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Stereochemical Consequences of the Lewis Acid-Promoted 3-Aza-Cope Rearrangement of *N*-Alkyl-*N*-Allyl Enamines

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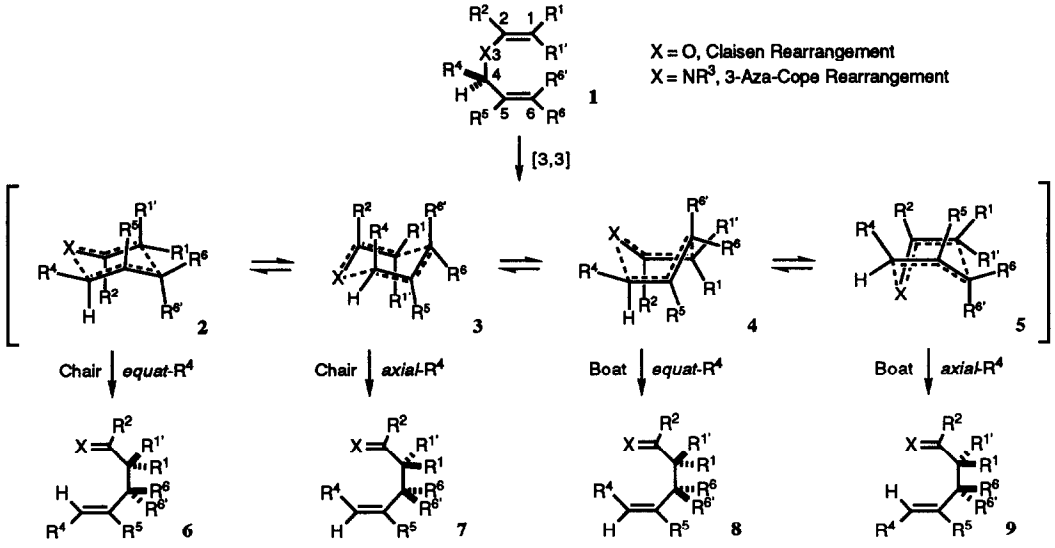
Abstract: Internal and relative asymmetric induction were examined for the electrophile promoted 3-aza-Cope rearrangement of substituted *N*-alkyl-*N*-allyl enamines. In general, internal asymmetric induction was highly variable, and was dependent both upon the nature of the electrophilic reagent and substrate. However, substitution at C-4 of the substrate served to anchor the transition state of the substrates, and product selectivity was typically >95:5. When the *N*-alkyl substituent was tethered to C-4, ring expansion from a five- to a nine-membered ring was obtained.

INTRODUCTION

The Claisen rearrangement, the [3,3] sigmatropic shift of allyl vinyl ethers (**1**, X = O), has been a powerful method for the regio- and stereochemically controlled formation of carbon-carbon bonds (Scheme I).[1] Valuable insight into this pericyclic process was obtained through analysis of the stereoselective product formation, which occurred as a result of the well-defined transition states for this intramolecular transformation. Thermal rearrangement of acyclic allyl vinyl ethers resulted in high internal asymmetric induction, the stereochemical relationship produced from simultaneous formation of vicinal stereocenters at C-1 and C-6. This high degree of stereoselectivity was demonstrated by a 95:5 ratio of [**6**+**7**]:[**8**+**9**], which directly corresponds to the conformational preference for the chair transition state topology over that of the boat ([**2**+**3**]:[**4**+**5**]).[2] Further differentiation between transition states has been made with the use of a substituent at C-4. During rearrangement of **1** (R^4 = iBu, $R^{6'}$ = Me), in which asymmetry at C-4 was transferred to C-6, the high equatorial preference for substituent R^4 was demonstrated by the selective formation of the *E* alkene product **6** (98:2, **6**:[**7**+**8**+**9**]).[3]

In contrast, less information has been obtained regarding the transition states of acyclic allyl vinyl ether rearrangements for systems promoted by alkyl aluminum reagents.[4] Introduction of these Lewis acids, which coordinated to the oxygen to accelerate the reaction, complicated the transition state analysis of this system. The aluminum reagents induced a planar geometry to the oxygen, and generated additional steric effects due to this new substitution at position 3.[5] The increased complexity of these systems was demonstrated through rearrangement of **1** (R^4 = nBu, R^6 = Me), which gave a 45:55 ratio of *E*:*Z* alkene products when promoted by $Al(iBu)_3$ to reflect the ratio of [**2**+**3**]:[**4**+**5**].[6] More recently, the use of $(ArO)_2AlMe$ reagents allowed for stereoselective control over rearrangement of **1** (R^4 = nBu, R^6 = Me) by varying the catalyst ligands.[7] The use of $(ArO)_2AlMe$ (ArO = 2,6-diphenylphenoxy) gave a 98:2 ratio of *E*:*Z* alkene products, while ArO = 4-bromo-2,6-ditertbutylphenoxy produced a complementary 16:84 *E*:*Z* ratio ([**6**+**9**]:[**7**+**8**]). Although the chair transition states **2** and **3** have been proposed, with product differentiation the result of axial or equatorial projection of R^4, substituents at C-1 have not yet been used to distinguish between the chair (leading to **6** and **7**) or boat (leading to **8** and **9**) transition state in these systems.

Scheme I. Stereochemical Features of The Claisen Rearrangement.



The stereochemical aspects of the analogous 3-aza-Cope rearrangement of acyclic *N*-alkyl-*N*-allyl enamines (**1**, X = NR^3) have not been studied as extensively as those of the Claisen rearrangement.[8] A high degree of internal asymmetric induction in the 3-aza-Cope rearrangement was suggested by the product distribution reported for the treatment of *N,N*-dialkyl enamines with crotyl bromide.[9] In the case in which R^2 was an oxygen anion substituent, the enolate of an allyl amide, stereoselective carbon-carbon bond formation revealed excellent chair to boat selectivity through internal asymmetric induction (99.5:0.5).[10] When substituted at the 4 position (R^4 = Me), thermal rearrangement resulted in a 90:10 *E*:*Z* alkene product selectivity for relative asymmetric induction.[11] An elegant example of 3-aza-Cope rearrangement has been the thermal transformation of *N,O*-ketene acetals, in which internal asymmetric induction was good (84:16), and asymmetric induction relative to a remote stereogenic center was high (97:3).[12] Other examples have reported stereoselective bond formation relative to an asymmetric alkyl substituent R^3 (X = NR^3). These reports have included allylation of *N,N*-dialkyl enamines (45-82%)[13] as well as rearrangement of asymmetric allyl amide enolates (89:11).[14] Interestingly, the *in situ* condensation of a secondary allyl amine with an aldehyde and subsequent $TiCl_4$ promoted rearrangement was found to give the same 90:10 *E* alkene selectivity[15] as well as good internal (85:15) and relative (95:5) asymmetric induction.[16]

