Aza-Claisen Rearrangements Initiated by Acid-Catalyzed Michael Addition

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*Received August 30, 1993**

Abstract: The reaction of allylic amines with dimethyl acetylenedicarboxylate is subject to protic acid catalysis and affords **15**, the product of Michael addition and aza-Claisen rearrangement. The sequence involves Michael addition of **4c** or **19–21** to generate an intermediate *N*-alkenyl ammonium salt **14** that undergoes a charge-accelerated rearrangement to **15**. Toluenesulfonic acid is a useful catalyst for the Michael addition step. Benzoic acid is not effective because the intermediate **14** is competitively dealkylated by the benzoate counterion. In one case, the intermediate *N*-alkenylammonium ion **18** has been detected by ^{1}H NMR spectroscopy and has been observed to undergo the aza-Claisen rearrangement at −20 °C. The sequence of Michael addition and rearrangement can also be catalyzed by Lewis acids. This variation affords **15** at temperatures below −40 °C. Finally, the Michael addition, aza-Claisen sequence has been applied to cyclic allylic amines **11** and **35**, resulting in ring expansion products **12**, **36**, and **37**.

Introduction

In 1931, Diels and Alder isolated an unusual 2:1 adduct from the reaction of dimethyl acetylenedicarboxylate (DMAD) and *N*-methylpyrrole **1**, but were unable to deduce the structure.[1a] Acheson and Vernon eventually identified the 2:1 adduct as **3** and suggested that this substance is formed from an intermediate 1:1 adduct **2** via a cyclic mechanism (Scheme 1, eq 1).[1b] This reaction is an early example of the aza-Claisen family of [3,3] sigmatropic shifts. Many related rearrangements involving the addition of allylic amines to acetylenic esters are now known, and recent papers by Kandeel and Vernon[2] and by Schwan and Warkentin[3] have explored the thermal reaction in depth. Mariano *et al.* have used analogous reactions of propiolate esters with allylic amines in alkaloid synthesis,[4] and several other groups have also made valuable contributions.[5] To quickly summarize this data (Scheme 2), the [3,3] rearrangement to **7** can take place by the equivalent of a cyclic transition state (eq 2) or by an ionic pathway involving C–N bond heterolysis to the ion pair **6** and recombination to **7** (eq 3). Depending on the conditions, **6** may decompose by enolate C-protonation or by nucleophilic capture of the cation, resulting in net N-dealkylation of **5** and the formation of **8** (eq 4). If the allylic fragment has additional substitution, then the cation can also decompose by elimination reactions.[5]

The DMAD-induced aza-Claisen rearrangement has found limited use for the synthesis of α-keto carboxylic acids via hydrolysis of **7** followed by decarboxylation,[2] but other applications remain largely unexplored. We have been interested in potential uses including the preparation of unsaturated acids **10** via controlled enamine hydrolysis (**7** to **9**) and base-induced oxaloyl cleavage and also the conversion of cyclic allylic amines such as **11** into medium ring amines **12**.[6] By comparison with other aza-Claisen techniques,[7] the DMAD–amine reactions are appealing for their experimental simplicity. On the other hand, the literature does not make clear why some reactions proceed at room temperature[1a,5c,d] while others require heating at 80 °C.[3-5] The empirical findings suggest either a pronounced dependence of rates on the substrate or the intervention of unknown catalysts.

At least some of the variations in the published reaction temperatures probably reflect medium effects. Thus, Kandeel and Vernon demonstrated that **4b** rearranges at room temperature (time scale of hours), provided that the experiment is done in acetonitrile solution.[2] The N-dealkylation process (eq 4) also competes, increasingly so as the water content of the acetonitrile is increased[2] or as the temperature is raised.[3] Using the best conditions (dry acetonitrile, room temperature), the distilled product **7b** contains ca. 10% of the byproduct **8b**. By comparison, the reaction of **4a** in deuteriochloroform has been reported to occur very slowly at room temperature (13% **7a** detected after 6 days).[3] Fragmentation to **8a** (eq 4) is the major pathway (37%), but additional byproducts are formed as the result of the amine-induced decomposition of chloroform. The authors recognized the possibility that proton transfer from chloroform could influence the mechanism of the aza-Claisen rearrangement.[3] Thus, protonation of **5** might give the cationic intermediate **14**, and subsequent [3,3] shift would benefit from acceleration by the cationic charge at nitrogen.[7] However, attempts to catalyze the reaction with a weak acid gave puzzling results. Treatment of **4a** and DMAD in chloroform with 5 mol % benzoic acid added actually *decreased* the yield of **7a**. These observations did not confirm the suspected conversion of **5** to **14**, but the authors left open the possibility that proton transfer may be involved in some unknown way.[3]

The findings from the benzoic acid experiments could be taken as evidence against other variants of an acid-induced process, such as the formation of **14** by the catalyzed Michael addition

* Abstract published in *Advance ACS Abstracts*, January 1, 1994.

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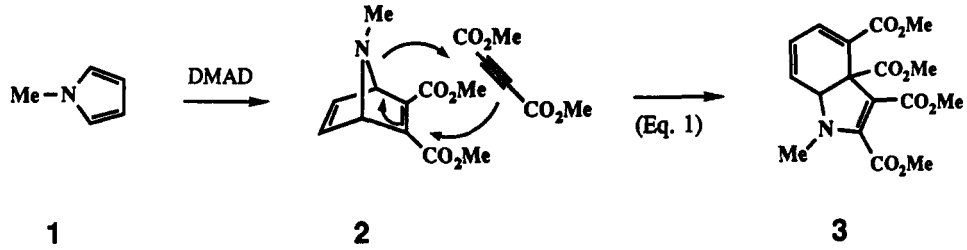
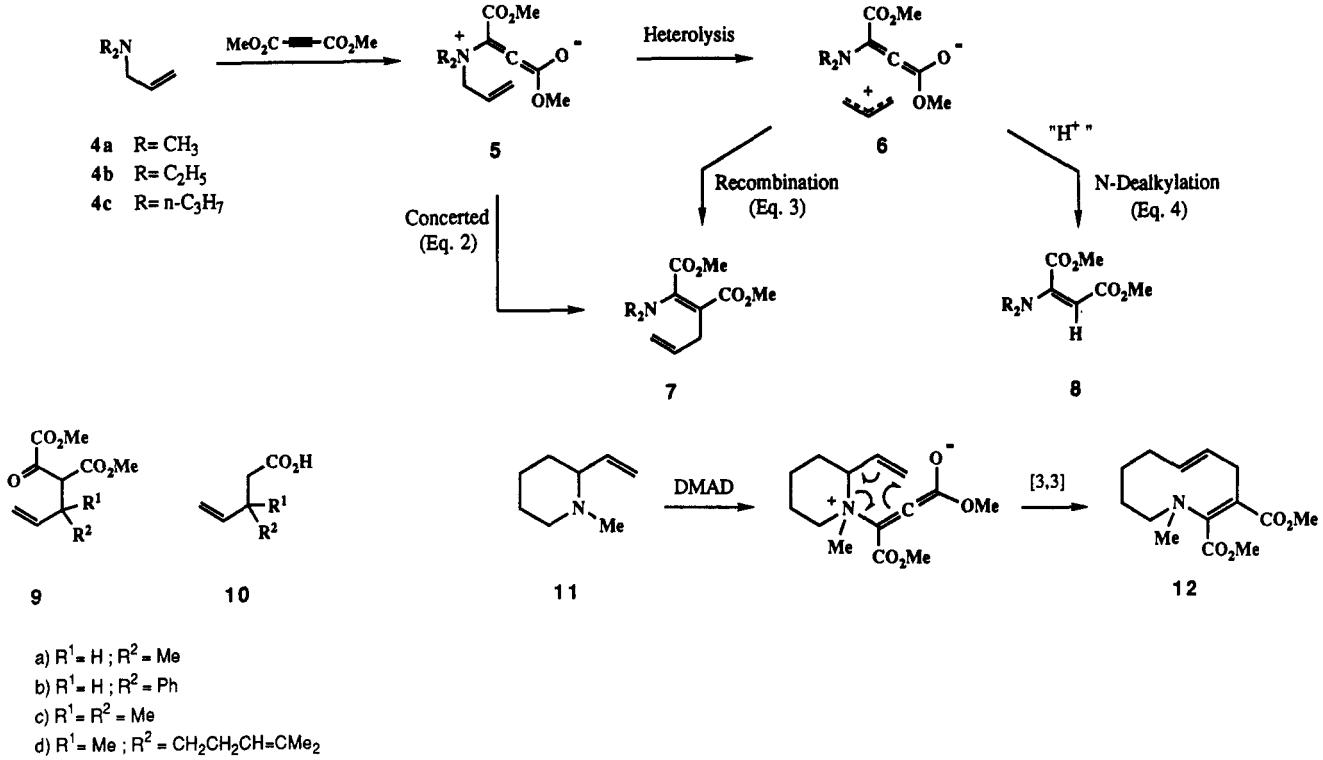
Scheme 1



Scheme 2



of the tertiary amine to the electron-deficient alkyne.[8] However, early experiments in our laboratory had shown that the hydrochloride salt of **4c** reacts with methyl propiolate at 20 °C in chloroform in a relatively fast reaction to give the aza-Claisen product **16** in >90% yield. This observation revives the issue of acid catalysis in the DMAD-induced aza-Claisen reactions. We now report conditions that make this process a viable, high-yielding method for C–C bond formation at room temperature or below.

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Results

Several different acids were explored as potential catalysts for the reactions of **4c** with DMAD (Table 1). It was found that 10 mol % toluenesulfonic acid (TsOH) induces conversion to **7c** in chloroform at room temperature in excellent yield. Trifluoroacetic acid was reasonably effective (entry 3), but benzoic acid gave only traces of **7c** together with other minor products that were difficult to isolate or identify because of the low conversion. Upon further investigation of reaction conditions, the reasons for this behavior became clear. When the reaction of **4c** with DMAD was repeated using 50 mol % benzoic acid (Table 1, entry 5), the usual product **7c** was formed (ca. 47% as a 3:1 mixture of isomers). However, **8c** was the major product (50%) according to NMR assay, and allyl benzoate (47%) was also present. This substance is probably formed by the N-dealkylation of **14a** by the nucleophilic benzoate counterion. Because this reaction destroys the intermediate as well as the catalyst, benzoic acid is not an effective catalyst for the conversion of **4** into aza-Claisen products. Acids having relatively non-nucleophilic counterions are necessary for good catalyst turnover.

