Intramolecular Diels−Alder Reaction of *N*-Alkyl-2-cyano-1-azadienes: A Study of the Eschenmoser Cycloreversion of Dihydrooxazines as a Route to *N*-Alkyl-2-cyano-1-azadienes

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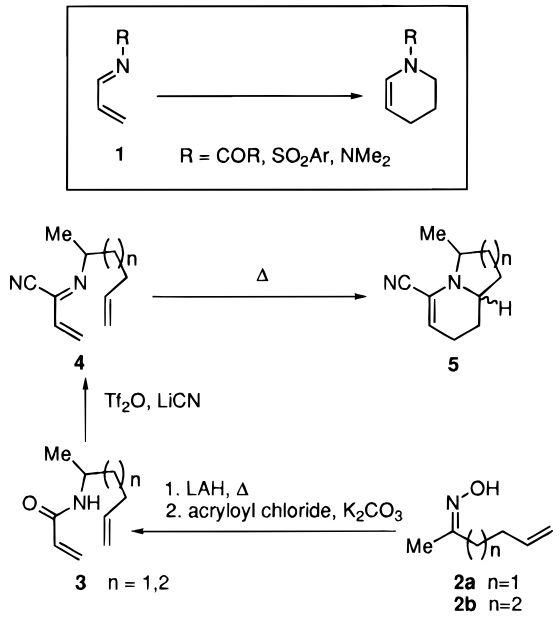
In connection with the development of the intramolecular Diels−Alder reaction (IMDA) of 1-azadienes, the 5,6-dihydro-4*H*-1,2-oxazine **12** has been evaluated as a synthon equivalent of the 2-cyano-1-azadiene system. It was found that the dihydrooxazonium salt **27**, generated *in situ* from the cyclic hydroxamic acid derivative **26**, is converted directly to azadiene **4a** *via* tautomerization to the corresponding enamine and a particularly facile Eschenmoser type cycloreversion process. Conditions were subsequently found for the preparation of synthon **12**. *N*-Alkylation of this intermediate with alkyl bromides in the presence of Ag^+ ion also resulted in direct formation of the 2-cyano-1-azadiene products **38a**−**d** and **4a**. Microwave irradiation of a benzene solution of azadiene **4a** proved to be a convenient means to effect its IMDA conversion to indolizidine **5a**. To avoid decomposition of azadiene **38c**, its intramolecular cycloaddition giving **40** (60%) was achieved by flash vacuum thermolysis.

The Diels−Alder reaction has proven to be an exceptionally powerful method for carbon−carbon bond formation in the synthesis of natural products and novel structures of both fundamental and applied interest. Indeed, in this process the simultaneous creation of two new C−C bonds is coupled with the possibility for regio- and stereocontrol at up to four carbon centers in the newly formed six-membered ring. Over the past decade considerable effort has also gone into the development of the Diels−Alder reaction of 1-azadienes **1**.[1] In particular, strategies have evolved to surmount the inherent problems associated with the lack of reactivity of these dienes in both the inter- and intramolecular Diels−Alder reactions. These include reinforcing the inverse electron demand nature of the azadiene system in $LUMO_{diene}$-controlled cycloadditions through *N*-SO_2AR and *N*-COR substitution and, alternatively, reversing the normal electrophilic character of these heterodienes by introduction of electron-donating *N*,*N*-dialkylamino groups onto nitrogen.[2−5]

In a continuation of our work on the [4 + 2] cycloaddition chemistry of 1-azadienes,[6] it was found that the intramolecular Diels−Alder (IMDA) reactions of the 2-cyano-substituted *N*-alkyl azadienes **4a,b** occur under mild conditions to give the fused bicyclic nitrogen heterocycles **5a,b** in up to 90% yield (Scheme 1).[7,8] These results indicate that a C-2 cyano substituent alone can serve to both accentuate the Diels−Alder reactivity of the 1-azadiene system and render the process efficient through stabilization of the starting diene and the derived Δ^2-piperideine product. Of greater synthetic interest, the

Scheme 1



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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) 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.

(3) (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.

(4) (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.

(5) Boger, D. L.; Corbett, W. L.; Allcock, S. J.; Gilchrist, T. L.; Shattleworth, S. J. *Tetrahedron* **1991**, *48*, 10053. See also ref 3a.

(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. (e) Sisti, N. J.; Motorina, I. A.; Tran Huu Dau, M.-E.; Claude, R.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1996**, *61*, 3715.

(7) Dufour, B.; Motorina, I.; Fowler, F. W.; Grierson, D. S. *Heterocycles* **1994**, *37*, 1455.

(8) Sisti, N. J.; Zeller, E.; Grierson, D. S.; Fowler, F. W. *J. Org. Chem.* **1997**, *62*, 2093.

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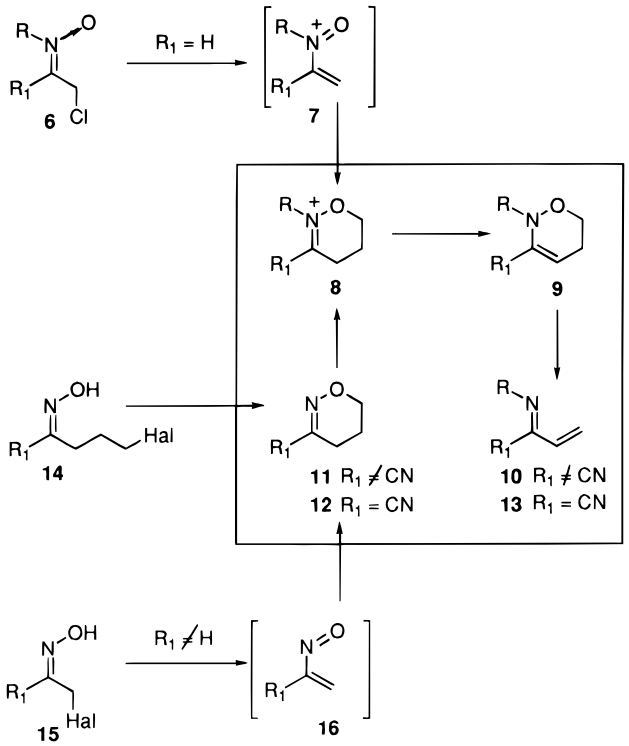
Scheme 2

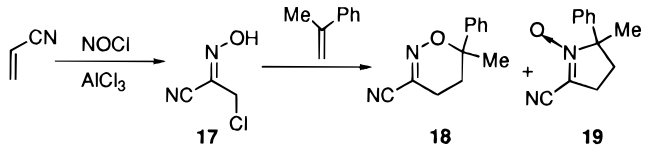


results suggest that the IMDA reaction of 2-cyano-1-azadienes can be integrated with confidence into strategies for the multistep synthesis of structurally complex heterocycles.

In this context, coordination of the timing and mode of construction of the azadiene component in the synthetic intermediate which is engaged in the intramolecular cycloaddition reaction is important. For the unfunctionalized compounds **4**, this was achieved by elaboration of the stable amides **3** followed by their reaction with triflic anhydride/LiCN.[6e,9] However, for more complicated target molecules the situation may well arise where the reaction conditions, and the linear type of approach taken to access **4**, are not applicable. Alternatives are thus required. A more convergent strategy is to construct the 2-cyano-1-azadiene and dienophile components separately and connect them only immediately prior to the programmed cycloaddition step. Anticipating the instability of 2-cyano-1-azadiene itself,[10] we have sought to develop this IMDA approach through the use of more stable 1-azadiene equivalents from which, ideally, the 2-cyano-1-azadiene unit can be generated *in situ* under the thermal conditions of the Diels−Alder reaction.

As demonstrated in elegant experiments conducted by Eschenmoser *et al.* in the early 1970s, dihydro-1,2-oxazines possess this potential.[11] It was observed that 5,6-dihydro-4*H*-1,2-oxazonium salts **8**, formed in the Diels−Alder reaction of transient vinylnitrosonium intermediates **7**, readily tautomerize in the presence of base producing the isomeric dihydrooxazines **9**. On gentle heating (50 °C) these intermediates undergo a very clean cycloreversion to give 1-azadienes **10** (Scheme 2). Further work by other groups has shown that the dihydrooxazonium salts **8** where R_1 = H or Ph can also be formed by *N*-alkylation of the corresponding dihydro-1,2-oxazines **11** with alkyl iodides and Meerwein reagents.[12] However, lacking suitable activation, the simple 1-azadienes obtained *via* the Eschenmoser retro Diels−Alder route have not found application as dienes in inter- or intramolecular Diels−Alder reactions.