Although the rearrangement of *N*-alkyl-*N*-allyl enamine substrates is similar in many respects to the Claisen rearrangement, there are several unique and advantageous properties of the complementary 3-aza-Cope rearrangement that make this transformation particularly attractive for application in organic synthesis. These features arise from the fluxional nitrogen heteroatom, and provide a number of opportunities for asymmetric induction in carbon-carbon bond formation. This fluxional nitrogen center provides a unique avenue for the introduction of asymmetry into the 3-aza-Cope rearrangement transition state framework by incorporation of either a vicinal stereocenter at C-4 or an asymmetric peripheral *N*-alkyl substituent. In addition, the

opportunity to tether the nitrogen to C-4 allows for the synthesis of heterocyclic products through sigmatropic ring expansion.

To conclude our investigations related to the formation and regioselective 3-aza-Cope rearrangement of *N*-alkyl-*N*-allyl enamines,[17] the internal and relative asymmetric induction of this reaction were investigated. In these studies, the dependence of the stereoselective formation of carbon-carbon bonds on the nature of the Lewis acid, and the effect of substrate substituent patterns on the product distribution have been probed.

RESULTS AND DISCUSSION

This series of studies was initiated by examination of the internal asymmetric induction for the 3-aza-Cope rearrangement of achiral *N*-alkyl-*N*-allyl enamines. Three different carbonyl compounds, butyraldehyde (**a**), 2-phenylpropionaldehyde (**b**), and cyclohexanone (**c**) were selected as substrates (Scheme II). Preparation of the desired allylic amine, **12**, was accomplished in three steps according to established procedure for stereoselective conversion of **10** to the *E* allyl amide **11** followed by hydrolysis to generate **12**.[17c,18] Condensation with the appropriate carbonyl group was accompanied by azeotropic removal of H_2O to generate **13**, and subsequent acylation of the imine produced **14**, which was isolated in 56 to 89% yield for the two step conversion of **12** to **14** (Table I). When formed from butyraldehyde or 2-phenylpropanal, the enamide intermediates were produced with poor *E* to *Z* alkene selectivity. However, as previously observed,[17] the reduction of **14** with $LiAlH_4$ produced a dramatic change in the *E* to *Z* isomer ratio under the conditions of the reaction, and gave **15** in excellent yield. Complete *E*:*Z* selectivity in enamine formation was observed for generation of **15a**, while an equilibrium 90:10 ratio of alkene isomers was obtained upon preparation of **15b**.

Scheme II. Preparation of *N*-Alkyl-*N*-Allyl Enamine Substrate **15**.

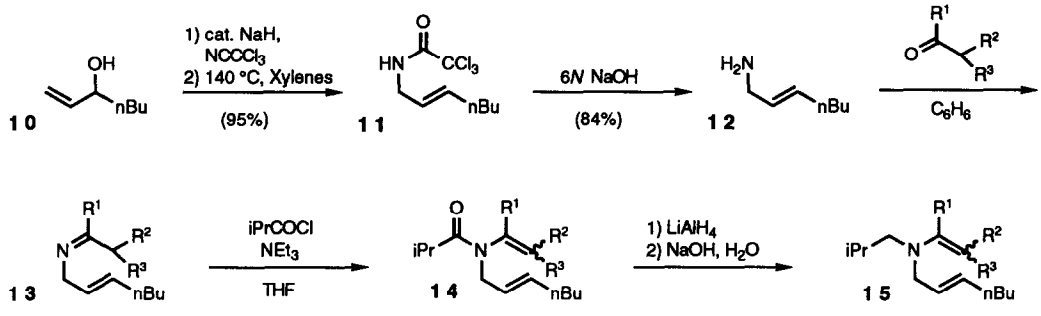


Table I. Yields and Isomer Ratios for the Preparation of *N*-Alkyl-*N*-Allyl Enamine Substrate **15**.

Substrate				Product Yields (%)[a]			
Carbonyl	R^1	R^2	R^3	**14**[b]	(*E*:*Z*)[c]	**15**	(*E*:*Z*)[c]
a	H	Et	H	66	(65:35)	99	(>98:2)
b	H	Ph	Me	56	(66:34)	99	(90:10)
c	-$(CH_2)_4$-		H	89		97	

[a]Isolated yields. [b]Yield from **12** to **14**. [c]Ratios were determined by ^1H NMR analysis.

Studies of the internal asymmetric induction produced by 3-aza-Cope rearrangement of *N*-alkyl-*N*-allyl enamines were performed by treating **15** with a variety of electrophilic reagents in toluene at reflux (111 °C). Because alkyl aluminum complexes have been established as the only effective electrophilic reagents for reactions with disubstituted enamines (R^2 or R^3 = H), the rearrangement of **15a** was limited to investigation with $AlMe_3$ and $AlClMe_2$.[17] In both cases, 3-aza-Cope rearrangement of **15a** produced a mixture of **16** and **17**. Subsequent reduction of this mixture with $LiAlH_4$ gave the corresponding amines, **18** and **19**, which were isolated to reveal poor product selectivity (Scheme III, Table II).

Scheme III. 3-Aza-Cope Rearrangement of **15**.

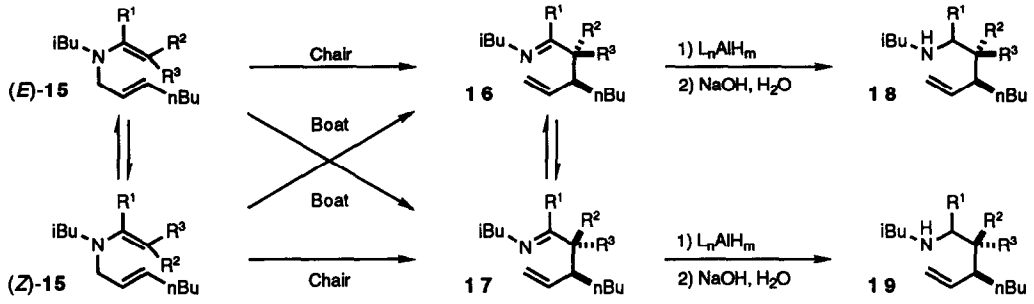


Table II. Electrophile-Promoted Rearrangement of **15** and Hydride Reduction to **18** and **19**.[a]

