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Highly Efficient Trapping of Short-Lived 1,4-Diradicals, The Order of First Bond Formation in the Intramolecular Photocycloaddition of 3-(4'-pentenyl)-cyclohex-2-enones.

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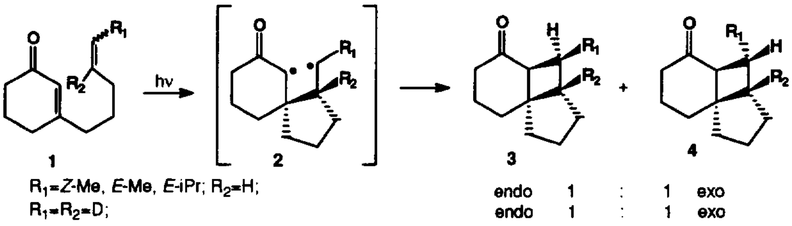
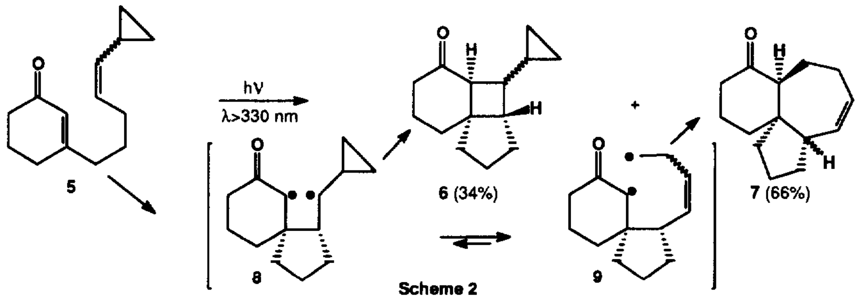
Abstract: Complete trapping of 1,4-diradical intermediates, formed in the intramolecular [2+2] photocycloaddition of **13**, provide direct evidence for the exclusive formation of the first bond at the C(β) of the cyclic enone. This result is found in full agreement with the previously studied compounds **1**.

The intramolecular photocycloaddition of alkenes to cyclic enones of type **1** has been extensively investigated by Becker and co-workers[1]. Systematic investigation revealed that similar ratio of the endo (**3**):exo (**4**) isomers was obtained in all cases, a 1:1 ratio was obtained upon irradiation at 25°C. In all cases, minor geometrical isomerization of the alkene in the starting material **1** was detected during the irradiation (ca. 10%). Based on these results, they concluded that first-bond formation in these compounds follow the "role of five"[2] and takes place exclusively *via* diradical **2**.



Scheme 1

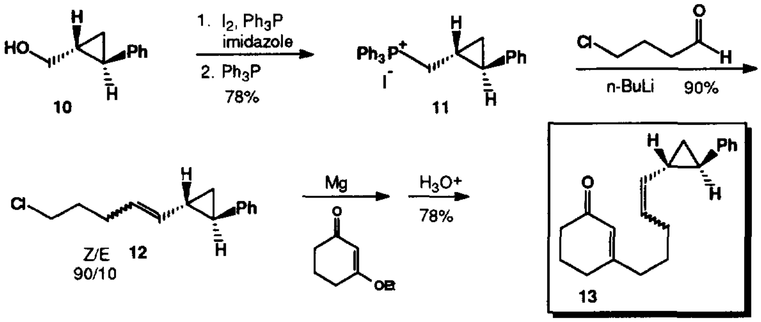
Successful trapping of a 1,4-diradical intermediate of type **2** (up to 66% of **7**), was first reported by Becker[3], providing direct evidence for its existence and its proposed structure. The trapping method is based on the fast rearrangement[4] (1×10^8 sec^{-1}) of cyclopropylcarbinyl radical intermediate **8** (scheme 2) to the corresponding homoallyl radicals **9**. This diradical underwent subsequent cyclization affording the trapping products **7**. Complete trapping of the diradical intermediate **8** would provide sufficient evidence for the above conclusion on the high regioselectivity of first-bond formation. Addition of vicinal phenyl substituent at the cyclopropyl ring, is known to facilitate the rearrangement of cyclopropyl carbinyl radicals[5] to the homoallyl radicals (1.8×10^{11} sec^{-1}) and was expected to provide complete trapping of 1,4-diradical intermediates of type **8**.



