The Catalytic Diastereo- and Enantioselective Claisen Rearrangement of 2-Alkoxycarbonyl-Substituted Allyl Vinyl Ether

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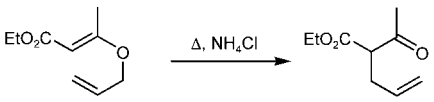
Dedicated to Prof. Johann Mulzer, an inspiring teacher of organic chemistry, on the occasion of his 60th birthday.

Abstract: The catalytic asymmetric Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers that contain two stereogenic double bonds is described. A combination of the highly Lewis acidic [Cu{(*S*,*S*)-*tert*-Bu-box}]$(H_2O)_2(SbF_6)_2$ complex and molecular sieves served as catalyst and afforded the Claisen rearrangement products, substituted and functionalized α-keto esters, in high yield with a remarkable diastereo- and enantioselectivity. The influence of ligand structure, counterion and allyl vinyl ether double bond configuration on the stereoselectivity of the rearrangement was briefly investigated. We propose an explanation for the rate accelerating effect of the Lewis acid as well as a stereochemical model which serve to explain and predict the stereochemical course of the copper bis(oxazoline) catalyzed Claisen rearrangement.

Keywords: allyl vinyl ether; asymmetric catalysis; Claisen rearrangement; α-keto ester; Lewis acids; sigmatropic rearrangement

Introduction

The thermal aliphatic Claisen rearrangement of allyl vinyl ethers has been in the focus of attention ever since the first example was reported by Ludwig Claisen in 1912 [Eq. (1)].[1]



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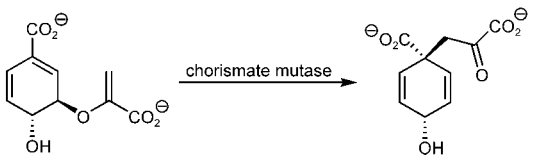
Methodical[2a–f] and theoretical[3a–j] studies were undertaken to elucidate the exact mechanism of this concerted [3,3]-sigmatropic rearrangement. The molecular mode of action of the chorismate mutase – an enzyme known to catalyze a Claisen rearrangement – is under intensive investigation [Eq. (2)].[4a–y]



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Numerous applications of the Claisen rearrangement and its named and unnamed relatives can be found in the literature.[5a–g] Many ingenious asymmetric versions which combine substrate- or reagent-induced diastereoselectivity with the inherent simple diastereoselectivity of the Claisen rearrangement have been devised.[6,7] Very recently, a comprehensive review article has been published on this topic by Nubbemeyer.[8] Although of outstanding potential, the catalysis of [3,3]-sigmatropic rearrangements in general and the asymmetric catalysis in particular has not yet matched its potential.[9–11] The catalytic asymmetric rearrangement of allylic imidates may be considered a noteworthy exception, however, it is not a C/C connecting rearrangement and it proceeds by a stepwise mechanism (Scheme 1).[12a–m]

It has been known for more than 20 years that achiral Al^{III} Lewis acids are able to accelerate the aliphatic Claisen rearrangement, however, their applicability as catalysts is prevented by product inhibition.[13a–k] Chiral Lewis acids based on aluminum(III),[14a–g] boron(III),[15a–d] and magnesium(II)[16] are more or less effective reagents, however a catalytic application has not been realized (Scheme 2). Kazmaier utilized stoichio-

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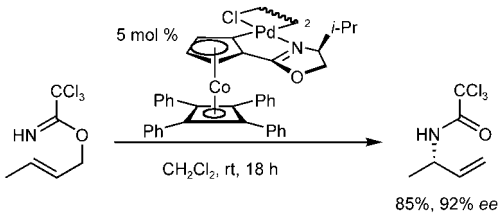
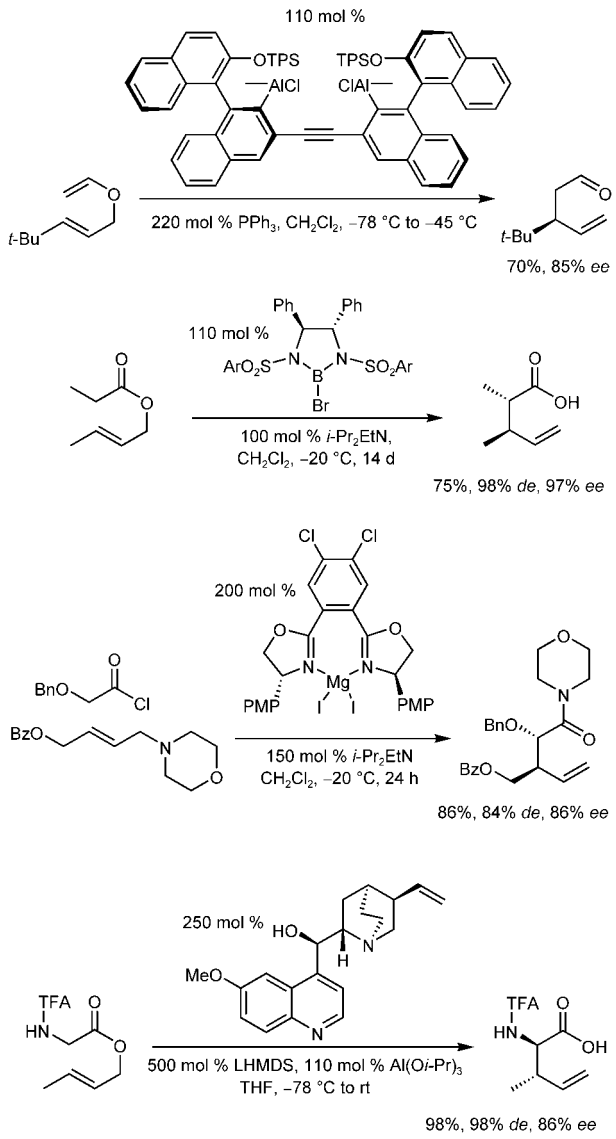


Scheme 1. Catalytic asymmetric rearrangement of allylic trichloroacetimidates according to Overman.[12j]



Scheme 2. Asymmetric Claisen rearrangements according to Maruoka (TPS = *t*-BuPh$_2$Si),[14f] Corey (Ar = 3,5-F$_3$C-C$_6$H$_3$),[15a] MacMillan (PMP = 4-CH$_3$O-C$_6$H$_4$)[16] and Kazmaier (TFA = CF$_3$CO).[17e]

metric amounts of a chiral Lewis base for an asymmetric enolate Claisen rearrangement (Scheme 2).[17a–e]

The catalysis of the Claisen rearrangement by Brønstedt acids was already exploited in Claisen's original

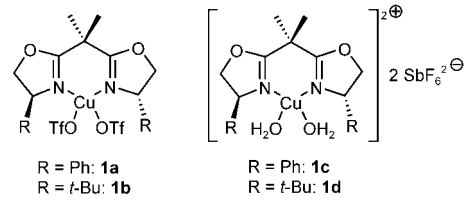
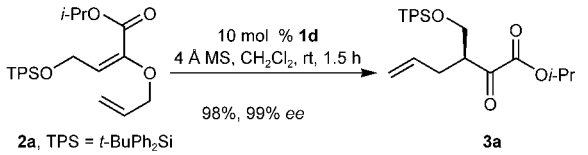


Figure 1. [Cu(II)box]-catalysts **1a–d** employed in this study.

work and has later been studied experimentally[18a–d] and theoretically.[19] A limited number of truly catalytic *achiral* metal catalysts that accelerate the Claisen rearrangement have been reported, most notably a Pd^{II} complex,[20a–k] lanthanide(III) complexes,[21a–d] and $TiCl_4$.[22a, b] Substituents on the allyl vinyl ether framework have a dramatic influence on the rate of the Claisen rearrangement. This seems to be true for metal-promoted and metal-catalyzed processes too. Therefore, the observation that a certain metal ion accelerates the Claisen rearrangement of a particular class of allyl vinyl ethers does not qualify this metal ion as a general catalyst. Consequently, substrate, product and catalyst structure (metal cation and ligands) have to be adjusted carefully in order to achieve sufficient reactivity, to avoid side reactions (e.g., ionization[23a–e]) and/or product inhibition of the catalyst. Following these considerations, we have initiated a research program directed toward the identification of an appropriate combination of substrate and catalyst structure. We have focused our efforts on 2-alkoxycarbonyl-substituted allyl vinyl ethers due to their convenient accessibility,[24] stability (storability) and because of the usefulness of the corresponding Claisen rearrangement products as a chiral building block. The breakthrough discovery was that several metal triflates [Cu^{II}, lanthanides(III), Sc^{III}] are useful catalysts for the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers.[25] The identification of $Cu(OTf)_2$ as an achiral Lewis acid catalyst guided us to the well known chiral copper(II) bis(oxazolines) **1a**,**b** as potential chiral catalysts for the Claisen rearrangement.[26a–c,27a–n] Our work culminated in the publication of the first catalytic asymmetric Claisen rearrangement.[28] Using [Cu^{II}-box](OTf)$_2$-complexes **1a**,**b** and 2-alkoxycarbonyl-substituted allyl vinyl ethers containing a variety of different substituents, we observed an enantiomeric excess of 80–90%.

