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Organocatalytic Claisen Rearrangement: Theory and Experiment

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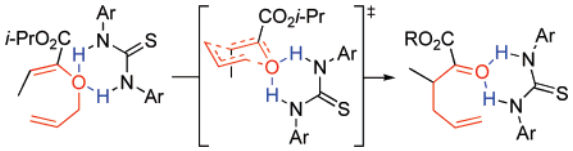

A combined computational and experimental study on the Claisen rearrangement of a 2-alkoxycarbonyl-substituted allyl vinyl ether in the presence of thioureas as potential noncovalent organocatalysts has been performed. DFT calculations employing different basis sets were utilized to predict a catalytic cycle for the thiourea-catalyzed Claisen rearrangement. The nature of the transition state in the presence and absence of thioureas was studied in detail. Critical geometrical data of the transition state that are indicators for the relative barrier height of the Claisen rearrangement are discussed. Although we did observe a significant transition state stabilization, due to endergonic conformational changes and endergonic complexation the overall effect on the barrier is small, in accordance with experimental results.

Introduction

Catalysis is a very important principle in chemistry and biochemistry. Many processes in industry use catalysts which, until recently, have frequently employed transition metals. However, a steadily increasing number of transformations that utilizes small "organic" molecules as organocatalysts are being reported.[1]

In noncovalent organocatalysis, the basic principle of activation is the selective stabilization of the transition state by hydrogen bonding.[2,3] Ureas and thioureas have been used frequently for this purpose because of their well-known ability of molecular recognition and complex formation.[4]

Before 1990, several research groups had noticed an accelerating effect of protic solvents[5] or Brønsted acids[6] on the rate of the thermal Claisen rearrangement. Jorgensen utilized quantum mechanical calculations to explain the accelerating effect of protic solvent systems (Figure 1).[7] On the HF/6-31G(d) level of theory Jorgensen found an enhanced polarization of the transition state compared to that of the allyl vinyl ether substrate. Proceeding from the substrate to the transition state, the partial negative charge on the ether oxygen atom increases, which promotes stronger hydrogen bonding. Furthermore, due to the elongation of the C/O bond in the transition state, the solvent accessibility of the ether oxygen atom is increased, which supports the hydrogen bonding of two water molecules instead of one water molecule in the substrate.[8,9] On the basis of these computational results, Jorgensen suggested a catalyst design that incorporates two hydrogen bond-donating sites in appropriate position to interact with the ether oxygen atom of the transition state of the Claisen rearrangement.

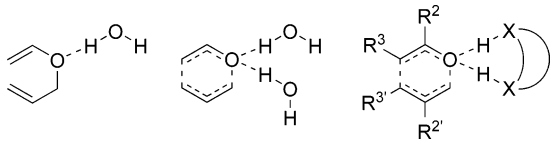

FIGURE 1. Specific interaction of water molecules with allyl vinyl ether and general catalyst design according to Jorgensen.

The first attempt to realize the Jorgensen catalyst design utilized the urea derivative **2a** and the 6-methoxy-substituted allyl vinyl ether **1** (Scheme 1).[10,11] Using catalytic amounts of **2a**, Curran et al. determined a small rate acceleration (k_{cat}/k_{uncat} = 2.7) at 80 °C by NMR experiments in benzene-d_6. The rate accelerating effect further increased in the presence of stoichiometric amounts of **2a** (k_{cat}/k_{uncat} = 22.4). It is worth mentioning that the thiourea derivative **2b** was less efficient probably due to its decomposition at the reaction temperature. In accordance

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(1) For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726−3748. (b) List, B. *Synlett* **2001**, 1675−1686. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138−5175. (d) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719−724. (e) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999−1010.

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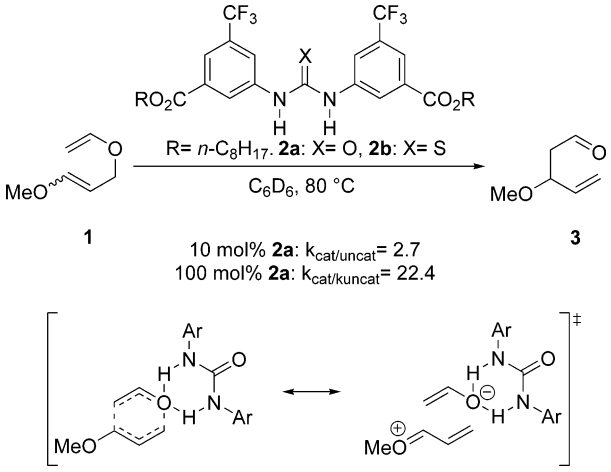
SCHEME 1. Urea-Catalyzed Claisen Rearrangement and Bis(hydrogen) Bonded Transition State Model According to Curran



with Jorgensen's suggestion, Curran proposed a bis(hydrogen) bonded transition state model based on a specific interaction between the urea **2a** and the partially negatively charged ether oxygen atom of the allyl vinyl ether **1** to explain the rate acceleration (Scheme 1).

The polarization of the transition state of the thermal aliphatic Claisen rearrangement in general has been confirmed by many computational studies at different levels of theory.[12] However, no detailed computational investigation to support the predicted transition state stabilization in the presence of a bis(hydrogen) bonded urea is currently available.[13]

It was shown before and particularly after the important work of Curran that a variety of different reactions may be catalyzed

(2) For hydrogen bond donors other than (thio)ureas, see: (a) Hine, J.; Linden, S. M.; Kanagasabapathy, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 1082−1083. (b) Hine, J.; Linden, S. M.; Kanagasabapathy, V. M. *J. Org. Chem.* **1985**, *50*, 5096−5099. (c) Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381−3384. (d) Raposo, C.; Almaraz, M.; Crego, M.; Mussons, M. L.; Pérez, N.; Caballero, M. C.; Morán, J. *Tetrahedron Lett.* **1994**, *35*, 7065−7068. (e) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *J. Am. Chem. Soc.* **1996**, *118*, 4910−4911. (f) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160. (g) Schuster, T.; Kurz, M.; Göbel, M. W. *J. Org. Chem.* **2000**, *65*, 1697−1701. (h) Schuster, T.; Bauch, M.; Dürner, G.; Göbel, M. W. *Org. Lett.* **2000**, *2*, 179−181. (i) Rowe, H. L.; Spencer, N.; Philp, D. *Tetrahedron Lett.* **2000**, *41*, 4475−4479. (j) Huang, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2002**, *124*, 9662−9663. (k) Dürner, S. B. G.; Bolte, M.; Göbel, M. W. *Eur. J. Org. Chem.* **2003**, 1661−1664. (l) Braddock, D. C.; MacGilp, I. D.; Perry, B. G. *Synlett* **2003**, 1121−1124. (m) Huang, Y.; Unni, A. K.; Thadani, A. N.; Rawal V. H. *Nature* **2003**, *424*, 146. (n) McDougal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094−12095. (o) Huang, J.; Corey, E. J. *Org. Lett.* **2004**, *6*, 5027−5029. (p) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906−9907. (q) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481−4483. (r) Gondi, V. B.; Gravel, M.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 5657−5660. (s) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 5473−5475. (t) Lou, S.; Taoka, B. M.; Ting, A.; Schaus, S. E. *J. Am. Chem. Soc.* **2005**, *127*, 11256−11257. (su) Unni, A. K.; Takenaka, N.; Yamamoto, H.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 1336−1337. (v) Nakashima, D.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 9626−9627. (w) Hansen, H. M.; Longbottom, D. A.; Ley, S. V. *Chem. Commun.* **2006**, 4838−4840.

(3) For Brønsted acid catalysis by chiral phosphoric acids, see: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. *Angew. Chem.* **2004**, *116*, 1592−1594. (b) Uraguchi, D.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357. (c) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804−11805. (d) Akiyama, T.; Morita, H.; Itoh, J.; Fuchibe, K. *Org. Lett.* **2005**, *7*, 2583−2585. (e) Rueping, M.; Sugiono, E.; Azap, C.; Theissmann, T.; Bolte, M. *Org. Lett.* **2005**, *7*, 3781−3783. (f) Uraguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2005**, *127*, 9360−9361. (g) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696−15697. (h) Hoffmann, S.; Seayad, A. M.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 7424−7427. (i) Terada, M.; Machioka, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 2254−2257. (j) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683−3686. (k) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796−4798. (l) Seayad, J.; Seayad, A. M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 1086−1087. (m) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070−13071. (n) Hoffmann, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074−13075. (o) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368−13369.

(4) (a) Etter, M. C.; Panunto, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5896−5897. (b) Wilcox, C. S.; Kim, E.-i.; Romano, D.; Kuo, L. H.; Burt, A. L.; Curran, D. P. *Tetrahedron* **1995**, *51*, 621−634. (c) Chien, C.-H.; Leung, M.-k.; Su, J.-K.; Li, G.-H.; Liu, Y.-H.; Wang, Y. *J. Org. Chem.* **2004**, *69*, 1866−1871.

