Catalysis of the Claisen Rearrangement of Aliphatic Allyl Vinyl Ethers

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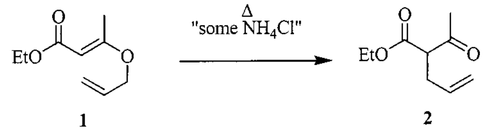
The thermal Claisen rearrangement of allyl vinyl ethers is generally regarded as high-performance method for diastereoselective C–C bond formation. Substrate-induced diastereoselectivity and reagent-induced enantioselectivity with stoichiometric amounts of external chiral auxiliaries have frequently been exploited to control the stereochemical course of the Claisen rearrangement. This review summarizes the attempts to catalyze the Claisen rearrangement of acyclic aliphatic allyl vinyl ethers with chiral and achiral catalysts. The best suited catalysts for the Claisen rearrangement so far identified are Lewis acids. Finally, bis(oxazoline)copper(II) complexes have found a further useful application as chiral catalysts for the first catalytic, enantioselective Claisen rearrangement – 90 years after Ludwig Claisen originally reported a [3,3]-sigmatropic rearrangement of an allyl vinyl ether.

Introduction

"*From what began as a casual introduction to a paper 76 years ago has blossomed a reaction of considerable significance. The Claisen rearrangement has stimulated the interest of several generations of chemists. Physical organic chemists have been provided with a mechanistic challenge, the synthetic organic community has had the opportunity to expand the scope of the reaction and apply it to complex syntheses, and bioorganic chemists have solved a formidable challenge in the chemistry of enzymes. Perhaps a new and imaginative generation will see new opportunities for this reaction and expand upon the chemistry discussed in this review.*" Frederick E. Ziegler, 1988.[1]

The first example of a thermal [3,3]-sigmatropic rearrangement of an aliphatic allyl vinyl ether was reported by Ludwig Claisen in 1912 (Scheme 1).[2] Claisen heated ethyl 3-allyloxybut-2-enoate (**1**) in the presence of solid NH_4Cl and isolated the β-oxo ester **2** as the product of a [3,3]-sigmatropic rearrangement.



Scheme 1. First published example of the Claisen rearrangement

Since Claisen's original report, the rearrangement now named after him has developed into one of the most soph-

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Martin Hiersemann was born in Berlin (Germany) in 1966. He studied chemistry at the Freie Universität Berlin. He received his Ph.D. in 1995 under the guidance of Johann Mulzer. As a postdoctoral fellow, he joined the group of Gary A. Molander for 18 months and worked on the total synthesis of cephalotaxine. In October 1997, he returned to Germany and started an independent research program at the Technische Universität Dresden. He submitted his habilitation thesis in August 2001. The research endeavors of his group are currently directed toward the development of chiral catalysts for sigmatropic rearrangements, metal-catalyzed cyclizations of 1,5-hexadienes, development of new artificial pyridoxamine analogues, and the total synthesis of biologically interesting or structurally challenging natural products.

Lars Abraham was born in Lauchhammer, Brandenburg (Germany) in 1974. He had his first contact with chemistry while working as a chemlab assistant in 1995 in the research department of BASF (Schwarzheide, Brandenburg). In 1996 – after his German civil equivalent of "Wehrdienst" – he decided to study chemistry at the Technische Universität Dresden. During his study he spent a year (1999/2000) at the University of Northumbria at Newcastle (UK). In October 2001 he obtained his diploma degree in chemistry. His thesis work was concerned with the catalytic enantioselective Claisen rearrangement of allyl vinyl ethers.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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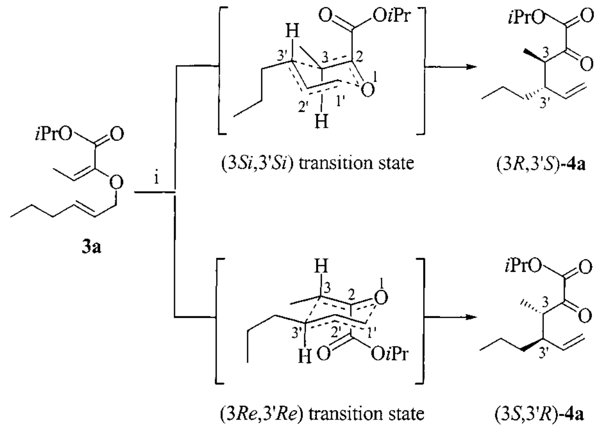
isticated synthetic methods for C−C bond formation. Over the years, a number of comprehensive review articles have been published, covering all the important features of the Claisen rearrangement and the numerous related [3,3]-sigmatropic rearrangements, such as mechanism, stereochemistry, and synthetic applications.[1,3] The purpose of this microreview is not to add another general review article concerning the Claisen rearrangement, but to provide an overview of catalysis of the Claisen rearrangement of aliphatic allyl vinyl ethers by metal catalysts. Only those catalysts that catalyze the Claisen rearrangement in substoichiometric amounts are taken into account.

The Challenge

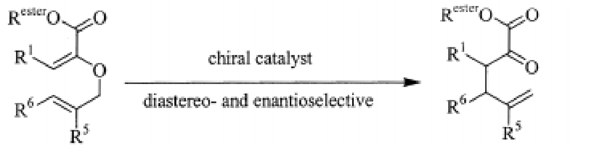
The utility of the Claisen rearrangement rests on its ability to transform an easily accessible C−O single bond into a less easily accessible C−C single bond, thereby generating up to two new chirality centers and a stereogenic double bond. Scheme 2 presents an instructive example; the 2-alkoxycarbonyl-substituted allyl vinyl ether **3a** was transformed into the α-oxo ester **4a** as a single diastereomer. The reaction temperature was moderate and the yield was almost quantitative.



i: $ClCH_2CH_2Cl$, 100 °C, 24 h, sealed tube (99 %, single diastereomer)

Scheme 2. Thermal Claisen rearrangement of the acyclic aliphatic allyl vinyl ether **3a**; the asynchronous nature of the transition state was not considered in the drawing

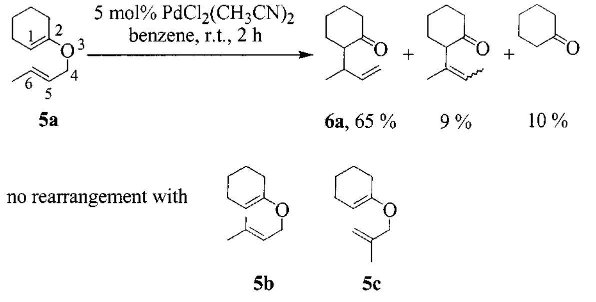
It is generally accepted that the stereochemical outcome of a thermal Claisen rearrangement of an acyclic allyl vinyl ether can be explained/predicted on the basis of a chair-like transition state conformation.[4] The inherent strength of the Claisen rearrangement is the reliable transformation of a given double bond configuration into a single relative configuration in the rearrangement product. Unfortunately, when the starting material is an achiral allyl vinyl ether (e.g., **3a**), the rearrangement proceeds through two enantiomeric transition states to afford a racemic product (e.g., **4a**). Several chiral reagents for an enantioselective Claisen rearrangement have been proposed.[5,6] Unfortunately, they all have to be used in at least stoichiometric amounts. In October 1997, we set out to combine the inherent diastereoselectivity of the thermal Claisen rearrangement with the potential of modern chiral catalysts for enantiofacial differentiation. We were seeking for a catalyst that would be able to catalyze the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers diastereo- and enantioselectively (Scheme 3).



Scheme 3. What is an appropriate catalyst for an enantioselective Claisen rearrangement?

