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

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Received August 6, 1992

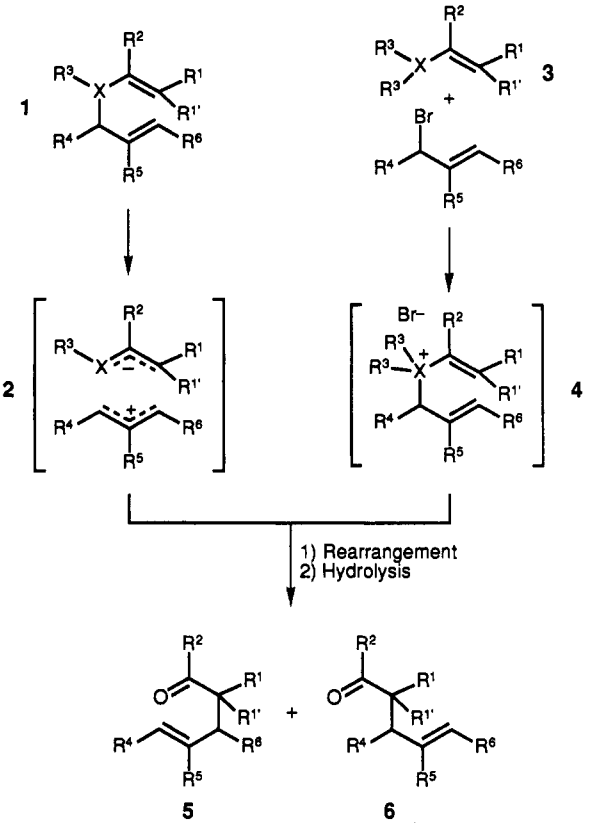
The 3-aza-Cope rearrangement of *N*-alkyl-*N*-allyl enamine substrates, which required temperatures of 250 °C to proceed thermally, was promoted at 111 °C in the presence of electrophilic reagents such as HCl (0.5 equiv), $TiCl_4$ (0.2 equiv), $AlMe_3$ (1.2 equiv), or $(ArO)_2AlMe$ (1.2 equiv). In order 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



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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.

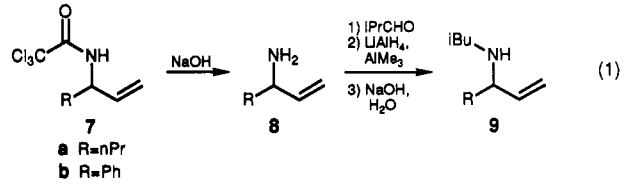
Acceleration of the 3-aza-Cope rearrangement has been achieved with titanium catalysts, and substrates having unsymmetrical allyl groups were investigated.[15] Both reports studied the rearrangement of enamines in which $R^1,R^{1'} \neq H$. In an example having R^4 = Me, **1** was transformed regiospecifically 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

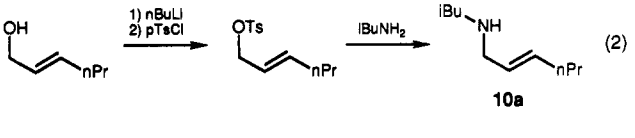
In order to examine the regioselectivity of the 3-aza-Cope rearrangement with aldehyde derived *N*-alkyl-*N*-allyl enamine substrates, two pairs of enamine substrates were selected. One pair had *n*-propyl (nPr) substituents at the allylic and terminal vinylic positions, while the other pair had phenyl 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)

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).



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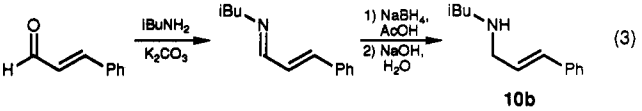

(3)

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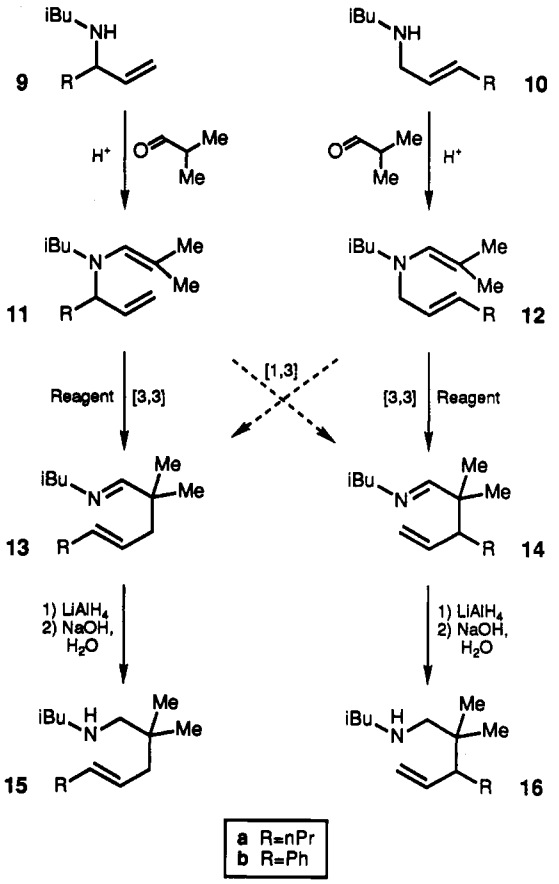
Scheme II. Charge-Accelerated Rearrangement of *N*-Alkyl-*N*-allyl Enamine Substrates



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.

