4-π-Photocyclization: Scope and Synthetic Applications

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Abstract: This minireview highlights the scope of 4-π-photocyclizations (photoinduced electrocyclizations that involve 4 pi electrons and generate bicyclic cyclobutenes from 1,3-dienes), including an overview of the historical progressions as well as recent developments. A range of 1,3-diene substrates is covered, including cycloheptatrienes, tropones, tropolones, cyclic 1,3-dienes, 2-pyrones, 2-pyridones, pyrimidines, 1,2-dihydropyridines and 1,2-dihydro-pyridazines. The bicyclic cyclobutene products formed through the photocyclizations are highly versatile synthetic intermediates, and examples of the application of these building blocks in the context of synthetic methodology development, natural product synthesis, medicinal chemistry and materials chemistry are featured throughout.

1. Introduction

Electrocyclization reactions are unimolecular pericyclic processes in which one pi bond is converted into a sigma bond. The reverse reaction (electrocyclic ring-opening) involves the opposite process, and both reaction types take place via cyclic transition states. Electrocyclic processes are reversible, and can be categorized according to the number of π electrons involved in the cyclization/ring-opening. According to the Woodward-Hoffmann rules,[1] all electrocyclic reactions are allowed based on orbital symmetry, although thermal reactions involving (4n) π electrons proceed in a conrotatory mode, whilst thermal reactions involving (4n + 2) π electrons take place in a disrotatory fashion. In the excited state, these preferences are reversed, thus the opposite stereochemical outcome is expected for a given reaction if it is carried out photochemically rather than thermally. Several reviews of electrocyclic reactions have appeared, including accounts of biosynthetic/biomimetic electrocyclizations,[2] asymmetric electrocyclic reactions,[3] and the application of electrocyclic reactions in complex natural product synthesis.[4]

4-π-Photocyclizations (often referred to in the literature as valence isomerizations) are a sub-type of electrocyclic reaction that involves the photoinduced cyclization of a 1,3-diene to give a cyclobutene. Whilst both thermal and photochemical 4-π cyclizations are theoretically possible, the conversion of a diene into a cyclobutene usually involves a significant increase in strain, and such energetically unfavorable reactions do not generally occur under thermal conditions. However, because conjugated dienes usually absorb longer-wavelength light than the cyclobutene products, it is possible to carry out a 4-π-electrocyclizations under photochemical conditions by selecting a wavelength of light that is absorbed by the conjugated diene but

not absorbed by the cyclobutene product. In acyclic 1,3-dienes (as well as medium/large-ring 1,3-dienes), the efficiency of the 4-π-photocyclization is usually lowered by competing E-Z isomerization, and depends strongly on the ability of the 1,3-diene to adopt a s-cis-diene conformation. In the case of trienes and higher polyenes, other electrocyclic reactions (most often 6-π ring–opening or ring–closing processes) may also compete with 4-π processes, therefore the most successful 4-π-photocyclizations tend to take place from small- or medium-ring cyclic 1,3-dienes, particularly from those with very rigid shapes. Despite the often rich synthetic potential of products deriving from 4-π-photocyclizations, this class of electrocyclic reaction has received much less attention than other types of pericyclic reactions, such as cycloadditions. A small number of reviews dedicated to 4-π-electrocyclic reactions have appeared, focusing mainly on thermal ring-opening reactions,[5-7] but no reviews dedicated specifically to 4-π-photocyclizations have emerged. Thus, this review aims to highlight the synthetic potential of 4-π-photocyclizations, providing an overview of the historical developments as well as more recent state-of-the-art work. The review is not intended to be comprehensive, but describes the most common substrate types as well as illustrating the use of the resulting photoproducts in various synthetic applications. Finally, it should be noted that this review is limited to 4π-electron-4-atom systems (i.e. 1,3-dienes), although other 4π cyclization systems are also possible. In particular, 4π-electron-5-atom species are implicated in photoinduced Nazarov-type cyclizations, of which several recent examples have emerged.[8]

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2. Cycloheptatriene Systems

The study of the photochemistry of cycloheptatriene systems has largely focused on tropones and tropolones, which provided some of the earliest examples of 4-π-photocyclization. Nevertheless, a number of examples of the 4-π-photocyclization of simple cycloheptatrienes has also been reported. As the photochemical behavior of these three substrate classes differs, each substrate type will be treated separately in this review.

2.1. Cycloheptatrienes and Tropylium Ions

The 4-π-photocyclization of the tropylium ion was first reported by van Tamelen and co-workers in 1968.[9] Irradiation of tropylium tetrafluoroborate (**1**) in aqueous sulfuric acid generated bicycle **2**, which was captured by a water molecule to give bicycle **3** (Scheme 1). Similarly, Childs and Taguchi proposed that upon irradiation at low temperature in fluorosulfuric acid, **1** initially isomerizes to **2** before thermal conversion into the norbornadiene-7-yl cation **4** at higher temperatures.[10]
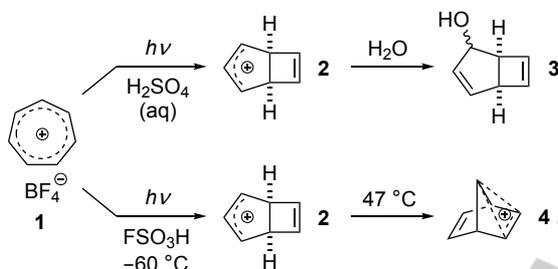
Scheme 1. 4-π-photocyclization of tropylium tetrafluoroborate.

In 1,3-cycloheptatriene derivatives, sigmatropic 1,7-hydrogen shifts can compete with 4-π-photocyclization.[11] These processes result in isomerization of the cycloheptatriene, and may well be the preferred pathway upon excitation. For 1,3,5-cycloheptatriene itself (**5**), the 1,7-hydrogen shift has been shown to take place 500 times faster than 4-π-photocyclization,[12] although in this case the bicycle **6** resulting from 4-π-photocyclization can be obtained in "excellent yield" upon extended irradiation (Scheme 2).[13]
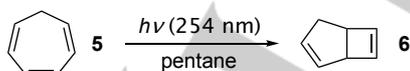
Scheme 2. 4-π-photocyclization of cycloheptatriene.

In their total synthesis of salvileucalin C (**7**), Ding and co-workers chose to employ the 4-π-photocyclization of a benzo-fused cycloheptatriene as a key step. Thus, **7** (likely a biosynthetic precursor to **8**) was cleanly converted into **8** in high yield upon irradiation at 365 nm (Scheme 3).[14]
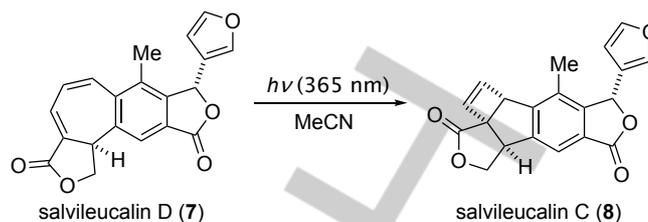
Scheme 3. 4-π-photocyclization in the total synthesis of salvileucalin C.

Examples of the 4-π-photocyclization of heteroelement-containing cycloheptatrienes have also appeared, and the electrocyclic chemistry of these systems has been reviewed by Lammertsma and co-workers.[15]

2.2. Tropone Systems

The photochemistry of tropone (**9**) is complex, with a variety of different photoproducts having been observed depending on the experimental conditions. Kende reported that upon irradiation in acetonitrile, tropone undergoes dimerization, producing a mixture of the formal [6+4], [6+2] and [4+2] dimers (Scheme 4).[16] Similarly, Mukai and co-workers reported that the [6+4] and [4+2] dimers were obtained upon irradiation in ether,[17] whilst the [6+6] dimer was produced selectively (albeit in low yield) in neutral and acidic aqueous solutions.[18]
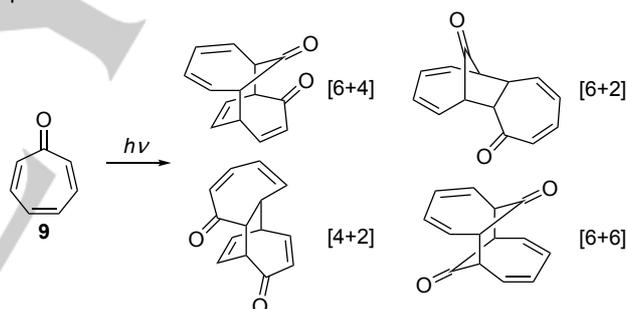
Scheme 4. Photoproducts obtained from irradiation of tropone.

In contrast, Childs and Taguchi provided the first report of a tropone system undergoing a 4-π-photocyclization. Hence, the hydroxytropylium cation (formed upon dissolution of tropone in fluorosulfonic acid) was subjected to irradiation in an NMR tube at around 300 nm. Two products were identified by NMR spectroscopy: the expected protonated 4-π-photocycloadduct **10**, and a related protonated norbornenone **11** (Scheme 5).[10]
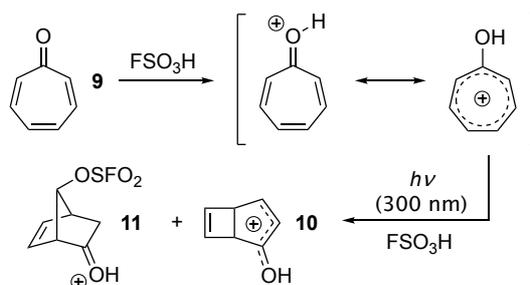
Scheme 5. 4-π-photocyclization of protonated tropone in fluorosulfuric acid.

Subsequently, Reingold and co-workers found that upon irradiation at low concentration in acidic organic solutions (trifluoroacetic acid gave the best results), the selective 4-π-photocyclization of tropone was possible, with tropone being cleanly converted into cyclobutene **12** (Scheme 6).[19] The photocyclization was very slow, with only around 33% conversion of **9** to **12** after 1 week of irradiation, although the authors suggested that longer irradiation times should lead to higher conversions. Similarly, Cavazza, Zandomeneghi and Pietra reported that complexation of tropone to Lewis acids also allowed selective 4-π-photocyclization rather than dimerization.[20] Thus, irradiation of BF₃·**9** in acetonitrile for 30 minutes resulted in 80% conversion, and the photocycloadduct **12** was isolated in 59% yield (Scheme 6).[21] Similar results were also observed through adding one equivalent of BF₃·Et₂O (or excess sulfuric acid) to a solution of tropone in acetonitrile, followed by irradiation under the above conditions. The authors showed that absorption peak at ~300 nm for the BF₃·**9** complex is more intense than that of uncomplexed **9**, although no significant absorption shift was observed upon complexation with BF₃.
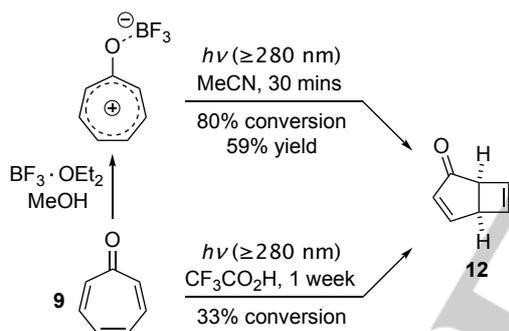
Scheme 6. 4-π-Photocyclization of tropone in acidic organic solutions.

