Reactivity of *N*-Phenyl-1-Aza-2-Cyano-1,3-Butadienes in the Diels−Alder Reaction

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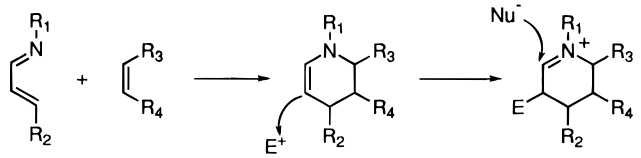
It is found that *N*-phenyl-2-cyano-1-azadiene **4**, prepared via a two-step, one-pot, sequence from acrylanilide, undergoes efficient [4 + 2] cycloaddition with a complete range of electron rich, electron poor, and neutral dienophiles under remarkably mild thermal conditions (90−120 °C for 20−48 h). Regiospecific formation of the α-cycloadduct wherein the dienophile substituent is α to nitrogen is observed for vinyl ethers and styrene, whereas the Diels−Alder reactions with methyl acrylate and methyl vinyl ketone (MVK) produce α/*β* mixtures in which the α-cycloadduct is the major regioisomer (approximately 4−5:1). An essentially identical reaction pattern was observed in the Diels−Alder reaction of *N*-(*p*-methoxyphenyl)-2-cyano-1-azadiene **18** and the 4-methyl-substituted azadiene **27**. For compound **19** derived from cycloaddition of **18** with ethyl vinyl ether, facile conversion to the dihydropyridine **21** through loss of EtOH on brief acid treatment was also noted. The 2,4-*cis*-disubstitution pattern confirmed by X-ray diffraction for the major cycloadduct **29** isolated from the reaction of **27** with styrene provides evidence for the endo mode of cycloaddition in the Diels−Alder reaction of *N*-phenyl(aryl)-2-cyano-1-azadienes. Calculation of the frontier orbital energies and coefficients, as well as the transition state geometries for the [4 + 2] cycloaddition of *N*-phenyl-2-cyano-1-azadiene **4** with methyl vinyl ether, styrene, and MVK were carried out at the RHF AM1 level (MOPAC, Version 5.0). The FMO treatment indicates that the reaction of **4** with methyl vinyl ether occurs under $LUMO_{diene}$ control, whereas in contrast, the corresponding cycloaddition with MVK occurs preferably under $HOMO_{diene}$ control. A high degree of asynchronicity is observed in the calculated transition states for reaction of **4** with the three representative dienophiles. In all cases the transition states leading to the α-cycloadducts are lower in energy than those giving the *β*-products. However, at the AM1 level the exo cycloaddition mode is found to be the preferred, this result contrasting with experimental results for azadiene **27**.

The Diels−Alder reaction of 1-azadienes provides a potentially powerful method for the construction of structurally defined polyfunctionalized six-membered heterocyles, as a result of regio- and stereocontrol during both the cycloadditon step and subsequent reaction of the enamine double bond (Scheme 1). However, the optimization of this hetero Diels−Alder reaction as a general synthetic method has required solving a number of problems, principal among which are the lack of reactivity of simple 1-azadiene systems in [4 + 2] cycloadditions and the inherent instability of the endocyclic Δ^2-piperideine enamines produced.[1] Indeed, due to the electrophilic nature of nitrogen, 1-azadienes are characteristically poor dienes in the normal [$HOMO_{diene}$ controlled] Diels−Alder reaction with electron deficient dienophiles. Important contributions by several groups have shown that this problem can be circumvented by introducing either electron-donating or withdrawing substituents onto the nitrogen atom. In the first instance, Ghosez *et al.* demonstrated that *N*,*N*-dimethylamino substitution alters the normal inverse electron demand character of 1-azadienes promoting their cycloaddition with electron deficient dienophiles.[2] However, considerable difficulties have been encountered in the extension of this approach to α,*β*-unsaturated oximes.[3,5d,6d] Approaching the problem from the opposite direction, Fowler[4] and Boger[5] have

Scheme 1



shown that substitution of the azadiene nitrogen by strong electron-withdrawing (*N*-acyl, *N*-sulfonyl) groups augments considerably the inverse demand Diels−Alder reactivity of the derived azadienes and effectively modulates the reactivity of the enamine system in the Δ^2-piperideine products.

In more recent work from our laboratories further attention has been drawn to the influence of a C-2 cyano group together wifh different nitrogen substituents (COR, phenyl, alkyl, OCH_3) on the Diels−Alder reactivity of the azadiene system.[6] Particularly interesting is the com-

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(1) For a general discussion of the Diels−Alder reaction of 1-azadienes; see: Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; Chapter 9.

(2) (a) Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261. (b) Ghosez, L.; Serckx-Poncin, B.; Rivera, M.; Bayard, P.; Sainte, F.; Demoulin, A.; Hesbain-Frisque, A.-M.; Mockel, A.; Munoz, L.; Bernard-Henriet, C. *J. Heterocycl. Chem.* **1985**, *22* Suppl. Issue (*Lect. Heterocycl. Chem.*, *8*, 69).

(3) (a) Wade, P. A.; Amin, N. B.; Yen, H.-K.; Price, D. T.; Huhn, G. F. *J. Org. Chem.* **1984**, *49*, 4595. (b) Kusurkar, R. S.; Bhosale, D. K. *Tetrahedron Lett.* **1991**, *32*, 3199. (c) Boger, D. L.; Zhu, Y. *Tetrahedron Lett.* **1991**, *32*, 7643.

(4) (a) Hwang, Y. C.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 2719. (b) Cheng, T.-S.; Lupo, A. T.; Fowler, F. W. *J. Am. Chem. Soc.* **1983**, *105*, 7696.

(5) (a) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517. (b) Boger, D. L.; Corbett, W. L.; Wiggins, J. M. *J. Org. Chem.* **1990**, *55*, 2999. (c) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1990**, *55*, 5439. (d) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713.

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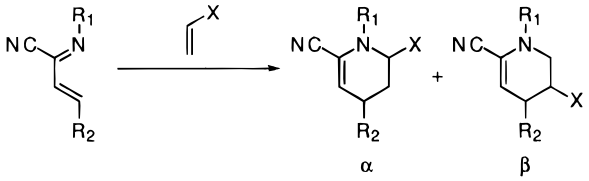
Table 1. Reaction of *N*-phenyl-2-cyano-1-azadienes with Selected Dienophiles



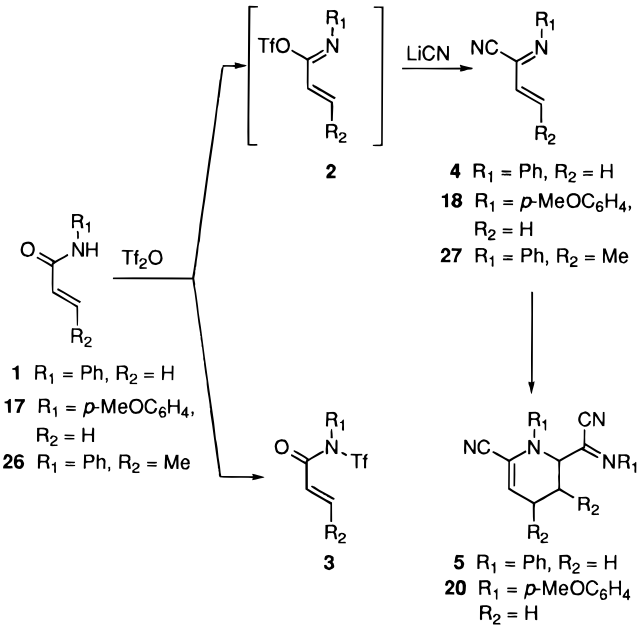
azadiene	dienophile	conditions	α	product (ratio)	β	yield, %
4	X = OEt	90 °C, 36 h	**6**		–	91
	2,3-dihydrofuran	90 °C, 22 h	**7**		–	87
	3,4-dihydro-2*H*-pyran	120 °C, 46 h	**8**		–	25
	X = CO_2Me	90 °C, 40 h	**9**	4:1	**10**	71
	X = COMe	90 °C, 20 h	**11**	4.4:1	**12**	65
	X = Ph	90 °C, 23 h	**13**		–	76
	X = $(CH_2)_3CH_3$	120 °C, 48 h	**14**		–	35
	trans-*β*-methylstyrene	90 °C, 20 h	**15**		–	75
	cis-*β*-methylstyrene	90 °C, 51 h	**16**		–	39
18	X = OEt	90 °C, 30 h	**19**		–	67
	X = CO_2Me	90 °C, 40 h	**22**	4:1	**23**	83
	X = COMe	75 °C, 24 h	**24**	8:1	**25**	63
27	X = Ph	120 °C, 30 h	**29**	4:1	**30**	77
	X = *m*-$O_2NC_6H_4$	90 °C, 22 h	**31**/**32**	2.8/1	–	60
	X = *p*-BrC_6H_4	90 °C, 44 h	**33**/**34**	2.8/1	–	68
	X = OEt	120 °C, 34 h	**35**/**36**	2/1	–	88
	X = CO_2Me	120 °C, 40 h	**37**/**38**	2.6/2:5/1	**39**/**40**	36

bined presence of the *N*-phenyl and C-2 cyano groups in azadiene **4**, as this compound is found to be unique in its capacity to undergo Diels–Alder reactions with electron rich, neutral, and electron deficient dienophiles.[6c,d] Following from these preliminary observations, a full account of the cycloaddition chemistry of *N*-phenyl-2-cyano-1-azadienes is presented in this paper, accompanied by the results of theoretical calculations carried out to gain insight into the electronic and structural properties of these heterodienes which govern their Diels–Alder reactivity.

Results and Discussion

Chemistry. *N*-Phenyl-1-aza-2-cyano-1,3-butadiene (**4**) was prepared by treatment of a solution of acrylanilide (**1**) in CH_2Cl_2 with trifluoromethanesulfonic anhydride at −60 °C, followed by reaction of the *in situ* generated *O*-triflyl imidate **2** with a suspension of lithium cyanide and 12-crown-4 in THF (Scheme 2).[7–9] Under these conditions competing N-triflation of amide **1** to give **3** as a byproduct occurs to only a very small extent.[10] Azadiene **4** was isolated in 70% yield after chromatographic purification (silica gel; heptane/EtOAc 10/1). Characteristic in the ^{13}C NMR of this compound were peaks at δ 148 and 109 for the C-2 and the cyano group of the imidoyl cyanide unit, and absorptions at 2221 and 1623 cm^{-1} in the IR spectrum. Although stable over relatively long periods if frozen in benzene at −20 °C, neat azadiene **4** was observed to decompose slowly at 0 °C to a more

Scheme 2



polar material (13% after 1 week). Isolation and structure elucidation of this crystalline product revealed that it corresponded to compound **5**, resulting from a Diels–Alder type dimerization of **4** in which one molecule reacts as the dienophile component (Scheme 2). More efficient conversion of **4** to **5** was subsequently achieved (60%) by heating in benzene (0.6 M solution) for 36 h. At higher concentrations of **4** (1.2 M) a similar yield of product was obtained after heating for only 15 h. However, under these conditions the azadiene was not completely consumed. This result provided the first indication that, in addition to the anticipated inverse electron demand reactivity of **4**, it would also react with electron poor dienophiles. To evaluate the scope of reactivity of this 1-azadiene a series of experiments were conducted, the results of which are presented in Table 1 and Schemes 3 and 4.

To begin with, azadiene **4** was heated in ethyl vinyl ether (40 equiv) at 90 °C in a closed tube for 36 h.[11] This led to very clean conversion to compound **6**, isolated as a

(6) (a) Teng, M.; Fowler, F. W. *Tetrahedron Lett.* **1989**, *30*, 2481. (b) Teng, M.; Fowler, F. W. *J. Org. Chem.* **1990**, *55*, 5646. (c) Sisti, N. J.; Fowler, F. W.; Grierson, D. S. *Synlett* **1991**, 816. (d) Trione, C.; Toledo, L. M.; Kuduk, S.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1993**, *58*, 2075.

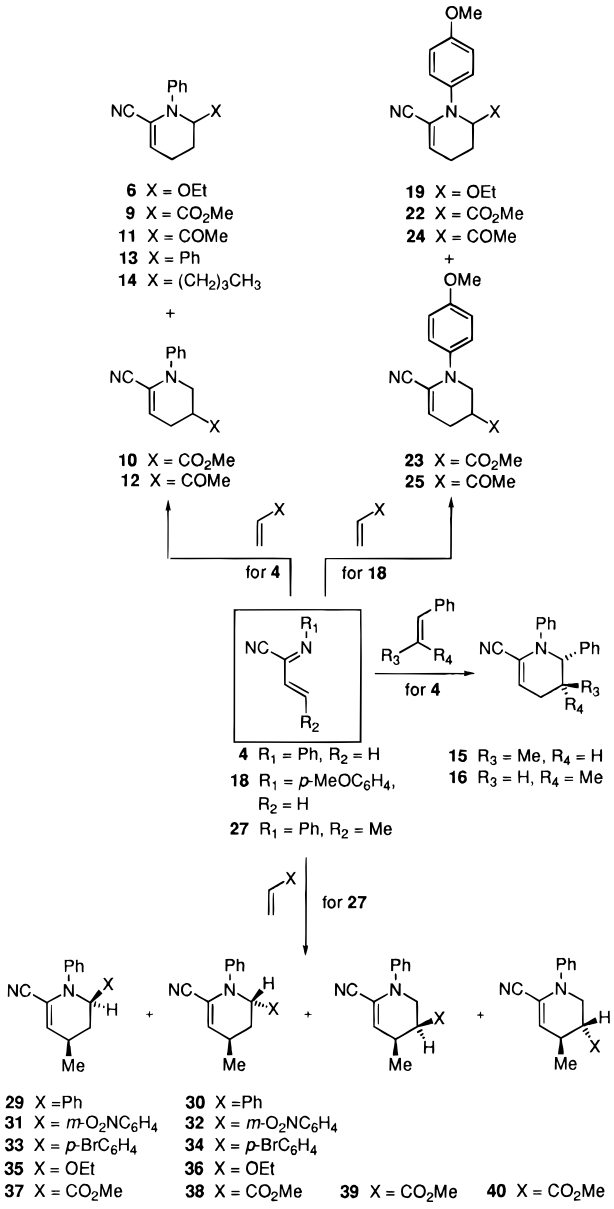
(7) Krutosikova, A.; Dandarova, M.; Konecny, V.; Kovac, *J. Chem. Papers* **1990**, *44*, 119.

