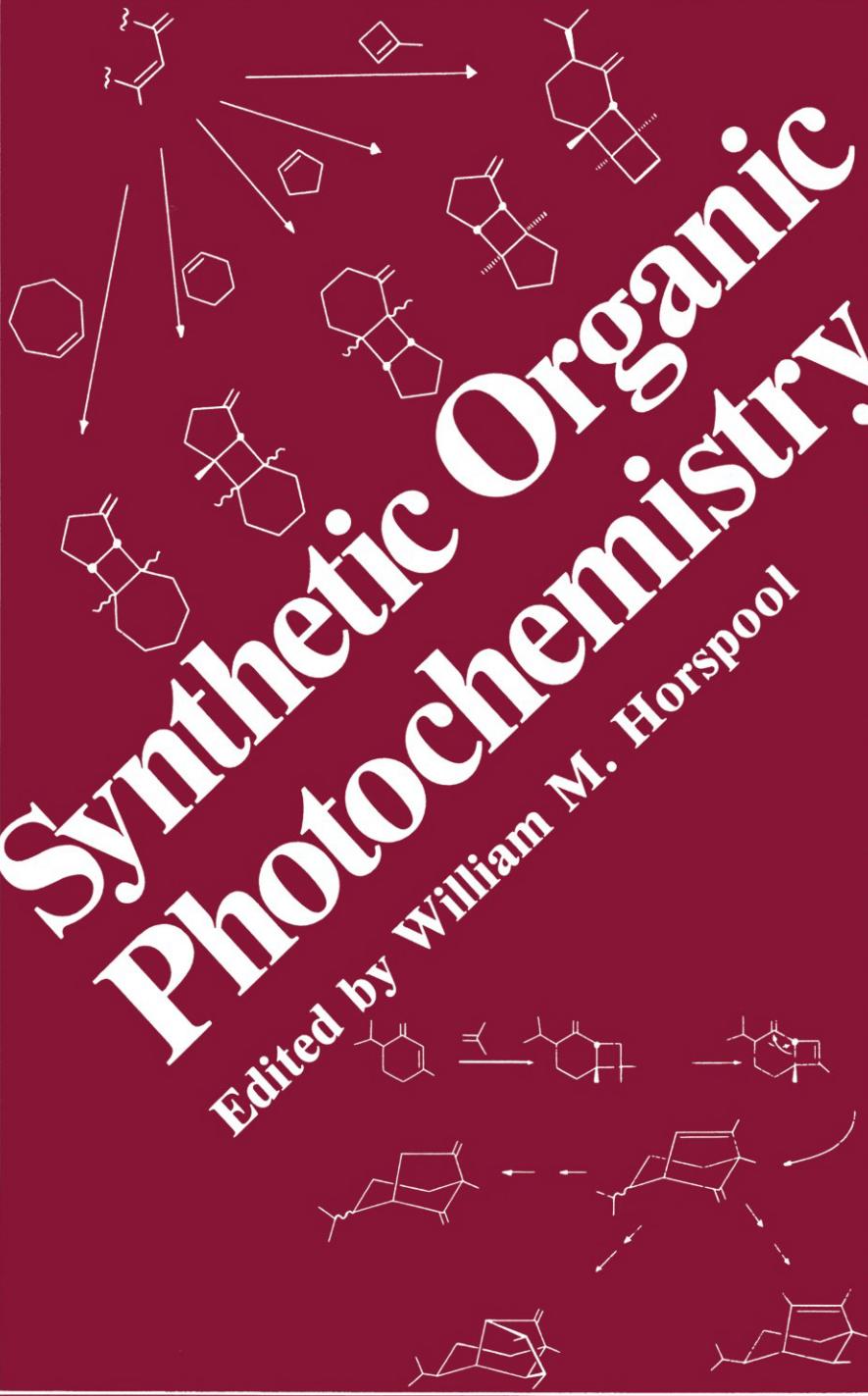


Synthetic Organic Photochemistry

Edited by William M. Horspool



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William M. Horspool

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To Una, Linda, and Andrew

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Foreword

Of all major branches of organic chemistry, I think none has undergone such a rapid, even explosive, development during the past twenty-five years as organic photochemistry. Prior to about 1960, photochemistry was still widely regarded as a branch of physical chemistry which might perhaps have occasional applications in the generation of free radicals. Strangely enough, this attitude to the subject had developed despite such early signs of promise as the photodimerization of anthracene first observed by Fritzsche in 1866, and some strikingly original pioneering work by Ciamician and Silber in the early years of this century. These latter workers first reported such varied photo-reactions as the photoisomerization of carvenone to carvone camphor, the photodimerization of stilbene, and the photoisomerization of *o*-nitrobenzaldehyde to *o*-nitrosobenzoic acid; yet organic chemists continued for another fifty years or so to rely almost wholly on thermal rather than photochemical methods of activation in organic synthesis—truly a dark age. When my colleagues and I first began in the 1950s to study the synthetic possibilities of photoexcitation in the chemistry of benzene and its derivatives, virtually all the prior reports had indicated that benzene was stable to ultraviolet radiation. Yet I think it fair to say that more different types of photoreactions than thermal reactions of the benzene ring are now known.

Comparable growth of knowledge has occurred in other branches of organic photochemistry, and photochemical techniques have in particular made possible or simplified the synthesis of numerous highly strained organic molecules.

Developments in organic photochemistry have been greatly stimulated by a growing understanding of the underlying mechanisms. In particular, the rules formulated by Woodward and Hoffmann have proved to have considerable predictive value despite the potentially complicating fact that most organic photoreactions are diabatic, i.e., the products are formed in their electronic ground states.

The development in Japan of a photochemical process for the manufac-

ture of caprolactam by photo-oximation of cyclohexane encouraged many workers to believe that further large-scale applications in organic synthesis lay just over the horizon. In fairness, it must be said that these expectations remain as yet unfulfilled, though there have been some useful applications within the pharmaceutical and insecticide industries. Although future larger scale developments remain a definite possibility, especially for those numerous photoreactions that proceed readily under the influence of solar radiation, the main future applications of synthetic photochemistry probably lie in the production of relatively small quantities of products having high intrinsic value, for example pharmaceutical intermediates. The situation could, however, be transformed by the introduction of improved radiation sources and, as noted above, use of the freely available quanta in solar radiation, especially in desert areas of the world unsuitable for agriculture. This latter approach was pioneered by Schönberg and Mustafa, but has not yet taken hold. For example, some twenty years ago a major chemical company seriously considered manufacturing the benzene/maleic anhydride photoadduct (a potentially valuable polymer intermediate which is also interesting in having biological activity as an analgesic) by a sensitized solar irradiation method in a desert area; but the idea seems to have been abandoned as involving a too unorthodox type of technology.

Despite the substantial failure of industry to capitalize on the exciting laboratory developments in organic photochemistry (often for good reasons, it must be said), the potential for successful exploitation is still undoubtedly very great. The worker in synthetic organic photochemistry soon finds himself or herself in a whole new world of chemistry where he must put aside most of his preconceptions about reactivity based upon the more conventional thermal chemistry, which still dominates most chemistry textbooks and teaching courses. I strongly support the objective of the present book to provide for synthetic chemists, both academic and applied, an up-to-date and broadly based account of the exciting opportunities available to those prepared to forsake the bunsen burner for the ultraviolet lamp, or even natural sunlight.

D. Bryce-Smith
Professor of Organic Chemistry

Preface

Organic photochemistry has in the last 30 years reached the full maturity of a scientific discipline. From its early beginnings the subject has continued to grow rapidly and hardly a month passes without the scientific literature announcing a novel photo-reaction or a new natural product synthesis using a photo-reaction as a key step. The steady development of the subject has seen its application to the synthesis of many compounds which could not have been synthesized by conventional routes and where often the photochemical path can be superior to existing ground-state steps. There is, however, a reluctance for the synthetic chemist to embrace the technique wholeheartedly regardless of the synthetic usefulness and the detailed understanding of many of the photochemical processes.

This textbook is aimed at the chemist who is looking for newer and superior methods. Sadly it is difficult to make a single volume totally comprehensive. However the contents have been selected with an eye for areas where there is currently active interest and where there is undoubtedly synthetic potential. The topics covered are aromatic compounds, enones, electron-transfer reactions, phthalimides, heterocycles, azirines, photo-protecting groups, oxetan formation, and a brief outline of equipment and techniques.

Where possible the authors have highlighted the synthetic value of the reactions under discussion. It is hoped, by this approach, that more investigators in academic life and, more importantly, in industry will be attracted to this exciting and worthwhile area.

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Photoaddition and Photocyclization Processes of Aromatic Compounds

Andrew Gilbert

1. Introduction

The present intensive interest in the photochemistry of aromatic systems has its origins in observations reported in the late 1950s that benzene, contrary to the widely held opinion of the time, was photolabile and would undergo both isomerization⁽¹⁾ and addition⁽²⁾ reactions when subjected to ultraviolet irradiation. From this time there has developed an awareness that the photochemical reactions of arenes have enormous potential both for the synthesis of novel compounds and the provision of convenient and versatile routes to systems, the thermal synthesis of which is, for one reason or another, troublesome. Photoisomerization reactions of arenes leading to benzvalenes, bicyclo[2.2.0]hexadienes, prismanes, and fulvenes have, for most systems, little synthetic application largely because of their low quantum and chemical yields of formation. This area of aromatic photochemistry has recently been reviewed,⁽³⁻⁵⁾ and the synthetic and mechanistic aspects of the photosubstitution reactions of arenes have been similarly treated.⁽⁶⁾

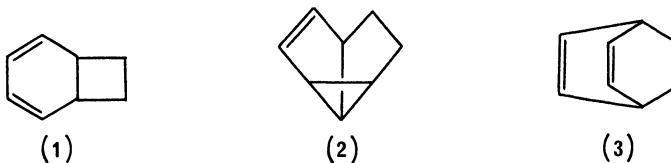
The published photochemistry of arenes involving addition and cyclization reactions is extensive. It is intended that the present review of such processes should illustrate the reaction types which may have potential as

synthetic procedures. Readers who require theoretical and mechanistic discussions of these intriguing processes, and a more exhaustive account of examples of the various reactions, should consult References 7–10. Reactions of photogenerated radicals with arenes are also not considered here.

2. Intermolecular Reactions

2.1 Arenes and Ethenes

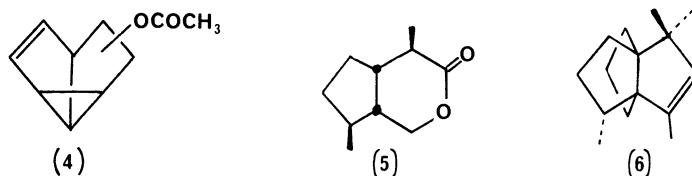
In principle ethenes may undergo *ortho*, *meta*, and *para* photocycloaddition to the benzene ring with the respective formation of **1**, **2**, and **3**. In



general, the *para* cycloaddition process is of relatively low efficiency and rarely constitutes more than a few percent of the total reaction pathway. The only exceptions to this statement are found in the photoaddition of benzene to 1,2-dienes,⁽¹¹⁾ the addition of S_1 naphthalene to dichlorovinylene carbonate, which yields the 1,2-(ortho) and 1,4-(para) cycloadducts in parallel processes via a common intermediate,⁽¹²⁾ and the additions of ethenes to the 9,10-positions of anthracenes.⁽¹³⁾

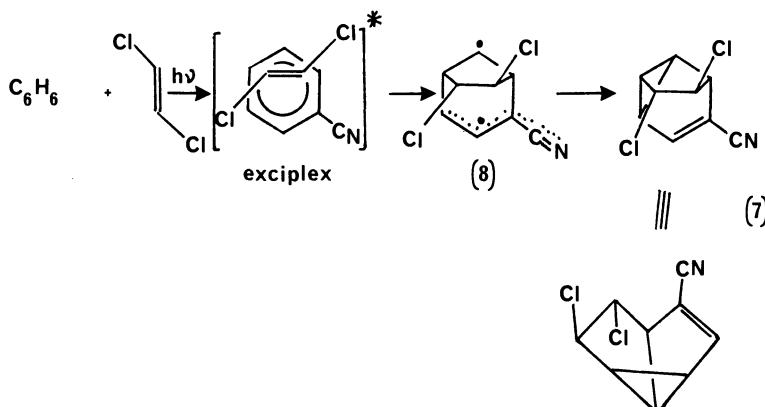
In contrast, both *ortho* and *meta* photocycloadditions of ethenes to the S_1 state of benzene and its simple derivatives can, dependent on the particular system, exhibit both high chemical and quantum yields. Occasionally both 1:1 adduct isomers are formed in approximately equal amounts, but in general the photoreaction shows selectivity and formation of one isomer is greatly favored. Synthetically relevant features of these reactions are that for all three modes of cycloaddition the ethene stereochemistry is preserved in the 1:1 adducts, the reactions proceed via the readily accessible S_1 manifold (254 nm) of the arene, and the *ortho* and *para* cycloadducts are more labile both thermally and photochemically than the *meta* isomers. This last aspect can be employed to allow the isolation of the *meta* products largely free from the structural isomers. However, for such reactions to have interest as synthetic procedures toward bicyclo[4.2.0]octa-2,4-dienes (**1**) and tricyclo[3.3.0.0^{2,8}]oct-2-enes (**2**), it is necessary to be able to predict the relative efficiencies of the two cycloaddition processes in particular cases. Thus the factors which affect such aspects of these reactions have been the subject of some discussions and investigations and, from an analysis of several systems, it has been proposed

that ethenes which have either strongly electron donor or acceptor properties favor the *ortho* process, whereas those which may be considered to be relatively "neutral" in this respect undergo *meta* cycloaddition to the arene.^(14,15) This proposal is supported by theoretical studies involving orbital symmetry correlation diagrams which show that although the *meta* cycloaddition is a concerted allowed reaction from the S_1 arene, the *ortho* process involves either the S_1 ethene or a charge transfer complex between the two addends.^(8,16) Subsequent study of numerous cases shows that for systems in which the ionization potential difference (Δ I.P.) between the addends is relatively large (electron donor and acceptor ethenes), the *ortho* cycloaddition is the favored or sole process, whereas in examples for which Δ I.P. tends to zero (simple alkenes) the *meta* reaction predominates.⁽⁹⁾ This general concept has good predictive capability but there are exceptions to the rigid application of ionization potentials of the ethenes to predict preferred modes of reaction.⁽¹⁷⁾ Nevertheless it has been established that within a series of structurally related ethenes as the Δ I.P. value increases so does the proportion of the *ortho* cycloadduct in the product mixture.^(9,18) Providing that the above features are considered, the *meta* photocycloaddition of ethenes to benzene can provide an excellent versatile one-step route to the synthesis of dihydrosemibullvalene systems **2**. The potential of such compounds as synthons for prostacyclin analogs and polycyclopentanoid terpenes has been noted,⁽¹⁹⁾ but they have been previously obtained by the oxa-di- π -methane rearrangement of bicyclo[2.2.2]octa-2-en-5-ones, and the present *meta* addition reaction has not been exploited in this context. Early reports of the *meta* process were largely concerned with the additions of hydrocarbon ethenes, but the reaction involving vinyl acetate allows functionalization of the skeleton **2** with the ready formation of the 1:1 adducts **4**.^(20,21) Formation of **4** and its conversion into tricyclo[3.3.0.0^{2,8}]oct-3-en-7-one are key steps in an elegant synthesis of \pm isoiridomyrmezin **5**,⁽²²⁾ and \pm modhephene **6** has been synthesized from the

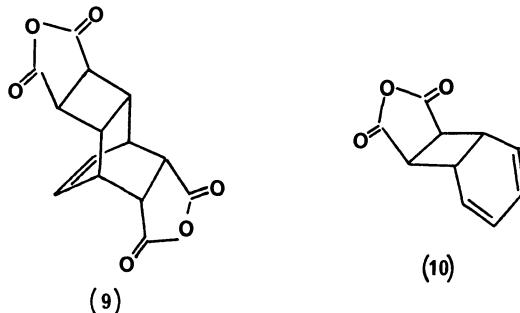


meta photocycloadduct of indane and vinyl acetate in six steps.⁽²³⁾ With alkyl and methoxy benzenes the position of the substituent in the *meta* cycloadduct is considered to be dictated by the orientation of the addends in the exciplex and by substituent radical stabilization in the addition intermediate.⁽²⁴⁾ These features lead to the formation of the 1-substituted isomer of **2** and such selectivity can be very useful in synthetic procedures. Substituent steric effects

and their ability to delocalize radical centers also appear to be important since the only *meta* cycloadduct from *trans* 1,2-dichloroethene and benzonitrile is **7** which is accounted for by the intermediacy of **8**.⁽²⁵⁾



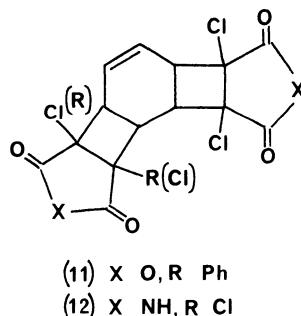
ortho Photocycloaddition of ethenes to arenes has been described for numerous systems and can offer an attractive route to bicyclo[4.2.0]octane derivatives. It was the first report⁽²⁾ of such a process in 1959 that initiated much of the research over the next twenty years into photoaddition reactions of aromatic systems. Thus it was observed that ultraviolet irradiation of solutions of maleic anhydride in benzene led to the novel 2:1 photoadduct **9**.^(2,26) The reaction was shown to be sensitized with compounds of triplet energy greater than approximately 275 kJ mol⁻¹⁽²⁷⁾ and to involve initial formation of the *exo,ortho* 1:1 cycloadduct **10** which is trapped by the second



addition of maleic anhydride in a thermal process.⁽²⁸⁾ The reaction has been extended to several alkyl benzenes, although for arenes other than toluene, photosensitization is essential.⁽²⁹⁾ The position of the arene substituent in the final product **9** is dependent upon light intensity and temperature of the

irradiation, factors which are considered to be a reflection of the photostabilities of, and rates of the second addition to, the 1:1 *ortho* adduct isomers, respectively.^(21,30) Since the 2:1 adducts crystallize from the irradiated solution, it is possible to obtain reasonable amounts of the photoproduct with good levels of purity, and with benzene, the reaction proceeds most satisfactorily in sunlight.⁽³¹⁾ The 2:1 adducts have excellent thermal stabilities, but their use as "monomers" in condensation polymerizations has apparently not been exploited. Not surprisingly maleimides yield similar 2:1 photoadducts with benzene and its derivatives, but in these systems, for successful reaction, it is essential that the maleimide does not have conjugative *N*-substituents.^(32,33) Use of bismaleimides in this reaction results in the formation of photoaddition polymers⁽³⁴⁾ and such exploitation has been reviewed.⁽³⁵⁾ In the case of the maleimide additions, the reaction proceeds by excitation of the addend, which may or may not be involved in ground-state complexation with the arene. On the other hand, a prerequisite for the additions of maleic anhydride is the formation with the arene of a ground-state complex having charge transfer absorption, as it is excitation within this band which is fruitful of reaction.^(8,36) The presence of such absorption, however, does not imply that the photo-reaction will necessarily occur.

Substitution of the ethenes of these dienophiles reduces the yields of photoadducts dramatically and in the case of dichloro maleic anhydride and maleimide, the final products **11** and **12** respectively, reflect two [2+2] cy-

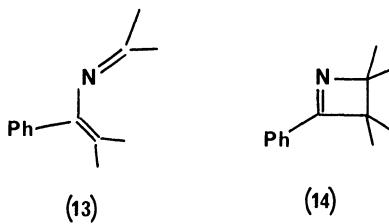


cloadditions rather than the consecutive *ortho* and *para* processes.⁽³⁷⁾ With the former dienophile, formation of phenylchloro-maleic anhydride precedes the addition process, but this apparently does not occur with the imide.

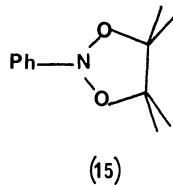
Consistent with the proposals concerning the electron donor-acceptor properties of the addends,⁽¹⁵⁾ *ortho* cycloadducts are the sole or major products from 254-nm irradiation of benzene with various simple dienophiles,^(9,21) 2,3-dimethylbut-2-ene,⁽¹⁴⁾ and enol ethers.⁽¹⁵⁾ For some systems the reaction is highly stereoselective yielding essentially either the *exo* or *endo* isomers, whereas in other cases a mixture of stereomers results.⁽⁹⁾ The *ortho* cycloadduct

of 1,1-dimethoxyethylene and benzene provides a convenient precursor for the synthesis of cyclo-octatrienone.⁽¹⁵⁾

Photoreactions of ethenes with substituted benzenes can yield complex mixtures of regio- and stereoisomers and this naturally limits the usefulness of such processes in synthetic pathways. However, in some cases regioselectivity of the addition can be achieved. Thus *ortho* cycloadditions of ethenes to anisole essentially involve the 1,2-positions for irradiations carried out in methanol solution, but this selectivity is markedly influenced by change in polarity of the solvent and in those of low polarity the products reflect 1,2-, 2,3-, and 3,4-addition of the ethene to the arene.^(21,38) The 1,2-cycloadducts of anisole with ethenes have some synthetic utility since they are readily converted in good yield with boron tribromide to benzocyclobutene derivatives.⁽³⁹⁾ The position of reaction of ethenes with benzonitrile depends markedly upon the former's electron donor properties. Ethenes having four alkyl substituents, two alkoxy, or two alkyl and one alkoxy, undergo photoaddition at the nitrile function leading to 2-azabutadienes **13** together with varying amounts of their azetine **14** precursor.⁽⁴⁰⁾ Other less electron-rich ethenes



undergo specific addition at the 1,2-positions of the phenyl ring. In contrast, irradiation of nitrobenzene and ethenes at room temperature gives a complex mixture of products, but at -70°C the unstable adduct **15** is formed.⁽⁴¹⁾

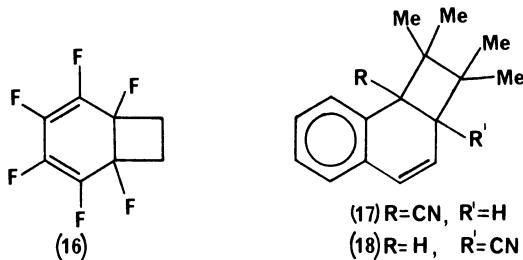


Hydrogenation of compounds of type **15** gives good yields of 1,2-diols and for example *cis* 1,2-dihydroxycyclohexane is formed from the cyclohexene addition product with less than 5% of the *trans* isomer.

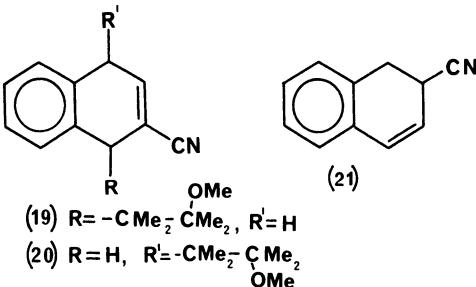
The formation of fluoro derivatives of **1** and **2** by the use of C_6F_6 as the arene in the above reactions is to some extent unpredictable and the success and selectivity of the reaction is very dependent upon the ethene. Thus although for several hydrocarbon ethenes the *ortho* cycloaddition to give **16** is the sole primary mode of reaction,⁽⁴²⁾ dienophilic ethylenes do not react and

cis cyclo-octene yields products which reflect both *ortho* and *meta* cycloaddition.⁽⁴³⁾

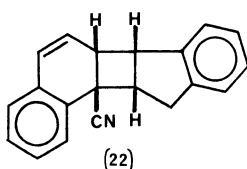
There is only one reported example of *meta* cycloaddition of an ethene to naphthalene,⁽⁴⁴⁾ but 1,2-additions to naphthalenes and in particular naphthonitriles is a general process and has been investigated with a variety of unsaturated systems.⁽⁷⁾ Such studies again emphasize the important effect of solvent on the course and selectivity of the addition process. Adducts **17** and **18** are the sole products from 2,3-dimethylbut-2-ene with 1- and 2-naphthon-



itriles, respectively, in hexane, benzene, and dimethoxyethane. In methanol solution, however, reduction products, for example, **19**, **20**, and **21** from the

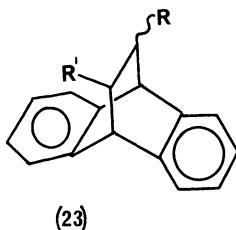


latter arene result.^(45,46) It is also important to note that the cyclobutane compounds are photolabile and undergo decomposition unless Pyrex apparatus is employed. Use of Corex filtered radiation along with high reactant conversions yields 2-azobutadienes and azetines (cf. **13** and **14**).⁽⁴⁷⁾ The exclusive formation of the *endo* head-to-head product **22** from 1-naphthonitrile

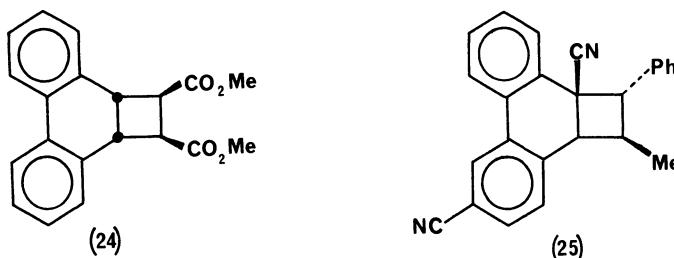


and indene in low-polarity solvents does, however, illustrate that for some systems this addition reaction can be regio- and stereo-specific, which renders the process most attractive as a synthetic procedure.⁽⁴⁸⁾

The thermal Diels–Alder reactions of anthracenes are well documented, but for weak dienophiles the process does require, on occasion, forcing conditions. To some extent, this inconvenience can be overcome by the corresponding photoprocess. Thus, for example, a range of dienophiles, styrenes, and 1,3-dienes have been shown to react, albeit nonstereospecifically, with electronically excited anthracene to give [4+2] adducts **23** with chemical and



quantum yields which are preparatively useful.⁽¹³⁾ It should, however, be noted that photodimerization of the anthracene (see Section 2.5) and in the case of the 1,3-diene [4+4] addition, do complete with the desired process. Phenanthrene and its derivatives also undergo photoreaction with dienophiles to yield compounds (e.g. **24**) of [2+2] addition to the arene 9,10-positions. Many of the studies of these systems have been concerned with mechanistic aspects and in particular the role of exciplexes in the process.⁽⁴⁸⁾ However, from the synthetic point of view, it is noteworthy that the addition of dichlorovinylene carbonate to phenanthrene is stereospecifically *exo*,⁽⁵⁰⁾ and that the product from the triplet manifold of 3,9-dicyanophenanthrene with *trans* 1-phenylpropene is the *exo* head-to-head isomer **25** whereas the reaction from the



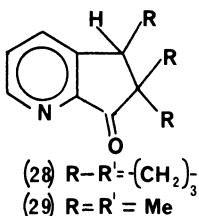
singlet state is nonspecific leading to head-to-head and head-to-tail products.⁽⁵¹⁾

Reports of photocycloaddition reactions of heteroaromatic compounds are few and far between, and in particular pyridine is a most unobliging

molecule photochemically. Ethene does, however, undergo photocycloaddition to the 3,4-positions of pentafluoropyridine to yield **26**, which at high addend pressures gives the 2:1 adduct **27**.⁵² Other ethenes undergo similar



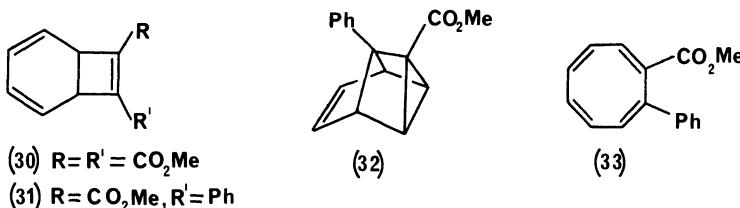
reaction but complex mixtures of 1:1 and 2:1 adducts can result and *cis* and *trans* but-2-enes, for example, give two 1:1 and six 2:1 ethylene:pentafluoropyridine adducts. 2-Cyanopyridine is reported to undergo photoreaction with cyclopentene and 2-methylbut-2-ene to yield, after work-up, the corresponding annelated ketones **28** and **29**⁽⁵³⁾ The process is, however, limited in scope for neither hex-1-ene nor vinyl acetate gives such products.



In view of the ease and convenience of ethene photoadditions to arenes, it is somewhat surprising that studies concerning the effects on polymer properties of polystyrenes by such reactions appear to be so limited. Photocycloadditions of maleic anhydride and maleimides do occur with the arene in such polymers,⁽⁵⁴⁾ and this may well be an area of more intensive synthetic study in the future.

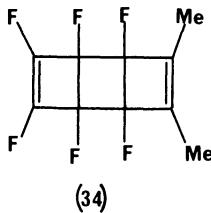
2.2. Arenes and Acetylenes

The *ortho* photocycloaddition of acetylenes to benzene was first reported in 1961⁽⁵⁵⁾ and has provided an important and convenient route to cyclo-octatetraenes.⁽⁵⁶⁾ For the majority of systems, it would appear that the first-formed product of the photoaddition, the 1:1 adduct **30**, is very labile and rapidly rearranges to the cyclo-octatetraene but in other systems the bicyclo[4.2.0]octatriene **30** has an appreciable lifetime and undergoes photocyclization competitive with ring-opening.⁽⁵⁷⁾ For example the adduct **31** from benzene and phenyl methyl propiolate yields the tricyclic compound **32** pho-



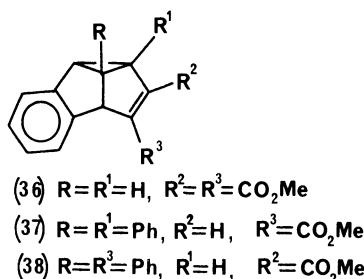
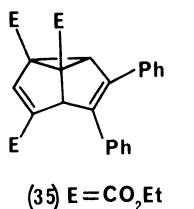
tochemically which in turn gives the cyclo-octatetraene **33** on thermolysis or in 92% yield using xanthone as the photosensitizer. It has been shown for the same system that, consistent with orbital symmetry considerations, it is the photoexcited acetylene which is responsible for the addition process.⁽⁵⁸⁾ This feature also probably accounts for the slow formation of the cyclo-octatetraenes from benzene and simple alkynes and must be taken into consideration when the process is intended for use in a synthetic pathway. Nevertheless, yields can make the reaction attractive, and even with cyclo-octyne, for example, it is observed that at 66% conversion the yield of the cyclo-octatetraene is 56%.

Formation of cyclo-octatetraenes from benzene by this method appears to be general for a number of acetylenes, but change of the arene leads in many cases to intractable mixtures⁽⁵⁹⁾; but for C_6F_6 the process is somewhat more predictable and simple alkynes⁽⁴³⁾ and phenyl acetylenes⁽⁶⁰⁾ yield both the cyclo-octatetraene and its bicyclic precursor, which in the case of the but-2-yne product gives both the cyclo-octatetraene and the intramolecular ring-closed isomer **34** on irradiation.⁽⁴³⁾ Again yields can be good and the phen-

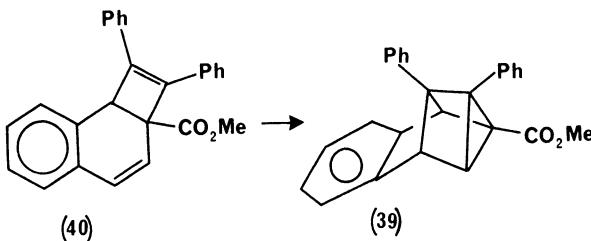


ylalkynes yield the polyfluoro bicyclic and monocyclic adducts in amounts of the order of 86%.⁽⁶⁰⁾

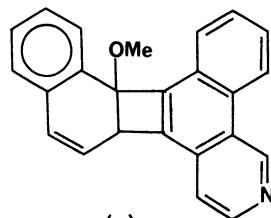
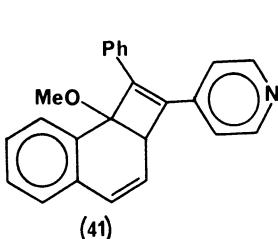
meta-Photocycloadditions of alkynes to benzenoid compounds would be an attractive route to the semibullvalene skeleton, but the only system in which this has been shown unambiguously to occur is that involving diphenyl acetylene and triethyl trimesate.⁽⁶¹⁾ Reaction times are long and yields of the adduct **35** even in an impure state are low. The 1,3-adduct **36** is reported to be present among the products from irradiation of naphthalene with dimethyl acetylene dicarboxylate,⁽⁶²⁾ but in general such additions to this arene involve the 1,2-positions. In confirmation of this it has been noted that the benzo-



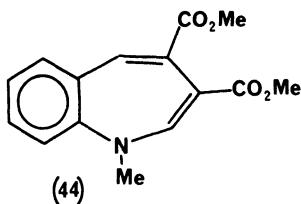
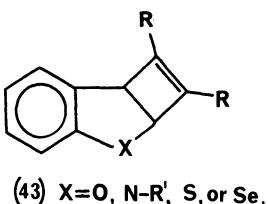
semibullvalenes **37** and **38** formed from methyl 2-naphthoate and diphenyl acetylene cannot result from 1,3- or 2,4-addition but rather are secondary photolysis products of **39**, which in turn results from the first-formed adduct **40**.⁽⁶³⁾ Such adducts as **39** and **40** are readily formed from a range of na-



phthalenes and diaryl acetylenes and the scope of this reaction has been well explored.⁽⁶⁴⁾ For the reaction involving some pyridyl acetylenes it is found that the secondary photolysis product of the primary 1:1 adduct (e.g., **41**) involves photo dehydrocyclization (Section 3.3.1) to give benzoquinoline derivatives (e.g., **42**). The mode of secondary reaction is clearly dependent upon the starting materials, and this makes the process versatile and potentially useful in synthesis.

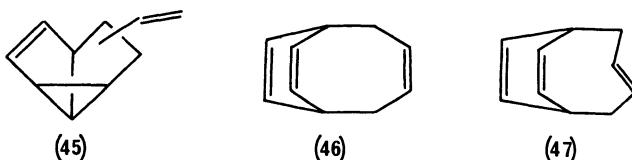


Acetylenes also yield [2+2] photocycloadducts **43** with benzo[b]furans, selenophenes, thiophens, and pyrroles, thiazoles, and isothiazoles.⁽⁶⁵⁾ However, as a result of unstable and rearranged products, the reaction mixtures can be complex, but **44** is formed in a 72% yield from dimethyl acetylene dicarboxylate and *N*-methylindole.⁽⁶⁶⁾

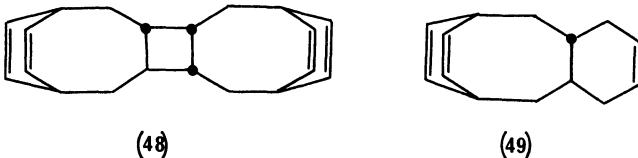


2.3. Arenes and 1,3-Dienes

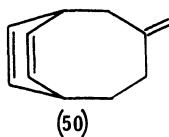
It should be recognized that, generally, the irradiation of arene-1,3-diene systems leads to a mixture of product types and frequently the yields are low.⁽⁶⁷⁾ Nevertheless the type of compound accessible by this one-step route would be difficult to obtain following even a multistep thermal pathway, and in particular cases, the photoprocess does display good selectivity or may be modified to do so. The potential complexity of the reaction mixture is typified by the products from the irradiation of benzene and buta-1,3-diene which comprise the *meta* 1,2- and *cis*- and *trans-para* 1,4-adducts **45**, **46**, and **47**, respectively, as well as the substitution product 1-phenylbut-2-ene.⁽⁶⁷⁾ Under



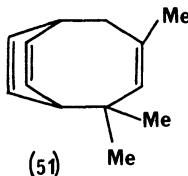
the experimental conditions, the *trans para* 1,4-adduct **47** undergoes both thermal dimerization and further reaction with the diene to give **48** and **49**,



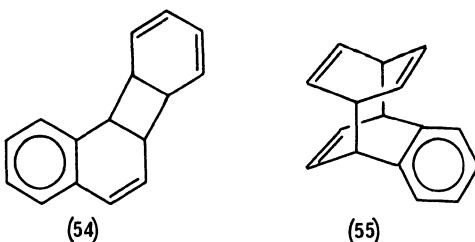
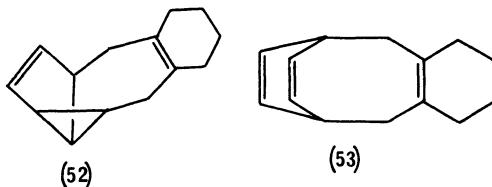
respectively. However, the presence of iodine dramatically affects the selectivity of the reaction. The very reactive *trans* adduct **47** is converted into the corresponding *cis* isomer **46** and this latter adduct is thus obtained in synthetically useful amounts and purity.⁽⁶⁸⁾ A similar effect of iodine is observed on the selectivity of the benzene-isoprene system,⁽⁶⁷⁾ which in the presence of the halogen produces only the rearranged *para* 1,4-adduct **50**⁽⁶⁹⁾: it is most surprising that these studies into the effects of halogens on the selectivity of the photoprocess do not appear to have been extended to other arene-diene systems.



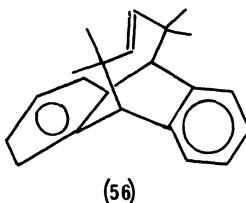
The ground-state conformation of the diene can also have a marked effect on the selectivity of the addition process. For example although irradiation of 2,3-dimethylbuta-1,3-diene and benzene yields three diene dimers, seven 1:1 adducts (none of > 10% of the reaction mixture), and polymeric material, *s-cisoid* 2,4-dimethylpenta-1,3-diene and benzene gives 37% of the *para* 1,4-adduct **51**,⁷⁰ and whereas yields of products from 3-methylenecyclohexene



with this arene are low and the mixture is comprised of adducts, diene dimers, and substitution products, irradiation of benzene with the conformationally fixed diene, 1,2-dimethylenecyclohexane, gives only the *meta* 1,4- and *para* 1,4-adducts **52** and **53** in a ratio dependent on reactant concentration.⁽⁷¹⁾ Similarly 1,2-dihydrophthalic anhydride undergoes *para* 1,4-photocycloaddition to both benzene and naphthalene, and the product from the latter has been converted into the benzene–naphthalene *ortho* *ortho* **54** and *para* *para* **55** cycloadducts which cannot be obtained directly.⁽⁷²⁾

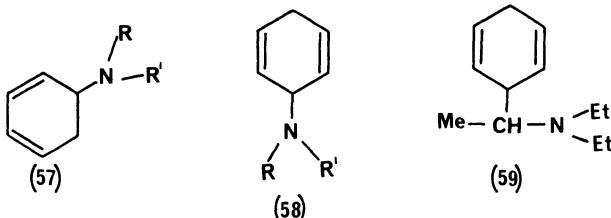


There have been several studies into the photoreactions of 1,3-dienes with polynuclear arenes, but again mixtures frequently result, which reduces the usefulness of such processes in synthesis.⁽⁷³⁾ There are, however, systems which do show selectivity in mode of reaction, and, for example, anthracene yields the [4 + 4] adduct **56** with 2,5-dimethylhexa-2,4-diene⁽⁷⁴⁾; and benz[a]anthracene, dibenz[a,h]anthracene, and dibenz[a,c]anthracene also give [4 + 4] adducts with cyclohexa-1,3-diene in respective yields of 69%, 82%, and 60%.⁽⁷⁵⁾

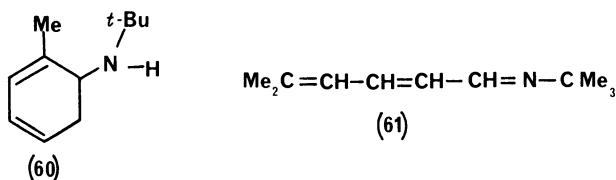


2.4. Acyclic Additions to Arenes and Reduction Processes

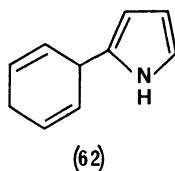
Light-induced electron transfer processes between arenes and amines have been the subject of many reports and several review articles in recent years,⁽⁷⁶⁾ and the resulting acyclic arene–amine photoaddition and arene photoreduction reactions have been described for many systems. By such processes benzene undergoes photoreaction with both primary and secondary aliphatic amines to give 1,2- and 1,4-acyclic adducts **57** and **58**, respectively, whereas tertiary aliphatic amines yield solely the 1,4-adduct **59**, which reflects arene attack at



the amine α -position.⁽⁷⁷⁾ In all cases the reduction products cyclohexa-1,4-diene and 1,4-1',4'-tetrahydrobiphenyl are formed in minor amounts. The reactions may be extended to alkyl benzenes but by-products can become significant in particular cases.⁽⁷⁸⁾ For example, the 1,2-acyclic adduct **60** of *t*-butylamine and toluene is thermally labile and during work-up undergoes ring opening to **61**. For methoxy, cyano, and halogeno benzenes, photonucleophilic substitution⁽⁶⁾ by the amines competes with varying degrees of

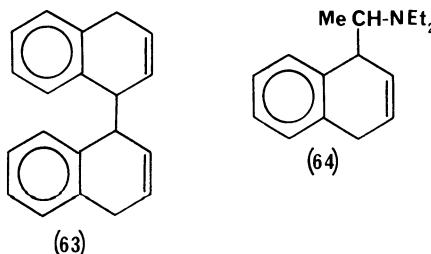


success with the acyclic addition process and generally complex mixtures result. Reaction of fluorobenzenes with amines yields *cine* substitution products which are accounted for by an addition-elimination mechanism, but again the complexity of the mixture discourages the consideration of such processes for synthetic purposes.⁽⁷⁹⁾ In contrast, the photoaddition of benzene to pyrrole is relatively efficient and reaction selectivity is good as the adduct **62** constitutes approximately 85% of the volatile products.⁽⁸⁰⁾ The photoadd-



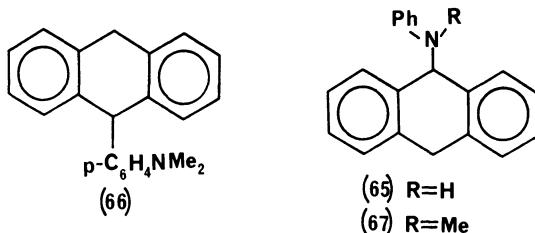
dition of both pyrrole and *tert* amines is markedly accelerated in the presence of methanol, and for the addition of *N*-methylpyrrole to benzene a proton source is essential.

The corresponding process with naphthalene as arene has been studied principally from the photoreduction aspect. The medium involves aqueous acetonitrile when both Birch and non-Birch reduction products are favored, although varying amounts of acyclic amine-arene adducts are also formed.⁽⁸¹⁾ Again the reaction selectivity can be very dependent upon the particular arene. For example, naphthalene and triethylamine yield 1,4-dihydronaphthalene, tetralin, the dihydro dimer **63**, as well as the 1:1 adduct **64** whereas

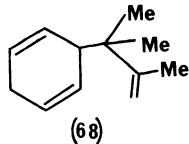


α -fluoronaphthalene gives 5-fluoro-1,4-dihydronaphthalene selectively and an unidentified basic product. Anthracene-amine systems have been investigated

under a variety of conditions by several groups of workers.⁽⁷⁾ Nonpolar solvents favor the formation of **65** from anthracene and aniline,⁽⁸²⁾ but the reaction with *N,N*-dimethyl aniline and this arene is dependent on reactant concentrations and solvent.⁽⁸³⁾ Thus whereas the 1:1 adduct **66**, 9,10-dihydroanthracene, and the 9,10-dihydroanthracene dimer are formed in acetonitrile, increase of reactant concentration and use of benzene as the solvent result in the formation of the dihydro dimer and **67**. The loss of the methyl group required in the formation of **67** was detected as formaldehyde.



It is relevant here to note that as well as yielding the cycloadducts described in Section 2.1, 1,1-dimethyl ethenes also undergo acyclic photoaddition to arenes to give "ene" products such as **68** from benzene and 2,3-

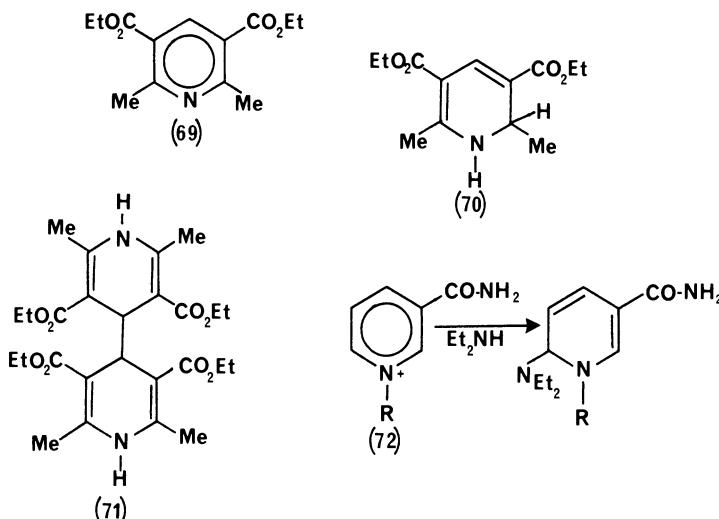


dimethylbut-2-ene.⁽¹⁴⁾ This acyclic photoaddition is promoted by proton donor solvents and this type of reaction increases in relative significance with increase in electron donor properties of the ethene.

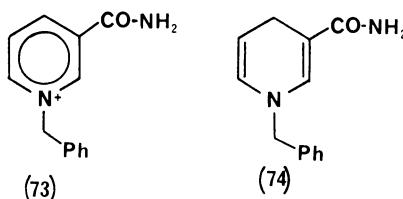
Photoreduction of arenes by sodium borohydride appears to be a general process, but yields and selectivities can be very variable. Phenols give poor yields of reduction products,⁽⁸⁴⁾ and benzene carboxylic esters yield complex mixtures,⁽⁸¹⁾ but naphthalenes,^(81,85) phenanthrene,⁽⁸⁵⁾ and anthracene⁽⁸⁵⁾ are efficiently photoreduced by sodium borohydride in the presence of 1,4-dicyanobenzene. Yields, based on unrecovered hydrocarbons, of the Birch products from the above polynuclear arenes are 30%, 70%, and 71%, respectively, in 10% aqueous acetonitrile. Use of deuterium oxide in these reactions generally produces the mono-deutero derivatives of the reduction products, which demonstrates the involvement of one proton from the water in the reduction sequence.

Acyclic addition-reduction of nitrogen heteroaromatic compounds has

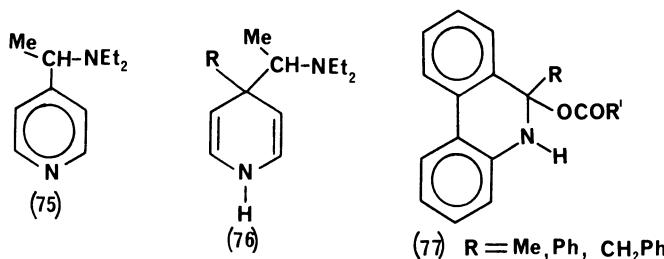
been achieved photochemically in certain systems. The following examples are illustrative of the types of compounds which have been examined and the reaction conditions employed. Other examples are described in References 7 and 86. Irradiation of the pyridine **69** in aqueous acetonitrile in the presence of diethylamine leads to the formation of the 1,2 reduction product **70** and the coupled 1,4 compound **71** in 13% and 19% yields, respectively.⁽⁸⁷⁾ Some pyridinium salts (e.g., **72**) undergo reductive amination in the dark, but



reduction of such compounds can be achieved photochemically by ascorbic acid in the presence of ammonia when for example the 1,4-dihydro product **74** is formed from **73**.⁽⁸⁸⁾ Dihydropyridines are frequently postulated as in-



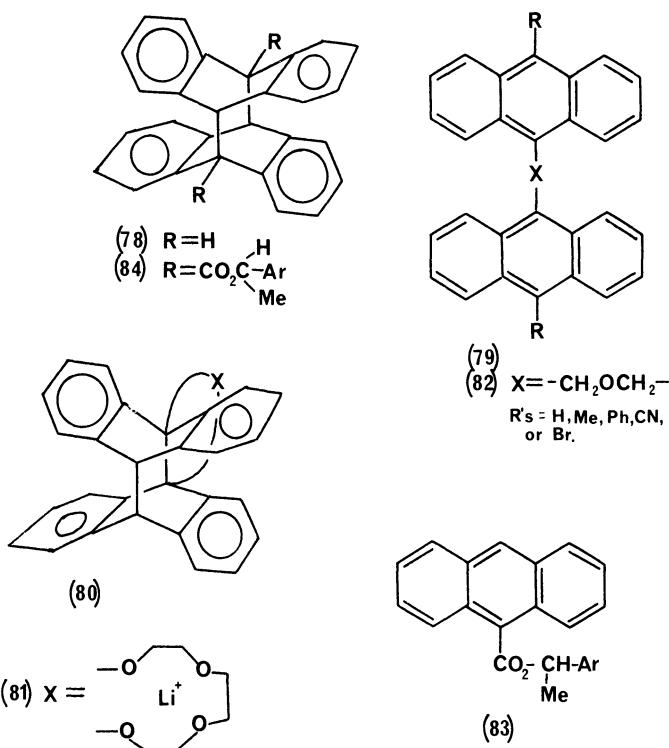
termediates in photosubstitution reactions of the heteroarene,⁽⁸⁶⁾ and a typical example of this involves the irradiation of 4-cyano- and 4-chloro-pyridines in the presence of triethylamine: thus **75** is formed via elimination of HCN and HCl, respectively, from the reductive amination addition product **76**.⁽⁸⁹⁾ Synthetically useful yields of 9,10-dihydrophenanthridines **77** are obtained by the photoaddition of carboxylic acids to the corresponding heteroarene.⁽⁹⁰⁾



2.5. Arene Photodimerizations

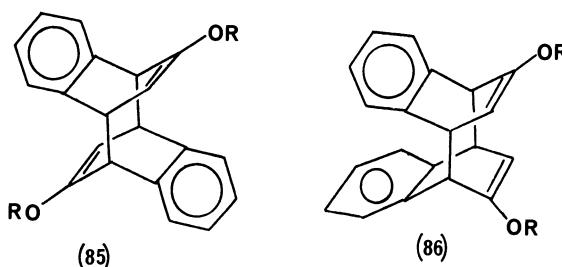
One of the earliest reports concerning a photochemical reaction involved the description of the photodimerization of anthracene in solution. The reaction has since been demonstrated to occur with a variety of derivatives of the arene, and the product **78** is frequently formed in good yield and purity. The photodimerization also occurs on irradiation of crystals of the monomer and is subject to topochemical control.⁽⁹¹⁾ Factors which affect the process, its scope, and limitations and utility have recently been reviewed and the photoreactions of linked 9,9'-bianthryls **79** have been subjected to similar treatment.^(92,93) The reactions of **79**, as with all nonconjugated bichromophoric molecules, are dependent upon the nature and length of the intervening chain. Intermolecular photoreaction in such a system as **79** can lead to addition polymerization whereas the intramolecular process yields **80**.⁽⁹²⁾ Such intramolecular photodimerization of linked anthracenes has been adapted for a synthesis of crown ethers.⁽⁹³⁾ Thus although irradiation of the compound 9-anthryl-X-CH₂-(CH₂-X-CH₂)₂-CH₂-X-9 anthryl for X = CH₂ produces essentially no chemical change, when X = oxygen, an intramolecular dimer results which has a half life of 3 min at room temperature. Irradiation of this latter system in the presence of lithium ions, however, produces the “cation-locked” isomer **81**, which is stable up to 206–210°C. Such “photocrowns” have been synthesized with four to seven oxygen atoms. Unlocking of **81** does not occur on heating but is readily accomplished by shaking the photoproducts in polar solvents such as acetonitrile.⁽⁹³⁾

Since anthracene dimers are well known to undergo retroaddition with short-wavelength (254-nm) radiation, the present reactions of these nonconjugated bichromophores clearly provide a basis for photochromic systems. This aspect of the photochemistry of bianthryls has been studied in some detail with a series of di(9-anthrylmethyl) ethers **82**.⁽⁹⁴⁾ The reactions were studied in fluid solution and both the forward (366-nm) and back (254-nm) reactions have good quantum efficiencies: interestingly the reactions were found to be more efficient in acetonitrile than in methylcyclohexane.



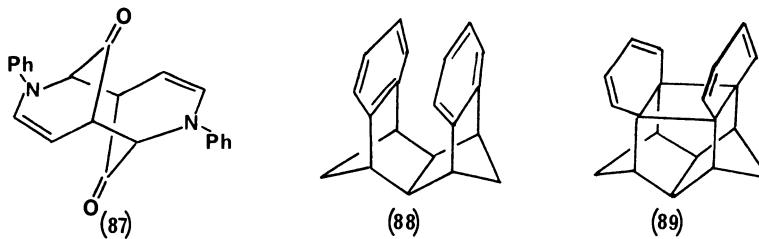
Methods for enantiomeric purification have obvious importance in many areas of pure and applied chemistry and the present photoprocess has been adapted for such a use.⁽⁹⁵⁾ The basic principle is as follows. The photodimerizable anthracene molecule is reacted with an enantiomerically enriched sample of an alcohol, amine, etc. The arene derivative now having the chiral group can crystallize in either the photodimerizable α -form or in the photostable γ form. The bulky chiral group effectively prevents crystallization in the β form which requires short intermolecular distances. Irradiation of the crystalline mixture gives the *meso* photodimer from the α form whereas the γ form is unaffected and readily separated from the mixture. Such procedures have been applied to the enantiomeric separation of 1-arylethanols which were irradiated as the 9-anthroates 83. The light-stable monomer was solvent extracted from the sparingly soluble dianthracenes 84, which revert to monomers at their melting points. Interest in a wider application of this method will doubtless be fostered by the chemical yields in excess of 80% and enantiomeric purities exceeding 90%.

Photodimerization of naphthalenes is largely restricted to β -substituted derivatives, particularly those bearing alkoxy groups. The reaction involves

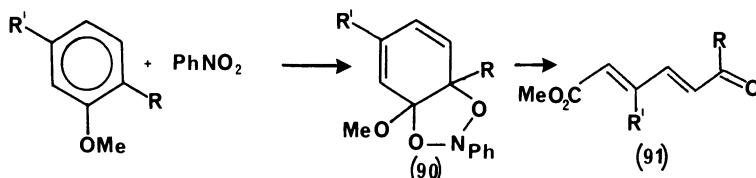


the 1,4-1'4'-positions and yields the ring systems **85** and/or **86**.⁽⁹⁶⁾ In general head-to-tail dimers predominate, a feature which reflects charge distribution in the ground state assuming that pairwise association occurs before excitation. Intramolecular photodimerization also occurs in the naphthalene series, and for example di(1-naphthylmethyl) ether yields both *exo* and *endo* [4+4] dimers.⁽⁹⁷⁾

Photodimerization of uncondensed benzene rings is an extremely rare process and has only been reported for one or two specialized cases. Thus 3-oxido-1-phenyl-pyridinium yields **87**,⁽⁹⁸⁾ and the bichromophore **88** undergoes [2+2] photocycloaddition to give **89**.⁽⁹⁹⁾ Irradiation of arene pairs substituted

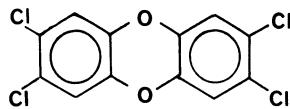


with electron donor-acceptor groups does not lead to addition products, although in some cases substitution processes are observed. However, selective addition of photoexcited nitroarenes to aromatic methoxy compounds does occur but results in ring-cleavage of the latter arene.⁽¹⁰⁰⁾ The first-formed product **90** is very labile and readily undergoes fission to give the diene **91**.



and the aryl nitrene, which dimerizes. It would appear that the reaction has not as yet been intensively studied, and while presently reported yields are

not good, the potential of the reaction for the synthesis of variously substituted dienes makes the process attractive and worthy of further study. Dioxin **92**



(92)

is a particularly obnoxious compound which has great stability and is extremely difficult to destroy and on occasion has been inadvertently released into the environment. It is interesting to consider whether this seemingly general and facile photocleavage reaction of aromatic ethers could be utilized for the decomposition (in sunlight?) of such pollutants as **92** to more readily degradable compounds.

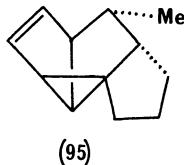
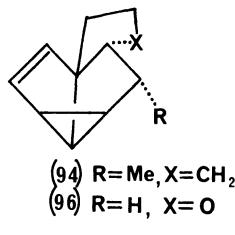
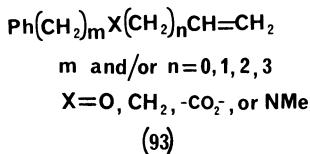
3. Intramolecular Cyclization Processes

3.1. Arene–Ethene and Arene–Ethyne Systems

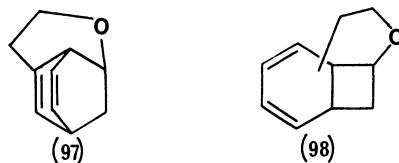
There is a considerable volume of literature which describes the photochemical reactions of compounds based on $\text{Ar}-\text{X}-\text{CH}=\text{CHR}$: by comparison very little is reported on the corresponding acetylenes. This section illustrates by selected examples the types of compounds which have been studied and the potential of the photoreactions as synthetic procedures. The photochemical reactions of aryl-ethenes have been the subject of two recent reviews, and although the content is largely restricted to hydrocarbon systems, general mechanistic aspects of the processes which are applicable to a variety of molecules are fully considered.⁽¹⁰¹⁾

3.1.1. Hydrocarbon Systems

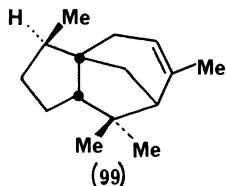
For phenyl–ethenyl nonconjugated bichromophoric systems **93** the photochemical reactivity is very dependent upon the length and nature of the flexible chain intervening between the chromophores. It has been observed for a variety of systems that interaction between the chromophores is maximized for three intervening units, although in some cases, for compounds with a greater number of units, interaction and reaction has been observed.⁽⁹²⁾ Irradiation (254 nm) of compounds which have three methylene units between the phenyl and ethenyl chromophores results in intramolecular *meta* cycloaddition. For example *cis* 6-phenylhex-2-ene yields the adducts **94** and **95** with



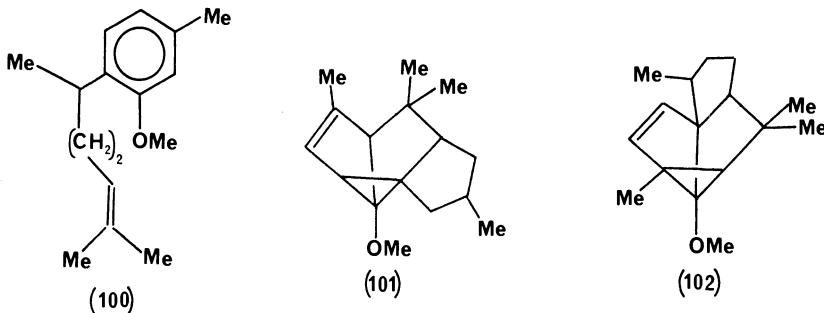
a total quantum yield of 0.26,⁽¹⁰²⁾ and whereas 5-phenylpent-1-ene behaves similarly, 6-phenylhex-1-ene cyclizes very inefficiently.^(9,103) Further, 2-phenethyl vinyl ether gives a 1:15 ratio of the *meta* and *para* intramolecular cycloadducts **96** and **97**, respectively, instead of the *ortho* product **98**, which



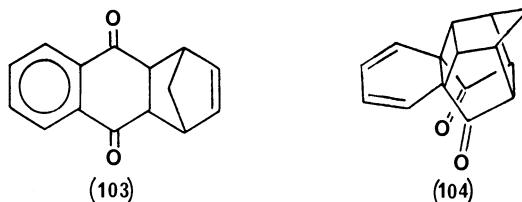
was expected from consideration of the corresponding intermolecular reaction.⁽¹⁰³⁾ From a study of space filling molecular models it is considered that the positions of intramolecular reaction and the reactivities observed with phenyl-ethenyl systems can be understood in terms of orientations of the chromophores dictated by preferred conformations of the intervening chains. The intramolecular *meta* photocycloaddition is a convenient process for the synthesis of a variety of polycyclic systems, particularly when it is appreciated that the positions of attack of the ethene onto the arene may be predictable from preferred ground-state conformations of the starting material and that the resulting adducts may be reactive and lead to compounds unavailable by more conventional routes. This synthetic potential has been recognized⁽¹⁰⁴⁾ and is well illustrated by formation of (\pm)- α -cedrene **99** from the phenyl



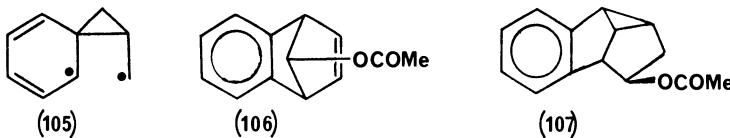
ethenyl bichromophoric system **100** using the latter's photoconversion to **101** and **102** as the key step. The conversion of **101** and **102** to the isomerically pure **99** is accomplished in two further steps.



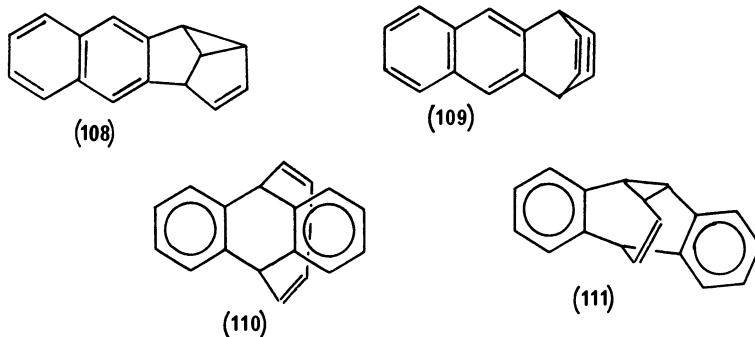
For compounds in which the orientation of the two chromophores is held by the molecular geometry, then, not surprisingly, this relative disposition in the ground state is reflected in the photoproduct and yields can be high. Thus the Diels–Alder adduct **103** of cyclopentadiene and 1,4-naphthoquinone is reported to be converted into the “caged” compound **104** in 94% yield⁽¹⁰⁵⁾. clearly the scope of such photorearrangements is very wide.



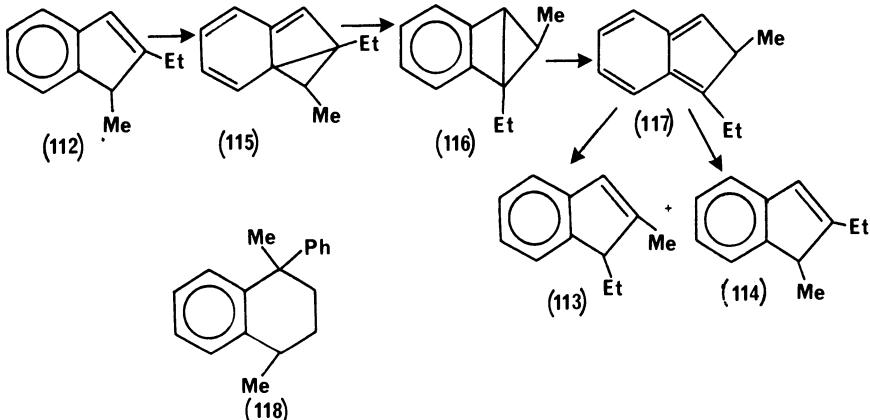
Photoaddition reactions of aromatic systems, in general, arise from the excited singlet state and hence intersystem crossing in the arene would appear to have little value to the synthetic photochemist except possibly to promote the formation of the T_1 ethene and hence induce $cis \rightleftharpoons trans$ interconversions. For bichromophoric systems intramolecular energy transfer has been noted and the ethene isomerization observed,⁽¹⁰¹⁾ but, in principle, any of the reactions typical of triplet excited ethenes may be expected.⁽¹⁰⁶⁾ More particularly, for allyl benzenes, as well as the T_1 ethene initiated reaction, the singlet and triplet states of the arene may undergo bond formation to the ethene to yield the biradical **105** and hence the di- π -methane rearrangement is initiated from the excited arene. Examples of this process resulting from the excited arene or ethene are numerous and include the stereospecific conversion of the benz-norbornadiene **106** to **107** in 85% yield,⁽¹⁰⁷⁾ the formation of naphthosemi-



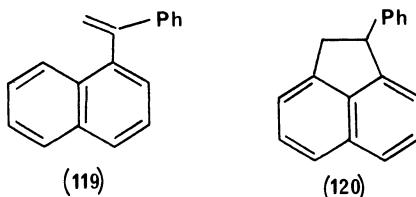
bullvalene **108** from naphthobarrelene **109** with 313 nm radiation or benzophenone sensitization,⁽¹⁰⁸⁾ and the rearrangement of **110** to **111** in 84% yield.⁽¹⁰⁹⁾



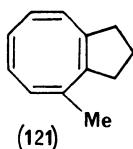
[2+2] Intramolecular bonding between the arene and ethene is the key step in the photorearrangement of indenes. For example the indene **112** is converted to the isomers **113** and **114** via the intermediates **115**, **116**, and **117**.⁽¹¹⁰⁾ Photodimerization-addition of styrenes to tetralin derivatives (e.g., **118**) has been observed, and interestingly the process has been shown to be accelerated by electron transfer agents such as pyromellitic dianhydride and Fe^{3+} and Mn^{2+} complexes with 2,2'-bipyridyl or 9,10-phenanthroline.⁽¹¹¹⁾



Other pathways are open to naphthyl derivatives and **119** yields the acenaphthene **120**: noteworthy in this reaction is the fortyfold enhancement in the yield of **120** when amines are present, but it is clear that the amine acts not to induce but to enhance the process.⁽¹¹²⁾

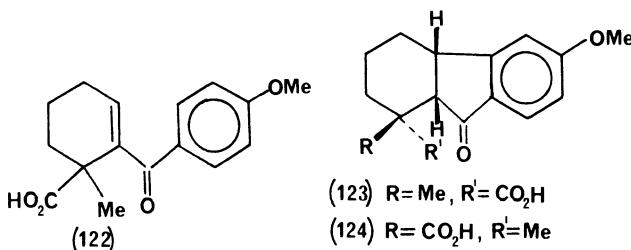


Since irradiation of ethyne–arene systems yields cyclooctatetraene derivatives (Section 2.2), the intramolecular nonconjugated analogs offer an attractive route into, for example, bicyclo[6.3.0]undecane derivatives. However, only one such example has been reported and involves the formation of **121** from 6-phenylhex-2-yne,⁽¹¹³⁾ thus the synthetic potential of this process remains unexplored.



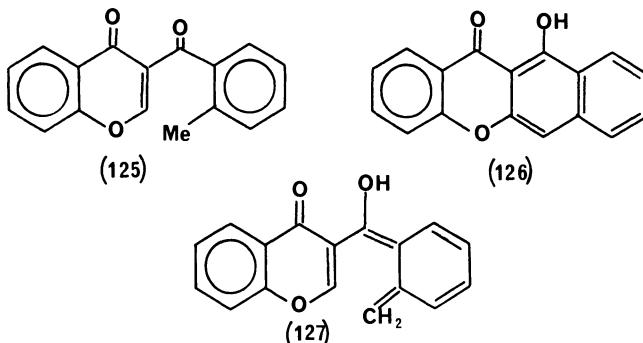
3.1.2. Aryl Enones

The first photocyclization of aryl enones such as **122** was reported in 1970.⁽¹¹⁴⁾ It was considered that the geminal disubstitution in **122** would inhibit dimerization and favorably orient the ring to cyclization. This appears to be the case, for the yield of the two epimers **122** and **124** is described as being nearly quantitative.

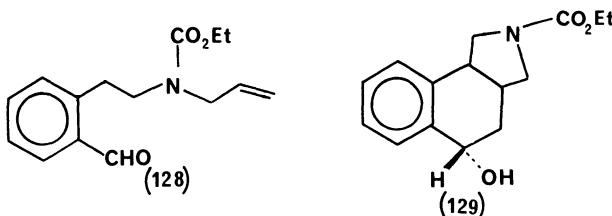


Cyclizations resulting from photoenolization are beyond the scope of the present treatment,⁽¹¹⁵⁾ but it is pertinent here to point out the synthetic pos-

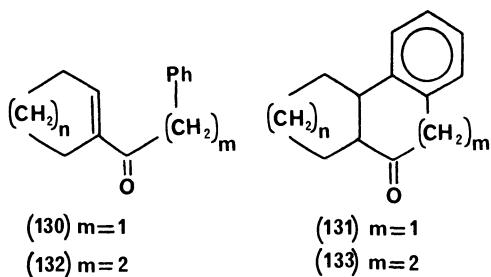
sibilities of the intramolecular process. Thus ethene cyclized compounds can be formed from aroylchromones following prior intramolecular hydrogen abstraction. The photocyclization is found to be very dependent on substituents present, and whereas 3-benzoyl-2-methylchromone is stable, its isomer 3-(*o*-toluoyl)chromone **125** readily yields benzoxanthene **126** via the enol **127**.

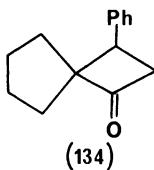


The general process of cyclization resulting from photoenolization is potentially useful and versatile and irradiation of the nonconjugated aryl-ethene **128** results in the formation of the *exo* and *endo* isomers of the intramolecular addition product **129**.⁽¹¹⁷⁾



Photocyclization of 3-benzyl-1-cycloalkenyl ketones **130** to yield **131** occurs only in the presence of boron trifluoride.⁽¹¹⁸⁾ For 1-cycloalkenyl phenethyl ketones **132** the reaction is very dependent upon the size of the cy-

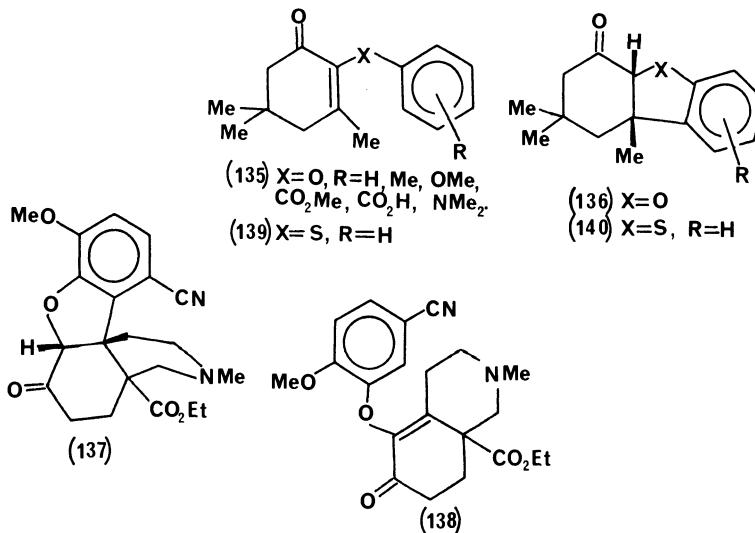




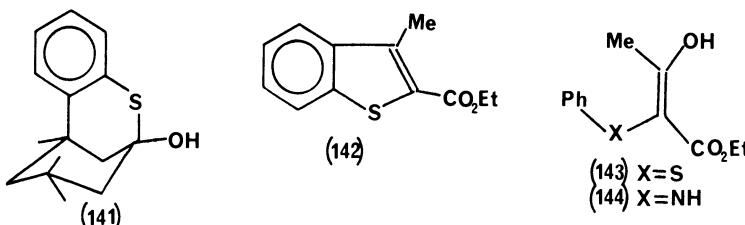
cloalkenyl ring, and whereas the cyclohexene derivative gives the cyclized compound **133** in the presence of the Lewis acid, methanol, or trifluoroacetic acid, the cyclopentene system, both in the absence and presence of the acid catalyst, forms the spiro compound **134**.⁽¹¹⁹⁾ Yields in the presence of the acid catalyst from the latter system are, however, low.

3.1.3. Aryl Ethenyl Ethers, Thioethers, and N-Aryl Enamines

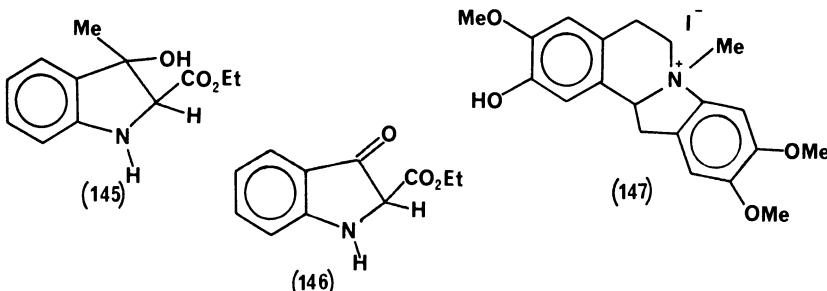
For several years there has been interest in the synthetic possibilities offered by the photoconversion of the above classes of compound into benzofurans, benzothiophens, and indoles. Both simple and complex examples of this seemingly general process have been reported and the scope of the reaction for particular systems has been explored. Thus irradiation of **135** in benzene:methanol:acetic acid (1:1:1) gives the cyclized products **136** in high yield (some quantitative) in which only the *cis* decalone ring fusion is observed.⁽¹²⁰⁾ This type of cyclization has been used in the synthesis of the tetracyclic morphine structural analog **137**.⁽¹²¹⁾ In this case, irradiation of the aryloxenone **138** in deaerated benzene produces the *trans* fused dihydrofuran, which in methanol saturated with sodium carbonate yields **137**. Thioanalogs



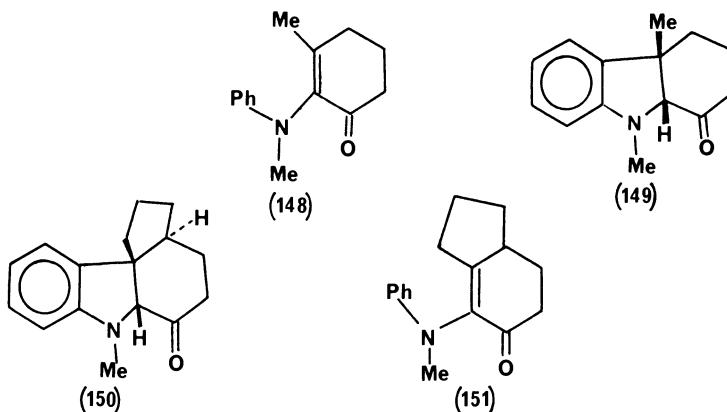
of **135** have also been studied in this cyclization reaction and again the process proved to be general with both high chemical and quantum efficiencies with a wide range of functional groups within the molecular system.⁽¹²²⁾ For example, irradiation of **139** in 3:1 benzene:methanol produces **140** in 91% yield. Compounds of type **140** are desulfurized with Raney nickel to give 3-aryl-cyclohexanones and treatment of **140** with zinc and acetic acid causes ring cleavage and the formation of *ortho*-substituted benzenethiols isolated in the hemithioketal form **141**. The process also occurs with naphthyl, 2-quinolyl, 3-indoyl, and 2-benzthiazolyl compounds,⁽¹²²⁾ and has been reported to yield the benzthiophen **142** in 66% yield from the thio ether **143**.⁽¹²³⁾



Anilino enols **144** derived from ethyl acetoacetate (i.e., nitrogen analogs of **143**) undergo photochemical cyclization and provide a route to indoles.^(124,125) The photoreaction is considered to be a realistic alternative to the traditional Bischler indole synthesis and has the versatility that in the absence of acid, the intermediate 3-hydroxydihydroindole **145** can be isolated prior to its dehydration, and treatment of **145** with lead tetra-acetate provides a high yield route to oxindoles **146**. The *N*-arylenamine cyclization has been applied to natural product syntheses and is the key step in the formation of (\pm)cryptostolone **147**⁽¹²⁶⁾: the scope of the process is at present somewhat



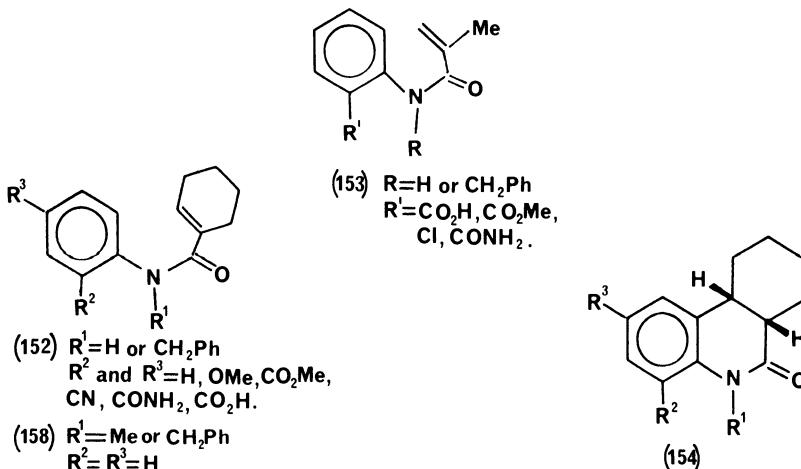
restricted by low yields. Such, however, is seemingly not the case with *N*-arylenamine ketones for the conversion of **148** to *cis* **149** occurs in 90% with 7% of the corresponding *trans* isomer and **150** is formed in 71% yield from **151**.⁽¹²⁷⁾ Readers concerned with mechanistic aspects of these cyclization reactions should consult Reference 128 and those cited therein.



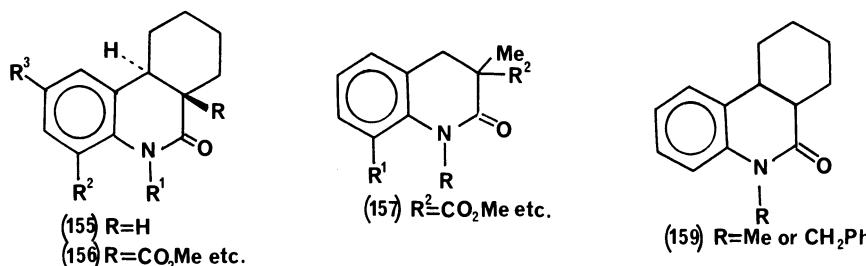
3.1.4. Cyclizations of *N*-Arylanilides and *N*-Benzoylenamines

In recent years there has been intense and widespread interest in the use of the photocyclization of the above two classes of compound for the synthesis of natural products which involve a variety of condensed ring systems.⁽⁷⁾ The process is extremely versatile as the ethene may be cyclic or acyclic and the arene phenyl, naphthyl, pyridyl, or their derivatives. Doubtless it is this feature and the generally good yields of the process which has persuaded synthetic chemists to look on these cyclizations with more than academic interest. The synthetic aspects of the photochemistry of enamides has been reviewed.⁽¹²⁹⁾

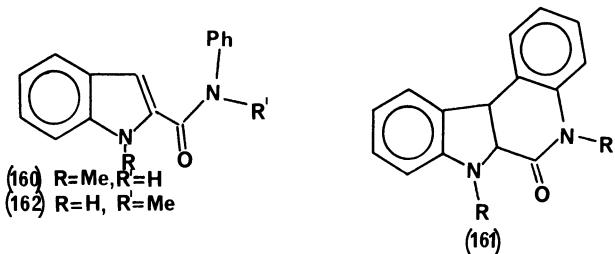
The scope of the process with acrylanilide is well illustrated by the successful photocyclization of numerous derivatives of the cyclic and acyclic systems **152** and **153**, respectively.⁽¹³⁰⁾ The former give a mixture of the *cis* and *trans* fused phenanthridinones **154** and **155**, but depending on the solvent



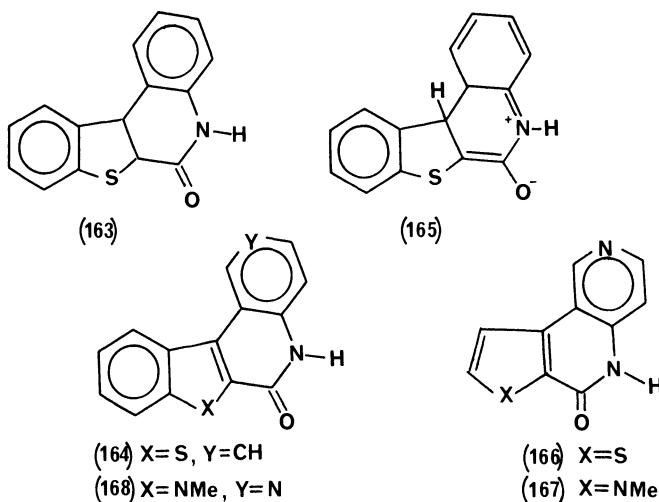
154 may be formed in up to 80% and **155** in up to 70% yields. Irradiation of **152** and **153** derivatives which have an *ortho* electron withdrawing substituent (CO_2Me , COMe , CN , CONH_2) results in a 1,5-migration of the group and the formation of the *trans* lactams **156** from **152** and dihydroquinolones **157** from **153**: decarboxylation occurs if the *ortho* group is CO_2H . The stereochemistry of the cyclization process can be markedly affected by the nature of the solvent. Thus irradiation of **158** in protic solvents favors formation of the *cis* isomer of the product **159** whereas in the presence of an aprotic solvent



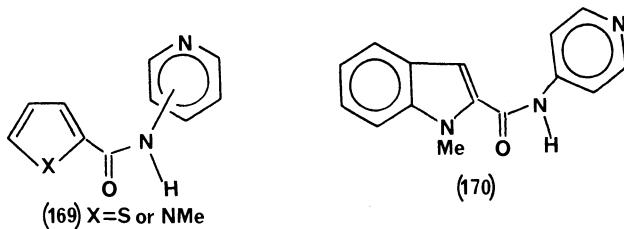
the cyclization yields the *trans* isomer.⁽¹³¹⁾ These results are considered to reflect a concerted hydrogen shift in the latter case, but for protic solvents the shift is suggested to be stepwise and involve a protonation–deprotonation sequence. This type of cyclization also occurs with the “ethene” in indoles and benzothiophenes, but the stereochemistry and selectivity of the process in the former case is seemingly remarkably influenced by the substitution on the nitrogen of the amide function.⁽¹³²⁾ For example, irradiation of **160** is reported to yield mainly the *cis* isomer of the product **161** whereas the *trans* isomer results exclusively from the *N*-methyl compound **162**.



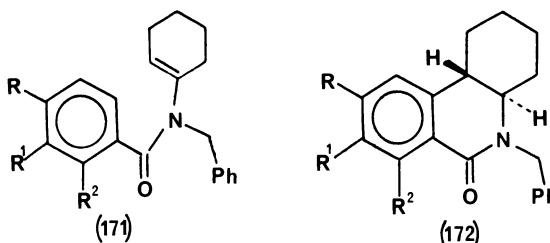
Benzo[b]thiophen-2-carboxamide, the sulfur analog of **160**, gives the two products **163** and **164** on irradiation in 15% and 40% yields, respectively, and this is rationalized in terms of the intermediate **165**, which under aerobic conditions is rapidly oxidized to **164** but which may also undergo a 1,5-shift to yield **163**.⁽¹³³⁾ Photocyclizations of heteroaromatic compounds have been used to synthesize the novel polycyclic systems thieno[2,3-*c*]-, pyrrolo



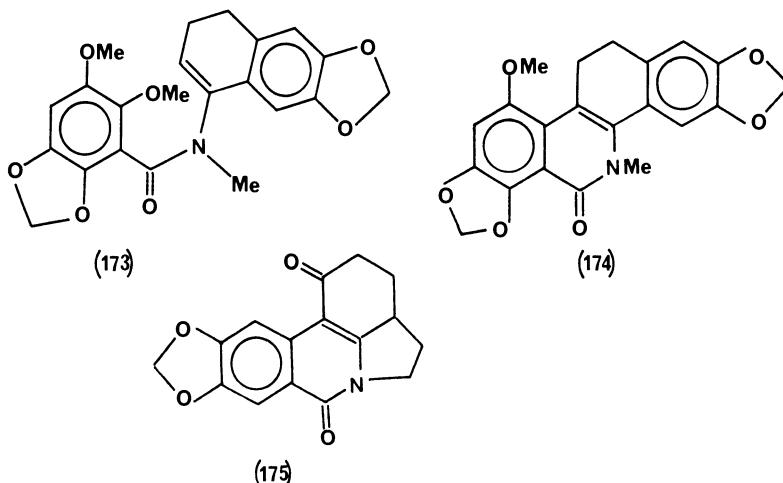
[2,3-c]-, and indolo[2,3-c]-diazonaphthalenes, **166**, **167**, and **168**, respectively.⁽¹³⁴⁾ Thus irradiation of the aroylaminopyridines **169** and **170** under oxidative conditions in 10% ethanol in benzene yields the corresponding cyclized systems **166**, **167**, and **168** or their isomers, depending upon the particular starting materials. Yields, however, are very variable and those quoted range between 8% and 62%.



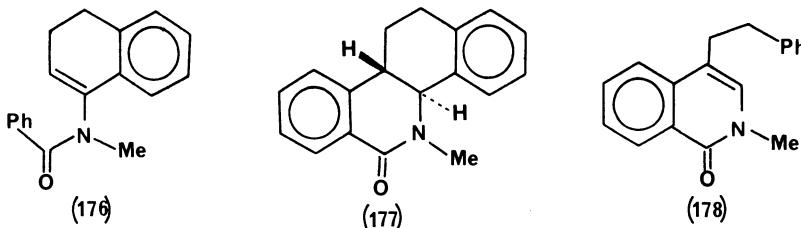
Isomeric fused lactams (hexahydrophenanthridones) with those outlined above are readily available from the photocyclization of *N*-benzoyl enamines (ArCONR—CH=CHR'). The cyclization process has been reviewed in a general consideration of the synthesis of lactams,⁽¹³⁵⁾ and the use in natural product synthesis has been summarized in a report concerned with the photochemistry of carboxylic acid derivatives.⁽¹³⁶⁾ General interest in synthetic routes to alkaloids has provided the impetus for many of these studies, and routes have, for example, been developed to corynoline systems.⁽¹³⁷⁾ A typical reaction involves the conversion of **171** to **172** with yields of 13%–71% dependent on the substituents.⁽¹³⁸⁾ As is common for many intramolecular cyclization processes (see Sections 3.1.3 and 3.3.1), *ortho* methoxy groups are



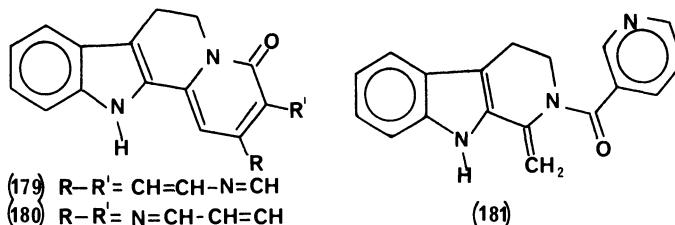
readily eliminated during the photoreaction and thus 173 yields 174 in a nonoxidative process.⁽¹³⁹⁾ The key intermediate 175 for the synthesis of α -lycorane is readily available via the photocyclization of the *N*-benzoyl derivatives of 1,2,3,3a,4,5-hexahydroindole-6-one,⁽¹⁴⁰⁾ and several instances of the



use of the process for the synthesis of benzo[b]phenanthridine alkaloids have been reported.⁽¹⁴¹⁾ For example irradiation of 176 in methanol yields the *trans* product 177 exclusively,⁽¹⁴¹⁾ and noteworthy here is that this ring system is also accessible by the photocyclization of the 4-substituted isoquinoline derivative 178.⁽¹⁴²⁾ *N*-Aroylenamine cyclizations also occur with the pyridine

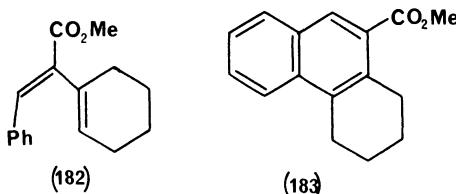


ring as the arene and for this the reaction is noteworthy. Thus both nauclefine **179** and isonauclefine **180** can be synthesized by the photocyclization of **181**.⁽¹⁴³⁾

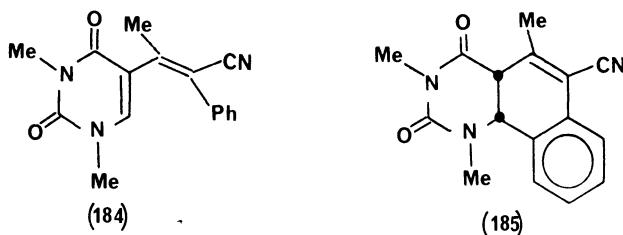


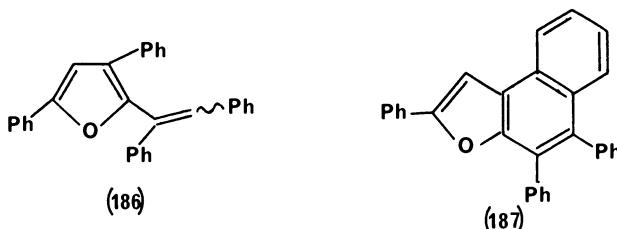
3.2 Aryl Butadiene and Butenyne Systems

As early as 1962 it was noted that photocyclization of 1-arylbuta-1,3-dienes led to naphthalene derivatives,⁽¹⁴⁴⁾ and since this time the potential of the process has been explored with many systems. For example, yields of 62%–88% are quoted for the conversion of the diene **182** to the naphthalene **183**,⁽¹⁴⁵⁾ but it should be noted that these efficiencies are very much better

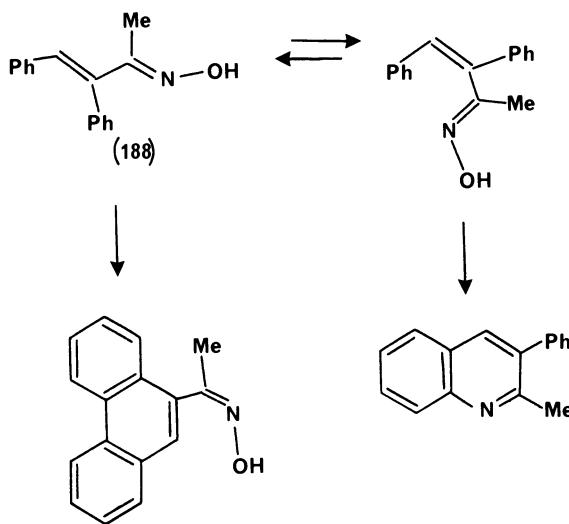


than those generally observed for 1,4-diphenylbuta-1,3-diene cyclizations. The diene moiety may be part of a complex system yet still the reaction proceeds: illustrative examples of this are found in the conversions of **184** to **185**⁽¹⁴⁶⁾ and of **186** to **187**.⁽¹⁴⁷⁾ The latter reaction is carried out in the presence of iodine as oxidant in order to form the naphthalene directly, and it is noteworthy that the process favored is that involving the phenylbutadiene cycli-

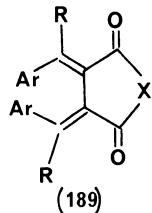




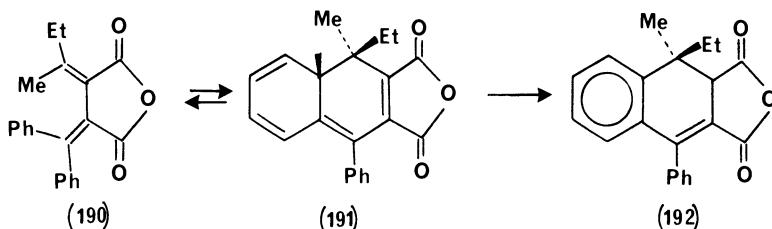
zation rather than a stilbene to phenanthrene type of conversion (see Section 3.3.1). The photoreactions of the oxime **188**, however, illustrate firstly that irradiation of arylazodienes can provide a synthesis for quinolines and secondly that the stereochemistry of the starting material is the deciding feature in determining the cyclization pathway.⁽¹⁴⁸⁾ Thus irradiation of *cis* **188** under oxidative conditions yields the phenanthrene derivative while *cis-trans* isomerism can occur which results in the formation of the quinoline.



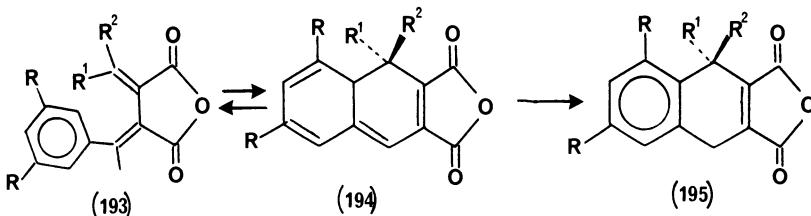
One of the major interests in the present cyclization has been in the photochromic properties that result from the reaction with certain systems. In particular the photochemistry of bis-arylmethylene succinic anhydrides and imides **189** have received much attention.⁽¹⁴⁹⁾ Substitution and substituent



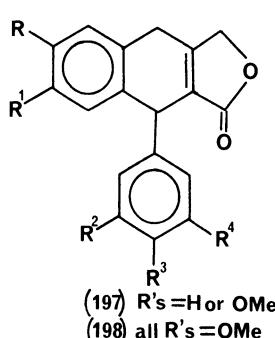
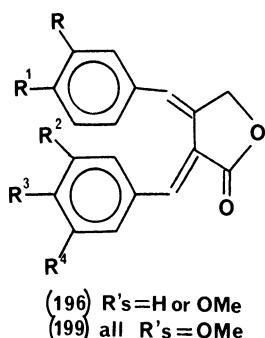
position in the arene can markedly affect the efficiencies of the photocyclization and rearrangement reactions and of the retro process. For example the derivative **190** undergoes photocyclization to yield the red 1,8a-dihydronaphthalene **191**, which in turn undergoes a facile 1,5-hydrogen shift to the 1,2-dihydronaphthalene **192**.⁽¹⁵⁰⁾ On the other hand, irradiation of the dime-



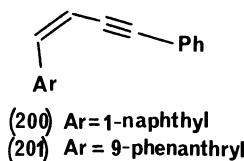
thoxyphenyl derivative **193** gives a reversible cyclization to the deep blue solvatochromic compound **194** which does not yield the analogous compound to **192** at room temperature but photochemically undergoes a 1,7-shift to the 1,4-dihydronaphthalene **195**. Many other examples of these intriguing and



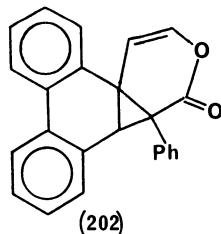
colorful reactions have been reported,^(7,151) and in this context it is interesting to note that the photocyclization reaction of 2,3-dibenzylidenebutyrolactones **196** has been used to synthesize β -apolignans **197**.⁽¹⁵²⁾ In particular, the trimethyl ether of β -apoplicatitoxin **198** has been formed in 34% yield, together with a small amount of regioisomer, from **199**.⁽¹⁵³⁾ Reports of the synthesis of other naphthalide lignans by this route have also been published.⁽¹⁵⁴⁾



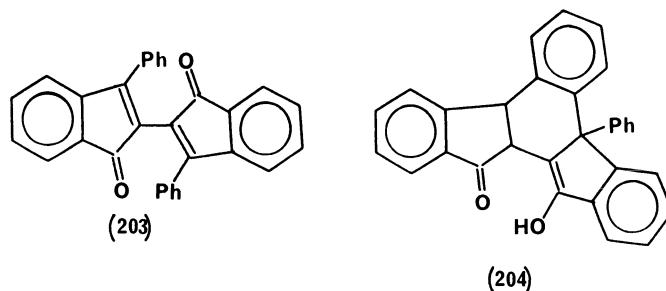
The photocyclization of 1-arylbut-1-en-3-ynes ($\text{Ar}-\text{CH}=\text{CH}-\text{C}\equiv\text{CH}$) to condensed arene systems in principle does not require a dehydrogenation step, but for several systems it has been observed that the presence of iodine or air is beneficial to product yields and also accelerates the process. Formation of 1-phenylphenanthrene from **200** has been accomplished in 45% yield and even very crowded polynuclear arenes (e.g., 4,5-diphenylphenanthrene) may be obtained quite specifically in this manner.⁽¹⁵⁵⁾ The mechanism and scope of this cyclization have been reported⁽¹⁵⁶⁾ and it has been observed that the pathway and by-product formation can be influenced by solvents⁽¹⁵⁷⁾: radical intermediates are favored in aprotic media whereas an ionic mechanism is considered to operate in alcoholic solvents. Care must also be taken concerning atmosphere, and with the arylbutenyne **201**, for example, although 1-phen-



yltriphenylene as expected is formed under nitrogen, in an oxygen atmosphere and in nonpolar solvents such as benzene, hexane, or diethyl ether, the main product is **202** although in methanol solvent and under oxygen, the triphen-



ylene is still preferred. The cyclization reaction of 3,3'-diphenyl-2,2'-bi-1H-indene-1,1'-dione **203** yields 70% of the blue-black crystals of **204** by way of a hydrogen migration in the expected dihydro intermediate.⁽¹⁵⁸⁾

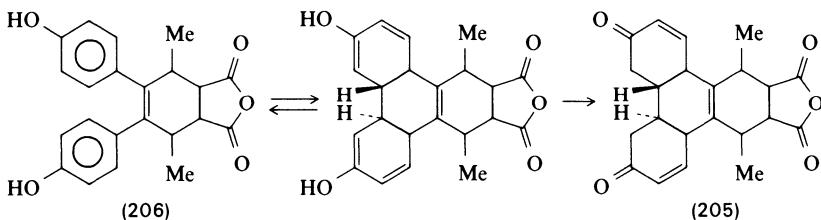


3.3. Intramolecular Photocoupling of Arenes

3.3.1. Stilbene–Phenanthrene-Type Cyclizations

Photooxidative cyclization of stilbenes to yield phenanthrenes *via* dihydronaphthalenes has been known for many years. In this section selected examples of the process are presented to illustrate the tremendous scope of the cyclization, the relevant features of the process, and the wide range of compounds which undergo this reaction. It is, however, firstly important to realize that there are criteria which may be used to assess if the photocyclization will occur. For many systems it has been shown that for successful reactions the sum of the free valence indices (ΣF^*) for the first excited state at atoms between which the cyclization may occur must be greater than unity. Other factors can override this consideration and the type of substitution on the stilbene may be very important as, in general, groups which promote intersystem crossing inhibit cyclization. One indication of an expected cyclization is the appearance in the mass spectrum of the stilbene of a “cyclization mass number.” Frequently the alternative mode of photoreaction of the stilbene is dimerization to yield the cyclobutane derivative.

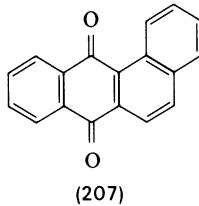
Early work on this cyclization largely assumed the intermediacy of a *trans* 4a,4b-dihydrophenanthrene but with the isolation of diketones (e.g. 205) from irradiation of 4,4'-dihydroxystilbenes, this has been proven⁽¹⁵⁹⁾: noteworthy here is that the quantum yield for the 206 to 205 conversion is in



excess of 0.85 and no side-products are formed. Such efficiencies and selectivities are not common for all stilbene–phenanthrene conversions, but the low yields and by-product formation can be seemingly overcome by carrying out the photocyclization in the presence of equimolar amounts of π -acceptors such as tetracyanoethylene, tetracyanoquinodimethane, chloranil, and bromanil in dichloromethane.⁽¹⁶⁰⁾ The photoreactions of stilbene, dimethoxystilbenes, naphthyl phenyl ethylenes, and dinaphthyl ethylenes have been examined in the presence of such additives and cyclization reaction rates are greatly increased from irradiation in the longest-wavelength absorption band. Practically complete conversions to the condensed arenes, which precipitate in excellent purity, are claimed and it is clear that if this modification proves to have general applicability in photocyclizations, this will undoubtedly in-

crease the attractiveness of these reactions as synthetic procedures. The addition of primary amines to irradiated solutions of stilbenes results in the formation of 1,4-dihydrophenanthrenes.⁽¹⁶¹⁾

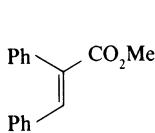
It is well established that in stilbene-phenanthrene conversions, for compounds in which the cyclization is blocked by substituents, either elimination of the group or its migration *may* result. Thus under oxidizing conditions 2,4,6-trimethylstilbene yields 1,3-dimethylphenanthrene.⁽¹⁶²⁾ Efficiencies are, however, very dependent upon the nature of the substituent, but elimination of methoxy is apparently a general facile process and for the cyclization of 2,6-dimethoxystilbene, 1-methoxyphenanthrene is formed in good yield under nonoxidizing conditions or in deoxygenated cyclohexane.⁽¹⁶³⁾ In cases where the cyclization can occur with or without such elimination, mixtures may result, but the conversion of 2,5-dimethoxystilbene to 1,4-dimethoxyphenanthrene is achieved in 71% yield and this reaction has been used as a step in the synthesis of 7,12-benz[a]anthraquinones **207**.⁽¹⁶⁴⁾ It is important to



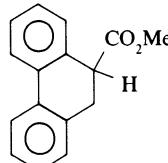
(207)

appreciate here that the loss of methoxy groups from positions of photocyclization is a very general phenomenon and occurs not only in the present type of conversion but also for examples of cyclizations of benzilides to phenanthridones⁽¹⁶⁵⁾ and of diphenyl ethers to dibenzofurans.⁽¹⁶⁶⁾ Such eliminations are considered to arise by the loss of methanol from dihydrointermediates.

Substitution on the ethylene bond of the stilbene by electron withdrawing groups such as carbomethoxy or cyano diverts the “normal” cyclization process and yields 9,10-dihydrophenanthrenes (e.g., **208** from **209**),^(167,168) but



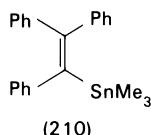
(209)



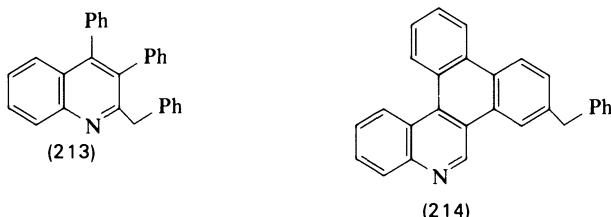
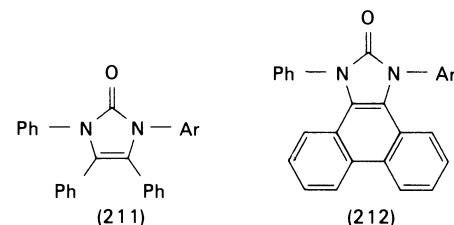
(208)

other substituents may have little effect and even the trimethylstannylethylene **210** is reported as giving the phenanthrene in reasonable yield.⁽¹⁶⁹⁾

There are many examples reported in the literature which demonstrate that for compounds in which the stilbene moiety is held in a *cis* configuration

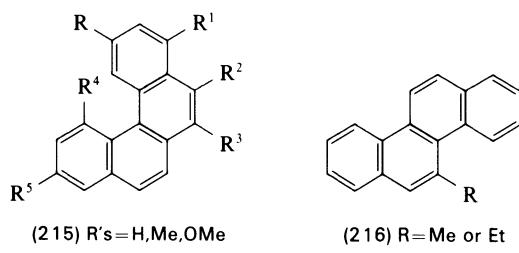


by the molecular structure, the photocyclization is an efficient high-yield process. The nature of the remainder of the molecule in such cases seems to have little or no effect on the success of the process which has been observed for a wide variety of compounds and is here illustrated by the high yield (70%–90%) conversions of **211** to **212**,⁽¹⁷⁰⁾ and **213** to **214**.⁽¹⁷¹⁾ The process has

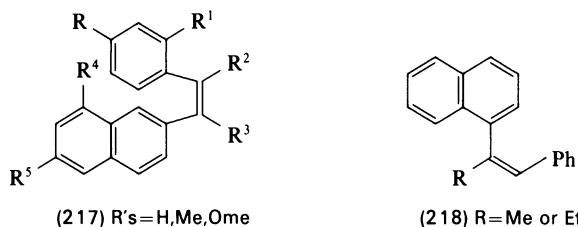


also been used as a key step in the efficient synthesis of phenanthrene-9,10-quinones which are intermediates in the formation of phenanthro-heterocycles and schizandrin-type lignans.⁽¹⁷²⁾

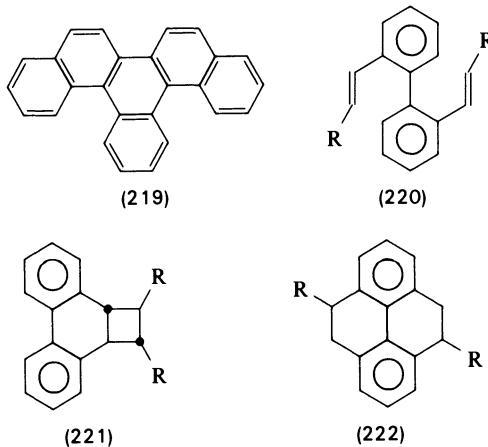
As indicated above,⁽¹⁶⁰⁾ this cyclization reaction occurs with aryl groups other than phenyl and this versatility has been exploited to synthesize a considerable number of polynuclear aromatic systems including helicenes and condensed heteroarenes. The key step in the synthesis of alkyl substituted benzo[c]phenanthrenes **215** and chrysenes **216** has involved such photocycli-



zation.⁽¹⁷³⁾ These condensed arenes result from irradiation of the β - and α -naphthyl compounds **217** and **218**, respectively, with yields of 66%–89%.

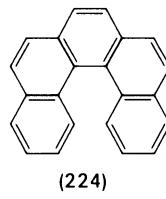
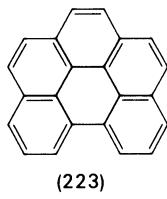


Product **215** is free from isomeric alkyl derivatives although approximately 1% of the benz[a]anthracene is formed in all cases as a result of cyclization to the β position of the naphthyl moiety. The formation of chrysene by this method has been developed to include the synthesis of derivatives with groups at the six substituent positions. Even the acetyl group, which normally inhibits cyclization in the stilbene series, can now be introduced into chrysene by this method.⁽¹⁷⁴⁾ This has also been used in an improved synthesis of the potent carcinogen 5-methyl-chrysene.⁽¹⁷⁵⁾ A further attraction of this one-step route to **215** and **216** is that the precursor molecules are readily synthesized by Wittig and Grignard procedures. The synthetic possibilities of two consecutive cyclizations have been investigated for various systems, and, for example, 5,6-benzopicene **219** can be obtained from 2,3-distyrylnaphthalene,⁽¹⁷⁶⁾ and 2,2'-divinylbiphenyls **220** may lead to the [2+2] intramolecular adduct **221** and tetrahydropyrene **222** dependent upon the vinyl substitution.⁽¹⁷⁷⁾

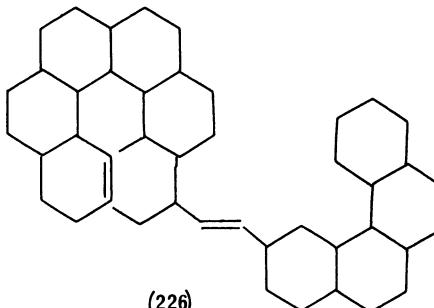
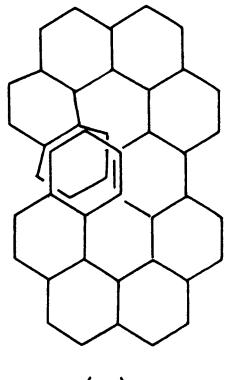


Cyclizations of the present type have been used in the synthesis of helicenes, but it should be realized that in the helicene products there is the possibility for further photoreaction, and, for example, benzoperylene **223**

results from irradiation of pentahelicene **224**.⁽¹⁷⁸⁾ However, the usefulness of the present reaction is illustrated by the synthesis of the double helicene



diphenanthro[4,3-a; 3'4'o]picene **225** by photocyclodehydrogenation of **226**.⁽¹⁷⁹⁾ It is deduced from spectroscopic measurements that of the two possible

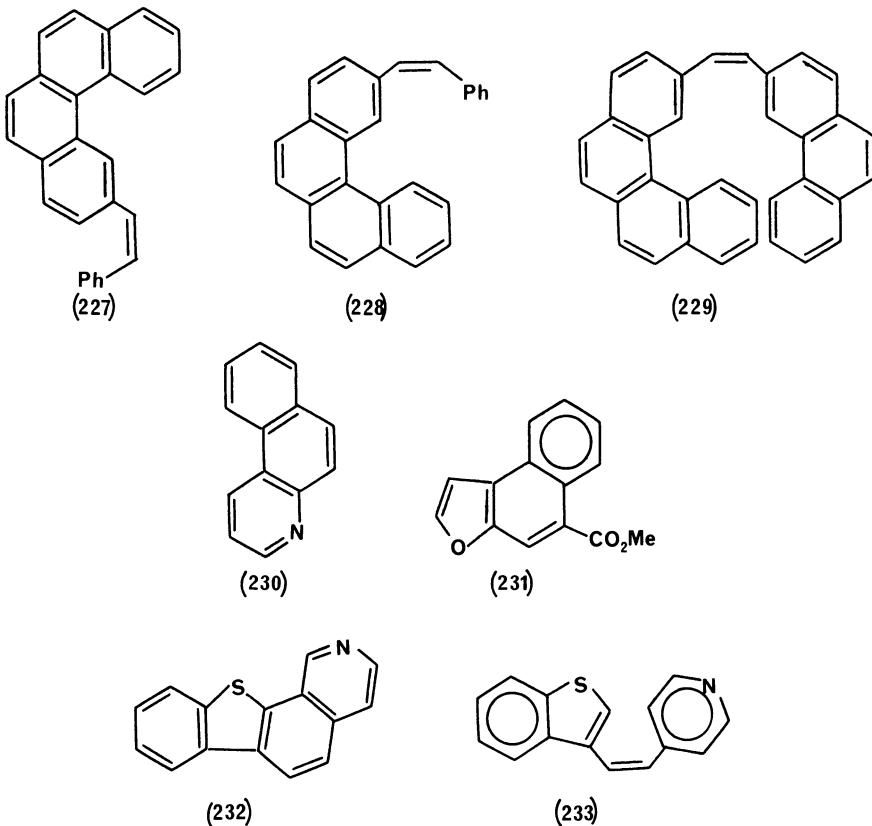


All rings aromatic

diastereoisomers of the product only **225** is formed as the racemate. One of the major interests in the use of this cyclization is, however, that it may provide a method for obtaining nonracemic mixtures of helicenes. Indeed the irradiation of 2-styrylbenzo[c]phenanthrene **227** in chiral solvents does produce the helicene with optical yields of between 0.2% and 2%,⁽¹⁸⁰⁾ and optically pure octa-, nona-, deca-, undeca-, and trideca-helicenes are reported to be formed by oxidative cyclization of the 1,2-diarylethylenes which have been prepared from optically pure 2-formylhexahelicene.⁽¹⁸¹⁾ An interesting development in this area is that irradiation of the hexahelicene and octahelicene precursors **228** and **229**, respectively, in a mechanically twisted nematic mesophase (1:1 mixture of *p*-cyanophenyl-*p*-butylbenzoate and *p*-cyanophenyl-*p*-heptylbenzoate) gives optically active helicenes, the chiralities of which are governed by the handedness of the twist⁽¹⁸²⁾: optical yields are variable and the highest quoted is 0.22%.

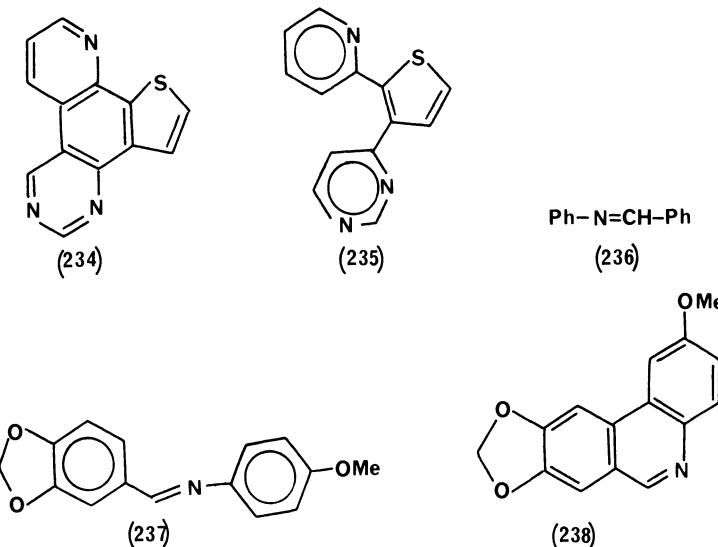
The stilbene cyclization is not greatly affected by the arenes being replaced by heteroarenes. Typically stilbazoles yield benzo[f]quinolines **230**,⁽¹⁸³⁾ and

naphtho[2.1-d]furan carboxylic acids **231** are obtained in up to 84% from oxidative photocyclization of substituted furylacrylic acid derivatives.⁽¹⁸⁴⁾ Similarly [1]benzothieno[3.2-h]isoquinolines **232** are formed from irradiation of **233**,⁽¹⁸⁵⁾ and noteworthy in these cyclizations is that the presence of electron

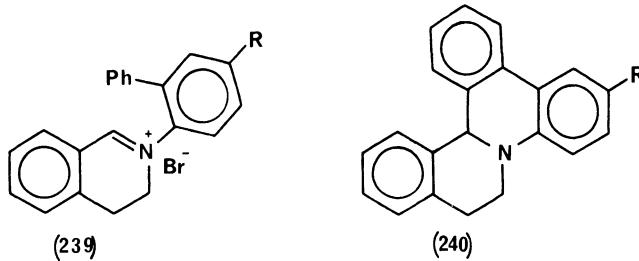


withdrawing substituents on the ethylene does not apparently affect the reaction (cf. References 167 and 168). This type of cyclization with heteroarenes has great potential for the synthesis of new condensed ring systems: this aspect is illustrated by the formation of **234** from **235**.⁽¹⁸⁶⁾

Photocyclization of simple benzylidene anilines **236** to phenanthridines generally requires the presence of strong acids, but the Schiffs base between α -naphthaldehyde and α -naphthylamine and anils having substituents with lone pair electrons yield the cyclized products in neutral solution.⁽¹⁸⁷⁾ From such results, it was deduced that for benzoylidene anilines with suitable substituents the cyclization would also occur in the absence of acid, and application of this approach has led to the successful synthesis of a phenanthridine alkaloid.⁽¹⁸⁸⁾ Thus irradiation of **237** yields **238**, which may be converted into the methobromide of ungeremine, an alkaloid from *Ungernia*.

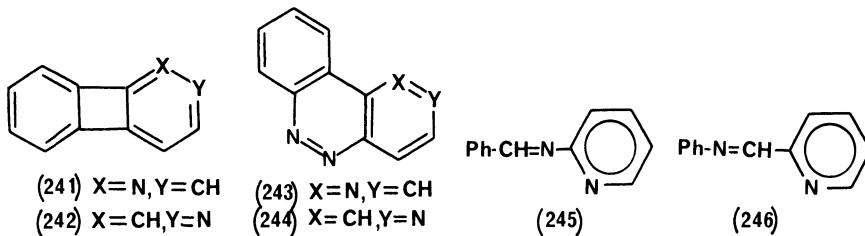


minor. Thermal cyclization of immonium salts such as **239** to the tri-benzo[a,c,h]quinolizine **240** occurs at 180°C in polyphosphoric acid but for **239** with R = NO₂, no reaction occurs. Such thermally stable immonium

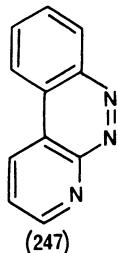


salts can, however, be induced to cyclize photochemically in ethanol solution in the presence of iodine⁽¹⁸⁹⁾: examples of this type of cyclization involving a C=N⁺ moiety are rare.⁽¹⁹⁰⁾ Failure of azobenzenes to yield benzo[c]cinnolines on irradiation in neutral solution has been considered to result from the fact that the lowest excited state is $n\pi^*$ in character, but protonation of the nitrogens or complexation with a Lewis acid results in $\pi\pi^*$ being the lowest state and cyclization occurs. For similar reasons, azobenzenes with suitably positioned substituents (i.e., 2,2'-dicarboxylic acids) yield the corresponding benzo[c]cinnolines in organic solvents, whereas their isomers (i.e., 3,3'- and 4,4'-dicarboxylic acids) are photostable under similar conditions.⁽¹⁹¹⁾ The photocyclodehydrogenation of phenylazopyridine in concentrated sulfuric acid has been used as a step in the synthesis of azabiphenylenes **241** and **242** via the azobenzocinnolines **243** and **244**,⁽¹⁹²⁾ and similarly diazophenanthrenes have been formed from the irradiation of benzylidenaminopyridine **245** and

pyridinalanilines **246** in similar media.⁽¹⁹³⁾ It is suggested that the lack of reaction of **245** and **246** in organic solvents is a consequence of a rapid *cis*–



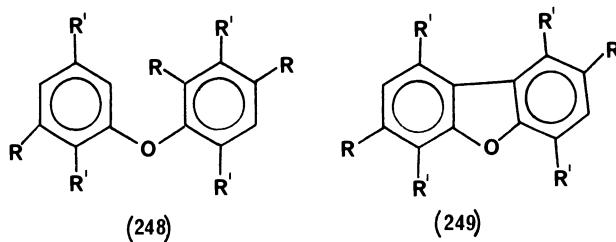
trans isomerization and the nonplanar geometry of the Schiffs base. In contrast to the requirements for acid media cited above, it is reported that 2-phenylazopyridine also reacts in neutral media to yield 4-pyrido[c]cinnoline 247. (194)



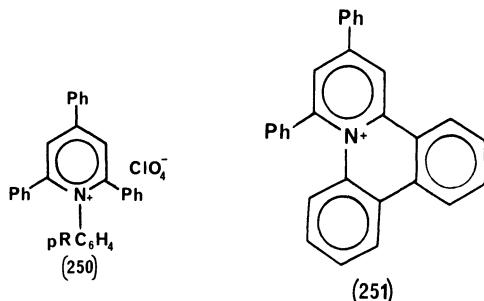
3.3.2 Photocoupling of Arenes with Intervening Units Other Than Ethylene

Compounds having proximate aryl groups which are separated by moieties other than ethylenes can also undergo both oxidative and nonoxidative photocyclization. The nature of the intervening unit(s) between the arenes does not apparently have a marked effect on the reaction, and hence this type of cyclization can be considered as having wide synthetic potential.

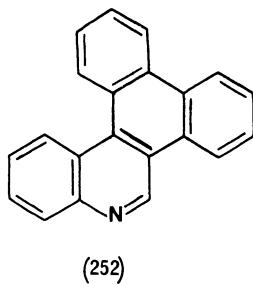
Photocyclization of diphenyl ethers provides a convenient synthesis of dibenzofurans, even those which are sterically hindered, and again the reaction occurs readily by elimination of substituent groups, particularly methoxy.⁽¹⁹⁵⁾ Thus the diphenyl ether **248** gives a 35% yield of the dibenzofuran **249**.⁽¹⁹⁶⁾



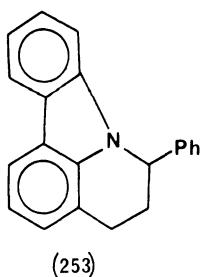
Yields of up to 80% are reported for the photoconversion of *N*-phenylpyridinium perchlorates **250** into the polynuclear compound **251**.⁽¹⁹⁷⁾ This process occurs in a number of solvents, and the efficiency is very dependent upon the nature of the R group in **250** with the rate order of R = Ph > Me > CO₂H:



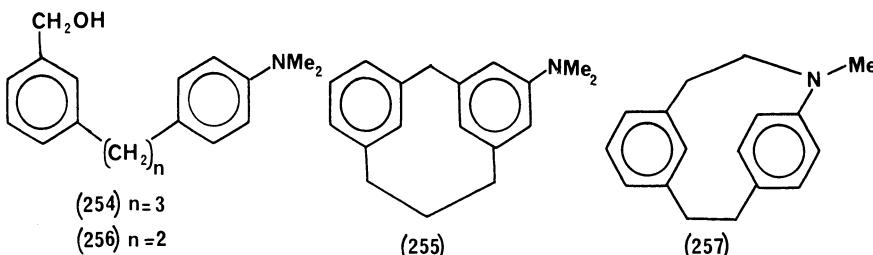
the process is, however, substantially slower when the substituent is halogen, nitro, or amino. This type of cyclization also occurs in the quinoline series, and 3,4-diphenylquinoline yields in dilute hydrochloric acid (not in neutral media) the condensed system **252** in 50% yield.⁽¹⁹⁸⁾ In contrast, the photo-



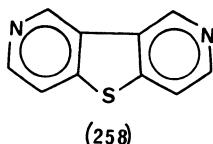
reaction of 1,2-diphenyl-1,2,3,4-tetrahydroquinoline under neutral conditions does lead to cyclization; however, this now involves the condensed arene function and gives 6-phenyl-4,5,6,7-tetrahydropyrido[3,2,1-j,k]carbazole 253.⁽¹⁹⁹⁾



Aryl groups separated by a simple *n*-alkane also cyclize on irradiation providing they have suitable substituents. For example the benzyl alcohol **254** gives the [3.1] *meta* cyclophane **255** in 54% yield by a process considered to involve electron transfer to the alcohol group followed by loss of hydroxide and radical cyclization.⁽²⁰⁰⁾ As may be expected, the efficiency and direction of the process is very dependent on the chain length separating the arenes, and for **256** the [3,2] *meta* cyclophane product **257** is formed by attack at the dimethylamino substituent but the yield has dropped dramatically to 3%.



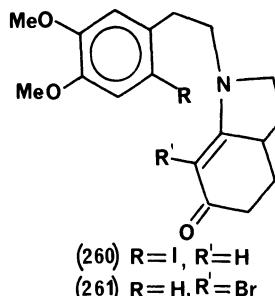
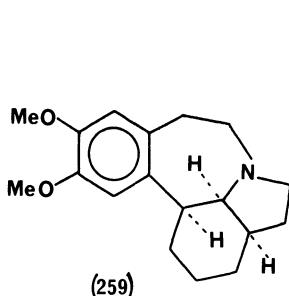
Cyclization occurs with heteroarenes, and, for example, one of the products from irradiation of 4,4'-dithiopyridine is the parent of the new heterocyclic system thieno [3,2-*c*, 4,5-*c'*]-dipyridine **258**.⁽²⁰¹⁾



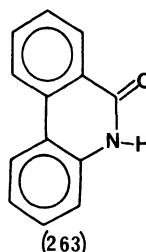
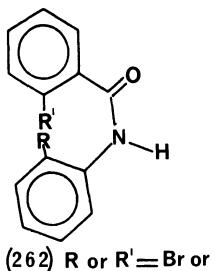
3.3.3. Coupling of Arenes as a Result of Halogen Acid Photoelimination

Although intermolecular arene coupling as a result of C–X bond homolysis and radical attack is outside the scope of the present treatment, it is considered that the corresponding intramolecular process is pertinent here as it is complimentary to the reactions cited above and for many systems is so selective as to be useful as a synthetic procedure towards polycyclic compounds.

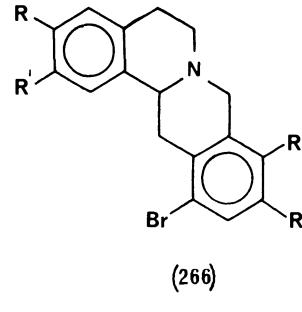
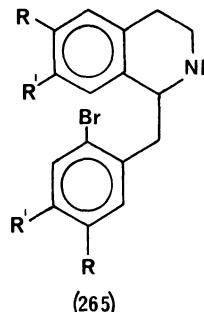
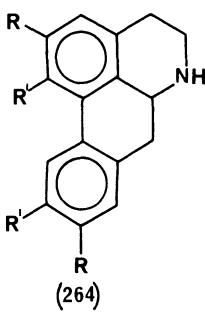
The literature abounds with reports of this general mode of cyclization, and again the limited number of examples cited here are chosen to demonstrate the scope of the reaction. Both arene–ethene and arene–arene coupling can be stimulated by the intramolecular photoelimination of halogen acid. The former process and its applicability is well illustrated by the novel synthesis of hexahydroapoerysopine dimethyl ether **259** using the photoinduced cyclization of the 6'-iodo- or 7-bromo derivatives **260** and **261** respectively, as the key step.⁽²⁰²⁾ The photoreaction occurs in dioxan or acetonitrile solution in



the presence of triethylamine in yields of 50% and 38%, respectively. Cyclization of the amides **262** has been used as a route to phenanthridones **263**.⁽²⁰³⁾ Interestingly the **262** to **263** conversion is facilitated by the presence of a *p*-hydroxy group, and the trends in product yields are a direct reflection of the C—X bond strengths. Aryl–aryl photocoupling finds extensive use in natural

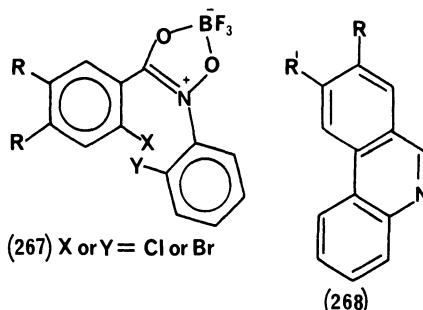


product synthesis⁽²⁰⁴⁾ and has been used, for example, in the formation of (\pm) laurolitsine **264** from the hydrochloride of **265**,⁽²⁰⁵⁾ although in this case the photooxidative cyclization product **266** is also observed. It is pertinent to

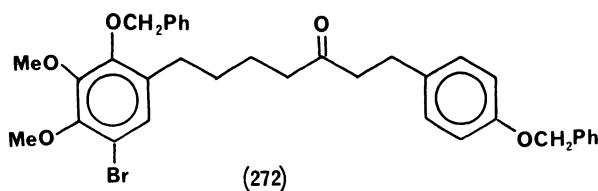
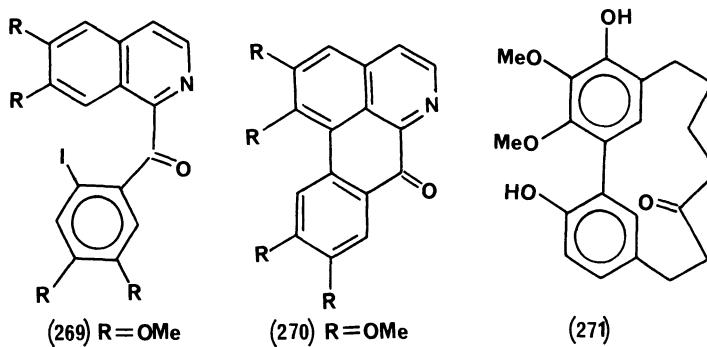


note here that these photodehydrohalogenation cyclizations generally involve Pyrex-filtered irradiation of the amine hydrochloride, but, for some systems, the process occurs in aqueous solution in the presence of sodium bisulfite.

Study of the boron complexes **267** of *N*-arylbenzohydroxamic acids in the present type of cyclization has led to the development of an improved route into the phenanthridine system.⁽²⁰⁶⁾ It is considered that the steric and electronic effects in **267** combine to result in an efficient cyclization and yields of **268** in the 76%–99% range are reported.

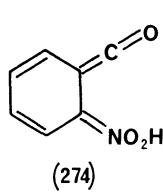
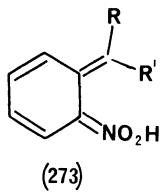


Heteroarenes can form part of the unit intervening between the coupling arenes and cyclization of **269** leads to the synthesis of aporphine **270** in 38% yield.⁽²⁰⁷⁾ Macrocycles which have the structure of the insect repellent myricanone **271** have been obtained by the photoelimination–cyclization process of **272**.⁽²⁰⁸⁾ Yields of the photoprocess are only 10%, but following debenzylation, the natural biphenyl is obtained.

