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Gosteli−Claisen Rearrangement: Substrate Synthesis, Simple Diastereoselectivity, and Kinetic Studies

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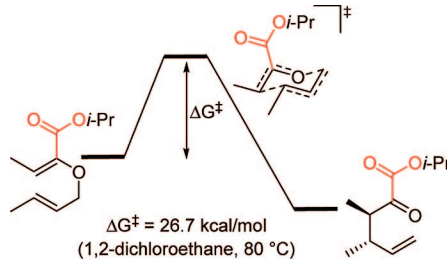

The results of kinetic studies on the uncatalyzed [3,3]-sigmatropic rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers are reported. Apparently first reported by Gosteli in 1972, this variation of a Claisen rearrangement enjoyed a shadowy existence for three decades until its potential for the development of a catalytic asymmetric Claisen rearrangement was discovered. Inspired by this development, we have studied substituent and solvent rate effects, and we provide evidence that a chairlike transition state is highly favorable for the uncatalyzed Gosteli−Claisen rearrangement.

Introduction

Aliphatic Claisen rearrangements are thermally allowed [3,3]-sigmatropic rearrangements of allyl vinyl ethers to γ,δ-unsaturated carbonyl compounds. The rearrangement is characterized by a concerted but asynchronous bond reorganization process via a cyclic, usually chairlike transition-state structure.[1−3] Substituent and solvent rate effects have been quantified by first-order kinetic studies.[4] Furthermore, a fairly large number of studies during the past two decades have been concerned with the elucidation of the mechanistic details of Claisen rearrangements by computational methods. Important topics have been studied at various levels of theory: (i) diradicaloid or dipolar character of the transition-state structure,[5] (ii) extension of bond making and bond breaking in the transition state structure,[5b,e,6] (iii) geometry of the transition-state structure,[5b,7] and (iv) substituent[5c,8] and solvent[8b,9] effects on the nature of the transition-state structure. Historically, the aliphatic Claisen rearrangement has been classified according to the substrate structure (Figure 1). Many of these Claisen rearrangements are named reactions and possess significant synthetic importance.[10,11]

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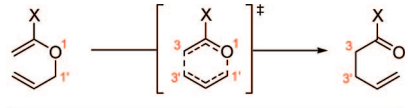
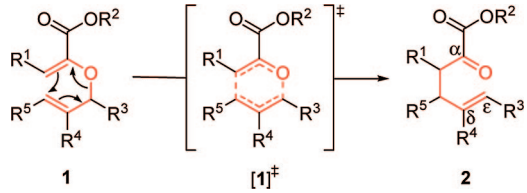


X	variant	reference 10
H	Claisen	a
C	Claisen	b
CO_2R	Gosteli-Claisen	c
OH	Carroll-Claisen	d
OMetal	Arnold-Claisen	e
NR_2	Eschenmoser-Claisen	f
OR	Johnson-Claisen	g
$OSiR_3$	Ireland-Claisen	h

FIGURE 1. Classification of aliphatic Claisen rearrangements.

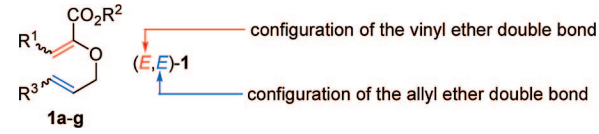
SCHEME 1. Claisen Rearrangement of 2-Alkoxycarbonyl-Substituted Allyl Vinyl Ethers



Each variant is characterized by the substrate synthesis, the rate range of the rearrangement, and the structure of the product. The Claisen rearrangement of acyclic 2-alkoxycarbonyl-substituted allyl vinyl ethers (**1**) to δ,ϵ-unsaturated α-keto esters (**2**) has so far found very limited attention (Scheme 1). The original study of Gosteli was followed by only isolated reports in the literature.[12] The first kinetic study on the Gosteli−Claisen rearrangement by Gajewski and co-workers was performed in the context of the chorismate-mutase research field.[4g] A general synthetic access to acyclic 2-alkoxycarbonyl-substituted allyl vinyl ethers was published in 2000,[13] and the first Lewis acid catalyzed Gosteli−Claisen rearrangement was revealed shortly thereafter.[14] Subsequent studies led to the discovery of efficient chiral Lewis acid catalysts and organocatalysts for enantioselective Gosteli−Claisen rearrangements.[15−17]

Here, we report an experimental study on the uncatalyzed Gosteli−Claisen rearrangement. Various 2-alkoxycarbonyl-substituted allyl vinyl ether **1** have been synthesized and pyrolized to provide product diastereoselectivities and activation parameters which enable us to draw conclusions about substituent and solvent rate effects as well as the stereochemical course of the Gosteli−Claisen rearrangement.

TABLE 1. Structure of Allyl Vinyl Ethers (TPS = *t*-$BuPh_2Si$, Bn = CH_2Ph)



compd	R^1	R^2	R^3
1a	H	Me	H
1b	H	*i*-Pr	H
(*E*)-**1c**	Me	*i*-Pr	H
(*Z*)-**1c**[17]	Me	*i*-Pr	H
(*E*)-**1d**	CH_2OTPS	*i*-Pr	H
(*Z*)-**1d**	CH_2OTPS	*i*-Pr	H
(*Z*)-**1e**	Me	H	H
(*Z*)-**1f**	Me	CH_2CF_3	H
(*E*,*E*)-**1g**	Me	*i*-Pr	Me
(*Z*,*E*)-**1g**	Me	*i*-Pr	Me
(*E*,*Z*)-**1g**	Me	*i*-Pr	Me
(*Z*,*Z*)-**1g**	Me	*i*-Pr	Me
(*Z*,*E*)-**1h**[13]	Me	*i*-Pr	*n*-Pr
(*E*,*Z*)-**1i**[31]	Me	Me	CH_2OBn
(*Z*,*Z*)-**1i**[31]	Me	Me	CH_2OBn

Results and Discussion

Allyl Vinyl Ether Synthesis. The allyl vinyl ethers **1a−i** utilized to study the simple (*syn*/*anti*) diastereoselectivity and the kinetics of the Gosteli−Claisen rearrangement are illustrated in Table 1. Synthesis of **1c** and **1g** could be accomplished in a concise manner as outlined in Scheme 2. Hydrometalation/protonation or hydrogenation of 2-butyn-1-ol provided (*E*)- or (*Z*)-2-buten-1-ol (**3**).[18] Subsequent etherification of the allylic alcohols **3** and **4** with bromoacetic acid afforded the α-allyloxy acetates **5** and **6**, which were converted to the isopropyl esters **7** and **8** utilizing Steglich's conditions.[19] Treatment of the esters **7** and **8** with LDA and freshly distilled acetaldehyde afforded the β-hydroxy esters **9** and **10**,[20] which were mesylated and

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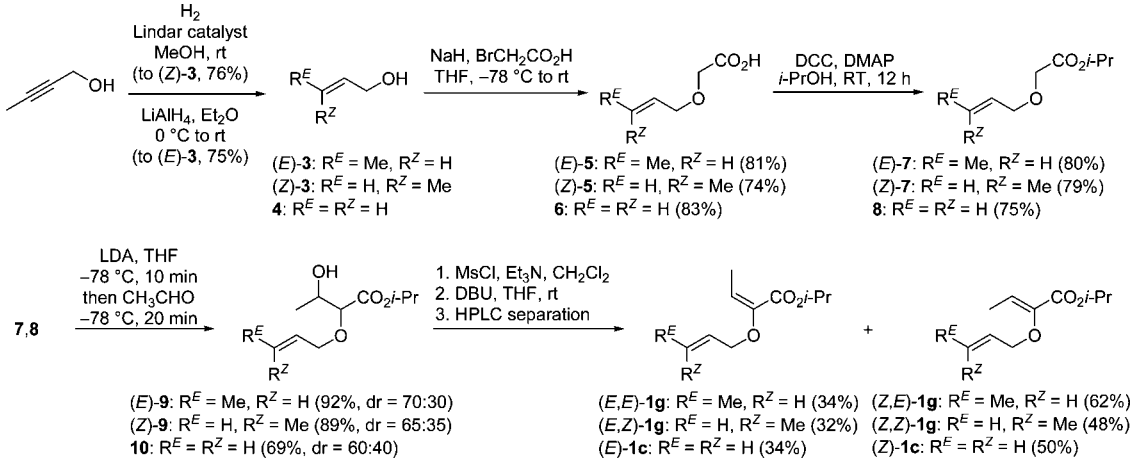
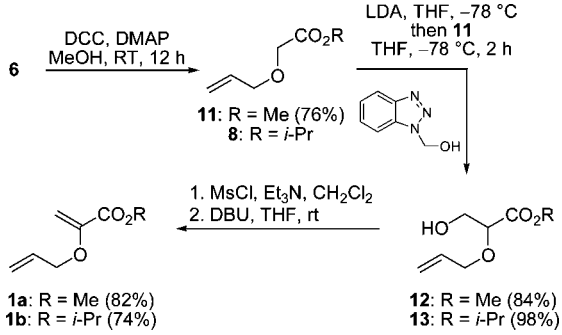
(20) Isolated as inseparable mixtures of diastereomers. The relative configuration of the major and minor diastereomer was not assigned.

