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Catalysis of the Claisen rearrangement

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Contents

Abbreviations: AAA, asymmetric allylic alkylation; BSA, benzene sulfonic acid; Bn, benzyl; Bpin, boron-substituted pinene; bim, 1-butyl-1*H*-imidazolium; box, bis(oxazoline); bmim, 1-butyl-3-methyl-1*H*-imidazolium; Cy, cyclohexyl; COD, cyclooctadienyl; CAC, catalytic asymmetric Claisen; DCM, dichloromethane; DEG, diethylene glycol; DIBAL-H, diisobutylaluminium hydride; DEA, *N*,*N*-DEA; DMA, *N*,*N*-DMA; DEGMEE, diethylene glycol monoethyl ether; dba, dibenzylidine acetone; DIPEA, *N*,*N*-diisopropylethylamine; dppe, diphenylphosphino ether; DBU, diazabicyclo[5,4,0]undec-7-ene; DCE, 1,2-dichloroethane; DMF, *N*,*N*-dimethylformamide; DIAD, diisopropyl azodicarboxylate; dr, diastereomeric ratio; ee, enantiomeric excess; FOD, 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione; HMPA, hexamethyl phosphoroustriamide; h, hour; ^{i}Pr, isopropyl; IL, ionic liquid; ICR, olefin isomerization–Claisen rearrangement; LA, Lewis acid; MS, molecular sieves; MWI, microwave irradiation; min, minute; MOM, methoxymethyl; MEM, methoxyethoxymethyl; min, minute; mim, 1-methyl-1*H*-imidazolium; mpy, 1-methyl pyrrolidium; $^{-}$OTf, trifluoromethanesulfonate; PMB, *p*-methoxybenzyl; Piv, pivaloyl; rt, room temperature; salen, (*s*,*s*)-(+)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediamino; TBDMS, *tert*-butyldimethylsilyl; TES, triethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TPP, tetraphenylporphyrin; THF, tetrahydrofuran; TMS, tetramethyl silane; TFAA, trifluoro acetic acid; TIPS, triisopropyl silyl; TPS, triphenyl silane; TFE, trifluoroethanol.

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1. Introduction

Since its discovery in 1912,[1] the Claisen rearrangement has become one of the most widely used synthetic tools for the organic chemist. For synthetic purposes, the Claisen rearrangement is being continuously studied to improve the yield of the rearrangement product, to shorten the reaction time and to perform the rearrangement under relatively milder conditions to prevent the undesired competitive side reactions and decomposition of the starting materials and/or products. Consequently, the catalysis of the Claisen rearrangement was developed to achieve milder conditions for the rearrangement and is now being applied extensively by synthetic organic chemists worldwide. Catalysis of the Claisen rearrangement has been known almost as early as the discovery of the Claisen rearrangement. Claisen[1] himself reported the apparent catalytic effect of ammonium chloride[2] on the Claisen rearrangement. Since then, numerous other substances such as transition-metal complexes, Lewis acids, Brønsted acids, bases, water and also some physical parameters have been developed to catalyze the Claisen rearrangement and accelerate the rearrangement rate dramatically.

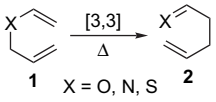
After the first review by Lutz[3] on the catalysis of the Cope and Claisen rearrangements, a number of comprehensive review articles[4,5] have appeared, covering the important features of the Claisen rearrangement and numerous related [3,3]-sigmatropic rearrangements, which include mechanism, stereochemistry and synthetic applications. Many of these review articles have only dealt with a few particular aspects of the catalysis of the Claisen rearrangement, although numerous developments have been made on the catalysis of the Claisen rearrangement by the application of various substances and physical parameters.

The purpose of this review is, therefore, to focus on the recent developments in the catalysis of the Claisen rearrangement by many metal complexes of the periodic table, and by Lewis acids, Brønsted acids, bases and water. The discussion has been extended to the microwave-accelerated Claisen rearrangement and the application of ionic liquids as alternative reaction media in promoting the Claisen rearrangement. The enzymatic version of the Claisen rearrangement has also been included briefly; this is being of interest in metabolic routes. In this review, the discussion has been limited mainly to the recent literature. Some earlier reports have also been included in order to emphasize a particular aspect of the Claisen rearrangement that the authors wish to highlight.

This report is not intended to be an exhaustive review of the different types of Claisen rearrangement reported in the literature and, therefore, some meritorious examples might have been excluded. The applications of the catalyzed Claisen rearrangement in the synthesis of a wide range of synthetically important building blocks and natural or biologically active compounds are highlighted in each section.

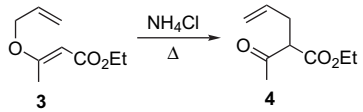
2. Definition and history

Classically, the Claisen rearrangement[1] can be defined as the thermal [3,3]-sigmatropic reorganization of an allyl vinyl ether (**1**, X=O) into a γ,δ-unsaturated carbonyl compound **2** by a concerted intramolecular process. This can be defined as a suprafacial, concerted and nonsynchronous pericyclic process. The definition has been extended to include any reorganization of the type **1** to **2** with X=N or S. One of the double bonds can be a part of the acetylenic group or a part of the aromatic ring. Replacement of both the double bonds can be involved in some cases. Other positions in **1** may be occupied by heteroatoms (Scheme 1).



Scheme 1.

The first report on the Claisen rearrangement involved the conversion of *O*-allylated ethyl acetoacetate **3** into the corresponding *C*-allyl isomer **4** during distillation in the presence of NH_4Cl (Scheme 2). The study of this conversion showed that solid NH_4Cl, in an apparently heterogeneous process, caused a slight increase in the rearrangement rate where NH_4Cl may function as a proton donor.[2] This marked the beginning of the catalysis of the Claisen rearrangement.



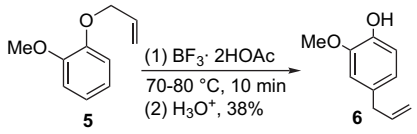
Scheme 2.

The synthetic utility of the Claisen rearrangement has stimulated the interest of several generations of chemists to find out suitable experimental conditions, which would allow the rearrangement to be performed on a wide variety of substrates, and achieve excellent chemo-, regio-, diastereo- and enantioselectivity to afford potentially useful polyfunctionalized products.

3. Catalysis of the Claisen rearrangement

3.1. Catalysis by derivatives of boron

The first reported example of Lewis acid catalysis in the Claisen rearrangement was the conversion of guaiacol allyl ether **5** into eugenol **6** using BF_3[6] (Scheme 3).



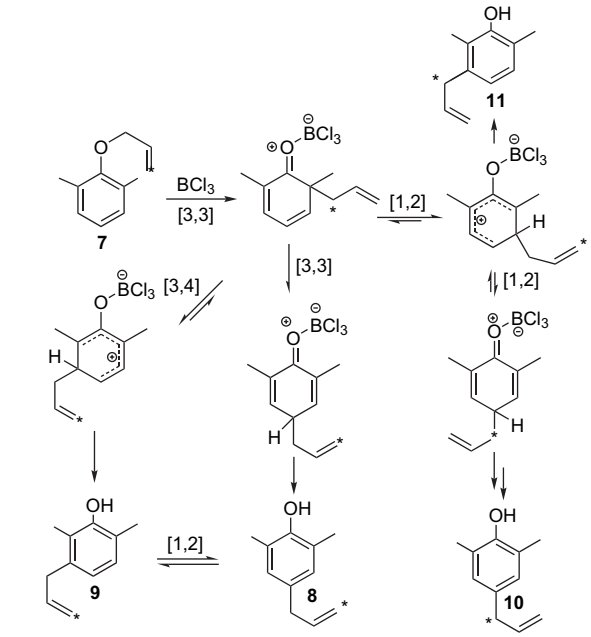
Scheme 3.

The BCl_3-catalyzed Claisen rearrangement of allyl aryl ethers was extensively studied by Schmid et al.[7,8] In the presence of BCl_3, the Claisen rearrangement of allyl aryl ethers having no electron-withdrawing substituents produced the corresponding *ortho*-allylphenols at low temperature in good yield. The charge induced at the reaction site by the catalyst caused a rate increase of ca. 10^{10} relative to the thermal Claisen rearrangement.

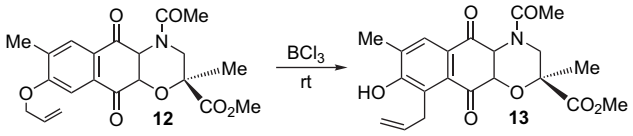
ortho-Substituted allyl aryl ethers under BCl_3-catalyzed conditions gave a mixture of *ortho*- and *para*-allyl phenol, the *para*-product being obtained in a higher ratio, compared to the thermal conditions. In the case of 2,6-dialkyl aryl allyl ether **7**, four different products **8**–**11** were obtained by the BCl_3-catalyzed Claisen rearrangement followed by a [1,2]-, [3,3]- or [3,4]-sigmatropic rearrangement of the allyl fragment[8] (Scheme 4).

The BCl_3-catalyzed aromatic Claisen rearrangement led to the formation of many undesired side products, which made BCl_3 a less attractive catalyst to synthetic organic chemists. The BCl_3-catalyzed Claisen rearrangement of a complex system such as compound **12**, however, afforded the product **13** at room temperature, whereas **12** decomposed under heating[9] conditions (Scheme 5).

During the synthesis of α-*C*-glycosides,[10] it was observed that the Claisen rearrangement of enol ether **14** under thermal conditions (PhCN, 180 °C) produced a mixture of both α- and β-*C*-glycoside products **15** and **16** (α/β=5:1). In addition, a small amount of the open-chain diene **17** was isolated. In order to obtain the anomerically pure α-*C*-glycoside, the Claisen rearrangement was performed in the presence of the Lewis acids, $NaBF_4$, $AlCl_3$, $BF_3{\cdot}OEt_2$, $Yb(OTf)_3$ and $TiCl_4$, at low temperature under a variety of reaction conditions, but, unfortunately, in all cases, mixtures of products **15** and **16** were obtained, although, in the case of $BF_3{\cdot}OEt_2$, the ratio of products

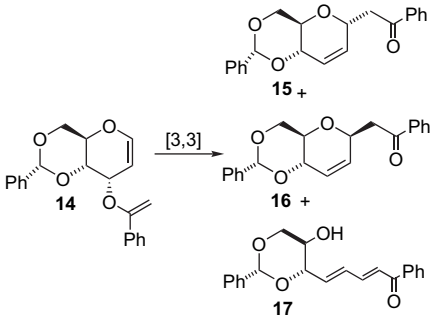


Scheme 4.



Scheme 5.

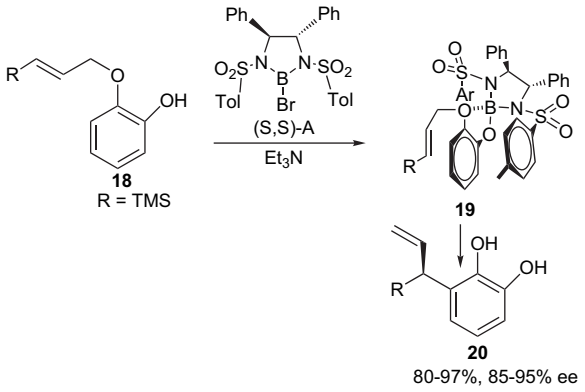
was favorable towards the desired α-anomer (α/β=16:1) and the yields were about 60%. Finally, the exclusive synthesis of the α-anomer was achieved by a thermal Claisen rearrangement in xylene in a sealed tube at 195 °C (Scheme 6).



Scheme 6.

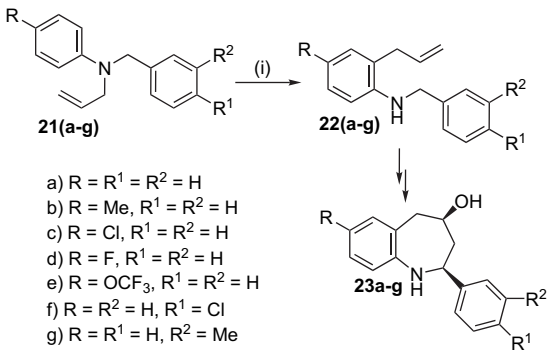
Enantioselective aromatic Claisen rearrangement was performed by Taguchi et al. using a chiral boron catalyst[11,12] (**A**). Various monoallyl ethers **18** of catechol were converted into the 3-allylcatechol derivatives **20** with complete regioselectivity and excellent ees (Scheme 7). The observed asymmetric induction was interpreted in terms of a five-membered cyclic intermediate **19** that was formed by a covalent bond between the boron atom and the phenolic hydroxyl group,

followed by coordination of the ether oxygen to the boron atom. In the cyclic intermediate, one of the arenesulfonyl groups may shield the *re* face of the phenyl ring, so that the allyl part may approach from the *si* face, resulting in an enantiotopic facial selectivity of the allyl double bond.



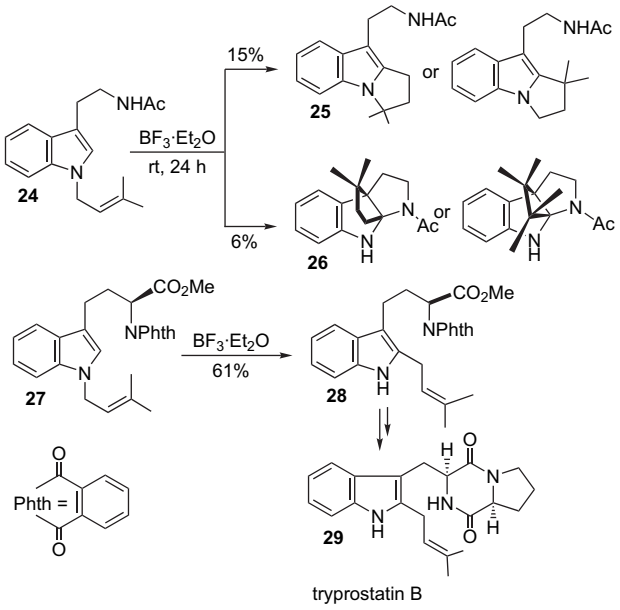
Scheme 7.

The Lewis acid, $BF_3 \cdot Et_2O$, also successfully catalyzed the amino-Claisen rearrangement. *N*-Allylanilines **21a–g** underwent an amino-Claisen rearrangement in the presence of 1.5 equiv $BF_3 \cdot Et_2O$, as an acid catalyst, at 140–150 °C and afforded the rearranged products **22a–g** in moderate-to-good yields[13] (55–75%). Products **22a–g** were then converted into the bioactive tetrahydro-1-benzazepine derivatives **23a–g** by an intramolecular 1,2-dipolar cycloaddition reaction (Scheme 8).



Scheme 8. Reagents and conditions: (i) $BF_3 \cdot Et_2O$ (1.5 equiv), 140–150 °C, 2–5 h.

$BF_3 \cdot Et_2O$ catalyzed the sigmatropic rearrangements of *N*-prenylindole derivatives[14] to form the basis of an enantiomerically pure synthesis of tryprostatin B **29**. Rearrangement of *N*-prenyl-*N*-acetyltryptamine **24**, induced by $BF_3 \cdot Et_2O$ at low temperature, led to a 2-prenyl derivative, and thence to the tricyclic tryptamine **25** and indoline **26** (Scheme 9). Similarly, *N*-prenyl-*N*-phthaloyl-L-tryptophan methyl ester **27** furnished the corresponding 2-prenyl derivative **28**, a known advanced precursor of the bioactive tryprostatin B. The thermal aza-Claisen rearrangement of some *N*-allyl-3-alkylindoles required very high temperatures of 450–470 °C to give their 2- and 3-alkylindolic derivatives.[14b]



Scheme 9.

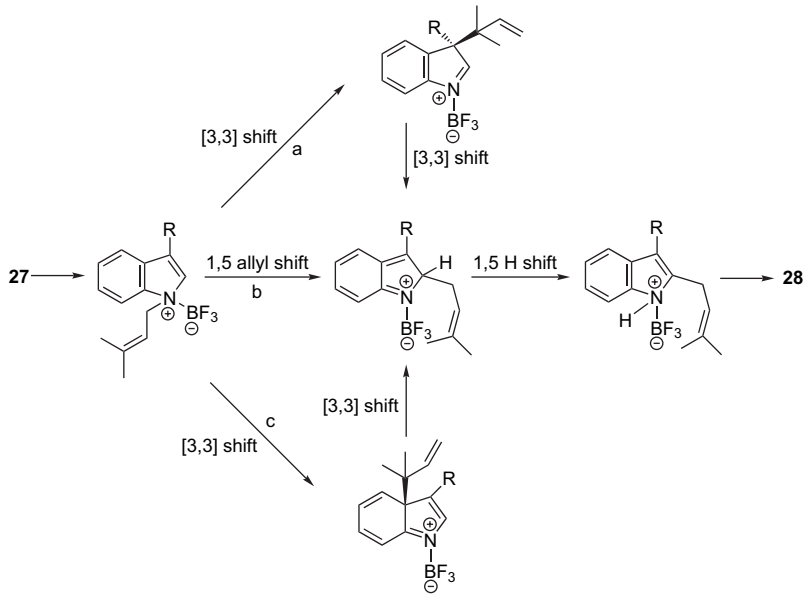
The rearrangement of **27** was carried at room temperature (or below) with an excess of $BF_3 \cdot Et_2O$ to furnish the desired product **28** in good yield and ee (Table 1).

The formation of the product **28** could be rationalized by considering three different sigmatropic rearrangement (of the prenyl group from the indole nitrogen–BF_3 complex) pathways (pathway a or b or c) followed by a [1,5]-sigmatropic hydrogen shift (Scheme 10).

Table 1
$BF_3 \cdot Et_2O$-catalyzed rearrangement of **27** to **28**

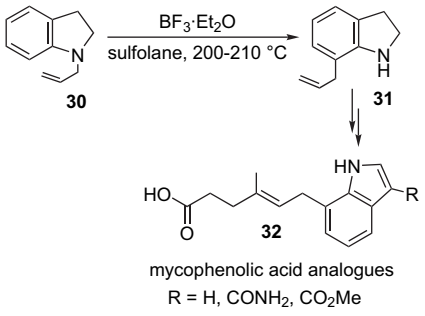
Entry	Starting material **27** (amount/mmol)	Equiv	Molar ratio $BF_3 \cdot Et_2O$/**27**	Temparature (°C)	Time (h)	Product **28**	
						Yield (%)	ee (%)
1	0.060	1[a]	7.2	rt	15.5	64	83
2	0.048	1[b]	7.2	−4	40	54	86
3	0.048	1[a]	14.8	−4	40	68	89
4	0.072	1[a]	23.6	−4	18	61	95
5	0.048	1[c]	23.6	−4	18	63	90
6	0.048	1[a]	36.3	−14	120	71	84

[a] DCM (0.024 M).
[b] DCM (0.019 M).
[c] DCM (0.012 M).



Scheme 10.

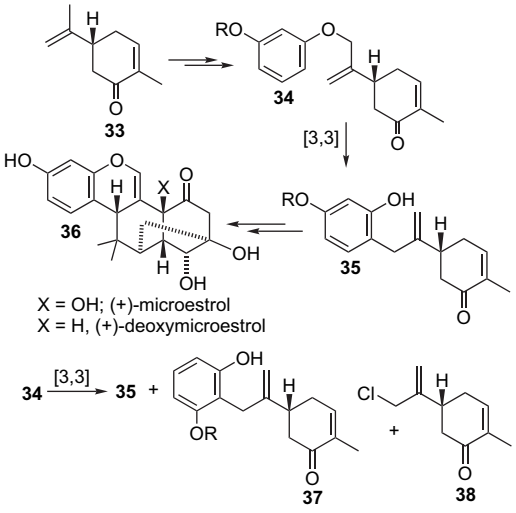
The syntheses of novel indole analogues of mycophenolic acid **32**, as potential antineoplastic agents, were carried out based on the $BF_3 \cdot Et_2O$-catalyzed amino-Claisen rearrangement and the *ortho*-ester-Claisen rearrangement as two key steps,[15,16] where the rearrangement of *N*-allylindoline **30** smoothly proceeded in the presence of $BF_3 \cdot Et_2O$ in sulfolane under argon at 200–210 °C to afford 7-allylindoline **31** in 47% yield (Scheme 11).



Scheme 11.

For the synthesis of strong phytoestrogens, (+)-microestrol and (+)-deoxymicroestrol **36**, from (*R*)-carvone **33**, the aromatic Claisen rearrangement of resorcinol allyl esters **34** was found to be the key step[17] (Scheme 12).

The thermal Claisen rearrangement of **34** in $PhNEt_2$ at 140–220 °C for 9.5 h afforded the rearranged products **35** and **37** in moderate yields, but with poor selectivity (**35**/**37**=1.2:1). The rearrangement proceeded much faster under microwave conditions at 250 °C and gave better yields in shorter reaction times (30–50 min), but the regioselectivity was not improved. If the reaction conditions were changed from thermal to catalytic by employing BCl_3 as the catalyst, the stereoselectivity was found to be good (ca. 13:1) and the



Scheme 12.

isomers **35a–e** were obtained from **34a–e** as the major products, along with the formation of the minor products **37a–e** and **38a–e** (Table 2).

Table 2
BCl_3-mediated Claisen rearrangement of resorcinol allyl ethers **34a–e**

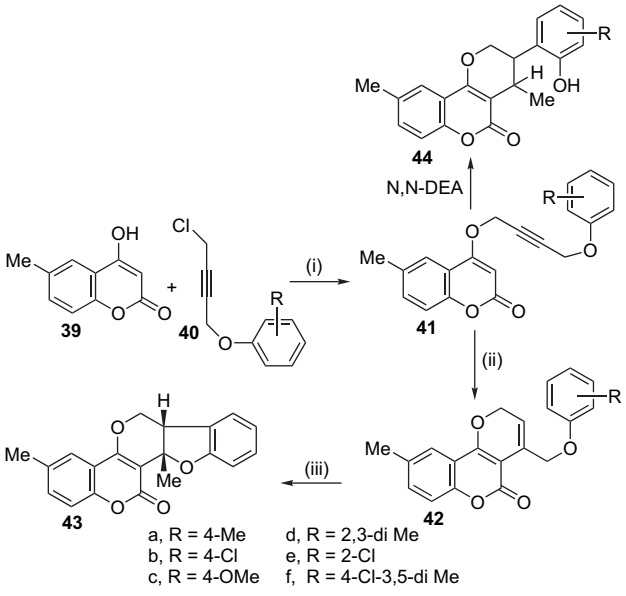
Run	Run in **34**: R	Conditions	Yield[a] (%)		
			35	**37**	**38**
1	**34b**: Me	−50 to −20 °C, 3 h	54	10	19
2	**34a**: H	−50 °C, 3 h	51	9	8
3	**34d**: benzoyl	−50 °C, 1 h	23	9	33
4	**34c**: 2-propyl	−50 °C, 1 h	5[b]		17
5	**34e**: TBDPS	−50 °C, 1 h	76[c]	6[c]	0

[a] Isolated yields from the corresponding **34**, unless otherwise noted.
[b] Mixture of **35c** and **37c** (4:1).
[c] Isolated yields from **34a** in two steps.

3.2. Catalysis by metal compounds

3.2.1. Catalysis by aluminium derivatives

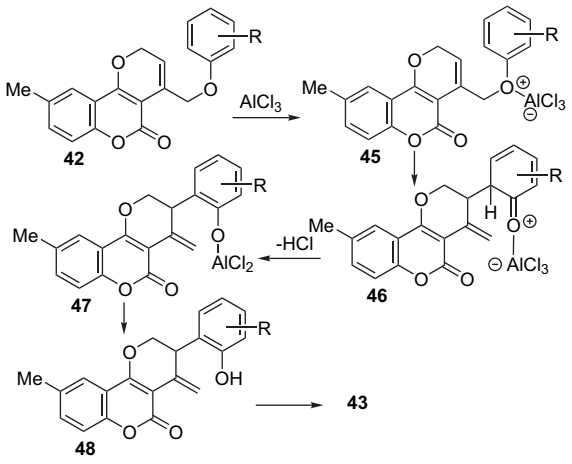
It has been observed that $AlCl_3$ catalyzes the Claisen rearrangement of bis-aryl ethers under mild conditions.[18] The overall reaction was rationalized by a series of steps involving an $AlCl_3$-catalyzed charge-accelerated sequential Claisen rearrangement and cyclization. Recently, we have reported[19] that several coumarin-annulated polyheterocycles have been regioselectively synthesized in 82–90% yield by an anhydrous $AlCl_3$-catalyzed charge-accelerated Claisen rearrangement of 4-aryloxymethyl[3,2-*c*]pyranobenzopyran-5-ones in dichloromethane solution at room temperature for 0.5 h. When the starting materials **41** prepared from **39** and **40** were subjected to a thermal Claisen rearrangement at 132 °C, the initial Claisen rearrangement products **42** were obtained. Products **42** still contained an allyl aryl ether moiety, well suited for a second Claisen rearrangement. Therefore, compounds **42** were treated with anhydrous $AlCl_3$[3,18] to afford the rearranged pentacyclic heterocycles **43** (Scheme 13), whereas the compounds **42** on heating in *N*,*N*-DEA (216 °C) gave the products **44**.



Scheme 13. Reagents and conditions: (i) dry Me_2CO–K_2CO_3, NaI; (ii) chlorobenzene, reflux; (iii) anhydrous $AlCl_3$, dry DCM, rt, 0.5 h.

The mechanism of the formation of the products **43** from **42** can be explained by a series of steps involving an initial charge-accelerated [3,3]-sigmatropic rearrangement. Substrates **42** form ether–$AlCl_3$ complexes **45**, which may undergo [3,3]-sigmatropic rearrangement through a charge-delocalized transition state to give the intermediates **46**. Elimination of HCl from the intermediates **46** gives intermediates **47**, which may afford the intermediate phenols **48**. These intermediate phenols **48** undergo 5-*exo*-cyclization to give the polyheterocyclic products **43** (Scheme 14).

We have also synthesized[20] various other polyheterocycles **51** by employing this methodology based on the 3-hydroxyquinolone moiety (i.e., from the starting materials **49** and **50**) by an $AlCl_3$-catalyzed Claisen rearrangement (Scheme 15).



Scheme 14.

Similarly, compounds **52a–f** and **54e–g** when subjected[21] to a catalyzed Claisen rearrangement gave the products **53a–f** and **55e–g** (Scheme 16).

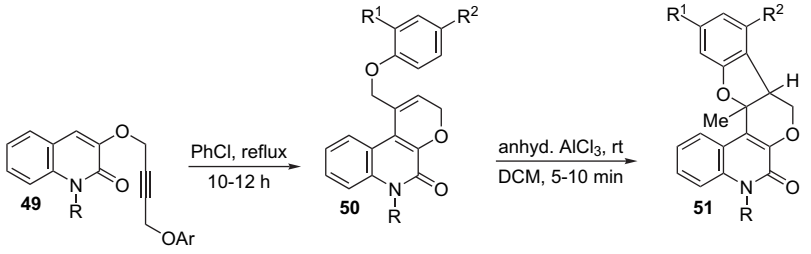
Compound **56** on treatment with an $AlCl_3$ catalyst afforded pentacyclic heterocycle[22] **57** along with a minor product **58** (Scheme 17). The mechanistic pathways for the formation of the compounds are the same as stated earlier.[19]

Recently, we have extended our efforts[23,24] in the regioselective synthesis of the polyheterocyclic compounds **60** and **61** by an aluminium chloride-catalyzed Claisen rearrangement, starting from the ethers **59a** and **59b** (Scheme 18).

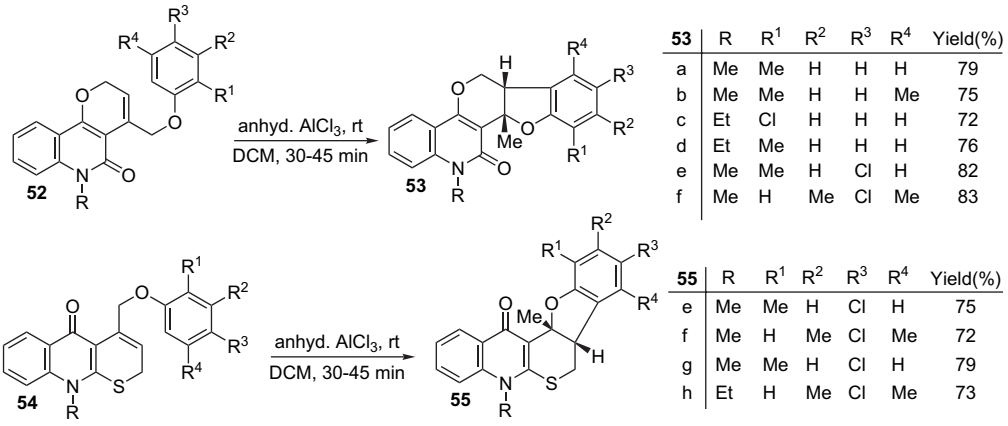
Pyrimidine heterocycles, interesting biologically active molecules, fused with a furothiopyran moiety at the C-5 and C-6 positions were synthesized regioselectively[25] by the application of a sequential Claisen rearrangement and an intramolecular hydroaryloxylation catalyzed by aluminium chloride. The first Claisen rearrangement products **62** still possessed an allyl aryl ether segment requisite for a further study of the sigmatropic rearrangement. In our earlier efforts, we found different regioselectivities with different substrates in the thermal second aromatic Claisen rearrangement. In some cases, a [1,3]-prototropic shift was an important side reaction, along with a [3,3]-sigmatropic rearrangement.[26] To avoid these undesired problems in the thermal Claisen rearrangement, we considered the Lewis acid-catalyzed Claisen rearrangement approach.

Among the different Lewis acid catalysts available for the aromatic oxy-Claisen rearrangement, aluminium chloride and its different derivatives have received the most attention.[3,18] Compounds **62a–f** were treated with $AlCl_3$ in DCM to afford the cyclized products **63a–e** in 90–96% yield (Scheme 19). No cyclized product corresponding to **63f** was obtained in the case of compound **62f**, as several other unwanted products were formed during the reaction and these were not characterized.

