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The $Cu(OTf)_2$- and $Yb(OTf)_3$-Catalyzed Claisen Rearrangement of 2-Alkoxycarbonyl-Substituted Allyl Vinyl Ethers

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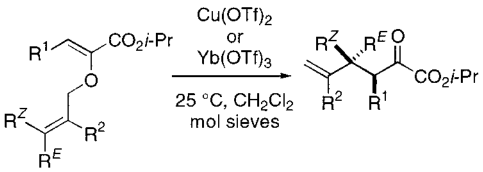
ABSTRACT



The $Cu(OTf)_2$- and $Yb(OTf)_3$-catalyzed Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers has been developed. Reactivity and stereoselectivity strongly depend on the substrate structure.

The development of catalytic enantioselective reactions plays a central role in current research efforts. In this regard, the Claisen rearrangement as one of the most powerful synthetic transformations has found only limited attention. Van der Baan and Bickelhaupt,[1] Nakai,[2] and our research group[3] have utilized a Pd(II)-catalyst to catalyze the Claisen Rearrangement of acyclic allyl vinyl ethers.[4] Very recently, Trost has shown that HoFOD can be used to catalyze the rearrangement of chiral aliphatic allyl vinyl ethers with very high efficiency.[5]

$Cu(OTf)_2$ and $Yb(OTf)_3$ in combination with the appropriate chiral ligands are useful Lewis acids for a number of catalytic enantioselective transformations.[6] As far as we know, neither $Cu(OTf)_2$ nor $Yb(OTf)_3$ has been used successfully to catalyze the Claisen rearrangement of aliphatic acyclic allyl vinyl ethers. Therefore, we set out to study the potential of $Cu(OTf)_2$ and of $Yb(OTf)_3$ in the catalysis of the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers. The purpose of this Letter is to describe our preliminary results concerning the nature of the catalyst system and the relationship between substrate structure, reactivity, and diastereoselectivity.

The 2-alkoxycarbonyl-substituted allyl vinyl ethers **1a−f** were synthesized by the application of our previously reported method.[7] The catalyzed Claisen rearrangement was performed by stirring a solution of an allyl vinyl ether (0.4 mmol) in dry CH_2Cl_2 (4 mL) at the appropriate temperature and in the presence of the catalyst and pulverized activated 3A molecular sieves (1 g/mmol).[8] We started our investigations with the *Z*,*E*-configured allyl vinyl ethers *Z*,*E*-**1a** and

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[2] Sugiura, M.; Nakai, T. *Chem. Lett.* **1995**, 697.
[3] Hiersemann, M. *Synlett* **1999**, *11*, 1823.
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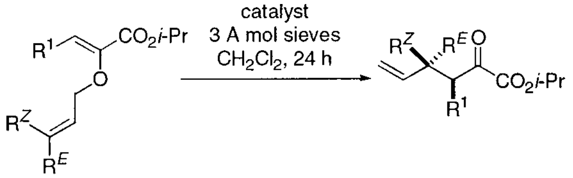
Z,*E*-**1c**. We were pleased to find that the presence of 5 mol % of $Cu(OTf)_2$ or of $Yb(OTf)_3$ led to complete transformation of the allyl vinyl ethers into the α-keto esters **2a** and **2c** (Table 1, entries 1, 2, 6, and 7). Unfortunately, the diastereoselectivities of the rearrangements were low and depended on the catalyst employed. The *anti*/*syn* preference was inverted by changing R^1 from Bn to *i*-Pr (Table 1, entries 1, 6 and 2, 7). The *Z*,*Z*-configured allyl vinyl ethers **1-a**,**c** surprisingly underwent the catalyzed rearrangement with high diastereoselectivities to give the *syn*-configured α-keto esters **2a**,**c** (Table 1, entries 3, 4, 5, 8, and 9). In these cases, to obtain complete product formation within the given reaction time, an increased catalyst loading was necessary. The variation of the amount of catalyst (from 1.25 mol % up to 10 mol %) did not alter the observed diastereoselectivities. Halogenated solvents (CH_2Cl_2, $CHCl_3$, CH_2ClCH_2Cl) and benzene were used without a significant change of reactivity and diastereoselectivity. Polar solvents (THF, DMF, acetonitrile) completely inhibited or decreased the rate of the catalysis of the rearrangement with $Yb(OTf)_3$.