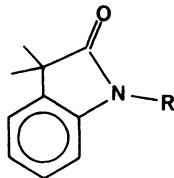


3.4. Photocyclizations of *o*-Substituted Arenes

Processes under this classification do not, in the final product, reflect a direct involvement of the aromatic ring. Nonetheless mention is made of such reactions here in order to give the reader a complete appraisal of the type of photocyclization reactions which may be expected from aromatic systems. Cyclization resulting from prior photoenolization of *o*-methyl ketones has been noted in Section 3.1.2, and an equally general reaction results from the irradiation of *o*-substituted aromatic nitro compounds. It has been known for some time that the photochromism of *o*-nitrotoluenes bearing α -hydrogen atoms occurs by hydrogen abstraction by the nitro group to yield 273,⁽²⁰⁹⁾ and that *o*-nitrobenzaldehyde yields *o*-nitrosobenzoic acid via a similar mechanism involving the intermediate 274.⁽²¹⁰⁾ Such intramolecular hydrogen ab-



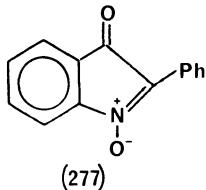
straction with *o*-*t*-butylnitrobenzenes does, however, lead to cyclization and 275 and 276 are the products.⁽²¹¹⁾ Such cyclization with an unsaturated side



(275) R=OH

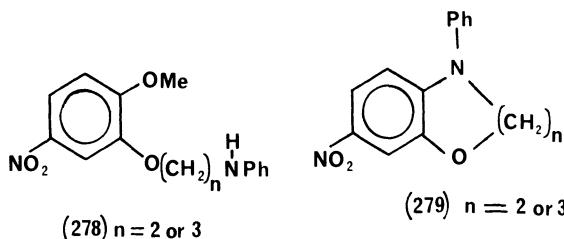
(276) R=H

chain in the *ortho* position has been used in a synthesis of isatogens and isatogenlike compounds.⁽²¹²⁾ Thus irradiation of *o*-nitrostilbene in benzene solution in the presence of iodine yields 2-phenylisatogen 277: the reaction



has been extended to include a variety of phenyl and naphthyl derivatives. Irradiation of *o*-allylanilines is a useful route to 2-methylindolines and yields

between 40% and 80% are reported.⁽²¹³⁾ The process is, however, very dependent upon the nitrogen substituent and for *N,N*-dialkylamino derivatives the photoproduct is 2-cyclopropyl-*N,N*-dialkylanilines. In view of the facile loss of the methoxy group following cyclization processes of aryl methyl ethers it may be surprising to note that no such reaction occurs on irradiation of allylanisoles which yield cyclopropylanisoles. However, such elimination does occur with 3-(ω -anilinoalkoxy) nitrobenzenes **278** which are reported to give good yields of oxazines or oxazepines **279** on irradiation.⁽²¹⁴⁾



The scope and mechanism of the light-induced cyclization of *ortho*-disubstituted benzene in which the substituents may be NH₂, OH, CN, CH=NOH, C≡CH, NPh, or NHMe, has been surveyed, and it does appear that this process could be a realistic route to benzoheterocyclic systems.⁽²¹⁵⁾

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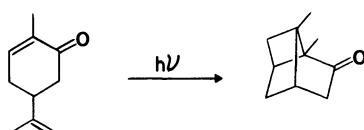
Enone Photochemical Cycloaddition in Organic Synthesis

Alan C. Weedon

1. Introduction

This chapter is concerned with the light-induced addition of the double bond of α,β -unsaturated ketones to alkenes to give cyclobutanes. The reaction is variously referred to as enone photoannelation, enone (2+2) cycloaddition, the de Mayo–Eaton reaction, or the de Mayo reaction. The last name is, however, usually reserved for the cycloaddition of enolized diketones to alkenes.

One of the first descriptions of this reaction appeared as early as 1908, when Ciamician reported the intramolecular photoreaction of carvone to give carvone-camphor⁽¹⁾ (Scheme 1). Despite this early start, little further investigation of the reaction occurred until the early 1960s, when, amongst others, de Mayo,⁽²⁾ Corey,⁽³⁾ and Eaton⁽⁴⁾ published results which suggested its synthetic potential for carbon–carbon bond formation. Since that time many papers have dealt with the reaction mechanism and its scope and limitations in synthesis, and many examples of its application to the preparation of natural products have appeared. Various aspects of the reaction have already been reviewed,^(5–13) and this chapter attempts to summarize what has been learned over the past 20 years with special emphasis given to those areas of interest to the organic chemist wishing to apply the reaction to organic synthesis.



SCHEME 1

2. The Reaction Mechanism

For synthetic organic chemists unfamiliar with the theory and practice of photochemistry, photochemical reactions often have a bad reputation in that it is commonly assumed that complex mixtures are frequently obtained. What is perhaps not realized is that with a proper understanding of functional group photochemistry and, more importantly, of photochemical mechanisms, it is frequently possible to achieve light-induced transformations as cleanly and in as high chemical yield as is the case in ground-state chemistry. For this reason some space will be given to a discussion of the mechanism of enone photocycloaddition.

The name enone (2+2) cycloaddition given to cyclobutane formation from irradiation of unsaturated ketones with alkenes is actually a misnomer because, with few exceptions, the reaction is not concerted as the name implies, but rather proceeds through a triplet biradical intermediate. An exception to this is the photoaddition of some α,β -unsaturated esters to alkenes where evidence exists that cyclobutane formation can proceed through a singlet exciplex.⁽¹⁴⁾

The generally accepted model for enone cycloaddition, as originally proposed qualitatively by Corey⁽³⁾ and in more detail by de Mayo,^(8,15) is shown in Figure 1. In this scheme, absorption of light by the enone, K, results in

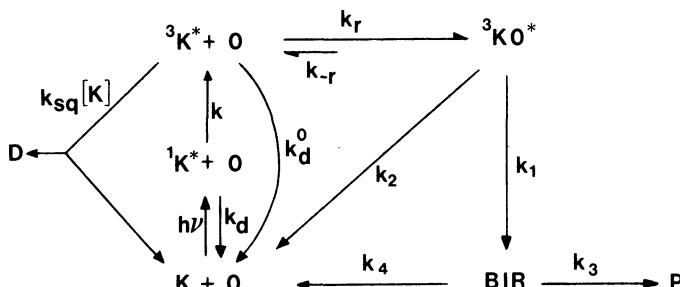
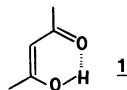


Figure 1. Mechanistic scheme for enone cycloaddition: K, enone; O, olefin; $^1\text{K}^*$, singlet excited state of enone; $^3\text{K}^*$, triplet excited state of enone; $^3\text{KO}^*$, triplet exciplex intermediate; BIR, biradical intermediate; P, enone/alkene adduct; D, dimer adduct.

formation of the singlet excited state, ${}^1\text{K}^*$. In flexible systems (i.e., acyclic enones), this can apparently decay rapidly and efficiently to the ground state by *cis*–*trans* isomerization of the double bond, and no other reaction is observed. This conclusion is based upon the reported inability of 0.53 M perylylene to quench 3-methylpent-3-en-2-one isomerization.⁽¹⁶⁾ It is possible, however, that the isomerization is a nonquenchable triplet process with a triplet excited-state lifetime of $\leq 10^{-10}$ s. This compares with a triplet lifetime for stilbene of 8×10^{-8} s.⁽¹⁷⁾

In less flexible enones (e.g., cyclic enones) intersystem crossing competes efficiently to produce the triplet excited state, ${}^3\text{K}^*$, with a quantum yield approaching unity in the cases of cyclopentenone and cyclohexenone.⁽¹⁸⁾ The triplet state is sufficiently long-lived in the less flexible enones (typically 2×10^{-8} for cyclopentenone and 3×10^{-9} for cyclohexenone⁽¹⁹⁾) that bimolecular processes such as enone cycloaddition can compete with nondiffusional processes leading to deactivation of the excited state. The latter, represented by process k_d^0 in Figure 1, includes *cis*–*trans* isomerization of the enone double bond. Because this process is rapid in acyclic or large-ring enones, photo-cycloaddition of α,β -unsaturated ketones is normally only observed for small-ring enones such as cyclopentenones and cyclohexenones, for enones such as 1 whose flexibility is reduced by intramolecular hydrogen bonding, or for



acyclic ketones conjugated with a double bond which is part of a small ring (e.g., 1-acylcyclopentenes).

The bimolecular fates of the triplet excited state of the enone include quenching by ground-state enone molecules⁽¹⁹⁾ or by other quenchers in the system provided they have lower triplet energies, and excited complex (exciplex) formation with alkenes. Self-quenching by enone molecules can lead to dimer formation which is essentially a special case of enone cycloaddition.⁽¹⁹⁾ The exciplex intermediate (${}^3\text{KO}^*$ in Figure 1) can decay back to the ground-state components or to a triplet biradical intermediate (BIR), which must then undergo spin inversion before closure to give the cyclobutane products, or fission to give back the starting enone and olefin.

The evidence for the existence of the postulated triplet exciplex intermediate is indirect, but it has been proposed in order to explain the regiochemistry of the alkene–enone cycloaddition products and to rationalize the observed reaction rates.^(8,15) The triplet-excited enone can be regarded as a biradical species from the point of view of its chemical reactivity; however, the observed rate of enone triplet quenching by olefins of higher triplet energy is far faster than would be predicted for normal radical additions to double

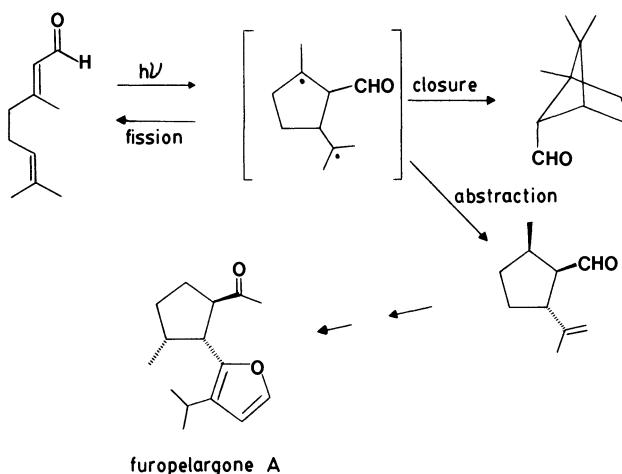
bonds. This difficulty can be avoided if an excited complex (the triplet exciplex) is first formed between the triplet enone and alkene which can then proceed to products unimolecularly. This reasoning is similar to that employed to rationalize the rapid rate of the Paterno-Büchi reaction of ketones with olefins.⁽²⁰⁾

The results of kinetic studies of enone photocycloaddition^(8,15) are consistent with the exciplex being formed irreversibly with a rate constant of 8.24×10^8 liter mol⁻¹ s⁻¹ for the cyclopentenone-cyclohexene reaction and 3.3×10^7 liter mol⁻¹ s⁻¹ for the cyclohexenone-cyclohexene reaction at room temperature. The activation energies for these processes are similar (1.3 and 0.96 kcal/mol, respectively) and the differences in rates between cyclopentenone and cyclohexenone are derived from changes in the preexponential factors in the Arrhenius equation. This has been interpreted in terms of greater flexibility in the excited cyclohexenone resulting in a reduced ability to form the exciplex.

Once formed, the exciplex apparently has a lifetime of less than 10⁻⁹ s as it cannot be intercepted by triplet quenchers, and its major pathway for decay is formation of a triplet biradical intermediate rather than collapse to starting materials.⁽¹⁵⁾

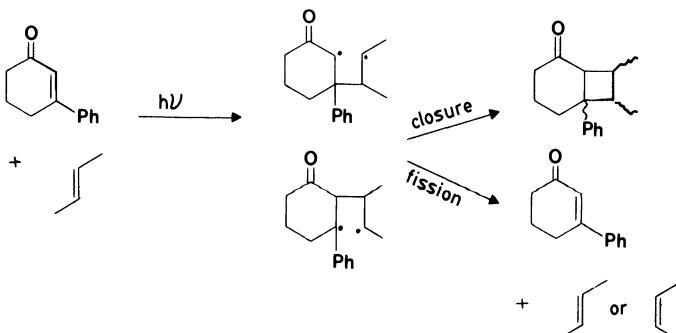
The evidence for biradical intermediates in enone cycloaddition is firmly based. It was found in early mechanistic studies of the reaction that, allowing for all observable modes of energy deactivation, a large proportion of the light energy absorbed by enones could not be accounted for and that this proportion varied with the olefin used. This could be explained if it was assumed that an intermediate (the biradical shown in Figure 1) was formed between the olefin and the triplet-excited enone which could then either proceed to products or alternatively dissipate the excited-state energy by collapsing back to the starting materials. Studies of the variation of quantum yield of cyclobutane formation as a function of temperature^(15,21,22,25) support this; for the reaction of cyclohexenone with various alkenes kinetic analysis of the quantum yield data indicates that the difference in activation energies for the two processes is less than 1 kcal mol⁻¹ (4 KJ mol⁻¹) and that approximately half of the biradicals proceed to product with the rest collapsing to starting materials.⁽¹⁵⁾

Evidence that the partitioning intermediate is a biradical species comes from studies of the products of enone cycloaddition: by-products frequently observed in the reaction are olefinic compounds which arise from intramolecular hydrogen abstraction through a six-centered transition state in the biradical intermediates. This process is normally inefficient, with fission to starting materials or closure to cyclobutanes proceeding more rapidly. An example is given in Scheme 2, which is unusual in that in this instance the major product arises from the abstraction reaction.⁽²³⁾ Use has been made of this in a synthesis of fupelargone A.⁽²⁴⁾

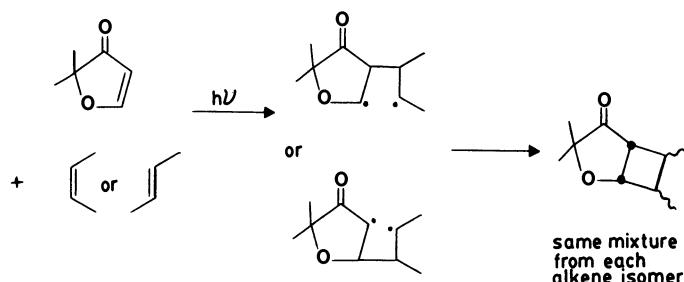


SCHEME 2

Other chemical evidence for the intermediacy of biradicals is the observation of isomerized unreacted olefin⁽²⁵⁾ (e.g., Scheme 3) and the formation of similar mixtures of products when starting from either pure *cis*- or pure *trans*- olefin^(3,26,27) (Scheme 4). The isomerized unreacted olefin is presumed to be formed by fission of the intermediate biradical which has a long enough lifetime to allow rotational equilibration around what was the olefinic double bond. This process is similar to the Schenk mechanism of isomerization of olefins by low-energy sensitizers.⁽²⁸⁾ The formation of identical mixtures of cyclobutane isomers from *cis*- or *trans*- is similarly explained by rotational equilibration in the intermediate biradicals (Scheme 4).

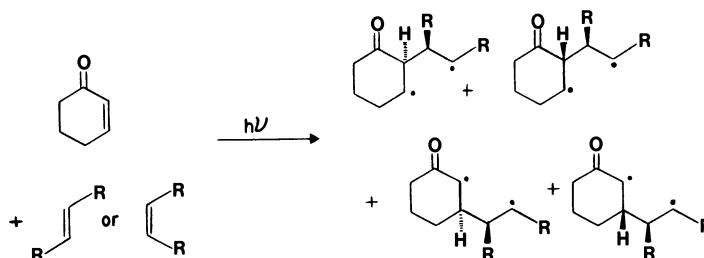


SCHEME 3



These results are not general, however, as others have found that *cis*- and *trans*-olefins do not always give the same distribution of products^(3,29,30,31) and that olefin isomerization at low conversion does not always occur.^(3,26) The latter may reflect the relative values of the rate constants k_3 and k_4 in the kinetic scheme shown in Figure 1; in some cases closure of the biradical may be efficient relative to fission with the consequence that little "unreacted" olefin isomerization is observed. The observation of identical mixtures of cyclobutene isomers from *cis*- and *trans*-olefins is probably the exception rather than the rule because of the possibility of isomeric biradicals being formed, as illustrated in Scheme 5. Thus, while each olefin isomer would be capable of giving all four possible biradicals, there is no reason to believe that their rates of formation should be the same for both olefins, so that an identical product distribution would not be expected. However, it is generally true that the stereochemistry of the olefin is lost in the cyclobutane products because of rotational equilibration in the biradical intermediates.

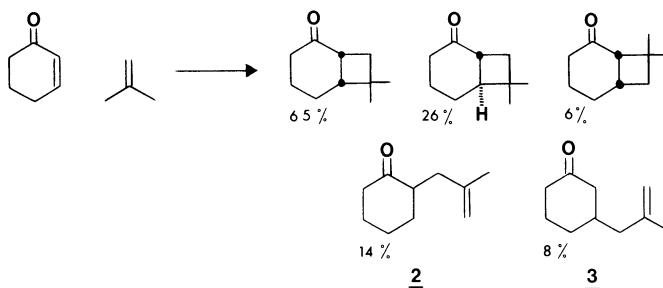
The question of whether the biradical intermediates are formed by bonding either to the α position or the β position, of the enone, or both, has not been fully resolved. Evidence has been presented to suggest that for simple enones the first bond is formed at the β position,^(29,30) although some of these



SCHEME 5

results have been shown to be incorrect.⁽³¹⁾ It has also been reasoned that the first bond is formed at the α position in an attempt to explain the regiochemistry of enone cycloaddition^(32,33); however, no evidence has been produced to support this, and the intermediacy of exciplexes can rationalize the observed regiochemistry satisfactorily, as will be discussed below. The frequent observation of olefinic products which appear to be derived from bonding to both the α position and the β position (e.g.,⁽³⁴⁾ structures **2** and **3** in Scheme 6) indicates that in all probability the initial bonding can be at both positions with the relative proportions depending upon the structures of the enone and alkene involved.

The relative efficiencies of enone cycloadditions with olefins of varying structure have been compared. The results of one of the earliest studies in this area,⁽³⁾ which have been confirmed by others,⁽³³⁾ are shown in Table 1. In competition experiments, the relative quantum yields of addition of various olefins to cyclohexenone were compared. It was found that the more electron-rich olefins apparently added to the enone fastest and this was taken to mean that the enone triplet excited state was electrophilic in nature. It has been pointed out by de Mayo⁽⁸⁾ that this is not necessarily a correct conclusion as the quantum yield of enone cycloaddition is not dependant upon the rate of attack of olefin upon excited enone so much as the relative efficiencies of competitive ring closure to give product and fission to starting materials in the intermediate biradical. That this is the case is supported by the data shown in Table 2. The actual rate of attack of olefin upon the enone triplet is controlled by the process k_3 in Figure 1, the rate constant for exciplex formation. This is also rate determining for the formation of the intermediate biradical since processes k_1 and k_2 are slow and k_3 is fast. The value of k_3 has been measured (Table 2) and is found to be similar for all olefins examined, irrespective of structure.⁽¹⁵⁾ Thus, the rate of reaction of excited enone is not enhanced by high electron density in the alkene π system and so its excited state is not necessarily electrophilic. However, the relative values of k_3 and



SCHEME 6

Table 1. Relative Efficiencies of Alkene-Enone Cycloaddition

Alkene	Enone	"Relative Rate" ^a	Ref.
		4.66	3
	"	1.57	3
	"	1.00	3
	"	0.40 ^b , 0.13 ^c	3
	"	0.234	3
	"	"VERY SLOW"	
		3.66	33
	"	1.00	33
	"	0.78	33

^a These numbers were determined in competition experiments where the alkene and cyclopentene were present simultaneously. The relative yields of the two possible adducts were taken as a measure of reaction rate.

^b Head-to-tail regioisomer.

^c Head-to-head regioisomer.

k_4 , the rate constants for biradical closure to product and reversion to starting materials, respectively, do vary substantially. For example, for cyclohexene addition to cyclohexenone, 48% of the biradicals close to products whilst in the case of cyclopentone only 26% close, the remainder undergoing fission.

The reactive excited state in enone cycloaddition can be $n-\pi^*$ or $\pi-\pi^*$ in nature. Simple enones (that is, those not possessing extended conjugation) exhibit weak maxima (ϵ ca. 10^2) around 300–320 nm in their ultraviolet absorption spectra and much more intense bands (ϵ ca. 10^4) at shorter wavelengths whose position can be predicted accurately by the Woodward-Fieser rules. The former corresponds to excitation into the $n-\pi^*$ singlet state and the latter to the $\pi-\pi^*$ singlet. Calculations suggest that the triplet $n-\pi^*$ and $\pi-\pi^*$ states are much closer in energy and that a state inversion may occur resulting in the $\pi-\pi^*$ state having lower energy.⁽³⁵⁾ However, the phospho-

Table 2. Rate Constants and Quantum Yields for Cyclopentenone Cycloadditions

Alkene	ϕ^a	$kr \times 10^{-8b}$	$\frac{k_3^c}{k_3 + k_4}$	Ref. ^d
	.19			44
	.23			44
	.24			44
	.54			44
	.29			44
	.46	8.24	.48	15
	.23	10.07	.26	15
	.22	2.14	.21	15
	.35	2.2	.36	15
	.36	6.73	.36	15

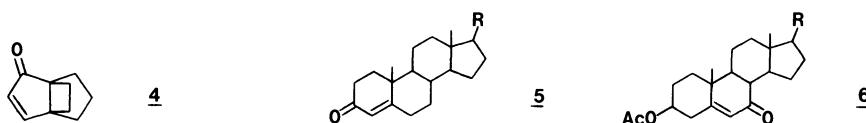
^a Quantum yield of adduct formation.

^b Rate of exciplex formation (see Figure 1).

^c k_3 , rate of biradical closure to product; k_4 , rate of biradical cleavage to starting materials.

^a Quantum yields from Reference 15 are extrapolated to infinite olefin concentration, those from Reference 44 are not and so are lower.

rescent emission spectrum of enone **4** suggests that the lowest triplet is $n-\pi^*$ in nature,⁽³⁶⁾ whilst the polarized phosphorescence spectra of compounds **5** and **6** suggest⁽³⁷⁾ that the lowest triplet for **5** is $\pi-\pi^*$ and for **6** is $n-\pi^*$.



It would seem probable that both electronic configurations are possible, depending upon enone structure, and it is also possible that the two states are close enough in energy that mixing can occur, blurring the distinction.

The current understanding of the mechanism of enone photocycloaddition is summarized in Figure 2 in the form of a potential energy surface diagram. Initial excitation produces the $n \rightarrow \pi^*$ singlet excited state which rapidly intersystem-crosses to the triplet excited state, which can traverse a small activation barrier to form an exciplex with the olefin in competition with quenching or radiationless decay back to starting enone. The exciplex can also decay back to starting materials, but the major reaction is rapid surface crossing to give a biradical which can partition between product formation and reversion to starting materials. The relative efficiencies of these last two processes depend upon the heights of the activation barriers present.

3. Regiochemistry of Enone Cycloaddition

When an unsymmetrical alkene undergoes cycloaddition to an excited enone, two orientations of addition are possible. It was demonstrated by Corey³ that for electron-rich alkenes the major regioisomer is that in which the polar group of the alkene is further from the carbonyl group of the enone, whilst for electron-deficient alkenes the reverse orientation is observed. Adducts in which the polar group is further from the ketone are normally referred to as head-to-tail isomers, and those with the opposite regiochemistry are referred to as head-to-head isomers.

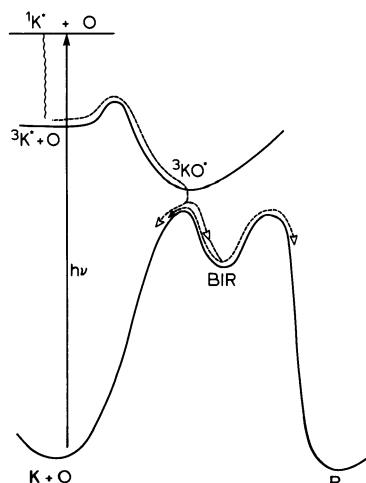
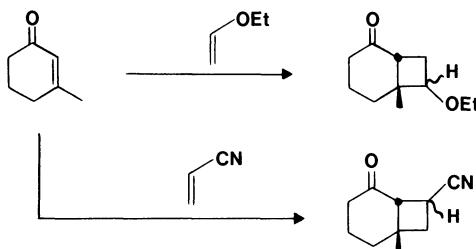


Figure 2. Potential energy surface diagram for enone cycloaddition: K, enone; O, olefin; $^1\text{K}^*$, singlet excited enone; $^3\text{K}^*$, triplet excited enone; $^3\text{KO}^*$, triplet exciplex intermediate; BIR, biradical intermediate; P, adduct.



SCHEME 7

The two modes of addition are illustrated in Scheme 7. In these examples none of the alternative possible regioisomers were observed.⁽³²⁾ The origin of this selectivity appears to be largely electronic, although steric factors can also affect the regiochemistry of the cycloaddition. One of the earliest rationalizations of the regiochemistry of enone cycloaddition was put forward by Corey,⁽³³⁾ who proposed that a “ π complex” be formed between the photoexcited enone and the alkene. The orientation of this complex is then reflected in the regiochemistry of the cycloadduct. This π complex can be regarded as identical with the exciplex intermediate postulated as being present in the mechanistic description of enone cycloaddition given in the previous section. Corey proposed that the more favorable orientation of the π complex is that in which the dipole of the alkene is opposed to that of the excited enone. For this purpose it was implicitly assumed that the excited state of the enone was $n \rightarrow \pi^*$ in nature and that consequently the dipole was reversed as compared with the ground-state enone because of movement of charge away from the carbonyl group (cf. Figure 3). This is usefully predictive, and cases where the rule breaks down can usually be accounted for by unfavorable steric interactions between enone and alkene in the more stable π complex

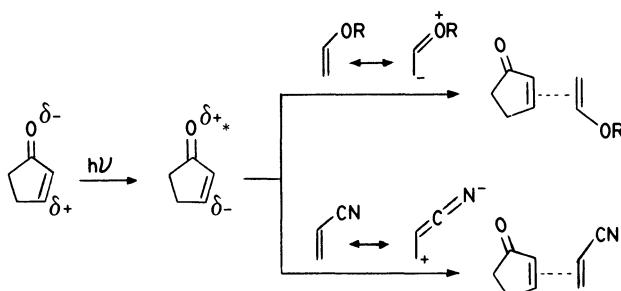


Figure 3. Rationalization of enone cycloaddition regiochemistry in terms of polarization of reacting species (ground-state olefin and $n \rightarrow \pi^*$ excited enone).

orientation. The occasional failure of Corey's proposal to predict correctly the observed regiochemistry may also arise from unequal partitioning of the different biradical intermediates derived from π complexes of differing stability; thus, in some instances, it is possible that the more stable π complex may yield a biradical which reverts to starting materials rather than progressing to product while a less stable π complex does the reverse, the overall result being formation of the "wrong" regioisomer.

Dipole-dipole interactions of the type postulated by Corey should be subject to solvent effects; this has been treated quantitatively by de Mayo,⁽³⁸⁾ who related the efficiency of the interaction to a function of the dielectric of the medium using an approach originally devised by Kirkwood and Onsager⁽³⁹⁾ and applied by Benson to the Diels-Alder reaction.⁽⁴⁰⁾ It was shown for two systems (Schemes 8 and 9) that the ratio of regioisomeric adducts does correlate with the Kirkwood-Onsager function of dielectric constant^(38,41) (Figures 4 and 5). These studies demonstrate that in order to maximize the proportion of the regioisomer predicted by the Corey rule a nonpolar solvent medium should be used, and conversely if the isomer with the opposite orientation is desired a highly polar medium should be employed.

An alternative rationalization of the regiochemistry of enone cycloaddition has been proposed which relates the stabilities of the biradicals leading to each regioisomer to the ratio of products obtained.⁽⁹⁾ In this approach, it is assumed that the more stable biradical intermediates preferentially revert to the starting materials and that the less stable biradicals proceed to cycloadducts, although it has also been suggested that the more stable biradicals

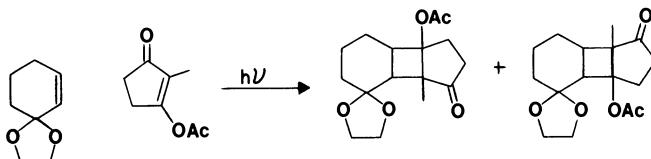
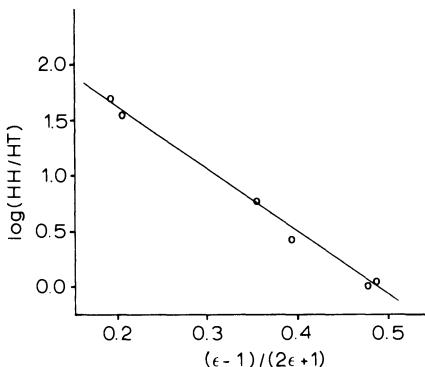


Figure 4. Regiochemistry of enone cycloaddition: Plot of the Kirkwood-Onsager function of solvent dielectric, $[(\epsilon - 1)/(2\epsilon + 1)]$, against logarithm of regioisomeric ratio of products for the reaction shown in scheme 8 (HH, amount of head-to-head product; HT, amount of head-to-tail product).

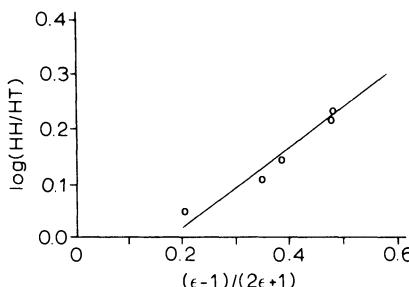


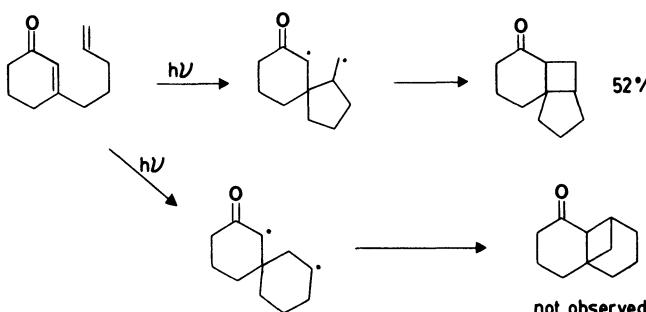
are the ones leading to products!⁽⁴²⁾ The difficulty in this approach lies in predicting the relative stabilities of the competing biradicals, which is not always straightforward. However, it does appear to have some value in predicting the outcome of intramolecular enone cycloadditions where strain and steric interactions within the molecule outweigh the effect of more stable π -complex formation. In intramolecular additions the general rule appears to be that the major regioisomeric product is that formed from closure of the biradical intermediate in which a five-membered ring has been formed. This “rule of five”⁽⁴³⁾ is illustrated in Scheme 10. Intramolecular enone-alkene additions will be considered in more detail in separate sections.

In Tables 3, 4, 5, and 6, the regiochemical outcome of photoaddition of representative unsymmetrical alkenes to cyclopentenones, cyclohexenones, heterocyclic enones, and acyclic enones, respectively, is summarized, whilst in Table 7, nonsymmetrical alkyne photoadditions are listed.

It can be seen from Tables 3–6 that for the more electron-rich alkenes (i.e., those bearing groups substituted on the double bond which are capable

Figure 5. Regiochemistry of enone cycloaddition: Plot of the Kirkwood-Onsager function of solvent dielectric, $[(\epsilon - 1)/(2\epsilon + 1)]$, against logarithm of regioisomeric ratio of products for the reaction shown in scheme 9 (HH, amount of head-to-head product; HT, amount of head-to-tail product).





SCHEME 10

of donating charge by resonance) the regioselectivity is usually very good with head-to-tail adducts predominating. However, as the electron-donating ability of the substituents on the alkene decreases, the regioselectivity of the reaction also falls, and for weakly electron-rich alkenes, such as those substituted by alkyl groups, the regiochemical control is less pronounced, much less predictable, and much more sensitive to effects of substitution on the enone, and the bulk of the alkene substituents. Thus, for example, addition of 2-methylpropene to cyclohexenone gives a mixture of head-to-tail and head-to-head adducts in the ratio 3.3:1,⁽³⁴⁾ respectively, whereas 3-methylcyclohexenone gives a similar mixture but in the ratio 1:2.3^(32,34) in the same solvent. In calculating these ratios, olefinic products are designated head-to-head or head-to-tail depending upon what products would have been formed from their biradical precursors had they undergone ring-closure to cyclobutanes rather than intramolecular hydrogen abstraction. It would seem probable that in this example the origin of the variation in regiochemistry is steric in nature, rather than electronic, in view of the fact that cyclohexenones substituted in the 3 position with either strongly electron-donating or electron-withdrawing groups continue to add to electron-rich alkenes with predominant head-to-tail regiochemistry, and to electron-deficient alkenes with predominant head-to-head regiochemistry.⁽⁶²⁾

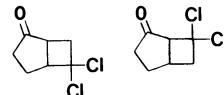
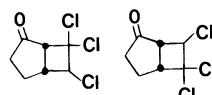
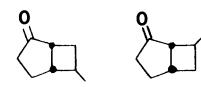
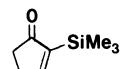
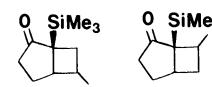
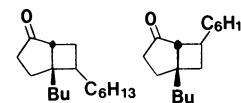
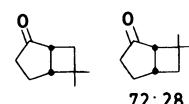
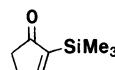
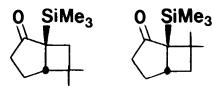
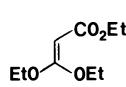
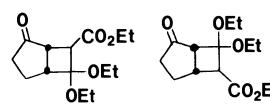
A further example, uncomplicated by the formation of unsaturated products arising from intramolecular hydrogen abstraction in biradical intermediates, and which also shows the effect of a bulky substituent on the alkene, involves the addition of vinyl acetates to 3-*n*-butylcyclopentenone. Addition of vinyl acetate itself yields a mixture of head-to-tail and head-to-head adducts in the ratio 3:1, while addition of 1-acetoxy-1-hexene is completely regioselective and gives head-to-tail adducts only.⁽⁴¹⁾ This effect must arise from an

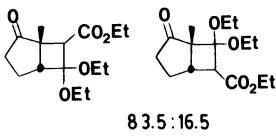
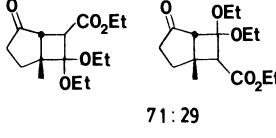
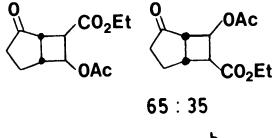
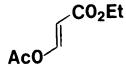
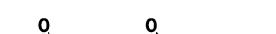
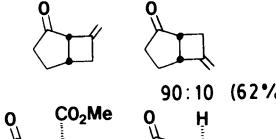
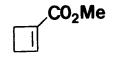
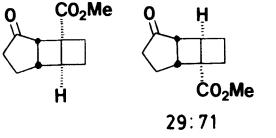
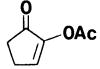
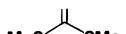
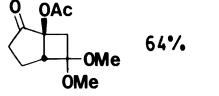
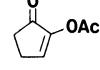
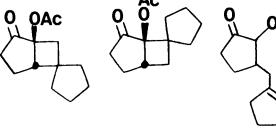
Table 3. Representative Photoadditions of Nonsymmetrical Alkenes to Cyclopentenones

Ref.	Enone	Alkene	Solvent	Products
44			pentane	
3, 44			pentane (-70°)	
44			pentane	
45			a	
44			pentane	
46			benzene	
41			cyclohexane	
41			cyclohexane	
47			pentane	
31			ether (-70°)	

(Continued)

Table 3. (Continued)

Ref.	Enone	Alkene	Solvent	Products
31				 84.2 : 15.8 70.7 : 29.3 80.5 : 19.5
31			ether acetonitrile alkene	 58:42 62:38 51:49
47, 48			a	 55:45
47			pentane	 50:50 (87%)
41			cyclohexane	 53:47
47, 48, 49			pentane	 72:28
47			pentane	 80:20 (82%)
50			pentane	 82.5:17.5

Ref.	Enone	Alkene	Solvent	Products
50		..	pentane	
50		..	pentane	
50			pentane	
51			benzene	
82		==	benzene	
52			dichloro-methane	
53			alkene	
54			benzene	

(Continued)

Table 3. (Continued)

Ref.	Enone	Alkene	Solvent	Products
38,55			cyclohexane	
41			cyclohexane	

^a Solvent not stated.^b Product ratio determined following chemical degradation.^c Product ratio includes contribution from secondary irradiation products.^d Includes olefinic products derived from common biradical.**Table 4. Representative Photoadditions of Nonsymmetrical Alkenes to Cyclohexenones**

Ref.	Enone	Alkene	Solvent	Products ^a
3			pentane	
32			ether	
61			benzene	
62			ether	

Ref.	Enone	Alkene	Solvent	Products
32			ether	
63			benzene	
64			b	
64			petroleum ether	

(Continued)

Table 4. (Continued)

Ref.	Enone	Alkene	Solvent	Products
34			pentane	<p>13:11 60%</p> <p>43 : 23 : 10</p>
3,32,34			pentane ether	<p>14 % 50% 27%</p>
66			cyclohexane	<p>38% 25% 23%</p>
66			cyclohexane	<p>7% 49% 43%</p>
67			pentane	<p>60:10</p> <p>18:3</p> <p>87:13 (78%)</p>
62			ether	<p>87:13 (78%)</p>
32			ether	<p>45%</p>

Ref.	Enone	Alkene	Solvent	Products
68			b	
69			benzene	
83				
32			ether	
52, 70 72, 73			b	
62			benzene	
32			ether	
32			ether	

(Continued)

Table 4. (Continued)

Ref.	Enone	Alkene	Solvent	Products
55			cyclohexane	 "minor" ^c
76			THF	 58%

^a Product stereochemistry specified.^b Solvent not stated.^c Products isolated as diketones following retro-aldol ring-opening.**Table 5. Representative Photoadditions of Nonsymmetrical Alkenes to Heterocyclic Enones^a**

Ref.	Enone	Alkene	Solvent	Products
26			pentane	 only
57			benzene	 14 : 86 (80%)
58			pentane	 95%
58	..		pentane	 73% 25%
58	 68%
58	 80 : 20 (99%)

Ref.	Enone	Alkene	Solvent	Products
59	..		hexane	
51			benzene	
57	
60			..	
26		..	pentane	
26	
74		..	b	
74		..	b	
75			hexane	

(Continued)

Table 5. (Continued)

Ref.	Enone	Alkene	Solvent	Products
75	
75	
75	
75	
60			ether	
33		..	alkene	
78			ethanol	

Ref.	Enone	Alkene	Solvent	Products
77			dioxane	
79			ethanol	
48			acetone	
34, 81			..	

^a Adduct stereochemistry specified where available.^b Solvent not stated.

Table 6. Regiochemical Outcome of Representative Photoadditions of Acyclic Enones to Nonsymmetrical Alkenes

Ref.	Enone	Alkene	Solvent	Products ^a
90			cyclohexane	
90, 91	..		alkene	
90	..		cyclohexane	
92			benzene	
92			benzene	
93			ethyl acetate	
94			pentane - dichloromethane	

^a Photoadducts are shown as primary products. In all cases, retro-aldol ring opening occurs to give 1,5-diketones as isolated products.

Table 7. Regiochemistry of Enone-Alkyne Photocycloadditions

Ref.	Enone	Alkyne ($R_1C \equiv CR_2$)		Products			
		R_1	R_2				
85, 88							
		n-Bu	H	69	:	31 ^a (35%)	
		t-Bu	H	87	:	13 (25%)	
		OEt	H	40	:	60 (20%)	
		CO ₂ Me	H	49	:	51 (8%)	
		Me ₃ Si	H	65	:	35	
		Me ₃ Si	Me	82	:	18	
85		n-Bu	H				
				R ₃ = H	88	:	12 (27%)
				R ₃ = Me	85	:	15 (40%)

^a Head-to-tail adducts were subject to a secondary photochemical reaction. In calculating the regiosomeric ratio the secondary product yield was combined with that of its primary product precursor.

unfavorable steric interaction between the alkyl group on the alkene and that on the enone rather than an electronic factor since the electron-donating effect of the alkene alkyl group would be expected to have the opposite result. The perturbing steric interaction presumably occurs either in the exciplex or in the biradical intermediates, or both. It would be expected that in bulkily substituted systems closure of the more hindered biradical intermediates would be inhibited with respect to reversion to starting material or intramolecular hydrogen abstraction. In the case of 2-methylpropene addition to cyclohexenone and 3-methylcyclohexenone, this is supported by the observation that for cyclohexenone the ratio of cyclobutane adducts to products resulting from intramolecular hydrogen abstraction is 1.75:1⁽³⁴⁾ whilst for 3-methylcyclohexenone the ratio is 1:5.5.^(32,34)

It can be seen from Table 7 that nonsymmetrical alkynes tend to add to enones to give head-to-head isomers preferentially, which is the reverse of the situation with comparable enone-alkene cycloadditions. However, the results of calculations⁽⁸⁴⁾ suggest that this is still consistent with the major product arising from the more stable exciplex formed between the ground-state alkyne and the $\pi-\pi^*$ triplet excited state of the enone. This is supported by the observation⁽⁸⁵⁾ of a correlation between the Kirkwood-Onsager function

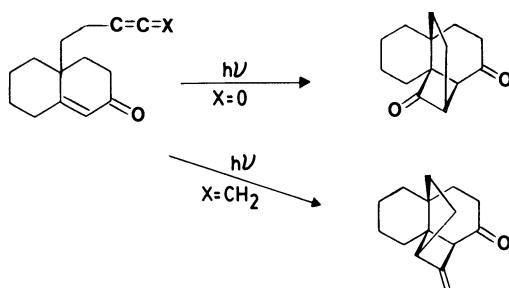
of solvent dielectric and regioisomeric ratio for alkyne additions; this correlation indicates that the proportion of head-to-head isomer increases at lower solvent polarity where the exciplex effect would be more pronounced.

An exception has been reported to the general rule concerning the regiochemistry of alkyne addition, and this involves the photoaddition of phenylacetylene to the enol form of an acyclic 1,3-diketone.⁽⁹²⁾ In this case, apparently only the head-to-tail isomer is obtained.

It has been found that whereas cyclopentenone additions to alkynes proceed with similar quantum efficiency to analogous additions to alkenes, the quantum yield of alkyne photoaddition to cyclohexenones is much lower.^(85,86) This is because in the latter case, the major fate of biradical intermediates is reversion to starting materials.⁽⁸⁵⁾ A consequence of this is that it is possible to add alkenes selectively to cyclohexenones in the presence of alkynes and this has been demonstrated in competition experiments.⁽⁶⁹⁾

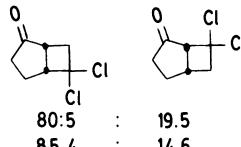
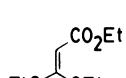
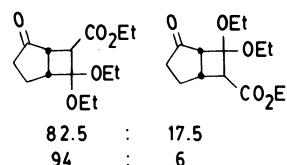
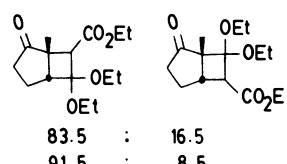
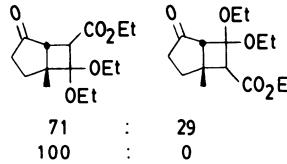
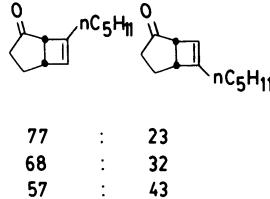
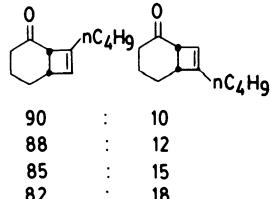
Allenes also add to enones in the opposite regiochemical sense to alkenes, giving the head-to-head adducts with very high selectivity,^(82,83) whilst ketenes have been shown to give the head-to-tail product preferentially⁽⁸⁷⁾ (Scheme 11).

The lack of control of regioselectivity in enone cycloaddition has been a limiting factor in its application in synthesis. To some extent solvent effects can be used to alter the product ratio; however, this is usually only capable of enhancing the observed regioselectivity rather than reversing it. Thus in the reaction shown in Scheme 8, the product is almost exclusively the head-to-tail isomer when the irradiation is performed in a nonpolar solvent whilst increasing polarity to its convenient limit does not raise the proportion of the head-to-head isomer above 50%.⁽³⁸⁾ Furthermore, the solvent effect is not usually this dramatic.⁽⁴¹⁾ Temperature also has an effect upon regioselectivity. Lowering temperature tends to increase the proportion of the regioisomer that would be expected if the product orientation is controlled by reaction of the more stable exciplex intermediate (Table 8).



SCHEME 11

Table 8. Temperature Effect upon Enone Photocycloaddition Regiochemistry

Ref.	Enone	Alkene	Temp.	Products
31			R.T. -75°C	
50			R.T. -40°C	
50		..	R.T. -40°C	
50		..	R.T. -40°C	
85		$\equiv nC_5H_{11}$	- 23°C 27 °C 77°C	
85		$\equiv nC_4H_9$	- 23°C 27 °C 77°C 127 °C	

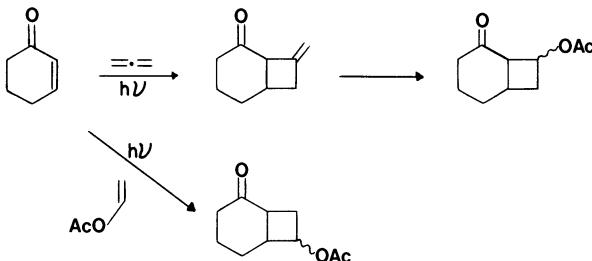
Attempts have been made to alter or enhance the regiochemistry of enone cycloaddition by placing directing groups on the alkene or enone which can later be removed. For example, a trimethylsilyl group placed in the 2 position of cyclopentenone increases the proportion of the head-to-tail isomer in its photoaddition with 2-acetoxypiprene and 2-methylpropene⁽⁴⁷⁾ (cf. Table 3). The silyl group can be removed subsequently with fluoride ion. However, the reaction fails for 2-trimethylsilylcyclohexenone⁽⁴⁷⁾ (the compound is inert to photochemical cycloaddition, as is commonly the case with 2-substituted cyclohexenones^(3,53)), and little change in product ratio occurs in the reaction between propene and 2-trimethylsilylcyclopentenone as compared with cyclopentenone itself.⁽⁴⁷⁾

An analogous perturbation has been found when the 2 position of the enone is substituted by a fluorine atom. In the case of uracil derivatives possessing a fluorine atom α to the enone carbonyl, head-to-tail isomers are obtained exclusively with 1,1-dialkylalkenes, whereas in the absence of the fluorine atom, substantial quantities of the head-to-head isomers are formed⁽⁴⁸⁾ (see Table 5). The photocycloaddition of 2-fluorocyclohexenones to 2-methylpropene has been observed to give the opposite result⁽⁶⁷⁾: whereas with cyclohexenone the major products have the head-to-tail orientation, with the 2-fluorocompound the major products are derived from the head-to-head mode of addition. However, the proportion of olefinic products arising from intramolecular disproportionation of the intermediate biradicals is greatly increased in the case where the fluorine substituent is present, reducing the synthetic utility of the reaction. Furthermore, the fluorine atom is difficult to remove.

The presence of halogen substituents at the 6 position of cyclohexenones has been shown to enhance the proportion of head-to-tail isomers in additions to 2-methylpropene; however, again the halogen atoms also appear to increase the amounts of olefinic by-products arising from biradical intermediate disproportionation.⁽⁶⁶⁾

A variation of the above approaches is to use disguised functionality on the alkene.⁽⁹⁶⁾ For example, cycloaddition between an enone and allene will yield the head-to-head regioisomer, which—following ozonolysis, selective reduction, and acetylation—will yield the regioisomer not obtained as the major product in the direct addition of vinyl acetate (Scheme 12).

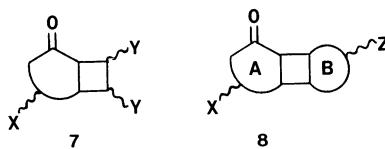
The regiochemical outcome of a number of enone cycloadditions has been altered and in some cases reversed by performing the reaction in micellar media.⁽⁴¹⁾ Under these conditions it appears that nonpolar substituents on both enone and alkene are solubilized in the interior of the micelle, and that this orienting effect dictates the regiochemistry of photoadducts (Figure 6). In Table 9, a comparison of the regiochemical outcome of a number of reactions in organic solvents and potassium dodecanoate micelles is given which demonstrates the magnitude of this effect.



SCHEME 12

4. Stereochemistry of Enone Cycloaddition

Structure **7** represents a typical photoadduct from a cyclic enone and an acyclic alkene and demonstrates the stereochemical possibilities which exist other than regioisomerism. The enone–cyclobutane ring junction can be *cis* or *trans*, substituents (Y) on the alkene can be *exo*- or *endo*-oriented and *cis* or *trans* with respect to each other, and remote substituents on the enone (X) can also adopt either of two configurations. In the case of adducts between cyclic enones and cyclic alkenes **8**, the cyclobutane–cycloalkene and cyclo-



butane–cycloalkanone ring fusions can be *cis* or *trans*, and if both cyclobutane ring junctions are *cis*, the enone- and cycloalkene-derived rings (A and B)

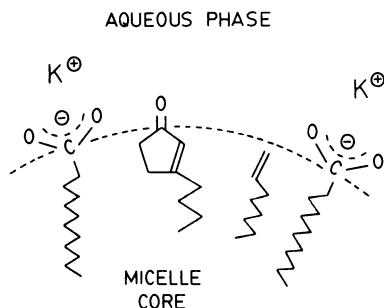


Figure 6. Rationalization of the effect of a micelle medium upon enone cycloaddition regiochemistry: hydrophobic groups on alkene and enone are oriented towards the micelle core, and so dictate the mode of approach of the reactants.

Table 9. Effect of a Micellar Medium upon Enone Photocycloaddition Regiochemistry^a

Enone	Alkene	Medium ^b	Products		
			51	:	49
			78	:	22
			53	:	47
			88	:	12
			75	:	25 ^c
			49	:	51 ^c
			100	:	0 ^c
			< 30	>	70 ^c
			88	:	9
			41	:	49

^a Taken from Reference 41.

^b Potassium dodecanoate was used as surfactant.

^c Product ratio determined following degradation.

can be *syn* or *anti* to each other. In addition, remote substituents (Z) on the cycloalkene ring can adopt either of two configurations.

Obviously, a large number of isomeric products can arise from a photocycloaddition reaction; however, usually not all the possible products are produced, and it is often possible to predict the stereochemical outcome of enone

additions. From the large number of enone photoadditions which have been reported, the following general statements concerning stereochemistry can be made:

(i) In the products from addition of cyclopentenone to alkenes, the cyclobutane-cyclopentanone ring fusion is always *cis*. Many examples are given in Table 3.

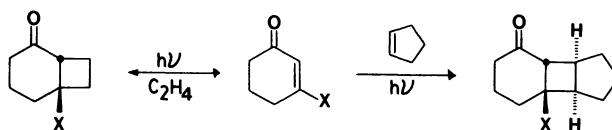
(ii) In the products from addition of cyclohexenone to alkynes, alenes, and cyclobutenes, the cyclobutane-cyclohexanone ring fusion is always *cis*. Examples can be seen in Tables 4 and 7.

(iii) In the products from addition of cyclohexenone to other alkenes other than those mentioned in (ii), the cyclobutane-cyclohexanone ring fusion can be *cis* or *trans*, and both configurations are often observed, giving mixtures of products. There is, however, a tendency for the *cis*-fused ring junction to predominate in adducts formed from highly electron-rich or electron-deficient alkenes; a number of examples are given in Table 4 and in Scheme 7.

There is also some evidence which suggests that adducts from cyclohexenones possessing charge or radical stabilizing functions at position 3 also give mainly *cis*-fused products (Scheme 13). However, the generality of these results has not been demonstrated, and they should be treated with care as it has been shown that epimerization of a *trans* adduct to give the *cis* isomer can occur very readily under mild acidic or basic catalysis,⁽³⁾ and in some cases can take place thermally during work-up.⁽⁹⁹⁾

(iv) In the products from the addition of alkenes to more rigid cyclohexenones the cyclobutane-cyclohexanone ring fusion is *cis*. Factors contributing to the rigidity of cyclohexenones are the presence of unsaturation or heteroatoms elsewhere in the ring, or fused rings adjoining the cyclohexenone ring (see Tables 4 and 5).

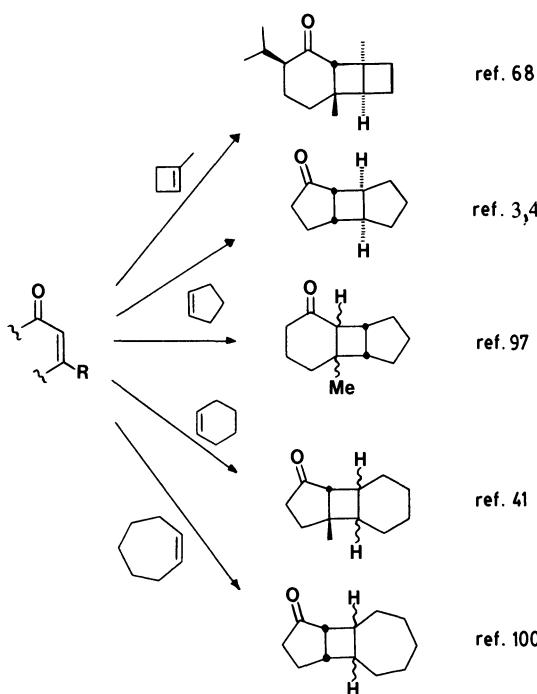
(v) In the products from the addition of enones to cyclobutenes and



X	Yield	Ref.
CO ₂ H	90%	98
CO ₂ Et	98%	..
CN	62%	..

X	Yield	Ref.
Ph	77%	97
OAc	68%	32,104
CN	63%	62
OMe	-	62

SCHEME 13



SCHEME 14

cyclopentenes, the cycloalkane–cyclobutane ring fusion is always *cis*, while with the larger cycloalkenes both *cis* and *trans* fusion is observed⁽¹⁰¹⁾ (Scheme 14).

(vi) In adducts between cycloalkenes and cyclic enones where the cyclobutane ring fusions to the enone and alkene derived rings are *cis*, the rings are preferentially *anti* to each other (Schemes 13 and 14).

(vii) In the adducts between enones and 1,2-disubstituted, acyclic alkenes the geometry of the alkene double bond is usually lost, giving a mixture of isomers (cf. Scheme 3). Similarly, addition of a mono-substituted alkene to an enone gives a mixture of adducts in which the substituent is *exo* or *endo*, often in approximately equal amounts (cf. Schemes 7,9,12).

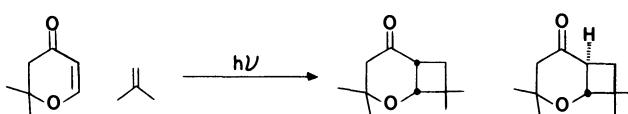
The mixtures of stereoisomers obtained in enone cycloaddition presumably arise because of the nonconcerted nature of the reaction; as depicted in Scheme 3 biradical intermediates can undergo rotation prior to closure to products, allowing loss of alkene stereochemistry, and the formation of *cis*- and *trans*-fused cyclobutane-cycloalkanone rings. With cyclic alkenes, small rings (cyclobutanes and cyclopentanes) can only close to give *cis*-fused prod-

ucts because of strain whereas large rings have sufficient conformational mobility that they can close to form a *trans*-ring fusion as well as *cis*.^(100,101) Similarly, when cyclopentenones add to alkenes, the biradical intermediate can only close onto the cyclopentanone ring to give a *cis*-ring fusion because of strain, whereas the six-membered ring containing biradical derived from a cyclohexenone has enough conformational mobility to form the *trans*-ring fused product.

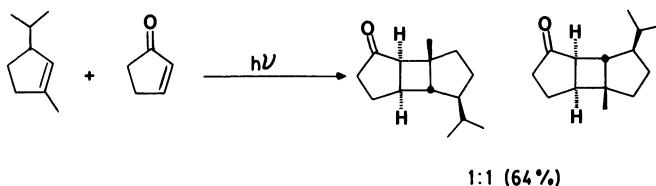
The formation of both *cis*- and *trans*-fused products from cyclohexenones and simple alkenes has been rationalized^(9,98) by assuming that the enone in its excited state is twisted about the carbon–carbon double bond and that this twisting is conserved for a short time in the biradical intermediate before the cyclohexanone ring relaxes to a more stable conformation. Short-lived biradicals might then be expected to close to *trans*-fused products if the activation energy for closure is not too high, whilst longer-lived biradicals could close to the *cis* fused product following conformational relaxation. However, the situation is complicated since in any enone cycloaddition there is always more than one possible biradical intermediate which may be involved and each has a choice of fates: reversion to starting materials or closure to give either *cis*- or *trans*-fused cyclobutanes. Since mixtures of products are usually obtained, the activation energies of these processes for the various biradicals involved must be quite similar, and consequently the stereochemistry of adducts produced from differently substituted enones and alkenes may never be more than qualitatively predictable using the empirical generalities (i)–(viii) given above.

As might be expected in a reaction where an intermediate biradical can partition to two products, the proportions of stereoisomers produced in a given cycloaddition reaction vary with temperature.^(15,22,31,102) For example, in the reaction shown in Scheme 15⁽²²⁾ the ratio of *trans*-fused to *cis*-fused product changes from approximately 1.65:1 at 200°K to 1.1:1 at 333°K corresponding to a difference in activation energies for closure of between 1 and 2 kcal mol⁻¹ (4 and 8 KJ mol⁻¹). This calculation assumes that there are only two biradical intermediates and not four (i.e., that the biradicals are formed by bonding to either the α or β position of the enone, but not both).

In alkenes where the two faces of the double bond are nonequivalent,



SCHEME 15

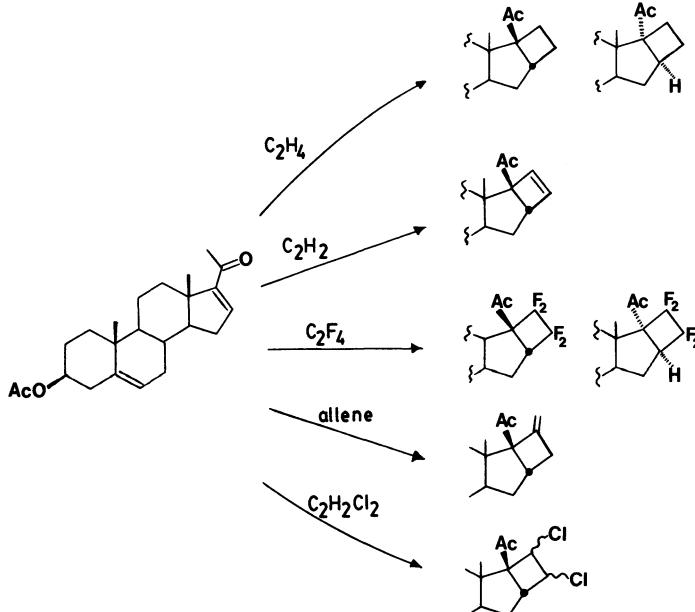


SCHEME 16

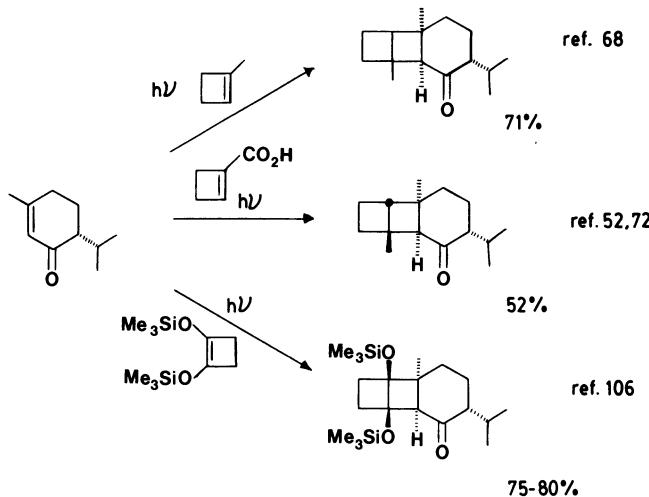
the major product of photoaddition to an enone is that arising from the approach of the enone from the least hindered side of the alkene. An example can be seen in Scheme 16⁽¹⁰⁵⁾.

Similarly, in enones where the two faces of the double bond are non-equivalent, the major product of photoaddition to an alkene is usually that arising from the least hindered mode of approach (Schemes 17, 18, and 19). A large number of additions of allene, and occasionally other alkenes, to a variety of rigid enone systems are known* where the alkene generally ap-

*Allene additions will be dealt with in detail in a separate section.

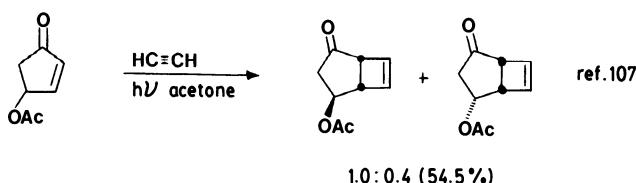


SCHEME 17

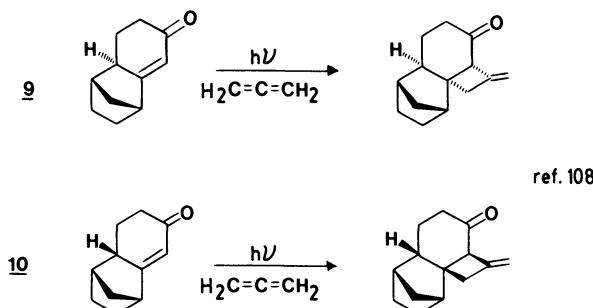


SCHEME 18

proaches from the less hindered face of the enone, but in a few cases the reverse is true and addition apparently occurs from the more hindered side. An example is shown in Scheme 20⁽¹⁰⁸⁾; the epimeric compounds **9** and **10** reacted photochemically with allene to give exclusively the products shown, where the alkene has added to **10** (Scheme 20) as might be expected on steric grounds, but has approached from the far more hindered face of the molecule in **9** (Scheme 20). Weisner has proposed an empirical rule, based upon many examples, to account for these directions of addition in cyclohexenones.⁽¹⁰⁸⁻¹¹⁰⁾ Wiesner's proposal is that in the α,β -unsaturated ketone excited state the α -carbon remains trigonal whilst the β -carbon becomes tetrahedral and is free to invert and select the more stable configuration. Overlap between the alkene and the orbital on the β -carbon then leads eventually to the observed product. Wiesner emphasizes that this proposal is a formalism which has



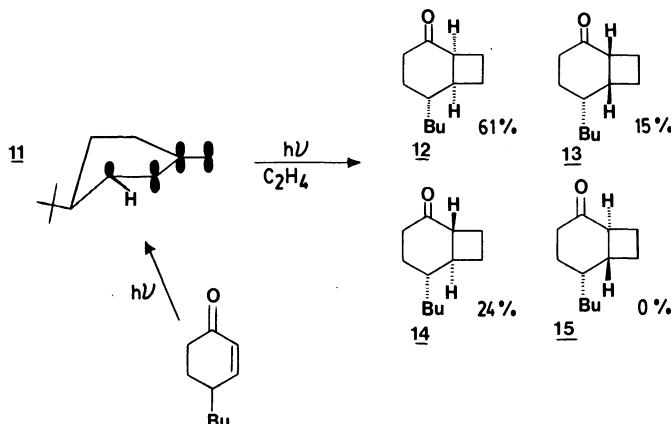
SCHEME 19



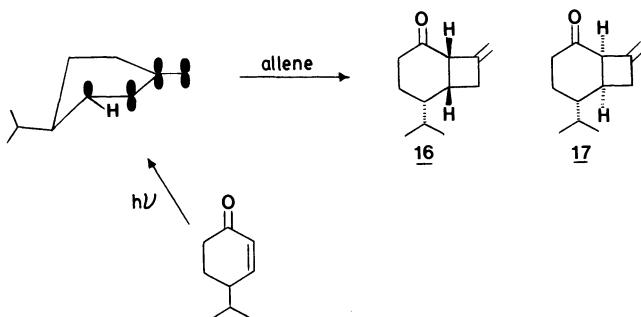
SCHEME 20

predictive value only, and is not meant to imply that the excited state exists in this form.

A consequence of Wiesner's proposal is that the stereochemistry of the β -carbon in the photoadduct should be similar to that of the product obtained by dissolving-metal reduction of the enone, and this can be used to predict the stereochemical outcome of a photoaddition.⁽¹⁰⁹⁾ In an attempt to test this empirical rule, Cargill has performed the photoaddition of 4-*t*-butylcyclohexenone with ethylene and obtained the products **12**, **13**, and **14** (Scheme 21). On the basis of Wiesner's proposal the enone would be expected to react from configuration **11** (Scheme 21) to give **13** (Scheme 21) or perhaps **15** (Scheme 21) as the major products, which is not in agreement with the



SCHEME 21



SCHEME 22

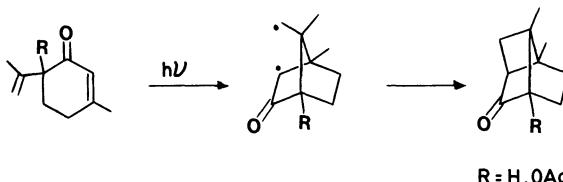
observed ratio.⁽¹¹¹⁾ Similarly, Wiesner has found that irradiation of 4-*i*-Pr-cyclohexenone with allene gives equal amounts of **16** and **17** (Scheme 22), although **17** (Scheme 22) would be expected as the major product.⁽¹¹¹⁾ These results are, however, consistent with a variation of Wiesner's proposal,⁽¹⁰⁸⁾ which is that the enone excited state is in fact planar and that pyrimidalization of the β -carbon occurs in the process of reaction with the olefin. This is more consistent with what is known about the geometry of relevant enone excited states.⁽³⁷⁾ In this case the stereochemical outcome of an addition will be decided by a combination of ease of steric approach and the energies of pyrimidalization which can be related to the stabilities of the configurational isomers produced.

Alternatively, it may be that the biradical intermediates formed by attack of alkene of either face of the enone revert to starting materials in differing proportions, with that leading to the product with the less stable configuration at C- β reverting more efficiently.

5. Intramolecular Enone Cycloadditions

The very first enone cycloaddition to be reported—the conversion of carvone to carvone-camphor⁽¹⁾ shown in Scheme 1—was an intramolecular reaction, and since that time many more intramolecular examples have been observed. Most of these involve alkene-substituted cyclopentenones or cyclohexenones in which the double bonds undergoing addition are separated by two or three atoms, although systems with greater separation have also been shown to react.

The regiochemistry of intramolecular addition appears to be quite predictable; with few exceptions, dienones in which the double bonds are 1,5 to



SCHEME 23

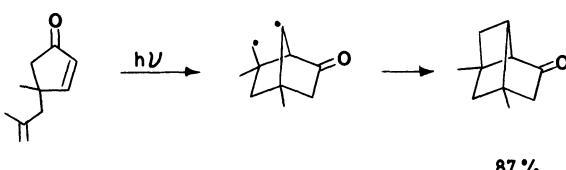
each other (i.e., separated by two atoms) obey what has been termed the “rule of five” which was described above and illustrated in Scheme 10. Further examples are shown in Schemes 23⁽¹¹²⁾ and 24⁽¹¹³⁾.

In dienones where the reacting double bonds are 1,6 to each other (i.e., separated by three atoms) the “rule of five” is usually adhered to, but products are also observed which are derived apparently from a biradical in which a six-membered ring has been formed, even though a five-membered ring isomer is possible (Scheme 25^(103,114-116) and Scheme 26^(66,117)). One of the products in Scheme 25 has been used in a synthesis of the natural product isocomene⁽¹¹⁵⁾ and another in a synthesis of the skeleton of the sesquiterpene modhephene⁽¹⁰³⁾ (Scheme 27).

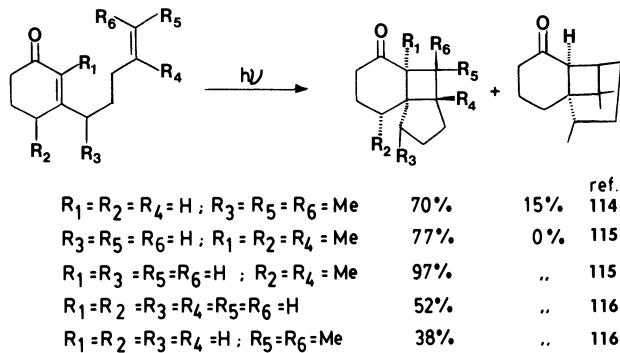
Allenes obey the rule, but with ketenes the carbonyl group dictates the regiochemistry of addition^(87,118) (Scheme 11). In some systems both orientations of double-bond addition can lead to biradical intermediates in which a five-membered ring has been formed. In these cases both possible regioisomeric products can be obtained.^(119,120) (e.g., Scheme 28).

A cycloaddition in a system where the double bonds are 1,4 to each other has been reported in a synthesis of the hirsutene ring system (Scheme 29). The product is thought to arise through opening of the intermediate cyclopropane by solvent.⁽¹²¹⁾

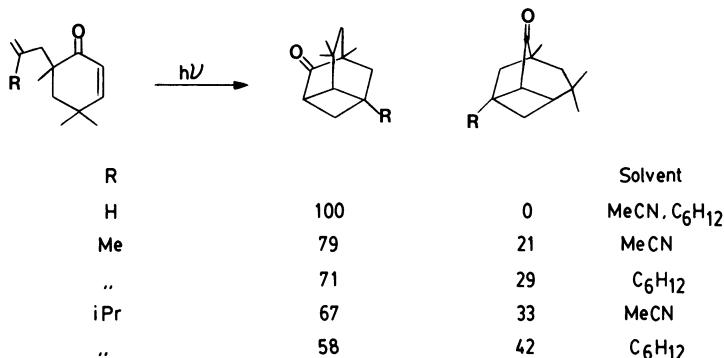
Normally, the photoaddition of alkenes to acyclic enones is very inefficient, to the point of being rarely observed. This is probably because of the short excited-state lifetime of these compounds; unimolecular decay by *cis*-



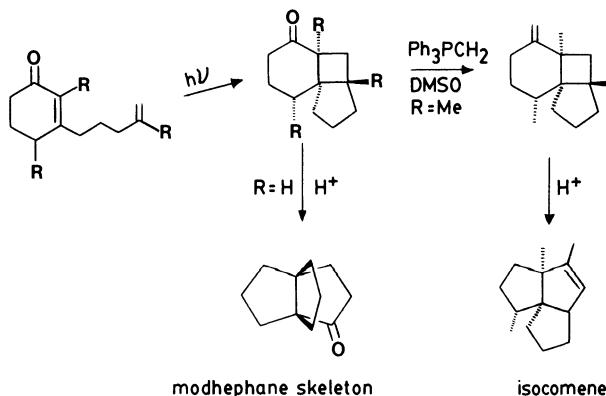
SCHEME 24



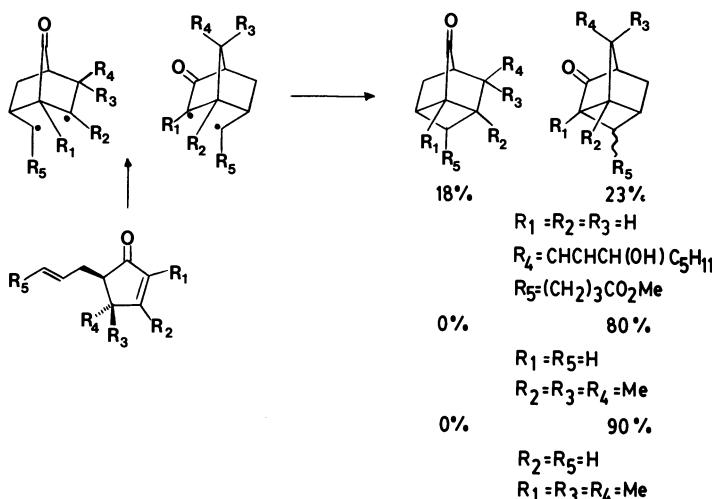
SCHEME 25



SCHEME 26

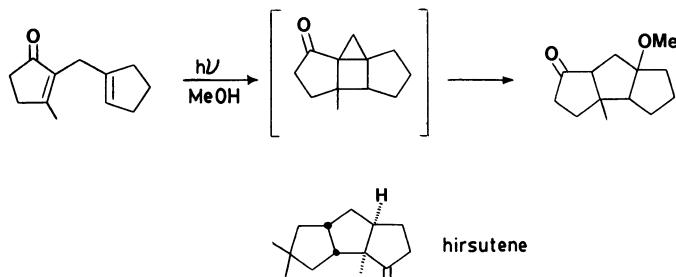


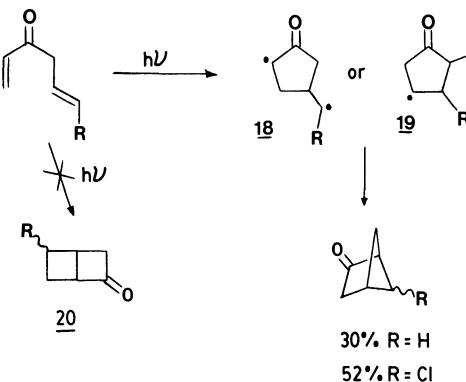
SCHEME 27



trans isomerization around the α,β -double bond is faster than biomolecular events. However, if an alkene is present in the same molecule the excited state can be trapped quite efficiently, and this has been the basis of a number of syntheses of bicyclo[2.1.1]hexane systems. Some examples are shown in Schemes 30⁽¹²²⁾ and 31^(123,124); the products can be visualized as being derived from the “rule of five” biradicals **18** and **19** depicted in Scheme 30 and none of the alternative bicyclo[2.2.0]hexanone isomer **20** (Scheme 30) is formed. The amino acid **21** (Scheme 31) is a naturally occurring insect antifeedant.

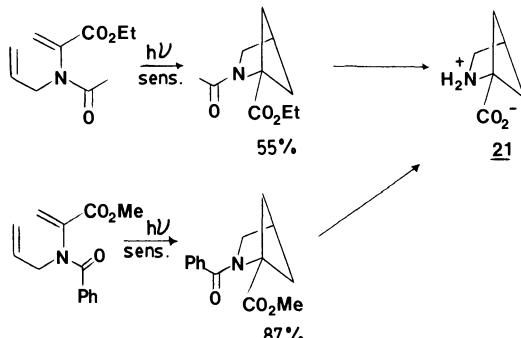
Another case of this mode of addition was seen in Scheme 2, except that the major product was derived from disproportionation of the intermediate biradical and only a minor amount of the bicyclo[2.1.1]hexane was formed.⁽²³⁾



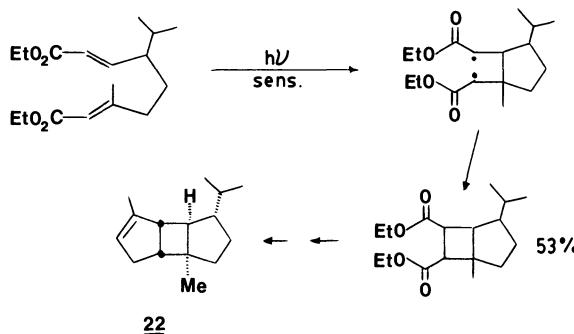


An analogous example of the “rule of five” in an acyclic system also occurs in Scheme 32 in a synthesis of the natural product α -Bourbonene **22**.⁽¹²⁵⁾ In this case the presumed intermediate biradical does not have as suitable a γ -hydrogen atom to abstract, and only ring closure is observed.

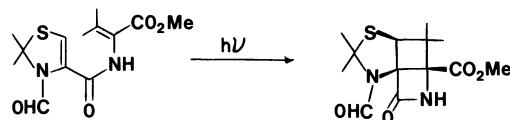
An example of disobedience to the “rule of five” is shown in Scheme 33⁽¹²⁶⁾ in a reaction leading to a β -lactam. Presumably, in this case where all the atoms involved are trigonal, strain prevents the normal mode of addition. In Scheme 34, a large-ring enone, which would normally be expected to be unreactive because of rapid *cis-trans* isomerization, undergoes intramolecular cycloaddition to give appreciable amounts of the non-“rule-of-five” product **23** (Scheme 34) along with the expected adduct **24** (Scheme 34) as the major component.⁽¹²⁷⁾ Another example is given in Scheme 35⁽¹²⁸⁾; in this case a concerted, singlet excited-state process is possible.



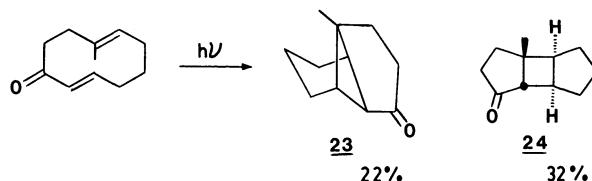
SCHEME 31



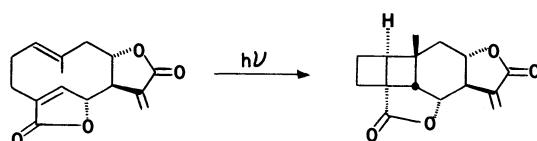
SCHEME 32



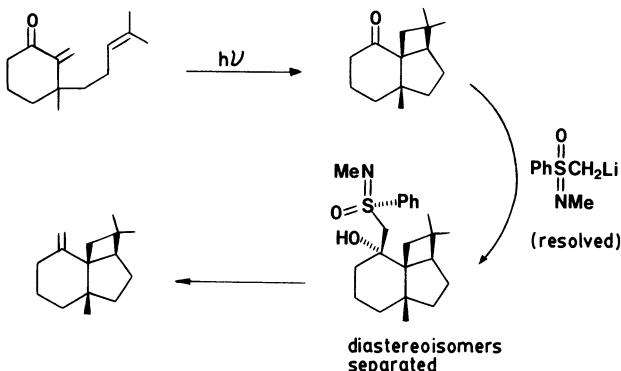
SCHEME 33



SCHEME 34



SCHEME 35



SCHEME 36

An intramolecular addition to a cyclohexenone possessing an exocyclic double bond has been published⁽¹²⁹⁾ in a synthesis of the natural product panasinsene (Scheme 36). The carbonyl group in the photoadduct is unreactive towards Wittig methylenation, but could be converted using the sulfonimide shown. Use of this was made in a resolution of the intermediate prior to elimination (see Scheme 36). This synthesis is especially interesting in that the direct photoaddition of 2-methylpropene to the enone **25** failed.⁽¹²⁹⁾

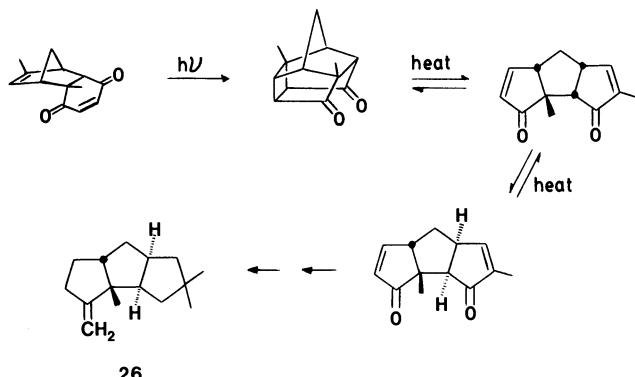


A large number of intramolecular cycloadditions of Diels–Alder adducts of cyclopentadiene with cyclopentenones and cyclohexenones to give cage compounds has been reported and the earlier work has been reviewed.⁽¹³⁰⁾ A recent example, utilized in a synthesis of the natural product hirsutene, **26**, is shown in Scheme 37.⁽¹³¹⁾

The intramolecular cycloaddition reactions of enolized 1,3-cyclopentanediones and 1,3-cyclohexanediones and their derivatives have been the subject of many studies and these will be discussed in the next section.

6. The de Mayo Reaction

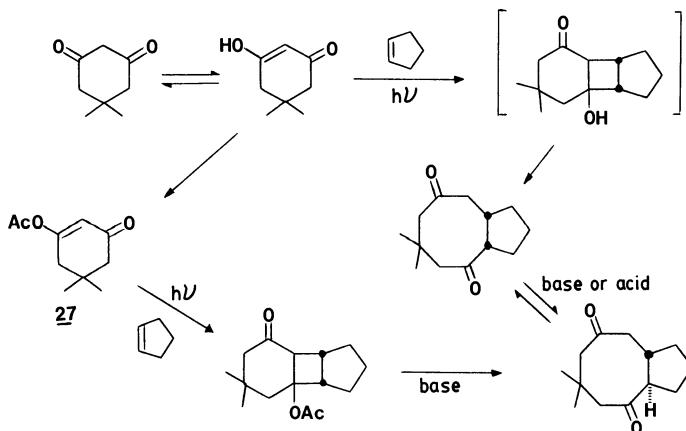
The photochemical addition of alkenes to enolized 1,2- or 1,3-diketones and their derivatives is often referred to as the de Mayo reaction. The reaction may be classified into three divisions: addition to enolized cyclic diones, addition to enolized acyclic diones, and intramolecular additions.



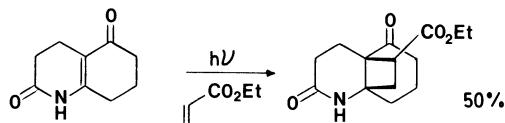
SCHEME 37

6.1. Cyclic Diketones

Cyclohexane-1,3-diones in solution are partially enolized, and exist in equilibrium with the corresponding 3-hydroxycyclohex-2-ene-1-ones. Whereas the nonenolized dione possesses a saturated carbonyl chromophore (λ_{max} ca. 290 nm), the enolized form exhibits an intense $\pi-\pi^*$ absorption at ca. 250 nm. When this band is irradiated in the presence of alkenes adduct formation is efficient^(32,55,102,104,132-135) (Scheme 38 and Table 4). Unless the enol has been



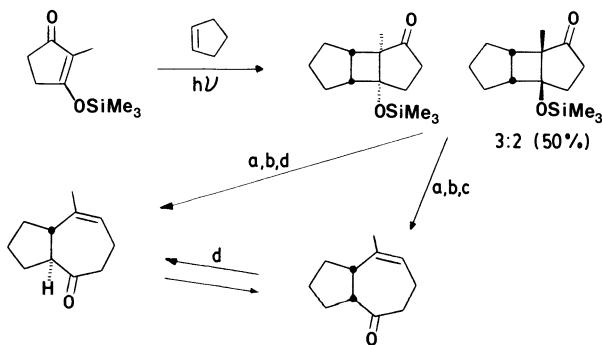
SCHEME 38



SCHEME 39

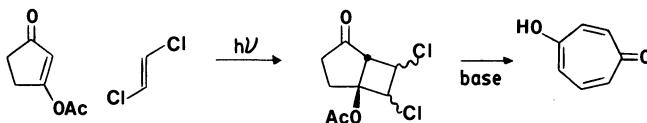
stabilized by derivatization, the primary adduct is not isolated, but undergoes retro-aldol opening to a cyclooctanedione. Cyclopentane-1,3-diones react similarly, giving cycloheptanediones as the ultimate products (cf. Table 3). Enolized cycloalkane-1,3-diones in which the 3-hydroxy group has been replaced by other heteroatoms also react^(41,62,76,136) (e.g., Scheme 39 and the last entry in Table 3).

In the addition of cyclopentene to dimedone (Scheme 38) the initial adduct is *cis*-fused at the cyclobutane–cyclopentane ring junction as expected, and this is maintained in the retro-aldolized product. However, if the latter is treated with acid or base, or heated, epimerization occurs to the more stable *trans*-fused cyclooctane–cyclopentane system.⁽¹³⁹⁾ Because cycloalkane-1,3-diones are rather insoluble, it is frequently advantageous to use the acylated analog (27 in Scheme 38); however, epimerization of the diketone product then becomes unavoidable during subsequent deacylation. This problem has been overcome by silylating the diketone rather than acylating, which allows the initial adduct to be deprotected and retroaldolized under non-epimerizing conditions⁽¹³⁷⁾ (Scheme 40).



a LAH, b MsCl, c KF, d base

SCHEME 40

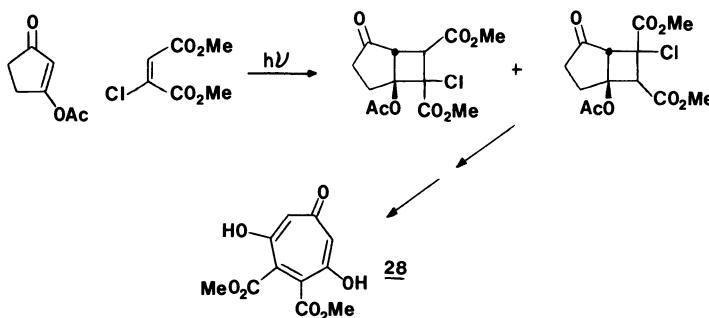


SCHEME 41

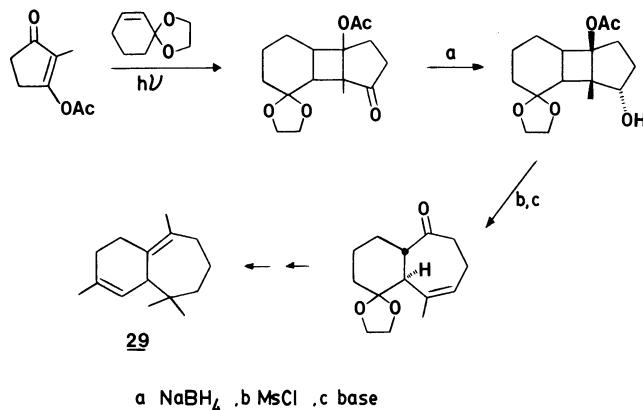
Alkene additions to cyclopentane-1,3-diones and cyclohexane-1,3-diones provide examples of some of the earliest natural product syntheses via enone cycloaddition. Irradiation of the acetyl stabilized enol of cyclopentane-1,3-dione in the presence of 1,2-dichloroethylene yields γ -tropolone after base treatment of the photoadducts⁽¹³²⁾ (Scheme 41), and an analogous reaction was applied⁽⁵⁵⁾ to the synthesis of stipitatic acid, **28** (Scheme 42).

The synthesis of β -himachalene, **29** (Scheme 43) makes use of the solvent effect upon regiochemistry described in an earlier section,⁽⁵⁵⁾ and a recent synthesis of the fungal metabolite hirsutene, **26**, utilizes essentially the same photoreaction⁽¹³⁸⁾ (Scheme 44). A much shorter route to the hirsutene skeleton, also using a de Mayo reaction, is shown in Scheme 45.⁽¹³⁹⁾

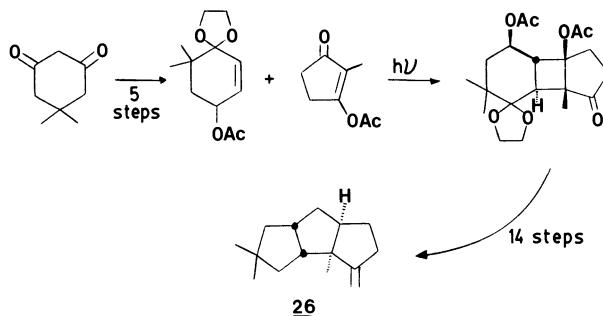
Photochemical cycloaddition to enolized 1,2-cyclohexanediones does not proceed⁽⁵³⁾; like other 2-substituted cyclohexenones it is inert when irradiated with alkenes. However, enolized cyclopentane-1,2-diones do undergo the reaction⁽⁵³⁾ (Scheme 46) and this has been applied in syntheses of methyl isomarasmine **30** (Scheme 47)⁽¹⁴⁰⁾ and acorenone, **31** (Scheme 48).⁽¹⁴¹⁾ A key step in these syntheses is the base-catalyzed rearrangement of the photoadduct following deacetylation to give a bicyclo[2.2.1]heptane system which can be cleaved with lead tetra-acetate to a 4-carboxycyclohexanone.



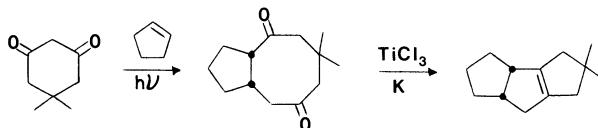
SCHEME 42



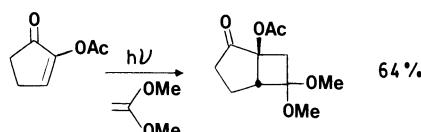
SCHEME 43



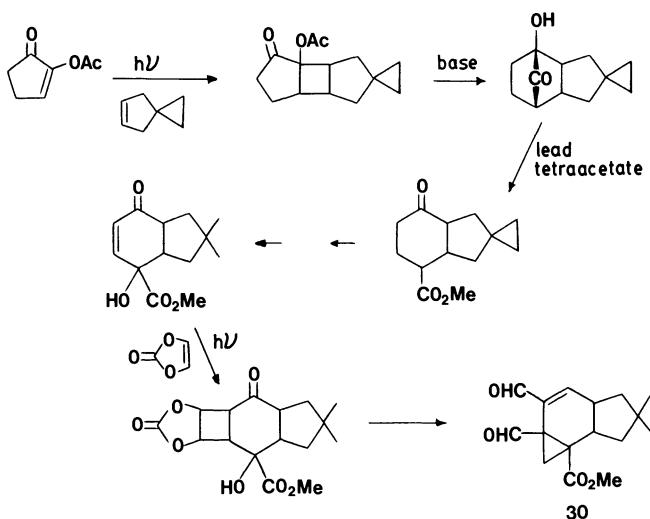
SCHEME 44



SCHEME 45



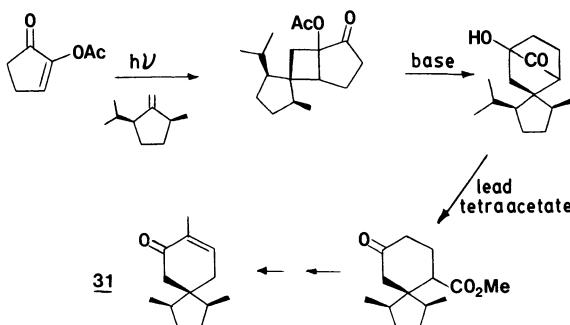
SCHEME 46



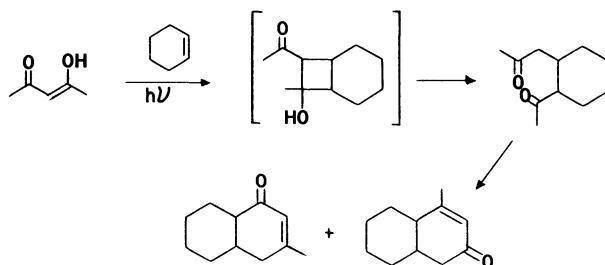
SCHEME 47

6.2. Acyclic 1,3-Diketones

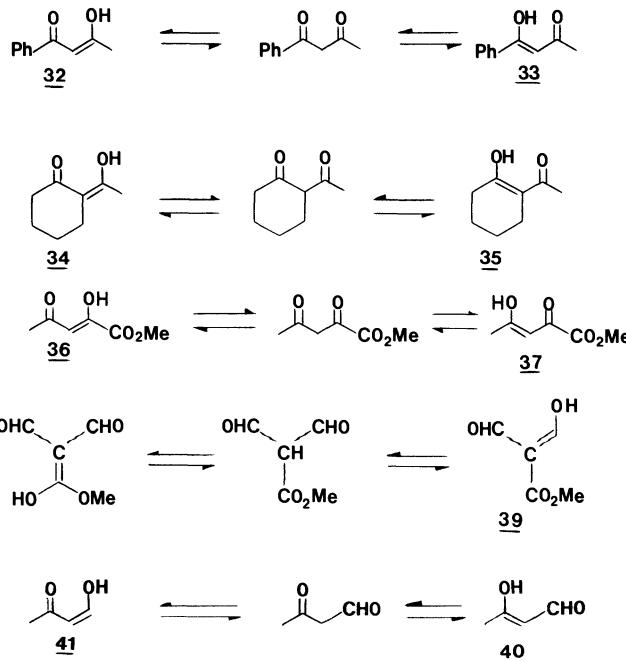
Irradiation of acetylacetone in the presence of an alkene results in cycloaddition to form an acyl cyclobutanol which undergoes a retro-aldol reaction to yield a 1,5-diketone (Scheme 49).^(2,90,142) The reaction proceeds via excitation of the enol form of the diketone, and adduct formation competes effectively with *cis-trans*-isomerization, presumably because the rate of the latter process is reduced by intramolecular hydrogen bonding between ketone and enol. The 1,5-diketones isolated as products can be cyclized in acid or base to yield cyclohexenones⁽²⁾ (Scheme 49).

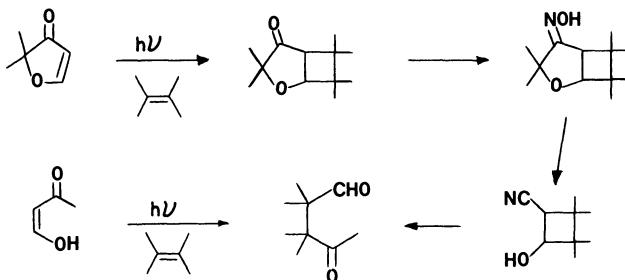


SCHEME 48



Nonsymmetrical β -diketones can enolize in two directions: in the systems which have been studied, reaction normally occurs preferentially from a single enol form, even though both may be present. For example, benzoyl acetone can enolize to give **32** and **33**, but the adducts obtained arise solely from addition to **33**.⁽⁹²⁾ With 2-acetylcyloalkan-1-ones, of the two possible enols **34** and **35**, only the exocyclic isomer **34** reacts to give isolable products⁽¹⁴²⁾ whilst methyl acetylpyruvate produces photoadducts derived from **36** and not from **37**.⁽¹⁴³⁾ Similarly, methyl diformylacetate yields adducts derived from **39** and not from **38**,^(94,95,144) and formyl acetone reacts from **41** and not **40**.^(145,146)



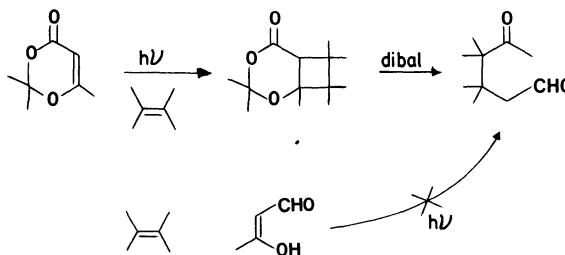


SCHEME 50

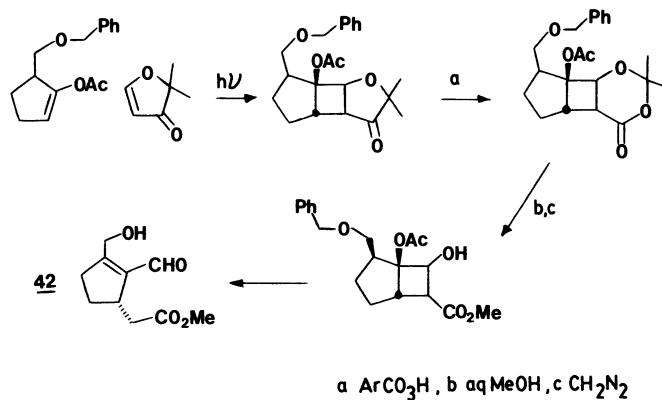
In the last example, improved yields and regiochemical control could be obtained by using a trapped form of the enol⁽⁵⁸⁾ (Scheme 50), and the product which would be derived from the alternative enol, **40**, if it were reactive, could be obtained by chemical transformation of the adduct from a similar trapped enol⁽⁷⁵⁾ (Scheme 51). The trapped enol in the last scheme is equivalent to a β -keto ester, and since these do not undergo enone cycloaddition⁽¹⁴⁷⁾ the procedure provides a route to adducts derived from them. This has been used in a synthesis of a compound whose structure, **42**, has previously been ascribed incorrectly to the natural product genipic acid⁽¹⁴⁸⁾ (Scheme 52).

It has been pointed out that pyrimidines can perform the same function and act as formyl acetate equivalents (Scheme 53).^(149,150) A related example can be seen in Scheme 54 in which the substituted pyrimidine **43** is prepared. This compound has been isolated from DNA.⁽¹⁹²⁾ Other examples of alkene photoaddition to trapped enols of β -dicarbonyl compounds are given in Table 5.

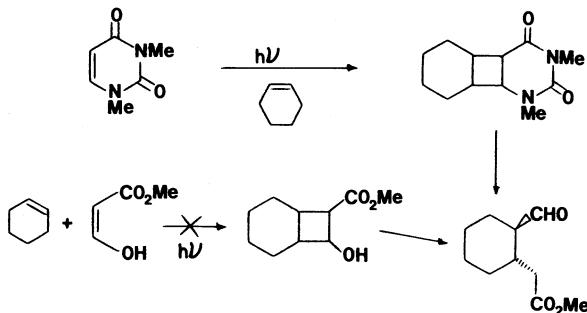
An efficient synthesis of valerane, **44**, and isovalerane, **45**, has been achieved by irradiating an enolized α -formyl acetone with 1,2-dimethylcyclohexene (Scheme 55); interestingly, not only is the chemical yield of ph-



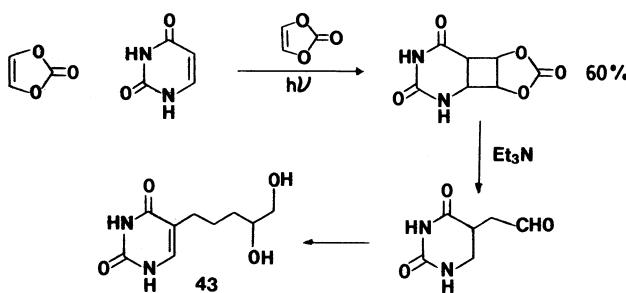
SCHEME 51



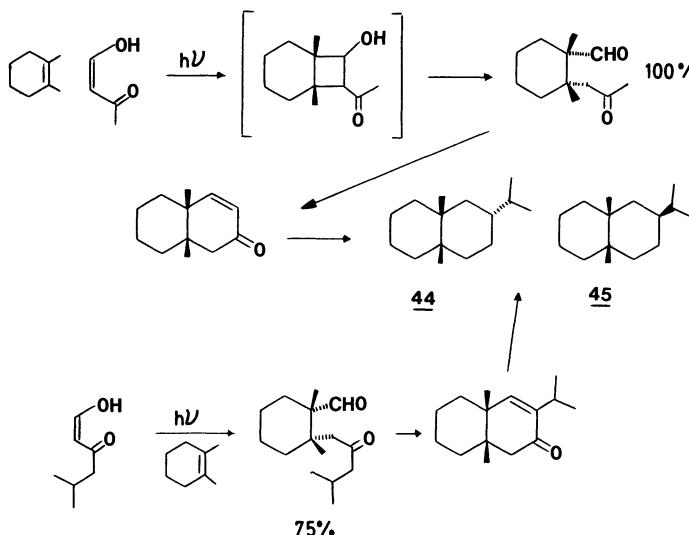
SCHEME 52



SCHEME 53



SCHEME 54



SCHEME 55

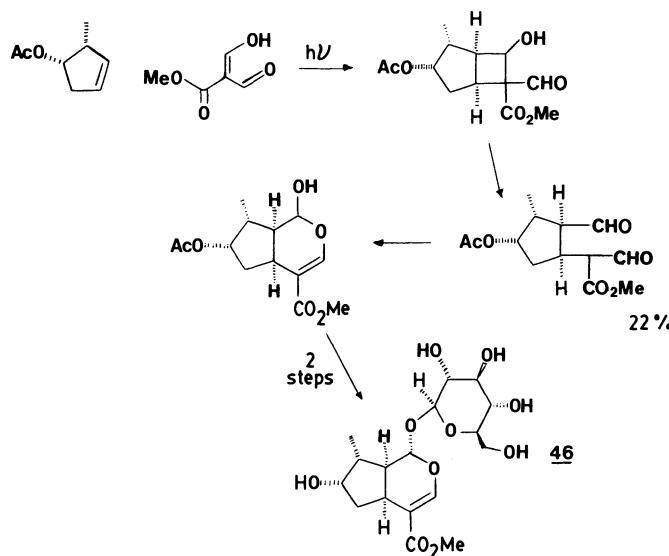
toadduct very high, but also the stereochemistry of the cyclobutane-cyclohexane ring junction is exclusively *cis*.⁽¹⁴⁶⁾

Two syntheses of loganin, **46**, have appeared using as their starting materials methyl diformylacetate, which, in its enolized form, is added photochemically to cyclopentene derivatives. The route shown in Scheme 56⁽⁹⁵⁾ is shorter, but the cycloaddition is less selective than the approach in Scheme 57.⁽¹⁴⁴⁾

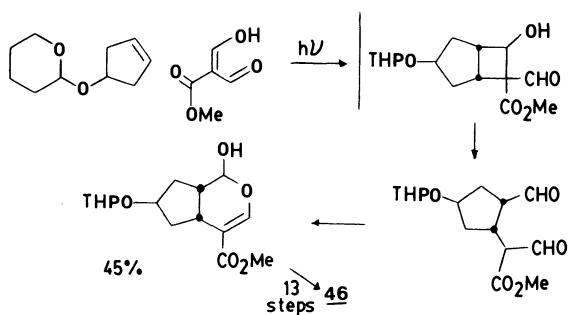
6.3. Intramolecular Additions of Enolized Diketones

As with other types of intramolecular enone cycloaddition described in the previous section, the regiochemistry of intramolecular addition of non-symmetrical alkenes to the double bond of enolized cyclohexane-1,3-diones and cyclopentane-1,3-diones is quite predictable, the major product being that formally derived from the biradical in which a five-membered ring has been constructed, or in which a six-membered ring has been formed if a five-membered ring is not possible. Examples involving cyclohexane-1,3-diones are illustrated in Schemes 58^(151,152) and 59^(153,154) and in Scheme 60 an example involving a cyclopentane-1,3-dione is shown which has been used in a synthesis of the natural product β -bulnesene, **47**.⁽¹⁵⁵⁾

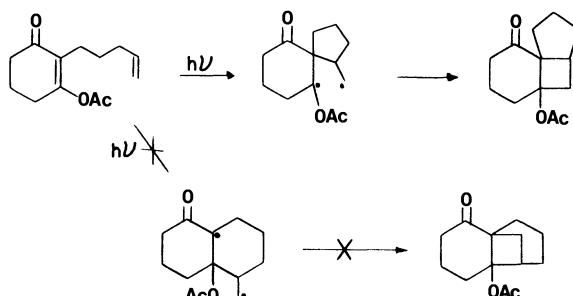
In some intramolecular additions to enolized cyclopentane-1,3-diones two products are possible, both obeying the "rule of five," corresponding to both regiochemical modes of addition of the alkene (Scheme 61). In the



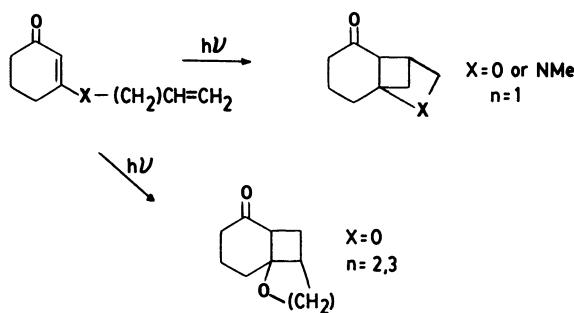
SCHEME 56



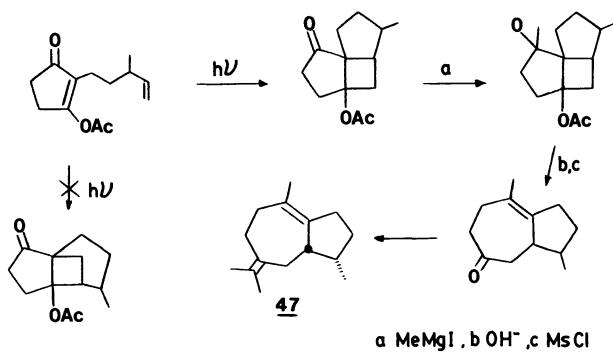
SCHEME 57



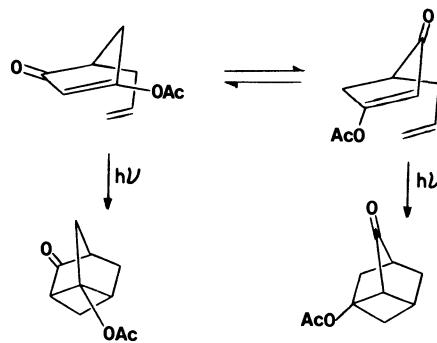
SCHEME 58



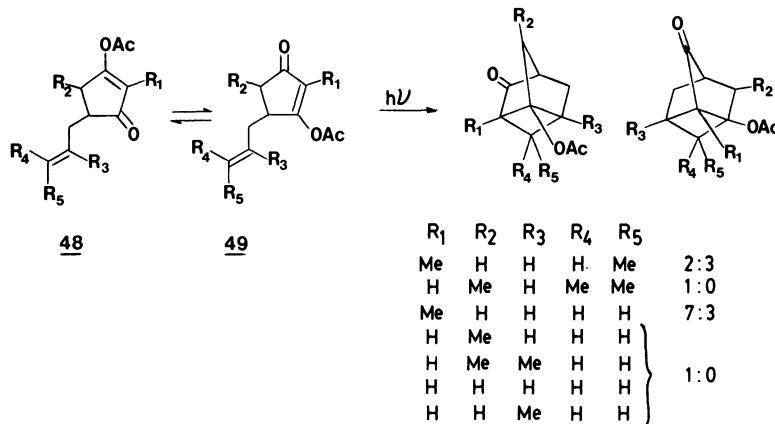
SCHEME 59



SCHEME 60



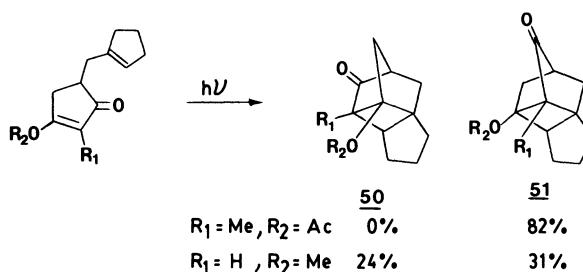
SCHEME 61



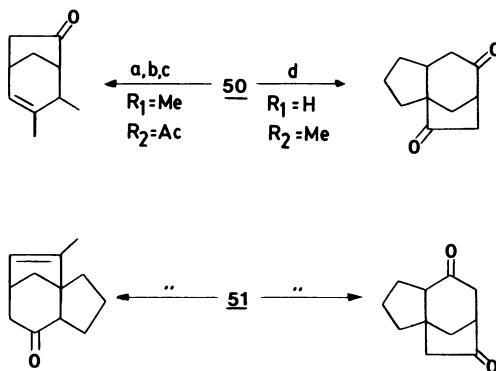
SCHEME 62

systems which have been investigated,^(156,157) it has been found that both products are obtained, their relative proportions depending upon the substituents on the enone and the alkene (Schemes 62 and 63). For the enolized cyclopentane-1,3-diones in Scheme 62, the two possible directions of enolization are nonequivalent and a mixture of 3-acetoxy-cyclopent-2-ene-1-ones are observed when the diketone is acetylated (structures 48 and 49). However, it is found that irradiation of the mixture yields, at high conversion, adducts derived from one isomer only, suggesting that 48 and 49 (Scheme 62) are in equilibrium under the reaction conditions.⁽¹⁵⁶⁾

The photoadducts shown in Scheme 63 have been fragmented to give the carbon skeleton of the zizaane and gibberellane groups of sesquiterpenes (Scheme 64).^(156,157)



SCHEME 63



a NaBH_4 , b MsCl , c OH^- , d $\text{BF}_3\text{Et}_2\text{O}$

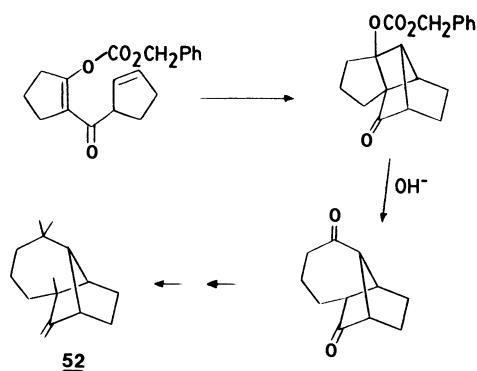
SCHEME 64

Longifolene, **52**, has also been synthesized by an intramolecular de Mayo reaction⁽¹⁵⁸⁾ and the route is shown in Scheme 65. The initial adduct is decarbobenzoylated with base and undergoes retro-aldol opening to yield the longifolene skeleton, which is then readily converted to the natural product.

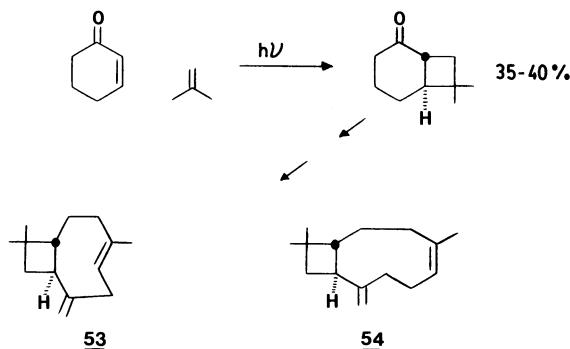
7. Intermolecular Enone Cycloaddition

The cycloaddition of enones to alkenes suggests an obvious route into cyclobutane-containing natural products. As well as determining the main stereochemical limitations of the reaction, Corey's group was one of the first to demonstrate its synthetic utility for this purpose. The synthetic targets were caryophyllene **53** and isocaryophyllene **54**, and the cyclobutane ring present in these compounds was generated by 2-methylpropene addition to cyclohexenone^(3,159) (Scheme 66).

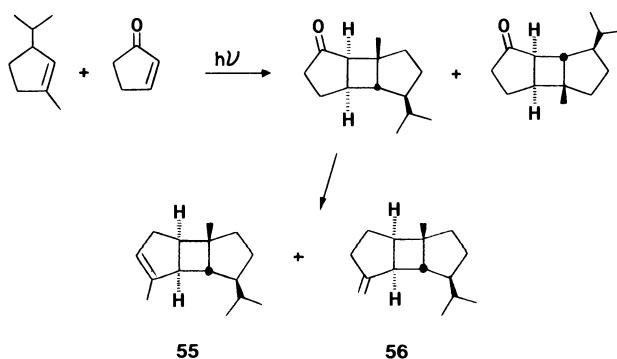
The sesquiterpenes α - and β -bourbonene, **55** and **56**, have also been prepared^(105,160) by intermolecular enone addition (Scheme 67), and of the many syntheses⁽¹⁶¹⁾ of the male boll weevil pheremone grandisol, **57**, no less than nine utilize enone cycloaddition for construction of the cyclobutane skeleton. One of the earliest of these syntheses, that shown in Scheme 68,⁽¹⁶²⁾ is unusual in two respects: it provides an example of an acyclic enone undergoing cycloaddition, and it involves addition to a diene, isoprene. Such a diene is of lower triplet energy than the enone and would be expected to quench its excited state rather than adding to it. This anomaly has been noted in other systems.⁽¹⁶³⁾



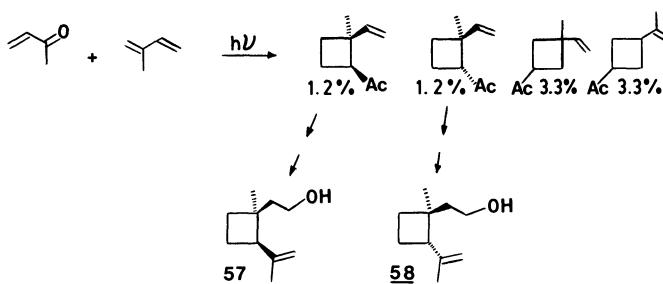
SCHEME 65



SCHEME 66



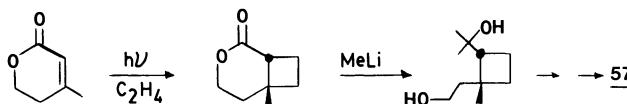
SCHEME 67



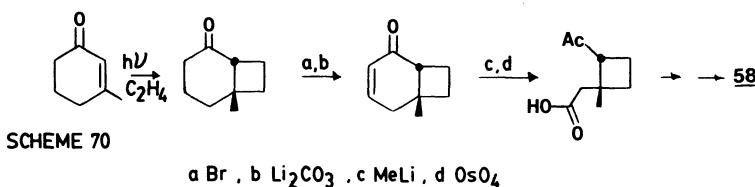
The above synthesis of grandisol suffers from poor regiochemical and stereochemical control, and the yields are very low, although it does lead to an isomeric natural product, fragrantol, **58**. An improved synthesis from the same laboratory⁽¹⁶⁴⁾ and others,^(60,165) utilizes a cyclic enone which adds efficiently to ethylene to give the desired *cis*-disubstituted cyclobutane skeleton (Scheme 69). A related route is shown in Scheme 70.⁽¹⁶⁶⁾

Two routes to grandisol have been developed from the photoadduct **59** formed by irradiation of 3-methylcyclopentene with ethylene^(167,168) (Scheme 71), and in a third route the adduct from 3-carboethoxycyclopentenone and ethylene is resolved prior to transformation into **59**, furnishing a synthesis of optically active grandisol.⁽¹⁶⁹⁾ Grandisol has also been prepared by an intramolecular cycloaddition of eucarvone⁽¹⁷⁰⁾ (Scheme 72).

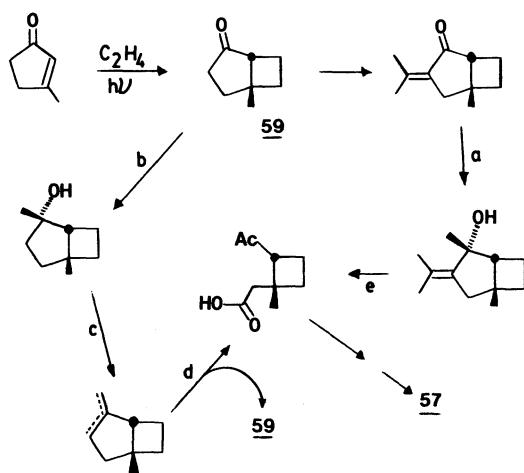
The synthesis of the terpene lineatin, **60**, demonstrates the problems of regiochemical and stereochemical control in enone cycloaddition (Scheme 73).⁽⁴⁶⁾ Addition of vinyl acetate to 3-methylcyclopentenone produces a mixture of stereo- and regioisomers, only one of which is required for the synthesis. Ketalization, hydrolysis, and oxidation produce a pair of separable regioisomers, and that corresponding to head-to-tail addition of vinyl acetate is stereoselectively reduced and acetylated to yield the original photoadduct with the desired stereochemistry and regiochemistry. This is then carried through to the natural product.



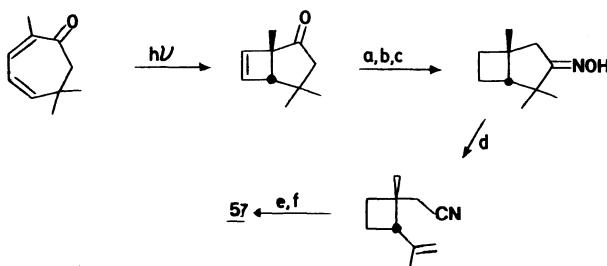
SCHEME 69



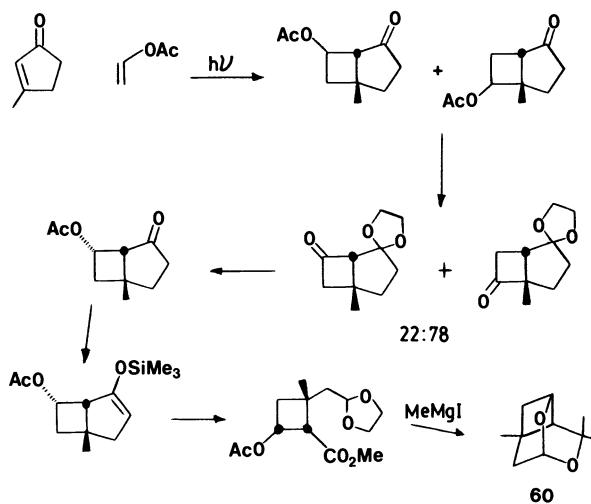
SCHEME 70



SCHEME 71

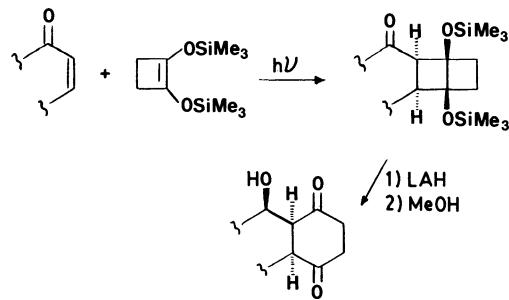


SCHEME 72

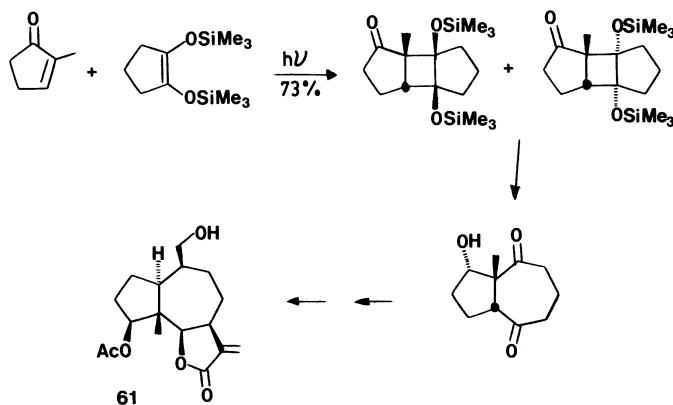


SCHEME 73

The photoaddition of cyclobutenes to enones followed by opening of the resulting bicyclo[2.2.0]hexanes has been used for the synthesis of a number of naturally occurring compounds. For example, addition of 1,2-bis(trimethylsiloxy)cyclobutene to cyclopentenones or cyclohexenones followed by an unusual oxidative opening with methanol provides an entry into the *cis*-fused hydrindane and decalin skeletons⁽¹⁰⁶⁾ (Scheme 74). If 1,2-bis(trimethylsiloxy)cyclopentene is used, the bicyclo[3.2.0]heptane adduct does not open upon treatment with methanol, but instead requires oxidative cleavage with lead tetraacetate.⁽¹⁷¹⁾ This has been used in a synthesis of the pseudoguaianolide hysterin, **61** (Scheme 75).⁽¹⁷²⁾

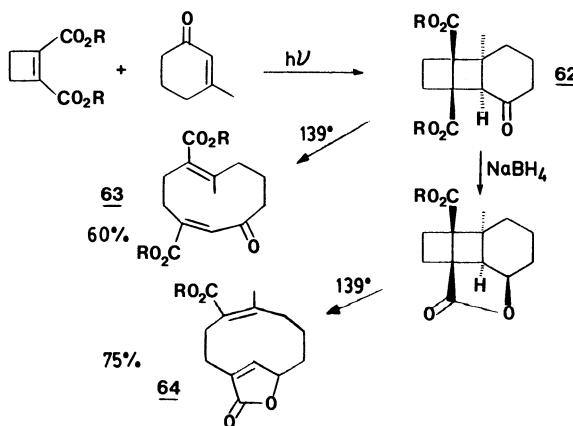


SCHEME 74

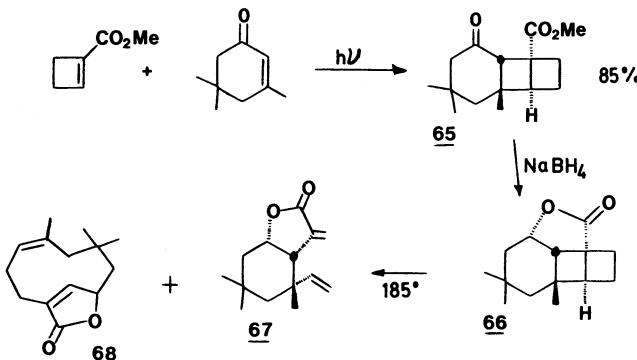


SCHEME 75

Thermal opening of bicyclo[2.2.0]heptane adducts derived from cyclobutene addition to cyclic enones has been investigated by three groups.^(52,68,70-73,173-175) The ring-opening reactions are thought to proceed through biradical intermediates rather than a concerted $\sigma_s^2 + \sigma_a^2$ electrocyclic reversion pathway⁽¹⁷⁷⁾; however, the ring opening often appears to proceed with a high degree of stereoselectivity. For example, addition of 1,2-bis(carbomethoxy)cyclobutene to 3-methylcyclohexenone gives an adduct **62** (Scheme 76) which when thermolized gives **63** in 60% yield. If, however, the cyclohexanone carbonyl is reduced prior to thermolysis, lactonization occurs



SCHEME 76

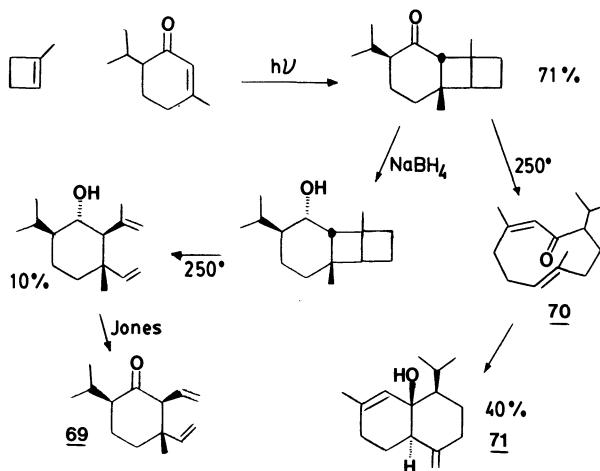


SCHEME 77

and ring opening gives **64** (Scheme 76) in 75% yield. Neither product corresponds to that which would be expected if ring opening was concerted. A related example is shown in Scheme 77⁽⁷³⁾; photoaddition of 1-carbomethoxy-cyclobutene to isophorone gave a single photoadduct isomer **65** which lactonized to **66** following reduction of the ketone function. Heating at 185° gave two products, **67** and **68**, in the ratio 1:2, derived from the two possible modes of opening of the bicyclo[2.2.0]hexane skeleton of **66**. It was shown that **67** and **68** must each have been formed directly from **66** (rather than either one being formed initially followed by equilibration to the other via a Cope rearrangement) because the product mixture was stable to the reaction conditions, and formed an equilibrium mixture of **67** and **68** in the ratio 2:1 when heated to 240° . It should be noted that concerted opening of **66** would give **68** with *Z, Z* or *E, E* double bond geometries rather than *E, Z*, which is obtained.

The ring-opening of a bicyclo[2.2.0]hexane to give a divinylcyclohexane such as **67** has been utilized⁽⁶⁸⁾ in a synthesis of the natural product shyobunone **69** (Scheme 78). In this case, if the cyclohexanone is not reduced prior to thermolysis, the alternative mode of opening of the bicyclohexane can also occur competitively to give an intermediate cyclodecadiene **70** analogous to **68**. This may be in equilibrium (Cope rearrangement) with its divinylcyclohexane isomer. Cyclodecadiene **70** then undergoes an irreversible transformation involving an intramolecular ene reaction to give **71**.^(68,72) This has been used in a synthesis of the cadinane group sesquiterpene calameon **72** (Scheme 79).⁽¹⁷⁴⁾

In a variation of this rearrangement, the carbonyl group has been replaced by a methylene function, and the thermal-opening-ene-reaction transforma-

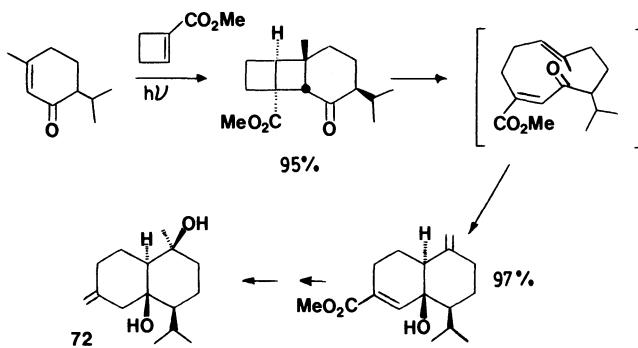


SCHEME 78

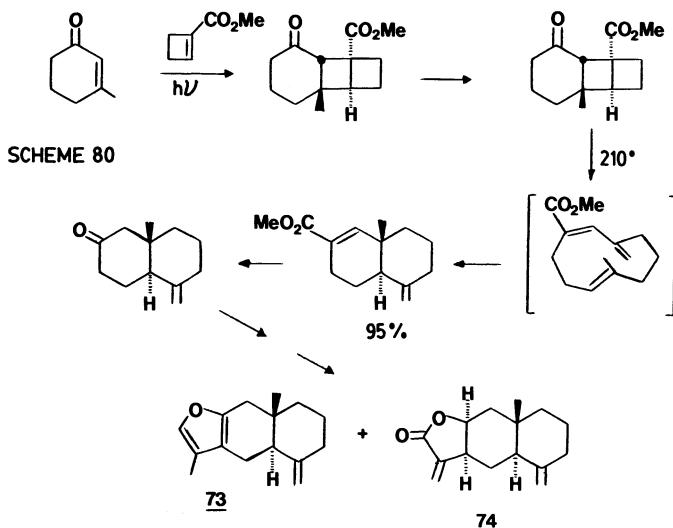
tion has been used in formal syntheses of the natural products atracylone, **73**, and isoalantolactone, **74** (Scheme 80).⁽¹⁷⁵⁾

Thermal opening of bicyclo[2.2.0]hexane-containing adducts to give cyclodecadienes provides a route into the germacrane ring system, and this has been applied to syntheses of an isomer of isoaristolactone⁽⁷¹⁾ (**75**, Scheme 81) and isabelin⁽¹⁷⁶⁾ (**76**, Scheme 82).

Bicyclo[2.2.0]hexane-containing photoadducts have also been opened reductively, and an example⁽⁵²⁾ is the preparation of the sesquiterpene epijunenol **77** (Scheme 83).