Scheme 3



We have undertaken a project to evaluate the reactivity and use of the dihydro-1,2-oxazine **12** functionalized at C-3 by a cyano group as a synthon equivalent of 2-cyano-1-azadiene. The initial objectives in this work have been to develop conditions for the preparation and *N*-alkylation of synthon **12**, as well as to demonstrate that the retro Diels−Alder reaction of the corresponding enamine tautomer **9** efficiently reveals the 2-cyano-1-azadiene system in **13**.

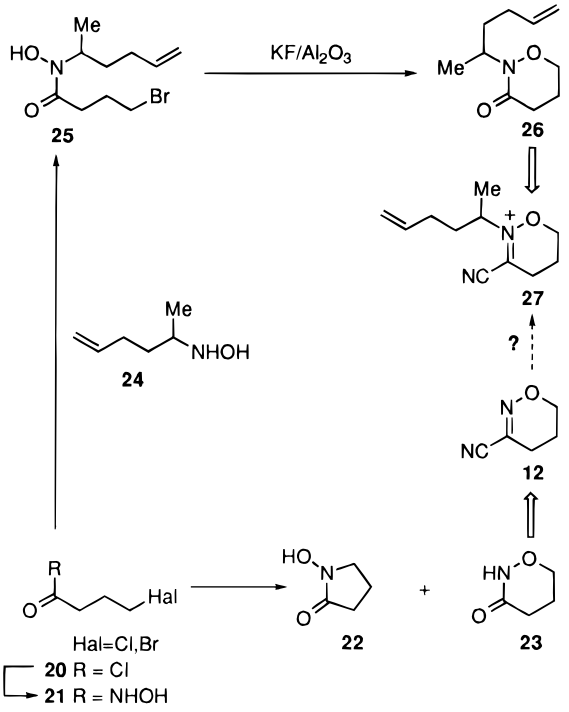
Results and Discussion

Two principal methods for the preparation of 5,6-dihydro-4*H*-1,2-oxazines include the cyclization of γ-halo oximes such as **14**[13] and the Diels−Alder reaction of nitrosoethylene derivatives **16**, generated from α-chloro-(bromo)methyl oximes such as **15**, with nucleophilic olefins (Scheme 2).[14] In view of the close parallel between the latter approach and Eschenmoser's work on α-chloronitrones **6**, we initially pursued this route to prepare 3-cyano-substituted dihydro-1,2-oxazines.

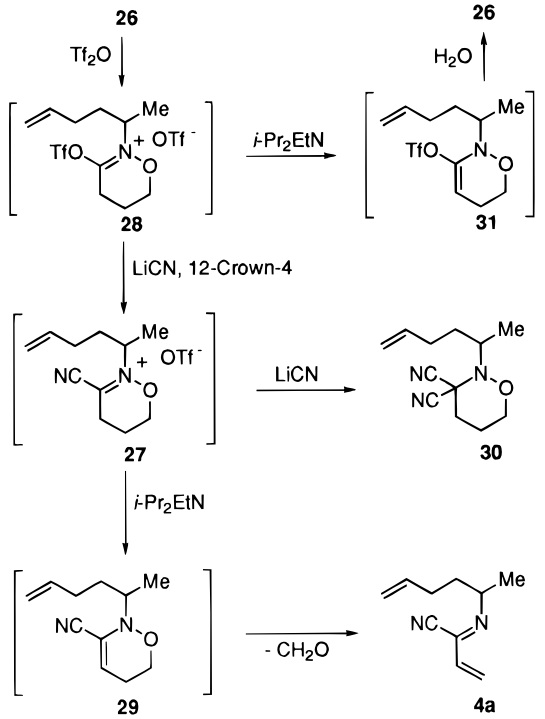
Ogloblin *et al.* showed that the starting cyano-substituted α-chloro oxime **17** could be prepared by reaction of nitrosyl chloride with acrylonitrile in ether/HCl.[15] However, under the reported conditions we found that product isolation was complicated due to concomitant formation of significant amounts of 2-chloropropionitrile through conjugate addition of HCl. Fortunately, by carrying out the reaction in the presence of catalytic quantities of $AlCl_3$, compound **17** was formed exclusively and isolated in 76% yield. Concerning the reactivity of this chlorooxime, Viehe *et al.* demonstrated that it reacts with cyclopentadiene in the presence of carbonate base to give the expected Diels−Alder product.[16] Furthermore, Gilchrist found that the related vinylnitroso intermediate **16** (R_1 = CO_2Et) reacts successfully with α-methylstyrene, but not with unactivated olefins such as ethylene.[14] For this reason we opted to prepare dihydrooxazine **18** by reaction of **17** with K_2CO_3 in CH_2Cl_2 containing 2 equiv of α-methylstyrene (20 °C, 15 h) (Scheme 3). This produced a separable mixture (1:1.2) of the desired

(9) For the preparation of LiCN, see: Livinghouse, T. *Org. Synth.* **1981**, *60*, 126.
(10) De Corte, B.; Denis, J.-M.; De Kimpe, N. *J. Org. Chem.* **1987**, *52*, 1147.
(11) (a) Gygax, P.; Das Gupta, T. K.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 2205. b) Kempe, U. M.; Das Gupta, T. K.; Blatt, P.; Gygax, P.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 2187.
(12) (a) Goldberg, I.; Saad, D.; Shalom, E.; Shatzmiller, S. *J. Org. Chem.* **1982**, *47*, 2192.; (b) Shatzmiller, S.; Shalom, E. *Liebigs Ann. Chem.* **1983**, 897. (c) Hardegger, B.; Shatzmiller, S. *Helv. Chim. Acta* **1976**, *59*, 2765.
(13) *Comprehensive Heterocyclic Chemistry*; Katritsky, A., Rees, C. W., Eds.; Pergamon: New York, 1984; Vol. 3, Chapter 2−27.
(14) Gilchrist, T. L. *J. Chem. Soc. Rev.* **1983**, *1*, 53.
(15) Ogloblin, K. A.; Semenov, V. P. *Z. Organich. Himii SSSR* **1965**, *1*, 1361, *Chem. Abstr.* **1966**, *64*, 588a.
(16) Francotte, E.; Merényi, R.; Vandenbulcke-Coyette, B.; Viehe, H.-G. *Helv. Chim. Acta* **1981**, *64*, 1208.

Scheme 4



Scheme 5



Diels−Alder adduct **18** (40%) and the more polar nitrone **19**, whose structure was confirmed by X-ray crystallography.[17]

In subsequent attempts to *N*-alkylate or *N*-acylate dihydrooxazine **18**, it was found that it does not react even with alkyl triflates or Meerwein's reagent. Indeed, by ^{1}H NMR it was revealed that, at best, a 2−5% yield of the desired *N*-alkylated enamine tautomer, or the azadiene resulting from retrocondensation, was formed in the case where **18** was treated with an excess of 4-pentenyl triflate and triethyloxonium tetrafluoroborate at temperatures up to 80 °C. In earlier work by Lee and Woodward,[18] similar difficulties were encountered to *N*-alkylate 3-carbethoxy-substituted dihydrooxazines. However, in the present case this problem is most probably aggravated by the sterically crowded neopentyl environment of the oxime ether nitrogen.

Several different options were thus considered at this point for the preparation of the unsubstituted 3-cyanodihydrooxazine **12** and the subsequent study of its *N*-alkylation/cycloreversion. Wade[19] previously showed that this synthon can be accessed by cyclization of the nitro-substituted halo oxime **14** ($R_1 = NO_2$), followed by displacement of the nitro group in the derived dihydrooxazine product by cyanide ion. This route is direct, but in terms of our objectives the approach illustrated in Scheme 4 potentially offered greater flexibility, since the Tf_2O/LiCN conditions used to convert **3** → **4** could be employed to prepare **12** and/or the dihydrooxazonium salt **27** from the cyclic hydroxamic acid derivatives **23** and **26**.