(5) Aromatic Claisen rearrangement, see: (a) White, W. N.; Gwynn, D.; Schlitt, R.; Girard, C.; Fife, W. *J. Am. Chem. Soc.* **1958**, *80*, 3271−3277. (b) Goering, L.; Jacobson, R. R. *J. Am. Chem. Soc.* **1958**, *80*, 3277−3285. (c) White, W. N.; Wolfarth, E. F. *J. Org. Chem.* **1970**, *35*, 2196−2199. (d) White, W. N.; Wolfarth, E. F. *J. Org. Chem.* **1970**, *35*, 3585−3585. (e) Bagnell, L.; Cablewski, T.; Strauss, C. R.; Trainor, R. W. *J. Org. Chem.* **1996**, *61*, 7355−7359. Aliphatic Claisen rearrangement, see: (f) Ponaras, A. A. *J. Org. Chem.* **1983**, *48*, 3866−3868. (g) Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636−6642. (h) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Curran, D. P.; Peck, D. R. *J. Am. Chem. Soc.* **1987**, *109*, 1160−1170. (i) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170−1186. (j) Brandes, E.; Grieco, P. A.; Gajewski, J. J. *J. Org. Chem.* **1989**, *54*, 515−516. (k) Grieco, P. A.; Brandes, E. B.; McCann, S.; Clark, J. D. *J. Org. Chem.* **1989**, *54*, 5849−5851. (l) Robertson, J.; Fowler, T. G. *Org. Biomol. Chem.* **2006**, *4*, 4307−4318.

(6) (a) Claisen, L. *Chem. Ber.* **1912**, *45*, 3157−3167. (b) Lauer, W. M.; Kilburn, E. I. *J. Am. Chem. Soc.* **1937**, *59*, 2586−2588. (c) Kincaid, J. F.; Tarbell, D. S. *J. Am. Chem. Soc.* **1939**, *61*, 3085−3089. (d) Ralls, J. W.; Lundin, R. E.; Bailey, G. F. *J. Org. Chem.* **1963**, *28*, 3521−3526. (e) Svanholm, U.; Parker V. D. *J. Chem. Soc., Chem. Commun.* **1972**, 645−646. (f) Widmer, U.; Hansen, H.-J.; Schmidt, H. *Helv. Chim. Acta* **1973**, *56*, 2644−2648. (g) Svanholm, U.; Parker, V. D. *J. Chem. Soc., Perkin Trans. 2* **1974**, 169−173. (h) Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1987**, *28*, 5879−5882. (i) Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4035−4037. (j) Paquette, L. A.; Moradei, O. M.; Bernardelli, P.; Lange T. *Org. Lett.* **2000**, *2*, 1875−1878. (k) Roe, J. M.; Webster, R. A. B.; Ganesan, A. *Org. Lett.* **2003**, *5*, 2825−2827. (l) Nakabayashi, K.; Ooho, M.; Niino, T.; Kitamura, T.; Yamaji, T. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 157−164.

(7) (a) Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1992**, *114*, 10966−10968. (b) Cramer, C. J.; Truhlar, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 8794−8799. (c) Jorgensen, W. L.; Blake, J. F.; Lim, D.; Severance, D. L. *J. Chem. Soc., Faraday Trans.* **1994**, *90*, 1727−1732. See also: (d) Davidson, M. M.; Hillier, I. H. *J. Phys. Chem.* **1995**, *99*, 6748−6751.

(8) For computational studies on solvent rate effects, see: (a) Gao, J. *J. Am. Chem. Soc.* **1994**, *116*, 1563−1564. (b) Davidson, M. M.; Hillier, I. H.; Hall, R. J.; Burton N. A. *J. Am. Chem. Soc.* **1994**, *116*, 9294−9297. (c) Sehgal, A.; Shao, L.; Gao, J. *J. Am. Chem. Soc.* **1995**, *117*, 11337−11340. (d) Hu, H.; Kobrak, M. N.; Xu, C.; Hammes-Schiffer, S. *J. Phys. Chem. A* **2000**, *104*, 8058−8066.

(9) For an insightful review on solvent rate effects, see: Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219−225.

(10) Curran, D. P.; Lung, H. K. *Tetrahedron Lett.* **1995**, *36*, 6647−6650. For the influence of diarylureas on the rate and the stereochemical course of a radical allylation, see: Curran, D. P.; Kuo, L. H. *J. Org. Chem.* **1994**, *59*, 3259−3261.

(11) The presence of the 6-methoxy group causes a slightly increased reactivity under thermal conditions ($k = 0.612 \times 10^{-5}$ s^{-1} in benzene-d_6 at 80 °C) compared to the unsubstituted allyl vinyl ether ($k = 0.0711 \times 10^{-5}$ s^{-1} in benzene-d_6 at 80 °C).

(12) (a) Yoo, H. Y.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 12047−12048. (b) Wiest, O.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 11628−11639. (c) Aviyente, V.; Yoo, H. Y.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 6121−6128. (d) Yoo, H. Y.; Houk, K. N. *J. Am. Chem. Soc.* **1997**, *119*, 2877−2884. (e) Meyer, M. P.; DelMonte, A. J.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 10865−10874. (f) Khanjin, N. A.; Snyder, J. P.; Menger, F. M. *J. Am. Chem. Soc.* **1999**, *121*, 11831−11846. (g) Aviyente, V.; Houk, K. N. *J. Phys. Chem. A* **2001**, *105*, 383−391. (h) Ozturk, C.; Aviyente, V.; Houk, K. N. *J. Org. Chem.* **2005**, *70*, 7028−7034.

(13) For recent computational studies on thiourea-catalyzed reactions, see: (a) Hamza, A.; Schubert, G.; Soos, T.; Papai, I. *J. Am. Chem. Soc.* **2006**, *40*, 13151−13160. (b) Zhu, Y.; Drueckhammer, D. G. *J. Org. Chem.* **2005**, *70*, 7755−7760.

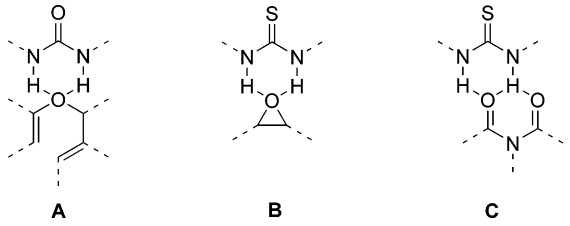


FIGURE 2. Bis(hydrogen) bond binding modes of thiourea catalysts according to Curran and Schreiner.

by ureas and thioureas.[14] However, despite its undisputed synthetic value, the Claisen rearrangement was apparently not further investigated. Therefore, we have initiated a research project aimed at the development of an organocatalytic asymmetric Claisen rearrangement (OCAC).[15] For the initial studies, we opted for the achiral 1,3-bis-(3,5-bis(trifluoromethyl)phenyl)-thiourea **5** as the potential noncovalent organocatalyst. This particular thiourea has been developed and utilized by Schreiner for the catalysis of a Diels−Alder reaction and, more recently, acetalization as well as nucleophilic epoxide ring opening.[16] On the basis of computational studies, Schreiner proposed the bis-(hydrogen) bond binding models **B** and **C** which complement Curran's initial binding model **A** for the Claisen rearrangement (Figure 2).

The substituent pattern of an allyl vinyl ether is pivotal for its accessibility, its inherent reactivity in the thermal and the catalyzed rearrangement, and most importantly, the synthetic value of the rearrangement product. Acyclic 2-alkoxycarbonyl-substituted allyl vinyl ethers are easily accessible on multigram scale, storable, and provide useful α-keto ester building blocks as products of the Claisen rearrangement.[17] Therefore, we selected the simple 2-isopropoxycarbonyl-1-methyl-substituted allyl vinyl ether **7**[18] as substrate for this study (Figure 3).[19]

Initially, we had to consider two general bis(hydrogen) bond binding modes between the transition state of the Claisen rearrangement and the thiourea catalyst (Figure 3). Complex **4** should be more favorable with respect to binding because of the involvement of the more Brønsted basic carbonyl oxygen atom. However, we expected that binding mode **6** would be more favorable with respect to selective transition state stabi-

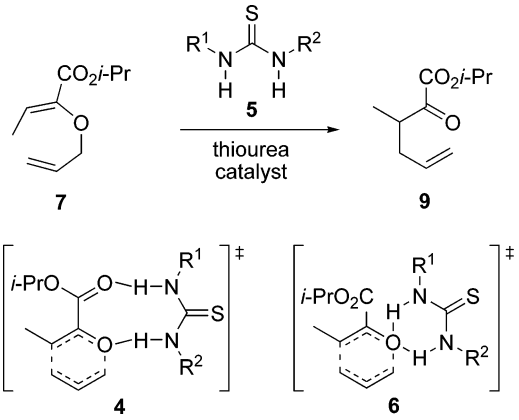


FIGURE 3. Proposed transition state stabilization for the Claisen rearrangement by bidentate thiourea coordination.

lization. A detailed computational study was performed to predict the consequences of the two binding modes on the nature of the transition state of the Claisen rearrangement. Here, we report the results of this endeavor and provide preliminary experimental data to support the conclusions from the computational study.

