The Acyl-Claisen Rearrangement.
Development of a Novel Metal-Catalyzed Claisen Rearrangement and Enantioselective Variants of the Acyl-Claisen Rearrangement

Thesis by

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Abstract

The development of a versatile new variant of the Claisen rearrangement is described. In this new Lewis acid-catalyzed process, the condensation of an allylic amine with a ketene (generated in situ from dehydrohaolgenation of an acid chloride) results in formation of a zwitterionic intermediate. Sigmatropic rearrangement via a highly organized cyclic transition state allows stereospecific access to a diverse range of α,β-disubstituted-γ,δ-unsaturated amides in excellent yields and diastereoselectivities for a range of alkyl-, aryl-, and heteroatom-substituted substrates. The ability of this new methodology to generate quaternary carbon stereocenters on both cyclic and acyclic carbon frameworks is demonstrated.

An enantioselective variant of the acyl-Claisen rearrangement employing a chiral magnesium(II)-bis(oxazoline) Lewis acid has been developed. The use of chelating acid chlorides provides excellent organizational control over the transition state, allowing the rearrangement of a range of allyl morpholine substrates to proceed in up to 97% ee. Excellent levels of complementary diastereocontrol can be achieved in a predictable and highly selective manner from the rearrangement of the (*E*)- and (*Z*)-isomers of the allyl amine substrates. This reaction is also proficient at accessing quaternary carbon stereocenters.

The scope of the enantioselective acyl-Claisen has been expanded by the use of a new chiral boron Lewis acid. This rearrangement does not require chelating acid chloride substrates for good enantioinduction. Thus, a range of α-alkyl-, α-alkoxy-, α-thio-, and α-halogen-substituted Claisen adducts can be produced in up to 93% ee.

Table of Contents

List of Schemes

List of Figures

List of Tables

Chapter 5

"Fate, it seems, is not without a sense of irony."

-Morpheus, *The Matrix*

Chapter 1

The Asymmetric Claisen Rearrangement

Introduction

Since its initial discovery in 1912,[1] the Claisen rearrangement has become recognized as one of the most powerful carbon-carbon bond-forming reactions available for the construction of complex organic molecules.[2] In its most basic formulation, this reaction is the [3,3]-sigmatropic rearrangement of an allyl vinyl ether to a γ,δ-unsaturated carbonyl compound (Figure 1). Formally, the bond reorganization event can be regarded as an intramolecular S_N' reaction between an enol ether (Claisen), thiocarbonyl enol (thio-Claisen), or enamine (aza-Claisen) and an allylic ether, sulfide, or amine, respectively. The formation of a new carbon-carbon bond in the rearrangement results in the concomitant formation of up to two new stereogenic carbon centers. As a result of its potential to generate dense stereochemical motifs on cyclic and acyclic frameworks in a predictable and highly diastereoselective manner, the Claisen rearrangement has found extensive application in the

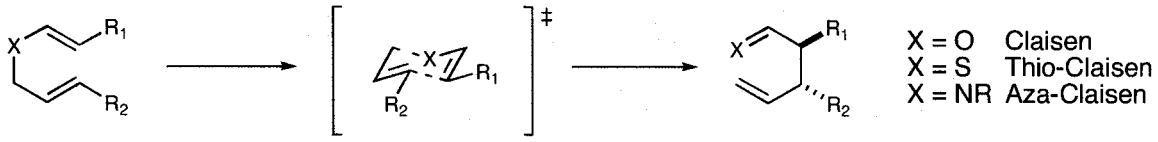

Figure 1. The Claisen rearrangement.

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1. Claisen, B. *Chem. Ber.* **1912**, *45*, 3157

2. For recent reviews of the Claisen rearrangement, see: (a) Moody, C. J. *Adv. Hetrocycl. Chem.* **1987**, *42*, 203. (b) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (c) Blechert, S.; *Synthesis* **1989**, 71. (d) Kallmerten, J.; Wittman, M. D. *Stud. Nat. Prod. Chem.* **1989**, *3*, 233. (e) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M. and Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, Chapter 7.2. (f) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron* **1996**, *7*, 1847.

total synthesis of natural products and has been the target of numerous methodological studies in the nine decades since its first report.

anion-accelerated Ireland Claisen

cation accelerated oxonia–Claisen

Figure 2. Charge-accelerated Claisen rearrangements.

The thermal sigmatropic rearrangement of allyl vinyl ethers typically occurs at elevated temperatures (ca. 150–200 °C). In contrast to the reversible Cope rearrangement of 1,5-dienes, the Claisen rearrangement results in the energetically favorable formation of a C=O π-bond. Therefore, the Claisen rearrangement is typically a strongly exothermic process (ca. 20 kcal/mol)[3,4] with a correspondingly earlier transition state and a lower activation barrier than the Cope rearrangement.[5] Incorporation of anionic charge at position 2a[6] or cationic charge at position 3[7] can accelerate the Claisen rearrangement, which has resulted in Claisen variants that occur at temperatures as low as –78 °C (Figure 2).

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3. (a) Schuler, F. W.; Murphy, G. W. *J. Am. Chem. Soc.* **1950**, *72*, 3155. (b) Vittorelli, P.; Winkler, T.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta.* **1968**, *51*, 1457.

4. Estimation of the enthalpy of transformation of allyl vinyl ether to 5-hexenal using Benson's group additivity method predicts ΔH° = –17 kcal/mol. Cohen, N.; Benson, S. W. *Chem. Rev.* **1993**, *93*, 2419.

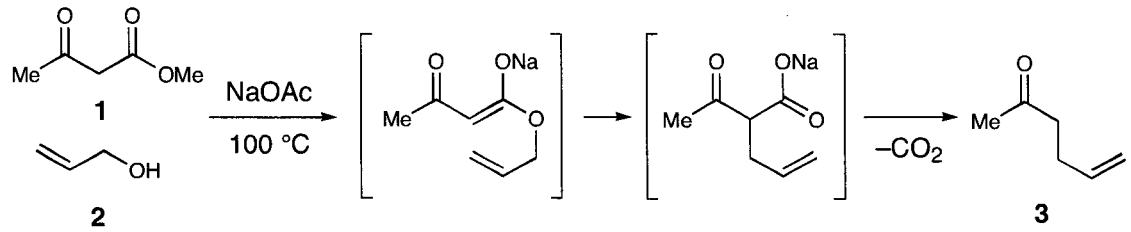
5. Aviyente, V.; Yoo, H. Y.; Houk, K. N. *J. Org. Chem.* **1997**, *62*, 6121.

6. (a) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Denmark, S. E.; Harmata, M. A. *J. Am. Chem. Soc.* **1982**, *104*, 4972.

Traditionally, the sensitive allyl vinyl ether moiety is generated by the mercury- or acid-catalyzed transetherification of enol ethers with allylic alcohols.[8] However, the toxicitiy of mercury salts and the low yields typically associated with these procedures limit their practical utility. The development of new Claisen methodology in the century since its initial discovery has been significantly assisted by the discovery of Claisen variants that allow the vinyl ether moiety to be generated in situ and the rearrangement to be conducted under milder conditions.

The first such variant of general utility was serendipitously discovered by Carroll in 1940 (Scheme 1).[9] An attempt to effect the base-promoted transesterification of β-ketoester **1** with allyl alcohol **2** resulted instead in the enolization of the allyl ester and subsequent [3,3]-rearrangement, resulting in the isolation of methyl ketone **3** after decarboxylation.

Scheme 1



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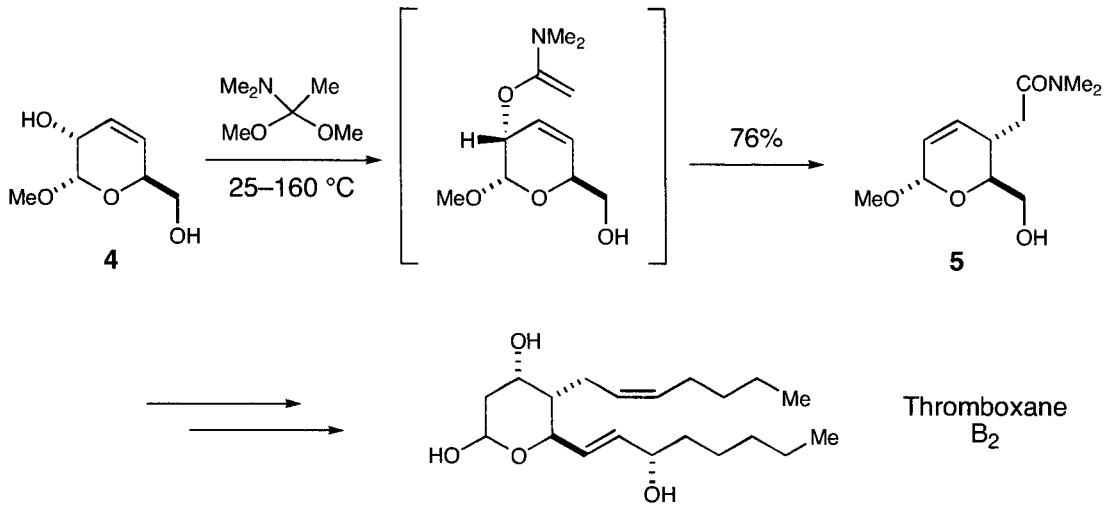
7. (a) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 3985. (b) Stevenson, J. W. S.; Bryson, *Tetrahedron Lett.* **1982**, *23*, 3143. (c) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 446. (d) Takai, K.; Mori, I.; Oshima, K.; Nozaki, H. *Tetrahedron* **1984**, *40*, 4013.

8. (a) Watanabe, W. H.; Conlon, L. E. *J. Am. Chem. Soc.* **1957**, *79*, 2828. (b) Burgstahler, A. W.; Nordin, I. C. *J. Am. Chem. Soc.* **1961**, *83*, 198. (c) Church R. F.; Ireland, R. E.; Marshall, J. A. *J. Org. Chem.* **1966**, *31*, 2526. (d) Thomas, A. F. *J. Am. Chem. Soc.* **1969**, *91*, 3281. (e) Dauben. W. G.; Dietsche, T. J. *J. Org. Chem.* **1972**, *37*, 1212.

9. (a) Carroll, M. F. *J. Chem. Soc.* **1940**, 704. (b) Carroll, M. F. *J. Chem. Soc.* **1940**, 1266. (c) Carroll, M. F. *J. Chem. Soc.* **1941**, 507.

In 1964, Eschenmoser[10] reported a Claisen variant in which the allyl vinyl ether moiety is generated in situ by condensation of an *N,O*-ketene acetal with an allylic alcohol (Scheme 2). The resulting transacetylated intermediate rearranges under the reaction conditions to produce a γ,δ-unsaturated amide. This Claisen variant was utilized as the key step in Corey's synthesis of thromboxane B_2, in which the cyclic allylic alcohol **4** was treated with *N,N*-dimethylacetamide dimethyl acetal at 160 °C to give the rearranged product **5**.[11]

Scheme 2

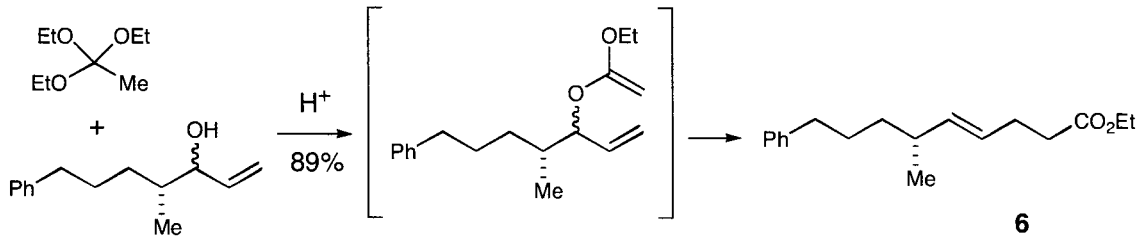


10. (a) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425. (b) Wick, A. E.; Felix, D.; Gschwend-Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030. (c) Jenkins, P. R.; Gut, R.; Wetter, H.; Eschenmoser, A. *Helv. Chim. Acta* **1979**, *62*, 1922.

11. (a) Corey, E. J.; Shibasaki, M.; Knolle, J.; Sugahara, T. *Tetrahedron Lett.* **1977**, 785. (b) Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, 1625.

Subsequently, Johnson[12] demonstrated that orthoesters also undergo acid-catalyzed condensation with allylic alcohols to afford ketene acetals. Rearrangement occurs under the reaction conditions necessary for transacetalization to afford ester products (Scheme 3). This reaction continues to be an important, operationally simple variant of the Claisen rearrangement, and has been featured recently in Santini's synthesis of the zaragozic acid C C(6) *O*-acyl sidechain **6** (Scheme 3).[13]

Scheme 3



The most influential advance in Claisen technology was the rearrangement of silylated ester enolates first introduced by Ireland and coworkers in 1972 (Scheme 4).[14] The key feature of the Ireland Claisen is the ability to direct the diastereoselectivity of the process in a highly predictable fashion by controlling the geometry of enolization. Thus, enolization of crotyl ester **7** with LDA in THF at –78 °C leads to selective formation of the

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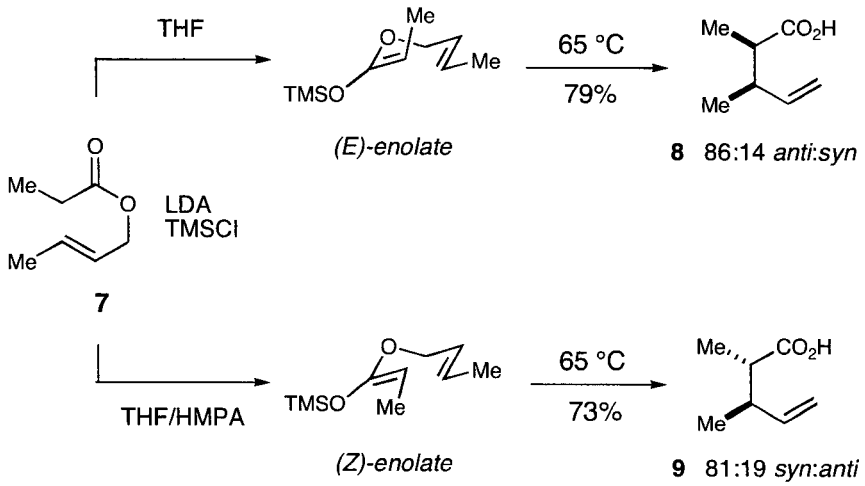
12. Johnson, W. S.; Werthemann, L. Bartlett, W. R.; Brockson, T. J.; Li, T.-T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

13. Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261.

14. (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, *3975*. (c) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(*E*)-silyl ketene acetal. In general, the transition state of the Claisen rearrangement of acyclic substrates demonstrates a strong preference for a highly organized, chair-like topography; therefore, the (*E*)-enolate methyl substituent adopts a pseudo-axial position in the chair-like transition state, leading predominantly to the *anti*-substituted product **8** in 79% yield and 87:13 dr. The complementary diastereomer can be similarly accessed by (*Z*)-selective enolization in a 23% HMPA/THF solvent system followed by rearrangement to *syn*-2,3-dimethyl-5-hexenoic acid (**9**) in 73% yield and 81:19 dr.[14c]

Scheme 4

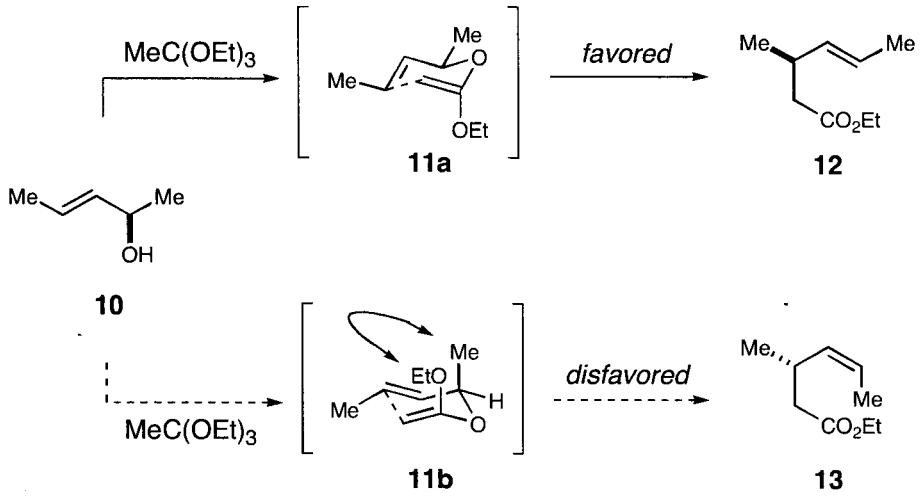


Stereoinduction in the Claisen Rearrangement

In addition to being highly diastereospecific, Claisen rearrangements with a stereogenic center at the oxygen-bearing allylic carbon are generally highly enantiospecific. In the Johnson orthoester Claisen rearrangement of the enantiopure secondary alcohol **10** depicted in Scheme 5, for example, the reaction proceeds predominantly through the transition state geometry depicted in **11a**, in which the allylic methyl substituent adopts an equatorial configuration, rather than through transition state **11b**, which is significantly

destabilized by the 1,3-diaxial interaction between the methyl and the alkoxy substituents. The rearranged product **12** can therefore be isolated from the reaction in >90% ee.[15] Importantly, loss of stereochemical fidelity in this process must be due to a small proportion of rearrangement through a high-energy boat topography, as the disfavored chair transition state **11b** leads to the isomeric (*Z*)-alkene **13**.

Scheme 5



The efficiency of stereochemical relay in the highly organized transition state of the Claisen rearrangement has enabled to the development of several highly asymmetric variants that employ chiral auxiliaries.[16] In 1985, Kurth[17] described an oxazoline-based aza-Claisen variant (Scheme 6). *N*-Alkylation of the valinol-derived oxazoline **14** with crotyl tosylate

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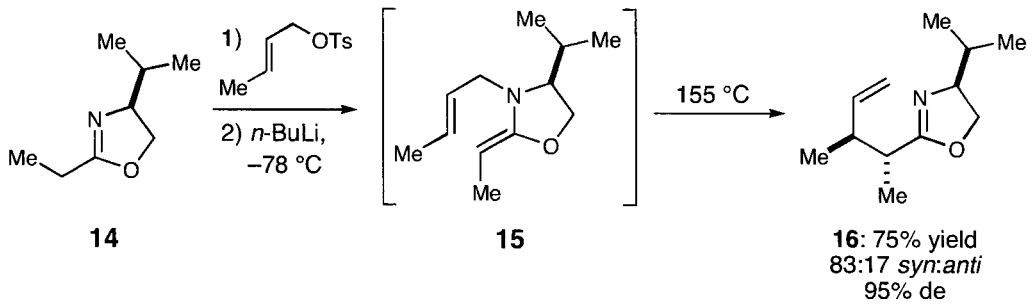
15. Hill, R. K.; Soman, R.; Sawada, S. *J. Org. Chem.* **1972**, *37*, 3737.

16. For reviews of asymmetric Claisen rearrangements, see: (a) Enders, D.; Knopp, M.; Schiffers, R. *Tetrahedron: Asymmetry* **1996**, *7*, 1847. (b) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43.

17. (a) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443. (b) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1985**, *50*, 5769.

followed by in situ deprotonation of the intermediate iminium salt gives (Z)-ketene acetal **15**. Rearrangement at 155 °C affords imidate **16** as a 83:17 mixture of *syn* to *anti* isomers in 75% yield, where the *syn* isomers are isolated in 95% de with respect to the chiral auxiliary.

Scheme 6



In 1997, Metz and coworkers[18] reported a chiral auxiliary strategy with greater generality (Scheme 7). Crotyl imidate **17**, derived from binaphthyl-derived amine **18**, can be deprotonated with lithium diethylamide at −78 °C. Upon warming the reaction to 0 °C, the resulting (Z)-ketene acetal **19** rearranges to the *anti*-substituted amide **20**, which can be isolated in 78% yield and 94% de. The chiral auxiliary can be cleaved and recovered by hydrolysis of the amide product to the carboxylic acid **21** via a two-step iodolactonization-reduction protocol.

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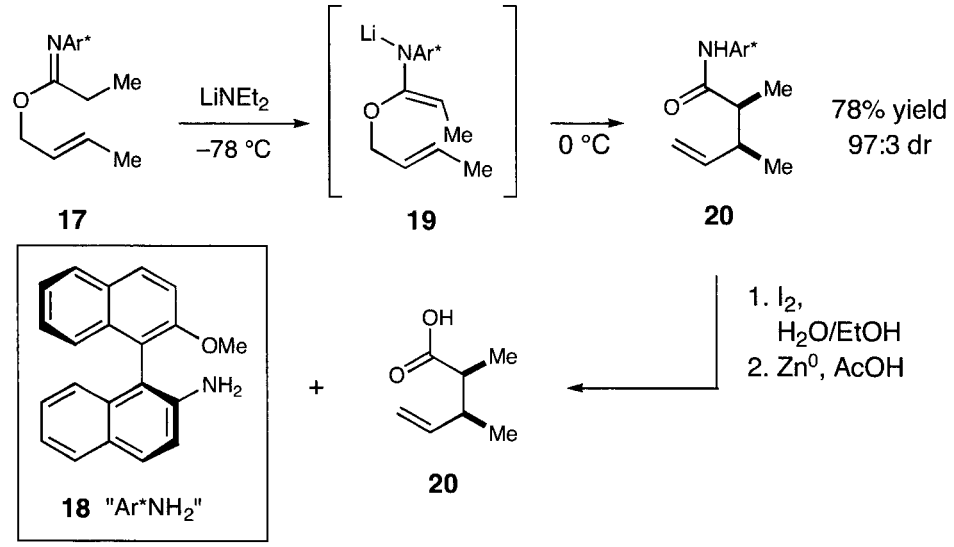
18. (a) Metz, P.; Hungerhoff, B. *GIT Fachz. Lab.* **1996**, *40*, 690. (b) Metz, P.; Hungerhoff, B. *J. Org. Chem.* **1997**, *40*, 690.

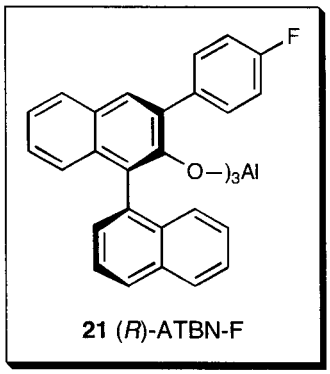
Scheme 7



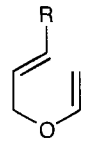
Enantioselective rearrangement of achiral allyl vinyl ethers has also been achieved. In 1995, Yamamoto[19] described a cation-accelerated Claisen rearrangement that employs the bulky aluminum(III) complex **21** as a chiral Lewis acid. Allyl vinyl ethers **22a–c** rearrange at –78 °C in the presence of a stoichiometric quantity of **21** to afford the corresponding γ,δ-unsaturated aldehydes **23a–c** in 70–97% yield and 76–92% ee. While enantioselectivities observed for substrates bearing bulky substituents (**22a**, R = *t*-Bu, 91% ee; **22b**, R = Me_3Si, 92% ee) are generally good, significantly lower selectivities are observed in the rearrangement of less sterically demanding allylic substrates (**22c**, R = Ph, 76% ee).

19. Maruoka, K.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 1165.

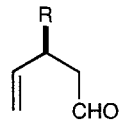
Scheme 8



21 (*R*)-ATBN-F



1.1–2 eq **21**



22a R = *t*-Bu
b R = $SiMe_3$
c R = Ph

23a 70% yield, 91% ee
b 78% yield, 92% ee
c 97% yield, 76% ee

A further brilliant advance in asymmetric Claisen technology is represented by Corey's[20] report of a chiral Lewis acid for the first enantioselective and diastereospecific rearrangement of achiral ester enolates (Scheme 9). In the presence of the stilbenediamine-derived bis(sulfonamido)boron Lewis acid **24**, crotyl propionate (**25**) is enolized by *i*-Pr_2NEt at –78 °C to afford (*E*)-ketene acetal **26**. Upon warming the reaction to –20 °C, the rearranged *syn*-2,3-dimethyl-5-hexenoic acid product **27** predominates over the *anti* diastereomer in a 99:1 ratio and may be isolated in 75% yield and >97% ee. Importantly, Corey's system allows the complementary *anti* diastereomer to be selectively generated by controlling the conditions under which the enolization event occurs. Thus, by deprotonating the Lewis acid-activated ester with triethylamine in a toluene-hexane solvent system, the (*Z*)-ketene acetal **28** can be generated selectively. After rearrangement of this geometric isomer at –20 °C, the *anti* isomer **29** predominates in a 90:10 ratio and can be isolated in 65% yield and 96% ee.

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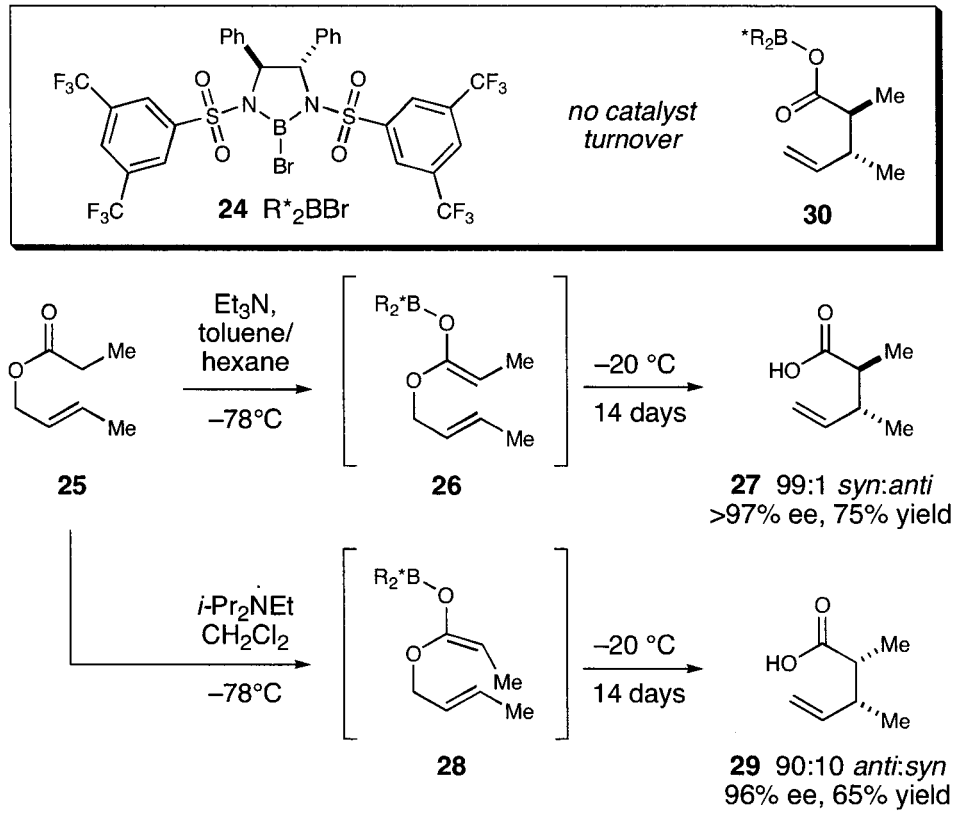
20. Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1986**, *113*, 4026.

Scheme 9



This methodology is successful with a range of alkyl-, aryl-, and heteroatom-substituted substrates, and Corey has demonstrated the synthetic utility of this reaction in elegant total syntheses of two natural products, (+)-fuscol[21] and dolabellatrienone.[22] In each synthesis, the key Claisen event is employed to install a quaternary carbon stereocenter in a

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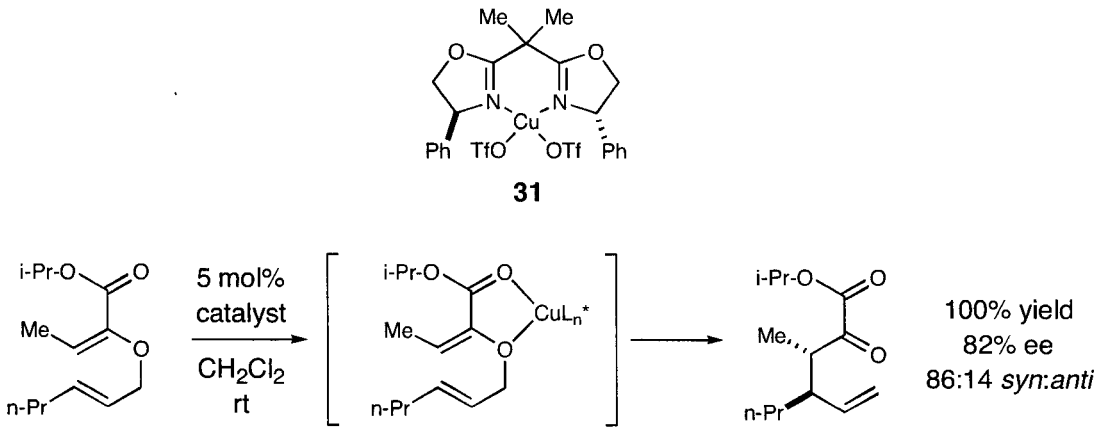
21. Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193.

22. Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.*, **1996**, *118*, 1229.

highly enantio- and diastereoselective manner.[23] However, stoichiometric quantities of the Lewis acid **24** are required for a successful reaction. Catalyst turnover in this reaction is likely inhibited by the formation of stable boron-carboxylate complex **30** as the direct product of the rearrangement event.

Scheme 10



Despite the synthetic importance of the Claisen rearrangement and the efforts of several groups towards the development of novel asymmetric Claisen variants, the development of catalytic asymmetric Claisen rearrangements has proven to be a difficult goal. In fact, the first example of an enantioselective Claisen rearrangement catalyzed by a chiral Lewis acid was only recently reported in the literature. Hiersemann[24] has demonstrated that copper(II) bisoxazoline complex **31** catalyzes the oxonia-Claisen rearrangement of allyl vinyl ethers capable of binding in a bidentate fashion to the metal

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23. Enantioselective construction of quaternary carbon stereocenters continues to be a challenging objective for synthetic organic chemists. For reviews of recent methods, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem. Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4591.

24. Abraham, L.; Czerwonka, R.; Hiersemann, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 4700.

center (Scheme 10). Enantioselectivities as high as 88% and diastereoselectivity as high as 97:3 can be achieved. However, the requirement for a chelating ester at the 2-position and the nontrivial synthesis of the allyl vinyl ether substrates limit the scope and synthetic utility of this reaction methodology.

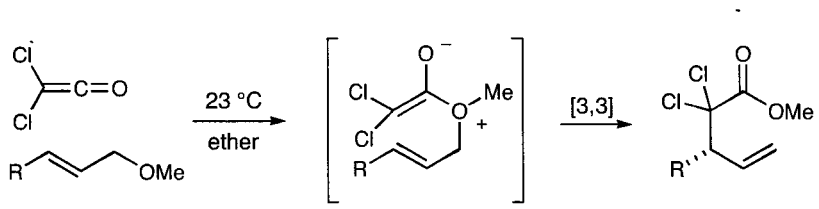
Thus, the development of a highly enantioselective catalytic Claisen variant of general synthetic utility continues to be an important yet elusive goal. Our approach to the discovery of an enantioselective catalytic Claisen rearrangement therefore begins with the design of a new Claisen variant that is more readily amenable to Lewis acid catalysis than the Ireland Claisen, with greater substrate scope and more facile substrate synthesis than the metal-mediated oxonia-Claisen reaction.

Chapter 2

Development of the Lewis Acid-Catalyzed Ketene Claisen Rearrangement

Reaction Design

The intial phase of this research program took its inspiration from the conceptually novel ketene-Claisen rearrangement reported by Bellus in 1978.[1] In an attempt to perform a [2+2] cycloaddition, the authors discovered that allylic ethers and sulfides will instead condense with dichloroketene to form zwitterionic enolates, which subsequently undergo [3,3]-sigmatropic rearrangement to produce γ,δ-unsaturated esters and thioesters, respectively (eq 1).



(1)

A broad range of allylic substrates can be used successfully in this Claisen rearrangement, including both cyclic and acyclic ethers and sulfides. The range of ketenes that could be used, however, was reported to be relatively narrow. Only highly electron-deficient ketenes such as dichloroketene and chloro(trichloroethyl)ketene were found to participate readily in the ketene-Claisen rearrangement. However, detailed inspection of these reports revealed that successful rearrangements only occurred when ketenes were

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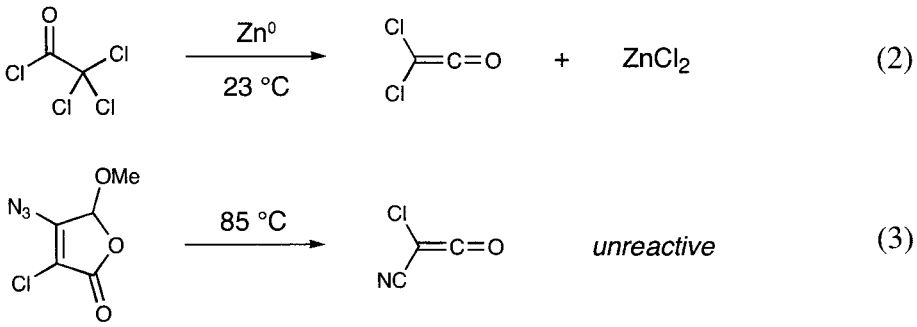
1. (a) Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096. (b) Malherbe, R.; Rist, G.; Bellus, D. *J. Org. Chem.* **1983**, *48*, 860.

generated in situ by zinc-promoted dehalogenation of α-chloro acid chlorides,[2] in which zinc(II) chloride is generated as a byproduct (eq 2). In fact, when the highly electron-deficient chlorocyanoketene was generated by thermolysis[3] in the absence of any metal species (eq 3), less than 5% of the product arising from Claisen rearrangement could be isolated, even at elevated temperatures.



These observations suggested that the $ZnCl_2$ byproduct of zinc-promoted ketene formation might constitute an integral component of the ketene-Claisen rearrangement, perhaps serving as a Lewis acid that activates ketenes towards nucleophilic attack. Indeed, Lewis acid activation of ketenes is well precedented,[4] and Brady[5] has suggested such a

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2. (a) Staudinger, H. *Chem. Ber.* **1905**, *38*, 1735. (b) Hassner, A.; Krepski, L. R. *J. Org. Chem.* **1978**, *43*, 2879. (c) Mehta, G.; Rao, H. S. P. *Synth. Commun.* **1985**, *15*, 991. (d) Depres, J.; Greene, A. E. *Org. Synth.* **1989**, *68*, 41. (e) Wulferding, A.; Wartchow, R.; Hoffmann, H. M. R. *Synlett.* **1992**, 476.

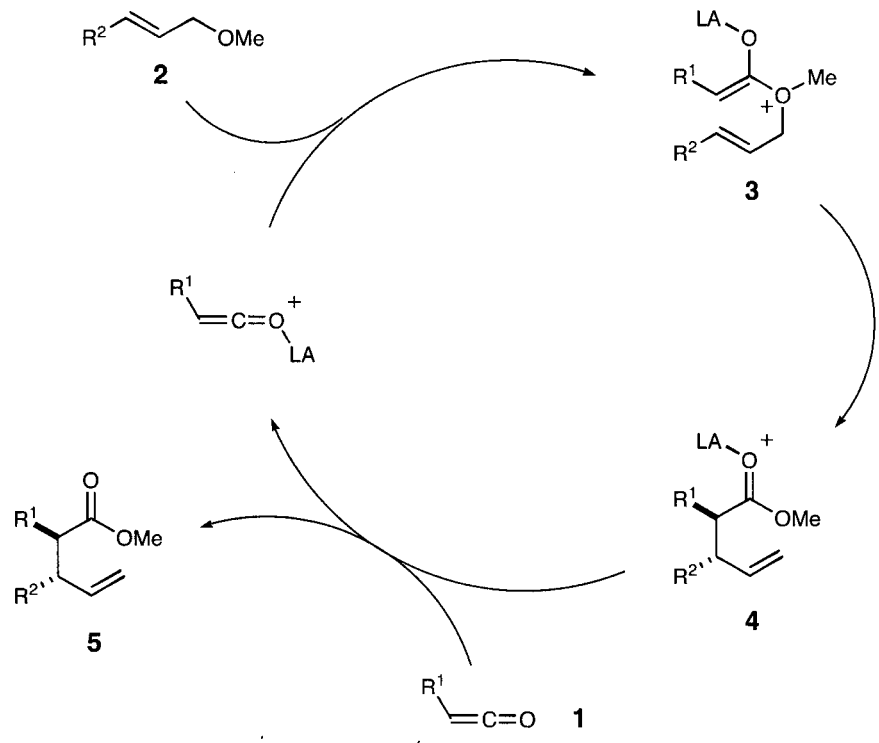
3. (a) Moore, H. W.; Hernandez, L.; Sing, A. *J. Am. Chem. Soc.* **1976**, *98*, 3728. (b) Moore, H. W.; Hernandez, L.; Chambers, R. *J. Am. Chem. Soc.* **1978**, *100*, 2245.

4. For example, BF_3•OEt_2 catalyzes the acylation of *t*-BuOH with trimethylsilylketene. Ruden, R. A. *J. Org. Chem.* **1974**, *39*, 3607.

5. (a) Brady, W. T.; Lloyd, R. M. *J. Org. Chem.* **1979**, *44*, 2 560. (b) Brady, W. T.; Lloyd, R. M. *J. Org. Chem.* **1980**, *45*, 2025.

mechanism in the [2+2] cycloaddition of dichloroketene with silyl enol ethers. Brady has reported that the cycloaddition proceeds smoothly when dichloroketene is generated in situ from zinc-promoted dehalogenation of trichloroacetyl chloride,[5a] while the reaction fails when the ketene is generated by amine-promoted dehydrohalogenation of dichloroacetyl chloride under metal-free conditions.[5b] Although the initial reports of the ketene-Claisen reaction did not make any mention of this mechanistic possibility, we speculated that a wider range of less electron-poor ketenes could potentially be induced to participate in the ketene-Claisen reaction by addition of the appropriate Lewis acid catalyst.

Scheme 1



We therefore proposed the hypothetical catalytic cycle for a general Lewis acid-catalyzed ketene-Claisen rearrangement shown in Scheme 1. Lewis acid activation of ketene

1 towards nucleophilic attack by allylic ether **2** should generate the metal-bound zwitterionic enolate species **3**. This intermediate should then undergo [3,3]-sigmatropic rearrangement to afford the metal-bound ester **4**. Release of the free ester product **5** would then regenerate the Lewis acid and complete the catalytic cycle.

If this hypothesis is correct, there are several features of the ketene-Claisen rearrangement that would render it an attractive platform for the development of a new asymmetric catalytic process. First, Claisen rearrangements are known to be accelerated both by cationic charge at the 3-position (e.g., the oxonia-Claisen) and by anionic charge at the 2a-position (e.g., the Ireland Claisen).[6] The zwitterionic intermediate generated by condensation of a ketene with an allylic ether will possess charge at both the 2a- and 3-positions, and should therefore be optimally poised to undergo charge-accelerated sigmatropic rearrangement.

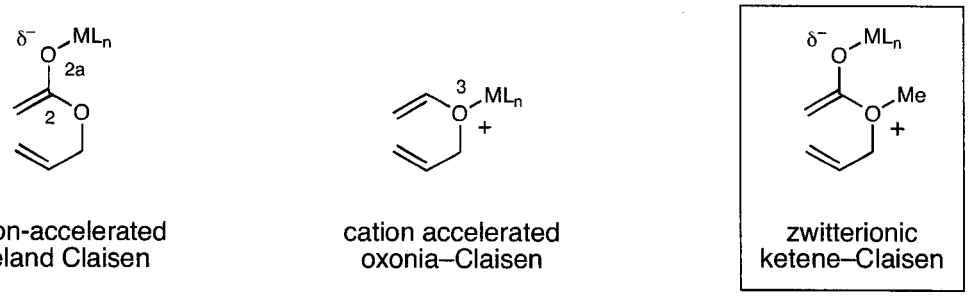


Figure 1. Dipole-accelerated ketene-Claisen rearrangement.

Second, we anticipated that the ketene-Claisen rearrangement should be amenable to catalysis using a substoichiometric amount of a Lewis acidic metal species. In Corey's

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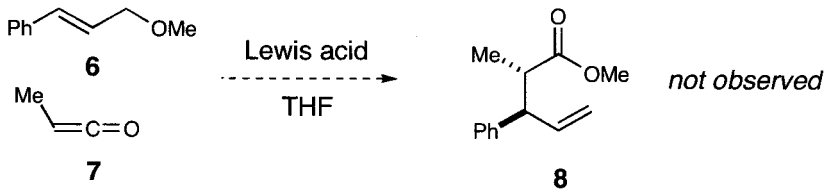
6. Chapter 1, Footnotes 6–7.

boron-mediated ester enolate Claisen rearrangement,[7] the anionic carboxylate product binds irreversibly to the boron Lewis acid, thereby inhibiting catalyst turnover (see Chapter 1, Scheme 9). The product of the ketene-Claisen reaction, on the other hand, is a neutral ester species (i.e., **5**) and should therefore be able to dissociate readily from a range of Lewis acidic metal salts.

Results and Discussion

We began our experiments by examining the reaction of methylketene (**7**) with cinnamyl methyl ether (**6**). Methylketene (**7**) can be generated free of metal salts by treatment of bromoacetyl bromide with zinc in THF and codistillation of the ketene-THF solution at reduced pressure into a liquid nitrogen-cooled Schlenk flask.[8] Unfortunately, the ether **6** failed to react with methylketene to produce the desired ester product **8** in the presence of a variety of Lewis acids (eq 4). As methylketene is considerably less electrophilic than the halogenated ketenes employed by Bellus, we reasoned that a more reactive nucleophile might be required to condense with the less reactive ketene.

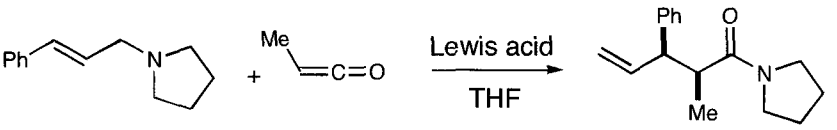


(4)

7. Chapter 1, Footnotes 19–21.

8. (a) Smith, C. W.; Norton, D. G. *Organic Syntheses*, Coll. Vol. IV; Rabjohn, N., Ed.; Wiley: New York, 1963, pp. 348–350. (b) McCarney, C. C.; Ward, R. S. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1600.

Table 1. Ketene-Claisen rearrangement between cinnamyl pyrrolidine and methylketene.



(5)

9 **7** **10**

entry	Lewis acid	equiv	% conv[a]	*syn*:*anti*[b]
1	--	--	NR	--
2	$AlCl_3$	1.0	90	>99:1
3	$MgBr_2$	1.0	80	>99:1
4	$Yb(OTf)_2$	1.0	90	>99:1
5	$ZnBr_2$	1.0	89	>99:1
6	$TiCl_4(THF)_2$	1.0	83[c]	>99:1
7	$ZnBr_2$	0.2	87	>99:1
8	$AlMeCl_2$	0.2	90[c]	>99:1
9	$TiCl_2(O\textit{i}\text{-}Pr)_2$	0.2	72[c]	>99:1
10	$TiCl_4(THF)_2$	0.1	83[c]	>99:1

[a] Conversion based on ^1H NMR analysis of the unpurified reaction mixture. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Isolated yield.

We therefore turned our attention to reactions involving allylic amine nucleophiles. Subsequent to the initial demonstration of the ketene-Claisen of allylic ethers by Bellus and Malherbe,[1] the ability of allylic tertiary amines to participate in this reaction was

demonstrated in studies by Mariano,[9a] Edstrom,[9b] Roberts,[9c] Vedejs,[9d] Nubbemeyer,[9e] and Hegedus.[9f] To our delight, we discovered that cinnamyl pyrrolidine undergoes an efficient ketene-Claisen rearrangement at room temperature under the influence of Lewis acid catalysts (Table 1). As illustrated by entries 2–10, a variety of oxophilic metal salts, including $AlCl_3$, $MgBr_2$, $Yb(OTf)_3$, $ZnBr_2$, $TiCl_2(O\textit{i}\text{-}Pr)_2$, and $TiCl_4(THF)_2$ successfully catalyze this process at catalyst loadings as low as 10 mol% (entry 10, $TiCl_4(THF)_2$). Importantly, reactions conducted in the absence of a Lewis acid catalyst failed to produce any observable Claisen product (entry 1).

Origins of Stereoselectivity in the Ketene-Claisen Rearrangement

This new Lewis acid-catalyzed ketene-Claisen rearrangement was found to be highly stereoselective. Only one diastereomer of the product was observable by ^1H NMR in each example listed in Table 1. Indeed, GC analysis demonstrated that the *syn* diastereomer was generated preferentially over the *anti* isomer with >99:1 diastereoselectivity in the presence of every Lewis acid that was successful in this process.

The high levels of stereoselectivity observed are the result of two sequential, highly selective steps. First, additions of nucleophiles to monosubstituted ketenes typically result in exclusive formation of the (*Z*)-enolate (Figure 2).[10] Because the lowest unoccupied molecular orbital (LUMO) is the C=O π^* orbital, which lies in the plane defined by the

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9. (a) Kunng, F.-A.; Gu, J.-M.; Chao, Y.; Mariano, P. S. *J. Org. Chem.* **1983**, *48*, 4262. (b) Edstrom, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6690. (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) Vedejs, E.; Gringas, M. *J. Am. Chem. Soc.* **1994**, *116*, 579. (e) Diederich, M.; Nubbemeyer, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1026. (f) Deur, C. J.; Miller, M. W.; Hegedus, L. S. *J. Org. Chem.* **1996**, *61*, 2871.

10. Seikaly, H. R.; Tidwell, T. T. *Tetrahedron* **1986**, *42*, 2613.

ketene,[11] nucleophiles that react with the ketene encounter a destabilizing steric interaction with one of the substituents on the terminal carbon. Thus, approach of the nucleophile occurs preferentially from the less-hindered trajectory opposite the bulkier substitutent of the ketene, resulting in selective formation of the (*Z*)-enolate.

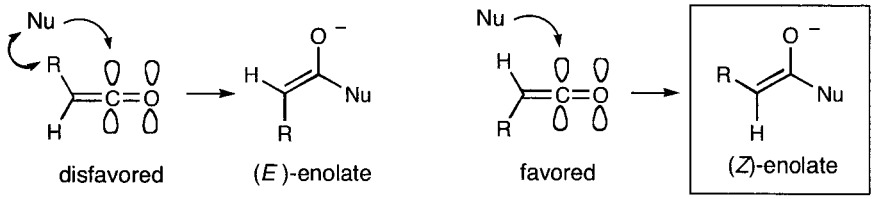

Figure 2. Origins of (*Z*)-enolate geometry in additions to monosubstituted ketenes.

