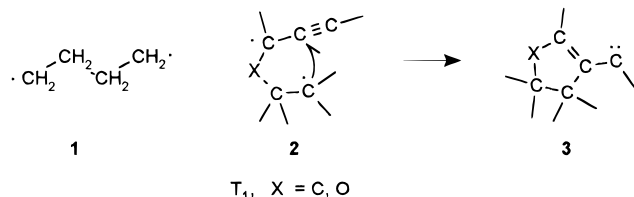# Exploring the 1,5 Cyclization of Alkyl Propargyl 1,4 Biradicals

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1,4 biradicals such as tetramethylene (**1**) are common short-lived intermediates in a variety of reactions. Since the spins of the electrons at the two radical centers of a biradical can be paired or unpaired, there are two species with structure **1** that differ only in electron spin. Typically, all the observed reactions of these biradicals take place from the species with paired electrons, which is known as the singlet state. Owing to the quantum-mechanical requirement that electron spin be conserved in chemical transforma-
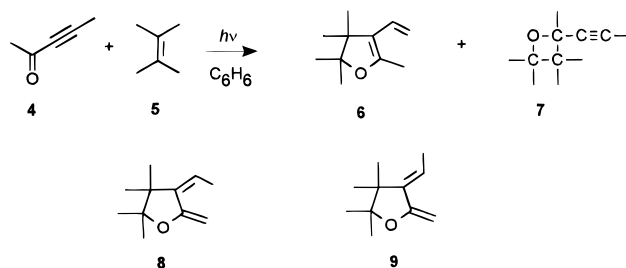

tions, the species with unpaired electrons, which is known as the triplet state, generally does not undergo chemical reactions. Thus, the two spin-paired electrons in singlet **1** can form a carbon−carbon bond, closing to ground state (S_0) singlet cyclobutane, but triplet **1** would have to close to *triplet* cyclobutane. Because excited state alkanes and cycloalkanes are highly energetic species (typically >150 kcal/mol above the ground state), such a cyclization would be endothermic, and consequently it does not take place. Typically, a triplet biradical simply undergoes a change in electron spin that converts it into the singlet, and chemical reactions then take place from this singlet species.[3] This change in multiplicity is called intersystem crossing.

Some years ago we discovered that triplet alkyl propargyl 1,4 biradicals (**2**) cyclize efficiently to the corresponding triplet unsaturated carbene **3** and, thus, form an exception to the general unreactivity of triplet biradicals.[4] This exception exists because, unlike

triplet **1** closing to triplet cyclobutane, closure of triplet **2** to triplet **3** is not only spin-allowed but also energetically feasible. Unlike the situation with cyclobutane, the energy gap between the lowest singlet and triplet states of carbenes is usually small, and rough calculations suggest that the triplet cyclization of **2** to **3** is somewhat exothermic. The carbene is of course an energetic, short-lived entity, and it is quickly stabilized by one of the several possible reactions of carbenes.[5]

Subsequent to our initial discovery of this cyclization, we have investigated several types of triplet alkyl propargyl biradicals, and in this Account we review their chemistry. Preparation of these biradicals nearly always requires photochemical reactions, so this work has led us into a number of mechanistic photochemical studies. From a synthetic point of view, many of the reactions we have uncovered provide simple access in a single step to relatively complex molecules containing a five-membered ring.

We first encountered these reactive triplet biradicals on irradiating a benzene solution of 3-pentyn-2-one (**4**) containing a few equivalents of tetramethylethylene (**5**).[4] Surprisingly, the major product was dihydrofu-

ran **6**, accompanied by only a small amount of oxetane **7**, which was the expected[6] [2 + 2] product. Careful isolation of the photoproducts with rigorous exclusion of acid indicated that the initial furan derivatives formed from **4** and **5** are the isomeric dienes **8** and **9**. These two very reactive compounds rearrange readily to the slightly more stable vinyldihydrofuran **6**.[7]

The simplest mechanism that accounts for formation of **8** and **9** involves biradical **10**, which is an interme-