The photochemistry of annelated tropones was investigated by Jones and co-workers.[22] Thus, benzo-fused tropones **13** underwent 4-π-photocyclization upon irradiation when R^1 and/or R^3 was an electron-donating group, generating tricyclic cyclobutenes **14** in low-moderate yields (Scheme 7). Interestingly, other benzotropones (bearing OH, NO₂, NH₂, Br substituents) gave only polymeric material upon irradiation.
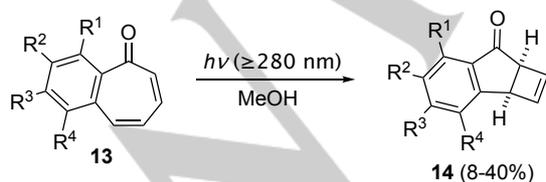
Scheme 7. 4-π-photocyclization of benzotropones **13** to give cyclobutenes **14**

Heterocyclic analogues of benzotropones **13** were also studied,[23] and in the case of thiophene-fused tropones, the substitution pattern on the tropone was found to strongly influence the reactivity. Hence, thienotropone **15** did not undergo 4-π-photocyclization; instead, dimerization took place, forming photodimer **16** in low yield (Scheme 8). In contrast, thienotropone **17** underwent selective 4-π-photocyclization, although the yield of product was not given. In this case, the methyl group on the tropone ring appears to suppress the dimerization pathway, favoring the generation of cyclobutene **18** (Scheme 8). Other heterocycle-fused tropones (including pyridine-, pyrrole-, indole- and furan-fused tropones) were also subjected to the irradiation conditions, but no 4-π-photocyclization products were observed, and the authors concluded that of the heterocyclic tropones tested, only thienotropones possess the required level of electron density on the tropone ring as well as sufficient stability of the heteroaromatic ring to avoid polymerization upon irradiation.
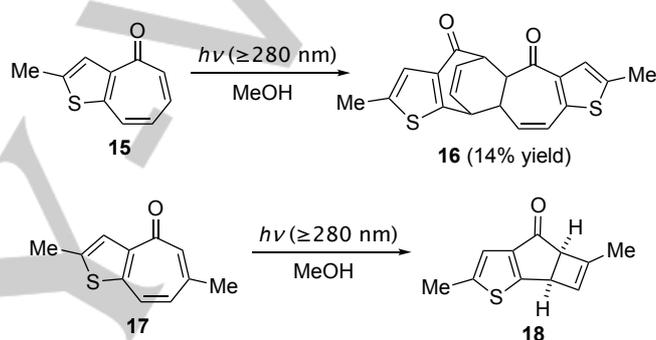
Scheme 8. Photochemical reactions of thienotropones **15** and **17**.

Carreño and co-workers described the 4-π-photocycliztion of a small family of 4-aminotropones **19** (Scheme 9), which displayed photochemical reactivity more similar to tropolone systems (*vide infra*) than the tropone systems discussed already.[24] Bicycles **20** were obtained in low-moderate yields, although it should be noted that these reactions were carried out on a very small scale.
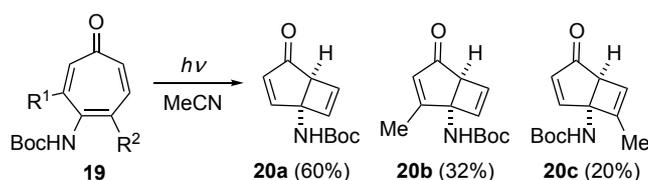
Scheme 9. 4-π-Photocyclization of 4-aminotropones.

Finally, perchlorinated[25] and perfluorinated[26] tropones have also been shown to undergo (reversible) 4-π-photocyclization upon irradiation, forming the corresponding [3.2.0]bicycles, although these reactions are unlikely to be of significant synthetic use.

2.3. Tropolone Systems

Tropolones are tropones that bear a hydroxy substituent at any point around the ring. Whilst their structure is very similar to tropones, their photochemistry is markedly different. Three isomers of tropolone are possible, depending on the position of the hydroxy group: the α-, β- and γ-tropolones (Figure 1).
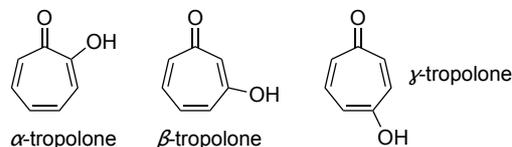
Figure 1. The α-, β- and γ-tropolones.

Chapman and Pasto outlined three possibilities for the electroisomerization of tropolone systems, namely the Type A, Type B and Type C cyclizations (Scheme 10). Type A (a 6-π-electrocyclization that gives a norcaradiene intermediate en route to benzene derivatives) is not particularly important in tropolone systems, but much more widespread in cycloheptatrienes. Conversely, Types B and C are both 4-π-cyclizations, and differ in the choice of the 4-π-system involved. Thus, in a Type B cyclization, the new bond forms at the carbon atom bearing the oxygen substituent, whilst in a Type C cyclization, the new bond is formed at a carbon atom *not* bearing the oxygen substituent.
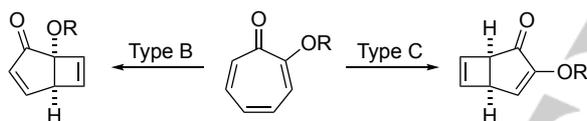
Scheme 10. Photocyclization of α-tropolone derivatives: Types B and C.

The first example of the 4-π-photocyclization of a simple tropolone derivative was reported by Chapman and Pasto in 1960.[27] An aqueous solution of γ-tropolone methyl ether **21** was slowly converted to bicycle **22** in a Type B photocyclization upon irradiation by use of a mercury lamp (Scheme 11). The isolated yield of **22** (24%) was relatively low, but the reaction had not reached completion, and starting material was re-isolated (60%) at the end of the reaction. Similar results could also be obtained by irradiating with natural sunlight.
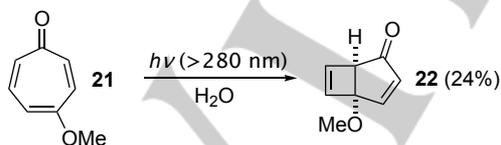
Scheme 11. Photocyclization of γ-tropolone methyl ether.

The following year, the groups of Dauben and Chapman disclosed the results of their study on the photochemistry of α-tropolone methyl ether (**23**), which turned out to be quite complex.[28] Although **23** initially underwent a Type B 4-π-photocyclization to produce bicycle **24**, continued irradiation led to rearrangement to

bicycle **25**, which, upon further irradiation in the presence of water, led to cyclopentenone **26** via a *retro*-aldol process (Scheme 12).
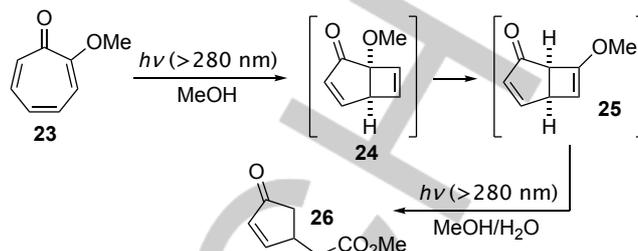
Scheme 12. Photochemistry of α-tropolone methyl ether.

The mechanism for the conversion of bicycle **24** into **25** was initially unclear, and was elucidated with the help of several substituted tropolones. The authors proposed that the bent shape of the bicycle **24** allows the interaction of the double bond in the cyclobutene with the enone chromophore, leading to an excited state intermediate best represented by zwitterion **27** (Scheme 13). From **27**, the acyl group of the cyclopentene undergoes migration to the neighboring cation, forming a new cation **28**, which is stabilized by the methoxy group. The collapse of **28** results in the re-formation of two double bonds, with the overall conversion of **24** to **25** essentially turning the molecule inside out. Later, a ketene intermediate was proposed for this transformation, based on low-temperature irradiation of **24**.[29]
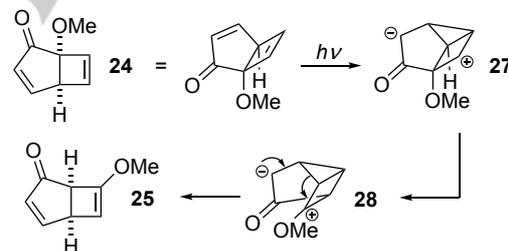
Scheme 13. Proposed mechanism for the transformation of **24** into **25**.

The remarkable transformation of **24** into **25** has been exploited by Winter and Trauner in the first step of their synthesis of (±)-hippolachnin A, in which the central carbon skeleton of the target molecule is formed in just one step (Scheme 14).[30]
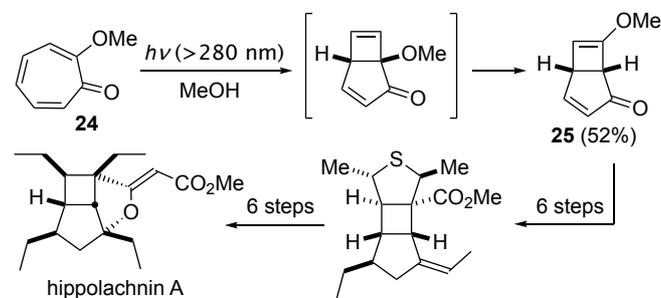
Scheme 14. Total synthesis of hippolachnin A.

In common with its methyl ether, α-tropolone itself (**29**) undergoes 4-π-photocyclization to give bicycle **30** upon irradiation, followed by photochemical rearrangement to give bicycle **31**, and *retro*-aldol reaction to furnish acid **32** (Scheme 15).[31] However, it is possible to stop the reaction after the first transformation by careful control of the irradiation conditions. Indeed, Wulff and co-workers obtained bicycle **30** in 83% yield through irradiation of a thin-layer solution of α-tropolone at 300 nm in dichloromethane.[32]
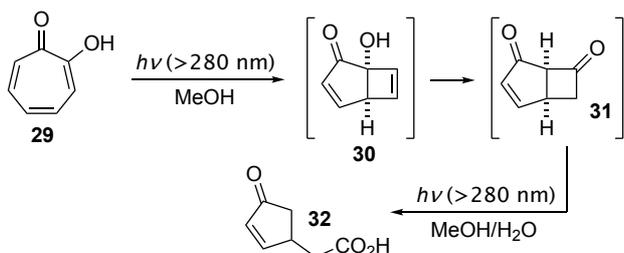
Scheme 15. Photochemistry of α-tropolone.

The bicyclic product formed upon irradiation of tropolone has wide synthetic potential. For example, Wulff and co-workers employed bicycle **30** in radical-mediated lactonizations and in metathesis sequences, generating complex tricycles such as **33** and spirocycles such as **34** (Scheme 16).[32]
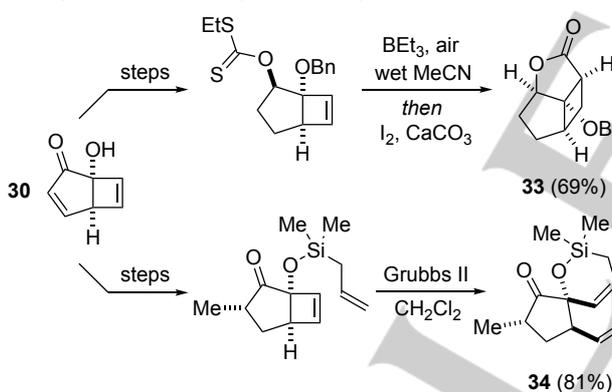
Scheme 16. Synthetic applications of phototropolone **30**.

It was noted above that the complexation of tropone with acids enables 4-π-photocyclization – reactivity that is not observed in other solvents. The same team also investigated the effect of acid on the photochemistry of α-tropolone methyl ether (**23**), and unearthed a surprising result. Thus, as already discussed, **23** undergoes Type B 4-π-photocyclization upon irradiation in a variety of solvents, such as acetonitrile. However, upon addition of boron trifluoride, a switch in selectivity occurred, and **23** instead underwent Type C 4-π-photocyclization (Scheme 17) to furnish bicycle **35**. After irradiating for 2 hours, **23** was 54% converted into bicycle **35**.
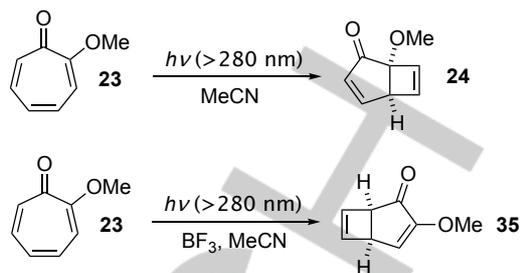
Scheme 17. Type B and C 4-π-photocyclization of tropolone methyl ether.

