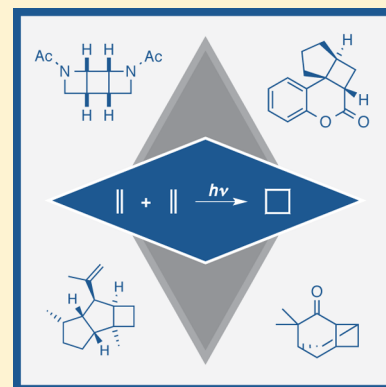


Recent Advances in the Synthesis of Cyclobutanes by Olefin [2 + 2] Photocycloaddition Reactions

Saner Poplata, Andreas Tröster, You-Quan Zou, and Thorsten Bach*

Department Chemie and Catalysis Research Center (CRC), Technische Universität München, D-85747 Garching, Germany

ABSTRACT: The [2 + 2] photocycloaddition is undisputedly the most important and most frequently used photochemical reaction. In this review, it is attempted to cover all recent aspects of [2 + 2] photocycloaddition chemistry with an emphasis on synthetically relevant, regio-, and stereoselective reactions. The review aims to comprehensively discuss relevant work, which was done in the field in the last 20 years (i.e., from 1995 to 2015). Organization of the data follows a subdivision according to mechanism and substrate classes. Cu(I) and PET (photoinduced electron transfer) catalysis are treated separately in sections 2 and 4, whereas the vast majority of photocycloaddition reactions which occur by direct excitation or sensitization are divided within section 3 into individual subsections according to the photochemically excited olefin.



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1. INTRODUCTION

Cycloaddition reactions enable a versatile and straightforward access to carbocyclic or heterocyclic organic compounds. Contrary to cyclization reactions, in which a single bond is formed, the hallmark of cycloaddition reactions is the formation of two or more bonds in a single operation. Commonly, olefins serve as one reaction partner in a cycloaddition reaction, and bond formation occurs at both carbon atoms of the double bond. Consequently, the double bond is sacrificed to form two new single bonds. Apart from the Diels–Alder reaction, in which a diene acts as the other cycloaddition component, the [2 + 2] photocycloaddition is the most frequently used cycloaddition reaction to access carbocyclic products. It involves two olefins, one of which is required to be excited by ultraviolet (UV) or visible light.

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1.1. Historical Note

Historically, the first $[2+2]$ photocycloadditions found in the chemical literature were formally $[2+2]$ photodimerization reactions, in which identical olefins would undergo formation of the central cyclobutane ring. Exposure of the respective monomeric olefins, frequently in the solid state, to sunlight led to the dimerization product. Thymoquinone was the first compound to show the above-mentioned dimerization as discovered by Liebermann in 1877.¹ Its dimer **1**² (Figure 1)

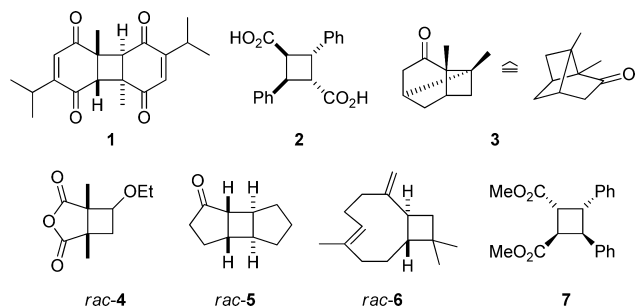


Figure 1. Structures of a few selected historically relevant $[2+2]$ photocycloaddition products.

represents the first $[2+2]$ photocycloaddition product ever described. The reaction was shown also to be successful in solution.³ α -Truxillic acid (**2**)^{4–6} represents another centrosymmetric photodimer, which was a few years later obtained by $[2+2]$ photodimerization of cinnamic acid.⁷ An array of similar $[2+2]$ photodimerization reactions were performed at the end of the 19th century and at the turn to the 20th century, the history of which has been summarized in an instructive review by Roth on the beginnings of organic photochemistry.⁸ The year 1908 marks the discovery of what we call today an intramolecular enone $[2+2]$ photocycloaddition reaction. Ciamician and Silber⁹ observed the formation of carvonecampor (**3**)¹⁰ when exposing (+)-carvone to sunlight.

The consecutive decades were dedicated mainly to studies of $[2+2]$ photodimerization and intramolecular $[2+2]$ photocycloaddition reactions. This time period is covered nicely in a book by Schönberg, which was first published in 1958¹¹ with an updated version published in 1968 with Schenck and Neumüller as co-authors.¹² The 1960s mark the advent of intermolecular $[2+2]$ photocycloaddition reactions. It was recognized that a second olefin can be employed as reaction partner and, if used in excess, enables formation of a defined $[2+2]$ cycloaddition product. Cyclobutanes *rac*-**4**, reported by Schenck et al.,¹³ and *rac*-**5**, reported by Eaton,¹⁴ represent early products obtained by this chemistry. Simultaneously, de Mayo et al. reported on a sequence of $[2+2]$ photocycloaddition/retro-aldol reaction when irradiating 1,5-diketones in the presence of alkenes.¹⁵ In 1963, Corey and co-workers employed the enone $[2+2]$ photocycloaddition for the first time in natural product synthesis when reporting their landmark syntheses of (\pm)-caryophyllene (*rac*-**6**) and (\pm)-isocaryophyllene.^{16,17} $[2+2]$ Photocycloaddition chemistry became a vibrant area of research, and a wealth of new information was collected in the 1960s and 1970s. The most comprehensive treatise covering the literature up to 1975 can be found in several chapters of the Houben-Weyl covering the topic of intramolecular $[2+2]$ photocycloaddition, $[2+2]$ photodimerization, and intermolecular $[2+2]$ photocycloaddition.¹⁸ Along with the data accumulated in synthetic studies,

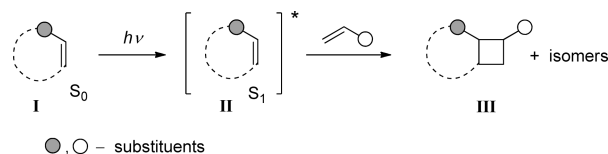
mechanistic work began simultaneously and helped to understand the main characteristics of photocycloaddition chemistry. The major mechanistic pathways, along which $[2+2]$ photocycloaddition reactions can progress, will be discussed in the next subsection. Of final historical note is the interest in controlling the absolute configuration of $[2+2]$ photocycloaddition products. In 1982, Tolbert and Ali showed that high auxiliary-induced diastereoselectivity could be achieved by employing chiral methyl *l*-bornyl fumarate in the intermolecular $[2+2]$ photocycloaddition to *trans*-stilbene.¹⁹ Upon cleavage of the auxiliary and esterification with methanol, dimethyl μ -truxinate (**7**)²⁰ was obtained in 90% enantiomeric excess (*ee*).

Over the years, many reviews have been written in the field of $[2+2]$ photocycloaddition chemistry. While the books mentioned above have covered more or less comprehensively the knowledge at the time of their publication, it appears nowadays impossible to discuss this vast area of chemical science in full depth. It is for this reason that most of the more recent reviews have focused on specific topics. Where applicable these reviews will be cited in the context of the next subsection.

1.2. Fundamental Mechanistic Considerations

Although the reaction pathways of $[2+2]$ photocycloaddition are discussed in many textbooks of photochemistry,^{21–24} a short summary seems appropriate to categorize the different mechanistic alternatives. The most straightforward reaction pathway $I \rightarrow III$ (Scheme 1) includes the direct excitation of a

Scheme 1. $[2+2]$ Photocycloaddition of an Olefin **I** via its First Excited Singlet State **II** (S_1)

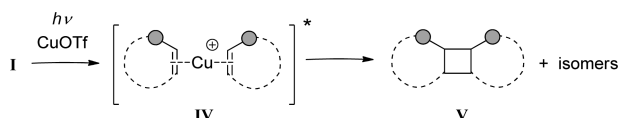


given olefin **I** from the ground state (S_0) to its first excited singlet state S_1 (**II**) and subsequent addition to another olefin. If no other olefin is present, olefin **I** can add to another molecule of itself leading to the product of $[2+2]$ photodimerization (vide infra). In either case, the addition can be envisaged to occur in a concerted fashion, although the intermediacy of excited complexes (exciplexes) in the case of $[2+2]$ photocycloaddition or of excited dimers (excimers) for $[2+2]$ photodimerization has been observed. The reaction is expected to be stereospecific for both olefinic reaction partners.

Of course, the reaction can also occur in an intramolecular fashion. Despite the fact that the reaction course seems straightforward and viable, there are several limitations. Nonconjugated alkenes have a high lying S_1 state, and excitation with commercially available irradiation sources ($\lambda \geq 250$ nm)²⁵ is not feasible. If, as is mostly the case, the first excited state is of $\pi\pi^*$ character, rotation around the C–C double bond can occur in **II** and leads to efficient energy dissipation. In addition, the S_1 state is normally short-lived with fluorescence and internal conversion (IC) being competitive photophysical pathways, which interfere with the efficiency of the desired $[2+2]$ photocycloaddition. Among the conjugated alkenes, it is mostly arylalkenes (e.g., styrenes and stilbenes), which follow this reaction pathway either in an intramolecular reaction, in a $[2+2]$ photodimerization, or in a $[2+2]$ photocycloaddition reaction to another olefin.²⁶

Upon complexation to a transition metal, olefins can be directly excited at a relatively long wavelength ($\lambda = 254$ nm) via a metal-to-ligand charge transfer (MLCT) or via a ligand-to-metal charge transfer (LMCT) excitation. In particular, copper(I) salts like CuOTf (Tf = trifluoromethanesulfonyl) have turned out to be effective catalysts for a subsequent [2 + 2] photocycloaddition.^{27–29} Mostly, this reaction is performed as a [2 + 2] photodimerization (Scheme 2) to

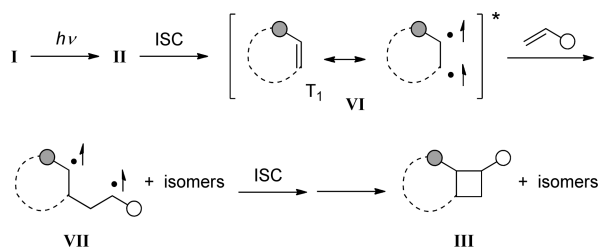
Scheme 2. [2 + 2] Photodimerization of an Olefin I via its Excited Cu(I) Complex IV



products V or as an intramolecular [2 + 2] photocycloaddition. In the latter instance, 1,6-heptadienes represent the preferred substrate class (vide infra). Albeit somewhat simplified, the reaction can be envisaged as a concerted reaction mediated by the copper(I) cation (cf. intermediate IV).

It is desirable for a successful intermolecular [2 + 2] photocycloaddition reaction to reach a relatively long-lived excited state, which is available for attack by another olefin. This prerequisite is ideally met by olefinic substrates, the double bond of which is conjugated to a carbonyl group.^{30–40} Typically, α,β -unsaturated ketones (enones) or α,β -unsaturated carboxylic acid derivatives can be directly excited to the respective S_1 state (II) from which intersystem crossing (ISC) (i.e., a spin flip) to the respective triplet state is rapid (Scheme 3). Photochemical reactions occur from the lowest-lying triplet state T_1 , which is frequently of $\pi\pi^*$ character (VI).⁴¹

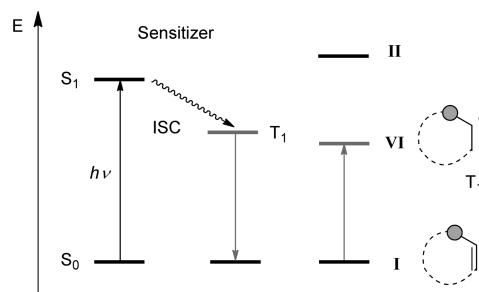
Scheme 3. [2 + 2] Photocycloaddition of an Olefin I via its First Excited Triplet State VI (T_1)



In this state, the double bond is not existent and free rotation is possible. It is therefore common to employ cyclic five- and six-membered α,β -unsaturated carbonyl compounds as substrates, the T_1 state of which is twisted but cannot completely dissipate its energy by rotation. The long lifetime of the triplet state, which can be in the μ s regime, allows an intermolecular attack of another olefin molecule to generate a 1,4-diradical intermediate VII,^{42–44} from which products are formed after ISC to the singlet hypersurface. Typical excitation wavelengths for enones are in the range of $\lambda = 300$ –350 nm, for α,β -unsaturated lactams and lactones at $\lambda \cong 250$ nm.

Population of the triplet state of an olefin is not only possible by direct excitation but it can also be induced by energy transfer from another photoexcited molecule. This process is called triplet energy transfer or sensitization (Scheme 4). An ideal triplet sensitizer is a compound with a low-lying S_1 and a high-lying T_1 state. In addition, it should show a high ISC rate so

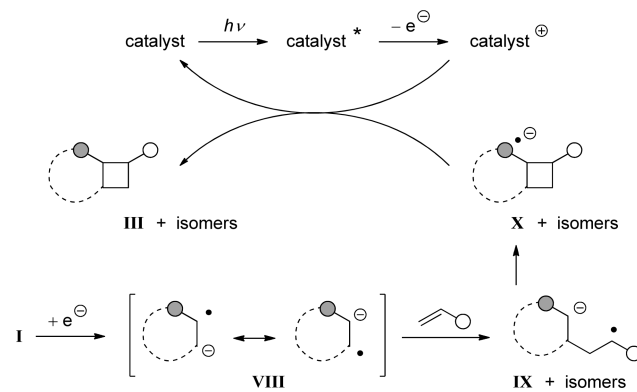
Scheme 4. Sensitization via Triplet Energy Transfer from a Sensitizer (left) to an Olefin I (right)



that the quantum yield of T_1 formation reaches unity. Once in the triplet state, the sensitizer can transfer its energy to an olefin by an electron exchange mechanism (Dexter mechanism⁴⁵). Requirements for the energy transfer to occur effectively are (a) a close spatial encounter of sensitizer and olefin and (b) an energetic preference for the process. In other words, the triplet energy of VI should be lower than the triplet energy of the sensitizer. The big advantage of sensitization versus direct excitation is the fact that it can be performed at long wavelength while direct excitation would require short-wavelength light. The situation depicted in Scheme 4 is typical. Direct excitation of the olefin ($I \rightarrow II$) would require significantly more energy than population of the triplet state by sensitization. Typically, aliphatic or aromatic ketones are used as triplet sensitizers. A convenient synthetic procedure is to run the reaction in acetone or to add the ketone (e.g., benzophenone and acetophenone) to a transparent solvent.

While sensitization requires the exchange of two electrons (i.e., one electron is transferred from the sensitizer to the olefin and one electron is transferred from the olefin to the sensitizer), it is also feasible to initiate a [2 + 2] photocycloaddition reaction by a catalyst, which transfers a single electron to the olefin (Scheme 5). In the literature before 2005,

Scheme 5. [2 + 2] Photocycloaddition of an Olefin I Mediated by Single Electron Transfer (SET) from a Catalyst (Top) to the Olefin I (Bottom)



this process has been described as photoinduced electron transfer (PET).^{46–56} In recent years, the term photoredox catalysis has become increasingly popular.^{57–64} In this type of catalysis, the olefin does not react from an excited singlet or triplet state but is rather reduced (reductive PET) or oxidized (oxidative PET) by the catalyst or by an additional electron transfer reagent, which acts as cocatalyst. Upon photochemical

reduction, intermediate radical anion **VIII** adds inter- or intramolecularly to another olefin to form radical intermediate **IX**, which cyclizes to cyclobutane **X** prior to back electron transfer. Alternatively, back electron transfer can occur before cyclization. In this case, a 1,4-diradical intermediate would be involved. If radical anion **X** transfers the electron directly to substrate **I**, a radical chain process is initiated. In an oxidative quench, the olefin forms the respective radical cation, which follows a similar sequence prior to back electron transfer.

It is apparent that upon photochemical excitation of **I** according to Schemes 1 and 3, a species can be generated, which is capable of SET to or from another olefin. In this rare instance, complete charge transfer can occur generating a radical cation/radical anion pair, the combination of which can also lead to products of [2 + 2] photocycloaddition (see section 4.3).

1.3. Scope

In this review, it is attempted to cover all aspects of recent [2 + 2] photocycloaddition chemistry with an emphasis on synthetically relevant, regio-, and stereoselective reactions. Most references refer to work performed in the last 20 years (i.e., from 1995 to 2015), but earlier work is mentioned when appropriate. Apart from the reviews already cited, very useful information about synthetically relevant [2 + 2] photocycloaddition chemistry can be found in reviews devoted to the application of photochemical reactions to natural product synthesis.^{65–67} Limited attention has been given in the present review to [2 + 2] photocycloaddition reactions, which occur in the solid state (mostly as [2 + 2] photodimerization),^{68–70} in biological systems,^{71,72} or in confined media.^{73–75} The [2 + 2] photocycloaddition to arenes, the *ortho*-photocycloaddition,^{76–79} is not covered in this review, either. The reaction was excluded from the discussion because it frequently occurs upon arene excitation and because the primary *ortho*-photocycloaddition products tend to undergo consecutive reactions, which do not meet the focus of this review. In fact, cyclobutane ring opening and ring expansion reactions^{80,81} are not extensively discussed.

A final remark seems warranted regarding the nomenclature of the newly formed cyclobutane ring. A regioisomer with two given substituents positioned in a 1,2-relationship is said to be the head-to-head (HH) isomer (Figure 2). If in a 1,3-relationship, the cyclobutane is called the head-to-tail (HT) isomer. The relative configuration along a cyclobutane single bond, which is annulated to another ring, is called *cis* versus *trans*. The relative configuration at the single bond, which is not annulated and which is frequently a result of the simple

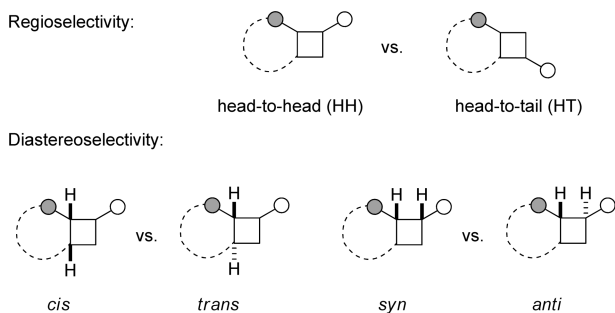


Figure 2. Nomenclature to describe regio- and diastereoisomers in [2 + 2] photocycloaddition reactions.

diastereoselectivity of the intermolecular [2 + 2] photocycloaddition, is referred to as *syn* versus *anti*.

Organization of the data follows a subdivision according to mechanism and substrate classes. Cu(I) and PET catalysis are treated separately in sections 2 and 4, whereas the vast majority of photocycloaddition reactions which occur by direct excitation or sensitization are divided within section 3 into individual subsections according to the photochemically excited olefin. Whenever possible, the emission wavelength of the irradiation source is specified in the schemes.⁸²

2. CU(I) CATALYSIS

The typical catalyst to be used in Cu(I)-catalyzed [2 + 2] photocycloaddition is CuOTf, which is commercially available as its benzene or toluene complex. In terms of handling, the use of Cu(OTf)₂ is more convenient, and it was shown that it exhibits similar catalytic activity, most likely by *in situ* reduction to Cu(I).⁸³ Ethers (Et₂O and THF) are typical solvents for the reaction, and the typical irradiation wavelength is $\lambda = 254$ nm. The reactions are performed intermolecularly as [2 + 2] photodimerization or intramolecularly to generate bicyclo[3.2.0]heptanes. Approaches to bicyclo[4.2.0]octanes have been reported and will be discussed in a separate section (section 2.3).

2.1. [2 + 2] Photodimerization

[2 + 2] Photodimerization reactions were shown by Malik et al. to proceed with high efficiency in ionic liquids (Figure 3).⁸⁴ It

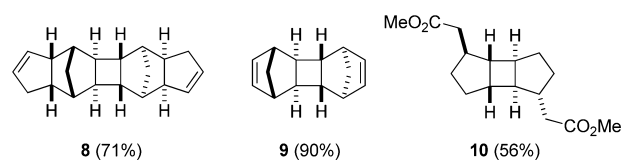
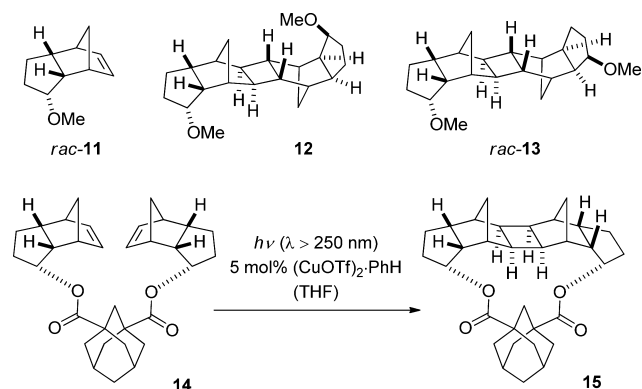


Figure 3. Products of CuOTf-catalyzed [2 + 2] photodimerization reactions performed at $\lambda = 254$ nm in the ionic liquid [tmba][NTf₂].

was found that trimethyl(butyl)ammonium bis-(trifluoromethylsulfonyl)imide ([tmba][NTf₂]) was an ideal solvent, which facilitates efficient product formation. Dicyclopentadiene for example was reported to give dimer **8** in 71% yield, whereas a yield of only 48% had been recorded⁸⁵ if the reaction was performed in THF. The central cyclobutane ring is typically formed in a *cis*-*anti*-*cis* fashion and is in *trans*(*exo*) position to the larger substituent at the existing ring. This stereochemical outcome is expected from preferred formation of the respective Cu(I) complex (*vide supra*). Related photodimers **9** and **10** were obtained in a similar fashion. Compound **10** was accompanied by another diastereoisomer in a diastereomeric ratio (d.r.) of 89/11. Intramolecular [2 + 2] photocycloaddition reactions could also be performed in [tmba][NTf₂] as the solvent.

It was shown by Galoppini et al. that the stereochemical outcome of the [2 + 2] photodimerization can be altered by tethering the two monomers (Scheme 6).^{86,87} Photodimerization of racemic dicyclopentadiene derivative *rac*-**11** gave exclusively the respective *cis*-*anti*-*cis* products **12** and *rac*-**13** with the cyclobutane in *exo*-position of the norbornane skeleton (62% yield). When tethering two enantiomers with opposite configuration via a dicarboxylic acid (e.g., compound **14**), the respective *cis*-*syn*-*cis* product **15** was obtained in good

Scheme 6. [2 + 2] Photodimerization Products from Norbornene *rac*-11 and Influence of a Tether on the Relative Configuration

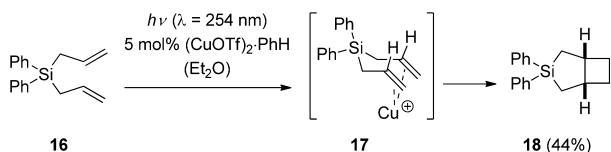


yield. The tether could be readily removed reductively to generate the respective diol.

2.2. Bicyclo[3.2.0]heptanes and Heterocyclic Analogues

A large variety of diolefins, the two alkene units of which are in a 1,6-relationship, undergo an intramolecular Cu(I)-catalyzed [2 + 2] photocycloaddition. The products are bicyclo[3.2.0]-heptanes or heterocyclic analogues thereof. An example from a recent study by Koenig and co-workers (Scheme 7),⁸⁸ in which

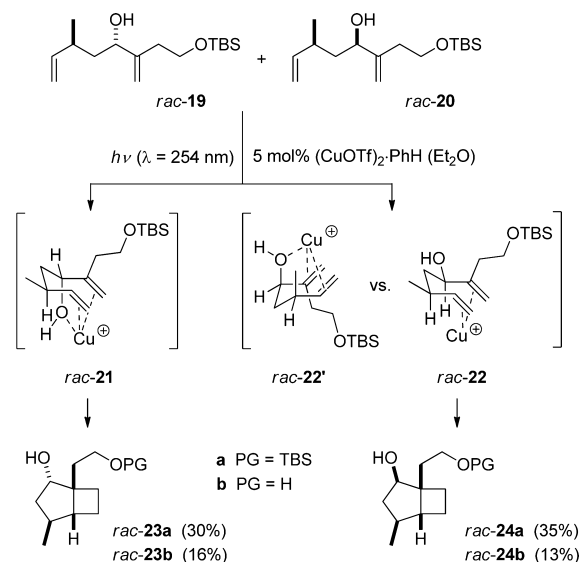
Scheme 7. Intramolecular Cu(I)-Catalyzed [2 + 2] Photocycloaddition of Diallylsilane 16



diallylsilane **16** was employed, illustrates the simple diastereoselectivity resulting in exclusive formation of the *cis*-product **18**. Coordination to the copper center occurs from both olefins in a putative complex **17**, in which the two hydrogen atoms are located in a *cis* relationship.

The facial diastereoselectivity in intramolecular Cu(I)-catalyzed [2 + 2] photocycloaddition reactions is determined by a preference for substituents to be equatorially positioned in the chairlike conformation, in which the 1,6-heptadienes bind to the copper cation. Oxygen substituents and, in particular, a hydroxy group can be positioned axially because this position facilitates additional binding to copper.⁸⁹ In the context of a synthetic approach to pseudolaric acid, Paquette and Pettigrew examined the [2 + 2] photocycloaddition of substrates *rac*-19 and *rac*-20, which were submitted to the Cu(I)-catalyzed photocycloaddition as a mixture of diastereoisomers (Scheme 8).⁹⁰ The resulting product mixture revealed that diastereoisomeric products *rac*-23 were formed via a copper complex *rac*-21, in which the methyl group is equatorially and the hydroxy group is axially positioned. The other set of diastereoisomeric products *rac*-24 resulted from copper complex *rac*-22. The binding of the hydroxy group to copper is not sufficiently strong to populate complex *rac*-22' in which the methyl group would be positioned axially. Products resulting from *rac*-22' were not observed. Partially deprotection of the *tert*-butyldimethylsilyl (TBS) group occurred, which resulted in the formation of alcohols *rac*-23b and *rac*-24b.

Scheme 8. Intramolecular Cu(I)-Catalyzed [2 + 2] Photocycloaddition of Chiral 1,6-Heptadienes *rac*-19 and *rac*-20 via the Putative Complexes *rac*-21 and *rac*-22



The group of Ghosh has extensively employed the Cu(I)-catalyzed [2 + 2] photocycloaddition as an entry to the synthesis and formal total synthesis of various natural products in racemic form. These studies include the synthesis of (\pm)-grandisol,^{91,92} (\pm)- α -cedrene,^{93,94} (\pm)- β -necrodol,⁹⁵ and (\pm)- $\Delta^{9(12)}$ -capnellene.⁹⁶ In our group, the total synthesis of (\pm)-kelsoene was achieved, employing the Cu(I)-catalyzed photocycloaddition as a key step.⁹⁷ For the synthesis of cyclobut-A (*rac*-27), a carbocyclic nucleoside analogue of oxetanocin, Ghosh and co-workers employed substrate *rac*-25 as starting material (Figure 4).⁹⁸ The facial diastereoselectivity

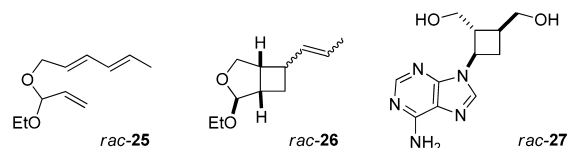


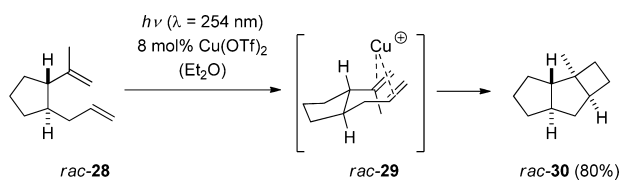
Figure 4. Intramolecular [2 + 2] photocycloaddition of substrate *rac*-25 to product *rac*-26 in the synthesis of the nucleoside analogue cyclobut-A (*rac*-27).

of the [2 + 2] photocycloaddition was high, but the exocyclic double bond turned out to cause a mixture of diastereoisomers *rac*-26 (70% yield). Its location at the cyclobutane ring (*exo*/*endo*) was not defined nor was its relative configuration (*E*/*Z*). Still, the mixture could be taken into the further steps of the synthesis, in the course of which the double bond was oxidatively cleaved, and the stereogenic center at the ring was epimerized.

There is extensive precedence in the recent literature that a high degree of diastereoselectivity can be achieved in the Cu(I)-catalyzed [2 + 2] photocycloaddition.^{99–101} Apart from the above-mentioned control by a stereogenic center in the linker, the preferred conformation of the starting material and its potential for complexation to copper are important issues to be considered. The disubstituted cyclopentane *rac*-28 for example can readily adopt a half-chair conformation *rac*-29, in which coordination to the copper atom is readily attained, while the two alkenyl substituents are in a pseudoequatorial position

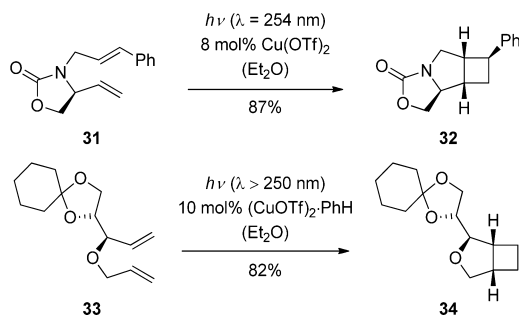
(Scheme 9).¹⁰² The reaction occurred with high diastereoselectivity to product *rac*-30.

Scheme 9. Conformational Control in the Intramolecular Cu(I)-Catalyzed [2 + 2] Photocycloaddition of Substrate *rac*-28



As already seen from Scheme 7 and Figure 4, the two alkene units do not need to be connected by a carbon chain to undergo an intramolecular Cu(I)-catalyzed [2 + 2] photocycloaddition. Instead, heteroatoms can be used to link the reaction partners. Scheme 10 shows two examples, in which a

Scheme 10. Diastereoselective Cu(I)-Catalyzed [2 + 2] Photocycloaddition with Heteroatoms in the 1,6-Heptadiene Structure

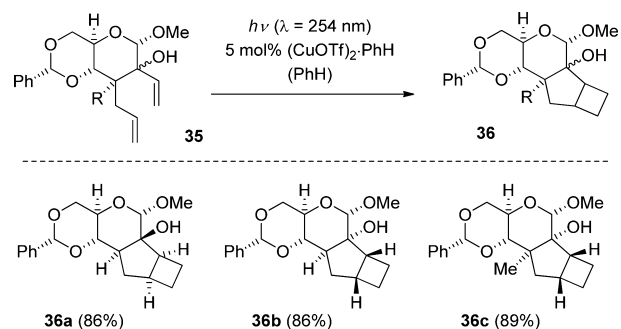


nitrogen atom or an oxygen atom was employed for this purpose. In the first example, enantiomerically pure *N*-cinnamyl-4-vinylloxazolidin-2-one (**31**) underwent a highly diastereoselective [2 + 2] photocycloaddition to product **32**.¹⁰³ The phenyl group formally retains its configuration, but it is known that Cu(I) induces a *cis/trans* isomerization. The preference for the *exo* products is thus rather a result of the steric demand of the phenyl group but an indication for a stereospecific reaction course. 3-Azabicyclo[3.2.0]heptanes as formed by this reaction represent useful scaffolds for medicinal chemistry. In the second example, the diallylether **33** derived from (*R*)-glyceraldehyde produced with high diastereoselectivity the 3-oxabicyclo[3.2.0]heptane **34**.^{104,105} Compounds of this type can be converted into natural products (*vide supra*). In the present study, which was performed in the Ghosh group, a formal synthesis of (+)-*β*-necrodol and (–)-*grandisol* was achieved.

Attempts were made by Langer and Mattay to generate enantiomerically pure bicyclo[3.2.0]heptanes employing chiral ligands in the Cu(I)-catalyzed photocycloaddition. Enantioselectivities remained low, however. A chiral auxiliary approach was more successful with a diastereomeric excess (*de*) of up to 60%.¹⁰⁶ The extensive pool of chiral enantiomerically pure compounds accessible from carbohydrates has been exploited by the Ghosh and Jenkins group to produce an array of new fused and spiro annulated structures by a Cu(I)-catalyzed [2 + 2] photocycloaddition.^{107–110} Scheme 11 illustrates an

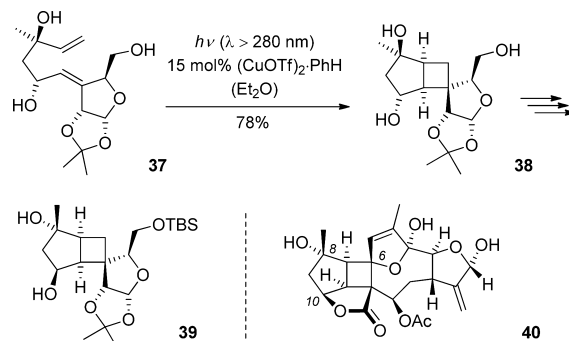
application of these experiments to the synthesis of new carbohydrate-type products **36** derived from precursors **35**.

Scheme 11. Cu(I)-Catalyzed [2 + 2] Photocycloaddition of Glucose-Derived 1,6-Heptadienes



A significant benefit of carbohydrate-based starting materials is their high enantiomeric purity, which enables an approach toward enantiomerically pure natural products via [2 + 2] photocycloaddition products. In 2011, Ghosh and co-workers reported¹¹¹ an approach toward the core structure of (–)-tricycloclavulone, employing a glucose-derived precursor. More recently, the same group disclosed an approach to the bicyclo[3.2.0]heptane core of bielschowskysin (**40**).^{112,113} Intramolecular Cu(I)-catalyzed [2 + 2] photocycloaddition of the glucose-derived 1,6-heptadiene **37** delivered in high yield and with excellent diastereoselectivity product **38** (Scheme 12).

Scheme 12. Intramolecular Cu(I)-Catalyzed [2 + 2] Photocycloaddition as an Approach to the Bicyclo[3.2.0]heptane Core of Bielschowskysin (40**)**



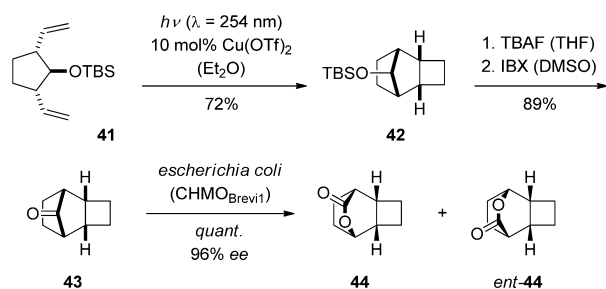
In subsequent steps, the relative configuration at carbon atoms C8 and C10 was adjusted so that the bicyclo[3.2.0]heptane ring of **39** coincided in all stereogenic centers with the natural product. In addition, successful photocycloaddition experiments with olefin precursors were undertaken, which also allow for introduction of the carbon chain attached to carbon atom C6.

2.3. Bicyclo[4.2.0]octanes

The intramolecular Cu(I)-catalyzed [2 + 2] photocycloaddition is limited to substrates with a three-atom tether between the reactive olefin units. Apparently longer or shorter tethers disfavor appropriate coordination to the electron deficient copper atom. Given the frequent occurrence of bicyclo[4.2.0]octane in natural products,¹¹⁴ attempts were made to synthesize these annulated cyclobutanes by Cu(I)-catalyzed [2 + 2] photocycloaddition. The key idea was to use a bicyclic

cyclopentane-type tether, with a cleavable bond in the ring, in order to attain the desired bicyclo[4.2.0]octane after a photocycloaddition/ring cleavage sequence. An advantage of this procedure is the fact that enantioselectivity can be induced in the ring cleavage step if the photocycloaddition product is a *meso* compound. [2 + 2] Photocycloaddition of 1,3-divinylcyclopentane **41** for example delivered product **42** (Scheme 13).¹¹⁵ Upon removal of the TBS group with tetrabutylammo-

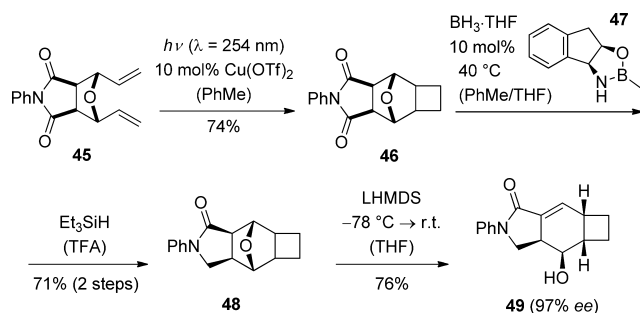
Scheme 13. Baeyer-Villiger Approach to Enantiomerically Pure Bicyclo[4.2.0]octanes from Bridged [2 + 2] Photocycloaddition Products



nium fluoride (TBAF) and oxidation with 2-iodoxybenzoic acid (IBX), ketone **43** was generated, which was subjected to an enzyme catalyzed Baeyer–Villiger oxidation.¹¹⁶ The cyclohexanone monooxygenase CHMO_{Brevi1} delivered lactone **44** in excellent enantioselectivity (96% *ee*). The enantiomer *ent*-**44** could be accessed in 86% *ee* by employing the cyclopentanone monooxygenase CPMO_{Coma}. Lactone ring opening was facile and was performed in quantitative yield as a transesterification with K₂CO₃ in MeOH.