The synthesis of hitherto unreported indole-annulated pentacyclic heterocycles[27] containing oxygen, nitrogen and sulfur by the thermal Claisen rearrangement followed by the



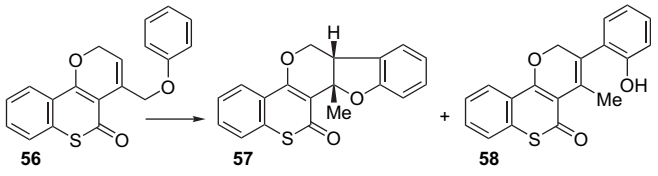
Scheme 15.



53	R	R^1	R^2	R^3	R^4	Yield(%)
a	Me	Me	H	H	H	79
b	Me	Me	H	H	Me	75
c	Et	Cl	H	H	H	72
d	Et	Me	H	H	H	76
e	Me	Me	H	Cl	H	82
f	Me	H	Me	Cl	Me	83

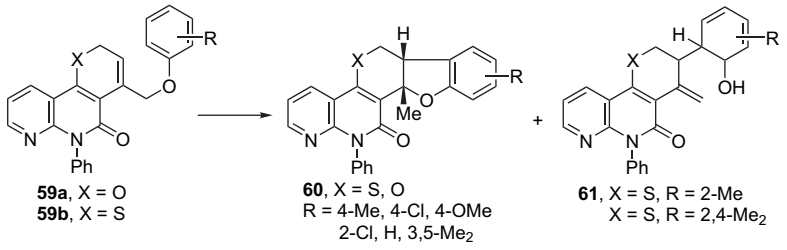
55	R	R^1	R^2	R^3	R^4	Yield(%)
e	Me	Me	H	Cl	H	75
f	Me	H	Me	Cl	Me	72
g	Me	Me	H	Cl	H	79
h	Et	H	Me	Cl	Me	73

Scheme 16.

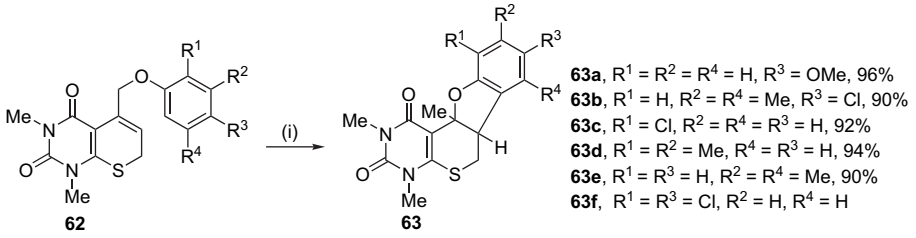


Scheme 17.

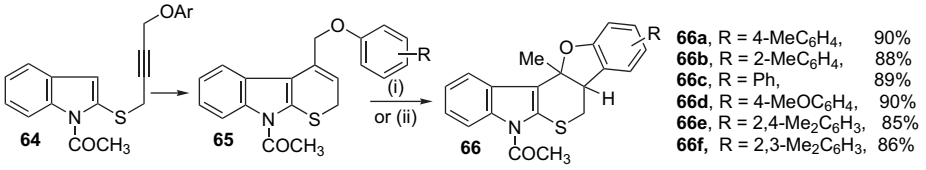
Lewis acid-catalyzed Claisen rearrangement has been described. 9-Acetyl-4-aryloxymethyl-2,9-dihydrothiopyrano-[2,3-*b*]indoles **65a–f** were regioselectively synthesized in 80–85% yields by thermal rearrangement of 2-(4′-aryloxy-but-2′-ynylthio)-1-acetylindoles **64a–f**. A second Lewis acid-catalyzed rearrangement of **65a–f** afforded compounds **66a–f** (Scheme 20).



Scheme 18.

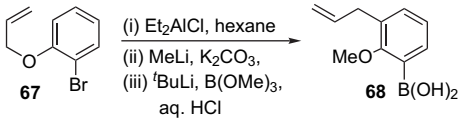


Scheme 19. Reagent and condition: (i) $AlCl_3$, DCM, rt, 1 h.



Scheme 20. Reagent and condition: (i) anhydrous $AlCl_3$ (1 equiv), dry DCM, rt, 0.5 h or (ii) *N*,*N*-DEA, reflux, 3 h.

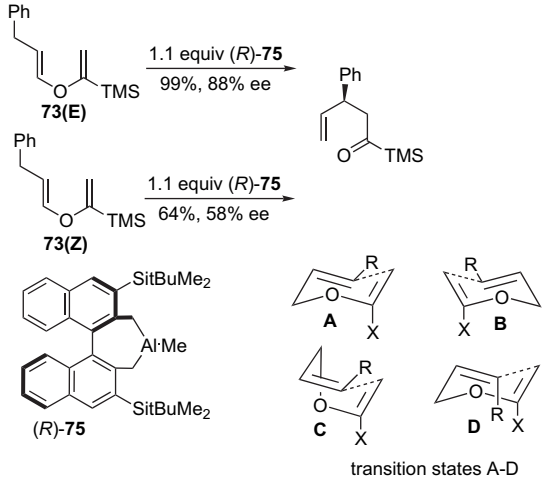
Dialkylaluminium halides (R_2AlCl, R=Et, ^tBu) catalyzed the Claisen rearrangement of allyl aryl ethers under mild condition and led to the formation of *o*-allyl phenols in almost quantitative yields and, in contrast to the catalyst BCl_3, the alkylaluminium derivatives effectively catalyzed the Claisen rearrangement of allyl aryl ethers having electron-withdrawing substituents on the aromatic ring. Diethylaluminium chloride catalyzed the Claisen rearrangement of allyl 2-bromophenyl ether **67** to furnish the *o*-allyl product **68** under mild conditions in excellent yield[28] (Scheme 21).



Scheme 21.

Al(III) complexes effectively catalyze the Claisen rearrangement of allyl vinyl ethers.[29] In the case of allyl vinyl ethers having two allyl fragments, the control of the regiochemistry during the Claisen rearrangement can be achieved by the use of an especially bulky organoaluminium Lewis acid reagent **72A** or **72B**. Compounds **69** under thermal conditions underwent a Claisen rearrangement to give **70** through the less hindered allyl group, whereas, in the presence of the catalyst **72A** or **72B**, the opposite regioselectivity was observed with the formation of **71**, due to minimization of the steric hindrance between the more substituted allyl group and the Lewis acid[30] (Scheme 22).

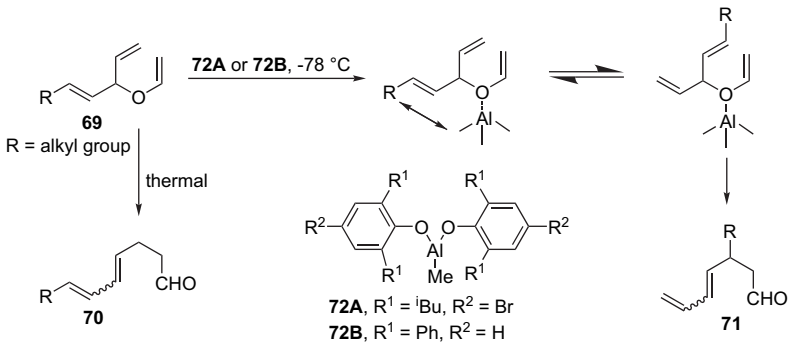
In 1990, Yamamoto et al.[31,32] reported the first example of a chiral Lewis acid-catalyzed enantioselective Claisen rearrangement. Allyl vinyl ether (*E*)-isomer **73**, in the presence of a Lewis acid chiral binaphthol–aluminium complex (*R*-**75**), underwent a Claisen rearrangement to give silyl ketone **74** in good yield with high enantioselectivity (88% ee). (*Z*)-Isomer **73** also gave the rearranged product having the same absolute stereochemistry (Scheme 23).



Scheme 23.

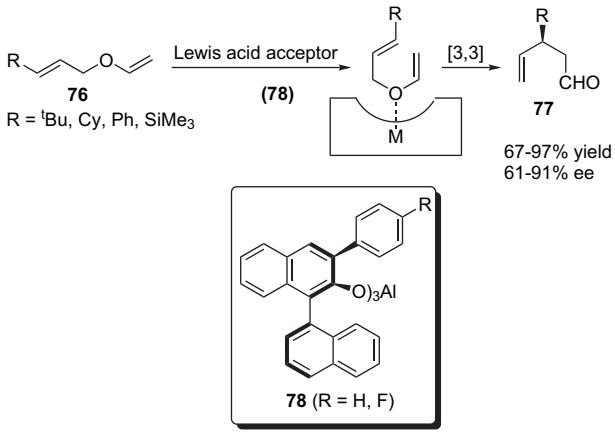
The Lewis acid-promoted Claisen rearrangement of **73** proceeds smoothly via a chair-like transition state. The reagent ((*R*)-**75**) efficiently discriminates between the two enantiotropic chair-like transition states and the transition state **A** is more favourable, as compared to the transition state **B** that leads to the high ee. The formation of the same product **74** from (*Z*)-**73** was explained by the fact that the boat-like transition state **C** is favourable over the chair-like transition state **D**, due to the steric repulsion between the allylic substituent and the bulky silyl group in **D**.

Further development of chiral Lewis acids for the enantioselective Claisen rearrangement has been conducted with C_3-symmetric aluminium complexes **78**, which act as chiral



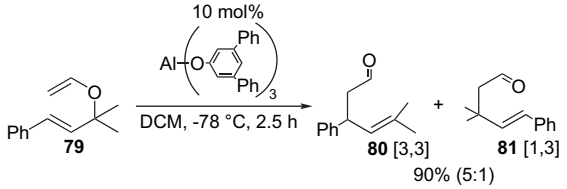
Scheme 22.

Lewis acid receptors capable of facilitating the rearrangement through a molecular recognition process and the formation of a transition state for a Claisen rearrangement of an allyl vinyl ether[33] **76** to give the rearranged product **77** (Scheme 24).



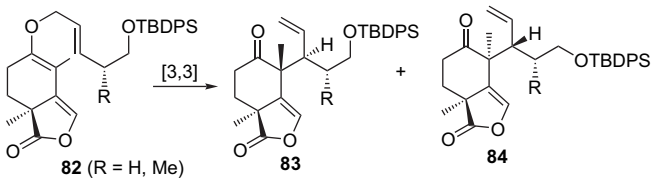
Scheme 24.

An Al(III)-based Lewis acid catalyzed the Claisen rearrangement of allyl vinyl ether **79**, leading to the formation of a mixture of products **80** and **81** arising from [3,3]- and [1,3]-rearrangements,[34] respectively (Scheme 25).



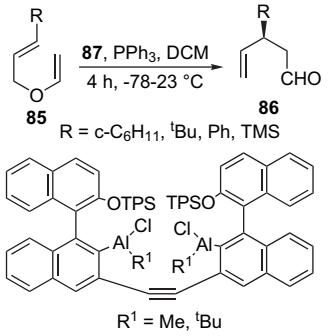
Scheme 25.

The bulky Lewis acid complex, $Et_2AlCl{\cdot}PPh_3$, has given moderate levels of diastereoselectivity from a remote asymmetric centre in the rearrangement of allyl vinyl ethers **82**. Thermal Claisen rearrangement of ethers **82** in toluene (105–125 °C) afforded the products **83** and **84** as a mixture of diastereomers (ranging from 1:1 to 1:3) in good yield (Scheme 26). The overall diastereoselectivity was significantly enhanced (5- to 8-fold) for the formation of the products **83** and **84** in moderate-to-excellent chemical yields in the presence of various Lewis acids. The stereoselectivity in the rearrangement of **82** appears to increase with (i) increasing steric bulk of the ligands on the Lewis acid and (ii) increasing electron deficiency of the Lewis acidic centre. Under optimal condition, the selectivity[35] is raised to 1:5.



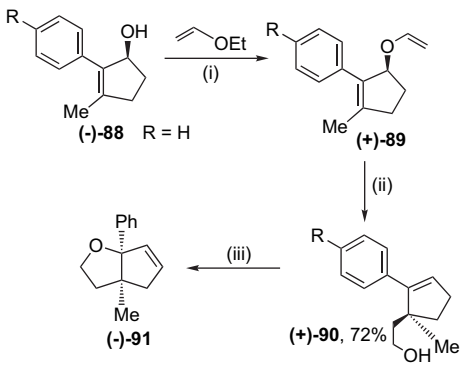
Scheme 26.

Moderate-to-good enantioselectivities were found for the Claisen rearrangement of allyl vinyl ethers **85** activated by chiral bis(organoaluminium) Lewis acids **87** prepared from (*S*)-binaphthol.[36] Treatment of the allyl vinyl ethers **85** with stoichiometric amounts of the aluminium reagents **87** at low temperature gave the chiral aldehydes **86** in 50–92% yields with 51–85% ee (Scheme 27).



Scheme 27.

$Hg(OAc)_2$-promoted vinylation of chiral allylic alcohol (−)-**88** followed by DIBAL-H-catalyzed Claisen rearrangement of (+)-**89** and subsequent reduction of the intermediate aldehyde led to the formation of the chiral primary alcohol (+)-**90** in good-to-excellent yields, which was further transformed into a 5,5-fused tetrahydrofuran derivative (−)**91**[37] (Scheme 28).

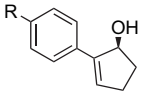
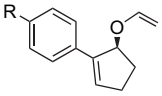
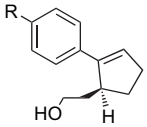
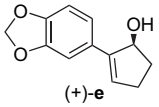
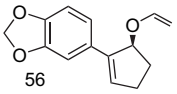
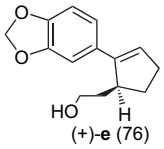
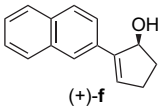
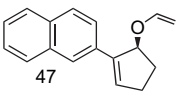
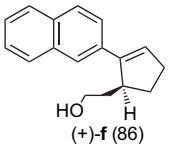
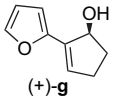
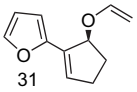
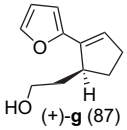
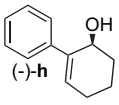
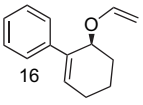
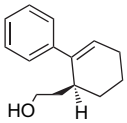


Scheme 28. Reagents and conditions: (i) $Hg(OAc)_2$ (0.28 equiv), 40 °C, 120 h, 61%; (ii) DIBAL-H, (1.1 equiv), DCM, −40 to 23 °C, 2 h, 72%; (iii) $Pd(TFA)_2$, (10 mol %), pyridine (40 mol %), O_2 (1 atm), Na_2CO_3 (4 equiv), MS (3 Å, PhMe, 80 °C, 17 h, 85%.

Allyl vinyl ethers derived from chiral allylic alcohols bearing a variety of aromatic groups also successfully underwent a DIBAL-H-promoted Claisen rearrangement and further transformation into enantio-enriched arylcyclopentenes. This reaction sequence additionally allowed access to cyclohexene (Table 3).

DIBAL-H and $Yb(OTf)_3$ were developed as alternative Lewis acids for achieving the Claisen rearrangement of allyl, crotyl and prenyl aryl ethers.[38] *para*-Substituted allyl aryl ethers **92** gave the *ortho*-Claisen products **93** and a small amount of the deallylated phenols in the presence of

Table 3
DIBAL-H-promoted Claisen rearrangement allylic alcohols

Entry	Allylic alcohol **88**[a]	Allyl vinyl ether, **89**, yield[b] (%)	Claisen product **90**,[c] yield[b] (%)
			
1	(+)-**a** (R=H)	55	(+)-**a** (36)
2	(+)-**b** (R=Me)	42	(+)-**b** (77)
3	(+)-**c** (R=OMe)	36	(+)-**c** (91)
4	(+)-**d** (R=CF_3)	37	(+)-**d** (82)
5	 (+)-**e**	 56	 (+)-**e** (76)
6	 (+)-**f**	 47	 (+)-**f** (86)
7	 (+)-**g**	 31	 (+)-**g** (87)
8	 (-)-**h**	 16	 (+)-**h** (83)

[a] Reaction conditions: $Hg(OAc)_2$ (0.28 equiv) in ethyl vinyl ether (0.08 M allylic alcohol), 40 °C, 120 h.
[b] Isolated yield.
[c] Reaction conditions: DIBAL-H (1.1 equiv, 1 M in PhMe) in DCM (0.08 M vinyl ether), −40 to 23 °C, 2 h.

10 mol % of $Yb(OTf)_3$ (Scheme 29a). *ortho*-Substituted allyl phenyl ethers afforded both the *ortho*- and the *para*-Claisen products and allyl-1-naphthyl ether gave the *ortho*-Claisen product. The rearrangement was complete in 40–72 h.

A $Yb(OTf)_3$-catalyzed Claisen rearrangement of aryl crotyl ethers **95** afforded the *ortho*-Claisen products **96** and the [1,3]-shift products **98** along with the corresponding cyclization products **99** and **100** (Scheme 29b). Crotyl-1-naphthyl ether gave the [1,3]-shift product in 60% yield. The rearrangements of crotyl phenyl ethers were complete in 3 h and this reaction time is less compared to that of allyl phenyl ethers (40–72 h). This may be due to the presence of the methyl group in the crotyl ethers.

DIBAL-H (1.5 equiv) catalyzed the Claisen rearrangement of allyl phenyl ethers **92** leading to the exclusive formation of **93** under mild conditions in a shorter reaction time of 24 h, along with the double-bond reduction product **94**, due to a hydroalumination and hydrolysis reaction (Scheme 29a). *o*-Substituted allyl aryl ethers gave the *ortho*-Claisen product as the major product along with the formation of the *para*-Claisen product. Crotyl phenyl ethers **95** in the presence of DIBAL-H afforded the *ortho*-Claisen products **96** (Scheme 29b). *p*-Methoxy- or *p*-fluoro-phenyl prenyl ether in the presence of DIBAL-H gave both the *ortho*- and the *meta*-Claisen products **96** and **97** at room temperature for 0.5 h, whereas 2,5-dimethylphenyl prenyl ether gave the *ortho*- and *para*-Claisen products. To summarize, the DIBAL-H-catalyzed Claisen rearrangement of allyl and crotyl ethers gave [3,3]-sigmatropic Claisen products, while the prenyl ethers provided [1,3]-shift products.

Me_2AlCl was found to catalyze the Claisen rearrangement of a bicyclic allyl vinyl ether **101** to afford the rearranged product **102** in good yields at 0 °C in 10 min (Scheme 30), whereas a much longer time, 24 h, was required under conventional heating in refluxing toluene.[39]

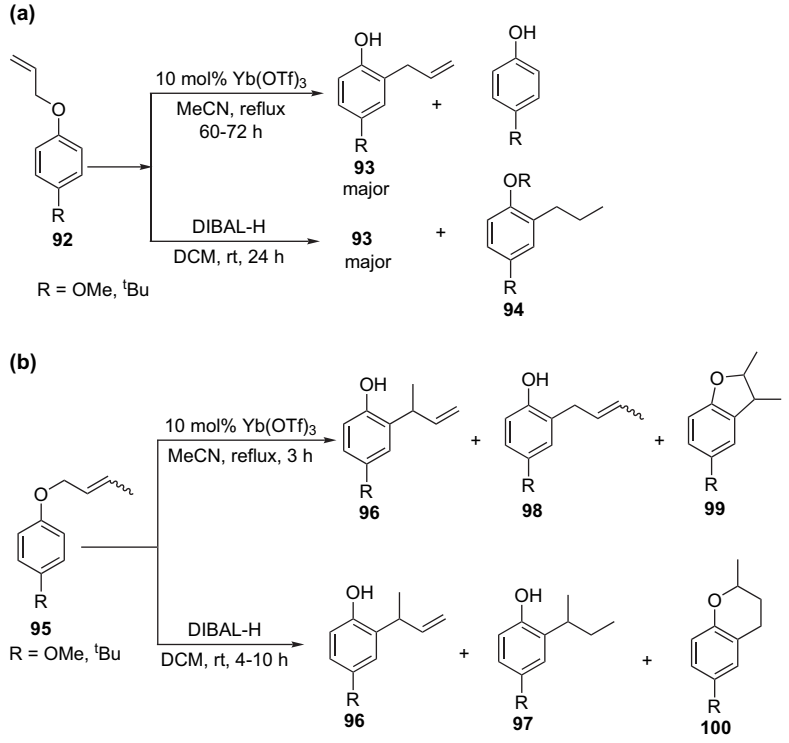
3.2.2. Catalysis by derivatives of chromium, manganese and iron

Lewis acids such as $Cu(OTf)_2$, $SnCl_4$, $TiCl_4$, $B(C_6F_5)_3$, and Al(III) and lanthanide(III) derivatives catalyzed the Claisen rearrangement of allyl vinyl ethers **103**.[36,40,41] For these rearrangements, stoichiometric amounts of the Lewis acid reagents or the allyl vinyl ethers were required and there is a lack of regioselectivity in the product formation, affording a regioisomeric mixture of [3,3] **104** and [1,3] **105** rearrangement products (Scheme 31).

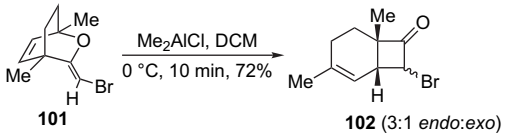
Rovis and Nasveschuk[42] reported that an increase in the strength of the Lewis acid and/or stability of the allyl cation results in increased [1,3]-selectivity. The metalloporphyrin-based weak Lewis acid catalyst Cr(TPP)Cl was developed to catalyze the Claisen rearrangement with high regioselectivity in order to obtain only the [3,3]-rearrangement product. Chromium complex catalyzed the Claisen rearrangement of allyl vinyl ethers[40] and enhanced the *E*/*Z* selectivity in the thermal Claisen rearrangement of 4,5- and 4,6-disubstituted allyl vinyl ethers.

Cr(TPP)Cl can effectively accelerate the Claisen rearrangement and efficiently depress the formation of ionic intermediates, and yet it enhances the concerted [3,3]-process, exhibiting high regioselectivity over a broad range of substrates, exclusively providing the corresponding Claisen products in high yields, in a fully catalytic fashion at low catalyst loading.[43]

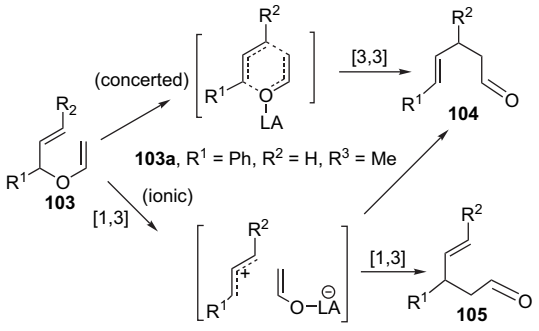
The Claisen rearrangement of the vinyl ether of 4-phenyl-3-buten-2-ol **103a** in the presence of Cr(TPP)Cl (5 mol %) in dichloroethane at 83 °C for 7 h led to the formation of only the [3,3]-Claisen rearrangement product **104a** in 94% yield. Such regioselective transformation of **103a** into **104a** could also be achieved by the use of other weak Lewis acid catalysts such as Fe(TPP)Cl, Mn(TPP)Cl, Cr(salen)Cl, and Mn(salen)Cl (Fig. 1) in good yield and a shorter reaction time, whereas in the absence of a catalyst, the rearrangement was quite sluggish and required a longer reaction time (58 h) to give only the product **104a** in 40% yield. In the presence of the stronger Lewis acid catalysts Cr(TPP)OTf and Fe(TPP)Otf, the undesired [1,3]-rearrangement product **105a** was observed as the major product, due to enhanced bond ionization of the substrate by these catalysts (Table 4).



Scheme 29.



Scheme 30.



Scheme 31. Putative mechanistic scheme for competitive formation of [3,3]- and [1,3]-adducts in the Lewis acid-mediated Claisen rearrangement of aliphatic allyl vinyl ethers.

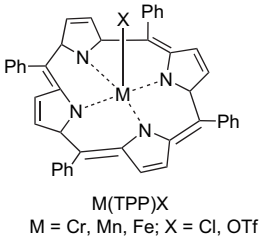
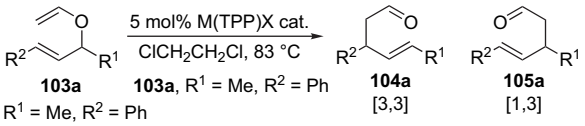


Figure 1.

Table 4
Porphyrin-based Lewis acid-catalyzed Claisen rearrangement of vinyl ethers 4-phenyl-3-buten-2-ol **103a**

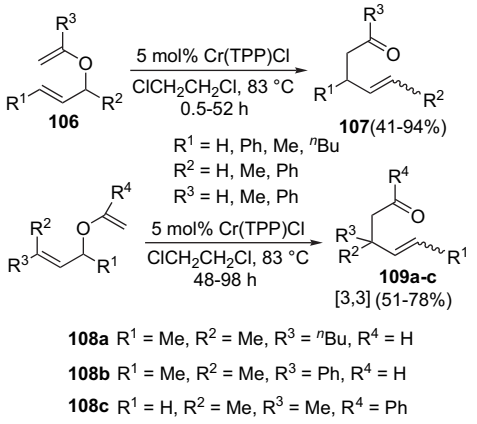


Entry	Catalyst	Time (h)	**104a** (%)[a] (*E*/*Z*)[b]	**105a** (%)[a]
1	Cr(TPP)Cl	7	94 (15:85)	—
2	None	58	40 (94:6)	—
3	Mn(TPP)Cl	24	62 (94:6)	—
4	Fe(TPP)Cl	24	83 (95:5)	—
5	Cr(salen)Cl	11	59 (85:15)	—
6	Mn(salen)Cl	24	62 (94:6)	—
7	Cr(TPP)OTf	24	19 (77:23)	26[c]
8	Fe(TPP)OTf	2	16(>99:1)	27[c]

[a] Isolated yield.
[b] *E*/*Z* ratios determined by 300 MHz ^{1}H NMR spectroscopy.
[c] Inseparable complex mixture of by-products was also produced in the catalytic rearrangement.

Cr(TPP)Cl was found to achieve excellent regioselectivity and the substituents on the vinyl moiety or on the allyl part or on the phenyl ring in the allyl vinyl ether substrates **106** did not affect the regioselectivity. The [3,3]-rearranged products **107** were always obtained in moderate-to-high yields (41–94%) and almost perfect regioselectivity at low catalyst loading (5 mol %) (Scheme 32).

In case of trisubstituted allyl vinyl ethers **108a–c**, the Cr(TPP)Cl catalyst afforded only the [3,3]-rearranged products **109a–c** without the formation of the corresponding [1,3]-products[43] via a concerted [3,3]-pathway with a minimal



Scheme 32.

degree of bond ionization (Scheme 32). With strong Lewis acids, such as $Cu(OTf)_2$, $SnCl_4$, $TiCl_4$, Me_2AlCl and $EtAlCl_2$, the formation of the [1,3]-rearranged product via the recombination of the metallo-enolate and allyl cation at the less hindered secondary position became fast, compared with the [3,3]-recombination to form a quaternary carbon center at the tertiary cation (Fig. 2), which hampered the regioselectivity.

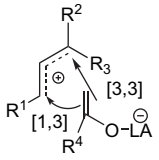


Figure 2.

3.2.3. Catalysis by derivatives of copper and lanthanides

Lanthanide triflates were found to catalyze the Claisen rearrangement of 1-isopropyl-6-propyl substituted allyl vinyl ether **110a** at room temperature in CH_2Cl_2 in the presence of molecular sieves with excellent chemoselectivity (Scheme 33). The rate of the reaction depended on the lanthanide(III) cation present in the reaction mixtures and decreased with increasing ionic radius.[5,44,45]

The less Lewis acidic (with increasing ionic radius) lanthanide triflates needed prolonged reaction times for complete conversion of the allyl vinyl ether **110a** into α-oxo ester **111a** (Table 5, entries 5 and 7). Thus, $Lu(OTf)_3$ and $Yb(OTf)_3$ were found to be the most reactive catalysts amongst other catalysts employed in the same reaction.

It was also observed that $Cu(OTf)_2$ and $Yb(OTf)_3$ catalyzed the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers **110** in the presence of molecular sieves. The reactivity and stereoselectivity strongly depended upon the substrate structure.[45] The (*Z*,*Z*)-configured allyl vinyl ethers **110a**–**c** underwent a catalyzed Claisen rearrangement with high diastereoselectivity to give the *syn*-configured α-keto ethers **111a**,**c** (Table 6, entries **3**, **4**, **7**, **8** and **9**), but the (*Z*,*E*)-configured allyl vinyl ethers underwent rearrangement with a significantly lower diastereoselectivity (Table 6).

Table 5
Ln(III)-catalyzed Claisen rearrangement of allyl vinyl ether **110a**

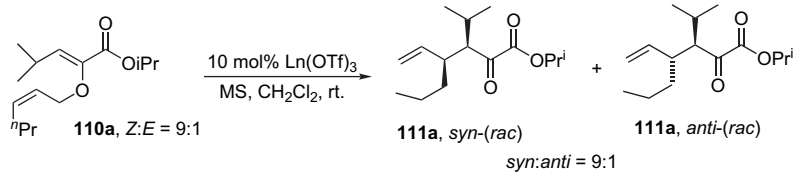
Entry	$Ln(OTf)_3$[a]	Ln^{3+} radius (Å)	*t* (h)	Yield[b] (%)	Conversion (%)
1	$Lu(OTf)_3$	0.848	6	98	100
2	$Yb(OTf)_3$	0.858	6	98	100
3	$Tm(OTf)_3$	0.869	6	100	93
4	$Er(OTf)_3$	0.881	6	99	82
5	$Er(OTf)_3$	0.881	24	100	100
6	$Ho(OTf)_3$	0.894	6	98	75
7	$Ho(OTf)_3$	0.894	24	98	100
8	$Dy(OTf)_3$	0.908	6	99	65
9	$Tb(OTf)_3$	0.923	6	100	66
10	$Gd(OTf)_3$	0.938	6	100	49
11	$Eu(OTf)_3$	0.950	6	100	44
12	$Sm(OTf)_3$	0.964	6	97	41
13	$Nd(OTf)_3$	0.995	6	99	29
14	$Pr(OTf)_3$	1.013	6	99	30
15	$Ce(OTf)_4 \cdot H_2O$	0.92 (Ce^{4+})	6	100	41
16	$La(OTf)_3$	1.061	6	98	7
17	$Y(OTf)_3$	0.88	6	100	61

[a] Reactions were performed with 0.4 mmol of the allyl vinyl ether in DCM (4 ml) containing 1–3 mol % of EtOH.
[b] Isolated yield after removal of the catalyst by filtration through 4×0.5 cm silica gel column.

