Development of a New Lewis Acid-Catalyzed Claisen Rearrangement

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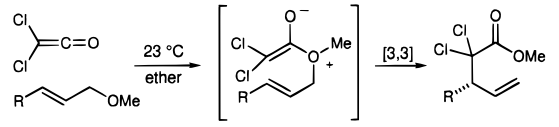
Since its discovery in 1912,[1] the Claisen rearrangement has become one of the most powerful tools for carbon−carbon bond formation in chemical synthesis.[2] This [3,3]-sigmatropic rearrangement, which involves the conversion of an allyl vinyl ether to an α,*β*-disubstituted *γ*,*δ*-unsaturated carbonyl, generally proceeds with high levels of stereocontrol, securing its widespread use in natural product and medicinal agent synthesis.[2] Activation of this rearrangement has traditionally been accomplished under thermal control; however, significant rate acceleration can be achieved through the incorporation of cationic[3] or anionic[4] charge in the bond reorganization event. Despite its prolific use in chemical synthesis and disposition toward charge acceleration, only two examples of catalytic Claisen variants have been reported.[5] In this paper we describe a broadly useful Lewis acid-catalyzed [3,3]-sigmatropic rearrangement that we expect will provide a new avenue for the development of an enantioselective catalytic Claisen process.[6]

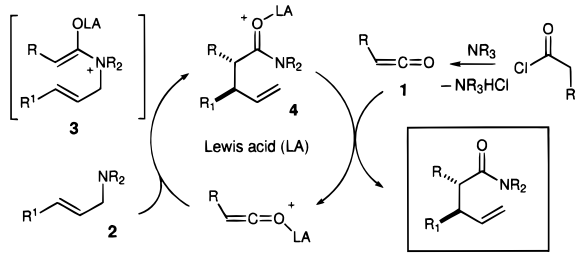
In 1978, Bellus and Malherbe reported the conceptually novel ketene-Claisen reaction.[7] In an attempt to perform a [2 + 2] cycloaddition, the authors discovered that treatment of an allyl ether with dichloroketene resulted instead in the formation of a 1,3-dipolar allyl vinyl ether, which subsequently underwent [3,3]-bond reorganization (eq 1). Although the scope of this reaction



(1)

was determined to be limited to highly electrophilic ketenes,[7] this study first demonstrated the capacity of zwitterionic 1,5-dienes to readily participate in charge-accelerated sigmatropic isomerization. Subsequently, the studies of Edstrom,[8a] Mariano,[9a] Roberts,[8c] Vedejs,[5a] Nubbemeyer,[9b] and Hegedus[9c] have demonstrated the utility of tertiary allylic amines in analogous [3,3]-sigmatropic rearrangements.

Scheme 1



We recently embarked upon the development of a catalytic Claisen process based upon design features derived from the Bellus-Claisen reaction. As outlined in Scheme 1, we envisioned that a broad range of ketenes (**1**) might be activated toward the addition of tertiary allyl amines (**2**) using Lewis acids. Accordingly, this activation−addition step would provide zwitterionic allyl-vinylammonium complexes (**3**) that exhibit the appropriate charge orientation to rapidly undergo [3,3]-bond reorganization to provide Claisen adducts (**4**). In contrast to a number of established Claisen variants, we expected this addition−rearrangement sequence to be catalytic in metal salt, providing an attractive platform for the development of an enantioselective process.

Bearing in mind that (i) ketenes are often prohibitively unstable toward isolation[10] and (ii) tertiary amine-promoted dehydrohalogenation of acid halides is a common method for cumulene production,[10,11] we selected acid chlorides as an *in situ* source of ketene for this survey.

Our catalytic Claisen strategy was first evaluated using propionyl chloride with (*E*)-crotyl morpholine[12] in the presence of *i*-Pr_2EtN and a series of metal salts. As revealed in Table 1, this addition−rearrangement sequence was successful with a variety of Lewis acids including $Yb(OTf)_3$, $AlCl_3$, $Ti(OiPr)_2Cl_2$, and $TiCl_4{\cdot}THF_2$. In all cases the 1,2-disubstituted Claisen adduct was formed in high yield (>75%, entries 2−5) and with excellent levels of stereocontrol (>99:1 *anti*/*syn*).[13] Notably, this reaction is contingent upon the use of Lewis acid (entry 1); control experiments performed in the absence of metal salt resulted only in the production of ketene dimer. Importantly, this procedure can be performed using only catalytic quantities of Lewis acid (5−10 mol %), an essential criterion for the development of an enantioselective catalytic process. The excellent levels of diastereoselectivity (>99:1 *anti*/*syn*) and catalyst efficiency (5 mol %) displayed by $TiCl_4{\cdot}THF_2$ to afford **5** in 92% yield (entry 5) defined this metal salt as the optimal catalyst for exploration of this new acyl-Claisen rearrangement.