Alternative ring opening modes for ketone **43** were pursued but turned out to be less enantioselective than the Baeyer–Villiger approach.¹¹⁷ More recently, it was shown in our laboratories that also an oxygen bridge can be employed as a possible position for ring opening. The sequence is illustrated for substrate **45**.¹¹⁸ Upon Cu(I)-catalyzed [2 + 2] photocycloaddition, the compound was converted into product **46**, which was obtained as an inseparable 82/18 mixture of *cis*-diastereoisomers with the cyclobutane ring *exo* or *endo* relative to the oxygen atom (Scheme 14). The imide was enantioselectively reduced employing oxazaborolidine **47** as the catalyst. Without purification, the product mixture was further reduced with triethylsilane in trifluoroacetic acid (TFA). Lactam **48** was isolated in 71% over two steps as a mixture of diastereoisomers (*d.r.* = *exo/endo* = 85/15). Upon base-

Scheme 14. Enantiomerically Pure Bicyclo[4.2.0]octanes by [2 + 2] Photocycloaddition and Enantioselective Reduction of an Imide



induced ring opening, the diastereomeric mixture became finally separable and product **49** was isolated as a single diastereoisomer in 76% yield. It was shown that the method is applicable to other *N*-substituted imides.

3. DIRECT EXCITATION AND SENSITIZATION

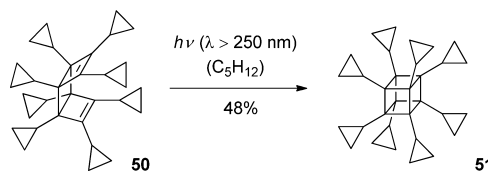
Most examples covered in this section follow mechanistically a pathway, in which the S₁ (Scheme 1) or T₁ (Scheme 3) state of the photoexcited alkene is attacked inter- or intramolecularly by a nonexcited alkene. The vast majority of these reactions has been performed with α,β -unsaturated carbonyl compounds and occurs on the triplet hypersurface. However, the discussion starts with nonconjugated and heteroatom-substituted alkenes as substrates followed by arene-conjugated alkenes. Chalcones are covered in the enone subsection (subsection 3.3.1.4).

3.1. Nonconjugated and Heteroatom-Substituted Alkenes

Strained nonconjugated alkenes have low-lying excited singlet and triplet states of $\pi\pi^*$ character, which can be accessed with conventional light sources ($\lambda \geq 250$ nm) or via sensitization. In this respect, cycloalkenes with a ring size of three to five are good substrates even more so because their cyclic skeleton avoids a *cis/trans* isomerization around the double bond, which is otherwise an efficient way of energy dissipation (*vide infra*). Heteroatom-substitution by oxygen, chlorine, nitrogen, etc. does not change the chromophore significantly, and alkenes of this type are also treated in this subsection unless the heteroatom substitution leads to extensive π -conjugation (*cf.* section 3.2).

De Meijere et al. successfully prepared octacyclopropylcubane (**51**) from diene **50** by an intramolecular [2 + 2] photocycloaddition (Scheme 15).¹¹⁹ The reaction was

Scheme 15. Synthesis of Octacyclopropylcubane (51) by Direct Excitation of Diene 50



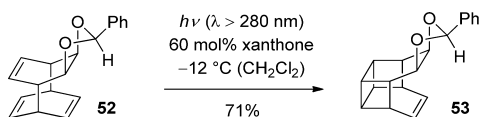
performed at $\lambda > 250$ nm without an additional sensitizer. Apparently, direct excitation is feasible at this wavelength and initiates the desired photocycloaddition.¹²⁰

Gleiter and Brand employed the intramolecular [2 + 2] photocycloaddition for the synthesis of octamethylcubane and related products by direct irradiation.^{121,122} In their work on the synthesis of pagodans and isopagodans, the Prinzbach group applied similar conditions to bridged dienes resulting in intramolecular [2 + 2] photocycloaddition reactions.¹²³ Further applications of photocycloaddition by direct excitation can be found in the field of belt compounds¹²⁴ and in cyclophane chemistry.¹²⁵

Sensitization of the photocycloaddition substrate is applicable if the triplet energy of the olefin is lower than the triplet energy of the sensitizer. The high triplet energy of acetone ($E_T = 332$ kJ mol⁻¹)¹²⁶ and its favorable properties as a solvent make it the most commonly used triplet sensitizer. Recent examples for this procedure can be found in the synthesis of basketenes en route to diademenes by de Meijere, Schreiner, and co-workers¹²⁷ or in the intramolecular [2 + 2] photocycloaddition of two cyclopentenes performed by Singh et al.¹²⁸

Xanthone ($E_T = 310 \text{ kJ mol}^{-1}$)¹²⁹ was applied by Gleiter, Yang, and colleagues as sensitizer to prepare the cage acetal **53** by intramolecular [2 + 2] photocycloaddition of substrate **52** (Scheme 16).¹³⁰ Sensitized intermolecular photocycloaddition

Scheme 16. Synthesis of Cage Acetal 53 by Xanthone-Sensitized Intramolecular [2 + 2] Photocycloaddition of Substrate 52

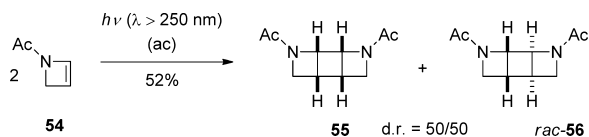


chemistry was successfully performed by Klimova et al. to obtain the *cis*-anti-*cis* photodimers of 3-ferrocenyl-substituted cyclopropenes.¹³¹

Sensitization can lead to *cis*/*trans* isomerization in cycloalkenes with a ring size of six atoms or more. Inoue and co-workers showed that cyclohexene undergoes isomerization to its (*E*)-isomer upon sensitization and adds to either an (*E*)- or (*Z*)-configured cyclohexene to form [2 + 2] cycloaddition products. Significant enantioselectivities were achieved for the *trans*-anti-*trans* products (up to 68% *ee*) in this process but the yields remained low (<1%).¹³²

[2 + 2] Photocycloaddition of heteroatom-substituted alkenes are mostly performed as an intramolecular reaction, often to form cage compounds, or as [2 + 2] photodimerization. A remarkable dimerization was observed when *N*-acetyl azetine (**54**) was irradiated in acetone solution (Scheme 17).¹³³

Scheme 17. Synthesis of Diazacyclooctanes 55 and *rac*-56 by Sensitized [2 + 2] Photocyclodimerization of *N*-acetyl Azetine (54)



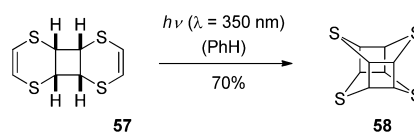
Exclusive formation of HH products was observed, the complete separation of which was impossible. The relative configuration of the diastereoisomers was elucidated to be *cis*-*syn*-*cis* (**55**) and *cis*-anti-*cis* (*rac*-**56**).

The related sensitized [2 + 2] photodimerization of *N,N*-diacetylimidazolinone, which had been originally reported by Steffan and Schenck in 1967,¹³⁴ was more recently used by Fischer et al. as a key step in the synthesis of 1,2,3,4-cyclobutanetetranitramine derivatives.¹³⁵

In work related to birdcaged hydrocarbons, Chou et al. performed the sensitized (acetone as solvent) intramolecular [2 + 2] photocycloaddition reaction of a cyclic 1,2-dichloroalkene to another cyclohexene in high yields.¹³⁶ Tetrathiatetraasterane (**58**) represents another aesthetically appealing compound, which was prepared by [2 + 2] photocycloaddition.¹³⁷ Precursor **57**, which was available by [2 + 2] photodimerization,¹³⁸ has a long wavelength absorption due to conjugation of the sulfur with the olefinic double bond. Irradiation was therefore performed at $\lambda = 350 \text{ nm}$ to deliver the desired product in good yield (Scheme 18).

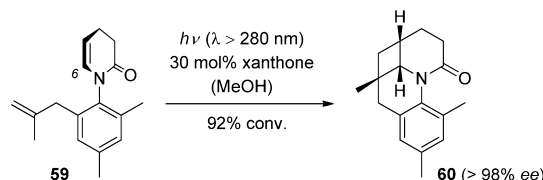
In the context of their continuing work on the photochemical chirality transfer from axially chiral compounds,¹³⁹ the Sivaguru group was concerned with the sensitized intramolecular [2 + 2]

Scheme 18. Synthesis of Tetrathiatetraasterane (58) by Intramolecular [2 + 2] Photocycloaddition of Dithiin 57



photocycloaddition of dihydropyridones such as **59** (Scheme 19).¹⁴⁰ Compounds of this type cannot rotate freely around the

Scheme 19. Diastereoselective Intramolecular [2 + 2] Photocycloaddition of Axially Chiral Substrate 59



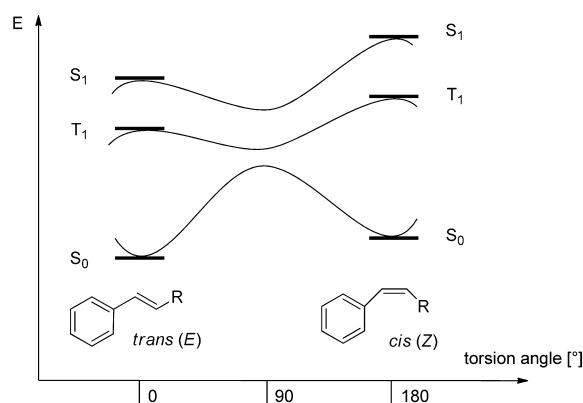
$N-C_{ar}$ bond due to steric hindrance. They exist in two separable atropisomeric forms, one of which was isolated and exposed to sensitized irradiation. After an irradiation time of 150 min, 92% conversion was achieved with a single product **60** being formed. Exclusive *re* face attack at carbon C6 was observed due to the axial chirality of the compound. The relative configuration reflects the higher stability of the *cis*-fused cyclobutane ring being annulated to two six-membered rings. Although yields were not reported, the mass balance (from ¹H NMR spectroscopy) was said to be 86% for this specific example.

3.2. Arene-Conjugated Alkenes

The conjugation of an aryl group with an alkene leads to a significant bathochromic shift. Both the S_1 state and the T_1 state are lowered in their energy (relative to S_0). For styrene, the energy of the S_1 state is tabulated as 415 kJ mol^{-1} and the T_1 state energy as 258 kJ mol^{-1} . For (*E*)-stilbene, there is a further bathochromic shift resulting in excited state energies of 358 kJ mol^{-1} (S_1) and 206 kJ mol^{-1} (T_1).¹⁴¹ It is evident from these figures that arene-conjugated alkenes can be excited to either state under appropriately chosen conditions (direct excitation or sensitization). A major side reaction, which competes efficiently with [2 + 2] photocycloaddition, is the *cis*/*trans* isomerization around the double bond. Since both T_1 and S_1 have $\pi\pi^*$ character, free rotation around the former $C=C$ double bond becomes feasible and the conformation minimum for both states is at a torsion angle of 90° (Scheme 20). Upon return to the S_0 hypersurface, the *cis* or *trans* isomer is formed irrespective from the configuration of the substrate. While *cis*/*trans* isomerization is beneficially used as a mode of action in cosmetic sunscreens¹⁴² or as a means to convert *trans* compounds selectively to their less stable *cis* isomers,¹⁴³ it significantly limits the number of potential synthetic applications for substituted aryl-conjugated alkenes. High reaction rates are required to compete against the rapidly occurring *cis*/*trans* isomerization. The latter limitation does not apply to cyclic alkenes which are found to undergo even intermolecular [2 + 2] photocycloaddition reactions readily.

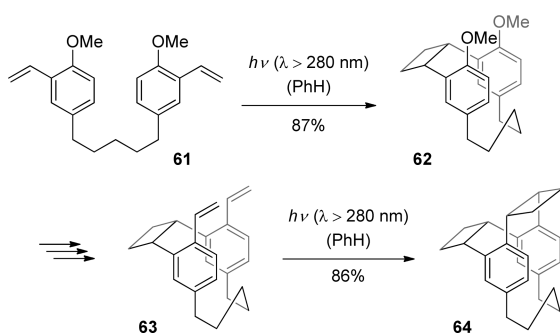
3.2.1. Styrenes and 1-Arylalkenes. If performed intramolecularly, many styrene [2 + 2] photocycloaddition reactions are initiated by direct excitation and are likely to occur from the S_1 state. The Nishimura group has over the years intensively

Scheme 20. Schematic Description of Photochemical *cis*/*trans* Isomerization via the S_1 or T_1 State



used this reaction type for the synthesis of cyclophanes.^{144–157} An example for this approach is shown in [Scheme 21](#).

Scheme 21. Synthesis of Cyclophane **64 by a Sequence of two Intramolecular Styrene [2 + 2] Photocycloaddition Reactions**

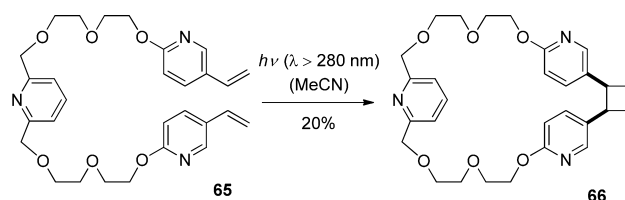


The reaction sequence commenced with the intramolecular [2 + 2] photocycloaddition of diolefin **61**, which gave the desired cyclobutane **62** in high yield.¹⁴⁴ The *ortho*-methoxy groups were responsible for the diastereocontrol and were subsequently transformed into electrophilic leaving groups (OTf). A second set of vinyl groups were introduced by Stille cross-coupling, and the resulting diolefin **63** underwent another intramolecular [2 + 2] photocycloaddition. In this instance, the cyclobutane rings of product **64** were not retained but were rather opened by Birch reduction to enable an access to triply bridged cyclophanes.

In another application, the Nishimura group employed the intramolecular [2 + 2] photocycloaddition for the synthesis of crown ethers, which contain apart from the ether groups three pyridine units in the macrocyclic ring. The di(vinylpyridine) **65** was subjected to Pyrex-filtered irradiation which resulted in formation of the desired product **66** ([Scheme 22](#)).¹⁵⁸ This compound and a related pyridinocrownophane showed a particularly high affinity to silver ions. Various other crown ethers were assembled by the Nishimura group employing related methods.^{159–165}

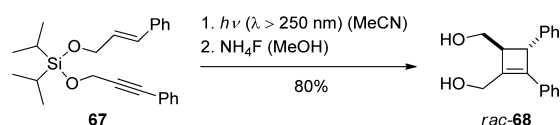
Shorter tethers connecting the reactive styrenes guarantee normally a higher yield and also an improved regio- and stereoselectivity. Fleming and co-workers used silyl-tethered 1-arylalkenes for the synthesis of diarylcyclobutanes by intramolecular [2 + 2] photocycloaddition.^{166,167} For dicinnamyloxysilanes, a high diastereoselectivity in favor of

Scheme 22. Synthesis of Pyridinocrownophane **66 by Intramolecular Vinylpyridine [2 + 2] Photocycloaddition**



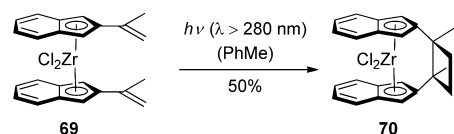
the *cis*-*anti*-*cis* products was found. The proximity of the reactive centers facilitated even reactions between a styrene and an adjacent alkyne as depicted for the reaction **67** → *rac*-**68** ([Scheme 23](#)).¹⁶⁸ Similarly, a highly strained cyclobutene was formed in the reaction of a styrene unit and an ethynylbenzene fragment within the framework of a pseudogeminal paracyclophane.¹⁶⁹

Scheme 23. Synthesis of Cyclobutene *rac*-68** by Intramolecular [2 + 2] Photocycloaddition of Silyl-Tethered Enyne **67** and Subsequent Removal of the Tether**



Remarkably, the cyclopentadienyl ring in bis-(cyclopentadienyl)metal complexes can serve like the phenyl ring as a suitable substituent to mediate intramolecular [2 + 2] photocycloaddition reactions. The Erker group employed this concept for the synthesis of novel *ansa*-metallocenes.^{170–172} The bis(2-alkenylindenyl)zirconium complex **69** for example gave upon direct excitation the cyclobutylene-bridged zirconocene **70** in a yield of 50% ([Scheme 24](#)).¹⁷⁰ A related behavior

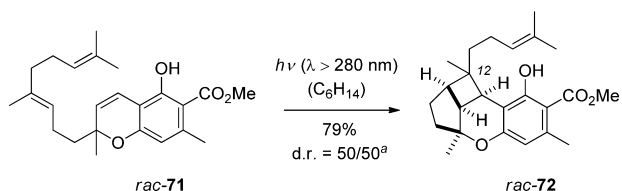
Scheme 24. Synthesis of Cyclobutylene-Bridged Zirconocene **70 by Intramolecular [2 + 2] Photocycloaddition**



was observed for alkenyl-substituted lithium cyclopentadienides.¹⁷³ Even a ladderane structure could be generated by employing a bis(butadienylcyclopentadienyl)zirconium complex.¹⁷⁴ Iwama et al. showed that intramolecular [2 + 2] photocycloaddition reactions are possible between two double bonds in bridged bis(azulenyl) zirconocenes.¹⁷⁵

Rhododaurichromanic acids A and B are two naturally occurring cyclobutanes, which were first described in 2001. It was shown that the compounds are likely derived from the respective daurichromenic acids, which can undergo an intramolecular [2 + 2] photocycloaddition.¹⁷⁶ With this biosynthetic consideration in mind, Hsung and co-workers synthesized the respective methyl ester *rac*-**71** of daurichromenic acid. Irradiation of this compound with a medium-pressure mercury lamp (Pyrex filter) gave the esters *rac*-**72** of (±)-rhododaurichromanic acids A and B as a 50/50 mixture of epimers at carbon atom C12 ([Scheme 25](#)).¹⁷⁷ The facial diastereoselectivity is high and governed by cyclic stereocontrol, which is exerted by the stereogenic center in the chromene

Scheme 25. Synthesis of the Methyl Esters *rac*-72 of (±)-Rhododaurichromanic Acids A and B by Intramolecular [2 + 2] Photocycloaddition Reaction^a

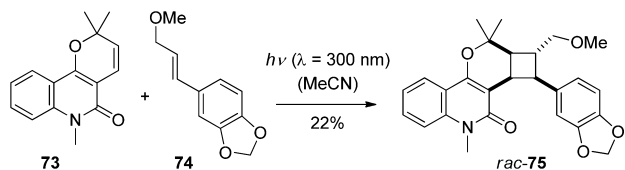


^aThe diastereomeric ratio refers to the stereogenic center at carbon atom C12. The methyl group can be either up (β) or down (α) relative to the cyclobutane. The former diastereoisomer is the methyl ester of (±)-rhododaurichromanic acid A, the latter of acid B.

skeleton. The authors stated that the epimerization occurs via *cis/trans* isomerization of the double bond prior to the [2 + 2] photocycloaddition. Saponification of esters *rac*-72 delivered (±)-rhododaurichromanic acids A and B in racemic form.

In 2012, Quinn and co-workers reported the synthesis of (±)-melicodenine C (*rac*-75) by an intermolecular [2 + 2] photocycloaddition. *N*-Methylflindersine (73) and an excess of cinnamyl ether 74 were irradiated for 72 h at $\lambda = 300$ nm (Scheme 26).¹⁷⁸ Excellent chemo- and regioselectivity was

Scheme 26. Synthesis of (±)-Melicodenine C (*rac*-75) by an Intermolecular [2 + 2] Photocycloaddition

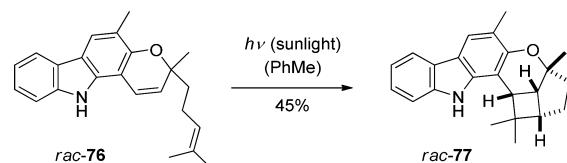


observed, although the mass balance of the reaction suggests that side reactions occur. By the same approach, the synthesis of (±)-melicodenes¹⁷⁹ D and E was accomplished. In a later report, it was disclosed that another naturally occurring pyranoquinoline, euodenine A, was an agonist of Toll-like receptor 4 (TLR), which bears relevance toward the treatment of the acute phase of asthma.¹⁸⁰ The intermolecular [2 + 2] photocycloaddition approach was taken as a general entry to this compound class.¹¹⁴

A third example for the recent use of 1-aryllalkene photocycloaddition reactions in natural product synthesis stems from the Knölker group. Studies in the field of pyrano[3,2-*a*]carbazoles led to the discovery that the conversion of (±)-mahanimbine (*rac*-76) into (±)-bicyclomahanimbine (*rac*-77) could be accomplished simply by sunlight irradiation (Scheme 27).¹⁸¹ The elegant photochemical approach to this natural product class was later also expanded to the synthesis of (±)-bicyclomahanimbicine and (±)-murrayamine-M.¹⁸²

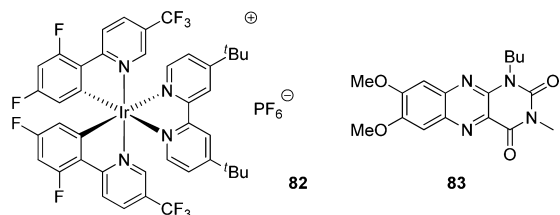
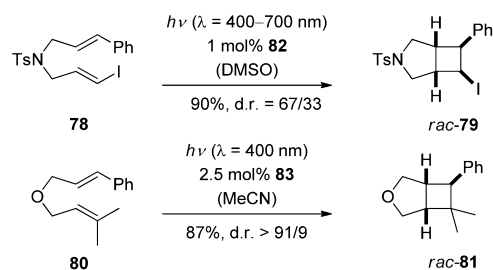
Despite the fact that the photocycloadditions discussed so far in this subsection were performed by direct excitation, it should be noted that sensitization is an efficient way to bring about intramolecular styrene [2 + 2] photocycloaddition at long wavelengths. For example, intramolecular reactions of cinnamylamines related to the reaction 31 → 32 (Scheme 10) can be efficiently performed employing acetophenone or acetone as sensitizers.^{183,184} Indeed, the triplet energy of styrenes is low enough so that sensitizers can be employed which absorb

Scheme 27. Conversion of (±)-Mahanimbine (*rac*-76) into (±)-Bicyclomahanimbine (*rac*-77) by Sunlight Irradiation



visible light. Lu and Yoon have recently described a versatile protocol to access bicyclo[3.2.0]heptanes and bicyclo[4.2.0]octanes by intramolecular [2 + 2] photocycloaddition of appropriately tethered 1-aryllalkenes.¹⁸⁵ Iridium catalyst 82 was found to be best suited to catalyze the reaction (Scheme 28). The synthesis of iodostituted 3-azabicyclo[3.2.0]-

Scheme 28. Visible Light Photocatalysis in the Intramolecular [2 + 2] Photocycloaddition of 1-Aryllalkenes



heptane *rac*-79 (Ts = *para*-toluenesulfonyl) from diallylamine 78 shows the compatibility of these conditions with photosensitive groups, which is not given upon direct excitation. Recently, Cibulka and co-workers showed that flavin derivatives such as 83 are also suitable catalysts for these reactions as exemplified by the conversion 80 → *rac*-81.¹⁸⁶

3.2.2. Stilbenes and 1,2-Diaryllalkenes. The intermolecular [2 + 2] photocycloaddition of this compound class suffers intrinsically from *cis/trans* isomerization as a competing reaction pathway. Still, [2 + 2] photodimerization reactions have been extensively explored in solution due to a continuous interest in generating tetrasubstituted cyclobutanes. Their potential activity as inhibitors of dipeptidyl peptidase III spurred interest in the synthesis of amidino-benzimidazoles such as compound 84 (Figure 5).¹⁸⁷ [2 + 2] Photodimerization was accomplished in water by Pyrex-filtered irradiation of the respective monomer (80% yield).

6-Styryl-substituted 2-pyranones were converted into the respective dimers by Copp and co-workers when searching for new compounds with antimalarial and antituberculosis activity.¹⁸⁸ In this case, as in the photodimerization of katsumadain to katsumadain C (85) performed by Zhang et al.,¹⁸⁹ the reactions were performed in the solid state, however. Investigations related to compounds with potential cytokinin activity led Andresen et al. to study the photodimerization of an (*E*)-6-styryl-purin-2-one. Product 86 was obtained in 48% yield

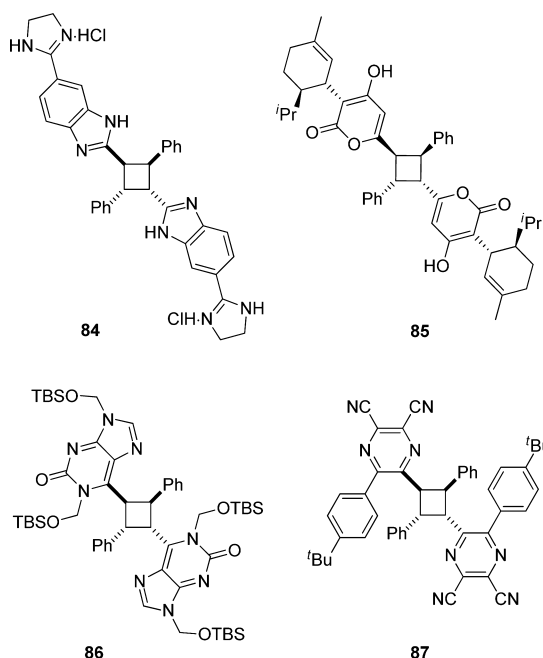


Figure 5. Tetrasubstituted cyclobutanes **84**, katsumadain C (**85**), **86**, and **87** obtained by [2 + 2] photodimerization.

by exposing the monomer as an oil to daylight irradiation.¹⁹⁰ Dimerization of styryl-substituted 2,3-dicyanopyrazines led to products like **87**, which are of interest in the context of new fluorescent materials.¹⁹¹ In all cases shown in **Figure 5**, the photodimerization occurred vertically (i.e., with a preference for the HT dimer in the trans-syn-trans configuration).

Preference for *syn* HT dimerization was found by both the Kim¹⁹² and the Ramamurthy group¹⁹³ as well as by Gromov et al.¹⁹⁴ in related reactions of charged 1,2-diaryllkenes when performed in cucurbit[8]uril under aqueous conditions. The templating effect of crown ethers on the [2 + 2] photodimerization was investigated in detail by the Gromov group^{195–197} and by Saltiel and co-workers.¹⁹⁸ Hydrogen bonding was shown by the group of Bassani to have an influence on the regioselectivity of stilbene-type photodimerization reaction.¹⁹⁹ A tremendous increase in regioselectivity was recorded for this reaction in favor of HH product **90d** when 5,5-dihexylbarbituric acid (**88**) was added. To account for this observation, an association of two molecules of olefin **89** was assumed as shown in **Figure 6**.

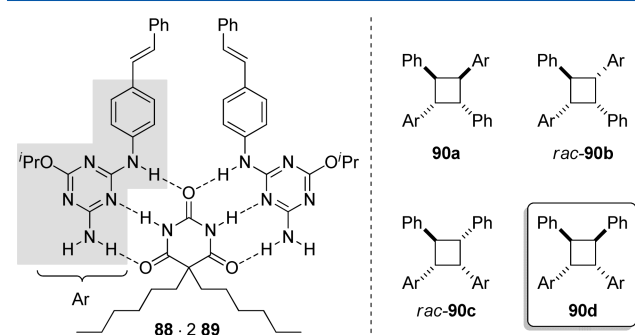
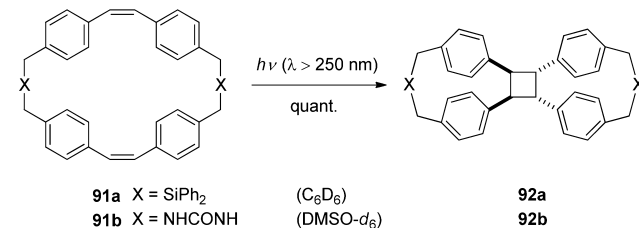


Figure 6. Association of two molecules of stilbene **89** to 5,5-dihexylbarbituric acid (**88**) leading to the preferred formation of photodimer **90d**.

Like for styrenes, intramolecular [2 + 2] photocycloaddition reactions of stilbene-type substrates are known. The group of Falk prepared a distyryl-substituted hypericin derivative, which underwent the reaction under sensitized conditions in acetone as the solvent.²⁰⁰ Transannular reactions of stilbene derivatives were investigated by the groups of Mizuno^{201,202} and Shimizu.²⁰³ In the former study, it was found that the silyl-tethered substrate **91a** underwent quantitative cyclobutane formation upon direct excitation in deuterated benzene (**Scheme 29**).²⁰¹ The same product **92a** was also obtained

Scheme 29. Intramolecular [2 + 2] Photocycloaddition of Tethered Stilbenes **91** upon Direct Excitation

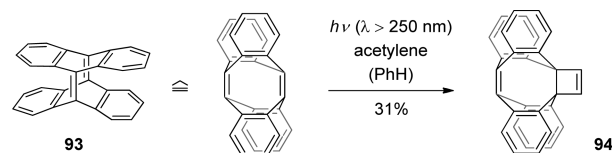


when a sensitizer was employed at longer wavelength irradiation ($\lambda > 360$ nm). In a similar fashion, the urea-tethered stilbene **91b** was found to give exclusively product **92b** upon direct excitation.²⁰³ In all cases, the formation of the respective trans-syn-trans product was explained by a photochemical *cis/trans* isomerization preceding the [2 + 2] photocycloaddition.

Dyker and co-workers observed a transannular [2 + 2] photocycloaddition as the main reaction pathway upon direct excitation of 1,3-substituted styrylcalix[4]arenes.²⁰⁴ In recent work, the Hahn group showed that it is possible to modify dicarbene-derived metallacycles postsynthetically by photocycloaddition chemistry. Silver(I) and gold(I) *N*-heterocyclic carbene (NHC) complexes, in which two stilbene units linked the imidazole-based ligands, underwent a formally intramolecular [2 + 2] photocycloaddition at $\lambda = 365$ nm to form the respective cyclobutane-bridged dinuclear tetrakis(NHC) complexes.²⁰⁵

Several cyclic stilbene derivatives are known, which undergo also [2 + 2] photocycloaddition reactions. One of the most unusual compounds of this type is 9,9',10,10'-tetrahydrodianthracene (**93**),²⁰⁶ in which the olefinic double bonds are located almost perpendicular to the anthracene plane (**Scheme 30**). Herges and co-workers studied several intermolecular

Scheme 30. Intermolecular [2 + 2] Photocycloaddition of 9,9',10,10'-Tetrahydrodianthracene (**93**) and Acetylene

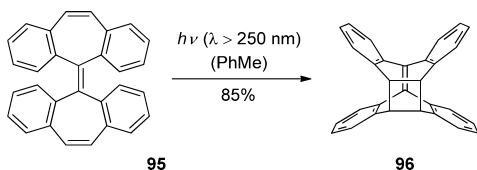


[2 + 2] photocycloaddition reactions of this compound. The compound has its longest wavelength absorption band at $\lambda = 282$ nm, and it reacts upon direct excitation not only with alkenes^{207,208} but even with acetylene to form the strained cyclobutene **94**.²⁰⁹ A remarkable feature of the cyclobutanes derived from **93** and cyclic olefins is the fact that they undergo ring fission to form formal olefin metathesis products. If

ladderane-type olefins are used, the cyclobutane ring fission can occur in a multiple fashion generating an extended π -system. This behavior was elegantly employed by Herges and co-workers to prepare a stable Möbius aromatic hydrocarbon.^{210,211}

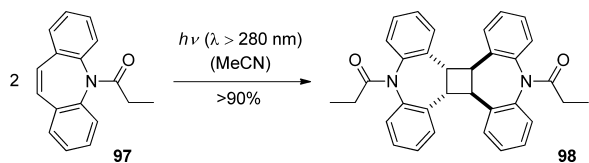
Another intriguing hydrocarbon is tetrabenzoheptafulvalene **95**, which had been claimed some years ago to undergo [2 + 2] photodimerization by forming two cyclobutane rings across the two double bonds within the seven-membered ring.^{212,213} On the basis of the observation that the reactions of carbon-linked benzosuberenones occurred intramolecularly but not intermolecularly, Dyker and co-workers reinvestigated this transformation and found the product to be indeed the intramolecular photocycloaddition product **96** but not the dimer (Scheme 31).²¹⁴

Scheme 31. Intramolecular [2 + 2] Photocycloaddition of Tetrabenzoheptafulvalene **95**



In the context of a mechanistic study on the sensitized [2 + 2] photodimerization of *N*-substituted dibenz[b,f]azepines, the group of Wolff discovered that the photodimerization can also be induced by direct excitation. Product **98** for example was formed as a single diastereoisomer in a yield of >90% from substrate **97** (Scheme 32).²¹⁵

Scheme 32. [2 + 2] Photodimerization of *N*-Propionyl Dibenz[b,f]azepine **97** upon Direct Excitation

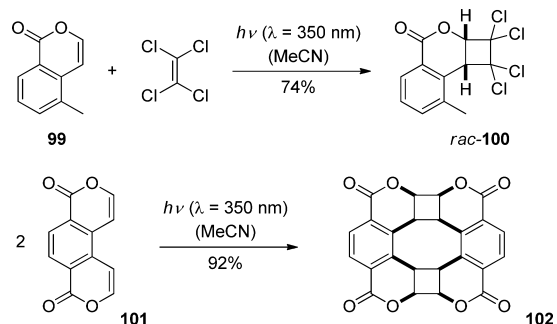


3.2.3. Isoquinolones and Isocoumarins. The intermolecular [2 + 2] photocycloaddition to isoquinolone was first reported in 1971,²¹⁶ while related reactions of isocoumarin (and isothiocoumarin) were reported more recently by the Margaretha group (Scheme 33).^{217–219} A remarkable feature of both compound classes is their propensity to react with electron-deficient olefins rather than with electron-rich olefins.^{220–222}

For the isocoumarins, this behavior was explained by a triplet exciplex, in which charge is preferably transferred from the excited styrene-type chromophore to the olefin. A smooth reaction occurred between isocoumarin **99** and tetrachloroethylene to give product **100** upon direct excitation.²¹⁹ Remarkably, 4*H*,7*H*-benzo[1,2-*c*:4,3-*c'*]dipyran-4,7-dione (**101**), which can be considered as a 2-fold isocoumarin, underwent a smooth 2-fold [2 + 2] photodimerization to product **102**.^{223,224} The authors pointed out, however, that this reaction should rather be envisaged as an initial 1,6-cycloaddition followed by a second (thermal) ring closure.