A comparative study of the Claisen rearrangement of allyl vinyl ether **110b** catalyzed by $Lu(OTf)_3$, $Sc(OTf)_3$, $Cu(OTf)_3$ and hydrated $LuCl_3$ and $YbCl_3$ showed that $Sc(OTf)_3$ was the most active Lewis acid followed by $Cu(OTf)_2$ and $Lu(OTf)_3$.[45] The $LuCl_3$- and $YbCl_3$-catalyzed Claisen rearrangement required a longer reaction time to afford the product **111b** with complete consumption of the substrate **110b** (Table 7).

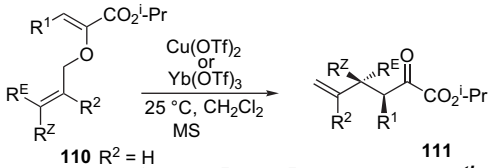
After a successful study of the Claisen rearrangement catalyzed by $Cu(OTf)_2$ and molecular sieve systems,[45] chiral Cu^{II}[bis(oxazoline)] complexes were used as potential catalysts for the enantioselective Claisen rearrangement[5] of 6,6-dimethyl-substituted allyl vinyl ethers **112** to afford the products **113a**,**b** with high enantioselectivities (Scheme 34).

The presence of an alkoxycarbonyl group (acceptor function) at the 2-position of the allyl vinyl ether was found to be crucial for improved reactivity and stereoselectivity. This acceptor function together with the allylic ether oxygen atom favours chelation of the Lewis acid, which allows the



Scheme 33.

Table 6
$Cu(OTf)_2$- and $Yb(OTf)_3$-catalyzed Claisen rearrangement



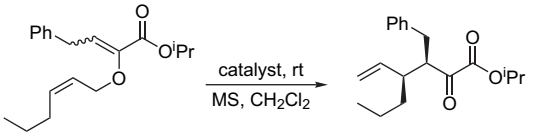
110 R^2 = H — **111**

***Z,E*-a**	R^1 = *i*-Pr, R^Z = H, R^E = *n*-Pr	***anti*-a**
***Z,Z*-a**	R^1 = *i*-Pr, R^Z = *n*-Pr, R^E = H	***syn*-a**
***Z,Z*-b**	R^1 = Bn, R^Z = *n*-Pr, R^E = H	***syn*-b**
***Z,E*-b**	R^1 = Bn, R^Z = H, R^E = *n*-Pr	***anti*-b**
***Z,Z*-c**	R^1 = Bn, R^Z = CH_2OBn, R^E = H	***syn*-c**

Entry	Substrate	Catalyst (equiv)	*T* (°C)	Yield[b] (%)	*syn*/*anti*[c]
1	*Z,E*-**a** (92:8)[a]	$Cu(OTf)_2$ (0.05)	25	97	55:45
2	*Z,E*-**a** (92:8)	$Yb(OTf)_3$ (0.05)	25	95	69:31
3	*Z,Z*-**a** (92:8)	$Cu(OTf)_2$ (0.05)	25	99	93:7
4	*Z,Z*-**a** (92:8)	$Yb(OTf)_3$ (0.075)	25	99	91:9
5	*Z,E*-**b** (96:4)	$Cu(OTf)_2$ (0.05)	25	99	22:71
6	*Z,E*-**b** (96:4)	$Yb(OTf)_3$ (0.05)	25	99	34:66
7	*Z,Z*-**b** (97:3)	$Cu(OTf)_2$ (0.05)	25	98	93:7
8	*Z,Z*-**b** (97:3)	$Yb(OTf)_3$ (0.075)	25	99	96:4
9	*Z,Z*-**c** (96:4)	$Yb(OTf)_3$ (0.1)	60	97[d]	94:6

[a] *Z*/*E* ratio of enol ether double bond.
[b] Isolated material after filtration through 4×0.5 cm silica gel column.
[c] Determined by ^1H NMR spectroscopy.
[d] Reaction was performed in a sealed tube in DCM.

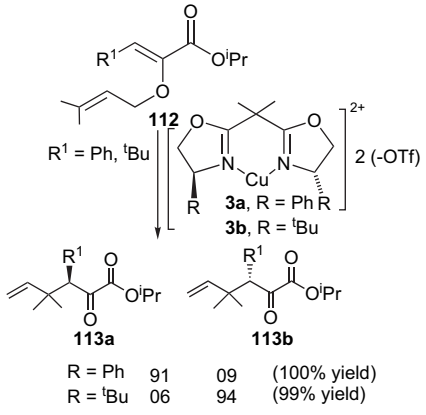
Table 7
Study of different Lewis acid catalysts for Claisen rearrangement of allyl vinyl ether **110b**



110b *Z*:*E* = 97:3 — **111b** *syn*:*anti* = 95:5

Entry	Catalyst (mol %)	*t* (h)	Yield[a] (%)
1	$Sc(OTf)_3$ (5)	0.5	98
2	$Cu(OTf)_2$ (10)	1	100
3	$Lu(OTf)_3$ (10)	3	98
4	$LuCl_3 \cdot 6H_2O$ (10)	18	98
5	$YbCl_3 \cdot 6H_2O$ (10)	18	97

[a] Isolated yield after removal of the catalyst by filtration through 4×0.5 cm silica gel column.



Scheme 34. [Cu(box)]$(OTf)_2$-catalyzed enantioselective Claisen rearrangement.

high stereoselectivity. The stereochemical outcome could be explained by the formation of a chair-like transition state arranging the Cu(II) as a chelate between the allyl ether and the side-chain carbonyl oxygen.

The catalyzed Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers **114** in the presence of 5–10 mol % bis(oxazoline)copper complex **3b** (Fig. 3) afforded the Claisen products **115a** and **115b** in very high yields and with moderate enantioselectivities. Coordination of the allyl vinyl ethers **114** with catalyst **3b** exhibiting a square planar geometry around the Cu(II) cation was proposed to account for the enantioselectivity of the rearrangement[46] (Scheme 35).

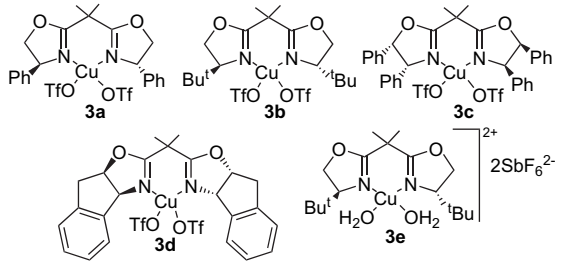
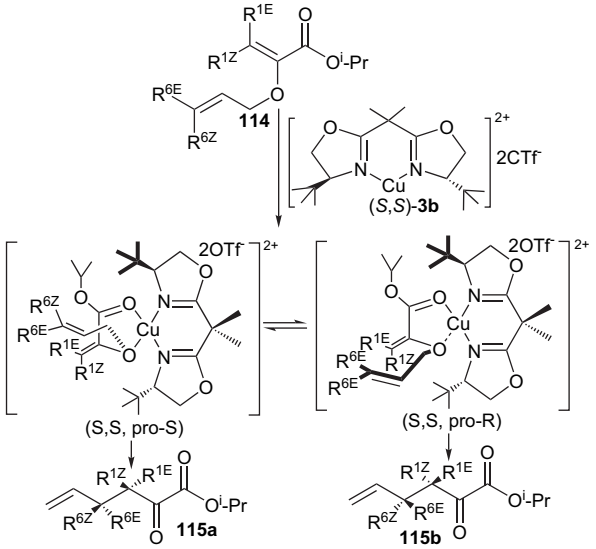


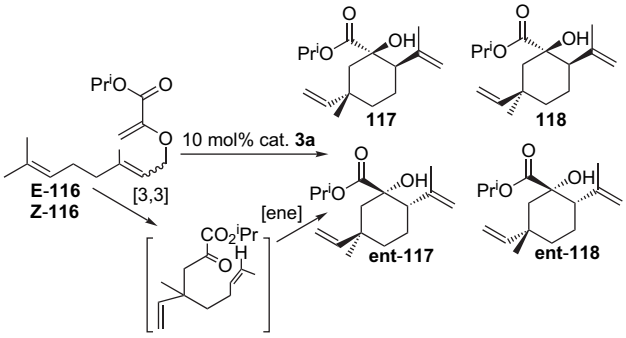
Figure 3. Catalysts for catalytic asymmetric Claisen rearrangement.



Scheme 35.

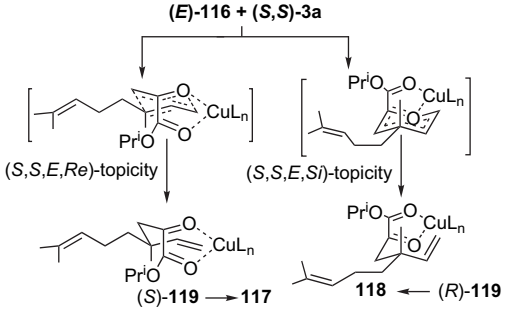
If a chair-like transition state is assumed for the Claisen rearrangement, the allyl fragment must approach the vinyl moiety opposite to the *tert*-butyl substituent at the bis(oxazoline). In this model, the catalyst differentiated the enantiomeric chair conformations by distinguishing between the enantiotopic electron pair [(*pro-R*) and (*pro-S*)] at the ether oxygen atom. From the results obtained (Scheme 34), 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 ethers, the absolute configuration of the major isomer of the rearrangement could be explained.

The first catalytic asymmetric domino Claisen rearrangement–carbonyl ene reaction was reported by Hiersemann and Kaden.[47] Chiral copper(II) bis(oxazoline) complex **3a**, [Cu(*S*,*S*)–Ph–box](OTf)$_2$ or [Cu(*R*,*R*)–Ph–box](OTf)$_2$ (Fig. 3), effectively catalyzed the Claisen rearrangement of an achiral allyl vinyl ether (*E*/*Z*)-**116** into substituted 1-hydroxycyclohexanecarboxylic esters **117**/**118** and *ent*-**117**/*ent*-**118** (Scheme 36).



Scheme 36.

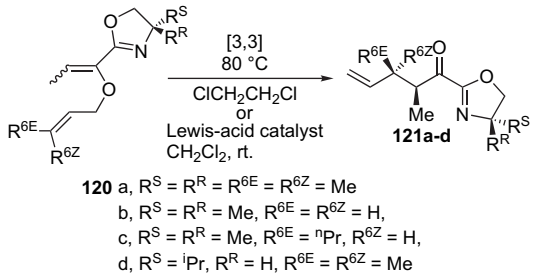
The reaction of (*E*)-**116** with catalyst **3a** afforded the product **117** and *ent*-**117** as the major product, while (*Z*)-**116** gave the ester **118** and *ent*-**118** as the major product. This reaction proceeded with a high catalyst-induced diastereo- and enantioselectivity. The formation of a stable chelate between the 2-alkoxycarbonyl-substituted allyl vinyl ether **116** and the catalyst **3a** controlled the high diastereoselectivity and enantioselectivity. The stereoselectivity of the rearrangement was rationalized by considering that the rearrangement of (*E*)-**116** in the presence of (*S*,*S*)-**3a** proceeded preferentially through a transition state with (*S*,*S*,*E*,*Re*)-topicity (*S*)-**119**.[47] The minor diastereomer (*R*)-**119** was formed by a Claisen rearrangement through a transition state with (*S*,*S*,*E*,*Si*)-topicity. Compounds (*S*)-**119** and (*R*)-**119** gave the products **117** and **118**, respectively (Scheme 37).



Scheme 37.

The Claisen rearrangement of 2-(1,3-oxazolin-2-yl)-substituted allyl vinyl ethers **120**, a novel type of 2-acceptor-substituted allyl vinyl ether, was studied thermally as well as in the presence of achiral and chiral Lewis acids[48] (Scheme 38).

The thermal Claisen rearrangement of **120a–d** at 80 °C required prolonged reaction times (39–95 h) and proceeded



Scheme 38.

with high chemoselectivity and simple diastereoselectivity to afford the rearrangement products **121a–d** in almost quantitative yield (96–99%).

The Claisen rearrangement of (*E*)-**120a** (R^S=R^R=R^{6E}=R^{6Z}=Me) was studied in the presence of different metal triflates (5 mol %) as achiral Lewis acid catalysts in CH_2Cl_2 at room temperature in the presence of activated molecular sieves to ensure the optimal chemoselectivity and reactivity (Table 8); Cu(OTf)$_2$ was found to be the most efficient catalyst in terms of reactivity. The substrate structure significantly influenced the reactivity and diastereoselectivity. The alkyl substituents on C-6 accelerated the Lewis acid-catalyzed Claisen rearrangement, presumably by stabilizing a partial positive charge in the highly polarized pericyclic transition state. The chiral bis(oxazoline)copper(II) complexes **3a**/**3b** catalyzed the Claisen rearrangement of **120** with low-to-moderate enantioselectivities. The reactivity and enantioselectivity were very low for the substrates **120a**,**b** as the bulky 1,3-oxazoline moiety decelerates the formation of the substrate–catalyst complex. The ^{i}Pr-substituted substrate **120d** was the most reactive allyl vinyl ether, due to decreased steric hindrance between **120d** and the Cu(II) catalyst.

Variation of the catalyst structure was attemped[49] in order to improve the enantioselectivity of the reaction to give **123** from **122** to a synthetically useful level. The use of Lewis acid catalysts (**3a–d**, Fig. 3), however, did not significantly improve the enantioselectivity, compared to the previous results[44–46] (Table 9).

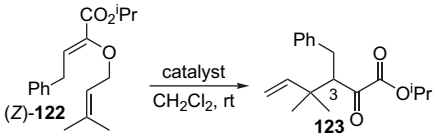
In order to differentiate between the enantiotopic faces of the vinyl ether double bond and, at the same time, to improve the reactivity of the catalyst by increasing the Lewis acidity of the copper, the triflate counterion of the catalyst **3b** was exchanged with a hexafluoroantimonate ion to give the catalyst [{Cu (^{t}Bu–box)(H$_2$O)$_2$}(SbF$_6$)$_2$, **3e**, Fig. 3)].

Table 8
Lewis acid (5 mol %)-catalyzed Claisen rearrangement of (*E*)-**120a**

Entry	Lewis acid	*t* (h)	Yield[a] (%)	**121a**/(*E*)-**120a**[b]
1	Cu(OTf)$_2$	3	92	1:0
2	Lu(OTf)$_3$	18	80	78:22
3	Lu(OTf)$_3$	89	80	78:22
4	Sc(OTf)$_3$	18	84	37:63
5	Sc(OTf)$_3$	89	84	43:57
6	Sn(OTf)$_2$	101	85	9:91

[a] Isolated yield.
[b] Ratio determined by ^{1}H NMR spectroscopy.

Table 9
Catalytic effect in the enantioselectivity of **123** from **122**

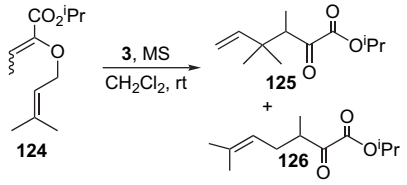


Entry[a]	Catalyst	*t* (h)	Yield (%)	3*S*/3*R*[b]
1	(*R*,*R*)-**3a**	0.5	100	88:12
2	(*S*,*S*)-**3b**	72	100	93:7
3	(4*R*,5*S*)-**3c**	24	99	86:14
4	(4*S*,5*R*)-**3d**	24	100	90:10

[a] All reactions carried out on 0.4 mmol scale.
[b] Determined by chiral HPLC: Chiracel OD 14025.

A comparison of the reaction time and enantioselectivity of the **3e**-catalyzed rearrangement of allyl vinyl ether **124** to **125** clearly showed that the use of **3e** led to a faster and more enantioselective Claisen rearrangement (Table 10).

Table 10
Highly enantioselective Claisen rearrangement of allyl vinyl ether **124**



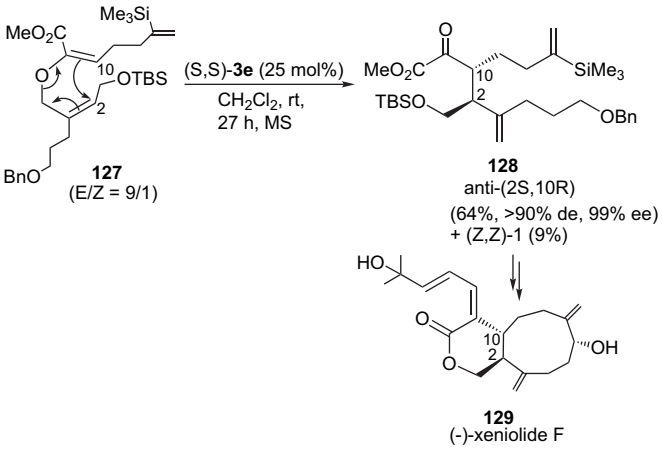
Entry[a]	**124**	Catalyst (mol %)	*t* (h)	Yield (%)	ee[b] (%, **125**)
1	(*Z*)	(*S*,*S*)-**3b** (10)	24[c]	100	94 (3*S*)
2	(*Z*)	(*S*,*S*)-**3e** (10)	24	95[d]	99 (3*S*)
3	(*Z*)	(*S*,*S*)-**3e** (5)	2	94[d]	99 (3*S*)
4	(*E*)	(*S*,*S*)-**3e** (5)	2[c]	100	99 (3*R*)

[a] All reactions were performed on 0.4 mmol scale.
[b] Determined by chiral HPLC: Chiracel OD 14025.
[c] Optimized reaction time and catalyst loading.
[d] Compound **126** of 5%, separated by chromatography; enantiomeric ratio not determined.

Although a small amount (5%) of the undesired [1,3]-rearranged product **126** was obtained by the application of **3e**, it attributed to a significant progress in the asymmetric Claisen rearrangement, compared to the previous results.[45,46]

The catalytic asymmetric Claisen rearrangement (CAC) of a highly substituted and functionalized α-alkoxycarbonyl-substituted allyl vinyl ether **127** using chiral Lewis acid catalyst **3e** was applied as the key step for the total synthesis of (−)-xeniolide F **129**, a bioactive natural product[50] (Scheme 39).

An *E*/*Z* (9:1) mixture of the allyl vinyl ether **127** under the above conditions furnished the desired rearrangement product *anti*-(2*S*,10*R*)-**128** in 64% yield as a single diastereo- and enantiomer from (*E*,*Z*)-**127**, but the minor component (*Z*,*Z*)-**127** did not rearrange even with a stoichiometric amount of (*S*,*S*)-**3e**; thermal conditions (80 °C for 32 h) gave (±)-*anti*-**128**



Scheme 39.

in 50% yield and (*Z*,*Z*)-**127** remained unreactive. The stereochemical outcome of the Claisen rearrangement and the different reactivities of (*E*,*Z*)-**127** and (*Z*,*Z*)-**127** were explained by considering the substrate–catalyst complexes **130** and **131** (Fig. 4), where the substrate coordinated with the catalyst in a bidentate fashion. The severe 1,3-diaxial interaction between the substituents at C-10 and C-3 in complex **130** prevented the rearrangement of (*Z*,*Z*)-**127**, but the destabilizing 1,3-diaxial interaction was absent in complex **131**, which catalyzed the rearrangement to give the product *anti*-(2*S*,10*R*)-**128**, and the configuration was due to a chair-like transition state geometry and to the privileged topicity[50] of the **3e**-catalyzed rearrangement of an allyl vinyl ether **127** containing an *E*-configured vinyl ether double bond.

Recently, a **3e**-catalyzed asymmetric Claisen rearrangement has been utilized as a key C–C bond-forming step for the total synthesis of the natural products, curvicollides A–C, which are fungicidal polyketides.[51] By an implementation of this methodology, the allyl vinyl ether (*E*,*Z*)-**132** underwent the desired Claisen rearrangement in the presence of 7.5 mol % of **3e** to afford the α-ketoester (3*R*,4*R*)-**133** as a single diastereomer and enantiomer in good yield (Scheme 40).

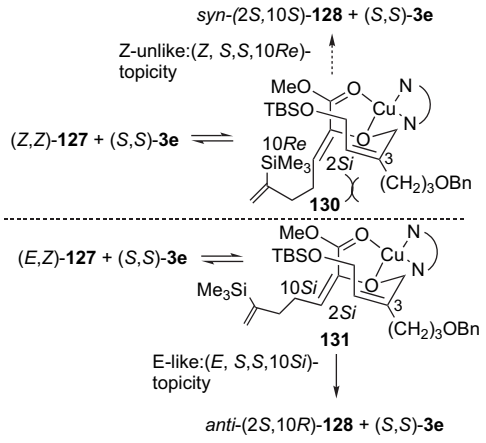
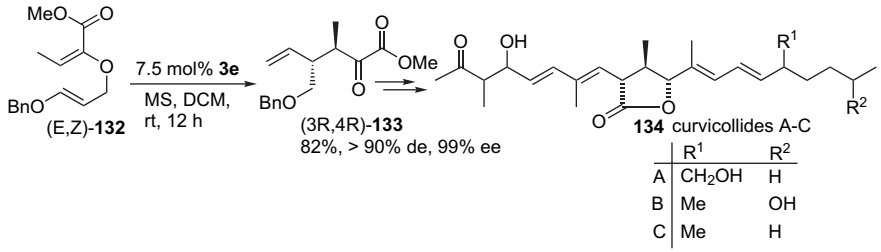


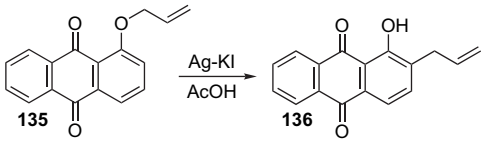
Figure 4. Stereochemical course of CAC.



Scheme 40.

3.2.4. Catalysis by derivatives of silver and gold

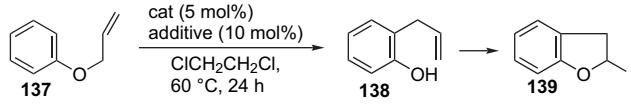
Silver tetrafluroborate ($AgBF_4$) and trifluoroacetate ($AgOCOCF_3$) catalyzed the Claisen rearrangement of aryl propargyl ethers.[3] A different type of accelerating effect in the Claisen rearrangement of **135** to **136** was observed where Ag–KI/HOAc system promoted the reductive rearrangement of allyloxyanthraquinone[52] (Scheme 41). The reduction of the anthraquinone to hydroquinone by Ag–KI might be responsible for the acceleration of the rearrangement.



Scheme 41.

A combination of $IrCl_3$ and AgOTf acts as an efficient catalyst for the tandem cyclization of allyl aryl ether **137** via **138** into dihydrobenzofuran **139** in 65% yield. Various metal catalysts were employed to carry out this transformation in the absence and presence of AgOTf (Table 11).

Table 11
Catalyst screening for Claisen hydroaryloxylation of **137**



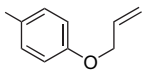
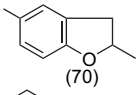
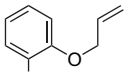
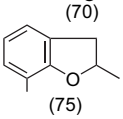
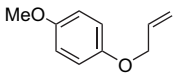
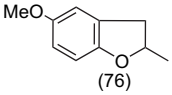
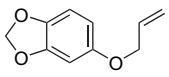
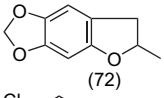
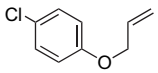
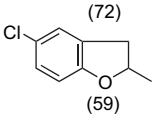
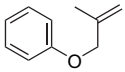
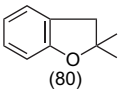
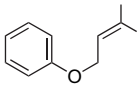
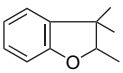
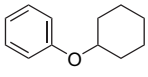
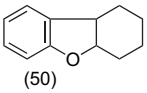
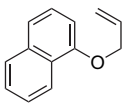
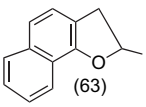
Entry	Catalyst	Additive	Yield[a] (%)
1	$RuCl_3$	None	0
2	$RuCl_3$	AgOTf	43
3	$PtCl_2$	None	0
4	$PtCl_2$	AgOTf	11
5	$PtCl_4$	AgOTf	12
6	$PtCl_2(CH_2{=}CH_2)$	Ph_3P	0
7	$Cu(OTf)_2$	None	44
8	$Cu(OTf)_2$	AgOTf	20
9	$Sc(OTf)_3$	None	0
10	$Sc(OTf)_3$	AgOTf	22
11	$Yb(OTf)_3$	None	0
12	$Yb(OTf)_3$	AgOTf	25
13	$IrCl_3$	None	0
14	$IrCl_3$	AgOTf	65
15	$PdCl_2(MeCN)_2$	None	0
16	None	AgOTf	0

[a] Reaction was performed at 0.5 M 1 in 1,2-dichloroethane at 60 °C for 24 h.

It was found that the addition of AgOTf promoted the transformation [except for the catalyst $Cu(OTf)_2$] and the $IrCl_3$/AgOTf system was found to be the most effective. Interestingly, neither $IrCl_3$ nor AgOTf alone was able to promote the conversion and the in situ-generated iridium catalyst might be responsible for this tandem intramolecular hydroaryloxylation.[52,53] The $IrCl_3$/AgOTf system was applied for the tandem Claisen rearrangement of a wide range of allyl aryl ethers and a variety of dihydrobenzofurans were obtained under mild conditions in moderate-to-good yields (Table 12).

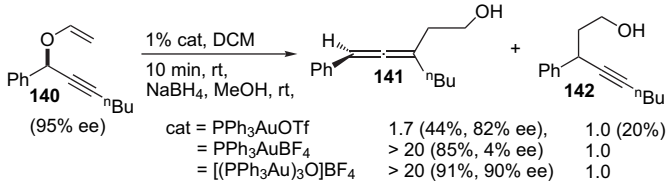
A gold(I) complex [$Ph_3PAuOTf$] catalyzed the Claisen rearrangement[54] of propargyl vinyl ether **140**, affording the

Table 12
Iridium-catalyzed Claisen hydroaryloxylation of aryl ethers

Entry	Substrate	Product[a] (%)
1		 (70)
2		 (75)
3		 (76)
4		 (72)
5[b]		 (59)
6[c]		 (80)
7		
8		 (50)
9		 (63)

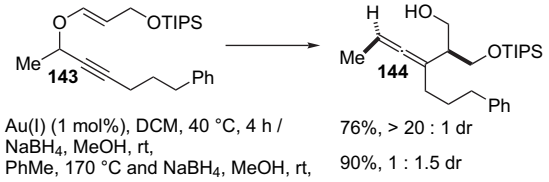
[a] All reactions were performed with 5 mol % $IrCl_3$ and 10 mol % AgOTf in $ClCH_2CH_2Cl$ (0.5 M) at 60 °C for 24 h, unless otherwise noted.
[b] Performed at 60 °C for 36 h.
[c] Performed at 60 °C for 4 h.

desired allene intermediate **141** with the formation of a small amount of the [1,3]-rearrangement product **142**. Interestingly, however, by changing the counterion from $^{-}$OTf to BF_4^-, the [3,3]-rearrangement product **141** was obtained exclusively, although it gave an almost racemic homoallenic alcohol **141** from enantio-enriched propargyl vinyl ether **140**. This problem was overcome by using a gold–oxo complex $[(Ph_3PAu)_3O]$-BF_4 and the product **141** was obtained in 91% yield and with nearly complete chirality transfer (90% ee) (Scheme 42).



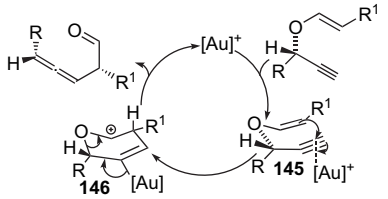
Scheme 42.

Gold(I)–oxo complex $[(Ph_3PAu)_3O]BF_4$ catalyzed the Claisen rearrangement of β-substituted vinyl propargyl ether **143** to afford a single diastereomer of **144** at 40 °C, whereas the thermal rearrangement at 170 °C gave a 1:1.5 diastereomeric mixture of **143** in favor of the opposite diastereomer (Scheme 43).



Scheme 43.

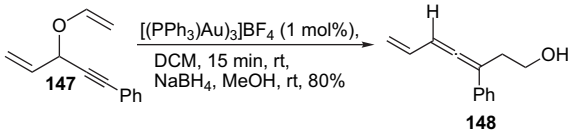
The Claisen rearrangement was mechanistically rationalized by considering a cyclization-induced rearrangement catalyzed by Au(I). A 6-*endo-dig* addition of the enol ether onto the gold(I)–alkyne complex **145** gave the intermediate **146**, which underwent a Grob-type fragmentation leading to the formation of the β-allenic aldehyde with the regeneration of the Au(I) catalyst (Scheme 44).



Scheme 44. Proposed mechanism for Au(I)-catalyzed rearrangement.

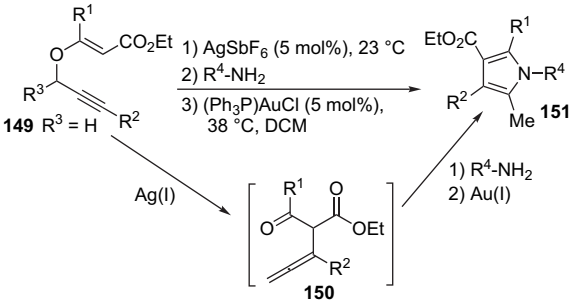
Interestingly, the Au(I)-catalyzed rearrangement of **147** afforded the product **148** by the acetylenic Claisen pathway, whereas the thermal[55a] and hard Lewis acid-catalyzed[55b] rearrangements gave the allyl vinyl ether rearranged product (Scheme 45).

