

## SYNOPSIS

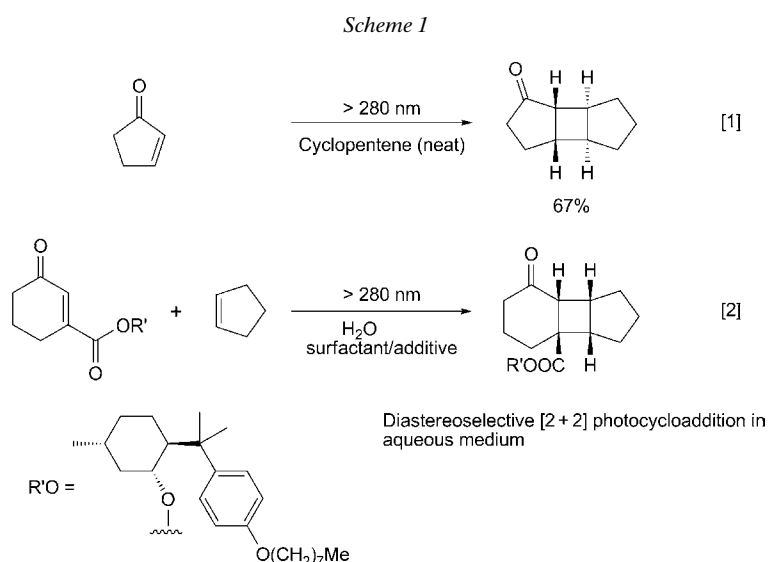
## Retrospective View on Recent Developments in Cyclobutane Synthesis via [2 + 2] Photocycloaddition of Unsaturated Ketones to Acyclic Dienes

by Paul Margaretha

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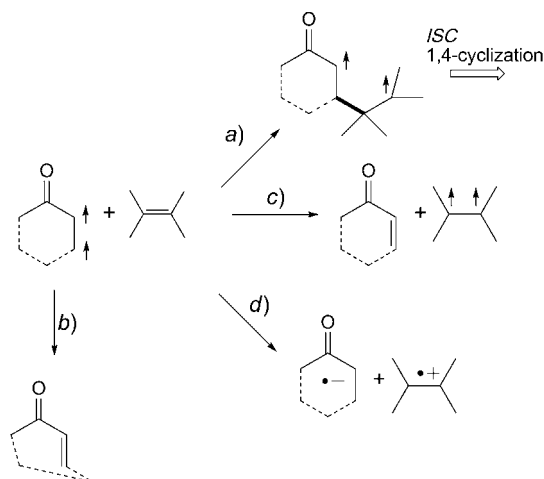
This synopsis addresses cyclobutane formation *via* light-induced [2 + 2] cycloaddition from both cyclic and acyclic unsaturated carbonyl compounds, and 2,3-dimethylbuta-1,3-diene

**Introduction.** – For more than 50 years, the photocycloaddition of five- and six-membered cyclic enones to alkenes affording cyclobutane derivatives represents one of – if not the – most important light-induced preparative organic transformations. One of the first representative examples [1], together with a very recent application [2] of such a reaction, are illustrated in *Scheme 1*.



As discussed in several reviews on this topic [3–7], the key step in these conversions (*Scheme 2*) is an efficient C,C-binding interaction between triplet-excited enone and the ground-state alkene leading to a triplet 1,4-biradical intermediate, which

Scheme 2



is then followed by spin inversion (*ISC*) and 1,4-cyclization (path *a*). The requirements for the efficiency of this addition step are straightforward. Regarding the enone, monomolecular deactivation by, *e.g.*, (*Z*)  $\rightarrow$  (*E*) isomerization becomes important for both acyclic unsaturated ketones and enone rings with seven or more members (path *b*), and, therefore, synthetic applications have at first remained limited to five- and six-membered cyclic enones. As for the alkene partner, a corresponding triplet energy below that of the excited enone, as generally observed for 1,3-dienes, will induce energy transfer to this latter (path *c*), whereas a very low oxidation potential, as found for tetramethoxyethene will favor electron transfer (path *d*) [8]. It is thus not surprising that, in most of the older reviews [3][4], it was generally stated that *a*) cyclohept-2-en-1-ones do not undergo photocycloaddition reactions with alkenes, and *b*) cyclopent-2-en-1-ones and cyclohex-2-en-1-ones do not undergo cycloaddition to 1,3-dienes due to efficient quenching.