The acyclic hydroxamic acid **21** was easily prepared in 95% yield by reaction of chloro- or bromobutyryl chloride **20** with hydroxylamine hydrochloride in the presence of K_2CO_3 (Scheme 4). Cyclization of **21** (Hal = Cl) was complicated by competing formation of **22**; however, compound **23** was obtained in 75% yield from the corresponding bromide derivative of **21** (Hal = Br). Somewhat suprizingly, different attempts to transform **23** to synthon **12** produced a mixture of unidentifiable products, leading us to focus all subsequent attention upon the preparation of *N*-alkylated hydroxamic acid **26** by ring closure of the bromo compound **25**. Compound **25** was itself prepared by reaction of bromobutyryl chloride with the hydroxylamine derivative **24**, which was in turn obtained by cyanoborohydride reduction of oxime **2a**.[20] Under typical solution reaction conditions (CH_2Cl_2, NaOH), cyclization of **25** was capricious, but by carrying out the reaction on alumina impregnated with KF in the absence of solvent,[21] a high-yield transformation to compound **26** was achieved (90%).

With intermediate **26** in hand, its reaction with triflic anhydride and LiCN at −60 °C was examined. Following our established protocol[6c] in which diisopropylethylamine is present in the reaction medium from the outset, only starting material was recovered. Recognizing that the amine base may tautomerize the initially formed *O*-triflyl imidate salt **28** to the *N*,*O*-triflyl ketene acetal **31** (Scheme 5), which is simply hydrolyzed upon reaction workup, the experimental procedure was modified such that the Hunig's base and LiCN are simultaneously added in equivalent amounts after the triflic anhydride. Under these new conditions two products were formed, and varying amounts of the starting hydroxylamine derivative were again recovered (up to 30%). Quite suprizingly, the major less polar reaction component (44%) corresponded to azadiene **4a** and not to the expected cyano enamine intermediate **29**. Indeed, direct conversion of amide **26** to this azadiene, presumably *via* the dihydrooxazonium salt **27** and its tautomer **29**, was shown by TLC to occur during the period in which the

(17) The authors have deposited atomic coordinates for compound **19** 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.
(18) Lee, V. J.; Woodward, R. B. *J. Org. Chem.* **1979**, *44*, 2487.
(19) Wade, P. *J. Org. Chem.* **1978**, *43*, 2020.
(20) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.
(21) Bergbreiter, D. E. *J. Org. Chem.* **1987**, *52*, 1601.

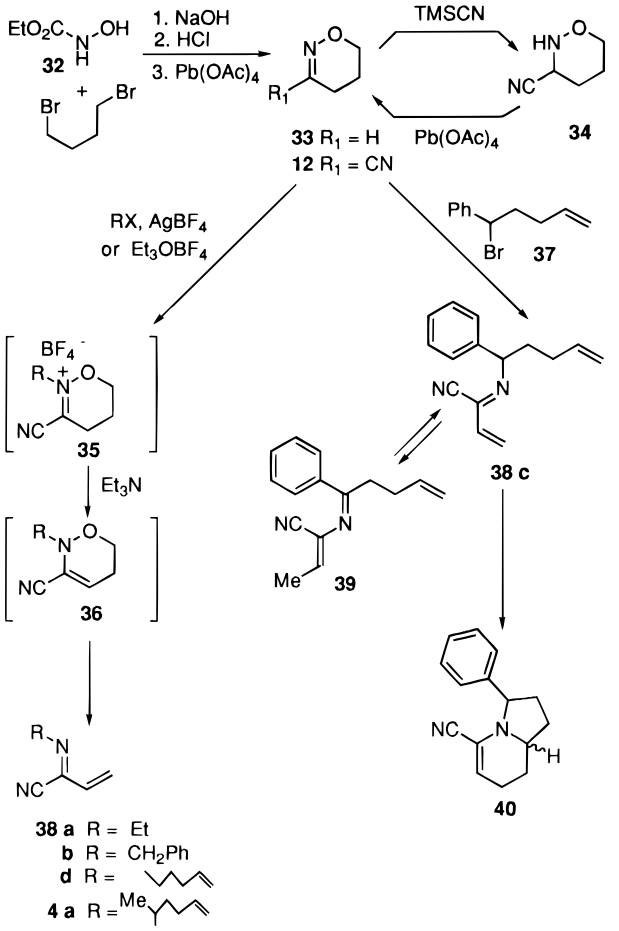
reaction was brought to room temperature. This result indicates that the dihydrooxazine isomer **29** bearing the electron-withdrawing cyano substituent at C-3 is remarkably prone to undergo the retro Diels−Alder process described by Eschenmoser, precluding therefore its isolation as a discrete product. The other more polar product (8%) of this reaction, also isolated by silica gel flash column chromatography, corresponded to the dicyano addition product **30**. Compound **30** most likely arises through competing reaction of the initially formed cyano imidate **27** with CN^- ion. In agreement with this mechanism was the observation that when **26** was treated with Tf_2O and LiCN in the absence of amine base azadiene **4a** was not produced, and the yield of the dicyano product **30** increased accordingly to 35%. Varying the reaction temperature and other parameters did not permit us to suppress completely the formation of the dicyano product **30**, or the process leading back to starting material, indicating that there is a very fine balance between the three different reaction pathways.

Having shown that the dihydrooxazonium salt **27** can be generated from hydroxamic acid **26**, and further that this intermediate transforms directly to azadiene **4a**, we returned to the preparation of synthon **12** in order to determine whether it could be successfully *N*-alkylated. A new route to this compound was devised based upon both the reported use of $Pb(OAc)_4$ to oxidize tetrahydrooxazine to the parent dihydro system **33** (**11**; $R_1 = H$)[22] and our own experience in the conversion of α-aminonitriles to imodyl cyanides using the same oxidant.[7] Thus, 5,6-dihydro-4*H*-1,2-oxazine (**33**) was synthesized in high overall yield by reaction of *N*-hydroxyurethane **32** with dibromobutane followed by ester hydrolysis−decarboxylation and $Pb(OAc)_4$ oxidation (Scheme 6).[23] By subsequent reaction of this sensitive intermediate with TMSCN, the stable aminonitrile **34** was obtained (84%). Finally, treatment of **34** with $Pb(OAc)_4$ provided a very convenient method to obtain gram quantities of **12**.

In marked contrast to **18**, synthon **12** reacted rapidly with triethyloxonium tetrafluoroborate, followed by Et_3N, to give directly the volatile *N*-ethyl-2-cyano-1-azadiene (**38a**) (71%) (Scheme 6). The same product was also formed, albeit in lower yield (29%), on reaction of **12** with EtBr in the presence of $AgBF_4$. In a similar way the reaction of **12** with benzyl bromide and silver ion gave the expected *N*-benzyl azadiene product **38b** in 72% isolated yield. Building upon this result, it was also found that reaction of **12** with the benzyl bromide derivative **37** was efficient, leading directly to formation of azadiene **38c** in 67% yield (along with 4% of the cyclic amide related to **26** produced by hydrolysis of the initially formed intermediate of type **35**/**36**). However, for reasons which have not been firmly established,[24] the corresponding Ag^+-promoted *N*-alkylation of **12** with 4-pentenyl bromide and 2-bromohex-5-ene produced the desired azadienes **38d** and **4a** in only 6−8% yields. Likewise, treatment of **12** with 4-pentenyl triflate did not result in formation of appreciable amounts of cyano enamine **36** or azadiene **38d**.

