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Supplementary Material Available: Tables of positional and thermal parameters and bond distances and angles (8 pages). Ordering information is given on any current masthead page.

The *N*-Acyl-α-cyano-1-azadienes. Remarkably Reactive Heterodienes in the Diels–Alder Reaction[1]

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A method for the prepartion of the *N*-acyl-α-cyano-1-azadienes has been developed and their Diels–Alder reactions have been studied. The intramolecular Diels–Alder reaction of these dienes with unactivated dienophiles occurs readily with a high preference for the exo (anti) reaction pathway. The *N*-acyl-α-cyano-1-azadienes are relatively stable allowing for their isolation and an investigation of their intermolecular Diels–Alder reactions. The azadiene **6** reacted with a range of dienophiles such as, ethyl vinyl ether, styrene, 1-hexene, and methyl acrylate. The reaction of **6** with *cis*- and *trans*-1-phenylpropene gave different products which was not consistent with a two-step reaction involving a common intermediate. The reactivity, regiochemistry, and stereochemistry of these reactions is interpreted in terms of a concerted mechanism with a transition state possessing a high degree of diradical character.

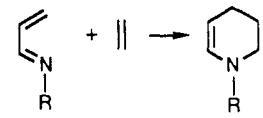
Introduction

A six-membered ring containing a nitrogen atom is a common structural feature in compounds of interest to synthetic chemists. Because of the efficiency of the Diels–Alder reaction for the preparation of six-membered rings with control of stereochemistry, much effort has been devoted to the development of aza analogues of this reaction for the preparation of nitrogen heterocycles.[2] The 1-azadienes are particularly attractive substrates for the hetero Diels–Alder reaction because, in addition to the normal advantages of the Diels–Alder reaction, they produce synthetically useful endocyclic enamine derivatives.

There are two problems that must be addressed in the development of 1-azadienes as reactants in the Diels–Alder reaction: (1) The reaction is less thermodynamically favorable than the all carbon dienes.[3] (2) The conditions necessary to induce the Diels–Alder reaction result in decomposition of the relatively sensitive endocyclic enamine functionality.[4]

There have been various creative solutions to overcome these difficulties for the development of a synthetically useful Diels–Alder reaction of 1-azadienes.[2] An early approach is the use of the *o*-quinone methide imine ring system.[5] Although restricted to the synthesis of quinoline derivatives, this reaction has been successfully incorporated into a scheme for the total synthesis of gephyrotoxin.[6] Other approaches to this problem have used activating substituents on the imine bond of these azadienes. These include the use of both electron-donating[7] or electron-withdrawing groups[8] on the nitrogen and electron-withdrawing groups on the carbon atom of the imine.[9] Among these approaches, the *N*-sulfonyl-1-azadienes have shown promise as reactive dienes in the Diels–Alder reaction.[8a]

Scheme I



We have previously observed that *N*-acyl-1-azadienes, generated as transient intermediates from *O*-acylhydroxamic acid derivatives under flash vacuum thermolysis conditions, will participate in the intramolecular version of the Diels–Alder reaction.[10] The utility of this approach was demonstrated by an efficient total synthesis of (−)-deoxynupharidine.[11]

(1) For a preliminary account of this work, see: Teng, M.; Fowler, F. W. *Tetrahedron Lett.* **1989**, *30*, 2481.

(2) *Hetero Diels-Alder Methodology in Organic Synthesis*; Boger, D. L., Weinreb, S. M., Eds.; Academic Press: San Diego, 1987.

(3) The primary reason that Diels–Alder reactions of 1-azadienes are less thermodynamically favorable than the all carbon dienes is because of the relative weakness of the carbon–nitrogen single bond in the product. The σ-bond strengths for ethane and methylamine are 85.8 and 84.8 kcal/mol, respectively,[3l] whereas the π-bond strengths for ethylene and methylene imine have been calculated to be 59.4 and 74.3 kcal/mol, respectively. (Shaw, R. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Wiley, New York, 1977; p 131.)

(4) Six-membered endocyclic enamine derivatives without substituents on the double bond are notoriously unstable. For example, attempts to prepare the simple *N*-methyl-Δ^2-piperidine usually result in formation of the dimer. (a) Martinez, S. J.; Joule, J. A. *Tetrahedron* **1978**, *34*, 3027. (b) Beeken, P.; Fowler, F. W. *J. Org. Chem.* **1980**, *45*, 1336.

(5) Burgess, E. M.;; McCullagh, L. *J. Am. Chem. Soc.* **1966**, *88*, 1580. With this example the problem of the thermodynamics of the reaction and the instability of the product are solved by the enamine double bond being part of an aromatic ring.

(6) Ito, Y.; Nakajo, E.; Nakatsuka, M; Saegusa, T. *Tetrahedron Lett.* **1983**, *24*, 2881.

(7) Poncin, B. S.; Frisque, A. M. H.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261.

(8) (a) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *11*, 1517. (b) Kim, J.-B.; Hall, H. K., Jr. *Macromolecules* **1988**, *21*, 1547.

(9) Whitesell, M. A.; Kyba, E. P. *Tetrahedron Lett*, **1984**, *25*, 2119.

(10) Cheng, Y.-S.; Lupo, A. T., Jr.; Fowler, F. W. *J. Am. Chem. Soc.* **1983**, *105*, 7696.

0022-3263/90/1955-5646$02.50/0

Table I

compd	R	X	4/5	yield, %	conditions
a	Ph	CH_2	>25:1	54[a]	refluxing benzene, 2 h
b	Ph	CH_2CH_2	15:1	32[a]	refluxing benzene, 12 h
c	Ph	O	8:1	61[b]	refluxing toluene, 12 h
d	CH_3	CH_2	19:1	58[b]	refluxing toluene, 9 h

[a] Yield calculated from compound 1. [b] Yield calculated from compound 2.

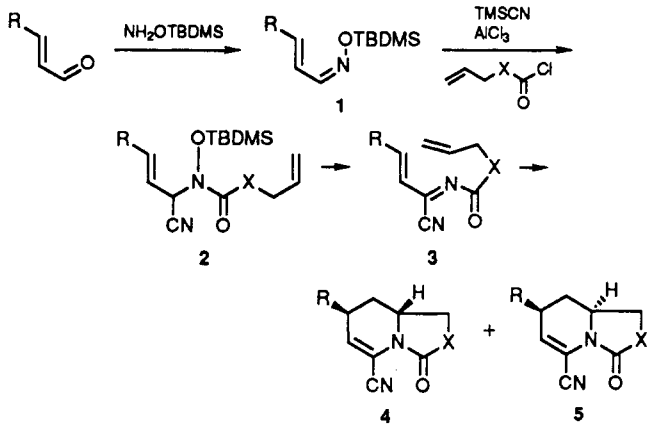
Although flash vacuum thermolysis has many advantages in synthetic chemistry, a difficulty of this method for inducing chemical reactions is that discrimination among possible reaction pathways at a kinetic branch, such as the Diels–Alder exo and endo reaction pathways, is lower at high temperature.[12] Our previous work demonstrated that it was the thermal elimination of the *O*-acylhydroxamic acid to produce *N*-acyl-1-azadienes and not the subsequent Diels–Alder reaction that was the slow step. This observation led us to consider the design of reactants that could be converted into *N*-acyl-1-azadienes at lower temperature. The α-cyanohydroxamic acids **2** appeared to be suitable candidates. In addition to activating α-hydrogen for the thermal elimination, there are other advantages to the cyano substituent. The electron-withdrawing properties of the α-cyano substituent should enhance the Diels–Alder reactivity of the azadiene **3** and the α-cyano enamine derivatives present in the Diels–Alder products should be useful for further structural elaboration.

Although *N*-acyl-α-cyanoimines appeared to have interesting synthetic potential, a search of the literature revealed only one report describing the preparation and some reactions of this functional group.[13] Unfortunately, the reported synthesis to the *N*-acyl-α-cyanoimines was not suitable for our purposes.

