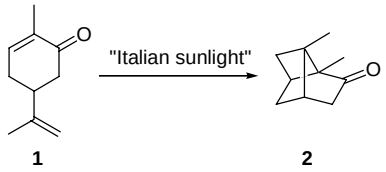
[2 + 2] PHOTOCYCLOADDITION OF ENONES TO OLEFINS

Reported by Timothy A. Boebel November 15, 2001

INTRODUCTION

The [2+2] photocycloaddition of enones to olefins is a classic reaction in synthetic organic chemistry. It was first reported by Ciamician in 1908 in the photo-induced conversion of carvone (**1**) to the highly strained carvonecamphor (**2**) (Scheme 1).[1] This example illustrates the potential for this transformation for the synthesis of mono and polycyclic ring systems containing a central, highly strained cyclobutane moiety under "reagentless" conditions.

Scheme 1.



1 **2**

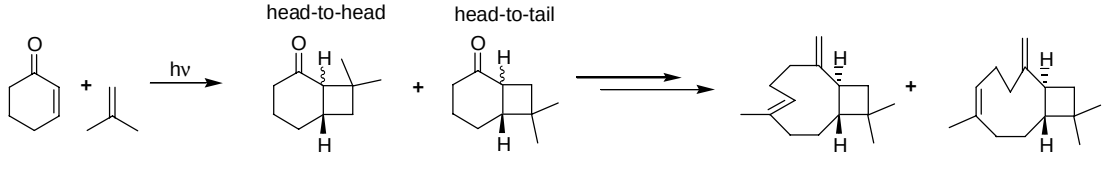
[2+2] Photocycloadditions have been a source of considerable interest for almost a century and has been extensively investigated.[2] Mechanistic studies have revealed much about the intermediates of the photocycloaddition,[3,4] but their high reactivity has made it difficult to control regio- and stereoselectivity. In addition, the general reaction pathway has yet to be fully elucidated. Despite these obstacles, this reaction has often been used in the total synthesis of natural products.[5,6,7,8] Also, new developments have overcome problems in both regio- and stereoselectivity. This report will summarize the reaction mechanism, recent developments in stereoselective photocycloadditions, and some applications of this methodology in the total synthesis of natural products.

MECHANISM

Background

In the landmark synthesis of caryophyllene (**3**) and isocaryophyllene (**4**) (Scheme 2), Corey and coworkers discovered that irradiation of enone **5** in the presence of isobutylene **6** resulted in the formation of a mixture of isomeric products: head-to-tail adducts **8** as the major products and head-to-head adducts **7** as minor constituents.[5] Intrigued by this observation, they examined several additional

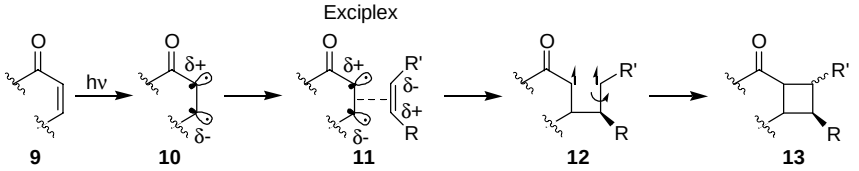
Scheme 2.



5 **6** **7** minor **8** major **3** **4**

intermolecular [2+2] photocycloadditions of cyclic enones to olefins with the goal of understanding the factors responsible for the regio- and stereoselectivity.[9] It was observed that in general, electron rich olefins yielded mainly head-to-tail cycloadducts with enones whereas electron deficient olefins provided head-to-head products. Also, it was observed that the use of either *cis* or *trans* 2-butene resulted in identical product mixtures. Corey concluded that upon excitation of the enone **9** to triplet **10,**[10] the reaction proceeded though an oriented π-complex or exciplex **11**, which defines the regioselectivity of bond formation to the olefin, affording triplet 1,4-biradical intermediate **12** (Scheme 3). Free rotation about the single bond results in scrambling of configuration before collapse to cyclobutane **13**.

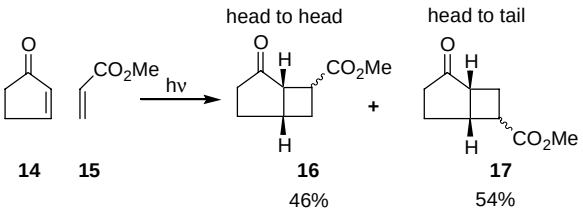
Scheme 3.