To finalize this preliminary study of the use of dihydrooxazine **12** as a 2-cyano-1-azadiene equivalent, it

Scheme 6



remained to effect the IMDA reaction of azadienes **4a** and **38c**. Although the conversion of **4a** to indolizidine **5a** (mixture of diastereomers) had already been achieved by heating in benzene overnight in a sealed tube at 110 °C,[8] it was found that reaction time could be reduced to a mere 14 min when this Diels−Alder reaction was carried out in a microwave oven (650 W). On the other hand, independent of the mode employed, heating **38c** in benzene solution did not result in its intramolecular cycloaddition to the indolizidine derivative **40**. NMR examination of the major isolable reaction components revealed that in several instances cleavage of the N−C(benzyl) bond in **38c** occurred, producing, among other things, compounds possessing a styrene type double bond. To suppress decomposition of this apparently sensitive azadiene *via* polar reaction pathways, its intramolecular cycloaddition reaction was subsequently examined under flash vacuum thermolysis conditions.[25] Indeed, by using the technique where the azadiene is brought into the gas phase by cosublimation with benzene, a very clean conversion to the desired Diels−Alder product **40** (mixture of 3,8a-*cis*/*trans* isomers) was observed at 470 °C. Note, however, that at slightly lower temperature (400 °C) the reaction took a different course, producing 2-azadiene **39**. Formation of this more highly conjugated azadiene results from a [1,5]-hydrogen shift, which is most likely reversible at the higher temperature at which conversion to cycloadduct **40** is observed.

In conclusion, it has been shown that dihydrooxazine **12** can be alkylated successfully using benzyl halides in

(22) Norman, R. O. C.; Purchase, R.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1701.
(23) King, H. *J. Chem. Soc* **1942**, 432.
(24) The lower yields observed for the formation of azadienes **38d** and **4a** may be the consequence of competing reactions of nonstabilized carbocation type intermediates formed on complexation of RBr with Ag^+ ion.
(25) Magrath, J.; Fowler, F. W. *Tetrahedron Lett.* **1988**, *29*, 2171.

combination with Ag^+ ion and that the resultant dihydrooxazonium salts undergo rearrangement to the corresponding enamine and very facile retro Diels−Alder reaction to give 2-cyano-1-azadienes. Further work to develop compound **12** as a stable 2-cyano-1-azadiene equivalent in IMDA reactions is in progress.

Experimental Section

Chloro Oxime 17. Procedure 1. Cold ether (150 mL) (dry ice bath) was transferred to NOCl (24.8 g, 0.38 mol) (prepared in 95% yield according to ref 26 and kept in a septum sealed flask at −73 °C), followed by acrylonitrile (24.8 g, 0.468 mol) and concd HCl (12 mL, 0.14 mol). The reaction vessel was then tightly sealed with a glass stopper, very slowly brought to room temperature, and stirred for 2 days (solution color fades and pressure drops to normal). Taking care to work in a well-ventillated fume hood, the reaction mixture was washed with water, and the aqueous layers were back-extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated. Distillation of the liquid residue *in vacuo* (bp 77−79 °C/1 mmHg) gave oxime **17** (14.91 g, 33%).

Procedure 2. To solution of NOCl (11.80 g, 0.18 mol) in Et_2O (80 mL) at −73 °C was added acrylonitrile (23.7 mL, 0.36 mol) and $AlCl_3$ (1.2 g, 0.009 mol). After the flask was tightly sealed, the reaction mixture was stirred at −20 °C for 2 h and then at room temperature for an additional 18 h. Taking care to work in a well-ventillated fume hood, the solvent volume was diminished to about 30 mL, and the residual liquid was washed with aqueous HCl (0.5 N) and water. The aqueous fractions were then back-extracted with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$ and concentrated. Distillation of the liquid residue *in vacuo* (bp 76−85°C/1 mmHg) gave chloro oxime **17** as a pale yellow liquid (16.18 g; 76%): R_f 0.58 (heptane−EtOAc, 3:1); ^{1}H NMR ($CDCl_3$) δ 4.34 (s, 2H), 10.20 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 33.47 and 40.32, 108.50 and 112.83, 129.86 and 135.38; IR (neat) 1688, 2250, 3331 cm^{-1}.

6-Methyl-6-phenyl-5,6-dihydro-4*H*-1,2-oxazine-3-carbonitrile (18) and 2-Cyano-5-methyl-5-phenyl-1-pyrroline 1-oxide (19). Chloro oxime **17** (510 mg, 4.3 mmol) in CH_2Cl_2 (10 mL) was added dropwise over 2 h to a stirred mixture of α-methylstyrene (1.016 g, 8.6 mmmol) in CH_2Cl_2 (20 mL) containing K_2CO_3 (0.912 g, 8.6 mmol). Stirring under nitrogen at room temperature was continued overnight, the solids were then removed by filtration, and the filtrate was concentrated under reduced pressure. Compound **18**, a colorless solid (215 mg; 25%), was obtained after silica gel column chromatography (gradient elution: heptane−EtOAc, 30:1 to 2:1).

In a separate experiment in which 3.56 g (30 mmol) of oxime **17** was engaged, Na_2CO_3 was employed as the base, and the reaction mixture was stirred at room temperature for 6 days, compound **18** (847 mg; 14%) and 2-cyano-5-methyl-5-phenyl-1-pyrroline 1-oxide (**19**) (1.00 g; 17%) were isolated by silica gel column chromatography (gradient elution: heptane−EtOAc, 30:1 to 1:1).

Dihydrooxazine 18: R_f = 0.46 (heptane−EtOAc, 3:1); mp 73−74 °C (heptane−EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.58 (s, 3H), 1.99 (m, 2H), 2.23−2.54 (m, 2H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.60, 27.73, 29.31, 81.92, 114.3, 124.60, 128.07, 129.15, 136.51, 141.86; IR (neat) 2231, 1575 cm^{-1}; MS (EI, 100 °C) 200 ($M^{\bullet+}$, 100), 183 (44), 168 (23), 156 (9), 154 (10), 131 (40), 118 (36); HRMS cald for $C_{12}H_{12}N_2O$ *m*/*z* 200.0949, found 200.0946. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.32; H, 6.07; N, 13.67.

1-Pyrroline 1-oxide 19: R_f = 0.21 (heptane−EtOAc, 3:1); mp 63 °C; R_f 0.21 (hexane−EtOAc, 3:1); ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3H), 2.48 (m, 1H), 2.70 (m, 1H), 2.81 (m, 2H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 25.47, 25.74, 35.95, 82.21, 112.04, 125.08, 128.49, 129.01, 139.74; IR (neat) 2219, 1538 cm^{-1}. Anal. Cald for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.85; H, 6.07; N, 13.76.

4-Bromobutyrohydroxamic Acid (21). 4-Bromobutyryl chloride (10.0 mL, 0.086 mol) in Et_2O (50 mL) was added dropwise to a stirred solution of hydroxylamine hydrochloride (6.0 g, 0.086 mol) in H_2O−ether (4:1; 250 mL) at a rate such that reflux was maintained. Stirring was then continued at room temperature for an additional 3 h. The ether layer was separated, and the aqueous layer was filtered to remove insoluble material. The water layer was extracted successively with CH_2Cl_2 and CH_2Cl_2−acetone. The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was silica gel flash column chromatographed (heptane−EtOAc, 1:3, followed by CH_2Cl_2, and CH_2Cl_2−acetone, 1:1). 4-Bromobutyrohydroxamic acid (**21**) (13.76 g, 88%) was obtained as a yellow oil, which slowly transformed to 1,2-oxazin-3-one (**23**) and decomposition products at room temperature and/or on prolonged contact with silica gel: ^{1}H NMR ($CDCl_3$) δ 2.18 (m, 2H), 2.58 (t, J = 7.1 Hz, 2H), 3.49 (t, J = 6.3 Hz, 2H), 8.4−9.2 (br, 2H); ^{13}C NMR ($CDCl_3$) δ 27.53, 32.26, 32.53, 178.29; IR (neat) 1175, 1438, 1713, 1734, 2975, 3156 cm^{-1}; MS (CI, isobutane, 170 °C) 102 ([M − HBr] + H)$^+$, 87, 86.

1,2-Oxazinan-3-one (23) and 1-Hydroxypyrrolidin-2-one (22). NaH [527 mg (60% suspension in mineral oil), 13.2 mmol] was added in portions to a solution of 4-bromobutyrohydroxamic acid (**21**) (2.00 g, 11 mmol) in dry THF (30 mL) at 0 °C under nitrogen, and stirring was continued for an additional 1 h at room temperature. H_2O (10 mL) was then added (ice bath), the organic layer was separated, and the aqueous layer was washed with CH_2Cl_2. The combined organic fractions were dried over Na_2SO_4 and concentrated without heating, and the residue was silica gel flash column chromatographed (heptane). 1,2-Oxazinan-3-one (**23**) was obtained as a colorless liquid (0.83 g, 75%) along with 3−5% of 1-hydroxypyrrolidin-2-one (**22**).