Substrate				Reagent	Products (18 and 19)	
Enamine	R^1	R^2	R^3	(equiv.)[b]	Yield (%)[c]	Ratio[d]
15a	H	Et	H	$AlMe_3$ (1.1)	88	(62:38)
				$ClAlMe_2$ (1.1)	94	(52:48)
15b[e]	H	Ph	Me	HCl (1.0)	54	(95:5)
				$TiCl_4$ (0.2)	48	(80:20)
				$AlMe_3$ (1.1)	86	(68:32)
				$(ArO)_2AlMe$ (1.1)[f]	58	(37:63)
15c	-$(CH_2)_4$-		H	HCl (1.0)	69	(54:46)
				$TiCl_4$ (0.2)	72	(55:45)
				$AlMe_3$ (1.1)	94	(67:33)
				$(ArO)_2AlMe$ (1.1)[f]	73	(77:23)

[a]Reduction of imines from **15a** and **15b** was performed with $LiAlH_4$; reduction of imine from **15c** was performed with DIBAH. [b]Rearrangements were performed at 111 °C. [c]Isolated yield. [d]Product ratio was determined by ^1H NMR analysis of the crude reaction mixture prior to purification (ref. 19). [e]Ratio of *E*:*Z* enamine isomers was 90:10 for **15b**. [f]ArO- = 2,6-diphenylphenoxy.

The poor selectivity obtained for the aluminum-promoted 3-aza-Cope rearrangement of **15a** could result from several reaction features (Scheme III). Based on the significant preference for (*E*)-**15a** over (*Z*)-**15a**, the relative amounts of **16a** and **17a** generated during the reaction could reflect the contributions of the chair *versus* boat transition states during product formation. Alternatively, the product distribution could reflect an equilibrium mixture of **16a** and **17a** formed by epimerization of the stereocenter α to the amine.

Potential changes in the diastereoselectivity due to α-imino epimerization prior to reduction were circumvented through the use of enamine **15b**. Generation of **15b** resulted in incomplete selectivity for enamine formation to give a 90:10 ratio of (*E*)- to (*Z*)-**15b**. Despite the lower selectivity observed for enamine formation, which was expected to result in less selective product formation, a slightly increased product selectivity was generated with $AlMe_3$ when compared to the same reaction with **15a**. Interestingly, when HCl was used to accelerate rearrangement, a 95:5 product ratio was generated at the same reaction temperature. Based on similar thermal[12] and electrophile-promoted[15,16] 3-aza-Cope rearrangements, the major isomer was assigned as **16b**, the product of rearrangement through the chair transition state. These results suggested that the larger electrophilic reagent ($AlMe_3$) resulted in poorer chair:boat transition state preference than the smaller reagent (H^+). As the effective size of the reagent was increased, from H^+ to $TiCl_4$, the product selectivity decreased, and greater steric hindrance of $(ArO)_2AlMe$ actually reversed the product selectivity. A study of the rearrangement of **15c** produced a similar trend from HCl to $(ArO)_2AlMe$. However, product selectivity was low, rearrangement appeared to be less sensitive to the different properties of the electrophilic reagents, and each reagent produced the same major isomer. In the case of **15c**, generation of the third contiguous stereocenter by reduction was carried out more selectively with DIBAH than $LiAlH_4$.

In order to provide greater conformational preference for the chair-like 3-aza-Cope transition state, an allylic amine with a methyl substituent at C-4 was used. The preparation of **22** was accomplished through the same route used for the synthesis of **12**,[18] and condensation with the appropriate carbonyl compound produced **23**, which was subsequently acylated to give enamide **24** (Scheme IV). In the formation of **24a**, selectivity for enamine alkene geometry was essentially complete, and $LiAlH_4$ reduction produced **25a** as a single isomeric product in excellent yield (Table III). However, formation of **24b** resulted in poor *E*:*Z* enamide selectivity, and reduction of **24b** did not improve the ratio of *E*:*Z* enamine isomers. The *E*:*Z* product ratios for **25b** varied only slightly as a result of $LiAlH_4$ reduction from 52:48 to 58:42.

Scheme IV. Preparation of *N*-Alkyl-*N*-Allyl Enamine Substrate **25**.

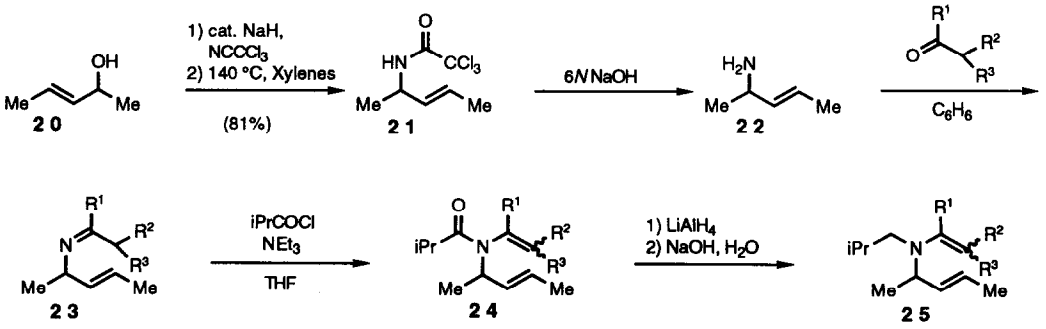


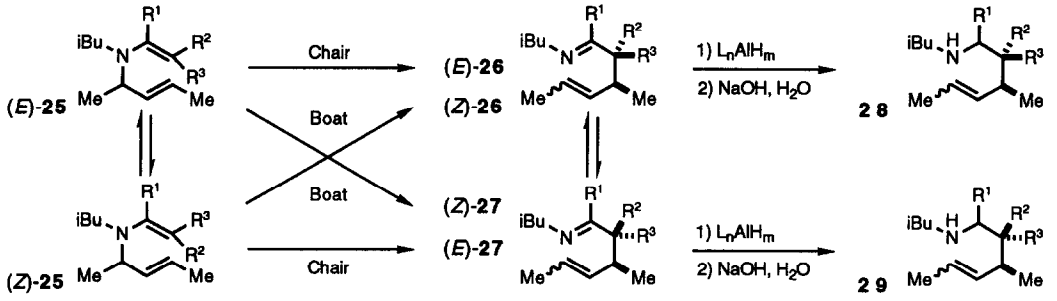
Table III. Yields and Isomer Ratios for the Preparation of *N*-Alkyl-*N*-Allyl Enamine Substrate **25**.[a]

Substrate				Product Yields (%)[a]			
Amine	R^1	R^2	R^3	**24**[b]	(*E*:*Z*)[c]	**25**	(*E*:*Z*)[c]
22a	H	Et	H	75	(>98:2)	88	(>98:2)
22b	H	Ph	Me	64	(55:45)[d]	96	(55:45)[d]
22c	-$(CH_2)_4$-		H	56		95	

[a]Isolated yields. [b]Yield of the three step sequence of **21** to **24**. [c]Ratios were determined by ^1H NMR analysis. [d]Product ratios varied from 52:48 to 58:42.

