Rearrangements of Substituted 3-Aza-1,2,5-hexatrienes. 3. The Scope and Versatility of an Extremely Mild 3-Aza-Cope Reaction

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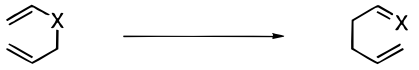
An investigation of the [3,3]-sigmatropic reaction of substituted 3-aza-1,2,5-hexatrienes to give 4-pentenenitriles is presented. This reaction has been found to occur under a wide variety of reactions conditions (10 are reported) starting from readily available *N*-allylamides. In contrast to other 3-aza-Cope reactions, this process occurs at room temperature, under essentially neutral conditions, allowing for the facile preparation of substituted nitrile products in moderate to excellent yields. The scope and versatility of this reaction are demonstrated by its use on a wide variety of substrates, including nitrogen- and oxygen-substituted amides. The rearrangements of *cis*- and *trans*-4-*tert*-butyl-*N*-allylcyclohexanecarboxamides **16a** and **16b** are reported and were found to give a ratio of axial to equatorial (A:E) products consistent with A:E ratios found for other related sigmatropic reactions. The stereochemical requirements for this reaction appear to be similar to other [3,3]-rearrangements even though the transition state for this rearrangement is most likely neither boat nor chairlike.

Introduction

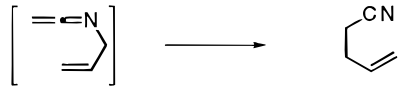
The stereochemical and regiochemical control of bond formation offered by the Claisen and Cope rearrangements has made these sigmatropic reactions powerful synthetic tools in the construction of both acyclic and cyclic molecules (eq 1).[1] Many heteroatom-substituted variations of these two fundamental reactions have been developed, largely in efforts to produce processes with the same useful characteristics but which might both occur at lower temperatures (Cope, 210−260 °C; Claisen, 180−255 °C) and offer better stereochemical control in the bond-forming step. With specific regard to nitrogen-substituted variations of these reactions, the 3-aza-Cope rearrangement has been especially well-investigated in the past few years.[2,3] In these studies, the potentially tetracoordinate nature of nitrogen has proven advantageous for the introduction of control elements which may influence both the stereochemical outcome and the catalysis of the reaction process.



(1)

X = CR_2; Cope
X = O; Claisen
X = NR; 3-Aza-Cope
X = N^+R_2; Cationic 3-Aza-Cope

The limited utility of the 3-aza-Cope for synthetic purposes has been due, in part, to the rather harsh conditions that are required to effect these transformations. The neutral 3-aza-Cope reaction occurs at temperatures of 120−250 °C,[2] while the positively charged variations usually are effected at 80−120 °C.[3,4] Substrates for the latter family of rearrangements have been derived from the neutral 3-amino-1,5-hexadiene framework by quaternization of the nitrogen or by the use of Lewis acids. Herein we report our investigations of a mild 3-aza-Cope reaction which occurs at room temperature under essentially neutral conditions. This reaction, which presumably proceeds via a 3-aza-1,2,5-hexatriene intermediate (eq 2), is the mildest neutral aza-Cope reaction reported to date and appears to have considerable synthetic potential.



3-aza-1,2,5-hexatriene
(N-allyl ketenimine)

(2)

Our interest in the 3-aza-Cope reaction was initiated

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(1) For reviews concerned with these and related [3,3]-sigmatropic rearrangements, see the following: (a) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423. (b) Blechert, S. *Synthesis* **1989**, *89*, 71. (c) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205. The ester enolate Claisen and the oxy-Cope reactions are perhaps the best examples of research directed along these lines. For general discussions of these processes, see: (d) Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Elmsford, NY, 1991; Vol. 5, pp 827−873, and (e) Bronson, J. J.; Danheiser, R. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Elmsford, NY, 1991; Vol. 5, pp 999−1035.

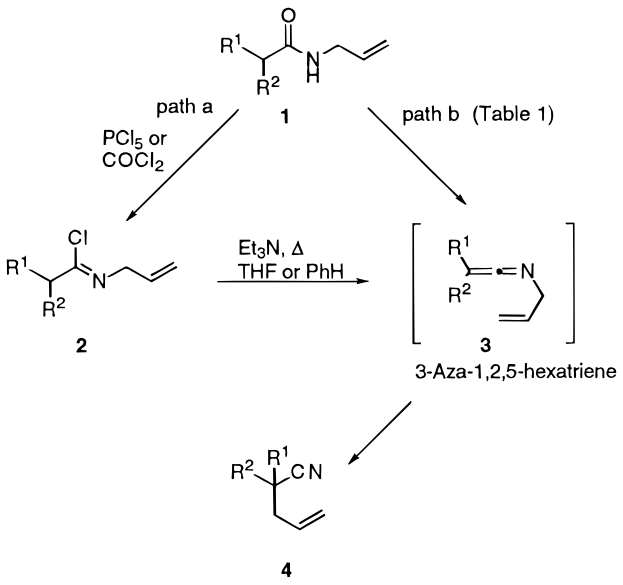
(2) (a) Kurth, M. J.; Brown, E. G. *Synthesis* **1988**, 362. (b) Kurth, M. J.; Decker, O. H. W.; Hope, H.; Yanuck, M. D. *J. Am. Chem. Soc.* **1985**, *107*, 443. (c) Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1985**, *50*, 5769. (d) Kurth, M. J.; Decker, O. H. W. *Tetrahedron Lett.* **1983**, *24*, 4535. (e) Ireland, R. E.; Willard, A. K. *J. Org. Chem.* **1974**, *39*, 421. (f) Hill, R. K.; Gilman, N. W. *Tetrahedron Lett.* **1967**, 1421. (g) Hill, R. K.; Newkome, G. R. *Tetrahedron Lett.* **1968**, 5059. (h) Tsunoda, T.; Tatsuki, S.; Akasaka, M.; Itô, S. *Tetrahedron Lett.* **1993**, 3297. (i) Tsunoda, T.; Sakai, M.; Sasaki, O.; Sako, Y.; Hondo, Y.; Itô, S. *Tetrahedron Lett.* **1992**, *33*, 1651. (j) Tsunoda, T.; Sasaki, O.; Itô, S. *Tetrahedron Lett.* **1990**, *31*, 727.

(3) (a) Gilbert, J. C.; Senaratne, K. P. A. *Tetrahedron Lett.* **1984**, *25*, 2303. (b) Brannock, K. C.; Burpitt, R. D. *J. Org. Chem.* **1961**, *20*, 3576. (c) Corbier, J.; Cresson, P. *C. R. Seances Acad. Sci., Ser. C* **1970**, *270*, 2077. (d) Barta, N. S.; Cook, G. R.; Landis, M. S.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 7188. (e) Danishefsky, S. J.; Phillips, G. B. *Tetrahedron Lett.* **1984**, *25*, 3159. (f) Hill, R. K. *Tetrahedron Lett.* **1978**, 4337. (g) Bailey, P. D.; Harrison, M. J. *Tetrahedron Lett.* **1989**, *30*, 5341. (h) Cook, G. R.; Barta, N. S.; Stille, J. R. *J. Org. Chem.* **1992**, *57*, 461. (i) Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1993**, *58*, 5095. The use of a Pd(0) catalyst to effect this transformation has also been reported. (j) Murahashi, S. I.; Makabe, Y. *Tetrahedron Lett.* **1985**, *26*, 5563. (k) Murahashi, S. I.; Makabe, Y.; Kunita, K. *J. Org. Chem.* **1988**, *53*, 4489.

(4) Exceptions to this temperature range have been observed. (a) Welch, J. T.; De Corte, B.; De Kimpe, N. *J. Org. Chem.* **1990**, *55*, 4981. Zwitterionic 3-aza-Cope examples have also been reported to occur at lower temperatures: (b) Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579. (c) Nubbemeyer, U. *J. Org. Chem.* **1995**, *60*, 3773.

