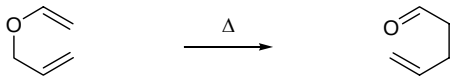
Chapter 1

The Lewis Acid–Catalyzed Ketene-Claisen Rearrangement

Introduction

In 1912, Claisen discovered that, at elevated temperatures, allyl vinyl ethers undergo a [3,3]-sigmatropic rearrangement to form γ,δ-unsaturated carbonyl compounds (equation 1).[1] Many elegant versions of this rearrangement have since been developed by Caroll, Eschenmoser, Johnson, Ireland, Bellus and others.[2] Consequently, the Claisen rearrangement now represents one of the most well-characterized and efficient methods available for the diastereoselective synthesis of structurally complex organic molecules. However, the development of enantioselective catalytic Claisen variants remains a valuable and challenging goal in synthetic chemistry.[3]



(eq. 1)

Asymmetric induction in the Claisen rearrangement has been achieved by the use of remote stereocontrol in chiral precursors or chiral auxillaries attached at various positions on the allyl vinyl ether.[2] In recent years, noteworthy enantioselective variants of the Claisen process involving external sources of chirality have also been achieved, by exploiting charge accelerated Claisen rearrangements.[3] While the thermal sigmatropic rearrangement of ally vinyl ethers require high temperatures (150 to 200 °C), charge accelerated rearrangements occur at temperatures as low as –78 °C. Incorporation of

either negative charge (at position 2a) or positive charge (at position 3) has been shown to facilitate this pericylic process (Figure 1).[2]

