Organocatalysis

DOI: 10.1002/anie.201005183

Catalytic Enantioselective Claisen Rearrangements of *O*-Allyl β-Ketoesters**

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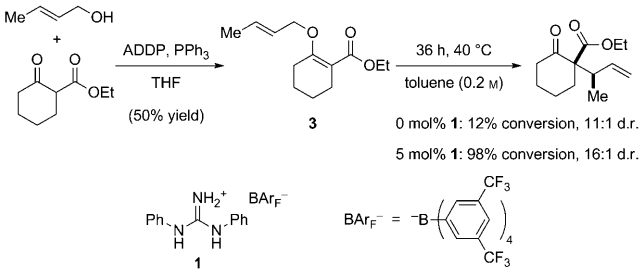
The selective construction of contiguous quaternary stereogenic centers, a motif found in many complex natural products, represents a significant synthetic challenge.[1] Among the limited number of approaches for the formation of bonds between such sterically congested carbon atoms, intramolecular processes such as polyene cyclizations,[2a,b] intramolecular cycloadditions,[2c] and sigmatropic rearrangements[2d,e] have been particularly effective. For addressing vicinal quaternary carbons, these transformations have only been applied in a diastereocontrolled manner using substrates containing pre-existing stereogenic centers, either as part of cleavable auxiliaries or structural features of the target molecule. The development of catalytic asymmetric methods for the direct and selective formation of such stereochemical arrays represents a highly desirable and challenging goal.

Since its discovery in 1912,[3] the [3,3]-sigmatropic rearrangement of allyl vinyl ethers (the Claisen rearrangement) has emerged as a proven strategy for the formation of carbon–carbon bonds between vicinal stereogenic centers.[4] Diastereoselectivity is generally predictable and high in these processes because of the concerted nature of the C–O bond-breaking and C–C bond-forming events as well as the large energetic preference for chair-like over boat-like transition states. Furthermore, important examples of enantioselective methods for Claisen rearrangements involving Lewis acid catalysis[5] have been identified recently for select substrates with chelating functional groups.

We reported recently that the achiral guanidinium ion **1**, bearing a non-coordinating tetraarylborate counterion, is a viable catalyst for the [3,3]-sigmatropic rearrangement of a wide range of substituted allyl vinyl ethers.[6] Rearrangements that proceed through highly dipolar transition structures were found to be particularly amenable to acceleration by hydrogen-bond donors. Substrates that meet this requirement possess either electron-donating substituents on the allyl group or electron-withdrawing substituents on the vinyl group in order to stabilize developing charge. In accord with this observation, the addition of **1** at 5 mol% loading induces rearrangement of β-ketoester derivative **3** to high levels of conversion. Notably, the diastereoselectivity is also enhanced under the guanidinium-catalyzed conditions (Scheme 1).



Scheme 1. *N,N′*-Diphenylguanidinium-catalyzed rearrangement of *O*-allyl β-ketoesters.

Here we report the discovery of chiral guanidinium-catalyzed Claisen rearrangements of cyclic *O*-allyl β-ketoesters as a method of broad scope for the formation of branched allylation products with both enantio- and diastereocontrol. While direct catalytic enantioselective allylations of β-ketoester nucleophiles, such as by phase-transfer alkylation[7a,b] or π-allyl metal chemistry,[7c–e] are highly effective with simple unsubstituted allyl electrophiles, regioselectivity for branched allylation and diastereoselectivity using more substituted electrophiles have proven to be difficult to achieve and highly dependent on the identity of the reaction partners.[8]

An extensive catalyst optimization study for the Claisen rearrangement was undertaken using representative 5- and 6-membered ring substrates (Table 1, entries 1a and 2). As was found previously in the rearrangement of *O*-allyl α-ketoesters,[6] catalyst **2** proved optimal among all catalysts studied in terms of both rate and enantioselectivity. Variation of the catalyst diamine backbone, heterocyclic component, or aryl substituent proved to be detrimental (see Supporting Information). The highest enantioselectivities were obtained in non-polar alkane solvents; however, toluene and dichloromethane also proved useful, affording products with only slightly diminished enantiomeric excess (*ee*).