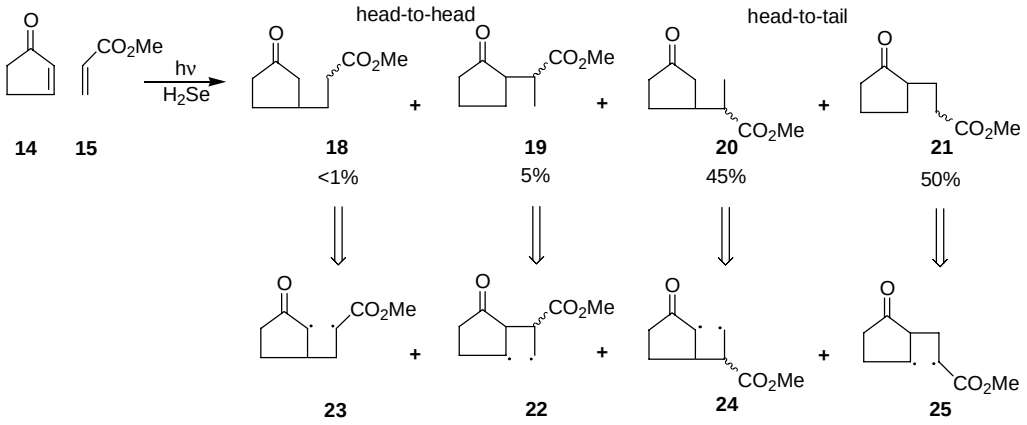
Trapping of Triplet 1,4-Biradical Intermediates

The intermediacy of a triplet 1,4-biradical intermediate **12** is central to the proposed mechanism of cycloaddition. Seeking evidence for this species, Weedon and coworkers designed a study to trap newly formed radical intermediates with hydrogen selenide before the cycloaddition could occur.[11] Irradiation of a solution of 2-cyclopentenone (**14**) and methyl acrylate **15** yielded a 1:1 mixture of head to head and head to tail products (Scheme 4). When the experiment was repeated in the presence of the radical trap H_2Se, a mixture of saturated esters **18-21** was isolated with no cycloadducts detected (Scheme 5). Each of these corresponded to a specific biradical intermediate **22-25**, giving strong evidence for the existence of the proposed intermediate **12**. Interestingly, the ratios of head to head and head to tail cycloaddition products did not match those of the trapped intermediates.[12] This suggests that the major cycloadducts do not come from those biradicals that form at the fastest rates; rather those products come from the biradicals that show a greater propensity to close and not revert to ground state starting material. As a result, the intermediacy of an exciplex intermediate may be incorrect, leaving no clear explanation for the observed regioselectivity.[11b]

Scheme 4.



Scheme 5.

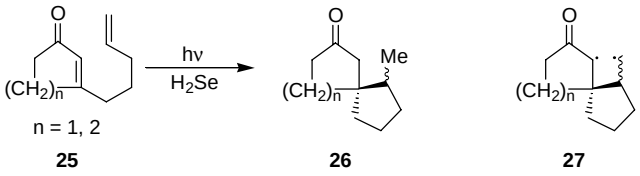


Intramolecular Photocycloadditions: The Rule of Five

The regioselectivity of intramolecular photocycloaddition is generally very high in systems where the two double bonds are connected by a three, or four atom tether. Generally, in these systems the initial radical addition to the olefin will preferentially form five-membered rings over larger rings.[2] This observation is known as the "Rule of Five"[13] and is likely due to the increasingly unfavorable entropies of cyclization that correspond to the formation of larger rings.[14]

This rule was tested by Weedon and coworkers in a second radical trapping study.[16] Irradiation of enone **25** (Scheme 6) in the presence of H_2Se resulted in exclusive formation of spiro ketone **26,** presumably formed from the biradical intermediate **27**, with no evidence of cycloaddition products. This experiment provided clear evidence for the validity of the Rule of Five.

Scheme 6.



ENANTIOSELECTIVE [2+2] PHOTOCYCLOADDITIONS

Enantioselective Photocycloadditions of Chiral Allenes

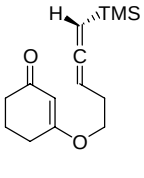
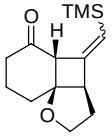
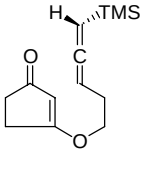
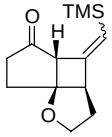
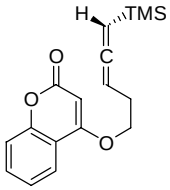
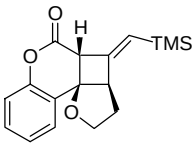
The use of allenes in [2+2] photocycloadditions with enones has been successfully demonstrated.[2,9,17] Recently, Carreira and coworkers developed a new strategy for the enantioselective intramolecular [2+2] photocycloaddition of enones to optically active silyl-substituted allenes.[18] Irradiation of cyclic enones **28-29** afforded a mixture of diastereomers with high enantioselectivity

(Table 1).[18b] Interestingly, irradiation of coumarin **30** resulted in the formation of **33** as a single diastereomer with excellent enantioselectivity. The authors proposed that this high diastereoselectivity was due to a conformational memory effect[19] in the closing of the putative 1,4-biradical intermediate. When the silyl group was replaced with a tertiary butyl group, greater enantioselectivities were realized.