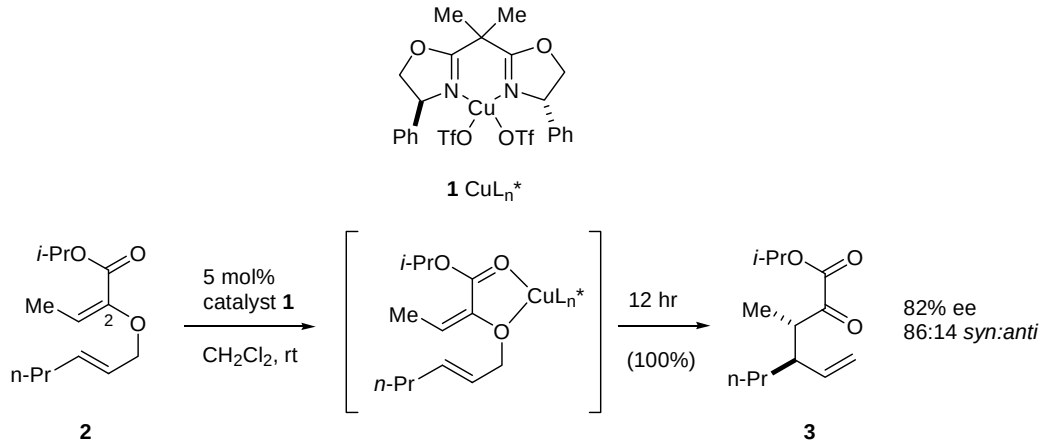
anion-accelerated
Ireland Claisen

cation accelerated
oxonia-Claisen

Figure 1. Charge-acceleration in the Claisen rearrangement

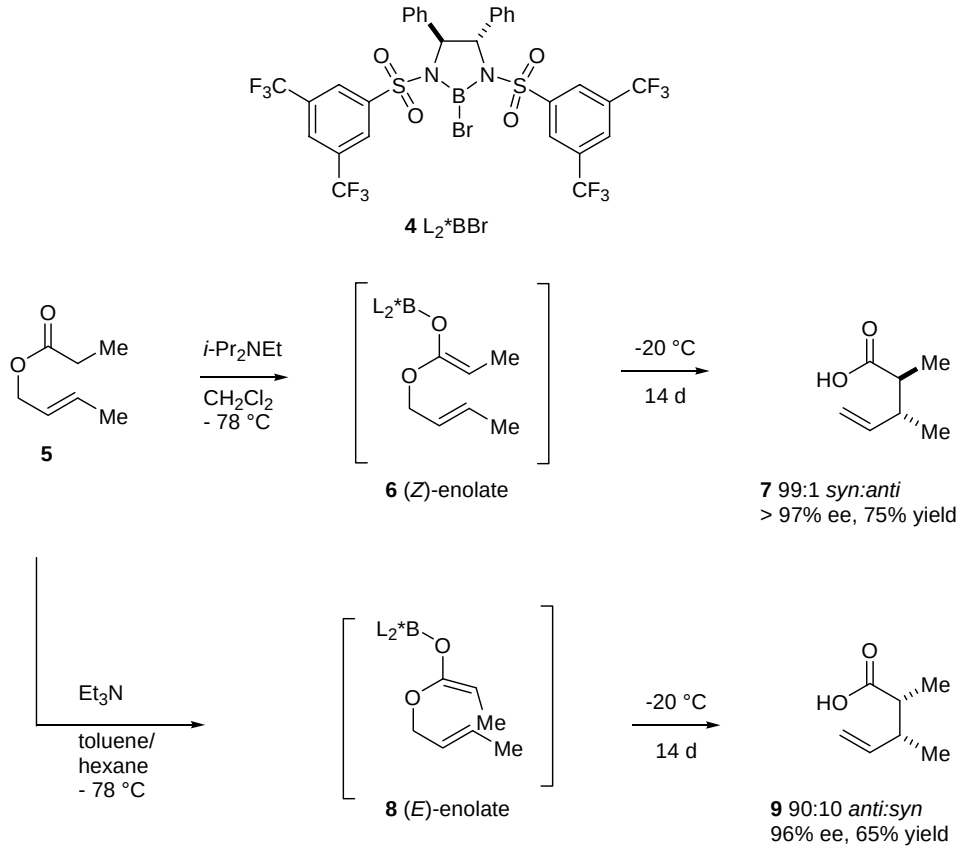
Despite the efforts of many research groups, only one asymmetric catalytic variant of the Claisen rearrangement has been demonstrated to date. In 2002, Hiersemann achieved the first enantioselective cation-accelerated Claisen rearrangement of allyl vinyl ethers (**1**) catalyzed by the copper bisoxazaline (**2**) to provide esters (**3**) (Scheme 1).[4] For acceptable levels of enantioselectivity to be obtained (72 to 88% e.e.), a chelating ester at the 2-position in the allyl vinyl ether substrates (**1**) is required. Although a breakthrough achievement, the inherent substrate limitation and the non-trivial synthesis of these precursors hinder the generality and synthetic utility of this method.

Scheme 1. First enantioselective catalytic Claisen rearrangement (Hiersemann, 2002)



Notably, a highly enantioselective and diastereoselective version of the Ireland-Claisen rearrangement of achiral esters has been developed by Corey (Scheme 2).[5] In the presence of the stillbenediamine derived bis(sulfonamide)boron Lewis acid **4**, crotyl propionate **5** is deprotonated by *i*-Pr_2NEt at –78 °C to furnish the (*Z*)-enolate **6** which upon warming rearranges to the *syn*-2,3-dimethyl-5-hexenoic acid **7** (97% e.e. and 99:1 dr). By simply changing the solvent system and the tertiary amine used for enolate formation, the (*E*)-enolate **8** can be accessed which subsequently rearranges to afford the *anti* isomer **9** in excellent enantio- and diastereoselectivity.

Scheme 2. Corey's enantioselective Ireland-Claisen promoted by boron complex **4**



Corey successfully applied this transformation in the total syntheses of natural products (+) fuscol[6] and dolabellatrienone.[7] Unfortunately, in addition to extended reaction times required (14 days), this methodology requires stoichiometric amounts of the chiral complex **4**. Turnover of the complex in this process is most likely inhibited by the formation of a stable boron-carboxylate complex **10** as the immediate product of the rearrangement (Figure 2).