Scheme 2

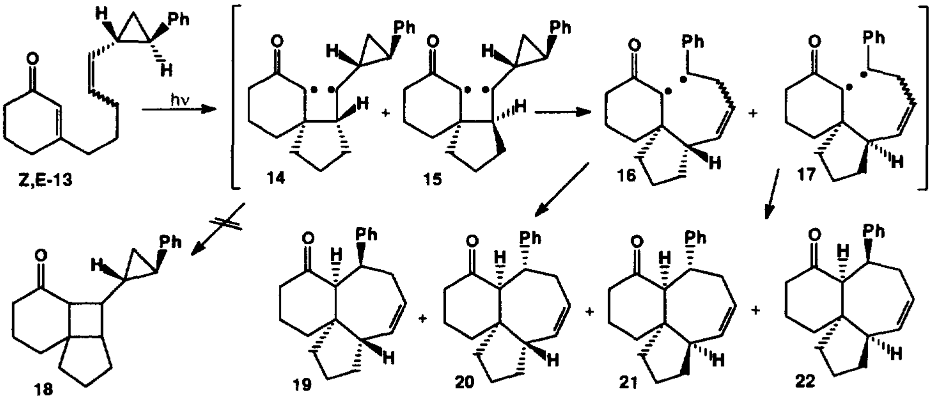
In continuation of this work, we present the first successful example on complete intramolecular[6] trapping of the 1,4-diradical intermediates formed in the photocycloaddition of **13**, possessing a phenyl substituent on the cyclopropyl ring. The results confirm the previously reported[1] high regioselectivity in the first-bond formation, obtained in the photocycloaddition studies of compounds **1** (scheme 1).

The synthesis of photosubstrates **13**, described in scheme 3, starts by converting the cyclopropyl subunit[7] **10** to the corresponding Wittig salt **11**. Condensation[8a] of **11** to 4-chlorobutyraldehyde[8b] afforded mixture of **Z-12** and **E-12** in the ratio of 90:10 respectively. The alkenyl chlorides mixture was converted to the desired photosubstrates **13** following the procedure of Conia et al.[9,1c].



Scheme 3

The photocycloaddition of compounds **13** (Z, E-mixture) was examined under the usual conditions[10], in the temperatures range of 55 to -55°C. In all cases, four trapping photoproducts **19-22** were obtained with no detectable amount of the corresponding [2+2] photoproducts **18** (scheme 4). The product ratio of **19+20** vs. **21+22** (entries 1-4, table 1) indicates a slight decrease in the ratio of "parallel" vs. "twisted" approach[3] (P/T) of the alkenyl side chain upon irradiation at lower temperature. Irradiation at -55°C (entry 5) afforded 43.3% of an undefined mixture of isomers, which possess lower mass than **18-22**, presumably formed *via* fragmentation of the 1,4- or the 1,7-diradical intermediates.



Scheme 4

The trapping products **19-22** were separated by flash chromatography and their structures determined by NMR experiments[11,12]. The structure of the major photoproduct **19** was confirmed by X-ray analysis[13]. MM2 calculations[14] of structures **20-22** and their corresponding epimers at the C(α) stereogenic center of the cyclohexanone revealed that the obtained compounds are more stable in 7.1, 13.1 and 3.62 kcal/mol respectively. Based on this result we anticipated no detectable epimerization of **20-22** upon treatment with base. Indeed, treatment of **20-22** with CD_3ONa/CD_3OD afforded their corresponding deuterated products with increase of three mass units and no detectable isomerization by GC/MS[3b].

Table 1: Irradiations of **13** (90% Z:10% E). **X**: undefined mixture of products, **P/T**: the ratio of "parallel" vs. "twisted" approach.

entry	T °C	**19**	**20**	**21**	**22**	**X**	**P/T**
1	55	66.3	11.5	7.5	15.2	--	3.4
2	25	66.8	9.6	5.6	18.0	--	3.2
3	2.5	66.5	7.5	5.6	20.4	--	2.8
4	- 14	64.2	6.8	5.9	23.1	--	2.4
5	- 55	35.2	4.2	5.5	11.6	43.3	--

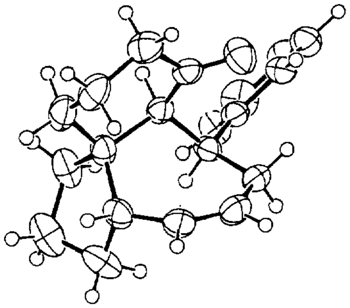


Figure 1: X-ray structure of **19**

In addition to the diradical intermediates **14** and **15**, three more 1,4-diradicals **23-25** should be considered. These diradicals could cyclize to the corresponding [2+2] photoproducts[15] and/or cleave back to the alkene-enones **Z-13** and **E-13**. Such an isomerization could easily be detected during the irradiation. Diradical **25** could also lead to trapping product(s).