A wide range of cyclic β-ketoester-derived substrates were synthesized and evaluated in order to determine the scope of the reaction. Many of the vinyl ether substrates could be prepared in modest yield by alkylation of the corresponding potassium enolate with allyl sulfonates in the presence of [18]crown-6. Mixtures of *C*- and *O*-allylated products were formed under these conditions, generally favoring the former. Higher selectivity for *O*-allylation was obtained under

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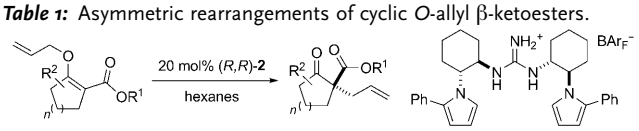
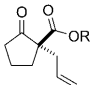
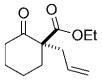
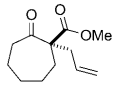
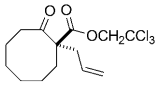
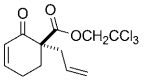
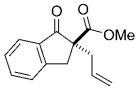
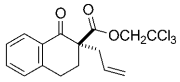
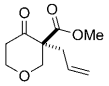
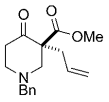
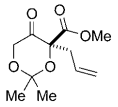
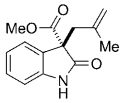
[**] This work was supported by the NIH (GM-43214). We acknowledge Matthew Rienzo for experimental assistance and Dr. Richard Staples for X-ray analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201005183.

Table 1: Asymmetric rearrangements of cyclic *O*-allyl β-ketoesters.



Entry	Product	*t*, *T*	Yield [%][a]	*ee* [%][b]
1a[c]	 R = Me	6 days, 30 °C	81	84
1b	R = allyl	6 days, 30 °C	82	83
1c	R = CH_2CCl_3	6 days, 30 °C	90	85
2		6 days, 22 °C	81	81[d]
3		5 days, 22 °C	98	87[d]
4		4 days, 22 °C	94	79
5		72 h, 22 °C	96	86
6		48 h, 22 °C	92	82
7		36 h, 22 °C	92	82
8		6 days, 22 °C	80	80
9		5 days, 22 °C	91	80
10		48 h, 22 °C	96	82
11		72 h, 22 °C	90	80[d]

[a] Yields of isolated products were determined for rearrangements run on a 0.1 mmol scale. [b] Enantiomeric excesses were determined by GC and HPLC analysis using commercial chiral columns. [c] A full screen of ester substituents was performed for the 5-membered ring substrate. Details are included in the Supporting Information. [d] The absolute configurations of the products in entries 2, 3, and 11 were determined by comparing the optical rotation to values reported in the literature (see Supporting Information).

Mitsunobu conditions using PPh_3 in conjunction with either diethyl azodicarboxylate (DEAD) or 1,1′-(azodicarbonyl)dipiperidine (ADDP).[9] This protocol afforded substrates for the enantioselective Claisen rearrangement in 40–52% isolated yield in a single step from the precursor alcohol and β-ketoester.

Simple carbocyclic substrates of a variety of ring sizes (Table 1, entries 1–4) were effective as were those containing unsaturation (entry 5), fused aromatic rings (entries 6 and 7), and heteroatoms (entries 8–10). In all cases, the products were isolated in high yield and enantiomeric excesses in the range of 79% to 87%. The Meerwein–Eschenmoser–Claisen rearrangement of a methallyloxyindole[10,5b] also proceeded with similar enantioselectivity, providing the allylated oxindole product (Table 1, entry 11). Indeed, the performance of catalyst **2** across a broad range of substrates is remarkably consistent, with the average enantioselectivity for all entries in Table 1 expressed in terms of free energy ($\Delta\Delta G^{\neq}$) being 1.38 kcal mol^{-1} with a relatively narrow standard deviation of 0.1 kcal mol^{-1}. Although the degree of asymmetric induction in these rearrangements is moderate, the broad substrate scope suggests a general and common basis for enantioinduction.