Computational Methods

All calculations were performed with Gaussian03.[20] The density functional hybrid model Becke3LYP[21] was used together with the valence double-ζ basis set 6-31G(d) as well as the valence triple-ζ basis sets 6-311+G(d,p) and 6-311++G(d,p). It has been shown that calculations with the Becke3LYP functional predict energies and geometries of hydrocarbon pericyclic reactions in general, and the aliphatic Claisen rearrangement in particular, with reasonable accuracy.[12e,22] No symmetry or internal coordinate constraints were applied during optimizations. All reported intermediates were verified as true minima by the absence of negative eigenvalues in the vibrational frequency analysis. Transition-state structures were located by using the Berny algorithm[23] until the Hessian matrix had only one imaginary eigenvalue. The identity of all transition states was confirmed by the presence of only one negative eigenvalue in the frequency analysis and animating this eigenvector

(14) For recent reviews, see: (a) Connon, S. J. *Chem. Eur. J.* **2006**, *12*, 5418−5427. (b) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299−4306. (c) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296. For recent reports on (thio)urea-catalyzed transformations, see: (d) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652−12653. (e) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366−6370. (f) De Rosa, M.; Citro, L.; Soriente, A. *Tetrahedron Lett.* **2006**, *47*, 8507−8510. (g) Berkessel, A.; Roland, K.; Neudörfl, J. M. *Org. Lett.* **2006**, *8*, 4195−4198. (h) Berkessel, A.; Mukherjee, S.; Müller, T. N.; Cleemann, F.; Roland, K.; Brandenburg, M.; Neudörfl, J.-M.; Lex, J. *Org. Biomol. Chem.* **2006**, *4*, 4319−4330.

(15) For the catalytic asymmetric Claisen rearrangement (CAC) based on Lewis acid *catalysis*, see: (a) Abraham, L.; Körner, M.; Schwab, P.; Hiersemann, M. *Adv. Synth. Catal.* **2004**, *346*, 1281−1294. (b) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4700−4703.

(16) (a) Schreiner, P. R.; Wittkopp, A. *Org. Lett.* **2002**, *4*, 217−220. (b) Wittkopp, A.; Schreiner, P. R. *Chem. Eur. J.* **2003**, *9*, 407−414. (c) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434−439. (d) Kleiner, C. M.; Schreiner P. R. *Chem. Commun.* **2006**, 4315−4317.

(17) (a) Körner, M.; Hiersemann, M. *Synlett* **2006**, 121−123. (b) Pollex, A.; Hiersemann, M. *Org. Lett.* **2005**, *7*, 5705−5708.

(18) Abraham, L.; Körner, M.; Hiersemann, M. *Tetrahedron Lett.* **2004**, *45*, 3647−3650.

(19) Experimentally determined activation parameters for thermal Claisen rearrangement of (*Z*)-**7**: $\Delta G^{\#} = 27.5$ kcal mol^{-1} at 298.15 K, $k = 2.8 \times 10^{-5}$ s^{-1} in benzene-d_6 at 80 °C.

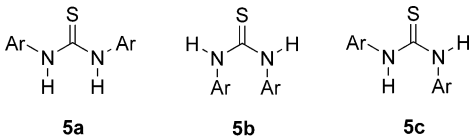
(20) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian03*, Rev. C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(21) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789. (c) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627. (d) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.* **1980**, *58*, 1200−1211.

(22) (a) Wiest, O.; Black, K. A.; Houk, K. N. *J. Am. Chem. Soc.* **1994**, *116*, 10336−10337. (b) Guner, V.; Khuong, K. S.; Leach, A. G.; Lee, P. S.; Bartberger, M. D.; Houk, K. N. *J. Phys. Chem. A* **2003**, *107*, 11445−11459.

(23) Peng, C.; Ayala, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **1998**, *17*, 49−56.

TABLE 1. Conformational Analysis of Thiourea 5 at Different Levels of Theory



		B3LYP free energy [kcal mol^{-1}]		
entry	compd	6-31G*	6-311+G**	6-311++G**
1	**5a**	+1.76	+0.87	+0.84 (0.00)[a]
2	**5b**	+0.79	+0.65	+0.78 (0.29)[a]
3	**5c**	0	0	0 (1.79)[a]

[a] Single-point energies (HF) with use of the PCM solvent model for dichloroethane (in parentheses).

coordinate with MOLDEN.[24] Approximate free energies were obtained through thermochemical analysis of the frequency calculation, using the thermal correction to the Gibbs free energy as reported by Gaussian03. This takes into account zero-point effects, thermal enthalpy corrections, and entropy. All energies reported in this paper, unless otherwise noted, are free energies (in kcal mol^{-1}) at 298 K and 1 atm. Frequencies remain unscaled. All transition states are maxima on the electronic potential energy surface. These may not correspond to maxima on the free energy surface.

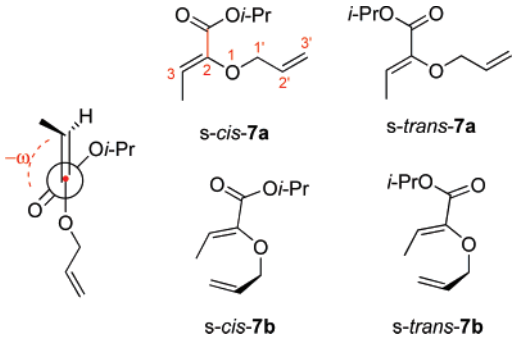
The charge separation between the positively charged allylic and negatively charge oxallylic fragments of the allyl vinyl ether was analyzed by Mullikan charges as well as the natural bond orbital (NBO) approach of Weinhold et al.[25a]

The free energy of solvation was calculated in terms of the polarizable continuum model (PCM).[25b] The self-consistent reaction field (SCRF) calculations with the PCM-UA0 solvation model[25c] were carried out as single-point calculations at the B3LYP/6-311++G** level of theory for the gas-phase optimized structures. The dielectric constant in the PCM calculations was set to $\epsilon = 10.36$ to simulate dichloroethane as one solvent medium frequently used in the experimental study.

Computational Results and Discussion

To predict a complete catalytic cycle for the thiourea-catalyzed Claisen rearrangement, a thorough conformational analysis of the thiourea **5**, the substrate **7**, and the α-keto ester **9** was required. We embarked on this endeavor with a conformational study of the thiourea derivative **5** (Table 1). [26] The conformer **5c** was found to be most stable for all basis sets in the gas phase, while solvent single-point calculations predict **5a** to be the most stable conformer. The proposed bis(hydrogen) bond binding mode requires the thiourea to adopt the conformation **5a**. In agreement with previous DFT calculations of Custelcean et al., the energetic difference between the conformers decreases when the basis set increases.[27] With the triple-ξ basis sets, the energetic difference between the thiourea conformers **5a**−**c** is very small and the conformers should be in a rapid equilibrium. Entropy and enthalpy changes for the conformational changes are given in the Supporting Information. Because the accurate description of hydrogen bonding[28] is pivotal for the computational analysis of the proposed catalytic cycle, we utilized the 6-311++G(d,p) basis set for further calculations.

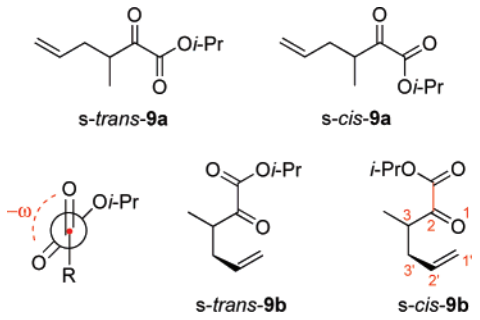
TABLE 2. Calculated (B3LYP/6-311++G) Geometric Data and Relative Free Energy of Relevant Conformers of the Allyl Vinyl Ether 7**



		bond distances [Å]			
entry	compd	O1−C1′	C3−C3′	dihedral angle ω [deg]	G_{rel} [kcal mol^{-1}]
1	*s-trans*-**7a**	1.45	5.53	−171	0 (0)[a]
2	*s-trans*-**7b**	1.45	4.57	−169	+0.47 (+0.44)[a]
3	*s-cis*-**7a**	1.44	5.49	+7	+0.55 (+0.08)[a]
4	*s-cis*-**7b**	1.45	4.34	+10	+0.98 (+0.56)[a]

[a] Single-point energies (HF) with use of the PCM solvent model dichloroethane (in parentheses).

TABLE 3. Calculated (B3LYP/6-311++G) Geometric Data and Relative Free Energy of Relevant Conformers of the α-Keto Ester 9**



		bond distances [Å]			
entry	compd	O1−C1′	C3−C3′	dihedral angle ω [deg]	G_{rel} [kcal mol^{-1}]
1	*s-trans*-**9a**	5.26	1.54	−144	0 (0)[a]
2	*s-cis*-**9a**	5.28	1.54	+49	+1.44 (+0.70)[a]
3	*s-trans*-**9b**	4.26	1.56	+160	+1.43 (+0.99)[a]
4	*s-cis*-**9b**	4.23	1.56	−52	+2.45 (+1.80)[a]

[a] Single-point energies (HF) with use of the PCM solvent model dichloroethane (in parentheses)

The conformational analysis of 2-alkoxycarbonyl-substituted allyl vinyl ethers **7** has to consider the *s-cis*/*s-trans* equilibrium of the α,β-unsaturated ester and the dihedral angle ω was assigned to denote the conformation (Table 2). Qualitatively, one would expect that a dihedral angle ω of 0° (synperiplanar)

(24) Schaftenaar, G.; Noordik, J. H. *J. Comput.-Aided Mol. Des.* **2000**, *14*, 123−124.