Second, the carbon-carbon bond-forming event is also highly diastereoselective. In a typical Claisen rearrangement of an acyclic allyl vinyl ether, the activation energy for rearrangement through a chair-like topography to the *syn* product is typically ~3 kcal/mol lower than that of the complementary boat transition state leading to the *anti* diastereomer.[12] At the elevated temperatures required for the traditional Claisen rearrangement of unactivated allyl vinyl ethers (150–200 °C), products can typically be isolated with up to 98:2 diastereoselectivity. However, this Lewis acid-promoted ketene-Claisen rearrangement proceeds smoothly at room temperature, presumably due to acceleration from the dipolar

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11. Cossio, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995.

12. (a) Vitorelli, P.; Winkler, T.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1457. (b) Vitorelli, P.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1293. (c) Vance, R. L.; Rondan, N. G.; Houk, K. N.; Hensen, F.; Borden, W. T.; Komornicki, A.; Wimmer, E. *J. Am. Chem. Soc.* **1988**, *110*, 2314.

charge distribution of the zwitterionic intermediate, and as a consequence, considerably higher levels of stereocontrol can be achieved.

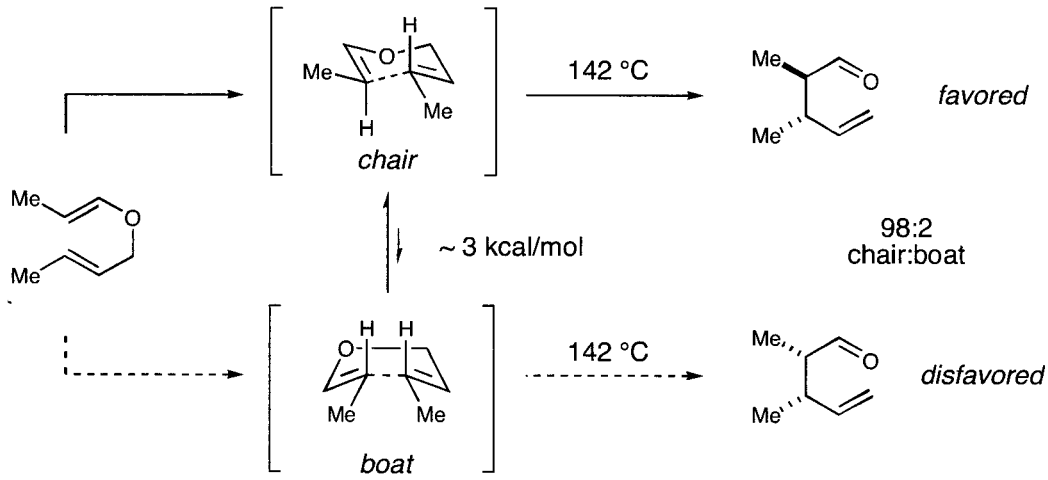
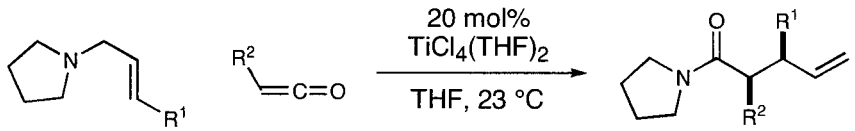


Figure 3. Origins of diastereoselectivity in acyclic Claisen rearrangements.

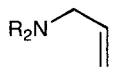
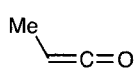
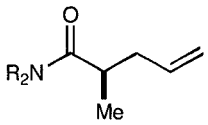
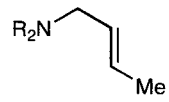
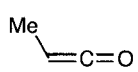
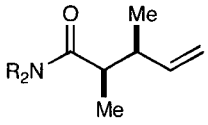
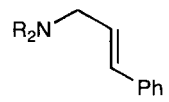
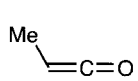
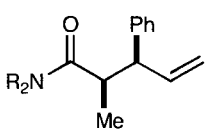
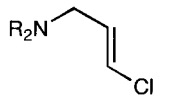
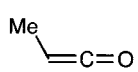
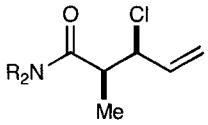
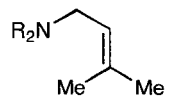
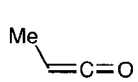
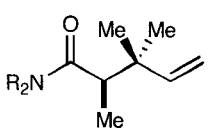
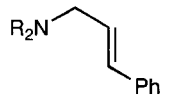
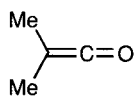
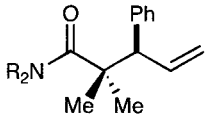
Scope of the Ketene-Claisen Rearrangement

The scope of this new ketene-Claisen reaction was investigated by Vy Dong, and the results of this investigation are summarized in Table 2. A range of substituted allylic pyrrolidines react with methylketene in the presence of 20 mol% $TiCl_4(THF)_2$, allowing access to alkyl-, aryl-, and even halogen-substituted products (entries 1–4). The diastereoselectivities observed in each case are uniformly excellent. In addition, a quaternary carbon center can be generated at the position β to the amide moiety in the Claisen adduct by starting with prenyl pyrrolidine as the allyl component (entry 5). Similarly, quaternary substitution at the α-position can be achieved by using dimethyl ketene as the electrophilic reaction partner (entry 6).

Table 2. Ketene-Claisen rearrangement of representative allyl pyrrolidines.



(6)

entry	amine[a]	ketene	product[a]	yield	*syn*:*anti*[b,c]
1				84	--
2				84	>99:1
3				85	>99:1
4				77	>99:1
5				68	--
6				86	--

[a] NR_2 = *N*-pyrrolidine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative configurations assigned by chemical correlation to known compounds (See Experimental section).

However, this reaction proved to be somewhat limited in the substrate scope. While *trans*-substituted allylic pyrrolidines rearrange efficiently with high levels of *syn* stereoselectivity, *cis*-alkenes appeared to react much more slowly. For example, as shown in eq 7, treatment of (*Z*)-2-pentenyl pyrrolidine (**11**) with methylketene in the presence of 20

mol% $TiCl_4(THF)_2$ resulted in <10% conversion to an amide product **12** of low diastereopurity (85:15 *anti*:*syn* as measured by ^1H NMR).

(7)

<10% conversion
85:15 *anti*:*syn*

A more critical limitation was the necessity of generating and isolating ketene solutions free of metal salts, which further limits the range and synthetic utility of this new methodology. First, because the ketenes used in this study are isolated by codistillation with ethereal solvents, only ketenes of relatively low molecular weight can be used. Second, because the concentrations of these solutions are difficult to ascertain, the ketene reaction partner is typically added to the reaction in vast excess. A more economical procedure would allow the ketene component to be added in only slight excess. Finally, the Lewis acidity of certain metal salts can be buffered by the presence of the strongly donating ethereal solvents in which the ketene is generated. These concerns led us to consider a new strategy that generates ketenes in situ from more readily available, bench-stable precursors.

Experimental Section

General Information. All non-aqueous reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. *N,N*-diisopropylethylamine and dichloromethane were distilled from calcium hydride prior to use. Air sensitive solids were dispensed in an inert atmosphere glovebox. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or $KMnO_4$ stain.

^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 (500 MHz and 125 MHz, respectively), AMX-400 (400 MHz and 100 MHz), or AMX-300 (300 MHz and 75 MHz) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^1H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C are reported in terms of chemical shift. IR spectra were recorded

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1. Perrin, D. D.; Armarego, W. L. F. *Purificaion of Laboratory Chemicals;* 3rd ed., Pregamon Press, Oxford, 1988.

2. Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

on an ASI React-IR 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Berkeley Mass Spectral facility. Gas chromatography was performed on Hewlett-Packard 5890A and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a C&C Column Technologies CC-1701 column (30 m x 0.25 mm).

General Procedure A: A round bottom flask containing $TiCl_4(THF)_2$ was charged with THF and the allyl pyrrolidine. The solution was stirred for 10 min before the ketene was added in portions of approximately 30 drops every 15 min via a 22 gauge teflon cannula. Addition of ketene (5–7 mL) was continued (1.5–2 h) until the allyl pyrrolidine was completely consumed (1.5–2 h) as determined by TLC (5% Et_3N:EtOAc). The resulting dark red solution was quenched with ether and aqueous 1 N NaOH. The aqueous layer was then extracted with ether, and the combined organic layers were washed with brine, dried, and concentrated. The resulting residue was purified by flash chromatography with 50% Et_2O/hexanes to provide the title compounds.

General Procedure B: A round-bottomed flask containing $TiCl_4(THF)_2$ was charged with CH_2Cl_2, then treated with the allyl morpholine, followed by iPr_2NEt. The solution was stirred for 5 min before a solution of the acid chloride in CH_2Cl_2 was added dropwise over 1 min. The resulting dark red solution was stirred until the allyl morpholine was completely consumed (2–6 h) as determined by TLC (EtOAc). The reaction mixture was then diluted with an equal volume of Et_2O and washed with aqueous 1 N NaOH. The aqueous layer was then extracted with ether, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by silica gel chromatography (Et_2O) to afford the title compounds.

General Procedure C: A round-bottomed flask containing $TiCl_4(THF)_2$ was charged with CH_2Cl_2, then treated with the allyl morpholine, followed by iPr_2NEt. The solution was stirred for 5 min before a solution of the acid chloride in CH_2Cl_2 was added slowly by syringe pump over 16 h. The resulting dark red solution was stirred until the allyl morpholine was completely consumed (2–5h) as determined by TLC (EtOAc). The reaction mixture was then diluted with an equal volume of Et_2O and washed with aqueous 1 N NaOH. The aqueous layer was then extracted with ether, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by silica gel chromatography (Et_2O) to afford the title compounds.

Methylketene: Methylketene was freshly prepared for each use according to the procedure of Ward.[3] Zinc powder was activated by washing with aqueous 1 N HCl, water, methanol, and ether and was subsequently dried under vacuum. The activated zinc powder (1.0 g, 15.3 mmol) was suspended in THF in a 100 mL receiving flask. The flask was fitted with a short-path distillation apparatus with a 50 mL Schlenk flask connected to the receiving end. The pressure within the apparatus was reduced to 110 torr, and a solution of freshly distilled 2-bromopropionyl bromide (0.52 mL, 5.0 mmol) in THF (3.5 mL) was then added dropwise via a 22 gauge teflon cannula tightened with a metal clamp. The ketene formed immediately and codistilled with the THF. The distillate was collected in the liquid nitrogen cooled Schlenk flask. After addition of acid bromide was complete (8–10 minutes), the distillation was continued for another 5 min. The distillate was then warmed to –78 °C in a dry ice/acetone bath under nitrogen, resulting in a bright yellow solution that was used without further purification. The IR spectrum of the solution displays an intense ketene band at 2130 cm^{-1}.

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3. McCarney, C. C.; Ward R. S. *J. Chem. Soc., Perkin Trans. 1*, **1975**,*16*, 1600.

***N*-(2-Methyl-4-pentenoyl)-pyrrolidine** (Table 2, entry 1). Prepared according to general procedure A from (*E*)-*N*-2-propenyl-pyrrolidine (76 mg, 0.68 mmol), $TiCl_4(THF)_2$, (44 mg, 130 μmol), and methylketene to provide the pure product as a yellow oil in 84% yield (96 mg, 0.57 mmol); IR 2980, 2880, 1629, 1463, 1440, 919 cm^{-1}; ^1H NMR (500 MHz) δ 5.76 (m, 1H, C**H**CH_2), 5.05 (dd, *J* = 1.5, 3.4 Hz, 1H, CHC**H**$_2$), 5.01 (dd, *J* = 1.5, 3.4 Hz, 1H, CHC**H**$_2$), 3.40-3.49 (m, 4H, (C**H**$_2$)$_2$N), 2.57 (m, 1H, C**H**C=O), 2.43 (m, 1H, C**H**$_2$CH=CH_2), 2.11 (m, 1H, C**H**$_2$CH=CH_2), 1.93 (m, 2H, C**H**$_2$$CH_2$N), 1.83 (m, 2H, C**H**$_2$$CH_2$N), 1.10 (d, *J* = 6.8 Hz, 3H, C**H**$_3$CH=O); ^{13}C NMR (125 MHz) δ 174.49, 136.27, 116.30, 46.38, 45.62, 38.02, 37.88, 26.08, 24.26, 16.86; LRMS (FAB) *m/z* 168 $(MH)^+$; HRMS (FAB) exact mass calcd for ($C_{10}H_{17}NO$) requires m/z 167.1310, found *m/z* 167.1308.

***N*-(2,3-Dimethy-4-pentenoyl)-pyrrolidine** (Table 2, entry 2). Prepared according to general procedure A from (*E*)-*N*-2-butenyl-pyrrolidine (94.4 mg, 0.753 mmol), $TiCl_4(THF)_2$, (50 mg, 150 μmol), and methylketene to provide the pure product as a yellow oil in 84% yield (114 mg, 0.628 mmol). All spectral data were in complete agreement with those previously reported for *N*-(2-methyl-4-pentenoyl)-pyrrolidine.[4]

(2R*,3R*)-*N*-(3-Phenyl-2-methyl-4-pentenoyl)-pyrrolidine (Table 2, entry 3). Prepared according to general procedure A from (*E*)-*N*-3-Phenyl-2-propenyl pyrrolidine (107 mg, 0.571 mmol), $TiCl_4(THF)_2$, (19 mg, 57 μmol), and methylketene to provide the pure product as a white solid in 80% yield (111 mg, 0.46 mmol); mp 85-86 °C;

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4. Welch, J. T.; Eswarakrishnan, S. *J. Org. Chem.* **1985**, 50, 26, 5909.

IR 2980, 2880, 1629, 1459, 1440, 923 cm^{-1}; ^1H NMR (400 MHz) δ 7.16-7.30 (m, 5H, Ph), 5.95-6.04 (ddd, *J* = 8.05, 10.9, 16.5 Hz, 1H, C**H**CH_2), 4.97 (d, *J* = 0.8 Hz, 1H, CHC**H**$_2$), 4.93-4.94 (m, 1H, CHC**H**$_2$), 3.56 (t, *J* = 9.0 Hz, 1H, C**H**CH=CH_2), 3.40-3.47 (m, 4H, (C**H**$_2$)O), 2.87 (m, 1H, C**H**C=O), 1.78-1.91 (m, 4H, C**H**$_2$$CH_2$N), 0.90 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz) δ 173.79, 141.90, 139.76, 128.45, 128.30, 126.44, 115.43, 53.46, 46.59, 45.60, 42.99, 26.01, 24.28, 16.14; LRMS (FAB) *m/z* 244 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{16}H_{21}NOH)^+$ requires m/z 244.1702, found *m/z* 244.1702; Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found C, 79.02; H, 8.41; N, 5.71.

***N*-3-Chloro-2-propenyl pyrrolidine** (Table 2, entry 4). Prepared according to the procedure of Butler.[5] (*E*)-1,3 dichloropropene was added dropwise to a refluxing mixture of pyrrolidine (6.3 mL, 110 mmol), $NaHCO_3$ (6.4 g, 76 mmol) and water (6 mL). After stirring the reaction at reflux for 3 h, the organic layer was separated from the aqueous layer and distilled to provide pure product as a colorless oil in 20 % yield (2.2 g, 15 mmol): bp (72 °C, 10 torr); IR 2814, 1637, 1455, 1297, 116, 907 cm^{-1}; ^1H NMR (400 MHz) δ 6.15 (dt, *J* = 13.2, 1.2 Hz, 1H, ClC**H**), 6.03 (m, 1H, ClCH=C**H**), 3.10 (d, *J* = 7.0 Hz, 1H, C**H**$_2$CH=CH), 2.50 (m, 4H, $(CH_2)_2$N), 1.80 (m, 4H, (C**H**$_2$$CH_2$)N); ^{13}C NMR (100 MHz) δ Anal. Calcd for $C_7H_{12}ClN$: C, 57.73; H, 8.31; N, 9.62. Found C, 57.41; H, 8.66; N, 9.85.

(2R*,3R*)-*N*-(3-Chloro-2-methyl-4-pentenoyl)-pyrrolidine (Table 2, entry 4). Prepared according to general procedure A from (*E*)-*N*-3-Chloro-2-propenyl-pyrrolidine (81.1 mg, 0.557 mmol), $TiCl_4(THF)_2$, (36 mg, 11 μmol), and methylketene to provide 77% yield of the pure product (86.4 mg, 0.431 mmol) as a yellow oil; IR 2980,

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5. Butler, G. B.; Ingley, F. L. *J. Am. Chem. Soc.* **1951**, 895.

2880, 1633, 1459, 1440, 934 cm^{-1}; ^1H NMR (500 MHz) δ 5.90 (ddd, *J* = 8.4, 10.2, 16.9 Hz, 1H, C**H**=CH_2), 5.29 (dt, *J* = 16.9, 0.9 Hz, 1H, CH=C**H**$_2$), 5.14 (dd, *J* = 10.3, 19.7 Hz, 1H, CH=C**H**$_2$), 4.50 (t, *J* = 8.8 Hz, 1H, CHCCl), 3.38-3.59 (m, 4H, (C**H**$_2$)$_2$N), 2.83 (m, 1H, CHC=O), 1.79-1.98 (m, 4H, (C**H**$_2$CH$_2$) N, 1.29 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (125 MHz) δ 171.47, 136.37, 117.83, 65.29, 46.74, 45.68, 45.53, 25.97, 24.25, 15.95; LRMS (FAB) *m/z* 201 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{10}H_{16}ClNO)^+$ requires m/z 201.0920, found *m/z* 201.0917.

(2-Methy-3,3-dimethyl-4-pentenoyl)-pyrrolidine (Table 2, entry 5). Prepared according to the general procedure A from (*E*)-*N*-3-methyl-2-butenyl-pyrrolidine (87 mg, 0.62 mmol), $TiCl_4(THF)_2$, (42 mg, 126 μmol), and methylketene to provide 68% yield of the pure product (81 mg, 0.42 mmol) as a yellow oil; IR 2976, 2880, 1725, 1629, 1455, 1436, 1193, 919 cm^{-1}; ^1H NMR (500 MHz) δ 5.93 (dd, *J* = 10.3, 17.9 Hz, 1H, C**H**=CH_2), 4.95 (dd, *J* = 1.4, 6.2 Hz, 1H, CH=C**H**$_2$), 4.92 (s, 1H, CH=C**H**$_2$), 3.38-3.52 (m, 4H, $(CH_2)_2N$), 2.44 (q, *J* = 7.0 Hz, 1H, (C**H**)C=O), 2.26 (m, 2H, C**H**$_2$CH$_2$N), 1.86 (m, 2H, C**H**$_2$CH$_2$N),), 1.07 (s, 3H, $(CH_3)_2C$), 1.03 (d, *J* = 5.6 Hz, 6H, $(CH_3)_2CH$=O); ^{13}C NMR (100 MHz) δ 174.04, 146.77, 111.25, 47.25, 45.91, 45.52, 39.35, 26.21, 24.71, 24.38, 23.80, 13.06; LRMS (FAB) *m/z* 195 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{12}H_{21}NO)^+$ requires m/z 195.1623, found *m/z* 195.1626.

(2,2 Dimethy-3-phenyl-4-pentenoyl)-pyrrolidine (Table 2, entry 6). Prepared according to general procedure A from (*E*)-*N*-3-phenyl-2-propenyl-pyrrolidine (68 mg, 0.36 mmol), $TiCl_4(THF)_2$, (22 mg, 66 μmol), and dimethylketene to provide 86% yield of the pure product (111 mg, 0.46 mmol) as a colorless oil; IR 3057, 2980, 2883, 1602, 1471, 1409 cm^{-1}; ^1H NMR (500 MHz) δ 7.18-7.27 (m, 5H, Ph), 6.30 (m, 1 H, C**H**CH_2), 5.13 (d, *J* = 10.1 Hz, 1H, CH=C**H**$_2$), 5.09 (d, *J* = 16.9 Hz, 1H, CH=C**H**$_2$), 3.64 (d, *J* = 9.6 Hz, 1H,

CHCH=CH_2), 3.07-3.48 (m, 4H, (C**H**$_2$)$_2$O), 1.65 (m, 4H, (C**H$_2$**CH_2)$_2$N), 1.27 (s, 3H, $(CH_3)_2$CC=O), 1.22 (s, 3H, $(CH_3)_2$CC=O); ^{13}C NMR (125 MHz) δ 174.86, 141.08, 137.16, 129.09, 127.89, 126.56, 117.09, 57.17, 48.56, 47.36, 27.18, 25.22, 23.61, 22.87; LRMS (FAB) *m/z* 257 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{17}H_{23}NO)^+$ requires m/z 257.1780, found *m/z* 258.1775; Anal. Calcd for $C_{17}H_{23}NO$: C, 79.33; H, 9.01; N, 5.44. Found C, 79.01; H, 9.28; N, 5.40.

Chapter 3

Development of the Acyl-Claisen Rearrangement[1]

Reaction Design

The research described in Chapter 2 successfully validated our hypothesis that the ketene-Claisen rearrangement is susceptible to Lewis acid catalysis. Indeed, a range of Lewis acidic metal salts were shown to catalyze the reaction of alkyl-substituted ketenes with a variety of allylic tertiary amine substrates. However, the inherent instability of most ketenes and the difficulty with which they are prepared, stored, and isolated limited the utility of this methodology and prompted us to investigate alternate methods of ketene generation.

In this context, the amine-promoted dehydrohalogenation of acid chlorides, first demonstrated by Staudinger,[2] is a widely used method of generating a broad range of mono- and disubstituted ketenes. Reactive ketenes generated in this manner have been trapped in situ with a variety of reaction partners, including alkenes, enol silanes, imines, and carbonyl compounds.[3] Importantly, this reaction generates ketenes without concomitant formation of a Lewis acidic metal byproduct. We reasoned that the utilization of acid chlorides as ketene surrogates in our Claisen methodology would (1) allow access to a

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1. Portions of the research described in this chapter have been published as a communication: Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726.

2. Staudinger, H. *Chem. Ber.* **1911**, *44*, 1619.

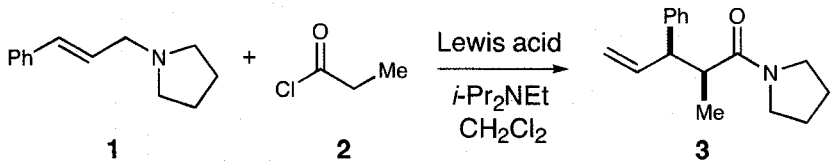
3. For recent comprehensive reviews of ketene cycloadditions, see: (a) Clemens, R. J. *Chem. Rev.* **1986**, *86*, 241. (b) Hyatt, J. A.; Raynolds, P. W. *Org. React.* **1994**, *45*, 159.

broader range of α-substituted Claisen adducts, (2) allow the reaction to be conducted without a large excess of the electrophilic reaction partner, and (3) permit the use of non-coordinating solvents that would be less likely to buffer the Lewis acidity of the catalytic metal salts.

Results and Discussion

This hypothesis was initially evaluated in the reaction of crotyl pyrrolidine (**1**) with propionyl chloride (**2**) in the presence of *i*-Pr_2NEt (Table 1). Gratifyingly, under the influence of 1 equiv dimethylaluminum chloride, the reaction proceeds smoothly to produce the desired Claisen adduct with good conversion (entry 2). Unfortunately, the reaction was

Table 1. Effect of Lewis acid on the acyl-Claisen rearrangement of cinnamyl pyrrolidine.



1 **2** **3** (1)

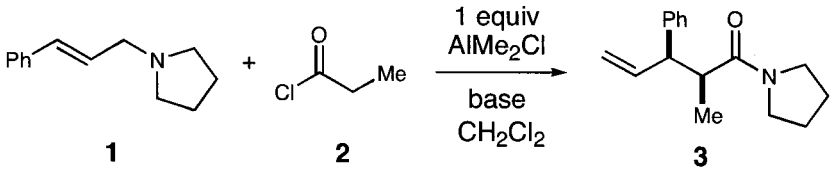
entry	Lewis acid	equiv	% conv[a]	*syn:anti*[b]
1	--	--	--	--
2	$AlMe_2Cl$	1.0	94	>99:1
3	$AlMe_2Cl$	0.1	34	>99:1
4	$MgBr_2$	0.1	20	>99:1
5	$Zn(OTf)_2$	0.1	<5	>99:1
6	$TiCl_4(THF)_2$	0.1	13	>99:1
7	$Yb(OTf)_3$	0.1	84	>99:1

[a] Conversion based on ^1H NMR analysis of the unpurified reaction mixture. [b] Product ratios determined by GLC using a Bodman CC1701 column.

less efficient using catalytic amounts of various Lewis acids (entries 3–6). When the catalyst loading of a range of Lewis acidic metal salts is lowered to 10 mol%, the level of conversion as measured by ^{1}H NMR is generally quite low. Good catalytic efficiency is only observed using $Yb(OTf)_3$ as the Lewis acid (entry 7).

We were concerned that the tertiary amine base might be interacting with the metal center and interfering with the course of the reaction. Table 2 summarizes the results of reactions investigating the effect of base structure on reaction efficiency. To our surprise, high levels of conversion were only observed when *i*-Pr_2NEt was used as the base (entry 1). The use of triethylamine resulted in lower conversion (entry 2), while only traces of the desired product could be observed in the presence of pyridine, DMAP, and DBU (entries 3–5). The success of the reaction did not seem to correlate well to the basicity of the amine used.

Table 2. Effect of amine base on the acyl-Claisen rearrangement of cinnamyl pyrrolidine.



(2)

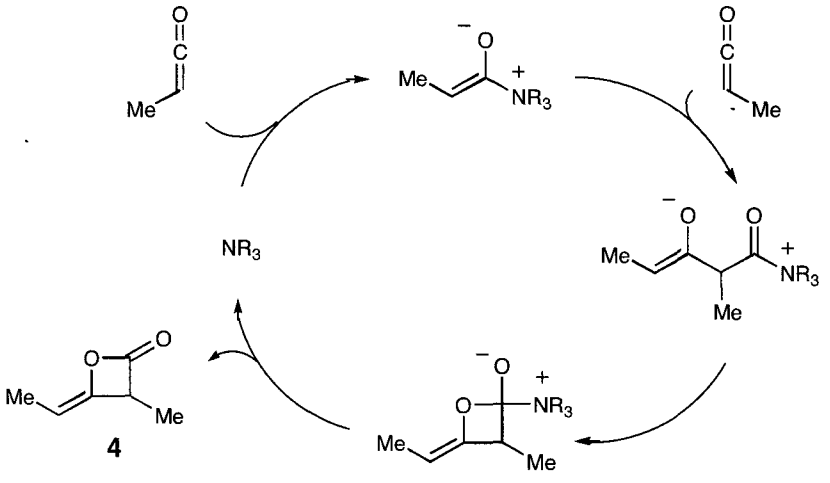
1 **2** **3**

entry	amine base	% conv[a]
1	*i*-Pr_2NEt	94
2	Et_3N	44
3	pyridine	<5
4	DMAP	5
5	DBU	<5

[a] Conversion based on ^{1}H NMR analysis of the unpurified reaction mixture.

More revealingly, TLC analysis of the unsuccessful reactions indicated that a new product was generated. Cinnamyl pyrrolidine could be recovered unchanged from the reaction, suggesting that the byproduct was the result of decomposition of the acid chloride component. Indeed, the formation of β-lactone **4** by dimerization of methylketene is known to be catalyzed by nucleophilic tertiary amines (Scheme 1).[4,5] Thus, we speculated that the poor conversions observed in the acyl-Claisen rearrangement could be due to consumption of the ketene intermediate in a nonproductive amine-catalyzed dimerization process that is competitive with the desired Claisen rearrangement.

Scheme 1



4. (a) Sauer, J. C. *J. Am. Chem. Soc.* **1947**, *69*, 2444. (b) Farnum, D. G.; Johnson, J. R.; Hess, R. E.; Marshall, T. B.; Webster, B. *J. Am. Chem. Soc.* **1965**, *87*, 5191. (c) Dehmlow, E. V.; Fastabend, U. *Synth. Commun.* **1993**, *23*, 79.

5. Enantioselective dimerization of ketenes has been achieved using a chiral tertiary amine catalyst: (a) Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006. (b) Calter, M. A.; Guo, X. *J. Org. Chem.* **1998**, *63*, 5308.

We became concerned that the *N*-cinnamyl pyrrolidine substrate itself could be serving as a nucleophilic catalyst for ketene dimerization. Because our initial investigations of the Lewis acid-catalyzed ketene-Claisen utilized ketene solutions added to the reaction in large excess, a competitive pyrrolidine-catalyzed ketene dimerization process would have been less detrimental to the overall yield of the reaction with respect to the limiting pyrrolidine substrate and may have gone unnoticed.

In order to investigate this concern, the reaction of propionyl chloride, *i*-Pr_2NEt, and crotyl pyrrolidine was investigated and monitored by ReactIR analysis. This in situ, real-time method of analyzing the course of a chemical reaction by IR spectroscopy proved to be ideal for the analysis of the acyl-Claisen reaction, as distinct characteristic IR signals could be observed for the acid chloride starting material (ca. 1790 cm^{-1}), the ketene intermediate (ca. 2115 cm^{-1}), and the amide product (ca. 1635 cm^{-1}).[6] By collecting a number of spectra at uniform intervals over the course of the reaction, the concentration of various species in solution can be monitored by observing changes in the absorbance of the corresponding peaks in the IR spectra.[7]

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6. Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tables of Spectral Data for Structure Determination of Organic Compounds*, 2nd ed.; Springer–Verlag: New York, 1989.

7. The concentration of a species in solution is linearly related to its absorbance by Beer's Law ($A=\varepsilon cl$, where A is absorbance, ε is the molar extinction coefficient, c is concentration, and l is the path length).

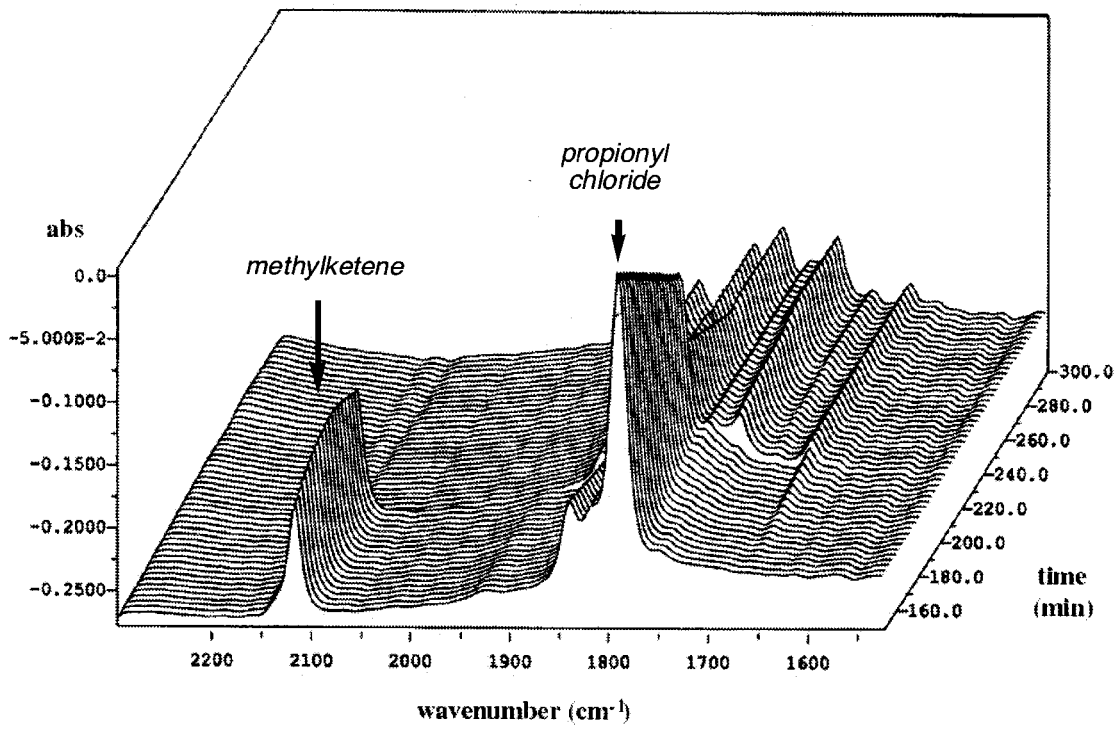

Figure 1. ReactIR spectrum of the crotyl pyrrolidine-catalyzed dimerization of ketene.

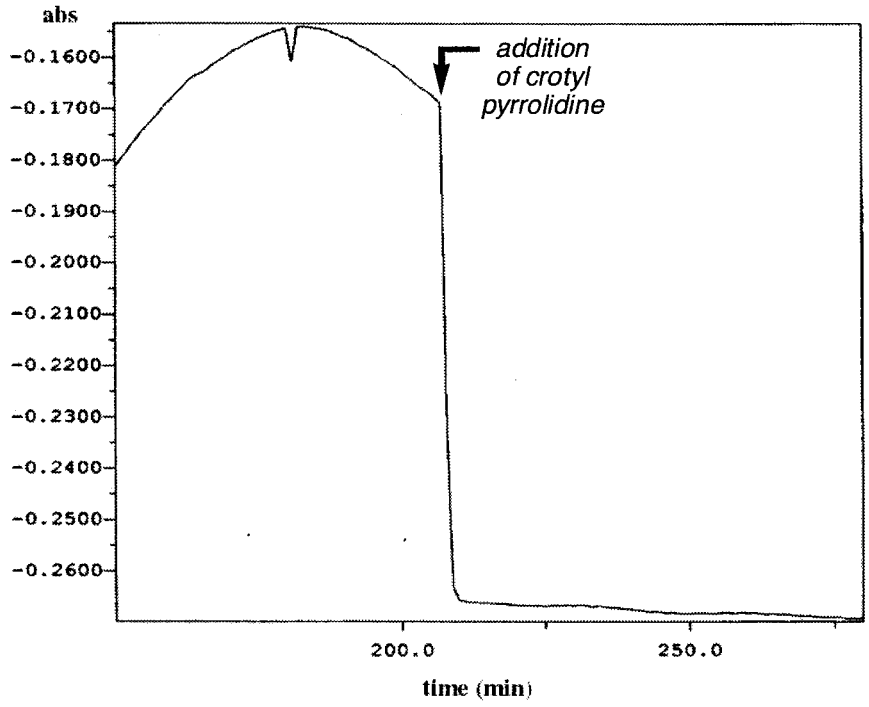

Figure 2. ReactIR profile of the absorbance of the ketene stretch (2115 cm^{-1}).

Upon addition of propionyl chloride to a solution of *i*-Pr_2NEt in CH_2Cl_2 at –20 °C, ReactIR analysis indicates the appearance of a strong stretch corresponding to the acid chloride carbonyl, which decays gradually as a peak corresponding to the methylketene stretch emerges (Figure 1). When crotyl pyrrolidine is added to the solution, the ketene stretch immediately disappears and the acid chloride stretch becomes greatly diminished in intensity. These results lend credence to our supposition that the *N*-allyl pyrrolidine substrates can cause ketene dimerization to occur competitively with the Claisen process. In addition, because ketene could be observed in the presence of the sterically encumbered *i*-Pr_2NEt base, it was clear that less nucleophilic amines would be poor catalysts for ketene dimerization and therefore could be present in the reaction without obstructing the Claisen process.

As a result, we began to consider other allylic amines that might engage in a facile acyl-Claisen rearrangement without significantly promoting a detrimental ketene dimerization process. In this context, *N*-allyl morpholine compounds appeared to be ideal candidates for investigation, as the presence of an electron-withdrawing oxygen in the six-membered ring reduces the basicity and nucleophilicty of the morpholine nitrogen relative to pyrrolidine.[8] Therefore, allyl morpholines are expected to be less efficient catalysts for the dimerization of ketenes (Scheme 2).

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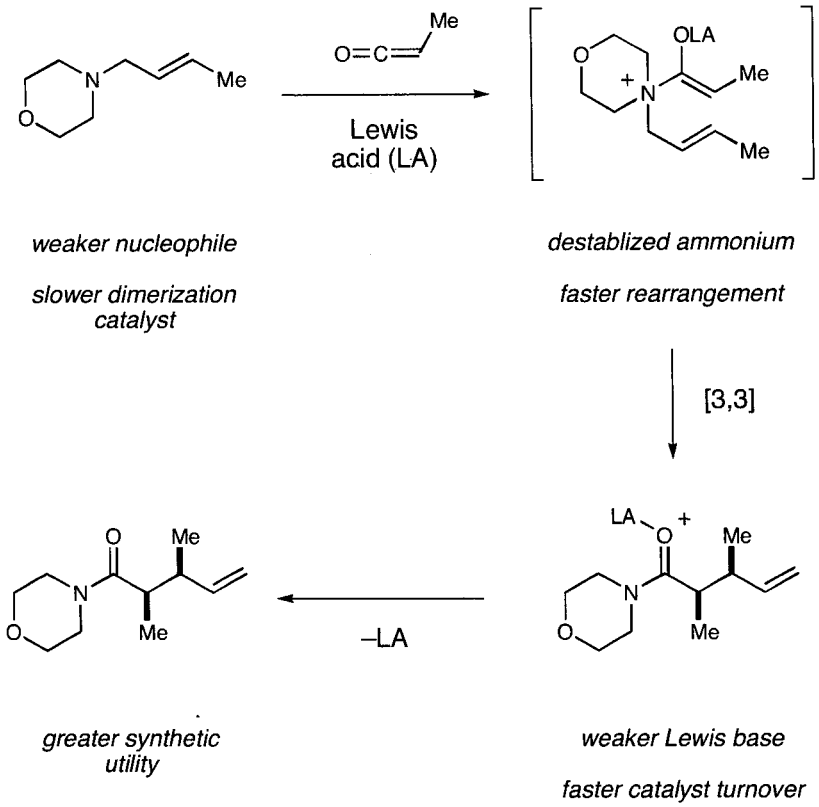
8. The p*Ka* of protonated *N*-methylpyrrolidine is 10.3, while protonated *N*-methylmorpholine exhibits a p*Ka* of 7.4. Perrin, D. D. *Dissociation Constants of Organic Bases in Aqueous Solution*; Butterworths: London, 1965.

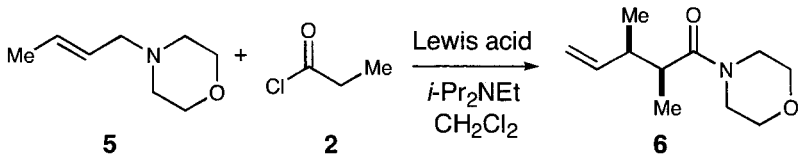
Scheme 2



In addition, the morpholine substrates would be superior to allyl pyrrolidines for several other reasons. First, the electron-withdrawing effect of the morpholine oxygen would destabilize the cationic charge on the nitrogen of the zwitterionic intermediate and could thereby increase the rate of the sigmatropic rearrangement. Second, the poorer electron-donating ability of the morpholine nitrogen should render the amide carbonyl of the product less Lewis basic, which would accelerate dissociation of the product from the metal center and improve catalyst turnover. Third, morpholine-derived amides possess

greater synthetic utility than their pyrrolidine-derived counterparts. Like Weinreb amides,[9] morpholine-derived amides can be directly converted to ketones by treatment with alkylmetal nucleophiles[10] and to aldehydes by reduction with LAH.[11]

Table 3. Effect of Lewis acid on the acyl-Claisen rearrangement of crotyl morpholine.



5 2 6 (3)

entry	Lewis acid	equiv	yield	*syn:anti*[a]
1	--	--	NR	--
2	$Y(OTf)_3$	0.1	59[b]	>99:1
3	$MgBr_2 \cdot OEt_2$	0.1	39[b]	>99:1
4	$Yb(OTf)_3$	0.1	80	>99:1
5	$AlCl_3$	0.1	90	>99:1
6	$Ti(O\textit{i}\text{-}Pr)_4$	0.1	76	>99:1
7	$TiCl_4(THF)_2$	0.1	99[b]	>99:1
8	$TiCl_4(THF)_2$	0.05	92	>99:1

[a] Product ratios determined by GLC using a Bodman CC1701 column. [b] Conversion based on ^1H NMR analysis of the unpurified reaction mixture.

9. (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815. (b) Sibi, M. P. *Org. Prep. Proc. Int.* **1993**, *25*, 15. (c) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1996**, *36*, 5461. (d) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685.

10. Martin, R.; Romea, P.; Tey, C.; Urpí, F.; Vilarrasa, J. *Synlett* **1997**, 1414.

11. Douat, C.; Heitz, A.; Martinez, J.; Fehrentz, J.-A. *Tetrahedron Lett.* **2000**, *41*, 37.

The results of experiments designed to test the effectiveness of morpholine-based substrates in the acyl-Claisen rearrangement are described in Table 3. In accord with our hypothesis, *N*-crotyl morpholine rearranges efficiently in the presence of catalytic quantities of a range of Lewis acids, including $Yb(OTf)_3$, $AlCl_3$, $Ti(O\textit{i}\text{-}Pr)_2Cl_2$, and $TiCl_4(THF)_2$. The desired Claisen product **6** was formed in high yield (>75%, entries 4–8) and with the same excellent levels of stereocontrol observed in previous experiments (>99:1 *syn:anti*). Notably, no products from Claisen rearrangement can be observed when the reaction is performed in the absence of a Lewis acid (entry 1).

In analogy to the ketene-Claisen methodology discussed in Chapter 2, $TiCl_4(THF)_2$ again proved to be the most effective Lewis acid for this transformation and could be used in as little as 5 mol% catalyst loading (entry 8). We therefore selected this metal salt for further exploration of the scope of the acyl-Claisen rearrangement.

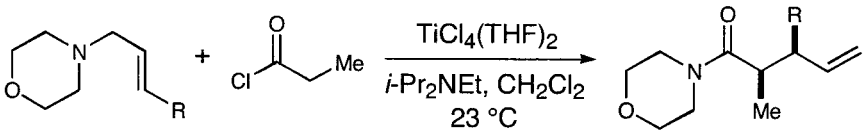
Scope of the Acyl-Claisen Rearrangement

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 in the reaction of *trans*-substituted allylic morpholines while maintaining good yields and excellent levels of diastereoselectivity (>76% yield, >99:1 *syn:anti*). Notably, the β-chloro-substituted morpholine amide **9** can be isolated in 95% yield without any observable decomposition to the conjugated α,β,γ,δ-unsaturated β-elimination product.

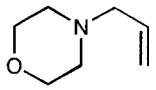
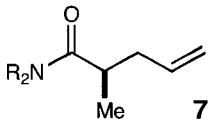
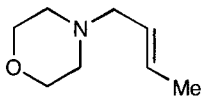
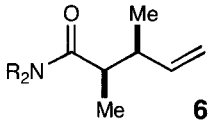
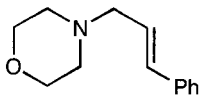
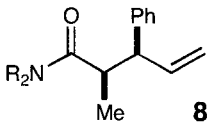
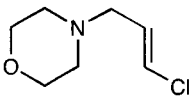
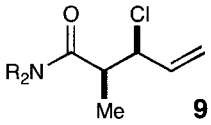
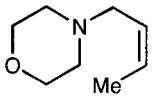
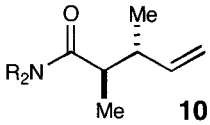
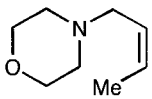
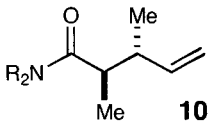
While *trans*-disubstituted allylic morpholines reacted smoothly with propionyl chloride under the influence of 5–10 mol% of $TiCl_4(THF)_2$, experiments involving the corresponding *cis* isomers were initially unsuccessful. Addition of propionyl chloride to *cis*-crotyl morpholine in the presence of 10 mol% $TiCl_4(THF)_2$ (entry 5) failed to produce the desired Claisen adduct, as indicated by TLC and ^1H NMR. However, when 1 equiv

$TiCl_4(THF)_2$ was used to promote the reaction, the desired *anti*-1,2-dimethyl-substituted Claisen product **10** was formed with >95% conversion after 2 h (entry 6).

Table 4. Acyl-Claisen rearrangement of representative allyl morpholines and propionyl chloride.



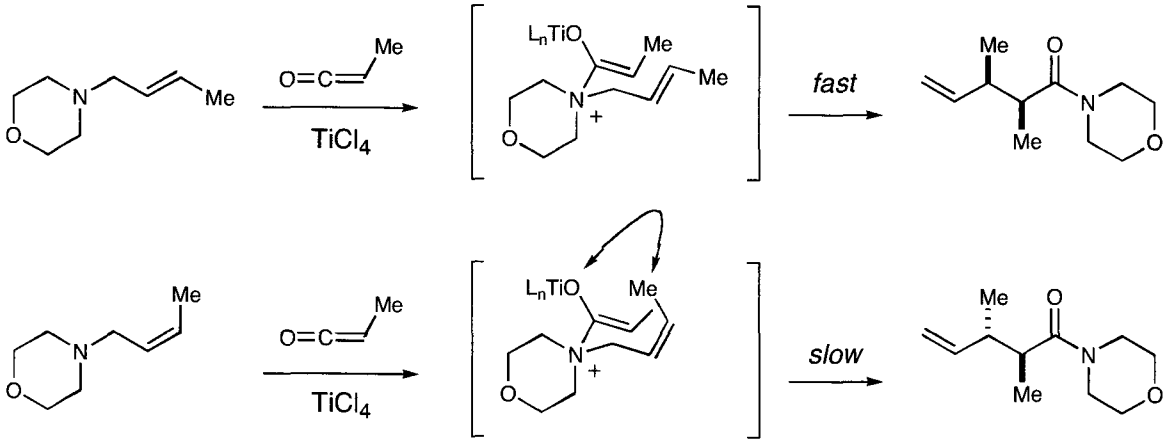
(4)

entry	amine	mol% cat	product[a]	yield	*syn*:*anti*[b,c]
1		10	 **7**	95	--
2		5	 **6**	92	>99:1
3		10	 **8**	76	>99:1
4		10	 **9**	95	>99:1
5		10	 **10**	NR	--
6		100	 **10**	>95[d]	<5:95[d]

[a] NR_2 = *N*-morpholine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative configurations assigned by chemical correlation to a known compound (See Experimental section). [d] Conversion and diastereoselectivity determined by ^1H NMR analysis of unpurified reaction mixture.

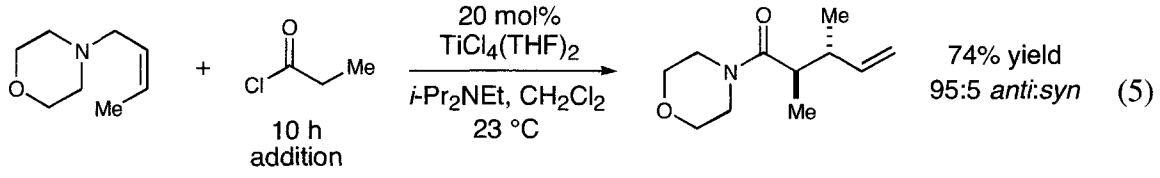
These results can be understood from an examination of the transition states involved in the rearrangement of each isomer (Scheme 3). Assuming that addition of the allylic morpholine occurs from the less hindered side of the ketene,[12] the zwitterionic enolate intermediate should be formed with high (*Z*) selectivity. In the case of the *trans*-crotyl morpholine, a low-energy chair-like transition state is accessible that places the methyl substituents in pseudo-equatorial orientations. The corresponding chair-like transition state for the rearrangement of the *cis* isomer, however, positions one of the methyl substituents in a pseudoaxial orientation, which suffers from a destabilizing 1,3-diaxial interaction with the bulky metal-bound enolate oxygen. Thus, the rate of rearrangement for the *cis*-crotyl morpholine would be expected to be slower than the rate of the *trans* isomer. As a result, ketene dimerization can compete with the desired rearrangement process, resulting in diminished yields of the desired acyl-Claisen adducts.