Enantioselectivity with a Chiral Host

Bach and coworkers have recently reported on the use of a chiral complexing reagent to effect enantioselective [2+2] photocycloadditions of a 2-quinolone substrate to olefins.[20] Irradiation of quinolone **34** and an olefin in the presence of chiral host **35** (Scheme 7) gave either exo-adduct **36** or endo-adduct **37** in high diastereo- and enantioselectivity (Table 2).[20b] Enantioselectivity is presumably controlled by a hydrogen-bonded complex of **34** with **35** which imparts a facial bias for olefin addition. When styrene was used, the reaction failed to go to completion, and 10% of endo-adduct **37** was recovered along with 65% of quinoline **34**.

Table 1

Entry	Photosubstrate	Photoadduct	Yield	Z:E	*ee*
1	 **28**	 **31**	86%	1.3:1	92% (Z) 86% (E)
2	 **29**	 **32**	67%	1.6:1	76% (Z) 78% (E)
3	 **30**	 **33**	90%	E only	99%

Scheme 7.

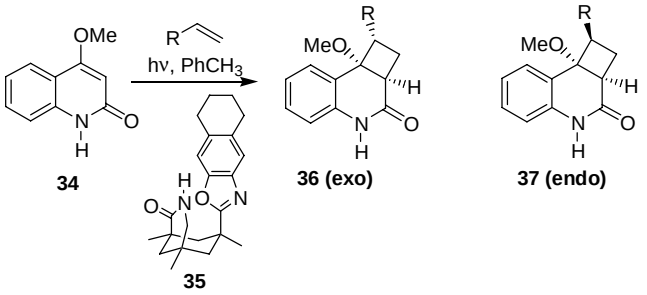


Table 2.

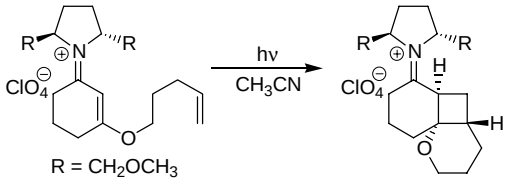
Entry	R	36/37	Yield	Product	*ee*
1	$CH_2CH_2CH_2OH$	>95/5	80%	**36**	81%
2	CH_2OAc	>95/5	80%	**36**	92%
3	Ph	<5/95	10%	**37**	83%
4	CO_2CH_3	90/10	84%	**36**	82%

Stereocontrol Through a Concerted Reaction Mechanism

A common disadvantage associated with [2+2] photocycloadditions is the scrambling of configuration associated with the putative 1,4-biradical intermediate **12**. However, if the cycloaddition occurred in a concerted manner, this problem would be nonexistent. Mariano and coworkers have recently reported a way to control the mechanism.[21] Their strategy employs the use of eniminium salts as enone surrogates. Since eniminium salts possess only π-π* excited states, intersystem crossing from singlet to triplet excited states should be slow. As a result, [2+2] cycloadditions of these substrates should occur from singlet excited states and thus follow a concerted mechanism.

A second key feature of their strategy was the incorporation of a chiral directing group to control facial selectivity in the cycloaddition. During their initial study, Mariano and coworkers found that irradiation of **38** led to formation of photoadduct **39** (Table 3).[21b] However, longer irradiation periods led to lower enantioselectivities. Also, it has yet to be determined whether this methodology will be successful in avoiding the scrambling of the configuration of the alkene.

Table 3.



