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Development of a New Lewis Acid-Catalyzed [3,3]-Sigmatropic Rearrangement: The Allenoate-Claisen Rearrangement

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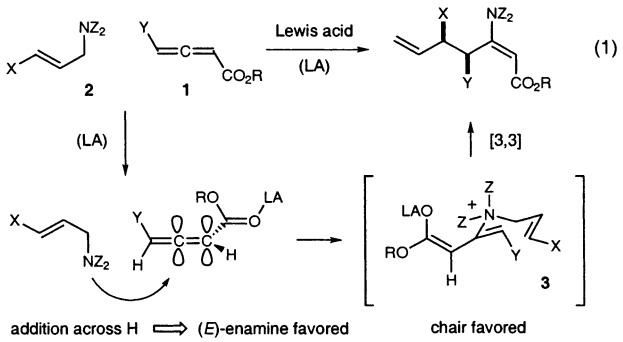
Over the last 90 years, the Claisen rearrangement has become a preeminent technology for the rapid construction of complex organic architecture, securing its widespread use in both natural product and medicinal agent synthesis.[1] To date, more than 15 variants of this powerful [3,3]-isomerization have been documented, including a variety of asymmetric methods;[2] however, only one example of an enantioselective catalytic Claisen has been accomplished.[2d] As part of an ongoing program to develop sigmatropic rearrangements that are amenable to enantioselective catalysis we recently reported the acyl-Claisen reaction,[3a] a metal-mediated addition−rearrangement sequence that is readily extended to enantioselective[3b] and iterative cascade sequences.[3c] In this communication we outline the design of a new Lewis acid-catalyzed Claisen rearrangement that allows the stereoselective production of β-amino-$\alpha,\beta,\epsilon,\zeta$-unsaturated-$\gamma,\delta$-disubstituted esters from simple allenoate esters and allylic amines (eq 1). We expect this catalytic addition−rearrangement sequence will also provide a valuable platform for the development of a new enantioselective Claisen protocol.

Allenoate–Claisen Rearrangement



As outlined in eq 1, we envisioned that a broad range of allenic esters[4] (**1**) might be activated toward the 1,4-conjugate addition of tertiary allylamines (**2**) using Lewis acids. Accordingly, this activation−addition step would provide zwitterionic allyl-vinylammonium complexes (**3**) that exhibit the appropriate charge orientation to rapidly participate in [3,3]-bond reorganization. As part of our design plan, we anticipated high levels of diastereoselection in the carbon−carbon bond-forming event on the basis of (i) π-facial discrimination in the cumulene addition step,[5] leading to selective formation of the (*E*)-enamine intermediate (**3**), and (ii) the propensity of [3,3]-bond isomerizations to populate chairlike transition states.[1] In the context of synthetic utility, this new Claisen process would allow rapid access to 1,2-disubstituted-β-enamino esters (eq 1), a versatile structural motif[6] with respect to reductive,[6a] oxidative,[6b] and π-nucleophile elaboration[6c] (see Supporting Information).

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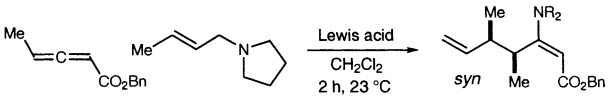
Table 1. Lewis Acid-Catalyzed Allenoate-Claisen Rearrangement



entry	Lewis acid	mol % cat.	% yield	*syn*:*anti*[a]
1	–	–	NR	–
2	$Yb(OTf)_3$	5	82	>98:2
3	$Sn(OTf)_2$	5	86	>98:2
4	$Cu(OTf)_2$	10	87	>98:2
5	$TiCl_4 \cdot THF_2$	10	86	>98:2
6	$AlCl_3$	10	83	>98:2
7	$MgBr_2 \cdot Et_2O$	10	81	>98:2
8	$FeCl_3$	10	83	>98:2
9	$Zn(OTf)_2$	10	95	>98:2
10	$Zn(OTf)_2$	5	93	>98:2

[a] Product ratios determined by ^{1}H NMR analysis.