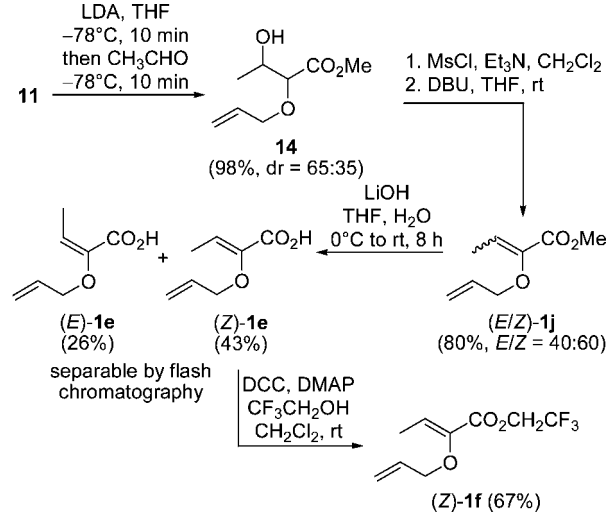
SCHEME 2. Synthesis of the Allyl Vinyl Ethers 1c,g



SCHEME 3. Synthesis of the Allyl Vinyl Ethers 1a,b



SCHEME 4. Synthesis of the Allyl Vinyl Ethers 1e,f



subsequently treated with DBU to provide the allyl vinyl ether **1c**,**g** as a mixture of double-bond isomers. Separation of the *E*/*Z*-diastereomers was accomplished by automated preparative HPLC on multigram scale.

The synthesis of **1a**,**b** required the hydroxymethylation of the ester enolate of **11** to provide the β-hydroxy esters **12** and **13** (Scheme 3).[21] After some experimentation with gaseous formaldehyde, we found the application of a procedure reported by Bischoff and co-workers more convenient and high yielding.[22] In the event, commercially available benzotriazolylmethanol was used for the in situ formation of formaldehyde. The synthesis of the unsubstituted parent allyl vinyl ether **1a**,**b** for the Gosteli−Claisen rearrangement was completed in two steps with the mesylation of the β-hydroxy esters **12** and **13** and base-mediated elimination of the crude mesylates.

The carboxyl-substituted allyl vinyl ether (*Z*)-**1e** was synthesized according to Scheme 4. (*E*/*Z*)-**1j** was prepared by the aldol condensation approach and subsequently treated with LiOH in a polar protic solvent system to afford the carboxylic acid (*E*/*Z*)-**1e**. Because of the well-established rate acceleration of the Claisen rearrangement in aqueous solution, the success of the saponification is noteworthy.[23] To avoid the undesired Claisen rearrangement of **1j**,**e**, particularly at prolonged reaction times, the progress of the reaction was carefully monitored by Tlc, and using optimized reaction times, the allyl vinyl ether **1e** was isolated in good yields. Notably, the double-bond isomers of **1e** were separable by flash chromatography, and (*Z*)-**1e** was then elaborated to the 2,2,2-trifluoroethyl ester (*Z*)-**1f** as described above. This route provides a strategically novel and expeditious access to carboxyl-derived functional groups at the 2-position of allyl vinyl ethers.

We have been able to prepare functionalized allyl vinyl ethers (**1**) by employing the aldol condensation approach.[16] In the present study, the aldol reaction between the lithium enolate of **8** and a siloxyacetaldehyde delivered the β-hydroxyester **15** which was further elaborated to the 1-siloxymethyl-substituted allyl vinyl ether **1d** (Scheme 5).

Simple Diastereoselectivity. The uncatalyzed Claisen rearrangement of achiral allyl vinyl ethers containing two stereogenic double bonds provides racemic γ,δ-unsaturated carbonyl compounds featuring two chiral carbon atoms. The relative configuration of the rearrangement products depends on the geometry of the corresponding transition-state structures (chair versus boat) as well as the double-bond configuration of the allyl vinyl ethers. Experimental results indicate a strong preference for a chairlike transition-state structure for the Claisen rearrangement of acyclic, aliphatic allyl vinyl ethers;[3] however, an unambiguous and general verification of this observation was not available for the Gosteli−Claisen rearrangement. Therefore, **1g**−**i** were pyrolized, and the *syn*/*anti* diastereoselectivities of the rearrangement were determined (Table 2). The rearrange-

(21) Care must be taken during the purification and isolation of the allyl vinyl ether **1a** and **1b** because of their volatility at reduced pressure.

(22) Deguest, G.; Bischoff, L.; Fruit, C.; Marsais, F. *Org. Lett.* **2007**, *9*, 1165–1167.

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SCHEME 5. Synthesis of the Allyl Vinyl Ether 1d (TPS = *t*-BuPh$_2$Si)

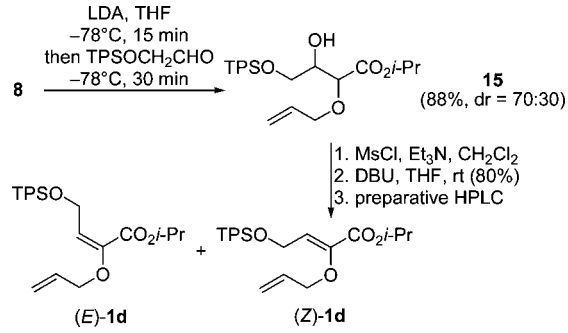
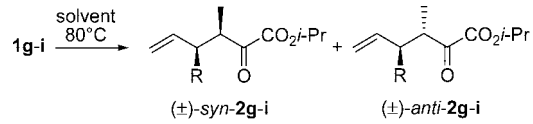


TABLE 2. Simple Diastereoselectivity of the Gosteli–Claisen Rearrangement



(±)-*syn*-**2g**-i (±)-*anti*-**2g**-i

entry	substrate	R	main product	solvent[a]	*syn*/*anti*[b]	yield [%][c]
1	(*E*,*E*)-**1g**	Me	(±)-*syn*-**2g**	DCE	>95/5	95
2	(*Z*,*E*)-**1g**	Me	(±)-*anti*-**2g**	DCE	97/3	96
3	(*E*,*Z*)-**1g**	Me	(±)-*anti*-**2g**	DCE	>95/5	95
4	(*Z*,*Z*)-**1g**	Me	(±)-*syn*-**2g**	DCE	>95/5	90
5	(*Z*,*E*)-**1h**	*n*-Pr	(±)-*anti*-**2h**	DCE	97/3	99
6	(*E*,*Z*)-**1i**	CH_2OBn	(±)-*anti*-**2i**	TFE	95/5	99
7	(*Z*,*Z*)-**1i**	CH_2OBn	(±)-*syn*-**2i**	TFE	95/5	95

[a] DCE = 1,2-dichloroethane, TFE = 2,2,2-trifluoroethanol. [b] Determined from ^{1}H NMR spectra. >95/5 = minor diastereomer not detectable. [c] Yield of isolated and purified material.

ment of the **1g** and **1h** proceeded in 1,2-dichloroethane (DCE) at 80 °C with a reasonable reaction rate (Table 2, entries 1–5) but was very slow for **1i**. We hoped to take advantage of the rate accelerating effect of polar protic solvents on the Claisen rearrangement,[4h] and a useful rate for the rearrangement of **1i** was finally achieved in 2,2,2-trifluoroethanol (TFE) at 80 °C (Table 2, entries 6 and 7). Generally, we obtained a complete mass balance and very high diastereoselectivities (≥95/5) for the uncatalyzed Gosteli–Claisen rearrangement of **1g–i**. Significant impurities were not detectable; the product diastereomers *syn*- and *anti*-**2g–i** are distinguishable in the ^{1}H NMR. The assignment of the relative configuration of *syn*-**2g** and *syn*-**2i** was corroborated by crystal structure analyses of synthetic derivatives.[24] The observed diastereoselectivities correspond to a difference in free energy ($\Delta\Delta G^{\ddagger}_{\text{chair/boat}}$) of ≥2.2 kcal/mol between the chair- and the boatlike transition states at 80 °C, a value that correlates well with the $\Delta\Delta G^{\ddagger}_{\text{chair/boat}}$ reported for the uncatalyzed Claisen rearrangement of crotyl propenyl ethers in heptane at 143 °C (2.9–3.1 kcal/mol, depending on the double-bond configuration).[3a]

Kinetic Studies. Kinetic measurements were conducted in a sealed glass tube. The degree of conversion was determined by ^{1}H NMR from the crude reaction mixture. The collected NMR data fitted to a first-order rate law over several half-life periods. No products other than the α-keto esters **2** could be detected. The first-order rate constants were determined from double experiments and analyzed according to the Arrhenius and the Eyring equations to provide the activation parameters. The experimentally determined rate constants (k) and free energies of activation ($\Delta G^{\ddagger}$) at 80 °C are summarized in Tables 3 and 4. For comparison, the kinetic parameters for the Claisen rearrangement of allyl vinyl ether (Table 3, entry 1) and the four double-bond isomers of crotyl propenyl ether **16** (Table 4, entries 2, 4, 6, and 8) are also included. The accuracy of the experimentally determined activation parameters is supported by the resemblance of our $\Delta G^{\ddagger}$ value for **1a** and the value reported by Gajewski and co-workers (Table 3, entries 2 and 3).