(8) For the corresponding vinyl triflate reaction, see: Piers, E.; Fleming, F. F. *J. Chem. Soc., Chem. Commun.* **1989**, 756.

(9) For the preparation of LiCN, see: Livinghouse, T. *Org. Synth.* **1981**, *60*, 126.

(10) In general, <3–5% of the *N*-triflyl product is formed under the experimental conditions employed. However, it is important to separate completely this contaminant from the product 2-cyano-1-azadienes, as in instances where trace quantities of this material remain extensive decomposition is observed in cycloaddition reactions with ethyl vinyl ether and methyl acrylate: Parly, F.; Motorina, I.; Fowler, F. W.; Grierson, D. S., manuscript in preparation.

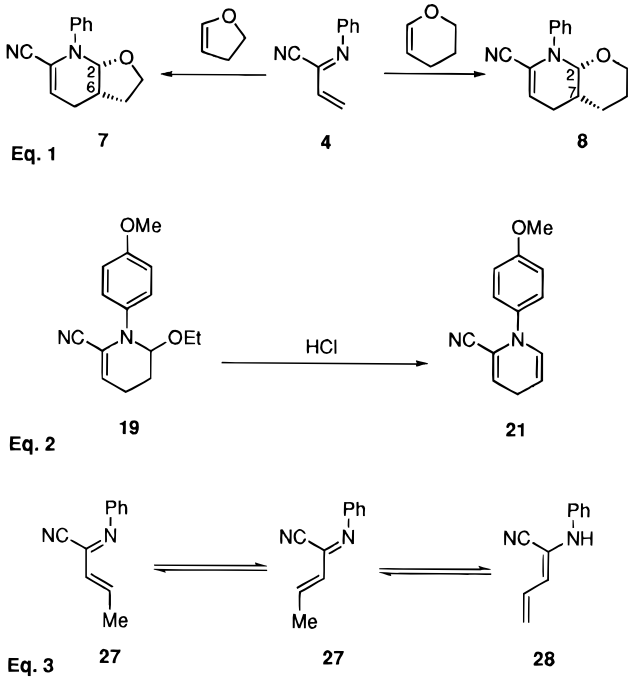
Scheme 3



pale yellow solid, in 91% yield. From the ^{1}H and ^{13}C NMR spectra for this product it was clear that the ethoxy group is present on the carbon center α to nitrogen and that it adopts a preferred axial position [δ 88.3 (C−2); δ 4.82 (t, J = 2.5 Hz, H-2)]. Further examination of the spectral data revealed that the alternate regiosisomeric cycloaddition product was not present in the crude product mixture; a minor component (approximately 2−6%) being identified as the dimer **5**.

The corresponding reactions using 2,3-dihydrofuran and 3,4-dihydro[2*H*]pyran as representative *Z*-enol ether type dienophiles gave very contrasting results. For the five-membered ring dienophile efficient conversion to the *N*-phenyl substituted bicyclic compound **7** was observed (90 °C, 22 h; 87%) (Scheme 4, eq 1). On the other hand, to induce appreciable reaction of **4** with dihydropyran required heating at 120 °C for 46 h. This was presumably necessary to overcome unfavorable steric interactions incurred in the kinetically preferred endo cycloaddition mode (*vide infra*). Under these somewhat harsher

Scheme 4



conditions, considerable decomposition of the dienophile and cycloadduct was observed, contributing to the problems encountered in purifying compound **8**, isolated in only 25−30% yield. The small $J_{2,7}$ = 0.8 Hz coupling for the H-2 proton doublet signal (δ 4.70) confirmed the *cis*-ring fusion in this product, and subsequent comparison of the $^1J13_{C-H}$ coupling constant for the C-2 methine system of **6** (158 Hz) and **8** (153 Hz) enabled us to deduce that it exists as an equilibrium mixture of conformers.[12]

As the formation of the self condensation product **5** suggests, azadiene **4** reacted with methyl acrylate at 90 °C for 40 h to give an approximately 4:1 mixture of the regioisomeric products **9** and **10** (71%) (Scheme 3). The positioning of the carbomethoxy substituent axial and α to nitrogen in the major isomer **9** was determined from the NMR data [δ 4.44 (dd, J = 2.8, 4.5 Hz, H-2); δ 61.3 C-2]. Similarily, the reaction of **4** with methyl vinyl ketone produced a 4.4:1 mixture of compounds **11** and **12** (65%). In this case the X-ray crystal structure of the major product **11** was obtained, definitively showing that the C-2 acetyl group was axial.[13]

A more quantitative idea as to the relative ease with which azadiene **4** reacts with ethyl vinyl ether and methyl vinyl ketone was obtained from a competition experiment performed using 20 equiv of each dienophile (90 °C, 24 h). By ^{1}H NMR it was ascertained that compounds **6** and **11/12** were produced in an approximate 7:5 ratio, and by heating compound **6** at the same temperature and duration in the presence of excess methyl vinyl ketone it was further verified that this ratio reflects a kinetic product distribution.

(11) As previously reported,[6c] good yields (75%) of cycloadduct **6** were obtained on heating azadiene **4** with ethyl vinyl ether for shorter periods (26 h), but under these conditions the azadiene **4** was not totally consumed.

(12) Measurement of $^1J13_{C-H}$ coupling constants for the "anomeric" methine center in carbohydrates and piperidine systems has proven to be a sensitive probe of both axial/equatorial stereochemistry and conformational mobility. In these systems $^1J13_{C-Heq}$ is larger than $^1J13_{C-Hax}$ by 10 ± 1 Hz. An only 5 Hz difference compared to a compound of known stereochemistry or the near identity of this coupling for compounds believed to be of opposite stereochemistry strongly indicates that such systems are not conformationally stable. For relevant applications of this technique, see: (a) Boch, K.; Pederson, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293. (b) Takeuchi, Y.; Chivers, P. J.; Crabb, T. A. *J. Chem. Soc., Chem. Commun.* **1974**, 210. (c) Bonin, M.; Chiaroni, A.; Riche, C.; Beloeil, J.-C.; Grierson, D. S. *J. Org. Chem.* **1987**, *52*, 382. (d) Reference 5d.

The Diels−Alder reaction of **4** with unactivated dienophiles such as styrene, 1-hexene, and *cis*- and *trans*-*β*-methylstyrenes were subsequently examined. In the styrene reaction (neat, 90 °C, 23 h) a single regioisomeric adduct **13** was produced, isolated in 76% yield as a pale yellow oil after chromatographic purification. In the reaction of **4** with 1-hexene prolonged heating (neat, 120 °C, 48 h) was required, and consequently there was formation of dimer **5** at the detriment of the C-2 alkyl substituted product **14** (35% yield).

As anticipated for a concerted Diels−Alder process, the stereochemistry of the dienophile was transferred to the cycloadduct formed in the reaction of **4** with *trans*- and *cis*-*β*-methylstyrenes. Furthermore, for the *trans* dienophile facile conversion (90 °C, 20 h) to give **15** (75% yield) was observed, whereas, for *cis*-*β*-methylstyrene, compound **16** was formed under more stringent conditions (90 °C, 51 h) and in characteristically lower yield (39%). In the proton NMR spectrum of compound **15** a diaxial arrangement of the phenyl and methyl substituents was discerned from the observed small $J_{2eq,3eq} = 2.8$ Hz coupling constant for H-2 (d, δ 4.59). Similarily, the *cis*-1,2 relative geometry in **16** was deduced from the larger $J_{2,3} = 4.1$ Hz constant. However, the observation that the $^1J13_{C-H}$ coupling constant for the C-2 phenyl-substituted center are essentially identical (139 ± 1 Hz) for compounds **16**, **13** (axial Ph attribution; $J_{2,3} = 3.4$ Hz), and in particular compound **29** (equatorial Ph from X-ray diffraction structure; $J_{2,3} = 4.1$ and 7.7 Hz) suggests that these 2-phenyl-substituted $\Delta^{5,6}$-piperideines are, in fact, conformationally mobile.

To determine the influence that an electron-donating group on the aromatic ring will have on the relative rates of these azadiene Diels−Alder reactions, the *N*-(*p*-methoxyphenyl)-2-cyano-1-azadiene **18** was prepared from amide **17**. From the X-ray structure of this compound it was determined that the azadiene component exists in the extended *s-trans* conformation, and that the *N*-phenyl group is twisted 46° out of plane so as to minimize steric interactions with the C-6 cyano group and to optimize the interaction of the aromatic ring π-electrons with both the conjugated imine system and the nitrogen lone pair of electrons.[13] Similar attempts to prepare azadienes bearing electron-withdrawing *p*-CN and *p*-CO_2Me substitutents from the corresponding amides were unsuccessful, due primarily to the insolubility of the starting amides in the reaction medium.

Although the reaction of **18** with ethyl vinyl ether (90 °C, 30 h) proved somewhat less efficient than the corresponding reaction of **4**, cycloadduct **19** was still isolated in good yield (67%) along with varying but small amounts of dimer **20**. In a subsequent competition experiment equimolar amounts of azadienes **4** and **18** were reacted in neat ethyl vinyl ether. After 5 h the ratio of compounds **6** and **19** was approximately 3:1. However, after continued heating for an additional 7 h, ^{1}H NMR integration of the peaks for the C-5 vinyl hydrogen revealed that the two products were present in the mixture in nearly equal proportions.

Interestingly, on several occasions compound **19** slowly transformed to a new product, whose structure was assigned to dihydropyridine **21** by proton NMR [δ 4.49 (ddd, H-3) and δ 5.99 (dt, H-2)] (Scheme 4, eq 2). It was deduced that trace quantities of acidic impurities in $CDCl_3$ catalyze this process. This was initially confirmed by reacting **19** with dry HCl in CH_2Cl_2 at room temperature for 1 h and isolation of **21** in 20% yield by preparative layer chromatography. Subsequently, treatment of **19** with acidic Al_2O_3 at 20 °C for 10 min was observed to produce dihydropyridine **21** in up to 94% yield.

The reaction of azadiene **18** with methyl acrylate (90 °C, 40 h) produced compounds **22** and **23**, obtained as an inseparable 4:1 mixture in high yield (83%). The major regioisomer **22** in this mixture once again corresponded to the product bearing the carbomethoxy group at the C-2 position, i.e. α to nitrogen. Similarily, diene **18** reacted with methyl vinyl ketone to give an approximately 8:1 mixture of cycloadducts **24** and **25**. In this case, silica column separation of the two regioisomeric products permitted their total characterization. Taking into consideration that the time required for complete consumption of azadienes **4** and **18** in their respective Diels−Alder reactions with methyl acrylate and methyl vinyl ketone are essentially the same, it is apparent that the presence of the *p*-methoxy substituent in **18** does not provide a large accelerating effect.

With the prospect in mind of employing more highly functionalized *N*-phenyl-2-cyano-1-azadienes in several synthetic projects, the [4 + 2] cycloaddition chemistry of compound **27** was next examined. Indeed, an important aspect of the reactivity of azadienes such as **27**, bearing a hydrogen on the C-4 substituent, is their propensity to equilibrate to the more highly conjugated enamine tautomer **28** (Scheme 4, eq 3). This rearrangement both destroys the azadiene system and opens up a competing Diels−Alder reaction pathway in which the derived enamine reacts as the diene in a normal $HOMO_{diene}$ controlled process.[14,15] Furthermore, the presence of two chiral centers in the products of the Diels−Alder reaction of **27** makes it a potentially easy matter to determine the endo/exo selectivity in these reactions. Compound **27** was prepared from crotonamide **26** and isolated as a low melting solid in 63% yield after flash column purification. In the ^{1}H NMR spectrum of this product two sets of signals (approximately 6:1 ratio) were present for the methyl group protons (δ 1.91 and 2.05; $J = 1.6$ and 6.8 Hz) and H-4 (δ 6.21 and 6.52; $J = 1.5$; 3.0 and 15.9 Hz). Several lines of evidence led us to conclude that compound **27** exists as an equilibrium mixture of *s-cis* and *s-trans* diene conformers. First of all, identical coupling constants were observed for the vinylic H-4 proton pair of signals, corresponding to a *trans* substitution pattern about the C_3-C_4 double bond. Secondly, contrary to what would be expected if **27** was comprized of a mixture of *cis* and *trans* 4-methyl isomers, the proportions of the two azadiene components remained unaltered during its reaction with selected dienophiles.[16]

(13) The authors have deposited atomic coordinates for the structures **11**, **18**, and **29** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(14) Snyder, H. R.; Robinson, J. C. Jr. *J. Am. Chem. Soc.* **1941**, *63*, 3279.

(15) (a) De Kimpe, N.; Stevens, C. *J. Org. Chem.* **1993**, *58*, 2904. (b) De Kimpe, N.; Verhé, R.; De Buyck, L.; Hasma, H.; Schamp, N. *Tetrahedron* **1976**, *32*, 3063.

(16) In an attempt to provide further evidence in favor of a conformational equilibrium for **27**, its proton spectrum was recorded in different solvents (DMSO-d_6, C_6D_6, CD_3OD). However, no appreciable variations in signal heights (integration) were detected. On heating the NMR probe to 100 °C the H-4 absorption for the minor component in **27** was observed to broaden, and additional signals appeared both in the olefinic region (δ 5.23−5.56 and 6.36) and for a third methyl group (δ 1.89). However, assignment of these signals to enamine **28** and to the *cis* 4-methyl isomer of **27** can only be considered tentatively, since treatment of the mixture with acid did not result in the expected dissapearance of the new olefinic signals (**28** → **27**).