Table 1. The Catalyzed Claisen Rearrangement



***Z*,*Z*-1a**	R^1= Bn, R^Z= *n*-Pr, R^E= H	***syn*-2a**
***Z*,*E*-1a**	R^1= Bn, R^Z= H, R^E= *n*-Pr	***anti*-2a**
***Z*,*Z*-1b**	R^1= Bn, R^Z= CH_2OBn, R^E= H	***syn*-2b**
***Z*,*E*-1c**	R^1= *i*-Pr, R^Z= H, R^E= *n*-Pr	***anti*-2c**
***Z*,*Z*-1c**	R^1= *i*-Pr, R^z= *n*-Pr, R^E= H	***syn*-2c**

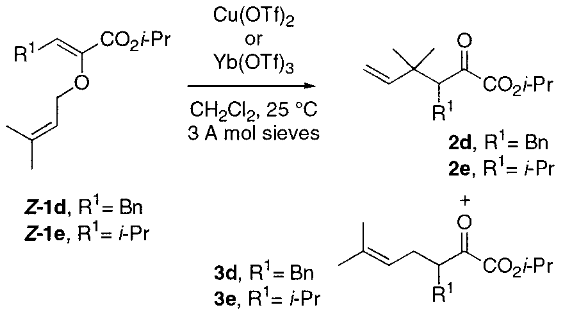
entry	substrate[a]	equiv of catalyst	*T* (°C)	yield (%)[b]	*syn*-**2**:*anti*-**2**[c]
1	*Z*,*E*-**1a** (96:4)	0.05 $Cu(OTf)_2$	25	99	22:71
2	*Z*,*E*-**1a** (96:4)	0.05 $Yb(OTf)_3$	25	99	34:66
3	*Z*,*Z*-**1a** (97:3)	0.05 $Cu(OTf)_2$	25	98	93:7
4	*Z*,*Z*-**1a** (97:3)	0.075 $Yb(OTf)_3$	25	99	96:4
5	*Z*,*Z*-**1b**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

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

Two experiments were performed in order to identify possible reasons for the low diastereoselectivities of the rearrangement of the *Z*,*E*-configured allyl vinyl ethers Z,*E*-**1a**,**c**. To exclude product epimerization, we stirred the α-keto ester *anti*-**2a** under the reaction conditions for the catalysis but observed no epimerization. *E*/*Z* isomerization of the enol ether double bond prior to the rearrangement could be a possible reason for the low diastereoselectivities. The enol ether *Z*-**4** (Figure 2) was stirred in the presence of the catalyst and molecular sieves, but we observed no enol ether double bond isomerization. Consequently, the low diastereoselectivities of the rearrangement of the *Z*,*E*-configured allyl vinyl ethers Z,*E*-**1a**,**c** should be a consequence of the rearrangement mechanism.

The *Z*,*Z*-configured allyl vinyl ether *Z*,*Z*-**1b** containing a benzyloxymethyl-substituted allyl ether double bond required 60 °C as reaction temperature and the presence of 10 mol % of $Yb(OTf)_3$ for a catalyzed rearrangement (Table 1, entry 5). A control experiment showed no rearrangement in the absence of the catalyst at 60 °C; 10 mol % of $Yb(OTf)_3$ or of $Cu(OTf)_2$ did not catalyze the rearrangement of *Z*,*Z*-**1b** at room temperature. Furthermore, $Cu(OTf)_2$ was inefficient as the catalyst even at 60 °C. Only 1.25 mol % of $Yb(OTf)_3$ or 5 mol % of $Cu(OTf)_2$ was necessary to catalyze the rearrangement of the allyl vinyl ether *Z*-**1d** (Table 2, entries 1 and 2). A very small amount of the corresponding [1,3]-rearrangement product could be detected. A significant amount of the [1,3]-rearrangement product was formed when the allyl vinyl ether *Z*-**1e** was treated with 5 mol % of Yb-$(OTf)_3$ ([3,3]:[1,3] = 4:1) (Table 2, entry 3). Employing 5 mol % of $Cu(OTf)_2$ as the catalyst for the same substrate *Z*-**1e** led to incomplete product formation (Table 2, entry 4).

