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Theoretical and Experimental Studies of the 3-Aza-Claisen Rearrangement[1]

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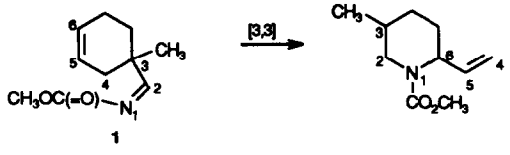
ABSTRACT: Semiempirical calculations support a spin-paired chair-like TS for the 3-aza-Claisen rearrangement, and yield the prediction that an anionic substituent on the nitrogen atom reduces the activation energies for the rearrangement. Attempts to demonstrate this experimentally have been unsuccessful.

INTRODUCTION

3,3-Sigmatropic rearrangements of 1,5-unsaturated moieties have long been used to form carbon-carbon bonds, often with high degrees of stereocontrol.[3] Rearrangement of an allylvinylamine, the 3-aza-Claisen rearrangement, has not been used extensively in this way, however, owing to the high temperatures required for thermolytic promotion,[4] and the limited number of catalysts available for promoting the reaction at more moderate temperatures.[5]

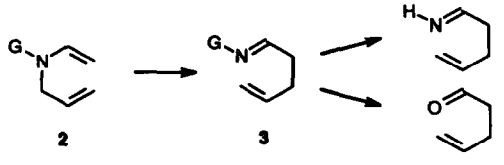
Several studies of *N*-substituted heterocyclic compounds have shown that acceleration of the reaction might well be induced by appropriate substitution on the nitrogen atom. For example, Makisumi and Sasaton have reported what appears to be the 3-aza-Claisen rearrangement of several heterocycles under conditions more moderate than those normally used for thermolysis (180 °C, 30 min).[6] Care must be taken, however, as some substituents are capable of reversing the thermodynamic preference of the rearrangement. This is evidenced by the successful 1-aza-Claisen rearrangement of the *N*-acyl compound, **1**, the *reverse* of the 3-aza-Claisen process (eq. 1).[7]



1 (1)

Thus, the introduction of an appropriate substituent on the nitrogen atom of the rearrangement skeleton (**2**, G = activating group) might well accelerate the desired rearrangement, permitting reaction at moderate temperatures. This substituent might then be removed by cleavage of the nitrogen-substituent bond on **3**, or by hydrolysis of the imine carbon-nitrogen double bond of the imine (Scheme 1). To support our experimental

Scheme 1

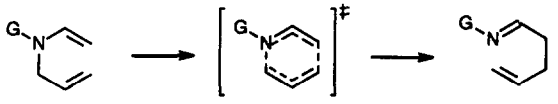


2 **3**

efforts in this area, we examined the rearrangement of a series of *N*-substituted allylvinylamines using the MNDO method. The MNDO method was chosen due to its documented usefulness in studying heteroatomic systems,[8] and in analogy to an earlier study of the Claisen rearrangement using MNDO.[9] To our knowledge, these calculations constitute the first computational study of the 3-aza-Claisen rearrangement.

COMPUTATIONAL METHODS

The reactions examined were the conversion of *N*-allyl-*N*-vinylamine, **2**, to imine **3** through transition state **2‡** (eq. 2). The calculations were performed using the MNDO method in the AMPAC (v. 1.0)[10] program. Starting geometries for the enamines and imines were assigned so that the two terminal atoms of the 1,5-unsaturated system were just beyond their respective van der Waals radii; the remaining atoms were arranged into "pre-chair" conformations that would require minimum molecular motion in order to reach a chair-like transition state (TS). Each approximate geometry was then optimized to the local structure of minimum energy, which was then characterized as a ground state (GS) structure by establishing that all eigenvalues were zero in the corresponding matrix of force constants.



(2)

2 **2‡** **3**

G = (**a**) H; (**b**) CH_2^-; (**c**) NH^-; (**d**) O^-; (**e**) F; (**f**) CH_3; (**g**) OH, (**h**) H, H^+; (**i**) NH_2; (**j**) NH_3^+; (**k**) "-".

The transition states (TS) for the reactions were located as follows. For the unsubstituted system (**2**, G = H), the SADDLE routine[11] in the AMPAC package[10] was used to locate an approximate saddle point, which was then fully optimized using the NLLSQ option.[12] Additional TSs were located by substituting the appropriate substituent for G = H on the first TS structure, and optimizing this new structure using either the NLLSQ[12] or the SIGMA[13] procedures in AMPAC. Each TS was then characterized by the presence of a single negative eigenvalue in the corresponding matrix of force constants.[13b] Entropies for the stationary state structures were calculated from the vibrational frequencies and moments of inertia, using the force constant routine in AMPAC.[14]

RESULTS AND DISCUSSION

A. *N*-Substituted Allylvinylamines

MNDO-calculated energies for the aza-Claisen rearrangement of allylvinylamines **2a-k** are reported in Table 1. These entries are ordered according to increasing free energies of activation ($\Delta\Delta G_0^{\ddagger}$), with the exception that the H-substituted system (**2a**) is listed first. The calculated activation barriers are relatively high, a prediction that is qualitatively consistent with experimental observations.[3a,b,d-g,i] In addition, one substituent is predicted to change the thermodynamic course of the reaction. The equilibrium for substrate **2k**, in which the substituent on the nitrogen atom is an additional electron pair, is calculated to favor starting material over product, so that the *reverse* reaction, which corresponds to a 1-aza-Claisen rearrangement, is expected in this case.