We elected to initially determine the substituent rate effect of an ester group at the 2-position of an allyl vinyl ether (Table 3, entries 1–3). The 2-CO_2Me substituent in **1a** lowers the activation barrier by 2.7 kcal/mol at 80 °C; this corresponds to a 35-fold rate acceleration compared to the unsubstituted allyl vinyl ether. Replacing the methyl ester (**1a**) by an isopropyl ester (**1b**) has only a small effect on the rate of the rearrangement (Table 3, entries 3 and 4). We next investigated the rate effect of an additional methyl substituent at the vinyl ether double bond and the influence of the double-bond configuration (Table 3, entries 5–10). For (*E*)-**1c**, the methyl substituent causes a rate-accelerating effect in benzene-d_6 (k_{rel} = 3.2) and 1,2-dichloroethane (DCE, k_{rel} = 4.8) compared to **1b**. For (*Z*)-**1c**, the rate-accelerating effect is attenuated but still evident for the rearrangement in DCE (k_{rel} = 1.3) and CD_3CN (k_{rel} = 1.6). The significant rate accelerating influence of TFE (k_{rel} = 15.2) on the Gosteli–Claisen rearrangement of (*Z*)-**1c** is remarkable (Table 3, entry 10).[25,26] In order to evaluate the responsiveness of the k_{rel} to the steric bulk of the substituent at C1 and the double-bond configuration, the methyl group (**1c**) was replaced by the *t*-BuPh$_2$SiOCH$_2$ group (**1d**). Somewhat surprisingly, we determined identical $\Delta G^{\ddagger}$ values for the rearrangement of (*E*)-**1d** and (*E*)-**1c** in DCE at 80 °C (Table 3, entries 6 and 11). Even more surprising was our finding that (*Z*)-**1d** (k_{rel} = 8.6) rearranges faster than (*E*)-**1d** (k_{rel} = 4.8) and (*E*)-**1c** (k_{rel} = 4.8) in DCE (Table 3, entries 6, 11, and 12). This result is difficult to interpret because intrinsic ground- or transition-state stabilizing or destabilizing effects of the substituents may be responsible. Therefore, the rate effects cannot be predicted or explained based solely on conventional resonance or steric effects. We next turned our attention to the influence of the nature of the ester alcohol on the rate of the rearrangement (Table 3, entries 13–15). We expected that a $CO_2CH_2CF_3$ substitutent should affect the rate of the rearrangement because of the electron withdrawing effect of the CF_3 group. However, a significant rate difference for the rearrangement of the trifluoroethyl ester (*Z*)-**1f** (k_{rel} = 2.1) and the isopropyl ester (*Z*)-**1c** (k_{rel} = 2.7) in CD_3CN at 80 °C was not observed (Table 3, entries 9 and 15). Consequently, and considering the results of a computational work (BLYP/6-31G*) by Houk and Wiest,[27] we expected a comparable reactivity of the acid (*Z*)-**1e** and the ester (*Z*)-**1c**. However, the acid (*Z*)-**1e** was more reactive than the ester (*Z*)-**1c** in DCE (k_{rel} = 11.4 versus 1.6) and CD_3CN (k_{rel} = 5.6 versus 2.7) (Table 3, entries 13, 14 versus 8, 9). Surprisingly, the more polar solvent CD_3CN (dielectric constant ϵ = 35.9) has a rate

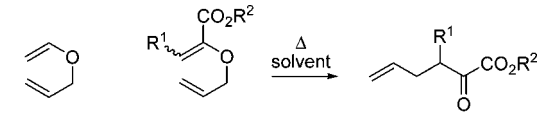
(24) (a) Gille, A.; Schürmann, M.; Preut, H.; Hiersemann, M. *Acta Crystallogr.* **2008**, *E64*, o1835. (b) Körner, M.; Schürmann, M.; Preut, H.; Hiersemann, M. *Acta Crystallogr.* **2008**, *E63*, o3012.

(25) A 25-fold rate acceleration in TFE compared to benzene has been experimentally determined for a Claisen rearrangement, see: Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515–516.

(26) Strassner and co-workers have calculated a gas-phase $\Delta G^{\ddagger}$ for (*Z*)-**1c** of 27.4 kcal/mol at the DFG B3LYP/6-311++G** level of theory; see ref 17. This value is in very good agreement with our experimentally determined values in benzene-d_6 (28.1 kcal/mol) or DCE (27.9 kcal/mol).

(27) Wiest, O.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 11628–11639.

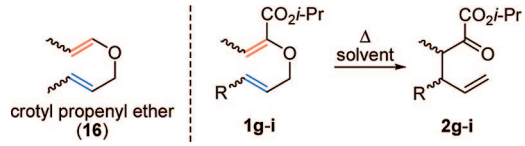
TABLE 3. Kinetic Data for the Costeli−Claisen Rearrangement of Disubstituted Allyl Vinyl Ethers at 80 °C (TPS = *t*-BuPh$_2$Si).



entry	compd	R^1	R^2	solvent[a]	T^b (°C)	$\Delta G^{\ddagger c}$	k^d	k_{rel}
1	parent[e]			C_6D_6	118−153	30.7	0.07	0.03
2	**1a**[f]	H	Me	CCl_4	41−80	28.0	3.4	1.4
3	**1a**	H	Me	C_6D_6	60−80	28.0	3.4	1.4
4	**1b**	H	*i*-Pr	C_6D_6	71−103	28.2	2.5	1
5	(*E*)-**1c**	Me	*i*-Pr	C_6D_6	60−90	27.4	7.9	3.2
6				DCE	60−100	27.1	12.1	4.8
7	(*Z*)-**1c**	Me	*i*-Pr	C_6D_6	60−90	28.1	2.9	1.2
8				DCE	80−100	27.9	3.4	1.3
9				CD_3CN	70−100	27.5	3.9	1.6
10				TFE	55−82	26.3	38.0	15.2
11	(*E*)-**1d**	CH_2OTPS	*i*-Pr	DCE	66−92	27.1	12.1	4.8
12	(*Z*)-**1d**	CH_2OTPS	*i*-Pr	DCE	66−94	26.7	21.5	8.6
13	(*Z*)-**1e**	Me	H	DCE	70−100	26.5	28.6	11.4
14				CD_3CN	70−91	27.0	14.0	5.6
15	(*Z*)-**1f**	Me	CH_2CF_3	CD_3CN	72−103	27.7	5.2	2.1

[a] DCE = 1,2-dichloroethane, TFE = 2,2,2-trifluoroethanol. [b] Temperature range of the kinetic measurements (temperature fluctuation ± 1 °C). [c] kcal mol^{-1} at 353.15 K. Determined from the Eyring plot and adjusted to one decimal place. [d] × 10^{-5} s^{-1} at 353.15 K. Calculated according to the Eyring equation and adjusted to one decimal place. [e] All-hydrogen-substituted, parent allyl vinyl ether. Value taken from ref 4i. [f] Value taken from ref 4i.

TABLE 4. Kinetic Data for the Costeli−Claisen Rearrangement of Trisubstituted Allyl Vinyl Ethers at 80°C. See Table *2* for Simple Diastereoselectivities



entry	compd	R	solvent[a]	T^b (°C)	$\Delta G^{\ddagger c}$	k^d	k_{rel}[e]
1	(*E*,*E*)-**1g**	Me	DCE	60−90	26.7	21.5	8.6
2	(*E*,*E*)-**16**[f]		gas phase	nr	30.5	0.095	(17.2)
3	(*Z*,*E*)-**1g**	Me	DCE	60−80	27.2	10.5	4.2
4	(*Z*,*E*)-**16**[f]		gas phase	nr	31.5	0.029	(5.3)
5	(*E*,*Z*)-**1g**	Me	DCE	60−80	27.4	7.9	3.2
6	(*E*,*Z*)-**16**[f]		gas phase	nr	31.8	0.015	(2.7)
7	(*Z*,*Z*)-**1g**	Me	DCE	60−80	28.2	2.5	1
8	(*Z*,*Z*)-**16**[f]		gas phase	nr	32.5	0.0053	(1)
9	(*Z*,*E*)-**1h**	*n*-Pr	DCE	68−103	27.6	6.0	2.4
10	(*E*,*Z*)-**1i**	CH_2OBn	TFE	50−80	27.1	12.1	7.1
11			EtOH	50−80	27.7	5.2	2.3
12	(*Z*,*Z*)-**1i**	CH_2OBn	TFE	50−80	27.9	3.9	3.0
13			EtOH	50−80	28.5	1.7	1.0

[a] DCE = 1,2-dichloroethane, TFE = 2,2,2-trifluoroethanol. [b] Temperature range of the kinetic measurements (temperature fluctuation ± 1 °C). nr = not reported. [c] kcal mol^{-1} at 353.15 K. Determined from the Eyring plot and adjusted to one decimal place. [d] ×10^{-5} s^{-1} at 353.15 K. Calculated according to the Eyring equation and adjusted to one decimal place. [e] Values in parentheses refer only to the relative reactivity of **16**. [f] Value taken from ref 3a.

decelerating effect on the rearrangement of the acid (*Z*)-**1e** (k_{rel} = 5.6) compared to DCE (k_{rel} = 11.4, ϵ = 10.4), which is in contrast to the experimental result for the ester (*Z*)-**1c** (k_{rel} = 1.6 in CD_3CN and 1.3 in DCE). So far, we have determined predictable and, more interestingly, less predictable rate constants for the Gosteli−Claisen rearrangement of **1a**−**f**. To explain the unexpected reactivity of **1d** (*t*-BuPh$_2$SiOCH$_2$ at C1) and **1e** (CO_2H at C2) and the remarkable solvent effect of 2,2,2-trifluoroethanol, knowledge of the relative product and transition-state stability as well as the detailed nature of the transition-state structure is required. Computational studies at an adequate level of theory could contribute crucial structural and energetic data for the analysis of the experimentally observed substituent and solvent rate effects.