Mukai and Miyashi studied the photochemistry of 5-phenyl-α-tropolone **38** and its methyl ether **36**. Interestingly, whilst **36** underwent selective Type C photocyclization to give bicycle **37**, **38** underwent slow Type B photocyclization and subsequent rearrangement and *retro*-aldol reaction as observed for the unsubstituted α-tropolone (Scheme 18).[33] This was the first example of Type C photocyclization in a simple tropolone, giving the opposite result to that obtained with 5-isopropyl-α-tropolone (which had been previously reported by Dauben), and illustrating that the nature of substituents can strongly affect the outcome of these reactions. On the other hand, 5-chlorotropolone methyl ether (**40**) gave a 2:3 mixture of Type B and Type C cyclization products upon irradiation in methanol (Scheme 18).[34] **41** underwent rearrangement in analogy with the parent compound, thus the ratio is based on the yield of all products derived from **41**.
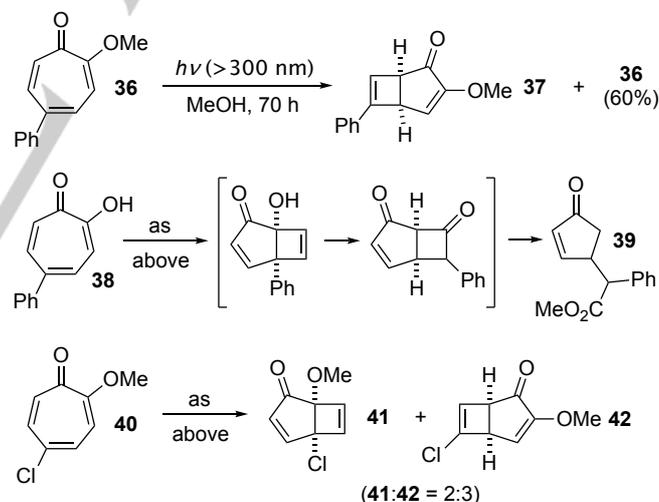
Scheme 18. Photochemistry of 5-substituted-α-tropolone derivatives.

The photochemistry of a limited range of benzo-fused tropolones has also been described. Forbes and co-workers reported that whilst benztropolone **43** underwent 4-π-photocyclization to generate tricycle **44** upon irradiation in aqueous ethanol (Scheme 19),[35] purpurogallin tetramethyl ether (**45**) was converted to a naphthoate product **46** under the same conditions.[36] Subsequent studies revealed that irradiation of **45** in aprotic solvents did lead to a tricyclic ketone, although it was not the product that would be

expected from 4-π-photocyclization.[36b] 3,4-Benzotropolone (**47**) underwent cyclization to give tricycle **49** in "good yield", with **48** proposed as a key intermediate (Scheme 19).
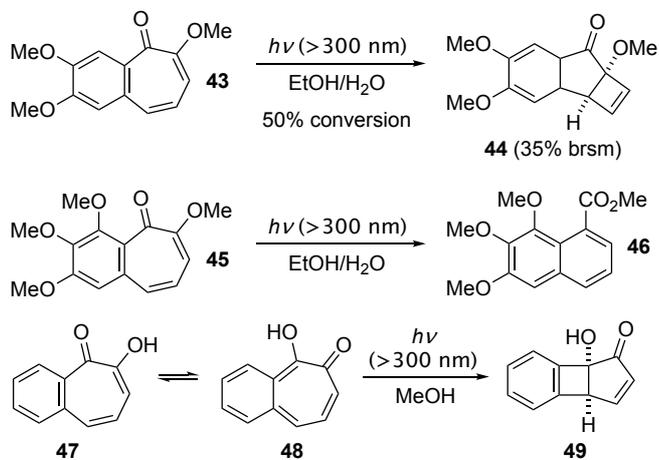
Scheme 19. Photochemistry of benzo-fused tropolones.
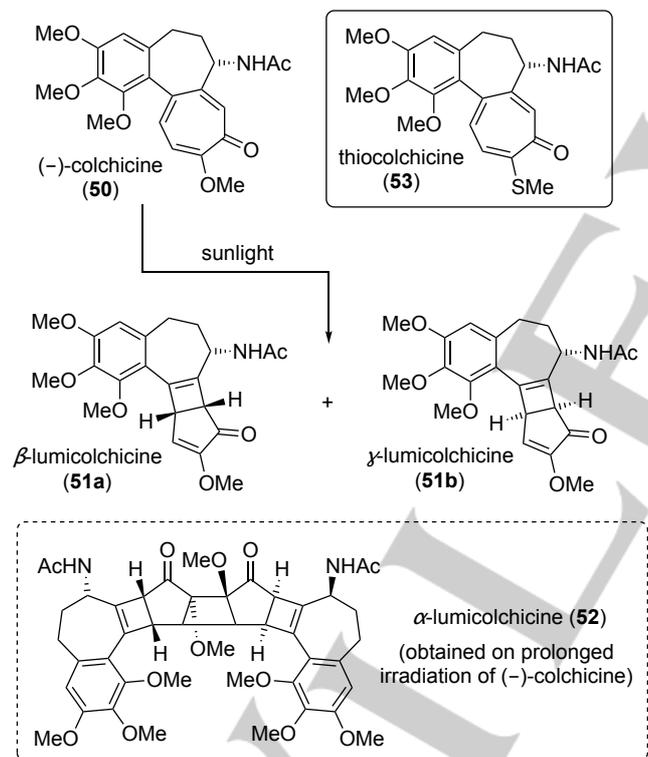
Scheme 20. (−)-Colchicine, thiocolchicine and the three photoproducts obtained from (−)-colchicine upon extended irradiation with sunlight.

Colchicine (**50**) is an interesting tropolone-containing alkaloid that can be isolated from *Colchicum autumnale*, the autumn crocus.[37] In 1951, Grewe and Wulf reported that the exposure of dilute aqueous solutions of colchicine to sunlight for 5-7 weeks gave a mixture of α-, β- and γ-lumicolchicines (Scheme 20), with all three products being obtained in similar amounts, although the

structures of the products were not reported.[38] Subsequently, Forbes repeated the experiment, obtaining the same three products, although this time β-lumicolchicine was obtained as the major product.[39] The structures of the β- and γ-lumicolchicines (**51a** and **51b**) were elucidated by Forbes,[39] by Gardner and co-workers,[40] and by Chapman and co-workers,[41] confirming that both products arise from a Type C photocyclization, and that they are diastereoisomers of each other. The third product, α-lumicolchicine, is obtained through [2+2] photocycloaddition of β-lumicolchicine upon extended irradiation.[42]

The mechanism of the 4-π-photocyclization of colchicine has been studied using transient absorption spectroscopy and computational modelling, the results of which support disrotatory cyclization of colchicine from its first excited singlet state.[43] The photochemistry of thiocolchicine (**53**, Scheme 20) was also investigated,[43] but in this case, no 4-π-photocyclization was observed, and only starting material was recovered. The failure of this cyclization was attributed to fast intersystem crossing from the singlet state to the triplet state, thereby suppressing the expected cyclization, which, by analogy with the photochemistry of colchicine, would be expected to occur from the singlet state. Using a variation of the irradiation conditions previously reported for the 4-π-photocyclization of colchicine, Li, Li and coworkers reported a concise synthesis of acetylcolchinol-*O*-methyl ether (NCME),[44] which is active against several cancer cell lines and exhibits greater inhibition of tubulin assembly than colchicine itself.[45] Thus, irradiation of (−)-colchicine through a Pyrex filter gave β-lumicolchicine (**51a**) selectively in 68% yield (Scheme 21), a significant improvement on the mixture of α-, β- and γ-lumicolchicines obtained under the original irradiation conditions (vide supra). Subsequent irradiation of **51a** under the same irradiation conditions gave NCME (**55**) in 54% yield, presumably through decarbonylation to form the Dewar benzene **54**, followed by *retro*-4π-electrocyclization to generate the aromatic ring. Interestingly, a one-pot conversion of **50** to **55** was not successful; upon extending the irradiation time of the first step, only traces of **55** were observed. The authors postulated that other, unidentified products generated in the first step had a deleterious effect on the decarbonylation/retro-cyclization step, with the two-step procedure (involving purification of **51a**) giving superior results.
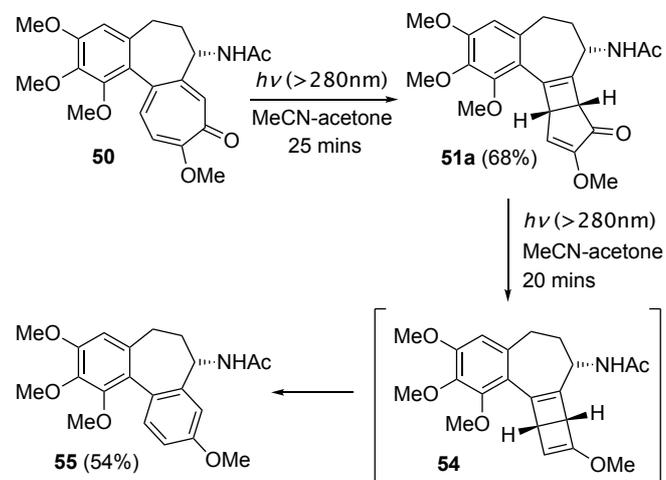
Scheme 21. Synthesis of NCME via 4-π-photocyclization.

The photochemistry of isocolchicine (**56**) has also been investigated (Scheme 22).[46] The major photoproduct was cyclobutene **58** (54% yield), accompanied by a minor product that was postulated to arise through initial formation of the methanol adduct (**57**) of isocolchicine, followed by 4-π-photocyclization to give **59** in 14% yield.

Scheme 22. 4-π-Photocyclization of isocolchicine and its methanol adduct.
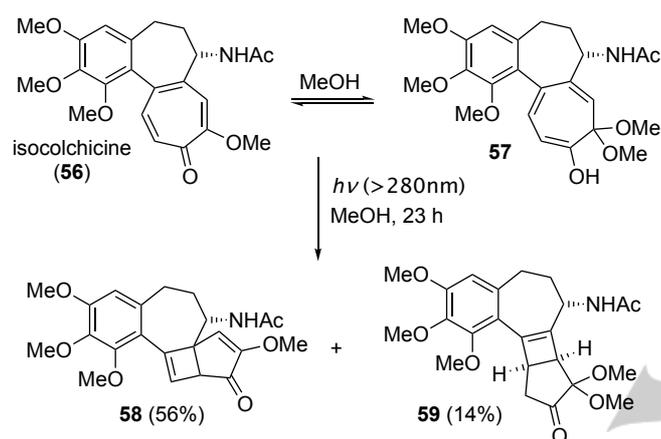
A number of approaches to enantioselective 4-π-photocyclizations of tropolones have also appeared,[3] but are beyond the scope of this review. So far, only moderate enantioselectivities have been obtained, using methods based on polymer microcapsules,[47] liquid crystals,[48] cyclodextrins,[49] zeolites,[50] and inclusion complexes.[51]

In summary, the photochemistry of cycloheptatriene systems (including tropones and tropolones) varies greatly with substrate structure, and earlier reports generally concentrated on the reaction feasibility and product distribution rather than preparative details. Therefore, with a few exceptions, the utility and potential of these 4-π-photocyclizations has not been firmly established, although recent applications to the synthesis of complex molecules are particularly compelling. Future work should focus on systematic studies, establishing "rules" to predict the reactivity of new substrates, and computational studies may prove particularly useful in this regard. In addition, diverse synthetic applications can be envisaged for the bicyclic products obtained through these photocyclizations, and more straightforward access to these products through improved 4-π-photocyclization protocols will enable further synthetic effort in this direction.