To predict such a quenching step, it is obviously crucial to know the effect of ring size or substituents on the triplet energies of enones. Representative data for such compounds are compiled in *Table 1*. As can be seen from these data, both the flexibility of the enone with respect to torsion around the C=C bond, as well as the extended conjugation have a decisive influence on the  $E_T$  values.

For comparative purposes, triplet energies of typical alkenes, dienes, and enynes are collected in *Table 2*. Independent of alkyl-substitution pattern, most conjugated alkenes have  $E_T$  values in the range of 58–62 kcal/mol.

Regarding the interaction of triplet excited cycloalk-2-enones with acyclic dienes, *e.g.* buta-1,3-diene, it was reported already in the early 1970s [14][15] that, by using a large excess (>20:1) of the diene, it was possible to obtain, on a preparative scale, good yields of [2+2] cycloadduct mixtures from cyclohex-2-en-1-one, although the latter were not separated, and thus the adducts themselves were not fully characterized. Some 15 years later, it was confirmed by transient absorption spectroscopy that *a*) the rates of quenching of cyclohex-2-en-1-one triplets by dienes are anomalously low, and *b*) that

Table 1. Triplet Energies [kcal/mol] of Selected Unsaturated Carbonyl Compounds

Compound	Triplet energy [kcal/mol]	Ref.
Prop-2-enal	58	[9]
Cyclopent-2-en-1-one	73	[10]
Cyclohex-2-en-1-one	63	[11]
Cyclohept-2-en-1-one	< 58	[11]
3-Methylcyclohex-2-en-1-one	70	[11]
1,2,3,5,6,7-Hexahydro-4 <i>H</i> -inden-4-one	74	[11]
3-Phenylcyclohex-2-en-1-one	58	[11]

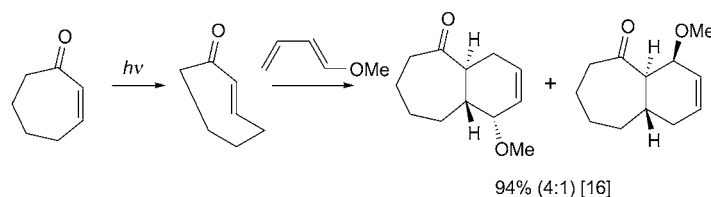
Table 2. Triplet Energies [kcal/mol] of Selected Conjugated Hydrocarbons

Compound	Triplet energy [kcal/mol]	Ref.
Ethene	79	[10]
Ethynylbenzene	62	[10]
But-1-en-3-yne	60	[12]
Buta-1,3-diene	58	[10]
2-Methylbuta-1,3-diene	60	[10]
2,3-Dimethylbuta-1,3-diene	< 61	[13]

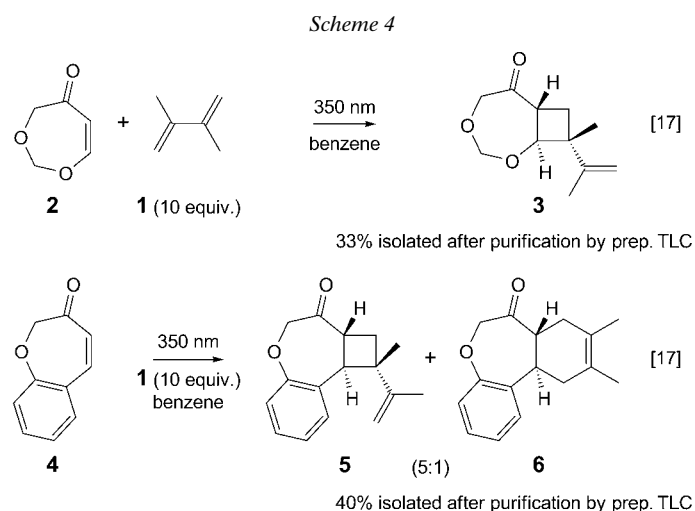
the corresponding *Stern–Volmer* plots show a pronounced curvature, probably due to competing cyclobutane formation [11]. Quite recently it was shown [16] that the [4 + 2] photocycloadducts exclusively formed on irradiation of cyclohept-2-en-1-one in the presence of 1-methoxybuta-1,3-diene arise from a reaction sequence wherein the first step is (*Z*)/(*E*) isomerization of the seven membered cyclic enone, which is then followed by a thermal *Diels–Alder* reaction between (*E*)-cyclohept-2-en-1-one and the diene (*Scheme 3*).