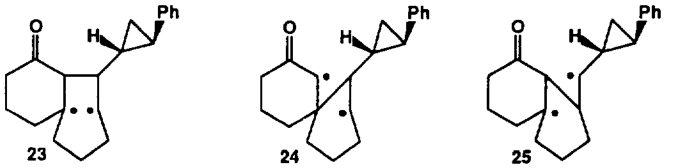


Figure 2

Kinetic studies on the irradiation of pure **Z-13** have shown *no geometrical isomerization* to its corresponding E-isomer (**E-13**), indicating no revision of diradical intermediates to starting materials. This result, along with the fact of absence of [2+2] photoproducts and/or trapping product(s) formed *via* diradical **25**, provide direct and unambiguous evidence that **14** and **15** are the only diradical intermediates obtained in the photocycloaddition reaction of **13**. This result is in full agreement with our previous conclusion[1a] that the intramolecular photocycloaddition of compounds **1** (scheme 1) takes place exclusively *via* first bond formation at the C(β) position of the cyclic enone, following the "rule of five".

Furthermore, the ratio of the "parallel" vs. "twisted" approach of the alkene to the cyclic enone, responsible for the formation of diradicals **14** and **15** respectively, could be determined from the product ratio of **18** and **19** vs. **20** and **21** respectively. The fact that no [2+2] *trans*-fused photoproducts were formed in the irradiation of **1**, indicates complete cleavage of its corresponding 1,4-diradical intermediate, formed *via* the "twisted" approach, back to the starting material *via* possible geometrical isomerization of the alkenyl side chain.

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\# Deceased, April, 1994.

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6. Intermolecular trapping of similar diradicals have recently been reported, using the **highly toxic** H_2Se as the trapping reagent: Maradyn, D. J.; Weedon, A. *J. Am. Chem. Soc.*, **1955**, *117*, 5359.
7. Chiral cyclopropyl **10** was prepared in an optically pure form, needed for further mechanistic studies, following Hacksell's procedure: Vallgarda, J.; Hacksell, U. *Tetrahedron Lett.*, **1991**, *32*, 5625; Vallgarda, J.; Appelberg, U.; Csoregh, I.; Hacksell, U. *J. Chem. Soc. Perkin Trans. 1*, **1994**, 461.
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10. 80-W Hanau mercury vapor lamp (Q-81) was used for irradiations *via* a Uranium glass filter ($\lambda > 330$). All irradiations were carried out in 18 mL of hexane as solvent under nitrogen atmosphere. The concentrations always kept below 0.05 M and the reactions followed by TLC or GC.
11. All new compounds were characterized by full spectroscopic data, yields refer to chromatographed materials with purity of >95%.
12. The relative stereochemical relationship of the stereogenic centers was determined by NOE-difference. The location of these protons determined by combination of COSY-45, XH-CORR, JMOD-XH methods and was supported by NOE experiments. For determination of similar structures by NMR cf.: ref. (3b) and (a) Becker, D.; Haddad, N. *Tetrahedron* **1993**, *49*, 947. Becker, D.; (b) Haddad, N. *Isr. J. Chem.* **1989**, *29*, 303.
13. X-ray analysis of **19**: Empirical formula $C_{20}H_{24}O$, F.W. 280.4, T = 293K, lattice monoclinic, space group $P2_{1/c}$, $a = 14.803(7)$, $b = 8.474(4)$, $c = 14.018(7)$ Å, $\beta = 93.95(5)°$, $V = 1568.6$ Å^3, $Z = 4$, F(000) = 608, Dx = 1.188 g.cm^{-3}, radiation Mo Kα, $\lambda = 0.71069$ Å, $\mu = 0.37$ mm^{-1}, θ range for data collection 2-25°, index ranges $-15 \leq h \leq 15$, $0 \leq k \leq 0$, $0 \leq 1 \leq 15$, No. of unique reflections 2644, structure solved by SHELXS86$^{(a)}$, and refined by SHELXL76$^{(b)}$ programs, refinement method full matrix least squares on F, 1864 reflections for which $Fo \geq 3\sigma (Fo)$, No. of parameters 286, R = 0.059, Rw = 0.065, largest diff. peak 0.19 eÅ^{-3}. (a) Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467; (b) Sheldrick, G. M. (1976) SHELX76, program for crystal structure determination. University of Cambridge, England. ^{1}H-NMR ($CDCl_3$) δ 7.41 (d, 2H), 7.27 (d, 2H), 7.15 (t, 1H), 5.68 (t, J=11.9 Hz, 1H), 5.48 (dt, J_1=12.1, J_2=4.5 Hz, 1H), 3.61 (q, J_1=12.1, J_2=5.8 Hz, 1H), 3.21 (m, 1H), 2.45 (m, 1H), 2.41 (s, 1H), 2.21 (m, 1H), 2.15 (m, 4H), 1.86-1.56 (m, 8H).
14. Calculated using the Macro model V-3.5X of Allinger MM2 program. The calculated conformations are in full agreement with the NOE results.
15. "Cross" photoproducts usually formed as major products in the intramolecular photocycloadditions of cyclicenones possessing shorter alkenyl side chain, cf.: Wolff, S.; Agosta, W. C. *J. Am. Chem. Soc.*, **1983**, *105*, 1292 and 1299.

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