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STUDIES OF THE 3-AZA-COPE REARRANGEMENT AND AZA-ANNULATION FOR THE CONSTRUCTION OF NITROGEN HETEROCYCLES

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Ph.D. degree in Chemistry

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Major professor

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STUDIES OF THE 3-AZA-COPE REARRANGEMENT AND AZA-ANNULATION FOR THE CONSTRUCTION OF NITROGEN HETEROCYCLES

By

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ABSTRACT

STUDIES OF THE 3-AZA-COPE REARRANGEMENT AND AZA-ANNULATION FOR THE CONSTRUCTION OF NITROGEN HETEROCYCLES

By

Gregory Richard Cook

General routes for the synthesis of alkaloids utilizing the charge-promoted 3-aza-Cope rearrangement and aza-annulation methodologies were explored. An efficient and general synthesis of *N*-alkyl-*N*-allyl enamines has been established through the condensation of allylamine with a carbonyl compound, followed by acylation with an acid chloride. Enamines of isobutyraldehyde, *n*-butanal, 2-phenylpropanal, cyclohexanone, and cyclopentanone were prepared in high yields. The *E* olefin selectivity of this process was high, giving only the *E* isomer with *n*-butanal, and a 86:14 *E:Z* ratio with 2-phenylpropanal. Acceleration of the aliphatic 3-aza-Cope rearrangement with a variety of electrophiles has been accomplished, and reduction of the imine products *in situ* provided high yields of δ,ε-unsaturated amines. Of the electrophiles examined, organoaluminum reagents afforded the broadest range of utility for this [3,3] rearrangement.

Examination of the degree of asymmetric induction in the charge-promoted 3-aza-Cope rearrangement was carried out. Relative asymmetric induction transferred from amino acid derived chiral auxiliaries was found to be very low (8-20% de). Internal asymmetric induction was determined to be highly dependent on the promoting reagent as well as the substitution of the enamine olefin. Diastereomer ratios ranged from 52:48 to 95:5. Selectivity was found to be very high with concomitant relative and internal asymmetric induction for some cases (>95:5). The [3,3] rearrangement of the enamine

derived from 2-phenylpropanal, with a variety of starting enamine olefin ratios, provided modest selectivity (54:37:9 - 89:8:2). Ring expansion reactions were accomplished, and yielded a nine-membered ring with complete stereoselectivity. The ring expansion process provided evidence of a reversible [3,3] rearrangement.

Aza-annulation quickly afforded six-membered nitrogen heterocyles, and methods for the modification of this δ-lactam template were investigated. This methodology was applied to the synthesis of hydroxylated alkaloids, and the first total synthesis of (±)-prosopinine was accomplished.

To my wife Lisa

and

my parents Clayton and Lucille

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LIST OF ABBREVIATIONS

Ac	Acetyl
ArO	2,6-Diphenylphenoxy
Bn	Benzyl
Boc	*t*-Butylcarboxy
i-Bu	Isobutyl
n-Bu	Normal Butyl
t-Bu	Tertiarybutyl
n-BuLi	*n*-Butyllithium
Bz	Benzoyl
Cbm	Carbomethoxy
Cbz	Carbobenzoxy
de	Diastereomeric Excess
DIBAH	Diisobutyl Aluminum Hydride
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DPPA	Diphenylphosphorylazide
E^+	Electrophile
ee	Enantiomeric Excess
Et	Ethyl
$LiAlH_4$	Lithum Aluminum Hydride
Me	Methyl

MOM	Methoxymethyl
NOE	Nuclear Overhauser Effect
Ph	Phenyl
i-Pr	Isopropyl
Pth	Phthalimide
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl
*p*TsOH	*p*-Toluenesulfonic Acid

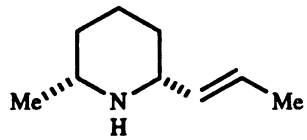
CHAPTER I. AN INTRODUCTION TO STRATEGIES FOR ALKALOID SYNTHESIS

Biological Importance of Alkaloids

Alkaloids, compounds which possess a nitrogen heteroatom, are prevalent in nature, and many that contain six-membered nitrogen heterocycles display a wide range of biological activity.[1] The piperidine alkaloids can have simple structures such as pinidine (**I-1**), or more complex features like the hydroxylated piperidines **I-2** and **I-3** (Figure I-1). These hydroxylated alkaloids display a broad range of physiological effects due to their ability to mimic carbohydrates and peptides in biological systems.[2] Alkaloids with the general structure of **I-4**, which bear a long aliphatic chain, also show interesting biological properties ranging from anesthetic and antibiotic to antitumor activity. These compounds include the *Prosopis* alkaloids ($R^2 = CH_2OH$)[3] as well as several others in which R^2 = Me.[4] Bicyclic alkaloids often show intriguing biological properties. The decahydroquinoline, pumiliotoxin C (**I-5**), isolated from *Dendrobates pumilio*, a Panamanian frog, displays toxicity at high concentrations.[5] Derivatives of lupinine (**I-6**) possess local anesthetic characteristics,[6] and swainsonine (**I-7**), which belongs to the indolizidine class of alkaloids, is another potent carbohydrate mimic.[1] The indolizidine, ipalbine (**I-8**), isolated from the seeds of *Ipomoea alba*, is structurally very similar to septicine (**I-9**), which was extracted from *Ficus septica*. These were the first simple, unfused, indolizidine alkaloids isolated from natural sources. Several reports of their total synthesis have appeared in the literature.[7]

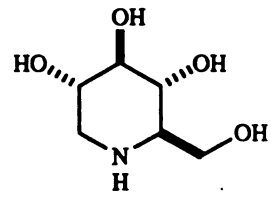
Clearly, piperidine alkaloids, especially those that are polyhydroxylated, will have a great impact on the treatment of many physiological anomalies. The development of facile and efficient new routes to these alkaloid skeletons, for the rational design of new drugs, has been a focus of synthetic efforts in our group.

Piperidine Alkaloids



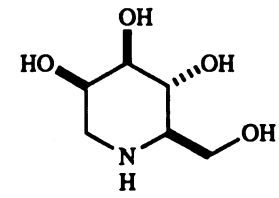
Pinidine

I-1



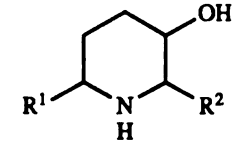
Deoxynorjirimycin

I-2



Deoxymannojirimycin

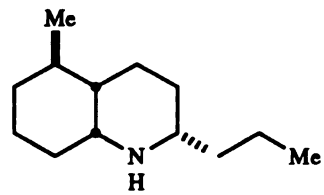
I-3



R^1 = lipid long chain
R^2 = Me, CH_2OH

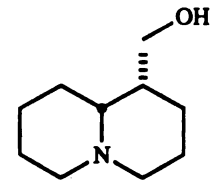
I-4

Hydroquinoline and Quinolizidine Alkaloids



Pumiliotoxin C

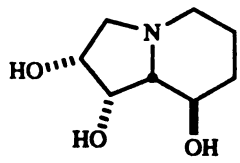
I-5



Lupinine

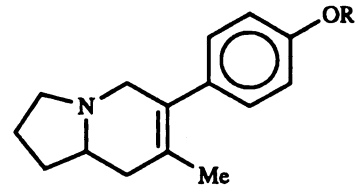
I-6

Indolizidine Alkaloids



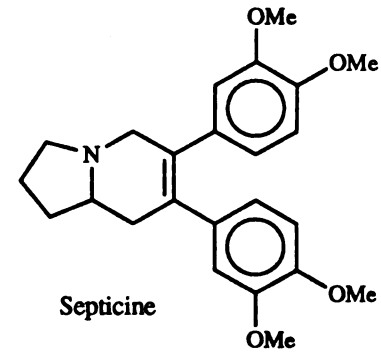
Swainsonine

I-7



Ipalbine (R = β-D-glucose)
Ipalbidine (R = H)

I-8



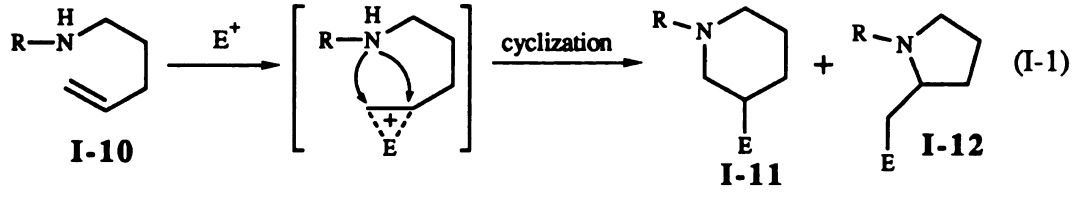
Septicine

I-9

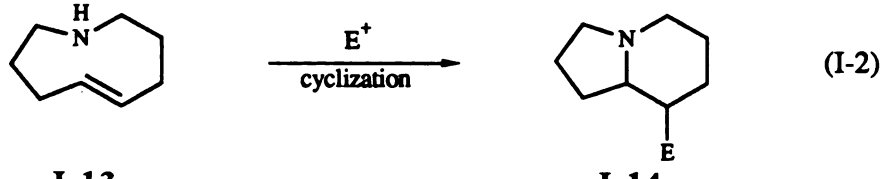
FIGURE I-1. Alkaloids Containing Six-Membered Nitrogen Heterocycles

3-Aza-Cope Strategy

The cyclization of δ,ε-unsaturated amines (**I-10**) has been studied and several reports have appeared in the literature (eq I-1).[8] Electrophilic reagents utilized for this cyclization include Hg(II) salts, I_2, Br_2, Pd(II) catalysts, as well as transition metal hydrides. In most cases the predominant product of this cyclization was the five-membered ring, **I-12**. The pyrrolidine, **I-12**, could be further elaborated, by extending the alkyl substituent containing E, to afford compounds which could be further cyclized to indolizidine skeletons. A more direct approach to indolizidines is the transannular cyclization[9] of **I-13**, which would afford the bicyclic **I-14** (eq I-2). Therefore, methods for the preparation of the requisite unsaturated amines would provide easy access to these nitrogen heterocycles.



I-10 **I-11** **I-12** (I-1)

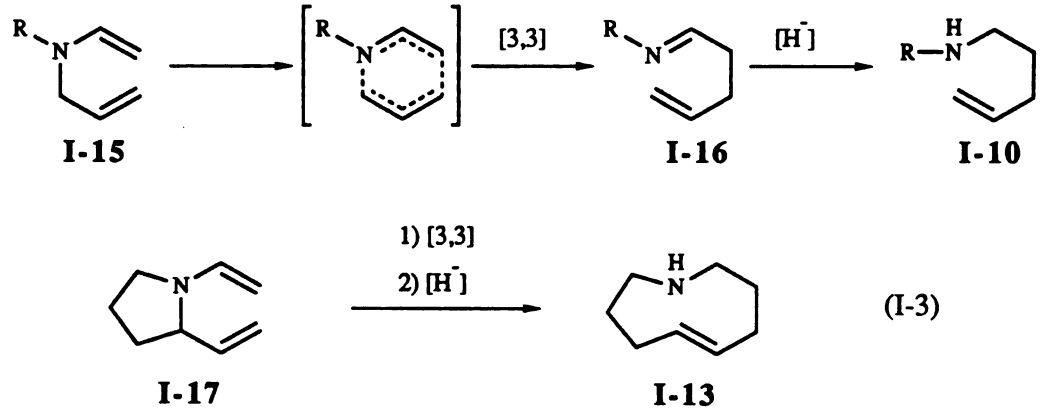


I-13 **I-14** (I-2)

Our approach to δ,ε-unsaturated amines (**I-10**) involved the use of the 3-aza-Cope rearrangement (Scheme I-1). Beginning with an *N*-allylenamine (**I-15**), [3,3] sigmatropic rearrangement would afford imine **I-16**. In most reported cases of 3-aza-Cope rearrangements, the imine products were hydrolyzed to give the corresponding aldehydes. Our approach was to reduce the imine functionality to provide the secondary amine, **I-10**. The cyclic amine, **I-13**, could be obtained by analogous rearrangement of enamines with

the general structure of **I-17** (eq I-3). To increase the diversity of substitution on the amines, a general and efficient route to the *N*-allylenamine substrates needed to be developed (Chapter II). As the thermal 3-aza-Cope rearrangement occurs at relatively high temperatures, methods for promoting the reaction to a synthetically useful range was required (Chapter III). In order to exploit the well-defined transition state of [3,3] rearrangements for stereochemical control, a detailed investigation of the factors that influence asymmetric induction was essential (Chapter IV).

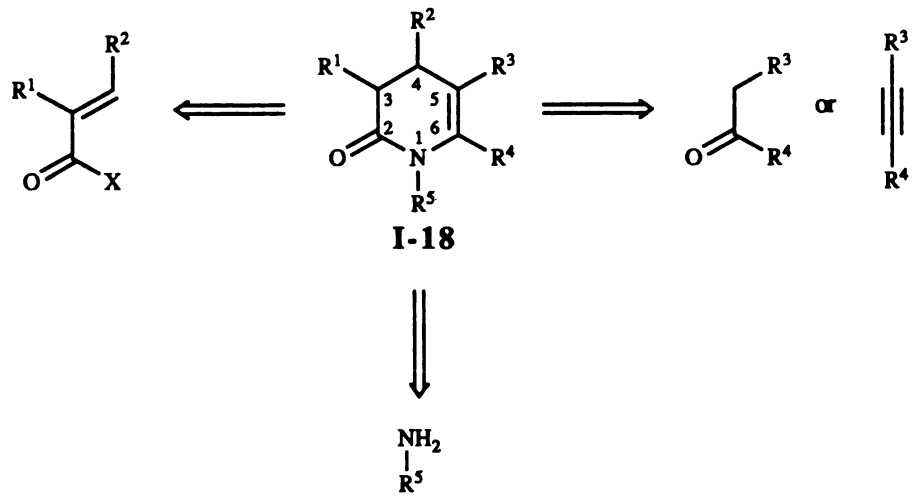
SCHEME I-1. 3-Aza-Cope Strategy for the Preparation of δ,ε-Unsaturated Amines



Aza-Annulation Strategy

Aza-annulation methodology, systematically investigated in our group, involved the convergent, one-pot synthesis of δ-lactams (**I-18**) from three common starting compounds (Figure I-2). The process entailed the addition of a primary amine to a carbonyl compound or alkyne (conjugated with an electron withdrawing group) to give an imine or enamine which was subsequently reacted with an α,β-unsaturated acid derivative. The reaction of imines derived from carbonyl compounds where R^3 = alkyl with acrylic acid derivatives has been explored, and a mixture of lactam and uncyclized enamides was obtained.[10] This

reaction has been investigated by our group, and evidence for an initial Michael addition followed by *N*-acylation mechanism has been obtained.[11a] If R^3 was an electron withdrawing group (ketone, ester, -CN), only lactam products were obtained.[12] This annulation methodology has been applied to the synthesis of (±)-lupinine (**I-6**),[11b] (±)-5-epipumiliotoxin,[11c] and (±)-tashiromine.[11d]



I-18

FIGURE I-2. Aza-Annulation: Convergent Synthesis of δ-Lactams

With an efficient and facile route to **I-18**, the preparation of a variety of alkaloids could be achieved. The δ-lactam template offers a wide range of possibilities for further modification (Figure I-3). If R^3 is an electron withdrawing group, the possibility for conjugate addition to C-6 exists. The double bond could be selectively reduced giving a *cis* disubstituted heterocycle.[11] The substituents that were in place during the annulation process could be further manipulated by functional group conversions. Enolate chemistry would provide the ability to functionalize the C-3 position, and oxidation could provide α,β-unsaturated lactams, which would allow modification of the C-4 position as well. The lactam carbonyl could be reduced to afford C-2 unsubstituted piperidines, or homologated

by a number of methods to allow the inclusion of a variety of groups found in natural piperidine alkaloids. Studies of the modification of this versatile compound are described in Chapter V.

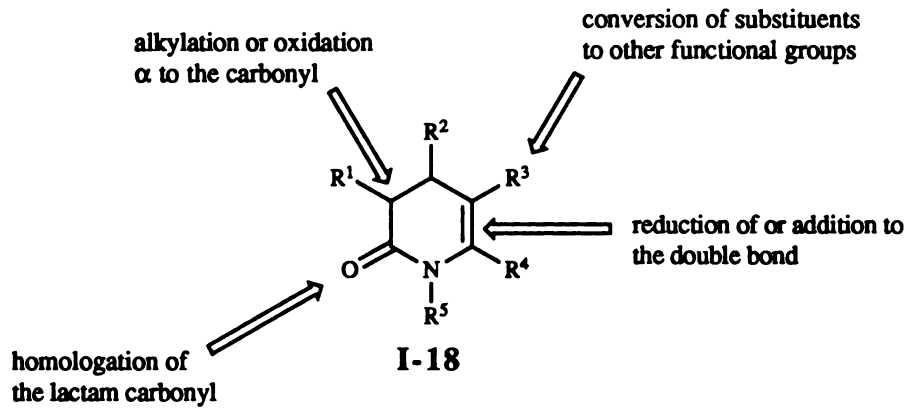


FIGURE I-3. Modification of the δ-Lactam Template

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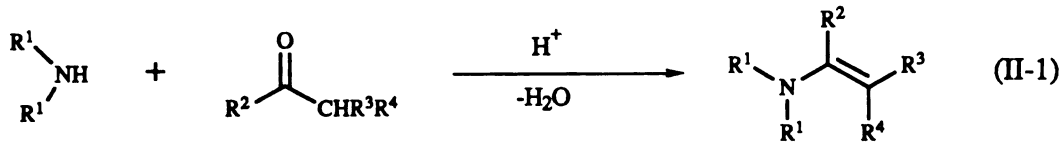
CHAPTER II: ENAMINE SYNTHESIS

Background: Enamine Synthesis

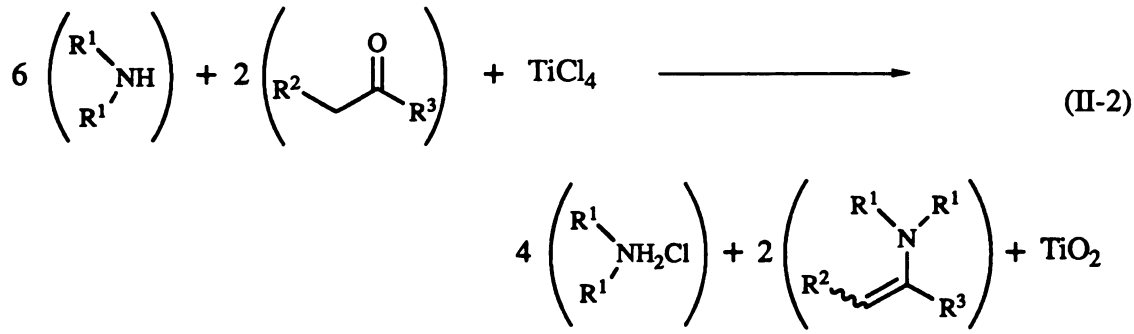
In order to fully utilize the 3-aza-Cope rearrangement in organic synthesis, efficient and facile methods for the preparation of a wide variety of enamines needed to be studied. A variety of methods for the synthesis of enamines have appeared.[1] The vast majority involve the condensation of a secondary amine with an aldehyde or ketone with various methods used for removal of the water formed in the reaction (eq II-1).



(II-1)

Mannich and Davidsen first reported that secondary amines and aldehydes condensed in the presence of potassium carbonate to give enamines,[2] and reactions proceeded at temperatures as low as 5 °C. Ketones required calcium oxide, higher temperatures and resulted in poor yields. Almost two decades later, Herr and Heyl reported that enamines of ketones and aldehydes could be more easily prepared in benzene with azeotropic removal of water.[3] In some cases, the addition of a catalytic amount of *p*-toluenesulfonic acid was required, and yields were generally good (60-90%). This procedure worked well with α,α-disubstituted aldehydes while straight chain aldehydes often reacted through aldol condensation pathways and gave only oligomeric products. Further, the preparation of enamines from ketones and acyclic secondary amines by this method was very sluggish. Other drying agents have been employed as well. Ketones and amines could be condensed over magnesium sulfate in the absence of any solvent and provided good yields (77-84%) of enamines at room temperature.[4]

In 1967, White and Weingarten reported that enamines could be obtained from secondary amines and carbonyl compounds in the presence of $TiCl_4$.[5] The Lewis acid acted both as a catalyst for the reaction and as a water scavenger (eq. II-2). This method has since been studied by Carlson and others, and has been optimized to provide good yields of enamines with short reaction times.[6]



(II-2)

While the $TiCl_4$ procedure worked well for the two most commonly studied amines (morpholine and pyrrolidine), as Hill demonstrated, the use of an allylic amine gave rearranged products rather than the pure enamines.[7] Furthermore, a large excess of the amine was required, and this method would not be efficient if a costly chiral amine were used. This method failed to produce good yields of enamines derived from aldehydes that have more than one α-hydrogen (straight chain aldehydes) and ketones.

Preparation of Enamines in the Presence of $AlMe_2Cl$

The studies described above for the preparation of enamines in the presence of $TiCl_4$ prompted us to explore the use of other Lewis acids in this condensation process. For this reaction, a secondary amine was first complexed with $AlMe_2Cl$ and then condensed with a carbonyl compound at room temperature (eq II-3). The reaction of amine-aluminum complexes with esters has been reported.[8] It was hoped that the use of an organoaluminum Lewis acid/water scavenger would allow for the use of stochiometric

amounts of amines due to the fact that methane would be produced as a byproduct rather than HCl.

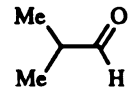
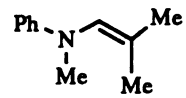
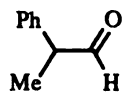
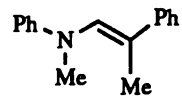
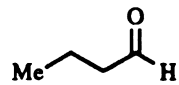
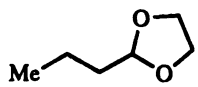
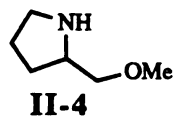
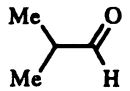
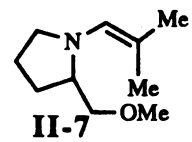
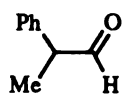
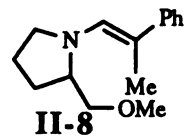
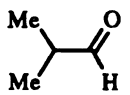
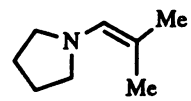
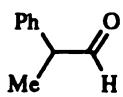
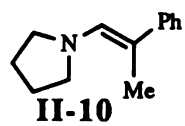
To probe the applicability of this condensation process, three amines were chosen to be condensed with a variety of carbonyl compounds. Table II-1 summarizes the results of this study. Reactions were carried out at ambient temperature for 1 hour, and enamine **II-5** was prepared from *N*-methylaniline and isobutyraldehyde in 75% yield. Condensation with 2-phenylpropionaldehyde provided enamine **II-6** in 85% yield as a mixture of isomers (*E*:*Z* 83:17). Unfortunately, attempts to prepare the enamine of butyraldehyde led to the formation of aldol products. It was hoped that the reaction would proceed with the acetal of butyraldehyde, but product formation was not observed.

Two other amines were tested with isobutyraldehyde and 2-phenylpropionaldehyde. Methoxyamine **II-4**, prepared as shown in Scheme II-1, and pyrrolidine gave similar results as *N*-methylaniline. Enamine **II-7** was prepared in 72% yield. Likewise, enamine **II-8** was obtained in 76% as a mixture of isomers (*E*:*Z* 90:10). The condensation of pyrrolidine with isobutyraldehyde gave enamine **II-9** in only 49% yield, perhaps due to its high volatility. However, enamine **II-10**, being less volatile, was prepared in respectable yield (76%, *E*:*Z* 84:16). Attempts to condense these amine-aluminum complexes with ketones gave no condensation products.

The use of $AlMe_2Cl$ in the condensation of secondary amines and carbonyl compounds was an efficient and facile process. Short reaction times (1 hour) and mild conditions (ambient temperature) have been employed and high yields of enamines were obtained. Unfortunately, this process, as in the $TiCl_4$ catalyzed process, was limited to the preparation of enamines derived from α,α-disubstituted aldehydes only. However, only one equivalent of amine was required eliminating the waste of costly amines.

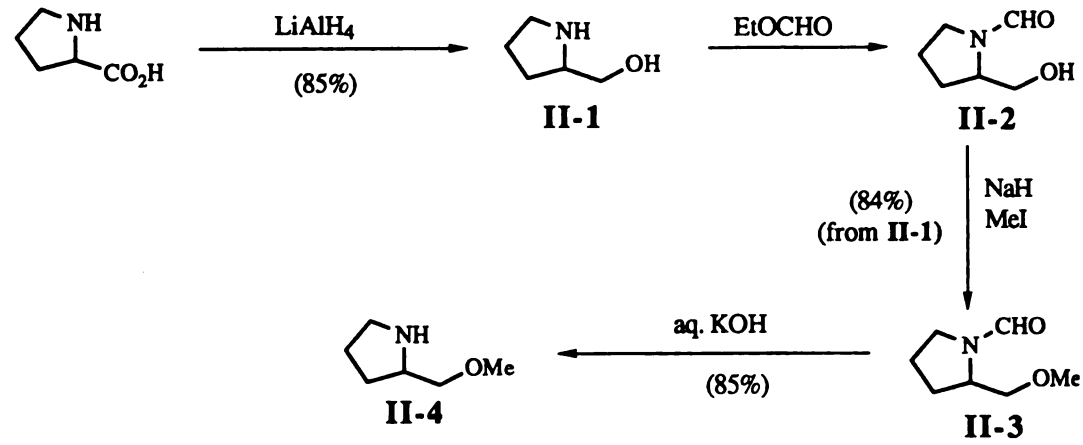
$$R_2NH + R'R''CHCHO \xrightarrow[\text{Toluene, RT}]{AlMe_2Cl\ (0.5\ eq)} R_2NCH{=}CR'R'' \qquad \text{(II-3)}$$

TABLE II-1: Preparation of Enamines in the Presence of $AlMe_2Cl$

Amine	Aldehyde	Enamine	Yield (*E*:*Z*)
		 **II-5**	75%
		 **II-6**	85% (83:17)
			Oligomers
			NR
 **II-4**		 **II-7**	72%
		 **II-8**	76% (90:10)
		 **II-9**	49%[a]
		 **II-10**	78% (84:16)

[a]This product was difficult to isolate due to its volatility.

SCHEME II-1. Preparation of Methoxymethly Pyrrolidine **II-4**



Preparation of *N*-Allyl-*N*-Isobutyl Enamines

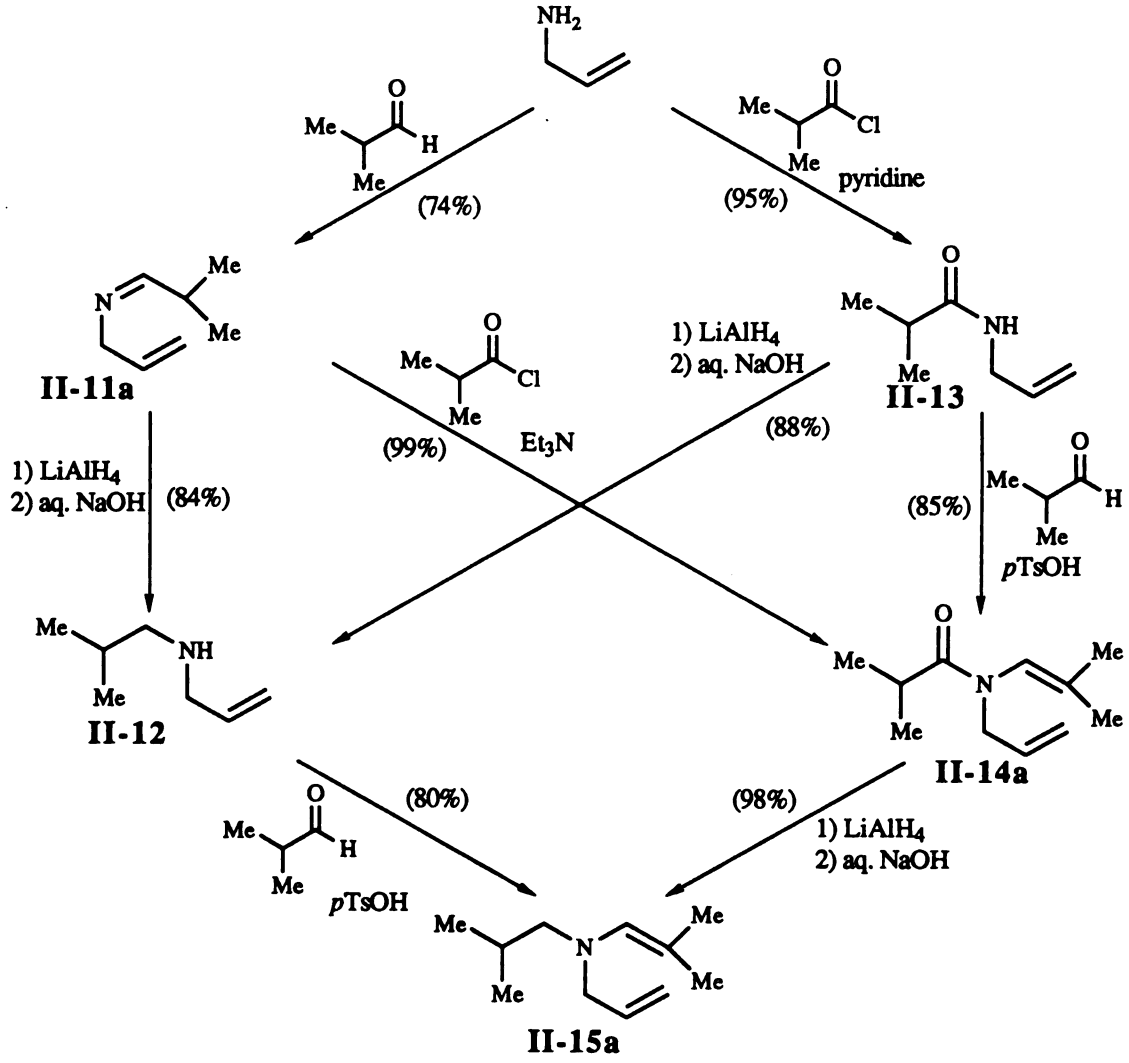
In order to study the scope and utility of the charge-promoted 3-aza-Cope rearrangement (Chapter III), an efficient and selective synthesis of a wide variety of *N*-alkyl-*N*-allyl enamines was required. Methods of forming enamines derived from ketones and aldehydes possessing a range of substitution variation was needed. Further, any methods developed should selectively produce a major isomer in the case where *E*:*Z* enamines could arise.

As shown in Scheme II-2, four different routes to the *N*-alkyl-*N*-allyl enamine **II-15a** were explored. Starting from allylamine, condensation with isobutyraldehyde resulted in the formation of **II-11a** in 74% isolated yield. Reduction of this imine with $LiAlH_4$ gave allylisobutylamine (**II-12**) in 84% yield. Condensation with isobutyraldehyde, catalyzed by *p*-toluenesulfonic acid (pTsOH), provided enamine **II-15a** in 80% distilled yield. The secondary amine **II-12** could also be prepared in high yield by acylation of allylamine with isobutyryl chloride (**II-13**, 95% yield) followed by reduction with $LiAlH_4$ (88% yield). It was thought that **II-15a** could be obtained by the reduction of enamide **II-14a**. The allylamide **II-13** could be condensed with

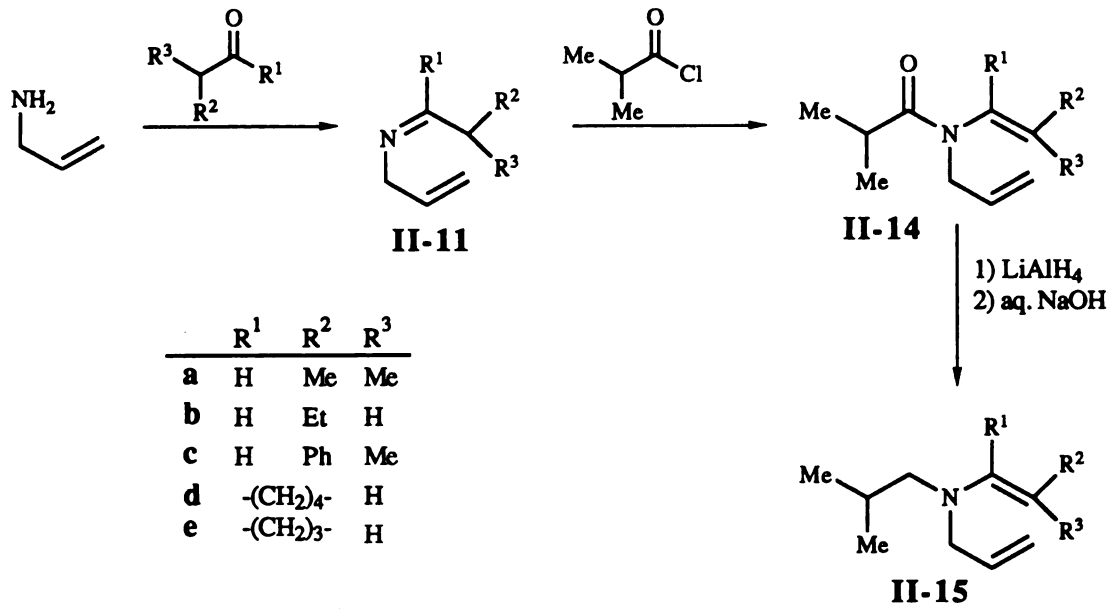
isobutyraldehyde to give the enamide in high yield, however long reaction times were required (66 hours for completion). Acylation of imine **II-11a** with isobutyryl chloride resulted in nearly quantitative yields of the desired enamide (99% yield). These enamide compounds were much more stable to hydrolysis than the corresponding enamines and could be purified by silica gel chromatography. This synthetic sequence provided for high yields of pure enamines upon reduction. Reduction of **II-14a** resulted in a 98% yield of the *N*-alkyl-*N*-allyl enamine. The efficiency of this route was improved by direct acylation of imine **II-11a**, prepared from allylamine without isolation, providing a 94% yield (for two steps) of enamine **II-14a**. Thus, the synthesis of enamine **II-15a** was achieved from allylamine in 92% overall yield.

With an optimal route for enamine synthesis, *N*-allyl-*N*-isobutyl enamines derived from butanal, 2-phenylpropanal, cyclohexanone, and cyclopentanone were prepared (Scheme II-3, Table II-2). In order to study the selectivity in the formation of the enamine-olefin geometry, *n*-butanal was employed in this sequence. As mentioned earlier, the use of linear aldehydes in the traditional condensation methods with a secondary amine gave aldol products. Similar products were observed while preparing the imine of allylamine and *n*-butanal in refluxing benzene. Therefore, it was necessary to prepare the imine **II-11b** at room temperature and isolate it by distillation. Since this compound was quite volatile, only a modest yield of 68% was obtained. Acylation with isobutyryl chloride provided a 90% yield of enamide **II-14b** as a 63:37 mixture of *E*:*Z* isomers, respectively. Employing pyridine as the base, this ratio increased slightly to 71:29. Reduction of this mixture of enamides gave a 95% yield of a single compound which was determined by ^{1}H NMR to be the *E* isomer. The mechanism by which this isomerization occurred is not fully understood, and probably resulted from the ability of the π-electrons to delocalize during the reduction process. This resonance would allow rotation around the enamine double bond, and lead to the more thermodynamically stable product.

SCHEME II-2. Different Synthetic Routes to Enamine **II-15a**



SCHEME II-3. Synthesis of *N* -Allyl-*N*-Isobutyl Enamine Substrates



	R^1	R^2	R^3
a	H	Me	Me
b	H	Et	H
c	H	Ph	Me
d	-$(CH_2)_4$-		H
e	-$(CH_2)_3$-		H

TABLE II-2. Isolated Yields for *N*-Allyl-*N*-Isobutyl Enamine Formation

	yield, %		
	II-11	**II-14**	**II-15**
a	*a*	94	98
b	68	90[b]	95
c	*a*	79[c]	96[d]
d	*a*	82	98
e	*a*	68	90

[a]Carried on to **II-14** without isolation. [b]Mixture of isomers *E*:*Z* (63:37). [c]Mixture of isomers *E*:*Z* (57:43). [d]Mixture of isomers *E*:*Z* (86:14).

Similar results were observed in the formation of the enamine derived from 2-phenylpropanal. *In situ* imine formation in benzene, followed by acylation with isobutyryl chloride gave enamide **II-14c** in 79% overall yield. A 57:43 mixture of enamine geometric isomers was obtained. The major isomer was determined by ^1H NMR Nuclear Overhauser Enhancement techniques to have the *E* enamine geometry, while the minor isomer had *Z* geometry. As was observed for the reduction of **II-14b**, this ratio changed upon treatment with $LiAlH_4$. Reduction provided a 96% yield of **II-15c** in a 86:14 (*E*:*Z*) ratio.

Enamines derived from cyclic ketones, cyclohexanone and cyclopentanone, were also prepared by this method. Reaction of allylamine with cyclohexanone gave imine **II-11d**, which was acylated without isolation to provide **II-14d** in 82% overall yield. Reduction with $LiAlH_4$ resulted in formation of **II-15d** in 98% yield. Cyclopentanone was more sluggish during the imine formation and **II-11e** showed a greater sensitivity towards hydrolysis than cyclohexanone. Nevertheless, *in situ* acylation with isobutyryl chloride gave enamide **II-14e** in 68% yield. The desired enamine **II-15e** was obtained in 90% yield after reduction.

Summary

A new method for the synthesis of enamines from secondary amines and aldehydes was developed employing $AlMe_2Cl$ as a water scavenger. Good yields of enamines were obtained, cleanly, without the loss of amine as by-products. This method appeared to be limited to α,α-disubstituted aldehydes, as linear aldehydes lead to aldol products and ketones did not react. An efficient and general synthesis of *N*-alkyl-*N*-allyl enamines has been established through the condensation of allylamine with the appropriate carbonyl compound, followed by acylation with acid chlorides. Enamines of isobutyraldehyde, *n*-butanal, 2-phenylpropanal, cyclohexanone, and cyclopentanone have

been prepared in high yields. Most notable was the fact that enamines of ketones and linear aldehydes could be prepared. The *E* olefin selectivity of this process was high, giving only the *E* isomer with *n*-butanal, and a 86:14 *E:Z* ratio with 2-phenylpropanal.

EXPERIMENTAL

General Methods

All reactions were carried out performing standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of either nitrogen or argon. Benzene, toluene, tetrahydrofuran (THF), and Et_2O were distilled from sodium/benzophenone immediately prior to use. Triethylamine, methylene chloride, dioxane, and pyridine were heated at reflux over calcium hydride for a minimum of 12 hours and then distilled immediately prior to use. Solutions of HCl (1.0 *M* in Et_2O) and $LiAlH_4$ (1.0 *M* in THF) were obtained from Aldrich Chemical Company. Solutions of $AlMe_3$ (2 *M* in toluene), Me_2AlCl (1 *M* in toluene), and DIBAL-H (1 *M* in THF) were prepared from neat organoaluminum compounds obtained from Aldrich Chemical Company. $TiCl_4$ were distilled prior to use. All other organic reagents were used as provided by the vender or purified by distillation. Additions were made with gas tight syringes, or via cannula transfer under nitrogen or argon. Unless specified, concentration of solutions after workup was performed on a Büchi rotary evaporator. Oven temperature ranges are reported for bulb to bulb (Kugelrohr) distillations.

Gas chromatographic (GLC) analyses were carried out on a Perkin-Elmer 8500 instrument with a 50 m RSL-200 capillary column (5% methyl phenyl silicone) and an FID detector at a 220 °C injector temperature, and a 300 °C detector temperature. Helium gas pressure was set at 15 psi with a flow rate of 2 mL/min. NMR spectra were obtained on Varian Gemini 300, VXR-300, or VXR-500 spectrometers with $CDCl_3$ as solvent. ^1H NMR data are reported as follows: chemical shift relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, m = multiplet), coupling, and integration. ^{13}C NMR data are reported as chemical shift relative to $CDCl_3$ (77.0 ppm).

Preparation of Prolinol (II-1):

To a suspension of $LiAlH_4$ (7.6 g, 200 mmol) in THF (400 mL) was added proline (11.51 g, 100 mmol), and the mixture was heated at reflux overnight. The reaction was quenched with 7.6 mL H_2O, 7.6 mL 15% aq. NaOH, followed by 22.8 mL H_2O, stirred for 15 minutes and then filtered. After concentration by rotary evaporation, the oil was dissolved in benzene and heated at reflux overnight with a Dean-Stark trap to collect water. The solution was concentrated, and the oil was distilled (Kugelrohr) to give **7** (8.608 g, 85 mmol) in 85% yield (oven temp 55-65 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.37 (m, 1H), 1.73 (m, 3H), 2.86 (m, 2H), 2.93 (bs, 2H), 3.24 (m, 1H), 3.28 (dd, J = 7.3, 10.1 Hz, 1H), 3.49 (dd, J = 3.4, 10.1 Hz, 1H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 25.9, 27.5, 46.4, 59.6, 64.8.

Preparation of Formate Protected Methylmethoxy pyrrolidine II-3:

To prolinol (8.092 g, 80 mmol) at 0 °C was added ethyl formate (6.519 g, 88 mmol), and the mixture was stirred at room temperature for one hour. The volatile materials were removed by rotary evaporation and the crude formamide (**II-2**) was dissolved in THF (100 mL). MeI (11.355 g, 80 mmol) was added, the solution was cooled to 0 °C, and NaH (2.112 g, 88 mmol) was added. After heating at reflux for 30 minutes, 100 mL of H_2O were added, and the methoxy formamide was extracted with 3 x 200 mL CH_2Cl_2, dried over $MgSO_4$, and concentrated. Kugelrohr distillation provided **II-3** (9.636 g, 67 mmol) in 84% yield (oven temp 75-85 °C, <1 mmHg).

Hydrolysis of IV-3 to Methylmethoxy Pyrrolidine II-4:

Formamide **II-3** (9.60 g, 67 mmol) was placed in 6 *M* aq. KOH (200 mL), and heated at reflux overnight. The amine was extracted with 3 x 200 mL of Et_2O, dried over Na_2SO_4, and concentrated. Distillation (Kugelrohr) gave **II-4** (6.553 g, 57 mmol) in 85% yield (oven temp 50-55 °C, 34 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.28 (m, 1H),

1.64 (m, 3H), 2.21 (bs, 1H), 2.75 (m, 1H), 2.84 (m, 1H), 3.16 (m, 2H), 3.24 (m, 1H), 3.26 (s, 3H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 25.1, 27.7, 46.3, 57.5, 58.8, 76.1.

General Procedure for $AlMe_2Cl$ Promoted Enamine Preparation:

To a solution of secondary amine (0.5 eq.) in toluene (0.2 *M*) was added $AlMe_2Cl$ (0.5 eq., 2 *M* in toluene) and the mixture was stirred at room temperature for one hour. The amine-Lewis acid complex was transferred via cannula to a solution of secondary amine (0.5 eq.) and aldehyde (1.0 eq.) in toluene (0.2 *M*). After stirring for one hour, solid K_2CO_3 was added and the mixture was stirred for 10 minutes. Filtration, rotary evaporation, and Kugelrohr distillation provided the pure enamine.

II-5: (1.202 g, 7.5 mmol) in 75% yield (oven temp 60-70 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.69 (d, J = 0.8 Hz, 3H), 1.81 (d, J = 1.4 Hz, 3H), 3.07 (s, 3H), 5.84 (qq, J = 0.8, 1.4 Hz, 1H), 6.78 (m, 3H), 7.28 (m, 2H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.8, 21.8, 38.5, 112.7, 117.0, 125.3, 128.2, 128.9, 129.2.

II-6: (1.903 g, 8.5 mmol) in 85% yield as a mixture of isomers (*E*:*Z* 83:17) (oven temp 100-120 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 2.07 (d, J = 1.3 Hz, 3H), 3.26 (s, 3H), 6.57 (q, J = 1.3 Hz, 1H), 6.81 (m, 3H), 7.39 (m, 5H), 7.55 (m, 2H), (*Z* isomer) 2.20 (d, J = 1.3 Hz, 3H), 2.84 (s, 3H), 6.35 (q, J = 1.3 Hz, 1H), 6.81 (m, 3H), 7.39 (m, 5H), 7.55 (m, 2H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 16.0, 38.9, 113.7, 118.2, 125.5, 126.6, 127.3, 128.3, 129.0, 132.5, 141.4, 148.0, (*Z* isomer) 14.6, 37.9, 113.1, 118.0, 125.5, 126.5, 127.3, 128.1, 129.0, 132.5, 140.5.

II-7: (1.223 g, 7.2 mmol) in 72% yield (oven temp 60-70 °C, 10 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.59 (s, 3 H), 1.65 (s, 3 H), 1.66-1.95 (m, 4 H), 2.62 (q, J = 7.1 Hz, 2 H), 2.80-2.98 (m, 2 H), 3.14 (dd, J = 7.8, 9.5 Hz, 1 H), 3.20-3.38 (m, 1 H), 3.30 (s, 3 H), 5.52 (s, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.9, 24.0, 28.8, 54.0, 57.7, 58.1, 64.1, 76.6, 116.6, 134.1.

II-8: (1.768 g, 7.6 mmol) in 76% yield as a mixture of isomers (*E*:*Z* 90:10) (oven temp >100 °C, <1 mmHg); ^{1}H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 1.50-2.0 (m, 4 H), 2.12 (s, 3 H), 3.23 (m, 1 H), 3.28 (m, 1 H), 3.35-3.50 (m, 2 H), 3.36 (s, 3 H), 3.61 (q, *J* = 7.1 Hz, 1 H), 6.47 (s, 1 H), 7.07-7.40 (m, 5 H), (*Z* isomer) 1.50-2.00 (m, 4 H), 2.01 (s, 3 H), 3.00 (m, 1 H), 3.28 (m, 1 H), 3.35-3.50 (m, 2 H), 3.40 (s, 3 H), 3.61 (q, *J* = 7.1 Hz, 1 H), 6.15 (s, 1 H), 7.07-7.40 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 15.7, 24.8, 28.8, 53.1, 59.2, 63.9, 76.8, 111.5, 124.5, 128.1, 128.2, 137.3, 143.9, (*Z* isomer) 14.6, 22.4, 18.0, 52.9, 57.6, 63.6, 77.2, 107.5, 124.5, 128.3, 129.0, 134.9, 142.4.

II-9: (0.616 g, 4.9 mmol) in 49% yield (oven temp 50-60 °C, 30 mmHg); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.59 (d, *J* = 0.8 Hz, 3 H), 1.66 (d, *J* = 1.3 Hz, 3 H), 1.74 (m, 4 H), 2.90 (m, 4 H), 5.57 (qq, *J* = 0.8, 1.3 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.9, 23.0, 24.9, 53.7, 114.0, 134.6.

II-10: (1.456 g, 7.8 mmol) in 78% yield as a mixture of isomers (*E*:*Z* 84:16) (oven temp 80-100 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 1.85 (m, 4H), 2.14 (d, *J* = 1.1 Hz, 3H), 3.28 (m, 4H), 6.45 (q, *J* = 1.1 Hz, 1H), 7.10 (m, 2H), 7.28 (m, 3H), (*Z* isomer) 1.70 (m, 4H), 2.02 (d, *J* = 1.1 Hz, 3H), 2.89 (m, 4H), 6.14 (q, *J* = 1.1 Hz, 1H), 7.10 (m, 2H), 7.28 (m, 3H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 15.6, 25.6, 53.1, 110.4, 124.4, 127.3, 128.1, 137.6, 144.1, (*Z* isomer) 14.7, 22.9, 52.8, 106.3, 124.4, 127.5, 128.3, 137.6, 144.1.

***N*-Allyl-*N*-isobutylideneamine (II-11a):**

A mixture of allylamine (3.54 g, 62 mmol), isobutyraldehyde (4.47 g, 62 mmol), and 4-Å molecular sieves in 100 mL of Et_2O was stirred for 2 hours at ambient temperature. The solution was then removed from the insoluble material via cannula and distilled at atmospheric pressure to give **II-11a** (5.11 g, 50.0 mmol) in 74% yield (bp 112-114 °C): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.05 (d, *J* = 6.9 Hz, 6 H), 2.42 (dsept, *J* =

4.9, 6.9 Hz, 1 H), 3.95 (d, J = 5.6 Hz, 2 H), 5.05 (dd, J = 1.8, 10.3 Hz, 1H), 5.10 (dd, J = 1.8, 17.2 Hz, 1H), 5.93 (ddt, J = 10.3, 17.2, 5.6 Hz, 1 H), 7.51 (d, J = 4.9 Hz, 1H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.3, 34.1, 63.2, 115.5, 136.1, 170.9; IR (neat) 3083, 3013, 2967, 2932, 2874, 2824, 1466, 1456, 1437, 1366, 1103, 1019, 995, 916 cm^{-1}.

_N_-Allylisobutyramide (II-13):

To a mixture of allylamine (9.02 g, 158 mmol) and pyridine (12.48 g, 158 mmol) in 600 mL of dry THF at 0 °C was added isobutyryl chloride (16.84 g, 158 mmol). After the addition was complete, the mixture was heated at reflux for 5 hours, cooled to ambient temperature, and washed with 50 mL of 15% aq. NaOH. The aqueous layer was extracted with 4 x 20 mL of Et_2O and the organic fractions were dried over $MgSO_4$. The solvents were removed by rotary evaporation, and the oil was distilled to give **II-13** (18.99 g, 149 mmol) in 95% yield (bp 78 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.13 (d, J = 6.9 Hz, 6 H), 2.37 (sept, J = 6.9 Hz, 1 H), 3.84 (ddd, J = 1.6, 1.6, 6.6 Hz, 2H), 5.09 (ddt, J = 1.4, 10.2, 1.6 Hz, 1 H), 5.14 (ddt, J = 1.4, 17.1, 1.6 Hz, 1 H), 5.81 (ddt, J = 10.2, 17.1, 6.6 Hz, 1 H), 5.85 (br s, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.3, 35.3, 41.5, 116.2, 134.5, 177.3; IR (neat) 3293, 2085, 3015, 2971, 1934, 1876, 1645, 1545, 1470, 1422, 1387, 1242, 1098, 988, 918 cm^{-1}. Anal. Calc'd for $C_7H_{13}NO$ C, 66.11; H, 10.30; N, 11.01; obsd C, 66.04, H, 9.91; N, 11.85.

Reduction of II-11a to _N_-Allyl-_N_-isobutylamine (II-12):

To a suspension of $LiAlH_4$ (1.37 g, 36 mmol) in 150 mL of Et_2O at 0 °C was slowly added **II-11a** (3.34 g, 30 mmol). After stirring for 2 hours at ambient temperature, the solution was cooled to 0 °C, and quenched by addition of 1.4 mL of H_2O, followed by 1.4 mL of 15% aq NaOH, and finally 4.1 mL of H_2O. The mixture was stirred for 1 hour and then filtered through Na_2SO_4. The solvent was removed, and the allylic amine was distilled at atmospheric pressure to give **II-12** (2.84 g, 25.1 mmol) in 84% yield (bp 122-

124 °C): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.87 (d, *J* = 6.7 Hz, 6 H), 1.00 (br s, 1 H), 1.70 (tsept, *J* = 6.8, 6.7 Hz, 1 H), 2.38 (d, *J* = 6.8, 2 H), 3.20 (ddd, *J* = 1.4, 1.4, 6.0 Hz, 2 H), 5.04 (ddt, *J* = 1.7, 10.2, 1.4 Hz, 1 H), 5.13 (ddt, *J* = 1.7, 17.2, 1.4 Hz, 1 H), 5.88 (ddt, *J* = 10.2, 17.2, 6.0 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.7, 28.3, 52.6, 57.5, 115.5, 137.2; IR (neat) 3407, 3081, 2959, 2934, 2874, 2811, 1646, 1466, 1385, 1368, 1129, 918 cm^{-1}. Anal. calcd for $C_7H_{15}N$ C, 74.27; H, 13.36; N, 12.37; obsd C, 74.43; H, 13.69; N, 12.21.

Reduction of II-13 to *N*-Allyl-*N*-isobutylamine (II-12):

To a suspension of $LiAlH_4$(1.85 g, 48.6 mmol) in 200 mL of Et_2O at 0 °C was slowly added **II-13** (5.62 g, 44.2 mmol). The mixture was heated at reflux for 3 hours, after which time the solution was cooled to 0 °C, and quenced by addition of 2 mL of water, followed by 2 mL of 15% aq NaOH, and again with 6 mL of water. After being stirred for 2 hours, the mixture was filtered through Na_2SO_4 and the solvents removed by rotary evaporation at 0 °C. The oil was distilled at atmospheric pressure to give **II-12** (4.38 g, 38.7 mmol) in 88% yield (bp 125 °C). Spectroscopic data were identical with that reported for the product obtained by reduction of **II-11a**.

Preparation of II-14a by Acylation of II-11a:

To 100 mL of dry THF were added **II-11a** (2.00 g, 18 mmol) and Et_3N (1.82 g, 18 mmol). Isobutyryl chloride (1.92 g, 18 mmol) was added dropwise. After being heated at reflux for 2 hours, the solution was cooled to ambient temperature and washed with 30 mL of 15% aq NaOH. The aqueous layer was extracted with 2 x 75 mL of Et_2O and then dried over Na_2SO_4. After removal of the solvent by rotary evaporation, the oil was distilled via Kugelrohr distillation under vacuum to give **II-14a** (3.24 g, 17.9 mmol) in 99% yield (oven temp 55-65 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.02 (d, *J* = 6.8 Hz, 6 H), 1.57 (s, 3 H), 1.70 (s, 3 H), 2.65 (sept, *J* = 6.8 Hz, 1 H), 3.89 (d, *J* = 6.2

Hz, 2 H), 5.04 (dd, J = 1.6, 11.3 Hz, 1 H), 5.06 (dd, J = 1.6, 16.0 Hz, 1 H), 5.74 (ddt, J = 11.3, 16.0, 6.2 Hz, 1 H), 5.85 (s, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.3, 18.8, 21.5, 30.9, 50.0, 116.9, 123.5, 133.4, 135.9, 177.7; IR (neat) 3083, 2975, 2936, 2876, 1653, 1472, 1404, 1242, 1208, 1092, 993, 920 cm^{-1}. Anal. calcd for $C_{11}H_{19}NO$ C, 72.88; H, 10.56; N, 7.73; obsd C, 72.84; H, 10.78; N, 7.72.

Formation of II-14a from II-13:

To 300 mL of benzene were added **II-13** (3.51 g, 27.6 mmol), isobutyraldehyde (2.38 g, 33.1 mmol), and pTsOH (0.48 g, 2.8 mmol). The reaction flask was fitted with a Dean-Stark trap containing 4-Å molecular sieves, and the solution was heated at reflux for 66 hours. After cooling, the solvents were removed and the oil was distilled under vacuum to give **II-14a** (4.24 g, 23.4 mmol) in 85% yield (oven temp 60-70 °C, <1 mmHg). Spectroscopic data were identical with that reported for the product obtained by acylation of **II-11**.

Preparation of II-15a by Condensation of Isobutyraldehyde with II-12:

A flask containing **II-12** (1.70 g, 15 mmol), isobutyraldehyde (1.08 g, 15 mmol), and pTsOH (0.007 g, 0.04 mmol) in 754 mL of benzene was fitted with a Dean-Stark trap containing 4-Å molecular sieves. The solution was heated at reflux for 28 hours and then cooled to ambient temperature. After removal of the solvent, the oil was distilled via Kugelrohr distillation to give **II-15a** (2.00 g, 12.0 mmol) in 80% yield (oven temp 45-50 °C, 8 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (d, J = 6.6 Hz, 6 H), 1.58 (d, J = 1.3 Hz, 3 H), 1.58 (tsept, J = 7.3, 6.6 Hz, 1 H), 1.65 (d, J = 1.3 Hz, 3 H), 2.25 (d, J = 7.3 Hz, 2 H), 3.15 (ddd, J = 1.6, 1.6, 6.2 Hz, 2 H), 5.02 (ddt, J = 2.0, 10.2, 1.6 Hz, 1 H), 5.08 (ddt, J = 2.0, 17.2, 1.6 Hz, 1 H), 5.22 (qq, J = 1.3, 1.3 Hz, 1 H), 5.81 (ddt, J = 2.0, 17.2, 1.6 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.4, 20.4, 22.0, 27.4, 59.6, 63.1, 115.9, 122.8, 135.8, 136.9; IR (neat) 3081, 3009, 2955, 2926, 2870, 2803, 1676, 1644, 1468,

1377, 1337, 1194, 1117, 1101, 995, 916 cm $^{-1}$. Anal. calcd for $C_{11}H_{21}N$ C, 78.98; H, 12.65; N, 8.37; obsd C, 79.18; H, 12.83; N, 8.48.

General Method for the Two-Step Synthesis of II-14 from Allylamine:

Allylamine (1.0 equiv), and the necessary aldehyde or ketone (1.0 equiv) were taken up in benzene (0.35 *M*). A Dean-Stark trap was fitted on the apparatus and the solution was heated at reflux to remove the water. After heating for 20 hours, the water was drained, the Dean-Stark trap was filled with 4-Å molecular sieves and reflux was continued for 2 hours. The solution was cooled to ambient temperature and Et_3N (1.0 equiv) and isobutyryl chloride (1.0 equiv) were added, sequentially. The mixture was heated at reflux for 3 hours, cooled, filtered to remove the Et_3N-HCl salts, and the solvent was evaporated. The crude oil was purified by flash column chromatography (silica, 230-400 mesh; eluent 70:30 Et_2O:petroleum ether). The solvents were evaporated, and the enamide was distilled under vacuum to give **II-14**.

II-14a: 42.68 g, (23.5 mmol, 94% yield), (bp 50-54 °C, <1 mmHg). Spectroscopic data were identical with that reported for the product obtained by acylation of **II-11a**.

II-14c: 9.56 g (*E*:*Z* 57:43), (39.3 mmol, 79% yield), (bp 112-115 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 1.10 (d, *J* = 6.7 Hz, 6 H), 2.02 (d, *J* = 1.4 Hz, 3 H), 2.80 (sept, *J* = 6.7 Hz, 1 H), 4.15 (ddd, *J* = 1.3, 1.3, 6.2 Hz, 2 H), 5.14 (ddt, *J* = 1.1, 10.4, 1.3 Hz, 1 H), 5.17 (ddt, *J* = 1.1, 17.0, 1.3 Hz, 1 H), 5.85 (ddt, *J* = 10.4, 17.0, 6.2 Hz, 1 H), 6.43 (q, *J* = 1.4 Hz, 1 H), 7.33 (m, 5 H), (*Z* isomer) 1.00 (d, *J* = 6.8 Hz, 6 H), 2.10 (d, *J* = 1.4 Hz, 3 H), 2.91 (sept, *J* = 6.8 Hz, 1 H), 3.84 (ddd, *J* = 1.3, 1.3, 6.0 Hz, 2 H), 4.99 (ddt, *J* = 1.2, 17.0, 1.3 Hz, 1 H), 5.06 (ddt, *J* = 1.2, 10.4, 1.3 Hz, 1 H), 5.70 (ddt, *J* = 10.4, 17.0, 6.0 Hz, 1 H), 6.26 (q, *J* = 1.4 Hz, 1 H), 7.33 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (both isomers) 15.6, 18.8, 18.9, 21.7, 31.3, 31.5, 49.2, 50.0, 116.7, 117.5, 124.2, 125.9, 126.2, 127.3, 127.9, 128.3, 128.7, 128.8, 133.2, 133.5, 134.2, 138.3,

138.8, 140.0, 177.5, 177.6; IR (neat) 3083, 3059, 2971, 2874, 1663, 1401, 1231, 995, 909 cm^{-1}. Anal. calcd for $C_{16}H_{21}NO$ C, 78.97; H, 8.70; N, 5.76; obsd (C, 78.96; H, 8.80; N, 5.70.

II-14d: 47.84 g, (247 mmol, 77% yield), (oven temp 80-120 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.03 (d, *J* = 6.8 Hz, 6 H), 1.52 (m, 2 H), 1.64 (m, 2 H), 2.02 (m, 4 H), 2.66 (sept, *J* = 6.8 Hz, 1 H), 3.87 (d, *J* = 6.3 Hz, 2 H), 5.04 (m, 2 H), 5.55 (t, *J* = 3.8, 1 H), 5.74 (ddt, *J* = 10.2, 17.0, 6.3 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.9, 21.2, 22.5, 24.4, 28.7, 31.0, 48.9, 117.0, 127.1, 134.3, 139.0, 176.9; IR (neat) 3081, 2967, 2936, 2863, 1649, 1480, 1400, 1360, 1245, 909 cm^{-1}. Anal. calcd for $C_{13}H_{21}NO$ C, 75.32; H, 10.21; N, 6.75; obsd C, 74.98; H, 9.85; N, 6.60.