Entry	Temperature	Conversion	Yield	*ee*
1	20 °C	90%	51%	63%
2	20 °C	56%	65%	75%
3	20 °C	40%	61%	82%
4	4 °C	60%	60%	78%
5	4 °C	46%	56%	80%

APPLICATIONS

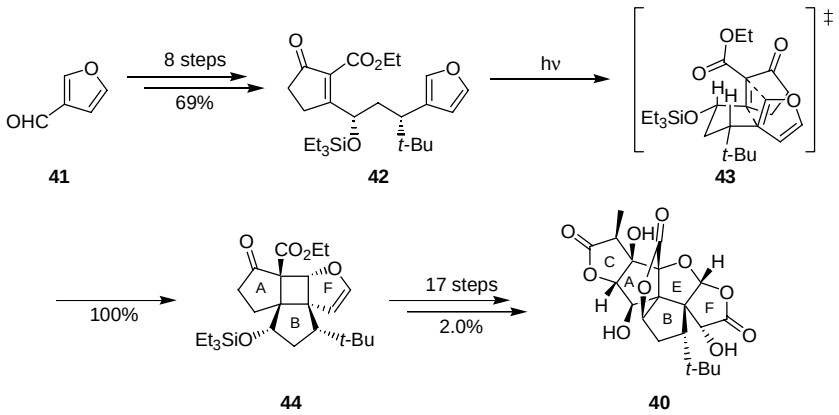
Total Synthesis of Ginkgolide B

Ginkgolide B (**40**) was first isolated from the root bark of *Ginko biloba* by Furukawa in 1932.[22] Because of its complex ring molecular architecture and biological activity as a potent platelet-activating antagonist,[23] Ginkgolide B is an attractive synthetic target.

Crimmins and coworkers reported a racemic synthesis of **40** using a double diastereoselective [2+2] photocycloaddition as the key step (Scheme 8).[7] Cycloaddition precursor **42** was prepared from

commercially available 3-furaldehyde in 8 steps. Irradiation of **42** provided the desired photoadduct **44** in quantitative yield, presumably through a chair-like transition state **43**. The natural product **40** was afforded from cycloadduct **44** in 17 steps, which included a regioselective cyclobutane cleavage and an acid-catalyzed closure of the E ring. This synthesis provides an excellent example of the utility of the [2+2] photocycloaddition of an enone to an olefin to set multiple stereocenters in a single step.

Scheme 8.

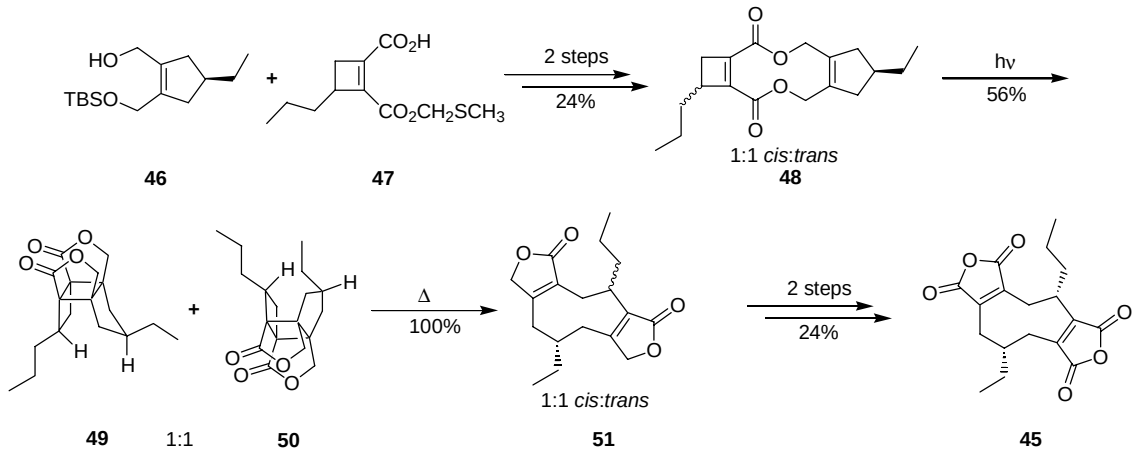


[2+2] Photocycloaddition/Thermal Fragmentation

The high ring strain associated with cyclobutanes typically allows for their efficient fragmentation to less strained products. If the cyclobutane is fused to one or more rings, this process can provide many ring expansion products. As a result, a tandem [2+2] photocycloaddition/fragmentation sequence offers a powerful route to medium-sized rings and has been extensively studied in the literature.[24, 25]

White and coworkers have recently reported the total synthesis of (+)-byssochlamic acid **45** (Scheme 9).[8] A [2+2] photocycloaddition/thermal fragmentation strategy for the construction of the nine-membered ring was employed. Coupling of **46** and **47** led to a 1:1 *cis*:*trans* mixture of photosubstrate **48** in 2 steps. Subsequent intramolecular [2+2] photocycloaddition of **48** yielded photoadducts **49** and **50** in 56% yield, which upon thermal fragmentation gave the desired cyclononadiene **51** as a 1:1 mixture of epimers in quantitative yield. Further elaboration and epimerization of the propyl group gave byssochlamic acid. The rapid construction of this fused macrocyclic ring system highlights the utility of the tandem [2+2] photocycloaddition/thermal fragmentation methodology.