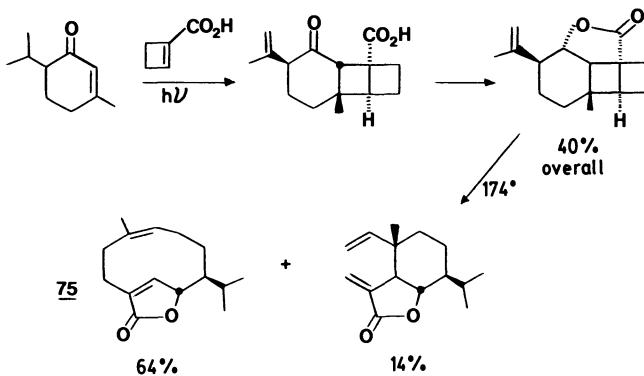


SCHEME 79

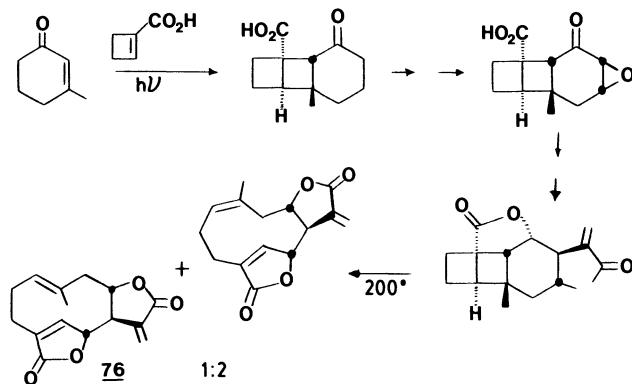


SCHEME 80

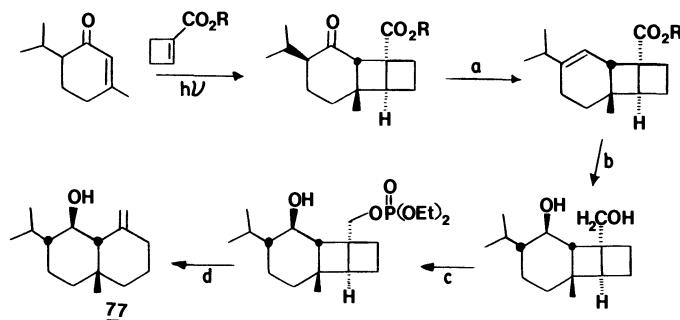
A number of syntheses have been reported which incorporate as key steps the photoaddition of cyclic or noncyclic alkenes to cyclic enones followed by ring expansion of the cyclobutane produced. The earliest of these⁽¹⁷⁸⁾ was Corey's synthesis of caryophyllene alcohol **78** (Scheme 84). The major adduct formed from irradiation of 3-methylcyclohexenone with 4,4-dimethylcyclopentene was converted to a tertiary alcohol with methyl lithium, and subsequent treatment with acid induced a carbonium ion rearrangement to the



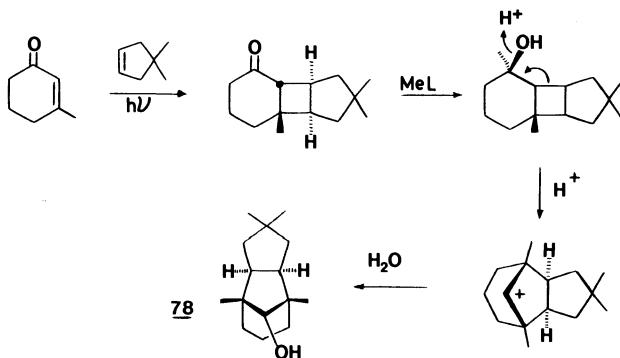
SCHEME 81



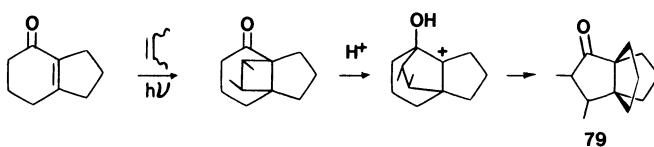
SCHEME 82

a Bamford-Stevens, b B_2H_6 , c $\text{ClP}(\text{O})(\text{OEt})_2$, d Li

SCHEME 83



SCHEME 84

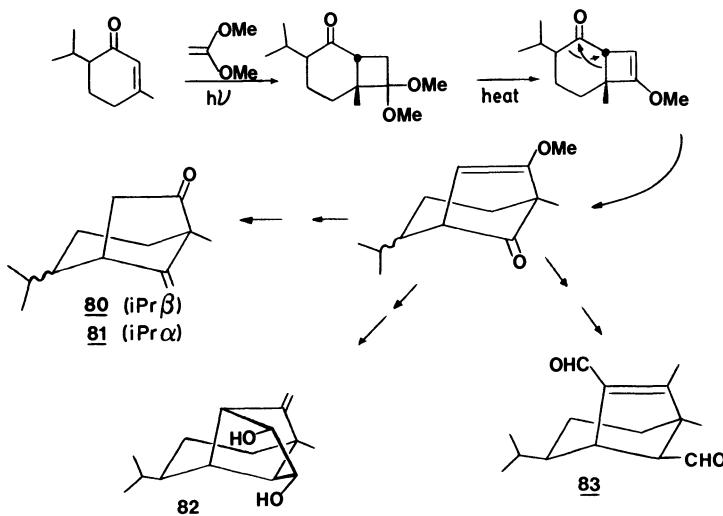


SCHEME 85

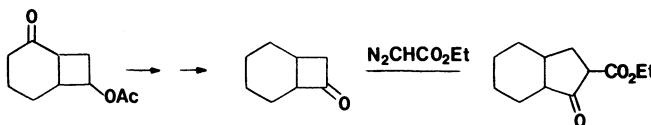
natural product. A related rearrangement⁽²⁹⁾ leads to the modhephane skeleton, **79** (Scheme 85; cf. Scheme 27) and thermolysis of the photoadduct from piperitone and 1,1-dimethoxyethylene results in an elimination-ring expansion sequence which has been used⁽¹⁷⁹⁾ to prepare the sesquiterpenes sativene, **80**, copacamphene, **81**, sativene diol, **82**, and helminthosporal, **88** (Scheme 86).

A cyclobutanone derived from an enone–vinyl acetate photoadduct has been ring-expanded using the diazoacetate method to yield the indane skeleton⁽⁶³⁾ (Scheme 87).

Many synthetic applications of enone cycloaddition involve cleavage of the initially formed cyclobutane. Examples of this were seen in the sections above concerning the de Mayo reaction (Schemes 40–60) and involved retro-aldol opening of the adduct. Closely related fragmentations have been observed for vinyl acetate adducts, and this has been utilized in the synthesis



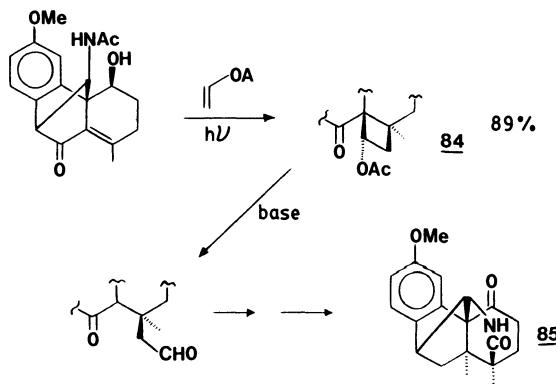
SCHEME 86



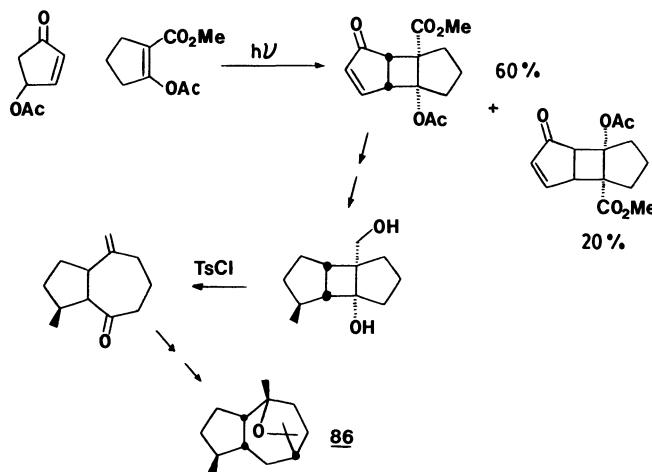
SCHEME 87

of the alkaloid songorine, **85** (Scheme 88); the photoadduct used for this fragmentation was derived from irradiation of enone **84** with vinyl acetate, and is anomalous in that the normal regiochemistry has been reversed.⁽¹⁸⁰⁾ An analogous transformation has been applied⁽¹⁸¹⁾ to the synthesis of sesquiterpene 5-epikessane, **86** (Scheme 89). Vinyl acetate photoadducts possessing the usual regiochemistry have been opened using a procedure which involves bromine oxidation of the cyclobutane ring at the position activated by the enone derived carbonyl function. This has been used in the synthesis^(64,182,183) of the alkaloids ormosamine, **87**, piptanthine, **88**, and panamine, **89** (Scheme 90). In cases where both the carbonyl group α positions are reactive towards bromination, the oxidation has been effected selectively using lead tetraacetate.⁽⁶⁴⁾

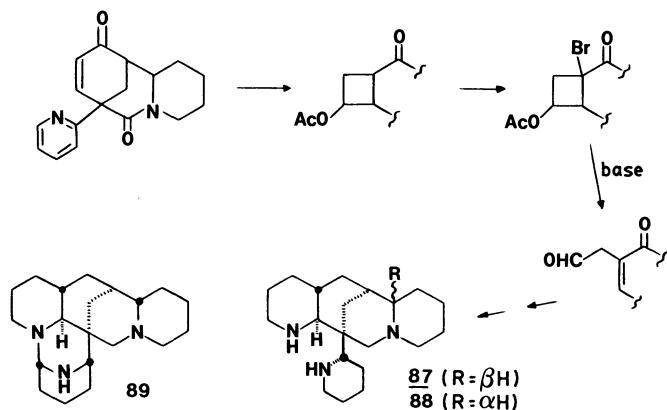
Suitably substituted cyclobutane rings derived from enone cycloaddition have been cleaved reductively,⁽¹⁸⁴⁾ and this has been used in the preparation of a prostoglandin synthon (Scheme 91). Baeyer–Villiger oxidative cleavage of photoadduct derived cyclobutanones has also been applied to prostoglandin synthesis⁽¹⁸⁵⁾ (Scheme 92).



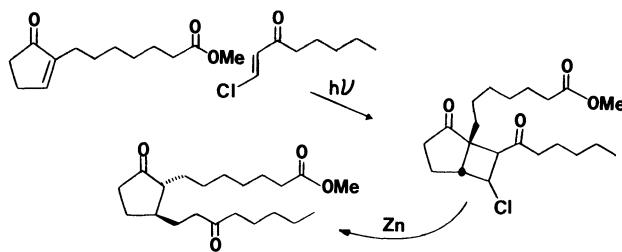
SCHEME 88



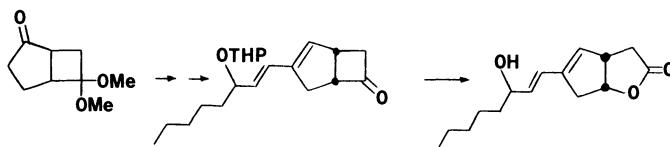
SCHEME 89



SCHEME 90



SCHEME 91

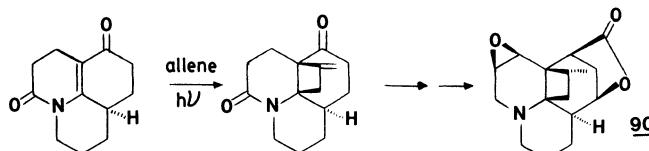
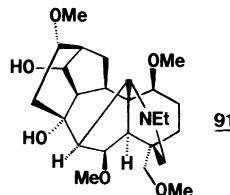


SCHEME 92

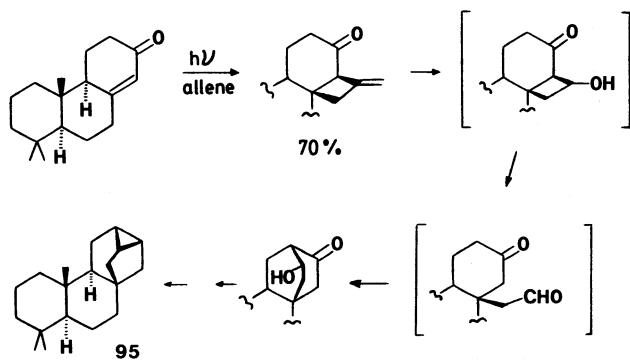
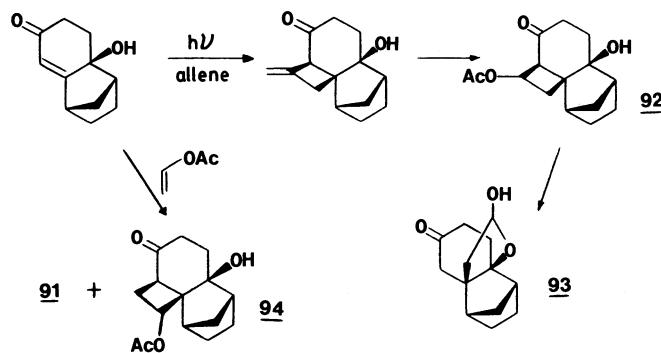
8. Photochemical Cycloaddition between Enones and Allenes

The addition of allene to photoexcited enones is highly stereoselective; the adduct obtained is invariably the head-to-head regioisomer, and with both cyclohexenones and cyclopentenones, the cyclobutane–cycloalkanone ring fusion is *cis*. In enones where the faces of the double bond are non-equivalent, the addition usually occurs from the least hindered face of the molecule; in rigid molecules the addition obeys Wiesner's empirical rule which correctly predicts the side of addition in the few exceptions where reaction occurs on the more hindered face. This selectivity has been used⁽¹⁸⁶⁾ in the total synthesis of the cyclobutane containing alkaloid annotinine, **90** (Scheme 93).

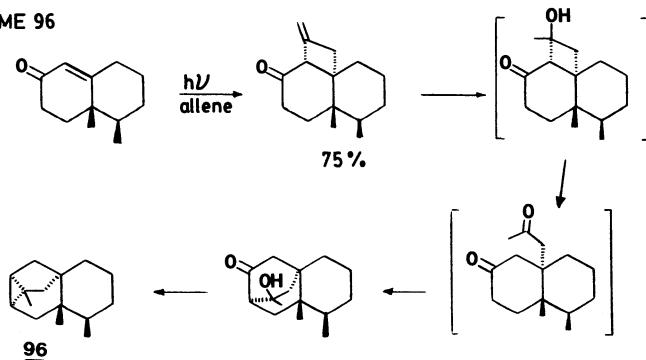
One of the advantages of allene cycloaddition is that the regiochemistry of the addition is the reverse of that observed in the addition of electron-rich alkenes such as vinyl acetate or alkoxy and 1,1-dialkoxy ethylenes, and that the allene–enone photoadduct is essentially a masked form of the adduct that would be derived from these alkenes. An example of this can be seen in the synthesis of part of the ring system of chasmanine, **91**, where allene addition

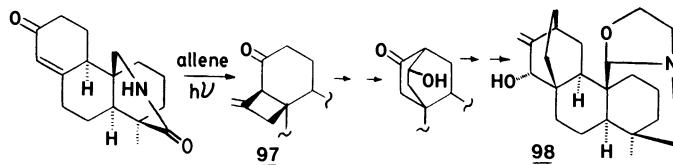


SCHEME 93



SCHEME 96

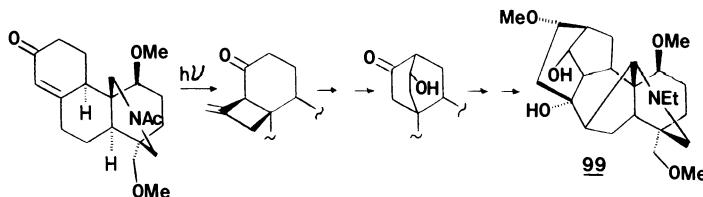




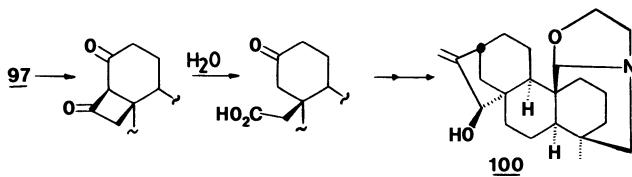
SCHEME 97

gives a single photoadduct which when ozonized, reduced with borohydride, and acetylated gives **92** and hence the desired skeleton **93**. Direct addition of vinyl acetate gives a mixture of regioisomers **92** and **94** in equal amounts (Scheme 94).⁽⁹⁶⁾

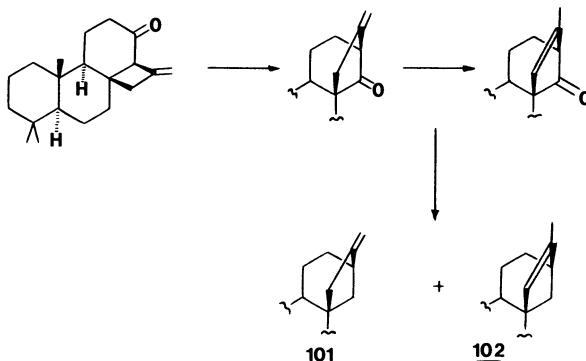
The conversion of **92** to **93** involves initial ester hydrolysis followed by a retro-aldol fragmentation of the acylcyclobutanol intermediate and intramolecular acetalization. This retro-aldol opening of the photoadduct is essentially identical to the fragmentation involved in the de Mayo reaction described in a previous section. Syntheses of trachylobane,⁽¹⁸⁷⁾ **95**, (Scheme 95), ishawarane,⁽⁸³⁾ **96** (Scheme 96), atisine,⁽¹⁸⁸⁾ **97** (Scheme 97), and talatamine,⁽¹⁸⁹⁾ **98** (Scheme 98) make use of this transformation. In these applications of enone–allene cycloaddition, the head-to-head adduct obtained is converted to an acyl cyclobutanol intermediate which undergoes an alternative aldol condensation following retro-aldol fragmentation. Recently, it has been shown that the ultimate aldol condensation product obtained in these syntheses can be produced directly from the allene–enone photoadduct by treatment with mercuric perchlorate.⁽¹⁹⁰⁾ The veatchin, **100**, has been prepared⁽¹⁹¹⁾ from the allene photoadduct **97** used in the synthesis of atisine (Scheme 97) by a similar fragmentation (Scheme 99) involving prior conversion of the allene-derived double to a ketone- and acid-catalyzed hydrolytic cleavage of the 1,3-diketone. A similar diketone, derived from the allene photoadduct used in the synthesis of trachylobane (Scheme 95), undergoes an acid-catalyzed cyclobutane ring expansion leading to a synthesis of phyllocladene, **101**, and isophyllocladene, **102** (Scheme 100).^(56,80)



SCHEME 98



SCHEME 99



SCHEME 100

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Synthetic Aspects of Photochemical Electron Transfer Reactions

Patrick S. Mariano and Jerome L. Stavinoha

1. Introduction

1.1. Synthetic Applications of Photochemical Reactions

The major applications of organic photochemical processes to synthetic problems have to date focused for the most part on the use of photocycloadditions and electrocyclizations in the preparation of strained ring compounds in target systems or key synthetic intermediates. The utility of these methods in selected preparative sequences for construction of natural and/or theoretically interesting products has been reviewed.⁽¹⁾ In general, these excited-state reactions share several unique features which make their utility in synthetic chemistry particularly advantageous. For example, photocycloadditions serve as useful methods for generating carbon–carbon bonds in strained ring systems which, due to their high energy content, are capable of participating in facile ring cleavage processes leading to desired intermediates. Similarly, electrocyclizations lead to the installation of difficultly prepared cyclic units from more readily available acyclic precursors. The applications of these reactions to synthetic problems is further broadened by their predictable regiochemical

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and stereochemical courses utilizing simple molecular orbital methods. Other classes of excited-state reactions have been used for the introduction and interconversion of functionality in molecular systems. Thus, several classes of photochemical processes appear compatible with the criteria established for evaluation of synthetically useful ground-state transformations.

In recent years exploratory and mechanistic photochemical studies have become increasingly focused on a new group of excited-state processes initiated by one-electron transfer from or to excited states of organic systems to acceptors or from donors. Many of the transformations uncovered appear to be particularly suited to synthetic practices due to their high chemical and quantum efficiencies and their structural and functional consequences. These new processes are the focus of this chapter, which will briefly outline introductory aspects of electron transfer in excited-state chemistry and then review selected examples of those reactions in which electron transfer mechanisms have been proven or are likely. Several excellent, earlier reviews of this subject have already appeared.^(2,4)

1.2. Electron Transfer in Excited-State Chemistry

1.2.1. *Exciplex Formation and Decay*

The concepts associated with excited-state complex formation and electron transfer have been discussed previously in contexts of a general description of the phenomena,^(4,6) the spectroscopic and photophysical characteristics of the systems,^(7,9) and chemical properties.^(2,3) Only the essential features of complex formation and its relationship to electron transfer in the excited-state chemistry of organic systems will be discussed here in order to establish a historical framework and the conceptual foundation for understanding the origin of chemical reactivity.

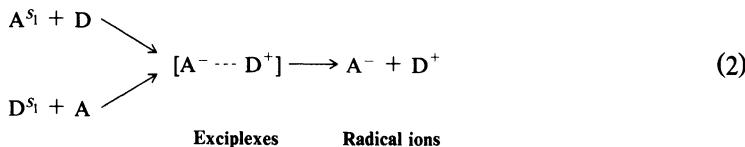
Over the past several decades a large body of evidence has been accumulated suggesting that a vast number of excited-state processes occur via the intervention of encounter complexes with charge or electron transfer characteristics. In earlier spectroscopic studies, Forster⁽¹⁰⁾ interpreted the concentration dependence of pyrene fluorescence in terms of complex formation between singlet excited and ground-state molecules. Similar observations by other groups^(11,12) support the view that excited homodimers, termed excimers by Stevens,⁽¹³⁾ are responsible for monomer fluorescence self-quenching and red-shifted dimer emission. The stability of excimers relative to the monomer singlet state as suggested by the relative emission maxima appears to derive in part from exciton resonance interactions involving delocalization of excitation over both components.⁽¹⁴⁾ However, subsequent to the early studies by Ferguson,⁽¹⁵⁾ it has become evident that the electronic states of excimers are

best described not only on the basis of resonance concepts but also in terms of intracomplex charge transfer. Accordingly, excimer stabilization is also the result of electrostatic attractions arising from partial electron transfer. The resonance formulation shown in equation (1) appears to best depict the excimer state.



Excimers

Excited-state complexation can also occur between two different species resulting in formation of excited heterodimers, termed exciplexes.⁽¹⁶⁾ Initial investigations by Hochstrasser⁽¹⁷⁾ of the pyrene-perylene system and later efforts by Weller⁽¹⁸⁾ on the perylene-dimethylaniline couple both suggest that the emitting exciplexes are stabilized by charge transfer between excited donors and ground-state acceptors or vice versa [equation (2)]. For the most part, singlet states have been found to be responsible for the quenching and emission characteristics attributed to exciplex formation and decay, although evidence is available supporting the intervention of triplets in complexation.⁽¹⁹⁻²²⁾ The postulate that exciplexes result from partial or complete electron transfer is substantiated by observations which demonstrate that the wavelength maxima for exciplex emission are dependent upon both the ionization potentials of donors and electron affinities of acceptors in the pair,⁽²³⁾ and the polarity of the medium.^(24,25) In addition, excitation of ground-state charge transfer complexes formed between donor and acceptor systems is known to directly populate the exciplex state.⁽²⁶⁾ Perhaps the most pertinent data on the nature of charge or electron transfer in exciplexes are found in the observed correlations existing between rate constants for fluorescence quenching and predicted rates of electron transfer. Weller^(27,28) has noted that semiempirical relationships exist connecting calculated rate constants with free energies for electron transfer in excited donor-acceptor systems. Accordingly, fluorescence quenching via exciplex formation should be controlled by electron transfer, the facility of which will be governed by polarographic oxidation and reduction potentials of the donors and acceptors along with the excited-state energy of the system.



One of the more important aspects of exciplex chemistry as it pertains to chemical reactivity concerns the nature of decay pathways available to excited-state complexes. The studies reviewed above suggest that complex

formation involves charge or electron transfer from donors to acceptors and that deactivation of the complex occurs through emission and radiationless decay including intersystem crossing.⁽²⁹⁾ However, exciplexes can serve as sources of radical ions. Accordingly, exciplex emission intensities are known to decrease in proceeding from solvents of low to high polarity.⁽³⁰⁾ This decrease in exciplex lifetime is associated with complete electron transfer resulting in production of radical ions [equation (2)] which have been detected by the use of a variety of spectroscopic techniques.⁽³¹⁻³⁵⁾ Importantly, the charged radical species formed in this way are capable of participating in a number of different chemical processes due to their high energy content. As will be seen, a variety of these processes are sufficiently selective to be applied in synthetic methodologies.

1.2.2. Electron Transfer Efficiencies and Rates

In order to develop a more thorough understanding of the chemical aspects of excited-state electron transfer processes and predictive capabilities, it is necessary to probe more deeply the factors which influence the efficiency and rate of electron transfer. A simplified molecular orbital view of redox systems depicted in Figure 1 serves to demonstrate the axiom that electronic excited states are better one-electron donors and acceptors than the corresponding ground-state species. Accordingly, the oxidation [$E_{1/2}(+)$] and reduction [$E_{1/2}(-)$] potentials of ground-state systems M^{S_0} reflect the respective energy differences between the doubly filled HOMO and unfilled LUMO orbitals and the source or sink for electrons. Transfer of electrons to or from excited species M^{S_1} on the other hand can occur from or to the respective high- and low-energy singly occupied molecular orbitals. Thus, the excitation energy ($\Delta E_{0,0}$) of M^{S_1} serves as the thermodynamic driving force for one-electron transfer.

The general scheme accepted for outer sphere, bimolecular electron transfer leading to excited-state quenching (k_q) or reaction (k_r) is shown for singlet

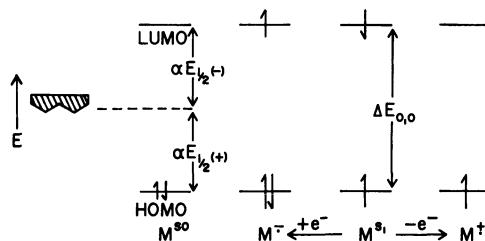
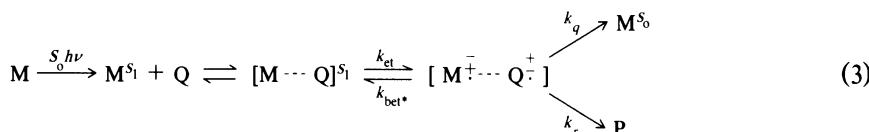


Figure 1. Molecular orbital schematic for one-electron transfer processes between ground and singlet excited species.

excited states in equation (3). The conversion of encounter complexes to ion pairs by this mechanism should have an associated free energy change ΔG_{et} which is dependent on the oxidation potential of the donor and reduction potential of the acceptor, the electronic excitation energy of $M(\Delta E_{0,0})$, and a Coulombic component related to solvent dielectric (ξ), encounter distance (r) and electron charge (e_0). The formulation of these relationships is found in equation (4). Moreover, both theoretical treatments and experimental observations suggest that the rate of outer sphere electron transfer is directly related to ΔG_{et} . In a classical study, Rehm and Weller⁽²⁸⁾ have shown that fluorescence quenching rate constants for more than 60 typical electron donor-acceptor systems correlate with ΔG_{et} . This correlation suggests that the free energy of activation for electron transfer $\Delta G_{\text{et}}^{\neq}$ is the monotonous function of ΔG_{et} shown in equation (5) and that the rate constant for electron transfer k_{et} in these systems is related to both ΔG_{et} and $\Delta G_{\text{et}}^{\neq}$ according to equation (6). Importantly, these empirically derived relationships indicate that k_{et} will approach the diffusion controlled limit of ca. $10^{10} \text{ M}^{-1} \text{ s}^{-1}$ when electron transfer is exothermic, i.e., when $\Delta G_{\text{et}} < 0$.



$$\Delta G_{\text{et}} = E_{\nu_2}^{(+)} - E_{\nu_1}^{(-)} - \Delta E_{0,0} - \frac{e_0^2}{\xi r} \quad (4)$$

$$\Delta G_{\text{et}}^{\neq} = \left[\left[\frac{\Delta G_{23}}{2} \right]^2 + (2.4 \text{ kcal/mol})^2 \right]^{1/2} + \frac{\Delta G_{23}}{RT} \quad (5)$$

$$k_{\text{et}} = \frac{2 \times 10^{10} \text{ M}^{-1} \text{ sec}^{-1}}{1 + 0.25 \left[\exp \frac{\Delta G_{\text{et}}^{\neq}}{RT} + \exp \frac{\Delta G_{\text{et}}}{RT} \right]} \quad (6)$$

Agreement between the calculated and experimentally determined quenching rate constants within a factor of less than 2 for systems in which ΔG_{et} varies between +5 and -60 kcal/mol is taken as evidence supporting the operation of electron transfer mechanisms for quenching in the systems studied by Rehm and Weller. This agreement appears to validate the relationships included in equations (5) and (6). Balzani, Scandola, and Schuster⁽³⁶⁻³⁸⁾ have recently shown that functions with the same general features as those empirically derived by Rehm and Weller can be derived on the basis

of free energy relationships first obtained by Marcus⁽³⁹⁾ for atom and proton transfer reactions and by Agmon and Levine^(40,41) from a thermodynamic treatment of reaction kinetics.

One of the more important consequences of the Rehm-Weller relationships is that they give the practicing organic photochemist simple methods for determining when electron transfer in excited-state systems will be thermodynamically feasible and, thus, kinetically significant. Accordingly, conclusions about the possible operation of electron transfer mechanisms in reacting systems can be made by considering the experimentally determined or empirically derived⁽⁴²⁾ electrochemical potentials and excited-state energies of donor-acceptor pairs, and solvent polarity. For this purpose, one can define a new set of electrochemical potentials for the excited-state species in terms of the conventional energy units for $E_{1/2}(+)$, $E_{1/2}(-)$ and $\Delta E_{0,0}$. Thus, the excited-state reduction potential is $E_{1/2}^*(-) = \Delta E_{0,0} + E_{1/2}(-)$, and the excited-state oxidation potentials become $E_{1/2}^*(+) = E_{1/2}(+) = \Delta E_{0,0}$. Electrochemical data for a large number of potential excited-state donors and acceptors are presented in this form in Tables 1 and 2. For convenience, an accumulation

Table 1. Approximate Excited-State Oxidation Potentials of Typical Donors

Compound	Singlet	Triplet	Compound	Singlet	Triplet
<i>Aromatic hydrocarbons</i>					
Benzene	-2.5	-1.3	Toluene	-2.6	-1.6
Naphthalene	-2.5	-1.1	<i>o</i> -Xylene	-2.7	-1.5
Anthracene	-1.8	-0.4	Hexamethylbenzene	-2.8	
<i>Aryl halides</i>					
1-Bromonaphthalene	-2.0	-0.7	1-Methyl-4-chlorobenzene	-2.6	
Chlorobenzene	-2.5				
<i>Aryl ethers</i>					
Anisole	-2.7		2-Methoxynaphthalene	-2.3	
1-Methoxynaphthalene	-2.3				
<i>Aryl amines</i>					
<i>N,N</i> -Dimethyl aniline	-3.3				
<i>Olefins</i>					
<i>t</i> -Stilbene	-2.6	-0.7	Indene	-2.7	
1,1-Diphenylethylene	-2.8		1,3-Butadiene		-0.6

Table 2. Approximate Excited-State Reduction Potentials of Typical Acceptors

Compound	Singlet	Triplet	Compound	Singlet	Triplet
<i>Aromatic systems</i>					
Naphthalene	+1.5	+0.2	Nitrobenzene		+1.4
Anthracene	+1.3	-0.1	Methyl <i>p</i> -cyanobenzoate	+2.9	
Phenanthrene	+1.1	+0.2	Chlorobenzene	+2.4	
<i>p</i> -Dicyanobenzene	+2.4	+1.1	1,4-Dicyanaphthalene	+2.1	
1-Cyananaphthalene	+1.5				
<i>Olefins</i>					
Styrene	+1.7	+0.1	<i>t</i> -Stilbene	+1.8	0.0
1,3-Butadiene		0.0	<i>c</i> -Stilbene	+2.0	+0.4
1,3-Cyclohexadiene	+1.3	-0.6			
<i>Heteroaromatic systems</i>					
Pyridinium-Br ⁻	+2.6		<i>N</i> -Ethyl-3-carbomethoxypyridinium-Br ⁻	+2.8	
Quinoline	+1.6	+0.3			
<i>N</i> -Ethylpyridinium-Br ⁻	+2.4		2-Phenyl-1-pyrrolinium-ClO ₄ ⁻	+2.5	
<i>Ketones</i>					
Acetophenone	+1.4	+1.3	<i>p</i> -Diacetylbenzene	+2.3	+2.1
Benzophenone	+2.0	+1.7	Benzil	+1.8	+1.3
<i>Quinones</i>					
Anthraquinone		+1.8	<i>p</i> -Benzoquinone	+1.9	+1.7
Phenanthraquinone	+2.5	+2.0			

of ground-state electrochemical potentials are included in Tables 3 and 4. The data in these tables can be used in developing rough estimates for ΔG_{et} and k_{et} in the excited chemistry of a variety of organic substrate classes.

1.3. Chemical Consequences of Electron Transfer

1.3.1. General Survey and Predictions

The driving force for classical photochemical processes is found in the high energy content of excited states arising by absorption of light. Furthermore, the different nuclear coordinant and energy distribution functions of

Table 3. Approximate Ground-State Oxidation Potentials of Typical Donors

<i>Aromatic systems</i>					
Benzene	+2.3	<i>o</i> -Xylene	+1.9	1-Bromonaphthalene	+1.9
Anthracene	+1.5	Hexamethylbenzene	+1.5	Chlorobenzene	+2.1
Naphthalene	+1.5	Bromobenzene	> +2.2	<i>p</i> -Chlorotoluene	+1.8
Toluene	+2.0				
<i>Olefins</i>					
Cyclohexene	+2.1	Indene	+1.2	<i>c,c</i> -1,5-Cyclooctadiene	+1.8
<i>t</i> -Heptene	+2.2	<i>t</i> -Stilbene	+1.5	<i>c,t</i> -1,5-Cyclooctadiene	+1.5
1-Octene	+2.7	2-Butene	+2.3	<i>c</i> -Cyclooctene	+1.8
Isoprene	+1.8	3-Ethyl-2-pentene	+1.6	<i>t</i> -Cyclooctene	+1.6
1,3-Butadiene	+2.0	2-Methylpropene	+2.2	1-Butene	+2.8
Cyclooctatetraene	+1.4	Vinylacetate	+2.8		
<i>Aromatic ethers</i>					
1,2-Dimethoxybenzene	+1.5	Anisole	+1.8	2,5-Diphenyl furan	
1,4-Dimethoxybenzene	+1.3	1-Methoxynaphthalene	+1.4	1,4-Dimethoxynaphthalene	+1.1
<i>Amines</i>					
Tri- <i>n</i> -propylamine	+0.6	<i>N,N</i> -Dimethylaniline	0.7	Pyrrole	+0.8
DABCO	+0.7	Pyridine	+1.8	Pyrrolidinyl-1-cyclopentene	+1.9
Aniline	+0.9				
<i>Sulfides</i>					
Dimethylsulfide	+1.4	Di- <i>n</i> -butylsulfide	+1.5	Thiophene	+1.8
<i>Alcohols and ethers</i>					
Methanol	+3.8	2-Propanol	+3.2	Furan	+1.5
Ethanol	+3.5	Diethyl ether	+2.5	THF	+1.9
2-Methyl-2-propanol	+2.5				
<i>Cyclopropanes and oxiranes</i>					
1,1,2,2-Tetraphenylcyclopropane	+1.2	<i>t</i> -2,3-Diphenyloxirane	+1.7		
<i>t</i> -1,2-Diphenylcyclopropane	+1.2	<i>c</i> -2,3-Diphenyloxirane	+1.8		
<i>c</i> -1,2-Diphenylcyclopropane	+1.4				

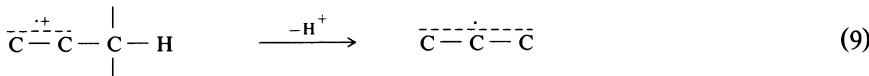
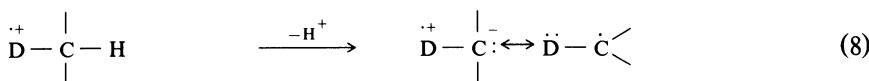
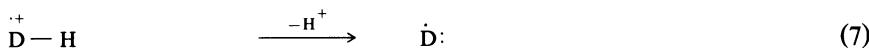
Table 4. Approximate Ground-State Reduction Potentials of Typical Acceptors

<i>Aromatic systems</i>					
Naphthalene	−2.5	<i>p</i> -Dicyanobenzene	−2.0	Benzyl bromide	−1.2
Anthracene	−2.0	<i>p</i> -Nitrobromobenzene	−1.1	<i>p</i> -Bromoanisole	−2.0
Phenanthrene	−2.5	Nitrobenzene	−1.2	Bromobenzene	−1.9
Benzonitrile	−2.7	Methyl benzenesulfonate	−2.5	<i>p</i> -Cyanobromobenzene	−1.4
Chlorobenzene	−2.1				
<i>Olefins</i>					
Styrene	−2.6	<i>c</i> -Stilbene	−2.1	TCNE	+0.2
1,3-Butadiene	−2.6	<i>t</i> -Stilbene	−2.2	Tetracyanoquino-dimethane	+0.1
1,3-Cyclohexadiene	−2.9	Acrylonitrile	−1.7		
<i>Ketones and quinones</i>					
Acetophenone	−2.0	Fluorenone	−0.9	<i>p</i> -Benzoquinone	−0.5
Benzalacetone	−1.0	Benzil	−1.0	1,4-Naphthoquinone	−0.6
Benzophenone	−1.3	Anthraquinone	−0.9	Phenanthraquinone	−0.3
<i>p</i> -Diacetylbenzene	−0.9				
<i>Anhydrides and imides</i>					
Maleic anhydride	−0.9	Phthalic anhydride	−1.3	Phthalimide	−1.5
<i>Heteroaromatic systems</i>					
Pyridinium-HCl	−1.1	<i>N</i> -Ethyl-3-carbomethoxy pyridinium-Br [−]	−0.9	Quinoline	−1.7
<i>N</i> -Methyl-pyridinium-Br [−]	−1.3			Isoquinoline	−2.3

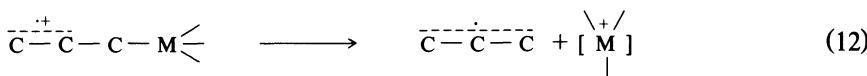
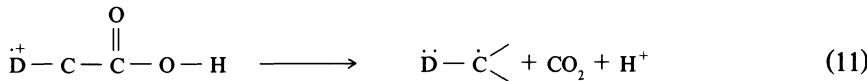
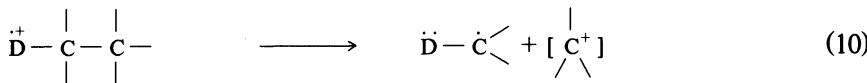
the excited systems compared to their ground-state precursors are responsible for the unique chemical properties of these species. Indeed, energy minima often exist on excited-state potential energy surfaces at nuclear coordinates corresponding to energy maxima on the ground-state surfaces. Thus, reaction barriers which normally prohibit certain reaction types in the ground-state manifold are in some cases easily surmounted by the excited-state systems. A typical example of this is found in the contrasting facility of photochemical π -bond isomerizations of alkenes due to the existence of energy minima and maxima for the respective excited and ground states at nuclear coordinates corresponding to perpendicular or twisted geometries.⁽⁴³⁾ Another pathway for activation of reaction pathways in excited-state chemistry is through the familiar process of exchange energy transfer. In the more common cases, excitation energy is conveyed from sensitizer to acceptors having lower-energy

excited states with multiplicity conservation and at rate near to the diffusion controlled limit. The excited acceptors are then capable of undergoing photochemical reactions controlled by the typical energy factors. It is important to note that the facility of exchange energy transfer processes is strongly dependent upon the relative energies of the sensitizer and acceptor excited states, i.e., the efficiency falls off dramatically when the energy transfer process is endothermic.

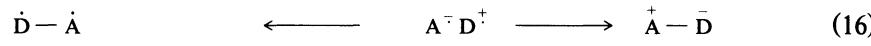
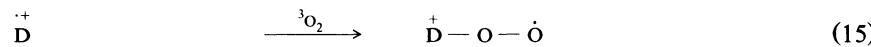
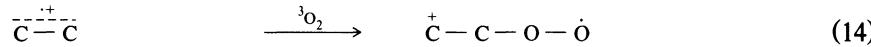
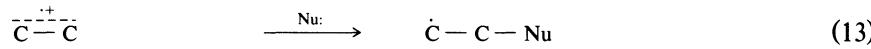
The factors controlling excited-state reactions proceeding by electron transfer mechanisms are distinctly different from those alluded to above. For example, in electron transfer sensitized processes the energetics of electron transfer described succinctly in the Rehm-Weller equation are important in determining the rate at which sensitizers activate acceptor molecules for reaction. Indeed, many examples exist in which electron transfer can occur from sensitizer to acceptor even though classical energy transfer would be greatly endothermic. More significantly, the reactivity of systems activated for reaction by electron transfer will be governed by principles applied in radical ion chemistry and not those describing excited states. With this in mind, it is possible to develop a framework for describing and predicting the chemical behavior of these systems by considering the reaction pathways available to radical cations and anions generated by electron transfer in primary events following excitation. A wealth of information in this area is found by inspecting the variety of chemical transformations associated with mass spectrometric fragmentations of molecular ions produced by electron impact or capture.⁽⁴⁴⁾ The body of knowledge concerning electroorganic chemical processes⁽⁴⁵⁾ also serves as an instructive guide to the types of solution phase transformations expected in electron transfer photochemistry. Thus, it is perhaps not surprising to find that the kinds of reactions observed for ion radicals produced in excited-state processes are quite few in number and simple to understand on the basis of organic chemical reasoning. For example, cation radicals generated by one-electron transfer from localized atomic or delocalized molecular orbitals undergo loss of protons from positions either α or β to the charged centers producing neutral radical species as depicted in equations (7)–(9). Other electrofugal groups, such as stabilized carbocations



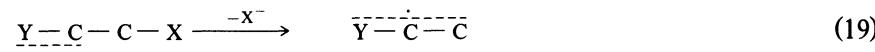
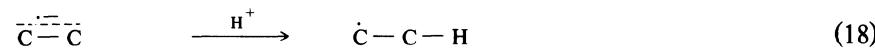
[equation(10)], carbon dioxide [equation (11)], and organometallic moieties [equation (12)] can be lost in conversion of radical cations to neutral radicals.



Because of the presence of the positive charge and vacant LUMO in delocalized radical cations, addition of nucleophiles occurs in a regiocontrolled fashion to generate carbon radicals [equation (13)]. The radical character of cation radicals is expressed in their reactions with species such as triplet dioxygen [equations (14) and (15)] and coupling with radical anions to generate zwitterionic intermediates [equation (16)]. Of course, ion radical pair coupling can also occur to form diradical species. Lastly, σ -type radical cations arising as a consequence of electron transfer from strained σ bonds will possess reduced σ -bond orders and, thus, should undergo ready carbon–carbon bond cleavage [equation (17)]. Radical anions produced by excited-state electron



transfer also appear to follow predictable reaction modes involving protonation [equation (18)], loss of nucleofugal groups from β [equation (19)] and α [equation (20)] positions, and coupling to form radical cations. Many examples of reactions activated in these ways will be discussed below.



1.3.2. Overview of Coverage

In the remaining sections of this chapter we have attempted to survey several classes of electron transfer photochemical reactions which in our judgement appear to hold synthetic potential. Of course, in doing this we were required to make decisions about synthetic applicability. A very broad set of criteria were applied. Thus, we have included for discussion those processes which occur with modest to high chemical yields, those that lead to carbon–carbon bond formation, to a major interconversion of functionality, or to a net oxidation or reduction, and those that bring about chemical changes for which no ground-state counterpart exists. Mechanistic discussion has been included since it serves as the substructure on which thoughts about the development of new processes are based. Lastly, the reader is reminded that the intent of this chapter is not to survey all examples of photochemical processes occurring by electron transfer mechanisms, and encouraged to consult other excellent reviews of this area.⁽²⁻⁴⁾

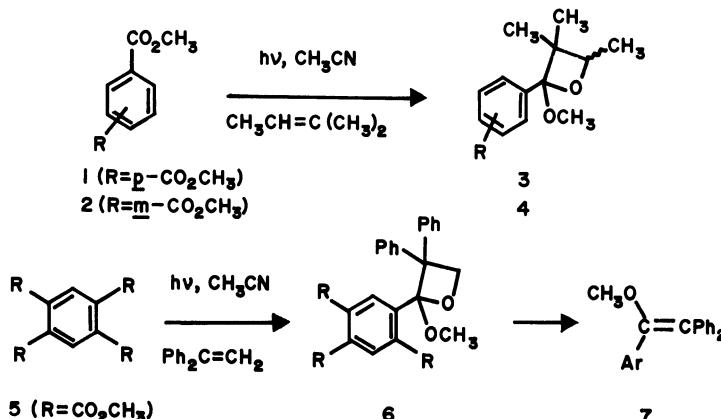
2. Reaction Pathways Followed in Electron Transfer Photochemistry

2.1. Alkenes and Strained Ring Hydrocarbons

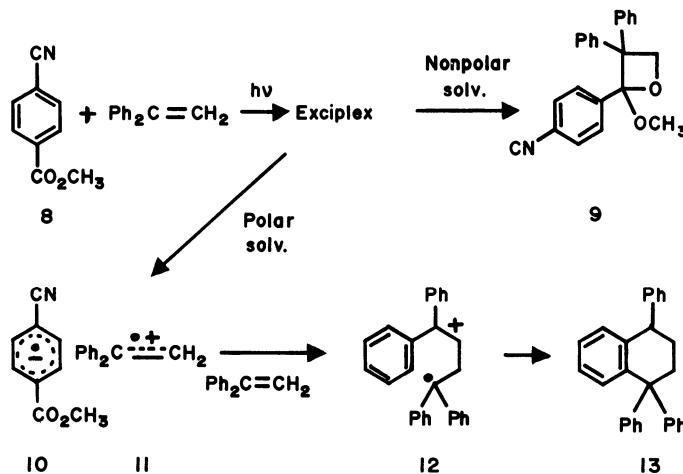
2.1.1. Alkenes as Electron Acceptors and Donors

Radical cations or anions are generated by one-electron transfer from or to alkenes in their $\Pi-\Pi^*$ excited states or through interaction of the ground-state species with excited states of electron acceptors or donors. As suggested earlier, the chemical reactivity of the charged radicals formed in these ways can be easily predicted on the basis of simple chemical principles. One such pathway followed by alkene-derived cation radicals involves nucleophilic addition. Early observations of photocycloaddition reactions between olefins and aromatic esters stimulated thought about the nature and degree of electron transfer in these systems. Shigemitsu⁽⁴⁶⁾ showed that irradiation of acetonitrile solutions of electron-poor aromatic esters in the presence of electron-rich alkenes leads to production of substituted oxetanes. For example, dimethyl ter- and isophthalate (**1** and **2**) smoothly photoadd trimethylethylene yielding the formal $\Pi_2 + \Pi_2$ adducts **3** and **4**. Tetramethyl pyromellitic ester **5** undergoes a similar addition with 1,1-diphenylethylene to produce the unstable oxetane **6** which rapidly deformylates to generate the vinyl ether **7**.⁽⁴⁷⁾ Cyclooctene and 2,3-dimethylbutadiene participate in similar cycloadditions all of which were attributed to processes occurring via electron transfer

through exciplexes and/or radical ion intermediates. Clarification of the mechanistic details of these processes has come from results of Arnold and his co-workers^(48,49) which demonstrate that the olefin-ester cycloadditions most probably involve intermediate exciplexes. Thus, oxetane **9** forming cycloaddition occurs when solutions of methyl *p*-cyanobenzoate **8** and 1,1-diphenylethylene in nonpolar solvents are irradiated. Photodimerization producing the tetralin **13** is the exclusive pathway followed when photoreactions are run in

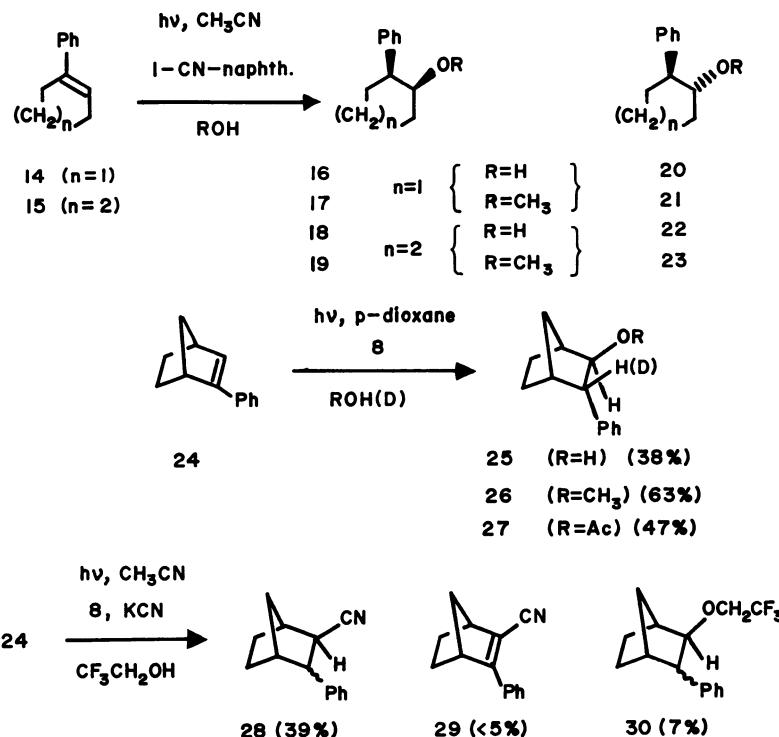


non-nucleophilic solvents of high polarity. The suggested mechanism for dimer formation involving one-electron transfer from olefin to excited ester received experimental support from uv spectroscopic observation of the radical cation **11** in flash photolysis experiments. In this case the ground-state olefin serves as a nucleophile toward the delocalized radical cation. Also, the direction of addition forming the separated cation radical **12** is fully consistent with

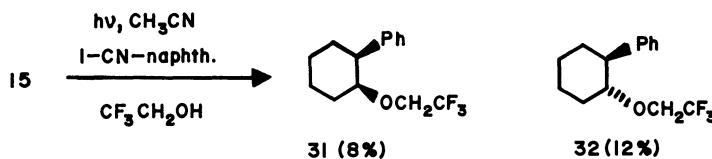


regiochemical predictions based upon steric, product stability, and FMO considerations. The final steps in dimer formation involve electron transfer between ion radicals **10** and **12** followed by carbon–carbon bond formation. Accordingly, methyl *p*-cyanobenzoate serves as an electron transfer photosensitizer in this process.

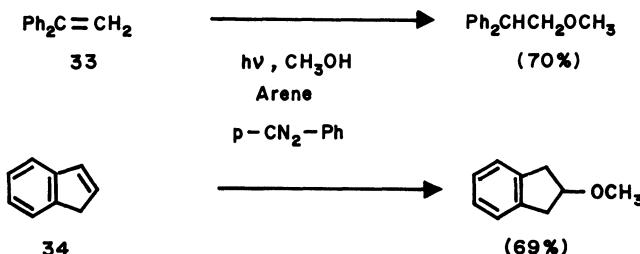
Olefin derived cation radicals are captured by other common nucleophiles as documented by the numerous examples of synthetically useful olefin additions described by Arnold.^(50,51) Photoadditions of water, alcohols, acids, and cyanide to the phenyl-substituted olefins **14**, **15**, and **24**, sensitized by aromatic electron acceptors such as 1-cyanonaphthalene and methyl *p*-cyanobenzoate, all proceed in modest yields to give products resulting from anti-Markovnikoff addition. The product regiochemistries and deuterium labeling patterns are fully consistent with mechanisms outlined above in which back electron transfer from photosensitizer radical anions to radicals, produced by nucleophile capture of the cation radicals, forms a carbanion precursor of the addition product. The synthetic utility of this methodology is further emphasized by its use in the preparation of β,β,β -trifluoroethyl ethers



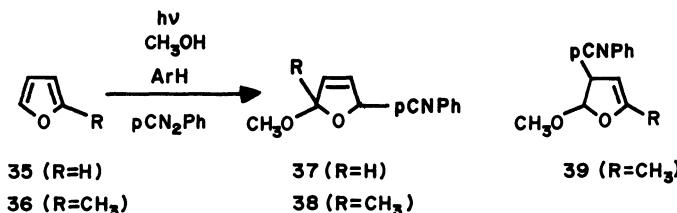
(**15** → **31** and **32**) which cannot be easily prepared by classical ether synthesis routes.⁽⁵²⁾



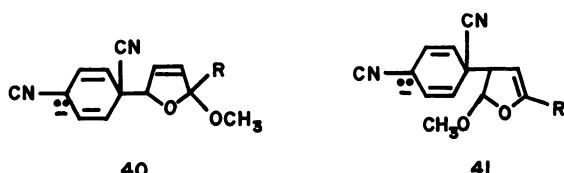
An indirect procedure for electron transfer sensitization of ether forming photoadditions of alcohols and olefins has been developed independently by Pac and Sakurai^(53,54) and Ansanuma.⁽⁵⁵⁾ In the indirect pathway, excitation of long-wavelength absorbing aromatic hydrocarbons such as naphthalene, anthracene, or phenanthrene is followed by electron transfer to the electron-poor acceptor *p*-dicyanobenzene present in the reaction mixture. The aromatic cation radicals then serve as electron acceptors in the key step transforming conjugated olefins such as 1,1-diphenylethylene (33) or indene (34) to reactive cation radical intermediates. Excellent yields are observed for anti-Markov-



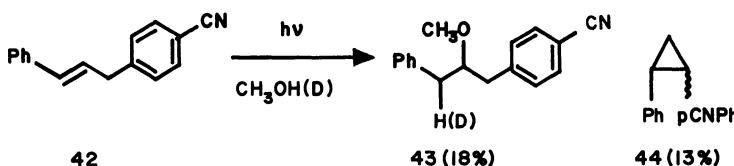
nikoff additions of methanol. The important advantages of the indirect method are found in its applicability in cases where the light absorbing characteristics of the olefin would prevent selective excitation of the acceptor and where low olefin concentrations are required. In the latter event, electron transfer efficiencies would still be large since the lifetimes of the aromatic cation radicals are normally longer than those of the acceptor excited states. Interesting examples of the utility of this method in sensitizing photoadditions to furans (35 → 37 and 36 → 38 + 39) have been provided by Pac and Sakurai.⁽⁵⁴⁾ The



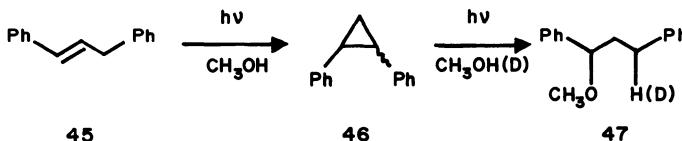
addition products formed in these processes result from radical coupling in the penultimate mechanistic steps followed by loss of cyanide from the anions 40 and 41.



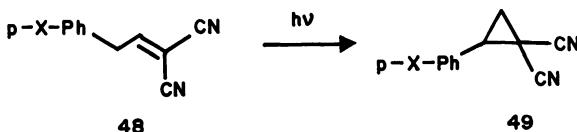
Intramolecular electron transfer sensitization appears to be responsible for methanol photoadditions to 1-phenyl-3-*p*-cyanophenylpropene **42** yielding the 1,2-diarylpropyl ether **43**.⁽⁵⁶⁾ The characteristics of this process are fully consistent with mechanisms for formation of **43** via electron transfer from the excited styrene to *p*-cyanophenyl chromophores followed by methanol attack, back electron transfer, and protonation (deuteration). The familiar di-



Π -methane rearrangement⁽⁵⁷⁾ competes with electron transfer in this system to generate the 1,2-diarylcyclopropane **44**. When the *p*-cyano-substituent is not present as in **45**, the di- Π -methane rearrangement pathway is followed

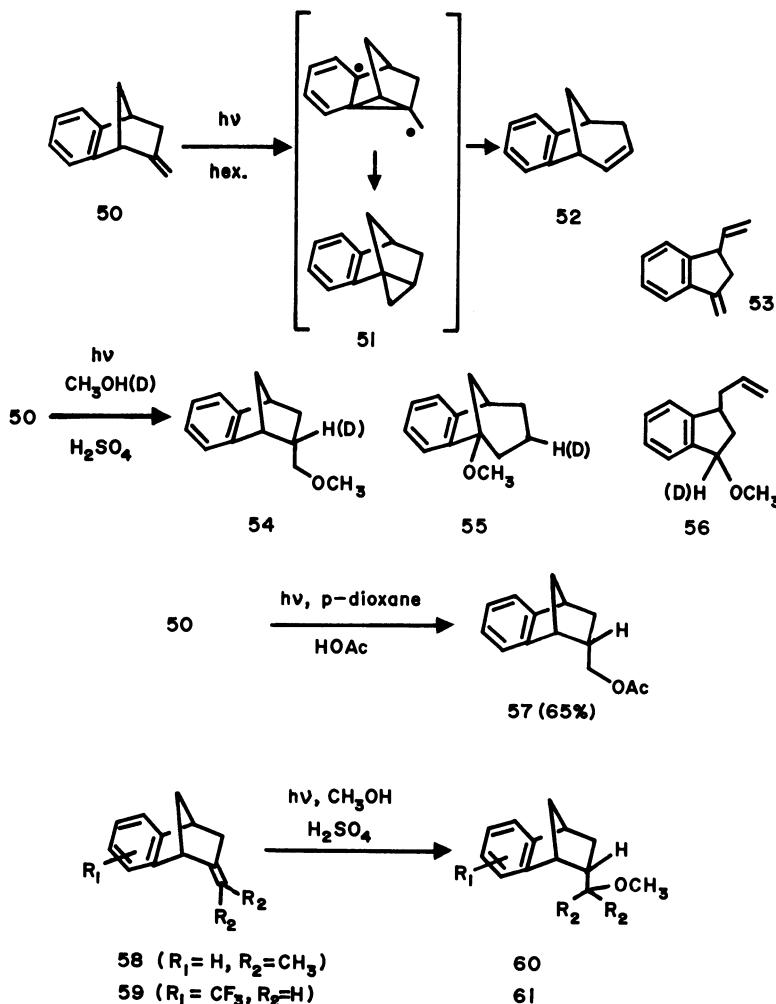


exclusively; the alcohol adduct **47** formed derives from secondary photoreaction of the initially produced 1,2-diphenylcyclopropane **46**. Additional infor-



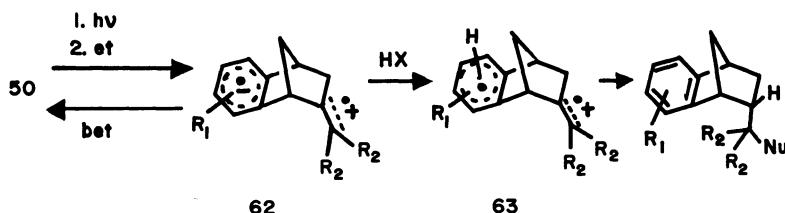
mation about the competitive nature of electron transfer and di-II-methane rearrangement in these bichromophoric systems is found in results of detailed studies conducted by Salisbury⁽⁵⁸⁾ on a series of 1,1-dicyano-3-*para*-substituted-phenylpropenes **48**. The efficiency of di-II-methane rearrangement (**48** → **49**) was found to vary with the nature of the *para*-substituent and solvent polarity in a fashion expected for excited state quenching by electron transfer from the aromatic ring to the electron-poor olefin moiety. For example, the quantum efficiency for rearrangement of *p*-CN-**48** is 40 times greater than that for *p*-CH₃O-**48** in cyclohexane and 200 times greater in the more polar

acetonitrile. Similar observations have been made in Morrison's investigation of the excited-state chemistry of the 2-methylenebenzonorbornenes. The parent bichromophoric system **50** undergoes a diverted di- Π -methane rearrangement from both singlet and triplet excited states to produce **52** and **53** when irradiated in hexane at 254 nm.⁽⁵⁹⁾ The chemistry changes considerably when irradiations are conducted on solutions of the norbornenes in polar solvents like methanol, especially when acid is present and the aromatic ring possesses electron withdrawing substituents.⁽⁶⁰⁾ This is illustrated by the conversion of **50** to a mixture of methyl ether **54** ($\Phi=0.03$) and the methanol capture

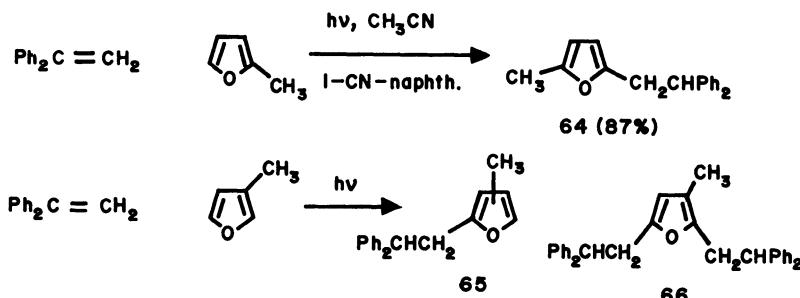


products **55** ($\Phi=0.01$) and **56** ($\Phi=0.004$) of a zwitterion precursor to or photoproduct of the strained cyclopropane **51**. The yields of anti-Markov-

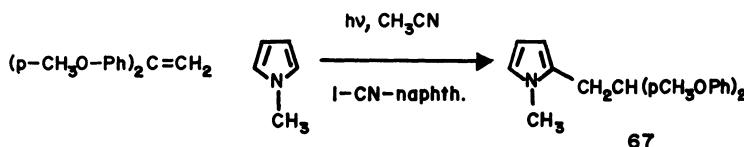
nikoff addition to the exocyclic methylene group are enhanced considerably when the reaction is conducted in the presence of acid or when electron-donating and -withdrawing groups are present on the exocyclic methylene and aromatic groups, respectively. Examples of this are found in the efficient transformations **50** → **57**, **58** → **60**, and **59** → **61**. These products appear to originate via intramolecular sensitized electron transfer mechanisms through the intermediacy of diradical ions **62**. The catalytic action of acid in these cases is most probably due to protonation producing the diradical cations **63**, species with longer lifetimes than **62** where back electron transfer should be exceedingly efficient.



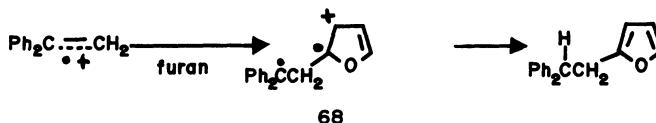
A number of other types of photoinduced electron transfer reactions are known to proceed through initial formation of olefin-derived cation radicals. Examples of these include the photoadditions of olefins to heteroaromatic and nitro compounds described below. Mizuno and Otsuji⁽⁶¹⁾ have shown that nucleophilic heteroaromatic compounds like furans and pyrroles can add to radical cations generated from olefins by electron transfer sensitization. Thus, irradiation of 1-cyanonaphthalene in acetonitrile solutions containing 1,1-diphenylethylene and a series of substituted furans gave mixtures of 1:1 and 1:2 adducts in high yields, as illustrated by transformations producing **64**–**66**. No olefin–furan crossed additions were observed when the bis-*p*-methoxyphenyl-substituted olefin was employed, owing presumably to the stability



of the intermediate cation radical toward nucleophilic attack. However, the electron transfer sensitized addition of this olefin to the more nucleophilic *N*-methylpyrrole proceeds smoothly to produce the adduct **67**. Detailed pho-

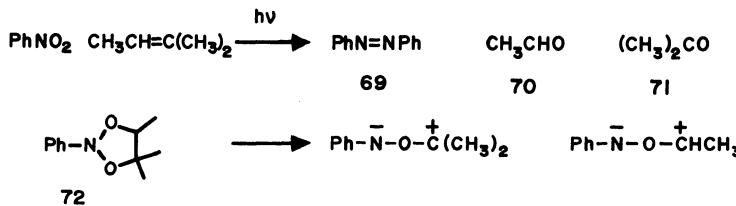


tophysical studies have shown that the initial step in the mechanism for these additions involves electron transfer from the olefin rather than the heteroaromatic system to the singlet excited sensitizer. This is then followed by

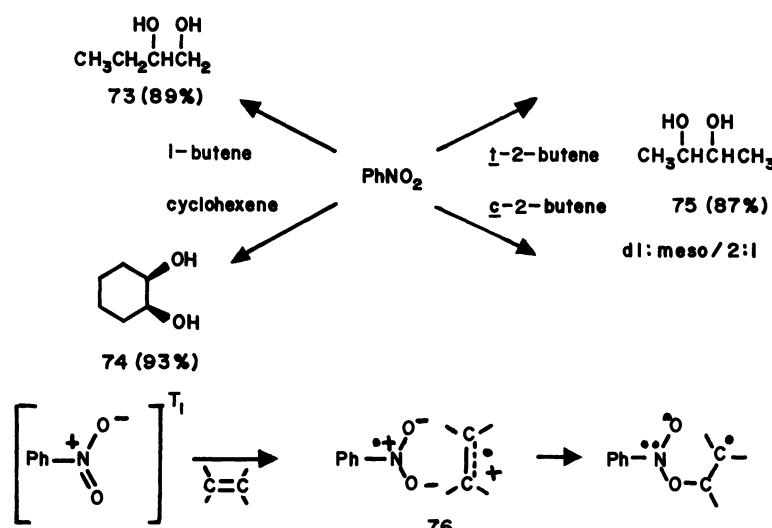


electrophilic addition forming 68, back electron transfer, and proton relocation.

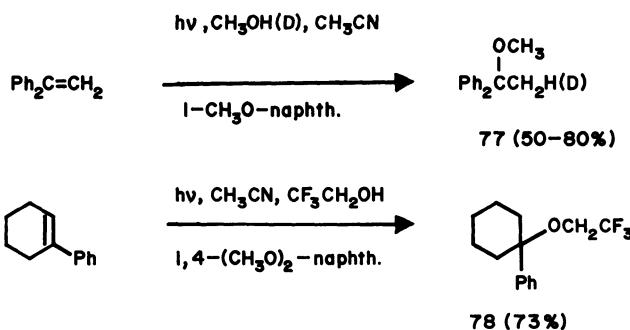
Studies of the olefin–nitrobenzene photoadditions date back to the early observations of Buchi and Ayer,⁽⁶²⁾ and include additional efforts of several notable photochemical research groups.^(63–65) The early investigations pointed out that nitrobenzene undergoes photoaddition to olefins such as cyclohexene and 2-methyl-2-butene to give carbonyl products and azobenzene, eg. 69–71.



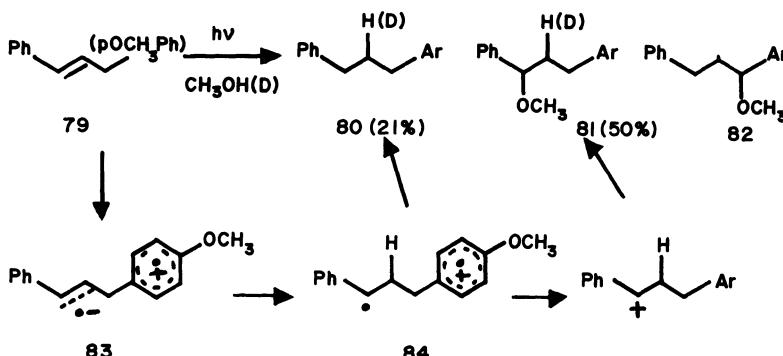
The products were rationalized as arising via intermediate 1,3-diox-3-azolidines 72. The proposed dioxazolidine intermediates have recently been isolated and characterized in careful studies by deMayo and his co-workers.⁽⁶⁵⁾ Moreover, deMayo has shown that irradiation of nitrobenzene–olefin mixtures at low temperature followed by catalytic hydrogenation of the crude photolysate leads to efficient production of vicinal diols and aniline. The examples of diol formation by this route starting with butadiene (→ 73), cyclohexene (→ 74) and *cis*- or *trans*-2-butene (→ 75) point out the synthetic utility of the methodology. Mechanistic studies have offered the following conclusions about 1,3-dioxazolidine production. The reaction is a nitrobenzene triplet state process, proceeding by a nonconcerted pathway. Significantly, the relative rates and quantum efficiencies for photoaddition are inversely dependent upon olefin ionization potential, suggesting the involvement of charge transfer in exciplex or ion radical intermediates 76 in pathways for these processes.



Thus far, we have reviewed several photoreactions in which olefins participate as electron donors in important mechanistic steps leading to production of cation radicals which serve as key reactive intermediates. Due to the availability of low-energy LUMO orbitals, olefins can serve as electron acceptors from excited states of appropriate electron-rich donors. This characteristic is expressed in the electron transfer sensitized, Markovnikoff additions of alcohols to phenyl conjugated olefins probed thoroughly by Arnold and Maroulis.^(66,52) Accordingly, 1,1-diphenylethylene and 1-phenylcyclohexene undergo photoaddition of methanol and trifluoroethanol to produce the respective substituted ethers, 77 and 78, upon irradiation with the electron-donating sensitizers 1-methoxynaphthalene, 1,4-dimethoxynaphthalene, or 1-methylnaphthalene. In these cases, the intermediate anion radicals are protonated by solvent yielding radicals which are oxidized by sensitizer radical



cation forming carbocation precursors of the ether products. An intramolecular counterpart of this process is found in the photoreduction and alcohol addition to 1-phenyl-3-*p*-methoxyphenylpropene **79**.⁽⁶⁷⁾ Thus protonation of the diradical ion **83**, arising from electron transfer from the anisyl moiety to the excited styrene chromophore, would give the radical **84**, which is capable of undergoing hydrogen atom abstraction from methanol (\rightarrow **80**) or back electron transfer followed by methanol addition (\rightarrow **81**). The trace quantity of the regiosomeric ether **82** also produced most probably arises by secondary photoreaction of the di- Π -methane rearrangement product, 1-phenyl-2-*p*-methoxyphenylcyclopropane.



One aspect of alkene electron transfer photochemistry which has received less attention over the years, yet one that might have synthetic importance, involves Π -bond isomerization through radical ion intermediates. To our knowledge, studies probing *cis-trans* isomerization of olefins catalyzed by reversible electron transfer in the excited-state manifold are sparse. However, the synthetic potential and mechanistic intricacies of the process appear sufficiently interesting to warrant brief discussion of expectations and existing experimental data. *Cis-trans* isomerization in excited triplet and singlet states is thought to result from twisting about the Π -bond to produce perpendicular states as energy minima on the excited-state surfaces. The energy lowering associated with twisting is a consequence of the olefin zero Π -bond order and electron-electron repulsion in the excited state. Crossover to the ground-state surface is thought to occur near or at the energy maximum for the ground state, funneling the system to both ground-state isomers with near equal probability (Figure 2).⁽⁶⁸⁾ Thus, photostationary state olefin isomer ratios should be dependent upon the efficiencies for excitation of the isomers by direct or sensitized pathways and the near equivalent partitioning of the excited-state to ground-state isomers. The factors controlling photostationary

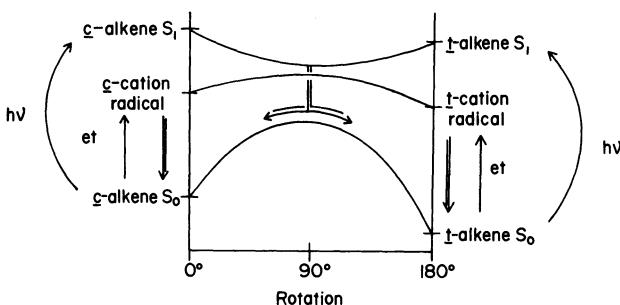
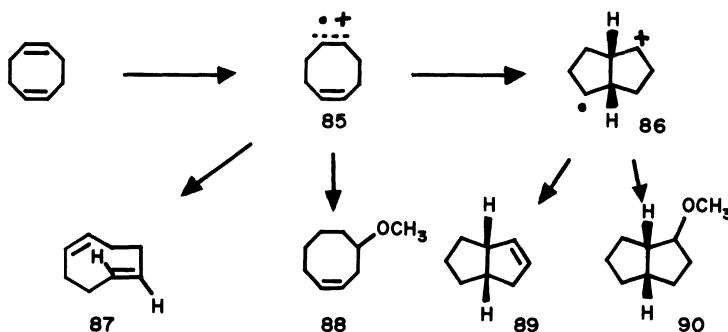


Figure 2. Energy profiles for carbon–carbon π -bond rotation in ground, singlet excited, and cation radical states of olefins.

state ratios in electron transfer sensitized processes should be different. Twisting in olefin-derived cation radicals for example should be less favorable since Π -bond orders, although lower than those for the ground states, are not zero as in the case of $\Pi-\Pi^*$ excited states. Also, back electron transfer would serve as the pathway for regeneration of the ground states. This process should be rapid, and, therefore, the relative efficiencies for *cis* and *trans* alkene formation should reflect the relative population of radical cation rotamers (Figure 2). Thus, photostationary state *cis-trans* isomer ratios obtained by electron transfer sensitization might differ considerably from those obtained by the other photochemical methods. Also, this method for photosensitized isomerization should be applicable even when photosensitization by energy transfer fails due to its endothermicity.

The literature contains some data on this point. Phillips⁽⁶⁹⁾ has found in a study of the gas phase *cis-trans* isomerization of 2-butene sensitized by a series of aromatic sensitizers unusual results for several highly electron withdrawing substituted systems. The decay ratios obtained from the photostationary state *cis-trans* isomer compositions are approximately unity for most substituted benzene sensitizers, reflective of the nearly equal partitioning of twisted olefin excited state to the isomeric ground-state species. However in the cases of *bis*-1,3 and 1,4-trifluoromethylbenzene, where electron transfer producing olefin radical cation is predicted to be energetically feasible, *trans-cis* isomer ratios are much greater than unity (ca. 1.5–2.0), a possible result of olefin radical cation formation in exciplexes or as free species and preferences for the *trans* cation-radical conformation. Similar observations of anomalous photostationary state ratios were made in studies of the solution phase, aromatic ester sensitized, *cis-trans* isomerization of cyclooctene.⁽⁷⁰⁾ Photoisomerization by direct irradiation via the singlet gives a near unity photostationary state ratio. On the other hand, singlet sensitization of this isomerization by a number of aromatic esters for which electron transfer should be efficient gave isomer ratios overwhelmingly favoring the thermo-

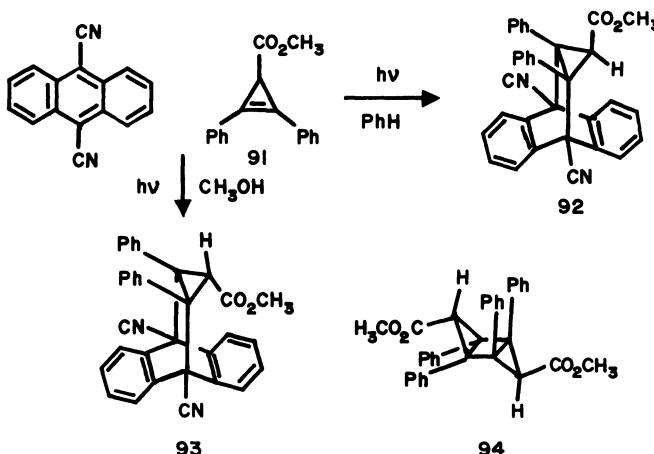
dynamically (ca. 9 kcal/mol, 38 kJ/mol) more stable *cis*-cyclooctene. For example, sensitization by dimethyl *o*-phthalate, tetramethyl pyromellitate, and *p*-dicyanobenzene gave *trans*-*cis* ratios of 0.07, 0.10, and 0.02, respectively. These results were interpreted as reflecting isomerization through exciplexes having charge transfer character. In related investigations, Takamuku and Inoue⁽⁷¹⁾ observed that the methyl benzoate singlet sensitized *cis*-*trans* isomerization of 1,5-cyclooctadiene in pentane gives the *cis*-*trans* diene **87**, predominantly. When this reaction is conducted in methanol, three additional products are generated, including the fused olefin **89**, ether **90**, and the methanol adduct **88**. Although mechanisms for generation of these adducts via **87** were proposed, alternate pathways through the cation radical **85** also appear



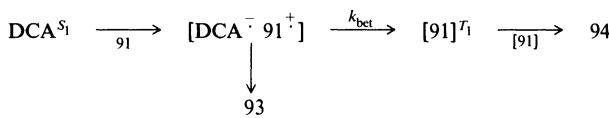
likely. Accordingly, intramolecular olefin-radical cation addition would produce **86**, a possible precursor to **89** and **90** by precedented routes already discussed in this section.

2.1.2. Cyclopropene Electron Transfer Photochemistry

Cyclopropenes contain olefinic II bonds in strained ring environments and, thus, should display types of reactivity similar to alkenes in electron transfer initiated photochemical processes. Accordingly, radical cations formed by electron transfer from the II system of cyclopropenes to acceptors should be susceptible to nucleophilic attack due to their electron deficiency and to ring-opening processes driven by the relief of ring strain. The results of several studies suggest that these predictions are correct. One of the first examples of reactions controlled in this way is found in studies by Farid and Brown⁽⁷²⁾ of cyclopropene-9,10-dicyanoanthracene (DCA) cycloadditions. Methyl 1,2-diphenylcyclopropene-3-carboxylate **91** has been shown to form an emitting exciplex with DCA in benzene, a solvent in which cycloaddition occurs upon irradiation at $\lambda > 405$ nm to yield mainly the dimer **92** ($\phi = 0.002$). In comparison, a mixture of hetero **93** and homo **94** dimers are produced when the photoreaction of **91** and DCA is conducted in the more polar

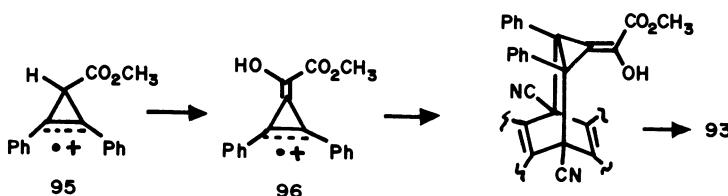


acetonitrile. Mechanistic information including concentration dependencies, 1,4-dimethoxynaphthalene quenching, 1,2,4,5-tetracyanobenzene activation, and classical triplet sensitization, led to the postulate that two mechanisms are operating in dimer formation: a reversible electron transfer process leading to the cyclopropene triplet excited state serving as a precursor to the homo dimer **94**, and radical ion generation and coupling to produce the hetero dimer **93**. A much more detailed analysis of this system has provided firm support for these conclusions and additional information about the stereochemistry of hetero dimer formation.⁽⁷³⁾ Specifically, dimer production in

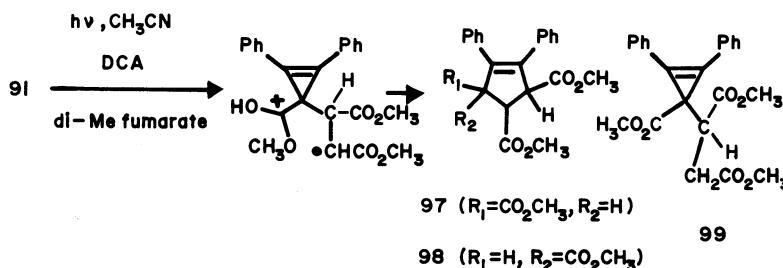


nonpolar solvents involves the intermediacy of an exciplex with the less crowded exo- CO_2CH_3 orientation. On the other hand, the cyclopropene cation radical **95** formed as a free species in the electron transfer process would derive stabilization through enolization (**95** → **96**). If cycloaddition of **96** occurs to produce the enolic adduct, ester stereochemistry would be controlled by delivery of a proton from the least hindered exo face during ketonization. This speculation rationalizing the preference for the endo ester containing cycloadduct has been given support by the observation that the mixed dimer arising via irradiation in 10% $(\text{CH}_3)_3\text{COD-CH}_3\text{CN}$ contains 80% deuterium incorporated at the ester α -position.

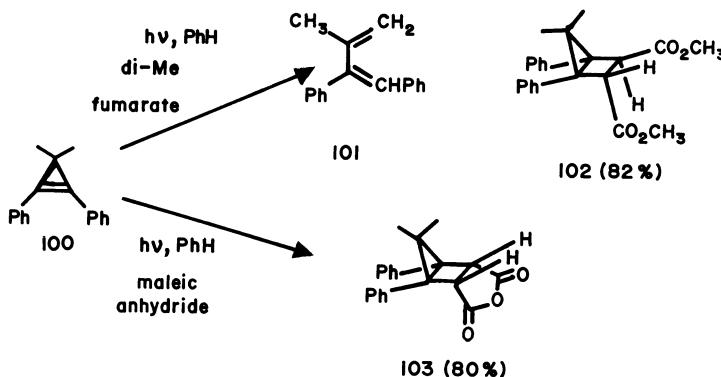
Farid⁽⁷³⁾ has also noted that the cation radical **95** generated under DCA electron transfer sensitized conditions can be trapped by electron deficient olefins, such as dimethyl fumarate, leading to formation of the adducts **97**–**99**. Similar results have been provided by Arnold and Morchat⁽⁷⁴⁾ with the



1,2-diphenyl-3,3-dimethylcyclopropene **100**-dimethyl fumarate and maleic anhydride systems. In these cases, long-wavelength irradiations ($\lambda > 350$ nm)

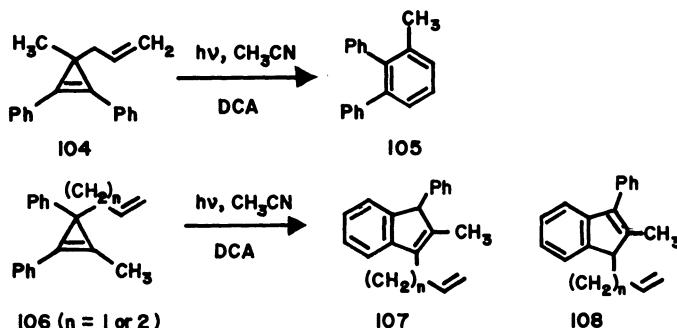


result in excitation of charge transfer states and in production of the dienes **101** and cycloadducts **102** and **103**. Cycloaddition here as in the Farid examples was shown to be the responsibility of the cyclopropene triplet excited states arising via reversible electron transfer whereas diene formation occurs by singlet state cyclopropene ring opening through a carbene intermediate. A complete analysis of the photophysical and chemical characteristics of these interesting electron transfer processes has been provided by Wong and Arnold.⁽⁷⁵⁾

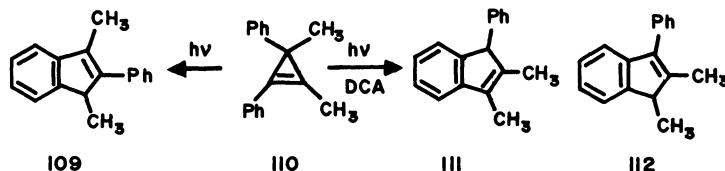


We have seen how reversible electron transfer in cyclopropene systems can lead to the production of the triplet states involved in cycloaddition processes. In addition, cyclopropene-derived cation radicals themselves undergo cycloadditions with olefins. Padwa and his co-workers⁽⁷⁶⁾ have de-

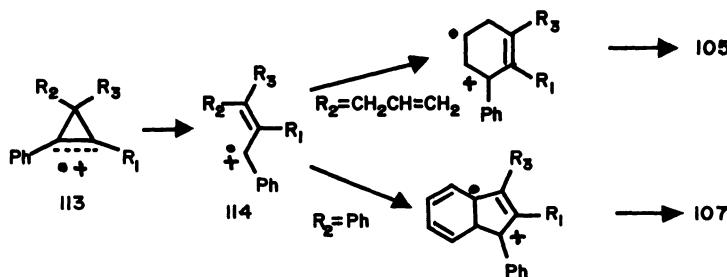
tected yet another reaction pathway available to these radical cations, exemplified by the DCA electron transfer sensitized conversions of alkenylcyclopropenes **104** and **106** to benzenoid **105** and indene, **107** (major) and **108** (minor) products, respectively. Another example of this novel chemistry is found in the comparable reactivity of the 1,3-diphenyl-2,3-dimethylcyclopropane **110** singlet state produced by direct irradiation \rightarrow **109** and cation radical state generated by DCA sensitization \rightarrow **111** and **112**. Indene formation in the singlet reaction of **110** has been attributed to excited-state funneling into the higher-energy carbene state through cleavage of the less phenyl substituted σ bond of **110** followed by Π -bond insertion. Cyclopropene bond cleavage



required to rationalize product formation in the electron transfer pathways should not be controlled by excited-state–ground-state surface crossing but



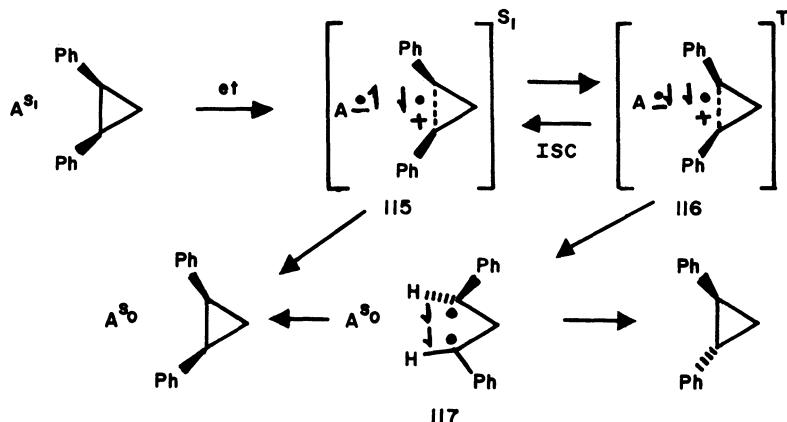
rather by preferential reaction of the intermediate cation radicals **113** to produce more delocalized allylic radical cations **114**. Thus, intramolecular



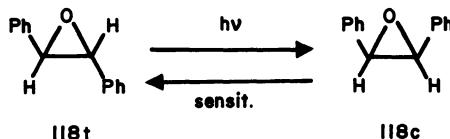
addition of the olefinic or phenyl moieties to the radical cation center in **114** would initiate conversion to the benzenoid or indene products. Importantly, rationalizations of the ring cleavage regiochemistries are more difficult on the basis of alternative mechanisms for these ring expansion processes in which intramolecular capture of the cyclopropene cation radical precedes σ -bond cleavage.

2.1.3. Cyclopropanes and Other Strained Ring Systems as Electron Donors

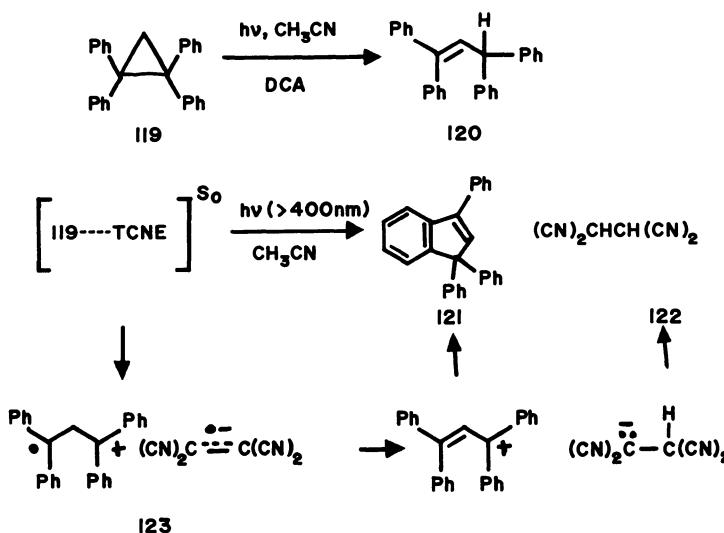
An evaluation of the electron-donating properties of aryl-substituted cyclopropanes and related oxiranes based upon measured and estimated oxidation potentials suggests that these substances should serve as reasonably efficient one-electron donors in photostimulated electron transfer processes. Earlier studies⁽⁷⁷⁻⁷⁹⁾ of these systems had concluded that photochemical *cis-trans* isomerization of 1,2-diphenylcyclopropane, sensitized by substituted naphthalenes, involves exciplex or electron transfer pathways. More recent efforts of Arnold^(80,81) and Roth⁽⁸²⁾ have probed the details of these isomerizations induced by electron transfer sensitization with the use of electrochemical and spectroscopic techniques. The results obtained are compatible with mechanisms involving electron transfer from the substituted cyclopropane σ bond to excited singlet acceptors, such as 1,4-dicyanonaphthalene and chloranil, generating the open shell radical cation as part of a singlet pair **115**. Return to nonisomerized reactant occurs through a multiplicity conserved back electron transfer. The triplet radical ion pair **116** formed by intersystem crossing, on the other hand, undergoes electron transfer to produce the triplet cyclopropane **117** of orthogonal geometry, capable therefore of partitioning to either the *cis* or *trans* isomer. Arnold⁽⁸³⁾ has found that the 1,2-diphenyloxi-



ranes **118** also undergo electron transfer sensitized *cis-trans* isomerization in polar, nonnucleophilic solvents such as acetonitrile. It appears that isomerization in these systems requires sensitizers with excited state reduction potentials greater than +2.0 eV. This is understandable in terms of the measured oxidation potentials of these oxiranes [$E_{1/2}$ (+) ca. 1.8 eV].

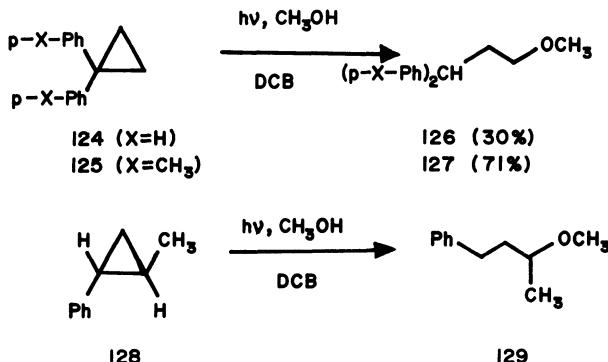


As expected, the cation radicals generated by electron transfer from these systems can participate in a variety of chemical processes which ultimately lead to ring cleavage. One example is found in the photochemistry of 1,1,2,2-tetraphenylcyclopropane **119** sensitized by 1,4-dicyanonaphthalene (DCN) in acetonitrile.⁽⁸⁴⁾ Under these conditions the propene **120** is formed through a pathway involving hydrogen transfer in the cation radical. In addition, excitation of the charge transfer complex of **119** and tetracyanoethylene (TCNE) in acetonitrile is apparently followed by electron transfer to produce the radical ion pair **123** which serves as a precursor for the indene **121** and reduced product **122** which are formed in this photoreaction. Cyclopropane-

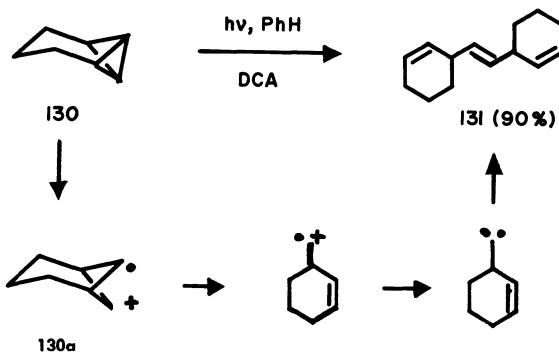


derived cation radicals can also react with nucleophiles as illustrated by Hixson's⁽⁸⁵⁾ observation that *p*-dicyanobenzene (DCB) effectively sensitizes the methanolytic ring opening reaction of a variety of 1,1-diarylcyclopropanes 124, 125, and 128. One of the intriguing aspects of these processes concerns the

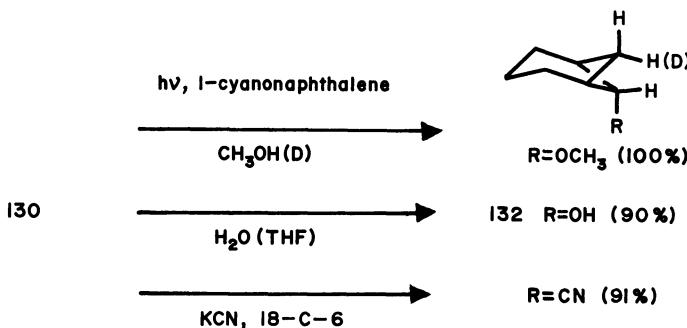
control of methanol addition regiochemistry. Apparently, the pathways involve the intermediacy of ring opened cation radicals or ones in which the cyclopropane σ bonds have acquired a large degree of charge radical separated character.



Other strained ring hydrocarbons appear to undergo similar electron transfer sensitized ring opening reactions leading to dimerization or nucleophilic solvent incorporation. Gassman⁽⁸⁶⁾ has found that a series of strained, saturated hydrocarbons with oxidation potentials lying between 0.4 and 2.1 eV serve as efficient quenchers of naphthalene fluorescence and that a reasonable correlation exists in these systems between observed k_q and predicted k_{et} values. The conclusion that electron transfer is involved in quenching is supported by observations made concerning the chemical reactivity of these systems. For example, 9,10-dicyanoanthracene sensitized irradiation of bicyclo[4.1.0.0^{2,7}] heptane (130) leads to the efficient production of dimer 131, the result of electron transfer induced ring opening followed by subsequent back electron transfer, and carbene coupling. When nucleophiles are included in this reaction mixture, stereocontrolled trapping of the initially formed cation radical 130a occurs to produce addition products, such as the ethers, alcohols,

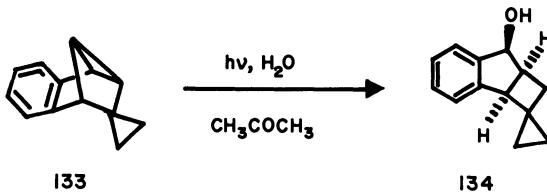


and nitriles **132**. A closely related example of photohydrolysis of a strained ring hydrocarbon is found in the conversion of **133** to the alcohol **134**.⁸⁷



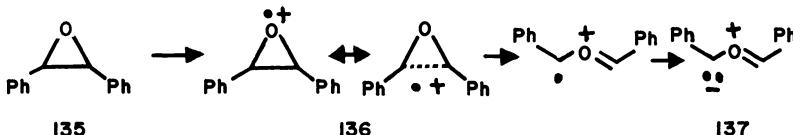
Acetone can serve as the electron-accepting sensitizer for this process which perhaps proceeds by an electron transfer mechanism analogous to those operating in the above cases even though the stereochemical outcome is unexpected.

The electron transfer photochemistry of 1,2-diphenyloxiranes **135** explored to date has yielded observations which demonstrate the potential of this method for carbonyl ylid generation. Accordingly, electron transfer sensitization of **135** results in ring opening through a cation radical intermediate **136** formed by either *n*- or σ -electron donation. Back electron transfer would then generate the familiar carbonyl ylid **137** capable of undergoing $\Pi_4 + \Pi_2$ cycloadditions with a variety of olefins. Arnold⁽⁸³⁾ has shown that this pathway



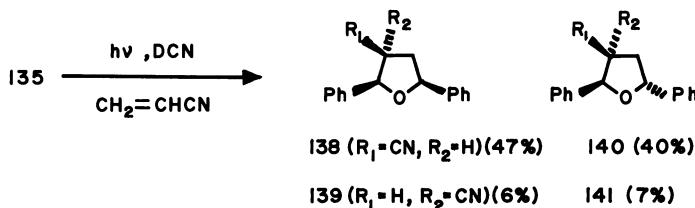
operates in the dicyanonaphthalene-sensitized additions of acrylonitrile to **135** furnishing the tetrahydrofurans **138–141**.

Still another strained ring system receiving attention due to its potentially interesting electron transfer properties is quadricyclene. NMR studies em-

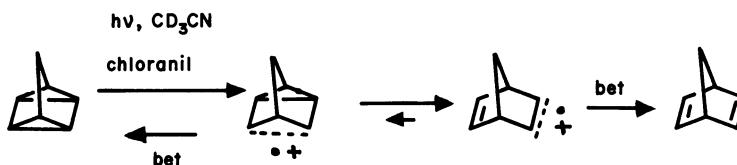


ploying the CIDNP technique conducted by Roth and Jones⁽⁸⁸⁾ have shown that the cation radical derived from quadricyclene by photochemical electron

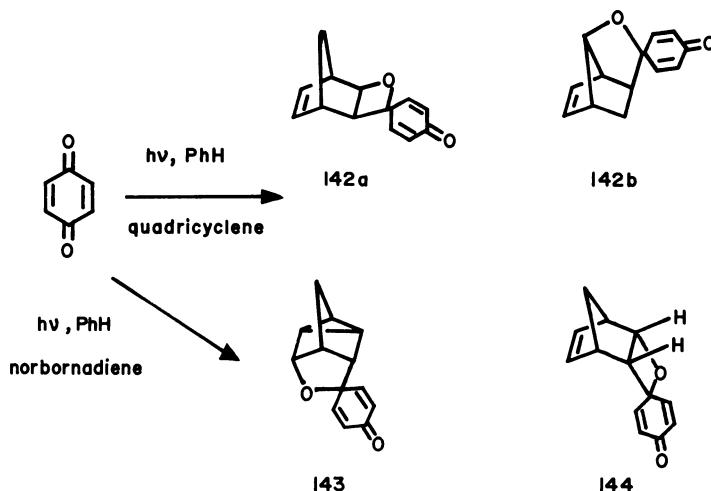
transfer is a discrete species with a lifetime on the order of several nanoseconds and that it undergoes irreversible conversion to the norbornadiene cation radical in competition with back electron transfer. Studies of the chemical consequences of these events have been less thorough. However, preliminary



information on which speculation can be based is provided in investigations by Fehnel and Brokaw⁽⁸⁹⁾ of *p*-benzoquinone photoadditions to quadricyclene



and norbornadiene. While the cycloadducts **142–144** are formed by irradiation of the quinone in benzene solutions of norbornadiene only two of these, **142a**



and **142b**, arise under similar conditions with quadricyclene. These results have been rationalized in terms of the intervention of biradical intermediates capable of undergoing rearrangement in competition with intramolecular coupling. Thus, the lack of adducts **143** and **144** in product mixtures arising

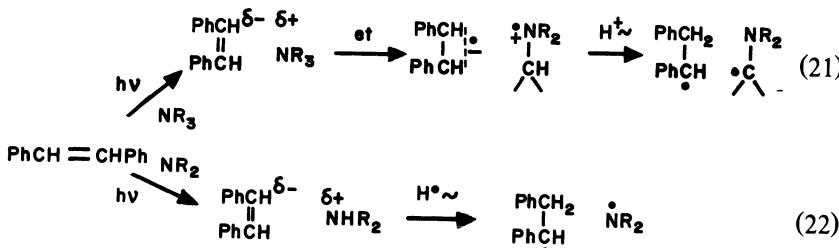
from quadricyclene was attributed to the inability of the system to produce the needed precursor diradical. In light of the results of Roth and Jones, an electron transfer mechanism via cation radical intermediates might be involved in these additions.

2.2. Amines

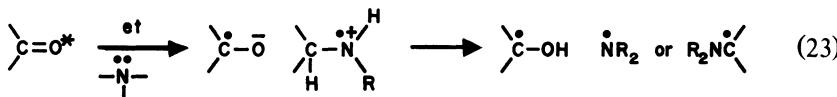
2.2.1. General Considerations

As a result of their low ionization and oxidation potentials amines serve as efficient electron donors in electron transfer processes with excited states of a variety of organic substrates including olefins, arenes, and carbonyl compounds. In this section, synthetic aspects of reactions resulting from amine–olefin and amine–ketone electron transfer processes will be discussed. Before doing this it is instructive to consider briefly the results of several photophysical studies which outline the principles involved and, more importantly, the factors that control reactivity. Information about the mechanistic details of amine–olefin photochemistry has been gained through the efforts of Lewis and his co-workers⁽⁹⁰⁾ with amine–stilbene systems. In general, emitting exciplexes are formed upon irradiation of nonpolar solutions of stilbene and tertiary amines. The efficiency for exciplex formation is coupled to the rate constant for quenching of stilbene fluorescence by amines, both of which are directly dependent upon the tertiary amine ionization potentials. Exciplex emission is quenched in polar solvents while addition product formation (*vide infra*) is enhanced as solvent polarity increases. These data strongly suggest that exciplex formation results in charge transfer and that decay of these complexes in polar solvents leads to production of ion-radical pairs which serve as key intermediates in product formation. Emitting exciplexes are not produced in secondary-amine stilbene systems although complexes with charge transfer characteristics have been proposed as intermediates in pathways for fluorescence quenching. Evidence for this comes from observations which suggest that secondary amine ionization potentials correlate with fluorescence quenching rate constants and addition reaction quantum efficiencies. For example, k_q values are directly dependent upon IP while ϕ , decrease with decreasing IP as well as with increasing solvent polarity. Thus, although electron transfer is involved in stilbene singlet excited-state deactivation by secondary amines, radical ions are apparently not involved in mechanisms for adduct formation. In summary, complete electron transfer in tertiary amine systems yields radical ions which can participate in a variety of chemical processes, including α -proton transfer [equation (21)]. On the other hand, exciplexes with charge transfer characteristics in secondary amine–

stilbene systems undergo direct reaction by N–H proton transfer in competition with complete electron transfer to produce chemically inert radical ions [equation (22)].



An abundance of evidence has been accumulated demonstrating that electron transfer occurs efficiently from a variety of primary, secondary, and tertiary amines to singlet and triplet excited states of ketones and that the radical ions formed undergo rapid proton transfer from the amine radical cation nitrogen or α -carbons of the amine [equation (23)].^(91,92) This mechanism for radical pair production in amine–ketone systems appears to dominate hydrogen atom abstraction pathways as evidenced by the following observations. Amines have been found to be powerful reducing agents of carbonyl excited states even in cases where the less active electron donor isopropyl alcohol is ineffective due to the existence of low-lying ketone $\pi-\pi^*$ or CT



states.^(93–97) The rates of ketone reduction by amines are much larger than by isopropyl alcohol^(98,99) and are well correlated with amine ionization potentials.⁽¹⁰⁰⁾ Most importantly, radical ions have been detected by spectroscopic methods in these systems.^(101–104) That singlet ketones also participate in electron transfer quenching is suggested by observations made in studies of biacetyl, fluorenone, and thioxanthone fluorescence quenching.^(105–107) Additional spectroscopic investigations have shown that proton transfer in radical ion pairs generated by electron transfer from tertiary amines to excited ketones occurs with near unit efficiency.^(92,102,108,109)

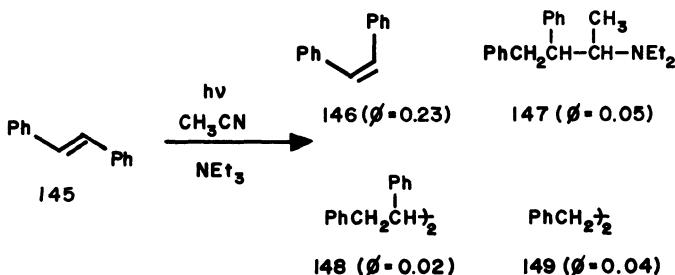
2.2.2. Amine–Olefin Electron Transfer Photochemistry

Detailed studies of the photochemistry of amine–stilbene systems have uncovered examples of photoaddition processes of interest due to their structural and regiochemical outcomes. For example, *trans*-stilbene (**145**) undergoes smooth photoreaction when irradiated in acetonitrile solutions of triethylam-

Amine	Coupling Products	
	%position a	%position b
CH ₃ CHN (CH (CH ₃) ₂) ₂	92	8
CH ₃ N (CH (CH ₃) ₂) ₂	> 95	< 5
CH ₃) ₂ N CH ₂ CH ₃	84	16
(CH ₃) ₂ N CH(CH ₃) ₂	83	17

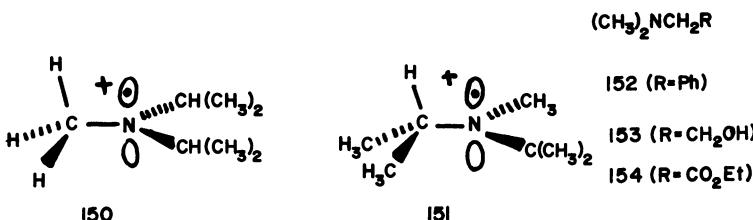
Figure 3. Yields of amine-stilbene coupling products arising from deprotonation at positions a or b, α to nitrogen in amine cation radicals.

ine producing the isomerized olefin **146**, coupling products **147** and **148**, and reduction of products **149**.⁽¹¹⁰⁾ The regiochemical course of the amine-olefin coupling process, probed through the use of a variety of unsymmetrically substituted tertiary amines, appears to depend on the nature of the alkyl substituents in a manner expected for control by stereoelectronic factors.⁽¹¹¹⁾ Accordingly, results from study of the tertiary amines listed in Figure 3 indicate preferences for coupling at the least alkyl-substituted amine α carbon. This selectivity has been attributed to stereoelectronic requirements of deprotonation of the amine cation radical resulting from the need to align σ -CH bonds parallel to the half-vacant p orbital on nitrogen. Steric considerations suggest that the transition state **150** should be of lower energy than **151** and, thus, that the deprotonation and coupling ratios should be greater than statistical at the methyl rather than isopropyl methine positions of methyl diisopropylamine. However, other factors, including kinetic acidity, may be important in controlling the regiochemistry of amine-stilbene photo-

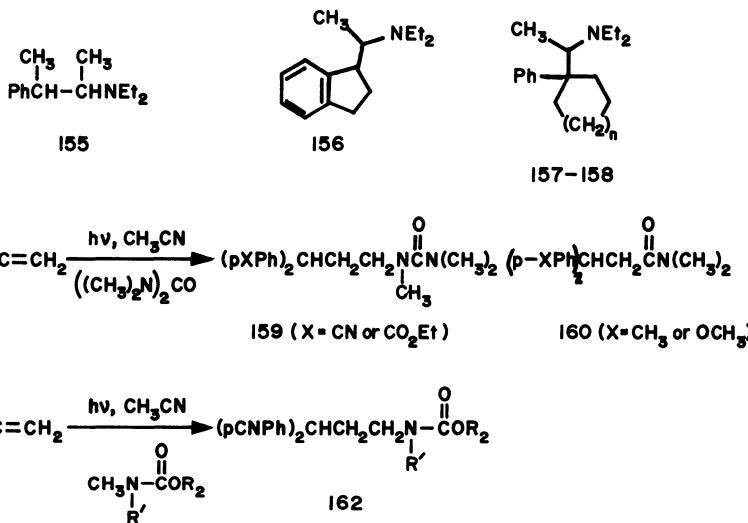


toadditions. This is illustrated by preferences for coupling at the more substituted methylene positions in amines **152**–**154**.^(112,113)

The synthetic utility of amino-olefin photoadditions is further exemplified by observations that triethylamine undergoes modestly efficient, regiocon-

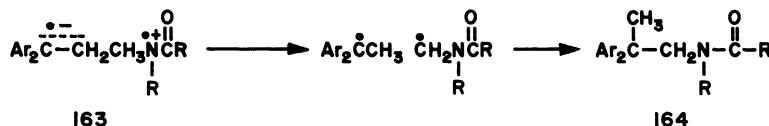


trolled addition to the styryl moieties of styrene, indene, 1-phenylcyclopentene, and 1-phenylcyclohexene yielding the adducts **155–158** along with reduced olefins.⁽¹¹⁴⁾ Product regiochemistries in these cases are nicely rationalized in terms of proton transfer in the initially produced ion radical pairs to yield

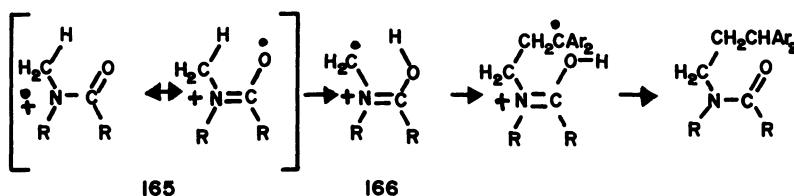


the more stable phenyl-conjugated radicals prior to coupling. Structurally related transformations have been observed in studies of carbamate and urea photoadditions to 1,1-diarylethylenes. Irradiation of the electron withdrawing substituted aryl olefins in acetonitrile solutions containing tetramethylurea results in the high yield (92%–95%) production of the addition products **159**.⁽¹¹⁵⁾ The efficiencies of this process are low in cases of *p*-CH₃ and *p*-OCH₃ substituted systems where reaction favors an alternate pathway leading to carbamates.⁽¹¹⁶⁾ Although the structural outcomes of these photoadditions mimic those of the amine–olefin electron transfer processes discussed above, it is doubtful that this similarity holds also for the mechanistic details. Thus, although electron transfers from ureas or carbamates to the excited olefins are highly probable initial events in these processes, the ensuing steps do not appear to involve proton transfer as the authors have suggested, since available data would suggest that protonation of the olefin-derived radical anions should

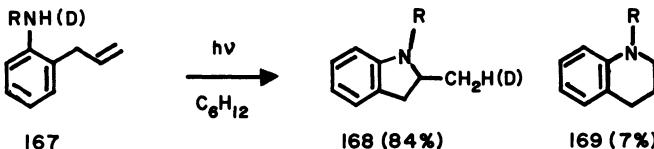
be at the terminal rather than the phenyl-substituted carbons. If proton transfer were to occur prior to coupling, formation of the benzylic substitution products **164** is expected. A possible rationale of this atypical regiochemistry



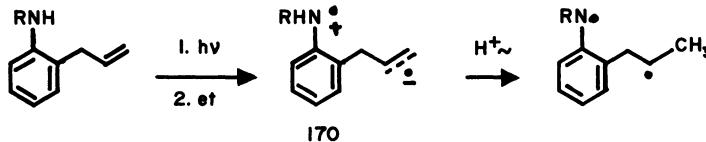
still based upon initial electron transfer involves invocation of intramolecular H-atom migrations via a 1,4-sigmatropic shift in the initially produced cation radicals **165** forming the more stable intermediate **166**. Coupling of **166** with the olefin radical anions followed by proton transfer would then lead to the observed urea and urethane products. Thus, the unusual regiochemistry observed in these additions might be due to the availability of intramolecular proton relocation pathways which can compete with the inter-radical ion route.



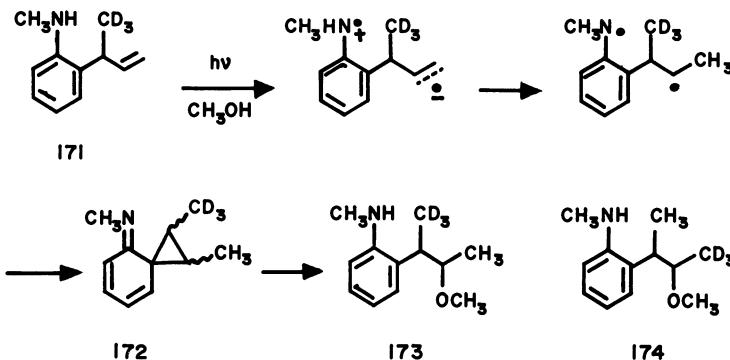
Investigations by several groups have demonstrated that intramolecular electron transfer initiated secondary amine–olefin photoreactions serve as useful cyclization methodologies. In independent efforts, Dallocq and Lattes⁽¹¹⁷⁾ and Schmid⁽¹¹⁸⁾ showed that the *o*-allylanilines **167** undergo efficient photocyclization to generate mainly the indolines **168** along with trace quantities of the tetrahydroquinolines **169**. The indoline forming process is quite general⁽¹¹⁹⁾ and occurs in competition with Π -bond isomerization⁽¹²⁰⁾ and Markovnikoff addition when conducted in methanol solution.^(118,121) Schmid and



his co-workers have proposed electron transfer mechanisms through intervention of diradical zwitterions **170** for these processes. A detailed study of

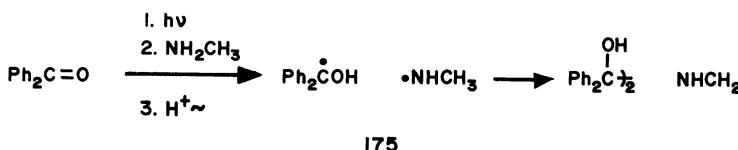


the methanol additions to these *o*-allylanilines and their para-isomers has been carried out recently by Hansen.⁽¹²²⁻¹²³⁾ The results demonstrate that simple mechanisms, involving electron transfer followed by protonation, back electron transfer, and methanol attack, are not operable in these cases. Rather, these photoadditions proceed via the spirocyclic dienimine intermediates 172 as illustrated by the conversion of 171 to a threo-erythro steroisomeric mixture of methanol adducts 173 and 174.



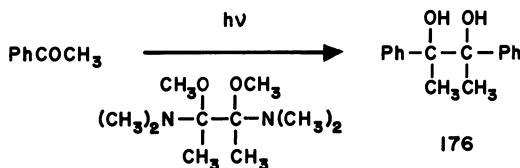
2.2.3. Amine-Ketone Electron Transfer Photochemistry

The chemical reaction pathways followed by amine-ketone systems which participate in photoinitiated electron transfer are controlled by the processes available to the radical ion intermediates. In most instances, proton transfer from the amine cation radicals to ketyl radical anions is exceptionally efficient, and, thus, radical pair formation dominates other possible reaction modes. The photoreductive dimerization observed for the benzophenone-methylamine system is a typical example of this reaction type in which N-H proton transfer leads to generation of benzhydrol radicals 175.⁽¹²⁴⁾ Dimerization re-

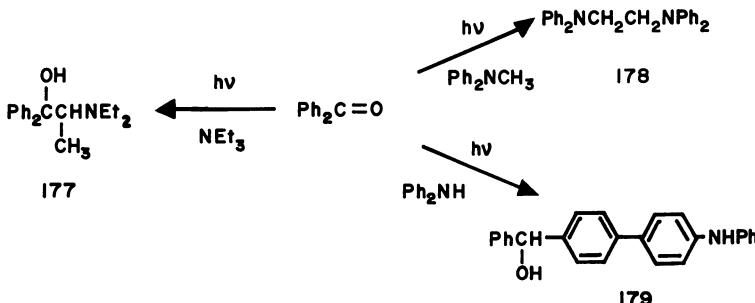


actions of this kind can also be initiated by α -CH proton transfer from tertiary amine radical cations. An intriguing example is found in studies by Seebach⁽¹²⁵⁾ targeted at the development of novel methods for chiral synthesis. Irradiation of solutions of acetophenone in the chiral amine (+)-2,3-bis(dimethylamino)-2,3-dimethoxybutane leads to production of a mixture of diol diastereomers containing 28% of the *dl*-isomer 176. The *dl*-pinacol was formed in a 6% optical yield, suggesting the involvement of the chiral amine in the radical

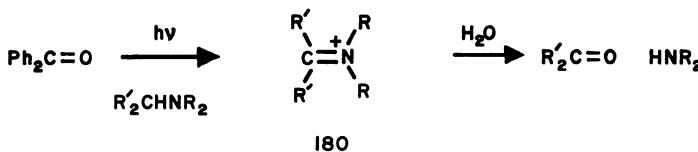
coupling step. Alternative modes of amine–ketone electron transfer photo-reaction dictated by the nature of radical coupling have been observed in



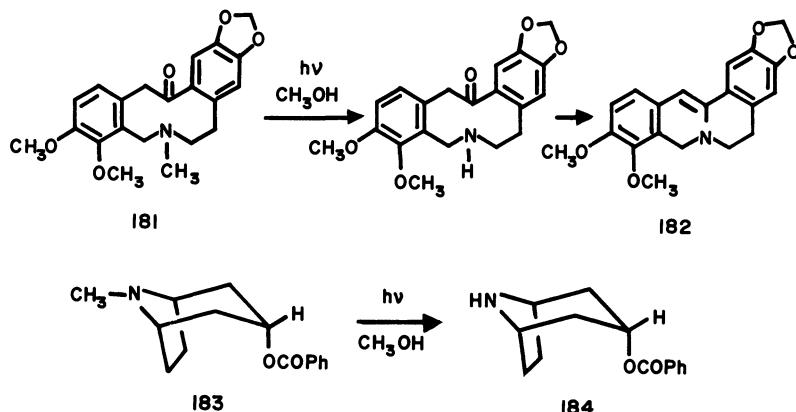
reaction pathways followed by benzophenone–triethylamine and diphenyl-amine systems.^(126,127) In these cases, the amino radicals arising by α -CH proton transfer undergo carbon–carbon bond formation to produce amino alcohol **177**, diaminoethane **178**, and biphenyl **179** products. Yet another reaction type detected for tertiary amine–ketone systems involves dealkylation. In these



cases, sequential electron and proton transfers are followed by back electron transfer to yield the iminium salts **180** which undergo hydrolysis on aqueous work-up of reaction mixtures giving carbonyl and secondary amine products.⁽⁹⁹⁾ Regiochemical control in these dealkylations appears to be governed by factors similar to those operating in the amine–olefin additions discussed earlier. Thus, loss of the less substituted alkyl group is dictated by preferential

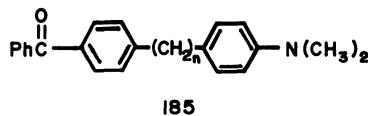


deprotonation at the less-branched amine cation radical α -carbon. This reaction appears to be quite general and, as a result, has been employed as a dealkylation method for transformation of a variety of naturally occurring amines.⁽¹²⁸⁾ Some examples, which illustrate its versatility, are found in the photodealkylative cyclodehydration of α -allocryptopine **181** producing berberine **182**⁽¹²⁹⁾ and the photodemethylation of benzoyltropine **183**.^(130,131) In

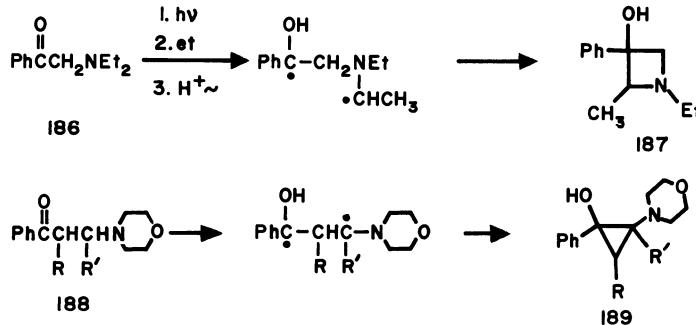


both of these processes, the initial electron transfer occurs intramolecularly from amine to excited aroyl groupings. Evidence for this postulate is provided by the observation that the nonbenzoyl tropine system is unreactive under the conditions used for the conversion of **183** to **184**.

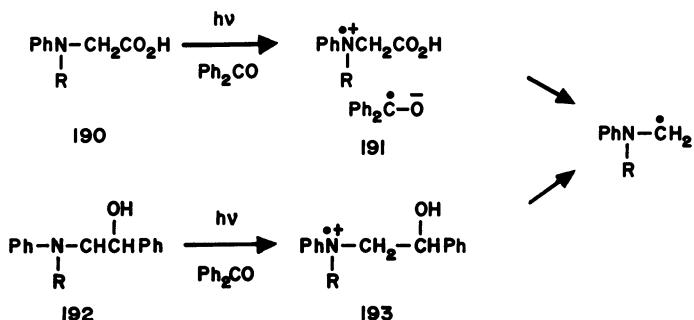
Photophysical aspects of intramolecular electron transfer in amine- κ -ketone systems have been probed in detailed spectroscopic studies by Masuhara and Mataga.⁽¹³²⁾ These investigations show that intramolecular singlet and triplet exciplexes form upon excitation of the polymethylene linked benzophenone-*N, N*-dimethylanilines **185**. As expected, complete electron transfer in these cases generates zwitterionic diradicals which can serve as intermediates



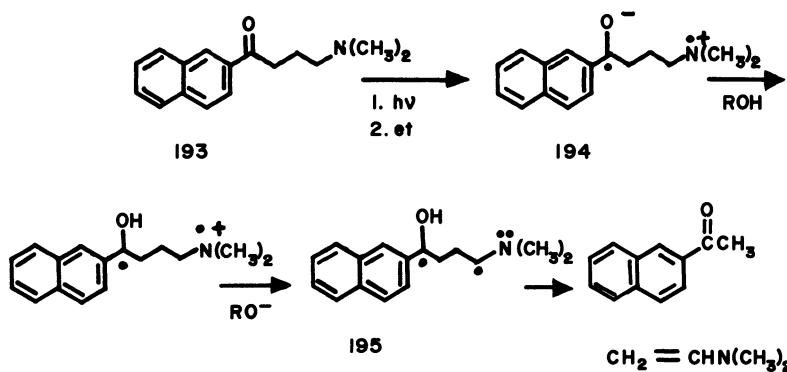
in routes for heterocyclic and carbocyclic product formation. Accordingly, the α -aminoacetophenone **186** undergoes efficient cyclization to generate the hydroxyazetidine **187**⁽¹³³⁾, while the cyclopropanols **189** are produced upon irradiation of the morpholinopropiophenones **188**.⁽¹³⁴⁾



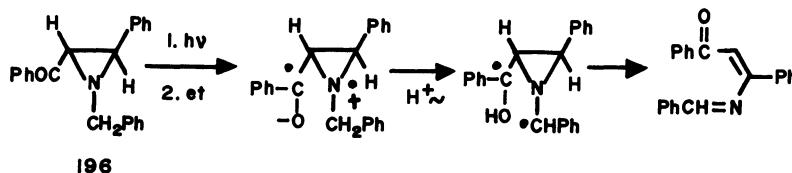
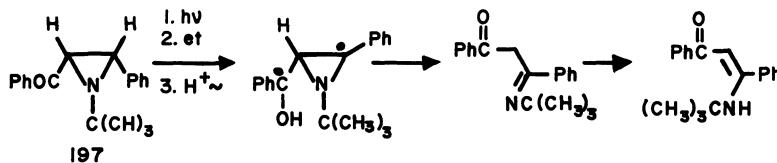
Thus far, we have seen that deprotonation of amine radical cations at α -carbons leads to generation of amino-alkyl radicals in pathways which dominate the electron transfer chemistry of amines. However, unusually interesting processes occur when electrofugal groups other than protons are attached to α -carbons of amine-derived radical cations. Davidson and his co-workers^(135,136) have uncovered two interesting examples of reactions initiated in this way. Irradiation of benzophenone in solutions containing the *N*-phenyl-*N*-alkylglycines **190** results in efficient decarboxylation. The rate of loss of CO₂ in these systems equals that of triplet quenching, suggesting that decarboxylation of the intermediate cation radical **191** must occur with near unit efficiency. In a similar fashion, retro aldol fragmentation of the anilinoethanols **192** occurs upon irradiation in the presence of benzophenone.



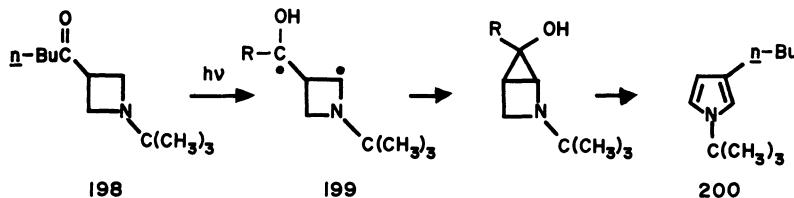
Another type of fragmentation process observed in the electron transfer photochemistry of amine-ketone systems is exemplified by the efficient Norrish type II cleavage of the amino-2-butyronaphthalene **193** induced by irradiation in polar, protic solvents.⁽¹³⁷⁾ The familiar intramolecular hydrogen atom abstraction mechanism for Norrish type II processes is probably not involved in this transformation since the lowest-energy excited state of **193** is of triplet $\Pi-\Pi^*$ rather than $n-\Pi^*$ character. Thus, an alternative route through 1,4-diradical **195** must be followed. It seems reasonable that se-



quential electron–proton transfers would also generate the intermediate diradical which then undergoes Grob-type fragmentation. An intriguing observation is that the efficiency of fragmentation is highly dependent upon the nature of the solvent employed, ranging from 0.08 in benzene to 0.17 in 5 M methanol in benzene. This dependence is attributed to the protic nature of methanol which allows it to serve as an acid–base catalyst in the proton transfer step converting the initially formed zwitterionic diradical **194** to **195**. The requirement for catalysis of this usually efficient process in intermolecular examples suggests a rather restricted geometry for **194** making intramolecular proton transfer difficult. Fragmentations analogous to the type II process observed for **193** have been detected in studies of aziridinylketone photochemistry with the arylketones **196** and **197**.^(138,139) A related pathway involving diradical coupling rather than bond cleavage is followed in the excited-state transformation of the azetidinylketone **198** to pyrrole **200**.⁽¹⁴⁰⁾

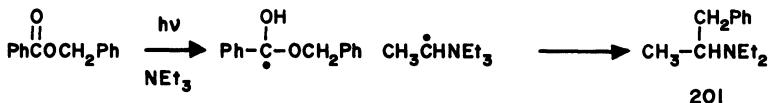
**196****197**

It appears important to review in this section an area of electron transfer photochemistry involving amines which to date has received much less attention than studies of amine–olefin and amine–ketone photochemistry. Evidence available from a variety of investigations suggests that amine–ester systems can participate in excited-state electron transfer and that synthetically interesting chemistry can result from the formed ion radical intermediates. For example, spectroscopic studies by Kokubun and Koizumu^(141,142) dem-

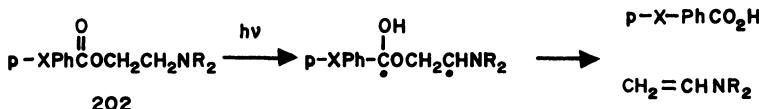


onstrate that radical ions are produced when mixtures of aromatic amines and aromatic esters are irradiated in polar solvents. The chemical processes

followed in these systems are exemplified by the tertiary amine photoalkylations initiated by irradiation of benzoic acid esters as illustrated by production of amine **201** from irradiation of solutions of benzyl benzoate in triethylamine.⁽¹⁴³⁾ Likewise, the quantum yields for fragmentation of the ami-



noethyl benzoates **202** depend on the nature of the *p*-phenyl substituents in a way expected for mechanisms involving initial intramolecular electron transfer from the amino to excited aryl group.⁽¹⁴⁴⁾



2.3. Ketones

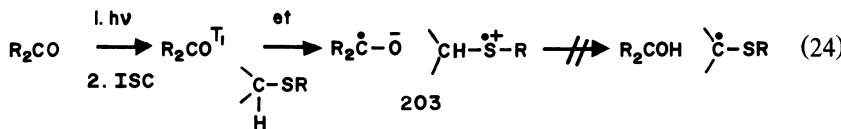
2.3.1. General Considerations

In the previous section we have discussed several observations which demonstrate that certain ketones and esters in their triplet and singlet excited states serve as electron acceptors in electron transfer reactions with good donors such as ground states of amines and that the radical-ion pairs formed in this way participate in efficient proton transfer or fragmentation processes. The chemical reaction pathways followed by these systems, including carbon–carbon bond formation or cleavage, are nicely rationalized on the basis of these initial steps. Electron transfer also appears to be efficient when ketone excited states interact with other electron donors with low oxidation potentials. Thioethers, disulfides, and phosphines are examples of donor systems which have been investigated. In addition, quinones, a class of carbonyl compounds with exceptionally high excited-state reduction potentials, are capable of serving as acceptors in one electron transfer processes with a variety of organic substrates. In this section we will briefly summarize the chemical aspects of ketone and quinone photochemistry which appear to be compatible with electron transfer mechanisms although in some cases experimental verification is lacking.

2.3.2. Ketone Electron Transfer Photochemistry

It has been known for some time that thioethers serve as reasonably efficient quenchers of ketone phosphorescence.^(145,146) Quenching in these cases does not appear to involve triplet ketone hydrogen atom abstraction since

the typical chemical reactions associated with this type of process are not followed by these systems. On the basis of these observations and the predicted free energies and rates for electron transfer, it seems reasonable to conclude that ketone triplet quenching by thioethers involves reversible electron transfer. Furthermore, the absence of ketone photoreduction is consistent with a mechanism where proton transfer from the thioether cation radicals to the ketyl radical anions is slow compared to back electron transfer [equation (24)]. As expected, photochemical reactivity is observed for these systems



when more efficient reaction pathways are available to the radical ions **203**. An example of this is found in the benzophenone sensitized photodecarboxylation of α -thioacetic acids **204** producing alkyl methyl sulfides **205**.^(135,147) In these systems, decarboxylation is initiated by proton transfer to the ketyl anion radical from the more acidic carboxylic acid group of the cation radical. The ketone-photosensitized cleavage of dialkyl disulfides appears to be another

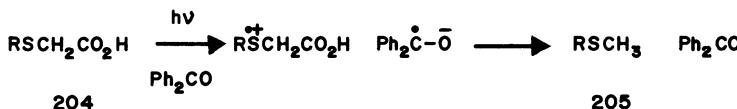
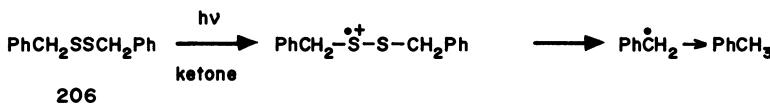
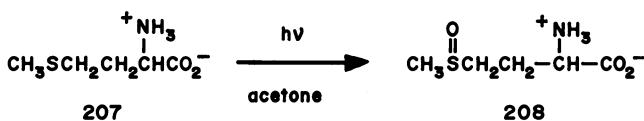


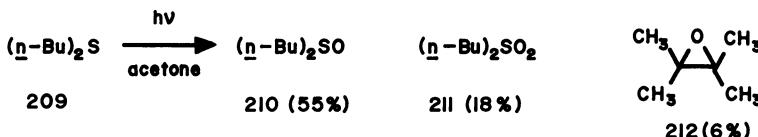
illustration of this phenomenon. Kampmeir's studies⁽¹⁴⁸⁾ have shown that the rates of triplet-sensitized decomposition of dibenzyl disulfide **206** are independent of the ketone triplet energy but directly related to the reduction potentials of the ketone sensitizers. When these photoreactions are conducted in the presence of free radical scavengers such as thiols, the benzyl radicals generated by homolytic cleavage of the cation radical intermediate are efficiently trapped.