As may be seen from the data in Table 1, appropriate substitution is indeed predicted to lower the activation energy for the 3-aza-Claisen rearrangement. In particular, the values for the free energies of activation for the rearrangement of substrates with adjacent anionic centers, **2b-d**, G = CH_2^-, NH^-, and O^-, are computed to be 2.5 to 12.5 kcal/mol lower than those for neutral substrates. This corresponds to an acceleration of up to 10^9 times at 298 K for the rearrangement of the anionic substrates.[15] Relative to the hydrogen atom substituent, the neutral *N*-substituents, **2e-g, i** (G = F, OH, CH_3, NH_2) have little effect on the activation barrier for the rearrangement, whereas a positively charged moiety (**2j**, G = NH_3^+) causes an *increase* in the activation barrier.

G =	Compound	ΔH_f^a (2)	S^b (2)	$\Delta\Delta H^{\ddagger a}$	$\Delta S^{\ddagger b}$	$\Delta\Delta G^{\ddagger a}$	$\Delta\Delta G_{rxn}{}^a$
H	**2a**	36.57	84.13	35.66	-11.15	38.98	-13.00
CH_2^-	**2b**	79.63	90.59	22.60	-9.71	25.49	-50.07
NH^-	**2c**	79.81	89.34	22.92	-9.5	25.75	-51.52
O^-	**2d**	33.04	87.62	34.25	-10.74	37.45	-44.88
F	**2e**	39.74	87.33	34.96	-10.42	38.07	-26.29
CH_3	**2f**	40.62	91.24	36.09	-10.57	39.24	-18.74
OH	**2g**	29.98	88.66	38.95	-11.12	42.26	-25.89
H, H^+	**2h**	199.92	84.41	39.18	-11.27	42.54	-15.26
NH_2	**2i**	62.00	90.08	40.26	-7.82	42.59	-26.04
NH_3^+	**2j**	232.24	89.82	41.26	-9.93	44.22	-21.81
"-"	**2k**	32.34	84.39	25.56	110.74	40.47[c]	+11.71[c]

(a) kcal mol^{-1}, 298 K; (b) cal mol^{-1} K^{-1}, 298 K; (c) Value given is for the *forward* reaction; $\Delta\Delta G^{\ddagger}$ for the reverse reaction is -28.76 kcal mol^{-1}.

Table 1. Calculated Thermodynamic Parameters for 3-Aza-Claisen Rearrangement of *N*-Allyl-*N*-vinylamines (**2**).

Inconsistent with experimental results, the protonated enamine **2h** (G = H, H^+) is predicted to exhibit a *higher* activation energy for rearrangement than does the neutral system. For example, allylvinylammonium ions have been shown to undergo rearrangement at temperatures much below those used for the corresponding thermolysis.[3d,16] This unexpected result may reflect errors inherent in the application of the MNDO method to the studies of charged species.

One source of error in the energies calculated for ions arises from the fact that the MNDO method ignores solvation effects. For cations, the errors in the calculated free energies due to ignoring solvation are as great as ±20 kcal/mol.[17] These errors were shown to be greatest for substrates bearing high degrees of localized charge. For the aza-Claisen rearrangement of substrate **2h**, however, only the *difference* between the localization of charge for the GS and TS structures, **2h** and **2h**‡ respectively, need be considered. The electronic component of the difference can be approximated by the difference between the total charge densities of **2h** and **2h**‡, which is only 0.06. As the charge densities for the two species are nearly identical, errors due to the electronic effects of solvation are probably quite similar. Thus the disagreement between the expected and calculated activation energies for the rearrangement of **2h** must be attributed to weaknesses in the MNDO method other than the electronic component of solvation energies.[18]

In fact, the neglect of solvation energies by the MNDO method must be considered for the aza-Claisen rearrangements of *all* systems, **2a-k**. Again, the activation energies will be affected by the electronic effects of solvation only in cases with significant differences between the total charge densities calculated for the GS, **2**, and corresponding TS, **2‡**; these differences are *less than 0.08 for all systems except two*, **2c** and **2g** (G = NH^-, OH), for which the difference is 0.15. Thus errors introduced in the activation energies calculated by neglecting electronic effects of solvation are expected to be negligible for all but two reactions. In addition, the *steric* effects of solvation would be similar for all the systems, as the GS and TS geometries for each are all quite similar. Thus, although the *absolute* activation energies might be affected by ignoring solvent effects, the errors in the *relative* activation energies should be small.

