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Highly enantioselective catalytic asymmetric Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers

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Abstract—Progress in the catalytic asymmetric Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ether is reported. Application of a more Lewis acidic catalyst, [Cu{(*S*,*S*)-*t*-Bu-box}]$(H_2O)_2(SbF_6)_2$, afforded β-chiral α-keto ester with an enantiomeric excess up to 99%. We suggest a highly polarized transition state for the Lewis acid-catalyzed Claisen rearrangement in order to explain the experimental results.

We have recently communicated the first catalytic asymmetric Claisen rearrangement of acyclic 2-alkoxycarbonyl-substituted allyl vinyl ether **1**.[1,2] The catalyzed rearrangement proceeded at room temperature yielding highly substituted α-keto ester **2** in a remarkable chemo- and an acceptable enantioselectivity (Fig. 1). The *tert*-butyl- and phenyl-substituted copper(II) bis(oxazolines) **3a**,**b** containing triflate counterions were employed as Lewis acid catalysts for the rearrangement (Fig. 2).[3,4] In this letter, we present the results of further work aimed at the improvement of the enantioselectivity to a synthetically useful level. We will illustrate that the variation of the catalyst structure can significantly increase the enantioselectivity of the catalyzed Claisen rearrangement.

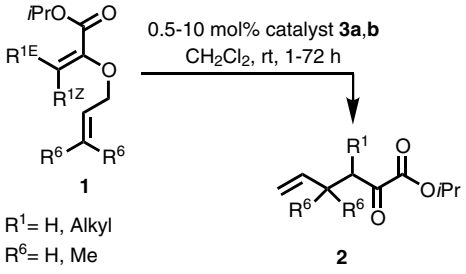

Figure 1. Previous work[1] afforded 94–100% yield and 72–88% ee, depending on the substrate and the catalyst structure (**3a**,**b**). For catalyst structures see Figure 2.

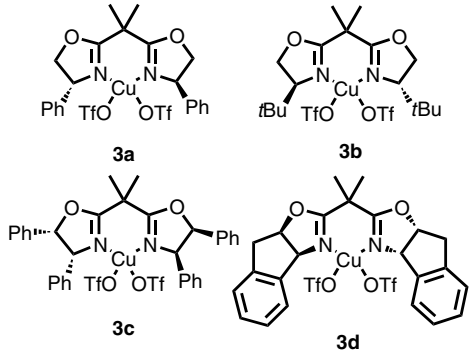

Figure 2. Catalysts for the catalytic asymmetric Claisen rearrangement.

In order to evaluate the influence of the ligand structure on the enantioselectivity of the rearrangement, a small number of commercially available bis(oxazoline) ligands were combined with $Cu(OTf)_2$ to afford the corresponding Lewis acid catalysts **3a**–**d** (Fig. 2). Employing these catalysts for the catalytic asymmetric Claisen rearrangement of the allyl vinyl ether (*Z*)-**1a** did not significantly improve the enantioselectivity compared to our previous results (Table 1). In accordance with our earlier observations,[1] the *tert*-butyl-substituted [Cu{(*S*,*S*)-*t*-Bu-box}]$(OTf)_2$ (**3b**) afforded the rearrangement product with the highest enantioselectivity but at the same time exerted the lowest reactivity (Table 1, entry 2).

Keywords: Claisen rearrangement; Asymmetric catalysis; Lewis acid; Copper(II)bis(oxazoline).
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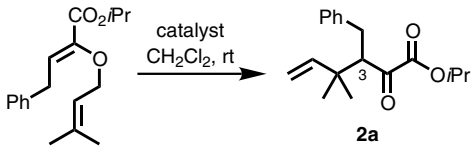
Table 1. Influence of the catalyst structure on reactivity and diastereoselectivity—a case study

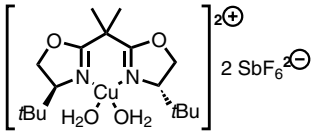


(*Z*)-**1a** **2a**

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

[a] All reactions were carried out on a 0.4 mmol scale. The catalyst was removed by filtrating the reaction mixture through a 4×5 cm silica gel column to obtain a colorless oil that was analytically pure.
[b] Determined by chiral HPLC: Chiracel OD 14025.

The next objective was to maintain the capability of the [Cu(*t*-Bu-box)](OTf)$_2$-complex (**3a**) to differentiate between the enantiotopic faces of the vinyl ether double bond and at the same time to improve the reactivity by increasing the Lewis acidity of the copper cation. Therefore, we decided to exchange the triflate counterion for the less coordinating hexafluoroantimonate. For this purpose, we selected the bench stable aqua complex [Cu(*t*-Bu-box)](H$_2$O)$_2$(SbF$_6$)$_2$ (**3e**), which was originally described by Evans et al.,[5] as potential catalyst.