II-14e: 39.55 g, (205 mmol, 68% yield), (oven temp 100-130 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.05 (d, *J* = 6.7 Hz, 6 H), 1.91 (m, 2 H), 2.33 (m, 4 H), 2.79 (sept, *J* = 6.7 Hz, 1 H), 3.99 (d, *J* = 5.9 Hz, 2 H), 5.06 (m, 2 H), 5.50 (s, 1 H), 5.74 (ddt, *J* = 10.2, 17.0, 5.9 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.8, 22.1, 30.1, 31.0, 33.1, 48.7, 116.8, 126.9, 134.1, 177.0; IR (neat) 3081, 2967, 2934, 2872, 2851, 1649, 1480, 1400, 1370, 1225, 995, 909 cm^{-1}. Anal. calcd for $C_{12}H_{19}NO$ C, 74.57; H, 9.91; N, 7.24; obsd C, 74.70; H, 10.07; N, 7.55.

General Method for Reduction of II-14 to *N*-Allyl-*N*-Isobutyl Enamines II-15:

To a suspension of $LiAlH_4$ (1.1 equiv) in Et_2O (0.2 *M*) was added **II-14** (1.0 equiv) slowly via syringe. After addition was complete, the reaction was stirred at ambient temperature for 3-4 hours, cooled to 0 °C, and quenched by addition of water (1 mL/g $LiAlH_4$), 15% aq NaOH (1 mL/g $LiAlH_4$), and finally water (3 mL/g $LiAlH_4$). The mixture was stirred for 2 hours, then filtered. The solvent was evaporated and the enamines **II-15** were distilled via short-path or Kugelrohr distillation.

II-15a: 9.84 g, (58.8 mmol, 98% yield), (bp 54-55 °C, 8 mmHg). Spectroscopic data were consistent with that reported for the preparation of **II-15a** by condensation of **II-13** with isobutyraldehyde.

II-15b: 3.64 g, (21.8 mmol, 95% yield), (bp 63-64 °C, 8 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.83 (d, 6 H, *J* = 6.7 Hz), 0.92 (t, 3 H, *J* = 7.4 Hz), 1.82 (tsept., 1 H, *J* = 7.3, 6.7 Hz), 1.94 (ddq, 2 H, *J* = 1.2, 6.7, 6.7 Hz), 2.62 (d, 2 H, *J* = 7.3 Hz), 3.49 (ddd, 2 H, *J* = 1.5, 1.5, 5.8 Hz), 4.12 (dt, 1 H, *J* = 13.8, 6.7 Hz), 5.07 (ddt, 1 H, *J* = 1.4, 10.2, 1.5 Hz), 5.09 (ddt, 1 H, *J* = 1.4, 17.1, 1.5 Hz), 5.77 (ddt, 1 H, *J* = 10.2, 17.1, 5.8 Hz), 5.89 (dt, 1 H, *J* = 13.8, 1.2 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 16.1, 20.2, 23.7, 27.0, 54.2, 59.8, 98.9, 116.2, 135.3, 137.7; IR (neat) 3079, 3052, 3009, 2957, 2930, 2070, 2847, 1653, 1468, 1389, 1368, 1223, 1203, 1175, 1117, 934, 918 cm^{-1}.

II-15c: 4.77 g (*E*:*Z* 86:14), (20.6 mmol, 95% yield), (bp 105 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 0.91 (d, 6 H, *J* = 6.6 Hz), 1.76 (tsept., 1 H, *J* = 7.4, 6.6 Hz), 2.09 (d, 3 H, *J* = 1.2 Hz), 2.63 (d, 2 H, *J* = 7.4 Hz), 3.53 (ddd, 2 H, *J* = 1.5, 1.5, 5.9 Hz), 5.13 (ddt, 1 H, *J* = 1.9, 10.2, 1.5 Hz), 5.20 (ddt, 1 H, *J* = 1.9, 17.2, 1.5 Hz), 5.91 (ddt, 1 H, *J* = 10.2, 17.2, 5.9 Hz), 6.15 (q, 1 H, *J* = 1.2 Hz), 7.30 (m, 5 H), (*Z* isomer) 0.86 (d, 6 H, *J* = 6.6 Hz), 1.75 (tsept., 1 H, *J* = 7.4, 6.6 Hz), 1.98 (d, 3 H, *J* = 1.2 Hz), 2.51 (d, 2 H, *J* = 7.4 Hz), 3.26 (ddd, 2 H, *J* = 1.4, 1.4, 5.9 Hz), 5.02 (m, 1 H), 5.68 (m, 1 H), 5.84 (q, 1 H, *J* = 1.2 Hz), 7.30 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 15.4, 20.2, 58.3, 62.4, 116.4, 125.2, 125.5, 128.2, 128.3, 136.4, 139.3, 143.5; IR (neat) 3079, 3059, 3029, 2955, 2936, 2870, 2813, 1632, 1597, 1495, 1480, 1445, 1204, 1121, 918 cm^{-1}.

II-15d: 1.52 g (7.8 mmol, 98% yield), (oven temp 50-60 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.82 (d, 6 H, *J* = 6.7 Hz), 1.49 (m, 2 H), 1.63 (m, 2 H), 1.84 (tsept., 1 H, *J* = 7.1, 6.7 Hz), 2.06 (m, 4 H), 2.66 (d, 2 H, *J* = 7.1 Hz), 3.57 (ddd, 2 H, *J* = 1.5, 1.5, 5.7 Hz), 4.41 (dd, 1 H, *J* = 3.4, 3.4 Hz), 5.04 (ddt, 1 H, *J* = 1.7, 10.3, 1.5 Hz), 5.06 (ddt, 1 H, *J* = 1.7, 17.3, 1.5 Hz), 5.75 (ddt, 1 H, *J* = 10.3, 17.3, 5.7); ^{13}C NMR (75.5

MHz) ($CDCl_3$) δ 20.4, 22.7, 23.4, 24.5, 26.5, 27.1, 52.6, 56.8, 96.7, 115.6, 136.1, 143.5; IR (neat) 3079, 2953, 2869, 1714, 1644, 1607, 1564, 1468, 1420, 1387, 1339, 1223, 1119, 993, 916 cm^{-1}.

II-15e: 1.29 g, (7.1 mmol, 90% yield), (oven temp 50-60 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (d, 6 H, *J* = 6.7 Hz), 1.86 (br. m, 3 H), 2.34 (br. m, 4 H), 2.74 (d, 2 H, *J* = 7.4 Hz), 3.61 (ddd, 2 H, *J* = 1.4, 1.4, 5.5 Hz), 4.08 (bs, 1 H), 5.05 (ddt, 1 H, *J* = 1.6, 10.5, 1.4 Hz), 5.07 (ddt, 1 H, *J* = 1.6, 17.0, 1.4 Hz), 5.77 (ddt, 1 H, *J* = 10.5, 17.0, 5.5 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.2, 26.9, 30.5, 32.3, 38.2, 53.8, 58.4, 92.3, 115.7, 135.6, 137.3; IR (neat) 3087, 2964, 2915, 2874, 1670, 1634, 1607, 1561, 1468, 1418, 1391, 1341, 1238, 1096, 991, 909 cm^{-1}.

Preparation of *N*-Allylbutylideneamine (II-11b):

To 20.70 g (150 mmol) of potassium carbonate and 2.855 g (50 mmol) of allylamine in 50 mL of dry diethyl ether were added dropwise 2.904 g (40 mmol) of *n*-butanal in 25 mL of dry diethyl ether over one half hour. The mixture was stirred for an additional 1.5 hours at ambient temperature. The solution was filtered, and the ether was removed by rotary evaporation at 0 °C. The imine was distilled via Kugelrohr under vacuum to give **II-11b** (3.02 g, 27.2 mmol) in 68% yield (oven temp 30-40 °C, 25 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.89 (t, 3 H, *J* = 7.4 Hz), 1.51, (tq, 2 H, *J* = 7.3, 7.4 Hz), 2.19 (dt, 2 H, *J* = 4.9, 7.3 Hz), 3.94 (ddd, 2 H, *J* = 1.3, 1.3, 5.7 Hz), 5.03 (ddt, 1 H, *J* = 1.7, 10.3, 1.3 Hz), 5.08 (ddt, 1 H, *J* = 1.7, 17.2, 1.3 Hz), 5.91 (ddt, 1 H, *J* = 1.03, 17.2, 5.7 Hz), 7.61 (t, 1 H, *J* = 4.9 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 12.9, 18.5, 37.1, 62.8, 115.1, 135.7, 165.8; IR (neat) 3081, 3013, 2963, 2938, 2874, 2832, 1673, 1644, 1470, 1440, 1375, 1305, 990, 905 cm^{-1}.

Acylation of Imine II-11b to Give Enamide II-14b:

To a solution of imine **II-11b** (12.52 g, 100 mmol) and pyridine (7.910 g, 100 mmol) in 500 mL of dry diethyl ether was slowly added isobutyryl chloride (10.660 g, 100 mmol). The solution was heated at reflux for six hours, then filtered and washed with 100 mL aqueous saturated sodium bicarbonate and 100 mL of water. The organic layer was dried over $MgSO_4$ and filtered. The ether was removed by rotary evaporation, and the enamide was distilled under vacuum to give **II-14b** (15.57 g, 85.9 mmol) in 86% yield as a 63:37 (*E*:*Z*) mixture of isomers (b.p. 57-62 °C/<1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 0.96 (t, 3 H, *J* = 7.4 Hz), 1.13 (d, 6 H, *J* = 6.7 Hz), 2.03 (ddq, 2 H, *J* = 1.3, 6.9, 7.4 Hz), 2.91 (sept., 1 H, *J* = 6.7 Hz), 4.20 (d, 2 H, *J* = 5.1 Hz), 5.08 (m, 3 H), 5.73 (m, 1 H), 6.78 (d, 1 H, *J* = 14.0 Hz), (*Z* isomer) 0.95 (t, 3 H, *J* = 7.4 Hz), 1.12 (d, 6 H, *J* = 6.7 Hz), 2.03 (ddq 2 H, *J* = 1.3, 6.9, 7.4 Hz), 2.70 (sept., 1 H, *J* = 6.7 Hz), 4.12 (d, 2 H, *J* = 5.1 Hz), 5.08 (m, 3 H), 5.73 (m, 1 H), 7.21 (d, 1 H, *J* = 12.8 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 14.3, 19.0, 19.4, 20.5, 23.3, 23.4, 30.7, 30.9, 46.0, 47.2, 113.9, 115.9, 116.0, 116.1, 125.7, 126.5, 132.8, 133.1, 175.5; IR (neat) 3347, 3085, 2967, 2934, 2874, 1673, 1647, 1480, 1405, 1315, 1205, 945 cm^{-1}. Anal. calcd for $C_{11}H_{19}NO$ C, 72.88; H, 10.56; N, 7.73; obsd C, 72.59; H, 10.93; N, 7.84.

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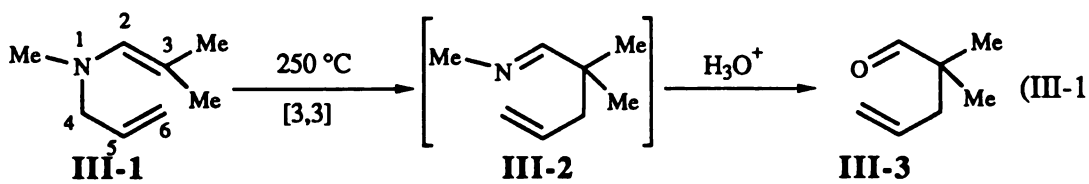
CHAPTER III: CHARGE-PROMOTED 3-AZA-COPE REARRANGEMENTS

Background: Acceleration of the 3-Aza-Cope Rearrangement

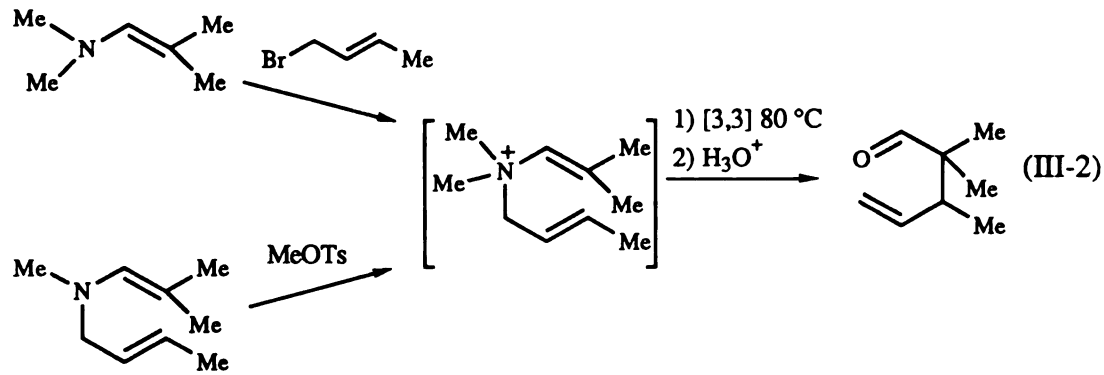
The *N*-allyl-*N*-methyl enamine **III-1** has been reported to undergo [3,3] sigmatropic rearrangement thermally at 250 °C, followed by hydrolysis of imine **III-2** to produce the γ,δ-unsaturated aldehyde **III-3** (eq III-1).[1] Because many sensitive functional groups cannot tolerate such harsh temperatures, promotion of this rearrangement at lower temperatures would lead to greater utility of this transformation in organic synthesis.



III-1 **III-2** **III-3** (III-1)

Modification of the electronic environment of the enamine has led to lower reaction temperatures. Increasing the electron density by placing an oxygen substituent on the C-2 position, as in the case of ketene *N*,*O*-acetals allowed for [3,3] rearrangement at 180-190 °C.[2] The [3,3] sigmatropic rearrangement of the enolate of an *N*-allyl amide proceeded at 135 °C.[3]

Acceleration of the 3-aza-Cope rearrangment could be accomplished through reduction of the electron density around the enamine as well. The addition of alkyl electrophiles resulted in the formation of a quaternary ammonium salt, which was reported to undergo [3,3] rearrangment at 80 °C (eq III-2).[4] In most cases where 3-aza-Cope rearrangment has been carried out on cationic quaternary enamines, the imine products were hydrolyzed to the corresponding aldehydes for isolation.



The use of Lewis acids for the promotion of [3,3] sigmatropic rearrangements has been extensively explored.[5] Although, aluminum complexes have been employed in the Claisen rearrangement of allyl vinyl ethers, the only Lewis acid reported to promote the 3-aza-Cope rearrangement, aside from the findings of this group,[6] was $TiCl_4$. During the $TiCl_4$ catalyzed formation of an *N*-allyl enamine, Hill discovered that [3,3] sigmatropic rearrangment occurred in refluxing benzene, and even slowly at room temperature.[5l] Bailey has used $TiCl_4$ catalysis in the stereoselective 3-aza-Cope rearrangement of chiral enamines at 55 °C.[5m] Again, in these cases, the imine products were hydrolyzed *in situ* to the corresponding aldehydes, and overall yields for the condensation, [3,3] rearrangement, and subsequent hydrolysis were low to moderate (15-68%). Further, the use of straight-chain aldehydes in this procedure resulted in low yields (20-30%), and condensation and rearrangement with ketones was unsuccessful. This methodology, condensation and *in situ* 3-aza-Cope rearrangment, was limited to α,α-disubstitued aldehydes, thus its utility for practical synthesis was low.

Charge-Promoted 3-Aza-Cope Rearrangments of *N*-Allyl-*N*-Isobutyl Enamines

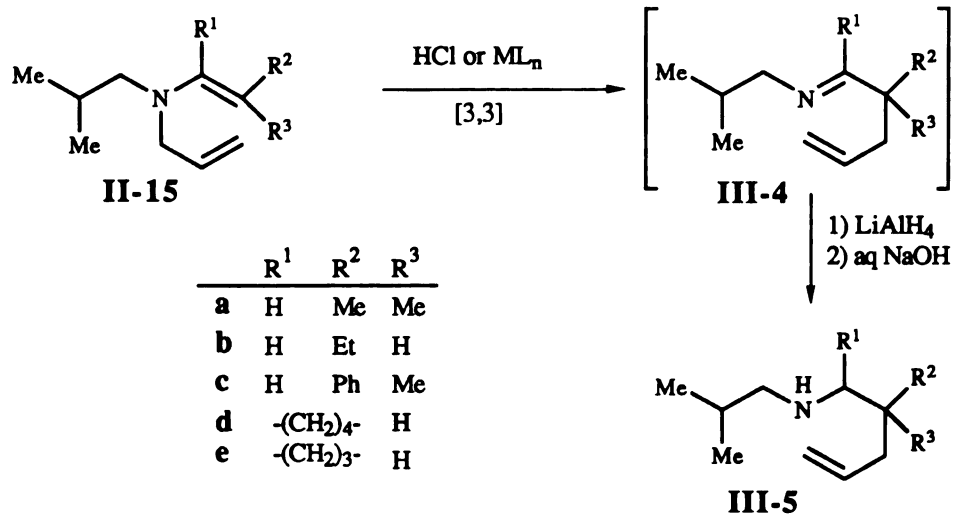
Several features were required for our study of the charge-promoted 3-aza-Cope rearrangement. First, electrophilic reagents were needed which would promote the reaction at temperatures that would be synthetically useful. Second, this charge-

promoted [3,3] sigmatropic rearrangement should be applicable to enamines derived from straight-chain aldehydes and ketones. And finally, the imine products should be reduced efficiently to δ,ε-unsaturated amines in order to preserve the nitrogen functionality for further manipulation.

Initial studies were focused on the use of methyl electrophiles (MeI and MeOTs) in refluxing acetonitrile or dioxane.[6a,7] While the [3,3] rearrangement proceeded well, clean reduction with $LiAlH_4$ or $NaBH_4$ could not be obtained, and further investigation was not carried out.

Acceleration of the [3,3] rearrangement of **II-15** by protic and Lewis Acids (HCl, $TiCl_4$, $AlMe_3$) was investigated (Scheme III-1, Table III-1). Treatment of **II-15a** with 1.0 eq. of HCl in dioxane at reflux, and subsequent reduction, provided **III-5a** in 81% isolated yield. Rearrangement promoted by catalytic $TiCl_4$ and stoichiometric $AlMe_3$ produced similar results. High yields were also obtained for the rearrangement and reduction of the geminally disubstituted enamine **II-15c** derived from 2-phenylpropanal. Substrate **II-15b**, monosubstituted on the nucleophilic enamine carbon, was found to be sensitive to the reaction conditions. Treatment with HCl and $TiCl_4$ gave only oligomeric products derived from aldol-type reactions, which indicated that the electrophilic reagent has a preference for the nucleophilic carbon over the nitrogen. In contrast, the organoaluminum electrophile produced clean rearrangement and **III-5c** was obtained in 84% yield.

SCHEME III-1. Proton and Lewis Acid Promoted 3-Aza-Cope Rearrangements



II-15

III-4

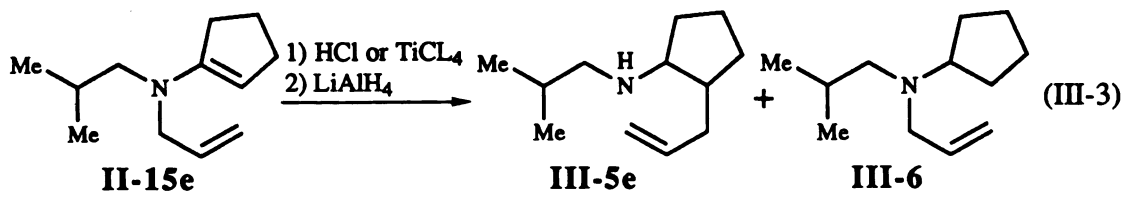
III-5

	R^1	R^2	R^3
a	H	Me	Me
b	H	Et	H
c	H	Ph	Me
d	$-(CH_2)_4-$		H
e	$-(CH_2)_3-$		H

TABLE III-1. Yields of Charge-Promoted 3-Aza-Cope Rearrangement

		Reagent (equiv.)		
Enamine	Product	HCl (1.0)	$TiCl_4$ (0.2)	$AlMe_3$ (1.0)
II-15a	**III-5a**	81	71	95
II-15b	**III-5b**	0	0	84
II-15c	**III-5c**	77	88	92
II-15d	**III-5d**	99	92	96
II-15e	**III-5e**	10	3	83

Successful rearrangement of ketone enamines **II-15d** and **II-15e** was found to be dependent upon the nature of the carbonyl compound. While **II-15d** was transformed into **III-5d** in nearly quantitative yields with all three electrophiles, **II-15e** gave mixed results. Rearrangement with HCl resulted in a mixture of unreacted **II-15e** (9%), **III-5e** (10%), and the reduced product **III-6** (36%) (eq. III-3). Reaction with $TiCl_4$ gave a similar mixture of **II-15e** (11%), **III-5e** (3%), and **III-6** (26%). **III-6** was prepared independently to confirm the structure. As was the case with **II-15b**, treatment of **II-15e** with stoichiometric $AlMe_3$ afforded clean rearrangement, and **III-5e** was obtained in high yield.



II-15e **III-5e** **III-6** (III-3)

The nature of the electrophilic reagent was critical for control over the outcome of the charge-promoted 3-aza-Cope rearrangement. $AlMe_3$ appeared to be unique in a number of ways. Organoaluminum reagents appeared to have a greater affinity for nitrogen *versus* the nucleophilic enamine carbon over the other reagents employed. This preference of aluminum was demonstrated by complete [3,3] rearrangement of **II-15b** and **II-15e** through an aza-Cope process while HCl and $TiCl_4$ reacted through alternate pathways. The nitrogen affinity of $AlMe_3$ was also demonstrated by the observation that stoichiometric quantities were required for complete conversion of enamine substrate. This suggested that the organoaluminum reagent formed a relatively stable complex with the nitrogen of the imine product **III-4** and was not available for further complexation with unreacted enamine substrate.

Summary

Acceleration of the aliphatic 3-aza-Cope rearrangement with a variety of electrophiles has been accomplished, which increases the utility of this process for organic synthesis. Reduction of the imine products *in situ* was carried out and provided high yields of δ,ε-unsaturated amines. Geminally disubstituted enamine substrates derived from isobutyraldehyde and 2-phenylpropanal as well as enamine substrates derived from ketones underwent efficient carbon-carbon bond formation through charge-promoted 3-aza-Cope rearrangment with HCl, $TiCl_4$, and $AlMe_3$. More sensitive enamine substrates derived from *n*-butanal and cyclopentanone would only undergo clean efficient rearrangment when $AlMe_3$ was employed as the electrophile.

EXPERIMENTAL

General Methods

For general experimental methods see General Methods in Chapter II.

General Procedure for the HCl-Promoted 3-Aza-Cope Rearrangement:

To a dried flask under argon or nitrogen was added **II-15** (1.0 eq.) and dry dioxane to make a 0.2 *M* solution. Anhydrous HCl (1.0 eq.) (1 *M* solution in Et_2O) was added at 0 °C and the mixture was heated at reflux for 6-12 hours. The solution was cooled to 0 °C, and $LiAlH_4$ (1.1 eq.) (1 *M* in THF) was added. After stirring for 2 hours at ambient temperature, the mixture was quenched by sequential addition of H_2O (1 mL/g $LiAlH_4$), 15% aq. NaOH (1 mL/g $LiAlH_4$), and H_2O (3 mL/g $LiAlH_4$). The solution was filtered after stirring for 1 hour, concentrated by rotary evaporation, and the amine product (**III-5e**) was purified by Kugelrohr distillation.

III-5a: (1.37 g, 8.1 mmol) in 81% yield (oven temp 50-60 °C, 8 mmHg); ^1H NMR (300 MHz) ($CDCl_3$) δ 0.85 (s, 6 H), 0.86 (d, *J* = 6.6 Hz, 6 H), 0.87 (bs, 1 H), 1.71 (tsept, *J* = 6.9, 6.6 Hz, 1 H), 1.98 (d, *J* = 7.5 Hz, 2 H), 2.29 (s, 2 H), 2.35 (d, *J* = 6.9 Hz, 2 H), 4.99 (m, 2 H), 5.79 (ddt, *J* = 9.2, 17.9, 7.5 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 25.5, 27.9, 34.4, 44.7, 59.1, 60.3, 116.6, 135.7; IR (neat) 3359, 3077, 3005, 2957, 2872, 2811, 1640, 1466, 1385, 1364, 1121, 995, 912 cm^{-1}. Anal. calcd for $C_{11}H_{23}N$ C, 78.04; H, 13.69; N, 8.27; obsd C, 77.64; H, 13.87; N, 7.68.

III-5c: (1.37 g, 5.9 mmol) in 77% yield (oven temp 60-70 °C, <1 mmHg); ^1H NMR (300 MHz) ($CDCl_3$) δ 0.75 (d, *J* = 6.6 Hz, 3 H), 0.77 (d, *J* = 6.6 Hz, 3 H), 0.88 (bs, 1 H), 1.34 (s, 3 H), 1.63 (tsept, *J* = 6.8, 6.6 Hz, 1 H), 2.29 (dd, *J* = 11.8, 6.8 Hz, 1 H), 2.32 (dd, *J* = 11.8, 6.8 Hz, 1 H), 2.35 (dd, *J* = 7.6, 13.8 Hz, 1 H), 2.52 (dd, *J* = 6.6, 13.8 Hz, 1 H), 2.63 (d, *J* = 11.5 Hz, 1 H), 2.80 (d, *J* = 11.5 Hz, 1 H), 4.94 (d, *J* = 10.0 Hz, 1 H), 4.99 (d, *J* = 17.1 Hz, 1 H), 5.57 (dddd, *J* = 6.6, 7.6, 10.0, 17.1 Hz, 1 H) 7.25 (m, 5 H);

^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.2, 23.2, 27.6, 41.7, 45.0, 58.6, 60.6, 117.2, 126.0, 126.7, 128.4, 135.3; IR (neat) 3337, 3061, 3025, 2957, 2928, 2872, 2811, 1640, 1601, 1497, 1466, 1447, 1379, 1123, 959 cm^{-1}. Anal. calcd for $C_{16}H_{25}N$ C, 83.06; H, 10.89; N, 6.05; obsd C, 82.73; H, 10.93; N, 6.08.

III-5d: (1.98 g, 10.1 mmol) in 99% yield as a 90:10 mixture of diastereomers (oven temp 40-50 °C, <1 mmHg); ^1H NMR (300 MHz) ($CDCl_3$, major diastereomer) δ 0.85 (s, 6 H), 0.86 (d, *J* = 6.6 Hz, 6 H), 0.87 (bs, 1 H), 1.71 (tsept, *J* = 6.9, 6.6 Hz, 1 H), 1.98 (d, *J* = 7.5 Hz, 2 H), 2.29 (s, 2 H), 2.35 (d, *J* = 6.9 Hz, 2 H), 4.99 (m, 2 H), 5.79 (ddt, *J* = 9.2, 17.9, 7.5 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 25.5, 27.9, 34.4, 44.7, 59.1, 60.3, 116.6, 135.7; IR (neat) 3359, 3077, 3005, 2957, 2872, 2811, 1640, 1466, 1385, 1364, 1121, 995, 912 cm^{-1}. Anal. calcd for $C_{11}H_{23}N$ C, 79.93; H, 12.90; N, 7.17; obsd C, 80.16; H, 12.03; N, 7.47.

III-5e/III-6: (0.98 g of a mixture of **II-15e** (9%), **III-5e** (10%, 90:10 mixture of diastereomers), and **III-6** (36%)) (oven temp 50-60 °C, 8 mmHg); ^1H NMR (300 MHz) ($CDCl_3$, **III-5e**, major diastereomer) δ 0.86 (d, *J* = 6.7 Hz, 6 H), 1.43 (m, 3 H), 1.65 (m, 4 H), 1.90 (m, 2 H), 2.17 (m, 2 H), 2.27 (dd, *J* = 6.9, 11.5 Hz, 1 H), 2.39 (dd, *J* = 6.6, 11.5 Hz, 1 H), 2.96 (dt, *J* = 5.8, 6.0 Hz, 1 H), 4.94 (dd, *J* = 1.2, 10.1 Hz, 1 H), 5.00 (dd, *J* = 1.2, 17.1 Hz, 1 H), 5.79 (ddt, *J* = 10.1, 17.1, 6.7 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 21.0, 28.3, 30.7, 32.7, 41.9, 56.5, 61.5, 115.1, 138.7; IR (neat) 3349, 3077, 2955, 2870, 2010, 1642, 1470, 1387, 1366, 1138, 993, 911 cm^{-1}.

General Procedure for $TiCl_4$-Promoted 3-Aza-Cope Rearrangement:

To a predried flask under argon or nitrogen was added **II-15** (1.0 eq.) and dry toluene to make a 0.2 *M* solution. $TiCl_4$ (0.2 eq.) was added at -78 °C and the mixture was heated at reflux for 24-48 hours. The solution was cooled to -78 °C and $LiAlH_4$ (1.1 eq.) (1 *M* in THF) was added. After 6 hours at -78 °C, the mixture was quenched at that temperature by sequential addition of H_2O (1 mL/g $LiAlH_4$), 15% aq. NaOH (1 mL/g

$LiAlH_4$), and H_2O (3 mL/g $LiAlH_4$) and allowed to warm to room temperature. The solution was filtered after 1 hour, concentrated by rotary evaporation, and the amine product (**III-5e**) was purified by Kugelrohr distillation.

III-5a: in 71% yield. Spectral data was identical to that obtained by the HCl-promoted rearrangmeent.

III-5c: in 88% yield. Spectral data was identical to that obtained by the HCl-promoted rearrangmeent.

III-5d: in 92% yield as a 90:10 mixture of diastereomers. Spectral data was identical to that obtained by the HCl-promoted rearrangmeent.

III-5e/III-6: Mixture of **II-15e** (11%), **III-5e** (3%, 90:10 mixture of diastereomers), and **III-6** (26%). Spectral data was identical to that obtained by the HCl-promoted rearrangmeent.

General Procedure for the $AlMe_3$-Promoted 3-Aza-Cope Rearrangement:

To a dried flask under argon or nitrogen was added **II-15** (1.0 eq.) and dry toluene to make a 0.2 *M* solution. $AlMe_3$ (1.0 eq.) (2 *M* solution in toluene) was added at -78 °C and the mixture was heated at reflux for 12-24 hours. The solution was cooled to 0 °C and $LiAlH_4$ (1.1 eq.) (1 *M* in THF) was added. After stirring for 2 hours at ambient temperature, the mixture was quenched by sequential addition of H_2O (1 mL/g $LiAlH_4$), 15% aq. NaOH (1 mL/g $LiAlH_4$), and H_2O (3 mL/g $LiAlH_4$). The solution was filtered after 1 hour, concentrated by rotary evaporation, and the amine product (**III-5e**) was purified by Kugelrohr distillation.

III-5a: in 95% yield. Spectral data was identical to that obtained by the HCl-promoted rearrangmeent.

III-5b: in 84% yield (oven temp 70-80 °C, 8 mmHg); ^1H NMR (300 MHz) ($CDCl_3$) δ 0.85 (t, J = 7.4 Hz, 3 H), 0.85 (d, J = 6.6 Hz, 6 H), 1.29 (m, 2 H), 1.48 (ddq, J = 6.4, 6.4, 7.4 Hz, 1 H), 1.50 (ddq, J = 6.4, 6.4, 7.4 Hz, 1 H), 1.69 (tsept, J = 6.7, 6.6. Hz,

1 H), 2.04 (ddt, J = 6.1, 7.2, 1.3 Hz, 1 H), 2.34 (d, J = 6.7 Hz, 1 H), 2.44 (d, J = 6.4 Hz, 1 H), 2.45 (d, J = 6.4 Hz, 1 H), 4.95 (ddt, J = 1.1, 10.0, 1.3 Hz, 1 H), 4.99 (ddt, J = 1.1, 17.2, 1.3 Hz, 1 H), 5.76 (ddt, J = 10.0, 17.2, 7.2 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 10.8, 20.4, 24.3, 28.0, 36.3, 39.3, 53.0, 58.3, 115.8, 137.5; IR (neat) 3418, 3079, 2959, 2928, 2874, 2813, 1640, 1466, 1381, 1366, 1125, 995, 911 cm^{-1}. Anal. calcd for $C_{11}H_{23}N$ C, 78.04; H, 13.69; N, 8.27; obsd C, 77.65; H, 13.66; N, 8.25.

III-5c: in 92% yield. Spectral data was identical to that obtained by the HCl-promoted rearrangmeent.

III-5d: in 96% yield as a 90:10 mixture of diastereomers. Spectral data was identical to that obtained by the HCl-promoted rearrangmeent.

III-5e: in 83% yield as a 90:10 mixture of diastereomers. Spectral data was identical to that obtained by the HCl-promoted rearrangement.

Preparation of Standard III-6:

Allylamine (5.71 g, 100 mmol), cyclopentanone (8.41 g, 100 mmol), and benzene (300 mL) were added to a flask fitted with a Dean-Stark trap, and the mixture was then heated at reflux for 15 hours. The water was drained from the trap and 4 Å molecular sieves were added. Reflux was continued an additional 2 hours to remove the final traces of water from the reaction mixture. The benzene was removed by distillation and the remaining oil was distilled via Kugelrohr to give *N*-allylcyclopentylideneamine (8.09 g, 66 mmol) in 66% yield (oven temp 50-70 °C, 15 mmHg).

To a suspension of $LiAlH_4$ (1.82 g, 48 mmol) in Et_2O (200 mL) was added *N*-allylcyclopentylideneamine (4.93 g, 40 mmol). The mixture was stirred for 4 hours at ambient temperature and was then quenched by sequential addition of H_2O (1.8 mL), 15% aq. NaOH (1.8 mL), and H_2O (5.4 mL). After stirring for 1 hour, the mixture was filtered to remove the aluminum salts, and the solution was concentrated to an oil, which was distilled under vacuum to give *N*-allyl-*N*-cyclopentylamine (4.36 g, 35 mmol) in

87% yield (oven temp 60-70 °C, 15 mmHg); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.28 (m, 2 H), 1.50 (m, 3 H), 1.64 (m, 2 H), 1.81 (m, 2 H), 3.06 (tt, *J* = 6.7, 6.8 Hz, 1 H), 3.20 (ddd, *J* = 1.2, 1.2, 6.1 Hz, 2 H), 5.03 (ddt, *J* = 10.2, 17.1, 6.1 Hz, 1 H), 5.12 (ddt, *J* = 1.3, 17.1, 1.2 Hz, 1 H), 5.89 (ddt, *J* = 10.2, 17.1, 6.1 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 24.0, 33.1, 51.3, 59.2, 115.5, 137.2.

To a mixture of *N*-allyl-*N*-cyclopentylamine (3.76 g, 30 mmol) and triethylamine (3.33 g, 33 mmol) in Et_2O (150 mL) was added isobutyryl chloride (3.20 g, 30 mmol) dropwise. The mixture was stirred at ambient temperature for 5 hours, and then filtered through a pad of silica. Removal of the solvent produced an oil, which was distilled via Kugelrohr to give *N*-allyl-*N*-cyclopentylisobutyramide (5.14 g, 26.4 mmol) in 88% yield (oven temp 75-85 °C, <1 mmHg).

To a suspension of $LiAlH_4$ (0.912 g, 24 mmol) in Et_2O (100 mL) was added *N*-allyl-*N*-cyclopentylisobutyramide (4.00 g, 20.4 mmol) in a dropwise manner. After addition was complete, the mixture was stirred at ambient temperature for 2 hours. The reaction was quenched by sequential addition of H_2O (0.9 mL), 15% aq. NaOH (0.9 mL), and H_2O (2.7 mL) and then stirred for 1 hour. After removal of the solids by filtration, the solvent was removed and the oil was distilled via Kugelrohr to give **III-6** (3.27 g, 20.4 mmol) in quantitative yield (oven temp 50-65 °C, 4 mmHg); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.84 (d, *J* = 6.6 Hz, 6 H), 1.35 (m, 2 H), 1.45 (m, 2 H), 1.59 (m, 2 H), 1.70 (m, 3 H), 2.14 (d, *J* = 7.1 Hz, 2 H), 3.00 (tt, *J* = 7.3, 7.4 Hz, 1 H), 3.11 (ddd, *J* = 1.9, 2.1, 6.4 Hz, 2 H), 5.04 (ddt, *J* = 1.6, 10.2, 2.1 Hz, 1 H), 5.12 (ddt, *J* = 1.6, 17.1, 1.9 Hz, 1 H), 5.87 (ddt, *J* = 10.2, 17.1, 6.4 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 21.0, 24.1, 26.9, 29.2, 55.7, 59.5, 63.7, 116.1, 136.8. Anal. calcd for $C_{12}H_{23}N$ C, 79.49; H, 12.79; N, 7.72; obsd C, 79.36; H, 12.79; N, 7.99.

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CHAPTER IV. ASYMMETRIC INDUCTION IN THE CHARGE-PROMOTED 3-AZA-COPE REARRANGEMENT

Background: Asymmetric Induction in 3-Aza-Cope Rearrangements

The formation of C-C bonds has significant importance in synthetic chemistry and the ability to control the stereochemical outcome of these reactions is the highest goal in synthetic research today. Concerted rearrangements have been at the forefront of efforts to control asymmetry in C-C bond forming reactions. While the Claisen rearrangement has been utilized extensively for the stereocontrolled synthesis of new molecules,[1] few reports of stereoselective 3-aza-Cope rearrangements have appeared in the literature.

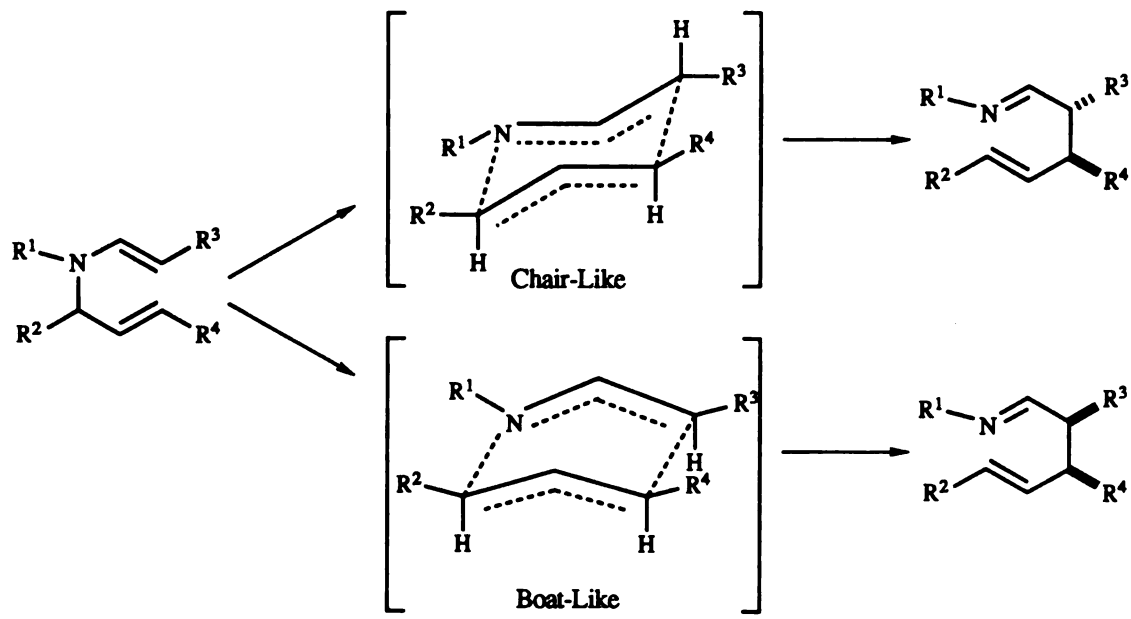
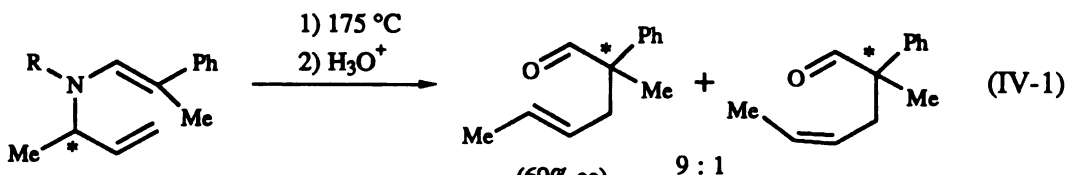


FIGURE IV-1. 3-Aza-Cope Transition States

In order to achieve asymmetric induction in the [3,3] sigmatropic rearrangement, two requirements must be met. First, there must be a preference for either a chair-like or boat-like conformation in the transition state. Secondly, the geometry of the olefins must

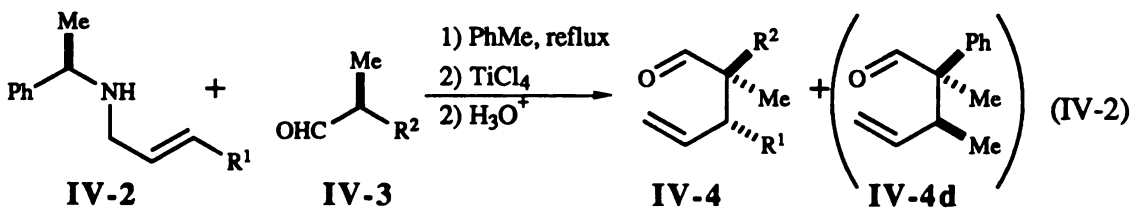
be fixed. The example of the 3-aza-Cope rearrangement in Figure IV-1 shows the stereochemical outcome of the rearrangement of a *N*-allylenamine which contains only *E* olefin geometry. Assuming the allylic substituent, R^2, would occupy an equatorial position in both transition states, the effect of the olefin geometries is clearly seen in the products obtained from each conformation.

The 3-aza-Cope rearrangement offers an advantage over the Claisen rearrangement in that a chiral auxiliary can be attached to the nitrogen. Hill first reported asymmetric induction in the thermal rearrangement of **IV-1a** (eq. IV-1).[2] Two aldehydes were obtained after hydrolysis of the reaction mixture which had opposite double bond geometries and opposite configurations at the newly formed stereogenic center. Asymmetric induction from the chiral auxiliary to the new center of chirality was determined to be 69%. A similar substrate (**IV-1b**), prepared *in situ* and rearranged with $TiCl_4$, was also studied by Hill, and asymmetric induction was found to be 67%.[3] This substrate did not contain a chiral auxiliary and asymmetry was imparted solely from the allylic stereocenter in the 3-aza-Cope framework. Hill concluded that the aliphatic 3-aza-Cope rearrangement, both thermal and $TiCl_4$ catalyzed, proceeded in a concerted fashion that favored a chair-like transition state. There is some doubt as to whether the catalyst for this rearrangement was $TiCl_4$ since the condensation process would produce water which would hydrolyze the Lewis acid. It is reasonable to conclude that the $TiCl_4$ was consumed, and that HCl was truly the catalyst in these studies.



IV-1 **a:** R = (*R*)-phenylethyl
b: R = phenyl

Bailey has extended the study of Hill's $TiCl_4$ catalyzed 3-aza-Cope rearrangement of *N*-alkyl-*N*-allylenamines (eq. IV-2) and the results are summarized in Table IV-1.[4] In probing 1,4- and 1,5-asymmetric induction (entries 1 and 2, respectively), very little stereoselection was observed. In contrast, simultaneous 1,4- and 1,5-asymmetric induction was relatively high (entries 3 and 4), although diastereoselectivity was only moderate (**IV-4c/IV-4d** 40-72% de). Temperature affected the asymmetric induction slightly, which provided greater selectivity at 55 °C than at 110 °C. A dramatic solvent effect was observed when the reaction was performed in benzene rather than toluene (entry 5), and asymmetric induction was reduced to almost zero. The authors provided no explanation for this phenomenon.



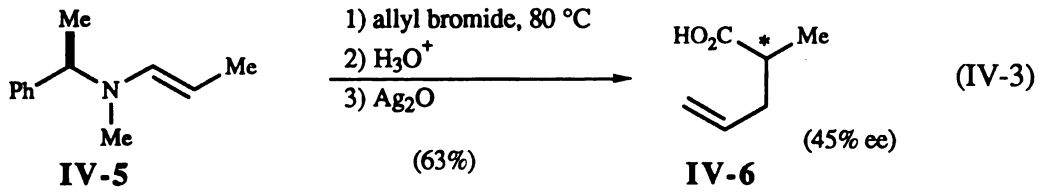
IV-2 **IV-3** **IV-4** **IV-4d** (IV-2)

a: R^1=H, R^2=Ph
b: R^1=Me, R^2=Me
c: R^1=Me, R^2=Ph

Table IV-1: Asymmetric 3-Aza-Cope Rearrangements Catalyzed by $TiCl_4$

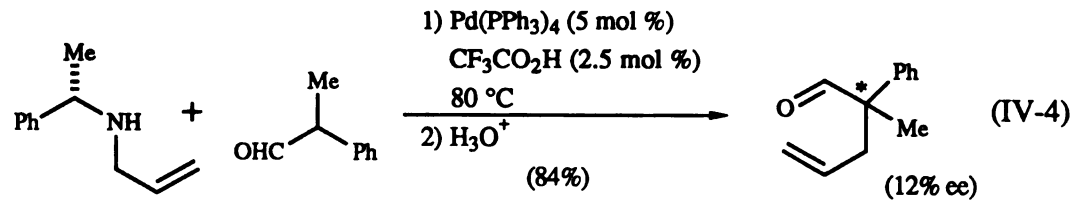
						%ee		
Entry	Amine	Aldehyde	Solvent	Temp.	%de	IV-4	IV-4d	%Yield
1	**IV-2a**	**IV-3a**	PhMe	110	----	30	----	16
2	**IV-2b**	**IV-3b**	PhMe	110	----	18	----	48
3	**IV-2b**	**IV-3a**	PhMe	110	72	81	76	56
4	**IV-2b**	**IV-3a**	PhMe	55	70	90	98	46
5	**IV-2b**	**IV-3a**	PhH	55	40	1	12	18

One example of an asymmetric 3-aza-Cope rearrangement, charge-promoted via a cationic quaternary amine, has appeared in the literature.[5] Alkylation of **IV-5** with allyl bromide in acetonitrile at reflux, followed by hydrolysis and subsequent oxidation, gave **IV-6** in 63% yield with 45% optical purity (eq IV-3).



IV-5 **IV-6** (IV-3)

Although not a true concerted 3-aza-Cope rearrangement, the intramolecular allylation of an enamine which contained a chiral auxiliary, catalyzed by palladium (0), has been explored. Amine **IV-7** was condensed with 2-phenylpropanal in the presence of catalytic $Pd(PPh_3)_4$ and protic acid, and heated in benzene with azeotropic removal of water. After hydrolysis, **IV-8** was obtained in excellent yield with low asymmetric induction (eq. IV-4).[6] A similar Pd(0) catalyzed allylation of chiral proline allyl ester enamines provided an enantiomeric excess which ranged from 5-16%, and chiral pyrrolidine enamines gave higher selectivity (6-88% ee).[7]

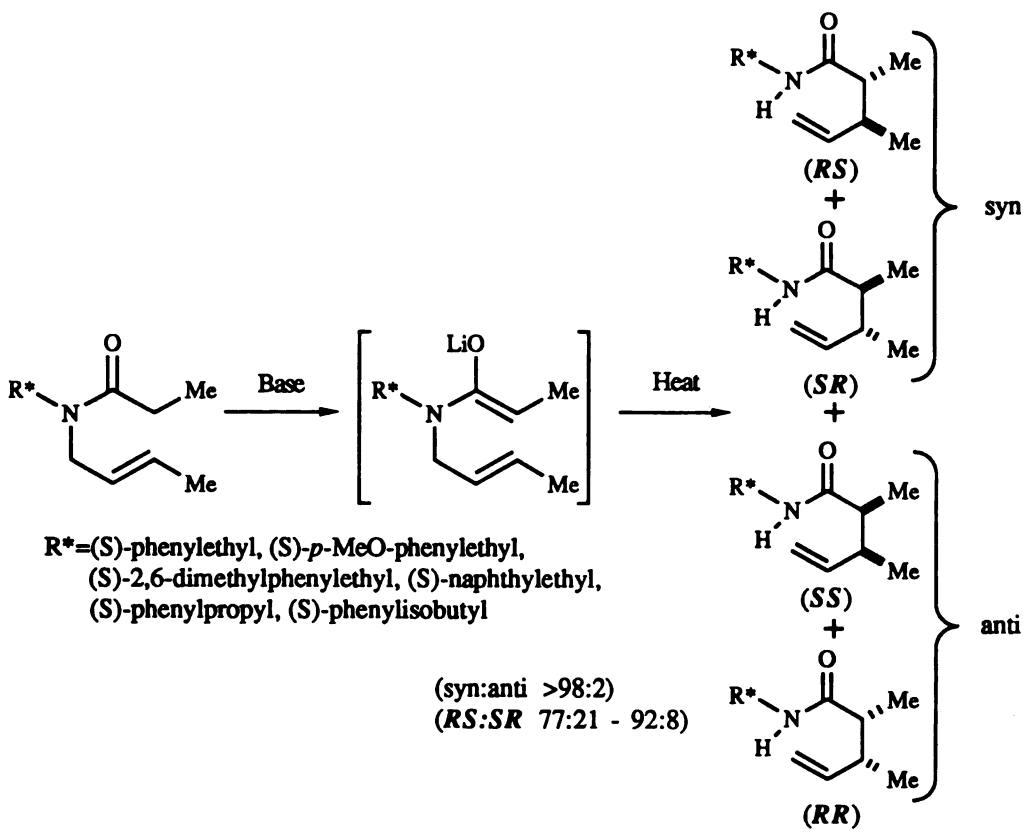


IV-7 **IV-8** (IV-4)

Much greater internal and relative asymmetric induction was observed in the thermal rearrangement of *N*-allyl amide enolates. Internal asymmetric induction from the reaction of the enolate derived from *N*-(2*E*)-butenyl-*N*-butylpropanamide was found to be as high as 199:1 (syn:anti).[8a,b] The utilization of chiral auxiliaries on the nitrogen

provided for high relative asymmetric induction (77:21 - 92:8) (Scheme IV-1).[8c] The high syn:anti ratios observed reflect the high *Z* selectivity in the formation of amide enolates.[9] It should be noted that longer reaction times (>6 hours) resulted in lower and even reversed syn:anti ratios due to base catalyzed isomerization of the amide products.

SCHEME IV-1. Asymmetric 3-Aza-Cope Rearrangements of *N*-Allylamide Enolates.



SCHEME IV-2. Asymmetric Induction in the 3-Aza-Cope Rearrangement of Ketene *N,O*-Acetals

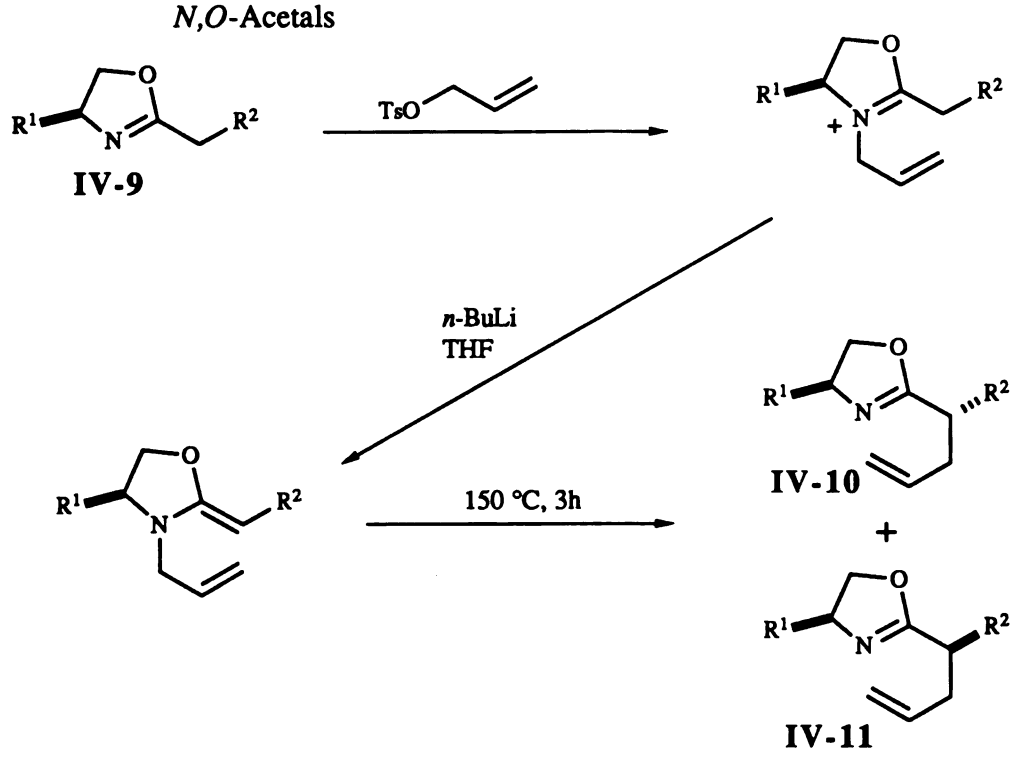


TABLE IV-2. Diastereoselective 3-Aza-Cope Rearrangement of Ketene *N,O*-Acetals

Entry	Substrate	R^1	R^2	IV-10/IV-11 Ratio	% Yield from IV-9
1	**IV-9a**	Et	Bn	92/8	67
2	**IV-9b**	Bn	Bn	94/6	53
3	**IV-9c**	*i*-Pr	Bn	97/3	81
4	**IV-9d**	*t*-Bu	Bn	98/2	58
5	**IV-9e**	Ph	Bn	78/22	34
6	**IV-9f**	*t*-Bu	Me	97/3	79
7	**IV-9g**	*t*-Bu	CMe_2Ph	98/2	81
8	**IV-9h**	*i*-Pr	Me	97/3	80

The chemistry of chiral auxiliary-mediated 3-aza-Cope rearrangements has been elegantly extended by Kurth with the utilization of oxazolines derived from α-amino acids.[10] As shown in Scheme IV-2 and summarized in Table IV-2, the covalent tethering of the auxiliary to the [3,3] rearrangement framework provided for excellent diastereoselection. A number of features made this a desirable process for C-C bond formation. The starting oxazolines (**IV-9**) were easily prepared from the appropriate carboxylic acid and amino alcohol. *N*-Alkylation with allyl tosylates provided high yields of the oxazolinium salt, and the oxazoline enamines required lower temperatures to affect [3,3] rearrangement in comparison to simple aliphatic enamines. Finally, the chiral auxiliary was readily recovered by hydrolysis of the rearrangement products. The high degree of asymmetric induction implied the selective formation of enamine olefin geometry. As demonstrated by entries 6-8, variation of the R^2 substituent had little effect on enamine olefin selectivity. The rearrangement appeared to be the controlled by the steric influence of the R^1 substituent, although both relatively small (Et) and relatively large (*t*-Bu) groups gave high selectivity (entries 1 and 4). This selectivity, concurrent with *E* or *Z* substituted allylic groups, afforded [3,3] rearrangement products (α,β-disubstituted) with 79-92% diastereoselectivity and 97-98% enantioselectivity from optically pure oxazolines.[10c] This methodology has been applied to the synthesis of (+)-dihydropallescensin-2.[11]

Amino Acid Derived Chiral Auxiliaries in the Charge-Promoted 3-Aza-Cope Rearrangement

Inspired by the work of Kurth, investigations were first directed toward the use of amino acid derived chiral auxiliaries. The possibility that auxiliaries bearing a methoxy substituent would allow for coordination of the promoting reagent (Lewis acid) with both the nitrogen and the oxygen (Figure IV-2) and effect a diastereofacial bias was explored.

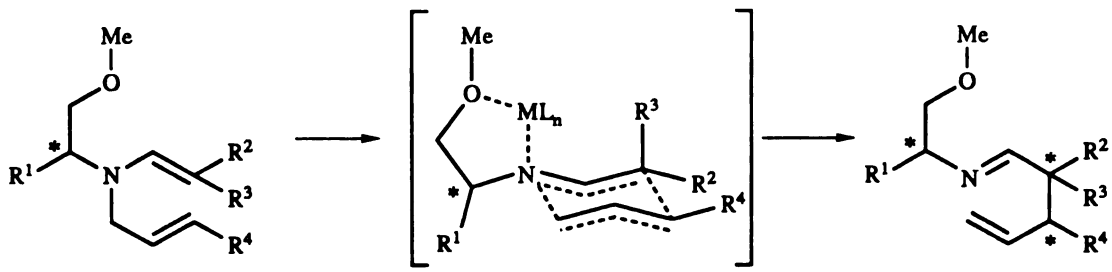
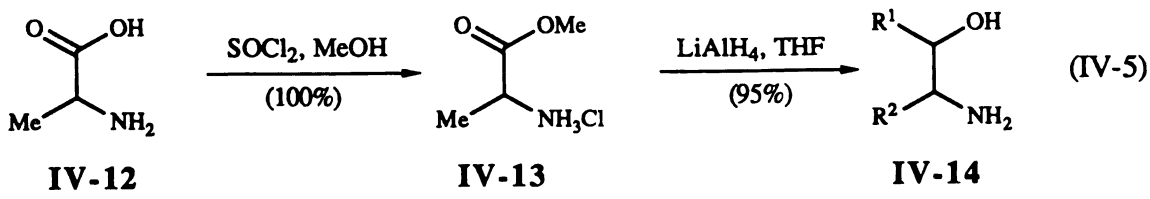


FIGURE IV-2. Expected Coordination of Electrophiles with Amino Acid Derived Chiral Auxiliaries

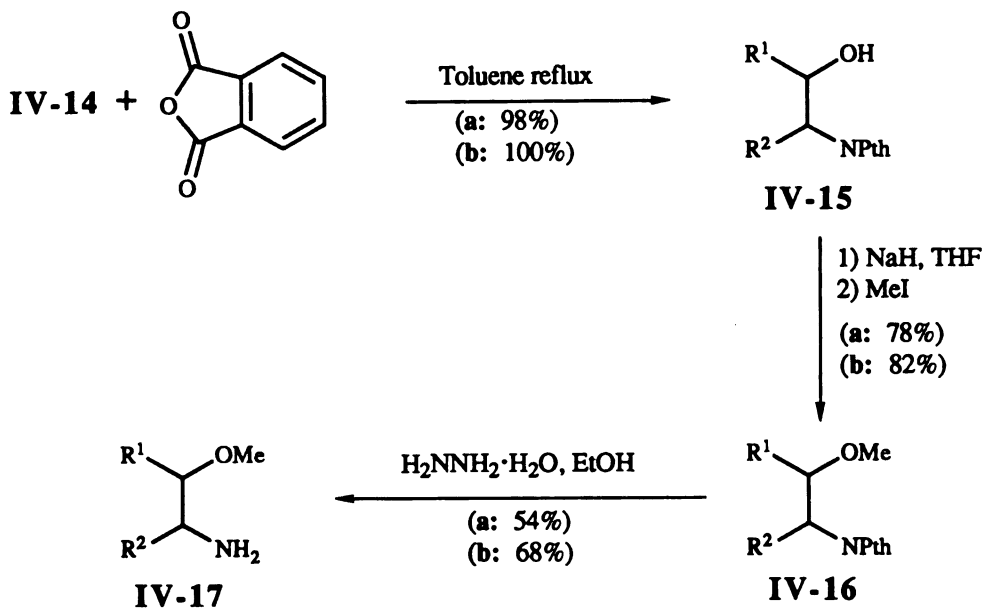
Two *N*-crotyl enamines were prepared from the requisite amino alcohols, which were obtained from commercial sources or from the amino acids (eq. IV-5). The amino acid alanine (**IV-12**) was converted into its ester hydrochloride salt upon treatment with thionyl chloride in methanol (100% yield).[12] Reduction with $LiAlH_4$ gave good yield of **IV-14a**. The amino alcohol **IV-14b** was obtained commercially. Methyl protection of the alcohol was carried out as shown in Scheme IV-3. The amine functionality was protected as the phthalimide by reaction with phthalic anhydride to provide **IV-15** in excellent yields. Methylation by treatment with NaH, followed by MeI, gave the methoxy phthalimides **IV-16** in good yield, and deprotection with hydrazine afforded **IV-17** in moderate yields. With the methoxy amines in hand, preparation of the *N*-crotyl enamines was straightforward (eq. IV-6). Condensation with crotonaldehyde followed by reduction with $NaBH_4$ gave **IV-18a** and **IV18b** in 47% and 70% yield respectively. Reaction with isobutyraldehyde afforded enamines **IV-19a** and **IV-19b** in excellent yield, which were obtained as a mixture of *E:Z* double bond isomers (85:15).