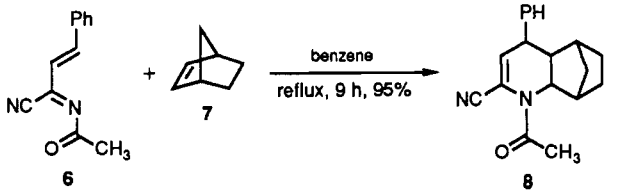
Intramolecular Diels–Alder Reactions. The *N*-acyl-α-cyanohydroxylamines needed for our studies appear to be unknown requiring the development of new synthetic methodology. After several unproductive attempts, the approach that proved to be successful initiates with an appropriate α,β-unsaturated aldehyde. Conversion of the aldehyde to the anti *O*-(*tert*-butyldimethylsilyl)-hydroxylamine derivative followed by treatment with trimethylsilyl cyanide, aluminum chloride, and the appropriate acid chloride produced the required α-cyano-hydroxamic acid derivatives **2**. These compounds proved to be relatively unstable with respect to the azadienes **3**. For example, attempted column chromatography of **2a** resulted in the formation of a yellow band on the silica gel column. This yellow band proved to be a mixture of the azadiene **3a** and the Diels–Alder adduct **4a**. A 61% conversion to the Diels–Alder adduct **4a** was realized by allowing the solution of the azadiene **3a** in $CDCl_3$ to stand at room temperature for 22 h. However, it was more convenient to effect this conversion by refluxing the azadiene **3a** in benzene for a short period of time. Only stereoisomer **4a** could be detected in the reaction mixture. Application of this scheme to other hydroxamic acid derivatives **2b–d** resulted in the formation of Diels–Alder adducts **4b–d** and **5b–d** (see Scheme II and Table I).

The structures assigned to the intramolecular Diels–Alder adducts are apparent from their spectral data. In particular, the vinyl enamine hydrogen occurs in the proton

Scheme II



Scheme III



NMR spectrum at δ 6.0–6.2 ppm. The magnitude of its *J* coupling with the adjacent hydrogen reveals the relative stereochemistry of the ring system. If the phenyl substituent is cis to the bridgehead hydrogen the coupling constant is approximately 5 Hz. If the phenyl group is trans to the bridgehead hydrogen then a smaller coupling constant of 2.1 Hz is observed.[10] Also, the infrared absorption of the cyano substituent in the Diels–Alder products has an extinction coefficient several times larger than the cyano substituent attached to saturated carbon which is consistent with it being attached to a double bond.[14]

The structure of **4a** was further established using X-ray crystallography.[15] The six-membered ring of **4a** assumes a half-chair conformation with the phenyl ring occupying a pseudoaxial position. Molecular mechanics calculations[16] on compound **4a** are in very close agreement with the crystallographically observed conformation.

Intermolecular Diels–Alder Reactions. Although the α-cyano substituent clearly enhances the Diels–Alder reactivity of the 1-azadiene, the appearance of the *N*-acyl-α-cyano-1-azadiene in the product mixture after chromatography indicates the α-cyano substituent has also stabilized the azadiene with respect to decomposition.[17] The stabilizing effect of the α-cyano substituent on the 1-azadiene allowed for their isolation and a study of their intermolecular Diels–Alder reactions, presently an unknown reaction for *N*-acyl-1-azadienes.[18]

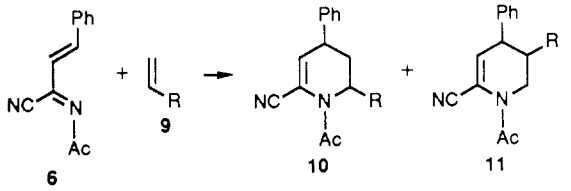
(11) Hwang, Y. C.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 2719.
(12) The ratio of the exo/endo reaction rates approaches $e^{\Delta S/R}$ as the temperature of a reacting system is increased.
(13) Fujimori, M.; Haruki, E.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 1372.
(14) Conley, R. T. *Infrared Spectroscopy*; Allyn and Bacon: Boston, 1972; p 122.
(15) All of the X-ray crystallography reported in this paper were performed by Yuh-Loo Chang, Department of Chemistry, State University of New York at Stony Brook. Full experimental details of the X-ray experiments will be published separately.
(16) The molecular mechanics calculations were performed using Macro Model version 2.5 distributed by C. Still of Columbia University.
(17) Previous attempts to prepare simple *N*-acyl-1-azadienes, such as *N*-acetyl-1-azadiene, using flash vacuum thermolysis were unsuccessful.[10] These simple *N*-acyl-1-azadienes appeared to be unstable and rapidly decomposed at room temperature. It is interesting to note that the *N*-methoxycarbonyl derivatives of 1-azadienes are sufficiently stable as to allow their isolation.
(18) A Diels–Alder reaction of a *N*-(methoxycarbonyl)-1-azadiene has been reported.[8b]

Table II

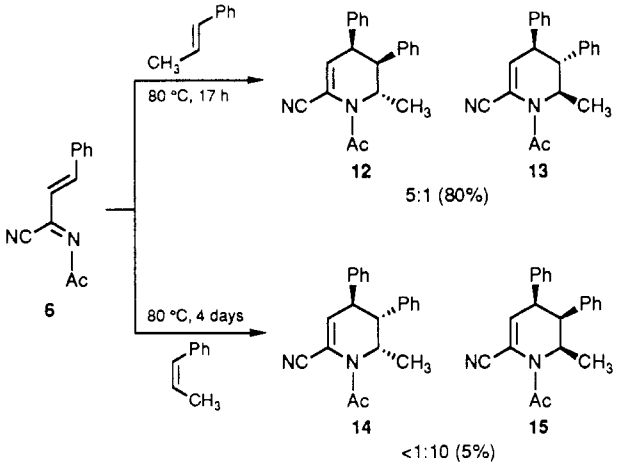
compd	R	product ratios[a] 10 (cis:trans)	11 (cis:trans)	yield, %	conditions
a	$CH_2CH_2CH_2CH_3$	3:8	3 (cis)	25	100 °C, 4 days
b	Ph	1 (cis)	6 (cis)	92	refluxing benzene, 48 h
c	OC_2H_5	cis isomer only	–	69	neat, rt,[b] 48 h
d	CO_2CH_3	–	8:1	92	neat, reflux, 24 h

[a] Cis and trans refer to the relative stereochemistry of the phenyl and R substituent. The cis isomer results from the reaction proceeding by the endo transition state and the trans results from the reaction proceeding by the exo transition state. [b] rt = room temperature.

Scheme IV



Scheme V



The *N*-acetyl-α-cyano-1-azadiene (**6**) was chosen for exploring the intermolecular Diels–Alder reactions. This compound was prepared by the treatment of acetyl chloride with oxime **1** according to Scheme II.

Because simple alkenes are notoriously poor dienophiles[19] it was our belief that their reaction with **6** would be an interesting test of the reactivity of this azadiene. Thus, heating norbornene with azadiene **6** in benzene for 9 h gave a 9:1:1 mixture of three Diels–Alder adducts in 95% yield (Scheme III). The major isomer could be separated from the minor isomers by chromatography and, from an analysis of its NMR spectrum, it was concluded that it was formed by a reaction pathway that was exo to the diene.

The reactivity of norbornene (**7**) led to an exploration the reaction of **6** with other dienophiles (see Table II). The data in Table II shows a remarkable range of reactivity for azadiene **6**, which reacts with a dienophile containing a strong electron-withdrawing group (**9d**), with a dienophile containing a strong electron-donating group (**9c**) and also reacts with dienophiles without significant activation (**9a** and **b**). The regio and stereochemistry of these Diels–Alder reactions provide further testimony to the unique reactivity of azadiene **6**.

The reaction of ethyl vinyl ether (**9c**) with **6** produced a single Diels–Alder adduct. Inspection of the proton NMR spectrum of the product clearly indicated that the reaction had given the regioisomer with the ethoxy substituent adjacent to the nitrogen atom.[20] However, the relative stereochemistry of the phenyl and ethoxyl substituents was not obvious from the spectral data. X-ray crystallography resolved this problem, demonstrating that **10a** possesses the cis stereochemistry as shown. These regio- and stereochemical results are consistent with those recently reported for analogous 1-azadienes.[8a]

From a consideration of the electron-deficient nature of the diene, the Diels–Alder reaction of **6** with methyl acrylate would be anticipated to be difficult. However, it is known that electron-deficient dienes also react with the electron-deficient dienophile, methyl acrylate.[21] Methyl acrylate and azadiene **6** gave a high yield of a single regioisomer as an 8:1 mixture of cis and trans stereoisomers. The regio- and stereochemistry of these products was apparent from proton NMR coupling constants and was confirmed by 2D NOE experiments.