Another source of error in the calculated energies is introduced by the over-correlation of lone pairs of electron on adjacent atoms by the MNDO method.[8] This over-correlation results in an artificial reduction in the calculated free energies of formation for compounds with adjacent lone pairs of electrons. Many of the substrates and TSs for the systems in this study involve π-donor groups adjacent to the nitrogen atom, e.g. **2b, c, d, e, g, i**, G = CH_2^-, NH^-, O^-, F, OH, NH_2, and hence the calculated free energies for these compounds will be erroneously lowered by over-correlation of adjacent electron pairs. The *activation* energies calculated for the reactions of substrates **2** will be affected only to the extent that the over-correlation errors for the GS and corresponding TS energies are significantly different. In fact, the over-correlation for any TS structure is likely to be slightly greater than that for the GS, as the lone pair of electrons on the nitrogen atom would be somewhat delocalized through the π-system of the former, but entirely orthogonal to the π-system for the latter. Thus the activation energies calculated for these systems might be somewhat smaller than experimental values.

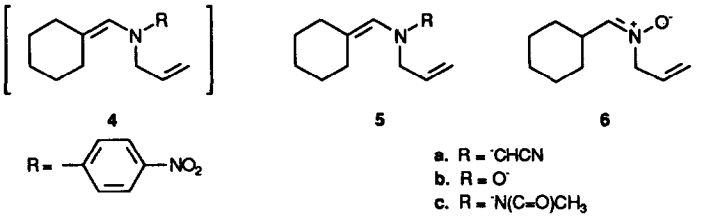
It is unlikely that the cumulative errors in the semiempirical predictions would be greater than the predicted decrease in activation energy afforded by the two most activating *N*-substituents (G = NH^-, CH_2^-). For a better understanding of the origin for this predicted energetic advantage, the geometric changes that the substrates undergo prior to reaching the TSs were examined. The most illustrative geometric changes are the elongation of the breaking N(3)–C(4) sigma bond, and the formation of the new C(1)–C(6) bond. The values for bond-breaking and bond-making can be expressed as the Pauling bond orders for the two bonds (n_{BB} and n_{BM}, respectively, Table 2); these are derived from calculated bond lengths of GS and TS structures.[19] The two anionic systems with the greatest kinetic advantage undergo little bond-making prior to reaching the TS, a result consistent with the calculated entropic advantages for these processes (Table 2, entries 2 and 3, $n_{BM} < 0.30$). These systems have an enthalpic advantage, too, as little of the energy requiring bond-breaking occurs during the same interval (Table 2, entries 2 and 3, $n_{BB} > 0.85$).

Thus, the computational analyses indicate that an anionic substituent on the nitrogen atom may indeed facilitate the 3-aza-Claisen rearrangement. This possibility was explored by preparation and attempted rearrangement of the *N*-allyl(cyclohexylidenemethyl)amines **4** and **5**, all of which carry an anionic site adjacent to the nitrogen atom of the 1,5-dienic system. Unfortunately, these efforts proved to be unsuccessful, as neither the expected imine products, the rearranged aldehyde resulting from hydrolysis, or the corresponding alcohol from hydrolysis and reduction were detected. It is believed that radical anion **4** and anion **5a** were indeed prepared, as indicated by color changes in the former system and deuterium corporation in the latter (see Experi-

Entry	G =	Compound	C(1)–C(6) (TS)	N(3)–C(4) (TS)	C(1)–C(6) imine	n_{BB}	n_{BM}	ΔG_{rxn}	$\Delta\Delta G^{\ddagger}$
1	H	**2a**	4.38 (1.91)	1.47 (1.52)	1.54	0.85	0.30	-13.00	38.98
2	CH_2^-	**2b**	4.34 (2.28)	1.48 (1.51)	1.55	0.905	0.088	-50.07	25.49
3	NH^-	**2c**	4.24 (2.14)	1.51 (1.54)	1.55	0.905	0.14.	-51.52	25.75
4	O^-	**2d**	4.25 (2.00)	1.55 (1.66)	1.55	0.69	0.22	-44.88	37.45
5	F	**2e**	4.15 (1.91)	1.51 (1.58)	1.54	0.79	0.30	-26.29	38.07
6	CH_3	**2f**	4.34 (1.90)	1.45 (1.50)	1.54	0.85	0.31	-18.74	39.24
7	OH	**2g**	4.27 (1.82)	1.50 (1.57)	1.54	0.79	0.39	-25.89	42.26
8	H, H^+	**2h**	4.34 (1.81)	1.54 (1.61)	1.55	0.82	0.42	-15.26	42.54
9	NH_2	**2i**	4.41 (1.83)	1.49 (1.55)	1.54	0.82	0.38	-26.04	42.59
10	NH_3^+	**2j**	4.24 (1.79)	1.51 (1.55)	1.55	0.87	0.45	-21.81	44.22
11	"-"	**2k**	5.31 (2.20)	1.43 (1.45)	1.54	0.94	0.11	+11.71	40.47

Table 2. MNDO-Calculated Bond Lengths for 3-Aza-Claisen Rearrangement.

mental Section). These intermediates did not undergo the desired rearrangement after long periods of heating, however; quenching the reaction mixtures allowed recovery of the respective conjugate acids in nearly quantitative yields. Attempts to produce the enamine corresponding to the conjugate acid of **5b** were unsuccessful, group. Treating nitrone **6** with a variety of bases afforded neither anion **5b** nor the rearranged product. Efforts to produce the enamine leading to **5c** led only to intractable mixtures of products.