Compound 23: R_f = 0.88 (heptane); ^{1}H NMR ($CDCl_3$) δ 2.18 (dt, J = 7.2, 7.4 Hz, 2H), 2.63 (t, J = 7.8 Hz, 2H), 4.37 (t, J = 6.8 Hz, 2H), 9.08 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.70, 26.12, 72.13, 160.41; IR (neat) 3480, 3367, 1771, 1645, 1377, 1173 cm^{-1}; MS (CI, isobutane, 170 °C) 102 (M + H), 87.

Compound 22: R_f = 0.17 (heptane−EtOAc, 3:1); ^{13}C NMR ($CDCl_3$) δ 15.62, 23.58, 25.99, 165.42.

Hex-5-en-2-one oxime.[20] Hydroxylamine hydrochloride (10.4 g, 15 mmol) and NaOAc (12.3 g, 15 mmol) were added to a solution of hex-5-en-2-one (4.9 g, 5 mmol) in H_2O (50 mL)−EtOH (3 mL), and the reaction mixture was stirred at reflux for 46 h. The mixture was then extracted with CH_2Cl_2, and the combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated. Oxime was obtained as a colorless liquid (4.73 g, 84%) by vacuum distillation: bp 59°C/2 mmHg; R_f 0.66 and 0.76 (heptane−EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.88 and 1.90 (s, 3H), 2.30 (s, 4H), 5.02 (m, 2H), 5.82 (m, 1H), 9.48 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ *anti* (major) 13.67, 28.04, 35.28, 115.41, 137.32, 157.92; *syn* (minor) 20.01, 29.52, 30.44, 115.26, 137.56, 158.30; IR (neat) 1649 and 1663, 3243 cm^{-1}.

***N*-(1-Methylpent-4-enyl)hydroxylamine (24).** In a modification of literature procedure,[20] a solution of MeOH−HCl (12 N) (8 mL; 1:1 v/v) was added dropwise over 30 min with stirring to a cooled (−20 °C) mixture of hex-5-en-2-one oxime (3.40 g, 30 mmol) and $NaBH_3CN$ (2.31 g, 33 mmol) in MeOH (30 mL) containing bromophenol blue (3 mg) (nitrogen atmosphere). The rate of addition was controlled such that the color of the reaction mixture remained yellow−yellow-green (pH 3−4). The reaction was then brought slowly to room temperature, and stirring under nitrogen was continued for an additional 1 h. After basification by the addition of aqueous KOH (until pH = 9), the reaction mixture was extracted successively with Et_2O and CH_2Cl_2. The combined organic phases were deoxygenated (N_2 bubbling) to prevent cyclization,[26] dried over Na_2SO_4, and concentrated *in vacuo*, affording hydroxylamine **24** (3.43 g, 99%) as a white solid in sufficiently pure form to be employed directly in the next operation. For analytical purposes the product was column chromatographed (silica gel; heptane−EtOAc, 1:3; 3.07 g, 89%): R_f 0.34 (heptane−EtOAc, 1:1); mp 39−40 (CH_2Cl_2−ether); ^{1}H NMR ($CDCl_3$)

(26) Doyle, M. P.; Bosch, R. J.; Seites, P. G. *J. Org. Chem.* **1978**, *43*, 4120.

δ 1.45 (d, J = 7.5 Hz, 3H), 1.76 (m, 1H), 2.16 (m, 3H), 3.53 (m, 1H), 5.06 (m, 2H), 5.77 (m, 1H), 9.52 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 14.45, 29.53, 29.67, 57.31, 116.10, 136.53; IR (neat) 2526, 3402 cm^{-1}; MS (EI, 160 °C) 115 (M^+, 35.9), 114 (6.4), 101 (100), 83 (5.1), 70 (15.4); HRMS calcd for $C_6H_{13}NO$ *m/z* 115.0997, found 115.1007.

4-Bromo-*N*-hydroxy-*N*-(1-methylpent-4-enyl)butyramide (25). To hydroxylamine **24** (3.16 g, 27.48 mmol) and Na_2CO_3 (8.75 g, 82.5 mmol, 3 equiv) in $Et_2O-CH_2Cl_2$ (150 mL; 1:1 v/v) was added a solution of 4-bromobutyryl chloride (3.18 mL, 5.10 g, 27.50 mmol) in CH_2Cl_2 (10 mL) with stirring under nitrogen at 0 °C. After further stirring for 1 h at room temperature, the mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was column chromatographed on silica gel (heptane−EtOAc, 1:1). Compound **25** was obtained as a colorless oil (6.56 g, 90%): R_f 0.58 (heptane−EtOAc, 1:1); ^{1}H NMR ($CDCl_3$)[28] δ 1.15 (d, *J* = 6.4 Hz), 1.29 (d, *J* = 6.5 Hz), 1.41 (d, *J* = 6.6 Hz), 1.47−1.75 (m, 1H), 1.96−2.22 (m, 5H), 2.49 and 2.67 (m, 2H), 3.47 (t, *J* = 6.3 Hz), and 3.40−3.84 (m, 2H), 3.99 and 4.38 and 4.56 (m, 1H), 4.98 (m, 2H), 5.76 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.38, 17.07, 17.56, 17.76, 18.63, 22.09−33.84 (19 peaks), 50.99, 54.14, 57.95, 59.64, 61.68, 61.89, 79.55 and 80.46, 114.76, 115.59, 116.02, 116.16, 116.32, 136.49, 136.67, 137.00, 137.52, 138.37, 165.75, 173.00, 178.56; IR (neat) 3144, 1631 and 1681, 1444 cm^{-1}; MS (CI, CH_4, 180 °C) 266 and 264 (31.3, 65.7), 264 and 262 (65.7, 32.8), 184 (16.4), 178 and 176 (6.7 (6.7)), 168 (25.4), 116 (10.4), 114 and 112 (35.8 (23.9)), 98 and 96 (100 (85.1)); HRMS calcd for $C_{10}H_{19}NO_2Br$ *m/z* 264.0600, found 264.0613.

2-(1-Methylpent-4-enyl)-1,2-oxazinan-3-one (26). Compound **25** (3.58 g, 13.6 mmol) in CH_2Cl_2 (20 mL) was adsorbed onto 15 g of KF/Al_2O_3,[21] and the solvent was removed under reduced pressure without heating. The resultant mixture was stirred for 5 h at room temperature. After the adsorbant was copiously washed with CH_2Cl_2, the combined washings were concentrated, giving a colorless volatile oil (2.24 g). Compound **26**, a colorless oil (1.57 g; 63%), was obtained after silica gel flash chromatography (pentane−Et_2O gradient): R_f 0.16 (heptane−EtOAc, 3:1); ^{1}H NMR ($CDCl_3$) δ 1.19 (d, *J* = 6.7 Hz, 3H), 1.53 (m, 1H), 1.75 (m, 1H), 2.06 (m, 4H), 2.47 (d, *J* = 7.3 Hz), 4.02 (m, 2H), 4.57 (m, 1H), 4.96 (ddd, *J* = 10.1, 1.7, 1.2 Hz, 1H), 5.02 (ddd, *J* = 17.1, 1.7, 1.5 Hz, 1H), 5.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.67, 22.52, 28.66, 30.80, 32.75, 50.56, 69.66, 115.00, 138.01, 170.15; IR (neat) 1413, 1450, 1644 cm^{-1}; MS (CI, isobutane, 170 °C) 184 (M + H (100)), 168 (18.2), 154 (2.8), 116 (21.0), 114 (29.4), 98 (46.2); HRMS calcd for $C_{10}H_{18}NO_2$ *m/z* 184.1338, found 184.1342.