The regiochemistry that was observed for methyl acrylate was also found for the reaction of azadiene **6** with styrene. The product consisted of an 6:1 mixture of regioisomers **11b** and **10b** with the major isomer being the one with the phenyl group derived from styrene on the carbon β to the heterocyclic nitrogen atom. The assigned regio- and stereochemistry of these compounds were suggested by their proton NMR spectra. However, it was desirable to confirm these assignments because of the unusual regiochemistry of these reactions. Single-crystal X-ray crystallography of the major product of the styrene reaction with azadiene **6** confirmed the assigned structure **11b**.

The crystallographic molecular structure for **11b** is in very good agreement with the molecular mechanics calculations.[16] These calculations further predict that **11b** is about 2 kcal/mol less stable than its isomer **10b**. This result suggested that the Diels–Alder reaction was under kinetic control. This assumption was supported by the observation that the minor isomer **10b** remained unchanged when subjected to the reaction conditions. It was not converted into the major isomer **11b**.

It was not surprising that 1-hexene was the least reactive and least selective among the dienophiles studied. Heating **6** with an excess of 1-hexene at 100 °C for 4 days gave a mixture of three compounds in relative low yield (25%). The regiochemistry of the major isomer is analogous to

(19) Wollwever, H. In *Methoden der Organischen Chemie (Houben-Weyl)*; Muller, E., Ed.; Thieme: Stuttgart, 1970; Teil 3, Vol. V/1c, p 981.

(20) Because of a significant steric interaction ($A^{1,3}$ strain) involving the *N*-acyl function the R substituent of the most stable conformation of **10** has the R substituent occupying the pseudoaxial position. This analysis is supported by molecular mechanics calculations[16] as well as X-ray crystallographic studies on **10b** and **c**. Thus, if the reaction proceeded by endo transition state the phenyl substituent on C-4 would be cis and also occupy the pseudoaxial position. If the reaction proceeded by an exo transition state the phenyl substituent would occupy the pseudoequatorial position. The coupling constant between the vinyl hydrogen and an equatorial hydrogen at C-4 is larger (3.8–3.9 Hz) than the coupling constant between the vinyl hydrogen and an axial hydrogen at C-4 (2.9–3.0 Hz).

(21) Two examples of electron deficient dienes reacting with methyl acrylate are α,β-unsaturated carbonyl compounds[26] and *trans*-penta-2,4-dienoic acid (Fleming, I.; Michael, J. P.; Overman, L. E.; Taylor, G. F. *Tetrahedron Lett.* **1978**, 1313).

ethyl vinyl ether but opposite to that observed for styrene and methyl acrylate.

In order to determine whether the Diels–Alder reaction conformed to the Alder cis principle, the reaction of **6** with *cis*- and *trans*-1-phenylpropenes was investigated. Each of these dienophiles gave different set of products. The *trans*-1-phenylpropene reacted (refluxing benzene, 17 h) to give the same regiochemistry as previously observed for styrene producing a mixture of Diels–Alder adducts **12** and **13** is a total yield of 80% (Scheme V).

In contrast to the trans isomer, the *cis*-1-phenylpropene was very slow to react with azadiene **6**. After heating for 4 days in refluxing benzene, only a 5% conversion to the Diels–Alder products **14** and **15** was observed (Scheme V).

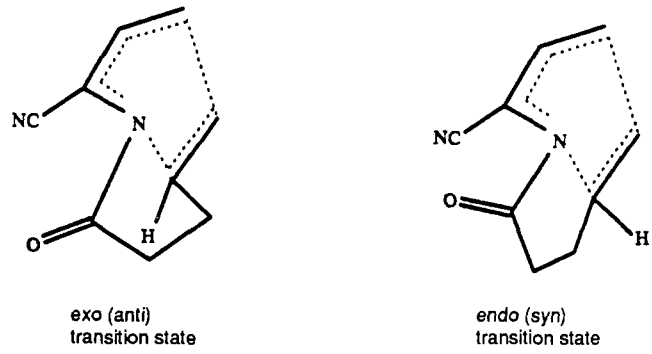


Figure 1. Exo and endo transition states.

Discussion

The high proportion of the reaction proceeding through the exo (anti) transition state in the intramolecular Diels–Alder reaction is unusual (Table I).[22] This observation is probably a result of two factors: (1) The α-cyano substitution, by a nonbonded interaction with the connecting side chain, raises the activation energy of the endo (syn) transition state.[22] (2) The stereoelectronic requirements of the developing amide function lowers the energy of the exo (anti) transition state. Molecular models as well as molecular mechanics calculations[16] clearly demonstrate that the constraints of the connecting chain prevent effective overlap between the nitrogen lone pair of electrons and the carbonyl group in the endo (syn) transition state.

The relative stereochemistry of the intermolecular Diels–Alder reaction shown in Table II are generally consistent with the Diels–Alder reactions of other dienes.[23] The endo transition state is favored with both electron-rich and electron-deficient dienophiles. However, there was little preference for the exo or endo transition state for 1-hexene. This would be anticipated because of the lack of any secondary overlap of the butyl substituent and the azadiene.

It is the regiochemistry of the Diels–Alder reactions of the α-cyano-*N*-acylazadienes that is unusual and without significant precedent. Attempts to understand the regiochemistry of the Diels–Alder reaction are as old as the reaction itself. Early approaches to rationalize the regiochemistry emphasized the importance of the dipolar or diradical nature of the reaction.[24,25] More recent analyses of this problem have emphasize the role of frontier molecular orbital theory.[26] All of these approaches have had varying degrees of success. Unfortunately, the difficulty of trying to understand the origins or the regiochemistry of the Diels–Alder reaction is that the observed product mixtures are the result of relatively small energy differences for the competing reaction pathways. It would be anticipated that the regiochemistry of the Diels–Alder reaction would be affected by relatively minor structural changes or changes in the reaction conditions. However, the persistency of certain regiochemical pattern have supported efforts directed toward their understanding.

It is informative to compare our results with those previously reported for α,β-unsaturated carbonyl compounds since there is an electronic analogy between the oxa and the azadienes. They both have an unshared electron pair and, because of the *N*-acyl function, the heteroatoms have similar electronegativities. The Diels–Alder reactions of 1-oxadienes are well known. These reactions have been valuable in total synthesis and have been the focus of theoretical studies.[2,23,27]

Acrolein, a heterodiene analogous to **6** has also been reported to react with the dienophiles shown in Table II.[28] However, these Diels–Alder reactions, with the exception of ethyl vinyl ether, proceeded in extremely poor yield. For example, acrolein and methyl acrylate, when heated at 195 °C for 1 h, gave only a 3% yield of the Diels–Alder product.

There is a significant difference between the regiochemistry of the Diels–Alder reactions of acrolein and azadiene **6**. Acrolein reacts with *all* of the dienophiles shown in Table II to give the same regiochemistry, that is, the substituent on the dienophile always occurs α to the heterocyclic oxygen atom. In contrast, only ethyl vinyl ether and 1-hexene react with azadiene **6** to give the regiochemistry that was observed with acrolein. Both styrene and methyl acrylate react with **6** to give the regioisomeric adduct with the substituent on the dienophile β to the heterocyclic nitrogen atom.