3. Carbocyclic 1,3-Diene Systems

For the 4-π-photocyclizations of 1,3-cyclohexadienes, the situation is complicated by competing 6-π-ring-opening to give trienes. The latter is usually the preferred pathway, unless the substrate structure prevents ring-opening. One of the earliest demonstrations of the competition between 4-π-ring-closure and 6-π-ring-opening was observed in the steroid series relevant to vitamin D production: whilst ergosterol undergoes 6-π-ring-opening upon irradiation to give previtamin D (followed by sigmatropic 1,7-hydrogen migration to give vitamin D), its C-10 stereoisomer pyrocalciferol undergoes 4-π-photocyclization to give photopyrocalciferol (Scheme 23). Dauben and co-workers suggested that in general, the conformation of the 1,3-diene controls the reaction pathway – conrotatory ring-opening occurs more efficiently from a half-chair conformation, whereas disrotatory ring-closure is preferred form a near-planar arrangement of the two double bonds.[52]
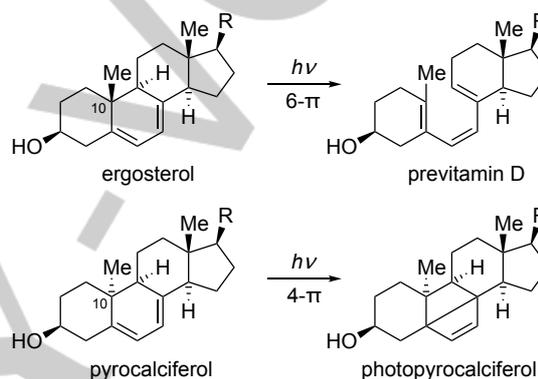
Scheme 23. 4-π-ring-closure versus 6-π-ring-opening in the steroid series.

4-π-Photocyclizations can prevail in a number of other cyclohexa-1,3-diene systems that do not allow 6-π-ring-opening – indeed, in strained bicyclic systems in which the fused ring is small (5- or 4-membered), 4-π-ring-closure is often preferred over ring-opening. For example, bicyclic diene **60** is smoothly converted into tricycle **61** upon irradiation in diethyl ether, whereas the related diacid **62** gives only triene **63** (Scheme 24).[53] Tricycle **61** has very recently been employed in approaches to *trans*-poly(acetylene),[54] as well as to benzoladderane mechanophores.[55]
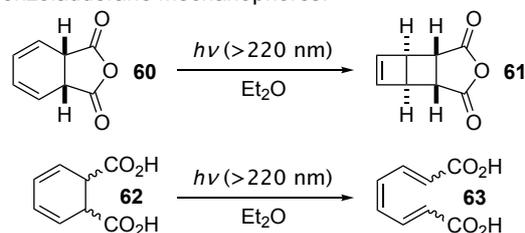
Scheme 24. 4-π-ring-closure versus 6-π-ring-opening in 1,3-cyclohexadienes.

Christl and Freund showed that strained 1,3-diene **64** undergoes selective 4-π-photocyclization upon irradiation, generating polycyclic cyclobutenes **65a** and **65b** with high stereoselectivity (Scheme 25). In addition, a number of perfluorinated cyclohexa-1,3-diene systems also undergo clean 4-π-photocyclization.[56]
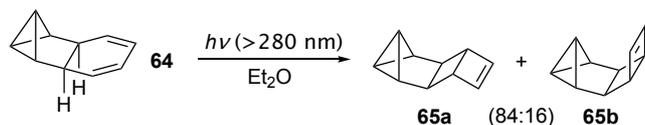
Scheme 25. 4-π-ring-closure of a strained cyclic 1,3-diene.

In 1,3-cycloheptadienes, although 6-π-ring-opening is not a problem, *E-Z* isomerization may compete efficiently with 4-π-photocyclization (as well as other processes), which may result in complex mixtures of photoproducts. Nevertheless, a number of examples of selective 4-π-photocyclization in cycloheptadiene systems have been reported, particularly in systems where *E-Z* isomerization is not favored. 1,3-Cycloheptadiene itself (**66**) underwent cyclization upon irradiation in diethyl ether to give bicycle **67** in 58% yield,[13,57] which could then be converted to the corresponding diacid upon treatment with potassium permanganate or through ozonolysis (Scheme 26).
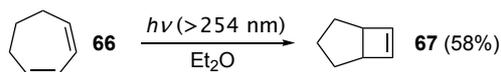
Scheme 26. 4-π-ring-closure of 1,3-cycloheptadiene.

Functionalised cycloheptadienes can also be employed in 4-π-photocyclizations, although the reaction outcome is highly dependent on the structure of the substrate. For example, cycloheptadienol **68** undergoes cyclization (with reasonable *endo* stereoselectivity) upon irradiation, whereas the related ketone **70** undergoes double α-cleavage, leading to 1,3,5-hexatriene and carbon monoxide (Scheme 27).[57] The latter reaction is thought to be initiated via n → π* excitation of the carbonyl chromophore, which is of course impossible in alcohol **68**.
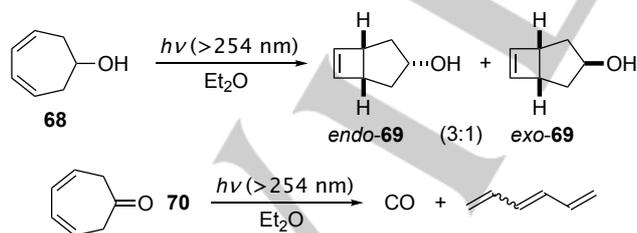
Scheme 27. Photochemistry of cycloheptadienol and cycloheptadienone.

Rigby and co-workers studied the 4-π-photocyclization of a series of complex bicyclic cycloheptadienes. For example, dienes **71** and **73** underwent stereoselective photocyclization upon irradiation, furnishing the corresponding cyclobutene products

(**72** and **74**) respectively in high yields (Scheme 28).[58] It was also demonstrated that the cyclobutene in **72** could be cleaved through ozonolysis, giving the corresponding diol after reduction.
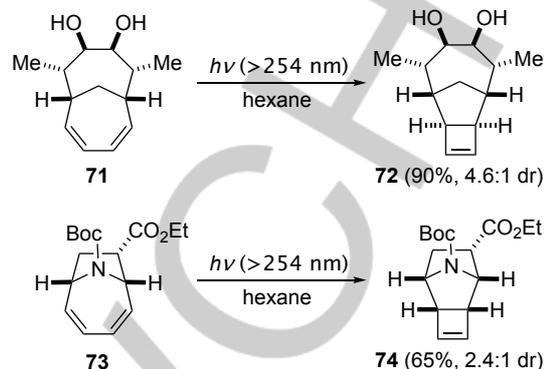
Scheme 28. 4-π-Photocyclization of bicyclic cycloheptadienes.

4. Heterocyclic 1,3-Diene Systems

4-π-Photocyclization is not restricted to carbocyclic frameworks – indeed, various heterocycles have been employed in such reactions. Arguably, the highly strained heterocyclic products obtained in these cyclizations have even higher synthetic potential than the carbocyclic examples previously discussed, as will be illustrated in the following sections. The review will concentrate on the photochemistry and applications of 2-pyrones and 2-pyridones, which have both received a great deal of attention, but will also describe the corresponding reactions of related heterocycles.

4.1. 2-Pyrones

The first 4-π-photocyclization of 2-pyrone itself (**75**) was described by Corey and Streith in 1964.[59] Quantitative yields of bicyclic lactone **76** could be obtained upon irradiation of a solution of 2-pyrone in diethyl ether (Scheme 29), and the product could be isolated in pure form simply by evaporation of the solvent under reduced pressure. However, the authors warned that the product is pyrophoric and can explode upon warming in air, and that solutions of the product must be kept cool at all times.
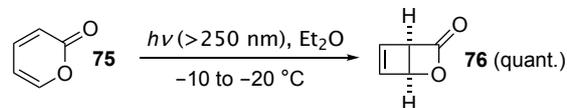
Scheme 29. 4-π-photocyclization of 2-pyrone.

Subsequent studies by a range of research groups focused on the irradiation of 2-pyrone at very low temperatures (8-20 K) in argon matrices.[60] Under these conditions, the initial product was not bicyclic lactone **76**, but aldoketene **77**, which is presumed to arise from a photochemical 6-π-ring-opening of **75** (Scheme 30). Upon prolonged irradiation, lactone **76** forms slowly, and finally **76** is converted to carbon dioxide and cyclobutadiene. Further irradiation causes photodecomposition of cyclobutadiene to acetylene, or dimerization may occur through Diels-Alder reaction of cyclobutadiene with itself upon warming of the matrix. Interestingly, at 77 K, aldoketene **77** is barely detectable, and lactone **76** is the major species, indicating a strong temperature dependence on the photostationary state between **75** and **76**.
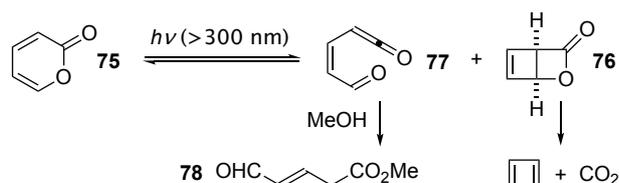
Scheme 30. Irradiation of 2-pyrone generates bicyclic lactone and ketene.

The outcome of irradiation of 2-pyrone in solution mirrors that observed in an argon matrix, but depends strongly on the solvent employed. Thus, irradiation in diethyl ether leads to quantitative formation of bicyclic lactone **76**, whilst irradiation in methanol furnishes methyl *trans*-4-formyl-3-butenoate (**78**) essentially quantitatively.[61] **78** is thought to arise from trapping of ketene **77** with methanol; although **77** is present only in very low concentration, the rate of its reaction with methanol appears to be competitive with cyclization to revert to 2-pyrone, resulting in constant consumption of ketene (Scheme 29). Interestingly, acetophenone-sensitized irradiation of 2-pyrone does not give **76**, but rather two Diels-Alder-like dimers.[61a] Since the rate of reaction of 2-pyrone upon irradiation in diethyl ether (to give **76**) or methanol (to give **78**) is not slowed by the addition of piperylene, and that the use of a triplet sensitizer suppresses the formation of these products, it seems safe to assume the formation of **76** and **77** occurs from a singlet excited state of **75**.

Maulide and co-workers have extensively exploited bicyclic lactone **76** in various synthetic applications, resulting in impressive approaches to substituted cyclobutenes and dienes through direct manipulation of **76**.[62] For example, the palladium-catalyzed alkylation of **76** using a range of active methylene compounds (e.g. malonate ester **79** or azlactone **81**) gave disubstituted cyclobutenes in good yields (Scheme 31).[63] In the case of azlactone **81**, the initial product underwent ring-opening then cyclization to form bicyclic cyclobutene **82**. Further studies allowed the development of catalytic asymmetric diastereo-divergent deracemization methodology, in which the judicious choice of ligand determined whether the two substituents on the cyclobutene products were oriented *cis* or *trans* to each other, and allowed the enantioselective preparation of a range of complex cyclobutene products.[64]
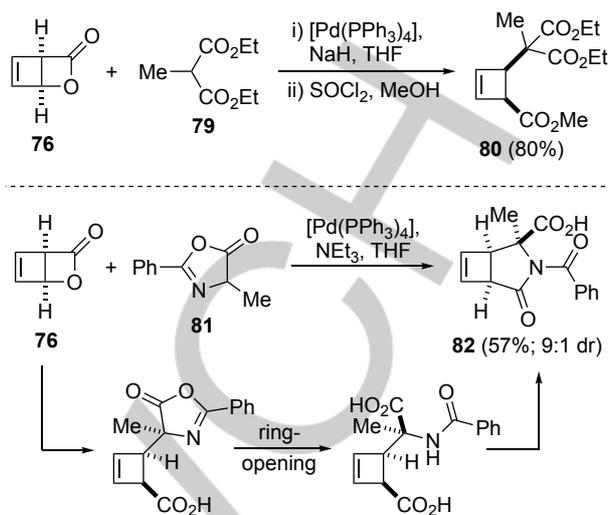
Scheme 31. Alkylation of bicyclic lactone **76** to give substituted cyclobutenes.