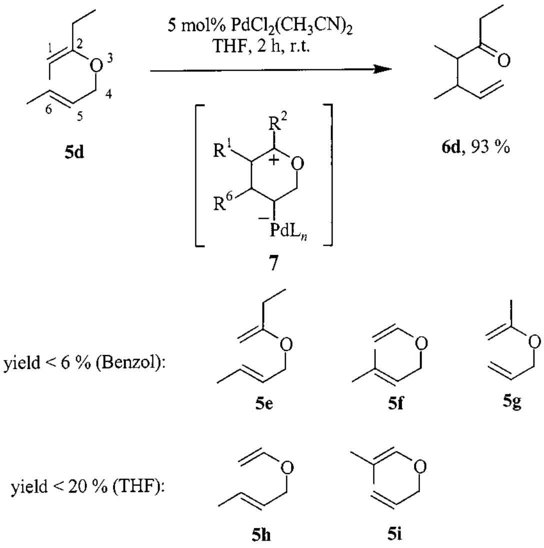
Achiral Catalysts

The number of known catalysts for Claisen rearrangements of aliphatic allyl vinyl ethers is amazingly limited; van der Baan and Bickelhaupt apparently reported the first successful example in 1986.[7] They utilized $[PdCl_2(CH_3CN)_2]$ as catalyst and studied how the substituents on the allyl vinyl ether **5** determined the reactivity (Schemes 4 and 5). Their study revealed that the cyclic allyl vinyl ether **5a** was transformed with 5 mol% of $[PdCl_2(CH_3CN)_2]$ at room temperature into the rearrangement product **6a** (Scheme 4), double bond migration and cleavage of the vinyl ether being the most important side reactions. The allyl vinyl ethers **5b** and **5c**, with a trisubstituted allylic ether double bond or a methyl group at C-5, were not reactive.



Scheme 4. Pd^{II}-catalyzed Claisen rearrangement

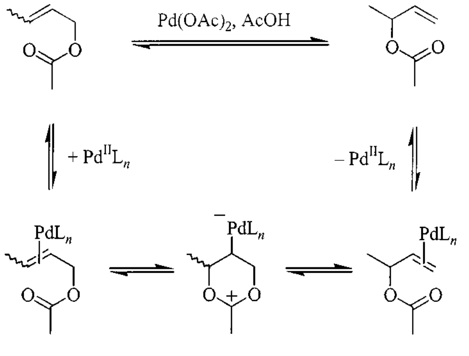
They also studied the $[PdCl_2(CH_3CN)_2]$-catalyzed Claisen rearrangement of acyclic allyl vinyl ethers **5d−i** and found that the Pd^{II} catalyst was efficient if certain structural demands were met (Scheme 5). To obtain an acceptable result from the rearrangement, C-1 and C-2 of the allyl vinyl ether **5** had to be substituted with alkyl groups. The authors explained this observation through the assumption of a "cyclization-induced" rearrangement mechanism. They argued that the substituent on C-1 prevents the unproductive coordination of the Pd^{II} catalyst to the vinyl ether double bond and that the alkyl group at C-2 stabilizes a positive charge in the intermediate Pd−C σ-complex **7**. Unfortunately, the stereochemical outcome of the catalyzed re-



Scheme 5. Pd^{II}-catalyzed Claisen rearrangement

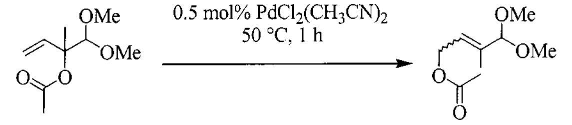
arrangement was not explicitly mentioned in their publication.

The work of van der Baan and Bickelhaupt was inspired by two review articles published by L. E. Overman and R. P. Lutz in 1984.[8,9] These comprehensive review articles summarize the early work concerning the catalysis of [3,3]-sigmatropic rearrangements. The seminal observation was apparently made by Winstein in 1966. He found that $Pd(OAc)_2$ in AcOH was able to promote the equilibration of allylic acetates (Scheme 6).[10] Henry thoroughly studied the mechanism of this reaction and found evidence for the "cyclization-induced" rearrangement mechanism (Scheme 6).[11]



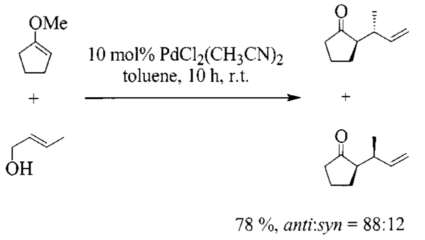
Scheme 6. The "cyclization-induced" rearrangement mechanism of the Pd^{II}-catalyzed rearrangement of allylic acetates

This specific mechanism is also believed to operate for the Pd^{II}-catalyzed [3,3]-sigmatropic rearrangement of allylic imidates and the Pd^{II}-catalyzed Cope rearrangement.[12,13] $[PdCl_2(CH_3CN)_2]$ was first utilized as a convenient catalyst for [3,3]-sigmatropic rearrangements by Meyer[14] (Scheme 7).



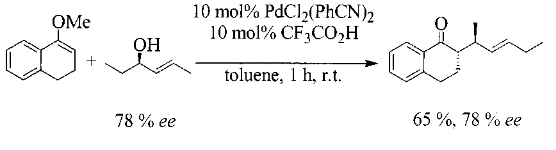
Scheme 7. First application of $PdCl_2(CH_3CN)_2$ for the catalysis of sigmatropic rearrangements

Winstein's seminal discovery,[11] followed by the work of Henry,[12] Meyer,[14] and Overman[8,15] culminated in the study by van der Baan and Bickelhaupt, summarized above.[7] Their investigation was followed by a series of papers of T. Nakai and co-workers, who developed an in situ vinyl ether exchange procedure to avoid the sometimes troublesome synthesis of an allyl vinyl ether. $[PdCl_2(CH_3CN)_2]$ catalyzes vinyl ether exchange between a methyl vinyl ether and an appropriate allylic alcohol and also the subsequent Claisen rearrangement of the intermediate allyl vinyl ether (Scheme 8).[16]



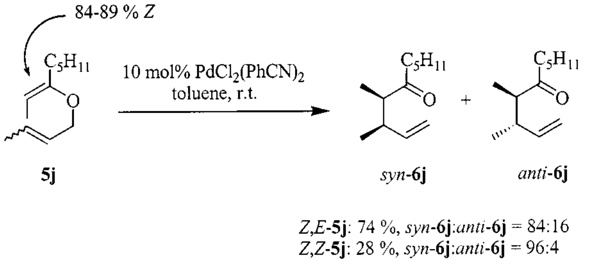
Scheme 8. Pd^{II}-catalyzed, in situ vinyl ether exchange/Claisen rearrangement

A combination of $[PdCl_2(CH_3CN)_2]$ and CF_3CO_2H was used if the substrates were reluctant to undergo the vinyl ether exchange reaction in situ (Scheme 9).[17] This procedure allowed the formation in situ and the catalyzed rearrangement of a chiral allyl vinyl ether with complete 1,3-chirality transfer. The relative and absolute configuration of the rearrangement product is best explained by the assumption of a boat-like transition state conformation in the Pd^{II}-catalyzed rearrangement. Regioisomeric products are possible if a methyl vinyl ether of an unsymmetrical ketone is used as substrate for the in situ vinyl ether exchange reaction.[18]



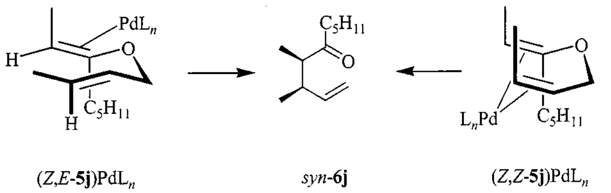
Scheme 9. Pd^{II}-catalyzed, in situ vinyl ether exchange/Claisen rearrangement

In 1995, Nakai and Sugiura reinvestigated the experiments of van der Baan and Bickelhaupt and determined the stereochemical result of the rearrangement (Scheme 10).[19] Somewhat surprisingly, they found that both the (*E*,*Z*)- and the (*Z*,*Z*)-configured acyclic allyl vinyl ethers **5j** underwent the Pd^{II}-catalyzed Claisen rearrangement with a preference for the same relative configuration in the rearrangement product **6j**.



