
(173) Coates, B.; Montgomery, D.; Stevenson, P. J. *Tetrahedron Lett.* **1991**, *32*, 4199.
(174) Lindström, U. M.; Somfai, P. *Chem. Eur. J.* **2001**, *7*, 94.
(175) Barrett, A. G. M.; Ahmed, M.; Baker, S. P.; Baugh, S. P. D.; Braddock, D. Ch.; Procopiou, P. A.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **2000**, *65*, 3716.
(176) Jacobi, P. A.; Li, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9307.
(177) Booker-Milburn, K. I.; Fedouloff, M.; Paknoham, S. J.; Strachan, J. B.; Melville, J. L.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 4657.
(178) (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. *J. Org. Chem.* **1984**, *49*, 4320. (b) Burke, S. D.; Armistead, D. M.; Fevig, J. M. *Tetrahedron Lett.* **1985**, *26*, 1163.
(179) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48.
(180) (a) Tokuhisa, H.; Nagawa, Y.; Uzawa, H.; Hiratani, K. *Tetrahedron Lett.* **1999**, *40*, 8007. (b) Nagawa, Y.; Fukazawa, N.; Suga, J.; Horn, M.; Tokuhisa, H.; Hiratani, K.; Watanabe, K. *Tetrahedron Lett.* **2000**, *41*, 9261.
(181) Koyama, E.; Yang, G.; Hiratani, K. *Tetrahedron Lett.* **2000**, *41*, 8111.
(182) Subramanian, R. S.; Balasuramanian, K. K. *Tetrahedron Lett.* **1988**, *29*, 6797.
(183) Yang, Z.-Y.; Xia, Y.; Xia, P.; Brossi, A.; Lee, K.-H. *Tetrahedron Lett.* **1999**, *40*, 4505.
(184) Macor, J. E.; Langer, O. D.; Gougoutas, J. Z.; Melley, M. F.; Cornelius, L. A. M. *Tetrahedron Lett.* **2000**, *41*, 3541.
(185) Cooper, J.; Knight, D. W. *Tetrahedron Lett.* **1987**, *28*, 3031.
(186) Mues, H.; Kazmaier, U. *Synlett* **2000**, 1004.
(187) Laabs, S.; Münch, W.; Bats, J. W.; Nubbemeyer, U. *Tetrahedron* **2002**, *58*, 1317.
(188) (a) Sabol, J. S.; Flynn, G. A.; Friedrich, D.; Huber, E. W. *Tetrahedron Lett.* **1997**, *38*, 3687. (b) Evans, M. C.; Johnson, R. L. *Tetrahedron* **2000**, *56*, 9801.
(189) Roucher, S.; Klein, P. *J. Org. Chem.* **1986**, *51*, 123.
(190) Bycroft, B. W.; Landon, W. *J. Chem. Soc., Chem. Commun.* **1970**, 967.
(191) Plate, R.; Theunisse, A. W. G.; Ottenheijm, H. C. J. *J. Org. Chem.* **1987**, *52*, 370.
(192) Majumdar, K. C.; Samanta, S. K. *Tetrahedron* **2001**, *57*, 4955.
(193) Majumdar, K. C.; Bhattacharyya, T. *Tetrahedron Lett.* **2001**, *42*, 4231.
(194) Majumdar, K. C.; Ghosh, M.; Jana, M.; Saha, D. *Tetrahedron Lett.* **2002**, *43*, 2111.
(195) Majumdar, K. C.; Ghosh, S. K. *Tetrahedron Lett.* **2002**, *43*, 2115.
(196) Ghosh, S. Ch.; De, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3705.
(197) Büchi, G.; Powel, J. E., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3126.
(198) (a) Agami, C.; Couty, F.; Evano, G. *Tetrahedron Lett.* **2000**, *41*, 8301. (b) Agami, C.; Couty, F.; Evano, G. *Eur. J. Org. Chem.* **2002**, 29.
(199) Lemieux, R. M.; Devine, P. N.; Mechelke, M. F.; Meyers, A. I. *J. Org. Chem.* **1999**, *64*, 3585.
(200) Abelman, M. M.; Funk, R. L.; Munger, J. D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030.
(201) Velker, J.; Roblin, J.-P.; Neels, A.; Tesouro, A.; Stoeckli-Evans, H.; Klaerner, F.-G.; Gehrke, J.-S.; Neier, R. *Synlett* **1999**, *S1*, 925.
(202) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371.
(203) Kang, H.-J.; Paquette, L. A. *J. Am. Chem. Soc.* **1990**, *112*, 3252.
(204) Ravi Kumar, J. S.; O'Sullivan, M. F.; Reisman, S. E.; Hulford, C. A.; Ovaska, T. V. *Tetrahedron Lett.* **2002**, *43*, 1939.
(205) Barriault, L.; Denissova, I. *Org. Lett.* **2002**, *4*, 1371.
(206) Reed, S. F., Jr. *J. Org. Chem.* **1965**, *30*, 1663.