Scheme 3



12. See Chapter 2, Figure 2.

We speculated that the reaction of the *cis*-crotyl morpholine isomer could be rendered catalytic in titanium if the rate of ketene dimerization could be diminished with respect to the rate of the desired acyl-Claisen process. Since ketene dimerization is presumably second-order with respect to ketene, while the acyl-Claisen rearrangement involves only one equivalent of ketene, we reasoned that the undesired dimerization process could be avoided by maintaining a relatively low concentration of ketene in solution. We further surmised that the concentration of ketene could be minimized by slow addition of the acid chloride precursor to the reaction over a long period of time. Indeed, as shown in eq 5, when propionyl chloride is added by syringe pump over the course of 10 h, the reaction of *cis*-crotyl morpholine proceeds smoothly to give the desired *anti* product in 74% yield (95:5 *anti*:*syn*) using only 20 mol% $TiCl_4(THF)_2$



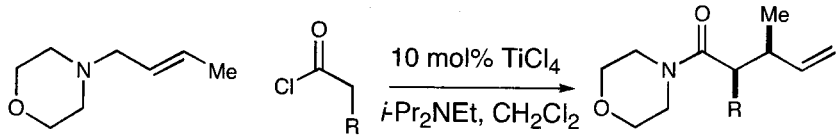
(5)

The scope of acid chlorides tolerated by the reaction was also investigated (Table 5). The reaction is successful using a variety of sterically unhindered alkyl-substituted acid chlorides, such as acetyl chloride, propionyl chloride, and hexenoyl chloride (entires 1–3). Sterically encumbered acid chlorides such as isovaleroyl chloride react much more sluggishly (entry 4), and the α-disubstituted isobutyroyl chloride produced no observable Claisen product (entry 5).[13]

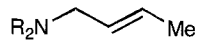
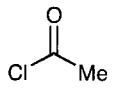
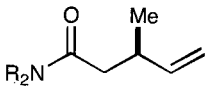
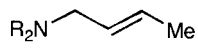
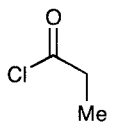
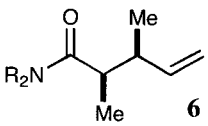
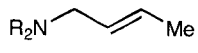
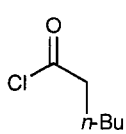
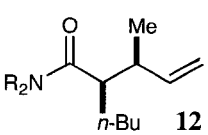
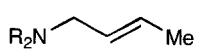
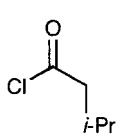
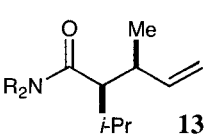
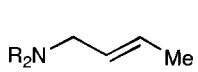
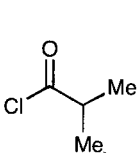
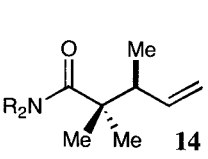
---

13. As dimethyl ketene participates readily in the ketene-Claisen (Chapter 2), we presume that the failure of isobutyroyl chloride in the acyl-Claisen is due to a slow rate of ketene formation. Indeed, ReactIR analysis of the reaction of isobutyroyl chloride with *i*-Pr_2NEt does not provide evidence of the

Table 5. Acyl-Claisen rearrangement of allyl morpholines and representative acid chlorides.



(6)

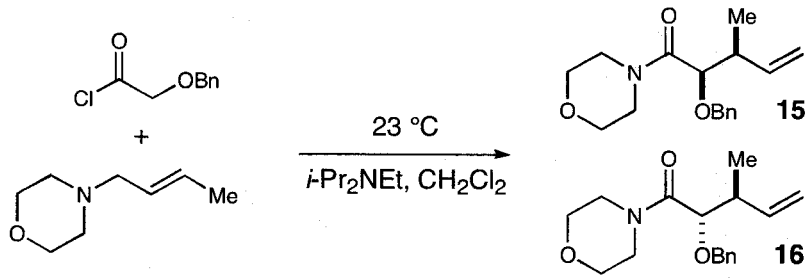
entry	allyl amine[a]	acid-Cl	product[a]	yield	*syn:anti*[b,c]
1			 **11**	81	--
2[d]			 **6**	92	>99:1
3			 **12**	93	>99:1
4			 **13**	28[d]	>99:1
5			 **14**	NR	--

[a] NR_2 = *N*-morpholine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative stereochemistry assigned by analogy to results summarized in Table 4. [d] Reaction conducted with 5 mol% $TiCl_4(THF)_2$. [e] 32% conversion as assayed by ^1N NMR of the unpurified reaction mixture.

formation of dimethylketene (Dong, V. M.; Hughes, C. H.; MacMillan, D. W. C., unpublished results).

As shown in Table 6, heteroatom-substituted acid chlorides also participate in the acyl-Claisen rearrangement. Initial experiments demonstrated that benzyloxyacetyl chloride reacts with *trans*-crotyl morpholine to afford the expected Claisen product **15** in good yield but with poor diastereoselectivity (entry 1, 92% yield, 67:33 *syn:anti*). Importantly, it was discovered that when employing the α-benzyloxy acid chloride as the ketene equivalent, Claisen rearrangement product was formed over 24 h even in the *absence* of a Lewis acid. This background reaction pathway was poorly selective for the production of the *anti* isomer **16** (entry 2, 26:74 *syn:anti*). However, when stoichiometric amounts of $TiCl_4(THF)_2$ were employed, good levels of *syn* selectivity were observed, suggesting that the Lewis acid-mediated process itself is highly diastereoselective (entry 3, 90:10 *syn:anti*). In attempts to diminish the non-Lewis acid-activated background process, the reaction was

Table 6. Optimization of reactions using benzyloxyacetyl chloride.



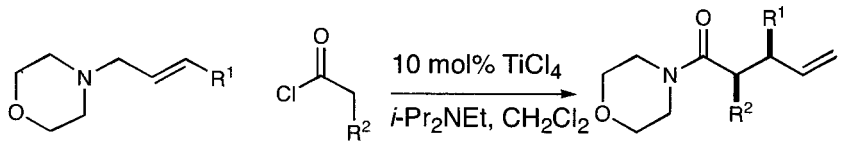
(7)

entry	conditions	% yield	**15:16**[a]
1	10 mol% $TiCl_4(THF)_2$	92	78:22
2	no Lewis acid	24[b]	26:74
3	100 mol% $TiCl_4(THF)_2$	83[b]	90:10
4	10 mol% $TiCl_4(THF)_2$, 10h addition	91	86:14[c]

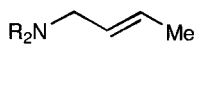
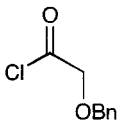
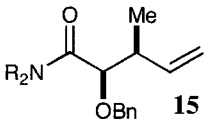
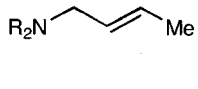
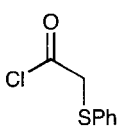
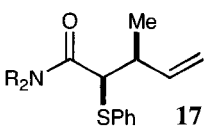
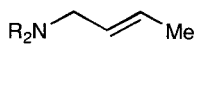
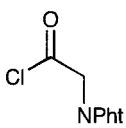
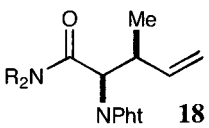
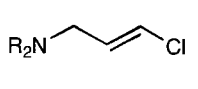
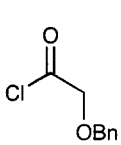
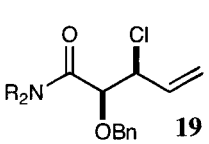
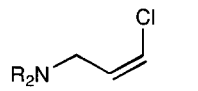
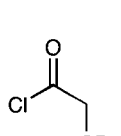
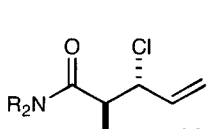
[a] Product ratios determined by ^1H NMR. [b] Conversions determined by ^1H NMR analysis of the unpurified reaction mixture. [c] Product ratio determined by GLC using a Bodman CC1701 column.

conducted with slow addition of the acid chloride. At lower concentrations of the reactive ketene component, the Lewis acid-catalyzed pathway is favored, resulting in formation of the Claisen product **15** in high yield and diastereoselectivity (91% yield, 86:14 *syn:anti*).

Table 7. Acyl-Claisen rearrangement of allylic morpholines with representative heteroatom-substituted acid chlorides.



(8)

entry	allyl amine[a]	acid-Cl	product[a]	yield	*syn:anti*[b,c]
1			 **15**	91	86:14
2			 **17**	81	92:8
3			 **18**	77	>99:1
4			 **19**	83	90:10
5			 **20**	70	10:90

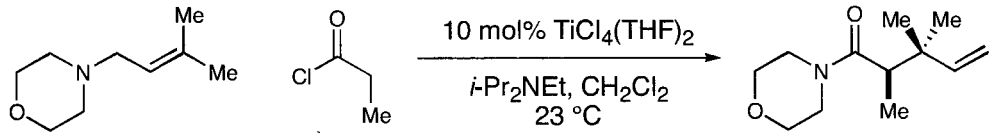
[a] NR_2 = *N*-morpholine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Relative stereochemistry assigned by analogy to results summarized in Table 4. [d] 32% conversion as assayed by ^{1}N NMR of the unpurified reaction mixture.

In addition to benzyloxyacetyl chloride, other α-heteroatom-substituted acid chlorides participate successfully in the acyl-Claisen rearrangement (Table 7). Thus, reaction of crotyl morpholine with benzyloxy- and phenylthio-substituted acid chlorides results in the formation of the corresponding α-alkoxy- and α-alkylthio-substituted Claisen adducts (entries 1–2, 81–91% yield, 86:14 to 92:8 *syn*:*anti*). This methodology also provides a new strategy for the catalytic production of unnatural β-substituted α-amino acids using α-phthalylglycyl chloride (entry 3, 77% yield, 98:2 *syn*:*anti*). Finally, both the *syn* and *anti* α-oxy-β-chloro Claisen isomers **19** and **20** can be accessed in high yield and stereoselectivity from chloro-substituted allyl morpholines and benzyloxyacetyl chloride (entries 4–5). The ability to easily generate halogen-bearing stereocenters on an acyclic carbon framework in a highly stereospecific manner using this new Claisen methodology further highlights its value in the construction of otherwise elusive structural motifs.[14]

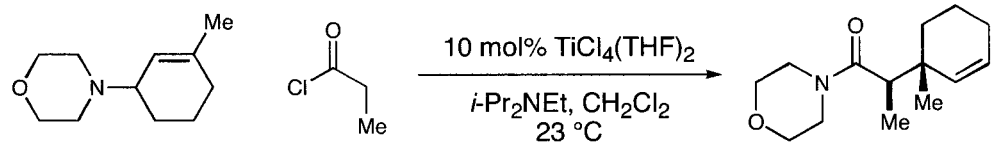
The success of both *cis*- and *trans*-disubstituted allyl morpholines in this reaction suggested to us that quaternary carbon centers might also be accessible using this methodology from the rearrangement of 3,3-disubstituted allyl morpholine substrates. Thus, *N*-prenyl morpholine **21** reacts with propionyl chloride to give 2,3,3-trimethyl-substituted Claisen product **22** in good yield (eq 9). In addition, the propensity for the acyl-Claisen rearrangement to proceed via a highly organized chair-like transition suggested that quaternary carbon stereocenters could be generated stereospecifically from 3,3-disubstuted allyl morpholine substrates. Indeed, as shown in eq 10, reaction of propionyl chloride with 1-methyl-3-*N*-morpholino-cyclohexene (**23**) provides very high levels of diastereocontrol in the formation of the quaternary carbon bearing cyclic adduct **24** (70% yield, 95:5 *anti*:*syn*). Finally, as illustrated in equation 3, the reaction is also highly

14. A review of chiral auxiliary-based methods for construction of halogenated stereocenters has recently been published: Duhamel, P. *Ind. Chem. Libr.* **1996**, *8*, 176.

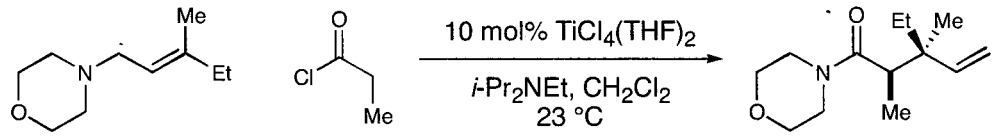
diastereoselective in the rearrangement of *acyclic* olefins, furnishing **26** with excellent *syn* selectivity (eq 11, >99:1 *syn*:*anti*).



21 **22** 70% yield (9)



23 **24** 75% yield
anti:*syn* 95:5 (10)

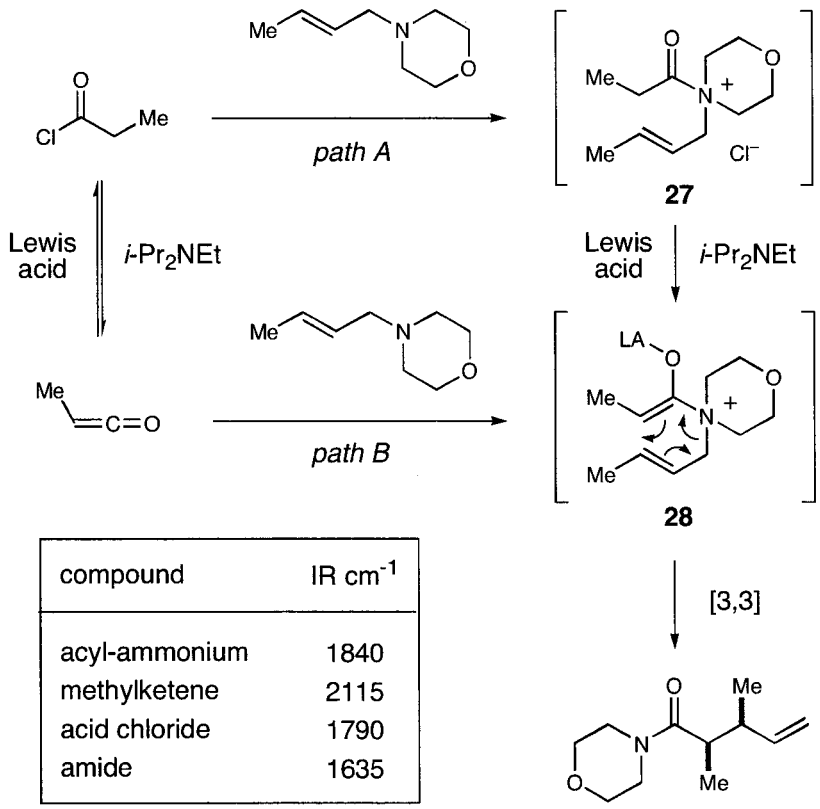


25 **26** 72% yield
syn:*anti* >99:1 (11)

Analysis of the Acyl-Claisen Rearrangement by ReactIR

Our initial investigations of the acyl-Claisen rearrangement were predicated on the mechanistic hypothesis shown in Scheme 4, path B. We surmised that acid chlorides would undergo rapid dehydrohalogenation in the presence of *i*-Pr_2NEt to produce ketenes, which would condense with allylic amines under the influence of a Lewis acid catalyst to generate a zwitterionic intermediate **28**. However, we could not rule out the possibility of an alternate mechanism in which the key zwitterionic intermediate **28** is produced instead by Lewis acid-promoted enolization of acyl ammonium species **27** (path A).

Scheme 4



compound	IR cm^{-1}
acyl-ammonium	1840
methylketene	2115
acid chloride	1790
amide	1635

As previously mentioned, the ketene (2115 cm^{-1}) and acyl ammonium carbonyl (1840 cm^{-1}) produce absorbance peaks in the IR spectrum that are strong and easily distinguishable both from one another and from the acid chloride starting material (1790 cm^{-1}) and amide product (1635 cm^{-1}) carbonyl stretches.[6] Consequently, we recognized that analysis of reaction progress by ReactIR could potentially identify which reactive intermediates are generated during the course of the reaction.

Thus, we monitored the $AlCl_3$-catalyzed reaction of crotyl morpholine and propionyl chloride by ReactIR. The region of the IR absorbance spectrum from 1600–2200 cm^{-1} is shown in Figure 3. Upon addition of propionyl chloride, a peak corresponding to the acid chloride carbonyl appears at 1790 cm^{-1} and decays as a peak corresponding to the product amide develops at 1635 cm^{-1}. Additionally, a third peak appears at 2115 cm^{-1}, indicating

that ketene is indeed generated under the reaction conditions and could lie along the reaction pathway.

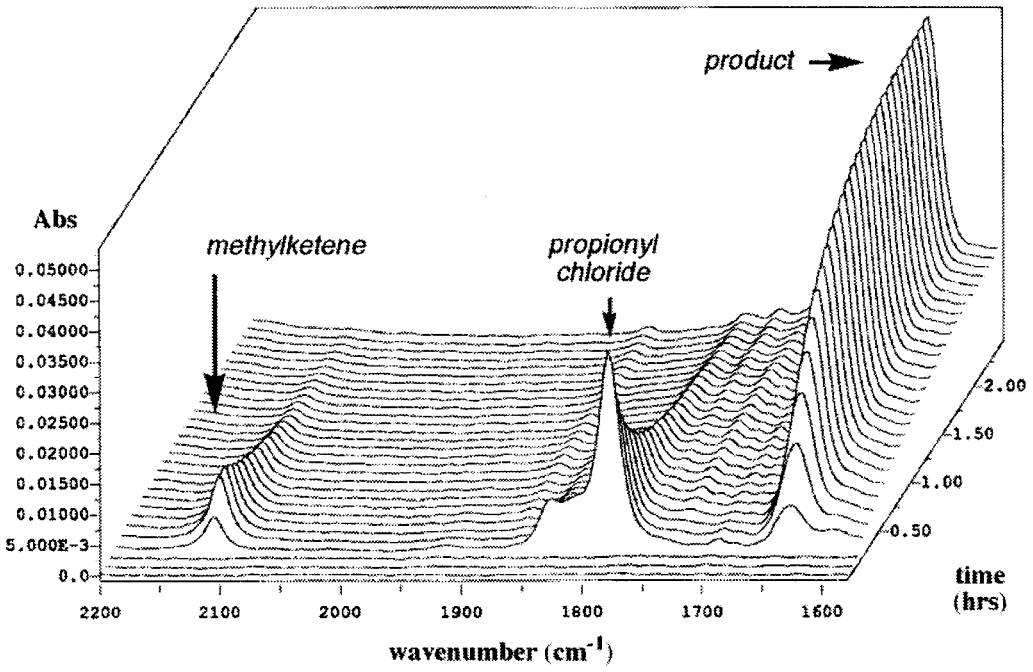


Figure 3. ReactIR analysis of the $AlCl_3$-catalyzed acyl-Claisen rearrangement.

However, the presence of ketene in the reaction solution does not necessarily demonstrate that ketene is directly involved as an intermediate in the reaction. The ketene peak observed under the reaction conditions could simply be the result of an equilibrium concentration of ketene that reverts to acid chloride before forming an acyl ammonium intermediate.[15] In fact, a plot of absorbance vs. time for the acid chloride and ketene peaks suggests that the ketene and the acid chloride are consumed at the same rate (Figure 4), which would be consistent with a rapid pre-equilibrium between the ketene and acid chloride species followed by a slow rate-determining step through either reaction manifold.

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15. Ketene formation is known to be reversible: Brady, W. T.; Scherubel, G. A. *J. Am. Chem. Soc.* **1973**, *95*, 7447.

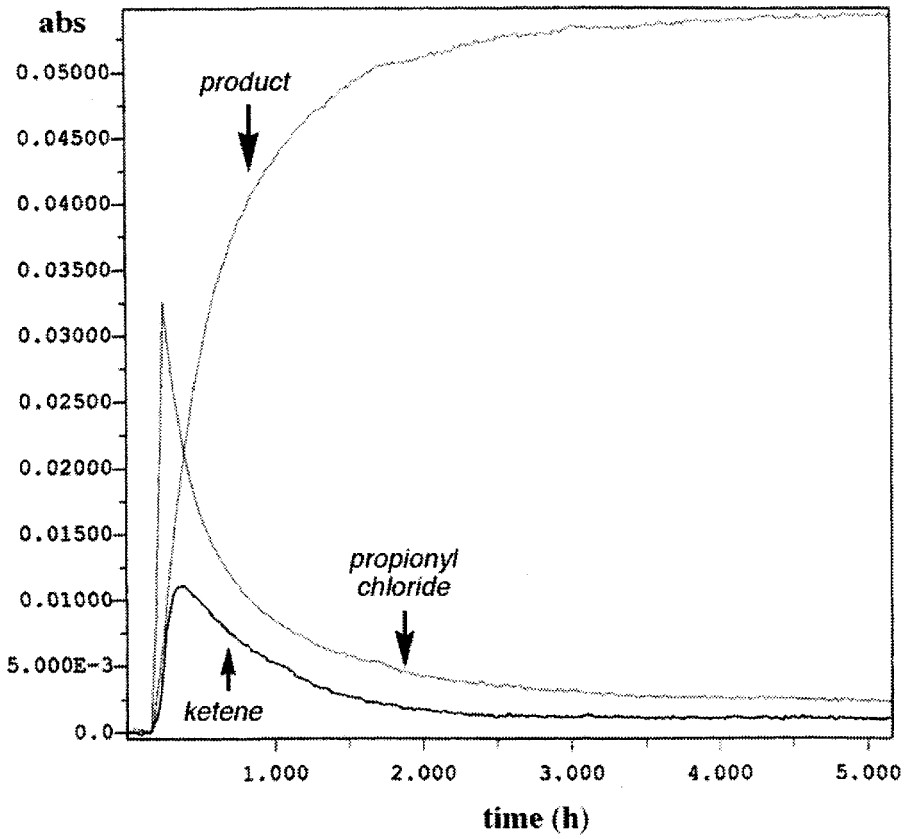

Figure 4. ReactIR profile of the $AlCl_3$-catalyzed acyl-Claisen rearrangement.

The analysis of the acyl-Claisen rearrangement catalyzed by $TiCl_4(THF)_2$ shown in Figure 5 is more informative. As in the $AlCl_3$-catalyzed reaction, addition of propionyl chloride results in the appearance of an acid chloride stretch that decays as an amide signal grows in. However, in this case, the ketene stretch remains constant at a relatively low absorbance throughout the course of the reaction (Figure 6). This profile is inconsistent with a mechanism in which ketene and acid chloride remain in equilibrium throughout the course of the reaction. It is more likely that the ketene is a steady-state intermediate that is generated and consumed rapidly in the subsequent formation of the zwitterionic intermediate **28**. Thus, these data discount the intermediacy of an acyl

ammonium species and lend additional support for the ketene mechanism we initially proposed.

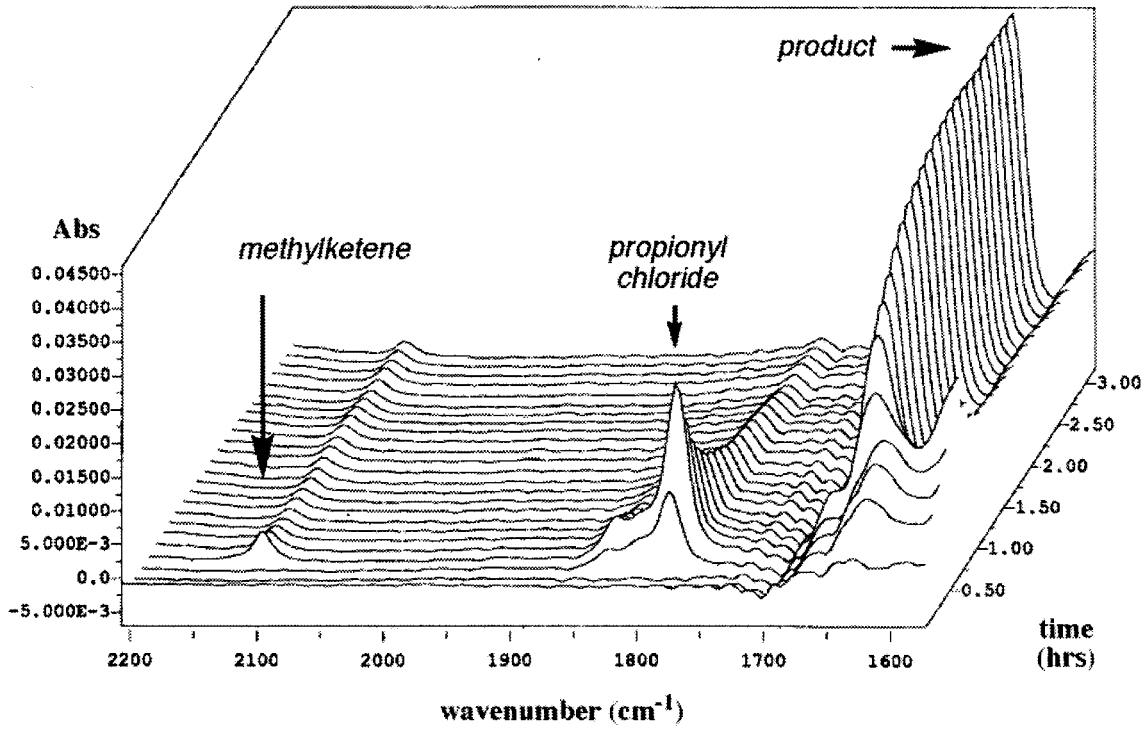

Figure 5. ReactIR analysis of the $TiCl_4(THF)_2$-catalyzed acyl-Claisen rearrangement.

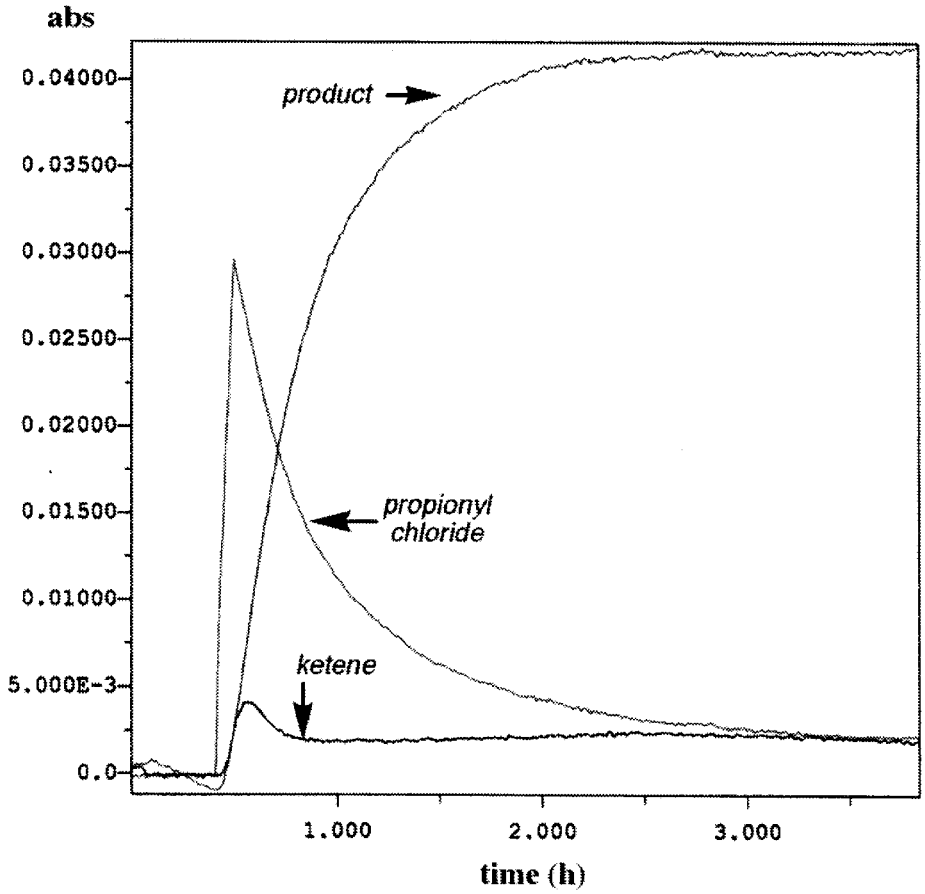

Figure 6. ReactIR profile of the $TiCl_4(THF)_2$-catalyzed acyl-Claisen rearrangement.

Conclusion

We have developed a powerful new acyl-Claisen rearrangement that susceptible to Lewis acid catalysis. This methodology tolerates a wide range of alkyl-, aryl-, and heteroatom-substituted acid chloride and allylic morpholine reaction partners. Slow addition of acid chloride to the reaction allows the successful rearrangement of less reactive allyl morpholine substrates without consumption of the intermediate ketene in a non-productive dimerization process. The acyl-Claisen rearrangement is highly stereospecific using allyl morpholine substrates bearing *cis*- and *trans*-disubstituted double bonds, and can be employed to establish quaternary carbon stereocenters in a highly diastereoselective manner on both cyclic and acyclic carbon frameworks. Analysis of the reaction by ReactIR

spectroscopy supports a mechanism in which ketene generated in situ is directly involved in the reaction pathway. Importantly, this reaction is catalytic in the presence of a variety of metal species and presents an attractive platform for the development of an asymmetric catalytic Claisen variant.

Experimental Section

General Information. All non-aqueous reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. *N,N*-diisopropylethylamine and dichloromethane were distilled from calcium hydride prior to use. Air sensitive solids were dispensed in an inert atmosphere glovebox. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or $KMnO_4$ stain.

^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 (500 MHz and 125 MHz, respectively), AMX-400 (400 MHz and 100 MHz), or AMX-300 (300 MHz and 75 MHz) instruments, as noted, and are internally referenced to residual protio solvent signals. Data for ^1H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C are reported in terms of chemical shift. IR spectra were recorded

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1. Perrin, D. D.; Armarego, W. L. F. *Purificaion of Laboratory Chemicals;* 3rd ed., Pregamon Press, Oxford, 1988.

2. Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

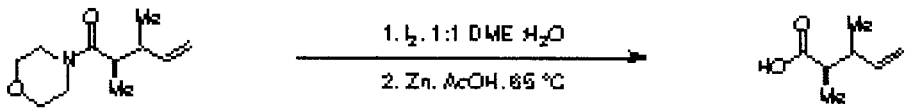
on an ASI React-IR 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Berkeley Mass Spectral facility. Gas chromatography was performed on Hewlett-Packard 5890A and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using the following columns: Bodman Chiraldex Γ-TA (30 m x 0.25 mm) and C&C Column Technologies CC-1701 (30 m x 0.25 mm).

General Procedure A: A round-bottomed flask containing $TiCl_4$•$(THF)_2$ was charged with CH_2Cl_2, then treated with the allyllic morpholine, followed by *i*-Pr_2NEt. The solution was stirred for 5 min before a solution of the acid chloride in CH_2Cl_2 was added dropwise over 1 min. The resulting dark red solution was stirred until the allyllic morpholine was completely consumed (2–6 h) as determined by TLC (EtOAc). The reaction mixture was then diluted with an equal volume of Et_2O and washed with aqueous 1*N* NaOH (5 mL). The aqueous layer was then extracted with ether, and the combined organic layers washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by silica gel chromatography (Et_2O) to afford the title compounds.

General Procedure B: A round-bottomed flask containing $TiCl_4$•$(THF)_2$ was charged with CH_2Cl_2, then treated with the allyllic morpholine, followed by *i*-Pr_2NEt. The solution was stirred for 5 min before a solution of the acid chloride in CH_2Cl_2 was added slowly by syringe pump over 4–10 h. The resulting dark red solution was stirred until the allyllic morpholine was completely consumed (2–6h) as determined by TLC (EtOAc). The reaction mixture was then diluted with an equal volume of Et_2O and washed with aqueous 1*N* NaOH (5 mL). The aqueous layer was then extracted with ether, and the combined organic layers washed with brine, dried (Na_2SO_4), and concentrated. The resulting residue was purified by silica gel chromatography (Et_2O) to afford the title compounds.

***N*-(2-Methyl-4-pentenoyl)-morpholine** (Table 4, entry 1). Prepared according to general procedure A from *N*-allyl morpholine (161 mg, 1.3 mmol), $TiCl_4$•$(THF)_2$ (42 mg, 0.13 mmol), *i*-Pr_2NEt (336 μL, 0.94 mmol), and propionyl chloride (1.5 mL, 1 M solution in CH_2Cl_2, 1.5 mmol) in CH_2Cl_2 (13 mL) to provide the pure product as a clear oil in 95% yield (221 mg, 1.2 mmol); IR (CH_2Cl_2) 2976, 2864, 1640, 1467, 1436 cm^{-1}; ^1H NMR (400 MHz) δ 5.66-5.77 (m, 1H, C**H**=CH_2), 4.96-5.05 (m, 2H, CH=C**H**$_2$), 3.47-3.64 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.64-2.72 (m, 1H, C**H**CH_3), 2.35-2.42 (m, 1H, C**H**$_2$CH=CH_2), 2.06-2.13 (m, 1H, C**H**$_2$CH=CH_2), 1.08 (d, 3H, CH_3); ^{13}C NMR (100 MHz) δ 174.5, 136.0, 116.7, 67.0, 66.8, 46.0, 42.1, 38.1, 35.1, 17.3; LRMS (FAB) *m/z* 183 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{10}H_{17}NO_2$) requires *m/z* 183.1259, found *m/z* 183.1253.

(2*R,3*S**)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine** (Table 4, entry 2). Prepared according to general procedure A from (*E*)-*N*-but-2-enyl morpholine (115 mg, 0.81 mmol), $TiCl_4$•$(THF)_2$ (27 mg, 81 μmol), *i*-Pr_2NEt (213 μL, 1.22 mmol), and propionyl chloride (980 μL, 1 M solution in CH_2Cl_2, 0.98 mmol) in CH_2Cl_2 (8.1 mL) to provide the pure product as a colorless oil in 92% yield (148 mg, 0.75 mmol); >99:1 *syn:anti*. *Syn* isomer: IR (CH_2Cl_2) 2972, 2926, 2860, 1633, 1459, 1436 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (ddd, *J* = 7.3, 10.4, 17.5 Hz, 1H, C**H**=CH_2), 4.87–4.96 (m, 2H, CH=C**H**$_2$), 3.34–3.60 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.52 (dq, *J* = 7.1, 7.1 Hz, 1H, C**H**CH_3), 2.37 (q, *J* = 7.1 Hz, 1H, C**H**CH_3), 1.01 (d, *J* = 6.7 Hz, 3H, CH_3), 0.94 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7, 142.3, 114.3, 67.3, 67.0, 46.5, 42.3, 40.5, 40.3, 16.3, 14.8; LRMS (FAB) *m/z* 197 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{11}H_{19}NO_2$) requires *m/z* 197.1416, found *m/z* 197.1414. Product ratio was determined by GLC with a Bodman Γ-TA column (70 °C, 2 °C/min gradient, 23 psi); *syn* adduct (2*R*,3*S* and 2*S*,3*R*) t_r = 39.7 min and 40.8 min, *anti* adduct (2*R*,3*R* and 2*S*,3*S*) t_r = 39.9 min and 40.5 min.



Determination of the Relative Configuration of (2*R,3*S**)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine by Correlation with (2*R**,3*S**)-2,3-Dimethyl-4-pentenoic acid.** A solution of (2*R**,3*S**)-*N*-(2,3-dimethyl-4-pentenoyl)-morpholine (22 mg, 0.11 mmol) in 1,2-DME (0.25 mL) and H_2O (0.25 mL) was placed in an 8 mL scintillation vial equipped with a magnetic stir bar. The solution was treated with iodine (61 mg, 0.24 mmol) and was stirred in the absence of light. After 30 min, the reaction was diluted with Et_2O (1 mL) and washed sequentially with 10% aqueous $Na_2S_2O_3$ (1 mL) and brine (1 mL). The resulting organic layer was dried (Na_2SO_4) and concentrated to give (2*S**,3*S**,4*R**)-4-iodomethyl-2,3-dimethyl-γ-butyrolactone as a yellow oil. This crude residue was dissolved in glacial AcOH (1 mL) and placed in an 8 mL scintillation vial equipped with a magnetic stir bar. The solution was treated with zinc dust (65 mg, 1.0 mmol) and stirred at 65 °C for 3 h. After allowing the reaction to cool to rt, 1 *N* HCl (aq) (1 mL) was added, and the mixture was extracted with ether (3 x 1 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to give a light pink oil that exhibited spectral data identical in all respects to those reported for (2*R**,3*S**)-2,3-dimethyl-4-pentenoic acid.[3]

(2*S,3*S**)-*N*-(2-Methyl-3-phenyl-4-pentenoyl)-morpholine** (Table 4, entry 3). Prepared according to general procedure A from (*E*)-*N*-(3-phenyl-2-propenyl)-morpholine (201 mg, 0.99 mmol), $TiCl_4$•$(THF)_2$ (33 mg, 99 μmol), *i*-Pr_2NEt (258 μL, 1.43 mmol), and propionyl chloride (1.48 mL, 1 M solution in CH_2Cl_2, 1.48 mmol) in CH_2Cl_2 (10 mL) at

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3. Metz, P. *Tetrahedron* **1993,** *49,* 6367.

0 °C to provide the pure product as white needles in 74% yield (194 mg, 0.75 mmol); >99:1 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 3057, 2988, 2968, 2930, 1637, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.15-7.31 (m, 5H, Ph), 5.99 (ddd, *J* = 7.8, 10.4, 17.9 Hz, 1H, C**H**=CH_2), 4.95–5.02 (m, 2H, CH=C**H**$_2$), 3.48–3.66 (m, 9H, N(C**H**$_2$C**H**$_2$)$_2$, C**H**Ph), 3.04 (dq, *J* = 6.8, 9.9 Hz, 1H, C**H**CH_3), 0.90 (d, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 141.7, 139.8, 128.6, 128.3, 126.7, 115.7, 67.0, 66.7, 53.4, 46.2, 42.1, 39.7, 16.7; LRMS (FAB) m/z 259; HRMS (FAB) exact mass calcd for ($C_{16}H_{21}NO_2$) requires *m/z* 259.1572, found *m/z* 259.1569. Diastereomer ratio was determined by GLC with a CC-1701 column (70 °C, 5 °C/min gradient, 25 psi); *syn* adduct t_r = 31.3 min, *anti* adduct t_r = 30.2 min.

(2*R,3*S**)-*N*-(3-Chloro-2-methyl-4-pentenoyl)-morpholine** (Table 4, entry 4). Prepared according to general procedure A from (*E*)-*N*-(3-chloro-2-propenyl) morpholine (112 mg, 0.69 mmol), $TiCl_4$•$(THF)_2$ (23 mg, 69 μmol), *i*-Pr_2NEt (181 μL, 1.04 mmol), and propionyl chloride (1.04 mL, 1 M solution in CH_2Cl_2, 1.04 mmol) in CH_2Cl_2 (7 mL) to provide the pure product as a pale yellow oil in 95% yield (143 mg, 0.66 mmol); >99:1 *syn*:*anti* . *Syn* isomer: IR (CH_2Cl_2) 3057, 2976, 2864, 1640, 1463, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 8.3, 10.2, 18.5 Hz, 1H, C**H**=CH_2), 5.12–5.31 (m, 2H, CH=C**H**$_2$), 4.51 (t, *J* = 8.4 Hz, 1H, C**H**Cl), 3.50–3.65 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.98 (dq, *J* = 6.8, 8.8 Hz, 1H, C**H**CH_3), 1.27 (d, *J* = 6.8, 3H, CH_3); ^{13}C NMR (75 MHz) δ 172.0, 136.6, 118.4, 67.2, 67.0, 65.4, 46.7, 42.7, 42.5, 16.7; LRMS (FAB) *m/z* 217 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{10}H_{16}ClNO_2$) requires *m/z* 217.0870, found *m/z* 217.0868. Product ratio was determined by GLC with a Bodman Γ-TA column (70 °C, 7 °C/min gradient, 23 psi); *syn* adduct (2*R*,3*S* and 2*S*,3*R*) t_r = 18.7 min and 19.2 min, *anti* adduct (2*R*,3*R* and 2*S*,3*S*) t_r = 19.6 min and 19.8 min. Relative configuration assigned by analogy.

(2*R,3*R**)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine** (eq 5). Prepared according to general procedure B from (*Z*)-*N*-but-2-enyl morpholine (88 mg, 0.62 mmol), $TiCl_4$•$(THF)_2$ (42 mg, 0.13 mmol), *i*-Pr_2NEt (163 μL, 0.94 mmol), and propionyl chloride (750 μL, 1 M solution in CH_2Cl_2, 0.75 mmol), added over 8h, in CH_2Cl_2 (4.2 mL) to provide the pure product as a clear oil in 74% yield (91 mg, 0.46 mmol); 95:5 *anti*:*syn*. *Anti* isomer: IR (CH_2Cl_2) 2976, 2864, 1637, 1463, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (ddd, *J* = 8.2, 10.2, 18.3 Hz, 1H, C**H**=CH_2), 4.96–5.12 (m, 2H, CH=C**H**$_2$), 3.44–3.66 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.36–2.49 (m, 2H, C**H**CH3), 1.02 (d, *J* = 6.5 Hz, 3H, CH_3), 0.94 (d, *J* = 6.3 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 141.6. 115.4, 67.4, 67.1, 46.5, 42.4, 41.8, 40.4, 19.3; LRMS (FAB) *m/z* 197 $(M)^+$; HRMS (FAB) exact mass for ($C_{11}H_{19}NO_2$) requires *m/z* 197.1416, found 197.1414. Product ratio was determined by GLC with a Bodman Γ-TA column (70 °C, 2 °C/min gradient, 23 psi); *syn* adduct (2*R*,3*S* and 2*S*,3*R*) t_r = 39.7 min and 40.8 min, *anti* adduct (2*R*,3*R* and 2*S*,3*S*) t_r = 39.9 min and 40.5 min.

***N*-(3-Methyl-4-pentenoyl)-morpholine** (Table 5, entry 1). Prepared according to general procedure A from (*E*)-*N*-but-2-enyl morpholine (147 mg, 1.04 mmol), $TiCl_4$•$(THF)_2$ (35 mg, 0.10 mmol), *i*-Pr_2NEt (255 μL, 1.56 mmol), and propionyl chloride (1.25 mL, 1 M solution in CH_2Cl_2, 1.25 mmol) in CH_2Cl_2 (10 mL) to provide the pure product as a clear oil in 81% yield (155 mg, 0.846 mmol); ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (ddd, *J* = 6.6, 10.3, 17.2 Hz, 1H, C**H**=CH_2), 4.91–5.03 (m, 2H, CH=C**H**$_2$), 3.43–3.65 (m, 8H. N(C**H**$_2$C**H**$_2$)$_2$), 2.61–2.74 (m, 1H, C**H**CH_3), 2.35 (dd, *J* = 6.8, 14.8 Hz, 1H C**H**$_2$CH), 2.23 (dd, *J* = 7.4 Hz, 14.8 Hz, 1H C**H**$_2$CH), 1.04 (d, *J* = 6.8 Hz, 3H, C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 143.3, 113.5, 67.3, 67.0, 46.5, 42.2, 39.9, 34.8, 20.1; LRMS (FAB) *m/z* 183 $(M)^+$; HRMS (EI) exact mass for ($C_{10}H_{17}NO_2$) requires *m/z* 183.1259, found 183.1254.

(2*R,3*S**)-*N*-(2-Butyl-3-methyl-4-pentenoyl)-morpholine** (Table 5, entry 3). Prepared according to general procedure A from (*E*)-*N*-but-2-enyl morpholine (129 mg, 0.914 mmol), $TiCl_4$•$(THF)_2$ (31 mg, 91 μmol), *i*-Pr_2NEt (239 μL, 1.37 mmol), and hexanoyl chloride (154 μL, 1.10 mmol) in CH_2Cl_2 (9 mL) to provide the pure product as a yellow oil in 93% yield (204 mg, 0.852 mmol); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (ddd, *J* = 7.5, 10.3, 17.3 Hz, 1H, C**H**=CH_2), 4.87–4.97 (m, 2H, CH=C**H**$_2$), 3.40–3.63 (m, 8H. N(C**H**$_2$C**H**$_2$)$_2$), 2.35–2.46 (m, 2H, C**H**CH_3, C**H**CH=CH_2), 1.63 (m, 1H, butyl), 1.42 (m, 1H, butyl), 1.02–1.24 (m, 4H, butyl), 0.97 (d, *J* = 6.7 Hz, 3H, C**H**$_3$), 0.82 (t, *J* = 6.8 Hz, 3H, C**H**$_3$$CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 142.3, 114.3, 67.5, 67.1, 46.7, 46.2, 42.3, 40.6, 30.3, 29.8, 23.2, 17.1, 14.3; LRMS (FAB) *m/z* 239 $(M)^+$; HRMS (EI) exact mass for ($C_{14}H_{25}NO_2$) requires *m/z* 239.1885, found 239.1886.

(2*R,3*S**)-*N*-(2-Benzyloxy-3-methyl-4-pentenoyl)-morpholine** (Table 7, entry 1). Prepared according to general procedure B from (*E*)-*N*-but-2-enyl morpholine (60 mg, 0.43 mmol), $TiCl_4$•$(THF)_2$ (14 mg, 43 μmol), *i*-Pr_2NEt (111 μL, 0.64 mmol), and benzyloxyacetyl chloride (0.51 mL, 1 M solution in CH_2Cl_2, 0.51 mmol), added over 2h, in CH_2Cl_2 (8.5 mL) to provide the pure product as a pale yellow oil in 91% yield (112 mg, 0.39 mmol); 86:15 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 3068, 2746, 2864, 1640, 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.36 (m, 5H, Ph), 5.68 (ddd, *J* = 8.3, 10.2, 18.5 Hz, 1H, C**H**=CH_2), 5.00–5.08 (m, 2H, CH=C**H**$_2$), 4.62 (d, *J* = 11.7, 1H, C**H**$_2$Ph), 4.43 (d, *J* = 11.7, 1H, C**H**$_2$Ph), 3.92 (d, *J* = 8.9, 1H, C**H**OCH_2Ph), 3.55–3.70 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.55–2.62 (m, 1H, C**H**CH_3), 1.15 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 138.9, 137.3, 128.5, 128.0, 115.8, 84.2, 72.2, 67.1, 66.8, 45.7, 42.5, 41.5, 17.0; LRMS (FAB) *m/z* 290 $(MH)^+$; HRMS (FAB) exact mass calcd for ($C_{17}H_{24}NO_3$) requires *m/z* 289.1756, found *m/z* 290.1755. Diastereomer ratios were determined by ^{1}H NMR analysis. Relative configuration assigned by analogy.