Due to the presence of the methyl group at C-4, the reaction had added complexity (Scheme V). In addition to the compounds formed through rearrangement similar to that of **15**, the potential for generation of the *Z* alkene isomers provided the possibility of an extra set of products. Rearrangement of **25** was therefore a much more sensitive probe of the mechanistic aspects of the electrophile-promoted 3-aza-Cope rearrangement.

Scheme V. 3-Aza-Cope Rearrangement of **25**.



When compared to the analogous reaction of **15**, a dramatic increase in the chair:boat transition state selectivity of the 3-aza-Cope rearrangement resulted from the presence of a methyl substituent at C-4. Rearrangement of **25a** gave essentially complete product selectivity to generate (*E*)-**28a** as the only product (Scheme V, Table IV). The rearrangement of **25c**, followed by selective hydride reduction with DIBAH, also resulted in formation of a single observable reaction product. Unfortunately, the analogous treatment of **25c** with HCl or $TiCl_4$ generated a wide variety of additional products.

Treatment of **25b** with different electrophiles produced more complicated results, and the increased complexity of the reaction with **25b** stemmed primarily from the incomplete selectivity of enamine formation. Although the enamine isomers were typically generated in nearly equal mixtures (Table III), treatment with HCl in $CHCl_3$ could be used to enhance the *E*:*Z* ratio through isomerization of **25b** without facilitating the sigmatropic rearrangement. As a result of this process, increased *E*:*Z* selectivity was obtained that gave mixtures of enamine isomers in ratios up to 83:17. Rearrangement of this mixture of isomers, by heating **25b** with electrophilic reagents at 111 °C, generated three rearrangement products. Despite the occurrence of this third product, the results obtained for this substrate appeared to be in line with those obtained for **25a** and **25c**, and could also be rationalized by invoking a high degree of chair:boat transition state selectivity.

Table IV. Electrophile-Promoted Rearrangement of **25** and Hydride Reduction to **28** and **29**.[a]

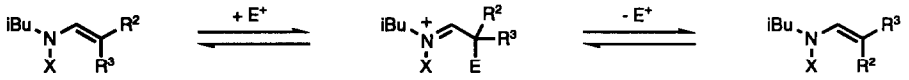
Substrate				Reagent	Products (28:29)	
Enamine	R^1	R^2	R^3	(equiv.)[b]	Yield (%)[c]	Ratio[d]
25a (>98:2)	H	Et	H	$AlMe_3$ (1.1)	78	(>98:2)
				$ClAlMe_2$ (1.1)	81	(>98:2)
25b (52:48)	H	Ph	Me	HCl (0.6)	92	([78:8]:14)
(52:48)				HCl (1.2)	91	([79:8]:13)
(83:17)				HCl (0.6)	94	([81:9]:10)
(83:17)				HCl (1.2)	98	([89:3]:8)
(58:42)				$TiCl_4$ (0.2)	84	([65:11]:24)
(55:45)				$AlMe_3$ (1.1)	97	([71:8]:21)
(70:30)				$AlMe_3$ (1.1)	98	([73:7]:20)
(58:42)				$(ArO)_2AlMe$ (1.1)[e]	84	([80:6]:14)
25c		$-(CH_2)_4-$		$AlMe_3$ (1.1)	95	(>95:5)

[a]Reduction of imines from **25a** and **25b** was performed with $LiAlH_4$; reduction of imine from **25c** was performed with DIBAH. [b]Rearrangements were performed at 111 °C. [c]Isolated yields. [d]Product ratio was determined by ^1H NMR analysis of the crude reaction mixture prior to purification (ref. 19). The products from **25b** represent the ratio of [(*E*)-**28b**:(*Z*)-**28b**]:(*E*)-**29b**. [e]ArO- = 2,6-diphenylphenoxy.

Based on previous studies of 3-aza-Cope rearrangements,[12,15,16] the major product isomer after $LiAlH_4$ reduction was expected to be (*E*)-**28**, the product of rearrangement through a chair transition state with an equatorial methyl substituent. Hydrogenation of the 79:8:13 product mixture (**28** and **29**) derived from HCl rearrangement gave approximately a 90:10 mixture of two diastereomers, and similar reduction of the 71:8:21 mixture produced by $AlMe_3$ rearrangement afforded an 80:20 mixture. The fourth possible product of 3-aza-Cope rearrangement was not detected by NMR. Based on these findings, the compound isomeric with (*E*)-**28** that contributed 8% to the product mixture was assigned structure (*Z*)-**28**, which could have been produced through a chair transition state with the C-4 methyl in an axial position (**3**). Based on these results, the 80:20 and 90:10 mixtures produced by rearrangement closely paralleled the 83:17 *E*:*Z* selectivity obtained for enamine equilibration of **25b** as well as the 90:10 equilibrium ratio of **15b**. The third isomeric product generated upon rearrangement and reduction was most probably (*E*)-**29**, formed through rearrangement of (*Z*)-**25** through the chair transition state. The results obtained for **25b** were consistent with those obtained for **25a** and **25c** in which high chair:boat selectivity was observed.

Equilibration of the enamine isomers prior to rearrangement appeared to provide an explanation for the relative independent nature of product formation on the initial ratio of (*E*)-**25b**:(*Z*)-**25b** used for this transformation. The fact that these results were not significantly different than the equilibrium ratio of (*E*)-**25b**:(*Z*)-**25b** (83:17), suggested that enamine equilibration occurred more rapidly than rearrangement, and that subsequent rearrangement did not occur at a rate that was affected significantly by enamine geometry. One possible means of enamine isomerization is illustrated in Scheme VI,[20] and an alternative route would be reversible equilibration through a 1-aza-Cope rearrangement reaction (*vide infra*).