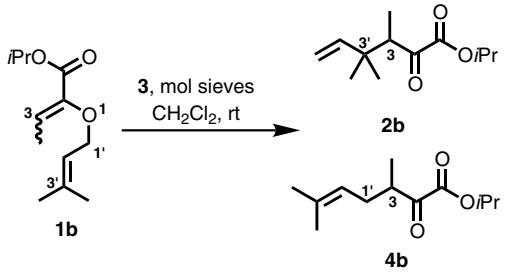


3e

Initially, the **3e**-catalyzed rearrangement of allyl vinyl ether (*E*)- and (*Z*)-**1b** was investigated. We switched the substrate structure from **1a** to **1b** because the rearrangement product **2b** represents the more useful synthetic building block and **1b** is available in both vinyl ether double bond configurations.[6]

Compound **1b** represents a sterically challenging system since its rearrangement would generate a quaternary carbon atom vicinal to the new chiral center at C-3. Furthermore, the *gem*-dimethyl group at C-3′ of the allyl vinyl ether could support the ionization of the allyl vinyl ether to an oxallylic anion and an allylic cation in the presence of the strong Lewis acid **3e**. For the sake of comparison, the rearrangement of (*Z*)-**1b** was catalyzed under identical conditions with (*S*,*S*)-**3b** and (*S*,*S*)-**3e**. The results are summarized in Table 2. The comparison of reaction time and enantioselectivity clearly demonstrates that the application of **3e** led to a faster and more

Table 2. Highly enantioselective Claisen rearrangement of allyl vinyl ether **1b**



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

AVE=allyl vinyl ether.
[a] All reactions were performed on a 0.4 mmol scale. The catalyst was removed by filtrating the reaction mixture through a 4×0.5 cm silica gel column to obtain a colorless oil that was analytically pure.
[b] Determined by chiral HPLC: Chiracel OD 14025.
[c] Optimized reaction time and catalyst loading.
[d] 5% **4b**, separated by chromatography. Enantiomeric ratio not determined.

enantioselective Claisen rearrangement compared to the **3b**-catalyzed rearrangement (Table 2, entries 1–3). However, due to the increased Lewis acidity and the carbenium ion-stabilizing ability of the *gem*-dimethyl group, we observed up to 5% of the undesired [1,3]-rearrangement product **4b** (Table 2, entries 2 and 3). The formation of **4b** is most likely a consequence of the homogenous cleavage of the O-1 to C-1′ bond, which generated an α-keto ester enolate and an allylic cation. The α-keto ester enolate then attacked the allylic cation at C-1′, the sterically less hindered position. It is however surprising, that the formation of the [1,3]-rearrangement product **4b** was not observed from the **3e**-catalyzed rearrangement of the (*E*)-configured allyl vinyl ether **1b** (Table 2, entry 4). Nevertheless, from these initial experiments we concluded that the application of $[Cu(t\text{-Bu-box})](H_2O)_2(SbF_6)_2$ (**3e**) does indeed represent a significant progress compared to our previous results.

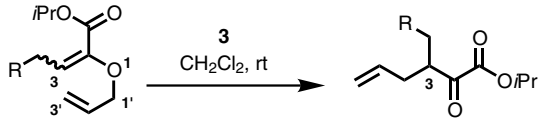
The catalysis of the rearrangement of (*E*)- and (*Z*)-**1b** with **3e** proceeded equally well in the presence or absence 4 Å molecular sieves. However, the **3b**-catalyzed rearrangement was significantly slower (80–85% conversion after 4 d with 10 mol% **3b**) in the absence of molecular sieves but afforded identical enantioselectivities.

As can be seen from Table 2, it is possible to control the absolute configuration of the newly generated chiral center at C-3 by changing the vinyl ether double bond configuration (Table 2, entries 3 and 4). Therefore, the availability of one enantiomer of the catalyst is sufficient in order to gain access to both enantiomeric rearrangement products. This fact further increases the utility of our catalytic asymmetric Claisen rearrangement, because a variety of (*E*)- and (*Z*)-configured 2-alkoxycarbonyl-substituted allyl vinyl ethers **1** are easily accessible according to our previously published procedure.[6]