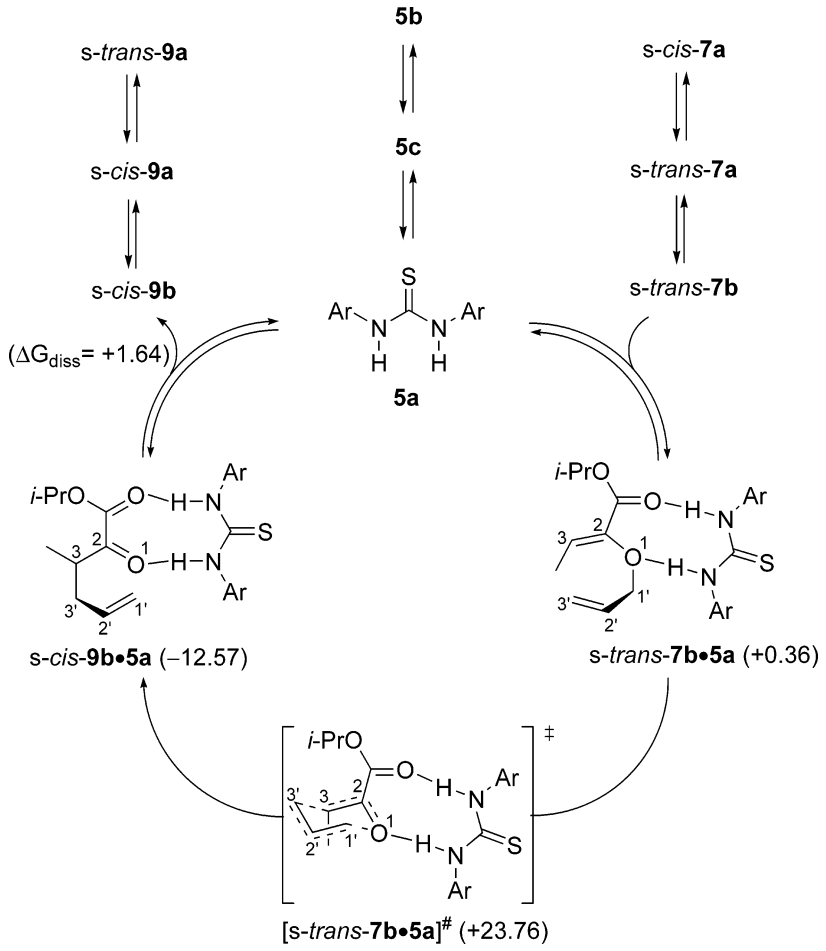
(25) (a) Reed, A. E.; Curtis, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926. (b) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117−129. (c) Barone, V.; Cossi, M.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3210−3221.

(26) For recent computational studies on the conformation of substituted ureas and thioureas, see: (a) Bryantsev, V. S.; Firman, T. K.; Hay, B. P. *J. Phys. Chem. A* **2005**, *109*, 832−842. (b) Bryantsev, V. S.; Hay, B. P. *J. Phys. Chem. A* **2006**, *110*, 4678−4688.

(27) Custelcean, R.; Gorbunova, M. G.; Bonnesen, P. V. *Chem. Eur. J.* **2005**, *11*, 1459−1466.

(28) (a) Zierkiewicz, W.; Jurecka, P.; Hobza, P. *Chem. Phys. Chem.* **2005**, *6*, 609−617. (b) Scheiner, S.; Grabowski, S. J.; Kar, T. *J. Phys. Chem. A* **2001**, *105*, 10607−10612. (c) Liu, Y.; Liu, W.-Q.; Li, H.-Y.; Yang, Y.; Cheng, S. *Chin. J. Chem.* **2007**, *25*, 44−52. (d) Wojtulewski, S.; Grabowski, S. J. *Chem. Phys.* **2005**, *309*, 183−188.

TABLE 4. Calculated (B3LYP/6-311++G) Geometric Data and Free Energy (kcal mol^{-1}) for the Proposed Catalytic Cycle (Ar = 3,5-CF_3-C_6H_3) of s-*trans*-7b**



entry	compd	bond distances [Å] H−O1	bond distances [Å] H−O=C	bond distances [Å] O1−C1′	bond distances [Å] C3−C3′	dihedral angle ω [deg]	G_{rel} [kcal mol^{-1}] at 298.15 K
1	s-*trans*-**7a** + **5c**						0 (+1.35)[c]
2	s-*trans*-**7b** + **5a**						+1.34 (0)[c]
3	s-*trans*-**7b·5a**	2.08	1.97	1.46	4.18	−165	+0.36 (−1.04)[c]
4	[s-*trans*-**7b·5a**]#	1.95	1.97	2.05	2.46	172	+23.76 (+20.81)[c]
5	*s-cis*-**9b·5a**	2.04	2.02	4.03	1.57	−7	−12.57 (−15.65)[c]
6	*s-cis*-**9b** + **5a**						−10.93[a] (−14.12)[c]
7	*s-trans*−**9a** + **5c**						−14.25[b] (−15.92)[c]

[a] Calculated according to the following: {G(*s-cis*-**9b**) + *G*(**5a**)} − {*G*(*s-trans*-**7a**) + *G*(**5c**)} [kcal mol^{-1}]. Not explicitly stated in the depicted catalytic cycle. [b] Calculated according to the following: {*G*(*s-trans*-**9a**) + *G*(**5c**)} − {*G*(*s-trans*-**7a**) + *G*(**5c**)} [kcal mol^{-1}]. Not explicitly stated in the depicted catalytic cycle. [c] Calculated single-point energies with use of the PCM solvent model in dichloroethane (in parentheses).

or 180° (antiperiplanar) should be favorable with respect to conjugative stabilization. However, all relevant conformers that have been studied computationally show a noticeable deviation from planarity of 7−11° (Table 2, entries 1−4). It is tempting to assume that the nonbonding interactions between the substituents on the highly substituted C2/C3 double bond are responsible for the predicted deviation from planarity. The *s-trans* conformers of **7a** and **7b** are more stable than their *s-cis* counterparts by 0.5 kcal mol^{-1}. As will be outlined later, the nature of the transition state of the Claisen rearrangement can be conveniently characterized by the length of the "breaking" (O1−C1′) and the "forming" (C3−C3′) σ bond. As expected, the length of the breaking bond is independent of the conformation of the allyl vinyl ether **7** (Table 2, entries 1−4). The conformers **7b** were calculated as reactive conformations in which the allylic ether double bond is directed toward the vinyl ether double bond. The reactive conformers **7b** are less stable by 0.5 kcal mol^{-1} compared to their stretched counterparts **7a** (Table 2, entries 1, 3 and 2, 4). Generally, as was the case for the thiourea **5**, the calculated energy differences between the conformers of **7** are rather small and we expect a rapid equilibrium between all possible conformers of the allyl vinyl ether **7**. This is also true for the solvent calculations given in parentheses (Table 2).

Selected geometric data and the relative free energy of relevant conformers of the α-keto ester **9** are summarized in Table 3. Enthalpic and entropic contributions are given in the Supporting Information. The dihedral angle ω was defined to denote the conformational preferences of the α-keto ester moiety (Table 3). A significant deviation from planarity is predicted for all calculated conformers. As expected, the stretched conformers *s-cis*- and *s-trans*-**9a** are more stable than the