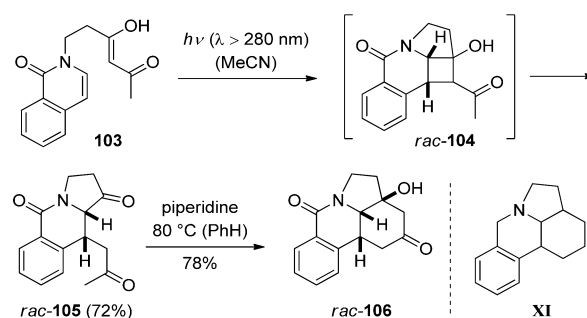
In work by Minter et al., the intramolecular [2 + 2] photocycloaddition of an isoquinolone was combined with a

Scheme 33. Intermolecular [2 + 2] Photocycloaddition of Isocoumarin **99** and [2 + 2] Photodimerization of 4*H*,7*H*-Benzo[1,2-*c*:4,3-*c'*]dipyran-4,7-dione (**101**)



retro-aldol cleavage in the spirit of the classic de Mayo reaction.^{225–227} Irradiation of substrate **103** gave via the [2 + 2] photocycloaddition product *rac*-**104** directly the ring-opened product *rac*-**105** in good yield (Scheme 34).^{228,229} Diketone

Scheme 34. De Mayo Reaction of Isoquinolone **103** to Diketone *rac*-**105** and its Transformation to Tetracyclic Product *rac*-**106** with a Galanthan Skeleton (XI)



rac-**105** underwent intramolecular aldol reaction to product *rac*-**106** with the tetracyclic galanthan skeleton XI, which in turn represents the core structure of lycorine-type Amaryllidaceae alkaloids.

Recent interest in the [2 + 2] photocycloaddition reaction of isoquinolones was stimulated by the discovery that lactam **107** and its enantiomer *ent*-**107**²³⁰ (Figure 7) serve as efficient chiral

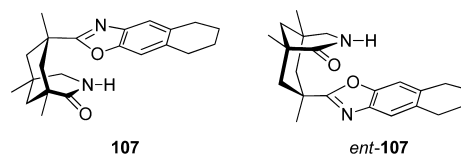


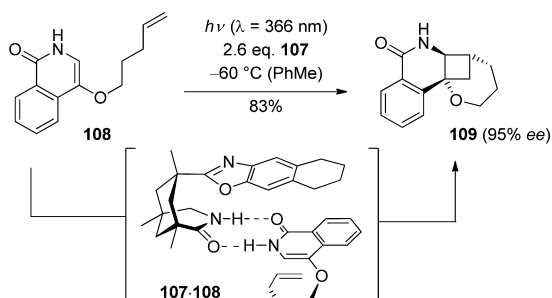
Figure 7. Structures of chiral template **107** and of its enantiomer *ent*-**107**.

templates for enantioselective photochemical reactions.^{231–238} It was shown in our laboratories that binding of these compounds to other lactams occurs with high binding constants at low temperature in a nonpolar solvent.²³⁹ This binding allows for efficient enantioface differentiation at prochiral substrates.

Initial work regarding an enantioselective intramolecular [2 + 2] photocycloaddition was performed with 4-substituted isoquinolones.²⁴⁰ It could be shown that reactions of this type occur with high enantioselectivity in the presence of chiral

template **107**. The reactions were run in toluene as the solvent at $-60\text{ }^{\circ}\text{C}$ and at an irradiation wavelength of $\lambda = 366\text{ nm}$. 4-(Pent-4-enyloxy)isoquinolone (**108**) for example underwent a clean reaction to cyclobutane annulated dihydroisoquinolone **109** upon direct irradiation (Scheme 35). The enantioselectiv-

Scheme 35. Enantioselective Intramolecular [2 + 2] Photocycloaddition of Isoquinolone 108

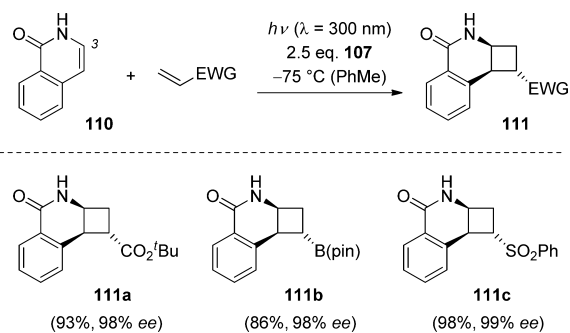


ity of the reaction was high, which is due to efficient shielding of one of the two enantiotopic isoquinolone faces by the bulky 5,6,7,8-tetrahydronaphtho[2,3-*d*]oxazole substituent of the template in a putative complex **107·108**. The template is transparent at longer wavelength ($\lambda > 280\text{ nm}$) and does not interfere with the photochemical process. It can be recovered in high yield without any loss of its enantiomeric purity.

The enantioface differentiation of template **107** is sufficiently strong to enable a kinetic resolution. It was found for a 4-alkenylisoquinolone with a stereogenic center in the alkenyl chain that one enantiomer is processed in the photochemical reaction while the other enantiomer reacts slowly or decomposes. In recent work, the intramolecular [2 + 2] photocycloaddition of isoquinolones was employed in a putative route to the skeleton of plicamine-type alkaloids.²⁴¹

In an extensive study, the intermolecular [2 + 2] photocycloaddition of isoquinolones with various alkenes was investigated.^{242,243} The reaction was shown to proceed well with a plethora of electron-deficient olefins, many of which had not been previously employed in [2 + 2] photocycloaddition reactions. The enantioselectivity achieved in the reactions was very high and frequently exceeded 90% *ee*. Scheme 36 depicts the reaction of isoquinolone (**110**) with a few selected olefins. The reaction is likely to proceed via the triplet state (see Scheme 3) which is populated by ISC from the singlet state. The preference for the shown product isomer **111** was explained by the nucleophilic nature of this state, which

Scheme 36. Enantioselective Intermolecular [2 + 2] Photocycloaddition of Isoquinolone (110) with Electron-Deficient Olefins

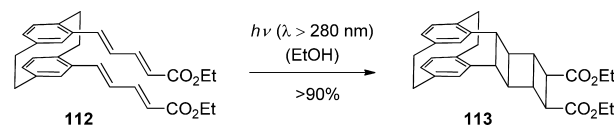


behaves like an α -amino radical at carbon atom C3. It was therefore postulated to add to the β -position of the olefin generating a 1,4-diradical. After ISC, the electron withdrawing group (EWG) adapts the less hindered trans position relative to the isoquinolone ring. The enantioselectivity is determined by the chiral template as depicted in Scheme 35. Several other isoquinolones were shown to undergo the reaction, and consecutive reactions of the resulting cyclobutanes were studied.²⁴³

3.2.4. Cinnamates and β -Arylacrylic Acid Derivatives.

The efficiency and robustness, with which cinnamates undergo *cis/trans* isomerization in the liquid phase, is emphasized by their continuous use as UV-B absorbers in cosmetic sunscreens.¹⁴² Only if rendered intramolecular and only if the reacting centers are spatially close is a [2 + 2] photocycloaddition with cinnamates and other β -arylacrylic acid derivatives possible. Against this background, research efforts have been devoted toward tethering either the aryl parts of cinnamates or their carboxylic acid parts by appropriate covalent or noncovalent binding. The rigidity of cyclophane provides the required proximity of the reacting center. Hopf, Desvergne, and colleagues used acrylates of cyclophanes for intramolecular [2 + 2] photocycloaddition reactions,^{244–249} which, as the transformation **112** \rightarrow **113**, frequently proceeded in high yield and with good stereocontrol (Scheme 37). In an analogous fashion, multibridged cyclophanes were prepared by the Nishimura group via the respective cinnamates.²⁵⁰

Scheme 37. Synthesis of Ladderane 113 by Intramolecular [2 + 2] Photocycloaddition of Cyclophane 112



Bassani and co-workers favorably employed hydrogen bonds for templating β -aryl acrylates with 5,5-dihexylbarbituric acid (**88**) (see Figure 6). The triazinyl group in substrate **114** (Figure 8) was used to enable template binding. An increase in

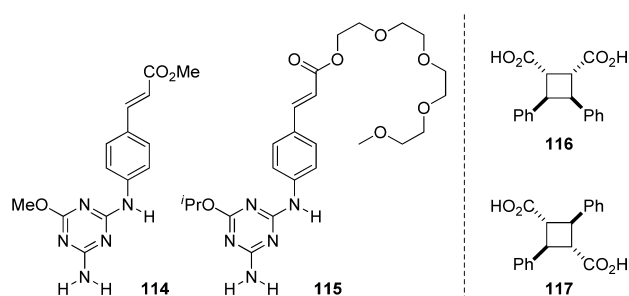
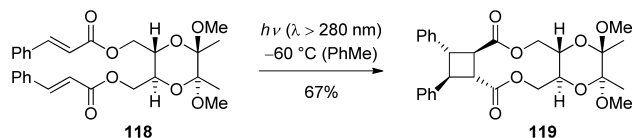


Figure 8. Structures of β -aryl acrylates **114 and **115** and of β -truxinic acid (**116**) and ϵ -truxillic acid (**117**).**

photodimerization quantum yields was recorded with the HH dimer of β -truxinic acid (**116**) configuration being the major product.^{251,252} In acrylate **115**, the crown ether-like ester enables a second templation mode. It was found that Ba^{2+} cations favor in combination with template **88** a [2 + 2] photodimerization to the HT product with the relative configuration of ϵ -truxillic acid (**117**).²⁵³

Templating at the carboxy terminus of cinnamic acid has been extensively studied in the last two decades. Scharf and co-workers showed that tartrate-derived diesters are suited to induce a high facial diastereoselectivity in the intramolecular [2 + 2] photocycloaddition of cinnamates. Employing diester **118**, they obtained the respective HH cyclobutane **119** as a single diastereoisomer (Scheme 38). The relative configuration

Scheme 38. Diastereoselective Synthesis of δ -Truxinate **119 by Intramolecular [2 + 2] Photocycloaddition of Chiral Dicinnamate **118****



was found to be the configuration of δ -truxinic acid, which the authors explained by invoking a triplet 1,4-diradical as an intermediate.²⁵⁴ Tethering the esters by more rigid linkers was found by König et al. to lead to β -truxinates (cf. Figure 8) as single products.²⁵⁵ A xylopyranoside was studied by Yuasa et al. as a covalent template to mediate the intramolecular [2 + 2] photocycloaddition of dicinnamates.²⁵⁶

Hopf and co-workers showed that cyclophanes can also be exploited as templating devices in a reverse fashion as compared to Scheme 37 (i.e., the cinnamoyl residues can be linked to the cyclophane by a heteroatom bond). 4,15-Diamino[2.2]paracyclophane turned out to be a suitable covalently bound template to induce formation of β -truxinic acid type dimers (cf. Figure 8) via the respective amide **120**.²⁵⁷ In more recent work, Ghosn and Wolf found the same regio- and stereoselectivity in cinnamic amide dimerization mediated by 1,8-bis(4'-anilino)naphthalene (shown as dicinnamoyl compound **121**) as the covalent linker (Figure 9).²⁵⁸

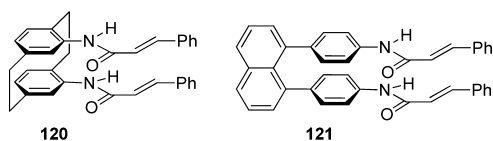
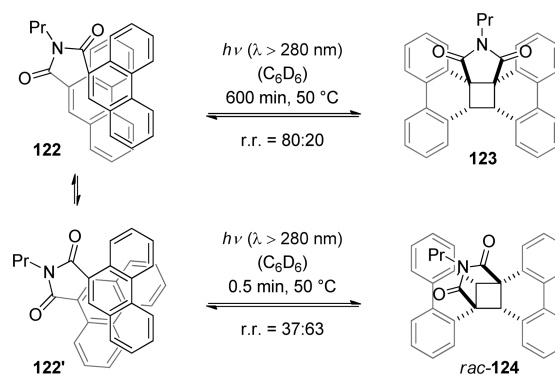


Figure 9. Structures of diamides **120** and **121**, in which a covalent linker induces stereoselective [2 + 2] photodimerization of cinnamic to β -truxinic acid derivatives.

Tethered approaches were also used to bring about the [2 + 2] photodimerization of more complex β -arylacrylic acids. Along these lines, Noh et al.²⁵⁹ and Kohmoto et al.²⁶⁰ studied the [2 + 2] photodimerization of phenanthrene-9-carboxylic acid derivatives. In the latter study, two acids were linked by a propylamino group via the respective imide **122**. The regioselectivity (r.r. = regioisomeric ratio = **123**/*rac*-**124**) of the intramolecular reactions was shown to be time-dependent, and it was proven that retro cycloaddition reactions intervene (Scheme 39). Conformation **122** of the substrate accounts for formation of the linear product **123**; conformation **122'** was said to lead to product *rac*-**124**. A preparative run was performed in acetone as the solvent at -78 °C, resulting in yields of 24% for **123** and 66% of *rac*-**124**.

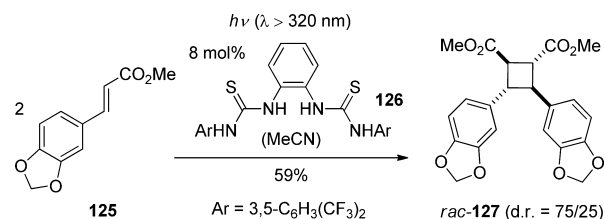
The ability of bis(thioureas) to template the [2 + 2] photodimerization of cinnamates was probed by the Beeler group in a flow chemistry setup.²⁶¹ They found an improved

Scheme 39. Intramolecular [2 + 2] Photocycloaddition of Imide **122 to Products **123** and *rac*-**124****



diastereoselectivity in favor of the δ -truxinate (e.g., **125** \rightarrow *rac*-**127**) versus the β -truxinate upon catalytic (8 mol%) addition of template **126** (Scheme 40). NMR studies suggested binding of

Scheme 40. Bis(thiourea)-Mediated Diastereoselective [2 + 2] Photodimerization of Cinnamate **125**

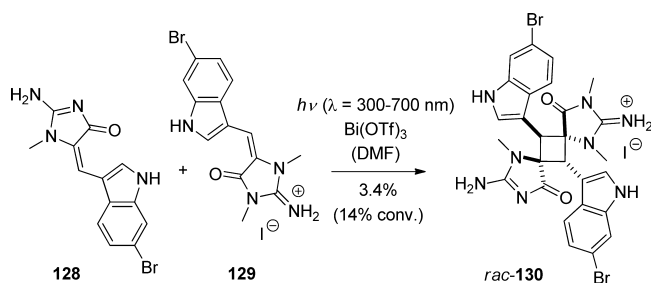


the cinnamate to the bis(thiourea) and supported the suggested templating effect. The photodimerization of cinnamic acid and derivatives in confined media (e.g. in cucurbit[8]uril) were studied by the Ramamurthy group.^{262,263}

Like for stilbene dimers (see Figure 5), synthetic interest in cyclobutanes, which derive from dimerization of β -aryl acrylates, has been spurred by their biological activity. Wang and colleagues reported on the [2 + 2] photodimerization of α -amido- β -arylacrylic acids to the respective cyclobutanes, which turned out to be potent glucagon-like peptide-1 (GLP-1) receptor agonists.²⁶⁴ D'Auria and co-workers continued their work on the synthesis of novel cyclobutanes with antibacterial and antimicrobial activity.²⁶⁵ In addition, the group performed many fundamental studies on the sensitized [2 + 2] photodimerization of various β -aryl acrylates.²⁶⁶ [2 + 2] Photodimerization of urocanic acid esters under sensitized conditions was found to lead mainly to dimers of the δ -truxinate type.²⁶⁷

Dictazole A and B are two recently discovered indole alkaloids with a cyclobutane core.²⁶⁸ Poupon and co-workers could show that a synthesis of (\pm)-dictazole B (*rac*-**130**) is feasible by an intermolecular [2 + 2] photocycloaddition of the closely related monomers **128** and **129** (Scheme 41).^{269,270} Apart from the desired photocycloaddition, [2 + 2] photodimerization of substrate **129** was observed. HT products were the only isolable cyclobutanes, indicating that the charged imino groups play a crucial role in the orientation of the two entities. Likewise, the simple diastereoselectivity could be attributed to a dipole minimization in the photocycloaddition event. In several related [2 + 2] photocycloaddition reactions, CuOTf was employed as a catalyst (see section 2).

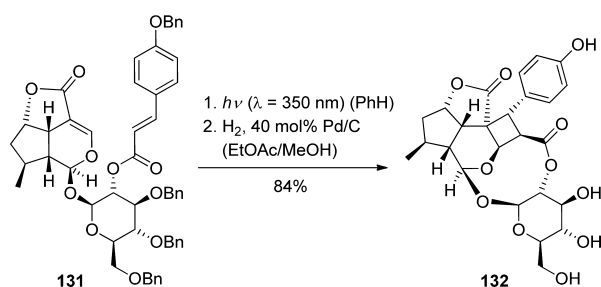
Scheme 41. Synthesis of (\pm)-Dictazole B (*rac*-130) by Intermolecular [2 + 2] Photocycloaddition



Poupon and co-workers showed further that cyclobutanes like *rac*-130 are precursors for other natural products and natural product-like compounds. A cyclobutane ring opening could be induced by heating which was followed by a Mannich-type ring closure to the six-membered ring core of (\pm)-tubastrindole B.²⁷⁰

The synthesis of (–)-littoralisone (132) by Mangion and MacMillan rests in its final steps on a potentially biomimetic intramolecular cinnamate [2 + 2] photocycloaddition (Scheme 42).²⁷¹

Scheme 42. Synthesis of (–)-Littoralisone (132) by Intramolecular [2 + 2] Photocycloaddition



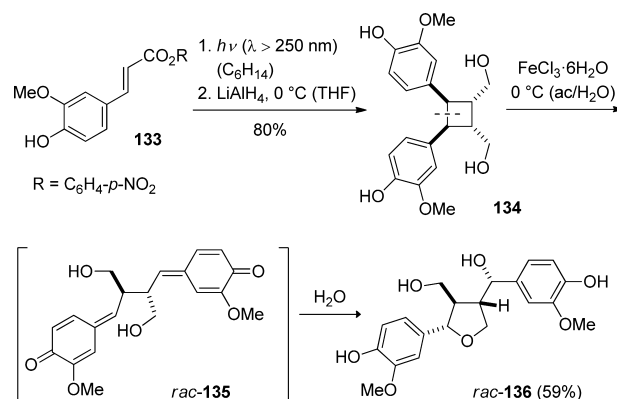
The precursor 131 is an *O*-cinnamoyl derivative of the natural product (–)-brassoside, and it is conceivable that the biosynthetic key step is, like in the total synthesis, mediated by light. Indeed, the desired photochemical reaction occurred in vitro at a remarkably long wavelength ($\lambda = 350\text{ nm}$), and it was observed that the reaction progressed slowly upon exposure of 131 to ambient light.¹¹⁴

Another recent bioinspired natural product synthesis by the Lumb group was based on a cinnamate photodimer as substrate. In this instance, solid-state irradiation of cinnamate 133 led via a β -truxinate intermediate to diol 134, which was subjected to oxidative conditions (Scheme 43).²⁷² When treated with iron(III)chloride, an oxidative cyclobutane fission occurred, which yielded via diquinone intermediate *rac*-135 the lignane natural product (\pm)-tanegool (*rac*-136).

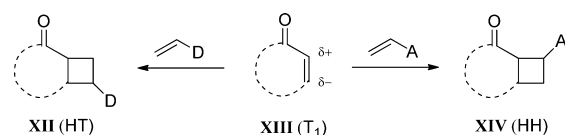
3.3. Enones

The photochemistry of α,β -unsaturated ketones (enones) is governed by rapid ISC from the first excited singlet state to the T_1 state, which is $\pi\pi^*$ in character. Most reactions of enones occur consequently on the triplet hypersurface (Scheme 3), and the nature of T_1 (XIII, Scheme 44) is responsible for the reactivity pattern.^{42–44} Although somewhat simplistic, the chemistry of the triplet state is determined by the fact that the π^* orbital is occupied by an electron, rendering the β -position nucleophilic and the α -position electrophilic.^{273,274}

Scheme 43. Synthesis of the Lignane Natural Product (\pm)-Tanegool (*rac*-136)



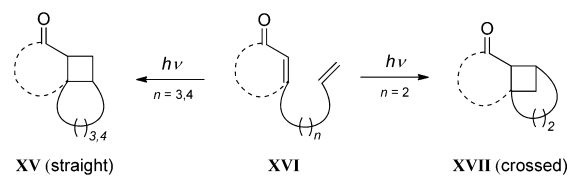
Scheme 44. Regioselectivity Preferences in the Intermolecular [2 + 2] Photocycloaddition of Enones



Excitation thus induces a polarity reversal (*Umpolung*) relative to the ground state. As a result, intermolecular [2 + 2] photocycloaddition reactions with donor-substituted olefins ($D = \text{donor}$) occur to the HT product XII, with acceptor-substituted olefins ($A = \text{acceptor}$) to the HH product XIV. The stability of the intermediate 1,4-diradicals (VII, Scheme 3) should also be considered. Indeed, enone [2 + 2] photocycloaddition reactions proceed via triplet 1,4-diradicals,²⁷⁵ which can not only form cyclobutane products but also cleave to the starting materials. It was established by Weedon and Andrew that the ratio, in which the 1,4-diradicals partition between products and ground state precursors, also influences the regioselectivity.²⁷⁶ The lifetime of the enone triplet state can vary from ca. 10 ns to several μs ,²⁷⁷ and an excess of olefin is normally employed to guarantee efficient quenching of the excited state.

The regioselectivity of intramolecular [2 + 2] photocycloaddition reactions depends less strongly on electronic parameters. Rather, the conformationally induced ring closure mode to a five-membered ring is the dominating factor (rule of five).^{278–280} Two regioisomers are conceivable as illustrated for a β -alkenyl substituted enone XVI in Scheme 45. If the tether length between the reacting olefins is only two atoms ($n = 2$), ring formation does not occur between the β -carbon and the internal olefin carbon atom because a strained four-membered ring would result. Instead, a crossed addition mode is preferred leading to product XVII. If the tether link is $n = 3$

Scheme 45. Regioselectivity Preferences in the Intramolecular [2 + 2] Photocycloaddition of Enones

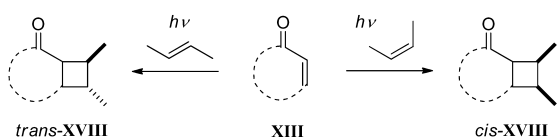


and in most cases also for $n = 4$, the former type of ring closure prevails, leading to a five-membered ring for $n = 3$ and a six-membered ring for $n = 4$ in the straight product **XV**. Exceptions are known, in particular if the tether is not attached to the α - or β -position of the enone. The 1,4-diradical intermediates have been invoked to influence the regioselectivity by "biradical conformation control".²⁸¹

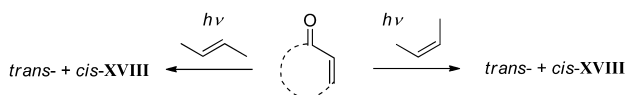
The intermediacy of a triplet 1,4-diradical en route to the cyclobutane product is consequential for the relative configuration of the former olefin carbon atoms. Free rotation around the single bond in the diradical intermediate renders the reaction nonstereospecific and often stereoconvergent. In **Scheme 46**, the reaction of a generic enone **XIII** with 2-butene

Scheme 46. Stereospecificity of [2 + 2] Photocycloaddition Reactions

• stereospecific:



• non-stereospecific:



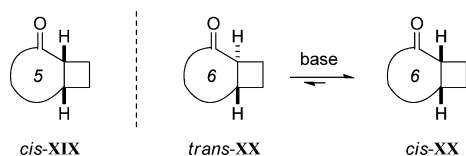
d.r. = *trans*-XVIII/*cis*-XVIII **XIII** d.r.' = *trans*-XVIII/*cis*-XVIII

• stereoconvergent: d.r. = *trans*-XVIII/*cis*-XVIII = d.r.'

is depicted to illustrate the different stereochemical possibilities. If *trans*-2-butene led exclusively to *trans*-product **trans**-XVIII and *cis*-2-butene exclusively to *cis*-product **cis**-XVIII, the reaction would be stereospecific. In [2 + 2] photocycloaddition chemistry, this outcome would strongly suggest a reaction via a singlet intermediate. A triplet reaction pathway leads typically to mixtures of products **trans**-XVIII and **cis**-XVIII in a nonstereospecific pathway. Still, the ratio of diastereoisomers d.r. and d.r.' (determined from the reaction of *trans*-2-butene and *cis*-2-butene) does not have to be identical as it depends on the 1,4-diradical lifetime and the rotational barriers within the 1,4-diradical. If the ratio is identical, the reaction is said to be stereoconvergent. The stereospecificity of a [2 + 2] photocycloaddition can serve as a mechanistic probe to elucidate the nature of the excited state (singlet vs triplet).

Finally, the fact that the former double bond is essentially nonexistent in the T_1 state (**Scheme 20**) leads to a significant twist around this bond even in cyclic enones. In enones with a ring size larger than five, the twisted nature of the T_1 state²⁸² can cause the formation of a *trans*-diastereoisomer **trans**-XX (**Scheme 47**, shown as product of ethylene addition) in the

Scheme 47. Product Diastereoisomers Formed from [2 + 2] Photocycloaddition Reactions of Cyclic Enones and Their Epimerization



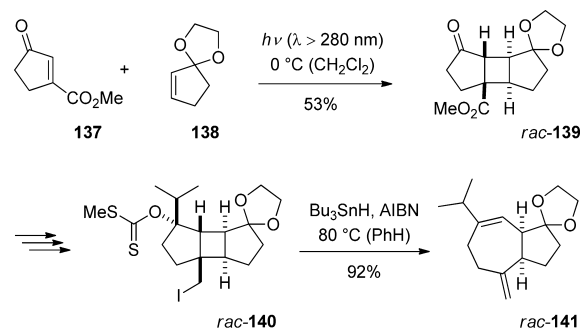
[2 + 2] photocycloaddition reaction. Epimerization of the *trans*- to the *cis*-product **cis**-XX can be induced by treatment with base. For five-membered enones, the relative configuration of the enone double bond is normally retained and *cis*-product **cis**-XIX is formed with a defined relative configuration.

3.3.1. Without Further Conjugation to Heteroatoms.

In this section, the reactions of the two most important classes of 2-cycloalkenones (2-cyclopentenones, 2-cyclohexenones) are treated. The discussion includes also [2 + 2] photocycloaddition products of quinones and benzoquinones, which are structurally closely related to the 2-cyclohexenone products. In addition, chalcones (subsection 3.3.1.4) and other enones (subsection 3.3.1.5) will be treated in this section.

3.3.1.1. 2-Cyclopentenones. There is continued interest in the photocycloaddition of the parent compound 2-cyclopentenone with olefins for the synthesis of cyclobutanes, which in turn serve as starting materials for further transformations.^{283–285} Intermolecular [2 + 2] photocycloaddition reactions of 2-cyclopentenones to cyclic olefins lead to *cis*-anti-*cis* cycloaddition products.²⁸⁶ Lange and co-workers used ester **137** in reactions with olefins.^{287–293} With ketal **138**, the HH product *rac*-**139** was the main product which exhibited the expected relative configuration at the cyclobutane ring [**Scheme 48**, AIBN = 2,2'-azobis(2-methylpropionitrile)]. Key idea of

Scheme 48. Intermolecular [2 + 2] Photocycloaddition of β -Functionalized 2-Cyclopentenone **137** and Consecutive Transformations

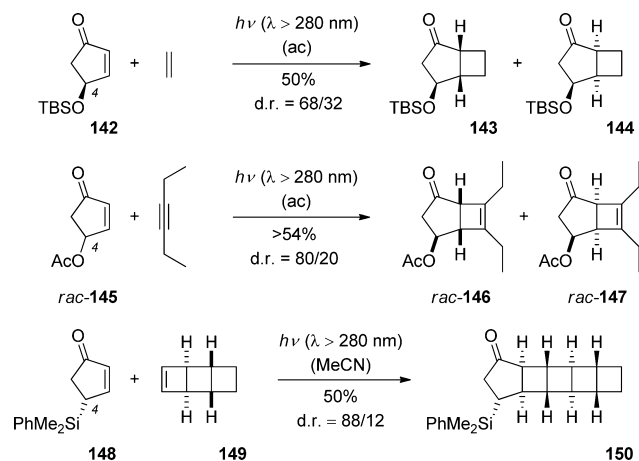


this work was to convert the ester group into a suitable leaving group to induce four-membered ring fragmentation. Along these lines, the iodide *rac*-**140** was prepared from *rac*-**139** and was successfully converted to bicyclic compound *rac*-**141**, which served as a precursor for the guaiane sesquiterpenoid (\pm)-alisol.^{287,291} In a similar fashion, the homologous 2-cyclohexenone derivative was employed by the Lange group for photocycloaddition/fragmentation sequences.²⁹⁴

The facial diastereoselectivity in intermolecular [2 + 2] photocycloaddition reactions of 2-cyclopentenones with a stereogenic center in the 4-position has in recent years been studied among others by the groups of Aitken,^{295,296} Carreira,²⁹⁷ and Corey.^{298,299} Aitken and co-workers investigated the reaction of 4-hydroxy-2-cyclopentenone derivatives, which are readily available in enantiomerically pure form. A moderate diastereoselectivity was recorded as shown exemplarily for the transformation **142** \rightarrow **143/144** (**Scheme 49**). Intramolecular [2 + 2] photocycloaddition reactions (vide infra)^{295,296} were found to proceed with higher diastereoselectivity.

In the synthesis of the polyketide natural product (\pm)-hippochachnin A, the initial step was the intermolecular [2 + 2]

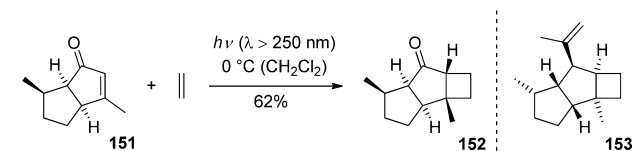
Scheme 49. Facial Diastereoselectivity in the Intermolecular [2 + 2] Photocycloaddition of Chiral 4-Substituted 2-Cyclopentenones



photocycloaddition of acetate *rac*-145 with 3-hexyne, which established the relative *cis* configuration of the target bicyclo[3.2.0]heptane skeleton. Since the photochemical reaction was followed by immediate acetic acid elimination, the facial diastereoselectivity in favor of *rac*-146 over *rac*-147 remained inconsequential.²⁹⁷ The 4-silyl-substituted 2-cyclopentenone 148 induced the highest diastereoselectivity in this series yielding in the photocycloaddition to cyclobutene 149 the ladderane-type product 150, which served as an enantiomerically pure precursor in the total synthesis of (+)-pentacycloanammoxic acid.^{298,299}

Bicyclic enones are attacked by an external alkene expectedly from their convex face. The construction of the tricyclic kelseene skeleton by the groups of Mehta,^{300–302} Schulz,³⁰³ and Piers³⁰⁴ relied on this strategy. Schulz and co-workers employed enone 151 for an enantioselective synthesis of this compound (Scheme 50). The absolute configuration of

Scheme 50. Intermolecular [2 + 2] Photocycloaddition of Bicyclic Enone 151 and Structure of (+)-Kelseene

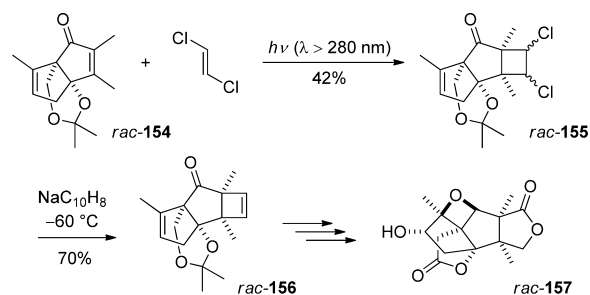


(+)-kelseene was independently established by the groups of Schulz and Mehta as 153. The formation of *rac*-152 by photochemical ethylene addition was a key step in the Piers synthesis.

The Mehta group employed 1,2-dichloroethene in many intermolecular [2 + 2] photocycloaddition reactions as an acetylene surrogate.^{305–309} In the total synthesis of (±)-merrilactone (*rac*-157), the addition to enone *rac*-154 was moderately diastereoselective and the d.r. was 67/33 in favor of diastereoisomer *rac*-155 (Scheme 51).^{310,311} Subjecting this product to reductive conditions (sodium naphthalenide) at low temperature led to clean 1,2-elimination to *rac*-156 without reduction of the carbonyl group.

Allene is another frequently used olefin component, which shows not only high HH selectivity but offers further options for functionalization. Examples can be found in the synthesis of

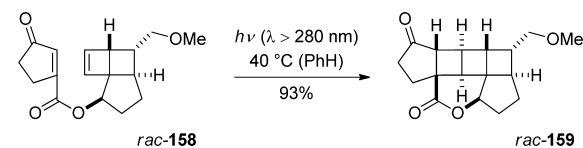
Scheme 51. Intermolecular [2 + 2] Photocycloaddition of Tricyclic Enone *rac*-154 En Route to the Synthesis of (±)-Merrilactone A (*rac*-157)



(±)-jiadifenin by Zhai and co-workers³¹² and in a new route for the construction of the AB-ring core of taxol by the Kakiuchi group.³¹³

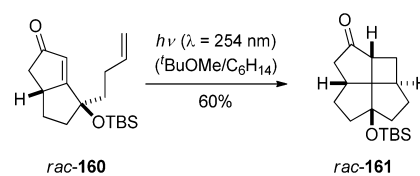
Benefits of an intramolecular [2 + 2] photocycloaddition as opposed to the intermolecular version are a better regiocontrol and often an improved chemo- and diastereoselectivity.^{314–316} In many approaches to new structural manifolds, intramolecular reactions have been employed. Snapper and co-workers presented an approach to an eight-membered ring system,^{317,318} which is based on retro-[2 + 2] cycloaddition of the central cyclobutane ring in ladderane-type product *rac*-159. The photocycloaddition of substrate *rac*-158 proceeded with high selectivity (Scheme 52). While related compounds could also be constructed by intermolecular [2 + 2] photocycloaddition chemistry, the regiocontrol depended on the choice of enone.³¹⁹

Scheme 52. Diastereoselective Intramolecular [2 + 2] Photocycloaddition of 2-Cyclopentenone *rac*-158



The synthesis of various fenestranes was accomplished in the Keese group^{320–322} by employing appropriately substituted bicyclo[3.3.0]octenones as photocycloaddition precursors. The diastereoselectivity [e.g., in the transformation *rac*-160 → *rac*-161 (Scheme 53)] was high as the rigid bicyclic ring system

Scheme 53. Access to [4.5.5]Fenestranes by Intramolecular [2 + 2] Photocycloaddition

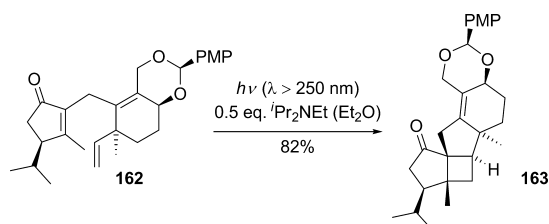


forces the tether to approach the enone from one diastereotopic face. In their synthesis of (–)-incarvilline, Kibayashi and co-workers employed a substrate with a tether at position C4 of a 2-cyclopentenone for a diastereoselective [2 + 2] photocycloaddition.³²³

Sorensen's synthesis of the diterpenes (+)-guanacastepenes A and E rested on an intramolecular [2 + 2] photocycloaddition

(Scheme 54) of chiral enone **162** (PMP = *para*-methoxyphenyl).^{324,325}

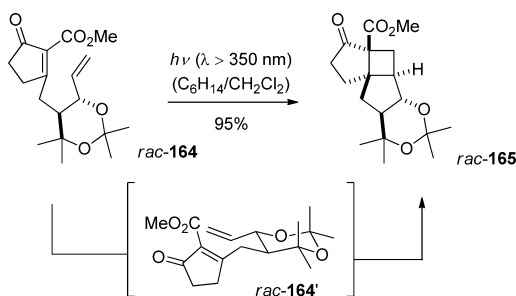
Scheme 54. Intramolecular [2 + 2] Photocycloaddition of Enone **162 En Route to (+)-Guanacastepenes A and E**



Facial diastereoselectivity is cooperatively induced by the stereogenic centers in the 2-cyclopentenone and the cyclohexene ring ensuring the formation of **163** as a single product. The regioselectivity is governed by the rule of five (see Scheme 45) with the straight addition mode being strongly preferred.