Based on the experimental results reported in this paper, the following working mechanistic hypothesis for the Diels–Alder reactions of α-cyano-1-azadienes is proposed. A concerted, asynchronous reaction pathway is consistent with the reaction of **6** with the *cis*- and *tran*-1-phenylpropenes (Scheme V) and the unsymmetrical nature of the azadiene. The transition state for this Diels–Alder reaction, like all pericyclic transition states, can be described by a series of both dipolar and diradical resonance structures (see Figure 2).[29] Because of the presence of the nitrogen in the diene, more stable dipolar electronic configurations (i.e. **16**) would result by bond formation between the carbon atoms 5 and 4. This bond formation would be favored because it allows for placement of th

(22) (a) Craig, D. *J. Chem. Soc. Rev.* **1987**, *16*, 187. (b) See also ref 34.
(23) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651.
(24) (a) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 16. (b) Woodward, R. B.; Katz, T. J. *Tetrahedron* **1959**, *5*, 70.
(25) More recently Dewar has proposed that Diels–Alder reactions in general proceed via very unsymmetrical transition states, close to biradicals in structure. Because these transition states are singlet closed-shell species derived from a biradical by a weak interaction between the radical centers the term *biradicaloid* has been introduced to distinguish these species from true biradicals. It is further proposed that these are polarizable species with large contributions from a corresponding zwiterionic electronic configurations. Thus, the ability of a substituent to stabilize both radical and polar centers is proposed to play a role in determining the regiochemistry of the Diels–Alder reaction. (Dewar, M. J. S.; Olivella, S.; Stewart, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 5771).
(26) (a) Kahn, S. D.; Pau, C. F.; Overman, L. E.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7381. (b) Houk, K. N. In *Pericyclic Reactions*; Marchand, A. P. N., Lehr, R. E., Eds.; Academic Press: New York, 1977; Vol. II, p 181 ff. (c) Eisenstein, O.; Lefour, J. M.; Anh, N. T.; Hudson, R. F. *Tetrahedron* **1977**, *33*, 523. (d) Fleming, I. *Frontier Orbitals and Organic Reactions*; Wiley: New York, 1976.
(27) See ref 2, pp 171–4.
(28) (a) Smith, C. W.; Norton, D. G.; Ballard, S. A. *J. Am. Chem. Soc.* **1951**, *73*, 5267. (b) *Ibid.* **1951**, *73*, 5270. (c) *Ibid.* **1951**, *73*, 5273.
(29) The degree of asynchronicity and the relative importance of diradical electronic descriptions of the transition state for the Diels–Alder reaction has been the focus of recent debate in the literature. For a recent and leading reference, see: Houk, K. N.; Loncharich, R. J.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 9172.

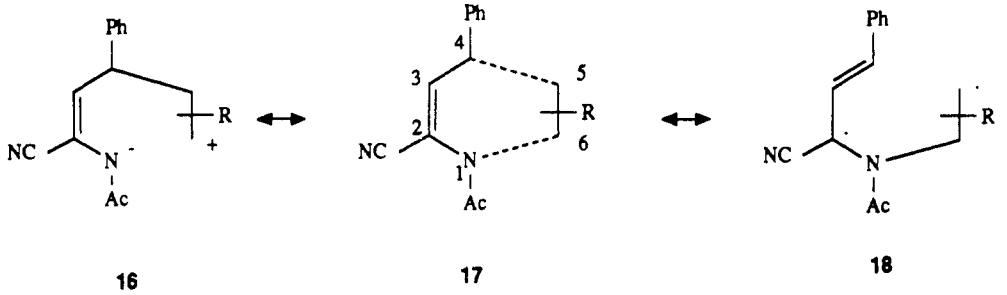


Figure 2. Electronic description of the Diels–Alder transition state.

negative charge on the electonegative nitrogen atom.

The most stable diradical electronic configurations results from bond formation between the nitrogen atom of the azadiene and the carbon atom of the dienophile (**18**). This bond formation allows for electronic configurations with the radical center adjacent to the phenyl substituent at C-4 and on C-2 of the diene. The electronic configuration with the radical center adjacent to the electron-donating nitrogen atom and the electron-withdrawing nitrile function are known to be particularly stable (capto-dative effect),[30] suggesting that the transition state for these Diels–Alder reactions may have considerable radical character.

The regiochemistry of the Diels–Alder reactions reported in Table II can be qualitatively understood by evaluating the relative stabilities of the two transition states resulting from the R substituent being on C-5 or C-6 (Figure 2). For this analysis homolytic bond energies are used to estimate the relative ability of a substituent to stabilize a radical center[31] and σ^+ values are used to estimate the relative ability of a substituent to stabilize a cationic center.[32]

The relative importance of the diradical vs dipolar character to the stability of the two transition states is provided by the dienophile styrene (R = Ph). The predominance of regioisomer **11b** reflects the greater stability of the transition state with the phenyl substituent being on C-5. If Figure 2 is a reasonable description of the transition state, it would have a large degree of diradical character.

An alkyl group is slightly more effective at stabilizing a cationic center but less effective at stabilizing a radical center than a phenyl group. An increase of the regioisomer **10a** would be predicted for hexene compared to styrene as a dienophile.

Compared to phenyl, an alkoxy group is analogous to an alkyl group except that it is much more effective at stabilizing a cationic vs a radical center. This fact is in agreement with the observation that only regioisomer **10c** was detected in the reaction mixture.

The reaction of methyl acrylate with azadiene **6** is particularly interesting. The relative ability of a carbonyl group to stabilize cationic vs radical centers is completely consistent with **11d** being the only regioisomer isolated from the reaction mixture.

All of the results reported in this paper suggest that the α-cyano-*N*-acyl-1-azadienes are very reactive dienes in the Diels–Alder reaction. Because the α-cyano substituent would further lower the LUMO of the electron-deficient *N*-acyl-1-azadienes, an increased reactivity was anticipated.[33] However, it was not anticipated that the intramolecular Diels–Alder reaction of **3a** would occur at room temperature[34] and that **6** would react with such a wide range of dienophiles.

Azadiene **6** reacts readily with dienophiles containing either an electron-withdrawing (**9d**) or a electron-donating group (9c). Only 1-hexene showed a reluctance to react with azadiene **6**, requiring heating to 100 °C for 4 days. Thus, it appears that the cyano substituent has further enhanced the reactivity of these *N*-acyl-1-azadienes by possibly increasing the importance of radical electronic configurations for stabilizing the transition state.

In summary, the α-cyano-1-azadienes have been observed to be reactive substrates in the Diels–Alder reaction. This process can provide an extremely efficient method for the preparation of synthetically useful piperidine derivatives. The regiochemistry of the intermolecular Diels–Alder reactions of 1-azadiene **6** are most readily accommodated by invoking a *single* transition state whose electronic character, dipolar or diradical, depends upon the nature of the substituents.

Experimental Section

***O*-(tert-Butyldimethylsilyl)cinnamaldoxime (1a).** To a solution of anti cinnamaldoxime (0.344 g, 2.34 mmol) and 4-(dimethylamino)pyridine (0.029 g, 0.24 mmol) in CH_2Cl_2 (15 mL) was added triethylamine (0.36 mL, 2.57 mmol). The mixture was cooled in an ice bath, and *tert*-butyldimethylsilyl chloride (0.387 g, 2.57 mmol) in CH_2Cl_2 (5 mL) was added. The reaction mixture was allowed to warm to room temperature. After thin-layer analysis indicated the starting material had been consumed (3 h), the reaction mixture was concentrated in vacuo and treated with hexanes. The undissolved TEA·HCl salt was removed by filtration through Celite, and the clear organic layer was concentrated in vacuo to afford pale yellow oil. Purification by column

(30) It has been proposed that there is a synergistic effect of the electron-donating and -withdrawing groups providing additional stabilization, often referred to as the captodative effect (Viehe, H. G.; Merenyi, R.; Stella, L.; Janousek, Z. *Angew. Chem.* **1979**, *91*, 982). For a recent paper with an excellent discussion on this controversial proposal, see: Bordwell, F. G.; Lynch, T.-Y. *J. Am. Chem. Soc.* **1989**, *111*, 7558.

(31) McMillen, D. F.; Golden, D. M. *Ann. Rev. Phys. Chem.* **1982**, *33*, 483.

(32) Exner, O. In *Correlation Analysis in Organic Chemistry*; Chapman, N. B., Shorter, J., Eds.; Research Studies Press: Chichester, 1982; p 439.

(33) Our work on the intramolecular ene reaction also demonstrated that the pericyclic reactivity of an *N*-acylimine could be enhanced by an electron-withdrawing group ($CO_2C_2H_5$) at the α-position. (Lin, J.-M.; Koch, K.; Fowler, F. W. *J. Org. Chem.* **1986**, *51*, 167).

(34) Ciganek, E. *Org. React.* **1984**, *32*, 1. Normally the intramolecular Diels–Alder reaction of an unactivated dienophile requires high temperature.