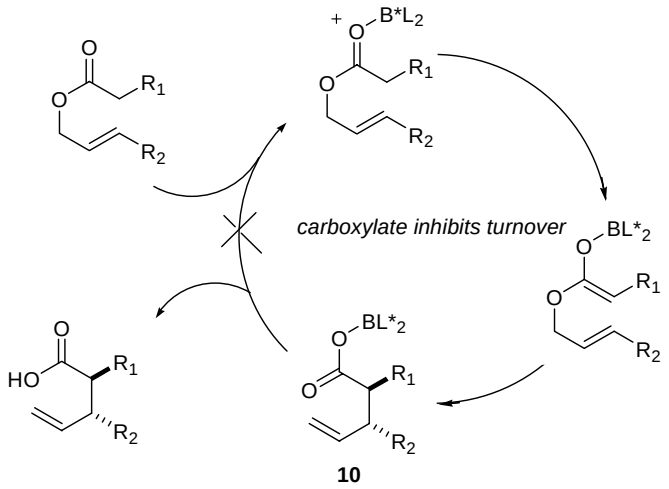


Figure 2. Carboxylate **10** inhibits catalytic turnover

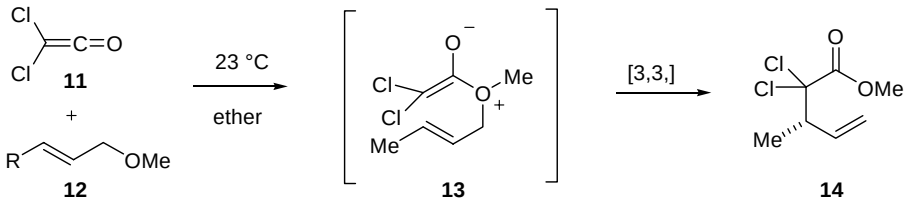
The development of enantioselective catalytic Claisen rearrangements with general synthetic versatility remains a valuable, yet unrealized goal. Our approach to this challenge begins with the design of a novel Claisen rearrangement that is amenable to Lewis acid catalysis (in contrast to the Ireland-Claisen reaction), and has greater substrate scope and a more facile starting material synthesis than the metal-catalyzed oxonia-Claisen methodology.

Reaction Design

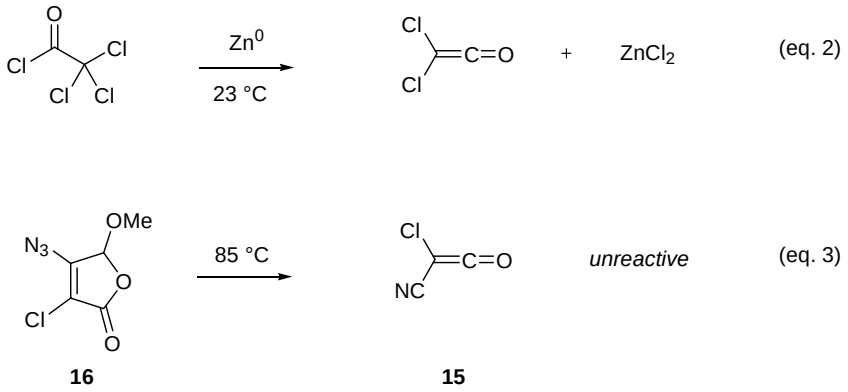
This research program was inspired by the conceptually novel ketene-Claisen rearrangement reported by Bellus in 1978 (Scheme 3).[8] Although expecting dichloroketene (**11**) and allyl ether (**12**) to participate in a [2+2] cycloaddition, the authors found instead that these reagents condense to form a zwitterionic enolate (**13**) which subsequently undergoes [3,3]-sigmatropic rearrangement to form γ,δ-unsaturated esters (**14**). The range of ketenes that could be used was reported to be limited to only

highly electron deficient ketenes, such as dichloroketene and chloro(trichloroethyl)ketene.

Scheme 3. Ketene-Claisen rearrangement by Bellus (1978)



However, detailed inspection of these reports revealed that the desired Claisen process occurred only when ketenes were generated *in situ* by the zinc-promoted dehalogenation of α-chloro acid chlorides, forming zinc(II) chloride as a byproduct (equation 2). For example, the highly electron deficient chlorocyanoketene **(15**) generated by thermolysis of lactone **16**, fails to participate in the ketene-Claisen rearrangement, even at elevated temperatures (equation 3).

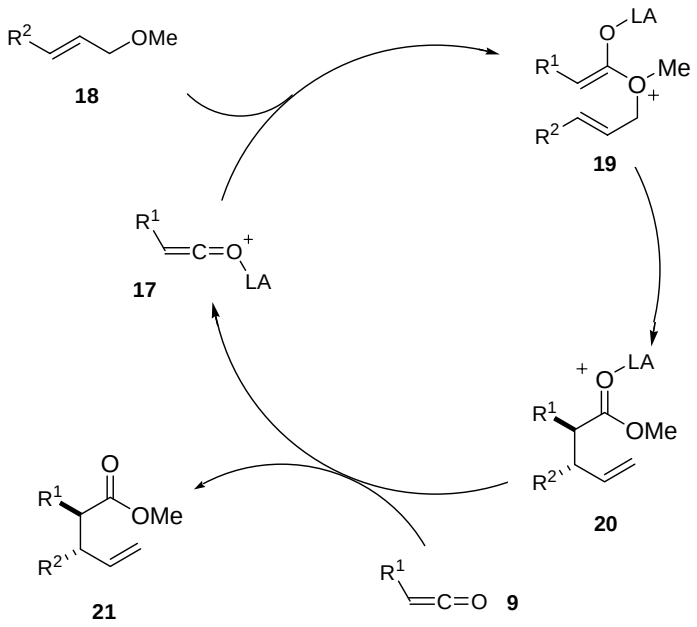


Based on these observations, we speculated that zinc chloride was a key component in this process, possibly activating the ketene towards nucleophilic attack. As such, we recognized the potential to use chiral Lewis acids as an attractive platform to induce asymmetry in the ketene-Claisen rearrangement. In contrast to Corey's boron-

mediated ester enolate Claisen reaction, where the anionic carboxylate product binds irreversibly to the boron Lewis acid, the product of the ketene-Claisen reaction is a neutral ester species which should therefore readily dissociate from a variety of Lewis acidic metals