B. The 3-Aza-Claisen Rearrangement and Related Reactions

Further understanding of factors governing the 3-aza-Claisen rearrangement was obtained by additional calculations on **2a** (G = H), and comparison of the results to data for other 3,3-sigmatropic rearrangements obtained from previous computational and experimental studies. The results of a number of investigators have suggested that Claisen-type rearrangements proceed through either *bis*-allylic[20] or biradical (diyl)[21] TSs, **7** and **8**, respectively. An open-shell system was not considered above, as a restricted Hartree-Fock (RHF) procedure treating all electrons as paired is used by default in MNDO calculations employing AMPAC. An unrestricted

Hartree-Fock (UHF) treatment or use of configuration interaction is required to calculate biradicals properly, as in the present case. To test the likelihood for the intervention of such entities in the aza-Claisen rearrangement of **2a**, the transition state **2a**‡ was optimized using the RHF basis set with configuration interaction.[22,23] This gave a new TS structure calculated to be 8.0 kcal/mol lower in enthalpy than that calculated without CI; this value is well within that expected when configuration interaction is applied to non-radical species;[23] this occurs because MNDO methodology accounts for correlation energy through parameterization. Further evidence that the TS is not biradical- or diyl-like is obtained by comparing the TS structures calculated with and without CI (*vide infra*). Thus, within the limits of MNDO, TS **2a**‡ is predicted to have little radical (*bis*-allylic or diyl) character.

The calculated parameters for the 3-aza-Claisen rearrangement of **2a** (G = H) were then compared to both experimental and calculated results for the Cope and Claisen rearrangements.[24] To provide an additional reference, values for the aromatic 3-aza-Claisen rearrangement (eq. 3) were also computed and compared to experimental results.[25]

(3)

A summary of the kinetic and thermodynamic parameters for the four reactions is presented in Table 3. As can be seen, the enthalpies of formation and of reaction agree well with the available experimental values. The calculated activation parameters, however, show significant deviation from values determined experimentally. The calculated free energies of activation ($\Delta\Delta G^{\ddagger}$) are consistently higher than for the available experimentally determined values. Moreover, the computed entropies ($\Delta S^{\ddagger}$) of activation for the Claisen and aromatic 3-aza-Claisen rearrangements are too high by 3.1 and 4.6 e.u., respectively, as are the activation enthalpies ($\Delta\Delta H^{\ddagger}$, 8.9 and 7.8 kcal/mol, respectively). The corresponding errors in the calculated values for the Cope rearrangement are smaller, probably because the AM1 force field was used for the all-carbon system. It is expected that errors in the calculated values for the 3-aza-Claisen rearrangement, for which experimental values are not available, should be similar to those for the Claisen and aromatic 3-aza-Claisen rearrangements.

Rearrangement	ΔH_f	$\Delta\Delta H^{\ddagger}$	$\Delta S^{\ddagger}$[b]	$\Delta\Delta G^{\ddagger}$[a]	ΔG_{rxn}[a]
3-Aza-Claisen	36.6	35.7	-11.9 (368K)	40.1	-12.3 (298 K)
Claisen (calc.)[c]	-7.24	39.5	-12.8 (373 K)	45.3	-20.8
Claisen (exp.)[d]	-8.7	30.6	-15.9 (373 K)	31.3	—
Cope (calc.)[e]	18.6	37.1	-15.6	45.4	0
Cope (exp.)	20.2[f]	33.3[g]	-13.0±1.0[g] (531 K)	40.8	0
Aromatic 3-aza-Claisen (calc.)	44.62	45.4	-12.4 (598 K)	52.8	14.7 (598 K)
Aromatic 3-aza-Claisen (exp.)[h]	–	37.6	-17 (583–613 K)	47.5	—

(a) kcal mol^{-1} K^{-1}; (b) e.u. = cal mol^{-1} K^{-1}; (c) Ref. 24c (d) Ref. 24b (e) Ref. 24e; (f) Ref. 24d (g) Ref. 24e (h) Ref. 25.

Table 3. Energetic Parameters for [3,3]-Sigmatropic Rearrangements

Correcting the activation entropy and enthalpy for the 3-aza-Claisen rearrangement by 8 kcal/mol and -3 e.u. respectively leads to a predicted activation enthalpy of approximately 28 kcal/mol, and entropy of about -15 e.u. at 298 K; the corresponding free energy of activation ($\Delta\Delta G^{\ddagger}$) would be about 32 kcal/mol. Thus, the predicted order of free energies of activation for these rearrangements, Claisen < 3-aza-Claisen < Cope < aromatic 3-aza-Claisen, is consistent with the increasing temperatures needed to promote these reactions.[26]

The calculated geometric parameters for the TSs for the Cope, Claisen, and 3-aza-Claisen rearrangements are presented in Figure 1. Structures **A** and **B** represent the TS structures calculated for the aza-Claisen rearrangement by MNDO without and with CI, respectively. Structure **C** illustrates the TS for the Claisen rearrangement calculated using MNDO.[24e] Structure **D** represents the TS for the Cope rearrangement calculated using AM1, and structure **E** corresponds to the diyl intermediate calculated for the same reaction.[24e] For each structure the Pauling bond orders, n_{BB} and n_{BM}, are listed in parentheses for the bonds being broken and formed in the reaction, X(3)–C(4) and C(1)–C(6), respectively.[27]