(35) **General.** Melting points were recorded in Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded with QE-300 instruments using tetramethylsilane (Me_4Si) as internal standard and $CDCl_3$ or CD_3CN as the solvent. Coupling constants are reported in hertz. All chemical shifts are reported on ppm units from the internal standard and described as being either singlet (s), doublet (d), triplet (t), quartet (q), quintet (q'), broad (b), or multiplet (m). Column chromatography was performed on silica gel 60, 200–400 mesh. IR spectra were measured on a Perkin-Elmer Model 727 infrared spectrophotometer and calibrated by polystyrene (1601 cm^{-1}). The thin-layer chromatography (TLC) was performed on Analtech thin-layer silica gel GF plates. Low-resolution mass spectra (MS) were recorded on a Hewlett-Packard 5980A spectrometer. High-resolution mass spectra (HRMS) were recorded on an AEI MS-80 spectrometer. Elemental analyses were performed by MHW laboratories, Phoenix, AZ.

chromatography (ethyl acetate/hexanes (1:8)) gave **1a** as a colorless oil (0.601 g, 98%): ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 6 H), 0.98 (s, 9 H), 6.83–6.88 (d, 1 H), 7.30–7.60 (m, 7 H); IR (neat) 2945, 1745, 1250, 920 cm^{-1}; MS *m/e* 262 (M^+ + 1), 261 (M^+), 246, 205, 204 (base peak), 130, 103.

Anal. Calcd for $C_{15}H_{23}NOSi$: C, 68.91; H, 8.73; N, 5.36. Found: C, 68.75; H, 9.01; N, 5.21.

***O*-(*tert*-Butyldimethylsilyl)crotonaldoxime (1d).** To crotonaldehyde (1.2 mL, 15 mmol) and molecular sieves (5.7 g, 4 Å)[36] in CH_2Cl_2 (10 mL) in an ice bath was added a solution of *O*-(*tert*-butyldimethylsilyl)hydroxylamine[37] (1.684 g, 11.44 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The molecular sieves were removed through filtration, and the reaction mixture was concentrated in vacuo. Purification of the product using column chromatography (ethyl acetate/hexanes (1:8)) gave **1d** as a colorless oil (1.82 g, 79.8%, 1:1 mixture of the anti and syn isomers): ^{1}H NMR (anti) δ 0.18 (s, 6 H), 0.95 (s, 9 H), 1.85–1.88 (dd, J_1 = 1.7, J_2 = 6.8, 3 H), 6.09–6.18 (dq, J_1 = 6.8, J_2 = 15.7, 1 H), 6.74–6.85 (ddq, J_1 = 1.6, J_2 = 9.2, J_3 = 15.7, 1 H), 7.14–7.18 (d, J = 9.3, 1 H); ^{1}H NMR (syn) δ 0.16 (s, 6 H), 0.93 (s, 9 H), 1.82–1.85 (dd, J_1 = 1.5, J_2 = 6.6, 3 H), 5.94–6.06 (dq, J_1 = 6.8, J_2 = 15.5, 1 H), 6.17–6.25 (ddq, J_1 = 1.5, J_2 = 6.7, J_3 = 15.5, 1 H), 7.78–7.81 (d, J = 9.6, 1 H); IR (neat of anti and syn) 2950, 2940, 2860, 1650, 1455, 1255, 970, 930, 840, 785 cm^{-1}; MS *m/e* 200 (M^+ + 1), 199 (M^+), 184, 142 (base peak).

Anal. Calcd for $C_{10}H_{21}NOSi$: C, 60.25; H, 10.62; N, 7.03. Found: C, 60.41; H, 10.70; N, 6.87.

1,7,8,8a-Tetrahydro-(7*S,8a*S**)-5-cyano-7-phenyl-3-(2*H*)-indolizinone (4a).** To a solution of trimethylsilyl cyanide (0.4 mL, 3.00 mmol) and catalytic amount of anhydrous $AlCl_3$ (0.12 mmol) in anhydrous CH_2Cl_2 (5 mL) at room temperature under nitrogen was added a solution of *O*-(*tert*-butyldimethylsilyl)-cinnamaldoxime (**1a**) (0.601 g, 2.30 mmol) in anhydrous CH_2Cl_2 (2 mL). To this reaction mixture was added a solution of 4-pentenoyl chloride (0.355 g, 3.0 mmol) in anhydrous CH_2Cl_2 (2 mL). After 12 h the reaction mixture was concentrated in vacuo, and the residue was treated with small amount of diethyl ether. The precipitate was removed by filtration through Celite. Column chromatography of the reaction mixture (ethyl acetate/hexanes (1:5)) gave a yellow oil which was dissolved in anhydrous benzene and used without further purification. Heating the benzene solution at reflux for 2 h produced, after purification by column chromatography (ethyl acetate/hexanes (1:1)), **4a** as colorless crystals from ethyl acetate (0.30 g, 54% from **1a**): mp 133–134 °C; ^{1}H NMR ($CDCl_3$) δ 1.65–1.73 (m, 1 H), 1.83–1.94 (m, 1 H), 2.13–2.19 (m, 2 H), 2.46–2.51 (m, 2 H), 3.58–3.68 (m, 1 H), 3.77–3.80 (t, J = 5.4, 1 H), 6.08–6.10 (d, J = 5.0, 1 H), 7.13–7.39 (m, 5 H); IR (KBr) 3070, 2220, 1705, 1615, 1400 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 25.0, 30.4, 36.1, 38.8, 51.0, 111.1, 113.6, 126.9, 126.9, 127.7, 128.5, 142.3, 171.0; MS *m/e* 238 (M^+, base peak), 183, 155, 140, 128, 115, 91, 77, 55, 51.

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.76. Found: C, 75.51; H, 5.95; N, 11.67.

1,2,3,8,9,9a-Hexahydro-(8*S,9a*S**)-6-cyano-8-phenyl-4-quinolizinone (4b).** Using the same procedure as was used for the preparation of **4a**, **1b** gave **4b** as colorless crystals (32% from **1b**): mp 131.5–132.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.41–1.53 (m, 1 H), 1.65–1.68 (m, 1 H), 2.08–2.71 (m, 4 H), 3.41–3.50 (m, 1 H), 3.69–3.74 (m, 1 H), 6.23–6.24 (d, J = 5.21, 1 H), 7.15–7.55 (m, 5 H); IR (KBr) 2925, 2220, 1675, 1390 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 18.8, 29.5, 32.9, 38.1, 38.2, 51.4, 114.4, 115.0, 127.2, 127.9, 128.8, 131.0, 142.9, 167.8; MS *m/e* 253 (M^+ + 1), 252 (M^+, base peak), 223, 196, 181.

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.35; N, 11.11. Found: C, 75.97; H, 6.50; N, 11.18.

***O*-(*tert*-Butyldimethylsilyl)-*N*-(1-cyanocinnamyl)-*N*-(carballyloxy)hydroxylamine (2c).** To a solution of trimethylsilyl cyanide (0.17 mL, 1.27 mmol) and catalytic amount of anhydrous $AlCl_3$ (0.1 mmol) in 5 mL of CH_2Cl_2 at room temperature under nitrogen was added a solution of **1a** (255 mg, 0.98 mmol) in anhydrous CH_2Cl_2 (2 mL). To this reaction mixture was added allyl chloroformate (0.135 mL, 1.27 mmol). The reaction mixture was allowed to stir for 72 h. The solvent was removed in vacuo, and the residue was dissolved in small amount of diethyl ether. The precipitate was removed by filtration through Celite, and the clear solution, after removal of the solvent, was purified by column chromatography (ethyl acetate/hexanes (1:20)) to afford **2c** as a pale yellow oil (153 mg, 42%): ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3 H), 0.24 (s, 3 H), 0.94 (s, 9 H), 4.69–4.71 (d, J = 5.9, 2 H), 5.28–5.32 (dd, J_1 = 0.96, J_2 = 10.2, 1 H), 5.35–5.41 (dq, J_1 = 1.4, J_2 = 17.2, 1 H), 5.70–5.73 (dd, J_1 = 1.4, J_2 = 6.2, 1 H), 5.87–5.96 (m, 1 H), 6.14–6.21 (dd, J_1 = 6.2, J_2 = 15.9, 1 H), 6.88–6.94 (dd, J_1 = 1.3, J_2 = 15.9, 1 H), 7.30–7.45 (m, 5 H); IR (neat) 2960, 2930, 2860, 1720, 1250, 835 cm^{-1}; MS *m/e* 315, 271, 248, 204, 142, 131, 115, 75 (base peak), 73.