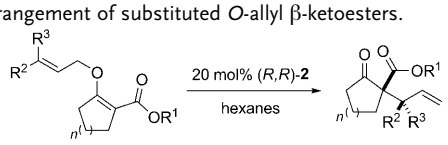
High conversion to product is observed for all rearrangements at or near room temperature using 20 mol% loadings of catalyst **2**. For substrates that require extended reaction times, higher rates can be obtained at higher temperatures with a small loss of enantioselectivity. For example, the cyclopentanone methyl ester substrate in entry 1a reached full conversion after 48 h at 40 °C, and the product was obtained in 80% *ee*.

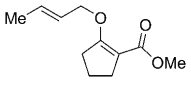
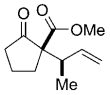
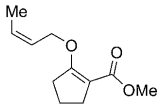
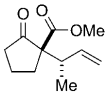
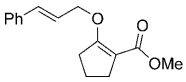
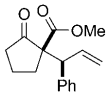
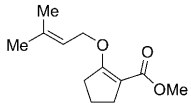
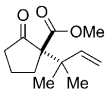
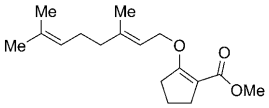
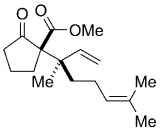
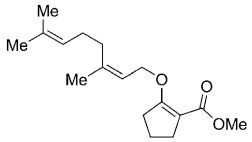
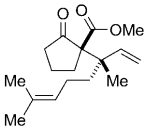
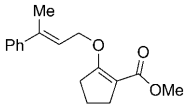
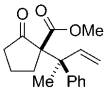
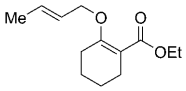
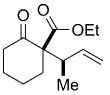
Due to the pericyclic nature of the [3,3]-sigmatropic rearrangement, substrates with substitution on the allyl component undergo rearrangement with complete regioselectivity for branched allylation. The scope for these substrates is illustrated in Table 2. Products of either diastereomeric series could be accessed using substrates with (*E*)- or (*Z*)-configured olefins (Table 2, entries 1 and 2). The relative configuration of the products is consistent with the rearrangement proceeding primarily through a chair-like transition state.[11] In addition to alkyl substitution, substrates possessing aryl groups were also effective (entries 3 and 7), providing products with similar enantioselectivity and slightly diminished diastereoselectivity. Finally, trisubstituted alkenyl substrates underwent rearrangement to generate products containing vicinal quaternary stereogenic centers (entries 5–7).

For three representative examples in Table 2, the catalyst loading was reduced to 10 mol% (see entries in parentheses). Although lower reaction rates were observed, all of the products were obtained in high yield and with only slightly diminished *ee*.

This method holds potential utility for addressing complex stereochemical relationships in natural product synthesis. A 0.5 mmol-scale rearrangement of the nerylated ethoxycyclohexenone substrate **4** was run under the standard reaction conditions (Scheme 2). After 72 h, 81% yield of the *C*-allylated product **5** was isolated with a 7:1 diastereomeric ratio and 81% *ee* for the major diastereomer. Upon completion of the reaction, analytically pure catalyst (*S*,*S*)-**2** was recovered in 95% yield. The particular stereochemical array formed in this rearrangement corresponds directly to the configuration of quaternary stereocenters found in hyperforin,[12] an important member of the polyprenylated phloroglucinol family of natural products. To date, only one enantioselective total synthesis has been reported.[13] The rearrangement product **5** was readily elaborated to the bicyclo[3.3.1]nonane core structure through an iodonium-induced carbocyclization.[14]

Table 2: Asymmetric rearrangement of substituted *O*-allyl β-ketoesters.