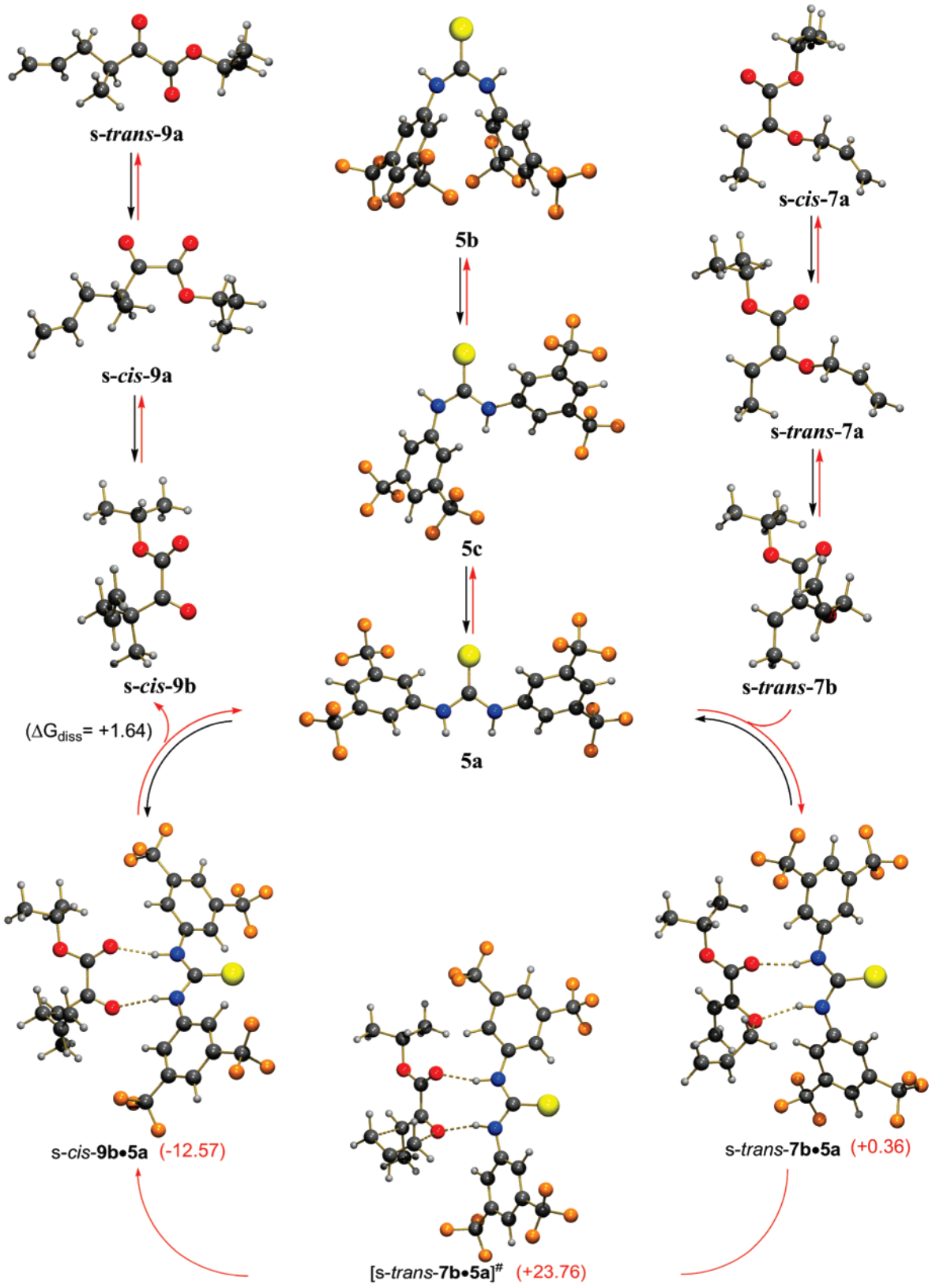


FIGURE 4. Optimized structures (B3LYP/6-311++G**) for stationary points of the catalytic cycle and conformers of the thiourea catalyst **5**, substrate **7**, and product **9**.

corresponding curved conformers *s-cis*- and *s-trans*-**9b** (Table 3, entries 1,3 and 2,4). *s-cis*-**9b** and *s-trans*-**9b** represent product conformations that originate directly from the Claisen rearrangement. *s-trans*-**9b** is more stable than *s-cis*-**9b** by 1 kcal mol^{-1} most likely due to the more favorable direction of the local carbonyl dipoles in opposite directions (Table 3, entries 3 and 4). Furthermore, the repulsion of the two carbonyl groups in *s-cis*-**9b** results in a dihedral angle of −52° thereby decreasing

TABLE 5. Comparison of Geometric and Energetic Data of the Transition State [*s-trans*-7b·5a]# at Different Levels of Theory

entry	B3LYP	bond distances [Å] H−O1	H−O=C	O1−C1′	C3−C3′	dihedral angle ω [deg]	charge separation δ[a]	$\Delta G^{\#}_{total}$ [kcal mol^{-1}][b]
1	6-31G(d)	2.01	2.02	2.01	2.39	171	0.62 (0.50)	24.54[c]
2	6-311+G(d,p)	1.95	1.98	2.05	2.46	173	0.67 (0.47)	23.77[d]
3	6-311++G(d,p)	1.95	1.97	2.05	2.46	172	0.66 (0.43)	23.76[d]

[a] NBO and Mulliken (in parentheses) charge separation between the allylic and the oxallylic segment of the transition state. See Table 6 for a definition. [b] At 298.15 K [c] Total activation barrier relative to the fully optimized lowest energy conformation of the **5a**·*s-trans*-**7b** complex. The barrier relative to the uncomplexed **5c** and *s-trans*-**7a** is 23.87 kcal mol^{-1}. [d] Total activation barrier relative to the fully optimized lowest energy conformation of the uncomplexed **5c** and *s-trans*-**7a**.

the stabilization by conjugation (Table 3, entry 4). Even for the *s-trans* conformers, a significant deviation from planarity was calculated most likely due to the unfavorable interaction between the isopropoxy group and the keto carbonyl oxygen atom (Table 3, entries 1 and 3). Generally, we expect a rapid equilibrium between the relevant conformers in which *s-trans*-**9a** should predominate. These conclusions are in agreement with the results of a recently published conformational analysis of α-keto esters by Baiker et al. based on FTIR spectroscopy and computational studies at the B3PW91/6-31++G(d,p) level of theory.[29]

The initial conformational studies established that the interconversion of the relevant substrate and catalyst conformers is fast and reversible. The actual Claisen rearrangement was investigated next. Starting points for our survey of the computationally predicted catalytic cycle are the lowest energy gas-phase conformations of the thiourea (**5c**) and the allyl vinyl ether (*s-trans*-**7a**) (Table 4, Figure 4). Formation of the "catalytically active" conformation of the thiourea (**5a**) and the allyl vinyl ether (*s-trans*-**7b**) is slightly endergonic in the gas phase, while *s-trans*-**7b·5a** is the lowest energy conformer according to the solvent single-point calculations. A summary of the relevant geometric properties of the complex *s-trans*-**7b·5a** is given in Table 4, entry 3. The hydrogen bond between the urea and the carbonyl oxygen atom (1.97 Å) is slightly shorter compared to the hydrogen bond to the ether oxygen atom (2.08 Å) as one would qualitatively expect based on the relative Brønsted basicity. The length of the O1−C1′ bond (1.46 Å) remains unchanged upon complex formation (see Table 2, entry 2 for comparison). The dihehydral angle ω decreases from −169° in the uncomplexed *s-trans*-**7b** to −165° in the *s-trans*-**7b·5a** complex in order to match the steric requirements of the bis-(hydrogen) bonding. Assuming that the barrier of the complex formation is easily accessible at room temperature, the complex s-*trans*-**7b·5a** should be part of a rapid and reversible equilibrium between hydrogen bonded and nonbonded catalyst and substrate conformers. The subsequent Claisen rearrangement of *s-trans*-**7b·5a** to *s-cis*-**9b·5a** via the transition state [*s-trans*-**7b·5a**]# is the rate determining and irreversible step of the calculated catalytic cycle. The rearrangement is exergonic by −12.6 kcal mol^{-1} and has a total activation barrier ($\Delta G^{\#}_{total}$) of 23.8 kcal mol^{-1}. The free energy of activation of the Claisen rearrangement step ($\Delta G^{\#}_{[3,3]} = 23.4$) is only slightly lower. The solvent single-point calculations provide an identical picture, with a little different (generally lower) numbers.

Important geometric data of the transition state are summarized in Table 4, entry 4. In proceeding from the complex *s-trans*-**7b·5a** to the transition state [*s-trans*-**7b·5a**]#, the length of the hydrogen bond between the thiourea **5a** and the oxygen atom O1 of *s-trans*-**7b** decreases. This could indicate an increasing negative charge on the oxygen atom and/or a better accessibility of O1 due to the elongated O1−C1 bond. Both interpretations are in accordance with the original transition state model of Jorgensen and Curran (vide supra).

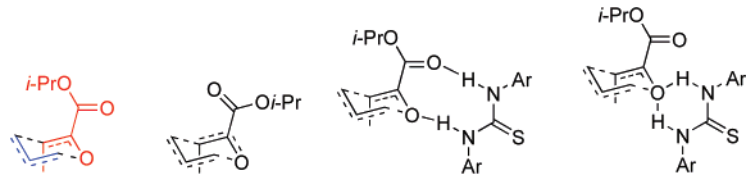
The α-keto ester·thiourea complex *s-cis*-**9b·5a** is characterized by a very small dihedral angle ($\omega = -7°$) (Table 4, entry 5). The small deviation from a perfect synperiplanar conformation of the two carbonyl groups in *s-cis*-**9b** is a consequence of the steric requirements of the two hydrogen bonds to the thiourea **5a** catalyst. The calculation predicts an endergonic dissociation process ($\Delta G_{diss} = +1.64$ kcal mol^{-1}) of *s-cis*-**9b·5a** to *s-cis*-**9b** ($\omega = -52°$) and **5a**. However, the exergonic formation (−2.45 kcal mol^{-1}) of *s-trans*-**9b** from *s-cis*-**9b** renders the overall dissociation process thermodynamically favorable and, therefore, product inhibition of the catalyst is not predicted by calculation.