The relatively facile ring-opening of cyclobutenes through a thermal 4-π-electro-*retro*-cyclization has also allowed the preparation of a variety of substituted dienes. For example, the addition of cuprates to bicyclic lactone **76** generates *trans*-disubstituted cyclobutenes in high yields, which can be converted to the corresponding dienes by heating (Scheme 32).[65] This approach has been applied to the synthesis of several natural products, including (−)-ieodomycin (Scheme 32), piperine[66] and inthomycin C.[67] Alternatively, the addition of phenols to bicyclic lactone **76** leads directly to diene products, via the corresponding cyclobutene intermediates. Here, 4-π-electro-*retro*-cyclization occurs readily at room temperature – no heating is necessary.[68]
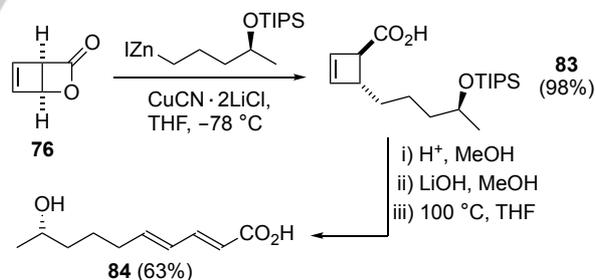
Scheme 32. Alkylation of bicyclic lactone **76** in the synthesis of (−)-ieodomycin.

The photochemistry of substituted 2-pyrones has also been investigated in detail, and the outcomes of these reactions depend strongly on the nature of the substituent(s). For example, Maulide and co-workers reported the 4-π-photocyclization of three 3-substituted 2-pyrones **85**, which proceeded in similar fashion to 2-pyrone itself, producing bicyclic lactones **86** in quantitative yield upon irradiation in diethyl ether −15 °C (Scheme

33). The photoproducts were not isolated in pure form, but were used as solutions in diethyl ether.[68]
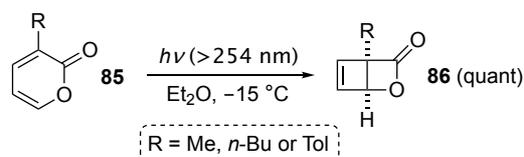
Scheme 33. 4-π-photocyclization of 3-substituted 2-pyrones.

The photochemistry of 4,6-dimethyl-2-pyrone (**87**) was first studied by de Mayo.[69] Irradiation in methanol gave an alkene product derived from a ketene, in line with the behavior of 2-pyrone itself, whereas irradiation of **87** in benzene led to two [4+4] dimers and a [2+2] dimer. Subsequently, Maier and Reisenauer reported further studies on this system, both in solution and at low temperature in an argon matrix.[70] Irradiation of a solution of **87** in diethyl ether at –50 °C gave bicyclic dienes **90** and **91** (Scheme 34), which presumably result from initial 4-π-photocyclization of **87** to give bicyclic lactone **88**, followed by loss of carbon dioxide to generate 1,3-dimethylcyclobutadiene **89**. Finally, **89** undergoes dimerization by Diels-Alder cycloaddition, producing **90** and **91**. This proposed sequence of events was supported by further study of the same system in an argon matrix at 10 K. Under these conditions, the irradiation of **87** with 313 nm or >320 nm light led to clean conversion to bicyclic lactone **88** (Scheme 34). Subsequent irradiation of **88** at 254 nm initially led to a mixture of 2-pyrone **87** and 1,3-dimethylcyclobutadiene **89**, which was entirely converted to **89** after 3 hours of irradiation. Cyclobutadiene **89** was reported to be photostable under these irradiation conditions.
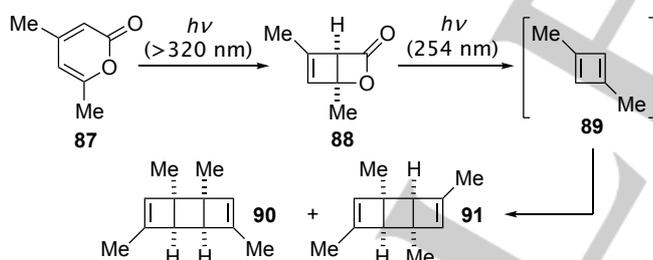
Scheme 34. 4-π-photocyclization of 4,6-dimethyl-2-pyrone.

The same authors also studied 3,4,5,6-tetramethyl-2-pyrone (**92**), expecting very similar reactivity to that of **87**.[70] Indeed, in an argon matrix, irradiation of **92** does lead to the formation of the corresponding bicyclic lactone **93** (Scheme 35), although in this case the competing ring-opening reaction (to form ketoketene **94**) is also observed, whereas the analogous ketoketene product was only formed in negligible amounts upon irradiation of **87**. Subsequent irradiation of bicycle **93** at 254 nm triggered rapid elimination of carbon dioxide, giving tetramethylcyclobutadiene.

Scheme 35. Photochemistry of 3,4,5,6-tetramethyl-2-pyrone.
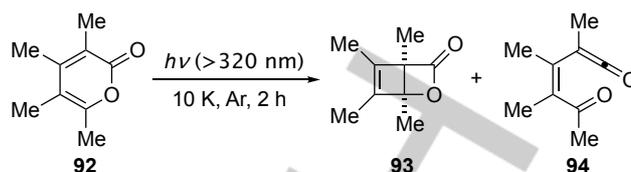
De Mayo and co-workers investigated the photochemistry of 4-methoxy-6-methyl-2-pyrone (**95a**), reporting that upon irradiation in benzene, both the ketene **96a** and the lactone **98a** were formed (from inspection of infrared data).[71] However, the addition of aqueous dioxane or methanol led to products thought to be derived from lactone **98a** rather than ketene **96a** (in contrast to the behavior of 2-pyrone itself), and the authors proposed that in **98a**, the presence of the methoxy group facilitates C-O bond cleavage to generate zwitterion **99a**, thus suppressing the reversion of **98a** to **95a** (Scheme 36). The cleavage of the C-O bond was assumed to be non-reversible, and the cyclization of ketene **96a** to pyrone **95a** was assumed to be fast, thus favoring the continual production (and consumption) of lactone **98a** rather than ketene **96a**. Irradiation at low temperature (83 K) led to characteristic peaks for lactone **98a** but not ketene **96a**, implying that the cyclization of ketene **96a** to regenerate **95a** is very fast even at this low temperature. Money and co-workers subsequently confirmed lactone **98a** rather than ketene **96a** as the important intermediate upon excitation of **95a**, and also reported similar outcomes for the related 2-pyrone **95b**.[72] Thus, the major products obtained from the irradiation of **95b** in methanol were thought to arise from lactone **98b**, although in this case a minor product was also obtained that was derived from the addition of methanol to ketene **96b** (Scheme 36).
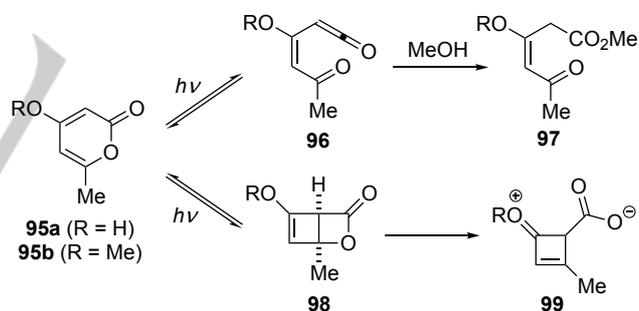
Scheme 36. Photochemistry of 2-pyrones bearing oxygen substituents.

Javaheripour and Neckers investigated the photochemistry of coumalic acid and several of its ester derivatives, both in solution and in the solid state.[73] Methyl coumalate (**100**) underwent clean 4-π-photocyclization upon irradiation at 300 nm in diethyl ether, generating bicyclic lactone **101** in quantitative yield (Scheme 37). Lactone **101** was reported to be more stable than the corresponding lactone obtained from 2-pyrone itself, and **101** could even purified by bulb-to-bulb distillation, although during the distillation around 10% reversion to methyl coumalate was observed. Irradiation in methanol led to the generation of the same products, but as these products were not stable in methanol,

secondary thermal reactions resulted in conversion of the primary photoproducts into a variety of derivatives.
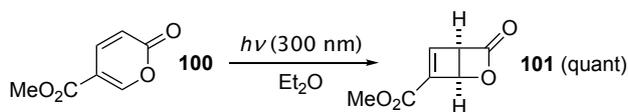
Scheme 37. 4-π-photocyclization of methyl coumalate.

In contrast, when **100** was irradiated in a KBr matrix, no 4-π-photocyclization was observed. Instead, dimeric [4+2] cycloadducts were obtained – the same products that were observed upon benzophenone-sensitized irradiation of **100** in diethyl ether, or upon irradiation in ethyl bromide, a heavy-atom solvent. The generation of these triplet-state-derived dimer products was described by the authors as the first example the external heavy atom effect in a KBr matrix, which in this case, appears to completely suppress the singlet-mediated 4-π-photocyclization observed upon direct excitation in diethyl ether. More recently, Gutekunst and Baran expanded on the work of Javaheripour and Neckers, by applying the 4-π-photocyclization of **100** as a key step in the total synthesis of piperarborenine B (Scheme 38).[74] Thus, irradiation of a solution of **100** in dichloromethane at 300 nm, cooled to −15 °C, gave bicyclic lactone **101** after 96 hours. Lactone **101** was not isolated, but underwent subsequent hydrogenation to produce cyclobutaneacid **102**, followed by coupling with aniline **103** to give disubstituted cyclobutane **104** in reasonable yield over three steps (the telescoped procedure was carried out on gram-scale). Cyclobutane **104** was finally converted into the target natural product piperarborenine B in a further six steps.
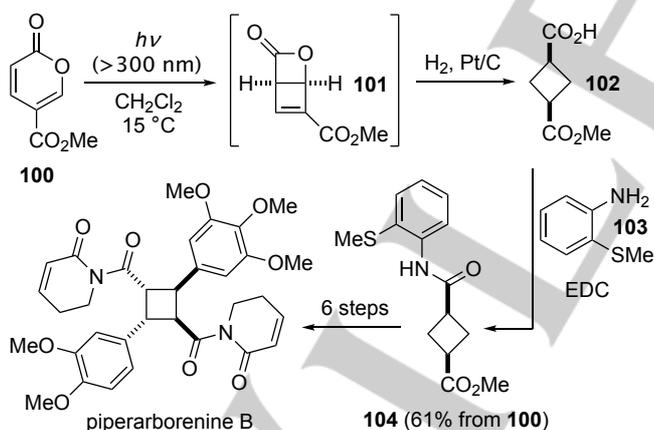
Scheme 38. 4-π-photocyclization in the total synthesis of piperarborenine B.

Similarly, Yamashita, Nishikawa and Kawamoto investigated the optimization of the 4-π-photocyclization of *tert*-butyl coumalate (**105**) in solution.[75] In this case, the use of a flow photoreactor allowed the clean conversion of **105** into **107** without any significant formation of other products – an improvement on the product profile observed in a batch reactor. Under the optimized conditions, substantial scale-up of the reaction was possible, and 13.5 grams of 2-pyrone **105** could be converted to 11.1 grams of

cyclobutane **107** (Scheme 37; 81% yield over two steps).
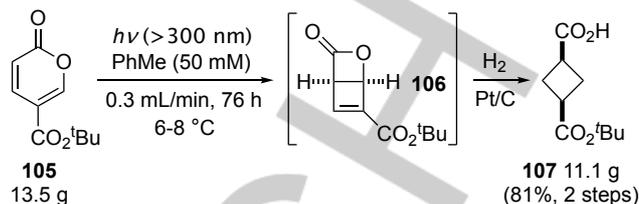
Scheme 39. 4-π-photocyclization of *tert*-butyl coumalate in flow.