Table 2. The Catalyzed Claisen Rearrangement



entry	substrate[a]	equiv of catalyst	yield (%)[b]	**1**:**2**:**3**[c]
1	*Z*-**1d** (97:3)	0.0125 $Yb(OTf)_3$	99	0:97:3
2	*Z*-**1d** (97:3)	0.05 $Cu(OTf)_2$	99	0:94:6
3	*Z*-**1e** (95:5)	0.05 $Yb(OTf)_3$	95	0:80:20
4	*Z*-**1e** (95:5)	0.1 $Cu(OTf)_2$	78	21:57:22

[a] In parentheses: *Z*/*E* ratio of the enol ether double bond. [b] Isolated material after filtration through a 4 × 0.5 cm silica gel column. [c] Determined by ^1H NMR spectroscopy.

Finally, we investigated the reactivity of the allyl vinyl ether *Z*-**1f**. Unfortunately, neither $Yb(OTf)_3$ nor $Cu(OTf)_2$

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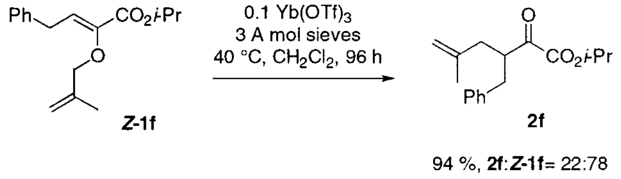
(8) **General procedure:** The allyl vinyl ether (4 mmol) was dissolved in dry CH_2Cl_2 (4 mL) under argon. Activated 3A molecular sieves (400 mg) and the catalyst (used as purchased) were added. The reaction mixture was stirred under argon for 24 h at the appropriate temperature. The molecular sieves were then removed by filtration. The solvent was then evaporated at reduced pressure. The crude product was then dissolved in heptane/ethyl acetate (1/1) and filtered through a 4 × 0.5 cm silica gel column. The solvent was then removed to afford the product as a colorless oil. The composition of the product was analyzed by ^1H and ^{13}C NMR spectroscopy. Commercially available 3A molecular sieves were activated by drying for several hours at 250 °C and at 5×10^{-2} mbar. Prior to use, they were stored at 200 °C.

was useful as catalysts for the Claisen rearrangement of this substrate. Mainly starting material *Z*-**1f** was isolated after stirring at 40 °C for 96 h in the presence of 10 mol % of $Yb(OTf)_3$ (Scheme 1). At 60 °C, the noncatalyzed thermal Claisen rearrangement becomes a significant side reaction.

Scheme 1



The available experimental data indicate a critical influence of the substitutent pattern at the allyl ether double bond. The substitution pattern determines the reactivity in the catalyzed rearrangement, and the double bond configuration is of pivotal importance for the observed diastereoselectivities. We propose the following mechanism for the catalyzed Claisen rearrangement in order to explain the different diastereoselectivities which we observed for the catalyzed rearrangement of the *Z*,*E*- and *Z*,*Z*-configured allyl vinyl ethers **1a**,**c** (Figure 1). We suggest that the Cu(II) or Yb(III) is coordinated between the ether and the carbonyl oxygen atom.[9] The ether bond would heterolytically be broken to generate an ion pair between the α-keto ester enolate and the corresponding allyl cation.