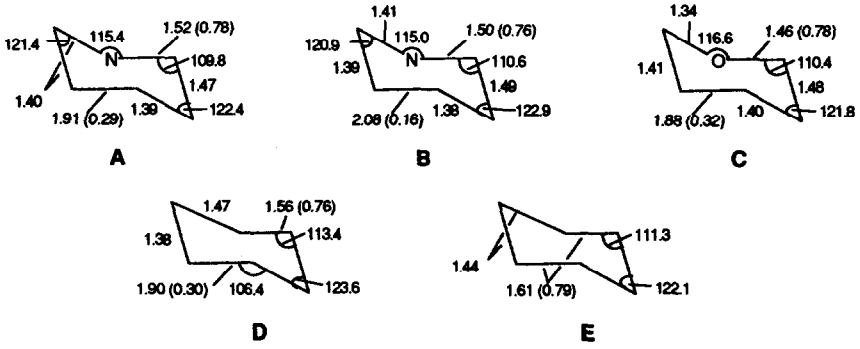


Figure 1. Calculated Transitions States for Several [3,3]-Sigmatropic Rearrangements (Bond Lengths in Angstroms, Angles in Degrees).

Structure **B**, calculated using configuration interaction, further supports the supposition that the TS for the 3-aza-Claisen rearrangement has little diyl or diradical character. In particular, if the TS were diyl-like, the bonds being formed and broken in structure **B** would have bond orders close to each other and to one, as do the changing bonds in structure **E**, the diyl intermediate in the Cope rearrangement.[24a] On the other hand, if the TS of the 3-aza-Claisen rearrangement were diradical-like the σ-bonds being broken and formed would have little integrity. In fact, the bond orders in **B** are very different from each other, the breaking N(3)–C(4) of high order ($n_{BB} = 0.76$), and the forming C(1)–C(6) bond of low order ($n_{BM} = 0.16$). Structure **B** is less unsymmetrical than is **A**, and therefore the TS structure calculated using CI is actually *less like either of the radicaloid structures than is the TS calculated for the all-paired system.*[22]

Clearly most of the bond lengths and angles for TS structures **A**, **C**, and **D**, are similar, as are the bond-orders for the bonds being broken and formed, as seen in the respective bond orders, n_{BB} and n_{BM}. The TS for the Claisen rearrangement is the most compact (highest bond orders), and TS for the Cope rearrangement most loosely associated. The degree of geometric association, Claisen < 3-aza-Claisen < Cope, is reflected in the

activation entropies of the systems, as Claisen TS is most ordered and Cope TS, least (Table 3). One interesting feature of the calculated geometries is that the all-carbon allylic portions of the TSs (atoms 4, 5, and 6) are virtually identical for TSs A, C, and D.

CONCLUSIONS

The results from semiempirical calculations reported herein indicate that the 3-aza-Claisen rearrangement occurs through a spin-paired chair-like TS. This transition state is predicted to be intermediate in geometry between the TSs for the Cope and Claisen rearrangements, and the predicted activation energy for the 3-aza-Claisen rearrangement falls between those calculated for the other two. Substitution on the nitrogen atom changes both the geometry and the energy of the corresponding transition-state structure, and appropriate substitution might well reduce the activation energies required for the rearrangement. The most promising substituents are predicted by MNDO calculations to be an atom or group bearing a negative charge adjacent to the nitrogen atom. However, attempts to demonstrate this experimentally have thus far been unsuccessful.

EXPERIMENTAL SECTION

All routine IR spectra were recorded on samples prepared as neat films unless otherwise noted. The polystyrene absorption at 1944 or 1601 cm^{-1} was used as a reference, and only major and characteristic absorptions are reported, in $cm.^{-1}$

^1H-NMR spectra were measured using either a Varian Associates EM-390 or a General Electric QE-300 spectrometer; routine ^{13}C-NMR spectra were obtained with the latter instrument. Chemical shifts are reported on the δ-scale, and coupling constants are reported in Hz. ^1H- and ^{13}C-NMR spectral data were obtained in $CDCl_3$, except where noted and either the solvent or tetramethylsilane was used for reference. The following abbreviations are used in reporting NMR data: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad).

Exact mass measurements using high resolution mass spectroscopy (HRMS) were obtained with a du Pont (CEC) 21-110 instrument. Low resolution electron impact mass spectra (LRMS) were obtained with a du Pont (CEC) 21-471 double-focusing mass spectrograph operating at 70 eV.

High-pressure liquid chromatography (HPLC) was performed on a Waters Associates 6000A instrument with two linked 2' x 1/4" columns packed with LC Porasil silica gel (Type A).

Electronic spectra were obtained using a Beckman D6-7 UV-Visible spectrophotometer with a single cell, using samples that were approximately 0.005 *M* concentration in $CHCl_3$. Melting and boiling points are uncorrected.