Very recently, the synthetic potential of the 4-π-photocyclization of 2-pyrones was further demonstrated by the Nelson group, in their elegant concise total synthesis of (±)-vibralactone (**112**).[76] Thus, 3-prenyl-2-pyrone (**108**) underwent photocyclization upon irradiation at 300 nm in benzene, producing bicyclic lactone **109** in 83% yield (yield determined by ^{1}H NMR spectroscopy; Scheme 40). Next, rhodium-catalyzed cyclopropanation of **109** delivered housane derivative in 18% isolated yield (over two steps from pyrone **108**). Subsequent base-mediated ring expansion followed by selective reduction of the exocyclic ester delivered (±)-vibralactone, representing a 4% overall yield of the natural product in only five steps from commercially available materials.
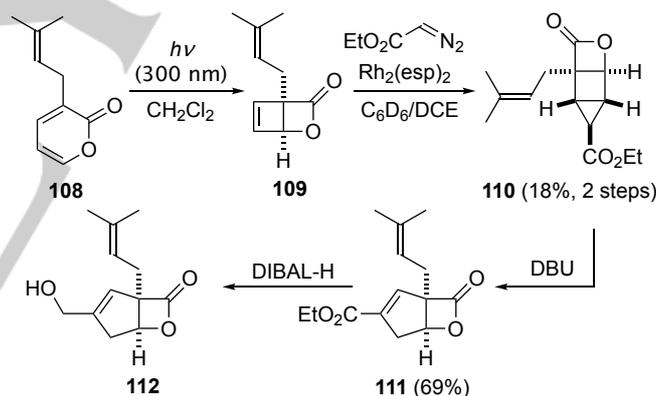
Scheme 40. Total synthesis of (±)-vibralactone (**112**).

In summary, the photochemistry of a range of different 2-pyrone derivatives has been studied. The major primary photoproducts upon direct irradiation are ketenes (resulting from 6-π-ring-opening) and bicyclic lactones (resulting from 4-π-photocyclization), whereas dimerization products are often observed upon triplet sensitization. The reaction conditions strongly affect the outcome of the reaction: if 4-π-photocyclization is desired, care should be taken to avoid nucleophilic solvents and triplet sensitisers (both suppress the desired cyclization by consuming the competing ketene photoproduct or by promoting dimerization respectively). Preference for 6-π-ring-opening or 4-π-ring-closure seems highly dependent on the structure of the pyrone, although many early studies did not focus on preparative aspects, and no systematic studies have appeared in which a

variety of 2-pyrones have been treated under exactly the same conditions. Therefore, it is difficult to predict the outcomes of irradiation of other 2-pyrones, and future work should focus on establishing "rules" for these reactions, in order to allow their widespread usage in synthesis. Nevertheless, several recent applications of the 4-π-photocyclizations of 2-pyrones serve to emphasize the rich synthetic potential of these reactions.

4.2. 2-Pyridones

The first example of a 4-π-photocyclization in the 2-pyridone series was reported by Corey and Streith, alongside their disclosure of the analogous reaction of 2-pyrone,[59] generating bicyclic lactam **114** in 20% yield upon irradiation (Scheme 41).
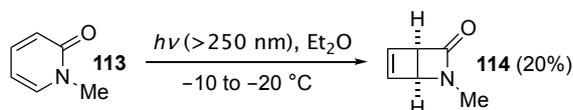
Scheme 41. 4-π-photocyclization of N-methyl-2-pyridone.

Interestingly, Corey and Streith made no mention of the formation of dimeric products, which several groups had previously obtained from the irradiation of 2-pyridones. For example, Taylor and Paudler reported that 2-pyridone **113** and N-methyl-2-pyridone **115** dimerized upon irradiation, although no yields were given, and the irradiation conditions were not specified.[77] The dimers were initially incorrectly identified as **116**, but subsequent reports confirmed the correct structure as **117** (Scheme 42).[78]
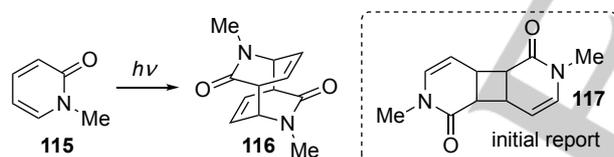
Scheme 42. Photochemical dimerization of 2-pyridones.

Subsequently, Paquette and Slomp investigated the photochemistry of a range of 2-pyridones (Figure 2), reporting that upon irradiation in aqueous alcoholic solution, dimeric products were obtained – no mention was made of bicyclic lactam products analogous to that obtained by Corey and Streith.
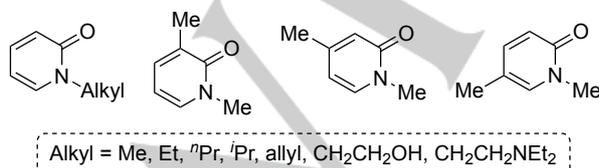
Figure 2. 2-Pyridones investigated by Paquette and Slomp.

On the other hand, De Selms and Schleigh reported that upon irradiation in methanol, a range of substituted 2-pyridones (some examples being the same substrates as studied by Paquette and Slomp) form mixtures of bicyclic lactams (resulting from 4-π-photocyclization) and dimeric products.[79] Lactams **118** were reported to be stable indefinitely at room temperature, but to revert to 2-pyridones upon heating above 100 °C. The yields of bicycles **118** were variable and highly dependent on the structure of the 2-pyridone, but two examples stand out in which yields of the bicycles are particularly high (Scheme 43); presumably dimerization is disfavored in these systems. The bicycles **118** were easily separated from the dimers, as **118** were all liquids or low-melting solids, whereas the dimers are crystalline solids melting above 200 °C. It seems likely, therefore, that in (some of) the previously reported experiments, the formation of bicyclic lactams may have overlooked, especially when products were purified solely by recrystallization. Although De Selms and Schleigh reported the yields of the bicyclic lactams obtained, the yields of the dimers were not given, thus it is difficult to accurately gauge the selectivity for 4-π-photocyclization versus dimerization.
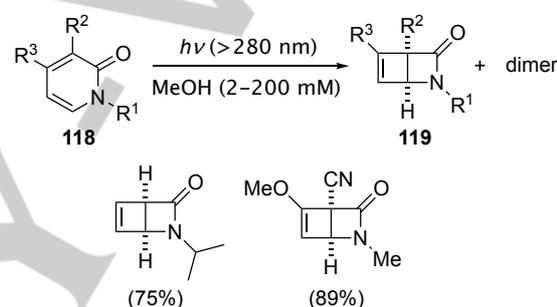
Scheme 43. 4-π-Photocyclization of substituted 2-pyridones in methanol.

Furrer carried out similar studies on a range of substituted 2-pyridones **120**, and in most cases bicyclic lactams were obtained in good yields (selected examples are shown in Table 1).[80] The conversion of **120** to **121** was relatively slow – several of the reactions did not reach completion despite very long irradiation times (Table 1, entries 3-5). In these cases the isolated yields reported for the bicyclic lactams are adjusted based on the amount of starting 2-pyridone recovered. In two examples, the yield of the dimer was also reported (Table 1, entries 1 and 3).
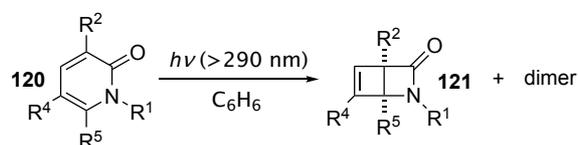
entry	R^1	R^2	R^3	R^4	Time (h)	Yield **120** (%)	Yield dimer (%)
1	vinyl	H	H	Me	n.r.	85	9
2	Ph	H	H	Me	88	90	n.r.

3	Me	H	H	Me	150	67[a]	24[a]
4	Me	Me	Me	Me	256	45[a]	n.r.
5	Me	NHAc	H	^{i}Pr	141	62[a]	n.r.

[a] Isolated yield is based on the amount of recovered starting material.

Table 1. 4-π-Photocyclization of substituted 2-pyridones in benzene.

Furrer also studied several standard synthetic transformations of bicycles **121**. For example, heating of the bicycles at reflux in chlorobenzene results in rapid regeneration of the 2-pyridone starting materials, and the hydrogenation of **121a** led to saturated bicycle **122** (Scheme 44). The attempted ozonolysis of **123** did not lead to the expected ketoaldehyde, but rather to bis-acetal **124** in 33% yield, and the attempted ring-opening of the lactam ring by heating in acidic ethanol was also unsuccessful (the cyclobutene ring was destroyed under these conditions, as only acyclic products were recovered).
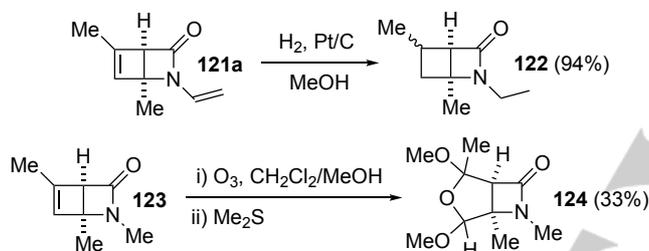
Scheme 44. Synthetic transformations of bicyclic lactams.

Kaneko and co-workers found that when the 4-position of the 2-pyridine was substituted with an *O*-alkyl or an acetoxy substituent, selective 4-π-photocyclization occurred, with no trace of dimeric products.[81] Varied examples were studied, and the corresponding bicyclic lactams were obtained in excellent yields (Scheme 45).
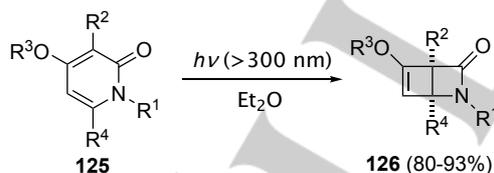
Scheme 45. 4-π-Photocyclization of 2-pyridones bearing oxygen substituents.

The total lack of dimerization observed for 4-oxygenated 2-pyridones is not well understood, although interestingly, Sieburth and co-workers found that although 4-methoxy-2-pyridone does not undergo dimerization upon irradiation, it *does* undergo [4+4] cycloaddition with other 2-pyridones such as 4-butyl-2-pyridone. Here, high concentrations of 2-pyridones were maintained in order to suppress the competing 4-π-photocyclization process.[82]

Only one report of the 4-π-photocyclization of a 3-oxygenated 2-pyridone has appeared. Somekawa and co-workers reported that upon direct irradiation, 2-pyridone **127** was converted into bicyclic lactam **128** in 50% yield, whilst upon triplet sensitization, [2+2] photocycloaddition involving the pendent alkyne took place, giving tricycle **129** in 25% yield (Scheme 46).[83]
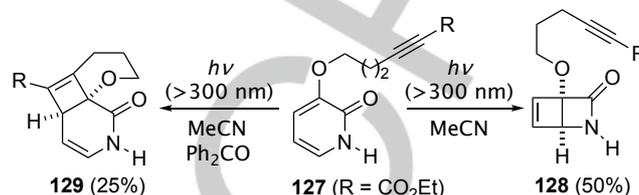
Scheme 46. Photochemistry of a 3-oxygenated-2-pyridone with alkyne tether.

From the examples presented so far, it is clear that the main limitation in the 4-π-photocyclization of 2-pyridones arises from competing dimerization. In some cases, dimerization is reported to dominate, whereas in other cases, 4-π-photocyclization is the favored pathway. Since 4-π-photocyclization is a unimolecular process and dimerization is a bimolecular process, it follows that the concentration of the substrate likely has a profound effect on the reaction outcome. Mariano and Leone demonstrated that substrate concentration does indeed strongly influence the photochemistry of *N*-vinyl-substituted 2-pyridones – at low concentrations (4 mM) in THF, 2-pyridones **130** were selectively converted to bicyclic lactams **131**, whilst more concentrated solutions (30-50 mM) led to selective dimerization (Scheme 47).[84]
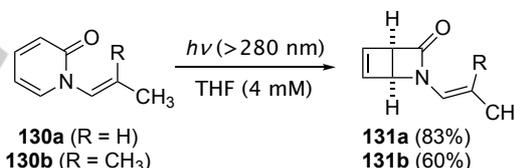
Scheme 47. Selective 4-π-photocyclization at low substrate concentration.