As shown in Scheme 4, we envisioned that a range of ketenes **9** could undergo Lewis-acid activation (see **17**) and condense with allyl vinyl ethers **18** to produce zwitterionic allyl–vinyl oxonium complexes **19** which would subsequently undergo [3,3]-sigmatropic rearrangement to afford the metal-bound ester **20**. Dissociation of the neutral ester product **21** would regenerate the catalytically active Lewis acid species.

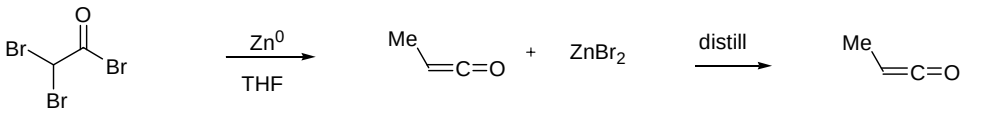
Scheme 4. Proposed Lewis acid–catalyzed ketene-Claisen rearrangement



Results and Discussion

In order to test whether or not the Lewis acid plays a catalytic role in the ketene-Claisen rearrangement, the ketene component needed to be isolated free from any salt byproducts prior to use. This was accomplished by Ward's procedure;[9] treatment of bromoacetyl bromide (**22**) with zinc produces methylketene (**23**) which can be co-distilled to provide a methylketene solution in THF (Scheme 5).

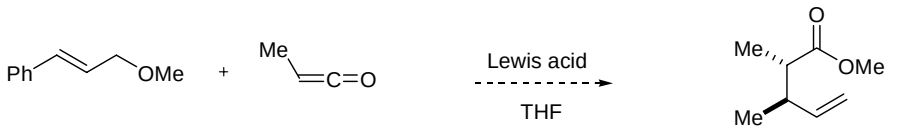
Scheme 5. Ward procedure for synthesizing methyl ketene



22 **23** *(**23** in THF)*

Our proposed ketene-Claisen rearrangement was first examined using cinnamyl methyl ether **24** and methylketene **23** (Scheme 6). In the presence of a variety of Lewis acids, the ether **24** failed to react with methylketene to produce the desired Claisen product **25** (Scheme 6).[10]

Scheme 6. Attempted Lewis acid–catalyzed ketene-Claisen rearrangement of **24**



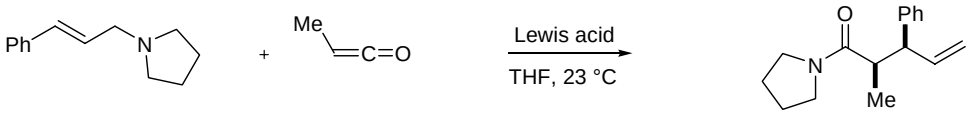
24 **23** **25** *not observed*

We reasoned that the allyl ether was not nucleophilic enough to condense with methyl ketene—a less electrophilic ketene than the halogenated ketenes used by Bellus. As a result, we considered using a more reactive nucleophile, such as an allylic amine.

The ability of allylic tertiary amines to participate in the ketene-Claisen has been previously studied by several groups.[11]

To our delight, we observed that cinammyl pyrrolidine **26** and methylketene **23** undergo an efficient ketene-Claisen rearrangement at room temperature under the influence of Lewis acids to provide Claisen adducts **27** (Table 1). A variety of oxophilic metal salts efficiently promote this transformation when used in stoichiometric amounts, including $ZnBr_2$, $AlMeCl_2$, $MgBr_2$, and $Yb(OTf)_2$ (entries 6–9). Moreover, this procedure can indeed be performed using catalytic quantities of Lewis acid with $AlCl_3$, $Ti(O\textit{i}\text{-}Pr)_2Cl_2$, $TiCl_4$, and $ZnBr_2$ (entries 2-5).