We next turned our attention to the allyl vinyl ether **1c** featuring a nonstereogenic, mono-substituted allylic ether double bond (Table 3). Compound **1c** represents a challenging substrate due to the absence of alkyl-substituents at C-3′. Lack of substituents on the allylic ether segment may cause a decreased reactivity due to a less efficiently stabilized positive partial charge in the proposed highly polarized transition state of the Lewis acid-catalyzed Claisen rearrangement. Consequently, the application of **3b** as the catalyst led to disappointing results. Generally, reaction times of several days and catalyst loadings up to 20 mol% of **3b** were not sufficient to obtain a complete conversion and consistently high enantioselectivities, even in the presence of 4 Å molecular sieves (Table 3, entry 1). Although the sterically less demanding **3a** catalyzed the rearrangement within an acceptable reaction time, the corresponding enantioselectivity remained improvable (Table 3, entry 2).[7] Finally, due to its increased Lewis-acidity, **3e** was found to be the most efficient catalyst affording the corresponding rearrangement product **2c** in high yield and enantioselectivity (Table 3, entry 3).[8]

The ability to introduce further functional groups in the allyl vinyl ether **1** would significantly increase the utility of the catalytic asymmetric Claisen rearrangement for the synthesis of α-keto esters **2** as synthetic building blocks. Consequently, the protected hydroxymethyl-substituted allyl vinyl ether **1d** was synthesized. The highly Lewis acidic catalyst **3e** tolerated the protecting group and afforded the rearrangement product, the functionalized α-keto ester **2d**, in a remarkable chemo- and enantioselectivity (Table 3, entries 5 and 6).[9]

Table 3. Highly enantioselective Claisen rearrangement of allyl vinyl ether **1c**,**d**



R= H: **1c**
R= OTPS: **1d**

R= H: **2c**
R= OTPS: **2d**

Entry[a]	AVE	Catalyst	*t* [d]	Yield [%]	Ee [%][b]
1	(*Z*)-**1c**	10 mol% (*S*,*S*)-**3b**	6	55[c]	24 (3*S*)-**2c**
2	(*Z*)-**1c**	10 mol% (*R*,*R*)-**3a**[d]	2	95	84 (3*S*)-**2c**
3	(*Z*)-**1c**	10 mol% (*S*,*S*)-**3e**	1	98	95 (3*S*)-**2c**
4	(*E*)-**1c**	10 mol% (*S*,*S*)-**3e**	1	96	97 (3*R*)-**2c**
5	(*Z*)-**1d**	10 mol% (*S*,*S*)-**3e**	1.5 h[e]	99	99 (3*R*)-**2d**
6	(*E*)-**1d**	10 mol% (*S*,*S*)-**3e**	1.5 h[e]	98	99 (3*S*)-**2d**

AVE=allyl vinyl ether.

[a] All reactions were performed on a 0.4 mmol scale in the presence of 100 mg pulverized and activated 4 Å molecular sieves. The catalyst was removed by filtrating the reaction mixture through a 4×0.5 cm silica gel column to obtain a colorless oil that was analytically pure.

[b] Enantiomeric excess determined by GC (**2c**: 50 m×0.25 mm hydrodex (*R*)-β-6-TBDM (heptakis-(6-*O*-*tert*-butyl-2,3-di-*O*-methyl)-β-cyclodextrine), 65 °C) or HPLC (**2d**: Chiracel OD 14052, 1 mL/min hexane/*i*-PrOH 99.5/0.5).

[c] 45% recovered starting material.

[d] Performed in the absence of molecular sieves. The presence of molecular sieves did not increase the enantioselectivity.

[e] Optimized reaction time.

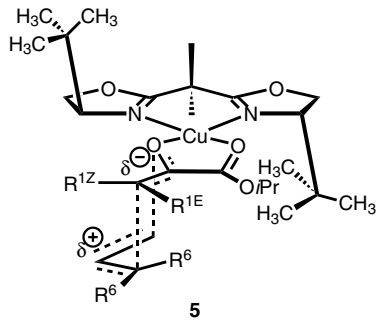


Figure 3. Proposed model for the transition state of the [Cu{(*S*,*S*)-*t*-Bu-box}]-catalyzed Claisen rearrangement.

The majority of the experimental data from this and from earlier studies support the assumption that the [Cu(box)]-catalyzed Claisen rearrangement proceeds through a highly polarized but nevertheless concerted pericyclic transition state **5** (Fig. 3). Based on extensive computational work, a polarized transition state has also been suggested for the noncatalyzed, thermal Claisen rearrangement.[10] Furthermore, the observation of the [1,3]-rearrangement product **4b** illustrated the existence of a rather small line between a highly polarized transition state **5** and the formation of an allylic cation/oxallylic anion ionpair that will recombine to the corresponding [1,3]-rearrangement product.