The rate of C−C-bond formation should then depend on the steric hindrance between the substituents at the two trigonal carbon atoms which approach each other for the C−C-bond formation. Therefore, the formation of the *syn*-**2a**,**c** diastereomer through the **ap-IP**, which features the R^1 and *n*-Pr substituents in an antiperiplanar arrangement, could be faster than the formation of the *anti*-**2a**,**c** diastereomer through the **sc-IP** (R^1 and *n*-Pr synclinal). The **sc-IP** and **ap-IP** could equilibrate by a C−C-bond rotation in the allylic cation.[10] Therefore, it might be feasible to explain the low diastereoselectivities of the catalyzed rearrangement of *Z*,*E*-**1a**,**c** by an equilibration of the corresponding allylic cations in the ion pairs **sc-IP** and **ap-IP**.[11]

This model of a stepwise rearrangement through an ion pair also accounts for the increased *syn* diastereoselectivity of the rearrangement of *Z*,*E*-**1c** (R^1 = *i*-Pr) in comparison to the rearrangement of *Z*,*E*-**1a** (R^1 = Bn). Increasing bulk of R^1 decreases the rate of the C−C-bond formation through **sc-IP** and facilitates the transition state equilibration which leads to increased amounts of *syn*-**2c**. The catalyzed rearrangement of the *Z*,*Z*-configured allyl vinyl ethers *Z*,*Z*-**1a**,**b**,**c** is realized with high diastereoselectivities through the more favorable **ap-IP** ion pair.

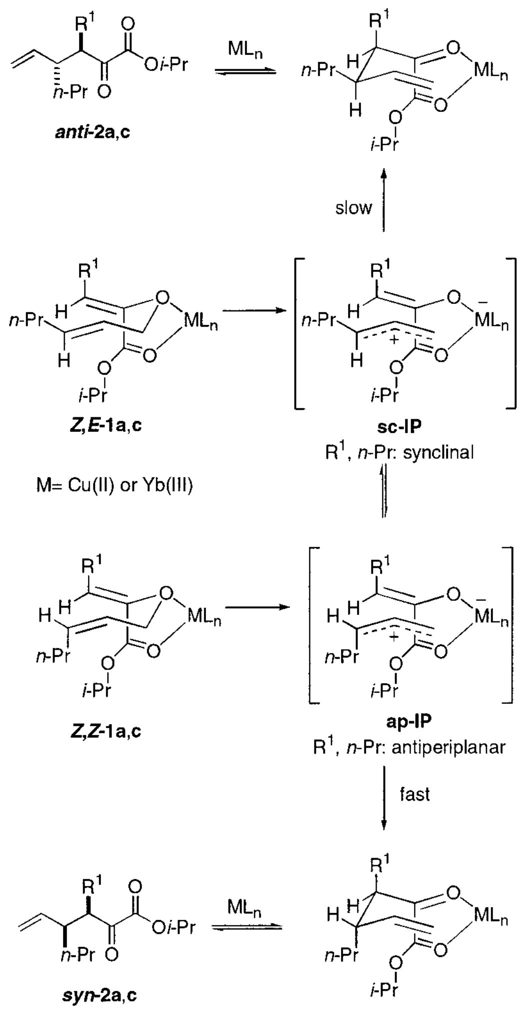


Figure 1. Suggested catalysis mechanism. The rearrangement of *Z*,*E*-**1a**,**c** leads to the formation of *syn*/*anti*-**2a**,**c** mixture, possibly through an equilibration of the allylic cations **sc-IP** and **ap-IP**.