0022-3263/96/1961-0055$12.00/0

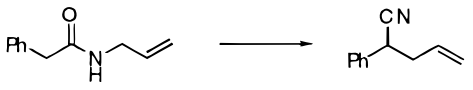
Scheme 1



by an infrequently cited paper by Brannock and Burpitt,[5] published in 1965, which describes an extremely mild example of this type of rearrangement. Treatment of the readily available *N*-allylamides with either phosgene or phosphorous trichloride (path a of Scheme 1) followed by reaction of the imidoyl chloride intermediates with triethylamine (TEA) in either benzene or tetrahydrofuran (THF) at reflux leads to the formation of the α-substituted pentenenitriles in moderate yields. The authors hypothesized a 3-aza-1,2,5-hexatriene, an *N*-allylketenimine, as the intermediate in this reaction process.[6] Remarkably, this neutral 3-aza-Cope reaction was reported to occur at temperatures 120−200 °C lower than that of the other known "neutral" version![2f]

Apparently, the synthetic potential of the *N*-allylketenimine rearrangement, and the observation of its facility relative to closely related rearrangements, lay dormant in the literature until our investigation of the transformation began a few years ago.[7] After our original report of a mild, one-pot variation of this reaction process, Molina[8] reported the synthesis of several substituted *N*-allylketenimines and their facile rearrangement to substituted 4-pentenenitriles. In other studies, Nubbemeyer[9] has investigated the diastereoselectivity of this reaction in a limited number of cases and Huisgen[10] has reported the equilibration of the ketenimine and nitrile isomers in highly-fluorinated substrates. We recently reported ab initio calculations that confirm that the intermediacy of a ketenimine in the transformation of an *N*-allylamide to a 4-pentenenitrile is sufficient to explain the relative facility of this reaction relative to the neutral and charged 3-aza-Cope reactions.[6] Presumably, this relative facility arises from the sterically-unencumbered nature of the ketenimine which allows it to approach the π-system of the tethered allyl system in an almost strain-free manner. Additionally, the almost linear nature of the ketenimine and the length of the C═N make the total distance the heterocumulene spans in the transition structure almost identical to that of counterpoised allylic system. Both of these factors combine to make the rearrangement particularly facile and thus particularly worthy of investigation.

Table 1. Reagent Combinations Employed To Effect the Transformation of *N*-Allylamides to Pentenenitriles



1a **4a**

entry	conditions[a]	yield (%)
A	$2PPH_3$, $2CCl_4$, $3Et_3N$	94
B	$[Ph_3PBr^+]Br^-$, $2Et_3N$	55
C	$2PPh_3$, $2CBr_4$, $3Et_3N$	66
D	PPh_3, I_2, $2Et_3N$	56
E	polymeric PPh_3, Br_2, $2Et_3N$	42
F	$3I_2$, $3P(OEt)_3$, $3Et_3N$	86
G	$3I_2$, $3P(OMe)_3$, $3Et_3N$	36
H	Tf_2O, $2(iPr)_2NEt$, Et_2O	67
H	Tf_2O, $2(iPr)_2NEt$, CH_2Cl_2	44
I	triphosgene (1/2), $3Et_3N$, rt	78
J	0 °C	85
K	−78 °C	40
L	$(COCl)_2$, $2Et_3N$	31
M	$PhCH_2NEt_3^+Cl^-$ (0.03%, $CHCl_3$, 50% NaOH/H_2O	39

[a] Reference 7b.

Our developement of this reaction into a more versatile process began with the investigation of the conditions required to bring about the rearrangement in a one-pot process. We accomplished this goal by the use of dehydrating conditions which had seen use in ketenimine-forming processes subsequent to the initial work of Brannock and Burpitt and the use of conditions for the transformation of amides into nitriles. Our work along these lines has demonstrated that the conversion of *N*-allylamides can be effected by a wide variety of reagents, is very general in substrate-tolerance, and occurs under much milder conditions than were originally reported.

Results and Discussion

Reaction Conditions. Our initial successful one-pot conversion involved treatment of amide **1a** with Ph_3P, CCl_4, and TEA, in CH_2Cl_2 or CH_3CN at room temperature[11] (Table 1, entry A). These conditions gave the nitrile **4a** in 94% yield as the sole reaction product. The conversion of **1a** to **4a** was used as a standard in the development of other reaction conditions, and Table 1 lists the yields obtained with a variety of reagent combinations. Although some of these reagent combinations have not yet been applied to the preparation of simple ketenimines,[12] their use as activating agents in this rearrangement suggests that they might be useful for that purpose.

Further comment is required for some of these reaction conditions. Elimination of the troublesome Ph_3P-containing side products was accomplished through the use

(5) Brannock, K. C.; Burpitt, R. D. *J. Org. Chem.* **1965**, *30*, 2564.
(6) Ab initio calculations confirm this as a reasonable hypothesis. See: Walters, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11618−11619.
(7) (a) Walters, M. A.; McDonough, C. S.; Brown, P. S., Jr.; Hoem, A. B. *Tetrahedron Lett.* **1991**, *32*, 179. (b) Walters, M. A.; Hoem, A. B.; Arcand, H. R.; Hegman, A. D.; McDonough, C. S. *Tetrahedron Lett.* **1993**, *34*, 1453. (c) Walters, M. A.; Hoem, A. B. *J. Org. Chem.* **1994**, *59*, 2645.
(8) (a) Molina, P.; Alajarin, M.; Lopez-Leonardo, C.; Alcantara, J. *Tetrahedron* **1993**, 5153. (b) Molina, P.; Alajarin, M.; Lopez-Leonardo, C. *Tetrahedron Lett.* **1991**, *32*, 4041.
(9) Nubbemeyer, U. *Synthesis* **1993**, 1120.
(10) Brückner, R.; Huisgen, R. *Tetrahedron Lett.* **1994**, *35*, 3281.
(11) (a) Appel, R.; Warning, K.; Ziehn, K.-D. *Chem. Ber.* **1973**, *106*, 3450. (b) Yamato, E.; Sugasawa, S. *Tetrahedron Lett.* **1970**, 4383.
(12) For a review of the synthesis of ketenimines, see: Krow, G. R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 435.

Table 2. Examples of the 3-Aza-Cope Rearrangement

1a-l 4a-l

amide	R^1	R^2	method	nitrile	yield (%)
1a	Ph	H	A	**4a**	94
1b	CH_2Ph	H	A	**4b**	67
1c	Ph	Me	A	**4c**	60
1d	Ph	Ph	A	**4d**	75
1e	*p*-$MeOC_6H_4$	H	A	**4e**	85
1f	*p*-$CF_3C_6H_4$	H	A	**4f**	73
1g	MeO_2CCH_2	H	A	**4g**	69
1h	CH_3CH_2	H	A	**4h**	36
1i	$Br(CH_2)_3$	H	B	**4i**	30
1j	$PhCH_2O$	H	F	**4j**	40
1k	$MeOCH_2O$	H	F	**4k**	59
1l	PthalN	H	B	**4l**	78
1l	PthalN	H	F	**4l**	66

of the reagents given in entries E, F, and G of Table 1. Non-phosphorus-based reagents were also successful in effecting the reaction (conditions H, I, L, and M). The conditions utilizing triphosgene/TEA appeared to be the most vigorous of all of the reagent combinations examined,[13] and under these reaction conditions the 3-aza-Cope transformation occurred at well below room temperature.

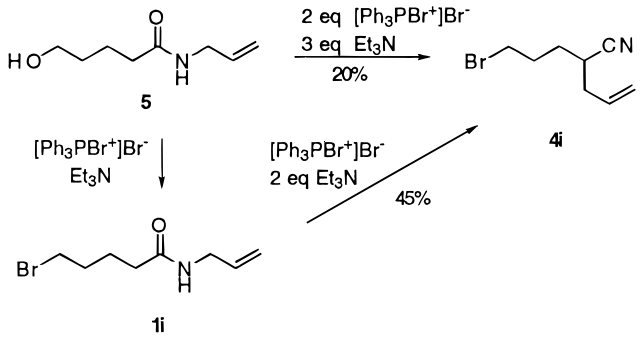
That this rearrangement is compatible with aqueous conditions is evidenced by the use of a phase-transfer reaction ($[PhCH_2NEt_3]^+Br^-/CHCl_3/NaOH/H_2O$, condition M) to generate the activating species.[14] This transformation presumably proceeds through the insertion of dichlorocarbene into the O−H bond in the imidoyl tautomer of the *N*-allylamide. Elimination of dichloromethanol leads to the transient formation of the ketenimine intermediate which rapidly (at least at a rate competitive with that of attack of other nucleophiles) rearranges to the nitrile.