(2*R,3*S**)-*N*-(3-Methyl-2-phenylthio-4-pentenoyl)-morpholine** (Table 7, entry 2). Prepared according to general procedure B from (*E*)-*N*-but-2-enyl morpholine (67 mg, 0.48 mmol), $TiCl_4$•$(THF)_2$ (15.9 mg, 47.5 μmol), *i*-Pr_2NEt (124 μL, 0.71 mmol), and phenylthioacetyl chloride (569 μL, 1 M solution in CH_2Cl_2, 0.57 mmol), added over 4h, in CH_2Cl_2 (9.5 mL) to provide the pure product as a light orange oil in 81% yield (107 mg, 0.39 mmol); *syn*:*anti* 92:8. *Syn* isomer: IR (CH_2Cl_2) 3053, 2976, 2864, 1640, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.49 (m, 2H, Ph), 7.28–7.30 (m, 3H, Ph), 5.75 (ddd, *J* = 7.5, 8.8, 16.3 Hz, 1H, C**H**=CH_2), 4.99–5.10 (m, 2H, CH=C**H**$_2$), 3.73 (d, *J* = 9.7 Hz, 1H, C**H**SPh), 3.11–3.58 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.76–2.82 (m, 1H, C**H**CH_3), 1.28 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 140.3, 134.0, 129.1, 128.4, 115.6, 78.3, 66.9, 66.4, 53.9, 46.4, 42.3, 39.7, 17.9; LRMS (FAB) *m/z* 292 $(MH)^+$; HRMS (FAB) exact mass calcd for ($C_{16}H_{22}NO_2S$) requires*m/z* 292.1371, found *m/z* 292.1373. Diastereomer ratios were determined by ^1H NMR analysis. Relative configuration assigned by analogy.

(2*R,3*S**)-*N*-(Methyl-2-phthalimido-4-pentenoyl)-morpholine** (Table 7, entry 3). Prepared according to general procedure B from (*E*)-*N*-but-2-enyl morpholine (75 mg, 0.53 mmol), $TiCl_4$•$(THF)_2$ (17.7 mg, 53 μmol), *i*-Pr_2NEt (139 μL, 0.80 mmol), and phthalylglycyl chloride (1.3 mL, 0.5 M solution in CH_2Cl_2, 0.64 mmol), added over 3h, in CH_2Cl_2 (10.6 mL) to provide the pure product as white crystals in 77% yield (134 mg, 0.41 mmol); 98:2 *syn*:*anti*. *Syn* isomer: IR (CH_2Cl_2) 3065, 2976, 2864, 1776, 1718, 1660, 1459, 1436, 1382, 1359 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.81 (m, 4H, Ph**H**), 5.79 (ddd, *J* = 7.6, 10.4, 17.5 Hz, 1H, C**H**=CH_2), 5.04–5.18 (m, 2H, CH=C**H**$_2$), 4.76 (d, *J* = 10.2 Hz, 1H, C**H**NR_2), 3.63–3.71 (m, 1H, C**H**CH_3), 3.39–3.56 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 0.95 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 166.5, 139.6, 134.4, 131.3, 123.6,

116.6, 66.8, 66.5, 54.5, 46.3, 42.5, 36.5, 16.5; LRMS (FAB) *m/z* 329 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{18}H_{21}N_2O_4)^+$ requires *m/z* 329.1501, found *m/z* 329.1504. Diastereomer ratio was determined by GLC with a CC-1701 column (50 °C, 5 °C/min gradient, 25 psi); *syn* adduct t_r = 51.8 min, *anti* adduct t_r = 49.2 min.

(2*R,3*S**)-*N*-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine** (Table 7, entry 4). Prepared according to the general procedure A from (*E*)-*N*-(3-chloro-2-propenyl)-morpholine (100 mg, 0.62 mmol), $TiCl_4$•$(THF)_2$, (21 mg, 62 μmol), *i*-Pr_2NEt (151 μL, 86.7 mmol), and propionyl chloride (0.74 mL, 1 M solution in CH_2Cl_2, 0.74 mmol) in CH_2Cl_2 (12 mL) to provide the pure product as a yellow oil in 84% yield (160 mg, 0.52 mmol); 90:10 *syn:anti*. *Syn* isomer: IR (CH_2Cl_2) 3053, 2976, 2907, 2864, 1648, 1444, 1274, 1247, 1116 cm^{-1}; ^1H NMR (400 MHz) δ 7.30-7.40 (m, 5H, Ph), 5.92 (ddd, *J* = 8.5 Hz, *J* = 10.1 Hz, *J* = 16.9 Hz, 1H, C**H**=CH_2) 5.39 (d, *J* = 16.9 Hz, 1 H, CH=C**H**$_2$), 5.26 (d, *J* = 10.2 Hz, 1 H, CH=C**H**$_2$), 4.72-4.73 (m, 1H, C**H**Cl), 4.71 (d, *J* = 11.7 Hz, 1H, C**H**$_2$Ph), 4.57 (d, *J* = 11.7 Hz, 1H, C**H**$_2$Ph), 4.33 (d, *J* = 7.4 Hz, 1H, C**H**OCH_2Ph), 3.50-3.65 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$); ^{13}C NMR (100 MHz) δ 167.0, 136.5, 134.4, 128.5, 128.3, 128.1, 119.5, 82.4, 72.5, 66.9, 66.7, 62.4, 45.8, 42.8; LRMS (FAB) *m/z* 310 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{16}H_{21}ClNO_3)^+$ requires m/z 310.1210, found *m/z* 310.1213. Diastereomer ratio was determined by GLC with a CC-1701 column (80 °C, 20 °C/min gradient for 1 min, then 10 °C/min, 23 psi); *syn* adduct t_r = 19.2 min, *anti* adduct t_r = 19.3 min.

(2*R,3*R**)-*N*-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine** (Table 7, entry 5). Prepared according to the general procedure A from (*Z*)-*N*-(3-chloro-2-propenyl)-morpholine (82 mg, 0.51 mmol), $TiCl_4$•$(THF)_2$, (17 mg, 51 μmol), *i*-Pr_2NEt (290 μL, 1.66 mmol), and propionyl chloride (1.52 mL, 1 M solution in CH_2Cl_2, 1.52 mmol) in CH_2Cl_2

(10 mL) to provide the pure product as a yellow oil in 71% yield (110 mg, 0.36 mmol); 90:10 *anti*:*syn*. *Anti* isomer: IR (CH_2Cl_2) 3057, 2976, 2907, 1652, 1444, 1239, cm^{-1}; ^1H NMR (400 MHz) δ 7.29-7.38 (m, 5H, Ph), 6.00 (ddd, *J* = 8.4 Hz, *J* = 10.1 Hz, *J* = 16.9 Hz, 1H, C**H**=CH_2), 5.48 (dd *J* = 0.9 Hz, *J* = 16.0 Hz, 1 H, CH=C**H**$_2$), 5.35 (d, *J* = 10.2 Hz, 1 H, CH=C**H**$_2$), 4.75 (t, *J* = 8.3 Hz, 1H, C**H**Cl), 4.63 (d, *J* = 12.0 Hz, 1H, C**H**$_2$Ph), 4.51 (d, *J* = 12.0 Hz, 1H, C**H**$_2$Ph), 4.33 (d, *J* = 8.3 Hz, 1H, C**H**OCH_2Ph), 3.50-3.70 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$); ^{13}C NMR (100 MHz) δ 167.3, 136.7, 134.5, 128.6, 128.3, 128.1, 119.8, 78.5, 71.9, 66.9, 66.6, 60.5, 46.0, 42.7; LRMS (FAB) *m/z* 310 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{16}H_{21}ClNO_3)^+$ requires m/z 310.1210, found *m/z* 310.1213. Diastereomer ratio was determined by GLC with a CC-1701 column (80 °C, 20 °C/min gradient for 1 min, then 10`°C/min, 23 psi); *syn* adduct t_r = 19.2 min, *anti* adduct t_r = 19.3 min.

***N*-(2,3,3-Trimethyl-4-pentenoyl)-morpholine (22).** Prepared according to general procedure B from (*E*)-*N*-(3,3-dimethyl-2-propenyl)-morpholine (150 mg, 0.97 mmol), $TiCl_4(THF)_2$, (32 mg, 96 μmol), iPr_2NEt (0.70 mL, 4.0 mmol), and propionyl chloride (2.5 mL, 1 M solution in CH_2Cl_2, 2.5 mmol) in CH_2Cl_2 (3 mL) to provide the pure product as a yellow oil in 70% yield (141 mg, 0.667 mmol); IR 2972, 2864, 1633, 1463, 1432, 1239, 1116, 1027, 919 cm^{-1}; ^1H NMR (400 MHz) δ 5.91 (dd, *J* = 11.0 Hz, 17.2 Hz, 1H, CH=CH_2), 4.99 (s, *J* = 1.47, 1H, CH=CH_2), 4.95 (dd, *J* = 8.72 Hz, 1H, CH=CH_2), 3.52-3.67 (m, 8H, morpholine), 2.63 (q, *J* = 6.9 Hz, 1H, CHC=O), 1.09 (s, 3H, C**H**$_3$CCH=CH_2), 1.07 (d, *J* = 6.0 Hz, 3H, CH_3CHC=O), 1.06 (s, 3H, C**H**$_3$CCH=CH_2); ^{13}C NMR (100 MHz) δ 174.03, 146.49, 111.59, 67.11, 66.74, 46.90, 42.34, 41.91, 39.35, 24.66, 24.10, 13.61; LRMS (FAB) *m/z* 212 $(MH)^+$; HRMS (FAB) exact mass calcd for $(C_{13}H_{23}NO_2H)^+$ requires m/z 212.1651, found *m/z* 212.1655.

3-Methyl-1-morpholinocyclohexene (**23**). To a solution of 3-methyl-2-cyclohexen-1-one (1.50 g, 13.7 mmol) and morpholine (3.57 g, 41.0 mmol) in CH_2Cl_2 (120 mL) was added Ti(O*i*-Pr)$_4$. The reaction was monitored by IR for disappearance of the ketone. After 6 h the solution was concentrated and EtOH (45 mL) was added followed by $Na(CN)BH_3$ (1.81 g, 28.8 mmol). The solution was stirred for 1 h before 1*N* NaOH (30 mL) was added. The resulting mixture was extracted with EtOAc (3 x 50 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated to give an orange oil. The residue was purified by column chromatography on silica gel using EtOAc to furnish the product as a brown oil in 19% yield (0.47 g). The spectral data for **24** were in complete agreement with previously reported literature values.[4]

(*E*)-*N*-(3-Ethyl-3-methyl-2-propenyl)-morpholine (**25**). 2-Methyl-3-penten-1-ol was prepared using a modification of the procedure outlined by Corey and coworkers:[5] To a solution of 2-pentyn-1-ol (2.5 mL, 27 mmol) in THF (100 mL) was added Red-Al (8.1 mL of a 3.5 M solution in toluene, 28 mmol). The resulting solution was warmed to reflux for 3.5 h and then cooled to –78 °C, before a solution of iodine (20.5 g, 81.0 mmol) in THF (50 mL) was added dropwise by syringe. The resulting solution was then allowed to warm to rt before Et_2O (200 mL) was added, and the reaction mixture washed with 5% Na_2SO_4 (3 x 200 mL), dried (Na_2SO_4), and concentrated to afford 3-iodo-2-penten-1-ol as a crude product that was used without further purification.

To a solution of copper(I)iodide (20.1 g, 0.11 mol) and methyl lithium (162 mL of a 1.3 M solution in Et_2O, 0.21 mol) in Et_2O (60 mL) at 0 °C was added a solution of the

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crude 3-iodo-2-penten-1-ol. The reaction mixture was stirred at 0 °C for 62 h and then washed with sat. aq. NH_4Cl (3 x 200 mL), dried (Na_2SO_4), and concentrated to provide 2-methyl-3-penten-1-ol in 91% yield (2.1 g, 21 mmol) as a pure oil by ^1H NMR analysis. Spectroscopic data of this material were in complete agreement with reported literature values.[6]

Morpholine **25** was prepared using a modification of the procedure outlined by Froyen and coworkers:[7] To a solution of 2-methyl-3-peten-1-ol (1.3 g, 13 mmol) and triphenylphosphine (3.6 g, 14 mmol) in THF (10 mL) was added *N*-bromosuccinimide (2.5 g, 14 mmol). After 15 min, morpholine (2.7 mL, 31 mmol) was added dropwise and the resulting brown solution was heated to 70 °C for 2.5 h. Upon cooling to rt, the reaction mixture was diluted with Et_2O (25 mL) and filtered through a pad of Celite©. The filtrate was then extracted with aqueous 1*N* HCl (100 mL). The product containing aqueous layer was then washed with Et_2O (3 x 100 mL), and then made alkaline by the addition of NaOH (4 g). The aqueous solution was then extracted with Et_2O (3 x 100 mL), the combined organic layers dried (Na_2SO_4), and then concentrated by rotary evaporation at 0 °C under reduced pressure. The resulting residue was then distilled (110 °C, 20 mm) to afford (*E*)-*N*-(3-ethyl-3-methyl-2-propenyl)-morpholine (**25**) as a colorless oil in 49% yield (1.0 g, 6.0 mmol); IR 2968, 1455, 1293, 1116, 1004, 907 cm^{-1}; ^1H NMR (400 MHz) δ 5.21-5.25 (m, 1H, C**H**=CCH$_3$), 3.65-3.77 (m, 4H, O(C**H**$_2$)$_2$), 2.96 (d, *J* = 7.0 Hz, 2H, C**H**$_2$C=CH), 2.44 (m, 4H, N(C**H**$_2$)$_2$), 2.01 (q, *J* = 7.3 Hz, 2H, CH$_3$C**H**$_2$), 1.63 (s, 3H, C**H**$_3$C=CH), 0.97-1.04 (m, 3H, CH$_3$C**H**$_2$); ^{13}C NMR (100 MHz) δ 141.1, 118.7, 67.0, 56.0, 53.5, 32.4, 16.4, 12.5;

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7. Froyen P.; Juvvik, P. *Tetrahedron Lett.* **1995**, *36*, 9555.

LRMS (FAB) *m/z* 169 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{10}H_{19}NO)^+$ requires *m/z* 169.1467, found *m/z* 169.1464.

(1′*S,2*R*)-*N*-(2-(1′-Methylcyclohex-2′-enyl)-propanoyl)-morpholine (24).** Prepared according to general procedure A from 1-methyl-3-*N*-morpholino-cycohexene **23** (50 mg, 0.28), $TiCl_4$•$(THF)_2$, (9 mg, 27 μmol), *i*-Pr_2NEt (71 μL, 0.41 mmol), and propionyl chloride (0.41 mL, 1M solution in CH_2Cl_2, 0.41 mmol) in CH_2Cl_2 (3 mL) to provide the product as a yellow oil in 72% yield (45 mg, 0.36 mmol); 95:5 dr. Major isomer: IR (CH_2Cl_2) 2968, 2934, 2864, 1633, 1459, 1432, 1239, 1116 cm^{-1}; ^1H NMR (400 MHz) δ 5.72 (d, *J* = 10.2 Hz, 1H, CH_2CH=C**H**), 5.64 (m, 1H, CH_2C**H**=CH), 3.54-3.70 (m, 8H, N(C**H**$_2C$**H**$_2)_2$), 2.62 (q, *J* = 6.9 Hz, 1H CHC=O), 1.92 (m, 2H, C**H**$_2$CH=CH), 1.68-1.73 (m, 1H, CH_2), 1.53-1.67 (m, 2H, CH_2), 1.34-1.39 (m, 1H, CH_2), 1.09 (d, *J* = 6.9Hz, 3H, C**H**$_3$CHC=O), 1.06 (s, 3H, C**H**$_3$CCH=CH); ^{13}C NMR (100 MHz) δ 174.5, 134.1, 126.4, 67.1, 66.8, 50.1, 46.9, 42.1, 37.4, 33.2, 25.0, 24.7, 19.2, 13.3; LRMS (FAB) *m/z* 237 $(M)^+$; HRMS (FAB) exact mass calcd for ($C_{14}H_{23}NO_2$) requires *m/z* 237.1729, found *m/z* 237.1731. Diastereomer ratios were determined by ^1H NMR analysis.

(2*R,3*R**)-*N*-(2,3-Dimethyl-3-ethyl-4-pentenoyl)-morpholine (26).** Prepared according to general procedure B from (*E*)-*N*-(3-ethyl-3-methyl-2-propenyl)-morpholine (135 mg, 0.80 mmol), $TiCl_4$•$(THF)_2$, (27 mg, 81 μmol), *i*-Pr_2NEt (0.56 mL, 3.2 mmol), and propionyl chloride (2.4 mL, 1 M solution in CH_2Cl_2, 2.4 mmol) in CH_2Cl_2 (2.7 mL) to provide the pure product as a yellow oil in 72% yield (130 mg, 0.58 mmol); >99:1 *syn:anti*. *Syn* isomer: IR (CH_2Cl_2) 2972, 1633, 1459, 1432, 1235 cm^{-1}; ^1H NMR (400 MHz) δ 5.88 (dd, *J* = 10.9 Hz, 17.6 Hz, 1H, CH=C**H**$_2$), 5.03 (dd, *J* = 1.5, 10.9 Hz, 1H, CH=C**H**$_2$), 4.88 (dd, *J* = 1.4, 17.6 Hz, 1H, CH=C**H**$_2$), 3.49-3.64 (m, 8H, N(C**H**$_2C$**H**$_2)_2$), 2.63 (q, *J* = 6.9 Hz, 1H, C**H**C=O), 1.32-1.49 (m, 2H, C**H**$_2$CH$_3$), 1.02 (d, *J* = 6.9 Hz, 3H, C**H**$_3$CHC=O), 0.99 (s, 3H, C**H**$_3$C), 0.73 (t, *J* = 7.5 Hz, 3H, C**H**$_3$CH$_2$); ^{13}C NMR (100 MHz) δ 174.1, 143.8, 67.0,

66.7, 66.6, 46.8, 42.7, 42.2, 41.8, 30.9, 18.7, 13.3, 8.3; LRMS (FAB) *m/z* 225 $(M)^+$; HRMS (FAB) exact mass calcd for $(C_{13}H_{23}NO_2)^+$ requires *m/z* 225.1710, found *m/z* 225.1727.

ReactIR Analysis of Ketene Dimerization (Figures 1–2). The ReactIR probe was fitted with a Schlenk flask, to which was added CH_2Cl_2 and *i*-Pr_2NEt. The reaction was cooled to –78 °C, and spectra were collected every 1 min. Propionyl chloride was added dropwise to the solution, and the reaction was then gradually allowed to warm to room temperature. After 210 min, crotyl pyrrolidine was added as a solution in CH_2Cl_2. Monitoring of the reaction was continued for an additional 90 min. The resulting spectra are displayed in Figures 1–2.

ReactIR Analysis of the $AlCl_3$-Catalyzed Acyl-Claisen Rearrangement (Figure 3–4). The ReactIR probe was fitted with a Schlenk flask containing (*E*)-crotyl moropholine (130 mg, 0.921 mmol), $AlCl_3$ (12.3 mg, 92 μmol), *i*-Pr_2NEt (240 μL, 1.39 mmol), and CH_2Cl_2 (9 mL). Spectra were collected every 1 min. Propionyl chloride (120 μL, 1.38 mmol) was added dropwise to the solution, and the reaction was monitored for 5 h. The resulting spectra are displayed in Figures 3–4.

ReactIR Analysis of the $TiCl_4$-Catalyzed Acyl-Claisen Rearrangement (Figure 5–6). The ReactIR probe was fitted with a Schlenk flask containing (*E*)-crotyl moropholine (196 mg,1.39 mmol), $TiCl_4(THF)_2$ (46 mg, 139 μmol), *i*-Pr_2NEt (362 μL, 2.08 mmol), and CH_2Cl_2 (14 mL). Spectra were collected every 1 min. Propionyl chloride (145 μL, 1.67 mmol) was added dropwise to the solution, and the reaction was monitored for 4 h. The resulting spectra are displayed in Figures 5–6.

Chapter 4

Development of a First-Generation Enantioselective Acyl-Claisen Rearrangement[1]

Reaction Design

The Lewis acid-catalyzed acyl-Claisen rearrangement described in Chapter 3 is a highly diastereospecific and functional group tolerant new methodology that is capable of generating a rapid increase in molecular complexity on both cyclic and acyclic carbon frameworks. A variety of Lewis acidic metal salts were shown to be capable of promoting this reaction. Consequently, we believed that this new methodology would be an attractive platform for the development of a new enantioselective variant of the Claisen rearrangement.

In the initial design of such a reaction, we drew inspiration from previous successful examples of chiral Lewis acid-mediated reactions.[2] In particular, chelation of a substrate to a metal center has been demonstrated to be a useful organizational control element in various enantioselective Lewis acid-catalyzed processes.[3] We speculated that an α-heteroatom-substituted acid chloride capable of two-point binding could provide a highly organized transition state for an enantioselective Claisen rearrangement. Our initial efforts therefore focused on the reaction involving benzyloxyacetyl chloride as the acid chloride component (Scheme 1).

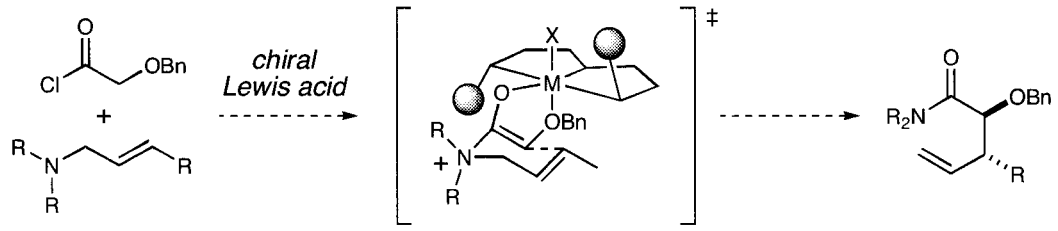
---

1. Portions of the research described in this chapter have been published as a communication: Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911.

2. For a recent survey of the field, see: *Comprehensive Asymmteric Catalysis*, Vol 1–3. Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. Springer, New York, 1999.

3. For example: Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

Scheme 1



Results and Discussion

A variety of metal-ligand combinations were assayed for their ability to produce the products of the acyl-Claisen rearrangement in enantioenriched form. The metal salts selected for this preliminary investigation were those that proved to be effective catalysts for the acyl-Claisen rearrangement in our initial metal screen, described in Chapter 3. We further chose to focus on chiral ligands that are members of "privileged" classes of ligands; that is, ligand architectures such as binaphthyls,[4] bis(oxazolines),[5] and salens[6] that have demonstrated the ability to generate an effective chiral environment about a metal center for a wide range of enantioselective processes.

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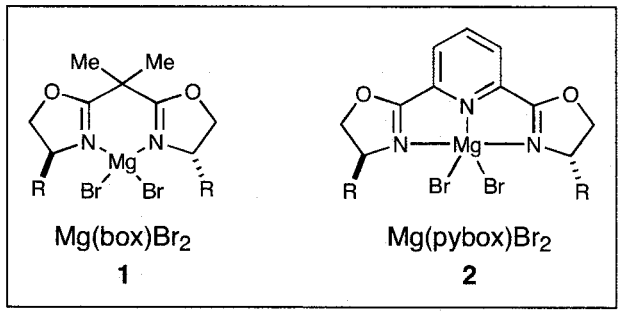
4. For recent reviews of binaphthyl derivatives as ligands in organic synthesis, see: (a) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (b) Akutaqawa, S. *App. Cat. A* **1995**, *128*, 171.

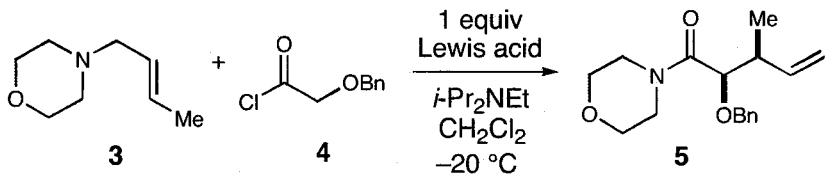
5. For recent reviews of chiral bis(oxazoline) ligands in organic synthesis, see: (a) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. (b) Pfaltz, A.; In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 3; Wiley: New York, 1995; p 2094. (b) Ghosh, A. K.; Packiarajan, M.; Cappiello, J. *Tetrahedron: Asymm.* **1998**, *9*, 1.

6. For a recent review of chiral metal(salen) colmplexes in organic synthesis, see: Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85.

An extensive screen of ligand-metal combinations revealed that magnesium bromide etherate complexes of various isopropylidene bisoxazoline (box) and pyridine bisoxazoline (pybox) ligands[7] could promote the acyl-Claisen reaction of benzyloxyacetyl chloride and

Table 1. Effect of chiral bis(oxazoline)•$MgBr_2$ Lewis acids on the enantioselective acyl-Claisen rearrangement.





3 4 5 (1)

entry	complex	ligand	R	% conv[a]	% ee[b]
1	**1a**	box	*t*-Bu	>95	21
2	**1b**	box	Ph	95	24
3	**2a**	pybox	*t*-Bu	37	18
4	**2b**	pybox	Ph	70	46
5	**2c**	pybox	*i*-Pr	51	15
6	**2d**	pybox	Bn	93	0

[a] Conversion of **3** determined by GLC on a Bodman CC1701 using an internal tridecane standard. [b] Enantiomeric excess was determined by chiral HPLC using a Chiralcel AD column.

7. Box and pybox ligands were purchased from Aldrich and used as supplied or were prepared by the method of Evans and coworkers: Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541.

crotyl morpholine with poor to moderate levels of enantioselectivity. The results of this survey of bis(oxazoline) ligands are summarized in Table 1. In general, the bidentate box ligands (entries 1–2) gave higher levels of conversion than the pybox ligands (entries 3–6). Notably, the phenyl-substituted pybox was the most enantioselective ligand in this preliminary assay, affording the Claisen product in 46% ee, while reactions employing other ligands proceeded in less than 25% ee.

Unfortunately, the complexes prepared in situ from phenyl pybox and $MgBr_2 \bullet OEt_2$ were only moderately soluble in methylene chloride and resulted in the formation of heterogeneous slurries. As a consequence, results of reactions employing this complex suffered from poor reproducibility, depending on the concentration of the reaction and the length of time the ligand was allowed to stir with $MgBr_2 \bullet OEt_2$ before the allylic morpholine and acid chloride reaction components were added to the solution.

The solubility of the magnesium pybox Lewis acid, however, proved to be dependent on the identity of the metal salt from which the complex was derived. Experiments probing the effect of counterion on the reaction are summarized in Table 2. In contrast to the bromide complex, the phenyl pybox$\bullet MgI_2$[8] complex was readily soluble in CH_2Cl_2, and reproducibly gave superior conversions without significantly impacting the enantioselectivity of the reaction. Other counterions were less successful in promoting the acyl-Claisen rearrangement.

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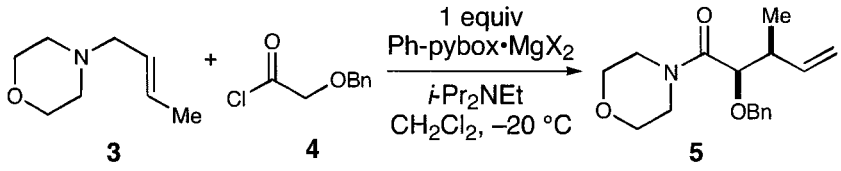
8. The purity of the MgI_2 used proved to be important for the reproducibility of the reaction. Optimal results could be obtained using anhydrous powdered MgI_2 (99.998%) available from Aldrich (catalog no. 46,610-7).

Table 2. Effect of magnesium(II) source on the enantioselective acyl-Claisen rearrangement.



(2)

3 **4** **5**

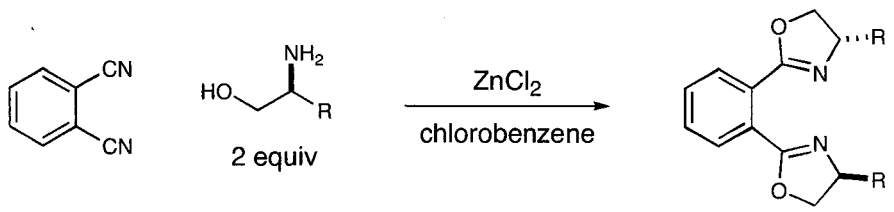
entry	MgX_2 salt	% conv[a]	% ee[b]
1[c]	$MgBr_2 \cdot OEt_2$	70	46
2[c]	$MgBr_2$	72	9
3	MgI_2	89	45
4	$Mg(OTf)_2$	52	30
5	$MgSO_4$	NR	--

[a] Conversion of **3** determined by GLC on a Bodman CC1701 using an internal tridecane standard. [b] Enantiomeric excess was determined by chiral HPLC using a Chiralcel AD column. [c] Heterogeneous reaction mixture.

Having identified the bis(oxazoline)• MgI_2 complex as a promising framework for the development of an enantioselective Lewis acid for the acyl-Claisen rearrangement, we next embarked on a more focused exploration of ligand architecture on the enantioselectivity of the reaction. In considering possible ligand designs, we speculated that the additional L-type nitrogen ligand present in the pybox complexes rendered them less Lewis acidic and consequently less efficient promoters than the corresponding box complexes. Thus, we focused our efforts in ligand design on bidentate bis(oxazoline) ligands.

In this context, we considered alternate ligand architectures in which the distance and bite angle between the oxazoline nitrogens can be adjusted by systematic variation of the backbone that links the oxazoline units. One of the ligand architectures that initially attracted our interest was the 1,2-bis(oxazolinyl)benzene (ArBox) ligands, first described by

Bolm and coworkers in 1991.[9] A variety of these ligands bearing different oxazoline substituents are readily accessible via condensation of 1,2-phthalonitrile with the appropriate enantiopure amino alcohol, as outlined in eq 3. Although the initial report describing this class of ligands reported the isolation and crystallographic determination of the zinc complex of the phenyl-substituted ArBox ligand, no successful enantioselective processes using these ligands had been reported in the literature prior to our disclosure of the present work.[10]



(3)

Table 3 summarizes the results of experiments using members of the ArBox class of ligands. A survey of various substituents on the oxazoline rings revealed that the phenyl-substituted ArBox complex (entry 1, ligand **6**) was more reactive and gave significantly higher levels of enantioinduction than the corresponding isopropyl, benzyl, and *t*-butyl analogs (entries 2–4), in analogy to the results of experiments employing the pybox family of ligands. We therefore speculated that the phenyl substituents could be exerting an electronic, rather than a purely steric, influence over the geometry of the transition state, perhaps through an attractive cation-π interaction with the ammonium cation.

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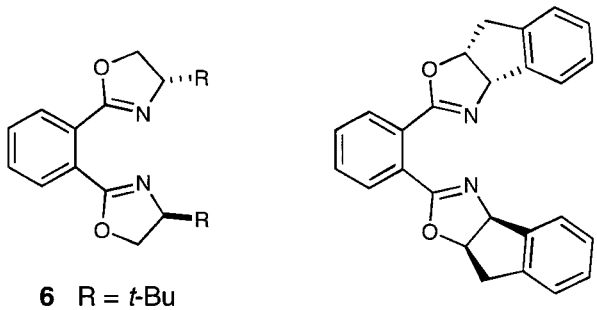
9. Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173.

10. ArBox ligands have given poor results in those reactions in which it has been assayed: (a) Diels–Alder (2% ee): Davenport, A. J.; Davies, D. L.; Fawcett, J.; Garratt, S. A.; Lad, L.; Russell, D. R. *Chem. Commun.* **1997**, 2347. (b) Diels–Alder (racemic): Takacs, J. M.; Quincy, D. A.; Shay, W.; Jones, B. E.; Ross, C. R., III. *Tetrahedron: Asymm.* **1997**, *8*, 3079. (c) Ketone hydrosilylation (10% ee): Mimoun, H.; de St. Laumer, J. Y.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158. (d) Aldol (13% ee): Wiener, J. J. M.; MacMillan, D. W. C.; unpublished results.

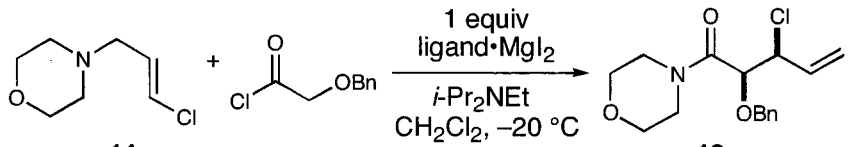


6 R = *t*-Bu
7 R = Ph
8 R = *i*-Pr
9 R = Bn

10

Figure 1. ArBox ligands assayed in the enantioselective acyl-Claisen rearrangement.

Table 3. Effect of ArBox ligands in the enantioselective acyl-Claisen rearrangement.



11 **12** (4)

entry	ligand	% conv[a]	% ee[b]
1	**6**	30	57
2	**7**	95	72
3	**8**	40	57
4	**9**	87	24
5	**10**	53	5

[a] Conversion of **11** determined by GLC on a Bodman CC1701 using an internal tridecane standard. [b] Enantiomeric excess was determined by chiral HPLC using a Chiralcel OJ column.

Thus, the effect of electron-withdrawing and -donating substituents on the ArBox framework was also investigated. The results of these experiments are summarized in Table 4.[11] In general, the reaction gives better results when 2 equiv of the chiral promoter is used. The presence of electron-withdrawing groups on the benzene backbone results in higher levels of enantioinduction (entries 2–3),[12] while electron-donating groups appear to diminish both the efficiency and enantioselectivity of the acyl-Claisen rearrangement (entry 6). Alkoxy groups on the phenyl oxazoline substituents further increased the selectivity of the reaction (entries 7–8). Thus, the *p*-methoxyphenyl-substituted 4,5-dichloro-1,2-bis(oxazolinyl)benzene ligand **16** resulted in optimal levels of reactivity and

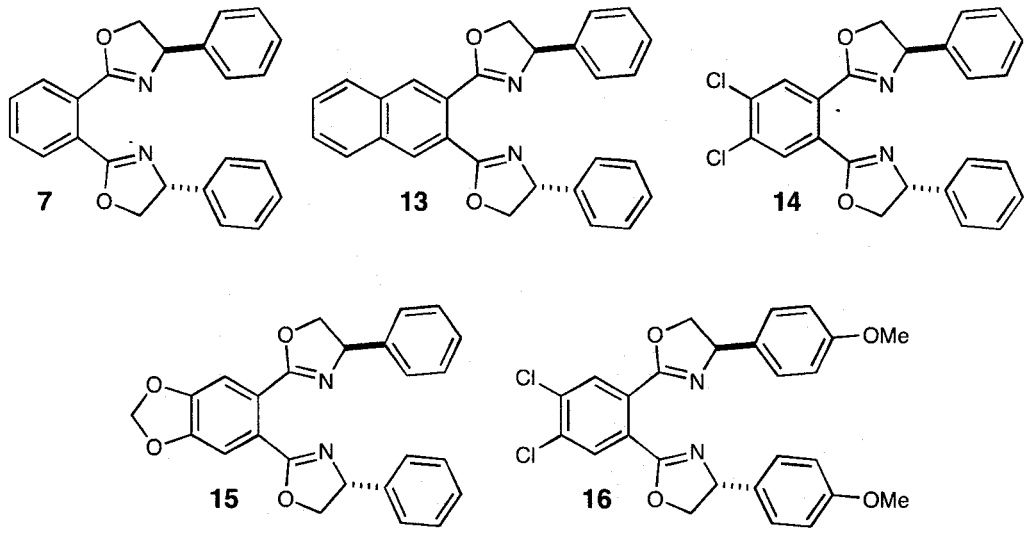


Figure 2. Modified ArBox ligands assayed in the acyl-Claisen rearrangement.

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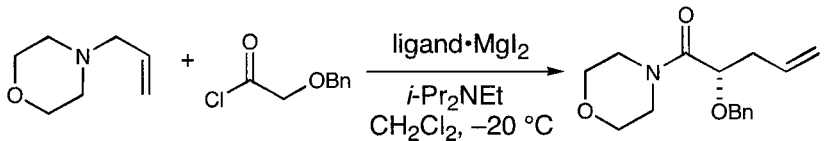
11. Synthesized by the method of Bolm by condensation of the appropriate amino alcohol with 2,3-naphthalenedicarbonitrile, 3,4-dichloro-1,2-phthalonitrile, or 3,4-dicyano-1,2-methylenedioxybenzene. See ref. 9.

12. Attempts to synthesize more electron-deficient ligands with a perchlorinated benzene backbone were unsuccessful, as the amino alcohols failed to cyclize with 2,3,4,5-tetrachlorophthalonitrile.

enantioselectivity and was selected for further investigation of the scope of this new enantioselective Claisen variant.

Table 4. Effect of electron-donating and -withdrawing ArBox substituents on the enantioselective acyl-Claisen rearrangement



(5)

17 **18**

entry	ligand	equiv ligand•MgI_2	% conv[a]	% ee[b]
1	**7**	2.0	87[c]	83
2	**13**	1.0	97	73
3	**13**	2.0	97	83
4	**14**	1.0	74	84
5	**14**	2.0	65[c]	86
6	**15**	2.0	12	17
7	**16**	1.0	63[c]	81
8	**16**	2.0	80[c]	91

[a] Conversion of **17** determined by GLC on a Bodman CC1701 using an internal tridecane standard. [b] Enantiomeric excess was determined by chiral HPLC using a Chiralcel OJ column. [c] Isolated yield.

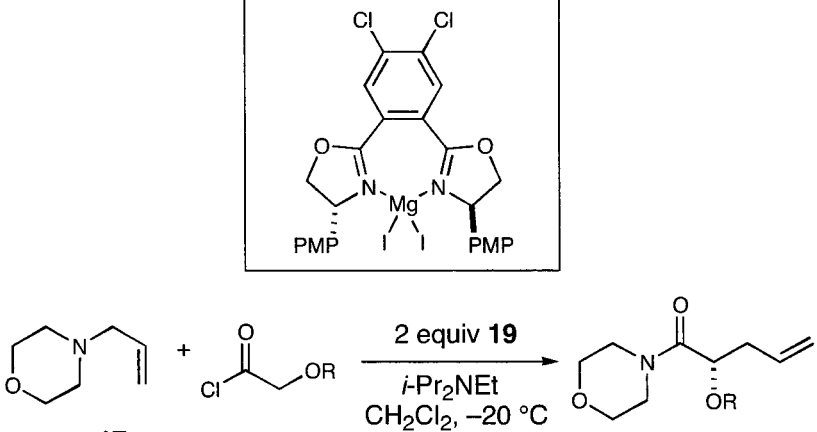
Scope of the First-Generation Enantioselective Acyl-Claisen Rearrangement.

Having identified ArBox•MgI_2 complex **19** as a successful asymmetric promoter of the acyl-Claisen rearrangement depicted in eq 6, we next investigated the effect of acid chloride structure on the selectivity of the reaction (Table 5). In line with our reaction design criteria, the level of enantioselectivity correlates with the ability of the acid chloride to participate in metal chelation. Thus, the highest levels of asymmetric induction were observed using those substrates bearing the most nucleophilic α-alkoxy substituents (entry 1, R=Bn, 91% ee; entry 2, R=Me, 80% ee). Conversely, poorly chelating substrates such as

acetoxyacetyl and (*t*-butyldimethylsilyloxy)acetyl chloride (entries 5 and 6) demonstrate only modest levels of selectivity (37% and 38% ee, respectively). Given this trend, benzyloxyacetyl chloride was chosen for further investigation of the reaction scope.

Table 5. Effect of acid chloride structure on the enantioselective acyl-Claisen rearrangement.

19 PMP-ClArBox•MgI_2



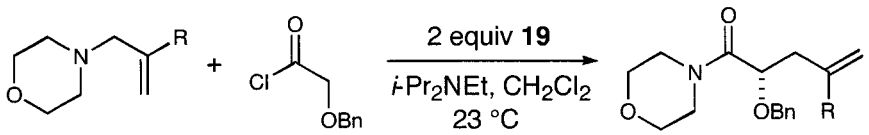
(6)

17

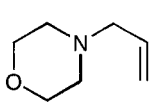
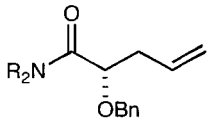
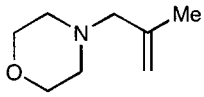
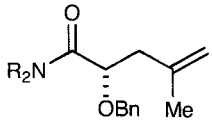
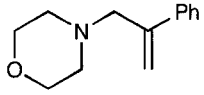
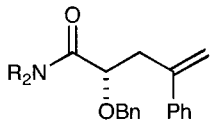
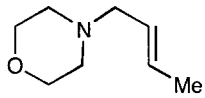
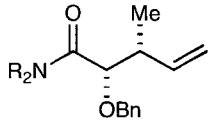
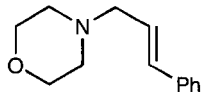
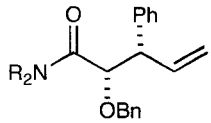
entry	OR	% yield	% ee[a]
1	OBn	80	91
2	OMe	28	80
3	OPh	48	78
4	OPhCl-4	59	71
5	OTBS	67	38
6	OAc	44	37

[a] Enantiomeric excess was determined by chiral GC or HPLC.

Table 6. Enantioselective acyl-Claisen rearrangement with alkyl- and aryl-substituted allyl morpholines



(7)

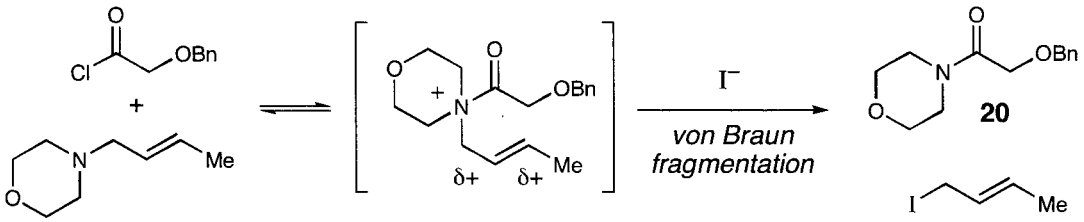
entry	amine	product[a]	% yield	% ee[b]
1			80	91
2			78	91
3[c]			79	91
4			<10[d]	--[e]
5[f]			26[d]	79

[a] NR_2 = *N*-morpholine. [b] Enantiomeric excess was determined by chiral GLC or HPLC. [c] Reaction performed using 3 equiv **19**. [d] Significant quantities of **20** were isolated from this reaction. [e] Not determined. [f] Reaction conducted at –40 °C using 1 equiv **19**.

The results of an investigation of allyl morpholine structure on the reaction are shown in Table 6. As demonstrated by entries 2 and 3, alkyl and aryl substituents at the methallyl position are tolerated. However, crotyl and cinnamyl morpholine (entries 4 and 5)

primarily undergo von Braun fragmentation[13] under the reaction conditions, evidenced by the formation of morpholine amide **20** (Scheme 2). We reasoned that electron-withdrawing substituents on the allylic amine would disfavor S_N2-type nucleophilic attack on the acyl ammonium species and partition the reaction towards the desired Claisen rearrangement pathway.[14]

Scheme 2



Indeed, as shown in Table 7, electron-deficient allylic morpholines are excellent substrates for this reaction, giving the desired Claisen rearrangement products in good yield with very high levels of enantio- and diastereoselectivity (entries 1-5, 74-95% yield, 86-97% ee, 92-99% dr). Moreover, we determined that relatively mild electronic perturbations on the allylic component could dramatically impact the course of the reaction; whereas crotyl morpholine undergoes predominantly von Braun fragmentation under the reaction conditions (Table 3, entry 4), the corresponding 4-benzoyloxy-substituted compound gives the desired Claisen-rearrangement product in good yield and selectivity (Table 4, entry 3,

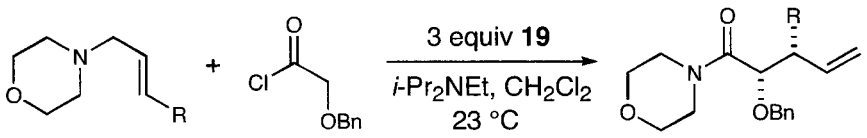
---

13. (a) Von Braun, J.; Engelbertz, P. *Ber.* **1923**, *56*, 1573. (b) von Braun, J.; Friedsam, A. *Ber.* **1930**, *63*, 2407. (c) von Braun, J.; May, M.; Michaelis, R. *Ann.* **1931**, *490*, 189. (d) Hagemann, H. A. *Org. React.* **1953**, *7*, 198.

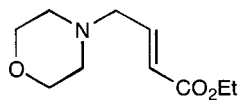
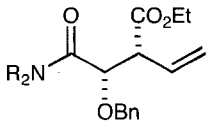
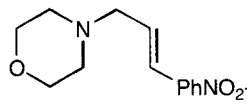
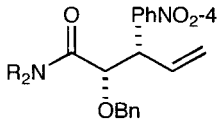
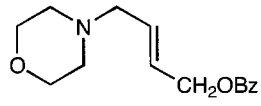
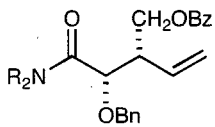
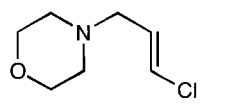
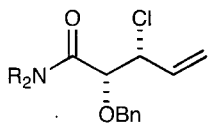
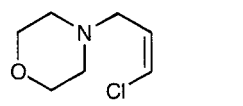
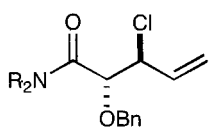
14. The benzyl ether is easily cleaved under mild conditions (BF_3•OEt_2, Me_2S). Ishizaki, M.; Hoshino, O.; Iitaka, Y. *Tetrahedron Lett.* **1991**, *32*, 7079. This method is being applied in our group in a total synthesis of callipeltoside A: Wiener, J. J. M.; Seo, J. B.; MacMillan, D. W. C., unpublished results.

95% yield, 98:2 *syn:anti*, 91% ee). Importantly, the enantioselective acyl-Claisen reaction remains diastereospecific. Thus, while (*E*)-(3-chloro-2-butenyl)morpholine yields predominantly the *syn* Claisen product (entry 4, 95% yield, 98:2 *syn:anti*, 91% ee), the (*Z*)-isomer affords the corresponding *anti* product with similar levels of stereocontrol (entry 5, 74% yield, 3:97 *syn:anti*, 91% ee). As in the corresponding $TiCl_4(THF)_2$-catalyzed reactions described in Chapter 3, formation of the α,β,γ,δ-unsaturated amide resulting from β-elimination of the chloride substituent is not observed in either case, highlighting the mild reaction conditions employed in this asymmetric Claisen process.

Table 7. Electron-deficient allyl morpholine substrates in the enantioselective acyl-Claisen rearrangement.