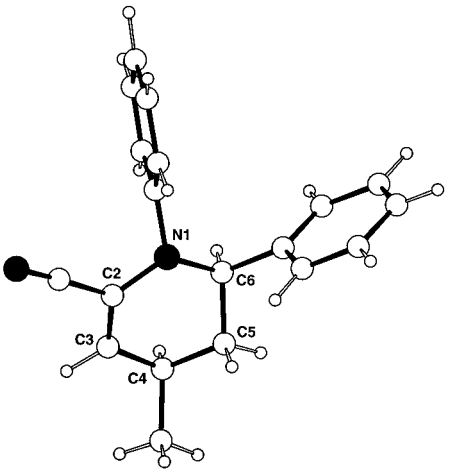


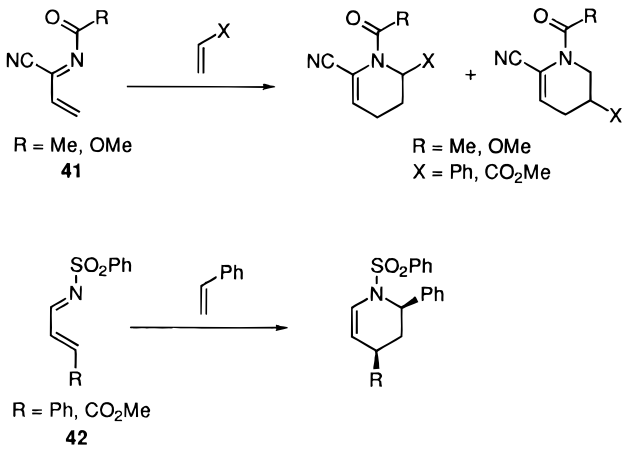
Figure 1. ORTEP drawing of cycloadduct **29**.

In the reaction with styrene, it was comforting to observe that azadiene **27** underwent the desired [4 + 2] cycloaddition (120 °C, 30 h) to give selectively a 4:1 mixture of the C-2 phenyl-substituted products **29** and **30** in 77% combined yield. Similarily the reaction of **27** with *m*-nitro and *p*-bromostyrene led to formation of the stereoisomeric α-cycloadducts **31**/**32** and **33**/**34**, respectively, isolated in 60−68% yields (2.8:1 ratio). Interpretation of the ^{1}H NMR spectrum of the major isomer **29** (as well as **31** and **33**) was complicated, since the value of the coupling constant for H-5 (δ 5.69, d, $J_{4,5} = 3.2$ Hz) is intermediate between that used on previous occasions to assign an axial (≥5 Hz) or equatorial (2.5 Hz) orientation to the C-4 substituent,[6b,d] and $J_{H2ax,H3ax} = 7.7$ Hz is smaller than the 10−12 Hz value which is generally observed. Furthermore, as mentioned above, measurement of the $^1J13_{C(2)-H}$ coupling constant indicated that the molecule possesses a conformationally mobile structure. Thus, even though the 2,4-*cis*-diequatorial structure of **29** was attributed on the basis of the ^{1}H/^{13}C NMR data, its structure had to be confirmed by X-ray crystallography. Indeed, the X-ray study shows that it possesses the predicted structure, the diequatorial conformation presumably being perferred in the solid state in order to diminish 1,3-diaxial type steric interactions at the expense of an reinforced interaction between the N- and C-2 phenyl groups [note that the *N*-phenyl substituent is almost perpendicular (99°) to the plane of the piperideine ring] (Figure 1).

Although complete separation of the minor isomers **30**, **32**, and **34** from the major cycloadducts in the three styrene cycloaddition reactions with **27** was not achieved, the H-5 vinyl and H-2 signals were clearly visible in the proton spectrum of each compound. This made it possible to assign the 2,4-*trans* relative stereochemistry to these products, with the Ph group oriented equatorially.

To complete our study, azadiene **27** was subsequently reacted with the more polar dienophiles ethyl vinyl ether and methyl acrylate. Surprisingly, in initial experiments with ethyl vinyl ether, extensive formation of decomposition products was observed. However, when particular care was taken to separate **27** from very minute amounts of the *N*-triflamide contaminants,[10] a clean reaction took place producing a (2:1) mixture of the α-cycloadducts **35** and **36** in 88% yield (the conformer with the OEt group axial being observed in each case). The reaction of **27** with methyl acrylate was complicated by the isolation of all four possible α (**37**:**38**; 1:5) and β-cycloadducts (**39**:**40**; 2.6:2) as an inseparable mixture (36%), but it remained possible to make regio- and stereochemical attributions based upon coupling constant measurements for the H-2 and H-5 absorptions in the proton spectrum.

Scheme 5



The formation of the 2,4-*cis* cycloadducts **29** (**31**, **33**), **35**, and **37** as the major products with the three representative dienophiles indicates that the principle Diels−Alder reaction mode of azadiene **27** involves an endo transition state. However, in light of the results of temperature variable NMR experiments,[16] a similar conclusion that the pathway leading to the minor α-cycloadducts in these reactions involves the alternative exo transition state cannot be made at present. This latter point will require further verification.

In summary, despite the reluctance of simple 1-azadienes to participate in Diels−Alder reactions, the *N*-phenyl-2-cyano-1-azadienes examined in our work all undergo efficient [4 + 2] cycloaddition with a complete range of dienophiles under remarkably mild thermal conditions (90−120 °C for 20−48 h). These findings are in agreement with earlier observations that N-acyl-2-cyano-1-azadienes **41** bearing phenyl substitution at C-4 also undergo Diels−Alder reactions with electron rich, poor, and neutral dienophiles (Scheme 5).[6b,17] In this regard the 2-cyano-1-azadiene system offers an advantage over the *N*-(phenylsulfonyl)-1-azadienes **42** studied by Boger *et al.*, which, although more reactive than **4** and **41** with respect to electron rich vinyl ethers, do not react with methyl acrylate or simple alkenes under a variety of conditions.[5c,18] It is clear from our results, and from a comparison of the relative rates of the intramolecular cycloadditions of 1-azadienes, with and without 2-cyano substitution,[6b,19] that the cyano group provides a cycloaddition rate accelerating capability, while at the same time stabilizing both the 1-azadiene system and the cycloadducts formed. However, in view of the electron-withdrawing nature of the CN group it is not intuitively obvious why the presence of this substituent should promote the inverse electron demand reaction with dienophiles like methyl acrylate. This point leads us to suggest that the cyano group together with the phenyl

(17) For a related papers on the propensity of *N*-aryl-3-cyano-substituted 1-azadienes to react with both electron rich and electron deficient dienophiles; see: (a) Sakamoto, M.; Nozaka, A.; Shimamoto, M.; Ozaki, H.; Suzuki, Y.; Yoshioka, S.; Nagano, M.; Okamura, K.; Date, T.; Tamura, O. *Chem. Pharm. Bull.* **1994**, *42*, 1367. (b) Sakamoto, M.; Nozaka, A.; Shimamoto, M.; Ozaki, H.; Suzuki, Y.; Yoshioka, S.; Nagano, M.; Okamura, K.; Date, T.; Tamura, O. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1759.

(18) *N*-(Phenylsulfonyl)-1-azadienes have recently been shown to react with unactivated dienophiles in intramolecular Diels−Alder reactions: Boger, D. L.; Corbett, W. L. *J. Org. Chem.* **1993**, *58*, 2068.

(19) Jung, M. E.; Choi, Y. M. *J. Org. Chem.* **1991**, *56*, 6729.

Table 2. Heats of Formation (DH, kcal/mol), AM1 HOMO, LUMO Energies (E, eV), and Coefficients for Ethylene, Methyl Vinyl Ketone, Styrene, and Methyl Vinyl Ether[a]

	ethylene		methyl vinyl ketone		styrene		methyl vinyl ether	
DH:	16.47		−23.99		38.72		−25.62	
	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO
E	−10.55	+1.44	−10.85	+0.05	−9.00	+0.02	−9.42	+1.46
C1′	+0.71	+0.71	+0.65	+0.62	+0.47	+0.45	+0.67	+0.68
C2′	+0.71	−0.71	+0.68	−0.42	+0.33	−0.30	+0.49	−0.70

[a] The molecules lie on the *XY* plane. The coefficients refer to the pz atomic orbitals. The HOMO and LUMO extend to the pz orbitals of the CO group, of the aromatic carbons, and of the oxygen of OMe group.

Table 3. Heats of Formation (DH, kcal/mol), AM1 HOMO, LUMO Energies (*E*, eV), and Coefficients for Butadiene and 1-Azadienes 43 to 45, 18, and 4[a]

	butadiene		**43**		**44**		**18**		**4**		**45**	
DH:	30.69		35.25		68.90		63.49		101.26		133.25	
	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO	HOMO	LUMO
E	−9.36	+0.46	−10.15	+0.40	−10.62	−0.43	−8.82	−0.88	−9.28	−0.86	−9.61	−1.30
C1(N1)	+0.56	+0.57	+0.46	+0.50	+0.45	+0.57	+0.19	+0.43	+0.23	+0.45	+0.22	+0.38
C2	+0.43	−0.42	+0.24	−0.45	+0.23	−0.49	+0.29	−0.47	+0.28	−0.48	+0.26	−0.45
C3	−0.43	−0.42	−0.59	−0.43	−0.59	−0.27	−0.14	−0.15	−0.17	−0.17	−0.18	−0.13
C4	−0.56	+0.57	−0.62	+0.60	−0.61	+0.46	−0.21	+0.33	−0.24	+0.36	−0.23	+0.31

[a] The molecules lie on the *XY* plane. The coefficients refer to the pz atomic orbitals.The HOMO and LUMO extend to the pz orbitals of the CN group and the aromatic carbons (including the oxygen of the OMe group in **18**).

substituent, also present in the azadienes of type **4** and **41**, determines their Diels−Alder reactivity. Indeed the subtle interplay of the electronic effects brought to the azadiene system by these electronically "opposite" functionalities may be at the origin of the differences in the α versus β-regiochemistry observed in the reactions of the *N*-phenyl and *N*-acyl-4-phenyl azadienes with the neutral dienophile styrene and methyl acrylate. Similarily, it may be that the strong electron-withdrawing nature of the *N*-phenylsulfonyl group in azadiene **42** overrides any contribution of the C-4 phenyl group in this system. To provide answers to some of the questions which issue from such speculation, we have undertaken a more detailed study of the Diels−Alder reaction of *N*-phenyl-2-cyano-1-azadiene **4** with ethyl vinyl ether, styrene, and methyl acrylate both at the FMO level and through calculation of the transition states for these reactions.

Computations. The calculation of frontier molecular orbitals, as well as the examination of orbital coefficients and secondary overlap, was used with success by Boger (AM1 and MNDO) to rationalize the observed endo selectivity and the preferred regiochemical formation of the α-cycloaddition products in reactions of *N*-(phenylsulfonyl)-1-azadienes of type **42**.[1,5d] Similarily, Nomura interpreted the increase in reactivity of phenyl-substituted 2-azadienes with electron deficient dienophiles using FMO arguments (CNDO/2),[20] and Orsini *et al.* have studied the electrophilic character of substituted 1,4-diaza-1,3-butadienes in Diels−Alder cycloadditions (MNDO).[21]

As the first step in our study, the ground state geometry of *N*-phenyl-2-cyano-1-azadiene **4** and the model azadienes **43** and **44**, were calculated at the RHF AM1 level (MOPAC, Version 5.0).[22,23] For the parent 1-azadiene **43** Bachrach has previously determined the *s-trans* conformer to be more stable than the *s-cis* form by between 2.55 kcal/mol (MP2/6-31G*) and 2.82 kcal/mol (HF/6-31G*), and the configuration with N−H *anti* to the C=N bond to be lower in energy than the corresponding *syn* isomer by about 0.82−0.87 kcal/mol.[24] The RHF AM1 calculations do not accurately reproduce this trend (ΔE = 0.09 kcal/mol for the two *anti* forms of **43**). However, as relative energies only are dealt with this does not introduce an error into our analysis. For azadienes **44** and **4** bearing a more bulky cyano substituent at C-2 there is a change in the relative energies of the *cis*/*trans* conformers, the *s-cis anti* forms which react in the Diels−Alder reaction being 0.96 and 0.99 kcal/mol more stable, respectively. In addition, for the *N*-phenyl-2-cyano-1-azadiene **4**, the optimal orientation of the phenyl ring with respect to the diene system was determined to be 42.32°. This value coincides well with the X-ray crystal data (46°) for azadiene **18**.[13]

Considering next the ground state structures of the dienophiles,[25] there is a discrepancy for methyl vinyl ketone (MVK). Ronayne *et al.* found that MVK exists as an equilibrium mixture at room temperature with the *s-trans* form predominating.[26] Similarily, UV spectroscopic experiments in liquid acrolein indicate that the *s-trans* conformer is the more stable by 2.1 kcal/mol.[27] These values are reproduced only at the 6-31G*/3-21G level [$E_{cis} - E_{trans} = 1.8$ kcal/mol].[28] Both lower level ab initio calculations (3-21G) and semiempirical methods give a preference for the *s-cis* conformer (0.94 kcal/mol; AM1). However, this is once again inconsequential, as the FMO energy levels and the corresponding coefficients are nearly the same for the *s-cis* and *s-trans* conformers.

The frontier orbital energies and coefficients determined for butadiene, azadienes **4**, **43**, **44**, and the *p*-OMe and -CN-substituted azadienes **18** and **45** (not synthesized) are presented along with the corresponding dienophile values (ethylene, MVK, styrene, and methyl vinyl ether) in Tables 2 and 3. It is seen, that by replacing the carbon C-1 in butadiene by nitrogen, as in **43**, the

(20) Nomura, Y.; Takeuchi, Y.; Tomoda, S.; Ito, M. M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2779.
(21) Orsini, F.; Sala, G. *Tetrahedron* **1989**, *45*, 6531.
(22) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(23) Stewart, J. J. P. MOPAC5.0, QCPE program number 455, and *J. Comput. Chem.* **1989**, *10*, 221.
(24) Bachrach, S. M.; Liu, M. *J. Am. Chem. Soc.* **1991**, *113*, 7929.
(25) To simplify the calculations ethyl vinyl ether was replaced by the corresponding methyl derivative: methyl vinyl ether (MVE).
(26) (a) Ronayne, J.; Sargent, M. V.; Williams, D. H. *J. Am. Chem. Soc.* **1969**, *88*, 5288; (b) Montaudo, G.; Librando, V.; Caccamese, S.; Maravigna, P. *J. Am. Chem. Soc.* **1973**, *95*, 6365.
(27) DeGroot, M. S.; Lamb, J. *Proc. R. Soc. London, Ser. A* **1957**, *242*, 36.
(28) Loncharich, R. J.; Schwartz, T. R., Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 14.