Although it appeared that almost any dehydrating agent could bring about this transformation, a number of reagents were not successful in converting the allylamide to the 4-pentenenitrile. Notably, the Misunobu conditions (DEAD, Ph_3P)[15] failed to facilitate the desired rearrangement. Other reagent combinations that failed to effect the reaction cleanly were TEA and CH_3COCl, Ac_2O, CH_3OCOCl, $(CF_3CO)_2O$, and 1-propylphosphonic acid cyclic anhydride.

Scope of the Reaction. The wide range of *N*-allylamides that were used as ketenimine precursors for this mild rearrangement is illustrated in Table 2. Amides **1c** and **1d** demonstrated that this reaction was useful for the synthesis of quaternary nitriles. Sensitive functionality that might be reactive under more vigorous conditions survived this mild rearrangement, as is evidenced by the successful reactions of the ester **1g** and bromide **1i**.

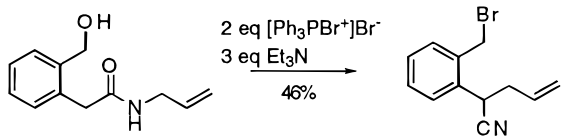
As a final note on the reaction conditions, it was possible to utilize some of the reagent combinations in a remote functional group interconversion which took place concomitantly with the rearrangement process (Scheme 2). For example, when amide **5** was treated with 2 equiv

Scheme 2



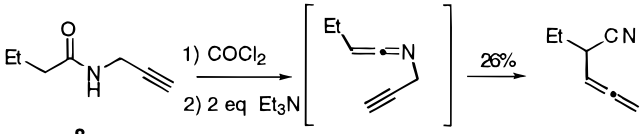
5 4i 1i

Scheme 3



6 7

Scheme 4



8 9 10

of $[Ph_3PBr^+]Br^-$ and 3 equiv of TEA, the conversion of the primary alcohol to the bromide was accomplished concurrently with the rearrangement, albeit in low yield.[16] Likewise, when amide **6**, derived from isochromanone, was treated under the same conditions, the desired bromonitrile **7** was obtained in 46% yield (Scheme 3). On the other hand, if amide **5** was treated with 1 equiv of $[Ph_3PBr^+]Br^-$ and TEA, the bromoamide **1i** could be obtained cleanly. This amide could then be induced to rearrange, in a separate step with the usual combination of reagents, to give the bromonitrile **4i** (45% yield).

Many of these same reagent combinations also proved to be effective in the rearrangement of both α-nitrogen- and α-oxygen-substituted *N*-allylamides. While the *N*-phthalimide protected derivative **1l** was converted quite smoothly to the α-aminonitrile **4l** (Table 2), the reactions of the $PhCH_2O$- and CH_3OCH_2O-substituted amides **1j** and **1k** proceeded only sluggishly to give the protected cyanohydrins **4j** and **4k**, respectively. The latter cases seemed to be much more dependent on the reaction conditions than were the other alkyl examples reported in Table 2 which proceeded using a wide variety of conditions.

One of the most intriguing results in the original Brannock and Burpitt manuscript was their reported conversion of *N*-propargylamide **8** to 3,4-pentadienenitrile **10** (26% yield) through what appears to be a highly-strained 3-aza-1,2-hexadien-5-yne **9** (Scheme 4). This transformation, however, appeared to be reasonably facile, even under the milder conditions which we had developed. For example, application of the standard rearrangement conditions to amide **11** converted it to the conjugated nitrile product **13**, presumably via the initially-

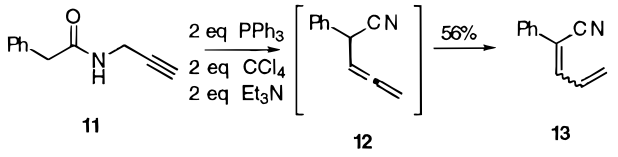
(13) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894−895.

(14) Saraie, T.; Ishiguro, T.; Kawashima, K.; Morita, K. *Tetrahedron Lett.* **1973**, 2121.

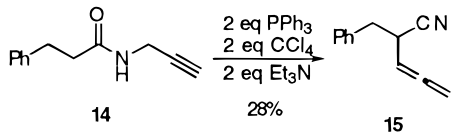
(15) For a review of the Mitsunobu reaction, see: Mitsunobu, O. *Synthesis* **1981**, 1.

(16) Bestmann, H. J.; Lienert, J.; Mott, L. *Liebigs Ann. Chem.* **1968**, *718*, 24−32.

Scheme 5



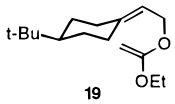
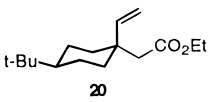
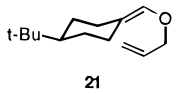
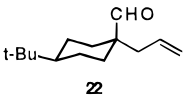
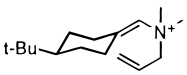
Scheme 6



formed allene **12** (Scheme 5).[17] Attempts to isolate intermediate **12** were unsuccessful. The aromatic system in this case no doubt facilitated the isomerization from the allene to the conjugated 1,3-diene system. Good evidence for this contention was obtained when no isomerization was observed subsequent to the rearrangement of **15** to the allenic nitrile **14** (Scheme 6).

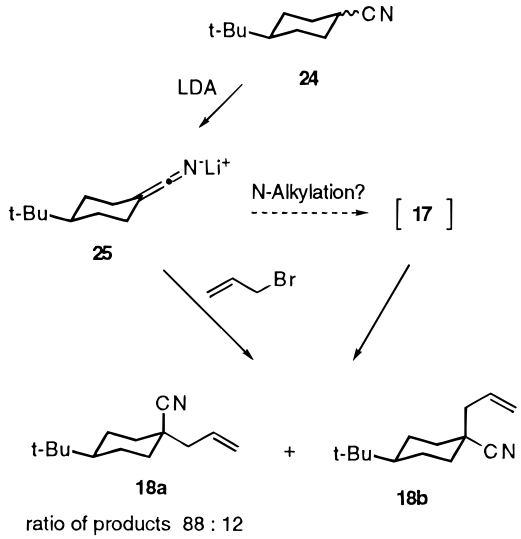
Stereochemistry. In addition to their ability to predictably form C−C bonds, another important feature of the Claisen and Cope rearrangements is their inherent stereochemical control.[1] This stereochemical control can be rationalized by invoking the intermediacy of an organized transition state which is chair- or boatlike. The attendant gauche and 1,3-diaxial interactions between the groups on the carbons involved in the bond-forming process and other substituents on the cyclic assembly of atoms can lead to marked differences between the various diastereomeric transition states for the reaction, thus allowing the potential for one diastereomer of the product to be formed preferentially. For the rearrangement of 3-aza-1,2,5-hexatrienes, the transition state fits neither the chair- nor boatlike paradigms. This situation raises important questions concerning the stereoselectivity associated with such a transition state. To gain some general understanding for the level of diastereocontrol which might be present in this process relative to other [3,3]-sigmatropic reactions, an investigation of the rearrangement of the conformationally-locked *N*-allylamides **16a**−**b** was undertaken. The rearrangement of related compounds has been investigated in the case of the Claisen[18] and cationic 3-aza-Cope[3a] reactions (Table 3, entries 2−4). These previous studies concluded that there was a marked preference for the bond-forming process to occur on the equatorial face of the π-system involved in the rearrangement process.[19] An additional impetus for determining the axial:equatorial (A:E) ratio for the rearrangement of **16a**−**b** was the report by House[18] that the reaction of the nitrile-stabilized anion **25** (derived from **24**) with allyl bromide favored the formation of the axial nitrile **18** in an 88:12 A:E ratio (Scheme 7). We speculated that this reaction might, alternatively, proceed through the 3-aza-1,2,5-hexatriene **17**, given that ketenimines have been formed by the