(207) (a) Parker, K. A.; Farmar, J. G. *Tetrahedron Lett.* **1985**, *26*, 3655. (b) Parker, K. A.; Farmar, J. G. *J. Org. Chem.* **1986**, *51*, 4023.
(208) Hong, S.; Lindsay, H. A.; Yaramasu, T.; Zhang, X.; McIntosh, M. C. *J. Org. Chem.* **2002**, *67*, 2042.
(209) Posner, G. H.; Kinter, C. M. *J. Org. Chem.* **1990**, *55*, 3967.
(210) Trost, B. M.; Pinkerton, A. B.; Seidel, M. *J. Am. Chem. Soc.* **2001**, *123*, 12466.
(211) Grigg, R.; Kongkathip, N.; Kongkathip, B.; Luangkamin, S.; Dondas, H. A. *Tetrahedron* **2001**, *57*, 7965.
(212) Khripach, V. A.; Zhabinskii, V. N.; Konstantinova, O. V.; Khripach, N. B. *Tetrahedron Lett.* **2000**, *41*, 5765.
(213) Stevenson, J. W.; Bryson, T. A. *Tetrahedron Lett.* **1982**, *23*, 3143.
(214) Kraft, P.; Eichenberger, W.; Fráter, G. *Eur. J. Org. Chem.* **1999**, 2781.
(215) de Koning, C. B.; Michael, J. P.; Rousseau, A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 787.
(216) Huang, K.-S.; Wang, E.-C. *Tetrahedron Lett.* **2001**, *42*, 6155.
(217) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3941.
(218) Ireland, R. E.; Wilcox, C. S. *Tetrahedron Lett.* **1977**, 2839.
(219) (a) Bartlett, P. A.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 623. (b) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933.
(220) Herold, P.; Duthaler, R.; Rihs, G.; Angst, C. *J. Org. Chem.* **1989**, *54*, 1178.
(221) Mohamed, M.; Brook, M. A. *Tetrahedron Lett.* **2001**, *42*, 191.
(222) Yokozawa, T.; Nakai, T.; Ishikawa, M. *Tetrahedron Lett.* **1984**, *25*, 3991.
(223) Konno, T.; Daitoh, T.; Ishihara, T.; Yamanaka, H. *Tetrahedron: Asymmetry* **2001**, *12*, 2743.
(224) Ito, Y.; Higuchi, N.; Murakami, M. *Tetrahedron Lett.* **1988**, *29*, 5151.
(225) Raucher, S.; Hwang, K.-J.; Macdonald, J. E. *Tetrahedron Lett.* **1979**, 3057.
(226) Elworthy, T. R.; Morgans, D. J., Jr.; Palmer, W. S.; Repke, D. B.; Smith, D. B.; Waltos, A. M. *Tetrahedron Lett.* **1994**, *35*, 4951.
(227) Peng, S.; Qing, F.-L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3345.
(228) Bao, R.; Valverde, S.; Herradón, B. *Synlett* **1992**, 217.
(229) Giardinà, A.; Marcantoni, E.; Mecozzi, T.; Petrini, M. *Eur. J. Org. Chem.* **2001**, 713.
(230) (a) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726. (b) Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2448.
(231) Feldman, K. S.; Masters, K. M. *J. Org. Chem.* **1999**, *64*, 8945.
(232) Bouvet, D.; Sdassi, H.; Ourévitch, M.; Bonnet-Delpon, D. *J. Org. Chem.* **2000**, *65*, 2104.
(233) Basavaiah, D.; Pandiaraju, S. *Tetrahedron Lett.* **1995**, *36*, 757.
(234) (a) Ireland, R. E.; Norbeck, D. W.; Mandel, G. S.; Mandel, N. S. *J. Am. Chem. Soc.* **1985**, *107*, 3285. (b) Gable, R. W.; McVinish, L. M.; Rizzacasa, M. A. *Aust. J. Chem.* **1994**, *47*, 1537. (c) Werschkun, B.; Thiem, J. *Synthesis* **1999**, 121.
(235) Vidal, T.; Haudrechy, A.; Langlois, Y. *Tetrahedron Lett.* **1999**, *40*, 5677.
(236) Godage, H. Y.; Fairbanks, A. J. *Tetrahedron Lett.* **2000**, *41*, 7589.
(237) Srikrishna, A.; Yelamaggad, C. V.; Kumar, P. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2877.
(238) Srikrishna, A.; Kumar, P. P. *Tetrahedron* **2000**, *56*, 8189.
(239) Srikrishna, A.; Nagaraju, S.; Venkateswarlu, S.; Hiremath, U. S.; Reddy, T. J.; Venugopalan, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2069.
(240) Kim, S.; Ko, H.; Kim, E.; Kim, D. *Org. Lett.* **2002**, *4*, 1343.
(241) Boeckman, R. K., Jr.; Rico-Ferreira, M. R.; Mitchel, L. H.; Shao, P. *J. Am. Chem. Soc.* **2002**, *124*, 190.
(242) Mandai, T.; Matsumoto, S.; Kohama, M.; Kawada, M.; Tsuji, J. *J. Org. Chem.* **1990**, *55*, 5671.