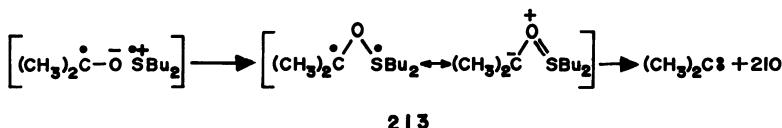
The photochemical behavior of acetone-dialkylsulfide systems serves as additional evidence for the operation of electron transfer mechanisms. In early studies, Gennari and Jori⁽⁴⁹⁾ had shown that methionine **207** is efficiently transformed to the corresponding sulfoxide **208** by irradiation [311 nm] in deoxygenated acetone solutions. The preliminary conclusion of this study as well as those probing the biacetyl-sensitized oxidations of this amino acid^(50,51) was that the carbonyl compounds serve as the sources of the oxygen transferred to methionine. This question has been investigated more thoroughly



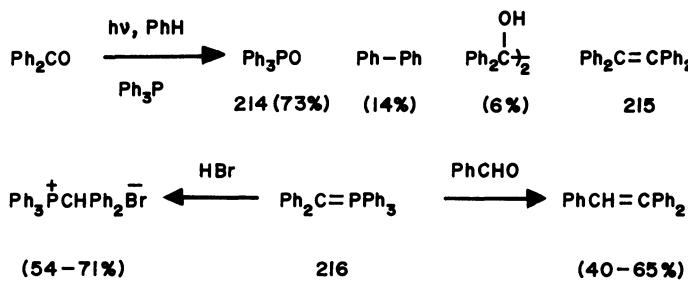
in recent studies by Fox and her co-workers,⁽¹⁵²⁾ who observed that irradiations of deoxygenated solutions of acetone and dialkylsulfides leads to production of oxidation products. This is exemplified by the conversion of dibutylsulfide **209** to the sulfoxide **210**, sulfone **211** and oxirane **212**. The relative rates of these oxygenation reactions are directly dependent upon the solvent polarity,



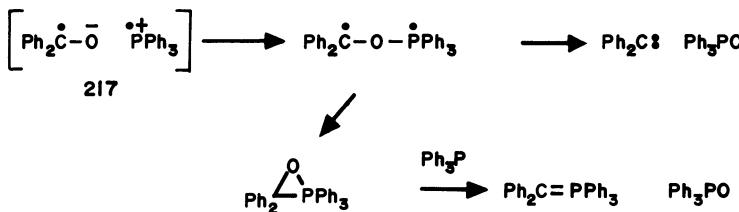
increasing by a factor of 2 in proceeding from benzene or cyclohexane to methanol. Mechanisms for production of **210** and **212**, consistent with these observations, involve radical ion production by electron transfer and coupling to produce the thiacarbonyl ylid **213**. Carbon–oxygen bond cleavage would then generate sulfoxide **210** and isopropylidene, the precursor to oxirane **212**.



Similar reaction pathways have been detected in ketone–phosphine photochemistry. Wescott⁽¹⁵³⁾ on the basis of preliminary results had suggested that irradiation of solutions of benzophenone containing triphenylphosphine leads to formation of diphenylmethylene triphenylphosphorane **216**. This material was identified in the crude photolysis mixture by its characteristic visible spectrum. Attempts to trap this ylid through its Wittig reaction with carbonyl compounds were unsuccessful. Analogous reactions occur in aryl ketone photodeoxygenations with trialkylphosphites⁽¹⁵⁴⁾ and diphosphines.⁽¹⁵⁵⁾ Studies which assist in clarifying mechanisms for these processes have recently been reported by Fox.⁽¹⁵⁶⁾ Careful analysis of the product mixture arising from irradiation of deoxygenated benzene solutions of benzophenone and triphenyl phosphine with wavelengths greater than 300 nm revealed the presence of triphenylphosphine oxide **214**, biphenyl, benzpinacol, and tetraphenylethylene **215**. The presence of the ylid **216** in the crude photolysate was proven through trapping reactions with benzaldehyde and aqueous hydrogen bromide. Additional mechanistic information is found in the observations that triphenylphosphine efficiently quenches benzophenone triplets and that 1,1-diphenyl-



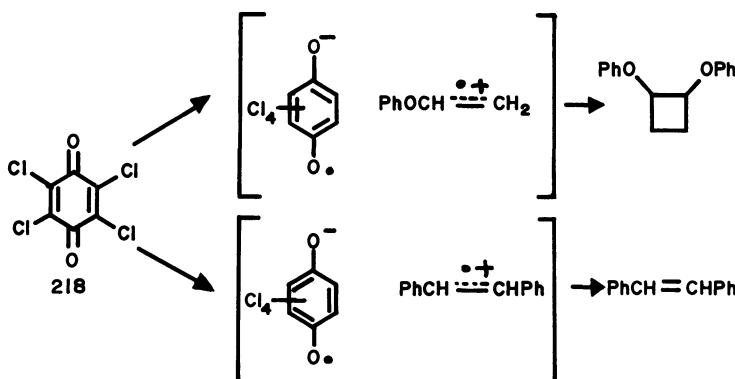
2,2-dimethylcyclopropane is produced in trace quantities when isobutylene is included in the reaction mixture. These results are consistent with several possible pathways for conversion of the initially formed radical ion pair **217** to the observed products. Diphenylcarbene and triphenylphosphine oxide, for example, could arise by ion pair coupling followed by phosphacarbonyl ylid cleavage. Alternately, a phosphaoxirane intermediate would be a reasonable precursor for triphenylphosphine oxide and the phosphorane **216** via a phos-



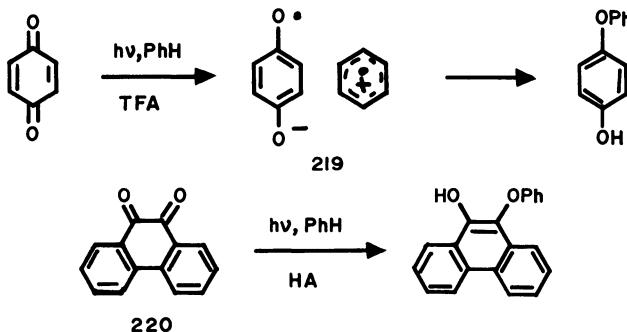
phine-induced deoxygenation pathway. Independently of the mechanistic complexity of the final steps for this reaction, it is clear that phosphine-induced photodeoxygenations of carbonyl compounds stand as further examples of interesting electron transfer processes.

2.3.3. Quinone Electron Transfer Photochemistry

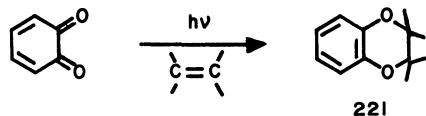
Suggestions about the intervention of electron transfer in the excited-state chemistry of quinones have come from a variety of spectroscopic and chemical studies. Evidence for exciplex formation between aromatic hydrocarbons and quinones is found in the early investigations of Bryce-Smith and his co-workers.^(157,158) More recently, Roth⁽¹⁵⁹⁾ has employed CIDNP techniques to demonstrate that radical ions are produced when chloranil **218** is irradiated in the presence of phenyl vinyl ether or the 1-phenylpropenes. Roth has further demonstrated that back electron transfer in these charged radical intermediates is competitive with dimerization and *cis-trans* isomerization. Similarly, electron transfer to excited quinones from aromatic hydrocarbons appears to be responsible for chemical processes which occur in these systems.



Illustrative of this are the interesting photophenylation reactions seen when *p*-benzoquinone⁽¹⁶⁰⁾ and 9,10-phenanthraquinone **220**⁽¹⁶¹⁾ are irradiated in benzene solutions containing strong acids. The catalytic role of acid in these systems most probably stems from the competitive nature of radical anion, e.g., **219**, protonation versus back electron transfer.

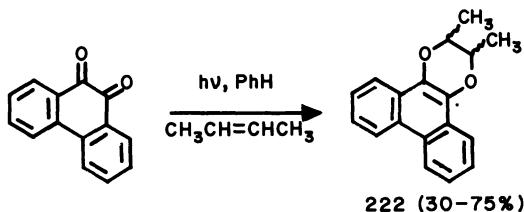


Synthetically relevant quinone–olefin photoaddition reactions appear also to follow electron transfer mechanisms. In early efforts, Schonberg and Mustafa⁽¹⁶²⁾ had observed that *o*-benzoquinone undergoes photoaddition to a variety of olefins producing 1,4-dioxene products **221**. A number of mechanistic studies of this reaction have been reported since that time.^(163,164) More recent investigations with phenanthraquinone have provided results consistent with

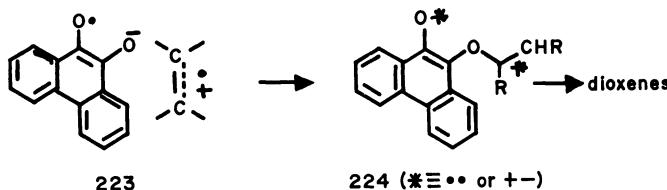


the electron transfer nature of the quinone olefin cycloadditions.⁽¹⁶⁵⁾ Thus, photoadditions of phenanthraquinone occur via the *n*– π^* triplet manifold and require that the olefin substrates be electron rich. Dioxene formation is

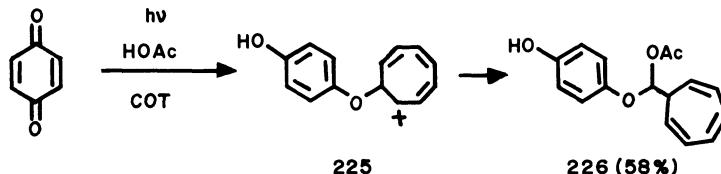
not observed with fumaronitrile and the quantum yields for dioxene production correlate qualitatively with olefin oxidation potentials. Finally a non-concerted cycloaddition mechanism is required on the basis of the observation that the same ratio of stereoisomeric dioxenes **222** is obtained when starting with either *cis* or *trans*-2-butene. Analogous results have been reported by



Bryce-Smith and Gilbert⁽¹⁶⁶⁾ for the *o*-chloranil–stilbene system. The combined observations suggest that 1,4-dioxene formation occurs through the intervention of the ion radical pairs **223**. Coupling to produce the diradical or zwitterionic intermediates **224** is then followed by carbon–oxygen bond formation, an apparently slow process relative to bond rotation.

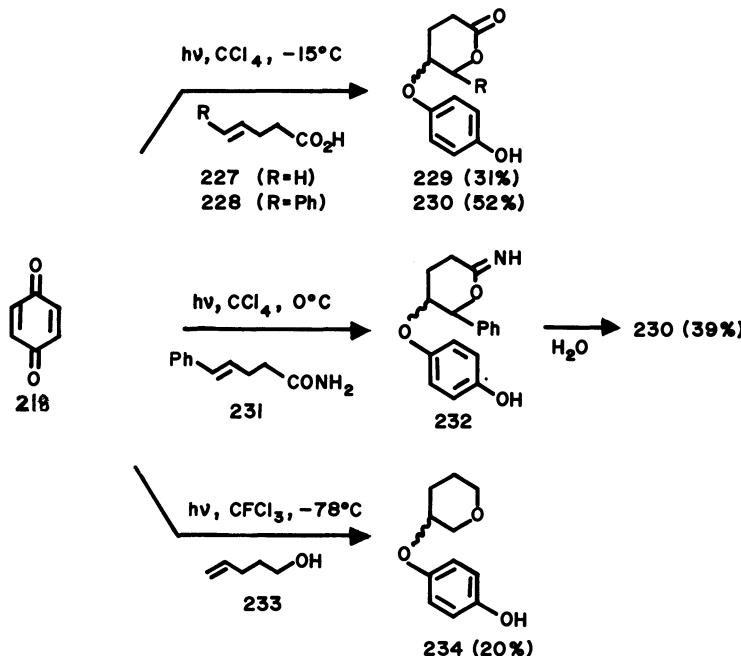


Further evidence for electron transfer in quinone-olefin photochemistry along with extremely interesting examples of synthetic applications are found in investigations by Wilson^(167,168) of the argon-laser-induced photoadditions of olefins to *p*-benzoquinone. Cyclooctatetraene, for example, has been observed to undergo efficient addition producing the acetal 226 when irradiations are conducted in acetic acid solutions.⁽¹⁶⁷⁾ A reasonable mechanism for this ring-contracting addition is through a stepwise pathway involving electron



transfer, protonation, and radical ion coupling forming the carbenium ion **225** which then rearranges to the cationic precursor to **226** by vinyl group migration. In an extension of this initial study, Wilson⁽¹⁶⁸⁾ has probed quinone photoadditions which employ olefin substrates possessing nucleophilic group-

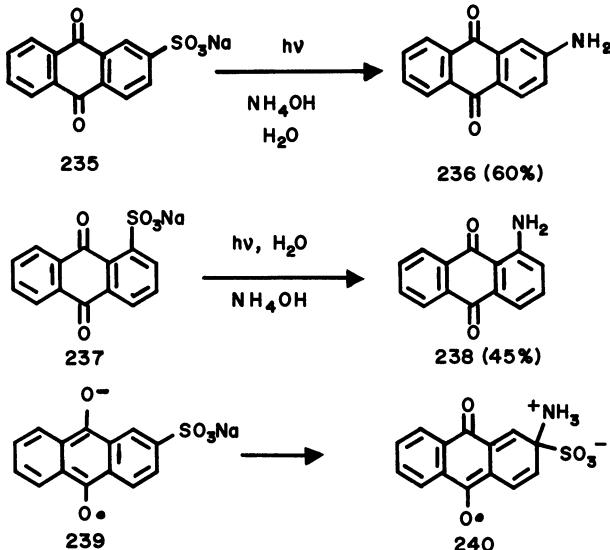
ings capable of internally trapping radical cations. Irradiation of solutions of *p*-benzoquinone **218** containing the pentenoic acids **227** and **228** leads to production of the lactones **229** and **230**, respectively. In an analogous fashion, the lactone **230** and cyclic ether **234** are produced from the electron transfer induced addition of the unsaturated amide **231** and alcohol **233** to *p*-benzoquinone. Several features of these cyclization reactions warrant further comment. First, if internal capture of the radical cation moieties by the nucleophilic acid, amide, or alcohol functions precedes coupling to the quinone fragment, an unusual source of regiochemical control must be at work. Thus, the product



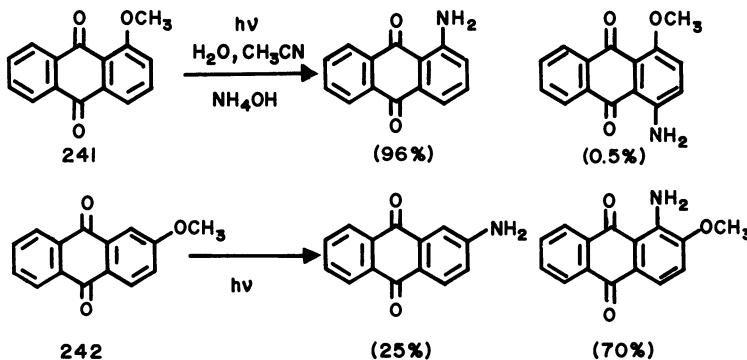
structures suggest that nucleophilic attack occurs to produce the less substituted radicals, a result differing from that predicted on the basis of earlier observations made in studies of electron transfer sensitized nucleophilic additions to olefins. However, this regiochemical outcome appears consistent with the stereoelectronic requirements for cyclization reactions through intramolecular nucleophilic addition to Lewis acid centres or with pathways in which radical ion coupling occurs prior to nucleophilic addition. Also, cyclization of the cation radical derived from the unsaturated amide **231** utilizes the amide oxygen rather than the nitrogen center. This is expected on the basis of the bidentate reactivity of amides with hard acids.

Radical anions arising by electron transfer to the excited states of substituted quinones have been postulated as intermediates in quinone photo-substitution reactions. Wubbels and his co-workers⁽¹⁶⁹⁾ have suggested mech-

anisms of this type to rationalize observations made in investigating the efficient photostimulated nucleophilic substitution processes followed by the 9,10-anthraquinone sulfonates **235** and **237**. Irradiation of these substances

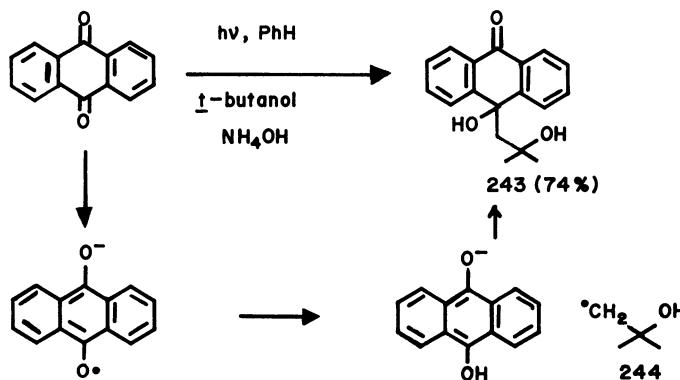


in aqueous ammonium hydroxide leads to formation of the aminoquinones **236** and **238**. When irradiations of **235** and **237** are conducted in aqueous diethylamine, no substitution reactions are observed. However, uv-spectroscopic methods have been used to show that the quinone radical anions are produced under the latter conditions. Analogous substitution reactions have been observed with the methoxy-substituted anthraquinones **241** and **242**.⁽¹⁷⁰⁾ In these cases, remarkably clean reactions occur to generate products of direct displacement at the methoxy bearing centers and at remote positions. Wubbels has concluded that these photosubstitution reactions follow electron transfer routes in which the intermediate radical anions, e.g., **239**, couple to the ammonia radical cation giving the intermediates **240** which then expel the



sulfite leaving group. The lack of reactivity of **235** and **237** with diethylamine is attributed to rapid proton transfer from the α -CH position of the amine cation radical giving radical pairs which efficiently return to reactant ground states by back hydrogen atom transfer.

In continuing efforts in this area, Wubbels⁽¹⁷¹⁾ has observed and interpreted the intriguing photoaddition to anthraquinone of the reluctant hydrogen atom donor, *t*-butyl alcohol. Ammonia serves a key role in the production of ketodiol **243** as evidenced by its effect on the reaction quantum efficiency which varies from 0.008 to 0.16 with changes in ammonia concentrations from 0 to 1 *M*. Kinetic studies have shown that ammonia is involved in the primary step following triplet anthraquinone production. It appears certain

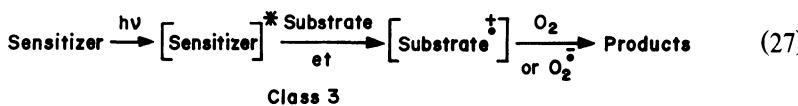
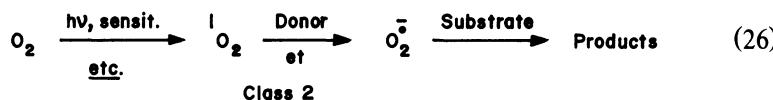
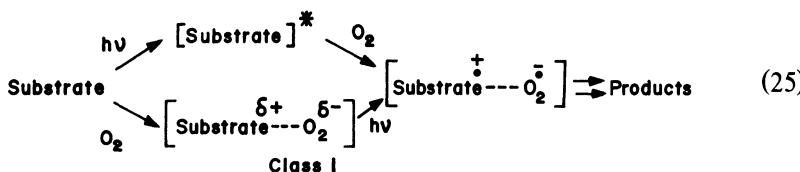


that the ammonium radical cation arising from electron transfer acts as the reactive hydrogen atom abstracting agent yielding the alkyl radical **244** in the key step in this transformation.

2.4. Electron Transfer Photooxygenations

2.4.1. General Considerations

Organic photooxygenation reactions have received intense study during the past decade as a result of major changes in mechanistic concepts brought about by thoughts about the availability of electron transfer pathways to the reacting systems. Many processes formerly rationalized in terms of the intermediacy of singlet molecular oxygen now seem more reasonably explained by electron transfer mechanisms. Radical ion intermediates in these pathways can be formed by electron transfer to ground-state triplet or singlet excited molecular oxygen or from substrates to excited states of photosensitizers. The initial steps in several possible electron transfer routes for photooxygenation

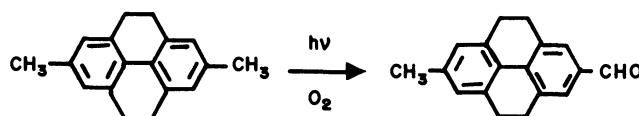
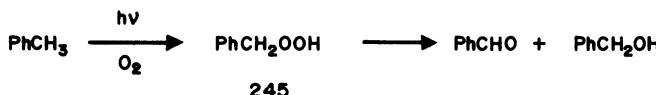


are outlined in equations (25)–(27) and for the purposes of this review are termed class 1–3 photooxygenations. These schemes point out the variety of pathways which can arise through electron transfer initiation and the mechanistic complexities which can be encountered.

2.4.2. Class 1 Photooxygenations

A variety of aromatic hydrocarbons are known to form weak ground-state complexes with triplet dioxygen^(172–175) which serve as precursors for excited complexes^(8,176) formed by irradiation in the charge transfer bands. Also, ground-state oxygen is an efficient quencher of aromatic hydrocarbon fluorescence. Solvent polarity^(177,178) and ionization potential^(179,180) correlations combine to suggest that the quenching mechanism involves the formation of excimers with charge transfer character. Quenching of aromatic hydrocarbon triplets, on the other hand, appears to be by energy transfer resulting in generation of singlet molecular oxygen.⁽¹⁸¹⁾

Several oxidation reactions appear to be initiated by electron transfer from triplet oxygen to aromatic hydrocarbons. Direct irradiation of oxygen-

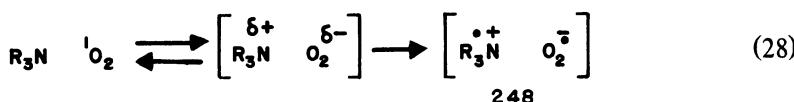


ated solutions of benzylic hydrogen containing aromatic hydrocarbons at wavelengths leading to excitation of the aromatic chromophores or charge transfer complexes leads to benzylic oxidation. Examples of this process are found in the photooxygenation of toluene to yield benzaldehyde and benzyl alcohol, products arising from dehydration and hydrolysis of benzylhydroperoxide **245**.⁽¹⁷³⁾ An analogous reaction is found in conversion of the linked bitolyl **246** to the corresponding aldehyde **247**.⁽¹⁸²⁾

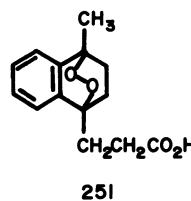
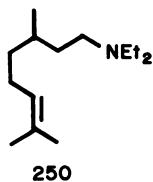
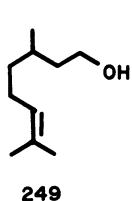
2.4.3. Class 2 Photooxygenations

Singlet molecular oxygen, a reactive intermediate produced by a number of methods including dye photosensitization of ground-state triplet oxygen, microwave discharge, or thermal decomposition of endoperoxides, serves as an efficient electron acceptor from a variety of organic donors. Electron transfer in these cases results in production of radical ion pairs containing the superoxide ion, O_2^- , and leads to quenching of 1O_2 and oxidation of organic substrates. An extensive review of the photophysical and photochemical aspects of this mode of photooxidation has been written by Bellus.⁽¹⁸³⁾ Thus, only a brief survey of a limited number of photooxygenations of this type applied to amine systems will be given here.

The area of amine-singlet oxygen chemistry is reasonably complex due to the multitude of mechanistic pathways possible. Useful information has been gained through investigations of singlet oxygen quenching by amines and of amine oxidations. Amines are known to quench the ${}^1\Delta_g$ state of molecular oxygen in both the gas and solution phases with rate constants which correlate with quencher ionization potential.⁽¹⁸⁴⁻¹⁸⁶⁾ Gollnick⁽¹⁸⁷⁾ has suggested that amine quenching and oxidation processes both proceed by electron transfer to produce the radical ion pairs **248** as shown in equation (28). Further evidence that ${}^1\text{O}_2$ is efficiently quenched by amines comes from the observation by Davidson⁽¹⁸⁸⁾ that the alkenol **249** undergoes normal ene-

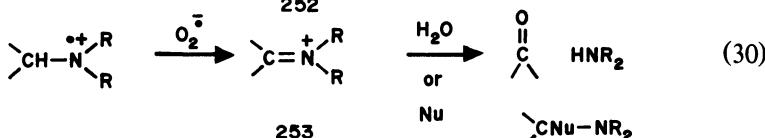
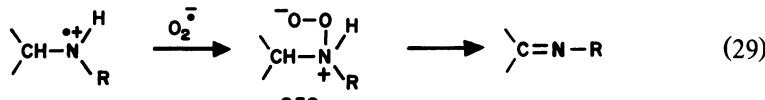


type reaction with singlet oxygen while the analogous enamine **250** is unreactive under dye-sensitized photooxygenation reaction conditions. Direct evidence for the production of the superoxide ion, O_2^- , by electron transfer from amines to singlet oxygen has come from recent, ingenious experiments by Saito and Inoue.⁽¹⁸⁹⁾ When deoxygenated solutions of the water soluble singlet oxygen generator **251** and *N,N*-dimethyl-*p*-anisidine in phosphate buffer containing *p*-nitro blue tetrazolium (NBT) are stirred at room temperature, diformazan, the superoxide oxidation product of NBT, is formed.

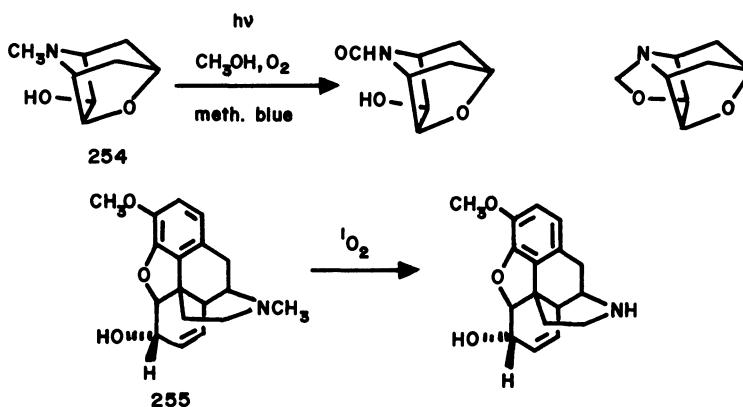


The presence of the superoxide-inhibiting enzyme, superoxide dismutase, in these mixtures blocks diformazan formation, confirming the intermediacy of O_2^- , arising from electron transfer between the amine and ${}^1\text{O}_2$ in the oxidation processes.

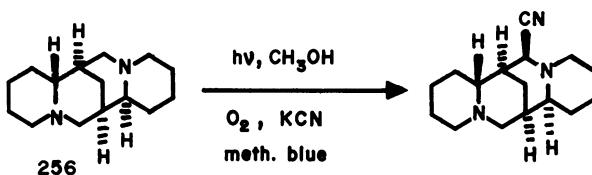
Amine oxidations initiated by electron transfer to ${}^1\text{O}_2$ can occur by several routes depending on the nature of the amine substrate. For primary and secondary amines with α -hydrogens, the radical ion pairs are converted to imines, perhaps through intervention of zwitterionic intermediates 252 [equation (29)]. Tertiary amines with α -hydrogens undergo related reactions to yield iminium salts 253 [equation (30)], which are susceptible to hydrolytic cleavage or nucleophilic addition. Numerous examples of amine dealkylations and additions document the generality of these electron transfer initiated



oxidation pathways.⁽¹²⁸⁾ Illustrative of these pathways are the oxidation of scopoline 254⁽¹⁹⁰⁾ under dye-sensitized photooxidation conditions and of codeine 255⁽¹⁹¹⁾ in viscous solution or on a solid support with ${}^1\text{O}_2$ in the gas phase. The photocyanation of sparteine 256⁽¹⁹²⁾ is another natural product



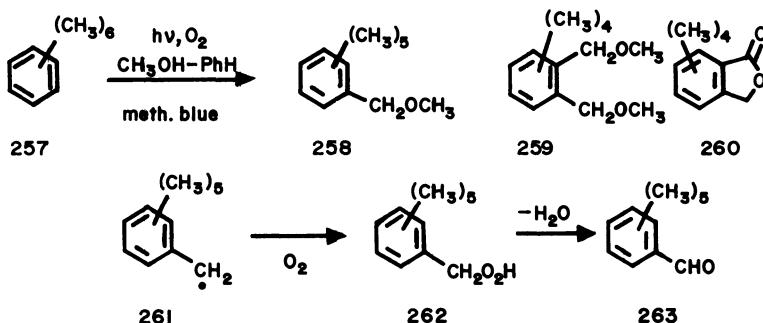
example of oxidation pathways involving iminium salt production by electron transfer to singlet molecular oxygen.



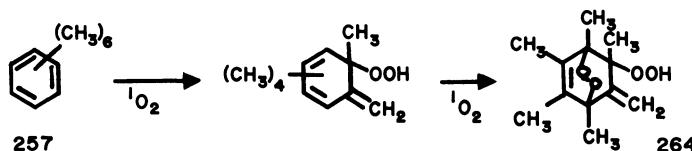
2.4.4. Class 3 Photooxygenations

In several cases of photosensitized oxidations, production of singlet oxygen by energy transfer is competitive with the direct interaction of organic substrate with excited sensitizer through electron transfer. This has been demonstrated by careful experimentation in studies of Davidson and Trethewey⁽¹⁹³⁾ which showed that substances which typically quench singlet oxygen via chemical reaction can also efficiently quench the excited states of common, singlet oxygen producing photosensitizers, including Rose Bengal and Methylene Blue. An example of this is found in the photooxidative decarboxylations of α -keto-acids which Davidson⁽¹⁹⁴⁾ has shown to involve direct electron transfer from substrate to sensitizer rather than singlet oxygen as the oxidant as previously thought. Lastly, a useful kinetic method has been developed^(195,196) enabling the distinction between photooxidation pathways via electron transfer from substrates to either $^1\text{O}_2$ or the excited photosensitizer.

The generality of oxidation pathways initiated by electron transfer from organic reactants to sensitizer is illustrated by the large number of examples of alkene and arene photooxygenations which have accumulated to date. In an early study, Wasserman and his co-workers⁽¹⁹⁷⁾ uncovered unusual benzylic oxidation reactions of hexamethylbenzene **257** and suggested mechanisms involving direct arene–sensitizer interaction in a primary event following excitation. A hydrogen atom abstraction mechanism was proposed to rationalize the Methylene Blue sensitized transformation of **257** to the mono **258** and bis **259** ethers and the phthalide **260**. Accordingly, capture of the benzylic radical formed in this way by triplet oxygen would yield the hydroperoxide **262**, a precursor by methanolysis and dehydration of the respective ether **258** and aldehyde **263**. The higher oxidation products, **259** and **260**, were shown to arise by secondary reaction of **258** and **263**, respectively. In retrospect, a more reasonable route for production of **261** appears to be by sequential electron–proton transfers. Indeed, both the observed solvent polarity dependence of the reaction quantum efficiency and the expected large negative free energy for electron transfer from **257** to Methylene Blue singlets

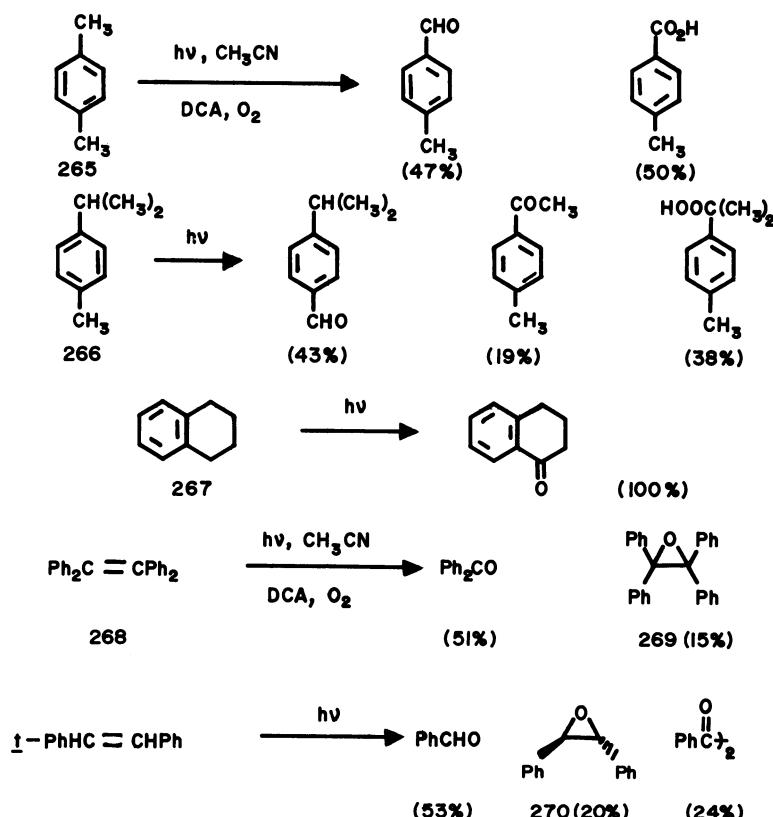


are in accord with this postulate. It should be noted that Van den Heuvel⁽¹⁹⁸⁾ has isolated the endoperoxide **264** from the reaction mixture arising by photooxidation of **257** under reaction conditions similar to those used in the earlier study by Wasserman. This substance most probably arises via singlet oxygen reaction pathways through consecutive ene and Diels–Alder additions.

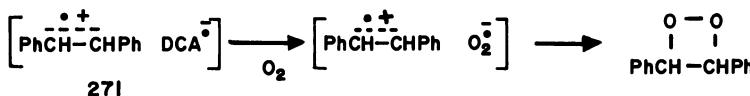


An interpretation of this dichotomy in terms of a wavelength dependence has been offered by Tokumaru.⁽¹⁹⁹⁾ An alternate rationale based upon a hexamethylbenzene concentration dependence controlling the relative rates of energy transfer producing singlet oxygen versus electron transfer yielding the arene radical cation has not yet been subjected to experimental test. However, recent efforts by Matsuura and Saito⁽²⁰⁰⁾ have provided indirect evidence to support the validity of this mechanistic postulate. These workers have demonstrated the operation of electron transfer mechanisms in the 9,10-dicyanoanthracene (9,10-DCN)-sensitized, benzylic photooxidations of a variety of substituted arenes, including **265–266**.

A variety of alkene photosensitized oxygenations appear to proceed via electron transfer rather than singlet oxygen mechanisms. One of the first examples of this reaction type was provided by Foote and his co-workers⁽²⁰¹⁾ in their study of 9,10-DCN-sensitized oxidations of tetraphenylethylene **268**, 1,3-cyclohexadiene, and *trans*-stilbene. Irradiation of oxygenated, acetonitrile solutions of these olefins containing 9,10-DCN led to formation of carbonyl and epoxide products, exemplified by the transformation of **268** to benzophenone **269**, and by conversion of *t*-stilbene to benzaldehyde, the oxirane **270**, and benzil. That electron transfer from the alkenes to singlet 9,10-DCN occurs in the primary step following excitation in these processes is suggested by the expected electron transfer rates, accumulated fluorescence quenching

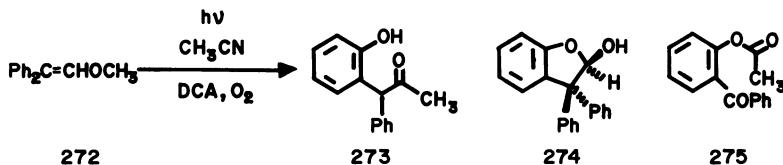


data, and the fact that these reactions do not take place under conditions which are known to produce singlet oxygen.^(201,202) Similar results and interpretations have arisen from studies by Schaap⁽²⁰³⁾ of 1,2-dioxetane formation via 9,10-DCN-sensitized oxidations of alkenes and by Foote⁽²⁰⁴⁾ of the methylene blue sensitized oxidative cleavage of *t*-stilbene. The detailed mechanisms for these oxidations appear to involve two key electron transfer steps, the first yielding the olefin cation radical-sensitizer anion radical pair (e.g., 271), and the second generating the superoxide ion and ground-state sensitizer by electron transfer to triplet oxygen. An alternate route involving capture of the olefin cation radical by ground-state oxygen is also possible.

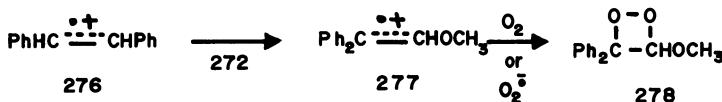


A subtle yet interesting mechanistic variant has been uncovered in studies of alkene electron transfer sensitized photooxidations. Foote⁽²⁰⁵⁾ noted that the enol ether 272 yields three products, 273–275, along with benzophenone

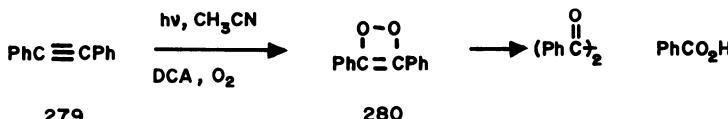
when subjected to 9,10-DCN-sensitized oxidation in acetonitrile. However, when *trans*-stilbene is present at high concentrations in the photolysis solution, the yield of benzophenone increases to > 95%. Data accumulated in this study demonstrate that the oxidation products **273–275** arise via singlet oxygen mechanisms. However, electron transfer to *trans*-stilbene effectively competes with energy transfer to oxygen and serves to catalyze formation of dioxetane **278**, the precursor of benzophenone. Thus, in this process electron transfer



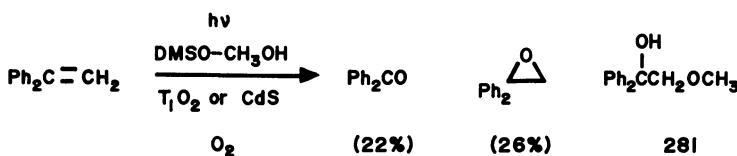
from **272** to the *t*-stilbene radical cation **276** is a more efficient route for generation of the reactive ion radical **277** than direct electron transfer from **272** to 9,10-DCN singlets. Farid and Mattes⁽²⁰⁶⁾ have observed that electron transfer sensitized photooxygenation of diphenylacetylene **279** leads to effi-



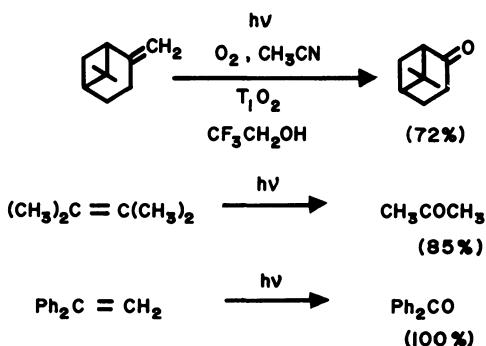
cient ($\Phi=0.15$) production of benzil and benzoic acid. In this study, firm evidence was gathered in support of a mechanism involving dioxetene **280** formation by coupling of the superoxide anion rather than triplet oxygen with the diphenylacetylene cation radical.



The area of semiconductor photocatalyzed olefin oxidation has received only brief attention in recent independent investigations by Tokumaru⁽²⁰⁷⁾ and Fox.⁽²⁰⁸⁾ In spite of this, the reaction efficiencies and simplicity of the technique combine to suggest that this method will become exceedingly useful for olefin oxidative cleavage. Therefore, we have included a brief review of preliminary results from these studies in this section. Band gap irradiation of semiconductors such as TiO_2 or CdS results in promotion of an electron into the conduction band and causes a hole in the valence band. In the case of TiO_2 , the conduction band edge is at a potential of +2.4 eV, thus, allowing the excited semiconductor to accept electrons from olefinic donors with oxidation potentials < 2.4 eV. This pathway would generate the same olefin cation radicals formed in the electron transfer sensitized photooxidations described



above or in electrocatalyzed oxidations which proceed via dioxetane intermediates.⁽²⁰⁹⁾ Tokumaru⁽²⁰⁷⁾ demonstrated that irradiation of suspensions of TiO_2 ($\lambda > 350$ nm) or CdS ($\lambda > 430$ nm) in solutions containing a variety of 1,1-diphenyl substituted alkenes under oxygen atmospheres leads to generation of oxirane and carbonyl products, as exemplified by the conversion of 1,1-diphenylethylene to benzophenone and 1,1-diphenyloxirane and its methanolysis product 281. Fox⁽²⁰⁸⁾ has shown that this method, utilizing TiO_2 as a catalyst, is synthetically useful by demonstrating its applications in the efficient oxidative cleavage of a variety of olefins including α -pinene, tetramethylethylene, and 1,1-diphenylethylene.

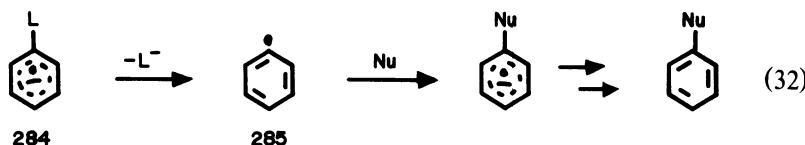
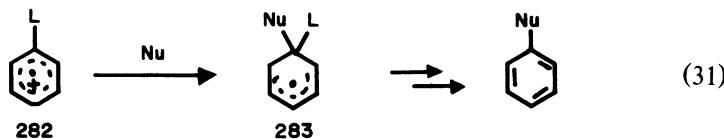


2.5. Aromatic Systems

2.5.1. Aromatic Photosubstitution Reactions

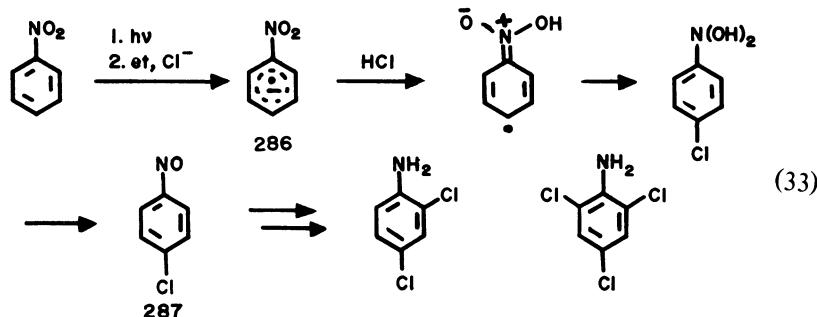
Photosubstitution appears to be an extremely general excited-state process of a variety of aromatic substances.⁽²¹⁰⁾ A number of mechanistic pathways including heterolytic and homolytic cleavage and two-step sequences through intermediate σ complexes appear to operate in these cases depending upon the nature of the aromatic substrate and electro- and nucleo-fugal groups involved. A class of these substitutions have the common mechanistic feature of activation by photostimulated electron transfer. Aryl radical cations 282 produced in this way are susceptible to nucleophilic attack giving radicals 283 which serve as intermediates in substitution pathways [equation (31)]. Alternatively, aryl radical anions 284 arising by electron transfer can undergo

expulsion of nucleofugal groups to produce aryl radicals **285** which are captured by nucleophiles in routes leading to formation of substitution products [equation (32)]. In the following sections, we will review several recent aro-



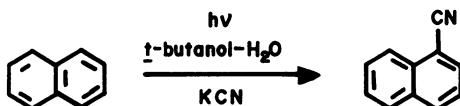
matic photosubstitution reactions which appear to proceed through routes of these types.

2.5.1.1. Photosubstitution of Hydrogen in Aromatic Systems. A number of recent studies⁽²¹⁻²¹³⁾ have demonstrated that the interesting conversion of nitrobenzene to a mixture of 2,4,6-trichloroaniline and 2,4-dichloroaniline induced by irradiation in aqueous hydrochloric acid proceeds by an electron transfer mechanism in which chloride ion serves as an electron donor [equation (33)]. Nitrosobenzenes (e.g., **287**), intermediates in these pathways, are transformed to the anilines in secondary dark processes. The catalytic effect of HCl noted in these photosubstitution reactions appears to have its origin in the competitive nature of back electron transfer and protonation of the initially formed radical anion **286**.

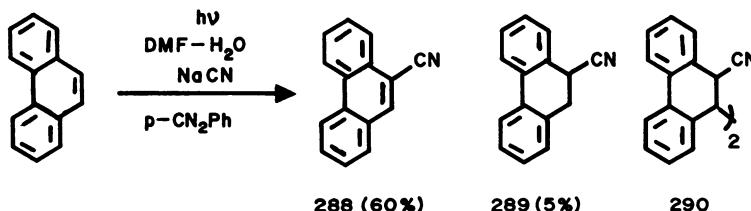


Photocyanation represents another interesting class of aromatic photo-substitution reactions in which hydrogen serves as the group undergoing displacement. The conversion of naphthalene to its 1-cyano derivative and of biphenyl to a mixture of *ortho*- and *para*-cyanated products by direct irradiation in aqueous *t*-butyl alcohol solutions containing potassium cyanide are

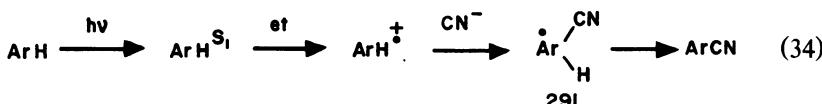
representative of the large number of examples of this reaction type.⁽²¹⁴⁾ Detailed investigations of reaction conditions have shown that solvent and phase



transfer catalysts have a marked effect on photocyanation yields which can be brought into the synthetically useful ranges of 90%–97%.^(215,216) The efficiency of aromatic hydrocarbon photocyanation is dramatically enhanced by conducting irradiations in the presence of electron acceptors such as 1,4-dicyanobenzene, as exemplified by the conversion of phenanthrene to 9-cyanophenanthrene **288** along with the reduced and dimeric cyanide adducts, **289** and **290**.⁽²¹⁷⁾ Similar photosubstitution processes have been observed for naphthalene and anthracene which yield 1- and 9-substituted derivatives, respectively.

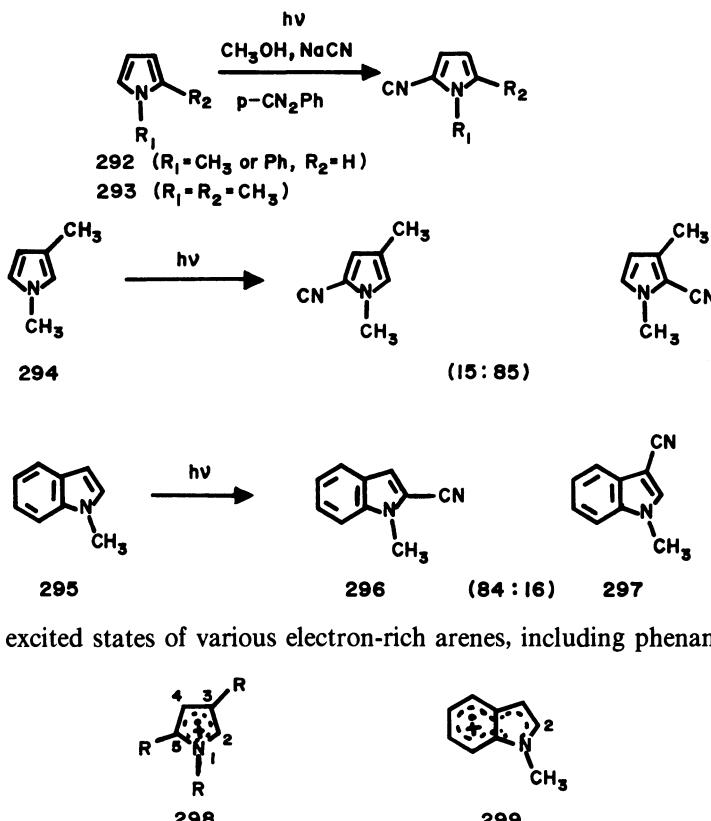


Mechanisms proposed for these cyanation reactions involve electron transfer from the hydrocarbon singlet states to dicyanobenzene to yield the aryl radical cations which react with cyanide ion forming the radical intermediates **291** [equation (34)]. Support for this postulate is found in the observation that the quantum efficiency is decreased by a factor of 15 when reactions are conducted in the absence of dicyanobenzene. Importantly, the unsensitized aromatic photocyanations, occurring albeit with reduced efficiency, might also proceed by electron transfer in or through excimer intermediates.



Analogous photocyanation reactions occur in the aromatic heterocycle series on substances containing the pyrrole and indole groupings.⁽²¹⁸⁾ Thus, irradiation of *p*-dicyanobenzene in solutions containing the pyrroles **292**–**294** and sodium cyanide results in formation of α -cyano products. Also, *N*-methylindole **295** is converted to a mixture of α - and β -cyano products, **296** and

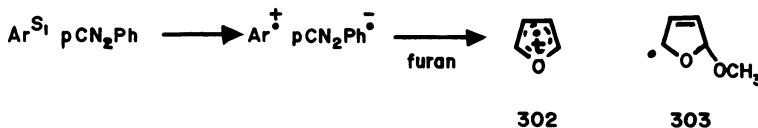
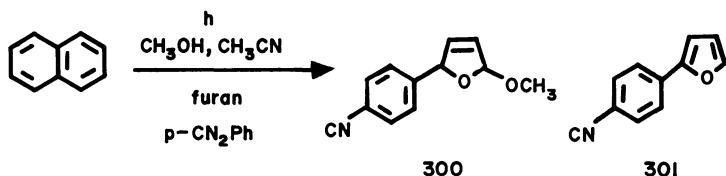
297, under these conditions. The regiochemical courses of these processes are in accord with predictions, arising from molecular orbital theory, of charge density minima at the 2 position in radical cation intermediates 298 and 299. Related heterocyclic cation radicals are intermediates in the aromatic hydrocarbon catalyzed, photoelectron transfer reaction of furans.⁽²¹⁹⁾ In these cases,



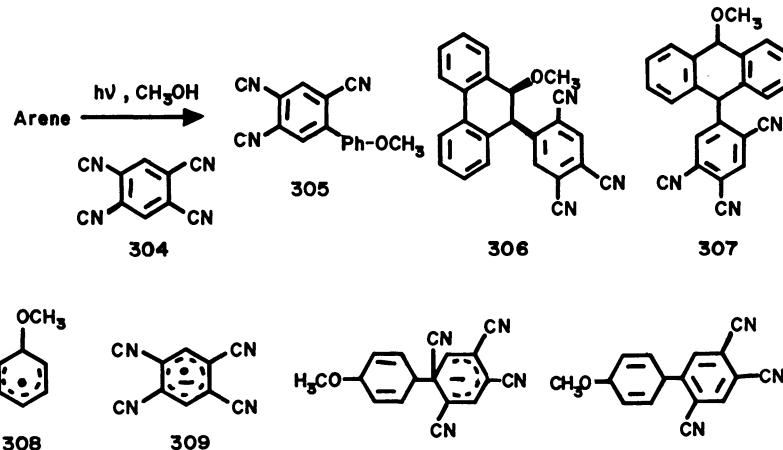
singlet excited states of various electron-rich arenes, including phenanthrene



and naphthalene, activate photoadditions of *p*-dicyanobenzene and methanol to furans, as illustrated by production of 300 and 301 under these conditions. Several observations are consistent with electron transfer routes through 302 for these processes. For example, these reactions are efficiently quenched by the electron donor, *p*-dimethoxybenzene, through competitive deactivation of the initially formed arene cation radical and by low solvent polarity which results in slow rate of electron transfer. Information on the details of routes converting 303 to the adduct 300 has come from study of 1,2,4,5-tetracyanobenzene photoadditions.⁽²²⁰⁾ Accordingly, the 1:1:1 adducts 305 and 307 resulting from irradiation of 304 in methanolic solutions containing benzene, phenanthrene, or anthracene appear to arise by coupling of the neutral radical

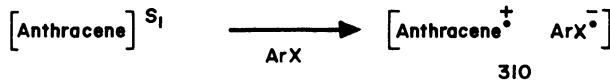


308 and ion radical 309 at a substituted carbon followed by loss of cyanide ions. The benzene adduct formed in this way is subject to rapid aromatization.



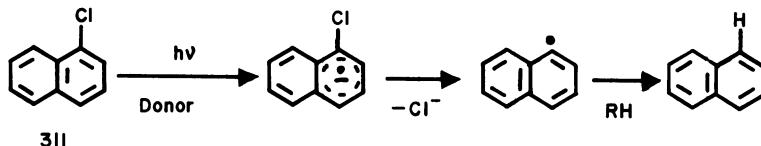
Thus, similar pathways must operate in converting the radical ion 303 to the furan adduct 300.

2.5.1.2. Aryl Halide Photosubstitutions. Strong evidence has been provided for the postulate that electron transfer mechanisms are operable in arylhalide photosubstitution reactions. Spectroscopic studies by Latkowski⁽²²¹⁾ have shown that halobenzenes quench the fluorescence of anthracene by pathways involving electron transfer to form the ion radical pairs 310. As expected on

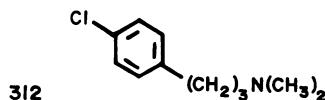


the basis of results from earlier work by Asirvatham and Hawley,⁽²²²⁾ the aryl halide radical anions formed in this way undergo rapid expulsion of halide ion to generate aryl radicals. Bunce and his co-workers⁽²²³⁾ have demonstrated

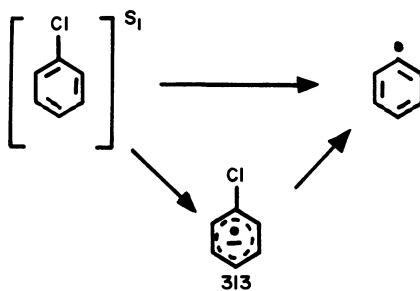
that this pathway is involved in photoreduction of 1-chloronaphthalene **311** via the intermediate 1-naphthyl radical. The efficiency of photoreduction is significantly enhanced when irradiation of **311** is conducted in the presence of electron donors, such as triethylamine, 4-chlorobiphenyl, and 1,3-cyclohexadiene, as illustrated by the seven-fold increase in quantum yield caused by addition of 0.01 *M* triethylamine and the linear dependence of ϕ^{-1} on $[\text{triethylamine}]^{-1}$. A similar conclusion has been reached for the triethylamine assisted photoreduction of 4-chlorobiphenyl.⁽²²⁴⁾



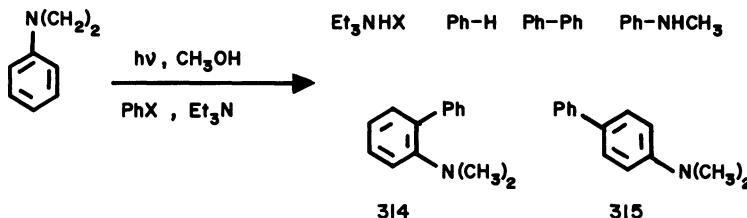
Photoreduction of 1-chloronaphthalene in the absence of electron donors appears to also involve electron transfer in an exciplex with charge transfer character. This conclusion comes from the observed seven-fold increase in reduction efficiency on changing aryl halide concentration from 3.2×10^{-5} to 3.2×10^{-2} *M*. An interesting comparison to reaction of the 1-chloronaphthalene system is found in photoreduction of 1-chlorobenzene.⁽²²⁵⁾ Here the reaction efficiency is diminished when irradiations are conducted at high aryl halide concentration or in the presence of intermolecular (triethylamine) or intramolecular (e.g., **312**) electron donors. Thus, two mechanisms are possible for aryl halide photoreduction, one involving direct photohomolysis



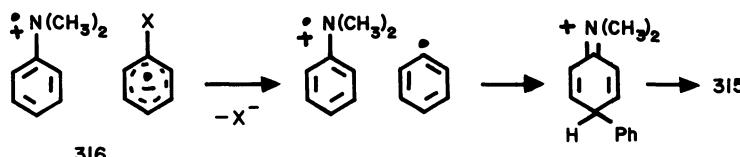
other proceeding through the anion radical **313**. The former route is more efficient in the chlorobenzene system and, as a result, electron transfer serves to quench photoreduction. The opposite mechanism hierarchy exists for 1-chloronaphthalene where photoreduction by the electron transfer pathway is more facile.



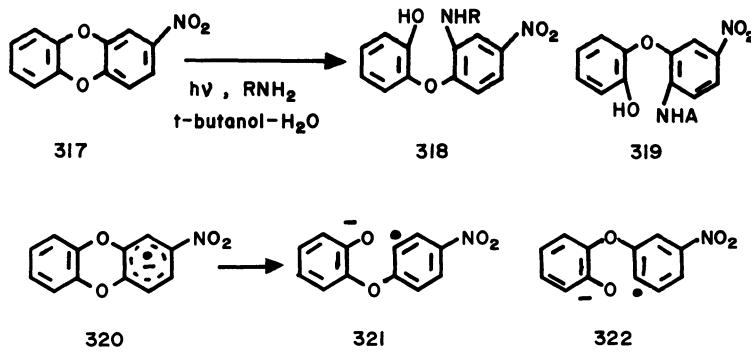
Electron transfer induced photohomolysis of aryl halides can be stimulated by indirect methods through irradiation of aromatic tertiary amines.⁽²²⁶⁾ Illustrative of this approach is the observation that irradiation of methanol solutions of dimethylaniline containing chloro- or bromobenzene and triethylamine gives triethylammonium halide in quantitative yields along with benzene, biphenyl, *N*-methylaniline, and aminobiphenyls 314 and 315. The products generated in these reactions are nicely rationalized by mechanisms



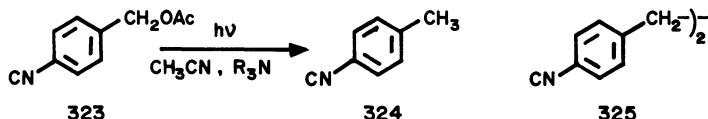
in which the initially formed radical ion pair **316** undergoes halide ion loss followed by hydrogen abstraction or radical coupling.



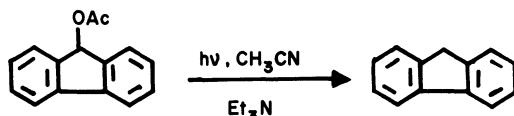
Three additional and closely related examples of arene photoreduction are worthy of mention at this point. The first is found in the ring opening processes followed by the 2-nitrobenzo[b,e] [1,4]dioxine **317** upon irradiation in *t*-butyl alcohol solution containing primary amines.⁽²²⁷⁾ The aminophenols, **318** and **319**, are formed in 2:1 ratio (80%) when polar solvents are used. Partitioning of the radical anion **320** serving as a key intermediate in this process appears to favor *meta* over *para* cleavage, yielding the radicals **321** and **322** in a ratio reflective of the final product distribution.



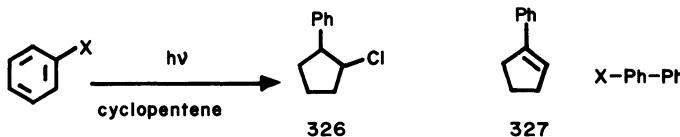
The versatility of electron transfer sensitized processes of aromatic compounds is demonstrated by another type of photostimulated reduction. Aromatic anion radicals possessing nucleofugal groups at benzylic positions are expected to expel the leaving group to produce benzyl radicals. A process exemplifying this reaction pattern has been provided by Ohashi⁽²²⁸⁾ in studies of the photochemistry of *p*-cyanobenzyl acetate **323**. Irradiation of **323** in acetonitrile solutions containing triethyl, *n*-butyl, or disopropyl amine leads to high yielding formation of the reduced **324** and dimeric **325** products. In



a similar fashion, fluorenyl acetate is transformed to fluorene upon irradiation in the presence of triethylamine.



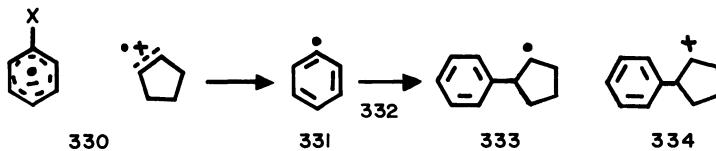
Aryl halide photoadditions to cyclopentene, recently uncovered by studies of Bryce-Smith,⁽²²⁹⁾ serve as the final example of interesting photosubstitution processes possibly proceeding through electron transfer mechanisms. Irradiation of chloro, iodo, or bromobenzene in cyclopentene under an oxygen atmosphere leads principally to products **326** and **327** derived from insertion of the olefin into the aryl halide carbon–halogen bonds. Importantly, irra-



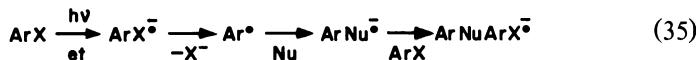
diation of fluorobenzene under identical conditions results in exclusive production of the meta and para cycloadducts **328** and **329**. (See chapter 1.) Although a number of mechanisms are possible for the C-X insertion processes, those involving electron transfer appear to more easily rationalize production of both saturated and unsaturated products. Accordingly, electron



transfer from cyclopentene to the aryl halide singlets generates sequentially the radicals **330** and **331**. Capture of **331** by cyclopentene **322** then serves to form the cyclopentyl radical **333** and, after back electron transfer, the ultimate cationic intermediate **334**. Deprotonation or chloride capture of **334** then complete the pathway for product formation. Closely related olefin and arene photoarylations have been observed in halopyridine⁽²³⁰⁾ and halobenzene⁽²³¹⁾ systems.



2.5.1.3. Photoarylations by the S_{RN_1} Mechanism. In the above sections we have outlined studies which show that aromatic halides and related systems containing nucleofugal groups on the aromatic nucleus serve as acceptors in photostimulated electron transfer processes and that the formed anion radicals efficiently eliminate the nucleofugal groups to generate aryl radicals. The aryl radicals formed in this way undergo hydrogen atom abstraction and olefin or arene additions. An alternate reaction pathway available to aryl radicals involves nucleophilic addition generating anion radicals. This reaction could serve as the key propagating step in radical chain mechanisms for nucleophilic aromatic substitution which are similar to the S_{RN_1} processes [equation (35)]



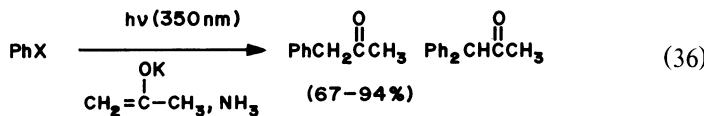
described earlier by Kornblum⁽²³²⁾ and Russell⁽²³³⁾ to explain observations made in studies of nucleophilic substitutions. The general features of aromatic substitution operating by S_{RN_1} mechanisms have been summarized in an excellent review by Bennett.⁽²³⁴⁾ As a result, observations providing information on the mechanistic details of these processes will not be surveyed in this chapter. It will be sufficient for our purposes to only outline a few of the general features of these substitution reactions. S_{RN_1} processes can be stimulated by a number of methods including electron transfer from alkali metal–ammonia solutions, electrochemical reduction, photoelectron transfer, or spontaneously from electron-rich nucleophiles. A variety of nucleofugal groups and aromatic ring substituents can be tolerated, the exceptions being those which either prevent initial electron transfer by their effect on arene reduction potentials or which stabilize the initially formed radical anion, thus preventing expulsion of the leaving groups. Steric effects do not appear to be important in controlling reactivity of these systems. Lastly, a variety of ar-

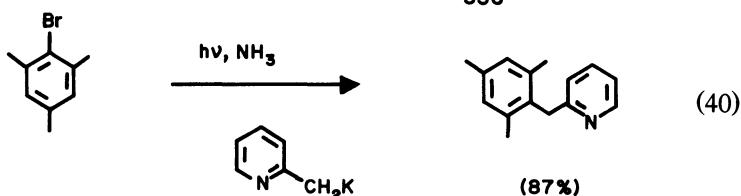
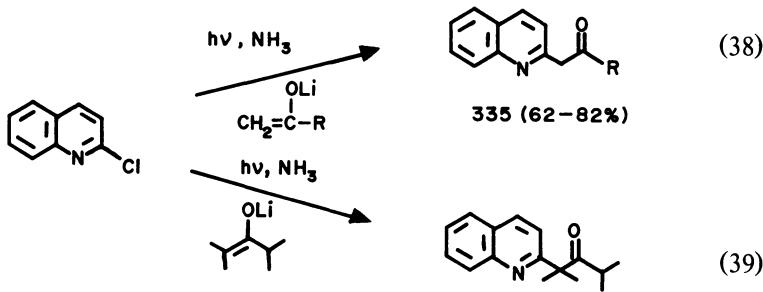
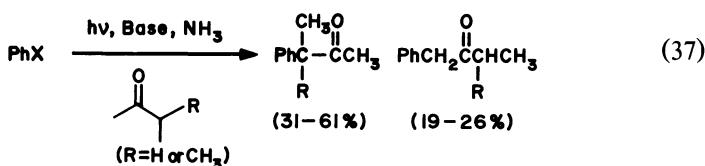
omatic systems participate in S_RN_1 processes including those in which leaving groups are bound to ring systems of aromatic hydrocarbons and their heteroaromatic counterparts.

The photostimulated version of S_RN_1 aromatic substitutions was first explored by Bunnett.⁽²³⁵⁾ In general, these processes can be initiated by irradiation through a Pyrex filter which leads to excitation of the nucleophile and electron transfer to the aromatic substrate. However, excitation of the aryl halide or charge transfer complexes formed between aryl halides and nucleophiles also leads to initiation of the chain process.⁽²³⁶⁾ As expected on the basis of the chain nature of the mechanism, the quantum yields for photosubstitution in some cases reach 20–50. The generality and synthetic applicability of reactions involving this mechanism are demonstrated by the examples cataloged in Bunnett's review.⁽²³⁴⁾ Attention will be given here to examples of carbon–carbon bond forming photoarylations which occur in synthetically useful yields.

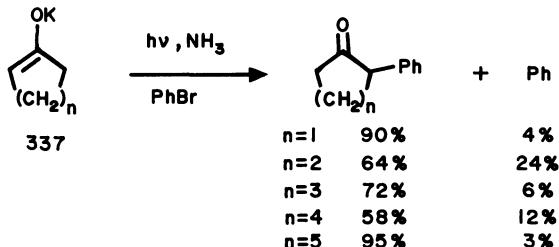
One of the first cases of ketone enolate photostimulated substitutions on aryl halides is found in early studies by Rossi and Bunnett.⁽²³⁵⁾ The potassium enolate of acetone was found to undergo photoarylation with a variety of substituted benzenes when irradiated in liquid ammonia solutions to form a mixture of mono- and di-phenylated acetones in yields of 67%–94% [equation (36)]. In continuing investigations,^(237,238) these workers showed that the potassium enolates of 2-butanone and 3-methyl-2-butanone participate in similar photoarylations to produce α -phenyl ketone mixtures [equation (37)] reflecting the relative population of regioisomeric enolates present in the starting solution. Ketone enolates undergo photosubstitution with haloheteroaromatic systems, as illustrated by the lithium enolate 2-chloroquinoline reactions to produce ketones 335 and 336 [equations (38) and (39)].^(259,241) 2-Chloropyridine participates in similar substitution reactions with ketone enolates.⁽²⁴³⁾ Finally, photoarylation of α -picolyl potassium by 2-bromomesitylene [equation (40)] serves to illustrate the absence of aryl halide steric effects in controlling S_RN_1 reaction efficiencies.⁽²⁴³⁾

A limitation⁽²⁴⁴⁾ of enolate anion photoarylations has been formed in Bunnett's studies⁽²⁴⁵⁾ on cyclic ketone enolates (337), which shows that the yields of α -phenylcycloalkanones and benzene are inversely related and dependent on ring size. It appears that steric crowding in the enolates controls the relative rates of nucleophilic addition to and hydrogen atom abstraction by the aryl radical intermediates in these reactions. This feature is further illustrated by the observation that photoarylation yields decrease and new

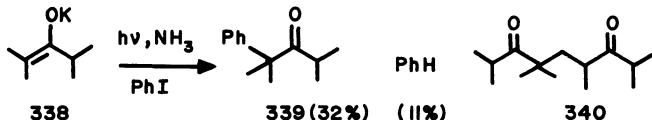




products arise when the ketone enolates become sterically bulky. For example, reaction of the crowded potassium enolate of diisopropyl ketone 338 with iodobenzene is exceptionally sluggish when compared to those of less bulky

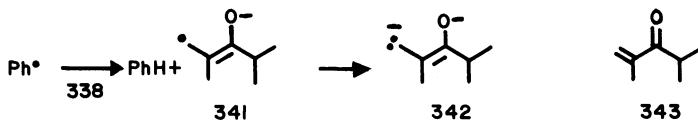


counterparts and leads to production of benzene and the dimer 340 along with the normal phenylated product 339. A mechanistic interpretation of



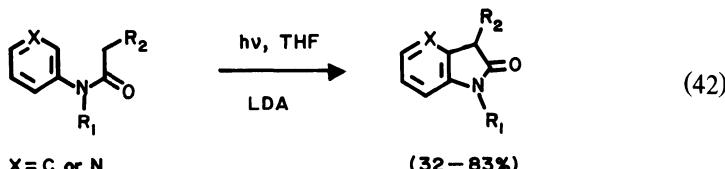
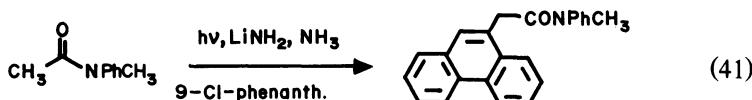
dimer formation has been provided in independent studies by Bennett⁽²⁴⁶⁾ and Semmelhack.⁽²⁴⁷⁾ Accordingly when the enolate is sterically crowded, addition

to the aryl radical is slow giving way to hydrogen abstraction to produce anion radical (e.g., 341). Disproportionation of 341 occurs to produce the dianion 342 and enone 343 which serve as precursors of the dimer 340. The contrasting behavior of enolate 338 with iodobenzene and 2-chloroquinoline [see equation (38)] is intriguing. The absence of dimer formation in the latter

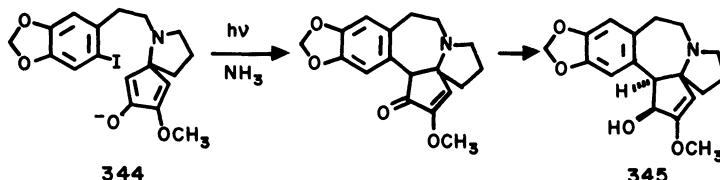


reaction might be due to the greater electrophilicity of the heteroaryl radical intermediate.

The synthetic utility of $S_{\text{R}}N_1$ photoarylations is illustrated further by examples in which amide enolates undergo inter- [equation (41)]⁽²⁴⁸⁾ and intra-[equation (42)]⁽²⁴⁹⁾ molecular carbon–carbon bond forming processes. Intramolecular enolate anion photoarylations, probed by Semmelhack,^(250,251) have found important application as a synthetically useful cyclization methodology.



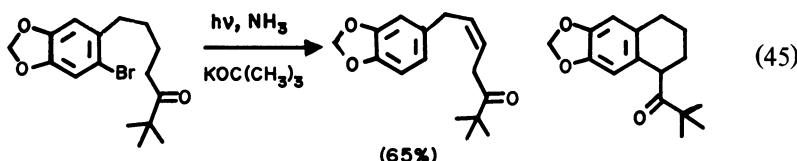
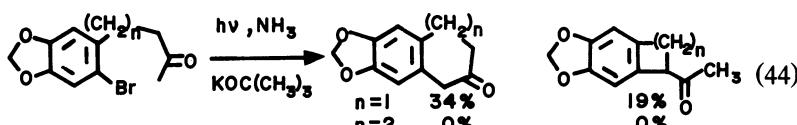
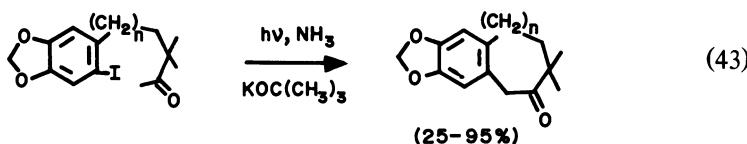
The first example of this reaction type was provided in cephalotaxine (345)



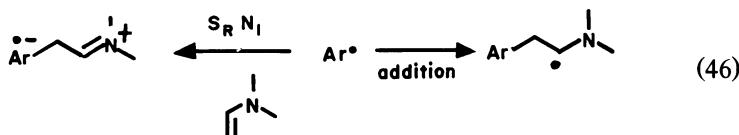
synthetic studies where cyclization of the iodoaryl-enolate 344 produced cephalotaxinone⁽²⁵⁰⁾. Additional reactions illustrating the versatility and limitations of the methodology are outlined in equations (43)–(45).⁽²⁵¹⁾

A structurally related class of intramolecular photoarylations in which carbon–carbon bond formation occurs between aryl halide and enamine, enamide, or β -enaminone groupings are known. The mechanisms for these

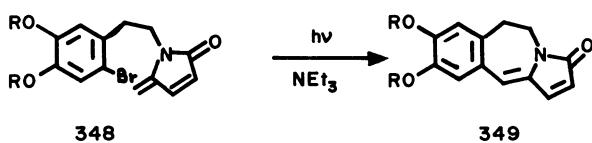
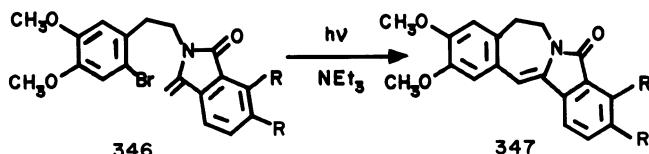
processes have not been probed in sufficient detail to determine if $S_R N_1$ or more simple radical coupling [equation (46)] routes are involved. The possible mechanistic similarities and acute synthetic utility of these processes encourage their brief review in this section. Snieckus and his co-workers^(252,253) have shown

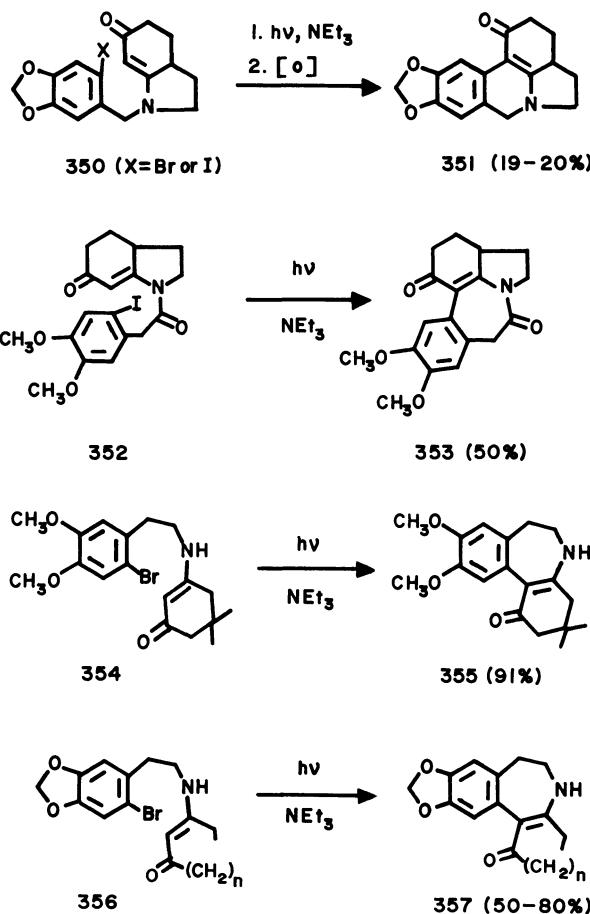


that the enamide containing aryl halides **346** and **348** undergo moderately efficient cyclization to produce the polycyclic amides **347** and **349**, when irradiated in solutions containing triethylamine. Enamino and enamidoketones participate in analogous photoarylate cyclizations as shown by the trans-



formations $350 \rightarrow 351$,^(254,255) $352 \rightarrow 353$,^(256,257) and $354 \rightarrow 355$,⁽²⁵⁵⁾ and $356 \rightarrow 357$.⁽²⁵⁸⁾

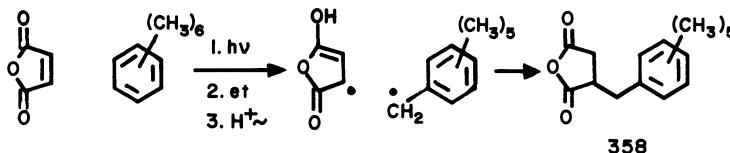
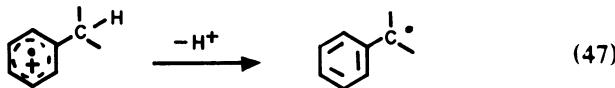




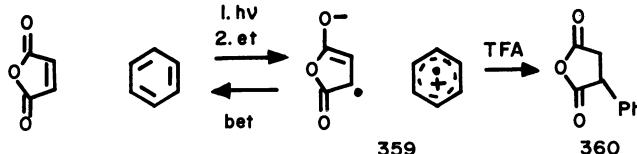
2.5.2. Photobenzylations by Electron Transfer Mechanisms

Radical cations generated by excited-state electron transfer from aromatic hydrocarbons containing benzylic hydrogens undergo efficient deprotonation to produce benzylic radicals [equation (47)]. This sequential electron–proton transfer process, formally corresponding to hydrogen atom transfer, is responsible for several interesting carbon–carbon bond forming reactions of aromatic hydrocarbons. An early example of a photobenzylation reaction through this route is present in investigations of Paciszewski^(259,260) of hexamethylbenzene-maleic anhydride photoadditions. Irradiation of this system under conditions which lead to excitation of the ground-state charge transfer complex results in generation of the adduct 358. It is interesting to note in this context that benzene participates in a related reaction with maleic an-

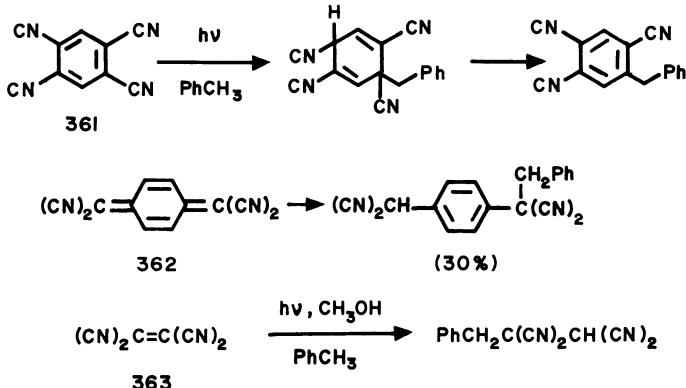
hydride to yield phenylsuccinic anhydride (**360**) when the ground-state CT-complex is irradiated strongly acidic solutions.^(261,60) In this case acid is



required to intercept the initially formed ion radical pair **359** which is efficiently deactivated by back electron transfer.

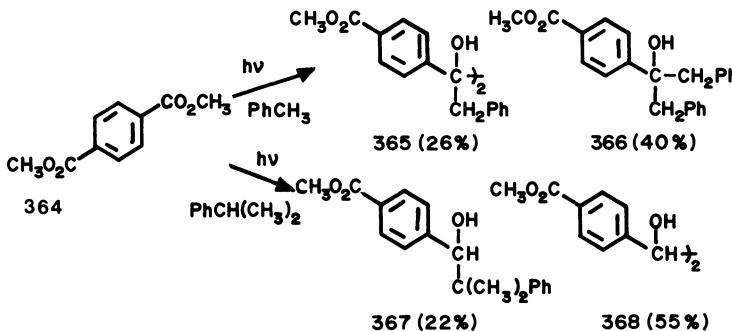


Analogous processes are followed in the photochemistry of cyano-substituted olefins and arenes and of aromatic esters. Illustrative of these reactions are the photobenzylations of 1,2,4,5-tetracyanobenzene **361**,⁽²⁶²⁾ the tetracyanoquinodimethane **362**,⁽²⁶³⁾ and tetracyanoethylene **363**⁽²⁶⁴⁾ occurring upon irradiation in toluene solutions. Sequential electron–proton transfer appears

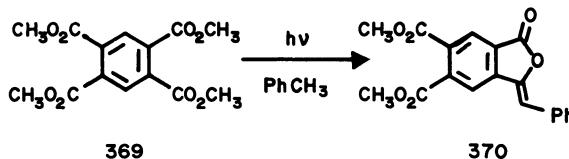


to be followed by a variety of secondary processes in the photochemistry of aromatic ester–toluene systems. Fukui^(265,266) has demonstrated that dimethyl terphthalate **364** undergoes smooth photoreductive addition of toluene to produce the dimeric **365** and benzylated adduct **366**. The nature of the reaction changes when cumene serves as the arene substrate. Here, simple addition to

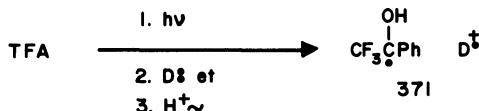
generate **367** accompanies pinacol **368** formation. The unusual and unpredictable nature of these electron transfer induced ester reactions is further



exemplified by formation of the benzylideneephthalide **370** upon irradiation of toluene solutions of tetramethyl pyromellitate **369**.⁽²⁶⁵⁾



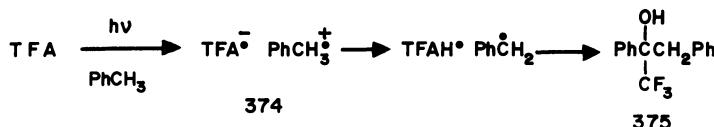
A series of interesting studies probing the detailed nature of sequential electron–proton transfer processes have been conducted with alkylbenzene-trifluoroacetophenone (TFA) systems. The triplet state of TFA like those of other aryl ketones can participate in chemical reactions with other molecules by a number of pathways including hydrogen atom abstraction and electron transfer. Wagner and his co-workers^(267–269) have shown by use of the CIDNP technique that irradiation of TFA in acidic solutions containing a variety of donors, such as DABCO and aromatic hydrocarbons results in formation of radical pairs **371**. The chemical consequences of this electron transfer process were suggested in earlier work⁽²⁷⁰⁾ by the photochemical transformation of TFA to the pinacol **372** and addition product **373** induced by irradiation in acidic methanol solutions containing benzene. An electron transfer mechanism



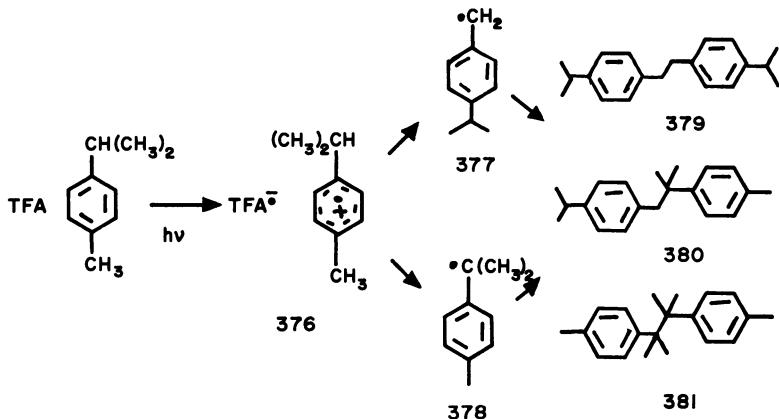
has been proposed to rationalize these reactions. As expected, irradiation of TFA-toluene solutions in the absence of acid leads to efficient production of



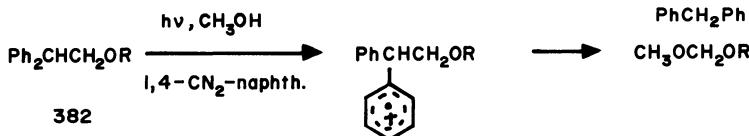
the benzyl-adduct **375**.⁽²⁷¹⁾ A detailed analysis of this system⁽²⁷²⁾ has uncovered strong evidence in support of a sequential electron–proton transfer mechanism for this process. TFA triplet quenching by toluene does not display a primary deuterium isotope effect, consistent with a pathway for excited-state deactivation which involves reversible electron transfer rather than hydrogen atom abstraction. Additionally, the deuterium isotope effect for adduct formation in this case is larger than that for triplet quenching, as expected for a reaction pathway in which proton transfer in the initially formed ion radicals **374**, required for product formation, is competitive with back electron transfer.

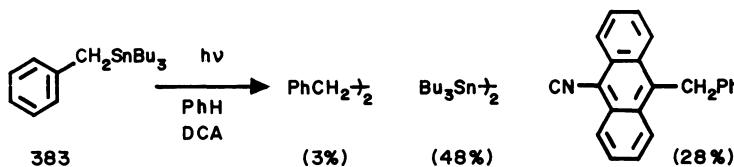


Further investigations utilizing *p*-cymene as the electron donor have provided additional information on the nature of electron and proton transfers in these systems.^(273,274) Analysis of the dimers **379**–**381** produced by irradiation of a benzene solution of TFA and *p*-cymene, shows that the primary **377** and tertiary **378** radicals were formed in a ratio of 3.4:1 in this process. This observation is fully consistent with a pathway in which benzyl radical for-



mation occurs by deprotonation of the intermediate radical cation **376** and not by hydrogen atom abstraction. Therefore, the selectivity in this case is governed by the relative kinetic acidities of the primary versus tertiary hydrogens in **376**.

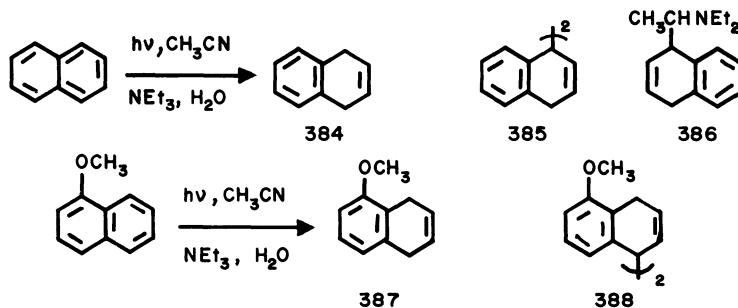




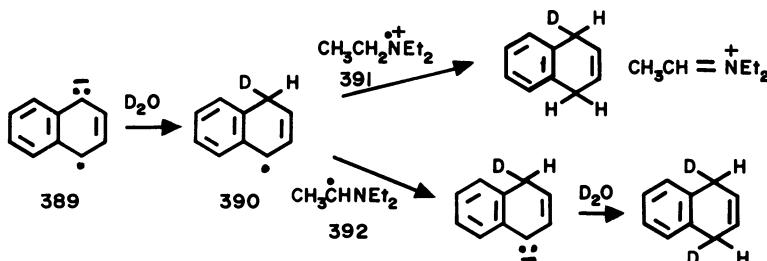
Thus far, we have presented examples of photobenzylation in which arene cation radicals undergo deprotonation from benzylic positions to produce benzylic radicals. However, radical formation can also occur by loss of other electrofugal groups. This is illustrated by the electron transfer photosensitized aryl ether **382** and benzylstannane **384** cleavage processes in independent efforts by Arnold⁽⁴⁹⁾ and Eaton.⁽²⁷⁵⁾

2.5.3. Birch and Related Photoreductions of Aromatic Compounds

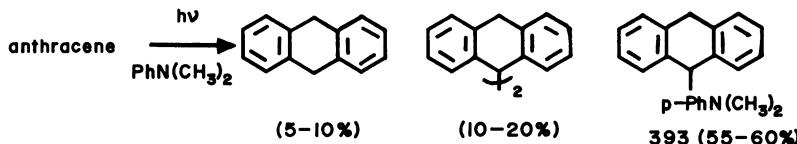
Classical studies probing the photophysical aspects of electron transfer photochemistry have been carried out with amine–aromatic systems. Through these efforts, the properties of exciplexes have been elucidated. We have outlined at an earlier point in this chapter the results of these investigations which show that the efficiency and wavelength of amine–arene exciplex emission is dependent on solvent polarity in a manner expected for decay of highly polar excited-state complexes by conversion to radical ion pairs. The arene radical anions formed by this route are identical to intermediates produced by electron donation from metals or solutions of solvated electrons to arenes in the familiar Birch reduction process. Thus, it is not surprising that the photochemistry of arene–amine systems is dominated by reduction pathways which mimic those of the ground-state counterparts. Benchmark studies in this area have been conducted by Barltrop and his co-workers.⁽²⁷⁶⁾ Examples illustrating the diverse nature of products arising in these reactions are found in photoreductions of naphthalene and 1-methoxynaphthalene occurring upon irradiation in aqueous acetonitrile solutions containing triethylamine. Birch-



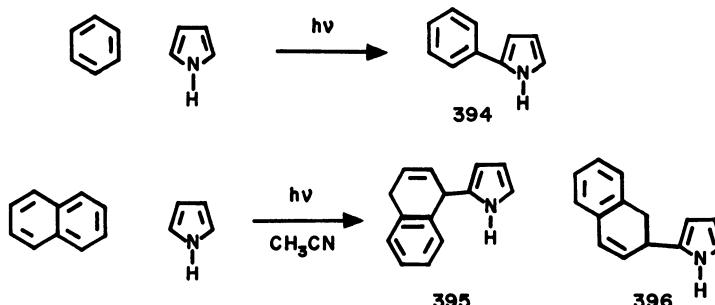
type reduction products **384** and **387** are produced under these conditions along with substances arising from dimerization **385** and **388** and amine addition **386**.^(277,278) Careful deuterium labeling studies have been used to probe the detailed mechanisms of these processes.^(276,277) Accordingly, irradiation of naphthalene in solutions containing deuterium oxide gives rise to the 1,4-dihydro-derivative **384** containing 1.6 deuteria per molecule. Thus, two mechanisms must operate here, one involving hydrogen atom abstraction from the amine cation radical **391** by the intermediate radical **390** and the other electron transfer from the amino radical **392** to **390**. In these cases, protonation of radical anion **389** at C-1 serves as the pathway for formation of **390**. Similar



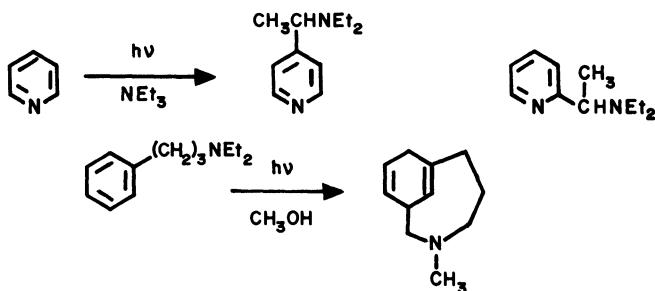
observations have been made in studies of *N,N*-dimethylaniline^(279,280) and triethylamine⁽²⁸¹⁾ induced photoreduction of anthracene. Interestingly, the major product formed in the former case is the amine *para*-adduct **393**. Electron



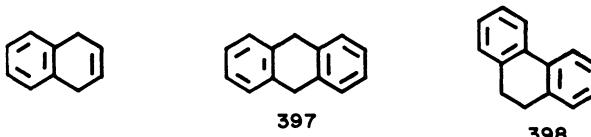
transfer mechanisms also appear to be responsible for the reductive additions of pyrrole to benzene⁽²⁸²⁻²⁸³⁾ and naphthalene^(285,286) yielding the adducts **394**–**396**. Finally, both intramolecular and heterocycle examples of tertiary amine



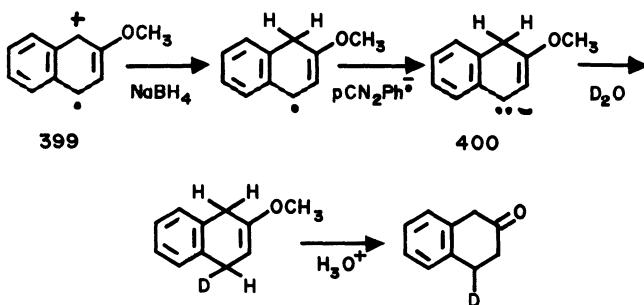
additions to aromatic substances activated by photostimulated electron transfer are present in studies by Bryce-Smith^(287,288) of pyridine and phenylpropylamine photochemistry.



The final reaction type that we will review in this section appears to possess the potential of becoming an extremely useful synthetic method for arene reduction. The process is based upon the anticipated ability of arene radical cations to react with hydride reducing agents. Pac⁽²⁸⁹⁾ has employed this reasoning in the development of a technique used for aromatic hydrocarbon reduction. Irradiation of the arenes, naphthalene, anthracene, or phenanthrene, in the presence of the electron acceptor 1,4-dicyanobenzene and sodium borohydride in aqueous acetonitrile leads to production of the dihydroproducts **384**, **397**, and **398**, respectively, in yields ranging from 50% to 88%. An analysis of deuterium incorporation in the tetralones arising by



aqueous acid hydrolysis of products from 2-methoxynaphthalene reduction conducted with $\text{NaBH}_4\text{-D}_2\text{O}$ and $\text{NaBD}_4\text{-H}_2\text{O}$ systems suggests that hydrogen delivery to the arene ring occurs both on the radical cation intermediate by borohydride and by protonation of the ultimate anion **400**. An important feature of this methodology is that it enables selective reduction of the electron-donating substituting rings of unsymmetrically substituted arenes such as 2-methoxynaphthalene. This should be contrasted to Birch-type procedures which favor reduction of the less electron-rich aromatic ring due to the intervention of radical anion rather than cation intermediates.



2.6. Electron Transfer Photochemistry of Nitrogen Heteroaromatic Salts and Related Systems

2.6.1. General Considerations

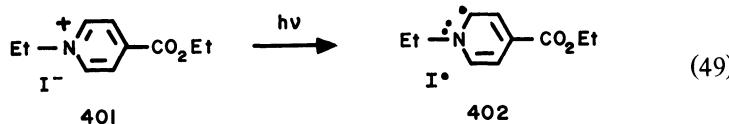
In this section synthetic aspects of the electron transfer photochemistry of *N*-heterocyclic and *N*-heteroaromatic systems which contain the iminium ion ($\text{R}_2\text{C}=\overset{+}{\text{N}}\text{R}_2$) functional group will be described. Considerable data have been accumulated to implicate electron transfer mechanisms in many of the photoreactions of these systems. The principal feature of excited states of substance containing the iminium salt grouping arises from the presence of the positive charge delocalized over nitrogen and the adjacent carbon. The ground states of these systems serve as excellent acceptors in one-⁽²⁹⁰⁾ and two-⁽²⁹¹⁾ electron transfer processes depicted in equation 48. The excited states of these systems are predicted to undergo one-electron reduction even more readily than the corresponding ground states. Accordingly, calculations⁽²⁸⁾ taking into account excited-state energies and reduction potentials of various iminium salts⁽²⁹⁰⁾ suggest that one-electron transfer to the excited species should occur rapidly from a number of unlikely one-electron donors such as simple olefins, aromatic hydrocarbons, alcohols, and ethers. Importantly,



electron transfer in these cases could serve as initial steps in pathways leading to quenching, photosensitization, and to the synthetically important processes involving reaction with donors. Indeed, many of the photochemical processes undergone by substances containing the iminium salt chromophore can be explained as occurring via electron transfer processes.

Before describing the synthetic applications of these reactions it is useful to review some of the spectroscopic evidence which implicates single-electron transfer in the excited-state chemistry of systems containing the imine and iminium salt function. Recent electron spin resonance studies by Castellano and co-workers⁽²⁹²⁾ have demonstrated that irradiation of six-membered monoazaaromatics in acidic (HCl) methanol or of quaternary salts of these systems results in the formation of semiquinone radical intermediates. These investigators concluded that the radicals were generated by electron transfer from methanol to the protonated heterocycles. It is noteworthy that the corresponding neutral systems in methanol, ether, or cyclohexane, generate the same or similar radicals when irradiated through mechanisms which most likely involve hydrogen atom abstraction. Flash photolysis studies by Kosower⁽²⁹³⁾ with 1-ethyl-4-carboethoxypyridinium iodide **401** and by Cozzens⁽²⁹⁴⁾ with 1-methylpyridinium, 1-methylcollidinium, and 1-methylquinolinium io-

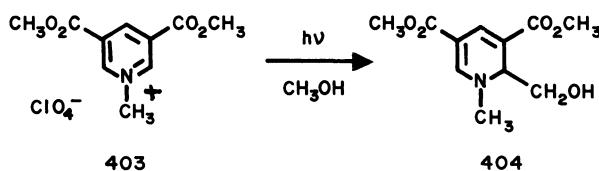
dides have shown that these systems undergo intramolecular electron transfer generating iodine atoms and the corresponding heterocyclic radicals [e.g., **402**, equation (49)].



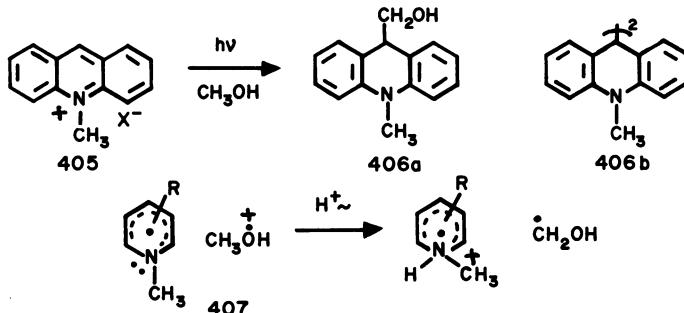
Charge transfer complexes which arise via single-electron transfer are also reported to be responsible for the fluorescence quenching of *N*-methylacridinium cation by various negatively charged counter ions.⁽²⁹⁵⁾ Similarly, fluorescence quenching involving electron transfer in pyridinium salts has also been reported by McCall and Whitten.⁽²⁹⁶⁾ Pyridinium⁽²⁹⁷⁾ and bipyridylium ions^(298,299) undergo photostimulated electron transfer in the presence of various neutral and anionic electron donors as indicated by their charge transfer spectra. In fact, the bipyridylium radical cation has been detected in flash photolysis studies by McKellar and Turner.⁽³⁰⁰⁾ Additionally, photochemical electron transfer between bipyridylium dication and oxalate, formate, and benzilate anions was observed by Ledwith.⁽³⁰¹⁾ Bipyridylium radical cations were produced in high quantum efficiencies. Ledwith^(302,303) and others⁽³⁰⁴⁾ have also investigated the photochemistry of bipyridylium salts in alcoholic solvents. Oxidation of the alcohol was observed with concomitant formation of the bipyridylium radical cation.

2.6.2. Electron Transfer Photochemistry of Pyridinium and Related Salts

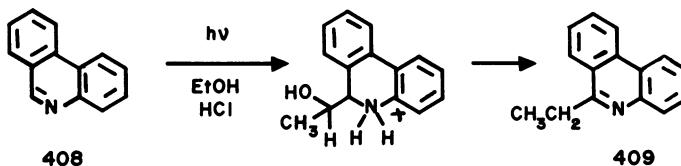
Pyridinium salts and related charged *N*-heteroaromatic systems participate in a variety of excited-state processes the more characteristic of which involve photoreduction and photoaddition. An excellent review of a number of these reactions has been written.⁽³⁰⁵⁾ Therefore, only a brief survey of several relevant examples will be included in this section. Van Bergen and Kellogg⁽³⁰⁶⁾ in studies of the photochemistry of carbomethoxy-substituted *N*-methylpyridinium salt **403** have observed reductive addition of methanol to the 2 position of **403** producing the 1,2-dihydropyridine **404**. Similar routes appear to be



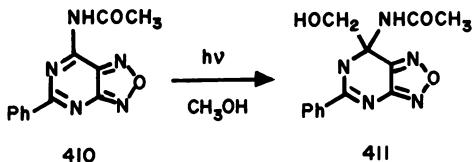
followed in the photochemistry of the acridinium salt **405** which is transformed to the methanol adduct **406a** and dimer **406b** upon irradiation in methanolic solution.⁽³⁰⁷⁾ The results of both of these reactions can be understood mechanistically in terms of initial electron transfer from methanol to the excited quaternary salts. Ensuing proton transfer of the formed radical–radical cation pairs related to **407** and coupling would lead to the observed products. Related pathways are involved in photoalkylations of quinoline⁽³⁰⁸⁾ and phenanthridine **408**^(309,310) occurring upon irradiation in acidic ethanol solutions. Thus, the



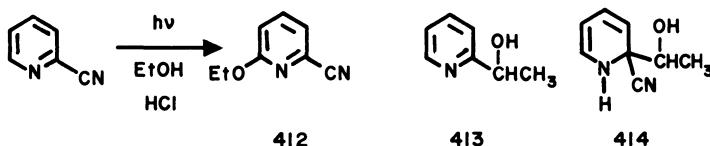
formation of 10-ethylphenanthridine **409** from **408** in near quantitative yield most probably involves addition to produce the intermediate aminoalcohol which then undergoes dehydration and tautomerization to generate **409**.⁽³⁰⁹⁾ A further example of alcohol addition is found in studies by Taylor⁽³¹¹⁾ of the pyrimidine **410** which adds methanol under irradiation conditions to produce adduct **411**. The diversity of pyridinium salt alcohol photoadditions is illustrated by the unusual course taken in the excited-state reaction of 2-cyano-



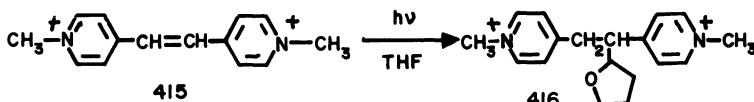
pyridine. In this case, irradiation in acidic ethanol solution leads to formation of adducts **412** and **413**, arising from both C- and O- addition by ethanol.⁽³¹²⁾ The ethoxide addition product is most likely the result of nucleophilic attack



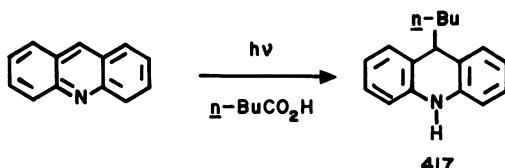
of ethanol on the highly electron deficient excited state cyanopyridinium salt occurring in competition with the electron transfer pathway to yield the cyano alcohol **414**, the precursor of **413**. Finally, analogous, sequential electron-



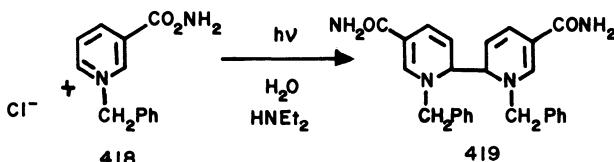
proton transfer pathways are involved in ether additions to the quaternary salts **415** of dipyridylethylene,⁽³¹³⁾ exemplified by formation of the adduct **416** through irradiation in tetrahydrofuran.



Radical pairs arising by photostimulated electron transfer in carboxylate salts of heteroaromatic substances can undergo rapid decarboxylation in a key mechanistic step leading to alkylation. Reductive alkylation processes occurring through this route have been investigated by Nozaki.⁽³¹⁴⁾ An example demonstrating the high efficiency of these reactions is found in the formation of 9-butylacridane **417** in 55% yield by irradiation of acridine in the presence of valeric acid.

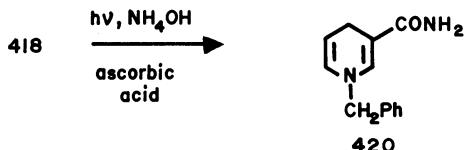


As pointed out by conversion of *N*-methylacridinium chloride **405** to dimer **406b** described above, electron transfer to *N*-heteroaromatic salts can lead to reductive dimerization through coupling of intermediate radicals. This process can be stimulated by irradiation of pyridinium salt, like **418**, in the presence of good electron donors, such as diethylamine. Accordingly irradiation of aqueous solutions of **418** under these conditions results in formation of the dimer **419**.⁽³¹⁵⁾ Radical coupling in this case is at C-6 of the 3-substituted



pyridinyl radical, a possible result of steric control. Additional studies by Matsuo⁽³¹⁶⁾ have shown that hemin is reduced in high yields by an electron transfer process involving formation of radicals from the pyridinium salts, **418**, 3,5-dicarboethoxy-2,6-dimethyl pyridinium chloride, beta-nicotinamideadenine dinucleotide (NAD⁺), or benzyl viologen. Matsuura⁽³¹⁷⁾ has also

reported that irradiation of **418** in the presence of excess ascorbic acid in aqueous ammonia gives the 1,4-dihydropyridine **420**.

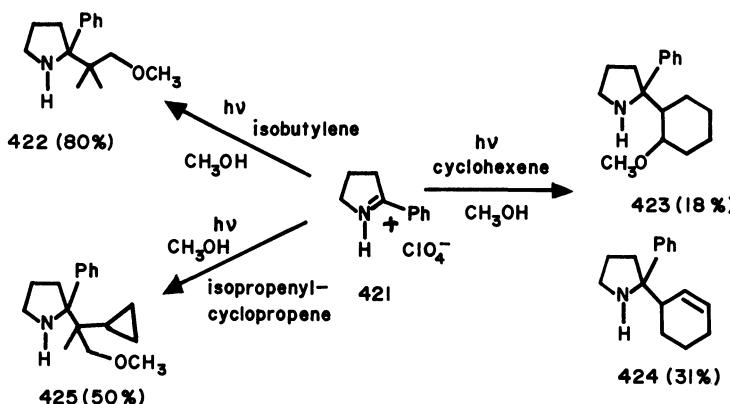


2.6.3. Iminium Salt Photochemistry

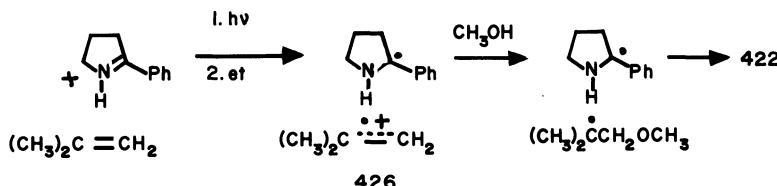
As mentioned earlier in this section, calculations taking into account excited-state energies and the reduction potential of a variety of iminium salts suggest that one-electron transfer to the excited species should occur rapidly from a number of unlikely one-electron donors such as simple olefins, aromatic hydrocarbons, alcohols, and ethers. A host of recent studies have shown that photostimulated electron transfer from these donors to compounds containing the iminium salt grouping serves to initiate a variety of photochemical processes. The structural and functional outcomes of these reactions allow them to be categorized as synthetically useful. In this section we will review these processes pointing out when appropriate how each can be applied to synthetic problems.

Mariano and Stavinoha,⁽³¹⁸⁻³²¹⁾ in investigations of olefin-pyrrolinium salt photochemistry have uncovered interesting carbon–carbon forming addition reactions which proceed by way of electron transfer mechanisms. Preliminary consideration of the free energies and rates of electron transfer to singlet excited states of C-phenyl conjugated iminium salts suggest that the process will be favorable when olefin donors with π -oxidation potentials lower than ca. 2.6 eV are used. Consistent with this expectation is the observation that several olefins of this type serve as excellent quenchers of 2-phenyl-1-pyrrolinium perchlorate **421** fluorescence. Rate constants for quenching were found to be near the diffusion-controlled limit in acetonitrile (ca. $1 - 10^{10} M^{-1} \text{ sec}^{-1}$).^(318,320) In addition, 2-phenyl-1-pyrrolinium perchlorate **421** undergoes addition of isobutylene in a high yielding, regiocontrolled fashion producing the adduct **422**. Similar pathways are followed in reaction of **421** with a number of other electron-rich olefins, including cyclohexene, butadiene, methyl β,β -dimethylacrylate, and isopropenylcyclopropane. The formation of **422** in high yield (80%) illustrates the synthetic potential of this process. The amino ether is the result of C–C bond formation between two quaternary centers, a rare occurrence in organic chemistry.

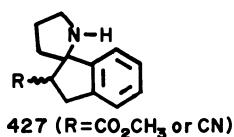
The structural and regiochemical aspects of these photoadditions appear nicely rationalized by electron transfer mechanisms. Accordingly, electron transfer from the electron-rich olefin isobutylene to **421^s** would result in the



production of radical cation–radical pair **426**. Attack by methanol on the charged fragment of this pair should occur with regiocontrol dictated by the stability of the resulting radical. Collapse of the radical pair by C–C bond formation would yield the observed amino ether **422**. Alternatively, competitive deprotonation of the cation radical intermediate can occur to produce



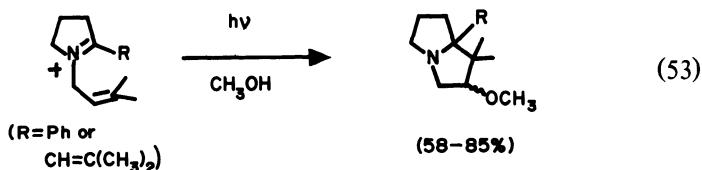
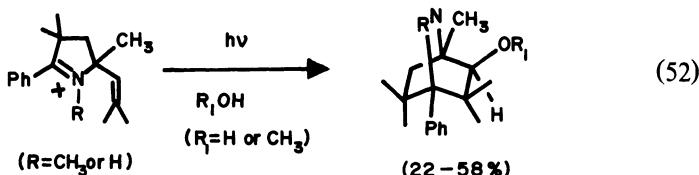
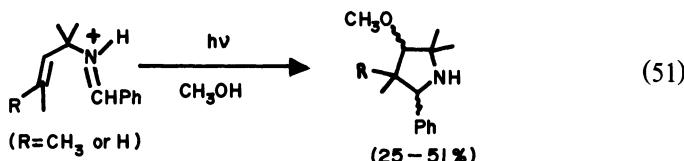
an allyl radical. The latter route is followed in production of the olefin adduct **424** by irradiation of **421** in the methanol solution containing cyclohexene. It is significant to note that rate constants for electron transfer from the electron-poor olefins, acrylonitrile, methyl acrylate, and methyl methacrylate to the singlet of **421** are predicted to be small. Interestingly, the typical aminoether adducts are not produced upon irradiation of **421** in the presence of these olefins. Instead, the epimeric spirocyclic amines **427** are generated through alternate $\pi_2 + \pi_2$ arene–olefin cycloaddition followed by ring expansion.^(320,322)



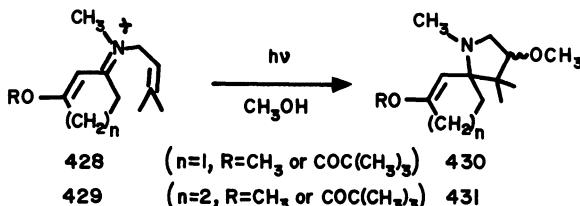
Intramolecular counterparts of olefin–iminium salt photoadditions serve as useful methods for heterocyclic ring construction. Results from investigations by Mariano and co-workers^(319,321) of *N*-allyliminium salts show that photocyclizations of these systems occur in moderate yields (40% to 60%) to

generate 3-pyrrolidinyl ethers or alcohols in monocyclic, and bridged and fused bicyclic structural environments. Examples demonstrating this aspect are presented in equations (51–53).

More recently, Mariano and his co-workers⁽³²⁴⁾ have found that *N*-allyliminium salt photocyclizations can be used to prepare spirocyclic-aminoethers. Iminium salts **428** and **429** produced by O-acylation and O-alkylation of precursor β -enaminones undergo electron transfer induced photocyclizations

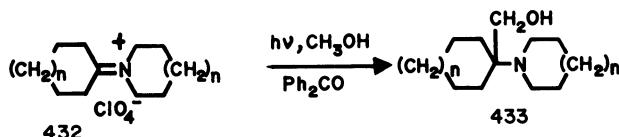


to form the enol ether and ester products **430** and **431** upon irradiation in methanol. Although the yields of these processes are low (ca. 20%–30%), their structural outcome illustrates the versatility of the process and suggest its potential in synthetic applications.

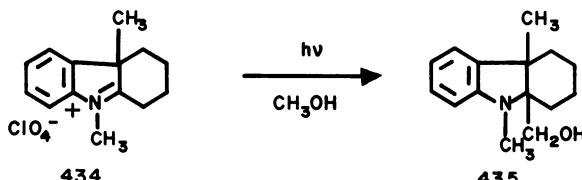


Thus far we have surveyed investigations of iminium salt photochemistry in which electron transfer from olefinic π -electron donors occurs and results in fluorescence quenching and photaddition reactions. Simple theoretical treatments permit the prediction that other types of substances should be capable of serving as one-electron reducing agents of iminium salt excited states. These include materials with such common functionality as alcohols, ethers, esters, carboxylic acid salts, and aromatic systems. Indeed, fluorescence quenching

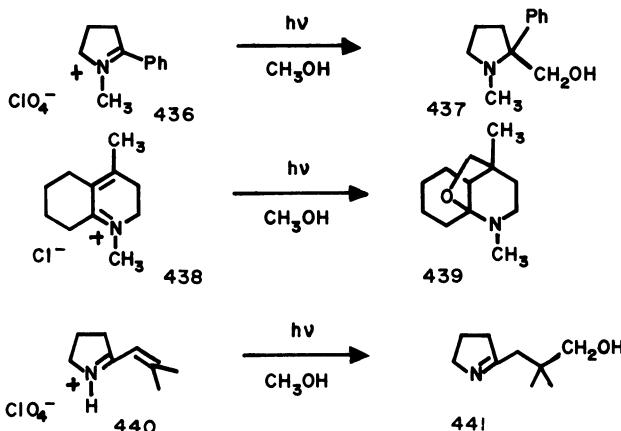
of the iminium salt excited state by alcohols and ethers apparently involves an electron transfer mechanism.^(322,324) Photoadditions of alcohols with α -hydrogens to iminium salts represent a potentially interesting and synthetically useful class of C-C bond-forming reactions. These processes, proceeding most



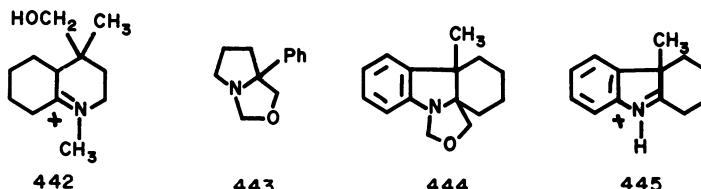
probably via electron–proton transfer mechanisms, result in the production of β -aminoalcohols. Several examples of this type of addition process are found in the chemical literature. Schmid⁽³²⁵⁾ observed that aminoalcohols **433** are formed in moderately good yields in the benzophenone-sensitized photolysis of the quaternary salts **432**. Schmid and Cerutti⁽³²⁶⁾ also reported that



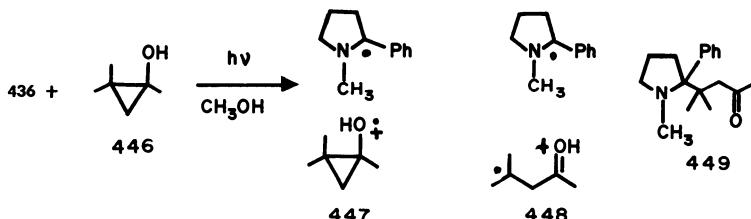
irradiation of the iminium salt **434** in methanol resulted in a 38% yield of the amino alcohol **435**. Related examples of alcohol additions to iminium salts, operating via sequential electron–proton transfer mechanisms,^(322,324) are found in the conversions of iminium salts, **436**,⁽³²²⁾ **438**,⁽³²⁷⁾ and **440**⁽³²⁴⁾ to corresponding adducts upon irradiation in methanol solutions. The tricyclic ether **439** is most likely a secondary product arising from ground-state cyclization of the initially formed alcohol **442**. Secondary dark reactions of



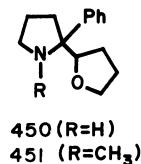
initially formed methanol adducts with formaldehyde formed in the photo-reaction mixtures appears to be responsible for formation of the oxazolidines **443** and **444** from irradiation of the protonated pyrrolinium **421**⁽³²²⁾ and indolenium salt **445**,⁽³²⁸⁾ respectively.



Normally, tertiary alcohols do not participate in iminium salt photoadditions since transfer of a proton on carbon α to oxygen in the initially formed radical cation must occur to produce the ultimate radical intermediate. However, Mariano and his co-workers⁽³²²⁾ have observed that the photoadduct **449** is obtained when the pyrrolinium salt **436** is irradiated in the presence of 1,2,2-trimethylcyclopropan-1-ol **446**. In this case, the alcohol-derived radical cation **447** is efficiently converted to the ring cleaved radical ion **448** in competition with back electron transfer.



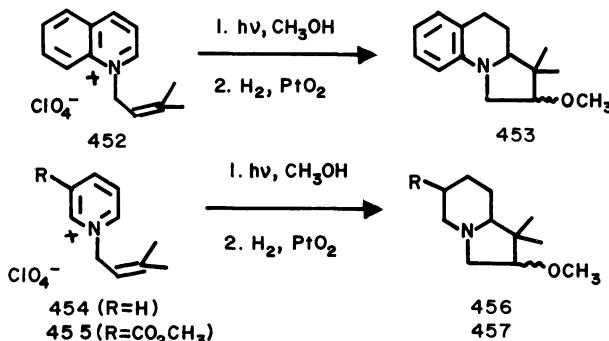
Photoadditions of ethers to iminium salts occur by mechanisms which closely parallel alcohol additions. β -Aminoethers **450** and **451** are formed when the 2-phenylpyrrolinium perchlorates **421** are irradiated in solutions of



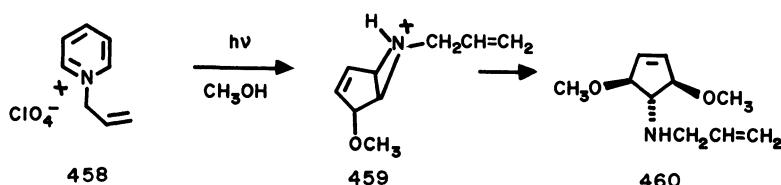
tetrahydrofuran and acetonitrile. The reasonably high yields (40%–60%) of these processes suggest potential synthetic applications.

As discussed earlier in this section, pyridinium and related heteroaromatic cations participate in interesting, electron transfer initiated alcohol photoadditions. An evaluation of electron transfer rate constants indicates that electron-rich olefins should also serve as electron donors to the singlet excited

states of pyridinium and quinolinium salts. Studies⁽³²⁹⁾ of *N*-allylpyridinium and quinolinium salt photochemistry show that this postulate is correct and that electron transfer reaction pathways serve as useful methods for construction of interesting heterocyclic systems. For example, the *N*-prenyl perchlorates **452** and **454** undergo efficient photocyclization upon irradiation in meth-



anol followed by catalytic hydrogenation to produce the indolizidines **453** and **456** in high yields. Similarly, the diastereomeric indolizidine esters **457** are formed when the corresponding methyl nicotinate derived salt **455** is irradiated under these conditions. Among the observations providing evidence in support of electron transfer mechanisms for these cyclization reactions, is one made in study of *N*-allylpyridinium perchlorate **458**. Intramolecular electron transfer from the monosubstituted olefinic unit in **458** to the singlet excited pyridinium moiety is predicted to be inefficient. As expected, excited-state reaction of this system does not appear to follow an electron transfer pathway. Rather, a precedented⁽³³⁰⁾ electrocyclization process leading through **459** to the aminocyclopentene **460** occurs in 80% yield.

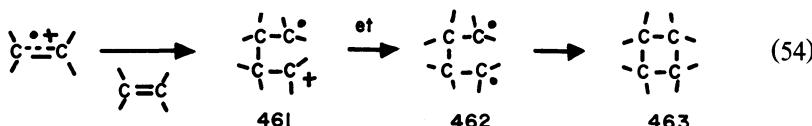


2.7. Other Electron Transfer Initiated Photoreactions

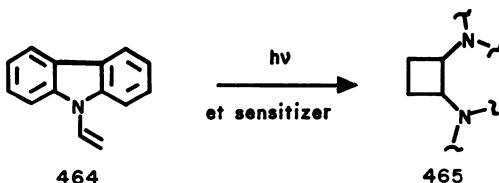
2.7.1. Olefin Cycloadditions and Retro Processes

One of the most widely studied and synthetically useful classes of photochemical reactions is that involving olefin $\pi 2 + \pi 2$ cycloaddition to olefinic,⁽³³¹⁾ carbonyl,⁽³³²⁾ and α,β -unsaturated carbonyl⁽³³³⁾ groupings. Concerted

mechanisms and two-step pathways through intermediate diradicals have been found to be operable for most of these cycloaddition reactions. A number of recent studies have uncovered examples of olefin cyclodimerization which proceed by an alternate route involving photostimulated or sensitized electron transfer. Accordingly, radical cations arising by electron transfer from olefin π systems can react with electron-rich olefins of the same or different identity to produce 1,4-diradical cations **461** [equation (54)]. Back electron transfer would then give rise to familiar 1,4-diradicals **462**, precursors of the cycloadducts **463**. Ledwith⁽³³⁴⁻³³⁶⁾ has provided a number of observations which show that olefin cyclodimerizations through this pathway are synthetically useful processes. *N*-Vinylcarbazole **464** is transformed to the trans-cyclobutane **465**

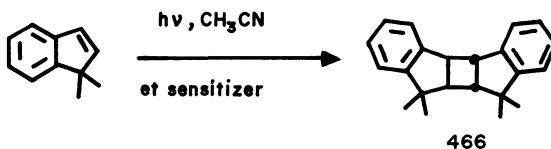


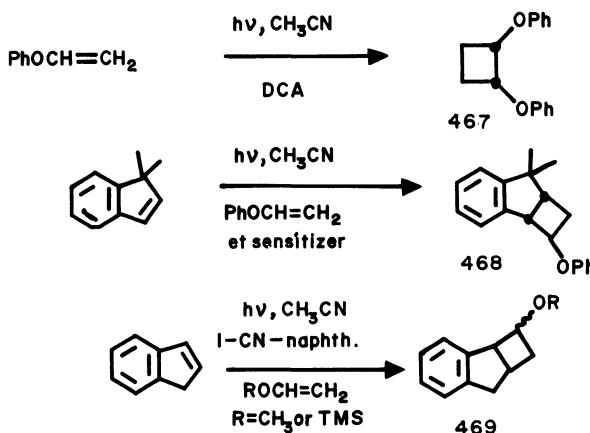
under electron transfer sensitized conditions with a variety of electron accepting sensitizers. The dimerization quantum efficiencies, which range up to 66, are enhanced by the presence of dissolved oxygen in the reaction media.



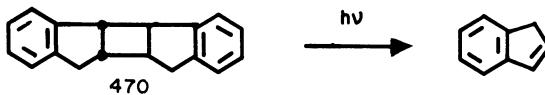
The effect of oxygen on reaction efficiency is most probably due to its reaction with sensitizer radical anions by electron transfer, thus preventing the radical anions from transferring electrons to the olefin cation radicals or intermediate 1,4-diradical cations. Intervention of either of these electron transfer steps would lead to termination of the chain processes.

A variety of other olefin cycloadditions have been uncovered as illustrated by production of the homo-dimers **466**⁽³³⁷⁾ and **467**,^(338,339) and heterodimers **468**⁽³⁴⁰⁾ and **469**⁽³⁴¹⁾ by electron transfer sensitized irradiation of corresponding olefin systems. It is interesting that cation radicals derived from conjugated olefins can also participate in $\pi_2 + \pi_2$ cycloaddition reactions.^(48,342,343)



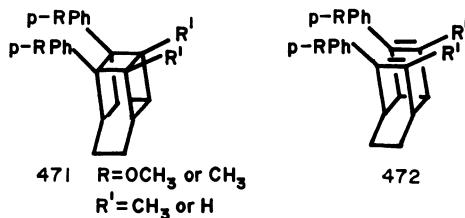


Cyclobutane cycloreversions to olefins can be performed under electron transfer sensitized conditions. Pac and co-workers⁽³⁴⁴⁾ have shown that the indene dimer **470** undergoes a cycloreversion to indene in yields of 75% to 80% by means of a redox photosensitization. Sensitizers such as triphenylene, naphthalene, chrysene, and dimethylnaphthalene were effective. The reaction system consisted of a mixture of a sensitizer (S), *p*-dicyanobenzene, the aryl-substituted cyclobutane, and acetonitrile as solvent. A novel mechanism involving catalysis by S^+ via a π complex was proposed. In another example,



Mukai⁽³⁴⁵⁾ has demonstrated that phenylated cage compounds **471** undergo photocatalyzed cycloreversions leading to dienes **472** in good yield (70%–90%) when *p*-benzoquinone or 9,10-phenanthraquinone was used as sensitizer.

Electron transfer sensitized irradiation of olefins at high concentration can lead to polymerization. The utilization of photoelectron transfer processes for the initiation of chain reaction polymerizations has potential application in many areas. These include uses in photoactive relief printing plates, printed

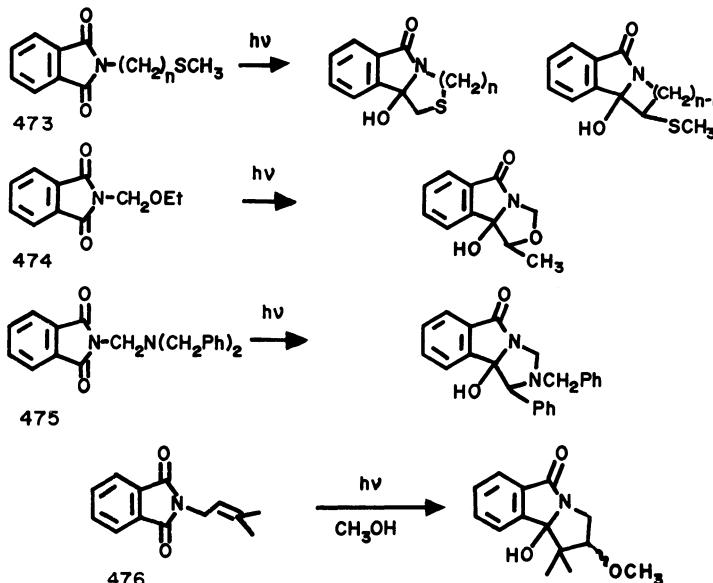


circuits, photochemical curable coatings, and printing inks, among others. Ledwith⁽³⁴⁵⁾ has demonstrated that an effective photoinitiation system for

radical polymerization is generated by the photolysis of fluorenone in the presence of suitable tertiary amines, such as *N,N*-dimethylethanolamine. Methyl methacrylate was studied as a model system. The utilization of pendant amine and fluorenone rings as photoinitiators was investigated. These studies suggest that the former were more effective for graft copolymer formation. Several workers⁽³⁴⁷⁾ have reported the cationic and radical photopolymerizations of *N*-vinylcarbazole which arise via charge transfer complexes. Other photopolymerizations involving electron transfer mechanisms have been reported. Examples include styrene polymerization⁽³⁴⁸⁾ and photocrosslinking of poly-*n*-(vinyloxyethoxy)styrene.⁽³⁴⁹⁾ The copolymerization of acrylonitrile and styrene also involves radical ion intermediates.⁽³⁵⁰⁾

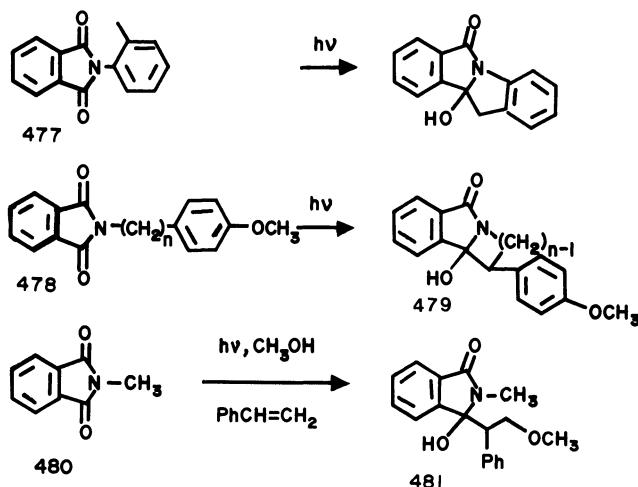
2.7.2. Phthalimide Photochemistry

Considerable attention has been given in the last decade to the excited-state chemistry of phthalimides. Two excellent reviews of this topic have appeared recently.^(351,352) Detailed aspects of this system will also be covered in another chapter (Chapter 4) of this book. However, a brief mention of the photochemical processes followed by phthalimides which involve photosti-



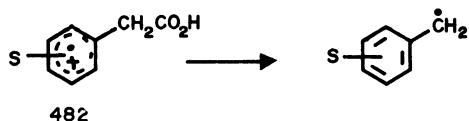
mulated electron transfer in this section seems in order. Photoreactions of phthalimides with electron-rich olefins^(353,354) and other potential electron donors, including sulfides, ethers, and amines, all appear to be activated by electron transfer and to lead to carbon–carbon bond formation. Examples

which illustrate the variety of reactions rationalized in this way are seen in the intramolecular cyclizations of phthalimides with *N*-thioalkyl^(355,356) **473**, *N*-alkoxyalkyl⁽³⁵⁷⁾ **474**, *N*-aminoalkyl⁽³⁵⁸⁾ **475**, *N*-alkenyl⁽³⁵⁹⁾ **476**, and *N*-aryalkyl^(360,361) **477** and **478** substituents. Intermolecular versions of these processes have been uncovered for olefin-*N*-methylphthalimide systems (e.g., **480**→**481**).⁽³⁵³⁾

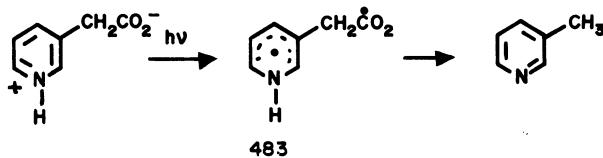


2.7.3. Photodecarboxylations

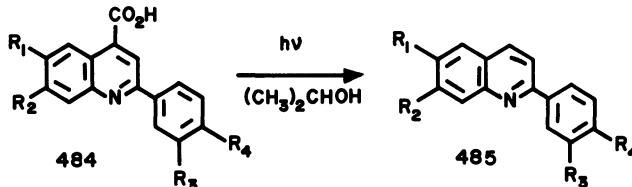
Photosensitized decarboxylation is a general excited-state process followed by a variety of substituted 2-arylacetic acids. A number of electron-accepting sensitizers, including quinones,⁽¹⁴⁷⁾ nitrogen heterocycles, dyes,⁽³⁶²⁾ and polycyclic aromatic hydrocarbons,⁽³⁶³⁾ have been employed as decarboxylation catalysts. The mechanism for these reactions appears to involve photochemically activated electron transfer to generate the arylacetic acid radical cations **482** which then readily lose carbon dioxide to form the corresponding benzyl radicals, a process analogous to the deprotonation route of arylalkyl cation radicals described earlier in this chapter (Section 1.2.5.2). This mechanistic pathway is involved in the photodecarboxylative transformation of



2-, 3-, and 4-pyridylacetic acids in aqueous solutions to the corresponding picolines.⁽³⁶⁴⁾ In this case, electron transfer from the carboxylate to pyridinium

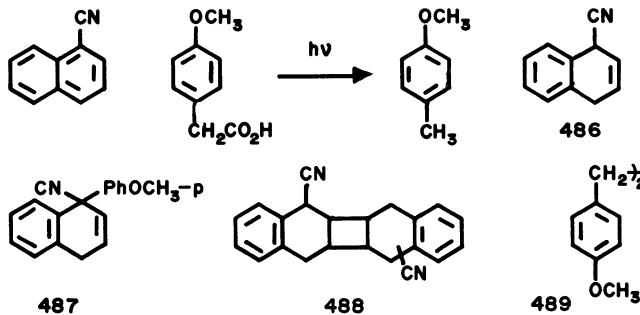


salt chromophores is an intramolecular process giving rise to diradicals related to **483**. The photochemical decarboxylation of 2-arylquinoline-4-carboxylic

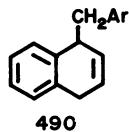


acids **484** observed by Epling and Yoon,⁽³⁶⁵⁾ which form the corresponding quinolines **485** in excellent yields, appear to follow similar routes.