Table 3. Comparison of the Rearrangement of 17 to Related [3,3]-Sigmatropic Processes

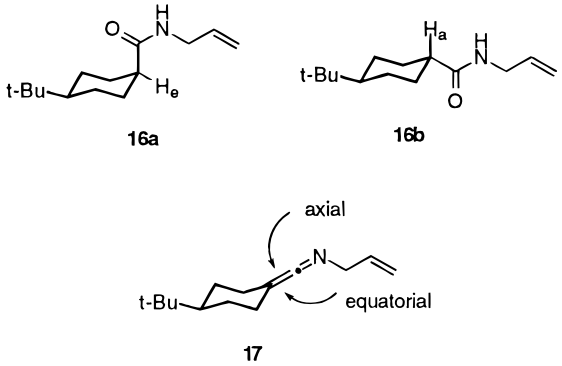
entry	starting material[a]	major product	ratio of products	ref
1	**17**	**18a**	75:25	
2	 **19**	 **20**	52:48	18
3	 **21**	 **22**	76:24	18
4	 **23**	**22**	77:23	3a

[a] Structures **17**, **21**, and **23** represent intermediates.

Scheme 7



N-alkylation of nitrile anions.[12,20] This process would lead to the same products as those formed by the direct C-alkylation reaction, but perhaps in a different A:E ratio. Determination of the A:E ratio in our case, wherein the ketenimine was to be formed by an alternative process, might allow us to rule out the exclusive intermediacy of this putative species in the case reported by House, but only if the ratio for the rearrangement of **17** turned out to be much different than 88:12.



A mixture of the axial and equatorial amide isomers **16a** and **16b** (the identities of which could be character-

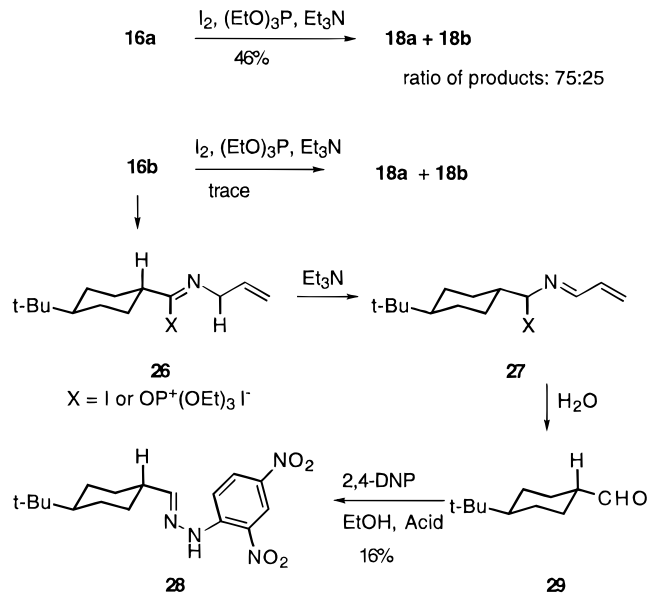
(17) The mixture of nitrile isomers **13** was converted to one isomer by treatment with mild acid or silica gel.

(18) House, H. O.; Lubinkowski, J.; Good, J. J. *J. Org. Chem.* **1975**, *40*, 862.

(19) [2,3]-Sigmatropic rearrangements evince a similar preference for bond formation on the equatorial face of the cyclohexane system. (a) Evans, D. A.; Sims, C. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453. (b) Mander, L. N.; V., T. J. *Aust. J. Chem.* **1980**, *33*, 1559−1568.

(20) Clarke, L. F.; Hegarty, A. F. *J. Org. Chem.* **1992**, *57*, 1940 and references cited therein.

Scheme 8



ized by the ^{1}H coupling constants of H_e and H_a) was readily prepared from 4-*tert*-butylcyclohexanecarboxylic acid (1. $SOCl_2$ 2. $CH_2{=}CHCH_2NH_2$). When this ~50:50 mixture of isomers was subjected to the rearrangement conditions, a rapid reaction of only one of the two isomers was observed. Fortunately, the amide isomers proved to be separable by radial chromatography, and each of these isomers was subjected, independently, to several of the standard rearrangement conditions which we had developed. The axial amide **16a** led to an identical 75:25 (±3%; integration of ^{1}H NMR resonances) mixture of the axial and equatorial isomers of the nitrile **18**, regardless of which method (Table 1: A, 41%; F, 46%; H, 42%; I, 27%) was employed. This ratio of isomers was in reasonable agreement with the results reported for comparable sigmatropic reactions (Table 3). Therefore, even though the rearrangement of this 3-aza-1,2,5-hexatriene proceeded via a fundamentally different transition state than in the other examples, it exhibited relatively the same diastereofacial selectivity. Since the A:E ratio was not drastically different from that which House reported for the reaction of carbanion **24**, we could draw no conclusions as to the intermediacy of **17** in the alkylation process.

In marked contrast to the smooth rearrangement of the axial isomer **16a**, the rearrangement of the equatorial amide isomer **16b** (Ph_3P/CCl_4/TEA) gave a very low yield of the product nitrile **18**, albeit in approximately the same A:E ratio as had resulted from the rearrangement of amide **16a** (Scheme 8). The difference in reactivity between **16a** and **16b** is most likely a manifestation of steric acceleration or assistance.[21] Both amides are probably converted to their respective imidoyl halides at a similar rate. Subsequent ketenimine formation from **26**, however, is slower than it is from the axially-disposed, and more sterically-encumbered, imidoyl halide derived from **16a**. Notably, the treatment of amide **16b** with I_2/$(EtO)_3P$/TEA led to only a trace amount of the nitrile mixture **18a**−**b**, even though little starting material could be isolated from the reaction.[22] When the quenched reaction mixture was treated with 2,4-dinitrophenylhydrazine reagent, a small amount of the 2,4-dinitrophenylhydrazone **28** was isolated (mp 169−170 °C; lit.[23] mp 170−171 °C). Apparently, the slower rate of elimination from imidoyl halide **26** (relative to the one derived from **16a**) allowed for an alternative reaction pathway, that of the removal of the allylic proton, to occur.[24] Thus, in the case of the reaction of **16b**, TEA-assisted isomerization of the imidoyl intermediate **26** would give the α-chloroimine **27** as the predominant product. Subsequent hydrolysis of this reactive species upon aqueous workup would account for the production of aldehyde **29**, which could then be isolated as its 2,4-DNP derivative.

Conclusions

In conclusion, we have expanded on the pioneering work of Brannock and Burpitt and developed what we consider to be the mildest 3-aza-Cope reaction reported to date. This reaction appears to be quite general, in that it is capable of transforming a wide variety of *N*-allylic amides into their corresponding substituted pentenenitriles. Additionally, this sigmatropic process can be effected by a wide variety of readily available reagent combinations and occurs under surprisingly mild temperatures relative to other 3-aza-Cope reactions. Finally, this rearrangement is comparable to other [3,3]-sigmatropic reactions in its selectivity for reacting preferentially from the equatorial face of conformationally-locked systems like **16a** and **16b**. This is in spite of the fact that this process most likely occurs via neither a chair- nor boatlike transition state and might, therefore, be expected to evince much lower diastereoselection. We are continuing our investigation into the diastereofacial selectivity of this process in both acyclic and cyclic systems. Our results along these lines will be reported in due course.