Scheme 9.



CONCLUSION

The [2+2] photocycloaddition of enones to olefins has been shown to be highly effective in the generation of cyclobutanes in an enantioselective fashion. In particular, Mariano's strategy shows great promise and has the capacity to develop into a general method for stereocontrol in [2+2] photocycloadditions. Furthermore, the [2+2] photocycloaddition/thermal fragmentation strategy provides a powerful method for the generation of medium sized rings which are frequently found in natural products.

REFERENCES

(1). (a) Ciamician, G.; Silber, P. *Chem. Ber.* **1908**, *41*, 1928. (b) Büchi, G.; Goldman, I. M., *J. Am. Chem. Soc.* **1957**, *49*, 4741.

(2) Crimmins, M. T. *Chem. Rev.* **1988**, *88*, 1453.

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

(4) For an excellent resource on photochemical mechanisms, see Turro, N. J. *Modern Molecular Photochemistry*. The Benajmin/Cummings Publishing Company Inc.: Menlo Park; 1978.

(5) Caryophyllene: Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485.

(6) Manzamine: Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425.

(7) Ginkgolide: Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **2000**, *122*, 8453.

(8) Byssochlamic Acid: White, J. D.; Kim, J.; Drapela, N. E. *J. Am. Chem. Soc*. **2000**, *122*, 8665.

(9) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. *J. Am. Chem. Soc.* **1964**, *86*, 5570.

(10) Broeker, J. L.; Eksterowicz, J. E.; Belk, A. J.; Houk, K. N. *J. Am. Chem. Soc.* **1995**, *117*, 1847.

(11) (a) Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8525. (b) Andrew, D.; Hastings, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1994**, *116*, 10870.

(12) Similar results were realized when ethyl vinyl ether was used as the olefin.

(13) (a) Srinivasan, R.; Carlough, K. H. *J. Am. Chem. Soc.* **1967**, *89*, 4932. (b) Liu, R. S. H.; Hammond, G. S. *J. Am. Chem. Soc.* **1967**, *89*, 4936.

(14) Capon, B. *Quart. Rev.* **1964**, *18*, 45.

(15) Fischer, E.; Gleiter, R. *Angew. Chem., Int. Ed.* **1989**, *28*, 925.

(16) Maradyn, D. J.; Weedon, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 5359.

(17) (a) Baker, W. R.; Senter, P. D.; Coates, R. M. *J. Chem. Soc., Chem. Commun.* **1980**, 1011. (b) Coates, R. M.; Senter, P. D.; Baker, W. R. *J. Org. Chem.* **1982**, *47*, 3697. (c) Becker, D.; Nagler, M.; Harel, Z.; Gillon, A. *J. Org. Chem.* **1983**, *48*, 2584. (d) Dauben, W. G.; Shapiro, G.; Luders, L. *Tetrahedron Lett.* **1985**, *26*, 1429.

(18) (a) Carreira, E. M.; Hastings, C. A.; Shepard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6622. (b) Shepard, M. S.; Carriera, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 2597. (c) Shepard, M. S.; Carriera, E. M. *Tetrahedron* **1997**, *53*, 16253.

(19) Griesbeck, A. G.; Mauder, H.; Stadtmuller, S. *Acc. Chem. Res.* **1994**, 27, 70.

(20) (a) Bach, T.; Bermann, H.; Harms, K. *Angew. Chem. Int. Ed.* **2000**, *39*, 2302. (b) Bach, T.; Bergmann, H. *J. Am. Chem. Soc.* **2000**, *122*, 11525.

(21) (a) Cia, X.; Chang, V.; Chen, C.; Kim, H.-J.; Mariaono, P. S. *Tetrahedron Lett.* **2000**, *41*, 9445. (b) Chen, C.; Chang, V.; Cai, X.; Duesler, E.; Mariano, P. S. *J. Am. Chem. Soc.* **2001**, *123*, 6433.

(22) Furukawa, S. *Sci. Papers Inst. Phys. Chem. Rev. Tokyo* **1932**, *19*, 2.

(23) Braquet, P. *Drugs Future* **1987**, *12*, 643.

(24) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003.

(25) (a) Randall, M. L.; Lo, P. C.-K.; Bonitatebus, P. J.; Snapper, M. L., *J. Am. Chem. Soc.* **1999**, *121*, 4534. (b) Lo, P. C.-K.; Snapper, M. L.; *Org. Lett.* **2001**, *3*, 2819.