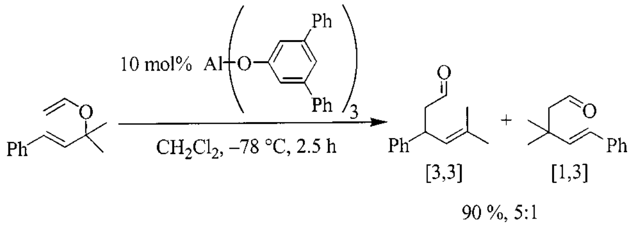
Scheme 10. Pd^{II}-catalyzed Claisen rearrangement of allyl vinyl ethers

They suggested that, depending on the double bond configuration of the allyl vinyl ether, the Pd^{II} catalyst could coordinate one or both double bonds and that boat- or chair-like transition states would therefore be possible (Scheme 11). Alternatively, it was also proposed that the Pd^{II} catalyst could induce a (*Z*)/(*E*) isomerization of the vinyl ether double bond of the (*Z*,*Z*)-configured substrate **5j**, followed by a rearrangement through a chair-like transition state.



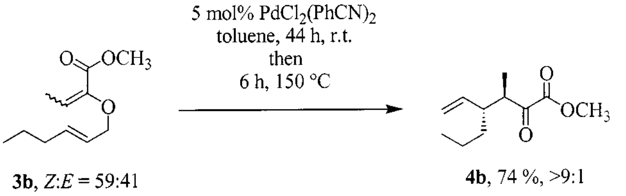
Scheme 11. Pd^{II}-catalyzed Claisen rearrangement of allyl vinyl ethers

Oshima apparently first reported that Al^{III} Lewis acids were able to promote the Claisen rearrangement of aliphatic allyl vinyl ethers in 1981.[20] Since then, Al^{III} Lewis acids have frequently been used and Yamamoto even developed an enantioselective Claisen rearrangement based on a chiral Al^{III} complex with BINOL derivatives.[21,22] Unfortunately, 1−2 equiv. of the Al^{III} Lewis acid are necessary to promote the Claisen rearrangement, the only exception so far having been published in 1996.[23] Significantly, catalysis with an achiral Al^{III} Lewis acid resulted in the formation of a mixture of [1,3]- and [3,3]-rearrangement products (Scheme 12).



Scheme 12. Al^{III}-catalyzed Claisen rearrangement of allyl vinyl ethers

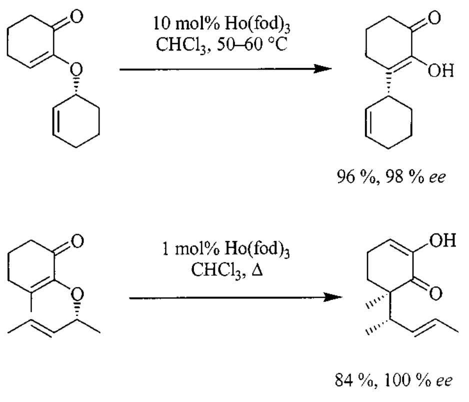
In 1999 we reported the first Pd^{II}-catalyzed rearrangement of a 2-alkoxycarbonyl-substituted allyl vinyl ether **3**.[24] At this early point in our work we were still using mixtures of vinyl ether double bond isomers to determine the reactivity of allyl vinyl ethers **3** with an ester group in the 2-position. In our hands, only the (*E*,*E*)-configured allyl vinyl ether **3b** underwent the $[PdCl_2(PhCN)_2]$-catalyzed rearrangement. The three other double-bond isomers were not reactive in the presence of $[PdCl_2(PhCN)_2]$. We took advantage of the different reactivities of the (*E*,*E*)- and (*Z*,*E*)-configured allyl vinyl ethers **3b** and effected a combination of Pd^{II}-catalyzed and thermal rearrangement as a one-pot procedure (Scheme 13). Application of this methodology transformed a mixture of the (*E*,*E*)- and (*Z*,*E*)-configured allyl vinyl ethers **3b** into the *anti*-configured rearrangement product **4b**. The (*E*,*E*)-configured substrate **3b** rearranged with Pd^{II} catalysis at room temperature to the *anti*-configured α-oxo ester **4b**, presumably through a boat-like transition state. At increased temperature, the remaining (*Z*,*E*)-configured substrate **3b** underwent the thermal Claisen rearrangement through a chair-like transition state to give the *anti*-configured rearrangement product **4b**.



Scheme 13. Pd^{II}-catalyzed Claisen rearrangement of the allyl vinyl ether **3b**

The strict requirements regarding substrate structure have so far prevented the development of a catalytic and enantioselective Claisen rearrangement of aliphatic allyl vinyl ethers based on a chiral Pd^{II} catalyst. Nevertheless, it should be mentioned that chiral Pd^{II} catalysts have successfully been employed to catalyze the [3,3]-sigmatropic rearrangement of allylic imidates.[25]

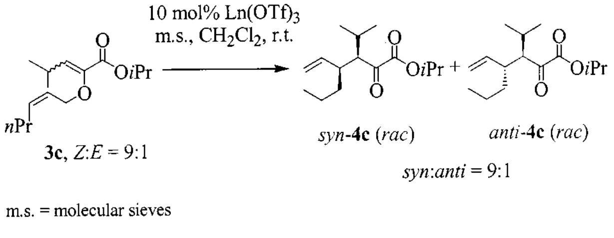
Seeking for alternative catalysts, Trost reported an interesting result in 2000. He was able to demonstrate that lanthanide(III) cations in combination with the FOD ligand were suitable as catalysts for the Claisen rearrangement of cyclic aliphatic allyl vinyl ethers (Scheme 14).[26,27]



Scheme 14. Ho^{III}-catalyzed Claisen rearrangement of cyclic allyl vinyl ethers

The [Ho(fod)$_3$]-catalyzed Claisen rearrangement of chiral allyl vinyl ethers proceeded with very high chemical yields and almost complete 1,3-chirality transfer. An appropriate Lewis acidity of the catalyst was critical to ensure a concerted process. More strongly Lewis acidic catalysts such as [Yb(fod)$_3$] gave partially racemized rearrangement products, and lanthanide(III) triflates were characterized as too reactive.

The apparent futility of developing a general Pd^{II} catalyst for the Claisen rearrangement of aliphatic acyclic allyl vinyl ethers made us turn our attention toward Lewis acids. At the beginning of our research program, we had decided to use 2-alkoxycarbonyl-substituted allyl vinyl ethers **3**. The application of this class of allyl vinyl ethers offers advantages in terms of synthesis, stability, and reactivity.[28] We performed a variety of different studies to determine the best Lewis acid in terms of reactivity and chemoselectivity. All the commercially available lanthanide(III) triflates and also Ce(OTf)$_4$ were tested as catalysts for the Claisen rearrangement of the 1-isopropyl-6-propyl-substituted allyl vinyl ether **3c** (Scheme 15, Table 1), used in our screening program as a (*Z*)/(*E*) = 9:1 mixture of vinyl ether double-bond isomers. We found that Ln(OTf)$_3$ and Ce(OTf)$_4$·H$_2$O all catalyzed the Claisen rearrangement at room temperature in CH$_2$Cl$_2$ in the presence of molecular sieves (MS) with superb chemoselectivity. No side reactions were observed and the product **4c** was isolated in analytically pure form after removal of the catalyst by filtration through a 4×0.5 cm silica gel column. The degree of conversion after a given reaction time depended on the lanthanide(III) cation and decreased with increasing ionic radius (decreasing Lewis acidity). Consequently, the most reactive catalysts were Lu(OTf)$_3$ and Yb(OTf)$_3$. Less Lewis acidic lanthanide triflates needed prolonged reaction times for complete conversion of the allyl vinyl ether **3c** into the α-oxo ester **4c** (Table 1, Entries 5, 7). The diastereoselectivity of the rearrangement was obviously determined by the stereoisomeric purity of the substrate **3c**. It should be pointed out that the presence of pulverized and activated molecular sieves was mandatory for optimal reactivity and chemoselectivity.