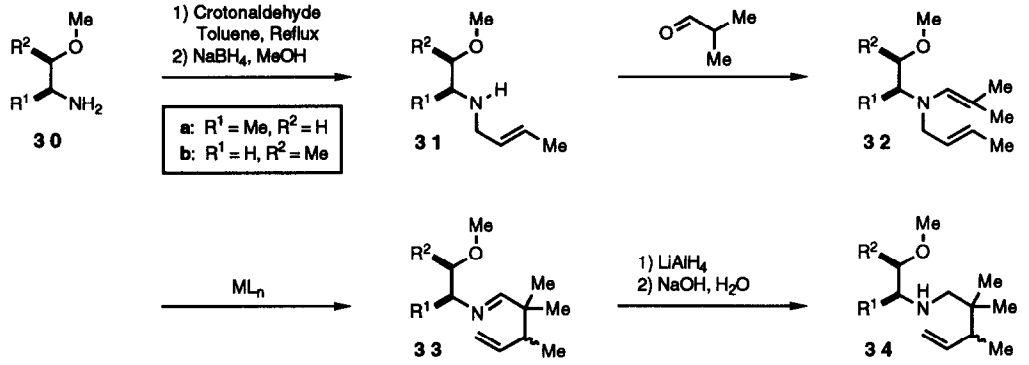
Scheme VI. Possible Route For Substrate Equilibration Prior to Rearrangement.



Comparison of the results obtained from rearrangement of substrates **15** and **25** under the same reaction conditions illustrated the key role of a substituent at C-4, in which increased product selectivity appeared to result from a greater conformational preference for a chair- *versus* boat-like transition state. An advantage to the use of these substrates for asymmetric induction in the 3-aza-Cope reaction is the availability of chiral allylic amine substrates, which have been prepared from a variety of amino acids through established procedures.[21] The above examples clearly illustrate the self-immolative nature of the reaction when the stereogenic center is part of the [3,3] sigmatropic rearrangement framework.

An alternative route to asymmetric induction is the selective generation of an asymmetric quaternary nitrogen through strategic placement of a stereocenter α to the nitrogen on the spectator ligand at position 3. Once generated, the asymmetric ammonium species could then serve to transfer stereochemistry to the nascent stereocenters at C-1 and C-6 without consumption of the original stereocenter on the auxiliary. In order to examine the effectiveness of this approach, chiral auxiliaries derived from amino acids were used in the preparation of two asymmetric allyl enamine substrates.[22] Condensation of readily available chiral auxiliaries (**30**) with crotonaldehyde, followed by $NaBH_4$ reduction, gave the asymmetric allyl amines **31a** and **31b** (Scheme VII).[16] Enamine formation with isobutyraldehyde produced **32**.

Scheme VII. Preparation and Rearrangement of Substrate **32**.

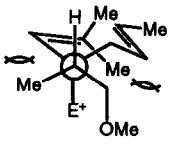


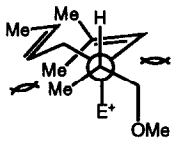
The most effective reagents for rearrangement, as well as the most selective reagents for internal asymmetric induction, were HCl and $TiCl_4$. Rearrangement of **32a** was promoted by treatment with $TiCl_4$, which resulted in formation of the corresponding imine **33a**. Although hydrolysis of **33a** could be employed to remove the chiral auxiliary at this point, **33a** was reduced instead to the corresponding amine so that the product could be readily isolated, and so that asymmetric induction could be determined by analysis of the diastereomeric mixture of products. This two step process generated a 77% yield of **34a**, but the

diastereomeric excess of **34a** was only 15%. Interestingly, rearrangement of the substrate with a methyl substituent at R^2 (**32b**) resulted in similar diastereoselectivity with $TiCl_4$ (72% yield, 20% de), and rearrangement promoted by HCl produced less selectivity (86% yield, 8% de).

The poor asymmetric induction in the charge-accelerated 3-aza-Cope rearrangement in this case can be rationalized by an insignificant steric difference between the *N*-crotyl and *N*-butenyl substituents as well as the lack of steric differentiation between the Me and -CH_2OMe substituents. As illustrated for **35a** and **35b**, the diastereomeric *gauche* interactions do not provide the energy differences necessary to generate a preference for one diastereomeric transition state over the other, despite the possibility for chelation control.[22b] In order to enhance asymmetric induction through this approach, greater steric differentiation between the *N*-crotyl and *N*-butenyl substituents would be essential. Although substitution at C-4 would accomplish this task, introduction of a stereocenter at this position produced successful asymmetric induction without the need for the peripheral chiral auxiliary. An alternative approach for differentiation of the allyl and alkene substituents on the nitrogen involved substitution at C-2. However, preparation of the corresponding cyclohexanone derived substrate was unsuccessful due to the steric hindrance encountered during attempted enamine formation with **31**.

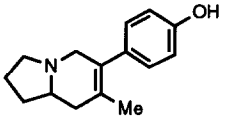
35a



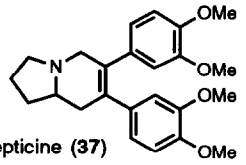


35b

The ability to place a substituent at the 3 position of the [3,3] sigmatropic rearrangement framework provided the opportunity to covalently tether the 3 and 4 positions for the (n) → (n+4) ring expansion of cyclic allyl amine substrates. Ring expansion of allyl enamine substrates has enormous potential in synthetic organic chemistry for the formation of medium ring cyclic amines,[23] or through a sequential [3,3] ring expansion, imine reduction, and transannular formation of indolizidine and quinolizidine ring systems such as the indolizidine skeletons of the naturally occurring alkaloids ipalbidine (**36**)[24] and septicine (**37**).[25]



Ipalbidine (**36**)

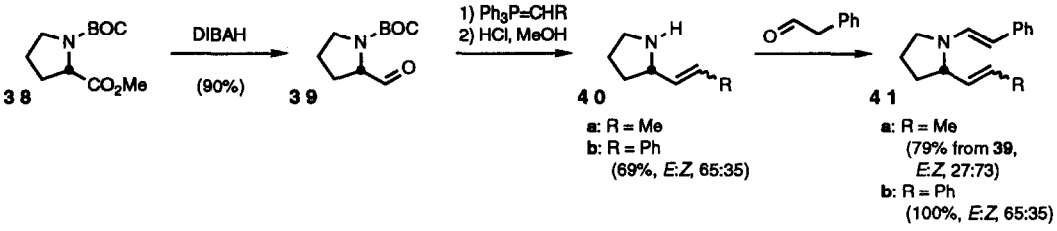


Septicine (**37**)