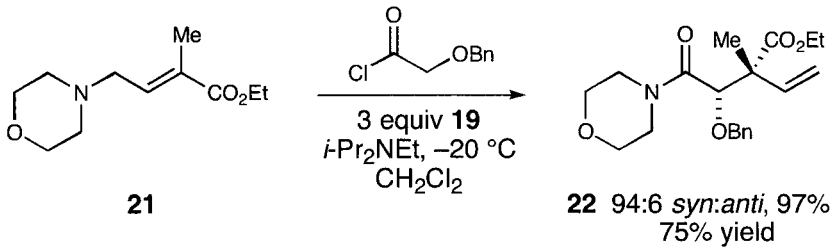


(8)

entry	amine	product[a]	% yield	*syn:anti*[b]	% ee[b]
1			84	97:3	96
2			82	99:1	97
3[c]			86	92:8	86
4			95	98:2	91
5			74	3:97	91

[a] NR_2 = *N*-morpholine. [b] Product ratios determined by chiral GLC or HPLC. Absolute stereochemistry determined by chemical correlation or by analogy. [c] Reaction performed using 2 equiv **19**.

A further example of the ability of this new asymmetric acyl-Claisen methodology to access elusive acyclic structural motifs is illustrated in eq 9. The rearrangement of the trisubstituted alkene **21** using 3 equiv **19** results in the formation of Claisen product **22** bearing a quaternary carbon stereogenic center. The geometry of the prochiral olefin is translated with excellent stereochemical fidelity, providing the expected Claisen adduct **22** in 97% ee and 94:6 *syn*:*anti* selectivity.



21 **22** 94:6 *syn*:*anti*, 97% ee, 75% yield (9)

Stereochemical Models[15]

On the basis of the excellent, predictable diastereoselectivity observed in these reactions, we presume that this asymmetric acyl-Claisen rearrangement proceeds via a cyclic chair-like transition state, in accord with previously established Claisen methodology (see Chapter 1). Additionally, the results of the acid chloride survey summarized in Table 5 strongly suggest that coordination of the α-alkoxy substituent. Taking these considerations into account, semiempirical computational modeling of the presumed transition state was performed at the PM3 level (Figure 3).[16] On the basis of the resulting minimized structure **23**, we have developed a preliminary working model to explain the origins the

15. Several attempts to produce crystals of complex **19** failed to provide crystals of sufficient quality for X-ray analysis. The ^{1}H NMR spectrum of **19** in CD_2Cl_2 indicated fluxional behavior in solution.

16. PM3 method, MacSpartan, Wavefunction, Inc.

enantioinduction observed in this reaction. Coordination of the transition state to the tetrahedral magnesium(II) center in a bidentate manner orients one of the PMP substituents over the enolate olefin, blocking the *si* face and leaving the *re* diastereoface open for attack, as shown. This model is consistent with the absolute sense of stereoinduction observed in this reaction.

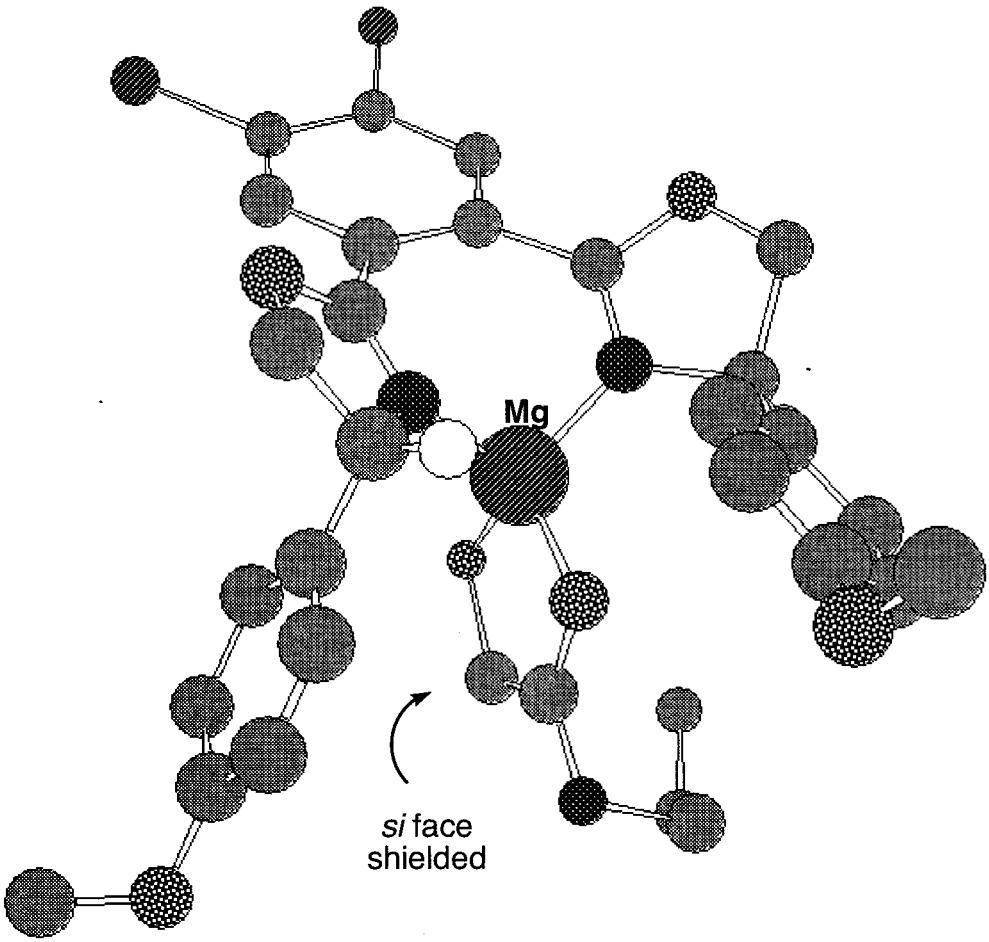
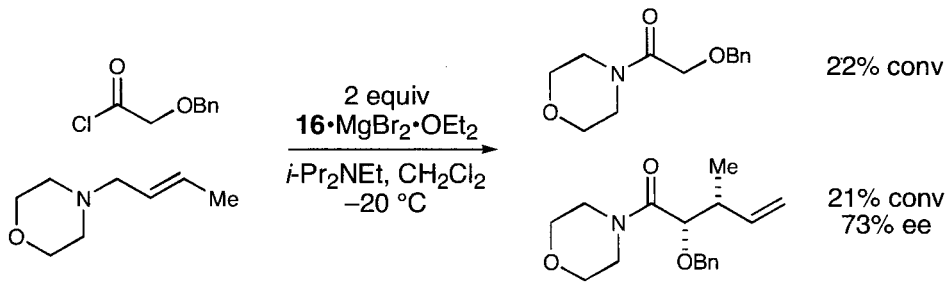


Figure 3. Transition state model generated by semiempirical computation (PM3).

Limitations of the First-generation Enantioselective Acyl-Claisen

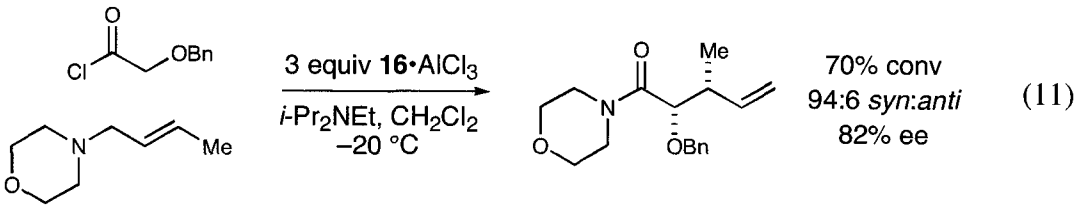
As demonstrated by the results outlined in Table 6, crotyl morpholine is not successful in the asymmetric acyl-Claisen rearrangement promoted by **19** because of the propensity of the acyl ammonium species to undergo von Braun fragmentation in the presence of the highly nucleophilic iodide counterion. We reasoned that a Lewis acidic metal species with less nucleophilic counterions might be able to successfully promote the acyl-Claisen rearrangement of crotyl morpholine. Unfortunately, the $Mg(OTf)_2$ and $MgCl_2$ complexes of **16** were not successful at promoting this reaction. Use of the corresponding $MgBr_2 \bullet OEt_2$ complex resulted in less von Braun fragmentation, but the reaction was less efficient (eq 10, 21% conv, 73% ee).



(10)

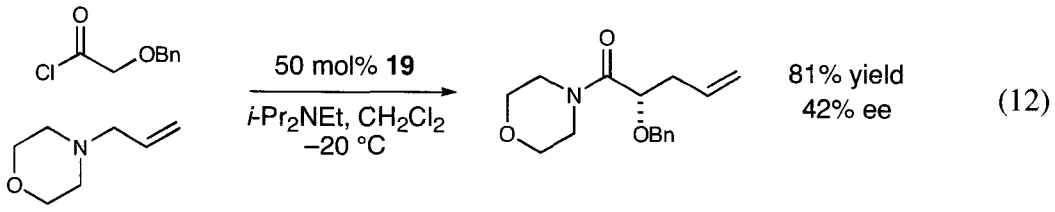
After a screen of alternate metal centers, we discovered that the complex of **16** with $AlCl_3$ could promote the reaction with promising levels of enantioinduction (eq 11, 82% ee). Importantly, no von Braun cleavage was observed by analysis of the unpurified reaction mixture by capillary GC. However, the reaction requires 3 equiv of the chiral promoter; reactions employing fewer equivalents of the chiral aluminum Lewis acid fail to yield products exhibiting substantial ee's.[17]

17. For example, use of 1 equiv **16**•$AlCl_3$ results in formation of a Claisen product in only 31% ee.



(11)

Indeed, enantioselective catalysis of acyl-Claisen rearrangements involving benzyloxyacetyl chloride proved to be an elusive goal in general. Reactions using only 50 mol% **19** gave the Claisen product in considerably poorer enantioselectivity (eq 12, 42% ee).



(12)

Because the *in situ* generation of ketenes from acid chlorides results in the formation of an ammonium chloride byproduct, we speculated that the MgI_2 promoter could undergo a detrimental salt metathesis reaction to a poorly reactive $MgCl_2$ species. In addition, as discussed in Chapter 3, acyl-Claisen reactions involving benzyloxyacetyl chloride exhibit a slow but significant background reaction in the absence of a Lewis acid catalyst. The uncatalyzed reaction of allyl morpholine with benzyloxyacetyl chloride, for example, afforded the Claisen adduct in 42% yield after 24 hours. These concerns prompted us to reconsider bidentate chelation as a design element in the investigation of our second-generation approach to an enantioselective acyl-Claisen rearrangement.

Conclusion

A first-generation approach to the development of an enantioselective variant of the acyl-Claisen has resulted in the discovery of a magnesium(II)•bis(oxazoline) complex **19**. The selectivity of the reaction is high when Lewis basic α-alkoxy-substituted acid chlorides are used. Although 2–3 equiv of the chiral promoter are required for optimal levels of enantioselectivity, this chiral Lewis acid successfully promotes the enantioselective and stereospecific reaction of a range of allyl morpholine substrates in 86–97% ee, including alkyl-, aryl-, ester-, and heteroatom-substituted substrates. Quaternary carbon stereocenters can also be accessed in a highly stereoselective fashion.

Experimental Section

General Information. All reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use according to the guidelines of Perrin and Armarego.[1] Non-aqueous reagents were transferred under nitrogen by syringe. Organic solutions were concentrated under reduced pressure using a Büchi rotary evaporator. Methylene choride and *N,N*-diisopropylethylamine were distilled from calcium hydride immediately prior to use. Chlorobenzene was used as supplied by Acros. (*R,R*)-1,2-bis(2-phenyloxazolin-4-yl)benzene was prepared as described by Bolm and coworkers.[2] Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[3] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or $KMnO_4$ stain.

^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500 (500 MHz and 125 MHz, respectively), AMX-400 (400 MHz and 100 MHz), AMX-300 (300 MHz and 75 MHz), Varian I500 (500 MHz and 125 MHz), or Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for

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1. Perrin, D. D.; Armarego, W. L. F. *Purificaion of Laboratory Chemicals;* 3rd ed., Pregamon Press, Oxford, 1988.

2. Bolm, C.; Weickhardt, K.; Zehnder, M.; Ranff, T. *Chem. Ber.* **1991**, *124*, 1173.

3. Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 1600 Series spectrometer using NaCl salt plates, and reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral Facility. Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm, 25°C). Gas chromatography was performed on Hewlett-Packard 5890A and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using the following columns: Bodman Chiraldex Γ-TA (30 m x 0.25 mm) and C&C Column Technologies CC-1701 (30 m x 0.25 mm). HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at 254nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm), OJ (25 cm) and OJ guard (5 cm).

(*R*,*R*)-1,2-Dichloro-4,5-bis(2-phenyloxazolin-4-yl)benzene (14). A solution of 4,5-dichloro-1,2-phthalonitrile (500 mg, 2.5 mmol), (*R*)-phenylglycinol (1.04 g, 7.6 mmol), and anhydrous $ZnCl_2$ (17 mg, 130 μmol) in chlorobenzene (9 mL) was warmed to reflux for 12 h. After cooling to room temperature, the solvent was removed by rotary evaporation, and the residue was partitioned between CH_2Cl_2 (15 mL) and water (15 mL). The organic phase was dried (Na_2SO_4), concentrated, and purified by flash chromatography (66:33 hexanes:EtOAc) to afford 579 mg (1.32 mmol, 52% yield) of **2b** as a viscous yellow oil. IR (thin film) 3061, 3030, 2898, 1652, 1505, 1488, 1393, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.33 (m, 10H, Ph**H**), 6.07 (s, 2H, ClPh**H**), 5.32 (dd, *J* = 9.2, 9.2 Hz, 2H, OCH_2CHN), 4.67 (dd, *J* = 8.5, 9.9 Hz, 2H, OCH_2CHN), 4.16 (dd, *J* = 8.2, 8.5 Hz, 2H, OCH_2CHN). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 142.4, 128.8, 128.6, 127.7, 127.1, 110.5, 102.5, 75.5, 70.8; HRMS (FAB) exact mass calcd for ($C_{24}H_{18}Cl_2N_2O_2$ + H^+) requires *m/z* 437.0824, found *m/z* 437.0817. $[\alpha]_D$ = +68.1 (c = 1.0, $CHCl_3$).

(*R*,*R*)-1,2-Dichloro-4,5-bis(2-(*p*-methoxyphenyl)oxazolin-4-yl)benzene (ArCl2-PMPBox **16**). (*R*)-(*p*-Methoxyphenyl)glycinol was prepared as previously described.[4] A solution of 4,5-dichloro-1,2-phthalonitrile (2.4 g, 12 mmol), (*R*)-(*p*-methoxyphenyl)glycinol (5.0 g, 30 mmol), and anhydrous $ZnCl_2$ (160 mg, 1.2 mmol) in chlorobenzene (120 mL) was warmed to reflux for 7 h. After cooling to room temperature, the solvent was removed by rotary evaporation, and the residue was partitioned between CH_2Cl_2 (15 mL) and H_2O (15 mL). The organic phase was dried (Na_2SO_4), concentrated, and purified by flash chromatography (66:33 to 50:50 hexanes:EtOAc gradient). The resulting solid was recrystallized from EtOAc and hexanes to give 4.0 g (8.0 mmol, 67%) of **2c** a white crystalline material. IR (thin film) 1955, 1906, 1833, 1669, 1649, 1514, 1247, 951, 832 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (s, 2H, ClPh**H**), 7.24 (d, *J* = 8.8 Hz, 4H, MeOPh**H**), 6.82 (d, *J* = 8.8 Hz, 4H, MeOPh**H**), 5.30 (dd, *J* = 8.5, 9.9 Hz, 1H, OCH_2CHN), 4.67 (dd, *J* = 8.5, 10.2 Hz, 2H, OC**H**(H)CHN), 4.18 (dd, *J* = 8.5, 8.5 Hz, 2H, OC**H**(H)CHN), 3.78 (s, 6H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 159.0, 134.9, 133.8, 131.8, 128.0, 127.9, 114.0, 75.6, 70.1, 55.3; HRMS (CI) exact mass calcd for ($C_{26}H_{22}Cl_2N_2O_4^+$) requires *m/z* 496.0957, found *m/z* 496.0956; $[\alpha]_D$ = +72.9 (c = 1.0, $CHCl_3$).

General Procedure. To a flask charged with $ArCl_2$-PMPBox **16** and anhydrous MgI_2 in an inert atmosphere, was added CH_2Cl_2 (4 mL) and the resulting pale yellow solution was stirred vigorously for 1 h under an inert atmosphere. The allyl morpholine (0.4 mmol) was then added via syringe as a solution in CH_2Cl_2 (1 mL). The syringe was rinsed with CH_2Cl_2 (3 x 1 mL), and the combined rinses were added to the reaction flask. The reaction mixture was then treated with *i*-Pr_2NEt, then cooled to –20 °C. At this point, a

4. Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1994**, *50*, 9457.

solution of the acid chloride (1.0 M in CH_2Cl_2) was added over 12 h. After a further 12 h at –20 °C, the reaction mixture was washed with a mixture of EtOAc (25 mL) and 1 N NaOH (25 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were then washed with saturated aq. NaCl (50 mL), dried (Na_2SO_4), and then concentrated. The resulting residue was then added to EtOH (15 mL) and set aside. After 6-10 h, the precipitated $ArCl_2$-PMPBox ligand was removed by filtration, and the resulting supernatant solution was concentrated by rotary evaporation. The resulting residue was then purified by preparative HPLC or by flash chromatography.

(2*S*)-*N*-(2-Benzyloxy-4-pentenoyl)-morpholine (Table 5, entry 1). Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and benzyloxyacetyl chloride (0.48 mL, 1.0 M solution in CH_2Cl_2, 0.48 mmol), using MgI_2 (222 mg, 0.80 mmol), $ArCl_2$-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr_2NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 80% yield (88 mg, 0.32 mmol); 91% ee. IR (thin film) 2916, 2854, 1643, 1457, 1436, 1114 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.37 (m, 5H, Ph**H**), 5.83 (ddd, *J* = 7.0, 10.2, 17.1 Hz, 1H, C**H**=CH_2), 5.10-5.17 (m, 2H, CH=C**H**$_2$), 4.62 (d, *J* = 11.7 Hz, 1H, C**H**$_2$Ph), 4.45 (d, *J* = 11.7 Hz, 1H, C**H**$_2$Ph), 6.54 (dd, *J* = 6.0, 8.0 Hz, 1H, C**H**OCH_2Ph), 3.57-3.83 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.47-2.62 (m, 2H, C**H**$_2CH=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 137.3, 133.4, 128.5, 128.0, 128.0, 118.0, 79.0, 71.4, 67.1, 66.8, 45.7, 42.6, 36.7; HRMS (CI) exact mass calcd for ($C_{16}H_{21}NO_3$ + H^+) requires *m/z* 276.1599, found *m/z* 276.1594; $[\alpha]_D$ = +30.2 (c = 1.0, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel OJ column and OJ guard column (10% EtOH:hexanes, 1 mL/min flow); t_r = 16.8 min and 19.3 min.

(2*S*)-*N*-(2-Methoxy-4-pentenoyl)-morpholine (Table 5, entry 2). Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and methoxyacetyl

chloride (0.48 mL, 1.0 M solution in CH_2Cl_2, 0.48 mmol), using MgI_2 (222 mg, 0.80 mmol), $ArCl_2$-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr_2NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 28% yield (22 mg, 0.11 mmol); 80% ee. IR (thin film) 2946, 2853, 2812, 1721, 1659, 1119 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 7.0, 10.2, 17.1 Hz, 1H, C**H**=CH_2), 5.09-5.16 (m, 2H, CH=C**H**$_2$), 4.07 (dd, *J* = 6.0, 7.8 Hz, 1H, C**H**OCH_3), 3.64-3.78 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 3.35 (s, 3H, C**H**$_3$), 2.44-2.55 (m, 2H, C**H**$_2$CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 133.4, 117.9, 81.1, 67.1, 66.9, 56.9, 45.6, 42.6, 36.4; HRMS (CI) exact mass calcd for ($C_{10}H_{17}NO_3^+$) requires *m/z* 199.1208, found *m/z* 199.1211; $[\alpha]_D$ = +2.1 (c = 1.0, $CHCl_3$). The enantiomeric purity was assayed by derivitization of a portion of the product to the iodolactone (I_2, 1:1 H_2O:DME, 15 min) and analysis by GC with a Bodman Chiraldex Γ-TA column (50 °C, 1 °C/min gradient, 1 mL/min); minor diastereomer, t_r = 92.9 min and 107.7 min.

(2*S*)-*N*-(2-Phenoxy-4-pentenoyl)-morpholine (Table 5, entry 3). Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and phenoxyacetyl chloride (0.48 mL, 1.0 M solution in CH_2Cl_2, 0.48 mmol), using MgI_2 (222 mg, 0.80 mmol), $ArCl_2$-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr_2NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 48% yield (50 mg, 0.19 mmol); 78% ee. IR (thin film) 3072, 2968, 2916, 2854, 1643, 1597, 1228 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.29 (m, 2H, Ph**H**), 6.96-7.00 (m, 1H, Ph**H**), 6.89 (d, *J* = 8.8 Hz, 2H, Ph**H**), 5.88 (ddd, *J* = 7.0, 10.0, 17.0 Hz, 1H, C**H**=CH_2), 5.14-5.22 (m, 2H, CH=C**H**$_2$), 4.85 (dd, *J* = 6.5, 7.5 Hz, 1H, C**H**$_2$OPh), 3.36-3.78 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.70-2.72 (m, 2H, C**H**CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.8, 157.2, 132.7, 129:8, 121.8, 118.5. 114.9, 78.5, 67.0, 66.7, 45.8, 42.9, 36.8; HRMS (CI) exact mass calcd for ($C_{15}H_{19}NO_3$ + H^+) requires *m/z* 262.1443, found *m/z* 262.1438; $[\alpha]_D$ = –26.3 (c = 1.0, $CHCl_3$). The enantiomeric purity

was determined by HPLC with a Chiralcel OJ column and OJ guard column (3% EtOH:hexanes, 1 mL/min flow); t_r = 28.3 min and 32.6 min.

(2*S*)-*N*-(2-(*p*-Chlorophenoxy)-4-pentenoyl)-morpholine (Table 5, entry 4). Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and (*p*-chlorophenoxy)acetyl chloride (0.48 mL, 1.0 M solution in CH_2Cl_2, 0.48 mmol), using MgI_2 (222 mg, 0.80 mmol), $ArCl_2$-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr_2NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 59% yield (70 mg, 0.24 mmol); 71% ee. IR (thin film) 3072, 2968, 2916, 2854, 1643, 1597, 1493, 1234 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 9.0 Hz, 1H, Ph**H**), 6.83 (d, *J* = 9.0 Hz, 1H, Ph**H**), 5.87 (ddd, *J* = 7.0, 10.0, 17.0 Hz, 1H, C**H**=CH_2), 5.15-5.23 (m, 2H, CH=C**H**$_2$), 4.80 (dd, *J* = 6.2, 7.5 Hz,, 1H, C**H**-O(PhCl)), 3.39-3.75 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.68-2.76 (m, 2H, C**H**CH=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 155.8, 132.4, 129.7, 118.7, 116.2, 114.9, 78.9, 67.0, 66.7, 45.8, 42.9, 36.7; HRMS (CI) exact mass calcd for ($C_{15}H_{18}NO_3Cl^+$) requires *m/z* 295.0975, found *m/z* 295.0969; $[\alpha]_D$ = −17.7 (c = 1.0, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel AD column and AD guard column (3% *i*-PrOH:hexanes, 1 mL/min flow); t_r = 36.2 min and 41.8 min.

(2*S*)-*N*-(2-(*t*-Butyldimethylsilyloxy)-4-pentenoyl)-morpholine (Table 5, entry 5) Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and (*t*-butyldimethylsilyl)oxyacetyl chloride (0.48 mL, 1.0 M solution in CH_2Cl_2, 0.48 mmol), using MgI_2 (222 mg, 0.80 mmol), $ArCl_2$-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr_2NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 67% yield (81 mg, 0.27 mmol); 38% ee. IR (thin film) 5/77, 2911, 2854, 1643, 1462, 1436, 1249, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.75 (ddd, 7.0, 10.1, 17.2 Hz, 1H, C**H**=CH_2), 5.06-5.10 (m, 2H, CH=C**H**$_2$), 4.38-4.45 (m, 1H, C**H**-OTBS), 3.56-3.85 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.24-2.45 (m,

2H, $CH_2CH=CH_2$), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.04 (s, 4H, $Si(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 133.5, 118.1, 75.7, 67.1, 67.0, 45.9, 42.7, 39.9, 25.7, 18.1, -4.7, -5.2; HRMS (CI) exact mass calcd for ($C_{15}H_{29}NO_3Si$ + H^+) requires *m/z* 300.1995, found *m/z* 300.1986; $[\alpha]_D$ = +6.2 (c = 1.0, $CHCl_3$). The enantiomeric purity was assayed by derivitization of a portion of the product to the deprotected secondary alcohol (2N HCl, MeOH, 30 min) and analysis by GC with a Bodman Chiraldex Γ-TA column (70 °C, 3 °C/min gradient, 1 mL/min); minor diastereomer, t_r = 34.5 min and 35.8 min.

(2*S*)-*N*-(2-Acetoxy-4-pentenoyl)-morpholine (Table 5, entry 6). Prepared by the general procedure from *N*-allyl morpholine (51 mg, 0.40 mmol) and acetoxyacetyl chloride (0.48 mL, 1.0 M solution in CH_2Cl_2, 0.48 mmol), using MgI_2 (222 mg, 0.80 mmol), $ArCl_2$-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr_2NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 44% yield (40 mg, 0.18 mmol); 37% ee. IR (thin film) 2968. 2926, 2864, 1737, 1654, 1451, 1239 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 7.1, 10.1, 17.1 Hz, 1H, $CH=CH_2$), 5.29 (m, 1H, CHOAc), 5.11-5.13 (m, 2H, $CH=CH_2$), 3.48-3.69 (m, 8H, $N(CH_2CH_2)_2$), 2.48-2.57 (m, 2H, $CH_2CH=CH_2$), 2.10 (s, 3H, OAc);); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 168.2, 132.3, 119.3, 69.6, 67.2, 66.8, 46.4, 42.8, 36.0, 21.0; HRMS (CI) exact mass calcd for ($C_{11}H_{17}NO_4^+$) requires *m/z* 227.1158, found *m/z* 257.1152; $[\alpha]_D$ = –4.3 (c = 1.0, $CHCl_3$). The enantiomeric purity was assayed by derivitization of a portion of the product to the deprotected secondary alcohol ($NaBH_4$, MeOH, 2 h) and analysis by GC with a Bodman Chiraldex Γ-TA column (70 °C, 3 °C/min gradient, 1 mL/min); minor diastereomer, t_r = 34.6 min and 35.9 min.

(2*S*)-*N*-(2-Benzyloxy-5-methyl-4-pentenoyl)-morpholine (Table 6, Entry 2). Prepared by the general procedure from *N*-methallyl morpholine (57 mg, 0.40 mmol) and benzyloxyacetyl chloride (0.48 mL, 1.0 M solution in CH_2Cl_2, 0.48 mmol), using MgI_2

(222 mg, 0.80 mmol), $ArCl_2$-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr_2NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 78% yield (90 mg, 0.31 mmol); 91% ee. IR (thin film) 3072, 3030, 2968, 2916, 2854, 1643, 1457, 1436 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21–7.34 (m, 5H, Ph**H**), 4.83 (s, 1H, CMe=C**H**$_2$), 4.77 (s, CMe=C**H**$_2$), 4.60 (d, 1H, *J* = 11.6 Hz, 1H, C**H**$_2$Ph), 4.43 (d, 1H, *J* = 11.6 Hz, 1H, C**H**$_2$Ph), 4.33 (dd, *J* = 5.5, 8.7 Hz, 1H, C**H**OCH$_2$Ph), 3.56-3.75 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.52 (dd, *J* = 8.7, 14.3 Hz, 1H, C**H**$_2$CMe=CH$_2$), 2.41 (dd, *J* = 5.4, 14.3 Hz, 1H, C**H**$_2$CMe=CH$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 141.1, 137.3, 128.5, 128.0, 128.0, 113.6, 78.5, 71.6, 67.1, 66.8, 45.7, 42.5, 40.6, 22.5; HRMS (CI) exact mass calcd for ($C_{17}H_{23}NO_3$ + H^+) requires *m/z* 290.1756, found *m/z* 290.1764; $[\alpha]_D$ = +30.0 (c = 1.0, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel OJ column and OJ guard column (6% *i*-PrOH:hexanes, 1 mL/min flow); t_r = 14.8 min and 16.4 min.

(2*S*)-*N*-(2-Benzyloxy-5-phenyl-4-pentenoyl)-morpholine (Table 6, entry 3). Prepared by the general procedure from *N*-(2-phenyl-2-propenyl)morpholine (81 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in CH_2Cl_2, 1.0 mmol), using MgI_2 (334 mg, 1.2 mmol), $ArCl_2$-PMPBox **2c** (597 mg, 1.2 mmol), and *i*-Pr_2NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 79% yield (111 mg, 0.32 mmol); 90% ee. IR (thin film) 3030, 1926, 1854, 1716, 1643, 1509, 1451, 1244 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.40 (m, 10H, Ph**H**), 5.39 (d, *J* = 1.4 Hz, CPh=C**H**$_2$), 5.20 (d, *J* = 1.1 Hz, CPh=C**H**$_2$), 4.55 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.35 (d, *J* = 11.5 Hz, 1H, C**H**$_2$Ph), 4.28 (dd, *J* = 6.9, 7.1 Hz, 1H, C**H**OCH$_2$Ph), 3.42-3.63 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 3.00 (dd, *J* = 0.8, 6.9 Hz, 2H, C**H**$_2$CPh=CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ169.6, 143.5, 139.9, 137.1, 128.3, 128.2, 127.8, 127.6, 126.0, 115.8, 99.9, 77.0, 71.4, 67.0, 66.6, 45.6, 42.4, 38.5; HRMS (CI) exact mass calcd for ($C_{22}H_{25}NO_3$ + H^+) requires *m/z* 352.1912, found *m/z* 352.1912; $[\alpha]_D$ = +4.9 (c = 1.0, $CHCl_3$). The enantiomeric purity was determined by

HPLC with a Chiralcel AD column and AD guard column (10% *i*-PrOH:hexanes, 1 mL/min flow); t_r = 13.4 min and 16.0 min.

(2*S*,3*S*)-*N*-(2-Benzyloxy-3-(ethoxycarbonyl)-4-pentenoyl)-morpholine

(Table 7, entry 1) Prepared by the general procedure from (*E*)-ethyl 4-morpholinocrotonate (74 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in CH_2Cl_2, 1.0 mmol), using MgI_2 (334 mg, 1.2 mmol), $ArCl_2$-PMPBox **2c** (597 mg, 1.2 mmol), and *i*-Pr_2NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 84% yield (111 mg, 0.32 mmol); *syn*:*anti* 97:3; *syn* 96% ee. *Syn* isomer: IR (thin film) 2968, 2916, 2864, 1737, 1649, 1457, 1441 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27-7.37 (m, 5H, Ph**H**), 5.75 (ddd, *J* = 9.1, 10.1, 17.1 Hz, 1H, C**H**=CH_2), 4.61 (d, *J* = 11.7 Hz, 1H, C**H**$_2$Ph), 4.60 (d, *J* = 10.5 Hz, 1H, C**H**-OBn), 4.51 (d, *J* = 11.7 Hz, 1H, C**H**$_2$Ph), 4.11-4.25 (m, 2H, OC**H**$_2$$CH_3$), 3.50-3.65 (m, 9H, **CH**-CH=CH_2), N(C**H**$_2$C**H**$_2$)$_2$), 1.24 (t, *J* = 7.1 Hz, OCH_2C**H**$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 167.6, 136.9, 130.7, 128.4, 128.1, 128.1, 120.6, 79.4, 72.3, 67.0, 66.7, 61.2, 54.0, 45.7, 42.5, 14.1; HRMS (CI) exact mass calcd for ($C_{19}H_{25}NO_5$ + H^+) requires *m/z* 348.1811, found *m/z* 348.1804; $[\alpha]_D$ = –31.8 (c = 1.0, $CHCl_3$). The enantiomeric purity and diastereomer ratio were determined by HPLC with a Chiralcel AD column and AD guard column (10% EtOH:hexanes, 1 mL/min flow); *syn* isomer, t_r = 15.5 min and 20.6 min; *anti* isomer, t_r = 14.1 min and 19.5 min.

(2*S*,3*S*)-*N*-(2-Benzyloxy-3-(*p*-nitrophenyl)-4-pentenoyl)-morpholine (Table 7, entry 2) Prepared by the general procedure from (*E*)-*N*-(*p*-nitrocinnamyl)morpholine (99 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in CH_2Cl_2, 1.0 mmol), using MgI_2 (334 mg, 1.2 mmol), $ArCl_2$-PMPBox **2c** (597 mg, 1.2 mmol), and *i*-Pr_2NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 82% yield (136 mg, 0.33 mmol); *syn*:*anti* 99:1; *syn* 97% ee. *Syn* isomer: IR (thin film) 3061, 2968, 2911, 2854,

1737, 1649, 1519, 1457, 1436, 1348, 1239 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.8 Hz, 2H, $(NO_2)PhH$), 7.35 (d, *J* = 8.8 Hz, 2H, $(NO_2)PhH$), 7.21-7.25 (m, 3H, CH_2PhH), 6.99 (d, *J* = 7.7 Hz, 2H, CH_2PhH), 5.94 (ddd, *J* = 8.8, 10.4, 17.0 Hz, 1H, $CH=CH_2$), 5.08-5.18 (m, 2H, $CH=CH_2$), 4.52 (d, *J* = 12.1 Hz, 1H, CH_2Ph), 4.44 (d, *J* = 9.6 Hz, 1H, CHOBn), 4.27 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 3.87 (dd, *J* = 9.1, 9.1 Hz, 1H, $CH-CH=CH_2$), 3.51-3.76 (m, 8H, $N(CH_2CH_2)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.0, 147.8, 146.6, 136.1, 135.1, 129.1, 128.3, 128.0, 127.8, 123.5, 118.7, 81.8, 72.0, 67.0, 66.6, 53.0, 45.6, 42.7; HRMS (CI) exact mass calcd for ($C_{22}H_{24}N_2O_5$ + H^+) requires *m/z* 397.1763, found *m/z* 397.1756; $[\alpha]_D$ = +4.0 (c = 1.0, $CHCl_3$). The enantiomeric purity and diastereomer ratio were determined by HPLC with a Chiralcel AD column and AD guard column (15% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer, t = 16.7 min and t = 26.1 min; *anti* isomer, t_r = 21.9 min and 29.5 min.

(2*S*,3*R*)-*N*-(2-Benzyloxy-3-(benzoyloxymethyl)-4-pentenoyl)-morpholine

(Table 7, entry 3). Prepared by the general procedure from (*E*)-*N*-(4-benzoyloxy-2-butenyl)morpholine (105 mg, 0.40 mmol) and benzyloxyacetyl chloride (0.48 mL, 1.0 M solution in CH_2Cl_2, 0.48 mmol), using MgI_2 (222 mg, 0.80 mmol), $ArCl_2$-PMPBox **2c** (398 mg, 0.80 mmol), and *i*-Pr_2NEt (0.11 mL, 0.60 mmol) to afford the product as a colorless oil in 86% yield (140 mg, 0.34 mmol); *syn*:*anti* 92:8; 86% ee. *Syn* isomer: IR (thin film) 3072, 3030, 2968, 2916, 2854, 1716, 1643, 1451, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.1 Hz, 2H, C(O)PhH), 7.53 (t, *J* = 7.4 Hz, 1H, C(O)PhH), 7.39 (dd, *J* = 7.9, 7.5 Hz, 2H, C(O)PhH), 7.18-7.28 (m, 5H, CH_2(PhH)), 5.78 (ddd, *J* = 9.3, 10.2, 17.1 Hz, 1H, , $CH=CH_2$), 5.15-5.21 (m, 2H, $CH=CH_2$), 4.65 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.49-4.51 (m, 2H, CH_2OBz), 4.42 (d, *J* = 11.7 Hz, 1H, CH_2Ph), 4.27 (d, *J* = 9.5 Hz, 1H, CHOBn), 3.54-3.73 (m, 8H, $N(CH_2CH_2)_2$), 2.91-2.96 (m, 1H, $CH-CH=CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 166.3, 136.8, 134.0, 133.0, 130.0, 129.6, 129.5, 128.5, 128.4, 128.2, 128.2,

120.3, 97.4, 72.3, 67.1, 66.7, 64.5, 46.7, 45.6, 42.6; HRMS (CI) exact mass calcd for ($C_{24}H_{27}NO_5$ + H^+) requires *m/z* 410.1967, found *m/z* 410.1952; $[\alpha]_D$ = +8.6 (c = 1.0, $CHCl_3$). The enantiomeric purity and diastereomer ratio were determined by HPLC with a Chiralcel OD-H column and OD guard column (10% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer, t_r = 20.1 min and 29.5 min; *anti* isomer, t_r = 23.2 min and 26.0 min.

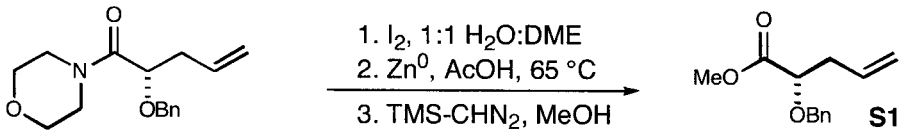
(2*S*,3*R*)-*N*-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine (Table 7, entry 4). Prepared by the general procedure from (*E*)-*N*-(3-chloro-2-propenyl)morpholine (65 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in CH_2Cl_2, 1.0 mmol), using MgI_2 (334 mg, 1.2 mmol), $ArCl_2$-PMPBox **2c** (597 mg, 1.2 mmol), and *i*-Pr_2NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 95% yield (118 mg, 0.38 mmol); *syn*:*anti* 98:2; 91% ee. ^1H NMR, ^{13}C NMR, IR, and mass spectral data for this compound were consistent with those previously reported.[5] $[\alpha]_D$ = –5.8 (c = 1.0, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel OJ column and OJ guard column (10% EtOH:hexanes, 0.5 mL/min); *syn* isomer, t = 53.0 min and t = 61.5 min. The diastereomer ratio was determined by GC with a CC-1701 column (70 °C, 7 °C/min gradient, 1 mL/min); *syn* isomer, t_r = 29.8 min, *anti* isomer, t_r =30.3 min.

(2*S*,3*S*)-*N*-(2-Benzyloxy-3-chloro-4-pentenoyl)-morpholine (Table 7, entry 5). Prepared by the general procedure from (*Z*)-*N*-(2-phenyl-2-propenyl)morpholine (81 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in CH_2Cl_2, 1.0 mmol), using MgI_2 (334 mg, 1.2 mmol), $ArCl_2$-PMPBox **2c** (597 mg, 1.2 mmol), and *i*-Pr_2NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 79% yield (111 mg, 0.32 mmol). ^1H NMR, ^{13}C NMR, IR, and mass spectral data for this compound were consistent

5. Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726.

with those previously reported.[5] $[\alpha]_D$ = +54.9 (c = 1.0, $CHCl_3$). The enantiomeric purity and diastereomer ratio were determined by HPLC with a Chiralcel OJ column and OJ guard column (6%:1% *i*-PrOH:EtOH:hexanes, 1 mL/min flow); *anti* isomer, t_r = 37.6 min and 51.0 min; *syn* isomer, t_r = 48.2 min.

(2*S*,3*S*)-*N*-(2-Benzyloxy-3-(ethoxycarbonyl)-3-methyl-4-pentenoyl)-morpholine (22). Prepared by the general procedure from ethyl (*E*)-4-morpholino-2-methylcrotonate (85 mg, 0.40 mmol) and benzyloxyacetyl chloride (1.0 mL, 1.0 M solution in CH_2Cl_2, 1.0 mmol), using MgI_2 (334 mg, 1.2 mmol), $ArCl_2$-PMPBox **2c** (597 mg, 1.2 mmol), and *i*-Pr_2NEt (0.21 mL, 1.2 mmol) to afford the product as a colorless oil in 75% yield (109 mg, 0.30 mmol); *syn*:*anti* 94:6; *syn* 97% ee. IR (thin film) 3093, 3051, 2968, 2906, 2854, 1732, 1654, 1457, 1441, 1239 cm^{-1}; ^1H NMR (300 MHz) δ 7.26-7.34 (m, 5H, Ph), 5.94 (dd, *J* = 10.7, 17.3 Hz, 1H, CH=C**H**$_2$), 5.11-5.18 (m, 2H, CH=C**H**$_2$), 4.76 (s, 1H, C**H**OBn), 4.59 (d, *J* = 11.8 Hz, C**H**$_2$Ph), 4.43 (d, *J* = 11.8 Hz, C**H**$_2$Ph), 4.06-4.21 (m, 2H, OC**H**$_2$CH$_3$), 3.34-3.60 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 1.44 (s, 3H, C**H**$_3$), 1.21 (t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 167.2, 137.1, 136.8, 128.2, 127.9, 127.9, 116.3, 79.2, 72.5, 67.0, 66.4, 61.3, 53.9, 46.4, 42.4, 15.4, 14.1; HRMS (CI) exact mass calcd for ($C_{20}H_{27}NO_5$ + H^+) requires *m/z* 362.1967, found *m/z* 362.1960; $[\alpha]_D$ = –33.6 (c = 1.0, $CHCl_3$). The enantiomeric purity and diastereomer ratio were determined by HPLC with a Chiralcel AD column and AD guard column (6% *i*-PrOH:hexanes, 1 mL/min flow); *syn* isomer, t_r = 15.7 min and 17.6 min; *anti* isomer, t_r = 16.5 min.



Determination of the absolute configuration of (2*S*)-*N*-(2-benzyloxy-4-pentenoyl)-morpholine by correlation with (2*S*)-2-benzyloxy-4-pentenoic acid methyl ester (S1). A solution of (2*S*)-*N*-(2-benzyloxy-4-pentenoyl)-morpholine (23 mg, 84 μmol) in 2 mL 1:1 water/ DME was placed in an 8 mL scintillation vial equipped with a magnetic stir bar. The solution was treated with iodine (53 mg, 0.21 mmol) and stirred at 23 °C for 10 min. The reaction was then quenched with 10% aqueous $Na_2S_2O_3$ (1 mL) and extracted into Et_2O. The resulting organic layer was dried (Na_2SO_4) and concentrated. The unpurified iodolactone product was then taken up in glacial AcOH (1 mL). The resulting solution was then treated with zinc dust (55 mg, 0.84 mmol) and stirred at 65 °C for 1.5 h. Upon cooling to ambient temperature, 1 *N* HCl (aq) (1 mL) was added, and the resulting mixture was extracted with Et_2O (3 x 1 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated. The resulting carboxylic acid was then taken up in MeOH and TMS-CHN_2 (2.0 M in hexanes) was added dropwise until a bright yellow color persisted. The reaction was then treated with a drop of AcOH and concentrated. The residue was purified by flash chromatography (5:1 hexanes:EtOAc) to afford 9.5 mg (43 μmol, 52% yield) of a clear oil that was spectroscopically identical in all respects to the compound (2*S*)-2-benzyloxy-4-pentenoic acid methyl ester.[6] $[\alpha]_D$ (literature) = +46 (c = 1.0, $CHCl_3$); $[\alpha]_D$ (observed) = +55 (c = 1.0, $CHCl_3$).

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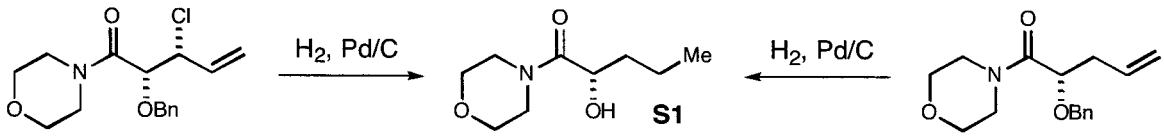
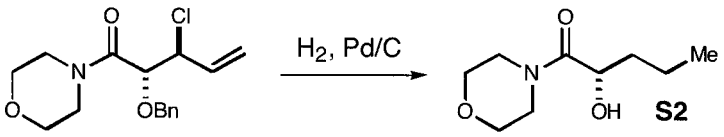
6. Kato, Y.; Ohta, H.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 1303.

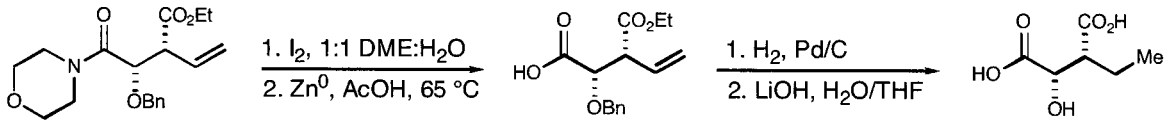


Determination of the absolute stereochemistry of (2*S*,3*S*)-*N*-(2-benzyloxy-3-chloro-4-pentenoyl)-morpholine by correlation with (2*S*)-*N*-(2-hydroxy-pentanoyl)-morpholine (S1). A suspension containing (2*S*)-*N*-(2-benzyloxy-4-pentenoyl)-morpholine (19 mg, 68 μmol) of known absolute configuration (*vide supra*) and 10% palladium on carbon (25 mg) in 1 mL ethanol was stirred under an atmosphere of H_2 for 30 min. The catalyst was removed by filtration through a short plug of celite, and the filtrate was concentrated. Purification of the residue by flash chromatography (1:1 hexanes:EtOAc) afforded 12 mg (68 μmol, 96% yield) of a colorless film. $[\alpha]_D$ = + 4.0 (c = 1.0, $CHCl_3$).

A suspension containing of (2*S*,3*S*)-*N*-(2-benzyloxy-3-chloro-4-pentenoyl)-morpholine (43 mg, 0.14 mmol) and 10% palladium on carbon (50 mg) in EtOH (2 mL) was stirred under at atmosphere of H_2 for 1 h. The catalyst was then removed by filtration through a short plug of celite, and the filtrate was concentrated. Purification of the residue by flash chromatography (1:1 hexanes:EtOAc) afforded 25.4 mg (0.14 mmol, 97%) of a colorless oil that was spectroscopically identical to **S1** in all respects. $[\alpha]_D$ = + 2.4 (c = 1.0, $CHCl_3$).



Determination of the absolute stereochemistry of (2*S*,3*R*)-*N*-(2-benzyloxy-3-chloro-4-pentenoyl)-morpholine by correlation with (2*S*)-*N*-(2-hydroxypentanoyl)-morpholine (S2). A suspension containing of (2*S*,3*R*)-*N*-(2-benzyloxy-3-chloro-4-pentenoyl)-morpholine (26.2 mg, 84.6 μmol) and 10% palladium on carbon (50 mg) in EtOH (2 mL) was stirred under at atmosphere of H_2 for 1.5 h. The catalyst was then removed by filtration through a short plug of celite, and the filtrate was concentrated. Purification of the residue by flash chromatography (1:1 hexanes:EtOAc) afforded 15 mg (81 μmol, 96% yield) of a colorless film that was spectroscopically identical to **S2**. $[\alpha]_D$ = + 1.0 (c = 1.0, $CHCl_3$).