Libman⁽³⁶⁶⁾ has demonstrated that 1-cyanonaphthalene undergoes photochemical reduction and reductive alkylation in the presence of electron-rich phenylacetic acid derivatives. Thus, irradiation of *p*-methoxyphenylacetic acid in the presence of 1-cyanonaphthalene resulted in quantitative conversion of the acid to *p*-methoxytoluene, the 1,4-dihydronaphthalenes **486** and **487**, dimer **488**, and the bibenzyl **489**. Libman's investigations indicate that the excited

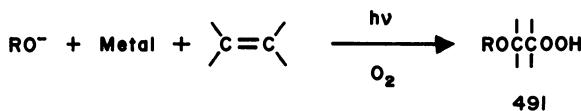


cyanonaphthalene reacts with electron-rich phenylacetic acids to give excited complexes which undergo electron transfer in acetonitrile solution leading to photoproducts. However, in nonpolar solvents such as benzene the excited complex deactivates via fluorescence. Libman⁽³⁶⁷⁾ has also investigated the photochemistry of 1-methoxynaphthalene in the presence of various phenylacetic acids. The major alkylation products were the dihydronaphthalenes



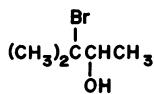
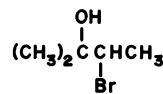
2.7.4. Metal Catalyzed Photoreactions

The utility of metal ions or semiconductors as catalysts for photochemical reactions has been demonstrated in recent years. Although only a few examples of these processes operating by electron transfer mechanisms have been explored in detail, they amply illustrate the synthetic potential of the method. Sato and his co-workers⁽³⁶⁸⁾ have reported that the photooxidation of olefins in the presence of uranyl acetate leads to production of β -hydroxyhydroperoxides in low yields by a mechanism involving interligand electron transfer which leads to the adduct **491**. Sata has shown that other substances capable



of trapping olefin-derived radicals can also participate in these processes as exemplified by the production of bromohydrins **492** and **493** by irradiation of solutions of 2-methyl-2-butene, uranyl acetate, and bromotrichloromethane.

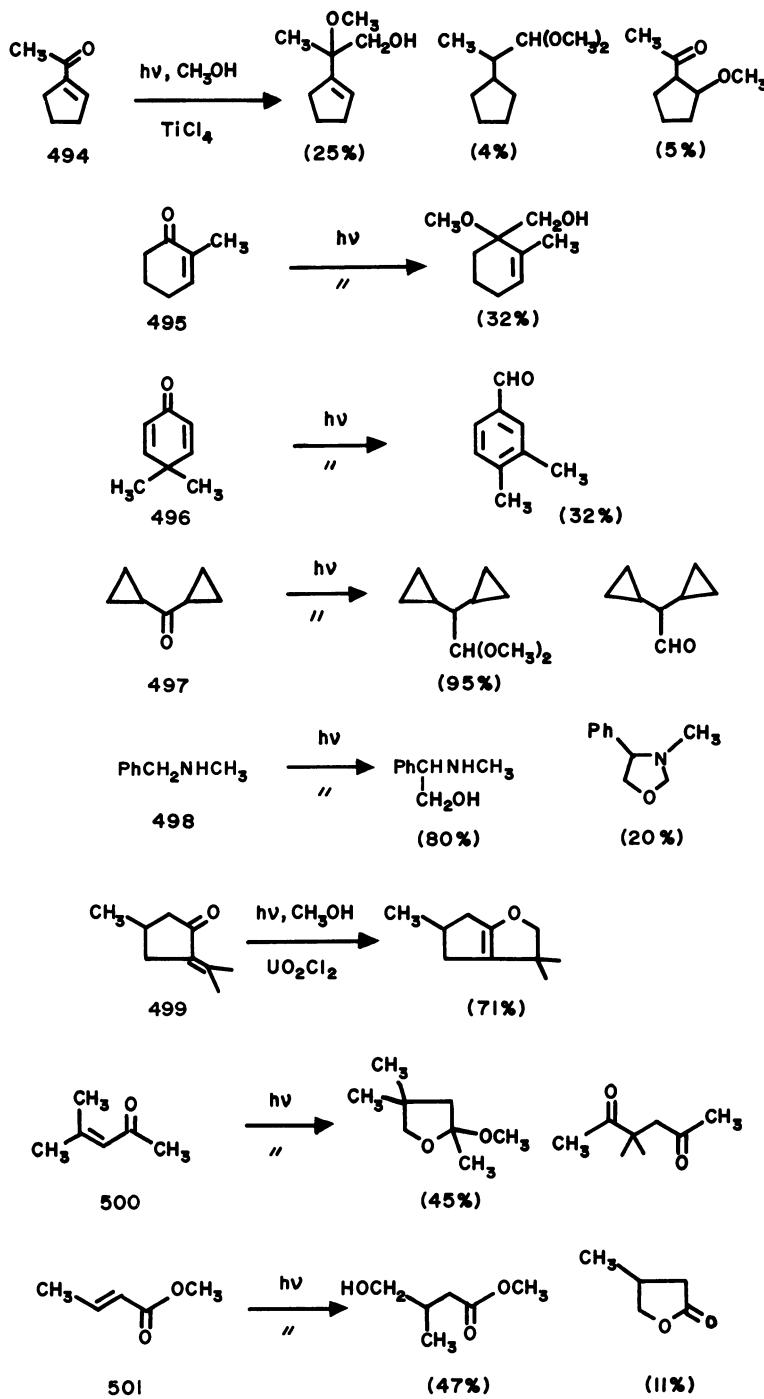
Sato has used a similar long-range electron transfer mechanism to explain the TiCl_4 and uranyl chloride initiated photoaddition of alcohols to α , β -unsaturated carbonyl compounds and esters, cyclopropyl ketones, β -diketones, Schiff's bases, and nitriles.⁽³⁶⁹⁾ These workers have shown that the α -

**492****493**

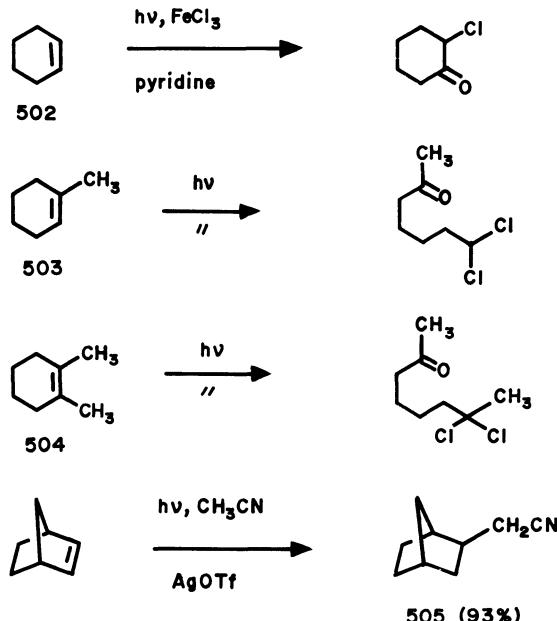
carbon of the primary alcohols undergoes bond formation with the $\text{C}=\text{X}$ (or $\text{C}=\text{N}$) carbon of the substrates when TiCl_4 is used as the photocatalyst. Illustrative examples are given in conversions of the enones **494–496**, ketone **497**, and imine **498** to the corresponding methanol adducts. Interestingly, adducts arising through bond formation to the olefinic moieties of α , β -unsaturated carbonyl compounds **499–501** are observed when uranyl chloride is employed as catalyst.

Other examples of metal-catalyzed reactions of olefins are found in the production of α -chloroketones upon irradiation of pyridine solutions in the presence of ferric chloride.⁽³⁷⁰⁾ Tri- and tetra-substituted olefins, such as **503** and **504**, yield ring cleaved products under these conditions.

Other synthetically useful metal-catalyzed olefin electron transfer induced transformations have been reported. Marks and co-workers⁽³⁷¹⁾ have reported that silver (I) can be used to photocatalyze addition of acetonitrile to norbornene. Accordingly, irradiation of an acetonitrile solution of norbornene and silver trifluoromethanesulfonate resulted in formation of the cyano adduct **505** along with minor amounts of norbornene dimers. The proposed mech-



anism for this addition involves ligand-to-metal charge transfer photoinitiation. A free radical chain process then ensues in which a cyanomethyl radical adds to norbornene.



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Phthalimide and Its Derivatives

John D. Coyle

1. Introduction

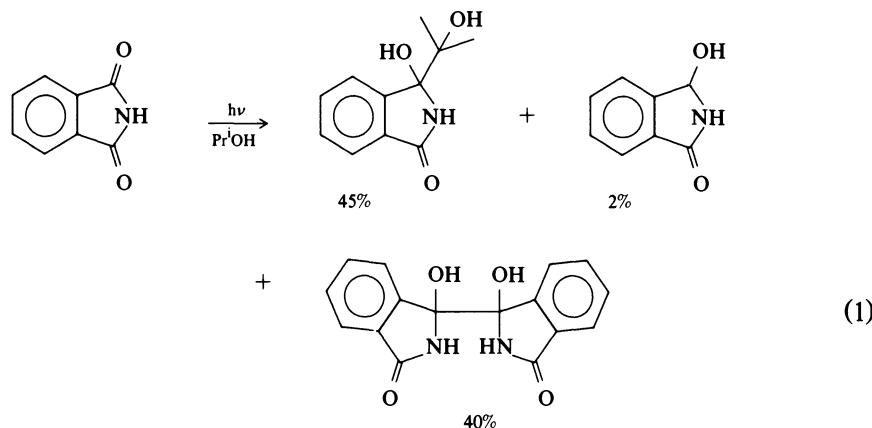
Organic carbonyl compounds featured prominently in the early period of mushrooming growth in the field of organic photochemistry. Initially much attention was focused on the photoreactions of ketones and, to a lesser extent, aldehydes. Subsequently carboxylic acids and their derivatives were investigated more extensively, and reviews of their photochemistry show a wide range of interesting reactions.^(1,2) Cyclic carboximides have emerged as showing a considerable variety of photochemical behavior, and many of the reactions can be put to good use in the synthesis of heterocyclic compounds. Reactions of the hydrogen abstraction/cyclization type have been reviewed by the director of the most active research group in this area,⁽³⁾ and a more comprehensive review of imide photochemistry is available.⁽⁴⁾ The purpose of this chapter is to describe the photochemical reactions of aromatic imides related to phthalimide, and to emphasize the synthetic applications of the processes. At various points in the discussion the main parallels and differences between aromatic and aliphatic imides will also be covered briefly.

2. Hydrogen Abstraction

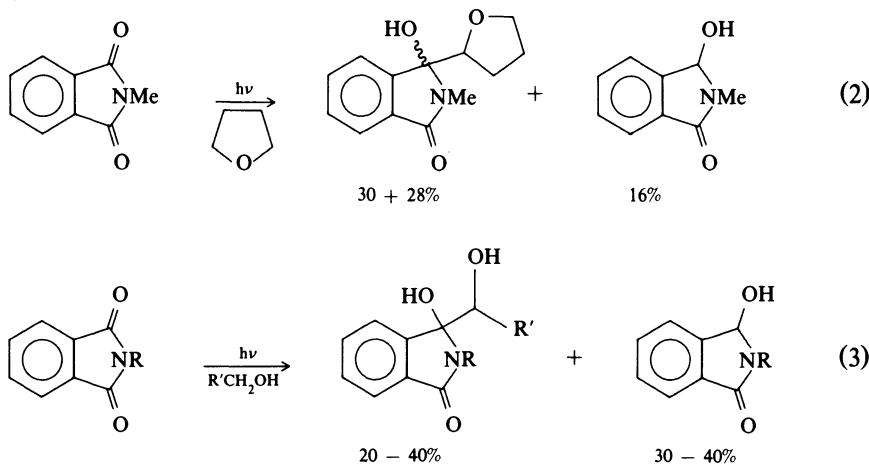
2.1. Photoreduction and Photoaddition

In their ability to abstract hydrogen from a suitable donor such as an alcohol, ether, alkene, amine, or alkylbenzene, phthalimides resemble aromatic ketones such as benzophenone. With phthalimide itself and isopropanol the

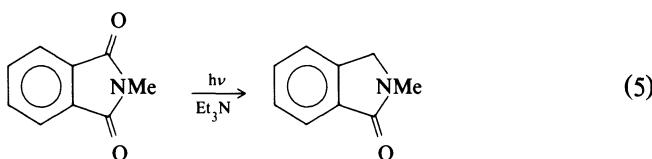
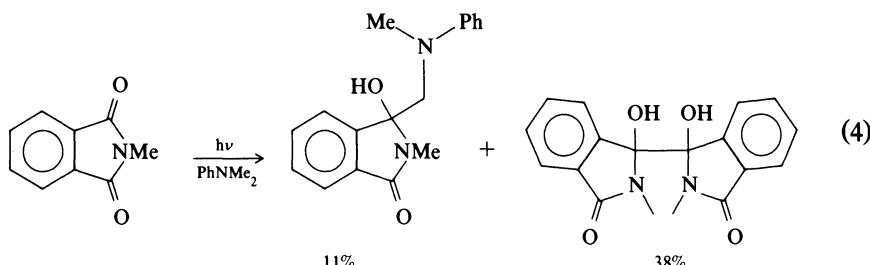
major products are a photoadduct and the pinacol-like reduction product (1), together with a small amount of 3-hydroxyisoindolinone.⁽⁵⁾ A similar distribution of products is found when the reducing agent is ethanol, dioxan, or tetrahydrofuran,⁽⁶⁾ with the photoadduct predominating. Methanol, however, gives only photoreduction products in low yield.



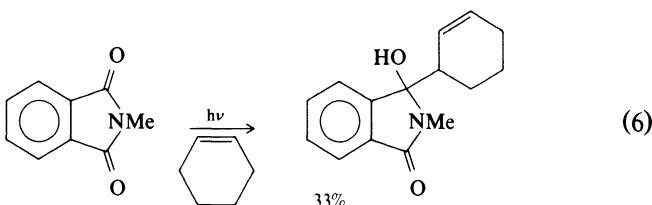
N-Methylphthalimide has been studied with a wide range of hydrogen donors. Typical of the reaction with ethers is the formation of diastereoisomeric photoadducts with tetrahydrofuran [equation (2)]; some 3-hydroxy-2-methylisoindolinone is also formed, but no dimeric photoreduction product.⁽⁷⁾ The same behavior is found with dioxan⁽⁷⁾ or with diethyl ether.^(7,8) In the same way, both *N*-methyl- and *N*-ethyl-phthalimide can be photoreduced with methanol or ethanol to give⁽⁹⁾ the corresponding 3-hydroxyisoindolinone and a similar amount of photoaddition product [equation (3)].

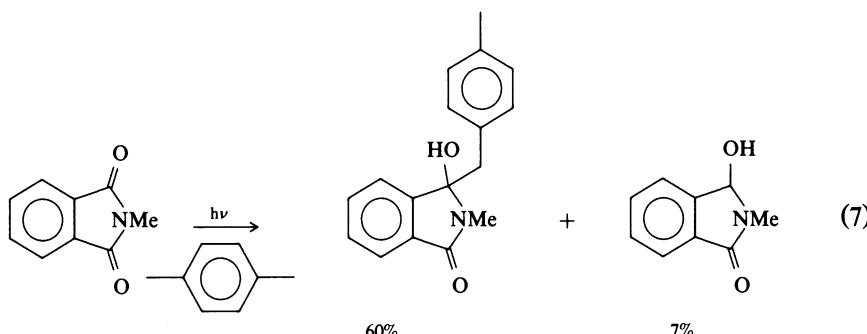


A report⁽¹⁰⁾ of the use of amines as hydrogen donors shows that under some conditions the pattern of products includes the dimeric photoreduced imide as well as the monomeric reduction product and the photoadduct [equation (4)]. An unusual feature of the reaction with amines is that triethylamine, and also *N,N*-dimethylcyclohexylamine in one experiment, gives the further reduced product 2-methylisoindolinone [equation (5)], although there is no comment on the factors that promote this type of photoreduction.

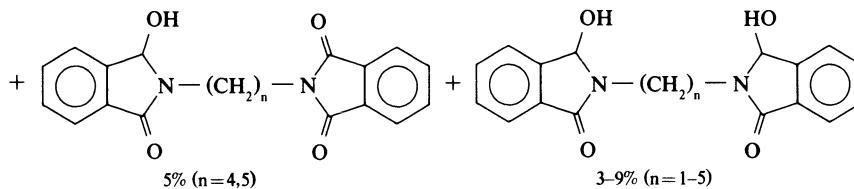
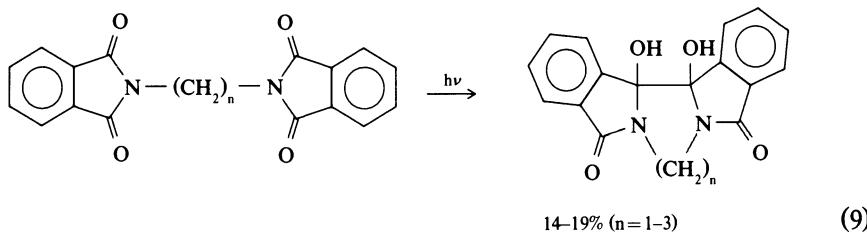
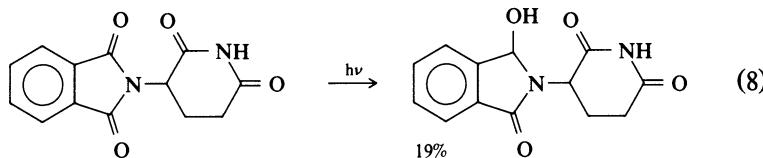


Alkenes with allylic hydrogen can take part in the photoaddition process, and the reaction of *N*-methylphthalimide with cyclohexene [equation (6)] or cyclopentene illustrates this.⁽⁷⁾ The yields are not high, and it is probable that other processes compete with the hydrogen abstraction (see Section 3). Higher yields of photoadduct are obtained with methyl-substituted benzenes,⁽¹⁰⁾ such as toluene, the xylenes [equation (7)], or mesitylene. It is significant that, as in so many of these photochemical hydrogen abstraction reactions of phthalimides, the major product is derived by cross-coupling of the initially formed pair of radicals. This is in contrast to the photoreduction of ketones, and it reflects, not a difference in the nature of the excited state involved, but different relative rate constants for combination, cross-combination, and disproportionation in the various radical pairs.

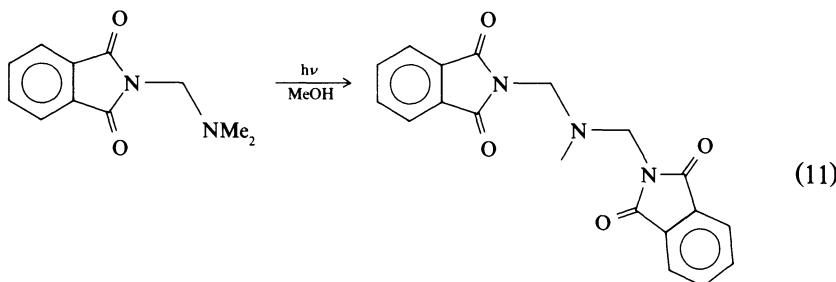
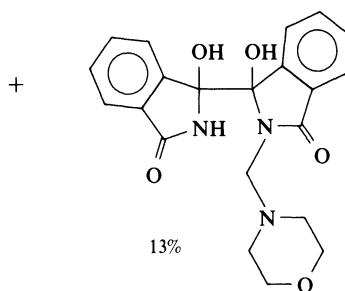
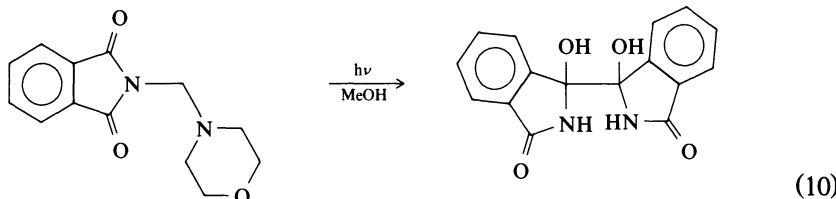




A number of phthalimides have been studied with substituents other than simple alkyl groups on the nitrogen. *N*-(Methoxymethyl)phthalimide and *N*(carboxymethyl)phthalimide give photoaddition products with tetrahydrofuran,⁽⁵⁾ but the only product isolated from the irradiation of thalidomide is the substituted 3-hydroxyisoindolinone [equation (8)]. A series of *N*-methylenebisphthalimides showed⁽¹¹⁾ that, with a suitable length of bridging group, the intramolecular pinacol-like product predominates over products in which one or both of the imide groups is separately reduced [equation (9)]. Rather surprisingly, no photoaddition products are reported in this system. The photochemistry of Mannich bases of phthalimide features largely in the next section, but one interesting report⁽¹²⁾ suggests that in some instances photo-reduction involving the Mannich base or the parent phthalimide takes place.



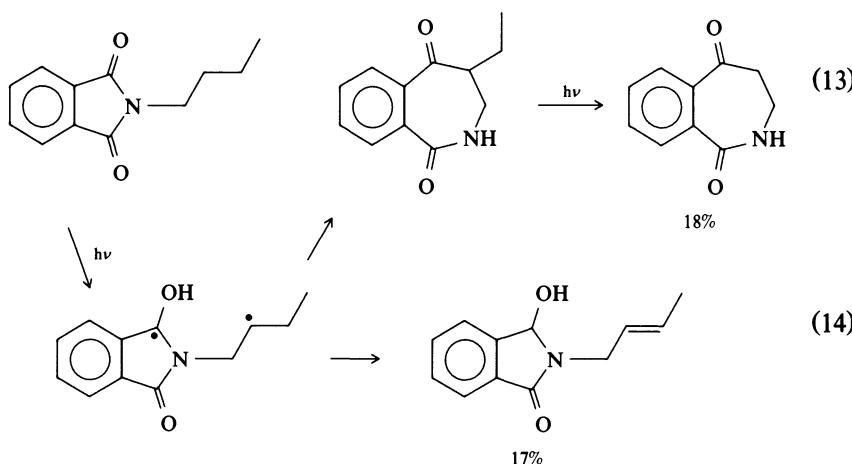
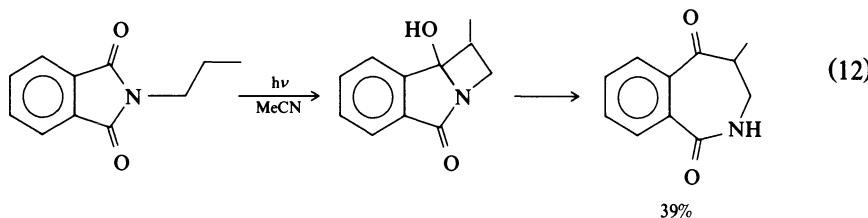
N-(Morpholinomethyl)phthalimide gives two dimeric photoreduced products [equation (10)], one involving phthalimide only and the other both phthalimide and the Mannich base. Other derivatives give bis(phthalimidomethyl) products that point to a fragmentation and recombination mechanism [equation (11)].



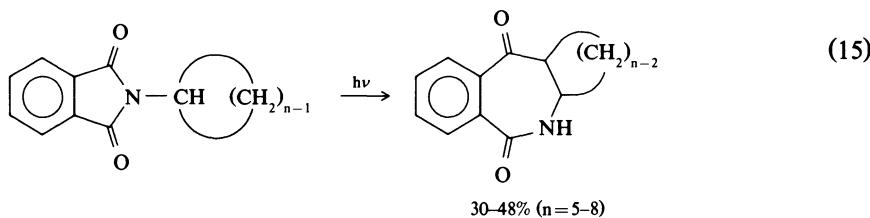
2.2 Intramolecular Photocyclization

Photochemical intramolecular hydrogen abstraction and cyclization is the subject of a large number of reports, and one of the main reasons for the interest in these reactions is the possibility of making a variety of polycyclic heterocyclic systems. Simple *N*-alkylphthalimides can give benzazepinediones [equation (12)] that arise by way of γ -hydrogen transfer and an intermediate fused azetidinol.⁽¹³⁾ This is the major reaction pathway for related alicyclic amides such as succinimides, glutarimides, or perhydrophthalimides,^(14,16) but

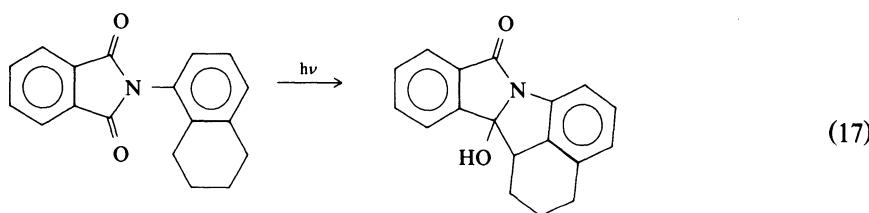
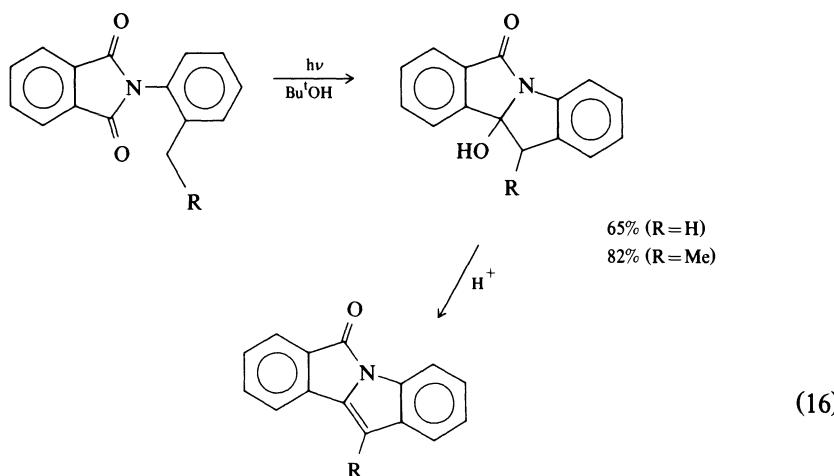
in the aromatic imide systems other processes compete effectively. The major alternative products arise either by a further Norrish type 2 photoelimination in the benzazepinedione [equation (13)] or by intramolecular disproportionation in a biradical intermediate to give an *N*-allylic 3-hydroxyisoindolinone [equation (14)]. Phthalimide itself is reported as a significant product only from *N*-*t*-butylphthalimide, and a product arising from abstraction at a position other than the γ -CH only from *N*-(3-methylbutyl)phthalimide.

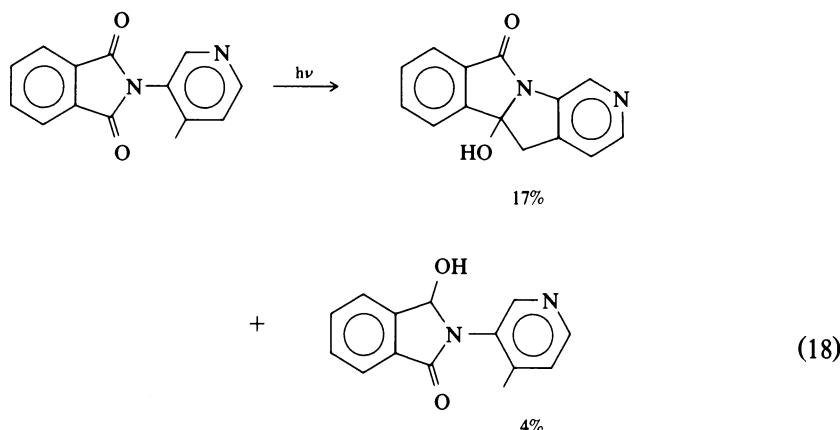


A study⁽¹⁷⁾ of the mechanistic aspects of some of these reactions shows that quantum yields are in the range 0.003 to 0.023, and that optical activity at the γ - position in the initial imide is preserved, indicating that there is no reversible formation of a long-lived biradical species. The reaction has been extended to a series of *N*-cycloalkylphthalimides,⁽¹⁸⁾ and for these compounds the formation of the polycyclic azepinedione is quite efficient [equation (15)].

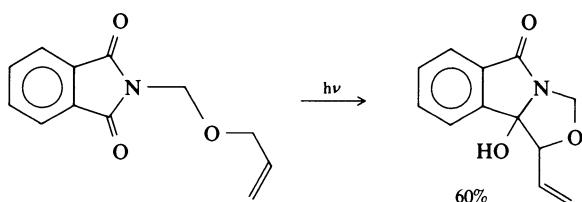
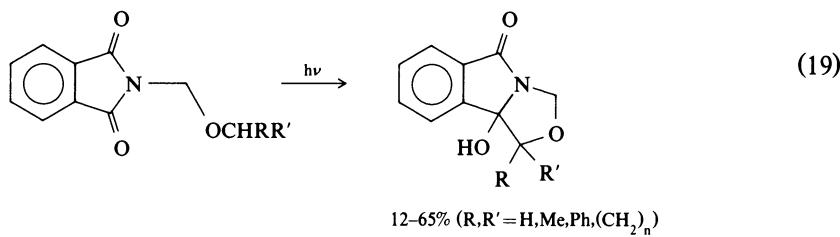


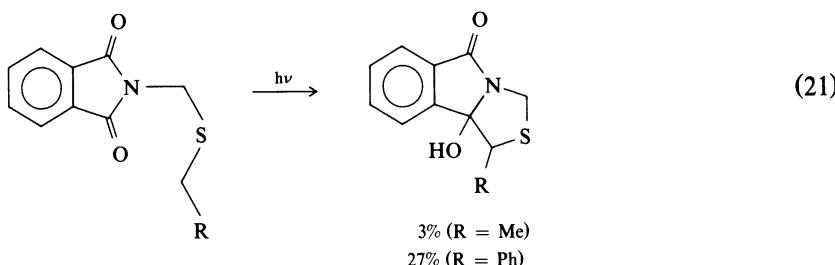
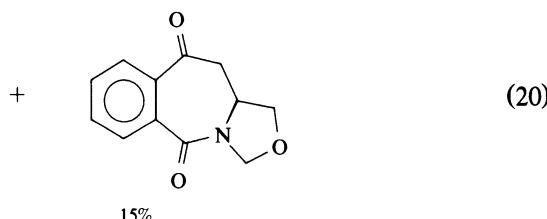
When there is no γ -hydrogen available in the substrate, reaction at a different position can occur to give more stable multicyclic systems. *N*-*o*-Tolylphthalimide and *N*-(*o*-ethylphenyl)phthalimide give fused-ring products, [equation (16)] that undergo ready dehydration to indole derivatives.⁽⁹⁾ The reaction has been extended to a tetrahydronaphthyl derivative [equation (17)],⁽¹⁹⁾ and to compounds with methylpyridyl groups on the imide nitrogen, as in equation (18).⁽²⁰⁾ Only in the case of the (3-methyl-2-pyridyl) compound is the intramolecular reaction unsuccessful—photoreduction of the imide occurs instead. This may be related to electronic effects in the excited state; a study⁽²¹⁾ of a wide range of *N*-*o*-tolylphthalimides with substituents on one or other of the aromatic rings concluded that the reaction was inhibited only by electron-donating groups ($-\text{OMe}$, $-\text{NR}_2$) on the aromatic ring of the phthalimide unit.



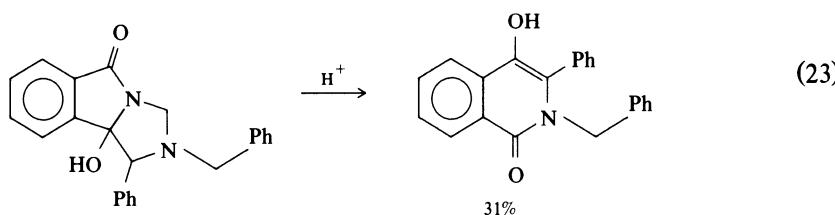
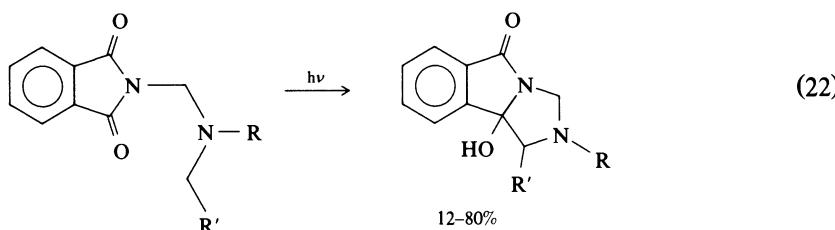


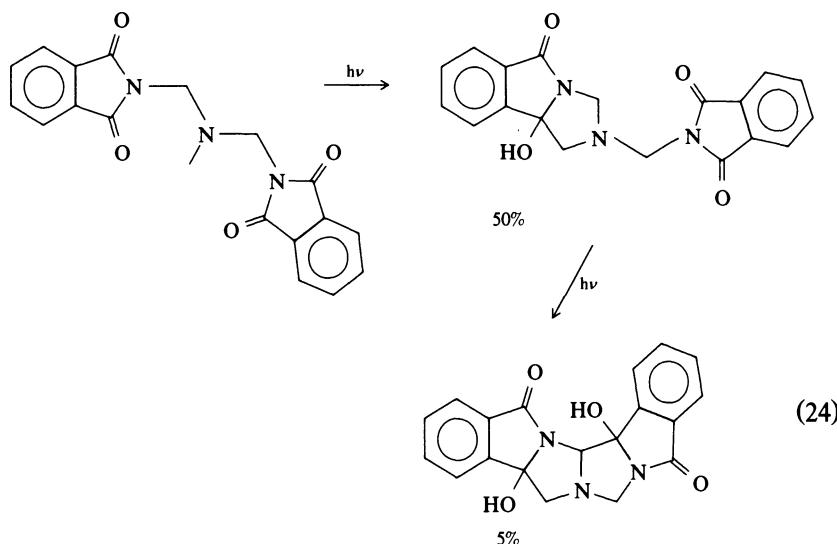
Substituted phthalimides in which there is a hetero-atom at the γ -position give rise to products with a new 5-membered heterocyclic ring. This is seen in the reactions of (alkoxymethyl)phthalimides [equation (19)],^(22,23) and of (allyloxymethyl)phthalimide [equation (20)],⁽²⁴⁾ although the latter also gives a product arising from an intramolecular imide–alkene reaction (see Section 3). A similar process occurs with (ethylthiomethyl)- or (benzylthiomethyl)-phthalimide,⁽²⁵⁾ to form a thiazolidine system [equation (21)].



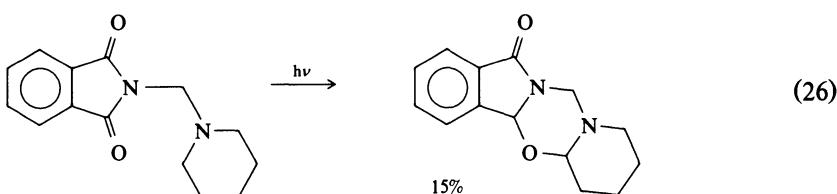
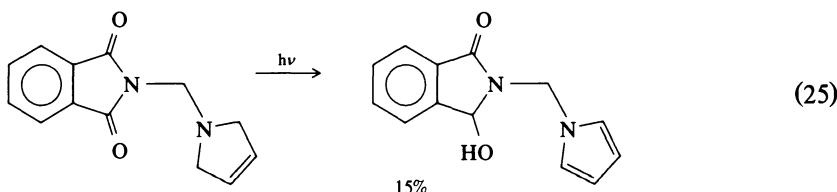


Mannich bases of phthalimide are relatively easy to prepare, and on photolysis they give reasonable yields of fused imidazolidines [equation (22)] as a result of reaction at the δ position.⁽²⁶⁻²⁸⁾ Treatment of some of the photoproducts with acid offers a route⁽²⁹⁾ to 4-hydroxyisoquinolinones [equation (23)]. The photoreaction has been extended⁽³⁰⁾ to bis(phthalimido-methyl)amines, where a second photocyclization can occur, to the original bridging methylene position rather than a second time to the amine substituent [equation (24)].

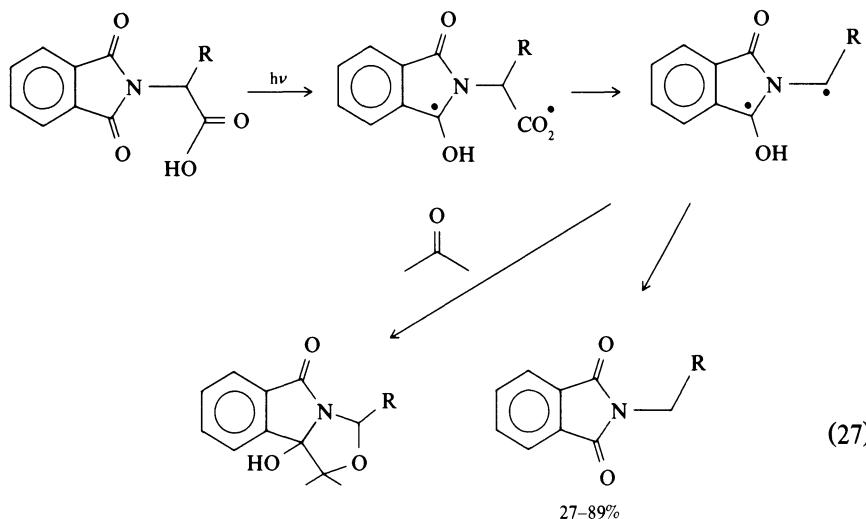




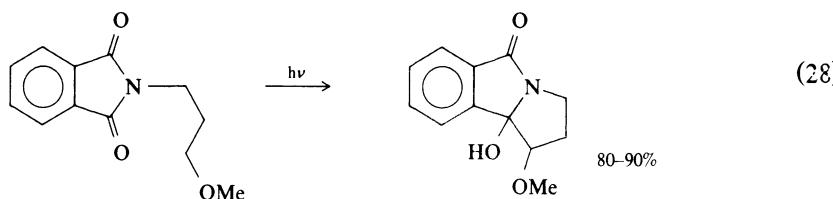
In a number of instances an alternative reaction competes effectively with the formation of cyclic alcohol. With the Mannich base from 3-pyrroline⁽²⁸⁾ the product is a pyrrolomethyl substituted hydroxyisoindoline [equation (25)], and this probably arises from disproportionation of an intermediate biradical. More unexpected is the isolation⁽²⁶⁾ of an oxadiazine as the major product from the piperidinomethyl compound [equation (26)]; this might be formed by a route involving a 1,2-hydrogen shift in a biradical, but it is difficult to account for the absence of similar products with very closely related substrates.

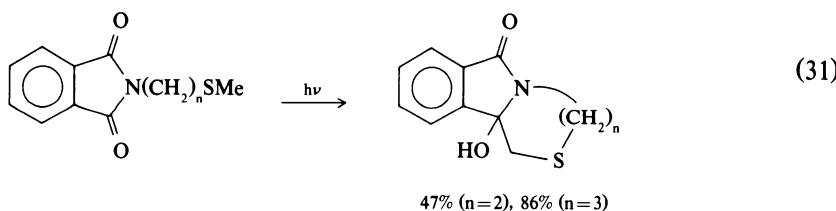
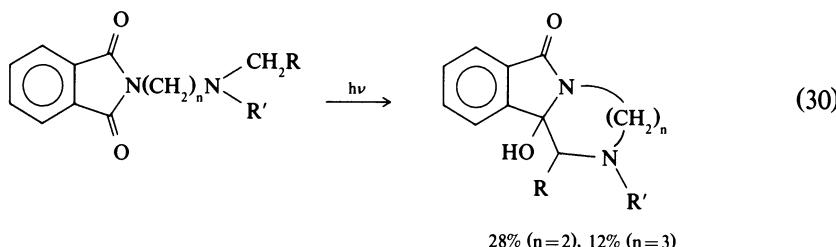
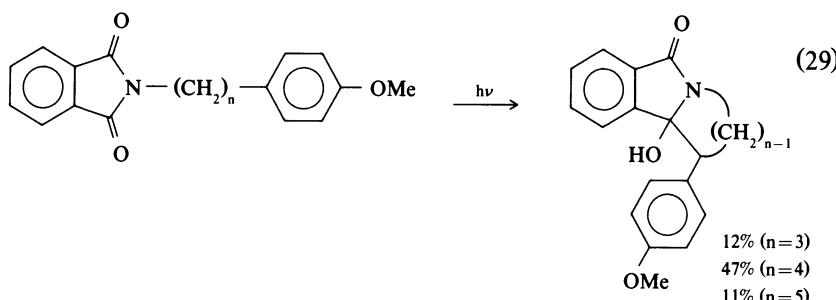


Part of the early interest in the photochemistry of phthalimides arose out of the observation that *N*-phthaloyl- α -aminoacids decarboxylate readily on irradiation.⁽³¹⁾ A mechanism involving loss of carbon dioxide from an intermediate biradical [equation (27)] seems plausible in the light of the oxazolidine that can be isolated in trapping experiments with acetone.

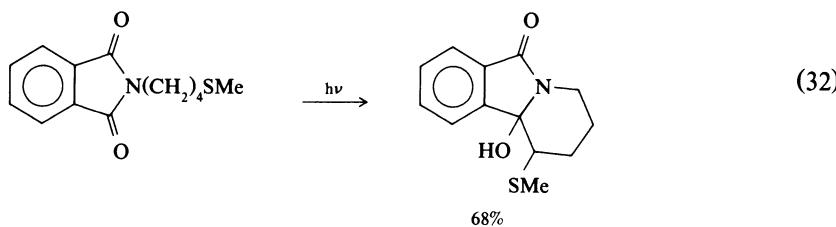


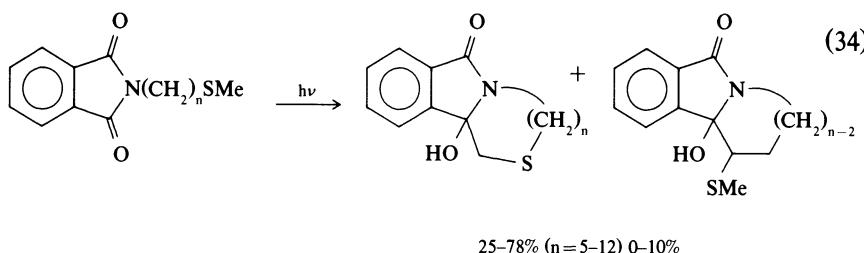
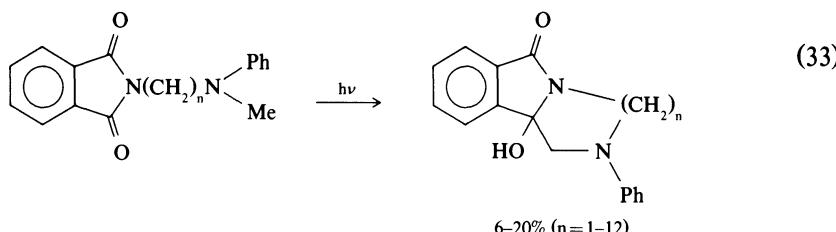
Considerable interest has been shown in systems where there is a choice of position for the initial site of attack. With an oxygen atom in the side chain⁽²²⁾ there is a strong preference for attack at the δ position [equation (28)] provided there is the possibility of stabilizing the intermediate formed in this process. When the stabilizing group is an aromatic ring,⁽³²⁾ this stabilisation seems to be the overriding factor, and products are formed by reaction at the γ , δ , or ϵ position according to the length of the bridging unit [equation (29)]. However, indications of different behavior for nitrogen- or sulfur-containing side-chains are seen in the ready formation^(33,34) of fused hexahydropyrazines and hexahydro-1,4-diazepines by photocyclization of aminoethyl- and aminopropyl-phthalimide systems [equation (30)], and the isolation of products with corresponding sulfur-containing ring systems [equation (31)] from the reaction of (thioalkyl)phthalimides.⁽²⁵⁾



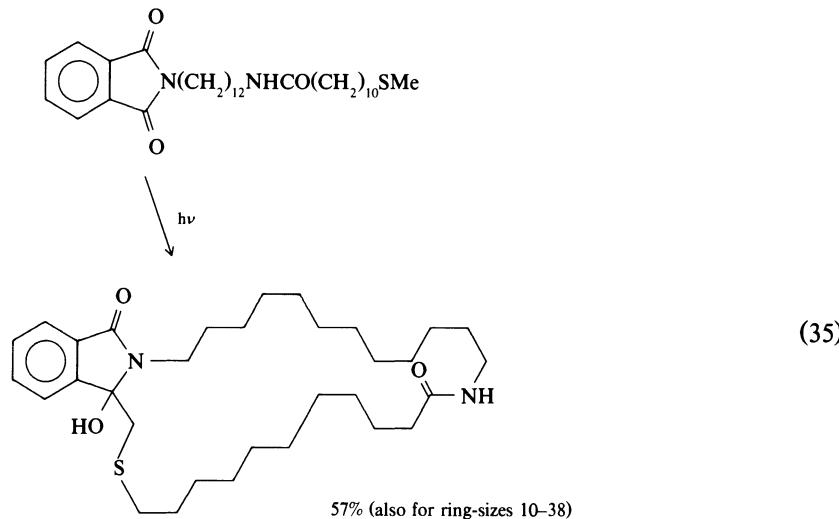


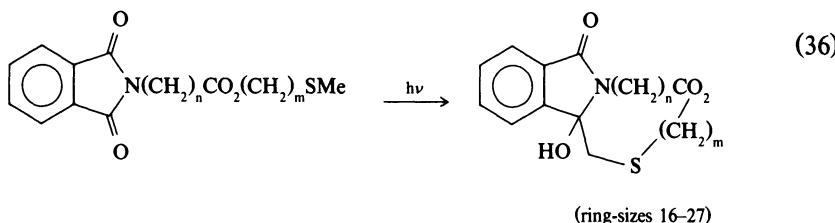
The report⁽²⁵⁾ that (alkylthiobutyl)phthalimides give products in which the sulfur group is exocyclic [equation (32)] seemed to suggest a limit to the ring sizes that could be achieved in this reaction. However, this is not the case. Irradiation of *N*-(ω -methylanilinoalkyl)phthalimides gives⁽³⁵⁾ moderate to low yields of medium- or large-ring diaza-systems [equation (33)] with ring sizes of up to 16 atoms, and related (methylthioalkyl)phthalimides^(36,37) give thiaza-systems up to the same ring size in better yield [equation (34)].





Even this is not the upper limit of ring size in these remarkable reactions. Phthalimides with an amide-containing [equation (35)] or ester-containing [equation (36)] substituent terminating in a methylthio group give macrocyclic lactams or lactones on irradiation in reasonably high yield.^(38,39) The outstanding feature of these cyclizations is that the process occurs in a nonrigid molecule with none of the precautions of high dilution that are associated with many conventional macrocyclic syntheses. The reason for the success of the reaction seems to lie in the establishment of charge transfer interactions in the excited state that lead to preferential conformations in which the sulfur (delta-plus) and imide (delta-minus) are in close proximity.

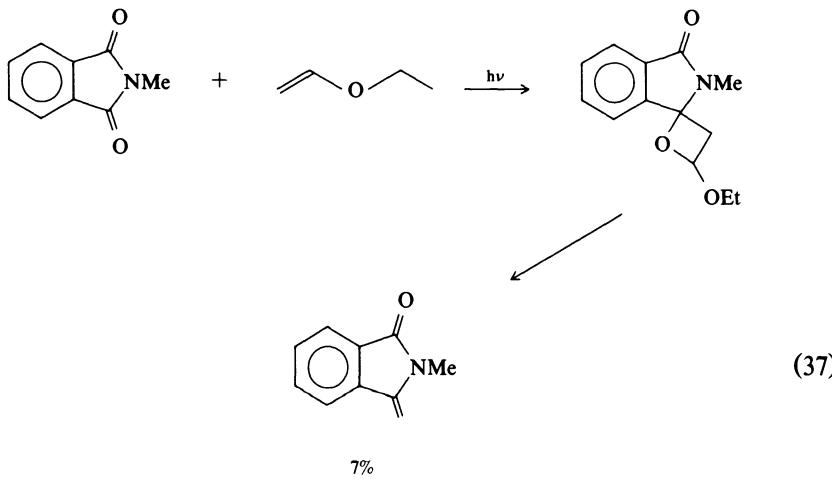




3. Reaction with Alkenes

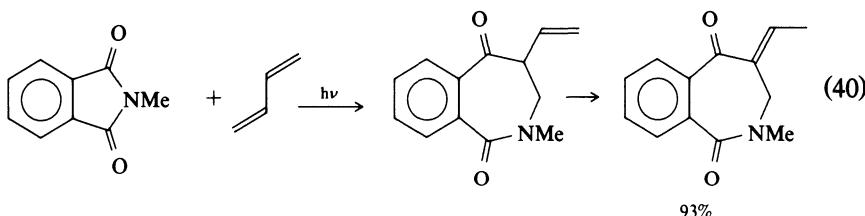
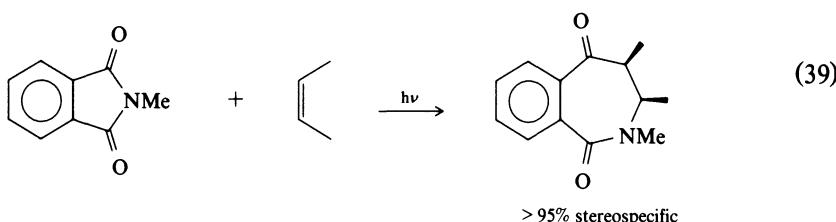
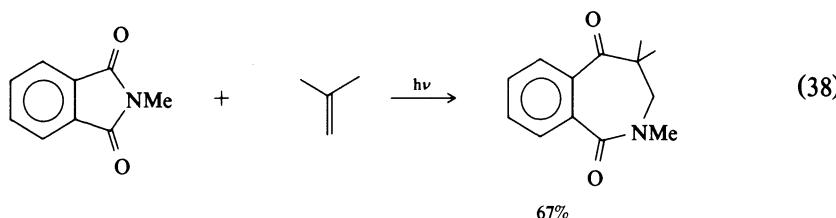
3.1 Ring Expansion

On irradiation of ketones or aldehydes with alkenes, oxetanes are formed by cycloaddition (see Chapter 2), and a similar process occurs with alicyclic imides such as succinimides or glutarimides.^(40,41) However, phthalimides behave differently towards alkenes, and only in the case of *N*-methylphthalimide with ethyl vinyl ether⁽⁴²⁾ is a product formed that is considered to be derived by decomposition of an initially formed oxetane [equation (37)].



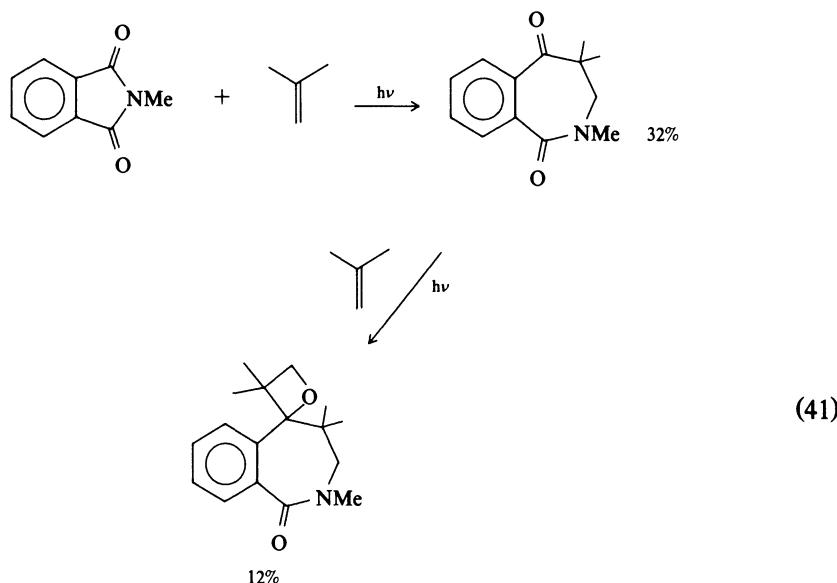
Phthalimide or *N*-methylphthalimide reacts with alkenes to give a benzazepinedione by ring expansion. The reaction is regiospecific [equation (38)]⁽²⁴⁾ and stereospecific [equation (39)].⁽⁴³⁾ It also occurs with conjugated dienes, and the reaction between *N*-methylphthalimide and butadiene [equation (40)] was the first reported example⁽⁴⁴⁾ of this unexpected photoaddition process. With the conjugated diene the product isolated in very high yield

has undergone a shift of the double bond compared with the structure expected on the basis of the alkene photoproducts.



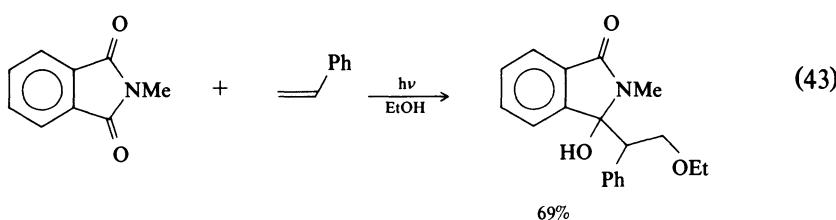
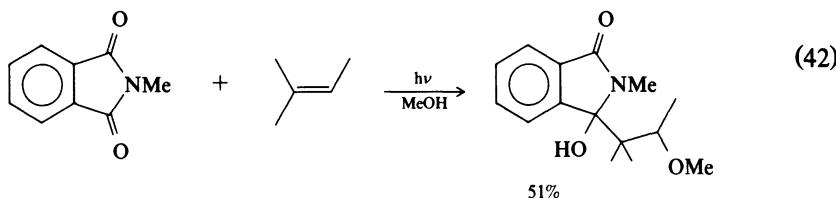
Because of its unusual nature, the mechanism of the reaction of phthalimides with alkenes has been studied more closely. Spectroscopic and quenching studies⁽⁴⁵⁾ show that the lowest triplet state of *N*-ethylphthalimide is quenched linearly by alkenes. The use of a range of alkenes with *N*-methylphthalimide⁽⁴⁶⁾ gives results consistent with an electron transfer mechanism, in that the reactivity of the alkene towards the imide excited state correlates with the ionization potential of the alkene. Formally the products could then be formed by cycloaddition of the alkene radical cation with the (partial) C–N double bond in the radical anion of phthalimide, and the orientation of addition is in accord with this idea.

The benzazepinedione, the normal product of the photoreaction of phthalimides with alkenes, can undergo further photochemical reaction with more of the alkene⁽⁴⁶⁾ to give a spirooxetane [equation (41)]. In this process the carbonyl group is behaving like that in a normal aromatic ketone.

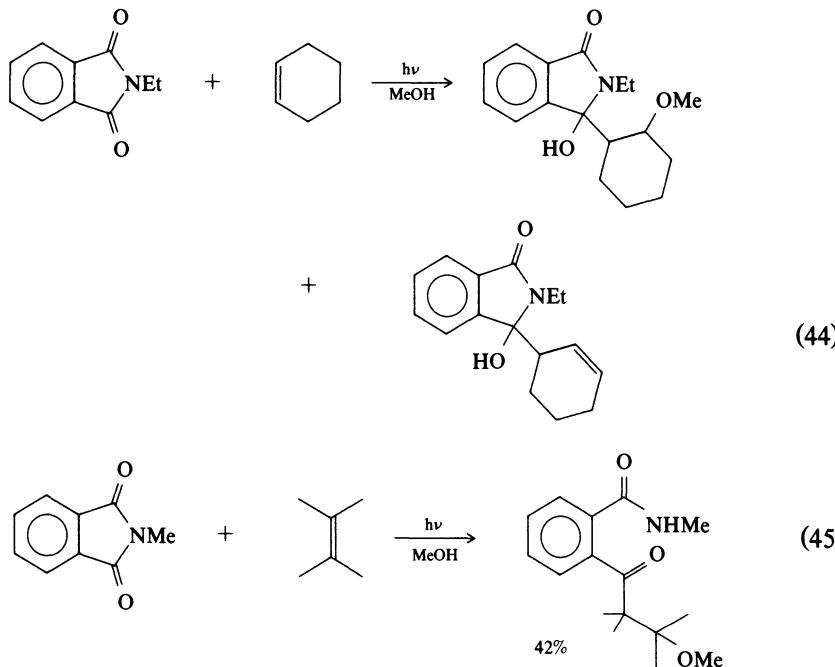


3.2. Solvent Incorporation

In the presence of a hydroxylic solvent, phthalimides and alkenes give a different type of product that is in keeping with the existence of charged (or zwitterionic) species in the photoaddition mechanism. The reaction is exemplified by the use of *N*-methylphthalimide with 2-methylbut-2-ene [equation (42)],⁽⁴⁷⁾ or with styrenes [equation (43)].⁽⁴⁸⁾

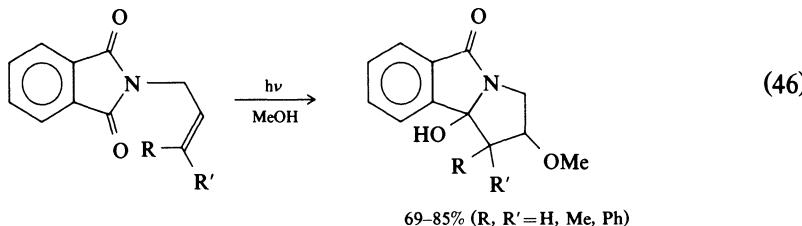


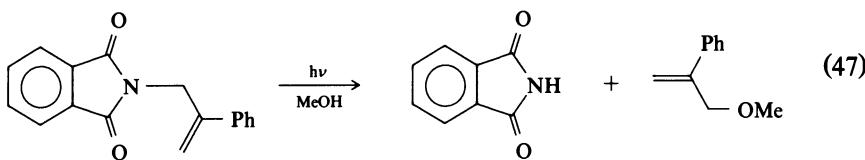
With cyclohexene it is reported⁽⁴⁹⁾ that a photoaddition product obtained (at least formally) by hydrogen abstraction accompanies the solvent-incorporated adduct [equation (44)], although it is possible that electron transfer also plays a part in the photoreduction–photoaddition reactions of phthalimides. When the alkene used is 2,3-dimethylbut-2-ene, solvent incorporation occurs, but the product isolated⁽⁴⁷⁾ is derived by ring opening in the 3-hydroxyisoindolinone system [equation (45)].



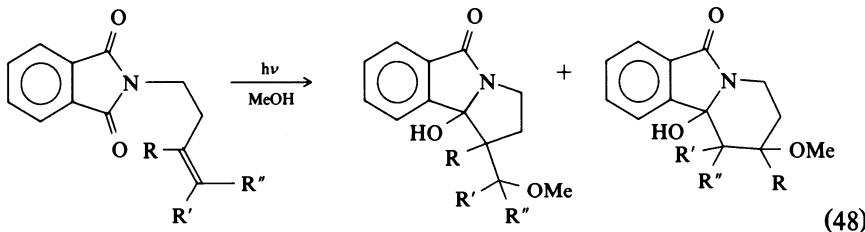
3.3. Intramolecular Reaction

Irradiation of *N*-allylic phthalimides in methanol gives^(50,51) good yields of products in which intramolecular addition of alkene with solvent incorporation has occurred [equation (46)]; radical ion intermediates are again postulated. In the case of the 2-phenylallyl compound⁽⁵¹⁾ no cyclization occurs, but rather cleavage to phthalimide and a methoxyalkene [equation (47)].

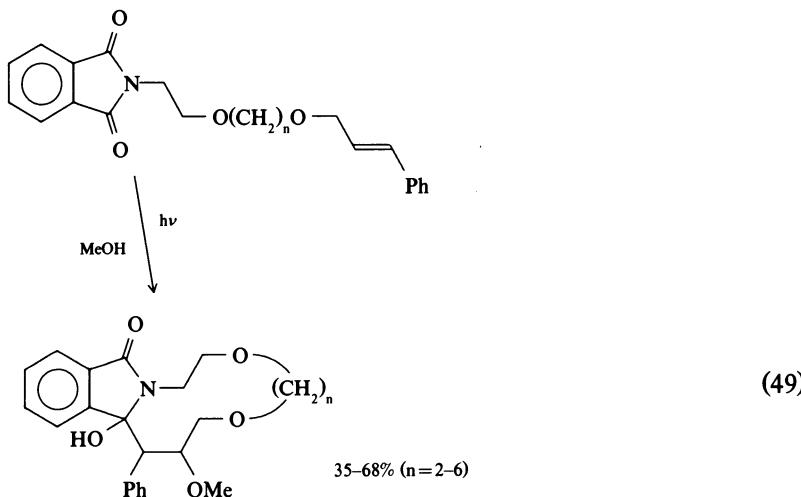




With but-3-enyl substituted phthalimides there is competition between formation of a new five- or six-membered ring [equation (48)]. The orientation is governed largely⁽⁵²⁾ by the substitution pattern at the double bond, and this can be rationalized in terms of stabilization of alternative biradical (or zwitterion) intermediates. Once again macrocyclic compounds can be synthesized using an extension of this reaction,^(53,54) and products with ring sizes up to 15 atoms have so far been prepared [equation (49)]. A rationalization in terms of electron transfer followed by interaction between imide radical anion and end-of-chain radical cation seems reasonable, analogous to that invoked for the cyclization of (methylthioalkyl)phthalimides and related compounds (Section 2.2).



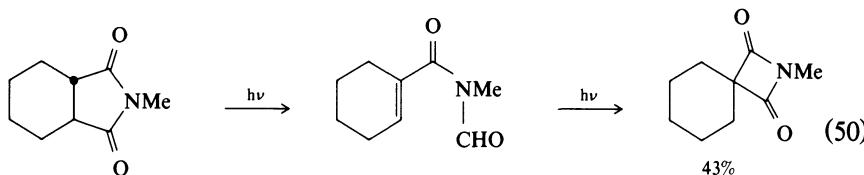
$R = Me; R' = H$	83%
$R, R'' = Me; R' = H$	32%
$R = H; R', R'' = Me$	39%
	83%



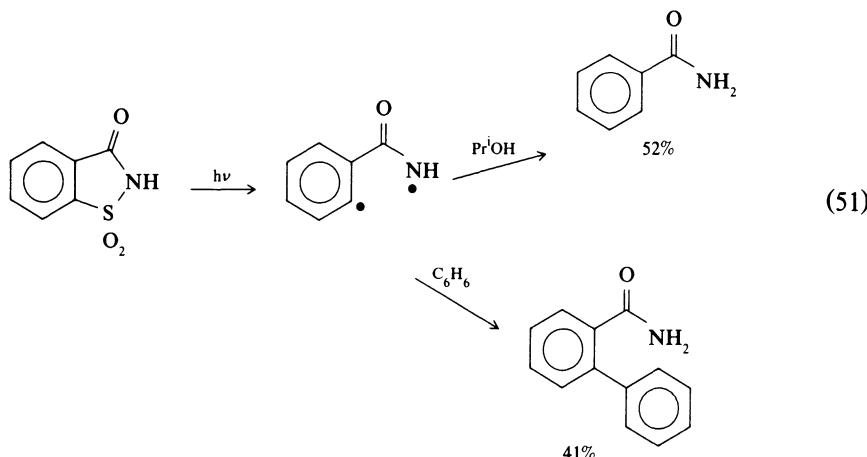
4. Cleavage Reactions

4.1. α -Cleavage

For aliphatic imides there are a number of interesting photoreactions that involve initial α -cleavage in the imide excited state. Most interesting from a synthetic point of view are the reactions by which succinimides generate ring-opened unsaturated amides (in a process that resembles the formation of unsaturated aldehydes from cycloalkanones), which then undergo further photochemical reaction [equation (50)] to give azetidinediones (malonimides).^(55,56)



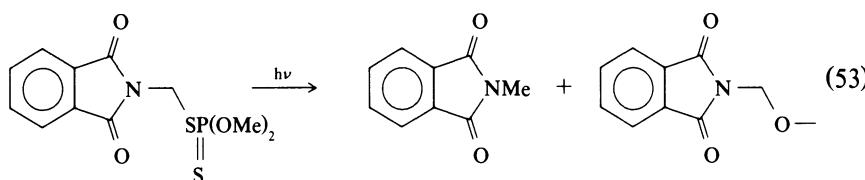
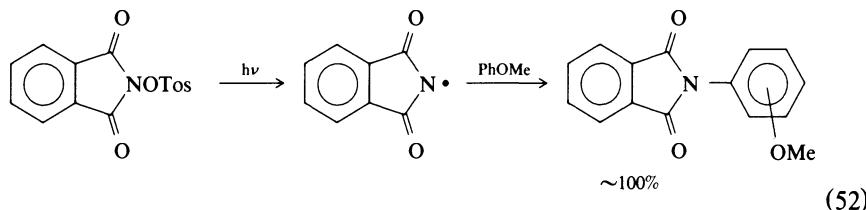
Other acyclic or cyclic aliphatic imides undergo decarbonylation^(57,58) or competing Norrish type-2 photoelimination,^(59,60) and diacylanilines or related compounds take part in photo-Fries rearrangements.^(61,62) Phthalimides undergo none of these reactions, and the only example of a related imide that takes part in an α -cleavage process is saccharin,⁽⁶³⁾ which loses sulfur dioxide on irradiation to give products derived from the resulting biradical [equation (51)].



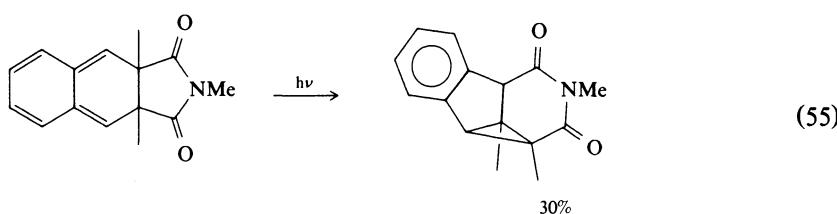
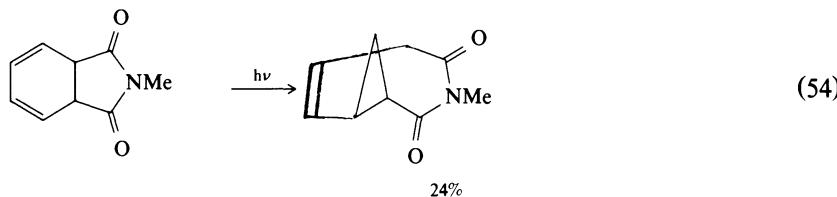
4.2. β -Cleavage

Cleavage of the bond between nitrogen and a substituent on nitrogen is an effective way of generating phthalimidyl radicals [equation (52)] if the bond is relatively weak, as it is in toslyloxy-imides.⁽⁶⁴⁾ A related γ -cleavage

reaction is also responsible⁽⁸⁾ for the products isolated in the photochemical degradation of the nonsystemic insecticide imidan [equation (53)], although this is not of any synthetic value.



A different type of β -cleavage occurs on irradiating 1,2-dihydro aromatic imides,⁽⁶⁵⁻⁶⁷⁾ and one of the products is an isomeric polycyclic imide [equation (54)]. Mechanistic studies⁽⁶⁷⁾ show that the reaction is not concerted but goes through biradical intermediates, and these may also be involved in the formation of the accompanying fragmentation products. The yield of the isomeric imide is moderate in the phthalimide series, and it is about the same⁽⁶⁸⁾ for the corresponding 2,3-naphthalimide compound [equation (55)].



5. Spectra and Excited States

The lowest excited states of aliphatic imides are almost certainly (n, π^*), since the absorption spectra show only weak bands in the near ultraviolet region. The situation with aromatic imides is more complex. Although there are conflicting reports^(6,69) about the existence of a distinct, long-wavelength absorption band for phthalimide, there is a distinct weak absorption above 300 nm for substituted phthalimides that is absent in the corresponding amides (isoindolinones).⁽⁷⁰⁾ The weak fluorescence of phthalimides⁽⁷⁰⁾ relates to the strong ($\pi \rightarrow \pi^*$) absorption band, and so there seems to be a lower-lying, nonfluorescent (n, π^*) singlet state. The phosphorescing state⁽⁷⁰⁾ is (π, π^*) in nature, and so the $T_1(\pi, \pi^*)$, $S_1(n, \pi^*)$, and $S_2(\pi, \pi^*)$ states can be located at around 288, 334, and 395 kJ mol⁻¹, respectively. These results are supported by photoelectron spectroscopy measurements,^(71,72) and by m.o. calculations,⁽⁷²⁾ which suggest that the nonbonding and highest occupied π orbitals are close in energy, but that the $n \rightarrow \pi^*$ transition is of lower energy. The luminescence of amino- and acyl-substituted phthalimides has been studied,⁽⁷³⁻⁷⁵⁾ and again singlet energy levels below that of the fluorescing state are postulated.

As far as the reactive excited states in the various photochemical processes are concerned, it seems that the weight of evidence in most cases favors the involvement of a singlet rather than a triplet state. The observations that lead to this conclusion include the lack of significant quenching by known triplet quenchers, the relatively long lifetime of the triplet states under normal conditions, and the detection of an intermediate derived from the triplet but not leading to normal photoproducts.⁽⁷⁶⁾ Inter- and intramolecular charge transfer absorption and emission have been observed in a number of phthalimide systems.⁽⁷⁷⁻⁷⁹⁾ This is of considerable relevance to the postulated electron transfer mechanisms for some of the photochemical reactions of phthalimides, but a discussion of the results is not appropriate in this review of synthetic applications.

6. Summary

Of the various types of photoreaction described for phthalimides and related aromatic imides, three stand out as being of general synthetic value. Intramolecular hydrogen abstraction and cyclization processes lead to the formation of new heterocyclic rings; the products may be of interest in themselves if they have particular polycyclic or polyheteroatom features, or if they can be modified chemically to give alternative heterocyclic systems; the formation of medium-ring or large-ring systems is especially noteworthy. The reaction of phthalimides with alkenes offers a route to 2-benzazepine-1,5-

diones with a variety of substituents in positions 3 and 4. Finally, the intramolecular reaction with alkenes that also involves incorporation of solvent offers another route to polycyclic systems, including those with new large rings.

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Photochemical Addition Reactions in the Benzo(b)Thiophene, Benzo(b)Furan, and Indole Series

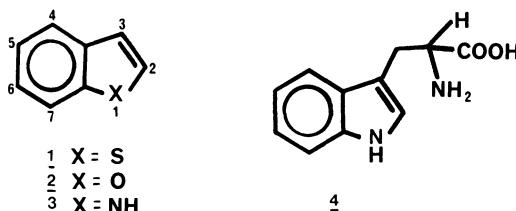
Douglas C. Neckers and Alois H. A. Tinnemans

1. Introduction

Benzo(b)thiophene (**1**), benzo(b)furan (**2**), and indole (**3**) are a group of fused aromatic heterocyclic compounds related to naphthalene.⁽¹⁾ All are natural products. Benzo(b)thiophene* was discovered by Boes⁽²⁾ and represents as much as 12%–15% of the sulfur content of the crude naphthalene fraction of some coal tars. It has also been isolated in various oil shales.⁽³⁾ Benzo(b)furan, called coumarone in older literature, is also found in coal tar and was synthesized first by Fittig and Ebert.[†] Benzo(b)furan derivatives have many pharmacodynamic applications including use as pesticides, bactericides, and antibiotics. A major group of natural benzo(b)furans, the furocoumarins, are used as skin photosensitizers. Psoralens are particularly active, with 8-

* Called thianaphthene in the older literature because it was originally isolated from the naphthalene fraction of brown coal tar.

† The chemistry of benzo(b)furan has been extensively reviewed: see Reference 4.



methoxypsoralen being used in many suntan lotions and in skin dyes—particularly in Middle Eastern countries.

Indole and its simple derivatives are metabolites of tryptophan (4) and are found in decayed animal and vegetable matter.⁽⁵⁾ Indole itself was synthesized first by Bayer in 1866 during studies of the degradation products of indigo.⁽⁵⁾ It is biogenetically related to many natural products such as toad poisons, alkaloids, and auxins. In most respects indole is the most ubiquitous of the three fused ring heterocycles discussed herein. Hundreds of indole derivatives are found in nature and many of these have important biogenetic, physiological, and pharmaceutical applications.

Some physical properties of these three, formally similar heterocyclic compounds are given in Table 1. Nothing is particularly unique about them, except their simplicity and the role they play in natural systems. In spite of their apparent structural similarity, the chemical properties of benzo(b)-thiophene, benzo(b)furan, and indole are rather different from each other and also from naphthalene, the closest carbocyclic relative. Benzo(b)thiophene, with a resonance energy of about 58 kcal mol⁻¹ (243 KJ mol⁻¹) is the “most aromatic” of the three compounds and smells like naphthalene. Benzo(b)furan is much like an enol ether in its chemistry. Indole, on the other hand, is susceptible to oxidation—both across the C-2, C-3 bond and at the nitrogen atom.

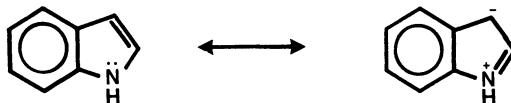
Electrophilic aromatic substitution in benzo(b)thiophene gives predominantly 3-substituted derivatives, the thiophene ring being more reactive than the benzene ring and 3-substitution being rationalized by the fact that having

Table 1. Properties of Fused Heterocycles 1-3

	Benzo(b)thiophene	Benzo(b)furan	Indole
Color	None	None	None when pure
Odor	Naphthalenelike	Pleasant	Pleasant when pure
Melting point(°C)	32	—	80
Boiling point(°C)	221–222	171	253
Resonance energy, kcal mol ⁻¹ (kJ mol ⁻¹)	58 (243)	50–52 (210–218)	47–49 (197–205)

a sulfur atom next to the positively charged carbon leads to an additional resonance contributor with aromatic stability.

Electrophilic reactions of benzo(b)furan occur under milder conditions and give 2-substituted products. Halogenation of benzo(b)furan, for instance, occurs via an addition-elimination mechanism. Oxidizing agents sever the ring giving salicylic acid derivatives. Indole, like the others, is a planar heteroaromatic compound. Self-consistent molecular orbital calculations⁽⁶⁾ show the 3-position of indole with the highest π -electron density, and, like the resonance picture, suggest electrophilic substitution should occur, as it does, preferentially at position 3. Unlike benzo(b)furan and benzo(b)thiophene,



indole can be easily protonated though the aromatic system removes electron density from the nitrogen atom making indole a relatively weak base, and protonation is more likely on C-3 than at nitrogen. Electrophilic aromatic substitution usually occurs on the conjugate acid.⁽⁷⁾

1.1. Absorption and Emission Characteristics

The absorption spectra of benzo(b)thiophene, benzo(b)furan, indole and naphthalene are compared in Figure 1. The spectra belie a practical reason for studying the compounds' photochemistry. The absorption maxima are in a convenient spectral region. The absorption spectra are characteristic of the compounds—particularly the indoles—and in the latter instance are used to identify indole alkaloids. The absorption of tryptophan is the most intense of the three natural aromatic amino acids, tryptophan, tyrosine, and phenylalanine,⁽⁸⁾ and the spectra of proteins is largely the result of their tryptophan content.⁽⁹⁾

Indole fluorescence is characteristic. Benzo(b)thiophene and benzo(b)furan do not emit efficiently from their excited singlet states.⁽¹⁰⁾ Benzo(b)furan, indole, and benzo(b)thiophene all phosphoresce very weakly with 0-0 bands corresponding to triplet energies of about 70 kcal mol⁻¹ (293 KJ mol⁻¹).⁽¹¹⁾

The fluorescence of indole and its derivatives is highly characteristic and forms the basis for several analytical methods. In water the 355-nm fluorescence band is 46% quantum efficient. This λ_{max} is highly solvent and substituent dependent. Tryptophan, for instance, does not fluoresce in strong acids, but between pH = 1 and pH = 4 the cation fluoresces at 345 nm; from pH = 4 to pH = 8.5 the zwitterion is predominant and emits at 352 nm. In alkaline solution (to pH = 11.0) the anion is the emitting specie ($\lambda_{\text{max}} = 420$ nm). The quantum yield of fluorescence increases with pH—from 0.085 at pH =

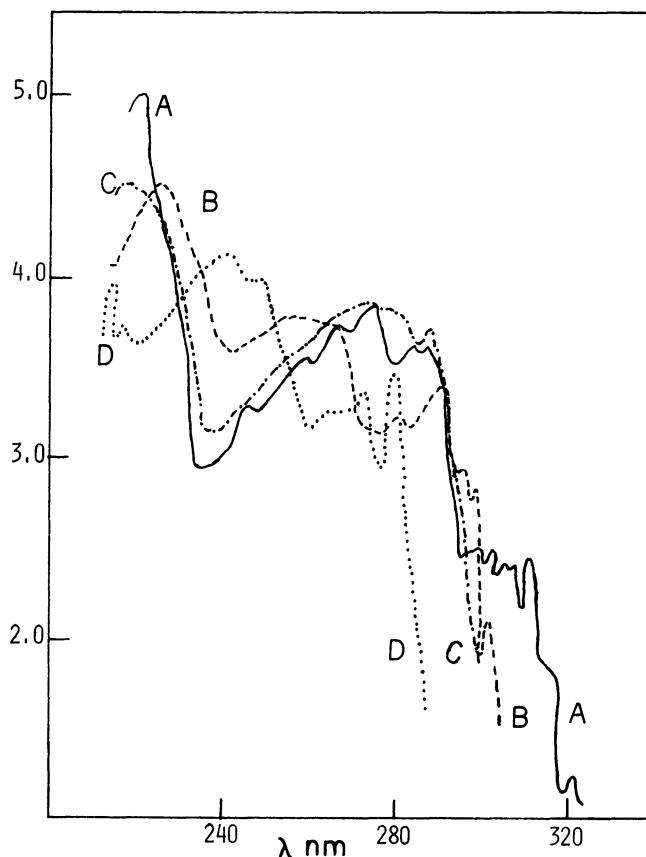


Figure 1. Absorption spectra of benzo(b)thiophene (A) (—), benzo(b)furan (C) (---), indole (D) (...) and naphthalene (B).

1.5 to 0.51 at pH = 10. The fluorescence of the indole nucleus is largely responsible for protein emission and finds many applications in biology and medicine. Extensive reviews of these applications have been published.⁽¹²⁾

2. Photochemistry

Photochemical reactions of benzo(b)thiophene, benzo(b)furan, and indole almost invariably involve the C-2, C-3 bond—both in the addition of their excited state to partner molecules, and in the addition of excited species to their ground state—such as in singlet oxidation and oxetan formation.*

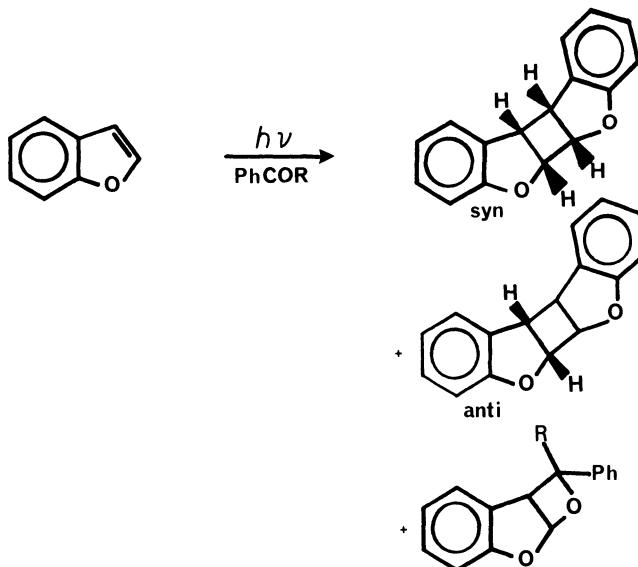
* The photochemical (2+2)-cycloaddition reactions and 2+2-cycloreversion of heterocyclic compounds have been reviewed: see Reference 29.

2.1. Oxetan Formation

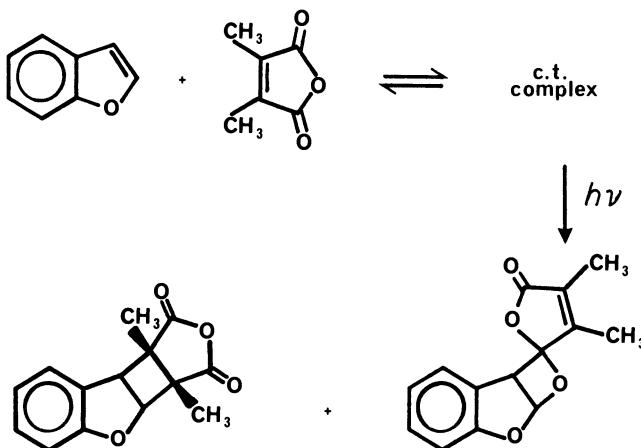
When benzo(b)furan is irradiated in the presence of the high-energy triplet sensitizers C_6H_5COR ($R = H, CH_3, C_2H_5, C_6H_5$), oxetan formation is observed in competition with dimerization to *syn* and *anti* head-to-head dimers (Scheme 1).^(9,13-17) Alkyl groups on the furan facilitate the electrophilic attack of the excited carbonyl group by stabilizing the proposed intermediate biradical,⁽¹⁵⁾ and by increasing the electron density of the double bond system. In contrast to benzo(b)furan, indole has been found to be inert to oxetan formation.⁽¹⁸⁾ This is likely ascribed to the quenching of the excited ketone by the non-bonding electrons on the nitrogen atom.^(18,19b) Reducing electron availability of the nonbinding electrons with an electron withdrawing group, such as benzoyl and acetyl, successfully leads to a cycloaddition product with the ketone.^(18,19a) Charge transfer excitation of a complex between benzo(b)furan and dimethylmaleic anhydride⁽²¹⁾ in nonpolar solvents leads to an oxetan mixture of two geometrical isomers, together with a cyclobutane formation (Scheme 2). Analogous (2 + 2) cycloadducts were obtained from quinones and benzo(b)furan and some of its derivatives.^(13,17)

2.2. Dimerization

In contrast to benzo(b)furan (**2**), 2-phenylbenzo(b)furan gives head-to-tail *syn* and *anti* adducts when irradiated with benzo(b)furan (Scheme 3).



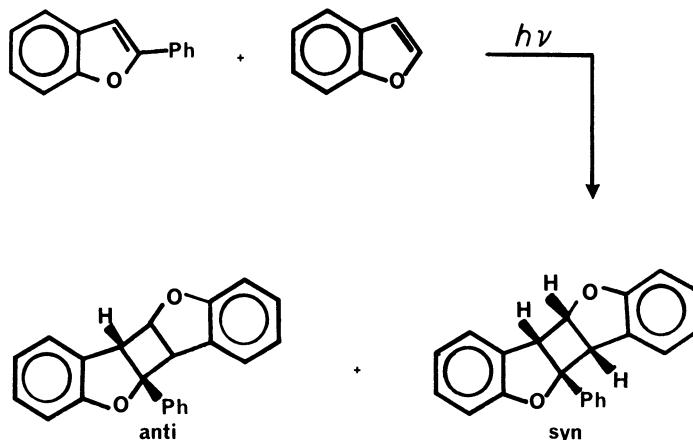
SCHEME 1



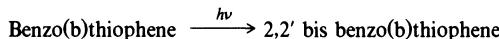
SCHEME 2

These head-to-tail dimers were shown to be formed from the singlet state of the furan. Their formation was neither sensitized by acetophenone nor quenched by 1,3-pentadiene.⁽²⁰⁾

Benzo(b)thiophene, reportedly, undergoes radical dimerization as well as addition with desulfurization (Scheme 4)⁽²²⁾; *sic*: “benzo(b)thiophene showed instability when stored in sunlight for one year.” The photochemical dimerization of 3-methylbenzo(b)thiophene 1,1-dioxide has also been reported,⁽²³⁾ and benzo(b)thiophene 1,1-dioxide and some of its derivatives generally photodimerize in both head-to-head and head-to-tail fashion.⁽²⁴⁻²⁶⁾ An exception



SCHEME 3



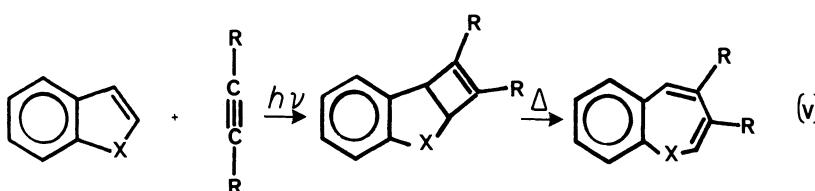
SCHEME 4

is benzo(b)thiophene-3-carboxylic acid 1,1-dioxide which gives only the *anti* head-to-head dimer.⁽²⁷⁾ Harpp has shown that the dimerization of benzo(b)thiophene 1,1-dioxide could be sensitized with triplet sensitizers [$E_T > 50 \text{ kcal mol}^{-1}$ (210 KJ mol⁻¹)] and quenched with α -methylstilbene—a triplet quencher [$E_T = 50 \text{ kcal mol}^{-1}$ (210 KJ mol⁻¹)]. Though the dioxide does not phosphoresce, it appears to have a triplet energy between 50 and 53 kcal mol⁻¹ (210 and 222 KJ mol⁻¹). The head-to-head dimer to head-to-tail dimer ratio is strongly solvent dependent, and the head-to-head transition state is strongly dipolar. Thus, whereas the component dipoles in the head-to-tail transition state would cancel, the same dipolar interactions should be favored in polar solvents for head-to-head dimerization. Schloman and Plummer investigated this dimerization in the presence of the heavy-atom solvent, bromoethane, and found the benzo(b)thiophene 1,1-dioxide intersystem crossing yield enhanced to unity.^(25,26)

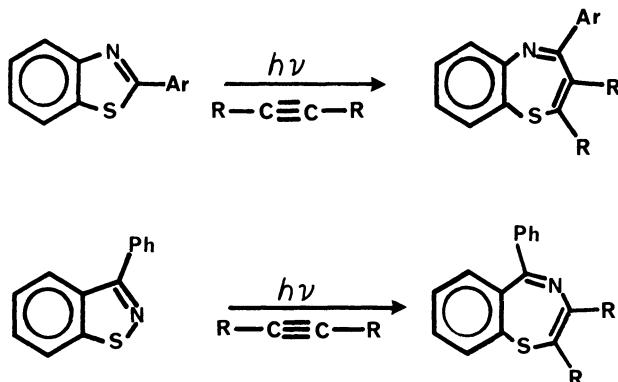
Strictly speaking benzo(b)thiophene sulfone is like cinnamic acid, a styrene chromophore with an electron withdrawing group at the terminus. As in the case of cinnamic acid, dimerization in the crystal has been reported⁽²⁸⁾ though the stereochemistry of the coal-black adduct thereby obtained has not been determined.

2.3. Photochemical Reactions with Acetylene Esters

Photochemical addition reactions of benzo(b)furan, benzo(b)thiophene, and indoles to acetylenes provide a synthetic device for building annelated seven-membered ring systems from readily accessible heteroaromatic derivatives. Thus, these reactions provide a direct single-step entry to benzoxepines, benzothiepines, and benzazepines via a coupled cyclobutene–butadiene ring opening rearrangement (Scheme 5).⁽²⁹⁾ The exploitation of this synthetic route



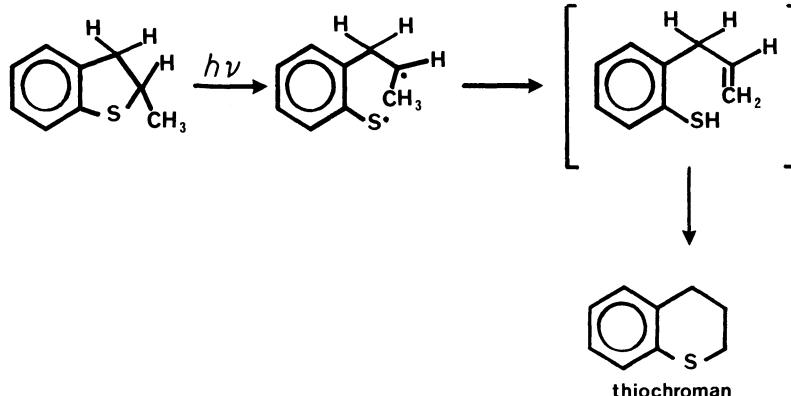
SCHEME 5



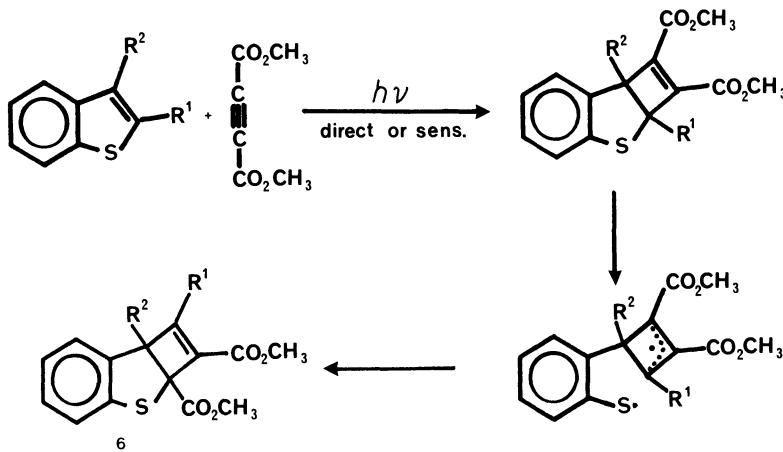
SCHEME 6

to the pharmacologically important benzthiazepines has been studied in detail by Sindler-Kulyk and Neckers (Scheme 6).⁽³⁰⁾

2-Methyl-2,3-dihydrobenzo(b)thiophene, when irradiated through quartz in carbon tetrachloride, gives thiochroman (Scheme 7),⁽³¹⁾ the reaction occurring through a biradical disproportionation, followed by an intramolecular addition of the intermediate thiophenol giving the favorable six-membered ring product. DeZwaan's result represented the first example of this mechanistic alternative: S—C bond homolysis followed by ring reclosure to give a more favorable cyclic derivative.



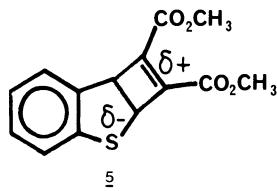
SCHEME 7



SCHEME 8

3. Benzo(b)thiophene

The photocycloaddition of dimethyl acetylenedicarboxylate (DMAD) to benzo(b)thiophene and its alkylated derivatives was first carried out by Dopper,⁽³²⁾ who isolated only a rearranged adduct **6** from the sensitized addition of DMAD to alkylbenzo(b)thiophenes. In our original communication on the work this product was suggested to derive from a secondary rearrangement of the $\pi^2s + \pi^2s$ cycloadduct **5** via an allylic biradical though we were unable to capture the unrearranged adduct in this system until some 10 years later^(33,38) (Scheme 8). Dopper's original work also indicated the facility of sulfur–carbon bond cleavage in these systems (*vide supra*), and we grew to expect this allylic rearrangement. That the rearrangement was due to the unusual absorption characteristics of $\pi^2s + \pi^2s$ adducts such as **5** was shown by Ditto and Davis.⁽³³⁾ They demonstrated that the initial adduct **5** absorbed at substantially longer wavelength than did the rearranged adduct **6**, a difference they attributed to formation of an intramolecular charge transfer complex between the electron-poor maleate of the cyclobutene and the electron-rich aryl-S system. The rearranged adduct shows no related charge transfer absorption



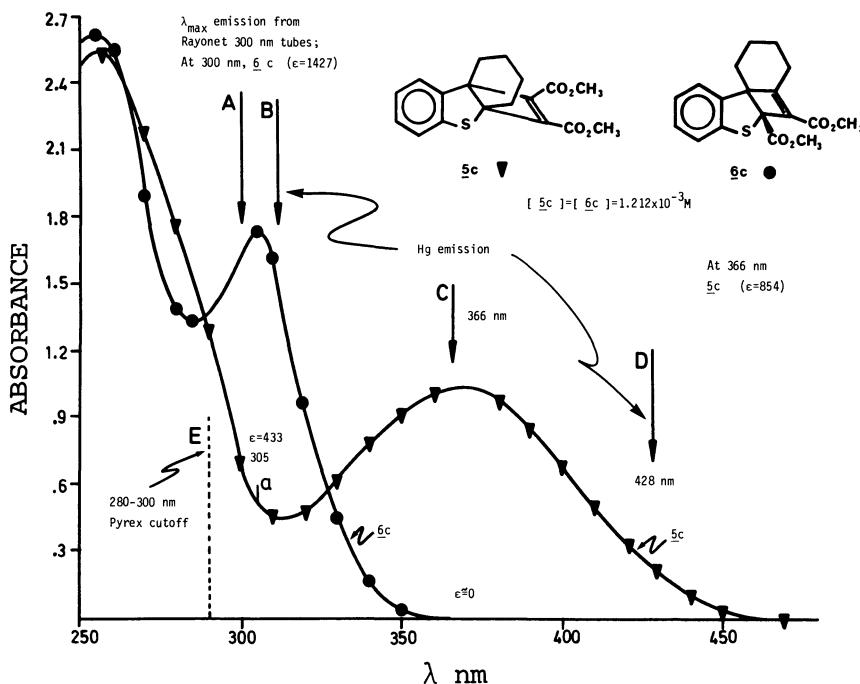
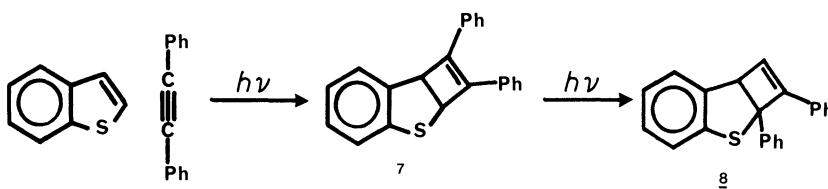


Figure 2. Absorption spectra of unrearranged adduct **5c** and rearranged adduct **6c** compared with the emission characteristics of Rayonet 300-nm lamps and medium-pressure mercury arcs. $[5c] = [6c] = 1.212 \times 10^{-3} M$. A, λ_{max} emission from Rayonet 300 nm tubes; B, C, D, Hg emission lines at 313, 366, and 428 nm, respectively; E, 280 nm cutoff by Pyrex. At 300 nm molar absorbance of **6c** is $\epsilon = 1427$; at 366 nm molar absorbance of **5c** is $\epsilon = 854$; at 366 nm absorbance of **6c** is 0.

(Figure 2). Thus the unrearranged adduct **5** absorbs the 360-nm radiation preferentially from the high-pressure mercury arc used in Dopper's experiments and is converted to the preferred rearranged adduct **6**. Only when light sources which produced no 360-nm radiation were used was the unrearranged adduct eventually isolated.

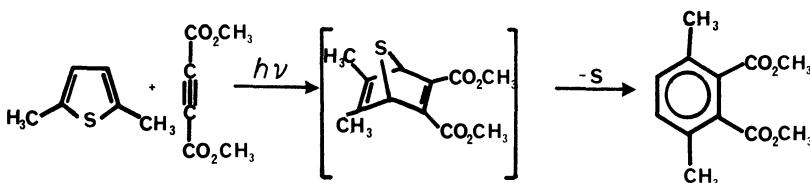
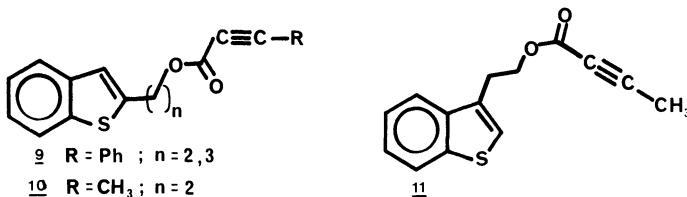
This photoaddition of benzo(b)thiophene to electron-poor alkynes proceeds from the triplet state of the benzo(b)thiophene [$E_T = 67.7-68.9 \text{ kcal mol}^{-1}$ (288-7KJ mol⁻¹)],^(34,35) and appears to be more efficient with alkynes containing one or more electron-withdrawing substituents. Thus, no reaction has been observed with but-2-yne,⁽³⁴⁾ 1,4-dimethoxybut-2-yne, or 1,4-dichlorobut-2-yne.⁽³²⁾ In general electron-poor alkynes react more rapidly than electron-rich alkynes with all the other heterocyclic compounds. The reaction of diphenylacetylene with benzo(b)thiophene proceeds slowly compared to the reaction with DMAD⁽³⁵⁾ and is quenched by oxygen. Since the triplet energy of the diphenylacetylene is only 61.8 kcal mol⁻¹ (258-9KJ mol⁻¹) it is likely



SCHEME 9

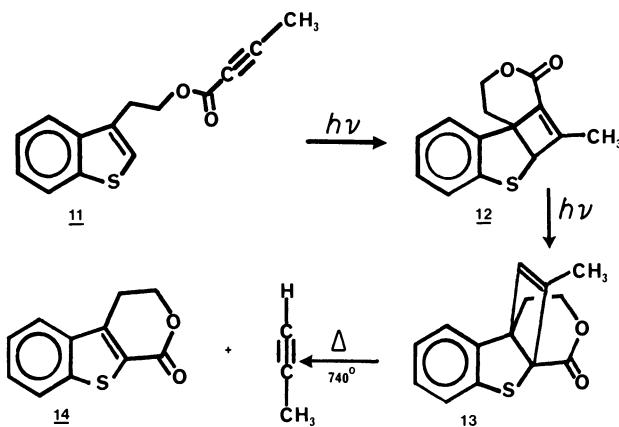
that benzo(b)thiophene triplets sensitize formation of diphenylacetylene triplets which add to ground-state benzo(b)thiophene. Triplet diphenylacetylene is very short lived and a high concentration of benzo(b)thiophene is required before any reaction is observed.

Sasse first isolated an unarranged adduct **7** from the reaction of benzo(b)thiophene with an alkyne, and he also demonstrated that the unarranged adduct **7** was converted to rearranged adduct, **8** (Scheme 9).⁽³⁶⁾ Sasse thus established what we initially did not—namely, that the rearranged adduct derived from the direct [2 + 2] π adduct **7**. Irradiation of alkylthiophenes⁽³⁴⁾ and benzoylthiophenes⁽³⁷⁾ with dimethyl acetylenedicarboxylate also gives unarranged adducts, but, more interestingly, phthalate ester is also formed presumably via a Diels–Alder pathway. 2,3-Dimethylthiophene, for instance, produces 3,6-dimethylphthalate by a Diels–Alder-type reaction followed by sulfur extrusion⁽³⁴⁾ (Scheme 10). The isolation of the unarranged adduct is often difficult. Tinnemans,⁽³⁸⁾ however, in order to exclude direct formation of rearranged adducts, studied the intramolecular $\pi^2s + \pi^2s$ addition of the benzo(b)thiophene alkyne esters **9–11**. In every case where both un-



SCHEME 10

rearranged and rearranged adducts resulted, the rearrangement process was slowed by the steric bulk of the appended group. Thus, sensitized irradiation of **11** gives **12** and **13**, both of which can be isolated. Of interest, too, is that **13** fails to ring-open thermally, the latter process being precluded by Bredt's rule.



Tinnemans also isolated an unarranged adduct from an intermolecular addition of an alkyne ester—methyl phenylpropionate—to benzo(b)thiophene, but it was still possible that the unarranged adduct derived from the triplet state of the alkyne ester.⁽³⁸⁾

The important generalization that in every case the preferred cyclobutene is formed with the least substituted double bond could be made after these experiments (see Table 2).

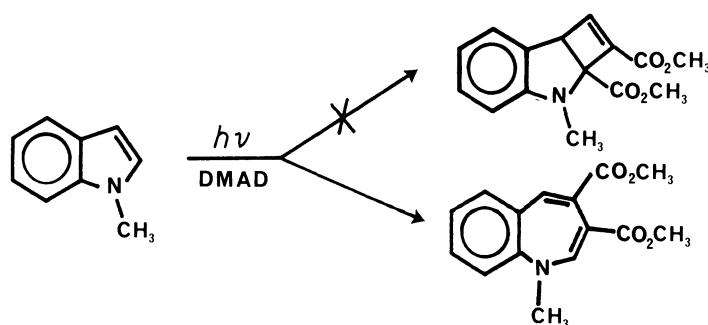
4. Indoles

The secondary allylic rearrangement, prevalent in the benzo(b)thiophene,⁽¹²⁾ and also, as we shall see later, in benzo(b)furan, does not occur in photocycloadditions to alkylated indoles. Thus the reaction of *N*-methylindole to DMAD yields no rearranged adduct but instead leads directly to *N*-methyl-3,4-dicarbomethoxybenzo(b)azepine (Scheme 11). This product derives from the direct $\pi^2s + \pi^2s$ cycloaddition process, and subsequent thermal rearrangement, the latter occurring at room temperature.⁽⁴¹⁾

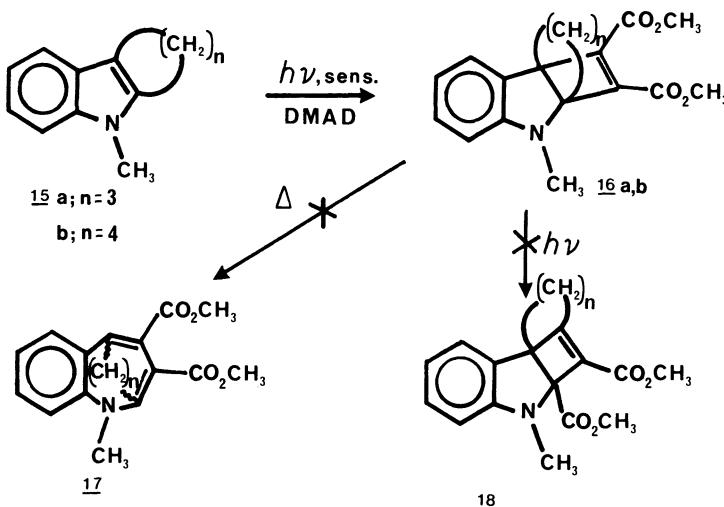
Isolation of cyclobutene adducts in the *N*-alkylindole system was accomplished by using fused indoles (**15a, b**) to prevent cyclobutene ring opening. The photoreactions of 1-methyl-2,3-trimethyleneindole (**15a**, $n = 3$) and 6,7,8,9-tetrahydro-1-methylcarbazole (**15b**, $n = 4$) demonstrate this point. Direct cycloaddition to produce the cyclic adducts **16** would not likely be

Table 2. Photorearrangements of 2-Thia-3,4-benzobicyclo[3.2.0]hepta-3,6-diene

Unrearranged product		Preferred, rearranged product		Ref.
R ₁	R ₂	R ₃	R ₄	
COOCH ₃	COOCH ₃	H or CH ₃	H	33,34
COOCH ₃	COOCH ₃	H or CH ₃	CH ₃	33
COOCH ₃	COOCH ₃	H	OH	40
COOCH ₃	COOCH ₃	—(CH ₂) ₄ —		34
COOCH ₃	COOCH ₃	C(CH ₃) ₃	H	<i>a</i>
COOCH ₃	H	H or CH ₃	H	33
COOCH ₃	C ₆ H ₅	H or CH ₃	H	33,39
C ₆ H ₅	COOCH ₃	H or CH ₃	H	33,39
C ₆ H ₅	—C(=O)OCH ₂ CH ₂ —		H	39
CH ₃	—C(=O)OCH ₂ CH ₂ —		H	39
C ₆ H ₅	C ₆ H ₅	H	H	33,37
C ₆ H ₅	H, CN, OAc,	H	OCH ₃	41
	OCH ₃			
<i>b</i>	CH ₃	H	<i>b</i>	39

a. A.H.A. Tinnemans and D.C. Neckers, unpublished results.*b.* R₄ and R₁ = —CH₂CH₂OC(=O)—.

SCHEME 11

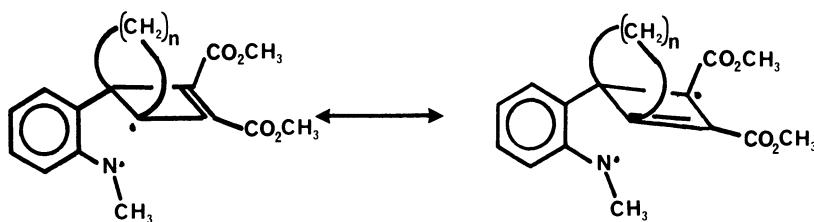


SCHEME 12

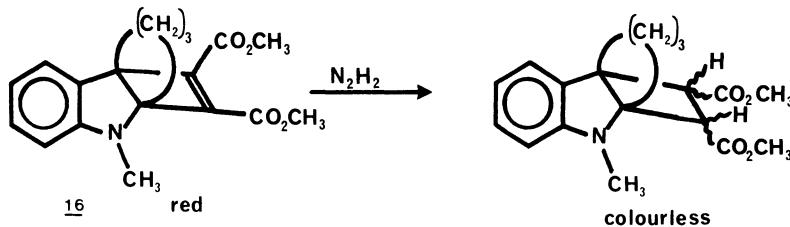
followed by ring opening to the benzazepines **17** since in these cases the derived benzazepine would have two bridgehead double bonds (Scheme 12).

This synthetic sequence had the added benefit of allowing a test for the secondary allylic rearrangement in indole photocycloadditions. The biradicals (Scheme 13), if they are formed, in addition to requiring the more difficult C—N bond homolysis for their formation, would suffer steric resonance inhibition, since one of them possesses a bridgehead double bond. In fact, photocycloaddition of DMAD to both **15a** and **b** produces the $\pi^2s + \pi^2s$ unarranged product in quantitative yield. The rearranged product is not observed. Neither, as expected, is the benzazepine.

The single product from the reaction of 1-methyl-2,3-trimethyleneindole **15a** with DMAD, the unarranged product **16a**, was blood red due to the



SCHEME 13



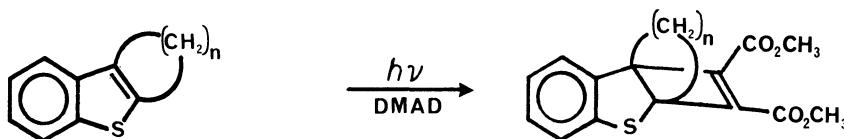
SCHEME 14

presence of a charge transfer band ($\epsilon = 758$; $\lambda_{\max} = 438$ nm). The band is the result of an intramolecular charge transfer interaction between the aniline donor and the maleate acceptor, as could be shown by concentration dependence studies and chemical tests. For instance, this charge transfer band disappears on diimide reduction of the double bond (Scheme 14).

5. Benzo(b)thiophenes

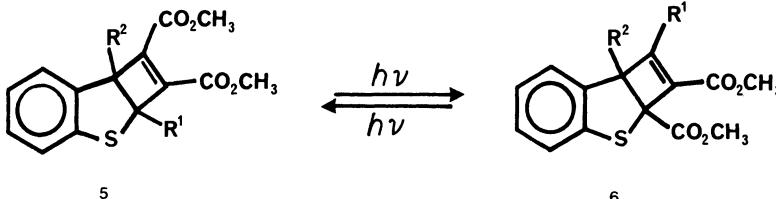
The concept of destabilizing the allylic biradical by forcing its formation at a bridgehead (Scheme 13) and the observation of charge transfer absorptions in the unrearranged cyclobutenes (Scheme 14) suggested an extension of the study to benzo(b)thiophenes analogous to the tetrahydrocarbazoles and looking for unrearranged cyclic adducts following the addition of DMAD.

Isolation of the $\pi^2s + \pi^2s$ unrearranged cycloadduct was successfully achieved by Ditto and Davis, who irradiated 2,3-tetramethylenebenzo(b)thiophene with 300-nm light sources, (Scheme 15). Subsequently, it was found out that the unrearranged adduct does not have a significant absorption at this wavelength (Figure 2).⁽³³⁾ Davis, Ditto, and Neckers⁽³³⁾ also isolated unrearranged adducts from the addition of DMAD to the parent benzo(b)thiophene and several of its alkylated derivatives, and demonstrated



SCHEME 15

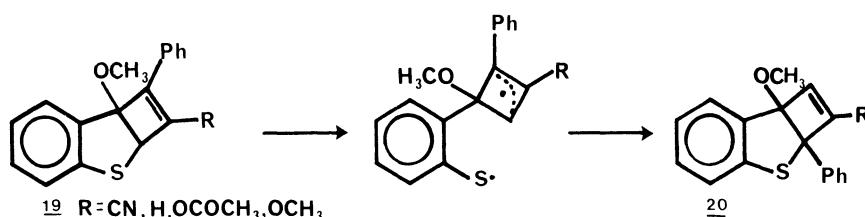
Table 3. Photoequilibrium Studies

		
	5(%)	6(%)
(a.) $R_2 = R_2' = H$	64%	36%
(b.) $R_1 = H; R_2 = CH_3$	70	30
(c.) R_1 and $R_2 = -(CH_2)_4-$	100	0

that a photostationary state existed between the rearranged and the unrearranged isomers (Table 3). These experimental results were achieved only after the differential absorption spectra of the rearranged and the unrearranged adducts were discovered. Each photoequilibration was carried out at ambient temperatures in a Rayonet photochemical reactor, using 300-nm lamps, and in benzene solvent (N_2 purged) using concentrations in the range $1.3\text{--}1.5 \times 10^{-3} M$.

In contrast, no photoequilibrium, **19**–**20**, was observed by Hofmann and Gaube on direct irradiation of **19**, though both **19** and **20** absorb at long wavelengths. The cyclobutene **19** irreversibly converts into the rearranged isomer **20**. This has been explained from the differential absorption characteristics of the cyclobutenes. The long-wavelength absorption of **19** is approximately an overlap of the absorption of a styrene chromophore with that of an aryl-S-alkyl chromophore. Photoexcitation of **19** leads to C_1-S bond rupture affording a mesomeric biradical intermediate. Photolysis of **20** at long wavelengths no longer causes C_1-S bond rupture since the absorption maximum of **20** is that of a dihydrobenzo(b)thiophene and as such is observed at shorter wavelengths (Scheme 16).⁽⁴⁰⁾ Taken together, these results clarify the relatively complex situation with respect to photocycloaddition reactions of benzo(b)thiophene to electron-poor acetylenes.

1. Photocycloadditions of benzo(b)thiophenes are triplet-state reactions.
2. Rearrangement of the initial (2+2)-adduct can be prevented by the selection of the proper irradiating wavelength.



SCHEME 16

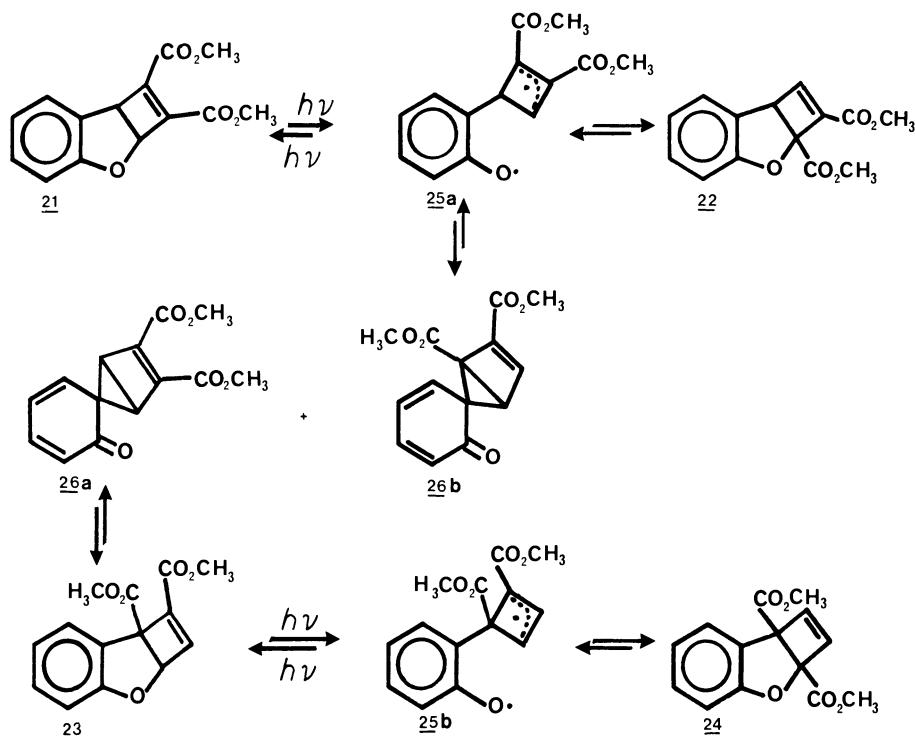
3. In every case where photocycloaddition partners lead to products, the unarranged adduct absorbs at longer wavelengths than the rearranged adduct. It must be that way since the functional groups which facilitate the addition reaction also make the double bond of the cyclobutene electron poor and set up the charge transfer interaction as a possibility.

6. Benzo(b)furans

Addition of alkyne esters to benzo(b)furan represents the intermediate case between benzo(b)thiophene, which gives photochemical rearrangements easily and needs to be forced to do otherwise, and alkylated indoles, which give no secondary photochemical rearrangement products.⁽⁴²⁾

Acetophenone-sensitized cycloaddition of DMAD to benzo(b)furan leads to all four possible cyclobutene adducts in which carboxymethyl groups occupy vicinal positions. Under the experimental conditions the cyclobutenes equilibrate photochemically, and all the isomers derive from each other when irradiated directly, though the reactions are much more efficient when acetophenone is used to sensitize them (Table 4).

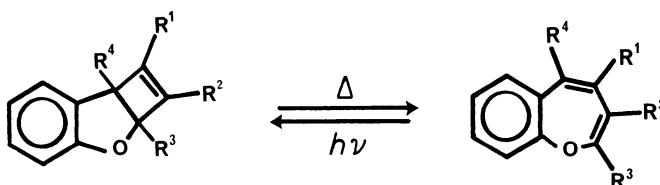
We have suggested the mechanism shown below to explain the observation that four stereoisomeric cyclobutenes, 21–24, derive from the photocycloaddition of DMAD to benzo(b)furan and the eight products which result from its 2-methyl derivative. Crucial in this mechanistic scheme is the formation of the 1,2-cyclobutenespiro[2,5]-octadienones, 26a and 26b. In 26b, cleavage at α would give biradical 25b and lead to the unexpected products 23 and 24. The spirodienones have not been isolated in these reactions and it could be that there are other mechanistic possibilities which could explain the results.



7. Thermal Reactions of the 2-Hetero-bicyclo[3.2.0]heptadienes

Synthetic applications of these photocycloaddition processes are conceivable and can be applied to the synthesis of fused ring systems in the azepine, thiepin, or oxepine series.

Ring openings of the cyclobutenes are temperature dependent. At temperatures over 180° 2-oxa-3,4-benzobicyclo[3.2.0]heptadienes are isomerized into benzoxepines (Scheme 17).^(42,43) The reaction is photochemically reversible.



SCHEME 17

Table 4. Products of Photocycloaddition of Dimethyl Acetylenedicarboxylate to Benzo(b)furan

Ia, b, R = H, CH₃

		Product			Yield isolated (%)
	R ¹	R ²	R ³	R ⁴	
R = H ^a	H	CO ₂ CH ₃	CO ₂ CH ₃	H	9
	CO ₂ CH ₃	CO ₂ CH ₃		H	8
	H	H	CO ₂ CH ₃	CO ₂ CH ₃	7
	CO ₂ CH ₃	H	H	CO ₂ CH ₃	1.5
R = CH ₃ ^b	CH ₃	CO ₂ CH ₃	CO ₂ CH ₃	H	5
	CO ₂ CH ₃	CO ₂ CH ₃	CH ₃	H	15
	H	CH ₃	CO ₂ CH ₃	CO ₂ CH ₃	6
	CO ₂ CH ₃	CH ₃	H	CO ₂ CH ₃	c
	H	CO ₂ CH ₃	CO ₂ CH ₃	CH ₃	1
	CO ₂ CH ₃	CO ₂ CH ₃	H	CH ₃	c
	CH ₃	H	CO ₂ CH ₃	CO ₂ CH ₃	2
	CO ₂ CH ₃	H	CH ₃	CO ₂ CH ₃	c

^aProducts equilibrate under the conditions of the experiment. The relative yields, therefore, depend on the irradiation time.

^bA photoequilibrium exists among the product isomers. The relative yields may therefore vary.

^cThese isomers are likely in reaction mixture but were not definitely identified.

ble.⁽⁴²⁻⁴⁴⁾ When irradiating at $\lambda > 300$ nm the benzoxepines are converted to the corresponding cyclobutenes via a disrotatory closure of the diene system.* The ring closure cannot be induced by triplet sensitizers and is therefore thought to proceed via the singlet state of the benzoxepine. A detailed study of the photochemical reaction of 4-phenylbenzo(b)oxepines with respect to differential substitution patterns has appeared.⁽⁴⁴⁾

Thermal ring openings of 2-azabicyclo[3.2.0]heptadienes are substituent dependent, but in general occur at much lower temperatures than either the oxygen or sulfur analogs.^{(46)†} Like the oxepine series the azepines ring close photochemically.⁽⁴⁸⁾ The benzazepines derive from each of the cyclobutenes

* We have deliberately omitted discussion of valence isomerization in oxepines. For extensive discussions of these unrelated reactions the reader is referred to Reference 45.

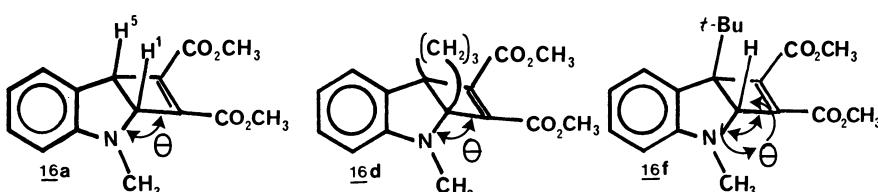
† For additional details regarding ring openings in the nitrogen system the reader is referred to Reference 47.

Table 5. Yield of Products from the Sensitized Irradiation of Indoles and DMAD

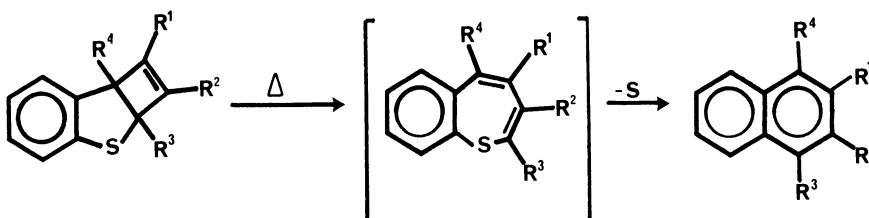
	% Yield	UV data in 95% ethanol	
		CT _{max}	Other
(a.) R ₁ =CH ₃ , R ₂ =R ₃ =H	72	375	—
(b.) R ₁ =R ₂ =CH ₃ , R ₃ =H	11	427	285, 253
(c.) R ₁ =R ₃ =CH ₃ , R ₂ =H	2-12	435(2.79)	302(3.14), 251(3.61)
(d.) R ₁ =CH ₃ , R ₂ and R ₃ =—(CH ₂) ₃ —	71	438(2.88)	304(3.18), 249(3.68)
(e.) R ₁ =CH ₃ , R ₂ and R ₃ =—(CH ₂) ₄ —	82	432	302, 250
(f.) R ₁ =CH ₃ , R ₂ =H, R ₃ = <i>t</i> -butyl	77	411(2.81)	295(3.21), 252(3.62)
(g.) R ₁ =R ₃ = <i>t</i> -butyl, R ₂ =H	85	408	—

in Table 5 except *d* and *e*, the opening of which violates Bredt's rule. The cyclobutenes in Table 5 were isolated by carefully controlling the temperature at which the irradiations were carried out.

It has been suggested that the position (λ_{\max}) of the charge transfer absorption maximum CT_{max} is related to the distance between interacting chromophores⁽⁴⁹⁾ as long as differences are not also accompanied by changes in electronic effects. The electronic similarity in the cyclobutenes (Table 5) suggests that the relative positions of the CT_{max} (*a, d*, and *f*: 375, 435, and 411 nm) may change because of a change in the angle due to the steric strain caused by groups at positions 1 and 5. This observation is further manifested in the ease of ring opening, in the indole systems, as a function of substituent. Ring opening to the benzazepine, precluded in **16d** by Bredt's rule considerations, is substantially slower in fused cyclobutene **16f** than in cyclobutene **16a** because of eclipsing of the *t*-butyl with the carboxylate which retards ring opening of the *t*-butyl derivative relative to the unsubstituted compound **16a** (Scheme 18).



SCHEME 18

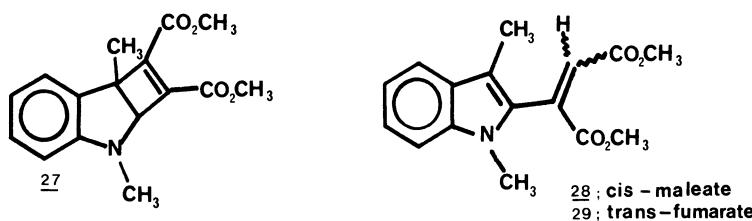


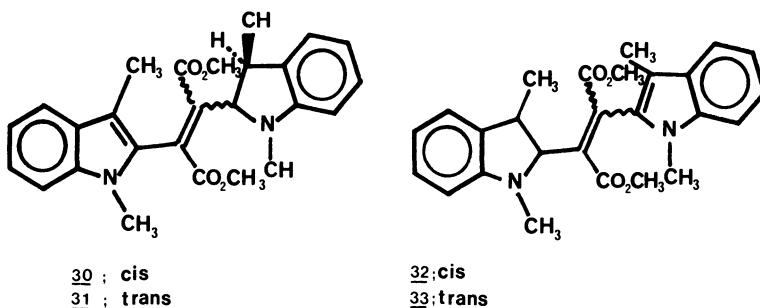
SCHEME 19

In many respects thermal ring opening of the 2-thiabicyclo[3.2.0]-heptadienes is more practically and synthetically interesting than are the ring openings in the nitrogen or oxygen series. In the former regard, Reinhoudt and Kouwenhoven used an electron-donating amino group at C₅ of the 2-thiabicyclo[3.2.0]heptadiene to isolate the first stable thiepin,⁽³⁹⁾ the isolation of the latter being previously precluded by sulfur elimination to produce naphthalene (Scheme 19). Isolated benzo(b)thiepines^(39,50) behave similarly to benzo(b)azepines or benzo(b)oxepines and ring close photochemically—to 2-thiabicyclo[3.2.0]heptadienes via a symmetry allowed disrotatory ring closure. The influence of π -donor, π -acceptor substituents on this photoreaction has been reported.⁽⁴⁰⁾

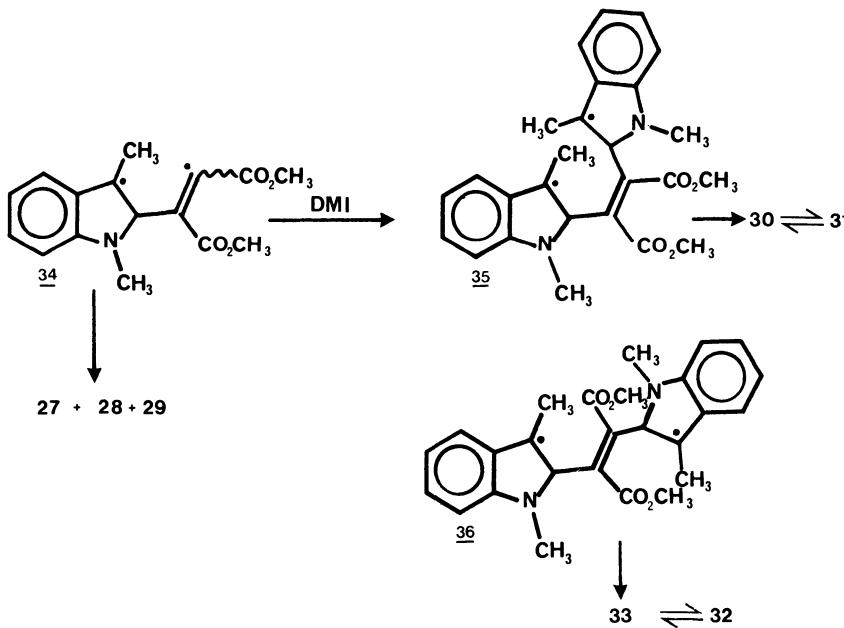
8. 1,3-Dimethylindole

In each family there is a black (or white) sheep, and in the photocycloaddition reaction of alkynes to indoles such may be said of 1,3-dimethylindole. An elaborate study⁽⁵¹⁾ of the photoreaction of DMAD with 1,3-dimethylindole (DMI) shows that there are seven products formed. The $[2+2]\pi$ cycloadduct, **27**, which is a minor product, is accompanied by two other 1:1 substitution products, **28** and **29** and four 2:1 substitution products, **30–33**, which together are the major products of the reaction. The photo-

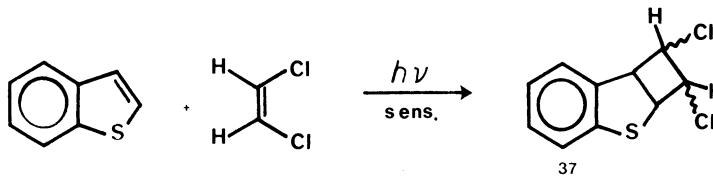




reaction is thought to occur via the 1,3-dimethylindole triplet, $^3[\text{DMI}]^*$, interacting with DMAD to form either an exciplex or radical ion pair. Adducts **28** and **29** have been rationalized as occurring via a 1,4-biradical **34** or a radical pair.^(41,47,51) From the concentration dependence of DMI addition to



DMAD, it is suggested that **34** has been chemically trapped with another molecule of DMI to give the two intermediate 1,6-biradicals **35** and **36**. The former would lead to the stereospecific formation of **30** by an intramolecular disproportionation process, whereas the latter is proposed to lead to **33** via an intermolecular H-atom transfer process. A similar biradical trapping has been observed in other indole/DMAD systems as well—e.g., 1-methyl-3-phenylindole. Trapping of biradicals in the case of 1,3-dimethylindole likely



SCHEME 20

is forced because ring closure of 34 is retarded by the 3-methyl substituent. Among all the indoles, 1,3-dimethylindole often gives unusual results, which can be useful in some cases, a nuisance in others.

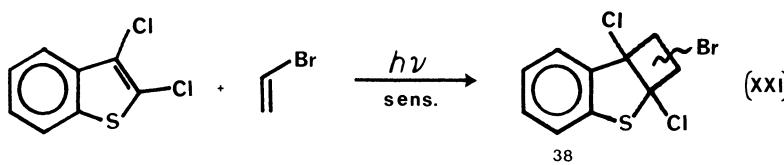
9. Photocycloadditions of Benzo(b)thiophene to Alkenes

The rationale for first selecting dichloroethylene as a partner for the reaction of what we now know to be triplet benzo(b)thiophene was based on an analysis made by one of us that relative to naphthalene, benzo(b)thiophene was nucleophilic. Our expectation in planning our first experiments in this area was, therefore, that an electrophilic partner olefin would react with benzo(b)thiophene triplets and give a [2 + 2]-cycloadduct.