A comparative study on the total barrier of the thermal and the thiourea-catalyzed Claisen rearrangement was performed next. Many studies use B3LYP/6-31G* as the standard basis set, sometimes in combination with high-level single-point calculations. We were therefore interested in the influence of the basis set on the geometry and the $\Delta G^{\#}_{total}$ of the catalytic cycle depicted in Figure 4. As can be seen from Table 5, the relevant geometric data that characterize the [*s-trans*-**7b·5a**]# transition state are not significantly dependent on the size of the utilized basis set. The total barrier is moderately higher for the double-ξ basis set due to an exergonic formation of **5a**·*s-trans*-**7b** from **5c** and *s-trans*-**7a**. The triple-ξ basis sets predict this transformation as endergonic. Although the double-ξ basis set 6-31G(d) can be considered a reasonable compromise between cost and accuracy, we decided to use the triple- ξ basis set 6-311++G**.

The thermal Claisen rearrangement of the allyl vinyl ether **7** was studied first (Table 6). The two competing transition states [*s-trans*-**7b**]# and [*s-cis*-**7b**]# are characterized by a concerted, but asynchronous bond reorganization process (Table 6, entries 1 and 2). The bond breaking is more advanced (+39%) than the bond making process (55% elongation of the C3−C3′ bond). Therefore, the transition state is polarized and a significant charge separation (δ) between the allylic and the oxallylic fragment is predicted by the calculations.[12] The barrier of the rearrangement via [*s-cis*-**7b**]# is 0.75 kcal mol^{-1} lower than that for the competing transition state [*s-trans*-**7b**]#. [*s-cis*-**7b**]# should be intrinsically favored due to the less significant deviation of the dihedral angle ω from planarity (+18° vs −147° for [*s-trans*-**7b**]#). Furthermore, [*s-cis*-**7b**]# leads directly to the thermodynamically more favorable rearrangement product [*s-trans*-**9b**]#, which should contribute to the lower activation barrier of the rearrangement via [*s-cis*-**7b**]# (see Table 3 for comparison). At the B3LYP/6-311++G(d,p) level of theory, the rearrangement via the bis(hydrogen) bonded transition state

(29) Ferri, D.; Bürgi, T.; Baiker, A. *J. Chem. Soc., Perkin Trans. 2* **2000**, 221−227.

TABLE 6. Comparison of Calculated (B3LYP/6-311++G) Geometric and Energetic Data for the Thermal and the Thiourea-Catalyzed Claisen Rearrangement of 7**



[s-*trans*-**7b**]# [s-*cis*-**7b**]# [s-*trans*-**7b**•**5a**]# [s-*cis*-**7b**•**5a**]#

entry	compd	bond distances [Å] H−O1	H−O=C	O1−C1′ [a]	C3−C3′ [b]	dihedral angle ω [deg]	NBO charge separation δ [c]	$\Delta H^{\#}/\Delta S^{\#}_{total}$ [kcal mol^{-1}] at 298.15 K	$\Delta G^{\#}_{total}$ [d] [kcal mol^{-1}] at 298.15 K	$\Delta G^{\#}_{total,\,solv}$ [e] [kcal mol^{-1}] at 298.15 K	$\Delta G^{\#}$ [f] $_{[3,3]}$ [kcal mol^{-1}] at 298.15 K
1	[*s-trans*-**7b**]#			2.00 (+39%)	2.39 (+55%)	−147	0.54 (0.37)	24.80/−8.5 × 10^{-3}	27.34	24.78	26.87
2	[*s-cis*-**7b**]#			1.98 (+38%)	2.39 (+55%)	18	0.52 (0.30)	24.49/−8.08 × 10^{-3}	26.90	24.52	25.45
3	[*s-trans*-**7b**•**5a**]#	1.95	1.97	2.05 (+42%)	2.46 (+60%)	+172	0.66 (0.43)	10.53/−44.36 × 10^{-3}	23.76	20.81	23.76
4	[*s-cis*-**7b**•**5a**]#	2.00, 2.01		2.05 (+42%)	2.50 (+62%)	−1	0.67 (0.52)	14.42/−42.29 × 10^{-3}	27.03	24.45	19.96

[a] In parentheses: elongation of the breaking bond relative to **7a** calculated according to $[(d(O1-C1')_{TS} - d(O1-C1')_{7a})/d(O1-C1')_{7a}] \times 100$. $d(O1-C1')_{7a}$= 1.44 Å at B3LYP/6-311++G(d,p). *b*In parentheses: Elongation of the forming bond relative to **9a** calculated according to $[(d(C3-C3')_{TS} - d(C3-C3')_{9a})/d(C3-C3')_{9a}] \times 100$. $d(C3-C3')_{9a}$= 1.54 Å at B3LYP/6-311++G(d,p). [c] NBO and Mulliken (in brackets) charge separation between the allylic (blue) and the oxallylic (red) segment of the transition state. [d] Total activation barrier relative to the fully optimized lowest energy conformation of the separated thiourea and allyl vinyl ether. [e] Calculated single-point energies with use of the PCM solvent model in dichloroethane. [f] Free energy of activation for the [3,3]-rearrangement step.

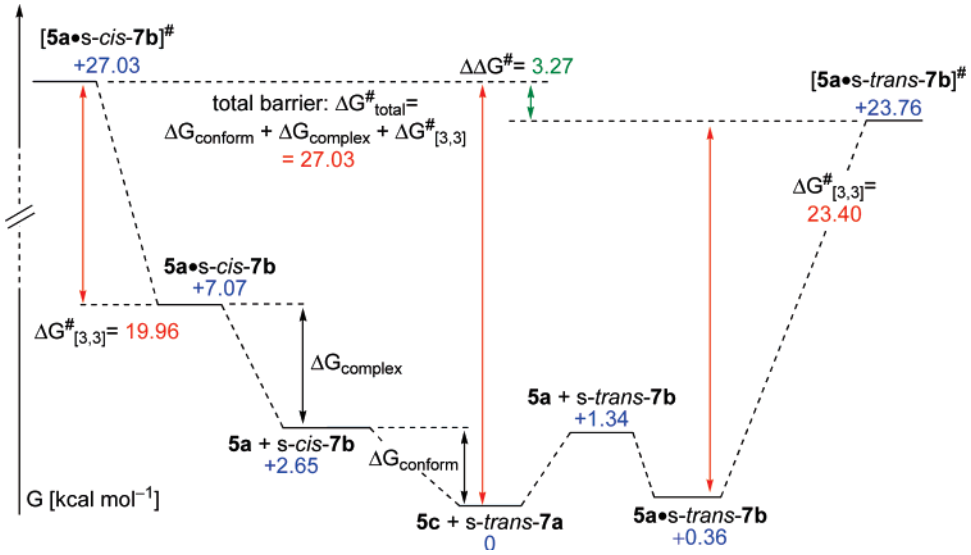
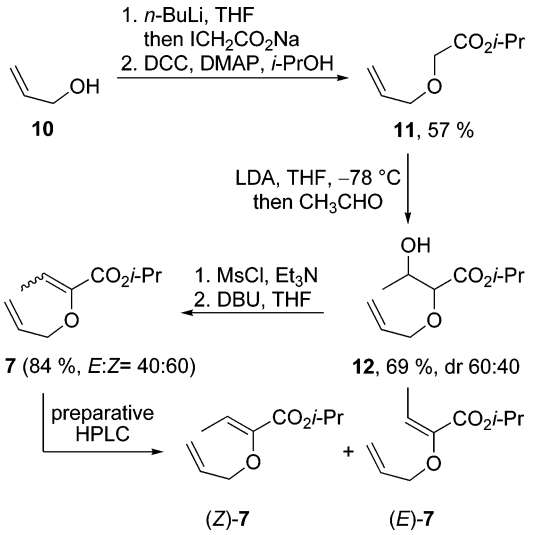


FIGURE 5. Gas-phase free energy diagram for the thiourea (**5**)-catalyzed Claisen rearrangement (B3LYP/6-311++G**).

[s-*trans*-**7b**•**5a**]# has a 3.3 kcal mol^{-1} lower $\Delta G^{\#}_{total}$ compared to the thermal rearrangement via [s-*cis*-**7b**]#. The presence of the coordinated thiourea significantly alters the relevant geometric data of the transition state (Table 6, entry 3). The asynchrony of the concerted bond reorganization is more pronounced leading to a looser and more polarized transition state compared to thermal rearrangement. Evidently, the dihedral angle ω is closer to planarity in [s-*trans*-**7b**•**5a**]# (+172°) compared to [s-*cis*-**7b**]# (+18°) (Table 6, entries 2 and 3). To evaluate the influence of the bis(hydrogen) bonding mode on the height of $\Delta G^{\#}_{total}$, the rearrangement via the transition state [s-*cis*-**7b**•**5a**]# was investigated next (Table 6, entry 4). The corresponding $\Delta G^{\#}_{total}$ for the rearrangement is 3.3 kcal mol^{-1} higher than that for the rearrangement via [s-*trans*-**7b**•**5a**]# and, furthermore, provides no rate acceleration compared to the thermal rearrangement via [s-*cis*-**7b**]# (Table 6, entries 2−4).