Our initial results can be considered as a proof of principle, however, a significant improvement of the *ee* and the investigation of a broader substrate spectrum, particularly with respect to highly functionalized allyl vinyl ethers, was necessary in order to establish a truly synthetically useful catalytic asymmetric Claisen rearrangement. Studies aimed at this objective led to the discovery that the known bench-stable [Cu{(*S*,*S*)-*tert*-Bu-box}](H$_2$O)(SbF$_6$)$_2$ complex,[29] which amalgamates efficient enantioface-differentiating capability and high

Lewis acidity, is an exceptionally powerful catalyst for the catalytic asymmetric Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers **2** featuring a stereogenic vinyl ether double bond [see, for example, Eq. (3)].[30,31]



(3)

As an extension to these encouraging results, we now report the details of the catalytic asymmetric Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers **2b – f** that contain two stereogenic double bonds.

Results and Discussion

The first question to answer was whether or not the highly Lewis acidic complex **1d** would be suitable to catalyze the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers **2** that contain two stereogenic double bonds with high chemo-, diastereo- *and* enantioselectivities. Our initial concern that the increased Lewis acidity of **1d** compared to the previously employed catalysts **1a**,**b** may cause extensive decomposition of the sensitive enol ether moiety turned out to be unjustified. The 1,6-dialkyl-substituted (*E*,*Z*)-configured allyl vinyl ether **3b** ($R^1 = H$, $R^6 = Et$) underwent the catalyzed rearrangement in the presence of 10 mol % **1d** and pulverized and activated molecular sieves[32] at room temperature in CH_2Cl_2 to afford the α-keto ester **3b** with an exceptionally high chemoselectivity along with a remarkable diastereo- and enantioselectivity (Table 1, Entry 1). Encouraged by these initial results the question was raised whether the same catalyst **1d** would tolerated protected hydroxy groups as part of the substrate. Consequently, a number of allyl vinyl ethers were synthesized that contain benzyl and silyl ether functionalities. For the sake of comparability and clear arrangement, the results for the (*E*,*Z*)-configured allyl vinyl ethers **2c – f** will be discussed first (Table 1). We selected the trifunctional allyl vinyl ether (*E*,*Z*)-**2c** ($R^{1,6} = OBn$) as a touchstone for the catalyst **1d**. The two Lewis basic benzyl ether oxygen atoms of **2c** may coordinate to the strong Lewis acid **1d** causing catalyst inhibition or ether cleavage (favored by the formation of a stabilized benzylic cation).[33a–d] Fortunately, **1d** catalyzed the Claisen rearrangement almost undisturbed by the presence of the benzyl ether functionalities to afford the α-keto ester **3c** as virtually one stereoisomer in very high yield (Table 1, Entry 2). Furthermore, scale-up of the reaction to 4 mmol of the allyl vinyl ether **2c** and optimizing the catalyst loading down to 2.5 mol % led to an identical result (Table 1, Entry 3). However, we noticed the formation of 1–2% of the undesired elimination product **4c** that was separated by flash chromatography. In a control experiment, the treatment of (3*S*,4*R*)-**3c** with 10 mol % of **1d** under the conditions of the rearrangement led to the time-dependent formation of up to 17% of **4c** (after 72 h). We conclude that the formation of the byproduct **4c** is a consequence of the interaction of the catalyst with the rearrangement product **3c** and can be minimized by an optimized reaction time in order to avoid superfluous catalyst-product interaction.

Although the α-keto ester **3b** does contain valuable protected functionalities for further transformations, the hydroxy groups should be protected orthogonally. Therefore, we continued our investigation with the allyl vinyl ether (*E*,*Z*)-**2d** containing one benzyl ($R^1 = OBn$) and one silyl ether ($R^6 = OTPS$) (Table 1, Entries 4–6). The (*S*,*S*)-**1d**-catalyzed rearrangement of (*E*,*Z*)-**2d** proceeded with high chemoselectivity, however, we noticed a decreased diastereoselectivity (86/14) in favor of the expected *anti*-(3*S*,4*R*)-**3d** diastereomer (Table 1, Entry 4). Interestingly, we observed an *ee* of 98% for the major [*anti*-(3*S*,4*R*)-**3d**] *and* the minor [*syn*-(3*S*,4*S*)-**3d**] diastereomer. This observation led to the hypothesis that the lack of *anti*/*syn* diastereoselectivity may be a consequence of a competing catalyzed rearrangement *via* a boat-like transition state arrangement caused by the bulkiness of the *tert*-butyl-substituted bis(oxazoline) ligand *and* the TPS-protecting group.[34] In an attempt to circumvent this problem, we employed the less sterically demanding catalyst [Cu{(*R*,*R*)-Ph-box}]$(OTf)_2$, (*R*,*R*)-**1a**, for the rearrangement of (*E*,*Z*)-**2d** (Table 1, Entry 5). In agreement with the decreased Lewis acidity of **1a**, the complete consumption of (*E*,*Z*)-**2d** required a significantly increased reaction time but afforded the rearrangement product with a diastereoselectivity of 99/1 in favor of the *anti*-(3*S*,4*R*)-**3d** diastereomer. Not unexpectedly based on our previous results, however, the enantioselectivity of the rearrangement was only moderate (74%). The observation that (*S*,*S*)-**1d** and (*R*,*R*)-**1a** both favor the formation of the rearrangement product with the same absolute configuration at C-3 is consistent throughout our work. It is furthermore in agreement with literature reports that are concerned with other Cu(box)-catalyzed reactions.[35] We next studied the effect of the counterion on the stereoselectivity of the [Cu(Ph-box)]-catalyzed rearrangement. For this purpose, the catalyzed rearrangement of (*E*,*Z*)-**2d** employing the highly Lewis acidic but moderately sterically demanding [Cu{(*R*,*R*)-Ph-box}]$(H_2O)_2$ $(SbF_6)_2$ complex **1c** was investigated (Table 1, Entry 6). As expected, **1c** was found to be the most reactive catalyst, almost instantaneously converting the allyl vinyl ether (*E*,*Z*)-**2d** into the rearrangement product **3d**. Although the observed *anti*/*syn* diastereoselectivity was quite good (97/3) in favor of the expected *anti*-(3*S*,4*R*)-**3d** diastereomer, the enantioselectivity remained moderate (76% ee). Lowering the reaction temperature to

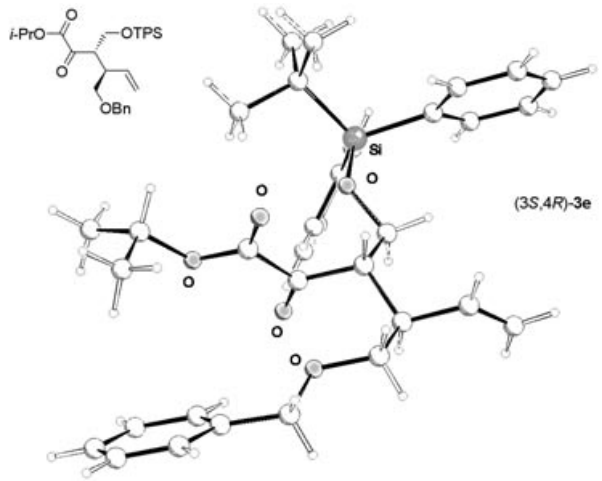


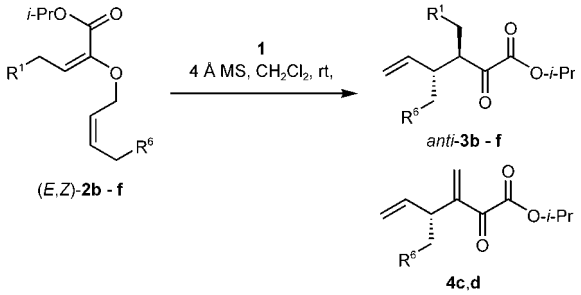
Figure 2. Crystal structure analysis of (3*S*,4*R*)-**3e**.

0 °C significantly slowed down the rate of the rearrangement but improved neither the diastereo- nor the enantioselectivity.