Matsushima and Terada carried out a systematic study on the photochemistry of a series of substituted 2-pyridones **132** (Figure 3), aiming to better understand the effect of substrate structure, temperature, concentration and solvent on the reaction
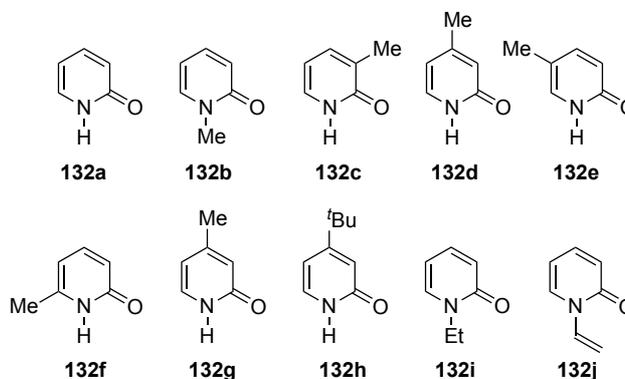
outcome.[85] As expected, lower concentration favors 4-π-photocyclization, whilst higher concentrations favor dimerization.

The quantum yields of the 4-π-photocyclization of **132** are low due to the very short-lived (< 1 ns) singlet excited states involved, and do not vary a great deal with solvent or with different substituent patterns (although it is notable that the quantum yield for 4-π-photocyclization is significantly higher for **132h** (0.07) and significantly lower for **132f** (0.01) than for the other examples (0.02-0.04). The chemical yield varied with solvent (EtOH, EtOAc, THF and hexane afford the highest yields of photocyclization product), and with substituent pattern, with the 4-alkylated pyridines (**132d**, **132g** and **132h**) giving the highest yields (the high yield of photocyclization product from **132h** had already been noted by Kanaoka and co-workers.[86] Matsushima and Terada also studied the ground-state association equilibria in 2-pyridones **132a-j**,[87] which were postulated to play an important role in the selectivity for unimolecular or bimolecular reaction of **132**. In general, *N*H-2-pyridones exist largely as hydrogen-bonded pairs in non-polar solvents, and partly so in polar solvents. On the other hand, it was shown that 2-pyridones (especially *N*-alkyl pyridines) likely associate through dipole-dipole pairing, whilst **132h** showed no tendency to associate in solution.

The preceeding examples of 2-pyridones invariably involve relatively electron-rich substituents – there are very few examples of the 4-π-photocyclization of 2-pyridones bearing electron-withdrawing groups. One such example was reported by Nakano and Hongo, in a study that looked at the photochemistry of the two isomeric 2-pyridones **133** and **135** (Scheme 48).[88] Interestingly, whilst **133** gave the expected bicycle **134** in 52% yield, **135** did not give the expected 4-π-photocyclization – instead, a dimer was formed in 80% yield (the dimer structure was not reported, and no rationale was provided for the difference in reactivity observed in these two very similar substrates).
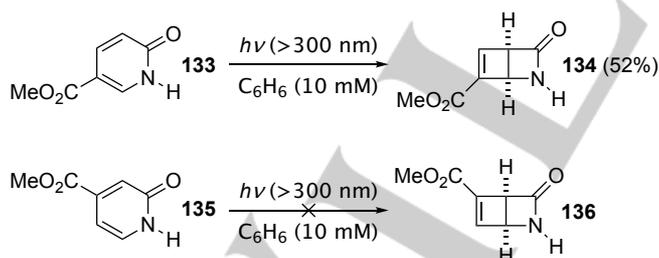
Scheme 48. Complementary photochemistry of methoxycarbonyl-2-pyridones.

Young and co-workers studied the 4-π-photocyclization of a range of related bicyclic 2-pyridones, producing tricyclic azetidinones related to the cephalosporins. For example, 2-pyridone **137** underwent successful 4-π-photocyclization upon irradiation in benzene, generating tricycle **138** in 74% yield (Scheme 49). The photoproduct was reported to be unstable

(undergoing thermal reversion to **137**), but the cyclobutene ring could be hydrogenated to produce a more stable derivative.[89]
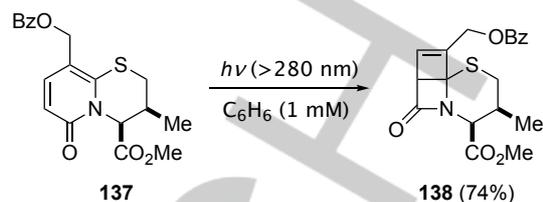
Scheme 49. 4-π-photocyclization of a bicyclic 2-pyridone.

Perhaps due to their obvious potential as useful precursors to β-lactam antibiotics, the bicyclic lactam products generated from the 4-π-photocyclization of 2-pyridones have received significant synthetic attention, and several approaches to polysubstituted monocyclic azetidinones have been described. For example, ozonolysis of the cyclobutene ring in bicycle **139**, followed by reduction of the resulting aldehyde was employed by Honda and co-workers to generate *trans*-azetidinone **140**,[90] whilst Brennan reported the production of *cis*-azetidinone **142** from bicycle **141** through ozonolysis with in-situ reduction of the intermediate molozonide (Scheme 50).[91]
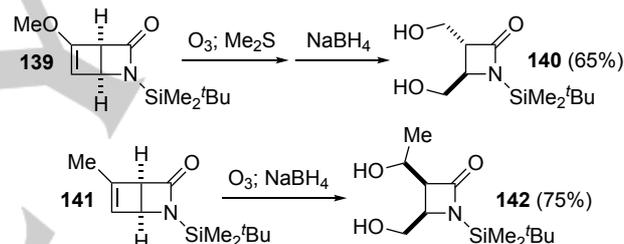
Scheme 50. The ozonolysis approach to monocyclic azetidinones.

Kaneko and co-workers pioneered a complementary approach to monocyclic azetidinones starting from 4-oxygenated-2-pyridones. For example, 4-π-photocyclization of such substrates generated bicycles **143** and **146**, which underwent retro-aldol cleavage of the original cyclobutene ring, resulting in substituted monocyclic azetidinones **145** and **148** respectively (Scheme 51).[81,92] This approach was later extended to more substituted 2-pyridones,[93] then further expanded by replacing the oxygen substituent with a chiral auxiliary, to enable access to enantiopure azetidinones.[94]
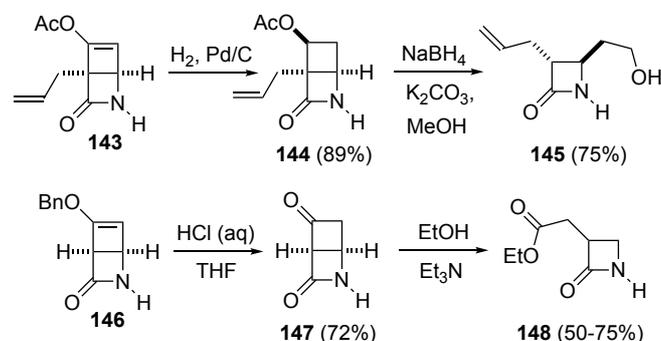
Scheme 51. The retro-aldol approach to monocyclic substituted azetidinones.

Adamo and co-workers prepared functionalized azetidinones from bicyclic lactams through ring-opening/cross metathesis sequences.[95] Thus, treatment of bicycle **149** with the Grubbs I catalyst in the presence of ethylene led to divinylazetidinone **150** in 50% yield (Scheme 48). Using styrene or 1-hexene, the yields of ring-opened products were much lower (12-28%), but much higher yields were obtained with silyl-protected bicycles. For example, bicycle **151** could be ring-opened using the above-described metathesis conditions to give divinylazetidinone **152** in 89% yield (Scheme 52).
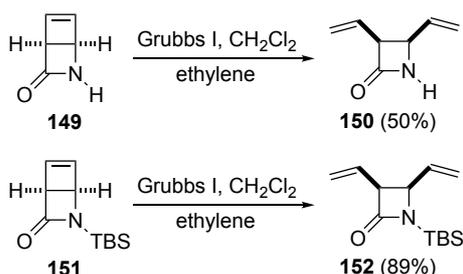
Scheme 52. The metathesis approach to monocyclic azetidinones.

On the other hand, Katagiri, Sato and Kaneko succeeded in ring-opening the azetidinone ring in **153**, through conversion to urea **154** followed by treatment with sodium methoxide, generating **155** (an analogue of oxetanocin) in excellent yield (Scheme 53).[96]
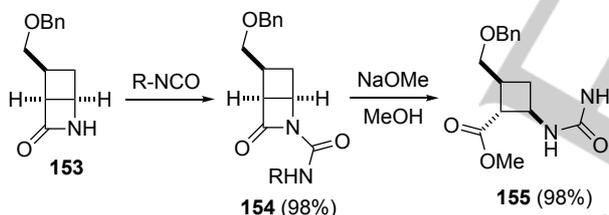
Scheme 53. Ring-opening of the azetidinone ring in a bicyclic azetidinone.

In a complementary application, Tsuchiya and co-workers employed the bicyclic lactam products **156** obtained from the 4-π-photocyclization of MOM-protected 2-pyridones as precursors to azepinone derivatives. Thus, the cyclobutene ring in **156** underwent epoxidation or aziridination to give the corresponding tricycles **157a** and **157b**, which could be converted into azepinone derivatives **158a** and **158b** respectively by heating (Scheme 54).

156a (X = O)   **157a** (95%)   **158a** (70%)
156b (X = N-CO₂Et)   **157b** (35%)   **158b** (72%)
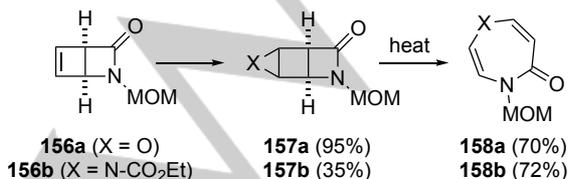
Scheme 54. Ring-opening tricycles to produce azepinone derivatives.

Given the demonstrated broad synthetic potential of the bicyclic lactam products obtained through the 4-π-photocyclization of 2-pyridones, it is not surprising that a number of studies directed towards the preparation of enantiopure bicyclic lactams have appeared. Earlier reports by Hongo and co-workers focused on the lipase-catalyzed resolution of racemic bicyclic lactams,[97] allowing relatively low yields (3-34%) of highly enantioenriched bicyclic lactams to be obtained (enantiomeric excesses of 81 to >98% were reported). Subsequently, a number of groups have reported approaches to enantioselective 4-π-photocyclization, including the use of a chiral template,[98] cyclodextrin inclusion complexes,[99] chiral auxiliaries within zeolites,[100] and direct irradiation of crystals or inclusion complexes in the solid state.[101] A detailed discussion of these processes is beyond the scope of this review, but it is fair to say that the enantioselectivity obtained using these methods remains moderate, and not yet at a level that would be considered useful in synthesis. More recently, Sivaguru and co-workers studied the 4-π-photocyclization of axially chiral 2-pyridones and achieved enantiomeric excesses of up to 95%.[102] This work was followed by a study on the effect of elevated pressure on the enantioselectivity, although the focus was directed more to theoretical aspects than preparative utility.[103]

In conclusion, the 4-π-photocyclization of 2-pyridones has received a great deal of attention over the years, at least partly due to the rich potential of the bicyclic lactam products formed as intermediates in the synthesis of β-lactam antibiotics. In general, to ensure high yields of the photocyclization product, irradiation should be carried out at low substrate concentration in order to suppress dimerization. The reaction is generally well-understood, although there is little understanding of the particular propensity for some 2-pyridones (in particular, 4-oxygenated 2-pyridones) to undergo 4-π-photocyclization rather than dimerization even at higher concentrations. To further advance the synthetic applications of the bicyclic azetidinones produced through these procedures, new approaches for *enantioselective* 4-π-photocyclization of 2-pyridones would be particularly useful.