Scheme 15. Ln^{III}-catalyzed Claisen rearrangement of the allyl vinyl ether **3c**

We next compared Lu(OTf)$_3$ with Sc(OTf)$_3$ and Cu(OTf)$_2$ and briefly studied the ability of the commercially available hydrates of LuCl$_3$ and YbCl$_3$ to catalyze the Claisen rearrangement.[29] Table 2 summarizes the results with the (*Z*,*Z*)-configured 1-benzyl-6-propyl-substituted allyl vinyl ether **3d** as substrate (Scheme 16).

Sc(OTf)$_3$ proved to be the most active Lewis acid, followed by Cu(OTf)$_2$ and Lu(OTf)$_3$. With LuCl$_3$ and YbCl$_3$, prolonged reaction times were required to obtain complete consumption of the allyl vinyl ether **3d**. The diastereoselectivity of the catalyzed rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers **3**, with a (*Z*)-configured allylic ether double bond, was uniformly high for all Lewis acid catalysts used. This situation changed dramatically if substrates with an (*E*)-configured allylic ether double bond were used. As demonstrated in Scheme 17 and Table 3, the (*Z*,*E*)-configured allyl vinyl ether **3e** underwent the Cu(OTf)$_2$/molecular sieves catalyzed rearrangement with a significantly lower diastereoselectivity than the corresponding (*Z*,*Z*)-configured allyl vinyl ether **3e** (Table 3, Entries 1, 6).

The ratio and sense of diastereoselectivity depends on the substituent R^1 on the allyl ether double bond and, to some extent, on the Lewis acid used to catalyze the rearrangement (Scheme 17, Table 3). We observed a modest influence of the Lewis acid on the diastereoselectivity, with Cu(OTf)$_2$ being the most selective catalyst. The most striking result was the *syn* diastereoselectivity observed for the rearrangement of the 1-isopropyl-substituted, (*Z*,*E*)-configured allyl vinyl ether **3c** (Table 3, Entries 8−10). The 1-benzyl- and 1-isopropenyl-substituted allyl vinyl ethers **3d** and **3e** showed a low diastereoselectivity in favor of the *anti* diastereomers **4d** and **4e**. The *anti*-configured product **4** would be expected on the assumption of a chair-like transition state for the rearrangement. At this point, it was evident that the configuration of the allyl ether double bond had the pivotal influence on the diastereoselectivity of the Lewis acid catalyzed rearrangement, the Lewis acid catalyst having, if any, then only a modest influence. We finally synthesized a complete set of double-bond isomers of the 1-methyl-6-propyl-substituted allyl vinyl ether **3a**. Again, only the allyl vinyl ethers **3a** with (*Z*)-configured allylic ether double bonds rearranged with high diastereoselectivities (Table 3, Entries 13, 14), the configuration of the vinyl ether double bond determining the sense of diastereoselectivity. This reaction proved to be the principal access to both diastereomers of the rearrangement product **4a** under Lewis acid catalysis conditions, simply by choosing the appropriate vinyl ether double bond configuration. The allyl vinyl ethers **3a** with (*E*)-configured allylic ether double bonds showed low to moderate diastereoselectivities in the Lewis acid catalyzed Claisen rearrangement (Table 3, Entries 12, 13). Interestingly, the vinyl ether double bond configuration determines not only the sense, but also the extent, of the diastereoselectivity.

The Lewis acid catalyzed Claisen rearrangement of 6,6-dimethyl-substituted allyl vinyl ethers **3f−h** was also studied (Scheme 18).[30] It was instructive to observe that this specific substituent pattern on the allylic ether double bond resulted in the formation of significant amounts of the [1,3]-rearrangement product **8f−h** (Table 4). The extent of formation of the [1,3]-rearrangement product **8f−h** was de-

Table 1. Catalysis of the Claisen rearrangement of **3c** with $Ln(OTf)_3$ (Scheme 15)

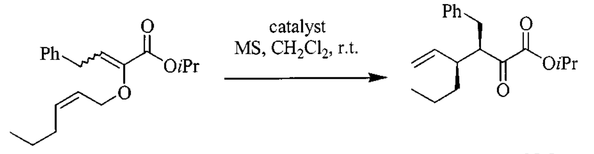
Entry	$Ln(OTf)_3$ [a]	Ln^{3+} radius [Å]	*t* [h]	Yield [%][b]	Conversion [%]
1	$Lu(OTf)_3$	0.848	6	98	100
2	$Yb(OTf)_3$	0.858	6	98	100
3	$Tm(OTf)_3$	0.869	6	100	93
4	$Er(OTf)_3$	0.881	6	99	82
5	$Er(OTf)_3$	0.881	24	100	100
6	$Ho(OTf)_3$	0.894	6	98	75
7	$Ho(OTf)_3$	0.894	24	98	100
8	$Dy(OTf)_3$	0.908	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	$Ce(OTf)_4·H_2O$	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] The reactions were performed with 0.4 mmol of the allyl vinyl ether in CH_2Cl_2 (4 mL) containing 1−3 mol % of EtOH. [b] Isolated yield after removal of the catalyst by filtration through a 4×0.5 cm silica gel column.

Table 2. Comparison of different Lewis acids as catalysts for the Claisen rearrangement (Scheme 16)

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

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



3d, *Z*:*E* = 97:3 **4d**, *syn*:*anti* = 95:5

Scheme 16. Lewis acid catalyzed Claisen rearrangement of the allyl vinyl ether **3d**

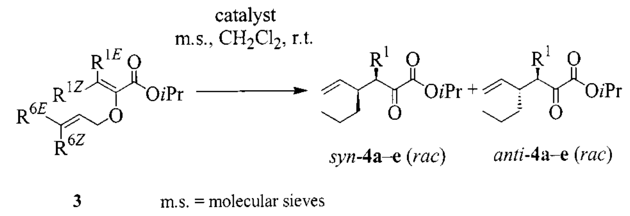
Table 3. Influence of substrate structure and Lewis acid catalyst on the diastereoselectivity of the Claisen rearrangement (Scheme 17)

Entry	Substrate	Catalyst	*t* [h]	Product	Yield [%][a]	*syn*/*anti*[b]
1	*Z*,*Z*-**3e**	5 mol % $Cu(OTf)_2$	6	**4e**	98	91:9
2	*Z*,*E*-**3d**	2.5 mol % $Sc(OTf)_3$	0.5	**4d**	98	46:54
3	*Z*,*E*-**3d**	2.5 mol % $Cu(OTf)_2$	0.5	**4d**	99	33:67
4	*Z*,*E*-**3d**	10 mol % $Lu(OTf)_3$	1	**4d**	99	37:63
5	*Z*,*E*-**3e**	2.5 mol % $Sc(OTf)_3$	0.5	**4e**	98	42:58
6	*Z*,*E*-**3e**	2.5 mol % $Cu(OTf)_2$	0.5	**4e**	99	31:69
7	*Z*,*E*-**3e**	10 mol % $Lu(OTf)_3$	1	**4e**	95	36:64
8	*Z*,*E*-**3c**	2.5 mol % $Sc(OTf)_3$	0.5	**4c**	98	76:24
9	*Z*,*E*-**3c**	2.5 mol % $Cu(OTf)_2$	0.5	**4c**	98	75:25
10	*Z*,*E*-**3c**	10 mol % $Lu(OTf)_3$	2	**4c**	100	74:26
11	*E*,*E*-**3a**	5 mol % $Sc(OTf)_3$	1[c]	**4a**	99	70:30
12	*Z*,*E*-**3a**	5 mol % $Sc(OTf)_3$	1[c]	**4a**	98	44:56
13	*E*,*Z*-**3a**	5 mol % $Sc(OTf)_3$	1[c]	**4a**	100	4:96
14	*Z*,*Z*-**3a**	5 mol % $Sc(OTf)_3$	1[c]	**4a**	95	96:4

[a] Isolated yield after removal of the catalyst by filtration through a 4×0.5 cm silica gel column. [b] Determined from ^1H NMR spectra. [c] Reaction time not optimized.