Table 4. Bond Lengths (Å), Bond Angles (deg) and Torsional Angles (deg) for the Transition States of 1-Azadiene with Ethylene and of 1-Methyl-1-azadiene with Propene

	1-azadiene + ethylene STO3G (MP2/6-31G)	1-azadiene + ethylene AM1	1-methyl-1-azadiene + propene STO3G	1-methyl-1-azadiene + propene AM1
C2′N1	2.108 (2.207)	1.889	2.195	2.670
C1′C4	2.188 (2.161)	2.255	2.122	1.695
C2′N1C2	107.88 (107.3)	111.03	105.64	91.40
C1′C4C3	103.51 (104.8)	97.50	105.91	111.34
C2′N1C2C3	−58.63	−54.94	−57.29	−46.27
C1′C4C3C2	60.46	55.52	62.43	74.88

HOMO energy (ΔE = 0.79 eV) is lowered to a much greater extent than the LUMO energy (ΔE = 0.06 eV). Azadiene **43** would thus be predicted to be more electrophilic than butadiene and consequently display little tendency to react in normal $HOMO_{diene}$-controlled Diels−Alder reactions. These AM1 calculations agree well with ab initio 6-31G results obtained by Bachrach [butadiene HOMO (−0.3305 au)/1-azadiene HOMO (−0.3558 au); Δ = 0.69 eV].[29] In fact, essentially the only difference between the two methods is that the decrease in the LUMO level is more important at the ab initio level than in the AM1 calculations [butadiene LUMO (0.1389 au)/ 1-azadiene LUMO (0.1147 au); Δ = 0.66 eV).

The presence of the electron-withdrawing cyano substituent in azadiene **44** results in a further lowering of the HOMO with respect to **43** (Δ = 0.47 eV) and an even larger drop in the LUMO energy level (Δ = 0.83 eV). This suggests that it may react efficiently (if not exclusively) with electron rich and neutral dienophiles such as vinyl ethers and styrene in the inverse electron demand Diels−Alder mode.

Striking is the further modification of the frontier orbital energies brought about by *N*-phenyl substitution of the 2-cyano-1-azadiene system.[20,30,31] This results in a major shift in the position of the HOMO to higher energy, and consequently, to a significant decrease in the difference between the HOMO and LUMO levels (Δ = 1.77 eV). Indeed, compared to azadiene **44**, the HOMO energy in **4** is raised by 1.34 eV, whereas the LUMO level continues to fall (Δ = 0.43 eV). Measurements of HOMO−LUMO energy differences show that the experimentally observed reaction of **4** with methyl(ethyl) vinyl ether [$LUMO_{diene\ control}$ = 8.56 eV; $HOMO_{diene\ control}$ = 10.74 eV] and styrene [$LUMO_{diene\ control}$ = 8.14 eV; $HOMO_{diene\ control}$ = 9.30 eV] occurs under $LUMO_{diene\ control}$, and alternatively, that the reaction of **4** with MVK can occur under both LUMO and HOMO diene control, the latter mode being the more favorable [*E* diene LUMO − E dienophile HOMO = 9.99 eV, and *E* diene HOMO − *E* dienophile LUMO = 9.33 eV].

The AM1 calculations also suggest that the reaction of the *p*-cyanophenyl azadiene **45** with electron rich dienophiles would be accelerated with respect to the corresponding reaction of **4**, due to a continued lowering of the LUMO energy level (ΔE LUMO = 0.44 eV). In contrast, the *p*-methoxyphenyl azadiene **18** should react with even greater ease with methyl vinyl ketone (ΔE HOMO = 0.46 eV). In fact, compared to the reaction of **4** with MVK, a small increase in reaction rate and yield is observed.

Concerning the orbital coefficients, compared to butadiene there is a decrease in the relative magnitude of the coefficient of the N-1 atom at the expense of the coefficient of C-4 in both the HOMO [+0.56 (C-1), −0.56 (C-4) → +0.46 (N-1), −0.62 (C-4)] and LUMO [+0.57, +0.57 → +0.50, +0.60] of 1-azadiene **43**. The introduction of the electron-withdrawing cyano group at C-2 inverses the relative size of the N-1 and C-4 coefficients in the LUMO of **44**, and this trend is maintained in *N*-phenyl-2-cyano-1-azadiene **4**. Furthermore, the coefficients in **4** are all reduced in value due to delocalization of the diene π-electrons through the phenyl ring, and the coefficients for N-1 and C-4 are nearly identical in both the HOMO and LUMO. An interpretation of the regiochemistry of the reaction of **4** with the three electronically different dienophiles is thus difficult to make on the basis of the relative magnitudes of the diene terminal atom coefficients. However, as suggested from Boger's work,[5d] the regioselective formation of the α-product in the reaction of **4** with ethyl vinyl ether and styrene can be rationalized to result from secondary orbital interactions, since the LUMO diene C-2 coefficient (-0.48) is significantly larger than the coefficient for C-3 (−0.17). Unfortunately, a similarily clear cut explanation for the selective (4 to 5:1) formation of the α-cycloadduct in the $HOMO_{diene\ controlled}$ reaction of **4** with MVK does not issue from secondary orbital considerations (C-2/3 = +0.28/−0.17). For this reason, plus the fact that neither the H_{ij} differential overlap integrals or steric effects are included in the FMO analysis, the transition states for the reactions of azadiene **4** were calculated.

The transition state for the prototype Diels−Alder reaction of 1-azadiene **43** with ethylene has been calculated at several levels of theory (MP2/6-31G*, RHF/6-31+G*, RHF/3-21G, RHF/STO3G). These calculations (Table 4) display similar features, excepting that the C2′−N1 distance (2.207 Å, 2.139 Å) is slightly longer than the C1′−C4 distance (2.161 Å, 2.082 Å) at the MP2/6-31G* and RHF/6-31+G* levels, respectively,[29,32] and is slightly shorter at RHF/3-21G and RHF/STO-3G (C2′-N1: 2.103 Å/2.108 Å; C1′−C4: 2.158 Å/2.188 Å).[33] Globally, in these studies the C2′−N1 and C1′−C4 distances differ by <0.11 Å, the other distances differ by less than 0.02 Å, and the bond angles differ by no more than 2°.

It is immediately obvious from the results of the RHF AM1 calculated transition state of the reaction of **43** with ethylene (Table 4) that the degree of asymmetry is much more pronounced: C2′−N1 = 1.889 Å and C1′−C4 = 2.255 Å.[34,36] As a better model to the Diels−Alder reactions of **4**, the endo approach of propene to N-methyl-1-azadiene **46** was also studied. At the STO-3G level[40] the distances (Table 4) between the reacting centers

(29) Bachrach, S. M.; Liu, M. *J. Org. Chem.* **1992,** *57*, 6736.
(30) Houk, K. N.; Strozier, R. H. *J. Am. Chem. Soc.* **1973**, *95*, 4072.
(31) Eisenstein, O.; Lefour, J. M.; Nguyen Trong Anh; Hudson, R. F. *Tetrahedron* **1977**, *33*, 523.
(32) Tietze, L. F.; Fennen, J.; Geissler, H.; Schulz, G.; Anders, E. *Liebigs Ann.* **1995**, 1681.
(33) Tran Huu Dau, M. E.; Flament, J. P.; Lefour, J.-M.; Riche, C.; Grierson, D. S. *Tetrahedron Lett.* **1992**, *33*, 2343.
(34) All the RHF AM1 transition structures were located using the procedures in MOPAC (Version 5.0). All variables were optimized by minimizing the sum of the squared scalar gradients (NLLSQ[35a] and SIGMA[35b]). Final values of the gradient norms were <1 kcal/Å and each transition structure had one negative eigenvalue in the Hessian matrix as required.

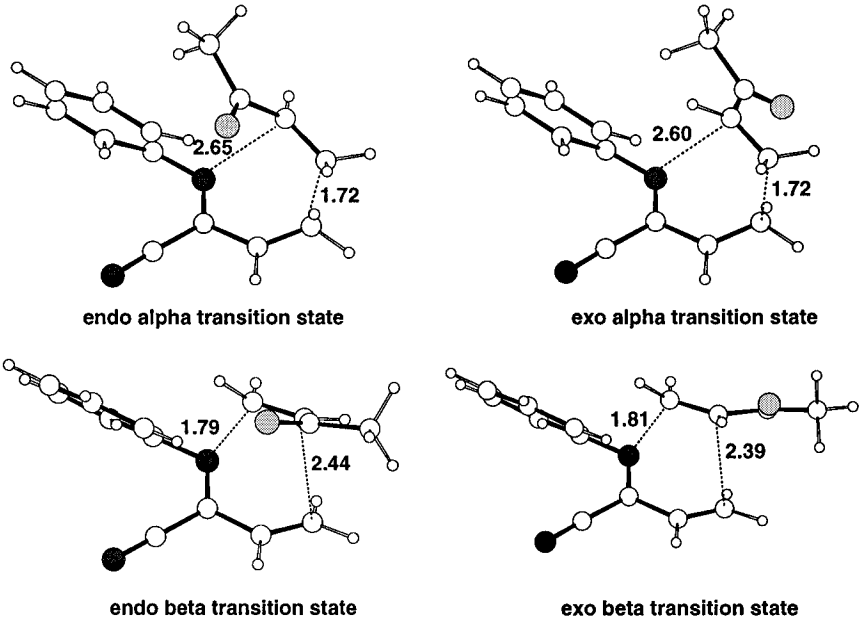


Figure 2. AM1 optimized geometries of the transition structures of *N*-phenyl-2-cyano-1-azadiene + methyl vinyl ketone. The distances are in angstroms.

Table 5. Activation Energies (AE, kcal/mol), Bond Lengths (Å), Bond Angles (deg), Torsional Angles (deg), Charges (*q* on atom or group of atoms), Quantities of Electron Given by the Dienophile to the Diene (*Q*, e), and Bond Orders (*b* (atom−atom)) for the Transition States of 4 with Different Dienophiles

	N-phenyl-2-cyano-1-azadiene **4**												
	methyl vinyl ketone				styrene				ethylene	methyl vinyl ether			
	α		*β*		α		*β*			α		*β*	
	endo	exo	endo	exo	endo	exo	endo	exo		endo	exo	endo	exo
AE	34.72	33.65	36.77	36.70	32.04	31.69	39.43	38.74	33.87	27.04	25.73	39.54	39.43
C2′N1	2.655	2.596			2.825	2.817			2.502	2.830	2.810		
C1′C4	1.720	1.724			1.753	1.742			1.771	1.797	1.793		
C2′N1C2	96.31	96.49			91.98	94.37			97.26	93.87	95.94		
C1′C4C3	109.91	107.98			111.46	109.55			108.37	111.06	109.73		
C2′N1C2C3	−44.53	−46.41			−44.95	−43.12			−47.74	−41.32	−39.54		
C1′C4C3C2	74.35	70.87			79.42	78.27			70.15	81.33	79.21		
C1′N1			1.786	1.813			1.842	1.865				1.870	1.869
C2′C4			2.443	2.391			2.342	2.300				2.309	2.307
C1′N1C2			117.95	115.38			113.55	110.09				110.85	108.76
C2′C4C3			93.91	93.93			95.38	96.73				94.99	98.22
C1′N1C2C3			−48.39	−50.58			−53.55	−56.40				−57.31	−58.52
C2′C4C3C2			57.02	59.29			57.31	57.85				57.74	55.71
*q*N1	−0.14	−0.13	−0.11	−0.11	−0.18	−0.18	−0.11	−0.11	−0.19	−0.25	−0.26	−0.08	−0.07
*q*C4	−0.10	−0.10	−0.08	−0.07	−0.06	−0.06	−0.10	−0.09	−0.05	−0.01	−0.01	−0.17	−0.17
*q*C1′	−0.14	−0.14	0.01	0.001	−0.20	−0.20	−0.07	−0.08	−0.22	−0.27	−0.27	−0.14	−0.15
*q*C2′	−0.19	−0.18	−0.39	−0.37	−0.03	−0.02	−0.22	−0.20	−0.09	0.09	0.10	−0.09	−0.07
*q*Phenyl	+0.05	+0.04	+0.06	+0.06	+0.02	+0.02	+0.04	+0.04	+0.02	−0.01	−0.01	+0.03	+0.03
*q*Cyano	−0.16	−0.16	−0.14	−0.15	−0.17	−0.17	−0.15	−0.15	−0.17	−0.18	−0.18	−0.16	−0.16
Q	0.03	0.05	−0.09	−0.06	0.18	0.19	0.03	0.04	0.18	0.28	0.30	0.11	0.12
b(C−O)(C−C)	1.01	0.99	1.02	1.01	1.12	1.11	1.05	1.04	−	1.16	1.16	1.03	1.03

corresponded closely to those found by Bachrach for the prototype reaction of **43**.[29] In the AM1 treatment there is similarily a trend toward a longer C2′−N1 distance [C2′−N1 = 2.670 Å, C1′−C4 = 1.695 Å], albeit clearly exaggerated. This is most probably due to an overestimation of core−core repulsion at intermediate distances.[37] In line with these results, Houk *et al.* found C−N and C−C distances of 1.982 and 2.266 Å, respectively, in the RHF/3-21G-calculated transition structure for the reaction of butadiene with formaldimine.[43] Houk further found that the concerted exo transition structure in the Diels−Alder dimerization of 1,3-butadiene is quite asynchronous with two partial σ bonds equal to 2.07 and 2.39 Å, at the CASSCF/3-21G level.[44]

The AM1 calculated ΔE_{act} for the cycloaddition of **43**

(35) (a) Bertels, R. H. Report CNA-44, University of Texas Center for Numerical Analysis: Austin, TX, 1972. (b) McIver, J. W.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

(36) As the energy minimization from the stationary point, initiated by a step along the C−N or C−C bond in one sense leads to the reactants and in the opposite sense to the product,[35] we are confident that the Diels−Alder reaction with azadiene **4** should be a single-step reaction analogous to the Diels−Alder reaction of butadienes (note that the experimental results obtained in the reaction of **4** with *cis*- and *trans*-*β*-methylstyrenes are also in accord with a concerted mechanism). The high degree of asymmetry is probably due in large part to the overestimation of the core−core repulsion of the method at intermediate distances. However, one should be extremely careful in drawing conclusions regarding reaction mechanisms from semi-empirical calculations.[37−39]

(37) Lehd, M.; Jensen, F. *J. Org. Chem.* **1990**, *55*, 1034.