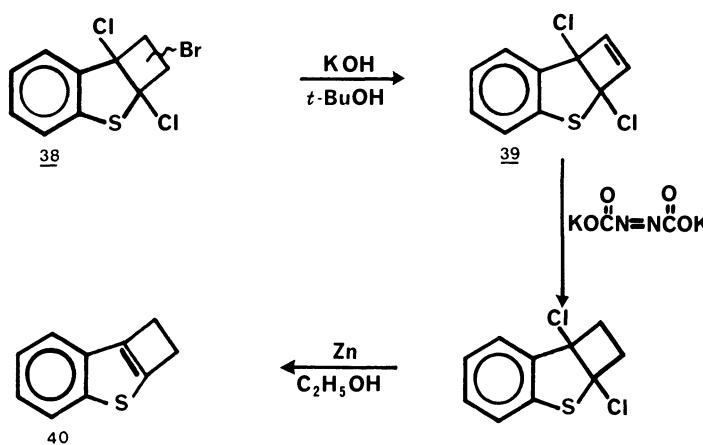
That such an addition occurred was first observed in 1968 with dichloroethylene as the partner olefin. The adducts 37 were the first isolated and characterized [2 + 2]-cycloaddition products to benzo(b)thiophene or for that matter to benzo(b)furan or indole. Our detailed studies of this system have been reported (Scheme 20).⁽⁵³⁾

Since then several reports have appeared on the formation of olefin cycloaddition products to these heteroaromatics.⁽⁵⁵⁻⁵⁷⁾

These cycloadditions can also be used to synthetic advantage. Photocycloaddition of 2,3-dichlorobenzo(b)thiophene to vinyl bromide gives either 1,5-dichloro-6-bromo-2-thia-3,4-benzobicyclo[3.2.0]hept-3-ene (38) or the 7-bromo isomer (Scheme 21). Treatment with base gives the olefin 39, which



SCHEME 21



SCHEME 22

following diimide reduction and treatment with Zn in ethanol affords the heretofore unknown benzo(b)thiophene derivative **40** (Scheme 22).⁽⁵⁴⁾ This result portends further fun in the benzo(b)thiophene cycloaddition series, and experiments, today, are in progress to synthesize the cyclobutadiene **41** or its isomer **42**.



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Azirine Photolysis and Cycloaddition Reactions

Albert Padwa

1. Introduction

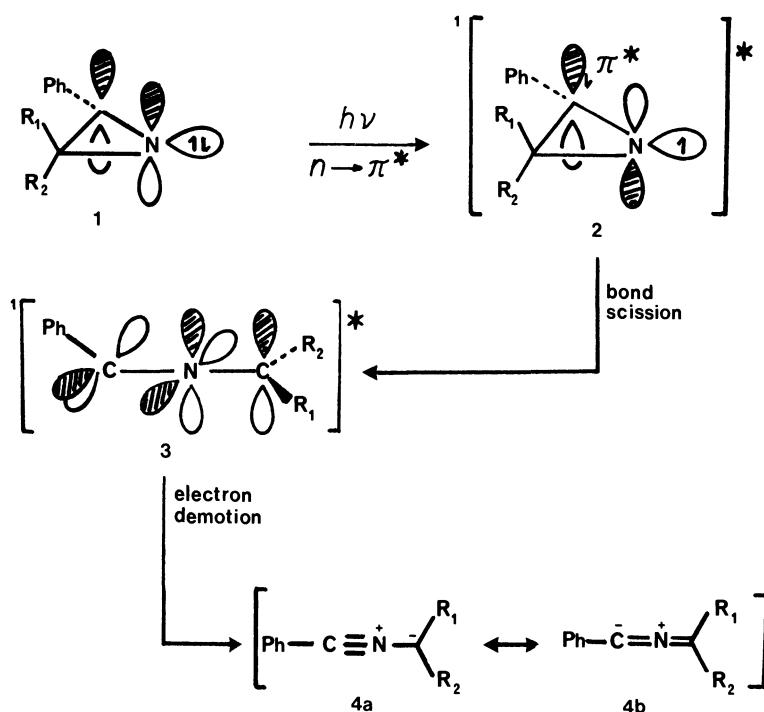
Photochemical cycloaddition reactions of alkenes⁽¹⁻⁹⁾ and carbonyl compounds⁽¹⁰⁻¹⁶⁾ have received considerable attention in recent years and have taken an important place among the best known and most reliable organic photochemical transformations. It is becoming increasingly clear that the photocycloaddition reaction is a versatile synthetic tool which can be used for the construction of complex molecules.⁽⁹⁾ In contrast to the wealth of data associated with excited-state cycloadditions of alkenes and ketones, the photoaddition reactions of the structurally related imine system have received little attention. This is surprising in view of the many studies that have been made dealing with the photochemistry of imines⁽¹⁷⁻¹⁹⁾ and of their spectroscopic behavior.⁽²⁰⁾

The possibilities of both $n-\pi^*$ and $\pi-\pi^*$ excitation of this chromophore promise a variety of interesting physical and chemical conversion processes. While chemical reaction of the excited state of an imine has often been observed, a more frequently encountered phenomenon for simple imines is fast, efficient, radiationless deactivation. The low photoreactivity of the imine system can be attributed to rotation about the π bond in the excited state, which allows dissipation of electronic energy.⁽²¹⁾ In rigid systems, this mode of energy dissipation is not available, and these cyclic imines have maximum opportunity to undergo reaction from an electronically excited state.

Investigations dealing with the photochemistry of small-ring cyclic imines have shown that the three-membered azirine ring⁽²²⁻²⁸⁾ undergoes photochemical cycloaddition with various carbon–carbon and hetero double bonds to give five-membered heterocyclic rings.^(29,30) With this system, syn–anti photoisomerization about the C–N double bond is a high-energy, structurally prohibited process. It is well known that 2*H*-azirines are versatile substrates which can serve as useful precursors for the synthesis of other heterocyclic rings.⁽³¹⁻³⁷⁾ An unusual feature of this three-membered heterocyclic ring is that it is susceptible to attack by both electrophilic and nucleophilic reagents.⁽³⁷⁾ Also, the 2*π* electrons present in the ring can participate in thermally allowed $[\pi_4S + \pi_2S]$ cycloadditions as dienophiles^(38,39) or as dipolarophiles.⁽⁴⁰⁾ The intent of this chapter is to provide an indication of the wide diversity and intriguing transformations that 2*H*-azirines undergo on photochemical excitation. It is hoped that an overview of the major developments and potentialities in this area will be attained.

1.1. UV Spectra of Arylazirines

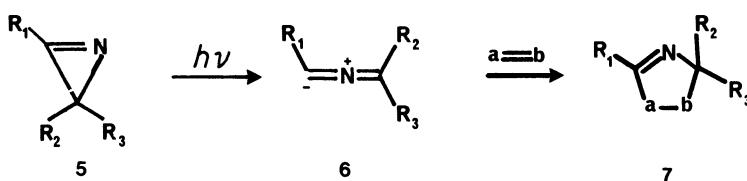
The ultraviolet absorption spectra of substituted arylazirines in cyclohexane exhibit strong ($\epsilon \sim 10,000$) absorption at ca. 240 nm with a weak inflection on the long-wavelength side of the principal absorption band [i.e., ca. 285 nm ($\epsilon \sim 500$)]. This weak band undergoes a hypsochromic shift with increasing polarity of the medium. By the empirical criteria of low intensity and shift of the absorption to shorter wavelengths in hydrogen-bonding solvents, this latter band can be attributed to an $n-\pi^*$ transition. The weakening of the C–C bond of the azirine ring as a result of this transition was rationalized⁽⁴¹⁻⁴³⁾ in terms of an electrocyclic transformation by analogy with the cyclopropyl \rightarrow allyl cation rearrangement. One may envisage the $n-\pi^*$ excitation process as leading to a species resembling structure 2, where the nonbonding orbital on nitrogen contains only one electron. The electron that was promoted to the antibonding π^* orbital will partially reside on the carbon atom and consequently the nitrogen atom will become somewhat electrophilic and begin to resemble an aziridinyl cation. The remaining nonbonding electron on nitrogen, which is in the plane of the σ bonds of the ring, will overlap with the back lobe of the saturated carbon and facilitate bond scission. Electron demotion would then result in the formation of nitrile ylide 4. A similar nonbonding orbital overlap with an adjacent σ bond has been postulated to account for the facile α cleavage (i.e., Norrish type I reaction) encountered with carbonyl compounds.⁽⁴⁴⁾



SCHEME 1

1.1.1. Evidence for Nitrile Ylide Formation

Schmid and co-workers^(45,46) have reported that the irradiation of a number of substituted arylazirines in a rigid matrix at -185°C gave rise to a new maximum in the ultraviolet spectrum (ca. 350 nm) which was attributed to a nitrile ylide. Their results showed that the dipole undergoes photochemical but not thermal reversion to the starting azirine. When the azirine was photolyzed at -185°C in the presence of a trapping agent such as methyl trifluoroacetate, the maximum at 350 nm was obtained again. This maximum vanished, however, upon increasing the temperature to -160°C , thereby indicating that cycloadduct formation is derived from a thermal 1,3-dipolar addition of the initially generated nitrile ylide with the added dipolarophile. The purely aliphatic 2,3-dipropyl-2*H*-azirine was also found to undergo efficient ring cleavage ($\Phi = 0.8$) to produce a nitrile ylide [λ_{max} 280 nm ($\epsilon > 15000$)].⁽⁴⁷⁾



SCHEME 2

Nitrile ylides, generated from the photolysis of $2H$ -azirines, may be classified as nitrilium betaines, a class of 1,3-dipoles containing a central nitrogen atom and a π bond orthogonal to the 4π allyl system. They can be intercepted with a wide variety of dipolarophiles to form five-membered heterocyclic rings. A number of other methods have also been used to generate nitrile ylides.⁽⁴⁸⁻⁵⁵⁾

2. Cycloaddition Reactions

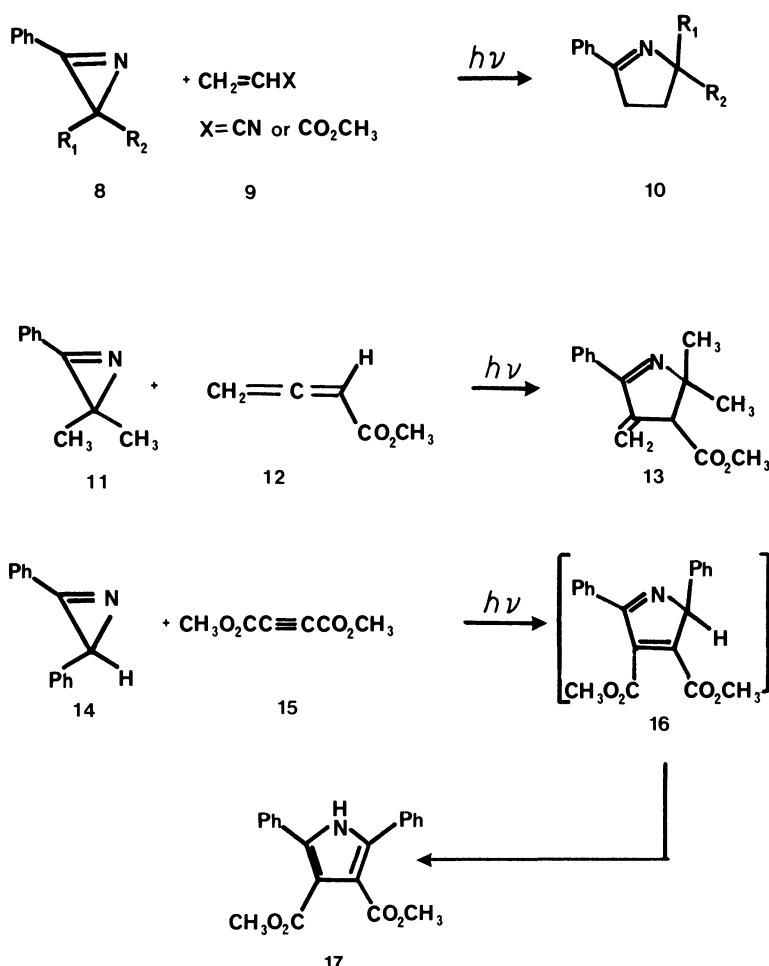
2.1. Addition with Electron-Deficient Olefins

The photocycloaddition of $2H$ -azirines with electron-deficient olefins produces Δ^1 -pyrrolines as primary photoproducts. Some of the dipolarophiles used include acrylic esters, acrylonitriles, fumaric and maleic esters, methyl allenecarboxylate, norbornene, and 1,2-dicyanocyclobutene.⁽⁵⁵⁻⁶⁰⁾ Similarly, styrenes⁽⁵⁸⁾ and vinyl pyridines⁽³⁰⁾ undergo smooth photocycloaddition with $2H$ -azirines. Addition of acetylene derivatives to the transient nitrile ylide gives $2H$ -pyrroles which rearrange to pyrroles if the C-2 atom is monosubstituted.⁽⁵⁶⁾ 3-Phenyl- $2H$ -azirines have been found to cycloadd to vinyl phosphonium salts and to vinyl sulfones. The initial adducts undergo ready loss of the phosphorous or sulfur substituent to give $2H$ -pyrroles.⁽⁶⁰⁻⁶²⁾

The photocycloadditions show all the characteristics of concerted reactions, including stereospecificity and regioselectivity.

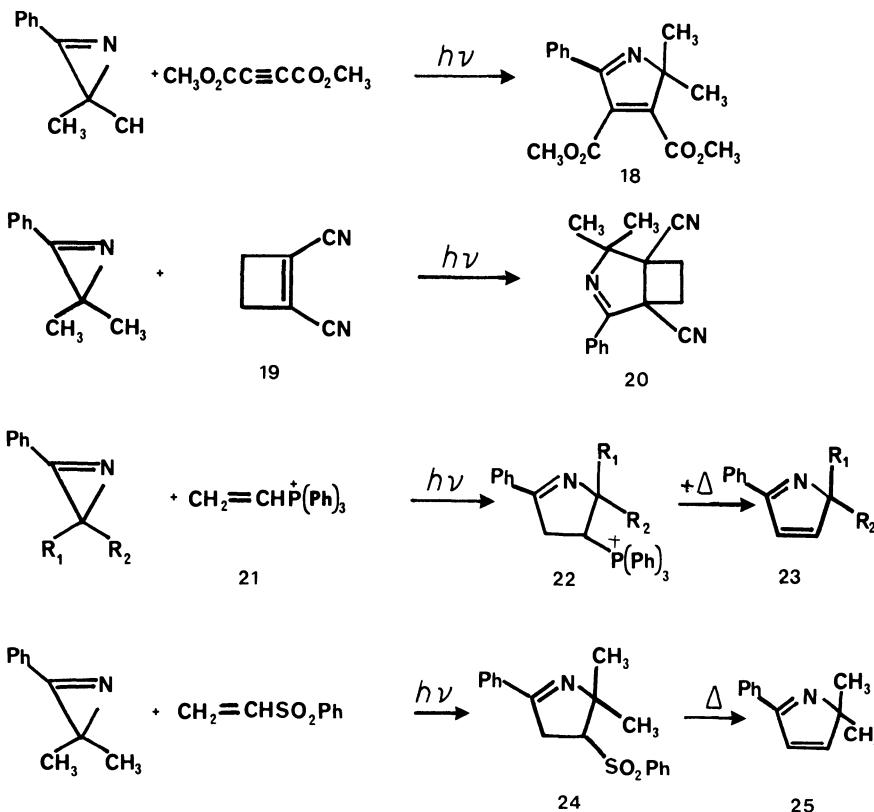
2.1.1. Mechanism of Cycloaddition to Olefins

Concerted 1,3-dipolar additions are known to proceed via a “two-plane” orientation complex.⁽⁶³⁾ For the case of diphenylazirine and methyl acrylate, there are two possible orientation complexes, **26** or **27**. The interaction of substituent groups in the *syn*-complex **26** can be of an attractive (π -overlap, dipole-dipole interaction) or of a repulsive nature (van der Waals strain). Both effects are probably negligible in the *anti* complex **27**. The ratio of the



two steric courses (*syn* and *anti*) functions as a probe and gives insights into the interplay of steric and electronic substituent effects in the transition state of 1,3-dipolar addition. The effect of π overlap and van der Waals strain was found to play an important role in controlling the stereochemical distribution of the products obtained.⁽⁵⁷⁾

2.1.1.1. Regiospecificity and Regioselectivity of Cycloaddition. The orientation of the groups in the Δ^1 -pyrrolines obtained from the photoaddition process is essentially identical with that observed by Huisgen in related 1,3-dipolar additions.⁽⁶³⁾ For example, treatment of *N*-(*p*-nitrobenzyl)benzimidoyl chloride (30) with triethylamine in the presence of acrylonitrile has been found



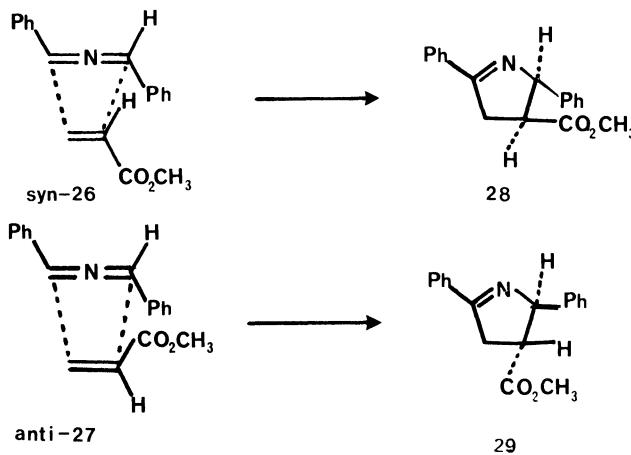
SCHEME 4

to give Δ^1 -pyrroline 31.⁽⁶⁴⁾ This reaction has been interpreted as proceeding via a nitrile ylide intermediate 32.

The regiospecificity of the olefin cycloaddition reaction depends on the substituent groups present on the double bond. Thus, acrylonitrile and methyl acrylate react with various nitrile ylides to give only the 4-substituted regioisomers (i.e., 16). Photocycloaddition of arylazirines to α -methylacrylonitrile and methyl methacrylate, on the other hand, give adducts to type 33 and 34 in a 3:2 ratio.⁽⁵⁷⁾

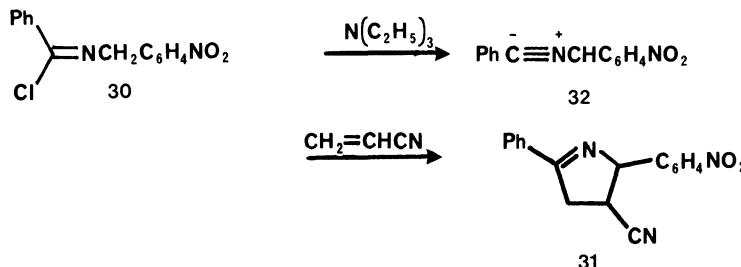
The regioselectivity is completely lost in the photocycloaddition of azirine 35 with diethyl vinyl phosphonate or dimethyl vinyl phosphine sulfide.⁽⁶⁰⁾ The two isomers, 36 and 37 as well as 38 and 39, are found in equal quantities.

The experimentally observed regioselectivity of these and other 1,3-dipolar cycloadditions has, until recently, been a most difficult phenomenon to explain. Rationalizations of regioselectivity based on a concerted transition

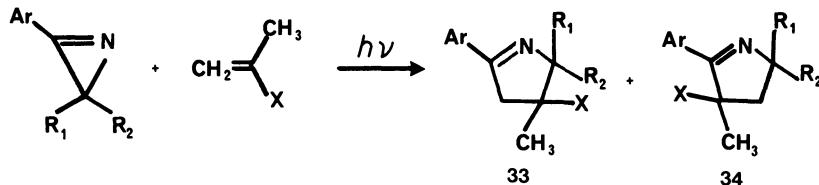


SCHEME 5

state model have invoked both electronic and steric effects.⁽⁶³⁾ A solution to the vexing problem of regioselectivity in 1,3-dipolar cycloadditions has recently been proposed by Houk and co-workers,⁽⁶⁵⁾ who used the frontier orbital method for rationalizing the effect of substituents on rates and regioselectivity of 1,3-dipolar cycloadditions. According to the frontier orbital treatment of 1,3-dipolar cycloadditions, the relative reactivity of a given 1,3-dipole towards a series of dipolarophiles will be determined primarily by the extent of stabilization afforded the transition state by interaction of the frontier orbitals of the two reactants.^(66,67) When nitrile ylides are used as 1,3-dipoles, the dipole highest occupied (HO) and dipolarophile lowest unoccupied (LU) interaction will be of greatest importance in stabilizing the transition state. The favored cycloadduct will be that formed by union of the atoms with the largest coefficient in the dipole HO and dipolarophile LU. An electron-deficient olefin

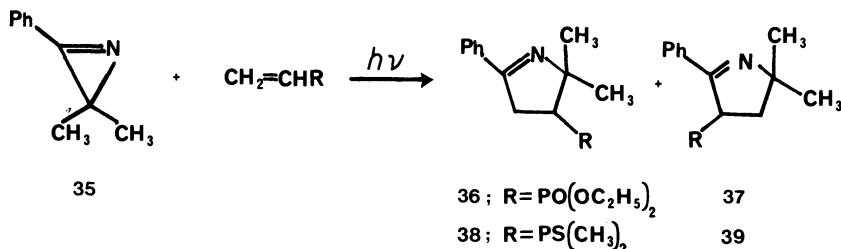


SCHEME 6

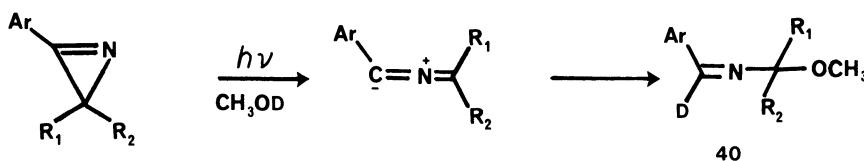


SCHEME 7

has the largest coefficient on the unsubstituted carbon in the LU orbital. In order to predict regioselectivity in the photocycloaddition of arylazirines, it is necessary to determine the relative magnitudes of the coefficients in the highest occupied orbital (HO) of the nitrile ylide. This problem was solved by carrying out the irradiation of several arylazirines in hydroxylic media.^(67,68) The photoconversion of arylazirines **1** to alkoxyimines (**40**) indicates that in the highest occupied orbital of the nitrile ylide, the electron density at the disubstituted carbon is greater than at the trisubstituted carbon atom. The preferred regioisomeric transition state will be that in which the larger terminal coefficients of the interacting orbitals are united. Houk has pointed out that with all dipolarophiles except for the very electron-rich, nitrile ylide reactions are HO-controlled.⁽⁶⁵⁾ Reactions of nitrile ylides with electron-rich dipolarophiles have not been observed, indicating that the dipole LU-dipolarophile HO interaction is not very large. The photochemical addition of methanol to the nitrile ylide clearly shows that the larger HO coefficient of the nitrile ylide is, in fact, on the disubstituted carbon atom. With this conclusion, all of the regiochemical data found in the photoaddition of arylazirines⁽⁶⁹⁻⁷¹⁾ with dipolarophiles can be explained. Thus, the formation of the 4-substituted Δ^1 -pyrroline **16** from the irradiation of acrylonitrile or methyl acrylate with various nitrile ylides is perfectly consistent with the regioselectivity being controlled by union of the atoms with the largest coefficients in the dipole



SCHEME 8



SCHEME 9

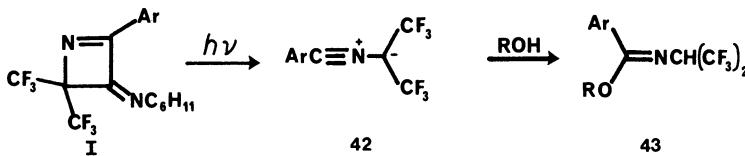
HO and dipolarophile LU. The formation of a mixture of 2*H*-azirines with α -methylacrylonitrile and methyl methacrylate can be attributed to the fact that whereas the cyano or ester group enhances the LU coefficient at the unsubstituted carbon atom of the dipolarophile, the methyl group has the opposite effect. The terminal coefficients in the LU of α -methylacrylonitrile and methyl methacrylate are more nearly the same than for the nonmethylated analogs, so that regioselectivity decreases for these dipolarophiles.

It should be noted that Schmid and co-workers⁷² have reported on the photoaddition of arylazirines with other active hydrogen compounds [e.g., 35 ($h\nu$) \rightarrow 41] which are complementary to the observations outlined above. A somewhat related case has also been described by Burger, who found that irradiation of azetine *I* in an alcohol solvent generated nitrile ylide 42 which could be trapped to give *N*-(hexafluoroisopropyl)-benzimidic ester 43.⁽⁷³⁾ It is interesting to note that the addition of alcohol to this nitrile ylide occurs in a manner opposite to that encountered in the irradiation of the arylazirines bearing alkyl groups in the 2-position of the ring. The effect of the *gem*-trifluoromethyl groups in Burger's system is apparently such that the coefficient at the trisubstituted carbon atom of the nitrile ylide is now the larger.

Dipolarophiles which contain an electron-deficient substituent undergo smooth cycloaddition reactions with nitrile ylides. The relative reactivity of the nitrile ylide toward a series of dipolarophiles is determined primarily by the extent of stabilization afforded the transition state by interaction of the dipole highest occupied (HO) and dipolarophile lowest unoccupied (LU) orbitals.^(65,66) Substituents which lower the dipolarophile LU energy accelerate



SCHEME 10

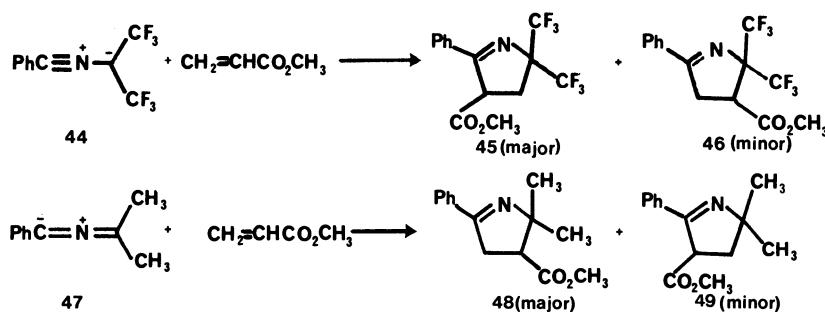


SCHEME 11

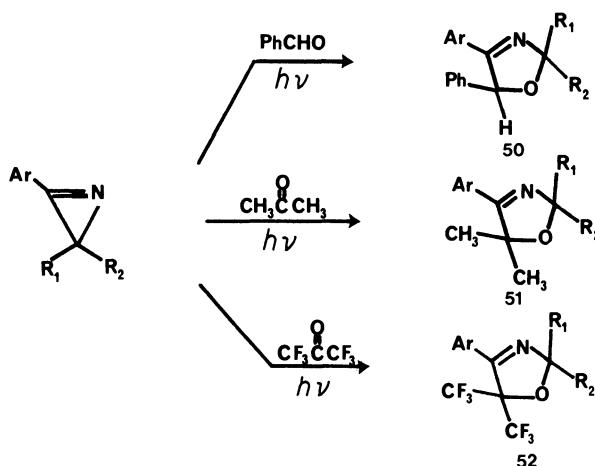
the 1,3-dipolar cycloaddition reaction.⁽⁷⁴⁾ For example, fumaronitrile undergoes cycloaddition at a rate which is 189000 times faster than methyl crotonate.⁽⁷⁴⁾ Ordinary olefins react so sluggishly that their bimolecular rate constants cannot be measured. The absolute reaction rate of methyl acrylate and the nitrile ylide derived from 2,3-diphenyl-2H-azirine at 25° has been estimated as $7.6 \times 10^8 M^{-1} s^{-1}$.⁽³⁹⁾ Inductive effects exerted by substituents on the nitrile ylide also have an important effect on the regioselectivity of the cycloaddition. Benzonitrilio-hexafluoro-2-propanide (**44**) and methyl acrylate yield products with inverse regioselectivity as compared with the reactions of the related benzonitrilio-2-propanide **47**.⁽⁴⁹⁾ The difference in regioselectivity has been attributed to the larger coefficient at the trisubstituted carbon atom of the *gem*-trifluoromethyl substituted nitrile ylide **44**. This result parallels the different mode of addition of alcohols to nitrile ylides **44** and **47**.

2.2. Addition to Aldehydes and Ketones

The photochemical addition of 2*H*-azirines to the carbonyl group of aldehydes, ketones and esters also shows complete regiospecificity.^(45,58,69-72,75-78) The cycloaddition of ketones with nitrile ylides proceeds much more slowly than the corresponding cycloaddition with aldehydes.⁽⁷²⁾ On the other



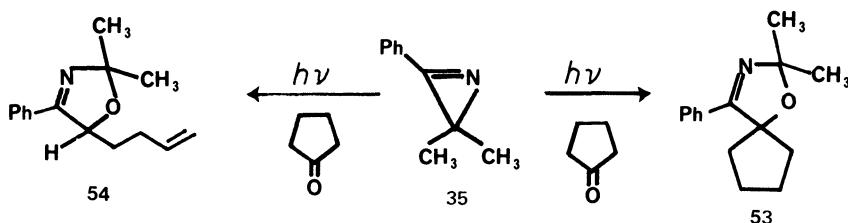
SCHEME 12



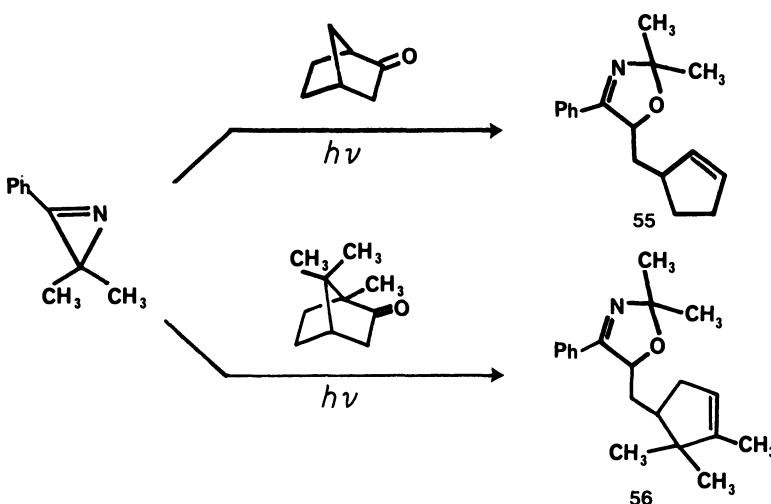
SCHEME 13

hand, ketones with electron-withdrawing groups like trifluoromethyl, ethoxycarbonyl, nitrile, or phosphonate in the α position react rapidly with the 1,3-dipole.⁽⁷²⁾ All of this is understandable in terms of frontier MO theory. Nitrile ylides react rapidly with the more electron-deficient carbonyl group since such a pair of addends possess a narrow dipole HO-dipolarophile LU gap.

The photochemical cycloaddition of azirine 35 with cyclopentanone has been found to depend on the experimental conditions. When 35 is irradiated and cyclopentanone is slowly added, the expected spiro-3-oxazoline 53 is the main product.⁽⁷²⁾ However, when the cyclopentanone is irradiated first and the irradiation is continued in the presence of azirine 35, the sole product is 3-oxazoline 54.⁽⁷²⁾ Under the latter conditions, cyclopentanone reacts first by a Norrish type I cleavage and hydrogen transfer to yield penten-4-al. This aldehyde reacts faster with the nitrile ylide than does the cyclic ketone still



SCHEME 14

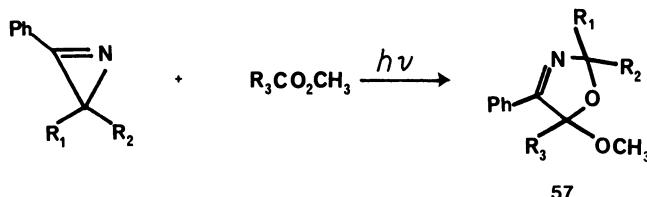


SCHEME 15

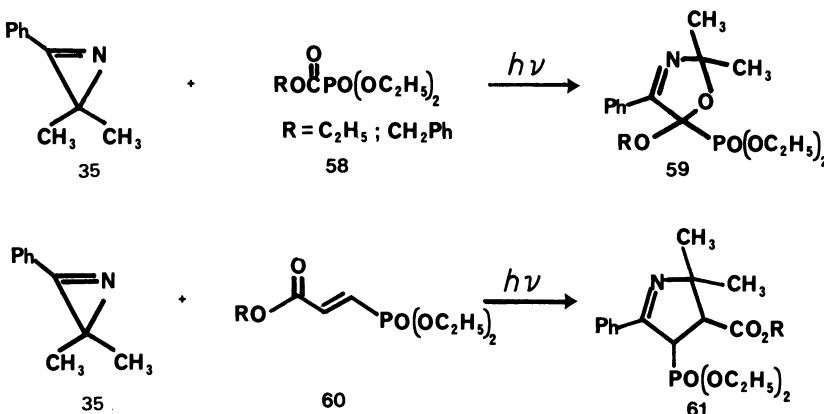
present, so that only **54** is formed. Norcamphor and camphor also react with azirine **35** under photolytic conditions via the Norrish type I reaction route to give 3-oxazolines **55** and **56**.

2.3. Addition to Esters

Esters of carboxylic acids which are activated by electron-withdrawing groups in the acyl or alkyl portion of the molecule also react with photochemically generated nitrile ylides to produce 5-alkoxy-3-oxazolines in high yield.⁽⁷²⁾ The addition to the carbonyl group occurs with the same regioselectivity as observed with aldehydes and ketones.⁽⁷⁶⁾ Esters which are not sufficiently activated like methyl acetate or benzoate do not undergo cycloaddition. Schmid and co-workers have reported that the ester carbonyl group can also be activated by a diethyl phosphonate residue.⁽⁶⁰⁾ Thus, irradiation



SCHEME 16



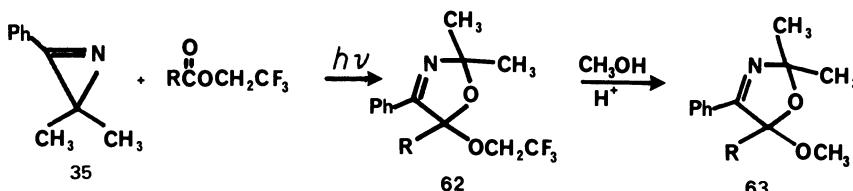
SCHEME 17

of **35** with alkoxy carbonyl phosphonate **58** produced oxazoline **59** in over 90% yield.⁽⁶⁰⁾ Photocycloaddition of **35** with the vinylogous phosphonate **60**, on the other hand, only occurred across the C—C bond to give cycloadduct **61**.

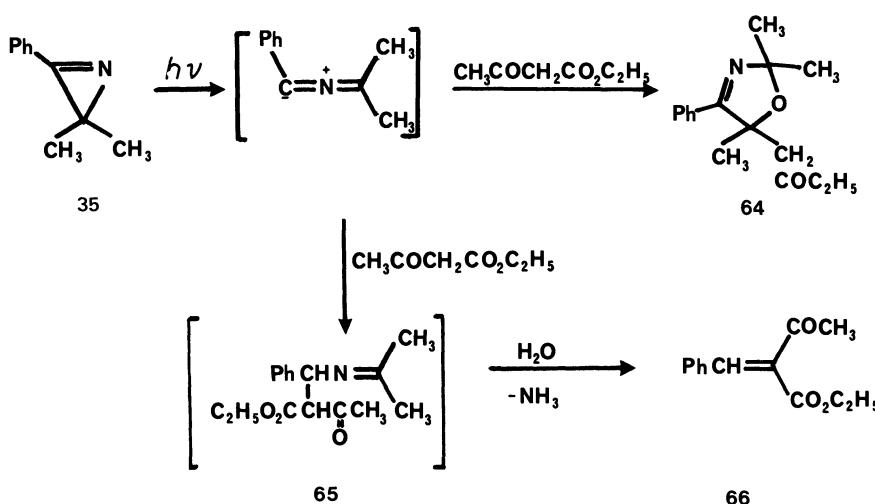
The Zurich group was also able to show that activation of carboxylic esters on the alkyl residue can best be achieved by esterification of the corresponding acid with 2,2,2-trifluoroethanol.⁽⁷²⁾ The advantage of the trifluoroethoxy moiety is that it can easily be exchanged with other alkoxy groups under acidic conditions. This procedure allows the preparation of a variety of 5-alkoxyoxazolines which are not accessible by the direct irradiation route.

The irradiation of 2*H*-azirine **35** in the presence of ethyl acetoacetate is of interest since, in this case, protonation of the nitrile ylide competes with cycloaddition. The protonation reaction is followed by hydrolysis and elimination of ammonia to eventually give ethyl benzylidene acetoacetate **66**.⁽⁷²⁾

The photocycloaddition reactions of arylazirines with a number of related carbonyl containing systems have also been studied.⁽³⁰⁾ 5-Methyl thiobenzoate



SCHEME 18

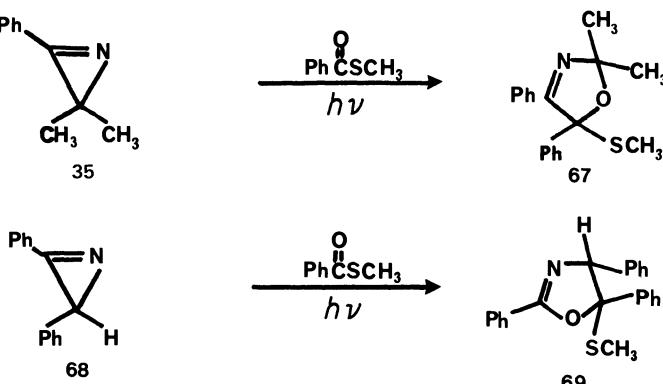


SCHEME 19

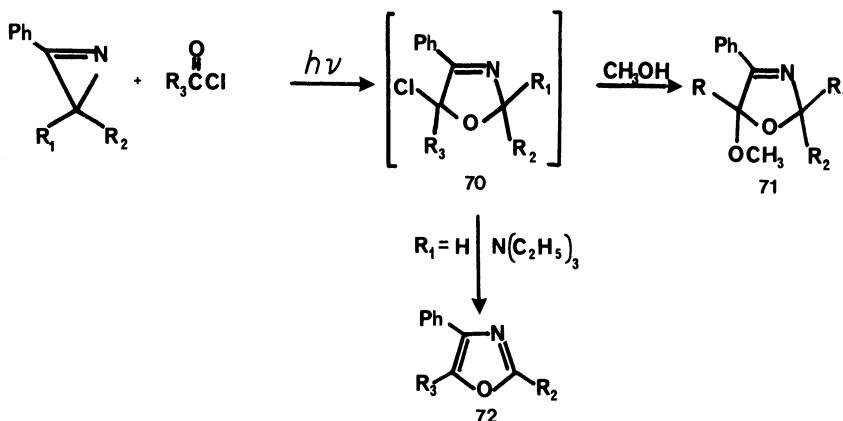
was found to photocycloadd with the same regiospecificity as was observed with the carboxylic ester.⁽⁷²⁾ In contrast to this, the reaction of methyl di-thiobenzoate with azirine 68 takes place at the thiocarbonyl group with inverse regiospecificity.⁽⁶⁹⁾

2.4. Additions to Acid Chloride and Anhydrides

Photocycloadditions have also been observed between 2*H*-azirines and acyl chlorides.⁽⁷⁹⁾ The primary cycloadducts (i.e., 70) are quite labile and can



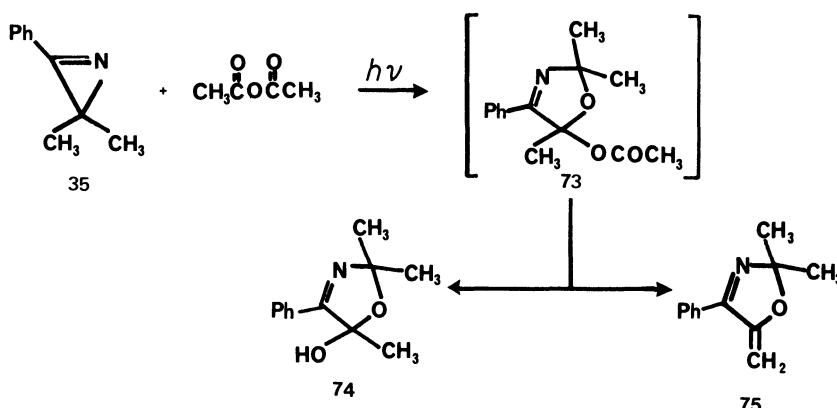
SCHEME 20



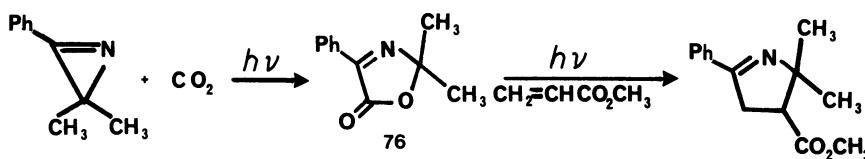
SCHEME 21

not be isolated directly. The 5-chloro substituent of the photoproduct could readily be exchanged with an alkoxy group. Cycloadducts **70**, which are monosubstituted at C-2, on treatment with tertiary amines undergo a 1,4-elimination of hydrogen chloride to form oxazoles in moderate yield.⁽⁷⁹⁾

A photoreaction similar to that observed with 2*H*-azirines and acyl chlorides also takes place with anhydrides.⁽⁷⁹⁾ Irradiation of azirine **35** and acetic anhydride, for example, initially produces the nonisolable cycloadduct **73**, which is subsequently converted to oxazolines **74** and **75** in 50% and 25% yield, respectively. Oxazoline **75** is formed as the sole product when **35** is irradiated in the presence of ketene.⁽⁷⁷⁾



SCHEME 22



SCHEME 23

2.5. Additions to Carbon Dioxide and Carbon Disulfide

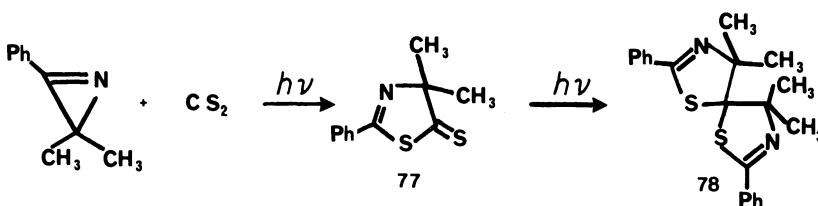
One of the more interesting photocycloaddition reactions in this series involves the photoinduced combination of 3-aryl-2*H*-azirines with carbon dioxide.^(54,80) This reaction is carried out by passing a finely dispersed carbon dioxide stream through a benzene solution of the 2*H*-azirine during irradiation and results in the formation of 3-oxazolin-5-ones **76** in good yield.⁽⁸¹⁾ The carbon dioxide cycloaddition with the photochemically generated nitrile ylide is reversible. Irradiation of the 3-oxazolin-5-one system (**76**) with 250–350-nm light regenerates the nitrile ylide which can be trapped in the usual way.^(47,54) A kinetic investigation, involving Stern–Volmer plots and relative reactivity studies, showed that the nitrile ylide generated from the photolysis of the 3-oxazolinone system is identical with that generated from the corresponding 2*H*-azirine.⁽⁵⁴⁾ Evidence was obtained which showed that the photochemically generated nitrile ylide derived from **76** did not thermally collapse back to the azirine ring.

When 2,2-dimethyl-3-phenyl-2*H*-azirine **35** was irradiated in the presence of carbon disulfide, a 2:1 adduct, 5,5-spirobis-(4,4-dimethyl-2-phenyl-2-thiazoline (**78**) was isolated.⁽⁵⁴⁾ Undoubtedly, the C–S double bond of the initially formed 1:1 adduct (i.e., **77**) reacts much faster than does the C–S double bond of carbon disulfide.^(54,82)

2.6. Additions to Ketenes, Carbodiimides, Isocyanates, and Isothiocyanates

Photoreactions have also been observed between 3-phenyl-2*H*-azirines and ketenes, carbodiimides, isocyanates, as well as isothiocyanates. The isocyanates and their thio-analogs react with the C–O and C–S double bond, respectively, and not with the C–N double bond.^(77,80)

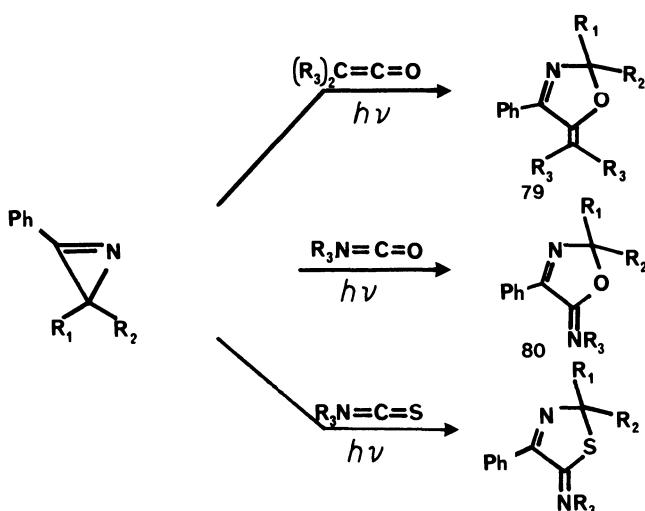
The photocycloaddition of 2*H*-azirines with a variety of other multiple π bonds proceeds in high yield and provides a convenient route for the synthesis of a variety of five-membered heterocyclic rings.^(83–87) Some of the dipolarophiles used include nitriles,⁽⁷¹⁾ azodicarboxylates,⁽⁸⁶⁾ and *p*-quinoles.^(47,87)



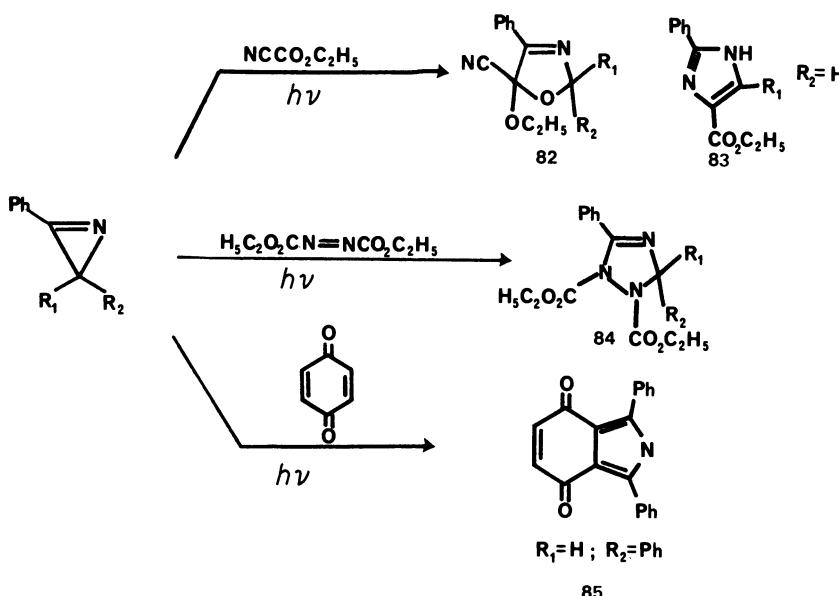
SCHEME 24

3. Photodimerization of Azirines

Irradiation of arylazirines with olefins of low dipolarophilic activity or in inert solvents produced no photoadduct but instead gave dimers.^(57,71,84) It was originally reported that photolysis of phenylazirine (**86**) gave azabicyclopentane (**87**).^(88,89) However, in the light of the foregoing mechanistic rationale developed for the photolysis of azirines, Padwa and Schmid's groups were able to show that the photodimer isolated is actually diazabicyclohexane **88**. Thus, in the absence of a dipolarophile, the nitrile ylide generated photochemically simply adds to a ground-state azirine molecule.⁽⁵⁷⁾ A cross dimerization of **89** to the ground state of **86** has also been realized.⁽⁹⁰⁾ Additional work showed that the photodimerization of arylazirines to 1,3-diazabicy-

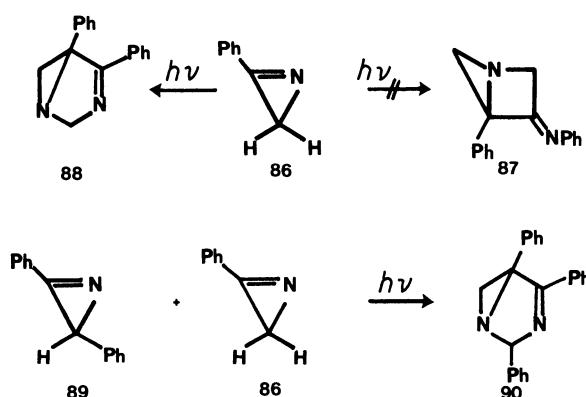


SCHEME 25

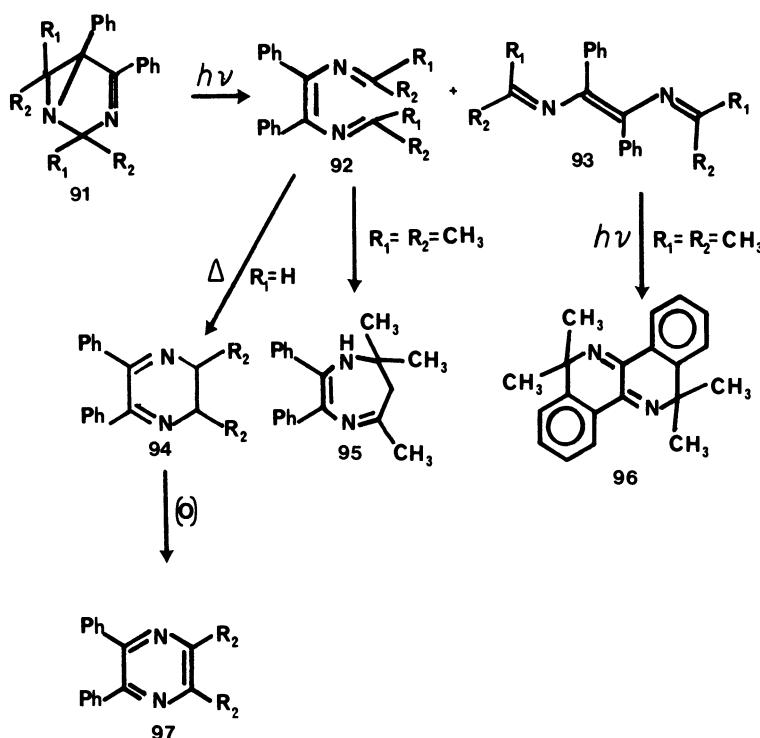


SCHEME 26

clo[3.1.0]hex-3-enes is a general reaction which is independent of the nature of the substituent groups attached to the C atom of the azirine ring.^(58,78) Care is required in the choice of solvent, photolysis time, and substituents since the 1,3-diazabicyclohexanes are themselves photochemically labile.⁽⁹¹⁾ Indeed, extended photolysis leads to complete ring opening and the formation of diazahexatrienes **92** which may be isolated when $\text{R}_1 = \text{R}_2 = \text{CH}_3$. Further



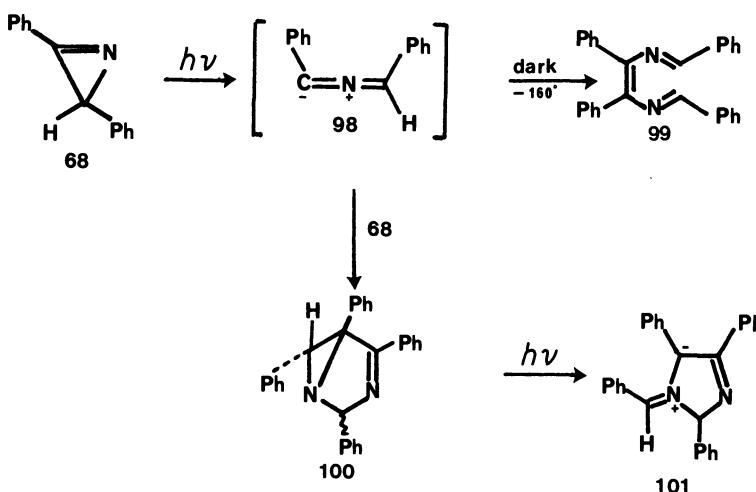
SCHEME 27



SCHEME 28

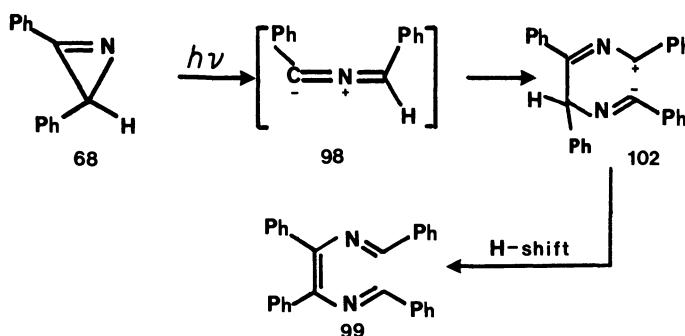
photolysis of *trans*-93 ($R_1 = R_2 = \text{CH}_3$) gives the diazachrysene 96.⁽⁹²⁾ The *cis* ($R_1 = R_2 = \text{CH}_3$) enedimine 92 very readily cyclizes to the diazepine 95 on standing. On the other hand, if $R_1 = \text{H}$ in *cis* 92 then cyclization gives first the dihydropyrazine 94 and eventually the pyrazine 97. The results indicate that the secondary photoproducts formed from the irradiation of the diazabicyclic hexenes (91) depend on the substituent groups, the time of irradiation, and the particular solvent employed.^(58,92,93)

Work by Schmid's group⁽⁴⁶⁾ has shown that the nitrile ylide derived from diphenylazirine (68) also undergoes quantitative dimerization to 1,3,5,6-tetraphenyl-2,5-dioda-1,3,5-hexatriene (99) at -160° . This result indicates that 99 is not only formed by the indirect route ($98 + 68 \rightarrow 100 \xrightarrow{h\nu} 101 \rightarrow 99$) but also by dimerization of 98 by a direct head-to-head coupling. The intermediacy of azomethine ylide 101 in the photochemical conversion of azabicyclic hexene 100 to diazahexatriene 99 was verified by low-temperature photolysis studies. Flash photolysis of a solution of 2,3-diphenyl-2*H*-azirine (68) in cyclohexane at room temperature allows one to monitor the disappearance of the nitrile ylide (i.e., 98) by uv spectroscopy.⁽⁴⁶⁾ At high concentrations of

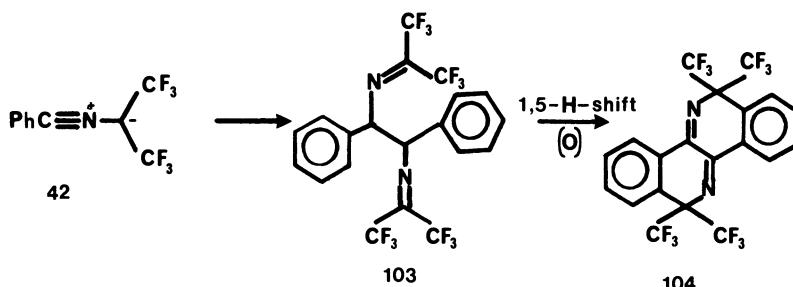


SCHEME 29

98 ($> 10^{-7} M$), the dipolar species was found to disappear with second-order kinetics with a specific rate constant $k = 5 \times 10^7 M^{-1}s^{-1}$. At low concentrations of **98** ($< 10^{-7} M$), the dipolar species was found to vanish with pseudo-first-order kinetics (**98** + **68** \rightarrow **100**). The specific pseudo-first-order rate constant is $k = 1 \times 10^4 M^{-1} \text{ sec}^{-1}$. The direct formation of **99** has been explained in terms of a head-to-head reaction of two molecules of the dipolar intermediate in a biradicaloid or carbenoid form.⁽⁴⁶⁾ Alternatively, a head-to-tail dimerization of the nitrile ylide could occur to give **102** which is then transformed into **99** via a subsequent hydrogen shift.⁽⁴⁶⁾



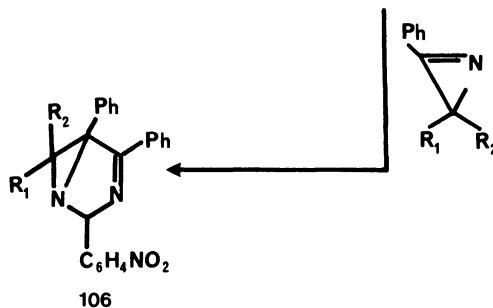
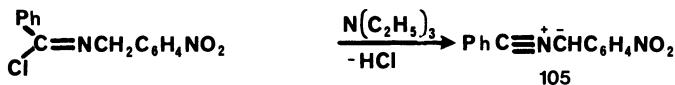
SCHEME 30



SCHEME 31

A head-to-head dimerization was also observed with benzonitriliohexafluoro-2-propanides (**42**) generated from the thermolysis of oxaphosphole **6**. The primary coupling product **103** was converted to structure **104** by cyclization followed by a 1,5-*H* shift and dehydrogenation by oxygen.

It was also shown that benzonitrilio-*p*-nitrophenyl methanide (**105**) generated chemically by the base-induced elimination of HCl from *N*-(*p*-nitrobenzyl)-benzimidoyl chloride **5**, adds across the C–N double bond of 2*H*-azirines to give the 1,3-diazabicyclo[3.1.0]hexene ring system.⁽⁸⁴⁾ The 1,3-diazabicyclohexene ring was also prepared by treating 2-acyl-aziridines with aldehydes and ammonia.^(94,95) This independent synthesis provides unequivocal support for the structures of the photodimers.

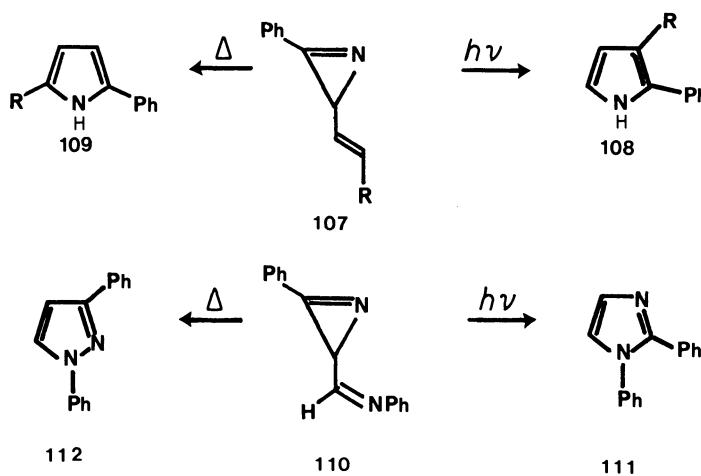


SCHEME 32

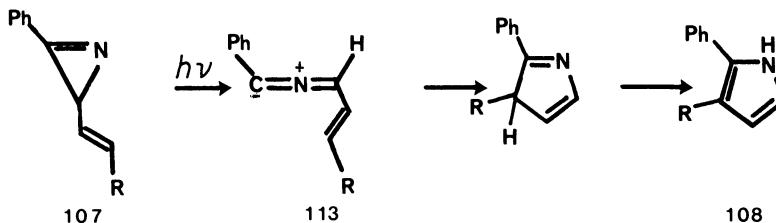
4. Intramolecular Cycloaddition Reactions

4.1. Rearrangement of 2-Vinylazirines

Whereas the cycloaddition of arylazirines with electron-deficient olefins produces Δ^1 -pyrrolines, a rearranged isomer is formed when the alkene and the azirine moieties are suitably arranged in the same molecule. This intramolecular electrocyclization reaction⁽⁹⁶⁾ was first observed by Padwa and Smolanoff using 2-vinyl-substituted 2*H*-azirines. Irradiation of 2*H*-azirine **107** afforded a 2,3-disubstituted pyrrole **108**, while thermolysis gave a 2,5-disubstituted pyrrole **109**. Photolysis of azirine **110** proceeded similarly and gave 1,2-diphenylimidazole **111** as the exclusive photoproduct. This stands in marked contrast to the thermal reaction of **110**, which afforded 1,3-diphenylpyrazole **112** as the only product. The evidence obtained clearly indicates that the above photorearrangements proceed via a mechanism involving a nitrile ylide intermediate since cycloadducts could be isolated when the irradiations were carried out in the presence of trapping agents.⁽⁹⁷⁾ Intramolecular electrocyclization of nitrile ylide **113** followed by a 1,3-sigmatropic hydrogen shift of the initially formed five-membered ring readily accounts for the formation of the final product. The thermal transformations observed with these systems have been rationalized in terms of an equilibration of the 2*H*-azirine with a transient vinyl nitrene which subsequently rearranges to the 2,5-disubstituted pyrrole (*vide infra*).



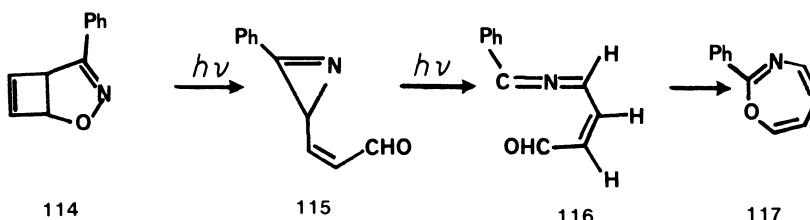
SCHEME 33



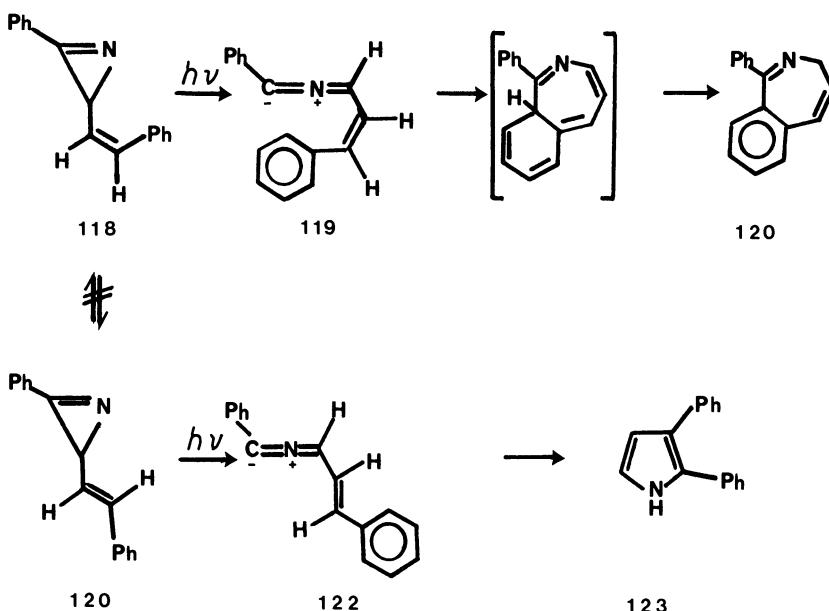
SCHEME 34

In the above examples only the *E* isomers of azirine **107** could be prepared. It is noteworthy that the photochemical conversion of the bicyclic isoxazoline **114** to oxazepin **117** is believed to involve the *Z* isomer of the azirine **115**.^(98,99) This species could not be isolated but goes on to give nitrile ylide **116**. 1,7-Electrocyclization of **116** leads to oxazepin **117** in 80% yield. Because of steric constraints it is clearly impossible for the *E*-vinyl nitrile ylide **107** ($R = \text{CHO}$) to undergo 1,7-cyclization.

Analogous results were obtained from the photochemical ring opening of *Z*-3-styryl-2*H*-azirine **118**.¹⁰⁰ The *Z*-strylnitrile ylide **119** formed in the irradiation of **118** affords benzazepine **120** in 80% yield by a 1,7-electrocyclization followed by a 1,5-sigmatropic shift. The photolysis of the isomeric *E*-styrylazirine **121** followed an entirely different course and produced 2,3-diphenylpyrrole **123** as the major photoproduct. This observation requires that opening of the azirine ring followed by intramolecular electrocyclization proceeds faster than isomerization about the C–C double bond. The formation of **120** indicates that the nitrile ylide obtained from **118** cyclizes more easily via a seven-membered transition state and leads to the preferential formation of benzazepine **120**. Cyclization of the nitrile ylide derived from the trans isomer to a seven-membered ring is precluded on structural grounds, and formation of 2,3-diphenylpyrrole occurs instead.



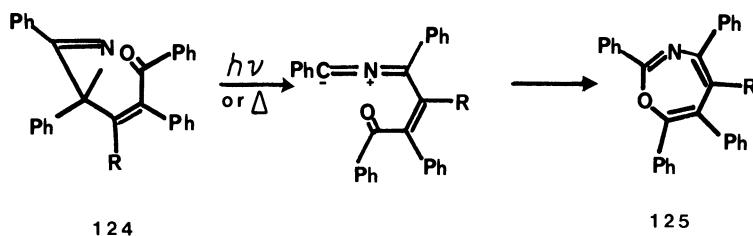
SCHEME 35



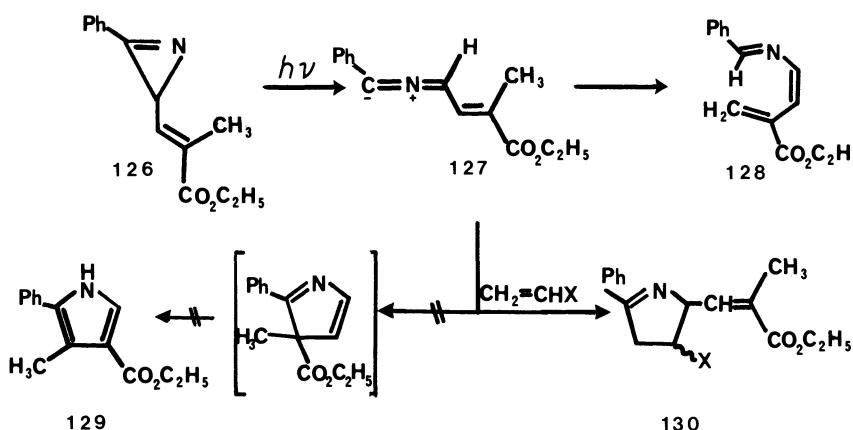
SCHEME 36

The photoconversion of the *Z*-benzoyl-substituted vinyl-azirine **124** to tetraphenyloxazepine **125** most likely involves ring opening to a nitrile ylide followed by 1,7-electrocyclization.⁽¹⁰⁾ The same product was also obtained from the thermolysis of **124**. All attempts to trap the nitrile ylide with methyl acrylate failed. This result indicates that if a nitrile ylide is formed at all during the rearrangement, it reacts much faster intramolecularly to give **125** than biomolecularly with methyl acrylate.

Irradiation of 3-vinyl-2*H*-azirine **126** gives, among other products, the azatriene **128** which arises via intramolecular hydrogen transfer of vinylnitrile



SCHEME 37



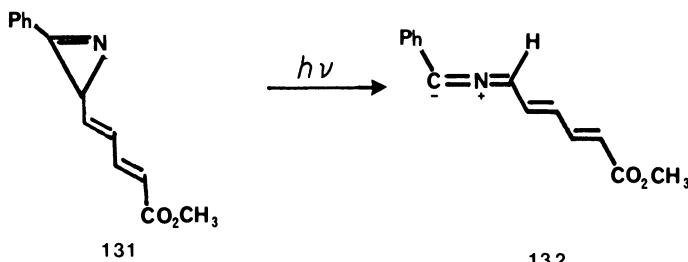
SCHEME 38

ylide **127**.⁽¹⁰²⁾ The pyrrole **129** derived from 1,5-dipolar cyclization of **127** was not found. When the reaction is run in the presence of acrylonitrile or methyl acrylate, the 1,3-dipolar cycloadducts **130** ($X = CN, CO_2CH_3$) are obtained in high yield, thus arguing for the intermediacy of the nitrile ylide.⁽¹⁰²⁾

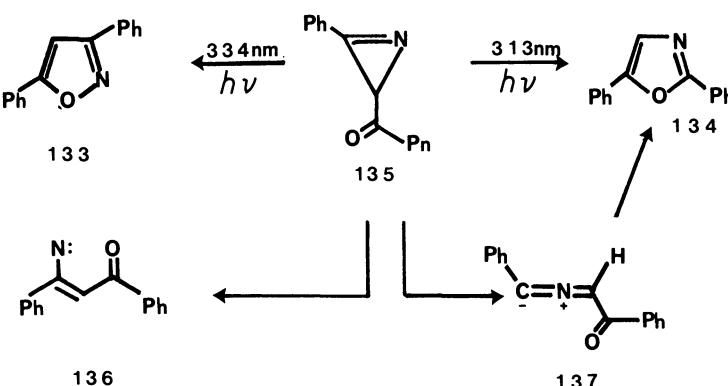
Attempts to effect a dipolar cyclization of the butadienyl nitrile ylide generated by photolysis of *2H*-azirine **131** failed; only a complex mixture of products was obtained.⁽¹⁰²⁾

4.2. Rearrangements of Isoxazoles and Oxazoles

A reaction which is closely related to the above cyclizations was uncovered by Ullmann and Singh back in 1966.⁽⁴¹⁾ While studying the photochemical rearrangement of 3,5-diphenylioxazole (**133**) to 2,5-diphenyloxazole (**134**), these workers observed the formation of an intermediate which proved to be



SCHEME 39

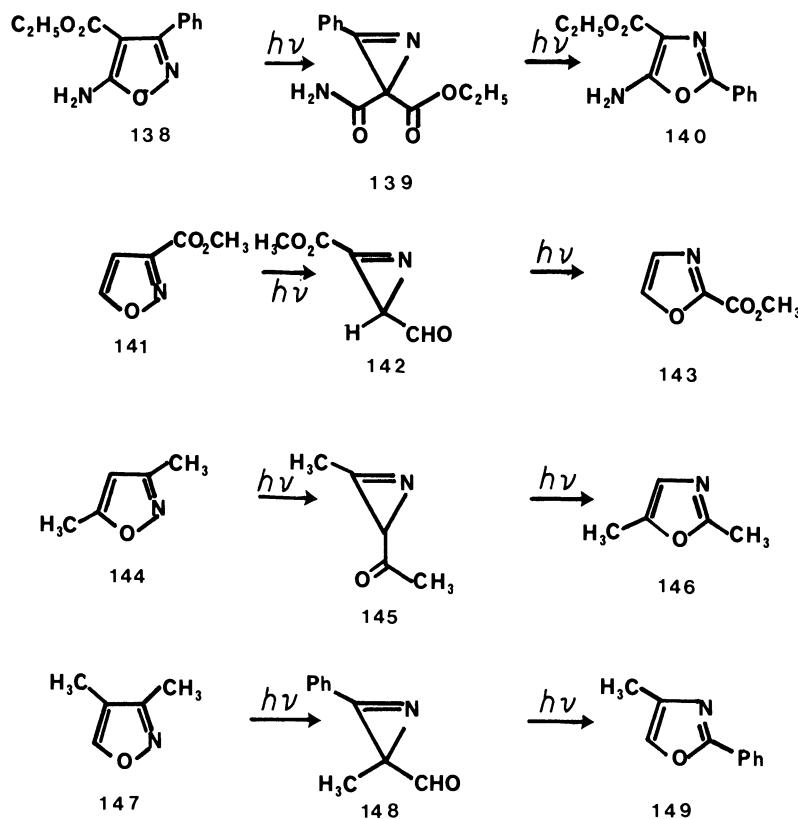


SCHEME 40

3-phenyl-2-benzoyl-2*H*-azirine (**135**). The photobehavior of azirine **135** was found to be dramatically controlled by the wavelength of the light used. With 3130-Å light, **135** rearranges almost quantitatively to oxazole **134**, whereas 3340-Å light causes rearrangement to isoxazole **133**. The formation of the isoxazole was suggested to occur via the $n-\pi^*$ ³ state of the carbonyl chromophore. Oxazole formation, on the other hand, was attributed to excitation of the $n-\pi^*$ state of the azirine ring. Selective $n-\pi^*$ excitation of the carbonyl group of **135** causes weakening of the C–N single bond. Cleavage of this bond leads to the vinyl nitrene **136** which collapses to isoxazole **133**. The $n-\pi^*$ excitation of the ketimine chromophore at shorter wavelengths leads to C–C bond cleavage generating the carbonylnitrile ylide **137**. 1,5-Dipolar cyclization of **137** gives oxazole **134**. This valence isomerization has subsequently aroused the interest of a number of investigators and much effort has been expended in outlining the scope and mechanism of this process.^(103–113) Some of the systems which have been studied in detail are outlined below. These reactions involve 3-carbonyl-substituted 2*H*-azirine intermediates which are not isolated but react further to give the oxazoles. The carbonylnitrile ylides do not give 1,3-dipolar cycloadducts with added dipolarophiles due to the facility with which they undergo electrocyclic ring closure.

Although the majority of oxazole photorearrangements involve the formal interchange of the C₂ and O atoms via the intermediacy of a 2*H*-azirine intermediate, two examples of ring interchange between the C₄ and C₅ atoms have been found.⁽¹¹³⁾ These transformations have been rationalized in terms of a 1*H*-azirine intermediate^(114,115) derived by cleavage of the C₅–O bond.⁽¹¹³⁾

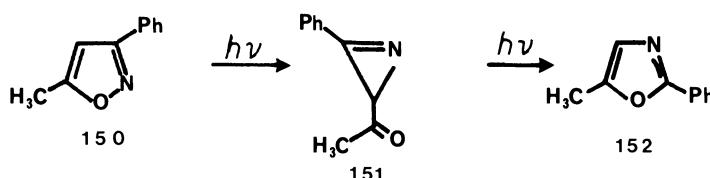
One case where an azirine intermediate is believed not to arise in the isoxazole photorearrangement has been reported by Padwa and co-workers.^(116,117) When 3-phenyl-4-benzoyl-5-methylisoxazole (**158**) or 3,5-diphenyl-4-



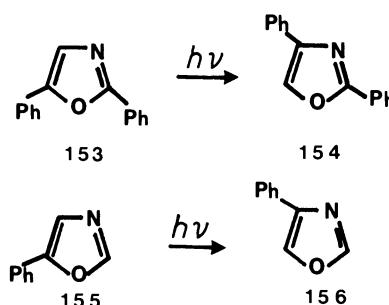
SCHEME 41

acetylisoazole (159) was thermolyzed (230°C), a 2*H*-azirine is presumably formed which subsequently opens to the nitrile ylide 160. Subsequent closure of 160 affords the isomeric oxazoles 161 and 162 in a ratio of 3:4.

In sharp contrast to the thermal results, the photolysis of 158 affords only oxazole 161. The authors postulated that the nitrile ylide 160 is formed



SCHEME 42



SCHEME 43

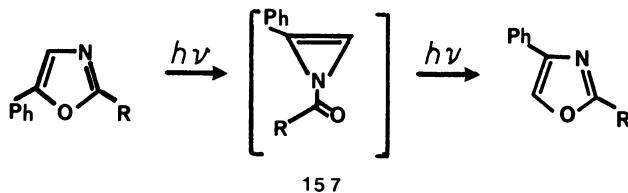
directly from the excited isoxazole in the conformation **160a**.⁽¹¹⁷⁾ Ring closure occurs before rotation around the C–N bond yielding only oxazole **161**. Some recent MINDO/3 calculations by Dewar and Turchi indicate that the CNC angle of nitrile ylides is less than 180°C and that rotation about the C–N bond in **160** is indeed slow relative to ring closure.⁽¹¹⁸⁾

It should be noted that Schmid and co-workers have postulated a 2*H*-azirine (i.e., **165**) as a transient intermediate in the photoreorganization of **163** to oxazoles **167** and **168** (1:1 mixture).⁽¹¹⁹⁾ This reaction is also accompanied by a slower transformation of **163** to **164**.

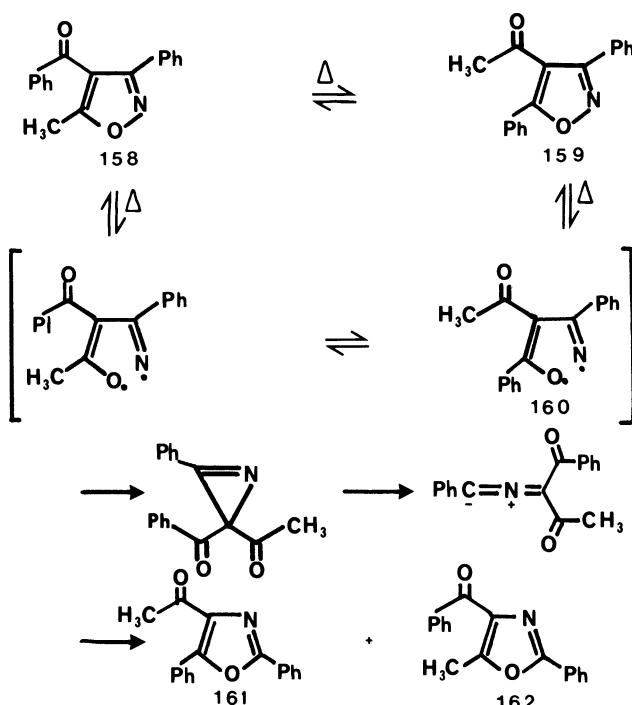
Photolysis of the pyrazole-4-carboxyaldehyde **169** has been found to afford imidazole **172**. This reaction is analogous to the isoxazole–oxazole photoisomerization discussed above. It is most likely that a 1,5-electrocyclic ring closure of iminonitrile imine **170** is responsible for imidazole formation.⁽¹²⁰⁾

5. Mechanisms for Cycloaddition Reactions of Nitrile Ylides

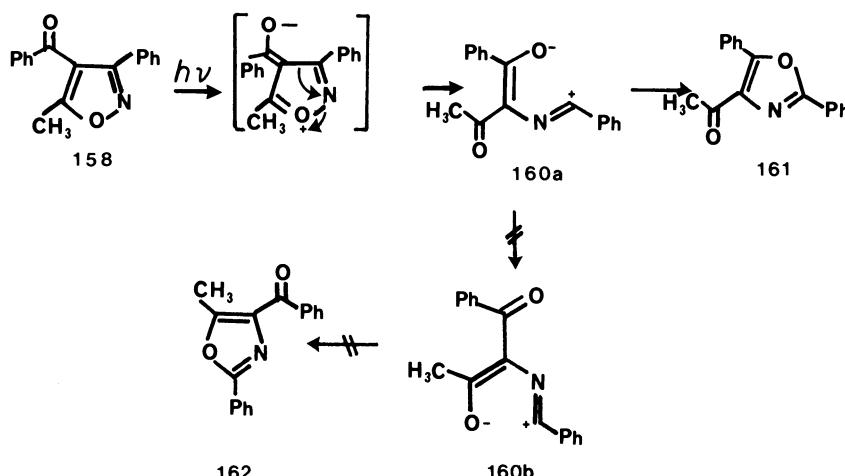
Nitrile ylides, generated from the photolysis of 2*H*-azirines, may be classified as nitrilium betaines,⁽¹²¹⁾ a class of 1,3-dipoles containing a central nitrogen atom and a π bond orthogonal to the 4π allyl system. As was



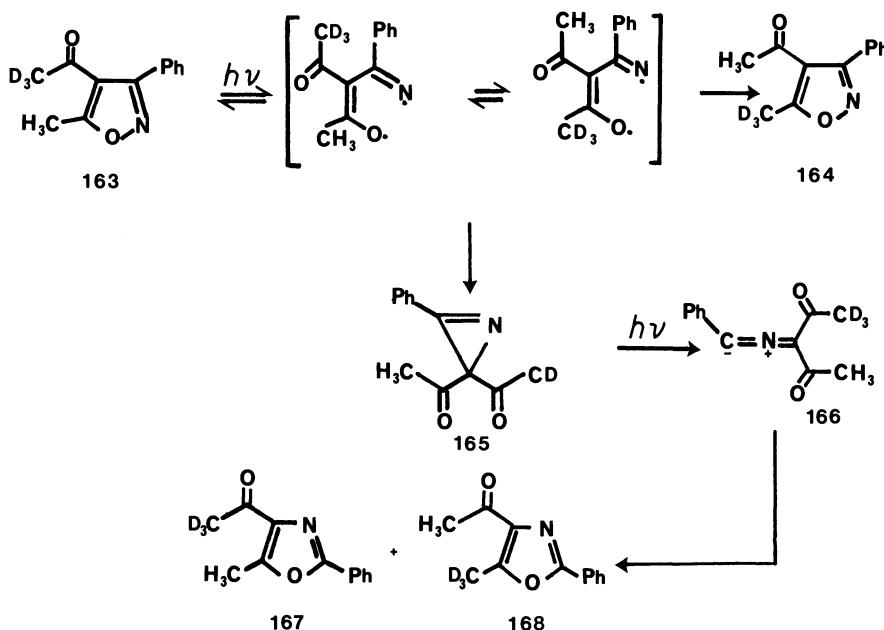
SCHEME 44



SCHEME 45

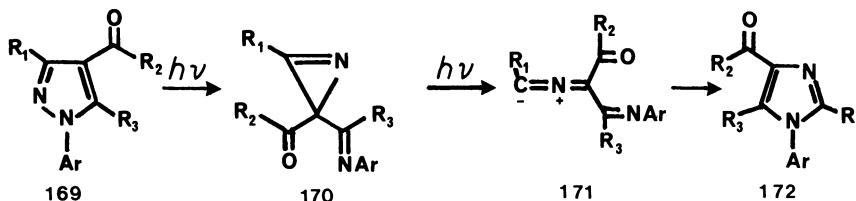


SCHEME 46

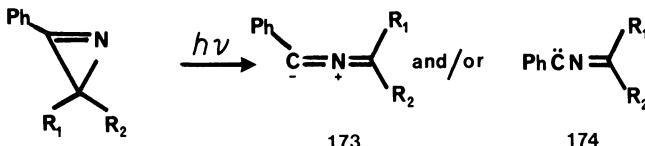


SCHEME 47

pointed out earlier, these species can be intercepted with a wide variety of dipolarophiles to form five-membered heterocyclic rings. Among the possible geometric forms of a nitrile ylide, a carbene structure (174) can be envisaged which makes a 1,1-cycloaddition of this 1,3-dipole conceivable. Huisgen has argued⁽¹²¹⁾ that the bent geometric form (174) of a nitrile ylide would be less stable than the linear form (173), since allyl resonance would be at a maximum with the linear arrangement. The bent form would have a lone pair of electrons in an orbital with some *s* character, but this was postulated to be of lesser importance.⁽¹²¹⁾ The extensive early literature dealing with nitrile ylide cycloadditions has generally been explained in terms of the linear arrangement



SCHEME 48

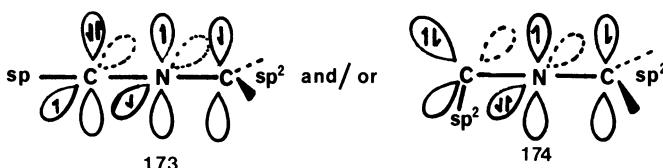


SCHEME 49

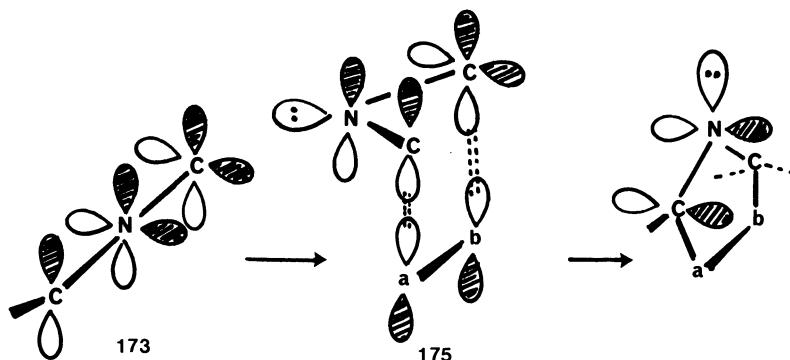
of this 1,3-dipole.⁽⁶³⁾ Thus, 1,3-dipolar cycloadditions of nitrile ylides have been suggested to proceed via a “two-plane” orientation complex in which the dipole and dipolarophile approach each other in parallel planes.⁽⁶³⁾ Formula 175 depicts the orientation complex involved in the addition of the linear nitrile ylide 173 with a dipolarophile. During the activation process, the linear bond system of the nitrile ylide must bend. This involves disruption of the orthogonal π bond at some modest energy costs but leaves the allyl anion π system undisturbed. The loss of π bond energy with 173 is partly compensated by a gain in energy resulting from rehybridization and accommodation of a lone pair of electrons in an orbital of high *s* character.

Another mechanism which could also account for the products obtained on dipolar cycloaddition of nitrile ylides with π bonds involves an initial 1,1-addition of the bent nitrile ylide (carbene form) with the dipolarophile to give a transient three-membered ring. This would be followed by a rapid intramolecular rearrangement to the five-membered heterocycle. This alternate possibility was discounted by Huisgen, however, who showed that three-membered rings are not primary products in the 1,3-dipolar additions leading to five-membered heterocycles with nitrilium betaines.⁽¹²²⁾

Recent *ab initio* LCAO-MO-SCF calculations by Salem,⁽¹²³⁾ Houk,^(124,125) and Devaquet⁽¹²⁶⁾ indicate that the geometry of the nitrile ylide is appreciably different from that suggested by Huisgen.⁽¹²¹⁾ Salem’s calculations indicate that the ring-opened intermediate should be capable of dual reactivity when it is intercepted by an added dipolarophile. The behavior of the system was predicted to be dependent on the geometry of the transient intermediate generated from the photolysis. Opening of the ring to an intermediate with

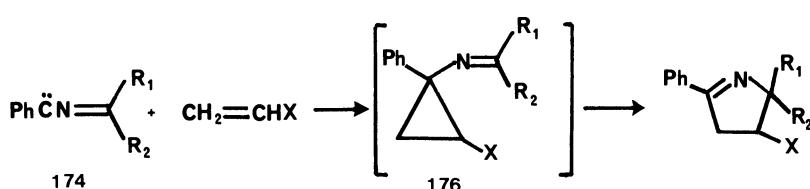


SCHEME 50



SCHEME 51

linear geometry will result in the formation of a 1,3-dipolar species having closed-shell zwitterionic character. Salem's calculations also indicate that if the ring is opened to give an intermediate with bent geometry, a diradical state with partial dipolar character will be obtained which may undergo reactions different from the linear species. According to Salem's calculations, the lowest-energy ground-state geometry of the nitrile ylide has a NCN angle of 156.7° and is ca. 18 kcal/mol (76 kJ/mol) more stable than the linear form. A similar conclusion was reached by Houk and Caramella.^(124,125) Their calculations show that the bent nitrile ylide geometry is favored over the linear, but otherwise optimized, geometry by 11.1 kcal/mol (46.6 kJ/mol). These findings indicate that the most stable form of a nitrile ylide resembles a bent allenyl anion rather than a linear propargyl anion. The HOMO and second LUMO of the bent ylide bear a strong resemblance to the HOMO and LUMO of a singlet carbene. It should be noted that the bent nitrile ylide geometry correctly rationalizes the regioselectivity encountered with the 1,3-dipolar cycloadditions of nitrile ylides with added dipolarophiles. Houk's calculations show that the bent nitrile ylide HOMO is heavily localized at C-1, but still resembles the normal three-orbital, four-electron π system pres-

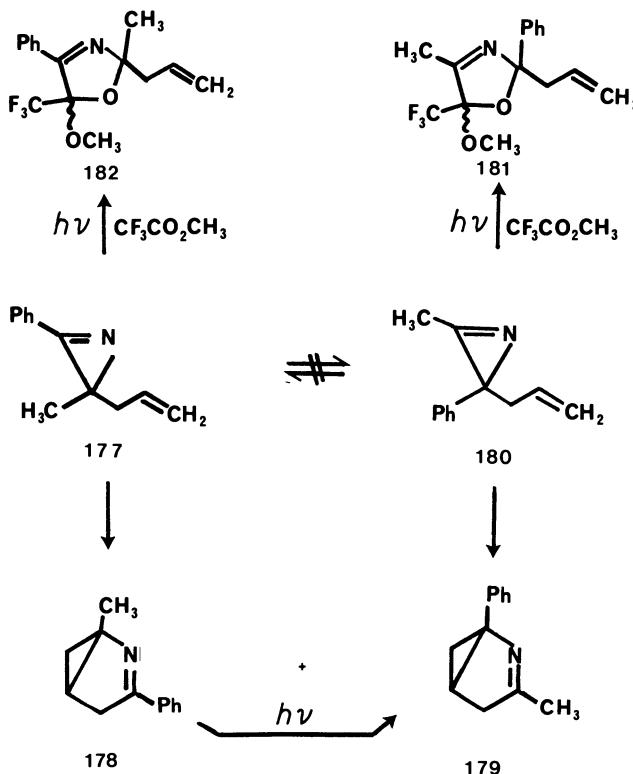


SCHEME 52

ent in other 1,3-dipoles so that concerted cycloadditions can still occur. As a consequence of the bent geometry, C-1 is the nucleophilic terminus of the nitrile ylide. According to the frontier orbital treatment of 1,3-dipolar cycloadditions,^(65,66) the relative reactivity of a given 1,3-dipole forward a series of dipolarophiles will be determined primarily by the extent of stabilization afforded the transition state by interaction of the frontier orbitals of the two reactants. When nitrile ylides are used as 1,3-dipoles, the dipole highest occupied (HO) and dipolarophile lowest unoccupied (LU) interactions will be of greatest importance in stabilizing the transition state. Regioselectivity will be controlled by union of the atoms with the largest coefficients in the dipole HO and LU. Using these generalizations, the regioselectivity of bimolecular nitrile ylide cycloadditions can readily be predicted. Protonation of the nitrile ylide is also known to occur at the C-1 carbon atom.⁽⁶⁷⁾ Thus, all the known reactions of nitrile ylides can be adequately accounted for in terms of a bent nitrile ylide.

5.1. The 1,1-Cycloaddition Process

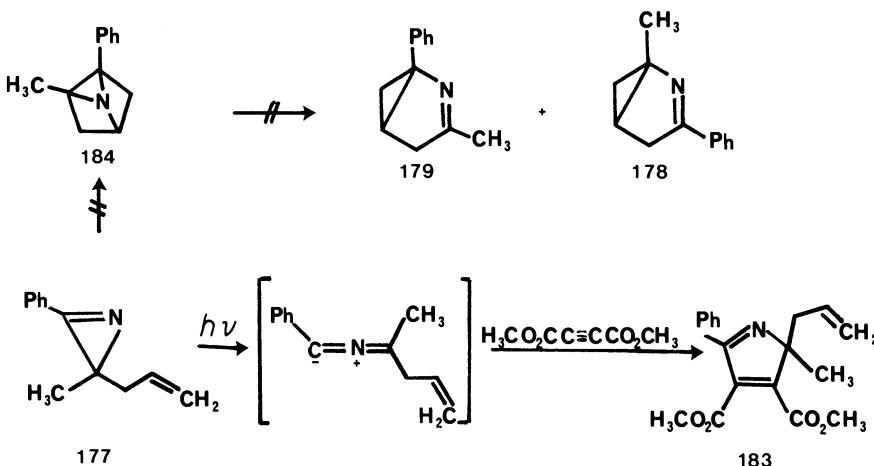
As was mentioned earlier, the HOMO and second LUMO of the bent nitrile ylide bear a strong resemblance to the HOMO and LUMO of a singlet carbene. Since carbenes are known to react readily with double bonds, a 1,1-cycloaddition reaction of nitrile ylides can be expected. Padwa and Carlsen uncovered the first example of such a process during an investigation of the photochemistry of a number of 2-allyl-substituted 2*H*-azirines.⁽¹²⁷⁾ When a thoroughly deaerated solution of 2-allyl-2-methyl-3-phenyl-2*H*-azirine (**177**) was irradiated in cyclohexane with light of wavelength > 280 nm for 15 min, an extremely rapid and clean conversion to 1-phenyl-3-methyl-2-azabicyclo[3.1.0]hex-2-ene (**179**) was observed. When the irradiation of **177** was carried out to 20% conversion, however, a 1:1 mixture of **179** and 1-methyl-3-phenyl-2-azabicyclo[3.1.0]hex-2-ene (**178**) was quantitatively isomerized to **179**. The photochemical behavior of the isomeric 2-allyl-2-phenyl-3-methyl-2*H*-azirine (**180**) afforded a quantitative yield of azabicyclohexene (**179**). A control experiment showed that **177** and **180** were not interconverted by a Cope reaction under the photolytic conditions. Photolysis of **180** in the presence of the very reactive dipolarophile, methyl trifluoroacetate, resulted in the trapping of a nitrile ylide and gave cycloadduct **181** in high yield. Under these conditions, the formation of **179**, which is produced in quantitative yield in the absence of a trapping agent, is entirely suppressed. Photocyclization of **177** with added methyl trifluoroacetate resulted in the formation of cycloadduct **182** in high yield. The isolation of **181** in the bimolecular trapping experiment eliminates a path by which **180** is partially isomerized to **177** which then rearranges **179** on further excitation. This possibility was initially



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considered to be reasonable since the extinction coefficient of **177** at 254 nm (ϵ 8700) is much larger than that of **180** (ϵ 220). It should be noted that no significant quantities of **178** were detected in a short-term irradiation of **180**. This is probably related to the fact that **178** possesses a much larger extinction coefficient than does **180** and is optically pumped to **179**, even at low conversions.

The formation of azabicyclohexenes **178** and **179** from the irradiation of azirine **177** clearly proceeds via a nitrile ylide intermediate since the formation of these compounds are entirely suppressed when the irradiation is carried out in the presence of an added dipolarophile. For example, when dimethyl acetylenedicarboxylate is used, cycloadduct **183** was the only product isolated. The fact that the photolysis of **177** produces a nitrile ylide intermediate which would be trapped by an added dipolarophile (i.e., as **183**) eliminates [2+2]-cycloaddition of the azirine C–N double bond with the olefin and subsequent rearrangement of a hypothetical azatricyclo[2.1.1.0^{2,5}]hexane intermediate

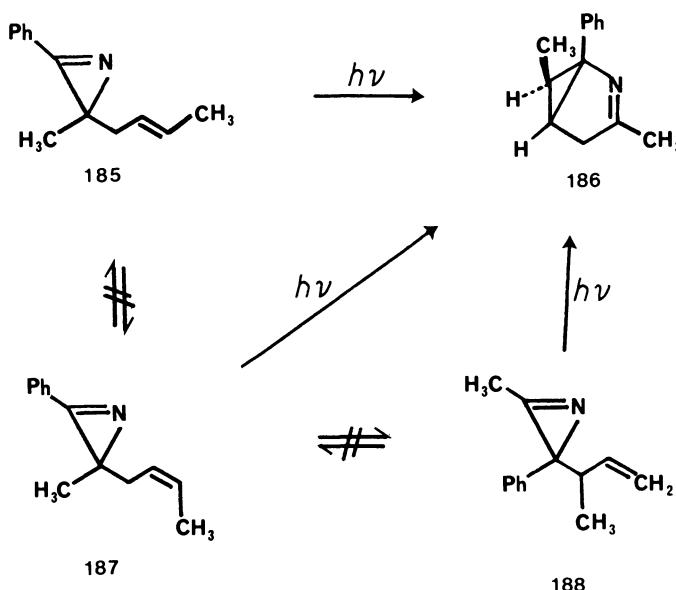


SCHEME 54

(184) as the mechanism for the formation of the azabicyclo[3.1.0]hex-2-ene system.

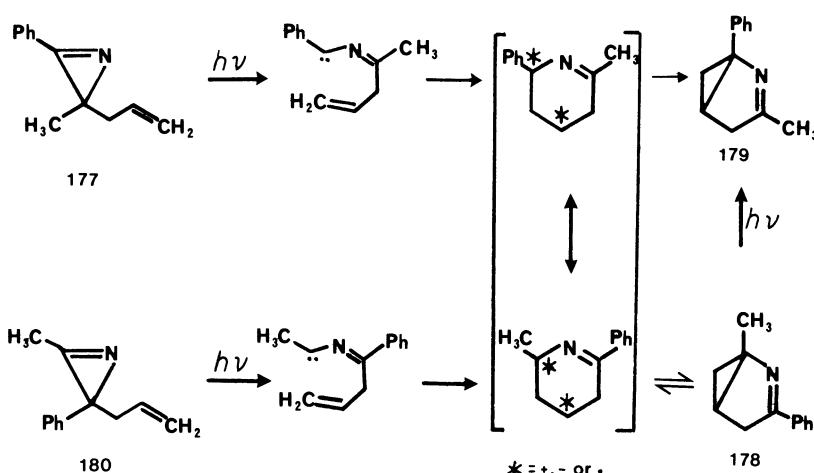
An unusual aspect of the intramolecular photocyclization of 2-allyl-substituted 2*H*-azirines was uncovered during a study of the photochemistry of (*E*)-2-(2-butenyl)-2-methyl-3-phenyl-2*H*-azirine (185). Irradiation of 185 in cyclohexane gave rise to one major product (> 95%) which was identified as endo-3,6-dimethyl-1-phenyl-2-azabicyclo[3.1.0]hex-2-ene (186). The formation of the thermodynamically less favored endo-isomer corresponds to a complete inversion of stereochemistry about the π system in the cycloaddition process. The only product obtained on irradiation of the isomeric *Z*-substituted 2*H*-azirine 187 was azabicyclohexene 186. Photoisomerization about the C–C double bond of starting azirine (185 or 187) did not occur during the course of the irradiation. Thus, azabicyclohexene 186 is the exclusive product obtained with both the (*E*) and (*Z*) isomers. Irradiation of 2-phenyl-2-(1-methallyl)-3-methyl-2*H*-azirine (188) in cyclohexane (100% conversion) also gave 186 as the exclusive photoproduct.

As was pointed out by Huisgen,⁽⁶³⁾ 1,3-dipolar additions generally proceed via a “two-plane” orientation complex in which the dipole and dipolarophile approach each other in parallel planes. Inspection of molecular models of the above 2-allyl substituted nitrile ylides indicates that the normal “two-plane orientation approach” of the nitrile ylide and the allyl π system is impossible as a result of the geometric restrictions imposed on the system. Consequently, the normal mode of 1,3-dipolar cycloaddition cannot occur here. The most reasonable mechanism to account for the cycloadditions observed with these



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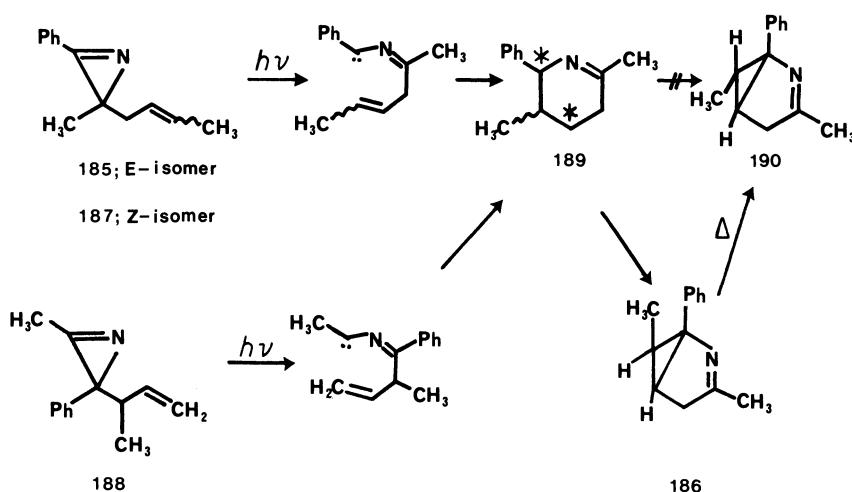
systems involves the reaction of a bent nitrile ylide intermediate (carbene like). Attack of the carbene carbon on the terminal position of the neighboring double bond generates a six-membered ring trimethylene intermediate. Collapse of this species results in the formation of the observed azabicyclohexene system. The photoconversion of the azabicyclicenes (i.e., **178** → **179**) has been rationalized in terms of a trimethylene derivative. It is particularly important to note that the above cycloaddition sequence proceeds in a non-concerted manner and bears a strong resemblance to the stepwise-diradical mechanism suggested by Firestone to account for bimolecular 1,3-dipolar cycloadditions.^(128,129) It is evident from the available data that unless the dipole and dipolarophile approach each other in parallel planes, an alternate nonconcerted mechanism for dipolar cycloadditions occurs. The possibility that other dipolar cycloadditions of nitrilium betaines occur via a stepwise process now merits serious attention. In fact, the cycloaddition of benzonitrile oxide to the arylidene double bond of 3-phenyl-4-arylideneisoxazol-5-ones has been proposed to proceed through the phenylnitrosocarbene form.⁽¹³⁰⁾ Since Padwa's original report of this phenomenon appeared,⁽¹²⁷⁾ a related intramolecular carbene-type of 1,1-cycloaddition of a nitrile imine has been reported by Garanti and co-workers.⁽¹³¹⁾



SCHEME 56

The above mechanism also accommodates the unusual stereochemical results observed with azirine **185**. As was pointed out earlier, the formation of the thermodynamically less favored *endo*-isomer **186** from **185** corresponds to a complete inversion of stereochemistry about the π system in the cycloaddition process. The stereochemical results have been rationalized by assuming that collapse of the trimethylene derivative **189** to the thermodynamically more favored *exo*-isomer **190** results in a severe torsional barrier on ring closure. Collapse of **189** to the thermodynamically less favored *endo*-isomer **186** moves the phenyl and methyl groups increasingly further apart and accounts for the formation of the less stable product. Supporting evidence for this rationale was obtained from the irradiation of the isomeric *Z*-2-butenyl-2*H*-azirine **188**. Photolysis of this azirine resulted in the quantitative formation of the same *endo*-azabicyclohexene (**186**) and is perfectly consistent with the preferred kinetic closure of intermediate **189**. The formation of **186** from 2*H*-azirine **188** also provides convincing support for this interpretation.

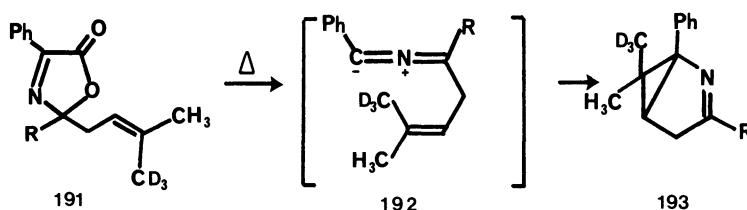
Fischer and Steglich were also able to generate an allyl-substituted nitrile ylide **192** by the thermal induced 1,3-dipolar cycloreversion reaction of 3-oxazolinone **191** with elimination of carbon dioxide.⁽¹³²⁾ The resulting ylide was found to undergo 1,1-cycloaddition to give 2-azabicyclo[3.1.0]hexene **193**. In this case the 1,1-cycloaddition of the thermally generated nitrile ylide proceeds with retention of configuration. That the nitrile ylide **192** is in fact generated in the thermolysis of **191** was demonstrated by trapping with dimethyl acetylenedicarboxylate.



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5.2. Summary of 1,1-Cycloaddition Mode

The results obtained to date suggest that there are two pathways by which nitrile ylides react with multiple π bonds. The most frequently encountered path involves a bimolecular “parallel-plane approach of addends” and can be considered to be an orbital-symmetry allowed [4+2]-concerted process. With this path, the relative reaction of dipolarophiles toward the nitrile ylide is controlled by the extent of stabilization afforded the transition state by interaction of the frontier orbitals of the two reactants. Electron-withdrawing substituents, which lower the dipolarophile LU energy, accelerate the reaction. The other path, which operates with the 2-allyl-substituted systems, occurs because the p orbitals of the olefinic group have been deliberately constrained to attack perpendicular to the nitrile ylide plane. Houk



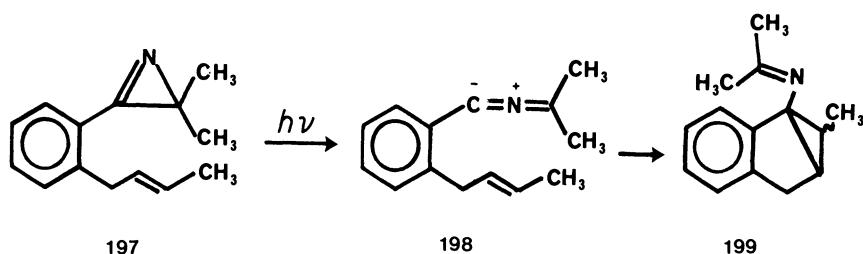
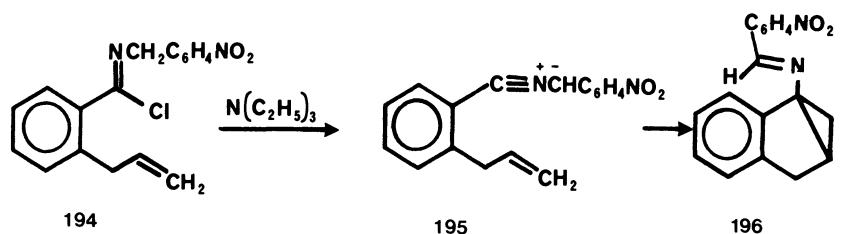
SCHEME 58

and Caramella have suggested that the 1,1-cycloaddition reaction is initiated by interaction of the terminal carbon of the olefin with the second LUMO of the nitrile ylide.⁽¹²⁵⁾ The second LUMO of the dipole is perpendicular to the ylide plane and presents a large vacancy at C₁ of the dipole for attack by the terminus of the neighboring double bond, without the possibility of simultaneous bonding at the C₃ carbon. In fact, the HOMO and second LUMO of the bent nitrile ylide bear a strong resemblance to the HOMO and LUMO of a singlet carbene. A factor which undoubtedly plays an important role in the intramolecular 1,1-cycloaddition reaction involves the interaction of the secondary orbitals of the dipole and dipolarophile. With nitrile ylides, the in-plane vacant orbital is of lower energy than the vacant π orbital. Consequently, stabilization of the transition state can be enhanced by interaction of this in-plane orbital with the dipolarophile HOMO orbital. For this to occur, a contortion away from the strictly parallel plane approach of the dipole and dipolarophile would be necessary. With the allyl-substituted 2*H*-azirines, the transition state actually involves a geometry where the *p* orbitals of the olefinic group have been deliberately constrained to attack perpendicular to the nitrile ylide plane. Thus, the 1,1-cycloaddition reaction involves appreciable interaction of both the in-plane and out-of-plane π -unoccupied orbitals of the dipole with the dipolarophile-filled orbitals. This secondary orbital interaction will significantly enhance the rate of the intramolecular 1,1-cycloaddition with unactivated olefins. Ordinary olefins react so sluggishly with nitrile ylides that their bimolecular rate constants cannot be measured. Clearly, there has been a marked enhancement of the rate of the intramolecular 1,1-cycloaddition. It should be noted, however, that while the secondary orbital effect is important, the relative reactivities of a series of π -substituted double bonds toward internal 1,1-cycloaddition is still controlled by the highest occupied molecular orbital of the nitrile ylide.⁽¹³³⁾

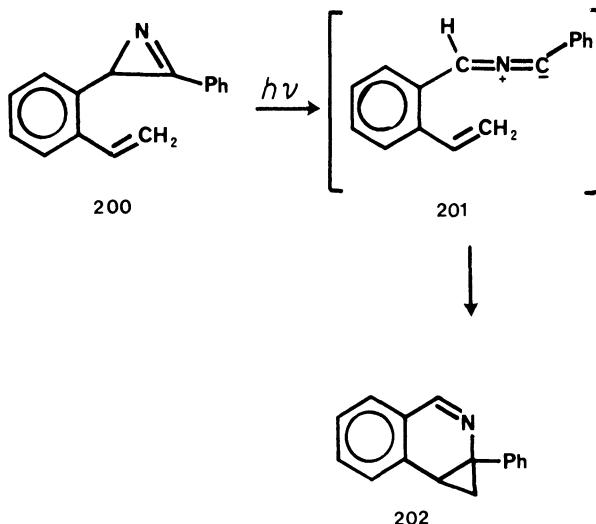
5.3. Other Examples of 1,1-Cycloaddition

Several additional examples in the literature demonstrate the generality of the 1,1-trapping of nitrile ylides.⁽¹³⁴⁻¹³⁶⁾ Thus, treatment of *o*-allyl-substituted imidoyl chloride **194** with triethylamine gave benzobicyclo[3.1.0]hex-2-ene **196**. Irradiation of the closely related methyl-substituted azirine system **197** produced a mixture of *endo*- and *exo*-benzobicyclohexenes **199** in quantitative yield.⁽¹³⁵⁾ No detectable quantities of the isomeric 1,3-dipolar adduct was observed in either system. In the case of **197**, the major product (*exo*-**199**) is the thermodynamically more favored *exo*-isomer.

Another system which was found to undergo smooth intramolecular 1,1-cycloaddition was 2*H*-azirine **200**.⁽¹³⁵⁾ The exclusive formation of a 1:1-cycloadduct with this system indicates that the nitrile ylide produced is capable



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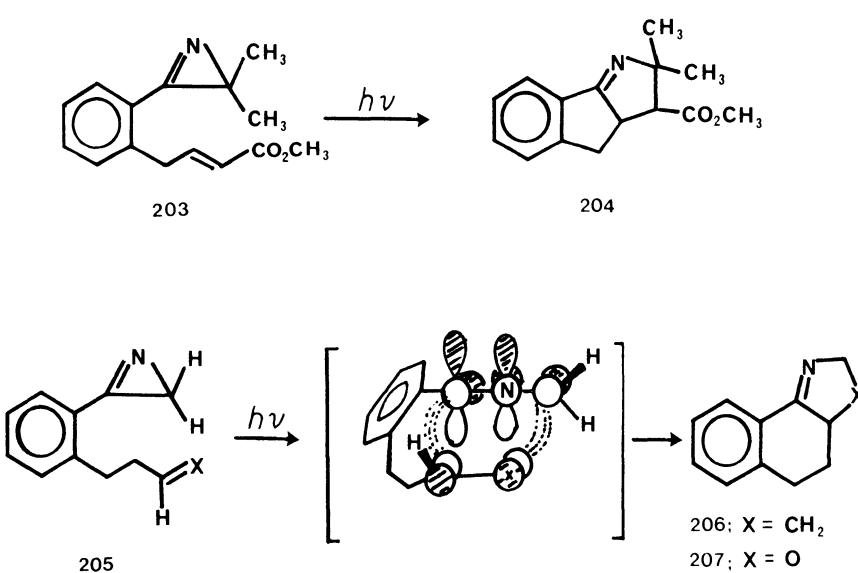
SCHEME 60

of undergoing carbene-type addition to a vinyl group just as long as there are no considerable bond distortions involved in the transition state for the intramolecular cycloaddition.

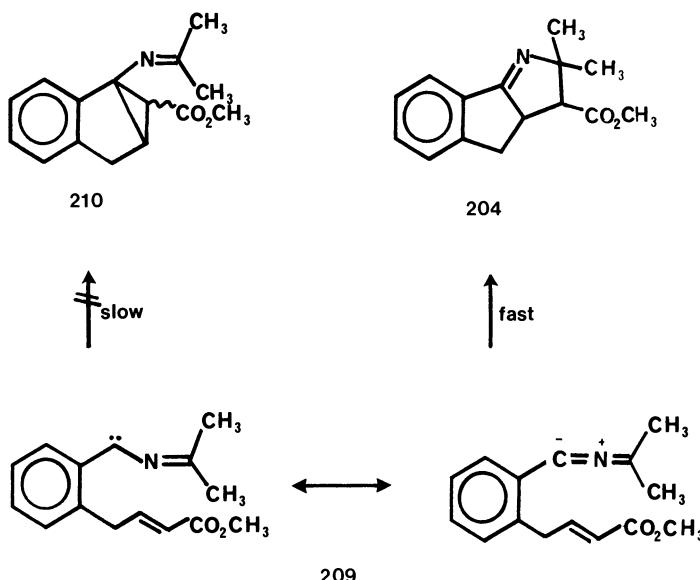
5.4. 1,1- and 1,3-Cycloaddition in Competition

In contrast to the above systems, irradiation of the 3-carbomethoxy-substituted 2*H*-azirine **230** resulted in an intramolecular 1,3-dipolar cycloaddition. Related intramolecular 1,3-cycloadducts were also isolated from the photolysis of azirines **205** and **207**. The transition state for cycloaddition with the nitrile ylides generated from the irradiation of azirines **205** and **207** allows easy attainment of the “parallel-plane approach” of the dipole and olefin and, consequently, intramolecular 1,3-dipolar cycloaddition readily occurs.

In contrast to the *o*-allylphenyl substituted 2*H*-azirines (**197** and **200**) which undergo 1,1-cycloaddition, azirine **203** cycloadds exclusively in the 1,3-sense. The formation of the 1,3-dipolar cycloadduct **204** is perfectly consistent with the principles of frontier MO theory. With this system the rate of internal 1,3-dipolar cycloaddition of the nitrile ylide derived from **203** proceeds much more rapidly than that of the ylides derived from **197** and **200**. This is to be expected since electron-withdrawing substituents on the double bond narrows



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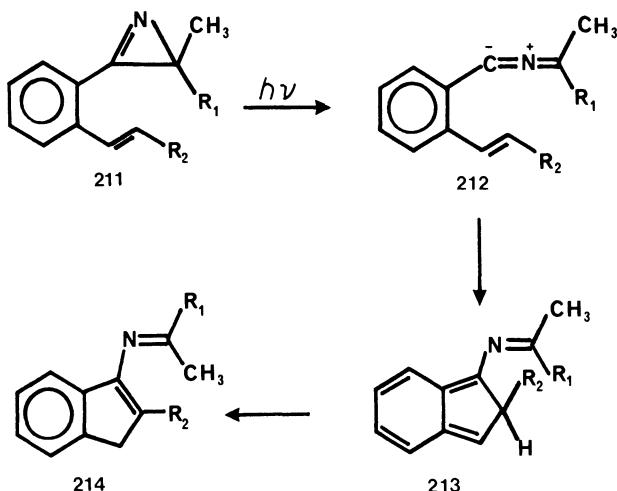


SCHEME 62

the HO dipole–LU dipolarophile gap. In order for the 1,3-dipolar cycloaddition of **209** to occur, a slight distortion away from the strictly parallel plane approach of the dipole and dipolarophile will be necessary. The interplay of entropy and enthalpy factors controls the rate-determining activation process. With azirine **203**, the enthalpy term is the dominant factor and the internal 1,3-dipolar cycloaddition process wins out.

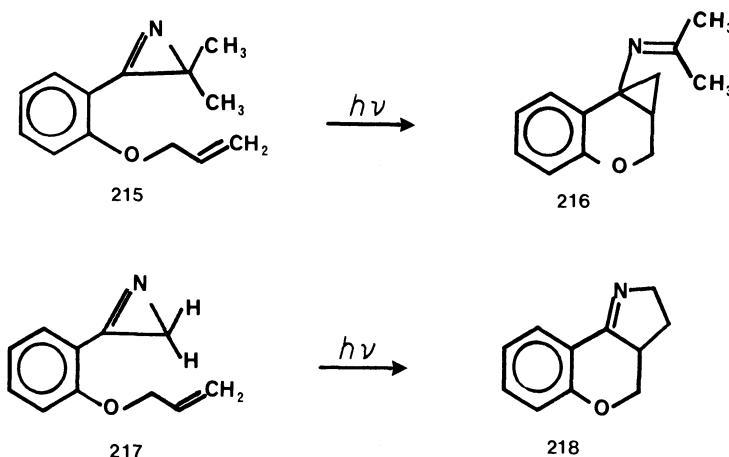
Attempts to prepare a benzobicyclo[2.1.0]pentane from the irradiation of a *o*-vinylphenyl-substituted 2*H*-azirine (**211**) resulted only in the isolation of an *N*-alkylideneindene-3-amine **214**. The formation of **214** has been suggested to proceed via a nitrile ylide intermediate (**212**) which undergoes dipolar electrocyclization followed by a 1,5-sigmatropic shift of the initially formed isoindene ring (**213**). This mechanism was supported by the trapping of nitrile ylide **212** with added dipolarophiles.

The intramolecular photocycloaddition reactions of a number of *o*-allyloxyphenyl-substituted 2*H*-azirines were also examined by Padwa's group.⁽¹³⁶⁾ These azirines were found to undergo intramolecular 1,1 and/or 1,3-cycloaddition depending on the substituent groups attached to the 2 position of the ring. Thus irradiation of the disubstituted 2*H*-azirine 215 resulted in the formation of a 1,1-cycloadduct whereas the related 2*H*-azirine 217 produced the 1,3-cycloadduct 218. The exclusive formation of a 1,3-dipolar cycloadduct from azirine 217 suggests that the mode of cycloaddition

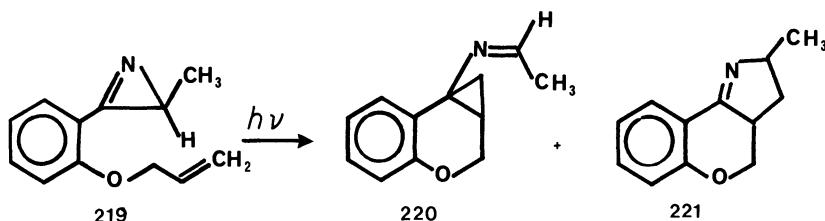


SCHEME 63

of the *o*-allyloxyphenyl system is markedly dependent on the nature of the substituent groups attached to C-2 of the nitrile ylide. This was further borne out by the irradiation of the monomethyl substituted 2*H*-azirine **219** which produced a 1:1 mixture of the 1,1- and 1,3-cycloadducts **220** and **221**. Another case where an oxyphenyl-substituted 2*H*-azirine was found to undergo both 1,1- and 1,3-dipolar cycloaddition was encountered in the photolysis of **222**.



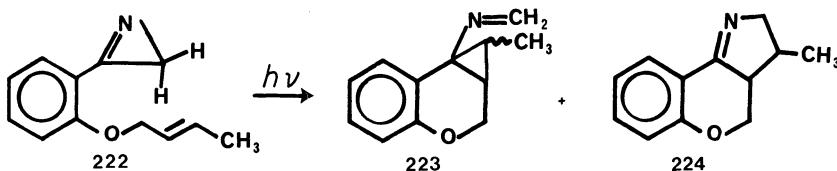
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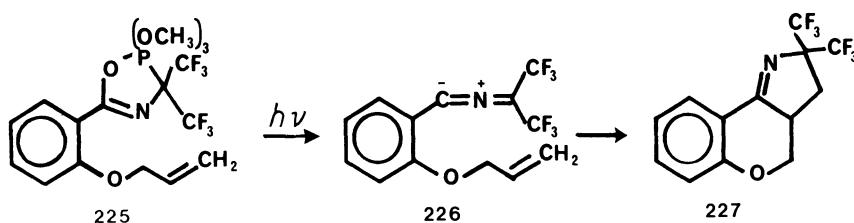
SCHEME 65

Irradiation of this compound afforded a 3:4 mixture of cycloadducts **223** and **224**. The isolation of cycloadduct **227** from the photolysis of **225** clearly establishes that the substituent effect encountered in these nitrile ylide cycloadditions is electronic rather than steric in nature. A steric effect would have been expected to produce a 1,1-cycloadduct since the trifluoromethyl group is larger than a methyl group.⁽¹³⁷⁾ This was clearly not the case.

Inspection of molecular models of these *o*-allyloxyphenyl-substituted nitrile ylides shows that two paths for cycloaddition are possible depending on the geometry of the nitrile ylide. The parallel plane approach of addends produces a 1,3-cycloadduct and occurs when the dipole possesses linear geometry. The alternate 1,1-cycloaddition process occurs when the dipole possesses bent geometry. Recent MINDO/3 calculations by Houk reveal that attachment of a phenyl group at the C₁ atom of the nitrile ylide significantly lowers the energy separation between the linear and bent forms by about 10–15 kcal/mol (42–63 KJ/mol).⁽¹²⁵⁾ The calculations indicate that the *o*-allyloxyphenyl-substituted nitrile ylide system will be less bent and easier to make linear than the corresponding parent system (i.e., HCNCH₂). As the dipole becomes less bent, the C₁N bond length will shorten and NC₃ will lengthen, as expected for going toward a propargyl-type structure. Since the energy difference between the nonplanar bent and linear forms is quite small with these *o*-oxyallylphenyl-substituted nitrile ylides, the preferred mode of approach is strongly dependent on the substituent groups present on the nitrile

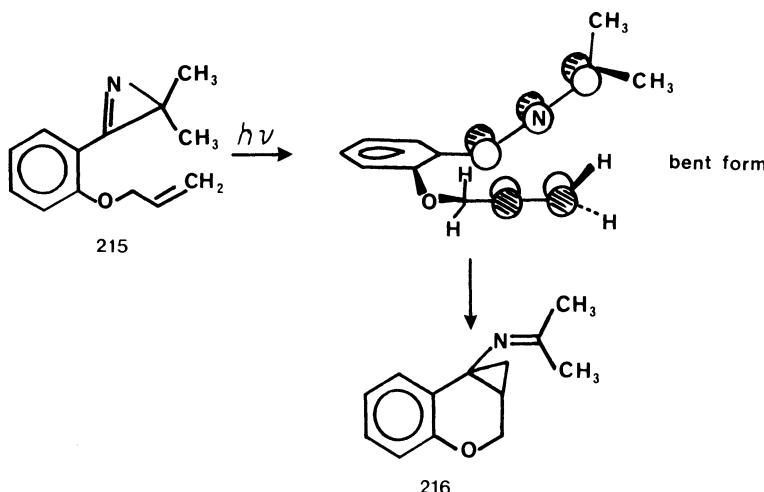


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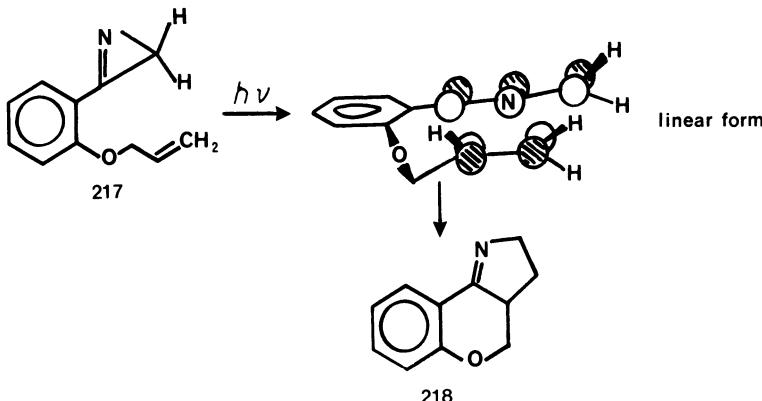


SCHEME 67

ylide. The nitrile ylide species becomes more carbene-like as methyl or electron donor groups are added and is more likely to undergo the 1,1-cycloaddition reaction. Placing electron-withdrawing groups at C_3 (i.e., H, CF_3 , $C_6H_4NO_2$) favors linearization of the nitrile ylide and promotes the 1,3-cycloaddition. The results show that when the energy difference between the nonplanar bent and linear forms is small, substituent effects can play an extremely important role in determining the course of the intramolecular cycloaddition reactions of nitrile ylides. The formation of a mixture of 1,1 and 1,3-cycloadducts from the irradiation of **219** has been attributed to the fact that the energy levels of the bent and linear forms must lie very close to each other.⁽¹³⁶⁾ The isolation of both 1,1- and 1,3-cycloadducts from the irradiation of **222** is related to the fact that the methyl substituent on the double bond diminishes the rate of 1,3-dipolar cycloaddition and enhances the rate of the 1,1-cycloaddition.



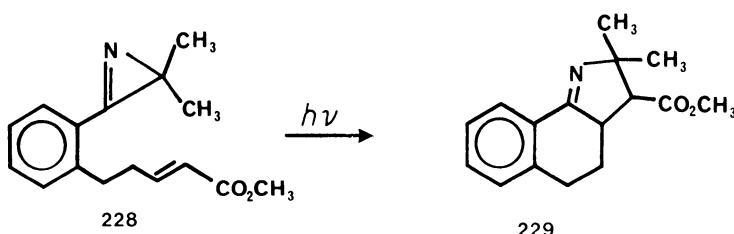
SCHEME 68



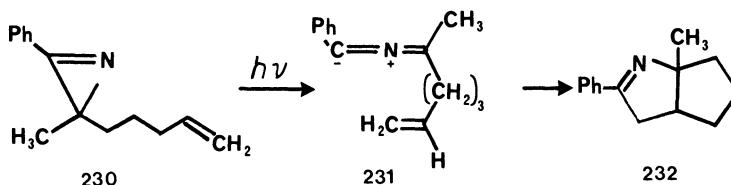
SCHEME 69

The exclusive formation of a 1,3-dipolar cycloadduct **229** from the irradiation of azirine **228** has been attributed to a significant lowering of the activation energy associated with the 1,3-cycloaddition reaction and to a substantial increase in the activation energy for the 1,1-cycloaddition process.⁽¹³⁶⁾

The isolation of 1,1- and 1,3-cycloadducts from the photolysis of *2H*-azirines bearing unsaturated π bonds clearly indicates that the spatial relationship of the dipole and dipolarophile plays an important role in controlling the intramolecular dipolar cycloaddition reactions of nitrile ylides. The primary spatial requirement for intramolecular 1,3-dipolar cycloaddition is that the distance between the two reacting centers should be short enough so that effective three-center overlap of the 1,3-dipole with the dipolarophile occurs. For concerted 1,3-dipolar cycloaddition to take place, the atoms of the dipolarophile should be arranged in such a way as to allow their *p*-orbitals to lie in a plane parallel to the plane of the nitrile ylide. This can happen when



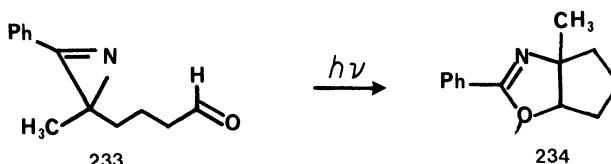
SCHEME 70



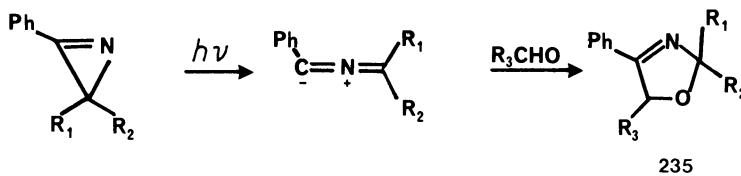
SCHEME 71

the methylene chain between the azirine ring and the alkene end is extended to three carbon atoms. For example, irradiation of azirine **230** gives Δ^1 -pyrrolidine **232** in quantitative yield.⁽¹³⁸⁾ In this case the methylene chain is sufficiently long to allow the dipole and olefinic portions to approach each other in parallel planes.

The exclusive orientation observed in this reaction is unusual and cannot be adequately accounted for on the basis of frontier orbital theory. A similar inconsistency was also found on irradiation of azirine **233**. The orientation of the cycloaddition reaction of aldehyde **233** proceeds in an alternate regiochemical sense from that observed with related bimolecular nitrile ylide-aldehyde cycloadditions where one obtains only Δ^3 -oxazolines **235**.^(69,70) In a somewhat related case, Schmid and co-workers reported on the photoisomerization of dihydroisoxazole **236** to dihydroxazole **239**.⁽⁷²⁾ The reaction was proposed to proceed via a transient azirine (i.e., **237**). This intermediate was not isolated, but was suggested to undergo rapid ring opening to nitrile ylide **238** which cyclized to the observed photoproduct via an intramolecular 1,3-dipolar cycloaddition. The intramolecular cycloaddition reactions of azirines **230** and **233** clearly indicate that geometrical factors can force the cycloaddition reaction to occur in a manner opposite to that normally encountered. The inversion of regiospecificity must be related to steric effects which destabilize the transition states for formation of the alternate bridged structures. Similar "orientation-inversions" have been reported with a number of other 1,3-dipoles which undergo intramolecular dipolar cycloadditions.⁽¹³⁹⁻¹⁴²⁾



SCHEME 72



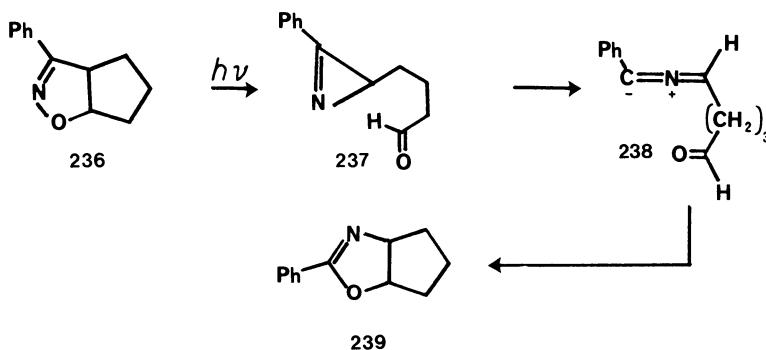
SCHEME 73

All of the reactions discussed above have involved the photocycloadditions of 2*H*-azirines with multiple π bonds. These studies have rigorously established nitrile ylides as useful intermediates in a variety of synthetic applications. Some recent work in the literature has shown that the photolysis of certain 2*H*-azirines can lead to new and interesting photochemistry.