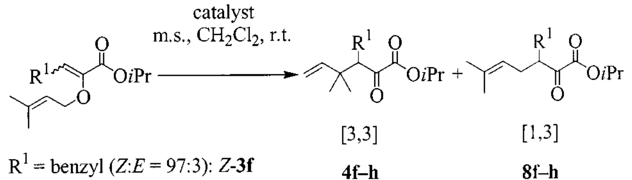
termined by the Lewis acidity of the catalyst and the substrate structure (Scheme 18, Table 4).

The most Lewis acidic catalyst, $Sc(OTf)_3$, required the shortest reaction times but at the same time resulted in the formation of the largest amount of the [1,3]-rearrangement product **8** (Table 4, Entries 1,5). The less Lewis acidic catalysts, such as $Cu(OTf)_2$ or $Lu(OTf)_3$, were less reactive than $Sc(OTf)_3$ and afforded smaller amounts of [1,3]-rearrangement product **8** (Table 4, Entries 2−4, 6−7). The 1-isopropyl-substituted allyl vinyl ether **3h** showed a greater propen-



R^{1E} = methyl, R^{6E} = *n*-propyl: *E,E*-**3a**
R^{1Z} = methyl, R^{6E} = *n*-propyl: *Z,E*-**3a**
R^{1E} = methyl, R^{6Z} = *n*-propyl: *E,Z*-**3a**
R^{1Z} = methyl, R^{6Z} = *n*-propyl: *Z,Z*-**3a**
R^{1Z} = isopropyl, R^{6E} = *n*-propyl: *Z,E*-**3c**
R^{1Z} = benzyl, R^{6E} = *n*-propyl: *Z,E*-**3d**
R^{1Z} = isopropenyl, R^{6E} = *n*-propyl: *Z,E*-**3e**
R^{1Z} = isopropenyl, R^{6Z} = *n*-propyl: *Z,Z*-**3e**

Scheme 17. Lewis acid catalyzed Claisen rearrangement of the allyl vinyl ethers **3a** and **3c**–**e**



R^1 = benzyl (*Z*:*E* = 97:3): *Z*-**3f**
R^1 = isopropenyl (*Z*:*E* = 96:4): *Z*-**3g**
R^1 = isopropyl (*Z*:*E* = 92:8): *Z*-**3h**

Scheme 18. Lewis acid catalyzed Claisen rearrangement of the allyl vinyl ethers **3f**–**h**

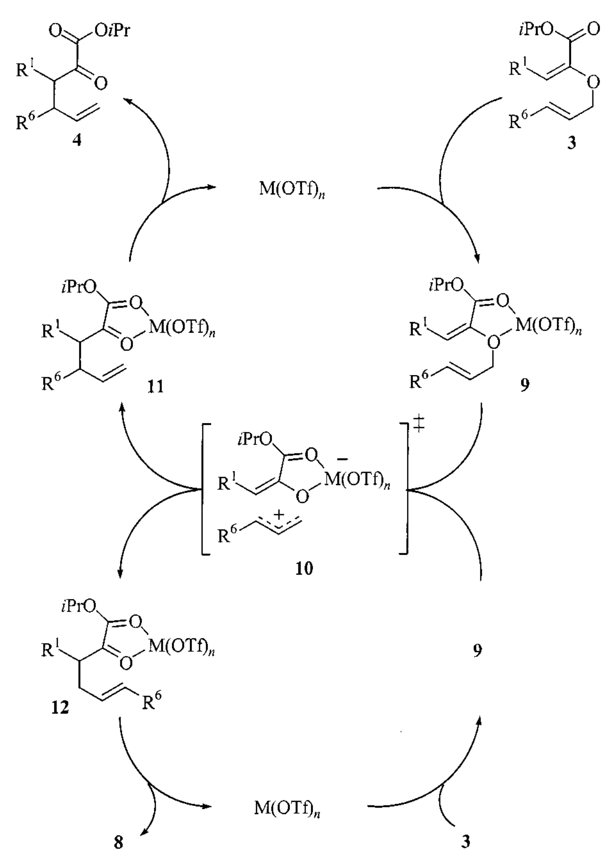
Table 4. The influence of substrate structure and catalyst on the periselectivity of the Lewis acid catalyzed Claisen rearrangement of 6,6-dimethyl-substituted allyl vinyl ethers **3f**–**h** (Scheme 18)

Entry	Substrate	Catalyst	*t* [h]	Yield [%][a]	**4f**–**h**/**8f**–**h** [3,3]/[1,3][b]
1	*Z*-**3f**	1 mol % Sc(OTf)$_3$	0.5	98	76:24
2	*Z*-**3f**	5 mol % Cu(OTf)$_2$	1	100	83:17
3	*Z*-**3f**	5 mol % Lu(OTf)$_3$	2	100	91:9
4	*Z*-**3f**	5 mol % Yb(OTf)$_3$	2	100	91:9
5	*Z*-**3g**	1 mol % Sc(OTf)$_3$	0.5	93	74:26
6	*Z*-**3g**	10 mol % Lu(OTf)$_3$ [c]	1	93	95:5
7	*Z*-**3h**	5 mol % Yb(OTf)$_3$	24[d]	97	80:20

[a] Isolated yield after removal of the catalyst by filtration through a 4×0.5 cm silica gel column. All reactions were run on a 0.4-mmol scale. [b] Determined from ^{1}H NMR spectra. [c] Catalyst loading not optimized. [d] Reaction time not optimized.

sity for the formation of the [1,3]-rearrangement product **8h.** Even if the reaction was performed with the less Lewis acidic catalyst Yb(OTf)$_3$, a large amount of the [1,3]-rearrangement product **8h** could still be detected (Table 4, Entry 7).

As a working model, we suggest the following simple mechanistic scheme for the Lewis acid catalyzed Claisen rearrangement (Scheme 19). It appears feasible to assume the formation of the chelate **9** between the metal cation and the allyl vinyl ether **3**. This arrangement could further increase the propensity of the allyl vinyl ether **3** to undergo the Claisen rearrangement through a transition state **10**, featuring a high degree of charge separation.[30] One could imagine the formation of a metal cation stabilized α-oxo ester enolate and an allylic cation, interacting in a pericyclic fashion.

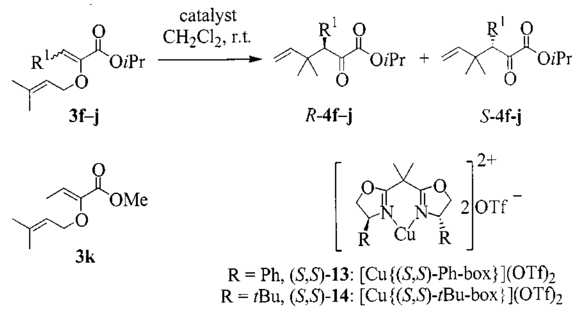


Scheme 19. Presumed catalytic cycle and mechanism for the Lewis acid catalyzed Claisen rearrangement of the allyl vinyl ethers **3**

The catalyst could accelerate the rearrangement by destabilizing the allylic ether O–C bond and by stabilizing the negative partial charge in the vinyl ether moiety formed in a transition state **10**, characterized by a high degree of charge separation. Increased Lewis acidity of the catalyst and charge stabilization by substituents, namely the stabilization of the allylic cation by alkyl substituents, could accelerate the rearrangement and, in an extreme scenario, induce the formation of the [1,3]-rearrangement product **8**. No apparent explanation is yet available for the low diastereoselectivities observed for the catalyzed Claisen rearrangement of allyl vinyl ethers **3** with (*E*)-configured allylic ether double bonds. Competition between boat- or chair-like transition state geometries may be responsible, but an (*E*)/(*Z*) equilibration of a separated allylic cation based on a mechanism in which an ion pair intermediate is involved cannot be ruled out. Further work using a combination of theoretical calculations and the accumulation of kinetic data will be necessary to elucidate the operating mechanism(s) precisely.