The stereochemical result of the **3e**-catalyzed rearrangement may be explained assuming an idealized square planar coordination sphere around the copper(II) ion (Fig. 3). The allylic ether segment will then approach the vinyl ether double bond from the face opposite to the *tert*-butyl group on the bis(oxazoline) ligand. Further experimental and theoretical work is currently underway to support our assumptions concerning the nature of the transition state and to further broaden the scope of the Lewis acid-catalyzed Claisen rearrangement.

Acknowledgements

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6. 2-Alkoxycarbonyl-substituted allyl vinyl ethers **2** were synthesized according to our previously published procedure: Hiersemann, M. *Synthesis* **2000**, 1279–1290, The vinyl ether double bond isomers have been separated by preparative HPLC. Details will be published elsewhere.
7. We had previously reported a low reactivity and a moderate enantioselectivity (68%) for the (*S*,*S*)-**3b**-catalyzed Claisen rearrangement of (*Z*)-**1c**.[1] A careful reinvestigation using a new charge of ligand and allyl vinyl ether (*Z*)-**1c** in the presence of molecular sieves afforded the rearrangement product **2c** with an increased enantioselectivity.
8. General procedure: (*S*,*S*)-**3e** was dissolved in dry CH_2Cl_2 (5 mL/mmol allyl vinyl ether) in a round bottom flask under an atmosphere of argon. After 5 min of stirring, pulverized and activated 4 Å molecular sieves (250 mg/mmol ave) was added. After an additional 5 min of stirring, a solution of the allyl vinyl ether in dry CH_2Cl_2 (5 mL/mmol ave) 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 a 20/1 mixture of heptane and ethyl acetate. The molecular sieves were removed subsequently by filtration and the filtrate was filtered again, then through a 4×0.5 cm plug of silica gel in order 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 **2c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.41 (ddd, $J = 17.0, 10.0, 7.1$ Hz, 1H), 5.14 (sept, $J = 6.3$ Hz, 1H), 5.09–5.04 (m, 1H), 5.02 (s, 1H), 3.28 (qdd, $J = 13.5, 7.3$ Hz, 1H), 2.39–2.51 (m, 1H), 2.09–2.21 (m, 1H), 1.34 (d, $J = 6.2$ Hz, 3H), 1.33 (d, $J = 6.4$ Hz, 6H), 1.13 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 197.7, 161.4, 134.7, 117.4, 70.4, 41.8, 36.0, 21.5, 14.8; IR (in substance) 2980–2940, 1720; $[\alpha]_D^{25}$ (3*S*)-**2c** −23, (*c* 1.52, $CHCl_3$, 95% ee), $[\alpha]_D^{25}$ (3*R*)-**2c** +24, (*c* 1.90, $CHCl_3$, 97% ee); analyt. GC (50 m × 0.25 mm hydrodex (*R*)-β-6-TBDM (heptakis-(6-*O*-*tert*-butyl-2,3-di-*O*-methyl)-β-cyclodextrine), 65 °C) R_t (3*S*)-**2c**=76.2 min, R_t (3*R*)-**2c**=74.7 min; Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.22; H, 8.84.
9. **2d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64–7.57 (m, 4H), 7.46–7.33 (m, 6H), 5.44 (ddt, $J = 17.1, 10.2, 7.0$ Hz, 1H), 5.11 (sept, $J = 6.3$ Hz, 1H), 5.03–4.93 (m, 2 H), 3.88 (d, $J = 5.8$ Hz, 2H), 3.59 (dt, $J = 12.9, 6.5$ Hz, 1H), 2.51–2.40 (m, 1H), 2.32–2.20 (m, 1H), 1.32 (d, $J = 6.2$ Hz, 3H), 1.31 (d, $J = 6.2$ Hz, 3H), 1.00 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 196.1, 184.5, 161.0, 135.6, 134.6, 133.1, 129.8, 127.7, 117.2, 70.5, 63.7, 49.8, 31.6, 26.7, 21.6, 19.2; IR (in substance) 3070–2860, 1720, 1470, 1425 cm^{-1}; $[\alpha]_D^{25}$ (3*S*)-**2d** −14, (*c* 1.02, $CHCl_3$, 98% ee), $[\alpha]_D^{25}$ (3*R*)-**2d** +15, (*c* 0.95, $CHCl_3$, 99% ee); analyt. HPLC (Chiracel OD 14052, flow 1 mL/min, 99.5% *n*-hexane/0.5% *iso*-propanol) R_t (3*S*)-**2d**=5.2 min, R_t (3*R*)-**2d**=4.7 min; Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 71.01, H, 7.84.
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