Since the acid-catalyzed reaction is facile, the possibility exists that previous experiments involving the DMAD or the methyl propiolate induced aza-Claisen rearrangements may have encountered adventitious catalysis. We therefore investigated several other conditions as listed in Table 1 (entries 6–11). Less than 2% rearrangement could be detected after 24 h in $CDCl_3$ that had been freshly purified by filtration over alumina. Rearrangements reported earlier using deuteriochloroform may

Table 1. Acid-Catalyzed Michael Addition and Aza-Claisen Rearrangements of 4 + $R^3C{\equiv}CCO_2Me$

entry	solvent	Michael acceptor	time (h)	catalyst (mol %)	R	R^1	R^2	R^3	% **15**[a]	% **8**[b]
1	CD_3CN	DMAD[c]	48	TsOH (10%)	*n*-Pr	H	H	CO_2Me	99%[b]	1%
2	$CDCl_3$	DMAD[c]	18	TsOH (10%)	*n*-Pr	H	H	CO_2Me	95%[d]	5%
3	$CDCl_3$	DMAD[c]	6.5	CF_3CO_2H (10%)	*n*-Pr	H	H	CO_2Me	92%[b]	8%
4	$CDCl_3$	DMAD[c]	4	CF_3SO_3H (10%)	*n*-Pr	H	H	CO_2Me	97%[b]	3%
5	$CDCl_3$	DMAD[c]	29	$PhCO_2H$ (50%)	*n*-Pr	H	H	CO_2Me	47%	50%
6	CH_3CH_2CN	DMAD[c]	54		*n*-Pr	H	H	CO_2Me	75%	2%
7	PhCN	DMAD[c]	168		*n*-Pr	H	H	CO_2Me	48%[b]	<1%
8	DMF	DMAD[c]	54		*n*-Pr	H	H	CO_2Me	31%[b]	0%
9	THF	DMAD[c]	54		*n*-Pr	H	H	CO_2Me	0%	
10	$CDCl_3$[e]	DMAD[c]	27		*n*-Pr	H	H	CO_2Me	<2%	
11	THF/H_2O 5:1	DMAD[c]	54		*n*-Pr	H	H	CO_2Me	0%	
12	$CDCl_3$	MP[c,f]	16.5	**4c** + HCl[g] (100%)	*n*-Pr	H	H	H	>90%[b]	1%
13	CH_2Cl_2	MP[c,f]	24	TsOH (5%)	*n*-Pr	H	H	H	95%[d]	trace
14	$CDCl_3$	DMAD[c]	16	TsOH (10%)	*n*-Pr	H	Me	CO_2Me	95%	4%[a]
15	$CHCl_3$	DMAD[h]	23	TsOH (10%)	$(CH_2)_4$	H	Me	CO_2Me	>89%[i]	*j*
16	$CHCl_3$	DMAD[h]	4.5	TsOH (5%)	$(CH_2)_4$	H	Ph	CO_2Me	>91%[i]	*j*
17	$CDCl_3$	DMAD[h]	18	TsOH (10%)	*n*-Pr	Me	Me	CO_2Me	64%[k]	12%[a]
18	Et_2O/CH_2Cl_2 5:1	DMAD[c]	45	TsOH (10%)	$(CH_2)_5$	H	Ph	CO_2Me	88%	*j*

[a] Experiments at room temperature; isolated yield unless otherwise noted. [b] Yield by NMR analysis vs internal standard. [c] 1.1 equiv. [d] Distilled yield. [e] Filtered through basic alumina. [f] MP = methyl propiolate. [g] 0.2 equiv of amine present in addition to 1 equiv of the hydrochloride salt. [h] 1.2 equiv. [i] Overall yield after hydrolytic cleavage to **9**. [j] Not assayed. [k] 24% unreacted **4**.

therefore have been influenced by traces of HCl as the catalyst.[3] In the absence of acid, the reaction is very slow unless higher dielectric solvents are used, such as DMF, acetonitrile,[2] and propionitrile (entries 6–8). The zwitterionic mechanism via **5** appears to be consistent with the available evidence in these solvents. However, high yields are difficult to obtain because the intermediate **5** is easily diverted into the undesired N-dealkylation pathway if good nucleophiles are present.

To define temperature limits for the cationic aza-Claisen rearrangement, the acid-catalyzed reactions were studied more thoroughly. First, a model compound was prepared by the addition of tri-*n*-propylamine to DMAD in the presence of TsOH.[8] This reaction produced a stable salt **17** having a characteristic low-field signal for the vinyl proton at δ 7.36 ppm ($CDCl_3$ solution). With **17** available as a reference compound, the reaction of the allylic amine **4c** could be probed by NMR methods. Upon mixing **4c** with 0.34 equiv of TsOH at –40 °C, a complex spectrum resulted containing residual signals of both reactants and traces of the product **15a**, together with distinct signals that could be assigned to an ammonium salt **18**. Since **18** could not be isolated, the strongest evidence for this structure is the similarity in chemical shifts for the characteristic vinyl proton in **17** and **18** and the transient nature of the signals assigned to **18**. Slow conversion from **18** to **15a** could be monitored over hours at –20 °C or minutes above –10 °C. This experiment shows that the charge-accelerated aza-Claisen rearrangement of **18** is sufficiently fast to account for the TsOH-catalyzed reactions observed at room temperature. Presumably, the electron-withdrawing ester groups contribute somewhat to lowering the activation barrier. Similar effects are seen in other [3,3] sigmatropic rearrangements.[9] Thus, **18** rearranges significantly faster than do simple *N*-alkenyl *N*-allylammonium salts.[7]

The acid-catalyzed reactions of Table 1 proceed with minor complications due to the N-dealkylation pathway. Traces of the byproduct **8** were detected in nearly all cases, but the side reaction was problematic only in the case of the benzoic acid catalyzed reaction (entry 5). Qualitatively, the ratio of **15** to **8** increased as the nucleophilicity of the counterion in **14** decreased. Thus, triflic acid gave somewhat cleaner reactions than did TsOH in deuteriochloroform (entry 4 vs entry 2).

These observations indicate that eq 2 and eq 4 have acid-mediated counterparts. Acid catalysts activate the alkyne for nucleophilic addition of the amine, and the resulting **14** can undergo the charge-assisted aza-Claisen rearrangement to **15** (Scheme 3). If the counterion is nucleophilic, then competing S_N2-dealkylation of **14** can occur to give **8**. In the case of the more highly substituted amine **20**, the corresponding intermediate **14** may also be capable of N-dealkylation by an S_N1 process. Formation of 12% of **8c** in this experiment is consistent with the expected increase in C–N heterolysis of **14** in the acid-mediated equivalent of eq 3.

One additional complication was detected with the γ-disubstituted amine **20**. This substrate gave the usual Claisen product **15c** in reasonable yield (64%), but traces (ca. 2%) of an isomeric product were also obtained. This material was identified as **22**, the product expected from heterolysis of **14c**, followed by cation recombination with **8** at the less hindered allylic position. The reaction was also unusual in that considerable unreacted starting material **20** was recovered (24%). This fact implicates catalyst deactivation due to the N-dealkylation process discussed above and suggests that the allylic cation derived from heterolysis of **14c** can be intercepted by the tosylate counterion of TsOH. Comparable results were observed with the geraniol-derived amine **23** (Scheme 4), but the rearrangement in this case was marginally better (73% isolated yield of **24**).

To summarize the above findings, acid catalysis suppresses the undesired fragmentation pathway (eq 4) in simple acyclic substrates. It also lowers the reaction temperature substantially. However, the mechanistic options remain in delicate balance. Structural changes that interfere with effective overlap in the six-center transition state can be expected to promote the alternative pathways. Thus, attempted conversion of **25** into **26** gave only the fragmentation product **27**, corresponding to the formation of **8** from the acyclic amines.

Having established conditions for reliable rearrangement of the simple substrates, we turned to the issue of hydrolytic cleavage of representative adducts. As expected, conversion to structures **9** and **10** could be demonstrated easily. Treatment of the rearranged products **15** with aqueous acid (room temperature; two-phase conditions) afforded the oxaloyl derivatives **9** in excellent yield (Table 2). The reactions of entries 1–4 were performed using purified enamine esters, but comparable results were obtained using a one-pot method (entries 5, 7, 8). In the latter examples, the acid-catalyzed aza-Claisen reaction was done in the usual way, and the crude product was treated directly with dilute acid. The neutral extract consisted of **9** and traces of impurities that could be removed by flash chromatography.

Base-induced oxaloyl cleavage and simultaneous saponification of **9** were accomplished using aqueous sodium hydroxide at room temperature to give **10a** or **10b** in nearly quantitative yield after

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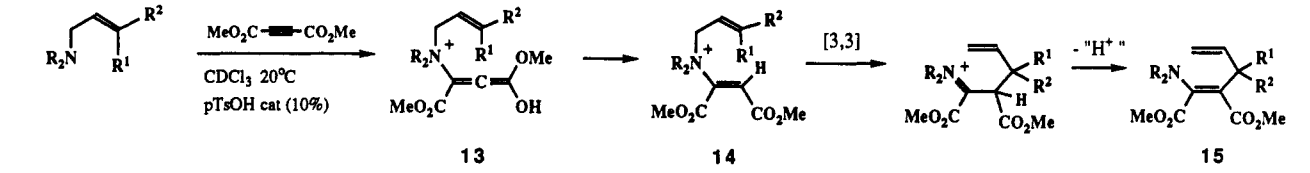
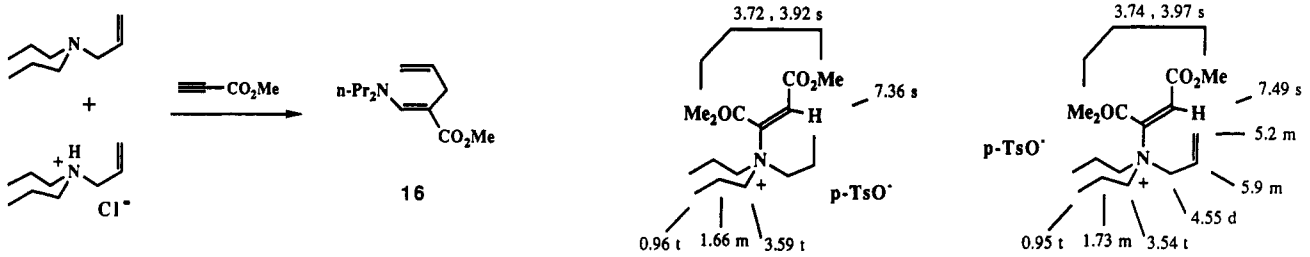
Scheme 3