(38) Sodupe, M.; Oliva, A.; Bertran, J.; Dannenberg, J. J. *J. Org. Chem.* **1989**, *54*, 2488.

(39) Tietze *et al.* (ref 32) calculated the energy surface for the reaction of azadiene **43** with ethylene at AM1/CI. They located two competing reaction channels, one corresponding to the concerted process, and the second to a preferred lower energy two-step reaction pathway.

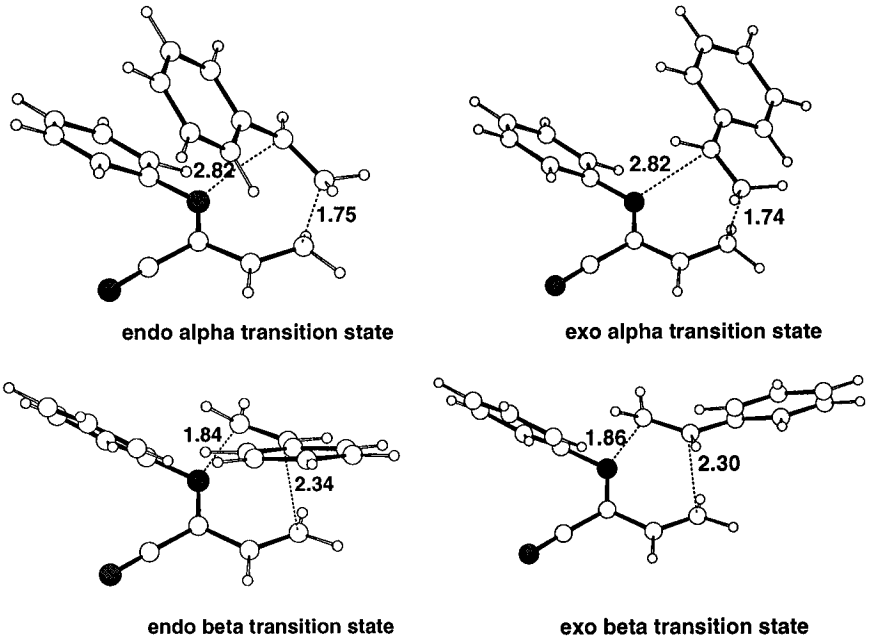


Figure 3. AM1 optimized geometries of the transition structures of *N*-phenyl-2-cyano-1-azadiene + styrene. The distances are in angstroms.

and ethylene (34.48 kcal/mol) agrees remarkably with the ab initio value of 31.80 kcal/mol (MP4SDQ/6-31G*//MP2/6-31G* with ZPE at HF/6-31G*//HF/6-31G*),[29] and is larger than the corresponding AM1 activation energy for the butadiene + ethylene reaction (32.99 kcal/mol). All factors considered, the AM1 transition states for the model Diels−Alder reactions coincide sufficiently well with ab initio treatments to provide the degree of confidence necessary to proceed with the calculation of the transition states for the observed [4 +2] cycloadditions of the more complex functionalized azadiene **4** with styrene, ethyl vinyl ether, MVK, and ethylene.[37,38] The activation energies (obtained by difference from the calculated enthalpies of the fully optimized reactants in their ground states), interatom distances, and angles, as well as other relevant parameters for the different transition structures involving azadiene **4** (α, *β*, and endo, exo orientations of the dienophiles) are presented in Table 5, and illustrated in Figures 2−5.

Looking first qualitatively at the calculated geometries of these transition states one sees that, as for the simpler model systems, there is a high degree of asymmetry. However, it is interesting that there are only slight differences between the exo and endo transition states leading to the α products, despite the greater steric interactions that would, *a priori*, be expected in the endo reactions. For the transition states leading to the *β* products the asymmetry is in the opposite sense, i.e. N-1−dienophile distance is less than that between C-4 and the requisite dienophile carbon center. This difference in the sense of asymmetry may be construed as reflecting mainly diminished steric interactions between the dienophile and the crowded N-1 center. However, this is an incomplete argument since the transition state for the reaction of **4** with ethylene (a model for hex-1-ene) has a geometry, which although somewhat less asymmetric, is clearly α like with a longer N_1−C distance.

The finding that the computed activation energies for formation of the α cycloadducts are lower than the corresponding energies for the *β* regioisomers correlates nicely with the experimental results. Furthermore, this agreement holds independently of whether the comparison is made between endo or exo modes for each of the regioisomeric transition states. Indeed, the differences in activation energies between the α and *β* reaction pathways involving methyl vinyl ether and styrene are 7−13 kcal/mol. The difference in the activation energies between the α and *β* reaction pathways is less important in the cycloaddition of **4** with MVK (approximately 2 kcal/mol) which is qualitatively consistent with the observed formation of a 4.4:1 mixture of regioisomers.

It is also noteworthy that in the α transition structures for the reactions of MVK and MVE, the forming bonds (C1′−C4/C2′−N1 = 1.724/2.596, 1.742/2.817, 1.771/2.502, 1.793/2.810 Å) are shorter in the MVK transition structure, suggesting that the transition state for this reaction is later than the corresponding α-TS with MVE. As observed by Lehd *et al.*,[37] the values of activation energy can be correlated with the lengths of the forming bonds: the longer are the forming bonds the lower the activation energy. Even though the relative differences in the AM1 calculated activation energies are too large, the observed trend between ΔE_{act} and approach distance provides an explanation why the *β* transition state energies are higher than those leading to the α products [MVK: C1′−C4/C2′−N1//C1′−N1/C2′−C4 = 1.724/2.596//1.813/2.391 Å, styrene: 1.742/2.817//1.865/2.300, MVE: 1.793/2.810//1.869/2.207 Å].

The agreement with experiment appears less satisfactory, however, concerning the question of endo versus exo

(40) The computation of the transition structure of the endo Diels−Alder reaction of 1-methyl-1-azadiene with propene was carried out using STO-3G basis set[41] and gradient techniques with optimization of all variables with the help of HONDO8 program.[42] The stationary point is characterized at the STO-3G restricted Hartree Fock level as a true transition state having a single negative Hessian eigenvalue. The convergence threshold on the maximum gradient component is 0.0006 Å.

(41) Hehre, W. J.; Stewart, R. F.; Pople, J. A. *J. Chem. Phys.* **1969**, *51*, 2657.

(42) Dupuis, M.; Johnston, F.; Marquez, A. HONDO 8.1 from CHEM-Station; IBM Corporation: Kingston, NY 12401.

(43) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330.

(44) (a) Yi Li; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 7478. (b) Houk, K. N.; Loncharich, R. J.; Blake, J. F.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 9172.

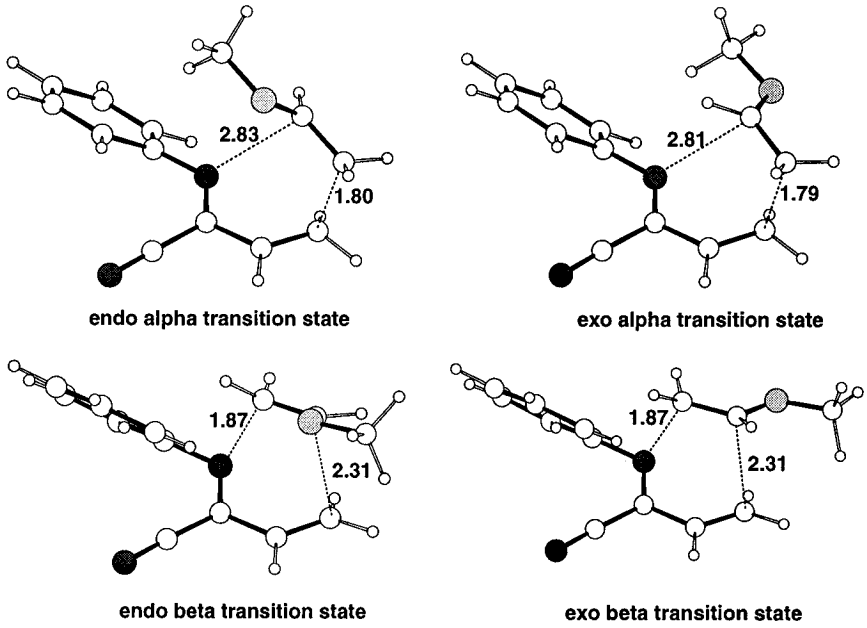


Figure 4. AM1 optimized geometries of the transition structures of *N*-phenyl-2-cyano-1-azadiene + methyl vinyl ether. The distances are in angstroms.

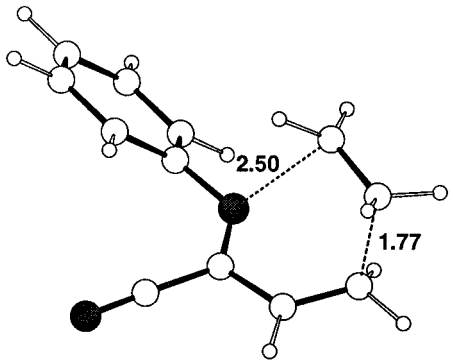


Figure 5. AM1 optimized geometry of the transition structure of *N*-phenyl-2-cyano-1-azadiene + ethylene. The distances are in angstroms.

Diels−Alder reactivity. NMR and X-ray data show that the endo product is formed in the Diels−Alder reaction of the *N*-phenyl-2-cyano-4-methyl-1-azadiene **27** with styrene, whereas the calculations for azadiene **4** indicate that the exo transition states are slightly lower in energy. Such preferences for the exo TS have been found in the theoretical treatment of other Diels−Alder processes, even at the RHF/3-21G and CASSCF levels. The study by Apeloig and Matzner provides the first systematic and quantitative evidence supporting the idea that secondary orbital interaction control the stereochemistry in the Diels−Alder reaction.[45] According to other theoretical studies, it is recognized that the calculations slightly underestimate the stability of the endo TS relative to the exo TS.[44] A further factor which may diminish the contribution of secondary orbital interaction in our calculations is the large distance between the diene and the C1′ center in the dienophile which bears the substituent.

Boger *et al.* have attributed the high endo selectivity observed in the reaction of their *N*-phenylsulfonyl azadiene systems with vinyl ethers to the combined influence of secondary overlap and anomeric type effects.[5d] According to Cieplak,[46] the consequence of an anomeric type n → σ^* interaction would be a reduction of the bond order in the electron−acceptor bond. In our case, there is no evidence for such stabilization, the bond orders of the electron acceptor bond in the endo transition structures being equivalent to the corresponding bond orders in the exo transition structures.

To have at least a partial appreciation of the electronic component which contributes, or more likely controls, the regiochemical sense of the Diels−Alder reactions of **4**, the charge distributions were examined. Mulliken population analysis shows that in all cases, except for the transition state leading to the β regioisomer with methyl vinyl ketone, the dienophile is globally donating a quantity of electron "*Q*" to the diene (i.e. $Q > 0$). It was deduced from this calculation that the Diels−Alder reaction of **4** with MVE, ethylene, styrene, *and methyl vinyl ketone* to give the α-product will occur under LUMO diene-control. As can be expected, the extent of electron donation increases with the electron-releasing property of the dienophile (0.03) MVK < styrene < ethylene < MVE (0.28). Examining the charge distributions on the individual atoms the inductive effects produced by variation in the dienophile substituent can be measured: i.e. the presence of an electron-withdrawing group at C2′ of the dienophile is inclined to decrease the negative charge on the adjacent atoms C1′ and N1 in the α transition states, and on C1′ and C4 in the β TS's, thereby augmenting the negative charge on C2′. Inversely, the presence of an electron-releasing group on C2′ is inclined to increase the negative charges on the adjacent atoms C1′ and N1 in the α TS's and C1′ and C4 in the β TS's, resulting in a reduction of the negative charge on C2′. For example, on going from MVK to MVE the negative charge on C1′ and N1 in the α transition structures increases from −0.14 and −0.13 to −0.27 and −0.26, respectively, and the charge on C2′ becomes positive (−0.18 to +0.10). Similarily, in the β transition structures for MVK and MVE the negative charge on C1′ and C4 increases from 0.0 and −0.07 to −0.15 and −0.17, respectively, and the negative charge on C2′ diminishes (−0.37 to −0.07). Furthermore, with respect to the

(45) Apeloig, Y.; Matzner, E. *J. Am. Chem. Soc.* **1995**, *117*, 5375.

(46) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

ground state charge on the phenyl ring (+0.06e) and the cyano group (−0.16e), one sees that there is a build-up of negative charge in the phenyl ring and that there is very little charge variation in the cyano substituent in the α transition state of the reaction of **4** with MVK (Ph: +0.04; CN: −0.16) and MVE (Ph: −0.01; CN: −0.18). However, in the *β* transition structures the charge on the phenyl ring (+0.06 to +0.04e) and the cyano group (−0.15 to −0.16e) do not vary significantly. This movement of electrons reveals that the charge given by the dienophile to the diene is better stabilized by the phenyl ring on nitrogen than by the cyano group at C2. This stabilization effect of the *N*-phenyl group rationalizes on the one hand the stability of the α transition states compared to the *β* transition states, and on the other hand the α-like orientation in the transition structure for the reaction of **4** with ethylene.