Even if the stereogenic centers are not within a ring system as in the previous examples (Schemes 52–54), high facial diastereoselectivity can be achieved in intramolecular [2 + 2] photocycloaddition reactions. Analysis of the preferred conformation of the respective substrate frequently leads to a reliable prediction about the stereochemical outcome. Substrate *rac*-**164**, which was employed by Crimmins et al. in their synthesis of (\pm)-lubiminol,^{326,327} contained two stereogenic centers in the tether, which connects the olefin with the 2-cyclopentenone core (Scheme 55). The preferred chair

Scheme 55. Diastereoselective Intramolecular [2 + 2] Photocycloaddition Due to Stereogenic Centers in the Tether

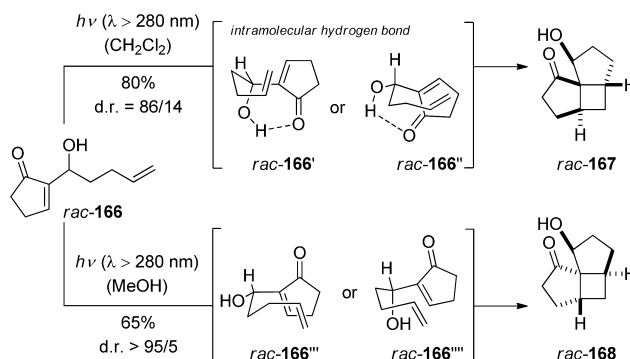


conformation *rac*-**164'** of the acetal enables a half-chair conformation for the five-membered ring to be formed in the [2 + 2] photocycloaddition. Product *rac*-**165** was obtained as single diastereoisomer. Similarly, stereogenic centers in the tether were favorably employed by the Crimmins group in a [2 + 2] photocycloaddition en route to (\pm)-ginkgolide B.^{328–331}

Crimmins and co-workers noted that the hydroxy group within the three-carbon tether of intramolecular enone photocycloaddition reactions adopts an axial position most likely due to hydrogen bonding to the carbonyl group.³³² Along the same lines, Snapper and co-workers observed a strong solvent influence on the diastereoselectivity of intramolecular [2 + 2] photocycloadditions if the tether contained a hydroxy group at a stereogenic center.³³³ The observation was explained by intramolecular hydrogen bonding of the hydroxy group to the carbonyl group, which becomes possible in nonpolar solvents. 2-Cyclopentenone *rac*-**166** for example produced

predominantly photocycloaddition product *rac*-**167** in CH₂Cl₂ as the solvent via hydrogen-bond induced conformations *rac*-**166'** or *rac*-**166''** (Scheme 56). In a polar solvent, such as

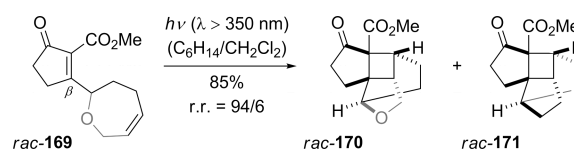
Scheme 56. Solvent Influence on the Intramolecular [2 + 2] Photocycloaddition of 2-Cyclopentenone *rac*-166****



methanol, there is no hydrogen-bond formation and the cyclopentenone moiety rotates in a conformation *rac*-**166'''** or *rac*-**166''''**, in which the opposite diastereotopic face of the enone double bond is exposed to the olefin. Product *rac*-**168** was found to be the major product.

An interesting way to access formal crossed intramolecular [2 + 2] photocycloaddition products was proposed by Crimmins and Hauser.³³⁴ In substrates like *rac*-**169**, the seven-membered ring offers two tethers between the β -carbon atom of the enone and the reacting olefin. A conformational preference for an oxygen atom within the tether (in gray) in a straight approach led with high preference to product *rac*-**170** versus its regioisomer *rac*-**171** (Scheme 57). Clearly, the alkyl

Scheme 57. Intramolecular [2 + 2] Photocycloaddition of Substrate *rac*-169** to the Formal Crossed Product *rac*-**170****

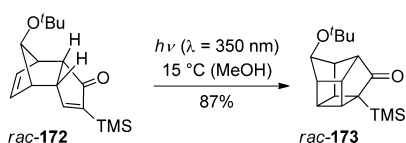


tether is in *rac*-**170** formally crossed and upon cleavage of the oxygen carbon bond in the tetrahydrofuran ring of *rac*-**170** (e.g., with NaI/Ac₂O), crossed products result.

Dating back to Eaton's landmark synthesis of cubane,³³⁵ the intramolecular [2 + 2] photocycloaddition of 2-cyclopentenones remains the method of choice for constructing cage molecules with cubane-like structure. Applications of these compounds in medicinal chemistry have spurred synthetic activities by the groups of Fokin³³⁶ and of Nilius.³³⁷ Likewise, interest in the thermochemical data and in the use of cubanes as chiral ligands led Prier and co-workers to employ [2 + 2] photocycloaddition chemistry.^{338,339} Riera and co-workers explored the consecutive chemistry of norbornadiene-derived Pauson–Khand reaction products.³⁴⁰ They found smooth intramolecular [2 + 2] photocycloaddition reactions occur for some enones [e.g., the reaction *rac*-**172** \rightarrow *rac*-**173** (Scheme 58)].

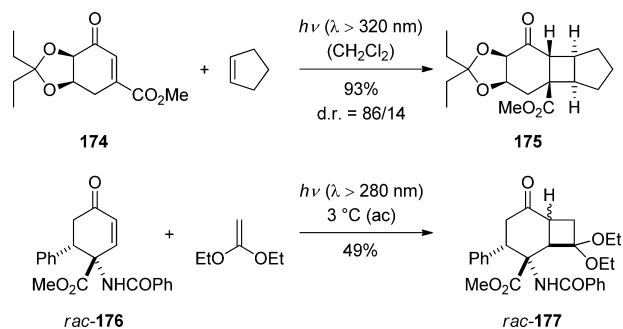
3.3.1.2. 2-Cyclohexenones. The regio- and stereoselectivity of the 2-cyclohexenone [2 + 2] photodimerization can be altered if performed in self-assembling bisurea macrocycles. As reported by the Shimizu group, almost exclusive formation of

Scheme 58. Synthesis of Cage Ketone *rac*-173 by Intramolecular [2 + 2] Photocycloaddition



the HT *cis*-*anti*-*cis* product was observed.³⁴¹ The regioselectivity of intermolecular addition reactions follows the principles explained in Scheme 44, but a ring-size effect was noted.³⁴² [2 + 2] Photocycloaddition reactions of enone acids and esters were studied by Piva and co-workers.^{343,344} Chiral 2-cyclohexenones with a stereogenic center within the six-membered ring exhibit a significant degree of facial diastereoselectivity based on cyclic stereocontrol.³⁴⁵ Lange and co-workers prepared the enone ester **174** and related esters from (–)-quinic acid and studied their intermolecular [2 + 2] photocycloaddition to cyclopentene (Scheme 59).³⁴⁶ The top

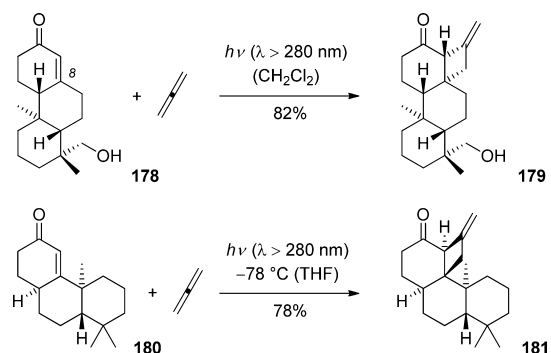
Scheme 59. Facial Diastereoselectivity in the Intermolecular [2 + 2] Photocycloaddition of Chiral 2-Cyclohexenones



face of the enone is shielded by the bulky acetal and attack of the olefin occurs preferentially from the bottom of the enone. Diastereocontrol in favor of product **175** was high (d.r. = 86/14), and the relative configuration at the cyclobutane core was expectedly *cis*-*anti*-*cis*. In a similar fashion, as reported by the Ortuño group,³⁴⁷ the bulky substituents in enone *rac*-176 allowed only for an attack from one diastereotopic face. Products *rac*-177 were shown to result from a HT addition and were obtained as an 81/19 mixture of *cis*/*trans* isomers (cf. Scheme 47). Epimerization to the pure *cis* isomer was performed with NaOMe in MeOH.

In polycyclic 2-cyclohexenones, the conformational flexibility of the skeleton and the 1,4-diradical stability influence the stereochemical outcome of an intermolecular [2 + 2] photocycloaddition. Substrate **178** exemplifies nicely the potential of photochemical reactions for creating C–C bonds at inaccessible positions (Scheme 60). In the synthesis of *ent*-kaurane and beyerane diterpenoids, Baran and co-workers explored numerous methods to generate the quaternary stereogenic center at C8 of enone **178** but only the [2 + 2] photocycloaddition turned out to be successful.³⁴⁸ Related work was performed by Abad et al.^{349,350} Allene addition³⁵¹ proceeded in the expected HH fashion to product **179**. The pyramidalization of the triplet state in a chairlike fashion^{352,353} is likely responsible for the facial diastereocontrol. The Marini-Bettolo group used a related approach in the synthesis of diterpenoid natural products such as (+)-13-stemarene,^{354,355} for which

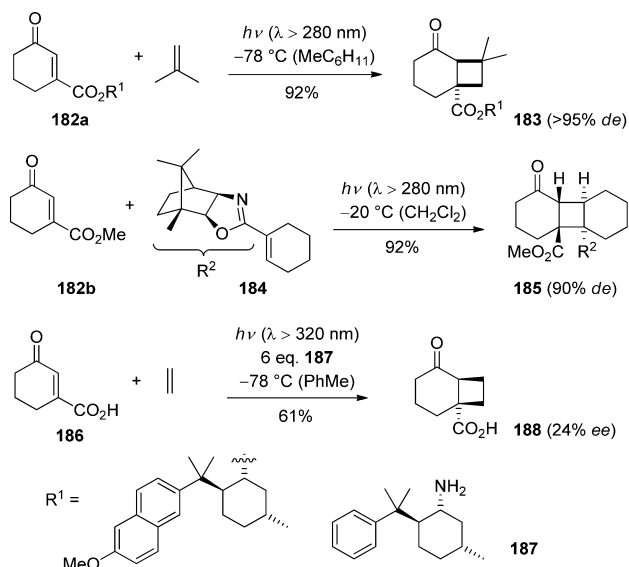
Scheme 60. Intermolecular Allene [2 + 2] Photocycloaddition to Tricyclic Enones **178 and **180****



enone **180** served as the precursor. Intermolecular [2 + 2] photocycloaddition to allene generated selectively product **181**.

Setting up the first stereogenic center in 2-cyclohexenone [2 + 2] photocycloaddition chemistry has so far been a domain of auxiliary- and template-based approaches. Initial studies on enone esters **182** derived from a chiral alcohol R^1OH were performed by the groups of Lange³⁵⁶ and Scharf.³⁵⁷ In recent years, Kakiuchi and co-workers extensively optimized the choice of chiral alcohols for this reaction^{358–360} and screened the best reaction conditions to boost the diastereoselectivity.^{361–369} With ester **182a**, a remarkable *de* was achieved in the reaction with olefins such as isobutene (Scheme 61). The formal HH product **183** was obtained as the sole regioisomer most likely for steric reasons.

Scheme 61. Enantioselective Approaches to [2 + 2] Photocycloaddition Products of 2-Cyclohexenone Employing Chiral Auxiliaries or Templates



An auxiliary can also be attached to the olefin part as proposed by Xia and co-workers.³⁷⁰ They found a remarkable *de* in the reaction of oxazoline **184** with enone ester **182b** ($\text{R}^1 = \text{Me}$). The HT product **185** was shown to have *cis*-*anti*-*cis* configuration. Recently, Kakiuchi and co-workers attempted to modify carboxylic acid **186** with chiral amines such as **187** to induce enantioselectivity via the chiral counterion.³⁷¹ Success

was limited, however, as seen from the enantiomeric excess of product **188** achieved under optimized conditions.

Margaretha and co-workers have greatly expanded the scope of possible substrates for enone photochemistry. Although a major focus of their work was on possible shifts of the spin centers in triplet intermediates (leading to products which are beyond the scope of this review), several enones also delivered conventional [2 + 2] photocycloaddition products. In Figure 10, some of the enones **189**–**196** are summarized which were

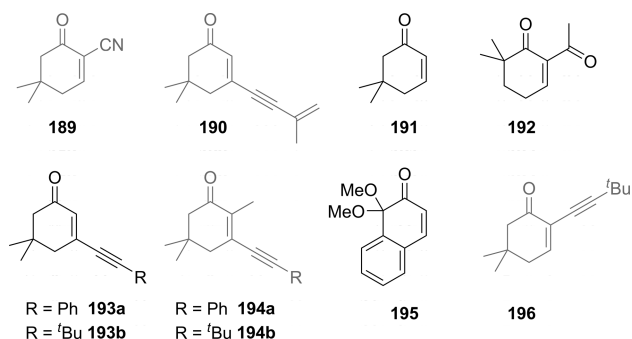


Figure 10. Structures of selected enones, which were studied by Margaretha et al. in [2 + 2] photocycloaddition reactions.

investigated in the last two decades.^{372–384} Compounds which exhibit a chemoselectivity preference in favor of [2 + 2] photocycloaddition products are drawn in black, compounds which followed mainly non-[2 + 2] pathways are shown in gray. Enones with a heteroatom in the ring are discussed in section 3.3.2. Photodimerization and photocycloaddition reactions of 4,4-dialkoxyated- and 4-hydroxylated 2-cyclohexenones were studied by Chen et al.³⁸⁵

Remarkably, several of the conjugated enones studied by the Margaretha group did undergo cyclobutane formation but not at the enone double bond. Instead the triplet character was transferred via the ethyne bridge to the terminal double bond. In Figure 11, the two major products from irradiation of

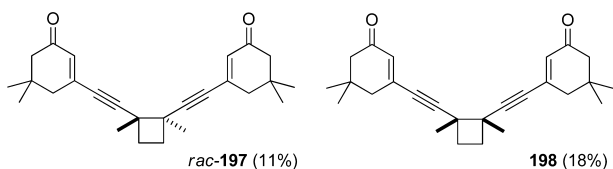


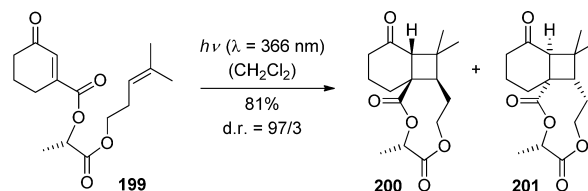
Figure 11. Photodimerization products of enone **190**.

substrate **190** (Figure 10) are depicted. [2 + 2] Photodimerization occurred to HH products with the relative configuration at the cyclobutane being trans (**rac-197**) or cis (**198**).³⁸⁰

A temporary tether between enone and olefin can not only be used to alter or enhance the regioselectivity of a [2 + 2] photocycloaddition, but it can also exert a significant diastereoselectivity if properly chosen. Piva and co-workers have studied the influence of various tethers on the course of intramolecular [2 + 2] photocycloaddition reactions.^{386–388} A lactic acid-based tether induced a high facial diastereoselectivity in the reaction of enone ester **199** (Scheme 62). The major product **200** clearly prevailed over the minor diastereoisomer **201**.

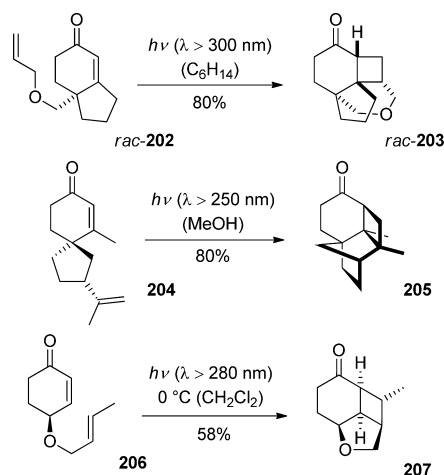
Excellent diastereoselectivities are obtained if the reacting olefin is tethered to a stereogenic center within the 2-

Scheme 62. High Diastereoselectivity in an Intramolecular [2 + 2] Photocycloaddition Reaction Mediated by a Chiral Tether



cyclohexenone core. Mattay and co-workers employed enone **rac-202** in the photocycloaddition to **rac-203**, which served as a precursor for a heterocyclic propellane (Scheme 63).^{389,390} A

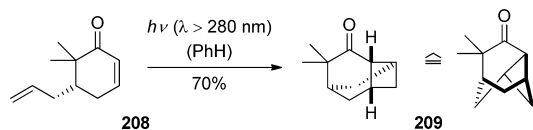
Scheme 63. Diastereoselective Intramolecular [2 + 2] Photocycloaddition of 2-Cyclohexenones



similar intramolecular addition with an amine linker was employed by Navarro and Reisman in the synthesis of an aza-propellane.³⁹¹ For the construction of the tricyclic core of several phytoalexins, Srikrishna et al. successfully used the diastereoselective [2 + 2] photocycloaddition of spiroenones (e.g., **204** → **205**).^{392,393} In their synthesis of (–)-huperzine A, White et al. employed a hydroxy group to link the olefin to the 2-cyclohexenone core of **206** via an ether bond.³⁹⁴ Product **207** was obtained with high regio- and diastereoselectivity. Intramolecular [2 + 2] photocycloaddition reactions of 4-alkenyl-substituted 2,5-cyclohexadienones were studied by Schultz and Lockwood.³⁹⁵ All reactions shown in Scheme 63 gave a single diastereoisomer (d.r. $\geq 95/5$).

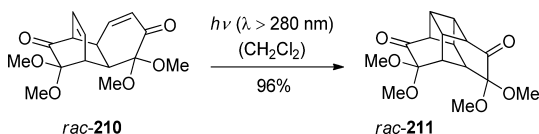
While in the synthesis of precursor **206**, (–)-quinic acid served as a chiral building block, it was (–)- α -pinene, which attracted the interest of Mehta et al. as a potential precursor of enone substrates.³⁹⁶ Compound **208** was readily available in enantiomerically pure form from the natural product and was shown to undergo the intramolecular [2 + 2] photocycloaddition to crossed product **209** (Scheme 64). Steric reasons were invoked to account for the fact that the straight product was not formed. Another example for a formal crossed photocycloaddition was found by Winkler and co-workers when investigating the reaction of an encarbamate intermediate, which was tethered to the 2-cyclohexenone via a phenyl group at the β -position and which was generated by photochemical desulfurization of a benzothiazoline precursor.³⁹⁷

Scheme 64. Unusual Regioselectivity in the Intramolecular [2 + 2] Photocycloaddition of (–)- α -Pinene-Derived 2-Cyclohexenone 208



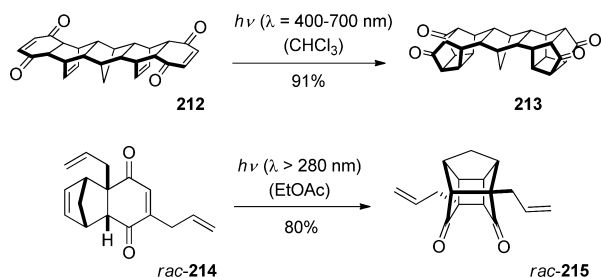
If 2-cyclohexenones are properly aligned to olefins they can also form cage compounds. For example, it was shown by the Quideau group that the Diels–Alder dimers of orthoquinone monoketals readily undergo an intramolecular [2 + 2] photocycloaddition [e.g., *rac*-210 \rightarrow *rac*-211 (Scheme 65)].³⁹⁸ A similar observation was made by Porco and co-workers with another polycyclic 2-cyclohexenone.³⁹⁹

Scheme 65. Synthesis of Cage Diketone *rac*-211 by Intramolecular [2 + 2] Photocycloaddition



3.3.1.3. *para*-Quinones and Related Substrates. While the photochemistry of *para*-benzoquinones depends on the nature of their lowest triplet state (vide infra), the respective dihydrocompounds, 1,4-cyclohex-2-enediones, behave like typical enone substrates. They absorb at long wavelength and react with olefins intra- or intermolecularly. An expedient way to construct cage compounds makes use of an initial Diels–Alder reaction of a *para*-quinone with a cyclopentadiene followed by an intramolecular [2 + 2] photocycloaddition (Scheme 66).^{400–407}

Scheme 66. Synthesis of Cage Diketones by Intramolecular [2 + 2] Photocycloaddition of 1,4-Cyclohex-2-enediones

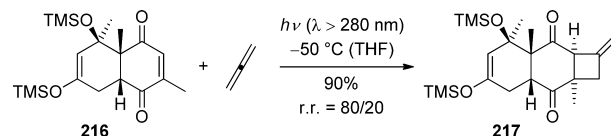


Chou et al. have used this approach for the construction of rack- and U-shaped polycyclic compounds as seen for example by the reaction 212 \rightarrow 213 (Scheme 66).^{408,409} The group of Kotha prepared new cage compounds by the same approach (e.g., *rac*-214 \rightarrow *rac*-215) utilizing pendant alkenes for subsequent ring-closing metathesis reactions.^{410–412}

If the diene employed in the Diels–Alder reaction with *para*-quinones is less rigid than cyclopentadiene, the resulting products can undergo intermolecular instead of intramolecular [2 + 2] photocycloaddition reactions. Following earlier work on the total synthesis of (\pm)-alloyathin B₃,^{413,414} Ward and co-workers employed enedione 216, which was available by an enantioselective Diels–Alder reaction, to perform an intermolecular [2 + 2] photocycloaddition en route to (–)-cyathin

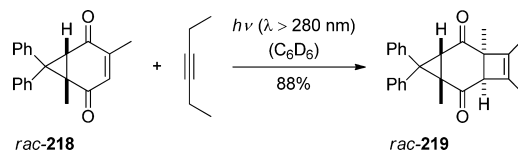
A₃ (Scheme 67). The approach of allene from the convex face of the molecule led predominantly to the desired diastereoisomer 217.⁴¹⁵

Scheme 67. Intermolecular [2 + 2] Photocycloaddition of Diels–Alder Product 216 with Allene



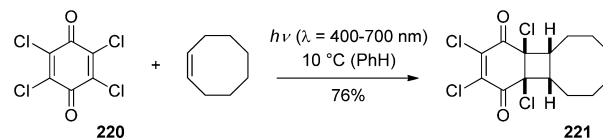
Of course, any other reaction that involves selectively one of the two *para*-quinone double bonds leads to products which are useful for intermolecular [2 + 2] photocycloaddition chemistry. The cyclopropanation product of 2,5-dimethylbenzoquinone *rac*-218 was studied intensively by Oshima and co-workers.^{416–418} The reaction with alkynes, such as 3-hexyne, occurred trans to the cyclopropane resulting in products like *rac*-219 (Scheme 68).

Scheme 68. Intermolecular [2 + 2] Photocycloaddition of 3-Hexyne to Homobenzoquinone *rac*-218



Parent *para*-benzoquinone ($n\pi^*$ triplet ca. 76 kJ mol^{–1} below $\pi\pi^*$ triplet) is known to undergo mainly spirooxetane formation. Electron-donating substituents at the quinone lead to an increased preference for [2 + 2] photocycloaddition by destabilizing the $n\pi^*$ triplet.^{419,420} Chloranil (220) and olefins with a low oxidation potential were shown to undergo oxetane formation by a SET mechanism.⁴²¹ The reaction of chloranil (220) with several olefins can be successfully conducted as a monoaddition reaction if the irradiation wavelength is properly chosen. Christl and co-workers^{422,423} isolated the intermolecular [2 + 2] photocycloaddition product 221 of cyclooctene when visible light was employed for excitation (Scheme 69). Irradiation at a shorter wavelength led to multiple addition and other side reactions.

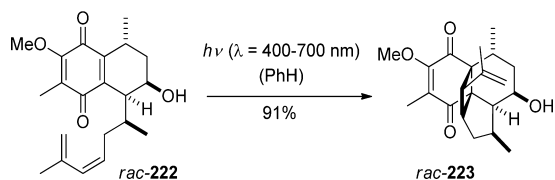
Scheme 69. Intermolecular [2 + 2] Photocycloaddition of Chloranil (220) to Cyclooctene



At times, visible-light-induced photoreactions of *para*-quinones can be undesired. For example, it was noted by Nicolaou and co-workers that compound *rac*-222, an intermediate in the total synthesis of (\pm)-colombiasin A, underwent an intramolecular [2 + 2] photocycloaddition to product *rac*-223 if simply exposed to daylight (Scheme 70).⁴²⁴

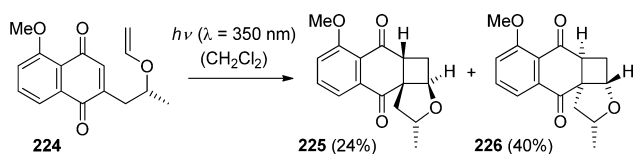
The natural product (–)-elecanacin (225) invited a photochemical approach for the construction of its cyclobutane core. Wege and co-workers prepared naphthoquinone 224 in

Scheme 70. Undesired Intramolecular [2 + 2] Photocycloaddition of *para*-Quinone *rac*-222, an Intermediate in the Synthesis of (±)-Colombiasin A



enantiopure form and submitted it to irradiation at $\lambda = 350$ nm (Scheme 71).⁴²⁵ Indeed, the natural product was produced but its isomer **226** turned out to be the major product.

Scheme 71. Intramolecular [2 + 2] Photocycloaddition of Naphthoquinone **224 to (–)-Elecanacin (**225**) and its Diastereoisomer **226****



3.3.1.4. Chalcones and Related Substrates. Due to fast *cis/trans* isomerization in the excited state, intermolecular [2 + 2] photocycloaddition reactions of chalcones in solution are rare. [2 + 2] Photodimerization reactions are more common. An improved chemoselectivity can be achieved in the molten state.⁴²⁶ In general and in agreement with what has been said above (Scheme 44), the [2 + 2] photodimerization occurs in a HH fashion with one chalcone acting as a nonexcited olefin reaction partner. If there are no constraints, the major product exhibits *trans-anti-trans* configuration. In Figure 12, the

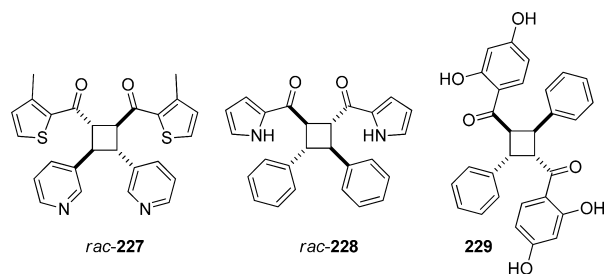


Figure 12. Structures of chalcone dimers *rac*-227, *rac*-228, and **229**.

medicinally relevant product dimers *rac*-227⁴²⁷ and *rac*-228⁴²⁸ of heterocyclic chalcones are depicted. Chalcone dimer **229** is a natural product (oxyfadichalcone A), which was found by Zhang et al. together with the two regioisomeric cyclobutanes oxyfadichalcone B and C in the Tibetan herb *Oxytropis falcata* Bunge (Leguminosae).⁴²⁹ Compound **229** and its diastereoisomer oxyfadichalcone B are unique because they represent the first naturally occurring chalcone HT dimers. Attempts to obtain them by [2 + 2] photodimerization failed because the HH product oxyfadichalcone C clearly prevailed under a variety of conditions.

Meier and co-workers studied the photochemistry of 1,3,5-tricinnamoylbenzene **230**, a trifold chalcone (Figure 13).^{430–432} Remarkably, they observed upon irradiation at $\lambda > 290$ nm in concentrated CH_2Cl_2 solution ($c = 0.14$ M) the formation of a dimer, which contained three cyclobutane rings and exhibited a

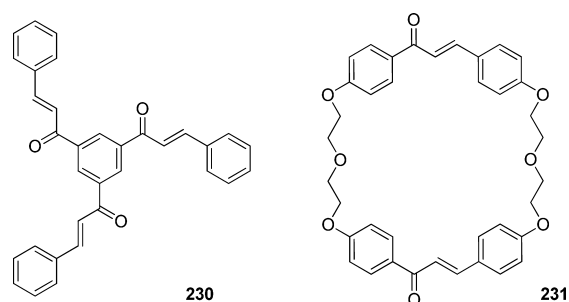
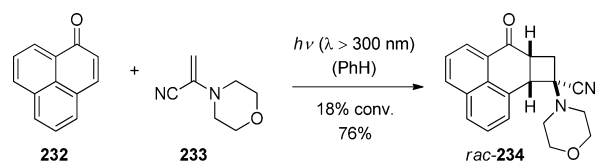


Figure 13. Structures of multifunctional chalcones **230** and **231** as employed in [2 + 2] photocycloaddition reactions.

C_3 symmetry axis. The [2 + 2] photodimerization of **230** was also studied in the crystalline state. The Doddi group observed a smooth intramolecular [2 + 2] photocycloaddition of two tethered chalcones in compounds such as **231**.^{433,434} The photoproduct was a formal HH product with *trans-syn-trans* configuration. In related work, Rusinov and co-workers showed that chalcones, which are tethered by an *ortho*-appended, oxyethylene bridge undergo an intramolecular [2 + 2] photocycloaddition reaction. The selectivity was improved by the addition of potassium cations, which have presumably a templating effect. The product in this case was the HH product with *trans-anti-trans* configuration.⁴³⁵ By this method, cyclobutane-containing benzocrown ethers were readily prepared.⁴³⁶

If the chalcone substructure is part of a cyclic array, there is an increased chance to obtain [2 + 2] photocycloaddition products. Döpp and co-workers successfully converted perinaphthenone (**232**) into [2 + 2] photocycloaddition product *rac*-**234** upon irradiation in the presence of enamine **233** (Scheme 72).⁴³⁷

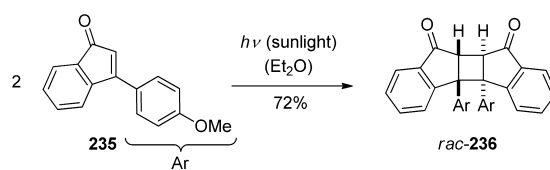
Scheme 72. Intermolecular [2 + 2] Photocycloaddition of **232**



With regard to the regioselectivity of their [2 + 2] photodimerization, the 3-arylidenedones behave as expected for cyclic chalcone analogues. A clear preference for the HH products was found in studies by the Sommer^{438,439} and the McMurry group.⁴⁴⁰ The relative configuration is dictated by the cyclic five-membered ring system to be *cis-anti-cis* as shown for the representative transformation **235** \rightarrow *rac*-**236** (Scheme 73).

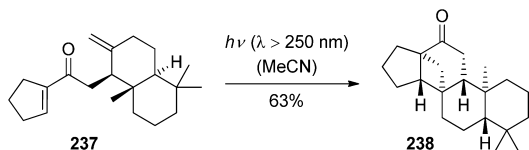
3.3.1.5. Others. If the carbonyl group of an α,β -unsaturated enone is exocyclic and the double bond is within a five-

Scheme 73. [2 + 2] Photodimerization of 3-Arylidenedone **235**



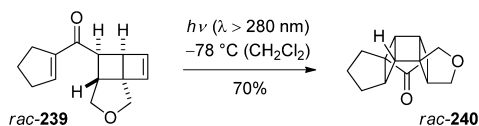
membered ring system, rotation around the double bond in the T_1 state is not possible and $[2+2]$ photocycloaddition chemistry can be expected from substrates of this type. De la Torre and co-workers used enantiomerically pure substrates derived from (+)-sclareolide for the synthesis of polycyclic terpene-like products by intramolecular $[2+2]$ photocycloaddition chemistry.⁴⁴¹ On the basis of cyclic stereocontrol exerted by the decaline ring system, acylcyclopentene **237** gave for example product **238** with high diastereoselectivity (Scheme 74).

Scheme 74. Intramolecular $[2+2]$ Photocycloaddition of (+)-Sclareolide-Derived Enone **237**



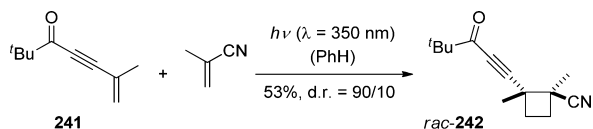
In their previously mentioned approach to annulated eight-membered rings (see Scheme 52), Snapper and co-workers found the respective all-cis-substituted (cis-syn-cis) cyclobutanes more effective to achieve the thermal ring-opening process. An access to this compound class was provided by intramolecular $[2+2]$ photocycloaddition of acylcyclopentenes such as *rac*-**239** (Scheme 75).³¹⁸ Upon irradiation of this substrate, the desired product *rac*-**240** was readily obtained.

Scheme 75. Intramolecular $[2+2]$ Photocycloaddition of Acylcyclopentene *rac*-239****



There are rare cases in which intramolecular $[2+2]$ photocycloaddition reactions were successfully performed with open-chain α,β -unsaturated aldehydes and ketones. The reactions typically include the formation of a bicyclo[3.2.0]-heptane skeleton with the first step being a fast five-membered ring closure, which successfully competes with cis/trans isomerization.^{442–444} A remarkable intermolecular $[2+2]$ photocycloaddition of enynones to olefins was reported by Inhülsen and Margaretha.⁴⁴⁵ Reactions occurred at the terminal olefin position to form HH type products as shown for the reaction **241** \rightarrow *rac*-**242** (Scheme 76).

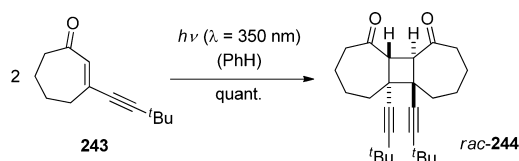
Scheme 76. Intermolecular $[2+2]$ Photocycloaddition of Enynone **241 with α -Acrylonitrile**



The Margaretha group was also able to successfully involve 3-alkynyl-2-cycloheptenones in $[2+2]$ photocycloaddition and photodimerization reactions.⁴⁴⁶ Yields of the photodimerization reactions were high, and cyclobutane *rac*-**244** was produced quantitatively from precursor enone **243** (Scheme 77). In line

with previous work,⁴⁴⁷ the HH product was formed in a trans-anti-trans configuration.

Scheme 77. $[2+2]$ Photodimerization of 3-Alkynyl-2-cycloheptenone **243**

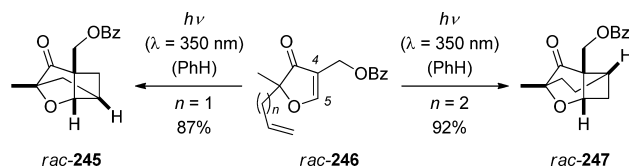


3.3.2. With Further Conjugation to Heteroatoms.

Endocyclic conjugation of the enone double bond to an oxygen, sulfur, or nitrogen atom has little influence on the absorption properties, if compared to the enones discussed in section 3.3.1. The regioselectivity outcome of intermolecular $[2+2]$ photocycloaddition reactions is also similar to the enone reactions, sometimes even improved in favor of the HT products. Compounds of this type (see subsections 3.3.2.1 and 3.3.2.2) absorb at a wavelength of $\lambda \cong 350$ nm, and their photocycloaddition reactions typically proceed via the T_1 state. While the latter is also true for enones with an exocyclic conjugation, their $n\pi^*$ (and $\pi\pi^*$) absorption is shifted hypsochromically. This shift makes it mandatory to use shorter wavelength irradiation or an appropriate sensitizer. In addition, the products from this substrate class have a higher tendency to undergo ring-opening reactions, some of which will be briefly discussed in subsections 3.3.2.3 and 3.3.2.4.