The First Catalytic Enantioselective Claisen Rearrangement

Bis(oxazoline)copper(II) complexes have emerged as useful chiral catalysts for a variety of different C−C bond-forming reactions.[31] The scope of reactions that can be catalyzed with [Cu^{II}box] [box = bis(oxazoline)] catalysts is still increasing,[32] and the first immobilized [Cu^{II}box] complexes have very recently been reported.[33] In view of the encouraging results involving catalysis of the Claisen rearrangement with the Cu(OTf)$_2$/molecular sieves system, we decided to study chiral [Cu^{II}box] complexes as potential catalysts for a catalytic and enantioselective Claisen rearrangement. The [Cu^{II}box]-catalyzed Claisen rearrangement of the 6,6-dimethyl-substituted allyl vinyl ethers **3i−n** was studied first (Scheme 20, Table 5).[34]



Scheme 20. [Cu^{II}(box)](OTf)$_2$-catalyzed enantioselective Claisen rearrangement

As detailed in Table 5, the [Cu(Ph-box)](OTf)$_2$ complex **13** catalyzes the Claisen rearrangement with very good enantioselectivity and outstanding chemoselectivity. Competing formation of the [1,3]-rearrangement product **8**, observed when the Cu(OTf)$_2$/molecular sieves system had been used, was insignificant. Different alkyl substituents and an alkenyl substituent were tolerated and only slightly influenced the enantioselectivity (Table 5). The rearrangement of the methyl ester **3k** did not improve the enantioselectivity of the process (Table 5, Entry 13). As expected, a change in the absolute configuration of the catalyst **13** or the vinyl ether double configuration in **3** inverted the absolute configuration of the preferred rearrangement product **4** (Table 5, Entries 1−3). In a scaled up reaction, only 0.5 mol % of (*R*,*R*)**-13** was sufficient to transform the allyl vinyl ether **3i** completely into the rearrangement product **4i** (Table 5, Entry 12). The [Cu(*t*Bu-box)](OTf)$_2$ catalyst **14** proved to be significantly less reactive, and incomplete consumption was observed even with an increased catalyst concentration and prolonged reaction times (Table 5, Entries 4, 10). Addition of molecular sieves increased the reactivity, however, with catalysis with the [Cu{(*S*,*S*)-*t*Bu-box}](OTf)$_2$/molecular sieves system resulting in the highest enantioselectivities so far observed (Table 5, Entries 5, 11). As has been reported in the literature for other [Cu^{II}box]-catalyzed reactions,[35] the (*S*,*S*)**-13** and the (*S*,*S*)**-14** catalysts induced opposite absolute configurations in the rearrangement product **4**. Generally, thanks to the outstanding chemoselectivity of the [Cu^{II}box](OTf)$_2$-catalyzed Claisen rearrangement, simple removal of the catalyst by filtration through a short plug of silica gel followed by evaporation of the solvent provided the analytically pure rearrangement product **4**. Undoubtedly, the observed enantioselectivities still need to be further improved by variation of the catalyst and the substrate structure. Nevertheless, the simplicity of the procedure opens an efficient route to a very interesting class of building blocks, difficult to synthesize even as racemates by other methods.

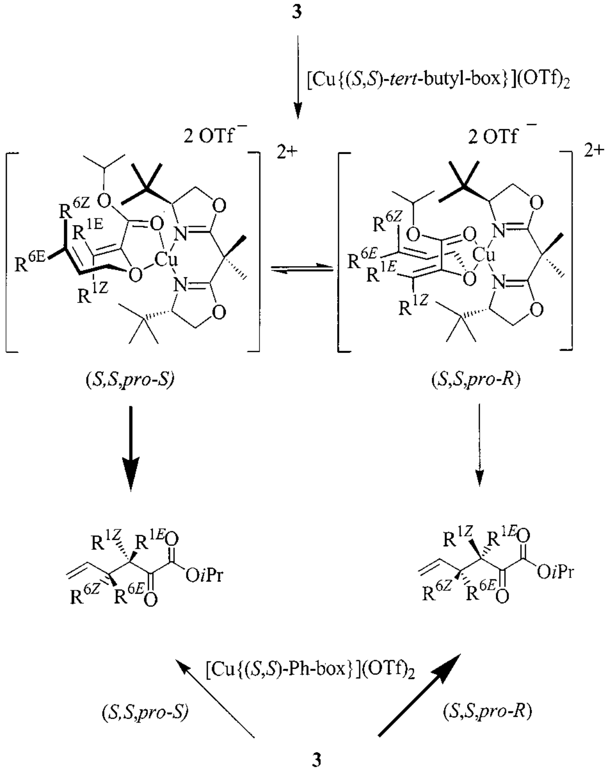
The enantioselectivity of the [Cu{(*S*,*S*)-*t*Bu-box}](OTf)$_2$-catalyzed Claisen rearrangement can be explained in analogy to previously proposed stereochemical models for other [Cu(box)]-catalyzed reactions.[31,32] We suggest a bidentate coordination of the allyl vinyl ether **3** on the [Cu(box)] complexes and a square-planar geometry around the copper(II) cation (Scheme 21). On the assumption of a

Table 5. The catalytic enantioselective Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers **3f−j** (Scheme 20)

	Substrate	R^1	(*Z*)/(*E*)	Catalyst	*t* [h]	Yield [%][a]	(*R*)/(*S*)[b]
1	*Z*-**3i**	methyl	96:4	5 mol % (*S*,*S*)-**13**	1	100	91:9
2	*Z*-**3i**	methyl	96:4	5 mol % (*R*,*R*)-**13**	1	100	9:91
3	*E*-**3i**	methyl	4:96	5 mol % (*S*,*S*)-**13**	1	99	9:91
4	*Z*-**3i**	methyl	96:4	10 mol % (*S*,*S*)-**14**	24	47[c]	6:94
5	*Z*-**3i**	methyl	96:4	10 mol % (*S*,*S*)-**14**, 4-Å m.s.	24	99	6:94
6	*Z*-**3j**	ethyl	100:0	5 mol % (*S*,*S*)-**13**	2	99	92:8
7	*Z*-**3h**	isopropyl	90:10	5 mol % (*S*,*S*)-**13**	24	98	89:11
8	*Z*-**3g**	isopropenyl	100:0	5 mol % (*S*,*S*)-**13**	1	100	93:7
9	*Z*-**3f**	benzyl	97:3	5 mol % (*S*,*S*)-**13**	1	99	88:12
10	*Z*-**3f**	benzyl	97:3	10 mol % (*S*,*S*)-**14**	72	7[d]	−
11	*Z*-**3f**	benzyl	97:3	10 mol % (*S*,*S*)-**14**, 4-Å m.s.	72	94[e]	8:92
12	*Z*-**3f**	benzyl	97:3	0.5 mol % (*R*,*R*)-**13**[f]	24	100	12:88
13	*Z*-**3k**	methyl	100:0	5 mol % (*S*,*S*)-**13**	3	99	90:10

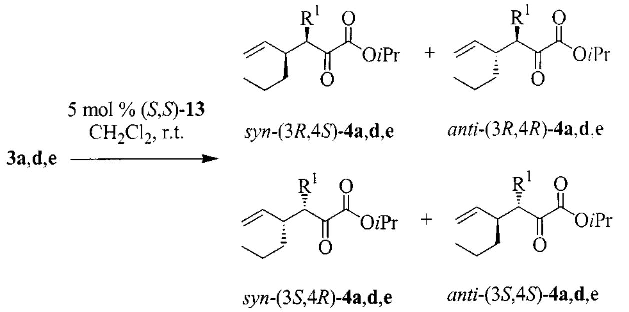
[a] Isolated yield after removal of the catalyst by filtration through a 4×0.5 cm silica gel column. All reactions were run on a 0.4-mmol scale. m.s.: molecular sieves. [b] Determined by HPLC: Daicel Chiracel OD14025, hexane/*i*PrOH (99.9:0.1). [c] 52% substrate isolated. [d] 93% substrate isolated. [e] 6% substrate isolated. [f] Reaction run on a 4-mmol scale. Reaction time not optimized.

chair-like transition-state geometry for the catalyzed Claisen rearrangement, the allylic ether moiety should approach the vinyl ether moiety from the direction opposite to the *tert*-butyl substituent on the box ligand. In this model, the [Cu(box)] catalyst differentiates between the two enantiomeric chair-like conformations by enantiotopos differentiation between the enantiotopic lone pairs [(*pro-R*) and (*pro-S*)] on the allylic ether oxygen atom. Our results so far indicate that [Cu{(*S*,*S*)-Ph-box}](OTf)$_2$ (**13**) preferentially coordinates the (*pro-R*) lone pair, whereas [Cu{(*S*,*S*)-*tert*-butyl-box}](OTf)$_2$ (**14**) prefers to coordinate the (*pro-S*) lone pair of the allylic ether oxygen atom. From this stereochemical relationship and the double-bond configuration of the allyl vinyl ether **3**, it should be possible to predict/explain the absolute configuration of the main isomer from the [Cu^{II}(box)]-catalyzed Claisen rearrangement. Further work to corroborate this model is currently underway.