Ag(I) salts effectively catalyzed the Claisen rearrangement of propargyl vinyl ethers at room temperature in CH_2Cl_2. A



Scheme 45.

one-pot synthesis of tetra- and penta-substituted pyrroles **151** has been accomplished from various substituted propargyl vinyl ethers **149** by the Ag(I)-catalyzed Claisen rearrangement in the presence of the catalyst $AgSbF_6$, followed by the condensation of the allenyl carbonyl intermediate **150** with an aromatic amine and a gold(I)-catalyzed 5-*exo-dig* heterocyclization[56] (Scheme 46).



Scheme 46.

This one-pot methodology has been successfully utilized for the synthesis of various substituted pyrrole derivatives. The reaction of propargyl vinyl ethers **149** with aryl or heteroaryl amines afforded the substituted pyrroles in 52–96% yields (Table 13). The reaction with aliphatic amines did not give the corresponding pyrroles.

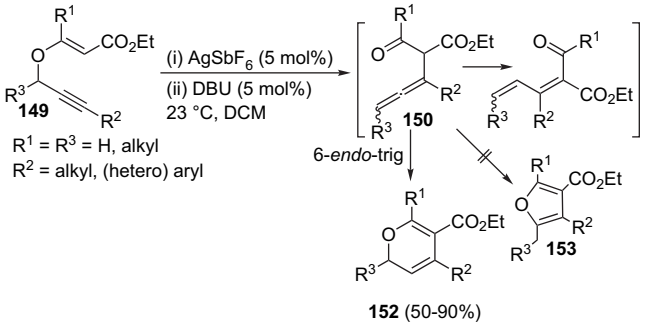
Table 13
Formation of pyrroles **151** from **149**[a]

Entry	R^1	R^2	R^4	**151**, Yield[b] (%)
1	Ph	Me	Ph	71
2	Ph	Me	*p*-MeO(C_6H_4)	75
3	Ph	Me	*m*-Cl(C_6H_4)	83
4	Ph	Me	1-Naphthyl	72
5[c]	Ph	Me	C	52
6	Ph	Me	*p*-Br(C_6H_4)	74
7	Ph	Me	*p*-^{i}Pr(C_6H_4)	73
8	Ph	Me	*o*-^{i}Pr(C_6H_4)	67
9	Ph	Me	*m*-NO_2(C_6H_4)	55
10	Me	Ph	Ph	75
11	Me	Ph	*p*-MeO(C_6H_4)	75
12	Me	*O*-MeO(C_6H4)	Ph	83
13	^{n}Pent	Me	Ph	68
14	Ph	Ph	Ph	65
15	Ph	3-Thienyl	Ph	74
16	Ph	CH_2–C_6H_{11}	Ph	96
17	Ph	CH_2–C_6H_{11}	1-Naphthyl	79
18	Ph	$(CH_2)_3$OTHP	Ph	70
19	Ph	H	Ph	52
20	Ph	TBDMS	Ph	77

[a] Conditions: 0.2 mmol of **11**, 5 mol % of $AgSbF_6$, 23 °C, DCM (0.4 M), 30 min, R^4–NH_2 (1.5 equiv), 23 °C; 5 mol % $(PPh_3)AuCl$, 38 °C, 30–240 min.
[b] Pure product after column chromatography.
[c] C=3-(2-carboxymethoxythiophene).

The cationic silver(I) salts effectively catalyzed the Claisen rearrangement of propargyl vinyl ethers to the corresponding allenyl carbonyl compounds.[57] An $AgSbF_6$-catalyzed Claisen rearrangement of propargyl vinyl ethers **149** was the key step for a one-pot synthesis of 2*H*-pyrans[58] **152**. It is interesting to note that this reaction did not give any five-membered product **153**.

The one-pot sequence proceeded via an Ag(I)-catalyzed propargyl-Claisen rearrangement, followed by a base (DBU)-catalyzed isomerization and 6π-oxa-electrocyclization leading to the formation of suitable 2*H*-pyrans **152** at room temperature in good-to-excellent yields (Scheme 47). Various substituted propargyl vinyl ethers were transformed into 2*H*-pyrans in up to 90% yields that depended upon the substituents present.

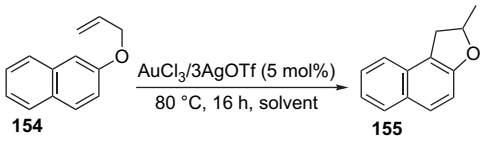


Scheme 47.

We have so far discussed the catalysis of the aliphatic Claisen rearrangement by the gold catalysts. The cationic gold species[59] $AuCl_3$/3AgOTf catalyzed the aromatic Claisen rearrangement of allyl 2-naphthyl ether **154**. $AuCl_3$/3AgOTf (5 mol %) catalyst system catalyzed the Claisen rearrangement of **154**, but the rearrangement was too slow at room temperature and required higher temperatures (80 °C) for completion. The rearrangement is followed by cyclization to give the dihydrobenzofuran **155** in moderate yields (45–73%)[60] (Table 14).

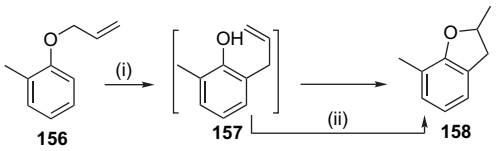
Gold(I) chloride in combination with a phosphine ligand and with silver(I) triflate [Ph_3PAuCl/AgOTf] was found to catalyze the Claisen rearrangement of **154** by the in situ-generated $Ph_3PAuOTf$ in excellent yield (>95%, entry 4, Table 14). The electron-donating group on the aromatic ring increases the yield. AgOTf and HOTf also catalyzed the Claisen rearrangement of **154**, affording the product **155** in 57–66% yields (Table 14). As the *ortho*-allyl product was not obtained from the catalyzed Claisen rearrangement of **154**, another set of experiments were carried out. The Au(I)-catalyzed Claisen rearrangement of **156** followed by cyclization afforded **158** in 24% yield at 85 °C after 24 h. Intermediate **157** was obtained after running the reaction for 12 h and **157** was transformed into **158** with the same catalyst at much higher efficiency (Scheme 48). This result proved that the cationic gold(I) complex can effectively catalyze the aromatic Claisen rearrangement.

Table 14
Aromatic Claisen rearrangement by cationic-gold species



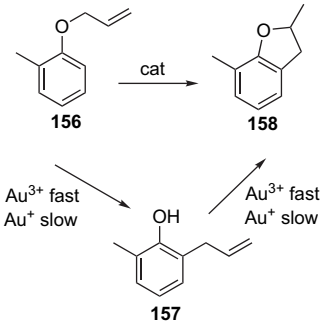
Entry	Catalyst	Solvent	**155**, Yield[a] (%)
1	$AuCl_3$/3AgOTf	Benzene	67
2	$AuCl_3$/3AgOTf	Toluene	(45)
3	$AuCl_3$/3AgOTf	CCl_4	(73)
4	Ph_3PAuCl/AgOTf	Toluene	>95 (82)
5	AuCl/AgOTf	Toluene	65
6	AgOTf	Toluene	57
7	HOTf	Toluene	66 (53)

[a] Based on ^1H NMR spectroscopy, using an internal standard; yields in parentheses represent isolated yields.



Scheme 48. Reagents and conditions: (i)$Ph_3PAuOTf$ (5 mol %), 85 °C, 24 h, toluene, 24%; (ii) $Ph_3PAuOTf$ (5 mol %), 24 h, toluene, 74%.

In an attempt to compare the rates of the two steps in the tandem reaction process (Scheme 49), it was found that the complete conversion of compound **157** into **158** occurs after 10 h, while the reaction of **156** to **158** proceeded to only about 50% conversion, even after 24 h, signifying that the Claisen rearrangement is the slow step in the process.

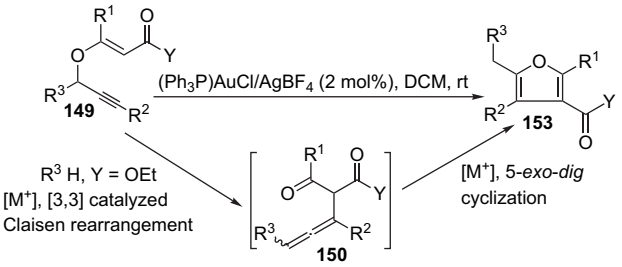


Scheme 49.

Interestingly, the gold(III) complex was able to catalyze the Claisen rearrangement of compound **154** at 0 °C to give the *ortho*-allyl product, whereas the gold(I) complex failed to mediate the rearrangement step at such a low temperature, indicating a difference in catalytic activity between the two oxidation states of gold. This difference was due to the increased oxophilicity of gold(III), as compared to gold(I).[61] Presumably, gold(III) binds to the phenol oxygen to speed up the rearrangement step.

A propargyl-Claisen rearrangement was the key step for the synthesis of tri- and tetra-substituted furans from various substituted propargyl vinyl ethers and this Claisen rearrangement was effectively catalyzed by a cationic triphenylphosphinogold(I)

complex [$(Ph_3P)AuCl/AgBF_4$] with a low catalyst loading[62] (2 mol %) (Scheme 50).



Scheme 50.

Besides the gold-catalyzed Claisen rearrangement of both the aliphatic and the aromatic systems, gold-promoted cycloisomerization is one of the new aspects discovered in recent years. It was found that the Au(I) catalyst system used for the Claisen rearrangement also promoted the cycloisomerization of the allenyl carbonyl intermediate **150** to the furan in a cascade reaction at ambient temperature and under neutral conditions.

Propargyl vinyl ether (**149a**, R^1=R^2=Me, R^3=H, Y=OEt) was completely converted into the allene **150** through the catalyzed Claisen rearrangement by the use of 10 mol % $AgBF_4$, but the furan **153** was not obtained. It was also observed that [$(Ph_3P)AuCl$] was unreactive, whereas this complex was active in the presence of $AgBF_4$ or $AgSbF_6$ or AgOTf (Table 15).

The cationic triphenylphosphinogold(I) complex was, therefore, the catalytically active species in both steps of the reaction cascade. In addition, the possibility of Ag(I) catalyzing the Claisen rearrangement step with the heterocyclization being catalyzed by Au(I) cannot be ruled out, and $PtCl_2$ and $AuCl_3$ also catalyzed the Claisen rearrangement of **149a** at room temperature. The rearrangement of **149a** by the use of $(Ph_3P)AuCl/AgBF_4$ (2 mol %) at room temperature followed the order: CH_2Cl_2 (97%, 40 min)>PhH (95%, 40 min)>C_6H_{12} (99%, 48 h)>MeCN (30%, 48 h)>THF (3%, 28 h) with DCM being the best solvent. A wide range of substituted furans **153** were synthesized by the triphenylphosphinogold(I)-catalyzed Claisen rearrangement of propargyl vinyl ethers **149** in DCM at room temperature (Table 16).

Table 15
Efficiency of catalysts for the conversion of **149a** into **153a**[a]

Entry	Catalyst (mol %)	Time	**153a**, Yield[b] (%)
1	CuI (5)	24 h	0
2	$PdCl_2(MeCN)_2$ (5)	24 h	0[c]
3	$PtCl_2$ (2)	24 h	52
4	$AgBF_4$ (10)	24 h	0
5	$K[AuCl_4]$ (5)	24 h	0
6	$AuCl_3$ (2)	24 h	7
7	$(Ph_3P)AuCl$ (2)	24 h	0
8	$(Ph_3P)AuCl$ (2)/$AgBF_4$ (2)	40 min	97
9	$(Ph_3P)AuCl$ (2)/$AgSbF_6$ (2)	40 min	83
10	$(Ph_3P)AuCl$ (2)/AgOTf (2)	40 min	60

[a] Conditions: 0.2 mmol of **149a**, 23 °C, DCM (0.2 M).
[b] Yield of pure **153a** after column chromatography.
[c] No starting material **149a** remained.

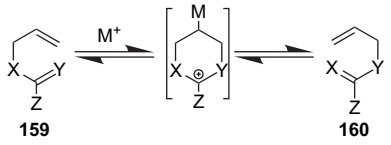
Table 16
Gold(I)-catalyzed formation of **153** from **149**[a]

Entry	R^1	Y	R^2	R^3	Isomer	*t* (h)	**153**, Yield[b] (%)
1	Me	OEt	Me	H	**a**	4	95
2	^{n}pent	OEt	Me	H	**b**	15	97
3	Ph	OEt	Me	H	**c**	2	90
4[c]	H	OEt	Me	H	**d**	4	75
5	Ph	Ph	Me	H	**e**	8	72
6	Me	OEt	H	H	**f**	12	82
7	^{n}pent	OEt	H	H	**g**	12	77
8	Me	OEt	Ph	H	**h**	2	87
9	Ph	OEt	Ph	H	**i**	4	90
10[c]	H	OEt	Ph	H	**j**	4	84
11	Me	OEt	2-OMe−phenyl	H	**k**	3	99
12	Ph	OEt	3-Thienyl	H	**l**	4	89
13[c]	Ph	OEt	2-Pyridyl	H	**m**	48	82
14	Ph	OEt	CH_2−C_6H_{11}	H	**n**	5	73
15	Ph	OEt	$CH_2CH_2OTBDMS$	H	**o**	3	72
16	Me	OEt	TBDMS	H	**p**	4	83
17[d]	Ph	OEt	Me	Me	**q**	25	45

[a] Conditions: 0.2 mmol of **149**, 2 mol % of [$(Ph_3P)AuCl/AgBF_4$], 23 °C, DCM (0.2 M).
[b] Pure product after column chromatography.
[c] Benzene used as solvent.
[d] Temperature: 38 °C, **a**–**q** are the different structures of **149**.

3.2.5. Catalysis by derivatives of palladium

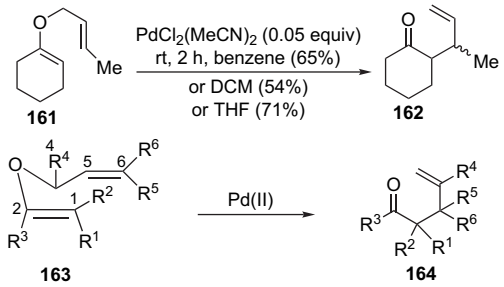
Pd(II)-catalyzed [3,3]-sigmatropic rearrangements of allylic esters,[63] allyl imidates[64] and *S*-allylthioimidates[65] occur under mild condition in high yield and with high regio- and stereoselectivity. These rearrangements (**159** to **160**) were rationalized via a cyclization-induced rearrangement pathway, which accounts for the action of the metal catalysts (Scheme 51).



Scheme 51.

The number of reported examples of Hg(II)- or Pd(II)-catalyzed Claisen rearrangements of 3-hetero-1,5-dienes such as allyl vinyl ethers **159** (X=O, Y=CR_2, Z=H, alkyl, phenyl) 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.[66] In contrast, those allyl vinyl ethers, e.g., **161** having a vinyl moiety protected by alkyl substitution from attack of the metal catalyst are able to rearrange to **162** in the presence[67] of $PdCl_2(MeCN)_2$, although they are unstable under thermal conditions (Scheme 52).

For both C_1- and C_2-substituted allyl vinyl ethers, e.g., **163**, the Claisen rearrangement products **164** were obtained in good yields after only 2 h, but the C_1- and C_2-unsubstituted allyl vinyl ethers gave only traces of the rearranged products and the C_1-unsubstituted substrate gave only 2–5% of the rearranged product, even after 24 h. This observation supported the hypothesis that Pd(II) strongly coordinates to the unsubstituted C_1 of the vinyl ether group and consequently, is not available



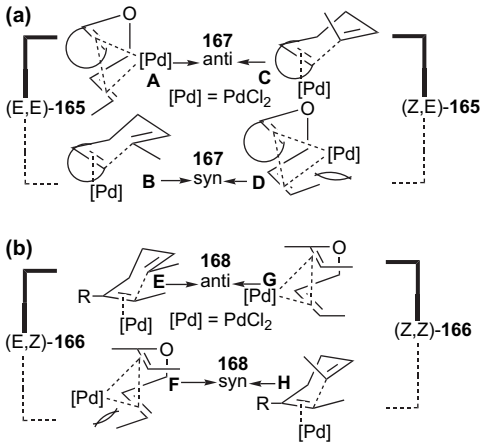
Scheme 52.

for coordination to the allyl group. As a result, the cyclization-induced rearrangement failed, whereas the presence of alkyl substituents at C_1 and C_2 sufficiently retard coordination of the catalyst to the vinyl group.

The Pd(II)-catalyzed Claisen rearrangement of various geometrical isomers of crotyl vinyl ethers was found to exhibit identical *anti*-diastereoselection, independent of the substrate geometries[68] (Scheme 53), while the thermal rearrangement showed a high stereospecificity, namely (*E*,*E*) or (*Z*,*Z*) to the *syn* product and (*E*,*Z*) or (*Z*,*E*) to the *anti* product. The thermal rearrangement passes through a chair-like transition state.

The stereochemical outcome from (*E*,*E*)-**165** to *anti*-**167** product could be visualized by a boat transition state (TS) **A**, where the Pd(II) coordinated to the two olefinic bonds. On the contrary, (*Z*,*E*)-**165** to *anti*-**167** was formed via the TS **C**, where the Pd(II) may coordinate to the enol part and the formation of TS **D** was disfavoured, due to the large steric repulsion (Scheme 54a). The chair TS **B** involves *syn* diastereoselection and is not visualized for the formation of the products.

Similarly, (*E*,*Z*)-**166** to *anti*-**168** was visualized by the chair TS **E** and not by boat TS **F**, similar to TS **C**, but, due to the considerable extent of geometrical isomerization, it was difficult to analyze (*Z*,*E*)-**166** to *anti*-**168** formation. The rearrangement through the boat TS **G** or the initial geometrical

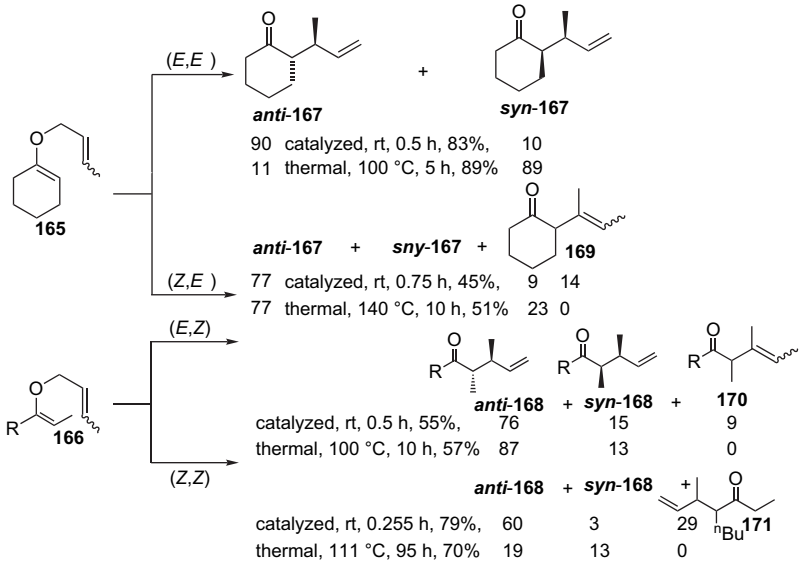


Scheme 54.

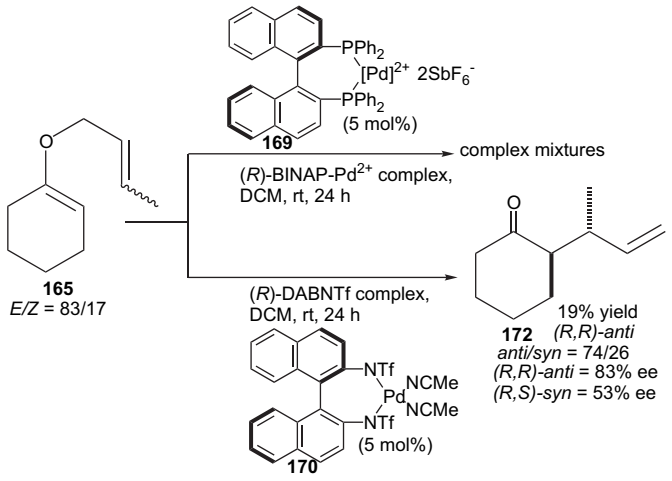
isomerization to (*Z*,*E*)-**166** followed by the rearrangement through the chair TS **E** may afford the *anti*-**168** product (Scheme 54b).

Mikami and Akiyama[69] used two types of palladium complexes, cationic (*R*)-BINAP–$Pd^{2+}(SbF_6^-)$ **169** and neutral (*R*)-BINAP–$Pd(MeCN)_2$ **170**, as chiral catalysts for the enantioselective Claisen rearrangement of the allyl cyclohexenyl ether **165** (Scheme 55).

The neutral (*R*)-BINAP–Pd complex gave the product (*R*,*R*)-*anti*-**172** with high enantioselectivity (83%) at room temperature but in low yield. The yield was improved by increasing the temperature and a better yield (69%) was obtained at 80 °C (Table 17), while the reaction of **165** with the cationic Pd complex gave a complex mixture. DABNTf–$Pd(MeCN)_2$ complex **171**, therefore, provided high enantio- and *anti*-diastereoselectivity and good yield. The reaction involving the neutral complex could have occurred via a six-membered boat-like transition state through bidentate coordination to the Pd catalyst by a similar mechanism to that described above.

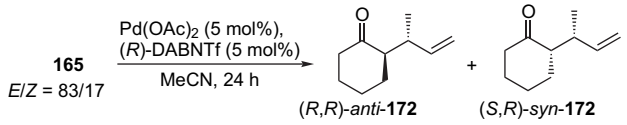


Scheme 53.



Scheme 55.

Table 17
Temperature effect of enantioselective Claisen rearrangement



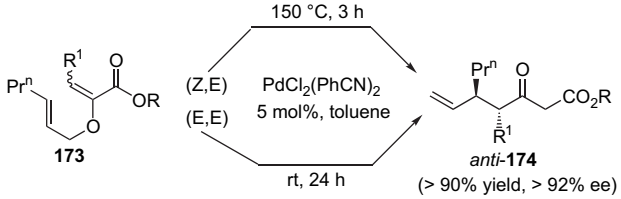
Entry	T (°C)	**172**, Yield[a] (%)	**172**, (*anti*/*syn*[b])	ee[c] (%)
1	−10	7	6:37	78:27
2	rt	24	85:15	84:50
3	40	42	85:15	83:57
4	60	54	82:18	81:53
5	80	69[d]	78:22	77:32

[a] Determined by NMR spectroscopy.
[b] Determined by GC.
[c] *anti* ee calculated by isomerization.
[d] Reaction time: 14 h.

Pd complexes effectively catalyzed the Claisen rearrangement of various allyl vinyl ethers.[70] The Pd(II)-catalyzed as well as thermal Claisen rearrangement of (*Z*,*E*)- and (*E*,*E*)-configured 2-alkoxycarbonyl-substituted allyl vinyl ethers **173** was carried out by Hiersemann[71] to give **174**.

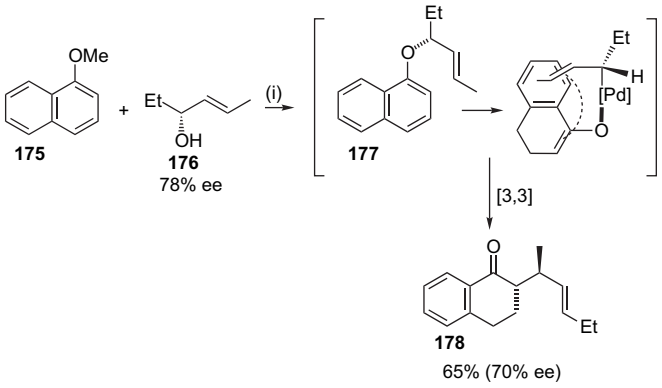
Under thermal conditions, the reaction required heating at 150 °C (sealed tube) in toluene for 4 h but, in the presence of $PdCl_2(PhCN)_2$, the 2-alkoxycarbonyl-substituted (*Z*,*E*)- and (*E*,*E*)-allyl vinyl ethers **173** exhibited markedly different activities. At ambient temperature, (*E*,*E*)-**173** in the presence of $PdCl_2(PhCN)_2$ rearranged through a boat-like transition state to give the *anti*-β,γ-alkyl-substituted-α-ketoesters, but (*Z*,*E*)-**173** did not rearrange under Pd(II) catalysis at room temperature. It was found that (*Z*,*E*)-**173** rearranged at higher temperatures, however, to afford the same *anti* product in a Pd(II)-catalyzed process via a boat-like transition state geometry (Scheme 56).

Nakai and Sugiura[72] reported a palladium-catalyzed alkylation–[3,3]-sigmatropic rearrangement reaction sequence, where the first step was the formation of the allyl vinyl ether by an in situ enol ether exchange between **175** and allylic alcohol **176** followed by an immediate [3,3]-sigmatropic



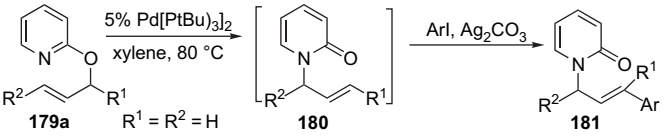
Scheme 56.

rearrangement to afford the γ,δ-unsaturated ketone **177** (Scheme 57). The use of an optically active allylic alcohol **176** in this transetherification and a Claisen rearrangement sequence generated *anti*-**178** via 1,3-chirality transfer and the stereochemical outcome was rationalized by the formation of a metal-stabilized boat-like transition state.



Scheme 57. Reagents and conditions: (i) $PdCl_2(MeCN)_2$ (10 mol %), TFA (10 mol %), PhMe, rt.

Itami et al.[73] reported the Pd-catalyzed one-pot rearrangement–arylation of 2-allyloxypyridine (Scheme 58).

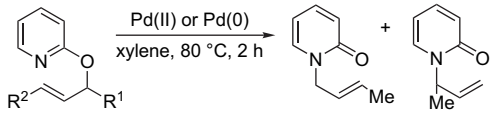


Scheme 58.

The Claisen rearrangement of **179a** to **181** via **180** was studied by employing various Pd(II) and Pd(0) complexes at 80 °C in xylene. Among the Pd(II) complexes investigated [$PdCl_2(PhCN)_2$, $PdCl_2$ and $Pd(OAc)_2$], $PdCl_2$ was found to be the best catalyst. $Pd(Ph_3P)_4$ and $Pd[P(^tBu)_3]_2$ were most effective Pd(0) catalysts than $Pd(PCy_3)_2$. When the Claisen rearrangement of **179b**,**c** was performed with $PdCl_2$ and $Pd(Ph_3P)_4$, it was found that $PdCl_2$ gave the [3,3]-rearrangement product **182**, whereas $Pd(Ph_3P)_4$ afforded the [1,3]-rearrangement product **183** (Table 18).

The Claisen rearrangement of **179** using a Pd(II) catalyst proceed through the cyclization-induced rearrangement pathway, whereas the Pd(0)-catalyzed rearrangement proceeds through the intermediacy of a (π-allyl)palladium complex (Scheme 59). Itami et al. also achieved a one-pot rearrangement–arylation of 2-allyloxypyridine **179a** in the presence

Table 18
Pd-catalyzed rearrangement of **179b** and **179c**[a]

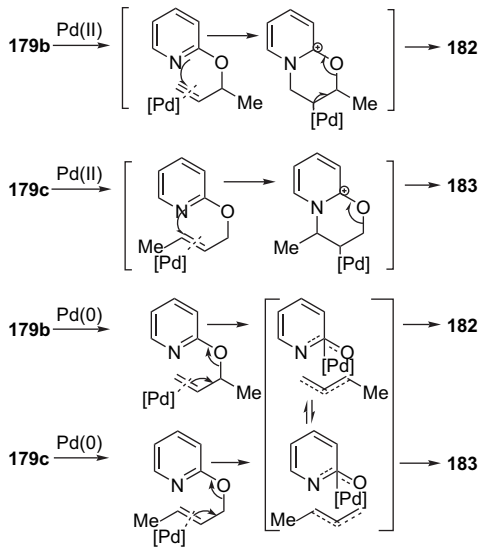


179b, R^1 = Me, R^2 = H,
179c, R^1 = H, R^2 = Me

Entry	Substrate	Catalyst	**182/183**
1	**179b**	$PdCl_2$	100:0[b]
2	**179c**	$PdCl_2$	0:100
3	**179b**	$Pd(PPh_3)_4$	33:67[c]
4	**179c**	$Pd(PPh_3)_4$	32:68[d]

[a] All reactions were performed at 80 °C in xylene using **179b**,**c** and Pd complex (5 mol %).
[b] Compound **182** was formed as a mixture of *E*/*Z* isomers (96:4).
[c] Compound **182** was formed as a mixture of *E*/*Z* isomers (79:21).
[d] Compound **182** was formed as a mixture of *E*/*Z* isomers (81:19).

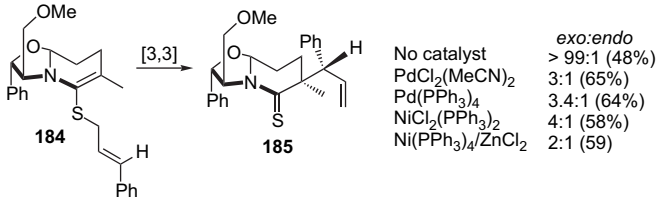
of a Pd catalyst using aryl iodide and base. The best results were obtained by using a $Pd[P(^tBu)_3]_2/AgCO_3$ catalytic system with 2-allyloxypyridine and aryl iodide.



Scheme 59.

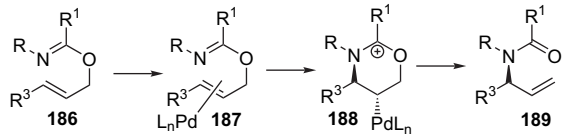
Pd(II) and Ni(II) were found to catalyze the thio-Claisen rearrangement of ketene *N*,*S*-acetals **184** under mild conditions.[74] Ketene *N*,*S*-acetal **184** in the presence of $PdCl_2(MeCN)_2$, $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $NiCl_2(PPh_3)_2$ or $Ni(PPh_3)_4/ZnCl_2$ underwent transition-metal-promoted [3,3]-sigmatropic rearrangement at lower temperature (25 °C) to afford the corresponding thiolactam **185**, whereas the thermal rearrangement required heating at 140 °C. In the presence of a catalyst, however, the *exo*-diastereoselectivity markedly decreased, compared to the thermal process (Scheme 60).