From all these data, it could be inferred that seven membered cyclic enones *constrained* from undergoing (*Z*)/(*E*) isomerization, and six-membered cyclic enones, either with a higher flexibility than cyclohex-2-enone itself, or bearing substituents allowing for an extension of the conjugated  $\pi$ -system *without increasing steric hindrance*, should be appropriate molecules for undergoing light-induced [2 + 2] cycloadditions to conjugated alkenes. A compilation of such reactions will follow. For all experiments described below, 2,3-dimethylbuta-1,3-diene (**1**) was used as diene due to *a*) the equivalence of its two C=C bonds, thus avoiding the formation of constitutional isomers, and *b*) NMR differentiation between [2 + 2] and [4 + 2] cycloadducts becomes straightforward.

Scheme 3



**Results.** – Cyclic enones without substituents at the C=C bond represent the most convenient starting compounds for exploratory cycloadditions to unsaturated hydrocarbons, as the analysis of the coupling constants by  $^1\text{H-NMR}$  spectroscopy usually allows a full assignment of constitution, configuration, and conformation of the photocycloadducts. Oxacycles tend to be less flexible than the corresponding carbacycles of the same ring size regarding torsion around a C=C bond due to the shorter C–O bond as compared to a C–C bond. Thus, dioxepinone **2** on irradiation in the presence of a tenfold molar excess of **1** is selectively converted into cyclobutane **3**, whereas benzoxepinone **4** under the same conditions affords a 5 : 1 mixture of [2 + 2] cycloadduct **5** and [4 + 2] cycloadduct **6** [17] (*Scheme 4*).



Both photocycloadducts **3** and **5** exhibit a newly formed *trans*-ring fusion (two pseudoaxial H-atoms on the bridge) and a preferential configuration/conformation wherein the Me group occupies the *pseudo-axial* and the methylethenyl group the *pseudo-equatorial* position (*Fig.*).

In contrast, C–S bonds are longer than C–C bonds, and, therefore, thiinone **7** on irradiation also reacts efficiently with **1** to afford – now *cis*-fused – thiabicyclooctanones **8** and **9** as major and *trans*-fused thiabicyclooctanone **10** as minor [2 + 2] cycloadduct besides traces of the [4 + 2] cycloadduct **11** [18] (*Scheme 5*). The

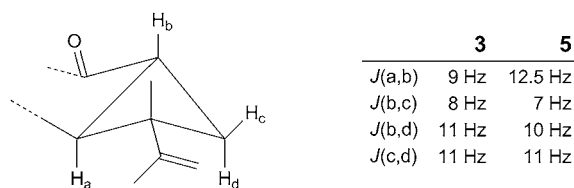
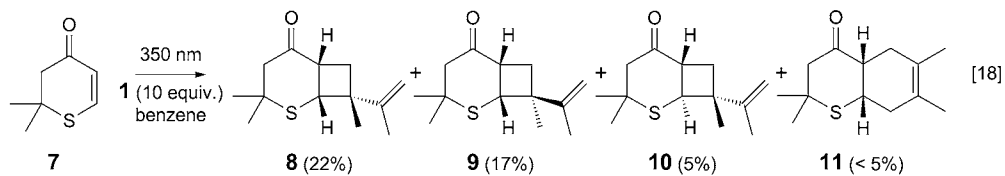
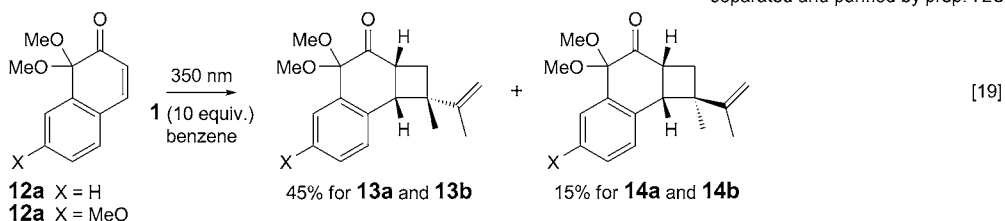