(1) The Rockefeller University.
(2) Universität Hamburg.
(3) Griesbeck, A. G.; Mauder, H.; Stadtmüller, S. *Acc. Chem. Res.* **1994,** *27*, 70.
(4) Hussain, S.; Agosta, W. C. *Tetrahedron* **1981,** *37*, 3301.
(5) *Methoden der Organischen Chemie (Houben-Weyl)*; Regitz, M., Ed.; Thieme Verlag: Stuttgart, 1989; Vol. 19b.
(6) Jorgenson, M. J. *Tetrahedron Lett.* **1966,** 5811. Kwiatkowski, G. T.; Selley, D. B. *Ibid.* **1968,** 3471.
(7) Saba, S.; Wolff, S.; Schröder, C.; Margaretha, P.; Agosta, W. C. *J. Am. Chem. Soc.* **1983,** *105*, 6902.

diate in the formation of oxetane **7**.[8] Closure of **10** on
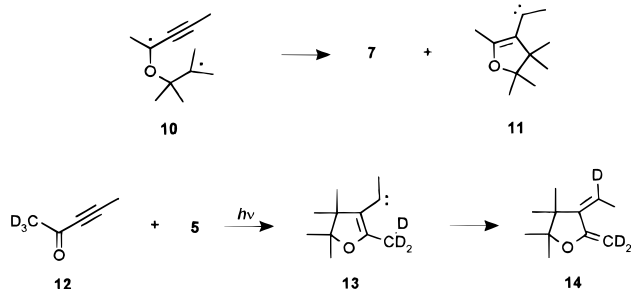
the triple bond in a 1,5 fashion gives vinyl carbene **11**, and a 1,4 hydrogen shift in **11** then yields dienes **8** and **9**. Experimental support for this mechanism came from the labeling pattern of **14** (≡**8**-d_3), which was formed on cycloaddition of **5** to pentynone-d_3 **12**. Such 1,4 shifts of hydrogen are known[9] to occur in vinyl carbenes (see **13** ≡ **11**-d_3).

We also investigated the excited states responsible for these reactions. When **4** is irradiated,[10] it is raised from its ground state (S₀) to its first excited singlet state (S₁). Two transformations of **4**(S₁) are important for our purposes. One is intersystem crossing to yield the first triplet state of **4**, which we can write as **4**(T₁), and the other is addition of **4** to **5**, forming **10**(S₁). In the same way, **4**(T₁) can add **5** to form **10**(T₁).

To investigate whether **4**(T₁) was involved in these cycloadditions, we employed a chemical tool known as a triplet quencher. In the presence of a triplet quencher, reactant triplet molecules transfer their energy exothermically to this species. The reactant triplets return to their ground state, and (generally unreactive) triplets of the quencher are formed. If the reactant triplets are the photochemically reactive species, their removal by energy transfer to the quencher will slow or stop (partially or completely) "quench") the photochemical reaction.

When we applied this triplet-quenching technique to the photocycloaddition between **4** and **5**, we found that the yield of **8** and **9** decreased, but the yield of oxetane **7** was unaffected. This indicated that the furans arise from a triplet of **4**, but that the oxetane does not. In general, both singlet and triplet states of various ketones form oxetanes with alkenes.[8] These experiments showed that, in the case of simple α,β acetylenic ketones, oxetanes come from the singlet state. Earlier workers had assumed that these were triplet reactions.[6]

Another experiment also supported the conclusion that 1,4 and 1,5 cycloadditions come from different excited states of the acetylenic ketone. This experiment showed that the relative yield of oxetane **7** increases at the expense of the furans as the concentration of tetramethylethylene (**5**) is increased. In neat **5** as solvent, over 80% of the product is oxetane. This is understandable if **5** interacts with short-lived **4**(S₁) to furnish **7**. At low concentrations of **5**, encounters between **5** and **4**(S₁) are less frequent, and **4**(S₁) has the opportunity to undergo intersystem crossing to longer-lived **4**(T₁) before reacting with **5**. When **5** interacts with **4**(T₁), the products are **8** and **9**. It has

been known for many years that the chemical behavior of singlet and triplet species of identical structure can be quite different, and the present system provides an excellent example of the course of chemical processes being controlled by electron spin. Thus, singlet **10** cyclizes to singlet **7**, while triplet **10** cyclizes to triplet **11**. Singlet **10** cannot yield singlet **11** presumably because competitive 1,4 closure to the more stable oxetane is too fast, while triplet **10** cannot yield triplet **7** because the reaction would be much too endothermic.