In view of the asymmetric nature of both the α and *β* transition states for the reaction of azadiene **4** it is tempting to try and deduce from the data something concerning the asynchronicity/synchronicity (mechanism) of these reactions.[36] However, the answer to this pertinant question is beyond the reach of the semiempirical approach which we have been constrained to employ because of the complexity of the system under study. Indeed, even at very high levels of theory this issue still remains open for the simple prototype reaction of 1-azadiene **43** with ethylene. In spite of this limitation the FMO analysis does permit an understanding of the observed reactivity and regiochemistry in the Diels−Alder reactions of *N*-phenyl-2-cyano-1-azadiene **4** with such electronically different dienophiles as methyl vinyl ketone, styrene, and ethyl(methyl)vinyl ether. Further exploration of the Diels−Alder reaction of 2-cyano-1-azadienes is in progress in our laboratories.

Experimental Section

***N*-Phenyl-2-cyano-1-aza-1,3-butadiene (4).** Triflic anhydride (4.4 g, 16.3 mmol) was added dropwise over 10 min to a cold (−60 °C) solution of acrylanilide (**1**) (prepared in 82% yield according to ref 7) (2.0 g, 13.6 mmol) and dry diisopropylethylamine (2.6 g, 20.4 mmol) in 40 mL of anhydrous CH_2Cl_2, and the resulting mixture was stirred for 1 h (argon atmosphere). A suspension of LiCN (0.6 g, 19.0 mmol; predried for 2 h at 80 °C; 0.01 mmHg) in 40 mL of anhydrous THF containing 12-crown-4 (0.27 g, 0.14 mmol) was then added dropwise over a period of 10 min, and stirring was continued at −60 °C for an additional 45 min. The reaction mixture was subsequently warmed to −20 °C over a period of 15 min and quenched with 50 mL of water. The organic layer was removed and the aqueous phase washed with ether. The combined organic layers were washed with water, dried over sodium sulfate, and concentrated. *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**) was obtained as a yellow oil (1.5 g, 70%) after flash column purification (silica gel, 10:1 heptane/EtOAc): IR (neat) 2221, 1623, 1581 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.09 (d, J = 10.5 Hz, 1H), 6.33 (d, J = 17.5 Hz, 1H), 6.75 (dd, J = 10.5, 7.0 Hz, 1H), 7.13 (dd, J = 7.4, 1.5 Hz, 2H), 7.25−7.47 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 109.8, 120.4, 127.7, 129.3, 129.6, 135.5, 140.5, 148.7; MS *m/z* 156 (M^+), 155, 130, 77; HRMS Calcd for $C_{10}H_8N_2$ 156.0687, found 156.0703.

***N*-phenyl-2-cyano-1-aza-1,3-butadiene dimer 5**. *N*-Phenyl-2-cyano-1-aza-1,3-butadiene (**4**) (75 mg, 0.48 mmol) in 0.4 mL of anhydrous benzene was placed in an argon-flushed 10-mL capacity thick glass-walled tube, equipped with a Rotoflo tap and a magnetic stirring bar, and heated under closed conditions at 90 °C (oil bath temperature) for 15 h. After cooling, the solvent was removed under vacuum, and the residue was flash column chromatographed (silica, 4:1 heptane ether). Compound **5** was obtained after subsequent recrystallization (pentane−ether) as a colorless solid (45 mg, 60%): mp 106−107 °C; IR (neat) 2263, 2228, 1623, 1595, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (m, 1H), 2.38 (m, 2H), 2.55 (m, 1H), 4.70 (t, J = 4.2, 3.5 Hz, 1H), 5.96 (t, J = 3.6, 4.1 Hz, 1H), 7.04 (d, J = 7.6 Hz, 2H), 7.19−7.45 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 19.8, 21.8, 64.5, 111.0, 115.4, 117.9, 120.1, 123.1, 123.5, 125.8, 127.8, 129.2, 129.5, 143.1, 145.1, 148.0; MS *m/z* 312 (M^+), 220, 183, 155, 92, 77. Anal. Calcd for $C_{20}H_{16}N_4$: C, 76.90; H, 5.16; N, 17.94. Found: C, 76.55; H, 5.42, N, 17.71.

***N*-Phenyl-1,2,3,4-tetrahydro-2-ethoxy-6-cyanopyridine (6).** *N*-Phenyl-2-cyano-1-aza-1,3-butadiene (**4**) (78 mg, 0.5 mmol) and ethyl vinyl ether (1.2 mL, 20 mmol) were placed in an argon-flushed 10-mL capacity thick glass-walled tube, equipped with a Rotoflo tap and a magnetic stirring bar, and heated under closed conditions at 90 °C (oil bath temperature) for 36 h. After cooling, the excess dienophile was removed under vacuum and the residue was flash column chromatographed (silica, 6:1 heptane/EtOAc). Compound **6** was obtained as a pale yellow solid (104 mg, 91%): mp 54−56°C (heptane−EtOAc); IR (neat) 2228, 1630, 1595, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.0 Hz, 3H), 1.61 (m, 1H), 1.97 (m, 1H), 2.19 (ddt, J = 19.3, 1.3, 5.1 Hz, 1H), 2.39 (m, 1H), 3.67 (m, 1H), 3.90 (m, 1H), 4.82 (t, J = 2.5 Hz, 1H), 6.02 (brt, 1H), 7.16 (m, 3H), 7.36 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 15.2, 18.9, 24.0, 63.0, 88.3, 115.5, 116.3, 123.3, 124.7, 125.2, 129.5, 144.9; MS *m/z* 228 (M^+), 199, 196, 183, 155, 104, 77, 51. Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N,12.27. Found: C, 73.66; H, 6.93; N, 12.35.

Diels−Alder Adduct 7. As described for **6**, a mixture of *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**) (100 mg, 0.64 mmol) in freshly distilled 2,3-dihydrofuran (1.94 mL, 25.6 mmol) was heated under closed conditions at 90 °C for 22 h. Compound **7** was obtained as a yellow oil (126 mg, 87%) after flash column chromatography (silica gel, 10:1 heptane/EtOAc): IR (neat) 2226, 1630, 1604, 1492, 1414 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (m, 1H), 2.22 (m, 2H), 2.35 (ddd, J = 4.7, 6.3, 17.5 Hz, 1H), 2.63 (m, 1H), 3.80 (dt, J = 8.3, 6.4 Hz, 1H), 5.23 (d, J = 5.9 Hz, 1H), 5.95 (t, J = 5.1 Hz, 1H), 7.12 (t, J = 7.3, 1H), 7.22 (d, J = 7.6, 2H), 7.34 (t, J = 7.9, 2H); ^{13}C NMR ($CDCl_3$) δ 24.0, 30.4, 37.7, 64.9, 89.9, 115.3, 121.6, 122.3, 124.5, 129.1, 143.9; MS *m/z* 226 (M^+), 225, 197, 195, 183, 181, 169, 155, 104, 77. HRMS calcd for $C_{14}H_{14}N_2O$ 226.1106, found 226.1095. Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N,12.38. Found: C, 73.81; H, 6.38; N, 11.96.

Diels−Alder Adduct 8. As described for **6**, a mixture of *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**) (70 mg, 0.45 mmol) in freshly distilled 3,4-dihydro-2*H*-pyran (4.6 g, 54 mmol) was heated under closed conditions at 120 °C for 46 h. Compound **8** was obtained as a yellow oil (27 mg, 25%) after flash column chromatography (silica gel, 4:1 heptane/ether): IR (neat) 2225, 1625, 1600, 1500, 1413 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (m, 1H), 1.83 (m, 3H), 2.10 (m, 2H), 2.56 (m, 1H), 3.61 (m, 1H), 4.09 (dd, J = 3.6, 11.6 Hz, 1H), 4.70 (d, J = 0.8 Hz, 1H), 5.71 (dd, J = 3.0, 5.0 Hz, 1H), 7.16−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.5, 22.7, 27.4, 30.7, 68.3, 88.4, 115.7, 116.3, 118.0, 123.9, 125.4, 129.2, 144.3; MS *m/z* 240 (M^+), 239, 181, 155, 97, 84, 77; HRMS calcd for $C_{15}H_{16}N_2O$ 240.1262, found 240.1262.

***N*-Phenyl-1,2,3,4-tetrahydro-2-carbomethoxy-6-cyanopyridine (9) and *N*-Phenyl-1,2,3,4-tetrahydro-3-carbomethoxy-6-cyanopyridine (10).** As described for **6**, a mixture of *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**) (45 mg, 0.29 mmol) and methyl acrylate (1.04 mL, 11.5 mmol) was heated under closed conditions at 90°C for 40 h. Compounds **9** and **10**, an inseparable 4:1 mixture of regioisomers, were obtained as a yellow oil (50 mg, 71%) after flash column chromatography (silica gel, 8:1 heptane/ethyl acetate). These regioisomers were separated by HPLC (silica gel; 93:7 heptane/ethyl acetate).

Compound **9**: IR (neat) 2227, 1742, 1622, 1596, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.93 (m, 1H), 2.20−2.39 (m, 3H), 3.78 (s, 3H), 4.44 (dd, J = 2.8, 4.5 Hz, 1H), 5.77 (dt, J = 1.1, 4.5 Hz, 1H), 7.12 (m, 3H), 7.34 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 20.2, 22.8, 52.6, 61.3, 115.7, 117.3, 120.5, 122.8, 124.7, 129.3, 145.1, 145.4, 171.7; MS *m/z* 242 (M^+), 184, 183, 181, 129, 104, 77, 51.

Compound **10**: IR (neat) 2228, 1736, 1621, 1596, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.53 (m, 2H), 2.78 (m, 1H), 3.58 (s, 3H), 3.65 (m, 1H), 3.87 (ddd, J = 0.7, 3.2, 12.6 Hz, 1H), 5.88 (t, J = 4.0 Hz, 1H), 7.07 (m, 3H), 7.34 (m, 2H); ^{13}C NMR ($CDCl_3$) δ

26.0, 37.0, 52.1, 64.6, 117.3, 120.1, 122.5, 124.4, 129.7, 145.2, 172.8; MS *m/z* 242 (M^+), 183, 181, 104, 77. Anal. of mixture of regioisomers: Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.79; H, 5.73; N, 11.77.

***N*-Phenyl-1,2,3,4-tetrahydro-2-acetyl-6-cyanopyridine (11) and *N*-Phenyl-1,2,3,4-tetrahydro-3-acetyl-6-cyanopyridine (12).** As described for **6**, a mixture of *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**) (55 mg, 0.35 mmol) and methyl vinyl ketone (1.0 g, 14 mmol) in 1.0 mL of anhydrous benzene was heated under closed conditions at 90 °C for 20 h. Compound **11** was obtained as a white solid (42 mg, 53%), and **12** was obtained as a yellow oil (10 mg, 12%) after flash column chromatography (silica gel, 3:1 heptane/ether and then 2:1 heptane/ether).

Compound **11**: mp 101−103 °C; IR (neat) 2225, 1712, 1593, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (m, 1H), 2.17 (m, 2H), 2.36 (s, 3H), 2.37 (m, 1H), 4.24 (dd, J = 3.2, 1.2 Hz, 1H), 5.92 (t, J = 4.0 Hz, 1H), 7.12 (m, 3H), 7.36 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 20.3, 20.9, 27.0, 68.7, 115.6, 117.3, 122.1, 124.2, 124.6, 129.5, 145.5, 208.7; MS *m/z* 226 (M^+), 183, 182, 166, 155, 143, 129, 104, 77, 51. Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.23; N, 12.38; O, 7.07. Found: C, 74.15; H, 6.28; N, 12.53; O, 7,28.

Spectral data for **12**: IR (neat) 2227, 1709, 1622, 1596, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15 (s, 3H), 2.47 (m, 2H), 2.83 (m, 1H), 3.49 (m, 1H), 3.86 (dd, J = 3.2 Hz, 1H), 5.89 (t, J = 4.1 Hz, 1H), 7.09 (m, 3H), 7.35 (t, 2H); ^{13}C NMR ($CDCl_3$) δ 25.8, 28.7, 44.2, 51.7, 115.4, 118.3, 120.9, 122.9, 124.5, 129.4, 145.3, 207.4; MS *m/z* 226 (M^+), 183, 155, 147, 105, 93, 77, 55; HRMS calcd for $C_{14}H_{14}N_2O$ 226.1106, found 226.1104.

***N*-Phenyl-1,2,3,4-tetrahydro-2-phenyl-6-cyanopyridine (13)**. As described for **6**, *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**) (64 mg, 0.41 mmol) and styrene (1.71 g, 16.4 mmol) were heated under closed conditions at 90 °C for 23 h. Compound **13** was obtained as a pale yellow oil (81 mg, 76%) after flash column chromatography (silica gel, heptane): IR (neat) 2227, 1622, 1596, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86 (m, 1H), 1.99−2.25 (m, 3H), 4.92 (t, J = 3.4 Hz, 1H), 5.76 (dt, J = 1.6, 4.8 Hz, 1H), 7.09 (m, 3H), 7.22−7.41 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 19.5, 25.6, 62.5, 116.2, 117.0, 121.9, 122.1, 124.0, 125.9, 127.3, 128.9, 129.2, 140.8, 146.1; MS *m/z* 260 (M^+), 196, 183, 155, 130, 104, 84, 77, 51. Anal. Calcd for $C_{18}H_{16}N_2$: C, 83.04; H, 6.19; N, 10.76. Found: C, 82.66; H, 5.81, N, 10.43.

***N*-Phenyl-1,2,3,4-tetrahydro-2-butyl-6-cyanopyridine (14)**. As described for **6**, a mixture of *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**) (50 mg, 0.3 mmol) and 1-hexene (3.4 g, 36 mmol) was heated under closed conditions at 120 °C for 48 h. Compound **14** was obtained as a light red oil (25 mg, 35%) after flash column chromatography (silica gel, 4:1 heptane/ether): IR (neat) 2227, 1625, 1595, 1492 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, J = 6.8 Hz, 3H), 1.50 (m, 4H), 1.69 (m, 2H), 2.21 (m, 2H), 3.68 (m, 1H), 5.90 (t, J = 4.0 Hz, 1H), 7.04 (m, 3H), 7.32 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.8, 22.9, 28.9, 30.6, 60.2, 116.2, 116.7, 122.4, 123.6, 123.7, 129.2, 146.7; MS *m/z* 240 (M^+), 183, 155, 130, 104, 77; HRMS calcd for $C_{16}H_{20}N_2$ 240.1627, found 240.1629.