Switching the positions of the Bn and the TPS protecting group might solve the problem of unsatisfactory diastereoselectivities caused by the steric bulk of the TPS group in the allylic ether segment of the allyl vinyl ether **3d**. Therefore, the allyl vinyl ether (*E*,*Z*)-**2e** (R^1 = OTPS, R^6 = OBn) was synthesized and treated with the catalyst (*S*,*S*)-**1d** (Table 1, Entry 7). We were pleased to find that the corresponding rearrangement proceeded very smoothly within an short time (1.5 h) to provide the α-keto ester (3*S*,4*R*)-**3e** as virtually one stereoisomer (99% *de*, 99% *ee*). We were able to obtain suitable crystals for an X-ray crystal structure analysis of the α-keto ester (3*S*,4*R*)-**3e** from the (*S*,*S*)-**1d** catalyzed rearrangement of (*E*,*Z*)-**2e**. The result of the X-ray crystal structure analysis is depicted in Figure 2 and further supports our earlier established relationship between catalyst configuration, allyl vinyl ether double configuration and relative as well as absolute configuration of the rearrangement product.[28]

The investigation of the (*S*,*S*)-**1d**-catalyzed rearrangement of the allyl vinyl ether (*E*,*Z*)-**2f** (R^1 = CH_2OBn, R^6 = OTPS) served to indicate the generality of our catalytic asymmetric Claisen rearrangement. We were pleased to find that the rearrangement afforded the α-keto ester *anti*-(3*R*,4*R*)-**3f** as an essentially enantio- and diastereomerically pure compound (98% *de*, 99% *ee*) in quantitative yield (Table 1, Entry 8). It is instructive to note that, in contrary to the (*S*,*S*)-**1d**-catalyzed rearrangement of (*E*,*Z*)-**2d**, the presence of the TPS protecting group in the allylic ether fragment did

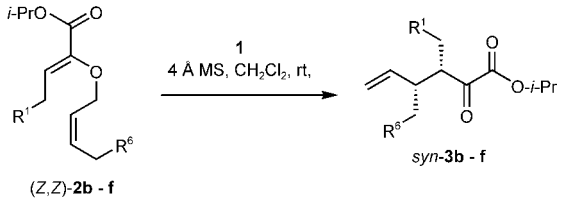
Table 1. The catalytic asymmetric Claisen rearrangement of (*E*,*Z*)-configured allyl vinyl ethers **2b–g.**



Entry	Substrate	R^1	R^6	cat.	mol %[a]	t [h]	Yield [%][d]	*anti*/*syn*[b]	*ee* [%][c]
1	(*E*,*Z*)-**2b**	H	Et	(*S*,*S*)-**1d**	10	3	99	97/3	98 (3*R*,4*R*)-**3b**
2	(*E*,*Z*)-**2c**	OBn	OBn	(*S*,*S*)-**1d**	10	24	98[e]	99/1	99 (3*S*,4*R*)-**3c**
3	(*E*,*Z*)-**2c**	OBn	OBn	(*S*,*S*)-**1d**	2.5[f]	24	96[e]	99/1	99 (3*S*,4*R*)-**3c**
4	(*E*,*Z*)-**2d**	OBn	OTPS	(*S*,*S*)-**1d**	5	8	97[e]	86/14	98 (3*S*,4*R*)-**3d**[g]
5	(*E*,*Z*)-**2d**	OBn	OTPS	(*R*,*R*)-**1a**	10	30	98[e]	99/1	74 (3*S*,4*R*)-**3d**
6	(*E*,*Z*)-**2d**	OBn	OTPS	(*R*,*R*)-**1c**	5	1	99	97/3	76 (3*S*,4*R*)-**3d**
7	(*E*,*Z*)-**2e**	OTPS	OBn	(*S*,*S*)-**1d**	2.5[h]	1.5	99	99/1	99 (3*S*,4*R*)-**3e**
8	(*E*,*Z*)-**2f**	CH_2OBn	OTPS	(*S*,*S*)-**1d**	5	6	99	99/1	99 (3*R*,4*R*)-**3f**

Bn = benzyl, TPS = *tert*-butyldiphenylsilyl.
[a] Unless otherwise noted, all reactions were carried out on a 0.4 mmol scale.
[b] Determined by ^{1}H NMR and/or chiral HPLC.
[c] Determined by chiral HPLC. For details see Experimental Section.
[d] Isolated yield of analytically pure material.
[e] Additionally, 1–2% of the elimination product **4c** was formed, separable by flash chromatography.
[f] 4 mmol (1.64 g) scale.
[g] The *syn*-(3*S*,4*S*)-**3d** diastereomer was also obtained in 98% *ee*.
[h] Optimized catalyst loading and reaction time.

Table 2. The catalytic asymmetric Claisen rearrangement of (*Z*,*Z*)-configured allyl vinyl ethers **2b** – **f**.



(*Z*,*Z*)-**2b - f** *syn*-**3b - f**

Entry	Substrate	R^1	R^6	cat.	mol %[a]	t [h]	Yield [%][d]	*anti*/*syn*[b]	*ee* [%][c]
1	(*Z*,*Z*)-**2b**	H	Et	(*S*,*S*)-**1d**	10	3	99	1/99	99 (3*S*,4*R*)-**3b**
2	(*Z*,*Z*)-**2c**	OBn	OBn	(*S*,*S*)-**1d**	5	12	99[e]	1/99	99 (3*R*,4*R*)-**3c**
3	(*Z*,*Z*)-**2c**	OBn	OBn	(*R*,*R*)-**1a**	10	24	95[e]	1/99	88 (3*R*,4*R*)-**3c**
4	(*Z*,*Z*)-**2d**	OBn	OTPS	(*S*,*S*)-**1d**	5	3	99[e]	1/99	98 (3*R*,4*R*)-**3d**
5	(*Z*,*Z*)-**2e**	OTPS	OBn	(*S*,*S*)-**1d**	2.5[f]	1.5[f]	99	1/99	99 (3*R*,4*R*)-**3e**
6	(*Z*,*Z*)-**2f**	CH_2OBn	OTPS	(*S*,*S*)-**1d**	10[g]	48[g]	98	1/99	99 (3*S*,4*R*)-**3f**

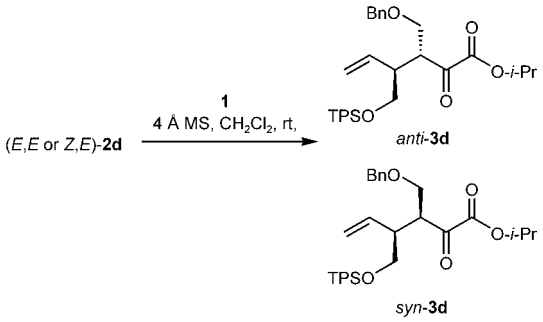
Bn = benzyl, TPS = *tert*-butyldiphenylsilyl.
[a] Unless otherwise noted, all reactions were carried out on 0.4 mmol scale.
[b] Determined by ^{1}H NMR and/or chiral HPLC.
[c] Determined by chiral HPLC. For details see Experimental Section.
[d] Isolated yield of analytically pure material.
[e] 1–3% of the elimination product **4c**, separable by flash chromatography.
[f] Catalyst loading and reaction time optimized.
[g] An attempt to catalyze the rearrangement with 5 mol % **1c** for three days led to an incomplete conversion.

not undermine the diastereoselectivity of the rearrangement.

Our synthetic strategy conveniently affords the 2-alkoxycarbonyl-substituted allyl vinyl ether **2** with either the *E*- or the *Z*-configured vinyl ether double bond.[24] Consequently, the present study was continued with the evaluation of the (*S*,*S*)-**1d**-catalyzed rearrangement of the (*Z*,*Z*)-configured allyl vinyl ethers **2b** – **f** (Table 2). Based on the assumption of a chair-like transition state geometry for the catalyzed rearrangement, we expected the preferential formation of the corresponding *syn*-configured α-keto esters **3b** – **f**. The 1,6-dialkyl-substituted allyl vinyl ether (*Z*,*Z*)-**2b** (R^1 = H, R^6 = Et) underwent the rearrangement in the presence of (*S*,*S*)-**1d** with a rate and selectivity comparable to those of the (*S*,*S*)-**1d**-catalyzed rearrangement of (*E*,*Z*)-**2b** (Table 2, Entry 1). As expected, we observed the formation of the *syn*-configured diastereomer which can be clearly distinguished by ^{1}H NMR from the corresponding *anti*-configured diastereomer. The **1d**-catalyzed rearrangement of (*Z*,*Z*)-**2c** afforded (3*R*,4*R*)-**3c** as a single diastereo- and enantiomer (Table 2, Entry 2). Employing the less Lewis acidic and less sterically demanding catalyst (*R*,*R*)-**1a** afforded *syn*-(3*R*,4*R*)-**3c** as a single diastereomer but with a decreased enantioselectivity (Table 2, Entry 3). The (*S*,*S*)-**1c**-catalyzed rearrangement of the synthetically more useful orthogonally protected allyl vinyl ethers (*Z*,*Z*)-**2d** (R^1 = OBn, R^6 = OTPS), (*Z*,*Z*)-**2e** (R^1 = OTPS, R^6 = OBn) and (*Z*,*Z*)-**2f** (R^1 = CH_2OBn, R^6 = OTPS) proceeded uneventfully to provide the corresponding α-keto esters *syn*-(3*R*,4*R*)-**3d**, *syn*-(3*R*,4*R*)-**3e** and *syn*-(3*S*,4*R*)-**3f** in high yield (98%) and stereoselectivity (98% *de*, 98–99% *ee*) (Table 2, Entries 4–6).