The difference in the reactivity of the studied allyl vinyl ethers can be explained on the basis of the corresponding ion pair structures (Figure 2). The catalyzed Claisen rearrangement of the allyl vinyl ether *Z*,*Z*-**1b** would proceed through the *Z*,*Z*-**1b-IP** ion pair. The benzyloxymethyl substituent presumably destabilizes the allylic cation. Therefore, the rearrangement requires elevated reaction temperatures in comparison to the rearrangement of the allyl vinyl ethers *Z*,*Z*-**1a**,**c**. The enhanced reactivity of the allyl vinyl ether *Z*-**1d** is a consequence of a more stable allylic cation in the ion pair *Z*-**1d-IP**. The catalyzed rearrangement of the allyl vinyl ether *Z*-**1e** led to significant amounts of [1,3]-rearrangement

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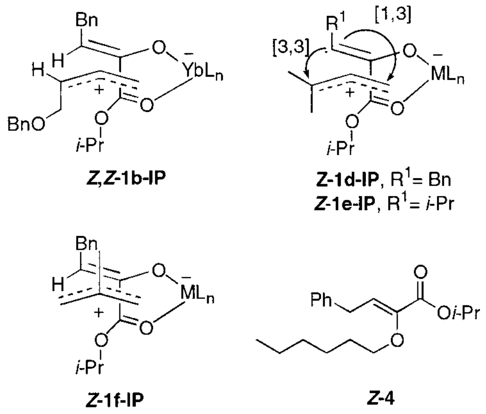
(9) For the coordination of Cu(II)-species to α-thio acrylates, see ref 5i.

(10) For rates of allyl cation isomerization, see: (a) Schleyer, P. v. R.; Su, T. M.; Saunders, M.; Rosenfeld, J. C. *J. Am. Chem. Soc.* **1969**, *91*, 5174. (b) Demo, N. C.; Haddon, R. C.; Nowak, E. N. *J. Am. Chem. Soc.* **1970**, *92*, 6691. (c) Allinger, N. L.; Siefert, J. H. *J. Am. Chem. Soc.* **1975**, *97*, 752.

(11) Assuming a concerted rearrangement, a boatlike transition state for the catalyzed Claisen rearrangement of *Z*,*E*-**1a**,**c** could also account for the formation of the *syn*-**2a**,**c** diastereomer. We found that the thermal Claisen rearrangement of *Z*,*E*-**1a** led to the exclusive formation of *anti*-**2a** whereas *Z*,*Z*-**1a** afforded *syn*-**2a**. Therefore, we conclude that the thermal rearrangement proceeds exclusively through chairlike transition states. To accept a boatlike transition state for the catalyzed Claisen rearrangement of *Z*,*E*-**1a**,**c**, it would be necessary to explain why the presence of Cu(II) or Yb(III) opens access to a boatlike transition state at room temperature for the rearrangement of *Z*,*E*-**1a**,**c**. Further experiments to clarify the mechanism of the catalyzed Claisen rearrangement are currently underway.



***Z*,*Z*-1b-IP**

***Z*-1d-IP**, R^1= Bn
***Z*-1e-IP**, R^1= *i*-Pr

***Z*-1f-IP**

***Z*-4**

Figure 2. Suggested ion pair structures **1b**−**f**-**IP** of the catalyzed Claisen rearrangement. Reactivity and regioselectivity as a consequence of steric and electronic factors. Enol ether double bond isomerization in *Z*-**4** in the presence of the catalyst was not obtained.

product in comparison to the rearrangement of the allyl vinyl ether *Z*-**1d**. This result can be explained by an increased steric bulk of the *i*-Pr group in comparison to the Bn group. That makes an attack at the less substituted carbon atom of the allylic cation more favorable. The reluctance of the methallyl vinyl ether *Z*-**1f** to undergo Claisen rearrangement could be the consequence of a less stable allylic cation in the ion pair *Z*-**1f**-**IP**.

In conclusion, the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers may be catalyzed by Cu(OTf)$_2$ and by Yb(OTf)$_3$ in the presence of 3A molecular sieves. Reactivity and stereoselectivity strongly depend on the substrate structure. Optimization of the catalyst concentration is necessary for each individual substrate. We suggest a stepwise reaction mechanism through an ion pair intermediate to explain the observed reactivity and stereoselectivity.

Further work is in progress to study other efficient catalysts and to investigate the catalytic asymmetric Claisen rearrangement.

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Supporting Information Available: Experimental procedures, characterization data of compounds *syn*-**2a**−**c** and **2d**, and selected copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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