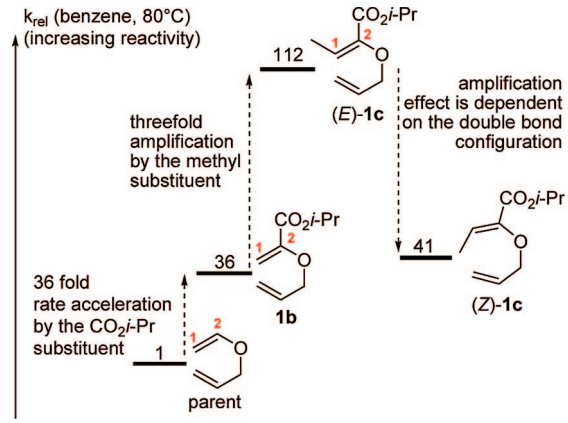


FIGURE 2. Substrate−reactivity relationship.

We expanded our kinetic study of the Gosteli−Claisen rearrangement to take trisubstituted allyl vinyl ethers into consideration. Table 4 summarizes the experimentally determined activation parameters for **1g**−**i**. For comparison, the reported kinetic data for crotyl propenyl ether (**16**) are included.[3a] We begin our discussion in reminiscence of some instructive results from Table 3. The relative rate constants enable a quantification of the rate effect of a CO_2i-Pr and a methyl group at the vinyl ether double bond. According to Figure 2, the CO_2i-Pr group has a significant rate accelerating influence which is further amplified by the additional methyl group in (*E*)-**1c**. The amplification effect is strongly dependent on the double-bond configuration, as (*Z*)-**1c** and **1b** show a comparable reactivity.

Using (*E*)-**1c** for comparison (k_{rel} = 1), the rate effect of a methyl at C6 was then studied and the results are illustrated in Figure 3. In the event, we found a small rate acceleration for

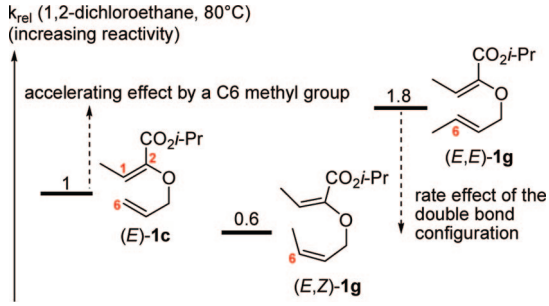


FIGURE 3. Substrate−reactivity relationship.

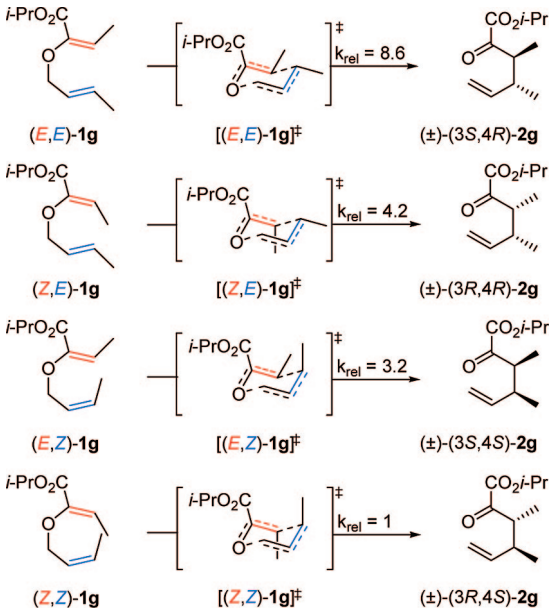


FIGURE 4. Qualitative transition-state model for the Gosteli−Claisen rearrangement of **1g**.

(*E*,*E*)-**1g** (k_{rel} = 1.8) and a small rate retardation for (*E*,*Z*)-**1g** (k_{rel} = 0.6) (Table 4, entries 1 and 5). A related statement is applicable for (*Z*)-**1c** (k_{rel} = 1) if compared to (*Z*,*E*)-**1g** (k_{rel} = 2.7) and (*Z*,*Z*)-**1g** (k_{rel} = 0.7) (Table 4, entries 3 and 7). These data support the conclusion that a C6 methyl group has a general rate accelerating effect, providing that the allylic ether double bond is *E*-configured.

We continued our study by comparing the relative reactivity of the double-bond isomers of **1g** (Table 4, entries 1, 3, 5, and 7). The experimentally determined substrate−reactivity relationship can be rationalized by a qualitative steric model that considers only the relative *stability* of the transition-state structures [**1g**]‡ to predict the relative *reactivity* of the corresponding substrates **1g** (Figure 4). Judging from the minimization of transanular interactions in the chairlike transition-state structure [**1g**]‡ as single qualitative criteria, [(*E*,*E*)-**1g**]‡ is the most stable transition state. The transition state structures [(*E*,*Z*)-**1g**]‡ and [(*Z*,*E*)-**1g**]‡ are less favorable because of the axial methyl group that causes 1,3-diaxial interactions. Therefore, (*E*,*Z*)-**1g** (k_{rel} = 3.2) and (*Z*,*E*)-**1g** (k_{rel} = 4.2) are less reactive than (*E*,*E*)-**1g** (k_{rel} 8.6). The slightly higher reactivity of (*Z*,*E*)-**1g** (k_{rel} = 4.2) compared to (*E*,*Z*)-**1g** (k_{rel} = 3.2) can be explained by the assumption that [(*E*,*Z*)-**1g**]‡ is less stable than [(*Z*,*E*)-**1g**]‡ due to the additional 1,3-diaxial interaction between the methyl and the CO_2i-Pr group. Unfavorable transanular 1,3-diaxial interactions are maximized in the transition state [(*Z*,*Z*)-**1g**]‡ and, therefore, (*Z*,*Z*)-**1g** is the least reactive (k_{rel} = 1) of

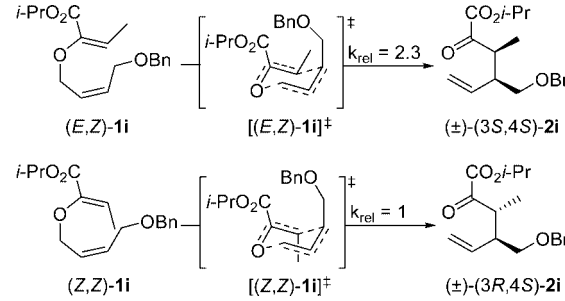


FIGURE 5. Qualitative transition-state model for the Gosteli−Claisen rearrangement of (*E*,*Z*)- and (*Z*,*Z*)-**1i**.

the allyl vinyl ethers **1g**. Although this simple qualitative analysis neglects the relative stability of substrates (**1g**) and products (**2g**) and does not account for the exact electronic nature of the transition state (polarization because of the asynchronous bond reorganization process) and solvent rate effects, it in fact predicts the relative reactivity of the four allyl vinyl ether **1g** correctly.

It is instructive to compare the kinetic data of **1g** with those of the crotyl propenyl ether **16** (Table 4, entries 1−8). Comparing the difference in the free energy of activation of allyl vinyl ethers with an identical double-bond configuration, the barrier for the Gosteli−Claisen rearrangement of **1g** is lower than for the Claisen rearrangement of **16** by 3.8−4.4 kcal/mol. The decreased barrier for the rearrangement of **1g** can be attributed to the substituent rate effect of the CO_2i-Pr group and the rate-accelerating solvent effect of DCE. The k_{rel} of the four crotyl propenyl ethers **16** obeys the same trend as observed for the Gosteli−Claisen rearrangement of **1g**. The analogy of k_{rel} for the (*Z*,*E*)-, (*E*,*Z*)-, and (*Z*,*Z*)-configured ethers **16** and **1g** is striking (Table 4, entries 3−6). However, the k_{rel} (8.6) of (*E*,*E*)-**1g** is less pronounced than the k_{rel} (17.2) for (*E*,*E*)-**16** (Table 4, entries 1 and 2). This discrepancy may be interpreted as experimental evidence for an increased "loosness" of the transition-state structure for the rearrangement of **1g** compared to **16**. A looser transition-state structure would attenuate transanular interactions and increase the relative reactivity of the allyl vinyl ethers that contain at least one *Z*-configured double bond.

We concluded our study by modifying the C6 substituent at the allylic ether double bond (Table 4, entries 9−13). Replacing the methyl group in (*Z*,*E*)-**1g** for a propyl group provides (*Z*,*E*)-**1h** (Table 4, entry 9). As anticipated for steric reasons, the propyl group has a rate decelerating effect ((*Z*,*E*)-**1h**: k_{rel} = 2.4) compared to the methyl group ((*Z*,*E*)-**1g**: k_{rel} = 4.3).[28] We further increased the steric bulk of the C6 substituent by introducing a $BnOCH_2$ group (Table 4, entries 10−13). In the event, we found that the rate of the rearrangement of (*E*,*Z*)- and (*Z*,*Z*)-**1i** in DCE was too slow to provide useful kinetic data. Therefore, the rate constants were experimentally determined in TFE and ethanol, again taking advantage of the rate accelerating effect of polar protic solvents. We than found in accordance with the simplified reactivity model discussed above, that (*E*,*Z*)-**1i** is more reactive than (*Z*,*Z*)-**1i** in TFE (k_{rel} = 7.1 versus 3.0) and ethanol (k_{rel} = 2.3 versus 1.0) (Figure 5). The relative reactivity of (*E*,*Z*)- and (*Z*,*Z*)-**1i** at 80 °C (k_{rel} = 2.3) is independent of the solvent and