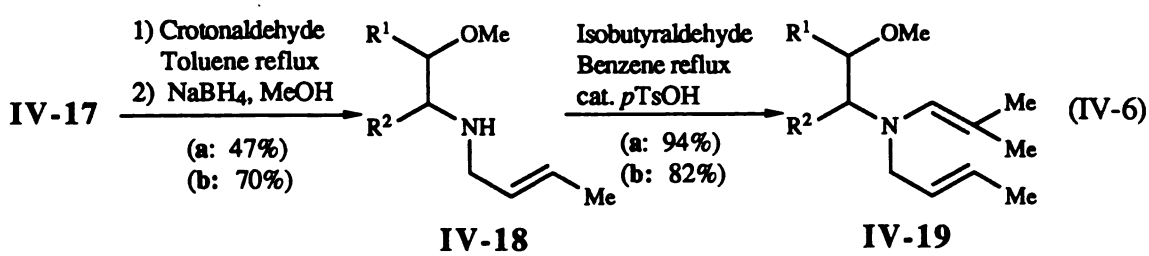


IV-12 **IV-13** **IV-14**

a: R^1=H, R^2=Me
b: R^1=Me, R^2=H

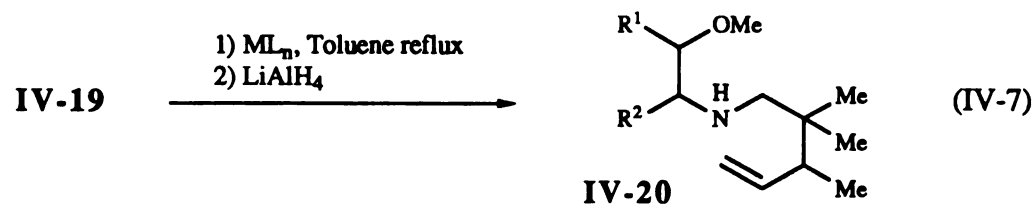
SCHEME IV-3. Methylation of Amino Alcohols





IV-18 **IV-19**

The charge-promoted 3-aza-Cope rearrangement of **IV-19a** and **IV-19b** promoted by protic and Lewis acids is summarized in eq. IV-7 and Table IV-3. Treatment of **IV-19a** with catalytic $TiCl_4$ in toluene at reflux and subsequent $LiAlH_4$ reduction afforded **IV-20a** in good yield, however, asymmetric induction was very low (15% de). This was surprising in light of the fact that the placement of a center of chirality α to the nitrogen has shown greater selectivity in the $TiCl_4$ promoted [3,3] rearrangement.[3,4] Rearrangement of **IV-19b**, bearing a center of chirality β to the nitrogen, showed improved selectivity (20% de) with $TiCl_4$ catalysis but lower selectivity when the reaction was promoted with protic acid (8% de). It was interesting that 1,6-asymmetric induction was greater than 1,5-asymmetric induction. These results hinted that some complexation of both heteroatoms had occurred with $TiCl_4$ since selectivity would be expected to be lowered by locating the stereogenic center further from the 3-aza-Cope framework.

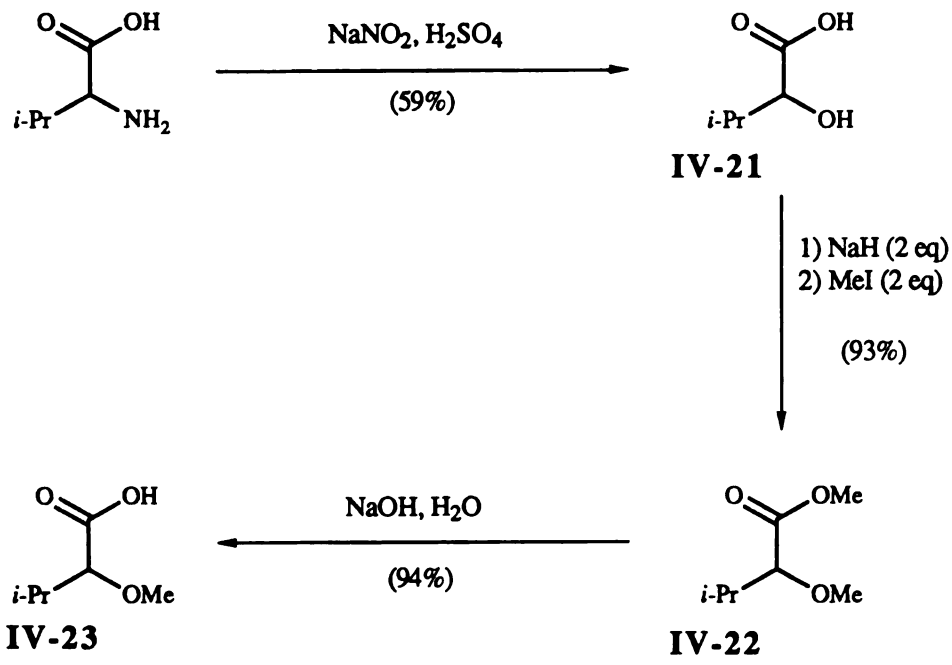


(IV-7)

TABLE IV-3. Asymmetric Induction with Chiral Auxiliaries

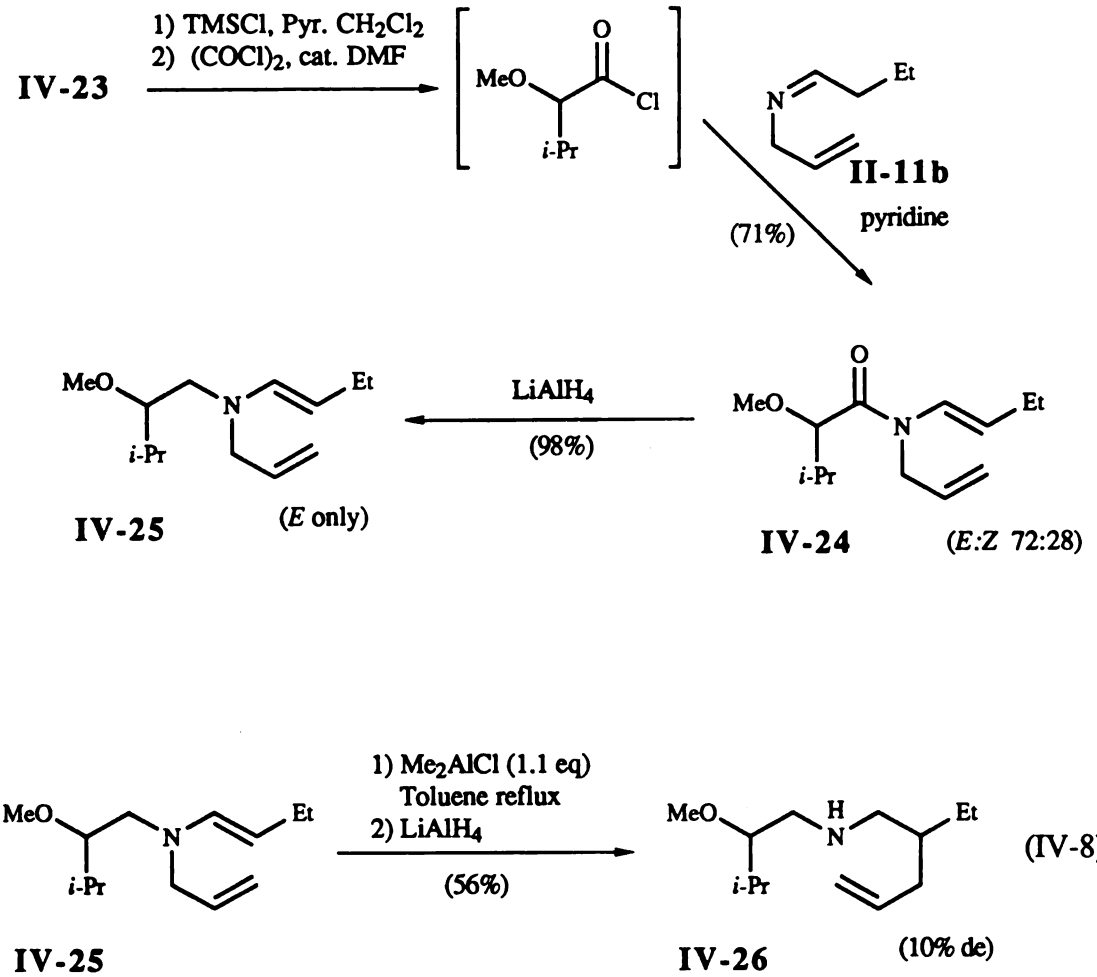
Substrate	R^1	R^2	ML_n	Product	%Yield	%de
IV-19a	H	Me	$TiCl_4$	**IV-20a**	77	15
IV-19b	Me	H	HCl	**IV-20b**	86	8
IV-19c	Me	H	$TiCl_4$	**IV-20c**	72	20

SCHEME IV-4. Preparation of α-Methoxy Acid **IV-23**



Since greater selectivity was observed by placing a substituent on the chiral auxiliary β to the nitrogen, enamine **IV-25** was studied in which the β-substituent was larger (*i*-Pr) and the newly formed stereogenic center was closer. The preparation of **IV-25** is described in Schemes IV-4 and IV-5. Starting with valine, conversion of the amino group to a hydroxyl group was carried out in 59% yield with $NaNO_2/H_2SO_4$. Methylation of **IV-21** gave methoxy ester **IV-22** in 93% yield and hydrolysis afforded the α-methoxy acid **IV-23** in 94% yield. Using a literature procedure for converting α-hydroxyl acids to α-hydroxyl amides,[13] **IV-24** was obtained in 71% yield as a 72:28 mixture of *E*:*Z* isomers. Reduction with $LiAlH_4$ gave **IV-25** in nearly quantitative yield as a single enamine olefin isomer having *E* geometry. Since enamines derived from linear aldehydes were observed to react through pathways other than [3,3] rearrangement when promoted by HCl or $TiCl_4$ (Chapter III), the rearrangement of **IV-25** was studied with an organoaluminum reagent. Treatment with Me_2AlCl followed by reduction gave **IV-26** in 56% yield. Asymmetric induction was very low giving only a 10% diastereomeric excess.

SCHEME IV-5. Preparation of Enamine **IV-25**

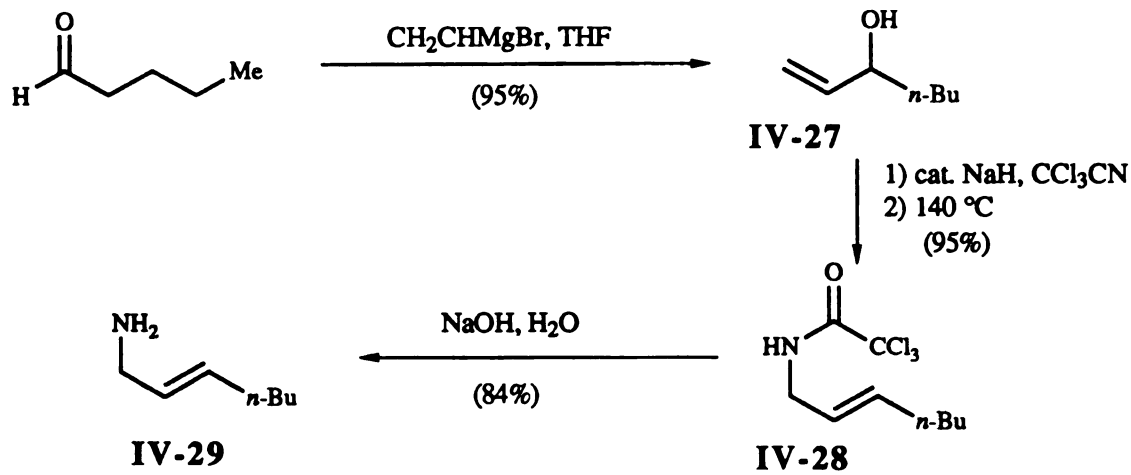


Internal Asymmetric Induction

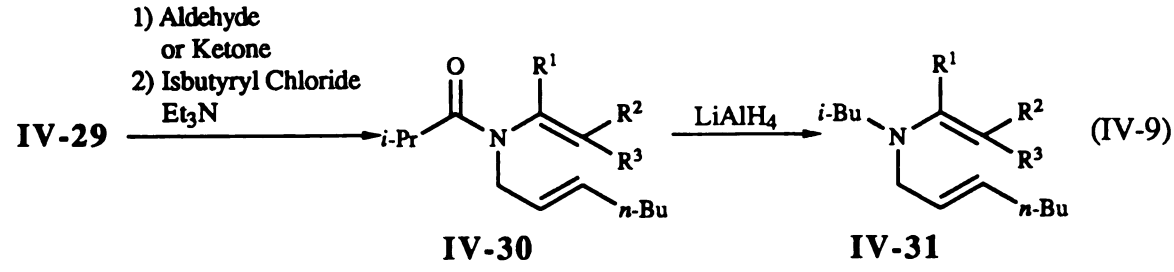
In order to study diastereoselectivity arising from chair- or boat-like conformations of the transition state, enamines containing an *n*-butyl group pendant on the allyl moiety (*N*-(*E*)-2-hepten-1-ylenamines) combined with a variety of substitution patterns on the enamine olefin were prepared. The preparations of these substrates were carried out from the primary allylic amine **IV-29** obtained as shown in Scheme IV-6. Addition of vinyl magnesium bromide to valeraldehyde gave the allyl alcohol **IV-27** in

95% yield. Treatment of **IV-27** with trichloroacetonitrile and catalytic NaH followed by thermal rearrangement in xylenes provided the trichloroacetamide **IV-28**[14] which was determined by ^{1}H NMR and IR to be only the *E* olefin isomer. Hydrolysis with NaOH cleaved the amide to give **IV-29** in 84% yield.

SCHEME IV-6. Synthesis of (*E*)-2-Hepten-1-ylamine

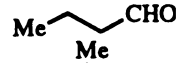
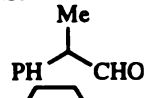
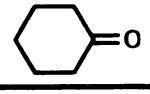


The synthesis of enamines **IV-31** is outlined and eq. IV-9 and summarized in Table IV-4. Condensation of **IV-29** with *n*-butanal followed by acylation with isobutyryl chloride gave the enamide **IV-30a** in 66% purified yield (enamine olefin *E:Z* 65:35). Reduction to **IV-31a** was carried out to give a single compound (*E* only). **IV-31b** was synthesized in a similar fashion. Condensation of 2-phenylpropanal with **IV-29** in benzene at reflux was followed by acylation with isobutyryl chloride to give the purified **IV-30b** in 56% yield as a mixture of *E:Z* isomers (66:34 respectively). Reduction provided **IV-31b** with a good selectivity of 90:10 (*E:Z*). Likewise, **IV-30c** was obtained from the condensation of **IV-29** and cyclohexanone in toluene at reflux followed by acylation with isobutyryl chloride. Reduction to **IV-31c** was accomplished in excellent yield (97%).



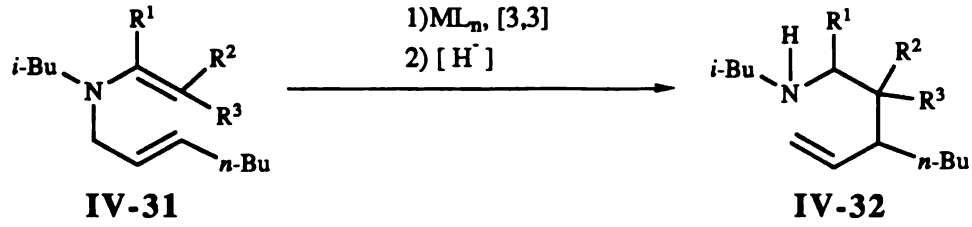
(IV-9)

Table IV-4. Yields of *N*-(*E*)-2-Hepten-1-yl Enamides and Enamines

	Starting Carbonyl	R^1	R^2	R^3	%Yield of **IV-30**	%Yield of **IV-31**
a		H	Et	H	66[a]	99[b]
b		H	Ph	Me	56[c]	99[d]
c		-$(CH_2)_4$-		H	89	97

[a]Ratio of *E:Z* 65:35. [b]Ratio of *E:Z* 100:0. [c]Ratio of *E:Z* 66:34. [d]Ratio of *E:Z* 90:10.

The [3,3] sigmatropic rearrangements of **IV-31a**, **IV-31b**, and **IV-31c** were accomplished using a variety of electrophiles to promote the reaction (eq. IV-10) and the results are summarized in Table IV-5. Determination of the exact configuration of each diastereomer has not been carried out. Enamine **IV-31a**, as previously noted, would not undergo [3,3] rearrangement with protic acids or $TiCl_4$, therefore, two organoaluminum catalysts were used. Rearrangement with $AlMe_3$ or Me_2AlCl followed by reduction gave good yields of **IV-32a**, however, the diastereoselectivity in both cases was low (62:38 and 52:48 respectively). There are two possible explanations for the low selectivity observed. Either the preference for a chair- or boat-like conformation in the transition state was low or the product, an imine, isomerized via imine-enamine tautomerization (Figure IV-3).



IV-31 IV-32 (IV-10)

TABLE IV-5. Internal Asymmetric Induction

Enamine	ML_n	[H^-]	%Yield	Product	Ratio of Diastereomers
IV-31a	$AlMe_3$	$LiAlH_4$	88	**IV-32a**	62:38
IV-31a	Me_2AlCl	$LiAlH_4$	94	**IV-32a**	52:48
IV-31b	HCl	$LiAlH_4$	54	**IV-32b**	95:5
IV-31b	$TiCl_4$	$LiAlH_4$	48	**IV-32b**	80:20
IV-31b	$AlMe_3$	$LiAlH_4$	86	**IV-32b**	68:32
IV-31b	$(ArO)_2AlMe^a$	$LiAlH_4$	58	**IV-32b**	37:63
IV-31c	HCl	DIBAH	69	**IV-32c**	54:46
IV-31c	$TiCl_4$	DIBAH	72	**IV-32c**	55:45
IV-31c	$AlMe_3$	DIBAH	94	**IV-32c**	67:33
IV-31c	$(ArO)_2AlMe^a$	DIBAH	73	**IV-32c**	77:23

^{a}ArO = 2,6-diphenylphenoxy

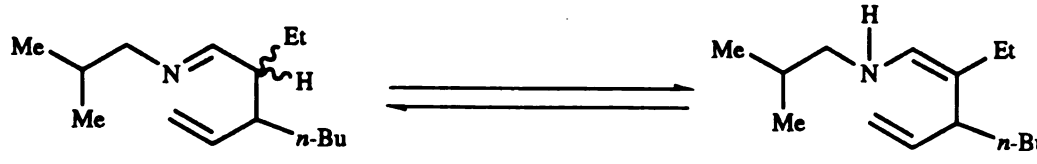


FIGURE IV-3. Possible Imine-Enamine Tautomerization

In order to probe whether tautomerization was playing a role, the disubstituted enamine **IV-31b**, whose rearrangement product could not undergo tautomerization, was subjected to rearrangement conditions with HCl, $TiCl_4$, $AlMe_3$, and bis-2,6-diphenylphenoxymethyl aluminum ($(ArO)_2AlMe$). Yields for these reactions were moderate and the selectivity varied markedly with catalyst. HCl provided the best selectivity (95:5) while the organoaluminum reagents gave much lower asymmetric induction. It is interesting to note that the bulky catalyst, $(ArO)_2AlMe$, gave opposite diastereoselectivity than was observed for all other promoting electrophiles. Indeed, the selectivity was equal and opposite the selectivity obtained from the $AlMe_3$ promoted rearrangement. Also of interest was the observation that HCl afforded a greater selectivity than would have been expected based on the starting enamine *E:Z* ratio (90:10). This implied that isomerization of the enamine or allylic olefin may have occurred under the reaction conditions.

Rearrangement of enamine **IV-31c**, derived from cyclohexanone, gave different results with regard to catalyst diastereoselectivity than **IV-31b**. The asymmetric induction of the HCl and $TiCl_4$ catalyzed reactions proved to be very low while the organoaluminum electrophiles provided increased selectivity. In this instance, the bis-phenoxy aluminum gave the greatest asymmetric induction and yielded the same major isomer as the other reagents. This substrate, while unable to have undergone enamine olefin isomerization due to ring constraints, could have equilibrated by tautomerization. In order to avoid complications from the third stereocenter in this substrate, selective reduction of the imine resulting from [3,3] rearrangement was carried out with diisobutylaluminum hydride (DIBAH) instead of $LiAlH_4$.

Concomitant Relative and Internal Asymmetric Induction

In order to examine concurrent relative and internal asymmetric induction in the 3-aza-Cope rearrangement, three enamines containing an allylic methyl substituent (**IV-35**) were prepared (Scheme IV-7, Table IV-6). Methyl magnesium bromide was added to crotonaldehyde to give an allylic alcohol which was carried on to **IV-33** in 81% overall yield. Hydrolysis of the amide and condensation with the appropriate carbonyl compound gave an imine which was acylated *in situ* affording **IV-34** in 56-75% yield. **IV-34a**, derived from *n*-butanal was obtained as a single olefin isomer having *E* geometry. Reduction with $LiAlH_4$ gave **IV-35a** in 88% yield as a single isomer. Condensation with 2-phenylpropanal provided a 55:45 (*E:Z*) ratio of **IV-34b**, and reduction gave **IV-35b** in the same ratio of *E:Z* isomers. Repeated attempts to reduce **IV-34b** gave similar selectivity, and ratios ranging from 52:48 to 58:42 were obtained. Isomerization of **IV-35b** with HCl in chloroform increased the amount of the *E* isomer, and afforded mixtures ranging from 70:30 to 83:17 (*E:Z*). **IV-35c** was prepared from **IV-34c** in 95% yield.

Results of the charge-promoted 3-aza-Cope rearrangement of **IV-35a**, **IV-35b**, and **IV-35c** are summarized in Table IV-7 (eq. IV-11). Treatment of **IV-35A** with $AlMe_3$ or Me_2AlCl, followed by reduction with $LiAlH_4$ gave **IV-36a** in good yield as a single isomer detectable by ^1H and ^{13}C NMR (>98:2). Although the exact configuration was not rigorously determined, the syn product was assumed based on the most favorable chair-like transition state (Figure IV-1). Use of the more bulky bis-2,6-diphenylphenoxy methyl aluminum reagent resulted in decreased selectivity (70:30). Likewise, asymmetric induction in the $AlMe_3$ promoted rearrangement of **IV-35c** was very high (>95:5) and **IV-36c** was obtained in almost quantitative yield. Products of the [3,3] rearrangement of **IV-35a** were not obtained under HCl or $TiCl_4$ catalyzed reaction conditions, thus asymmetric induction with these reagents could not be ascertained.

SCHEME IV-7. Synthesis of *N*-(*E*)-3-Penten-2-yl Enamines

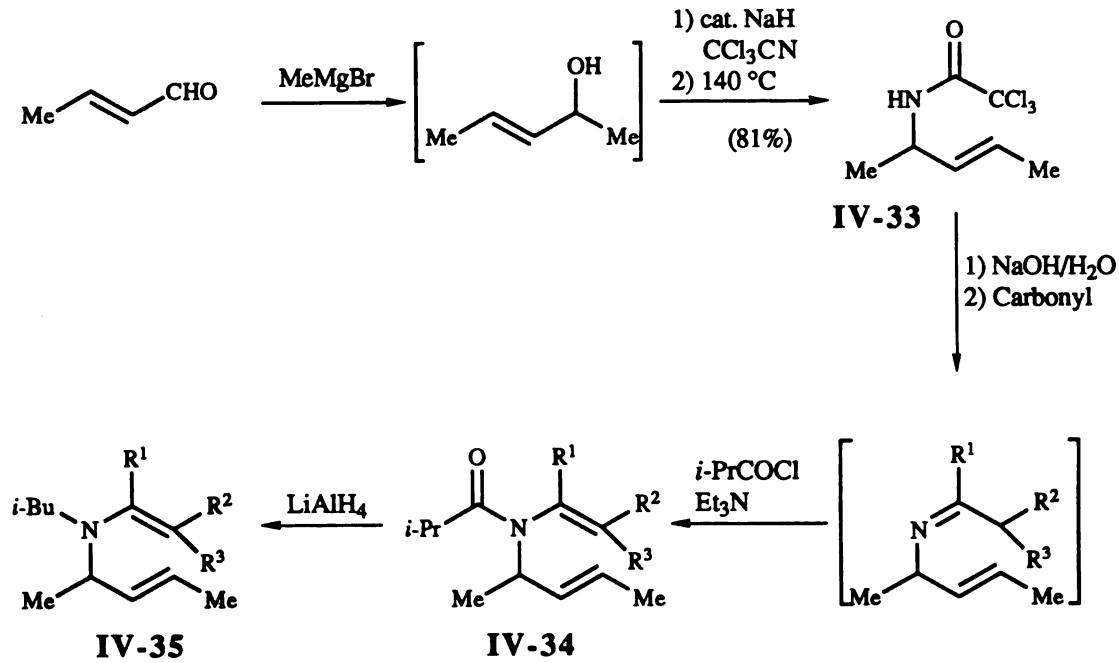
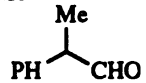
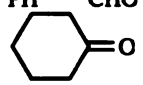
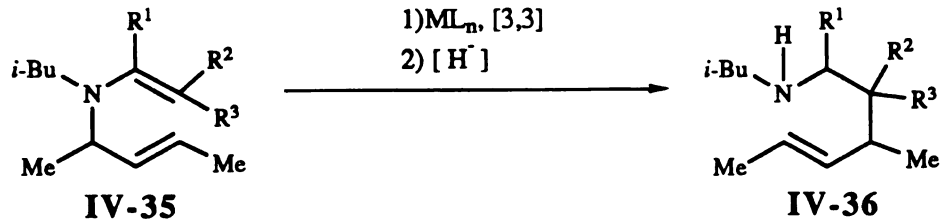


TABLE IV-6. Yields of *N*-(*E*)-3-penten-2-yl Enamides and Enamines

	Starting Carbonyl	R^1	R^2	R^3	%Yield of **IV-34**	%Yield of **IV-35**
a		H	Et	H	75[a]	88[b]
b		H	Ph	Me	64[c]	96[d]
c		-$(CH_2)_4$-		H	56	95

[a]Ratio of *E*:*Z* 100:0. [b]Ratio of *E*:*Z* 100:0. [c]Ratio of *E*:*Z* 55:45. [d]Ratio of *E*:*Z* 55:45.



IV-35 **IV-36** (IV-11)

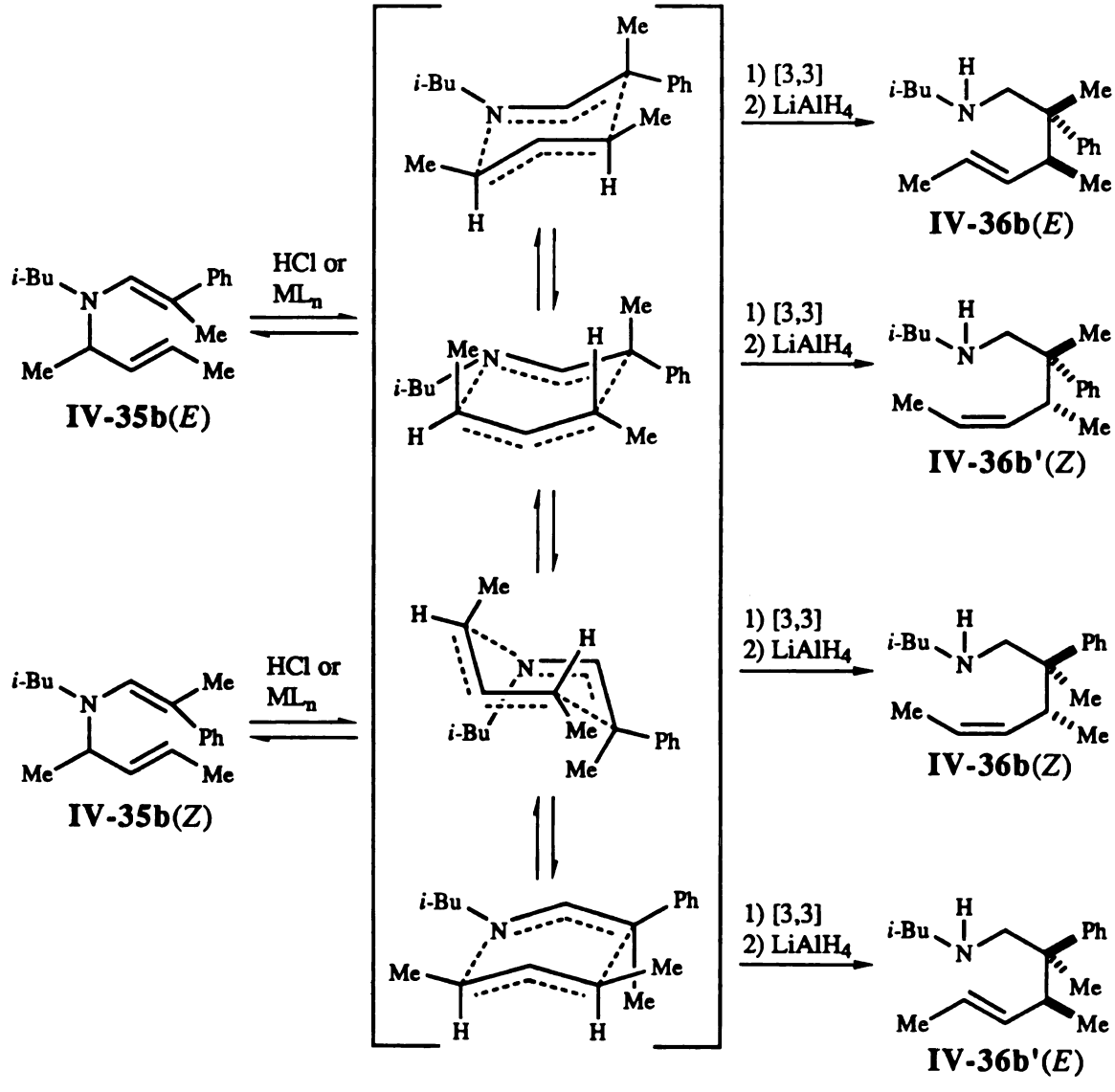
TABLE IV-7. Concomitant Relative and Internal Asymmetric Induction

Enamine	*E*:*Z*	ML_n	[H^-]	%Yield	Product	Ratio of Diastereomers
IV-35a	100:0	$AlMe_3$	$LiAlH_4$	78	**IV-36a**	>98:2
IV-35a	100:0	Me_2AlCl	$LiAlH_4$	81	**IV-36a**	>98:2
IV-35a	100:0	$(ArO)_2AlMe$[a]	$LiAlH_4$	60	**IV-36a**	70:30
IV-35b	55:45	HCl[b]	$LiAlH_4$	75	**IV-36b**[f]	79:13:8
IV-35b	70:30	HCl[b]	$LiAlH_4$	78	**IV-36b**[f]	54:37:9
IV-35b	58:42	HCl[c]	$LiAlH_4$	85	**IV-36b**[f]	70:20:10
IV-35b	52:48	HCl[d]	$LiAlH_4$	92	**IV-36b**[f]	78:14:8
IV-35b	52:48	HCl[e]	$LiAlH_4$	91	**IV-36b**[f]	79:13:8
IV-35b	83:17	HCl[d]	$LiAlH_4$	94	**IV-36b**[f]	81:10:9
IV-35b	83:17	HCl[e]	$LiAlH_4$	98	**IV-36b**[f]	89:8:3
IV-35b	52:48	$TiCl_4$	$LiAlH_4$	38	**IV-36b**[f]	65:24:11
IV-35b	55:45	$AlMe_3$	$LiAlH_4$	97	**IV-36b**[f]	71:21:8
IV-35b	70:30	$AlMe_3$	$LiAlH_4$	98	**IV-36b**[f]	73:20:7
IV-35b	58:42	$(ArO)_2AlMe$[a]	$LiAlH_4$	84	**IV-36b**[f]	80:14:6
IV-35c	-----	$AlMe_3$	DIBAH	95	**IV-36c**	>95:5

[a]ArO = 2,6-diphenylphenoxy. [b]1.0 eq. [c]1.1 eq. [d]0.6 eq. [e]1.2 eq. [f]Products have been assigned as **IV-36b**(*E*), **IV-36b'**(*E*), and **IV-36b**(*Z*), respectively based on transition state analysis (Scheme IV-8).

The variety of *E:Z* ratios obtained in the preparation of **IV-35b**, afforded an opportunity for in depth examination of the factors that influence selectivity in the charge-promoted [3,3] sigmatropic rearrangement. With a nearly equal mixture of isomers (*E:Z* 55:45), promotion with 1.0 equivalent HCl provided a 79:13:8 mixture of three rearrangement products. If one transition state conformation dominated in the course of this reaction, the highest selectivity expected would have been equal to the starting isomer ratio. Since **IV-35b** could not undergo imine-enamine tautomerization, it was clear that another factor must have been involved. It was possible that one isomer could have been reacting predominantly through a chair-like conformation while the other reacted through a boat-like conformation. However, with **IV-35b** as an *E:Z* mixture of 70:30 lower selectivity was obtained (54:37:9). If a chair-boat preference was the only controlling feature, this selectivity should have been at least as high as that obtained in the first case. Another possible explanation for the results obtained was that isomerization of the olefin by HCl had occurred. To probe this theory, low (52:48) and high (83:17) starting ratios of **IV-35b** were reacted with either 0.6 or 1.2 equivalents of HCl. The use of less than one equivalent of protic acid would allow for intermolecular proton transfer from one protonated enamine to the carbon of another enamine, which would facilitate proton catalyzed isomerization. By the addition of excess HCl, all enamines would have been protonated and proton transfer would not occur, thus reducing the possibility of acid catalyzed isomerization.[15] The results of this study indicated that the probability of proton catalyzed olefin isomerization as the feature controlling asymmetric induction was low. In all cases, almost the same ratio of diastereomers of **IV-36b** was obtained (78:14:8 to 89:8:2). Analogous results were found for the $TiCl_4$ promoted rearrangement of **IV-35b**. A slightly lower 65:24:11 ratio of diastereomers of **IV-36b** was obtained from the treatment of **IV-35b** (*E:Z* 58:42) with $TiCl_4$ followed by reduction. Reaction of **IV-35b**, having either a 55:45 or 70:30 mixture of *E:Z* isomers, with $AlMe_3$ gave consistent product mixtures, and moderate selectivity was obtained (71:21:8 and 73:20:7). A higher selectivity (80:14:6) resulted from use of the more bulky aluminum reagent.

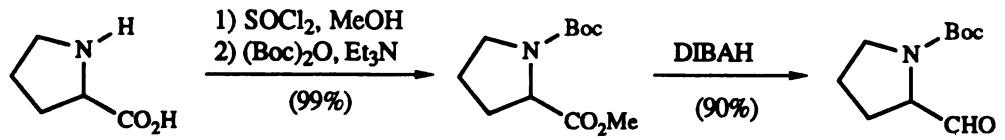
SCHEME IV-8. Transition States for the 3-Aza-Cope Rearrangement of **IV-35b**.



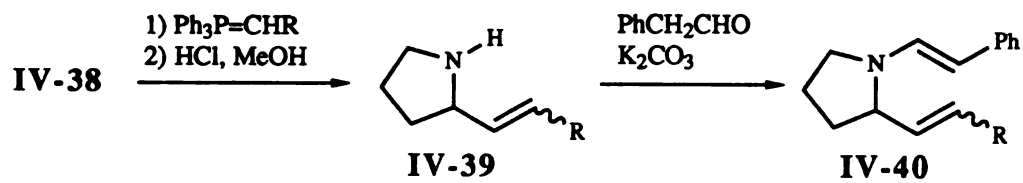
While protic acid isomerization of enamines **IV-35b** remained a possibility with HCl, and even with $TiCl_4$ by hydrolysis to produce protic acid, the results of the organoaluminum promoted rearrangement clearly indicated that an additional factor was involved. The most probable explanation was that olefin isomerization occurred via a reversible [3,3] sigmatropic rearrangement. The reverse of the 3-aza-Cope rearrangement, the 1-aza-Cope has been shown to occur in some cases.[16] This would have been more likely to be the case with **IV-35b** than the other two enamines examined due to the stabilization of the enamine olefin by conjugation with the phenyl group. Also, with substrate **IV-35b**, the presence of a third product was observed, which was not detected in the rearrangement products from **IV-35a** and **IV-35c**. The products have been assigned the structures **IV-36b**(*E*) (major isomer), **IV-36b'**(*E*) (intermediate isomer), and **IV-36b**(*Z*) (minor isomer) based on the possible transition states shown in Scheme IV-8. **IV-36b**(*E*) was derived from the most favored transition state in which a chair-like conformation was adopted with the allylic methyl group in an equatorial position. The minor product was assigned as described for two reasons. First, the chair-like conformation with the allylic methyl group axial would have predominated over the boat-like conformation. Secondly, hydrogenation of the product mixture increased the amount of the major product over the minor product. Reduction of the 79:13:8 mixture derived from HCl rearrangement, gave approximately a 90:10 mixture of two diastereomers, and reduction of the 71:21:8 mixture from $AlMe_3$-promoted rearrangement afforded a 80:20 mixture. These results indicated that the minor isomer possessed the same relative stereochemistry at the two asymmetric centers as the major product, and reduction of the double bond would have made these two compounds identical. The intermediate isomer resulted from the chair-like conformation with an equatorial allylic methyl substituent, and had opposite relative stereochemmistry as the major isomer. The fourth possible isomer, **IV-36b'**(*Z*), was not detectable by NMR.

Asymmetric Ring Expansion Reactions

As a possible route to indolizidine alkaloids, the charge-promoted 3-aza-Cope rearrangement with concurrent ring expansion was examined.[17] Treatment of the amino acid proline with thionyl chloride in methanol, followed by *N*-protection gave **IV-37** in 99% yield (eq. IV-12). DIBAH reduction afforded aldehyde **IV-38**. Two enamines were prepared as shown in eq. IV-13. **IV-38** was olefinated with benzylidenetriphenylphosphine and deprotected with HCl in methanol to afford **IV-39a** as a 65:35 ratio of *E*:*Z* isomers. Condensation with phenylacetaldehyde gave **IV-40a** in quantitative yield with complete *E* selectivity of the enamine olefin. Enamine **IV-40b** was obtained by same sequence with ethylidenetriphenylphosphine. Due to its volatility, **IV-39b** was not isolated, and **IV-40b** was prepared in 79% overall yield from **IV-38**. Again, complete enamine selectivity was achieved, while the allylic olefin was procured as a 27:73 mixture of *E*:*Z* isomers.



(IV-12)

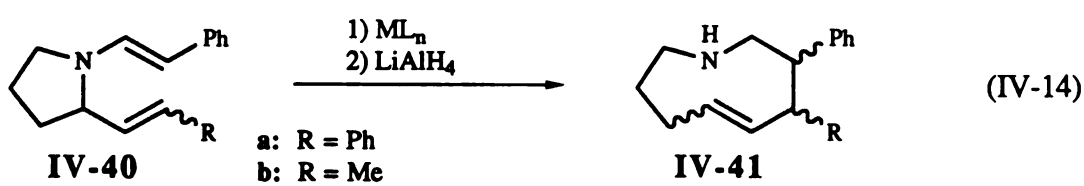


(IV-13)

a: R = Ph (69%)
(*E*:*Z* 65:35)
b: R = Me

a: R = Ph (100%)
(*E*:*Z* (enamine) 100:0)
(*E*:*Z* (allylic) 65:35)
b: R = Me (79% from **IV-38**)
(*E*:*Z* (enamine) 100:0)
(*E*:*Z* (allylic) 27:73)

Success in the charge-promoted 3-aza-Cope rearrangement/ring expansion of the pyrrolidine enamines (eq. IV-14) was found to be very dependent on the electronic demands of the substituents. Treatment of **IV-40a**, where R was a phenyl group, with organoaluminum reagents and subsequent reaction with $LiAlH_4$ did not provide the ring-expanded product. Instead, **IV-40a** was recovered quantitatively, and the allylic olefin had been isomerized to a single isomer (*E*) (Figure IV-4). This result provided further evidence that olefin isomerization through reversible sigmatropic rearrangement had occurred under the charge-promoted reaction conditions. Only two possibilities could be formulated to explain the isomerization. Either the aluminum species had added to the allylic olefin, which would have allowed for single bond rotation, or the proposed reversible reaction had occurred. Since addition of aluminum to the double bond was highly unlikely, the reversible [3,3] rearrangement was assumed to have taken place. The quantitative recovery of starting material indicated that the equilibrium lay far on the side of **IV-40a** in which both olefins were in conjugation with the phenyl groups. In contrast, replacing one of the phenyl groups with a methyl group allowed for complete rearrangement with Me_2AlCl, and reduction afforded **IV-41b** in 85% yield. A 27:73 mixture of isomers was produced, and the double bond geometry was determined by ^1H NMR to have *Z* geometry. To determine that the product ratio was due to the cis/trans relationship of the phenyl and methyl substituents rather than possible *E*:*Z* isomers of the olefin, **IV-41b** was hydrogenated over 10% palladium on carbon, and a 27:73 mixture of isomers was obtained. This result demonstrated that the 3-aza-Cope rearrangement/ring expansion reaction promoted by Me_2AlCl was completely stereoselective. Thus, the product ratio was solely dependent on the starting olefin geometries.



IV-40 **IV-41** (IV-14)

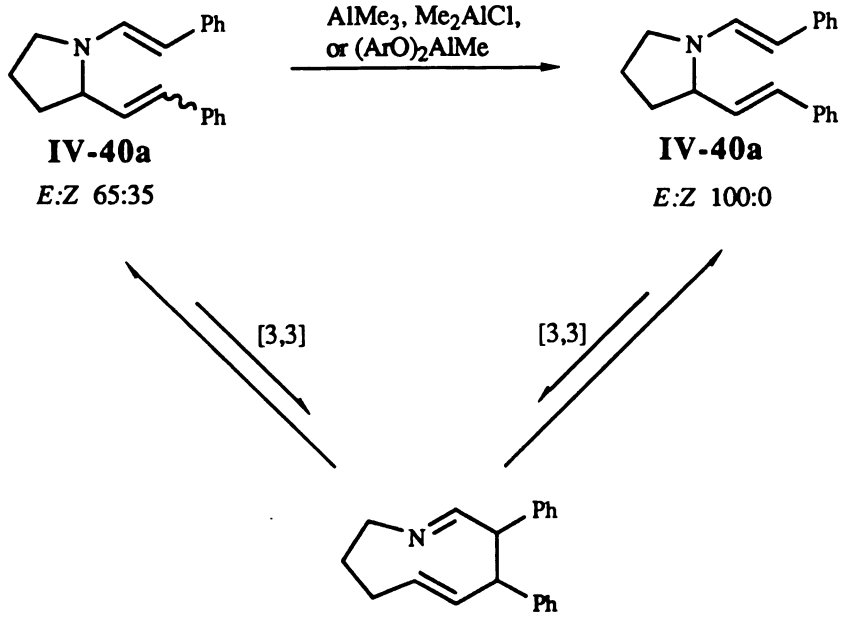


FIGURE IV-4. Reversible Ring Expansion Reaction

Summary

Studies of the stereoselectivity of the charge-promoted 3-aza-Cope rearrangement were carried out by examining diastereomer ratios of the resulting products. Relative asymmetric induction transferred from amino acid derived chiral auxiliaries was found to be very low (8-20% de). Internal asymmetric induction was determined to be highly dependent on the promoting reagent as well as the substitution of the enamine olefin. The enamine derived from *n*-butanal provided low selectivity when promoted with organoaluminum reagents (52:48 - 62:38). With the disubstituted enamine (**IV-31b**) asymmetric induction was very high with protic acids yielding a 95:5 ratio of isomers. Organoaluminum reagents gave lower selectivity, and the more bulky bis-phenoxy methyl aluminum reagent gave the opposite ratio of the same magnitude as $AlMe_3$. The rearrangement of **IV-31c** provided contrasting results, giving the highest selectivity upon reaction with organoaluminum reagents, and lower selectivity with HCl and $TiCl_4$. A

more thorough investigation of the features which control selectivity was carried out by the study of concurrent relative and internal asymmetric induction. Selectivity was found to be very high with enamines derived from *n*-butanal and cyclohexanone (>98:2 and >95:5 respectively). [3,3] rearrangement of the enamine derived from 2-phenylpropanal, with a variety of starting enamine olefin ratios, provided evidence that the 3-aza-Cope rearrangement was a reversible process. This substrate provided modest selectivity in all cases (54:37:9 - 89:8:2). Ring expansion reactions were accomplished with **IV-40b** yielding a nine-membered ring with complete stereoselectivity. The ring expansion process was also found to be reversible with **IV-40a**, and the degree of the reverse reaction was dependent on the electronic demands of the enamine.

EXPERIMENTAL

General Methods

For general experimental methods see General Methods in Chapter II.

Preparation of IV-13:

L-Alanine (17.819 g, 200 mmol) was placed in anhydrous methanol (200 mL) and cooled to 0 °C. Thionyl chloride (59.584 g, 500 mmol) was added dropwise over 30 min. The solution was warmed to room temperature and allowed to stir for 12 hours. The mixture was concentrated by rotary evaporation under reduced pressure and the crystals were triturated with ether. The solid was filtered and allowed to dry in the air to afford **IV-13** (27.90 g, 200 mmol) in 100% yield: ^{1}H NMR (300 MHz) (D_2O) δ 1.41 (d, J = 7.3 Hz, 3 H), 3.68 (s, 3 H), 4.06 (q, J = 7.3 Hz, 1 H); ^{13}C NMR (75.5 MHz) (D_2O) δ 21.1 54.8, 59.6, 177.3.

Preparation of Amino Alcohol IV-14a:

IV-13 (27.90 g, 200 mmol) was slowly added to a cooled suspension of $LiAlH_4$ (19.0 g, 500 mmol) in THF (750 mL). After addition, the mixture was allowed to warm to room temperature and stir overnight. The reaction was quenched at 0 °C by the addition of H_2O (19 mL), then 15% NaOH (19 mL), and finally H_2O (57 mL). After 2 hours, the mixture was filtered, concentrated and the resulting oil was distilled (Kugelrohr) under vacuum to afford **IV-14a** (14.30 g, 190 mmol) in 95% yield (oven temp 60-80 °C, 10 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.93 (d, J = 6.5 Hz, 3 H), 2.75 (bs, 3 H), 2.89 (ddq, J = 3.9, 7.8, 6.5 Hz, 1 H), 3.13 (dd, J = 7.8, 10.7 Hz, 1 H), 3.42 (dd, J = 3.9, 10.7 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.4, 48.2, 67.8.

General Method for the Phthalimide Protection of Amino Alcohols:

The amino alcohol (1 eq.) and phthalic anhydride (1 eq.) were placed in toluene (0.3 *M*). The solution was heated at reflux for 48 hours with azeotropic removal of water. The mixture was concentrated by rotary evaporation under reduced pressure. The crystals were washed with petroleum ether and dried under vacuum.

IV-15a: (15.69 g, 76 mmol) in 98% yield, (yellow crystals): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.41 (d, J = 7.0 Hz, 3 H), 3.08 (bs, 1 H), 3.86 (dd, J = 3.8, 11.8 Hz, 1 H), 4.01 (dd, J = 7.5, 11.8 Hz, 1 H), 4.48 (ddq, J = 3.8, 7.5, 7.0 Hz, 1 H), 7.68 (m, 2 H), 7.80 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 14.8, 49.3, 64.2, 123.3, 131.9, 134.1, 168.9.

IV-15b: (40.86 g, 199 mmol) in 100% yield (yellow crystals, mp 87-89 °C): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.24 (d, J = 6.3 Hz, 3 H), 2.28 (bs, 1 H), 3.70 (dd, J = 7.1, 14.2 Hz, 1 H), 3.76 (dd, J = 4.0, 14.2 Hz, 1 H), 4.09 (ddq, J = 4.0, 7.1, 6.3 Hz, 1 H), 7.71 (m, 2 H), 7.83 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 21.1, 45.5, 66.8, 123.4, 131.9, 134.1, 168.9.

General Method for the Methylation of the IV-15:

The phthalimide (1 eq.) was slowly added to a 1.2 *M* suspension of NaH (1.2 eq.) in THF. The mixture was allowed to stir for one hour, and then was heated at reflux for one hour. The solution was cooled, MeI (1.2 eq.) was added, and the solution was stirred for one hour and then heated at reflux for an additional hour. The mixture was concentrated and washed with water. The methylated phthalimide was extracted with ether and the organic layer was dried over potassium carbonate. Concentration by rotary evaporation afforded yellow crystals which were washed with petroleum ether and dried under vacuum.

IV-16a: (13.703 g, 62.4 mmol) in 78% yield (yellow wax): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.40 (d, J = 7.0 Hz, 3 H), 3.28 (s, 3 H), 3.49 (dd, J = 5.3, 9.8 Hz, 1 H),

3.93 (dd, J = 9.8, 9.8 Hz, 1 H), 4.56 (ddq, J = 5.3, 9.8, 7.0 Hz, 1 H), 7.66 (m, 2 H), 7.77 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 15.0, 46.2, 58.6, 72.8, 123.0, 132.0, 133.7, 168.4.

IV-16b: (62.76 g, 286 mmol) in 82% yield (yellow crystals, mp 72-74 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.16 (d, J = 6.0 Hz, 3 H), 3.30 (s, 3 H), 3.61 (dd, J = 4.5, 12.6 Hz, 1 H), 3.67 (ddq, J = 4.5, 6.2, 6.0 Hz, 1 H), 3.78 (dd, J = 6.2, 12.6 Hz, 1 H), 7.68 (m, 2 H), 7.82 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.2, 42.4, 56.4, 74.3, 123.2, 132.0, 133.9, 168.4.

General Method for the Deprotection of Phthalimides IV-16:

Phthalimide **IV-16** (1 eq.) and hydrazine hydrate (2 eq.) were placed in 100% ethanol (0.1-0.2 *M*). The solution was heated at reflux for a minimum of 6 hours. The mixture was then filtered to remove the phthalhydrazide and treated with excess conc. HCl. The solution was concentrated, and the amine-hydrochloride salt was dissolved in a minimum amount of water. Additional insoluble phthalhydrazide was filtered and the water solution was treated with NaOH pellets until the pH reached 14. The amine was extracted with ether and the combined organic layers were dried over potassium carbonate. The ether was removed by distillation and the amine was distilled at normal pressure.

IB-17a: (2.872 g, 32 mmol) in 54% yield (bp 95-97 °C, 760 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.98 (d, J = 6.2 Hz, 3 H), 3.05 (d, J = 5.3 Hz, 1 H), 3.07 (ddq, J = 5.0, 5.3, 6.2 Hz, 1 H), 3.25 (d, J = 5.0 Hz, 1 H), 3.32 (s, 3 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.8, 46.3, 58.8, 79.7.

IV-17b: (1.812 g, 20 mmol) in 68% yield (bp 102-105 °C, 760 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.03 (d, J = 6.1 Hz, 3 H), 2.56 (dd, J = 6.8, 13.2 Hz, 1 H), 2.65 (dd, J = 4.0, 13.2 Hz, 1 H), 3.21 (ddq, J = 4.0, 6.8, 6.1 Hz, 1 H), 3.28 (s, 3 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 16.4, 47.2, 56.1, 78.3.

General Method for the Synthesis of IV-18:

IV-17 (1 eq.) and crotonaldehyde (1 eq.) were placed in toluene (0.2-0.4 *M*) and heated at reflux for 1-2 hours with azeotropic removal of water. The solution was cooled, and $NaBH_4$ (1-2 eq.) was added. The mixture was cooled to 0 °C and MeOH (half the volume of toluene) was added dropwise. The solution was allowed to stir for 16-24 hours. Solvents were removed by rotary evaporation, and the white solids were treated with 15% NaOH. The amine was extracted with ether, and the organic layer was dried over potassium carbonate. Ether was removed by rotary evaporation at 0 °C and the amines were distilled.

IV-18a: (1.663 g, 12 mmol) in 47% yield (bp 45-55 °C, 16 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (major isomer) 0.96 (d, J = 6.4 Hz, 3 H), 1.55 (bs, 1 H), 1.62 (m, 3 H), 2.84 (ddq, J = 4.2, 7.5, 6.4 Hz, 1 H), 3.06 (m, 1 H), 3.17 (dd, J = 7.5, 9.2 Hz, 1 H), 3.20 (m, 1 H), 3.26 (dd, J = 4.2, 9.2 Hz, 1 H), 3.30 (s, 3 H), 5.43-5.62 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 16.9, 17.7, 49.1, 51.8, 58.8, 77.3, 127.1, 129.6; IR (neat) 3330, 3020, 2969, 2926, 2880, 2828, 1673, 1453, 1375, 1109, 966 cm^{-1}; HRMS calcd for $C_8H_{17}NO$ *m/e* 143.1310, obsd *m/e* 143.1308.

IV-18b: (5.013 g, 35 mmol) in 70% yield (bp 165-167 °C, 760 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (major isomer) 1.09 (d, J = 6.2 Hz, 3 H), 1.39 (bs, 1 H), 1.64 (bd, J = 4.8 Hz, 3 H), 2.49-2.62 (m, 2 H), 3.10-3.15 (m, 2 H), 3.32 (s, 3 H), 3.42 (ddq, J = 4.7, 7.6, 6.2 Hz, 1 H), 5.42-5.64 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 17.0, 17.7, 51.7, 54.9, 56.2, 76.2, 127.1, 129.5; IR (neat) 3332, 3020, 2973, 2930, 2880, 2822, 1672, 1453, 1374, 1090, 968 cm^{-1}; HRMS calcd for $C_8H_{17}NO$ *m/e* 143.1310, obsd *m/e* 143.1372.

General Method for the Preparation of IV-19:

The crotyl amine **IV-18** (1 eq.), isobutyraldehyde (1 eq.), and *p*-toluenesulfonic acid (0.0025 eq.) were placed in benzene and heated at reflux 24-48 hours with azeotropic

removal of water. The benzene was removed by rotary evaporation under reduced pressure and the enamine was distilled (Kugelrohr) under vacuum.

IV-19a: (1.850 g, 9.4 mmol) in 94% yield (oven temp 60-80 °C, 5 mmHg): This enamine was extremely sensitive to hydrolysis and full spectral characterization could not be obtained. ^{1}H NMR (500 MHz) ($CDCl_3$) δ (major isomer) 0.98 (d, J = 6.7 Hz, 3 H), 1.59 (bs, 3 H), 1.63 (bs, 3 H), 1.64 (d, J = 4.7 Hz, 3 H), 3.01 (sext, J = 6.8 Hz, 1 H), 3.12 (dd, J = 7.2, 9.3 Hz, 1 H), 3.16-3.25 (m, 2 H), 3.29 (s, 3 H), 3.40 (dd, J = 5.8, 9.3 Hz, 1 H), 5.36-5.62 (m, 3 H).

IV-19b: (4.843 g, 25 mmol) in 82% yield (oven temp 75-80 °C, 6 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (major isomer) 1.08 (d, J = 6.2 Hz, 3 H), 1.58 (bs, 3 H), 1.64 (bs, 3 H), 1.65 (d, J = 4.6 Hz, 3 H), 2.39 (dd, J = 6.6, 12.8 Hz, 1 H), 2.64 (dd, J = 5.9, 12.8 Hz, 1 H), 3.10-3.16 (m, 2 H), 3.25 (q, J = 6.2 Hz, 1 H), 3.31 (s, 3 H), 5.25 (m, 1 H), 5.38-5.62 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 17.6, 17.8, 17.9, 22.2, 56.5, 59.1, 60.0, 76.1, 122.7, 127.5, 128.7, 135.2; IR (neat) 3077, 2971, 2932, 2865, 2822, 1682, 1451, 1377, 1098, 966 cm^{-1}.

Synthesis of 2-Hydroxy-3-methylbutanoic Acid (IV-21):

L-valine (19.916 g, 170.0 mmol) was dissolved in a solution of 10 mL conc. sulfuric acid in 250 ml water and cooled to 0 °C. A solution of $NaNO_2$ (17.595 g, 255.0 mmol) in 40 mL water was slowly added over 0.5 hours. The mixture was stirred at 0 °C for 4 hours and then allowed to warm to room temperature. The acid was extracted with 5 x 150 mL Et_2O and dried over $MgSO_4$. The solution was concentrated and then placed under high vacuum to give **IV-21** (11.74 g, 99.4 mmol) as white crystals in 59% yield: ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.89 (d, J = 6.7 Hz, 3 H), 1.02 (d, J = 7.0 Hz, 3 H), 2.13 (ddq, J = 3.4, 6.7, 7.0 Hz, 1 H), 4.12 (d, J = 3.4 Hz, 1 H), 6.00-8.00 (bs, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 15.9, 18.7, 32.0, 74.9, 179.2.

Synthesis of Methyl 2-Methoxy-3-methylbutyrate (IV-22):

To a suspension of NaH (5.952 g, 248.0 mmol) in 200 mL DMSO cooled in an ice bath was added dropwise a solution of **IV-21** (11.74 g, 99.0 mmol) in 150 mL DMSO. The mixture was stirred at room temperature for 2 hours, then cooled again and MeI (35.201 g, 248 mmol) was added over a 0.5 hour period. The mixture was allowed to stir at room temperature for 12 hours. Water (300 mL) was carefully added and the methoxy ester was extracted with 4 x 300 mL pentane. The organic layers were combined and washed with 100 mL sat. NaCl, dried over $MgSO_4$, and concentrated to give **IV-22** (13.53 g, 92.6 mmol) in 93% yield as a yellow oil. The ester was hydrolyzed without further purification: ^1H NMR (300 MHz) ($CDCl_3$) δ 0.89 (d, J = 6.8 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H), 1.99 (ddq, J = 5.5, 6.8, 6.9 Hz, 1 H), 3.3 (s, 3 H), 3.47 (d, J = 5.5 Hz, 1 H), 3.72 (s, 3 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.6, 18.5, 31.5, 51.6, 58.5, 85.9, 172.8.

Hydrolysis of IV-22 to 2-Methoxy-3-methylbutanoic Acid (IV-23):

The 2-methoxy ester (**IV-22**) was placed in 100 mL 6 *N* NaOH and heated at reflux for 24 hours. The heterogeneous mixture was brought to a pH < 2 by careful addition of conc. HCl with external cooling in an ice bath. The acid was extracted with 3 x 100 mL Et_2O and dried over $MgSO_4$. Solvents were evaporated and the oil was distilled to give **IV-23** (5.191 g, 39.3 mmol) in 96% yield (bp 92-94 °C, 8 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.95 (d, J = 6.9 Hz, 3 H), 1.00 (d, J = 6.9 Hz, 3 H), 2.10 (ddq, J = 4.7, 6.9, 6.9 Hz, 1 H), 3.42 (s, 3 H), 3.56 (d, J = 4.7 Hz, 1 H), 6.60-7.90 (bs, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.2, 18.6, 31.4, 59.1, 85.4, 176.7.

Preparation of IV-24:

To 60 mL of CH_2Cl_2 was added the methoxy acid **IV-23** (5.286 g, 40.0 mmol) and pyridine (3.322 g, 42.0 mmol). Trimethylsilyl chloride (4.563 g, 42.0 mmol) was

slowly added and the mixture was allowed to stir for 3.5 hours. DMF (5 drops) was added and the solution was cooled to 0 °C. Oxalyl chloride (5.331 g, 42.0 mmol) was added dropwise, and the mixture was stirred at 0 °C for 1 hour, then at room temperature for 30 minutes. The mixture was again cooled to 0 °C and pyridine (4.746 g, 60.0 mmol) followed by a solution of imine **II-11b** (5.259 g, 42.0 mmol) in 40 mL CH_2Cl_2 were added. After stirring 5 hours the reaction mixture was filtered through a pad of silica gel/alumina and concentrated. The enamide was purified by flash column chromatography (silica gel, 70:30 Et_2O:petroleum ether) and concentrated. Kugelrohr distillation gave **IV-24** (6.389 g, 28.4 mmol) in 71% yield as a mixture of isomers (*E*:*Z* 72:28) (oven temp 60-70 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 0.87 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 2.02 (m, 3 H), 3.23 (s, 3 H), 3.62 (d, *J* = 7.7 Hz, 1 H), 4.23 (m, 2 H), 5.09 (m, 3 H), 5.72 (m, 1 H), 6.88 (d, *J* = 13.9 Hz, 1 H), (*Z* isomer) 0.87 (d, *J* = 6.8 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 3 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 2.02 (m, 3 H), 3.28 (s, 3 H), 3.72 (d, *J* = 7.9 Hz, 1 H), 4.23 (m, 2 H), 5.09 (m, 3 H), 5.72 (m, 1 H), 7.20 (d, *J* = 14.6 Hz, 1 H); ^3C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 14.4, 18.6, 18.9, 23.4, 30.6, 46.3, 57.4, 87.9, 115.6, 116.3, 125.9, 132.7, 169.6, (*Z* isomer) 14.4, 18.2, 19.1, 23.5, 30.4, 46.6, 57.3, 86.4, 114.8, 116.2, 125.3, 132.8, 169.7; IR (neat) 3080, 3020, 2967, 2934, 2876, 2828, 2645, 1520, 1464, 1408, 1368, 1318, 1200, 1136, 1102, 988, 949 cm^{-1}; HRMS calcd for $C_{13}H_{23}NO_2$ *m/e* 225.1728, obsd *m/e* 225.1770.