Earlier studies have revealed that 2-alkoxycarbonyl-substituted allyl vinyl ethers **2** containing an *E*-configured allylic ether double bond frequently undergo the **1a**-catalyzed Claisen rearrangement to provide the rearrangement products **3** with only moderate diastereoselectivities.[28] The question remained whether the application of the more Lewis acidic and sterically demanding catalyst **1d** would lead to the same result. We selected the novel, highly functionalized allyl vinyl ethers (*Z*,*E*)- and (*E*,*E*)-**2d** in order to answer this question. Our choice was guided by the observation that the diastereoselectivity of the catalyzed rearrangement of (*E*,*Z*)-**2d** was already sensitive to the nature of the bisoxazoline ligand (Table 1, Entry 4). We expected an even more pronounced effect of the catalyst structure on the diastereoselectivity of the rearrangement of (*Z*,*E*)- and (*E*,*E*)-**2d**. The results of the catalyzed Claisen rearrangement of (*Z*,*E*)- and (*E*,*E*)- **2d** are summarized in Table 3 and impressively illustrate this surprising effect. The first three Entries in Table 3 are concerned with the influence of the catalyst structure on the diastereo- and enantioselectivity of the rearrangement of (*E*,*E*)-**2d**. Employing (*S*,*S*)-**1d** afforded the rearrangement product as a 9/1 mixture of *syn*-(3*S*,4*S*)-**3d** and *anti*-(3*R*,4*S*)-**3d** (Table 3, Entry 1). Significantly, the *ee* of *syn*-(3*S*,4*S*)-**3d** did not decrease dramatically indicating the uniformly efficient ability of the catalyst to differentiate between the enantiotopic faces of the enol ether double bond. We had demonstrated earlier, that the exchange of the substituent on the bis(oxazoline) ligand (Ph *vs.*

Table 3. The catalytic asymmetric Claisen rearrangement of (*Z*,*E*)- or (*E*,*E*)-configured allyl vinyl ethers **2d**.

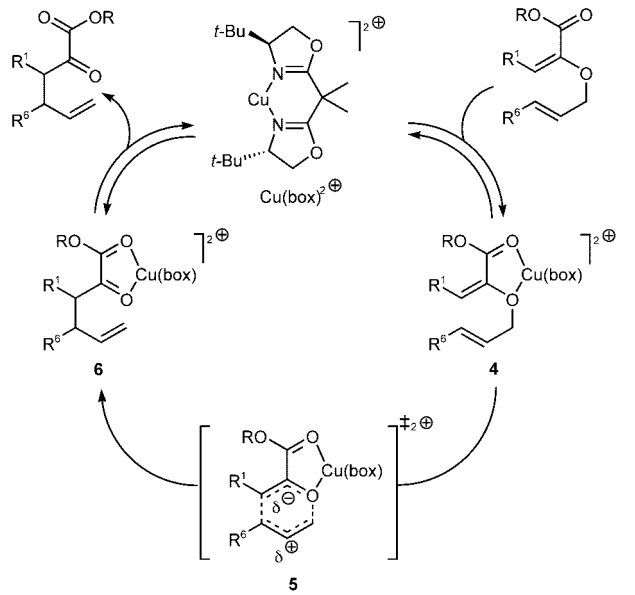


Entry	Substrate	cat.	mol %[a]	t [h]	Yield [%][d]	*anti*/*syn*[b]	*ee anti* [%][c]	*ee syn* [%][c]
1	(*E*,*E*)-**2d**	(*S*,*S*)-**1d**	5	4	99	11/89	–[e]	94 (3*S*,4*S*)-**3d**
2	(*E*,*E*)-**2d**	(*R*,*R*)-**1a**	10	12	99	2/98	–[e]	84 (3*S*,4*S*)-**3d**
3	(*E*,*E*)-**2d**	(*R*,*R*)-**1c**	5	1.5	99	3/97	–[e]	78 (3*S*,4*S*)-**3d**
4	(*Z*,*E*)-**2d**	(*S*,*S*)-**1d**	5	4	98	37/63	95 (3*R*,4*S*)-**3d**	99 (3*R*,4*R*)-**3d**
5	(*Z*,*E*)-**2d**	(*R*,*R*)-**1a**	10	3	99	69/31	88 (3*R*,4*S*)-**3d**	88 (3*R*,4*R*)-**3d**
6	(*Z*,*E*)-**2d**	(*R*,*R*)-**1c**	5	1	99	70/30	76 (3*R*,4*S*)-**3d**	74 (3*R*,4*R*)-**3d**

Bn = benzyl, TPS = *tert*-butyldiphenylsilyl.
[a] Unless otherwise noted, all reactions were carried out on a 0.4 mmol scale.
[b] Determined by ^{1}H NMR and/or chiral HPLC.
[c] Determined by chiral HPLC. For details see Experimental Section.
[d] Isolated yield of analytically pure material.
[e] Not unambiguously determinable.

tert-Bu) may have a beneficial effect on the diastereoselectivity of the rearrangement (Table 1, Entries 4 and 5). Accordingly, we observed an increased diastereoselectivity by the application of either [Cu{(*R*,*R*)-Ph-box}]$(H_2O)_2(SbF_6)_2$ (**1a**) or [Cu{(*R*,*R*)-Ph-box}]$(OTf)_2$ (**1c**) as catalysts. Only a very small amount of the minor *anti*-**3d** diastereomer could be detected by HPLC in both cases (Table 3, Entries 2 and 3). Unfortunately, the increased diastereoselectivity was accompanied by a decreased enantioselectivity (**1a**: 84% *ee*, **1c**: 78% *ee*) in accordance with previous results (Table 1, Entries 5 and 6). An even more pronounced dependence between catalyst structure and diastereoselectivity was observed for the (*Z*,*E*)-configured allyl vinyl ether **2d** (Table 3, Entries 4–6). The **1d**-catalyzed rearrangement proceeded with a disappointingly low diastereoselectivity of 2/1 in favor of *syn*-(3*R*,4*R*)-**3d** (Table 3, Entry 4). The preferred formation of the *syn*-diastereomer is particularly surprising because *it implies the preference for a boat-like transition state arrangement*. The observation that both diastereomers [*anti*-(3*R*,4*S*)-**3d** and *syn*-(3*R*,4*R*)-**3d**] were obtained in almost equally high enantioselectivity (95% and 99% *ee*, respectively) again demonstrated the powerful enantioface-differentiating capability of **1d**. Application of the Ph-box-derived catalysts **1a** and **1c** reversed the diastereoselectivity in favor of *anti*-(3*R*,4*S*)-**3d** indicating the intrinsic preference of the Ph-box-derived catalysts for a chair-like transition state (Table 3, Entries 5 and 6). The **1a, c**-catalyzed rearrangement afforded *syn*-(3*R*,4*S*)-**3d** and *anti*-(3*R*,4*R*)-**3d** with moderate, however, identical enantioselectivities. This observation is in agreement with our assumption that the lack of diastereoselectivity is solely a consequence of the competition between boat- and chair-like transition state geometries. This competition is a direct consequence of the catalytic process. The thermal Claisen rearrangement of either (*E*,*E*)-**2d** or (*Z*,*E*)-**2d** afforded the corresponding α-keto ester *syn*- or *anti*-**3d** with a diastereoselectivity exceeding 95/5. As one would expect, the preference of the thermal Claisen rearrangement of these acyclic allyl vinyl ethers for a chair-like transition state is very dependable. A stepwise, non-concerted process *via* an ion pair may be considered as reason for the low diastereoselectivity of the catalyzed rearrangement. However, we never observed the characteristic formation of the corresponding [1,3]-rearrangement products which is usually the consequence of a dissociative process.

A working hypothesis for the catalytic cycle of the Cu(box)-catalyzed Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ether **2** is depicted in Scheme 3. We propose, in accordance with the catalytic cycle of other Cu(box)-catalyzed processes,[26] the formation of the complex **4** between the catalyst and the allyl vinyl ether in which the copper ion coordinates simultaneously the allylic ether and the ester carbonyl oxygen atom. The strong inductive effect of the copper ion then polarizes the allylic ether oxygen/carbon bond and, thereby, facilitates the formation of the highly polarized transition state **5**. The assumption of a polarized transi-



Scheme 3. Proposed catalytic cycle for the (*S*,*S*)-**1d**-catalyzed Claisen rearrangement.

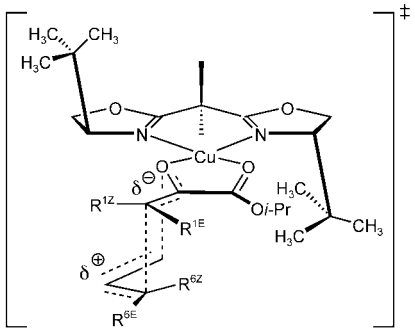
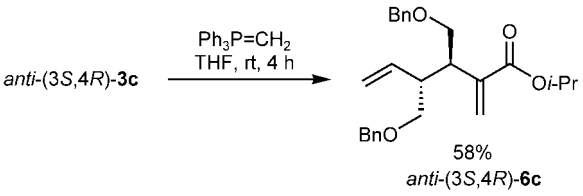


Figure 3. Schematic presentation of the proposed transition state for the (*S*,*S*)-**1d**-catalyzed Claisen rearrangement that proceeded *via* a chair-like transition state.

tion state has been employed earlier to explain the accelerating influence of substituents and solvents on the rate of the thermal Claisen rearrangement.[2c, d,f;3b, g] Theoretical work by Houk and coworker later confirmed this proposal.[3d, h] Wiest and Houk also studied by calculation the effect of an ammonium ion and a proton bond to the allylic ether oxygen atom of the parent allyl vinyl ether.[19] They found significantly decreased activation energies and a highly polarized transition state. The polarization of the transition state was particularly pronounced in the presence of a proton, the calculated transition state was described as a "loose complex between an enol and an allyl cation". Based on these results, we suggest that the catalytic activity of the copper ion is a consequence of its strong Lewis acidity which enables the Claisen rearrangement to proceed *via* a highly polarized transition state with considerably lower activation energy. Whether or not the catalytic activity of Cu(box) is also a consequence of a selective binding of the allyl vinyl ether in a conformation that resembles the transition state of the Claisen rearrangement, in analogy to a proposed mechanism of action of the chorismate mutase, remains speculative. Work is currently underway to gain more insights into the exact mechanism of the Cu(box)-catalyzed Claisen rearrangement.