2-(1-Methylpent-4-enyl)-1,2-oxazinane-3,3-dicarbonitrile (30). Triflic anhydride (171 μL, 1.5 equiv) was added dropwise over 10 min to a cold (−60 °C) solution of 2-(1-methylpent-4-enyl)-1,2-oxazinan-3-one (**26**) (124 mg, 0.68 mmol) in anhydrous CH_2Cl_2 (5 mL), and the resulting mixture was stirred for 1.5 h (nitrogen atmosphere). A suspension of LiCN (112 mg, 5 equiv; predried for 2 h at 80 °C *in vacuo*) in anhydrous THF (3 mL) containing 12-crown-4 (12 mg, 11 μL, 0.1 equiv) was then added, and stirring was continued at −60 °C for 1 h. After this period diisopropylethylamine (355 μl, 2.04 mmol, 3 equiv) was added, and the reaction was subsequently warmed to −20 °C over 15 min before the addition of H_2O (5 mL). The organic layer was removed and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, and concentrated. Oxazinane **30** was obtained as a yellow oil (52 mg, 35%) after silica gel flash column purification (pentane−Et_2O, 4:1): R_f 0.56 (heptane−EtOAc, 3:1); ^{1}H NMR ($CDCl_3$) δ 1.31 (d, *J* = 6.5 Hz, 3H), 1.52 (m, 1H), 1.76−2.09 (m, 3H), 2.14 (dd, *J* = 7.3, 14.4 Hz, 2H), 2.44 (m, 2H), 3.38 (m, 1H), 3.94 (dt, *J* = 3.2, 10.3 Hz, 1H), 4.07 (dt, *J* = 4.0, 11.2 Hz, 1H), 5.00 (d, *J* = 7.6 Hz, 1H), 5.08 (dd, *J* = 1.6, 17.0 Hz, 1H), 5.81 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.96, 21.33, 30.55, 33.76, 36.68, 54.06, 59.75, 70.37, 113.18, 115.29, 137.96; IR (neat) 2238, 1438 cm^{-1}; MS (CI, isobutane, 180 °C) 220 (M + H (1.4)), 193 (100), 166 (8.6), 136 (20.7), 84 (5.7); HRMS calcd for $C_{12}H_{18}N_3O$ *m/z* 220.1451, found 220.1432. Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.73; H, 7.81; N, 19.16. Found: C, 65.26; H, 7.75; N, 18.54.

1-(1-Methylpent-4-enyl)-2-cyano-1-aza-1,3-butadiene (4a). Triflic anhydride (447 mg, 1.59 mmol) was added dropwise over 10 min to a cold (−60 °C) solution of (1-methylpent-4-enyl)-1,2-oxazinan-3-one (**26**) (223 mg, 1.22 mmol) in anhydrous CH_2Cl_2 (10 mL), and the resulting mixture was stirred for 2 h under nitrogen. A suspension of LiCN (242 mg, 6 equiv) in anhydrous THF (10 mL) containing 12-crown-4 (21 mg, 0.12 mmol) and diisopropylethylamine (410 mg, 3.18 mmol) was then added dropwise over 20 min, and stirring was continued at −60 °C for 1 h. The reaction mixture was subsequently warmed to −20 °C over 15 min and stopped by the addition of H_2O (20 mL). The organic layer was removed, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O, dried over Na_2SO_4, and concentrated without heating. The resulting oil was flash column chromatographed on silica gel (pentane−Et_2O, 9:1). The less polar component in the product mixture corresponded to azadiene **4a** (colorless volatile liquid; 86 mg; 44%), and the more polar component to oxazinane **30** (20 mg; 8%): R_f 0.70 (heptane−EtOAc, 3:1). Spectral characteristics of compound **4a** are identical to those published earlier (ref 8).

3-Methyl-1,2,3,7,8,8a-hexahydroindolizine-5-carbonitrile (5a). A solution of azadiene **4a** (54 mg, 0.33 mmol) in 2.5 mL of dry degassed toluene in a 10-mL capacity thick-walled glass tube, equipped with a Rotoflo tap and a magnetic stirring bar was placed in a beaker filled with vermiculite and irradiated in a microwave oven for 6 + 8 min (650 W, Philips microwave oven 900 W).[29] After cooling, the solvent was evaporated and the residue was flash column chromatographed (silica gel; hexane−Et_2O, 4:1). Compound **5a** was isolated as an inseparable mixture of diastereoisomers (1:2.2) (38 mg, 70%):[30] R_f 0.73 (heptane−EtOAc, 3:1). Spectral characteristics of compound **5a** are identical to those published earlier (ref 8).

1,2-Oxazinane-3-carbonitrile (34). To 5,6-dihydro-4*H*-1,2-oxazine (**33**) (240 mg, 2.8 mmol)[22,23] were added TMSCN (307 mg, 3.1 mmol) and anhydrous $ZnBr_2$ (16 mg, 0.07 mmol), and the resultant mixture was stirred under nitrogen at room temperature for 3 h. The reaction was then stopped by the addition of H_2O and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was column chromatographed on silica gel (heptane−EtOAc, 3:1). Compound **34** was obtained as a colorless oil (260 mg, 84%): R_f = 0.17 (heptane−EtOAc, 3:1); ^{1}H NMR ($CDCl_3$) δ 2.06 (m, 4H), 3.90 (m, 1H), 4.03 (m, 2H), 5.06 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.03, 26.53, 48.55, 70.28, 118.71; IR (neat) 3297, 2938, 2235, 1680, 1638, 1441 cm^{-1}; MS (EI, 150 °C) 112 ($M^{\bullet+}$, 100), 111 (5.0), 100 (3.9), 97 (11.1), 86 (19.0), 81 (12.4), 80 (32.0); HRMS calcd for $C_5H_8N_2O$ *m/z* 112.0637, found 112.0632. Anal. Calcd for $C_5H_8N_2O$: C, 53.56; H, 7.19; N, 24.98. Found: C, 53.41; H, 6.93; N, 24.99.

5,6-Dihydro-4*H*-1,2-oxazine-3-carbonitrile (12). To a solution of 1,2-oxazinane-3-carbonitrile (**34**) (230 mg, 2.05 mmol) in CH_2Cl_2 (10 mL) was added a solution of $Pb(OAc)_4$ (1.00 g, 2.25 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 1 h at room temperature, pentane (30 mL) was added, and the mixture was filtered through a short Celite pad. The solvent was evaporated, and the oily residue was

(27) In the presence of air, hydroxylamine **24** readily cyclizes to 2,5-dimethyl-*N*-hydroxypyrrolidine; see ref 20 and the following: (a) Oppolzer, W.; Siles, S.; Snowden, L.; Baker, B. H.; Petrzilka, M. *Tetrahedron*, **1985**, *41*, 3497. (b) House, H. O.; Manning, D. T.; Mellio, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem*. **1976**, *41*, 855.

(28) Note that multiple signals are observed for the same hydrogens/carbons in the ^{1}H/^{13}C NMR spectra for compound **25**. This is ascribed to both amide rotamers and the presence of H-bonded species in the sample analyzed.

(29) *CAUTION*: As the internal pressure increases in the closed tube upon heating, the cycloaddition reaction should be carried out in an isolated fume cupboard and behind a protective screen. Open only after cooling the tube to room temperature.

(30) Separation of the diastereoisomers may be achieved by HPLC. For conditions, see ref 8.

flash chromatographed on silica gel (pentane−Et_2O, 4:1). 5,6-Dihydro-4*H*-1,2-oxazine-3-carbonitrile (**12**) was isolated as a colorless oil (158 mg, 70%): $R_f = 0.55$ (heptane−EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.04 (m, 2H), 2.42 (t, J = 6.7 Hz, 2H), 4.18 (t, J = 5.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 17.17, 23.17, 67.90, 114.49, 137.00; IR (neat) 2945, 1882, 2235, 1567, 1448, 1173, 1026 cm^{-1}; MS (EI, 150 °C) 110 ($M^{\bullet+}$, 31.4), 101 (3.3), 97 (9.2), 80 (21.6), 69 (22.5), 65 (13.1), 57 (22.2), 55 (19.6), 53 (100); HRMS calcd for $C_5H_6N_2O$ *m/z* 110.0480, found 110.0484. Anal. Calcd for $C_5H_6N_2O$: C, 54.54; H, 5.49. Found: C, 54.31; H, 5.57.