Reduction of IV-24 to Enamine IV-25:

To a suspension of $LiAlH_4$ (0.920 g, 24.2 mmol) in 100 mL Et_2O was added enamide **IV-24** (4.957 g, 22.0 mmol). The mixture was stirred at room temperature for 3 hours, and then quenched by addition of 0.92 mL H_2O, then 0.92 mL 15% aq. NaOH, and finally 2.76 mL H_2O. After filtration, the solution was concentrated and distilled (Kugelrohr) to give **IV-25** (4.534 g, 21.5 mmol) in 98% yield as a single isomer (oven

temp 45-60 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.87 (d, *J* = 6.9 Hz, 3 H), 0.88 (d, *J* = 6.9 Hz, 3 H), 0.91 (t, *J* = 7.4 Hz, 3 H), 1.76 (dqq, *J* = 4.6, 6.9, 6.9 Hz, 1 H), 1.94 (ddq, *J* = 1.2, 6.8, 7.4 Hz, 2 H), 2.85 (dd, *J* = 7.7, 14.4 Hz, 1 H), 2.95 (dd, *J* = 3.8, 14.5 Hz, 1 H), 3.06 (ddd, *J* = 3.8, 7.4, 7.7 Hz, 1 H), 3.35 (s, 3 H), 3.54 (ddd, *J* = 1.4, 1.7, 5.7 Hz, 2 H), 4.14 (dt, *J* = 13.8, 6.8 Hz, 1 H), 5.07 (ddt, *J* = 3.5, 10.4, 1.4 Hz, 1 H), 5.10 (ddt, *J* = 3.5, 17.1, 1.7 Hz, 1 H), 5.77 (ddt, *J* = 10.4, 17.1, 5.7 Hz, 1 H), 5.89 (dt, *J* = 13.8, 1.2 Hz, 1 H); ^{3}C NMR (75.5 MHz) ($CDCl_3$) δ 16.3, 17.5, 18.5, 23.8, 30.1, 52.9, 54.6, 58.8, 84.1, 99.2, 116.2, 135.1, 137.0; IR (neat) 3081, 2965, 2875, 2828, 1676, 1606, 1389, 1285, 1186, 1094, 995, 970, 924 cm^{-1}.

Synthesis of 3-Hydroxy-1-heptene (IV-27):

To a flask containing 100 mL THF was added vinyl magnesium bromide (220 mL, 1 *M* in THF), and the solution was cooled in an ice bath. Valeraldehyde (17.227 g, 810.0 mmol) was slowly added, and the mixture was stirred for 30 min at 0 °C then 30 min at room temperature. The mixture was quenched with 50 g sat. aq. NH_4Cl and then dried with K_2CO_3. Filtration and concentration provided an oil which was distilled to give **IV-27** (21.56 g, 188.8 mmol) in 95% yield (bp 61 °C, 15 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3 H), 1.30 (m, 4 H), 1.50 (m, 2 H), 1.75 (s, 1 H), 4.05 (dddt, *J* = 1.2, 1.2, 6.5, 6.3 Hz, 1 H), 5.06 (ddd, *J* = 1.2, 1.5, 10.2 Hz, 1 H), 5.17 (ddd, *J* = 1.2, 1.5, 17.2 Hz, 1 H), 5.84 (ddd, *J* = 6.5, 10.2, 17.2 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 14.0, 22.6, 27.5, 36.7, 73.2, 114.4, 141.3; IR (neat) 3357 (br), 3081, 2960, 2933, 2874, 2862, 1646, 1468, 1425, 1380, 1319, 1276, 1146, 1089, 1052, 992, 920 cm^{-1}.

Synthesis of Trichloroacetamide IV-28:

To a suspension of NaH (0.571 g, 23.8 mmol) in 200 mL THF was added **IV-27** (18.10 g, 158.5 mmol). After stirring for 1 hour at room temperature the alkoxide/alcohol

mixture was transfered to a cooled solution of CCl_3CN (22.886 g, 158.5 mmol) in 200 mL Et_2O. The mixture was stirred for 1.5 hours at 0 °C and then concentrated. Methanol (2 mL) in 100 mL pentane was added to the thick oil and shaken for 1 min. The solution was filtered and concentrated. The dark oil was dissolved in 600 mL xylenes and heated at reflux for 20 hours. The amide solution was filtered through a pad of silica gel and eluted with toluene and then concentrated. Kugelrohr distillation provided **IV-28** (39.05 g, 151.0 mmol) in 95% yield (oven temp 85-100 °C, >1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (t, J = 7.2 Hz, 3 H), 1.32 (m, 4 H), 2.03 (m, 2 H), 3.89 (dd, J = 1.2, 6.5 Hz, 2 H), 5.45 (m, 1 H), 5.70 (m, 1 H), 6.60-6.80 (bs, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 13.9, 22.1, 31.1, 31.9, 43.3, 123.5, 135.7, 161.5; IR (neat) 3411 (br), 3022, 2959, 2930, 2873, 1718, 1495, 1457, 1263, 1050, 972, 839, 728, 671 cm^{-1}.

Hydrolysis of IV-28 to 2-Heptenylamine (IV-29):

The trichloroacetamide **IV-28** was placed in 6 *N* aq. NaOH (300 mL) and heated at reflux for 36 hours. The amine was extracted from the aqueous mixture with 4 x 150 mL Et_2O and dried over K_2CO_3. The oil was concentrated and distilled (Kugelrohr) to give **IV-29** (14.268 g, 126.0 mmol) in 84% yield (oven temp 60-70 °C, 22 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.84 (t, J = 7.4 Hz, 3 H), 1.25 (m, 6 H), 1.97 (m, 2 H), 3.19 (m, 2 H), 5.50 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 13.9, 22.1, 31.5, 31.9, 44.1, 130.7, 131.2; IR (neat) 3371, 3300, 2959, 2928, 2858, 1467, 1379, 969 cm^{-1}.

General Method for the Synthesis of Enamides IV-30:

The amine **IV-29** and an equimolar amount of the appropriate carbonyl compound were condensed in either Et_2O with K_2CO_3 at room temperature (for *n*-butanal) or in benzene (for 2-phenylpropanal) or toluene (for cyclohexanone) at reflux to prepare the corresponding imines which were used without isolation. After imine formation the solution was treated with Et_3N (1 eq.), and isobutyryl chloride (1 eq.) was slowly added.

The mixture was stirred for a minimum of 4 hours at room temperature and then filtered through a pad of silica gel/alumina. The enamide was concentrated and purified by flash chromatography (silica gel, 70:30 Et_2O/petroleum ether) and then distilled (Kugelrohr).

IV-30a: (2.63 g, 11.1 mmol) in 66% yield as a mixture of *E*:*Z* enamine olefin isomers (65:35 respectively) (oven temp 60-90 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (mixture of isomers) 0.84 (t, *J* = 7.0 Hz, 3 H), 0.98 (t, *J* = 7.4 Hz, 3 H), 1.11 (d, *J* = 6.6 Hz, 6 H), 1.19-1.35 (m, 4 H), 1.92-2.05 (m, 2 H), 2.04 (ddq, *J* = 1.3, 6.7, 7.5 Hz, 2 H), 2.75 (sept, *J* = 6.6 Hz, 1 H, *Z* isomer), 2.89 (sept, *J* = 6.6 Hz, 1 H, *E* isomer), 4.05 (bd, *J* = 2.9 Hz, 2 H, *Z* isomer), 4.14 (bd, *J* = 5.3 Hz, 2 H), 5.02 (dt, *J* = 13.8, 7.4 Hz, 1 H, *Z* isomer), 5.12 (dt, *J* = 13.8, 6.7 Hz, 1 H, *E* isomer), 5.34 (m, 1 H), 5.46 (m, 1 H), 6.52 (d, *J* = 13.8 Hz, 1 H, *E* isomer), 7.19 (d, *J* = 14.8 Hz, 1 H, *Z* isomer); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 13.8, 14.6, 19.2, 22.0, 23.7, 30.8, 31.3, 31.8, 45.5, 116.0, 124.4, 126.4, 133.0, 175.2, (*Z* isomer) 13.8, 14.6, 19.7, 22.1, 23.6, 31.0, 31.3, 31.8, 46.7, 113.7, 124.1, 125.6, 132.7, 175.9; IR (neat) 3081, 2965, 2874, 1734, 1651, 1545, 1468, 1379, 1240, 1099, 970 cm^{-1}; HRMS cald for $C_{15}H_{27}NO$ *m/e* 237.2092, obsd *m/e* 237.2100.

IV-30b: (8.937 g, 29.8 mmol) in 56% yield as a mixture of *E*:*Z* enamine olefin isomers (66:34 respectively) (oven temp 80-140 °C, 0.05 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 0.86 (t, *J* = 6.9 Hz, 3 H), 1.07 (d, *J* = 6.6 Hz, 6 H), 1.20-1.34 (m, 4 H), 1.91-2.04 (m, 2 H), 1.97 (d, *J* = 1.4 Hz, 3 H), 2.75 (sept, *J* = 6.6 Hz, 1 H), 4.06 (d, *J* = 6.0 Hz, 2 H), 5.24-5.62 (m, 2 H), 6.36 (bq, *J* = 1.4 Hz, 1 H), 7.18-7.58 (m, 5 H), (*Z* isomer) 0.83 (t, *J* = 7.1 Hz, 3 H), 0.94 (d, *J* = 6.9 Hz, 6 H), 1.20-1.34 (m, 4 H), 1.91-2.04 (m, 2 H), 2.07 (d, *J* = 1.4 Hz, 3 H), 2.85 (sept, *J* = 6.9 Hz, 1 H), 3.78 (d, *J* = 5.8 Hz, 2 H), 5.24-5.62 (m, 2 H), 6.17 (bq, *J* = 1.4 Hz, 1 H), 7.18-7.58 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 13.8, 19.1, 22.1, 31.2, 31.4, 31.7, 31.9, 49.4, 124.4, 126.0, 127.1, 128.0, 128.5, 134.7, 138.0, 139.9, 177.1, (*Z* isomer) 15.8, 19.0, 21.8, 31.2, 31.4, 31.7, 31.8, 48.6, 124.1, 125.8, 127.1, 127.7, 128.5, 134.0, 138.6, 139.9, 177.0; IR (neat) 3083,

3058, 3029, 2965, 2930, 2874, 1734, 1663, 1470, 1445, 1406, 1227, 1090, 970, 758, 698 cm^{-1}; HRMS calcd for $C_{20}H_{29}NO$ *m/e* 299.2249, obsd *m/e* 299.2239.

IV-30c: (3.755 g, 14.3 mmol) in 89% yield (oven temp 90-100 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.82 (t, *J* = 7.2 Hz, 3 H), 1.03 (d, *J* = 6.7 Hz, 6 H), 1.25 (m, 4 H), 1.54 (m, 2 H), 1.64 (m, 2 H), 1.98 (m, 4 H), 2.06 (m, 2 H), 2.71 (sept, *J* = 6.7 Hz, 1 H), 3.90 (bs, 2 H), 5.40 (m, 2 H), 5.52 (m, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 13.8, 20.1, 21.5, 22.0, 22.7, 24.7, 29.0, 31.2, 31.3, 31.8, 48.1, 125.5, 127.0, 134.0, 138.5, 176.4; IR (neat) 3027, 2960, 2931, 2873, 1651, 1469, 1438, 1400, 1361, 1246, 1234, 1139, 1092, 970, 922 cm^{-1}; HRMS calcd for $C_{17}H_{29}NO$ *m/e* 263.2249, obsd *m/e* 263.2248.

Preparation of Trichloroacetamide IV-33:

To a solution of crotonaldehyde (14.018 g, 200 mmol) in Et_2O (250 mL) at -78 °C was added methyl magnesium bromide (66.67 mL, 3 *M* in Et_2O). The solution was allowed to warm to room temperature overnight, and quenched with saturated aq. NH_4Cl (100 mL) and water (100 mL). The alcohol was extracted with 3 x 100 mL Et_2O, and dried over $MgSO_4$. The solution was filtered and concentrated to half its volume by distillation. To the alcohol solution was added NaH (0.72 g, 30 mmol), and the mixture was stirred for 30 minutes. The alkoxide solution was added to a 0 °C solution of CCl_3CN in THF (400 mL). The mixture was stirred at ambient temperature overnight, concentrated. The residue was taken up in pentane/MeOH (200 mL/20 mL) and filtered. The solvents were evaporated, and the oil was placed in xylenes (400 mL). The solution was heated at reflux for 20 hours, filtered through silica with toluene as eluant, and concentrated. The trichloroacetamide was distilled via Kugelrhor to give **IV-33** (37.10 g, 162 mmol) in 81% yield (oven temp 80-120 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.27 (d, *J* = 6.8 hz, 3 H), 1.67 (dd, *J* = 1.6, 6.4 Hz, 3 H), 4.42 (ddq, *J* = 1.3, 5.8, 6.8 Hz, 1 H), 5.43 (ddq, *J* = 5.8, 15.4, 1.6 Hz, 1 H), 5.66 (ddq, *J* = 1.3, 15.4, 6.4 Hz, 1

H), 6.58 (s, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.6, 20.1, 48.8, 92.7, 127.2, 130.5, 160.7; IR (neat) 3333, 3035, 2978, 2938, 2921, 2830, 1696, 1518, 1453, 1379, 1240, 1167, 1130, 1078, 966, 823, 740, 683 cm^{-1}.

General Method for the Preparation of Enamides IV-34:

Amide **IV-33** was heated at reflux for at least 12 hours in 6 *M* NaOH, extracted with either Et_2O or benzene, and dried with K_2CO_3. The amine solution and an equimolar amount of the appropriate carbonyl compound were condensed in either Et_2O with K_2CO_3 at room temperature (for *n*-butanal) or in benzene (for 2-phenylpropanal and cyclohexanone) at reflux to prepare the corresponding imines which were used without isolation. After imine formation the solution was treated with Et_3N (1 eq.), and isobutyryl chloride (1 eq.) was slowly added. The mixture was stirred for a minimum of 4 hours at room temperature and then filtered through a pad of silica gel/alumina. The enamide was concentrated and purified by flash chromatography (silica gel, 70:30 Et_2O/petroleum ether) and then distilled.

IV-34a: (25.44 g, 121.2 mmol) in 75% yield (bp 83-95 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.01 (t, *J* = 7.4 Hz, 3 H), 1.05 (d, *J* = 6.6 Hz, 6 H), 1.15 (d, *J* = 6.6 Hz, 3 H), 1.64 (d, *J* = 5.2 Hz, 3 H), 2.07 (quint, *J* = 7.4 Hz, 2 H), 2.86 (sept, *J* = 6.6 Hz, 1 H), 5.13 (m, 1 H), 5.35-5.57 (m, 3 H), 5.95 (d, *J* = 13.7 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 13.8, 17.5, 17.7, 19.2, 23.3, 31.4, 50.4, 124.5, 126.1, 131.5, 132.4, 176.3; IR (neat) 3030, 2969, 2936, 2876, 1645, 1458, 1395, 1237, 968 cm^{-1}; HRMS calcd for $C_{13}H_{23}NO$ *m/e* 209.1779, obsd *m/e* 209.1781.

IV-34b: (6.101 g, 22.4 mmol) in 64% yield as a mixture of isomers (*E*:*Z* 55:45) (oven temp 95-110 °C, <1 mmHg): ^1H NMR: (300 MHz) ($CDCl_3$) δ (*E* isomer) 0.75 (d, *J* = 6.7 Hz, 3 H), 1.07 (d, *J* = 6.7 Hz, 3 H), 1.16 (d, *J* = 6.9 Hz, 3 H), 1.61 (d, *J* = 6.1 Hz, 3 H), 2.11 (d, *J* = 1.3 Hz, 3 H), 2.75 (sept, *J* = 6.7 Hz, 1 H), 5.05 (quint, *J* = 6.9 Hz, 1 H), 5.35-5.61 (m, 2 H), 6.00 (d, *J* = 1.3 Hz, 1 H), 7.16-7.42 (m, 5 H), (*Z* isomer) 0.72 (d, *J* =

6.7 Hz, 3 H), 1.05 (d, J = 6.7 Hz, 3 H), 1.17 (d, J = 6.9 Hz, 3 H), 1.65 (d, J = 6.4 Hz, 3 H), 1.96 (d, J = 1.3 Hz, 3 H), 2.73 (sept, J = 6.7 Hz, 1 H), 5.29 (quint, J = 6.9 Hz, 1 H), 5.40-5.67 (m, 2 H), 6.23 (d, J = 1.3 Hz, 1 H), 7.16-7.42 (m, 5 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 17.2, 17.8, 18.6, 19.0, 22.2, 31.4, 52.2, 121.5, 126.0, 126.9, 127.3, 128.3, 131.0, 135.5, 140.0, 177.1, (*Z* isomer) 16.0, 17.6, 18.8, 19.3, 22.2, 31.5, 51.4, 122.8, 126.0, 127.0, 127.6, 128.5, 130.7, 135.5, 138.6, 176.8; IR (neat) 3083, 3058, 3029, 2971, 2934, 2874, 1655, 1447, 1402, 1246, 1192, 1090, 970, 864, 764, 698 cm^{-1}; HRMS calcd for $C_{18}H_{25}NO$ *m/e* 271.1936, obsd *m/e* 271.1936.

IV-34c: (3.317 g, 14.0 mmol) in 56% yield (oven temp 80-90 C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.02 (m, 6 H), 1.14, (m, 3 H), 1.43-1.72 (m, 4 H), 1.62 (d, J = 5.8 Hz, 3 H), 1.80-2.18 (m, 4 H), 2.62 (sept, J = 6.5 Hz, 1 H), 4.93 (m, 1 H), 5.35-5.60 (m, 3 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.8, 18.6, 19.9, 20.4, 21.5, 22.9, 24.9, 32.0, 51.0, 126.4, 128.2, 131.9, 136.7, 176.1; IR (neat) 3031, 2967, 2934, 2874, 2842, 1647, 1393, 125, 972 cm^{-1}; HRMS calcd for $C_{15}H_{25}NO$ *m/e* 235.1936, obsd *m/e* 235.1917.

General Method for the Reduction of Enamides to Enamines IV-31 and IV-35:

Enamide **IV-31** or **IV-35** was slowly added to a suspension of $LiAlH_4$ (1.2 eq.) in Et_2O (0.2 *M*) and stirred at room temperature for a minimum of 2 hours. The mixture was quenched by careful addition of H_2O (1 mL/g $LiAlH_4$), then 15% aq. NaOH (1 mL/g $LiAlH_4$), and finally H_2O (3 mL/g $LiAlH_4$), stirred for 1 hours, and filtered. The was concentrated, and the enamine was distilled (Kugelrohr).

IV-31a: (1.94 g, 8.7 mmol) in 99% yield as a single enamine olefin isomer (oven temp 60-70 °C, <1 mmHg): This enamine was extremely sensitive to hydrolysis and full spectral characterization could not be obtained. Characteristic enamine olefin resonances; ^{1}H NMR (300 MHz) ($CDCl_3$) δ 4.11 (dt, J = 6.7, 13.9 Hz, 1 H), 5.88 (bd, J = 13.9 Hz, 1 H).

IV-31b: (7.129 g, 25.0 mmol) in 99% yield as a mixture of *E*:*Z* enamine olefin isomers (90:10 respectively) (oven temp 95-120 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (mixture of isomers) 0.89 (d, *J* = 6.6 Hz, 6 H), 0.91 (t, *J* = 6.4 Hz, 3 H), 1.25-1.40 (m, 4 H), 1.76 (non, *J* = 6.6 Hz, 1 H), 1.97 (d, *J* = 1.1 Hz, 3 H, *Z* isomer), 2.00-2.10 (m, 2 H), 2.09 (d, *J* = 1.1 Hz, 3 H, *E* isomer), 2.49 (d, *J* = 7.2 Hz, 2 H, *Z* isomer), 2.61 (d, *J* = 7.4 Hz, 2 H, *E* isomer), 3.46 (d, *J* = 5.1 Hz, 2 H), 5.44-5.64 (m, 2 H), 5.82 (d, *J* = 1.1 Hz, 1 H, *Z* isomer), 6.14 (d, *J* = 1.1 Hz, 1 H, *E* isomer); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 13.9, 15.6, 20.4, 22.2, 28.3, 31.5, 32.0, 57.5, 62.1, 117.7, 124.9, 125.1, 127.4, 128.0, 133.1, 139.3, 143.4, (*Z* isomer) 13.9, 15.6, 20.7, 22.7, 28.3, 31.4, 31.9, 56.1, 61.5, 117.7, 124.9, 125.1, 127.6, 127.9, 133.0, 136.7, 142.0; IR (neat) 3085, 3050, 3028, 2957, 2928, 2870, 1632, 1495, 1466, 1120, 970, 756, 696 cm^{-1}.

IV-31c: (2.901 g, 11.6 mmol) in 97% yield (bp 75-90 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.82 (d, *J* = 6.6 Hz, 6 H), 0.86 (t, *J* = 7.2 Hz, 3 H), 1.29 (m, 4 H), 1.49 (m, 2 H), 1.65 (m, 2 H), 1.84 (dsept, *J* = 7.1, 6.6 Hz, 1 H), 1.98 (m, 2 H), 2.06 (m, 4 H), 2.63 (d, *J* = 7.1 Hz, 2 H), 3.49 (d, *J* = 5.5 Hz, 2 H), 4.41 (dd, *J* = 1.2, 3.6 Hz, 1 H), 5.40 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 13.9, 20.6, 22.1, 22.9, 23.6, 24.7, 26.6, 27.3, 31.6, 32.0, 51.8, 56.3, 96.5, 126.9, 132.3, 143.5; IR (neat) 3022, 2958, 2929, 2872, 1685, 1653, 1646, 1466, 1437, 1367, 1120, 970 cm^{-1}.

IV-35a: (4.277 g, 22.0 mmol) in 88% yield (bp 75-85 °C, 8 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.83 (d, *J* = 6.7 Hz, 6 H), 0.92 (t, *J* = 7.4 Hz, 3 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 1.65 (m, 3 H), 1.84 (non, *J* = 6.7 Hz, 1 H), 1.95 (ddq, *J* = 1.1, 6.6, 7.4 Hz, 2 H), 2.49 (d, *J* = 7.1 Hz, 2 H), 3.5 (m, 1 H), 4.11 (dt, *J* = 13.9, 6.6 Hz, 1 H), 5.42-5.53 (m, 2 H), 5.92 (dt, *J* = 13.9, 1.1 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 16.3, 17.3, 17.8, 20.6, 24.2, 26.6, 56.0. 58.7, 100.1, 125.2, 133.4, 135.0; IR (neat) 3020, 2959, 2932, 2870, 1649, 1453, 1379, 1080, 972, 938 cm^{-1}.

IV-35b: (2.949 g, 11.52 mmol) in 96% yield as a mixture of isomers (*E*:*Z* 55:45) (bp 80-90 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) (mixture of isomers) δ 0.86 (d,

J = 6.7 Hz, 3 H), 0.87 (d, J = 6.7 Hz, 3 H), 1.15 (d, J = 6.8 Hz, 3 H), 1.63 (m, 1 H), 1.64 (dd, J = 1.3, 4.7 Hz, 3 H, *Z* isomer), 1.69 (dd, J = 1.1, 4.8 Hz, 3 H, *E* isomer), 1.97 (d, J = 1.2 Hz, 3 H, *Z* isomer), 2.08 (d, J = 1.2 Hz, 3 H, *E* isomer), 2.41 (dd, J = 7.3, 12.7 Hz, 1 H), 2.44 (dd, J = 7.3, 12.7 Hz, 1 H), 3.48 (m, 1 H), 5.25-5.60 (m, 2 H), 5.77 (bq, J = 1.2 Hz, 1 H, *Z* isomer), 6.08 (bq, J = 1.2 Hz, 1 H, *E* isomer), 7.08-7.55 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) (*E* isomer) δ 15.8, 17.6, 17.9, 20.5, 28.6, 57.0, 57.7, 60.0, 113.9, 125.1, 127.7, 128.1, 129.1, 133.5, 138.8, 143.0, (*Z* isomer) 16.6, 17.6, 17.9, 22.6, 28.7, 55.9, 57.8, 60.0, 111.4, 125.6, 127.6, 128.3, 129.1, 133.3, 136.8, 141.9; IR (neat) 3028, 2965, 2870, 1686, 1450, 1360, 1285, 972, 760, 698 cm^{-1}.

IV-35c: (2.532 g, 11.4 mmol) in 95% yield (oven temp 60-70 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.78 (d, J = 6.6 Hz, 6 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.46-1.56 (m, 2 H), 1.57-1.68 (m, 2 H), 1.66 (dd, J = 1.5, 4.7 Hz, 3 H), 1.80 (non, J = 6.6 Hz, 1 H), 1.99-2.11 (m, 4 H), 2.35 (dd, J = 6.8, 10.7 Hz, 1 H), 2.42 (dd, J = 6.8, 10.7 Hz, 1 H), 3.87 (m, 1 H), 4.48 (t, J = 3.8 Hz, 1 H), 5.34-5.50 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 16.2, 17.9, 20.8, 20.9, 23.1, 23.7, 24.9, 25.2, 27.9, 51.4, 53.0, 101.7, 124.5, 134.4, 142.2; IR (neat) 3027, 2957, 2938, 2868, 1717, 1450, 1119, 970 cm^{-1}.

Preparation of IV-37:

Proline (8.635 g, 75.0 mmol) was dissolved in MeOH (75 mL), cooled to 0 °C and $SOCl_2$ (22.307 g, 187.5 mmol) was slowly added. The solution was allowed to stir at room temperature overnight and was then concentrated. The crude ester hydrochloride was dissolved in THF (150 mL) and Et_3N (16.665 g, 165.0 mmol) was added followed bydi-*tert*-butyldicarboxylate (17.242 g, 79.0 mmol). After stirring 4 hours, the mixture was filtered, concentrated, and distilled (Kugelrhor) under vacuum to give **IV-37** (17.10 g, 74.6 mmol) in 99% yield as a mixture of two amide isomers (oven temp 90-100 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (major isomer) 1.38 (s, 9 H), 1.90 (m, 3 H), 2.17 (m, 1 H), 3.46 (m, 2 H), 3.69 (s, 3 H), 4.19 (dd, J = 4.0, 8.5 Hz, 1 H), (minor isomer)

1.43 (s, 9 H), 1.85 (m, 3 H), 2.17 (m, 1 H), 3.40 (m, 2 H), 3.70 (s, 3 H), 4.29 (dd, J = 4.0, 8.5 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 23.6, 28.2, 30.8, 46.2, 51.8, 59.0, 79.7, 152.7, 173.7, (minor isomer) 24.2, 28.3, 29.8, 46.5, 52.0, 58.6, 79.6, 154.3, 173.4; IR (neat) 2978, 2882, 1752, 1701, 1455, 1397, 1367, 1258, 1202, 1161, 1122, 1088, 1001, 889, 774 cm^{-1}.

DIBAH Reduction of IV-37 to Aldehyde IV-38:

IV-38 (8.025 g, 35.0 mmol) was placed in toluene (100 mL) and cooled to -78 °C. DIBAH (36 mL, 2 *M* in hexane) was added. The mixture was stirred at -78 °C for 2 hours, and quenched by addition of $Na_2SO_4(10\ H_2O)$. The solution was filtered, concentrated, and the oil was distilled under vacuum to give **IV-38** 6.30 g, 31.6 mmol) in 90% yield as a mixture of amide resonance isomers (bp 88-90 °C <1 mmHg): .^1H NMR (300 MHz) ($CDCl_3$) δ (major isomer) 1.40 (s, 9 H), 1.8-2.2 (m, 4 H), 3.42 (m, 2 H), 4.0 (m, 1 H), 9.42 (d, J = 2.8 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 23.9, 28.2, 28.3, 46.7, 65.0, 80.6, 153.9, 200.4, (minor isomer) 24.6, 28.0, 28.4, 46.8, 64.8, 80.2, 154.7, 200.6; IR (neat) 2978, 2930, 2882, 2813, 1738, 1698, 1480, 1456, 1397, 1256, 1167, 1123, 984, 912, 858, 774 cm^{-1}.

Wittig Reaction and Deprotection of IV-38 to give IV-39:

To a solution of benzyltriphenylphosphonium or ethyltriphenylphosphonium bromide (1 eq.) in DMSO (0.5 *M*), was added NaH (1.1 eq.), and the mixture was stirred for 15 minutes. A solution of **IV-38** (1 eq.) in DMSO (2 *M*) was added. The mixture was stirred for 30 minutes, and washed with water. The mixture was extracted with pentane and dried over K_2CO_3. The organic layer was concentrated and the crude olefin was dissolved in MeOH (1 *M*). Excess concentrated HCl was added and the solution was allowed to stir overnight. The mixture was brought to pH 14 by addition of NaOH pellets, extracted with ether, dried over K_2CO_3, concentrated and distilled (Kugelrohr).

IV-39a: (1.401 g, 8.11 mmol) in 69% yield as a mixture of isomers (*E*:*Z* 65:35) (oven temp 85-95 °C, <1 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 1.50 (m, 1 H), 1.65 (bs, 1 H), 1.70-1.90 (m, 2 H), 1.98 (m, 1 H), 2.90 (m, 1 H), 3.07 (m, 1 H), 3.68 (bq, *J* = 7.1 Hz, 1 H), 6.20 (dd, *J* = 7.2, 15.7 Hz, 1 H), 6.49 (d, *J* = 15.7 Hz, 1 H), 7.15-7.40 (m, 5 H), (*Z* isomer) 1.50 (m, 1 H), 1.65 (bs, 1 H), 1.70-1.90 (m, 2 H), 2.85 (m, 1 H), 1.98 (m, 1 H), 3.07 (m, 1 H), 3.96 (dt, *J* = 9.3, 7.1 Hz, 1 H), 5.62 (dd, *J* = 9.3, 11.4 Hz, 1 H), 6.46 (d, *J* = 11.4 Hz, 1 H), 7.15-7.40 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 25.1, 32.2, 46.3, 60.7, 126.1, 127.0, 128.3, 129.3, 132.7, 137.0, (*Z* isomer) 25.7, 33.0, 46.6, 55.6, 126.7, 128.0, 128.5, 129.4, 135.4, 136.9; IR (neat) 3275, 3080, 3058, 3025, 2961, 2870, 1493, 1449, 1399, 1073, 965, 748, 694 cm^{-1}.

IV-39b: carried on to **IV-40b** without isolation.

Condensation of IV-39 with Phenylacetaldehyde to give IV-40:

Amine **IV-39** (1 eq.) and phenylacetaldehyde (1 eq.) were dissolved in Et_2O (0.3 *M*). Potassium carbonate or magnesium sulfate was added and the mixture was stirred for 1-6 hours, filtered, and concentrated. If necessary the enamine was distilled under vacuum.

IV-40a: (0.826 g, 3.0 mmol) in 100% yield as a mixture of isomers at the allylic double bond (*E*:*Z* 65:35): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 1.87-2.36 (m, 4 H), 3.34 (m, 1 H), 3.47 (m, 1 H), 4.15 (q, *J* = 6.8 Hz, 1 H), 5.28 (d, *J* = 14.0 Hz, 1 H), 6.22 (dd, *J* = 7.4, 15.7 Hz, 1 H), 6.65 (d, *J* = 15.7 Hz, 1 H), 6.99-7.07 (m, 2 H), 7.12 (d, *J* = 14.0 Hz, 1 H), 7.21-7.26 (m, 2 H), 7.30-7.70 (m, 6 H), (*Z* isomer) 1.87-2.36 (m, 4 H), 3.34 (m, 1 H), 3.47 (m, 1 H), 4.49 (dt, *J* = 6.9, 9.5 Hz, 1 H), 5.16 (d, *J* = 13.9 Hz, 1 H), 5.70 (dd, *J* = 9.5, 11.5 Hz, 1 H), 6.78 (d, *J* = 11.5 Hz, 1 H), 6.99-7.07 (m, 2 H), 7.04 (d, *J* = 13.9 Hz, 1 H), 7.21-7.26 (m, 2 H), 7.30-7.70 (m, 6 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 23.5, 32.9, 47.7, 63.6, 98.2, 122.9, 123.3, 126.4, 127.5, 128.4, 128.5, 131.3, 131.4, 134.5, 136.6, 139.9, (*Z* isomer) 23.9, 33.3, 47.7, 58.1, 98.2, 122.8, 123.2, 126.4,

127.1, 128.2, 128.6, 131.3, 134.1, 134.3, 136.6, 139.9; IR (neat) 3080, 3056, 3025, 2969, 2872, 1636, 1597, 1495, 1370, 1142, 968, 936, 747, 693 cm^{-1}.

IV-40b: (3.19 g, 14.93 mmol) in 79% yield (from **IV-38**) (oven temp 100-110 °C, <1 mmHg) as a mixture of isomers at the allylic double bond (*E*:*Z* 27:73): ^1H NMR (300 MHz) ($CDCl_3$) δ (*E* isomer) 1.53-1.68 (m, 1 H), 1.72 (dd, *J* = 1.7, 6.9 Hz, 3 H), 1.81-2.12 (m, 3 H), 3.16 (m, 1 H), 3.28 (m, 1 H), 3.80 (q, *J* = 7.2 Hz, 1 H), 5.11 (d, *J* = 13.8 Hz, 1 H), 5.32 (m, 1 H), 5.68 (m, 1 H), 6.92 (m, 1 H), 6.93 (d, *J* = 13.8 Hz, 1 H), 7.11-7.23 (m, 4 H), (*Z* isomer) 1.53-1.68 (m, 1 H), 1.75 (dd, *J* = 1.8, 6.9 Hz, 3 H), 1.81-2.12 (m, 3 H), 3.16 (m, 1 H), 3.28 (m, 1 H), 4.20 (bq, *J* = 7.1 Hz, 1 H), 5.11 (d, *J* = 13.8 Hz, 1 H), 5.32 (ddq, *J* = 9.0, 10.8, 1.8 Hz, 1 H), 5.66 (ddq, *J* = 1.1, 10.8, 6.9 Hz, 1 H), 6.92 (m, 1 H), 6.93 (d, *J* = 13.8 Hz, 1 H), 7.11-7.23 (m, 4 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*E* isomer) 23.4, 32.9, 46.7, 56.7, 63.8, 97.5, 122.8, 123.3, 127.7, 128.1, 132.9, 135.0, 140.2, (*Z* isomer) 23.8, 32.9, 46.7, 56.7, 63.6, 97.8, 122.8, 123.3, 126.8, 128.1, 132.3, 134.5, 140.1; IR (neat) 3080, 3061, 3029, 2975, 2924, 2875, 1690, 1634, 1601, 1495, 1453, 1121, 1030, 970, 752, 700 cm^{-1}.

General Procedure for HCl Promoted Rearrangement and Reduction:

The procedure was identical to the the general HCl promoted rearrangement procedure in Chapter III with the exception that toluene was used as the solvent and reduction of the cyclohexanone derived substrate was carried out with DIBAH (3 eq.).

IV-20b: 0.687 g (3.4 mmol, 86% yield, 8% de), (oven temp 60-70 °C, 5 mmHg): ^1H NMR (500 MHz) ($CDCl_3$) (major isomer) δ 0.81 (s, 3 H), 0.83 (s, 3 H), 0.91 (d, *J* = 7.0 Hz, 3 H), 1.10 (d, *J* = 6.2 Hz, 3 H), 2.14 (quint, *J* = 7.4 Hz, 1 H), 2.31 (d, *J* = 11.5 Hz, 1 H), 2.37 (d, *J* = 11.5 Hz, 1 H), 2.51 (dd, *J* = 4.1, 10.7 Hz, 1 H), 2.58 (dd, *J* = 7.6, 10.7 Hz, 1 H), 3.32 (s, 3 H), 3.44 (m, 1 H), 4.89-4.98 (m, 2 H), 5.76 (ddd, *J* = 8.6, 10.3, 18.9 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) (major isomer) δ 14.7, 17.1, 22.9, 23.0, 36.2, 44.4, 56.1, 56.5, 59.6, 76.0, 114.0, 141.7; (minor isomer) 14.7, 17.0, 23.0, 22.9, 36.2,

44.5, 56.2, 56.4, 59.5, 75.9, 114.0, 141.8; IR (neat) 3343, 3075, 2973, 2878, 2822, 1636, 1458, 1373, 1128, 1088, 999, 912, 812 cm^{-1}; HRMS calcd for $C_{12}H_{25}NO$ *m/e* 199.1936, obsd *m/e* 199.1922.

IV-32b: (0.465 g, 1.6 mmol) in 54% yield as a mixture of diastereomers (95:5) (oven temp 85-100 °C, <1 mmHg): ^1H NMR (500 MHz) ($CDCl_3$) δ (major isomer) 0.71 (d, *J* = 6.6 Hz, 6 H), 0.81 (t, *J* = 6.6 Hz, 3 H), 0.86-1.32 (m, 7 H), 1.34 (s, 3 H), 1.59 (non, *J* = 6.6 Hz, 1 H), 2.19-2.30 (m, 2 H), 2.60 (d, *J* = 11.5 Hz, 1 H), 2.83 (d, *J* = 11.5 Hz, 1 H), 5.07 (dd, *J* = 2.3, 16.9 Hz, 1 H), 5.11 (dd, *J* = 2.3, 9.9 Hz, 1 H), 5.63 (dt, *J* = 16.9, 9.9 Hz, 1 H), 7.15-7.36 (m, 5 H); (minor isomer) 0.73 (d, *J* = 6.6 Hz, 6 H), 0.83 (t, *J* = 6.6 Hz, 3 H), 0.86-1.32 (m, 7 H), 1.39 (s, 3 H), 1.66 (non, *J* = 6.6 Hz, 1 H), 2.27-2.43 (m, 2 H), 2.72 (d, *J* = 11.5 Hz, 1 H), 3.01 (d, *J* = 11.5 Hz, 1 H), 4.78 (dd, *J* = 2.1, 17.1 Hz, 1 H), 4.92 (dd, *J* = 2.1, 10.3 Hz, 1 H), 5.42 (dt, *J* = 17.1, 10.3 Hz, 1 H), 7.15-7.36 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 13.9, 17.7, 20.4, 20.5, 22.3, 27.5, 28.3, 29.9, 44.8, 53.2, 58.6, 60.6, 116.8, 125.7, 126.8, 128.1, 139.6, 146.0; (minor isomer) 14.0, 17.7, 20.6, 21.1, 22.6, 27.7, 28.2, 30.3, 44.7, 53.8, 58.1, 58.9, 116.3, 125.6, 127.1, 127.8, 139.3, 145.4; IR (neat) (neat) 3341, 3061, 3025, 2957, 2932, 2872, 2809, 1684, 1466, 1379, 1121, 912, 700 cm^{-1}; HRMS calcd for $C_{20}H_{33}N$ *m/e* 287.2613, obsd *m/e* 287.2614.

IV-32c: (0.692 g, 2.8 mmol) in 69% yield as a mixture of diastereomers (54:46) (oven temp 75-85 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ (major isomer) 0.85 (t, *J* = 6.7 Hz, 3 H), 0.89 (d, *J* = 6.5 Hz, 6 H), 1.0-1.74 (m, 16 H), 1.79-2.00 (m, 2 H), 2.14 (dd, *J* = 6.7, 11.2 Hz, 1 H) 2.47 (dd, *J* = 6.4, 11.2 Hz, 1 H), 2.82 (q, *J* = 2.5 Hz, 1 H), 4.91 (dd, *J* = 2.2, 17.0 Hz, 1 H) 4.93 (dd, *J* = 2.2, 10.1 Hz, 1 H), 5.47 (ddd, *J* = 9.8, 10.1, 17.0 Hz, 1 H); (minor isomer) 0.83 (t, *J* = 6.7 Hz, 3 H), 0.86 (d, *J* = 6.7 Hz, 6 H), 1.0-1.74 (m, 16 H), 1.79-2.00 (m, 2 H), 2.06 (dd, *J* = 6.7, 11.2 Hz, 1 H) 2.38 (dd, *J* = 6.4, 11.2 Hz, 1 H), 2.67 (q, *J* = 2.8 Hz, 1 H), 4.94 (dd, *J* = 2.2, 17.0 Hz, 1 H) 4.96 (dd, *J* = 2.2, 10.1 Hz, 1 H), 5.53 (ddd, *J* = 9.8, 10.1, 17.0 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major

isomer) 14.1, 19.9, 20.9, 21.0, 22.8, 25.4, 26.7, 28.7, 29.3, 31.1, 45.1, 46.7, 53.7, 55.9, 114.9, 143.0; (minor isomer) 14.0, 20.0, 20.8, 21.0, 22.8, 24.8, 26.7, 28.8, 29.4, 31.8, 45.6, 46.4, 54.1, 55.7, 114.4, 142.3; IR (neat) 3360, 3074, 2955, 2930, 2857, 1640, 1469, 1377, 1105, 998, 909 cm^{-1}; HRMS calcd for $C_{17}H_{33}N$ *m/e* 251.2613, obsd *m/e* 251.2606.

IV-36b: (0.778 g, 3.0 mmol) in 75% yield as a mixture of diastereomers (90:10) (oven temp 80-100 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ (mixture of isomers) 0.40 (bs, 1 H), 0.63 (d, J = 6.7 Hz, 3 H), 0.69 (d, J = 6.7 Hz, 3 H), 0.72 (d, J = 6.7 Hz, 3 H), 1.29 (s, 3 H), 1.57 (m, 1 H), 1.67 (d, J = 5.3 Hz, 3 H), 2.16-2.34 (m, 2 H), 2.47 (quint, J = 7.8 Hz, 1 H), 2.59 (d, J = 11.4 Hz, 1 H), 2.83 (d, J = 11.4 Hz, 1 H, major isomer), 2.96 (d, J = 11.4 Hz, 1 H, minor isomer), 5.09-5.29 (m, 2 H, minor isomer), 5.30-5.58 (m, 2 H, major isomer), 7.11-7.21 (m, 2 H), 7.24-7.37 (m, 3 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 15.9, 17.4, 18.1, 20.4, 20.5, 27.6, 45.0, 45.7, 58.8, 60.4, 125.4, 125.6, 126.8, 128.1, 133.6, 146.2, (minor isomer) 15.1, 17.2, 18.0, 20.1, 20.6, 27.7, 44.8, 45.4, 58.3, 59.8, 124.7, 125.7, 127.1, 127.8, 133.5, 145.6; IR (neat) 3375, 3090, 3059, 3025, 2959, 2925, 2876, 2809, 1497, 1464, 1379, 1121, 1030, 970, 764, 700 cm^{-1}; HRMS calcd for $C_{18}H_{29}N$ *m/e* 259.2300, obsd *m/e* 259.2286.

General Procedure for the $TiCl_4$ Promoted Rearrangement and Reduction:

The procedure was identical to the the general $TiCl_4$ promoted rearrangement procedure in Chapter III with the exception that reduction of the cyclohexanone derived substrate was carried out with DIBAH (3 eq.).

IV-20a: (0.923 g, 4.6 mmol) in 77% yield (15% de) (oven temp 60-70 °C, 5 mmHg): ^1H NMR (500 MHz) ($CDCl_3$) δ 0.82 (s, 3 H), 0.83 (s, 3 H), 0.92 (d, J = 7.0 Hz, 3 H), 0.96 (d, J = 6.4 Hz, 3 H), 1.40 (bs, 1 H), 2.14 (dq, J = 8.5, 7.0 Hz, 1 H), 2.31 (d, J = 11.3 Hz, 1 H), 2.42 (d, J = 11.3 Hz, 1 H), 2.73 (m, 1 H), 3.22-3.25 (m, 2 H), 3.32 (s, 3 H), 4.92-4.99 (m, 2 H), 5.76 (ddd, J = 8.5, 10.3, 17.1 Hz, 1 H), (minor isomer) 0.81 (s, 3 H), 0.83 (s, 3 H), 0.91 (d, J = 7.0 Hz, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 1.40 (bs, 1 H), 2.14 (dq,

J = 8.6, 7.0 Hz, 1 H), 2.28 (d, J = 11.5 Hz, 1 H), 2.41 (d, J = 11.5 Hz, 1 H), 2.73 (m, 1 H), 3.22-3.25 (m, 2 H), 3.32 (s, 3 H), 4.92-4.99 (m, 2 H), 5.77 (ddd, J = 8.5, 10.3, 17.1 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 14.7, 17.2, 22.9, 35.9, 44.2, 53.3, 56.9, 58.6, 77.2, 114.0, 141.5; (minor isomer) 14.6, 17.3, 22.8, 35.9, 44.2, 53.3, 56.7, 58.7, 77.1, 114.0, 141.6; IR 3341, 3075, 2967, 2874, 2826, 1635, 1474, 1458, 1370, 1111, 912 cm^{-1}; HRMS calcd for $C_{12}H_{25}NO$ *m/e* 199.1936, obsd *m/e* 199.1940.

IV-20b: (0.854 g, 4.3 mmol) 72% yield (20% de) (oven temp 60-70 °C, 5 mmHg): Spectral data were consistent with that reported for the HCl promoted rearrangement.

IV-32b: (0.411 g, 1.4 mmol) in 48% yield as a mixture of diastereomers (80:20) (oven temp 85-100 °C, <1 mmHg): Spectral data were consistent with that reported for the HCl promoted rearrangement.

IV-32c: (0.635 g, 2.5 mmol) in 72% yield as a mixture of diastereomers (55:45) (oven temp 75-85 °C, <1 mmHg): Spectral data were consistent with that reported for the HCl promoted rearrangement.

IV-36b: (0.65 g, 2.52 mmol) in 84% yield as a mixture of diastereomers (90:10) (oven temp 80-90 °C, <1 mmHg): Spectral data were consistent with that reported for the HCl promoted rearrangement.

General Procedure for the $AlMe_3$ Promoted Rearrangement and Reduction:

The procedure was identical to the the general $AlMe_3$ promoted rearrangement procedure in Chapter III with the exception that reduction of the cyclohexanone derived substrate was carried out with DIBAH (3 eq.).

IV-32a: (0.693 g, 3.1 mmol) in 88% yield as a mixture of diastereomers (62:38) (oven temp 55-65 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ (major isomer) 0.84-0.89 (m, 12 H), 1.05-1.47 (m, 3 H), 1.51 (sept, J = 6.3 Hz, 2 H), 1.89 (dsept, J = 6.8, 5.6 Hz, 1 H), 2.06 (t, J = 7.2 Hz, 2 H), 2.42-2.62 (m, 4 H), 3.06 (m, 1 H), 3.38 (s, 3 H), 4.95-

5.04 (m, 2 H), 5.73-5.82 (m, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 10.7, 17.5, 18.2, 24.3, 29.2, 36.1, 39.3, 49.9, 53.1, 57.8, 85.2, 115.5, 138.8, (minor isomer) 10.8, 17.5, 18.2, 24.1, 29.2, 36.0, 39.2, 49.8, 53.0, 57.8, 85.2, 115.5, 138.8; IR (neat) cm^{-1}; HRMS calcd for $C_{15}H_{31}N$ *m/e* 225.2456, obsd *m/e* 225.2439.

IV-32b: (0.740 g, 2.6 mmol) in 86% yield as a mixture of diastereomers (68:32) (oven temp 85-100 °C, <1 mmHg): Spectral data were consistent with that reported for the HCl promoted rearrangement.

IV-32c: (0.940 g, 3.7 mmol) in 94% yield as a mixture of diastereomers (67:33) (oven temp 75-85 °C, <1 mmHg): Spectral data were consistent with that reported for the HCl promoted rearrangement.

IV-36a: (0.771 g, 3.9 mmol) in 78% yield as a single diastereomer (>98:2) (oven temp 65-75 °C, 5 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (bs, 1 H), 0.84 (t, J = 7.0 Hz, 3 H), 0.86 (d, J = 6.4 Hz, 6 H), 0.91 (d, J = 7.0 Hz, 3 H), 1.20-1.40 (m, 3 H), 1.61 (d, J = 4.5 Hz, 3 H), 1.70 (non, J = 6.7 Hz, 1 H), 2.18 (m, 1 H), 2.36 (d, J = 6.7 Hz, 2 H), 2.39 (dd, J = 6.0, 11.7 Hz, 1 H), 2.50 (dd, J = 5.5, 11.7 Hz, 1 H), 5.25-5.42 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 11.6, 17.3, 18.0, 20.6, 22.1, 28.1, 37.5, 45.1, 50.9, 58.4, 123.6, 135.8; IR (neat) 3360, 3025, 2981, 2934, 2874, 2815, 1464, 1379, 1125, 968, 742 cm^{-1}; HRMS calcd for $C_{13}H_{27}N$ *m/e* 197.2143, obsd *m/e* 197.2147.

IV-36b: (1.002 g, 3.88 mmol) in 97% yield as a mixture of diastereomers (80:20) (oven temp 80-90 °C, <1 mmHg): Spectral data were consistent with that reported for the HCl promoted rearrangement.

IV-36c: (0.847 g, 3.8 mmol) in 95% yield as a mixture of diastereomers (>95:5) (oven temp 55-65 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ (major isomer) 0.81 (d, J = 7.0 Hz, 3 H), 0.85 (d, J = 6.7 Hz, 6 H), 0.90-1.25 (m, 7 H), 1.50-1.68 (m, 3 H), 1.60 (d, J = 4.5 Hz, 3 H), 1.95 (m, 1 H), 2.14-2.25 (m, 2 H), 2.47 (dd, J = 6.7, 11.2 Hz, 1 H), 2.56 (m, 1 H), 5.25-5.43 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 13.5, 18.0, 20.7, 20.8, 25.0, 25.4, 25.9, 28.7, 32.6, 34.8, 47.5, 54.9, 57.9, 122.9, 137.0,

(minor isomer) 13.5, 18.0, 20.7, 20.9, 25.2, 25.7, 26.1, 28.7, 32.4, 36.0, 47.9, 54.8, 58.4, 124.1, 134.0; IR (neat) 3380, 3025, 2955, 2928, 2870, 2859, 1470, 1458, 1377, 1105, 968, 702 cm^{-1}. HRMS calcd for $C_{15}H_{29}N$ *m/e* 223.2300, obsd *m/e* 223.2300.

General Procedure for the Me_2AlCl Promoted Rearrangement and Reduction:

The procedure was identical to the the general $AlMe_3$ promoted rearrangement procedure in Chapter III with the exception that $AlMe_2Cl$ was used instead of $AlMe_3$, and reduction of the cyclohexanone derived substrate was carried out with DIBAH (3 eq.).

IV-26: (0.955 g, 4.5 mmol) in 56% yield as a mixture of diastereomers (55:45) (oven temp 65-75 °C, 4 mmHg): ^1H NMR (500 MHz) ($CDCl_3$) δ (major isomer) 0.86 (d, J = 7.6 Hz, 3 H), 0.87 (t, J = 8.2 Hz, 3 H), 0.91 (d, J = 7.0 Hz, 3 H), 1.33 (m, 4 H), 1.51 (sept, J = 6.3 Hz, 2 H), 1.89 (dsept, J = 6.8, 5.6 Hz, 1 H), 2.06 (t, J = 7.2 Hz, 2 H), 2.42-2.62 (m, 4 H), 3.06 (m, 1 H), 3.38 (s, 3 H), 4.95-5.04 (m, 2 H), 5.73-5.82 (m, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 10.7, 17.5, 18.2, 24.3, 29.2, 36.1, 39.3, 49.9, 53.1, 57.8, 85.2, 115.5, 138.8, (minor isomer) 10.8, 17.5, 18.2, 24.1, 29.2, 36.0, 39.2, 49.8, 53.0, 57.8, 85.2, 115.5, 138.8; IR (neat) 3345, 3077, 2961, 2932, 2876, 2822, 1640, 1464, 1385, 1094, 995, 910, 771 cm^{-1}; HRMS calcd for $C_{13}H_{27}NO$ *m/e* 213.2092, obsd *m/e* 213.2084.

IV-32a: (0.724 g, 3.2 mmol) in 94% yield as a mixture of diastereomers (52:48) (oven temp 55-65 °C, <1 mmHg): Spectral data were consistent with that reported for the $AlMe_3$ promoted rearrangement.

IV-36a: (1.284 g, 6.48 mmol) in 81% yield as a single diastereomer (>98:2) (oven temp 65-75 °C, 5 mmHg): Spectral data were consistent with that reported for the $AlMe_3$ promoted rearrangement.

IV-41b: (0.712 g, 3.32 mmol) in 85% yield as a mixture of diastereomers (73:27) (oven temp 95-100 °C, <1 mmHg): ^1H NMR (500 MHz) ($CDCl_3$) δ (mixture of isomers) 0.79 (d, J = 7.9 Hz, 3 H, minor isomer), 0.82 (d, J = 6.6, 3 H, major isomer),

0.93 (bs, 1 H), 1.53 (m, 1 H, major isomer), 1.65 (m, 1 H, minor isomer), 1.77 (m, 1 H), 1.93 (m, 1 H), 2.24 (ddd, J = 2.2, 4.3, 10.8 Hz, 1 H), 2.56-2.72 (m, 2 H), 2.75-2.98 (m, 2 H), 3.02 (dd, J = 6.5, 13.1 Hz, 1 H), 3.51 (m, 1 H, major isomer), 3.63 (m, 1 H, minor isomer), 5.09 (t, J = 10.7 Hz, 1 H, minor isomer), 5.26 (t, J = 10.6 Hz, 1 H, major isomer), 5.56 (ddd, J = 6.0, 10.6, 17.0 Hz, 1 H, major isomer), 5.70 (ddd, J = 6.8, 10.7, 17.3 Hz, 1 H, minor isomer), 7.16-7.35 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 19.7, 22.6, 28.0, 32.3, 47.1, 48.2, 51.2, 52.5, 53.5, 126.0, 128.1, 128.4, 131.3, 135.4, 145.6, (minor isomer) 19.0, 21.9, 26.8, 30.4, 47.1, 49.0, 51.2, 52.5, 53.5, 126.1, 127.7, 129.1, 131.5, 135.4, 141.7; IR (neat) 3380, 3061, 3027, 2996, 2926, 2870, 1603, 1493, 1453, 1372, 1354, 1142, 763, 739, 702 cm^{-1}; HRMS calcd for $C_{15}H_{21}N$ *m/e* 215.1674, obsd *m/e* 215.1689.

General Procedure for the $(ArO)_2AlMe$ Promoted Rearrangement and Reduction:

To 2,6-diphenylphenol (2.2 eq.) in toluene was added a solution of $AlMe_3$ (1.1 eq, 2 *M* in toluene). The mixture was stirred for a minimum of 5 hours at room temperature and the enamine (1 eq.) was added The mixture was heated at reflux for 24 hours, then cooled to room temperature and $LiAlH_4$ (1.2 eq, 1 *M* in THF) or DIBAH (3 eq., 2 *M* in hexane) was added. The mixture was stirred for 2 hours (for $LiAlH_4$) or 24 hours (for DIBAH) and then quenched by careful addition of H_2O (1 mL/g $LiAlH_4$ or 3.7 g DIBAH), then 15% aq. NaOH (1 mL/g $LiAlH_4$ or 3.7 g DIBAH), and finally H_2O (3 mL/g $LiAlH_4$ or 3.7 g DIBAH), stirred for 1 hours, and filtered. The amines were purified by flash column chromatography where necessary (silica gel washed with Et_3N/Et_2O then washed with Et_2O, 50:50 Et_2O/petroleum ether) and distilled.

IV-32b: (1.003 g, 3.5 mmol) in 58% yield as a mixture of diastereomers (37:63) (oven temp 85-100 °C, <1 mmHg): Spectral data were consistent with that reported for the HCl promoted rearrangement.

IV-32c: (0.547 g, 2.2 mmol) in 73% yield as a mixture of diastereomers (77:23) (oven temp 75-85 °C, <1 mmHg): Spectral data were consistent with that reported for the HCl promoted rearrangement.

IV-36a: (0.592 g, 3.0 mmol) in 60% yield as a mixture of diastereomers (70:30) (oven temp 65-75 °C, 5 mmHg): Spectral data were consistent with that reported for the $AlMe_3$ promoted rearrangement.

IV-36b: (0.65 g, 2.52 mmol) in 84% yield as a mixture of diastereomers (90:10) (oven temp 80-90 °C, <1 mmHg): Spectral data were consistent with that reported for the HCl promoted rearrangement.

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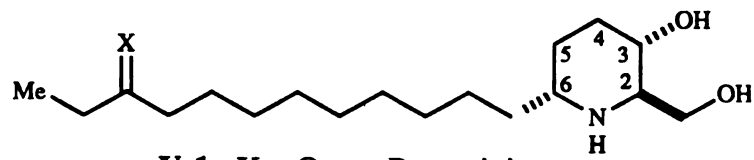
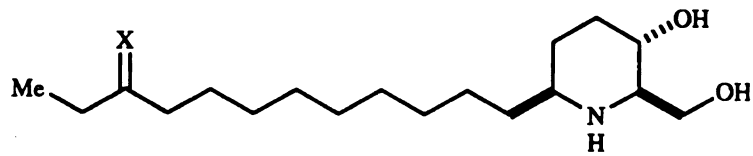
CHAPTER V. AZA-ANNULATION AS A ROUTE TO HYDROXYLATED ALKALOIDS. THE TOTAL SYNTHESIS OF (±)-PROSOPININE

Background: Isolation and Synthesis of *Prosopis Africana* Alkaloids

Seven piperidine alkaloids were isolated from *Prosopis africana* (African mimosa) over two decades ago, and their structures have been rigorously determined.[1] Two of these alkaloids, prosopinine (**V-1**) and its C-6 epimer prosophylline (**V-3**) (Figure V-1), have been a target for the synthetic efforts in this group. **V-1** has been shown to exhibit biological activities, including antibiotic and local anesthetic properties.[2] These alkaloids possess structural similarities to sphingosine (**V-5**) and deoxynorjirimycin (**V-6**) (Figure V-2). All of these compounds have an arrangement of hydroxyl groups with a stereochemical relationship indentical to glucose (**V-7**). **V-5** is a common membrane lipid, and **V-6** has exhibited antitumor and anti-HIV-1 properties through inhibition of α-glucosidase.[3] Compounds which combine the two structural features present in **V-5** and **V-6**, a polar head group and a lipophilic tail, may provide beneficial biological properties with the ability to penetrate cell membranes while simultaneously acting as a carbohydrate mimic. The *Prosopis* alkaloids contain both structural features, and more in-depth study of their properties is warranted.