With our investigation of ring expansion reactions directed toward construction of the bicyclic alkaloid skeleton of **36** and **37**, and the use of Ph substituents to model the aromatic functionality of these naturally occurring products, allyl amines **40a** and **40b** were prepared from the proline derivative **38** (Scheme VIII).[26] Partial reduction of the ester carbonyl efficiently produced aldehyde **39**. Homologation with the appropriate Wittig reagent gave a mixture of the corresponding alkene isomers, and subsequent removal of the nitrogen protecting group resulted in formation of allyl amines **40a** and **40b**. In each case, incomplete selectivity was obtained for generation of the alkene, and optimization of alkene selectivity was not pursued. Condensation of **40** with phenylacetaldehyde generated **41**, in which enamine formation occurred with >98:2 selectivity for the

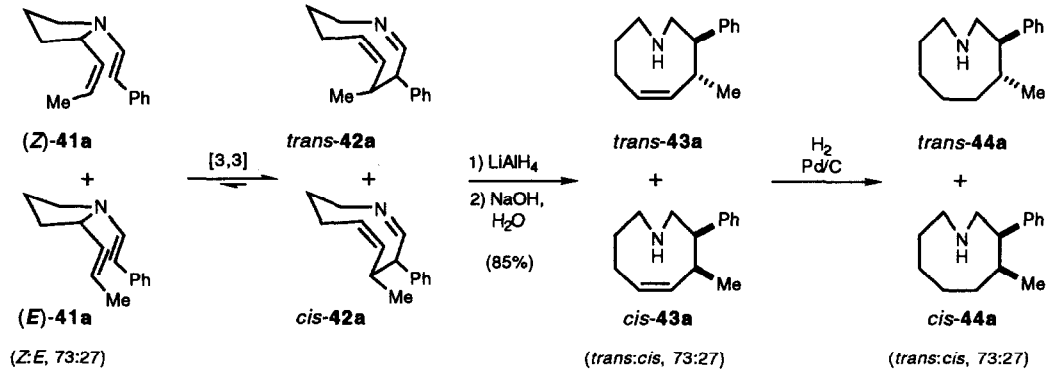
E geometry for both isomers, and the ratios of *E*:*Z* alkene isomers were 27:73 and 65:35 for **41a** and **41b**, respectively.

Scheme VIII. Preparation of Proline Derived Substrates (**41**) For 3-Aza-Cope Ring Expansion.



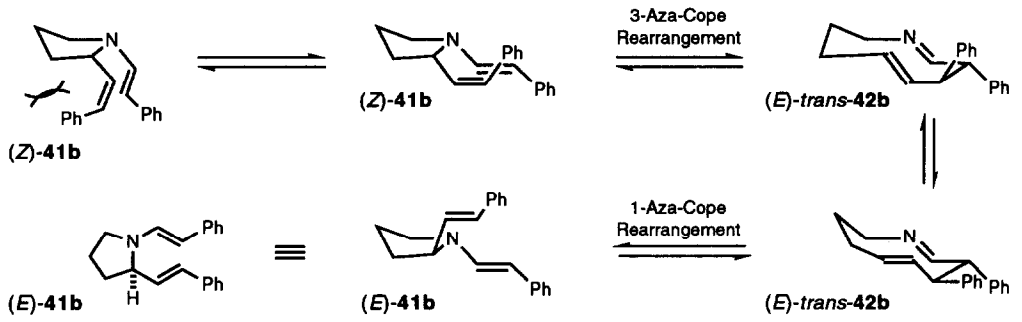
Rearrangement of **41a** with Me_2AlCl resulted in efficient formation of **42a**, and reduction of the imine functionality gave **43a** in 85% yield as a 27:73 mixture of isomers (Scheme IX). Through ^1H NMR ($^3J_{HC=CH}$ = 10.6 Hz) and IR (*cis*-C=C, 739 cm^{-1}) analysis, the geometry of the double bonds in both isomeric products was determined to be *Z*. Hydrogenation of this mixture produced **44a** with the same 27:73 isomeric product ratio to support the assignment of this mixture as trans and cis diastereomeric products. This selectivity was opposite that observed for the charge-accelerated [3,3] sigmatropic ring expansions of both the analogous oxygen[27] and nitrogen[23b] systems. In these cases, the less thermodynamically stable *E* isomers were generated from 2-vinyltetrahydropyran,[27] furan,[27] and pyrrole[23] substrates, while our studies more closely parallel the results observed for the Cope rearrangement.[28] When promoted by Me_2AlCl, coordination with the nitrogen probably resulted in reaction through the more favorable boat transition state to give **42a** as the *Z* isomer.[28] The 73:27 isomer ratio could represent the thermodynamic equilibrium of *cis*-**42a**:*trans*-**42a**, which could result from epimerization of the benzylic position α to the imine.[29] However, under the same rearrangement and reduction conditions as those used for reaction of **25a**, the product mixture correlated directly to the initial allyl amine alkene geometry.

Scheme IX. Stereoselective 3-Aza-Cope Ring Expansion of **41a**.



In contrast, treatment of **41b** with $AlMe_3$, Me_2AlCl, or $(ArO)_2AlMe$ did not result in the transformation to the corresponding ring expanded product. Instead, reaction under the same conditions that produced rearrangement of **41a** resulted only in quantitative recovery of (*E*)-**41b** as the only isomeric product. Although the products of 3-aza-Cope rearrangement were not observed, a rearrangement equilibrium can be used to rationalize the geometric isomerization of the alkene (Scheme X). Due to steric restrictions in the transition state through which **41a** was found to rearrange, **41b** could proceed through an alternative boat transition state to produce **42b**. This energetically less stable intermediate, due to the trans alkene in the aza-nonene ring system as well as the loss of alkene conjugation with the aromatic rings, has the potential to produce (*E*)-**41b** through the reverse reaction, 1-aza-Cope rearrangement.[30] Conformational change to the chair transition state, and nitrogen-carbon bond formation from the other face of the *E* alkene intermediate would result in generation of (*E*)-**41b**. Although this isomerization process would result in epimerization of the allylic position, changes in optical activity from substrate to product were not explored.

Scheme X. Proposed 1-Aza-Cope Rearrangement for Alkene Isomerization of (*Z*)-**41b** to (*E*)-**41b**.