(243) Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4035.
(244) Srikrishna, A.; Chandrasekhar Babu, N. *Tetrahedron Lett.* **2001**, *42*, 4913.
(245) Chandrasekhar, S.; Venkat Reddy, M. *Tetrahedron* **2000**, *56*, 6339.
(246) Thrash, T. P.; Welton, T. D.; Behar, V. *Tetrahedron Lett.* **2000**, *41*, 29.
(247) Pettus, T. R. R.; Inoue, M.; Chen, X.-T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6160.
(248) Mcandrew, B. A.; Riezebos, G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 367.
(249) Snider, B. B.; Beal, R. B. *J. Org. Chem.* **1988**, *53*, 4508.
(250) Amano, S.; Takemura, N.; Ohtsuka, M.; Ogawa, S.; Chida, N. *Tetrahedron* **1999**, *55*, 3855.
(251) Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, 1625.
(252) Masaki, Y.; Arasaki, H.; Itoh, A. *Tetrahedron Lett.* **1999**, *40*, 4829.
(253) Stork, G.; Raucher, S. *J. Am. Chem. Soc.* **1976**, *98*, 1583.
(254) Schlama, T.; Baati, R.; Gouverneur, V.; Valleix, A.; Falck, J. R.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2085.

(255) Srikrishna, A.; Ramachary, D. B. *Tetrahedron Lett.* **2002**, *43*, 2765.
(256) Srikrishna, A.; Vijaykumar, D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1265.
(257) (a) Fukuda, Y.; Sakurai, M.; Okamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 4173. (b) Fukuda, Y.; Okamoto, Y. *Tetrahedron* **2002**, *58*, 2513.
(258) White, J. D.; Amedio, J. C., Jr. *J. Org. Chem.* **1989**, *54*, 736.
(259) Ng, F. W.; Lin, H.; Tan, Q.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 545.
(260) Amano, S.; Ogawa, N.; Ohtsuka, M.; Chida, N. *Tetrahedron* **1999**, *55*, 2205.
(261) Hatcher, M. A.; Posner, G. H. *Tetrahedron Lett.* **2002**, *43*, 5009.
(262) Julia, S.; Julia, M.; Linstrumelle, G. *Bull. Soc. Chim. Fr.* **1964**, *25*, 2693.
(263) Funk, R. L.; Munger, J. D., Jr. *J. Org. Chem.* **1985**, *50*, 707.
(264) Abelman, M. M.; Funk, R. L.; Munger, J. D., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 4030.
(265) Funk, R. L.; Abelman, M. M. *J. Org. Chem.* **1986**, *51*, 3247.
(266) Paterson, I.; Hulme, A. N. *Tetrahedron Lett.* **1990**, *31*, 7513.
(267) Mapp, A. K.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 23.
(268) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771.
(269) Gilbert, J. C.; Kelly, T. A. *J. Org. Chem.* **1986**, *51*, 4485.
(270) Ceccarelli, S.; Piarulli, M.; Gennari, C. *Tetrahedron Lett.* **1999**, *40*, 153.
(271) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205.
(272) Ireland, R. E.; Smith, M. G. *J. Am. Chem. Soc.* **1988**, *110*, 854.
(273) Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.
(274) Ireland, R. E.; Häbich, D.; Norbeck, D. W. *J. Am. Chem. Soc.* **1985**, *107*, 3271.
(275) Ireland, R. E.; Maienfisch, P. *J. Org. Chem.* **1988**, *53*, 640.
(276) Hong, S.; McIntosh, M. C. *Org. Lett.* **2002**, *4*, 19.
(277) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193.
(278) Kurth, M. J.; Soares, C. J. *Tetrahedron Lett.* **1987**, *28*, 1031.
(279) Suh, Y.-G.; Kim, S.-A.; Jung, J.-K.; Shin, D.-Y.; Min, K.-H.; Koo, B.-A.; Kim, H.-S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3545.
(280) Tsunoda, T.; Nishii, T.; Yoshizuka, M.; Yamasaki, C.; Suzuki, T.; Itô, S. *Tetrahedron Lett.* **2000**, *41*, 7667.
(281) Wenkert, E.; Dave, K. G.; Haglid, F. *J. Am. Chem. Soc.* **1965**, *87*, 5461.
(282) (a) Chao, S.; Kunng, F.-A.; Gu, J.-M.; Ammon, H. L.; Mariano, P. S. *J. Org. Chem.* **1984**, *49*, 2708. (b) Baxter, E. W.; Labaree, D.; Ammon, H. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 7682.
(283) Tubéry, F.; Grierson, D. S.; Husson, H.-P. *Tetrahedron Lett.* **1990**, *31*, 523.
(284) Boeckman, R. K., Jr.; Zhang, J.; Reeder, M. R. *Org. Lett.* **2002**, *4*, 3891.
(285) Tokuhisa, H.; Koyama, E.; Nagawa, Y.; Hiratani, K. *Chem. Commun.* **2001**, 595.

CR020703U