13 14 15

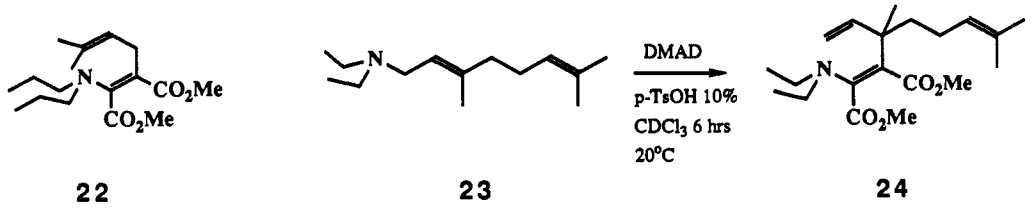
4c $R^1 = R^2 = H$; R = n-Pr
19 $R^1 = H$; $R^2 = Me$; R = n-Pr
20 $R^1 = R^2 = Me$; R = n-Pr
21a $R^1 = H$; $R^2 = Ph$; R = Et
21b $R^1 = H$; $R^2 = Me$; R = $(CH_2)_4$
21c $R^1 = H$; $R^2 = Ph$; R = $(CH_2)_4$
21d $R^1 = H$; $R^2 = Ph$; R = $(CH_2)_5$

a) $R^1 = R^2 = H$; R = n-Pr
b) $R^1 = H$; $R^2 = Me$; R = n-Pr
c) $R^1 = R^2 = Me$; R = n-Pr
d) $R^1 = H$; $R^2 = Ph$; R = Et
e) $R^1 = H$; $R^2 = Me$; R = $(CH_2)_4$
f) $R^1 = H$; $R^2 = Ph$; R = $(CH_2)_4$
g) $R^1 = H$; $R^2 = Ph$; R = $(CH_2)_5$

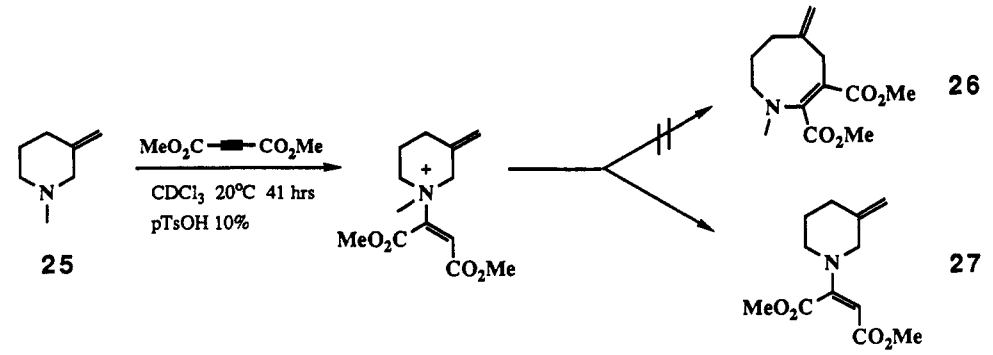


16 17 18

Scheme 4



22 23 24



25 26 27

neutralization. The overall conversion from **15b** to **10a** could be achieved in >90% yield if care was taken to purify **9a**. However, the oxaloyl cleavage did not take place cleanly in the more highly substituted **9c**. The product was a 1:2 mixture of **10c** and the α-keto acid derived from **9c** by complete saponification and decarboxylation.

Lewis Acid Catalysis

In the course of the low-temperature experiments with **4c** we noticed that a small amount of rearrangement had already occurred at −30 °C. Since the subsequent rearrangement by the observable intermediate **18** was too slow to account for the conversion at −30 °C, we suspected that the initially formed allenol **13** may be the species responsible for the −30 °C rearrangement. Conclusive proof for this conjecture has not been found. However, the above result suggested that the fastest rearrangements should be observed using catalysts that are less likely to proceed from the reactive allene intermediate to the enoate tautomer corresponding to **14**. Lewis acid catalysis was therefore investigated. The Lewis acid coordinated Michael adduct **28** should be capable of direct rearrangement to a Lewis acid complex **29** of the product enamine ester (Scheme 5). The overall conversion would benefit not only from the cationic charge but also from the conversion of an allene subunit into the highly delocalized vinylogous amide **29**. In the case of simple hydrocarbon systems, the corresponding transformation from an allene into a conjugated 1,3 diene is favored by >10 kcal/mol in terms of overall free energy.[10,11] A

(10) Thermodynamic data needed to compare the stability of the allene with **29** are not available. In the simple hydrocarbon analogue, the free energies of formation of 1,2-butadiene (47.8 kcal/mol) vs 1,3-butadiene (35.75 kcal/mol) strongly favor the latter.[11] The aza-analogue should be at least as favorable, and some fraction of this free energy advantage should be felt in the transition state for [3,3] shift.

Table 2. Acid Hydrolysis of Enamine Esters to α-Keto Esters 9

entry	enamine	solvent	acid	time (h)	R^1	R^2	yield[a]
1	**15a**	THF	5% HCl	16	H	H	86%[b]
2	**15b**	THF	5% HCl	17	H	Me	99%
3	**15c**	THF	5% HCl	5	Me	Me	91%
4	**24**	THF	5% HCl	22	$(CH_2)_2CH{=}CMe_2$	Me	93%
5	**15d**	$CHCl_3$	2 M H_2SO_4	36	H	Ph	93%[c]
6	**15e**	EtOAc/hexane	SiO_2	<1[d]	H	Me	89%[c]
7	**15f**	$CHCl_3$	1 M H_2SO_4	36	H	Ph	98%[c]
8	**15g**	Et_2O	2 M H_2SO_4	11	H	Ph	88%[c]

[a] Yields after flash chromatography unless otherwise noted. [b] Distilled yield. [c] Overall yield from allylic amine; enamine ester was not isolated. [d] Hydrolysis occurred on the time scale of flash chromatography using 1:4 ethyl acetate/hexane.

Scheme 5

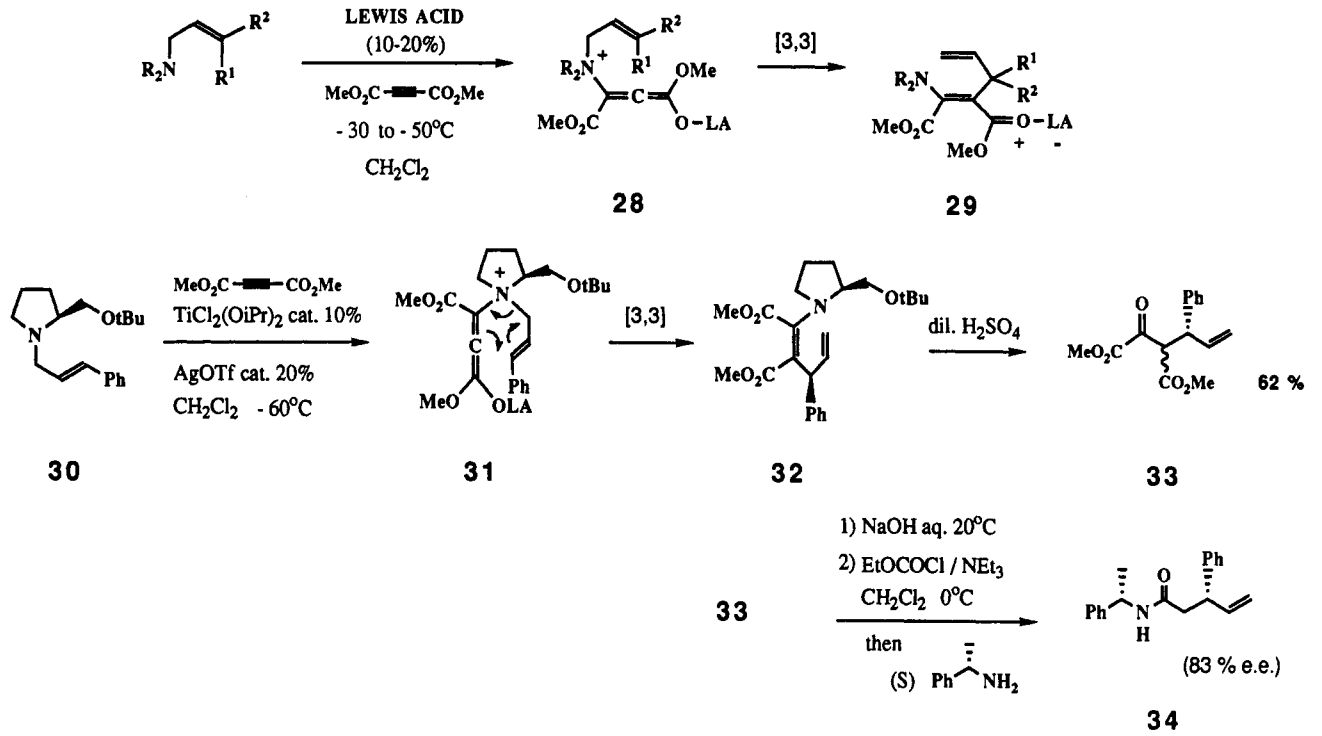


Table 3. Lewis Acid Catalyzed Michael Addition and Aza-Claisen Rearrangement to 15 Using 1.1 equiv of DMAD/CH_2Cl_2

entry	amine	catalyst (mol %)	time (h)	temp (°C)	R	R^1	R^2	R^3	% 7
1	**19**	$TiCl_2(OiPr)_2$ (20%)	0.3	0	*n*-Pr	H	Me	CO_2Me	51%[a]
2	**19**	$TiCl_2(OiPr)_2$ (27%)	14	−40	*n*-Pr	H	Me	CO_2Me	66%[a]
3	**19**	(catechol)AlMe (10%)	18	20	*n*-Pr	H	Me	CO_2Me	52%[a,b]
4	**19**	(BINOL)$TiCl_2$[c] (27%)	18	−40	*n*-Pr	H	Me	CO_2Me	93%[d]
5	**21c**	$TiCl_2(OiPr)_2$ (10%)	18	−40	$(CH_2)_4$	H	Ph	CO_2Me	83%[d]
6	**21c**	(BINOL)$TiCl_2$[c] (27%)	18	−40	$(CH_2)_4$	H	Ph	CO_2Me	92%[d]
7	**21a**	$TiCl_2(OiPr)_2$ (10%) AgO_3SCF_3 (25%)	24	−60[e]	Et	H	Ph	CO_2Me	83%[d]

[a] Isolated yield of **15**. [b] 28% of **8** was also formed. [c] Powdered 4-Å molecular sieves were present. [d] Overall yield after hydrolysis to **9**. [e] Bath temperature; some reaction occurs upon warming.

fraction of this free energy advantage in the transition state for [3,3] sigmatropic rearrangement should lower the activation barrier for the aza-Claisen process.