V-1: X = O Prosopinine
V-2: X = H,H Desoxoprosopinine



V-3: X = O Prosophylline
V-4: X = H,H Desoxoprosophylline

FIGURE V-1. Structures of Some *Prosopis* Alkaloids

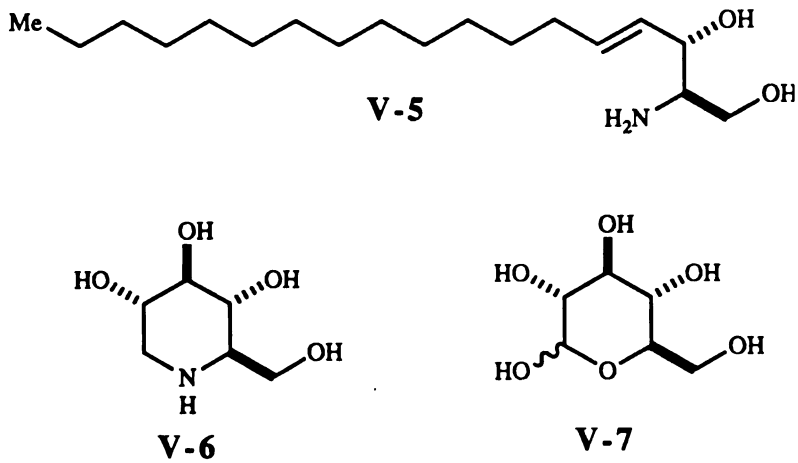
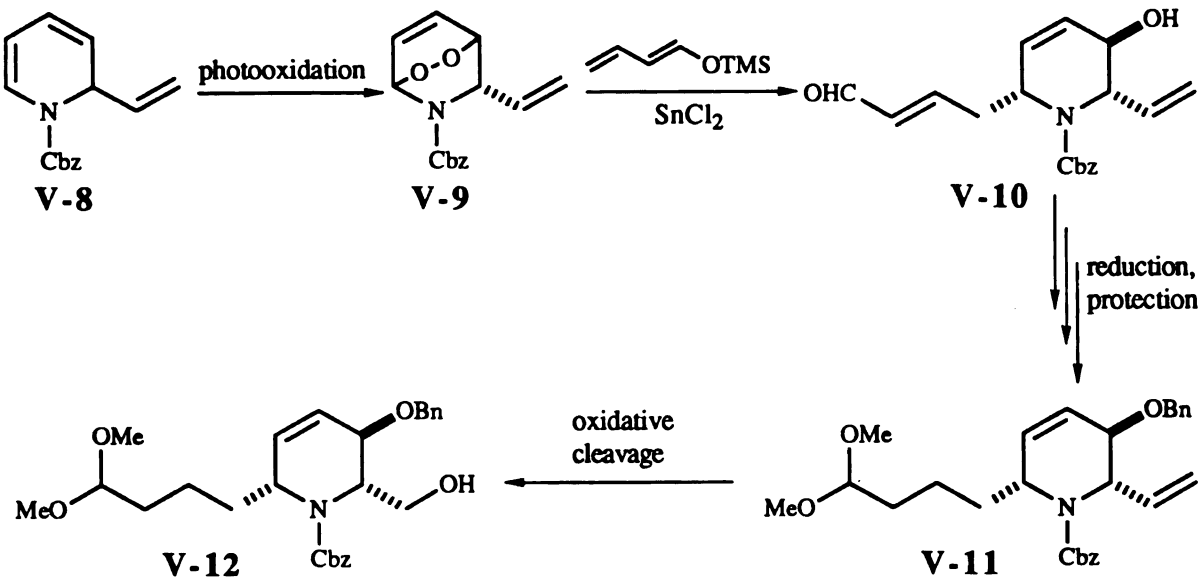


FIGURE V-2. Compounds with Similar Structural Features to *Prosopis* Alkaloids

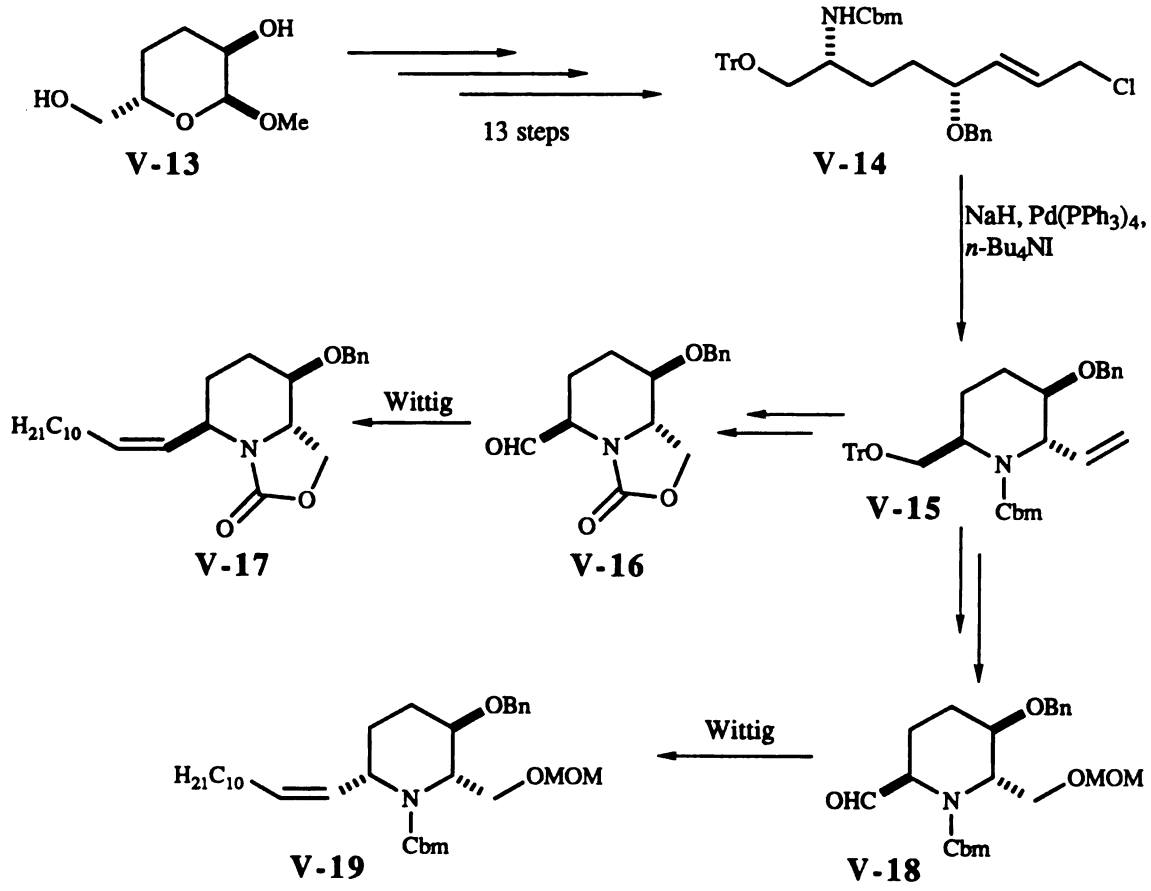
While prosopinine has not been prepared synthetically, the total synthesis of prosophylline (**V-3**),[4] desoxoprosopinine (**V-2**),[5] and desoxoprosophylline (**V-4**)[5a,5d,5e] has been reported. Three main objectives must be integrated in the design of a synthesis of *Prosopis* alkaloids. These include 1) construction of the piperidine ring, 2) establishment of the stereochemistry around the ring, and 3) the attachment of the aliphatic side chain. The key steps in the synthesis of prosophylline reported by Natsume[4] are shown in Scheme V-1. The nitrogen heterocycle **V-8** was prepared from pyridine, vinylmagnesium bromide, and benzyl chloroformate. Photooxidation gave an endoperoxide (**V-9**) which was opened by a $SnCl_2$-promoted addition of trimethylsilyloxybutadiene to give **V-10** with the proper stereochemical relationship for prosophylline. Selective reduction of the conjugated olefin and two protection steps afforded **V-11**. The vinyl group was cleaved under oxidative conditions to give hydroxylated derivative **V-12**. The synthesis of prosophylline was completed by homologation via a Wittig reaction, reduction, and deprotection in 2.7% overall yield from pyridine. The synthesis began with the 6-membered ring intact, and used the bicycloperoxide as a template to direct the stereochemistry. Since this was accomplished early, the total synthesis was comprised mainly of functional group manipulations.

SCHEME V-1. Synthetic Route to Prosophylline.



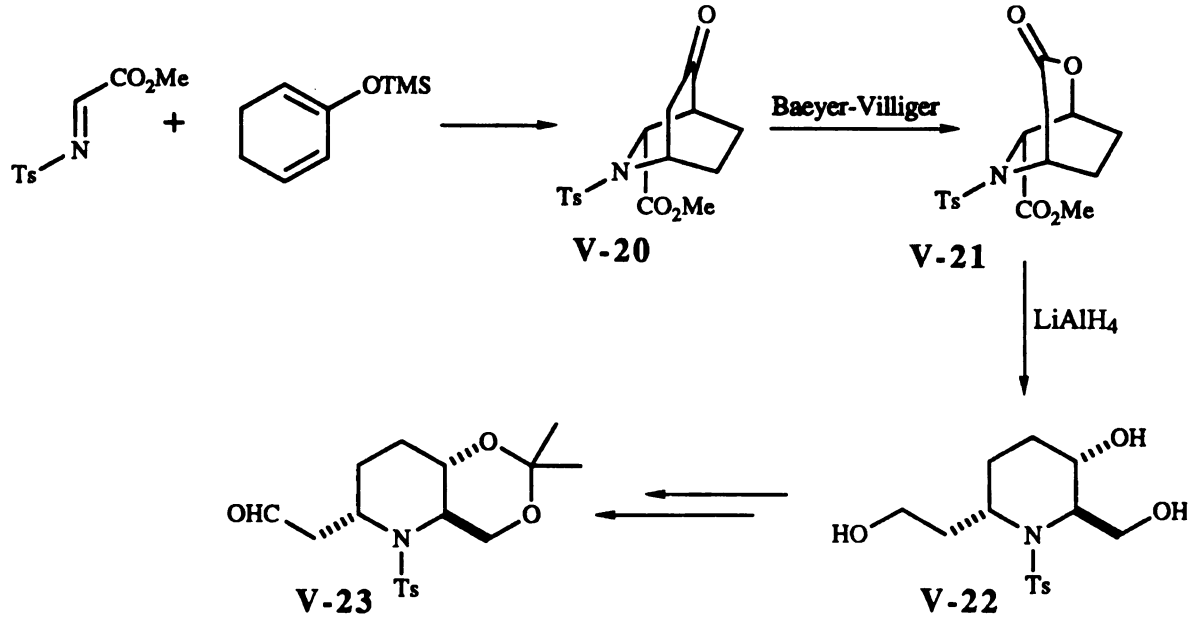
Tadano has reported a synthesis of (-)-desoxoprosopinine and (-)-desoxoprosophylline in which the piperidine ring was formed late in the synthetic sequence (Scheme V-2).[5a] Starting with **V-13**, prepared from D-glucose, **V-14** was obtained after 13 steps. Palladium (0) cyclization of **V-14** led to **V-15** as a 10:1 mixture of diastereomers. Oxidative cleavage of the olefin and protecting group modification afforded either **V-16** or **V-18**. Wittig olefination of **V-16** gave **V-17** as a mixture of olefin isomers, which was carried on to **V-2** in 11.6% overall yield from **V-13**. Interestingly, when **V-18**, which only differed from **V-16** in the protecting groups, was subjected to Wittig conditions, complete epimerization of the C-6 center was obtained. Thus, **V-19** was carried on to **V-4** in 8.3% overall yield. While the overall yields were very good, the synthesis was long, requiring 21 steps from **V-13**, over half of which were manipulations of the sugar derivative to prepare the cyclization precursor **V-14**. Another route to **V-2** and **V-4** was reported by Takahashi, in which an aminomercuration cyclization was used to prepare the piperidine ring very late in the synthesis.[5d, 5e]

SCHEME V-2. Route to (-)-Desoxoprosopinine and (-)-Desoxoprosophylline.



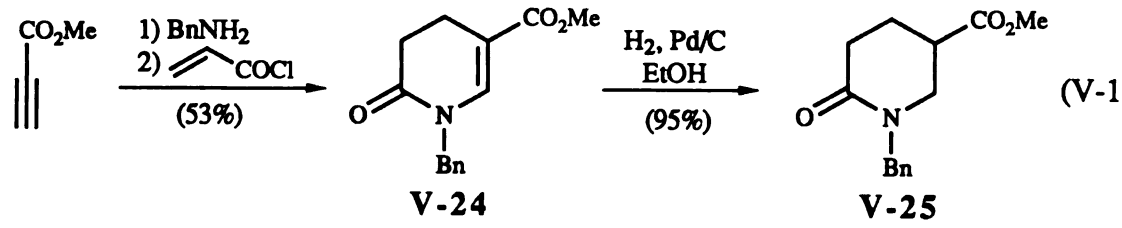
Holmes has reported a synthesis of **V-2** in which the nitrogen heterocycle was constructed via a hetero-Diels-Alder reaction to give **V-20** (Scheme V-3).[5c] The bicycloketone was obtained as a mixture of exo and endo isomers (57% and 24% respectively). Baeyer-Villiger oxidation provided the bicyclolactone **V-21** with the proper placement of oxygen functionality. Reduction with $LiAlH_4$ afforded triol **V-22** which was protected and oxidized to **V-23**. The aldehyde **V-23** was homologated, again, by Wittig olefination, and desoxoprosopinine (**V-2**) was obtained in 2.2% overall yield after reduction and deprotection. Here, as in the synthesis of prosophylline described above, the relative stereochemistry was controlled by utilizing a rigid bicyclic template. Although the selectivity of the Diels-Alder reaction was not optimal, this route consisted of only ten steps, and quick facile construction of the nitrogen heterocycle with the proper stereochemistry was accomplished.

SCHEME V-3. Route to (±)-Desoxoprosopinine.

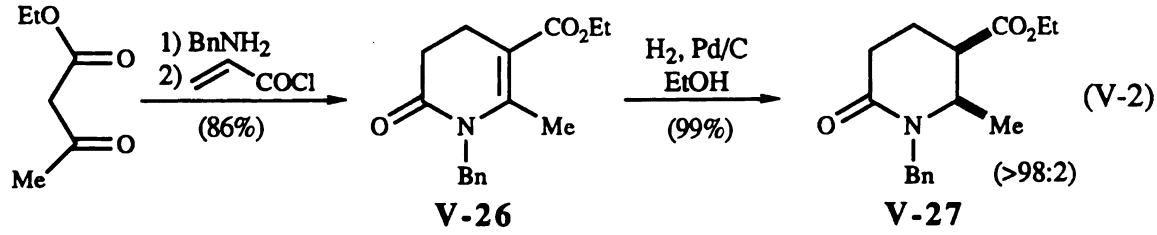


Model Studies for Alkaloid Synthesis

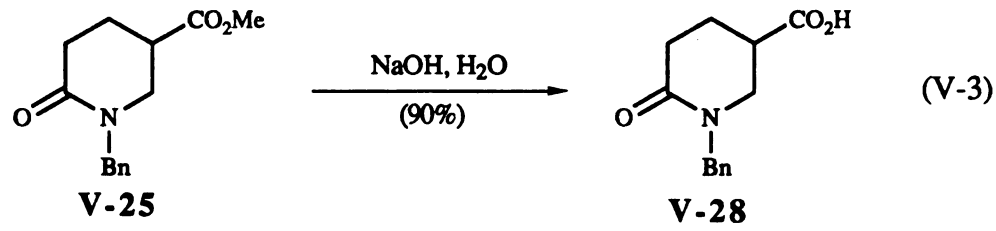
Aza-annulation methodology, recently developed in this group, quickly and efficiently provided suitably substituted piperidine derivatives for the construction of *Prosopis* alkaloids (see Chapter I). As models for the synthesis of **V-1** and **V-3**, compounds **V-25** and **V-27** were prepared (eq. V-1 and eq. V-2). Conjugate addition of benzylamine to methyl propiolate resulted in the formation of an enamine, which was annulated with acryloyl chloride to give **V-24** in 53% yield. **V-26** was prepared in an analogous manner by annulation of the enamine derived from benzylamine and ethyl acetoacetate. Reduction of the double bond gave lactams **V-25** and **V-27** in nearly quantitative yield. **V-27** was obtained as a single isomer detectable by NMR (*cis:trans*, >98:2). With the model substrates prepared, three aspects of the target synthesis were explored. These three requirements were 1) introduction of the C-2 substituent with proper stereochemical relationship to the C-3 substituent, 2) conversion of the C-3 carboxylate functionality to a hydroxyl group, and 3) homologation of the lactam carbonyl to append the lipid tail of the target compounds. Initial efforts were applied to the introduction of the C-2 substituent via conjugate addition. Treatment of **V-24** or **V-26** with a variety of cuprate reagents[6] failed to give addition products, and the starting lactams were recovered unchanged. Hydride reduction ($NaBH_4$) of the olefin was attempted as an alternate route to **V-27**, and, again, only starting materials were recovered. Apparently, the vinylogous carbamate was very stable, and would not succumb even to reaction with strong nucleophiles. Therefore, any functionality at this site needed to be in place prior to annulation.

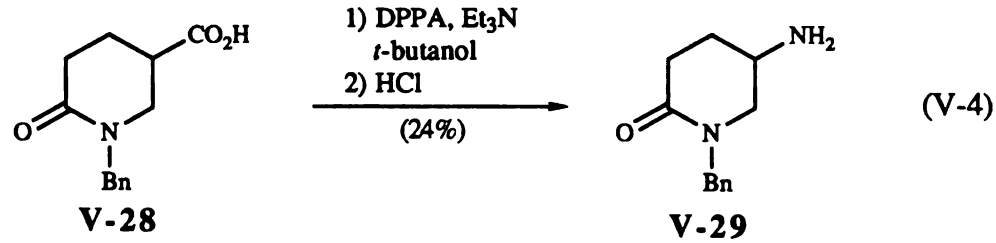


V-24 **V-25** (V-1)



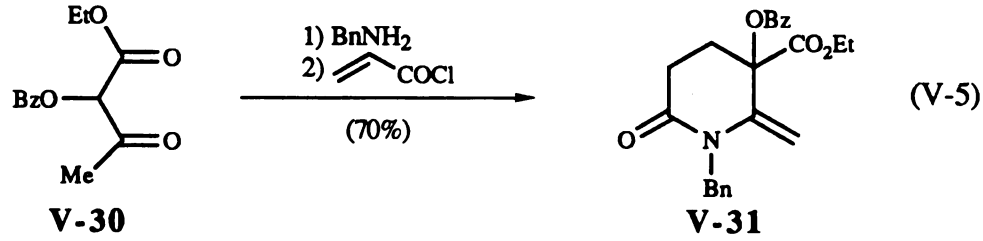
Attention was next directed toward conversion of the carboxylate group to a hydroxyl group. Several reports of oxidative decarboxylation of carboxylic acids have appeared,[7] thus **V-25** was hydrolyzed to **V-28** with NaOH (eq. V-3). Submission of the acid **V-28** to these literature reaction conditions resulted in the formation of complex product mixtures, from which a hydroxylated compound could not be isolated. A similar oxidative procedure for the introduction of an amino group was utilized (eq. V-4).[8] **V-28** was treated with DPPA in *t*-butanol at reflux, and the intermediate *t*-butylcarbamate was cleaved with HCl to give the primary amine **V-29** in low yield (24%).



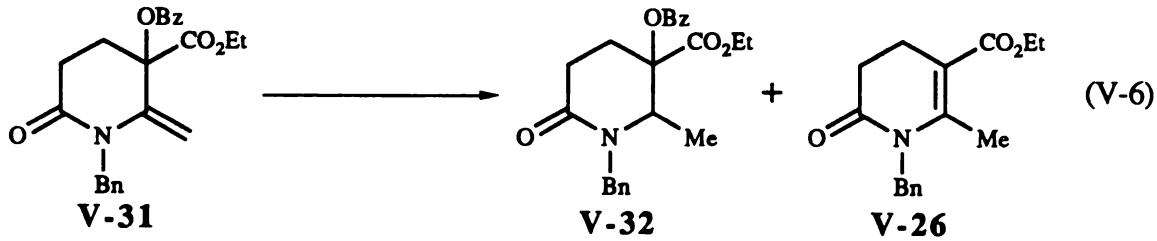


Periodate oxidation of diols[9] was another possible route for introducing the oxygen functionality. Toward this goal, the oxygenated lactam **V-31** was prepared. The ketoester **V-30** was obtained from benzoyl peroxide and ethyl acetoacetate by a known procedure.[10] Submitting **V-30** to the two-step annulation conditions afforded **V-31** in 70% yield (eq.

V-5). Attempts to hydrogenate the olefin resulted in the formation of two products (eq. V-6). Hydrogenation with 10% palladium on carbon gave the reduced lactam **V-32** and the enamide **V-26** in a 49:51 ratio respectively (ratio of diastereomers of **V-32**; 58:42). Reduction under basic conditions (Na_2CO_3), which has been reported to prevent deprotection of hydroxyl groups,[11] resulted in a decreased amount of the desired lactam (29:71, **V-32**:**V-26**). The use of platinum oxide as the reduction catalyst afforded similar mixtures (40:60, **V-32**:**V-26**). The elimination product, **V-26**, most likely arose from a π-allyl palladium intermediate. The chemistry of palladium-allyl species has been well documented.[12] It was unclear why **V-26** would not undergo further reduction to give **V-27** under these conditions. Perhaps the catalyst was poisoned by the presence of benzoate, or was tied up as π-allyl palladium species, and was unavailable for hydrogenation. Further studies on this substrate were not carried out.



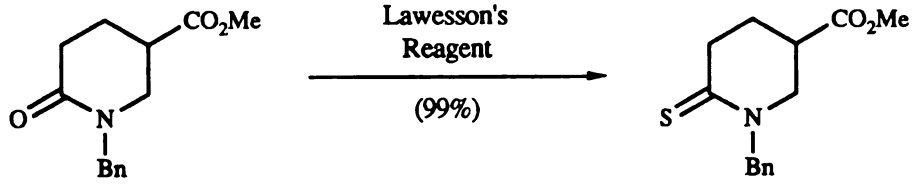
V-30 **V-31** (V-5)



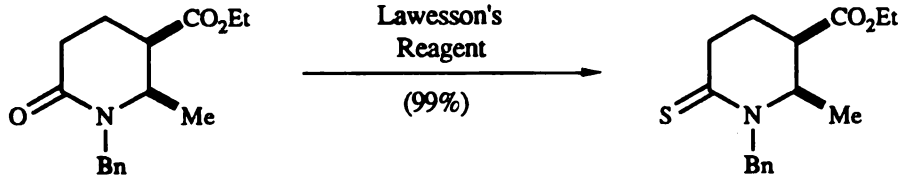
V-31 **V-32** **V-26** (V-6)

H_2, 10% Pd/C, EtOH	49 (58:42)	51
H_2, 10% Pd/C, EtOH, Na_2CO_3	29 (24:76)	71
H_2, PtO_2, EtOAc	40 (48:52)	60

While there are various methods reported for the homologation of lactam carbonyls, many of these procedures were found to be unproductive for our substrates. One such procedure was the selective addition of an alkynylborane to an amide carbonyl, followed by *in situ* reduction.[13] This borane reagent appeared ideal for our situation, as it was reported to react solely with the amide carbonyl in the presence of an ester. However, treatment of **V-25** or **V-27** to the reported conditions gave only traces of alkylated products, and the reaction mixture consisted mainly of starting lactam.



V-25 **V-33** (V-7)

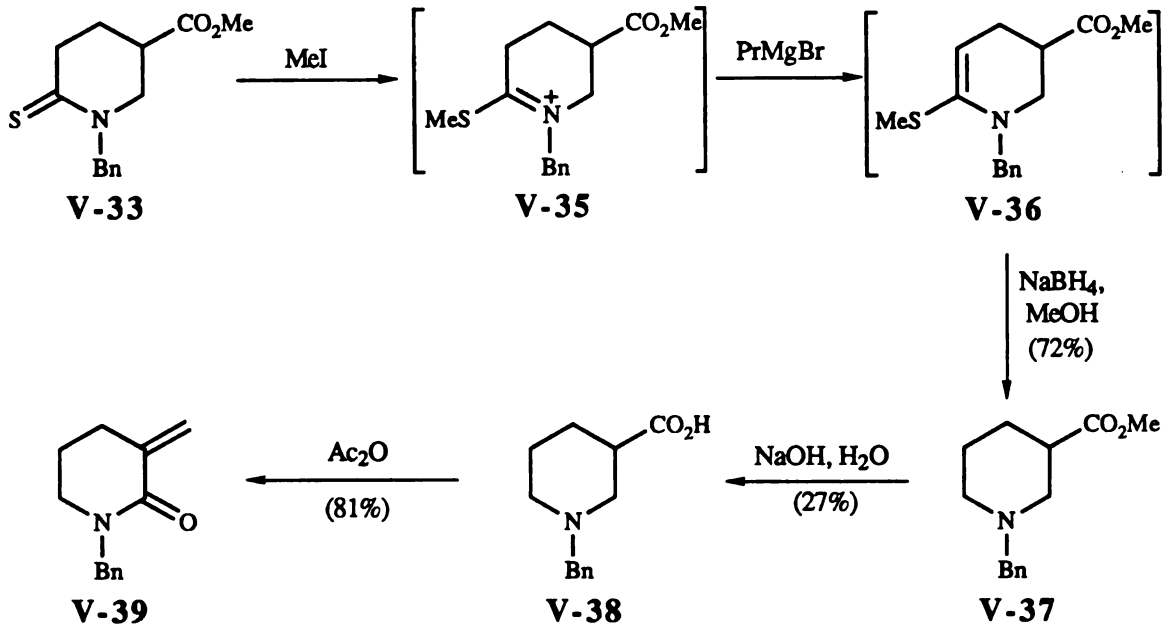


V-27 **V-34** (V-8)

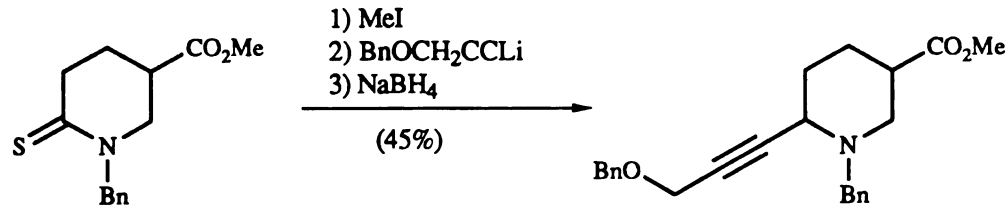
In order to explore other homologation routes, the thiolactams **V-33** and **V-34** were prepared in excellent yield (eq. V-7 and eq. V-8).[14] Methylation of **V-33** with MeI afforded a thioiminium salt (**V-35**) (Scheme V-4).[14] Attempts to introduce a C-6 alkyl substituent by Grignard addition to **V-35**, followed by reduction, led only to the formation of the reduced **V-37**. The Grignard reagent did not add to the electrophilic carbon, but simply deprotonated in the α position to give a *N,S*-ketene acetal (**V-36**). Although a C-6 alkylated product was not obtained, the formation of **V-37** afforded an opportunity to explore an interesting β-amino acid rearrangement.[15] Thus, **V-37** was hydrolyzed with base to the acid **V-38** in low yield. The acid was heated at reflux in acetic anhydride to give the α,β-unsaturated lactam **V-39** in good yield. Compounds with this structure have

been oxidized with ozone to give a C-3 oxygenated piperidine ring.[15] Therefore, if homologation of the lactam carbonyl of **V-25** or **V-33** could be accomplished, this rearrangement could be utilized to introduce functionality at C-3 once the C-6 substituent were in place.

SCHEME V-4. β-Amino Acid Rearrangement

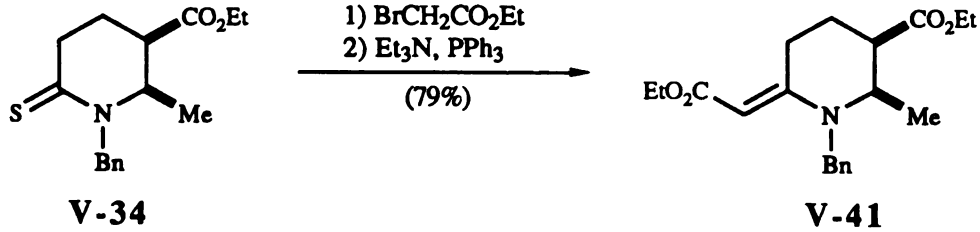


The addition of alkynyllithium reagents to thioiminium salts has been reported,[16] and this procedure was explored as a route to the target compound. Methylation of the thiolactam **V-33** was followed by addition of the alkynyl lithium reagent derived from benzyl protected propargyl alcohol. *In situ* reduction with $NaBH_4$ provided the piperidine **V-40** in 45% isolated yield as a mixture of diastereomers (63:37). The fully reduced **V-37** was a major by-product of this process. While the yield was only moderate, the alkylated product was obtained cleanly after silica gel chromatography. Unfortunately, treatment of **V-34**, which had a methyl substituent at C-2, under the same reaction conditions gave no alkylated product, and the only isolable material was the reduced piperidine analog of **V-37**.

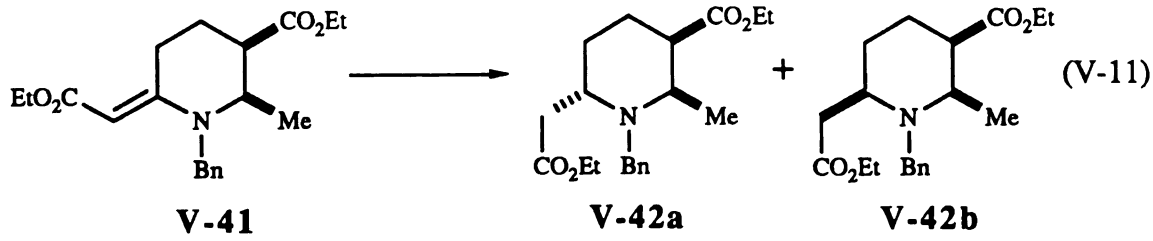


V-33 V-40 (V-9)

The homologation of thiolactams by an Eschenmoser sulfide contraction was next investigated. The thiolactam **V-34** was treated with ethyl bromoacetate to form an intermediate thioiminium salt, and the contraction/sulfide extrusion was accomplished with Et_3N and PPh_3 to afford the enaminoester **V-41** in 79% purified yield (eq. V-10).[17] **V-41** was obtained as a single isomer and was assumed to have *E* olefin geometry due to steric constraints. Hydride reduction at pH 4.0 selectively produced **V-42a** and **V-42b** in quantitative yield (92:8 respectively) (eq. V-11). The selectivity could be reversed by catalytic hydrogenation to give a 15:85 mixture of **V-42a** and **V-42b**.[18] The stereochemistry of each isomer was determined by NMR nuclear Overhauser enhancement (NOE) techniques (Figure V-3). The ability to selectively produce either isomer was opportune as **V-42a** possesed the proper stereochemical relationship between C-2 and C-6 as prosopinine (**V-1**), and **V-42b** was analogous to prosophylline (**V-3**).



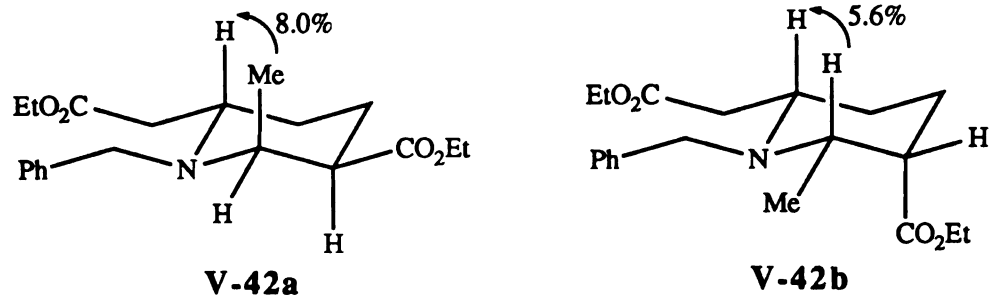
V-34 V-41 (V-10)



(V-11)

V-41 **V-42a** **V-42b**

$NaBH_3CN$, pH 4.0 (100%)	92	8
H_2, 10% Pd/C, Na_2CO_3	15	85

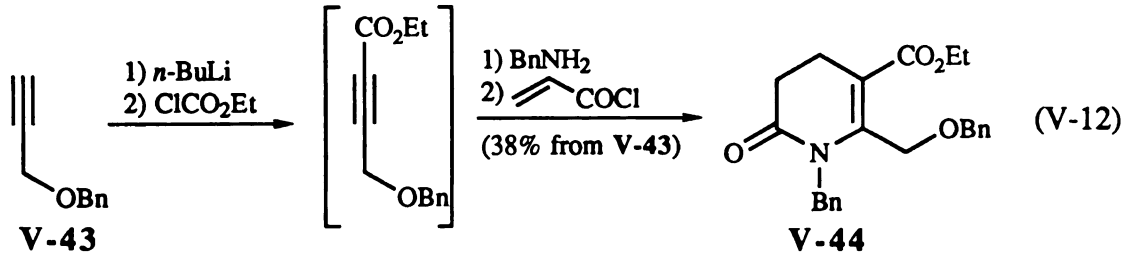


V-42a **V-42b**

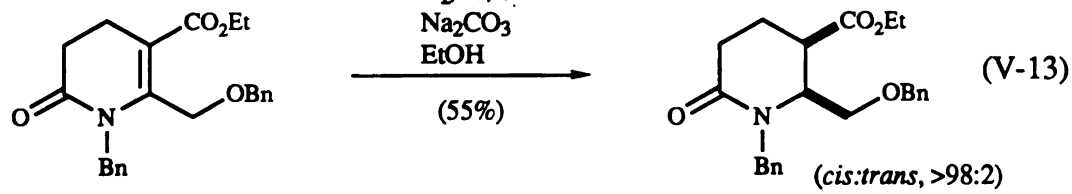
FIGURE V-3. NOE for **V-42a** and **V-42b**

Total Synthesis of (±)-Prosopinine

With an efficient method for homologation of the lactam carbonyl, the total syntheses of prosopinine (**V-1**) and prosophylline (**V-3**) were undertaken. The preparation of the six-membered nitrogen heterocycle with the hydroxyl functionality in place at the C-2 methylene is shown in eq. V-12 and eq. V-13. The benzyl protected propargyl alcohol (**V-43**) was deprotonated with *n*-BuLi, and acylation with ethyl chloroformate afforded an alkynyl ester. The ester was subjected to the two step condensation/aza-annulation conditions without purification to provide **V-44** in 38% overall yield. This yield has been increased to 55% overall by another member of this group[19] with the use of acrylic anhydride rather than acryloyl chloride. Hydrogenation with 10% Pd/C in the presence of Na_2CO_3, to preserve the benzyl protecting groups, gave lactam **V-45** in 55% yield (optimized to 80%[19]).

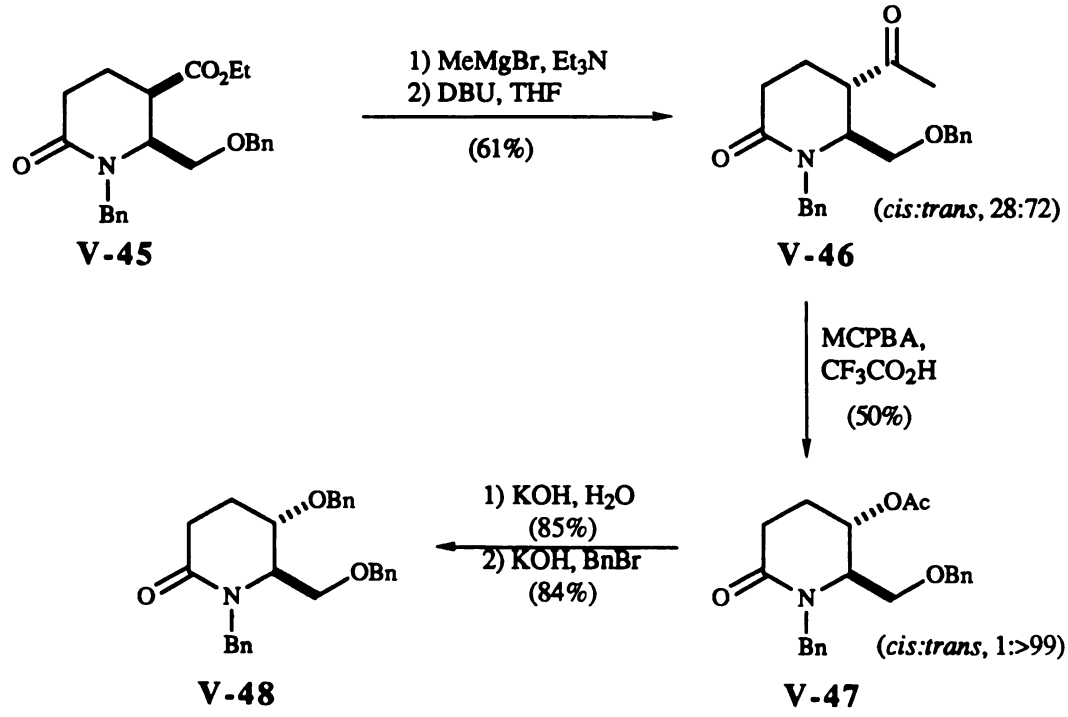


V-43 V-44



V-44 V-45

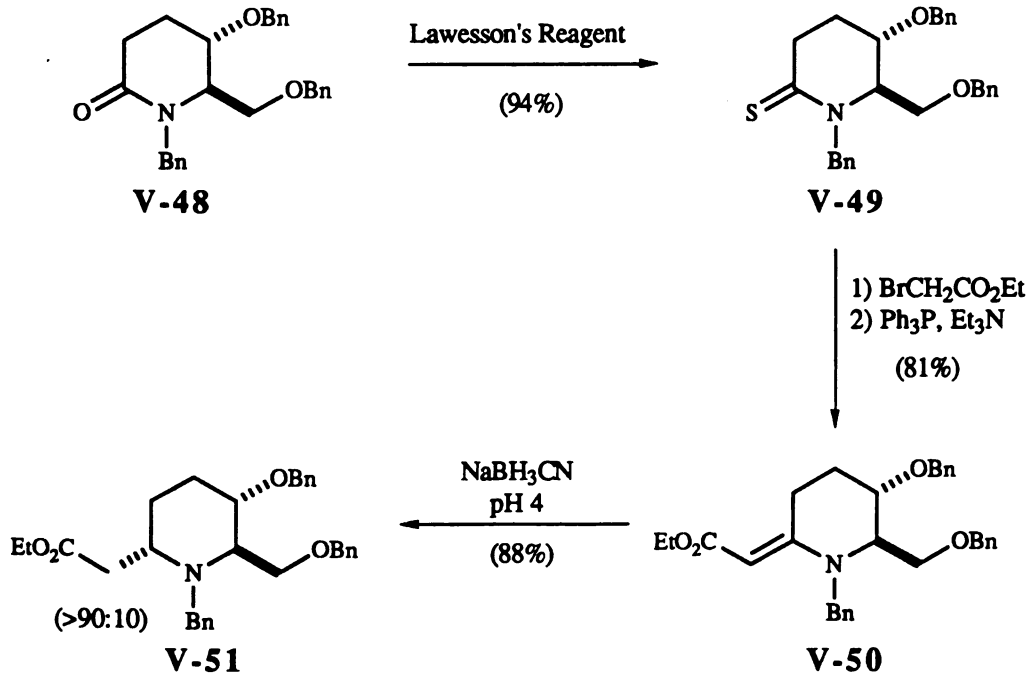
SCHEME V-5. Introduction of the C-3 Hydroxyl Substituent of Prosopinine[19]



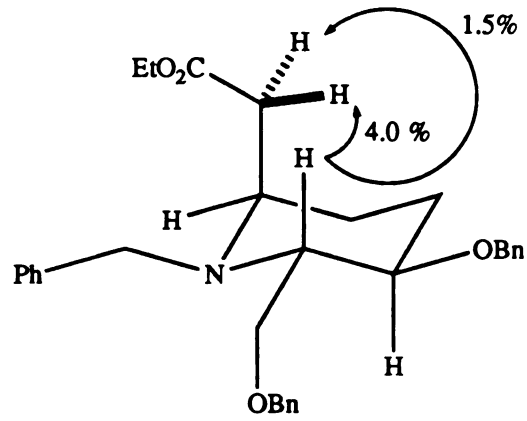
V-45 V-46 V-47 V-48

Since placement of the C-3 hydroxyl group could not be obtained directly from the carboxylate functionality, the ester was first converted to a ketone, and then subjected to Baeyer-Villiger oxidation conditions (Scheme V-5).[19] Careful addition of methyl magnesium bromide to **V-45**, in the presence of Et_3N,[20] was followed by base catalyzed isomerization at room temperature to give ketone **V-46** as mostly the *trans* isomer (*cis:trans*, 28:72). Baeyer-Villiger oxidation selectively produced *trans* **V-47** in 50% yield.[21] The acetate was hydrolyzed with KOH, and protected as the benzyl ether **V-48**. The δ-lactam template afforded the ability to control the relative stereochemistry of the C-2 and C-3 substituents for the synthesis of the target *Prosopis* alkaloids.

SCHEME V-6. Homologation of the Lactam Carbonyl

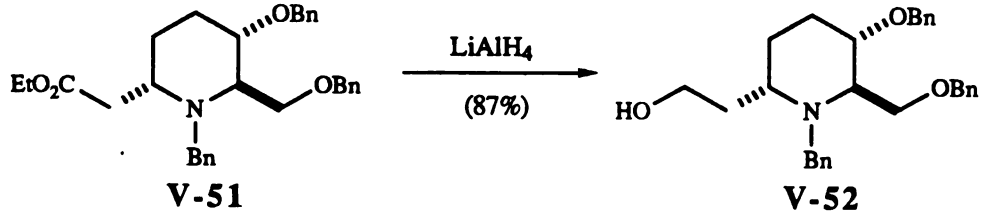


The C-6 alkyl substituent was introduced via the sulfide contraction process as described previously for **V-34**. Conversion of lactam **V-48** to **V-49** was accomplished in excellent yield (Scheme V-6), and the two step Eschenmoser sulfide contraction provided an 81% yield of **V-50**. $NaBH_3CN$ reduction gave the reduced piperidine **V-51** as the major isomer (>90:10), and the stereochemistry was established by NOE (Figure V-4). Unfortunately, **V-50** did not react in an analogous fashion towards catalytic hydrogenation as **V-41**, and the same major isomer (**V-51**) was obtained (67:33). The ester was reduced with $LiAlH_4$ to alcohol **V-52** in 87% yield in preparation for subsequent Wittig homologation.



V-51

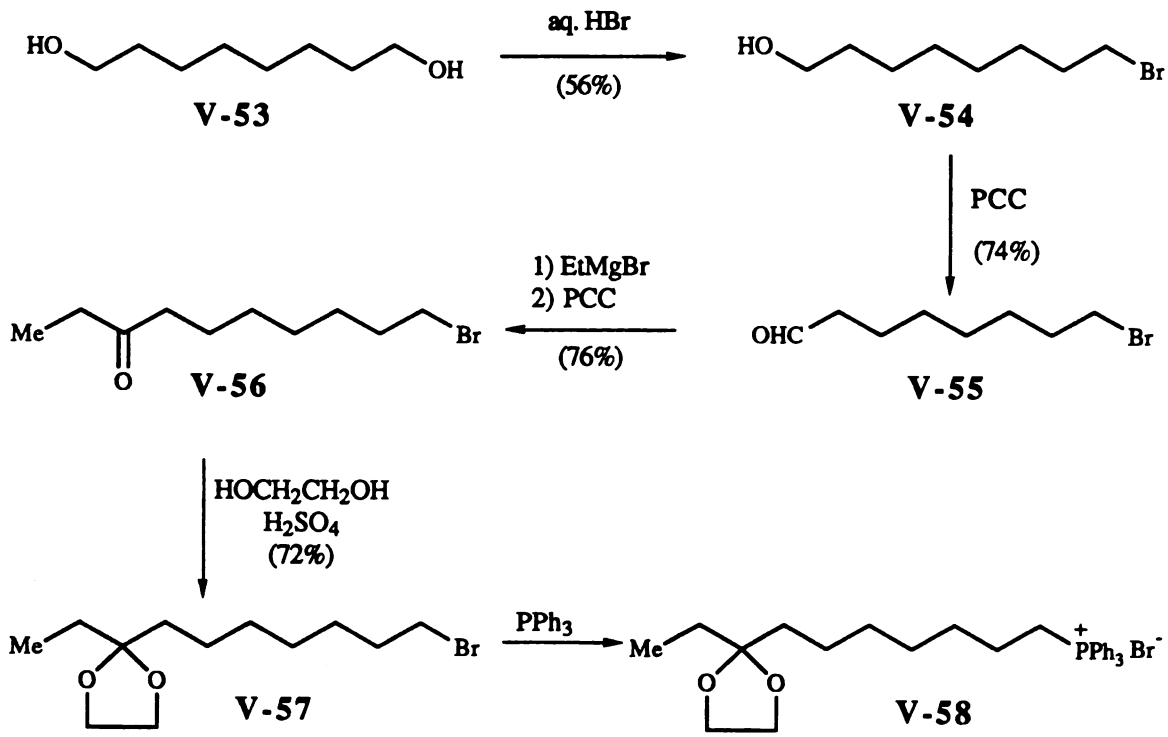
FIGURE V-4. NOE for **V-51**



V-51 **V-52** (V-14)

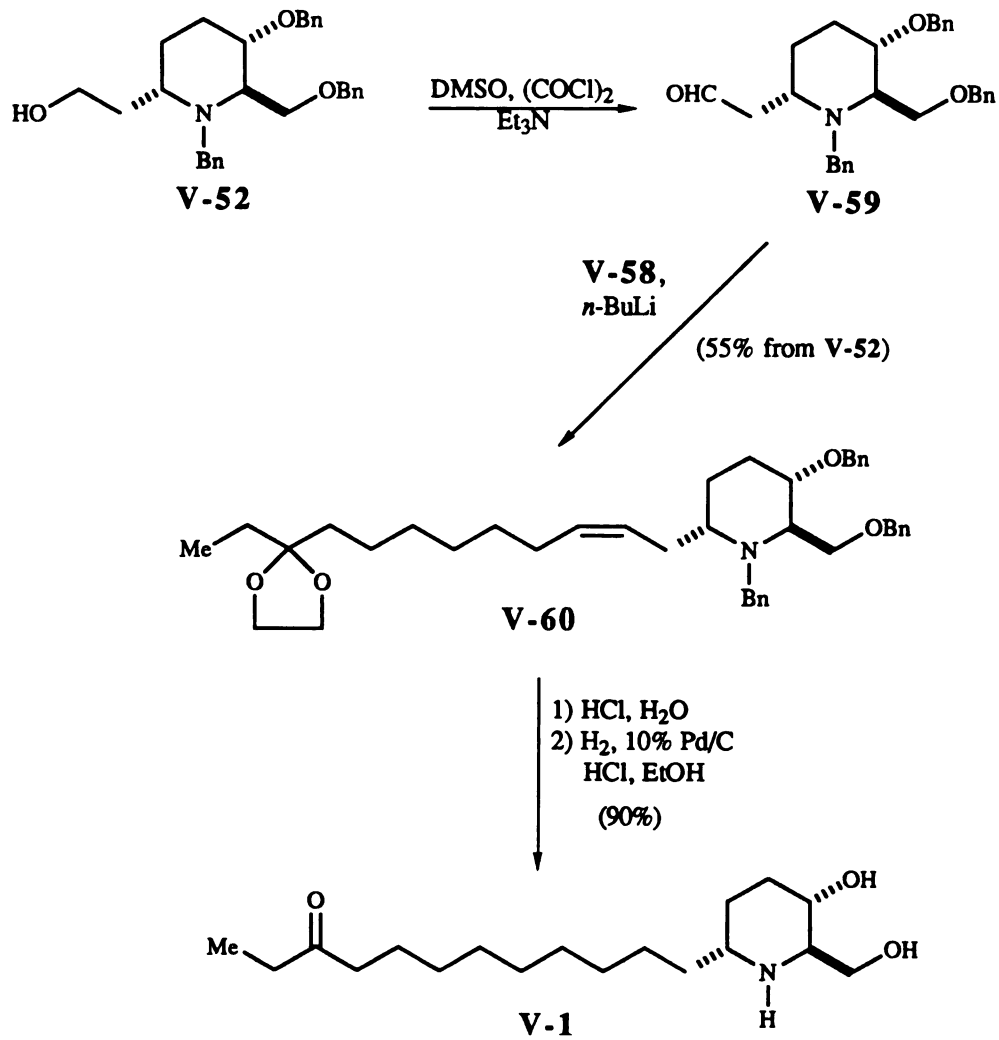
The aliphatic side chain was introduced via a Wittig olefination, and the preparation of the requisite phosphonium salt is described in Scheme V-7. Monobromination of diol **V-53** gave **V-54**,[22] which was oxidized with PCC to afford the corresponding aldehyde. The aldehyde was treated with ethyl magnesium bromide, and subsequent oxidation gave ketone **V-55** in 76% yield for the two steps. The ketone functionality was protected as the dioxolane, and treatment with PPh_3 gave the corresponding phosphonium salt **V-58**, which was used without isolation.

SCHEME V-7. Preparation of the Aliphatic Wittig Reagent



Completion of the synthesis of **V-1** is shown in Scheme V-8. Alcohol **V-52** was oxidized under Swern conditions to **V-59**, and olefination with the ylide of **V-58** gave **V-60** in 55% overall yield as an 85:15 mixture of *cis* and *trans* alkenes. Deprotection of the ketal was carried out with aq. HCl, and hydrogenation affected reduction of the alkene, with simultaneous removal of the benzyl groups, to give **V-1** in 90% yield. Thus, the total synthesis of prosopinine was accomplished in 3% overall yield from **V-43**.

SCHEME V-8. Wittig Homologation and Deprotection to Give (±)-Prosopinine (**V-1**)



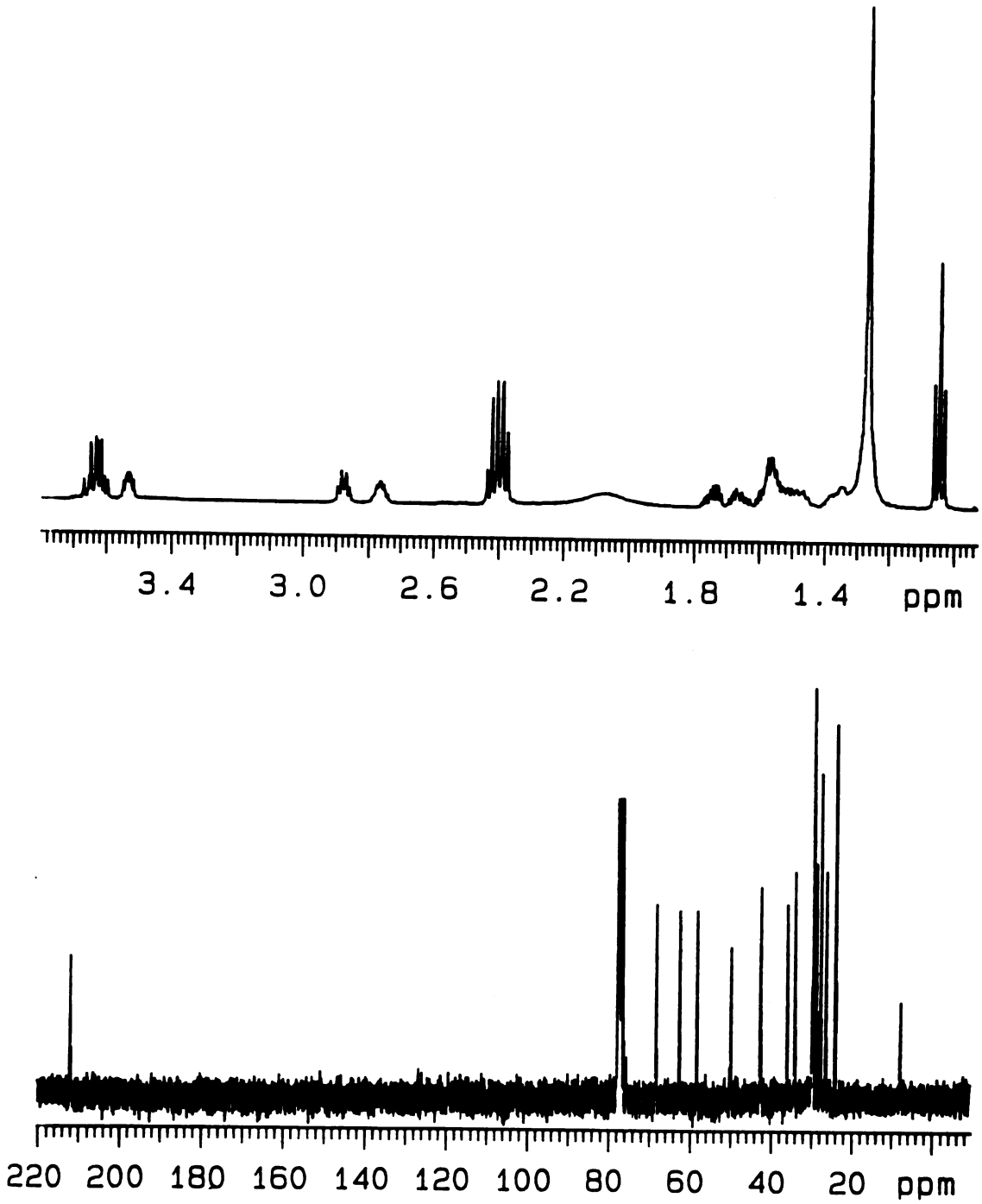


FIGURE V-5. ^{1}H and ^{13}C NMR of Prosopinine V-1

Summary

Model studies for the synthesis of *Prosopis* alkaloids were carried out on δ-lactams prepared by aza-annulation of keto and alkynylesters. Direct conversion of the C-3 carboxyl group to a hydroxyl substituent could not be accomplished, but introduction of amino functionality at that site was obtained in low yield. Aza-annulation produced a lactam bearing a C-3 quaternary center in good yield (70%), but clean reduction of the enamide could not be effected. Treatment of δ-lactams with Lawesson's reagent afforded quantitative yields of the corresponding lactams. Methylation provided methyl thioiminium salts. These salts would not undergo alkylation upon treatment with Grignard reagents, and subsequent reduction gave only reduced piperidine products, which were hydrolyzed and subjected to a β-amino acid rearrangement. Treatment of the salts with alkynyl lithium reagents afforded modest yields of alkylated products with **V-33**, however, if a C-2 alkyl substituent was present (**V-34**), alkylation could not be obtained. Homologation of the lactam carbonyl was carried out via an Eschenmoser sulfide contraction to give good yields of enaminoesters. Reduction of **V-41** with $NaBH_3CN$, or catalytic hydrogenation provided for the selective formation of either of the two stereoisomers. The optimal routes for modification of the aza-annulation product for the model compounds, were applied to the total synthesis of (±)-prosopinine. Aza-annulation from **V-43** provided **V-44** with the appropriate placement of hydroxyl functionality on the C-2 methylene substituent. The C-3 hydroxyl was introduced by conversion of the carboxylate to ketone, and subsequent Baeyer-Villiger oxidation, utilizing the δ-lactam template to effect stereochemical control. Thiolactam formation and Eschenmoser contraction was applied with analogous results to the model compounds. Hydride reduction gave the proper stereochemical relationship for the synthesis of prosopinine, however, hydrogenation was not analogous to the model compound, and the isomer for the preparation of prosophylline could not be obtained selectively. Wittig homologation, deprotection, and reduction completed the synthetic sequence. Thus, the first total synthesis of **V-1** was accomplished.

EXPERIMENTAL

General Methods

For general experimental methods see General Methods in Chapter II.

Preparation of V-24:

Benzyl amine (10.716 g, 100 mmol) was added to a cooled (0 °C) solution of methyl propiolate (8.407 g, 100 mmol) in Et_2O (100 mL). The mixture was warmed to ambient temperature, stirred for 12 hours, and the solvent was evaporated. The crude enamine was dissolved in THF (600 mL), and acryloyl chloride (9.917 g, 110 mmol) was added. After heating for 16 hours, the solution was washed with sat. aq. $NaHCO_3$ (200 mL), and the aqueous layer was extracted with 3 x 200 mL Et_2O. The combined organic layers were dried over $MgSO_4$. Purification by silica gel chromatography (70:30, petroleum ether:Et_2O) gave **V-24** (13.118 g, 53 mmol) in 53% yield as a viscous oil: ^1H NMR (300 MHz) ($CDCl_3$) δ 2.61 (s, 4 H), 3.68 (s, 3 H), 4.71 (s, 2 H), 7.19-7.35 (m, 6 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.8, 30.7, 49.8, 51.5, 108.8, 127.6, 127.8, 128.8, 136.4, 139.4, 166.6, 169.6; IR (neat) 3080, 3065, 3032, 2951, 2905, 2849, 1690, 1649, 1439, 1377, 1294, 1254, 1184, 1121, 729, 700 cm^{-1}.

Preparation of V-26:

Benzyl amine (10.716 g, 100 mmol), ethyl acetoacetate (13.014 g, 100 mmol), and a catalytic amount of *p*-toluenesulfonic acid were heated in benzene (600 mL) with azeotropic removal of water for 5 hours. The solvent was evaporated and the crude enamine was dissolved in THF (600 mL). Acryloyl chloride (9.015 g, 100 mmol) was added and the mixture was heated at reflux for 16 hours. The solvent was evaporated, and purification by silica gel chromatography (70:30, petroleum ether:Et_2O) gave **V-26** (23.37 g, 86 mmol) in 86% yield as a white solid (mp 74-76 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ

1.27 (t, J = 7.1 Hz, 3 H), 2.33 (bs, 3 H), 2.55-2.69 (m, 4 H), 4.15 (q, J = 7.1 Hz, 2 H), 5.00 (s, 2 H), 7.11 (bd, J = 6.9 Hz, 2 H), 7.17-7.33 (m, 3 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 14.3, 16.4, 21.2, 31.3, 44.9, 60.3, 109.4, 126.1, 127.1, 128.7, 137.5, 148.4, 167.5, 171.1; IR (neat) 3087, 3063, 3032, 2978, 2903, 2847, 1686, 1622, 1385, 1365, 1271, 1184, 1121, 1049, 725, 696 cm^{-1}.

General Method for the Hydrogenation of Enamides:

A mixture of enamide (1 eq.) and 10% palladium on carbon (0.1 g/mmol enamide) in EtOH (0.05-0.2 *M*) was stirred under an atmosphere of H_2 (45 psi) for 16-48 hours. Na_2CO_3 (3.0 eq.) was added to the reaction mixture to avoid deprotection of *O*-benzyl groups, if present. The solids were removed by filtration and the solvent evaporated to afford the lactam.

V-25: (5.225 g, 21.66 mmol) in 95% yield as a viscous oil: ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.98 (ddt, J = 6.0, 13.5, 9.6 Hz, 1 H), 2.12 (m, 1 H), 2.45 (ddd, J = 6.3, 9.6, 17.8 Hz, 1 H), 2.59 (ddd, J = 5.2, 6.3, 17.8 Hz, 1 H), 2.76 (dddd, J = 3.9, 5.8, 9.9, 12.4 Hz, 1 H), 3.36 (ddd, J = 1.1, 5.8, 12.4 Hz, 1 H), 3.42 (dd, J = 8.5, 12.4 Hz, 1 H), 3.63 (s, 3 H), 4.50 (d, J = 14.7 Hz, 1 H), 4.67 (d, J = 14.7 Hz, 1 H), 7.20-7.36 (m, 5 H) ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 23.8, 30.6, 38.9, 47.9, 50.0, 52.0, 127.4, 128.0, 128.5, 136.6, 168.8, 172.4; IR (neat) 3086, 3063, 3030, 2953, 2875, 1736, 1642, 1495, 1454, 1437, 1381, 1356, 1332, 1264, 1204, 1171, 1013, 727, 700 cm^{-1}.

V-27: (5.20 g, 18.90 mmol) in 99% yield as a white solid (mp 52-53 °C): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.09 (d, J = 6.6 Hz, 3 H), 1.17 (t, J = 7.1 Hz, 3 H), 1.97-2.18 (m, 2 H), 2.43 (ddd, J = 1.4, 9.1, 18.4 Hz, 1 H), 2.56 (ddd, J = 2.8, 6.9, 18.4 Hz, 1 H), 2.76 (dt, J = 11.8, 4.9 Hz, 1 H), 3.77 (quint, J = 6.3 Hz, 1 H), 3.94 (d, J = 15.1 Hz, 1 H), 4.08 (q, J = 7.1 Hz, 2 H), 5.22 (d, J = 15.1 Hz, 1 H), 7.17-7.31 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 14.0, 15.0, 18.1, 30.3, 43.8, 48.2, 52.1, 60.8, 127.3,

127.7, 128.5, 137.3, 169.0, 171.4; IR (neat) 3087, 3065, 3031, 2978, 2930, 2875, 1734, 1644, 1468, 1451, 1260, 1235, 1173, 1030, 696 cm^{-1}.

V-45: (0.63 g, 1.65 mmol) in 55% yield as a viscous oil: ^1H NMR (300 MHz) ($CDCl_3$) δ 1.12 (t, *J* = 7.2 Hz, 3 H), 2.04 (m, 1 H), 2.21 (m, 1 H), 2.46 (dd, *J* = 8.2, 18.4 Hz, 1 H), 2.60 (dd, *J* = 7.7, 18.4 Hz, 1 H), 2.78 (dt, *J* = 13.2, 4.4 Hz, 1 H), 3.51 (d, *J* = 4.9 Hz, 2 H), 3.87-4.06 (m, 3 H), 4.13 (d, *J* = 15.1 H, 1 H), 4.36 (s, 2 H), 5.22 (d, *J* = 15.1 Hz, 1 H), 7.17-7.37 (m, 10 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 13.9, 19.3, 30.2, 42.5, 49.3, 56.3, 60.8, 68.8, 73.3, 127.3, 127.5, 127.7, 127.8, 128.3, 128.6, 137.3, 137.4, 169.7, 171.2; IR (neat) 3088, 3063, 3031, 2980, 2960, 2938, 2905, 2870, 1786, 1734, 1647, 1497, 1464, 1453, 1414, 1379, 1306, 1235, 1200, 1171, 1105, 1030, 737, 698 cm^{-1}.