Determination of the absolute stereochemistry of (2*S*,3*S*)-*N*-(2-benzyloxy-3-(ethoxycarbonyl)-4-pentenoyl)-morpholine by correlation with (2*S*,3*R*)-3-ethylmalic acid. A solution of (2*S*,3*S*)-*N*-(2-benzyloxy-3-(ethoxycarbonyl)-4-pentenoyl)-morpholine (34 mg, 0.1 mmol) in 2.4 mL 1:1 H_2O/DME was treated with iodine (64 mg, 0.25 mmol) and stirred at 23 °C for 1 h. The resulting solution was then treated with 10% aqueous $Na_2S_2O_3$ (1 mL) and extracted into Et_2O. The resulting organic layer was dried (Na_2SO_4) and concentrated. The iodolactone residue was then taken up in glacial AcOH (2.5 mL) and treated with zinc dust (65 mg, 1.0 mmol) and stirred at 65 °C for 1.5 h. Upon cooling to ambient temperature, 1 *N* HCl (aq) (1 mL) was added, and the mixture was

extracted with Et_2O (3 x 1 mL). The organic extracts were combined, dried (Na_2SO_4), and then concentrated.

The resulting carboxylic acid was taken up in THF (4 mL) and treated with 10% palladium on carbon (50 mg) and stirred under an H_2 atmosphere for 1 h. The catalyst was then removed by filtration through a short plug of celite, and the filtrate was concentrated. The resulting residue was then taken up in 3:1 THF:H_2O (4 mL) and treated with LiOH•H_2O (42 mg, 1.0 mmol). The solution was warmed to 65 °C for 14 h. After cooling to ambient temperature, the reaction mixture was added to Dowex 50X80-200 (H^+ form) resin. The resin was removed by filtration and washed with H_2O. The combined filtrate was concentrated to afford 7 mg of a yellow oil (43 μmol, 43% for 4 steps) that was identical to (2*R*,3*S*)-3-ethylmalic acid[7] in all regards except for optical rotation, which was opposite in sign. $[\alpha]_D$ (literature) = -3.1 (c = 1.0, H_2O); $[\alpha]_D$ (observed) = +1.4 (c = 1.0, H_2O).

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7. Kakinuma, K.; Terasawa, H.; Li, H.-Y.; Miyazaki, K.; Oshima, T. *Biosci. Biotech. Biochem.*, **1993**, *57*, 1916.

Chapter 5

Development of a Second-Generation Enantioselective Acyl-Claisen Rearrangement

Reaction Design

The design of our first-generation approach to an enantioselective acyl-Claisen rearrangement focused on the use of benzyloxyacetyl chloride in order to take advantage of the well-established ability of bidentate chelating substrates to confer a high level of organizational control in the transition state of Lewis acid-catalyzed transformations.[1] Indeed, the research described in Chapter 4 employs this strategy to produce Claisen products in up to 97% ee. However, the requirement for an acid chloride substrate capable of two-point binding to a metal center limits the scope of the reaction to transformations using benzyloxyacetyl chloride as the ketene precursor; reactions employing acid chlorides with less Lewis basic α-substitutents gave poorer results, and the use of propionyl chloride resulted in racemic products. In addition, benzyloxyacetyl chloride suffers from a significant uncatalyzed background reaction that significantly reduces the enantioselectivity of the products when a substoichiometric quantity of the chiral Lewis acid is used.

Acyl-Claisen rearrangements using non-chelating acid chlorides such as propionyl chloride, on the other hand, suffer from neither of these disadvantages. As demonstrated in Chapter 3, propionyl chloride does not participate in an uncatalyzed background reaction. Furthermore, chiral Lewis acids that achieve high levels of organizational control over the transition state without a specific requirement for two-point binding could potentially be

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1. Chapter 4, reference 3.

tolerant of a range of α-substituents on the acid chloride component of the reaction, greatly expanding the utility of this process (Figure 1).

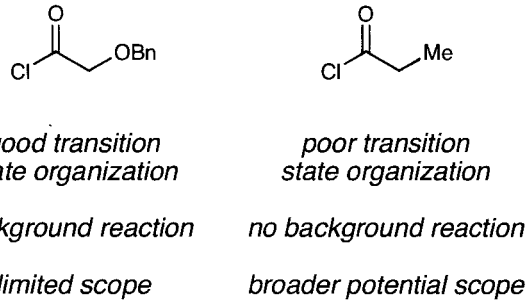


Figure 1. Comparison of benzyloxyacetyl chloride and propionyl chloride.

Initially, we speculated that electronic interactions between the zwitterionic intermediate and the metal center could be exploited to diminish the conformational flexibility of the transition state. In particular, we predicted that the presence of an energetically low-lying empty *p*-orbital on the metal center could potentially induce anisotropy about the enolate oxygen-metal bond (Figure 2). Therefore we chose to focus on Group 13 Lewis acids in our initial investigations toward the development of a second-generation enantioselective acyl-Claisen rearrangement involving non-chelating acid chlorides.

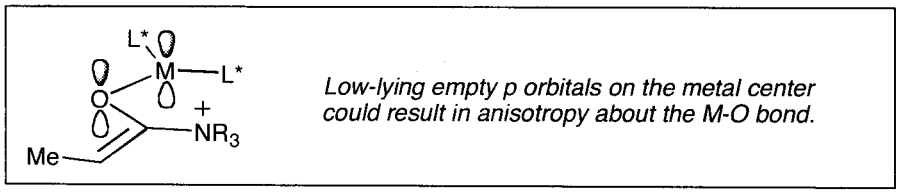
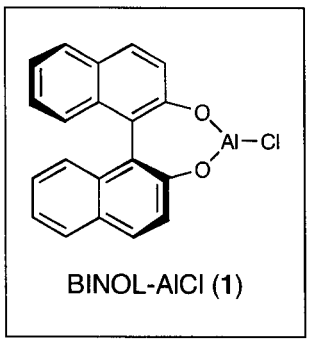


Figure 2. Rationale for design of propionate acyl-Claisen around Group 13 Lewis acids.

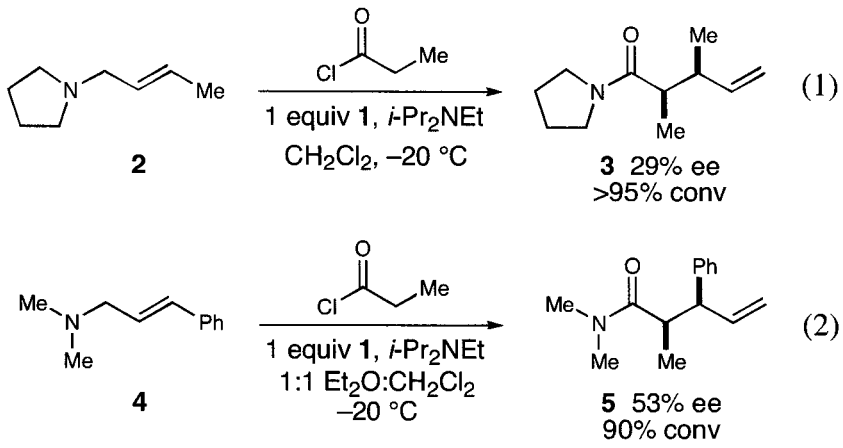
BINOL-Aluminum-Promoted Enantioselective Acyl-Claisen Rearrangements

In our preliminary studies of the acyl-Claisen rearrangement described in Chapter 3, $Bu_2B(OTf)$ did not successfully catalyze the acyl-Claisen rearrangement of propionyl chloride and crotyl morpholine, while $AlCl_3$ proved to be a very effective catalyst for this reaction. Consequently, chiral aluminum Lewis acids were first screened for their ability to promote the asymmetric reaction.

A screen of ligand-metal salt combinations revealed that BINOL-AlCl complex **1**, generated in situ by the reaction of BINOL and dimethylaluminum chloride in methylene chloride, exerted promising levels of enantiocontrol over the reaction of crotyl pyrrolidine (**2**) with propionyl chloride (eq 1, 29% ee).[2,3] Upon further optimization, involving variation of the amine substituents as well as reaction conditions, the enantioselectivity of the reaction could be improved to 53% ee (eq 2).[2]



BINOL-AlCl (**1**)



2. Relative stereochemistry shown. The absolute sense of stereoinduction was not determined.

3. Surprisingly, the reaction of crotyl morpholine was racemic under these conditions.

However, optimization of this system was complicated by two factors. First, the success of the reaction was highly dependent on the order of addition and the solvent in which the Lewis acid complex was generated. In particular, optimal results were obtained when the BINOL-aluminum complex was generated in Et_2O and the allyl amine substrate was next added as a solution in CH_2Cl_2. This behavior is consistent with the formation of complex aluminum-BINOLate aggregates in solution.[4] Second, the BINOL ligand structure is relatively difficult to functionalize, rendering the optimization of ligand architecture in this system synthetically intensive.[5]

Boron-Bis(sulfonamide)-Promoted Enantioselective Acyl-Claisen Rearrangements

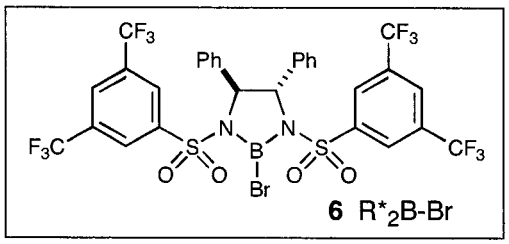
We therefore sought a new Lewis acid bearing a ligand framework that was modular and correspondingly more easily derivatized than BINOL. We also considered Lewis acid systems that had proven successful in other asymmetric reactions involving one-point binding between substrates and the metal center. In particular, Corey's[6] chiral boron Lewis acid-promoted ester enolate Claisen rearrangement appears to meet both of these criteria. Corey has shown that the boron bromide complex **6** can be used to promote the Ireland-

4. Related aluminum-BINOLate complexes demonstrate complex aggregation behavior in solution: (a) Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymm.* **1997**, *8*, 3403. (b) Arai, T.; Sasai, H.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 441. Similar behavior has also been observed for other Group 13 BINOLate complexes: (c) Chitsaz, S.; Neumüller, B. *Organometallics* **2001**, *20*, 2338. Titanium BINOLates are similar: (d) Davis, T. J.; Balsells, J.; Carroll, P.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 699.

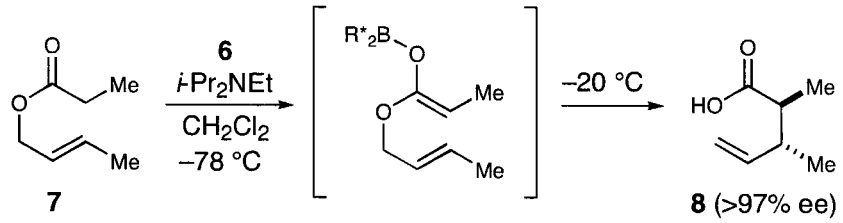
5. (a) Sogah, G. D. Y.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3035. (b) Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975. (c) Yamamoto, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938. (d) Ishihara, K.; Kurihara, H.; Matsumoto, M.; Yamaoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 6920. (e) Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 1095.

6. Chapter 2, references 19–21.

Claisen rearrangement of the monodentate propionate substrate **7** to give the rearranged carboxylic acid **8** with excellent levels of enantiocontrol (eq 3, >97% ee). We speculated that a structurally similar Lewis acid could provide similarly high levels of organizational control in acyl-Claisen rearrangements with propionyl chloride.



6 R^*_2B-Br



(3)

The synthesis of the boron complex described by Corey[6] is straightforward (Scheme 1). Chiral ligand **11** can be produced by condensation of commercially available stilbenediamine (stein, **9**) with 2 equiv sulfonyl chloride **10**. The boron bromide complex **6** is generated by complexation of ligand **11** with BBr_3. Importantly, this synthesis is modular and can be easily modified by variation of either the parent diamine[7] or the sulfonyl chloride[8] component. Additionally, the halide component of the Lewis acid can be exchanged for more labile counterions (e.g., triflate or perchlorate) by treatment of the bromide with the appropriate silver salt.[9]

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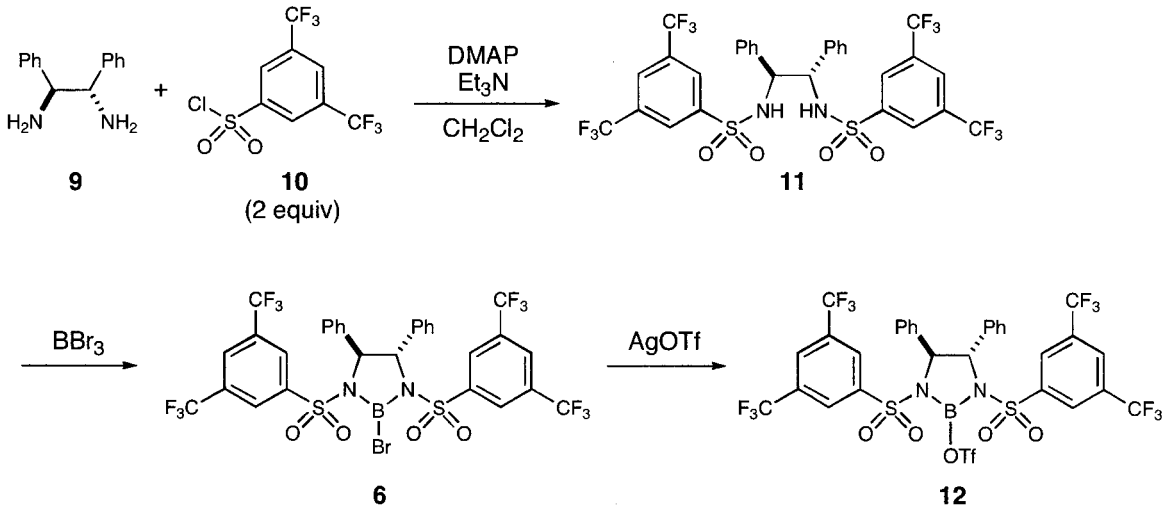
7. Corey, E. J.; Lee, D. H.; Sarshar, S. *Tetrahedron: Asymm.* **1995**, *6*, 1995.

8. Guo, C.; Qiu, J.; Zhang, X.; Verdugo, D.; Larter, M. L.; Christie, R.; Kenney, P.; Walsh, P. J. *Tetrahedron* **1997**, *53*, 4145.

Scheme 1



Results and Discussion

The results of a survey of Lewis acid structures in the acyl-Claisen reaction of propionyl chloride and allyl-morpholine (**13**) are summarized in Table 1. As shown in entry 1, the boron complex most useful for Corey's Ireland Claisen was not a competent promoter for the asymmetric acyl-Claisen rearrangement. The toluene sulfonamide derivative was more successful, providing the desired Claisen adduct **14** in 44–70% ee, albeit with very low conversion due to the undesired formation of propionyl morpholine (**15**) through a von Braun fragmentation process (entries 2–3). We speculated that this nucleophilic cleavage pathway could be avoided by replacement of the bromide counterion with a less nucleophilic anion. Indeed, no products from von Braun fragmentation were observed in reactions using the boron chloride, triflate, and perchlorate complexes, which promoted the reaction in 50–77% ee (entries 4–6). However, the PF_6^- and BF_4^- complexes were not successful promoters for the acyl-Claisen rearrangement (entries 7–8).

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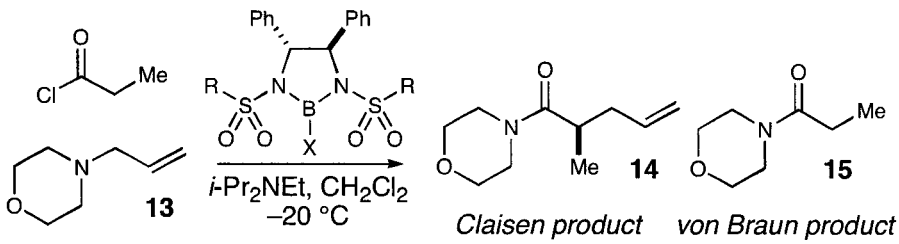
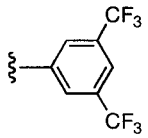
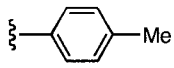
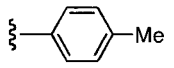
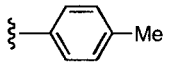
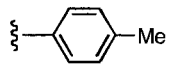
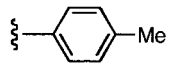
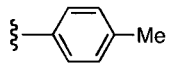
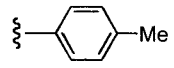
9. Evans has demonstrated that weakly coordinating counterions can be beneficial to Lewis acid-catalyzed enantioselective processes: Evans, D. A.; Murry, J. A.; von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.

Table 1. Effect of boron complex structure on enantioselective acyl-Claisen rearrangement.



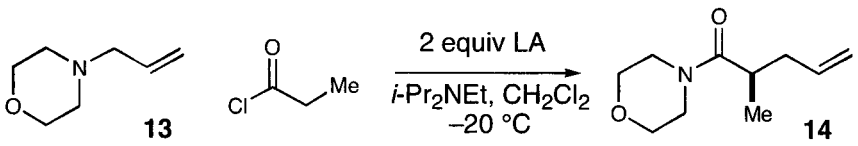
(4)

entry	R	X	equiv LA	% **14**[a]	% ee[b]	% **15**[c]
1		Br	1	50	5	0
2		Br	1	30	44	53
3		Br	2	35	70	48
4		Cl	2	>99	50	0
5		OTf	2	>99	71	0
6		ClO_4	2	>99	77	0
7		BF_4	2	40	0	0
8		PF_6	2	9	*c*	0

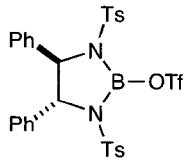
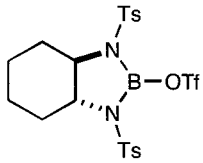
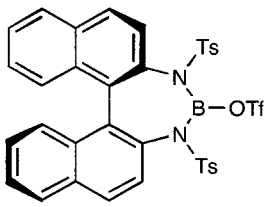
[a] Product ratios determined by GLC using a Bodman CC1701 column. [b] Enantiomeric excess was determined by chiral GLC using a Chiraldex Γ-TA column. [c] Not determined.

Several ligands containing alternate diamino backbones were also synthesized, and the results of experiments assaying their effectiveness in the enantioselective acyl-Claisen rearrangement are summarized in Table 2. Both the *trans*-1,2-diaminocyclohexane and 2,2'-diaminobinaphthyl backbones resulted in boron complexes that were less enantioselective than the stilbene diamine-derived boron Lewis acids (entires 2–3, 8–19% ee). Thus, ligands containing the stien backbone were chosen for further investigation of this reaction.

Table 2. Effect of diamino ligand backbone structure on the enantioselective acyl-Claisen rearrangement.



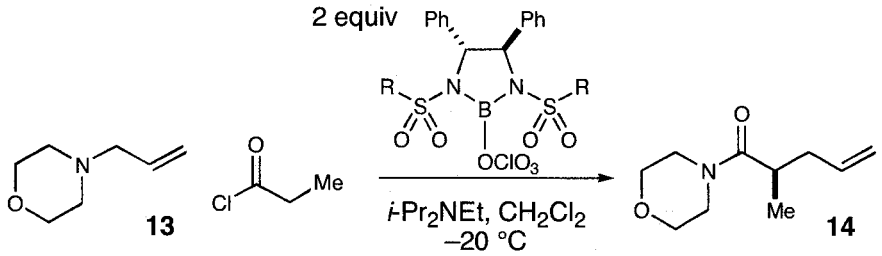
13 14 (5)

entry	LA	% conv[a]	% ee[b]
1		>99	71
2		75	19
3		61	8

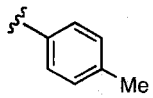
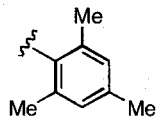
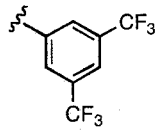
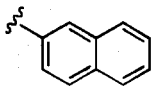
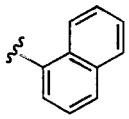
[a] Product ratios determined by GLC using a Bodman CC1701 column. [b] Enantiomeric excess was determined by chiral GLC using a Chiraldex Γ-TA column.

Experiments probing variations on the sulfonamide portion of the ligand structure are summarized in Table 4. Electron-deficient ligands give poor results; the 3,5-bis(trifluoromethyl)benzene-substituted ligand gives very poor conversion and ee. As demonstrated in entry 2, the enantioselectivity of the reaction could be increased slightly at

Table 3. Effect of sulfonamide structure on the enantioselective acyl-Claisen rearrangement.



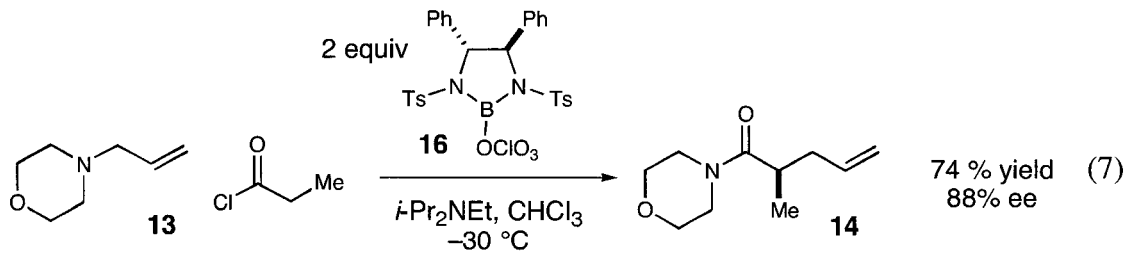
13 14 (6)

entry	R	% conv[a]	% ee[b]
1		>99	71
2		41	80
3		15	--[c]
4		48	0
5		43	0
6[d]		72	7

[a] Conversion of **13** determined by GLC using a Bodman CC1701 column. [b] Enantiomeric excess determined by GLC using a Chiraldex Γ-TA column. [c] Not determined. [d] Reaction conducted using boron triflate complex.

the expense of reaction efficiency by using bulkier sulfonamide groups (41% conv, 80% ee). Surprisingly, naphthylene sulfonamide-derived ligands gave poor conversions and no enantioselectivity under identical conditions (entries 3–4). Given these results, we selected the bis(toluenesulfonamido) boron species (entry 1) as the optimal Lewis acid for further exploration of this reaction process.

Upon further optimization of the reaction conditions, we found that the use of $CHCl_3$ as solvent and a lower reaction temperature of –30 °C resulted in improved yields and selectivities (eq 7). Under these conditions, allyl morpholine reacts with propionyl chloride in the presence of the boron perchlorate complex **16** to give the Claisen adduct **14** in 88% ee (74% isolated yield). These conditions were employed in reactions to examine the scope of this second-generation enantioselective acyl-Claisen methodology.

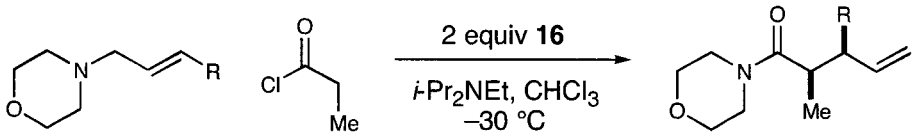


Evaluation of Reaction Scope

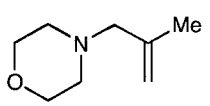
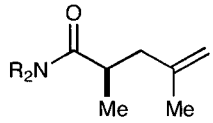
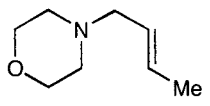
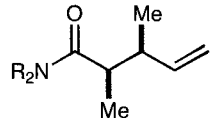
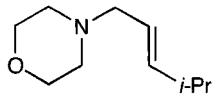
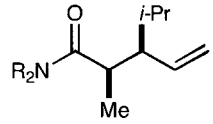
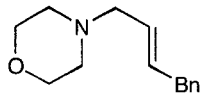
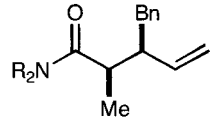
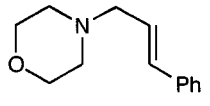
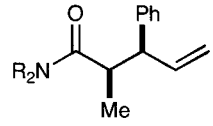
The scope of this methodology was investigated by Dr. Sung-Gon Kim. Table 4 summarizes the results of experiments probing the range of alkyl- and aryl-substituted allyl morpholine structures tolerated in the reaction. In accord with the results of our first-generation magnesium-promoted asymmetric acyl-Claisen rearrangement, a variety of alkyl-substituted morpholines rearrange with good levels of enantio- and diastereocontrol (entries 1–4, 86–92% ee, >99:1 *syn*:*anti*). The enantioselectivity of the reaction increases slightly with increasing steric bulk of the alkyl substituent. However, carbocation-stablizing

substituents had a deleterious effect on the rearrangement, and reaction of cinnamyl morpholine resulted in decomposition of the morpholine substrate (entry 5).

Table 4. Enantioselective acyl-Claisen rearrangement of representative alkyl- and aryl-substituted allyl morpholines.



(8)

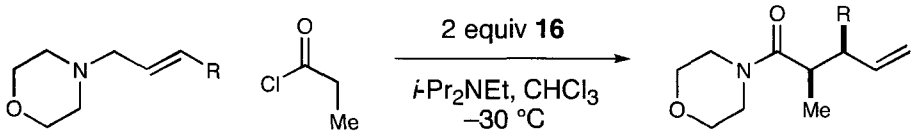
entry	amine	product[a]	% yield	*syn*:*anti*[b]	% ee[c]
1			66	--	86
2[d]			81	>99:1	91
3[d]			84	>99:1	92
4[d]			83	>99:1	90
5			0[e]	--	--

[a] NR_2 = *N*-morpholine. [b] Product ratios determined by GLC using a Bodman CC1701 column. [c] Enantiomeric excess determined by chiral HPLC or GLC. [d] Reaction conducted using *c*-Hex_2NMe as amine base. [e] Substrate decomposition observed.

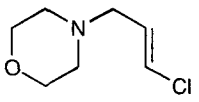
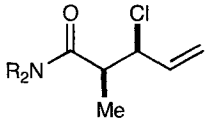
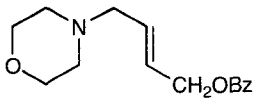
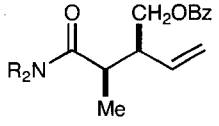
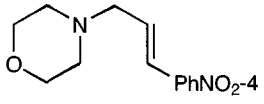
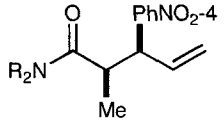
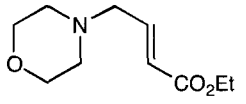
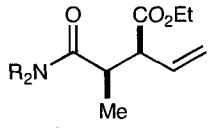
Heteroatom-substituted allyl morpholine substrates were also investigated (Table 5). As demonstrated by entry 1, halogen-substituted allyl morpholines react successfully, providing the β-chloro-substituted amide in 93% ee (>99:1 *syn*:*anti*, 77% yield) without any observable products of β-elimination. Although cinnamyl morpholine decomposes under

the reaction conditions, the electron-poor *p*-nitrocinnamyl derivative rearranges efficiently, providing the expected Claisen adduct in 84% yield and 90% ee (entry 3). Finally, the ester-substituted allyl morpholine substrate shown in entry 4 reacts sluggishly, requiring higher temperatures for reasonable reaction times, and consequently providing the desired Claisen product in diminished enantioselectivity (entry 4, 79% ee), albeit with excellent diastereoselectivity.

Table 5. Enantioselective acyl-Claisen rearrangement of representative heteroatom-functionalized allyl morpholines.



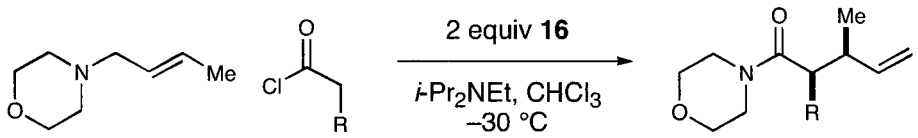
(9)

entry	amine	product[a]	% yield	*syn*:*anti*[b]	% ee[c]
1			77	>99:1	93
2			72	>99:1	87
3			90	>99:1	90
4[d]			45	>99:1	79

[a] NR_2 = *N*-Morpholine. [b] Product ratio determined by GLC using a Bodman CC1701 column. [c] Enantiomeric excess determined by chiral GLC or HPLC. [d] Reaction performed at –10 °C.

In accord with our design plan, a range of acid chlorides participate in this reaction and rearrange with moderate to good levels of enantioselectivity (Table 6). As demonstrated by the results of entries 2–4, a variety of alkyl-substituted acid chlorides participate in the reaction, although the enantioselectivity of the process seems to decrease as the bulk of the alkyl substituent increases (entry 2, R = Me, 91% ee; entry 3, R = Et, 84% ee; entry 4, R = Bn, 74% ee; entry 5, R = Ph, 10% ee). Acetyl chloride gave only von Braun fragmentation products.

Table 6. Enantioselective acyl-Claisen rearrangement with representative alkyl- and aryl-substituted acid chlorides.



(10)

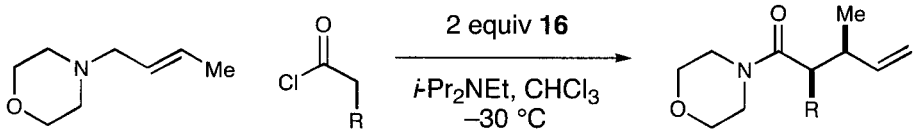
entry	R	% yield	*syn:anti*[a]	% ee[b]
1	H	--[c]	--	--
2	Me	81	>99:1	91
3[d]	Et	71	>99:1	84
4[d]	Bn	44	97:3	74
5	Ph	71	99:1	10

[a] Product ratios determined by GLC using a Bodman CC1701 column. [b] Enantiomeric excess determined by chiral HPLC or GLC. [c] Allyl morpholine decomposition observed. [d] Reaction conducted using *c*-Hex_2NMe as amine base.

Heteroatom-substituted acid chlorides were also assayed. Benzyloxyacetyl chloride, which proved to be the optimal acid chloride for the magnesium-promoted chemistry described in Chapter 4, gave poor results under these conditions; the powerful Lewis acidity of the boron perchlorate Lewis acid **11** facilitated cleavage of the benzyl group, and the resulting α-hydroxyamide product was isolated with only 18% ee (entry 1). The Claisen

products resulting from rearrangement of α-phenoxy-derived acid chlorides, which are not susceptible to a similar fragmentation process, were formed in higher ee (entries 2–3, 53–69% ee). As evidenced by entries 4–5, reasonable levels of stereocontrol could be achieved in rearrangements that produce α-halogenated products (entry 4, R = Cl, 80% ee; entry 5, R = Br, 79% ee). These results establish that this new boron Lewis acid provides a promising chiral environment for the further development of a general enantioselective Claisen rearrangement.

Table 7. Enantioselective acyl-Claisen rearrangement of representative heteroatom-substituted acid chlorides.



(11)

entry	R	% yield	*syn:anti*[a]	% ee[b]
1	OBn	55[c]	97:3	18
2[d]	OPh	84	92:8	69
3[d]	OPhCl-4	69	98:2	53
4	SPh	75	>99:1	77
5[d]	Cl	78	>99:1	80
6[e]	Br	74	99:1	79

[a] Product ratios determined by GLC using a Bodman CC1701 column. [b] Enantiomeric excess determined by chiral HPLC or GLC. [c] The debenzylated α-hydroxyamide (R = OH) was isolated. [d] Reaction conducted using *c*-Hex_2NMe as amine base. [e] The acid halid used in this reaction was bromoacetyl bromide.

Stereochemical Model

The transition state geometry about the Lewis acidic center of boron halide-mediated Lewis acidic processes can be either tetrahedral (**17**)[10] or trigonal (**18**),[6] depending on whether the counterion is dissociated or covalently bound to the boron center (Figure 3).[11] While the neutral trigonal species should possess greater Lewis acidicty than the anionic tetrahedral *ate* complex, boron-halogen bonds are generally very strong (B-Cl = 128 kcal /mol),[12] and dissociation of the halide counterion could be energetically prohibitive. However, in our new enantioselective acyl-Claisen methodology, the perchlorate and triflate counterions that provide optimal results are excellent leaving groups and should dissociate easily from boron. Indeed, addition of 2 equiv $NaClO_4$ results in slower reaction rates without significantly impacting the enantioselectiivty of the rearrangement, which is consistent with a mechanism requiring dissociation of the perchlorate counterion prior to the rate-limiting rearrangement event. Therefore, we speculate that the boron center likely adopts a trigonal geometry in the transition state of the sigmatropic event.

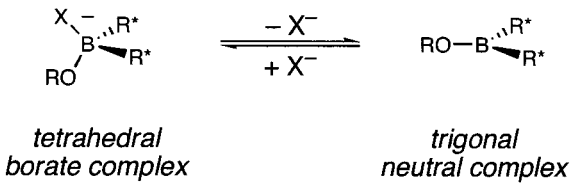


Figure 3. Tetrahedral and trigonal geometries for boron Lewis acids.

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10. For example: (a) Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794. (b) Hawkins, J. M.; Loren, S.; Nambu, M. *J. Am. Chem. Soc.* **1994**, *116*, 1657.

11. Corey has investigated divergent stereochemical consequences from the trigonal and tetrahedral geometries of boron Lewis acids in the context of the aldol reaction: Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976.

12. Barrow, R. F. *Trans. Faraday Soc.* **1960**, *56*, 962.

Based on this assumption, we have proposed a preliminary transition state model based on PM3 semiempirical calculations to explain the observed sense of stereoinduction. As shown in Figure 4, the lowest energy structure computed for complex **16** displays an attractive π–π interaction between the aryl groups of the sulfonamide substituent and the stien backbone. In this conformation, the *re* face of a bound enolate is effectively shielded by one of the oxygen atoms of the sulfonamide, leaving the *si* face open for rearrangement. An attempt to enforce rearrangement from the *si* face forces the sulfonamide substituent to rotate 107° out of alignment, disrupting the attractive π–π interaction. The sense of enantioenduction predicted by this model is consistent with the observed outcome.

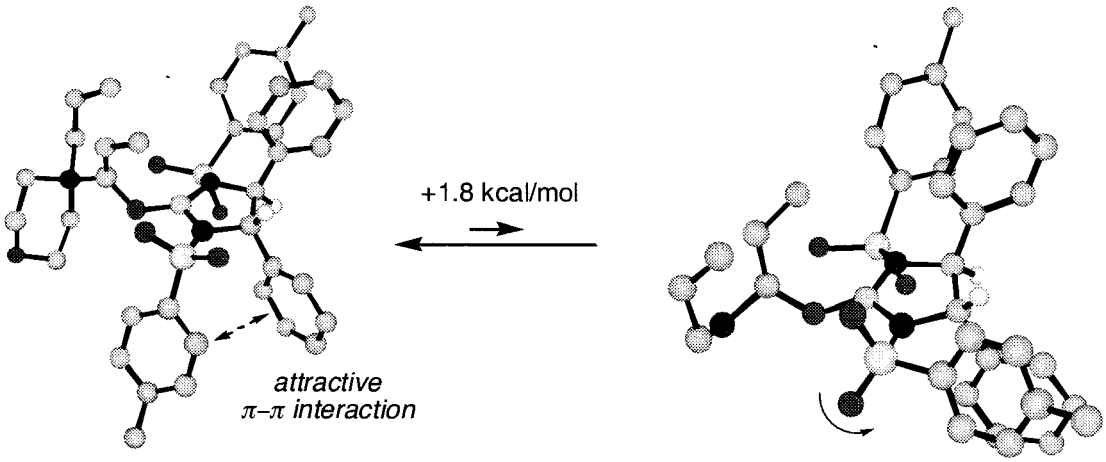
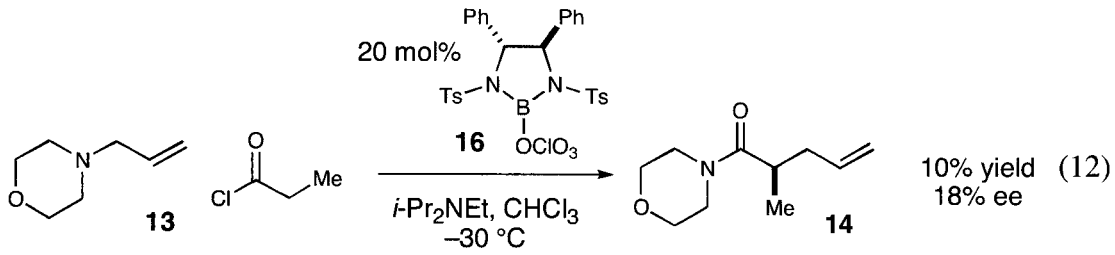


Figure 4. Preliminary rationale for the observed sense of stereoinduction.[13]

13. The opposite antipode of the ligand is shown.

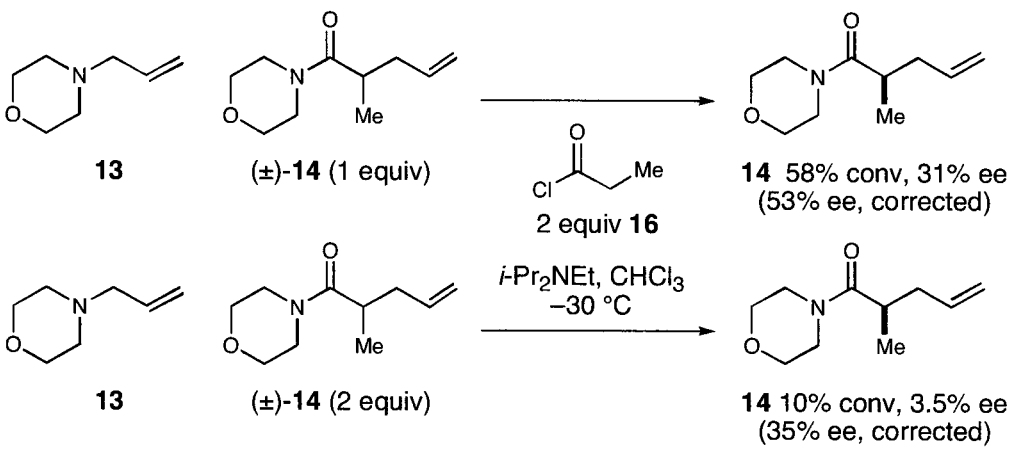
Limitations of the Methodology

At present, stoichiometric quantities of the Lewis acid promoter are required for optimal yields and levels of enantioselectivity. While the reaction of allyl morpholine and propionyl chloride proceeds in the presence of 2 equiv **16** under our optimized conditions to give the rearranged product in 88% ee and 74% yield (eq 7), the reaction gives dramatically poorer results when the stoichiometry of the Lewis acid is reduced to 20 mol% (eq 12).



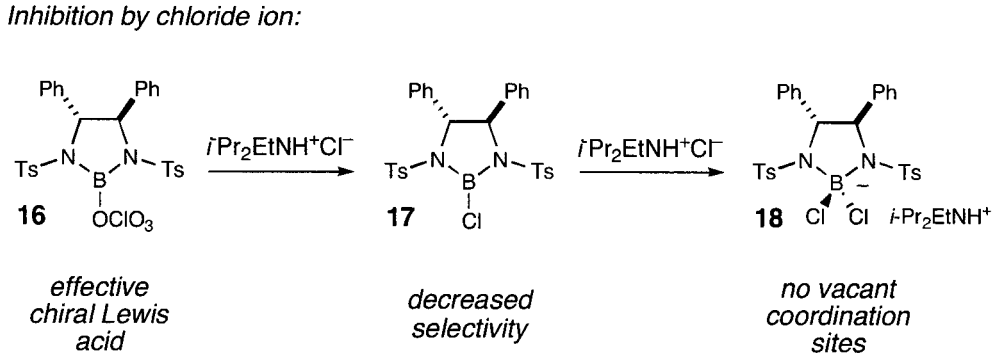
We speculate that there are two key reasons that explain the finding that **16** does not serve as a competent Claisen catalyst in substoichiometric quantities. First, the catalyst suffers from product inhibition. As outlined in Scheme 2, the progress of the reaction is impeded by the addition of the product to the reaction mixture. When conducted in the presence of 1 equiv of racemic **14**, the reaction proceeds to 58% conversion. Amide **14** is isolated from the reaction in 31% ee, indicating that the product formed in the course of the reaction is generated in 53% ee. Conducting the reaction in the presence of 2 equiv of **14** resulted in even poorer results (10% conversion, 35% ee).

Scheme 2



Second, we speculate that the ammonium chloride salt generated from dehydrohalogenation of the acid chloride can inhibit the reaction by participating in a salt metathesis reaction with the boron perchlorate Lewis acid (Scheme 3). As demonstrated by the results summarized in Table 1, the boron chloride salt **17** is a less effective promoter of the acyl-Claisen rearrangement. Furthermore, in the presence of an excess of ammonium chloride, the vacant coordination site on boron in **17** can accept a second halide ligand to afford the boron *ate* complex **18**, which is coordinatively saturated and cannot act as a Lewis acid. A competent acyl-Claisen catalyst based on this system, therefore, will likely require a method of removing chloride ion from the solution. Experiments are underway in our group to explore this possibility.

Scheme 3



Conclusion

Our investigations of a second-generation strategy towards an enantioselective acyl-Claisen rearrangement have resulted in the discovery that stilbenediamine-derived boron Lewis acid **16** is an effective enantioselective promoter for acyl-Claisen rearrangements involving propionyl choride. In analogy to the magnesium-ArBox-promoted variant disclosed in Chapters 3–4, this boron-mediated process enables the rearrangement of a variety of allyl morpholine substrates with good enantiocontrol. In addition, bidentate chelation is not an essential criterion for effective control of transition state geometry, and a range of alkyl-, aryl-, and heteroatom-substituted acid chlorides participate in this reaction with moderate to good levels of enantioselectivity. This new methodology provides convenient access to complex, stereochemically dense acyclic motifs and represents an important step towards the development of the first enantioselective catalytic Claisen rearrangement of general utility.

Experimental Section

General Information. All non-aqueous reactions were performed using flame- or oven-dried glassware under an atmosphere of dry nitrogen. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. diisopropylethylamine, dicyclohexylmethylamine, dichloromethane, and chloroform were distilled from calcium hydride prior to use. Air-sensitive solids were dispensed in an inert atmosphere glovebox. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or $KMnO_4$ stain.

Melting points were determined on a Tomas Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^1H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin-Elmer 1600 Series spectrometer using NaCl salt plates,

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1. Perrin, D. D.; Armarego, W. L. F. *Purificaion of Laboratory Chemicals;* 3rd ed., Pregamon Press, Oxford, 1988.

2. Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.

and reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral Facility. Optical rotations were recorded on a Jasco P-1010 polarimeter (WI lamp, 589 nm). Gas chromatography was performed on Hewlett-Packard 5890A gas chromatograph equipped with a split-mode capillary injection system and flame ionization detectors using the following columns: Bodman Chiraldex Γ-TA (30 m x 0.25 mm). HPLC analysis was performed on a Hewlett-Packard 1100 Series HPLC at 254nm using the following Chiralcel columns: OD-H (25 cm) and OD guard (5 cm), AD (25 cm) and AD guard (5 cm).

Bis(sulfonamide) ligands. (*R*,*R*)-Bis(3,5-ditrifluoromethyl-benzenesulfonyl)-1,2-diphenyl-1,2-diaminoethane[3] and (*R*,*R*)-bis(4-methylbenzene-sulfonyl)-1,2-diphenyl-1,2-diaminoethane[4] were synthesized as previously described and were spectroscopically identical in all respects to the reported materials. The syntheses of other bis(sulfonamide) ligands were accomplished analogously by condensation of the appropriate diamine with a sulfonyl chloride.

(*R*,*R*)-2-Bromo-4,5-diphenyl-1,3-bis-(toluene-4-sulfonyl)-[1,3,2]diaza-borolidine (16). In a flame-dried 250 mL round-bottomed Schlenk flask was placed (*R*,*R*)-bis(4-methylbenzene-sulfonyl)-1,2-diphenyl-1,2-diaminoethane (2.28g, 4.38 mmol). The flask was sealed with a rubber septum and then evacuated and flushed three times with nitrogen. The flask was then charged with 50 mL dry CH_2Cl_2. A 1.0 M solution of boron tribromide in hexanes (8.8 mL, 8.8 mmol) was added by syringe, and the reaction mixture

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3. Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976.

4. Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xing, Y.J. *J. Am. Chem. Soc.* **1989**, *111*, 5493.

was stirred at 23 °C for 24 h. The flask was immersed in a water bath, and the solvent and residual boron compounds were carefully removed under reduced pressure through a sodium hydroxide trap. After admission of nitrogen, the flask was charged with 20 mL dry CH_2Cl_2, and the suspension was stirred until the solution became homogenous. The solvent was removed under reduced pressure, and the residue was dried under vacuum for 8 h to provide an orange amorphous solid in 99% yield (2.63 g, 4.32 mmol). This material was used in acyl-Claisen rearrangements without further purification.

General Procedure A. A dry flask in an inert atmosphere glovebox was charged with **16** and anhydrous $AgClO_4$. The flask was sealed with a rubber septum and removed from the glovebox. $CHCl_3$ (1 mL) was introduced by syringe, and the resulting pale yellow mixture was stirred vigorously for 1 h under nitrogen. The resulting mixture was take up in a disposable 2.5 mL syringe, which was then fitted with an Acrodisc® PTFE syringe filter and an 18 gauge disposible needle. The filtered solution was added directly to a solution of allyl morpholine (0.2 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was then treated with *i*-Pr_2NEt or Cy_2MeN, and cooled to –30 °C. The solution was stirred for 10 min before acid chloride was added dropwise over 0.5 min. After 18 h at –30 °C, the reaction mixture was poured onto a mixture of EtOAc (5 mL) and 20% sodium potasium tartrate solution (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with saturated aq. NaCl (50 mL), dried (Na_2SO_4), and concentrated by rotory evaporation. The resulting residue was purified by silica gel chromatography to afford the title compounds and recovered *R,R*)-bis(4-methylbenzene-sulfonyl)-1,2-diphenyl-1,2-diaminoethane.

General Procedure B. A dry flask in an inert atmosphere glovebox was charged with **16** and anhydrous $AgClO_4$. The flask was sealed with a rubber septum and removed

from the glovebox. $CHCl_3$ (1 mL) was introduced by syringe, and the resulting pale yellow mixture was stirred vigorously for 1 h under nitrogen. The resulting mixture was take up in a disposable 2.5 mL syringe, which was then fitted with an Acrodisc® PTFE syringe filter and an 18 gauge disposible needle. The filtered solution was added directly to a solution of allyl morpholine (0.2 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was then treated with *i*-Pr_2NEt or Cy_2MeN, and cooled to –30 °C. The solution was stirred for 10 min before a solution of the acid chloride in $CHCl_3$ was added by syringe pump over 12 h. After addition was complete, the reaction was stirred 6 h at –30 °C then quenched by pouring onto a mixture of EtOAc (5 mL) and 20% sodium potasium tartrate solution (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with saturated aq. NaCl (50 mL), dried (Na_2SO_4), and concentrated by rotory evaporation. The resulting residue was purified by silica gel chromatography to afford the title compounds and recovered *R,R*)-bis(4-methylbenzene-sulfonyl)-1,2-diphenyl-1,2-diaminoethane.