It is generally accepted that L_2Cu(*tert*-Bu-box)-complexes adopt a distorted square planar geometry. Consequently, the stereochemical course of several Cu(*tert*-Bu-box)-catalyzed processes have been successfully interpreted by assuming a square planar substrate-catalyst complex. Two-point binding of the substrate on the Cu(box)-catalyst is of pivotal importance in order to take advantage of the enantioface-differentiating capability of the catalyst. Figure 3 depicts our proposal for an idealized three-dimensional structure of the polarized transition state **5** of the catalyzed Claisen rearrangement (Scheme 3). We assume that, based on a chair-like transition state arrangement, the allylic ether segment favorably approaches the vinyl ether segment from the face opposite to the bulky *tert*-Bu substituent on the box ligand. This model is fully consistent with the obtained absolute configuration at C-3 of the rearrangement products **3a** – **f**. However, it remains to be determined why for certain double bond configurations and substituent patterns the rearrangements proceeds partially through a boat-like transition state.

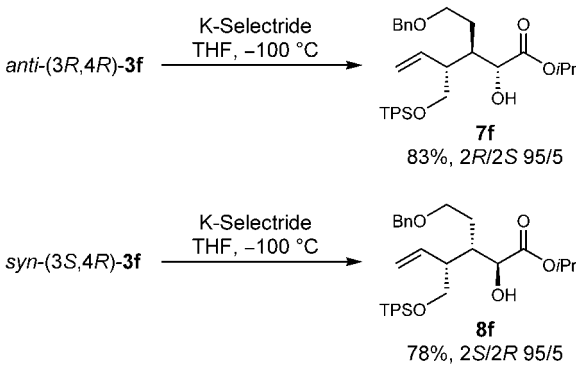
The presence of the ester function at the 2-position of the allyl vinyl ether **2** is not only pivotal for their accessibility, stability and reactivity, its presence furthermore increases the usefulness of the rearrangement products, the α-keto esters **3**, as building blocks in natural product synthesis.[36] For instance, the α-keto function of the α-keto ester *anti*-(3*S*,4*R*)-**3c** has been successfully employed in a Wittig olefination affording the α,β-unsaturated ester *anti*-(3*S*,4*R*)-**6c** in moderate yield under non-optimized conditions [Eq. (4)].



(4)

We also investigated the reduction of the α-keto ester function by hydride donors.[37a–f] K-Selectride was particularly useful and reduced *anti*-(3*R*,4*R*)-**3f** and *syn*-(3*S*,4*R*)-**3f** into the corresponding α-hydroxy esters (2*R*,3*R*,4*R*)-**7f** and (2*S*,3*S*,4*R*)-**8f** in good yield (Scheme 4).

The high diastereoselectivities of ≥95/5 in favor of the 2,3-*anti* diastereomers (2*R*,3*R*,4*R*)-**7f** and (2*S*,3*S*,4*R*)-**8f** may be explained by an 1,2-asymmetric induction and,



Scheme 4. Diastereoselective reduction of enantiomerically pure rearrangement products.

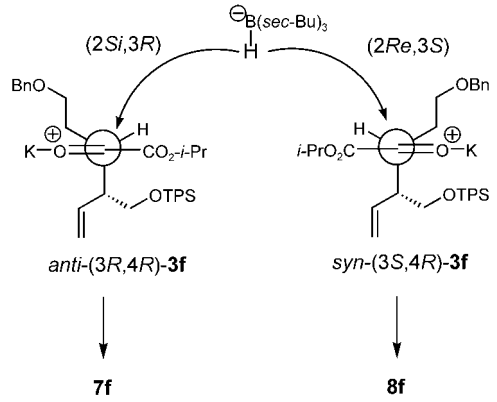


Figure 4. The substrate-induced diastereoselectivity of the reduction can be explained by the application of the Cram–Felkin–Anh model.

consequently, by the application of the Cram–Felkin–Anh model (Figure 4).[38,39]

Conclusion

This paper illustrates the scope and limitations of the (*S*,*S*)-**1d**-catalyzed Claisen rearrangement of the 2-alkoxycarbonyl-substituted allyl vinyl ethers **2b** – **f** containing two stereogenic double bonds. The results summarized in Tables 1 and 2 clearly demonstrate that, if one thoughtfully chooses the appropriate combination of substrate structure and catalyst configuration, the catalytic asymmetric Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ether **2** provides an access to highly functionalized δ,ε-unsaturated α-keto ester **3b – f** in high yield, as well as high diastereo- *and* enantioselectivity. The results summarized in Table 3 illustrate a remarkable influence of the configuration of the allylic ether double bond of the allyl vinyl ether and the nature of the catalyst on the stereoselectivity of the rearrangement. Generally, the catalyzed rearrangement of allyl vinyl ethers **2b** – **f** containing an *E*-configured allylic ether double bond frequently provides decreased diastereoselectivities, particularly if the catalyst **1d** is employed. Considering earlier work on the nature of the transition state of the thermal Claisen rearrangement, we proposed that the catalytic activity of the Cu(box)-complex **1** is a consequence of the ability to open a rearrangement pathway *via* a highly polarized pericyclic transition state of significantly lower activation energy. Work aimed at the confirmation of our proposed mechanism and the application of the catalytic asymmetric Claisen rearrangement in natural product synthesis is currently underway in our laboratory.

Experimental Section

General Remarks

CH_2Cl_2 was freshly distilled from CaH_2 under an atmosphere of N_2. Pulverized 4 Å molecular sieves were activated at 200 °C/0.1 mbar for 2 h and stored at 80 °C under an atmosphere of argon. Metal salts, ligands, molecular sieves and allyl vinyl ethers were weighed under a non-inert atmosphere. NMR spectra (^1H at 300/500 MHz, ^{13}C at 75/125 MHz) were recorded in $CDCl_3$ as solvent and chemical shifts were expressed in parts per million relative to the signals for $CHCl_3$ (7.26 ppm) or $CDCl_3$ (77.0 ppm). Column chromatography was performed on silica gel 60 (Merck, 40–63 μm mesh) using a mixture of heptane and ethyl acetate as eluent. Enantiomeric excess (*ee* [%]) was determined by HPLC (Hewlett Packard HP 1090, DAD detection at 210 and 220 nm employing Chiracel OD 14025, 4.6 × 250 mm, 10 μm mesh and mixtures of 2-propanol and hexane as eluent).

General Procedure for the (*S*,*S*)-1d-Catalyzed Rearrangement

The catalyzed rearrangements were generally performed in flame-dried septum-sealed round-bottom flasks with magnetic stirring under an atmosphere of argon at room temperature. The appropriate amount of (*S*,*S*)-**1d** was dissolved in dry CH_2Cl_2 (5 mL/mmol allyl vinyl ether). After 5 min of stirring, pulverized and freshly activated 4 Å molecular sieves (250 mg/mmol) were added. After additional 5 minutes of stirring, a solution of the allyl vinyl ether **2a** – **f** in dry CH_2Cl_2 (5 mL/mmol) was added. The flask was then sealed with a rubber septum and the reaction mixture was stirred for the appropriate time. The reaction mixture was then diluted with CH_2Cl_2 and the molecular sieves were removed by filtration. The filtrate was passed through a 4 × 0.5 cm plug of silica gel using CH_2Cl_2 as eluent (small scale, regular flash chromatography following reactions on large scale: heptane/ethyl acetate 20/1) to remove the catalyst. The solvents were evaporated and the colorless oil was dried at reduced pressure to provide the analytical pure α-keto ester.