(28) The $\Delta G^{\ddagger}$ (29.6 kcal/mol) for the uncatalyzed Gosteli−Claisen rearrangement of (*E*,*Z*)-**7h** was predicted at the IEFPCM(solvent = CH_2Cl_2)//B3LYP/6-31G* level of theory; see: Öztürk, C.; Balta, B.; Aviyente, V.; Vincent, M. A.; Hillier, I. H. *J. Org. Chem.* **2008**, *73*, 4800–4809.

corresponds well with the relative reactivity ($k_{rel} = 3.2$) of the methyl-substituted derivatives (*E*,*Z*)- and (*Z*,*Z*)-**1g**. In accordance with an experimental study of Grieco and Gajewski, we found that the rate accelerating influence of TFE is more pronounced compared to ethanol.[4h] Whether the observed solvent rate effects are attributable to a selective transition-state stabilization by increased dipole stabilization, hydrogen bonding to the ether oxygen atom, or by the hydrophobic effect can not be deduced from our experimental data.[29]

Conclusion

The Gosteli−Claisen rearrangement has lately attracted attention in connection with the development of catalyzed Claisen rearrangements. Lewis acids and organocatalysts have been successfully utilized to establish a *catalytic* asymmetric aliphatic Claisen rearrangement,[15,16] an elusive quest for many decades. Computational studies have emerged that provide structural models for the stereodifferentiation of the catalyzed Gosteli−Claisen rearrangement.[15,17] The present work has collected fundamental information on the uncatalyzed Gosteli−Claisen rearrangement. We provide experimental details for a general synthetic strategy to 2-alkoxycarbonyl-substituted allyl vinyl ethers (**1**), the simple diastereoselectivity of the rearrangement, and experimental activation parameter that should be useful for the validation of future computational studies on the catalyzed Gosteli−Claisen rearrangement. A computational study on the uncatalyzed Gosteli−Claisen rearrangement could be a crucial step forward to a fundamental understanding of the experimentally observed substituent and solvent rate effects. Success in this venture will be reported in due course.

Experimental Section

General Procedure A: Aldol Addition. A cooled (−78 °C) solution of the ester (1 equiv) in THF (3 mL/mmol of the ester) was added to a solution of LDA [prepared *in situ* from diisopropylamine (1.3 equiv) and *n*-BuLi (2.3 M in hexanes, 1.2 equiv) in THF (3 mL/mmol of the ester) at −78 °C] at −78 °C. The solution was stirred for 15 min at −78 °C before freshly distilled and cooled (−78 °C) acetaldehyde (5 equiv) was added. After the reaction mixture was stirred for 15 min at −78 °C, a saturated aqueous NH_4Cl solution (5 mL/mmol of the ester) was added at −78 °C, the reaction mixture was warmed to ambient temperature, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic phases were dried ($MgSO_4$) and concentrated at reduced pressure, and the residue was purified by chromatography (silica gel).

General Procedure B.[22] A cooled (−78 °C) solution of the ester (1 equiv) in THF (1 mL/mmol of the ester) was added to a solution of LDA in THF [prepared from diisopropylamine (3.0 equiv) and *n*-BuLi (2.0 M in hexanes, 2.1 equiv) in THF (1 mL/mmol of the ester) at −78 °C] at −78 °C. The solution was stirred for 15 min at −78 °C before benzotriazolylmethanol (2 equiv) in THF (2 mL/mmol of ester) was added at −78 °C over a period of 20 min. After 2 h at −78 °C, saturated aqueous NH_4Cl solution was added, and the resulting suspension was warmed to room temperature. The organic phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (4×). The combined organic phases were dried ($MgSO_4$), the solvents were removed under reduced pressure, and the residue was purified by chromatography (silica gel).

***β*-Hydroxy Ester (*E*)-9.** Prepared according to general procedure A from (*E*)-**7** (5.9 g, 34.4 mmol, 1 equiv), diisopropylamine (6.3 mL, 44.7 mmol, 1.3 equiv), *n*-BuLi (2.0 M in hexanes, 20.6 mL, 41.3 mmol, 1.2 equiv), and acetaldehyde (9.6 mL, 172 mmol, 5 equiv). (*E*)-**9** was isolated after chromatographic purification (cyclohexane/ethyl acetate 10/1) as a yellowish oil (6.8 g, 92%, 7/3 mixture of diastereomers): $R_f = 0.7$ (cyclohexane/ethyl acetate 1/1); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 1.18 (d, $J = 7.0$ Hz, 3H) 1.25 (d, $J = 6.2$, 6H), 1.68 (d, $J = 6.78$, 3H), 3.63 (d^{minor}, $J = 6.02$, 1H), 3.83 (d^{major}, $J = 4.52$ Hz, 1H) 3.85−3.95 (m, 1H), 4.01−4.15 (m, 2H), 5.09 (sept, $J = 6.2$, 1H), 5.50−5.59 (m, 1H), 5.65−5.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 18.2, 18.8, 21.9, 68.4, 68.8, 72.0, 81.8, 82.5, 118.5, 118.7, 133.8, 133.9, 170.4, 170.8; IR (film on KBr) 3480 (broad), 1740 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.0; H, 9.3.

***β*-Hydroxy Ester (*Z*)-9.** Prepared according to general procedure A from (*Z*)-**7** (1.1 g, 6.2 mmol, 1 equiv), diisopropylamine (1.1 mL, 8 mmol, 1.3 equiv), *n*-BuLi (2.1 M in hexanes, 3.5 mL, 7.4 mmol, 1.2 equiv), and acetaldehyde (0.7 mL, 12.4 mmol, 2 equiv). (*Z*)-**9** was isolated after chromatographic purification (cyclohexane/ethyl acetate 10/1) as a yellowish oil (1.2 g, 89%, 65/35 mixture of diastereomers): $R_f = 0.6$ (cyclohexane/ethyl acetate 1/1); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 1.20 (dd, $J = 6.4$, 3.7 Hz, 3H) 1.27 (d, $J = 6.3$, 6H), 1.65 (d, $J = 6.8$ Hz, 3H) 2.17 (broad s, 1H), 3.65 (d^{minor}, $J = 5.7$ Hz, 1H) 3.84 (d^{major}, $J = 4.4$ Hz, 1H), 4.06 (m, 2H), 4.24 (m, 1H), 5.12 (sept, $J = 6.1$, 1H), 5.53 (m, 1H), 5.70 (m, 1H); ^{13}C NMR (75.475 MHz, $CDCl_3$, mixture of diastereomers) δ 13.1, 18.2, 18.7, 21.8, 65.8, 68.4, 68.7, 81.4, 82.4, 125.6, 125.8, 129.2, 129.4, 170.4, 170.6; IR (film on KBr) 3460 (broad), 1730 cm^{-1}. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.2; H, 9.3.

***β*-Hydroxy Ester 12.**[30] Prepared according to general procedure B from **11** (1.3 g, 10 mmol, 1 equiv), diisopropylamine (4.2 mL, 30 mmol, 3 equiv), *n*-BuLi (2.0 M in hexanes, 15 mL, 30 mmol, 2.1 equiv), and benzotriazolylmethanol (3 g, 20 mmol, 2 equiv). Compound **12** was isolated after chromatographic purification (hexanes/ethyl acetate 10/1) as a colorless oil (1.34 g, 84%): $R_f =$ 0.4 (hexanes/ethyl acetate 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.13 (broad s, 1H), 3.75 (s, 3H), 3.80−3.90 (m, 2H), 3.96−4.06 (m, 2H), 4.26 (dd, $J = 12.4$, 5.4 Hz, 1H), 5.21 (d, $J = 9.5$, 1H), 5.28 (dd, $J = 17.2$, 1.4, 1H), 5.84−5.96 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 52.0, 63.3, 71.8, 78.2, 118.3, 133.5, 170.9; IR (film on KBr) 3445 (broad), 1740 cm^{-1}. Anal. Calcd for $C_7H_{12}O_4$: C, 52.5;, H, 7.6. Found: C, 52.3; H, 7.7.

***β*-Hydroxy Ester 13.** Prepared according to general procedure B from **8** (0.64 g, 4 mmol, 1 equiv), diisopropylamine (1.7 mL, 12 mmol, 3 equiv), *n*-BuLi (2.0 M in hexanes, 6 mL, 12.0 mmol, 2.1 equiv), and benzotriazolylmethanol (1.2 g, 8 mmol, 2 equiv). Compound **13** was isolated after chromatographic purification (hexanes/ethyl acetate 10/1) as a colorless oil (0.75 g, 98%): $R_f =$ 0.4 (hexanes/ethyl acetate 1/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, $J = 6.3$ Hz, 3H), 1.26 (d, $J = 6.3$ Hz, 3H), 2.21 (broad s br, 1H), 3.74−3.90 (m, 2H), 3.95−4.02 (m, 2H), 4.24 (d, $J = 5.3$ Hz, 1H), 5.08 (sept, $J = 6.3$ Hz, 1H), 5.20 (d, $J = 10.0$, 1H), 5.29 (dd, $J = 17.1$, 1.5 Hz, 1H), 5.85−5.95 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.7, 63.4, 68.8, 71.7, 78.4, 118.2, 133.7, 170.0; IR (film on KBr) 3465 (broad), 1725 cm^{-1}.