The palladium(II) complex-catalyzed rearrangement of α-allylimidates **186** to *N*-allylamides **189** has been extensively studied[75] by Overman et al. The rearrangement proceeds via a stepwise pathway involving the initial complex formation of **187** through intramolecular aminopalladation of the double



Scheme 60.

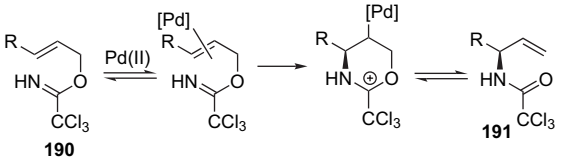
bond (oxidative addition) to give **188** followed by a final reductive elimination to afford the product amide **189** (Scheme 61). This rearrangement was extensively studied by variation of the Pd(II) catalysts and the development of bidentate cationic Pd(II) catalysts.[76] Chiral ferrocene-derived bis(palladacycle) catalysts[77] were employed to get a better yield and ee, and chiral Pd(II) complexes derived from tridentate ligands[78] were also used. The first example of an asymmetric transformation catalyzed by a cyclopalladated ferrocene derivative that exhibited only central chirality was introduced by Moyano et al.[79]



Scheme 61.

Cyclopalladated ferrocene derivatives are interesting[80] as they are planar chiral compounds with increasing applications in the materials science, asymmetric synthesis and catalysis fields.[81]

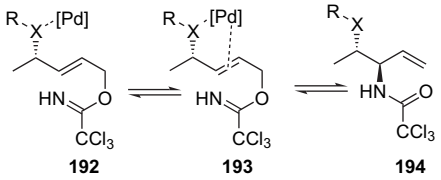
The thermal and metal-catalyzed [3,3]-sigmatropic rearrangements of allylic trichloroacetimidates to afford allylic trichloroamides have found widespread use in synthetic organic chemistry, due to the ease of transformation of the more readily available allylic alcohols under mild conditions to the less available allylic amines and their derivatives.[4d] The Pd(II)-catalyzed aza-Claisen reaction has been shown to follow a cyclization-induced rearrangement mechanism involving intramolecular aminopalladation of the alkene followed by reductive elimination to generate the amide products **191**[82] (Scheme 62).



Scheme 62.

Overman[75a,83] reported that the best results could be achieved with the chiral palladium diamine complexes based on the development of an asymmetric palladium(II) catalyst in the above-mentioned reaction sequences. A highly stereoselective aza-Claisen rearrangement of allylic trichloroacetimidates **192** to allylic trichloroimidates **194** via **193** has, however, been achieved using adjacent chiral functional

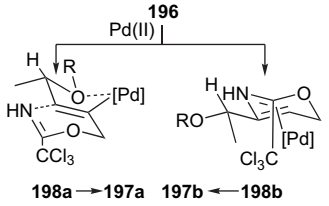
groups (ether groups) to direct facial coordination of the Pd(II) catalyst.[84] The chiral functional group may initially coordinate with the Pd(II) catalyst and then direct the catalyst intramolecularly to one face of the alkene, resulting in the diastereoselective rearrangement (Scheme 63).



Scheme 63. Directed aza-Claisen rearrangement.

Allylic trichloroacetimidates **196a** prepared from allylic alcohol **195**, under $PdCl_2(MeCN)_2$-catalyzed rearrangement afforded the amides **197a** and **197b**, and the diastereoselectivity depended upon the ether group (Table 19).

The bulky ether groups (entries 1–3, Table 19) prevent an efficient initial coordination to the Pd(II) catalyst, resulting in **197a** and **197b** in low diastereoselectivity. The smaller methyl group allowed an effective coordination to the catalyst, resulting in a much-increased diastereoselectivity. To increase the initial coordination of the ether group with the Pd(II) catalyst, an additional oxygen-containing MOM group was used, which gave **197a** and **197b** in an excellent 10:1 ratio (entry 5). Good selectivity was also obtained using an MEM group. The formation of the major diastereomer **197a** was rationalized by considering the reacting conformer **198a**, which may direct the catalyst to the back face of the alkene, resulting in a chair-like conformation in which the 1,3-allylic strain is minimized and where intramolecular attack can only take place from the front face of the alkene leading to **197a**. The minor diastereomer **197b** was formed via the reacting conformer **198b**, where the catalyst can coordinate directly to the least hindered, front face of the alkene, forcing the rearrangement to proceed from the back face. Thus, for a bulky ether group containing **196**, this second pathway became more competitive (Scheme 64).



Scheme 64.

A further study on the aza-Claisen rearrangement of various (*E*)-allylic trichloroacetimidates **196** and **199–202** having a methoxymethyl (MOM) ether group was carried out at room temperature using $PdCl_2(MeCN)_2$ as the catalyst (Table 20).

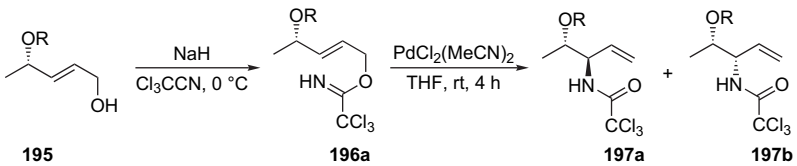
As previously reported, the $PdCl_2(MeCN)_2$-catalyzed rearrangement of **196** (R=Me) gave an excellent 10:1 ratio of **197a** and **197b** in 64% yield and the reaction was complete in 4 h. Surprisingly, similar treatment of **199** (R=^{i}Pr) required 48 h for complete conversion of the substrate and yielded the (3*S*,4*S*)-diastereomer **203b** and **203c** in a 1:2 ratio. The usual (3*R*,4*S*)-diastereomer **203a** was not obtained. Further treatment of the allylic imidates **200–202** gave the desired (3*R*,4*S*)-diastereomers **204a–206a** in good yields and excellent stereoselectivities up to 14:1 with respect to **204b–206b** (Table 20) and the *anti*-Claisen products **204c** and **206c** were also obtained.[85]

A study on the metal-catalyzed rearrangement of allylic imidates using both Pd(II) and Pd(0) complexes[86] showed that the use of Pd(II) gave exclusively the [3,3]-product (Claisen), while Pd(0) via a nonconcerted ionization pathway produced predominantly the [1,3]-product (*anti*-Claisen) (Scheme 65).

The formation of [1,3]-products via the Pd(0) pathway was effectively inhibited by using *p*-benzoquinone as an oxidant of Pd(0), resulting in the isolation of only the [3,3]-products **204–206** in 73, 70 and 69% yields and with excellent stereoselectivities of 14:1, 12:1 and 9:1 (**a/b**), respectively. In addition to the Pd(II) catalyst several metal catalysts[87] were employed in the aza-Claisen rearrangement (Table 21) of **196**.

Ni(II), Ru(II), Hg(II) and PdI_2 catalysts, however, showed no catalytic activity. Platinum(II) chloride and hydrogen-

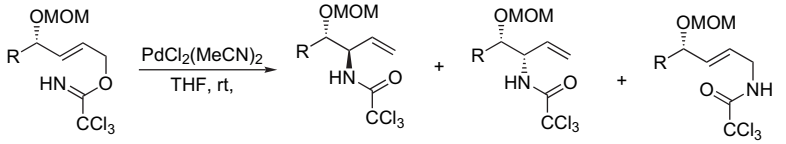
Table 19
Palladium-catalyzed rearrangement of trichloroacetimidates **196a**



Entry	R	Yield[a] (%)	Ratio[b] (**197a/197b**)
1	TBDMS	68	2:1
2	Tr	70	3:1
3	Bn	62	3:1
4	Me	49	7:1
5	MOM	64	10:1
6	MEM	60	8:1

[a] Isolated combined yields of **197a** and **197b** from allylic alcohol.
[b] Ratio in crude reaction mixture.

Table 20
Aza-Claisen rearrangement of (*E*)-allylic trichloroacetimidates **196** and **199–202**

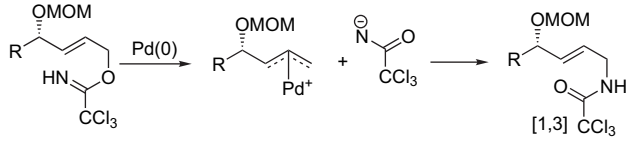


196, R = Me **199**, R = ^{i}Pr **200**, R = ^{t}Bu
201, R = $PhCH_2$ **202**, R = $PhCH_2CH_2$

197, R = Me **203**, R = ^{i}Pr **204**, R = ^{t}Bu
205, R = $PhCH_2$ **206**, R = $PhCH_2CH_2$

Entry	R	Yield[a] (%)	Ratio[b] (**a/b/c**)
1	Me (**197**)	64	10:1:0
2	^{i}Pr (**203**)	58	0:1:2
3	^{t}Bu (**204**)	60	14:1:1
4	$PhCH_2$ (**205**)	54	12:1:0
5	$PhCH_2CH_2$ (**206**)	65	9:1:4

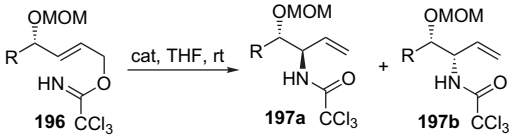
[a] Isolated combined yields of **a–c** from (*E*)-allylic alcohol.
[b] Ratio in crude reaction mixture.



Scheme 65. Pd(0)-catalyzed formation of 1,3 products (*anti*-Claisen).

tetrachloroaurate(III) hydrate gave the rearrangement products **197a** and **197b** in good yields and high stereoselectivity. Among the various soft metal catalysts of Pd(II), Pt(II) and Au(III), $PdCl_2(MeCN)_2$ was the best catalyst for this directed aza-Claisen rearrangement reaction. The same rearrangement was investigated in different solvents in the presence of $PdCl_2(MeCN)_2$ (Table 22). The best yield (64%) was obtained by using THF as a solvent, but an excellent diastereoselectivity was observed in toluene, which gave **197a** and **197b** in a 15:1 ratio in good yield (56%). This may be explained by the assumption that THF may compete with the MOM ether for the coordination of the Pd(II) catalyst, restricting the directing effect, whereas the noncoordinating solvent, toluene, allows a more effective coordination of the MOM ether to the Pd(II) catalyst, enhancing the directing effect and resulting in a more selective rearrangement.

Table 21
Rearrangement of allylic trichloroacetimidate **196** using various catalysts



Entry	Catalyst	*t* (h)	Yield[a] (%)	Ratio[b] (**a/b**)
1	$PdCl_2(MeCN)_2$	24	64	10:1
2	$PdCl_2(PhCN)_2$	24	57	9:1
3	$PdCl_2$	120	45	11:1
4	$PdBr_2$	72	44	9:1
5	PdI_2	120	—	—
6	$Pd(OAc)_2$	96	18	9:1
7	$NiCl_2$	120	—	—
8	$Cl_2Ru(PPh_3)_3$	120	—	—
9	$Hg(OTf)_2$	120	—	—
10	$PtCl_2$	48	49	10:1
11	$HAuI_4 \cdot 2H_2O$	144	49	6:1

[a] Isolated combined yields of **197a** and **197b** from (*E*)-allylic alcohol.
[b] Ratio in crude reaction mixture.

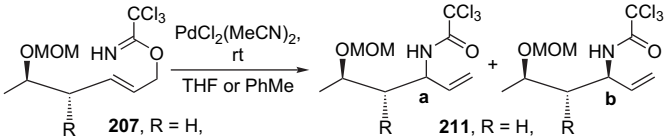
Table 22
Catalytic effects in different solvents for the conversion of **196** to **197**

Entry	Solvent	*t* (h)	Yield[a] (%)	Ratio[b] (**a/b**)
1	THF	24	64	10:1
2	Et_2O	24	47	12:1
3	MeCN	24	32	9:1
4	CH_2Cl_2	24	49	12:1
5	PhMe	24	56	15:1
6	$(bmim)BF_4$	148	37	5:1

[a] Isolated combined yields of **197a** and **197b** from (*E*)-allylic alcohol.
[b] Ratio in crude reaction mixture.

A further extension of the aza-Claisen rearrangement along these lines was carried out on δ,ε-disubstituted acetimidates **207–209**. The rearrangement was studied in both THF and toluene in the presence of $PdCl_2(MeCN)_2$ (Table 23) and the expected high diastereoselectivity was observed when toluene was used as the solvent. In the case of a THF solvent,

Table 23
Aza-Claisen rearrangement of **207–209** to **211–213** in two different solvents

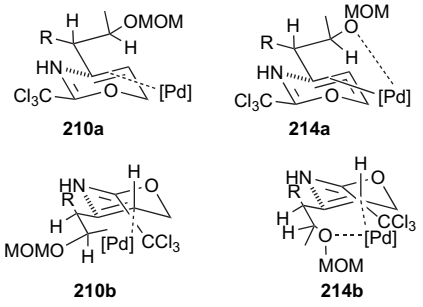


207, R = H,
208, R = Me,
209, R = Bn

211, R = H,
212, R = Me,
213, R = Bn

Entry	R	Solvent	Yield (%)	Ratio (**a/b**)
1	H (**211**)	THF	50	1:1
2	Me (**212**)	THF	49	3:1
3	Bn (**213**)	THF	72	6:1
4	H (**211**)	Toluene	71	3:1
5	Me (**212**)	Toluene	66	13:1
6	Bn (**213**)	Toluene	82	11:1

introduction of substituents at the δ-position, as for **208** and **209**, results in the destabilization of the transition state **210b**, due to 1,3-allylic strain between the 2-H and the R group. This leads to the preferred formation of diastereomer **a** via **210a** with increasing steric bulk of the R group. In the case of toluene as the solvent, for **207** the transition state **214b** is destabilized, due to the directing effect, causing the methyl group to adopt an axial position and leading to the preferred formation of **211a**. In the case of **208** and **209**, the transition state **214b** is destabilized by 1,3-allylic strain, and the positioning of the axial methyl group, due to MOM ether coordination to Pd(II), adds to this destabilization, leading to an enhancement of the diastereoselectivity. The combination of both the 1,3-allylic strain and the MOM ether-directing effect led to an excellent 13:1 and 11:1 diastereoselectivity in favour of **212a** and **213a**, respectively[88] (Scheme 66).

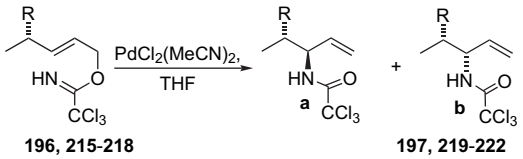


Scheme 66.

Recently, in order to find out the origin of the high degree of diastereoselectivity observed for the MOM ether-directed palladium(II)-catalyzed aza-Claisen rearrangement, some δ-substituted allylic trichloroacetimidates **196** and **215–218** were studied[89] to give products **197** and **219–222** (Table 24).

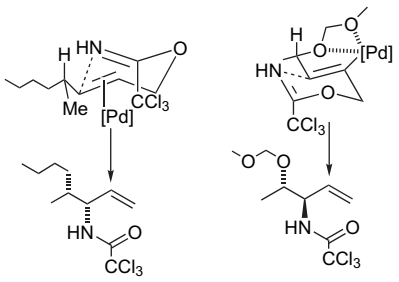
Rearrangement of **215** (R=OH) gave the corresponding trichloroacetimides **219** in 33% yield (from the allylic alcohol) and in only a 4:1 (**a/b**) ratio in favour of the *anti*-diastereomer **219a**. The corresponding MOM ether **196**, however, gave the product **197** in 64% yield and in a 10:1 (**a/b**) ratio.[84] This substantial change in selectivity in the case of **215** indicated that the free hydroxyl group is unable to direct the catalyst as effectively as the MOM group. This led to the proposal that both oxygen atoms of the MOM group participate in coordination with the Pd(II) catalyst. The rearrangement of **217** shows a similar type of selectivity 5:1 (**a/b**), but substrate **218** with the oxygen atom at the 7-position was unable to direct the rearrangement and gave the product **222** in a 1:2 (**a/b**) ratio like the carbon analogue **216** giving the *syn*-diastereomer as the major product. These results clearly showed that, without an oxygen atom immediately adjacent to the alkene (i.e., at the 5-position), the diastereoselective outcome of the reaction was particularly low (Scheme 67).

Table 24
Degree of diastereoselectivity observed for the MOM ether-directed palladium(II)-catalyzed aza-Claisen rearrangement



Entry	R	Yield[a] (%)	Ratio[b] (**a/b**)
1	OH (**219**)	33	4:1
2	OCH_2OCH_3 (**197**)	64	10:1
3	$CH_2CH_2CH_2CH_3$ (**220**)	59	1:2
4	$OCH_2CH_2CH_3$ (**221**)	77	5:1
5	$CH_2CH_2OCH_3$ (**222**)	60	1:2

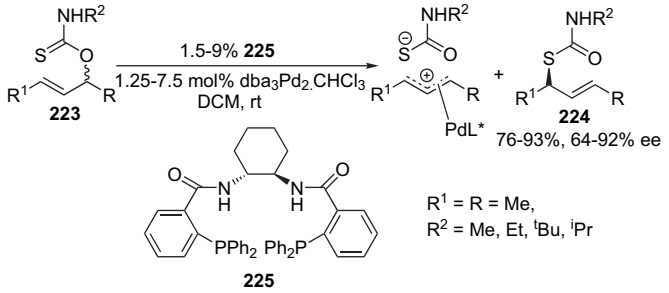
[a] Isolated combined yields of **a** and **b** from (*E*)-allylic alcohol.
[b] Ratio in crude reaction mixture.



Scheme 67. Transition states for the noncoordinating and MOM ether-directed aza-Claisen rearrangement.

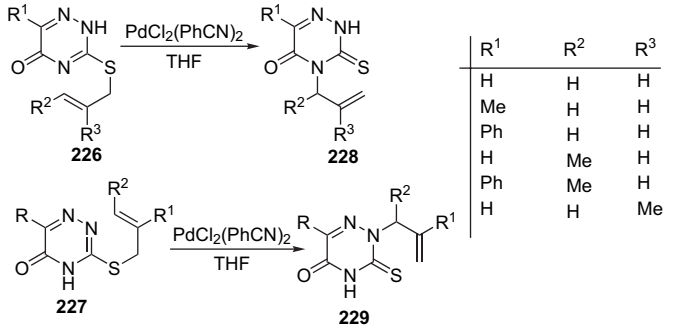
From these experimental results, it is observed that **215** and **217** showed a similar diastereoselectivity, although they are very different in size. This indicated that these rearrangements are controlled by a directing effect and not by the steric bulk. The diastereoselectivity observed for the rearrangement of **196** was much higher than those for **215** and **217**, which indicated that the second oxygen atom assists in coordinating the palladium(II) catalyst, resulting in a highly diastereoselective process.

Practically, highly active and enantioselective ferrocenylimidazoline palladacycle catalysts (FIPs) for the aza-Claisen rearrangement of *N*-*para*-methoxyphenyl trifluoroacetimidates have recently been reported.[90,91] The optically active compounds **224** were synthesized by the rearrangement of racemic *o*-allylthionocarbamates **223** in 93% yield with up to 92% ee using the palladium(0) catalyst[92] and the ligand **225** (Scheme 68).



Scheme 68.

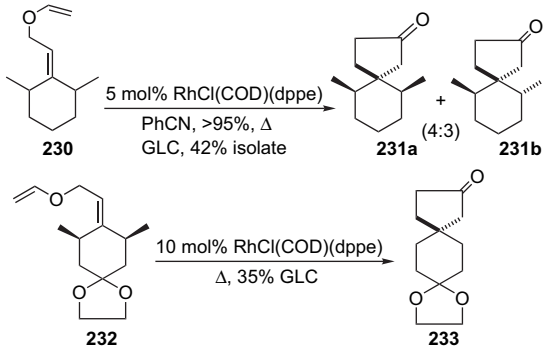
3-(Allylthio)-1,2,4-triazin-5(2*H*)ones **226** and **227** in the presence of $PdCl_2(PhCN)_2$ underwent a thio-Claisen rearrangement under milder conditions than those of the uncatalyzed reaction to give **228** and **229**, respectively[93] (Scheme 69).



Scheme 69.

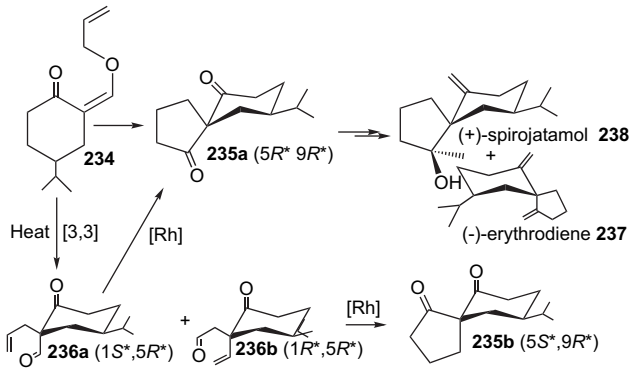
3.2.6. Catalysis by derivatives of rhodium

A one-pot combination of the Claisen rearrangement of allyl vinyl ethers followed by an intramolecular hydroacylation catalyzed by RhCl(COD)(dppe) was applied as a key step in the synthesis of *meso*-dimethyl-1,4-dioxa-dispiro[4.2.4.2]tetradecan-10-one **233**, a potential precursor in the synthesis of solavetivone.[94] The model compound **230** on treatment with 5 mol % RhCl(COD)(dppe) in benzonitrile under heating conditions afforded the corresponding spiroannelated cyclopetanone **231** in more than 95% yield and a 4:3 diastereomeric mixture of **231a** and **231b**. The target product **233** was obtained similarly from **232**, but in much lower yield (35%) (Scheme 70).



Scheme 70.

This one-pot reaction sequence was also used in the formal total synthesis of acoradienes.[95] The reaction sequence was tested in the synthesis of 9-isopropyl-spiro[4.5]decane-1,6-dione **235a**[96] from **234**, which had been used in the total synthesis of *erythro*-diene (**237**) and spirojatamol (**238**) (Scheme 71).

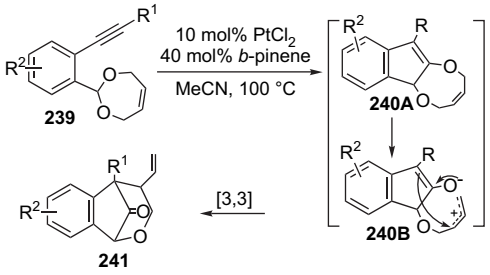


Scheme 71.

The Rh-catalyzed reaction sequence afforded the desired compound **235a**, along with the undesired product **235b**. Therefore, this one-pot methodology was not used; rather, the isomers **236a** and **236b** obtained in a 1:1 ratio by the thermal rearrangement were separated to conduct the cyclization step separately.

3.2.7. Catalysis by derivatives of platinum

The platinum-catalyzed tandem carboalkoxylation–Claisen rearrangement reaction of arylalkynes **239** bearing an *ortho*-1,5-dihydro-3*H*-2,4-dioxepine group in the presence of $PtCl_2$ (10 mol %) and β-pinene (40 mol %) in acetonitrile at 100 °C gave the corresponding tricyclic compounds **241** in good-to-excellent yields[97] (Scheme 72).



Scheme 72.

Intermediate **240A** could not be isolated under the reaction conditions and was converted in situ into the product **241**. Since the distance between the 3- and 3′-carbon atoms is too long for a concerted Claisen rearrangement, the product **241** could have been formed through the zwitterionic intermediate **240B**. Various substituted arylalkynes **239a–k** were transformed into different tricyclic products **241a–k** and the yield depended upon the substituents present on the aryl and alkyne groups (Table 25).

Extensive investigations showed that other catalysts such as $PtBr_2$, $Pt(Ph_3P)_4$, $Ni(dppp)Cl_2$, $RhCl_3$ and $Y(OTf)_3$ did not promote this type of reaction and that other solvents such as DCM, benzene, toluene and THF were totally ineffective.

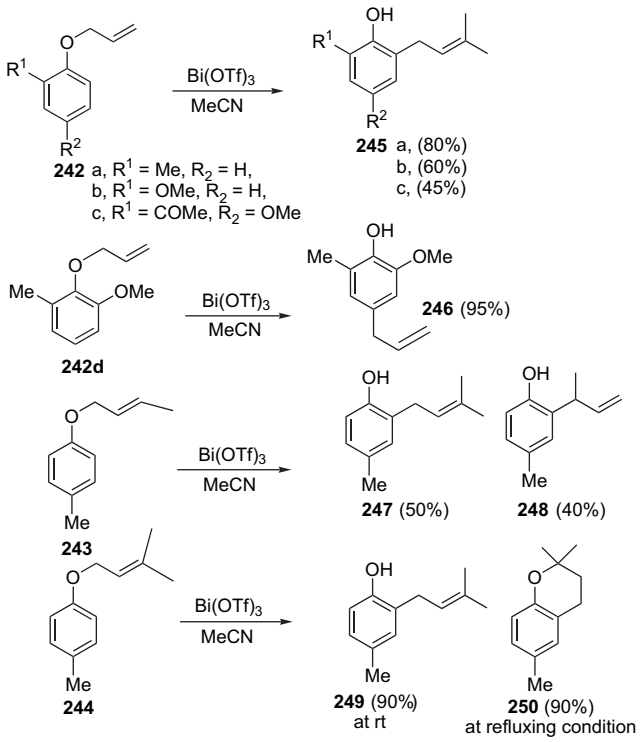
Table 25
Pt-catalyzed tandem carboalkoxylation–Claisen rearrangement of **239**[a]

Entry	**239**	R^1	R^2	**241**	Yield[b] (%)
1	**a**	^{n}Pr	H	**a**	69
2	**b**	^{n}Bu	H	**b**	56
3	**c**	^{n}Hex	H	**c**	63
4	**d**	Ph	H	**d**	50
5	**e**	*p*-Tolyl	H	**e**	52
6	**f**	*p*-Anisyl	H	**f**	51
7	**g**	*p*-BrC_6H_4	H	**g**	35
8	**h**	H	H	**h**	20
9	**i**	^{n}Pr	5-CF_3	**i**	53
10	**j**	^{n}Pr	4-CF_3	**j**	45
11	**k**	^{n}Pr	5-OMe	**k**	23
12	**1**	^{n}Pr	4-OMe	—	NR

[a] Reaction of **239** carried out in the presence of 10 mol % $PtCl_2$ and 40 mol % β-pinene in MeCN at 100 °C for 17–90 h.
[b] Isolated yield of **241**.

3.2.8. Catalysis by derivatives of bismuth

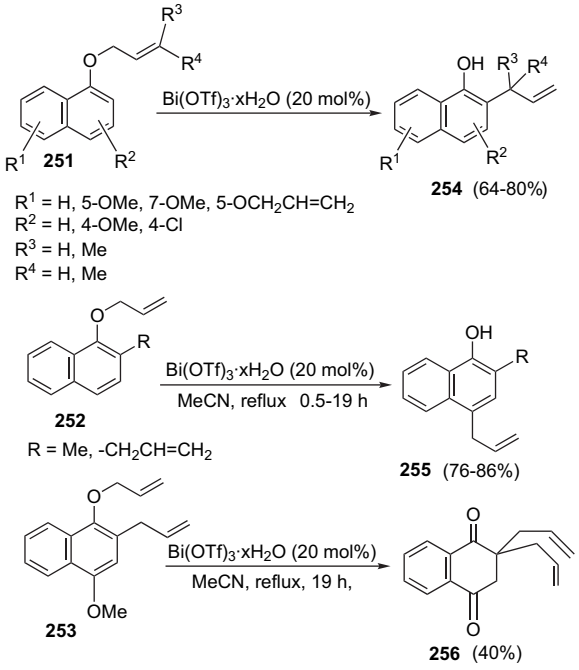
Recently, sigmatropic rearrangements[98–100] catalyzed by bismuth compounds have attracted considerable attention, due to the low toxicity,[101] low cost and good stability of these derivatives. Bismuth(III) triflate effectively catalyzed the Claisen rearrangement of allyl phenyl ethers.[98] Initially, the rearrangement of allyl *p*-cresyl **242**, crotyl **243** and prenyl phenyl ether **244** with 5 mol % $Bi(OTf)_3$ in methanol or benzene was very sluggish and only 5–10% conversion was observed, even after 24 h. The rearrangement of allyl phenyl ethers **242a–c** with 5 mol % of $Bi(OTf)_3$ in acetonitrile under refluxing conditions afforded the *ortho*-allyl products **245a–c** (Scheme 73).



Scheme 73.

The presence of an electron-releasing group in the aryl ring increased the yield of the rearranged products, while an electron-withdrawing group decreased the yield. 2,6-Dimethoxyphenyl allyl ether **242d** afforded the *para*-Claisen product **246**. Both the [3,3]- and [1,3]-rearrangement products **247** and **248** were obtained from the crotyl ether **243**. *p*-Cresyl prenyl ether **244** efficiently rearranged to the *o*-substituted product **249** at room temperature with $Bi(OTF)_3$, but, under refluxing conditions, 2,2-dimethylchroman **350** was obtained in 90% yield. Allyl *p*-nitrophenyl ether failed to give any rearranged product, even after 24 h, but *p*-nitrophenol was obtained as a result of the cleavage of the allyl ether bond. Bismuth triflate hydrate $[Bi(OTf)_3 \cdot xH_2O]$ $(2.5<x<4)$ was found to be an effective catalyst for the Claisen rearrangement of allyl naphthyl ether.[99]

The rearrangement of **251** proceeded smoothly with a catalytic amount of bismuth triflate (20 mol %) in a polar coordinating solvent such as acetonitrile to afford the corresponding *ortho*-allylnaphthols **254** in moderate-to-good yields (64–80%). In the case of allyl 2-substituted naphthyl ethers **252**, the corresponding *p*-allyl products **255** were obtained in 76–86% yields. For the 2,4-disubstituted naphthylallyl ether **253**, under $Bi(OTf)_3$-catalyzed conditions, the only *ortho*-Claisen rearrangement product, 2,2-diallyl-2,3-dihydronaphthalene-1,4-dione **256** was obtained, due to acidic hydrolysis of the enol ether part (Scheme 74).