Hydrolysis of V-25 to Acid V-28:

V-25 (3.00 g, 12 mmol) and NaOH (0.96 g, 24 mmol) were placed in a mixture of THF (50 mL) and water (200 mL). The solution was stirred for 20 hours, and brought to pH >3.0 by addition of conc. HCl. The mixture was extracted with 3 x 75 mL of $CHCl_3$, and the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded **V-28** (2.68 g, 10.8 mmol) in 90% yield as a white solid (mp 156-157 °C): ^1H NMR: (300 MHz) ($CDCl_3$) δ 1.96 (m, 1 H), 2.13 (m, 1 H), 2.50 (ddd, *J* = 6.3, 9.3, 17.9 Hz, 1 H), 2.63 (dt, *J* = 17.9, 5.5 Hz, 1 H), 2.76 (m, 1 H), 3.38 (dd, *J* = 5.8, 12.5 Hz, 1 H), 3.43 (dd, *J* = 8.5, 12.5 Hz, 1 H), 4.43 (d, *J* = 14.6 Hz, 1 H), 4.74 (d, *J* = 14.6 Hz, 1 H), 7.16-7.35 (m, 5 H), 11.24 (br s, 1 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ 23.6, 30.4, 38.8, 48.0, 50.5, 127.6, 128.1, 128.7, 136.2, 170.0, 175.7; IR (neat) 3070, 3029, 2930, 2872, 2780, 2670, 2492, 1940, 1713, 1591, 1455, 1421, 1375, 1302, 1223, 980, 752, 698 cm^{-1}.

Curtius Rearrangement of V-28 to Give V-29:

To a solution of **V-28** (0.748 g, 3.0 mmol) in *t*-butanol (10 mL) was added DPPA (0.826 g, 3.0 mmol) and Et_3N (0.303 g, 3.0 mmol). The mixture was heated at reflux for 18 hours, diluted with toluene (30 mL), and sequentially washed with 2 x 10 mL 5% aq. citric acid, 2 x 10 mL, sat. aq. $NaHCO_3$, and finally 10 mL sat. aq. NaCl. The organic layer was dried over Na_2CO_3, and the solvent was evaporated. The oil was dissolved in MeOH (70 mL), and conc. HCl (5 mL) was added. The mixture was stirred for 4 hours, brought to pH >12 by addition of solid NaOH, extracted with 3 x 50 mL CH_2Cl_2, and dried over K_2CO_3. The solvent was evaporated and Kugelrohr distillation provided **V-29** (0.149 g, 0.72 mmol) in 24% yield (oven temp 140-160 °C, <1 mmHg): ^1H NMR: (300 MHz) ($CDCl_3$) δ 1.58 (m, 3 H), 1.86 (m, 1 H), 2.34 (ddd, *J* = 6.6, 9.9, 17.9 Hz, 1 H), 2.49 (ddd, *J* = 4.9, 6.3, 17.9 Hz, 1 H), 2.82 (dd, *J* = 8.2, 11.8 Hz, 1 H), 3.07 (m, 1 H), 3.19 (ddd, *J* = 1.7, 4.9, 11.8 Hz, 1 H), 4.45 (d, *J* = 14.7 Hz, 1 H), 4.53 (d, *J* = 14.7 Hz, 1 H), 7.12-7.30 (m, 5 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ 29.7, 30.2, 45.5, 49.8, 54.3, 127.2, 127.8, 128.3, 136.7, 168.9; IR (neat) 3330, 3285, 3061, 3031, 2930, 2872, 1716, 1638, 1541, 1495, 1455, 1422, 1358, 1260, 1196, 747, 704 cm^{-1}.

Preparation of V-30:

Ethyl acetoacetate (13.014 g, 100 mmol) was added to a slurry of NaH (1.20 g, 50 mmol) in benzene (250 mL), and the mixture was stirred for 20 minutes. Benzoyl peroxide (12.112 g, 50 mmol) and the mixture was stirred for 3.5 hours. The solution was diluted with $CHCl_3$ (200 mL) and washed with 1 *M* aq. H_3PO_4 (200 mL), sat. aq. $NaHCO_3$ (200 mL), and sat. aq. NaCl (200 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. The excess ethyl acetoacetate was removed under vacuum (<1 mmHg) at 55 C. Purification by silica gel chromatography (50:50, petroleum ether:Et_2O) afforded **V-30** (11.162 g, 44.5 mmol) in 89% yield as an oil: ^1H NMR (300 MHz) ($CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 1 H), 2.39 (s, 3 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 5.69 (s, 1 H), 7.44 (m, 2 H),

7.59 (tt, J = 1.1, 7.7 Hz, 1 H), 8.20 (m, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 14.0, 27.3, 62.5, 78.2, 128.2, 128.7, 130.0, 133.8, 164.5, 165.0, 197.7; IR (neat) 3065, 3036, 2986, 2942, 2911, 2876, 1730, 1601, 1452, 1360, 1277, 1179, 1117, 1055, 1022, 858, 712, 687 cm^{-1}.

Annulation of V-30 to Give V-31:

Benzyl amine (1.072 g, 10 mmol), **V-30** (2.503 g, 10 mmol), and a catalytic amount of *p*-toluenesulfonic acid were heated in benzene (50 mL) with azeotropic removal of water for 14 hours. The solvent was evaporated and the crude enamine was dissolved in THF (50 mL). Acryloyl chloride (0.902 g, 10 mmol) was added and the mixture was heated at reflux for 16 hours. The solution was washed with sat. aq. $NaHCO_3$ (50 mL), the aqueous layer was extracted with 3 x 50 mL Et_2O, and the organic layer was dried over $MgSO_4$. The solvent was evaporated, and silica gel chromatography (50:50, petroleum ether:Et_2O) gave **V-31** (2.76 g, 7 mmol) in 70% yield as a pale yellow solid (mp 106-108 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.20 (t, J = 7.1 Hz, 3 H), 2.62 (m, 1 H), 2.74-2.91 (m, 3 H), 4.19 (dq, J = 12.9, 7.1 Hz, 1 H), 4.23 (dq, J = 12.9, 7.1 Hz, 1 H), 4.71 (d, J = 3.0 Hz, 1 H), 4.78 (d, J = 3.0 Hz, 1 H), 4.99 (d, J = 15.8 Hz, 1 H), 5.06 (d, J = 15.8 Hz, 1 H), 7.18-7.36 (m, 5 H), 7.43 (m, 2 H), 7.58 (tt, J = 1.1, 7.7 Hz, 1 H), 7.96 (m, 2 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ 13.8, 26.5, 28.3, 47.2, 62.2, 79.7, 98.3, 126.8, 127.2, 128.5, 128.6, 129.1, 129.8, 133.6, 136.4, 141.5, 165.1, 168.3, 168.6; IR (neat) 3085, 3063, 3032, 2982, 2930, 2890, 2875, 1746, 1725, 1680, 1630, 1452, 1377, 1360, 1287, 1267, 1200, 1096, 1071, 1026, 712 cm^{-1}.

Preparation of Thioamides V-33, V-34, and V-49:

Lawesson's reagent (0.5 eq.) was added to a solution of the lactam (1.0 eq.) in THF (0.4 *M*), and the mixture was stirred for 4-12 hours. The solvent was evaporated, diluted with EtOAc (3 times the volume of THF), and the solution was washed sequentially

with 3 portions of aq. sat. $NaHCO_3$ (1/3 the volume of EtOAc) followed by 2 portions of sat. aq. NaCl (1/5 the volume of EtOAc). The aqueous layers were combined and extracted with 2 portions of EtOAc (1/2 the volume of EtOAc). The organic layers were combined and dried over Na_2SO_4. Silica gel chromatography (Et_2O) afforded the pure thiolactam.

V-33: (5.410 g, 20.4 mmol) in 99% yield as a white solid (mp 63-65 °C): ^1H NMR: (300 MHz) ($CDCl_3$) δ 1.87 (ddt, *J* = 5.8, 13.7, 9.1 Hz, 1 H), 2.00 (dq, *J* = 13.7, 5.8 Hz, 1 H), 2.78 (m, 1 H), 2.97 (ddd, *J* = 6.3, 8.8, 18.2 Hz, 1 H), 3.14 (dt, *J* = 18.2, 5.8 Hz, 1 H), 3.42-3.56 (m, 2 H), 3.56 (s, 3 H), 5.12 (d, *J* = 14.5 Hz, 1 H), 5.40 (d, *J* = 14.5 Hz, 1 H), 7.18-7.29 (m, 5 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ 23.0, 38.6, 40.3, 50.0, 52.0, 57.1, 127.6, 127.7, 128.5, 134.8, 172.0, 199.7; IR (neat) 3080, 3030, 2951, 2860, 1734, 1514, 1453, 1348, 1200, 1169, 1043, 704 cm^{-1}.

V-34: (2.280 g, 7.82 mmol) in 99% yield as a viscous oil: ^1H NMR (300 MHz) ($CDCl_3$) δ 1.17 (d, *J* = 6.6 Hz, 3 H), 1.18 (t, *J* = 7.1 Hz, 3 H), 1.93-2.13 (m, 2 H), 2.77 (ddd, *J* = 4.7, 5.8, 11.5 Hz, 1 H), 3.14 (dt, *J* = 8.5, 19.5 Hz, 1 H), 3.29 (ddd, *J* = 3.3, 6.6, 19.5 Hz, 1 H), 3.98 (dq, *J* = 5.8, 6.6 Hz, 1 H), 4.09 (q, *J* = 7.1 Hz, 2 H), 4.45 (d, *J* = 14.8 Hz, 1 H), 6.23 (d, *J* = 14.8 Hz, 1 H), 7.23-7.35 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 14.0, 14.7, 18.3, 40.0, 43.5, 54.9, 55.8, 61.0, 127.5, 127.7, 128.7, 135.3, 170.8, 199.8; IR (neat) 3087, 3061, 2980, 2938, 1732, 1497, 1452, 1348, 1171, 961, 708 cm^{-1}.

V-49: (1.453 g, 3.36 mmol) in 94% yield as a yellow solid (mp 81-82 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.83-2.05 (m, 2 H), 3.10 (ddd, *J* = 4.4, 6.1, 19.0 Hz, 1 H), 3.30 (ddd, *J* = 7.1, 9.6, 19.0 Hz, 1 H), 3.49 (dd, *J* = 6.6, 10.2 Hz, 1 H), 3.58 (dd, *J* = 4.4, 10.2 Hz, 1 H), 3.85 (m, 1 H), 3.91 (m, 1 H), 4.24 (d, *J* = 11.8 Hz, 1 H), 4.35 (d, *J* = 11.8 Hz, 1 H), 4.40-4.50 (m, 3 H), 6.45 (d, *J* = 15.1 Hz, 1 H), 7.14-7.40 (m, 15 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 22.7, 37.3, 55.5, 61.1, 69.1, 70.0, 72.2, 73.3, 127.2, 127.4, 127.5, 127.6, 127.9, 128.2, 128.5, 135.2, 137.1, 137.7, 201.8; IR (neat) 3100, 3090, 3031, 2940, 2867, 1497, 1453, 1345, 1173, 1073, 1028, 733, 696 cm^{-1}.

Preparation of V-37:

Thiolactam **V-33** (1.245 g, 4.72 mmol) and MeI (6.714 g, 47.2 mmol) were stirred for 3 hours. The excess MeI was removed under vacuum and the salt was dissolved in THF (20 mL). *N,N,N',N'*-Tetramethyl ethylenediamine (4 mL) was added to help solubilize the salt. The mixture was cooled to -78 °C and a solution of propyl magnesium bromide (4.72 mmol) in Et_2O (10 mL) was added. The solution was stirred for 20 minutes, warmed to 0 °C over 20 minutes, and stirred an additional 15 minutes. $NaBH_4$ (0.893 g, 23.6 mmol) followed by MeOH (10 mL) were added. After 6 hours, the solution was washed with water (50 mL), and extracted with 3 x 50 mL CH_2Cl_2. The organic layers were combined, dried over Na_2SO_4, and concentrated. The oil was purified by silica gel chromatography (60:40, petroleum ether:Et_2O) to give **V-37** (0.790 g, 3.4 mmol) in 72% yield: ^1H NMR: (300 MHz) ($CDCl_3$) δ 1.38-1.64 (m, 2 H), 1.70 (m, 1 H), 1.90 (m, 1 H), 2.03 (dt, J = 2.7, 10.7 Hz, 1 H), 2.20 (t, J = 10.4 Hz, 1 H), 2.57 (tt, J = 3.8, 10.2 Hz, 1 H), 2.71 (dt, J = 11.3, 3.8 Hz, 1 H), 2.93 (ddd, J = 1.7, 3.6, 11.3 Hz, 1 H), 3.47 (d, J = 13.3 Hz, 1 H), 3.53 (d, J = 13.3 Hz, 1 H), 3.63 (s, 3 H), 7.19-7.31 (m, 5 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ 24.5, 26.9, 41.8, 51.4, 53.5, 55.3, 63.2, 126.9, 128.1, 128.9, 138.2, 174.6; IR (neat) 3087, 3063, 3029, 2950, 2855, 2803, 2768, 1736, 1455, 1435, 1221, 1194, 1179, 1152, 1134, 739, 698 cm^{-1}.

Hydrolysis of V-37 to Acid V-38:

V-37 (0.79 g, 3.38 mmol) and NaOH (0.27 g, 6.76 mmol) were heated at 66 °C in a mixture of THF (20 mL) and water (60 mL) for six hours, and then stirred at ambient temperature for 12 hours. The THF was evaporated and the solution was brought to pH 6 by careful addition of conc. HCl. The solution was saturated with NaCl, extracted with 4 x 50 mL $CHCl_3$, and dried over Na_2SO_4. The solvent was evaporated to give **V-38** (0.20 g, 0.91 mmol) in 27% yield as a white solid (mp 172-175 °C): ^1H NMR: (300 MHz) ($CDCl_3$) δ 1.64-1.89 (m, 4 H), 2.50-3.00 (m, 5 H), 3.80 (s, 2 H), 7.32 (s, 5 H), 11.0

(br. s, 1 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ 22.1, 26.2, 40.5, 52.2, 54.3, 61.5, 128.4, 128.6, 130.1, 133.0, 176.7; IR (neat) 3085, 3070, 3031, 2980, 2932, 2870, 2541, 1962, 1715, 1578, 1456, 1399, 1254, 1011, 954, 752, 702 cm^{-1}.

β-Aminoacid Rearrangement of V-38 to V-39:

V-38 (0.175 g, 0.798 mmol) was dissolved in acetic anhydride and heated to reflux. After 3 hours, the solution was cooled to 0 °C and a solution of K_2CO_3 (10 g) in water (20 mL) was added. The mixture was stirred for 2 hours, extracted with 3 x 20 mL CH_2Cl_2, and dried over Na_2SO_4. Purification by silica gel chromatography (60:40, petroleum ether:Et_2O) provided **V-39** (0.130 g, 0.646 mmol) in 81% yield as a viscous oil: ^1H NMR: (300 MHz) ($CDCl_3$) δ 1.77 (quint, J = 6.1 Hz, 2 H), 2.52 (tt, J = 1.4, 6.3 Hz, 2 H), 3.24 (dd, J = 5.8, 6.0 Hz, 2 H), 4.62 (s, 2 H), 5.27 (q, J = 1.8 Hz, 1 H), 6.23 (q, J = 1.8 Hz, 1 H), 7.17-7.31 (m, 5 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ 23.0, 30.0, 47.7, 50.6, 121.8, 127.2, 127.9, 128.5, 137.1, 137.7, 164.2; IR (neat) 3087, 3063, 3031, 2932, 2865, 1658, 1615, 1487, 1452, 1341, 1294, 1223, 1198, 1080, 938, 801, 737, 704 cm^{-1}.

Preparation of V-40:

Thiolactam **V-33** (0.633 g, 2.4 mmol) and MeI (0.546g, 3.85 mmol) were stirred in THF (2.5 mL) at room temperature, and then cooled to -78 °C. A solution of the alkynyl lithium (1.2 eq., 2.88 mmol), prepared by *n*-BuLi addition to benzyl protected propargyl alcohol, in THF (2.5 mL) was added. After 2 hours, $NaBH_4$ (0.454 g, 12.0 mmol) followed by MeOH (5 mL) was added, and the solution was allowed to warm to room temperature. The mixture was stirred for 12 hours, washed with H_2O (10 mL), and extracted with 3 x 10 mL CH_2Cl_2. Silica gel chromatography (80:20, petroleum ether:Et_2O) afforded **V-40** (0.405 g, 1.08 mmol) in 45% yield as a viscous oil (63:37 mixture of diastereomers): ^1H NMR: (300 MHz) ($CDCl_3$) δ 1.77 (m, 1 H), 1.80-1.99 (m,

2 H), 2.11 (m, 1 H), 2.53-2.77 (m, 2 H), 2.89 (dt, J = 11.8, 3.6 Hz, 1 H), 2.91 (t, J = 3.6 Hz, 1 H, minor isomer), 3.50 (m, 1 H), 3.60 (d, J = 13.5 Hz, 1 H), 3.60-3.72 (m, 2 H, minor isomer), 3.66 (s, 3 H), 3.84 (d, J = 13.5 Hz, 1 H), 4.29 (d, J = 1.7 Hz, 2 H), 4.31 (d, J = 1.7 Hz, 2 H, minor isomer), 4.67 (s, 2 H), 4.70 (s, 2 H, minor isomer) 7.23-7.45 (m, 10 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ (major isomer) 23.0, 29.8, 40.1, 41.8, 49.9, 51.9, 57.3, 59.9, 71.2, 81.6, 82.8, 126.9, 127.9, 128.0, 128.1, 128.3, 128.8, 137.4, 138.0, 174.0, (minor isomer) 22.7, 29.1, 40.1, 41.8, 49.6, 51.3, 57.3, 60.0, 71.1, 82.6, 84.4, 127.0, 127.7, 127.9, 128.0, 128.1, 128.3, 128.8, 137.4, 138.1, 174.1; IR (neat) 3087, 3063, 3031, 2951, 2853, 1736, 1495, 1455, 1437, 1356, 1292, 1217, 1191, 1173, 1123, 1074, 1028, 982, 739, 698 cm^{-1}.

General Method for Eschenmoser Sulfide Contraction:

The thiolactam (1.0 eq.) and ethyl bromoacetate (1.2 eq,) were stirred in Et_2O (1 *M*) for 24-36 hours. The solvent was evaporated and the thionium salt was dissolved in CH_3CN (0.2 *M*). Triphenylphosphine (1.2 eq.) was added and the mixture was allowed to stir for 10 minutes. Triethylamine (1.5 eq.) was added and the solution was heated to reflux. After 26 hours, the solids were filtered and the resultant solution was concentrated. Silica gel chromatography (90:10 - 70:30, petroleum ether:Et_2O) provided the pure enaminoesters.

V-41: (0.426 g, 1.23 mmol) in 79% yield as a white solid (mp 69-71 °C): ^{1}H NMR: (300 MHz) ($CDCl_3$) δ 1.12 (d, J = 6.4 Hz, 3 H), 1.18 (t, J = 7.0 Hz, 3 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.89-2.11 (m, 2 H), 2.86-3.00 (m, 2 H), 3.62 (ddd, J = 3.1, 6.7, 18.7 Hz, 1 H), 3.80 (quint, J = 6.3 Hz, 1 H), 3.99 (dq, J = 3.4, 7.0 Hz, 2 H), 4.02 (dq, J = 3.4, 7.0 Hz, 1 H), 4.14 (q, J = 7.0 Hz, 2 H), 4.26 (d, J = 16.5 Hz, 1 H), 4.55 (d, J = 16.5 Hz, 1 H), 4.63 (s, 1 H), 7.17 (d, J = 7.0 Hz, 2 H), 7.22-7.37 (m, 3 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ 14.0, 14.5, 14.6, 17.0, 25.4, 44.1, 54.0, 54.8, 58.2, 60.6, 85.7,

126.4, 127.1, 128.6, 136.1, 159.8, 168.6, 171.8; IR (neat) 3100, 3080, 3030, 2978, 2920, 2870, 1734, 1682, 1561, 1136, 1060, 1030, 966, 791, 727, 696 cm^{-1}.

V-50: (1.22 g, 2.51 mmol) in 81% yield as a viscous oil: ^1H NMR (300 MHz) ($CDCl_3$) δ 1.17 (t, *J* = 7.1 Hz, 3 H), 1.85 (m, 1 H), 1.95 (m, 1 H), 2.95 (dt, *J* = 18.1, 6.2 Hz, 1 H), 3.41 (dd, *J* = 6.7, 9.7 Hz, 1 H), 3.50 (m, 1 H), 3.51 (dd, *J* = 4.5, 9.7 Hz, 1 H), 3.61 (ddd, *J* = 2.8, 4.4, 7.1 Hz, 1 H), 3.86 (ddd, *J* = 3.0, 4.4, 6.9 Hz, 1 H), 3.98 (dq, *J* = 3.8, 7.1 Hz, 1 H), 4.01 (dq, *J* = 3.8, 7.1 Hz, 1 H), 4.35 (d, *J* = 16.5 Hz, 1 H), 4.41 (s, 2 H), 4.43 (d, *J* = 14.6 Hz, 1 H), 4.52 (d, *J* = 14.6 Hz, 1 H), 4.53 (d, *J* = 16.5 Hz, 1 H), 4.60 (s, 1 H), 7.18-7.36 (m, 15 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 14.6, 22.2, 22.3, 53.9, 58.2, 62.5, 70.1, 70.2, 73.2, 73.3, 84.8, 126.6, 127.0, 127.4, 127.5, 127.6, 127.8, 128.3, 128.4, 128.5, 136.3, 137.6, 138.2, 161.7, 168.9; IR (neat) 3100, 3080, 3031, 2980, 2934, 2867, 1680, 1561, 1497, 1455, 1362, 1142, 1094, 1073, 735, 696 cm^{-1}.

General Method for the $NaBH_3CN$ Reduction of Enaminoesters:

The enaminoester (1.0 eq.) was dissolved in MeOH (0.2 *M*) with a trace of bromocresol green as indicator. $NaBH_3CN$ (1.0 eq) was added. A 5% methanolic HCl solution was added drowpise until a yellow color persisted. The solution was stirred for 2 hours, with the periodic addition of HCl to maintain a yellow color. The mixture was diluted with CH_2Cl_2 (5 times the volume of MeOH), washed with 10% aq. $NaHCO_3$ (0.5 times the volume of CH_2Cl_2), and the organic phase was dried over Na_2SO_4. The solvent was evaporated and silica gel chromatography (70:30, petroleum ether:Et_2O) afforded the pure piperidines.

V-42: (0.113 g, 0.318 mmol) in 100% yield as a viscous oil (mixture of diastereomers, **V-42a**:**V-42b**, 92:8): ^1H NMR: (300 MHz) ($CDCl_3$) δ (major isomer) 0.98 (d, *J* = 6.9 Hz, 3 H), 1.13 (t, *J* = 7.1 Hz, 3 H), 1.14 (t, *J* = 7.1 Hz, 3 H), 1.37 (dq, *J* = 5.2, 12.4 Hz, 1 H), 1.56 (dq, *J* = 13.2, 3.0 Hz, 1 H), 1.72-1.92 (m, 2 H), 2.19 (dd,

J = 7.4, 14.8 Hz, 1 H), 2.46 (dd, J = 6.9, 14.8 Hz, 1 H), 2.78 (dt, J = 4.9, 11.8 Hz, 1 H), 3.22 (dq, J = 4.7, 6.9 Hz, 1 H), 3.34 (m, 1 H), 3.67 (s, 2 H), 3.93-4.12 (m, 4 H), 7.12-7.31 (m, 5 H), (minor isomer) 0.93 (d, J = 7.0 Hz, 3 H), 1.19 (t, J = 7.3 Hz, 3 H), 1.20 (t, J = 7.3 Hz, 3 H), 1.62-1.77 (m, 3 H), 1.84 (m, 1 H), 2.34 (dd, J = 10.3, 14.2 Hz, 1 H), 2.65 (dd, J = 3.4, 14.2 Hz, 1 H), 2.73 (m, 1 H), 3.22-3.35 (m, 2 H), 3.72 (d, J = 14.3 Hz, 1 H), 3.78 (d, J = 14.3 Hz, 1 H), 4.06 (q, J = 7.3 Hz, 2 H), 4.08 (q, J = 7.3 Hz, 2 H), 7.17-7.34 (m, 5 H); ^{13}C NMR: (75.5 MHz) ($CDCl_3$) δ (major isomer) 10.4, 14.1, 21.2, 28.2, 40.1, 41.5, 50.7, 51.9, 53.2, 60.1, 60.4, 126.6, 127.8, 128.2, 140.6, 172.1, 174.1; IR (neat) 3087, 3063, 3029, 2980, 2940, 2874, 2853, 1734, 1495, 1453, 1370, 1200, 1152, 1034, 733, 698 cm^{-1}.

V-51: (0.6148 g, 1.267 mmol) in 88% yield (mixture of isomers, >90:10): ^{1}H NMR (300 MHz) ($CDCl_3$) δ (major isomer) 1.17 (t, J = 7.2 Hz, 3 H), 1.53-1.78 (m, 3 H), 1.99 (m, 1 H), 2.43 (dd, J = 8.7, 14.2 Hz, 1 H), 2.60 (dd, J = 5.3, 14.2 Hz, 1 H), 2.95 (dt, J = 7.0, 4.5 Hz, 1 H), 3.24 (m, 1 H), 3.54 (dt, J = 4.2, 7.5 Hz, 1 H), 3.71 (m, 3 H), 4.03 (m, 1 H), 4.04 (q, J = 7.2 Hz, 2 H), 4.36 (s, 2 H), 4.42 (d, J = 11.4 Hz, 1 H), 4.55 (d, J = 11.4 Hz, 1 H), 7.16-7.38 (m, 15 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (major isomer) 14.1, 24.7, 25.4, 33.9, 52.7, 59.2, 60.2, 68.8, 70.8, 72.9, 74.2, 126.5, 127.3, 127.4, 127.5, 127.6, 128.0, 128.2, 128.3, 128.4, 138.4, 138.8, 140.7, 172.6; IR (neat) 3087, 3063, 3031, 2980, 2936, 2865, 1732, 1495, 1452, 1368, 1290, 1157, 1096, 1028, 737, 698 cm^{-1}.

Preparation of V-44:

To a solution of **V-43** (5.84 g, 40 mmol) in THF (100 mL), cooled to -78°C, was added *n*-BuLi (16 mL, 40 mmol, 2.5 *M* in hexane). The solution was stirred for 15 minutes, and ethyl chloroformate (4.341 g, 40 mmol) was added. Afert 15 minutes, the mixture was warmed to room temperature, and stirred an additional 20 minutes. The solution was washed with water (100 mL), extracted with 3 x 100 mL of Et_2O, and dried

over $MgSO_4$. Concentration afforded the crude ester which was dissolved in benzene (20 mL). Benzyl amine (4.286 g, 40 mmol) was added, and the mixture was stirred for 12 hours. The solvent was removed by rotary evaporation, and the crude enamine was dissolved in THF (300 mL). Acryloyl chloride (3.606 g, 40 mmol) was added, and the mixture was heated at reflux for 12 hours. The solution was washed with sat. aq. $NaHCO_3$, extracted with 3 x 200 mL Et_2O, and concentrated. The enamide was purified by silica gel chromatography (60:40, petroleum ether, Et_2O) to afford **V-44** (5.82 g, 15.3 mmol) in 38% yield as a yellow solid (mp 85-86 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3 H), 2.50-2.59 (m, 2 H), 2.64-2.72 (m, 2 H), 4.18 (1, *J* = 7.1 Hz, 2 H), 4.58 (s, 2 H), 4.62 (s, 2 H), 5.13 (s, 2 H), 7.0 (m, 1 H), 7.03 (m, 1 H), 7.17-7.40 (m, 8 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 14.1, 21.6, 30.7, 44.4, 60.7, 63.5, 72.6, 113.5, 126.0, 126.9, 128.0, 128.3, 128.6, 137.6, 137.9, 146.0, 166.6, 170.8; IR (neat) 3085, 3063, 3031, 2980, 2905, 2870, 1688, 1628, 1497, 1455, 1373, 1323, 1287, 1267, 1183, 1125, 1071, 727, 696 cm^{-1}.

Reduction of V-51 to V-52:

V-51 (0.167 g, 0.342 mmol) was dissolved in Et_2O and $LiAlH_4$ (0.1 g, 2.63 mmol) was added. The mixture was stirred for 2 hours and quenched by addition of H_2O (0.1 mL), 15% aq. NaOH (0.1 mL), and H_2O (0.3 mL). After 1 hour, the mixture was filtered and the solvents were evaporated to give **V-52** (0.1325 g, 0.297 mmol) in 87% yield as a viscous oil: ^1H NMR (300 MHz) ($CDCl_3$) δ 1.16 (m, 1 H), 1.27 (s, 1 H), 1.41 (m, 1 H), 1.68 (m, 1 H), 1.94 (m, 1 H), 2.09 (m, 1 H), 2.27 (m, 1 H), 2.91 (m, 1 H), 3.40 (dt, *J* = 2.2, 10.5 Hz, 1 H), 3.48-3.68 (m, 3 H), 3.62 (d, *J* = 13.2 Hz, 1 H), 3.74 (dd, *J* = 8.0, 9.9 Hz, 1 H), 3.86 (dd, *J* = 3.7, 9.9 Hz, 1 H), 4.11 (d, *J* = 13.2 Hz, 1 H), 4.41 (d, *J* = 11.5 Hz, 1 H), 4.46 (d, *J* = 12.1 Hz, 1 H), 4.58 (d, *J* = 12.1 Hz, 1 H), 4.61 (d, *J* = 11.5 Hz, 1 H), 7.20-7.38 (m, 15 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 22.6, 26.6, 30.9, 50.6, 54.4, 57.1, 62.9, 68.2, 70.4, 72.3, 73.3, 126.9, 127.3, 127.4, 127.6,

128.3, 129.0, 138.2, 138.7, 140.0; IR (neat) 3405, 3087, 3063, 3029, 2936, 2861, 1495, 1455, 1100, 1075, 733, 698 cm^{-1}.

Preparation of V-54:

1,8-Octanediol (28.78 g, 196.8 mmol) and 48% aq. HBr (24.6 mL, 236.2 mmol HBr) were heated at reflux in benzene (400 mL) for 16 hours with azeotropic removal of water. The solvent was evaporated and the bromoalcohol was purified by silica gel chromatography (60:40, petroleum ether:Et_2O). Distillation provided **V-54** (23.67 g, 110.2 mmol) in 56% yield (oven temp 85-90 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.23-1.32 (m, 6 H), 1.33-1.43 (m, 2 H), 1.50 (m, 2 H), 1.79 (quint, *J* = 6.9 Hz, 2 H), 2.07 (s, 1 H), 3.35 (t, *J* = 6.9 Hz, 2 H), 3.56 (t, *J* - 6.6 Hz, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 25.5, 28.0, 28.6, 29.1, 32.5, 32.7, 33.9, 62.7; IR (neat) 3337, 2932, 2857, 1464, 1437, 1246, 1057, 723, 644 cm^{-1}.

Preparation of V-55:

To a solution of PCC (21.556 g, 100 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added **V-54** (10.456 g, 50 mmol). The mixture was warmed to ambient temperature and allowed to stir for 10 hours. The chromium salts were removed by filtration through a celite/silica gel mixture, and the aldehyde was purified by silica gel chromatography (Et_2O). The solvent was evaporated to give **V-55** (7.624 g, 37 mmol) in 74% yield: ^1H NMR (300 MHz) ($CDCl_3$) δ 1.23-1.45 (m, 6 H), 1.59 (m, 2 H), 1.81 (quint, *J* = 7.0 Hz, 2 H), 2.39 (dt, *J* = 1.8, 7.4 Hz, 2 H), 3.36 (t, *J* = 6.8 Hz, 2 H), 9.72 (t, *J* = 1.8 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 21.8, 27.8, 28.4, 28.8, 32.5, 33.8, 43.7, 202.6; IR (neat) 2934, 2859, 2679, 1709, 1464, 1429, 1412, 1279, 1244, 1215, 941, 725, 644 cm^{-1}.

Preparation of V-56:

Ethyl bromide (3.923 g, 36 mmol) was added over a 1 hour period to magnesium (4.4 g, 180 mmol) in Et_2O (40 mL) at ambient temperature. The mixture was allowed to stir for an additional 45 minutes, and then added to a cooled (-30 °C) solution of **V-55** (6.213 g, 30 mmol) in Et_2O (50 mL). The solution was warmed to 0 °C over 45 minutes, and then quenched by addition of sat. aq. NH_4Cl (40 mL). 10% aq. HCl was added until all the solids had dissolved. The mixture was extracted with 3 x 100 mL Et_2O, and the organic layers were combined and dried over $MgSO_4$. The solvent was evaporated and the crude alcohol was added to a cooled (0 °C) mixture of PCC (9.7 g, 45 mmol) in CH_2Cl_2 (100 mL). The solution was warmed to ambient temperature, stirred for 3 hours, and filtered through a mixture of celite/silica gel. Kugelrohr distillation provided **V-56** (5.339 g, 22.8 mmol) in 76% yield (oven temp 75-90 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.02 (t, J = 7.3 Hz, 3 H), 1.20-1.45 (m, 6 H), 1.55 (m, 2 H), 1.82 (quint, J = 7.1 Hz, 2 H), 2.37 (t, J = 7.4 Hz, 2 H), 2.39 (q, J = 7.3 Hz, 2 H), 3.37 (t, J = 6.8 Hz, 2 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 7.7, 23.6, 27.9, 28.4, 28.9, 32.6, 33.8, 35.8, 42.2, 211.7; IR (neat) 2938, 2857, 1715, 1460, 1375, 1113, 725, 644 cm^{-1}.

Preparation of V-57

V-56 (5.13 g, 21.8 mmol), ethylene glycol (1.354 g, 21.8 mmol), and H_2SO_4 (2 drops) were heated at reflux in benzene (75 mL) with azeotropic removal of water for 5 hours. The solution was washed with sat. aq. $NaHCO_3$ (40 mL), extracted with 3 x 50 mL Et_2O, and dried over Na_2SO_4. Evaporation afforded an oil which was purified by silica gel chromatography (90:10, petroleum ether:Et_2O) to give **V-57** (4.361 g, 15.7 mmol) in 72% yield: ^1H NMR (300 MHz) ($CDCl_3$) δ 0.85 (t, J = 7.5 Hz, 3 H), 1.23-1.44 (m, 8 H), 1.54 (m, 2 H), 1.58 (q, J = 7.5 Hz, 2 H), 1.80 (quint, J = 7.0 Hz, 2 H), 3.35 (t, J = 6.9 Hz, 2 H), 3.88 (s, 4 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 8.1, 23.6, 28.0,

28.6, 29.6, 29.7, 32.7, 33.9, 36.6, 64.9, 112.0; IR (neat) 2938, 2880, 2859, 1464, 1202, 1163, 1074, 947, 920, 646 cm^{-1}.

Swern Oxidation of V-52 to V-59:

To a solution of oxalyl chloride (0.057 g, 0.45 mmol) in CH_2Cl_2, cooled to -70 °C, was added a solution of DMSO (0.070 g, 0.90 mmol) in CH_2Cl_2 (1 mL). After 10 minutes, **V-52** (0.133 g, 0.297 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was allowed to stir for 45 minutes at -65 °C, and Et_3N (0.182 g, 1.8 mmol) was added. The mixture was stirred for 20 minutes at -65 °C and warmed to ambient temperature for 1 hour. The mixture was washed with 10% aq. $NaHCO_3$ and extracted with 3 x 10 mL CH_2Cl_2. The solvents were evaporated and the aldehyde was used immediately without further purification.

Wittig Homologation of V-59 to V-60:

The bromide **V-57** (0.1675 g, 0.6 mmol) and triphenylphosphine (0.1574 g, 0.6 mmol) were heated at reflux in toluene (2 mL) for 48 hours. The solvent was removed under vacuum and THF (2 mL) was added. The solution was cooled to -78 °C and *n*-BuLi (2.5 *M* in hexane, 0.24 mL, 0.6 mmol) was added. The mixture was stirred for 15 minutes at -78 °C and 1 hour at ambient temperature. The ylide solution was cooled to -78 °C and a solution of **V-59** in THF (1 mL) was added. The mixture was warmed to -45 °C over 2 hours, stirred at that temperature for an additional hour, warmed to 0 °C for 3 hours, and stirred an aditional 2 hours at ambient temperature. The solution was washed with H_2O (10 mL) and extracted with 3 x 20 mL CH_2Cl_2, dried over Na_2SO_4, and concentrated. The oil was purified by silica gel chromatography (90:10 - 80:20, petroleum ether:Et_2O) to give **V-60** (0.1029 g, 0.163 mmol) in 55% yield as a viscous oil (*cis:trans* 85:15): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.89 (t, *J* = 7.4 Hz, 3 H), 1.20-1.38 (m, 8 H), 1.44-1.75 (m, 6 H), 1.88-2.20 (m, 4 H), 2.22-2.35 (m, 2 H) 2.58 (m, 1 H, *trans* isomer),

2.69 (m, 1 H), 2.83 (dt, J = 7.4, 3.8 Hz, 1 H, *trans* isomer), 3.01 (dt, J = 7.4, 4.3 Hz, 1 H), 3.54 (m, 1 H), 3.68-3.78 (m, 3 H), 3.91 (s, 4 H), 4.06 (d, J = 14.0 Hz, 1 H, *trans* isomer), 4.08 (d, J = 13.7 Hz, 1 H), 4.39 (s, 2 H), 4.42 (d, J = 11.5 Hz, 1 H), 4.43 (d, J = 11.5 Hz, 1 H, *trans* isomer), 4.55 (d, J = 11.5 Hz, 1 H, *trans* isomer), 4.56 (d, J = 11.5 Hz, 1 H), 5.21 (m, 1 H), 5.34 (m, 1 H), 7.16-7.41 (m, 15 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ (*cis* isomer) 8.1, 23.7, 25.0, 25.4, 27.4, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 29.8, 52.5, 55.0, 58.9, 64.9, 68.7, 70.8, 72.9, 74.6, 112.1, 126.4, 127.2, 127.3, 127.4, 127.6, 128.0, 128.3, 128.4, 131.1, 138.4, 138.8, 141.1, (*trans* isomer) 8.1, 23.5, 25.0, 27.2, 29.1, 29.2, 29.4, 29.5, 29.6, 29.7, 29.8, 52.4, 54.8, 58.8, 64.9, 68.7, 70.8, 72.9, 74.6, 112.0, 126.2, 126.9, 127.3, 127.4, 127.7, 127.8, 128.2, 128.3, 128.4, 131.3, 138.4, 138.9, 141.2; IR (neat) 3100, 3080, 3029, 2930, 2855, 1453, 1075, 733, 696 cm^{-1}.

Preparation of V-1:

V-60 (0.0989 g, 0.158 mmol) was dissolved in THF (8 mL) and 10% aq. HCl (4 mL) was added. The mixture was stirred for 2 hours, washed with sat. aq. $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2. The organic layers were dried over Na_2CO_3, and concentrated. The residue was dissolved in EtOH (10 mL), and conc. HCl (20 drops) was added. 10% Pd on carbon (0.05 g) was added and the mixture was stirred under H_2 (50 psi) for 24 hours. The solution was filtered, and the solvents were evaporated. The residue was washed with sat. aq. $NaHCO_3$, extracted with 4 x 20 mL $CHCl_3$, and dried over Na_2SO_4. The residue was filtered through basic alumina with $CHCl_3$ and MeOH and the solvents were evaporated. The crystals were washed with a minimum amount of acetone and dried under vacuum to give **V-1** (0.043 g, 0.142 mmol) in 90% yield as white crystals (mp 88-89 °C): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 1.05 (t, J = 7.3 Hz, 3 H), 1.23-1.41 (m, 13 H), 1.44-1.61 (m, 5 H), 1.66 (m, 1 H), 1.74 (m, 1 H), 2.07 (br. s, 3 H), 2.39 (t, J = 7.5 Hz, 2 H), 2.41 (q, J = 7.3 Hz, 2 H), 2.76 (m, 1 H), 2.87 (dt, J = 5.5, 7.7

Hz, 1 H), 3.53 (ddd, J = 4.0, 5.6, 6.9 Hz, 1 H), 3.61 (dd, J = 5.4, 10.5 Hz, 1 H), 3.65 (dd, J = 7.8, 10.5 Hz, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 7.8, 23.9, 26.3, 27.4, 28.6, 29.2, 29.3, 29.4, 29.6, 33.9, 35.8, 42.4, 49.7, 58.1, 62.3, 68.1, 212.0; IR (neat) 3320, 2926, 2855, 1717, 1460, 1377, 1275, 1119, 1073, 723 cm^{-1}.

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18. Hydrogenation of **V-41** at 1 atm H_2 only proceeded to ~50% conversion after 48 hours. The crude products consisted of a mixture of **V-41**, **V-42a** and **V-42b** (15:85, respectively), and a small amount of the *N*-debenzylated analog. Reduction at higher pressures (50 psi) resulted in nearly complete removal of the benzyl group, and gave the deprotected analogs of **V-42a** and **V-42b** in the same ratio (15:85, respectively).
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Preparation and 3-Aza-Cope Rearrangement of *N*-Alkyl-*N*-allyl Enamines

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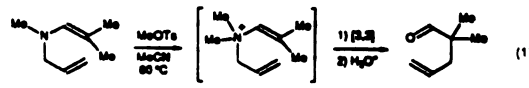
The [3,3] charge-accelerated rearrangement of *N*-allyl-*N*-isobutyl enamine substrates to γ,δ-unsaturated imine products and subsequent reduction to the corresponding *N*-alkyl δ,ε-unsaturated amines is reported. Several routes to the *N*-allyl-*N*-isobutyl enamines were established for the enamine prepared from isobutyraldehyde. With use of the most efficient route developed, enamines derived from butanal, 2-phenylpropanal, cyclohexanone, and cyclopentanone were prepared in 58 to 92% overall yield in three steps from allylamine. In the case of butanal, the *E* isomer was formed exclusively, while the enamine from 2-phenylpropanal was prepared with an *E* to *Z* selectivity of 86:14. Heating these *N*-allyl-*N*-isobutyl enamines in refluxing dioxane with 0.5 equiv of HCl produced [3,3] rearrangement for substrates derived from isobutyraldehyde, 2-phenylpropanal, and cyclohexanone; the enamines of *n*-butanal and cyclopentanone were found to react through alternate pathways.

The study of the Claisen rearrangement, the [3,3] sigmatropic shift of allyl vinyl ethers, has provided many valuable contributions to the areas of mechanistic and synthetic chemistry.[1] Several features, including the convergent nature of the allyl enol ether preparation and subsequent C–C bond formation, have contributed to the extensive use of this reaction in organic synthesis. The products of this pericyclic process, γ,δ-unsaturated carbonyl compounds, are valuable synthons with different functionality at each terminus. Because of the different reactivity at each end, subsequent synthetic elaboration or incorporation of this fragment into a larger target molecule can be efficiently accomplished.

The nitrogen analogue of the Claisen rearrangement, the 3-aza-Cope rearrangement of **1**, has been reported to undergo thermally induced [3,3] sigmatropic rearrangement to the corresponding imine at 250 °C, and subsequent hydrolysis of the imine produced **3**.[2] Several approaches to rate enhancement of this transformation have been made through the electronic modification of the enamine functionality. Thermal rearrangement of the aniline-derived *N*-phenyl-*N*-allyl enamine was found to occur at a somewhat reduced temperature of 205 °C.[2] Rearrangement at lower reaction temperatures could be achieved by substrates with oxygen substituents at C-2. For example, ketene *N*,*O*-acetals underwent thermal sigmatropic transformation at 180 °C,[3] and allylamide enolates were found to rearrange at 130 °C.[4] The temperatures necessary for rearrangement to occur have been a major limiting feature of the 3-aza-Cope rearrangement. At the elevated temperatures for thermal rearrangement, technical difficulties commonly arise in setting up the reaction, monitoring its progress, and workup of the reaction mixture. Typically, in these cases the [3,3] transformation must be incorporated into multistep synthetic sequences early, so as not to disturb sensitive functionality.

Methods of promoting the aza-Cope rearrangement at even lower temperatures have involved the formation of cationic quaternary nitrogen centers. As shown in eq 1, one way to access an intermediate such as **2** has been accomplished by methylation of the *N*-alkyl-*N*-allyl enamine **1**. Under the 80 °C conditions for methylation of



(1)

1 **2** **3**

allyl enamines, which has only been successfully performed on enamine substrates formed from 2-substituted aldehydes, rearrangement also occurred and hydrolytic workup of the reaction mixture produced **3**.[5] A modification of the methylation procedure, methylation of an *N*-allylimine

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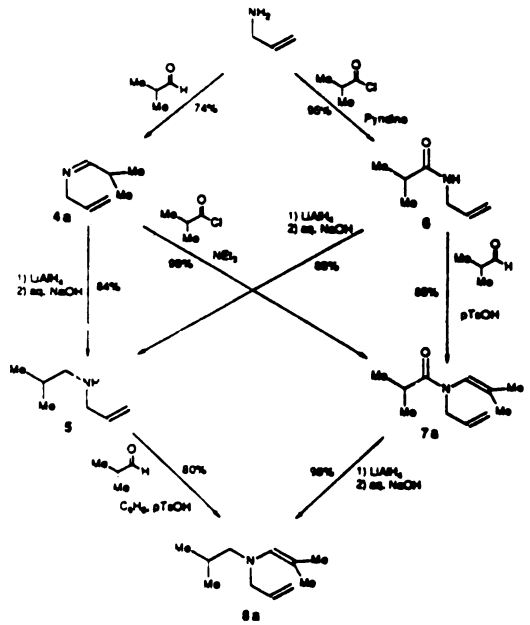
followed by the addition of a base, was found to produce rearrangement at 25 °C.[5c] More commonly, these quaternary ammonium intermediates have been obtained by allylation of *N,N*-dialkyl enamines at 80 °C, but problems involving N- versus C-allylation have limited the synthetic utility of this route to the use of symmetrical allyl groups.[6] Conjugate addition of a tertiary amine to ethyl propiolate has also been reported to produce [3,3] rearrangement through a charge-accelerated process.[7] Through these methods of rearrangement acceleration, reaction temperatures have been reduced by over 150 °C. In most cases, access to synthetically useful products was gained by hydrolytic removal of the amine functionality to form the corresponding carbonyl compound.

In a similar manner of reaction acceleration, Lewis acid catalysis of the aliphatic aza-Cope rearrangement has been reported.[8] In a landmark paper by Hill, *N*-phenyl-*N*-allyl enamines were found to rearrange at 80 °C when treated with 0.25 equiv of $TiCl_4$.[9] Coordination of the amine to the Lewis acid, generating an electron-deficient nitrogen center analogous to 2, has been suggested to produce this rate acceleration. Hill found that the in situ condensation of a carbonyl compound with a secondary amine, [3,3] rearrangement, and workup generally gave as high as 68% yield using aldehydes having only one α hydrogen. Unfortunately, only a 27% yield was obtained when straight chain aldehydes were used, and the reaction did not proceed with ketones as the carbonyl source. Bailey extended this chemistry to chiral substrates and was able to obtain asymmetric induction as high as 90% ee.[10] The use of $Pd(PPh_3)_4$ also has been reported to catalyze the rearrangement of either *N*-phenyl- or *N*-methyl-*N*-allyl enamines at 50 °C.[11] Although this reaction was found to work well for enamines derived from ketones or α-disubstituted aldehydes, π-allyl palladium intermediates were involved and the reaction did not proceed through a pericyclic reaction.

Two aspects of this chemistry have prevented the general application of the 3-aza-Cope rearrangement in organic synthesis. The first involves the limited methods available for preparation of the *N*-alkyl-*N*-allyl enamine substrates. Two methods have been reported for the synthesis of the required alkylallyl enamines. The most commonly used method is simply condensation of an acyclic secondary *N*-alkyl-*N*-allyl amine with aldehydes, accompanied by removal of water, to form the corresponding enamine.[5a,11] In practice, this works well for aldehydes that are branched at the α carbon but has been less effective at enamine formation from straight-chain aldehydes or ketones. In a second method, an *N*-alkyl-*N*-allyl amine has been used in condensation with ketones and diethyl (diazomethyl)-phosphonate to again produce the *N*-alkyl-*N*-allyl enamine of a 2-substituted aldehyde.[5b] The second limiting feature of the 3-aza-Cope reaction has been the difficulty in promoting the reaction at a reasonable temperature to obtain, upon reduction of the resulting imine, δ,ϵ-unsaturated amine products. A related system, the charge-accelerated 2-aza-Cope rearrangement developed by Overman, also has been promoted at mild temperatures. This methodology has led to many valuable contributions to synthetic organic chemistry including a number of elegant syntheses of biologically active alkaloids.[12]

Scheme I. Different Synthetic Routes to 8a



Our interests have focused on the use of the 3-aza-Cope rearrangement as an effective and convergent method of forming carbon–carbon bonds. This report describes the various routes used to efficiently prepare a variety of *N*-alkyl-*N*-allyl enamines, the proton-catalyzed [3,3] rearrangement of these compounds, and subsequent reduction of the intermediate imines to δ,ϵ-unsaturated amine products.

Results and Discussion

Substrate Synthesis. Four different routes for the synthesis of substrate 8a starting from allylamine were explored. Starting from allylamine, two approaches were studied for the formation of 5, which has been the standard intermediate for previous synthetic approaches to compounds similar to 8a (Scheme I). The condensation of allylamine with isobutyraldehyde resulted in the formation of the desired imine 4a, which could be isolated in 74%

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Table I. Isolated Yields for *N*-Alkyl-*N*-allyl Enamine Formation and Rearrangement

	yield, %			
	4	7	8	10
a	a	94	96	81
b	68	90[b]	95	0
d	a	79[c]	96[d]	77
f	a	82	98	99
g	a	68	90	10

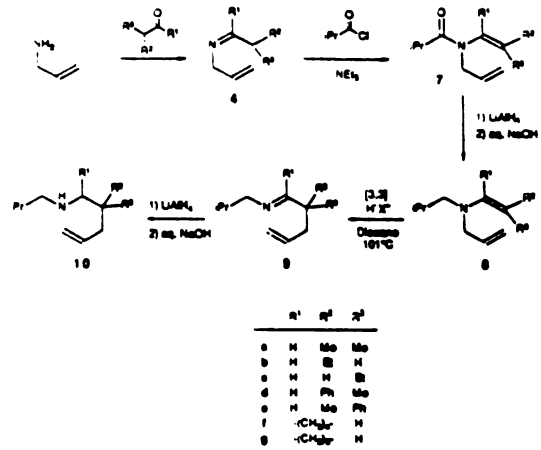
[a] Carried on to 7 without isolation. [b] Mixture of isomers b:c (63:37). [c] Mixture of isomers d:e (57:43). [d] Mixture of isomers d:e (86:14).

distilled yield. Reduction of this imine gave the corresponding amine 5 in 84% isolated yield. Alternatively, intermediate 5 could be prepared by acylation of allylamine with isobutyryl chloride to provide 6 in 95% yield, and subsequent $LiAlH_4$ reduction gave 5 in 88% isolated yield. Enamine formation by condensation of isobutyraldehyde with 5, catalyzed by *p*-toluenesulfonic acid, produced 8a in 80% distilled yield. Amide 6 could also be used for enamide formation with isobutyraldehyde, which gave an 85% yield of 7a, but the reaction took 66 h to reach completion. A third route to 8a was completed by the $LiAlH_4$ reduction of 7a in 98% isolated yield. The final route was found to be the most efficient for the general preparation of *N*-alkyl-*N*-allyl enamine substrates. This route involved acylation of imine 4a to form enamide 7a in 99% isolated yield. The efficiency of this route could be optimized by initial formation of imine 4a in benzene. Subsequent addition of NEt_3 and isobutyryl chloride, without isolation of the intermediate imine, resulted in a 94% isolated yield of enamide 7a from allylamine. These enamide intermediates were more resistant to hydrolysis than the corresponding enamines and could be purified by silica gel chromatography. The previously described reduction with $LiAlH_4$ completed the synthesis of 8a in 92% overall yield in the three-step process from allylamine.

With use of the optimum sequence for the synthesis of 8a, the *N*-alkyl-*N*-allyl enamine derivatives of butanal, 2-phenylpropanal, cyclohexanone, and cyclopentanone were also prepared (Scheme II, Table I). The *N*-alkyl-*N*-allyl enamine of butanal was prepared through the standard three-step process in order to investigate the selectivity of enamine formation. Reaction of *n*-butanal with allylamine gave predominantly the corresponding imine 4b. Due to the volatility of the compound, isolation of 4b was limited to 68% yield, but purification was necessary prior to acylation due to minor amounts of dimeric byproducts generated during imine formation. Acylation produced a 63:37 mixture of two enamine geometric isomers in 90% isolated yield. From ^1H NMR analysis using nuclear Overhauser enhancement, the major isomer was 7b, the *E* enamine isomer, with the minor isomer 7c having *Z* geometry. Acylation employing a different base, pyridine, produced a slightly higher 71:29 ratio of 7b:7c in 86% yield. Reduction of the enamide mixture with $LiAlH_4$ gave a 95% yield of a single enamine isomer having *E* geometry (8b). The nature of the isomerization process of the minor product to the more thermodynamically stable enamine, whether during reduction conditions or workup of the reaction, has not yet been determined.

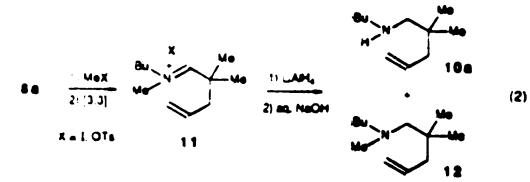
Similar results were observed for selective enamine formation using 2-phenylpropanal as the carbonyl source. Imine formation with allylamine in benzene, followed by reaction with isobutyryl chloride and NEt_3 without isolation of 4d, gave 7d in 79% overall yield for the two-step process. As was observed for the preparation of 7b, the product was isolated as a 57:43 mixture of geometric enamine isomers. On the basis of nuclear Overhauser enhancement NMR experiments, the major enamine isomer was assigned as 7d with *E* enamine geometry. Reduction of this mixture with $LiAlH_4$ also produced a change in the isomeric ratio. From reduction of the 57:43 mixture of isomers, an 86:14 mixture of isomers 8d:8e was obtained.

Scheme II. Synthesis and Rearrangement of *N*-Allyl-*N*-isobutyl Enamine Substrates



Enamine formation from cyclic ketones was also studied by using cyclohexanone and cyclopentanone. The reaction of allylamine with cyclohexanone produced imine 4f, which could be taken on without purification to enamide 7f in 82% overall yield from allylamine. Hydride reduction efficiently produced 8f in 98% yield. Preparation of the cyclopentanone imine was more difficult to drive to completion and displayed somewhat greater sensitivity toward hydrolysis. As a result, acylation of the intermediate imine 4g gave a reduced 68% yield of isolated 7g. A 90% yield of the desired enamine 8g was obtained upon reduction with $LiAlH_4$.

Rearrangement and Reduction of *N*-Alkyl-*N*-allyl Enamines. An initial approach to the δ,ϵ-unsaturated amine product 10a utilized the known methylation of 8a to produce acceleration of the [3,3] rearrangement and formation of 11 (eq 2). Methylation with MeI or MeOTs



(2)

in refluxing dioxane produced complete rearrangement to 11 within 17 h. Although treatment of each reaction mixture with $NaBH_4$ at ambient temperature gave multiple products, the use of $LiAlH_4$ under the same conditions gave more selective reduction of 11. Reduction of the MeI-promoted rearrangement using $LiAlH_4$ produced an 89:11 mixture of 10a:12 in 59% isolated yield, and the corresponding reaction with MeOTs gave a lower 72:28 ratio of 10a:12 in 68% yield.[13]

An alternate method, the proton-catalyzed rearrangement of 8a to 9a followed by $LiAlH_4$ reduction to 10a was much more effective. Initial evidence for this transfor-

(13) This tertiary amine was prepared independently by methylation of 10a to give 12.

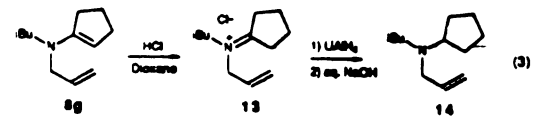
Table II. Various Conditions for HCl-Catalyzed Rearrangement of 8a to 9a

HCl, equiv	time, h	solvent, temp, °C	GLC yield, %
0.3	20	dioxane/101	74
0.3	6	toluene/111	70
0.5	6	dioxane/101	82
0.5	3	toluene/111	82
0.5	6	toluene/80	63
0.8	6	toluene/111	82

mation under protic conditions was observed when the reaction of 5 to 8a was performed in toluene instead of benzene. Through azeotropic removal of water with refluxing benzene at 80 °C, 8a was the only product of the acid-catalyzed enamine formation. However, at the higher temperature required for removal of water with refluxing toluene (111 °C), small amounts of acid-catalyzed rearrangement were observed after an extended period of time. In order to optimize reaction acceleration as well as facilitate reaction workup, anhydrous HCl was studied as a means of promoting these reactions.[14] Table II summarizes the results of the rearrangement of 8a to 9a using different equivalents of HCl, various reaction temperatures, and dioxane or toluene as solvent for the reaction. Optimum conditions were found to require 0.5 equiv of HCl at reflux in either toluene or dioxane. These conditions produced 9a as the only volatile product in 82% yield by GLC analysis and, on a preparative scale, in situ reduction of 9a allowed isolation of 10a in 81% yield for the two-step process from 8a. At lower temperatures (80 °C) or fewer equivalents of HCl (0.3 equiv), GLC reaction yields were slightly lower.

The rearrangement of 8 to 10 was highly dependent on the properties and substituent pattern of the enamine functionality. For the aldehyde substrates 8b and 8d, success was mixed. Substrate 8d, which was similar in substitution pattern to 8a, underwent complete rearrangement promoted by 0.5 equiv of HCl and, following $LiAlH_4$ reduction, 10d was isolated in 77% yield. When a straight-chain aldehyde enamine such as 8b was treated with HCl, a mixture of products resulted that did not contain 10b after reduction. Although N-protonation of enamines has been reported to be kinetically favored by hard acids such as HCl, the thermodynamic product was the iminium ion resulting from C-protonation.[15] If the resulting iminium salts were unsubstituted α to the nitrogen and had minimal steric hindrance at the nucleophilic carbon of the corresponding enamine, rapid oligomerization was found to occur.[16] Similar N- versus C-alkylation pathways have led to reduced product selectivity during the previously mentioned allylation of related enamines[6] and have limited the methylation charge-acceleration studies of *N*-alkyl-*N*-allyl enamines to the derivatives of 2-substituted aldehydes.[5]

Similarly, proton-catalyzed rearrangement of the two ketone-derived substrates was found to be highly dependent on the properties of the carbonyl compound. Rearrangement of the cyclohexanone derivative 8f proceeded quantitatively to 9f. Subsequent reduction of this imine without prior isolation gave 10f, which was obtained in 99% yield as a 90:10 mixture of diastereomers resulting from reduction with $LiAlH_4$. The use of more selective reducing agents was not pursued. In contrast, the results obtained for the cyclopentanone enamine 8g were poor. As was found for the enamine of *n*-butanal, protonation at the nucleophilic carbon of the enamine to form 13 appeared to dominate over N-protonation. Because intermolecular oligomerization pathways were less favorable for the more sterically hindered iminium salt 13, as compared to that of the aldehyde iminium salt produced by protonation of 8b, alternate monomeric products were formed. Upon reduction of the reaction mixture containing 13 and 8g with $LiAlH_4$, 14 (36%), 10g (10%), and unreacted 8g (9%) were obtained as a mixture of the only volatile products (eq 3).[17] Increasing the amount of catalyst to 1.0 equiv of HCl gave increased oligomerization of the substrate and, thus, resulted in reduced product recovery.