Experimental Section

General Methods. Unless otherwise noted, all nonaqueous reactions were carried out under a dry argon or nitrogen atmosphere in flame-dried glassware. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Dichloromethane and acetonitrile were distilled from calcium hydride. Triethylamine (Et_3N) was distilled and stored over solid potassium hydroxide. Dimethylformamide (DMF) was dried over activated 4 Å molecular sieves. Triphenylphosphine polymer bound was purchased from Fluka Chemicka-BioChemika Analytika. Chemical shifts, for ^{1}H NMR spectra, are reported in δ units downfield from internal Me_4Si or from the $CHCl_3$ solvent peak at 7.26 ppm relative to Me_4Si. ^{13}C NMR spectra were referenced to the $CDCl_3$ peak at 77.2 ppm relative to Me_4Si. Multiplicities are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), ABq (AB quartet), app (apparent), unresolved, and br (broad). An ABq was reported as the center of the two doublets and the splitting distance of each doublet. An apparent (app)

(21) This concept has been employed to explain the effect of substituent conformation on a closely analogous reaction, that of the formation of exocyclic alkenes by elimination of HBr. For example, *cis*-4-*tert*-butylcyclohexanemethyl bromide (axial) undergoes elimination to 1-*tert*-butyl-4-methylenecyclohexane at a rate nine times faster than does the corresponding *trans* (equatorial) epimer. King, J. F.; Coppen, M. J. *Can. J. Chem.* **1971**, *49*, 3714−3723. We thank a referee for bringing this concept to our attention.

(22) The crude reaction mixture showed a resonance (^{1}H) consistent with the presence of an aldehyde which we presumed to be **29**. Attempts to isolate this compound from the crude mixture were unsuccessful.

(23) Cross, B.; Whitham, G. H. *J. Chem. Soc.* **1960**, 3895.

(24) This proposed mechanism is reminiscent of a published synthetic process in which the allylic deprotonation of nonenolizable *N*-allyl imidoyl chlorides is found to lead to good yields of substituted pyrroles. Engel, N.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 676.

splitting pattern was defined as a splitting pattern that was less complicated than predicted, usually due to coincidentally identical splitting from chemically nonequivalent protons. Substances for which C, H, N analyses are not reported were purified as specified and gave spectroscopic data consistent with being >95% of the assigned structure. Microanalysis were performed by Spang Microanalytical Laboratory, Galbraith Laboratories, Inc., Schwarzkopf Microanalytical Laboratory, or Atlantic Microlab, Inc.

Amide Preparation. All amides were produced by standard synthetic techniques. Unless otherwise noted, amides were synthesized by the condensation of allylamine (AA) or propargylamine with the appropriate acid chloride. Amides **1e**, **1f**, and **13** were produced by conversion of the appropriate acid to the acid chloride with thionyl chloride, followed by reaction with AA. Amides **1i** and **1k** were produced by the ring-opening reaction of δ-valerolactone or isochromanone with AA. Amide **1n** was produced by condensation of the *N*-phthalylglycine with pivaloyl chloride, followed by treatment of the mixed anhydride with AA. Amide **1m** was produced by a two-step procedure from butyl glycolate. The glycolate was protected as the methoxymethyl ether (MOMCl, Hunig's Base), and the resulting ester was converted to the amide by heating with AA.

Standard Purification Procedure. All reactions were partitioned between water and ether when deemed complete. The organic layer was then washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Chromatography of the residue on silica gel (10% EtOAc/hexane) gave the nitrile product.

General Procedures for the Conversion of *N*-Allylamides to 4-Pentenenitriles. Preparation of 2-Phenyl-4-pentenenitrile (4a): IR (neat) 3090, 2833, 2240, 1649, 1493, 1451, 996, 925, 759, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44−7.30 (m, 5H), 5.90−5.72 (m, 1H), 5.24−5.14 (m, 2H), 3.86 (t, 1H, J = 7.7 Hz), 2.73−2.57 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 132.5, 128.9, 128.1, 127.3, 120.2, 119.3, 39.8, 37.4; MS (EI) *m/e* 157 (42), 117 (37), 116 (100), 104 (18), 92 (42), 77 (22). Anal. Calcd for $C_{11}H_{11}N$: C, 84.03; H, 7.06. Found: C, 84.06; H, 7.09.

Procedure A. To a solution of 98.3 mg of amide **1a** (0.561 mmol), 0.309 g of Ph_3P (1.17 mmol), and 0.235 mL of Et_3N (1.68 mmol) in 2.24 mL of dry CH_2Cl_2 was added 0.162 mL of CCl_4 (1.68 mmol) via syringe. After the solution was stirred for 15 h at rt, purification gave 83.1 mg of nitrile **4a** (94%).

Procedure B. To a solution of 53.5 mg of amide **1a** (0.305 mmol) and 0.149 g of $[Ph_3PBr^+]Br^-$ (0.351 mmol) in 1.22 mL of dry CH_2Cl_2 at rt was added 0.106 mL of Et_3N (0.763 mmol) via syringe. After the solution was stirred for 15 h, purification gave 26.3 mg of nitrile **4a** (55%).

Procedure C. To a solution of 52.5 mg of amide **1a** (0.300 mmol), 0.165 g of Ph_3P (0.630 mmol), and 0.129 mL of Et_3N (0.930 mmol) in 1.20 mL of dry CH_2Cl_2 at room temperature was added 0.308 g of CBr_4 (0.930 mmol). After the solution was stirred for 15 h at rt, purification gave 31.1 mg of nitrile **4a** (66%).

Procedure D. To a solution of 82 mg of I_2 (0.324 mmol) in 1.3 mL of dry CH_2Cl_2 was added PPh_3 (0.330 mmol) until the solution was colorless. To this solution was added 57.8 mg of amide **1a** (0.324 mmol). The solution was then stirred for 5 min at rt before the addition of 0.093 mL of Et_3N (0.664 mmol) via syringe. This solution was then stirred overnight. Purification gave 29.2 mg of nitrile **4a** (56%).

Procedure E. To a solution of 0.126 g of Ph_3P−polymer (~3 mmol of Ph_3P/g of polymer, 0.376 mmol) in 1.4 mL of CH_2Cl_2 was added slowly, via syringe, 0.018 mL of Br_2 (0.351 mmol). To this solution was added 60.0 mg of amide **1a** (0.342 mmol) and, after the reaction was stirred for 5 min, 0.105 mL of Et_3N (0.752 mmol). After the solution was stirred for 15 h at rt, purification gave 22.6 mg of nitrile **4a** (42%).

Procedure F. A solution of 0.2230 g of I_2 (0.879 mmol) in 0.5 mL of dry CH_2Cl_2 was titrated via syringe with triethyl phosphite (0.153 mL, 0.894 mmol) until the solution was colorless. This solution was transferred, via cannula, to a solution of 51.3 mg of amide **1a** (0.293 mmol) in 0.72 mL of dry CH_2Cl_2. After being stirred for 5 min at rt, the solution was treated with 0.122 mL of Et_3N (0.879 mmol) via syringe. The reaction was stirred for a further 45 min before purification gave 39.5 mg of nitrile **4a** (86%).

Procedure G. A solution of 0.229 g of I_2 (0.903 mmol) in 0.5 mL of dry CH_2Cl_2 was titrated via syringe with trimethyl phosphite (0.107 mL, 0.918 mmol) until the solution was colorless. The solution was transferred, via cannula, to a solution of 53.8 mg of amide **1a** (0.301 mmol) in 0.73 mL of CH_2Cl_2. After being stirred for 15 min at rt, the solution was treated with 0.126 mL of Et_3N (0.903 mmol) via syringe. The reaction was stirred for a further 1 h before purification gave 16.6 mg of nitrile **4a** (36%).

Procedure H. To a solution of 58.1 mg of amide **1a** (0.332 mmol) and 0.121 mL of diisopropylethylamine (0.697 mmol) in 1.66 mL of dry ethyl ether at room temperature was added slowly 0.059 mL of triflic anhydride (0.347 mmol) via syringe. This solution was stirred for 20 min before the reaction was quenched with the addition of 3 mL of brine. Purification gave 35.0 mg of nitrile **4a** (67%).