1,7,8,8a-Tetrahydro-(7*S,8a*R**)-2-oxa-5-cyano-7-phenyl-3(2*H*)-indolizinone (4c) and 1,7,8,8a-Tetrahydro-(7*S**,8a*S**)-2-oxa-5-cyano-7-phenyl-3(2*H*)-indolizinone (5c).** A solution of **2c** (55 mg, 0.148 mmol) in dry toluene (5 mL) was refluxed for 1 h. The heat was removed, and silica gel (50 mg) was added. The solution turned yellow and was refluxed for another 8 h. The silica gel was removed by filtration, and the toluene was removed in vacuo. The residue was purified by column chromatography (ethyl acetate/hexanes (1/1)) to afford two products as colorless crystals (22 mg, 61%, 8:1 mixture of **4c** and **5c**). Compound **4c**: mp 139.5–141 °C; ^{1}H NMR ($CDCl_3$) δ 2.00–2.16 (m, 2 H), 3.82–3.95 (m, 2 H), 4.00–4.05 (t, J = 8.2, 1 H), 4.50–4.56 (t, J = 8.5, 1 H), 6.16–6.17 (d, J = 5.3, 1 H), 7.15–7.50 (m, 5 H); IR (KBr) 3070, 2950, 2235, 1760, 1615, 1415, 1265, 1085, 1005, 855 cm^{-1}; MS *m/e* 240 (M^+), 195, 181, 168, 154, 140, 128, 115, 103, 91, 77, 51.

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.00; N, 11.67. Found: C, 70.06; H, 5.07; N: 11.50.

Compound **5c** (colorless oil): ^{1}H NMR ($CDCl_3$) δ 1.73–1.85 (m, 1 H), 2.35–2.41 (m, 1 H), 3.74–3.81 (m, 1 H), 4.03–4.08 (dd, J_1 = 7.5, J_2 = 8.7, 1 H), 4.22–4.32 (m, 1 H), 4.61–4.67 (t, J = 8.5, 1 H), 6.05–6.06 (d, J = 2.1, 1 H), 7.10–7.50 (m, 5 H); IR (KBr) 3062, 3027, 2921, 2231, 1770, 1620, 1417, 1261, 1071, 763 cm^{-1}; MS *m/e* 240 (M^+, base peak), 195, 181, 168, 155, 154, 140, 129, 128, 115, 103, 91, 77; HRMS calcd for $C_{14}H_{12}N_2O_2$ 240.0900, found 240.0897.

O-(*tert*-Butyldimethylsilyl)-*N*-(1-cyano-2-butenyl)-*N*-4-pentenoylhydroxylamine (2d). Using the same procedure as was used for the preparation of **2c**, **1d** gave **2d** as colorless oil (71%). This product was purified by column chromatography (ethyl acetate/hexanes, (1:15)): ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 3 H), 0.28 (s, 3 H), 0.98 (s, 9 H), 1.77–1.80 (dt, J_1 = 1.5, J_2 = 6.6, 3 H), 2.34–2.41 (m, 2 H), 2.52–2.57 (m, 2 H), 4.99–5.08 (m, 2 H), 5.46–5.55 (ddq, J_1 = 1.7, J_2 = 5.8, J_3 = 15.4, 1 H), 5.68–5.71 (dq, J_1 = 1.3, J_2 = 5.8, 1 H), 5.77–5.90 (m, 1 H), 5.98–6.10 (m, 1 H); IR (neat) 2980, 2950, 1700, 1480, 1270, 850 cm^{-1}; MS *m/e* 282, 251, 200, 172, 142, 100, 83, 65, 63.

1,7,8,8a-Tetrahydro-(7*S,8a*S**)-5-cyano-7-methyl-3-(2*H*)-indolizinone (4d).** Using the same procedure as was used for the preparation of **4c**, **2d** gave **4d** as colorless crystals (58%): mp 80.5–81.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.11–1.14 (d, J = 7.3, 3 H), 1.56–1.77 (m, 2 H), 1.86–1.91 (m, 1 H), 2.29–2.60 (m, 4 H), 3.66–3.76 (m, 1 H), 5.97–5.99 (dd, J = 1.0, J' = 5.2, 1 H); IR (neat) 2970, 2897, 2240, 1715, 1625, 1420 cm^{-1}; MS *m/e* 176 (M^+), 161, 133, 121 (base peak), 119, 106, 94, 93, 84, 55; HRMS calcd for $C_{10}H_{12}N_2O$ 176.0951, found 176.0951.

***N*-Acetyl-2-cyano-4-phenyl-1-aza-1,3-butadiene (6).** To a solution of trimethylsilyl cyanide (0.1 mL, 0.75 mmol) and anhydrous $AlCl_3$ (9.2 mg, 0.97 mmol) in anhydrous CH_2Cl_2 (3 mL) at room temperature under nitrogen was added a solution of **1a** (154 mg, 0.59 mmol) in anhydrous CH_2Cl_2 (2 mL). To this reaction mixture was added acetyl chloride (0.05 mL, 0.76 mmol). The reaction mixture turned green-yellow immediately and returned to colorless within a few seconds. The reaction mixture was stirred at room temperature for 12 h. The solvent was removed in vacuo, and the pale yellow oil was dissolved in small amount of diethyl ether. The precipitate was removed by filtration. The clear solution was concentrated in vacuo and purified by column chromatography (ethyl acetate/hexanes (1:5)) to yield **6** as a yellow solid (75 mg, 63% from **1a**): mp 45–47.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3 H), 6.80–6.86 (d, J = 16.5, 1 H), 7.45–7.60 (m, 5 H), 7.65–7.71 (d, J = 16.5, 1 H); IR (neat) 3060, 2920, 2225, 1708, 1600, 1250, 1185, 963, 750 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 24.6, 104.9, 122.5, 128.7, 129.3, 131.8, 133.5, 148.7, 152.1, 183.4; MS *m/e* 198 (M^+),

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183, 179, 157, 156, 155, 140, 129, 128, 102, 77; HRMS calcd for $C_{12}H_{10}N_2O$ 198.0794, found 198.0794.

***N*-Acetyl-1,2,3,4-tetrahydro-(2*R**,4*S**)-2-ethoxy-4-phenyl-6-cyanopyridine (10c).** A solution of **6** (124 mg, 0.626 mmol) in freshly distilled ethyl vinyl ether (1.2 mL, 12.55 mmol) was stirred at room temperature under nitrogen for 48 h. The ethyl vinyl ether was removed in vacuo, and the residue was purified by column chromatography (ethyl acetate/hexanes (1:1)) to afford **10c** as colorless crystals (116 mg, 69%): mp 92.5–94 °C; ^{1}H NMR ($CDCl_3$) δ 1.11–1.16 (t, J = 6.99, 3 H), 2.36 (s, 3 H), 2.36–2.45 (m, 2 H), 3.36–3.48 (m, 1 H), 3.50–3.62 (m, 2 H), 5.71 (b, 1 H), 6.50–6.51 (d, J = 3.39, 1 H), 7.20–7.40 (m, 5 H); IR (KBr) 3000, 2940, 2240, 1680, 1420, 1400, 1315, 90, 1080, 950 cm^{-1}; MS m/e 270 (M$^+$), 228, 199, 183, 182, 181, 155, 105.

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.11; H, 6.67; N, 10.37. Found: C, 70.99; H, 6.89; N, 10.36.

***N*-Acetyl-1,2,3,4-tetrahydro-(2*S**,3*S**,4*S**)-2,3-(1′,3′-cyclopentanediyl)-4-phenyl-6-cyanopyridine (8) and Its Two Diastereomers.** A solution of **6** (56.2 mg, 0.284 mmol), norbornene (135 mg, 1.43 mmol), and anhydrous benzene (1 mL) was refluxed for 7 h. After concentration in vacuo, the reaction mixture was purified by column chromatography (ethyl acetate/hexanes (1:5)) to yield 64.9 mg (78.3%) of **8** and 13.9 mg (16.8%) of two diastereomers of **8**. The ratio of the two minor products is 1:1 (by ^{1}H NMR). Compound **8**: mp 131.5–132 °C; ^{1}H NMR (CD_3CN) δ 1.18–1.28 (m, 3 H), 1.49–1.54 (dt, J_1 = 1.79, J_2 = 8.57, 2 H), 1.84–1.89 (dt, J_1 = 1.93, J_2 = 10.62, 1 H), 2.23 (s, 3 H), 2.30–2.31 (m, 1 H), 2.52–2.55 (m, 2 H), 3.70–3.72 (d, J = 7.8, 1 H), 4.04–4.07 (d, J = 8.55, 1 H), 6.60–6.63 (d, J = 7.79, 1 H), 7.18–7.38 (m, 5 H); IR (KBr) 2969, 2871, 2228, 1657, 1493, 1396, 1338, 1318, 1184, 967 cm^{-1}; MS m/e 293 (M$^+$ + 1), 292 (M$^+$), 250, 249, 183, 182, 181, 173, 155, 140.

Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.08; H, 6.85; N, 9.59. Found: C, 78.21: H, 6.84; N, 9.51.

The Two Isomers of 8 (colorless oil). The mixture of the two isomers showed only one spot by thin-layer chromatography: ^{1}H NMR ($CDCl_3$) δ 0.90–1.05 (m), 1.25–1.40 (m), 1.61–1.86 (m), 2.02–2.05 (m), 2.33 (s), 2.37 (s), 2.46 (m), 2.59 (m), 2.60–2.64 (m), 3.59–3.61 (m), 3.62–3.70 (m), 3.90–3.93 (d, J = 8.23), 4.59–4.62 (d, J = 9.28), 6.69–6.70 (d, J = 2.87), 6.84–6.85 (d, J = 3.61), 7.20–7.45 (m); IR (neat) 2960, 2874, 2223, 1673, 1619, 1405, 1329, 1267, 967, 734, 704 cm^{-1}; MS m/e 292 (M$^+$), 251, 250, 249, 204, 183, 181, 155, 131, 116, 105, 103, 91; HRMS calcd for $C_{19}H_{20}N_2O$ 292.1577, found 292.1575.

***N*-Acetyl-1,2,3,4-tetrahydro-(3*S**,4*S**)-3,4-diphenyl-6-cyanopyridine (11b) and *N*-Acetyl-1,2,3,4-tetrahydro-(2*S**,4*S**)-2,4-diphenyl-6-cyanopyridine (10b).** A solution of **6** (28.8 mg, 0.145 mmol), freshly distilled styrene (0.5 mL, 4.36 mmol), and anhydrous benzene (1 mL) was refluxed for 48 h. After concentration, the reaction mixture was purified by column chromatography (ethyl acetate/hexanes (1:2)) to afford 5.7 mg (13%) of **10b** and 34.5 mg (78.8%) of **11b**. Compound **11b**: mp 153.5–155 °C; ^{1}H NMR (CD_3CN) δ 2.20 (b, 3 H), 3.57–3.63 (ddd, J_1 = 3.44, J_2 = 6.32, J_3 = 9.56, 1 H), 3.79–3.88 (dd, J_1 = 9.46, J_2 = 12.76, 1 H), 3.92–4.00 (d, J = 12.87, 1 H), 4.06–4.09 (dd, J_1 = 4.77, J_2 = 6.1, 1H), 6.40–6.42 (d, J = 4.53, 1 H), 6.80–7.20 (m, 10 H); IR (KBr) 3047, 2886, 2228, 1666, 1627, 1491, 1390, 1346, 1114, 1032, 995, 951, 871 cm^{-1}; MS m/e 303 (M$^+$ + 1), 302 (M$^+$), 260, 212, 181, 155, 140, 105, 104, 103, 91.

Anal. Calcd for $C_{20}H_{18}N_2O$: C, 79.43; H, 6.01; N, 9.27. Found: C, 79,27; H, 6.05; N, 9.31.

Compound **10b** (colorless oil): ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3 H), 2.28–2.38 (m, 1 H), 2.67–2.75 (m, 1 H), 3.58–3.63 (m, 1 H), 5.33–5.38 (t, J = 6.93, 1 H), 6.91–6.94 (d, J = 2.54, 1 H), 7.08–7.26 (m, 10 H); IR ($CDCl_3$) 2225, 1678, 1494, 1451, 1398, 1323, 1186, 1103, 1031, 911 cm^{-1}; MS m/e 302 (M$^+$), 260, 259, 220, 181, 169, 145, 142, 140, 104; HRMS calcd for $C_{20}H_{18}N_2O$ 302.1420, found 302.1422.

***N*-Acetyl-1,2,3,4-tetrahydro-(2*S**,3*S**,4*S**)-2-methyl-3,4-diphenyl-6-cyanopyridine (12) and *N*-Acetyl-1,2,3,4-tetrahydro-(2*R**,3*R**,4*S**)-2-methyl-3,4-diphenyl-6-cyanopyridine (13).** A solution of **6** (33.8 mg, 0.171 mmol), *trans*-β-methylstyrene (1 mL, 7.71 mmol), and dry benzene (2 mL) was refluxed for 17 h. The benzene was removed in vacuo, and the residue was purified by column chromatography (ethyl acetate/hexanes (1:2)) to yield 36 mg (67%) of **12** and 7.0 mg (13%) of **13**. Compound **13** (colorless oil): ^{1}H NMR (CD_3CN) δ 1.18–1.20 (d, J = 6.64, 3 H), 2.20 (s, 3 H), 3.23–3.26 (t, J = 5.67, 1 H), 3.85–3.88 (dd, J_1 = 3.73, J_2 = 5.95, 1 h), 4.20–4.24 (m, 1 H), 6.88–6.89 (d, J = 3.79, 1 H), 7.20–7.40 (m, 10 H); IR (CH_2Cl_2) 3060, 3028, 2226, 1674, 1619, 1495, 1452, 1402, 1325, 1267, 1202, 1139, 1031, 987 cm^{-1}; MS m/e 317 (M$^+$ + 1), 316 (M$^+$), 274, 230, 223, 222, 119, 118, 117, 115, 91; HRMS calcd for $C_{21}H_{20}N_2O$ 316.1577, found 316.1577.

Compound **12**: mp 157.5–158 °C; ^{1}H NMR (CD_3CN) δ 1.52–1.54 (d, J = 6.81, 3 H), 2.20 (b, 3 H), 3.54–3.57 (dd, J_1 = 0.78, J_2 = 7.62, 1 H), 4.25 (b, 1 H), 4.35–4.38 (dd, J_1 = 3.05, J_2 = 7.19, 1 H), 6.74–6.75 (dd, J_1 = 0.79, J_2 = 2.97, 1 H), 6.89–7.22 (m, 10 H); IR (KBr) 3059, 3024, 2934, 2230, 1667, 1402, 1332, 1246, 1125, 1032, 988, 770, 701 cm^{-1}; MS m/e 317 (M$^+$ + 1), 316 (M$^+$), 274, 178, 140, 119, 118, 117, 115, 91.

Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.71; H, 6.37; N, 8.86. Found: C, 76.71; H, 6.46; N, 8.35.

***N*-Acetyl-1,2,3,4-tetrahydro-(2*S**,3*R**,4*S**)-2-methyl-3,4-diphenyl-6-cyanopyridine (14) and *N*-Acetyl-1,2,3,4-tetrahydro-(2*R**,3*S**,4*S**)-2-methyl-3,4-diphenyl-6-cyanopyridine (15).** A solution of **6** (267 mg, 1.35 mmol), *cis*-β-methylstyrene (1.5 mL, 11.56 mmol), and anhydrous benzene (3.5 mL) was refluxed. The reaction proceeded slowly, and most of the azadiene **6** still remained after 4 days. The benzene was removed, and the rest of the azadiene **6** was recovered from the reaction mixture by column chromatography (ethyl acetate/hexanes (1:5)). Also, from the column chromatography (ethyl acetate/hexanes (1:2)) were obtained 2.1 mg (0.5%) of **14** and 17.4 mg (4%) of **15**. Compound **15** (colorless oil): ^{1}H NMR ($CDCl_3$) δ 1.33–1.36 (d, J = 6.9, 3 H), 2.33 (s, 3 H), 3.66–3.70 (dd, J_1 = 4.75, J_2 = 7.41, 1 H), 3.93–3.97 (dd, J_1 = 3.88, J_2 = 7.38, 1 H), 4.52–4.58 (m, 1 H), 6.58–6.59 (d, J = 3.86, 1 H), 6.72–7.50 (m, 10 H); IR (neat) 2926, 2226, 1670, 1495, 1450, 1402, 1328, 1030 cm^{-1}; MS m/e 317 (M$^+$ + 1), 316 (M$^+$), 274, 231, 230, 157, 153, 140, 118, 117, 91; HRMS calcd for $C_{21}H_{20}N_2O$ 316.1577, found 316.1569.