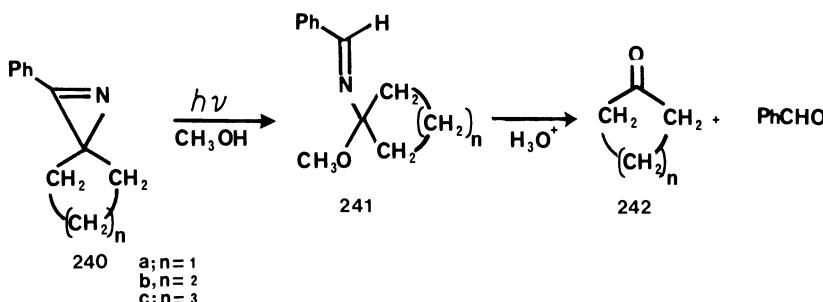
A new synthesis of cycloalkanones was devised and is based upon the photolysis of spiroazirines in alcohol followed by aqueous hydrolysis.⁽¹⁴³⁾ Irradiation of spiroazirine **240** in methanol resulted in the quantitative formation of imine **241**. Clean conversion to benzaldehyde and the corresponding cycloalkanone (**242**) was accomplished by treating the photoproduct with a 10% aqueous hydrochloric acid solution.

6. Fragmentation Reactions

In contrast to the above findings, irradiation of 2-phenyl-1-aza-spiro[2.2]pent-1-ene (**243**) in methanol resulted in a Griffin-type fragmentation⁽¹⁴⁴⁾ and produced ethylene and 2-phenylazirinylidene (**244**).⁽¹⁴⁵⁾ Three-membered rings are known to undergo [3 \rightarrow 2+1]-cycloelimination on

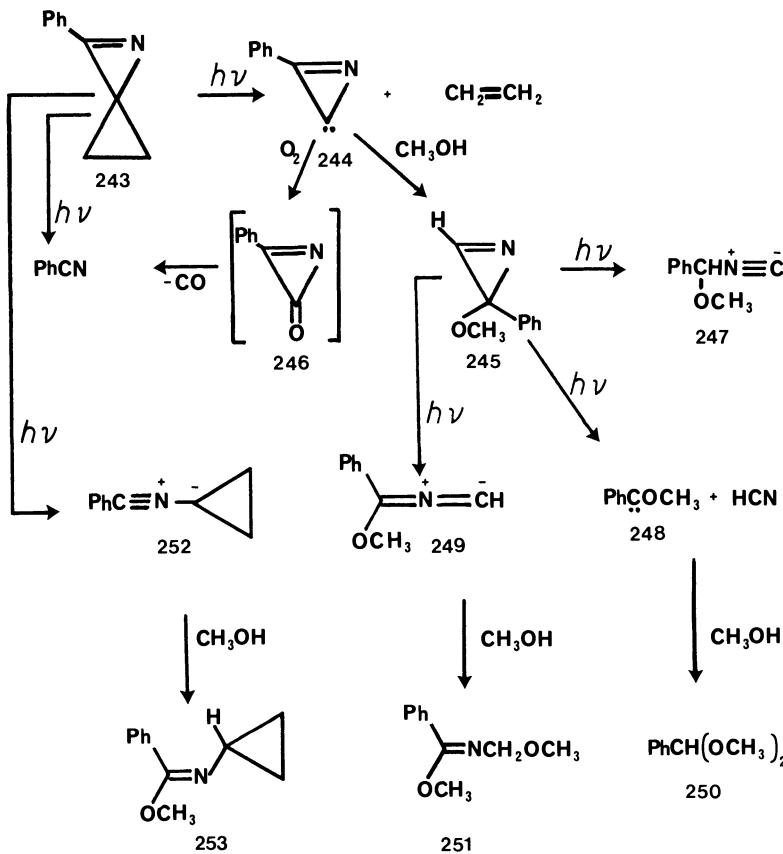


SCHEME 74

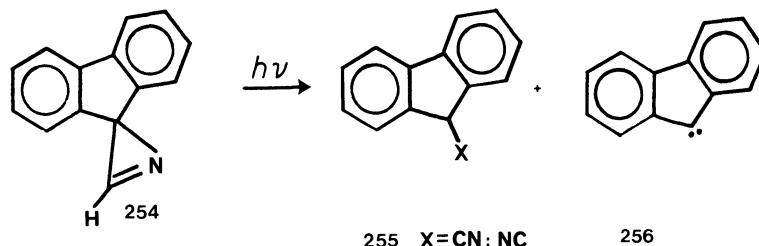


SCHEME 75

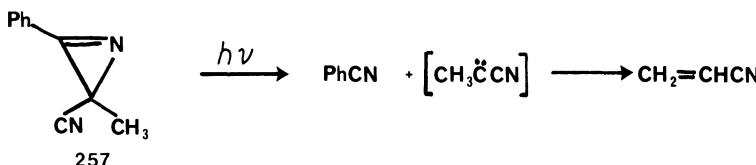
irradiation.^(144,146) For example, cyclopropane has been photolyzed in the vapor phase and gives methylene and ethylene⁽¹⁴⁷⁾ while photolysis of benzylcyclopropane leads to extensive fragmentation⁽¹⁴⁸⁾ and produces a number of hydrocarbons including ethylene and benzylcarbene. A comprehensive review of the generation of carbenes by photochemical cycloelimination from cyclopropanes has appeared.⁽¹⁴⁹⁾ The formation of the major products produced from the irradiation of spiroazirine **243** has been attributed to an initial photocycloelimination step.⁽¹⁴⁵⁾ This photocycloelimination generates ethylene and the extremely novel carbene, 2-phenylazirinylidene (**244**) which is subsequently trapped by methanol to give azirine **245**. 2-Phenylazirinylidene (**244**), by analogy with diphenylcyclopropenylidene,⁽¹⁵⁰⁾ is a carbene whose normal electrophilicity is suppressed as a result of conjugation of the double bond electrons of the azirine ring with the vacant *p*-orbital of the carbene. When the irradiation of **243** is carried out in the presence of oxygen, benzonitrile and carbon monoxide are formed. In the absence of oxygen, an extremely small quantity of benzonitrile is produced and is presumably derived from **243** by competitive cycloelimination. The formation of benzonitrile has been attributed to the intermediacy of 2-phenylazirinone **246** as a transient intermediate. Hassner and Taylor have previously shown that azirinones are unstable and readily lose carbon monoxide to form nitriles⁽¹⁵¹⁾ thereby providing good analogy for this reaction. On further photolysis, azirine **245** is converted into isocyanide **247**, phenylmethoxy carbene **248**, and nitrile ylide **249**. Both the carbene **248** and the 1,3-dipole were trapped with methanol to give **250** and **251**, respectively. Hafner and Bauer have reported that the related spiro-[2*H*-azirine-2,9¹-fluorene] (**254**) leads to a mixture of 9-cyano and 9-isocyanofluorene on photolysis.⁽¹⁵²⁾ These workers also found that **254** undergoes loss of HCN and generates 9-fluorenylidene **256**, thereby providing good precedent for the transformations observed with azirine **245**.



SCHEME 76



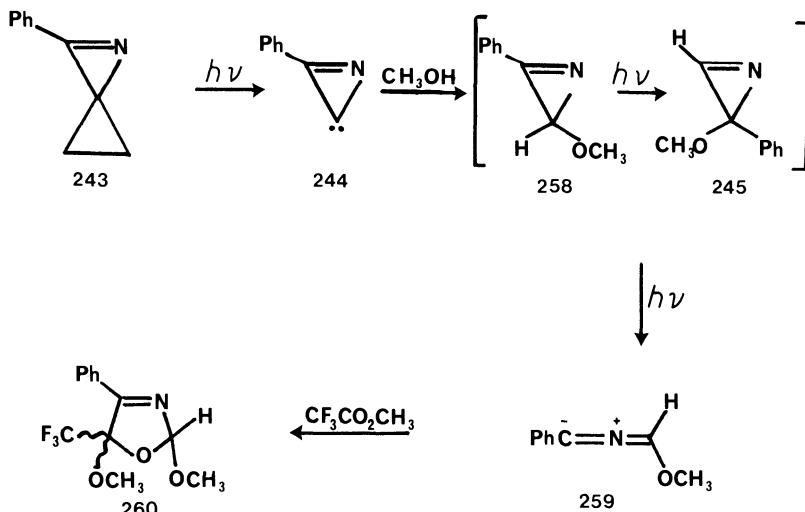
SCHEME 77



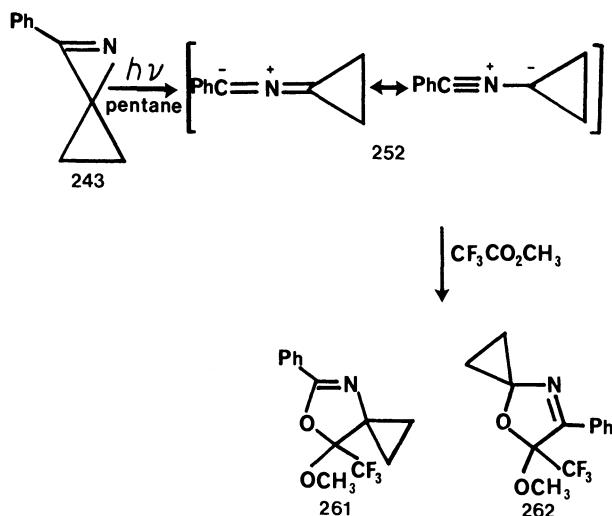
SCHEME 78

A similar fragmentation of a 2*H*-azirine has been reported by Shechter and Magee, who found that the irradiation of 2-cyano-2-methyl-3-phenyl-2*H*-azirine (**257**) gave benzonitrile and acrylonitrile. These two products are derived from carbenic collapse of **257** and hydrogen migration in the methylcyanocarbene generated.⁽¹⁵³⁾

A most unusual result was encountered when the irradiation of (243) was carried out in pentane in the presence of both methanol and methyl trifluoroacetate (excess).⁽¹⁴⁵⁾ Under these conditions, a mixture of the two stereoisomers of 3-oxazoline (260) were the only cycloadducts observed. This result suggests that 2-phenylazirinylidene (244) reacts with methanol to give mainly azirine 258 which is subsequently converted to nitrile ylide 259 (and thus cycloadduct 260) on further irradiation. The formation of 245 has been explained in terms of a photoinduced methoxy migration of 258 which com-



SCHEME 79

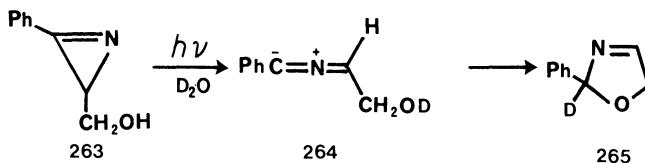


SCHEME 80

petes with C–C bond cleavage of the azirine ring. Ciabattoni and Cabell⁽¹⁵⁴⁾ have previously reported that 2-chloro-2*H*-azirines undergo ready isomerization at room temperature via a 2*π*-electron azacyclopropenyl cation. A similar mechanism would rationalize the apparent photoconversion of azirines **258** and **245**. The results obtained with this spiro azirine system indicate that cycloelimination of ethylene from **243** is much more efficient than C–C bond scission of the azirine ring. Undoubtedly, the stability of the aromatic carbene **244** contributes to this mode of cleavage.

6.1 Competitive Involvement of Ylide Formation

The formation of small quantities of methyl *N*-cyclopropylbenzimidate (**253**) from the irradiation of azirine **243** in methanol has been formulated as proceeding via nitrile ylide **252** which undergoes subsequent addition of methanol. The trapping of this ylide with methanol occurs in a different sense from that observed with most other nitrile ylides. The isolation of **253** implies that the largest HO coefficient of nitrile ylide **252** rests on the cyclopropyl carbon atom. The reluctance to develop a positive charge on the cyclopropyl carbon atom presumably contributes to this reversal in regioselectivity. The major cycloadduct **261** obtained from carrying out the irradiation of azirine **243** in pentane in the presence of methyltrifluoroacetate corresponds to the



SCHEME 81

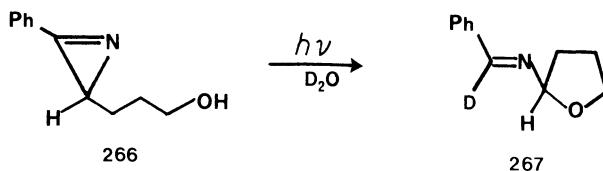
trapping of the nitrile ylide **252** in the reverse fashion from that normally observed.

The formation of oxazoline **265** from the irradiation of azirine **263** has been formulated as proceeding via a nitrile ylide intermediate **264** which transfers a proton from the neighboring hydroxyl group and then collapses to the observed product.⁽¹⁴⁵⁾ Support for the nitrile ylide intermediate was provided by the irradiation of **263** in benzene which had been saturated with D₂O. A single deuterium atom was incorporated at the 2-position of the oxazoline ring, as expected for an intermediate corresponding to **264** in this reaction. The complete absence of the isomeric *N*-benzylidene epoxide would suggest that the zwitterion produced on transfer of the proton from the nitrile ylide prefers to collapse to a five-membered rather than a three-membered ring.

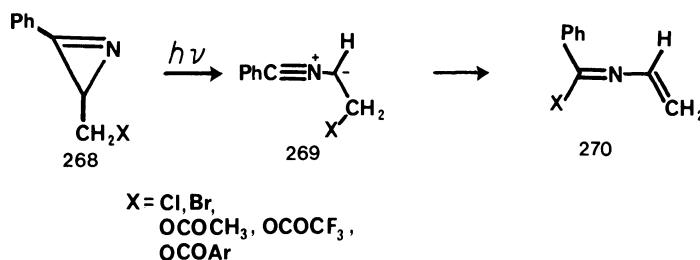
Photolysis of the hydroxyazirine with two additional methylene units afforded furanamine **267** as the only product. The formation of **267** was also explained in terms of an internal trapping of a transient nitrile ylide.⁽¹⁴⁵⁾

7. Group Migration Reactions

Irradiation of a series of hydroxymethyl-2*H*-azirine derivatives **268** which contain good leaving groups was found to give *N*-vinylimines **270** via a novel 1,4-substituent shift.⁽¹⁵⁵⁾ The results indicate that the migrating substituent

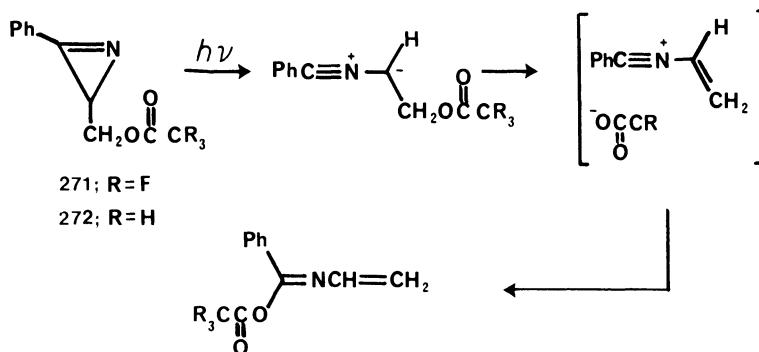


SCHEME 82



(X) must be a reasonably good leaving group in order for the rearrangement to occur. Irradiation of a nitrile ylide intermediate **269** in these reactions was demonstrated by trapping experiments.

The observation that the rearrangement of the nitrile ylide derived from 3-phenyl-2-trifluoroacetoxyethyl-2*H*-azirine **271** proceeds at a faster rate (200 times) than that of the ylide derived from 3-phenyl-2-acetoxyethyl-2*H*-azirine **272** provides support for the intermediacy of an ion pair in the rearrangement of these hydroxymethyl-2*H*-azirine derivatives. The rate of rearrangement of a series of substituted 3-phenyl-2*H*-azirine-2-methanolbenzoate derivatives were also studied.⁽¹⁵⁶⁾ Electron-withdrawing substituents in the *para*-position were found to facilitate the rearrangement while electron-donating groups retard the 1,4-substituent shift. Both the sign and magnitude of the reaction constant ($\rho = +2.15$) indicates that the transition state for the rearrangement has substantial negative charge development. Stern–Volmer treatment of the reaction rates clearly demonstrates that the rate of the rearrangement is directly related to leaving group ability and that the mi-



grating substituent must be a reasonably good leaving group in order for the reaction to occur.

In conclusion, the photochemical reactions of the 2*H*-azirine ring have been summarized. The photocycloaddition behavior of a large number of azirines have been described and general outlines and potential analogies for these reactions noted. Significant progress has been made toward understanding the factors which determine the photochemical behavior in a given system. Further work will be needed to clarify the mechanistic features of some of the systems.

ACKNOWLEDGMENTS

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Photoremovable Protecting Groups

Roger W. Binkley and Thomas W. Flechtner

1. Introduction

Selective reaction in molecules which contain more than a single functional group is an essential element in nearly all organic synthesis. Achieving this selectivity can be a challenging problem in reactions of compounds which contain a number of functional groups, particularly if those functional groups are all of the same type (e.g., carbohydrates). Perhaps the most common method for obtaining selective reaction is through the use of protecting groups. One indication of the importance of these groups is the continuing rise in the number of new protecting groups described each year. At present this number appears to be doubling every decade.⁽¹⁾

The effectiveness of a protecting group is usually judged by how well it satisfies a set of well-established criteria.^(1,2) These criteria may be summarized in the following way. A protecting group should be (a) easily introduced in high yield using readily available reagents; (b) capable of being removed in high yield from the molecule being protected; (c) stable throughout the reaction sequence; (d) easily separated from the protected molecule following deprotection. A desirable but less essential criterion is that introduction of a protecting group should not create a new chiral center in the molecule being protected.

It is possible to categorize protecting groups in a number of different ways. The common feature which brings together the groups discussed here

is that they can be removed from a molecule by photolysis. Significant use of photochemical reaction for protecting group removal is a relatively recent phenomenon. Its importance is increasing rapidly because it adds a new dimension to the protection/deprotection process; that is, photochemical reaction allows a set of potentially valuable protecting groups, ones which meet the established criteria except that they cannot be easily removed, to realize their potential because they can be removed by photolysis. Also, since photochemical reactions can be conducted under quite mild reaction conditions, photolysis can be a nondestructive deprotection process even for relatively unstable molecules.

The majority of reports of the use of photochemically reactive protecting groups are concerned with highly functionalized natural products. A number

Table 1. Standard Abbreviations Used in This Chapter

Me	Methyl
Bn	Benzyl
Ph	Phenyl
Tr	Triphenylmethyl
Ts	<i>p</i> -Toluenesulfonyloxy
Tf	Trifluoromethanesulfonyloxy
Ac	Acetyl
ONB	<i>o</i> -Nitrobenzyl
NVOC	6-Nitroveratryloxycarbonyl
NBOC	2-Nitrobenzyloxycarbonyl
DNBOC	2,2'-Dinitrodiphenylmethoxycarbonyl
Ddz	α,α -Dimethyl-3,5-dimethoxybenzyloxycarbonyl
Cbz	Benzylloxycarbonyl
Boc	<i>t</i> -Butyloxycarbonyl
Dms	5-Dimethylamino-1-naphthalenesulfonyl
(P)	Polymer chain
Ala	Alanine
Arg	Argine
Cys	Cysteine
Glu	Glutamic acid
Gly	Glycine
His	Histidine
Ile	Isoleucine
Leu	Leucine
Lys	Lysine
Met	Methionine
Phe	Phenylalanine
Pro	Proline
Ser	Serine
Trp	Tryptophan
Tyr	Tyrosine
Val	Valine

of standard abbreviations exist which make description of these systems more convenient.⁽³⁾ Those abbreviations used in this review are listed in Table 1.

Finally, it should be noted that four reviews containing information on photoremovable protecting groups have been published.⁽⁴⁻⁷⁾ Two of these^(5,6) are devoted exclusively to photochemical reactions of protecting groups while the others^(4,7) are broader in scope but contain pertinent sections. The present review is distinguished from earlier ones in that it is a comprehensive treatment of the subject which includes discussion of reaction mechanisms as well as advantages and disadvantages of particular protecting groups.

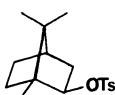
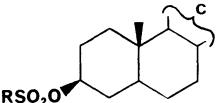
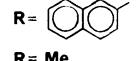
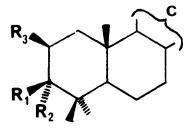
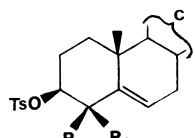
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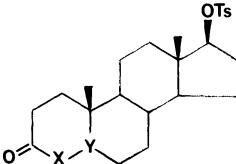
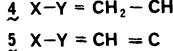
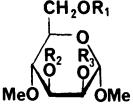
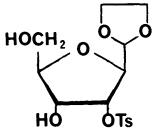
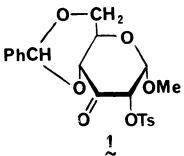
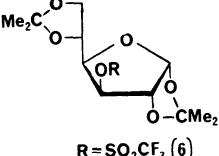
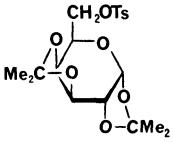
2.1. Sulfonic Acid Esters

Esters of sulfonic acids are one of the most frequently used of the photoremovable, hydroxyl protecting groups. Most of the synthetic applications of these esters as protecting groups involve carbohydrates since hydroxyl protection is an essential process of these polyhydroxy compounds. Protecting by the sulfonyloxy (usually *p*-toluenesulfonyloxy) group is particularly attractive in carbohydrate synthesis because sulfonate displacement in these highly functionalized molecules typically requires vigorous reaction conditions; consequently, the probability of an undesired solvolysis or other displacement of a sulfonate anion during a synthetic step is quite low. Even though sulfonyloxy group protection has been used most often for carbohydrates, irradiation of several sulfonate esters derived from steroids as well as a few derived from simple organic molecules has been reported (Table 2). Photolyses of these noncarbohydrate systems has been concerned primarily with the investigation of the mechanism of the photochemical process.

Current understanding of the mechanism of the photochemical reaction of sulfonic acid esters arises from the extensive investigations of Pète, Portella, and co-workers⁽⁸⁻¹⁰⁾ and from the work of Izawa and Kuromiya.⁽¹¹⁾ The findings from these two research groups indicate that reaction occurs from an excited singlet state. The quantum yield for alcohol formation ranges from 0.02 to 0.07 and depends upon the ester being irradiated and the reaction conditions. The formation of benzene (and biphenyl) from irradiation of benzene sulfonates⁽¹¹⁾ and toluene from *p*-toluenesulfonates^(10,11) argues in favor of a homolytic carbon-sulfur bond cleavage (Scheme 1). This fragmentation is thought to be followed by loss of sulfur dioxide to produce an alkoxy radical, although alkoxy radical formation has not been demonstrated. Even though initial homolysis of the sulfur-oxygen bond (Scheme 1) is an *a priori* possibility, this fragmentation is not thought to be the first bond-breaking process because such a cleavage is believed to be energetically unfavorable.^(10,11)

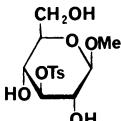
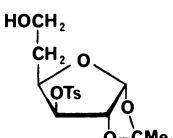
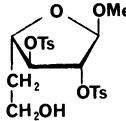
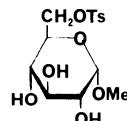
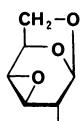
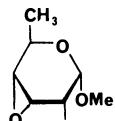
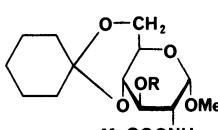
Table 2. Photochemical Deprotection of Alcohols Protected as Sulfonic Acid Esters

Protected compound ^a	Percent yield of deprotected alcohol	Reference
$\text{C}_6\text{H}_{11}\text{OTs}$	43	8,9
	78	10
PhSO_2OMe	b	11
	83	8,10
		
$\text{R} = p\text{-MeC}_6\text{H}_4$	95	9,10
$\text{R} = \text{Ph}$	75	9,10
$\text{R} = p\text{-MeOC}_6\text{H}_4$	80	9
	82	10
	95	10
$\text{R} = \text{Me}$	0	10
		
$\text{R}_1 = \text{OTs}, \text{R}_2 = \text{R}_3 = \text{H}$	85	8
	83	10
$\text{R}_1 = \text{R}_3 = \text{H}, \text{R}_2 = \text{OTs}$	70	8
$\text{R}_1 = \text{R}_2 = \text{H}, \text{R}_3 = \text{OTs}$	50	8,10
		
$\text{R}_1 = \text{R}_2 = \text{H}$	40	8,10
$\text{R}_1 = \text{R}_2 = \text{Me}$	40	8,10

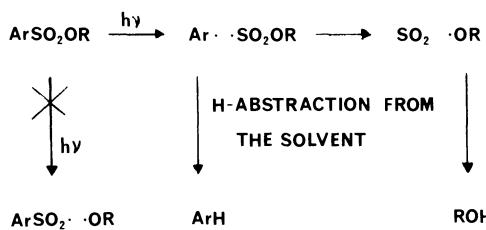
Protected compound ^a	Percent yield of deprotected alcohol	Reference
	0	8
	0	8
		
$R_1 = R_2 = Me, R_3 = Ts$	87	12
$R_1 = H, R_2 = Me, R_3 = Ts$	62	12
$R_1 = Me, R_2 = R_3 = Ts$	61	13
	70	14
	0	15
	0	16
$R = SO_2CF_3$ (9)	0	16
$R = Ts$	100	17
	100	17

(Continued)

Table 2. (Continued)

Protected compound ^a	Percent yield of deprotected alcohol	Reference
	80	17
	> 50	18
	63	18
	90	17
	80	19, 20, 21
	60	22
	91	23
	86	23

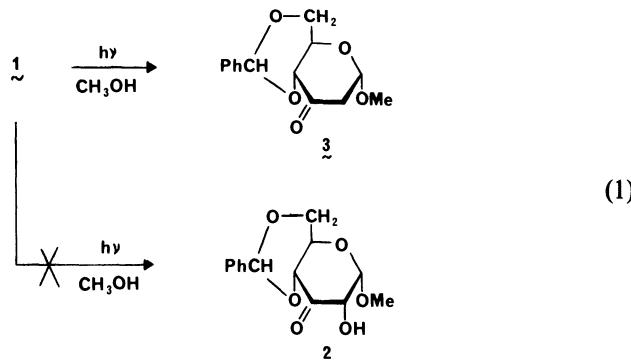
^a See Table 1 for abbreviations.^b Yield not reported.^c Cholestan derivative.



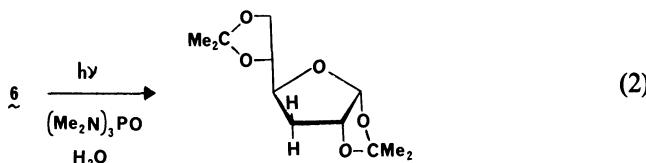
SCHEME 1. Proposed Mechanism for Photochemical Reaction of Sulfonic Acid Esters.

The *p*-toluenesulfonyloxy (tosyloxy) group meets the normal criteria for an effective protecting group.⁽¹⁾ It is easily introduced using readily available starting materials and its formation does not create a new chiral center in the molecule being protected. The tosyloxy group is stable under a variety of reaction conditions including treatment with acids and bases,^(12,13) alkylation,^(12,13) hydrogenation,⁽¹⁴⁾ and nitrous acid deamination.⁽¹⁴⁾ In general, this group is removed by photolysis in good to excellent yield (Table 2).

Photochemical deprotection of sulfonic acid esters sometimes is thwarted by the presence of other functional groups, ones which alter the photochemical reactivity in the molecule under consideration. For example, irradiation of 4,6-*O*-benzylidene-2-*O*-tosyl- α -D-ribohexopyranosid-3-ulose (**1**) (Table 2) does not yield the corresponding deprotected sugar **2** but rather the deoxy sugar **3**⁽¹⁵⁾ [equation (1)]. This unexpected reaction is attributed to the presence of



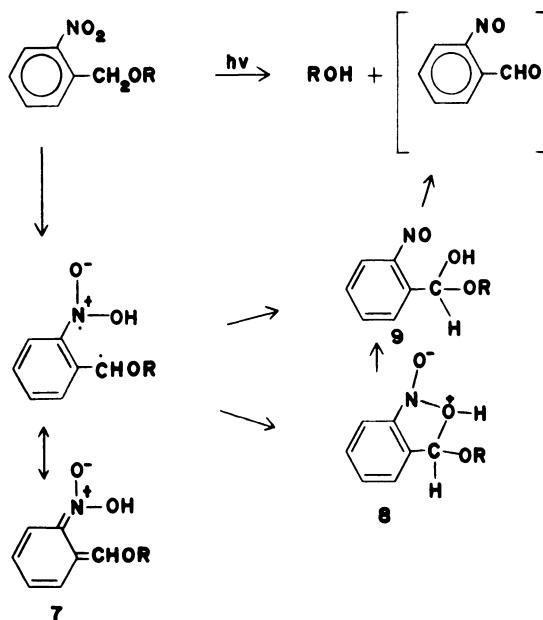
the photochemically reactive carbonyl group in **1**. A similar explanation⁽⁸⁾ is offered for the lack of simple deprotection of compounds **4** and **5** (Table 2). Irradiation of 1,2:5,6-di-*O*-isopropylidene-3-*O*-trifluoromethanesulfonyl- α -D-glucofuranose (**6**) in hexamethylphosphoric triamide also results in deoxy sugar formation⁽¹⁶⁾ [equation (2)], although it is possible in this case that this unexpected behavior is attributable, at least in part, to the unusual photolysis



solvent. Finally, sulfonates in which the aromatic ring is substituted with bromo, nitro, and amino substituents experience complex photochemical reactions in which there is little or no simple deprotection.⁽⁹⁾ Even when these reactions which do not produce simple deprotection are taken into consideration, the sulfonyloxy group remains an excellent photoremoveable protecting group.

2.2. *o*-Nitrobenzyl Ethers

The development of the *o*-nitrobenzyl group as a photoremoveable protecting group for alcohols has its origins in several early studies which describe the photolyses of simple *o*-nitrophenyl compounds.⁽²⁴⁻²⁶⁾ These studies led to the finding that when alkyl *o*-nitrobenzyl ethers were irradiated, they were converted into *o*-nitrosobenzaldehyde and the alcohol resulting from removal of the *o*-nitrobenzyl group (Scheme 2). (Complete characterization of *o*-ni-



SCHEME 2. Proposed Mechanism for the Photochemical Cleavage of *o*-Nitrobenzyl Ethers.

etrosobenzaldehyde is difficult; consequently, although there is little doubt of its formation, its isolation and characterization are rarely attempted.) *o*-Nitrobenzyl ethers now have been used to protect the hydroxyl groups in carbohydrates and the carbohydrate portions of nucleosides and oligoribonucleotides (Table 3).

The proposed mechanism for the photoreaction of *o*-nitrobenzyl ethers (Scheme 2) has been discussed many times in the literature. This information has been collected and described in several reviews.⁽⁴³⁻⁴⁶⁾ Excitation of the *o*-nitrophenyl group is thought to result in a transfer of a hydrogen atom to one of the oxygens of the nitro group to produce the resonance stabilized

Table 3. Photochemical Deprotection of Alcohols Protected as *o*-Nitrobenzyl Ethers

Protected compound	Percent yield of free alcohol	Reference
	100 ^a	28
	100 ^a	"
	100 ^b	27
	100 ^b	"
	"very high" ^c	29

(Continued)

Table 3. (Continued)

Protected compound	Percent yield of deprotected alcohol	Reference
R = H, B = URACIL	93 ^e	30
" "	100 ^e	31
" "	Not GIVEN	35
R = H, B = ADENINE	100	31
R = H, B = CYTOSINE	100	"
R = H, B = HYPOXANTHINE	100	"
R = H, B = GUANINE	Not GIVEN	34
R = URIDYL(3'-5'), B = URACIL	94-95 ^e	30
R = ADENYL(3'-5'), B = URACIL	94-95 ^e	30
TRINUCLEOSIDE DIPHOSPHATES WITH ONE Q-NITROBENZYL GROUP ON A RIBOSE 2' OXYGEN AND CONTAINING CYTIDINE AND ADENOSINE RESIDUES	95 ^e	33
DI AND TRINUCLEOSIDE PHOSPHATES WITH ONE Q-NITROBENZYL GROUP ON A RIBOSE 2' OXYGEN AND CONTAINING CYTIDINE, URIDINE, ADENINE AND GUANINE RESIDUES	NOT GIVEN	36
TRI, HEXA, AND NONAADENYLIC ACID OLIGORIBONUCLEOSIDES WITH ONE 2' Q-NITROBENZYL GROUP FOR EVERY THREE ADENINE RESIDUES	NOT GIVEN	37
OLIGORIBONUCLEOTIDES (UP TO HEPTA) WITH A 2'-Q-NITROBENZYL GROUP ON EACH RIBOSE AND CONTAINING THE FOUR MAJOR BASE RESIDUES	NOT GIVEN	38
OLIGORIBONUCLEOTIDES (UP TO DECA) WITH A 2'-Q-NITROBENZYL GROUP ON EACH RIBOSE AND CONTAINING THE FOUR MAJOR BASE RESIDUES	NOT GIVEN	39
A DIRIBONUCLEOTIDE PHOSPHORO- THIOATE WITH ONE 2'-Q-NITROBENZYL GROUP AND ADENINE AS THE BASE RESIDUE	30(OVERALL)	40
OLIGOMERS OF 3'-Q-NITROBENZYL ADENOSINE-5'-PHOSPHATE	40 (TRIMER)	42

^a Determined by "viewing the chromatograms."^b Determined enzymatically.^c The basis for this statement is not given. The completely deprotected disaccharide was obtained in 12.5% yield.^d Styrene-divinylbenzene copolymer.^e Estimated by thin-layer and/or paper chromatography.

intermediate **7** (Scheme 2). This species (**7**) cyclizes to form **8**, an intermediate which ring opens to give the hemiacetal **9**. Decomposition of **9** gives the deprotected alcohol.

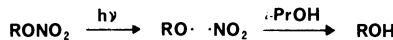
Several successful methods have been developed for synthesis of *o*-nitrobenzyl protected hydroxyl groups. *o*-Nitrobenzyl glycosides have been prepared by reaction of *o*-nitrobenzyl alcohol with the appropriate glycosyl bromide.⁽²⁷⁻²⁹⁾ Protected nucleoside and nucleotide syntheses have been reported using both *o*-nitrobenzyl bromide^(30,33,34) and *o*-nitrophenyl diazomethane.^(31,40,42) All protecting reactions for nucleosides have produced mixtures of the 2' and 3' ethers which have had to be separated chromatographically.

Even though *o*-nitrobenzyl ethers can be cleaved by Pyrex filtered irradiation, they are stable under a variety of reaction conditions. The photochemical deprotection itself can be conducted on molecules containing unprotected hydroxyls,^(27,28) esters,^(27,28) benzyl ethers,⁽²⁹⁾ and phosphates.⁽³⁰⁾ Also, reactions conducted on *o*-nitrobenzyl protected compounds without altering the protecting group include: base-catalyzed deesterification,^(27,28) acid-catalyzed isopropylidenation and deisopropylidenation,⁽²⁸⁾ tosylation^(30,34,35) in the presence of dicyclohexylcarbodiimide, and various kinds of ribonucleic acid oligomerizations.^(36-39,41) When the stability of the *o*-nitrobenzyl group toward this variety of reagents is combined with its facile photochemical reaction, it easily equals the sulfonic acid esters as a photoremovable protecting group for alcohols.

2.3. Nitrates, Nitrites, Dimethylthiocarbamates, and Aryl Azides

In addition to sulfonic acid esters and *o*-nitrobenzyl ethers, other compounds containing potentially useful photoremovable hydroxyl protecting groups have been irradiated. Among this group, which includes nitrates,⁽⁴⁷⁾ nitrites,⁽⁴⁸⁾ dimethylthiocarbamates,⁽⁴⁹⁾ and aryl azides,⁽⁵⁰⁾ only the nitrates have appeared to be promising candidates since deprotection is not the major photochemical pathway for the other compounds. (Nitrites and dimethylthiocarbamates experience other, synthetically valuable photochemical reactions.)

Nitrates are formed in high yield by reaction of the corresponding alcohol with acetyl nitrate.⁽⁵¹⁾ They are stable under a variety of reaction conditions including esterification, methylation, acetal formation, and treatment with strong acid.⁽⁵¹⁾ Photolysis of nitrates leads to homolysis of the nitrogen–oxygen bond⁽⁵²⁾ and, in the presence of a hydrogen-donating solvent such as 2-propanol, to quantitative or nearly quantitative alcohol formation.⁽⁴⁷⁾ The proposed mechanism for the photochemical process is shown in Scheme 3. Since only a few examples of this reaction have been reported (Table 4), its generality is uncertain. A limiting factor in nitrate photolysis as a deprotection



SCHEME 3. Proposed Mechanism for Photochemical Reaction of Nitrates.

process is the possibility for epimerization at a chiral center as a result of photolysis. A reaction of this type has been observed (Table 4).

3. Diols

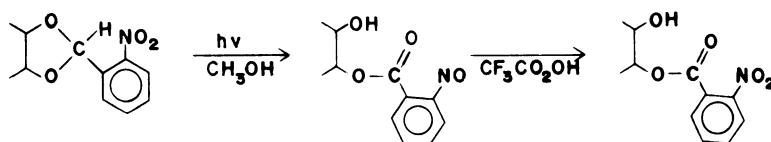
Over fifty years ago, Tanesescu and co-workers explored the photochemistry of *o*-nitrobenzylidene acetals of ethylene glycol and glycerol⁽⁵³⁾ and of several carbohydrates.⁽⁵⁴⁻⁵⁸⁾ (This work had been inspired by an even earlier report that photolysis of acetals of *o*-nitrobenzaldehyde liberated alcohols and *o*-nitrosobenzoic acid esters.⁽⁵⁹⁾) Unfortunately, difficulties in product isolation and purification prevented exact structural determination for the carbohydrates studied.

More recent work by Collins and co-workers⁽⁶⁰⁻⁶²⁾ demonstrates that the compounds produced by irradiation of *o*-nitrobenzylidene acetals of carbohydrates can be isolated and characterized, if the nitroso groups present in the photoproducts are oxidized to nitro groups (Scheme 4). The photochemical

Table 4. Photochemical Deprotection of Alcohols Protected as Nitrates

Protected compound	Percent yield of deprotected alcohol	Reference
	100 ^a	47
$R_1 = \text{ONO}_2, R_2 = \text{H}$	92	47
	100	47

^a Complete inversion at C₃.



SCHEME 4. Photochemical Cleavage of an *o*-Nitrobenzylidene Acetal and Oxidation of the Nitroso Product.

reaction can be conducted without difficulty in the presence of acetoxy, hydroxy, methoxy, tosyloxy, and epoxy groups. *o*-Nitrobenzylidene acetals are cleaved rapidly by acids but are stable under neutral and mildly basic conditions. The considerable number of compounds studied by the Collins group are tabulated in Table 5.

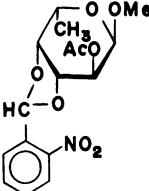
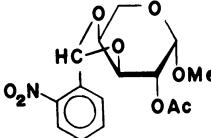
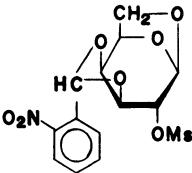
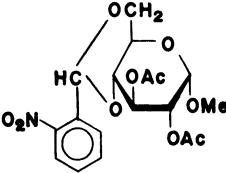
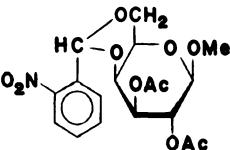
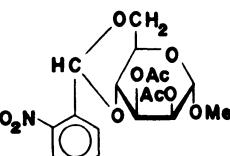
The mechanism proposed for *o*-nitrobenzylidene acetal photoreaction (Scheme 5) is analogous to that pictured for *o*-nitrobenzyl ethers (Scheme 2). The reaction is viewed as starting with a hydrogen atom abstraction, followed by a hydroxyl group transfer, and then by a ring opening (Scheme 5).

Table 5. Photochemical Deprotection of Carbohydrates Protected as *o*-Nitrobenzylidene Acetals

Protected compound	Position of free hydroxyl	Percent yield	Reference
	a	not reported	53
	3 2	95 5	60, 61
	2 3	93 < 5	61

(Continued)

Table 5. (Continued)

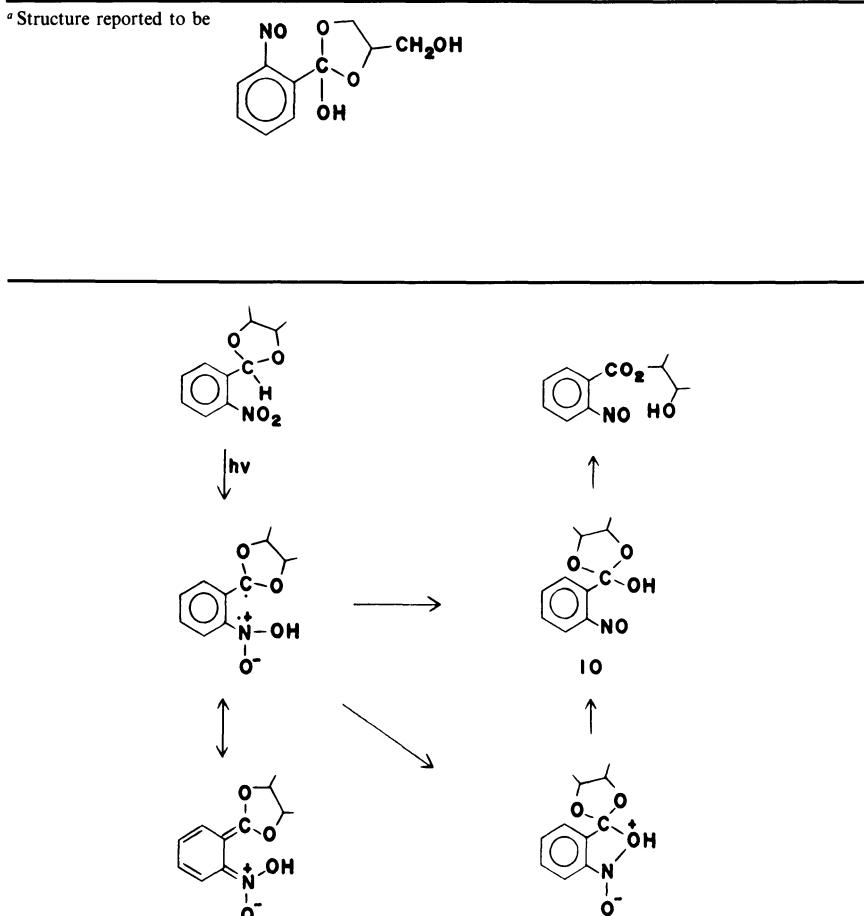
Protected compound	Position of free hydroxyl	Percent yield	Reference
	3 4	93 <5	60,61
	3 4	95 5	61
	4 3	89 <5	"
	4 6	59 30	60,62
	6 4	50 23	60,62
	4 6	59 32	62

Protected compound	Position of free hydroxyl	Percent yield	Reference
	4 6	60 40	"
	6 4	50 20	"
	6 4	48 17	62
	not reported	96 (total)	60, 62
	not reported	—	62

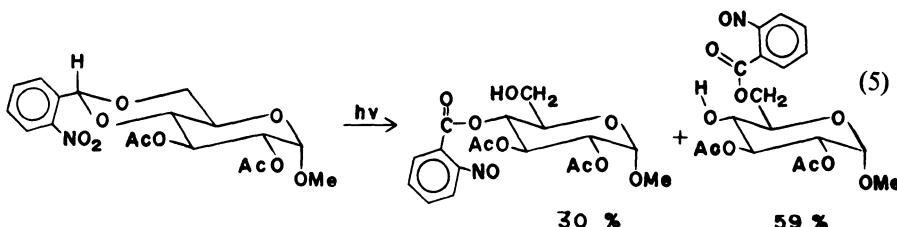
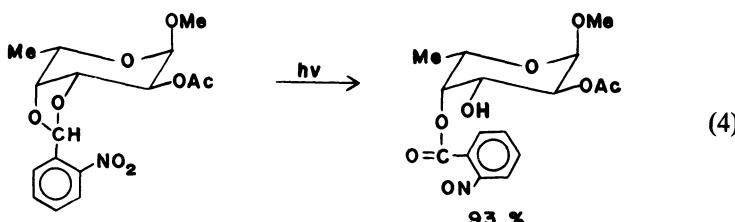
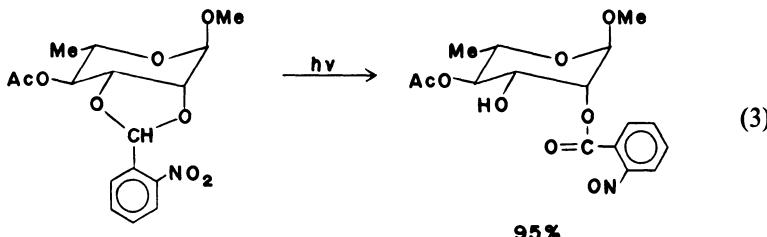
(Continued)

Table 5. (Continued)

Protected compound	Position of free hydroxyl	Percent yield	Reference
	3,4 3,6	45 32	
^a Structure reported to be			

SCHEME 5. Proposed Mechanism for the Photochemical Rearrangement of *o*-Nitrobenzylidene Acetals to *o*-Nitrosobenzoates.

An important difference between the *o*-nitrobenzylidene group and other photoremovable hydroxyl protecting groups is that photolysis produces only partial deprotection; that is, the reaction product contains an unprotected hydroxyl group and a protected one in the form of an *o*-nitrosobenzoate ester. The direction of acetal ring opening is critical. According to the mechanism depicted in Scheme 5, ring opening occurs in the last (nonphotochemical) step. Analysis of the examples reported^(60,62) (Table 5, all pyranose derivatives) indicates the following generalizations: (a) an *o*-nitrobenzylidene acetal of a *cis* vicinal diol (2,3 or 3,4) ring opens to give an excellent yield of the product with an equatorial free hydroxyl and an axial *o*-nitrosobenzoate [equations (3) and (4)]; (b) nonvicinal acetals (derived from 4,6-diols) provide mixtures containing approximately equal amounts of the two possible ring open products [equation (5)]. A full explanation including the basis for these two



generalizations has not been made; however, Collins has proposed that the factors governing the direction of the ring opening of **10** (Scheme 5) are similar to those involved in the hydrolysis of cyclic orthoesters. Cyclic orthoester hydrolysis has been considered in detail by King and Abutt.⁽⁶³⁾

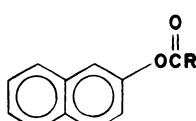
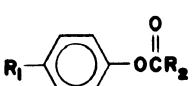
Although the *o*-nitrobenzylidene acetal is potentially a useful photolabile protecting group, its use is limited to a relatively small number of situations. The cases in which it can be synthetically attractive are those in which the direction of acetal ring opening is immaterial or in which there is a decided preference for formation of one of the two ring-opened products.

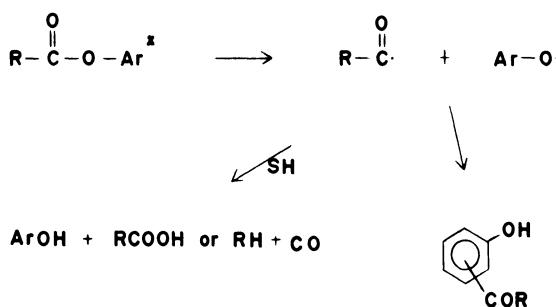
4. Phenols

Relatively little has been published on photoremovable protecting groups for phenols. Specifically, certain esters⁽⁶⁴⁻⁶⁶⁾ and the *o*-nitrobenzyl ether group⁽⁶⁷⁾ have been studied. Those phenol derivatives which have been deprotected photochemically are listed in Table 6.

Considerable information exists concerning the mechanism of the photochemical reactions of esters of phenols.⁽⁶⁸⁻⁷⁰⁾ Acyl and phenoxy radicals are

Table 6. Photochemical Deprotection of Phenolic Hydroxyl Groups Protected as Carboxylic Acid Esters

Protected compound	Percent yield of free phenol	Reference
		
R = Ph	8	64, 65
R = CH ₃	41	" "
R = CCl ₃	29	" "
R = CPh ₃	46	" "
R = 9-Fluorenyl	67	" "
 		
R ₁ = CH ₃ , R ₂ = 9-Fluorenyl	58	64, 65
R ₁ = R ₂ = H	49	66
R ₁ = C(CH ₃) ₃ , R ₂ = H	80	"
R ₁ = C(CH ₃) ₃ , R ₂ = CH ₃	34	"

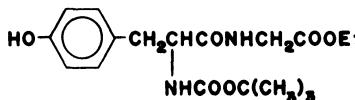
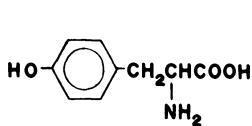


SCHEME 6. Proposed Mechanism for the Photochemical Cleavage and Rearrangement of Aryloxy Esters.

produced by photochemical bond homolysis. These radicals either recombine to produce nuclear substituted phenols (the photo-Fries reaction) or they diffuse apart and abstract hydrogen from the solvent (Scheme 6). Formation of substituted phenols as a side reaction is one of the principal problems with esters as photoremovable protecting groups. A second difficulty with these protecting groups is that esters typically must be irradiated at wavelengths at which the desired (and photochemically reactive) phenols also absorb.

Photochemical reactions of alcohols protected as *o*-nitrobenzyl ethers are described in Section 2.2. Presumably, the same kind of cleavage mechanism which operates for alcohol deprotection (Scheme 2) also operates for the *o*-nitrobenzyl ether of a phenol.

The *o*-nitrobenzyl group is capable of protecting phenolic hydroxyls during peptide synthesis.⁽⁶⁷⁾ Photochemical deprotection yields of 98% for tyrosine (**11**) and 80% for *N*-Boc-L-tyrosyl-glycine ethyl ester (**12**) are obtained.



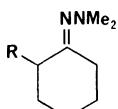
Use of *o*-nitrobenzyl ethers as photoremovable protecting groups for phenols has the advantages of (a) no competition from rearrangement; (b) irradiation at a wavelength (> 350 nm) which should not affect most other substituents; (c) the hydrolytic stability of an aromatic ether.

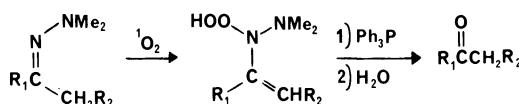
5. Aldehydes and Ketones

Even though three promising methods for protection and photochemical deprotection of aldehydes and ketones have been reported, none of these has become an important synthetic tool. Two of these methods^(71,72) require irradiation in the presence of molecular oxygen, while the third⁽⁷³⁾ takes advantage of the reactivity of an aromatic ring with a nitro group ortho to a benzylic hydrogen. The photochemical deprotection in all three cases takes place in good yield.

Dye-sensitized photooxygenation (conditions which generate singlet oxygen) of *N,N*-dimethylhydrazones in a variety of solvents regenerates the ketones from which the hydrazones were synthesized⁽⁷¹⁾ (Table 7). A significant feature of the photochemical process from a synthetic point of view is that it is conducted under neutral reaction conditions. Although mechanistic investigation of the photolysis of these hydrazones has not been conducted, a

Table 7. Photochemical Deprotection of Aldehydes and Ketones Protected as *N,N*-Dimethylhydrazones

Protected compound	Percent yield of deprotected ketone		Reference
$\begin{array}{c} \text{NNMe}_2 \\ \parallel \\ \text{R}_1\text{CR}_2 \end{array}$			
R_1	R_2		
$(\text{CH}_2)_{10}\text{CH}_3$	H	52	71
$(\text{CH}_2)_4\text{CH}_3$	CH_3	80	71
$\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	CH_2CH_3	67	71
$(\text{CH}_2)_2\text{CO}_2\text{CH}_2\text{CH}_3$	CH_3	88	71
$\text{CH}_2\text{CH}(\text{OH})\text{CH}(\text{CH}_3)_2$	$\text{CH}(\text{CH}_3)_2$	48	71
$\text{CH}_2\text{CH}(\text{OH})\text{CH}_3$	CH_3	63	71
			
$\text{R} = \text{H}$	52		71
$\text{R} = \text{CH}_3$	59		71



SCHEME 7. Proposed Mechanism for Photochemical Reaction of *N,N*-Dimethylhydrazones.

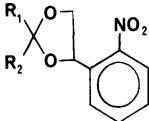
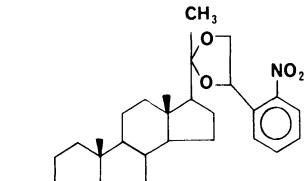
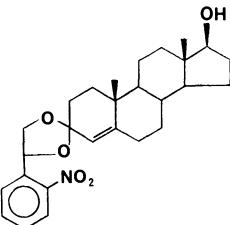
reasonable proposal⁽⁷¹⁾ is that a hydroperoxide intermediate is involved (Scheme 7).

The second type of photochemically reactive, carbonyl protecting group which has been investigated is the dithioacetal.⁽⁷²⁾ The protected carbonyl compound is regenerated in good yield (Table 8) from the appropriate dithioacetal by photolysis in an oxygen saturated hexane solution containing

Table 8. Photochemical Deprotection of Ketones Protected as Dithioacetals

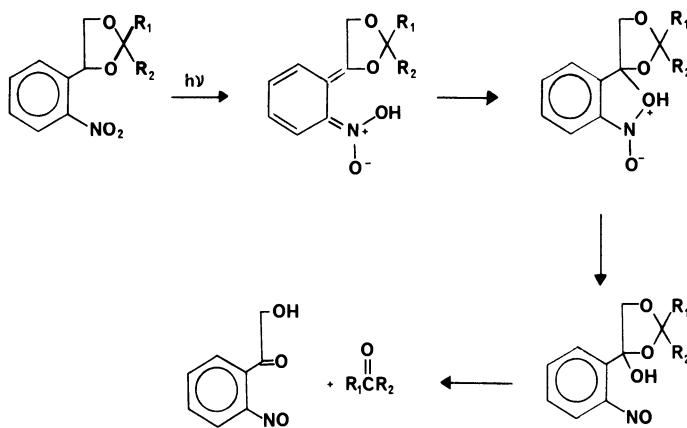
Protected compound	Percent yield of deprotected ketone	Reference
$\text{R}_1 = \text{R}_2 = \text{R}_3 = \text{H}$	65	72
$\text{R}_1 = \text{Me}$, $\text{R}_2 = \text{R}_3 = \text{H}$	70	72
$\text{R}_1 = \text{R}_3 = \text{H}$, $\text{R}_2 = \text{CMe}_3$	60	72
$\text{R}_1 = \text{CHMe}_2$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{Me}$	87	72
R_1	R_2	
$-\text{SCH}_2\text{CH}_2\text{S}-$	$\alpha\text{-H}$	77
$-\text{SCH}_2\text{CH}_2\text{S}-$	4,5 DOUBLE BOND	57
$-\text{SCH}_2\text{CH}_2\text{S}-$	$\beta\text{-H}$	75
$(\text{PhCH}_2\text{S})_2$	$\alpha\text{-H}$	80
$-\text{SCH}_2\text{CH}_2\text{O}-$	$\alpha\text{-H}$	61

Table 9. Photochemical Deprotection of Ketones Protected as Ketals of 1-(*o*-Nitrophenyl)-1,2-ethanediol

Protected compound	Percent yield of deprotected ketone or aldehyde	Reference
		
$R_1, R_2 = -CH_2(CH_2)_3CH_2-$	85	73
$R_1 = R_2 = Ph$	90	73
$R_1 = H, R_2 = p\text{-NO}_2C_6H_4$	86	73
	83	73
	31	73

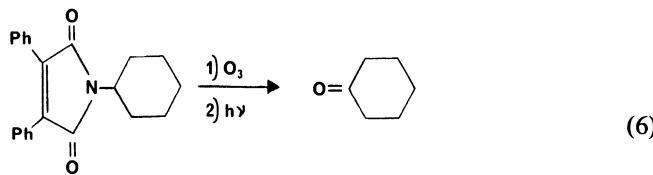
the triplet sensitizer benzophenone. The mechanism for this reaction is not known.

Photochemical removal of acetal and ketal protecting groups, formed from 1-(*o*-nitrophenyl)-1,2-ethanediol, is part of a protection-deprotection process⁽⁷³⁾ (Table 9). The essential element in reforming a carbonyl compound protected as this unusual acetal or ketal is the well-established photochemical reaction of the *o*-nitrobenzyl group. The mechanism proposed for this reaction (Scheme 8) is analogous to that suggested for *o*-nitrobenzyl ethers (Scheme 2). Chromatography of the reaction mixture is necessary to remove the nitroso compound (Scheme 8) produced by photolysis.



SCHEME 8. Proposed Mechanism for Photochemical Reaction of Acetals and Ketals Derived from 1-(*o*-Nitrophenyl)-1,2-ethanediol.

Finally, 1,2-diphenylmaleimides (**13**) have been suggested as photoreactive protecting groups for carbonyl compounds⁽⁷⁴⁾; however, the product yields from removal of these groups are too low to be of value [equation (6)].



13

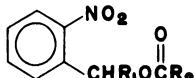
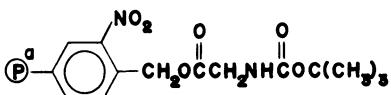
6. Carboxylic Acids and Amides

Protection of carboxylic acids by photoremovable groups has been accomplished with the *o*-nitrobenzyl,⁽⁷⁵⁻⁷⁷⁾ *o*-nitrophenylamino,⁽⁷⁸⁻⁸¹⁾ phenacyl,^(82,83) and 2,4-dinitrophenylthio^(64,65) groups. Also, ethers derived from aryl azides⁽⁵⁰⁾ and esters derived from benzoin⁽⁸⁴⁾ have been used. In addition, polymerlinked *o*-nitrobenzyl⁽⁸⁵⁻⁸⁸⁾ and phenacyl⁽⁸⁹⁾ groups have been found to be effective in protecting carboxylic acids. This use of polymer-bound *o*-nitrobenzyl groups also has been extended to protection of amides.⁽⁹⁰⁻⁹²⁾

6.1. *o*-Nitrobenzyl Esters

Those situations in which the *o*-nitrobenzyl group has been used to protect carboxylic acids and amides are given in Table 10. Because photo-removable protecting groups have been most frequently used with highly functionalized natural products, it is not surprising that many of the compounds listed in Table 10 are peptides. Peptide protection presents a challenging test for the *o*-nitrobenzyl group because it requires (a) stability under the various conditions of peptide synthesis; (b) compatibility with other pro-

Table 10. Photochemical Deprotection of Carboxylic Acids and Amides Protected as *o*-Nitrobenzyl Ester and Amide Derivatives

Protected compound	Percent yield of free acid or amide	Reference
		
R ₁ = H, R ₂ = Ph	17	75
R ₁ = R ₂ = Ph	90	"
R ₁ = Ph, R ₂ = (CH ₂) ₁₄ CH ₃	95	"
R ₁ = Ph, R ₂ = CH ₂ Ph	87	"
R ₁ = Ph, R ₂ = CH ₂ N(Phthalimido)	75	"
R ₁ = <i>o</i> -Nitrophenyl, R ₂ = Ph	100	76
" , R ₂ = CH ₂ Ph	100	"
" , R ₂ = CH ₂ Naphthyl	100	"
" , R ₂ = Boc-Ala	100	"
" , R ₂ = Boc-Phe	100	"
R ₁ = H, R ₂ = a carbapenam derivative	19	77
		
(P-ONB-Gly-Boc)	71	85
P-ONB-Leu-Boc	65	"

Protected compound	Percent yield of free acid or amide	Reference
P-ONB-(D,L)-Phe-Boc	66	"
P-ONB-Phe-Boc	60	"
P-ONB-Tyr(OBz)-Boc	53	"
P-ONB-Trp-Boc	57	"
P-ONB-Protected Tripeptide	62	"
P-ONB-Protected Tetrapeptide	32	86
R = Protected tetra, penta, hepta or decapeptides	50-64	86
R = Protected amino acids and di, tri, and tetrapeptides	98 86-95	87 92
R = Boc-Gly	100 ^c	90
R = Boc-Val	100 ^c	"
R = a protected decapeptide	65 ^c	"
R = Protected amino acids and di, tri, and tetrapeptides	90-97 ^c	91, 92

^a Cross-linked polystyrene.^b Polyethylene glycol.^c Amide.

pecting groups; and (c) efficiency in removal. The report of Rich and Gurwara⁽⁸⁶⁾ that a decapeptide can be synthesized while attached to a resin bound *o*-nitrobenzyl group and isolated in 64% yield after photochemical removal provides an excellent example of the versatility and effectiveness of this protecting group. Clearly, photochemically removed, polymer-bound, *o*-nitrobenzyl groups, particularly those bound to soluble polyethylene,^(88,91) satisfy well the requirements for a protecting group. Their principal drawback is the difficulty experienced in reusing the polymer.

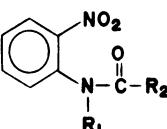
The mechanism by which the *o*-nitrobenzyl group undergoes photochemical reaction has been discussed in Section 2.2.

6.2. *o*-Nitrophenylamino Derivatives

The initial application of the *o*-nitrophenylamino group as a photoremoveable protecting group for carboxylic acids was made by Amit and Patchornik⁽⁷⁸⁾ and involved the synthesis and photolysis of *o*-nitroanilides and 4,5-dimethoxy-2-nitroanilides (nitroveratramides). The use of this group now has been extended to include *N*-acyl-1,2,3,4-tetrahydro-8-nitroquinolines⁽⁸⁰⁾ and *N*-acyl-7-nitroindolanes^(79,81) (Table 11).

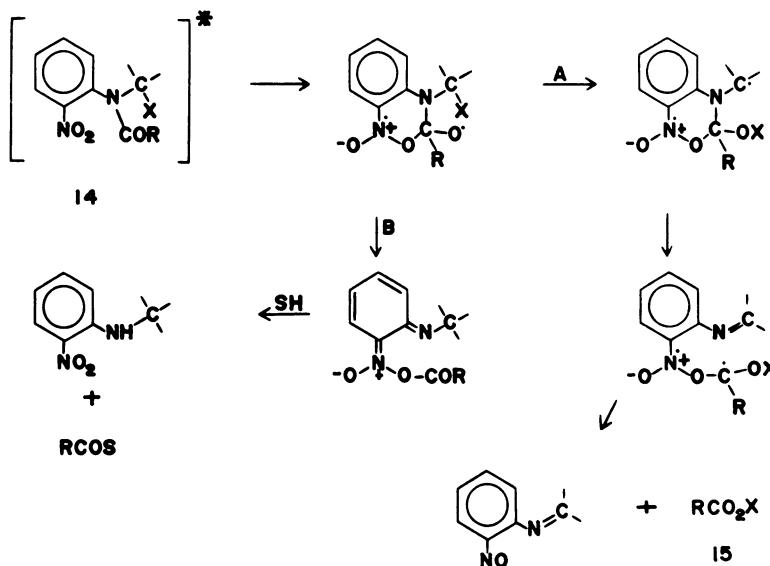
Mechanistic investigations indicate two different pathways for photochemical reaction of these compounds. The primary factor determining which

Table 11. Photochemical Deprotection of Carboxylic Acids Protected as *o*-Nitroanilide Derivatives

Protected compound	Percent yield of free acid	Reference
	0	78
R ₁ = H, R ₂ = Ph	90	"
R ₁ = CH ₂ Ph, R ₂ = CH ₃	95	"
R ₁ = Ph, R ₂ = CH ₃	95	"
R ₁ = R ₂ = CH ₃	90	"
R ₁ = CH ₃ , R ₂ = Ph	90	"
R ₁ = CH ₃ , R ₂ = 2-Naphthyl	90	"
R ₁ = Cyclohexyl, R ₂ = 2-Naphthyl	80	"

Protected compound	Percent yield of free acid	Reference
R ₁ = Cyclohexyl, R ₂ = CH ₃	90	78
R ₁ = (CH ₂) ₅ CH ₃ , R ₂ = CH ₃	70	"
R ₁ = CH ₂ Ph, R ₂ = CH ₃	90	"
R ₁ = CH ₂ Ph, R ₂ = 3,4-Cl ₂ C ₆ H ₃	85	"
R ₁ = Cyclohexyl, R ₂ = 3,4-Cl ₂ C ₆ H ₃	93	78
R ₁ = CH ₃ , R ₂ = 2-ClC ₆ H ₄	93	"
R ₁ = (CH ₂) ₅ CH ₃ , R ₂ = 2-Naphthyl	80	"
R ₁ = Ph, R ₂ = Br	100, 100 ^a , 70 ^b	79
R ₁ = 4-CH ₃ OC ₆ H ₄ , R ₂ = Br	100, 100 ^a	"
R ₁ = 3-NO ₂ C ₆ H ₄ , R ₂ = Br	87, 0 ^a	"
R ₁ = 3,4-Cl ₂ C ₆ H ₃ , R ₂ = Br	87, 61 ^a	"
R ₁ = 2-Naphthyl, R ₂ = Br	100, 100 ^a	"
R ₁ = 2-Furyl, R ₂ = Br	90, 90 ^a	"
R ₁ = (CH ₂) ₆ CH ₃ , R ₂ = Br	100, 100 ^a	"
R ₁ = Ph, R ₂ = NO ₂	100, 95 ^a , 70 ^b	"
R ₁ = Protected tri and tetra peptides, R ₂ = Br	70-97	81
R = Ph	91 ^c , 85 ^d , 80 ^e	80
R = 3,4-Cl ₂ C ₆ H ₃	95 ^c , 80 ^e	"

^a Ester from irradiation in 6:1 dichloromethane:alcohol.^b Benzamide from irradiation in 10:20:1 dichloromethane:dioxane:concentrated ammonia.^c In methanol or ethanol.^d In isopropanol.^e In benzene.



SCHEME 9. Proposed Mechanism for the Photochemical Cleavage of *o*-Nitroanilide Derivatives.

pathway is followed is whether the "X" group in structure **14** (Scheme 9) is an "available" hydrogen. An available hydrogen is one attached to a carbon which is either not in a ring system or is part of a relatively flexible ring (six-membered or larger). If the carbon containing X is part of a relatively rigid (e.g., five-membered or smaller) ring system, the X hydrogen is not available; that is, it is held too far away from the carbonyl group (see structure **14**, Scheme 9) for hydrogen abstraction.

When X is an available hydrogen, the reaction is thought to follow path A in Scheme 9 and has the characteristics that one oxygen in the deprotected carboxyl group in **15** comes from the nitro group and that X becomes the carboxyl proton. When X is not an available hydrogen, the solvent provides one of the oxygen atoms attached to the carbonyl carbon of the product (path B, Scheme 9) and the nitro group does not lose an oxygen. This information on the photolysis of *o*-nitrophenylamino derivatives is accounted for in the mechanistic proposal given in Scheme 9.

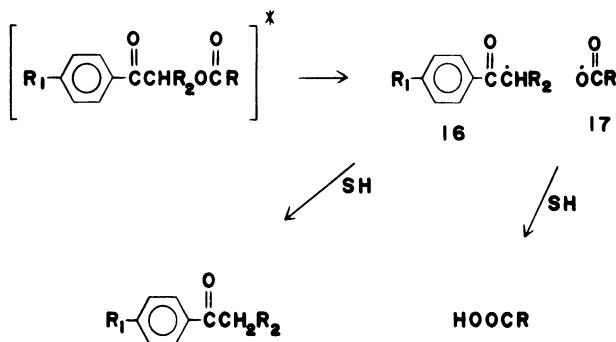
Photolysis of compounds with the general structure **14** (Scheme 9) in solvents which are effective hydrogen atom donors creates the possibility for hydrogen abstraction from the solvent; consequently, reaction pathways in addition to those described above may be operative. Even though the same

type of photochemical deprotection observed in non-hydrogen-donating solvents (Scheme 9) does occur in hydrogen-donating solvents, the reaction mechanism may be different and, therefore, at present must be considered undetermined.

In general, *o*-nitrophenylamino-protected compounds contain an excellent photoremovable group, one which affords good yields of photocleavage products (see Table 11) and, otherwise, is quite stable. The primary drawback to use of compounds containing this group appears to be the difficulty in their synthesis.^(80,81) Also, a more thorough understanding of the mechanism of photochemical reaction of these compounds would be valuable in evaluating situations in which the *o*-nitrophenylamino group could be used.

6.3. Phenacyl Esters

Sheehan and Umezawa⁽⁸²⁾ initially examined both the *p*-methoxyphenacyl and the α -methylphenacyl groups as photoremovable protecting groups. Both already have proven to be useful. The *p*-methoxyphenacyl group has been used in the synthesis of the natural product gibberellin⁽⁸³⁾ and the α -methylphenacyl group has been incorporated into a resin for application in peptide synthesis.⁽⁸⁹⁾ The mechanism for the photoremoval of either of these two groups involves an excited triplet state which α -cleaves to give the radicals **16** and **17** (Scheme 10). Hydrogen abstraction from the solvent by **17** completes the deprotection process. The evidence⁽⁸²⁾ in favor of the proposed mechanism (Scheme 10) includes isolation of *p*-methoxyacetophenone (or propiophenone), the effect of various hydrogen atom donors on the reaction, and the observation that decarboxylation occurs when stable radicals result.⁽⁸²⁾



SCHEME 10. Proposed Mechanism for the Photochemical Cleavage of Phenacyl Esters.

Compounds containing these two phenacyl esters which have been photochemically deprotected are shown in Table 12.

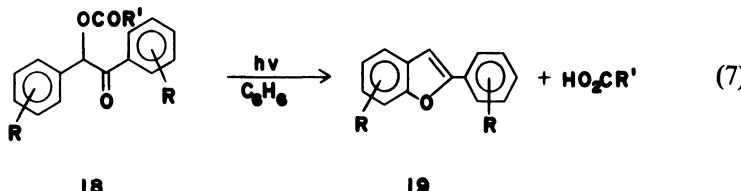
The phenacyl group seems to be the principal alternative to the *o*-nitrobenzyl group for carboxyl protection. As an alternative, it is inferior because it requires shorter-wavelength radiation for reaction and risks decarboxylation during removal. The phenacyl group is, however, removed more rapidly by photolysis than the *o*-nitrobenzyl group.

6.4. 2,4-Dinitrophenylthio Esters, Benzoin Esters, and Aryl Azides

Three other possibilities for the photoremoveable protection of carboxylic acids have been reported. These are the 2,4-dinitrophenylthio group,^(64,65) the methoxyl substituted benzoin ester group,⁽⁸⁴⁾ and the aryl azido ether.⁽⁵⁰⁾ Among these three, photolysis of the aryl azides produced such low yields of carboxylic acids that this azido group will not be discussed as a photoremoveable protecting group.

Barton and co-workers have studied the photolysis of the compounds containing the dinitrophenylthio group which are listed in Table 13. Investigation of the mechanism of this reaction^(65,94) has favored that shown in Scheme 11. These studies have provided evidence that neither a carboxyl radical nor a free sulfenium ion is involved in the reaction.⁽⁹⁴⁾

Sheehan and co-workers⁽⁸⁴⁾ have reported on an exploration of methoxy-substituted benzoin esters. Their investigation began with the observation that the benzoin esters **18** photocyclize to produce the benzofurans **19** with release of the free carboxylic acids⁽⁹⁴⁾ [equation (7)]. The methoxy-substituted



esters (**18**, $\text{R}=\text{OMe}$) were the compounds which liberated carboxylic acids in the best yields (see Table 13). In spite of a substantial amount of effort, no mechanism for this photoreaction has been established; however, it has been shown that the basic cleavage is probably heterolytic because there is no decarboxylation accompanying photolysis.⁽⁸⁴⁾

Neither of these two final carboxylic acid protecting groups has been studied sufficiently to allow a proper evaluation of their advantages and disadvantages.

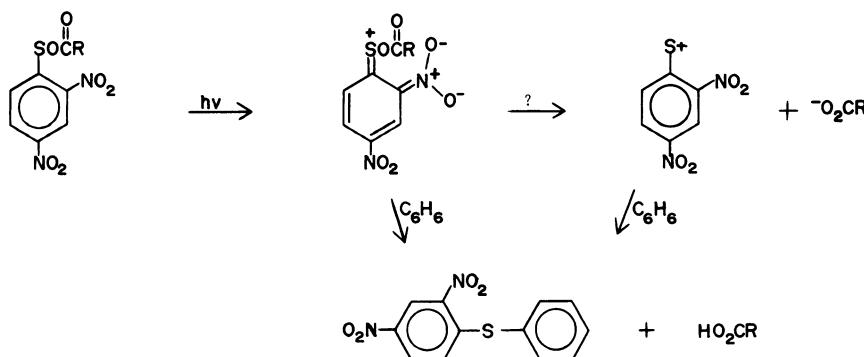
Table 12. Photochemical Deprotection of Carboxylic Acids Protected as Phenacyl Esters

Protected compound	Percent yield of free acid	Reference
R = Ph	78-96	82
R = Boc-Ala	82-93	"
R = Boc-Gly	94	"
R = Boc-Phe	89	"
R = Cbz-D,L-Ala	84	"
R = Phthaloyl-Gly	80 ^a	"
R = Ph ₃ C-Gly	58	"
R = Cbz-Trp	33	"
R = Cbz-Gly-Gly	77	"
R = Cbz-Asp-OBz L-Ser	49	"
R = 3 Gibberellin derivatives	32-62 ^b	83
R = Ph	78-87	82
R = Boc-Gly	87	"
R = Boc-Ala	93-96	"
R = Boc-Phe	86-96	"
R = Phthaloyl-Gly	71	"
R = Cbz-Lys(Cbz)-Phe-Phe-Gly	70 ^d	89

^a N-methylphthalimide also isolated.^b Photochemical reactions in the gibberellin portion also occurred with another derivative; see also Reference 93.^c Styrene-divinylbenzene copolymer.^d Overall yield analytically pure.

Table 13. Photochemical Deprotection of Carboxylic Acids Protected as Dinitrophenylthio Derivatives and as Benzoin Esters

Protected compound	Percent yield of free acid	Reference
R = CH ₃	92	64
R = (CH ₂) ₄ CH ₃	83	"
R = CH ₂ Ph	88	"
R1' = 3,5-(OMe) ₂ , R2' = H	87	84
R1' = R2' = 2,3-(OMe) ₂	76	"
R1' = R2' = 3,4-(OCH ₂ O)	75	"

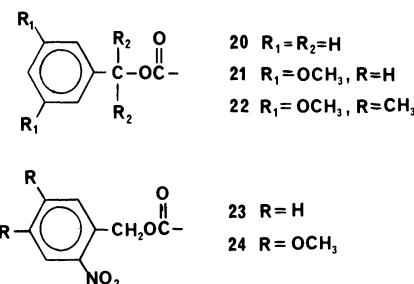


SCHEME 11. Proposed Mechanism for the Photochemical Cleavage of Dinitrophenylthio Derivatives of Carboxylic Acids.

7. Amines

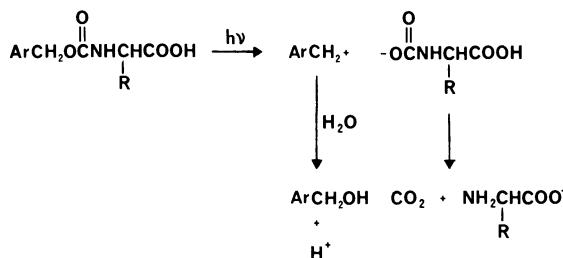
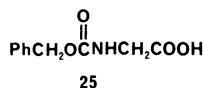
7.1. Benzyloxycarbonyl Compounds

Several photochemically reactive groups are effective in protecting amino functions. Compounds containing one of the benzyloxycarbonyl structural units **20–24** are used most frequently. The principal interest in these groups is in protection of amino acids and aminodeoxy sugars. The benzyloxycarbonyl substituents **20–24** draw their effectiveness from their stability in the presence



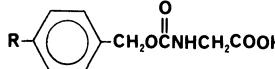
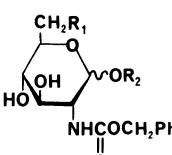
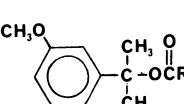
of dilute acids and bases combined with their facile removal by stronger acids or by photolysis. Photochemical deprotection generally takes place in high yield (see Tables 14 and 15), although yields are reduced, at least in some instances, by a competing rearrangement process. Photochemical deprotection is sufficiently rapid and uncomplicated for these groups to permit protected amino acids to be used in automated peptide synthesis.^(102,103)

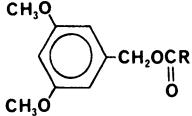
An ionic mechanism (Scheme 12) supported primarily by photoproduct identity is favored for the photochemical removal of groups **20–22**.^(96,97,101–103) The photolysis of an aqueous solution of benzyloxycarbonylglycine (**25**), the



SCHEME 12. Proposed Mechanism for the Photochemical Cleavage of Benzyloxycarbonyl Derivatives.

Table 14. Photochemical Deprotection of Amines Protected as Benzyloxycarbonyl Derivatives (Excluding *o*-Nitro Derivatives)

Protected compound ^a	Percent yield of deprotected amine	Reference
		
R=H	10, b	96, 97, 98
R=NO ₂	b	96, 97
R=Br	b	96, 97
R=OMe	b	96, 97
		
R ₁ , R ₂		
OH OH	70	100
Br OH	70	100
OH OCH ₃	70	100
		
R = Phe	b	101
R = Trp	b	101
R = Ala-Phe-t-Bu	86	102
R = Pro-Ala-Phe-o-t-Bu	49	102
$\text{PhCH}=\text{CHOCH}_2\text{NHCH}_2\text{CO}_2^- \text{Na}^+$	b	96
$m\text{-NO}_2\text{C}_6\text{H}_4\text{OC(=O)NHPh}$	b	104, 105

Protected compound ^a	Percent yield of deprotected amine	Reference
		
R = Gly	85	98,99
R = Met	60	98
R = Gly(Ph)	66	98
R = Ser	72	98
R = Lys	42	98
R = Leu	b	99
R = Val	b	99
R = Phe	b	99
R = Pro	b	99
R = Phe-Ala-OMe	b	99

^a See Table 1 for abbreviations.

^b Chemical yields not reported.

most extensively studied of these compounds, produces benzyl alcohol, carbon dioxide, and glycine as the major products.^(96,97) If ethanol is used as the reaction solvent, benzyl ethyl ether is formed.⁽⁹⁷⁾ This solvent effect on product identity provides a persuasive argument in favor of a carbocation being produced by photolysis. A second observation, one which is consistent with an ionic mechanism but does not require one, is that the quantum yield for reaction increases in polar solvents.

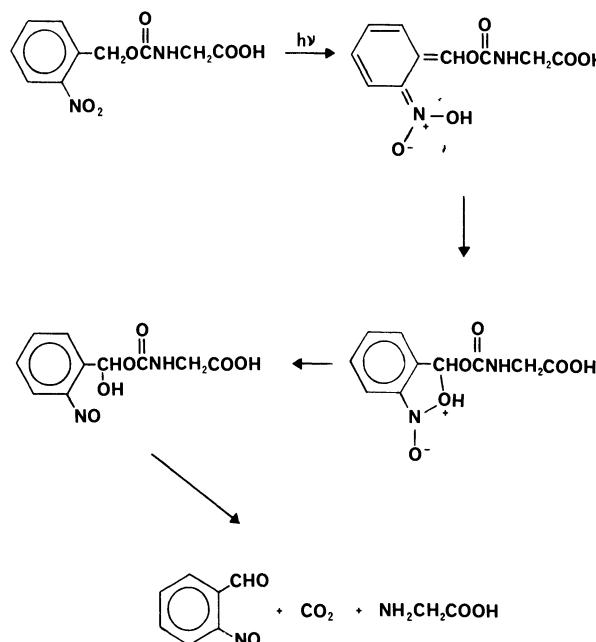
The basic photochemical process for compounds containing the *o*-nitrobenzyloxycarbonyl groups **23** and **24** appears to be quite different from that just considered (Scheme 12). The photochemical reactivity of compounds containing the groups **23** and **24** appears to be dictated by the facile, intramolecular abstraction of a benzylic hydrogen by one of the nitro group oxygens. The mechanism proposed for this reaction⁽⁷⁶⁾ (Scheme 13) is quite similar to that described earlier for the photochemical reaction of *o*-nitrobenzyl ethers (Scheme 2) and *o*-nitrobenzylidene acetals (Scheme 5).

The formation of an *o*-nitrosobenzaldehyde during photolysis of compounds containing either of the protecting groups **23** or **24** presents a significant experimental problem since an aldehyde reacts readily with the deprotected amine. This difficulty can be overcome by conducting the photochemical reaction in the presence of a reagent (e.g., semicarbazide hydrochloride) which combines with aldehydes (Table 15). One effective solution to this problem is to conduct the photochemical deprotection in the presence

Table 15. Photochemical Deprotection of Amines Protected as *o*-Nitrobenzyloxycarbonyl Derivatives

Protected compound ^a	Percent yield of deprotected amine	Reference
R = Val	100 ^b	76
R = Met	100 ^b	76
R = Pro	100 ^b	76
R = Trp	100 ^b	76
R = Phe - Gly	100 ^b	76
R = Ala	100 ^b , 80	76
R = Phe	100 ^b , 35	76
R = Gly	100 ^b	76
R = Ala	100 ^b , 35	76
R = Phe	17	76
R = Ala	95	76
R = Phe	70	76
R = Glu	94	75
R = D-Leu	70	75
R = Leu-Gly	84	75
 	100	106

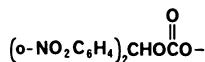
Protected compound ^a	Percent yield of deprotected amine			Reference
R ₁	R ₂	R ₃		
OH	H	H	96	107
OH	H	OCH ₃	100	107
H	OH	H	97	107
H	OH	OCH ₃	98	107

^a See Table 1 for abbreviations.^b Sulfuric acid present during reaction.

SCHEME 13. Proposed Mechanism for Photochemical Reaction of *o*-Nitrobenzyl oxy carbonyl Derivatives.

of a polymer-bound hydrazine derivative.⁽¹⁰⁷⁾ If a photochemically generated aldehyde is immediately removed from the reaction mixture, the yields of deprotected amines are excellent (Table 15).

The 2,2'-dinitrodiphenylmethyloxycarbonyl group **26**, a group quite similar to those just discussed (**23** and **24**), also has been tested as a photore-

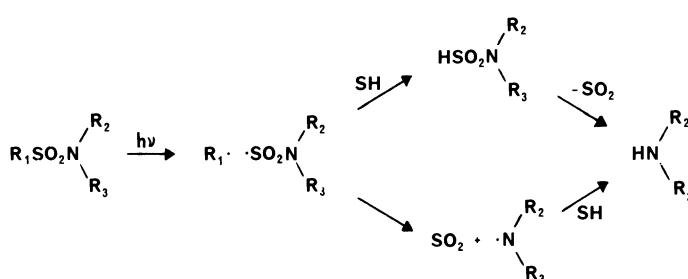


26

movable protecting group⁽⁷⁶⁾ (Table 15). If no aldehyde trapping agents are added to the reaction mixture, higher yields of deprotected amines are realized from the photochemical removal of **26** when compared to removal of **23** and **24**. If, however, aldehydes generated photochemically are removed immediately from the reaction mixture, this protecting group (**26**) has no particular advantage.

7.2. Sulfonamides

In addition to the various benzyloxycarbonyl groups **20–24**, a second important type of amino protection by a photoremovable group is as the sulfonamide.^(8,108–110) Sulfonamides have the advantages that they are easily formed and are resistant to acid and base hydrolysis. Also, amines protected in this fashion are not readily oxidized and are much less nucleophilic. A significant drawback to sulfonamides is, however, that the yields from their photochemical reaction are quite dependent upon compound structure and are sometimes poor (Table 16). A mechanism for the photochemical deprotection process, analogous to that proposed for the reaction of sulfonate esters, is given in Scheme 14.



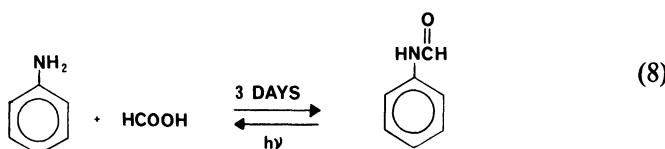
SCHEME 14. Proposed Mechanism for Photochemical Reaction of Sulfonamides.

Table 16. Photochemical Deprotection of Amines Protected as Sulfonamides

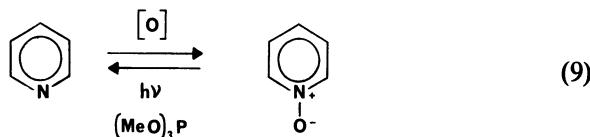
Protected compound	Percent yield of deprotected amine	Reference
PhCH₂SO₂R		
R= N(C ₄ H ₉) ₂	40-78	108
R= NH(CH ₂) ₆ CH ₃	81	108
R= NH(CH ₂) ₅ CH ₃	98	108
R= NHPh	10	108
PhSO ₂ N(C ₄ H ₉) ₂	63-81	108
PhSO ₂ N(C ₂ H ₅) ₂	36	8
p-CH₃C₆H₄SO₂R		
R= Leu	22-48	109
R= His	46-57	109
R= Arg	31	109
R= Cys	29-41	109
R= N(C ₂ H ₅) ₂	33	8
R= N(CH ₂) ₅ CH ₃	30	8
R= Al-Leu	34	110
R= Gly-Asp	64	110
R= Gly-Tyr	59	110
R= Gly	95	110

7.3. Formamides, N-Oxides, and 4,5-Diaryl-4-oxazoline-2-ones

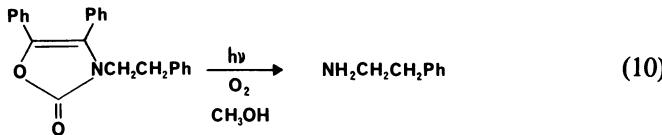
Several other photoremovable protecting groups, ones for which use appears to be restricted to certain types of amines, have been investigated. Formanilides, easily prepared from formic acid and the appropriate amine, are converted quantitatively upon irradiation to the corresponding aniline derivatives⁽¹¹¹⁾ [equation (8)]. Photolysis of N-oxides (formed by oxidation of



pyridine, quinoline, or their derivatives) in the presence of trimethylphosphite removes the protecting oxygen bound to nitrogen⁽¹¹²⁾ [equation (9)]. Finally,

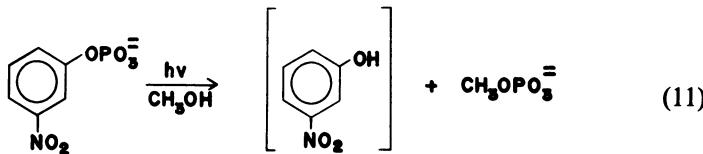


conversion of a primary amine into a 4,5-diaryl-4-oxazoline-2-one can be reversed by photolysis in the presence of oxygen⁽¹¹³⁾ [equation (10)].



8. Phosphates

Two groups for phosphate protection, the *m*-nitrophenyl^(114,115) and the *o*-nitrobenzyl⁽¹¹⁶⁻¹¹⁸⁾ have been studied. The photosensitivity of the *m*-nitrophenyl esters was originally noted by Havinga, De Jongh, and Dorst.⁽¹¹⁹⁾ Although the detailed mechanism of the cleavage has not been studied, it is clear that the process involves a solvolysis of a phosphorus–oxygen bond in which a solvent-derived nucleophile becomes attached to phosphorus,⁽¹²⁰⁻¹²²⁾



as illustrated in equation (11).⁽¹²³⁾ The results reported^(114,115) on phosphate deprotection are given in Table 17.

The *o*-nitrobenzyl group seems to be the protecting group of choice. Two comments need to be made about limitations on the use of both of these groups. The isolation of good yields of the protected mononucleotides using the *o*-nitrobenzyl ester is only possible when a carbonyl-trapping reagent (an insoluble polystyrene-linked semicarbazide) is present during irradiation.⁽¹¹⁶⁾ In the use of the *m*-nitrophenyl ester care must be taken that, if free phosphate is desired, other nucleophiles do not compete with water or hydroxide [note equation (11)].

Table 17. Photochemical Deprotection of Phosphates Protected as *m*-Nitrophenyl and *o*-Nitrobenzyl Esters

Protected compound	Percent yield of free phosphate	Reference
	a	114
	40-50 ^b	"
	a	115
R = H	95	116
R = 3'-O-acetylthymidine	70	"
R = 2',3'-O-isopropylideneuridine	91	"

(Continued)

Table 17. (Continued)

Protected compound	Percent yield of free phosphate	Reference
$R_1 = -, R_2 = H$	90	117
$R_1 = -, R_2 = CH_3$	90	"
$R_1 = ADP, R_2 = H$	25	"
$R_1 = ADP, R_2 = CH_3$	80	"
$R = G-A-U$	a	118
$R = G-A-U_p-G-A-U$	a	"
$R = U(OBz)$	a	41

^a Not given.^b Not isolated.

9. Conclusion

Among photoremoveable protecting groups, the tosyl, phenacyl, *o*-nitrophenylamino, benzyloxycarbonyl, and *o*-nitrobenzyl have been studied in enough detail and have been found to be sufficiently useful to be generally recommended. Each of the first four of these is effective in protecting one type of functional group. The fifth one, the *o*-nitrobenzyl group, is an excellent protecting group for a wide variety of compounds, including alcohols, diols, phenols, carboxylic acids, amides, amines, and phosphates. In addition to its versatility, the *o*-nitrobenzyl group is frequently the best choice for protecting a particular functional group.

The reasons for the success of the *o*-nitrobenzyl group are several. The relatively long-wavelength light (e.g., Pyrex-filtered radiation) which can be absorbed by this protecting group is sufficiently energetic to cause deprotection, but in general, is low enough in energy either not to be absorbed by the deprotected compound or, if absorbed, not to cause reaction. The basic

photochemical process which initiates removal of the *o*-nitrobenzyl group (hydrogen atom transfer) is intramolecular. As a result, deprotection is favored over other possible photochemically initiated reactions. Finally, the actual separation of the protecting group from the molecule being protected is a ground-state process which does not generate reactive intermediates, ones which might follow several different pathways.

The use of photochemically removable protecting groups now should be considered a standard synthetic technique. It provides yet another means for chemical modification of organic compounds under mild and selective conditions. There is still a need for further investigation of the properties of known protecting groups, discovery of new ones, and exploration of new ways in which photoremovable protecting groups may be used.

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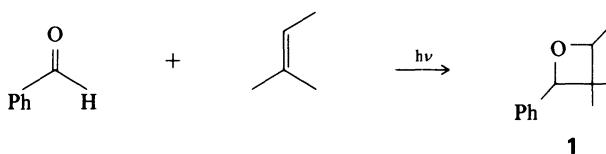
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Photochemical Synthesis of Oxetans

Howard A. J. Carless

1. Introduction

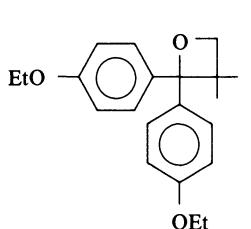
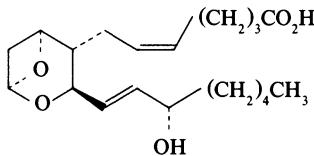
The photoaddition of benzaldehyde to 2-methylbut-2-ene in sunlight to give an oxetan (Scheme 1) represents one of the pioneering experiments in photochemistry, reported in 1909 by Paterno and Chieffi.⁽¹⁾ This synthesis went unnoticed until 1954 when Büchi and co-workers⁽²⁾ investigated the scope of the reaction and were able to confirm the structure of the oxetan adduct as **1**. Since that date, the production of oxetans by photocycloaddition of carbonyl compounds to alkenes has been the subject of much research; hundreds of examples are known, and the scope and limitations of the reaction are now fairly well understood.^(3,4)



SCHEME 1

Nowadays, the photochemical synthesis of oxetans in this manner is often referred to as the Paterno–Büchi reaction; it is a standard reaction of organic photochemistry which has found its way into textbooks.^(5–7) Much effort has been put into understanding the mechanism of this photochemical reaction; in the present chapter, this work will only be mentioned in sufficient detail to give an overall view of the mechanism which is predictively useful. Existing reviews take up the mechanism in greater detail.^(3,4)

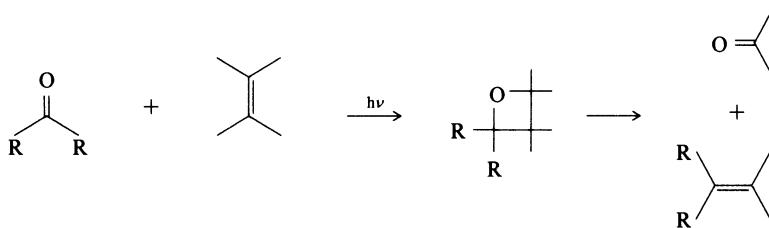
Although oxetans are not commonplace as natural products, they may have significant properties: the oxetan **2** for example, made from 4,4'-dieethoxybenzophenone and 2-methylpropene, has insecticidal activity.⁽⁸⁾ The much sought after thromboxane A₂ molecule **3**,⁽⁹⁾ the biological “counterpart”

**2****3**

of the prostaglandins, is an example of a naturally occurring bicyclic oxetan which might be approached by photochemical reactions. Alternatively, oxetans may serve as intermediates in organic synthesis, and various chemical reactions of oxetans which have been developed are summarized at the end of this chapter.

Büchi's original proof⁽²⁾ of the structure of the oxetan **1** was achieved by acid-catalyzed cleavage of the ring of **1** to give acetaldehyde and benzaldehyde, as well as olefins; no acetone could be detected. This cleavage was the first transposition reaction of a photochemically generated oxetan, and it has been followed in the last 30 years by other examples in which an oxetan is first formed in a photochemical reaction, and then cleaved in a retro-[2+2] manner (Scheme 2). Reagents such as acid, transition-metal ions, or heating have been used to varying effect for this purpose, as will be discussed. If regiochemical control can be achieved in this reaction, it represents a powerful *metathesis* reaction. The general approach of [2+2] photochemical reactions, followed by retro-cleavage, has been extensively and successfully applied to organic synthesis^(10,11) and it has potential in oxetan chemistry.

Photochemical oxetan formation is a versatile reaction, which often proceeds in very high yield. The present classification is mainly based on the types of alkenes which undergo the reaction, followed by the variously substituted carbonyl compounds which have been investigated. The emphasis is



SCHEME 2

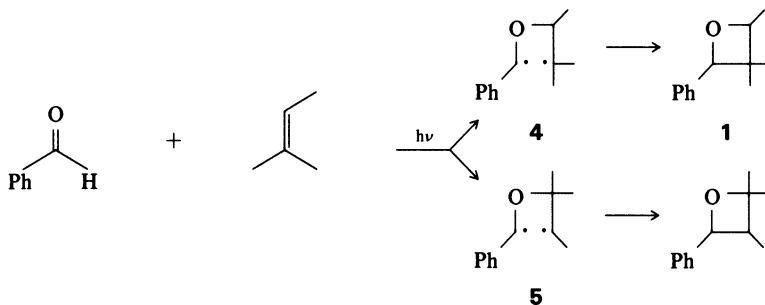
on synthetic chemistry, and chemical or quantum yields are given where possible.

The oxetan ring can also be produced in nonphotochemical reactions (e.g., by intramolecular nucleophilic substitution of 3-halogeno-alcohols), but the strain energy of the four-membered ring means that such reactions are slow (thus being subject to competition with elimination, etc.) and of low yield. Searles⁽¹²⁾ has reviewed general methods for oxetan synthesis, and recent specialized methods have appeared.⁽¹³⁻¹⁵⁾ Thermal [2+2] additions are only usually possible for alkene–carbonyl combinations of strong electron donors and acceptors.⁽¹⁶⁾ For these reasons, photocycloaddition is generally the method of choice for oxetan synthesis.

2. Reaction Mechanism

There is no doubt that the light-absorbing species in these reactions is generally the carbonyl component: alkanones and aromatic carbonyl compounds have a weak ($\log \epsilon = 1-2$) $n \rightarrow \pi^*$ absorption band at 280–350 nm in their uv spectra. While the carbonyl component is initially formed in the singlet excited state, it can rapidly undergo intersystem crossing to become the corresponding triplet (n, π^*) state. Examples of oxetan formation are known from either the singlet or the triplet excited state, or from both in some instances. For aliphatic compounds, the intersystem crossing rate ($k = 10^8$ – 10^9 s $^{-1}$) is much slower than for aromatic carbonyls ($k > 10^{10}$ s $^{-1}$), and this means that there is often a basic distinction in reaction pathway between these two types of compound. Only in the rarest of cases has the excited state of the alkene been shown to be responsible for oxetan formation.^(17,18)

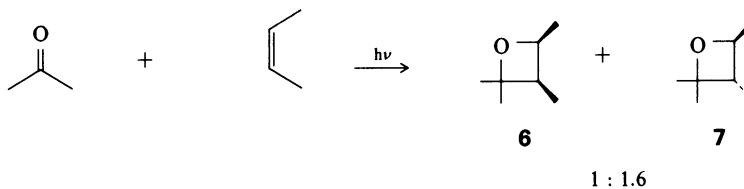
When an excited carbonyl compound reacts with an unsymmetrically substituted alkene, two or more oxetan isomers can result, depending on the orientation of addition. The dominant product in Scheme 1 was rationalized by Büchi⁽²⁾ as arising from a 1,4-biradical intermediate (Scheme 3). The elec-



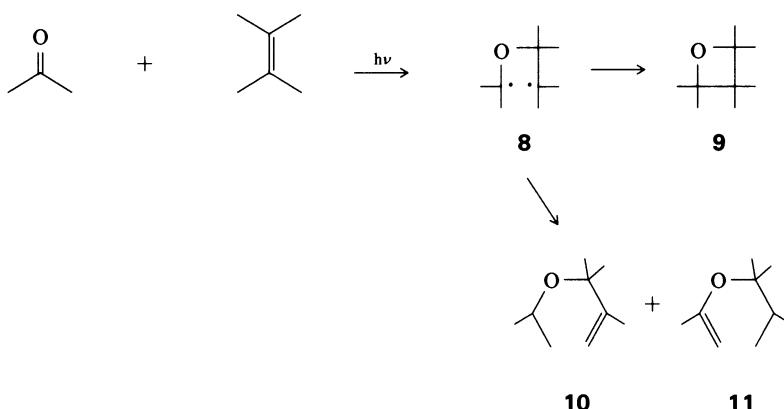
SCHEME 3

triphilic oxygen atom of the excited carbonyl compound could attack the electron-rich alkene to generate 1,4-biradicals such as **4** and **5**. These biradicals might then undergo C–C bond formation to yield oxetan, or undergo bond breakage to regenerate starting materials. Büchi proposed that the reaction occurred through the more stable biradical **4** having a tertiary rather than a secondary radical centre, and thus led to the formation of **1** as the dominant product.

The concept of a biradical intermediate in the Paterno–Büchi reaction has proved itself predictively very useful, and it has received indirect support from several investigations since then. For example, in the photocycloaddition of acetone to *cis*- or *trans*-but-2-ene, a mixture of the *cis*- and *trans*-oxetans **6** and **7** is produced, even before a significant fraction of the but-2-ene has isomerized (Scheme 4).⁽¹⁹⁾ This loss of stereochemistry upon cycloaddition is what is expected from a reaction intermediate such as the 1,4-biradical which exists for long enough to undergo bond rotations before the final ring closure step.

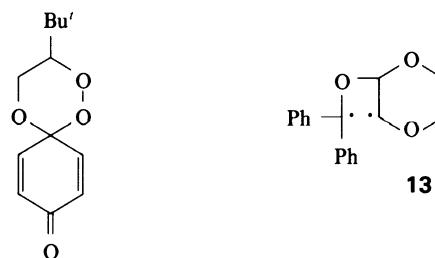


SCHEME 4



SCHEME 5

In the photochemical reaction of acetone with 2,3-dimethylbut-2-ene, several products are formed.⁽²⁰⁾ Alongside the oxetan **9** are found the allyl and vinyl ethers **10** and **11** (Scheme 5), and it is likely that these latter two arise by 1,5-hydrogen shifts in the biradical intermediate **8** in processes which compete with biradical ring closure. Other research has shown that during the photocycloaddition reactions of *p*-benzoquinone to alkenes, 1,4-biradicals may be intercepted by added oxygen^(21,22) or by sulfur dioxide.⁽²³⁾ For example, laser irradiation of *p*-benzoquinone and *t*-butylethylene in solution under oxygen (1 atm) gives predominantly oxetans (69%), while a higher pressure of oxygen (11 atm) reduces the oxetan yield in favor of the 1,2,4-trioxan **12** (66%).⁽²¹⁾ Very recently, spectroscopic studies of the photocycloaddition of benzophenone to 1,4-dioxene have provided direct evidence for the biradical **13**, having a lifetime of 1.6 ns.⁽²⁴⁾



There are indications from several laboratories that an excited-state complex of carbonyl compound with alkene (an exciplex) is a necessary precursor of the biradical intermediate.⁽²⁵⁻²⁷⁾ In such a complex, the alkene appears to act as electron donor and the excited carbonyl compound is the electron acceptor. Compelling evidence for exciplex formation comes from such diverse observations as deuterium isotope effects on oxetan formation,⁽²⁵⁾ studies of the quantum yields of alkene isomerization,⁽²⁶⁾ and the temperature dependence of alkanone fluorescence quenching by alkenes.⁽²⁷⁾ Exciplex formation also allows an energy-wasting route which helps to explain the low-to-moderate quantum yields (e.g., $\Phi = 0.05-0.5$) typically observed for oxetan production.

Despite all the above, it must be stated that there are examples of the Paterno-Büchi reaction which do appear to bypass the biradical intermediate, and they may proceed via concerted mechanisms: the photocycloaddition of alkanones to electron-deficient alkenes⁽²⁸⁾ is a case in point which will be mentioned later.

There are several important considerations which may limit efficient oxetan formation in a particular system. Broadly, these are (1) the nature of the carbonyl excited state; (2) triplet state energy considerations; (3) competing unimolecular pathways for carbonyl reaction; and (4) hydrogen abstraction reactions.

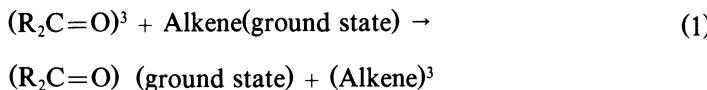
2.1. Carbonyl Excited States

One of the earliest generalizations to emerge from studies of the Paterno-Büchi reaction was that carbonyl compounds which were reduced on irradiation in propan-2-ol were also capable of forming oxetans efficiently in the presence of alkenes.⁽²⁹⁾ Since photoreduction was a known property of the carbonyl $n\pi^*$ excited state, it was reasoned that this must also be the state involved in oxetan production. Both types of reaction are easily understandable if one views the $n\pi^*$ excited state of the carbonyl compound as having an electrophilic oxygen atom. The carbonyl $n\pi^*$ state has analogies in its behavior to the chemistry of alkoxy radicals.^(5,7) Benzaldehyde, for example, undergoes efficient photocycloaddition to 2-methylbut-2-ene (oxetan yield 64%, $\Phi = 0.45$)⁽³⁰⁾ and efficient photoreduction.⁽³⁾ Quenching experiments confirm that it is the triplet state of benzaldehyde which is involved in photocycloaddition to alkenes.⁽³¹⁾ The consistent mechanistic picture is completed by phosphorescence emission spectra, which show a lowest $n\pi^*$ triplet state for benzaldehyde. Those aromatic carbonyl compounds which have lowest $\pi\pi^*$ triplet states are generally much less reactive or totally unreactive towards oxetan formation: thus 2-acetonaphthone⁽³⁰⁾ and 4-phenylbenzophenone⁽³⁾ do not react on irradiation in the presence of 2-methylbut-2-ene and 2-methylpropene, respectively.

In comparison with phenyl ketones, polycyclic aromatic carbonyl systems (e.g., 2-naphthaldehyde, 9-anthraldehyde)^(30,31) have a reduced intersystem crossing rate as a consequence of the larger singlet-triplet energy splitting. The possibility then arises of a *singlet nπ** reaction (as for alkanones): in these circumstances, the oxetan formation is highly stereoselective⁽³²⁾ although usually of low quantum yield. For example, 2-naphthaldehyde reacts with 2-methylbut-2-ene (oxetan yield 70%, but $\Phi = 0.05$).⁽³⁰⁾ From a synthetic point of view, such low quantum yields are not a serious disadvantage since it is easy to compensate for them by continuing irradiations for a longer period of time; generally it is more important to have a high chemical yield of oxetan to allow for its easy isolation from the photoproducts.

2.2. Triplet Energies

Singlet energy transfer from an excited carbonyl compound to an alkene is not energetically possible, but the same cannot be said for the triplet state. When the triplet state energy of the alkene falls below that of the carbonyl compound, triplet-triplet energy transfer [equation (1)] becomes fast (up to the diffusion-controlled rate) and efficient.



The triplet state of the alkene will not give oxetan, but usually leads to *cis-trans* isomerization and other unwanted reactions such as alkene dimerization. The occurrence of triplet energy transfer thus provides a major limitation to oxetan formation. Some triplet state energies of potential addends in the Paterno-Büchi reaction are given in Table 1, and they are valuable in understanding the limitations of the reaction. More extensive tables of triplet energies are available,^(3,33,34) but because alkenes do not phosphoresce, there is a lack of reliable data on their triplet energies. The quenching of triplet phenyl ketones by alkenes has been carefully studied in an attempt to disentangle charge transfer and triplet-triplet energy transfer components of the quenching.⁽³⁵⁾

Norbornene has been used as a probe for triplet-triplet energy transfer, because the norbornene triplet gives dimers. When carbonyl compounds are irradiated in the presence of norbornene, the ratio of oxetan to norbornene dimers depends critically upon the triplet energy of the carbonyl compound, as has been demonstrated by Arnold.⁽³⁾ Ketones with triplet energies greater than 72 kcal mol⁻¹ (301 kJ mol⁻¹) (e.g., acetophenone, see Table 1) yield some oxetan but mainly dimers.⁽³⁶⁾ Conversely, those ketones with triplet energies lower than this value (e.g., benzophenone) give largely oxetan.

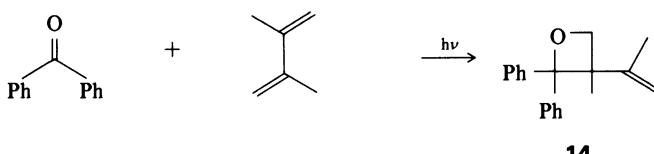
Table 1. Triplet State Energies (E_T) of Components in the Paterno–Büchi Reaction

Carbonyl compound	Alkene	E_T	
		(kcal mol ⁻¹)	(kJ mol ⁻¹)
Acetone	Ethene	82	(343)
	But-2-ene	82–79	(343–330)
Acetophenone		78	(326)
	Norbornene	73.5	(307)
Benzaldehyde		72	(301)
	Benzophenone	68.5	(286)
Styrene		61.5	(257)
	Penta-1,3-diene	59–57	(247–238)
Biacetyl		56	(234)
<i>p</i> -Benzoquinone		50	(209)

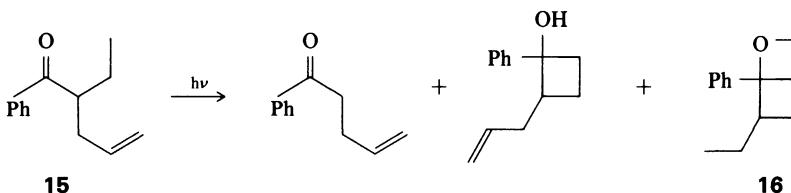
Conjugated dienes (e.g., penta-1,3-diene) have low triplet energies and thus make good quenchers of the triplet state of carbonyl compounds; they have traditionally been used for this purpose in mechanistic studies. Nevertheless, examples of oxetan formation involving dienes are known (see Section 3.2); they usually arise from the singlet excited carbonyl compound. Otherwise, the reactions occur with very low quantum efficiencies: benzophenone and 2,3-dimethylbuta-1,3-diene, for example, give the oxetan **14** in reasonable yield (40%), but with a quantum yield of only 0.0003 (Scheme 6).⁽³⁷⁾

2.3. Competing Reactions

Photochemical oxetan formation requires a bimolecular reaction in which an excited-state carbonyl compound attacks ground-state alkene. If there are efficient unimolecular processes which deactivate or destroy the excited carbonyl moiety, then oxetan formation will be less dominant.⁽³⁹⁾ Thus, the unsaturated ketone **15** shown in Scheme 7 undergoes Norrish type-II reaction ($\Phi = 0.0014$) and cyclobutanol formation ($\Phi = 0.0010$) by intramolecular

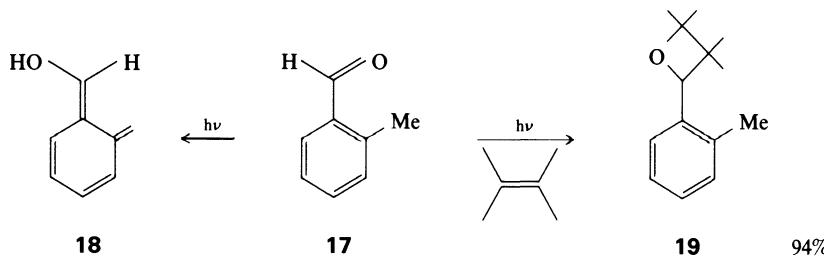


SCHEME 6



SCHEME 7

γ -hydrogen abstraction, and these processes are in competition with the intramolecular formation of an oxetan **16** and its decomposition products ($\Phi = 0.0061$, in total).⁽³⁸⁾ Photoenolization of *ortho*-alkyl substituted aromatic carbonyl compounds is usually thought of as an efficient photochemical reaction [e.g., **17** \rightarrow **18** in Scheme 8],⁽⁴⁰⁾ but the possibility of its occurrence does not detract from the photocycloaddition of *o*-methyl substituted benzaldehydes to 2,3-dimethylbut-2-ene, which is so efficient that the quantum yield of oxetan **19** formation from *o*-tolualdehyde **17** ($\Phi = 0.53$) is not reduced below that found from benzaldehyde.⁽⁴¹⁾ However, those carbonyl compounds which undergo rapid Norrish type-I (e.g., cyclobutanone) or type-II (e.g., 5-methylhexan-2-one) reactions will make relatively unsuitable partners in the Paterno–Büchi reaction. Rate constants for γ -hydrogen abstraction are generally 10^7 – 10^9 s^{−1}, and have been usefully summarized for alkanones.⁽³⁹⁾ Since rate constants for exciplex formation (leading to oxetan) are typically 10^7 – 10^9 liters mol^{−1} s^{−1}, it is possible to use a high concentration of alkene (≥ 1 mol liter^{−1}) to assist the *bimolecular* reaction and thus give higher yields of oxetan. Relatedly, if oxetan formation occurs from the singlet excited state of the carbonyl compound, it may be better to use a high concentration of alkene to allow photocycloaddition to compete more effectively with the unimolecular process of intersystem crossing to the carbonyl triplet state.⁽⁴²⁾



SCHEME 8

2.4 Hydrogen Abstraction

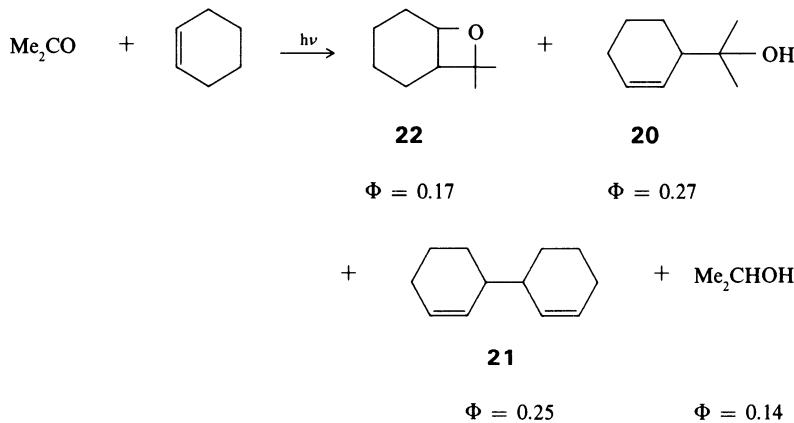
A final limitation on oxetan production arises from the fact that $n\pi^*$ photoexcited carbonyl compounds are generally good abstractors of hydrogen atoms, and they may react with alkenes in this alternative manner. The resulting radical pairs can combine in various ways to give unsaturated alcohols and hydrocarbons. These abstraction reactions can compete with or even dominate over oxetan formation, but generally they present a relatively minor problem because of the low rate constants for hydrogen abstraction (10^5 – 10^6 liters mol $^{-1}$ s $^{-1}$)^(33,39) in comparison with the photocycloaddition reaction. Hydrogen abstraction is particularly favored from allylic positions of the alkene, if the resulting allylic radical is resonance stabilized.

Acetone reacts with cyclohexene on irradiation,^(43,44) for example, to give various hydrogen-abstraction products (e.g., **20** and **21**) in competition with oxetan **22** formation (Scheme 9). Four similar hydrogen-abstraction products are formed from the photoreaction of acetone with 2,3-dimethylbut-2-ene.⁽²⁰⁾

Aliphatic aldehydes (RCHO) are prone to a related intermolecular hydrogen abstraction; at high concentration, an excited-state aldehyde may react with another molecule of ground-state aldehyde to give an α -ketol [RCH(OH)COR].⁽⁴⁵⁾

3. Alkene Addends

Many investigators have examined the range of alkenes which will add photochemically to simple carbonyl compounds in the Paterno–Büchi reaction. It is proposed to summarize these results according to the type of alkene



SCHEME 9

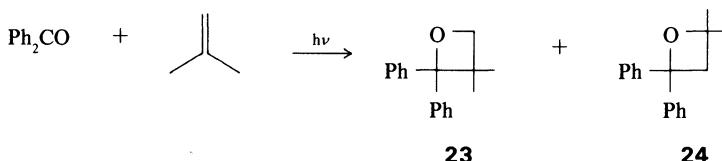
involved, because alkene substitution pattern directly controls the mechanism of the photoreaction.

There is little need to give details of the experimental conditions required for these photocycloadditions, since these are well summarized, with experimental procedures,⁽³⁾ in previous reviews.^(3,4,46) Typical conditions would involve the uv irradiation of solutions of the reactants in an inert solvent such as benzene, using a medium-pressure mercury arc and quartz apparatus. The lack of a chromophoric grouping in the oxetan product ensures that it is normally photochemically inert once formed. Nitrogen is often bubbled through the solution during irradiation, to keep it stirred and to prevent photooxidation reactions.

3.1. Simply Substituted Alkenes

The earliest reports of oxetan formation dealt with the photocycloaddition of aldehydes and ketones to acyclic alkenes.^(1,2) Arnold *et al.*,⁽²⁹⁾ for example, examined the photochemical reaction of benzophenone with a variety of methyl-substituted alkenes, and found good yields of oxetans (58%–93%) from all cases except that of propene (5%). The scope of the reaction was shown by the fact that methyl, methoxy, and chloro-substituted benzophenones added efficiently to 2-methylpropene (74%–81%). Photoreaction did not occur for aromatic ketones having $\pi\pi^*$ (xanthone) or charge-transfer lowest excited states [4,4'-bis(dimethylamino)benzophenone]. Some idea of the *regioselectivity* of the reaction can be gained from their results on the addition of benzophenone to 2-methylpropene in which the oxetans **23** and **24** were formed in a 9:1 ratio (Scheme 10). This clear preference for the oxetan **23** which arises from the more stable biradical intermediate is also seen in the photoaddition of acetone to 2-methylpropene, where 3-substituted oxetan dominates over the 4-substituted isomer (4.5:1).⁽¹⁹⁾

It is generally the *triplet* excited state which is responsible for these additions; they probably occur via a relatively long-lived triplet biradical and reaction is therefore nonstereoselective. Thus, irradiation of benzophenone

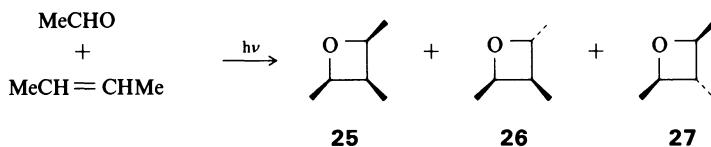


SCHEME 10

and *cis*-but-2-ene gives a mixture of *cis*- and *trans*-oxetans (ratio, 1:6),⁽²⁵⁾ as also found for acetone and *cis*-but-2-ene (Scheme 4).⁽¹⁹⁾

In contrast, Yang and Eisenhardt⁽⁴⁷⁾ found that the photocycloaddition of acetaldehyde to but-2-ene was highly stereoselective. As shown in Scheme 11, three stereoisomeric oxetans 25–27 were formed in the reaction in reasonable quantum yields ($\Phi = 0.13\text{--}0.16$ at 5 mol liter⁻¹ alkene). The use of *cis*-but-2-ene gave an 8:1 preference for those oxetans 25 and 26 in which the stereochemistry of the original *cis*-butene unit was maintained. *Trans*-but-2-ene led to an even higher preference (27:1) for the *trans*-arranged oxetans 26 and 27. This was the first of several observations to suggest that alkanals are more reactive towards photocycloaddition than alkanones. In the initially formed singlet excited state, alkanals are thus able to react with alkene (especially at high alkene concentration) at a rate which is competitive with intersystem crossing to the carbonyl triplet. Thus, the photoreaction of acetaldehyde with 2,3-dimethylbut-2-ene gives an oxetan quite cleanly,^(47,48) whereas the photoreaction of acetone with the same alkene leads to a complex mixture of seven products which arise from both the singlet and triplet excited states of acetone.⁽²⁰⁾ In summary, photocycloaddition reactions of alkanals to alkenes and alkadienes are therefore often highly stereoselective singlet state reactions.^(40,49) By contrast, reactions of alkanones occur by triplet or a mixture of singlet and triplet pathways.^(20,50)

Yang and Eisenhardt⁽⁴⁷⁾ also noted that propanal reacted with various alkenes to give oxetans as the major products, with the exception of the monosubstituted alkene hex-1-ene which yielded the saturated ketone, nonan-3-one, as the major product. Such free-radical addition of aldehydes to alk-1-enes under the influence of uv light had previously been reported by Kharasch⁽⁵¹⁾ and it doubtless involves generation of alkanoyl radicals (RCO^\cdot) and their subsequent addition to the alkene. It is generally an important pathway only in the photoaddition of aldehydes to monosubstituted alkenes, although an early note on the photoreaction of acetone with norbornene⁽⁵²⁾ reported 2-acetonylnorbornane (45%) as the major product, presumably formed by a free-radical pathway.

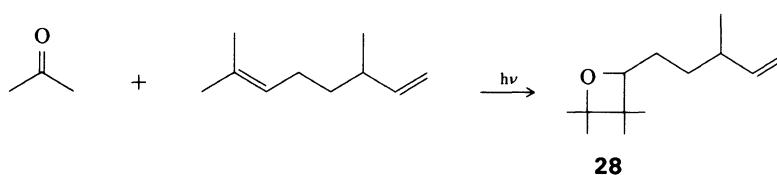


SCHEME 11

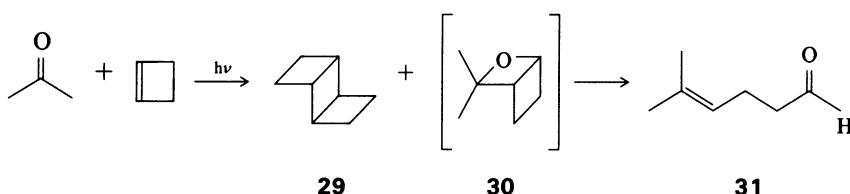
For alkanones, it is clear that the rate constant for exciplex formation (and thus for oxetan production) depends on the substitution pattern of the alkene addend. Increased alkyl substitution lowers the ionization potential of the alkene, and increases the rate of *singlet* exciplex formation (as can be studied from the quenching effects of the alkenes on the fluorescence of the alkanone).⁽²⁷⁾ Selectivity of attack at more substituted double bonds of alkenes is therefore likely, as evidenced by the formation of the oxetan **28** (20%) from irradiation of acetone in the presence of 3,7-dimethylocta-1,6-diene (Scheme 12).⁽⁵³⁾

In these photocycloadditions, it is possible to have some variety in the substituents on the alkene without undue detraction from the oxetan yield. The chloromethyl-substituted alkene, 3-chloro-2-methylpropene, reacts with aromatic aldehydes to give oxetans of the expected orientation in fair yields (18%–39%),⁽⁵⁴⁾ although chloro-substituted alkenes themselves do not give the Paterno–Büchi reaction.⁽³⁾ Fluoroalkenes such as tetrafluoroethene undergo photocycloaddition to acetaldehyde as a minor process (1.1%–2.8%) in competition with the formation of saturated ketones.⁽⁵⁵⁾ This last example is notable as one of the rare cases of photochemical oxetan formation in the gas phase. Despite their low triplet energies (see Table 1), styrenes (phenylalkenes) will undergo photocycloaddition to aldehydes.⁽⁵⁶⁾ On irradiation, acetaldehyde reacts with the *cis*- and *trans*- isomers of 1-phenylprop-1-ene to yield 2,4-dimethyl-3-phenyl oxetans in reasonable yield (60%) and in a highly stereo-selective reaction ($\geq 95\%$ and $\geq 98\%$ retention of stereochemistry, respectively), probably via the singlet excited state of the aldehyde.⁽⁵⁷⁾ Even aromatic aldehydes will react with styrenes, though the reaction appears less stereo- and regioselective. In the simplest example, benzaldehyde reacts with styrene itself to give *cis*- and *trans*-2,3-diphenyloxetan in a 1:1 ratio (31% isolated yield).⁽⁵⁸⁾

The photocycloaddition of carbonyl compounds to cycloalkenes produces bicyclic oxetans which have proved themselves useful as synthetic intermediates. Often, the nature of the reaction products depends upon alkene concentration. Irradiation of a solution of cyclobutene in acetone led, at low

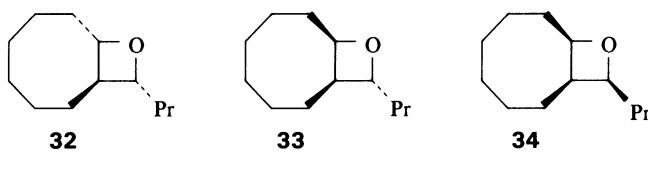


SCHEME 12



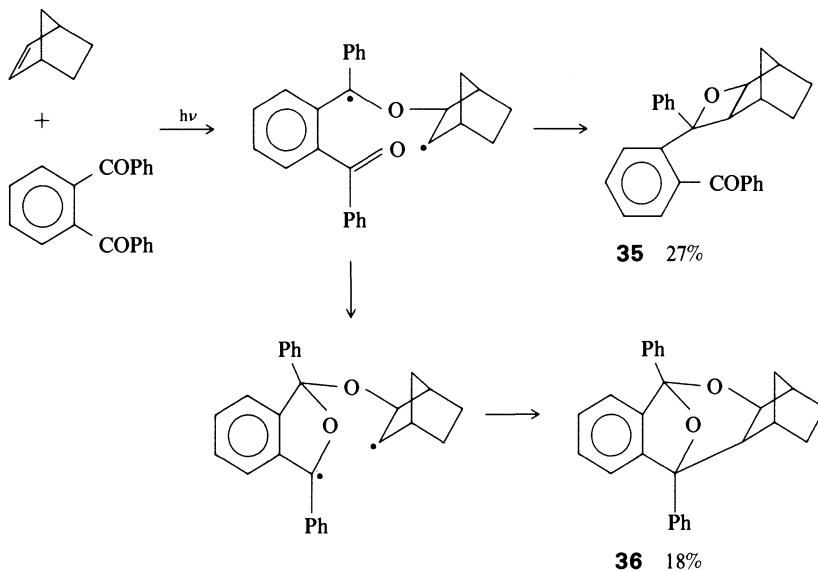
SCHEME 13

cyclobutene concentration, to the free-radical product, cyclobutylacetone; at high alkene concentration, cyclobutene dimer **29** and unsaturated aldehyde **31** were isolated as the main products (Scheme 13).⁽⁵⁸⁾ The aldehyde **31** was believed to be formed from decomposition of the oxetan **30**; thermal instability of such strained bicyclic oxetans is taken up in detail later. The yield of oxetan from acetone and cyclopentene is increased from 16% to 28% on irradiation at low temperature (-78°C),⁽⁵⁹⁾ while cyclohexene is a more reluctant partner (8% oxetan).⁽⁴³⁾ Cyclooctene is claimed to give a “good” yield of two stereoisomeric oxetans on irradiation with acetone.⁽⁵⁰⁾ In the photoreactions of butanal and cyclopentene, Jones⁽⁴⁾ has emphasized that the ratio of oxetans to unsaturated alcohols (see Section 2.4) is dependent on alkene concentration; only at high alkene concentrations do the oxetan stereoisomers become dominant. Moreover, Jones and co-workers⁽⁴²⁾ have shown how reactions of this type become more stereoselective at higher alkene concentrations, as summarized in Scheme 14 for the distribution of oxetans **32**–**34** from butanal and *cis*-cyclooctene. From the results, it appears that formation of the *trans*-fused cyclooctane ring of **32** is favored at low alkene concentrations (via the triplet biradical), but that at high concentrations a stereoselective, singlet reaction prevails.