***N*-Phenyl-1,2,3,4-tetrahydro-*trans*-2-phenyl-3-methyl-6-cyanopyridine (15).** As described for **6**, a mixture of *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**) (50 mg, 0.32 mmol) and *trans*-β-methylstyrene (1.5 g, 12.8 mmol) was heated under closed conditions at 90 °C for 20 h. Compound **15** was obtained as a light red oil (66 mg, 75%) after flash column chromatography (silica gel, 5:1 heptane/ether): IR (neat) 2227, 1616, 1596, 1496 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (d, J = 6.8 Hz, 3H), 1.92 (m, 1H), 2.43 (m, 2H), 4.59 (d, J = 2.8 Hz, 1H), 5.62 (dd, J = 3.7 Hz, 1H), 7.04 (m, 3H), 7.30 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 19.3, 26.4, 32.3, 68.0, 115.9, 116.5, 118.4, 121.6, 123.9, 125.7, 127.3, 128.9, 129.1, 141.7, 146.2; MS *m/z* 274 (M^+), 194, 179, 176, 161, 136, 121, 105, 86, 84, 77. Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.17; H, 6.66; N, 9.92.

***N*-Phenyl-1,2,3,4-tetrahydro-*cis*-2-phenyl-3-methyl-6-cyanopyridine (16)**. As described for **6**, *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**) (50 mg, 0.32 mmol) and *cis*-β-methylstyrene (1.5 g, 12.8 mmol) were heated under closed conditions at 90°C for 51 h. Compound **16** was obtained as a light yellow oil (34 mg, 39%) after flash column chromatography (silica gel, 10:1 heptane/ethyl acetate): IR (neat) 2225, 1724, 1616, 1597, 1495 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, J = 6.8 Hz, 3H), 1.81 (ddd, J = 2.8, 11.8, 18.8 Hz, 1H), 2.13−2.34 (m, 2H), 4.57 (d, J = 4.1 Hz, 1H), 5.77 (dd, J = 2.8, 5.5 Hz, 1H), 7.05 (m, 3H), 7.29 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 18.4, 27.4, 30.2, 68.5, 118.2, 118.8, 121.6, 122.7, 124.4, 125.8, 127.7, 127.8, 128.7, 129.0, 129.1, 139.8, 146.2; MS *m/z* 274 (M^+) 259, 156, 103, 91, 77; HRMS calcd for $C_{19}H_{18}N_2$ 274.1470, found 274.1463.

***N*-(*p*-Methoxyphenyl)-2-cyano-1-aza-1,3-butadiene (18)**. Following the procedure described for the preparation of *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**), *p*-methoxyacrylanilide (**17**) (1.0 g, 5.65 mmol) in CH_2Cl_2 (40 mL) containing diisopropylethylamine (1.75 g, 13.56 mmol) was treated with triflic anhydride (1.91 g, 1.14 mL, 6.78 mmol) at −73 °C, and then with LiCN (0.56 g, 16.95 mmol) and 12-crown-4 (0.10 g, 0.57 mmol). *N*-(*p*-Methoxyphenyl)-2-cyano-1-aza-1,3-butadiene (**18**) was obtained as a yellow low melting crystalline solid (0.83 g, 79%) after flash column purification (silica gel, 5:1 heptane/EtOAc): mp 52−54 °C; IR (neat) 2220, 1609, 1503, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H), 6.05 (d, J = 10.5 Hz, 1H), 6.29 (d, J = 17.5 Hz, 1H), 6.75 (dd, J = 10.6, 17.5 Hz, 1H), 6.94 (m, 2H), 7.27 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 55.6, 110.7, 114.6, 123.3, 128.2, 136.0, 137.5, 141.4, 159.1; MS *m/z* 186 (M^+), 171, 160, 143, 85. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.65; H, 5.24; N, 14.76.

***N*-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydro-2-ethoxy-6-cyanopyridine (19).** As described for **6**, a mixture of *N*-(*p*-methoxyphenyl)-2-cyanoazadiene (**18**) (100 mg, 0.54 mmol) and ethyl vinyl ether (1.6 g, 21.6 mmol) was heated under closed conditions at 90 °C for 30 h. Compound **19** was obtained as a pale yellow oil (93 mg, 67%) after flash column chromatography (silica gel, 4:1 heptane/ether): IR (neat) 2227, 1622, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7.0 Hz, 3H), 1.59 (m, 1H), 1.95 (m, 1H), 2.16 (ddt, J = 19.3, 1.3, 5.1 Hz, 1H), 2.40 (m, 1H), 3.62 (m, 1H), 3.79 (s, 3H), 3.90 (m, 1H), 4.68 (t, J = 2.4 Hz, 1H), 5.90 (dd, J = 3.0, 1.0 Hz, 1H), 6.89 (m, 2H), 7.08 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.3, 18.6, 23.9, 55.6, 63.1, 88.4, 114.8 × 2, 116.5, 122.7, 125.7, 138.3, 157.4; MS *m/z* 259 (M^+), 214, 187, 172; Anal. Calcd for $C_{15}H_{19}N_2O_2$: C, 69.47; N, 7.38; N, 10.80. Found: C, 69.57; H, 7.08; N, 10.89.

***N*-(*p*-Methoxyphenyl)-2-cyano-1-aza-1,3-butadiene Dimer 20**. *N*-(*p*-Methoxyphenyl)-2-cyanoazadiene (**18**) (206 mg, 1.10 mmol) in 3.0 mL of anhydrous benzene was placed in an argon-flushed 10-mL capacity thick glass-walled tube, equipped with a Rotoflo tap and a magnetic stirring bar, and heated under closed conditions at 100 °C (oil bath temperature) for 36 h. After cooling, the solvent was removed and the residue was flash column chromatographed (silica; 6/1 heptane/ether). Compound **20** was obtained after subsequent recrystallization (pentane−ether) as a bright yellow solid (127 mg, 62%). mp = 97−98 °C; IR (neat) 2227, 2221, 1622, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (m, 1H), 2.34 (m, 2H), 2.47 (m, 1H), 3.78 (s, 3H), 3.81 (s, 3H), 4.53 (t, J = 4.0 Hz, 1H), 5.82 (t, J = 4.0 Hz, 1H), 6.92 (m, 4H), 7.20 (m, 4H). ^{13}C NMR ($CDCl_3$) δ 19.8, 22.2, 55.6, 65.1, 111.9, 114.6, 114.9, 115.6, 118.9, 120.5, 122.9, 126.3, 138.4, 140.0, 140.6, 158.0, 160.0; MS, *m/z* 373 (M^+), 250, 213, 123; HRMS calcd for $C_{22}H_{20}N_4O_2$ 372.1587, found 372.1590. Anal. Calcd for $C_{22}H_{20}N_4O_2$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.85; H,5.65; N, 15.10.

***N*-(*p*-Methoxyphenyl)-2-cyano-1,4-dihydropyridine (21).** Procedure 1: *N*-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydro-2-ethoxy-6-cyanopyridine **(19)** was treated with dry HCl in CH_2Cl_2 for 1 h at room temperature. The mixture was then concentrated and separated by preparative TLC on SiO_2 (heptane−EtOAc, 5:1). Compound **21** was obtained as a colorless oil (20%).

Procedure 2: *N*-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydro-2-ethoxy-6-cyanopyridine **(19)** (57 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was absorbed on 1.0 g of acidic Al_2O_3 (Janssen Chimica, 50−200 μm). The solvent was then evaporated under reduced pressure, and the mixture was stirred under nitrogen at room temperature for 10 min. The adsorbent was washed several times with CH_2Cl_2, and the combined washings were evaporated giving compound **21** (44 mg, 94%) (TLC and NMR pure): IR (film) 2231, 1669, 1606, 1513 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.11 (m, 2H), 3.80 (s, 3H), 4.49 (ddd, J = 8.1, 5.5, 3.0 Hz, 1H), 5.39 (m, 1H), 5.99 (dt, J = 8.1, 1.2 Hz, 1H), 6.89 (d, J = 8.9 Hz, 2H), 7.14 (d, J = 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.82, 55.62, 98.20, 114.72, 115.77, 118.57, 126.70, 128.35, 131.75,

136.28, 158.45; MS (CI, isobutane, 170 °C), *m/z* 269 (M + 57), 213 (M + H), 124, 105.

***N*-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydro-2-carbomethoxy-6-cyanopyridine (22) and *N*-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydro-3-carbomethoxy-6-cyanopyridine (23).** As described for **6**, a mixture of *N*-(*p*-methoxyphenyl)-2-cyanoazadiene (**18**) (110 mg, 0.59 mmol) and methyl acrylate (2.03 g, 2.13 mL, 23.7 mmol) was heated under closed conditions at 90 °C for 40 h. Compounds **22** and **23**, an inseparable 7:1 mixture of regioisomers, were obtained as a yellow oil (134 mg, 83%) after flash column chromatography (silica gel, 4:1 heptane/ethyl acetate).

Compound **22**: ^{1}H NMR ($CDCl_3$) δ 1.95 (m, 1H), 2.17−2.34 (m, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 4.33 (dd, J = 3.1, 4.4 Hz, 1H), 5.64 (dt, J = 1.1, 4.2 Hz, 1H), 6.87 (dt, J = 2.7, 8.9 Hz, 2H), 7.10 (dt, J = 2.7, 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.0, 22.7, 55.5, 61.7, 114.5, 115.8, 117.7, 125.6, 138.5, 157.4, 171.8.

Compound **23**: ^{1}H NMR ($CDCl_3$) δ 2.50 (m, 2H), 2.77 (m, 1H), 3.54 (m, 2H), 3.62 (s, 3H), 3.78 (s, 3H), 5.78 (t, J = 4.0, 1H), 6.87 (dt, J = 2.1, 8.9 Hz, 2H), 7.01 (dt, J = 2.1, 8.9 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 25.8, 36.7, 52.5, 52.7, 61.7, 115.8, 118.3, 118.9, 124.7, 138.9, 157.3, 173.0.

For the mixture of regioisomers: IR (neat) 2225, 1744, 1613, 1506, 1450 cm^{-1}; MS *m/z* 272 (M^+), 257, 213, 134, 92; HRMS calcd for $C_{15}H_{16}N_2O_3$ 272.1161, found 272.1151.

***N*-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydro-2-acetyl-6-cyanopyridine (24) and *N*-(*p*-Methoxyphenyl)-1,2,3,4-tetrahydro-3-acetyl-6-cyanopyridine (25)**. As described for **6**, a mixture of *N*-(*p*-methoxyphenyl)-2-cyanoazadiene **18** (100 mg, 0.54 mmol) and methyl vinyl ketone (1.1 g, 21.6 mmol) was heated under closed conditions at 75 °C for 24 h. Compound **24** was obtained as a white solid (78 mg, 56%) and **25** as a yellow oil (10 mg, 7%) after flash column chromatography (silica gel, 4:1 heptane/ether).

Compound **24**: IR (neat) 2259, 2227, 1717, 1618, 1508 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (m, 1H), 2.17 (m, 3H), 2.33 (s, 3H), 3.79 (s, 3H), 4.11 (t, J = 4.0 Hz, 1H), 5.79 (t, J = 4.0 Hz, 1H), 6.88 (m, 2H), 7.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.2, 20.7, 27.1, 55.6, 114.8, 115.8, 118.3, 121.5, 124.7, 139.1, 157.3, 208.8; MS *m/z* 256 (M^+), 213, 134, 92. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.28; H, 6.29; N, 10.93. Found: C, 69.88; H, 6.46; N, 10.78.

Compound **25**: IR (neat) 2228, 1711, 1621, 1514 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.44 (m, 2H), 2.82 (m, 1H), 3.44 (m, 1H), 3.75 (dd, J = 3.0, 10.0 Hz, 1H), 3.80 (s, 3H), 5.81 (t, J = 4.2 Hz, 1H), 6.89 (m, 2H), 7.01 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.4, 28.6, 44.1, 52.4, 55.6, 114.8, 118.7, 115.5, 119.3, 124.9, 139.0, 157.3, 207.6; MS *m/z* 256 (M^+), 213, 134, 84; HRMS calcd for $C_{15}H_{16}N_2O_2$ 256.1212, found 256.1210.

***N*-Phenyl-2-cyano-4-methyl-1-aza-1,3-butadiene (27)**. Following the procedure described for the preparation of *N*-phenyl-2-cyano-1-aza-1,3-butadiene (**4**), crotanilide **26** (1.777 g, 11.04 mmol) in CH_2Cl_2 (60 mL) containing diisopropylethylamine (3.418 g, 26.50 mmol) was treated with triflic anhydride (3.735 g, 2.23 mL, 13.25 mmol) at −73 °C, and then with LiCN (1.093 g, 33.12 mmol) and 12-crown-4 (0.194 g, 1.1 mmol). *N*-Phenyl-2-cyano-4-methyl-1-aza-1,3-butadiene (**27**), a 5:1 mixture of isomers, was obtained as a yellow low melting crystalline solid (1.181 g, 63%) after flash column purification (silica gel, 15:1 heptane/EtOAc): mp 35 °C; IR (neat) 2228, 1645, 1581, 1490, 1441, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$) major isomer δ 2.05 (dd, J = 1.6, 6.8 Hz, 3H), 6.52 (ddd, J = 1.5, 3.0, 15.9 Hz, 1H), 6.96 (m, 1H), 7.08 (d, J = 7.3, 2H), 7.27 (t, J = 7.4, 1H), 7.42 (t, J = 7.3, 2H); minor isomer δ 1.91 (dd, J = 1.6, 6.9 Hz, 3H), 6.21 (ddd, J = 1.5, 3.1, 15.6 Hz, 1H), 6.90 (m, 1H), 7.08 (d, J = 7.3, 2H), 7.27 (t, J = 7.4, 1H), 7.42 (t, J = 7.3, 2H); ^{13}C NMR ($CDCl_3$) δ 18.8, 110.3, 119.9, 120.4, 122.8, 125.9, 127.2, 129.3, 130.8, 140.4, 144.6, 146.1, 147.9, 149.1; MS (CI) *m/z* 227 (M + 57$^+$), 171 (M + H), 144. Anal. Calcd for $C_{11}H_{10}N_2$: C, 77.62; H, 5.92; N, 16.46. Found: C, 77.50; H, 5.81; N, 16.41.