Entry	Substrate	Product[a]	*t*, *T*	Yield [%][b]	d.r.[c]	*ee* [%][d]
1			48 h, 22 °C (72 h, 22 °C)[e]	99 (99)	16:1 (15:1)	83 (81)
2			6 days, 40 °C	82	16:1	81
3			48 h, 4 °C (72 h, 4 °C)[e]	99 (99)	5:1 (5:1)	83 (80)
4			48 h, 40 °C (72 h, 40 °C)[e]	87 (99)	– (–)	82 (81)
5			6 days, 30 °C	99	10:1	82
6			6 days, 30 °C	99	10:1	85
7			4 days, 22 °C	99	5:1	78
8[11]			48 h, 22 °C	98	> 20:1	85

[a] Major diastereomer. [b] Yields of isolated products were determined for rearrangements run on a 0.1 mmol scale. [c] Diastereomer ratios were determined by ^{1}H NMR spectroscopy. [d] Enantiomeric excesses were determined by chiral GC and HPLC analysis using commercial chiral columns. [e] The yield, d.r., and *ee* in parentheses were obtained using 10 mol% of the catalyst under the reactions conditions shown.

Computational studies were conducted in order to probe the nature of the catalyst–substrate interaction and the basis for the observed accelerations. Calculated lowest energy structures for the substrate, product, and transition state for both the uncatalyzed and *N*,*N*′-dimethylguanidinium-catalyzed reaction pathways are depicted in Figure 1.

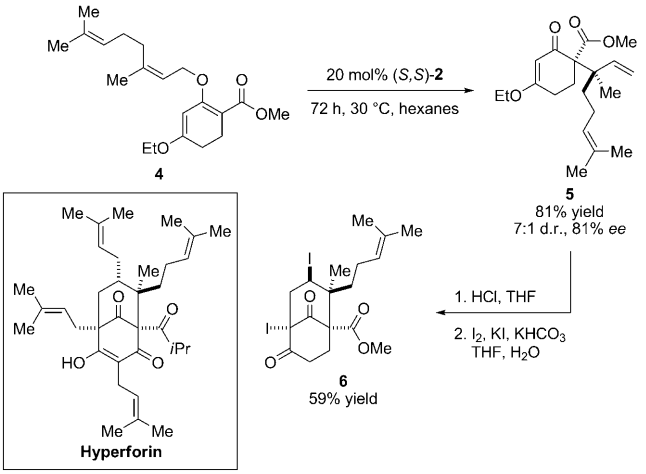
While a slight energetic preference for the *s-trans* conformation of the α,β-unsaturated ester was calculated for the uncatalyzed pathway, there is a large preference for the *s-cis* conformation in the catalyzed pathway. This geometry permits simultaneous interactions between the catalyst and both the ester and vinyl ether oxygen atoms. While the substrate is bound primarily through the more Lewis basic ester group, binding is biased toward the ether oxygen in the transition state. It is likely that both the developing negative charge on the ether oxygen as well as alleviation of steric hindrance by partial C–O bond-breaking contribute to this change in geometry. This transition state binding mode is remarkably similar to that calculated for the rearrangement of a model *O*-allyl α-ketoester substrate,[6] and provides a rationale for the observation that catalyst **2** is capable of high levels of asymmetric induction for both substrate classes.

The overall calculated effect of the guanidinium ion is a 5.3 kcal mol^{-1} lowering of the activation barrier for the rearrangement. Additionally, binding of the product β-ketoester is predicted to be 1.4 kcal mol^{-1} less favorable than binding of the substrate, consistent with the observation of catalyst turnover.

Ongoing efforts are directed at applying insights gleaned from this system to other fundamental transformations that are amenable to asymmetric catalysis by hydrogen-bond donors.