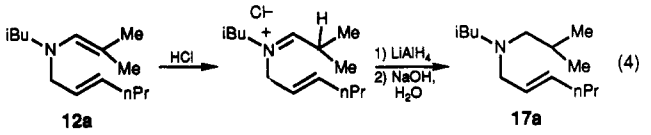
Rearrangement of **11a** and **12a** was investigated using the three types of reagents previously reported to efficiently promote the 3-aza-Cope rearrangement (Table I).[17] The reagents examined in this regiochemical study were the protic acid HCl (0.5 equiv), the metal halide Lewis acid catalyst $TiCl_4$ (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]	product formation 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]



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-

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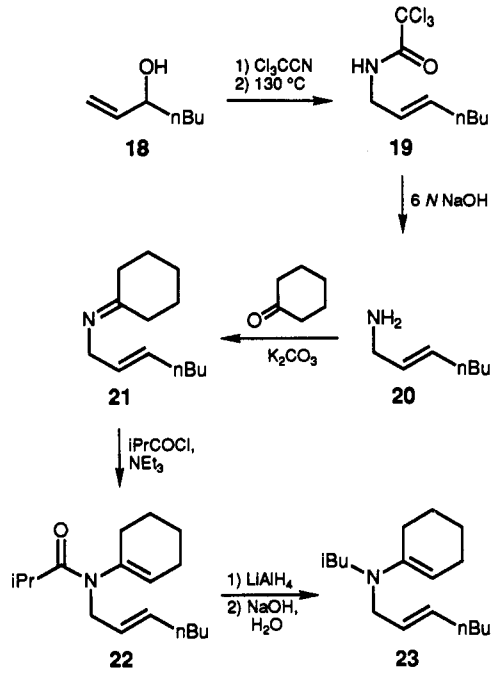
(19) Compound **12a** could also be prepared in a manner similar to that illustrated in Scheme III. Hydrolysis of the appropriate trichloroacetamide,[18] followed by condensation with isobutyraldehyde and acylation with isobutyryl chloride produced the corresponding enamide. $LiAlH_4$ reduction gave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

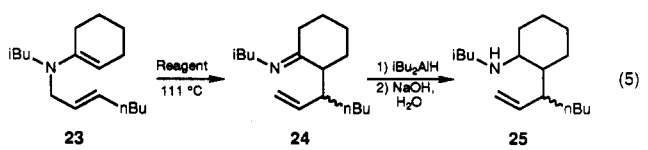
(20) For discussions of N- versus C-protonation of enamines, see: (a) Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. (b) Hinman, R. L. *Tetrahedron* **1968**, *24*, 185, and references therein.

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.[18] 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)[18] 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), 4.98–5.07 (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)[18] 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), 5.40–5.58 (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)amino)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)[18] 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, 2–5 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 **10a**) 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.[26]

was purified by silica gel flash column chromatogaphy[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.

(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.

Acknowledgment. We are grateful to Michigan State University for financial support of this research. Michigan State University is gratefully acknowledged for a College of Natural Sciences Research Fellowship to N.S.B. and a Ronald E. McNair Undergraduate Research Fellowship for M.S.L. Spectral product characterization was performed on NMR instrumentation purchased in part with funds from NIH Grant 1-S10-RR04750-01 and from NSF Grant CHE-88-00770. Mass spectral data were obtained at the Michigan State University Mass Spectrometry Facility, which is supported, in part, by a grant (DRR-00480) from the Biotechnology Resources Branch, Division of Research Resources, National Institutes of Health.

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.

Ester Homologation Revisited: A Reliable, Higher Yielding and Better Understood Procedure

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Received August 31, 1992

Enolate anions **3** and **6**, prepared via enolization of α-bromo and dibromo ketones **4** and **5** were converted in high yield to ynolate anions **10** by respective addition of lithium tetramethylpiperidide (to effect deprotonation, **3** → **7**) or butyllithium (to effect metal–halogen exchange, **6** → **7**). Mixtures of such enolates were also obtainable from esters **1** on a large-scale (25 mmol) via in situ formation and addition of lithiodibromomethane (from methylene bromide and lithium tetramethylpiperidide), followed by treatment of the resulting adducts with lithium hexamethyldisilazide to ensure complete enolization. Addition of *sec*-butyllithium and *n*-butyllithium to effect ynolate anion formation, followed by quenching of the reaction mixtures into acidic ethanol, reproducibly afforded homologated esters **8** in 67–90% yield. Demonstrated for ethyl esters **1** having the carbethoxy moiety attached to primary, secondary, tertiary, aryl, and alkenyl groups, this general procedure provides a convenient, large-scale alternative to the classical Arndt–Eistert sequence.

Introduction

Previously, we published a straightforward procedure for the direct homologation of esters (i.e., **1** → **8**). Proceeding via rearrangement of carbenoid **7** to ynolate anion **10**, and quench via the ketene **9**, it occurred with retention of stereochemistry at the migrating R group.[2] Just enough attention was devoted to this novel chemistry at the time to establish a fairly general and reproducible method, but it was not thoroughly examined since our focus turned to exploration of the synthetic utility of the little studied ynolate anion species.[3] Indeed, these efforts were rewarded when subsequently it was found that ynolates **10** could be utilized in other reactions as well,[4] most significantly to prepare siloxyacetylenes **11**,[4c] which have been shown to be useful synthetic intermediates themselves.[5]

Upon repeated application of this original chemistry to prepare ynolate anions **10** for our various studies, however, two limitations became apparent. First, only moderate yields were obtained for either ester homologation or siloxyacetylene formation (i.e., about 50–75%).[2,4c] Second,

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0022-3263/92/1957-7194$03.00/0