Other findings supported our mechanistic conclusions. We prepared alkyl propargyl biradical **16** specifically in its *singlet* state from diazene **15**. The
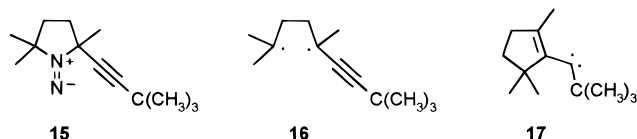
diazene is quite unstable, and it loses N₂ at −90 °C to furnish singlet **16**. Singlet biradicals react chemically much too fast for intersystem crossing to their triplet counterparts to compete, so all products from **16** come directly from the singlet. Biradical **16** gave several products typical of such species, but unlike the behavior of all other alkyl proparagyl biradicals we have encountered, there were no products from the derived carbene **17**.[11] This is the result expected if **17** can arise only from triplet **16**, and it underscores the importance of spin control in these cyclizations.

With these mechanistic details established, we focused attention on the behavior of triplet alkyl propargyl biradicals from other sources. Since irradiation of ortho-substituted aromatic ketones leads to efficient abstraction of γ hydrogen by the carbonyl group of the triplet ketone,[12] it was attractive to examine the photochemistry of **18**, where the expected hydrogen abstraction should yield triplet alkyl propargyl biradical **19**. In the event, light converted **18**
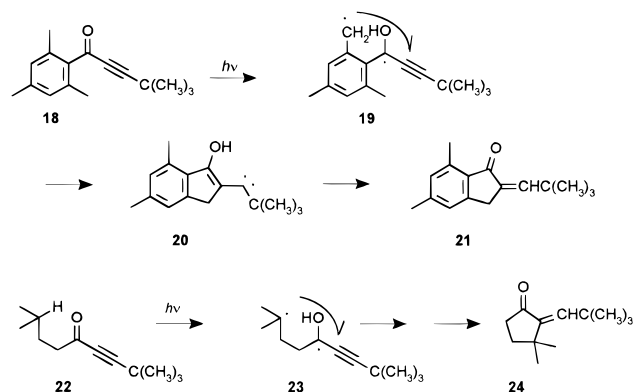
into indanone **21** (79%), indicating that **19** had efficiently cyclized in a 1,5 fashion to **20**.[13,14] Parallel reactions take place with simple open-chain ketones (as **22** → **23** → **24**), but only in low yield. Here the biradical formed on hydrogen abstraction preferen-

(8) Jones, G., II. *Org. Photochem.* **1981**, *5*, 1.

(9) Closs, G. L.; Closs, L. E.; Böll, W. A. *J. Am. Chem. Soc.* **1963**, *85*, 3796. Pincock, J. A.; Morchat, R.; Arnold, D. R. *Ibid.* **1973**, *95*, 7536.

(10) We used the output from a medium-pressure mercury arc filtered through uranium glass throughout this work, so that for all irradiations, λ > 340 nm.

(11) Horner, M. G.; Rudolph, M. J.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1992**, *114*, 6034.

(12) Wagner, P. J.; Park, B. S. *Org. Photochem.* **1991**, *11*, 227.

(13) Rao, V. B.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1985**, *107*, 521.

(14) Agosta, W. C.; Caldwell, R. A.; Jay, J.; Johnson, L. J.; Venepalli, B. R.; Scaiano, J. C.; Singh, M.; Wolff, S. *J. Am. Chem. Soc.* **1987**, *109*, 3050.

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tially fragments and cyclizes to the cyclobutanol rather than undergoing 1,5 closure.[13]

The triple bond can equally well be on the other end of the biradical. In methanol, biradical **26**, formed on illumination of **25**, gives both diastereomers of **28**, the products of capture of **27** by solvent.[15]
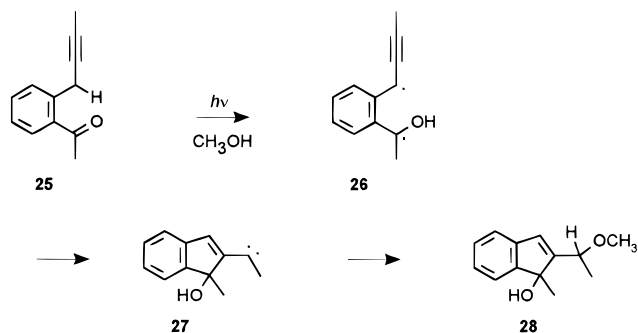