The proposed allenoate-Claisen reaction was first evaluated using (*E*)-crotyl pyrrolidine with benzyl 2,3-pentadienoate and a variety of Lewis acids. As outlined in Table 1, this new rearrangement was successful with a broad range of metal salts of diverse Lewis acidity including $AlCl_3$, $Cu(OTf)_2$, $FeCl_3$, and $Zn(OTf)_2$. Importantly, high levels of reaction efficiency and diastereocontrol were observed in all metal-mediated cases (entries 2−10, 81−95% yields, ≥98:2 *syn*:*anti*), while rearrangement adducts were not detected in the absence of Lewis acid (entry 1). The superior catalytic efficiency exhibited by $Zn(OTf)_2$ prompted us to select this metal salt for further exploration.

Experiments that probe the scope of the allylamine substrate are summarized in Table 2. Considerable variation in the steric demand of the olefin substituent (R_1 = H, Me, *i*-Pr, and Ph, entries 1−5) is possible without loss in efficiency or stereocontrol (80−97% yield, >94:6 *syn*:*anti*). The reaction also appears quite general with respect to the tertiary amine moiety (entries 3, 6, and 7, 81−97% yield, ≥94:6 dr). In accord with established Claisen protocols,[1] the relative sense of stereoinduction can be dictated by judicious selection of olefin geometry on the allyl component. While high levels of *syn*-stereocontrol can be secured with *trans*-allylic amines (entries 1, 3, and 4, >94:6 *syn*:*anti*), the *anti*-adduct is readily accessed using the *cis*-isomer (entry 2, <2:98 *syn*:*anti*).

As revealed in Table 3, significant modification in the allenoate structure can be tolerated. Steric and electronic variation of the allenic substituent (R_2 = H, Cl, Me, allyl, *i*-Pr, and Ph, entries 1−6) has apparently little influence on reaction selectivity (≥93:7 dr). Moreover, the stereoselective installation of γ-amino substituents can be accomplished using γ-phthalyl allenic esters (entry 7, 75% yield, 91:9 *syn*:*anti*).

The proficiency of the allenoate-Claisen rearrangement to rapidly construct synthetically challenging structural motifs has been examined. As highlighted with the isomeric substrates geranyl (**4**) and

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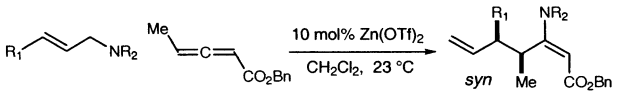
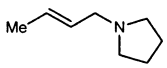
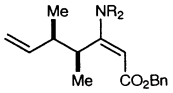
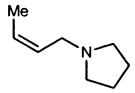
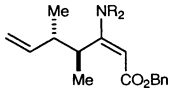
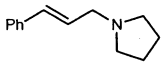
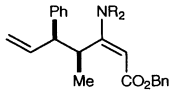
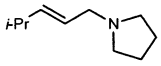
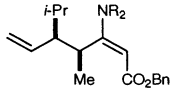
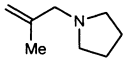
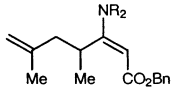
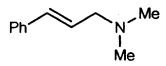
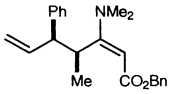
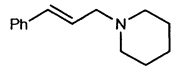
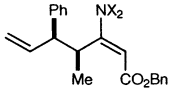
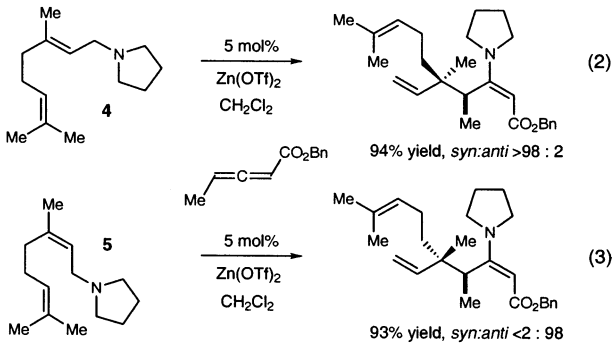
Table 2. Catalyzed Allenoate-Claisen Rearrangement between Benzyl 2,3-Pentadienoate and Representative Allyl Pyrrolidines