***β*-Hydroxy Ester 14.** Prepared according to general procedure A from **11** (4.3 g, 33.4 mmol, 1 equiv), diisopropylamine (7.4 mL, 43.4 mmol, 1.3 equiv), *n*-BuLi (2.0 M in *n*-hexanes, 20.1 mL, 40.1 mmol, 1.2 equiv), and acetaldehyde (9.4 mL, 167 mmol, 5 equiv). Compound **14** was isolated after chromatographic purification (cyclohexane/ethyl acetate 10/1) as a colorless oil (5.7 g, 98%, 65/35 mixture of diastereomers): $R_f = 0.4$ (cyclohexane/ethyl acetate 1/1); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 1.19 (d^{major}, $J = 6.5$ Hz, 3H) 1.21 (d^{minor}, $J = 7.0$, 3H), 2.31 (broad

(29) For an insightful discussion on this topic, see: Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219–225.

(30) Eichelberger, U.; Mansourova, M.; Hennig, L.; Findeisen, M.; Giesa, S.; Müller, D.; Wetzel, P. *Tetrahedron* **2001**, *57*, 9737–9742.

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s^{major}, 1H), 2.43 (broad s^{minor}, 1H), 3.74 (s, 3H) 3.90 (d, J = 4.5 Hz, 1H), 3.91−4.98 (m, 1H), 4.00−4.10 (m, 1H), 4.17−4.24 (m, 1H), 5.2 (m, 1H), 5.20 (dd, J = 17.3, 1.5 Hz), 5.83−5.94 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) 18.2, 18.7, 51.8, 51.9, 68.1, 68.2, 72.0, 72.3, 81.6, 82.0, 118.0, 118.3, 133.4, 133.5, 171.1, 171.3; IR (film on KBr) 3425 (broad), 2880, 1740 cm^{-1}. Anal. Calcd for $C_8H_{14}O_4$: C, 55.2; H, 8.1. Found: C, 55.5; H, 8.1.

***β*-Hydroxy Ester 15.** Imidazole (0.55 g, 8 mmol, 1 equiv) and *t*-BuPh_2SiCl (2.2 g, 8 mmol, 1 equiv) were successively added to a solution of ethylene glycol (2.60 g, 42 mmol, 6 equiv) in THF (21 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight and then diluted by the addition of saturated aqueous $NaHCO_3$ solution. The layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the solvents were evaporated at reduced pressure. The residue was purified by chromatography (cyclohexane/ethyl acetate 5/1) to provide the mono-TPS-protected diol as colorless oil (87%, 2.1 g, 7 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (s, 9H), 2.31 (broad s, 1H), 3.67 (d, J = 4.8 Hz, 2H), 3.75 (d, J = 4.8 Hz, 2H), 7.35−7.45 (m, 6H), 7.66 (d, J = 6.3 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 26.7, 63.6, 64.8, 127.6, 129.5, 133.1, 134.7, 135.4; IR (film on KBr) ν 3425 (broad) cm^{-1}. To a solution of the mono-TPS-protected alcohol (3 g, 10 mmol, 1 equiv) in DMSO (8.5 mL, 120 mmol, 12 equiv) and CH_2Cl_2 (10 mL) were added Et_3N (5.6 mL, 40 mmol, 4 equiv) and SO_3·pyridine complex (3.18 g, 20 mmol, 2 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and at ambient temperature for 2.5 h. The progress of reaction was monitored by TLC (heptane/ethyl acetate 1/1; alcohol: R_f = 0.5, white spot; aldehyde: R_f = 0.6, blue spot; anisaldehyde staining). The reaction mixture was diluted with water (10 mL), the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), the solvents were evaporated at reduced pressure, and the residue was purified by flash chromatography (heptane/ethyl acetate 5/1) to provide the aldehyde as a pale yellow oil (92%, 2.76 g, 9.2 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (s, 9H), 4.20 (s, 2H), 7.40 (m, 6H), 7.65 (dd, J = 7.7, 1.7 Hz, 4H), 9.71 (s, 1H). According to general procedure A, the ester **8** (1.33 g, 8.6 mmol, 1 equiv) was treated with diisopropylamine (1.6 mL, 11.1 mmol, 3 equiv), *n*-BuLi (2.16 M in hexanes, 4.8 mL, 10.3 mmol, 2.1 equiv), and the freshly prepared aldehyde (2.8 g, 9.4 mmol, 1.1 equiv). The residue was purified by chromatography (heptane/ethyl acetate 20/1) to provide the β-hydroxy ester **15** as a colorless oil (2.25 g, 88%, 7/3 mixture of diastereomers): R_f = 0.5 (heptane/ethyl acetate 1/1); ^{1}H NMR (300.1 MHz, $CDCl_3$, mixture of diastereomers) δ 1.10 (s, 9H), 1.22 (d, J = 6.2 Hz, 3H), 1.27 (d, J = 6.2 Hz, 3H), 3.65−4.17 (series of m, 6H), 5.10 (sept, J = 6.3, 1H), 5.19 (ddt, J = 10.4, 1.5 Hz, 1H), 5.26 (ddt, J = 17.2, 1.6 Hz, 1H), 5.88 (ddt, J = 17.2, 10.4, 5.9 Hz, 1H), 7.33−7.44 (m, 6H), 7.61−7.69 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$, mixture of diastereomers) δ 19.1, 21.7, 21.8, 26.6, 26.9, 64.0, 68.7, 71.7, 72.5, 78.8, 117.9, 127.7, 129.8, 133.1, 133.8, 134.8, 135.5, 170.5; IR (film on KBr) 3430 (broad), 1740 cm^{-1}. Anal. Calcd for $C_{26}H_{36}O_5Si$: C, 68.39; H, 7.95. Found: C, 68.59; H, 7.99.

General Procedure C: Mesylation and Elimination. To a solution of the β-hydroxy ester (1.0 equiv) in CH_2Cl_2 (3 mL/mmol of β-hydroxy ester) at 0 °C were added Et_3N (1.3 equiv) and MsCl (1.2 equiv). The ice bath was removed, and the white suspension was stirred at ambient temperature for 30 min. The reaction mixture was then diluted with saturated aqueous $NaHCO_3$ solution, the layers were separated, the aqueous phase was extracted with CH_2Cl_2 (3×), the combined organic phases were dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. The residue was then dissolved in THF (2 mL/mmol of the β-hydroxy ester) and cooled to 0 °C, and DBU (3 equiv) was added. The reaction mixture was allowed to warm to room temperature overnight and then diluted with water. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (3×), the combined organic phases were dried ($MgSO_4$), the solvents were evaporated under reduced pressure, and the residue was purified by chromatography (silica gel).

Allyl Vinyl Ether 1a.[4g] Prepared according to general procedure C from **12** (1.21 g, 7.6 mmol, 1 equiv), Et_3N (1.4 mL, 9.9 mmol, 1.3 equiv), MsCl (0.7 mL, 9.1 mmol, 1.2 equiv), and DBU (3.4 mL, 22.8 mmol, 3 equiv). Chromatographic purification (hexanes/ethyl acetate 100/1) delivered **1a** as a colorless liquid (0.89 g, 82%): R_f = 0.8 (hexanes/ethyl acetate 1/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.33(d, J = 5.8 Hz, 2H), 4.61 (d, J = 2.7 Hz, 1H), 5.27 (dd, J = 10.5, 1.2 Hz, 1H), 5.33−5.39 (m, 2H), 5.93−6.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 69.3, 94.8, 118.4,131.9, 150.6, 163.4; IR (thin film) 1740, 1625 cm^{-1}. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.19; H, 7.14.

Allyl Vinyl Ether 1b. Prepared according to general procedure C from **13** (0.83 g, 4.7 mmol, 1 equiv), Et_3N (0.86 mL, 6.1 mmol, 1.3 equiv), MsCl (0.4 mL, 5.6 mmol, 1.2 equiv), and DBU (2.2 mL, 14.1 mmol, 3 equiv). Chromatographic purification (hexanes/ethyl acetate 100/1) provided **1b** as a colorless liquid (0.55 g, 74%): R_f = 0.7 (hexanes/ethyl acetate 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (d, J = 6.3 Hz, 6H), 4.33 (dt, J = 5.3, 1.4 Hz, 2H), 4.58 (d, J = 2.5 Hz, 1H), 5.09 (sept, J = 6.3 Hz, 1H), 5.25−5.33 (m, 3H), 5.93−6.03 (m, 1H); ^{13}C NMR (80 MHz, $CDCl_3$) δ 21.7, 69.0, 69.2, 94,0, 118.0, 132.0, 151.0, 162.0; IR (film on KBr) 2980, 1730 cm^{-1}. Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.58; H, 8.22.