SUMMARY

The key features necessary for the stereoselective [3,3] rearrangement of *N*-alkyl-*N*-allyl enamines were determined through these studies. In the absence of a substituent at C-4, internal asymmetric induction that resulted from chair:boat transition state selectivity was highly variable, and was dependent both on the nature of the electrophilic reagent and substrate. In general, poor selectivity was obtained in these studies, and placement of a chiral peripheral substituent on the nitrogen did not improve selectivity through relative asymmetric induction. Substitution at C-4 was critical to the stereoselective rearrangement of these substrates, and incorporation of a methyl group at C-4 served to anchor the transition state of the acyclic substrates in the chair conformation. In these examples, chair:boat selectivity was typically >95:5, and resulted in selective product formation. Rearrangement of a cyclic substrate, tethered at the C-4 and nitrogen positions, also generated products with a high degree of control over transition state geometry. Based on these studies, the scope and limitations of the charge accelerated [3,3] rearrangement of *N*-alkyl-*N*-allyl enamines has been outlined for future use.

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) and $LiAlH_4$ (1.0 *M* in THF) were obtained from Aldrich Chemical Co. Solutions of $AlMe_3$ (2 *M* in toluene), Me_2AlCl (1 *M* in toluene), and DIBAH (1 *M* in THF) were prepared from neat organoaluminum compounds obtained from Aldrich Chemical Co. $TiCl_4$ was distilled prior to use. $(ArO)_2AlMe$ was prepared as previously described.[17c] Additions were made with gas tight syringes, or *via* cannula transfer under nitrogen or argon. Unless specified, concentration of solutions after work up was performed on a Büchi rotary evaporator.

NMR Spectra were obtained on a Varian Gemini or VXR-300 instrument with $CDCl_3$ as the solvent. ^1H NMR spectral data are reported as follows: chemical shifts relative to residual $CHCl_3$ (7.24 ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, b = broad), coupling, and integration. ^{13}C signals are reported in ppm relative to the residual $CHCl_3$ (77.0 ppm). Infrared spectra were recorded on a Nicolet 42 FT-IR instrument. Mass spectra were recorded on a Finnigan 9610 instrument. Capillary gas chromatography was carried out on a Perkin Elmer 8500 equipped with a 50 m RSL-200 column (methyl 5% phenylsilicone) and a Hewlett Packard 5880A equipped with an RTX-1 column.

General Method for the Synthesis of Enamides 14. A mixture of **12** and 1 equiv. of the appropriate carbonyl compound was condensed (**14a**, Et_2O/K_2CO_3/25 °C; **14b**, benzene, 80 °C; **14c**, toluene, 111 °C) to prepare the corresponding imines, which were used without isolation. After imine formation, the solution was treated with Et_3N (1 equiv.), and isobutyryl chloride (1 equiv.) was slowly added. The mixture was stirred for a minimum of 4 h at room temperature and then filtered through a pad of silica gel/basic alumina. The enamide was concentrated, purified by flash chromatography (silica gel, 70:30 Et_2O/petroleum ether), and distilled (Kugelrohr).

14a: (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 Torr): ^1H 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, *E* isomer), 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.

14b: (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, <1 Torr): ^1H 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.

14c: (3.755 g, 14.3 mmol) in 89% yield (oven temp 90-100 °C, <1 Torr): ^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.

General Method for the Preparation of Enamides 24. Amide **21** was heated at reflux for at least 12 h in 6 *M* NaOH, extracted with either Et_2O or benzene, and dried with K_2CO_3. This solution was then combined with 1 equiv. of the appropriate carbonyl compound and then condensed (**24a**, Et_2O/K_2CO_3/25 °C; **24b** and **24c**, benzene, 80 °C) to prepare the corresponding imines, which were used without isolation. After imine formation, the solution was treated with Et_3N (1 equiv.), and isobutyryl chloride (1 equiv.) was slowly added. The mixture was stirred for a minimum of 4 h at room temperature and then filtered through a pad of silica gel/basic alumina. The enamide was concentrated, purified by flash chromatography (silica gel, 70:30 Et_2O/petroleum ether), and distilled (Kugelrohr).

24a: (25.44 g, 121.2 mmol) in 75% yield (bp 83-95 °C, <1 Torr): ^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.

24b: (6.101 g, 22.4 mmol) in 64% yield as a mixture of isomers (*E:Z* 55:45) (oven temp 95-110 °C, <1 Torr): ^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.

24c: (3.317 g, 14.0 mmol) in 56% yield (oven temp 80-90 C, <1 Torr): ^1H 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, 1258, 972 cm^{-1}; HRMS calcd for $C_{15}H_{25}NO$ *m/e* 235.1936, obsd *m/e* 235.1917.

General Method For Formation of Enamines 15 and 25. Enamide **14** or **24** 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 h. The mixture was quenched by careful sequential addition of H_2O (1 mL/g $LiAlH_4$), 15% aq. NaOH (1 mL/g $LiAlH_4$), and H_2O (3 mL/g $LiAlH_4$). After the mixture was stirred for 1 h, the solids were removed by filtration. The mixture was concentrated, and the enamine was distilled (Kugelrohr).

15a: (1.94 g, 8.7 mmol) in 99% yield as a single enamine olefin isomer (oven temp 60-70 °C, <1 Torr): This enamine was extremely sensitive to hydrolysis and full spectral data could not be obtained. Characteristic enamine olefin resonances; ^1H 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).

15b: (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 Torr): ^{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}.

15c: (2.901 g, 11.6 mmol) in 97% yield (bp 75-90 °C, <1 Torr): ^{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}.

25a: (4.277 g, 22.0 mmol) in 88% yield (bp 75-85 °C, 8 Torr): ^{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}.

25b: (2.949 g, 11.52 mmol) in 96% yield as a mixture of isomers (*E:Z* 55:45) (bp 80-90 °C, <1 Torr): ^{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}.

25c: (2.532 g, 11.4 mmol) in 95% yield (oven temp 60-70 °C, <1 Torr): ^{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}.

General Method for the Synthesis of 31. Equimolar amounts of **30** and crotonaldehyde were added to toluene (0.2-0.4 *M*) and heated at reflux for 1-2 h accompanied by azeotropic removal of H_2O. After the solution was cooled to room temperature, $NaBH_4$ (1-2 equiv.) was added, the mixture was cooled to 0 °C, MeOH (half the volume of the toluene) was added dropwise, and the solution was allowed to stir for 16-24 h. Subsequent removal of solvents produced white solids, which were treated with 15% NaOH. The amine was extracted with Et_2O, the organic layer was dried (K_2CO_3), solvents were removed at 0 °C, and the amines were distilled.

31a: (5.013 g, 35 mmol) in 70% yield (bp 165-167 °C, 760 Torr): ^{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.

31b: (1.663 g, 12 mmol) in 47% yield (bp 45-55 °C, 16 Torr): ^{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.