3.3.2.1. 4-Hetero-2-cyclopentenones. The $[2+2]$ photocycloaddition chemistry of five-membered enones like 3(2*H*)-furanones, 3(2*H*)-thiophenones, and dihydro-1*H*-pyrrole-3-ones was studied intensively by Margaretha and co-workers in the 1970s and in the 1980s.⁴⁴⁸ In a more recent study, the intramolecular $[2+2]$ photocycloaddition of 2-(alk-2-enyl)-furan-3(2*H*)-ones and 2-(alk-2-enyl)thiophen-3(2*H*)-ones was investigated. Major products were the bridged tricyclic hydrocarbons with a 7-oxa- or 7-thia-bicyclo[3.2.1.0^{3,6}]-octan-2-one skeleton.⁴⁴⁹ In agreement with this result, it was found in our laboratories that 2-(prop-2-enyl)furan-3(2*H*)-one *rac*-**246a** ($n = 1$) gave product *rac*-**245** with perfect regio- and diastereoselectivity (Scheme 78).⁴⁵⁰ The homologue *rac*-**246b**

Scheme 78. Divergent Regioselectivity in the Intramolecular $[2+2]$ Photocycloaddition of Furan-3(2*H*)-ones *rac*-246****

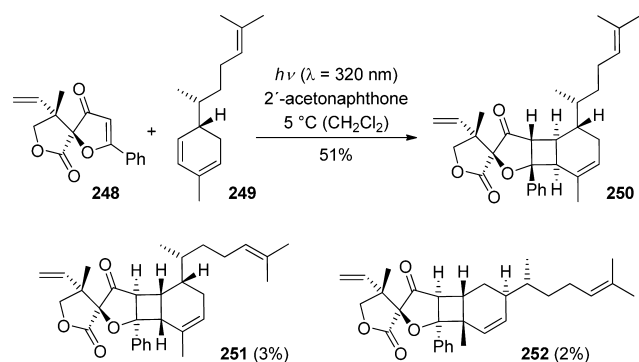


($n = 2$) surprisingly delivered under the same conditions not the expected 7-oxabicyclo[4.2.1.0^{3,8}]nonanone but its regioisomer *rac*-**247**. The dramatic change in selectivity was explained by the conformation of the side chain, which enables initial C–C bond formation in the former case between carbon atom C5 of the furanone and the internal olefin carbon atom and in the latter case between C4 and the internal olefin carbon atom.

The intermolecular $[2+2]$ photocycloaddition between the 5-phenylfuran-3(2*H*)-one **248** (hyperolactone C) and an

appropriate olefin **249** was used by the Nicolaou group (Scheme 79)^{451,452} and by the Xie group⁴⁵³ for the synthesis of (–)-biyouyanagin A (**250**).

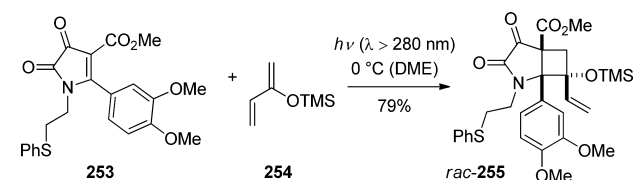
Scheme 79. Synthesis of Biyouyanagins A (**250**) and B (**251**) by Intermolecular [2 + 2] Photocycloaddition



In addition, Nicolaou and co-workers could show that the naturally occurring (–)-biyouyanagin B (**251**) is a side product in this photocycloaddition, which led to a revision of its structure.⁴⁵⁴ The authors also isolated a third compound **252**, which they speculated might also be a natural product.

Sano and co-workers successfully employed the intramolecular [2 + 2] photocycloaddition of dioxopyrrolines as an efficient entry to the synthesis of erythrin and homoerythrin alkaloids.^{455–457} Reaction of enone **253** with diene **254** occurred at the more electron-rich double bond and favored the HT product *rac*-**255** (Scheme 80). Key step in the further

Scheme 80. Intermolecular [2 + 2] Photocycloaddition of Enone **253** with Diene **254** En Route to a Formal Total Synthesis of (±)-Erystrine

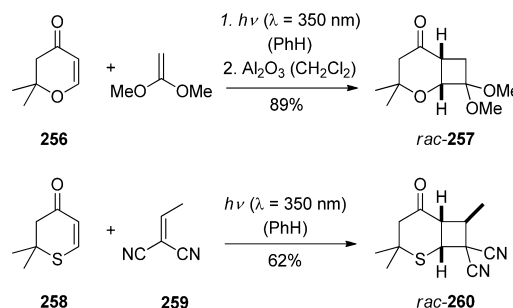


synthetic sequence was an anionic 1,3-rearrangement to expand the four-membered to a six-membered ring. The intermolecular [2 + 2] photocycloaddition of 5-methoxy-1-phenyl-pyrrole-2,3-dione was investigated by Abd El-Nabi.⁴⁵⁸

3.3.2.2. 4-Hetero-2-cyclohexenones. Extensive studies by the Margaretha group aimed to elucidate the intermolecular [2 + 2] photocycloaddition chemistry of 2,3-dihydro-4*H*-pyran-4-ones^{377,459–461} and 2,3-dihydro-4*H*-thiopyran-4-ones.^{462–464} An immense data set has been generated, out of which two examples are given in Scheme 81. Dihydropyranone **256** produced with high regioselectivity the respective HT photocycloaddition product. A mixture of *cis* and *trans* products (see Scheme 47) was formed, which was converted into the pure *cis* isomer *rac*-**257** upon treatment with basic alumina (Scheme 81).⁴⁶¹

Dihydrothiopyranone **258** underwent a smooth [2 + 2] photocycloaddition to the dinitrile **259**. The HT product *rac*-**260** was formed. It was argued that the high stabilization of the radical center next to the sulfur atom results in formation of a thermodynamically preferred 1,4-diradical intermediate, which

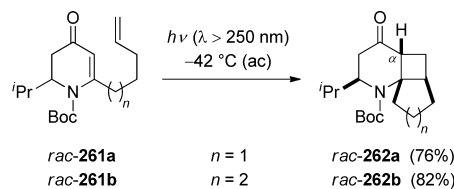
Scheme 81. Representative Intermolecular [2 + 2] Photocycloaddition Reactions of 4-Hetero-2-cyclohexenones **256** and **258**



undergoes ring closure to the observed product.⁴⁶³ White and co-workers used the diastereoselective intermolecular [2 + 2] photocycloaddition of acetylene to a chiral 2,3-dihydro-4*H*-pyran-4-one as a key step in a formal synthesis of (±)-verrucarol.⁴⁶⁵

The intermolecular [2 + 2] photocycloaddition reaction of 2,3-dihydropyridin-4(1*H*)-one was discovered by Neier and co-workers in the 1980s.^{466–469} The intramolecular variant of this reaction was used by the Comins group for the synthesis of various alkaloids.^{470–475} They observed a high facial diastereoselectivity in the intramolecular [2 + 2] photocycloaddition if a stereogenic center was present within the dihydropyridone ring. The reaction of substrates *rac*-**261** delivered for example exclusively products *rac*-**262** in good yields (Scheme 82).⁴⁷⁵

Scheme 82. Facial Diastereoselectivity in the Intramolecular [2 + 2] Photocycloaddition of Dihydropyridones *rac*-**261**

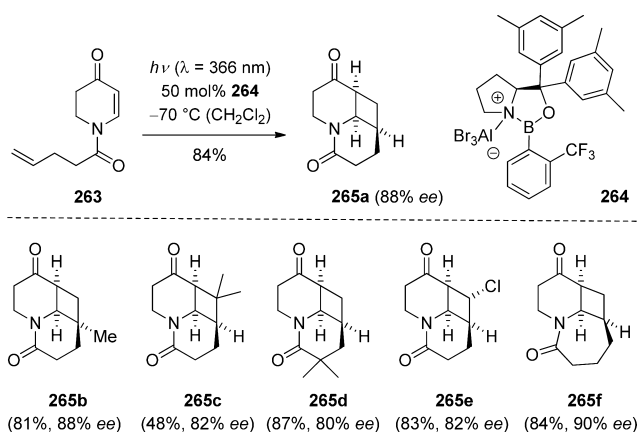


Ring-opening reactions of the cyclobutane ring were performed reductively with SmI_2 as the reductant. Cleavage of the bond between the α -carbon atom and the methylene carbon led to spiro compounds.

Typically, enone [2 + 2] photocycloaddition reactions are performed by irradiation of the longest wavelength absorption ($\lambda = \text{ca. } 280\text{--}360 \text{ nm}$), which corresponds to a S_1 state with $n\pi^*$ character. ISC to the $\pi\pi^*$ T_1 state is rapid as this process is allowed by El-Sayed's rule.^{476,477} An intense absorption at shorter wavelength ($\Delta\lambda \cong 60 \text{ nm}$) corresponds to a singlet state with $\pi\pi^*$ character, which is normally not involved in [2 + 2] photocycloaddition chemistry. It was found in our laboratories that the latter absorption band is shifted bathochromically upon coordination of the enone to a Lewis acid. In the case of dihydropyridone **263**, the above-mentioned absorption maxima occur in a noncomplexed substrate at $\lambda \cong 360 \text{ nm}$ ($n\pi^*$; $\epsilon = 70 \text{ M}^{-1} \text{ cm}^{-1}$) and at $\lambda = 291 \text{ nm}$ ($\pi\pi^*$; $\epsilon = 17400 \text{ M}^{-1} \text{ cm}^{-1}$) in CH_2Cl_2 ($c = 0.5 \text{ mM}$).^{478,479} Upon complexation with EtAlCl_2 , the latter band is shifted to $\lambda = 343 \text{ nm}$ ($\epsilon = 21400 \text{ M}^{-1} \text{ cm}^{-1}$). Since the absorption coefficient of the Lewis acid complex is by a factor of ca. 200 higher than for the uncomplexed substrate at $\lambda = 360 \text{ nm}$, it was considered possible to catalyze the reaction enantioselectively⁴⁸⁰ in the

presence of a chiral Lewis acid. Indeed, this hypothesis turned out to be correct, and the oxazaborolidine-AlBr₃ complex **264** was found to be the best-suited catalyst for the reaction. Several cyclobutane⁴⁸¹ products **265** were obtained in good yields and with high enantioselectivity (Scheme 83). Product **265e** was

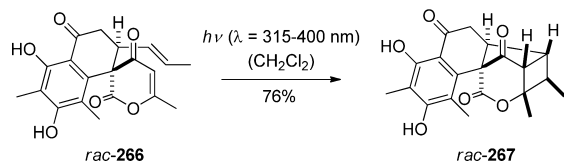
Scheme 83. Enantioselective Lewis Acid Catalysis in Intramolecular [2 + 2] Photocycloaddition Reactions of 2,3-Dihydropyridin-4(1H)-ones



employed as starting material for the total synthesis of (+)-lupinine and for the formal total synthesis of (+)-thermosine.⁴⁷⁸ Evidence was collected that the reactions occur from the T₁ level and recent calculations by Wang et al. suggest that the ISC in the Lewis acid is induced by the relativistic heavy atom effect of the bromine atoms in **264**.⁴⁸²

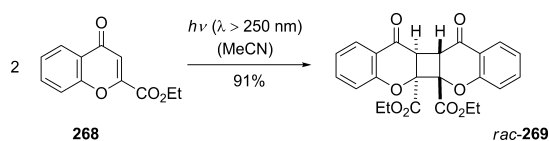
The intramolecular [2 + 2] photocycloaddition of 2,3-dihydro-4H-pyran-4-ones was applied by Haddad and Salman to the synthesis of (+)-ligundentol.^{483–485} More recently, Porco Jr. and co-workers employed the intramolecular [2 + 2] photocycloaddition of the pyran-2,4-dione *rac*-**266** to elucidate its constitution and relative configuration via a crystal structure of product *rac*-**267** (Scheme 84).⁴⁸⁶

Scheme 84. Intramolecular [2 + 2] Photocycloaddition of Pyran-2,4-dione *rac*-266



The [2 + 2] photodimerization and [2 + 2] photocycloaddition of chromones (benzo- γ -pyrones) was studied by the Sakamoto group.^{487–489} Ester **268** provided exclusively the HH product *rac*-**269** in the expected cis-anti-cis configuration (Scheme 85). The regioselectivity could be completely reverted if the reaction was performed in the solid state.⁴⁸⁸ A diastereoselective [2 + 2] photodimerization was achieved

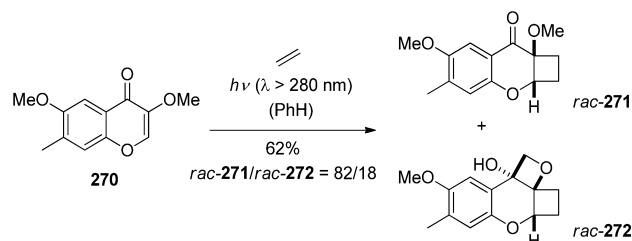
Scheme 85. [2 + 2] Photodimerization of Chromone 268



with chiral amides.^{490,491} The related [2 + 2] photodimerization of pyrano[2,3-*c*]pyrazole-4-(1H)-ones was studied by Pavlik et al.,⁴⁹² and the [2 + 2] photodimerization of 5-substituted 2-styryl-4-pyrones was investigated by Jakopčić and co-workers.⁴⁹³

In some cases, the carbonyl group of [2 + 2] photocycloaddition products may give rise to further photoinduced reactions. Sabui and Venkateswaran for example observed in the intermolecular [2 + 2] photocycloaddition of chromone **270** that, apart from the desired product *rac*-**271**, the oxetane *rac*-**272** was isolated (Scheme 86).⁴⁹⁴ Its formation can be

Scheme 86. Photochemical Reaction of Chromone 270 and Ethylene

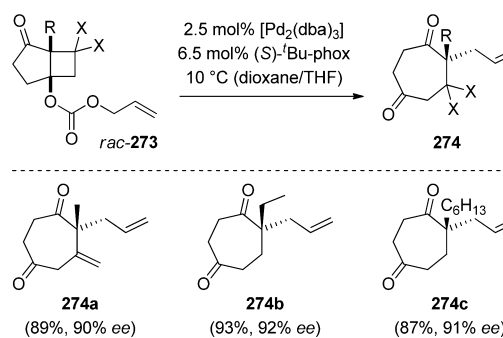


explained by a Norrish-Yang cyclization of ketone *rac*-**271** upon excitation. In this specific case, the side reaction turned out to be inconsequential because both products were converted to a common intermediate in the synthesis of (\pm)-heliannuol D.

Intermolecular [2 + 2] photocycloaddition and photodimerization reactions of seven-membered benzoxepinones and dioxepinones have recently been studied by the Margaretha group.^{461,464,495} The reactions follow the pathways previously discussed for related six-membered enones in this subsection.

3.3.2.3. Exocyclic Heteroatom at β -Position. In this subsection, cyclic enones are treated, which bear an exocyclic heteroatom at the β -position. Mechanistically, their mode of [2 + 2] photocycloaddition is identical to the addition mode of other enones. Their longest wavelength absorption is shifted somewhat hypsochromically relative to the parent compounds. In the photocycloaddition products, the exocyclic heteroatom can be more easily activated than an endocyclic heteroatom, which facilitates cyclobutane ring opening of the bond between former α - and β -carbon atoms. Typically, this reaction is a retro-aldol or a retro-Mannich reaction (vide infra).^{65,225–227} Schulz and Blechert showed that this type of ring-opening mode can be combined with an enantioselective Pd-catalyzed allylation reaction (Scheme 87).⁴⁹⁶

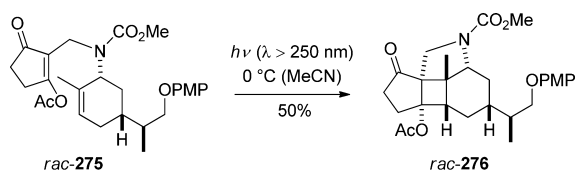
Scheme 87. Enantioselective Ring Opening/Allylation of [2 + 2] Photocycloaddition Products *rac*-273



[2 + 2] Photocycloaddition products *rac*-273 were readily accessible by reaction of the respective 3-allyloxycarbonyloxy-2-cyclopentenones with allene or ethylene. Ring opening and allylation were induced by treatment with a chiral palladium complex [(*S*)-^tBu-phox = (*S*)-4-(*tert*-butyl)-2-(2-(diphenylphosphanyl)phenyl)-4,5-dihydrooxazole] furnishing products 274 with high enantioselectivity.

Wang and co-workers employed β -acetoxy-substituted enones for intramolecular [2 + 2] photocycloaddition reactions.^{497,498} Product *rac*-276 was for example obtained in 50% yield from substrate *rac*-275 (Scheme 88). The comparably low

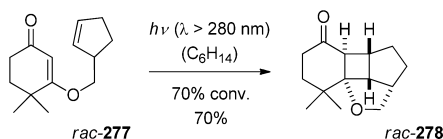
Scheme 88. Intramolecular [2 + 2] Photocycloaddition of β -Acetoxy-2-cyclopentenone *rac*-275



yield was due to a retro-aldol fragmentation of acetate *rac*-276,⁴⁹⁹ which led to the respective seven-membered ring product in 29% yield. After reduction of the carbonyl group in *rac*-276 and mesylation of the resulting alcohol, the originally planned Grob fragmentation of the cyclobutane ring could be performed and was shown to be an efficient entry to the tetracyclic core of calyciphylline alkaloids.

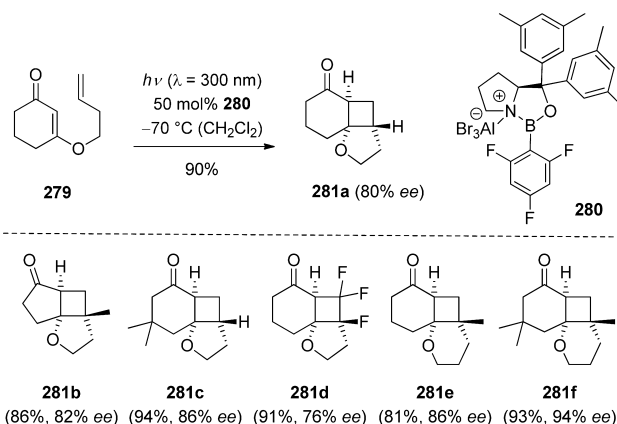
Tedaldi and Baker noted undesired Norrish type I cleavage products when performing intramolecular [2 + 2] photocycloaddition reactions of 3-alkenyloxy-2-cyclopentenones. It was recommended to reduce the product in situ to avoid complications.⁵⁰⁰ In related 2-cyclohexenones consecutive reactions seem less problematic, and Inouye et al. successfully employed the [2 + 2] photocycloaddition of ketone *rac*-277 to *rac*-278 in a formal total synthesis of (\pm)-precapnelladiene (Scheme 89).⁵⁰¹

Scheme 89. Intramolecular [2 + 2] Photocycloaddition of 3-Alkenyloxy-2-cyclohexenone *rac*-277



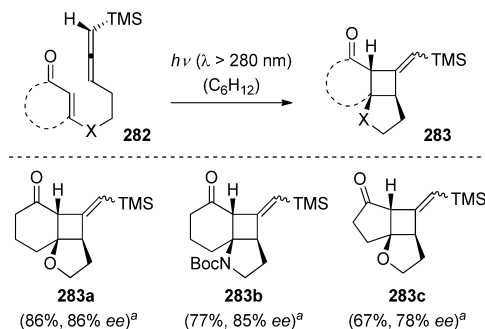
On the basis of the previously mentioned concept of Lewis acid catalysis (see Scheme 83), enantioselective intramolecular [2 + 2] photocycloaddition reactions of 3-but-3-enyloxy- and 3-pent-4-enyloxy-substituted 2-cyclopentenones and 2-cyclohexenones were successfully performed in our laboratories.⁵⁰² In this instance, the $\pi\pi^*$ absorption maximum of the prototypical substrate 279 was shifted from $\lambda = 245$ nm ($\epsilon = 21790$ M⁻¹ cm⁻¹) to $\lambda = 281$ nm ($\epsilon = 27270$ M⁻¹ cm⁻¹) upon Lewis acid coordination in CH₂Cl₂ ($c = 0.5$ mM). Due to the high cross section of the latter absorption, the $n\pi^*$ transition of the uncomplexed substrate at $\lambda = 299$ nm ($\epsilon = 90$ M⁻¹ cm⁻¹) did not significantly contribute to product formation. Lewis acid 280 was found optimal for high asymmetric induction and several products (e.g., 281b–281f) were formed in analogy to the conversion 279 \rightarrow 281a (Scheme 90).

Scheme 90. Enantioselective Lewis Acid Catalysis in Intramolecular [2 + 2] Photocycloaddition Reactions of 3-Alkenyloxy-Substituted Enones



Another approach to enantio-enriched cyclobutanes was described by Carreira and co-workers (Scheme 91).⁵⁰³ They

Scheme 91. Chirality Transfer in the Intramolecular [2 + 2] Photocycloaddition of Axially Chiral Allenes 282^a



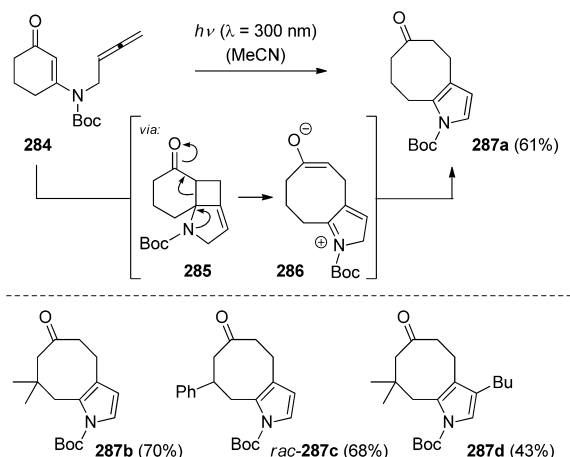
^aTotal yield of (*E*)- and (*Z*)-diastereoisomers, the *ee* refers to the respective (*E*)-diastereoisomer.

employed an efficient chirality transfer from the chiral axis in substrates 282 to a center of chirality in products 283. Key step is the cyclization to the intermediate 1,4-diradical, which occurs at the allene axis antiperiplanar to the trimethylsilyl (TMS) group. The TMS group in products 283 could readily be removed by protodesilylation.

As pointed out in the beginning of this subsection, retro-Mannich fragmentation reactions can follow the [2 + 2] photocycloaddition reaction of β -amino-substituted enones.⁵⁰⁴ The Hiemstra group isolated *tert*-butoxycarbonyl (Boc)-protected pyrroles such as 287a upon irradiation of enone allenes like 284 (Scheme 92).^{505,506} Presumably, the [2 + 2] photocycloaddition proceeds in a straight fashion to highly strained intermediate 285, which cleaves in a retro-Mannich fashion to zwitterion 286. The corresponding crossed [2 + 2] photocycloaddition products were isolated in yields of 10–20% accounting in part for the apparent deficiencies in the mass balance. The reaction could be applied to the synthesis of furans employing oxygen-tethered enone allenes. Very similar findings were made simultaneously by Winkler and Ragains when studying the reaction of *N*-unprotected vinylogous amides and imides.⁵⁰⁷

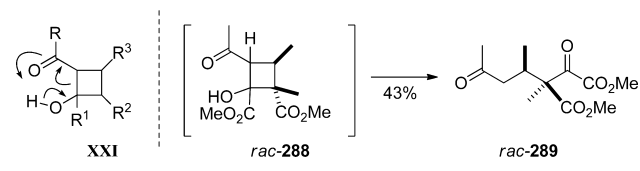
3.3.2.4. Others. The classic de Mayo reaction^{225–227} employs enols of 1,3-dicarbonyl compounds as substrates

Scheme 92. Synthesis of Pyrroles 287 by a Sequence of Intramolecular [2 + 2] Photocycloaddition and retro-Mannich Fragmentation



(see also Scheme 34), and retro-aldol reaction occurs from hydroxycyclobutanes **XXI** as indicated in Scheme 93. The

Scheme 93. De Mayo Reaction as an Entry to 1,5-Dicarbonyl Compounds such as *rac*-289



Takeshita group introduced several acyclic ketoesters for applications in intermolecular de Mayo reactions.^{508–510} [2 + 2] Photocycloaddition intermediate *rac*-288 for example led immediately to 1,5-dicarbonyl product *rac*-289 by retro-aldol cleavage. Compound *rac*-289 in turn was used as a key intermediate in the total synthesis of (±)-sollasin a and (±)-sollasin d.⁵¹⁰

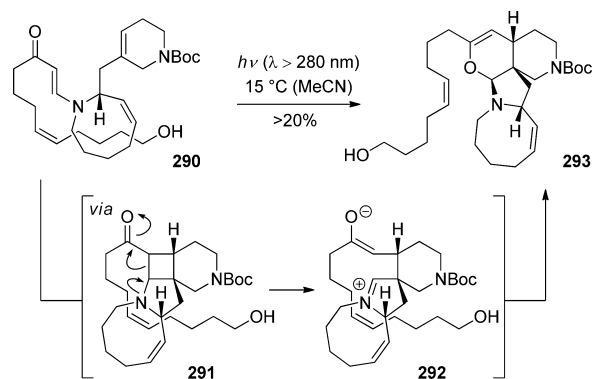
Acyclic β -aminoenones were employed by Winkler and co-workers for sequences of [2 + 2] photocycloaddition reactions and Mannich reactions.^{511–516} In their synthesis of (–)-ircinol A, (+)-ircinal A, (+)-manzamine A, and (+)-manzamine D, Winkler and Axten subjected enone **290** to Pyrex-filtered UV irradiation (Scheme 94). Upon intramolecular [2 + 2] photocycloaddition, the putative intermediate **291** underwent a sequence of retro-Mannich reaction (to **292**) and *N,O*-acetal formation (to **293**).⁵¹¹

More recently, Winkler and Fitzgerald applied a photocycloaddition–retro-Mannich–Mannich cascade to the synthesis of 8-substituted 6-azabicyclo[3.2.1]octan-3-ones. Intramolecular [2 + 2] photocycloaddition of enaminone **294** gave crossed product *rac*-295 in high yields (Scheme 95). Conversion of orthoester *rac*-295 into methyl ester *rac*-296 set the stage for the acid-induced cascade, which proceeded via intermediate *rac*-297 to the desired bicyclic product *rac*-298.⁵¹⁶

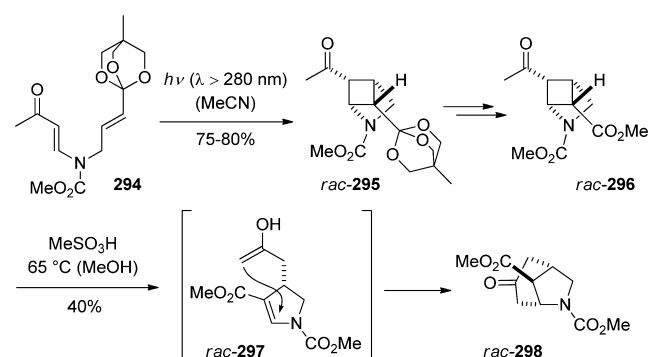
3.4. α,β -Unsaturated Carboxylic Acid Derivatives

For lactones/esters and lactams/amides with an unsaturated double bond in the α,β -position, the longest wavelength absorption is shifted to $\lambda \cong 250$ nm (i.e., hypsochromically relative to the respective enones). This absorption is weak and corresponds to an $n\pi^*$ transition. Stronger absorption bands

Scheme 94. Intramolecular [2 + 2] Photocycloaddition of Enone **290** as a Pivotal Step in the Synthesis of Manzamine Alkaloids



Scheme 95. Synthesis of 6-Azabicyclo[3.2.1]octan-3-one *rac*-298 by a Photocycloaddition–retro-Mannich–Mannich Cascade



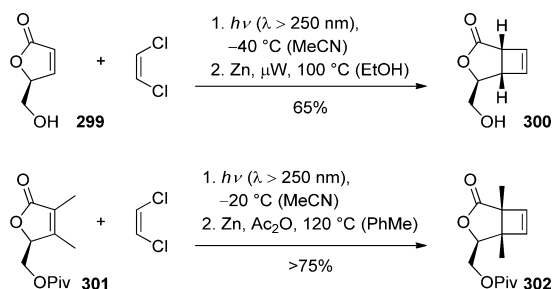
are recorded below 250 nm, which are, however, of lesser relevance for the photochemistry of this compound class. [2 + 2] Photocycloaddition reactions of α,β -unsaturated carboxylic acid derivatives can be induced by direct excitation (see Scheme 3), frequently employing low-pressure mercury lamps in quartz vessels. Alternatively, sensitization can be attempted (see Scheme 4). The triplet energy of many compounds of this class is below the triplet energy of acetone ($E_T = 332$ kJ mol^{−1}). Consequently, acetone can serve simultaneously as a solvent or cosolvent and as a triplet sensitizer.

3.4.1. α,β -Unsaturated Lactones. Most compound classes of section 3.4 represent typical α,β -unsaturated lactones (subsections 3.4.1.1 and 3.4.1.4–3.4.1.6) as described in the introduction (vide supra). Some compound classes, however, are somewhat different in their photochemical properties due to extensive conjugation (subsection 3.4.1.2) or due to the existence of another carbonyl group (subsection 3.4.1.3). All compounds, however, have a low triplet energy in common, which invites excitation via sensitization. In addition, the presence of an olefinic bond in the α,β -position to a carboxy unit remains a recurring theme in all substrates.

3.4.1.1. Without Further Conjugation. Initial work on [2 + 2] photocycloaddition reactions of nonconjugated α,β -unsaturated lactones was performed in the 1970s.^{517,518} Five-membered ring compounds [i.e. 2(*SH*)-furanones (butenolides)] have long been in the center of interest as they behave relatively well both in inter- and intramolecular [2 + 2] photocycloaddition reactions.⁵¹⁹ A substituent in the 5-position

creates a stereogenic center, and studies on the facial diastereoselectivity of the respective 5-substituted 2(*SH*)-furanones commenced in the late 1980s. Initial work on 5-alkyl-2(*SH*)-furanones was performed by the groups of Koga⁵²⁰ and Font,^{521–523} while 5-alkoxy-2(*SH*)-furanones were investigated by Scharf, Hoffmann, and co-workers.^{524–528} Koga and his group employed enantiopure 2(*SH*)-furanone substrates in the synthesis of (+)-stoechospermol⁵²⁹ and (+)-spatol.⁵³⁰ The facial diastereoselectivity in intermolecular [2 + 2] photocycloaddition reactions of 2(*SH*)-furanones is variable and depends on the nature of the substituent in the 5-position and on the olefinic component.⁵³¹ In the last two decades, Alibés, Figueredo, Font, and co-workers widely employed free and oxygen-protected 5-hydroxymethyl-2(*SH*)-furanones.^{532–539} Significant diastereoselectivities were recorded in several intermolecular [2 + 2] photocycloaddition reactions, and numerous applications were disclosed for the enantioselective synthesis of terpenoid natural products^{540–545} and new nucleoside analogues (Scheme 96).^{546–549}

Scheme 96. Intermolecular [2 + 2] Photocycloaddition Reactions of 5-Substituted 2(*SH*)-Furanones 299 and 301

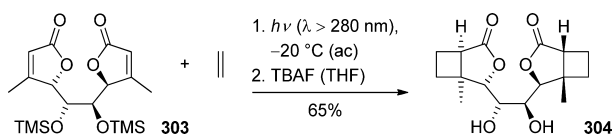


In the latter context, 2(*SH*)-furanone **299** and *cis*-1,2-dichloroethene were shown to react with high facial diastereoselectivity (Scheme 96) to intermediate dichlorocyclobutanes, which gave upon reductive dechlorination cyclobutene **300**.⁵⁴⁸ Inoue et al. employed the pivaloyl (Piv)-protected 5-hydroxymethyl-2(*SH*)-furanone **301** in a similar sequence to generate cyclobutene **302**, which served as a key intermediate in the synthesis of (–)-merrilactone A (**157**, see Scheme 51).⁵⁵⁰

Twofold intermolecular [2 + 2] photocycloaddition reactions to *C*₂-symmetric bis(butenolides) were studied by Figueredo, Font, and co-workers.^{551–553} Compounds of this type, such as **303**, can readily be obtained in enantiomerically pure form from *D*-mannitol. High diastereoselectivities were obtained in the photochemical reaction with olefins. The reaction of **303** with ethylene gave after silyl deprotection with tetrabutylammonium fluoride (TBAF) diol **304** as a single product (Scheme 97), which was converted into the insect pheromone (+)-grandisol.

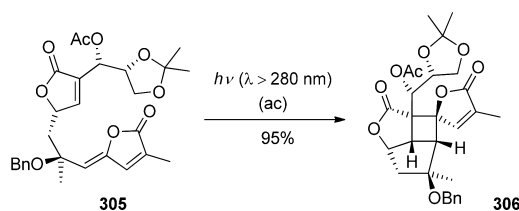
The group of Figueredo and Font also investigated intramolecular [2 + 2] photocycloaddition reactions of 5-but-

Scheme 97. Intermolecular [2 + 2] Photocycloaddition of Ethylene to Bis(butenolide) 303



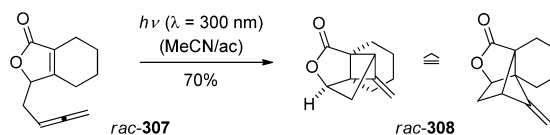
3-enyl-2(*SH*)-furanones which yielded the respective straight product.^{554,555} Reactions of this type bear relevance to the construction of the core structure of bielschowskysin (**40**, see Scheme 12). After studies on less complex model substrates,⁵⁵⁶ Sulikowski and co-workers recently found a very efficient intramolecular [2 + 2] photocycloaddition of 2(*SH*)-furanone **305**, which cleanly gave under sensitizing conditions the elaborated intermediate **306** (Scheme 98).⁵⁵⁷ Related intramolecular photocycloaddition approaches to the bielschowskysin core were reported by the Lear⁵⁵⁸ and the Mulzer group.^{559,560}

Scheme 98. Construction of the Bielschowskysin Core by Intramolecular [2 + 2] Photocycloaddition



If the tether between the reacting olefin and the enone double bond of a 5-substituted 2(*SH*)-furanone is too short to allow for a straight [2 + 2] photocycloaddition, the crossed addition mode prevails. Hiemstra and co-workers studied this reaction class intensively in possible approaches toward the synthesis of (±)-solanoeclepin A.^{561–566} A representative model reaction *rac*-**307** → *rac*-**308** is depicted in Scheme 99.⁵⁶¹

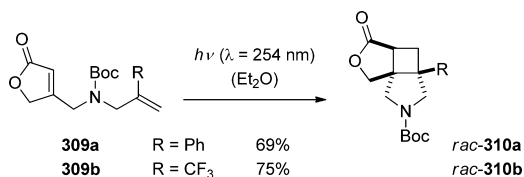
Scheme 99. Crossed Intramolecular [2 + 2] Photocycloaddition Reaction of *rac*-**307** as an Approach toward the Core Fragment of Solanoeclepin A



In an approach to conformationally rigid pyrrolidines and bis-pyrrolidines the intramolecular [2 + 2] photocycloaddition of various 4-(allylaminomethyl)-2(*SH*)-furanones was investigated.^{567–569} The reactions (e.g. **309** → *rac*-**310**) were found to proceed best under conditions of direct irradiation (Scheme 100).

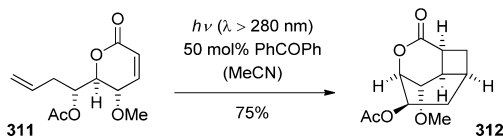
The six-membered analogues of 2-(*SH*)furanones, the respective 5,6-dihydro-2(*2H*)-pyranones, have in recent years been less extensively used for [2 + 2] photocycloaddition reactions.⁵⁷⁰ Carbohydrate-derived precursors for an intramolecular reaction were studied by Tenaglia et al.⁵⁷¹ and by Gómez et al.⁵⁷² The latter group discovered that 6-but-3-enyl-

Scheme 100. Intramolecular [2 + 2] Photocycloaddition of *N*-Boc-Protected 4-(Allylaminomethyl)-2(*SH*)-furanones 309



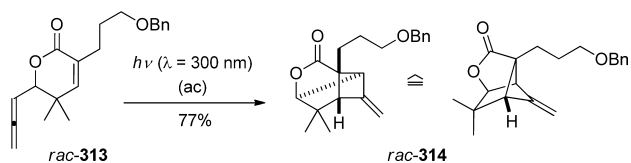
substituted pyranone **311** gave the straight product **312** with high regio- and diastereoselectivity (Scheme 101). 6-Allyl-substituted pyranones give a mixture of regioisomers, while the respective 6-vinyl derivative produced only the crossed photocycloaddition product.