A comparative free energy diagram for the thiourea-catalyzed Claisen rearrangement of s-*trans*-**7a** via either [s-*trans*-**7b**•**5a**]# or [s-*cis*-**7b**•**5a**]# is depicted in Figure 5. The $\Delta G^{\#}_{total}$ for the thiourea (**5**)-catalyzed Claisen rearrangement is the sum of three free energies, namely the free energy of the formation of the "catalytically active" conformation of the thiourea (**5a**) and the allyl vinyl ether (s-*trans*-**7b** or s-*cis*-**7b**) ($\Delta G_{conform}$), the complex formation between the thiourea and the catalyst ($\Delta G_{complex}$), and finally, the actual free energy of activation of the [3,3]-rearrangement step ($\Delta G^{\#}_{[3,3]}$). It is apparent that $\Delta G^{\#}_{[3,3]}$ for the rearrangement via [s-*cis*-**7b**•**5a**]# is significantly lower than the rearrangement via [s-*trans*-**7b**•**5a**]# ($\Delta\Delta G^{\#}_{[3,3]} = -3.8$ kcal mol^{-1}) or the thermal rearrangement via [s-*cis*-**7b**]# ($\Delta\Delta G^{\#}_{[3,3]} = -5.5$ kcal mol^{-1}). However, the decreased $\Delta G^{\#}_{[3,3]}$ is due to "substrate destabilization", namely an endergonic conformational process ($\Delta G_{conform} = +2.7$ kcal mol^{-1}) and an endergonic complex formation ($\Delta G_{complex} = +4.4$ kcal mol^{-1}). Therefore, $\Delta G^{\#}_{total}$ remains almost unchanged compared to thermal rearrangement. With respect to the geometry of the transition state, it should be noted that [s-*cis*-**7b**•**5a**]# is even "looser" than [s-*trans*-**7b**•**5a**]# and, therefore, the charge separation between the allylic and the oxallylic segment is more pronounced than

SCHEME 2. Synthesis of the Allyl Vinyl Ether 7



the charge separation in [*s-trans*-**7b·5a**]$^{\#}$. Furthermore, the dihedral angle ω in [*s-cis*-**7b·5a**]$^{\#}$ shows only a small deviation from planarity (−1°) compared to [*s-trans*-**7b·5a**]$^{\#}$ (+172°).

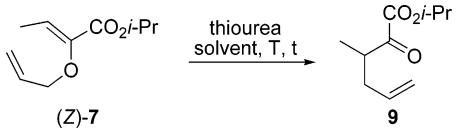
Experimental Results and Discussion

Our aldol condensation approach was employed for the synthesis of (*Z*)-**7** (Scheme 2).[30] Allylic alcohol **10** was first converted into the allyloxy acetate **11** by etherification followed by esterification with *i*-PrOH in the presence of *N*,*N*-dicyclohexylcarbodiimide (DCC). Subsequent aldol addition with acetaldehyde provided the β-hydroxy ester **12**. Mesylation followed by 1,8-diazabicyclo[5,4,0]undecene (DBU)-mediated elimination provided **7** as a mixture of double bond isomers. Subsequent separation by preparative HPLC led to isolation of (*Z*)-**7** on a multigram scale.

To qualitatively determine a rate accelerating effect of thiourea **5** on the Claisen rearrangement, the allyl vinyl ether (*Z*)-**7** was treated with varying amounts of the corresponding thiourea in different solvents and at different temperatures. Due to the limited solubility of **5** in dichloroethane (DCE), chloroform was utilized as aprotic solvent. Trifluoroethanol was employed as the polar protic solvent system for which a rate accelerating solvent effect on the Claisen rearrangement may be expected.[5] The results are summarized in Table 7. Control experiments in $CHCl_3$ and trifluoroethanol were performed to determine the intrinsic reactivity of the allyl vinyl ether (Z)-**7** in the absence of the thiourea **5** (Table 7, entries 1−4). Stirring (*Z*)-**7** in $CHCl_3$ or DCE for 5 days at room temperature led to small but significant conversions (Table 7, entries 1 and 4). An impressive solvent effect was observed when (*Z*)-**7** was stirred in trifluoroethanol. After 5 days at room temperature, a 41% conversion was determined by ^{1}H NMR (Table 7, entry 2). The same conversion was obtained after 6 h at 45 °C (Table 7, entry 3). Next, we studied the influence of 20 mol % of the thiourea **5** on the conversion (Table 7, entries 5−9). As was predicted by the calculation, the conversion in the presence of the thiourea **5** was almost unchanged compared to that of the control experiments. Change of solvent or reaction temperature was not suitable to improve the observed conversion.

(30) Hiersemann, M. *Synthesis* **2000**, 1279−1290.

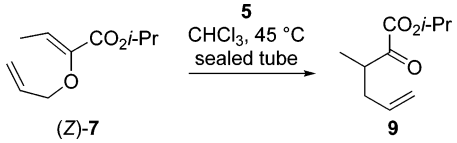
TABLE 7. Thiourea-Catalyzed Claisen Rearrangement



entry	thiourea	mol %	solvent [a]	*T* [°C]	*t*	conv.[b] [%]
1			$CHCl_3$	25	5 d	10
2			CF_3CH_2OH	25	5 d	41
3			CF_3CH_2OH	45	6 h	41
4			DCE	25	5 d	7
5	**5**	20	$CHCl_3$	25	5 d	17
6	**5**	20	CF_3CH_2OH	25	5 d	44
7	**5**	20	$CHCl_3$	45	6 h	15
8	**5**	20	CF_3CH_2OH	45	6 h	44
9	**5**	20	DCE	25	5 d	14

[a] DCE= 1,2-dichloroethane. [b] For entries 5−8, 0.1 mmol of **7** was dissolved in 2 mL of the indicated solvent. Conversion was determined by NMR. For experimental details see the Experimental Section.

Table 8. Thiourea 5-Accelerated Claisen Rearrangement



		conversion [%]	
entry	*t* [d]	100 mol % **5**	no **5**
1	1	41	23
2	2	63	41
3	3	72	52
4	5	84	57
5	7	87	74

In an attempt to elucidate a potential rate accelerating effect of stoichiometric amounts of the thiourea **5**, we determined the conversion in chloroform at 45 °C over a period of several days (Table 8). Comparison of the conversion in the presence and absence of 100 mol % of **5** clearly indicates a small and reproducible rate accelerating effect.[31]

Conclusions

A computational study concerning the nature of the transition state of the Claisen rearrangement in the presence and absence of the thioureas 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea (**5**) was performed. Although thiourea **5** is capable of lowering the barrier for the actual Claisen rearrangement step based on a bis(hydrogen) bond interaction with the ether oxygen atom of (*Z*)-**7**, a detailed computational investigation of a conceivable catalytic cycle for the thiourea-catalyzed Claisen rearrangement at the B3LYP/6-311++G(d,p) level of theory indicates that the transition state stabilization is not significant enough to overcome the energetic costs of conformational changes and complexation required for the formation of the reactive complex *s-cis*-**7b·5a**. The corresponding transition state [*s-cis*-**7b·5a**]$^{\#}$ is characterized by a concerted but asynchronous bond reorganization process that leads to its polarization. The calculated reduction of the total barrier $\Delta G^{\#}_{total}$ for the Claisen rearrange-

(31) Judging from a progressively yellowish colored reaction mixture, the thiourea **5** is apparently unstable at the reaction temperature. A thermal decomposition would diminish the effective concentration of **5**.

ment in the presence of **5** can be neglected. Solvent calculations confirm this finding. They do predict lower activation energies compared to the gas-phase values, but this is also true for the uncatalyzed, thermal reaction. Our experimental efforts validate that thioureas are ineffective as catalysts for the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers.

As initially suggested by Jorgensen, the design of a noncovalent organocatalyst for the Claisen rearrangement must clearly focus on a significant polarization of the transition state by strong hydrogen bonding to the ether oxygen atom. Increasing polarization, indicated by the charge separation between the allylic and the oxallylic segment of the transition state, is reflected in increasing lengths of the breaking and the forming bonds. An increasing polarization of the transition state apparently indicates (not causes) a decreasing rearrangement barrier. Last but not least, the choice of a suitable catalyst/substrate combination should avoid energetic costs for conformational changes and/or complex formation.