General Method for the Preparation of 32. Crotyl amine **31** (1 equiv.), isobutyraldehyde (1 equiv.), and *p*-toluenesulfonic acid (0.0025 equiv.) were placed in benzene and heated at reflux 24-48 h accompanied by azeotropic removal of H_2O. The mixture was concentrated, and the enamine was distilled (Kugelrohr) under vacuum.

32a: (4.843 g, 25 mmol) in 82% yield (oven temp 75-80 °C, 6 Torr): ^{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}.

32b: (1.850 g, 9.4 mmol) in 94% yield (oven temp 60-80 °C, 5 Torr): This enamine was extremely sensitive to hydrolysis and full spectral data 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).

DIBAH Reduction of 38 to Aldehyde 39. Ester **38** (8.025 g, 35.0 mmol) was dissolved in toluene (100 mL), and the mixture was cooled to -78 °C. DIBAH (36 mL, 2 *M* in hexane) was added, the mixture was stirred at -78 °C for 2 h, and then quenched by the addition of Na_2SO_4•10 H_2O. The solution was filtered, concentrated, and the resulting oil was distilled under vacuum to give **39** (6.30 g, 31.6 mmol) in 90% yield as a mixture of amide resonance isomers (bp 88-90 °C <1 Torr): ^{1}H 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 39 to give 40. To a solution of benzyltriphenylphosphonium or ethyltriphenylphosphonium bromide (1 equiv.) in DMSO (0.5 *M*), was added NaH (1.1 equiv.), and the mixture was stirred for 15 min. A solution of **39** (1 equiv.) in DMSO (2 *M*) was added, the mixture was stirred for 30 min, and then washed with H_2O. The mixture was extracted with pentane, the combined organic fractions were dried (K_2CO_3), concentrated, and the crude olefin was dissolved in MeOH (1 *M*). Excess conc. 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 Et_2O, and the combined organic extractions were dried (K_2CO_3), concentrated, and distilled (Kugelrohr).

40a: Used for the preparation of **41** without isolation.

40b: (1.401 g, 8.11 mmol) in 69% yield as a mixture of isomers (*E:Z* 65:35) (oven temp 85-95 °C, <1 Torr): ^{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}.

Condensation of 40 with Phenylacetaldehyde to give 41. Amine **40** (1 equiv.) and phenylacetaldehyde (1 equiv.) were dissolved in Et_2O (0.3 *M*), and either K_2CO_3 or $MgSO_4$ was added to consume H_2O. The mixture was stirred for 1-6 h, filtered, and concentrated. When necessary, the enamine was distilled under vacuum.

41a: (3.19 g, 14.93 mmol) in 79% yield (from **39**) (oven temp 100-110 °C, <1 Torr) as a mixture of isomers at the allylic double bond (*E*:*Z* 27:73): ^{1}H 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}.

41b: (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}.

General Procedure for the Electrophile-Promoted 3-Aza-Cope Rearrangement and Subsequent Reduction. The desired *N*-alkyl-*N*-allyl enamine (1.0 equiv.) was dissolved in toluene (0.2 *M* solution), and the appropriate reagent was added (HCl, 0 °C; $TiCl_4$, $AlMe_3$ and Me_2AlCl, -78 °C) (see Tables for equiv. of reagents). The reaction mixture was then heated at reflux for 6-48 h, cooled to 0 °C, and $LiAlH_4$ (1.1 eq.) (1 *M* in THF) was added.[31] The mixture was stirred for 2 h at ambient temperature, and then 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 stirred for 1 h, filtered, concentrated, and the corresponding amine product was purified by Kugelrohr distillation.

General Procedure for Rearrangement/Reduction of 15c. To a 0.2 *M* solution of **15c** (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, cooled to room temperature, and DIBAH (1.2 equiv., 2*M* in hexanes) was added slowly.[32] The mixture was stirred for 24 h at room temperature and then quenched by sequential addition of H_2O (1 mL/0.3 g DIBAH), 15% w/v aq. NaOH (1 mL/0.3 g DIBAH), and then H_2O (3 mL/0.3 g DIBAH), stirred for 1 h, and filtered.[33] The amine was purified by silica gel flash column chromatography[34] (eluent: 50:50 Et_2O/petroleum ether) and purified by Kugelrohr distillation to give a mixture of **18c** and **19c** (see Table II for yields and diastereomer ratios): (bp 75-85 °C, <1 Torr):

18a and **19a:** (0.693 g, 3.1 mmol) in 88% yield as a mixture of diastereomers (62:38) (oven temp 55-65 °C, <1 Torr): ^{1}H NMR (300 MHz) ($CDCl_3$, major isomer) δ 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.

18b and **19b:** (0.465 g, 1.6 mmol) in 54% yield as a mixture of diastereomers (95:5) (oven temp 85-100 °C, <1 Torr): ^{1}H 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.

18c and **19c:** (0.692 g, 2.8 mmol) in 69% yield as a mixture of diastereomers (54:46) (oven temp 75-85 °C, <1 Torr): ^{1}H 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.

28a and **29a:** (0.771 g, 3.9 mmol) in 78% yield as a single diastereomer (>98:2) (oven temp 65-75 °C, 5 Torr): ^{1}H 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.

28b and **29b:** (0.778 g, 3.0 mmol) in 75% yield as a mixture of diastereomers (90:10) (oven temp 80-100 °C, <1 Torr): ^{1}H NMR (300 MHz) ($CDCl_3$, Mixture of isomers) δ 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.

28c and **29c:** (0.847 g, 3.8 mmol) in 95% yield as a mixture of diastereomers (>95:5) (oven temp 55-65 °C, <1 Torr): ^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.

34a: 0.687 g (3.4 mmol, 86% yield, 8% de), (oven temp 60-70 °C, 5 Torr): ^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.

34b: (0.923 g, 4.6 mmol) in 77% yield (15% de) (oven temp 60-70 °C, 5 Torr): ^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.

43a: (0.712 g, 3.32 mmol) in 85% yield as a mixture of diastereomers (73:27) (oven temp 95-100 °C, <1 Torr): ^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.

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32. The mixture resulting from rearrangement promoted by $TiCl_4$ was quenched with a 10% solution of NaOMe in MeOH prior to the addition of the aluminum hydride reagent.[31]
33. 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-diphenyl phenol. The product was then eluted with 95:5 ether:Et_3N to remove **25** from the column, the solvent removed, and the product distilled.
34. Silica gel was washed with a solution of 5% Et_3N in Et_2O prior to loading the products on the column in order to enhance resolution of the eluting compounds.

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