Compound **14** (pale yellow oil): ^{1}H NMR ($CDCl_3$) δ 1.25–1.26 (d, J = 1.94, 3 H), 2.30 (s, 3 H), 3.29–3.32 (dd, J_1 = 1.03, J_2 = 8.89, 1 H), 4.20–4.24 (dd, J_1 = 3.15, J_2 = 7.42, 1 H), 4.41–4.44 (m, 1 H), 6.56–6.57 (d, J = 2.85), 6.82–7.05 (m, 10 H); IR (neat) 3060, 3029, 2226, 1680, 1496, 1401, 1332, 1270, 1034, 765, 736, 703 cm^{-1}; MS m/e 317 (M$^+$ + 1), 316 (M$^+$), 274, 257, 232, 231, 178, 140, 118, 117, 103, 91; HRMS calcd for $C_{21}H_{20}N_2O$ 316.1577, found 316.1580.

***N*-Acetyl-1,2,3,4-tetrahydro-(2*S**,4*S**)-2-butyl-4-phenyl-6-cyanopyridine (10a) and Its Two Isomers.** A solution of **6** (82.7 mg, 0.418 mmol) in freshly distilled 1-hexene (5 mL) in a sealed tube was heated to 100 °C in an oil bath for 4 days when the reaction mixture turned dark brown. The 1-hexene was removed in vacuo, and the residue was purified by column chromatography (ethyl acetate/hexanes (1:2)) to furnish 16.6 mg (14%) of **10a** and 13.6 mg (11.5%) of two diastereomers of **10a**. The ratio for the two minor diastereomers of **10a** is 1:1 (by ^{1}H NMR). Compound **10a**: mp 98–99 °C; ^{1}H NMR ($CDCl_3$) δ 0.94–0.98, (t, J = 6.44, 3 H), 1.39–1.41 (m, 4 H), 1.55–1.80 (m, 2 H), 1.80–1.90 (m, 1 H), 2.15–2.25 (m, 1 H), 2.30 (b, 3 H), 3.58–3.66 (m, 1 H), 4.13 (b, 1 H), 6.17 (s, 1 H), 7.20–7.40 (m, 5 H); IR (KBr) 3060, 2931, 2225, 1673, 1401, 1337, 1178, 760, 735, 701 cm^{-1}; MS m/e 282 (M$^+$), 240, 184, 183, 176, 156, 140, 128, 115; HRMS calcd for $C_{18}H_{22}N_2O$ 282.1734, found 282.1726.

The Two Diastereomers of 10a (colorless oil). The mixture of the two isomers showed only one spot by thin-layer chromatography: ^{1}H NMR ($CDCl_3$) δ 0.73–0.96 (m), 1.13–1.25 (m), 2.02–2.08 (m), 2.32 (s), 2.41–2.50 (m), 3.37–3.44 (dd, J_1 = 9.39, J_2 = 12.85), 3.54–3.56 (m), 3.73–3.76 (t, J_1 = 5.35, J_2 = 10.44), 4.39 (b), 6.16–6.17 (d, J = 4.43), 6.64–6.66 (d, J = 3.73), 7.20–7.40 (m); IR (neat) 3059, 3027, 2930, 2224, 1676, 1400, 1341, 1032, 702 cm^{-1}; MS m/e 282 (M$^+$), 267, 240, 184, 183, 163, 156, 155, 140, 130, 129, 128, 115, 105, 91; HRMS calcd for $C_{18}H_{22}N_2O$ 282.1734, found 282.1724.

Methyl *N*-Acetyl-1,2,3,4-tetrahydro-(3*S,4*S**)-4-phenyl-6-cyanonicotinate (11d).** A solution of **6** (117 mg, 0.59 mmol) is methyl acrylate (1.5 mL, 16.66 mmol) was refluxed for 27 h. The methyl acrylate was removed in vacuo, and the residue was purified by column chromatography (ethyl acetate and hexanes (1:1)) to afford 17.5 mg (10.5%) of a diastereomer of **11d** and 137 mg (81.8%) of **11d**. Compound **11d**: mp 120.5–121.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (b, 3 H), 3.10–3.16 (m, 1 H), 3.47 (b, 3 H), 3.65–3.67 (m, 1 H), 4.02–4.08 (dd, J_1 = 7.73, J_2 = 12.49, 1 H), 6.18–6.19 (d,

J = 4.54, 1 H), 7.10–7.34 (m, 5 H); IR (KBr) 3028, 2950, 2227, 1735, 1680, 1396, 1305, 1198, 1086, 704 cm^{-1}; MS m/e 284 (M^+), 242, 183, 182, 181, 155, 128, 115, 105, 91.

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.86. Found: C, 67.67; H, 5.69; N, 9.95.

Isomer of 11d (colorless oil): ^{1}H NMR ($CDCl_3$) δ 2.35 (b, 3 H), 2.84–2.90 (m, 1 H), 3.70 (s, 3 H), 3.85–3.88 (m, 2 H), 4.11 (b, 1 H), 6.18–6.19 (d, J = 3.48, 1 H), 7.16–7.37 (m, 5 H); IR (CH_2Cl_2) 3028, 2952, 2226, 1734, 1683, 1435, 1395, 1331, 1031, 702 cm^{-1}; MS m/e 285 (M^+ + 1), 284 (M^+), 242, 241, 232, 183, 182, 181, 155, 129, 128, 127, 115, 105, 91; HRMS calcd for $C_{16}H_{16}N_2O_3$ 284.1162, found 284.1160.

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Supplementary Material Available: NMR spectra of **2c,d 4d, 5c, 6**, isomers of **8, 10a,b**, isomers of **10a, 11d**, and **13–15** (13 pages). Ordering information is given on any current masthead page.

Notes

Kinetic Isotope Effects and Possible Brønsted Curvature in a Simple Enolization Reaction

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Among the methods used to probe transition-state structure and to assess the changes in such structures that are brought about by substitution, two of the most important are (i) the Brønsted relationship and the matter of curvature of therein[1-9] and (ii) kinetic isotope effects and the question of changes in their magnitude.[8-12]

We have previously conducted an exhaustive examination of the enolization of acetone catalyzed by general acids and bases,[13-15] using both carboxylic and phosphonic species, and in those systems that could be examined, we have observed neither curvature of the Bønsted line for any individual system nor variations in the magnitude of the deuterium kinetic isotope effect. It should be noted, however, that in most instances where Brønsted curvature has been reported, it was necessary to embrace a wider range of catalyst acid or base strengths than we had been able to use. With regard to kinetic isotope effects, one expects to find pronounced changes therein only when base strengths of the species removing the proton from the substrate are considerably different from the base strengths of the species formed in the reaction, that is, when the proton in question could not be described as being half-transferred in the transition state. In the carboxylic acid catalyzed enolization of acetone (where we observed no significant change in the isotope effect), the species formed in the reaction (acetone enol) and the base that removed the proton in the rate-controlling step (a carboxylate ion) have comparable base strengths.[13]

We here report the results of our final study of the enolization of acetone, in which we have used a series of phosphonate dianions of widely varying base strength, and for which we could obtain kinetic isotope effects in regions far removed from those in which the proton is expected to be half-transferred in the transition state. The rate-

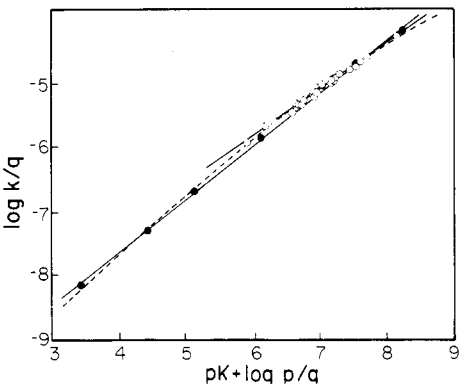

Figure 1. Brønsted plots for the reaction given in eq 1. The dotted line represents a quadratic equation and includes all points; the solid lines for alkylphosphonates (closed circles) and arylphosphonates (open circles) are the least-squares straight lines.

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