Procedure I. A solution of 53.3 mg of amide **1a** (0.304 mmol) dissolved in 0.5 mL of dry CH_2Cl_2 was transferred, via cannula, to a solution of 46.3 mg of triphosgene (0.152 mmol) in 0.72 mL of dry CH_2Cl_2. This solution was treated slowly with 0.127 mL of Et_3N (0.912 mmol) via syringe. The reaction was stirred for 5 min before purification gave 37.0 mg of nitrile **4a** (77%).

Procedure J. A solution of 51.5 mg of amide **1a** (0.294 mmol) dissolved in 0.5 mL of dry CH_2Cl_2 was transferred via cannula to a solution of 43.6 mg of triphosgene (0.147 mmol) in 0.7 mL of dry CH_2Cl_2 and cooled to 0 °C. This solution was treated slowly with 0.123 mL of Et_3N (0.882 mmol) via syringe. This solution was stirred for 30 min before the reaction was diluted with 3 mL of brine. Purification gave 39.1 mg of nitrile **4a** (85%).

Procedure K. A solution of 54.6 mg of amide **1a** (0.312 mmol) dissolved in 0.5 mL of dry CH_2Cl_2 was transferred via cannula to a solution of 46.2 mg of triphosgene (0.156 mmol) in 0.75 mL of dry CH_2Cl_2 which had previously been cooled to −78 °C. The external temperature of this solution was maintained at <−70 °C while 0.130 mL of Et_3N (0.936 mmol) was added slowly via syringe. This solution was held at constant temperature for 4.5 h, without being checked by TLC, before the reaction was quenched by 3 mL of brine. Purification gave 19.4 mg of nitrile **4a** (40%).

Procedure L. To a solution of 59.8 mg of amide **1a** (0.341 mmol) and 0.119 mL of Et_3N (0.853 mmol) in 1.37 mL of dry CH_2Cl_2 at room temperature was added slowly 0.037 mL of oxalyl chloride (0.426 mmol) via syringe. This solution was stirred for 30 min before being quenched with 3 mL of brine. Purification gave 16.7 mg of nitrile **4a** (31%).

Procedure M. A solution of 50.9 mg of amide **1** (0.290 mmol), 1.5 mL of chloroform (0.2M), 6.6 mg of benzyltriethylammonium chloride (0.029 mmol), and 0.16 mL of 50% NaOH/H_2O was stirred overnight at room temperature. Purification gave 17.8 mg of nitrile **2** (39%).

***N*-Allyl-2-phenylacetamide (1a):** IR (CH_2Cl_2) 3432, 3031, 1671, 1514 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.22 (m, 5H), 5.83−5.60 (m, 2H), 5.10−5.00 (m, 2H), 3.83 (tt, 2H, J_{app} = 5.6, 1.6 Hz), 3.58 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 135.0, 134.2, 129.5, 129.1, 127.5, 116.1, 43.9, 42.0; MS (EI) *m/e* 175 (35), 118 (17), 93 (37), 91 (100), 84 (70), 65 (81). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.39; H, 7.48. Found: C, 75.43; H, 7.35.

***N*-Allyl-3-phenylpropanamide (1b):** IR (neat) 3296, 3079, 2929, 1647, 1545, 1260, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.10 (m, 5H), 6.02 (br s, 1H), 5.82−6.68 (m, 1H), 5.10−5.00 (m, 2H), 3.82 (tt, 2H, J_{app} = 5.7, 1.5 Hz), 2.95 (t, 2H, J = 7.8 Hz), 2.49 (t, 2H, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 140.7, 134.0, 128.3, 128.1, 126.0, 116.0, 41.7, 38.2, 31.6; MS (EI) *m/e* 190 (9.32), 189 (44), 133 (13), 131 (23), 105 (86), 91 (93), 77 (73), 57 (100). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.14; H, 7.99. Found: C, 75.27; H, 8.01.

***N*-Allyl-2-phenylpropanamide (1c):** IR (neat) 3293, 3075, 2978, 1651, 1546, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.18 (m, 5H), 5.82−5.66 (m, 1H), 5.58 (br s, 1H), 5.06−4.95 (m, 2H), 3.81 (tt, 2H, J_{app} = 5.6, 1.5 Hz), 3.58 (q, 1H, J =

7.2 Hz), 1.53 (d, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 141.3, 134.1, 128.8, 127.6, 127.2, 115.8, 47.0, 41.8, 18.4. Anal. Calcd for $C_{12}H_{15}NO$: C, 76.14; H, 7.99. Found: C, 75.99; H, 7.95.

***N*-Allyl-2,2-diphenylacetamide (1d):** IR (CH_2Cl_2) 3428, 3029, 1670, 1510 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.16 (m, 10H), 5.90−5.70 (m, 2H), 5.10−5.00 (m, 2H), 4.94 (s, 1H), 3.89 (tt, 2H, J_{app} = 5.6, 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 139.6, 134.2, 129.0, 128.9, 127.4, 116.4, 59.3, 42.2; MS (GC−E/I) *m*/*e* 251 (M^+, 4), 168 (100), 152 (21), 41 (26). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.33; H, 6.85; N, 5.70.

***N*-Allyl-2-(4-methoxyphenyl)acetamide (1e):** IR (CH_2Cl_2) 3428, 2936, 1670, 1513, 1249 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18, 6.90, (app t ABq, 4H, J = 2.6 Hz, J_{AB} = 8.8 Hz), 5.83−5.70 (m, 1H), 5.45 (br s, 1H), 5.09−5.00 (m, 2H), 3.87−3.80 (m, 2H), 3.81 (s, 3H), 3.55 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 158.8, 134.0, 130.5, 126.7, 115.9, 114.4, 55.2, 42.8, 41.8; MS (GC−E/I) *m*/*e* 205 (M^+, 17), 121 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.20; H, 7.37; N, 6.82. Found: C, 70.07; H, 7.34; N, 6.52.

***N*-Allyl-2-(4-(trifluoromethyl)phenyl)acetamide (1f):** IR (CH_2Cl_2) 3428, 3336, 2922, 1677, 1514, 1327, 1168, 1127 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61, 7.41 (ABq, 4H, J_{AB} = 8.2 Hz), 5.87−5.70 (m, 1H), 5.60 (br s, 1H), 5.13−5.05 (m, 2H), 3.89−3.83 (m, 2H), 3.63 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 139.3, 133.9, 129.7, 129.3, 125.7 (unresolved q, J = 4 Hz), 124.2 (q, J = 272 Hz), 116.4, 43.2, 42.2. Anal. Calcd for $C_{12}H_{12}F_3NO$: C, 59.26; H, 4.94; N, 5.76; MS (GC−E/I) *m*/*e* 243 (M^+, 17), 158 (70), 84 (53), 57 (35), 41 (100). Found: C, 59.03; H, 4.93; N, 5.54.

Methyl 3-(*N*-Allylcarbamoyl)propanoate (1g): IR (neat) 3301, 3085, 2950, 1738, 1653, 1549, 1167 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.26 (br s, 1H), 5.84−5.66 (m, 1H), 5.20−4.98 (m, 2H), 3.80 (tt, 2H, J_{app} = 5.7, 1.5 Hz), 3.62 (s, 3H), 2.61 (t, 2H, J = 6.7 Hz), 2.45 (t, 2H, J = 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 171.2, 134.0, 115.9, 51.6, 41.8, 30.6, 29.2; MS (EI) *m*/*e* 157 (17), 116 (100), 89 (23), 87 (21), 63 (18), 57 (44). Anal. Calcd for $C_8H_{13}NO_3$: C, 56.11; H, 7.66. Found: C, 55.04; H, 7.86.

***N*-Allyl-5-bromopentanamide (1i):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.15 (br s, 1H), 5.91−5.78 (m, 1H), 5.24−5.10 (m, 2H), 3.87 (tt, 2H, J_{app} = 5.7, 1.5 Hz), 3.43 (t, 2H, J = 6.5 Hz), 2.26 (t, 2H, J = 7.2 Hz), 1.97−1.74 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 134.3, 116.4, 42.0, 35.5, 33.4, 32.2, 24.3.