(3)

Summary

An efficient and general synthesis of *N*-allyl-*N*-isobutyl enamines 8 from allylamine has been established. Initial condensation of the appropriate carbonyl compounds with allylamine formed the intermediate imines 4, which were treated with isobutyryl chloride to produce the corresponding enamide substrates 7. Reduction of the enamide intermediates with $LiAlH_4$ gave 8 in good yield. For substrates that could produce isomeric (*E*)- and (*Z*)-8, dominant formation of the enamine with *E* geometry was observed. The *E* isomeric selectivity for the 2-phenylpropanal enamine was 86:14 while that of *n*-butanal was observed to produce exclusively the *E* enamine isomer. Proton-catalyzed [3,3] rearrangement and subsequent imine reduction to form the corresponding δ,ϵ-unsaturated amines was efficiently accomplished for the substrates prepared from isobutyraldehyde (81%), 2-phenylpropanal (77%), and cyclohexanone (99%). However, the enamines derived from butanal and cyclopentanone did not undergo high-yielding charge-accelerated [3,3] rearrangement but instead gave mixtures of products resulting predominantly from protonation at carbon.

Experimental Section

General Methods. All reactions were carried out by using standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of either nitrogen or argon. Benzene, toluene, tetrahydrofuran (THF), and Et_2O were distilled from sodium/benzophenone immediately prior to use. Dichloromethane, acetonitrile, pyridine, and triethylamine were heated at reflux over calcium hydride for a minimum of 12 h and then distilled immediately prior to use. 1,4-Dioxane was dried over $LiAlH_4$ and distilled. Solutions of HCl (1 M in Et_2O) and $LiAlH_4$ (1 M in THF) were obtained from Aldrich Chemical Co. Unless specified, concentration of mixtures was performed on a Büchi rotary evaporator.

Gas chromatographic (GLC) analyses were carried out on a Perkin-Elmer 8500 instrument using a 50-m RSL-200 capillary column (5% methyl phenyl silicone) and an FID detector using a 220 °C injector temperature and 300 °C detector temperature. Helium gas pressure was set at 15 psi with a flow rate of 2 mL/min. NMR spectra were obtained on Varian Gemini 300 or VXR-300 spectrometers using $CDCl_3$ as solvent. Data are reported as follows: chemical shift relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet), integration, and coupling. Infrared spectra were recorded on a Nicolet 42 FT-IR instrument.

(14) HCl is available as a 1 M solution in Et_2O from Aldrich Chemical Co.

(15) Hickmott, P. W. *Tetrahedron* 1982, *38*, 1975. Protonation of enamines is discussed on pages 1998–2000.

(16) Hinman, R. L. *Tetrahedron* 1968, *24*, 185, and references therein.

(17) This tertiary amine was prepared independently by $LiAlH_4$ reduction of the imine formed from allylamine and cyclopentanone, followed by reaction with isobutyryl chloride and reduction to give 14.

N-Allyl-N-isobutylideneamine (4a). A mixture of allylamine (3.54 g, 62 mmol), isobutyraldehyde (4.47 g, 62 mmol), and 4-Å molecular sieves in 100 mL of Et_2O was stirred for 2 h at ambient temperature. The solution was then removed from the insoluble material via cannula and distilled at atmospheric pressure to give 4a (5.11 g, 50.0 mmol) in 74% yield (bp 112–114 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.05 (d, 6 H, J = 6.9 Hz), 2.42 (dsept, 1 H, J = 4.9, 6.9 Hz), 3.95 (d, 2 H, J = 5.6 Hz), 5.05 (dd, 1 H, J = 1.8, 10.3 Hz), 5.10 (dd, 1 H, J = 1.8, 17.2 Hz), 5.93 (ddt, 1 H, J = 10.3, 17.2, 5.6 Hz), 7.51 (d, 1 H, J = 4.9 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.3, 34.1, 63.2, 115.5, 136.1, 170.9; IR (neat) 3083, 3013, 2967, 2932, 2874, 2824, 2674, 1466, 1456, 1437, 1366, 1103, 1019, 995, 916 cm^{-1}.

N-Allylisobutyramide (6). To a mixture of allylamine (9.02 g, 158 mmol) and pyridine (12.48 g, 158 mmol) in 600 mL of dry THF at 0 °C was added isobutyryl chloride (16.84 g, 158 mmol) at a dropwise rate. After addition was complete, the mixture was heated at reflux for 5 h, cooled to ambient temperature, and then washed with 50 mL of 15% aqueous NaOH. The aqueous layer was then extracted with 4 × 20 mL of Et_2O, and the organic fractions were combined and dried over $MgSO_4$. After removal of solvents by rotary evaporation, the resulting oil was distilled to give 6 (18.99 g, 149 mmol) in 95% yield (bp 78 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.13 (d, 6 H, J = 6.9 Hz), 2.37 (sept, 1 H, J = 6.9 Hz), 3.84 (ddd, 2 H, J = 1.6, 1.6, 6.6 Hz), 5.09 (ddt, 1 H, J = 1.4, 10.2, 1.6 Hz), 5.14 (ddt, 1 H, J = 1.4, 17.1, 1.6 Hz), 5.81 (ddt, 1 H, J = 10.2, 17.1, 6.6 Hz), 5.35 (br s, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.3, 35.3, 41.5, 116.2, 134.6, 177.3; IR (neat) 3293, 3085, 3015, 2971, 2934, 2876, 1645, 1545, 1470, 1422, 1387, 1242, 1098, 988, 918 cm^{-1}. Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.04; H, 9.91; N, 11.85.

Reduction of 4a to N-Allyl-N-isobutylamine (5). To a suspension of $LiAlH_4$ (1.37 g, 36 mmol) in 150 mL of Et_2O at 0 °C was slowly added 3.34 g (30 mmol) of N-allyl-N-isobutylideneamine (4a). After being stirred for 2 h, the solution was cooled to 0 °C and quenched by addition of 1.4 mL of H_2O, followed by 1.4 mL of 15% aqueous NaOH, and finally 4.1 mL of H_2O. The mixture was stirred for 1 h and then filtered through Na_2SO_4. Solvent was removed and the allylic amine was distilled at atmospheric pressure to give 5 (2.84 g, 25.1 mmol) in 84% yield (bp 122–124 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.87 (d, 6 H, J = 6.7 Hz), 1.00 (br s, 1 H), 1.70 (tsept, 1 H, J = 6.8, 6.7 Hz), 2.38 (d, 2 H, J = 6.8), 3.20 (ddd, 2 H, J = 1.4, 1.4, 6.0 Hz), 5.04 (ddt, 1 H, J = 1.7, 10.2, 1.4 Hz), 5.13 (ddt, 1 H, J = 1.7, 17.2, 1.4 Hz), 5.88 (ddt, 1 H, J = 10.2, 17.2, 6.0 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.7, 28.3, 52.6, 57.5, 115.5, 137.2; IR (neat) 3407, 3081, 2959, 2934, 2874, 2811, 1646, 1466, 1385, 1368, 1129, 918 cm^{-1}. Anal. Calcd for $C_7H_{15}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.43; H, 13.69; N, 12.21.

Reduction of 6 to N-Allyl-N-isobutylamine (5). To a suspension of $LiAlH_4$ (1.85 g, 48.6 mmol) in 200 mL of Et_2O at 0 °C was slowly added 5.62 g (44.2 mmol) of N-allylisobutyramide (6). The mixture was heated at reflux for 3 h, after which the solution was cooled to 0 °C and quenched by addition of 2 mL of water, followed by 2 mL of 15% aqueous NaOH, and again with 6 mL of water. After being stirred for 2 h, the solution was filtered through Na_2SO_4 and the solvent was removed by rotary evaporation at 0 °C. The residue was distilled at atmospheric pressure to give 5 (4.38 g, 38.7 mmol) in 88% yield (bp 125 °C). Spectroscopic data were identical with that reported for the product obtained by reduction of 4a.

Synthesis of 7a by Acylation of 4a. To 100 mL of dry THF were added 2.00 g (18 mmol) of N-allyl-N-isobutylideneamine (4a) and 1.82 g (18 mmol) of NEt_3. The mixture was cooled to 0 °C and 1.92 g (0.018 mmol) of isobutyryl chloride was added dropwise. After being heated at reflux for 2 h, the solution was cooled to ambient temperature and washed with 30 mL of 15% aqueous NaOH. The aqueous layer was extracted with 2 × 75 mL of Et_2O and then dried over Na_2SO_4. The solvents were removed under reduced pressure, and the resulting enamide was distilled via Kugelrohr distillation under vacuum to give 7a (3.24 g, 17.9 mmol) in 99% yield (bp 55–65 °C, <1 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.02 (d, 6 H, J = 6.8 Hz), 1.57 (s, 3 H), 1.70 (s, 3 H), 2.65 (sept, 1 H, J = 6.8 Hz), 3.89 (d, 2 H, J = 6.2 Hz), 5.04 (dd, 1 H, J = 1.6, 11.3 Hz), 5.06 (dd, 1 H, J = 1.6, 16.0 Hz), 5.74 (ddt, 1 H, J = 11.3, 16.0, 6.2 Hz), 5.85 (s, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.3, 18.8, 21.5, 30.9, 50.0, 116.9, 123.5, 133.4, 135.9, 177.7; IR (neat) 3083, 2975, 2936, 2876, 1653, 1472, 1404, 1242, 1208, 1092, 993, 920 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.84; H, 10.78; N, 7.72.

Preparation of 8a by Condensation of Isobutyraldehyde with 5. A flask containing 5 (1.70 g, 15 mmol), isobutyraldehyde (1.08 g, 15 mmol), and p-toluenesulfonic acid (0.007 g, 0.04 mmol) in 75 mL of benzene was fitted with a Dean–Stark trap containing 4-Å molecular sieves. The solution was heated at reflux for 28 h and the cooled to ambient temperature. After removing the benzene under reduced pressure, the resulting oil was distilled via Kugelrohr distillation under vacuum to give 8a (2.00 g, 12.0 mmol) in 80% yield (bp 45–60 °C, 8 mmHg): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (d, 6 H, J = 6.6 Hz), 1.58 (d, 3 H, J = 1.3 Hz), 1.58 (tsept, 1 H, J = 7.3, 6.6 Hz), 1.65 (d, 3 H, J = 1.3 Hz), 2.25 (d, 2 H, J = 7.3 Hz), 3.15 (ddd, 2 H, J = 1.6, 1.6, 6.2 Hz), 5.02 (ddt, 1 H, J = 2.0, 10.2, 1.6 Hz), 5.08 (ddt, 1 H, J = 2.0, 17.2, 1.6 Hz), 5.22 (qq, 1 H, J = 1.3, 1.3 Hz), 5.81 (ddt, 1 H, J = 10.2, 17.2, 6.2 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.4, 20.4, 22.0, 27.4, 59.6, 63.1, 115.9, 122.8, 135.8, 136.9; IR (neat) 3081, 3009, 2955, 2926, 2870, 2803, 1676, 1644, 1468, 1449, 1377, 1337, 1194, 1117, 1101, 995, 916 cm^{-1}. Anal. Calcd for $C_{11}H_{21}N$: C, 78.98; H, 12.65; N, 8.37. Found: C, 79.18; H, 12.83; N, 8.48.

Formation of 7a from Condensation of Isobutyraldehyde with 6. To 300 mL of benzene were added N-allylisobutyramide (3.51 g, 27.6 mmol), isobutyraldehyde (2.38 g, 33.1 mmol), and p-toluenesulfonic acid (0.48 g, 2.8 mmol). The reaction flask was fitted with a Dean–Stark trap containing 4-Å molecular sieves, and the solution was heated at reflux for 66 h. After cooling the mixture, the volatiles were removed under reduced pressure, and the enamide was distilled under vacuum to give N-allyl-N-isobutylideneisobutyramide (7a, 4.24 g, 23.4 mmol) in 85% yield (bp 60–70 °C, <1 mmHg). Spectroscopic data were identical with that reported for the product obtained by acylation of 4a.

General Method for Two-Step Synthesis of 7 from Allylamine. Allylamine (50 to 250 mmol, 1.0 equiv) and the necessary aldehyde (1.0 equiv) were taken up in benzene (0.35–0.375 M solution). A Dean–Stark trap was fitted on the apparatus and the solution was heated to reflux to azeotropically remove the resulting water. After heating for 19–22 h, the water was removed, 4-Å molecular sieves were added to the Dean–Stark trap, and reflux was continued for 2 h. The solution was cooled to ambient temperature and NEt_3 (1.0 equiv) and isobutyryl chloride (1.0 equiv) were added, sequentially, and then heated at reflux for 3 h. The mixture was filtered to remove solids, and after benzene was removed under reduced pressure, the crude oil was purified by flash column chromatography (silica, 230–400 mesh; eluent 70:30 Et_2O:petroleum ether). The solvents were evaporated and the enamide was distilled under vacuum to give 7.

7a: 42.68 g, (23.5 mmol, 94% yield) (bp 50–54 °C, <1 mmHg). Spectroscopic data were identical with that reported for the product obtained by acylation of 4a.

General Method for Reduction of 7 to N-Allyl-N-isobutyl Enamines 8. To a suspension of $LiAlH_4$ (1.1 mmol/1.0 mmol 7) in Et_2O (0.2 M solution) at 0 °C was added 7 (1.0 equiv, 9 to 66 mmol reaction scale) slowly via syringe. After addition was complete, the reaction was warmed to ambient temperature and stirred for 2–3 h. The resction was then cooled to 0 °C and quenched by addition of water (1 mL/g $LiAlH_4$), 15% aqueous NaOH (1 mL/g $LiAlH_4$), and then again water (3 mL/g $LiAlH_4$). The mixture was stirred for 2 h and then filtered through Na_2SO_4. Solvent was removed under reduced pressure and enamine 8 was distilled via short-path or Kugelrohr distillation.

8a: 9.84 g (58.8 mmol, 98% yield) (bp 54–55 °C, 8 mmHg). Spectroscopic data were consistent with that reported for the preparation of 8a by condensation of 5 with isobutyraldehyde.

General Procedure for HCl Rearrangement of 8 Followed by Reduction to 10. Enamine 8 (1.0 equiv) was dissolved in 1,4-dioxane (0.2 M solution) and 0.5 equiv of HCl (1 M solution of HCl in Et_2O) and then heated to reflux. After 9–10 h, the solution was cooled to ambient temperature and $LiAlH_4$ (1.1 equiv, 1 M in THF) was added. After being stirred for 2 h, the solution was then cooled to 0 °C and quenched by addition of water (1 mL/g $LiAlH_4$), 15% aqueous NaOH (1 mL/g $LiAlH_4$), and then again water (3 mL/g $LiAlH_4$). The mixture was allowed to stir for 1 h and then filtered to remove aluminum salts.[10] Solvent

was removed under reduced pressure and the oil was Kugelrohr distilled under vacuum to give **10**.

10a: 1.37 g (8.1 mmol, 81% yield) (bp 50–60 °C, 8 mmHg); ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.85 (s, 6 H), 0.86 (d, 6 H, J = 6.6 Hz), 0.87 (bs, 1 H), 1.71 (tsept, 1 H, J = 6.9, 6.6 Hz), 1.98 (d, 2 H, J = 7.5 Hz), 2.29 (s, 2 H), 2.35 (d, 2 H, J = 6.9 Hz), 4.99 (m, 2 H), 5.79 (ddt, 1 H, J = 9.2, 17.9, 7.5 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 25.5, 27.9, 34.4, 44.7, 59.1, 60 3, 116.6, 135.7; IR (neat) 3359, 3077, 3005, 2957, 2872, 2811, 1640, 1466, 1385, 1364, 1121, 995, 912 cm^{-1}. Anal. Calcd for $C_{11}H_{23}N$: C, 78.04; H, 13.69; N, 8.27. Found: C, 77.64; H, 13.87; N, 7.68.

***N*-Methyl-*N*-isobutyl-2,2-dimethylpent-4-enamine (12).** To 25 mL of dry acetonitrile were added 0.847 g (5 mmol) of **10a** and 0.710 g (5 mmol) of MeI. The solution was heated to reflux for 12.5 h and then cooled to ambient temperature. Solvent was removed under reduced pressure and the residue was washed with 10 mL of 15% aqueous NaOH and extracted with 3 × 50 mL portions of Et_2O. The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Kugelrohr distillation under vacuum gave 0.739 g (4.0 mmol, 81% yield) of **12** (bp 60–70 °C, 10 mmHg): ^{1}H NMR (300 MHz) ($CDCl_3$) δ 0.82 (s, 6 H), 0.87 (d, 6 H, J = 6.6 Hz), 1.65 (tsept, 1 H, J = 7.4, 6.6 Hz), 1.97 (d, 2 H, J = 7.4 Hz), 2.07 (s, 2 H), 2.10 (d, 2 H, J = 7.4 Hz), 2.18 (s, 3 H), 4.97 (m, 2 H), 5.81 (ddt, 1 H, J = 11.0, 18.8, 7.4 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 25.4, 26.8, 36.0, 44.9, 45.0, 69.5, 70.2, 116.6, 136.4; IR (neat) 3077, 2978, 2843, 2786, 1640, 1470, 1385, 1366, 1250, 1105, 1040, 993, 909, 850 cm^{-1}. Anal. Calcd for $C_{12}H_{25}N$: C, 78.62; H, 13.74; N, 7.64. Found: C, 78.55; H, 13.48; N, 7.70.

(18) In the case of the more volatile compounds **10a** and **10b**, an excess of aqueous HCl was added, and the solution was concentrated under reduced pressure. The residue was treated with 15% aqueous NaOH to a pH of 14, the amine was extracted with 3 × 50 mL portions of Et_2O, and the organic layers were dried ($MgSO_4$) prior to distillation.

MeI-Promoted Rearrangement of 8a Followed by $LiAlH_4$ Reduction. To 15 mL of 1,4-dioxane were added 1.34 g (8 mmol) of enamine **8a** and 1.14 g (8 mmol) of MeI. The solution was heated to reflux for 17 h and then cooled to 0 °C. The reaction was reduced by addition of $LiAlH_4$ (16.0 mL, 1 M in THF, 16 mmol), warming to ambient temperature, and then stirring for 2 h. The solution was then cooled to 0 °C and quenched by addition of 0.6 mL of water, 0.6 mL of 15% aqueous NaOH, and 1.8 mL of water. After being stirred for 1 h, the mixture was filtered and then treated with an excess of aqueous HCl. The solution was concentrated under reduced pressure and the residue was treated with 15% aqueous NaOH to a pH of 14. The amine products were extracted with 3 × 50 mL portions of Et_2O and the organic layer was dried ($MgSO_4$). Volatiles were removed by rotary evaporation and the oil was Kugelrohr distilled under vacuum to give 0.81 g (59% yield) of an 89:11 mixture of *N*-isobutyl-2,2-dimethylpent-4-enamine (**10a**) and *N*-methyl-*N*-isobutyl-2,2-dimethylpent-4-enamine (**12**) (bp 60–65 °C, 10 mmHg).

MeOTs-Promoted Rearrangement of 8a Followed by $LiAlH_4$ Reduction. The reaction was performed under conditions identical with those described above, using 1.49 g (8 mmol) of MeOTs. Distillation after workup gave 0.96 g (68% yield) of a 72:28 mixture of *N*-isobutyl-2,2-dimethylpent-4-enamine (**10a**) and *N*-methyl-*N*-isobutyl-2,2-dimethylpent-4-enamine (**12**) (bp 60–65 °C, 10 mmHg).

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Supplementary Material Available: Experimental procedures and physical data for the series of compounds **b–g** (5 pages). Ordering information is given on any current masthead page.

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Lewis Acid-Promoted 3-Aza-Cope Rearrangement of *N*-Alkyl-*N*-allylenamines

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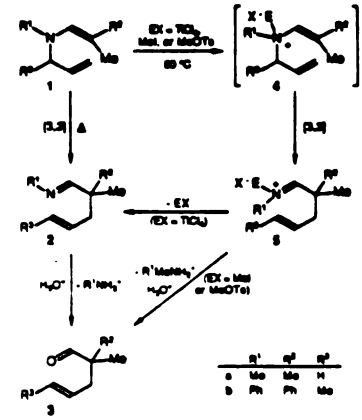
The 3-aza-Cope rearrangement of the *N*-alkyl-*N*-allylenamines derived from isobutyraldehyde, which proceeds thermally at 250 °C, has been accelerated by a variety of electrophilic reagents to give γ,δ-unsaturated imines. Protic acids, such as HCl (0.5 equiv), and the Lewis acidic reagents $TiCl_4$ (0.1–0.2 equiv), $Et_2O{\cdot}BF_3$ (0.5 equiv), and $AlMe_3$ (1.0 equiv) produced complete [3,3] rearrangement of substrates at 111 °C. By increasing the Lewis acidity of the aluminum reagents, this transformation was achieved at 50 °C with $ClAlMe_2$, Cl_2AlMe, and methylaluminum bis(2,6-diphenylphenoxide). Reaction conditions were studied initially by GLC analysis of the *N*-isobutyl derivative. These optimum conditions were then used to obtain isolated yields of 59–99% for rearrangement and in situ $LiAlH_4$ reduction of the analogous *N*-methylcyclohexyl substrate to the corresponding δ,ε-unsaturated amine. Substrates derived from 2-phenylpropanal, *n*-butanal, cyclohexanone, and cyclopentanone were used to examine the general effectiveness of HCl, $TiCl_4$, and $AlMe_3$ as reagents for acceleration of the [3,3] rearrangement. The most versatile and efficient reagent for promoting this reaction, $AlMe_3$, produced overall yields of 83–96% for the two-step rearrangement and reduction of these substrates.

Introduction

The [3,3] sigmatropic shift of allyl vinyl ethers, the Claisen rearrangement, has had significant impact on the regio- and stereochemically controlled formation of carbon–carbon bonds, and mechanistic studies of this rearrangement have provided important insight into these and related pericyclic processes.[1] While the analogous 3-aza-Cope rearrangement of allylenamine substrates has many of the same advantages, there are intrinsic properties of this nitrogen system that provide for some unique synthetic opportunities (1 to 2, Scheme I). Included in these features are the higher *E*–*Z* control of enamine geometry, which presents a valuable alternative to the less selective enol ether formation,[2] and the availability of optically active allylamines from amino acid sources.[3] A rather intriguing feature of this substrate is the presence of an asymmetric heteroatom at the 3-position, a property which the allyl vinyl ether substrates lack.[3]

Scheme I



Despite the attractive possibilities of this reaction, the 3-aza-Cope rearrangement has been of limited synthetic utility due, in part, to the elevated temperatures required for thermally induced rearrangement, 250 °C for **1a** to **2a** and 205 °C for **1b** to **2b**.[4] In order to overcome these limitations, a number of methods for accelerating this rearrangement have appeared involving manipulation of the electron density of the atoms in the six-membered transition state. An increase in electron density at the enamine functionality through the use of *N*-allylketene *N,O*-acetals produced rearrangement at 180–190 °C, a significant decrease from the 250 °C required for the corresponding enamines.[3,5] A similar [3,3] rearrangement occurred for a substrate with a dialkylamine substituent.

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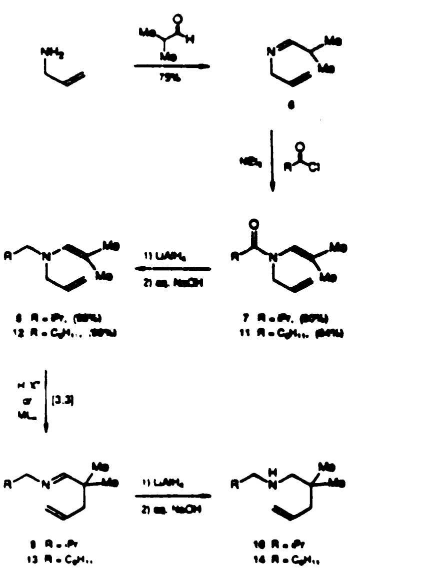
an N-alkylketene N,N-acetal, at 200 °C.[5a] Increasing electron density at the enamine by formation of the N-allylamide enolates further reduced the temperature required for rearrangement to 135 °C.[6]

Other methods of promoting the 3-aza-Cope rearrangement through charge-accelerated processes have included reducing the electron density on the nitrogen. The effectiveness of this approach is apparent from the slightly lower reaction temperature required for the less Lewis basic aniline derivative **1b** (205 °C) than for the rearrangement of **1a** (Scheme I).[4] Further reduction in the electron density at nitrogen, by forming a cationic quaternary nitrogen center, has produced rearrangement at a temperature as low as 80 °C. The quaternary ammonium intermediate **4a** has been accessed by methylation of **1a** as shown in Scheme I,[7] and a modification of the methylation procedure, methylation of an N-allylimine followed by the addition of a base, has been found to produce rearrangement at 25 °C.[8] A more common route to **4** has been the allylation of N,N-dialkylenamines.[9] Unfortunately, symmetrical allyl groups must be used to avoid problems associated with N- versus C-allylation in this method. Another type of route has been reported that used conjugate addition of a tertiary amine to ethyl propiolate to form the cationic nitrogen species.[10] In most of these cases in which the tetraalkyl ammonium species was generated, product isolation was limited to hydrolysis of the iminium ion **5** to the corresponding aldehyde **3**, the same product accessible through Claisen rearrangement.

The use of non-carbon electrophiles, in the form of Lewis acid catalysts, have been explored as well.[11] Although Lewis acid catalysis of the Claisen rearrangement has been studied extensively,[12] only one method of promoting the aliphatic 3-aza-Cope sigmatropic rearrangement has been reported. In this case, the use of 0.25 equiv of $TiCl_4$

Scheme II



promoted transformation of **1b** to **2b** at 80 °C.[13] Complexation of the enamine to the Lewis acid, generating an electron-deficient nitrogen center, has been suggested to produce this rate enhancement. However, this in situ carbonyl condensation and rearrangement procedure was less effective for straight-chain aldehydes (20–30%) and was unsuccessful for ketones. A recent report by Bailey has extended the use of $TiCl_4$ to obtain asymmetric induction as high as 90% ee for substrates where R^1NH_2 was (*R*)-(+)-α-methylbenzylamine.[14] In each case, this methodology has been limited to the use of enamines formed from 2-substituted aldehydes.[15]

Our own research interests have focused on the use of the aliphatic 3-aza-Cope rearrangement in organic synthesis. In order to develop this method into a useful synthetic carbon–carbon bond-forming reaction, we found it necessary to determine which of a variety of catalysts would promote the rearrangement of **1** to **2** most efficiently. The generality of the electrophilic reagents was investigated for a variety of enamine substrates prepared from the aldehydes 2-methylpropanal, 2-phenylpropanal, and *n*-butanal and from the ketones cyclohexanone and cyclopentanone. Hydride reduction of imine **2** would then provide a route to the corresponding δ,ε-unsaturated amine, which has found creative use in the formation of nitrogen heterocycles.[16]

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Results and Discussion

Substrate Preparation. Determination of the ability of Lewis acid catalysts to accelerate the 3-aza-Cope rearrangement required the preparation of two *N*-allyl-*N*-alkylenamine substrates (Scheme II). For the purposes of optimizing reaction conditions by capillary gas chromatography (GLC), **8** was ideal for analysis of the reaction progress and product formation. However, the product of rearrangement and reduction, **10**, proved to be somewhat volatile, and the use of substrate **12** was preferable to facilitate the process of obtaining optimum isolated yields for the δ,ε-unsaturated amine.

Synthesis of **8** and **12** was accomplished from allylamine through the route illustrated in Scheme II. Imine formation from the reaction of allylamine with isobutyraldehyde gave **6** in 75% yield, and subsequent reaction of **6** with isobutyryl chloride and NEt_3 produced a 90% yield of reported.[17] Reduction of enamide **7** with $LiAlH_4$ gave **8** as the only product in 98% distilled yield. In the same manner, compound **11** was prepared by reaction of **6** with cyclohexanecarbonyl chloride in 84% yield or, if the reaction mixture containing **6** was acylated without prior isolation of the imine, **11** was isolated in 68% yield in two steps from allylamine. Reduction of enamide **11** with $LiAlH_4$ produced a 99% yield of the desired enamine **12**. Substrates **15**, **18**, **21**, and **24** (eqs 1 and 2), which vary in enamine substituent pattern, were prepared by the same route from the corresponding carbonyl compound as previously reported.[17]

Rearrangement Promoted by Proton Sources. Catalysis of the [3,3] rearrangement by protic acids was first observed during the preparation of **8** through a more established route for enamine formation.[17] Heating *N*-allyl-*N*-isobutylamine and isobutyraldehyde in the presence of 0.0025 equiv of *p*-toluenesulfonic acid, with azeotropic removal of H_2O, produced the corresponding enamine **8**. If the enamine condensation reaction mixture was heated to reflux in benzene (80 °C), the reaction was found to give **8** in 80% yield as the only product. However, with the use of toluene to azeotrope the water (111 °C), the rearrangement product **9** was formed from **8** to an extent of 10–15% over the course of 72 h. In order to enhance the conversion to **9**, increased amounts of a stronger acid were required.[18]

HCl as the proton source produced efficient transformation of **8** to **9**, and conditions of the reaction were optimized by GLC analysis (Table I). This acid-promoted rearrangement required only 0.3 equiv of HCl for complete conversion to **9** within 6 h in refluxing toluene.[19] The use of 0.5 equiv of HCl produced a slight increase in yield, optimized at 82%, but further increase in the amount of catalyst to 0.8 equiv of HCl offered no synthetic advantage. Complete conversion was achieved at a lower temperature (80 °C) with 0.5 equiv of HCl, but the yield was significantly reduced. Product isolation by in situ reduction of the imine with $LiAlH_4$ gave the corresponding amine **10** in 81% yield.[20] Rearrangement and reduction of the less volatile **12** under the same conditions produced a slightly improved 85% isolated yield of **14**.[21]

Table I. Catalytic Acceleration of the 3-Aza-Cope Rearrangement[a]

reagent	equiv	time/temp (h/°C)	yields (%) GLC[b]	yields (%) isolated[c]
HCl	0.3	6/111	70	
	0.5	3/111	82	85
	0.5	6/80	64	
	0.8	6/111	82	
$TiCl_4$	0.1	24/111	83	73[d]
	0.3	24/111	64	
	0.5	24/111	56	
	0.5	24/80[e]	8	
$(ArO)_2TiCl_2$	0.5	24/111	80	71
	0.5	48/111	87	
$Et_2O{\cdot}BF_3$	0.5	24/80[f]	59	
	0.5	24/111	82	59
	1.0	9/111	75	
	1.5	5/111	70	
$SnCl_4$	0.1	48/111[g]	14	
$ZnCl_2$	1.0	12/111	86	
	1.0	24/111	74	

[a] All reactions were run 0.2 M in toluene. [b] Rearrangement of **8** to **9** was performed on a 1.0 mmol scale. Yields were determined by capillary gas chromatographic (GLC) analysis of the quenched reaction mixture (10% w/v MeONa/MeOH) using internal standards and correcting for detector response (ref 19). Values were based on reacted substrate. [c] Isolated yield of **14** after rearrangement of **12** (5 mmol) followed by in situ reduction of **13**. [d] 0.2 equiv of catalyst required on 5.0 mmol scale. [e] 18% conversion. [f] 97% conversion. [g] 84% conversion.

Rearrangement by Metal Halides. The use of $TiCl_4$, which has been reported to promote rearrangement in similar systems,[13] was examined as a means of promoting the transformation of **8** to **9** under a variety of conditions.[22] Carbon–carbon bond formation was found to proceed within 24 h in refluxing toluene with as little as 0.1 equiv of Lewis acid. Increasing the quantity of $TiCl_4$ still produced a single volatile product, but caused a decrease in yield presumably through enhanced substrate oligomerization. At a lower reaction temperature of 80 °C, 0.5 equiv of this Lewis acid only produced 18% conversion to **9** within 24 h. On a larger reaction scale, 0.2 equiv of $TiCl_4$ was typically required to achieve complete conversion to imine product.[23] Catalysis of the rearrangement of **8** to **9** with 0.2 equiv of $TiCl_4$, followed by in situ reduction of the resulting imine with $LiAlH_4$, produced **10** in 71% isolated yield.[20] Similarly, transformation of **12** to **14** was accomplished in 73% yield. Steric and electronic modification of the titanium catalyst, by the exchange of ligands to form bis(2,6-diphenylphenoxy)$TiCl_2$,[24] promoted rear-

(17) Cook, G. R.; Stille, J. R. *J. Org. Chem.* **1991**, *56*, 5578.

(18) Weaker acid catalysts, such as phenol or 2,6-diphenylphenol (0.5 equiv), produced only minor amounts of **9** at 111 °C during consumption of **8** under a variety of reaction conditions.

(19) Reaction mixtures were quenched with a 10% w/v solution of NaOMe/MeOH for analysis by GLC. Under the quenching conditions, loss of **8** or **9** was not observed even after an extended period of time (24 h).

(20) In the case of the more volatile compound **10**, an excess of aqueous HCl was added, and the solution was concentrated under reduced pressure. The residue was treated with 15% aqueous NaOH to a pH of 14, the amine was extracted with 3 × 50 mL portions of Et_2O, and the organic layers were dried ($MgSO_4$) prior to distillation.

(21) For transformations with some of the electrophilic reagents containing halogens (HCl, $ClAlMe_2$, and Cl_2AlMe), GLC yields were lower than isolated yields in some cases due possibly to ammonium chloride salt formation prior to analysis.

(22) Because hydrolysis of $TiCl_4$ could produce up to 4 equiv of HCl, which was also found to promote rearrangement, the $TiCl_4$ was distilled prior to use and rigorous measures were taken to exclude oxygen and water from the reaction mixtures. In each case, the characteristics of the $TiCl_4$-catalyzed rearrangements were very different from those of the HCl reactions.

(23) The addition of $TiCl_4$ to the enamine produced an oil on the sides of the flask, which could be a mixture of the salts corresponding to **4** and **5**. The increased amount of catalyst required to get complete conversion of **8** to **9** could be due to the decreased surface area/volume ratio of the reaction vessel as the reaction is scaled up. As a result, the surface area of the oily intermediate was decreased, and the reaction slowed.

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Table II. Studies of [3,3] Rearrangement Promoted by Aluminum Reagents[a]

reagent	equiv	time, temp (h, °C)	yields (%) GLC[b]	isolated[c]
$AlMe_3$	0.5	24, 111	100	
	1.0	12, 111	100	99
	1.5	6, 111	100	
	1.5	24, 80	100	
$ClAlMe_2$	0.2	24, 111	50[d]	
	0.5	24, 80	71[e]	
	1.0	24, 25	54	
	1.0	24, 40	67	
	1.0	24, 50	88	91
	1.0	9, 60	83	
	1.0	5, 80	96	96
Cl_2AlMe	1.0	24, 50	79	87
	1.0	12, 80	91	84
$(ArO)_2AlMe$	1.0	24, 40	87	80
	1.0	12, 60	84	
Cl_3Al	1.0	24, 50	36	
	1.0	24, 80	63	

[a] All reactions were run 0.2 M in toluene. [b] Rearrangement of 8 to 9 was performed on a 1.0 mmol scale. Yields were determined by capillary gas chromatographic (GLC) analysis of the quenched reaction mixture (10% w/v MeONa–MeOH) using internal standards are correcting for detector response (ref 19). Values were based on reacted substrate. [c] Isolated yield of 14 after rearrangement of 12 (5 mmol) followed by in situ reduction of 13. [d] 19% conversion to product. [e] 80% conversion to product.

rangement of 8 to 9 at 111 °C in 87% yield by GLC analysis. Rearrangement of 12 to 13, followed by reduction with $LiAlH_4$, gave 14 in 71% isolated yield with use of this catalyst.

Although there has been one report in which BF_3 was used as a catalyst for formation of an *N*-allyl *N,N*-ketene acetal at 30 °C, there was no evidence for charge accelerated rearrangement under the reaction conditions.[25] However, rearrangement of substrate 8 was promoted by Et_2O-BF_3 at a higher temperature of 111 °C. For complete conversion to 9 within 24 h, a minimum of 0.5 equiv of catalyst was required, and increasing quantities of Et_2O-BF_3 gave progressively decreasing yields. At a milder temperature of 80 °C, conversion to 9 by using 0.5 equiv of Et_2O-BF_3 was only 97% complete after 24 h with a somewhat lower yield of 59%. With use of the optimum conditions, transformations of 12 to 14 was achieved in 59% isolated yield. Rearrangement promoted by $ZnCl_2$, one of the most effective catalysts reported for the rearrangement of allylaniline substrates,[11a] produced less selective transformation of 8 to 9. When 1.0 equiv of the Lewis acid was used, rearrangement required 12 h to reach completion with 86% GLC yield of 9, but 8–15% of an unidentified side product was unavoidably generated in the process. Further exposure to the reaction conditions caused degradation of 9 over the course of time.

Rearrangement by Organoaluminum Complexes. As found for the Claisen rearrangement, complexes of aluminum were the most effective catalysts for the 3-aza-Cope rearrangement.[12] Acceleration of the 3-aza-Cope rearrangement with aluminum reagents also paralleled that of the Claisen rearrangement in that stoichiometric amounts of the complexes were necessary to produce complete transformation of 8 to 9. For example, the use of 0.5 equiv of $AlMe_3$ at 111 °C produced 59% conversion of 8 to 9 after 6 h, but the reaction only progressed to 68%

(25) Ficini, J.; Barbara, C. *Tetrahedron Lett.* 1966, 6425.

Table III. Yields of the 3-Aza-Cope Rearrangement/Reduction as a Function of Reagent and Enamine Substitution Pattern[a]

substrate	product	reagent (equiv) HCl (0.5)	$TiCl_4$ (0.2)	$AlMe_3$ (1.0)
8	10	81	71	95
12	14	85	73	99
15[b]	17	77	88	92
18	20	0	0	84
21	23	99	92	96
24	26	10[c]	3[c]	83

[a] Isolated yields of reactions performed 0.2 M in refluxing toluene followed by treatment with $LiAlH_4$. [b] *E:Z* = 86:14. [c] Purified yields (ref 29).

conversion after an additional 18 h (Table II). Increasing the initial amount of Lewis acid to 1.0 equiv, produced complete transformation within 12 h at 111 °C in 100% GLC yield. Under these optimum conditions, the rearrangement and reduction of 8 produced 10 in 95% yield,[20] and the same transformation with 12 gave a 99% isolated yield of 14. Complete conversion to product was also achieved at a temperature as low as 80 °C within 24 h, but required the use of 1.5 equiv of $AlMe_3$. Although the Claisen rearrangement of allyl vinyl ethers with $AlMe_3$ was found to result in addition of a methyl group to the resulting aldehyde, addition of a methyl group to the imines 9 or 13 was not observed after the analogous 3-aza-Cope transformation.[26]

As expected, increasing the Lewis acidity of the aluminum catalyst produced conversion of 8 to 9 with reduced reaction times or at lower reaction temperatures (Table II). By the use of 1.0 equiv of $ClAlMe_2$ at 80 °C, the reaction was complete within 5 h in 96% yield by GLC analysis. With the use of these conditions for rearrangement of 12 and subsequent reduction of 13 gave a 96% yield of the corresponding secondary amine.[21] Complete conversion of 12 to 13 also was achieved within 24 h at a temperature of 50 °C in 88% yield by GLC. This reaction temperature represents an overall decrease of 200 °C from the conditions necessary for thermal rearrangement! As was discussed for $AlMe_3$, $ClAlMe_2$ also was required in stoichiometric amounts. Rearrangement of 8 at 111 °C with 0.2 equiv of catalyst was only 19% complete after 24 h. The use of 0.5 equiv of Lewis acid at 80 °C gave a 57% conversion to 9 in 3 h, but the reaction advanced to only 60% conversion after an additional 21 h. Further increase of the aluminum Lewis acidity, by the use of Cl_2AlMe, produced results similar to those observed for $ClAlMe_2$. At 80 °C, a 91% GLC yield of 8 to 9 was obtained, and the reaction of 12 under these same conditions gave an 84% isolated yield of 14. Comparable yields were obtained at 50 °C.

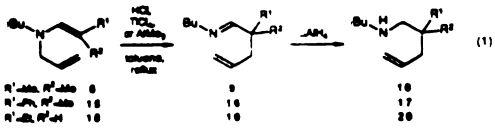
An aluminum catalyst of similar oxidation state, methylaluminum bis(2,6-diphenylphenoxide),[12b] was also a very efficient catalyst for facilitating the 3-aza-Cope rearrangement. Rearrangement of 8 to 9 using this catalyst was complete within 24 h at 25 °C to give a 59% yield, and a yield of 87% was obtained by promoting the reaction at 40 °C. Similarly, the rearrangement and reduction of 12 under these conditions produced an 80% yield of 14. To

(26) The preparation of the product of methyl addition to 9, *N*-(2-methyl-1-propyl)-*N*-(1,2,2-trimethylpent-4-en-1-yl)amine, was performed by the addition of methylmagnesium bromide to 9 followed by aqueous workup.

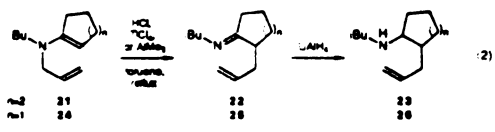
complete the methyl- and chloro-substituted series of aluminum Lewis acids, Cl_3Al was used as a catalyst for the transformation of **8** to **9**. This catalyst produced significantly lower yields of product under the same rearrangement conditions as those used for Cl_2AlMe.

Variation of Enamine Substitution. In order to determine the versatility of the different types of reagents (protic acids, metal halides, and organoaluminum species) on various substrates, three representative reagents were studied. These reagents, HCl, $TiCl_4$, and $AlMe_3$, were each used to promote rearrangement of substrates **15**, **18**, **21**, and **24**, which all differed in enamine substitution pattern. The results are shown in Table III.

The 3-aza-Cope rearrangement of the aldehyde enamines was highly dependent on both the enamine substituent pattern and the type of electrophile used. With the traditionally successful geminally disubstituted enamine substrates,[7,9] such as **8** and **12**, rearrangement and subsequent reduction gave good yields of **10** and **14**, as previously discussed. The substrate derived from 2-phenylpropanal, **15**, gave similar results (eq 1). Rearrangement of **15** to **16** followed by $LiAlH_4$ reduction produced isolated yields which ranged from 77% to 92% for the three reagents. Substrate **18**, with only one alkyl substituent on the nucleophilic enamine carbon, was much more sensitive toward these reaction conditions. Treatment with HCl (0.5 or 1.0 equiv) or $TiCl_4$ (0.1 to 1.0 equiv) under a variety of conditions produced complete degradation of **18** to oligomeric products. In contrast, treatment of **18** with $AlMe_3$ resulted in rearrangement to **19** as the only volatile product, and reductive workup gave an 84% isolated yield of **20**.



The properties of the carbonyl compound had an enormous effect on the success of the acceleration of the 3-aza-Cope rearrangement for the ketone-derived substrates. The transformation of **21** to **22** proceeded quantitatively with each electrophilic reagent used, and reduction of the intermediate imine with $LiAlH_4$ gave **23** as a 90:10 mixture of diastereomers (eq 2).[27] For each reagent, isolated yields of greater than 92% were obtained. However, the results obtained for rearrangement and reduction of **24** were poor with the use of HCl or $TiCl_4$. Rearrangement with HCl for lengthy reaction times, followed by reduction with $LiAlH_4$, resulted in a mixture of unreacted **24** (9%), *N*-isobutyl-*N*-allylcyclopentylamine (**27**, 36%),[28] and **26** (10%) as the only distillable products.[29]



The reaction with $TiCl_4$ resulted in a similar mixture of **24** (11%), **27** (26%), and **26** (3%), and the use of an alternate catalyst, Et_2O-BF_3 (0.5 equiv), gave a somewhat improved mixture of **27** (11%) and **26** (43%). As was found for **18**, the other substrate sensitive to HCl and $TiCl_4$ conditions, a stoichiometric amount of $AlMe_3$ successfully promoted the 3-aza-Cope rearrangement of **24**. Carbon–carbon bond formation and imine reduction produced an 83% yield of **26** as a 90:10 mixture of diastereomers.[27]

There are several features that made $AlMe_3$ a rather unique reagent for the acceleration of the 3-aza-Cope rearrangement. The most apparent difference was that $AlMe_3$ must be used in stoichiometric quantities for 3-aza-Cope rearrangement to reach completion. These observations suggest that the aluminum reagent formed a complex with the nitrogen of the imine product (**5**) that was not easily recycled to form the complex with substrate **4**. Although requiring 1.0 equiv of $AlMe_3$ places a limitation on this methodology, this same affinity for nitrogen may be directly related to the effectiveness of this reagent. As has been demonstrated, enamine substrates which were more subject to electrophilic attack at carbon, such as **18** and **24**, react through alternate pathways with HCl and $TiCl_4$.[30] However, the differing properties of the Lewis acid/base interaction of the aluminum with the enamines made this reagent much more compatable with sensitive enamine substrates. As a result, $AlMe_3$ was a versatile and efficient reagent for carbon–carbon bond formation through the charge-accelerated 3-aza-Cope rearrangement with all substrates tested.

Summary

Acceleration of the 3-aza-Cope rearrangement of the *N*-alkyl-*N*-allylenamines derived from isobutyraldehyde was accomplished at temperatures as low as 25 °C, which represents a decrease in reaction temperature of greater than 200 °C from that of the thermal rearrangement. A variety of catalysts, including protic acids (HCl), transition-metal halides ($TiCl_4$, BF_3, $ZnCl_2$), and organometallic reagents ($X_nAlMe_{(3-n)}$), effectively promoted rearrangement of the *N*-alkyl-*N*-allylenamine to the corresponding imine. Each type of electrophilic reagent demonstrated different stoichiometry requirements, from 0.1 to 1.0 equiv, for complete conversion of substrate to product. Reduction of the intermediate imine, without prior isolation, gave **14** in 59 to 99% isolated yields for the two-step process from **12**. The substitution pattern of the enamine substrates was critical to successful 3-aza-Cope rearrangement by HCl and $TiCl_4$, but $AlMe_3$ produced efficient product formation with even the most sensitive enamine substrates.

Experimental Section

General Methods. All reactions were carried out performing standard inert atmosphere techniques to exclude moisture and oxygen, and reactions were performed under an atmosphere of either nitrogen or argon. Benzene, toluene, tetrahydrofuran (THF), and Et_2O were distilled from sodium/benzophenone immediately prior to use. Triethylamine was heated at reflux over calcium hydride for a minimum of 12 h and then distilled immediately prior to use. Solutions of HCl (1.0 M in Et_2O), $LiAlH_4$ (1.0 M in THF), and Cl_2AlMe (1.0 M in hexanes) were obtained from Aldrich Chemical Co. Solutions of $AlMe_3$ and $ClAlMe_2$ (1.0 M in toluene) were prepared from neat organoaluminum compounds obtained from Aldrich Chemical Co. Cyclohexanecarbonyl chlorides, isobutyryl chloride, allyl amine, $TiCl_4$, and Et_2O-BF_3 were distilled prior to use. Additions were made with gas tight

(27) The use of other hydride reducing agents to achieve greater selectivity is currently being investigated.

(28) Tertiary amine **18** was prepared through an independent route. *N*-allylcyclopentylamine was made by $LiAlH_4$ reduction of the imine formed from allylamine and cyclopentanone. Reaction with 2-methylpropanoyl chloride and NEt_3 gave the corresponding secondary amide, which was reduced to **18** with $LiAlH_4$.

(29) A mixture of products was obtained by distillation (40–44% mass recovery), and the individual yields were calculated on the contribution of each compound to this purified product mixture.

(30) For discussions of N- versus C-protonation of enamines, see: (a) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. (b) Hinman, R. L. *Tetrahedron* **1968**, *24*, 185, and references therein.

syringes or via cannula transfer under nitrogen. Unless specified, concentration of solutions after workup was performed on a Büchi rotary evaporator.

Gas chromatographic (GLC) analyses were carried out on a Perkin-Elmer 8500 instrument with a 50 m RSL-200 capillary column (5% methyl phenyl silicone), an FID detector at a 220 °C injector temperature, and a 300 °C detector temperature. Helium gas pressure was set at 15 psi with a flow rate of 2 mL/min. NMR spectra were obtained on Varian Gemini 300 or VRX-300 spectrometers with $CDCl_3$ as solvent. Data are reported as follows: chemical shift relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet), integration, and coupling. Infrared spectra were recorded on a Nicolet 42 FT-IR instrument.

N-Allylisobutylideneamine (6). Allylamine (3.54 g, 62 mmol) was added to a flask containing 100 mL of Et_2O and 14 g of 4-Å molecular sieves. Over the period of 10 min, isobutyraldehyde (4.47 g, 62 mmol) was added dropwise at 25 °C. After being stirred at ambient temperature overnight, the solution was filtered and the remaining solids were washed with two 50-mL portions of Et_2O. The mixture then was distilled under nitrogen at atmospheric pressure to give 6 (5.13 g, 46.0 mmol) in 75% yield (bp 112–114 °C): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.05 (d, 6 H, J = 6.9 Hz), 2.42 (dsept, 1 H, J = 4.9, 6.9 Hz), 3.95 (d, 2 H, J = 5.6 Hz), 5.05 (dd, 1 H, J = 1.8, 10.3 Hz), 5.10 (dd, 1 H, J = 1.8, 17.2 Hz), 5.93 (ddt, 1 H, J = 10.3, 17.2, 5.6 Hz), 7.51 (d, 1 H, J = 4.9 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 19.3, 34.1, 63.2, 115.5, 136.1, 170.9; IR (neat) 3083, 3013, 2967, 2932, 2874, 2824, 2674, 1466, 1456, 1437, 1366, 1103, 1019, 995, 916 cm^{-1}.

Synthesis of 7 by Acylation of 6. To 50 mL of dry THF were added 6 (3.34 g, 30 mmol) and NEt_3 (3.54 g, 33 mmol). The solution was cooled to 0 °C, and isobutyryl chloride (3.50 g, 33 mmol) in 20 mL of THF was added dropwise over a 30-min period. After being heated at reflux for 1.5 h, the solution was cooled to ambieng temperature and filtered through a pad of silica on a glass frit, and the solids were washed with two portions of Et_2O. The solvents were removed under reduced pressure, and the crude oil was purified by flash column chromatography (silica, 230–400 mesh; eluent 50:50 Et_2O–petroleum ether). The solvents were evaporated, and the enamide was isolated via Kugelrohr distillation under vacuum to give 7 (4.88 g, 27 mmol) in 90% yield (bp 55–65 °C (<1 mmHg)): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.02 (d, 6 H, J = 6.8 Hz), 1.57 (s, 3 H), 1.70 (s, 3 H), 2.65 (sept, 1 H, J = 6.8 Hz), 3.89 (d, 2 H, J = 6.2 Hz), 5.04 (dd, 1 H, J = 1.6, 11.3 Hz), 5.06 (dd, 1 H, J = 1.6, 16.0 Hz), 5.74 (ddt, 1 H, J = 11.3, 16.0, 6.2 Hz), 5.85 (s, 1 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.3, 18.8, 21.5, 30.9, 50.0, 116.9, 123.5, 133.4, 135.9, 177.7; IR (neat) 3083, 2975, 2936, 2876, 1653, 1472, 1404, 1242, 1208, 1092, 993, 920 cm^{-1}. Anal. Calcd for $C_{11}H_{19}N$: C, 74.27; H, 13.36; N, 12.37. Found: C, 74.43; H, 13.69; N, 12.21.

Reduction of 7 to 8. To a flask containing $LiAlH_4$ (2.51 g, 66 mmol) was added 300 mL of Et_2O, and the suspension was cooled to 0 °C. Amide 7 (10.87 g, 60 mmol) in 30 mL of Et_2O was added dropwise over a 45-min period. The solution was warmed to room temperature and stirred for 6 h. After the solution was cooled to 0 °C, the reaction was quenched by addition of 2.5 mL of H_2O, followed by 2.5 mL of 15% aqueous NaOH, and then again by 7.5 mL of H_2O. The solution was stirred for 1.5 h and then dried with K_2CO_3. The solids were removed by filtration, and the solvent was removed under reduced pressure. Enamine 8 was isolated via Kugelrohr distillation (bp 54–55 °C (8 mmHg), 9.84 g, 98% yield): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (d, 6 H, J = 6.6 Hz), 1.58 (d, 3 H, J = 1.3 Hz), 1.58 (tsept, 1 H, J = 7.3, 6.6 Hz), 1.65 (d, 3 H, J = 1.3 Hz), 2.25 (d, 2 H, J = 7.3 Hz), 3.15 (dt, 2 H, J = 1.6, 1.6, 6.2 Hz), 5.02 (ddt, 1 H, J = 2.0, 10.2, 1.6 Hz), 5.08 (ddt, 1 H, J = 2.0, 17.2, 1.6 Hz), 5.22 (qq, 1 H, J = 1.3, 1.3 Hz), 5.81 (ddt, 1 H, J = 10.2, 17.2, 6.2 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.4, 20.4, 22.0, 27.4, 59.6, 63.1, 115.9, 122.8, 135.8, 136.9; IR (neat) 3081, 3009, 2955, 2928, 2870, 2803, 1676, 1644, 1468, 1449, 1377, 1337, 1194, 1117, 1101, 995, 916 cm^{-1}.

General Procedure for Rearrangement of 8 to 9. All flasks used in rearrangement studies were heated under vacuum for 20–30 min and then purged with argon for 10 min. A solution containing 8 (0.167 g, 1 mmol), *o*-xylene (0.121 mL, 1 mmol, internal GLC standard), and 5 mL of toluene was cooled to −78 °C. After an initial gas chromatograph was taken, the Lewis acid reagents (see Tables I and II for equiv) were added at −78 °C or the HCl was added at 0 °C or the HCl was added at 0 °C. For Cl_3Al and $(ArO)_2AlMe$ accelerated reactions, a solution of 8 was added to the catalyst in 25 mL of toluene via cannula at −78 °C. All aliquots for analysis were removed from the reaction vessel via cannula, quenched in Et_2O with 10% w/v solution of NaOMe in MeOH, and dried over Na_2SO_4 or K_2CO_3 prior to GLC analysis.

Preparation of 11 by Acylation of 6. Imine 6 (2.44 g, 22 mmol) and NEt_3 (3.69 mL, 26.4 mmol) were taken up in 150 mL of THF and cooled to 0 °C. Cyclohexanecarbonyl chloride (3.50 g, 24 mmol) in 35 mL of THF was added dropwise over a 2-h period. The reaction was allowed to warm to room temperature during the addition and then was brought to reflux for 2.5 h. After the solution was cooled to ambient temperature, solids were removed by filtration through a pad of silica on a glass frit and then washed with two portions of Et_2O. The solvents were removed via rotary evaporation, and the remaining oil was purified by column chromatography (silica, 230–400 mesh; eluent 30:70 Et_2O–petroleum ether) and isolated via Kugelrohr distillation to give 11 (75–100 °C, (<1 mmHg), 3.35 g, 69% yield): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.21 (m, 4 H), 1.43 (m 2 H), 1.61 (m, 4 H), 1.60 (s, 3 H), 1.75 (s, 3 H), 2.38 (m, 1 H), 3.96 (d, 1 H, J = 6.2 Hz), 5.02 (d, 1 H, J = 11.5 Hz), 5.04 (d, 1 H, J = 15.8 Hz), 5.72 (ddt, 1 H, J = 11.5, 15.8, 6.2 Hz), 5.82 (s, 1 H). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.6, 21.8, 25.7, 28.9, 41.5, 50.0, 116.7, 123.3, 133.3, 135.9, 176.0. IR (neat) 3101, 2930, 2855, 1653, 1451, 1427, 1342, 1256, 1206, 1123, 990, 918, 895, 831 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO$: C, 72.88; H, 10.56; N, 7.73. Found: C, 72.54; H, 10.28; N, 7.72.

Two-Step Synthesis of 11 from Allylamine. Allylamine (2.20 g, 30.0 mmol) and isobutyraldehyde (1.74 g, 30.0 mmol) were taken up in 85 mL of benzene. A Dean-Stark trap was fitted on the apparatus, and the solution was heated to reflux to azeotropically remove the resulting water. After being heated 19–22 h, the water was removed, 4-Å molecular sieves were added to the Dean-Stark trap, and reflux was continued for 2 h. The solution was cooled to ambient temperature, and NEt_3 (3.03 g, 30.0 mmol) and cyclohexanecarbonyl chloride (4.40 g, 30.0 mmol) were added, sequentially, and then heated at reflux for 3 h. After benzene was removed under reduced pressure, the crude oil was purified by flash column chromatography (silica, 230–400 mesh; eluent 30:70 Et_2O–petroleum ether). The solvents were evaporated, and the enamide was distilled under vacuum to give 4.53 g of 11 (20.5 mmol, 68% yield). Spectroscopic data was identical to that reported for the product obtained by acylation of isolated 6.

Reduction of 11 to 12. Enamide 11 (4.71 g, 21.0 mmol) in 40 mL of Et_2O was added dropwise to a suspension of $LiAlH_4$ (0.89 g, 23.0 mmol) in 300 mL of Et_2O at 0 °C over a 1-h period. The reaction mixture was warmed to room temperature and then stirred for 5 h. The $LiAlH_4$ was quenched at 0 °C through slow addition of 0.9 mL of H_2O, 0.9 mL of 15% NaOH, and then 2.7 mL of H_2O. After being stirred for 1 h, the solids were removed by filtration, and the solvents were removed via rotary evaporation to give an oil. The oil was isolated via Kugelrohr distillation to give 4.15 g of 12 (70–80 °C (5 mmHg), 95% yield): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.83 (m, 2 H), 1.15 (m 4 H), 1.30 (m, 1 H), 1.59 (s, 1 H), 1.65 (s, 3 H), 1.75 (s, 3 H), 2.30 (d, 2 H, J = 7.2 Hz), 3.14 (d, 2 H, J = 6.1 Hz), 5.02 (dd, 1 H, J = 10.2, 2.0 Hz), 5.09 (dd, 1 H, J = 17.3, 2.0 Hz), 5.22 (s, 1 H), 5.81 (ddt, 1 H, J = 17.3, 10.2, 6.1). ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 17.6, 22.3, 26.2, 26.9, 31.6, 37.1, 59.6, 61.9, 115.7, 122.0, 135.7, 136.8; IR (neat) 3091, 2923, 2851, 2797, 1650, 1600, 1449, 1374, 1337, 1283, 1263, 1178, 1123, 993, 9163, 843 cm^{-1}.

Representative Procedure for Charge-Accelerated 3-Aza-Cope Rearrangement and Reductive Workup (12 to 14). All flasks used in rearrangement studies were heated under vacuum for 20–30 min and purged with argon for 10 min. The electrophilic reagents (see Tables I and II for equiv) were added to a solution containing 12 (1.04 g, 5.0 mmol) in 25 mL of toluene to give a final concentration of 0.2 M of 12. Lewis acids were added at −78 °C, and HCl was added at 0 °C. For Cl_3Al and $(ArO)_2AlMe$ accelerated reactions, a solution of 12 was added to the catalyst in 25 mL of toluene via cannula at −78 °C. The reaction mixture was heated until complete conversion of 12 to 13 had occurred

(see Tables I and II for temperatures and reaction times). Following rearrangement, the reaction was placed in an ice bath, and 5.5 mL of 1.0 M $LiAlH_4$ solution was added.[31] After 3 h, the reduction was quenched at 0 °C through slow addition of 0.2 mL of H_2O, 0.2 mL of 15% NaOH, and then 0.6 mL of H_2O. The solids were removed by filtration through sodium sulfate on a glass frit. Solvents were removed by rotary evaporation and the oil was isolated via Kugelrohr distillation to give **14**.

14: (bp 70–80 °C (<1 mmHg)): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.89 (s, 6 H), 1.31 (m 4 H), 1.40 (m, 1 H), 1.72 (m, 6 H), 1.96 (d, 2 H, J = 7.5 Hz), 2.28 (s, 2 H), 2.37 (d, 2 H, J = 6.8 Hz), 4.97 (d, 1 H, J = 16.6 Hz), 4.98 (d, 1 H, J = 12.2 Hz), 5.78 (ddt, 1 H, J = 16.6, 12.2, 7.5 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 25.5, 26.2, 26.8, 31.4, 37.6, 44.7, 57.8, 60.5, 116.6, 135.7; IR (neat) 3350, 3074, 2923, 2853, 2807, 2753, 1639, 1462, 1447, 1364, 1127, 995, 913 cm^{-1}. Anal. Calcd for $C_{14}H_{27}N$: C, 80.31; H, 13.00; N, 6.70. Found: C, 79.00; H, 12.49; N, 6.85.

16: (bp 50–60 °C (8 mmHg)): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.85 (s, 6 H), 0.86 (d, 6 H, J = 6.6 Hz), 0.87 (bs, 1 H), 1.71 (tsept, 1 H, J = 6.9, 6.6 Hz), 1.98 (d, 2 H, J = 7.5 Hz), 2.29 (s, 2 H), 2.35 (d, 2 H, J = 6.9 Hz), 4.99 (m, 2 H), 5.79 (ddt, 1 H, J = 9.2, 17.9, 7.5 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 25.5, 27.9, 34.4, 44.7, 59.1, 60.3, 116.6, 135.7; IR (neat) 3359, 3077, 3005, 2957, 2872, 2811, 1640, 1466, 1385, 1364, 1121, 995, 912 cm^{-1}. Anal. Calcd for $C_{11}H_{23}N$: C, 78.04; H, 13.69; N, 8.27. Found: C, 77.64; H, 13.87; N, 7.68.