We next turned to the photochemical addition of unsaturated ketones to alkenes as a source of triplet biradicals. Such biradicals are intermediates in the well-known [2 + 2] cycloadditions between these reactants,[16] and it appeared possible that we could alter the course of reaction by adding a triple bond to the system. The success of this idea is illustrated by the behavior of 3-(1-propynyl)-2-cyclohexen-1-one (**29**).
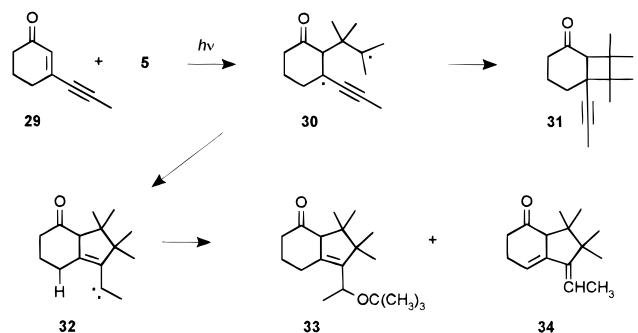

Irradiation of **29** and **5** presumably leads to the expected triplet biradical **30**. This species can either spin-invert to the singlet and close 1,4 to cyclobutane **31** or else close 1,5 directly to triplet carbene **32**. In fact, >99% of the products formed on irradiating **29** in *tert*-butyl alcohol came from **32**.[17] The major photoproduct was solvent adduct **33**, which was accompanied by the 1,4 hydrogen transfer product **34** and double-bond isomers derived from it. Other 3-alkynyl-substituted cyclohexenones and cyclopentenones underwent analogous reactions, although 1,4 cyclization sometimes took place as well. In methanol or *tert*-butyl alcohol as solvent, the carbene could frequently be trapped efficiently as an ether. In inert solvent, the carbene rearranged to a mixture of products.

There is an interesting temperature dependence in the competition between 1,4 and 1,5 cyclization here, such that closure in the 1,5 sense is favored with increasing temperature. This observation fits nicely with the mechanism for 1,5 closure outlined above. The rate-controlling step in normal processes involving

(15) Kravitz, J. I.; Margaretha, P.; Agosta, W. C. *Tetrahedron Lett.* **1991**, *32*, 31

(16) Schuster, D. I.; Lem, G.; Kaprinidis, N. A. *Chem. Rev.* **1993**, *93*, 3.

(17) Rathjen, H.-J.; Margaretha, P.; Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1991**, *113*, 3904.

triplet biradicals, including 1,4 closure, is spin inversion to the singlet, and the rate of this spin inversion shows very little dependence on temperature.[18] Consequently, the rate of 1,4 cyclization should change little with temperature. On the other hand, direct 1,5 closure of a triplet biradical such as **30** should require activation, as do most other bond-forming reactions. The rates of activated reactions increase with temperature, so that the rate of 1,5 cyclization should be greater at higher temperatures. In the reaction of cyclopentenone **35** with **5**, the ratio of 1,4 cyclization (**36**) to 1,5 cyclization (**37** and related compounds) is 87:13 at −55 °C but decreases to 17:83 at +35 °C.[17]
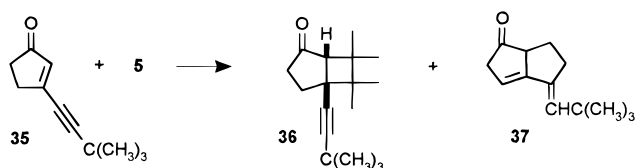

A synthetically useful sequence based on these reactions is provided by the irradiation of **38** in the presence of dimethylketene dimethyl acetal (**39**).[19]
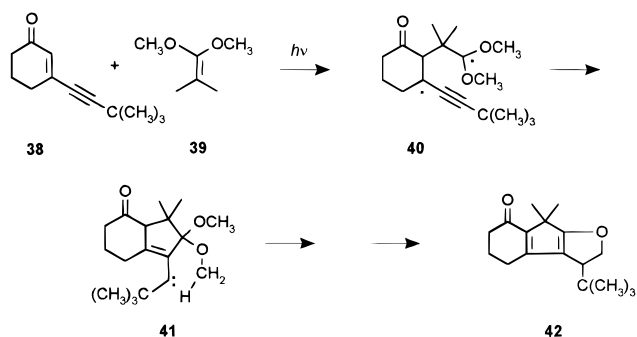
Here carbene **41**, formed on 1,5 cyclization of biradical **40**, inserts into the C−H bond of a methoxy group to yield a new tetrahydrofuran ring. Elimination of methanol then affords the final tricyclic product **42** in 22% yield. Other cyclohexenones behave similarly, and these adducts are the only cyclopentadienes known to us that are stabilized by 1,4 oxygen and carbonyl substituents in this fashion.