Table 1. Lewis acid–promoted ketene-Claisen rearrangement between cinnamyl pyrrolidine and methyl ketene



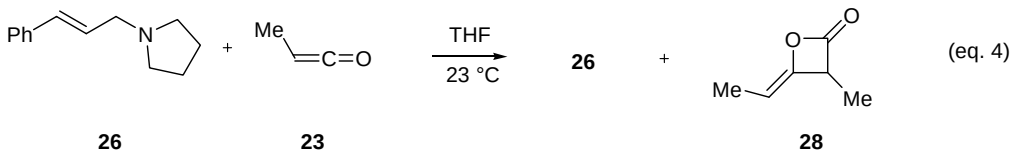
26 **23** **27**

entry	Lewis acid	equiv	% conv[a]	*syn:anti*[b]
1	--	--	NR	--
2	$AlCl_3$	0.20	90	>99:1
3	$TiCl_2(O\textit{i}\text{-}Pr)_2$	0.20	88	>99:1
4	$TiCl_4$	0.10	80[c]	>99:1
5	$ZnBr_2$	0.20	60	>99:1
6	$ZnBr_2$	1.0	89	>99:1
7	$AlMeCl_2$	1.0	80	>99:1
8	$MgBr_2$	1.0	80	>99:1
9	$Yb(OTf)_2$	1.0	90	>99:1

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

Role of the Lewis acid. The success of the ketene-Claisen rearrangement is contingent on the use of Lewis acids. In experiments conducted without metal salts, Claisen product **27** was not observed (Table 1, entry 1). Instead, these experiments

resulted in the recovery of the starting amine **26** and isolation of a β-lactone product **28** (equation 4).



26 **23** **28**

Product **28** presumably arises from the dimerization of methylketene, by a pathway known to be catalyzed by tertiary amines.[12] As shown in Figure 3, in the absence of Lewis acids, allyl amine **26** condenses with ketene **23** to form a zwitterionic enolate **29** which adds to a second equivalent of ketene **23**. The resulting zwitterionic intermediate **30** eventually undergoes intramolecular cyclization via **31** to form the observed ketene dimer **28**.

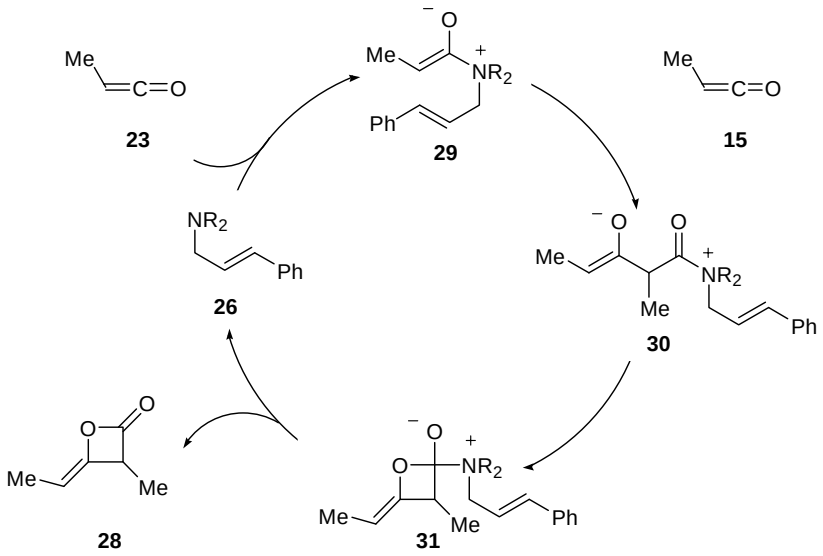
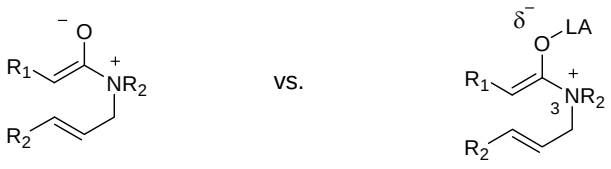


Figure 3. Amine catalyzed ketene dimerization pathway

As such, contrary to what we had previously speculated, the Lewis acid does not appear necessary for activation of ketene towards nucleophilic addition by allyl pyrrolidine. *What role then does the Lewis acid play in catalyzing the ketene-Claisen*

rearrangement? We proposed that binding of the Lewis acid to the resulting allyl-vinyl ammonium complex **29** helps deter ketene dimerization by attenuating the nucleophilicity of this zwiterrionic enolate (Figure 4). In addition, the Lewis acid bound zwitterion **32** is presumably more activated towards [3,3]-sigmatropic rearrangement than zwitterions **29** because **32** posses greater cationic character at the 3 position. This increased positive charge should accelerate rearrangement, as in the cation-accelerated oxonia Claisen (see Figure 1).



29 favors ketene dimerization

32 favors [3,3] rearrangement

Figure 4. Role of the Lewis acid (LA) in catalyzing the ketene-Claisen rearrangement

Origins of stereoselectivity. This new Lewis acid–catalyzed ketene-Claisen rearrangement was found to be highly stereoselective (Table 1, entries 2–9). Based on GC and ^{1}H NMR analysis, the *syn* diastereomer was observed to be favored over the *anti* isomer with >99:1 diastereoselectivity in the presence of every Lewis acids that was successful in this rearrangement. The high levels of stereoselectivity observed result from two sequential and highly selective steps.