In the event, Lewis acids based on the titanium blend reagents[12,13] were found to catalyze the conversion of allylic amines into the DMAD-derived aza-Claisen products. Thus, treatment of **19** or **21c** with DMAD and 10–20% $TiCl_2(OiPr)_2$ gave the expected products of aza-Claisen rearrangement. These reactions were assayed after dilute acid cleavage to give **9a** or **9b**, and overall conversions of ca. 90% were demonstrated using the catalyst obtained from BINOL and $TiCl_2(OiPr)_2$ (Table 3).

A low-temperature experiment was also performed to probe the temperature limits for the process. Thus, a CD_2Cl_2 solution of **21a** was treated with DMAD and the catalyst generated from $TiCl_2(OiPr)_2$ + AgOTf.[12] Analysis at −50 °C by ^1H NMR revealed traces of rearrangement, and further progress of the reaction could be monitored at −40 °C over a time scale of hours, ca. 50% conversion after 2 h. Relatively rapid reaction was observed upon warming the sample to −20 °C. The Lewis acid catalyzed reactions are the fastest aza-Claisen rearrangements observed to date. Presumably, the rate advantage reflects a combination of the cationic acceleration mentioned earlier, together with the added driving force due to the conversion of an allene into the conjugated enamine. We are aware of one previous example of an aza-Claisen rearrangement that proceeds rapidly at 0 °C, a reaction that involves rearrangement of a vinyl aziridine

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(12) Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1403.
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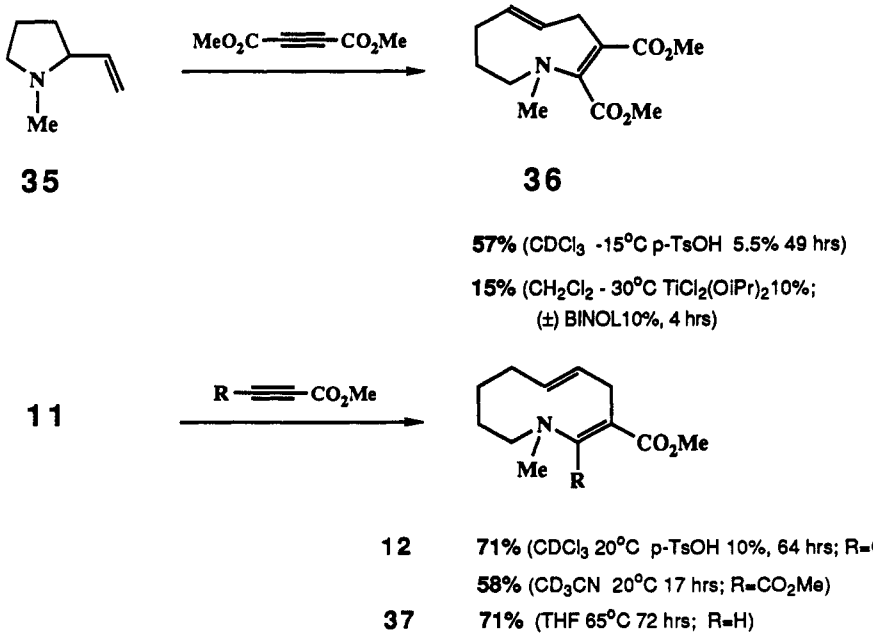
Scheme 6



to a seven-membered ring.[5b] This transformation is accelerated by release of aziridine ring strain.[5b,14] Thus, the Lewis acid catalyzed reactions of DMAD with simple allylic amines can be recommended for applications where the temperature of reaction is critical. However, for routine synthetic applications, the protic acid catalyzed reactions are more practical.

The potential of the Lewis acid catalyzed reactions for asymmetric synthesis was briefly explored. Conversion of an achiral allylic amine into **28** results in the creation of a chiral allene structure and suggests the possibility of control by a chiral Lewis acid catalyst. Alternatively, a chiral allylic amine such as **30** might allow the synthesis of enantiomerically enriched products under conditions of substrate control. In this case, the chiral amine subunit would serve in the less desirable role of a covalently bound auxiliary, and recycling of the amine obtained after hydrolysis of **32** would be necessary. Both of these options have been probed starting with the chiral substrate **30**.

The inherent capacity of **30** for relaying stereochemical information to the newly created stereogenic carbon in **32** was evaluated using the simple achiral catalyst $TiCl_2(OiPr)_2$. A value of 83% ee was determined after the hydrolytic cleavage to **33** and conversion into the (*S*)-α-methylbenzylamine-derived amide **34** for NMR assay, and absolute stereochemistry was assigned by X-ray analysis. The rearrangement was then repeated using a variety of Lewis acid catalysts modified with chiral ligands. The catalyst obtained from (*R*)- or (*S*)-1,1′-bi-2-naphthol and 10% $TiCl_2(OiPr)_2$[12] gave the most promising results with achiral substrates, but ee values in excess of 30% were not obtained with **21a**. In the case of the chiral substrate **30**, the evidence for double asymmetric induction in the derived **33** proved to be vanishingly small, and ee values of 80% and 86% were obtained with the (*S*) and the (*R*) 1,1′-bi-2-naphthol-derived titanium catalysts, respectively. So far, we have not found conditions where catalyst control is effective by comparison to the best examples of substrate control.[15] The distance between the metal ligands and the bonding sites in the intermediate **31** may be too large to control the initial Michael addition process.

Ring Expansions

With a variety of catalyzed and uncatalyzed reaction conditions available, the ring expansion applications were explored. Both the five- and the six-membered amine substrates **35** and **11** were studied using DMAD as the Michael acceptor (Scheme 6). In contrast to the products from acyclic amines, ring-expanded enamines such as **12** were sensitive to hydrolysis during isolation, and they also were easily destroyed by acid catalysts. These problems were most severe in the case of the nine-membered ring system. Thus, the toluenesulfonic acid catalyzed DMAD reaction of **35** was performed at −15 °C, followed by chromatography over neutral alumina. The product **36** decomposed on attempted purification on silica gel, but it was obtained sufficiently pure for conclusive characterization by ^1H and ^{13}C NMR (57% recovery). The geometry of the *E*-disubstituted double bond was clear from the characteristic 15.5-Hz coupling in the ^1H NMR spectrum. Attempts to perform the reaction under conditions of Lewis acid catalysis were complicated by decomposition during workup, but some product was detected at −40 °C.

The six-membered amine **11** gave rearrangement products that were better behaved. The simple noncatalyzed reaction of **11** with DMAD in acetonitrile proceeded slowly at room temperature and gave **12** in 58% yield. Toluenesulfonic acid catalysis provided an improved 71% isolated yield of **12** under the usual conditions in deuteriochloroform. The reaction proceeded slowly between −10 and 0 °C according to NMR assay. A similar reaction catalyzed by $TiCl_2(OiPr)_2/AgOTf$[12] was significantly faster and could be monitored −35 °C. As in the nine-membered ring example, the *E*-disubstituted alkene was the exclusive initial product according to the NMR evidence. The enamine geometry is not rigorously known, but the more stable *E*-configuration as illustrated is supported by ^{13}C NMR chemical shift comparisons with acyclic analogues.[2]

The methyl propiolate reaction was also investigated. This reaction was more troublesome due to increased product sensitivity, and the acid-catalyzed process could not be performed in satisfactory yield. However, the noncatalyzed reaction occurred upon prolonged heating in THF, and the product **37** could be obtained in 71% yield and reasonable purity (ca. 90% by NMR assay) after distillation. All of these rearrangements follow the

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usual preference for *E*-disubstituted alkene products that has also been reported by Edstrom in the case of the dichloroketene-induced aza-Claisen ring expansions of similar substrates.[6]

Summary

The acid-catalyzed conversion from tertiary allylic amines and DMAD into products of aza-Claisen rearrangement has been achieved with both acyclic and cyclic substrates. Examples of the preparative utility of the aza-Claisen process have been demonstrated by the hydrolytic conversion into α-keto esters **9** and unsaturated acids **10** and by the extension to synthesis of medium ring amines **12**, **36**, and **37**. The reaction takes place at temperatures as low as −40 to −50 °C in optimal cases and is mechanistically distinct from the previously reported noncatalyzed reactions.[2-5] The Lewis acid catalyzed variation is accelerated by the free energy advantage resulting from conversion of an allene derivative into a stabilized conjugated enamine. We have recently encountered other examples of sigmatropic rearrangement where the transition state benefits from a similar allene driving force.[16]

Experimental Section

General. Analytical thin layer chromatography (TLC) was performed on precoated aluminum-backed silica gel (Merck 60F-254) or neutral alumina (Merck 150F-254). Flash chromatography was done on Merck 60 230–400-mesh silica gel. Melting points are uncorrected (Meltemp apparatus). All reactions were run under a N_2 atmosphere except for hydrolysis or oxaloyl cleavage reactions. THF, toluene, and Et_2O were distilled from sodium/benzophenone. Acetonitrile was distilled over P_2O_5 and then redistilled over K_2CO_3. Chloroform used in experiments on acid catalysis was passed over basic alumina. Deuterated chloroform was dried over 4-Å sieves. Methylene chloride was distilled over P_2O_5. DMF, PhCN, and CH_3CH_2CN were distilled over CaH_2. Allylic amines **4c**, **11**, **19**, **20**, **21**, **27**, and **35** were prepared using literature methods.[2,3,17]

1-(*N*,*N*-Di-*N*-propylamino)-2-carbomethoxy-1,4-pentadiene. Method A: *N*,*N*-Di-*n*-propylallylammonium Chloride Addition to Methyl Propiolate. A stream of HCl was bubbled into a solution of *N*,*N*-di-*n*-propylallylamine (0.050 mL, 39.8 mg, 0.28 mmol) in Et_2O (2.0 mL). Removal of Et_2O by slow evaporation under a N_2 stream followed by drying under vacuum afforded the crude hydrochloride salt. Di-*n*-propylallylamine (0.090 mL, 0.517 mmol) was then injected via a syringe, followed by $CDCl_3$ (2.0 mL), methyl propiolate (22.3 mg, 0.0236 mL, 0.265 mmol), and 2-bromomesitylene (Aldrich, 53 mg, 0.041 mL, 0.268 mmol) as internal standard. After the reaction mixture was stirred for 16.5 h at 20 °C, the yield of enamine ester **16** was estimated by ^1H NMR (99% vs 2-bromomesitylene).