Scheme 21. Stereochemical model for the [Cu^{II}(box)](OTf)$_2$-catalyzed enantioselective Claisen rearrangement

The highly diastereoselective generation of two vicinal chirality centers is an inherent strength of the thermal aliphatic Claisen rearrangement. Consequently, we set out to investigate whether or not it would be possible to combine the inherent diastereoselectivity of the thermal Claisen rearrangement with the ability, as shown above, of [Cu^{II}(box)] complexes to catalyze the Claisen rearrangement enantioselectively. Our previous results with the Cu(OTf)$_2$/molecular sieves system had revealed an amazing dependence of the diastereoselectivity on the configuration of the allylic ether double bond (Scheme 17, Table 4).[29] This observation was confirmed when [Cu{(*S*,*S*)-Ph-box}](OTf)$_2$ (**13**) was used as a catalyst for the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers **3a**, **3d**, and **3e**, containing two stereogenic double bonds (Scheme 22, Table 6).



Scheme 22. [Cu^{II}(box)](OTf)$_2$-catalyzed enantioselective Claisen rearrangement

The diastereoselectivity of the catalyzed Claisen rearrangement of the allyl vinyl ether **3a** with an (*E*)-configured allylic ether double bond was moderate (Table 6, Entries 1, 2). The allyl vinyl ethers **3a**, **3d**, and **3e**, each with a (*Z*)-configured allylic ether double bond, rearranged with very good diastereoselectivities and acceptable enantioselectivities (Table 6, Entries 3−6). It was possible to control the relative configuration of the rearrangement product **4** by choosing the appropriate vinyl ether double-bond configuration (Table 6, Entries 3, 4). The reaction times are quite

Table 6. Diastereo- and enantioselectivities of the [Cu{(*S*,*S*)-Ph-box}](OTf)$_2$-catalyzed Claisen rearrangement (Scheme 22)

Entry	Substrate	*t* [h][a]	Yield [%][b]	*syn*/*anti*[c]	*ee* [%][d]	Absol. config.[e]
1	*E*,*E*-**3a**	12	100	86:14	82	(3*S*,4*R*)
2	*Z*,*E*-**3a**	4	100	28:72	72	(3*R*,4*R*)
3	*E*,*Z*-**3a**	38	99	3:97	88	(3*S*,4*S*)
4	*Z*,*Z*-**3a**	38	98	99:1	84	(3*R*,4*S*)
5	*Z*,*Z*-**3d**	48	100	95:5	82	(3*R*,4*S*)
6	*Z*,*Z*-**3e**	24	98	92:8	86	(3*R*,4*S*)
7	*Z*,*Z*-**3a**	12[f]	99	96:4	76	(3*R*,4*S*)

[a] Reaction times not optimized. [b] Isolated yield after removal of the catalyst by filtration through a 4×0.5 cm silica gel column. All reactions were run on a 0.4-mmol scale. [c] Determined from ^{1}H NMR spectra. [d] Determined by HPLC: Daicel Chiracel OD14025, hexane/*i*PrOH (99.9:0.1). [e] Absolute configuration of the major enantiomer. Configuration assigned by assumption of an (*S*,*S*,1*Z*,1*Si*) or (*S*,*S*,1*E*,1*Re*) topicity of a chair-shaped transition state. [f] Reaction run with 10 mol % of (*S*,*S*)-**13**.

long in some cases but can be shortened significantly by increased catalyst loading (Table 6, Entry 7).

Conclusion

In the 90 years since Claisen's original report, the Claisen rearrangement and related [3,3]-sigmatropic rearrangements have been objects of dynamic development. Nevertheless, problems such as the understanding of the mechanism, the development of new variations, and possible applications in complex natural product synthesis still attract chemists. Somewhat surprisingly, catalysis of [3,3]-sigmatropic rearrangements, specifically of the Claisen and the Cope rearrangement, is underdeveloped. Furthermore, with the exception of the [3,3]-sigmatropic rearrangement of allylic imidates, no catalytic and enantioselective [3,3]-sigmatropic rearrangement had been developed until very recently. This microreview summarizes the available methods for catalysis of the Claisen rearrangement. It is now clear that well-known Lewis acids are suitable catalysts for the Claisen rearrangement under very simple reaction conditions, if certain structural demands are met. 2-Alkoxycarbonyl-substituted allyl vinyl ethers are apparently a substrate of choice for catalysis of the Claisen rearrangement. Use of the established chiral bis(oxazoline)copper(II) catalysts and the chelation ability of the 2-alkoxycarbonyl-substituted allyl vinyl ethers have allowed us to develop the first catalytic, enantioselective Claisen rearrangement. Outstanding chemoselectivity combined with acceptable enantioselectivities provides a good basis for further developments.

Acknowledgments

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[1] F. E. Ziegler, *Chem. Rev.* **1988**, *88*, 1423–1452.

[2] L. Claisen, *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157–3166.

[3] [3a] H. Frauenrath, *Methods Org. Chem. (Houben-Weyl)* **1995**, vol. E 21d, p. 3301–3756. [3b] S. Blechert, *Synthesis* **1989**, 71–82.

[4] [4a] M. P. Meyer, A. J. DelMonte, D. A. Singleton, *J. Am. Chem. Soc.* **1999**, *121*, 10865–10874. [4b] J. J. Gajewski, *Acc. Chem. Res.* **1997**, *30*, 219–225. [4c] V. Aviyente, H. Y. Yoo, K. N. Houk, *J. Org. Chem.* **1997**, *62*, 6121–6128. [4d] A. Sehgal, L. Shao, J. Gao, *J. Am. Chem. Soc.* **1995**, *117*, 11337–11340. [4e] R. L. Vance, N. G. Rondan, K. N. Houk, F. Jensen, W. Thatcher Borden, A. Komornicki, E. Wimmer, *J. Am. Chem. Soc.* **1988**, *110*, 2314–2315. [4f] R. M. Coates, B. D. Rogers, S. J. Hobbs, D. R. Peck, D. P. Curran, *J. Am. Chem. Soc.* **1987**, *109*, 1160–1170. [4g] C. S. Wilcox, R. E. Babston, *J. Am. Chem. Soc.* **1986**, *108*, 6636–6642. [4h] C. J. Burrows, B. K. Carpenter, *J. Am. Chem. Soc.* **1981**, *103*, 6983–6984.

[5] For review articles on enantioselective Claisen rearrangements, see: [5a] D. Enders, M. Knopp, R. Schiffers, *Tetrahedron: Asymmetry* **1996**, *7*, 1847–1882. [5b] H. Ito, T. Taguchi, *Chem. Soc. Rev.* **1999**, *28*, 43–50.

[6] T. P. Yoon, D. W. C. McMillan, *J. Am. Chem. Soc.* **2001**, *123*, 2911–2912.

[7] J. L. van der Baan, F. Bickelhaupt, *Tetrahedron Lett.* **1986**, *27*, 6267–6270.

[8] L. E. Overman, *Angew. Chem.* **1984**, *96*, 565–573; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 579–587.

[9] R. P. Lutz, *Chem. Rev.* **1984**, *84*, 205–247.

[10] W. Kitching, Z. Rappoport, S. Winstein, W. G. Young, *J. Am. Chem. Soc.* **1966**, *88*, 2054–2055.