First, addition of nucleophiles to monosubstituted ketenes usually results in exclusive formation of the (*Z*)-enolate (Figure 5).[13] As the lowest unoccupied molecular orbital (LUMO) is the C=O π^* orbital that lies in the plane defined by the ketene,[14] nucleophiles encounter a destabilizing steric interaction with the bulky R substituent on

the terminal carbon. Consequently, approach of the nucleophile occurs preferentially from the opposite side to the bulkier substituents, resulting in selective formation of the (*Z*)-enolate.

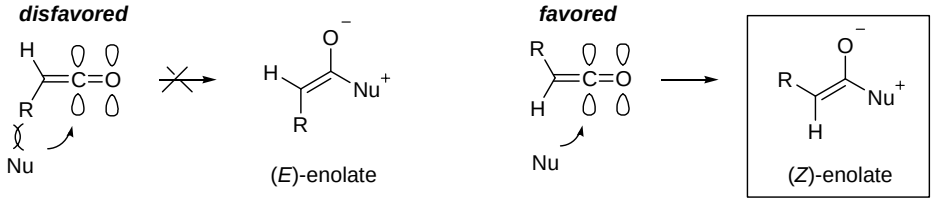


Figure 5. Origins of (*Z*)-enolate geometry control in additions to monosubstituted ketenes

Second, based on previous Claisen studies,[2] we predict that the zwitterionic enolate undergoes rearrangement through a highly ordered chair-like transition state to form the carbon-carbon σ bond in a diastereoselective fashion (Figure 6). The sense of diastereoselectivity is consistent with the model depicted. Notably, as the ketene-Claisen rearrangement proceeds at lower temperatures (room temperature) than a typical thermal aliphatic Claisen rearrangement (150 to 200 °C), higher levels of stereocontrol are achieved (>99:1 *syn:anti*).

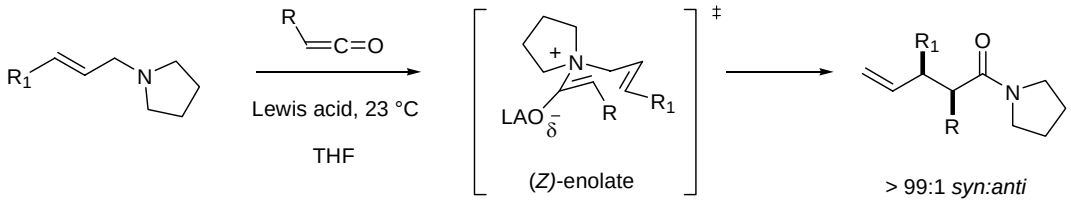
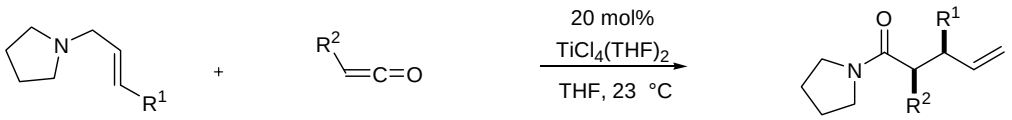


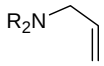
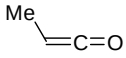
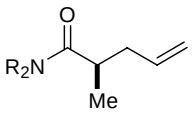
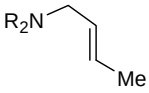
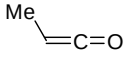
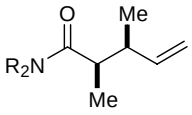
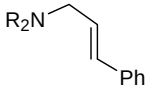
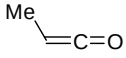
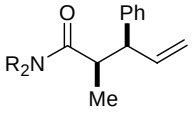
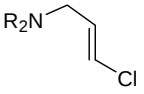
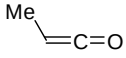
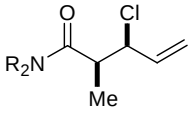
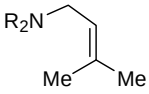
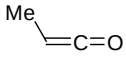
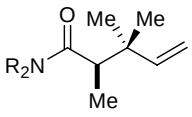
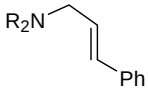
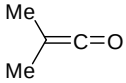
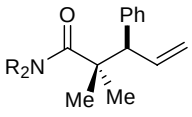
Figure 6. Origins of diastereoselectivity in the ketene-Claisen rearrangement

Scope of the ketene-Claisen rearrangement. Experiments that probe the scope of the ketene-Claisen rearrangement are outlined in Table 2. Variation in the allyl substituent (R = hydrogen, alkyl, aryl or halogen) was possible without loss in yield or diastereoselectivity (> 75% yield, > 99:1 *syn*:*anti*). Notably, access to quaternary carbons

at both the α and β positions to the amide moiety in the Claisen adduct are possible (entry 6 and 5, respectively).