Method B: TsOH-Catalyzed Addition. Dried *p*-toluenesulfonic acid (195 mg, 1.13 mmol, 5 mol % relative to amine) was dissolved in dichloromethane (35 mL), and freshly distilled *N*,*N*-di-*n*-propylallylamine (4.00 mL, 3.180 g, 22.5 mmol) was added by syringe. Methyl propiolate was then injected while stirring vigorously. A black color developed rapidly. After 24 h at 23 °C, an aliquot was taken and the solvent evaporated. ^1H NMR indicated complete consumption of the starting amine. After removal of solvent (aspirator), the residue was purified by distillation under reduced pressure (short-path apparatus) and **16** was collected as a pale yellow liquid, bp 93–94 °C (0.08 mmHg) (4.81 g, 95%): IR (neat (NaCl), cm^{-1}) 1682, C=C; 1598, C=C; 1195, CO, 200-MHz NMR ($CDCl_3$, ppm) δ 7.49 (1 H, s), 5.92 (1 H, ddt, J = 16.7, 10.4, 5.2 Hz), 4.99 (1 H, ddt, J = 16.7, 2.0, 2.0 Hz), 4.95 (1 H, ddt, J = 10.4, 2.0, 2.0 Hz), 3.66 (3 H, s), 3.17–3.05 (6 H, m), 1.67–1.47 (4 H, m), 0.88 (6 H, t, J = 7.4 Hz); ^{13}C NMR (67.93 MHz {H}, $CDCl_3$, ppm) δ 170.7, 148.2, 138.2, 113.3, 91.5, 54.2, 50.5, 28.8, 22.2, 10.4.

Table 1. Acid-Catalyzed Reaction of 4c with DMAD: Preparation of 15a. The same procedure as described for method B, above, was used but with the addition of the indicated amount (usually 10 mol % relative to the amine) of acids (CF_3CO_2H, CF_3SO_3H, or $PhCO_2H$) in $CDCl_3$ as solvent. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel (85:15 hexane/acetone eluent) to give **15a** as an oil: analytical TLC on silica gel, 1:4 acetone/hexane, R_f = 0.36; molecular ion calcd for $C_{15}H_{25}NO_4$, 283.17834; found m/e = 283.1780, error = 1 ppm; base peak = 254 amu; IR (neat (NaCl), cm^{-1}) 1734, C=O; 1699, C=C; 1570, C=C; 200-MHz NMR ($CDCl_3$, ppm) δ 5.88 (1 H, ddt, J = 17.1, 10.3, 5.3 Hz), 5.2–5.0 (2 H, m), 3.82 (3 H, s), 3.66 (3 H, s), 3.13 (2 H, ddd, J = 5.3, 1.9, 1.9 Hz), 3.00 (4 H, t, J = 7.3 Hz), 1.55–1.40 (4 H, m), 0.85 (6 H, t, J = 7.4 Hz); ^{13}C NMR (67.93 MHz {H}, $CDCl_3$, ppm) δ 169.2, 167.6, 153.0, 135.9, 114.9, 106.9, 53.8, 52.2, 51.5, 32.6, 21.9, 11.0.

The following compounds were prepared similarly. **15b**: a 3.3:1.0 mixture of *E*/*Z* enamines was obtained as an oil. Data for the major isomer: molecular ion calcd for $C_{16}H_{27}NO_4$, 297.193 97; found m/e = 297.1937, error = 1 ppm; base peak = 238 amu; IR (neat (NaCl), cm^{-1}) 1732, C=O; 1569, C=C; 1256, C—O, 270-MHz NMR ($CDCl_3$, ppm) δ 6.10–5.90 (1 H, m), 5.08–4.91 (2 H, m), 3.76 (3 H, s), 3.67 (3 H, s), 2.90–2.75 (5 H, m), 1.62–1.40 (4 H, m), 1.29 (3 H, d, J = 7.0 Hz), 0.87 (6 H, t, J = 7.3 Hz); ^{13}C NMR (125.76 MHz {H} DEPT 135, $CDCl_3$, ppm) δ 168.4 s, 166.9 s, 148.7 s, 140.7 d, 126.2 s, 113.5 t, 55.2 t, 51.7 q, 51.1 q, 37.5 d, 21.9 t, 18.5 q, 11.2 q. **15c**: oil, analytical TLC on silica gel, 1:9 acetone/hexane, R_f = 0.55; molecular ion calcd for $C_{17}H_{29}NO_4$, 311.209 62; found m/e = 311.2095, error = 0 ppm; base peak = 242 amu; IR (neat (NaCl), cm^{-1}) 1731, C=O; 1229, CO; 270-MHz NMR ($CDCl_3$, ppm) δ 5.88 (1 H, dd, J = 10.6, 17.5 Hz), 5.2–5.0 (2 H, m), 3.72 (3 H, s), 3.63 (3 H, s), 2.75–2.42 (4 H, m), 1.52–1.32 (4 H, m), 1.24 (6 H, s), 0.82 (6 H, t, J = 7.4 Hz); ^{13}C NMR (67.93 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 168.4 s, 165.6 s, 144.7 d, 140.1 s, 139.8 s, 111.4 t, 55.9 t, 50.8 q, 50.3 q, 38.6 s, 26.5 q, 21.2 t, 11.3 q. Isomer **22**: oil, analytical TLC on silica gel, 3:7 Et_2O/hexane, R_f = 0.24; molecular ion calcd for $C_{17}H_{29}NO_4$, 311.209 62; found m/e = 311.2056, error = 12 ppm; IR (neat (NaCl), cm^{-1}) 1735, C=O; 1698, C=C; 1572, C=C; 270-MHz NMR ($CDCl_3$, ppm) δ 5.09–5.00 (1 H, m), 3.80 (3 H, s), 3.67 (3 H, s), 3.05 (2 H, d, J = 6.0 Hz), 3.05–2.90 (4 H, m), 1.69 (3 H, s), 1.66 (3 H, s), 1.65–1.40 (4 H, m), 0.85 (6 H, t, J = 7.4 Hz); ^{13}C NMR (67.93 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 169.3 s, 167.7 s, 151.7 s, 132.3 s, 122.1 d, 110.6 s, 54.1 t, 52.1 q, 51.5 q, 27.7 t, 25.6 q, 21.9 t, 17.9 q, 11.1 q. **24**: analytical TLC on silica gel, 94:5:1 hexane/acetone/NEt_3, R_f = 0.33. The product was obtained as a viscous pale yellow oil: molecular ion calcd for $C_{20}H_{33}NO_4$, 351.240 97; found m/e = 351.2396, error = 4 ppm; base peak = 268 amu; IR (neat (NaCl), cm^{-1}) 1730, C=O; 1232, CO; 1204, CO; 270-MHz NMR ($CDCl_3$, ppm) δ 5.87 (1 H, dd, J = 10.8, 17.5 Hz), 5.12–4.95 (2 H, m), 3.72 (3 H, s), 3.64 (3 H, s), 2.58 (2 H, q, J = 7.2 Hz), 2.57 (2 H, q, J = 7.2 Hz), 2.05–1.90 (2 H, m), 1.66 (3 H, br s), 1.58 (3 H, br s), 1.55–1.45 (2 H, m), 1.28 (3 H, s), 1.01 (6 H, t, J = 7.2 Hz); ^{13}C NMR (125.76 MHz {H}, $CDCl_3$, ppm) δ 168.6, 165.4, 142.0, 141.3, 139.1, 131.1, 124.3, 113.0, 51.0, 51.0, 48.0, 42.3, 39.6, 25.5, 23.0, 22.9, 17.4, 13.4.

Zwitterionic 3-Aza-Claisen Rearrangement to 15a (Solvent Studies): Typical Procedure. To a flask washed with a NaOH solution, rinsed with distilled H_2O, and oven-dried was added *N*,*N*-di-*n*-propylallylamine (0.090 mL, 0.517 mmol), followed by CH_3CH_2CN (1.50 mL) and DMAD (0.071 mL, 0.577 mmol). After stirring for 53.5 h at 20 °C, the solvent was removed (aspirator), and flash chromatography on silica gel was done to purify the product using 1:9 acetone/hexane as eluent. The enamine ester **15a** was obtained (87.2 mg, 75%). The same procedure was applied to similar reactions with different solvents.

Benzoic Acid Induced Reaction of 4c with DMAD. Benzoic acid (51 mg, 0.418 mmol, 50 mol %) was dissolved in $CDCl_3$ (2.0 mL), and *N*,*N*-di-*n*-propylallylamine (119 mg, 0.150 mL, 0.844 mmol) and DMAD (132 mg, 0.114 mL, 0.929 mmol) were added. After stirring for 29 h, 2-bromomesitylene (56.0 mg, 0.043 mL, 0.281 mmol) as internal ^1H NMR standard was added. Formation of the products **15a**, **8c**, and allyl benzoate was confirmed by comparison with authentic spectra. Allyl benzoate was present in 47% yield on the basis of NMR assay vs the internal standard. After removal of the solvent (aspirator), the residue was purified by flash chromatography on silica gel, 1:9 EtOAc/hexane. The first fractions provided a mixture of allyl benzoate and 2-bromomesitylene, whereas the second fractions gave a 3:1 mixture of **15a** and a contaminant assumed to be the *Z*-isomer (109 mg, 0.386 mmol, 46% combined). The *Z*-isomer of **15a** could not be separated, and the tentative structure assignment rests on carbomethoxy ^1H NMR signals at δ 3.71 and 3.79 ppm and other NMR signals partially overlapping analogous signals of **15a** with the correct integral ratio. The third fraction provided

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8c (dimethyl 2-[*N*,*N*-di-*n*-propylamino]maleate), 112 mg (54%): analytical TLC on silica gel, 1:9 acetone/hexane, R_f = 0.11. The product **8c** was obtained as a colorless liquid: molecular ion calcd for $C_{12}H_{21}NO_4$, 243.147 02; found m/e = 243.1467, error = 1 ppm; base peak = 214 amu; IR (neat (NaCl), cm^{-1}) 1745, C=O; 1695, C=C; 1571, C=C; 200-MHz NMR ($CDCl_3$, ppm) δ 4.58 (1 H, s), 3.92 (3 H, s), 3.63 (3 H, s), 3.15–3.00 (4 H, m), 1.8–1.5 (4 H, m), 0.88 (6 H, t, J = 7.4 Hz); ^{13}C NMR (67.93 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 168.2 s, 166.0 s, 154.2 s, 83.0 d, 52.7 q, 52.6 t, 50.5 q, 20.4 t, 11.1 q.