Allyl Vinyl Ether 1d. Prepared according to general procedure C from **15** (2.62 g, 5.8 mmol, 1 equiv), Et_3N (1.1 mL, 7.5 mmol, 1.3 equiv), MsCl (0.5 mL, 6.9 mmol, 1.2 equiv), and DBU (2.7 mL, 17.4 mmol, 3 equiv). Chromatographic purification (heptane/ethyl acetate 20/1) delivered **1d** (2.17 g, 86%, Z/E = 70/30) as a colorless liquid. The double-bond diastereomers were separated by preparative HPLC: Nucleosil 50-7, 32 mm × 250 mm, heptane/ethyl acetate 98/2, flow 25 mL/min, 32 × 10^{-1} MPa, (*Z*)-**1d** = 11.6 min, (*E*)-**1d** = 12.9 min. R_f = 0.7 (heptane/ethyl acetate 1/1). (*Z*)-**1d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.30 (d, J = 6.2 Hz, 6H), 4.21 (ddd, J = 5.9, 1.2 Hz, 2H), 4.44 (d, J = 5.8 Hz, 2H), 5.21 (m, 3H), 5.83 (ddt, J = 17.0, 10.4, 6.2 Hz, 1H), 5.25 (t, J = 6.0 Hz, 1H), 7.33−7.44 (m, 6H), 7.64−7.71 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 21.8, 26.8, 59.1, 67.5, 68.7, 72.8, 118.1, 127.0, 129.7, 133.6, 135.6, 144.4, 162.9; IR (film on KBr) 1720 cm^{-1}. Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 71.30; H, 7.79. (*E*)-**1d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.15 (d, J = 6.2 Hz, 6H), 4.26 (ddd, J = 5.3, 1.2 Hz, 2 H), 4.65 (d, J = 5.2 Hz, 2H), 4.97 (sept, J = 6.3 Hz, 1H), 5.27 (ddt, J = 10.4, 1.3 Hz, 1H), 5.32 (ddt, J = 17.2, 1.5 Hz, 1H), 5.40 (t, J = 5.4 Hz, 1H), 6.01 (ddt, J = 17.2, 10.5, 5.2 Hz, 1H), 7.33−7.42 (m, 6H), 7.62−7.69 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.2, 21.7, 26.9, 61.1, 68.8, 69.6, 72.8, 117.6, 127.7, 129.6, 132.8, 133.8, 135.6, 143.8, 162.8; IR (film on KBr) 1720 cm^{-1}. Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 71.17; H, 8.19.

Allyl Vinyl Ether (*E*,*Z*)- and (*Z*,*Z*)-1g. Prepared according to general procedure C from (*Z*)-**9** (0.84 g, 3.9 mmol, 1 equiv), Et_3N (0.7 mL, 5 mmol, 1.3 equiv), MsCl (0.4 mL, 4.6 mmol, 1.2 equiv), and DBU (1.7 mL, 11.6 mmol, 3 equiv). Chromatographic purification (heptane/ethyl acetate 100/1) afforded (*E*/*Z*,*Z*)-**1g** (0.62 g, 87%, Z/E = 60/40) as a colorless liquid. The double-bond diastereomers were separated by automated preparative HPLC (Nucleosil 50-7, 32 mm × 250 mm, heptane/ethyl acetate 99/1, flow 20 mL/min, pressure 31 × 10^{-1} MPa, (*Z*,*Z*)-**1g** = 23.5 min (48%), (*E*,*Z*)-**1g** = 27.3 min (32%), baseline separation with 100 mg/injection). R_f = 0.84 (heptane/ethyl acetate 1/1). (*Z*,*Z*)-**1g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (d, J = 6.3 Hz, 6H), 1.65 (d, J = 6.3 Hz, 3H), 1.74 d, J = 7.1 Hz, 3H), 4.39 (d, J = 6.3 Hz, 2H), 5.06 (sept, J = 6.3 Hz, 1H), 5.58−5.74 (m, 1H), 6.31 (q, J = 7.1 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.3, 13.0, 21.8, 66.8, 68.1, 123.9, 125.7, 129.0, 145.9, 163.5; IR (film on KBr) 1720, 1650 cm^{-1}. (*E*,*Z*)-**1g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 6.3 Hz, 6H), 1.65 (d, J = 6.3 Hz, 3H), 1.92 (d, J = 7.4 Hz, 3H),

4.30 (d, J = 6.3 Hz, 2H), 5.11 (sept, J = 6.3 Hz, 1H), 5.38 (q, J = 7.4 Hz, 3H), 5.55−5.72 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.2, 12.6, 21.8, 68.4, 70.1, 112.6, 126.2, 130.1, 145.7, 163.6; IR (film on KBr) 1725, 1645 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.6; H, 9.2. Found: C, 66.6; H, 9.2.

Allyl Vinyl Ether (*Z*,*E*)-1g and (*E*,*E*)-1g. Prepared according to general procedure C from (*E*)-**9** (3.1 g, 14.3 mmol, 1 equiv), Et_3N (2.6 mL, 18.6 mmol, 1.3 equiv), MsCl (1.3 mL, 17.2 mmol, 1.2 equiv), and DBU (6.5 mL, 42.9 mmol, 3 equiv). Chromatographic purification (isohexanes/ethyl acetate 100/1) furnished (*Z*/*E*,*E*)-**1g** (2.71 g, 96%, *Z*/*E* = 60/40) as a colorless liquid. The double-bond diastereomers were separated by automated preparative HPLC: Nucleosil 50-7, 32 mm × 250 mm, heptane/ethyl acetate 99/1, flow 20 mL/min, pressure 31 × 10^{-1} MPa, (*Z*,*E*)-**1g** = 23.5 min (62%), (*E*,*E*)-**1g** = 27.3 min (34%), baseline separation with 100 mg/injection. R_f = 0.9 (isohexanes/ethyl acetate 1/1). (*Z*,*E*)-**1g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J = 6.0 Hz, 6H), 1.65 (d, J = 5.8 Hz, 3H), 1.73 (d, J = 7.2 Hz, 3H), 4.22 (d, J = 6.27 Hz, 2H), 5.05 (sept, J = 6.3 Hz, 1H), 5.60−5.78 (m, 2H), 6.29 (q, J = 7.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 11.3, 17.7, 21.6, 21.8, 68.2, 72.7, 123.7, 126.8, 130.7, 145.9, 163.5; IR (film on KBr) 1720, 1650, 1450 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.6; H, 9.2. Found: C, 66.6; H, 9.1. (*E*,*E*)-**1g**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (d, J = 6.3 Hz, 6H), 1.69 (dq, J = 6.3, 0.7 Hz, 3H), 1.90 (d, J = 7.3 Hz, 3H), 4.14 (d, J = 5.8 Hz, 2H), 5.10 (sept, J = 6.27 Hz, 1H), 5.36 (q, J = 7.3 Hz, 1H), 5.58−5.66 (m, 1H), 5.69−5.79 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 9.2, 12.6, 21.8, 68.4, 70.1, 112.6, 126.2, 130.1, 145.7, 163.6; IR (film on KBr) 1725, 1645 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.6; H, 9.2. Found: C, 66.6; H, 9.1.

Allyl Vinyl Ether 1j.[15] Prepared according to general procedure C from **14** (5.3 g, 30.4 mmol, 1 equiv), Et_3N (5.2 mL, 36.5 mmol, 1.3 equiv), MsCl (2.8 mL, 39.5 mmol, 1.2 equiv), and DBU (13.7 mL, 91.2 mmol, 3 equiv). Chromatographic purification (cyclohexane/ethyl acetate 100/1) furnished **1j** (3.8 g, 80%, *Z*/*E* = 60/40) as a colorless liquid. The double-bond diastereomers were separated by automated preparative HPLC: Nucleosil 50-7, 32 mm × 250 mm, heptane/ethyl acetate 95/5, flow 20 mL/min, pressure 31 × 10^{-1} MPa, (*Z*)-**1j** = 12.3 min (51%), (*E*)-**1j** = 13.1 min (34%), baseline separation with 100 mg/injection. R_f = 0.9 (cyclohexane/ethyl acetate 1/1). (*Z*)-**1j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (d, J = 7.0 Hz, 3H), 3.75 (s, 3H), 4.31 (d, J = 6.0 Hz, 2H), 5.20 (dt, J = 10.1, 0.5 Hz, 1H), 5.30 (dd, J = 17.1, 1.5 Hz, 1H), 5.92−6.04 (m, 1H), 6.35 (q, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 51.7, 72.9, 118.0, 124.7, 133.6, 145.2, 162.0; IR (thin film) 1725, 1650 cm^{-1}. (*E*)-**1j**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (d, J = 7.0 Hz, 3H), 3.75 (s, 3H), 4.31 (d, J = 6.0 Hz, 2H), 5.20 (dt, J = 10.1, 0.5 Hz, 1H), 5.30 (dd, J = 17.1, 1.5 Hz, 1H), 5.92−6.04 (m, 1H), 6.35 (q, J = 7.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 51.7, 69.7, 112.8, 117.8, 132.8, 151.3, 162.0; IR (film on KBr) 1725, 1640 cm^{-1}.

Allyl Vinyl Ether (*Z*)-1e. To a cooled solution (0 °C) of **1j** (1.28 g, 8.2 mmol, 1 equiv) in THF (5 mL) and H_2O (2.5 mL) was added $LiOH \cdot H_2O$ (0.69 g, 16.4 mmol, 2 equiv). The resulting suspension was stirred vigorously for 30 min at 0 °C and then at room temperature (∼6 h) until TLC indicated complete consumption of the ester (**1j**: R_f = 0.9, **1e**: R_f = 0.1−0.4, cyclohexane/ethylacetate 1/1). The yellow reaction mixture was then cooled to 0 °C, acidified with diluted aqueous HCl (pH 4), and extracted with $CHCl_3$ (6 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure, and the residue was purified by flash chromatography (cyclohexane/ethyl acetate 100/1 to 1/1) to afford (*Z*)-**1e** as white solid (0.5 g, 3.5 mmol, 43%) and (*E*)-**1e** as yellowish oil (0.31 g, 2.5 mmol, 26%). (*Z*)-**1e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.76 (d, J = 7.2 Hz, 3H), 4.34 (d, J = 6.0 Hz, 2H), 5.20 (d, J = 10.4 Hz, 1H), 5.32 (dd, J = 17.2, 1.2 Hz, 1H), 5.92−6.04 (m, 1H), 6.53 (q, J = 7.2 Hz, 1H); ^{13}C NMR (apt, 75 MHz, $CDCl_3$) δ 11.5, 73.3, 118.4, 127.2, 133.5, 144.7, 168.1; IR (film on KBr) 3450, 2925, 1710, 1650 cm^{-1}. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.19; H, 7.14. (*E*)-**7e**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.06 (d, J = 7.0 Hz, 3H), 4.29 (dt, J = 5.6, 1.2 Hz, 2H), 5.25 (d, J = 1.2 Hz, 2H), 5.37 (dd, J = 10.1, 1.2 Hz, 1H), 5.50 (q, J = 7.0 Hz, 1H), 5.92−6.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 69.7, 112.8, 117.8, 132.8, 151.3, 162.0; IR (film on KBr) 1725, 1640 cm^{-1}. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.13; H, 7.16.