(1-Bromo-pent-4-enyl)benzene (37). Potassium hydride (6.7 g, 30% suspension in mineral oil, 50 mmol), in a round bottom flask flushed with nitrogen, was washed with dry THF (3 × 40 mL). THF (100 mL) was then added, followed, after cooling to 0 °C, by slow addition of acetophenone (5.71 g, 47.6 mmol in 20 mL of THF). The mixture was stirred for 20 min at room temperature before addition of triethylborane (59.5 mL of 1 M solution in THF; 59.5 mmol) in several portions. After the mixture was stirred for a further 20 min, allyl bromide (8.64 g, 71.4 mmol) was added, and the mixture was stirred for 4 h. A 1:1 mixture of 30% H_2O_2 and 30% NaOH (50 mL) was then added dropwise with cooling in an ice bath. The reaction mixture was diluted with H_2O, and the organic fraction was separated and washed with water. The aqueous fractions were subsequently extracted with CH_2Cl_2, and the combined organic fractions were dried over Na_2SO_4, concentrated, and distilled *in vacuo*. 1-Phenylpent-4-en-1-one[31] (6.03 g, 79%) was obtained as a colorless liquid: bp 65−78 °C/2 mmHg; R_f 0.76 (heptane−ethyl acetate, 3:1); ^{1}H NMR ($CDCl_3$) δ 2.50 (dd, J = 7.0, 14.3 Hz, 2H), 3.08 (t, J = 7.4 Hz, 2H), 5.01 (dd, J = 1.2, 10.1 Hz, 1H), 5.09 (dd, J = 1.6, 17.2 Hz, 1H), 5.91 (m, 1H), 7.46 (t, J = 7.8 Hz, 2H), 7.56 (t, J = 7.3 Hz, 1H), 7.97 (d, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 28.14, 37.72, 115.26, 128.01, 128.28, 128.58, 132.98, 137.30, 199.35; IR (neat): 3529, 3353, 3072, 2924, 1688, 1645, 1588, 1448, 1363, 1265, 1209 cm^{-1}; MS (CI, isobutane, 180 °C) 161 (M + H), 145, 121, 105. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.21; H, 7.81.

To a solution of 1-phenylpent-4-en-1-one (4.00 g, 25 mmol) in methanol (50 mL) at 0 °C under nitrogen was added $NaBH_4$ (1.43 g, 37.5 mmol) in portions over 30 min. The reaction mixture was stirred for an additional 1 h at 0 °C and 3 h at room temperature. The mixture was then cooled to 0 °C, and the excess reducing agent was destroyed by slowly adding water (30 mL). Following extraction with ether and CH_2Cl_2, the combined organic fractions were dried over Na_2SO_4 and concentrated. 1-Phenylpent-4-en-1-ol (2.90 g, 72%) was obtained as a colorless liquid after column chromatography on silica (heptane−ethyl acetate, 5:1): R_f 0.53 (heptane−ethyl acetate, 3:1); ^{1}H NMR ($CDCl_3$) δ 1.83 (m, 2H), 2.12 (m, 2H), 2.23 (d, J = 3.0 Hz, 1H), 4.64 (dt, J = 2.8, 6.5 Hz, 1H), 5.01 (m, 2H), 5.82 (m, 1H), 7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.99, 38.11, 74.02, 114.99, 125.96, 127.59, 128.50, 138.25, 144.71; IR (neat) 3374, 2938, 1638, 1497, 1462, 1061, 913 cm^{-1}; MS (CI, isobutane, 170 °C) 163, 147, 145, 130; HRMS (CI, isobutane, 170 °C) calcd for $C_{11}H_{15}O$ (M + H) *m/z* 163.1123, found 163.1097.

PPh_3 (3.90 g, 14.9 mmol) was added in portions over 10 min to a solution of CBr_4 (4.93 g, 14.9 mmol) and 1-phenylpent-4-en-1-ol (2.19 g, 13.5 mmol) in dry ether (50 mL) at 0 °C under nitrogen.[32] The mixture was stirred for 20 min at 0 °C and for an additional 0.5 h at room temperature. The mixture was then diluted with pentane (100 mL), the white precipitate was filtered off, and the solution was concentrated under reduced pressure without heating. (1-Bromopent-4-enyl)benzene (**37**) (2.91 g, 96%) was obtained as a colorless liquid after distillation in *vacuo*: bp 47 °C/2 mmHg; R_f 0.70 (heptane−ethyl acetate, 3:1); ^{1}H NMR ($CDCl_3$) δ 2.10−2.24 (m, 3H), 2.36 (m, 1H), 4.95 (dd, J = 6.0, 8.2 Hz, 1H), 5.01 (d, J = 1.7 Hz, 1H, 5.06 (dd, J = 1.2, 10.3 Hz, 1H), 5.77 (m, 1H), 7.26−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 32.25, 39.01, 54.86, 116.05, 127.39, 128.42, 128.78, 136.72, 142.07; IR (neat): 3072, 2938, 1638, 1497, 1455, 920 cm^{-1}. Anal. Calcd for $C_{11}H_{13}Br$: C, 58.69; H, 5.82. Found: C, 58.64; H, 5.81.

1-Ethyl-2-cyano-1-aza-1,3-butadiene (38a). Procedure 1. To a solution of **12** (58 mg, 0.53 mmol) in dry CH_2Cl_2 (5 mL) at −60 °C under nitrogen was added triethyloxonium tetrafluoroborate (200 mg, 1.06 mmol). The mixture was brought to room temperature and stirred for 2 h before recooling to −60 °C and addition of Et_3N (107 mg, 1.06 mmol). The solution was then concentrated without heating, and the residue was flash column chromatographed on silica gel (pentane). Azadiene **38a** was obtained as a colorless volatile liquid (41 mg, 71%), which quickly decomposed at room temperature (1−2 h).

Procedure 2. To a solution of **12** (68 mg, 0.62 mmol) in dry CH_2Cl_2 (2 mL) at room temperature under nitrogen were added ethyl bromide (202 mg, 1.85 mmol) and $AgBF_4$ (360 mg, 1.85 mmol). The mixture was stirred for 10 min at room temperature and at 40 °C for an additional 5 min. The reaction mixture was then cooled to −60 °C, and Et_3N (187 mg, 1.85 mmol) was added. The mixture was concentrated without heating, and subsequent flash column chromatography on silica gel (pentane−Et_2O, 4:1) provided azadiene **38a** (19 mg, 29%) plus recovered **12** (34 mg, 50%).

Compound 38a: $R_f = 0.74$ (heptane−EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 1.35 (t, J = 7.3 Hz, 3H), 3.89 (q, J = 7.3 Hz, 2H), 5.99 (d, J = 10.5 Hz, 1H), 6.17 (d, J = 17.6 Hz, 1H), 6.58 (dd, J = 10.5, 17.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.45, 53.39, 127.84, 134.92, 142.31; IR (neat) 2931, 2225, 1631, 1456, 1375 cm^{-1}.

1-Benzyl-2-cyano-1-aza-1,3-butadiene (38b). To a solution of **12** (46 mg, 0.42 mmol) in dry CH_2Cl_2 (5 mL) at room temperature under nitrogen were added benzyl bromide (79 mg, 0.46 mmol) and $AgBF_4$ (90 mg, 0.46 mmol). The mixture was stirred for 2 h at room temperature and then for an additional 5 min at 40 °C before cooling to −60 °C and addition of Et_3N (46 mg, 0.46 mmol). The reaction mixture was concentrated without heating, and the residue was flash column chromatographed on silica gel (pentane−Et_2O, 4:1). 1-Benzyl-2-cyano-1-aza-1,3-butadiene (**38b**) was obtained as a colorless liquid (51 mg, 72%): $R_f = 0.73$ (heptane−EtOAc, 1:1); ^{1}H NMR ($CDCl_3$) δ 5.02 (s, 2H), 6.01 (d, J = 10.5 Hz, 1H), 6.22 (d, J = 17.6 Hz, 1H), 6.63 (dd, J = 10.5, 17.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 62.60, 108.87, 127.80, 128.24, 128.66, 128.89, 134.92, 137.24, 143.07; IR (neat) 2225, 1625, 1588, 1494, 1456 cm^{-1}; MS (EI, <150 °C) 170 ($M^{\bullet+}$), 169, 155, 142, 115, 107, 104, 92, 91, 77; HRMS calcd for $C_{11}H_{10}N_2$ *m/z* 170.0844, found 170.0835.