All reagents and solvents were purified according to standard methods unless otherwise specified. Skelly B was stirred over concentrated H_2SO_4 for 24 h, over anhydrous Na_2CO_3 for 12 h, and then was filtered and distilled. Inert atmosphere was maintained by the use of a positive pressure of in-house N_2, evaporated from liquid N_2, and was passed through a tower containing anhydrous $CaSO_4$ and silica gel (14-20 mesh, blue-indicating, Aldrich) prior to use.

Potassium hydride (KH) and sodium hydride (NaH) were obtained as suspensions in mineral oil (approximately 30% by weight), and were rinsed 3 times with hexane prior to use, as follows: the oily

suspension was transferred to a oven-dried one-necked flask under an atmosphere of N_2; a portion of hexane was added to the flask, via syringe, and the suspension was allowed to stir for several minutes; after the stirring was ceased and the solid KH (NaH) had been allowed to settle, the liquid was removed using a syringe; following removal of the final portion of hexane, the solid KH (NaH) was subjected to a stream of N_2 for several minutes.

N-Allyl-(*N*-cyclohexylidenemethyl)-*p*-nitroaniline Anion Radical (4)

N-Allyl-*p*-nitroaniline[28] was treated with cyclohexanecarbaldehyde and a catalytic amount of *p*-toluenesulfonic acid, according to a reported procedure.[29] After 24 h of heating, an additional equivalent of aldehyde was added, and heating was continued for 48 h, at which time TLC analysis indicated that *N*-allyl-*p*-nitroaniline remained. The reaction mixture was cooled to RT and concentrated *in vacuo* to give a yellow oil. The crude N-allyl-(*N*-cyclohexylidenemethyl)-*p*-nitroaniline was purified by column chromatography over activated basic alumina using 20% EtOAc/80% Skelly B as eluent. The enamine was isolated as a yellow solid (41% yield) whose spectral data were consistent with the expected structure.

Spectral data: ^{1}H-NMR 8.1 (d, 2H), 6.85 (d, 2H), 5.85 (m, 1H), 5.80 (s, 1H), 5.2 (dd, 2H), 4.1 (d, 2H), 2.2 (t, 2H), 2.05 (t, 2H), 1.45-1.65 (m, 6H); ^{13}C-NMR δ 152.9, 148.9, 140.9, 138.0, 132.2, 125.8, 122.8, 117.1, 111.9, 54.4, 32.9, 28.5, 28.1, 26.7, 26.3; HRMS: (M+, $C_{16}H_{20}N_2O_2$) calculated: 272.15247, found: 272.15214.

To a magnetically stirred solution of the enamine (1.00 mmol) in 15 mL of dry 1,2-dimethoxyethane (DME) held under an atmosphere of nitrogen was added 10 mL of a 0.15 *M* solution of sodium naphthide in DME[30] via cannula. The combined solution turned from bright yellow to deep red immediately. A number of trials were performed during which the reaction mixture was stirred for between 2 and 20 h at either RT, 50 °C or reflux, after which time the red solution was quenched with 10 mL of 0.1 *N* HCl. The crude, bright yellow mixture was neutralized with 1 *N* NaOH, saturated with NaCl, and extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4), and concentrated to give a yellow oil, which was subjected to analysis by ^{1}H-NMR spectroscopy, and TLC (Al_2O_3, 10% EtOAc/Skelly B). The major product from each run was unchanged starting material. The enamine was also treated with two equivalents of sodium naphthide, and reaction mixture heated to reflux for 40 h, after which time no starting material was detected by TLC analysis.

The crude yellow oil from each of the reactions was hydrolyzed by treatment with HCl (0.5 *N*) for 12 h at reflux. The resulting solution was neutralized using 1 *N* NaOH, saturated with NaCl, and extracted with Et_2O. The combined and concentrated organic fractions were subjected to analysis by GLC, but the expected aldehyde, (1-allylcyclohexane)carbaldehyde,[31,32] was not detected

An authentic sample of the imine expected from the aza-Claisen rearrangement of **4** followed by electron loss was prepared by dissolving 20 mg of the enamine in 0.5 mL of C_6D_6 contained in a thick-walled 5-mm NMR tube, which had been base-washed, rinsed with deionized water, and dried in an oven at 110 °C. The solution was subjected to three freeze-thaw cycles, sealed under vacuum, and heated at 250 °C for 8 h. Complete conversion to a single product, characterized by ^{1}H NMR spectroscopy as the expected imine, was observed. Attempts to isolate the imine for full characterization were unsuccessful as were attempts to prepare it from (1-allylcyclohexane)carbaldehyde and *p*-nitroaniline by known procedures.[33]

Spectral data: ^{1}H-NMR for enamine (C_6D_6) 8.1 (d, 2H), 6.35 (d, 2H), 5.5 (m, 1H), 5.35 (s, 1H), 4.9 (dd, 2H), 3.5 (d, 2H), 1.6-1.9 (m, 4H), 1.15-1.4 (m, 6H). ^{1}H-NMR for imine (C_6D_6) 7.85 (d, 2H), 6.45 (d, 2H), 5.55 (m, 1H), 4.85 (dd, 2H), 1.95 (d, 2H), 1.55-1.8 (m, 2H), 1.1-1.35 (m, 8H).