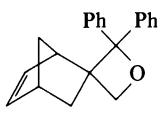
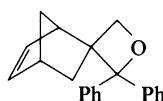
Alkene, 0.5M	65%	17%	18%
Alkene, neat	3%	47%	50%

SCHEME 14

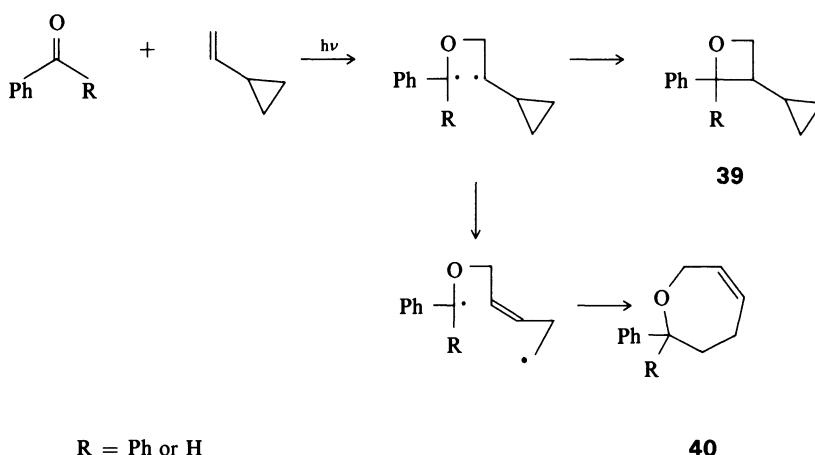


SCHEME 15

As already mentioned, norbornene gives efficient photocycloaddition to carbonyl compounds of suitable triplet energy^(3,36): benzophenone, for example, gives the oxetan expected from *exo*-attack in 80% yield.⁽⁶⁰⁾ On occasions, the 1,4-biradical intermediate in cycloaddition may be intercepted by another functional group, as in the formation of the dioxans **36** in competition with oxetan **35** from irradiation of *o*-dibenzoylbenzene in the presence of norbornene (Scheme 15).⁽⁶¹⁾ Interestingly, 5-methylenenorborn-2-ene gives the oxetans **37** and **38** (55% and 15%, respectively) in a regiospecific attack at the exocyclic double bond.^(62,63)

**37****38**

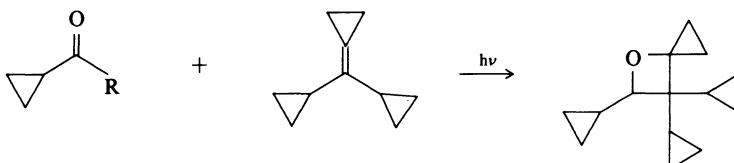
The well-known tendency of the cyclopropylcarbinyl radical to rearrange to the allylcarbinyl radical has been used as a test for the involvement of 1,4-biradicals in the Paterno–Büchi reaction. Thus, uv irradiation of a benzene solution of cyclopropylethene and benzophenone or benzaldehyde produced the expected oxetan **39** and a rearranged tetrahydroooxepin **40** (Scheme 16).⁽⁶⁴⁾



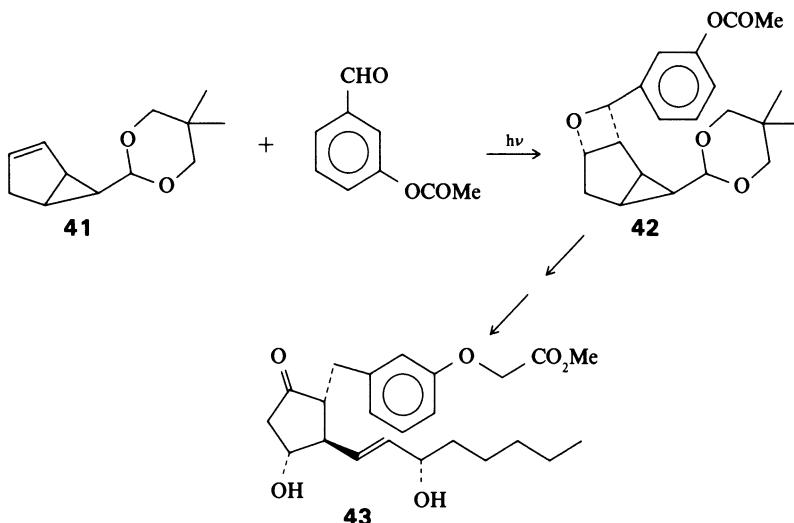
SCHEME 16

The formation of these products can be explained by competition between direct ring closure of the triplet biradical intermediate to yield **39**, and cyclopropylcarbinyl-type radical rearrangement followed by ring closure to produce **40**. At room temperature the oxetan **39** predominates, but increased temperature favors the product of radical rearrangement. Whether this rearrangement occurs in competition with oxetan formation depends critically on the cyclopropylalkene substitution pattern.⁽⁶⁵⁾ The remarkable addition shown in Scheme 17 demonstrates that such rearrangement is less prevalent in the cycloaddition of aliphatic cyclopropyl aldehydes and ketones, possibly because of a singlet reaction mechanism.⁽⁴⁹⁾

Photocycloaddition of the optically active cyclopentene **41** and *m*-acetoxybenzaldehyde (Scheme 18) has been used in an ingenious approach to the synthesis of an aromatic prostaglandin analog, **43**.⁽⁶⁶⁾ The oxetan ring of the tricyclic adduct **42** was opened by reductive cleavage using palladium and



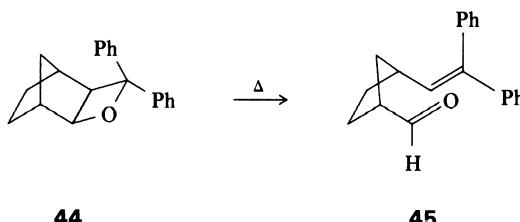
SCHEME 17



SCHEME 18

hydrogen, in 30% overall yield from **41**; further synthetic transformations gave the optically active prostanoid **43**. Benzylic cleavage of the oxetan ring could also be effected in a simpler model system using dissolving metal reduction ($\text{Na}/n\text{-BuOH}$).

It is possible to form an oxetan by [2+2] photocycloaddition and then to cleave it in the reverse mode, resulting in a metathesis reaction (Scheme 2). Thus, the oxetan **44** from benzophenone and norbornene shown in Scheme 19 is cleaved in an entirely regiospecific manner on heating to yield the unsaturated aldehyde **45**.⁽⁶⁷⁾ Such thermal fission of oxetans is often a clean reaction, occurring at 300–450°C.⁽⁶⁸⁾ For simply substituted oxetans, such as



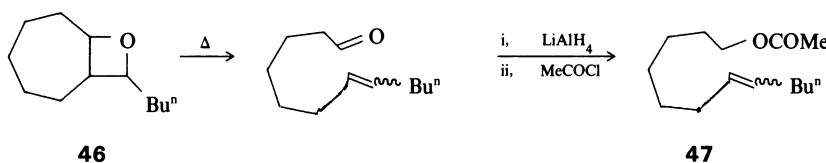
SCHEME 19

the stereoisomers of 2,3,4-trimethyloxetan, the 1,4-biradicals formed by both C—C and C—O bond cleavage are implicated in the reaction.⁽⁶⁹⁾ The stereoselectivity of such cleavage is therefore not marked in the case of alkyl-substituted oxetans, although a highly stereoselective thermal cleavage of 2-aryl substituted oxetans has been noted.^(70,71) A study of the regio- and stereochemical aspects of the thermal cleavage of several oxetans has produced no evidence for polar intermediates in the reaction.^(72,73) The use of this metathesis reaction is particularly appropriate for the synthesis of insect pheromones, such as dodec-7-enol acetate **47** (Scheme 20). Photolysis of pentanal and cycloheptene in acetonitrile solution gave stereoisomers of the oxetan **46** (30%); pyrolysis at 550°C and subsequent conventional steps converted the oxetans into a 1:1 mixture of the *cis*- and *trans*-isomers of dodec-7-enol acetate **47**, active as moth attractants.⁽⁴⁾

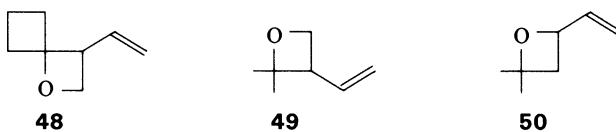
As an alternative to thermolysis, it is possible to cleave the oxetan ring by the use of transition-metal catalysts such as Rh(I) or Ag(I) compounds.^(74–76) For alkyloxetans, it may be useful to note that the cleavage may have different consequences from thermolysis, having been shown to be highly stereoselective using $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ or AgBF_4 at 80°C.⁽⁷⁵⁾ Nevertheless, there are limitations to the use of Rh(I) catalysis in oxetan cleavage, as shown by the failure of compound **46** to react even at 140°C.⁽⁴⁾

3.2. Dienes and Trienes

Despite the low triplet energy of conjugated dienes (Section 2.2), several examples of oxetan formation involving them have been observed, often in respectable chemical yields. For cycloaddition to aliphatic carbonyl compounds, these reactions have been shown to involve attack of the *singlet* excited carbonyl state on the diene.^(27,45,77) Early examples to be noted include the reaction of photolabile cyclobutanone with buta-1,3-diene at –78°C to give an oxetan **48** in 20% yield.⁽⁷⁸⁾ Acetone and butadiene react on irradiation to give the oxetans **49** and **50** in 8% and 2% yields, respectively, along with diene dimers.⁽⁷⁷⁾ Photocycloaddition of acetone to conjugated dienes appears



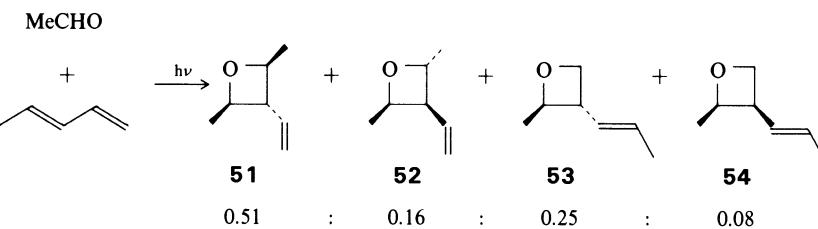
SCHEME 20



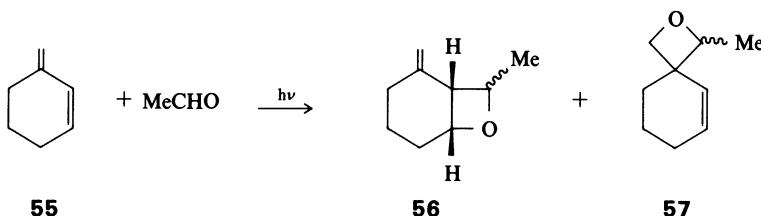
to be a fairly general reaction, although the above is the only example in which a 4-enyloxetan has been found: the orientation of addition is such that the reaction specifically gives 3-enyloxetans analogous to **49**. The cycloaddition is relatively efficient, since pentan-2-one reacts with buta-1,3-diene to give oxetan formation in competition with the products of Norrish type-II reaction of the ketone.

If the triplet state of the diene is formed, it is likely to lead on to the production of diene dimers. The higher reactivity of aliphatic aldehydes towards photocycloaddition in comparison with aliphatic ketones means that diene dimer production is much more important when ketones are the addends.^(49,79) Nevertheless, the singlet reaction mechanism ensures that oxetan yields are at their best relative to diene dimers when a high concentration of diene is used.^(80,81)

In view of the widespread use of penta-1,3-diene (piperlylene) as a quencher of triplet carbonyl compounds, photocycloadditions to this diene are of interest. These reactions clearly indicate that some singlet quenching of carbonyl excited states is also possible. 3-Methylenecyclobutanone adds to *cis*- or *trans*-penta-1,3-diene in a stereospecific manner.⁽⁷⁸⁾ This point has been examined in more detail in a study of the photocycloaddition of acetaldehyde to the same diene.⁽⁷⁹⁾ Seven oxetan products were formed, and it was possible to show that cycloaddition was highly stereoselective, giving more than 97% retention of configuration of the diene geometry in the oxetan products. For example, *trans*-penta-1,3-diene gave the oxetans **51**–**54** in the ratios shown in Scheme 21. These results show a regioselective attack at the more substituted double bond (ca. 65%), and a preference (ca. 77%) for a



SCHEME 21



SCHEME 22

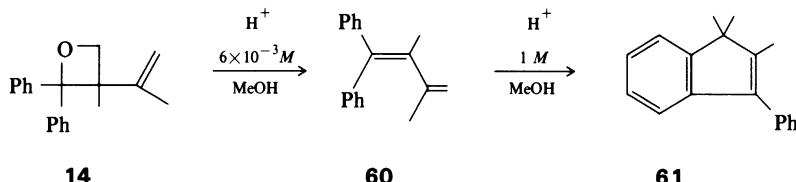
trans-arrangement of the diene enyl grouping and the acetaldehyde methyl in the oxetans produced. Independent work suggests that other alkanals, as well as isopropyl and cyclopropyl methyl ketone, react similarly with pent-1,3-diene.⁽⁴⁹⁾ In the reactions of butanal, pentanal, and 2-methylpropanal with 2,5-dimethylhexa-2,4-diene, the derived rate constants for oxetan formation are found to be close to those for fluorescence quenching of the aldehydes by the diene.⁽⁴⁵⁾

In attack on the conjugated diene **55** (Scheme 22), the photoaddition of acetaldehyde occurs at the terminal methylene group as readily as at the endocyclic double bond, as judged from the distribution (52:48) of the oxetan isomers **56** and **57** which are together produced in 23.5% yield on irradiation in pentane solution.⁽⁸²⁾ Turro and co-workers^(27,83) have reported a similar lack of selectivity in the attack of singlet excited acetone on *trans*-2-methylhexa-2,4-diene: the di- and tri-substituted double bonds are attacked with equal ease (but by stereospecific reactions), to yield oxetans.

Aliphatic aldehydes (e.g., propanal) react with cyclohexa-1,3-diene to give *exo* and *endo* isomers of bicyclic oxetans, such as **58** and **59** formed in



yields of 70% and 10%, respectively, plus a small amount of diene dimers.⁽⁸¹⁾ Jones⁽⁷⁶⁾ has used these oxetans in an ingenious approach to *trans*-non-6-enol, a sex attractant of the Mediterranean fruit fly. The individual steps are photocycloaddition, hydrogenation of the mixture of oxetans **58** and **59**, rhodium(I)-catalyzed cleavage of the oxetans, and lithium aluminum hydride reduction, and proceed in 40%–50% overall yield (cf. Scheme 20). This indirect approach was used because the oxetan yield from cyclohexa-1,3-diene is much



SCHEME 23

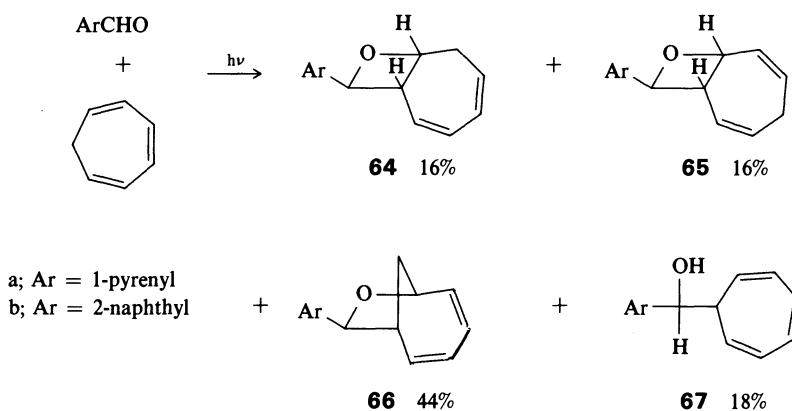
higher than from cyclohexene, in line with the greater ease of exciplex formation for the diene. Analogous oxetans are the favored products from photolysis of pentanal and cyclopentadiene at high diene concentrations, and from 3-acetoxypalanal and cyclopentadiene (38% yield).⁽⁴⁾ They can be cleaved by rhodium(I) catalyzed reaction to give straight-chain unsaturated aldehydes. UV irradiation of acetone in the presence of the "twisted" diene, cycloocta-1,3-diene, gives two stereoisomeric oxetans which are *cis* and *trans* fused about the ring junction⁽⁵⁰⁾: in this case, there is evidence that cycloaddition may occur by a triplet mechanism.⁽⁸⁴⁾

In the rarer cases of photocycloaddition of aromatic ketones to conjugated dienes (e.g., Scheme 6), it has been shown that the triplet state of the carbonyl compound is responsible for reaction, which is in inefficient competition with triplet energy transfer from carbonyl compound to diene.⁽³⁷⁾ These oxetans are sensitive to cleavage by acids, which had led to the failure by previous workers to isolate them.⁽⁸⁵⁾ The oxetan **14**, formed on irradiation of benzophenone and 2,3-dimethylbuta-1,3-diene, is easily converted by dilute perchloric acid to the diphenylbutadiene **60** in high yield (92%) (Scheme 23).⁽³⁷⁾ Stronger acid produces a useful route to the substituted indene **61** (91%). Oxetans analogous to **14** are formed by irradiation of benzophenone with buta-1,3-diene, 2-methylbuta-1,3-diene, and 2,5-dimethylhexa-2,4-diene. Photoexcited benzophenone attacks the conjugated enyne, 2-methylbut-1-en-3-yne, preferentially at the double bond, to give oxetan **62** in 58% yield. Treatment of **62** with dilute acid produces (58%) the aromatic conjugated enyne **63**.⁽⁸⁶⁾



62

63



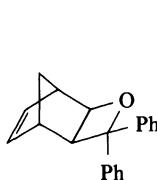
SCHEME 24

Yang and Chiang⁽⁸⁷⁾ have shown that aromatic aldehydes can give photocycloaddition to cyclohepta-1,3,5-triene. The products, shown in Scheme 24 with their yields from 1-pyrene-carboxaldehyde, include the two *exo*-oxetans **64** and **65**, as well as the remarkable [2+6] adduct **66**, and an alcohol arising from hydrogen abstraction **67**. The stereoselectivity of the formation of **66** is advanced as evidence for a concerted $[\pi 6_s + \pi 2_s]$ cycloaddition. Significantly, the photocycloaddition of these aldehydes to cycloheptene adopts a different route, giving both *exo*- and *endo*-oxetans.

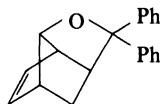
Homoconjugated dienes, such as norbornadiene **68**, are of interest because of their triplet-sensitized isomerizations (e.g., of **68** to quadricyclane **69**), which have potential as a means of storage of solar energy.^(88,89) However,



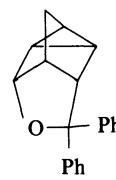
some sensitizers, such as aliphatic⁽⁴⁸⁾ and aromatic carbonyl compounds,⁽⁹⁰⁻⁹²⁾ can undergo photocycloaddition to these systems: irradiation of benzophenone and **68**, for example, gives the *exo*-oxetan **70** as the major product (32%), and the ethers **71** and **72** (15% and 3%, respectively).⁽⁹⁰⁾ The formation of these latter two products is easily understood in terms of the well-known homoallyl-cyclopropylcarbinyl rearrangement in the norbornenyl radical end of the 1,4-biradical intermediate. Gorman and co-workers^(63,91) have shown that it is in fact quadricyclane **69** rather than norbornadiene which is re-



70

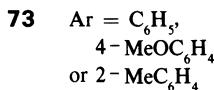
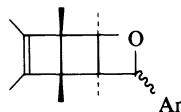


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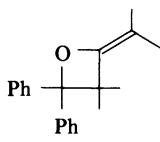
72

sponsible for these reactions. Aromatic aldehydes will even give photocycloaddition to hexamethyl(Dewar benzene) to produce the oxetans **73** 20%–29%, in competition with the triplet-energy transfer process which gives hexamethylbenzene.⁽⁹³⁾

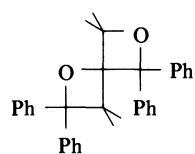


3.3. Allenes and Ketenimines

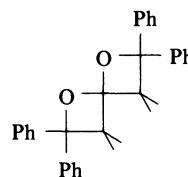
Photocycloaddition of aliphatic and aromatic ketones to allenes provides a route to usefully functionalized oxetans which may then be converted to cyclobutanones.^(94,95) For example, irradiation of benzophenone and tetramethylallene gives a 1:1 adduct **74** (37%), and two 2:1 adducts **75** and **76**



74



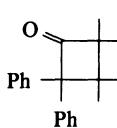
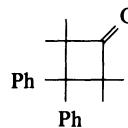
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76

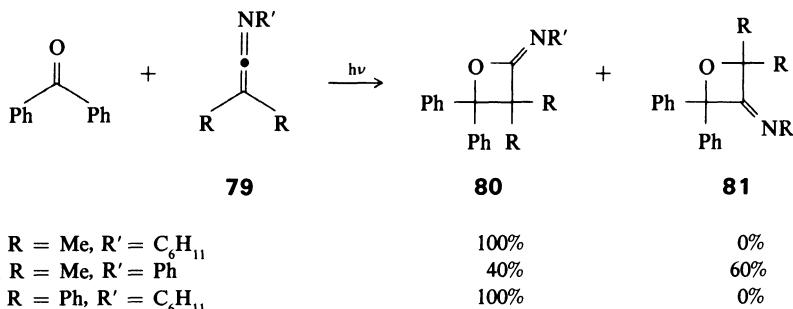
(28% and 15%, respectively).^(94,96) The initial addition of triplet benzophenone to the allene is regiospecific, with attack of the electron-deficient oxygen atom on the central carbon of the allene, leading to alkylideneoxetan **74**. Further attack of excited benzophenone on **74** to give the two bis(oxetans) is less selective, as would be expected from the presence of the vinylic ether functional group in **74** (see Section 3.5). In contrast, the irradiation of benzophenone

and allene gives only a bis(oxetan) (38%) having orientation analogous to **75**.^(96,97) Treatment of the isopropylideneoxetan **74** with neutral alumina leads cleanly (97% yield) to a 78:22 ratio of the cyclobutanones **77** and **78**, pre-

**77****78**

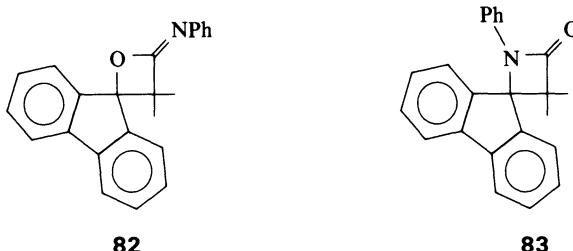
sumably by a ring opening–reclosure route.⁽⁹⁷⁾ There are indications that a similar rearrangement to cyclobutanones can occur upon triphenylene-sensitized photolysis of alkylideneoxetans.⁽⁹⁴⁾

Ketenimines have also been found to make good addends in the Paterno–Büchi reaction, adding to both aromatic⁽⁹⁸⁾ and aliphatic ketones.⁽⁹⁹⁾ Benzophenone reacts by a route shown to involve attack of the triplet carbonyl compound on ground-state ketenimine in competition with triplet energy transfer,⁽⁹⁸⁾ whilst fluorenone reacts from both singlet and triplet excited states.⁽¹⁰⁰⁾ Adducts with the α - **80** and β -imino-oxetan **81** structure are possible, and their relative proportions depend on the nature of the ketone and on the substitution pattern of the ketenimine. Scheme 25 shows some examples of the product distribution from benzophenone with the ketenimines **79a–c**.⁽¹⁰¹⁾ There is also a trend towards β -adduct **81** formation for higher triplet energy carbonyl compounds; acetone, for example, adds to **79a** to give an equimolar mixture of α - and β -adducts.⁽⁹⁹⁾ The α -adducts from photochemical reaction of fluorenone with ketenimines undergo ring cleavage on photolysis or heating to yield isocyanates and arylalkenes.⁽¹⁰²⁾ Alternatively, treatment



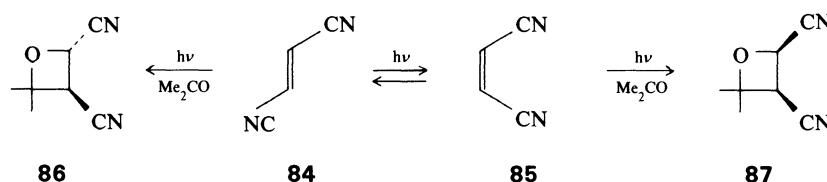
SCHEME 25

of the α -iminooxetan **82** with lithium bromide in acetonitrile solution at 70°C gives a four-membered ring rearrangement to yield a β -lactam **83** in high yield (91%),⁽¹⁰³⁾ in a reaction related to that described above for isopropylideneoxetans such as **74**.



3.4. Electron-Deficient Alkenes

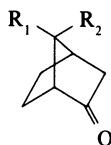
The first example of photocycloaddition of a carbonyl compound to an alkene having electron-withdrawing substituents was reported in detail in 1965.⁽¹⁰⁴⁾ Irradiation of a solution of fumaronitrile **84** in acetone (Scheme 26) led to the formation of a *trans*-oxetan **86**, as well as *trans*- to *cis*-isomerization of the alkene. Only when an appreciable concentration of the *cis*-isomer, maleonitrile **85** had been formed was any of the stereoisomeric oxetan **87** detectable. The implication of these experiments is that oxetan formation is stereospecific, and occurs in competition with *cis*-*trans*-isomerism of the alkene. Other ketones such as pentan-2-one, hexan-2-one, cyclopentanone, and cyclohexanone,⁽¹⁰⁵⁾ as well as adamantanone,⁽¹⁰⁶⁾ react in a stereospecific manner on irradiation in the presence of **84** to give oxetans in good yield (53%–89%). Later research showed that *cis*-*trans*-isomerization of **84** and **85** dominates at low alkene concentration, and is sensitized by triplet acetone.⁽¹⁰⁷⁾ Attempted triplet-quenching experiments and fluorescence studies show that it is the *singlet* excited state of the ketone which is responsible for the cycloaddition. The intervention of an excited state complex of ketone and alkene would



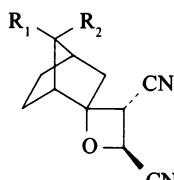
SCHEME 26

account for the low quantum yield of formation of oxetans ($\Phi = 0.01$ – 0.08).^(108,109)

In the photocycloadditions of **84** to the norcamphors **88a–c**, four oxetans are formed in stereospecific reactions from each ketone.⁽¹¹⁰⁾ The two major products in each case arise by approach of the alkene from the *exo*-side of the ketones (e.g., giving **89**). In this series of bicyclic ketones, it appears that



88 a; $R_1 = R_2 = H$
b; $R_1 = R_2 = Me$
c; $R_1 = R_2 = CH_2CH_2$

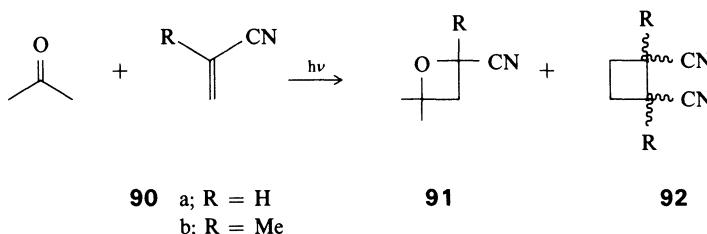


89

an increase in steric hindrance towards *exo*-approach reduces the rate of fluorescence quenching by fumaronitrile **84**,⁽¹¹¹⁾ although the efficiency of oxetan formation from the exciplex is increased.⁽¹¹⁰⁾ A stereoelectronic preference for reaction is revealed by such investigations, which show that attack on the excited-state ketone by electron-deficient alkene is easiest from above or below the plane of the carbonyl group. This may readily be understood in terms of a model of partial electron transfer from $n\pi^*$ singlet excited ketone to ground-state alkene: attack thus occurs in the electron-rich region of the π^* orbital of the ketone.^(109,112)

Irradiation of acetone, cyclohexanone, and cyclopentanone in the presence of maleic anhydride gives oxetans in fair yield (34%–67%), in competition with dimerization of the maleic anhydride.^(105,113) Oxetans are also formed on irradiation of acetone solutions of dimethyl maleate or dimethyl fumarate⁽¹⁷⁾; however, recent work⁽⁴⁾ has cast doubt on the originally proposed mechanism which involved attack of excited alkene on ground-state ketone. Other less electron-deficient alkenes, including chloroethenes and methyl acrylate,⁽³⁾ appear to be unreactive in the Paterno–Büchi cycloaddition.

Interesting results are obtained by uv irradiation of alkanones such as acetone in the presence of the $\alpha\beta$ -unsaturated nitriles, acrylonitrile **90a** or methacrylonitrile **90b** (Scheme 27). Two classes of product are observed: oxetans **91** (26%–55%) and alkene dimers **92**.^(28,114) Mechanistic studies show that the precursor of the oxetan is a singlet exciplex of excited ketone with ground-state $\alpha\beta$ -unsaturated nitrile, while the dimers are formed by photo-sensitized dimerization of **90** initiated by the triplet ketone. Only the oxetan having the orientation shown by **91** is formed in these photocycloadditions, and this is clearly the reverse of what would be expected on the basis of a 1,4-biradical intermediate. However, it is possible to rationalize the orientation



SCHEME 27

of addition by applying a simple perturbational molecular orbital treatment to the approach of singlet excited ketone and ground-state unsaturated nitrile.^{28,115}

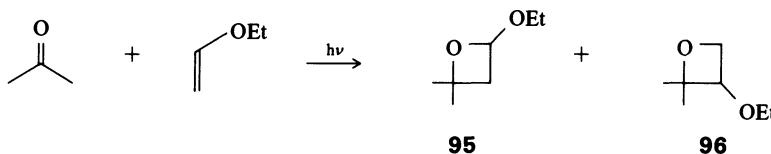
Irradiation of acetone and crotononitrile (1-cyanoprop-1-ene) leads cleanly to the *cis*- and *trans*-oxetans **93** and **94**, respectively, with competing *cis*-*trans*-isomerization of the alkene. Examining the reaction products before significant alkene isomerization has occurred shows that the oxetan formation is highly stereoselective (> 98%) if not stereospecific, because *cis*-crotononitrile gives the *cis*-oxetan **93**, while *trans*-crotononitrile yields oxetan **94**.²⁸



It is worth noting that the direction of electron transfer in these reactions is from excited ketone to electron-deficient alkene, in contrast to the examples of the Paterno–Büchi reaction mentioned in earlier sections where the alkene acts as electron donor. Another difference in mechanism is shown by the absence of any evidence for a biradical intermediate in oxetan formation involving electron-deficient alkenes.

3.5. Vinyl Ethers

Simple aliphatic and aromatic carbonyl compounds give efficient photocycloaddition reactions with vinyl ethers, producing oxetans in yields of 49%–99% in the earliest examples studied.⁽¹¹⁶⁾ Two orientations of addition are possible; thus, acetone reacts with ethyl vinyl ether to give the 2-alkoxyoxetan **95** and 3-alkoxyoxetan **96** in the ratio of 30:70 (Scheme 28). Aldehydes such as propionaldehyde appear to react with ethyl vinyl ether with slightly

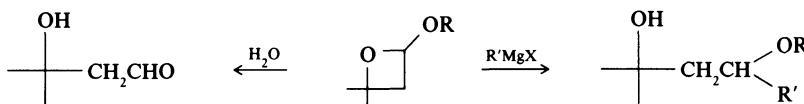


SCHEME 28

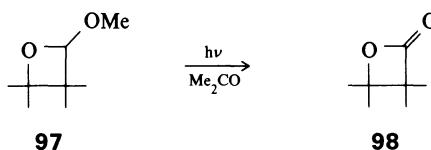
higher selectivity (19:81) favoring 3-alkoxyxetan.^(116,117) In comparison with simple alkenes (Section 3.1), the directing effect of the alkoxy group is small, acetone reacting with the substituted vinyl ether $\text{Me}_2\text{C}=\text{CH}(\text{OPr}^n)$ to give a 70:30 ratio of 2-alkoxy- to 3-alkoxy-isomers.⁽¹¹⁸⁾

Turro and co-workers have studied in detail the mechanism of photo-reaction of acetone and 1-methoxybut-1-ene ($\text{EtCH}=\text{CHOMe}$), which yields two stereoisomers of 2-methoxyoxetan and two of 3-methoxyoxetan.^(119,120) Both singlet and triplet excited states of the ketone are involved in oxetan formation. Using the *cis*-vinyl ether, the stereoselectivity arising from each excited state can be studied. The *cis*-stereochemistry of the initial vinyl ether is partially retained in the isomeric 3-methoxyoxetans when singlet acetone is the reacting species (*cis*- to *trans*-oxetan ratio = 4.5:1), but no stereoselectivity is found following attack by triplet acetone (*cis* : *trans*-oxetan = 1:1). At high vinyl ether concentration, oxetan formation is therefore mainly a selective singlet reaction, while at low concentration the production of acetone triplets leads to stereorandom cycloaddition, accompanied by *cis*-*trans*-isomerization of the vinyl ether. It seems likely that 1,4-biradical intermediates are involved in these photocycloadditions. Again, little selectivity is found in the orientation of attack (2-methoxy : 3-methoxy-oxetan = 1.25:1); this applies to reaction from both the singlet and triplet excited states.

Vinyl ethers are, of course, electron rich, and the direction of partial electron transfer in the exciplex leading to oxetan is believed to be from vinyl ether to excited carbonyl compound. Such a model fits in with studies of ketone fluorescence quenching by vinyl ethers,⁽¹²¹⁾ and would predict that attack by the vinyl ether on the photoexcited ketone occurs in the plane of the carbonyl group (i.e., the *n* orbital).^(7,109)



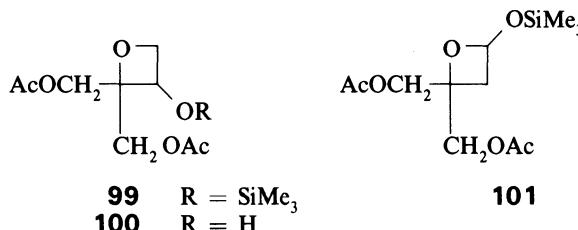
SCHEME 29



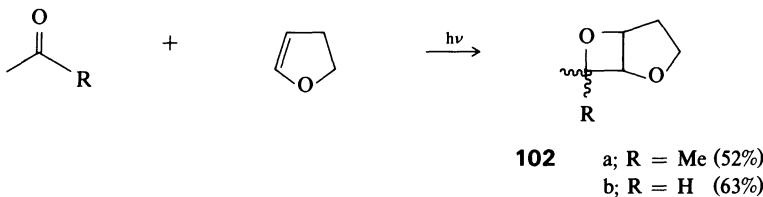
SCHEME 30

There is an important difference in the chemical reactions of the 3-alkoxy and 2-alkoxyoxetans: while the 3-alkoxyoxetans are only slightly strained ethers (and therefore relatively inert), the 2-alkoxy isomers are cyclic acetals and react rapidly with several reagents.^(116,122) Thus, 2-alkoxyoxetans react quantitatively with water to give 3-hydroxyaldehydes, and in high yield with Grignard reagents to give 3-hydroxyethers (Scheme 29). In 2-alkoxyoxetans, the acetal hydrogen is highly activated towards radical abstraction, so that irradiation of acetone solutions of the oxetan 97 leads to the β -lactone 98 in fair yield (37%) (Scheme 30).⁽¹²³⁾ 3-Alkoxyoxetans can be made to undergo ring opening on heating in the presence of dilute acids.⁽¹²²⁾ A potentially useful preparation of substituted vinyl ethers depends on photocycloaddition which yields 3-alkoxyoxetans, followed by thermolysis (above 300°C) to cleave the oxetan ring in the reverse mode.⁽¹²⁴⁾

Aldehydes and ketones are easily converted to their silyl enol ethers, and these latter make good "enol equivalents" in [2+2] photocycloaddition reactions. On irradiation, 1,3-diacetoxypalan-2-one will add to (trimethylsilyloxy)ethene to yield the oxetan **99** (57%).⁽¹²⁵⁾ The trimethylsilyl group can subsequently be removed. Thus, the oxetan **99** is converted quantitatively to oxetanol **100** on treatment with acetic acid in methanol. In the photochemical addition, the alternative oxetan **101** could not be isolated, although there was indirect evidence for its formation in ca. 22% yield.

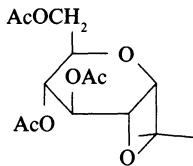


Cyclic vinyl ethers may behave rather differently to their acyclic counterparts. The photocycloaddition of aliphatic carbonyl compounds to 2,3-dihydrofuran (Scheme 31) has been shown to proceed with an orientational selectivity which is exceptionally high (at least 200:1), to yield 2,6-dioxabi-

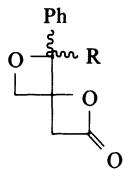


SCHEME 31

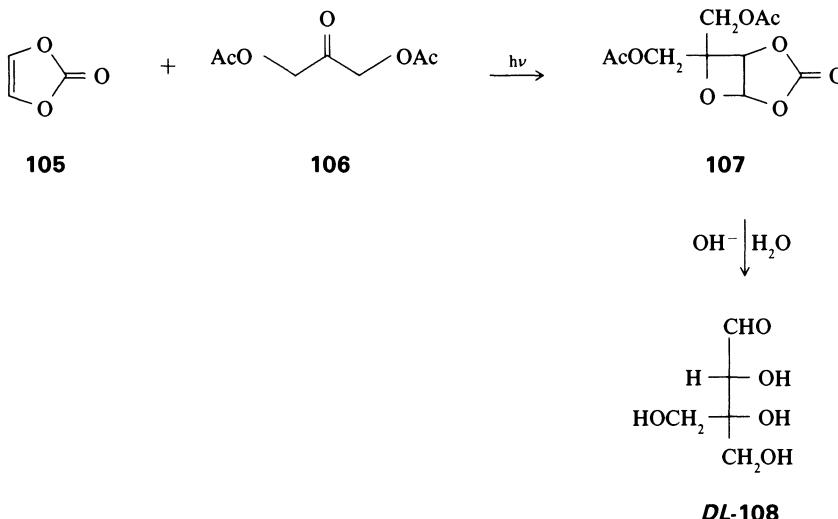
cyclo[3.2.0]heptanes **102**.⁽¹²⁶⁾ Irradiation of acetone solutions of the carbohydrate vinyl ether, 3,4,6-tri-*O*-acetyl-D-glucal, gives the oxetan **103** in good yield.⁽¹²⁷⁾ Benzophenone and acetone react on irradiation in the presence of 1,4-dioxene to give oxetans in 82% and 66% yield, respectively.⁽¹²⁸⁾

**103**

Likewise, the carbon–carbon double bond of α -methylenelactones is reactive towards photoexcited carbonyl compounds^(129,130); diketene and benzophenone or benzaldehyde are sources of the oxetans **104a** and **104b** in 25%

**104** a; R = Ph
b; R = H

and 21% isolated yields, respectively.⁽¹²⁹⁾ Vinylene carbonate **105** also makes a successful addend in photocycloadditions to carbonyl compounds. Thus, irradiation of a benzene solution of 1,3-diacetoxypalan-2-one **106** and **105** gives an oxetan product **107** in 55% yield (actually 81%, if based on converted **105**).⁽¹³¹⁾ Benzene was found to give the best yield of the seven solvents tried. Alkaline hydrolysis, using an ion-exchange resin, then converted **107** to the branched-chain sugar, DL-apiose **108** (Scheme 32).

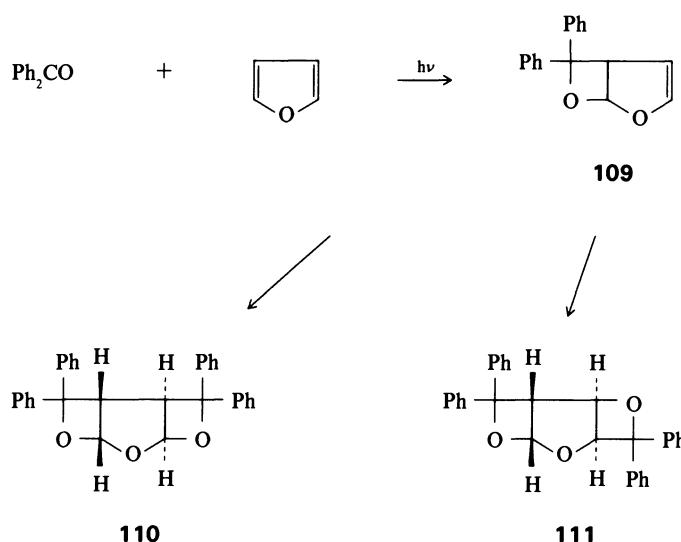


SCHEME 32

3.6. Heteroaromatics

The photocycloaddition of benzophenone to furan occurs in excellent yield and with high stereoselectivity, to give a 1:1 adduct having the orientation of the cyclic acetal **109** (Scheme 33).⁽¹³²⁾ The double bond of this product is relatively reactive towards further photocycloaddition and longer irradiation produces the 2:1 adducts having *anti*-stereochemistry **110** and **111** (27% and 18% overall yields from benzophenone).^(133,134) The reactions apparently involve attack of $n\pi^*$ triplet benzophenone on the ground-state double bond, via biradical intermediates.⁽¹³⁵⁾

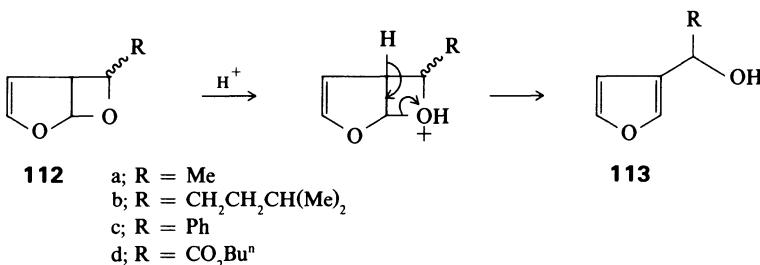
Various aliphatic aldehydes (including those which are capable of giving the Norrish type-II reaction) react photochemically with excess furan to give, in 70%–80% yield, 1:1 adducts which are analogous to the oxetan **109**.⁽¹³⁶⁾ Zamojski⁽¹³⁷⁾ has used the instability of such oxetans as an interesting method for the synthesis of 3-substituted furans (Scheme 34). Treatment of the oxetans **112**, which are mainly *exo*-isomers,^(4,48) with *p*-toluenesulphonic acid in diethyl ether gives the isomeric 3-furylmethanols **113** in good yield (58%–73%). Oxidation of the secondary alcohol in **113b** to ketone by Jones reagent thus achieves a synthesis of the naturally occurring furan, perillaketone. Other workers⁽¹³⁸⁾ have combined these reactions into a one-step synthesis of 3-substituted furans by uv irradiation of the aldehyde and excess furan in dioxan in the presence of a catalytic amount of methanesulfonic acid. In contrast,



SCHEME 33

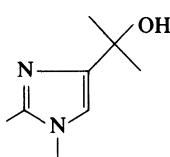
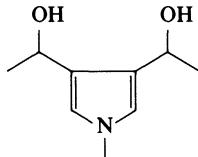
treatment of esters such as **112d** with Lewis acids can lead to the rearranged 2-substituted furan as the main product.⁽¹³⁹⁾ Acetophenone and propiophenone react on irradiation in the presence of benzofuran, leading both to oxetan formation and to dimerisation of the benzofuran.⁽¹⁴⁰⁾

Access to 3-substituted pyrroles can be difficult by conventional routes, but the similar photolysis of a series of pyrroles in the presence of alkanals or alkanones gives 3-(1-hydroxyalkyl)pyrroles in variable yield (5%–85%).⁽¹⁴¹⁾ In these examples, the oxetan adducts are less stable and proceed directly to alcohols; however, evidence for an intermediate oxetan was obtained in the acetone-*N*-methylpyrrole reaction. It has been known for some time that



SCHEME 34

imidazoles may react in this manner: thus, photoreaction of acetone and 1,2-dimethylimidazole gave adduct **114** in 70% yield.⁽¹⁴²⁾ Extended irradiation of pyrroles with excess carbonyl compound can produce 1:2 adducts such as **115**, formed in ca. 50% yield from *N*-methylpyrrole and acetaldehyde.⁽¹⁴¹⁾

**114****115**

Recent work suggests that it is the *singlet* excited state of the aliphatic carbonyl compound which is responsible for these reactions.⁽⁴⁾ The initially formed oxetans do appear to be stable when the nitrogen atom of the pyrrole is attached to electron-withdrawing groups, as in its *N*-benzoyl derivatives.⁽¹⁴³⁾ On irradiation in the presence of aromatic ketones, *N*-acylindoles also yield oxetans by cycloaddition of the ketone at the indole 2,3-double bond.⁽¹⁴⁴⁾

Although the parent heterocycles thiophen, pyrrole, oxazole, and isoxazole are unreactive towards photoaddition with benzophenone,⁽¹⁴⁵⁾ many of their derivatives will add. Benzophenone gives an oxetan (60%) on irradiation in the presence of 2,3-dimethylthiophen,⁽¹⁴⁵⁾ and it also reacts with 3,5- and 4,5-dimethylisoxazole (40% and 65% yields of oxetan, respectively), and with 2,4-dimethylthiazole (25%).⁽¹⁴⁷⁾

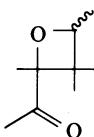
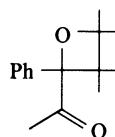
4. Carbonyl Addends

The discussion of oxetan formation so far has been restricted to the use of aldehydes and ketones as the carbonyl components in photocycloaddition. However, the Paterno–Büchi reaction is compatible with quite a wide variety of functionality within the carbonyl component. In such cases, this may lead to the possibility of other photochemical reactions competing with oxetan formation, as will be outlined in the present Section.

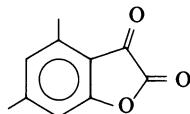
4.1. α -Dicarbonyls

Acyclic α -dicarbonyl compounds such as biacetyl behave similarly to acetone in their photocycloaddition reactions with alkenes. The reaction of biacetyl with 2-methylbut-2-ene,^(148,149) for example, leads to an oxetan **116** (21%) in addition to an allyl ether (54%) by a mechanism exactly analogous to that outlined for acetone in Scheme 5.⁽²⁰⁾ Curiously, no oxetan has been isolated in the photoreaction of biacetyl with 2,3-dimethylbut-2-ene.^(148,150) The

main products are allyl and vinyl ethers, and it appears that ring closure of the 1,4-biradical intermediate is unfavorable with respect to hydrogen transfer to yield unsaturated ethers. These competing pathways for biradical reaction depend critically on the substituents present, since 1-phenylpropane-1,2-dione is reported to react with 2,3-dimethylbut-2-ene to give the oxetan **117** exclusively.⁽¹⁵¹⁾

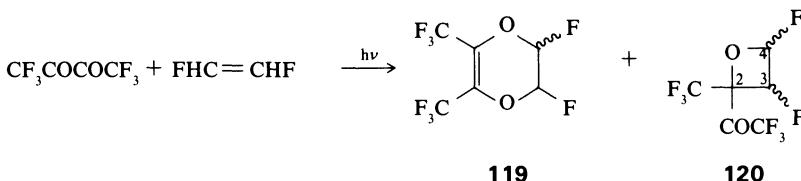
**116****117**

Other photocycloadditions of biacetyl, such as those to 2-phenylpropene and 2-ethoxypropene, give oxetans in better yields (48% and 57%, respectively).⁽¹⁴⁸⁾ It is worth noting that biacetyl reacts photochemically with indene, furan, and ethyl vinyl ether to give oxetans as the main products, in additions which have higher orientational selectivity than those of monoketones.⁽¹⁴⁹⁾ The low triplet state energy of α -diketones such as biacetyl (Table 1) removes one impediment in the photocycloaddition reaction: triplet energy transfer to alkene is less likely than for the corresponding reaction of the mono-carbonyl compounds. The photoaddition of biacetyl to 1,2-dimethoxyethene gives oxetans in a nonstereospecific reaction involving the triplet excited state of the α -diketone.⁽¹⁵²⁾ It appears that the photocycloaddition of biacetyl to 7-*syn*-norbornenes is subject to normal steric effects, because the ratio of *exo*-: *endo*-oxetan products decreases as the size of the 7-*syn*-substituent increases.⁽¹⁵³⁾ Photoreaction of the benzofurandione (**118**) with cyclohexene, ethyl vinyl

**118**

ether, and 2-methylbut-2-ene occurs at the carbonyl group adjacent to the aromatic ring to give oxetans (2%, 69%, and 40% yields, respectively), together with hydrogen abstraction products.⁽¹⁵⁴⁾

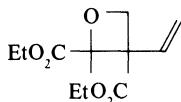
Less commonly, acyclic α -diketones may undergo competing 1,2- and 1,4-additions to alkenes. Irradiation in the vapor phase of a mixture of hexafluorobiacetyl and either *cis*- or *trans*-1,2-difluoroethene gives essentially the same mixture of dihydrodioxins **119** (65%–69%) and oxetans **120** (20%–23%) (Scheme 35).⁽¹⁵⁵⁾ Three stereoisomers of the oxetans are present in approximately equal proportions, with the fourth possible oxetan (having 2-CF₃, 3-F, and 4-F groups *cis* to each other) being noticeably absent from the reaction



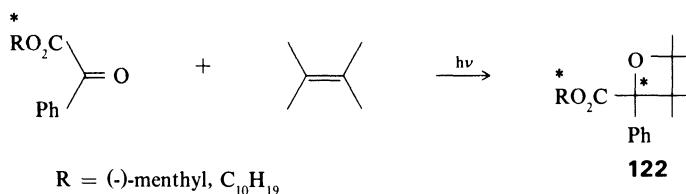
SCHEME 35

product. Cyclic α -diketones (in which the carbonyl groups are held in the *syn* arrangement) may undergo photocycloaddition to alkenes to give competing oxetan formation and 1,4-addition which yields dihydro-1,4-dioxins.⁽¹⁵⁶⁾

Other α -keto-carbonyl compounds may react photochemically at the keto-group to give oxetans, as shown in the early report of Japanese workers who obtained oxetans (42%–97%) by photocycloaddition of diethyl oxomalonate to various alkenes and dienes; the oxetan **121** was thus obtained in

**121**

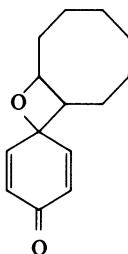
90% yield by irradiation of diethyl oxomalonate in the presence of excess isoprene.⁽¹⁵⁷⁾ The uv irradiation of methyl pyruvate (MeCOCO_2Me) and methyl-substituted alkenes in acetonitrile gave oxetans (15%–54%) as well as allylic ethers and alcohols⁽¹⁵⁸⁾; however, once again, the fully substituted alkene 2,3-dimethylbut-2-ene failed to provide an oxetan (cf. biacetyl^(148,150)).⁽¹⁵⁹⁾ The photoaddition of pyruvamide (MeCOCONH_2) to 2,3-dimethylbut-2-ene led only to products of the hydrogen-abstraction type.⁽¹⁶⁰⁾ The use of an optically active carbonyl compound such as the (-)-menthyl ester of phenylglyoxylic acid in a photocycloaddition reaction to 2,3-dimethylbut-2-ene can lead to a substantial degree of asymmetric induction in the oxetan ring **122** which is formed, as shown in Scheme 36 (optical purity up to 53%).⁽¹⁶¹⁾



SCHEME 36

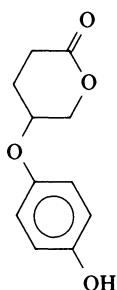
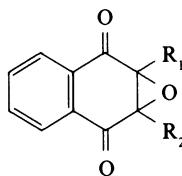
4.2. Quinones

It was Bryce-Smith, Gilbert, and Johnson⁽¹⁶²⁾ who found that irradiation of *p*-benzoquinone and alkenes in benzene solution gave spiro-oxetans (e.g., cyclooctene gave the oxetan **123**) in excellent yield. It appears that the triplet state of the quinone is responsible for cycloaddition; the low triplet energy of *p*-benzoquinone (Table 1) implies little competition from triplet energy transfer and thus a high yield of oxetan. In contrast, Barltrop and Hesp⁽¹⁶³⁾ reported that the main products from irradiation of *p*-benzoquinone and acyclic dienes were spiro-pyrans (e.g., **124**, formed from *p*-benzoquinone and

**123****124**

buta-1,3-diene), possibly formed by a biradical mechanism. Photocycloadditions of quinones proceed efficiently with light of wavelength 400–500 nm, which is helpful in ensuring the photostability of the products.⁽¹⁶⁴⁾ Visible light ($\lambda > 420$ nm) can be used to produce acid-sensitive oxetans with reasonable efficiency, by irradiation of 1-aminoanthraquinone in the presence of conjugated dienes.⁽¹⁶⁵⁾ Bunce and Hadley⁽¹⁶⁶⁾ confirmed that the triplet state of *p*-benzoquinone is responsible for photocycloaddition to simple alkenes, with reaction occurring via an exciplex and a biradical intermediate. It is particularly significant that the photocycloaddition of *p*-benzoquinone to either *cis*- or *trans*-but-2-ene gave the same mixture of spiro-oxetan stereoisomers. Later theoretical calculations suggested that oxetan formation is associated with those quinones which have lowest $n\pi^*$ triplet states (e.g., *p*-benzoquinone), whereas quinones having lowest $\pi\pi^*$ triplets (e.g., duroquinone) lead to cyclobutane formation by addition of the alkene to the quinone C=C bond.⁽¹⁶⁷⁾ Methyl substitution of the quinone significantly lowers the energy of the $\pi\pi^*$ triplet state.⁽¹⁶⁴⁾

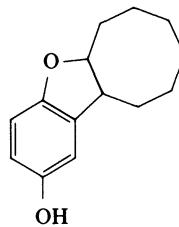
One limitation of the Paterno–Büchi reaction of quinones with alkenes concerns the exciplex, which has appreciable ionic character. An intermediate having properties of an alkene radical cation can be intercepted in suitable cases by intramolecular reaction. Thus, irradiation of *p*-benzoquinone and pent-4-enoic acid gives the δ -lactone **125** rather than an oxetan adduct.⁽¹⁶⁸⁾

**125****126**

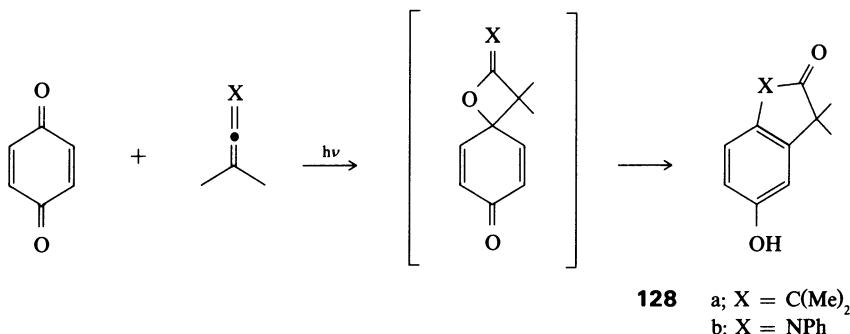
- a; $R_1 = R_2 = H$
- b; $R_1 = H, R_2 = Me$
- c; $R_1 = R_2 = Me$

p-Benzoquinone reacts photochemically with norbornadiene to give *exo*- and *endo*-norbornenyl oxetan adducts (in the ratio 48:15, respectively), along with ethers which arise by typical rearrangements of the 1,4-biradical intermediate, giving structures analogous to formulas 71 and 72.⁽¹⁶⁹⁾ On irradiation in the presence of norbornene, the epoxyquinones 126a and 126b give oxetans in good yields (60% and 86%, respectively), with an attack on 126b occurring at the carbonyl group which is remote from the methyl substituent.⁽¹⁷⁰⁾ In contrast, the more substituted 126c does not give oxetans under these conditions, but yields products derived from epoxide ring opening.

The cyclohexadienone structure of the adducts from quinone–alkene photoreactions makes them susceptible to a useful dienone–phenol rearrangement in acidic conditions. Oxetan 123, for example, is converted to phenol 127 in quantitative yield on treatment with hydrogen chloride in ethanol.⁽¹⁶²⁾

**127**

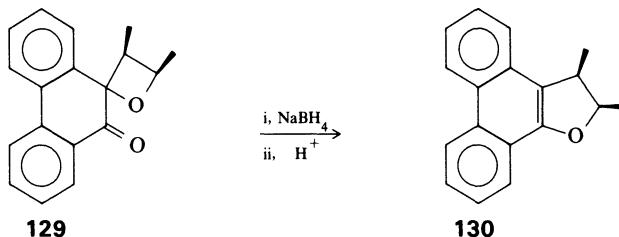
It is also possible to use allenes to form adducts with quinones. The products from photocycloaddition of *p*-benzoquinone with allenes such as 2,4-dimethylpenta-2,3-diene are unstable and undergo a dienone–phenol rearrangement to yield indanones 128a (78% yield), as shown in Scheme 37; 1,4-naphthoquinone behaves similarly (40% overall yield).⁽¹⁷¹⁾ The latter rearrangement of spiro-oxetans to indanones can be induced either photochemically, or by



SCHEME 37

treatment with acid.⁽¹⁷²⁾ Even ketenimines can replace allenes as partners in these photocycloadditions, yielding unstable spiro-oxetans which are readily converted to indolinones such as (128b), formed from dimethyl-*N*-phenylketenimine.⁽¹⁷³⁾ Curiously, photochemical addition of *N*-substituted ketenimines has recently been found to occur at the carbonyl group of duroquinone, in spite of its lowest $\pi\pi^*$ triplet state.⁽¹⁷⁴⁾

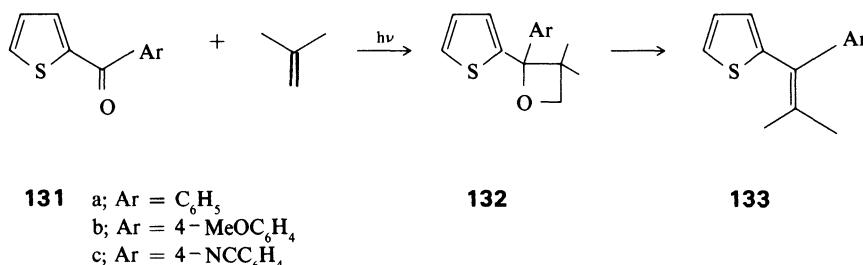
o-Quinones have their two carbonyl groups held in a *syn* arrangement which is suitable for dihydrodioxin formation in competition with normal oxetan production (see Section 4.1 and Scheme 35). Consequently, the photocycloaddition of 9,10-phenanthraquinone with alicyclic alkenes has generally been found to lead to mixtures of α -ketooxetans, dihydrodioxins, and hydrogen-abstraction products.⁽¹⁷⁵⁾ The situation is complicated by the ready isomerization of the α -ketooxetans to dihydrodioxins by light of wavelengths $\lambda < 420$ nm; hence the dihydrodioxins may in some cases be secondary photoproducts derived from an initial undetected oxetan. In contrast, additions of phenanthraquinone to bicyclic alkenes (e.g., norbornene) gave α -ketooxetans quite cleanly (21%–90%), and the authors⁽¹⁷⁶⁾ suggest that the ratio of oxetan to dihydrodioxin is dependent upon the *s* character of the intermediate biradicals. However, 9,10-phenanthraquinone reacts with a surprisingly wide range of substituted allenes to yield dihydrodioxins (15%–54%) as the only reported products.⁽¹⁷⁷⁾ The α -ketooxetans from *o*-quinones can be made to undergo a ring expansion reaction, via hydroxyoxetans, as shown in Scheme 38 for the oxetan from phenanthraquinone and *cis*-but-2-ene. Reduction of the ketooxetan 129 with sodium borohydride, followed by treatment with acid, leads to rearrangement and dehydration to give the dihydrophenanthrofuran 130 in a stereospecific reaction.⁽¹⁷⁸⁾



SCHEME 38

4.3. Miscellaneous Carbonyls

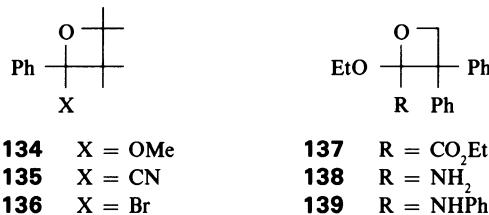
The use of heteroaromatic carbonyl compounds in photocycloaddition reactions presents possibilities for addition of an alkene at the aromatic ring (in either [2+4] or [2+2] modes), as well as oxetan formation. The benzoyl substituent appears to be the group most conducive to oxetan formation; 2-benzoylthiophen reacts on irradiation with 2,3-dimethylbut-2-ene to give oxetan efficiently (76%, $\Phi = 0.21$), and 2-benzoylfuran behaves similarly.⁽¹⁷⁹⁾ However, 2-acetylthiophen gives mainly [2+4] addition of the same alkene to the furan ring, whilst 2-acetylfuran gives mainly [2+2] cyclobutane formation with minor amounts of oxetan. The 2- and 3-aryloylthiophens (e.g., 131 in Scheme 39) react with 2-methylpropene on irradiation to give cycloaddition at the carbonyl group, irrespective of whether the lowest triplet state is $n\pi^*$ or $\pi\pi^*$.⁽¹⁸⁰⁾ As for many 2-aryloxetans, the resulting adducts 132 are unstable, and undergo ring fission before isolation to yield the arylalkenes 133; this cycloaddition-cleavage reaction provides an alternative to the conventional



SCHEME 39

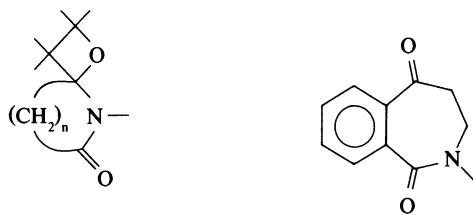
Wittig reaction. It appears in the thiophen and furan series that aldehydes are more reactive than the corresponding ketones towards oxetan formation. Thus, 3-formylthiophen and 3-formylfuran react with 2,3-dimethylbut-2-ene on irradiation to give oxetans as major products, in contrast to 3-acetyl furan which yields three other products.⁽¹⁸¹⁾ Even the presence of a methyl group adjacent to the carbonyl group (which might be expected to lead to photoenolisation, cf. Scheme 8) does not apparently hinder these photocycloadditions, as evidenced by the reaction of 2-methylpropene with 2-benzoyl-3-methylthiophen⁽¹⁸²⁾ or with related 3-benzoylthiophens.⁽¹⁸³⁾

Examples of the Paterno-Büchi reaction involving carboxylic ester derivatives are much rarer than those for simple carbonyl compounds.⁽¹⁸⁴⁾ This may be due to the greater tendency for the esters to have $\pi\pi^*$ lowest excited states. Nevertheless, examples of photocycloaddition are known, especially where it is feasible for an electron transfer mechanism to be involved. Methyl benzoate adds photochemically to 2,3-dimethylbut-2-ene to give oxetan 134 in reasonable yield (43%, $\Phi = 0.034$), though there is some competition with hydrogen abstraction reactions by the ester from the alkene.⁽¹⁸⁵⁾ Benzoyl cyanide and the same alkene react on irradiation to give the oxetan 135 in 22% yield, and there is even the interesting suggestion that benzoyl bromide may add to form the unstable oxetan 136.⁽¹⁸⁶⁾ In an analogous photoaddition of benzoic acid to 2,3-dimethylbut-2-ene, the ester $\text{PhCOOC(Me)}_2\text{CHMe}_2$ is formed in fair yield (46%), which could be the result of a 1,5-hydrogen transfer (from oxygen to carbon) in the normal 1,4-biradical intermediate.⁽¹⁸⁷⁾ The absence of any triplet quenching suggests that a singlet excited state is the



likely precursor in these reactions. There have been other isolated reports of oxetan formation involving photoaddition of the alkene 1,1-diphenylethene to ester and amide functions, such as those involving diethyl oxalate to give the oxetan 137,⁽¹⁸⁸⁾ and ethyl carbamate and its *N*-phenyl derivative to give the unusual oxetans 138 and 139, respectively (64% and 52%).⁽¹⁸⁹⁾

It has even been noted that unsaturated anhydrides such as dimethylmaleic anhydride are capable of undergoing photocycloaddition to indene, 1,1-dimethylindene, or benzofuran in nonpolar solvents, though in these cases there was some evidence for excitation of a ground-state complex.⁽¹⁹⁰⁾ Recently,

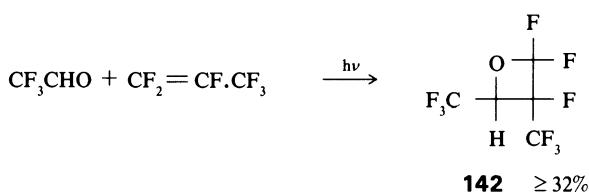


140 a; n = 2
b; n = 3

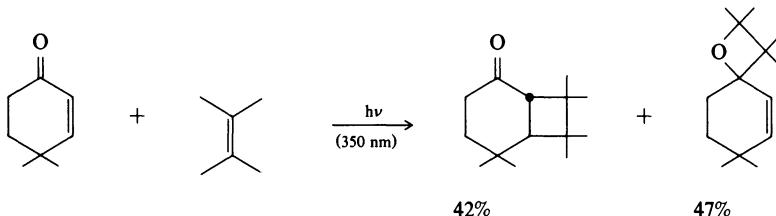
141

cyclic imides have been shown to yield oxetans: thus, aliphatic imides such as *N*-methylsuccinimide and *N*-methylglutarimide gave oxetans **140a** and **140b** in yields of 65% and 71% on irradiation in the presence of 2,3-dimethylbut-2-ene.⁽¹⁹¹⁾ In contrast, aromatic imides give ring-expanded products (e.g., the benzazepinedione **141** from *N*-methylphthalimide and ethoxyethene) in competition with⁽¹⁹²⁾ or to the exclusion of⁽¹⁹¹⁾ oxetan formation.

An interest in polyfluorooxetan chemistry led Harris and Coffman in 1962 to report that fluoroaldehydes, fluoroketones, and fluoroacid fluorides underwent photocycloaddition with highly fluorinated alkenes in reasonable yields (e.g., Scheme 40).⁽¹⁹³⁾ The efficiency of formation of the oxetan **142** stands in contrast to similar unfluorinated cases^(47,51) which give mainly products derived by a free radical mechanism, rather than oxetan. Related to the above is the report by Czech workers⁽¹⁹⁴⁾ that oxetan formation results from the uv irradiation of 3,4-dichloro-3,4,4-trifluorobutan-2-one in the presence of 2-methylbut-2-ene. A recent study by Barlow, Coles, and Haszeldine⁽¹⁹⁵⁾ showed that oxetan formation from chlorofluoroketones with 1,2-difluoroethene becomes subject to increasing competition with free radical reactions (arising from ketone photolysis) as the chlorine content of the molecule is increased. Perfluoroaldehydes react with *cis*- or *trans*-1,2-difluoroethene non-stereospecifically, to give three of the four possible isomeric oxetans in high yields (78%–94%) (cf. Reference 155).



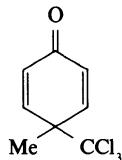
SCHEME 40



SCHEME 41

4.4. Enones and Ynones

At first sight, conjugated enones make unattractive carbonyl components in the Paterno–Büchi reaction; acyclic enones give efficient dissipation of energy by *cis*–*trans*-photoisomerization, whilst the well-known photoreactivity of cyclic enones with alkenes generally leads to cyclobutane formation.^(5,7) Nevertheless, there are examples where oxetan formation can compete with cyclobutane production, as shown for the cyclohexenone in Scheme 41.⁽¹⁹⁶⁾ Schuster⁽¹⁹⁷⁾ has reported the ability of the cyclohexadienone **143** to form an

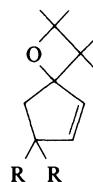


143

oxetan on irradiation in the presence of 2-methylbut-2-ene, with the reaction evidently proceeding from the dienone $n\pi^*$ triplet state. Irradiation of cyclohex-2-enone and ethene at low temperature also gives an oxetan as a very minor product (3%).⁽¹⁹⁸⁾

Margaretha and co-workers^(199–201) have investigated, in a series of papers, the additional factors which influence the oxetan-to-cyclobutane ratio in the addition of cyclic enones to alkenes. Oxetan formation is assisted by high electron density on the alkene, and by electron-withdrawing groups adjacent to the carbonyl group of the enone (as in the photoreaction of 6-fluoro-4,4-dimethylcyclohex-2-enone with 2,3-dimethylbut-2-ene, where the oxetan to cyclobutane ratio is 90:10).⁽¹⁹⁹⁾ The corresponding fluorocyclopentenone leads specifically in nonpolar solvents to oxetan stereoisomers.⁽²⁰⁰⁾ However, the amount of oxetan formed is much smaller for the reaction of the same alkene with analogous chloro-enones such as 6-chloro-4,4-dimethylcyclohex-2-enone (oxetan:cyclobutane = 10:90).⁽²⁰¹⁾

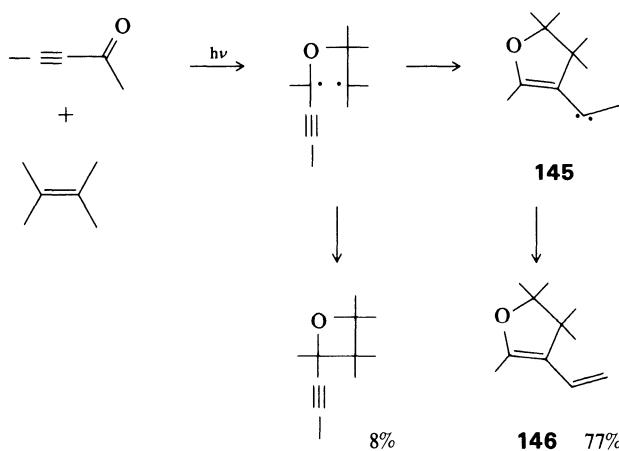
On irradiation, the carbonyl group of cyclopent-4-en-1,3-dione is reactive towards 2,3-dimethylbut-2-ene, giving exclusive oxetan **144a** formation in excellent yield; the product distribution of oxetan stereoisomers from the similar addition to but-2-ene clearly shows that the reaction is nonstereoselective.⁽²⁰²⁾ Likewise, 4-substituted cyclopentenones represent exceptions which on irradiation in the presence of 2,3-dimethylbut-2-ene give predominantly oxetans such as **144b** and **144c**.⁽²⁰³⁾ The oxetan-to-cyclobutane ratio in such



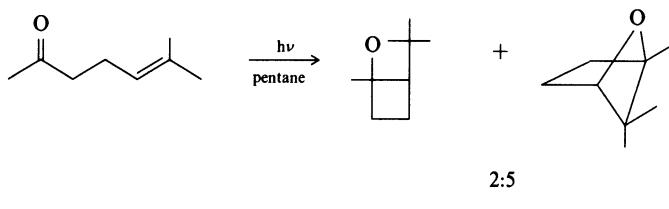
144 a; R—R = O
b; R = Me
c; R—R = —OCH₂CH₂O—

cases is solvent dependent, and the relative amount of oxetan decreases as the solvent polarity increases.

$\alpha\beta$ -Acetylenic ketones such as but-3-yn-2-one will add to alkenes on irradiation to give alkynyloxetans (64%–82%) rather than the possible acylcyclobutenes.⁽²⁰⁴⁾ However, a novel photochemical reaction has recently been found for substituted yrones such as pent-3-yn-2-one in the presence of alkenes.⁽²⁰⁵⁾ As shown by the example in Scheme 42, the main product is a



SCHEME 42

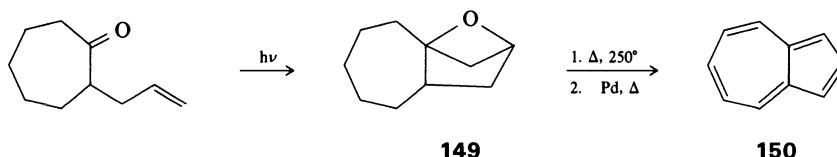


SCHEME 43

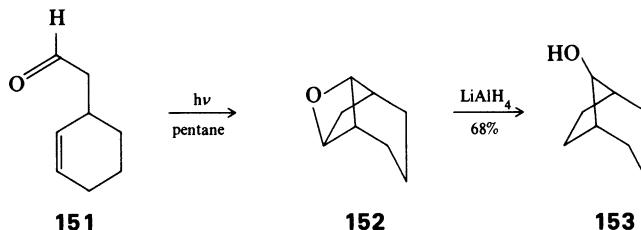
vinyldihydrofuran **146** whose formation can best be understood as arising from closure of the oxetan 1,4-biradical in an alternative manner via the carbene **145**.

5. Intramolecular Cycloadditions

Attack of the excited carbonyl group on an alkene can occur in an intramolecular manner, as was first shown in gas phase studies of hex-5-en-2-one photolysis by Srinivasan in 1960.⁽²⁰⁶⁾ Later solution-phase studies by Yang and co-workers⁽²⁰⁷⁾ showed, for example, that irradiation of 6-methyl-hept-5-en-2-one leads to the oxetans **147** and **148** (56%) which result from the two possible orientations of addition of the carbonyl group to the alkene (Scheme 43). In other examples of the irradiation of γ,δ -unsaturated ketones, bicyclic oxetans with the ring structure of **148** were thought to be formed, but were thermally unstable and defied isolation. Oxetans of this latter type, however, are sufficiently stable to be isolated following irradiation of 2-allylcycloalkanones.⁽²⁰⁸⁾ Thermal decomposition of these oxetans can be put to good synthetic use; the oxetan **149** which is analogous to **148**, but derived from 2-allylcycloheptanone (Scheme 44) is converted above 80°C mainly (ca. 90%) to a mixture of unsaturated alcohols and their corresponding dienes having the azulene-type skeleton of a bicyclo[5.3.0]decane system.⁽²⁰⁹⁾ Azulene



SCHEME 44



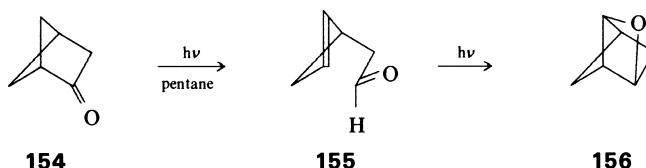
SCHEME 45

(150) itself could be obtained in 25% yield by dehydrogenation over palladium.⁽²¹⁰⁾

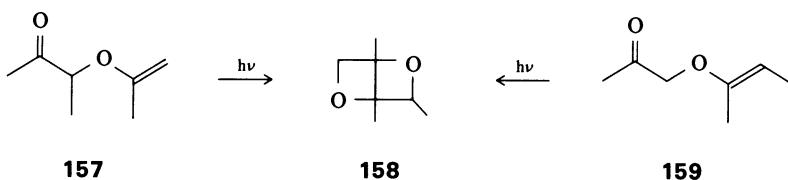
Early mechanistic work on intramolecular oxetan formation was done by Morrison.⁽²¹¹⁾ Irradiation of *trans*-hept-5-en-2-one led to *trans*-*cis*-isomerization ($\Phi = 0.02$) as well as oxetan formation ($\Phi = 0.016$) in which the oxetan has a structure analogous to 147. Curiously, the *cis*-isomer underwent isomerization, but gave no oxetan. It appears that a singlet intramolecular exciplex is involved in this reaction, and is responsible for the energy-wasting process which reduces quantum yields of reaction. Nevertheless, a triplet exciplex can be involved when necessary, as shown by the irradiation of 1-phenylhex-4-en-1-one, where oxetan derived products are still observed.⁽²¹²⁾

The intramolecular photoreaction of cyclohexenylacetaldehyde 151 is selective, giving only the tricyclic oxetan having the orientation of addition shown by 152 (40%) in Scheme 45.⁽²¹³⁾ Moreover, subsequent reduction of oxetans can lead to a specific C—O bond disconnection, so that reaction of lithium aluminum hydride with oxetan 152 provides a convenient entry to 153, having the bicyclo[3.2.1]octanol ring system.

Quite often, the unsaturated carbonyl reactants are themselves derived from photolysis of bicyclic or tricyclic ketones, via the process of Norrish type-I reaction. Irradiation of bicyclo[2.1.1]hexan-2-one 154 led to the cyclobut enyl aldehyde 155, which, on further irradiation, was converted to the oxetan 156 in 60% overall yield (Scheme 46).⁽²¹⁴⁾ The orientation of the ph-



SCHEME 46



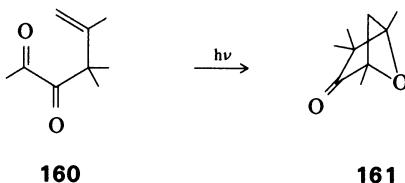
SCHEME 47

tocycloaddition to give oxetan **156** thus shows a reasonable preference for cyclopentane over cyclobutane ring formation, which is shared by many of the analogous intramolecular examples of cyclization of $\gamma\delta$ -unsaturated carbonyl compounds. Irradiation of camphor in solution gives rise to an oxetan as a secondary photoproduct, in a related process via an unsaturated aldehyde.⁽²¹⁵⁾

The known propensity for excited carbonyl compounds to attack vinyl ethers (cf. Section 3.5) has led to novel syntheses of dioxabicycloalkanes by intramolecular reaction of $\gamma\delta$ -unsaturated ketones in which oxygen replaces a β -methylene group.⁽²¹⁶⁻²¹⁸⁾ Irradiation of either of the β -oxa- $\gamma\delta$ -enones **157** or **159** thus produces the [2.2.0]dioxabicyclohexane **158** shown in Scheme 47 (56%–59% yield; $\Phi = 0.12$ – 0.13).⁽²¹⁷⁾ In the closely related example of 1-(cyclopentenyoxy)-propan-2-one, oxetan formation (15%) is accompanied by the product of a 1,3-acetonyl shift (60%).⁽²¹⁸⁾

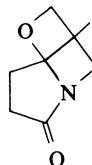
The low triplet energy of α -dicarbonyls (Section 4.1) makes unsaturated 1,2-diketones likely to react well in intramolecular photocycloadditions, subject to the limitation that such ketones are still likely to give photochemical γ -hydrogen abstraction where possible.^(219,220) The irradiation of **160** to give the bicyclic oxetan **161** (100%, Φ ca. 0.6) is a good example of the application of this reaction (Scheme 48).

Other examples of efficient oxetan formation have been noted on irradiation of $\gamma\delta$ -unsaturated carbonyl compounds such as 2-(cyclopentenyl-

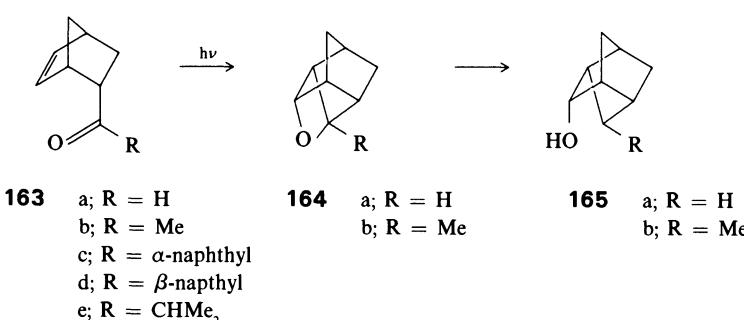


SCHEME 48

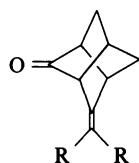
methyl)-cyclopentanone⁽²²¹⁾ and dihydro- β -ionone.⁽²²²⁾ On irradiation, *N*-(2-methylallyl)-succinimide underwent intramolecular ring closure to yield the remarkable oxetan **162** (ca. 100%).⁽²²³⁾

**162**

Over a period of ten years, Sauers and co-workers have investigated the intramolecular Paterno-Büchi reaction applied to *endo*-5-acylnorbornenes, with interesting results. The $\gamma\delta$ -unsaturated aldehyde **163a**, for example, undergoes cycloaddition on irradiation to give the polycyclic oxetan **164a** in 57% yield (Scheme 49).⁽²²⁴⁾ These photocycloadditions are unusually efficient, as shown by the quantum yields from the α - and β -naphthyl ketones **163c** and **163d** ($\Phi = 0.135$ and 0.175, respectively) being much higher than those for related intermolecular examples.⁽²²⁵⁾ A singlet reaction mechanism is suggested and, rather surprisingly, the quantum yield of cyclization is favored by increasing bulk in the substituent (R in formula **163**).⁽²²⁶⁾ Reductive cleavage of oxetan **164a** by lithium aluminum hydride occurs selectively to allow a synthesis of the tricyclic alcohol **165a** (61%).⁽²²⁴⁾ Lithium in liquid ammonia is more effective in reducing the oxetan **164b** to alcohol **165b** in good yield (81%).⁽²²⁷⁾ A similar cycloaddition-cleavage sequence starting from chiral ketones **163b** or **163e** has been used by Japanese workers as a key connection step in the synthesis of the optically active tricyclo[3.3.0.0^{3,7}]octanes **166a** and **166b**, respectively.⁽²²⁸⁾ Likewise, the corresponding *endo*-5-formylbicyclo[2.2.2]octene reacts on irradiation to give an oxetan (65%) which can be



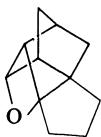
SCHEME 49



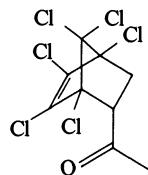
166 a; R = H
b; R = Me



167

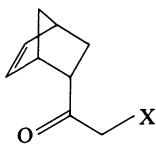


168



169

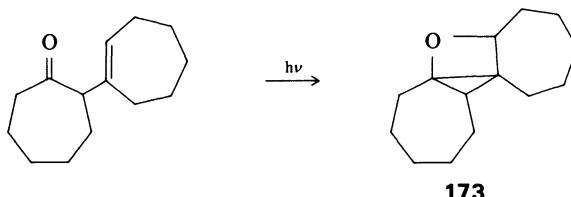
cleaved and deoxygenated to provide a synthesis of the parent twist-brendane system **167**.⁽²²⁹⁾ The unusual polycyclic oxetan **168** (44%) has been prepared by a similar intramolecular photocycloaddition of the corresponding *endo*-spiro-ketone.⁽²³⁰⁾ Even a chlorinated double bond appears reactive in these Paterno–Büchi additions, as shown by the fact that irradiation of ketone **169** gives a polychlorinated oxetan in 55% yield.⁽²³¹⁾ Recently, Sauers and Lynch⁽²³²⁾ have looked at the effects of an α -substituent on the formation of oxetans from 5-acylnorbornenes **170**. Intramolecular oxetans were the major products



170 a; X = OH
b; X = Cl
c; X = SCH₂Ph
d; X = NEt₂

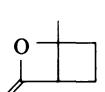
from irradiation of the hydroxyketone **170a** ($\Phi = 0.18$) and from the chloroketone **170b** ($\Phi = 0.29$), but the corresponding thioketone **170c** and aminoketone **170d** preferred competing pathways such as bond homolysis or intramolecular charge transfer, and consequently gave no detectable oxetan.

Intramolecular photocycloaddition is not necessarily restricted to ketones having unsaturation at the $\gamma\delta$ -position. In a norbornenyl ketone having both $\beta\gamma$ - and $\gamma\delta$ -unsaturated sites, intramolecular addition at the $\gamma\delta$ double bond has been found to be preferred over $\beta\gamma$ -attack.⁽²³³⁾ In contrast, uv irradiation of an acyclic allenic ketone, 3,3,6-trimethylhepta-4,5-dien-2-one, gives an oxetan product (70%) derived from cycloaddition of the carbonyl group at the $\beta\gamma$ - rather than $\gamma\delta$ -position.⁽²³⁴⁾ Crandall and Mayer⁽²³⁵⁾ have investigated the



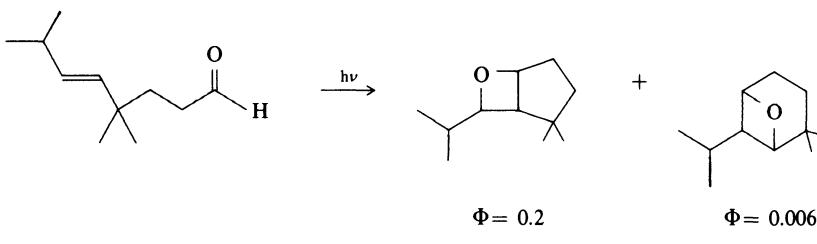
SCHEME 50

photochemistry of another allenic ketone, hepta-5,6-dien-2-one. Their finding that the oxetan **171** formed 91% of the volatile photoproducts suggests $\gamma\delta$ -attack is favored over $\delta\epsilon$ -addition. Irradiation of 3-methylenehex-5-en-2-one gives the thermally unstable oxetan **172** (54%) by intramolecular reaction at the $\gamma\delta$ -position, without interference from the $\alpha\beta$ double bond.⁽²³⁶⁾

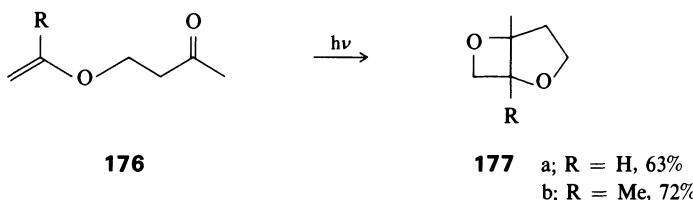
**171****172**

The variety of photochemical pathways open to $\beta\gamma$ -unsaturated carbonyl compounds (especially the oxa-di- π -methane rearrangement),⁽²³⁷⁾ makes oxetan formation only one of the possibilities for reaction. Nevertheless, examples of oxetan formation have been recorded,⁽²³⁸⁾ often in compounds derived from seven- and eight-membered ring cycloalkenes.^(239,240) For example, the formation of the remarkable oxetan **173** (32%) shown in Scheme 50 has been noted, but has not yet been put to synthetic use.⁽²⁴⁰⁾

Kossanyi and colleagues^(241,242) have examined the intramolecular photochemical reaction of $\delta\epsilon$ -unsaturated aldehydes. Oxetans are formed as major products, as shown by the example in Scheme 51. For the other cases studied,



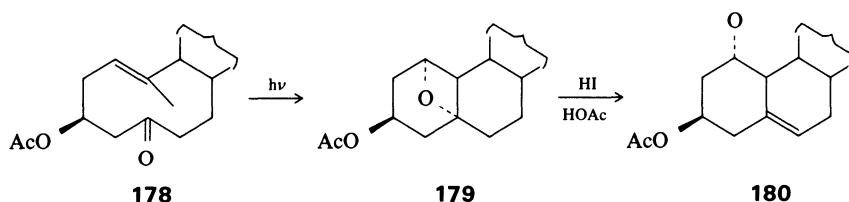
SCHEME 51



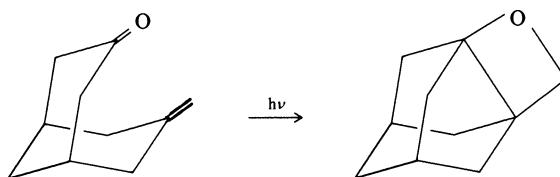
SCHEME 52

the major orientation of addition was such as to give the 6-oxabicyclo[3.2.0]heptane system of **174** rather than the 6-oxabicyclo[3.1.1]system of **175**. In a related reaction, uv irradiation of β -vinyloxy-ketones **176** gives 2,6-dioxabicyclo[3.2.0]heptanes **177** in reasonable yields (Scheme 52).⁽²⁴³⁾ It would not be possible to produce these oxetans in intermolecular additions of dihydrofurans to formaldehyde (cf. Section 3.5), since the latter has never been observed to give the Paterno-Büchi reaction.

Intramolecular attack of a carbonyl group on an alkene in medium-sized rings can be a useful synthetic reaction. Thus, the unsaturated ketone **178**, which can readily be prepared from cholesterol, gives, on irradiation in acetone solution, the oxetan **179** in 52% yield (Scheme 53).⁽²⁴⁴⁾ Subsequent acidic cleavage of the oxetan ring converts **179** to the 1-hydroxycholesterol derivative **180** (82%). This work could be seen as a development of the earlier finding that irradiation of *trans*-cyclodec-5-enone gave the parent tricyclic oxetan in 55% yield.⁽²⁴⁵⁾ Bicyclic $\delta\epsilon$ -unsaturated carbonyl compounds in which the carbonyl and olefinic groups are in suitable proximity can also undergo intramolecular oxetan formation.⁽²⁴⁶⁾ The example of Nozaki *et al.* (Scheme 54)⁽²⁴⁷⁾ is significant, because it requires a face-to-face approach of the reactants which is not in agreement with predictions for the allowed photochemical reaction.⁽⁷⁾ Other examples of intramolecular Paterno–Büchi reaction of $\delta\epsilon$ -unsaturated aldehydes have been recorded.^(248,249)



SCHEME 53



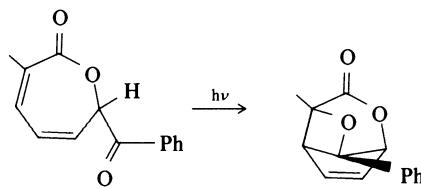
SCHEME 54

Photocycloaddition of a carbonyl group to a dienyl double bond may even occur, as shown in Scheme 55 for the dienyl ketone **181**; irradiation in acetone solution at -60°C leads to the bridged oxetan **182** in 30% yield.⁽²⁵⁰⁾ There is an exact analogy here both in position and orientation of attack to that previously found in the intramolecular Paterno–Büchi reaction of (*E*)-*retro*- γ -ionone.⁽²⁵¹⁾

6. Chemical Reactions of Oxetans

Much of the earlier work on oxetan reactions has been well reviewed by Searles.⁽¹²⁾ Both acid-catalyzed and nucleophilic pathways for opening of the oxetan ring are possible, and this greatly extends the possible use of oxetans as organic synthons. In this section are mentioned only those transpositions which promise to be generally applicable; in some cases the starting oxetans have not been produced photochemically, and thus the reactions have not been mentioned so far.

Ring expansion reactions of oxetans can lead to substituted tetrahydrofurans, as in the attack of carbethoxycarbene on 2-phenyloxetan.⁽²⁵²⁾ Alternatively, Lewis-acid catalysis is particularly valuable in oxetan ring ex-

**181****182**

SCHEME 55

pansions, leading to tetrahydrofurans from 2-*t*-butyloxetans,⁽²⁵³⁾ and to 1,3-dioxans from oxetans and acetone.⁽²⁵⁴⁾ Isocyanides react with oxetans in the presence of boron trifluoride to give α -iminotetrahydrofurans.⁽²⁵⁵⁾

Nucleophilic opening of the oxetan ring, whilst undoubtedly less facile than for epoxides, is a useful reaction.⁽¹²⁾ Oxetans thus react with Grignard reagents^(116,122) and with imine salts derived from cyclohexanone.⁽²⁵⁶⁾ Nucleophilic opening of the oxetan ring is now possible under mild conditions using alkylolithium reagents catalyzed by copper(I) iodide.⁽²⁵⁷⁾ An elegant total synthesis of humulene relies upon opening of an oxetan ring using diethylaluminium *N*-methylanilide to yield a homoallylic alcohol.⁽²⁵⁸⁾ Recently, the use of α -selenoalkyllithiums has been developed to convert oxetans to tetrahydrofurans in a ring homologation which formally resembles carbene insertion.⁽²⁵⁹⁾

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Equipment and Techniques

William M. Horspool

Two distinct groups of researchers are operative in photochemical research at the present time. One group is made up of physical chemists and physical-organic chemists, and the aim in this area is the elucidation of the detailed mechanisms involved in a photochemical process. The other group is composed of organic chemists whose aim is the application of photochemical methods to the synthesis of new molecules or the synthesis of known compounds by unique methods. The equipment employed by these groups can differ markedly. The investigator of reaction mechanisms requires elaborate equipment, often involving the use of monochromatic light, a filter train, a beam collimator, and means of measuring both the incident light and the amount of light absorbed by the molecule under study. On the other hand, the synthetic organic photochemist is primarily interested in a high-intensity light source abundant in the wavelengths absorbed by the reacting molecule. Ideally the apparatus should be easy to use and should have a variety of flask sizes so that preparative runs do not need the redesign of the equipment. It is to this latter group that the present chapter is directed. Clearly it is impossible to be comprehensive. The literature is full of many methods⁽¹⁻³⁾ which have been devised specifically for a certain experiment. The apparatus described in this chapter is in the main available from commercial suppliers, although some reference will be made to specially designed systems which can be readily constructed and which have some general applicability.

1. Mercury Vapor Lamps

Light has to be absorbed by a molecule to bring about a photochemical reaction. Thus the light source to be used for the experiment is determined by the absorption spectrum of the molecule under study. The most widely used light sources are those based on mercury. These lamps are extremely convenient to use and are both dependable and capable of supplying steady illumination of both ultraviolet and visible light covering the range from 200 nm (599 kJ mol^{-1}) to 750 nm (159 kJ mol^{-1}) and above. There are three main types of mercury lamps designated as low, medium, and high pressure and each has different spectral characteristics. The low-pressure or resonance lamp has a mercury vapor pressure of 0.005–0.1 Torr and operates at room temperature. Emission from these lamps is mainly at 253.7 and 184.9 nm corresponding to the transitions $\text{Hg}({}^3P_1) \rightarrow \text{Hg}({}^1S_0) + h\nu$ and $\text{Hg}({}^1P_1) \rightarrow \text{Hg}({}^1S_0) + h\nu'$. The high-energy emission at 184.9 nm is not transmitted unless ultrapure quartz, referred to as Suprasil, is used. The fractions of light emitted at the various wavelengths in such a lamp are presented in Table 1. The amount of light emitted at longer wavelengths is dependent upon the manufacturer of the lamp, and Table 1 should only be taken as a general guide to the situation. Medium-pressure lamps operate at 1–10 atm and at relatively high temperatures and consequently the lamp requires a few minutes to warm up to operational temperature, at which point the output is relatively stable. The emission from such lamps is usually a weak continuum with the superimposition of spectral lines. The higher operating pressures and temperatures

Table 1. Relative Spectral Energy Distribution of a Low-Pressure Mercury Lamp^a

Wavelength	Hanovia SC 2537
248.2	0.01
253.7	100.00
265.2–265.5	0.05
275.3	0.03
280.4	0.02
289.4	0.04
296.7	0.20
302.2–302.8	0.06
312.6–313.2	0.60
334.1	0.03
365.0–366.3	0.54
404.5–407.8	0.39
435.8	1.00
546.1	0.88
577.0–579.0	10.14

^a Reference 1, p. 696.

result in diminished intensity of the 253.7- and 184.9-nm lines. Indeed, lamps operating in the medium-pressure range have what is known as reversed radiation at 253.7 nm. In fact the center of the 253.7-nm line is missing because of self-absorption at the higher pressures of mercury used. Thus medium-pressure arc lamps are not useful for initiating mercury-sensitized reactions but can be used as useful sources for direct irradiations. The spectral lines at 265.4, 310, and 365 nm have reasonably high relative intensity (Table 2) and are in a useful part of the spectrum for the excitation of organic compounds. The high-pressure lamps (sometimes referred to as super-high-pressure lamps) operate at about 200 atm. The large increase in pressure and in working temperature introduces many more spectral lines and so a stronger continuum is obtained with broadening of the principal emission lines mentioned previously. Emission below 280 nm is very weak.

The use of mercury vapor lamps provides a highly versatile means for

Table 2. Relative Spectral Energy Distribution of a Medium Pressure Mercury Arc Lamp^a

Wavelength (nm)	Relative energy
222.4	14.0
232.0	8.0
236.0	6.0
238.0	8.6
240.0	7.3
248.2	8.6
253.7	16.6
257.1	6.0
265.2–265.5	15.3
270.0	4.0
275.3	2.7
280.4	9.3
289.4	6.0
296.7	16.6
302.2–302.8	23.9
312.6–313.2	49.9
334.1	9.3
365.0–366.3	100.0
404.5–407.8	42.2
435.8	77.5
546.1	93.0
577.0–579.0	76.5
1014.0	40.6
1128.7	12.6
1367.3	15.3

^a Reference 1, p. 696.

irradiation in preparative experiments. Other lamps have found application and both the xenon-mercury lamp and phosphor-coated lamps with output at, e.g., 350 or 410 nm have found application for general irradiative procedures.[†]

2. Lamps in Conjunction with Filters

The choice of lamp for a reaction depends upon two main considerations. The one of major importance is the need for spectral overlap between the lamp and the absorption spectrum of the compound to be irradiated. Ideally one should aim for maximum overlap between the output of the lamp and the compound. This condition can be achieved in the majority of cases by the use of a medium-pressure lamp which adequately covers the range between 250 and 450 nm. A greater degree of selectivity may be required if irradiation into one of the absorption bands of the molecule is desired, or if the product of the irradiation is sensitive to a wavelength different from the one used to excite the starting material. This requirement can be met by using a monochromatic source, i.e., a mercury arc lamp and a diffraction grating or else, less expensively, by a system of filters (either glass or solution). The simplest filter which can be applied is by the use of quartz, Vycor, Corex, or Pyrex for the vessel in which the irradiation is to be carried out. Approximate values of the wavelength transmission of these are given in Table 3.

The alternative to glass filters, which provide only minimum selectivity, is the use of solution filters, many of which can be prepared from readily available chemicals. These solution filters fall into two main classes: (a) those which slightly improve the use of the glass filter listed in Table 3, and (b) combinations of solutions which provide narrow band-pass irradiation suitable for quantum yield measurements. The first type are often classed as short and long cutoff filters, which serve the same purpose as the glasses. Some filter solutions of this type are listed in Table 4 and have been used by

[†] Phosphor-coated lamps are commercially available from Applied Photophysics, 20 Albemarle Street, London W1X 3HA.

Table 3. Light Transmission for Several Glasses^a

Glass	% Transmission for a thickness of 1 mm		
	20%	50%	90%
Quartz	< 200 nm	< 200 nm	240 nm
Vycor	200 nm	220 nm	280 nm
Corex	270 nm	290 nm	360 nm
Pyrex	290 nm	300 nm	360 nm

^a Reference 3, p. 107; Reference 4.

Table 4. Short and Long Cutoff Filter Solutions^a

Wavelength (nm) of cutoff	Chemical composition
Below 250	Na_2WO_4
Below 305	SnCl_2 in HCl (0.1 M in 2:3 $\text{HCl}-\text{H}_2\text{O}$)
Below 330	2M Na_3VO_4
Below 355	BiCl_3 in HCl
Below 400	KH phthalate + KNO_2 (in glycol at pH 11)
Below 460	0.1 M K_2CrO_4 (in $\text{NH}_4\text{OH}-\text{NH}_4\text{Cl}$ at pH 10)
Above 360	1 M NiSO_4 + 1 M CuSO_4 (in 5% H_2SO_4)
Above 450	CoSO_4 + CuSO_4

^a Reference 5.

Zimmerman's group at Wisconsin.⁽⁵⁾ Some of these systems have been developed for specific equipment. Thus the solutions for a three-component filter system listed in Table 5 have been used by Zimmerman and his co-workers for the "black-box" apparatus.⁽⁵⁾ Each solution is contained in a 2.4-cm path length cell, and the whole gives band widths of about 50 nm. The composition of the filter assemblies and the concentration of the solutions

Table 5. Filter Solution Combinations^a

Wavelength (nm)	Solution 1	Solution 2	Solution 3
232–268	2 M NiSO_4^b	0.25 M CoSO_4^b	$9.0 \times 10^{-3} M$ 2,7-dimethyl-3,6-diaza-cyclohepta-1,6-diene perchlorate ^d
260–300	2 M NiSO_4^c	0.8 M CoSO_4^c	$1.23 \times 10^{-3} M$ BiCl_3^c
255–305	2 M NiSO_4^b	2 M CoSO_4^b	$2.0 \times 10^{-4} M$ BiCl_3^c
250–325	2 M NiSO_4^c	0.8 M CoSO_4^c	$2.46 \times 10^{-4} M$ BiCl_3^c
290–350	2 M NiSO_4^c	0.8 M CoSO_4^c	0.1 M CuSO_4^c
282–356	2 M NiSO_4^c	1.0 M CoSO_4^c	0.1 M CuSO_4^c
300–350	1.71 M NiSO_4^c	1.0 M CoSO_4^b	0.0133 M $\text{SnCl}_2^{e,f}$
310–355	2 M NiSO_4^c	0.8 M CoSO_4^c	$2.2 \times 10^{-2} M$ $\text{SnCl}_2^{e,f}$
310–375	0.5 M NiSO_4^g	2 M CoSO_4^b	1.0 M CuSO_4^c
328–388	2 M NiSO_4^b	1.0 M CoSO_4^b	0.01 M NaVO_3^h
330–440	0.14 M NiSO_4^b	1.0 M CoSO_4^b	0.33 M $\text{SnCl}_2^{e,f}$
335–450	1.0 M CoSO_4^c	0.023 M CuSO_4^c	0.004 M KVO_3^h
370–450	1.0 M CoSO_4^b	1.0 M CuSO_4^b	0.10 M NaVO_3^h
375–470	$2.5 \times 10^{-3} M$ FeCl_3^i	0.20 M CoSO_4^b	Saturated ($\sim 1.25 M$) CuSO_4^h

^a References 5, 6.^b In 10% H_2SO_4 .^c In 5% H_2SO_4 .^d This solution decomposes during a 3-h photolysis.^e In 2:3 $\text{HCl}-\text{H}_2\text{O}$.^f SnCl_2 solution decomposes after 24 h contact with air.^g In 1.5% H_2SO_4 .^h In 0.1 M NaOH .ⁱ In 10% HCl .

Table 6. Selection of Filter Solutions Used in Conjunction with a Four- or Three-Cell Filter Train^a

Wavelength (nm)	Cell 1 (path length, cm)	Cell 2 (cm)	Cell 3 (cm)	Cell 4 (cm)
245-270	1.05 <i>M</i> NiSO ₄ · 6H ₂ O (5)	0.3 <i>M</i> CoSO ₄ · 7H ₂ O (5)	4 × 10 ⁴ <i>M</i> I ₂	Cl ₂ (5)
245-280	1.05 <i>M</i> NiSO ₄ · 6H ₂ O (5)	0.16 <i>M</i> CoSO ₄ · 7H ₂ O (5)	9 × 10 ⁻⁴ <i>M</i> KI (1) 2 × 10 ⁻⁴ <i>M</i> 1,4-diphenylbutadiene in ether (1)	—
370-440	1.8 × 10 ⁻² <i>M</i> CuSO ₄ · 5H ₂ O, 2.7 <i>M</i> NH ₃ (10)	3.0 × 10 ⁻² <i>M</i> I ₂ in CCl ₄ (1)	0.14 <i>M</i> quinone hydrochloride (1)	—
410-490	1.8 × 10 ⁻² <i>M</i> CuSO ₄ · 5H ₂ O, 2.7 <i>M</i> NH ₃ (10)	1.09 <i>M</i> NaNO ₂ (10)	—	—

^a Reference 1, pp. 728-747; Reference 3, pp. 97-104.

are mutually dependent. Other systems have been developed using different path length filter cells and some of the combinations possible are listed in Table 6. Many of the solutions used in these assemblies are themselves light sensitive, and care has to be exercised in their use to avoid overirradiation.

3. Photochemical Apparatus

Preparative organic photochemistry can be carried out using two methods: either (a) with the solution of the reactant surrounding the lamp or (b) with a battery of lamps surrounding the solution of the reactant.

The former method allows for a higher capture of the lamp's output and as such is more economical. A typical example of an immersion apparatus is shown in Figure 1. These reactors are highly efficient since the lamp is surrounded by the solution to be irradiated, a mode of operation which assures maximum light capture. The lamps are contained in a double-walled immersion well constructed of either quartz or borosilicate glass. The well is fitted with a standard taper joint which allows it to be used with a variety of reactor sizes. Pyrex is less expensive but can only be used with light of $\lambda > 300$ nm. Quartz, on the other hand, is transparent to 200 nm and is consequently more versatile. The use of a quartz immersion well can be made in conjunction with filter sleeves which fit around the lamp, and this permits the exclusion of short-wavelengths radiation. The double surface of the immersion well allows the solution of reactant to be insulated from the heat of the medium-pressure arc lamp by the circulation of cooling water. Alternatively, a cooled filter solution can be circulated, again permitting the selection of the appropriate wavelength for the reaction. The construction of the immersion well allows for the use of medium- or low-pressure mercury lamps which are commercially available. The outer vessel of such an apparatus is usually made of Pyrex and can be varied in size and also in the number of outlets and inlets attached to it. The various reaction flasks which can be constructed enable irradiations to be carried out under aerobic or anaerobic conditions or at constant, low, or high temperature.

It is usually essential, especially with the large reactors, to stir the reaction mixture since the light will not penetrate the entire solution. Either a mechanical stirrer or a nitrogen gas stream is sufficient, with the added advantage that the use of nitrogen also excludes oxygen from the reaction. One drawback of such a method of stirring is the loss of solvent or volatile products by vaporization.

The design of the outer part of the immersion well apparatus is clearly open to the ingenuity of the experimenter and many reactors have been designed for a specific purpose, only one of which will be mentioned here.

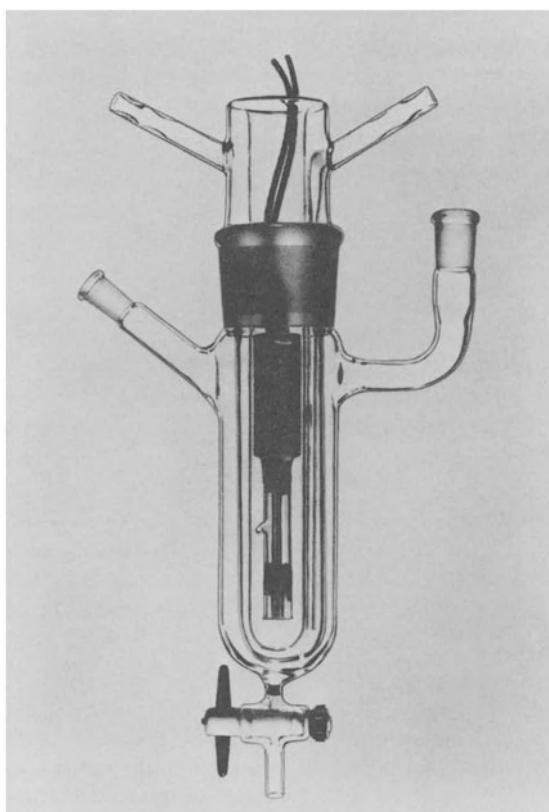


Figure 1. Immersion apparatus for solution phase photochemistry. (Reproduced by permission of Applied Photophysics Ltd.)

This relates to the difficulty of carrying out low-temperature irradiations. The problem with this procedure is that at low temperatures medium-pressure mercury arc lamps fail to strike and consequently if the experimenter is to carry out a photochemical reaction at a temperature much below that of cold water then difficulties will be encountered. This can be got around by using an unmirrored quartz Dewar as the immersion well. This effectively insulates the lamp from the cooling solution. Details for the construction are to be found in the original literature.⁽⁷⁾

The alternative mode of irradiating a solution is with an external lamp arrangement. In this type of reactor the solution to be irradiated is surrounded by a battery of lamps within a chamber. Obviously it is possible to construct these reactors oneself, but commercial models are available and one of these is shown in Figure 2. This example of a multilamp reactor can be used with



Figure 2. Multilamp reactor for solution phase photochemistry. (Reproduced by permission of Applied Photophysics Ltd.)

low-pressure, medium-pressure, or phosphor-coated lamps. The space within the lamp housing is cooled by a circulation fan, but if lower temperatures are needed a quartz or borosilicate Dewar can be used for this purpose.

A variant on this type of irradiation system is shown in Figure 3. This equipment utilizes the immersion well lamp housing in conjunction with a carrousel assembly which can take 12 sample tubes. Such an arrangement is ideal for carrying out preliminary studies on a variety of compounds or else for the determination of the quantum yield of a photochemical reaction. A more detailed treatment of this will be discussed later. The one essential feature of sample preparation for a "merry-go-round" experiment is to ensure that the light incident upon the sample or the actinometer is completely

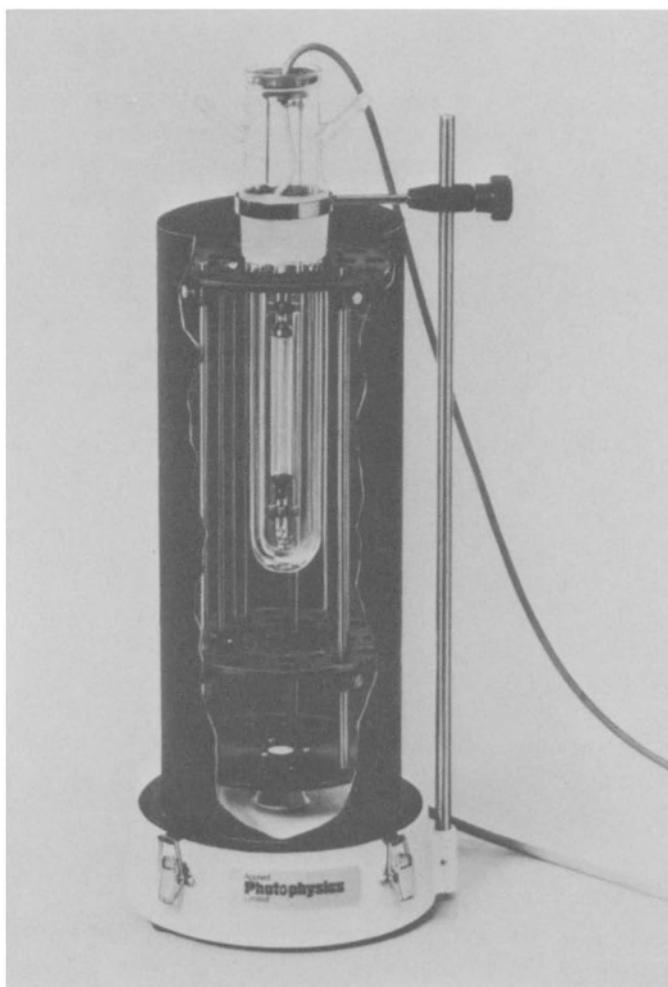


Figure 3. Annular photoreactor. (Reproduced by permission of Applied Photophysics Ltd.)

absorbed. This usually means making solutions where the optical density is > 5 . The need to ensure total light capture arises from the fact that if light capture is not complete then a method for measuring the fraction of light passing through the sample has to be devised. One further experimental drawback is the use of cylindrical sample cells. Such cells are used for economy since it is relatively inexpensive to construct sample cells from Pyrex or quartz

tubing of 13–16 mm diameter. These, when sealed—usually under vacuum since a sizable fraction of organic photochemistry takes place from the triplet state, which can be readily quenched by dissolved oxygen—hold about 3 ml of the solution and are a convenient size for handling. However, cylindrical sample cells do have the disadvantage of varying path length from the edge to the middle of the tube. Also, if the solvents in the sample and the actinometer are different, the amount of light refracted at the glass–sample interface will be different from that refracted at the glass–actinometer interface. A further complication is the fact that the angle of incidence of the light is not uniform, e.g., with water, as solvent light impinging at $> 57^\circ$ will not cause a reaction, while it does if benzene is the solvent. This leads to erroneous results with an apparent increase in the quantum yield of a reaction but it can be circumvented by restricting the angle at which the light can strike the tubes. A practical method of doing this is by using slits.⁽⁸⁾

The light capture by the solution is poorer in this mode of irradiation than in the immersion mode. There are, however, advantages in using such a system since degassing sampling and irradiation under vacuum are much easier. A more efficient utilization of the available light energy can be achieved by focusing the light from a source by means of a mirror. Such an apparatus for 5–50 g material has been designed using light from a 1-kW high-pressure arc focused by an aluminum parabolic mirror into a 14-cm beam.⁽⁵⁾ A relatively narrow band pass can be achieved using filter solution combinations (Table 5) in a three-stage filter solution cell interposed between the lamp and the sample to be irradiated. For quantum yield determinations the light incident on the face of the sample cell can be measured prior to irradiation of the sample and can also be monitored during the irradiation by using a beam splitter to deflect about 10% of the incident light at right angles to a separate monitoring cell. The light which passes through the irradiation cell can also be monitored. Such a system has obvious advantages over the annular photoreactor described previously in that not all the light need be trapped by the solution undergoing irradiation. Nevertheless the carrousel type of quantum yield reactor does find favor and a commercial example is shown in Figure 4. This equipment is similar to the Wisconsin black box or the microbench⁽⁵⁾ described above and utilizes a focused lamp and a three-compartment filter cell prior to the sample undergoing irradiation.

Yet another mode of irradiation, that of thin film, has found application in the irradiation of small volumes of reactant or for the irradiation of concentrated solutions where radiation penetrates only a fraction of a millimeter. This system shown in Figure 5 pumps the solution to be irradiated from a reservoir through a jet which allows a thin film of the solution to fall under gravity over a quartz or borosilicate tube containing the lamp.

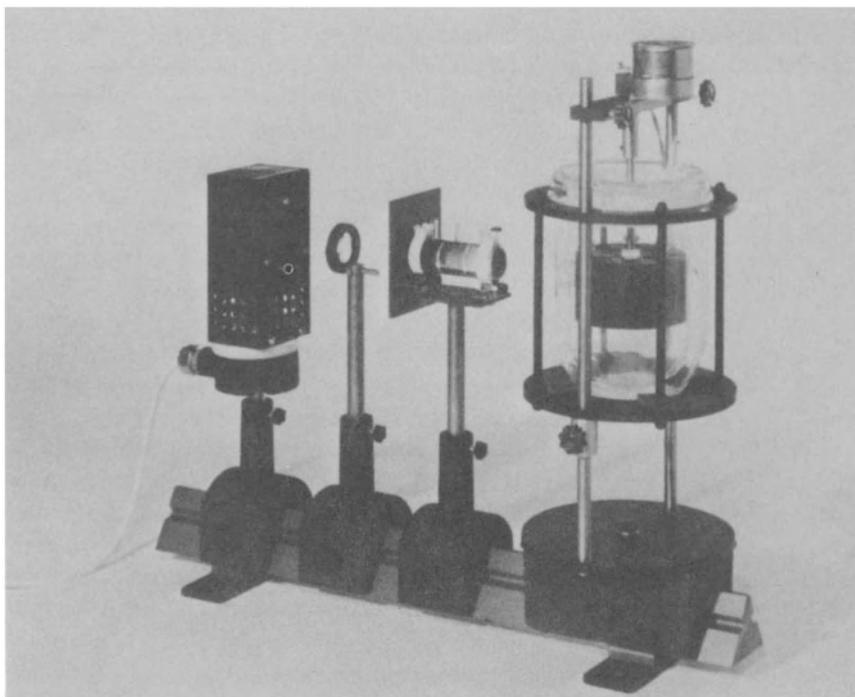


Figure 4. Quantum yield reactor. (Reproduced by permission of Applied Photophysics Ltd.)

4. Actinometry

The accurate measurement of a quantum yield depends mainly on the accuracy of the actinometer (the method of photon measurement), although analytical determination of the product (or reactant) consumed is also important.

4.1 Solution Phase Systems

Ideally a chemical actinometer should have the following features; thermal stability, availability, reproducibility, uniform response over a large wavelength range, and ease of analysis of chemical change.

In the range 250–450 nm, the normal range for solution photochemistry, the ferrioxalate actinometer is of paramount importance.⁽⁹⁾ This actinometer, used in aqueous solution as $6 \times 10^{-3} M$ solution without need for degassing,

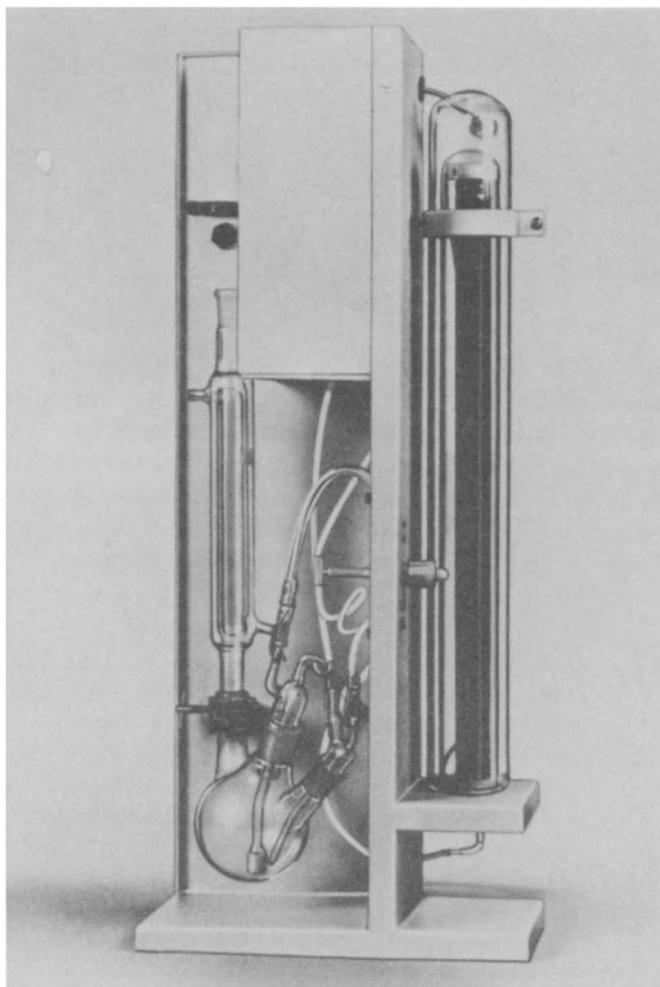


Figure 5. Thin-film reactor. (Reproduced by permission of Applied Photophysics Ltd.)

reacts with light to produce Fe^{2+} (as ferrous oxalate which does not absorb the light) and CO_2 as shown in the equations (1):

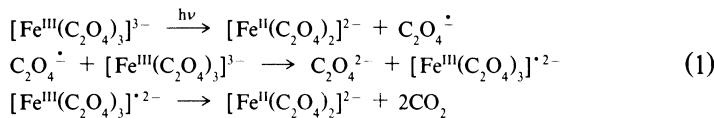
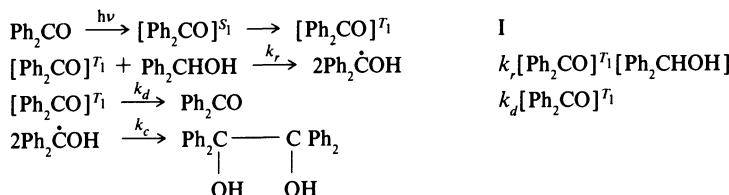


Table 7. Quantum Yield of Ferrous Ion Production for 0.006 M Solution of Potassium Ferrioxalate

λ (nm)	ϕ
254	1.25
267	1.24
312	1.24
334	1.24
361	1.21
365	1.21

These equations show that although only one photon is absorbed [equation (1)] the oxalyl radical anion produces, by a dark reaction, another molecule of potassium ferrous oxalate. Thus the observed quantum yield is twice the quantum yield of the primary photochemical process. The actinometer is monitored by measuring the amount of Fe^{2+} formed by complexation with 1,10-phenanthroline which produces a red complex analyzed spectrophotometrically at 510 nm. The formation of Fe^{2+} is almost constant at short wavelengths (Table 7). Full details of the values can be obtained elsewhere.[†] More recent investigations of this actinometer system have shown that an improvement in performance can be achieved using deoxygenated 0.15 M potassium ferrioxalate solutions.⁽¹⁰⁾ Other studies have shown that care has to be exercised in the use of the 1,10-phenanthroline since these solutions can be photooxidized under fluorescent lights.⁽¹¹⁾

Another actinometer which has gained support is the benzophenone-benzhydrol system. This actinometer uses the photoreduction of benzophenone by benzhydrol when irradiated in vacuum-degassed benzene solution.^{t(12)} The major advantages of this actinometer are (a) it does not absorb above 390 nm and (b) the quantum yield is redetermined each time and consequently most of the errors will be eliminated. The relevant equations and the kinetic treatment of the actinometer are as follows:



[†]Reference 1, p. 784.

[†]Reference 2, pp. 331-332.

Using the steady-state approach

$$\frac{d[\text{Ph}_2\text{CO}]^T}{dt} = I - k_r[\text{Ph}_2\text{CO}]^T[\text{Ph}_2\text{CHOH}] - k_d[\text{Ph}_2\text{CO}]^T$$

then when

$$\frac{d[\text{Ph}_2\text{CO}]^T}{dt} = 0$$

$$I = k_r[\text{Ph}_2\text{CO}]^T[\text{Ph}_2\text{CHOH}] + k_d[\text{Ph}_2\text{CO}]^T$$

Now the quantum yield for benzophenone disappearance ($\phi_{-\text{Ph}_2\text{CO}}$) is defined as

$$\phi_{-\text{Ph}_2\text{CO}} = \frac{k_r[\text{Ph}_2\text{CO}]^T[\text{Ph}_2\text{CHOH}]}{I}$$

$$\phi_{-\text{Ph}_2\text{CO}} = \frac{k_r[\text{Ph}_2\text{CO}]^T[\text{Ph}_2\text{CHOH}]}{k_r[\text{Ph}_2\text{CO}]^T[\text{Ph}_2\text{CHOH}] + k_d[\text{Ph}_2\text{CO}]^T}$$

$$= \frac{k_r[\text{Ph}_2\text{CHOH}]}{k_r[\text{Ph}_2\text{CHOH}] + k_d}$$

or

$$\frac{1}{\phi_{-\text{Ph}_2\text{CO}}} = \frac{k_r[\text{Ph}_2\text{CHOH}] + k_d}{k_r[\text{Ph}_2\text{CHOH}]} \quad (2)$$

$$= 1 + \frac{k_d}{k_r[\text{Ph}_2\text{CHOH}]}$$

This scheme shows that the disappearance of the benzophenone is related to the concentration of the benzhydrol. Several samples of benzophenone-benzhydrol mixtures with the benzophenone concentration kept constant are irradiated in a “merry-go-round”—see Section 3—and one of the samples is chosen as the actinometer. The amount of benzophenone which has been consumed in each sample is measured spectrophotometrically at 330, 335,

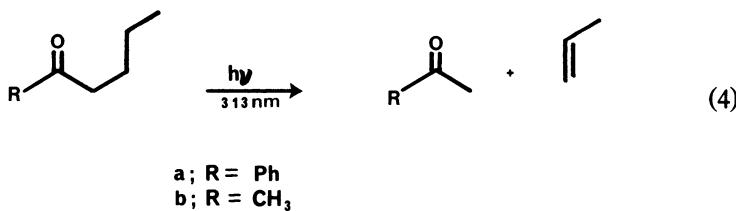
340, 345, and 350 nm. The evaluation of the system is then achieved by modification of equation (2) by multiplying by $\phi_{\text{actinometer}}$ to give equation (3):

$$\frac{\phi_{\text{act}}}{\phi_{-\text{Ph}_2\text{CO}}} = \phi_{\text{act}} + \frac{k_d}{k_r} \frac{\phi_{\text{act}}}{[\text{Ph}_2\text{CHOH}]} \quad (3)$$

a graphical solution of which is then obtained by plotting $\phi_{\text{act}}/\phi_{-\text{Ph}_2\text{CO}}$ against $1/[\text{Ph}_2\text{CHOH}]$. This gives the quantum yield for the actinometer as the intercept and the slope gives $k_d\phi_{\text{act}}/k_r$.

The photoreduction of decafluorobenzophenone in isopropanol has also been suggested as an actinometer for the 290–370-nm range. The disappearance of the benzophenone in this instance is measured spectrophotometrically and the quantum yield for the reaction is 0.60. Nitrogen purging of the solution is adequate.⁽¹⁴⁾ The system has some drawbacks in that decomposition, which is both wavelength and light intensity dependent, occurs.^(15,16)

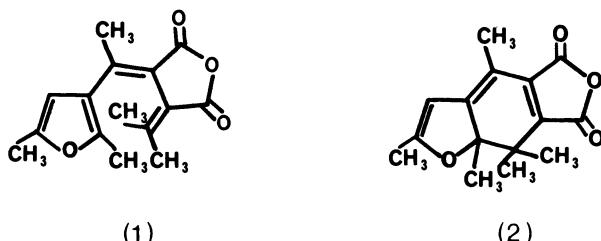
Many other systems can be used as actinometers, and often it is convenient to use a reaction whose quantum yield has been determined with reference to ferrioxalate. The Norrish type-II elimination of valerophenone is one such system. This reaction [equation (4)] produces acetophenone with a quantum yield of 0.33 when the valerophenone is irradiated at 313 nm in vacuum-degassed benzene solution.^(17,18)



The quantity of acetophenone formed is measured by gas–liquid chromatography (GLC). The hexan-2-one system is of the same type undergoing fragmentation at 313 nm to afford acetone and propene. Both of these can be measured quantitatively by GLC, although it is more customary to quantify the amount of acetone which has a quantum yield of appearance of 0.22.⁽¹⁹⁾ Such systems have the advantage that they can be used throughout a long irradiation and thus will take into account any light intensity fluctuations.

Recently a reusable chemical actinometer has been described⁽²⁰⁾ which is operative in the 310–370- and 436–545-nm ranges. The system is based on the photochromic compound **1**, named Aberchrome 540. This compound on irradiation in the 310–370-nm region is converted into the isomer **2**.

The use of a magnetically stirred solution of **1** in toluene in a cuvette allows the system to be used as an actinometer with analysis in the visible range at



494 nm for the isomer 2. The photon flux (I) can be obtained from equation (5):

$$I = \frac{\text{increase in absorbance at } 494\text{nm} \times \text{volume irradiated in ml}}{\phi \text{ for process } 1 \rightarrow 2} \times \frac{\text{Avogadro's number}}{8200^a \times \text{time (s)}} \text{ photons s}^{-1} \quad (5)$$

$a = \epsilon \text{ value for (2) at } 494 \text{ nm}$

The solution can then be irradiated with white light to reverse the reaction ($2 \rightarrow 1$) and it is then ready for reuse. Provided the photostability of such systems is beyond doubt, the reagents of type 1 and 2 are obviously of great use.

4.2 Electronic Actinometers

In two of the devices described in Section 3 the conventional method of actinometry involves solution-phase actinometers to analyze both the beams through the sample and the 90° reference beam separated by the beam splitter. This means that each quantitative run involves several actinometer solutions and determinations to monitor the light absorbed by the sample undergoing irradiation. For convenience two groups have felt it worthwhile to develop electronic actinometers. Schaffner and his co-workers⁽²¹⁾ have developed an integrating actinometric system to measure the light through the sample and to compare this with the light deflected by the beam splitter. The two beams are analyzed using fluorescent cells with silicon photodiodes to measure the output from the fluorescing material. The authors⁽²¹⁾ claim good agreement when the system is checked against potassium ferrioxalate actinometry in the 254–366-nm range. It has been suggested that such systems can suffer from possible sources of error in that there should be some correction for reflected light in the sample cell^(22,23) and also for changes in penetration with wavelength. Chemical actinometry has one major advantage over electronic methods in that the solution of actinometer can be irradiated under conditions similar to those of the solution of reactant under study. This eliminates the

need for corrections resulting from reflectance and nonuniformity of the incident light beam.

The device developed by Zimmerman and his group⁽²⁴⁾ utilizes IP28 photomultiplier tubes and a voltage-to-frequency converter to monitor the light through the reactant cell and the light reflected by the beam splitter. The design of the apparatus has ensured that errors due to differential drift in the amplifiers are minimized. One drawback of the system is that the photomultipliers have wavelength-dependent sensitivity, which means that the apparatus has to be calibrated for each wavelength used. There is also the problem associated with fatigue and drift in the photomultipliers at anode currents above 10 μ A. However, this was not found to be a problem in this instance, and the authors⁽²⁴⁾ claim excellent operational stability over a range of light intensities of 10⁵.

Quite clearly there are many actinometer systems, which all have their advantages and disadvantages. Which one is chosen is dependent on the type of apparatus being used and on the personal preference of the worker.

5. Purity of Solvents and Gases

Solvents can play an important part in the photoreaction of organic molecules. Primarily dilution of a neat compound prevents the accumulation of high concentrations of excited species which if produced near the walls of the containing vessel can lead to side-reactions including polymerization. Dilution also allows for reasonable penetration of the light into the solution and so reasonable reaction rates can be achieved. The optimum concentration for a reactant can only be found by trial and error and is a balance between too dilute a solution, where most of the incident light passes through the solution, and too concentrated a solution, where side-reactions such as undesirable dimerization take place.

Many solvents are used in irradiations. The spectral transmissions of some of the more common ones are shown in Table 8. From these data and more detailed information available from other sources it is possible to select the best solvent with appropriate optical transparency at the wavelength to be used.⁽²⁵⁾

Hydrocarbons such as cyclohexane are relatively trouble free since they do not have low-lying excited states which can interfere with the reaction of the solute and they are essentially chemically unreactive. They are also free from impurities, which can often be a problem when ethers and alcohols are used. Care has to be taken to ensure that the ethers are free of peroxides and that the alcohol used is acid free since these impurities could lead to undesirable reactions.

Table 8. Transmission Characteristics of Various Solvents^a

Solvent	10% Transmission	100% Transmission
Acetone	329	366
Acetonitrile	190	313
Benzene	280	366
Carbon tetrachloride	265	313
Cyclohexane	205	254
Diethyl ether	215	313
Dimethyl sulfoxide	262	366
Ethanol	205	313
Hexane	195	254
Propan-2-ol	205	313
Tetrahydrofuran	233	366

^a Measured for a 1 cm path length of pure solvent.

The exclusion of air (oxygen) from a photoreaction is essential, particularly when a triplet reaction is suspected. Table 9 shows the concentration of oxygen present in nondegassed solvents.[†] Even though the values are small there is sufficient dissolved oxygen to quench a triplet reaction. Thus it is essential to outgas the solvent prior to irradiation.

Degassing by a vacuum technique (3 or 4 freeze-pump-thaw cycles) at $< 10^{-4}$ Torr is effective. However, for many qualitative and preparative studies such a degassing is not practical and an alternative method has to be employed. The method most often used is one involving an inert gas such as helium, argon, or nitrogen. For most purposes nitrogen should suffice, but nitrogen, even of the highest purity supplied in large cylinders, contains appreciable quantities of oxygen and water. Thus it is desirable to scrub out these impurities by passing gas through a scrubbing chain. A few methods are available for the removal of oxygen from nitrogen, the simplest of which is the use of

[†] Reference 2, p. 89

Table 9. Concentration of Oxygen in Nondegassed Solvents

Solvent	Oxygen concentration (mol ter ⁻¹)
Acetone	0.0024
Benzene	0.0019
Carbon tetrachloride	0.0026
Cyclohexane	0.0023
Diethyl ether	0.0040
Ethanol	0.0021
Hexane	0.0031
Propan-2-ol	0.0021

a solution of vanadous sulfate.⁽²⁶⁾ The degassing is carried out by passing the purified nitrogen through the solution of the reactant for 0.5–1 h, which is usually sufficient time to reduce the level of the dissolved oxygen to below a concentration of $10^{-4} M$. The apparatus is then sealed or else the nitrogen purge is continued throughout the irradiation.

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