***α-Keto ester syn-*(3*S*,4*R*)-3b:** According to the general procedure, the (*S*,*S*)-**1d**-catalyzed (10 mol %, 34.6 mg) rearrangement of allyl vinyl ether (*Z*,*Z*)-**2b** (91 mg, 0.4 mmol) in the

presence of 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) afforded *syn*-(3*S*,4*R*)-**3b**; yield: 90 mg (99%, 98% *de*, 99% *ee*); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.61 (ddd, 1H, *J* = 16.9, 10.4, 9.1 Hz), 5.13 (sept, 1H, *J* = 6.3 Hz), 5.03 (dd, 1H, *J* = 10.2, 1.8 Hz), 5.00 (dd, 1H, *J* = 17.1, 1.5 Hz), 3.30 (dq, 1H, *J* = 6.8 Hz), 2.26–2.39 (m, 1H), 1.45–1.01 (m, 4H), 1.35 (d, 3H, *J* = 6.4 Hz), 1.33 (d, 3H, *J* = 6.2 Hz), 1.11 (d, 3H, *J* = 7.0 Hz), 0.87 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 198.0, 168.6, 139.5, 116.7, 70.4, 46.0, 45.9, 32.8, 21.6, 21.5, 20.1, 13.9, 12.4; IR (in substance): ν = 2980–2940, 1720 cm^{-1}; anal. calcd. for $C_{13}H_{22}O_3$: C 68.99, H 9.80; found: C 68.82, H 9.75; $[\alpha]_D^{25}$ (*3S,4R*)-**3b**: −54.6 (*c* 1.22, $CHCl_3$; 98% *de*, 99% *ee*); HPLC: R_t (*n*-hexane/*i*-PrOH, 99.9/0.1, flow = 1 mL/min) (*3S,4R*)-**3b** = 5.6 min, (*3R,4S*)-**3b** = 7.2 min.

α-*Keto ester anti*-(3*R*,4*R*)-3b: According to the general procedure, the (*S*,*S*)-**1d**-catalyzed (10 mol %, 34.6 mg) rearrangement of allyl vinyl ether (*E*,*Z*)-**2b** (91 mg, 0.4 mmol) in the presence of 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) afforded *anti*-(3*R*,4*R*)-**3b**; yield: 91 mg (100%, 96% *de*, 99% *ee*); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.41 (ddd, 1H, *J* = 17.1, 10.1, 9.3 Hz), 5.13 (sept, 1H, *J* = 6.3 Hz), 5.07 (dd, 1H, *J* = 10.2, 1.8 Hz), 4.98 (dd, 1H, *J* = 16.9, 1.9 Hz), 3.22 (dq, 1H, *J* = 6.8 Hz), 2.42–2.54 (m, 1H), 1.45–1.01 (m, 4H), 1.36 (d, 3H, *J* = 2.3 Hz), 1.34 (d, 3H, *J* = 2.3 Hz), 1.05 (d, 3H, *J* = 6.1 Hz), 0.88 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ = 198.3, 161.6, 139.5, 116.7, 70.4, 46.0, 45.9, 32.8, 21.6, 21.5, 20.1, 13.8, 12.4; IR (in substance): ν = 2980–2930, 1720 cm^{-1}; anal. calcd. for $C_{13}H_{22}O_3$: C 68.99, H 9.80; found: C 68.79, H 9.80; $[\alpha]_D^{25}$ (*3R,4R*)-**3b**: +66.7 (*c* 1.47, $CHCl_3$; 96% *de*, 99% *ee*); HPLC: R_t (*n*-hexane/*i*-PrOH, 99.9/0.1, flow = 1 mL/min) (*3S,4S*)-**3b** = 5.7 min, (*3R,4R*)-**3b** = 6.5 min.

α-*Keto ester anti*-(3*S*,4*R*)-3c: According to the general procedure, the (*S*,*S*)-**1d**-catalyzed (10 mol %, 34.6 mg) rearrangement of allyl vinyl ether (*E*,*Z*)-**2c** (164 mg, 0.4 mmol) in the presence of 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) afforded *anti*-(3*S*,4*R*)-**3c**; yield: 162 mg (98%, 99% *de*, 99% *ee*);^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.17 (m, 10H), 5.62 (ddd, 1H, J_1 = 17, J_2 = J_3 = 10 Hz), 5.12 (d, 1H, *J* = 17 Hz), 5.09 (d, 1H, *J* = 10 Hz), 4.98 (sept, 1H, *J* = 6.3 Hz), 4.47 (d^{AB}, 1H, *J* = 12.0 Hz), 4.4 (d^{AB}, 1H, *J* = 12.0 Hz), 4.34 (s, 2H), 3.83–3.60 (m, 3H), 3.43–3.31 (m, 2H), 2.97–2.84 (m, 1H), 1.23 (d, 3H, *J* = 6.5 Hz), 1.16 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 194.6, 185.3, 160.4, 137.9, 137.7, 135.3, 128.3, 128.2, 127.6, 127.5, 127.4, 127.3, 118.3, 73.1, 72.6, 72.5, 70.9, 70.1, 48.6, 45.3, 21.5; IR (in substance): ν = 3065–2860, 1720, 1495, 1450 cm^{-1}; anal. calcd. for $C_{25}H_{30}O_5$: C 73.15, H 7.37; found: C 73.13, H 7.42; $[\alpha]_D^{25}$: +57.5 (*c* 1.05, $CHCl_3$; 98% *de*, 99% *ee*); HPLC: R_t (*n*-hexane/*i*-PrOH, 95/5, flow = 1 mL/min) (*3S,4R*)-**3c** = 5.8 min, (*3R,4S*)-**3c** = 6.0 min.

α-*Keto ester syn*-(3*R*,4*R*)-3c: According to the general procedure, the (*S*,*S*)-**1d**-catalyzed (5 mol %, 17.3 mg) rearrangement of allyl vinyl ether (*Z*,*Z*)-**2c** (164 mg, 0.4 mmol) in the presence of 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) afforded *syn*-(3*R*,4*R*)-**3c**; yield: 162 mg (98%, 99% *de*, 99% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.21 (m, 10H), 5.89 (ddd, 1H, *J* = 16.9, 10.6, 8.9 Hz, 1H), 5.13–4.97 (m, 3H), 4.45 (s, 2H), 4.42 (s, 2H), 3.94 (ddd, 1H, J_1 = 8.2, J_2 = J_3 = 6.3 Hz), 3.74 (dd, 1H, *J* = 8.9, 8.2 Hz), 3.66 (dd, 1H, *J* = 8.9, 5.8 Hz), 3.54 (dd, 1H, *J* = 9.4, 4.6 Hz), 3.44 (dd, 1H, *J* = 9.4, 5.2 Hz), 2.91–2.80 (m, 1H), 1.27 (d, 3H, *J* = 6.2 Hz), 1.22 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.9, 184.8, 137.9, 136.0, 128.3, 127.6, 127.4, 117.7, 73.3, 73.0, 71.6, 70.3, 69.2, 48.3, 44.3, 21.5, 21.4; IR (in substance): ν = 3090, 3030, 2980, 2860, 1720, 1098, 735, 700 cm^{-1}; anal. calcd. for $C_{25}H_{30}O_5$: C 73.15, H 7.37; found: C 73.11, H 7.00; $[\alpha]_D^{25}$: 1.5 (*c* 1.23, $CHCl_3$; 99% *de*, 99% *ee*); HPLC: R_t (*n*-hexane/*i*-PrOH, 99/1, flow = 1 mL/min) (*3R,4R*)-**3c** = 9.1 min, (*3S,4S*)-**3c** = 6.0 min.

α-*Keto ester anti*-(3*S*,4*R*)-3d. According to the general procedure, the (*S*,*S*)-**1d**-catalyzed (5 mol %, 17.3 mg) rearrangement of allyl vinyl ether (*E*,*Z*)-**2d** (224 mg, 0.4 mmol) in the presence of 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) afforded *anti*-(3*S*,4*R*)-**3d**; yield: 223 mg (99%, 72% *de*, 99% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65–7.58 (m, 4H), 7.42–7.19 (m, 11H), 5.66 (ddd, 1H, J_1 = 17.6, J_2 = J_3 = 9.5 Hz), 5.10–4.93 (m, 3H), 4.46 (d^{AB}, 1H, *J* = 12.0 Hz), 4.36 (d^{AB}, 1H, *J* = 12.0 Hz), 3.97 (ddd, 1H, J_1 = 8.8, J_2 = J_3 = 5.2 Hz), 3.70–3.64 (m, 2H), 3.60 (d, 2H, *J* = 5.8 Hz), 2.90–2.78 (m, 1H), 1.26 (d, 3H, *J* = 6.5 Hz), 1.24 (d, 3H, *J* = 6.2 Hz), 1.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.6, 184.9, 160.9, 137.9, 135.9, 135.6, 133.4, 133.3, 129.64, 129.61, 128.3, 127.6, 127.5, 127.4, 117.9, 73.3, 70.3, 70.0, 65.8, 48.1, 45.7, 26.8, 21.5, 19.2; IR (in substance): ν = 3070–2860, 1720, 1470, 1430 cm^{-1}; anal. calcd. for $C_{34}H_{42}O_5Si$: C 73.08, H 7.58; found: C 72.76, H 7.65; HPLC: R_t (*n*-hexane/*i*-PrOH, 99/1, flow = 1 mL/min) (*3S,4R*)-**3d** = 7.0 min, (*3R,4S*)-**3d** = 5.5 min.