(2*R*)-*N*-(2-Methyl-4-pentenoyl)-morpholine (14). Prepared by general procedure A from *N*-allyl morpholine (25 mg, 0.20 mmol) and propionyl chloride (21 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and *i*-Pr_2NEt (53 μL, 0.30 mmol) to afford the product as a colorless oil in 74% yield (27 mg); 88% ee. ^1H NMR, ^{13}C NMR, IR, and mass spectral data for this compound were consistent with those previously reported.[5] $[\alpha]_D^{23} = -21.2$ (c = 0.9, $CHCl_3$). The enantiomeric purity was determined by GC with a Bodman Chiraldex Γ-TA column (100 °C, 2.0 mL/min, 25 psi); t_r = 37.1 min and 39.7 min.

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5. Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726.

(2*R*)-*N*-(2-Methyl-4-methyl-4-pentenoyl)-morpholine (Table 4, entry 1). Prepared by general procedure A from *N*-methallylmorpholine (28 mg, 0.20 mmol) and propionyl chloride (21 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and *i*-Pr_2NEt (53 μL, 0.30 mmol) to afford the product as a colorless oil in 66% yield (26 mg); 86% ee. IR (thin film) 2968, 2918, 2856, 1643, 1433, 1233, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.78 (s, 1H, $CH_2CCH_3=CH_2$), 4.68 (s, 1H, $CH_2CCH_3=CH_2$), 3.53-3.69 (m, 8H, $N(CH_2CH_2)_2$), 2.80-2.91 (m, 1H, $CHCH_3$), 2.41 (dd, *J* = 7.2, 14.7 Hz, 1H, $CH_2CCH_3=CH_2$), 2.07 (dd, *J* = 7.2, 14.1 Hz, 1H, $CH_2CCH_3=CH_2$), 1.72 (s, 3H, $CH_2CCH_3=CH_2$), 1.11 (d, *J* = 6.6 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 143.2, 112.1, 67.3, 67.1, 46.3, 42.4, 42.0, 33.6, 23.1, 17.7; $[\alpha]_D^{23}$ = -6.8 (c = 1.1, $CHCl_3$). The enantiomeric purity was determined by GC with a Bodman Chiraldex Γ-TA column (115 °C, 2.0 mL/min, 25 psi); t_r = 36.5 min and 42.3 min.

(2*R*,3*S*)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine (Table 4, entry 2). Prepared by general procedure A from (*E*)-*N*-but-2-enyl morpholine (28 mg, 0.20 mmol) and propionyl chloride (21 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to afford the product as a colorless oil in 81% yield (32 mg); *syn*:*anti* >99:1 *syn* 91% ee. ^1H NMR, ^{13}C NMR, IR, and mass spectral data for this compound were consistent with those previously reported.[5] $[\alpha]_D^{22}$ = -39.8 (c = 1.3, $CHCl_3$). The enantiomeric purity and diastereomer ratio was determined by GC with a Bodman Chiraldex Γ-TA column (115 °C, 2.0 mL/min, 25 psi); *syn* isomer, t_r = 32.7 min and 39.5 min; *anti* isomer, t_r = 41.9 min and 43.0 min.

(2*R*,3*S*)-*N*-(2-Methyl-3-isopropyl-4-pentenoyl)-morpholine (Table 4, entry 3). Prepared by general procedure A from (*E*)-*N*-4-methylpent-2-enyl morpholine (34 mg, 0.20 mmol) and propionyl chloride (23 μL, 0.26 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to afford the product as a colorless oil in 84% yield (38 mg); *syn*:*anti* >99:1 *syn* 92% ee. *Syn* isomer: IR (thin film) 2961, 2925, 28541641, 1432, 1267, 1250, 1117, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.63 (ddd, *J* = 10.2, 17.1, 20.1 Hz, 1H, C**H**=CH_2), 5.03 (ddd, *J* = 2.4, 10.2, 20.1 Hz, 2H, CH=C**H**$_2$), 3.50-3.66 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.81 (dq, *J* = 6.6, 9.6 Hz, 1H, C**H**CH_3), 2.20 (ddd, *J* = 3.9, 9.6, 17.1 Hz, 1H, C**H**CH=CH_2), 1.81-2.02 (m, 1H, C**H**$(CH_3)_2$), 1.10 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$), 0.83 (dd, *J* = 6.6, 21.6 Hz, 6H, CH(C**H**$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 136.6, 117.8, 67.3, 67.0, 53.2, 46.6, 42.3, 36.7, 27.0, 22.0, 16.8, 16.1; $[\alpha]_D^{23}$ = +4.5 (c = 1.6, $CHCl_3$). The enantiomeric purity and diastereomer ratio was determined by GC with a Bodman Chiraldex Γ-TA column (125 °C, 1.7 mL/min, 23 psi); *syn* isomer, t_r = 37.5 min and 40.0 min; *anti* isomer, t_r = 41.5 min and 43.0 min.

(2*R*,3*S*)-*N*-(3-Benzyl-2-methyl-4-pentenoyl)-morpholine (Table 4, entry 4). Prepared by general procedure A from (*E*)-*N*-4-phenylbut-2-enyl morpholine (44 mg, 0.20 mmol) and propionyl chloride (23 μL, 0.26 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to afford the product as a white solid in 83% yield (45 mg); *syn*:*anti* >99:1 *syn* 90% ee. *Syn* isomer: mp 69-70 °C; IR (thin film) 2967, 2931, 2856, 1641, 1433, 1267, 1227, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10-7.29 (m, 5H, CH_2C_6**H**$_5$), 5.81 (ddd, *J* = 8.1, 10.2, 16.8 Hz, 1H, C**H**=CH_2), 4.90 (ddd, *J* = 1.8, 10.2, 16.8 Hz, 2H, CH=C**H**$_2$), 3.38-3.66 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.89-2.96 (m, 1H, C**H**CH_3), 2.71-2.75 (m, 1H, C**H**CH=CH_2), 2.50-2.60 (m, 2H, C**H**$_2C_6H_5$), 1.19 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 140.3, 139.7, 129.4, 128.3, 126.1, 116.5, 67.3, 67.0, 49.2, 46.5, 42.3, 38.6, 38.0, 15.7. The

enantiomeric purity was determined by HPLC with a Chiralcel AD column and AD guard column (3% *i*-PrOH:hexanes, 1 mL/min flow); t_r = 17.7 min and 22.8 min.

(2*R*,3*R*)-*N*-(3-Chloro-2-methyl-4-pentenoyl)-morpholine (Table 5, entry 1). Prepared by general procedure A from (*E*)-*N*-(3-chloro-2-propenyl) morpholine (32 mg, 0.20 mmol) and propionyl chloride (21 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to afford the product as a colorless oil in 77% yield (33 mg); *syn*:*anti* >99:1 *syn* 93% ee. ^1H NMR, ^{13}C NMR, IR, and mass spectral data for this compound were consistent with those previously reported.[5] $[\alpha]_D^{23}$ = -42.8 (c = 1.5, $CHCl_3$). The enantiomeric purity and diastereomer ratio was determined by GC with a Bodman Chiraldex Γ-TA column (135 °C, 1.7 mL/min, 24 psi); *syn* isomer, t_r = 26.3 min and 32.8 min; *anti* isomer, t_r = 28.9 min and 31.0 min.

(2*R*,3*S*)-*N*-(3-(Benzoyloxymethyl)-2-methyl-4-pentenoyl)-morpholine (Table 5, entry 2). Prepared by general procedure B from (*E*)-*N*-(4-benzoyloxy-2-butenyl)morpholine (104 mg, 0.40 mmol) and propionyl chloride (480 μL, 1.0 M solution in $CHCl_3$, 0.48 mmol), using $AgClO_4$ (168 mg, 0.80 mmol), (*R,R*)-bromoborane reagent **16** (488 mg, 0.80 mmol), and *i*-Pr_2NEt (106 μL, 0.60 mmol) to afford the product as a colorless oil in 72% yield (92 mg); *syn*:*anti* >99:1 *syn* 87% ee. *Syn* isomer: IR (thin film) 2969, 2923, 2857, 1718, 1641, 1451, 1273, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-8.02 (m, 5H, $CH_2OCOC_6\mathbf{H}_5$), 5.89 (ddd, *J* = 8.1, 10.5, 17.1 Hz, 1H, $C\mathbf{H}{=}CH_2$), 5.14 (ddd, *J* = 1.2, 10.5, 17.1 Hz, 2H, $CH{=}C\mathbf{H}_2$), 4.37-4.48 (m, 2H, $C\mathbf{H}_2OCOC_6H_5$), 3.51-3.65 (m, 8H, $N(C\mathbf{H}_2C\mathbf{H}_2)_2$), 2.91-3.00 (m, 1H, $C\mathbf{H}CH_3$), 2.82-2.86 (m, 1H, $C\mathbf{H}CH{=}CH_2$), 1.20 (d, *J* = 6.9 Hz, 3H, $CHC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 166.4, 137.0, 133.2, 130.3, 129.7, 128.6, 117.9, 67.3, 67.0, 65.5, 46.6, 46.2, 42.4, 36.5, 15.7; $[\alpha]_D^{23}$ = -30.6 (c = 1.0,

$CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel AD column and AD guard column (5% *i*-PrOH:hexanes, 1 mL/min flow); t_r = 25.5 min and 27.4 min.

(2*R*,3*R*)-*N*-(2-Methyl-3-(p-nitrophenyl)-4-pentenoyl)-morpholine (Table 5, entry 3). Prepared by general procedure A from (*E*)-*N*-4-phenylbut-2-enyl morpholine (50 mg, 0.20 mmol) and propionyl chloride (21 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **2#** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to afford the product as a colorless oil in 87% yield (89 mg); *syn*:*anti* >99:1 *syn* 90% ee. *Syn* isomer: IR (thin film) 3081, 2970, 2923, 2858, 1637, 1529, 1463, 1435, 1352, 1245, 1220, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.06-8.13 (m, 2H, $CH_2C_6\mathbf{H}_4NO_2$), 7.47-7.57 (m, 2H, $CH_2C_6\mathbf{H}_4NO_2$), 5.98 (ddd, *J* = 7.8, 10.5, 18.0 Hz, 1H, $C\mathbf{H}{=}CH_2$), 5.04 (ddd, *J* = 1.2, 10.5, 18.0 Hz, 2H, $CH{=}C\mathbf{H}_2$), 3.82 (dd, 1H, *J* = 3.6, 7.8 Hz, $C\mathbf{H}CH{=}CH_2$), 3.58-3.74 (m, 8H, $N(C\mathbf{H}_2C\mathbf{H}_2)_2$), 3.10 (dq, 1H, *J* = 3.6, 6.9 Hz, $C\mathbf{H}CH_3$), 0.91 (d, *J* = 6.9 Hz, 3H, $CHC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 148.6, 144.0, 138.8, 135.4, 129.7, 123.0, 122.0, 117.0, 67.3, 67.0, 53.0, 46.6, 42.6, 40.0, 16.9; $[\alpha]_D^{23}$ = -53.4 (c = 1.9, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel AD column and AD guard column (5% *i*-PrOH:hexanes, 1 mL/min flow); t_r = 35.5 min and 42.0 min.

(2*R*,3*R*)-*N*-(3-(Ethoxycarbonyl)-2-methyl-4-pentenoyl)-morpholine (Table 5, entry 4). Prepared by general procedure A from (*E*)-ethyl 4-morpholinocrotonate (40 mg, 0.20 mmol) and propionyl chloride (21 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and *i*-Pr_2NEt (53 μL, 0.30 mmol) to afford the product as a colorless oil in 45% yield (23 mg); *syn*:*anti* >99:1 *syn* 79% ee. *Syn* isomer: IR (thin film) 2977, 2935, 2868, 1731, 1643, 1435, 1252, 1173, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.80 (ddd, *J* = 8.7, 10.5, 17.1 Hz, 1H, $C\mathbf{H}{=}CH_2$), 5.16 (ddd, *J* = 1.8, 10.5, 17.1 Hz, 2H, $CH{=}C\mathbf{H}_2$), 4.11-4.22 (m, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.49-3.658 (m, 8H,

$N(CH_2CH_2)_2$), 3.38 (dd, J = 8.7, 9.0, Hz, 1H, CHCH=CH_2), 3.10-3.20 (m, 1H, $CHCH_3$), 1.27 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.13 (d, J = 7.2 Hz, 3H, $CHCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 172.7, 134.2, 119.0, 67.3, 67.1, 61.1, 53.9, 46.6, 42.5, 38.0, 16.7, 14.6; $[\alpha]_D^{23}$ = -52.1 (c = 1.0, $CHCl_3$). The enantiomeric purity was determined by GC with a Bodman Chiraldex Γ-TA column (130 °C, for 40 min, then 1 °C/min, 1.7 mL/min, 23 psi); t_r = 57.9 min and 58.7 min.

(2*R*,3*R*)-*N*-(2-Ethyl-3-methyl-4-pentenoyl)-morpholine (Table 6, entry 3). Prepared by general procedure A from (*E*)-*N*-but-2-enyl morpholine (28 mg, 0.20 mmol) and butyryl chloride (25 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to afford the product as a colorless oil in 71% yield (30 mg); *syn*:*anti* >99:1 *syn* 84% ee. *Syn* isomer: IR (thin film) 2945, 2928, 2857, 1637, 1442, 1271, 1225, 1117 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (ddd, J = 7.8, 10.5, 17.7 Hz, 1H, CH=CH_2), 5.10 (ddd, J = 1.8, 10.5, 17.7 Hz, 2H, CH=CH_2), 3.40-3.67 (m, 8H, $N(CH_2CH_2)_2$), 2.35-2.43 (m, 1H, $CHCH_2CH_3$), 1.44-1.70 (m, 2H, CHCHCH=CH_2), 0.97 (d, J = 6.0 Hz, 3H, $CHCH_3$), 0.78 (dd, J =3.3, 7.8 Hz, 3H, $CHCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 142.1, 114.2, 67.5, 67.1, 47.9, 46.7, 42.3, 40.4, 23.1, 17.2, 12.6; $[\alpha]_D^{23}$ = -9.90 (c = 1.2, $CHCl_3$). The enantiomeric purity and diastereomer ratio was determined by GC with a Bodman Chiraldex Γ-TA column (120 °C, 2.0 mL/min, 25 psi); *syn* isomer, t_r = 28.5 min and 29.7 min; *anti* isomer, t_r = 36.6 min and 37.5 min.

(2*S*,3*R*)-*N*-(2-Benzyl-3-methyl-4-pentenoyl)-morpholine (Table 6, entry 4). Prepared by general procedure A from (*E*)-*N*-but-2-enyl morpholine (28 mg, 0.20 mmol) and hydrocinnamoyl chloride (36 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to

afford the product as a white solid in 44% yield (24 mg); *syn*:*anti* 97:3 *syn* 74% ee. *Syn* isomer: mp 69-70 °C; IR (thin film) 2960, 2917, 2857, 1622, 1460, 1266, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.14-7.28 (m, 5H, $CH_2C_6\mathbf{H}_5$), 5.77 (ddd, *J* = 7.8, 10.5, 17.7 Hz, 1H, $C\mathbf{H}{=}CH_2$), 4.99 (ddd, *J* = 1.5, 10.5, 17.7 Hz, 2H, $CH{=}C\mathbf{H}_2$), 2.56-3.69 (m, 12H, $N(C\mathbf{H}_2C\mathbf{H}_2)_2$, $C\mathbf{H}C\mathbf{H}_2C_6H_5$, $C\mathbf{H}CH{=}CH_2$), 1.15 (d, *J* = 6.6 Hz, 3H, $CHC\mathbf{H}_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 141.7, 140.2, 129.3, 128.6, 126.5, 114.6, 67.1, 66.5, 49.2, 46.4, 42.2, 40.7, 37.2, 17.7; $[\alpha]_D^{23}$ = +28.7 (c = 1.0, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel ODH column and ODH guard column (1% *i*-PrOH:hexanes, 1 mL/min flow); t_r = 22.7 min and 26.5 min.

(2*S*,3*R*)-*N*-(3-Methyl-2-phenyl-4-pentenoyl)-morpholine (Table 6, entry 5). Prepared by general procedure A from (*E*)-*N*-but-2-enyl morpholine (28 mg, 0.20 mmol) and phenylacetyl chloride (32 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R*,*R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and $i\mathrm{Pr}_2\mathrm{NEt}$ (59 μL, 0.30 mmol) to afford the product as a white solid in 77% yield (40 mg); *syn*:*anti* 99:1 *syn* 10% ee. *Syn* isomer: mp 72-73 °C; IR (thin film) 2964, 2922, 2856, 1641, 1456, 1430, 1224, 1115 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08-7.33 (m, 5H, $CHC_6\mathbf{H}_5$), 5.91 (ddd, *J* = 7.2, 10.5, 17.4 Hz, 1H, $C\mathbf{H}{=}CH_2$), 5.04 (ddd, *J* = 1.2, 10.5, 17.4 Hz, 2H, $CH{=}C\mathbf{H}_2$), 3.36-3.69 (m, 8H, $N(C\mathbf{H}_2C\mathbf{H}_2)_2$), 3.02-3.18 (m, 2H, $C\mathbf{H}C\mathbf{H}CH_3$), 0.77 (d, *J* = 6.9 Hz, 3H, $CHC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 142.7, 138.2, 128.9, 128.7, 127.4, 114.3, 67.1, 66.7, 54.6, 46.6, 42.7, 40.5, 17.7; $[\alpha]_D^{22}$ = +2.35 (c = 1.7, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel AD column and AD guard column (5% *i*-PrOH:hexanes, 1 mL/min flow); t_r = 11.5 min and 12.4 min.

(2*R*,3*S*)-*N*-(3-Methyl-2-phenyloxy-4-pentenoyl)-morpholine (Table 7, entry 2). Prepared by the general procedure A from (*E*)-*N*-but-2-enyl morpholine (28 mg, 0.20

mmol) and phenyloxyacetyl chloride (33 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to afford the product as a white solid in 84% yield (46 mg); *syn*:*anti* 92:8 *syn* 69% ee. *Syn* isomer: mp 65-66 °C; IR (thin film) 2967, 2922, 2857, 1641, 1599, 1588, 1495, 1439, 1227, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.89-7.31 (m, 5H, $OC_6\mathbf{H}_5$), 5.80 (ddd, *J* = 8.4, 9.9, 17.1 Hz, 1H, $C\mathbf{H}{=}CH_2$), 5.12 (ddd, *J* = 1.5, 9.9, 17.1 Hz, 2H, $CH{=}C\mathbf{H}_2$), 4.57 (d, *J* = 9.0 Hz, 1H, $C\mathbf{H}OC_6H_5$), 3.34-3.85 (m, 8H, $N(C\mathbf{H}_2C\mathbf{H}_2)_2$), 2.70-2.84 (m, 1H, $C\mathbf{H}CH_3$), 1.24 (d, *J* = 6.6 Hz, 3H, $CHC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 157.7, 138.5, 129.9, 121.9, 116.5, 115.1, 83.8, 67.3, 67.0, 46.1, 43.2, 42.1, 17.6; $[\alpha]_D^{23}$ = -12.2 (c = 2.0, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel ODH column and ODH guard column (3% *i*-PrOH:hexanes, 1 mL/min flow); t_r = 11.2 min and 12.1 min.

(2*R*,3*S*)-*N*-(3-Methyl-2-*p*-chlorophenyloxy-4-pentenoyl)-morpholine (Table 7, entry 3). Prepared by general procedure A from (*E*)-*N*-but-2-enyl morpholine (28 mg, 0.20 mmol) and *p*-chlorophenyloxyacetyl chloride (37 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and iPr_2NEt (59 μL, 0.30 mmol) to afford the product as a white solid in 86% yield (53 mg); *syn*:*anti* 97:3 *syn* 47% ee. *Syn* isomer: mp 85-86 °C; IR (thin film) 2968, 2924, 2857, 1642, 1595, 1491, 1439, 1232, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.81-7.24 (m, 4H, $OC_6\mathbf{H}_4Cl$), 5.78 (ddd, *J* = 8.1, 9.9, 17.1 Hz, 1H, $C\mathbf{H}{=}CH_2$), 5.12 (ddd, *J* = 1.2, 9.9, 17.1 Hz, 2H, $CH{=}C\mathbf{H}_2$), 4.50 (d, *J* = 9.0 Hz, 1H, $C\mathbf{H}OC_6H_4Cl$), 3.36-3.74 (m, 8H, $N(C\mathbf{H}_2C\mathbf{H}_2)_2$), 2.64-2.82 (m, 1H, $C\mathbf{H}CH_3$), 1.21 (d, *J* = 6.6 Hz, 3H, $CHC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2, 156.3, 138.5, 130.7, 128.9, 116.7, 115.6, 83.3, 67.3, 67.0, 46.0, 43.1, 41.7, 17.5; $[\alpha]_D^{23}$ = -46.0 (c = 1.5, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel ODH

column and ODH guard column (2% EtOH:hexanes, 1 mL/min flow); t_r = 15.2 min and 16.1 min.

(2*R*,3*S*)-*N*-(3-Methyl-2-phenylthio-4-pentenoyl)-morpholine (Table 7, entry 4). Prepared by general procedure A from (*E*)-*N*-but-2-enyl morpholine (28 mg, 0.20 mmol) and phenylthioacetyl chloride (36 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to afford the product as a white solid in 86% yield (50 mg); *syn*:*anti* >99:1 *syn* 72% ee. ^1H NMR, ^{13}C NMR, IR, and mass spectral data for this compound were consistent with those previously reported.[5] $[\alpha]_D^{23}$ = +68.4 (c = 2.0, $CHCl_3$). The enantiomeric purity was determined by HPLC with a Chiralcel ODH column and ODH guard column (1% *i*-PrOH:hexanes, 1 mL/min flow); t_r = 36.7 min and 43.2 min.

(2*R*,3*R*)-*N*-(2-Chloro-3-methyl-4-pentenoyl)-morpholine (Table 7, entry 5). Prepared by general procedure A from (*E*)-*N*-but-2-enyl morpholine (28 mg, 0.20 mmol) and chloroacetyl chloride (19 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R,R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to afford the product as a white solid in 78% yield (34 mg); *syn*:*anti* >99:1 *syn* 80% ee. *Syn* isomer: mp 47-48 °C; IR (thin film) 2969, 2925, 2858, 1655, 1458, 1439, 1276, 1234, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (ddd, *J* = 7.5, 10.2, 17.4 Hz, 1H, C**H**=CH_2), 5.12 (ddd, *J* = 2.4, 10.2, 17.4 Hz, 2H, CH=C**H**$_2$), 4.21 (d, *J* = 8.7 Hz, 1H, C**H**Cl), 3.46-3.79 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.90-3.02 (m, 1H, C**H**CH=CH_2), 1.24 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 138.9, 117.0, 67.0, 66.8, 58.5, 46.9, 43.0, 40.8, 17.0; $[\alpha]_D^{23}$ = -46.0 (c = 1.5, $CHCl_3$). The enantiomeric purity and diastereomer ratio was determined by GC with a Bodman Chiraldex Γ-TA column (135 °C, 1.7 mL/min, 24 psi); *syn* isomer, t_r = 23.0 min and 27.4 min; *anti* isomer, t_r = 28.7 min and 31.7 min.

(2*R*,3*R*)-*N*-(2-Bromo-3-methyl-4-pentenoyl)-morpholine (Table 7, entry 6). Prepared by general procedure A from (*E*)-*N*-but-2-enyl morpholine (28 mg, 0.20 mmol) and bromoacetyl bromide (21 μL, 0.24 mmol), using $AgClO_4$ (84 mg, 0.40 mmol), (*R*,*R*)-bromoborane reagent **16** (244 mg, 0.40 mmol), and Cy_2MeN (64 μL, 0.30 mmol) to afford the product as a white solid in 88% yield (46 mg); *syn*:*anti* >99:1 *syn* 76% ee. *Syn* isomer: mp 48-49 °C; IR (thin film) 2968, 2923, 2857, 1650, 1457, 1438, 1274, 1232, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (ddd, *J* = 7.2, 10.5, 17.4 Hz, 1H, C**H**=CH_2), 5.10 (dd, *J* = 10.5, 17.4 Hz, 2H, CH=C**H**$_2$), 4.20 (d, *J* = 9.0 Hz, 1H, C**H**Br), 3.42-3.76 (m, 8H, N(C**H**$_2$C**H**$_2$)$_2$), 2.94-3.05 (m, 1H, C**H**CH=CH_2), 1.26 (d, *J* = 6.6 Hz, 3H, CHC**H**$_3$)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 138.8, 117.0, 67.0, 66.6, 49.1, 47.0, 42.9, 40.5, 18.6; $[\alpha]_D^{23}$ = -50.7 (c = 2.0, $CHCl_3$). The enantiomeric purity and diastereomer ratio was determined by GC with a Bodman Chiraldex Γ-TA column (135 °C, 1.7 mL/min, 24 psi); *syn* isomer, t_r = 33.2 min and 37.6 min; *anti* isomer, t_r = 42.0 min and 45.8 min.

Determination of the absolute configuration of (2*R*,3*S*)-*N*-(2,3-Dimethyl-4-pentenoyl)-morpholine by Correlation with (2*R*,3*S*)-2,3-Dimethyl-4-pentenoic acid. A solution of (2*R*,3*S*)-*N*-(2,3-dimethyl-4-pentenoyl)-morpholine (16 mg, 81 μmol) in 1,2-DME (0.8 mL) and H_2O (0.8 mL) was placed in a 2 mL scintillation vial equipped with a magnetic stir bar. The solution was treated with iodine (52 mg, .203 μmol) and was stirred in the absence of light. After 30 min, the reaction was diluted with Et_2O (mL) and washed sequentially with 10% aqueous $Na_2S_2O_3$ (2 mL) and brine (2 mL). The resulting organic layer was dried (Na_2SO_4) and concentrated to give 4-iodomethyl-2,3-dimethyl-γ-butyrolactone as a yellow oil. The residue was dissolved in glacial AcOH (0.8 mL) and placed in a 2 mL scintillation vial equipped with a magnetic stir bar. The solution was treated with zinc dust (53 mg, 810 μmol) and stirred at 65 °C for 3 h. After allowing the reaction to cool to rt, 1 *N* HCl (aq) (2 mL) was added, and the mixture was extracted with

ether (5 x 2 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated to give a light pink oil that exhibited spectral data identical in all respects to those reported for (2*R*,3*S*)-2,3-dimethyl-4-pentenoic acid.[6] $[\alpha]_D$ (literature) = –48.9 (c = 1.0, $CHCl_3$); $[\alpha]_D$ (observed) = –29.9 (c = 1.0, $CHCl_3$).

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6. Tsunoda, T.; Sakai, M.; Sasaki, O.; Sako, Y.; Hondo, Y.; Ito, S. *Tetrahedron Lett.* **1992**, *33*, 1651.

Sample: tpyii92

P.O. # 1736

X-ray Structure Report

for

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204 Lewis Hall

3-8419

MacMillan

Thu Apr 1 1999

Introduction

The compound $C_{16}NO_2H_{20}$ crystallizes in the non-centrosymmetric space group $Pna2_1$ with four
molecules in the unit cell. The correct enantiomorph of the space group could not be determined. This ambiguity is inconsequential, however, as both enantiomorphs of the molecule are present in the space group regardless of the handedness of the space group.

The relative stereochemistry of the molecule is as expected. There are no unusually close intermolecular contacts.

-DLC

Experimental

Data Collection

A fragment of a colorless plate-like crystal of $C_{16}NO_2H_{20}$ having approximate dimensions of 0.35 x 0.30 x 0.12 mm was mounted on a quartz fiber using Paratone N hydrocarbon oil. All measurements were made on a SMART[10] CCD area detector with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix , obtained from a least-squares refinement using the measured positions of 99 reflections in the range $3.00 < 2\theta < 52.00°$ corresponded to a primitive orthorhombic cell with dimensions:

$$a = 10.343(2)\ \mathring{A}$$
$$b = 14.736(4)\ \mathring{A}$$
$$c = 9.399(2)\ \mathring{A}$$
$$V = 1432.5(6)\ \mathring{A}^3$$

For Z = 4 and F.W. = 258.34, the calculated density is 1.20 g/cm^3. Based on the systematic absences of:

$$0kl:\ k+l \neq 2n$$
$$h0l:\ h \neq 2n$$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$$Pna2_1\ (\#33)$$

The data were collected at a temperature of -135 $\pm$ 1°C. Frames corresponding to an arbitrary hemisphere of data were collected using ω scans of 0.3° counted for a total of 10.0 seconds per frame.

Data Reduction

Data were integrated by the program SAINT[11] to a maximum 2θ value of 52.3°. The data were corrected for Lorentz and polarization effects. Fourteen reflections with $\Delta I/\sigma I > 7$ were treated as outliers, resulting in 0.20% of the data being removed. Data were analyzed for agreement and possible absorption using XPREP[12]. An absorption correction was not necessary.

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in calculated idealized positions but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 1640

observed reflections ($I > 3.00\sigma(I)$) and 171 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.034$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2/\Sigma wFo^2)} = 0.037$$

The standard deviation of an observation of unit weight[4] was 1.37. The weighting scheme was based on counting statistics and included a factor (p = 0.030) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.12 and -0.13 $e^-/\AA^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2/(No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(6) Ibers, J. A. & Hamilton, W. C.; Acta Crystallogr., 17, 781 (1964).

(7) Creagh, D. C. & McAuley, W.J .; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, pages 219-222 (1992).

(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C.

Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

(10) SMART: Area-Detector Software Package, Siemens Industrial Automation, Inc.: Madison, WI, (1995)

(11) SAINT: SAX Area-Dectector Integration Program, V4.024; Siemens Industrial Automation, Inc.: Madison, WI, (1995)

(12) XPREP:(v 5.03) Part of the SHELXTL Crystal Structure Determination Siemens Industrial Automation, Inc.: Madison, WI, (1995)

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{16}NO_2H_{20}$
Formula Weight	258.34
Crystal Color, Habit	colorless, plates
Crystal Dimensions	0.35 X 0.30 X 0.12 mm
Crystal System	orthorhombic
Lattice Type	Primitive
Lattice Parameters	a = 10.343(2)$\AA$ b = 14.736(4) $\AA$ c = 9.399(2) $\AA$ V = 1432.5(6) $\AA^3$
Space Group	$Pna2_1$ (#33)
Z value	4
D_{calc}	1.198 g/cm^3
F_{000}	556.00
μ(MoKα)	14.08 cm^{-1}

B. Intensity Measurements

Diffractometer	SMART CCD
Radiation	MoKα (λ = 0.71069 $\AA$) graphite monochromated
Detector Position	60.00 mm
Exposure Time	10.0 seconds per frame.
Scan Type	ω (0.3 degrees per frame)
$2\theta_{max}$	52.3°

No. of Reflections Measured	Total: 6560 Unique: 1658 (R_{int} = 0.047)
Corrections	Lorentz-polarization

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	1640
No. Variables	171
Reflection/Parameter Ratio	9.59
Residuals: R; Rw; Rall	0.034 ; 0.037; 0.053
Goodness of Fit Indicator	1.37
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.12 $e^-/\mathring{A}^3$
Minimum peak in Final Diff. Map	-0.13 $e^-/\mathring{A}^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq}

atom	x	y	z	B_{eq}
O(1)	0.59157(14)	0.18906(10)	0.9976	2.55(4)
O(2)	0.90038(16)	0.13627(13)	0.6126(3)	3.53(5)
N(1)	0.77688(17)	0.16092(13)	0.8791(3)	2.27(5)
C(1)	0.7711(2)	0.35837(16)	1.3063(3)	2.31(6)
C(2)	0.6941(2)	0.38136(16)	1.4214(4)	2.61(6)
C(3)	0.7457(3)	0.42685(18)	1.5374(3)	3.28(7)
C(4)	0.8758(3)	0.44891(17)	1.5399(3)	3.49(7)
C(5)	0.9530(3)	0.42585(16)	1.4266(4)	3.23(7)
C(6)	0.9019(2)	0.38096(16)	1.3103(3)	2.74(6)
C(7)	0.7110(2)	0.31772(17)	1.1739(3)	2.57(6)
C(8)	0.6949(2)	0.39285(17)	1.0639(4)	2.71(6)
C(9)	0.7625(3)	0.40555(18)	0.9492(4)	3.61(7)
C(10)	0.7850(2)	0.23570(16)	1.1152(3)	2.36(6)
C(11)	0.8044(2)	0.16220(16)	1.2303(4)	2.98(6)
C(12)	0.7104(2)	0.19376(16)	0.9918(3)	2.13(5)
C(13)	0.9168(2)	0.15072(17)	0.8681(3)	2.85(6)
C(14)	0.9622(2)	0.18423(17)	0.7258(4)	3.39(7)
C(15)	0.7639(3)	0.1495(2)	0.6224(3)	3.15(7)
C(16)	0.7103(2)	0.11646(15)	0.7620(4)	2.45(6)
H(1)	0.6050	0.3658	1.4208	3.1331
H(2)	0.6918	0.4429	1.6153	3.9349
H(3)	0.9114	0.4798	1.6194	4.1916
H(4)	1.0423	0.4409	1.4282	3.8708
H(5)	0.9563	0.3654	1.2326	3.2831
H(6)	0.6269	0.2974	1.1989	3.0858
H(7)	0.6276	0.4353	1.0813	3.2485
H(8)	0.7434	0.4552	0.8882	4.3376
H(9)	0.8311	0.3652	0.9264	4.3376
H(10)	0.8672	0.2552	1.0820	2.8295
H(11)	0.7227	0.1390	1.2587	3.5773
H(12)	0.8468	0.1881	1.3103	3.5773
H(13)	0.8557	0.1143	1.1928	3.5773
H(14)	0.9574	0.1849	0.9412	3.4165
H(15)	0.9390	0.0885	0.8782	3.4165
H(16)	0.9426	0.2470	0.7176	4.0721
H(17)	1.0530	0.1757	0.7189	4.0721

Table 1. Atomic coordinates and B_{iso}/B_{eq} (continued)

atom	x	y	z	B_{eq}
H(18)	0.7231	0.1173	0.5472	3.7789
H(19)	0.7458	0.2125	0.6132	3.7789
H(20)	0.6206	0.1301	0.7667	2.9378
H(21)	0.7223	0.0527	0.7689	2.9378

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0.0244(9)	0.0369(10)	0.0355(10)	-0.0020(8)	0.0016(8)	-0.0074(8)
O(2)	0.0420(11)	0.0541(12)	0.0381(12)	-0.0069(9)	0.0083(9)	-0.0144(9)
N(1)	0.0232(11)	0.0352(12)	0.0279(13)	-0.0003(9)	-0.0013(10)	-0.0090(11)
C(1)	0.0312(14)	0.0267(14)	0.0297(16)	-0.0043(10)	0.0011(13)	-0.0016(12)
C(2)	0.0384(15)	0.0316(15)	0.0291(16)	-0.0059(12)	0.0037(13)	-0.0002(13)
C(3)	0.063(2)	0.0370(16)	0.0245(17)	-0.0037(13)	0.0062(14)	-0.0015(13)
C(4)	0.070(2)	0.0332(15)	0.0293(18)	-0.0017(14)	-0.0175(16)	-0.0050(13)
C(5)	0.0421(16)	0.0372(16)	0.0432(18)	0.0019(12)	-0.0151(14)	-0.0059(15)
C(6)	0.0354(15)	0.0331(16)	0.0354(17)	0.0013(11)	-0.0037(13)	-0.0061(12)
C(7)	0.0245(13)	0.0390(16)	0.0343(16)	-0.0042(11)	0.0004(11)	-0.0041(13)
C(8)	0.0379(14)	0.0310(15)	0.0339(17)	0.0012(11)	-0.0120(14)	-0.0032(13)
C(9)	0.060(2)	0.0335(15)	0.043(2)	-0.0036(13)	-0.0044(16)	0.0050(14)
C(10)	0.0256(13)	0.0353(16)	0.0287(15)	-0.0016(11)	0.0004(12)	-0.0041(12)
C(11)	0.0455(15)	0.0326(15)	0.0352(17)	-0.0010(11)	-0.0018(15)	-0.0022(13)
C(12)	0.0285(14)	0.0263(13)	0.0262(14)	-0.0003(11)	-0.0023(12)	0.0001(11)
C(13)	0.0275(14)	0.0440(17)	0.0367(17)	0.0025(12)	-0.0007(13)	-0.0143(13)
C(14)	0.0356(14)	0.0478(17)	0.046(2)	-0.0069(11)	0.0092(14)	-0.0130(16)
C(15)	0.0451(17)	0.0466(18)	0.0280(17)	-0.0054(13)	-0.0045(14)	-0.0030(14)
C(16)	0.0318(13)	0.0291(14)	0.0321(16)	-0.0008(10)	-0.0010(13)	-0.0052(12)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(1)	C(12)	1.232(2)	O(2)	C(14)	1.428(3)
O(2)	C(15)	1.428(3)	N(1)	C(12)	1.352(3)
N(1)	C(13)	1.459(3)	N(1)	C(16)	1.455(3)
C(1)	C(2)	1.385(3)	C(1)	C(6)	1.394(3)
C(1)	C(7)	1.515(4)	C(2)	C(3)	1.387(4)
C(3)	C(4)	1.384(4)	C(4)	C(5)	1.374(4)
C(5)	C(6)	1.383(4)	C(7)	C(8)	1.524(4)
C(7)	C(10)	1.533(3)	C(8)	C(9)	1.299(4)
C(10)	C(11)	1.544(3)	C(10)	C(12)	1.524(3)
C(13)	C(14)	1.500(4)	C(15)	C(16)	1.505(4)

Table 4. Bond Lengths($\mathring{A}$)

atom	atom	distance	atom	atom	distance
C(2)	H(1)	0.95	C(3)	H(2)	0.95
C(4)	H(3)	0.95	C(5)	H(4)	0.95
C(6)	H(5)	0.95	C(7)	H(6)	0.95
C(8)	H(7)	0.95	C(9)	H(8)	0.95
C(9)	H(9)	0.95	C(10)	H(10)	0.95
C(11)	H(11)	0.95	C(11)	H(12)	0.95
C(11)	H(13)	0.95	C(13)	H(14)	0.95
C(13)	H(15)	0.95	C(14)	H(16)	0.95
C(14)	H(17)	0.95	C(15)	H(18)	0.95
C(15)	H(19)	0.95	C(16)	H(20)	0.95
C(16)	H(21)	0.95			

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(14)	O(2)	C(15)	109.1(2)	C(12)	N(1)	C(13)	126.7(2)
C(12)	N(1)	C(16)	120.86(17)	C(13)	N(1)	C(16)	111.67(18)
C(2)	C(1)	C(6)	118.6(2)	C(2)	C(1)	C(7)	120.2(2)
C(6)	C(1)	C(7)	121.0(2)	C(1)	C(2)	C(3)	120.7(2)
C(2)	C(3)	C(4)	120.0(2)	C(3)	C(4)	C(5)	119.6(2)
C(4)	C(5)	C(6)	120.6(2)	C(1)	C(6)	C(5)	120.4(2)
C(1)	C(7)	C(8)	108.4(2)	C(1)	C(7)	C(10)	113.8(2)
C(8)	C(7)	C(10)	112.5(2)	C(7)	C(8)	C(9)	127.5(2)
C(7)	C(10)	C(11)	111.5(2)	C(7)	C(10)	C(12)	109.94(18)
C(11)	C(10)	C(12)	108.4(2)	O(1)	C(12)	N(1)	121.5(2)
O(1)	C(12)	C(10)	119.6(2)	N(1)	C(12)	C(10)	118.91(18)
N(1)	C(13)	C(14)	109.9(2)	O(2)	C(14)	C(13)	111.18(18)
O(2)	C(15)	C(16)	112.1(2)	N(1)	C(16)	C(15)	109.85(18)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	C(2)	H(1)	119.6	C(3)	C(2)	H(1)	119.6
C(2)	C(3)	H(2)	120.0	C(4)	C(3)	H(2)	120.0
C(3)	C(4)	H(3)	120.2	C(5)	C(4)	H(3)	120.2
C(4)	C(5)	H(4)	119.7	C(6)	C(5)	H(4)	119.7
C(1)	C(6)	H(5)	119.8	C(5)	C(6)	H(5)	119.8
C(1)	C(7)	H(6)	107.3	C(8)	C(7)	H(6)	107.3
C(10)	C(7)	H(6)	107.3	C(7)	C(8)	H(7)	116.2
C(9)	C(8)	H(7)	116.2	C(8)	C(9)	H(8)	120.0
C(8)	C(9)	H(9)	120.0	H(8)	C(9)	H(9)	120.0
C(7)	C(10)	H(10)	109.0	C(11)	C(10)	H(10)	109.0
C(12)	C(10)	H(10)	109.0	C(10)	C(11)	H(11)	109.5
C(10)	C(11)	H(12)	109.5	C(10)	C(11)	H(13)	109.5
H(11)	C(11)	H(12)	109.5	H(11)	C(11)	H(13)	109.5
H(12)	C(11)	H(13)	109.5	N(1)	C(13)	H(14)	109.4
N(1)	C(13)	H(15)	109.4	C(14)	C(13)	H(14)	109.4
C(14)	C(13)	H(15)	109.4	H(14)	C(13)	H(15)	109.5
O(2)	C(14)	H(16)	109.0	O(2)	C(14)	H(17)	109.0
C(13)	C(14)	H(16)	109.0	C(13)	C(14)	H(17)	109.0
H(16)	C(14)	H(17)	109.5	O(2)	C(15)	H(18)	108.8
O(2)	C(15)	H(19)	108.8	C(16)	C(15)	H(18)	108.8
C(16)	C(15)	H(19)	108.8	H(18)	C(15)	H(19)	109.5
N(1)	C(16)	H(20)	109.4	N(1)	C(16)	H(21)	109.4
C(15)	C(16)	H(20)	109.4	C(15)	C(16)	H(21)	109.4
H(20)	C(16)	H(21)	109.5				

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
O(1)	C(12)	N(1)	C(13)	-170.7(2)	O(1)	C(12)	N(1)	C(16)	-1.7(3)
O(1)	C(12)	C(10)	C(7)	-38.7(3)	O(1)	C(12)	C(10)	C(11)	83.3(3)
O(2)	C(14)	C(13)	N(1)	-58.2(3)	O(2)	C(15)	C(16)	N(1)	56.2(3)
N(1)	C(12)	C(10)	C(7)	142.5(2)	N(1)	C(12)	C(10)	C(11)	-95.5(2)
C(1)	C(2)	C(3)	C(4)	-0.7(4)	C(1)	C(6)	C(5)	C(4)	0.0(4)
C(1)	C(7)	C(8)	C(9)	106.4(3)	C(1)	C(7)	C(10)	C(11)	54.1(3)
C(1)	C(7)	C(10)	C(12)	174.3(2)	C(2)	C(1)	C(6)	C(5)	-0.4(3)
C(2)	C(1)	C(7)	C(8)	99.2(2)	C(2)	C(1)	C(7)	C(10)	-134.9(2)
C(2)	C(3)	C(4)	C(5)	0.3(4)	C(3)	C(2)	C(1)	C(6)	0.8(4)
C(3)	C(2)	C(1)	C(7)	-173.5(2)	C(3)	C(4)	C(5)	C(6)	0.1(4)
C(5)	C(6)	C(1)	C(7)	173.8(2)	C(6)	C(1)	C(7)	C(8)	-75.0(3)
C(6)	C(1)	C(7)	C(10)	51.0(3)	C(8)	C(7)	C(10)	C(11)	177.9(2)
C(8)	C(7)	C(10)	C(12)	-62.0(3)	C(9)	C(8)	C(7)	C(10)	-20.3(4)
C(10)	C(12)	N(1)	C(13)	8.0(3)	C(10)	C(12)	N(1)	C(16)	177.1(2)
C(12)	N(1)	C(13)	C(14)	-135.3(2)	C(12)	N(1)	C(16)	C(15)	135.9(2)
C(13)	N(1)	C(16)	C(15)	-53.5(2)	C(13)	C(14)	O(2)	C(15)	60.1(3)
C(14)	O(2)	C(15)	C(16)	-59.3(3)	C(14)	C(13)	N(1)	C(16)	54.8(3)

Table 8. Non-bonded Contacts out to 3.75 $\AA$

atom	atom	distance	ADC	atom	atom	distance	ADC
O(1)	C(13)	3.213(3)	45504	O(1)	C(14)	3.435(3)	45504
O(1)	C(10)	3.537(3)	45504	O(1)	C(4)	3.577(3)	64403
O(1)	C(6)	3.681(3)	45504	O(1)	C(9)	3.706(3)	45504
O(2)	C(2)	3.540(3)	55404	O(2)	C(11)	3.747(3)	55401
O(2)	C(8)	3.748(3)	64403	C(4)	C(16)	3.703(4)	65503
C(4)	C(12)	3.744(3)	65503	C(5)	C(16)	3.625(4)	65503
C(6)	C(16)	3.687(3)	65503	C(8)	C(13)	3.474(4)	45504
C(9)	C(13)	3.749(4)	45504	C(11)	C(15)	3.714(4)	55601

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	-X,	-Y,	1/2+Z
(3)	1/2-X,	1/2+Y,	1/2+Z	(4)	1/2+X,	1/2-Y,	Z

Table 9. Least Squares Planes

Plane number 1

Atoms defining plane	Distance
C(1)	-0.003(3)
C(2)	0.004(3)
C(3)	-0.003(3)
C(4)	-0.001(3)
C(5)	0.001(3)
C(6)	0.000(2)
Additional Atoms	**Distance**
C(7)	-0.144

Plane number 2

Atoms defining plane	Distance
C(7)	0.0
C(8)	0.0
C(9)	0.0
Additional Atoms	**Distance**
C(10)	-0.491

Plane number 3

Atoms defining plane	Distance
C(10)	0.002(3)
C(12)	-0.007(2)
O(1)	0.0011(14)
N(1)	0.001(2)
Additional Atoms	**Distance**
C(13)	0.181
C(16)	0.056

Summary

plane	mean deviation	χ^2
1	0.0020	5.4
2	0.0000	0.0
3	0.0028	11.1

Dihedral angles between planes (°)

plane	1	2
2	98.71	
3	8.26	104.31

Sample: tpy128

P.O. # 1736

X-ray Structure Report

for

Tehshik Yoon

204 Lewis Hall

3-8419

MacMillan

Thu May 20 1999

Introduction

The compound $C_{18}N_2O_4H_{19}$ crystallizes in the triclinic space group $P\bar{1}$ with four molecules in the unit cell. There are two crystallographically unique but chemically identical molecules in the asymmetric unit.

The relative stereochemistry of the molecule is as expected. The morpholine moiety on one of the molecules is disordered over two possible chair conformations. The disorder was modeled using half occupancy isotropic carbon and oxygen atoms and one full occupancy anisotropic nitrogen atom.

There are no unusually close intermolecular contacts.