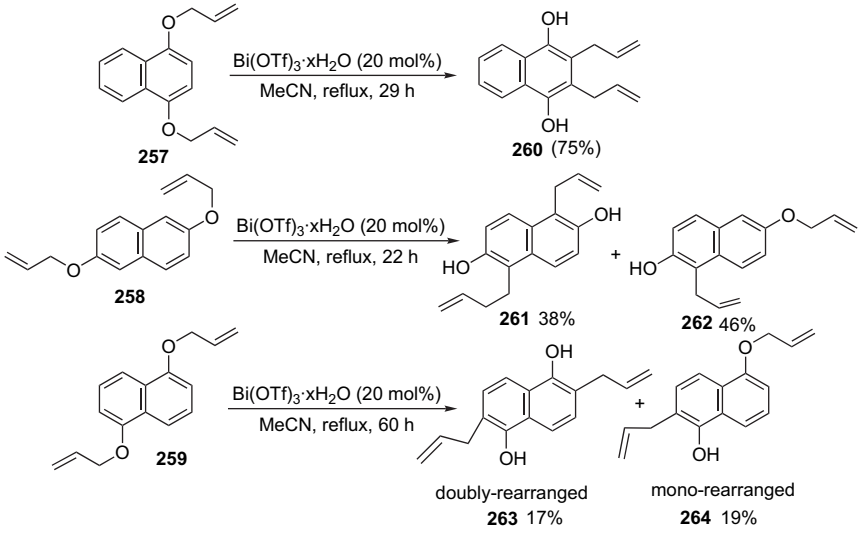
Scheme 74.

Accordingly, the $Bi(OTf)_3$-catalyzed Claisen rearrangement of 1,4-di(allyloxy)naphthalene **257** gave only the corresponding doubly rearranged product **260**, whereas 2,6-di(allyloxy)-naphthalene **258** and 1,5-di(allyloxy)naphthalene **259** rearranged slowly and a mixture of di-rearranged product (**261** or **263**) and mono-rearranged product (**262** or **264**) was obtained (Scheme 75). Interestingly, in the case of 1,5-di(allyloxy)naphthalene **259**, a 0.1 M concentration of the ether was necessary to obtain the doubly rearranged product **263** along with the formation of the mono-rearranged product **264**, since a higher concentration (0.5 M) gave only the mono-rearranged product.

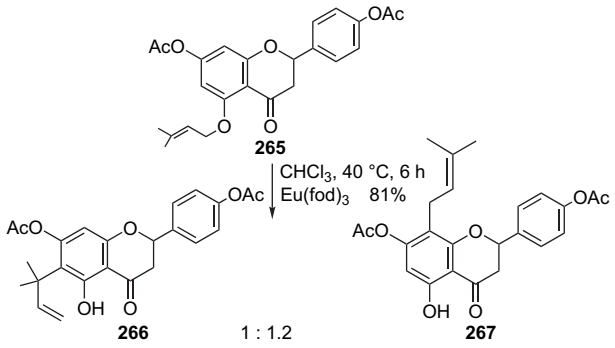
3.2.9. Catalysis by derivatives of europium and holmium

The catalytic activity of $Eu^{III}(fod)_3$ has been well studied and this complex was found to be a suitable catalyst for the aromatic Claisen rearrangement of the aryl phenyl ether **265** to give the *ortho*-Claisen product **266** and *para*-Claisen product **267** in a 1:1.2 ratio and 81% yield,[102] which, on treatment with base, afforded the flavonoids, 6-(1,1-dimethyl allyl)-naringenin and 8-prenyl-naringenin, respectively (Scheme 76).

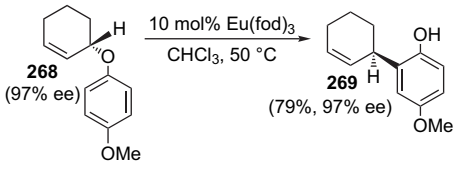
The Lewis acid, $Eu(fod)_3$, catalyzed the aromatic Claisen rearrangement of the *para*-substituted chiral allyl aryl ether **268** with an excellent intramolecular chirality transfer, leading to the formation of the chiral product **269** in good yield and excellent ee[103] (Scheme 77).



Scheme 75.

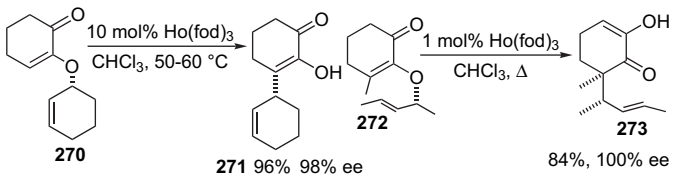


Scheme 76.



Scheme 77.

Trost and Schroeder reported that $Ho(fod)_3$ catalyzed the Claisen rearrangement of chiral allyl vinyl ethers **270** and **272** associated with a 1,3-chirality transfer and the chiral products **271** and **273**, respectively, were obtained in high yield with excellent ee[104] (Scheme 78).



Scheme 78.

3.3. Catalysis of the olefin isomerization–Claisen rearrangement (ICR)

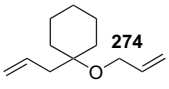
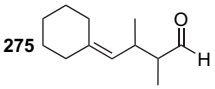
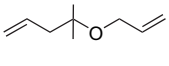
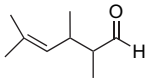
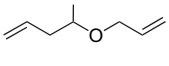
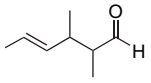
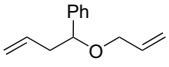
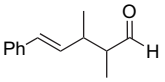
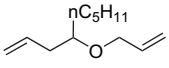
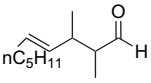
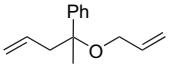
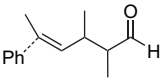
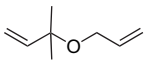
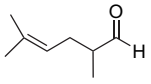
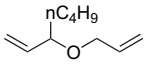
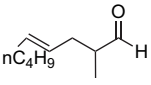
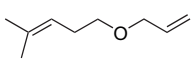
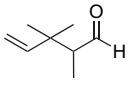
The aliphatic Claisen rearrangement of allyl vinyl ethers has been adopted as a valuable tool in organic chemistry for the synthesis of γ,δ-unsaturated carbonyl compounds.[1,3] Iridium complexes are found to catalyze the isomerization of olefinic double bonds. Therefore, the Claisen rearrangement was performed through the in situ generation of allyl vinyl ethers from allyl homoallyl ethers or diallyl ethers. Diallyl ethers were converted into the γ,δ-unsaturated aldehydes by heating in the presence[105] of $[Ir(C_8H_{12})(PMePh_2)_2]$ or $[RuCl_2(Ph_3P)_3]$. Usually, these reactions are carried out at a higher temperature (>160 °C).

It was observed that allyl homoallyl ethers or diallyl ethers were converted into the γ,δ-unsaturated aldehydes in the presence of a catalytic amount of $[Ir(COD)Cl]_2$ combined with PCy_3 and Cs_2CO_3 through double-bond migration followed by the Claisen rearrangement.[106] This method provides a novel route to γ,δ-unsaturated aldehydes under relatively mild conditions, these compounds being difficult to synthesize by conventional methods. Thus, various allyl homoallyl ethers were converted into the corresponding γ,δ-unsaturated aldehydes by the $[Ir(cod)Cl]_2/PCy_3/Cs_2CO_3$ system in moderate-to-good yields (Table 26).

Treatment of **274** with $[Ir(COD)Cl]_2$ (1 mol %), PCy_3 (2 mol %) and Cs_2CO_3 (1 mol %) in toluene at 100 °C for 15 h (entry 1, Table 26) gave 4-cyclohexylidene-2,3-dimethylbutanal **275** in 74% yield, together with a small amount of 1-allyl-propenyloxycyclohexane **276**. This observation indicates that the reaction might be initiated by the double-bond migration of **274** to 1-propenyloxycyclohexane **277** through the formation of **276** and that the resulting **277** underwent a Claisen rearrangement to give **275** (Scheme 79).

It is notable that 4-allyoxy-1-pentene was converted (path a) into (*E*)-2,3-dimethyl-4-hexenal without the formation of the (*Z*)-isomer (entry 3). This suggested that the

Table 26
Claisen rearrangement of allyl homoallyl and diallyl ethers catalyzed by $[Ir(COD)Cl]_2$[a]

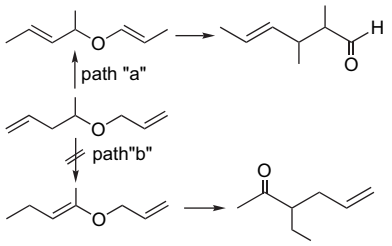
Entry	Substrate	Product	Yield (%)
1			74
2			68
3			78
4			81
5			72
6			81[b]
7			78
8			48
9[c]			78

[a] Substrate (0.5 mmol) was allowed to react in the presence of catalytic amounts of $[Ir(COD)Cl]_2$ (0.005 mmol), PCy_3 (0.01 mmol) and Cs_2CO_3 (0.005 mmol) in toluene (0.5 ml) at 100 °C for 15 h under Ar.
[b] Ratio of *E*/*Z* isomer was **275/274.**
[c] Reaction was carried out in *p*-xylene at 140 °C.

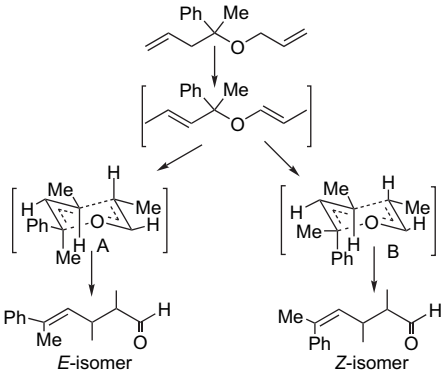
rearrangement took place in a regio- and stereoselective fashion to give the sole rearranged product having (*E*)-geometry. As, for example, 3-ethyl-5-hexen-2-one was expected to be formed from 4-allyloxy-1-pentene through an alternate *path b*, but no such product could be obtained (Scheme 80).

4-Allyloxy-4-phenyl-1-pentene (entry 6), however, led to a 2:1 stereoisomeric mixture of (*E*)- and (*Z*)-2,3-dimethyl-5-phenyl-4-hexenal. This ratio may be dependent upon the free energy difference between the six-membered transition states **A** and **B**, in the case of a common aliphatic Claisen rearrangement (Scheme 81).

Since the allyl homoallyl ethers can be more easily prepared than the allyl vinyl ethers, the present method provides a novel route to γ,δ-unsaturated aldehydes, which are difficult to prepare by conventional methods. Dixneuf et al. reported that the aliphatic Claisen rearrangement of allyl homoallyl and diallyl



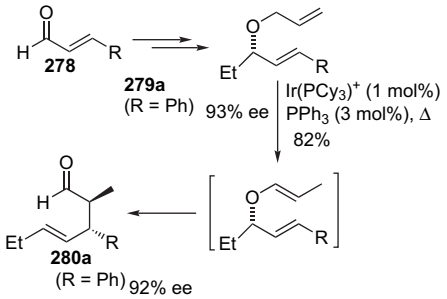
Scheme 80.



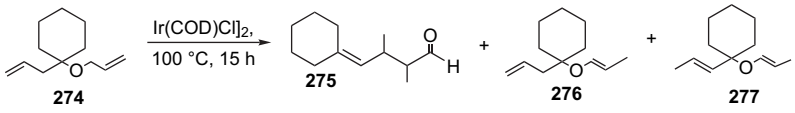
Scheme 81.

ethers was promoted by a catalytic amount of a Ru complex, giving the γ,δ-unsaturated aldehydes in a manner similar to the Ir-catalyzed reactions.[107] The $[Ir(PCy_3)_3]^+$-catalyzed olefin isomerization–Claisen rearrangement (ICR) reaction sequence provides a convenient access to an enantioselective aliphatic Claisen rearrangement from easily obtainable starting materials.[108] Diallyl ether **279** derived from **278** (R=Ph) in the presence of $[Ir(CPy_3)_3]^+$ (1 mol %) and PPh_3 (3 mol %) underwent an ICR and furnished the 2,3-*syn*-Claisen adduct **280** (R=Ph) with an enantiomeric purity paralleling that of the diallyl ether precursor (92% ee)[109] (Scheme 82).

Various diallyl ethers were converted into the corresponding aldehydes (Table 27).

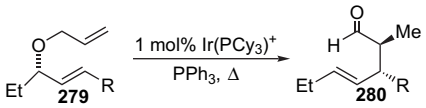


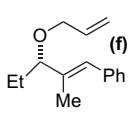
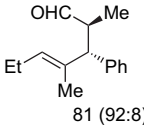
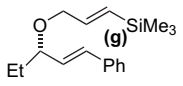
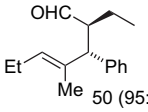
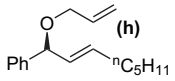
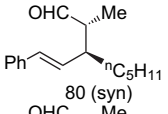
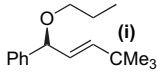
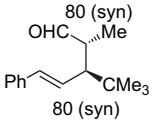
Scheme 82.



Scheme 79.

Table 27
ICR of enantio-enriched diallyl ethers **279**



Entry	**279**	Yield (%) (*syn*/*anti*)[a]	**280**,[b] ee (%)
1	R=Ph (**a**)	82 (95:5)	92
2	R=2-furyl (**b**)	75 (95:5)	96
3	R=(*E*)-CHCHPh (**c**)	77 (95:5)	93
4	R=$^{n}C_5H_{11}$ (**d**)	70 (97:3)	87
5	R=CH_2OBn (**e**)	60 (96:4)	92
6		 81 (92:8)[c]	97
7		 50 (95:5)	91
8		 80 (syn)	86
9		 80 (syn)	93

[a] Diastereomeric ratios determined by ^{1}H NMR spectroscopy of the crude product mixtures.
[b] Enantiomer ratios were determined by chiral HPLC.
[c] Claisen product **280f** was obtained as an 83:17 (*E*/*Z*) mixture of olefin isomers; enantiomer and diastereomer ratios are reported for the (*E*)-isomer.

The ICR[108–110] step has been applied as the key step in various multistep transformations. An enantioselective synthesis of the (+)-calopin dimethyl ether **283** from **281** via **282** highlights the potential utility of the ICR methodology in asymmetric syntheses[108,111,112] (Scheme 83).

Boron-substituted diallyl ethers provide an efficient conduit for expanding the structural diversity available from the ICR reaction. Easily prepared allyl propargyl ethers **284** underwent chemoselective Zr(IV)-catalyzed hydroboration to afford the boron-substituted ICR substrates **285**. Boron-substituted allyl residues **285** underwent chemoselective Ir(I)-catalyzed olefin isomerization and in situ Claisen rearrangement in the presence of $[Ir(PCy_3)_3]^+$ (2 mol %) in 25:1 CH_2Cl_2/acetone followed by the addition of PPh_3 (3 mol %) and heating at 83 °C to afford stereo-defined β-boryl aldehyde products **286** (Table 28). Further functionalizations of the C–B linkage by oxidation or Suzuki cross-coupling provide a route to the Claisen adducts previously inaccessible from the ICR methodology.[113]

Schmidt reported an interesting observation that diallyl and allyl homoallyl ethers **287** in the presence of Grubbs' catalyst $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (5 mol %) and $CH_2{=}CHOEt$ (4 equiv) in refluxing toluene afforded[114] pent-4-enals **288** (Scheme 84).

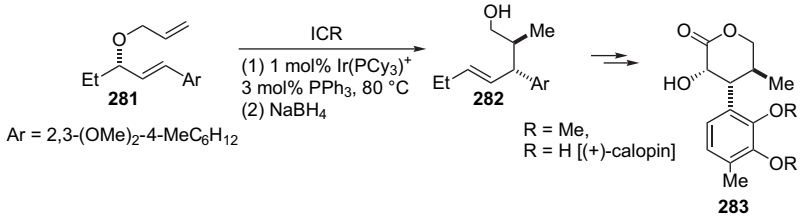
The rationalization for the formation of pent-4-enals is that the ruthenium–carbene complex $[Cl(PCy_3)_2Ru{=}CHPh]$ reacts with the electron-rich olefin, ethyl vinyl ether, to from a Fischer-type carbene complex such as $[Cl_2(PCy_3)_2Ru{=}CHOEt]$, which on heating decomposes to the ruthenium–hydride complex,[115,116] $[RuHCl(CO)(PCy_3)_2]$. Ruthenium–hydride complex rapidly reacts with the diene and promotes the double-bond isomerization followed by Claisen rearrangement leading to the formation of pent-4-enals **288**. Different types of pent-4-enals were synthesized from a wide variety of dienes using this protocol (Table 29). All pent-4-enals were obtained with a very high degree of (*E*)-selectivity.

Recently, an iridium-catalyzed ICR reaction has been applied to the enantioselective synthesis of the natural product, milbemycin β_3 **293**. In the presence of the Ir catalyst, the allylic ether **290** derived from **289** cleanly rearranged to the (*E*)-enol ether **291**. Addition of 6 mol % Ph_3P to **291** at 83 °C for 24 h afforded the aldehyde product **292** in 83% yield[117] (Scheme 85).

Echavarren and Nevado[118] observed that diallyl ethers **294** bearing an enol ether underwent selective isomerization by formal 1,2-H migration at the more substituted allyl part to give **295** in the presence of Pd(II) followed by Claisen rearrangement to give α-allyl α-alkoxy ketones **296** (Scheme 86).

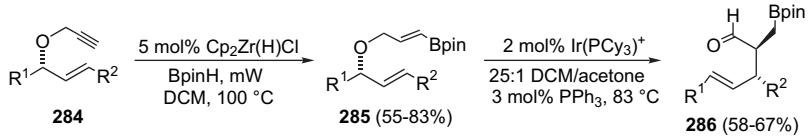
These workers achieved the conversion of **297** into **298** using different types of Pd compounds, among which the reaction with $Pd[Me(CN)_2Cl_2]$ in toluene at 110 °C afforded the ketone product in moderate yield (Scheme 87). The best results were obtained by using $PdCl_2$ in refluxing toluene, but no reaction took place with Pd(II) complexes bearing Ph_3P or $AsPh_3$ as the ligand and the Pd(0) catalyst was ineffective for this type of reaction sequence.

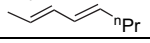
$AuCl_3$ and $IrCl_3$ were found to catalyze the reaction, although the yields were lower and the reactions were not as clean as those catalyzed by $PdCl_2$. An interesting observation in the $PdCl_2$-catalyzed olefin isomerization–Claisen rearrangement sequence is that **294** underwent selective isomerization by a formal 1,2-H migration at the more substituted allyl part, whereas the ICR described by Nelson et al.[108–110,113] using cationic Ir(I) complexes underwent isomerization by initial formal 1,2-H migration at the least substituted allyl part. This $PdCl_2$-catalyzed transformation of various



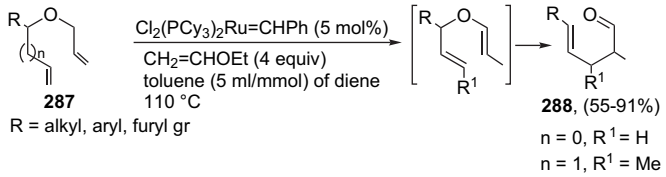
Scheme 83.

Table 28
ICR reaction of boron-substituted di(allyl) ethers



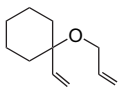
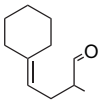
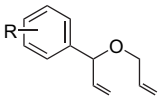
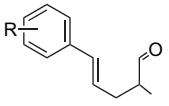
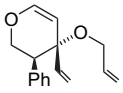
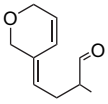
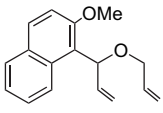
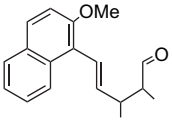
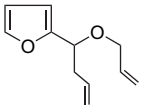
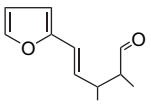
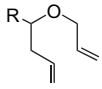
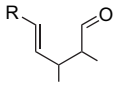
R^1	R^2	**285**, Yield (%)	**286**, dr (*syn*/*anti*)
^{n}Bu	Ph	67	92:8
Ph	Me	65	92:8
1-Np	Me	61	91:9
Et		58	88:12[a]

dr=diastereomeric ratio (*syn*/*anti*).
[a] *anti*/*syn*.



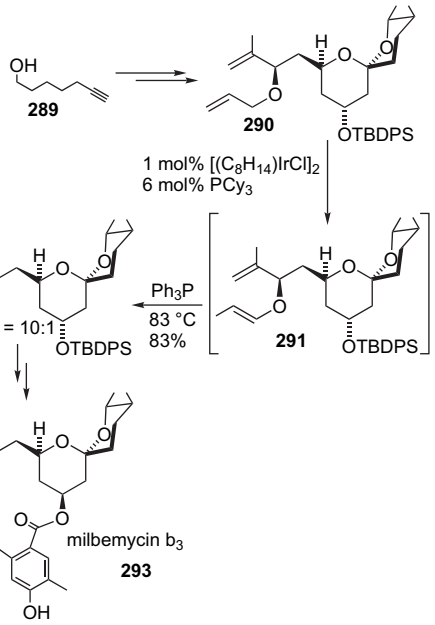
Scheme 84. Tandem isomerization–Claisen rearrangement.

Table 29
Pent-4-enals **288** from diene **287**

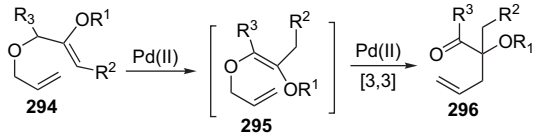
Entry	Dienes **287**	Pent-4-enals **288**	Yield (%)
1			78
2			
	R=H		91
	R=2-OMe		60
	R=3-OMe		53
3			52
4			84
5			70
6			
	$R = C_5H_{11}$		70
	$R = CH_2OBn$		55

substituted diallyl ethers afforded various functionalized ketones (Table 30).

Recently, Trost and Zhang[119] reported that, in the presence of an Ir catalyst, the hydroxyl group-protected bis-allyl ether

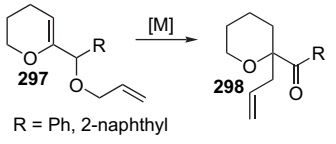


Scheme 85.



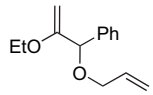
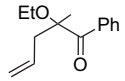
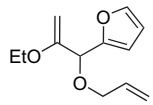
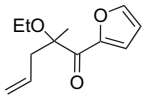
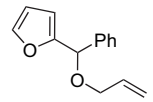
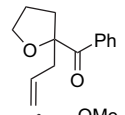
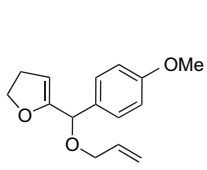
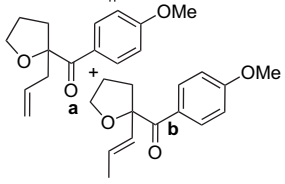
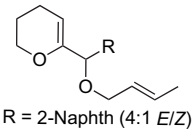
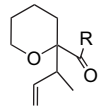
Scheme 86.

301 underwent olefin isomerization and in situ Claisen rearrangement (ICR) to give an α-chiral aldehyde **303**. The requisite substrates **301** were synthesized via Pd-catalyzed asymmetric allylic alkylation (AAA) from the easily available starting materials **299** and **300** followed by hydroxyl group

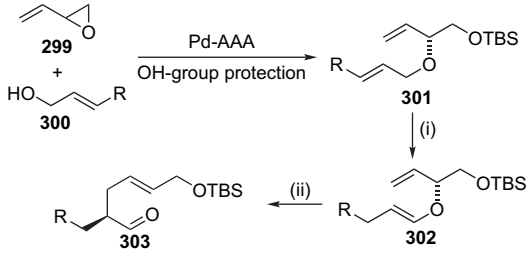


Scheme 87.

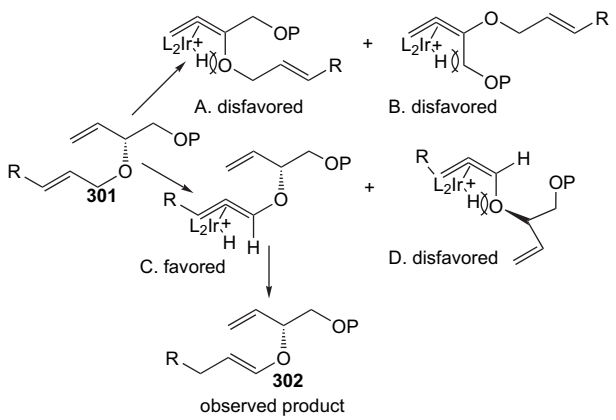
Table 30
Palladium-catalyzed isomerization–Claisen rearrangement[a]

Entry	Substrate	Product	Isomeric ratio	Yield (%)
1			—	76
2			—	80
3			—	88
4			1:1	70
5	 R = 2-Naphth (4:1 *E*/*Z*)		6:1	80

[a] Reaction was carried out with $PdCl_2$ (10 mol %) in toluene at 110 °C for 12 h.



Scheme 88. Reagents and conditions: (i) 2.5 mol % $[Ir(COD)_2Cl]_2$, 15 mol % PCy_3, 5% $NaBPh_4$, 50:1 (DCE/acetone), rt, 5 h; (ii) 15 mol % PPh_3, BSA (1 equiv), MWI, 140 °C, 15 min.



Scheme 89. Chemoselectivity of double-bond isomerization.

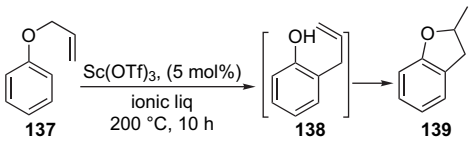
protection (Scheme 88). An unprecedented Ir-catalyzed olefin isomerization of the more substituted allyl part was observed. The isomerization at this 1,2-disubstituted double bond in **301** took place with a high (*E*)-selectivity, which could be rationalized by considering the allylic strain in a 1,1-disubstituted allyl complex, compared to a 1,3-disubstituted complex (Scheme 89).

The Claisen rearrangement of **302** was carried out under different conditions. Simple heating was found to be ineffective for both the conversion and the selectivity. The Claisen rearrangement was, however, carried out successfully under microwave irradiation conditions to give the product **303** in good yield and high ee. The best result was obtained when 1 equiv of *O*,*N*-bistrimethylsilylacetamide (BSA) was added, which also inhibited the racemization of the α-chiral aldehyde **303**.

3.4. Ionic liquid-mediated Claisen rearrangement

Recent studies of ionic liquids as new alternative, safe and recyclable reaction media are having an important impact in organic synthesis. Kitazume and Zulfiqar[120] reported a Lewis acid-catalyzed tandem Claisen rearrangement and cyclization using an ionic liquid as the reaction medium. On heating allyl phenyl ether **137** at 200 °C for 4 h in an ionic liquid (8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate) in the presence of a Lewis acid [anhydrous $Sc(OTf)_3$ (5 mol %)], 2-allyl phenol, 2-methyl-2,3-dihydrobenzo[*b*]-furan and the starting material (1:1:1) were detected by ^1H NMR spectroscopy, but, when the reaction was continued for 10 h at 200 °C, 2-allylphenol **138** was not obtained, but afforded **139**, which was produced by a domino Claisen rearrangement and an intramolecular cyclization of 2-allylphenol catalyzed by the Lewis acid. The Claisen rearrangements of various substituted allyl aryl ethers were studied in different ionic liquid media (Table 31).

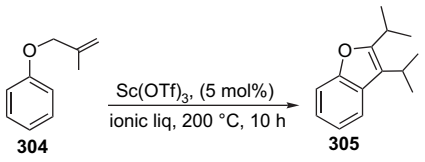
Table 31
Claisen rearrangement of substituted aryl allyl ether in different ionic liquid media



Entry	Substrate	Ionic liquid[a]	Yield (%)
1	Allyl phenyl ether	**A** [(EtDBU)OTf]	62
2		**B** [(MeDBU)OTf]	20
3	Allyl *p*-tolyl ether	**A**	88
4		**B**	40
5		**C** [bmim][BF_4]	12
6		**D** [bmim][PF_6]	9
7	Allyl *o*-tolyl ether	**A**	91
8		**B**	51

[a] **A**, 8-ethyl-1,8-diazabicyclo[5,4,0]-7-undecenium trifluoromethanesulfonate; **B**, 8-methyl-1,8-diazabicyclo[5,4,0]-7-undeceniumtrifluoromethanesulfonates; **C**, 1-butyl-3-methyl-1*H*-imidazoliumtetrafluoroborate; **D**, 1-butyl-3-methyl-1*H*-imidazolium hexafluorophosphate.

In the case of 2-methyl-2-propenyl phenyl ether **304** as a starting material, an unusual product 2,3-diisopropylbenzo-[*b*]furan **305** was obtained in 15% yield (Scheme 90).



Scheme 90.

Successive re-use of the recovered ionic liquid (**1**, see Fig. 5) in the same reaction yielded amounts of the product as those recovered high as in the first cycle in the conversion of **306** to **307** (Table 32).

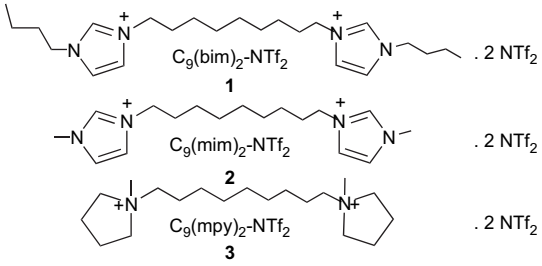


Figure 5.

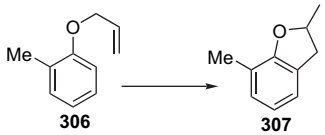
The high stability and high degradation–volatilization onset temperatures (330 to >400 °C) of the dicationic ionic liquids have made them promising solvents for high-temperature organic reactions. The Claisen rearrangement of allyl phenyl ether **137** was investigated in various types of dicationic ionic liquids[121] **1** or **2** or **3** (Fig. 5).