α-Keto ester *syn*-(3*R*,4*R*)-**3d**. According to the general procedure, the (*S*,*S*)-**1d**-catalyzed (5 mol %, 17.3 mg) rearrangement of allyl vinyl ether (*E*,*Z*)-**2d** (224 mg, 0.4 mmol) in the presence of 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) afforded *syn*-(3*R*,4*R*)-**3d** (223 mg, 99%, 99% *de*, 99% *ee*). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65–7.58 (m, 4 H), 7.43–7.19 (m, 11 H), 5.89 (ddd, 1 H, *J* = 17.0, 10.5, 9.0 Hz), 5.13–4.97 (m, 3 H), 4.40 (s, 2 H), 4.01 (ddd, 1 H, J_1 = 8.3, J_2 = J_3 = 5.7 Hz), 3.76–3.58 (m, 4 H), 2.72–2.62 (m, 1 H), 1.27 (d, 6 H, *J* = 6.2 Hz), 1.03 (s, 9 H); ^{13}C (75 MHz, $CDCl_3$) δ 195.9, 185.0, 160.9, 137.9, 136.5, 135.9, 135.7, 135.6, 133.4, 133.3, 129.7, 128.3, 127.7, 127.6, 127.5, 117.7, 73.2, 70.3, 69.5, 65.1, 48.5, 45.9, 26.8, 21.5, 19.3; IR (in substance) 3070–2860, 1720, 1470, 1430. Anal. calcd for $C_{34}H_{42}O_5Si$: C, 73.08; H, 7.58; found: C 72.91, H 7.59; $[\alpha]_D^{25}$ (*3R,4R*)-**3d**: +3.5 (c = 1.005 ($CHCl_3$ 99% *de*, 99% *ee*); HPLC: R_t (*n*-hexane/*i*-PrOH, 99/1, flow = 1 mL/min) (*3S,4S*)-**3d** = 7.5 min, (*3R,4R*)-**3d** = 5.9 min.

α-*Keto ester anti*-(3*S,4R*)-3e: According to the general procedure, the (*S*,*S*)-**1d**-catalyzed (2.5 mol %, 8.7 mg) rearrangement of allyl vinyl ether (*E*,*Z*)-**2e** (224 mg, 0.4 mmol) in the presence of 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) afforded *anti*-(3*S*,4*R*)-**3e**; yield: 223 mg (99%, 99% *de*, 99% *ee*). The progress of the rearrangement can be followed by TLC (heptane/ethyl acetate, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.54 (m, 4H), 7.54–7.18 (m, 11H), 5.44 (ddd, 1H, J_1 = 17.1, J_2 = J_3 = 9.7 Hz), 5.04–4.9 (m, 3H), 4.32 (s, 2 H), 4.00–3.89 (m, 1H), 3.82–3.71 (m, 2H), 3.39–3.28 (m, 2H), 2.92–2.77 (m, 1H), 1.25 (d, 3H, *J* = 6.2 Hz), 1.15 (d, 3H, *J* = 6.2 Hz), 0.95 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.8, 185.2, 160.3, 137.8, 135.6, 133.2, 133.1, 129.7, 128.3, 127.6, 127.5, 118.1, 72.8, 72.6, 70.1, 64.8, 50.8, 45.2, 31.8, 26.6, 22.7, 21.5, 19.0; IR (in substance): ν = 3070–2860, 1720, 1470, 1425 cm^{-1}; anal. calcd. for $C_{34}H_{42}O_5Si$: C 73.08, H 7.58; found: C 73.25, H 7.66; $[\alpha]_D^{25}$: +44.8 (*c* 1.065, $CHCl_3$; 99% *de*, 99% *ee*); HPLC: R_t (*n*-hexane/*i*-PrOH, 99/1, flow = 1 mL/min) (*3S,4R*)-**3e** = 5.3 min, (*3R,4S*)-**3e** = 5.2 min.

α-*Keto ester syn*-(3*R*,4*R*)-3e: According to the general procedure, the (*S*,*S*)-**1d**-catalyzed (2.5 mol %, 8.7 mg) rearrangement of allyl vinyl ether (*Z*,*Z*)-**2e** (224 mg, 0.4 mmol) in the presence of 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) afforded *syn*-(3*R*,4*R*)-**3e**; yield: 223 mg (99%, 99% *de*, 99% *ee*). The progress of the rearrangement can be followed by TLC (heptane/ethyl acetate, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.56 (m, 4H), 7.43–7.15 (m, 11H), 5.89 (ddd, 1H, *J* = 16.9, 10.4, 9.1 Hz), 5.06–4.97 (m, 3H), 4.33 (s, 2H), 4.00–3.78 (series of m, 3H), 3.44 (dd^{AB}, 1H, *J* = 9.1, 4.9 Hz), 3.38 (dd^{AB}, 1H, *J* = 9.1, 4.9 Hz), 2.80–2.71 (m, 1H), 1.29 (d, 3H, *J* = 6.5 Hz), 1.23 (d, 3H, *J* = 6.2 Hz), 0.97 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.3, 185.2, 160.6, 137.9, 136.2, 135.6, 135.2, 134.7, 133.2, 133.1, 129.7, 128.3, 127.7, 127.6, 127.5, 127.4, 117.5, 73.0, 71.9, 70.3, 63.5, 50.5, 44.2, 26.7, 21.5, 19.1; IR (in substance): ν = 3070–2860, 1720, 1470, 1425 cm^{-1}; anal. calcd. for $C_{34}H_{42}O_5Si$: C 73.08, H 7.58; found: C 72.84, H 7.48; $[\alpha]_D^{25}$: −2 (*c* 1.015, $CHCl_3$; 99% *de*, 99% *ee*); HPLC: R_t (*n*-hexane/*i*-PrOH, 99/1, flow = 1 mL/min) (*3R,4R*)-**3e** = 5.3 min, (*3S,4S*)-**3e** = 5.1 min.

α-*Keto ester anti*-(3*R*,4*R*)-3f: According to the general procedure, the (*S*,*S*)-**1d**-catalyzed (5 mol %, 17.3 mg) rearrangement of allyl vinyl ether (*E*,*Z*)-**2f** (229 mg, 0.4 mmol) in the presence of 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) afforded *anti*-(3*R*,4*R*)-**3f**; yield: 228 mg (99%, 98% *de*, 99% *ee*). The progress of the rearrangement can be followed by TLC (heptane/ethyl acetate, 3/1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.60 (m, 4H), 7.43–7.21 (m, 11H), 5.64 (ddd, 1H, J_1 = 16.9, J_2 = J_3 = 9.7 Hz), 5.11–4.96 (m, 3H), 4.37 (s, 2H), 3.72–3.58 (m, 3H), 3.47–3.38 (m, 2H), 2.79–2.67 (m, 1H), 2.09–1.94 (m, 1H), 1.93–1.81 (m, 1H), 1.24 (d, 3H, *J* = 6.2 Hz), 1.20 (d, 3H, *J* = 6.2 Hz), 1.04 (s, 9H); ^{13}C (75 MHz, $CDCl_3$): δ = 195.8, 184.9, 160.8, 138.2, 136.3, 135.6, 133.4, 133.3, 129.61, 129.58, 128.2, 127.7, 127.6, 127.5, 127.4, 118.2, 72.5, 70.1, 68.3, 65.6, 48.4, 45.6, 30.0, 26.8, 21.5, 19.2; IR (in substance): ν = 3070–2860, 1720, 1470, 1430; anal. calcd. for $C_{35}H_{44}O_5Si$: C 73.39, H 7.74; found: C 73.46, H 7.87; $[\alpha]_D^{25}$: +2.5 (*c* 1.12, $CHCl_3$; 98% *de*, 99% *ee*); HPLC: R_t (*n*-hexane/*i*-PrOH ,99/1, flow = 1 mL/min) (*3R,4R*)-**3f** = 5.7 min, (*3S,4S*)-**3f** = 5.3 min.

α-*Keto ester syn*-(3*S*,4*R*)-3f: According to the general procedure, the (*S*,*S*)-**1d**-catalyzed (10 mol %, 34.6 mg) rearrangement of allyl vinyl ether (*Z*,*Z*)-**2f** (229 mg, 0.4 mmol) in the presence of 4 Å molecular sieves (100 mg) in CH_2Cl_2 (4 mL) afforded *syn*-(3*S*,4*R*)-**3f**; yield: 228 mg, 99%, 98% *de*, 99% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.66–7.58 (m, 4H), 7.43–7.22 (m, 11H), 5.93 (ddd, 1H, *J* = 17.1, 10.3, 9.2 Hz), 5.07–4.93 (m, 3H), 4.37 (s, 2H), 3.79–3.65 (m, 3H), 3.43 (d^{AB}, 1H, *J* = 4.9 Hz), 3.39 (d^{AB}, 1H, *J* = 5.2 Hz), 2.61–2.50 (m, 1H), 2.14–1.99 (m, 1H), 1.80–1.70 (m, 1H), 1.24 (d, 3H, *J* = 6.2 Hz), 1.21 (d, 3H, *J* = 6.2 Hz), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.3, 185.0, 160.8, 138.2, 137.0, 135.7, 133.5, 133.4, 129.7, 128.3, 127.7, 127.6, 127.5, 117.6, 72.7, 70.1, 68.4, 64.8, 48.5, 45.5, 29.9, 26.9, 21.5, 19.3; IR (in substance): ν = 3070–2860, 1720, 1470, 1430 cm^{-1}; anal. calcd. for $C_{35}H_{44}O_5Si$: C 73.39, H 7.74; found: C 73.42, H 7.78; $[\alpha]_D^{25}$: +30.5 (*c* 1.11, $CHCl_3$; 98% *de*, 99% *ee*); HPLC: R_t (*n*-hexane/*i*-PrOH, 99/1, flow = 1 mL/min) (*3S,4R*)-**3f** = 6.8 min, (*3R,4S*)-**3f** = 6.1 min.