Scheme 101. Intramolecular [2 + 2] Photocycloaddition of Carbohydrate-Derived 5,6-Dihydro-2(2H)-pyranone **311**



The crossed [2 + 2] photocycloaddition of 6-allyl-5,6-dihydro-2(2H)-pyranone *rac*-**313** (Scheme 102) was found by

Scheme 102. Approach to the Tricyclic Skeleton of (±)-Aquatolide by Intramolecular [2 + 2] Photocycloaddition



Hiemstra and co-workers to be an efficient key step in the total synthesis of the sesquiterpene lactone (±)-aquatolide.⁵⁷³ Product *rac*-**314** was formed very efficiently with acetone acting as triplet sensitizer.

3.4.1.2. 2-Pyrones and Coumarins. The chemistry and photochemistry of 2-pyrones (α -pyrones) and olefins are complex. There is the option of a thermal or photochemical [4 + 2] cycloaddition and of [2 + 2] photocycloaddition reactions at either one of the two 2-pyrone double bonds (3,4- vs 5,6-addition). Furthermore, 2-pyrones can undergo a [4 π] photocyclization upon direct excitation. Many photocycloaddition reactions of 2-pyrones were studied by Shimo, Somekawa, and co-workers, who reviewed the topic in 2004.⁵⁷⁴ In general, triplet sensitization is the preferred way of excitation. The mode of the photocycloaddition depends on the substitution pattern of the 2-pyrone and the nature of the olefin. Figure 14 shows

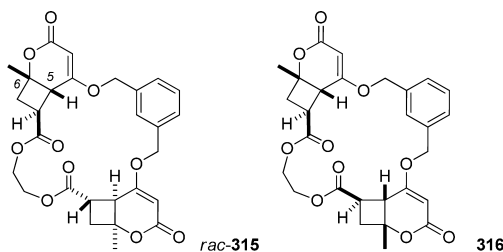


Figure 14. Structures of intermolecular [2 + 2] photocycloaddition products of di- α -pyrones.

cyclobutanes *rac*-**315** and **316**, which were obtained in a recent study on intermolecular 2-fold [2 + 2] photocycloaddition to di-2-pyrones.^{575,576} Addition to the 5,6-position was the main reaction pathway.

Sensitization is also the preferred way to promote coumarin and many of its derivatives into the excited state. In the absence

of an external olefin, [2 + 2] photodimerization occurs with the HH cis-anti-cis product (*rac*-**317**, Figure 15) being the major

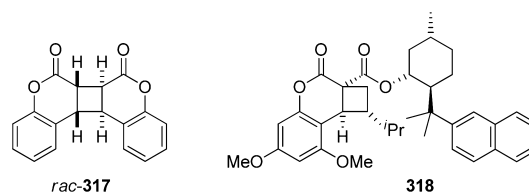


Figure 15. Structures of coumarin dimer *rac*-**317** and of [2 + 2] photocycloaddition product **318**.

product.⁵⁷⁷ In benzene as the solvent and with benzophenone as triplet sensitizer, yields over 90% were achieved by Ding and co-workers. Compound *rac*-**317** served as the starting material for the synthesis of new phosphane ligands.^{578,579} The selectivity of the [2 + 2] photodimerization was found to be altered for certain coumarins in micellar solutions⁵⁸⁰ or in the presence of a template.⁵⁸¹ The enantioselective formation of coumarin dimer **317** was observed in the presence of a chiral template but with low chemical yield.⁵⁸² A racemic coumarin photodimer was employed as a probe for the mechanochemical scission within poly(methyl acrylate) polymers.⁵⁸³

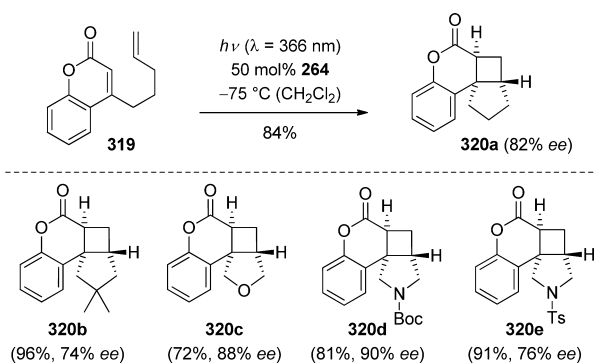
There are several recent reports on intermolecular [2 + 2] photocycloaddition reactions of coumarins which aim at improving the selectivity.^{584–586} As an example, photocycloaddition product **318** is depicted in Figure 15. The compound was obtained in significant diastereomeric excess (78% *de*) from the reaction of a chiral coumarin with 3-methyl-1-butene and served as a key intermediate in the Ohta synthesis of (–)-linderol A.^{587–591}

Direct excitation of coumarin is not suitable to initiate a photochemical reaction because the decay from S_1 to S_0 is extremely rapid.⁵⁹² Görner and Wolff showed in a comprehensive time-resolved UV–Vis spectroscopy study that the previously observed catalytic effect of Lewis acids on the [2 + 2] photodimerization of coumarin⁵⁹³ is due to an increased lifetime of S_1 and an enhanced ISC rate.⁵⁹⁴ They confirmed earlier work by Lewis and co-workers who had observed a catalytic effect of Lewis acids on the rate of [2 + 2] photocycloaddition reactions.⁵⁹² The latter study led our group to investigate a possible enantioselective [2 + 2] photocycloaddition to be mediated by chiral Lewis acids. It was found that oxazaborolidine- $AlBr_3$ complex **264** (Scheme 83) promotes the intramolecular reaction of 4-substituted coumarins such as **319**. Several products **320** were obtained with high enantioselectivity (Scheme 103).^{595,596} The reaction was shown to occur on the triplet hypersurface, while the uncatalyzed reaction, which occurs upon direct excitation, is a (slow) singlet process.⁴⁷⁹

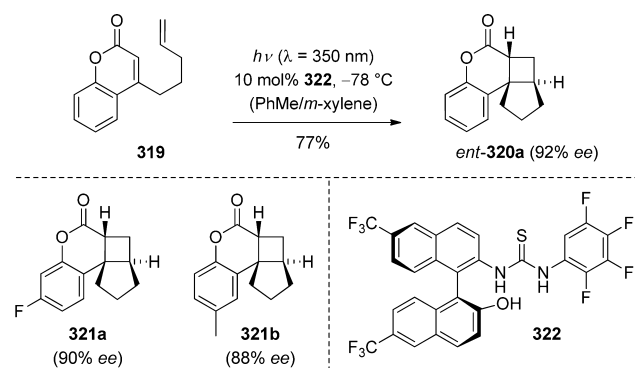
In a related catalysis study, which was published recently, Sivaguru, Sibi, and co-workers were guided by similar considerations. They designed a chiral thiourea **322**, which can act as hydrogen-bonding template to activate coumarin **319** (Scheme 104).⁵⁹⁷

A triplet mechanism was suggested to operate at low catalyst loading, according to which the catalyst-substrate complex can be directly excited at long wavelength. The enantioface differentiation is effected by 3-fold hydrogen bonding of the urea to the substrate with the carbonyl group being bound via the two NH protons of the thiourea and the lactone oxygen being additionally fixed by the naphthol hydroxy group. In

Scheme 103. Enantioselective [2 + 2] Photocycloaddition of Coumarins Mediated by a Chiral Lewis Acid



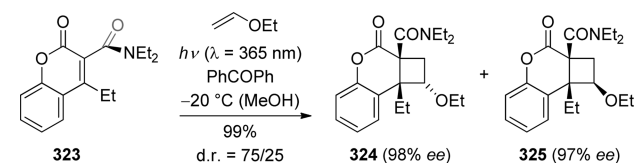
Scheme 104. Enantioselective [2 + 2] Photocycloaddition of Coumarins Mediated by Chiral Thiourea **322**



addition to product *ent*-**320a**, substituted coumarin photo-products **321** were also obtained with high ee.⁵⁹⁸

A completely different approach to enantioselective coumarin [2 + 2] photocycloaddition chemistry was taken by Sakamoto and co-workers.⁵⁹⁹ They generated an axially chiral coumarin **323** in enantiopure form by spontaneous crystallization. Upon dissolution at low temperature, the compound retains its chirality, and the intermolecular [2 + 2] photocycloaddition with ethyl vinyl ether occurred with high chirality transfer to the two diastereoisomers **324** and **325** (Scheme 105).

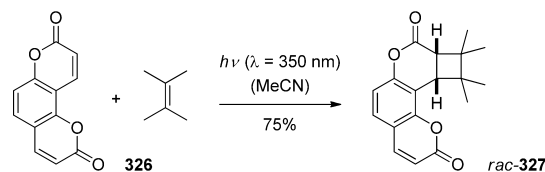
Scheme 105. Enantioselective Intermolecular [2 + 2] Photocycloaddition Reaction of Axially Chiral Amide **323**



Intramolecular [2 + 2] photocycloaddition reactions of coumarins were studied in the context of a combinatorial approach to new scaffolds⁶⁰⁰ and as a way to reversibly modify dicarbene-derived metallacycles.⁶⁰¹ Margaretha and co-workers investigated intramolecular reactions of this type in the context of a possible spin-center shift, which would enable the formation of other but cyclobutane photoproducts.^{602,603} The same group prepared also several coumarins with a second chromophore annulated to the arene ring of the coumarin.^{604,605} The regioselectivity of the addition reactions was investigated. Benzodipyrandione **326** was found to undergo

only a single [2 + 2] photocycloaddition upon direct excitation (Scheme 106).⁶⁰⁴ The reluctance of product *rac*-**327** toward a second photocycloaddition can be understood by the rapid internal conversion of the coumarin chromophore (vide supra).

Scheme 106. Intermolecular [2 + 2] Photocycloaddition of Benzodipyrandione **326**



3.4.1.3. Maleic Anhydride and Related Substrates. The triplet energy of maleic anhydride was reported⁶⁰⁶ as 302 kJ mol⁻¹, and triplet sensitization is therefore a viable way to populate the T₁ state, from which [2 + 2] photocycloaddition reactions can occur. Parent maleic anhydride was employed by Aitken and co-workers to access trisubstituted cyclobutanes as precursors for conformationally restricted amino acids.^{607–610} Cyclobutene *rac*-**328** was quantitatively obtained from maleic anhydride and propargyl alcohol upon irradiation of a MeCN solution in the presence of acetophenone (Figure 16).⁶⁰⁹ A

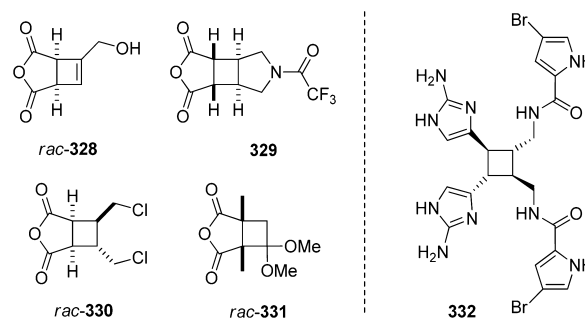


Figure 16. Structures of various maleic anhydride [2 + 2] photocycloaddition products and of (–)-sceptrin (**332**).

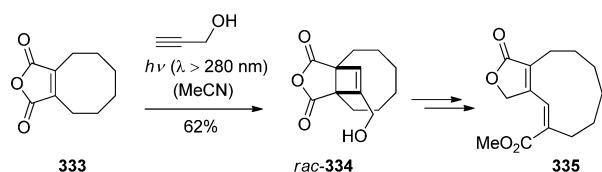
similar approach to amino acid derivatives based on maleic anhydride-derived cyclobutanes was reported by the Ortuño group.⁶¹¹ Wanner and co-workers prepared product **329** from an *N*-trifluoroacetyl protected 3-pyrroline en route to γ -aminobutyric acid analogues.⁶¹² Due to the symmetry of maleic anhydride, there is no regioselectivity issue and the relative configuration is *cis*-*anti*-*cis* for cyclic olefins and *cis*-*anti*-*trans* for acyclic olefins. An example for the latter relative configuration is found in photocycloaddition product *rac*-**330** obtained from 1,4-dichloro-2-butene. The compound was used as a key intermediate in the first synthesis of (\pm)-sceptrin (*rac*-**332**) by Birman et al.⁶¹³

There is ample precedence for maleic anhydride photocycloaddition products⁶¹⁴ as precursors in natural products synthesis. Cyclobutane *rac*-**331** served this purpose in Greaney's total synthesis of (\pm)-merrilactone A and (\pm)-anisactone A.⁶¹⁵ Further examples for synthetic applications include an access to erythrinan alkaloids by the Simpkins group,⁶¹⁶ another approach to (\pm)-merrilactone A by Inoue et al.,^{617,618} and the preparation of novel 2-azabicyclo[2.1.1]hexanes by Huet and co-workers.^{619,620}

The group of Booker-Milburn has a long-standing interest in the intermolecular [2 + 2] photocycloaddition of cycloalkane-

annulated maleic anhydrides.^{621–623} This interest was originally spurred by the idea to generate the eight-membered ring system of sesquiterpenes by ring opening of appropriate cyclobutane precursors, which were in turn prepared from 3,4,5,6-tetrahydrophthalic anhydride. In more recent work, Booker-Milburn and co-workers showed that cyclobutene products obtained from propargylic alcohol (e.g., **333** → *rac*-**334**) can serve as precursors for a thermally induced conrotatory ring opening.⁶²⁴ In the case of *rac*-**334**, this sequence led to trans-configured ten-membered ring **335** (Scheme 107). When the precursor compounds contained

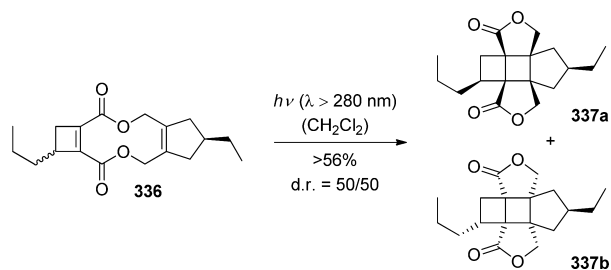
Scheme 107. Formation of Cyclobutene Photocycloaddition Product *rac*-334** and its Consecutive Reaction to Cyclodecadiene **335****



smaller rings, formal disrotatory ring-opening products were isolated, which are likely to be formed, however, by a sequence of conrotatory ring opening/rearrangement.

White et al. employed an intriguing sequence of [2 + 2] photocycloaddition and thermal [2 + 2] cycloreversion for the synthesis of (+)-byssochlamic acid.^{625,626} The pivotal photochemical step was the intramolecular reaction of enantiopure diesters **336**, which were used as 50/50 mixture of epimers (Scheme 108). The photocycloaddition gave consequently a

Scheme 108. Pivotal Photochemical Step in the Synthesis of (+)-Byssochlamic Acid



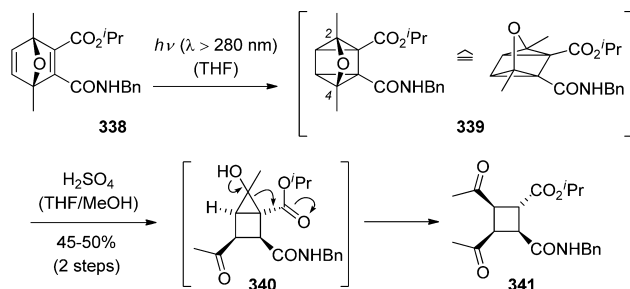
diastereomeric product mixture of **337a** and **337b** based on the respective *exo* approach of the olefins relative to the existing stereogenic centers. The [2 + 2] cycloreversion occurred horizontally to produce immediate the respective di-2-(*5H*)-furanones, which could be stereoconvergently transformed into the natural product.

The reaction of diesters **336** is reminiscent of the intermolecular [2 + 2] photocycloaddition of dimethyl-1-cyclobutene-1,2-dicarboxylate and cyclohexene as reported by Williams et al.⁶²⁷ The cyclobutane product underwent rapid ring opening to a cyclodecadiene intermediate, which in turn was converted into the respective trans-cyclohexyl-1,2-bisacrylate by a Cope rearrangement.

The intramolecular [2 + 2] photocycloaddition of oxabicyclic maleic acid derivatives^{628,629} was a key feature in a comprehensive synthetic approach to (–)-sceptrin (**332**, Figure 16) and several related dimeric pyrrole-imidazole alkaloids by the Baran group.^{630–632} The protocol is illustrated by the

reaction of the enantioenriched (75% *ee*) ester amide **338** (Scheme 109), which was obtained via the acid from the *meso*-

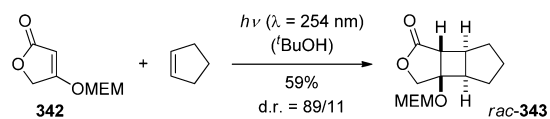
Scheme 109. Access to Cyclobutane **341 via Oxaquadricyclane **339****



dimethylester by hydrolytic desymmetrization with pig liver esterase. Intramolecular [2 + 2] photocycloaddition led to oxaquadricyclane **339**, which was immediately subjected to an acid-catalyzed fragmentation cascade. In the event, protonation of the basic amide oxygen atom leads to scission of the adjacent C–C bond and of the bond between the bridging oxygen atom and carbon atom C2. The resulting cation forms alcohol **340**, which undergoes retro-aldol cleavage to generate the desired cyclobutane **341**. The compound was enantiopure (>95% *ee*) after recrystallization.

3.4.1.4. Tetric Acid Derivatives. Esters of tetric acid (tetricates) were investigated by our group when searching for UV-active enolether surrogates.⁶³³ Although originally conceived to react in an intramolecular [2 + 2] photocycloaddition reaction, intermolecular reactions were found to be feasible and occurred with cyclic olefins expectedly to the *cis*-anti-*cis* products (e.g., **342** → *rac*-**343**, MEM = methoxyethoxymethyl; Scheme 110).^{634–636} Surprisingly, direct excitation at short

Scheme 110. Intermolecular [2 + 2] Photocycloaddition of Tetricate **342**

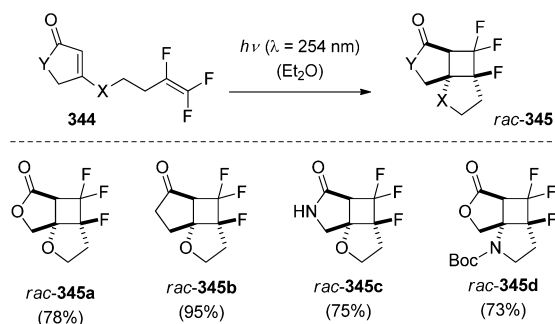


wavelength ($\lambda = 254$ nm) turned out to be superior to a sensitized protocol. If appropriately protected, tetricic amides turned out also to be suitable substrates.⁶³⁷

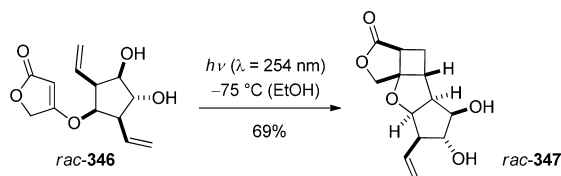
The lactone unit provides intrinsically two exit vectors for further functionalization. In view of an increasing interest in fluorinated scaffolds for pharmaceutical applications, it was attempted to involve fluorinated olefins in intramolecular [2 + 2] photocycloaddition reactions (Scheme 111).⁶³⁸ It was found that even the highly electron-deficient trifluorovinyl group was prone to attack by photoexcited enones. Products *rac*-**345** were obtained in high yields by intramolecular [2 + 2] photocycloaddition of substrates **344**.

In studies toward the total synthesis of the sesquiterpene (\pm)-punctaporonin C, various enantio- and diastereoselective photocycloaddition approaches were investigated.^{639–641} An intriguing result was the observation that the tetricic acid ester *rac*-**346** of a divinylcyclopentane triol underwent a diastereotopos-selective intramolecular [2 + 2] photocycloaddition, which yielded product *rac*-**347** in 69% yield (Scheme 112). Attack occurred selectively at one of the two diastereotopic

Scheme 111. Intramolecular [2 + 2] Photocycloaddition of Various Enones to a Trifluoro-Substituted Olefin



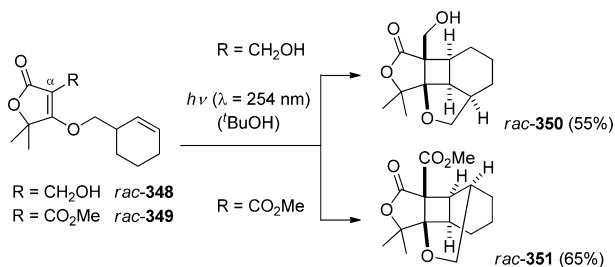
Scheme 112. Diastereotopos-Differentiating [2 + 2] Photocycloaddition of Tetronate *rac*-346



bonds, presumably due to a preferred conformation of the substrate in the polar solvent ethanol. The other diastereoisomer was formed in 20% yield (total yield 89%, d.r. = 78/22). A protected analogue of product *rac*-347 served as key intermediate in the total synthesis of the natural product.

Synthetic studies related to cembranoid diterpenes included the [2 + 2] photocycloaddition of several α -substituted tetronates.^{642–644} With various R groups, the expected straight regioselectivity was observed (e.g., *rac*-348 \rightarrow *rac*-350). An ester group in α -position altered the regioselectivity completely, and substrate *rac*-349 delivered exclusively the crossed product *rac*-351 (Scheme 113). It was speculated that the ester group

Scheme 113. Divergent Regioselectivity in the Intramolecular [2 + 2] Photocycloaddition of Tetronates *rac*-348 and *rac*-349

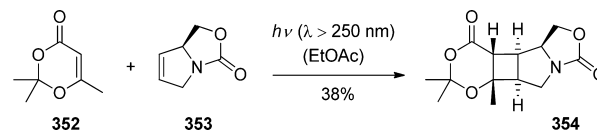


stabilizes the intermediate 1,4-diradical and enables a better selection toward the sterically less hindered product via retrocleavage pathways.

3.4.1.5. 1,3-Dioxin-4-ones. 1,3-Dioxin-4-ones represent ideal surrogates for the enol form of β -ketoacids and are bound, in the spirit of the de Mayo reaction, to undergo retro-aldol fragmentation upon hydrolysis. In the last decades, interest in 1,3-dioxin-4-ones with a stereogenic center in 2-position has ceased, but it should be mentioned as an option to obtain enantiopure photocycloaddition products.⁶⁴⁵ The sequence of [2 + 2] photocycloaddition/retro-aldol reaction has, however, remained a useful tool in organic synthesis. Parsons and co-

workers employed the intermolecular [2 + 2] photocycloaddition in an access to kainic acid and its derivatives (Scheme 114).^{646,647} 3-Pyrroline 353 was shown to react with 1,3-dioxin-

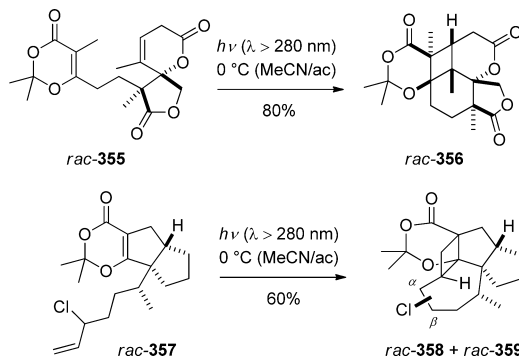
Scheme 114. Intermolecular [2 + 2] Photocycloaddition of 1,3-Dioxin-4-one 352 with a Chiral 3-Pyrroline



4-one 352 in a diastereoselective fashion to produce cyclobutane 354. The yield from the fact that the relatively valuable olefin 353 was employed only in moderate excess relative to the dioxinone. While the use of 5–10 equiv of an olefin is not uncommon in intermolecular [2 + 2] photocycloaddition reactions, only two equivalents were used in the present case. Subsequent retro-aldol cleavage was successful under basic or acidic conditions.

The total syntheses of (\pm)-saudin^{648,649} and (\pm)-ingenol^{650–653} by Winkler and co-workers are classics in the application of dioxinone/retro-aldol chemistry.²²⁷ They have been discussed in more detail in previous reviews,^{30,65} and it may thus be sufficient to depict here only the photochemical key steps. Sensitized conditions (acetone as cosolvent) were employed in both reactions, and the facial diastereoselectivity was excellent. While the reaction *rac*-355 \rightarrow *rac*-356 to the saudin intermediate proceeded smoothly, an unexpected complication was found in the reaction of the chlorinated substrate *rac*-357, which was employed as a mixture of diastereoisomers (Scheme 115). The chlorine atom was

Scheme 115. Photochemical Key Steps En Route to (\pm)-Saudin and (\pm)-Ingenol

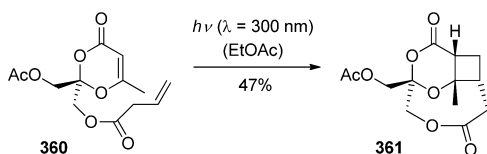


found not only at the expected carbon atom in α -position (product *rac*-358) to the cyclobutane ring but also at the β -position (product *rac*-359; r.r. = *rac*-358/*rac*-359 = 71/29). The result was explained by an intramolecular hydrogen abstraction which occurred in one diastereoisomer of the starting material and which led to isomerization. The other diastereoisomer reacted cleanly to *rac*-358.

An enantioselective access to chiral dioxinones was described by Sato and co-workers from the respective *meso*-2,2-hydroxymethyl-1,3-dioxin-4-ones.^{654,655} Lipase-catalyzed acetylation led to the respective chiral monoacetates with high enantioselectivity. Attachment of an alkenoyl group to the free hydroxy group generated substrates for an intramolecular

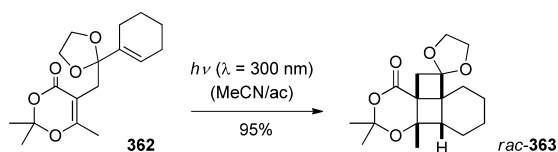
[2 + 2] photocycloaddition (Scheme 116). Compound **360** for example gave with high cyclic stereocontrol cyclobutane **361**.

Scheme 116. Diastereoselective Intramolecular [2 + 2] Photocycloaddition of 1,3-Dioxin-4-one **360**



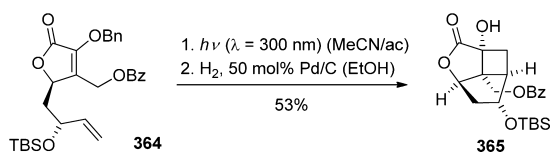
The Hiemstra group has employed 2(*5H*)-furanone as a chromophore in their quest to construct the strained bicyclo[2.1.1]hexane core of solanoeclepin A (see Scheme 99). The chromophore was also attached as 1,3-dioxin-4-one to the other end of the 2(*5H*)-furanone unit.⁵⁶⁴ In other approaches the 1,3-dioxin-4-one was employed as the only chromophore.⁶⁵⁶ In a methodology-oriented study, it was found⁶⁵⁶ that the crossed photocycloaddition product is not always preferred when a C₂-fragment was employed as a linker. Substrate **362** for example gave exclusively the straight product *rac*-**363** with a bicyclo[2.2.0]hexane core (Scheme 117).

Scheme 117. Formation of a Strained Bicyclo[2.2.0]hexane Core by an Intramolecular [2 + 2] Photocycloaddition



3.4.1.6. Others. Conjugation of a heteroatom in 3-position of a 2(*5H*)-furanone leads to minimal changes in the photochemical properties of the substrate. An example for an intramolecular [2 + 2] photocycloaddition under sensitized conditions is shown in Scheme 118. The reaction of substrate

Scheme 118. Intramolecular [2 + 2] Photocycloaddition of 3-Benzyloxy-2(*5H*)-furanone **364 En Route to (+)-Lactiflorin**



364 (Bn = benzyl, Bz = benzoyl) gave two regioisomers in a ratio of r.r. = 75/25. Separation of the major straight isomer was best achieved after hydrogenolysis. Alcohol **365** was obtained as a single product and served as the aglycon in the synthesis of the terpene glycoside (+)-lactiflorin.^{657,658}

In the intermolecular [2 + 2] photocycloaddition of 3-halo-(*5H*)-furanones **366** and **367** (Figure 17), an improved facial diastereoselectivity was recorded compared to the parent compound (**299**, Scheme 96, X = H). However, the chemoselectivity and also the yield were found to decrease.⁵⁴⁸ Piva and co-workers studied the intramolecular [2 + 2] photocycloaddition of bis-*O,O*-alkenyl ascorbic acid derivatives such as **368**.⁶⁵⁹ The compounds can be envisaged as tetronate analogues, and the same irradiation conditions ($\lambda = 254$ nm)

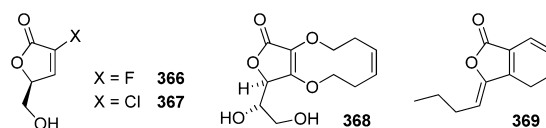
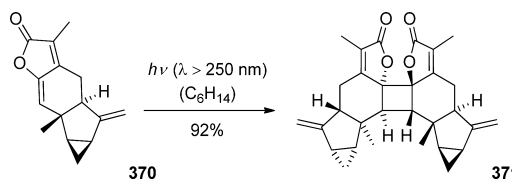


Figure 17. Structures of 3-halo-2(*5H*)-furanones **366**, **367**, of ascorbic acid derivative **368**, and of (*Z*)-ligustilide (**369**).

were employed as for this compound class. The expected transannular reactions occurred with high yield but with low facial diastereoselectivity.

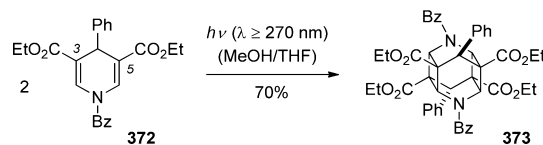
There is an increasing number of $\alpha,\beta,\gamma,\delta$ -unsaturated lactones, which are found in nature and which are speculated to undergo [2 + 2] photodimerization reactions. Delgado and co-workers studied the photochemistry of (*Z*)-ligustilide (**369**) and found among other products riligustilide, a naturally occurring photodimer.⁶⁶⁰ Along the same lines, Zhu, Ye, Chen, and co-workers isolated the natural product (–)-flueggeidine, a C₂-symmetric indolizidine alkaloid dimer, and established its formation by [2 + 2] photodimerization of (+)-virosecurinine.^{661,662} The natural product (+)-chloranthalactone F (**371**) was synthesized by Qian and Zhao from (+)-chloranthalactone A (**370**) following a biomimetic photochemical route (Scheme 119).⁶⁶³

Scheme 119. Synthesis of (+)-Chloranthalactone F (371**) from (+)-Chloranthalactone A (**370**) by [2 + 2] Photodimerization**



The photophysical properties of α,β -unsaturated esters do not differ significantly from α,β -unsaturated lactones. Since *cis*/*trans*-isomerization is not a viable pathway for energy dissipation in cyclic olefins, α,β -unsaturated esters with an endocyclic double bond can react smoothly in [2 + 2] photodimerization or [2 + 2] photocycloaddition reactions. Hilgeroth and co-workers have extensively studied the [2 + 2] photodimerization of 4-aryl-1,4-dihydropyridines with ester groups in the 3- and 5-position (Scheme 120).^{664–671} Upon

Scheme 120. Sequence of [2 + 2] Photodimerization/Intramolecular [2 + 2] Photocycloaddition upon Irradiation of Dihydropyridine **372**

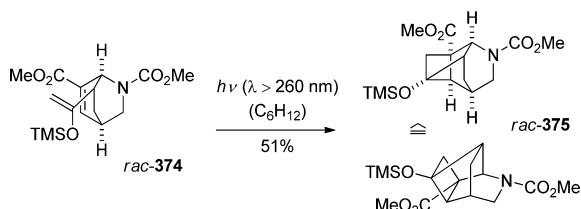


short wavelength irradiation, a sequence of [2 + 2] photodimerization/intramolecular [2 + 2] photocycloaddition was initiated, which led to the respective cage dimers (e.g., **372** → **373**). At longer wavelength irradiation, the reaction could be stopped at the stage of the [2 + 2] photodimer with a single cyclobutane ring. Various derivatives of the former compound class showed activity as nonpeptidic HIV-1 protease inhibitors^{664,666} or as P-glycoprotein (P-gp) inhibitors.^{669–671}

Similar photodimerization reactions to cage compounds were reported by Yan and co-workers for dihydropyridine compounds and for 4-aryl-4*H*-pyrans.^{672,673}

Intramolecular [2 + 2] photocycloaddition reactions of α,β -unsaturated esters were investigated by Choi and White in the context of a photochemical access to azatetracyclodecanes.⁶⁷⁴ They found the regioselectivity to vary depending on the substitution pattern of the 2-azabicyclo[2.2.2]octene substrates. Silyl enol ether *rac*-374 was reported to give exclusively the thermally stable crossed product *rac*-375 with an azatetracyclo[6.1.1.0^{2,7}.0^{5,9}]decane skeleton (Scheme 121). Intramolecular

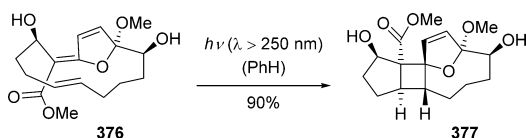
Scheme 121. Intramolecular [2 + 2] Photocycloaddition of 2-Azabicyclo[2.2.2]octene *rac*-374



[2 + 2] photocycloaddition reactions of related acrylic acids or acrylates with an endocyclic double bond were studied by Booker-Milburn et al.,^{675,676} Hsu et al.,⁶⁷⁷ and by the Panek group.⁶⁷⁸

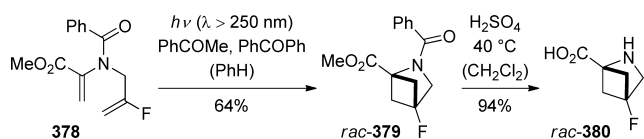
It has been speculated that bielschowskysin (**40**, Scheme 12) is formed from (+)-rubifolide by oxidation and a subsequent transannular [2 + 2] cycloaddition reaction.^{679,680} The Nicolaou group showed that an intramolecular [2 + 2] photocycloaddition of an appropriate ester is indeed feasible, and cyclobutane **377** was obtained upon irradiation of substrate **376** with high diastereoselectivity (Scheme 122).⁶⁸¹

Scheme 122. Synthesis of the Bielschowskysin Core by Intramolecular [2 + 2] Photocycloaddition



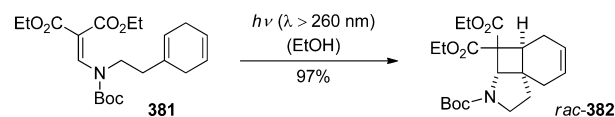
If rapid five-membered ring closure is feasible, even noncyclic α,β -unsaturated esters can undergo intramolecular [2 + 2] photocycloaddition. In this context, several studies were concerned with an improved photochemical access⁶⁸² to 2,4-methanoproline and its derivatives.^{683–685} Mykhailiuk et al. employed an intramolecular [2 + 2] photocycloaddition reaction to the synthesis of 4-fluoro-2,4-methanoproline (*rac*-380).⁶⁸⁶ Sensitized irradiation of acrylate **378** led to the ester of the *N*-protected product *rac*-379, which was hydrolyzed to the target compound *rac*-380 (Scheme 123).