General Method for Hydrolysis and Reduction of Products from Rearrangements of 5 The crude organic product from most of the reactions below were subjected to hydrolysis by stirring with 0.5 *N* HCl at RT for 4 h.[34] The aqueous phase was then neutralized using 1 *N* NaOH, saturated with NaCl, and extracted with three portions of Et_2O. The combined extracts were concentrated, dried (Na_2SO_4), and concentrated. For some runs, the crude product of hydrolysis was treated with $NaBH_4$ (4 eq.) in CH_3OH at 0 °C, according to published procedures.[35]

[*N*-Allyl-(*N*-cyclohexylidenemethyl)amino]acetonitrile Anion (5a)

(*N*-Allylamino)acetonitrile was prepared (98% yield) by the procedure of Kirino, et al.[36]

Spectral data:[37] ^{1}H-NMR 5.65 (m, 1H), 5.05 (br dd, 2H), 3.4 (s, 2H), 3.2 (d, 2H), 1.45 (br s, 1H); ^{13}C-NMR δ 134.8, 117.5, 50.5, 36.0; IR 3250–3400 (s), 3100 (m) 3000 (m), 2950 (s), 2860 (s), 2260 (w),1660 (s), 1440, 1475 (s).

[*N*-Allyl-(*N*-cyclohexylidenemethyl)amino]acetonitrile was prepared by treatment of the above acetonitrile with dimethyl diazomethylphosphonate[38] potassium *tert*-butoxide and cyclohexanone in THF at -78 °C, according to the procedure reported by Gilbert and Weerasooriya.[31a] The crude product was subjected to column chromatography on silica gel (5% EtOAc/95% Skelly B).

An alternate preparation followed a procedure reported by Taguchi and Westheimer.[33] In a 50-mL flask were combined (*N*-allylamino)acetonitrile (10.0 mmol) and cyclohexanecarbaldehyde (10.0 mmol) in 17 mL of benzene. To this solution was added 6 g of 4 Å molecular sieves, which had been activated by heating in an oven at 110 °C for at least 12 h. The resulting mixture was stirred under N_2 for 20 h, at which time TLC analysis of the mixture (Al_2O_3 plates, 100% EtOAc) indicated complete consumption of starting material. The solution was filtered, concentrated *in vacuo*, and the residual oil was subjected to column chromatography on silica gel (5% EtOAc/1% TEA/94% Skelly B) to give the desired product (60% yield).

Spectral data: ^{1}H-NMR 5.75 (m, 1H), 5.35 (s, 1H), 5.15 (dd, 2H), 3.5 (s, 2H), 3.2 (d, 2H), 2.2 (br s, 2H), 1.95 (br s, 2H), 1.45 (m, 6H); ^{13}C-NMR 135.9, 133.8, 128.4, 118.0, 115.1, 58.6, 42.7, 33.1, 28.1, 28.0, 27.0, 26.3; IR 3060 (w), 2920, 2850 (s), 2280 (w) 1690 (m), 1670 (m), 1450, 1475 (s); LRMS: 175 (M-1), 136, 135, 55, 41, 39, 28, 18 .

The nitrile was treated separately with KH, LDA or KHMDS at temperatures between -78 °C and room temperature. The major product isolated after quenching with water was found to be starting material (^{1}H-NMR spectroscopy); quenching the reaction mixture with D_2O afforded incorporation of a single deuterium atom α to the nitrile function. The crude products of all trials were subjected to hydrolysis, but this produced no detectable (1-allylcyclohexane)carboxaldehyde (^{1}H-NMR spectroscopy). Reduction of the hydrolysis mixtures also failed to yield 1-(2-propenylcyclohexyl)methanol.

Attempted Preparation of Precursor to 5b

N-Acetoxy-*N*-allylacetamide[39] was converted to *N*-allylhydroxylaminium chloride[40] by treating it with 3 *N* HCl and heating to reflux for 3 h. The crude product was dissolved in water, and the solution was brought to pH>10 by adding 1 *N* NaOH dropwise. The aqueous layer was washed with three portions of Et_2O, and the

combined organic extracts were dried (Na_2SO_4) and concentrated to give compound *N*-allylhydroxylamine as a white crystalline solid (60% yield). The amine decomposed when heated to 40 °C, and at RT in the presence of O_2.

Spectral data: ^{1}H-NMR 6.45 (br m, 1H), 5.9 (m, 1H), 5.25 (dd, 2H), 3.55 (d, 2H); ^{13}C-NMR 133.7, 118.1, 56.5; IR (CH_2Cl_2) 3550 (m), 3200 (br, s), 3050 (m), 2900 (s), 1650 (w), 1420 (m), 1350 (m); LRMS: 73 (M+), 70, 69, 68, 57, 56, 55, 54, 44, 42, 41, 39; mp (HCl salt) 198-199 °C (lit. 198-199 °C).[40]

Using a reported procedure,[41] *N*-allylhydroxylamine (4.47 mmol) was added to a solution of *t*-butyldimethylsilyl chloride (9.83 mmol) and imidazole (15.6 mmol) in 5 mL of dry DMF. The crude product was purified by column chromatography on silica gel (5% EtOAc/95% Skelly B) to give *N*-allyl-*N*-(*tert*-butyldimethylsiloxy)amine as a colorless liquid (bp 185 °C, 760 torr, 76% yield).