Table 2. Ketene-Claisen rearrangement of representative allyl pyrrolidines

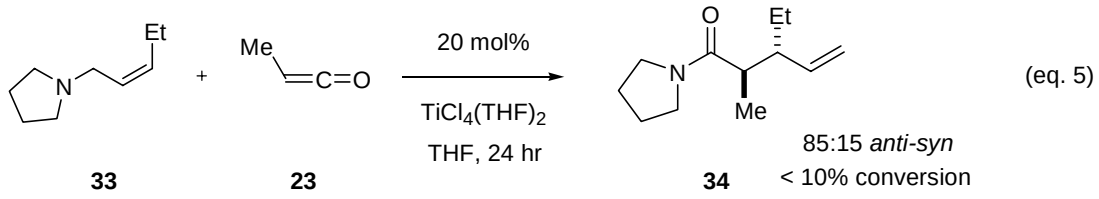


entry	amine[a]	ketene	product[a]	yield	*syn:anti*[b,c]
1				84	--
2				84	>99:1
3				85	>99:1
4				77	>99:1
5				68	--
6				86	--

[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 methods).

While excellent levels of *syn* stereoselection and reaction efficiency were observed with *trans*-allyl pyrrolidines (Table 2, entries 2–4, and 6), the *cis*-allylic pyrrolidines react less efficiently. For example, subjecting the (Z)-*N*-2-pentenyl-

pyrrolidine **33** to the standard reaction conditions resulted in only trace amounts of rearrangement product **34** as detected by ^{1}H NMR (equation 5).



These results can be understood by examining the transition states involved in the rearrangement of the *trans*- versus *cis*- allylic pyrrolidines (Figure 7). In the case of the *trans*-crotyl pyrrolidine **35**, a low-energy chair-like transition state **36** is accessible that places all substituents in pseudo-equatorial orientations. However, for the *cis* isomer **37,** the corresponding chair-like transition state **38** positions the R substituent in a pseudoaxial orientation, resulting in destabilization from the resulting 1,3-diaxial interaction of this substituent with the metal-bound enolate oxygen. As such, the rate of rearrangement for **37** to product **39** would be expected to be slower than the rate of rearrangement for the **35** to product **40**. As a consequence, ketene dimerization can compete with the desired rearrangement process, resulting in diminished yields of the desired **39**.

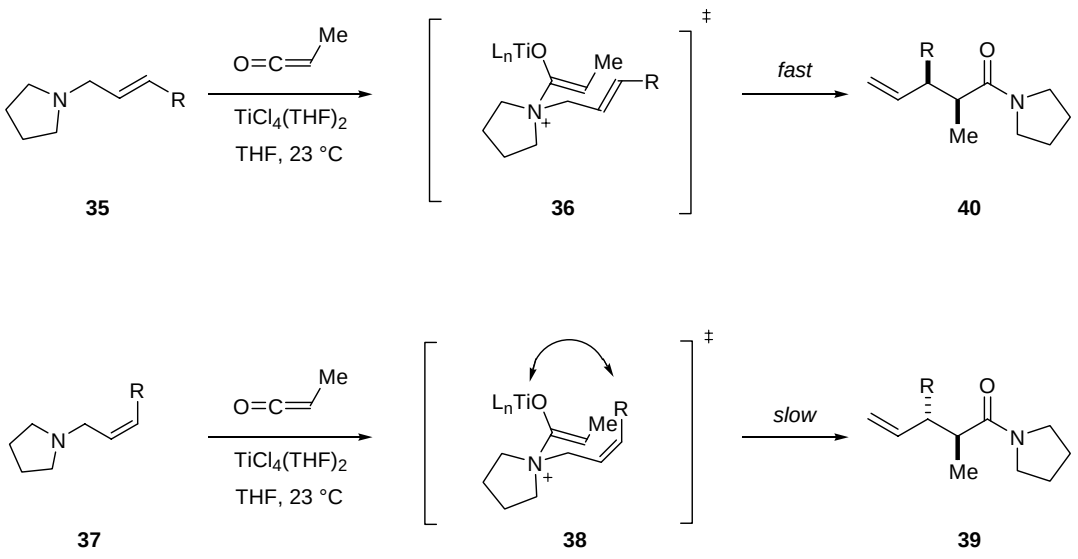


Figure 7. Rationale for relative rates of rearrangement for the *trans* vs. *cis* allyl amines

Concluding Remarks

A novel Lewis acid–catalyzed ketene Claisen rearrangement has been accomplished. A variety of allylic pyrrolidines can be tolerated by this methodology. However, demonstrating diversity in the ketene component was difficult to achieve. In the Ward procedure for generating ketenes, ketenes are isolated by codistillation with ethereal solvents. As such, only ketenes of low molecular weight, such as methylketene or dimethylketene can be accessed by this protocol. This limitation prompted us to explore a new strategy that generates ketenes *in situ* from readily available and bench-stable precursors (Chapter 2).