Figure. Preferred configurations/conformations of photocycloadducts **3** and **5**

Scheme 5



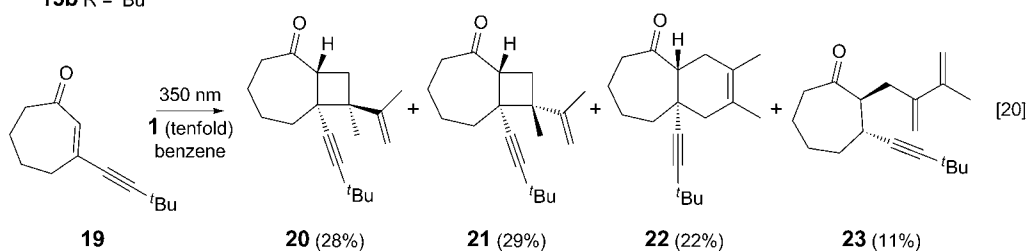
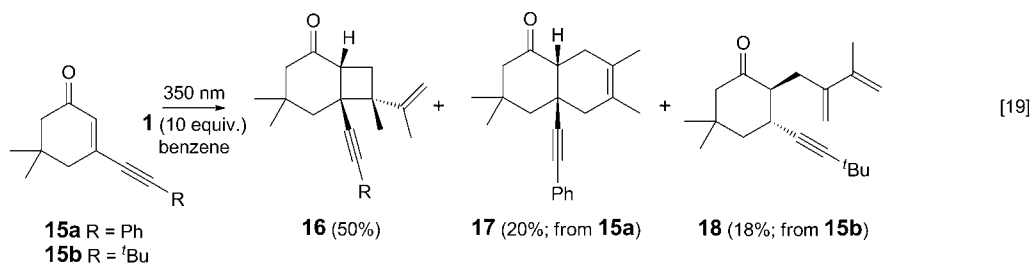
separated and purified by prep. TLC



configuration/conformation of the four-membered ring in **10** parallels that of cycloadducts **3** and **5** (*Fig.*). Under the same reaction conditions, naphthalenone **12** is quantitatively converted into a 3:1 mixture of [2+2] cycloadducts **13** and **14** (*Scheme 5*) [19]. Here, the extended conjugation due to benzoannellation is the reason for a lower triplet-energy value as compared to the (parent) cyclohex-2-enone.

Regarding substituents at C( $\beta$ ) of the enone ring system capable of extending the delocalization of the  $\pi$ -system, alkynyl groups seem most appropriate as they usually only exhibit very restricted steric requirements. Thus, both 3-alkynyl substituted cyclohex-2-en-1-ones **15a** and **15b** on irradiation in the presence of **1** afford [2+2] cycloadducts **16** as major products [19] (*Scheme 6*). Whereas the minor product for **15a**