The rearrangement was completed in 10 min in these ionic liquids when heated at 250 °C and afforded the *ortho*-allyl phenol **138** in 35–75% yields, whereas the thermal rearrangement gave the rearranged product in lower yield at 300 °C (Table 33).

The Claisen rearrangement of *meta*-substituted phenyl allyl ethers **308** in these dicationic ionic liquids at 250 °C gave two types of *ortho*-rearranged products **309** and **310** in good yields.[121] The nature of the ionic liquid had a substantial effect on both the yield and the product ratio, but no significant regioselectivity was observed for the rearrangement when different dicationic ionic liquids were used (Table 34).

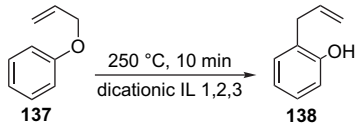
Among these three types of ionic liquids, the best solvent for the Claisen rearrangement was $C_9(mim)_2{-}NTf_2$ (**2**). The Claisen rearrangement in $C_9(mim)_2{-}NTf_2$ has significant advantages over the reaction in traditional mono cationic ionic liquids.[120] Firstly, there is no need for a Lewis acid catalyst to produce the Claisen rearrangement products in the dicationic ionic liquid, whereas the corresponding cyclization product, dihydrobenzo[*b*]furan (of the rearranged product) can be obtained in the case of mono cationic ionic liquids in the presence of a Lewis acid catalyst and, secondly, the reaction time is very short (10 min), compared to 10 h in the case of mono cationic ionic liquids.

Table 32
Recycling ionic liquids



Cycle	Yield (%)	Recovered (%) ionic liquid and Lewis acid
1	91	>99
2	95	>99
3	90	>99

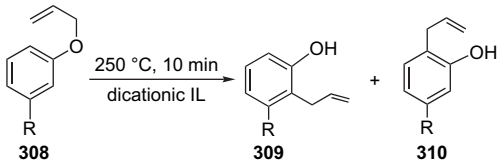
Table 33
Dicationic IL-mediated aromatic Claisen rearrangement



Entry	Ionic liquid	*T* (°C)	**138**, Yield[a] (%)
1	1	250	63
2		300	10
3	2	250	75
4		300	20
5	3	250	35
6		300	18

[a] Isolated yield.

Table 34
Claisen rearrangement of *meta*-substituted phenyl allyl ethers in dicationic ionic liquids



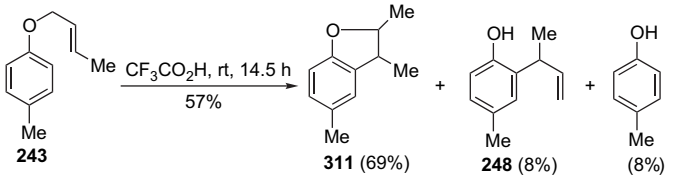
Entry	R	Ionic liquid	**309/310**	Yield[a] (%)
1	OMe	1		
2		2	1:1.8	82
3		3	1:2.4	34
4	Me	1		
5		2	4:5	87
6		3	1:1	44
7	CF_3	1		
8		2	1:1.2	77
9		3	1:1	74

[a] Isolated yield.

3.5. Catalysis by Brønsted acid

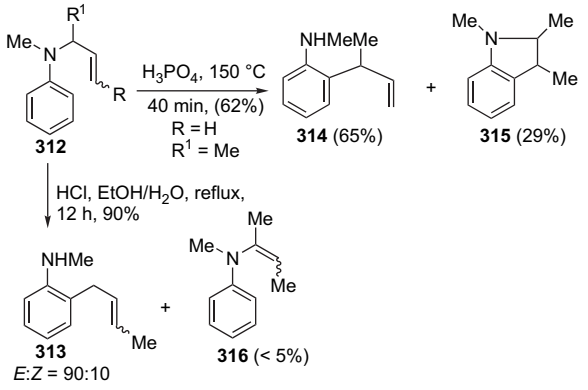
Trifluoroacetic acid and sulfuric acid considerably accelerate[3,122] the Claisen rearrangement rate of allyl aryl ethers and the corresponding cyclization product of allyl phenol was

obtained along with the rearranged allyl phenol and allyl-cleavage phenol under acidic reaction conditions. Thus, the Claisen rearrangement of crotyl ether **243** in CF_3CO_2H afforded cumaran **311**, resulting from the cyclization of the Claisen rearrangement product[122a,b] (Scheme 91).



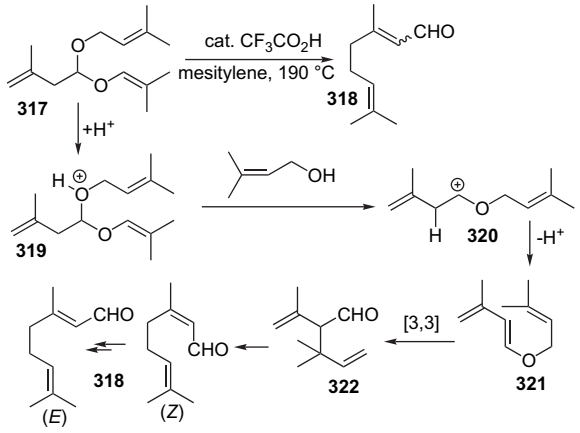
Scheme 91.

Sulfuric acid was found to catalyze the aza-Claisen rearrangement of different *N*-allylanilines under relatively mild conditions, giving *ortho*-allylanilines. 2,6-Disubstituted *N*-allylanilines afforded the corresponding *para*-Claisen product.[3] *N*-Methyl-*N*-(α-methylallyl)aniline **312** (R=H, R^1=Me) underwent facile aza-Claisen rearrangement in a concentrated HCl/ethanol medium (reflux, 12 h) to give the *ortho*-allyl amine **313** in 90% yield. The corresponding *N*-crotyl substrate **312** (R=H, R^1=Me) required drastic conditions for the rearrangement and, in H_3PO_4, it underwent a Claisen rearrangement to give the rearranged product **314** with the indoline[3,122c] **315** and the double-bond isomerization product **316** (Scheme 92).



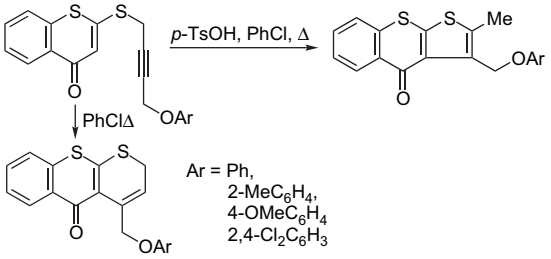
Scheme 92.

Citral **318** was synthesized by a CF_3CO_2H-catalyzed reaction of 3-methyl-3-butenal di(*trans*-2-pentenal)acetate **317** in good yield. The reaction proceeded by protonation of **317** to give **319**, followed by elimination of 3-methyl-2-butenyl alcohols to give **320**. Deprotonation of **320** gave **321**, Claisen rearrangement of **321** afforded **322**, Cope-rearrangement sequence and, finally, cis–trans isomerization (Scheme 93). The reaction was studied in different solvents in the presence of a catalytic amount of CF_3COOH. Aromatic solvents exhibited good results and mesitylene showed the best yield (60%) with high *E*/*Z* ratio of 57:43. Between the temperature range 150–210 °C, the best yield (60%) was obtained at 190 °C with an *E*/*Z* ratio of 57:43 and the *E*/*Z* ratio increased with increasing temperature. This indicated that cis–trans isomerization occurred after the Claisen and Cope rearrangements.[123]



Scheme 93.

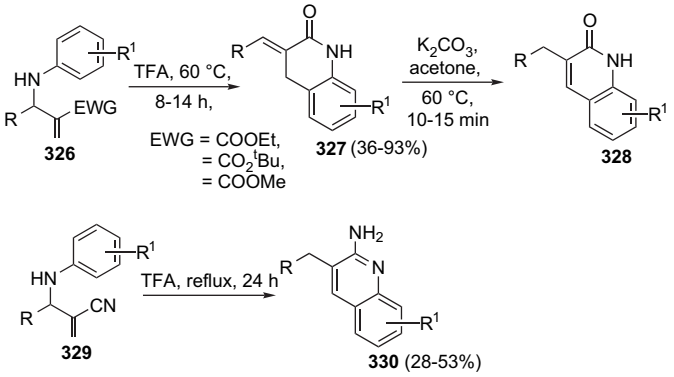
We have reported that the thio-Claisen rearrangement of 2-(4′-aryloxybut-2′-ynylthio)-thiochromen-4-ones **323** in the presence of a catalytic amount of 4-toluenesulfonic acid in refluxing chlorobenzene afforded 3-aryloxymethyl-2-methylthieno[2,3-*b*]thiochromene-4-ones[124] **324**, whereas in the absence of 4-toluenesulfonic acid, thiopyrano[2,3-*b*]benzothiopyran-5(2*H*)-ones[125] **325** were obtained (Scheme 94). Here, the acid catalysis was responsible for the dramatic alteration in the structural architecture of the product.



Scheme 94.

Trifluoroacetic acid was found to be a highly effective and efficient reagent for the tandem Claisen rearrangement and cyclization reaction to synthesize 3-arylmethylene-3,4-dihydro-1*H*-quinolin-2-ones **327** and 3-arylmethyl-2-amino-quinolines[126] **330**, from the Baylis–Hillman derivatives **326** and **329**, respectively. Product **327** was converted to **328** by treatment with potassium carbonate in acetone (Scheme 95).

Products **327** were obtained by an aza-Claisen rearrangement followed by cyclization. The formation of the products **330** was explained by considering that the aza-Claisen rearrangement may lead to a free aromatic amine, which may then attack the cyano group to yield the product **330** in a single step. Here, the Claisen rearrangement, cyclization and isomerization occurred in one step. Various substituted products **327** and **330** were synthesized in moderate-to-good yields (Tables 35 and 36).



Scheme 95.

Table 35
Yields of products **327** from **326**

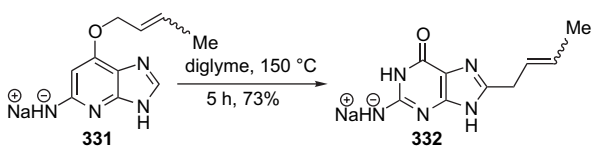
Entry	R in **326**	R^1 in **326**	EWG	**327**, Yield (%)
1	Ph	H	CO_2Et	88
2	2-ClC_6H_4	H	CO_2Et	71
3	4-BrC_6H_4	H	CO_2Et	80
4	Ph	6-Cl	CO_2Et	88
5	2-FC_6H_4	6-Cl	CO_2Et	79
6	4-BrC_6H_4	6-Cl	CO_2Et	85
7	Ph	4-F	CO_2Et	93
8	2-ClC_6H_5	4-F	CO_2Et	70
9	4-BrC_6H_4	4-F	CO_2Et	76
10	Ph	4-Br	CO_2Et	79
11	Ph	2-Me	CO_2Et	36
12	Ph	3,4,5-$(OMe)_3$	CO_2Et	63
13	Pyridyl-2-yl	4-F	CO_2Et	68
14	Ph	4-Me	CO_2Me	78
15	2-ClC_6H_4	4-Cl	CO_2Me	70
16	2-FC_6H_4	H	CO_2Me	73
17	2-FC_6H_4	H	$CO_2{}^tBu$	53
18	2-FC_6H_4	4-Cl	$CO_2{}^tBu$	85
19	2-FC_6H_4	4-F	$CO_2{}^tBu$	85
20	2-FC_6H_4	4-OMe	$CO_2{}^tBu$	77

Table 36
Synthesis of products **330** from **329**

Entry	R (**329**)	R^1 (**329**)	Yield (%)
1	Ph	4-Cl	28
2	2-FC_6H_4	4-Cl	48
3	2,4-$Cl_2C_6H_3$	H	46
4	2,4-$Cl_2C_6H_3$	4-Cl	53

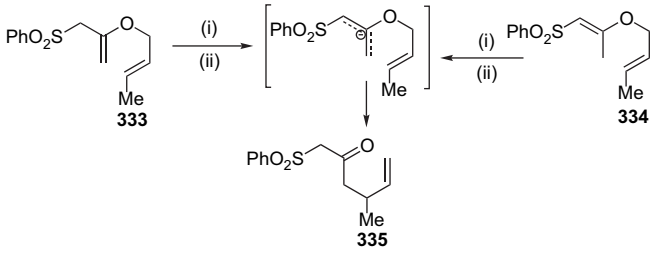
3.6. Catalysis by bases

So far, little work on the base-catalyzed[3,127,128] Claisen rearrangement has been reported in the literature. Leonard and Frihart[127] found a moderate rate enhancement in the anion as compared to the neutral substrate in the rearrangement of the guanine derivative **331** to **332** (Scheme 96). This observation was explained by potentially involving a Claisen rearrangement followed by a second [3,3]-sigmatropic shift and tautomerization.



Scheme 96.

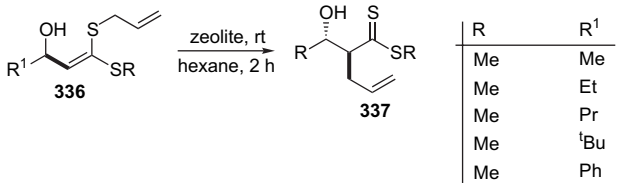
A considerable rate acceleration in the aliphatic Claisen rearrangement was observed in the presence of base, which converts the substrate into the corresponding anion with a rate enhancement relative to the neutral species. Both the substrates **333** and **334** underwent a Claisen rearrangement to give the product **335** in the presence of KH in 18-crown-6[128] (Scheme 97). The thio-Claisen rearrangement was considerably accelerated in the presence of neutral or anionic nucleophiles.[129]



Scheme 97. Reagents and conditions: (i) KH (1.5 equiv) in 18-crown-6, 50 °C, 5 h; (ii) H_2O.

3.7. Catalysis by zeolites

Zeolites have been found to catalyze the Claisen rearrangement in terms of yield and reaction time, contributing to an improvement in the yield and a shortening of the reaction time. *S*-Allyl-γ-hydroxyketenedithioacetals **336** underwent a facile and diastereoselective thio-Claisen rearrangement into 2-allyl-3-hydroxydithioesters **337** over different zeolites (Scheme 98). This zeolite-induced rearrangement gives predominantly the *anti*-isomer, in contrast to the *syn*-isomer obtained predominantly in the uncatalyzed reaction.



Scheme 98.

Adsorption of **336** in the channels of zeolites can occur in such a way that the bulky groups lie away from the catalytic surface (Fig. 6) and this type of arrangement may be responsible for the observed diastereoselectivity.[130]

A one-pot tandem Claisen rearrangement–cyclization of allyl aryl ethers using HY zeolite as the catalyst has been

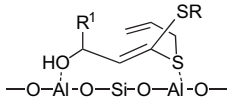
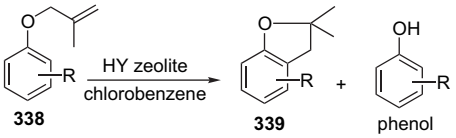


Figure 6.

achieved.[131] Aryl allyl ethers **338** when treated with HY zeolite in chlorobenzene furnished the dihydrobenzofuran derivatives **339** as the major product. The presence of electron-donating substituents in the aromatic ring increased the yield of **339** (Scheme 99).

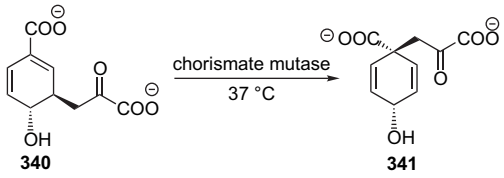


Substrate	Yield (%)	
R	**339**	Phenol
2-Cl-4,5-Me_2	86	14
3,4,5-Me_3	86	14
3,5-Me_2	84	16
2,3-Me_2	48	52
2,5-Me_2	47	55
4-Me	65	35
4-OMe	55	45
2-Cl	35	29

Scheme 99.

3.8. Catalysis by enzymes

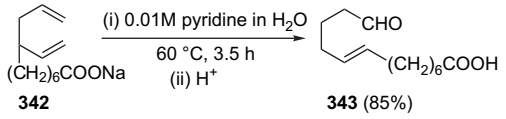
The Claisen rearrangement of chorismate **340** into prephenate **341** in vivo was catalyzed by the enzyme chorismate mutase (Scheme 100).[132] The rearrangement was accelerated by a factor of 2×10^6 at 37 °C and pH 7.5. The related compounds having an allyl vinyl ether moiety were not, however, affected by the enzyme. This Claisen rearrangement could be catalyzed by monoclonal antibodies and the rate of the antibody-catalyzed reaction was 10^4-fold faster at 10 °C, pH 7.0, compared with the uncatalyzed thermal rearrangement.[133]



Scheme 100.

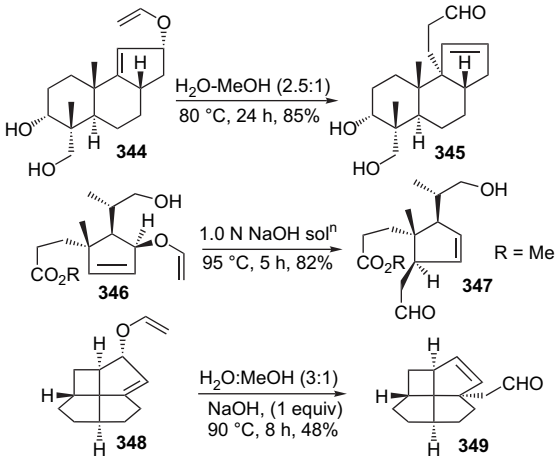
4. Water-accelerated Claisen rearrangement

Water has emerged as a versatile solvent in organic reactions in recent years. The small size and high polarity of a water molecule, as well as the three-dimensional hydrogen bonded network system of bulk water, provide unique and remarkable properties that include a large amount of cohesive energy density, a high surface tension and a hydrophobic effect. These unique properties are believed to be solely responsible for the rate and selectivity enhancements of pericyclic reactions. In addition, the hydrogen bonding between water and organic molecules is believed to play an important role in the rate accelerations of some organic reactions in water. Grieco et al. observed that allyl vinyl ether **342** underwent a facile Claisen rearrangement in water to **343** and the accelerating influence of water as the solvent was studied by measuring the first-order rate constant of the rearrangement in solvents of increasing polarity[134] (Scheme 101).



Scheme 101.

The first-order rate constant in water (18×10^{-5} s^{-1}) is much higher compared to that of pure methanol (0.79×10^{-5} s^{-1}) and the relative rate decreases in the order: water> TFAA>methanol>ethanol>2-propanol>MeCN>acetone> PhH>cyclohexane. Similarly, the corresponding methyl ester underwent a facile Claisen rearrangement. Allyl vinyl ether **344** smoothly underwent Claisen rearrangement in water–methanol (2.5:1) at 80 °C to afford the rearrangement product **345**, which was not obtained under thermal Claisen rearrangement conditions, due to decomposition.[135] The Claisen rearrangement of allyl vinyl ethers **346** and **348** also occurred smoothly in water, to give the rearrangement products **347** and **349**, respectively[135] (Scheme 102).



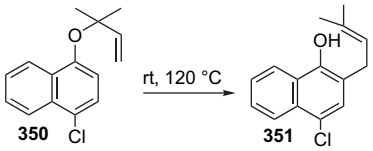
Scheme 102.

A rate acceleration of the aromatic Claisen rearrangement was additionally observed in an aqueous medium. The Claisen rearrangement of allyl naphthyl ether **350** to **351** in aqueous suspension was completed within 5 days at room temperature, whereas the reaction was much slower in organic solvents (Table 37). The neat reaction is slower than the aqueous reaction.[136]

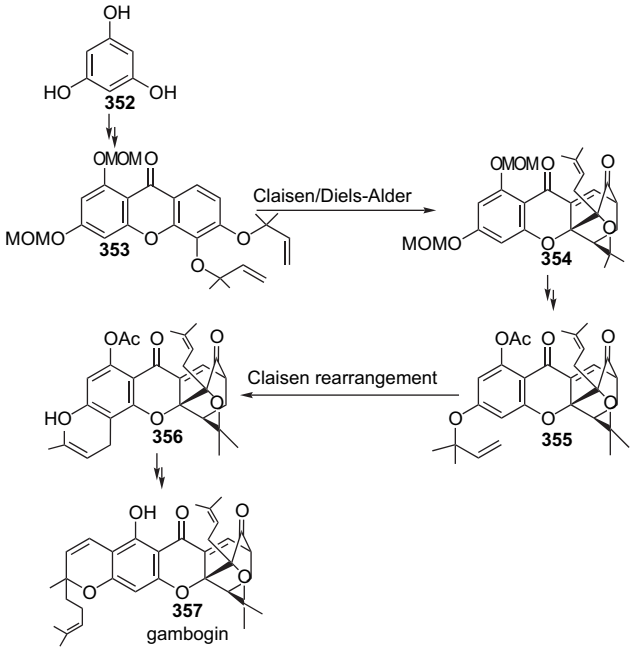
A total synthesis of the biologically active compound, gambogin **357**, includes two key steps of a Claisen rearrangement and a Claisen/Diels–Alder cascade reaction (Scheme 103).

The Claisen/Diels–Alder cascade reaction from **353** to **354** showed a dramatic rate acceleration in aqueous solution. Substrate **353** was derived from phloroglucinol **352**. The large rate enhancement of the Claisen rearrangement of **355** to **356** was also observed in aqueous solution[137] (Table 38).

Table 37
Role of solvents for aromatic Claisen rearrangement



Solvent	Yield (%)
PhMe	16
MeCN	27
MeOH	56
DMF	21
Neat	73
H_2O	**100**



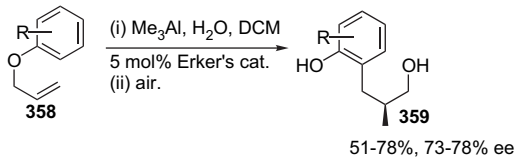
Scheme 103.

The rearrangements of chorismic acid and related compounds were observed to be 100-fold faster in water than in methanol.[138]

Wipf and Ribe[139] reported that the addition of stoichiometric quantities of water accelerated both the trimethylaluminium-mediated aromatic Claisen rearrangement and the chiral zirconocene-catalyzed asymmetric carboalumination of terminal alkenes **358**, leading to the branched alkanols **359** in good yields and high enantiomeric excess. The two reactions occurred in a tandem sequence (Scheme 104).

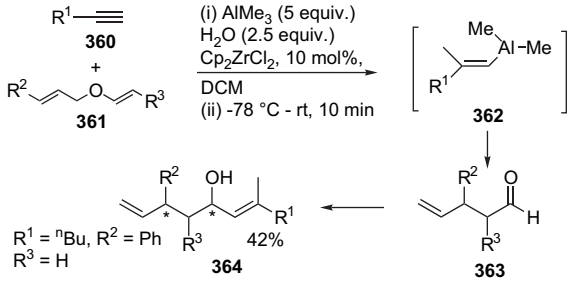
Table 38
Rate acceleration of the Claisen rearrangement from **355** to **356**

Solvent	T (°C)	t (h)	Conversion (%)
MeOH	50	4.5	50
TFE	25	4	0
EtOH	25	4	0
MeOH/H_2O (1:1)	50	2.5	100
TFE/H_2O (1:1)	25	75	100
EtOH/H_2O (1:1)	25	75	100



Scheme 104.

A three-step cascade reaction involving a water-accelerated catalytic carboalumination, a Claisen rearrangement and a nucleophilic carbonyl addition was found to convert the terminal alkynes **360** and allyl vinyl ethers **361** into allylic alcohols **364** containing up to three contiguous chiral centers via **362** and **363**. Stoichiometric quantities of water as an additive increased the rate of the Claisen rearrangement[140] (Scheme 105).



Scheme 105.

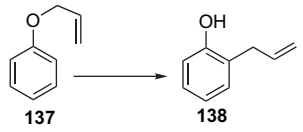
5. Microwave-assisted Claisen rearrangement

Recently, it has been found that the use of microwave irradiation to assist organic reactions has considerable advantages over thermal reactions. Reactions that typically require high temperatures and extended reaction times have been considerably accelerated using microwave irradiation. The Claisen rearrangement can be accelerated by microwave irradiation and the rearrangement was accomplished in a very short time, compared to the conventional thermal rearrangement under heating conditions. The use of microwave irradiation eliminated the problem of long thermal treatment in the case of decomposition of the substrates or products during the reaction.

The Claisen rearrangement can be carried out by microwave irradiation in the presence or absence of a solvent (DMF, *N*,*N*-diethylaniline, dichlorobenzene, THF, etc.). In the absence of a solvent, the Claisen rearrangement (in the solid phase) took a longer irradiation time to obtain comparable yields with the same reaction in a solvent. The rate of the reaction dramatically accelerated by polar aprotic media such as DMF, which absorbs more microwave energy and generates heat energy to promote the rearrangement.

The Claisen rearrangement of allyl phenyl ether **137** was carried out by the use of microwave irradiation in heating conditions in the absence or presence of DMF, which accelerated the Claisen rearrangement and allowed the rearrangement in a very short time,[141] as shown in Table 39.

Table 39
Aromatic Claisen rearrangement accelerated by microwave irradiation



Entry	Irradiation	*t*	*T* (°C)	Solvent	Yield (%)
1		6 h	220		85
2	μW	10 min	325–361		21
3	μW	6 min	300–315	DMF	92

The microwave-induced aromatic Claisen rearrangement of **366** prepared from **365**, regioselectively afforded the *para*-Claisen product **367** at room temperature, whereas **366** under thermal conditions underwent decomposition (Scheme 106).[142]

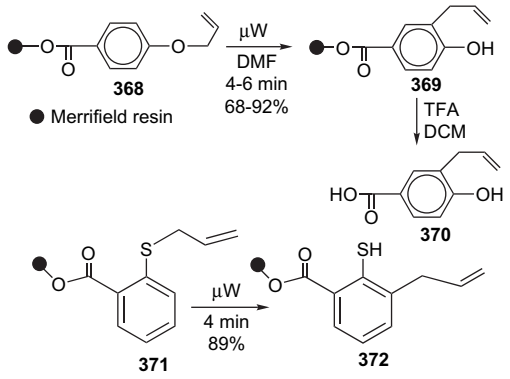
The microwave-assisted Claisen rearrangement of *o*-allylsalicylic acids **368** anchored to a Merrifield resin afforded the corresponding *ortho*-allyl products **369** in high yields in 4–6 min, compared to 10–16 h required under thermal conditions. 3-Allyl-4-hydroxy benzoic acid **370** was obtained by treatment with TFA in DCM. The Claisen rearrangement on the solid phase was carried out by irradiating the resin-bound *o*-allyl aryl ethers in DMF in an Erlenmeyer flask. *o*-Allyl aryl sulfides **371** also underwent a Claisen rearrangement to give the *ortho*-allylthiosalicylic acid[143] **372** (Scheme 107).

The microwave-assisted[144] solvent-free instantaneous Claisen rearrangement of bis(4-allyloxyphenyl) sulfone **373** afforded bis(3-allyl-4-hydroxyphenyl) sulfone **375** in 87% yield at 553 K in 5 min, whereas conventional heating[145] at 481–532 K required 2–30 h (Scheme 108).

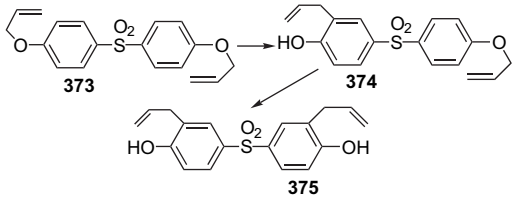
The Claisen rearrangement of **373** to **375** was complete in two steps via the formation of 3-allyl-4-hydroxy-4′-allyloxydiphenyl sulfone **374** and the conversion of **373** into **375** monotonously increased in the temperature range from 503 to 553 K (Table 40).

A one-pot synthesis of 2,3-bisallyl-1,4-quinones **377** from 1,4-bis-allyloxybenzene derivatives **376** was conducted by a microwave-assisted Claisen rearrangement on a silica gel support under solvent-free conditions.[146] *o*-Allylated ethers **378** and **380** under microwave irradiation (800 W) rearranged to the corresponding bis-allylated ketones **379** and **381** in 65–78% yields, respectively, in 5–15 min, whereas, under thermal conditions,[146b] the rearranged product was obtained in low yield (26%), even after heating for 12 h (Scheme 109).

Microwave irradiation also accelerates the aliphatic Claisen rearrangement of various allyl vinyl or propargyl vinyl ethers. The Claisen rearrangement of allyl vinyl ether **382** under microwave irradiation for 5 min gave **383** in high yield and high



Scheme 107.



Scheme 108.

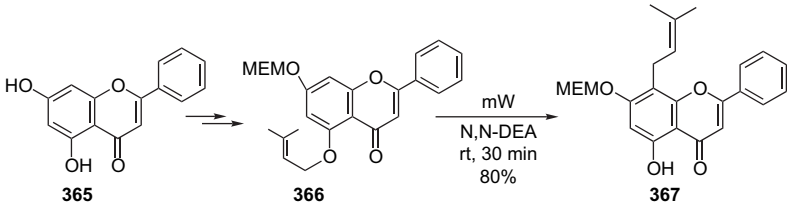
diastereoselectivity,[147,148] whereas the thermal Claisen rearrangement required 24 h to complete the rearrangement[149] (Scheme 110).

The microwave-assisted Claisen rearrangement of propargyl enol ether **384** to **385** was successful in the synthesis of the skeleton present in the triterpenoid azadirachtin **386** (Scheme 111), whereas no rearrangement was observed under thermal or catalytic conditions.[150]

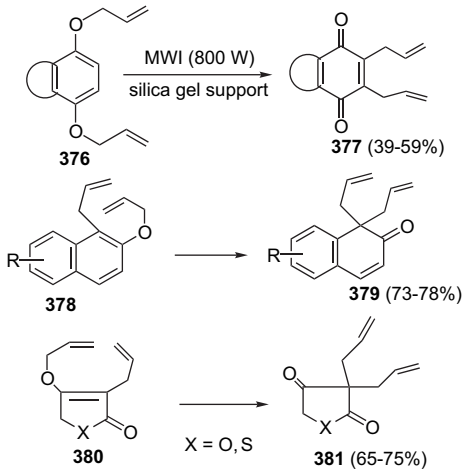
Table 40
Solvent-free Claisen rearrangement of **373** at 503–553 K under microwave irradiation

Entry	(K)	*t* (min)	Conversion[a] (%)		
			373	**374**	**375**
1	503	5	82	16	1
2	503	30	15	44	37
3	503	60	1	16	76
4	513	5	57	35	6
5	513	30	1	15	76
6	523	5	13	43	41
7	523	20	<1	7	81
8	533	5	7	34	54
9	533	10	1	10	83
10	543	5	1	13	77
11	553	5	<1	2	87

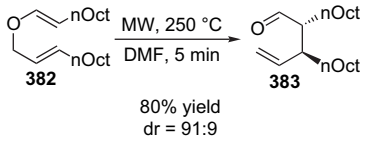
[a] Determined by HPLC analysis.