Attempted Conversion of 25 to 26: Isolation of 27. Dried *p*-toluenesulfonic acid (8.0 mg, 0.046 mmol, 14 mol %) was dissolved in $CDCl_3$ (1.5 mL), and freshly distilled 1-methyl-3-methylenepiperidine (**25**) (48 mg, 0.058 mL, 0.325 mmol) and DMAD (55 mg, 0.048 mL, 0.39 mmol) were added by syringe. The solution was stirred at 20 °C for 41 h. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel, 1:4 acetone/hexane eluent; analytical TLC on silica gel, 1:4 acetone/hexane, R_f = 0.25. The product **27** obtained was an oil (18.5 mg, 24%): molecular ion calcd for $C_{12}H_{17}NO_4$, 239.115 72; found m/e = 239.1163, error = 2 ppm; base peak = 180 amu; IR (neat (NaCl), cm^{-1}) 1744, C=O; 1695, C=C; 1576, C=C; 200-MHz NMR ($CDCl_3$, ppm) δ 4.98–4.80 (2 H, m), 4.76 (1 H, s), 3.93 (3 H, s), 3.67 (2 H, s), 3.64 (3 H, s), 3.26–3.21 (2 H, m), 2.33 (2 H, t, J = 6.4 Hz), 1.80–1.66 (2 H, m); ^{13}C NMR (67.93 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 168.0 s, 165.9 s, 153.9 s, 140.6 s, 111.4 t, 85.5 d, 53.7 t, 52.7 q, 50.7 q, 48.0 t, 31.8 t, 25.7 t.

Table 2: Acid Hydrolysis of Enamine Esters to α-Keto Diesters 9. Dried *p*-toluenesulfonic acid (94 mg, 0.546 mmol, 5 mol %) was dissolved in $CHCl_3$ (30 mL). While stirring freshly distilled *N*-cinnamylpyrolidine **21c** (2.056 g, 10.98 mmol) was added to the solution. After 4.5 h, TLC (SiO_2, 1:9 MeOH/$CHCl_3$) indicated consumption of the amine and a new intense spot was present (I_2 as developer). Hydrolysis of the crude enamine ester was performed by the addition of H_2SO_4 (5%, 50 mL) while vigorously stirring the two-phase mixture at 20 °C. The $CHCl_3$ phase was separated and the product further extracted with 2 × 50 mL of $CHCl_3$. After combining the organic phases, drying on Na_2SO_4/$MgSO_4$, filtration, and removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel, 1:4 EtOAc/hexane eluent; analytical TLC on silica gel, 3:7 EtOAc/hexane, R_f = 0.41. The keto diester **9b** was obtained as an inseparable (1:1) mixture of diastereoisomers (2.76 g, 91% overall): molecular ion calcd for $C_{15}H_{16}O_5$, 276.0998; found m/e 276.0991, error = 2.5 ppm; base peak = 117 amu; IR (neat (NaCl), cm^{-1}) 1754, C=O; 1735, C=O; 1256, CO; 200-MHz NMR ($CDCl_3$, ppm) δ 7.40–7.15 (5 H, m), 6.14–5.89 (1 H, m), 5.19–5.04 (2 H, m), 4.7 (1 H, d, J = 10.3 Hz), 4.27–4.11 (1 H, m), 3.89 (1.5 H, s), 3.79 (1.5 H, s), 3.71 (1.5 H, s), 3.48 (1.5 H, s); ^{13}C NMR (67.93 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 187.0 s, 186.7 s, 167.1 s, 166.8 s, 160.3 s, 160.0 s, 139.6 s, 139.1 s, 137.5 d, 137.0 d, 128.4 d, 128.3 d, 127.9 d, 127.7 d, 126.9 d, 116.9 t, 116.3 t, 58.6 d, 58.3 d, 53.0 q, 52.8 q, 52.3 q, 52.1 q, 48.9 d.

The following were prepared similarly. **9a**: oil, analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.32. The product was obtained as a 1:1 inseparable mixture of diastereoisomers: molecular ion calcd for $C_{10}H_{14}O_5$, 214.084 04; found m/e = 214.0838, error = 1 ppm; IR (neat (NaCl), cm^{-1}) 1754, C=O; 1733, C=O; 1261, CO; 270-MHz NMR ($CDCl_3$, ppm) δ 5.88–5.70 (1 H, m), 5.30–4.97 (2 H, m), 4.11 (0.5 H, d, J = 7.3 Hz), 4.08 (0.5 H, d, J = 7.3 Hz), 3.89 (1.5 H, s), 3.87 (1.5 H, s), 3.73 (1.5 H, s), 3.70 (1.5 H, s), 3.12–2.96 (1 H, m), 1.13 (3 H, d, J = 6.5 Hz); ^{13}C NMR (67.93 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 187.7 s, 167.9 s, 167.8 s, 160.6 s, 160.5 s, 140.0 d, 139.3 d, 115.7 t, 115.4 t, 59.2 q, 58.6 q, 53.0 q, 52.1 q, 37.1 d, 36.7 d, 17.6 q. **9c**: analytical TLC on silica gel, 1:4 EtOAc/hexane, R_f = 0.46. The product was obtained as a colorless liquid: molecular ion calcd for $C_{11}H_{16}O_5$, 228.099 70; found m/e = 228.1009; error = 5 ppm; IR (neat (NaCl), cm^{-1}) 1756, C=O; 1736, C=O; 1263, CO; 270-MHz NMR ($CDCl_3$, ppm) δ 6.01 (1 H, dd, J = 10.6, 17.6 Hz), 5.03 (1 H, dd, J = 0.5, 17.6 Hz), 5.02 (1 H, dd, J = 10.6, 0.5 Hz), 4.27 (1 H, s), 3.86 (3 H, s), 3.70 (3 H, s), 1.24 (6 H, d, J = 4.9 Hz); ^{13}C NMR (67.93 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 187.8 s, 167.5 s, 161.1 s, 144.3 d, 112.8 t, 61.2 d, 53.2 q, 52.1 q, 39.5 s, 25.7 q, 24.0 q. **9d**: oil, analytical TLC on silica gel, 3:7 EtOAc/hexane, R_f = 0.59; molecular ion calcd for $C_{16}H_{24}O_5$, 296.162 29; found m/e = 296.1652, error = 10 ppm; IR (neat, cm^{-1}) 1757, C=O; 1734, C=O; 200-MHz NMR ($CDCl_3$, ppm) δ 6.01 (0.33 H, dd, J = 10.8, 17.5 Hz), 5.92 (0.66 H, dd, J = 10.8, 17.5 Hz), 5.16–4.92 (3 H, m), 4.43 (0.67 H, s), 4.28 (0.33 H, s), 3.86 (1 H, s), 3.85 (2 H, s), 3.70 (2 H, s), 3.68 (1 H, s), 2.01–1.79 (2 H, m), 1.75–1.40 (2 H, m), 1.66 (3 H, s), 1.57 (3 H, s), 1.26 (2 H, s), 1.24 (1 H, s); ^{13}C NMR (25.8 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 187.7 s, 167.4 s, 161.0 s, 142.6 d, 131.6 s, 123.8 d, 114.5 t, 60.9 q, 53.2 q, 42.7 s, 39.3 t, 25.5 d, 22.5 t, 19.9 q, 18.7 q, 17.4 q.

Oxaloyl Cleavage, Typical Procedure. Methyl 2-oxo-3-carbomethoxy-4-methyl-5-hexenoate (**9a**) (67.0 mg, 0.313 mmol) was dissolved in THF (2.0 mL), and an aqueous NaOH solution (5 M, 1.0 mL) was added. After the mixture was stirred vigorously at 20 °C for 19.5 h, a white precipitate appeared. Chloroform (15 mL) was added followed by slow addition of aqueous 1 M HCl to pH ≈ 1 (pH paper). The organic phase was kept, and the aqueous layer was further extracted (2 × 10 mL of $CHCl_3$). Combination of the organic phases, drying on Na_2SO_4/$MgSO_4$, filtration, and evaporation of the solvent (aspirator) afforded 3-methyl-4-pentenoic acid (**10a**) (35.5 mg, 99%). The acid **10b** was similarly prepared. The structures were confirmed by comparison of NMR data with literature data.[18]

One-Pot Aza-Claisen Rearrangement and Oxaloyl Cleavage: Preparation of Methyl 3-Phenyl-4-pentenoate and 3-Phenylpentenoic Acid. To freshly distilled *N*-cinnamylpiperidine (3.41 g, 3.37 mL, 16.9 mmol) was added dried *p*-toluenesulfonic acid (146 mg, 0.85 mmol). Diethyl ether (90 mL) and sufficient CH_2Cl_2 (ca. 16 mL) to dissolve the ammonium salt were added. The reaction vessel was immersed in a water bath (15 °C), and DMAD (2.526 g, 2.19 mL, 17.77 mmol) was injected over 2–3 min. A bright yellow color appeared almost instantly. After 23 h, TLC analysis indicated incomplete reaction, so a second portion of *p*-toluenesulfonic acid was added (146 mg). After a total of 45 h, the reaction was complete. To hydrolyze the enamine, H_2SO_4 (2 M, 50 mL) was added, and the mixture was stirred vigorously for 11 h at 23 °C. An aliquot was evaporated and found to contain the keto ester **9b** and traces of DMAD (singlet at δ 3.85 ppm) by NMR analysis. The aqueous layer was discarded, and the ethereal layer was washed with 2 × 40 mL of H_2SO_4 2 M. The ether layer was then stirred vigorously with aqueous NaOH solution (5 M, 40 mL) at 23 °C for 24 h. A white precipitate appeared after a few hours, and its volume increased with time. After cooling in an ice-bath, a solution of H_2SO_4 (6 M, 25 mL) was added dropwise (exothermic). The mixture was then filtered, and the ethereal phase was kept. Further extractions of the aqueous layer (5 × 50 mL of $CHCl_3$), and combination of the organic phases, drying on Na_2SO_4/$MgSO_4$, filtration, and removal of the solvents (aspirator) afforded methyl 3-phenyl-4-pentenoate (2.84 g, 88% overall from *N*-cinnamylpiperidine) as a colorless liquid with >95% purity by NMR comparisons with authentic material.[18]

A portion of the methyl 3-phenyl-4-pentenoate (2.332 g, 12.26 mmol) was dissolved in ether (25 mL) and stirred with 5 M NaOH (34 mL) for 40 h. The same workup described above for the 3-methyl analogue gave 2.16 g of the acid **10b**[18] (>95% yield), >95% pure by NMR assay.