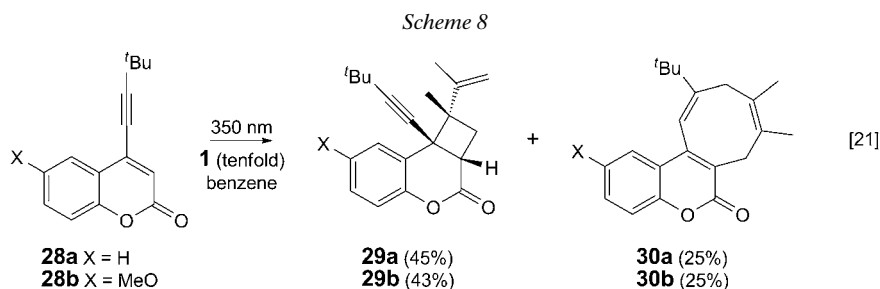
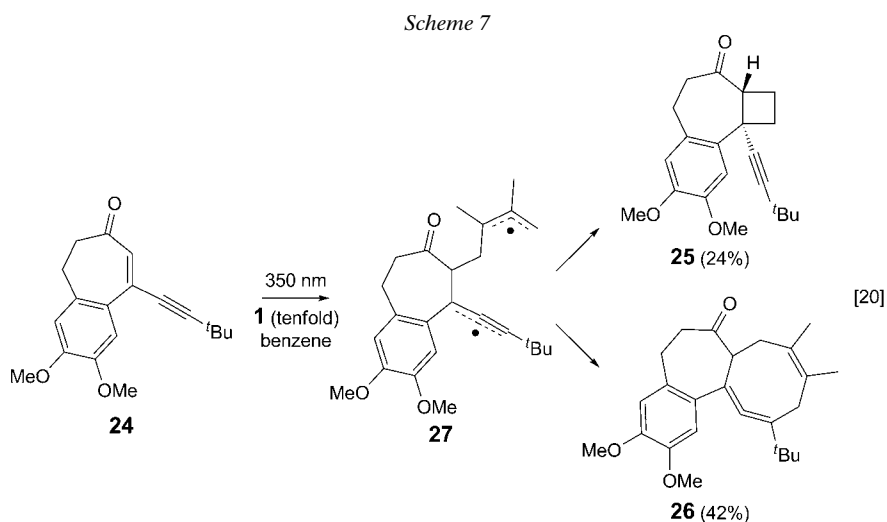
Scheme 6



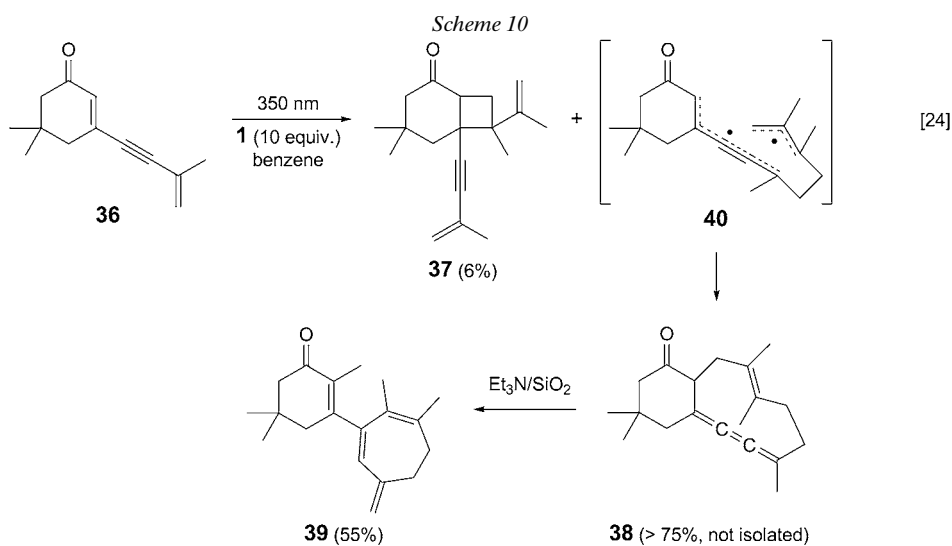
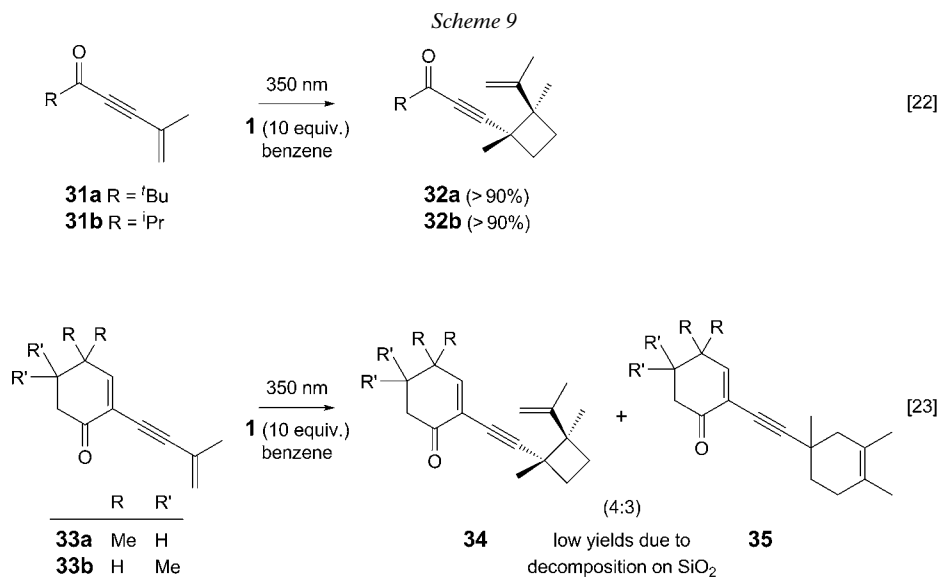
is the *cis*-fused [4+2] cycloadduct **17**, cyclohexanone **18** is formed from **15b**. Very similarly, 3-alkynylcyclohept-2-enone **19** affords cyclobutanes **20** and **21** as major products, and both the *trans*-fused [4+2] cycloadduct **22** and cycloheptanone **23** as minor products [20] (*Scheme 6*). Not unexpectedly the ring-fusion in bicyclooctanones **16** is *cis*, whereas that of bicyclononanones **20** and **21** is *trans*, reflecting the higher flexibility of a seven-membered ring compared to a six-membered one.