Experimental Section

Allyloxy Acetate 11. A solution of allylic alcohol (2.13 g, 36.6 mmol, 1.0 equiv) in THF (37 mL, 1 mL/mmol of allylic alcohol) was cooled to −78 °C. *n*-BuLi (16.5 mL, 36.6 mmol, 1.0 equiv) was added and the solution was stirred for 15 min at −78 °C. Solid sodium iodoacetate (8 g, 38.5 mmol, 1.05 equiv) was subsequently added at 0 °C. The resulting yellow suspension was allowed to warm to room temperature overnight. Aqueous 1 N KOH (40 mL) was added to the brownish suspension until the solid was completely dissolved. The two phases were then separated and the organic layer was extracted three times with aq 1 N KOH (10 mL). The combined aqueous phases were cooled to 0 °C and aq conc HCl (approximately 5 mL) was added carefully until pH 2 was reached. $CHCl_3$ (30 mL) was added and the layers were separated. The aqueous layer was extracted eight times with $CHCl_3$ (10 mL). The combined organic layers were dried over $MgSO_4$ and the solvents were removed under reduced pressure (40 °C, 300 mbar). The crude product was purified by kugelrohr distillation (5 mbar, 85 °C) to afford (allyloxy)acetic acid (2.13 g, 71%) as a colorless oil (R_f 0.1 hexanes/ethyl acetate 1/1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (d, J = 6.02 Hz, 2H), 4.11 (s, 2H), 5.25 (d, J = 10.3 Hz, 1H), 5.30 (dt, J = 16.7, 0.8 Hz, 1H), 5.83−5.95 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 66.6, 72.6, 118.9, 133.4, 175.6; IR (in substance) ν 1735, 3453 cm^{-1}. Anal. Calcd for $C_5H_8O_3$: C, 51.72, H, 6.94. Found: C, 51.7, H, 6.3.

(Allyloxy)acetic acid (2.0 g, 17.2 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (45 mL, 2.5 mL/mmol of (allyloxy)acetic acid) and cooled to 0 °C. *N*,*N*-(dimethylamino)pyridine (DMAP, 105 mg, 0.86 mmol, 0.05 equiv) and a solution of *N*,*N*′-dicyclohexylcarbodiimide (DCC, 3.90 g, 18.92 mmol, 1.1 equiv) in CH_2Cl_2 (7 mL, 0.4 mL/mmol (allyloxy)acetic acid) was successively added. After the reaction mixture was stirred for 5 min at 0 °C, *i*-PrOH (2.6 mL, 34.4 mmol, 2 equiv) was added to the brownish suspension. The reaction mixture was allowed to warm to room temperature overnight. The white precipitate was removed by filtration and washed with CH_2Cl_2. The solvents were then evaporated under reduced pressure (40 °C, 620 mbar) and the crude product was purified by kugelrohr distillation (2 mbar, 80 °C) to provide the ester **11** (2.18 g, 80%) as a colorless oil (R_f 0.8 hexanes/ethyl acetate 1/1).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (d, J = 6.27 Hz, 6H), 4.02 (s, 2H), 4.07 (d, J = 5.77 Hz, 2H), 5.08 (sept, J = 6.40 Hz, 1H), 5.23 (dt, J = 16.3, 10.3 Hz, 2H), 5.89 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.8, 67.5, 68.7. 72.5, 118.3, 134.1, 169.9; IR (in substance) ν 1750 cm^{-1}. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74, H, 8.92. Found: C, 60.85, H, 9.06.

β-Hydroxy Ester 12. A cooled (−78 °C) solution of **11** (7.36 g, 46.5 mmol, 1 equiv) in THF (3 mL/mmol of **11**) was added via syringe to a solution of LDA [prepared from diisopropylamine, (8.5 mL, 60.5 mmol, 1.3 equiv) and *n*-BuLi (2.3 M in *n*-hexane, 28 mL, 55.8 mmol, 1.2 equiv) in THF (3 mL/mmol) at −78 °C] in THF (139 mL) at −78 °C. The bright yellow solution was stirred for 15 min at −78 °C. Freshly distilled and cooled (−78 °C) acetaldehyde was then added to the reaction mixture at −78 °C. After the pale yellow solution was stirred for 15 min, saturated aq NH_4Cl solution (80 mL) was added at −78 °C. The mixture was warmed to room temperature, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were then dried with $MgSO_4$ and the solvents were evaporated at reduced pressure. Purification by flash chromatography (hexanes/ethyl acetate 10/1) provided the β-hydroxy ester **12** (6.5 g, 69%, dr = 60/40 relative configuration not assigned) as a yellowish oil (R_f 0.5 hexanes/ethyl acetate 1/1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (d, J = 6.3 Hz, 6H) 1.26 (d, J = 5.0 Hz, 3H), 2.30 (br s^{major}, 1H), 2.46 (br s^{minor}, 1H), 3.67 (d^{minor}, J = 5.5 Hz, 1H) 3.85 (d^{major}, J = 4.3 Hz, 1H), 3.90−4.00 (m, 1H), 4.03−4.11 (m, 1H), 4.19 (m, 1H), 5.10 (sept, J = 6.21 Hz, 1H), 5.20 (d, J = 10.3 Hz), 5.27 (dd, J = 17.31, 1.25 Hz), 5.82−5.96 (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 (in substance) ν 1729, 3469 cm^{-1}. Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39, H, 8.97. Found: C, 59.04, H, 9.11.

Allyl Vinyl Ether (*E*)- and (*Z*)-7. Et_3N (5.52 mL, 39 mmol, 1.2 equiv) was added at 0 °C to a solution of **12** in CH_2Cl_2 (60 mL). MsCl (2.8 mL, 36 mmol, 1.2 equiv) was then added at 0 °C. The ice bath was subsequently removed and the white suspension was stirred at room temperature for 30 min. The reaction was quenched by the addition of saturated aq $NaHCO_3$. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with $MgSO_4$ and the solvents were evaporated under reduced pressure. The crude product was then dissolved in THF (60 mL) and cooled to 0 °C. DBU (13.6 mL, 90 mmol, 3 equiv) was added and the reaction mixture was allowed to warm to room temperature overnight. The progress of product formation may be followed by TLC (R_f mesylate 0.75, R_f allyl vinyl ether 0.9, hexanes/ethyl acetate 1/1). The reaction mixture was then diluted with water and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried with $MgSO_4$ and the solvents were evaporated under reduced pressure. Purification by flash chromatography (hexanes/ethyl acetate 100/1) afforded the allyl vinyl ether **7** (4.61 g, 84%, colorless liquid) as a mixture of double bond isomers (*Z*/*E* = 60/40). The two diastereomers were separated by preparative HPLC: Nucleosil 50-7, 32 mm × 250 mm, *n*-heptane/ethyl acetate 99/1, flow 20 mL/min, pressure 31 × 10^{-1} MPa, (*Z*)-**4** = 23.5 min, (*E*)-**4** = 27.3 min, baseline separation with 100 mg (*E*/*Z*)-**4**/injection.

(*Z*)-**7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, J = 6.3 Hz, 6H), 1.75 (d, J = 7.0 Hz, 3H), 4.31 (d, J = 6.0 Hz, 2H), 5.06 (sept, J = 6.3 Hz, 1H), 5.19 (d, J = 10.3 Hz, 1H), 5.30 (dd, J = 17.1, 1.3 Hz, 1H), 5.92−6.04 (m, 1H), 6.31 (q, J = 7.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.7, 22.2, 68.7, 73.3, 118.4, 124.4, 134.3, 145.9, 163.5; IR (in substance) ν 1743 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19, H, 8.75. Found: C, 65.29, H, 8.71.

(*E*)-**7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, J = 6.27 Hz, 6H), 1.92 (d, J = 7.28 Hz, 3H), 4.23 (d, J = 5.27 Hz, 2H), 5.11 (sept, J = 6.27 Hz, 1H), 5.20 (dd, J = 10.54, 1.51 Hz, 1H), 5.31 (dd, J = 17.19, 1.63 Hz, 1H), 5.38 (q, J = 7.45 Hz, 3H), 6.01−5.89 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 12.6, 21.8, 68.5, 70.1, 112.7, 117.46, 133.3, 145.5, 163.5; IR (in substance) ν 1744 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19, H, 8.75. Found: C, 65.11, H, 8.92.

General Procedure for the Thiourea-Catalyzed Claisen Rearrangement. The thiourea was dissolved in the minimum amount of solvent required and the allyl vinyl ether (*Z*)-**7** was added via syringe under an atmosphere of argon. Reactions at elevated

temperature were performed in a sealed tube (as specified in the Methods and Materials section). The progress of the reaction was monitored by NMR. For this purpose, samples were taken from the reaction mixture at the indicated reaction times and the solvent was removed from the sample at reduced pressure at room temperature. The thiourea was then separated from the crude product mixture by short column chromatography (3 cm × 0.5 cm, hexanes/ethyl acetate 50/1). The conversion was determined by integration of suitable ^{1}H resonances (quartet at 6.31 ppm of (*Z*)-**7** vs multiplet at 2.39−2.51 ppm of **9**).

α-Keto Ester 9. ^{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, 1 H), 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 (in substance) ν 1724 cm^{-1}. Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19, H, 8.75. Found: C, 65.22, H, 8.84.

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Supporting Information Available: Cartesian coordinates for ground and transition states, number of imaginary frequencies, total electronic energies, and zero-point vibrational energies of all stationary points reported in the text; catalytic cycles for the three different basis sets 6-31G(d), 6-311+G(d,p), and 6-311++G(d,p) (Tables SI-1 to SI-4); experimental procedures for the synthesis of thiourea **5**; and copies of NMR spectra of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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