Scheme 106.



Scheme 109.

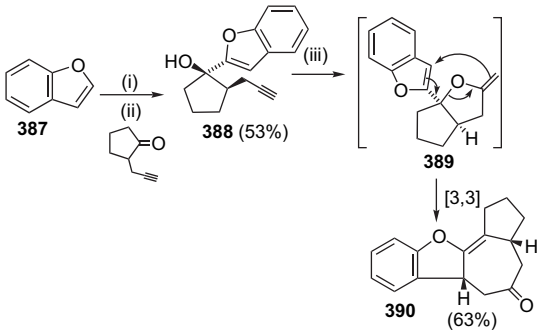


Scheme 110. Thermal conditions and results: 120 °C, 24 h, 90% yield, dr=94:6.

A one-pot reaction sequence involving a base-catalyzed 5-*exo* cyclization of appropriately substituted 4-alkyn-1-ols and subsequent Claisen rearrangement of the intermediate 2-methylenetetrahydrofuran derivatives was found to be significantly accelerated by the application of microwave irradiation[151] (Scheme 112).

Tetracyclic ketone **390** was synthesized by this methodology. Initial metallation of benzofuran **387** followed by reaction of the resulting organocerium species with 2-propargylcyclopentanone afforded acetylenic alcohol **388**, which, on irradiation for 30 min at 200 °C in phenetole via allyl vinyl ether **389**, gave the product **390** in 63% isolated yield (Scheme 112).

Various cycloheptanoid ring systems were synthesized using this microwave reaction sequence. Under microwave irradiation conditions, the products were obtained within a few minutes (Table 41), whereas a much longer time was needed



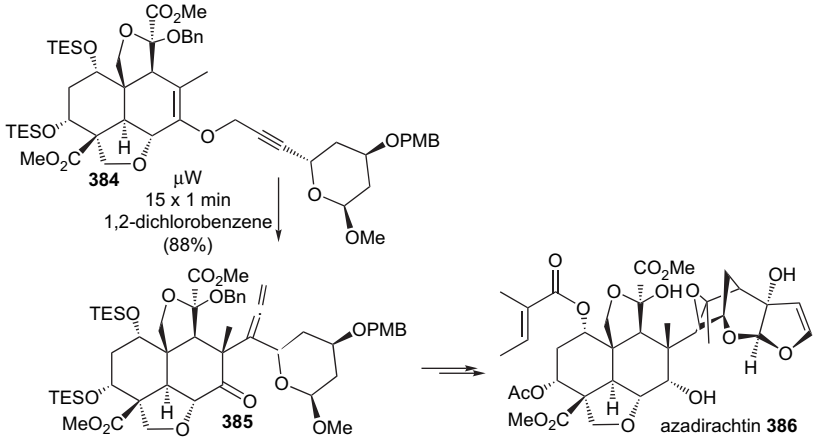
Scheme 112. Reagents and conditions: (i) ^{t}BuLi, −78 °C; (ii) $CeCl_3$; (iii) cat. MeLi, PhOEt, MWI, 30 min, 200 °C.

in the case of conventional heating for the same transformation (catalytic amount of ^{t}BuOK in DMF was also effective in place of MeLi in DMF). Ovaska et al. successfully applied this microwave-assisted 5-*exo* cyclization–Claisen rearrangement sequence of **394** to **392** for the total synthesis of the frondosin C system[152] **393** (Scheme 113). Their contribution is important in this reaction sequence for the cycloheptane-containing polycyclic ring structure synthesis.[153–157]

Recently, this methodology was successfully applied to the first total synthesis of (±)-frondosin C (**393**) and (±)-8-*epi*-frondosin C[158] (**395**). Frondosin C is one of the five related novel sesquiterpene hydroquinone derivatives that were isolated from the Micronesian marine sponge, *Dysidea frondosa*.[159] All members of this family are antagonists of interleukin-8 and inhibitors of protein kinase C in the low micromolar range.[159]

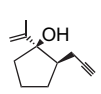
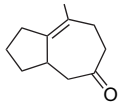
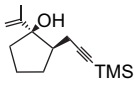
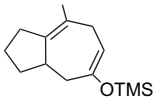
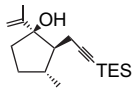
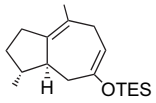
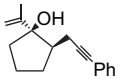
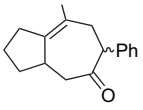
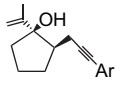
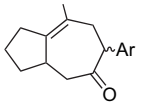
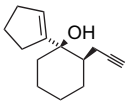
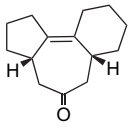
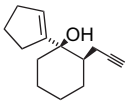
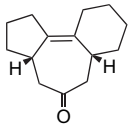
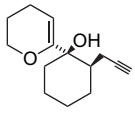
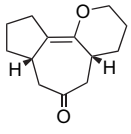
The microwave-assisted anionic 5-*exo-dig* cyclization Claisen rearrangement sequence of **391** afforded **392a** and **392b**, which were further transformed into the products **393** and **395** (Scheme 114).

A microwave-assisted combined Mitsunobu reaction, Claisen rearrangement and phenol oxidation sequence was used for the rapid synthesis of the 2,6-disubstituted-1,4-benzoquinone natural products, primin **397a** and 2-methoxy-6-pentadecyl-1,4-benzoquinone **397b** from *o*-methoxy phenol **396**, with a total reaction time of 1 h in overall yields of 43 and 28%, respectively[160] (Scheme 115).

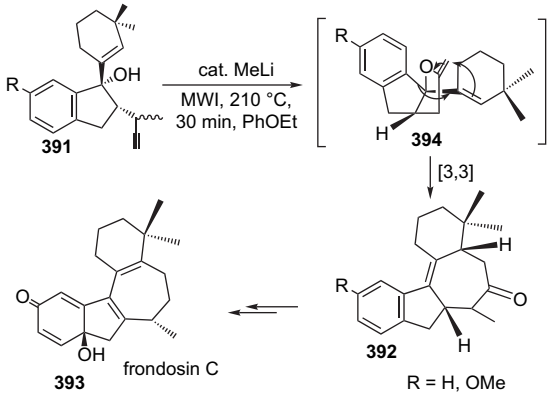


Scheme 111.

Table 41
Tandem cyclization–Claisen rearrangement reactions of 4-alkyn-1-ols under microwave irradiation

Entry	4-Alkyn-1-ol	Conditions[a]	Product	Yield[b] (%)
1		DMF, 150 °C, 12 min		72
2		PhOEt, 200 °C, 15 min		65[c]
3		PhOEt, 200 °C, 15 min (8×15 min required without MWI)		71
4		PhOEt, 200 °C, 20 min		85
5		DMF, 175 °C, 15 min, Ar=1-naphthyl		60
6		DMF, 200 °C, 4 min (50 min at 200 °C without MWI)		82
7		No solvent, 200 °C, 30 min		93
8		DMF, 200 °C, 15 min		90

[a] All reactions were done in the presence of catalytic (ca. 10 mol %) MeLi.
[b] Isolated yields of analytically pure products.
[c] Isolated yields reflect that of the hydrolyzed ketone product (entry 1).



Scheme 113.

The acceleration of the Claisen rearrangement by microwave irradiation was also confirmed by an experiment in which the allyl aryl ethers **398** under microwave irradiation in DMF for 30 min at 220–290 °C gave the rearrangement products **399** in good yields whereas conventional heating required 72 h in refluxing DMF or 4 h in DMA to give the phenols **399**. Application of the microwave-assisted tandem Claisen–Mislow–Evans rearrangement for the synthesis of A,G-spiroimine of pinnatoxins, member of marine natural products, was developed and found to be a viable alternative, significantly reducing the reaction time. The tandem rearrangement of **400** using microwave conditions[161] at 50 W and 170 °C gave the product **401**, an useful intermediate in the synthesis of pinnatoxin A **402**, in 82% yield in 20 min, whereas the thermal conditions at 150 °C required 15 h (Scheme 116).

6. Miscellaneous

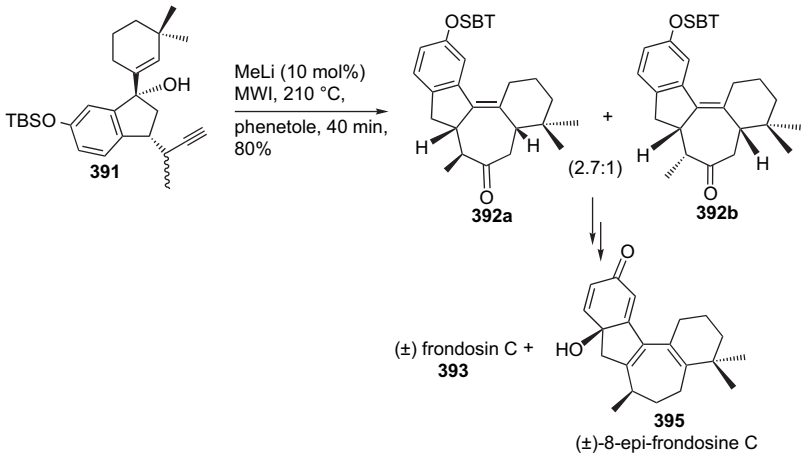
6.1. Lewis acid-catalyzed acyl-Claisen rearrangement

The acyl-Claisen rearrangement is a charge-accelerated and Lewis acid-promoted[162] version of the aza-Claisen rearrangement that belongs to a large group of zwitterionic [3,3]-sigmatropic rearrangements known under the name ketene or Bellus–Claisen rearrangements.[163] MacMillan et al.[162] studied this zwitterionic aza-Claisen rearrangement in the presence of a number of Lewis acids and a remarkable catalytic effect was observed. (Allyl) vinylammonium complexes **406**, generated by the reaction of ketenes **407** (derived from acyl chlorides **403**) with tertiary allyl amines **404** in the presence of a Lewis acid, rearranged to afford the 2,3-disubstituted Claisen products **405** in good yields (>75%) and excellent stereocontrol (>99:1 *anti*/*syn*) via the Lewis acid complex **408**. The best results were obtained with $Yb(OTf)_3$, $AlCl_3$, $Ti(O^iPr)_2Cl_2$ and $TiCl_4\cdot(THF)_2$. Mechanistically, this rearrangement could be rationalized via the formation of charged intermediates **406** and a six-centre cyclic transition state (Scheme 117).

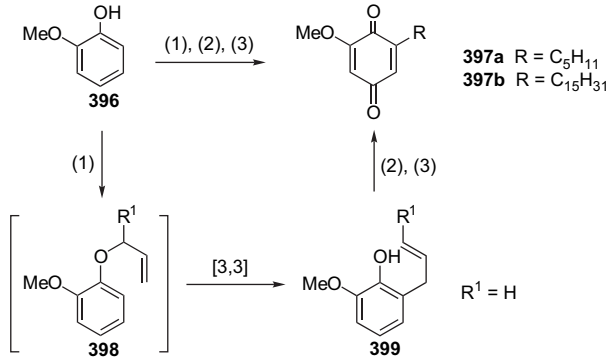
The Lewis acid-catalyzed acyl-Claisen rearrangement between various allylmorpholines and propionyl chloride in the presence of 5–10 mol % $TiCl_4\cdot(THF)_2$, $^iPr_2NEt$ and CH_2Cl_2 at 23 °C afforded the rearrangement products in good yields with good diastereoselectivity. This rearrangement is also effective for oxygen and sulfur substituents on the acyl chloride component.

In 2001, MacMillan et al.[164] reported the first enantioselective catalytic acyl-Claisen rearrangement using the chiral Lewis acid catalysts, [Mg–py box](I)$_2$ **409** and [Mg–Arbox](I)$_2$ **410a–c** (Fig. 7).

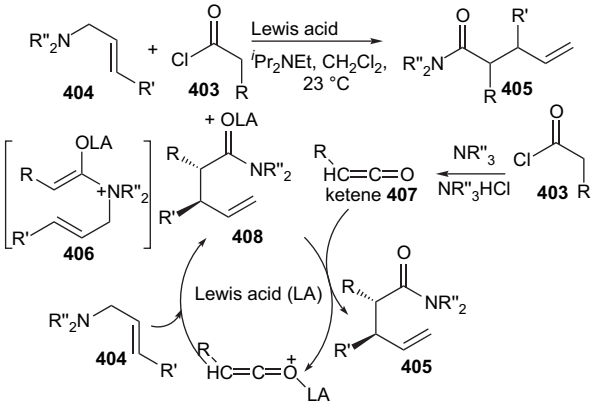
The architecture of the catalyst was found to play a vital role in the rearrangement process. Catalyst **409** (200 mol %, −20 °C, 24 h, entry 1, Table 42) gave the product (*S*)-**413** in 87% yield and 56% ee while the catalyst **410a** (200 mol %) was more effective in affording (*S*)-**413** from **411** and **412** in 88% yield and 83% ee, (entry 2, Table 42). Catalysts **410a–c** provided a highly efficient environment for the substrates to bind and rearrange asymmetrically.



Scheme 114.



Scheme 115. Reagents and conditions: (1) Ph_3P, DIAD, toluene, 300 W, 220 °C, 30 min, $CH_2{=}CHCHR^1(OH)$; (2) NH_4OCHO, Pd/C, 10 W, 10 min; (3) Fermy's salt, NaH_2PO_4, aq acetone, 10 W, 20 min, or salcomine, O_2, MeCN, 10 W, 20 min.

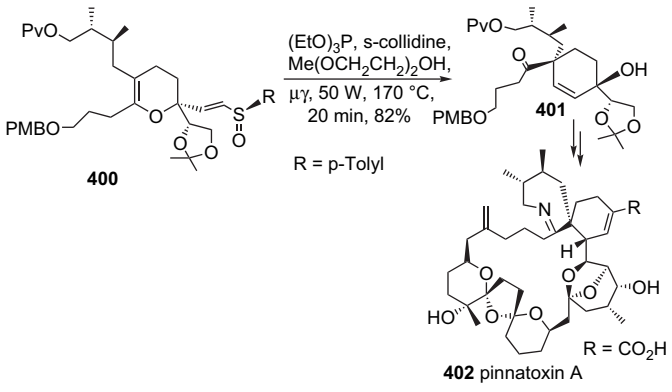


Scheme 117.

Catalyst **410c** was the most effective and substoichiometric quantities of **410c** afforded a lower enantioselectivity (entry 4, Table 42). An acyl-Claisen rearrangement was found to be the key step in a new and efficient asymmetric synthesis of chiral enantiomerically pure *trans*-3,4-dialkyl-γ-lactones[165] such as **418**, which are versatile synthetic intermediates and structural units of natural products and modified nucleosides.

Treatment of compound **415** with benzyloxyacyl chloride **414** in the presence of a $TiCl_4$ catalyst afforded the desired unsaturated amide **417** in 70% yield. The use of the Lewis acid catalyst $Zr(OSO_2CF_3)_2$ gave the amide **417** in 64% yield. Amide **417** was then transformed into the lactone **418**. Compounds **414** and **415** were prepared from easily available starting materials. Mechanistically, the acyl-Claisen rearrangement is believed to proceed through a charged intermediate **416** and a six-centre cyclic transition state (Scheme 118).

Recently, the stereoselective synthesis of a 3,4,5-trisubstituted tetrahydropyran **424**, a potent human NK_1 receptor antagonist, was achieved via an acyl-Claisen rearrangement.[166] In this synthesis, compound **421** was prepared by the application of a Lewis acid-catalyzed acyl-Claisen rearrangement from compounds **419** and **420**. Compound **421** was then transformed into compound **422**. Finally, reductive amination of the aldehyde **422** with piperidine **423** in the presence of sodium triacetoxyborohydride followed by saponification of the



Scheme 116.

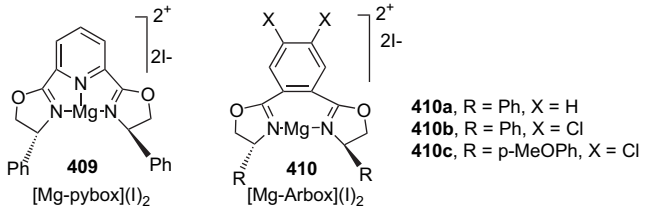
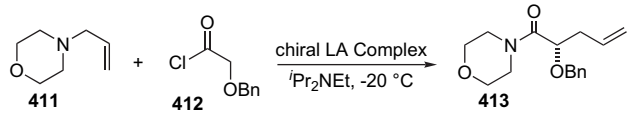
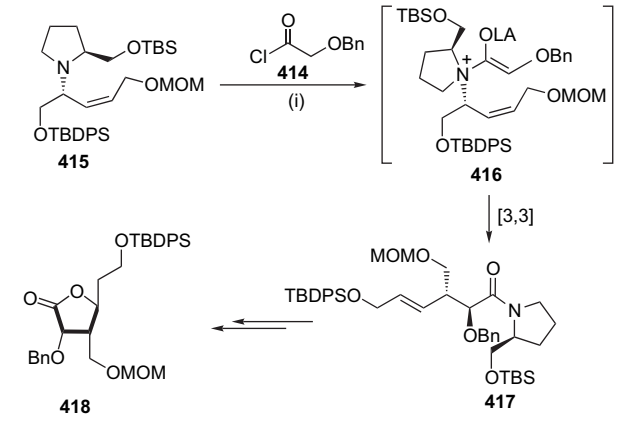


Figure 7.

Table 42
Effect of chiral Lewis acid structures on the enantioselective acyl-Claisen rearrangement



Entry	Complex	R	X	LA (mol %)	*t* (h)	Yield (%)	ee (%)
1	**409**	—	—	200	24	87	56
2	**410a**	Ph	H	200	24	88	83
3	**410b**	Ph	Cl	200	24	65	86
4	**410c**	*p*-MeOPh	Cl	50	24	81	42
5	**410c**	*p*-MeOPh	Cl	100	24	63	81
6	**410c**	*p*-MeOPh	Cl	200	24	80	91

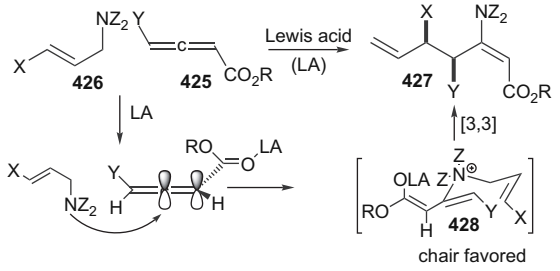


Scheme 118. Reagents and conditions: (i) cat. $TiCl_4$, $^{i}Pr_2NEt$, 70%, or $Zr(OSO_2CF_3)_2$, $^{i}Pr_2NEt$ (2 equiv), 64%.

camphanate ester furnished product **424** in 50% yield (Scheme 119). Compounds **419**, **420** and **423** were prepared from suitable starting materials.

6.2. Lewis acid-catalyzed allenoate-Claisen rearrangement

In the context of the Lewis acid-catalyzed Claisen rearrangement, the allenoate-Claisen rearrangement is a very important method for the diastereoselective preparation of 4,5-disubstituted-β-enamino esters.[167] The reaction of a Lewis acid-activated allenic ester **425** with a tertiary allylamine **426** proceeded with a high π-facial discrimination to give an (allyl) vinylammonium complex **428** exhibiting (*E*)-stereochemistry at the enamine double bond. This complex evolved through a chair-like transition state to afford the [3,3]-rearranged product **427** (Scheme 120).



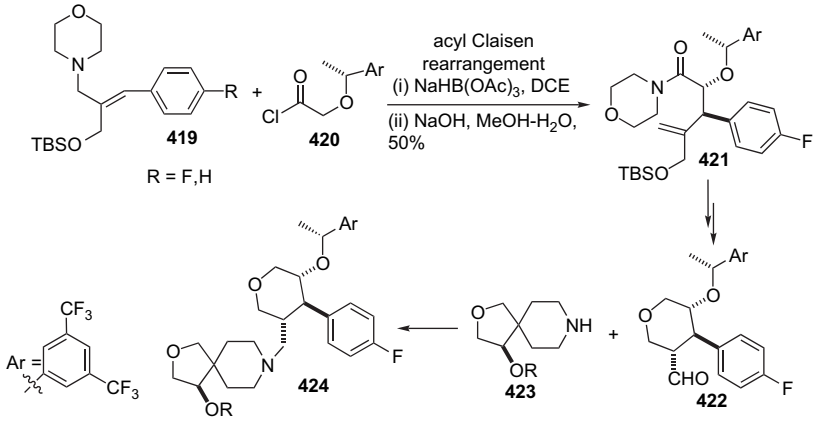
Scheme 120.

Excellent yields and stereoselectivities were obtained in the presence of $Yb(OTf)_3$, $Sn(OTf)_2$, $Cu(OTf)_2$ or $Zn(OTf)_2$ (Table 43).

Table 43
Lewis acid-catalyzed allenoate-Claisen rearrangement

Entry	Lewis acid	cat. (mol %)	Yield (%)	*syn*/*anti*[a]
1	—	—	NR	—
2	$Yb(OTf)_3$	5	82	>98:2
3	$Sn(OTf)_2$	5	86	>98:2
4	$Cu(OTf)_2$	10	87	>98:2
5	$TiCl_4\cdot(THF)_2$	10	86	>98:2
6	$AlCl_3$	10	83	>98:2
7	$MgBr_2\cdot Et_2O$	10	81	>98:2
8	$FeCl_3$	10	83	>98:2
9	$Zn(OTf)_2$	10	95	>98:2
10	$Zn(OTf)_2$	5	93	>98:2

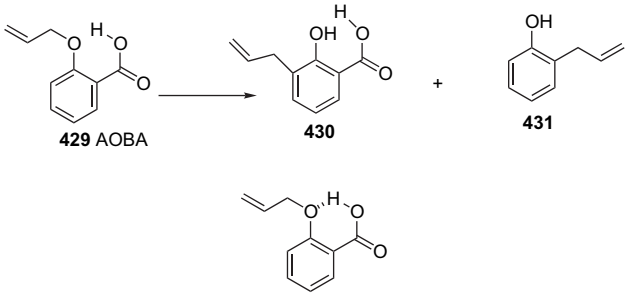
[a] Product ratios were determined by ^{1}H NMR analysis.



Scheme 119.

6.3. Other examples

The Claisen rearrangement of 2-allyloxybenzoic acid (AOBA) **429** afforded **430** and **431**. Claisen rearrangement of AOBA and its alkali and alkaline earth metal salts was studied in diethylene glycol (DEG), diethylene glycol monoethyl ether (DEGMEE) and decalin (Scheme 121).[168]



Scheme 121. Intramolecular H-bond is free in AOBA.

The rate of rearrangement was higher in the polar solvents than that in the nonpolar solvents and should be in the order DEG>DEGMEE>decalin. The order of reactivity in polar solvents was free: AOBA>alkali metal salts>alkaline earth metal salts, whereas in nonpolar solvents, the reactivity order changed to: alkaline earth metal salts>free AOBA>alkali metal salts. In nonpolar solvents, no rate acceleration was observed for the metal salts compared to free AOBA, due to loss of the intramolecular hydrogen bond (Fig. 8) between the carbonyl group and the ethanol oxygen that accelerates the Claisen rearrangement by decreasing the higher electron density on the ethereal oxygen in the transition state. In nonpolar solvents, however, a sufficiently high reactivity was observed for the alkaline earth metal salts, due to the chelate ring formation between the ethereal oxygen and the carboxyl group (Fig. 9). As the complex-forming ability of the alkali metals is much lower than that of the alkaline earth metals, they cannot form chelate rings and, as a result, no rate enhancement occurs, compared to free AOBA.[168]

Various homoallylic α-ketoacids such as **434** were synthesized from the reaction of aldehyde **432** with phosphonate **433** by a Horner–Wadsworth–Emmons (HWE) olefination reaction to **435** followed by Claisen rearrangement to **436** and saponification reaction sequence with an overall yield of 69% and a combined reaction time of 12 h. The one-pot tandem process

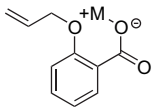


Figure 8. M=Li, Na, K; no interaction in alkali metal salts of AOBA.

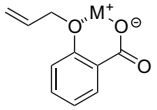
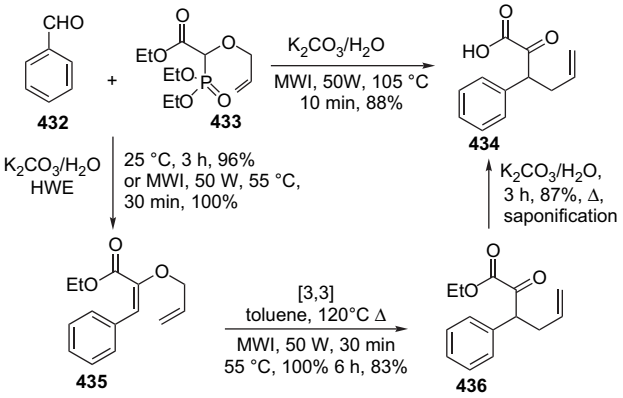


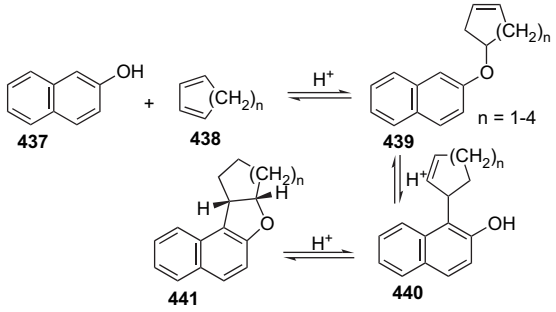
Figure 9. M=Ca, Ba; chelate ring in alkaline earth metal salt of AOBA.



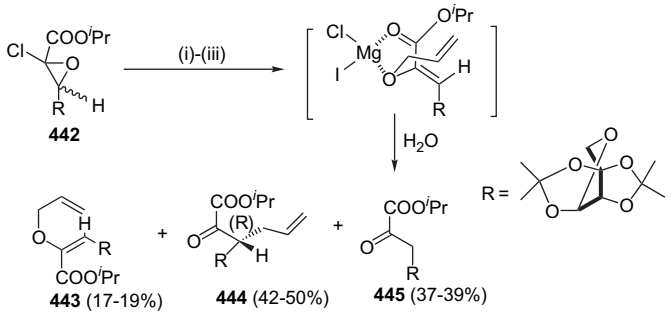
Scheme 122.

under microwave irradiation (50 W) at 105 °C for 10 min in the presence of an equimolecular heterogeneous mixture of **432** and **433** in aqueous K_2CO_3 afforded **434** directly in an excellent overall yield (88%)[169a] (Scheme 122). Here, the aqueous medium employed for the tandem sequence presumably assisted the Claisen rearrangement via a hydrophobic acceleration effect[169b] and also affected the saponification process.

Cycloalkanonaphthofurans **441** were prepared in a one-pot TsOH–H_2O-catalyzed reaction from 2-naphthol **437** and cycloalka-1,3-dienes **438** (Scheme 123).[170] The mechanism of the formation of **441** could be rationalized by an initial [1,3]- or [3,3]-rearrangement of the in situ-generated allyl aryl ethers **439**, followed by a concomitant intramolecular cyclization of **440**. 1-Naphthol also reacted in a similar fashion to give the corresponding cycloalkanonaphthofurans.



Scheme 123.



Scheme 124. Reagents and conditions: (i) MgI_2 (1 equiv), Mg (1 equiv), Et_2O, 2 h, 33 °C; (ii) Et_2O, 15 h, 20 °C; (iii) $CH_2{=}CH{-}CH_2Br$ (3.3 equiv), HMPA (4 equiv), 48 h, 33 °C.

The magnesium dihalide-catalyzed Claisen rearrangement[171] of 2-alkoxycarbonyl allyl vinyl ethers derived from α-chloroglycidic esters **442** afforded the rearranged products **444** in good yield after 48 h reaction at 33 °C, whereas in the absence of MgI_2, in refluxing xylene, only degradation of the substrate was observed. Products **444** were obtained as a unique diastereomer (100% stereoselectivity), which could be explained by considering the chair-like transition state and products **443** and **445** were also obtained in lower yield (Scheme 124). The first application of this strategy allowed access to the biologically active, ulosonic acid.

7. Conclusions

From the early 1960s, the Claisen rearrangement has been a topic of dynamic development. The problems of the conventional thermal technique have, however, prompted chemists to explore the catalysis of this reaction. In this review, we have discussed the catalysis of the Claisen rearrangement of a wide variety of suitable aliphatic and aromatic substrates using achiral and chiral nonmetal and metal catalysts, acids, bases, zeolites, water, enzymes, physical parameters such as microwave irradiation and ionic liquids as alternative reaction media to afford the rearranged products under mild condition with regio-, diastereo- and enantio-control, which offers an efficient means for the synthesis of different types of synthetically important organic compounds. This review has mostly included the work published during the last decade covering the catalysis of the Claisen rearrangement and related synthetic and mechanistic aspects. The recent findings and synthetic applications reported here still offer an enormous challenge and will provide a firm basis and scope for further studies on the topic.

Acknowledgements

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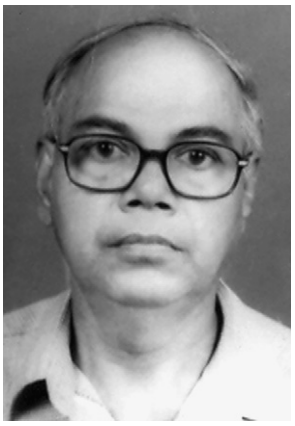
Biographical sketch



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