The success with **29**, **35**, and related ketones made it attractive to investigate biradicals from isomeric 2-(1-alkynyl)cycloalkenones such as **43**. As before,
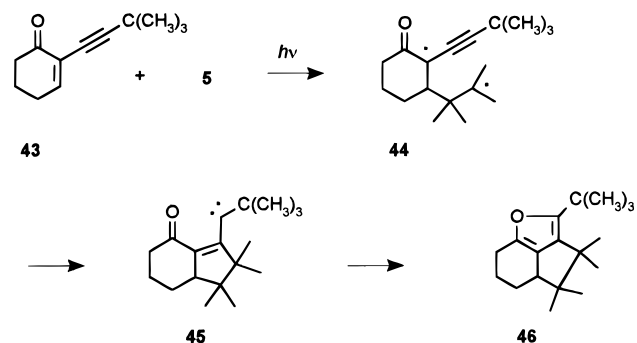
only one of the two possible biradicals is of interest for 1,5 cyclization, in this case the one from initial β bonding (as **44**).[20] We were pleased to find that irradiation of **43** with **5** led smoothly and in high yield to a single product, identified as the tricyclic furan **46**. Biradical **44** had formed and cyclized 1,5 to the desired

vinyl carbene **45**, and this carbene had then cleanly closed on the γ carbonyl group to furnish the furan. Analogous high-yield reactions leading to furans took place between other 2-alkynylcyclohexenones and either tetramethylethylene (**5**) or isobutylene, indicating that a γ carbonyl group serves as an efficient internal trap for the carbene.[21] This cyclization of β-acylvinyl carbenes to furans has been reported in the past,[22] but there are few previous examples of it.

The ability of a nearby carbonyl group to control the fate of the carbene suggested that we investigate the photochemistry of conjugated acetylenic α-diketones, such as **47,** in the presence of alkenes. Simple α-dike-
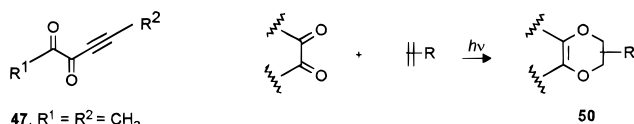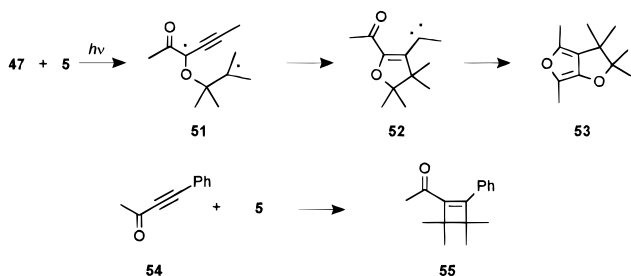

47, R^1 = R^2 = CH$_3$

48, R^1 = Ph, R^2 = CH$_3$

49, R^1 = CH$_3$, R^2 = Ph

tones react photochemically with alkenes to give 1,4-dioxenes (as **50**) along with photoproducts typical of monoketones.[23] We prepared ketone **47**[24] and found that it resembled a typical α-diketone in having a low-intensity absorption maximum at 420 nm, but that it also absorbed further into the visible, with $\lambda_{max} \sim$444 nm. On irradiation with **5**, this new ynedione was rapidly converted into furan **53** in $\sim$85% yield, in line with the intermediacy of **51** and **52**.[25] Phenyl-

substituted ketones **48** and **49** behaved analogously. By means of quenching experiments similar to those described above, we showed that the reactive excited state of **49** is a low-energy triplet (E_T 43−59 kcal/mol).

(18) Johnston, L. J.; Scaiano, J. C. *Chem. Rev.* **1989**, *89*, 521. Caldwell, R. A. In *Kinetics and Spectroscopy of Carbenes and Biradicals*; Platz, M. S., Ed.; Plenum Press: New York, 1990; Chapter 4, p 77.

(19) Margaretha, P.; Rathjen, H.-J.; Agosta, W. C. *Tetrahedron Lett.* **1990**, *31*, 3245.

(20) In general, initial bonding of enone and alkene can occur at either the α or β positions. Reference 16 contains further details.