Scheme 123. Synthesis of 4-Fluoro-2,4-methanoproline (*rac*-380) by Intramolecular [2 + 2] Photocycloaddition



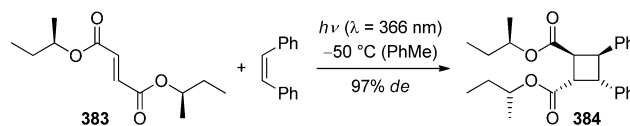
While the synthesis of 4-fluoro-2,4-methanoproline (*rac*-380) requires a crossed photocycloaddition, straight photocycloaddition reactions are observed if the tether between the α,β -unsaturated ester and the olefin contains three atoms. Pyrrolidine derivative *rac*-382 was generated smoothly from acyclic precursor **381** upon irradiation with Corex-filtered UV light (Scheme 124). White and co-workers employed compounds such as *rac*-382 as precursors for spiropyrrolines upon retro-Mannich cleavage.⁶⁸⁷

Scheme 124. Intramolecular [2 + 2] Photocycloaddition of β -Aminoalkylidene Malonate **381**



Unlike maleic acid derivatives, the respective fumarates cannot be embedded in a cyclic array. Intermolecular [2 + 2] photocycloaddition reactions have still been observed. Xiao and co-workers reported recently on the sensitized [2 + 2] photodimerization of alkoxy carbonyl-substituted 3-methylideneoxindoles.⁶⁸⁸ The Inoue group carefully investigated the influence of various physical parameters (e.g., irradiation wavelength, temperature, and solvent polarity) on the intermolecular [2 + 2] photocycloaddition of chiral fumarate **383** (Scheme 125).^{689–691} It was found that direct excitation via the stilbene

Scheme 125. Intermolecular [2 + 2] Photocycloaddition of Fumarate **383 and *cis*-Stilbene upon Irradiation of the CT Complex**



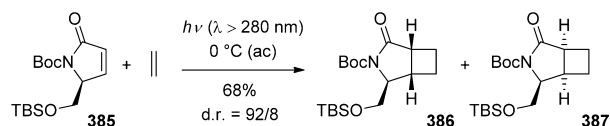
chromophore led to a different facial diastereoselectivity than excitation of the charge-transfer (CT) complex at long wavelength, which gave with *cis*-stilbene at low conversion exclusively product **384**. The results support the hypothesis that the excited CT complex and the conventional exciplex differ in structure and reactivity.

3.4.2. α,β -Unsaturated Lactams. In comparison to the analogous lactones, the photocycloaddition chemistry of α,β -unsaturated lactams has been less extensively used. Mechanistically, there is little difference to lactone [2 + 2] photocycloaddition chemistry. The large majority of the substrates discussed in this chapter react via the corresponding T_1 state. As in section 3.4.1, the discussion of section 3.4.2 starts with nonconjugated substrates (subsection 3.4.2.1) and moves via the heterocycles 2-pyridones, quinolones (subsection 3.4.2.2) and maleimides (subsection 3.4.2.3) to 4-pyrimidinones (subsection 3.4.2.4) and others (subsection 3.4.2.5).

3.4.2.1. Without Further Conjugation. Initial work on the intermolecular [2 + 2] photocycloaddition of α,β -unsaturated γ -lactams was performed by Meyers and Fleming in the context of a synthetic approach to (–)-grandisol.⁶⁹² Margaretha and co-workers studied the intermolecular [2 + 2] photocycloaddition chemistry of an *N*-unprotected γ -lactam, 5,5-dimethyl-1*H*-pyrrol-2(5*H*)-one, and of its *N*-acyl derivatives.^{693,694} In later work, the Ohfuné group found a high facial diastereoselectivity in the [2 + 2] photocycloaddition reactions of chiral *N*-Boc

protected pyrrol-2(*SH*)-ones such as **385** (Scheme 126). Cyclic stereocontrol guides the attack of ethylene to the more

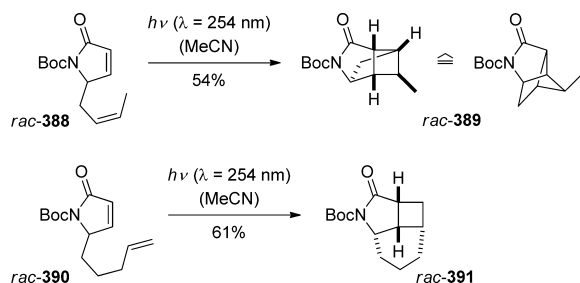
Scheme 126. Facial Diastereoselectivity in the Intermolecular [2 + 2] Photocycloaddition of Pyrrol-2(*SH*)-one **385**



accessible bottom face of the molecule, and the formation of diastereoisomer **386** was preferred over **387**.⁶⁹⁵ Similar results were recently found for substrate **385** in synthetic efforts toward cyclobutane-fused azanucleosides.⁶⁹⁶ A chiral phenylethyl substituent at the nitrogen atom of an otherwise unsubstituted pyrrol-2(*SH*)-one resulted in only low facial diastereoselectivity. Nonetheless, as disclosed by Aitken and co-workers, the intermolecular [2 + 2] photocycloaddition products can be nicely employed for the synthesis of all stereoisomers of 2-(aminomethyl)cyclobutane-1-carboxylic acid.^{697,698}

The intramolecular [2 + 2] photocycloaddition of various *N*-Boc protected pyrrol-2(*SH*)-ones was investigated by Margaretha and co-workers.^{699,700} They found for several substrates not only a high facial diastereoselectivity but also a clear regioselectivity preference. As expected from the rule of five (see Scheme 45),^{278–280} a but-2-enyl substituent in the 5-position (Scheme 127, substrate *rac*-**388**) led upon direct

Scheme 127. Intramolecular [2 + 2] Photocycloaddition of Pyrrol-2(*SH*)-ones *rac*-388** and *rac*-**390****

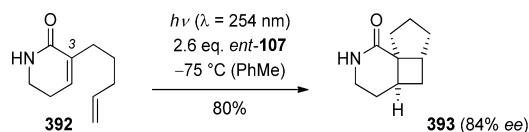


irradiation exclusively to the crossed product *rac*-**389**.⁷⁰¹ The relative configuration of the double bond was not retained, which supports a triplet reaction pathway (see Scheme 46). The pent-4-enyl substituted pyrrol-2(*SH*)-one *rac*-**390** yielded the straight product *rac*-**391**.

Five- and six-membered α,β -unsaturated lactams were probed in our laboratories toward a potential enantioselective photocycloaddition in the presence of template **107** and *ent*-**107** (Figure 7).^{702–704} It was found that significant enantioselectivities could be obtained for substrates with the alkenyl side chain in the 3-position such as 3-(pent-4-enyl)-5,6-dihydro-1*H*-pyridin-2-one (**392**). The reaction led with high enantioselectivity to photocycloaddition product **393** (Scheme 128).

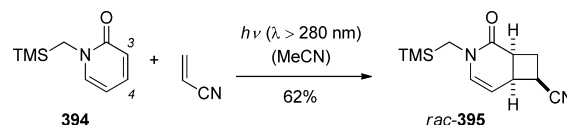
3.4.2.2. 2-Pyridones and Quinolones. Somekawa and co-workers studied the [2 + 2] photocycloaddition of 2-pyridones both in its intermolecular⁷⁰⁵ and its intramolecular⁷⁰⁶ version. The regioselectivity of the intermolecular [2 + 2] photocycloaddition is variable and, like for the related 2-pyridones, it

Scheme 128. Enantioselective Intramolecular [2 + 2] Photocycloaddition of 5,6-Dihydro-1*H*-pyridin-2-one **392 in the Presence of Chiral Template *ent*-**107****



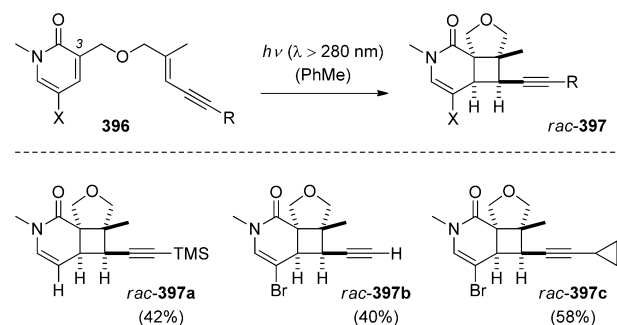
is complicated by [4 π] photocyclization, [4 + 4] photodimerization, and formal [4 + 2] cycloaddition reactions. Free 2-pyridones reacted with electron-deficient alkynes at the 5,6-double bond (vide infra) but yields remained low.⁷⁰⁷ In recent work by Mariano, Yoon, and co-workers, the trimethylsilyl substituted pyridone **394** was found to react with acrylonitrile to produce *rac*-**395** in good yield (Scheme 129).⁷⁰⁸

Scheme 129. Intermolecular [2 + 2] Photocycloaddition of Pyridone **394 with Acrylonitrile**



During the past decade, the Sieburth group investigated the inter- and intramolecular [2 + 2] photocycloaddition of pyridones with enynes.^{709–711} The intramolecular reaction variant turned out to deliver in several cases a reliable access to [2 + 2] photocycloaddition products. The 3-substituted pyridones **396** for example reacted to the respective straight cyclobutane products *rac*-**397** in moderate yields and with high diastereoselectivity (Scheme 130).⁷¹¹

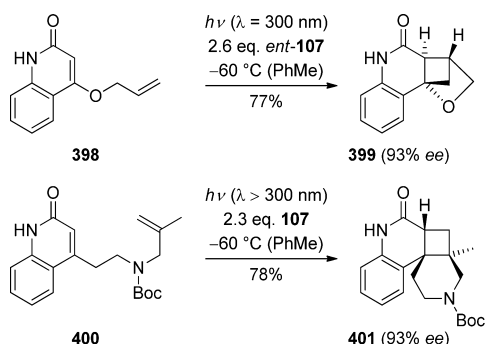
Scheme 130. Intramolecular [2 + 2] Photocycloaddition of 2-Pyridones **396**



Initial work on the photocycloaddition chemistry of quinolones dates back to the 1960s when the first [2 + 2] photodimerization^{712–714} and [2 + 2] photocycloaddition^{715,716} reactions were reported. Mechanistically, it has been well-established that direct excitation of quinolones leads via an effective ISC to the T₁ state, from which subsequent reactions occur.⁷¹⁷ Inter- and intramolecular [2 + 2] photocycloaddition reactions of quinolones were intensively studied in the 1980s by the groups of Naito and Kaneko and of Sugimoto.^{718–723} Interest in quinolone photochemistry was spurred in the last two decades by the discovery that this compound class is well-suited to bind to chiral templates **107** and *ent*-**107** (see Figure 7) via hydrogen bonds. In 2000, it was found in our laboratory that the reaction of 4-allyloxyquinolone (**398**) could be

performed with high enantioselectivity in the presence of *ent*-**107**, and product **399** was obtained with high enantioselectivity (Scheme 131).⁷²⁴ The key to the success of this and related

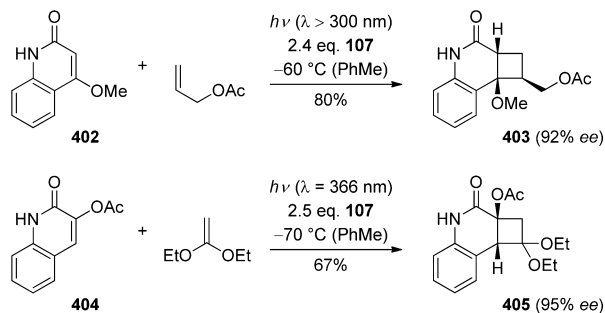
Scheme 131. Enantioselective Intramolecular [2 + 2] Photocycloaddition of 4-Substituted Quinolones



reactions was the use of a nonpolar solvent and a low reaction temperature. Both factors favor hydrogen bonding between substrate and template. Immobilized chiral templates could be used with similar success to mediate the enantioselective transformation **398** → **399**.⁷²⁵ Other intramolecular reactions were studied,^{726–728} and it was shown that not only crossed photocycloaddition products such as **399** but also straight products (e.g., **400** → **401**) could be cleanly obtained.

The concept of template-based enantioselective [2 + 2] photocycloaddition chemistry was expanded to intermolecular reactions. Many olefins added cleanly to quinolones with a general preference in the reaction of 4-methoxyquinolone (**402**) for HT products such as **403** (Scheme 132).⁷²⁹ The

Scheme 132. Enantioselective Intermolecular [2 + 2] Photocycloaddition of Quinolones **402** and **404**

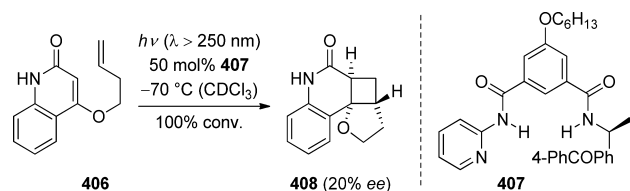


intermolecular [2 + 2] photocycloaddition to a 4-aminoethyl-substituted quinolone was employed as a key step in the first enantioselective synthesis of the *Melodinus* alkaloid (+)-melo-scine.^{730–732} 3-Acetoxyquinolone (**404**) underwent clean enantioselective photocycloaddition reactions to ketene acetals. A product related to **405** was employed as the key intermediate in the first total synthesis of (–)-pinolinone.⁷³³

The relatively low triplet energy of quinolones⁷³⁴ invites an indirect excitation of the quinolone triplet chromophore by sensitization. If a chiral sensitizer could be devised to exert sufficient enantioface differentiation in the [2 + 2] photocycloaddition, an enantioselective catalytic approach to chiral cyclobutanes would be feasible. Previous attempts to employ chiral ketones for enantioselective photochemical reactions had seen little success, however.^{480,735–737} In 2003, Krische and co-

workers reported a low enantioselectivity for the intramolecular reaction **406** → **408**, employing the chiral benzophenone **407** as the catalyst (Scheme 133).⁷³⁸

Scheme 133. Intramolecular [2 + 2] Photocycloaddition of Quinolone **406** in the Presence of Chiral Sensitizer **407**



Simultaneously, work in our laboratories was devoted toward the synthesis of chiral sensitizers, which would incorporate the 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeleton of templates **107** and *ent*-**107**. In successive order, the benzophenone **409**,⁷³⁹ the xanthenes **410** and *ent*-**410**,⁷⁴⁰ and the thioxanthone **411**⁷⁴¹ were synthesized (Figure 18).

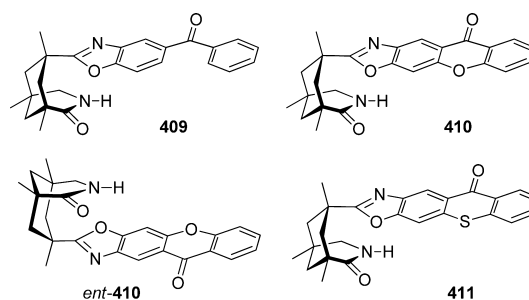
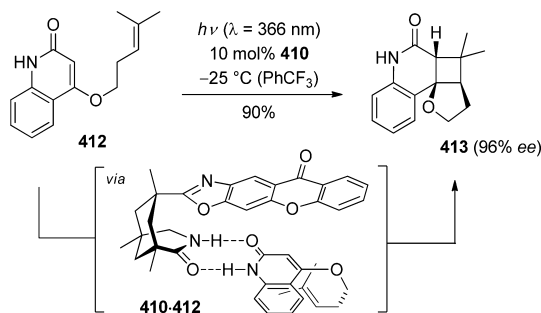


Figure 18. Structures of chiral sensitizers **409**–**411** with a 1,5,7-trimethyl-3-azabicyclo[3.3.1]nonan-2-one skeleton.

While benzophenone **409** was less suitable for quinolone [2 + 2] photocycloaddition reactions, xanthone **410** and its enantiomer *ent*-**410** turned out to be efficient chiral catalysts. The previously mentioned reaction **406** → **408** (Scheme 133) could be performed in 91% *ee* at a catalyst loading of 10 mol%.⁷⁴⁰ Related reactions (e.g., **412** → **413**) (Scheme 134)

Scheme 134. Catalytic Enantioselective Intramolecular [2 + 2] Photocycloaddition of Quinolone **412**

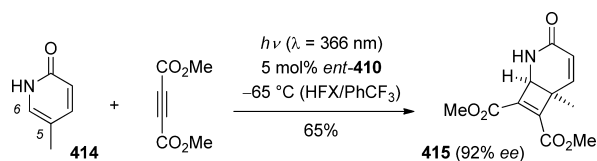


proceeded with even higher enantioselectivity.⁷⁴² It turned out that several factors contribute to the success of the chiral sensitizers in quinolone [2 + 2] photocycloaddition reactions. Not only is a high association required but also the subsequent reaction (i.e., the cyclization of the T_1 intermediate to the respective diradical) must be more rapid than the dissociation of the substrate from a complex such as **410**–**412**.⁷⁴³ In

addition, the irradiation wavelength must be chosen such that the substrate is not directly excited. Rather, energy transfer by electron exchange⁴⁵ has to be the exclusive pathway to generate a photoexcited triplet quinolone. Solvents must not contain labile C–H bonds to avoid destruction of the xanthere by hydrogen abstraction.

The solvent of choice for xanthone-sensitized quinolone [2 + 2] photocycloaddition was trifluorotoluene, which solidifies, however, at $-29\text{ }^{\circ}\text{C}$. It was found that a solvent mixture of hexafluoro-*meta*-xylene (HFX) and trifluorotoluene has a significantly lower melting point. In this solvent mixture, the enantioselective intermolecular [2 + 2] photocycloaddition of various acetylenedicarboxylates to 2-pyridones was successfully performed (Scheme 135).⁷⁴⁴ Yields and regioselectivities in

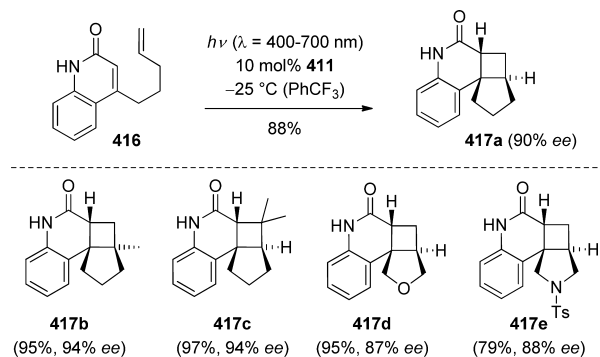
Scheme 135. Catalytic Enantioselective Intermolecular [2 + 2] Photocycloaddition of Pyridone 414



favor of the 5,6-addition product were significantly improved as compared to the original racemic protocol.⁷⁰⁷ Most notable is perhaps that the catalyst loading could be decreased to 2.5–5 mol%, while the enantioselectivity remained high and exceeded in several cases 90% *ee* (e.g., **414** → **415**).

The triplet energy of thioxanthere, which is tabulated⁷⁴⁵ for the parent compound as $E_T = 265\text{ kJ mol}^{-1}$, is lower than the triplet energy of xanthone but still appeared sufficiently high to catalyze [2 + 2] photocycloaddition reactions of quinolones. Indeed, it could be recently shown that 4-alkenyl-substituted quinolones such as **416** are amenable to an enantioselective intramolecular [2 + 2] photocycloaddition reaction in the presence of thioxanthere **411** (Scheme 136).⁷⁴¹ Products

Scheme 136. Visible-Light-Induced Enantioselective [2 + 2] Photocycloaddition to Products 417 Catalyzed by Chiral Thioxanthere 411

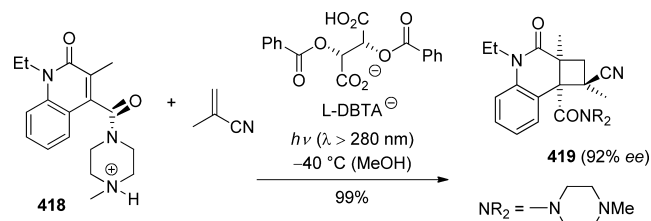


417 were obtained in high yield with excellent enantioselectivity. A benefit of catalyst **411** is its long wavelength absorption, which enabled the reactions to be performed with visible light.

An alternative route to enantioselectively access quinolone photocycloaddition products relies on the chirality transfer from an axially chiral substrate. Sakamoto and co-workers successfully employed the “frozen chirality” approach (see

Scheme 105) to the intermolecular [2 + 2] photocycloaddition of several quinolones (Scheme 137).^{746,747}

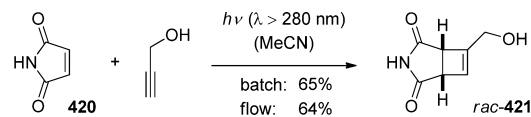
Scheme 137. Frozen Chirality Approach to the Intermolecular [2 + 2] Photocycloaddition of Quinolone Ammonium Salt 418



One recent example includes the use of a quinolone,⁷⁴⁸ which was crystallized as ammonium salt **418** of *L*-dibenzoyltartaric acid (DBTA). The chiral environment secured formation of the compound in a single enantiomeric form. Upon solvation at low temperature, the chirality was retained and a high enantioselectivity was observed for formation of product **419**.

3.4.2.3. Maleimides and Related Substrates. Intermolecular [2 + 2] photocycloaddition reactions of maleimides are long known¹⁸ but continue to attract attention from the synthetic community. The reaction with allene was employed by Mittendorf et al. for the synthesis of antifungal β -amino acids.⁷⁴⁹ Fujita and co-workers studied the intermolecular [2 + 2] photocycloaddition of *N*-cyclohexyl maleimide and fluoranthenes within a self-assembled chiral cage (up to 50% *ee*).⁷⁵⁰ *N*-Phenyl maleimide was employed to access a natural product-inspired scaffold by photocycloaddition to a tricyclic diene.⁷⁵¹ Very recently, Booker-Milburn and co-workers employed the reaction of maleimide (**420**) and propargylic alcohol, which they had first studied in the 1990s,^{621–623} as one of many photochemical reactions to quantify the productivity of a batch versus a flow process (Scheme 138).⁷⁵² The group had

Scheme 138. Comparison of Batch vs Flow in the Intermolecular [2 + 2] Photocycloaddition of Maleimide (420)

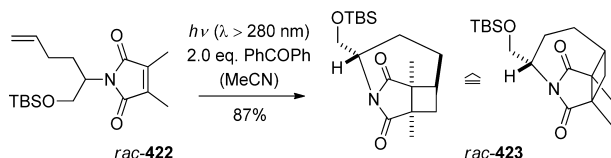


previously developed a practical flow reactor for continuous organic photochemistry,⁷⁵³ which was now compared to a batch reactor. Yields for product *rac*-**421** were essentially identical irrespective of whether the reaction was performed in batch or in flow. The same observation was made for several other photochemical (including [2 + 2] photocycloaddition) reactions. The authors stress, however, the advantage of flow photochemistry for large scale reactions, while batch photochemical reactors are said to be ideal for first-time reactions and their optimization.

In a combination of intermolecular and intramolecular [2 + 2] photocycloaddition reactions, Booker-Milburn and co-workers generated imide-cyclobutene containing macrocycles from *N*-alkynyl substituted maleimides.⁷⁵⁴ Continuing their interest in intramolecular maleimide [2 + 2] photocycloaddition,^{755–757} the same group could show that the reaction mode

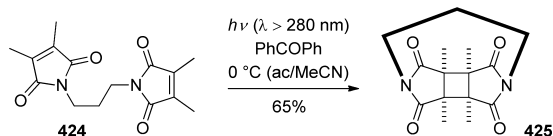
of the maleimide photocycloaddition can be altered by the mode of excitation.⁷⁵⁸ Direct irradiation of substituted maleimides such as *rac*-**422** led to [5 + 2] photocycloaddition products via a singlet pathway. If the reaction was performed in the presence of benzophenone, a triplet pathway was followed, which favored [2 + 2] photocycloaddition. In the present example (Scheme 139), the exclusive irradiation product was the cyclobutane *rac*-**423**.

Scheme 139. Sensitized Intramolecular [2 + 2] Photocycloaddition of Dimethylsubstituted Maleimide *rac*-**422**



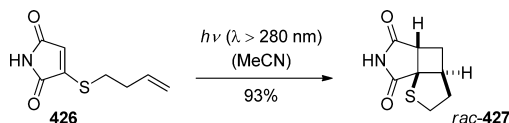
The intramolecular [2 + 2] photocycloaddition of carbon-tethered maleimides was investigated by Santelli and co-workers.⁷⁵⁹ Employing sensitizing conditions with acetone as cosolvent and a crystal of benzophenone, they achieved the synthesis of cage diimides from the respective maleimides (e.g., **424** → **425**) (Scheme 140).

Scheme 140. Intramolecular [2 + 2] Photocycloaddition of Tethered Maleimides **424** to Cage Diimide **425**



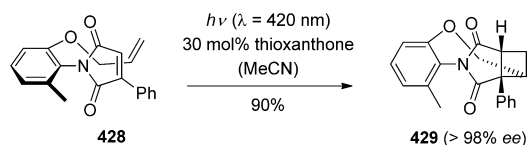
If maleimides carry an additional donor atom at the double bond, the longest wavelength absorption is shifted bathochromically and becomes more intense. The effect is particularly strong upon thio substitution as noted by Baker and co-workers.⁷⁶⁰ They observed smooth inter- and intramolecular [2 + 2] photocycloaddition reactions of thiomaleimides upon direct excitation. As an example, the intramolecular reaction of substrate **426** to cyclobutane *rac*-**427** is depicted in Scheme 141. Earlier observations on the facile photodimerization of oxygen-substituted maleimides may be explained similarly.⁷⁶¹

Scheme 141. Intramolecular [2 + 2] Photocycloaddition of Thiomaleimide **426** upon Direct Excitation



A general approach to enantiomerically pure maleimide photocycloaddition products was presented by the Sivaguru group.⁷⁶² Axially chiral *N*-aryl maleimides were separated into their enantiomers by chiral HPLC. Subsequent intramolecular [2 + 2] photocycloadditions were shown to proceed with excellent chirality transfer to deliver the respective cyclobutanes (e.g., **428** → **429**) (Scheme 142).

Scheme 142. Chirality Transfer in the Intramolecular [2 + 2] Photocycloaddition of Axially Chiral Maleimide **428**



3.4.2.4. 4-Pyrimidinones. The [2 + 2] photocycloaddition chemistry of thymine and uracil derivatives continues to be investigated in the context of DNA damage.^{763,764} As stated earlier, this work is not in the focus of the present review. Emphasis is rather put on synthetically relevant reactions. In this context, it is interesting to note that the [2 + 2] photocycloaddition reaction of isolated nucleosides shows relatively little facial diastereoselectivity.^{765–768} Haga, Ogura, and co-workers for example studied the reaction of 2'-deoxyuridine (**430a**) and thymidine (**430b**) with 2,3-dimethyl-2-butene.^{769,770} The former reaction was completely unselective giving products **431a** and **432a** in a ratio of 50/50 (Figure 19). The latter reaction showed a minor preference for

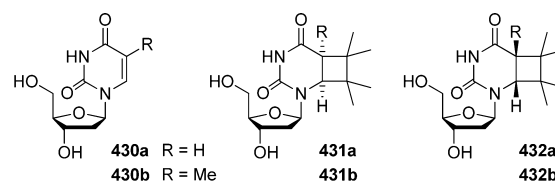


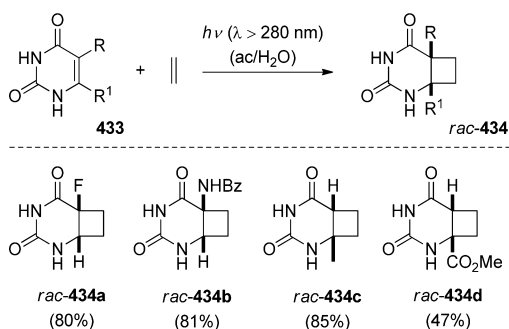
Figure 19. Structures of 2'-deoxyuridine (**430a**) and thymidine (**430b**) and of their [2 + 2] photocycloaddition products to 2,3-dimethyl-2-butene.

product **431b** (d.r. = 71/29) when performed under sensitized conditions. The rate constants for the intermolecular reactions were determined as $1.3\text{--}1.6 \times 10^9 \text{ M}^{-1} \text{ s}^{-1}$ and $4\text{--}5 \times 10^7 \text{ M}^{-1} \text{ s}^{-1}$.⁷⁷¹

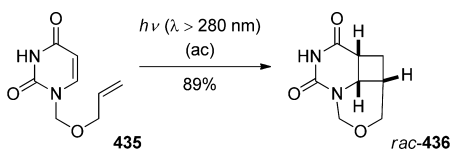
The diastereoselectivity of intramolecular reactions in which the olefin component was tethered to a hydroxy group of the nucleoside was found to be high.⁷⁷² The intramolecular [2 + 2] photocycloaddition of thymine glycoconjugates was used by Lindhorst and co-workers to prepare multivalent carbohydrates.⁷⁷³ The [2 + 2] photodimerization of isothiuronium-functionalized thymines exhibited high *syn* diastereoselectivity if performed in the presence of an appropriate anionic template.⁷⁷⁴

The group of Aitken has in recent years extensively explored the [2 + 2] photocycloaddition reaction of 4-pyrimidinones as an entry to conformationally constrained β -amino acids. The intermolecular reaction was studied with several 4-pyrimidinones.^{775–780} Upon irradiation in an acetone/water solution, uracil^{781,782} and thymine were shown to react with ethylene in good yield to the respective cyclobutanes. An array of substituted uracils **433** reacted equally well, and a few representative products *rac*-**434** are shown in Scheme 143. Methyl orotate underwent competitive [2 + 2] photodimerization, which reduced the yield of product *rac*-**434d**. The preparation of enantiomerically pure compounds was performed by a chiral auxiliary approach.^{775,783} In the absence of an external olefin, 4-pyrimidinones underwent [2 + 2] photodimerization as observed for 5- and 6-phenyluracil.⁷⁸⁴

The use of a labile tether enabled Aitken and co-workers to prepare 3-hydroxymethylated cyclobutanes with high simple

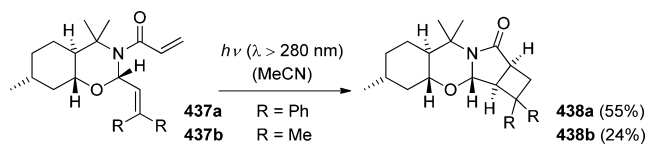
Scheme 143. Intermolecular [2 + 2] Photocycloaddition of 4-Pyrimidinones 433 and Ethylene


diastereoselectivity. Compound 435 for example delivered cleanly the desired tricyclic product *rac*-436 (Scheme 144).⁷⁸⁵

Scheme 144. Intramolecular [2 + 2] Photocycloaddition of 4-Pyrimidinone 435


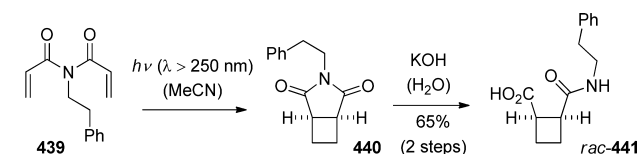
Very recently, it was shown in our laboratories that but-3-enyl orotates undergo an intramolecular [2 + 2] photocycloaddition reaction upon direct excitation at $\lambda = 300$ nm. At shorter wavelength, consecutive reactions were observed, which were initiated by Norrish type I cleavage.⁷⁸⁶

3.4.2.5. Others. Acyclic α,β -unsaturated amides were subjected successfully to intramolecular [2 + 2] photocycloaddition reactions. Pedrosa et al. prepared 3-azabicyclo[3.2.0]heptan-2-ones by a chiral auxiliary approach.⁷⁸⁷ High facial diastereoselectivity was observed in the reaction of 8-amino-menthol-derived acryloyl amides 437 (Scheme 145). The yield for the dimethylcyclobutane 438b was low due to photodecomposition.

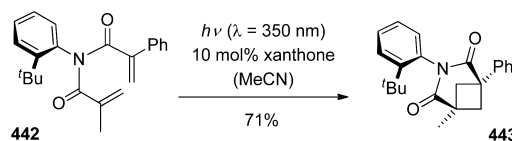
Scheme 145. Auxiliary-Induced Diastereoselectivity in the [2 + 2] Photocycloaddition to 3-Azabicyclo[3.2.0]heptan-2-ones 438


When searching for a method to prepare an unsymmetrically substituted 1,3-cyclobutandicarboxylic acid derivative, Miller et al. surprisingly found that imide 439 formed the straight photocycloaddition product 440 but not the expected crossed product (Scheme 146).⁷⁸⁸ The structure was proven by conversion to the monoamide *rac*-441, which was subjected to single-crystal X-ray analysis.

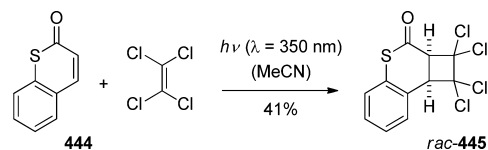
If the acryloyl units in related imides are α -substituted crossed intramolecular [2 + 2] photocycloaddition reactions prevail.⁷⁸⁹ This reaction was utilized by Sivaguru and co-workers as an entry to amino-bridged cyclobutanes.⁷⁹⁰ The axially chiral substrate 442 reacted with high facial diaster-

Scheme 146. Intramolecular [2 + 2] Photocycloaddition of Imide 439 to the Straight Product 440


eoselectivity to provide exclusively cyclobutane 443 (Scheme 147).

Scheme 147. Diastereoselective Intramolecular [2 + 2] Photocycloaddition of Axially Chiral Diimide 442


3.4.3. Thiolactones. Recent work on sulfur analogues of the compounds discussed in section 3.4.1 has been mainly concerned with thiocoumarins. Margaretha and co-workers studied the [2 + 2] photocycloaddition chemistry of 1-thiocoumarin (444) and of isothiocoumarin.^{217–219,602,603,791} Reactions of the former compound with olefins (e.g., with tetrachloroethylene to *rac*-445) (Scheme 148) were initiated by

Scheme 148. Intermolecular [2 + 2] Photocycloaddition of 1-Thiocoumarin (444) and Tetrachloroethylene


direct excitation, indicating that the ISC is more efficient than for coumarin. Isothiocoumarin reacted in solution only with electron deficient olefins and resembled isocoumarin in its reactivity (see Scheme 33).

The Margaretha group also investigated the site selectivity in several thiocoumarin-containing bichromophoric compounds.^{604,605,792,793} A few examples 446–448 are shown in Figure 20, with the more reactive bonds toward a [2 + 2] photocycloaddition with 2,3-dimethyl-2-butene being marked.

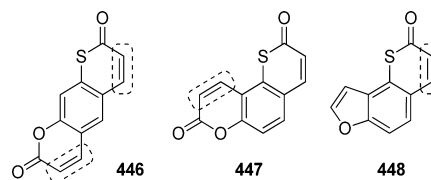


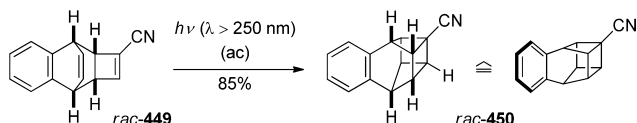
Figure 20. Structures of thiocoumarin-containing bichromophoric compounds and preferred site of [2 + 2] photocycloaddition reactions.

The preferred reaction at the coumarin site in compound 447 added further evidence to the hypothesis that the C=C bond closer to the heteroatom of the second heterocycle was more reactive.

3.5. Heteroanalogous Enones and Dienes

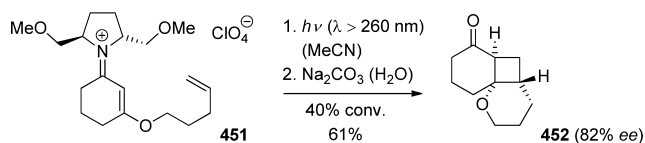
Although they can be formally envisaged as heteroanalogous enynes, acrylonitriles resemble in their photochemical behavior the respective α,β -unsaturated esters and amides. If the conjugated double bond is part of a cyclic ring, [2 + 2] photocycloaddition reactions can occur by sensitized excitation. Balci and co-workers employed the intramolecular reaction of various mono- and dicyanostituted cyclobutenes (e.g., *rac*-449 \rightarrow *rac*-450) (Scheme 149), as an entry to substituted benzobasketene derivatives.⁷⁹⁴

Scheme 149. Intramolecular [2 + 2] Photocycloaddition of Cyano-Substituted Cyclobutene *rac*-449



Iminium salts of α,β -unsaturated ketones have photochemically little in common with the respective carbonyl compounds. There is no $n\pi^*$ transition at long wavelength but only a strong $\pi\pi^*$ absorption ($\epsilon = 2-4 \times 10^4 \text{ M}^{-1} \text{ cm}^{-1}$) at $\lambda \cong 280 \text{ nm}$. With the expectation that consecutive intramolecular [2 + 2] photocycloaddition should occur at the singlet hypersurface, Mariano and co-workers studied initially the stereospecificity of this reaction.⁷⁹⁵ With dependence on the nature of the tether, it could be demonstrated that retention of the configuration was indeed possible (see Scheme 46). A remarkable degree of auxiliary-induced diastereoselectivity was found for the reaction of iminium ions derived from C_2 -symmetric chiral amines (Scheme 150).⁷⁹⁶ Compound 451 produced after hydrolysis

Scheme 150. Diastereoselective Intramolecular [2 + 2] Photocycloaddition of Iminium Salt 451



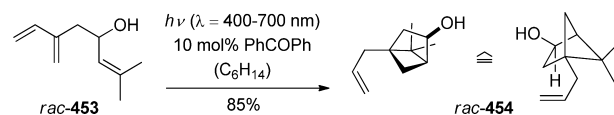
ketone 452 with 82% *ee* provided that the reaction was stopped at 40% conversion. Longer reaction times led to a decrease of the enantioselectivity.