Allyl Vinyl Ether (*Z*)-1f. A solution of the acid (*Z*)-**1e** (0.30 g, 2.1 mmol, 1 equiv) in CH_2Cl_2 (5 mL) was treated with DCC (0.47 g, 2.3 mmol, 1.1 equiv), DMAP (0.01 g, 0.1 mmol, 0.05 equiv), and 2,2,2-trifluoroethanol (0.52 mL, 4.2 mmol, 2 equiv) at 0 °C. The reaction mixture was allowed to warm to room temperature overnight; the white precipitate was removed by filtration and rinsed with CH_2Cl_2. The filtrate was concentrated under reduced pressure (40 °C, 620 mbar), and the residue was purified by flash chromatography (heptane/ethyl acetate 20/1) to deliver the ester (*Z*)-**1f** (67%, 0.3 g, 1.4 mmol) as a pale yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (d, J = 7.16 Hz, 3H), 4.32 (dt, J = 6.2, 1.1 Hz, 2H), 4.53 (q, J = 8.4 Hz, 1H), 5.22 (dd, J = 10.3 1.2 Hz, 1H), 5.28 (dd, J = 17.2, 5.3 Hz, 1H), 5.97 (m, 1H), 6.44 (q, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.8, 60.7, 73.3, 118.7, 127.6, 133.4, 144.1, 162.2; IR (film on KBr) 1740 cm^{-1}. Anal. Calcd for $C_9H_{11}F_3O_3$: C, 48.22; H, 4.95. Found: C, 48.2; H, 4.9.

General Procedure F: Kinetic Measurements. A solution of the allyl vinyl ether (0.4 mmol) in the specified solvent (2 mL) in a commercially available glass pressure tube was submerged into a preheated oil bath. The time measurement was started with a delay of 30 s for temperature equilibration (measured with a commercially available internal thermometer). The maximum temperature fluctuation during the kinetic measurements was ± 0.5 °C. Samples were taken by syringe (0.3 mL) and were immediately transferred into a cooled (0 °C) flask (1,2-dichloroethane, 2,2,2-trifluoroethanol, EtOH) or NMR tube (C_6D_6, CD_3CN). Nondeuterated solvents were evaporated at reduced pressure and ambient temperature. The substrate/product ratio was determined from the ^{1}H NMR spectra of the crude product. The obtained data were analyzed according to a first-order rate law. Eyring and Arrhenius parameters were generated from the resulting k values.

α-Keto ester 2a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (dd, J_1 = J_2 = 6.9 Hz, 2H), 2.93 (t, J = 7.3 Hz, 2H), 3.84 (s, 3H), 4.99 (dd, J = 10.3, 1.25 Hz, 1H), 5.05 (m, J = 17.3, 1.51 Hz, 1 H), 5.74−5.85 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 26.9, 38.5, 53.1, 116.0, 136.1; IR (film on KBr) 1725 cm^{-1}. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.31; H, 7.16.

α-Keto ester 2b: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (d, J = 6.3 Hz, 6H), 2.36 (dd, J_1 = J_2 = 6.7 Hz, 2H), 2.91 (t, J = 7.4 Hz, 2H), 4.99 (dd, J = 10.3, 1.3 Hz, 1H), 5.04 (dd, J = 17.1, 1.3 Hz, 1H), 5.10 (sept, J = 6.3 Hz, 1H), 5.70−5.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.9, 38.3, 70.6, 115.7, 136.1; IR (film on KBr) 1730 cm^{-1}. Anal. Calcd for $C_9H_{14}O_3$: C, 63.5; H, 8.3. Found: C, 64.7; H, 8.3.

α-Keto ester (±)-2c: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (d, J = 7.1 Hz, 3H), 1.34 (d, J = 6.2 Hz, 6H), 2.09−2.22 (m, 1H), 2.39−2.51 (m, 1H), 3.28 (tq, J = 17.5, 7.3 Hz, 1H), 5.00−5.09 (m, 2H), 5.14 (sept, J = 6.3 Hz, 1H), 5.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 21.6, 36.1, 41.9, 70.5, 117.4, 134.8, 161.5, 197.8; IR (film on KBr) 1725 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.22; H, 8.84.

α-Keto ester (±)-2d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (s, 9H), 1.31 (d, J = 6.2 Hz, 3H), 1.32 (d, J = 6.2 Hz, 3H), 2.20−2.32 (m, 1H), 2.40−2.51 (m, 1H), 3.59 (dt, J = 12.9, 6.5 Hz, 1H), 3.88 (d, J = 5.8 Hz, 2H), 4.93−5.03 (m, 2H), 5.11 (sept, J = 6.3, 1H), 5.69 (ddt, J = 17.1, 10.2, 7.0 Hz, 1H), 7.33−7.46 (m, 6H), 7.58−7.64 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 19.2, 21.5, 26.7, 31.5, 49.7, 63.7, 70.4, 117.2, 127.7, 129.7, 134.6, 135.5, 160.9, 184.5; IR (film on KBr) 1730 cm^{-1}. Anal. Calcd for $C_{26}H_{34}O_4Si$: C, 71.19; H, 7.81. Found: C, 71.01; H, 7.84.

α-Keto acid (±)-2e: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, J = 7.0 Hz, 3H), 2.19 (ddd, J_1 = J_2 = J_3 = 7.2 Hz, 1H), 2.47 (ddd,

$J_1 = J_2 = J_3 = 6.8$ Hz, 1H), 3.4 (tq, $J_1 = J_2 = 7.8$ Hz, 1H), 5.0 (s, 1H), 5.05 (d, $J = 4.0$ Hz, 1H), 5.64−5.75 (m, 1H), 6.3−7.0 (broad s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.1, 25.6, 68.0, 117.8, 134.5, 160.5, 199.0; IR (film on KBr) 3020, 1720 cm^{-1}. Anal. Calcd for $C_7H_{10}O_3$: C, 59.1; H, 7.1. Found: C, 58.8; H, 7.1.

α-Keto ester (±)-2f: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (d, $J = 7.0$ Hz, 3H), 2.13−2.25 (m, 1H), 2.41−2.52 (m, 1H), 3.28 (dq, $J_1 = J_2 = 6.9$ Hz, 1H), 4.61 (q, $J = 8.1$ Hz, 2H), 5.02−5.10 (m, 2H), 5.64−5.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ.14.3, 35.9, 42.1, 60.9, 117.9, 134.1, 159.7; IR (film on KBr) 1730 cm^{-1}.

α-Keto ester (±)-*syn*-2g: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, $J = 7.0$ Hz, 3H), 1.05 (d, $J = 6.7$ Hz, 3H), 1.31 (dd, $J = 6.0$, 5.0 Hz, 6H), 2.55 (m, 1H), 3.23 (m, $J = 6.8$ Hz, 1 H), 4.99 (d, $J = 9.8$ Hz, 2H), 5.11 (sept, $J = 6.2$ Hz, 1H), 5.68−5.78 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 11.3, 15.5, 21.4, 39.0, 46.3, 70.4, 114.8, 141.0, 161.4, 198.1; IR (film on KBr) 1720 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.6; H, 9.1. Found: C, 66.6; H, 9.1.

α-Keto ester (±)-*anti*-2g: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (d, $J = 7.0$ Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H), 1.32 (d, $J = 6.2$ Hz, 6H), 2.57 (m, 1H), 3.14 (m, 1H), 4.98 (d, $J = 6.8$, 2H), 5.13 (sept, $J = 6.2$ Hz, 1H), 5.61 (ddt, $J = 18.7$, 13.5, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 18.2, 21.6, 39.5, 47.0, 70.4, 115.5, 139.9, 186.9, 198.1; IR (film on KBr) 1720, 1640 cm^{-1}. Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.6; H, 9.1. Found: C, 66.7; H, 9.2.

α-Keto ester (±)-*anti*-2h: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 6.1$ Hz, 3H), 1.19−1.43 (m, 4H), 1.34 (d, $J = 6.3$ Hz, 3H), 1.35 (d, $J = 7.3$ Hz, 3H), 2.42−2.54 (m, 1H), 3.22 (dq, $J_1 = J_2 = 6.8$ Hz, 1H), 4.98 (ddd, $J = 16.9$, 1.9, 0.8 Hz, 1H), 5.07 (dd, $J = 10.2$, 1.8 Hz, 1H), 5.16 (sept, $J = 6.3$ Hz, 1H), 5.46 (ddd, $J = 17.1$, 10.1, 9.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 13.9, 20.1, 21.5, 21.6, 34.8, 44.9, 46.0, 70.4, 117.2, 138.1, 161.6, 184.0; IR (film on KBr) 1720 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.78; H, 9.70. Found: C, 68.79; H, 9.80.

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Supporting Information Available: Additional experimental procedures, copies of ^{1}H NMR and ^{13}C NMR spectra for new compounds, and Arrhenuis and Eyring plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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