17: (bp 60–70 °C (<1 mmHg)): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.75 (d, 3 H, J = 6.6 Hz), 0.77 (d, 3 H, J = 6.6 Hz), 0.88 (bs, 1 H), 1.34 (s, 3 H), 1.63 (tsept, 1 H, J = 6.8, 6.6 Hz), 2.29 (dd, 1 H, J = 11.8, 6.8 Hz), 2.32 (dd, 1 H, J = 11.8, 6.8 Hz), 2.35 (dd, 1 H, J = 7.6, 13.8 Hz), 2.52 (dd, 1 H, J = 6.6, 13.8 Hz), 2.63 (d, 1 H, J = 11.5 Hz), 2.80 (d, 1 H, J = 11.5 Hz), 4.94 (d, 1 H, J = 10.0 Hz), 4.99 (d, 1 H, J = 17.1 Hz), 5.57 (dddd, 1 H, J = 10.0, 17.1, 7.6, 6.6 Hz), 7.25 (m, 5 H); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.2, 23.2, 27.6, 41.7, 45.0, 58.6, 60.6, 117.2, 126.0, 126.7, 128.4, 135.3, 146.5; IR (neat) 3337, 3061, 3025, 2957, 2928, 2872, 2811, 1640, 1601, 1497, 1466, 1447, 1379, 1123, 959 cm^{-1}. Anal. Calcd for $C_{16}H_{25}N$: C, 83.06; H, 10.89; N, 6.05. Found: C, 82.73; H, 10.93; N, 6.08.

20: (bp 70–80 °C (8 mmHg)): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.85 (t, 3 H, J = 7.4 Hz), 0.85 (d, 6 H, J = 6.6 Hz), 1.29 (m, 2 H), 1.48 (ddq, 1 H, J = 6.4, 6.4, 7.4 Hz), 1.50 (ddq, 1 H, J = 6.4, 7.4 Hz), 1.69 (tsept, 1 H, J = 6.7, 6.6 Hz), 2.04 (dddd, 2 H, J = 1.3, 1.3, 6.1, 7.2 Hz), 2.34 (d, 2 H, J = 6.7 Hz), 2.44 (d, 1 H, J = 6.4 Hz), 2.45 (d, 1 H, J = 6.4 Hz), 4.95 (ddt, 1 H, J = 1.1, 10.0, 1.3 Hz), 4.99 (ddt, 1 H, J = 1.1, 17.2, 1.3 Hz), 5.76 (ddt, 1 H, J = 10.0, 17.2, 7.2 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 10.8, 20.4, 24.3, 28.0, 36.3, 39.3, 53.0, 58.3, 115.8, 137.5; IR (neat) 3418, 3079, 2959, 2928, 2874, 2813, 1640, 1466, 1381, 1366, 1125, 995, 911 cm^{-1}. Anal. Calcd for $C_{13}H_{25}N$: C, 78.04; H, 13.69; N, 8.27. Found: C, 77.65; H, 13.66; N, 8.25.

23: (bp 40–50 °C (<1 mmHg)): ^1H NMR (300 MHz) ($CDCl_3$, major diastereomer) δ 0.87, (d, 6 H, J = 6.6 Hz), 1.30 (m, 4 H), 1.50 (m, 4 H), 1.67 (m, 3 H), 1.95 (m, 1 H), 2.15 (m, 1 H), 2.26 (dd, 1 H, J = 6.8, 11.3 Hz), 2.38 (dd, 1 H, J = 6.8, 11.3 Hz), 2.59 (m, 1 H), 4.93 (ddt, 1 H, J = 1.1, 10.3, 1.4 Hz), 4.98 (ddt, 1 H, J = 1.1, 16.8, 1.4 Hz), 5.75 (ddt, 1 H, J = 10.3, 16.8, 6.7 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 22.5, 23.0, 27.1, 28.4, 28.8, 33.4, 39.1, 55.4, 57.1, 115.3, 138.6; IR (neat) 3359, 3077, 2928, 2859, 2805, 1642, 1470, 1366, 1130, 1103, 993, 909 cm^{-1}. Anal. Calcd for $C_{17}H_{25}N$: C, 79.93; H, 12.90; N, 7.17. Found: C, 80.16; H, 12.03; N, 7.47.

26: (bp 30–40 °C (<1 mmHg)): ^1H NMR (300 MHz) ($CDCl_3$, major diastereomer) δ 0.86 (d, 6 H, J = 6.7 Hz), 1.43 (m, 3 H), 1.65 (m, 4 H), 1.90 (m, 2 H), 2.17 (m, 2 H), 2.27 (dd, 1 H, J = 6.9, 11.5 Hz), 2.39 (dd, 1 H, J = 6.6, 11.5 Hz), 2.96 (dt, 1 H, J = 5.8, 6.0 Hz), 4.94 (dd, 1 H, J = 1.2, 10.1 Hz), 5.00 (dd, 1 H, J = 1.2, 17.1 Hz), 5.79 (ddt, 1 H, J = 10.1, 17.1, 6.7 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 20.6, 21.0, 28.3, 30.7, 32.7, 41.9, 56.5, 61.5, 115.1, 138.7; IR (neat) 3349, 3077, 2955, 2870, 2011, 1642, 1470, 1387, 1366, 1138, 993, 911 cm^{-1}. Anal. Calcd for $C_{12}H_{23}N$: C, 79.49; H, 12.79; N, 7.72 Found: C, 79.17; H, 12.70; N, 7.68.

Preparation of *N*-Allyl-*N*-cyclopentylamine. Allylamine (5.71 g, 100 mmol), cyclopentanone (8.41 g, 100 mmol), and benzene (300 mL) were added to a flask fitted with a Dean-Stark trap, and the solution was then heated at reflux for 15 h. The water was drained from the trap, and 4-Å molecular sieves were added. Reflux was continued for 2 h more to remove the final traces of water from the reaction mixture. The benzene was removed by distillation, and the remaining oil was isolated via Kugelrohr distillation to give *N*-allylcyclopentylideneamine (8.09 g, 66 mmol) in 66% yield (50–70 °C (10–15 mmHg)).

To a suspension of 1.82 g (48 mmol) $LiAlH_4$ in 200 mL of Et_2O was added 4.93 g (40 mmol) of *N*-allylcyclopentylideneamine. The solution was stirred for 4 h at ambient temperature and was then quenched with 1.8 mL of H_2O, followed by 1.8 mL of 15% aqueous NaOH, and then by 5.4 mL of H_2O. After being stirred for 1 h, the solution was filtered to remove the aluminum salts and the solvent concentrated to an oil, which was distilled under vacuum to give *N*-allyl-*N*-cyclopentylamine (4.36 g, 35 mmol) in 87% yield (60–70 °C (15 mmHg)): ^1H NMR (300 MHz) ($CDCl_3$) δ 1.28 (m, 2 H), 1.50 (m, 3 H), 1.64 (m, 2 H), 1.81 (m, 2 H), 3.06 (tt, 1 H, J = 6.7, 6.8 Hz), 3.20 (ddd, 2 H, J = 1.2, 1.2, 6.1 Hz), 5.03 (ddt, 1 H, J = 1.3, 10.2, 1.2 Hz), 5.12 (ddt, 1 H, J = 1.3, 17.1, 1.2 Hz), 5.89 (ddt, 1 H, J = 10.2, 17.1, 6.1 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 24.0, 33.1, 51.3, 59.2, 115.5, 137.2.

***N*-Allyl-*N*-isobutylcyclopentylamine (27).** To a solution of *N*-allyl-*N*-cyclopentylamine (3.76 g, 30 mmol) and triethylamine (3.33 g, 33 mmol) was added isobutyryl chloride (3.20 g, 30 mmol) dropwise. The solution was stirred at ambient temperature for 5 h and then filtered through a pad of silica. Removal of solvent produced an oil, which was isolated via Kugelrohr distillation to give *N*-allyl-*N*-cyclopentylisobutyramide (5.14 g, 26.4 mmol) in 88% yield (75–85 °C (<1 mmHg)).

To a suspension of $LiAlH_4$ (0.912 g, 24 mmol) in 100 mL of Et_2O was added *N*-allyl-*N*-cyclopentylisobutyramide (4.00 g, 20.4 mmol) in a dropwise manner. After addition was complete, the solution was stirred at ambient temperature for 2 h. The reaction was quenched by addition of 0.9 mL of H_2O, followed by 0.9 mL of 15% aqueous NaOH, followed by 2.7 mL of H_2O, and was then stirred for 1 h. After removal of solids by filtration, the solvent was removed and the resulting oil was isolated via Kugelrohr distillation to give **27** (3.27 g, 20.4 mmol) in quantitative yield (50–65 °C (4 mmHg)): ^1H NMR (300 MHz) ($CDCl_3$) δ 0.84 (d, 6 H, J = 6.6 Hz), 1.35 (m, 2 H), 1.45 (m, 2 H), 1.59 (m, 2 H), 1.70 (m, 3 H), 2.14 (d, 2 H, J = 7.1 Hz), 3.00 (tt, 1 H, J = 7.3, 7.4, Hz), 3.11 (ddd, 2 H, J = 1.9, 2.1, 6.4 Hz), 5.04 (ddt, 1 H, J = 1.6, 10.2, 2.1 Hz), 5.12 (ddt, 1 H, J = 1.7, 17.1, 1.9 Hz), 5.87 (ddt, 1 H, J = 10.2, 17.1, 6.4 Hz); ^{13}C NMR (75.5 MHz) ($CDCl_3$) δ 21.0, 24.1, 26.9, 29.2, 55.7, 59.5, 63.7, 116.1, 136.8. Anal. Calcd for $C_{12}H_{23}N$: C, 79.48; H, 12.79; N, 7.72. Found: C, 79.36; H, 12.79; N, 7.99.

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(31) In situ reduction of rearrangements catalyzed by $TiCl_4$ were performed at −78 °C to avoid reduction of the alkene functionality by titanium hydride species.

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Studies of the Regiospecific 3-Aza-Cope Rearrangement Promoted by Electrophilic Reagents

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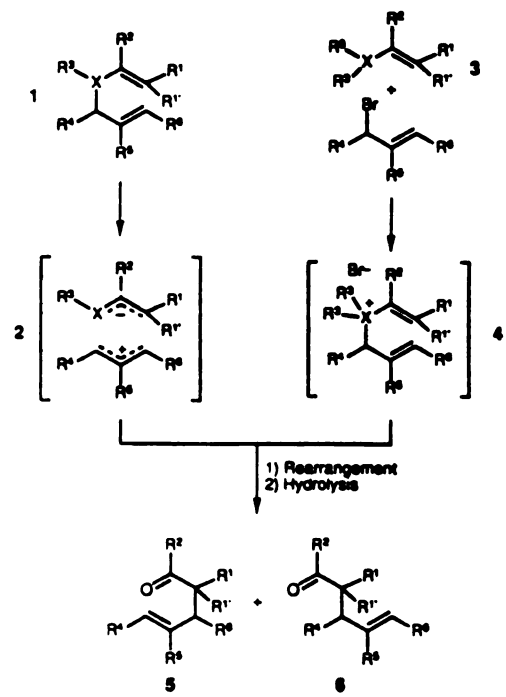
The 3-aza-Cope rearrangement of *N*-alkyl-*N*-allyl enamine substrates, which required temperatures of 250 °C to proceed thermally, was promoted at 111 °C in the presence of electrophilic reagents such as HCl (0.5 equiv), $TiCl_4$ (0.2 equiv), $AlMe_3$ (1.2 equiv), or $(ArO)_2AlMe$ (1.2 equiv). In order to probe the regioselectivity of this accelerated carbon–carbon bond forming process under these reaction conditions, several enamine substrates were prepared from both isobutyraldehyde and cyclohexanone. Each substrate used in these studies was prepared having an unsymmetrical N-allylic group, substituted with either an alkyl or phenyl substituent at the 4 or 6 position of the 3-aza-Cope framework. In all cases examined, reaction acceleration by the electrophilic reagent produced regiospecific [3,3] rearrangement to the corresponding imines; products resulting from [1,3] rearrangement were not observed. Hydride reduction of the resulting imines generated the δ,ε-unsaturated amines in 55–94% overall yield in the three-step condensation–rearrangement–reduction process from the secondary allylamine.

Introduction

Regiochemical control is an essential feature of any successful carbon–carbon bond forming process, and intramolecular approaches have been important strategies for achieving regioselective methodologies. A prominent example of this strategy has been the Claisen rearrangement, the [3,3] sigmatropic shift of allyl enol ether substrates (1, R^3–X = O Scheme I).[1] In a sense, this reaction constitutes a concerted S_N2' allylation of a carbonyl derivative, and such intramolecular thermal rearrangements have led to regiospecific carbon–carbon bond formation. Thermal 3-aza-Cope rearrangement of *N*-alkyl-*N*-allyl enamine substrates (1, X = N), the nitrogen analog of the Claisen rearrangement, also resulted in regiospecific formation of 5 after hydrolysis.[2] Because the Claisen and 3-aza-Cope rearrangements typically proceed at temperatures ranging from 180 to 250 °C, studies have been directed toward acceleration of these reactions in order to promote substrate rearrangement at lower reaction temperatures.[3]

Acceleration of the [3,3] sigmatropic rearrangement of allyl vinyl ethers having unsymmetrical allyl groups has been achieved primarily through the use of stoichiometric aluminum reagents. One group of aluminum reagents, the di- and trialkylaluminum complexes including Et_2AlX, $AlMe_3$, and $Al(iBu)_3$, has produced regiospecific rearrangement of substrates followed by reduction of the resulting carbonyl functionality.[4] In addition to alkyl substitution on the allyl group (R^4 or R^6 = alkyl), regiospecific [3,3] rearrangement occurred even when R^4 = Ph.[4a,c,d] Recent advances in this area have been reported for reagents of the type $(ArO)_2AlMe$[5] as well as the closely related binapthol reagent, which promoted rearrangement at temperatures as low as −78 °C without subsequent reduction of the carbonyl product.[6] However, although complete [3,3] rearrangement was achieved with R^4 or R^6 = alkyl, substrates having R^4 = Ph or vinyl and those with R^6 = vinyl resulted in mixtures of 5 and 6, the products

Scheme I. Approaches to the Allylation of Carbonyl Derivatives



(1) For reviews on [3,3] sigmatropic rearrangements see: (a) Rhoads, S. J.; Raulins, N. R. *Org. React. (N.Y.)* **1975**, *22*, 1. (b) Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. (c) Bennett, G. B. *Synthesis* **1977**, 589. (d) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3. (e) Gajewski, J. *Hydrocarbon Thermal Isomerizations*; Academic: New York, 1981. (f) Hill, R. K. Chirality Transfer via Sigmatropic Rearrangements. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, p 503. (g) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (h) Blechert, S. *Synthesis* **1989**, 71.

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of both [1,3] and [3,3] rearrangement. A nonconcerted reaction was proposed in which initial bond breakage generated ionic intermediate 2 followed by recombination to give the observed product distribution. Regiospecific [3,3] rearrangement of 1 ($R^2 \neq H$, R^3–X = O), in which regiochemical control was proposed to result from initial C–C bond formation followed by C–O bond cleavage, has also been promoted by Pd(II) catalysis.[7] A different reaction pathway was followed for the tetrahydrofuran substrates ($R^1 = CO_2Et$, $R^2,R^4 = -CH_2CH_2-$), which generated products of [1,3] and [3,3] rearrangement resulting from π-allylpalladium intermediates.[8]

Comparatively, the 3-aza-Cope reaction has been investigated far less extensively than the Claisen rearrangement. In part, the high temperatures required for thermal rearrangement when X = N (250 °C)[9] or with *N*-allyl-*N*,*O*-ketene acetal substrates ($R^2 = OR$, 180 °C)[10] has placed limitations on this synthetic method. Charge acceleration of the 3-aza-Cope rearrangement, by quaternization of the nitrogen (4), has been accomplished by allylation of dialkyl enamine substrates (3, X = N). When crotyl bromide (R^6 = Me) was used to alkylate dialkyl enamine substrates in which $R^1,R^{1'} \neq H$, products from initial N-alkylation (4) and subsequent [3,3] rearrangement produced 5 after hydrolysis.[11] However, when enamines derived from cyclopentanone,[12] cyclohexanone,[13] or butanal[14] were treated with crotyl bromide, the products of C-alkylation (6) contributed from 10 to 100% of the final reaction mixture. Studies of unsymmetrical allyl substrates were limited to the crotyl group, and have not included substrates with R^4 = alkyl.

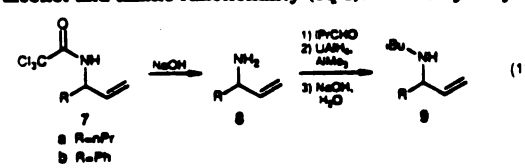
Acceleration of the 3-aza-Cope rearrangement has been achieved with titanium catalysts, and substrates having unsymmetrical allyl groups were investigated.[15] Both reports studied the rearrangement of enamines in which $R^1,R^{1'} \neq H$. In an example having R^4 = Me, 1 was transformed regiospecifically to 5 as a 90:10 ratio of *E*:*Z* olefin isomers.[15a] In contrast, acceleration of the 3-aza-Cope rearrangement by reaction with $Pd(PPh_3)_4/CF_3CO_2H$ proceeded through a π-allyl intermediate, and only products of [1,3] rearrangement were observed when R^6 = Me.[16]

Recently, we reported the electrophile-promoted 3-aza-Cope rearrangement for *N*-alkyl-*N*-allyl enamine substrates.[17] In these studies, the effectiveness of protic and Lewis acids in accelerating the rearrangement of substrates was examined for a variety of enamine substitution patterns; a symmetrical allyl group was used in each case. A study of the regiochemical selectivity of this charge-accelerated reaction, with respect to the [1,3] or [3,3] nature of this rearrangement, is presented. Acceleration of the 3-aza-Cope rearrangement with HCl, $TiCl_4$, $AlMe_3$, and $(ArO)_2AlMe$ was examined for substrates derived from isobutyraldehyde and cyclohexanone and having a phenyl or alkyl substituent at the R^4 (allylic) or R^6 (terminal vinylic) position.

Results and Discussion

In order to examine the regioselectivity of the 3-aza-Cope rearrangement with aldehyde derived *N*-alkyl-*N*-allyl enamine substrates, two pairs of enamine substrates were selected. One pair had *n*-propyl (nPr) substituents at the allylic and terminal vinylic positions, while the other pair had phenyl substituents at those positions (Scheme II). Rearrangement of these substrates through a [3,3] process would transform 11 to 13 and 12 to 14. These related sets of enamine substrates were designed so that if [1,3] rearrangement occurred to any extent during the charge-accelerated rearrangement, then 11 would produce 14, and the rearrangement of 12 would give 13. In order to generate substrates 11 and 12 by enamine condensation with isobutyraldehyde, amines 9 and 10 were prepared.

Synthesis of the required secondary amines was accomplished using several different routes. The amines substituted in the allylic position, 9a and 9b, were made from products obtained through Overman's 1,3 transposition of alcohol and amine functionality (eq 1).[18] The hydrolysis



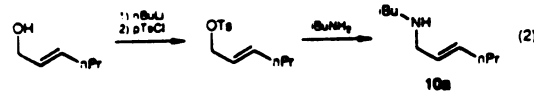
(1)

7
a R=nPr
b R=Ph

8

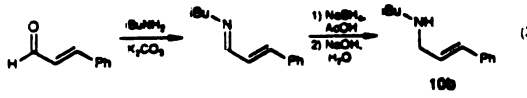
9

of 7a produced 8a, which was then alkylated by sequential treatment with isobutyraldehyde and then $LiAlH_4$ to yield 9a. In a similar manner, imine formation followed by reduction gave 9b from 8b in 81% yield. Secondary amine 10a was obtained in 86% overall yield by tosylation of 2-hexen-1-ol and subsequent reaction with isobutylamine (eq 2). The reduction of the imine formed from treatment of cinnamaldehyde with isobutylamine provided 10b (eq 3).



(2)

10a



(3)

10b

Formation of enamines 11 and 12 was most effectively accomplished by the reaction of 9 or 10 with isobutyraldehyde and pTsOH in benzene, and the condensation was driven to completion by azeotropic removal of H_2O. Under these conditions, conversion of 9a to 11a was achieved without formation of 13a or 14a. Amine 10a required the use of toluene as the solvent for effective formation of 12a, and production of 14a as a result of

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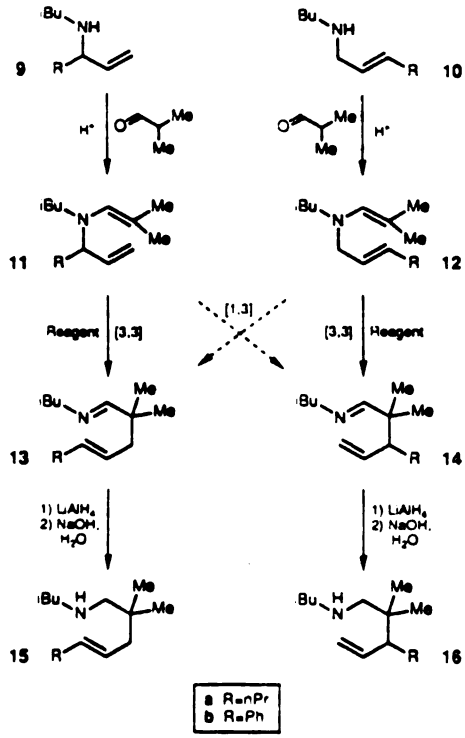
Scheme II. Charge-Accelerated Rearrangement of *N*-Alkyl-*N*-allyl Enamine Substrates



catalysis by pTsOH at these higher temperatures was not observed. Complications arose with the condensation of isobutyraldehyde with **9b**; under the conditions used to generate the enamine in benzene at reflux (80 °C), facile rearrangement of **11b** to **13b** occurred. Although a solution of **11b** was never obtained for separate rearrangement studies, the regiochemistry of this two-step process, the condensation reaction coupled to the sigmatropic rearrangement, was investigated for selected catalysts. In contrast to the reactivity observed for **9b**, formation of **12b** from **10b** was achieved through azeotropic removal of H_2O with benzene; even with the use of toluene as solvent, heating the mixture at reflux in the presence of pTsOH did not promote rearrangement of **14b**. In preparation for the rearrangement studies, benzene was removed in vacuo from substrates **11a** and **12** and replaced with toluene.

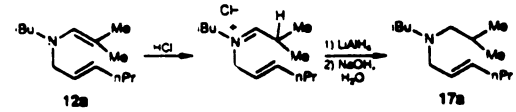
Rearrangement of **11a** and **12a** was investigated using the three types of reagents previously reported to efficiently promote the 3-aza-Cope rearrangement (Table I).[17] The reagents examined in this regiochemical study were the protic acid HCl (0.5 equiv), the metal halide Lewis acid catalyst $TiCl_4$ (0.2 equiv), and the organoaluminum complexes $AlMe_3$ and [bis(2,6-diphenylphenoxy)methyl]aluminum, which were required in a stoichiometric amount to achieve complete conversion of substrate to product. In each case, heating the substrate and reagent to reflux in

Table I. Regiospecific 3-Aza-Cope Rearrangement and Reduction of 11 and 12

substrate[a]	reagent[b]	conditions[c] [time(h)/ temp (°C)]	product formation 15:16[d]	yield (%)[e]
11a	HCl	6/111	>99:1	69
	$TiCl_4$	24/111	>99:1	79
	$AlMe_3$	24/111	>99:1	80
	$(ArO)_2AlMe$[f]	24/111	>99:1	61
12a	HCl	30/111	1:>99	76
	$TiCl_4$	30/111	1:>99	78[g]
	$AlMe_3$	8/111	1:>99	87
	$(ArO)_2AlMe$[f]	30/111	1:>99	85[g]
11b	HCl	48/80	>99:1	81
	pTsOH	48/80	>99:1	80
	$TiCl_4$	48/80	>99:1	80
12b	HCl	24/111		h
	$TiCl_4$	24/111		i
	$AlMe_3$	5/111	1:>99	56
	$(ArO)_2AlMe$[f]	18/111	1:>99	55

[a] Substrates were generated in situ by condensation of **9** or **10** with isobutyraldehyde in either benzene or toluene catalyzed by pTsOH. [b] Reagent (equiv): HCl (0.5), pTsOH (0.05), $TiCl_4$ (0.2), $AlMe_3$ (1.1), and $(ArO)_2AlMe$ (1.1). [c] Rearrangements were run 0.2 M at reflux in toluene (111 °C) or benzene (80 °C). [d] In each case, the product of [1,3] rearrangement was not detected by ^1H NMR or capillary GC. [e] Overall isolated yield of condensed, rearranged, and reduced products from **9** or **10**. [f] ArO = 2,6-diphenylphenoxy. [g] See ref 19. [h] Destruction of starting material. [i] Formation of **13** or **14** was not observed.

toluene promoted regiospecific rearrangement of **11a** to **13a** and **12a** to **14a** (Scheme II).[19] Reduction of the imines produced **15a** and **16a**, respectively, which were then isolated in 61–87% yield for the three-step condensation–rearrangement–reduction process from **9a** and **10a**. As a result of the rearrangement and reduction of **11a**, only the *E* alkene isomer of **15a** was observed. Evidence for the formation of the *E* isomer was the characteristic *E* alkene absorbance at 970 cm^{-1}, and the absence of the corresponding *Z* alkene absorbance around 690 cm^{-1}. Interestingly, at reaction times insufficient to produce complete conversion of **12a** to **14a**, reduction of the reaction mixture generated from **12a** with HCl or $TiCl_4$ resulted in formation of small amounts of **17a** (eq 4).[20] Evidence of [1,3]



(4)

rearrangement through an intermediate such as **2** or by a [1,3] sigmatropic shift, by formation of **14** from **11** or **13** from **12**, was not detected by capillary gas chromatography or ^1H NMR spectral analysis.

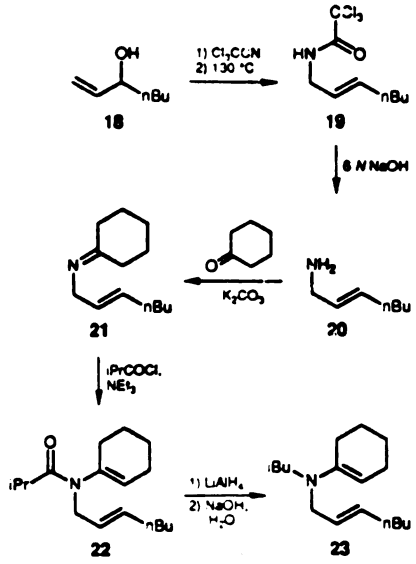
The phenyl-substituted allyl substrates, **11b** and **12b**, also rearranged to give exclusive formation of [3,3] products **13b** and **14b**, respectively, but these substrates were much more sensitive to the reaction conditions. A phenyl substituent in the allylic position produced significant acceleration of the reaction. During the condensation of **9b** to **11b**, facile rearrangement to **13b** was promoted by either HCl or pTsOH in benzene at 80 °C. Because **11b** could not be isolated, the charge-accelerated 3-aza-Cope rearrangement of **11b** was not examined. However, the use of the $TiCl_4$ reaction conditions reported by Hill, en-

(18) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.

(19) Compound **12a** could also be prepared in a manner similar to that illustrated in Scheme III. Hydrolysis of the appropriate trichloroacetamide,[18] followed by condensation with isobutyraldehyde and acylation with isobutyryl chloride produced the corresponding enamide. $LiAlH_4$ reduction gave enamine **12a**. This source of **12a** was used for the rearrangement studies with $TiCl_4$ and $(ArO)_2AlMe$.

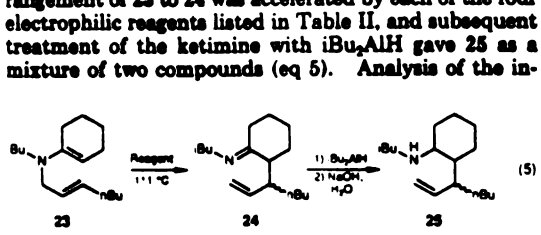
(20) For discussions of N- versus C-protonation of enamines, see: (a) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. (b) Hinman, R. L. *Tetrahedron* **1968**, *24*, 185, and references therein.

Scheme III. The Synthetic Route to 23



amine formation driven by 0.25 equiv $TiCl_4$ and subsequent 3-aza-Cope rearrangement accelerated by the product(s) of the $TiCl_4$ with 1 equiv of H_2O (generated during the enamine condensation), could be tested. These same conditions also produced **13b** stereospecifically from **9b**. For each catalyst studied, the condensation, rearrangement, and reduction of **9b** produced only the *E* olefin isomer of **15b**, as evidenced by the 16-Hz coupling constant measured for the olefinic protons. Substrate **12b**, which was prepared by condensation of **10b** in benzene, was very sensitive to the conditions for promoting rearrangement due to the styrene-like moiety in the molecule. Treatment with HCl (80 °C) or $TiCl_4$ (80 or 111 °C) resulted only in the destruction of **12b** without formation of **13b** or **14b**, and pTsOH would not cause rearrangement at 111 °C. However, both organoaluminum catalysts effectively generated **14b** at 111 °C, and reduction with $LiAlH_4$ gave exclusively **16b** in moderate yield.

In order to examine the regiospecificity of the 3-aza-Cope rearrangement with enamines derived from ketones, substrate **23** was prepared by the route illustrated in Scheme III. Although enamine formation by condensation of cyclohexanone with the corresponding secondary amine could not be used to obtain **23**, the reaction of cyclohexanone with **20** efficiently produced **21**. Acylation of **21** with isobutyryl chloride/NEt_3 gave **22** in 89% yield for the two-step process from **20**, and $LiAlH_4$ reduction of **22** generated the desired enamine substrate **23**. The rearrangement of **23** to **24** was accelerated by each of the four electrophilic reagents listed in Table II, and subsequent treatment of the ketimine with iBu_2AlH gave **25** as a mixture of two compounds (eq 5). Analysis of the intermediate reaction mixture revealed that rearrangement occurred in a regiospecific manner to generate a mixture



(5)

Table II. Regiospecific 3-Aza-Cope Rearrangement in Reduction of 23

reagent[a]	reaction time[b] (h)	25 diastereomer ratio[c]	25 yield (%)[d]
HCl	24	54:46	69
$TiCl_4$	48	55:45	72
$AlMe_3$	24	67:33	94
$(ArO)_2AlMe$[e]	24	77:23	73

[a] Reagent (equiv): HCl (1.0), $TiCl_4$ (0.15), $AlMe_3$ (1.1), and $(ArO)_2AlMe$ (1.1). [b] Rearrangements were run 0.2 M at reflux in toluene. [c] Ratio determined by ^1H NMR. [d] Isolated yield of rearranged and reduced products **25** from **23**. [e] ArO = 2,6-diphenylphenoxy.

of diastereomeric imines (**24**), and then hydride reduction with iBu_2AlH was directed completely by the bulky α-imine substituent to stereoselectively produce **25** as the same mixture of allylic diastereomers.

Summary

The value of the electrophile-promoted 3-aza-Cope rearrangement is evident from the unique features of this process. There have been a number of problems typically associated with the 3-aza-Cope rearrangement. One of these limitations has been the lack of regiospecific carbon–carbon bond formation by systems such as allylation of dialkylenamines derived from ketones as well as the rearrangement promoted by Pd catalysis. In addition, problems have been encountered with enamine substrates derived from ketones. Ketone-derived enamines produce low yields from in situ titanium condensation and rearrangement, and the regioselectivity resulting from enamine allylation was poor. The inability to stereospecifically produce *E* olefins from dialkyl enamine allylation has also provided a limitation, and the in situ titanium reaction produced only a 90:10 ratio of *E*:*Z* olefin isomers.

Acceleration of the 3-aza-Cope rearrangement with HCl, $TiCl_4$, $AlMe_3$, or $(ArO)_2AlMe$ provided a complementary method to these procedures. When substrates having unsymmetrical *N*-allyl groups, having an alkyl or aryl substituent at either the 4 or 6 position of the rearrangement framework, were treated with these electrophilic reagents, regiospecific [3,3] rearrangement occurred. Substrates derived from either isobutyraldehyde or cyclohexanone were found to produce regiospecific carbon–carbon bond formation, and for substrates with an alkyl or phenyl substituent at C-4, only the *E* olefin isomer was produced. The use of the aluminum reagents, especially $AlMe_3$, was particularly advantageous. $AlMe_3$ promoted the 3-aza-Cope rearrangement with the highest yields for each of the enamine substrates obtained.

Experimental Section

General Methods. All reactions were carried out performing standard inert atmosphere techniques to exclude moisture and oxygen.[21] Benzene, toluene, tetrahydrofuran (THF), and Et_2O were distilled from sodium/benzophenone immediately prior to use. Triethylamine was heated at reflux over calcium hydride for a minimum of 12 h and then distilled immediately prior to use. Solutions of HCl (1 M in Et_2O) and $LiAlH_4$ (1 M in THF) were obtained from Aldrich Chemical Co. Solutions of $AlMe_3$ (2 M in toluene) and iBu_2AlH (2 M in hexanes) were prepared from neat $AlMe_3$ and iBu_2AlH obtained from Aldrich Chemical Co. $(ArO)_2AlMe$ was prepared by dissolving 2,6-diphenylphenol (2.0 equiv) in toluene (2 M) followed by the slow addition of $AlMe_3$

(21) For more detailed General Experimental procedures from these labs, see ref 17b.

(1.0 equiv); the mixture was stirred at room temperature for 30–60 min prior to addition to the enamine solution.[6] Compound 19 was prepared according to a literature procedure.[16] Unless specified, concentration of mixtures after workup was performed using a Büchi rotary evaporator.

3-(*N*-(2-Methylprop-1-yl)amino)-1-hexene (9a). Trichloroacetamide 7a (25 g, 102 mmol)[15] was hydrolyzed in 200 mL of 6 N NaOH for 48 h. The organic portion was extracted using 3 × 100 mL of Et_2O, and the solution was carefully concentrated on a rotary evaporator below 0 °C. A flask containing the resulting amine, 8a, and isobutyraldehyde (7.3 g, 101 mmol) in benzene (0.2 M) was equipped with a Dean–Stark trap that contained 4-Å molecular sieves. The mixture was heated to reflux until imine formation was complete. Solid $LiAlH_4$ (3.86 g, 102 mmol) was added slowly over 20 min at 0 °C, the solution was stirred for 1 h, and then $AlMe_3$ (25.4 mL, 2.0 M in toluene, 50.8 mmol) was added dropwise via cannula over a period of 30 min at 0 °C. After 24 h, the solution was quenched at 0 °C by the sequential addition of 4.0 mL of H_2O, 4.0 mL of 15% w/v aqueous NaOH, and 12.0 mL of H_2O, and then the mixture was stirred for 4 h. The aluminum salts were removed by filtration, and the combined filtrate and washings were concentrated and distilled (80 °C, 35 mmHg) to give 9a (3.2 g, 20.5 mmol) in 20% overall yield; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (d, J = 6.6 Hz, 6 H), 0.87 (t, J = 6.9 Hz, 3 H), 1.2–1.5 (m, 4 H), 1.65 (nonet, J = 6.6 Hz, 1 H), 2.26 (dd, J = 11.5, 6.6 Hz, 1 H), 2.38 (dd, J = 11.5, 7.1 Hz, 1 H), 2.90 (dt, J = 5.5, 7.5 Hz, 1 H), 4.96–5.07 (m, 2 H), 5.53 (ddd, J = 17.6, 9.5, 8.1 Hz, 1 H), NH not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 19.1, 20.7, 20.8, 28.4, 37.9, 55.4, 61.8, 115.3, 141.9; IR (neat) 3337, 3077, 2959, 2872, 1641, 1117 cm^{-1}; HRMS calcd for $C_{10}H_{21}N$ m/z (MH$^+$) 156.1676, found 156.1762.

3-(*N*-(2-Methylprop-1-yl)amino)-3-phenyl-1-propene (9b). A flask containing 8b (7.0 g, 53 mmol)[15] and isobutylaldehyde (3.79 g, 53 mmol) in benzene (0.2 M) was equipped with a Dean–Stark trap that contained 4-Å molecular sieves. The mixture was heated at reflux for 2 h until imine formation was complete as judged by gas chromatographic analysis. Solid $LiAlH_4$ (2.0 g, 53 mmol) was added at 0 °C, and the mixture was warmed to room temperature and stirred for 10 h. The reaction was quenched at 0 °C by the sequential addition of 2.0 mL of H_2O, 2.0 mL of 15% w/v aqueous NaOH, and 6.0 mL of H_2O. After stirring for 4 h, the aluminum salts were removed by filtration, and the combined filtrate and washings were concentrated and distilled to give 9b (8.1 g, 42.8 mmol) in 81% yield (65 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6.6 Hz, 6 H), 1.34 (bs, 1 H), 1.65 (nonet, J = 6.6 Hz, 1 H), 2.19 (dd, J = 6.9, 11.4 Hz, 1 H), 2.35 (dd, J = 6.6, 11.4 Hz, 1 H), 4.14 (d, J = 7.1 Hz, 1 H), 5.06 (ddd, J = 0.9, 1.5, 10.1 Hz, 1 H), 5.19 (dt, J = 17.1, 1.6 Hz, 1 H), 5.85 (ddd, J = 7.1, 10.1, 17.1 Hz, 1 H), 7.22–7.39 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.67, 20.72, 28.4, 55.6, 66.2, 114.7, 127.0, 127.2, 128.2, 141.4, 143.2; IR (neat) 3310, 3027, 2955, 2870, 1620, 1116 cm^{-1}; HRMS calcd for $C_{13}H_{19}N$ m/z 189.1513, found 189.1520.

(*E*)-1-(*N*-(2-Methylprop-1-yl)amino)hex-2-ene (10a). A small amount of 1,10-phenanthraline was added to a solution of 2-hexen-1-ol (4.01 g, 40 mmol) in 250 mL of THF.[22] The solution was cooled to −78 °C, and *n*-BuLi (28 mL, 1.6 M in hexanes) was added until the orange, 1,10-phenanthralene endpoint was visible. Tosyl chloride (7.63 g, 40 mmol) was added in a single portion, and the mixture was stirred at −78 °C for 72 h. The reaction was worked up by diluting with 500 mL of cold petroleum ether, and washing with 2 × 100 mL of cold 50% saturated aqueous $NaHCO_3$ followed by 1 × 100 mL of saturated aqueous $NaHCO_3$. The aqueous layer were combined and extracted with 1 × 70 mL of petroleum ether, and the combined organic fractions were dried over K_2CO_3. After filtration and concentration of the mixture, the tosylate was taken up in 200 mL of Et_2O, dried, filtered, and concentrated in the same manner. The crude tosylate was then added to isobutylamine (17.5 g, 240 mmol) at 0 °C, and stirred at room temperature for 24 h. Excess isobutylamine was removed in vacuo, and the remaining oil was purified by Kugelrohr distillation (25 mmHg, 80–100 °C) to give 10a (5.47 g, 35.3 mmol) in 88% yield; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 7.4 Hz, 3 H), 0.85 (d, J = 6.8 Hz, 6 H), 1.33 (sext, J = 7.4 Hz, 2 H), 1.68 (nonet, J = 6.8 Hz, 1 H), 1.94 (m, 2 H), 2.35 (d, J = 6.8 Hz, 2 H), 3.12 (d, J = 5.0 Hz, 2 H), 5.40–6.58 (m, 2 H), NH not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 20.7, 22.4, 28.3, 34.4, 52.0, 57.5, 128.6, 132.3; IR (neat) 3301, 2959, 2872, 2810, 1670, 1121, 970 cm^{-1}; HRMS calcd for $C_{10}H_{21}N$ m/z 155.1669, found 155.1683.

(*E*)-3-(*N*-(2-Methylprop-1-yl)amine)phenylprop-1-ene (10b). A mixture of cinnamaldehyde (15 g, 114 mmol) and isobutylamine (8.1 g, 111 mmol) in 380 mL of Et_2O was stirred over K_2CO_3 (≈15 g) for 12 h. The mixture was filtered, and the solids were washed with 50 mL of Et_2O. Acetic acid (34 g, 570 mmol) was added to the combined organic fractions and the solution was stirred at room temperature for 30 min. $NaBH_4$ (1.12 g, 29 mmol) was added slowly over 20 min at 0 °C, and the mixture was warmed to room temperature and stirred for 8 h. The reaction was quenched at 0 °C with a mixture of saturated aqueous NaOH/solid NaOH, and the organic layer was separated and dried (K_2CO_3). The solution was concentrated and then purified via column chromatography by eluting the column first with a petroleum ether/Et_2O (80:20) to remove nonpolar impurities, and then with Et_2O to give the crude 10b. Short-path distillation gave 10b (3.2 g, 16.9 mmol) in 15% yield (bp 90–95 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, J = 6.7 Hz, 6 H), 1.33 (bs, 1 H), 1.76 (nonet, J = 6.7 Hz, 1 H), 2.42 (d, J = 6.7 Hz, 2 H), 3.38 (dd, J = 6.3, 1.2 Hz, 2 H), 6.31 (dt, J = 15.9, 6.2 Hz, 1 H), 6.51 (bd, J = 15.9 Hz, 1 H), 7.16–7.39 (m, 5 H); ^{13}C (75.5 MHz, $CDCl_3$) δ 20.7, 28.4, 52.1, 57.5, 126.2, 127.2, 128.4, 128.7, 131.0, 137.1; IR (neat) 3316, 3026, 2955, 2870, 2810, 1599, 1119, 966 cm^{-1}; HRMS calcd for $C_{13}H_{19}N$ m/z 189.1513, found 189.1510.

Preparation of *N*-(2-Methyl-1-propenyl)-*N*-(*E*)-hex-2-en-1-yl-2-methylpropanamide. The trichloroacetamide (33.7 mmol, 8.20 g)[15] was added to 200 mL of 6 N NaOH, and heated at reflux for 15 h. Following hydrolysis, the amine was separated, and the aqueous layer was washed with 2 × 15 mL portions of benzene. The organic layers were combined with 15 mL of additional benzene, isobutyraldehyde (100 mmol, 7.21 g) was added, and the mixture was heated at reflux with azeotropic removal of water using a glass trap containing molecular sieves. After 20 h, Et_3N (36 mmol, 5.03 mL) was added, and the mixture was cooled to 0 °C. Isobutyryl chloride was added via syringe over a 10-min period. The reaction was then stirred for 36 h, filtered through a pad of silica, and washed with petroleum ether. The solvents were concentrated, and the crude enamide was purified by column chromatography (1:9 EtOAc/petroleum ether). Kugelrohr distillation (60–70 °C, <1 mmHg) gave 3.28 g of the enamide (44% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.2 Hz, 3 H), 1.01 (d, J = 6.7 Hz, 6 H), 1.32 (sext, J = 7.2 Hz, 2 H), 1.54 (s, 3 H), 1.70 (s, 3 H), 1.92 (q, J = 6.9 Hz, 2 H), 2.68 (hept, J = 6.7 Hz, 1 H), 3.91 (d, J = 6.3 Hz, 2 H), 5.35 (dt, J = 15.3, 6.3 Hz, 1 H), 5.47 (dt, J = 15.3, 6.5 Hz, 1 H), 5.79 (bs, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.5, 17.6, 19.1, 21.8, 22.2, 31.1, 34.2, 49.3, 123.3, 124.7, 133.8, 135.6, 177.2; IR (neat) 2967, 2874, 1736, 1653, 1406, 1236, 970 cm^{-1}. HRMS calcd for $C_{14}H_{25}NO$ m/z 223.1936, found 223.1940.

Preparation of *N*-(*E*)-Hex-2-en-1-yl-*N*-(2-methyl-1-propyl)-2-methylpropenylamine (12a). The enamide (4.0 mmol, 0.89 g) was taken up in 5 mL of dry Et_2O, and LAH (5.0 mmol, 5 mL, 1.0 M in THF) was added dropwise over a 15-min period. After 1.5 h, the mixture was cooled to 0 °C and quenched as described for the workup of the $LiAlH_4$ reduction to make 9a. After 1.5 h, $MgSO_4$ was added, and the mixture was stirred for an additional 30 min. The solids were removed by filtration, and the mixture was concentrated. The enamine was purified by Kugelrohr distillation (60–65 °C, <1 mmHg) to give 0.83 g of 12a (99% yield): ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.7 Hz, 6 H), 0.89 (t, J = 7.4 Hz, 3 H), 1.30–1.42 (m, 3 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 1.96 (m, 2 H), 2.22 (d, J = 7.3 Hz, 2 H), 3.08 (d, J = 4.3 Hz, 2 H), 5.19 (bs, 1 H), 5.36–5.56 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.6, 17.7, 20.7, 22.3, 22.5, 27.6, 34.5, 58.9, 62.9, 122.4, 128.1, 132.4, 135.7; IR (neat) 2965, 2803, 1673, 1468, 1377, 1188, 970 cm^{-1} (in heptane); HRMS calcd for $C_{14}H_{27}N$ m/z 209.2143, found 209.2126.

General Procedures for Isobutyraldehyde Condensation and 3-Aza-Cope Rearrangements with 9 and 10. A mixture of the secondary amine (1.0 equiv, 2–6 mmol, 0.2 M in solvent),

(22) For a similar procedure, see: Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1985**, *50*, 5769.

isobutyraldehyde (3.0 equiv, 6–15 mmol), and pTsOH (0.0025 equiv) was taken up in benzene (or toluene for 10e) and heated to reflux. The mixture was heated to reflux with azeotropic removal of water,[23] and reaction progress was monitored by GLC for disappearance of amine.[24] Once the condensation was complete (12–24 h),[25] the mixture was cooled to room temperature and the benzene was removed in vacuo. The crude enamine was taken up in toluene (0.2 M), and the appropriate reagent was added at room temperature (see Table I). After complete rearrangement in refluxing toluene,[24] the imine was reduced at 0 °C by the addition of $LiAlH_4$ (1.1 equiv, 1.0 M in THF).[26] After stirring for 6 h, the reaction was quenched by the sequential addition of H_2O (1 mL/1.0 g $LiAlH_4$), 15% w/v aqueous NaOH (1 mL/1.0 g $LiAlH_4$), and then H_2O (3 mL/1.0 g $LiAlH_4$). The quenched mixture was stirred at room temperature overnight, filtered through K_2CO_3, concentrated, and purified by Kugelrohr distillation to give the corresponding product of condensation, rearrangement, and reduction (see Table I for yields).

(*E*)-1-(*N*-(2-Methylprop-1-yl)amino)-2,2-dimethyl-4-octene (15a): bp 70–80 °C (<1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (s, 6 H), 0.86 (t, J = 7.3 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 6 H), 1.35 (sextet, J = 7.2 Hz, 2 H), 1.72 (nonet, J = 6.6 Hz, 1 H), 1.87–1.99 (m, 4 H), 2.28 (s, 2 H), 2.35 (d, J = 6.9 Hz, 2 H), 5.35–5.41 (m, 2 H), NH not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 20.6, 22.8, 25.6, 28.0, 34.4, 34.8, 43.4, 59.1, 60.4, 126.9, 132.7; IR (neat) 3352, 2959, 2872, 2810, 1670, 1120, 970 cm^{-1}; HRMS calcd for $C_{14}H_{29}N$ m/z 211.2293, found: 211.2281.

(*E*)-1-(*N*-(2-Methylprop-1-yl)amino)-2,2-dimethyl-5-phenyl-4-pentene (15b): bp 70–80 °C (<1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6.7 Hz, 6 H), 0.93 (s, 6 H), 1.74 (nonet, J = 6.7 Hz, 1 H), 2.15 (dd, J = 7.3, 0.8 Hz, 2 H), 2.36 (s, 2 H), 2.39 (d, J = 6.9 Hz, 2 H), 6.25 (dt, J = 7.3, 15.9 Hz, 1 H), 6.38 (bd, J = 15.9 Hz, 1 H), 7.15–7.37 (m, 5 H), NH not observed; ^{13}N NMR (75.5 MHz, $CDCl_3$) δ 20.6, 25.7, 27.9, 35.1, 43.8, 59.0, 60.4, 125.9, 126.8, 127.7, 128.4, 131.9, 137.8; IR (neat) 3325, 3083, 3061, 3027, 2955, 2870, 2811, 1599, 1117, 966 cm^{-1}; HRMS calcd for $C_{17}H_{27}N$ m/z 245.2143, found 245.2172.

1-(*N*-(2-Methylprop-1-yl)amino)-2,2-dimethyl-3-propyl-4-pentene (16a): bp 70–80 °C (<1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.78 (s, 6 H), 0.85 (d, J = 6.1 Hz, 6 H), 0.86 (t, J = 6.7 Hz, 3 H), 0.99–1.19 (m, 2 H), 1.30–1.42 (m, 2 H), 1.69 (nonet, J = 6.6 Hz, 2 H), 4.90 (dd, J = 10.3, 2.4 Hz, 1 H), 4.98 (dd, J = 10.3, 2.4 Hz, 1 H), 5.55 (dt, J = 17.0, 10.3 Hz, 1 H), NH not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.1, 20.6, 21.1, 23.3, 23.6, 27.9, 30.5, 36.2, 51.0, 59.1, 59.6, 115.7, 140.2; IR (neat) 3310, 3075, 2959, 2872, 2811, 1638, 1119, cm^{-1}. HRMS calcd for $C_{14}H_{29}N$ m/z 211.2293, found 211.2264.

1-(*N*-(2-Methylprop-1-yl)amino)-2,2-dimethyl-3-phenyl-4-pentene (16b): bp 70–80 °C (<1 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3 H), 0.87 (d, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 0.90 (s, 3 H), 1.70 (nonet, J = 6.7 Hz, 1 H), 2.20 (d, J = 11.7 Hz, 1 H), 2.31 (d, J = 7.0 Hz, 2 H), 2.34 (d, J = 11.7 Hz, 1 H), 3.25 (bd, J = 10.1 Hz, 1 H), 5.01–5.09 (m, 2 H), 6.28 (m, 1 H), 7.10–7.30 (m, 5 H), NH not observed; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 20.7, 23.6, 23.7, 28.1, 37.6, 57.3, 59.0, 59.3, 116.2, 126.0, 127.8, 129.3, 138.8, 142.5; IR (neat) 3320, 3077, 3069, 3029, 2057, 2872, 2811, 1636, 1601, 1117 cm^{-1}; HRMS calcd for $C_{17}H_{27}N$ m/z 245.2143, found 245.2206.

(*E*)-1-(*N*,*N*-Bis(2-methylprop-1-yl)amino)-2-hexene (17a). Isobutyryl chloride (0.106 g, 1.0 mmol) was added slowly to a mixture of amine 10a (0.155 g, 1.0 mmol) and NEt_3 (0.15 g, 1.1 mmol) in toluene at 0 °C. The reaction mixture was allowed to warm to room temperature and stir for 48 h. The solution was washed through a plug of silica gel, concentrated, and purified by Kugelrohr distillation (70–85 °C, <1 mmHg) to give 17a (0.144 g, 0.66 mmol) in 66% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J = 6.6 Hz, 12 H), 0.88 (t, J = 7.3 Hz, 3 H), 1.31–1.43 (m, 2 H), 1.59–1.74 (m, 2 H), 1.93–2.08 (m, 1 H), 2.05 (d, J = 7.2 Hz, 4 H), 2.91 (d, J = 5.4 Hz, 2 H), 5.34–5.54 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.7, 20.9, 22.6, 26.5, 34.5, 57.1, 60.2, 128.2, 132.6; IR (neat) 3301, 2959, 2872, 2810, 1670, 1121, 971 cm^{-1}; HRMS calcd for $C_{14}H_{29}N$ m/z 211.2300, found 211.2297.

(*E*)-Hept-2-en-1-ylamine (20). Compound 19 (38.79 g, 150 mmol) was treated with 6 N aqueous NaOH (300 mL) and heated to reflux for 36 h. The amine was extracted from the aqueous mixture with 4 × 150 mL of Et_2O, and the combined organics were dried over K_2CO_3. The oil was concentrated and distilled to give 20 (14.27 g, 126.0 mmol) in 84% yield (bp 60–70 °C, 22 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J = 7.4 Hz, 3 H), 1.15–1.35 (m, 6 H), 1.97 (m, 2 H), 3.19 (m, 2 H), 5.50 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 22.1, 31.5, 31.9, 44.1, 130.7, 131.2; IR (neat) 3371, 3300, 3020, 2959, 2928, 2873, 2859, 1669, 969 cm^{-1}.

***N*-Cyclohexenyl-*N*-(*E*)-hept-2-en-1-yl-2-methylpropanamide (22)**. Amine 20 (1.81 g, 16 mmol) and cyclohexanone (1.57 g, 16 mmol) were condensed in refluxing toluene with azeotropic removal of water to form 21, which was used without isolation. To the imine solution was added NEt_3 (1.78 g, 17.6 mmol), followed by the slow addition of isobutyryl chloride (1.71 g, 16 mmol). The mixture was stirred for 3 h at room temperature and then filtered through a pad of silica gel/alumina. The enamide was concentrated, purified by silica gel flash chromatography (70:30 Et_2O/petroleum ether), and then distilled to give 22 (3.76 g, 14.3 mmol) in 89% yield (bp 90–100 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (t, J = 7.2 Hz, 3 H), 1.03 (d, J = 6.7 Hz, 6 H), 1.17–1.34 (m, 4 H), 1.54 (m, 2 H), 1.64 (m, 2 H), 1.90–2.10 (m, 6 H), 2.71 (sept, J = 6.7, 1 H), 3.90 (bs, 2 H), 5.29–5.53 (m, 2 H), 5.52 (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.8, 20.1, 21.5, 22.0, 22.7, 24.7, 29.0, 31.2, 31.3, 31.8, 48.1, 125.5, 126.9, 134.0, 138.5, 176.4; IR (neat) 3027, 2960, 2931, 2873, 1651, 970 cm^{-1}; HRMS calcd for $C_{17}H_{29}NO$ m/z 263.2249, found 263.2248.

(*E*)-*N*-(2-Methylprop-1-yl)-*N*-hept-2-en-1-yl-1-cyclohexenamine (23). Compound 22 (3.16 g, 12 mmol) was slowly added to a suspension of $LiAlH_4$ (0.502 g, 13.2 mmol) in Et_2O (50 mL) and stirred at room temperature for 2 h. The solution was quenched at 0 °C by the sequential addition of 3.0 mL of H_2O, 3.0 mL of 15% w/v aqueous NaOH, and 9.0 mL of H_2O. After stirring for 4 h, the aluminum salts were removed by filtration, and the combined filtrate and washings were concentrated and distilled to give 23 (2.90 g, 11.6 mmol) in 97% yield (bp 75–90 °C, <1 mmHg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (d, J = 6.6 Hz, 6 H), 0.86 (t, J = 7.2 Hz, 3 H), 1.22–1.37 (m, 4 H), 1.49 (m, 2 H), 1.65 (m, 2 H), 1.84 (nonet, J = 6.9 Hz, 1 H), 1.93–2.11 (m, 6 H), 2.63 (d, J = 7.1 Hz, 2 H), 3.49 (d, J = 5.5 Hz, 2 H), 4.41 (dd, J = 1.2, 3.6 Hz, 1 H), 5.29–5.56 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 13.9, 20.6, 22.1, 22.9, 23.6, 24.7, 26.6, 27.3, 31.6, 32.0, 51.8, 56.3, 96.5, 126.9, 132.3, 143.5; IR (neat) 3022, 2958, 2929, 2872, 1685, 1653, 1646, 970 cm^{-1}.

General Procedure for Rearrangement of 23 and Reduction of 24 To Give 25. To a 0.2 M solution of 23 (3–7 mmol) in toluene was added the reagent for promoting the 3-aza-Cope rearrangement (see Table II for equiv of reagent). The mixture was heated at reflux until the rearrangement was complete (see Table II for reaction times). After cooling to room temperature, iBu_2AlH (1.2 equiv, 2 M in hexanes) was added slowly.[27] The mixture was stirred for 24 h at room temperature and then quenched by sequential addition of H_2O (1 mL/0.3 g of iBu_2AlH), 15% w/v aqueous NaOH (1 mL/0.3 g iBu_2AlH), and then H_2O (3 mL/0.3 g of iBu_2AlH), stirred for 1 h, and filtered.[28] The amine

(23) Under these conditions, 9b was transformed to 13b, the product of condensation with isobutyraldehyde followed by [3,3] rearrangement. The addition of HCl or $TiCl_4$ also resulted in the formation of 13b from 9b under these reaction conditions (see text and Table I).

(24) Samples of the reaction mixture were quenched with a 10% w/v solution of NaOMe/MeOH for analysis by GC. Under the quenching conditions, loss of 11, 12, 13, or 14 was not observed even after extended exposure (24 h).

(25) In the examples in which 9b was transformed into 13b in a "one-pot" condensation and rearrangement, some hydrolysis of 13b to the corresponding aldehyde occurred under the reaction conditions. When hydrolysis occurred, enough isobutylamine was added during the azeotropic removal of H_2O to regenerate 13b from the corresponding aldehyde.

(26) Rearrangements promoted by $TiCl_4$ were first partially reduced with $LiAlH_4$ at −78 °C for 1 h, quenched at −78 °C, and then allowed to warm to room temperature. After stirring for 1–12 h, the solution was filtered to remove the aluminum and titanium salts. This modified procedure was performed in order to avoid reduction of the alkene functionality as a result of titanium hydride species.[17] The crude solution of imine was then reduced as described in the general procedure.

(27) The mixture resulting from rearrangement promoted by $TiCl_4$ was quenched with a 10% sodium of NaOMe in MeOH prior to the addition of the aluminum hydride reagent.[28]

was purified by silica gel flash column chromatography[29] (eluent, 50:50 Et_2O/petroleum ether) and purified by Kugelrohr distillation to give **25** as a mixture of diastereomers (see Table II for yields and diastereomer ratios) (bp 75–85 °C, <1 mmHg): ^1H NMR (300 MHz, $CDCl_3$) (major isomer) δ 0.85 (t, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.5 Hz, 6 H), 1.00–1.74 (m, 16 H), 1.79–2.00 (m, 2 H), 2.14 (dd, J = 6.7, 11.2 Hz, 1 H) 2.47 (dd, J = 6.4, 11.2 Hz, 1 H), 2.82 (bq, J = 2.5 Hz, 1 H), 4.91 (dd, J = 2.2, 17.0 Hz, 1 H), 4.93 (dd, J = 2.2, 10.1 Hz, 1 H), 5.47 (ddd, J = 9.8, 10.1, 17.0 Hz, 1 H); (minor isomer) δ 0.83 (t, J = 6.7 Hz, 3 H), 0.86 (d, J = 6.7 Hz, 6 H), 1.00–1.74 (m, 16 H), 1.79–2.00 (m, 2 H), 2.06 (dd, J = 6.7, 11.2 Hz, 1 H), 2.38 (dd, J = 6.4, 11.2 Hz, 1 H), 2.67 (bq, J = 2.8 Hz, 1 H), 4.94 (dd, J = 2.2, 17.0 Hz, 1 H), 4.96 (dd, J = 2.2, 10.1 Hz, 1 H), 5.53 (ddd, J = 9.8, 10.1, 17.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) (major isomer) δ 14.1, 19.9, 20.9, 21.0, 22.8, 25.4, 26.7, 28.7, 29.3, 31.1, 45.1, 46.7, 53.7, 55.9, 114.9, 143.0; (minor isomer) δ 14.0, 20.0, 20.8, 21.0, 22.8, 24.8, 26.7, 28.8, 29.4, 31.8, 45.6, 46.4, 54.1, 55.7, 114.4, 142.3; IR (neat) 3360, 3074, 2955, 2930, 2857, 1640 cm^{-1}; HRMS calcd for $C_{17}H_{33}N$ m/z 251.2613, found 251.2606.

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Supplementary Material Available: Copies of ^1H and ^{13}C NMR spectra of all compounds in the Experimental Section (30 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the Journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(28) After rearrangement promoted by $(ArO)_2AlMe$ and reduction of **24**, amine **25** was treated with HCl (3 mL, 1 M in Et_2O), loaded on silica gel, and washed with 90:10 petroleum ether/Et_2O to remove the 2,6-diphenylphenol. The product was then eluted with 95:5 ether/NEt_3 to remove **25** from the column, the solvent removed, and the product distilled.

(29) Silica gel was washed with a solution of 5% NEt_3 in Et_2O prior to loading the products on the column in order to enhance resolution of the eluting compounds.