entry	amine	product[a]	yield	*syn*:*anti*[b,c]
1			95	>98:2
2			94	<2:98
3			97	94:6
4			81	> 98:2
5			80	--
6			81	94:6
7			87	94:6

[a] NR_2 = *N*-pyrrolidine, NX_2 = *N*-piperidine. [b] Ratios determined by GLC or ^{1}H NMR analysis. [c] Relative configurations assigned by X-ray analysis, chemical correlation or by analogy.

neryl (**5**) pyrrolidine (eqs 2 and 3), complementary access to both *syn* and *anti* configurations of 1,2-tertiary-quaternary carbon stereogenicity[7] can be accomplished in excellent yield and selectivity (eq 2, 94% yield, >98:2 *syn*:*anti*; eq 3, 93% yield, <2:98 *syn*:*anti*).

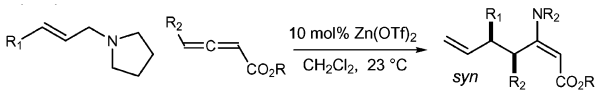


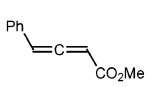
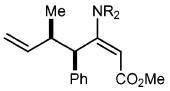
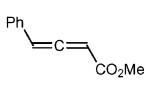
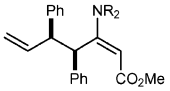
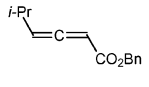
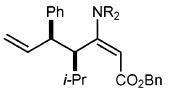
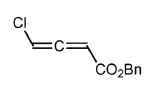
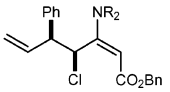
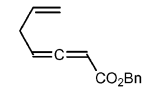
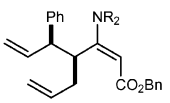
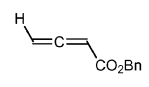
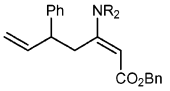
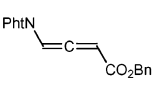
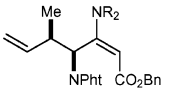
Finally, preliminary studies have revealed that the allenoate-Claisen rearrangement is a suitable platform for enantioselective catalysis. Studies toward this goal as well as a full account of this survey are forthcoming.

Acknowledgment. Support was provided by the NIHGMS (R01 GM61214-01) and the UC-AIDS Research Program. We are grateful to Dr. T. P. Yoon (Harvard University) for helpful discussions.

Supporting Information Available: Experimental procedures, structural proofs, and spectral data for all new compounds are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

Table 3. Catalyzed Allenoate-Claisen Rearrangement between Allyl Pyrrolidines and Representative Allenic Esters



entry	R_1	allene	product[a]	yield	*syn*:*anti*[b,c]
1	Me			86	97:3
2	Ph			94	94:6
3	Ph			94	94:6
4	Ph			84	93:7
5	Ph			96	95:5
6	Ph			84	--
7	Me			75	91:9

[a] NR_2 = *N*-pyrrolidine. [b] Product ratios determined by GLC or ^{1}H NMR analysis. [c] Relative configurations assigned by X-ray analysis or analogy.

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(2) (a) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026. (b) Kazmaier, U.; Krebs, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2012. (c) Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 1165. (d) Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 4700.

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