Synthesis of 30. *tert*-Butyl Ether of *N*-Cbz-Prolinol. In a thick-wall glass tube was weighed the Cbz-prolinol[19] (679 mg, 2.886 mmol). After cooling at −78 °C (acetone/CO_2 bath), isobutylene was condensed in the tube until the volume of liquid was ca. 2.0 mL. CH_2Cl_2 (9.0 mL) was then added (N_2 atmosphere), and concentrated H_2SO_4 was injected (0.060 mL). After sealing the tube, the bath was removed and stirring was continued for 8 h at 20 °C. TLC analysis of a sample indicated half conversion, so more isobutylene was condensed into the tube (1 mL), H_2SO_4 was added (0.100 mL), and the tube was resealed. After a total of 25.5 h the tube was cooled (−78 °C) and opened, and K_2CO_3 (0.50 g) was added while stirring vigorously. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel, 1:4 acetone/hexane eluent; analytical TLC on silica gel, 3:7 acetone/hexane, R_f = 0.43. The product was obtained as a colorless oil (818 mg, 97%): molecular ion calcd for $C_{17}H_{25}NO_3$, 291.183 44; found m/e 291.1853, error = 6 ppm; $[\alpha]_D$ = −58.2° (c = 10.89 g/100 mL, MeOH); IR (neat (NaCl), cm^{-1}) 1703, C=O; 200-MHz NMR ($CDCl_3$, ppm) δ 7.50–7.20 (5 H, m), 5.28–5.01 (2 H, m), 4.04–3.80 (1 H, br s), 3.65–3.07 (4 H, m), 2.09–1.70 (4 H, m), 1.15 (4 H, s), 1.09 (5 H, s); ^{13}C NMR (125.76 MHz {H}, $CDCl_3$, ppm) δ 154.55, 136.8, 136.6, 128.1, 127.7, 127.6, 127.5, 72.5, 66.4, 66.2, 62.3, 61.6, 57.7, 57.1, 46.7, 46.5, 28.5, 27.7, 27.3, 27.2, 23.5, 22.6.

***tert*-Butyl Ether of Prolinol.** Pure *tert*-butyl ether of CBz-protected (*S*)-(+)-prolinol (2.24 g, 7.69 mmol) was dissolved in MeOH (30 mL), and a small amount of Pd/C (50 mg, Degussa type E101 NO/W, Aldrich Co.) was added. After the system was flushed with N_2 and H_2, hydrogenation was carried out with a Parr apparatus (20 °C, 40 psi H_2) for 24 h. After filtration on a pad of Celite, rinsing, and removal of

(18) Guenther, H. J.; Guntrum, D. P.; Jaeger, V. *Liebigs Ann. Chem.* **1984**, 15.

(19) Cassal, J.-M.; Fürst, A.; Meier, W. *Helv. Chim. Acta* **1976**, *59*, 1917.

MeOH, distillation of the product gave a clear liquid (1.156 g, 96%): bp 100–105 °C, 20 mm, Kugelrohr; $[\alpha]_D = -3.8°$ (c = 5.95 g/100 mL, $CHCl_3$); IR (neat (NaCl), cm^{-1}) 3300, NH; 2972, CH; 1197, CO; 200-MHz NMR ($CDCl_3$, ppm) δ 3.45–3.10 (3 H, m), 3.08–2.78 (2 H, m), 2.55 (1 H, s), 1.95–1.65 (3 H, m), 1.52–1.30 (1 H, m), 1.18 (9 H, s); ^{13}C NMR (67.93 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 72.0 (s), 64.4 (t), 58.1 (d), 45.8 (t), 27.4 (q), 27.2 (t), 24.6 (t).

***tert*-Butyl Ether of *N*-Cinnamyl Prolinol 30.** The *tert*-butyl ether of (*S*)-prolinol (51.5 mg, 0.328 mmol) was dissolved in CH_2Cl_2 (2.0 mL), and *N*,*N*-diisopropylethylamine (50.9 mg, 0.069 mL, 0.394 mmol) was added by syringe. Under a N_2 atmosphere, cinnamyl bromide (64.5 mg, 0.328 mmol) was added and stirring continued for 24 h at 20 °C. After removal of solvent (aspirator), the residue was purified by flash chromatography on silica gel, 1:9 MeOH/$CHCl_3$ eluent; analytical TLC on silica gel, 1:9 MeOH/$CHCl_3$, R_f = 0.46. The product was obtained as a viscous oil (67.8 mg, 76%): molecular ion calcd for $C_{18}H_{27}NO$; 273.209 29; found m/e = 273.2092, error = 0 ppm; $[\alpha]_D = -76.6°$ (c = 5.20 g/100 mL, $CHCl_3$); IR (neat (NaCl), cm^{-1}) 3025, =CH; 2971, CH; 1198, CO; 200-MHz NMR ($CDCl_3$, ppm) δ 7.40–7.15 (5 H, m), 6.53 (1 H, d, J = 15.9 Hz), 6.34 (1 H, ddd, J = 5.6, 7.3, 15.8 Hz), 3.75 (1 H, ddd, J = 1.2, 5.7, 14.6 Hz), 3.50 (1 H, dd, J = 5.2, 8.9 Hz), 3.25 (1 H, dd, J = 6.9, 8.8 Hz), 3.21–3.06 (2 H, m), 2.72–2.57 (1 H, m), 2.39–2.21 (1 H, m), 2.05–1.49 (4 H, m), 1.18 (9 H, s); ^{13}C NMR (125.76 MHz {H}, $CDCl_3$, ppm) δ 137.0, 131.6, 128.3, 127.8, 127.0, 126.0, 72.5, 65.6, 63.2, 57.7, 54.6, 28.7, 27.4, 22.7.

Lewis Acid Catalysis: General Procedure Using $TiCl_2(OiPr)_2$ for Catalysis of the DMAD Reaction with 19. DMAD (81.3 mg, 0.070 mL, 0.57 mmol) was added via syringe to a solution of the *N*,*N*-di-*n*-propylcrotylamine (0.100 mL, 0.52 mmol) in CH_2Cl_2 (4.0 mL). After cooling at –40 °C (Cryocool bath) for a few minutes, a toluene solution (0.86 M) of $TiCl_2(OiPr)_2$[12,13] (0.120 mL, 0.103 mmol) was injected and stirring was continued for 14 h. After warming to room temperature, the solution was filtered over a plug of basic alumina with $CHCl_3$. After removal of the solvent (aspirator), the residue was purified by flash chromatography as described earlier to give enamine ester **15b** (101 mg, 66%).

(±)-(BINOL)$TiCl_2$ Procedure.[12] (±)-BINOL (Aldrich, 28.6 mg, 0.10 mmol) and 4-Å powdered molecular sieves (350 mg) were dissolved in CH_2Cl_2 (1.8 mL). After stirring for 5–10 min, a toluene solution of $TiCl_2(OiPr)_2$ (0.85 M, 0.116 mL, 0.10 mmol) was added. A deep red wine color appeared instantly, and stirring was continued for 60 min at 20 °C. *N*-Cinnamylpyrrolidine **21c** (98.4 mg, 0.100 mL, 0.525 mmol) was then added, and the mixture was cooled (Cryocool) to –40 °C. After 5 min, DMAD (81 mg, 0.070 mL, 0.57 mmol) was injected. After 18.5 h the reaction was quenched with HCl 5%/MeOH (1:1) (0.20 mL) for 30 min at –40 °C. After filtration and rinsing with $CHCl_3$, the solvents were partially removed (aspirator) and the residue was hydrolyzed with HCl (5%) (1.5 mL) while stirring vigorously at 20 °C for 28 h. The product **9b** was extracted with 3 × 10 mL of $CHCl_3$ and was purified as described above, 132 mg, 92% overall.

Lewis Acid Catalysis with $TiCl_2(OiPr)_2$: Conversion of 30 to 33 via 32. The catalyst was prepared according to the method of Mikami, Nakai, *et al.*[12] In a glovebox was weighed AgOTf (27 mg, 0.105 mmol, 21 mol %, Aldrich), (*R*)-(+)-BINOL (14.3 mg, 0.050 mmol, 10 mol %, Aldrich), and powdered 4-Å sieves (260 mg, Aldrich). CH_2Cl_2 (2.0 mL) was then injected via a syringe, followed by a freshly prepared toluene solution of $TiCl_2(OiPr)_2$ (0.86 M, 0.058 mL, 0.050 mmol, 10 mol %). The system was kept under N_2, and the mixture was stirred vigorously for 7 h at 20 °C. After cooling at –70 °C in a temperature-regulated bath (Cryocool), the amine **30** was injected (137 mg, 0.127 mL, 0.50 mmol). DMAD (77.5 mg, 0.067 mL, 0.55 mmol) was added after 10–15 min at –70 °C. Stirring was continued for 23 h, and the temperature was raised to –65 °C for an additional 47.5 h and finally quenched with a 1:1 solution of 0.1 M NaOH/MeOH (0.50 mL). Chromatography on a silica gel plug was used to remove residual starting amine, 3:7 EtOAc/hexane eluent. After removal of solvents (aspirator), the residue was dissolved in $CHCl_3$ (5.0 mL) and hydrolyzed at 20 °C with H_2SO_4 (1 M, 3.0 mL) for 30 h. Separation of the $CHCl_3$ layer, further extraction of the aqueous phase (2 × 5 mL of $CHCl_3$), drying of the combined organic phases on $Na_2SO_4/MgSO_4$, filtration, and removal of solvent (aspirator) provided the crude product, which was purified by flash chromatography on silica gel, 1:5 EtOAc/hexane. Pure **33** was obtained (91 mg, 66% overall). Basic oxaloyl cleavage under the conditions described before afforded the enantio-enriched acid **10b**, which was further coupled with (*S*)-benzylmethylamine using the mixed anhydride method (see below) to give **34** (86% ee by ^1H NMR assay of the amide mixture).