1-(1-Phenylpent-4-enyl)-2-cyano-1-aza-1,3-butadiene (38c) and 2-(1-Phenylpent-4-enyl)-1,2-oxazinan-3-one. To a solution of **12** (108 mg, 0.98 mmol) in dry CH_2Cl_2 (5 mL) at room temperature under nitrogen was added (1-bromopent-4-enyl)benzene (**37**) (265 mg, 1.18 mmol) and $AgBF_4$ (230 mg, 1.18 mmol). The mixture was stirred for 0.5 h at room temperature and then for an additional 3−5 min at 40 °C before cooling to −60 °C and addition of Et_3N (119 mg, 1.18 mmol). The solution was concentrated without heating and the resulting azadiene separated by flash column chromatography on silica gel (gradient pentane → pentane:ether, 1:1). 1-(1-Phenylpent-4-enyl)-2-cyano-1-aza-1,3-butadiene (**38c**) (146 mg, 67%) was obtained as a pale yellow liquid along with 2-(1-phenylpent-4-enyl)-1,2-oxazinan-3-one (9 mg, 4%).

Compound 38c: R_f 0.83 (heptane−ethyl acetate, 3:1); ^{1}H NMR ($CDCl_3$) δ 2.03 (m, 4H), 4.87 (t, J = 5.6 Hz, 1H), 4.98 (s, 1H), 5.05 (d, J = 7.0 Hz, 1H), 5.81 (m, 1H), 5.98 (d, J = 10.5 Hz, 1H), 6.25 (d, J = 17.5 Hz, 1H), 6.62 (dd, J = 10.5, 17.6 Hz, 1H), 7.25−7.42 (m, 5H); ^{13}C NMR ($CDCl_3$) δ (major isomer) 30.44, 37.49, 72.52, 108.96, 115.56, 127.35, 127.87, 128.23, 128.83, 134.99, 137.38, 141.81, 141.52; (minor isomer) 29.80, 35.52, 75.59, 115.32, 126.63, 126.78, 128.55, 141.51; IR (neat): 3072, 2924, 2221, 1736, 1645, 1588, 1455, 1251 cm^{-1}; MS (CI, isobutane, 170 °C) 225 (M + H), 145; HRMS (CI, isobutane, 170 °C) calcd for $C_{15}H_{17}N_2$ (M + H) *m/z* 225.1392, found 225.1378.

2-(1-Phenylpent-4-enyl)-1,2-oxazinan-3-one: yellow liquid; R_f 0.38 (heptane−ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$) δ 2.07 (m, 6H), 2.48 (m, 2H), 3.68 (m, 1H), 3.87 (m, 1H), 5.03

(31) Negishi, E. *Tetrahedron Lett.* **1979**, *N10*, 845.
(32) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86.

(m, 1H), 5.56 (m, 1H), 5.84 (m, 1H), 7.28−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.34, 28.69, 30.15, 30.75, 57.44, 69.70, 115.41, 127.85, 127.98, 128.52, 137.60, 139.27, 170.23; IR (neat) 2931, 1666, 1406 cm^{-1}; MS (CI, isobutane, 170 °C) 246 (M + H), 216, 176; HRMS (CI, isobutane, 170 °C) calcd for $C_{15}H_{20}NO_2$ (M + H) *m*/*z* 246.1494, found 246.1486.

1-Pent-4-enyl-2-cyano-1-aza-1,3-butadiene (38d). To a solution of 5,6-dihydro-4*H*-1,2-oxazine-3-carbonitrile (**12**) (68 mg, 0.62 mmol) in dry CH_2Cl_2 (5 mL) at room temperature under nitrogen was added 1-bromopent-4-ene (101 mg, 0.68 mmol) and $AgBF_4$ (132 mg, 0.68 mmol). The mixture was stirred for 3.5 h at room temperature and then for an additional 10 min at 40 °C. The reaction mixture was then cooled to −50 °C, and triethylamine (69 mg, 0.68 mmol) was added. The solvent was evaporated under reduced pressure without heating, and the residue was flash column chromatographed on silica gel (pentane−Et_2O, 4:1). Compound **38d** was obtained as a volatile colorless liquid (6 mg, 6%, recovered starting material 48 mg, 71%): ^{1}H NMR ($CDCl_3$) δ 1.60−1.91 (m, 2H), 2.14 (m, 2H), 3.86 (t, J = 6.9 Hz, 1H), 4.18 (m, 1H), 5.12 (m, 2H), 5.84 (m, 1H), 5.99 (dd, J = 2.2, 10.5 Hz, 1H), 6.18 (dd, J = 4.2, 17.6 Hz, 1H), 6.58 (ddd, J = 4.9, 10.5, 17.5 Hz, 1H); IR (neat) 2931, 2221, 1659, 1462 cm^{-1}; MS (CI, isobutane, 150 °C): 149 (M + H), 122; HRMS (CI, isobutane, 170 °C) calcd for $C_9H_{13}N_2$ (M + H) *m*/*z* 149.1079, found 149.1072.

1-(1-Methylpent-4-enyl)-2-cyano-1-aza-1,3-butadiene (4a). As described for **38a**, alkylation of 5,6-dihydro-4*H*-1,2-oxazine-3-carbonitrile (**12**) with 2-bromohex-5-ene (rt, 3 h) produced azadiene **4a** (8%) plus recovered starting material (68%).

1-Phenyl-1-but-3-enyl-3-cyano-2-aza-1,3-pentadiene (39). 1-(1-Phenylpent-4-enyl)-2-cyano-1-aza-1,3-butadiene (**38c**) (6 mg, 0.03 mmol) in frozen benzene (0.5 mL) was flash vacuum thermolyzed at 400 °C according to ref 25. 2-Azadiene **39** (2 mg, 30%) was separated from residual starting material and decomposition products by preparative layer chromatography on silica gel (heptane−EtOAc, 3:1): R_f 0.60 (heptane−AcOEt, 3:1); ^{1}H NMR ($CDCl_3$) δ 1.74 (d, J = 7.3 Hz, 3H), 2.29 (m, 2H), 2.87 (m, 2H), 5.03 (m, 2H), 5.81 (m, 1H), 6.03 (q, J = 7.1 Hz, 1H), 7.37 (m, 4H), 7.86 (m, 1H); IR (neat) 2931, 2225, 1644, 1606, 1450, 1413 cm^{-1}; MS (CI, isobutane, 160 °C: 225, 216, 161, 145, 73.

3-Phenyl-1,2,3,7,8,8a-hexahydroindolizidine-5-carbonitrile (40). 1-(1-Phenyl-pent-4-enyl)-2-cyano-1-aza-1,3-butadiene (**38c**) (10 mg, 0.04 mmol) in frozen benzene (0.5 mL) was flash vacuum thermolyzed at 470 °C according to ref 25. 3-Phenyl-1,2,3,7,8,8a-hexahydroindolizidine-5-carbonitrile (**40**) (6 mg, 60%) was obtained as a yellow oil after preparative TLC on silica gel (heptane−EtOAc, 3:1) (3:1 mixture of diastereomeres): R_f 0.59 (heptane−AcOEt, 3:1); ^{1}H NMR ($CDCl_3$), δ: 1.68−2.42 (m, 8H), 2.70 and 3.18 (m, 1H), 4.57 and 4.77 (m, 1H), 5.01 (m, 1H), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.24, 27.38, 29.84, 30.82, 34.41, 34.83, 37.43, 57.97, 72.67, 115.51, 126.38, 127.25, 127.77, 128.56, 128.77, 137.49; IR (neat) 2925, 2219, 1613, 1450, 1269 cm^{-1}; MS (CI, isobutane, 160 °C) 225, 145, 73.

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Supporting Information Available: NMR spectral data (56 pages). ORTEP drawing and X-ray experimental data for **19** (5 pages; see ref 17). 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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