Experimental Section

5: 167.2 g of the substrate **4** (1.0 equiv, 0.5 mmol) was weighed into a 20 mL screw-top vial and dissolved in 10 mL of hexanes. 137.0 mg of (*S*,*S*)-**2** (20 mol%, 0.1 mmol) was added as a solid, and the vial was sealed under air. The heterogeneous reaction was stirred in a temperature-controlled aluminum heating block at 30 °C for 72 h. The crude mixture was concentrated under reduced pressure and loaded directly onto a silica gel column. The product was eluted using a solvent gradient of 0–50% Et_2O in hexanes. The catalyst was then recovered from the column by eluting with 4% MeOH in CH_2Cl_2. 130.8 mg of (*S*,*S*)-**2** (95% recovery) was isolated after drying under reduced pressure (0.5 torr). 135.5 mg of the rearranged product **5** (0.41 mmol, 81% yield) was isolated as a 7:1 mixture of diastereomers (determined by ^{1}H NMR integration). The major diastereomer was determined to be 81% *ee* by chiral HPLC analysis (OD-H, 1 mL min^{-1}, 2% isopropyl alcohol (IPA)/hexanes, t_r(major) = 21.6 min, t_r(minor) = 15.9 min), and the minor diastereomer was determined to be 40% *ee* (OD-H, 1 mL min^{-1}, 2% IPA/hexanes, t_r(major) = 23.9 min, t_r(minor) = 18.0 min). $[\alpha]_D^{23} = -74.2°$ ($c = 0.37$, CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 6.25$ (br. m, 1H), 5.30 (s, 1H), 5.10 (d, $J = 11.0$ Hz, 1H), 5.06 (t, $J = 7.0$ Hz, 1H), 4.92 (d, $J = 17.1$ Hz, 1H), 3.85 (q, $J = 7.0$ Hz, 2H), 3.65 (s, 3H), 2.48–2.30 (m, 2H), 2.30–2.21 (m, 1H), 2.20–1.71 (m, 4H), 1.64 (s, 3H), 1.55 (s, 3H), 1.46–1.36 (m, 1H), 1.33 (t, $J = 7.0$ Hz, 3H), 1.16 ppm (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 195.7$, 175.3, 171.4, 143.8, 131.1, 125.0, 113.9, 104.6, 64.4, 62.2, 52.1, 46.1, 35.9, 27.9, 27.0, 25.8, 23.2, 17.7, 17.3,



Scheme 2. Claisen rearrangement to establish the vicinal quaternary stereogenic centers found in hyperforin and subsequent elaboration to the bicyclo[3.3.1]nonane core structure.

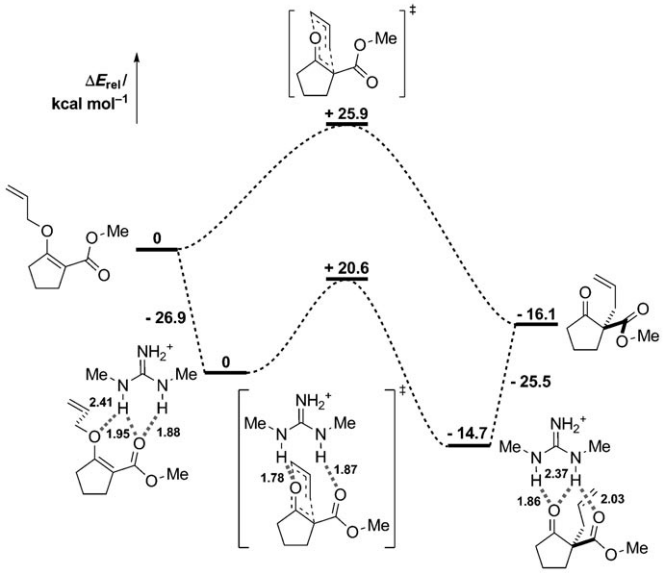


Figure 1. Calculated reaction coordinate for the uncatalyzed (top) and *N*,*N*′-dimethylguanidinium-catalyzed (bottom) rearrangement at the B3LYP/6-311 + G(d,p) level of DFT. Relative energies are in kcal mol^{-1}, and key hydrogen-bond distances are shown in Angstroms.

14.2 ppm; LRMS (APCI-ESI): 357.2 [*M*+Na]$^+$; FTIR (neat): $\tilde{\nu}$ = 2980 (w), 1724 (m), 1660 (m), 1614 (s), 1431 (w), 1381 (m), 1314 (w), 1231 (m), 1189 (s), 1035 (w), 897 cm^{-1} (w).

Received: August 18, 2010
Published online: November 15, 2010

Keywords: asymmetric catalysis · Claisen rearrangement · hydrogen bonding · keto esters · organocatalysis

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