The same procedure as described above was repeated using (*S*)-(–)-BINOL in place of (*R*)-(+)-BINOL. The keto diester **33** was obtained (101 mg, 73% overall). The same assay as before indicated 80% ee.

In a third experiment, the same procedure was used except that no molecular sieves or BINOL was used. Thus, the reaction was performed with AgOTf (65 mg, 0.25 mmol, 50 mol %), $TiCl_2(OiPr)_2$ (crystallized from toluene at –78 °C, 23.6 mg, 0.10 mmol, 20 mol %), CH_2Cl_2 (1.50 mL), DMAD (85.5 mg, 0.074 mL, 0.60 mmol), and **30** (137 mg, 0.127 mL, 0.50 mmol). The reaction time for preforming the Lewis acid was 3 h at 20 °C, and the reaction was performed at –60 °C for 4 days. Following H_2SO_4 hydrolysis, the keto diester **9b** was obtained (85.6 mg, 62% overall) and oxaloyl cleavage afforded the acid **33** (83% ee, determined as described above).

Preparation of 34. To racemic 3-phenyl-4-pentenoic acid (**10b**) (84.5 mg, 0.477 mmol) was added CH_2Cl_2 (3.0 mL) and NEt_3 (72 mg, 0.100 mL, 0.716 mmol). After cooling in an ice-bath (3 °C), freshly distilled ethyl chloroformate (57 mg, 0.050 mL, 0.525 mmol) was injected. After stirring for 12 min, (*S*)-(–)-methylbenzylamine (Aldrich, 63.6 mg, 0.068 mL, 0.525 mmol) was added, and the bath was removed after 30 min. Stirring was continued at 20 °C for 18 h. After removal of solvent (aspirator), the diastereoisomers were purified by flash chromatography on silica gel, 1:3 EtOAc/hexane (95.5 mg, 72%). The mixture of products was then separated by an additional flash chromatography on silica gel, 1:4 EtOAc/hexane eluent. The less polar diastereomer (*S*,*R*)-*N*-benzylmethyl-3-phenyl-4-pentenamide was obtained in the first fractions, analytical TLC on silica gel, 3:7 EtOAc/hexane, R_f = 0.25. Pure material was obtained by crystallization from chloroform, mp 146–146.5 °C, colorless needles. An X-ray structure determination established the absolute stereochemistry: molecular ion calcd for $C_{19}H_{21}NO$; 279.162 32; found m/e = 279.1622, error = 0 ppm; base peak = 105 amu; $[\alpha]_D = -62.5°$ (c = 3.53 g/100 mL, $CHCl_3$); IR (neat (NaCl), cm^{-1}) 3437, NH; 1663, C=O; 200-MHz NMR ($CDCl_3$, ppm) δ 7.40–7.20 (10 H, m), 6.10–5.90 (1 H, m), 5.52–5.33 (1 H, br d, J = 7.1 Hz), 5.12–4.92 (3 H, m), 3.94–3.80 (1 H, q, J = 6.9 Hz); ^{13}C NMR (90.56 MHz {H}, $CDCl_3$, ppm) δ 170.1, 142.9, 142.5, 140.3, 128.6, 128.4, 127.6, 127.1, 126.6, 126.1, 114.8, 48.4, 46.1, 42.9, 21.2. The second fractions contained the more polar diastereomer: analytical TLC on silica gel, 3:7 EtOAc/hexane, R_f = 0.19; molecular ion calcd for $C_{19}H_{21}NO$; 279.162 32; found m/e = 279.1624, error = 0 ppm; base peak = 105 amu; $[\alpha]_D = -36.5°$ (c = 2.73 g/100 mL, $CHCl_3$); 200-MHz NMR ($CDCl_3$, ppm) δ 7.40–7.20 (8 H, m), 7.05–6.88 (2 H, m), 6.10–5.92 (1 H, m), 5.65–5.50 (1 H, br d, J = 7.3 Hz), 5.13–4.95 (3 H, m), 3.96–3.80 (1 H, m), 2.65 (1 H, dd, J = 7.0, 13.9 Hz), 2.50 (1 H, dd, J = 8.3, 13.9 Hz), 1.39 (3 H, d, J = 6.9 Hz); ^{13}C NMR (90.56 MHz {H}, $CDCl_3$, ppm) δ 170.1, 142.8, 142.4, 140.5, 128.6, 128.4, 127.6, 126.9, 126.6, 125.9, 114.7, 48.3, 46.0, 42.8, 21.5. The crystalline diastereomer **33** corresponded to the major product from the reaction of **30** with DMAD described above. The assay of ee was based on integration of the C-methyl signals at δ 1.23 vs 1.39 ppm for the minor diastereomer.

1-Methyl-3-carbomethoxy-1-azacyclodeca-2,5-diene (37) from 11 and Methyl Propiolate. To distilled 1-methyl-2-vinylpiperidine (185 mg, 0.200 mL, 1.47 mmol) was added THF (10.0 mL) via a syringe, followed by an excess of methyl propiolate (520 mg, 0.550 mL, 6.18 mmol). A condenser was used, and the solution was refluxed under N_2 for 72 h. After cooling to room temperature, the solvent was evaporated through a stream of N_2, and the volatiles were evaporated overnight with a vacuum pump (0.1 mmHg). Distillation of the product gave **36** as a thick, pale yellow oil: 220 mg (71%), bp 150–170 °C, 0.005 mm; molecular ion calcd for $C_{12}H_{19}NO_2$; 209.141 57; found m/e = 209.1416, error = 0 ppm; base peak = 136 amu; IR (neat (NaCl), cm^{-1}) 1680, C=C; 1610, C=C; 200-MHz NMR ($CDCl_3$, ppm) δ 7.42 (1 H, s), 5.42–5.12 (2 H, m), 3.82–3.30 (2 H, m), 3.67 (3 H, s), 3.20–2.55 (2 H, m), 2.97 (3 H, s), 2.45–0.80 (6 H, m); ^{13}C NMR (67.93 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 171.4 s, 148.8 d, 131.3 d, 123.7 d, 93.5 d, 51.6 t, 51.0 q, 44.5 q, 33.4 t 29.1 t, 26.2 t, 21.5 t.

1-Methyl-2,3-bis(carbomethoxy)-1-azacyclodeca-2,5-diene (12) from 11 and DMAD with Acid Catalysis. Dried *p*-toluenesulfonic acid (11.0 mg, 0.066 mmol, 10 mol %) was dissolved in dry $CDCl_3$ (2.0 mL), and *N*-methyl-2-vinylpiperidine (83.1 mg, 0.090 mL, 0.663 mmol) and DMAD (122 mg, 0.106 mL, 0.862 mmol) were added. After 41 h at room temperature, the solvent was removed (aspirator) and the residue was purified by flash chromatography on silica gel, 1:40:59 NEt_3/EtOAc/hexane eluent, to give **12** as a pale yellow viscous oil (125 mg, 71%): analytical TLC on silica gel, 3:7 EtOAc/hexane, R_f = 0.41; molecular ion calcd for $C_{14}H_{21}NO_4$, 267.141; found, 266.1400 (M – 1), error = 0 ppm; base peak = 208 amu; IR (neat (NaCl), cm^{-1}) 1733, C=O; 1685,

C=C; 1558, C=C; 270-MHz NMR ($CDCl_3$, ppm) δ 5.40–5.20 (2 H, m), 3.81 (3 H, s), 3.67 (3 H, s), 3.60–3.20 (2 H, m), 2.90–2.70 (1 H, m), 2.65 (3 H, s), 2.30–2.20 (1 H, m), 2.00–1.45 (3 H, m), 1.40–1.10 (3 H, m); ^{13}C NMR (67.93 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 169.4 s, 167.4 s, 153.3 s, 132.7 d, 121.4 d, 108.3 s, 56.2 t, 52.2 q, 51.3 q, 40.9 q, 33.0 t, 29.4 t, 28.3 t, 26.3 t.

1-Azacyclononana-2,5-diene Derivative 36 from 35 and DMAD by Acid Catalysis. Dried *p*-toluenesulfonic acid (10 mg, 0.058 mmol, 5.5%) was dissolved in $CDCl_3$ (1.50 mL), and 1-methyl-2-vinylpyrrolidine was added (117 mg, 0.140 mL, 1.05 mmol). After cooling to −78 °C (acetone/CO_2 bath), DMAD (179 mg, 0.155 mL, 1.26 mmol) was injected, and the solution was stored at −15 °C for 48 h (freezer). After warming to room temperature and removal of solvent (aspirator), the residue was purified by chromatography on neutral alumina, 1:9 EtOAc/hexane eluent. The product was obtained as a pale yellow viscous liquid (145 mg, 57%; purity ca. 90% by NMR assay of the ester signals): molecular ion calcd for $C_{13}H_{19}NO_4$, 253.131 38; found m/e = 253.1312, error = 1 ppm; base peak = 194 amu; analytical TLC on alumina, 3:7 EtOAc/hexane, R_f = 0.70; IR (neat (NaCl), cm^{-1}) 1726, C=O; 1554, C=C; 1245, CO; 200-MHz NMR ($CDCl_3$, ppm) δ 5.69 (1 H, ddd, J = 15.5, 11.0, 4.0 Hz), 5.36 (1 H, ddd, J = 15.5, 9.1, 4.5 Hz), 3.75 (3 H, s), 3.71 (3 H, s), 3.18–3.04 (1 H, m), 3.03–2.68 (2 H, m), 2.45–2.21 (2 H, m), 2.39 (3 H, s), 2.20–1.95 (1 H, m), 1.84–1.47 (2 H, m); ^{13}C NMR (125.76 MHz {H}, DEPT 135, $CDCl_3$, ppm) δ 170.0 s, 166.1 s, 152.0 s, 135.6 d, 127.5 s, 125.3 d, 56.8 t, 51.8 q, 51.5 q, 38.0 q, 33.6 t, 31.7 t, 27.6 t.

Acknowledgment. This work was supported by the National Institutes of Health (CA17918). The authors also thank Prof. R. J. Kazlauskas for a gift of BINOL, and NSERC for a fellowship for M.G.