***N*-Allyl-2-(benzyloxy)acetamide (1j):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.28 (m, 5H), 6.72 (br s, 1H), 5.90−5.76 (m, 1H), 5.26−5.10 (m, 2H), 4.56 (s, 2H), 4.00 (s, 2H), 3.91 (tt, 2H, J_{app} = 5.9, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 136.8, 134.0, 128.7, 128.3, 128.0, 116.4, 73.6. 69.5, 41.2. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.82; H, 7.47; N, 6.78.

***N*-Allyl-(2-methoxymethoxy)acetamide (1k):** IR (neat) 3336, 2934, 1666, 1538, 1152, 1115, 1055, 920 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (br s, 1H), 5.94−5.77 (m, 1H), 5.28−5.11 (m, 2H), 4.69 (s, 2H), 4.07 (s, 2H), 3.95 (tt, 2H, J_{app} = 5.7, 1.5 Hz), 3.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 134.0, 116.5, 96.6, 67.1, 55.8, 41.2.

***N*-Allyl-2-phthalylacetamide (1l):** ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (br s, 1H), 7.96−7.81 (m, 4H), 5.87−5.69 (m, 1H), 5.19−5.00 (m, 2H), 4.21 (s, 2H), 3.70 (br t, 2H, J_{app} = 5.2 Hz); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (m, 4H), 5.90−5.68 (m, 2H), 5.28−5.10 (m, 2H), 4.37 (s, 2H), 3.92 (tt, 2H, J_{app} = 5.7, 1.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.6, 165.9, 134.8, 134.5, 131.8, 123.2, 115.2, 40.9, 40.1. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.78; H, 4.95; N, 11.23.

2-Benzyl-4-pentenenitrile (4b). Procedure A was used (67%): IR (neat) 3038, 2927, 2243, 1503, 1459, 924, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30−7.12 (m, 5H), 5.85−5.68 (m, 1H), 5.20−5.06 (m, 2H), 2.90−2.70 (m, 3H), 2.33−2.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 132.5, 129.0, 128.7, 127.2, 121.2, 119.2, 37.6, 35.6, 33.5; MS (GC−E/I) *m*/*e* 171 (2.31), 129 (4.66), 103 (2.21), 92 (13.82), 91 (100), 77 (4.34), 65 (9.44), 51 (3.91). Anal. Calcd for $C_{12}H_{13}N$: C, 84.16; H, 7.66. Found: C, 83.81; H, 7.76.

2-Methyl-2-phenyl-4-pentenenitrile (4c). Procedure A was used (60%): IR (neat) 2987, 2241, 1498, 1451, 927, 765, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−18 (m, 5H), 5.71−5.55 (m, 1H), 5.12−5.01 (m, 2H), 2.65−2.46 (m, 2H), 1.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 131.8, 128.8, 127.8, 125.5, 123.1, 120.1, 46.26, 42.11, 26.5; MS (GC−E/I) *m*/*e* 171 (18.68), 131 (10.06), 130 (100), 103 (40.30), 77 (13.62), 51 (4.71).

2,2-Diphenyl-4-pentenenitrile (4d). Amide **1d** (158.7 mg, 0.830 mmol) was submitted to procedure A above. Purification gave 107.4 mg of the nitrile (75%): IR (neat) 3062, 2237, 1493, 1449, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.20 (m, 10H), 5.80−5.61 (m, 2H), 5.27−5.10 (m, 2H), 3.13 (dt, 2H, J_{app} = 6.8, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.8, 131.9, 129.0, 128.1, 127.2, 122.1, 120.5, 51.8, 44.0; MS (GC−E/I) *m*/*e* 233 (M^+, 9), 192 (73), 165 (100). Anal. Calcd for $C_{17}H_{15}N$: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.78; H, 6.46; N, 5.80.

2-(4-Methoxyphenyl)-4-pentenenitrile (4e). Amide **1e** (127.2 mg, 0.620 mmol) was submitted to procedure A above. The standard pruification procedure gave 100.0 mg of the nitrile (85%): IR (neat) 2961, 2241, 1513, 1256 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24, 6.90 (ABq, 4H, J_{AB} = 8.9 Hz), 5.90−5.69 (m, 1H), 5.24−5.11 (m, 2H), 3.80 (s, 3H), 2.66−2.53 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 132.8, 128.6, 127.3, 120.7, 119.4, 114.5, 55.4, 40.0, 36.8; MS (GC−E/I) *m*/*e* 187 (M^+, 1), 158 (9), 91 (100), 65 (9).

2-(4-(Trifluoromethyl)phenyl)-4-pentenenitrile (4f). Amide **1f** (133.2 mg, 0.548 mmol) was submitted to procedure A above. Purification gave 90.6 mg of the nitrile (73%): IR (neat) 2926, 2243, 1326, 1168, 1128, 1069^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66, 7.47 (ABq, 4H, J_{AB} = 8.06 Hz), 5.90−5.60 (m, 1H), 5.31−5.13 (m, 2H), 3.94 (t, 1H, J = 7.08 Hz), 2.72−2.59 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 132.0, 130.5, 128.0, 126.2 (unresolved q, J = 3 Hz), 123.9 (q, J = 273 Hz), 120.2, 119.8, 39.7, 37.5; MS (GC−E/I) *m*/*e* 225 (M^+, 98), 184 (100), 134 (80), 41 (99). Anal. Calcd for $C_{12}H_{10}F_3N$: C, 64.00; H, 4.48; N, 6.22. Found: C, 63.96; H, 4.74; N, 6.07.

Methyl 3-Cyano-5-hexenoate (4g). Procedure A was used (69%): IR (neat) 2959, 2244, 1740, 1438, 1212, 1176 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88−5.72 (m, 1H), 5.29−5.16 (m, 2H), 3.73 (s, 3H), 3.16−3.04 (m, 1H), 2.75−2.53 (m, 2H), 2.45−2.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 132.1, 120.5, 119.8, 52.2, 35.6, 27.1. Anal. Calcd for $C_8H_{11}NO_2$: C, 62.71; H, 7.24. Found: C, 62.64; H, 7.16.

2-(3-Bromopropyl)-4-pentenenitrile (4i). Amide **1i** (145.9 mg, 0.663 mmol) was submitted to procedure B above. The standard purification procedure gave 59.7 mg of the nitrile (45%): IR (neat) 3085, 2946, 2871, 2240, 1649, 1442, 1250, 995, 922 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88−5.73 (m, 1H), 5.23−5.15 (m, 1H), 3.43 (t, 2H, J = 6.4 Hz), 2.69−2.57 (m, 1H), 2.36 (t, 2H, J = 6.9 Hz), 2.20−1.88 (m, 2H), 1.88−1.65 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.7, 121.1, 119.1, 36.1, 32.3, 30.7, 30.0, 29.8; MS (E/I) *m*/*e* 203 (1.4), 202 (0.5), 201 (1.5), 122 (34), 95 (20), 94 (79), 81 (11), 80 (30), 53 (100). Anal. Calcd for $C_8H_{12}BrN$: C, 47.76; H, 6.02. Found: C, 47.50; H, 5.84.

2-(Benzyloxy)-4-pentenenitrile (4j). Amide **1j** (59.3 mg, 0.288 mmol) was submitted to procedure F above. Purification gave 21.8 mg of the nitrile (40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42−7.28 (m, 5H), 5.90−5.74 (m, 1H), 5.32−5.20 (m, 2H), 4.86, 4.54 (ABq, 2H, J_{AB} = 11.5 Hz, 1H), 4.19 (t, 1H, J = 6.5 Hz), 2.61 (tt, 2H, J_{app} = 6.8, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 130.8, 128.8, 128.7, 128.4, 120.2, 118.0, 72.4, 67.5, 37.8.