Spectral data: ^{1}H-NMR 5.8 (br m, 1H), 5.1 (br dd, 2H), 3.4 (br d, 2H), 0.8 (s, 9H), 0.0 (s, 6H); ^{13}C-NMR 134.1, 118.0, 57.3, 26.8, 18.7, -5.40; IR 3240 (m), 3070 (m), 2950 (s), 2930 (s), 2890 (s), 2860 (s), 1850 (w), 1645 (m), 1470 (s), 1430 (s), 1400 (s), 1375, (s), 1265 (s); LRMS 181 (M+1; no M+) 111, 97, 85, 84, 83, 71, 70, 69, 57, 55.

Attempts to produce enamines from *N*-allylhydroxylamine or *N*-allyl-*N*-(*tert*-butyldimethylsiloxy)amine by a variety of methods[29,31a,33,42] were unsuccessful. The crude reaction mixtures were subjected to TLC analysis and to ^{1}H-NMR and IR spectral analysis in an attempt to detect the desired enamines. In each case either unchanged starting material or nitrone **6** was the major product, and no enamine was detected.

α-Cyclohexyl-*N*-allylnitrone (6)

Equimolar amounts of *N*-allylhydroxylamine and cyclohexanecarbaldehyde in CH_3OH were allowed to react according to a reported procedure.[43] The volatile components were removed from the reaction mixture under vacuum (oil pump, 1 torr) to give **6** as an colorless oil (87% yield).

Spectral data: ^{1}H-NMR 6.5 (d, 1H), 6.05 (m, 1H), 5.35 (dd, 2H), 4.35 (d, 2H), 2.95 (m, 1H), 1.9 (br d, 2H), 1.75 (br s, 4H), 1.35 (m, 2H), 1.15 (br t, 2H); ^{13}C-NMR 142.4, 130.4, 120.8, 67.9, 34.8, 28.7, 25.8, 25.1; IR 3080 (w), 2920 (s) 2850 (s), 1650 (w), 1600 (m), 1420 (m), 1460 (s), 1250, 1235 (m); LRMS: 167 (M+), 96, 95, 86, 83, 75, 55, 41; HRMS: (M+, $C_{10}H_{17}NO$) calc. 167.13101, fnd. 167.13138.

Additionally, **6** was converted to *N*-allylcyclohexanecarboxamide according to a published procedure.[44] Melting point and spectral data for the amide were in accord with those obtained by others.[45]

Attempts to Deprotonate and Rearrange α-Cyclohexyl-*N*-allylnitrone (6): A number of reactions were tried in which nitrone **6** (0.315 mmol) was treated with a base (0.1–5 eq.) at temperatures from -78 °C to RT for varying times. Bases used were potassium *tert*-butoxide, lithium diisopropylamide,[46] potassium hexamethyldisilazide,[47] KH, and NaH. Analysis of the crude reaction mixtures by ^{1}H-NMR and/or TLC indicated the presence of unchanged starting material, and/or of unknown compounds giving rise to a series of broad signals in the ^{1}H-NMR spectrum. Following aqueous work-up, the crude products from all runs were analyzed (^{1}H-NMR spectroscopy), and most aliquots were subjected to hydrolysis, the products of which failed to show the presence of rearranged aldehyde (TLC); some product mixtures were subsequently reduced, but no 1-(2-propenylcyclohexyl)methanol was detected in the resulting mixtures. Attempts to document the desired deprotonation by quenching with D_2O failed, as did attempts to trap deprotonated **6** with trimethylsilyl chloride.

Attempted Preparation of Precursor to 5c

N'-Allylacetohydrazide was prepared by modifying a procedure reported by Wieland, et al.[48] *N*-Allylhydrazine[49] (80.0 mmol) was combined with 4.3 mL of EtOAc (44 mmol) in a dry, base-washed thick-walled glass tube. The sealed tube was heated to 150 °C (oil bath) for 19 h. The reaction mixture was cooled and concentrated, and the residual oil was distilled under vacuum (oil pump). The desired carboxylate (92% yield) had bp 74–78 °C, 0.5 torr (lit.[50] 103–104 °C, 6 torr).

The hydrazide was treated according to a number of different procedures that have been used to prepare enamines.[29,31,33,51] In addition, it was subjected to the following procedure, a modification of a previously reported method.[52] A solution comprised of equimolar amounts of the hydrazide and cyclohexanecarbaldehyde was stirred under an atmosphere of N_2 for 12–24 h. Sufficient K_2CO_3 was then added to saturate the mixture, and stirring was continued for 12 h. The slurry was diluted with Et_2O and filtered, and the resulting ethereal layer was isolated and concentrated to give crude product. The crude product was analyzed by TLC and/or ^{1}H-NMR spectroscopy, and in several runs the crude product was subjected to chromatographic separation (HPLC or column) on basic alumina before analysis. No evidence was obtained for the desired enamine.

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