***N*-Phenyl-1,2,3,4-tetrahydro-*cis*-2-phenyl-4-methyl-6-cyanopyridine (29) and Its *Trans* Isomer 30**. As described for **6**, *N*-phenyl-2-cyano-4-methyl-1-aza-1,3-butadiene (**27**) (141 mg, 0.83 mmol) and styrene (3.45 g, 33.2 mmol) were heated under closed conditions at 120 °C for 30 h. Compound **29** was obtained as a white solid (141 mg, 62%), and **30** (admixture with **29**) as a pale yellow oil (33 mg, 15% from NMR) after flash column chromatography (silica gel, heptane/EtOAc, 97:3, then 95:5).

Compound **29** (major isomer): IR (neat) 2228, 1616, 1602, 1497, 1413 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (d, J = 7.2 Hz, 3H), 2.05 (m, 1H), 2.25 (ddd, J = 4.5, 5.8, 13.5 Hz, 1H), 2.61 (ddd, J = 3.4, 6.8, 13.4 Hz, 1H), 4.70 (dd, J = 4.1, 7.7 Hz, 1H), 5.69 (d, J = 3.2 Hz, 1H), 7.03 (m, 3H), 7.25 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 20.9, 28.3, 38.6, 63.2, 116.2, 119.2, 124.5, 125.2, 126.4, 127.1, 127.4, 128.6, 129.0, 141.2, 145.4; MS *m/z* 274 (M^+), 259, 180, 168, 104, 91, 77. Anal. Calcd for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.16; H, 6.85; N, 10.16.

Compound **30** (minor isomer): ^{1}H NMR ($CDCl_3$) δ 1.07 (d, J = 6.9 Hz, 3H), 1.77 (m, 1H), 1.96−2.28 (m, 2H), 4.88 (t, J = 3.5 Hz, 1H), 5.61 (d, J = 1.5 Hz, 1H), 6.87−7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 19.5, 25.3, 34.8, 63.0, 116.3, 119.2, 124.1−129.2, 7 peaks, 141.4, 145.9.

***N*-Phenyl-1,2,3,4-tetrahydro-*cis*-2-(3-nitrophenyl)-4-methyl-6-cyanopyridine (31) and Its *Trans* Isomer 32**. As described for **6**, *N*-phenyl-2-cyano-4-methyl-1-aza-1,3-butadiene (**27**) (37 mg, 0.22 mmol) and 3-nitrostyrene (1.3 g, 8.8 mmol) were heated under closed conditions at 90 °C for 22 h. Compounds **31** (31 mg, 44%) and **32** (11 mg, 16%) were obtained as yellow oils after two flash column chromatographies (silica gel, 50:1 heptane/EtOAc):

Compound **31** (major isomer): IR (neat) 2228, 1609, 1595, 1532, 1356 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (d, J = 7.2 Hz, 3H), 2.02 (dt, J = 8.4, 13.6 Hz, 1H), 2.26 (dddd, J = 0.6, 3.8, 5.7, 13.7 Hz, 1H), 2.71 (m, 1H), 4.77 (dd, J = 3.7, 8.7 Hz, 1H), 5.69 (dd, J = 2.5, 3.7 Hz, 1H), 6.98−7.61 (m, 8H), 8.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 28.4, 39.0, 63.0, 115.7, 119.8, 122.3, 122.4, 122.7, 125.5, 125.8, 126.3, 129.4, 129.7, 133.2, 143.7, 144.8, 148.5; MS *m/z* 319 (M^+), 304, 197, 169, 155, 93, 77. HRMS calcd for $C_{19}H_{17}N_3O_2$ 319.1321, found 319.1302.

Compound **32** (minor isomer): IR (neat) 2228, 1602, 1532, 1497, 1349 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.13 (d, J = 6.9 Hz, 3H), 1.84 (ddd, J = 4.2, 11.4, 12.9, 1H), 2.02 (m, 1H), 2.26 (m, 1H), 4.96 (t, J = 3.5 Hz, 1H), 5.68 (dd, J = 1.4, 2.5 Hz, 1H), 7.04−7.73 (m, 8H), 8.17 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 19.5, 25.2, 34.3, 62.7, 115.8, 116.6, 121.0, 122.4, 122.6, 125.0, 127.5, 129.5, 130.0, 132.2, 143.7, 145.6, 148.9.

***N*-Phenyl-1,2,3,4-tetrahydro-*cis*-2-(4-bromophenyl)-4-methyl-6-cyanopyridine (33) and Its *Trans* Isomer 34**. As described for **6**, *N*-phenyl-2-cyano-4-methyl-1-aza-1,3-butadiene (**27**) (116 mg, 0.68 mmol) and 4-bromostyrene (5.0 g, 27.2 mmol) were heated under closed conditions at 90 °C for 44 h. Compounds **33** (120 mg, 50%) and **34** (43 mg, 18%) were obtained as pale yellow oils after repetitive flash column chromatography (silica gel, 97:3 heptane/EtOAc):

Compound **33** (major isomer): IR (neat) 2228, 1623, 1595, 1497 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.86 (d, J = 7.2 Hz, 3H), 1.97 (m, 1H), 2.20 (ddd, J = 4.1, 5.9, 13.6 Hz, 1H), 2.61 (ddd, J = 3.2, 7.3, 13.7 Hz, 1H), 4.64 (dd, J = 3.9, 8.0 Hz, 1H), 5.67 (d, J = 3.1 Hz, 1H), 6.97 (d, J = 7.4, 2H), 7.04 (t, J = 7.4, 1H), 7.11 (d, J = 8.4, 2H), 7.21 (t, J = 7.7, 2H), 7.38 (d, J = 8.4, 2H, 2H); ^{13}C NMR ($CDCl_3$) δ 20.9, 28.2, 38.5, 62.7, 116.0, 119.3, 121.2, 124.7, 125.5, 126.2, 128.8, 129.1, 131.7, 140.3, 145.1; MS *m/z* 354, 352 (M^+), 353, 351, 339, 337, 231, 182, 184, 169, 77. Anal. Calcd for $C_{19}H_{17}N_2Br$: C, 64.60; H, 4.85; N, 7.93. Found: C, 64.44; H, 5.01; N, 7.64.

Compound **34** (minor isomer): IR (neat) 2228, 1625, 1595, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (d, J = 6.8 Hz, 3H), 1.77 (ddd, J = 4.3, 11.0, 12.6, 1H), 2.06 (m, 1H), 2.19 (m, 1H), 4.83 (dd, J = 3.3, 3.6 Hz, 1H), 5.62 (dd, J = 1.6, 2.5 Hz, 1H), 7.02-7.33 (m, 7H), 7.50 (d, J = 8.5, 2H); ^{13}C NMR ($CDCl_3$) δ 19.5, 25.2, 34.6, 62.6, 116.0, 120.4, 121.2, 124.4, 127.4, 127.7, 129.3, 132.0, 140.5, 145.8; MS *m/z* 354, 352 (M^+), 353, 351, 339, 337, 231, 195, 182, 169, 93, 77.

***N*-Phenyl-1,2,3,4-tetrahydro-*cis*-2-ethoxy-4-methyl-6-cyanopyridine (35) and Its *Trans* Isomer 36**. As described for **6**, *N*-phenyl-2-cyano-4-methyl-1-aza-1,3-butadiene (**27**) (60 mg, 0.35 mmol) and ethyl vinyl ether (1.02 g, 14.0 mmol) were heated under closed conditions at 120 °C for 34 h. Compounds **35** and **36** (73 mg, 88%) were obtained as a 2:1 mixture of isomers after flash column chromatography (silica gel, 20:1 heptane/EtOAc):

Compound **35** (major isomer): ^{1}H NMR ($CDCl_3$) δ 1.23 (d, J = 5.8 Hz, 3H), 1.26 (d, J = 5.3 Hz, 3H), 1.95 (m, 1H), 2.42

(m, 1H), 3.58 (m, 1H), 3.84 (m, 1H), 4.88 (t, J = 2.9 Hz, 1H), 6.03 (d, J = 4.2 Hz, 1H), 7.06−7.45 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.3, 21.6, 26.3, 31.9, 63.1, 88.8, 119.9, 120.4, 122.7, 124.4, 127.2, 129.3, 129.5, 130.8, 131.7, 144.5.

Compound **36** (minor isomer): ^{1}H NMR ($CDCl_3$) δ 1.14 (d, J = 7.2 Hz, 3H), 1.23 (d, J = 6.7 Hz, 3H), 1.77−2.07 (m, 1H), 2.72 (m, 1H), 3.59 (m, 1H), 3.87 (m, 1H), 4.75 (t, J = 2.6 Hz, 1H), 5.83 (dd, J = 1.4, 2.5 Hz, 1H), 7.11 (m, 3H), 7.37 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 18.9, 19.4, 24.8, 33.0, 63.2, 89.1, 116.4, 120.4, 123.6, 124.9, 129.6, 130.5, 131.8, 144.5.

For the mixture of isomers: IR (neat) 2228, 1645, 1631, 1595, 1490 cm^{-1}; MS (FAB) m/z 242 (M^+). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.29; H, 7.20; N, 11.78.

***N*-Phenyl-1,2,3,4-tetrahydro-*cis*-2-carbomethoxy-4-methyl-6-cyanopyridine 37, Its *Trans* Isomer 38, and *N*-Phenyl-1,2,3,4-tetrahydro-*cis*-3-carbomethoxy-6-cyanopyridine (39) and Its *Trans* Isomer 40.** As described for **6**, *N*-phenyl-2-cyano-4-methyl-1-aza-1,3-butadiene (**27**) (120 mg, 0.70 mmol) and methyl acrylate (2.43 g, 28.0 mmol) were heated under closed conditions at 120 °C for 40 h. Compounds **37**−**40** (64 mg, 36%, mixture of isomers, 5:1:2.6:2) were obtained as a yellow oil after flash column chromatography (silica gel, 20:1 heptane/EtOAc):

For the mixture of isomers: IR (neat) 2231, 1738, 1619, 1606, 1500 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, J = 7.3 Hz, 4-Me), 1.03 (d, J = 6.6 Hz, 4-Me), 1.14 (d, J = 6.9 Hz, 4-Me), 1.29 (dd, J = 6.4, 13.3 Hz, H-4), 1.43 (d, J = 6.7 Hz, H-3), 1.64 (ddd, J = 4.7, 11.3, 13.1 Hz, H-3), 2.21 (t, J = 5.1 Hz, H-3), 2.30−2.54 (m, H-5), 2.85 (m, H-2, H-3), 3.56 (dd, J = 11.1, 12.8 Hz, H-2), 3.59 (s, Me), 3.68 (s, Me), 3.73 (s, Me), 3.77 (s, Me), 3.82 (dd, J = 1.3, 2.7 Hz, H-2), 4.36 (t, J = 5.0 Hz, H-2), 4.41 (dd, J = 2.9, 4.6 Hz, H-2), 5.58 (dd, J = 1.5, 2.5 Hz, H-5), 5.72 (d, J = 4.1 Hz, H-5), 5.76 (d, J = 3.8 Hz, H-5), 5.79 (d, J = 4.5 Hz, H-5), 7.10 (m, ArH), 7.26 (m, ArH), 7.34 (m, ArH); ^{13}C NMR ($CDCl_3$) δ 15.9, 17.4, 19.8, 21.2, 26.2, 26.6, 27.8, 30.0, 31.5, 31.7, 32.2, 41.5, 44.6, 47.4, 50.4, 51.6, 51.8, 52.1, 52.4, 52.7, 57.2, 59.8, 61.8, 115.5, 115.7, 116.6, 117.2, 117.7, 119.7, 119.9, 120.0, 122.2, 122.4, 122.6, 122.9, 123.0, 123.5, 123.9, 124.5, 124.9, 125.0, 125.5, 125.7, 125.8, 127.1, 127.3, 128.4, 129.3, 129.6, 129.8, 134.2, 144.8, 145.0, 145.4, 172.0; MS m/z 256 (M^+), 241, 205, 197, 181, 169, 93, 77. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.49; H, 6.25; N, 10.99.

X-ray Structure Analysis of Compound 29. Crystal data. $C_{19}H_{18}N_2$, molecular weight 274.37; monoclinic system; space group $P2_1/n$; Z = 4; a = 12.699(4), b = 7.909(2), c = 16.149(5) Å, β = 107.55(5)°; V = 1546(1) Å^3; d_c = 1.18 g cm^{-3}; $F(000)$ = 584; l (Cu Kα) = 1.5418 Å; μ = 0.50 mm^{-1} (absorption ignored). Data were collected on a CAD4 Enraf-Nonius diffractometer using graphite monochromated Cu Kα radiation . From the 3804 reflexions measured by the (θ−2θ) scan technique up to θ = 66, 2697 were independent (R_{int} = 0.024) and 1842 were considered as observed with $I > 3.0\sigma(I)$, $\sigma(I)$ from counting statistics.

The structure was solved by direct methods using SHELXS86[47] and refined by full matrix least-squares with SHELX76,[48] minimizing the function $\Sigma w(F_o - |F_c|)^2$. The hydrogen atoms, located in difference Fourier maps, were introduced in theoretical position (d(C−H) = 1.00 Å) and assigned an isotropic thermal factor equivalent to that of the bonded carbon atom, plus 10%. Convergence was reached at R = 0.053 and R_w = 0.090 (with $R_w = \{\Sigma w(F_o - |F_c|)^2/\Sigma w F_o^2\}^{1/2}$ and $w = 1/[\sigma^2(F_o) + 0.0058F_o^2]$. No residual was higher than 0.29 e Å^{-3} in the final difference map.[49]

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Supporting Information Available: ^{1}H and ^{13}C NMR data with complete peak assignments for all compounds, and an ORTEP drawing for **18** (12 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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(47) TEXAN (1985). *TEXRAY* Structure Analysis Package Molecular Structure Corporation.

(48) Sheldrick, G. M. *SHELXS86*. Program for the solution of crystal structures. Univ. of Göttingen, Germany, 1986.

(49) Sheldrick, G. M. *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England, 1976.