2-(Methoxymethoxy)-4-pentenenitrile (4k) via Procedure F. Amide **1k** (0.2570 g, 1.61 mmol) was submitted to procedure F above. Purification gave 134.4 mg of the nitrile (59%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.92−5.76 (m, 1H), 5.34−5.22 (m, 2H), 4.85, 4.68 (ABq, 2H, J_{AB} = 7.1 Hz), 4.41 (t, 1H, J = 6.6 Hz)), 3.42 (s, 3H), 2.61 (tt, 2H, J_{app} = 6.8, 1.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.8, 120.4, 118.1, 95.7, 64.6, 56.4, 38.0.

2-Phthalyl-4-pentenenitrile (4l) via Procedure B. Amide **1l** (46.8 mg, 0.192 mmol) was submitted to procedure B above. Purification gave 33.8 mg of the nitrile (78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90−7.70 (m, 4H), 5.75−5.62 (m, 1H), 5.25−5.10 (m, 3H), 3.00−2.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 134.7, 131.0, 130.2, 123.9, 121.1, 115.5, 39.1, 35.5. Anal.

Calcd for $C_{13}H_{10}N_2O_3$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.92; H, 4.52; N, 12.30.

Nitrile 4l via Procedure F. Amide **1l** (56.2 mg, 0.231 mmol) was submitted to procedure F above, with the addition of 0.002 mL of DMF. Purification gave 34.2 mg of the nitrile (66%).

***N*-Allyl-5-hydroxypentanamide (5):** IR (neat) 3294, 2936, 1642, 1551, 1421, 1263, 1065, 989, 922 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.60 (br s, 1H), 5.87−5.73 (m, 1H), 5.23−5.08 (m, 2H), 3.85 (app tt, 2H, J_{app} = 5.7, 1.5 Hz), 3.61 (t, 3H, J = 6.3 Hz), 2.26 (t, 2H, J = 7.3 Hz), 1.80−1.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 134.3, 116.2, 61.8, 42.0, 36.0, 32.0, 22.0.

***N*-Allyl-2-(2-(hydroxymethyl)phenyl)acetamide (6):** IR (CH_2Cl_2) 3435, 3299, 3079, 2872, 1652, 1523, 1013 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30−7.15 (m, 4H), 5.80−5.62 (m, 1H), 5.20 (t, 1H, J = 5.5 Hz), 5.11−5.00 (m, 2H), 4.62 (d, 2H, J = 5.6 Hz), 3.81−3.72 (m, 2H), 3.62 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 139.5, 134.5, 133.8, 130.5, 130.4, 128.5, 127.7, 116.2, 63.5, 42.1, 40.6. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.49; H, 7.31; N, 7.10.

2-(2-(Bromomethyl)phenyl)-4-pentenenitrile (7). Amide **6** (44.4 mg, 0.216 mmol) was submitted to procedure B above, with an extra equivalent of $[Ph_3PBr^+]Br^-$, and gave 24.0 mg of the nitrile (46%): IR (neat) 3062, 2237, 1493, 1449, 697 cm^{-1}. Mixture of rotomers: ^1H NMR (300 MHz, $CDCl_3$) δ 7.58−7.28 (m, 4H), 5.98−5.80 (m, 1H), 5.36−5.20 (m, 2H), 4.68−4.44 (m, 2H), 4.20 (t, 1H, J = 7.3 Hz)), 2.75−2.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 134.7, 132.6, 131.3, 130.1, 128.9, 128.8, 120.4, 119.8, 43.7, 39.5, 39.2, 33.6, 30.4.

2-Phenyl-*N*-(2-propynyl)acetamide (11): IR (CH_2Cl_2) 3434, 3302, 3031, 1675, 1508 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.21 (m, 5H), 6.02 (br s, 1H), 3.98 (q, 2H, J_{app} = 2.6 Hz), 3.56 (s, 2H), 2.18 (t, 1H, J = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 134.6, 129.5, 129.1, 127.5, 79.6, 71.6, 43.4, 29.4; MS (GC−E/I) *m*/*e* 173 (M^+, 15), 92 (100), 65 (27), 39 (53). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.23; H, 6.44; N, 8.06.

2-Phenyl-2,4-pentadienenitrile (13). Amide **11** (63.6 mg, 0.367 mmol) was submitted to procedure A above. Purification gave 31.7 mg of the nitrile (56%) as a mixture of isomers: IR (neat) 3061, 2216, 1450, 761, 692 cm^{-1}. Major isomer: ^1H NMR (300 MHz, $CDCl_3$) δ 7.64−7.56 (m, 2H), 7.46−7.32 (m, 3H), 7.24 (d, 1H, J = 11.0 Hz) 7.10−6.60 (m, 1H), 5.85−5.50 (m, 2H). Mixture of isomers: ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1, 141.9, 133.7, 131.7, 129.6, 129.4, 129.2, 129.1, 129.0, 127.3, 126.5, 125.9; MS (GC−E/I) *m*/*e* 155 (M^+, 96), 154 (100), 140 (54), 127 (59), 115 (45).

3-Phenyl-(*N*-propynyl)propanamide (14): ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.17 (m, 5H), 6.31 (br s, 1H), 3.99 (dd, 2H, J = 5.4, 2.5 Hz), 2.95 (t, 2H, J = 7.8 Hz), 2.49 (t, 2H, J = 7.8 Hz), 2.18 (t, 1H, J = 2.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 140.7, 128.5, 128.3, 126.2, 79.7, 71.4, 37.9, 31.5, 29.1. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.13; H, 7.07; N, 7.42.

2-Benzyl-3,4-pentadienenitrile (15). Amide **14** (212.3 mg, 1.13 mmol) was submitted to procedure A above. Purification gave 53.5 mg of the nitrile (28%): IR (neat) 3030, 2241, 1958, 1497, 1455, 858, 742, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.19 (m, 5H), 5.16 (app q, 1H, J_{app} = 6.6 Hz), 4.96 (d, 1H, J = 6.8 Hz), 4.95 (d, 1H, J = 7.1 Hz), 3.50−3.40 (m, 1H), 3.07−2.92 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.3, 136.4, 129.3, 128.9, 119.8, 87.0, 79.3, 39.2, 33.4; MS (GC−E/I) *m*/*e* 169 (M^+, 1), 142 (44), 91 (100).

***cis*-4-*tert*-Butyl-*N*-allylcyclohexanecarboxamide (16a):** IR (neat) 3314, 2940, 1652, 1532 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.92−5.77 (m, 2H), 5.31−5.08 (m, 2H), 3.91 (app tt, 2H, J_{app} = 5.6, 1.5 Hz), 2.52−2.45 (m, 1H), 2.19−2.09 (m, 2H), 1.69−1.44 (m, 4H), 1.24 (qd, 2H, J = 12.6, 3.5 Hz), 1.00 (tt, 1H, J = 12.0, 3.1 Hz), 0.83 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6, 134.6, 115.8, 48.0, 41.7, 39.2, 32.5, 28.5, 27.4, 23.6; MS (GC−E/I) *m*/*e* 223 (M^+, 6), 166 (100), 57 (83), 41 (98). Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.07; H, 11.49; N, 6.24.

***trans*-4-*tert*-Butyl-*N*-allylcyclohexanecarboxamide (16b):** IR (CH_2Cl_2) 3445, 2944, 1668, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.56 (br t, 1H, J = 5.1 Hz), 5.90−5.75 (m, 1H), 5.20−5.06 (m, 2H), 3.85 (app tt, 2H, J_{app} = 5.7, 1.5 Hz), 2.11 (tt, 1H, J = 12.2, 3.4 Hz), 1.99−1.80 (m, 4H), 1.56−1.39 (m, 2H), 1.06−0.96 (m, 3H), 0.84 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 134.4, 115.5, 47.1, 45.2, 41.4, 32.2, 29.9, 27.3, 26.4; MS (GC−E/I) *m*/*e* 223 (M^+, 13), 166 (93), 57 (100), 41 (64). Anal. Calcd for $C_{14}H_{25}NO$: C, 75.28; H, 11.28; N, 6.27. Found: C, 75.63; H, 11.52; N, 6.20.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **1i**, **1k**, **4c**, **4e**, **4j**, **4k**, **5**, **7**, **13**, and **15** (20 pages). This material is contained in 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.

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