(21) Margaretha, P.; Reichow, S.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1992**, 797; *J. Org. Chem.* **1994**, *59*, 5393.

(22) Tomer, K. B.; Harrit, N.; Rosenthal, I.; Buchardt, O.; Kumler, P. L.; Creed, D. *J. Am. Chem. Soc.* **1973**, *95*, 7402 and references cited therein. Hamaguchi, M.; Ibuta, T. *Chem. Lett.* **1976**, 287. Huntsman, W. D.; Yin, T.-K. *J. Org. Chem.* **1983**, *48*, 3813.

(23) Rubin, M. B. *Top. Curr. Chem.* **1985**, *129*, 1; **1969**, *13*, 251. Monroe, B. M. *Adv. Photochem.* **1971**, *8*, 77.

(24) Our synthesis followed the preparation of the only previously described conjugated acetylenic α-diketone known to us: Leyendecker, J.; Niewöhner, U.; Steglich, W. *Tetrahedron Lett.* **1983**, *24*, 2375.

(25) Mukherjee, A. K.; Agosta, W. C. *J. Chem. Soc., Chem. Commun.* **1994**, 1821.

(26) Turro, N. J.; Shima, K.; Chung, C.-J.; Tanielian, C.; Kanfer, S. *Tetrahedron Lett.* **1980**, *21*, 2775.

(27) Fujita, K.; Yamamoto, K.; Shono, T. *Nippon Kagaku Kaishu* **1974**, 86.

(28) Andresen, S.; Margaretha, P. *J. Chin. Chem. Soc.*, in press.

(29) Gruenanger, P.; Vita-Finzi, P. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Ed.; J. Wiley & Sons: New York, 1991; Vol. 49, p 218.

To what extent this state is comparable to the reactive triplet of simple α-diketones ($E_T \sim$56 kcal/mol)[23,26] is still an open question.

It is interesting that there are no other significant photoproducts in these reactions. Even a stabilizing phenyl group on one carbonyl (as **48**) or on the triple bond (as **49**) has no apparent effect on the course of reaction. In contrast, ynone **54** reacts with alkenes only at the triple bond, adding **5** to yield cyclobutene **55**, for example.[27]

There still remain interesting mechanistic problems in our studies on alkyl propargyl biradicals. For example, there is good chemical evidence for the carbene, but efforts to identify it spectroscopically have so far been unsuccessful.[14] We have little understanding of why cyclopentenones and cyclohexenones behave differently in some of the reactions we have examined, but not in others. Another matter of interest concerns the possible reversibility of the observed closure of biradical **2** to carbene **3**. At present, we have no information on the possible opening of **3** to **2**, and this makes independent preparation of triplet vinyl carbenes an attractive goal. If the decomposition products from a triplet vinyl carbene should include products derivable only from the corresponding biradical, this result would provide chemical evidence that vinyl carbenes can open to alkyl propargyl biradicals. Fundamental physical and theoretical studies on the triplet states of acetylenic α-diketones would also be worthwhile.

Finally, we have begun to extend our studies to systems in which the acetylenic bond is replaced by a cyano group. Cyanocyclohexenone **56**, for example, reacts on irradiation in the presence of an excess of **5** to afford a nearly quantitative yield of isoxazole **59** by way of biradical **57** and β-acylvinyl nitrene **58**.[28]
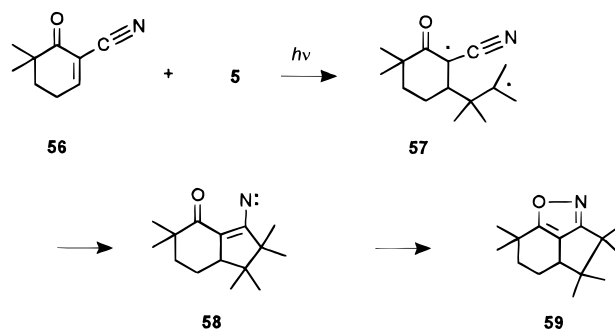
There are few previous examples of cyclization of such nitrenes to isoxazoles,[29] and we are unaware of other tricyclic isoxazoles of this sort. Experiments to trap nitrene **58** and to generate this intermediate from the corresponding azide are currently in progress.

Our exploration of alkyl propargyl biradicals has now been a fruitful area of research for many years. It continues to provide worthwhile mechanistic problems as well as to furnish simple and unusual photochemical routes to a variety of products containing five-membered rings.