Direct excitation of 1,3-dienes is normally not feasible, and photocycloaddition of this compound class is preferentially performed in the presence of a sensitizer. For studies on the thermal fragmentation of various cyclobutenes, the group of von E. Doering utilized the benzophenone-mediated [2 + 2] photodimerization of various dienes.^{797,798} Inoue and co-workers studied the enantioselectivity of the [2 + 2] photodimerization of 1,3-cyclohexadiene upon sensitization with chiral arene(poly)carboxylates (up to 8% *ee*).⁷⁹⁹ The extended chromophore of benzocarborane allowed for its direct excitation, which led in the absence of oxygen and hydrogen donors to a clean [2 + 2] photodimerization.⁸⁰⁰

An intramolecular variant of the [2 + 2] photocycloaddition between a diene and an olefin was investigated by the Pulido group.⁸⁰¹ The natural product (\pm)-ipsdienol (*rac*-453) was synthesized and subjected to visible light irradiation in the presence of benzophenone (Scheme 151). The crossed photoproduct *rac*-454 was formed as the major regioisomer,

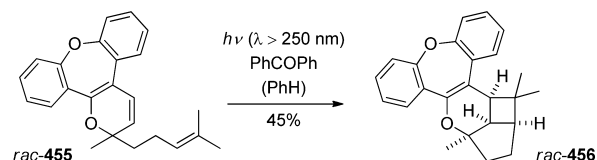
while the straight verbenol-type photoproduct was only detected as a side product.

Scheme 151. Intramolecular [2 + 2] Photocycloaddition of (\pm)-Ipsdienol (*rac*-453)



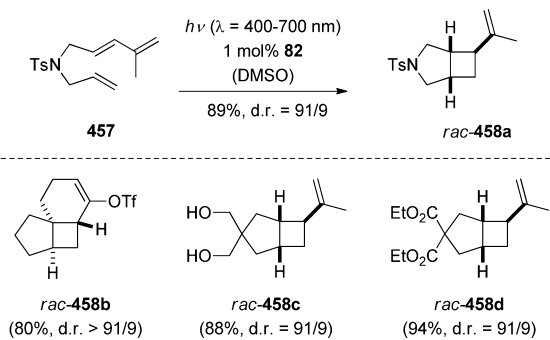
The polycyclic ring system of (\pm)-artocarpol A was accessed by Paduraru and Wilson by the intramolecular [2 + 2] photocycloaddition of the conjugated pyran *rac*-455 (Scheme 152).⁸⁰² Product *rac*-456 with the core fragment of the natural product was formed with high facial diastereoselectivity.

Scheme 152. Intramolecular [2 + 2] Photocycloaddition as an Entry to the Core Fragment of (\pm)-Artocarpol A



Recently, the Yoon group reported that not only aromatic ketones can serve as triplet sensitizers for 1,3-dienes but also certain iridium complexes. Complex 82 (Scheme 28) for example absorbs visible light and still exhibits a triplet energy of $E_T = 251 \text{ kJ mol}^{-1}$.⁸⁰³ With this compound as a catalyst, several intramolecular [2 + 2] cycloaddition reactions of dienes 457 to products *rac*-458 could be performed (Scheme 153). The method was applied to a short synthesis of the sesquiterpene (\pm)-epiraikovenal.

Scheme 153. Ir-Catalyzed Intramolecular [2 + 2] Photocycloaddition Reaction of Dienes 457



4. PET CATALYSIS–PHOTOREDOX CATALYSIS

Besides Cu(I) catalysis, direct excitation, and sensitization, photoinduced electron transfer (PET) is another powerful and straightforward strategy for the rapid construction of cyclobutenes.⁴⁶⁻⁶⁴ In this context, olefins are first converted to the corresponding reactive radical cations or radical anions (Scheme 5) by photocatalysts such as ketones, pyrylium salts, organic dyes, metal-polypyridyl complexes, etc. Recent work on photoredox catalysis also includes PET processes. All the advances in this field are attributed to the remarkable oxidative or reductive potential of electron transfer photocatalysts. Figure

21 shows some representative compounds 459–464, which have been widely used in PET catalysis for the preparation of

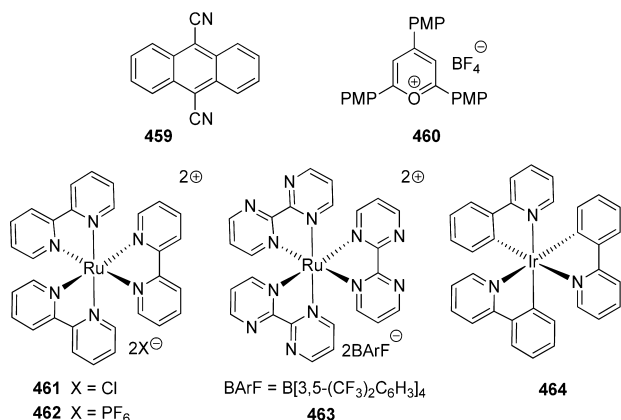


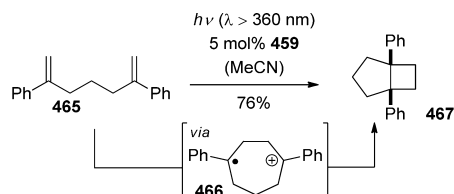
Figure 21. Structures of representative electron transfer photocatalysts 459–464.

cyclobutanes and their derivatives. There are other cases, however, in which the two coupling partners generate a radical cation/radical anion pair to furnish the [2 + 2] photoadducts without the aid of a catalyst. Reactions of this type will also be discussed in this chapter.

4.1. Radical Cation Intermediates

The PET-induced intramolecular [2 + 2] cycloaddition of 2,6-diphenylhepta-1,6-diene (465) was described by Takahashi et al.⁸⁰⁴ By using 9,10-dicyanoanthracene (459) as the catalyst,^{805–807} the desired *cis*-product 467 could be obtained in 76% yield (Scheme 154). Oxygen-trapping experiments

Scheme 154. Intramolecular [2 + 2] Photocycloaddition Reaction of 2,6-Diphenylhepta-1,6-diene (465)

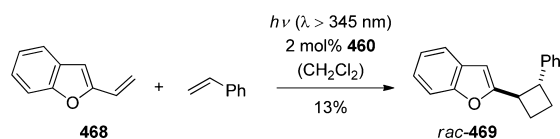


indicated that this reaction proceeded through the cyclic 1,4-radical cation intermediate 466. The same group also investigated the stereochemical outcome in the [2 + 2] photocycloaddition of 2,6-diarlylocta-1,6-dienes.⁸⁰⁸

2,4,6-Triarylpyrylium salts can be easily excited by UV–Vis irradiation.⁴⁸ Excited pyrylium salts exhibit a strong oxidative power which leads to the oxidation of various electron-rich olefins to highly reactive radical cation species and triggers subsequent cycloaddition reactions. In 1998, Steckhan and co-workers successfully introduced tri(4-methoxyphenyl)pyrylium tetrafluoroborate (460) to catalyze the reaction between 2-vinylbenzofuran 468 and styrene (Scheme 155).^{809,810} Only the 1,2-*trans* disubstituted product *rac*-469 was observed when dichloromethane was used as the reaction medium. The authors proposed that the 2-vinylbenzofuran was oxidized to a radical cation by the photoexcited catalyst 460.

Work by Cuppoletti et al. revealed that the intramolecular [2 + 2] photocycloaddition of norbornadiene to quadricyclane proceeds via a radical cation (paired with the radical anion of

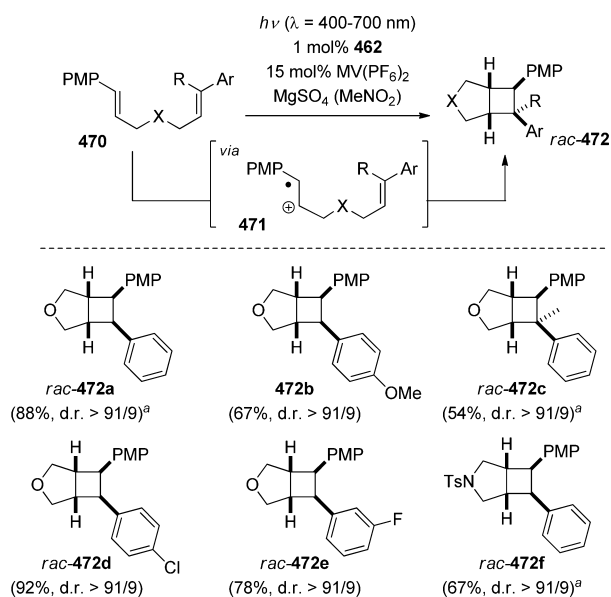
Scheme 155. Intermolecular [2 + 2] Photocycloaddition Reaction of 2-Vinylbenzofuran (468) and Styrene



the catalyst) if catalyzed by 3,3',4,4'-benzophenonetetracarboxylic dianhydride,⁸¹¹ but not, as with many other catalysts, by triplet sensitization.⁸¹²

In 2010, Yoon and co-workers reported an intramolecular [2 + 2] photocycloaddition reaction of bis(styrenes) 470 by means of visible light photoredox catalysis (Scheme 156).⁸¹³ In

Scheme 156. Visible-Light-Induced Intramolecular Oxidative [2 + 2] Photocycloaddition Reactions of Bis(styrenes) 470^a



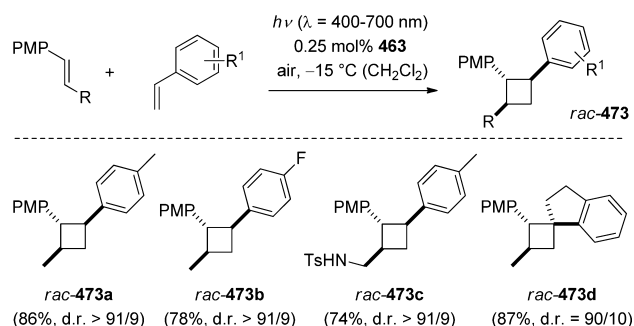
^a5 mol% 462 was used.

the presence of 1 mol% 462 and 15 mol% methyl viologen (MV) bis(hexafluorophosphate), many bis(styrenes) were shown to cyclize to the 3-oxabicyclo[3.2.0]heptanes *rac*-472 in moderate-to-good yields with excellent diastereoselectivity.

It is worth mentioning that the protected nitrogen atom in *N*-tethered bis(styrene) 470f was tolerated under the optimized conditions and afforded the corresponding 3-azabicyclo[3.2.0]heptane *rac*-472f in 67% yield. Mechanistic studies showed that at least one styrene of the substrate must bear an electron-donating methoxy group to facilitate oxidation to the key radical cation intermediate 471. The oxidative [2 + 2] photocycloaddition reaction of 470b could be conducted on gram scale using ambient sunlight without any loss of reaction efficiency.

In 2012, the Yoon group disclosed a visible-light-induced intermolecular [2 + 2] cycloaddition protocol (Scheme 157), according to which different styrenes were coupled smoothly to give the cyclobutanes *rac*-473.⁸¹⁴ Heteroatom substituents such as tosylamino, hydroxy, and chloro were also tolerated. Notably, 1-methylene-2,3-dihydro-1*H*-indene was also compatible with the optimal conditions and delivered the cyclobutane *rac*-473d with three contiguous stereogenic centers, especially one quaternary center. The success of this strategy is due to the

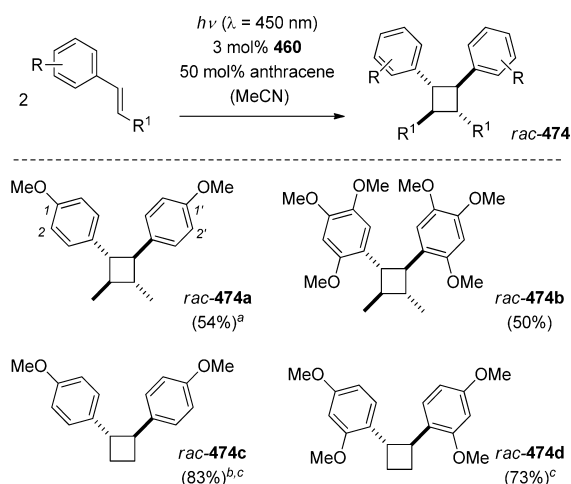
Scheme 157. Intermolecular [2 + 2] Photocycloaddition Reaction of Styrenes



choice of catalyst. Ruthenium complex **463** not only acts as the electron transfer photocatalyst, which oxidizes the styrenes, but also impedes the cycloreversion of the cycloadducts.

Shortly after, Nicewicz et al. showed that tris(4-methoxyphenyl)pyrylium tetrafluoroborate (**460**) was a very robust catalyst for the visible-light-induced [2 + 2] photodimerization of aromatic alkenes via a single electron transfer pathway (Scheme 158).⁸¹⁵ Anthracene or naphthalene (serving

Scheme 158. Visible-Light-Induced [2 + 2] Photodimerization of Aromatic Alkenes^{a,b,c}



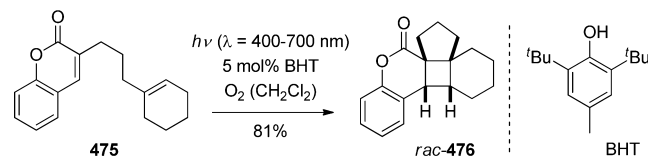
^a50 mol% Naphthalene was used as the electron relay compound. ^b75 mol% Anthracene was used. ^cThe reaction was performed in acetone at $-45\text{ }^{\circ}\text{C}$.

as electron relay compounds) was added to the reactions, which could inhibit the cycloreversion process and increase the yields of the cyclobutanes. The significance of this photodimerization reaction was demonstrated by the synthesis of (\pm)-magnosalin and (\pm)-endiandrin A, two bioactive lignin natural products. Using (*E*)-asarone as the styrene starting material, the natural product (\pm)-magnosalin (*rac-474b*) could be isolated in 50% yield under the best conditions. (\pm)-Endiandrin A could be easily constructed from the dimer *rac-474a* via bromination at C2 and C2', demethylation of the two methoxy groups at C1 and C1', followed by methoxy-debromination (59% yield over 3 steps).

Coumarins are common substrates in olefin [2 + 2] photocycloaddition reactions, which are normally excited by sensitization to their first excited triplet state (see subsection 3.4.1.2). An excited molecule of the respective coumarin reacts

with another olefin to furnish cyclobutane derivatives (see Scheme 3). In 2012, Schmalz, Griesbeck, and co-workers discovered that the intramolecular [2 + 2] photocycloaddition of coumarin **475** followed a PET pathway (Scheme 159).⁸¹⁶

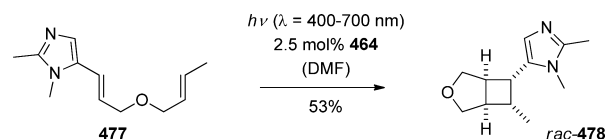
Scheme 159. Visible-Light-Induced Intramolecular [2 + 2] Photocycloaddition Reaction of Coumarin 475



The authors found that common photosensitizers such as Rose Bengal, tetraphenylporphyrin, or **460** did not improve the yield of *rac-476*. However, under aerobic conditions, the conversion was remarkably increased, particularly in the presence of BHT (3,5-di-*tert*-butyl-4-hydroxytoluene). Product *rac-476* was obtained in 81% yield. A striking feature of this transformation is the fact that molecular oxygen served as a redox catalyst. The authors used transient absorption spectroscopy and electrochemical techniques to shed some light on the mechanism of this reaction. The protocol provides an alternative way for the [2 + 2] photocycloaddition of coumarin and its derivatives.

Recently, the group of Chen employed the intramolecular Ir-catalyzed [2 + 2] photocycloaddition reaction for a biomimetic synthesis of the core skeleton of (\pm)-nakamuric acid (Scheme 160).⁸¹⁷ Upon treatment of vinylimidazole **477** in the presence

Scheme 160. Synthesis of the Core Skeleton of (\pm)-Nakamuric Acid by Visible-Light-Induced Intramolecular [2 + 2] Photocycloaddition Reaction of Vinylimidazole 477



of 2.5 mol% **464** under irradiation with visible light, the oxabicyclo[3.2.0]heptane *rac-478* was isolated as the major product. During this process, the vinylimidazole **477** was first oxidized by the excited photocatalyst to generate the corresponding radical cation intermediate. Subsequently, intramolecular radical addition and back electron transfer occurred to give the final product.

Prior to this work, the same group had taken a similar approach to construct the core skeleton of dimeric pyrrole-imidazole alkaloids, such as (+)-scepterin (*ent-332*, Figure 16), by a diastereoselective Ir-catalyzed [2 + 2] photocycloaddition.⁸¹⁸ This and the previous approach to (\pm)-nakamuric acid were based on biosynthetic experiments, which suggested a SET to induce the desired cycloaddition.⁸¹⁹

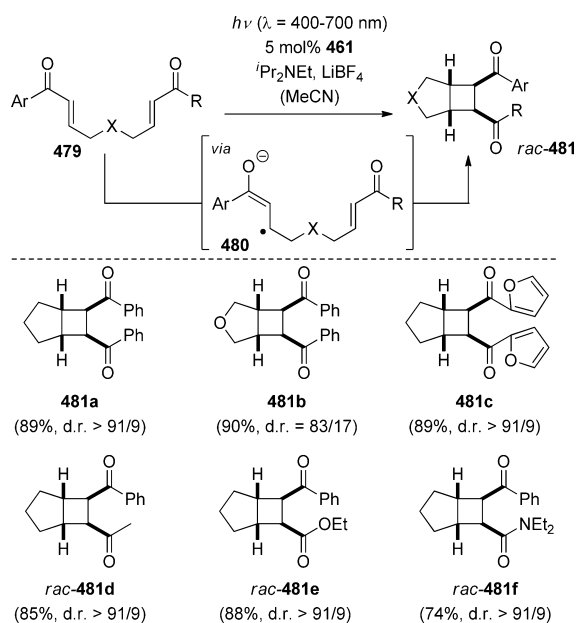
Oxidative PET catalysis was applied by Miranda and co-workers to [2 + 2] photocycloaddition reactions at the terminal part of poly(vinyl cinnamate).⁸²⁰ Employing 2,4,6-triphenylpyrylium tetrafluoroborate as the catalyst, photochemical cross-linking of poly(vinyl cinnamate) took place and gave the HH dimer as the major product.

4.2. Radical Anion Intermediates

Compared to the ground state, the excited state of photocatalysts significantly alters their redox properties. In PET-induced reactions, the excited photocatalysts frequently function both as good electron acceptors and donors, which could be easily oxidized or reduced by oxidative or reductive quenchers.^{821–827} For instance, methyl viologen (MV) bis-(hexafluorophosphate) could oxidize the excited ruthenium complex **462** to the high oxidation ground-state species, which was discussed in section 4.1. On the other hand, electron-rich organic molecules such as triethylamine can reduce the excited photocatalyst to the low oxidation ground state and initiate consecutive reactions. Recent [2 + 2] photocycloaddition reactions designed by Yoon and co-workers involve a reductive PET pathway.⁸²⁸

Inspired by Krische's work on reductive [2 + 2] cycloaddition reactions of bis(enone),^{829–833} the Yoon group developed a visible-light-induced [2 + 2] photocycloaddition reaction of enones.⁸³⁴ As shown in Scheme 161, a series of substituted

Scheme 161. Intramolecular [2 + 2] Photocycloaddition Reactions of Bis(enones) 479

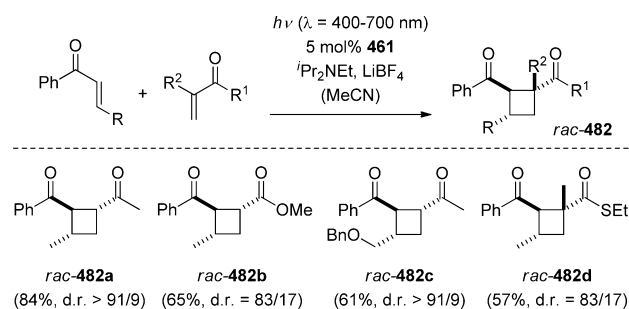


aryl and heteroaryl bis(enones) **479** cyclized in the presence of 5 mol% **461** and delivered the bicyclo[3.2.0]heptanes or their heterocyclic analogues *rac*-**481** in good-to-high yields with excellent diastereoselectivities (d.r. > 91/9). Mechanistic studies indicated that Hünig's base was essential for this transformation, which served as a reductive quencher to reduce the photoexcited $*\text{Ru}(\text{bpy})_3^{2+}$ to $\text{Ru}(\text{bpy})_3^+$ (bpy = 2,2'-bipyridine). LiBF_4 was also required and acts as a Lewis acid to activate the enone. Subsequently, the activated enone was reduced to the key radical anion intermediate **480** by $\text{Ru}(\text{bpy})_3^+$.^{835–839} As a limitation of this protocol, aliphatic enones and enoates did not cyclize. Their more negative reduction potential seemed to prevent reduction to the radical anions. Recent work showed that this [2 + 2] photocycloaddition proceeds by a radical chain mechanism. The quantum yield for the formation of product **481a** was determined as $\Phi = 77$.⁸⁴⁰ This high number suggests that electron transfer occurs

after cycloaddition directly to the substrate but not to the oxidized catalyst.

Intermolecular [2 + 2] photocycloaddition reaction of two different enones often suffers from homodimerization of each component. The development of an effective method for the intermolecular [2 + 2] photocycloaddition reactions is therefore desirable. Toward this goal, Yoon and co-workers successfully realized the intermolecular [2 + 2] photocycloaddition of acyclic enones by visible light catalysis (Scheme 162).⁸⁴¹

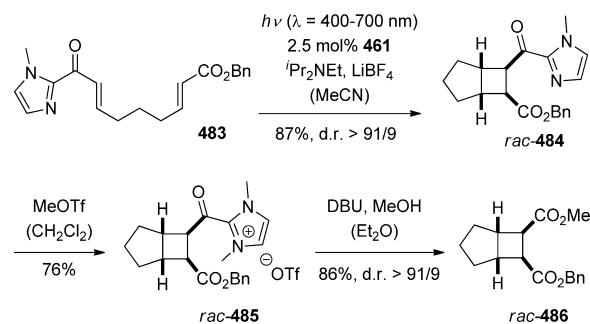
Scheme 162. Intermolecular [2 + 2] Photocycloaddition Reactions of Acyclic Enones



The key factor of this reaction is the rational design of the substrates. One coupling partner should be an aryl enone which is susceptible to the radical anion, and the other must be a more reactive Michael acceptor to facilitate the heterodimerization reaction to products *rac*-**482**.

The requirement of an aryl enone was a fundamental obstacle in the [2 + 2] photocycloaddition reactions, which limited the application of this methodology. In order to overcome this problem, the Yoon group described a visible-light-induced [2 + 2] photocycloaddition reaction of α,β -unsaturated 2-imidazolyl ketones such as **483** (Scheme 163),

Scheme 163. Intramolecular [2 + 2] Photocycloaddition Reaction of Enone 483 Bearing a Cleavable Redox Auxiliary



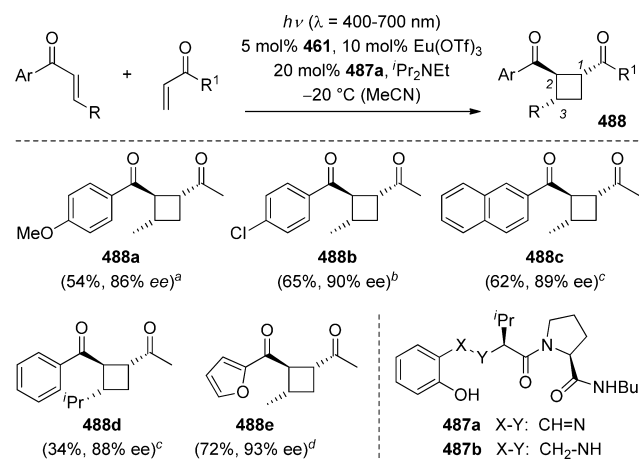
DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene).⁸⁴² Under the reductive PET conditions, the desired [2 + 2] products (e.g., *rac*-**484**) were isolated in high yields with good diastereoselectivity. The *N*-methylimidazol-2-yl moiety of the substrate functioned as a redox auxiliary and could easily be converted to the corresponding imidazolium salt *rac*-**485** for elaboration into many useful compounds. For instance, treatment of *rac*-**485** with methanol afforded the dicarboxylate *rac*-**486**, which could not be obtained from the direct [2 + 2] photocycloaddition reaction.

Chiral cyclobutanes are prevalent in pharmaceuticals and natural products. Given the importance of these cyclobutane

derivatives and their potential biological properties, the development of [2 + 2] photocycloaddition reactions in an enantioselective fashion is of great importance.

Recently, Yoon and co-workers reported a dual catalysis strategy for the enantioselective [2 + 2] photocycloadditions by combination of visible light photocatalysis and chiral Lewis acid catalysis (Scheme 164).⁸⁴³ By using **461** as the photocatalyst,

Scheme 164. Dual Catalysis Strategy in Enantioselective [2 + 2] Photocycloaddition Reactions of Enones^{a,b,c,d}



^ad.r. = 86/14. ^bd.r. = 88/12. ^cd.r. = 75/25. ^dd.r. = 89/11.

$\text{Eu}(\text{OTf})_3$ as the Lewis acid and **487a** as the chiral ligand, a diverse set of enones with a variety of functional groups on the aromatic ring reacted smoothly and provided the chiral cyclobutanes **488** in moderate-to-good yields with good enantioselectivities. Remarkably, 1,2-cis-2,3-trans chiral cyclobutanes could also easily be obtained by using **487b** as the chiral ligand.

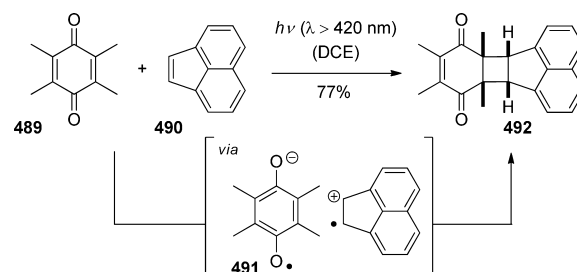
4.3. Radical Cation/Radical Anion Pairs

PET processes occur between an electron donor and an electron acceptor under the irradiation of light leading to a radical cation/radical anion pair. Various organic reactions can possibly take place in the radical cation/radical anion pair, including [2 + 2] photocycloaddition reactions.^{46–56} Unlike radical ion reactions, these reactions are more atom-economic, and external photocatalysts are not involved. In this context, aromatic hydrocarbons such as acenaphthylene and fullerene (C_{60}) are widely employed in [2 + 2] photocycloaddition reactions.

As part of their ongoing research interest in the development of PET reactions between acenaphthylene (**490**) and electron-deficient alkenes,^{844–848} Haga and co-workers used *para*-benzoquinone **489** as the reaction partner.⁸⁴⁹ As shown in Scheme 165 (DCE = 1,2-dichloroethane), the [2 + 2] photoadduct **492** was obtained in 77% yield (based on the consumption of **490**). The authors proposed that this reaction proceeds via a radical anion/radical cation pair **491**. Related findings regarding the formation of ion pairs were also made in [2 + 2] photocycloaddition reactions of chloranil with 1,1-diarylethenes.⁴²¹

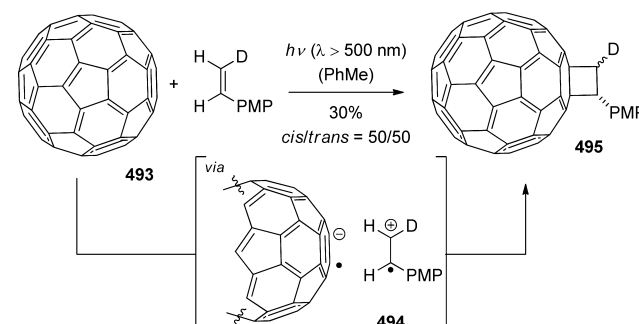
The intermolecular [2 + 2] photocycloaddition of C_{60} to an electron-rich alkyne (*N*-diethylpropynylamine) was reported by Foote and co-workers.^{850,851} Under the irradiation of light ($\lambda > 530\text{ nm}$), the C_{60} -fused cyclobutenamine was monitored as a single photocycloaddition product (>50% HPLC yield), which

Scheme 165. Intermolecular [2 + 2] Photocycloaddition between *para*-Benzoquinone **489** and Acenaphthylene (**490**)



could be further photooxidized to a ketoamide by molecular oxygen. Lately, the same group further employed this method for the synthesis of fullerene anhydrides.⁸⁵² The Orfanopoulos group studied the stereochemistry and possible isotope effects of the [2 + 2] photocycloaddition between C_{60} (**493**) and 4-vinylanisole (Scheme 166).^{853–855} The lack of any stereo-

Scheme 166. Intermolecular [2 + 2] Photocycloaddition Reaction between C_{60} (**493**) and 4-Vinylanisole



selectivity (cis-**495**/trans-**495** = 50/50) indicated that this transformation may involve the radical anion/radical cation complex **494** and a dipolar intermediate. A diradical pathway could not be completely ruled out, however.

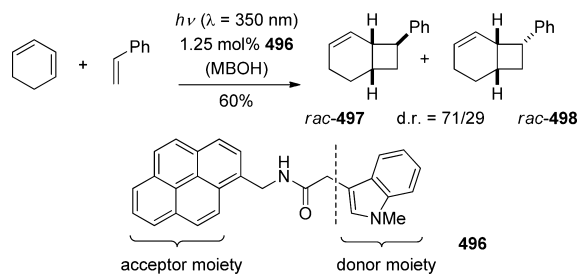
4.4. Others

Bichromophoric compounds were used as the photocatalysts in [2 + 2] photocycloaddition reactions performed by Pérez-Prieto and co-workers. In 2007, they developed a pyrene-benzoylthiophene bichromophoric system, which catalyzed the [2 + 2] photocycloaddition reaction of 1,3-cyclohexadiene and styrenes.⁸⁵⁶ The key point in this strategy is the intramolecular fluorescence quenching within the pyrene-benzoylthiophene complex that delivered an exciplex. Subsequently, the exciplex reacts with cyclohexadiene or styrene to give an excited triplet that undergoes [2 + 2] photocycloaddition to the final products *rac*-**497** and *rac*-**498**. Two years later, the same group showed that the pyrene-indole bichromophoric complex **496** could also catalyze the above-mentioned [2 + 2] photocycloaddition (Scheme 167, MBOH = 2-methyl-2-butanol).⁸⁵⁷ Within complex **496**, pyrene served as the acceptor moiety, and indole acted as the donor moiety. Mechanistic studies indicated that this reaction proceeded through a photoinduced charge separation in complex **496**.

5. CONCLUSION

Despite its history of over 100 years, [2 + 2] photocycloaddition chemistry has remained a topic of scientific interest and continues to be a vibrant area of chemical research.

Scheme 167. [2 + 2] Photocycloaddition Reaction of 1,3-Cyclohexadiene and Styrene Catalyzed by the Pyrene-Indole Bichromophoric Complex 496



Traditional applications of [2 + 2] photocycloaddition chemistry (e.g., in natural product synthesis or in the synthesis of cage compounds) flourish with the advent of new technologies for irradiation (e.g., light emitting diodes and flow chemistry). Indeed, practicing of photochemistry has never been as easy as it is today, and an array of commercially available equipment is on the market that fits almost every need. [2 + 2] Photocycloaddition receives increasing attention from medicinal chemists who have recognized that, if properly designed, the reactions can generate complex scaffolds in a single reaction step. Enantioselective catalysis is likely to enable the use of [2 + 2] photocycloaddition reactions as key steps in the very beginning of a synthesis to set up the first stereogenic center(s). Visible light photochemistry will make reactions feasible which are meant to occur in lower layers of biological or artificial matter. Since visible light sources are readily available, the practicability of [2 + 2] photocycloaddition reactions will be further increased. This review is meant to stimulate the interest of a larger audience in [2 + 2] photocycloaddition chemistry. It is hoped that the number of chemists to explore these reactions will continue to grow.

AUTHOR INFORMATION

Corresponding Author

*E-mail: thorsten.bach@ch.tum.de.

Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

Biographies

Saner Poplata studied chemistry at the Technische Universität München, where he received his M.Sc. degree in 2014. In his Ph.D. work, which he performs in the group of T. Bach, he focuses on the enantioselective Lewis acid catalysis of [2 + 2] photocycloaddition reactions.

Andreas Tröster studied chemistry at the Julius-Maximilians-Universität Würzburg, where he received his M.Sc. degree in 2014. During his Master's studies, he spent six months on a research internship at the Heriot-Watt University (M. Bebbington) in Edinburgh (UK). He received the faculty award for his M.Sc. studies in Würzburg. After obtaining his M.Sc., he carried out a research internship at Syngenta Crop Protection AG (Stein, CH). Currently, he performs his Ph.D. work as a fellow of the graduate college 1626 in the group of T. Bach on enantioselective catalysis of photochemical reactions by triplet sensitization.

You-Quan Zou studied chemistry at Luoyang Normal University (China), where he received his B.Sc. degree in 2008. He obtained his Ph.D. degree in 2014 under the direction of Professor Wen-Jing Xiao at Central China Normal University. He is currently working as a Humboldt postdoctoral fellow with Professor Thorsten Bach at the Technische Universität München.

Thorsten Bach obtained his education at the University of Heidelberg and at the University of Southern California, where he conducted his *Diplom* thesis with G. A. Olah. He received his Ph.D. in 1991 from the University of Marburg with M. T. Reetz and did postdoctoral work as a NATO fellow with D. A. Evans at Harvard University. He completed his *Habilitation* at the University of Münster in 1996, moved to the University of Marburg as an associate professor in 1997 and was appointed to the Chair of Organic Chemistry I at the Technische Universität München (TUM) in 2000. He has been an elected member of the German Academy of Sciences (Leopoldina) since 2006 and of the Bavarian Academy of Sciences since 2009.

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ABBREVIATIONS

AIBN	2,2'-azobis(2-methylpropionitrile)
Bn	benzyl
Bz	benzoyl
bpy	2,2'-bipyridine
BHT	3,5-di- <i>tert</i> -butyl-4-hydroxytoluene
Boc	<i>tert</i> -butoxycarbonyl
CT	charge-transfer

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
d.r.	diastereomeric ratio
de	diastereomeric excess
DCE	1,2-dichloroethane
DME	1,2-dimethoxyethane
dba	dibenzylideneacetone
DBTA	L-dibenzoyltartaric acid
EWG	electron-withdrawing group
ee	enantiomeric excess
eq	equivalents
E _T	triplet energy
HH	head-to-head
HT	head-to-tail
HFX	hexafluoro- <i>meta</i> -xylene
IC	internal conversion
ISC	intersystem crossing
IBX	2-iodoxybenzoic acid
LMCT	ligand-to-metal charge-transfer
MLCT	metal-to-ligand charge-transfer
MEM	methoxyethoxymethyl
MV	methyl viologen
MBOH	2-methyl-2-butanol
NHC	N-heterocyclic carbene
NTf ₂	bis(trifluoromethylsulfanyl)imide
PET	photoinduced electron transfer
PMP	<i>para</i> -methoxyphenyl
Piv	pivaloyl
r.r.	regioisomeric ratio
SET	single-electron transfer
(S)- ^t Bu-phox	(S)-4-(<i>tert</i> -butyl)-2-(2-(diphenylphosphanyl)-phenyl)-4,5-dihydrooxazole
Ts	<i>para</i> -toluenesulfonyl
Tf	trifluoromethanesulfonyl
tmba	trimethyl(butyl)ammonium
TBS	<i>tert</i> -butyldimethylsilyl
TBAF	tetrabutylammonium fluoride
TFA	trifluoroacetic acid
TMS	trimethylsilyl

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