The combined effect of an alkynyl group at C( $\beta$ ) of the enone ring *and* an additional benzo fusion leads to an unexpected novel cyclization step of the biradical intermediate besides the well established 1,4-cyclization, affording cyclobutane derivatives. Thus, of the irradiation of benzocycloheptenone **24** in the presence of **1**, cyclobutane **25** is now the minor product, whereas cyclooctatriene **26** now represents the major product [20]. The eight-membered cyclic allene results from 1,8, *i.e.*, end-to-end, cyclization of the – doubly delocalized – biradical **27** (*Scheme 7*).

Quite similarly, 4-alkynylcoumarins **28** under the same conditions afford a – now major – cyclobutane derivative **29** in addition to the minor cyclooctatriene derivative **30**, which in turn is formed *via* a H-shift from a cyclic allene intermediate corresponding to **26**, which is not detected in this reaction [21] (*Scheme 8*).



Finally, irradiation of appropriate *acyclic* enyne systems conjugated to a C=O group in the presence of **1** also leads to efficient and diastereoselective cyclobutane formation. Thus, enynones **31** are cleanly and almost quantitatively converted to 1-cyclobutylalk-1-yn-3-ones **32** [22], whereas 2-(alk-3-en-1-ynyl)cyclohexenones **33** afford mixtures of (major) [2 + 2] and (minor) [4 + 2] photocycloadducts **34** and **35**, respectively [23] (Scheme 9). Interestingly, 3-(alk-3-en-1-ynyl)cyclohex-2-en-1-one **36**, which represents a constitutional isomer of **33**, under the same conditions affords only



traces of [2 + 2] cycloadduct **37**, the major product now being cyclodecatetraene **38**, which contains both a butatriene moiety and a (*E*)-configured C=C bond in the ten-membered ring [24] (*Scheme 10*). Not surprisingly, **38** decomposes on contact with SiO<sub>2</sub>, but in the presence of base, *e.g.* Et<sub>3</sub>N, it isomerizes quantitatively to cycloheptadienylcyclohex-2-enone **39**. Compound **38** is formed from biradical **40** *via* 1,10-cyclization.

**Conclusions.** – The ‘enone + alkene photocycloaddition library’ has been significantly expanded in the last five years. Not only seven-membered cyclic enones containing heteroatoms, but also cyclohex-2-en-1-ones with substituents, which allow for a higher degree of delocalization of the  $\pi$ -system, and even acyclic enynones, on irradiation in the presence of 2,3-dimethylbuta-1,3-diene (as a representative acyclic 1,3-diene), afford [2 + 2] photocycloadducts with high efficiency. Furthermore, in some of these reactions, highly interesting larger-ring by-products result from competitive end-to-end-cyclization of the intermediate doubly delocalized biradicals. These results suggest that photocycloadditions of enones to alkenes will remain attractive in future preparative organic photochemistry.

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