Experimental Methods

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.[15] 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.[16] 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.

^{1}H 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 ^{1}H 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 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).

Methyl ketene (23): Methyl ketene was freshly prepared for each use according to the procedure of Ward.[9] Zinc powder was activated by washing with aqueous 1 *N* HCl, water, methanol and ether, followed by drying *in vacuo*. The activated zinc powder (1.00 g, 15.3 mmol) was suspended in THF in a 100 mL receiving flask and attached to 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. A solution of freshly distilled 2-bromopropionyl bromide (0.52 mL, 5.0 mmol) in THF (3.5 mL) was 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 N_2 (l) cooled Schlenk flask. After addition of acid bromide was complete (8–10 minutes), the distillation was continued for another 5 minutes. The distillate was then warmed to –78 ^oC in a CO_2/acetone bath under N_2 (g) resulting in a bright yellow solution which was used without further purification. The IR spectrum of the solution displays an intense ketene band at 2130 cm^{-1}.

General Procedure: A round-bottomed 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 then diluted 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.

***N*-(2-Methyl-4-pentenoyl)-pyrrolidine (Table 2, entry 1).** Prepared according to the general procedure from (*E*)-*N*-2-Propenyl pyrrolidine (76 mg, 0.68 mmol), $TiCl_4(THF)_2$, (44 mg, 130 μmol), and methyl ketene 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}; ^{1}HNMR (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 Dimethyl-4-pentenoyl)-pyrrolidine (Table 2, entry 2).** Prepared according to the general procedure from (*E*)-*N*-2-butenyl pyrrolidine (94.4 mg, 0.753 mmol), $TiCl_4(THF)_2$, (50 mg, 150 μmol), and methyl ketene 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.[17]

(2R*, 3R*)-*N*-(3-Phenyl-2-methyl-4-pentenoyl)-pyrrolidine (Table 2, entry 3). Prepared according to the general procedure from (*E*)-*N*-3-Phenyl-2-propenyl pyrrolidine (107 mg, 0.571 mmol), $TiCl_4(THF)_2$, (19 mg, 57 μmol), and methyl ketene to provide 80% yield of the pure product (111 mg, 0.46 mmol) as a white solid: mp 85–86 ^oC; 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-propenylpyrrolidine (Table 2, entry 4).** Prepared according to the procedure of Butler.[18] (*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 ^oC, 10 torr); IR 2814, 1637, 1455, 1297, 116, 907 cm^{-1}; ^1HNMR (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, $(CH_2)_2N$), 1.80 (m, 4H, (C**H**$_2$$CH_2$)N); ^{13}C NMR

(100 MHz) 131.20, 119.86, 55.71, 53.85, 23.46; 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.

(2*R, 3*R**)-*N*-(3-Chloro-2-methy-4-pentenoyl)-pyrrolidine (Table 2, entry 4).** Prepared according to the general procedure from (*E*)-*N*-3-chloro-2-propenyl pyrrolidine (81.1 mg, 0.557 mmol), $TiCl_4(THF)_2$, (36 mg, 11 μmol), and methyl ketene to provide 77% yield of the pure product (86.4 mg, 0.431 mmol) as a yellow oil; IR 2980, 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-Methyl-3,3-dimethyl-4-pentenoyl)-pyrrolidine (Table 2, entry 5). Prepared according to the general procedure from (*E*)-*N*-3-methyl-2-butenyl pyrrolidine (87 mg, 0.62 mmol), $TiCl_4(THF)_2$, (42.0 mg, 126 μmol), and methyl ketene 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_2N), 1.86 (m, 2H, C**H$_2$**CH_2N),), 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 Dimethyl-3-phenyl-4-pentenoyl)-pyrrolidine (Table 2, entry 6). Prepared according to the general procedure from (*E*)-*N*-3-phenyl-2-propenyl pyrrolidine (68 mg, 0.36 mmol), $TiCl_4(THF)_2$, (22 mg, 66 μmol), and dimethyl ketene to provide 86% yield of the pure product (110 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, C**H**CH=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.

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