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(4) (a) Arnold, R. T.; Searles, S. *J. Am. Chem. Soc.* **1949**, *71*, 1150. (c) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc*. **1972**, *94*, 5897. (d) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc*. **1982**, *104*, 4972. (e) Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722. (f) Buchi, G.; Vogel, D. E. *J. Org. Chem*. **1985**, *50*, 4664. (g) Alker, D.; Mageswaren, S.; Ollis, W. D.; Shahriari-Zavareh, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1623.

(5) (a) Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579. (b) Saito, S.; Shimada, K.; Yamamoto, H. *Synlett* **1996**, 720.

(6) An asymmetric catalytic variant of the Claisen rearrangement has yet to be realized. Enantioselective Clasien rearrangements involving stoichiometric chiral promoters have been documented: (a) Maruoka, K.; Susumu, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 1165. (b) Maruoka, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 7791. (c) Corey, E. J.; Lee, D. H. *J. Am. Chem. Soc.* **1991**, *113*, 4026. (d) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193.

(7) (a) Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096. (b) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem*. **1983**, *48*, 860.

(8) (a) Edstrom, E. D. *J. Am. Chem. Soc*. **1991**, *113*, 6690. (b) Ishida, M.; Muramaru, H.; Kato, S. *Synthesis* **1989**, 562. (c) Maruya, R.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Thomas, R. J.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1617. (d) Rosini, G.; Spinetti, G. G.; Foresti, E.; Pradella, G. *J. Org. Chem*. **1981**, *46*, 2228.

(9) For conceptually related zwitterionic aza-Claisen rearrangements see: (a) Kunng, F.-A.; Gu, J.-M.; Chao, Y.; Mariano, P. S. *J. Org. Chem*. **1983**, *48*, 4262. (b) Diederich, M.; Nubbemeyer, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1026. (c) Deur, C. J.; Miller, M. W.; Hegedus, L. S. *J. Org. Chem*. **1996**, *61*, 2871. See also ref 5a.

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(11) Staudinger, H. *Chem. Ber.* **1905**, *38*, 1735.

(12) Preliminary studies indicate pyrrolidine- and dimethylamine-derived allyl systems to be less general in this process.

(13) In a representative procedure the allyllic morpholine (0.8 mmol) and *i*-Pr_2EtN (1.2 mmol) were added sequentially to a catalyst solution (0.08 mmol) in CH_2Cl_2 at 23 °C. To the resulting solution was added the acid chloride as a 1.0 M solution in CH_2Cl_2 (0.98 mmol) over 5 min. After the reaction was complete (2−6 h), the mixture was then diluted with Et_2O and washed with 1 N NaOH. The organics were dried (Na_2SO_4), concentrated, and then purified by flash chromatography.

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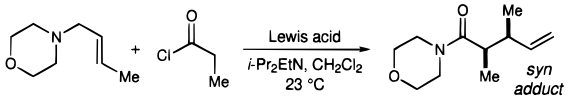
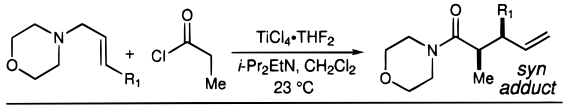
Table 1. Catalyzed Acyl-Claisen Rearrangement between Crotyl Morpholine and Propionyl Chloride

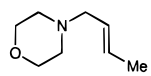
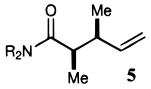
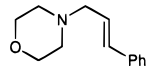
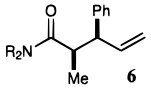
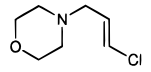
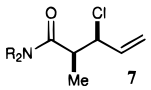
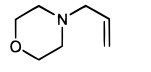
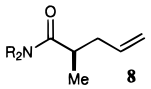
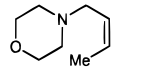
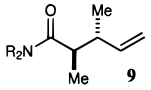


entry	Lewis acid	mol% cat	% yield	*syn*:*anti*[a]
1	--	--	NR	--
2	$Yb(OTf)_3$	10	80	>99:1
3	$AlCl_3$	10	90	>99:1
4	$Ti(O\textit{i}\text{-}Pr)_2Cl_2$	10	76	>99:1
5	$TiCl_4{\bullet}THF_2$	5	92	>99:1

[a] Product ratios determined by GLC using a Bodman CC1701 column.