[11] [11a] P. M. Henry, *J. Am. Chem. Soc.* **1972**, *94*, 5200–5206. [11b] P. M. Henry, *J. Am. Chem. Soc.* **1972**, *94*, 1527–1532. [11c] P. M. Henry, *J. Am. Chem. Soc.* **1971**, *94*, 3853–3859.

[12] [12a] J. Ammenn, K. Altmann, D. Bellus, *Helv. Chim. Acta* **1997**, *80*, 1589–1606. [12b] J. Gonda, A. Helland, B. Ernst, D. Bellus, *Synthesis* **1993**, 729–722. [12c] P. Metz, C. Mues, A. Schoop, *Tetrahedron* **1992**, *48*, 1071–1080. [12d] M. Mehmandoust, Y. Petit, M. Larcheveque, *Tetrahedron Lett.* **1992**, *33*, 4313–4316. [12e] T. G. Schenk, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2058–2066. [12f] T. Ikariya, Y. Ishikawa, K. Hirai, S. Yoshikawa, *Chem. Lett.* **1982**, 1815–1818.

[13] [13a] L. E. Overman, A. F. Renaldo, *J. Am. Chem. Soc.* **1990**, *112*, 3945–3949. [13b] N. Bluthe, M. Malacria, J. Gore, *Tetrahedron Lett.* **1983**, *24*, 1157–1160. [13c] L. E. Overman, E. J. Jacobsen, *J. Am. Chem. Soc.* **1982**, *104*, 7225–7231. [13d] L. E. Overman, F. M. Knoll, *J. Am. Chem. Soc.* **1980**, *102*, 865–867.

[14] K. Meyer, *Chem. Abstr.* **1976**, *84*, 89634s.

[15] L. E. Overman, F. M. Knoll, *Tetrahedron Lett.* **1979**, 321–324.

[16] K. Mikami, K. Takahashi, T. Nakai, *Tetrahedron Lett.* **1987**, *28*, 5879–5882.

[17] M. Sugiura, M. Yanagisawa, T. Nakai, *Synlett* **1995**, 447–448.

[18] M. Sugiura, T. Nakai, *Tetrahedron Lett.* **1996**, *37*, 7991–7994.

[19] M. Sugiura, T. Nakai, *Chem. Lett.* **1995**, 697–698.

[20] K. Takai, I. Mori, K. Oshima, H. Nozaki, *Tetrahedron Lett.* **1981**, *22*, 3985–3988.

[21] [21a] J. W. S. Stevenson, T. A. Bryson, *Tetrahedron Lett.* **1982**, *23*, 3143–3146. [21b] K. Takai, I. Mori, K. Oshima, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 446–451. [21c] K. Maruoka, K. Nonoshita, H. Banno, H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 7922–7924. [21d] K. Maruoka, H. Banno, K. Nonoshita, H. Yamamoto, *Tetrahedron Lett.* **1989**, *30*, 1265–1266. [21e] K. Maruoka, J. Sato, H. Banno, H. Yamamoto, *Tetrahedron Lett.* **1990**, *31*, 377–380. [21f] K. Nonoshita, H. Banno, K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc.* **1990**, *112*, 316–322. [21g] L. A. Paquette, D. Friedrich, R. D. Rogers, *J. Org. Chem.* **1991**, *56*, 3841–3849.

[22] [22a] K. Maruoka, H. Banno, H. Yamamoto, *J. Am. Chem. Soc.* **1990**, *112*, 7790–7791. [22b] K. Maruoka, H. Yamamoto, *Synlett* **1991**, 793–794. [22c] K. Maruoka, H. Banno, H. Yamamoto, *Tetrahedron: Asymmetry* **1991**, *2*, 647–662. [22d] K. Maruoka, S. Saito, H. Yamamoto, *J. Am. Chem. Soc.* **1995**, *117*, 1165–1166.

[23] S. Saito, K. Shimada, H. Yamamoto, *Chem. Lett.* **1996**, 720–722.

[24] M. Hiersemann, *Synlett* **1999**, 1823–1825.

[25] [25a] M. Calter, T. K. Hollis, L. E. Overman, J. Ziller, G. G. Zipp, *J. Org. Chem.* **1997**, *62*, 1449–1456. [25b] T. K. Kollis, L. E. Overman, *Tetrahedron Lett.* **1997**, *38*, 8837–8840. [25c] Y. Uozumi, K. Kato, T. Hayashi, *Tetrahedron: Asymmetry* **1998**, *9*, 1065–1072. [25d] F. Cohen, L. E. Overman, *Tetrahedron: Asymmetry* **1998**, *9*, 3213–3222. [25e] Y. Donde, L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 2933–2934. [25f] Y. Jiang, J. M. Longmire, X. Zhang, *Tetrahedron Lett.* **1999**, *40*, 1449–1450.

[26] B. M. Trost, G. M. Schroeder, *J. Am. Chem. Soc.* **2000**, *122*, 3785–3786.

[27] For the Eu(fod)$_3$-catalyzed aromatic Claisen rearrangement, see: [27a] B. M. Trost, F. D. Toste, *J. Am. Chem. Soc.* **1998**, *120*, 815–816. [27b] S. Gester, P. Metz, O. Zierau, G. Vollmer, *Tetrahedron* **2001**, *57*, 1015–1018.

[28] M. Hiersemann, *Synthesis* **2000**, 1279−1290.

[29] M. Hiersemann, L. Abraham, *Org. Lett.* **2001**, *3*, 49−52.

[30] For the influence of substituents on the nature of the transition state of the thermal Claisen rearrangement, see ref.[4]

[31] For reviews, see: [31a] J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325−335. [31b] K. A. Jørgensen, *Angew. Chem.* **2000**, *112*, 3702−3733; *Angew. Chem. Int. Ed.* **2000**, *39*, 3558−3588. [31c] D. A. Evans, T. Rovis, J. S. Johnston, *Pure Appl. Chem.* **1999**, *71*, 1407−1415. [31d] A. K. Gosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.

[32] [32a] D. A. Evans, J. M. Janey, *Org. Lett.* **2001**, *3*, 2125−2128. [32b] W. Zhuang, N. Gathergood, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **2001**, *66*, 1009−1013. [32c] D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras, T. Vojkovsky, *J. Am. Chem. Soc.* **2000**, *122*, 7936−7943. [32d] D. A. Evans, T. Rovis, M. C. Kozlowski, C. W. Downey, J. S. Tedrow, *J. Am. Chem. Soc.* **2000**, *122*, 9134−9142. [32e] H. Audrain, J. Thorhauge, R. G. Hazell, K. A: Jørgensen, *J. Org. Chem.* **2000**, *65*, 4487−4497. [32f] D. A. Evans, J. S. Johnston, E. J. Olhava, *J. Am. Chem. Soc.* **2000**, *122*, 1635−1649. [32g] V. K. Aggrawal, D. Elfyn-Jones, A. M. Martin-Castro, *Eur. J. Org. Chem.* **2000**, 2939−2945.

[33] [33a] K. Hallman, C. Moberg, *Tetrahedron: Asymmetry* **2001**, *12*, 1475−1478. [33b] D. Rechavi, M. Lemaire, *Org. Lett.* **2001**, *3*, 2493−2496. [33c] R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi, M. Pitillo, *J. Org. Chem.* **2001**, *66*, 3160−3166. [33d] M. I. Burguete, J. M. Fraile, J. I. Garcia, E. Garcia-Verdugo, *Org. Lett.* **2000**, *2*, 3905−3908. [33e] M. Glos, O. Reiser, *Org. Lett.* **2000**, *2*, 2045−2048.

[34] L. Abraham, R. Czerwonka, M. Hiersemann, *Angew. Chem.*, **2001**, *113*, 4835−4837; *Angew. Chem. Int. Ed.* **2001**, *40*, 4700−4703.

[35] [35a] M. Johannsen, K. A. Jørgensen, *J. Org. Chem.* **1995**, *60*, 5757−5762. [35b] D. A. Evans, J. S. Johnston, C. S. Burgey, K. R. Campos, *Tetrahedron Lett.* **1999**, *40*, 2879−2882.

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