α,β-Unsaturated Ester *anti*-(3*S*,4*R*)-6c

A solution of lithium diisopropylamide [generated from diisopropylamine (0.14 mL, 1.06 mmol) and *n*BuLi (0.4 mL of a 2.35 M solution in hexanes, 0.91 mmol)] in THF (2 mL) was added to a solution of Ph_3PMeBr (350 mg, 0.99 mmol) in THF (5 mL) at −10 °C. After 30 min of stirring at −10 °C, a solution of the α-keto ester *anti*-(3*S*,4*R*)-**3c** (300 mg, 0.73 mmol) in THF (5 mL) was added. The reaction mixture was subsequently allowed to warm to room temperature and the stirred at room temperature for 4 h. The reaction was then quenched by the addition of saturated aqueous $NHCl_4$ solution. The reaction mixture was diluted with an excess of CH_2Cl_2 and H_2O. The phases were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried and the solvents were removed under reduced pressure to afford the crude product that was purified by flash chromatography (heptane/ethyl acetate, 20/1 to 10/1) to provide the α,β-unsaturated ester *anti*-(3*S*,4*R*)-**6c** as a colorless oil; yield: 174 mg (58%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 10H), 6.25 (d, 1H, *J* = 1.3 Hz), 5.80 (ddd, 2H, *J* = 18.2, 9.1 Hz), 5.59 (s, 1H), 5.12–5.04 (m, 2H), 5.02 (sept, 1H, *J* = 6.3 Hz), 4.48 (d^{AB}, 1H, *J* = 6.3 Hz), 4.43 (s, 2H), 4.40 (d^{AB}, 1H, *J* = 12.3 Hz), 3.60–3.55 (m, 2H), 3.45–3.41 (m, 2H), 3.06–2.97 (m, 1H), 2.73–2.61 (m, 1H), 1.24 (d, 3H, *J* = 6.2 Hz), 1.22 (d, 3H, *J* = 6.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.5, 140.7, 138.6, 138.4, 128.9, 127.6, 127.44, 127.41, 126.1, 116.9, 72.9, 72.8, 72.2, 71.0, 67.9, 45.5, 42.5, 21.8; IR (in substance): ν = 3065–2860, 1710, 1630, 1495, 1450 cm^{-1}; anal. calcd. for $C_{26}H_{32}O_4$: C 76.44, H 7.90; found: C 76.66, H 8.12. $[\alpha]_D$ (*2S,3S,4R*): +12.4 (*c* 1.455, $CHCl_3$; *de* > 95%).

α-Hydroxy Ester (2*R*,3*R*,4*R*)-7f

A cold (−100 °C) solution of the α-keto ester *anti*-(3*R*,4*R*)-**3f** (309 mg, 0.54 mmol) in THF (5 mL) was treated with a solution of K-Selectride (1.6 mL of 1 M solution in THF, 1.6 mmol) under an atmosphere of argon. The reaction mixture was stirred at −100 °C for 5 min and then immediately treated with an aqueous NH_4Cl solution. The cooling bath was removed and the reaction mixture diluted with water and CH_2Cl_2. The phases were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic phases were dried and the solvents were removed under reduced pressure to afford the crude product that was purified by flash chromatography (heptane/ethyl acetate, 5/1) to provide the α-hydroxy ester (2*R*,3*R*,4*R*)-**7f** as a colorless oil; yield: 257 mg (83%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.68–7.59 (m, 4H), 7.45–7.27 (m, 11H), 5.76 (ddd, 1H, *J* = 17.1, 10.1, 9.0 Hz), 5.12–5.01 (m, 3H), 4.53 (d, 1H, *J* = 12 Hz), 4.47 (d, 1H, *J* = 12 Hz), 4.28 (broad s, 1H), 3.62–3.49 (m, 4H), 2.88 (broad s, 1H), 2.52–2.39 (m, 2H), 1.91–1.67 (m, 2H), 1.27 (d, 3H, 6.2 Hz), 1.25 (d, 3H, *J* = 6.2 Hz), 1.03 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 138.5, 137.7, 135.7, 135.6, 133.6, 129.6, 128.3, 127.6, 127.5, 120.9, 117.5, 72.9, 72.7, 69.2, 68.7, 65.0, 47.1, 39.1, 26.8, 25.9, 21.8, 19.3; IR (in substance): ν = 3530, 3070, 2930, 2860, 1725, 1100, 700 cm^{-1}; anal. calcd. for $C_{35}H_{46}O_5Si$: C 73.13, H 8.07; found: C 73.13, H 8.07; $[\alpha]_D^{25}$: +1.6 (*c* 0.83, $CHCl_3$).

α-Hydroxy Ester (2*S*,3*S*,4*R*)-8f

According to previous procedure, the α-keto ester *syn*-(3*S*,4*R*)-**3f** (360 mg, 0.63 mmol) was treated with K-Selectride (1.9 mL of 1 M solution in THF, 1.9 mmol) in THF (5 mL) at −100 °C to afford the α-hydroxy ester (2*S*,3*S*,4*R*)-**8f**; yield: 282 mg (78%) as colorless oil after flash chromatography (heptane/ethyl acetate, 5/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.72–7.62 (m, 4H), 7.46–7.22 (m, 11H), 5.71 (ddd, 1H, *J* = 17.0, 10.6, 8.0 Hz), 5.09 (sept, 1H, *J* = 6.3 Hz), 4.98 (dd, 1H, *J* = 8.0, 1.6 Hz), 4.97 (d, 1H, *J* = 17 Hz), 4.52 (d, *J* = 12 Hz, 1H), 4.46 (d, 1H, *J* = 12 Hz), 4.22 (broad s, 1H), 4.14 (broad s, 1H), 3.66 (dd, 1H, *J* = 10.4, 6.5 Hz), 3.58 (dd, 1H, *J* = 10.4, 4.6 Hz), 3.54 (dd, 2H, $J_1 = J_2 = 6.5$ Hz), 2.46–2.32 (m, 2H), 1.88–1.66 (m, 2H), 1.28 (d, 3H, *J* = 6.3 Hz), 1.27 (d, 3H, *J* = 6.3 Hz), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.2, 138.6, 138.5, 135.7, 133.2, 133.1129.8, 128.3, 127.7, 127.6, 127.5, 121.0, 116.6, 72.9, 72.2, 68.9, 68.5, 64.8, 46.5, 40.9, 27.2, 26.9, 21.9, 21.8, 19.2, 14.1; IR (in substance): ν = 3510, 3390, 3070, 2930, 2860, 1725, 1105, 700 cm^{-1}; anal. calcd. for $C_{35}H_{46}O_5Si$: C 73.13, H 8.07; found: C 73.09, H 8.11; $[\alpha]_D^{25}$: +26.8 (*c* 0.29, $CHCl_3$).

X-ray Crystallographic Study of (3*S*,4*R*)-3e

Empirical formula: $C_{34}H_{42}O_5Si$, formula weight: 558.77, temperature: 198(2) K, wavelength: 0.71073 Å, crystal system: orthorhombic, space group: *P*2(1)2(1)2(1), unit cell dimensions: *a* = 7.485(1) Å, α = 90°, *b* = 10.229(2) Å, β = 90°, *c* = 41.910(4) Å γ = 90°, volume: 3208.6(8) Å^3, *Z* = 4, density (calculated): 1.157 mg/m^3, absorption coefficient: 0.111 mm^{-1}, F(000): 1200, crystal size: 0.40 × 0.25 × 0.09 mm^3, diffractometer type: Nonius-CCD, theta range for data collection: 4.81 to 23.00°, index ranges: −8 <= h <= 7, −11 <= k <= 11, −46 <= l <= 46, reflections collected: 20277, independent reflections: 4386 [R(int) = 0.0392], completeness to theta = 23.00°: 98.5%, absorption correction: semi-empirical from equivalents, max. and min. transmission: 0.9901 and 0.9570, structure solution: direct method, refinement method: full-matrix least-squares on F^2, data/restraints/parameters: 4386/0/366, Goodness-of-fit on F^2: 1.090, final R indices [I > 2sigma(I)]: R1 = 0.0392, wR2 = 0.0827, R indices (all data): R1 = 0.0472, wR2 = 0.0864, absolute structure parameter: −0.13(14), largest diff. peak and hole: 0.323 and −0.174 e · Å^{-3}, treatment of H-atoms calculated by geometry/diffmap, used programs: Collect (Nonius BV, 1997–2000), Dirax/lsq (Duisenberg & Schreurs, 1989–2000), SHELXS-97 (Sheldrick, 1990), EvalCCD (Duisenberg & Schreurs 1990–2000), SADABS version 2.03 (Sheldrick, Bruker AXS Inc.), SHELXL-97 (Sheldrick, 1997), Schakal-99 (E. Keller 1999).

CCDC-216445 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internat.) +44–1223/336–033; E-mail: deposit@ccdc.cam.ac.uk].

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