Table 2. Catalyzed Acyl-Claisen Rearrangement between Representative Allyl Morpholines and Propionyl Chloride



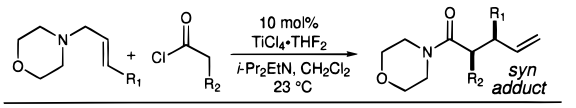
entry	amine	mol% cat	product[a]	yield	*syn*:*anti*[b,c]
1		5	 **5**	92	>99:1
2		10	 **6**	76	>99:1
3		10	 **7**	95	>99:1
4		10	 **8**	95	--
5		20	 **9**	74	5:95

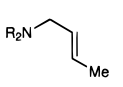
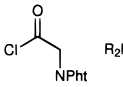
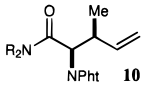
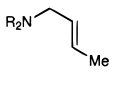
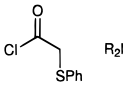
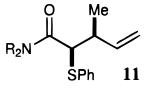
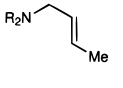
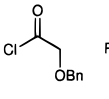
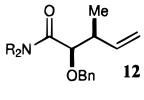
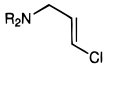
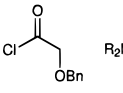
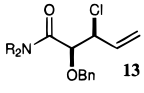
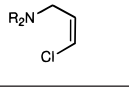
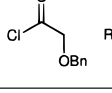
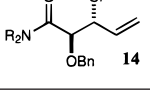
[a] NR_2 = *N*-morpholine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative configurations assigned by single-crystal X-ray analysis or chemical correlation to a known compound (Supporting Information).

Experiments that probe the scope of the allyl morpholine reaction component are summarized in Table 2. Significant structural variation in the allyl substituent (R_1 = H, alkyl, aryl, or halogen, entries 1−4) is possible without loss in yield or diastereoselectivity (>76% yield, >99:1 *syn*/*anti*). In accord with established Claisen methodology,[2a] complementary stereocontrol can be accessed through the appropriate selection of double bond geometry on the allyl component. While excellent levels of *syn* stereoselection are observed with *trans*-allyllic morpholines (entries 1−3), the *anti* Claisen adduct is readily furnished (95:5 *anti*:*syn*) using the *cis* double bond isomer (entry 5).

The reaction is also quite general with respect to the acid chloride structure (Table 3). As highlighted in entry 1, this methodology provides a new strategy for the catalytic production of unnatural β-substituted α-amino acids using α-phthalylglycyl chloride (77% yield, 98:2 *syn*/*anti*). This process is also tolerant of oxygen and sulfur substituents on the acyl chloride component (>81% yield, 86:14 to 92:8 *syn*/*anti*, entries 2−3). A powerful feature of this new Claisen process is the capacity to build diverse functional and stereochemical arrays that are not readily available using conventional catalytic methods. For example, both the *syn* and *anti* α-oxy, β-chloro Claisen isomers **13** and **14** can be accessed in high yield and stereospecificity from chloro-substituted allyl morpholines and α-benzyloxyacetyl chloride (entries 4−5).

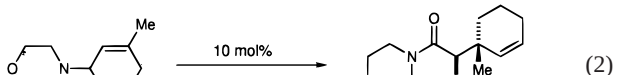
Table 3. Catalyzed Acyl-Claisen Rearrangement between Allyl Morpholines and Representative Acid Chlorides



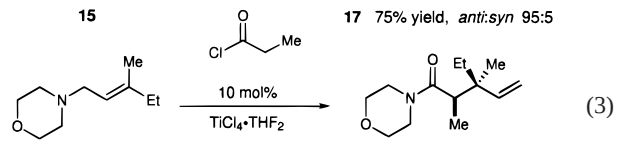
entry	amine[a]	acid-Cl	product[a]	yield	*syn*:*anti*[b,c]
1			 **10**	77	>99:1
2			 **11**	81	92:8
3			 **12**	91	86:14
4			 **13**	83	90:10
5			 **14**	70	10:90

[a] NR_2 = *N*-morpholine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative configurations assigned by single-crystal X-ray analysis or chemical correlation to a known compound (Supporting Information).

A further illustration of the proficiency of this reaction to provide catalytic access to elusive structural motifs is presented in the rearrangement of 3,3-disubstituted allyl morpholines **15** and **16** (eqs 2 and 3). The principal issue in these reactions is



(2)



(3)

that of transition state-controlled π-facial discrimination to selectively build quaternary carbon stereocenters on both cyclic and acyclic architecture. The reaction of propionyl chloride with 1-methyl-3-*N*-morpholino-cyclohexene (**15**) provides excellent levels of diastereocontrol in the formation of the quaternary carbon bearing cyclic adduct **17** (eq 2, 95:5 *anti*/*syn*). As illustrated in eq 3, the reaction can also translate the subtle methyl versus ethyl substitution pattern on morpholine **16** to furnish the acyclic framework **18** with complete stereospecificity (>99:1 *syn*/*anti*).

Finally, preliminary studies have recently been conducted that establish this new Claisen methodology as a suitable platform for enantioselective catalysis. Details of this work along with a full account of this survey will be forthcoming.

Acknowledgment. This research has been supported by Boehringer-Ingelheim (NIA) and Johnson and Johnson (FGA) and kind gifts from Merck, Roche-Biosciences, and Warner-Lambert.

Supporting Information Available: Experimental procedures, spectral data for all compounds, stereochemical proofs, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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