-DLC

Experimental

Data Collection

A fragment of a colorless blocky crystal of $C_{18}N_2O_4H_{19}$ having approximate dimensions of 0.35 x 0.17 x 0.05 mm was mounted on a quartz fiber using Paratone N hydrocarbon oil. All measurements were made on a SMART[10] CCD area detector with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix , obtained from a least-squares refinement using the measured positions of 2880 reflections in the range $3.00 < 2\theta < 46.00°$ corresponded to a primitive triclinic cell with dimensions:

a = 9.1819(9) $\AA$	α = 90.855(2)°
b = 11.3667(10) $\AA$	β = 90.623(2)°
c = 16.8867(17) $\AA$	γ = 110.369(2)
V = 1651.8(3) $\AA^3$	

For Z = 4 and F.W. = 327.36, the calculated density is 1.32 g/cm^3. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

$P\bar{1}$ (#2)

The data were collected at a temperature of -122 $\pm$ 1°C. Frames corresponding to an arbitrary hemisphere of data were collected using ω scans of 0.3° counted for a total of 10.0 seconds per frame.

Data Reduction

Data were integrated by the program SAINT[11] to a maximum 2θ value of 49.4°. The data were corrected for Lorentz and polarization effects. Data were analyzed for agreement and possible absorption using XPREP[12]. An empirical absorption correction based on comparison of redundant and equivalent reflections as applied using SADABS[13] (Tmax = 0.96, Tmin = 0.76).

Structure Solution and Refinement

The structure was solved by direct methods[1] and expanded using Fourier techniques[2]. The full occupancy non-hydrogen atoms were refined anisotropically, while the partial occupancy non-hydrogen atoms were refined isotropically. The disordered morpholine moiety was modeled as described in the Introduction. Hydrogen atoms were included in calculated idealized positions but not refined. The final cycle of full-matrix least-squares refinement[3] was based on 3025 observed reflections ($I > 3.00\sigma(I)$) and 428 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc||/\Sigma|Fo| = 0.052$$

$$R_w = \sqrt{(\Sigma w(|Fo| - |Fc|)^2 / \Sigma w Fo^2)} = 0.062$$

The standard deviation of an observation of unit weight[4] was 2.06. The weighting scheme was based on counting statistics and included a factor (p = 0.030) to downweight the intense reflections. Plots of $\Sigma w(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin θ/λ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.36 and -0.19 $e^-/\mathring{A}^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[5] . Anomalous dispersion effects were included in Fcalc[6]; the values for Δf' and Δf" were those of Creagh and McAuley[7]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[8]. All calculations were performed using the teXsan[9] crystallographic software package of Molecular Structure Corporation.

References

(1) SIR92: Altomare, A., Cascarano, M., Giacovazzo, C., Guagliardi, A. (1993). J. Appl. Cryst., 26, 343.

(2) DIRDIF94: Beurskens, P.T., Admiraal, G., Beurskens, G., Bosman, W.P., de Gelder, R., Israel, R. and Smits, J.M.M. (1994). The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands.

(3) Least-Squares:

Function minimized: $\Sigma w(|Fo| - |Fc|)^2$

(4) Standard deviation of an observation of unit weight:

$$\sqrt{\Sigma w(|Fo| - |Fc|)^2 / (No - Nv)}$$

where: No = number of observations

Nv = number of variables

(5) Cromer, D. T. & Waber, J. T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

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(8) Creagh, D. C. & Hubbell, J.H..; "International Tables for Crystallography", Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, pages 200-206 (1992).

(9) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992).

(10) SMART: Area-Detector Software Package, Siemens Industrial Automation, Inc.: Madison, WI, (1995)

(11) SAINT: SAX Area-Dectector Integration Program, V4.024; Siemens Industrial Automation, Inc.: Madison, WI, (1995)

(12) XPREP:(v 5.03) Part of the SHELXTL Crystal Structure Determination Siemens Industrial Automation, Inc.: Madison, WI, (1995)

(13) SADABS: Siemens Area Detector ABSsorption correction program, George Sheldrick, (1996). Advance copy, private communication.

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{18}N_2O_4H_{19}$
Formula Weight	327.36
Crystal Color, Habit	colorless, blocks
Crystal Dimensions	0.35 X 0.17 X 0.05 mm
Crystal System	triclinic
Lattice Type	Primitive
Lattice Parameters	a = 9.1819(9)$\AA$ b = 11.3667(10) $\AA$ c = 16.8867(17) $\AA$ α = 90.855(2)° β = 90.623(2)° γ = 110.369(2)° V = 1651.8(3) $\AA^3$
Space Group	$P\bar{1}$ (#2)
Z value	4
D_{calc}	1.316 g/cm^3
F_{000}	692.00
μ(MoKα)	16.21 cm^{-1}

B. Intensity Measurements

Diffractometer	SMART CCD
Radiation	MoKα (λ = 0.71069 $\AA$) graphite monochromated
Detector Position	60.00 mm
Exposure Time	10.0 seconds per frame.
Scan Type	ω (0.3 degrees per frame)

$2\theta_{max}$	49.4°
No. of Reflections Measured	Total: 8645 Unique: 5563 (R_{int} = 0.028)
Corrections	Lorentz-polarization Absorption (Tmax = 0.96 Tmin = 0.76)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR92)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$w = \frac{1}{\sigma^2(Fo)} = [\sigma_c^2(Fo) + \frac{p^2}{4}Fo^2]^{-1}$
p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	3025
No. Variables	428
Reflection/Parameter Ratio	7.07
Residuals: R; Rw; Rall	0.052 ; 0.062; 0.105
Goodness of Fit Indicator	2.06
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.36 $e^-/\mathring{A}^3$
Minimum peak in Final Diff. Map	-0.19 $e^-/\mathring{A}^3$

Table 1. Atomic coordinates and B_{iso}/B_{eq} and occupancy

atom	x	y	z	B_{eq}	occ
O(1)	0.1090(3)	0.7756(3)	0.72420(17)	3.41(7)	
O(2)	-0.1954(4)	0.8561(3)	0.51169(17)	3.87(8)	
O(3)	0.1956(3)	0.5541(3)	0.79701(17)	3.79(8)	
O(4)	-0.1124(3)	0.3896(2)	0.57795(16)	2.91(7)	
O(5)	0.4106(3)	0.2483(3)	0.22739(17)	3.30(7)	
O(6)	0.7248(7)	0.1527(6)	0.0221(4)	2.83(14)	1/2
O(7)	0.6627(8)	0.1088(6)	0.0110(4)	3.38(15)	1/2
O(8)	0.6300(3)	0.5987(3)	0.08320(17)	3.52(7)	
O(9)	0.2862(3)	0.4628(3)	0.28574(16)	3.56(7)	
N(1)	-0.0551(4)	0.7387(3)	0.61895(18)	2.32(8)	
N(2)	0.0568(4)	0.5034(3)	0.67708(18)	2.33(8)	
N(3)	0.5224(5)	0.2363(3)	0.1116(2)	3.95(10)	
N(4)	0.4424(4)	0.4976(3)	0.1744(2)	2.57(8)	
C(1)	0.4673(6)	0.8858(4)	0.6007(3)	4.39(13)	
C(2)	0.3613(5)	0.7797(4)	0.5815(2)	3.08(11)	
C(3)	0.3033(4)	0.6702(3)	0.6349(2)	2.44(9)	
C(4)	0.1249(4)	0.6195(4)	0.6318(2)	2.37(9)	
C(5)	0.0580(5)	0.7177(4)	0.6621(3)	2.41(10)	
C(6)	-0.1352(5)	0.6720(4)	0.5480(2)	2.84(10)	
C(7)	-0.1295(5)	0.7664(4)	0.4851(3)	3.40(11)	
C(8)	-0.1180(5)	0.9187(4)	0.5823(3)	3.61(12)	
C(9)	-0.1239(5)	0.8286(4)	0.6475(2)	2.87(10)	
C(10)	0.3687(5)	0.5699(4)	0.6095(3)	3.83(11)	
C(11)	0.0954(5)	0.4823(4)	0.7552(3)	2.87(11)	
C(12)	-0.0086(5)	0.3532(4)	0.7738(2)	2.55(10)	
C(13)	-0.0224(5)	0.2858(4)	0.8424(3)	3.41(12)	
C(14)	-0.1263(6)	0.1642(4)	0.8416(3)	3.64(12)	
C(15)	-0.2130(5)	0.1117(4)	0.7742(3)	3.72(12)	
C(16)	-0.2017(5)	0.1802(4)	0.7057(3)	3.04(11)	
C(17)	-0.0990(4)	0.3018(4)	0.7070(2)	2.43(10)	
C(18)	-0.0591(5)	0.3975(4)	0.6451(3)	2.36(10)	
C(19)	0.0490(7)	0.1072(5)	0.0990(3)	5.95(15)	
C(20)	0.1375(5)	0.2147(4)	0.0747(3)	3.21(11)	
C(21)	0.1958(5)	0.3318(4)	0.1249(2)	2.69(10)	
C(22)	0.3756(5)	0.3820(4)	0.1274(2)	2.49(10)	
C(23)	0.4384(5)	0.2835(4)	0.1590(3)	2.65(10)	

Table 1. Atomic coordinates and B_{iso}/B_{eq} and occupancy (continued)

atom	x	y	z	B_{eq}	occ
C(24)	0.6181(12)	0.1633(9)	0.1461(6)	3.2(2)	1/2
C(25)	0.5555(11)	0.1239(9)	0.1400(5)	2.6(2)	1/2
C(26)	0.7190(10)	0.1453(7)	0.1087(5)	2.76(16)	1/2
C(27)	0.5956(11)	0.0597(8)	0.0855(6)	4.0(2)	1/2
C(28)	0.6825(11)	0.2576(9)	-0.0019(5)	3.5(2)	1/2
C(29)	0.5935(11)	0.1973(8)	-0.0198(5)	3.26(18)	1/2
C(30)	0.6077(11)	0.3025(8)	0.0364(5)	3.05(17)	1/2
C(31)	0.5108(11)	0.2345(9)	0.0212(6)	3.8(2)	1/2
C(32)	0.5692(5)	0.5984(4)	0.1466(3)	2.77(11)	
C(33)	0.6062(5)	0.6984(4)	0.2085(3)	2.78(10)	
C(34)	0.7166(5)	0.8179(4)	0.2104(3)	3.63(12)	
C(35)	0.7239(6)	0.8919(4)	0.2777(3)	4.47(13)	
C(36)	0.6276(6)	0.8460(4)	0.3408(3)	3.95(13)	
C(37)	0.5151(5)	0.7260(4)	0.3382(3)	3.35(11)	
C(38)	0.5061(5)	0.6546(4)	0.2705(3)	2.56(10)	
C(39)	0.3969(5)	0.5273(4)	0.2488(3)	2.77(11)	
C(40)	0.1361(5)	0.4315(4)	0.0920(3)	3.91(12)	
H(1)	0.4983	0.9514	0.5635	5.2730	
H(2)	0.5142	0.8981	0.6520	5.2730	
H(3)	0.3171	0.7708	0.5297	3.6965	
H(4)	0.3373	0.6971	0.6876	2.9334	
H(5)	0.0931	0.6006	0.5780	2.8403	
H(6)	-0.0855	0.6164	0.5296	3.4075	
H(7)	-0.2403	0.6254	0.5598	3.4075	
H(8)	-0.0243	0.8091	0.4716	4.0828	
H(9)	-0.1859	0.7233	0.4396	4.0828	
H(10)	-0.0124	0.9638	0.5707	4.3338	
H(11)	-0.1665	0.9756	0.5998	4.3338	
H(12)	-0.0670	0.8732	0.6925	3.4381	
H(13)	-0.2287	0.7857	0.6616	3.4381	
H(14)	0.3347	0.5422	0.5569	4.5967	
H(15)	0.4790	0.6039	0.6115	4.5967	
H(16)	0.3334	0.5009	0.6441	4.5967	
H(17)	0.0377	0.3219	0.8886	4.0910	
H(18)	-0.1387	0.1158	0.8881	4.3734	
H(19)	-0.2816	0.0270	0.7749	4.4604	

Table 1. Atomic coordinates and B_{iso}/B_{eq} and occupancy (continued)

atom	x	y	z	B_{eq}	occ
H(20)	-0.2625	0.1444	0.6598	3.6522	
H(21)	0.0167	0.0369	0.0636	7.1431	
H(22)	0.0159	0.0982	0.1524	7.1431	
H(23)	0.1681	0.2202	0.0210	3.8508	
H(24)	0.1590	0.3128	0.1772	3.2324	
H(25)	0.4102	0.3994	0.0746	2.9826	
H(26)	0.7848	0.8482	0.1675	4.3576	
H(27)	0.7963	0.9753	0.2803	5.3683	
H(28)	0.6382	0.8972	0.3870	4.7436	
H(29)	0.4476	0.6949	0.3812	4.0254	
H(30)	0.1740	0.5054	0.1243	4.6949	
H(31)	0.1716	0.4504	0.0394	4.6949	
H(32)	0.0258	0.4007	0.0918	4.6949	

$$B_{eq} = \frac{8}{3}\pi^2(U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha)$$

Table 2. Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
O(1)	0.051(2)	0.051(2)	0.0322(18)	0.0240(16)	-0.0086(16)	-0.0103(16)
O(2)	0.069(2)	0.054(2)	0.039(2)	0.0409(18)	-0.0025(17)	0.0012(16)
O(3)	0.049(2)	0.044(2)	0.039(2)	0.0004(16)	-0.0158(17)	0.0058(15)
O(4)	0.0373(17)	0.0360(17)	0.0334(18)	0.0082(14)	-0.0029(15)	-0.0032(14)
O(5)	0.0442(18)	0.056(2)	0.0292(18)	0.0222(16)	0.0075(15)	0.0106(15)
O(8)	0.0386(17)	0.054(2)	0.038(2)	0.0120(16)	0.0078(16)	0.0106(16)
O(9)	0.046(2)	0.040(2)	0.040(2)	0.0037(16)	0.0142(16)	-0.0025(15)
N(1)	0.031(2)	0.029(2)	0.030(2)	0.0121(17)	-0.0028(17)	-0.0006(16)
N(2)	0.030(2)	0.029(2)	0.027(2)	0.0067(17)	-0.0004(16)	0.0040(16)
N(3)	0.082(3)	0.067(3)	0.024(2)	0.055(3)	0.012(2)	0.009(2)
N(4)	0.034(2)	0.032(2)	0.031(2)	0.0092(18)	0.0064(18)	-0.0003(17)
C(1)	0.060(3)	0.049(3)	0.053(3)	0.013(3)	0.002(3)	0.011(3)
C(2)	0.033(3)	0.040(3)	0.040(3)	0.006(2)	-0.004(2)	0.002(2)
C(3)	0.029(2)	0.027(2)	0.034(3)	0.006(2)	-0.001(2)	0.003(2)
C(4)	0.032(2)	0.032(2)	0.023(2)	0.008(2)	-0.002(2)	0.003(2)
C(5)	0.032(2)	0.027(2)	0.029(3)	0.005(2)	0.004(2)	0.007(2)
C(6)	0.034(2)	0.037(3)	0.037(3)	0.014(2)	-0.003(2)	-0.003(2)
C(7)	0.052(3)	0.045(3)	0.036(3)	0.023(3)	0.000(2)	-0.003(2)
C(8)	0.060(3)	0.044(3)	0.042(3)	0.028(3)	0.007(3)	0.004(2)
C(9)	0.039(3)	0.041(3)	0.033(3)	0.019(2)	0.003(2)	0.000(2)
C(10)	0.030(2)	0.047(3)	0.067(3)	0.013(2)	-0.002(2)	-0.003(3)
C(11)	0.034(3)	0.041(3)	0.036(3)	0.015(2)	0.000(2)	0.004(2)
C(12)	0.036(2)	0.030(3)	0.035(3)	0.016(2)	0.006(2)	0.009(2)
C(13)	0.042(3)	0.046(3)	0.046(3)	0.020(3)	0.004(2)	0.009(3)
C(14)	0.048(3)	0.042(3)	0.051(3)	0.018(3)	0.017(3)	0.018(3)
C(15)	0.041(3)	0.033(3)	0.066(4)	0.010(2)	0.017(3)	0.007(3)
C(16)	0.035(3)	0.032(3)	0.047(3)	0.009(2)	0.009(2)	0.004(2)
C(17)	0.028(2)	0.028(3)	0.037(3)	0.011(2)	0.008(2)	0.003(2)
C(18)	0.027(2)	0.033(3)	0.032(3)	0.012(2)	0.002(2)	-0.002(2)
C(19)	0.119(5)	0.047(3)	0.044(3)	0.008(4)	-0.013(3)	-0.002(3)
C(20)	0.046(3)	0.040(3)	0.035(3)	0.014(2)	-0.004(2)	0.002(2)
C(21)	0.038(3)	0.035(3)	0.031(3)	0.014(2)	0.002(2)	0.002(2)
C(22)	0.036(2)	0.034(3)	0.025(2)	0.013(2)	0.004(2)	0.000(2)
C(23)	0.036(3)	0.036(3)	0.030(3)	0.014(2)	0.000(2)	0.002(2)
C(32)	0.032(3)	0.041(3)	0.035(3)	0.016(2)	0.002(2)	0.008(2)
C(33)	0.033(2)	0.033(3)	0.041(3)	0.013(2)	-0.007(2)	0.004(2)

Table 2. Anisotropic Displacement Parameters (continued)

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C(34)	0.034(3)	0.034(3)	0.066(3)	0.006(2)	-0.003(3)	0.006(3)
C(35)	0.047(3)	0.036(3)	0.080(4)	0.007(3)	-0.008(3)	-0.002(3)
C(36)	0.047(3)	0.043(3)	0.064(4)	0.022(3)	-0.018(3)	-0.016(3)
C(37)	0.045(3)	0.040(3)	0.046(3)	0.019(3)	-0.005(2)	-0.002(2)
C(38)	0.034(2)	0.029(3)	0.036(3)	0.015(2)	-0.001(2)	0.001(2)
C(39)	0.035(3)	0.036(3)	0.035(3)	0.014(2)	0.004(2)	0.000(2)
C(40)	0.043(3)	0.043(3)	0.065(3)	0.019(2)	-0.001(3)	-0.001(3)

The general temperature factor expression:

$$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$$

Table 3. Bond Lengths($\AA$)

atom	atom	distance	atom	atom	distance
O(1)	C(5)	1.228(4)	O(2)	C(7)	1.424(5)
O(2)	C(8)	1.427(5)	O(3)	C(11)	1.207(4)
O(4)	C(18)	1.220(4)	O(5)	C(23)	1.228(4)
O(6)	O(7)	0.636(7)	O(6)	C(26)	1.467(9)
O(6)	C(27)	1.691(11)	O(6)	C(28)	1.438(10)
O(6)	C(29)	1.620(11)	O(7)	C(26)	1.724(10)
O(7)	C(27)	1.439(10)	O(7)	C(28)	1.655(11)
O(7)	C(29)	1.463(9)	O(8)	C(32)	1.212(5)
O(9)	C(39)	1.212(5)	N(1)	C(5)	1.352(5)
N(1)	C(6)	1.454(5)	N(1)	C(9)	1.454(5)
N(2)	C(4)	1.477(5)	N(2)	C(11)	1.408(5)
N(2)	C(18)	1.396(5)	N(3)	C(23)	1.345(5)
N(3)	C(24)	1.521(10)	N(3)	C(25)	1.497(9)
N(3)	C(30)	1.559(9)	N(3)	C(31)	1.528(10)
N(4)	C(22)	1.459(5)	N(4)	C(32)	1.410(5)
N(4)	C(39)	1.402(5)	C(1)	C(2)	1.292(5)
C(2)	C(3)	1.494(5)	C(3)	C(4)	1.535(5)
C(3)	C(10)	1.521(6)	C(4)	C(5)	1.534(5)
C(6)	C(7)	1.510(5)	C(8)	C(9)	1.505(5)
C(11)	C(12)	1.486(5)	C(12)	C(13)	1.382(5)
C(12)	C(17)	1.388(5)	C(13)	C(14)	1.379(6)
C(14)	C(15)	1.383(6)	C(15)	C(16)	1.389(6)
C(16)	C(17)	1.376(5)	C(17)	C(18)	1.474(5)
C(19)	C(20)	1.285(6)	C(20)	C(21)	1.496(5)
C(21)	C(22)	1.547(5)	C(21)	C(40)	1.530(5)
C(22)	C(23)	1.527(5)	C(24)	C(25)	0.600(12)
C(24)	C(26)	1.199(11)	C(24)	C(27)	1.505(13)
C(25)	C(26)	1.536(12)	C(25)	C(27)	1.300(12)
C(26)	C(27)	1.263(10)	C(28)	C(29)	0.909(10)
C(28)	C(30)	1.182(11)	C(28)	C(31)	1.560(13)
C(29)	C(30)	1.484(12)	C(29)	C(31)	1.208(11)
C(30)	C(31)	0.982(10)	C(32)	C(33)	1.480(6)
C(33)	C(34)	1.383(5)	C(33)	C(38)	1.380(6)
C(34)	C(35)	1.390(6)	C(35)	C(36)	1.381(7)
C(36)	C(37)	1.395(6)	C(37)	C(38)	1.377(6)
C(38)	C(39)	1.483(5)			

Table 4. Bond Lengths($\mathring{A}$)

atom	atom	distance	atom	atom	distance
C(1)	H(1)	0.95	C(1)	H(2)	0.95
C(2)	H(3)	0.95	C(3)	H(4)	0.95
C(4)	H(5)	0.95	C(6)	H(6)	0.95
C(6)	H(7)	0.95	C(7)	H(8)	0.95
C(7)	H(9)	0.95	C(8)	H(10)	0.95
C(8)	H(11)	0.95	C(9)	H(12)	0.95
C(9)	H(13)	0.95	C(10)	H(14)	0.95
C(10)	H(15)	0.95	C(10)	H(16)	0.95
C(13)	H(17)	0.95	C(14)	H(18)	0.95
C(15)	H(19)	0.95	C(16)	H(20)	0.95
C(19)	H(21)	0.95	C(19)	H(22)	0.95
C(20)	H(23)	0.95	C(21)	H(24)	0.95
C(22)	H(25)	0.95	C(34)	H(26)	0.95
C(35)	H(27)	0.95	C(36)	H(28)	0.95
C(37)	H(29)	0.95	C(40)	H(30)	0.95
C(40)	H(31)	0.95	C(40)	H(32)	0.95

Table 5. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(7)	O(2)	C(8)	110.5(3)	O(7)	O(6)	C(26)	102.8(10)
O(7)	O(6)	C(27)	56.3(9)	O(7)	O(6)	C(28)	98.3(10)
O(7)	O(6)	C(29)	64.4(8)	C(26)	O(6)	C(27)	46.5(4)
C(26)	O(6)	C(28)	108.9(6)	C(26)	O(6)	C(29)	115.7(6)
C(27)	O(6)	C(28)	112.0(6)	C(27)	O(6)	C(29)	92.3(6)
C(28)	O(6)	C(29)	33.9(4)	O(6)	O(7)	C(26)	56.1(9)
O(6)	O(7)	C(27)	102.1(11)	O(6)	O(7)	C(28)	59.3(8)
O(6)	O(7)	C(29)	92.5(10)	C(26)	O(7)	C(27)	46.0(4)
C(26)	O(7)	C(28)	88.8(5)	C(26)	O(7)	C(29)	110.1(6)
C(27)	O(7)	C(28)	114.0(6)	C(27)	O(7)	C(29)	110.8(7)
C(28)	O(7)	C(29)	33.2(4)	C(5)	N(1)	C(6)	128.3(3)
C(5)	N(1)	C(9)	119.9(3)	C(6)	N(1)	C(9)	111.5(3)
C(4)	N(2)	C(11)	126.9(3)	C(4)	N(2)	C(18)	122.2(3)
C(11)	N(2)	C(18)	110.9(3)	C(23)	N(3)	C(24)	120.6(5)
C(23)	N(3)	C(25)	117.3(5)	C(23)	N(3)	C(30)	124.2(4)
C(23)	N(3)	C(31)	123.6(5)	C(24)	N(3)	C(25)	22.9(4)
C(24)	N(3)	C(30)	107.0(6)	C(24)	N(3)	C(31)	115.3(6)
C(25)	N(3)	C(30)	117.9(5)	C(25)	N(3)	C(31)	110.6(5)
C(30)	N(3)	C(31)	37.1(4)	C(22)	N(4)	C(32)	121.0(3)
C(22)	N(4)	C(39)	128.4(3)	C(32)	N(4)	C(39)	110.6(3)
C(1)	C(2)	C(3)	124.7(4)	C(2)	C(3)	C(4)	109.0(3)
C(2)	C(3)	C(10)	109.5(4)	C(4)	C(3)	C(10)	111.3(3)
N(2)	C(4)	C(3)	113.0(3)	N(2)	C(4)	C(5)	108.8(3)
C(3)	C(4)	C(5)	111.5(3)	O(1)	C(5)	N(1)	121.8(4)
O(1)	C(5)	C(4)	119.4(4)	N(1)	C(5)	C(4)	118.8(4)
N(1)	C(6)	C(7)	108.8(3)	O(2)	C(7)	C(6)	111.7(3)
O(2)	C(8)	C(9)	112.2(3)	N(1)	C(9)	C(8)	108.3(3)
O(3)	C(11)	N(2)	126.4(4)	O(3)	C(11)	C(12)	127.7(4)
N(2)	C(11)	C(12)	105.9(4)	C(11)	C(12)	C(13)	130.4(4)
C(11)	C(12)	C(17)	108.3(4)	C(13)	C(12)	C(17)	121.3(4)
C(12)	C(13)	C(14)	117.6(4)	C(13)	C(14)	C(15)	121.0(4)
C(14)	C(15)	C(16)	121.4(4)	C(15)	C(16)	C(17)	117.4(4)
C(12)	C(17)	C(16)	121.1(4)	C(12)	C(17)	C(18)	108.0(3)
C(16)	C(17)	C(18)	130.8(4)	O(4)	C(18)	N(2)	124.5(4)
O(4)	C(18)	C(17)	128.5(4)	N(2)	C(18)	C(17)	106.9(3)
C(19)	C(20)	C(21)	124.8(4)	C(20)	C(21)	C(22)	109.8(4)

Table 5. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
C(20)	C(21)	C(40)	110.2(3)	C(22)	C(21)	C(40)	110.0(3)
N(4)	C(22)	C(21)	113.4(3)	N(4)	C(22)	C(23)	109.0(3)
C(21)	C(22)	C(23)	111.1(3)	O(5)	C(23)	N(3)	121.2(4)
O(5)	C(23)	C(22)	119.2(4)	N(3)	C(23)	C(22)	119.7(4)
N(3)	C(24)	C(25)	76.2(14)	N(3)	C(24)	C(26)	121.0(8)
N(3)	C(24)	C(27)	102.8(7)	C(25)	C(24)	C(26)	112.9(19)
C(25)	C(24)	C(27)	58.8(15)	C(26)	C(24)	C(27)	54.2(6)
N(3)	C(25)	C(24)	80.8(15)	N(3)	C(25)	C(26)	103.0(7)
N(3)	C(25)	C(27)	115.4(8)	C(24)	C(25)	C(26)	46.0(14)
C(24)	C(25)	C(27)	98.0(17)	C(26)	C(25)	C(27)	52.1(6)
O(6)	C(26)	O(7)	21.1(3)	O(6)	C(26)	C(24)	122.5(8)
O(6)	C(26)	C(25)	112.3(6)	O(6)	C(26)	C(27)	76.1(6)
O(7)	C(26)	C(24)	111.3(7)	O(7)	C(26)	C(25)	96.1(6)
O(7)	C(26)	C(27)	55.0(5)	C(24)	C(26)	C(25)	21.1(6)
C(24)	C(26)	C(27)	75.3(8)	C(25)	C(26)	C(27)	54.3(6)
O(6)	C(27)	O(7)	21.6(3)	O(6)	C(27)	C(24)	94.0(6)
O(6)	C(27)	C(25)	112.4(8)	O(6)	C(27)	C(26)	57.4(5)
O(7)	C(27)	C(24)	111.3(7)	O(7)	C(27)	C(25)	124.8(8)
O(7)	C(27)	C(26)	79.0(7)	C(24)	C(27)	C(25)	23.3(5)
C(24)	C(27)	C(26)	50.4(6)	C(25)	C(27)	C(26)	73.6(7)
O(6)	C(28)	O(7)	22.4(3)	O(6)	C(28)	C(29)	84.1(9)
O(6)	C(28)	C(30)	124.3(9)	O(6)	C(28)	C(31)	109.4(7)
O(7)	C(28)	C(29)	61.7(8)	O(7)	C(28)	C(30)	119.1(8)
O(7)	C(28)	C(31)	92.5(6)	C(29)	C(28)	C(30)	89.4(11)
C(29)	C(28)	C(31)	50.6(8)	C(30)	C(28)	C(31)	39.0(5)
O(6)	C(29)	O(7)	23.1(3)	O(6)	C(29)	C(28)	62.0(8)
O(6)	C(29)	C(30)	96.6(7)	O(6)	C(29)	C(31)	119.2(8)
O(7)	C(29)	C(28)	85.1(9)	O(7)	C(29)	C(30)	113.0(7)
O(7)	C(29)	C(31)	120.6(8)	C(28)	C(29)	C(30)	52.8(8)
C(28)	C(29)	C(31)	93.9(11)	C(30)	C(29)	C(31)	41.2(5)
N(3)	C(30)	C(28)	121.0(8)	N(3)	C(30)	C(29)	104.0(6)
N(3)	C(30)	C(31)	69.8(8)	C(28)	C(30)	C(29)	37.8(5)
C(28)	C(30)	C(31)	91.8(10)	C(29)	C(30)	C(31)	54.2(8)
N(3)	C(31)	C(28)	101.5(7)	N(3)	C(31)	C(29)	121.9(8)
N(3)	C(31)	C(30)	73.2(8)	C(28)	C(31)	C(29)	35.5(5)
C(28)	C(31)	C(30)	49.2(7)	C(29)	C(31)	C(30)	84.6(10)

Table 5. Bond Angles(°) (continued)

atom	atom	atom	angle	atom	atom	atom	angle
O(8)	C(32)	N(4)	124.4(4)	O(8)	C(32)	C(33)	129.1(4)
N(4)	C(32)	C(33)	106.4(4)	C(32)	C(33)	C(34)	130.4(4)
C(32)	C(33)	C(38)	108.1(4)	C(34)	C(33)	C(38)	121.4(4)
C(33)	C(34)	C(35)	117.3(4)	C(34)	C(35)	C(36)	121.0(4)
C(35)	C(36)	C(37)	121.4(4)	C(36)	C(37)	C(38)	117.1(4)
C(33)	C(38)	C(37)	121.6(4)	C(33)	C(38)	C(39)	108.5(4)
C(37)	C(38)	C(39)	129.9(4)	O(9)	C(39)	N(4)	126.1(4)
O(9)	C(39)	C(38)	127.6(4)	N(4)	C(39)	C(38)	106.3(4)

Table 6. Bond Angles(°)

atom	atom	atom	angle	atom	atom	atom	angle
C(2)	C(1)	H(1)	120.0	C(2)	C(1)	H(2)	120.0
H(1)	C(1)	H(2)	120.0	C(1)	C(2)	H(3)	117.6
C(3)	C(2)	H(3)	117.6	C(2)	C(3)	H(4)	109.0
C(4)	C(3)	H(4)	109.0	C(10)	C(3)	H(4)	109.0
N(2)	C(4)	H(5)	107.8	C(3)	C(4)	H(5)	107.8
C(5)	C(4)	H(5)	107.8	N(1)	C(6)	H(6)	109.6
N(1)	C(6)	H(7)	109.6	C(7)	C(6)	H(6)	109.6
C(7)	C(6)	H(7)	109.6	H(6)	C(6)	H(7)	109.5
O(2)	C(7)	H(8)	108.9	O(2)	C(7)	H(9)	108.9
C(6)	C(7)	H(8)	108.9	C(6)	C(7)	H(9)	108.9
H(8)	C(7)	H(9)	109.5	O(2)	C(8)	H(10)	108.8
O(2)	C(8)	H(11)	108.8	C(9)	C(8)	H(10)	108.8
C(9)	C(8)	H(11)	108.8	H(10)	C(8)	H(11)	109.5
N(1)	C(9)	H(12)	109.8	N(1)	C(9)	H(13)	109.8
C(8)	C(9)	H(12)	109.8	C(8)	C(9)	H(13)	109.8
H(12)	C(9)	H(13)	109.5	C(3)	C(10)	H(14)	109.5
C(3)	C(10)	H(15)	109.5	C(3)	C(10)	H(16)	109.5
H(14)	C(10)	H(15)	109.5	H(14)	C(10)	H(16)	109.5
H(15)	C(10)	H(16)	109.5	C(12)	C(13)	H(17)	121.2
C(14)	C(13)	H(17)	121.2	C(13)	C(14)	H(18)	119.5
C(15)	C(14)	H(18)	119.5	C(14)	C(15)	H(19)	119.3
C(16)	C(15)	H(19)	119.3	C(15)	C(16)	H(20)	121.3
C(17)	C(16)	H(20)	121.3	C(20)	C(19)	H(21)	120.0
C(20)	C(19)	H(22)	120.0	H(21)	C(19)	H(22)	120.0
C(19)	C(20)	H(23)	117.6	C(21)	C(20)	H(23)	117.6
C(20)	C(21)	H(24)	108.9	C(22)	C(21)	H(24)	108.9
C(40)	C(21)	H(24)	108.9	N(4)	C(22)	H(25)	107.7
C(21)	C(22)	H(25)	107.7	C(23)	C(22)	H(25)	107.7
C(33)	C(34)	H(26)	121.3	C(35)	C(34)	H(26)	121.3
C(34)	C(35)	H(27)	119.5	C(36)	C(35)	H(27)	119.5
C(35)	C(36)	H(28)	119.3	C(37)	C(36)	H(28)	119.3
C(36)	C(37)	H(29)	121.4	C(38)	C(37)	H(29)	121.4
C(21)	C(40)	H(30)	109.5	C(21)	C(40)	H(31)	109.5
C(21)	C(40)	H(32)	109.5	H(30)	C(40)	H(31)	109.5
H(30)	C(40)	H(32)	109.5	H(31)	C(40)	H(32)	109.5

Table 7. Torsion Angles(°)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
O(1)	C(5)	N(1)	C(6)	-175.0(4)	O(1)	C(5)	N(1)	C(9)	-2.4(6)
O(1)	C(5)	C(4)	N(2)	78.3(4)	O(1)	C(5)	C(4)	C(3)	-46.9(5)
O(2)	C(7)	C(6)	N(1)	-57.0(4)	O(2)	C(8)	C(9)	N(1)	57.3(4)
O(3)	C(11)	N(2)	C(4)	-3.3(6)	O(3)	C(11)	N(2)	C(18)	176.7(4)
O(3)	C(11)	C(12)	C(13)	3.0(7)	O(3)	C(11)	C(12)	C(17)	-176.2(4)
O(4)	C(18)	N(2)	C(4)	1.3(6)	O(4)	C(18)	N(2)	C(11)	-178.8(4)
O(4)	C(18)	C(17)	C(12)	-179.9(4)	O(4)	C(18)	C(17)	C(16)	1.5(7)
O(5)	C(23)	N(3)	C(24)	-15.1(7)	O(5)	C(23)	N(3)	C(25)	10.8(7)
O(5)	C(23)	N(3)	C(30)	-159.4(5)	O(5)	C(23)	N(3)	C(31)	155.6(5)
O(5)	C(23)	C(22)	N(4)	61.9(5)	O(5)	C(23)	C(22)	C(21)	-63.7(5)
O(8)	C(32)	N(4)	C(22)	1.1(6)	O(8)	C(32)	N(4)	C(39)	-178.6(4)
O(8)	C(32)	C(33)	C(34)	1.0(7)	O(8)	C(32)	C(33)	C(38)	-179.6(4)
O(9)	C(39)	N(4)	C(22)	-4.2(7)	O(9)	C(39)	N(4)	C(32)	175.5(4)
O(9)	C(39)	C(38)	C(33)	-174.5(4)	O(9)	C(39)	C(38)	C(37)	4.5(7)
N(1)	C(5)	C(4)	N(2)	-102.2(4)	N(1)	C(5)	C(4)	C(3)	132.5(3)
N(2)	C(4)	C(3)	C(2)	174.6(3)	N(2)	C(4)	C(3)	C(10)	53.8(4)
N(2)	C(11)	C(12)	C(13)	-178.7(4)	N(2)	C(11)	C(12)	C(17)	2.1(4)
N(2)	C(18)	C(17)	C(12)	0.8(4)	N(2)	C(18)	C(17)	C(16)	-177.7(4)
N(3)	C(23)	C(22)	N(4)	-118.4(4)	N(3)	C(23)	C(22)	C(21)	116.0(4)
N(4)	C(22)	C(21)	C(20)	179.1(3)	N(4)	C(22)	C(21)	C(40)	57.7(4)
N(4)	C(32)	C(33)	C(34)	-177.9(4)	N(4)	C(32)	C(33)	C(38)	1.5(4)
N(4)	C(39)	C(38)	C(33)	2.8(4)	N(4)	C(39)	C(38)	C(37)	-178.2(4)
C(1)	C(2)	C(3)	C(4)	132.7(5)	C(1)	C(2)	C(3)	C(10)	-105.4(5)
C(2)	C(3)	C(4)	C(5)	-62.5(4)	C(3)	C(4)	N(2)	C(11)	48.7(5)
C(3)	C(4)	N(2)	C(18)	-131.4(3)	C(4)	N(2)	C(11)	C(12)	178.4(3)
C(4)	N(2)	C(18)	C(17)	-179.4(3)	C(4)	C(5)	N(1)	C(6)	5.6(6)
C(4)	C(5)	N(1)	C(9)	178.1(3)	C(5)	N(1)	C(6)	C(7)	-129.1(4)
C(5)	N(1)	C(9)	C(8)	128.5(4)	C(5)	C(4)	N(2)	C(11)	-75.7(4)
C(5)	C(4)	N(2)	C(18)	104.3(4)	C(5)	C(4)	C(3)	C(10)	176.7(3)
C(6)	N(1)	C(9)	C(8)	-57.8(4)	C(6)	C(7)	O(2)	C(8)	57.0(4)
C(7)	O(2)	C(8)	C(9)	-57.5(4)	C(7)	C(6)	N(1)	C(9)	57.9(4)
C(11)	N(2)	C(18)	C(17)	0.5(4)	C(11)	C(12)	C(13)	C(14)	-177.5(4)
C(11)	C(12)	C(17)	C(16)	176.9(4)	C(11)	C(12)	C(17)	C(18)	-1.8(4)
C(12)	C(11)	N(2)	C(18)	-1.6(4)	C(12)	C(13)	C(14)	C(15)	0.4(6)
C(12)	C(17)	C(16)	C(15)	1.0(6)	C(13)	C(12)	C(17)	C(16)	-2.4(6)
C(13)	C(12)	C(17)	C(18)	178.9(4)	C(13)	C(14)	C(15)	C(16)	-1.8(7)

Table 7. Torsion Angles(°) (continued)

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
C(14)	C(13)	C(12)	C(17)	1.6(6)	C(14)	C(15)	C(16)	C(17)	1.0(6)
C(15)	C(16)	C(17)	C(18)	179.4(4)	C(19)	C(20)	C(21)	C(22)	120.7(5)
C(19)	C(20)	C(21)	C(40)	-118.0(5)	C(20)	C(21)	C(22)	C(23)	-57.7(4)
C(21)	C(22)	N(4)	C(32)	-135.8(4)	C(21)	C(22)	N(4)	C(39)	43.9(5)
C(22)	N(4)	C(32)	C(33)	-179.9(3)	C(22)	N(4)	C(39)	C(38)	178.4(3)
C(22)	C(23)	N(3)	C(24)	165.2(5)	C(22)	C(23)	N(3)	C(25)	-168.9(5)
C(22)	C(23)	N(3)	C(30)	20.9(7)	C(22)	C(23)	N(3)	C(31)	-24.1(7)
C(23)	C(22)	N(4)	C(32)	99.9(4)	C(23)	C(22)	N(4)	C(39)	-80.4(5)
C(23)	C(22)	C(21)	C(40)	-179.2(3)	C(32)	N(4)	C(39)	C(38)	-1.9(4)
C(32)	C(33)	C(34)	C(35)	179.9(4)	C(32)	C(33)	C(38)	C(37)	178.3(4)
C(32)	C(33)	C(38)	C(39)	-2.6(4)	C(33)	C(32)	N(4)	C(39)	0.3(4)
C(33)	C(34)	C(35)	C(36)	1.9(7)	C(33)	C(38)	C(37)	C(36)	1.4(6)
C(34)	C(33)	C(38)	C(37)	-2.3(6)	C(34)	C(33)	C(38)	C(39)	176.8(3)
C(34)	C(35)	C(36)	C(37)	-2.8(7)	C(35)	C(34)	C(33)	C(38)	0.6(6)
C(35)	C(36)	C(37)	C(38)	1.1(6)	C(36)	C(37)	C(38)	C(39)	-177.5(4)

Table 8. Non-bonded Contacts out to 3.75 Å

atom	atom	distance	ADC	atom	atom	distance	ADC
O(1)	C(26)	3.178(8)	66602	O(1)	C(24)	3.190(10)	66602
O(1)	C(35)	3.550(5)	67602	O(1)	C(25)	3.657(10)	66602
O(1)	O(9)	3.697(4)	56602	O(1)	C(21)	3.699(5)	56602
O(2)	C(36)	3.277(5)	45501	O(2)	C(8)	3.528(5)	57602
O(2)	C(1)	3.575(6)	45501	O(3)	C(24)	3.196(10)	66602
O(3)	N(3)	3.205(5)	66602	O(3)	C(23)	3.292(5)	66602
O(3)	C(32)	3.345(5)	66602	O(3)	C(30)	3.396(9)	66602
O(3)	O(8)	3.412(4)	66602	O(3)	O(5)	3.563(4)	66602
O(3)	C(26)	3.574(9)	66602	O(3)	N(4)	3.599(4)	66602
O(3)	C(40)	3.644(6)	56602	O(3)	C(25)	3.709(10)	66602
O(4)	C(6)	3.369(5)	56602	O(4)	C(7)	3.457(5)	56602
O(4)	O(9)	3.533(4)	56602	O(4)	C(4)	3.541(5)	56602
O(4)	C(2)	3.581(5)	56602	O(5)	C(9)	3.275(5)	56602
O(5)	C(3)	3.358(4)	66602	O(5)	C(10)	3.572(5)	66602
O(5)	C(1)	3.641(5)	66602	O(6)	C(14)	3.339(8)	65401
O(6)	C(19)	3.439(8)	65501	O(6)	C(27)	3.549(11)	65502
O(6)	C(20)	3.701(7)	65501	O(7)	C(27)	2.935(11)	65502
O(7)	O(7)	3.161(14)	65502	O(7)	C(14)	3.414(8)	65401
O(7)	C(29)	3.463(12)	65502	O(7)	C(25)	3.677(12)	65502
O(7)	C(31)	3.695(11)	65502	O(8)	C(31)	3.183(9)	66502
O(8)	C(30)	3.433(9)	66502	O(8)	C(22)	3.567(5)	66502
O(8)	C(13)	3.583(5)	66602	O(8)	C(20)	3.648(5)	66502
O(9)	N(1)	3.023(4)	56602	O(9)	C(18)	3.245(5)	56602
O(9)	C(5)	3.252(5)	56602	O(9)	C(6)	3.299(5)	56602
O(9)	C(9)	3.342(5)	56602	O(9)	N(2)	3.366(4)	56602
O(9)	C(17)	3.649(5)	56602	O(9)	C(10)	3.745(5)	66602
C(1)	C(36)	3.579(7)	67602	C(1)	C(8)	3.711(7)	65501
C(7)	C(36)	3.616(6)	45501	C(7)	C(18)	3.676(6)	56602
C(7)	C(8)	3.713(6)	57602	C(8)	C(8)	3.651(9)	57602
C(10)	C(39)	3.634(6)	66602	C(11)	C(40)	3.693(6)	56602
C(13)	C(34)	3.520(6)	66602	C(13)	C(28)	3.732(10)	45601
C(14)	C(28)	3.536(10)	45601	C(14)	C(19)	3.554(7)	55602
C(14)	C(29)	3.608(10)	45601	C(15)	C(25)	3.676(11)	55602
C(16)	C(37)	3.476(6)	56602	C(19)	C(26)	3.213(10)	45501
C(20)	C(26)	3.698(9)	45501	C(27)	C(29)	3.019(13)	65502
C(27)	C(27)	3.373(18)	65502	C(27)	C(31)	3.591(13)	65502
C(28)	C(40)	3.700(10)	66502	C(31)	C(32)	3.642(10)	66502

The ADC (atom designator code) specifies the position of an atom in a crystal. The 5-digit number shown in the table is a composite of three one-digit numbers and one two-digit number: TA (first digit) + TB (second digit) + TC (third digit) + SN (last two digits). TA, TB and TC are the crystal lattice translation digits along cell edges a, b and c. A translation digit of 5 indicates the origin unit cell. If TA = 4, this indicates a translation of one unit cell length along the a-axis in the negative direction. Each translation digit can range in value from 1 to 9 and thus ± 4 lattice translations from the origin (TA=5, TB=5, TC=5) can be represented.

The SN, or symmetry operator number, refers to the number of the symmetry operator used to generate the coordinates of the target atom. A list of symmetry operators relevant to this structure are given below.

For a given intermolecular contact, the first atom (origin atom) is located in the origin unit cell and its position can be generated using the identity operator (SN=1). Thus, the ADC for an origin atom is always 55501. The position of the second atom (target atom) can be generated using the ADC and the coordinates of the atom in the parameter table. For example, an ADC of 47502 refers to the target atom moved through symmetry operator two, then translated -1 cell translations along the a axis, +2 cell translations along the b axis, and 0 cell translations along the c axis.

An ADC of 1 indicates an intermolecular contact between two fragments (eg. cation and anion) that reside in the same asymmetric unit.

Symmetry Operators:

(1)	X,	Y,	Z	(2)	-X,	-Y,	-Z

Table 9. Least Squares Planes

Plane number 1

Atoms defining plane	Distance
N(2)	0.000(4)
C(11)	0.035(5)
C(12)	-0.008(4)
C(13)	-0.023(5)
C(14)	-0.010(5)
C(15)	0.024(5)
C(16)	0.011(4)
C(17)	-0.015(4)
C(18)	-0.023(5)

Additional Atoms	Distance
O(3)	0.116
O(4)	-0.032
C(4)	-0.012

Plane number 2

Atoms defining plane	Distance
N(4)	0.001(5)
C(32)	0.027(5)
C(33)	0.008(5)
C(34)	-0.018(6)
C(35)	-0.034(6)
C(36)	0.016(5)
C(37)	0.024(5)
C(38)	0.005(5)
C(39)	-0.041(5)

Additional Atoms	Distance
O(8)	0.041
O(9)	-0.148
C(22)	0.013

Summary

plane	mean deviation	χ^2
1	0.0165	156.0
2	0.0194	188.1

Dihedral angles between planes (°)

plane	1
2	43.63