4.3. 1,2-Dihydropyridines

Fowler and co-workers were the first to study the 4-π-photocyclization of 1,2-dihydropyridines.[104] **159** was prepared directly from pyridine in approximately 60% yield, and could be converted to bicyclic azetidine **160** either by irradiating at 300 nm in dichloromethane, or at 350 nm in acetone (Scheme 55). The corresponding azetidine product was also produced starting from 3-ethylpyridine, but no yields were given. The authors envisaged the application of this methodology in alkaloid synthesis, and described **160** as a "masked 1,2-dihydropyridine" since it is much more stable than **159** (which is relatively unstable towards oxidation and polymerization).

159 (~60%)   **160** (50%)
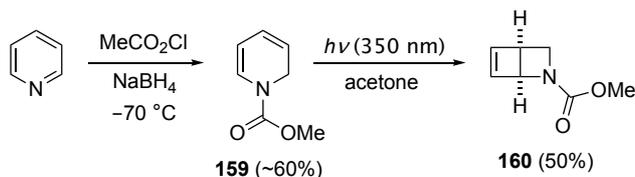
Scheme 55. 4-π-photocyclization of a 1,2-dihydropyridine.

Fowler reported that bicyclic azetidine **160** could be easily transformed to the *N*-methyl derivative using lithium aluminium hydride, and other alkyl protecting groups could be introduced by first removing the methyl carbamate upon exposure to methyllithium (Scheme 56). More recently, Opatz and co-workers prepared quaternary azetidinium salt **163** in 86% yield (over two steps from bicyclic azetidine **160**) upon reaction of **161** with methyl triflate (Scheme 56).[105]

162 (49%) **160** **163** (86%)

161 (quant.)
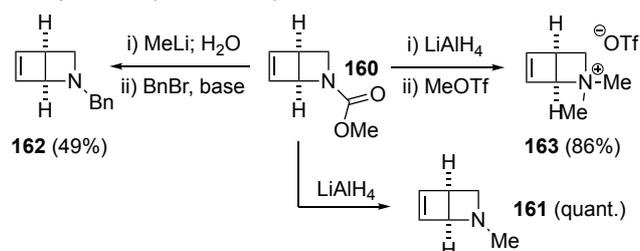
Scheme 56. Derivatization of bicyclic azetidine **160**.

Tsuchiya and co-workers extended Fowler's work to prepare a range of bicyclic azetidines **165** (Scheme 57).[106] The 1,2-dihydropyridines **164** were prepared from (substituted) pyridine using Fowler's method, or by addition of phenyl magnesium bromide to pyridine in the presence of benzyl chloroformate, and irradiation of **164** in dichloromethane for 10-18 hours gave the bicyclic azetidines **165**, albeit in low yields.

164 $h\nu$ (>280 nm) CH_2Cl_2 **165** (15-26%)

$R^1 = H/Me$, $R^2 = H/Me/Ph$, $R^3 = H/Ph$, $R^4 = Me/Bn$
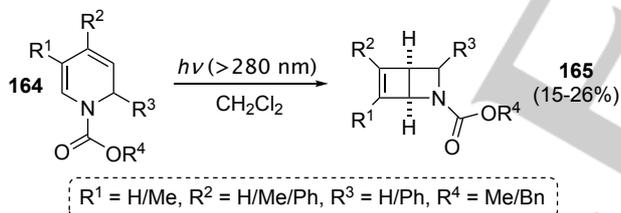
Scheme 57. 4-π-photocyclization of substituted 1,2-dihydropyridines.

The bicyclic diazetidines **165** prepared by Tsuchiya were transformed into azepine derivatives in a two-step procedure. For example, functionalization of the cyclobutene in bicycle **165a** (to the corresponding epoxide, aziridine, thiirane or cyclopropane), followed by heating furnished a range of (hetero)azepine derivatives, in good yields over two steps when X = O (85%) and when X = S (58%). The aziridination and cyclopropanation of **165a** proceeded in low yields, resulting in lower isolated yields of **167** when X = N-CO$_2$Et or CH$_2$ (Scheme 58).

165a **166** heat **167**

X = O, N-CO$_2$Et, S or CH$_2$
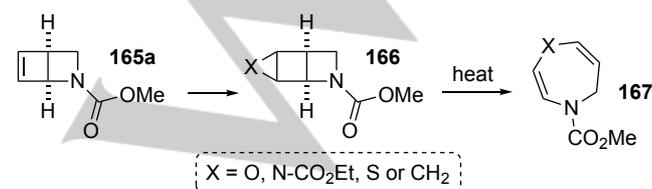
Scheme 58. Two-step conversion of bicyclic azetidines to azepine derivatives.

Arakawa and co-workers reported the 4-π-photocyclization of **159** using Fowler's conditions, generating bicyclic azetidine **160** in an excellent 85% yield – significantly higher than the yields reported by Fowler and Tsuchiya.[107] RuO$_4$-mediated oxidative cleavage of the cyclobutene ring followed, yielding the disubstituted monocyclic azetidine **168** in reasonable yield after esterification of the initially formed diacid (Scheme 59).

159 $h\nu$ (>280 nm) CH_2Cl_2 **160** (85%) i) RuO$_4$ ii) CH$_2$N$_2$ **168** (58%)
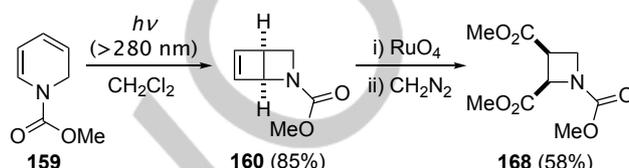
Scheme 59. Oxidative cleavage of the cyclobutene ring in bicycle **160**.

Krow and co-workers investigated the 4-π-photocyclization of a range of substituted 1,2-dihydropyridines **169** (Table 2) upon irradiation at 300 nm in acetone.[108] The highest yield of bicyclic azetidine was obtained from the unsubstituted 1,2-dihydropyridazine **169a**, whilst the addition of substituents led to decreased yields. When $R^3 \neq H$, the photocyclization is torquoselective, placing the R^3 substituent in the *endo* position.

169 $h\nu$ (300 nm) acetone **170**
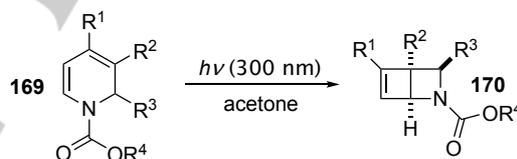
starting material	R^1	R^2	R^3	R^4	Yield **170** (%)
169a	H	H	H	Et	50
169b	H	Me	H	Et	16
169c	H	H	Me	Et	21
169d	H	Me	Me	Et	13
169e	H	H	Ph	Et	15
169f	Me	H	H	Et	25
169g	H	H	CH$_2$OH	Me	20
169h	CH$_2$OH	H	H	Me	17
169i	H	H	CH$_2$SiMe$_2$Ph	Bn	30

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Table 2. 4-π-photocyclization of substituted 1,2-dihydropyridines.

Krow and co-workers also investigated the functionalization of the cyclobutene ring in bicycles **170**. When R^3 = H, mixtures of dibromides **171** and rearranged dibromides **172** were obtained, with the latter proposed to arise via an aziridinium ion formed through attack of the nitrogen lone pair on the initially formed bromonium ion (Scheme 60).[108b,c] In contrast, when $R^3 \neq H$, only the rearranged bromides were observed in excellent yields. The treatment of bicyclic azetidine **173** under similar conditions generated acetoxy bromide **174** in 89% yield (Scheme 60).
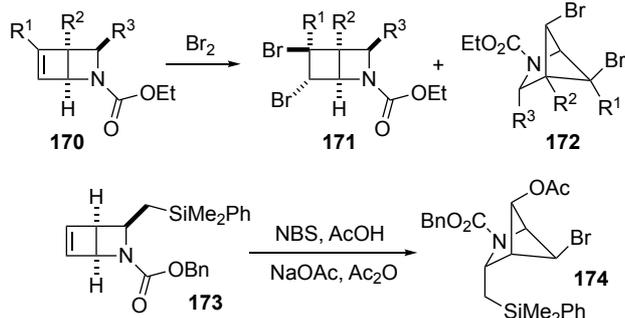
Scheme 60. Functionalization of the cyclobutene ring in bicycles **170** and **173**.

In summary, the 4-π-photocyclization of a range of substituted 1,2-dihyropyridines has been studied. The bicyclic azetidine products represent versatile synthetic intermediates that have, as yet, been underexploited in synthesis. The low-moderate yields reported for these photocyclizations have limited the wider appreciation of the synthetic utility of this transformation, and the cause of the low yields has not been clearly explained in previous work. Future endeavors should focus on optimizing the photocyclization, allowing a full understanding of side reactions, as well as enabling the derivatization of the bicyclic azetidine products to produce varied interesting molecular architectures.

4.4. Other Heterocyclohexadiene Systems

Due to its role in UV-induced DNA damage, the 4-π-photocyclization of the pyrimidin-2(1H)-one chromophore has been studied by various chemical biologists and biochemists.[109] The transformation has also been extensively studied using simple pyrimidin-2(1H)-ones by the Nishio group. Thus, upon irradiation in benzene, trisubstituted pyrimidin-2-ones such as **175** underwent photocyclization, generating the corresponding bicyclic diazetidinone products **176** in moderate-high yields (Scheme 61).[110] Bicycles **176** could be transformed into substituted quinolines **177** simply by heating (Scheme 61).[111] In contrast, less substituted pyrimidinones underwent ring opening to N-aryl imines rather than photocyclization.[112]

Scheme 61. Photochemistry of substituted pyrimidin-2-ones.
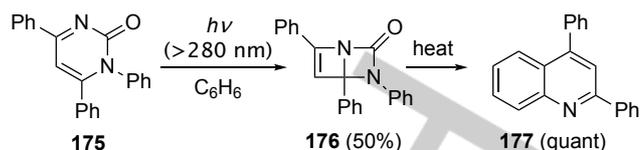
Nanjia, Desiraju and co-workers investigated the 4-π-photocyclization of pyrimidin-2-one **178** in an approach to non-natural β-lactam analogues.[113] Thus, irradiation for three hours in benzene led to a photostationary state (~1:1 ratio of **178**:**179**; Scheme 62). Bicycle **179** was obtained in excellent yield considering the ~50% conversion, and the azetine ring could subsequently be cleaved through ozonolysis to give aldehyde **180** in good yield. From **180**, a wide variety of different β-lactam mimics (including **181**-**184**) were prepared (Scheme 62).
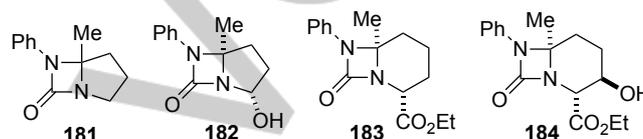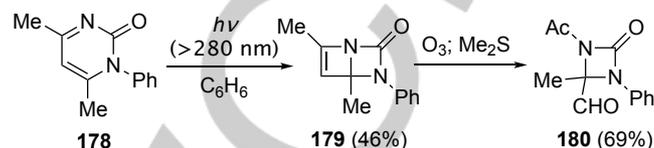
Scheme 62. Photochemistry and applications of pyrimidin-2-ones.

The 4-π-photocyclization of 1,2-dihydropyridazines has also been investigated, albeit in limited detail. The first example was published by Altman and co-workers, who prepared bicyclic diazetidine **186a** through irradiation of 1,2-dihydropyridazine **185a** (Scheme 63).[114] A reasonable yield of **186a** was reported (61%) along with a lower yield of pyrrole **187a**, which was proposed to arise through a 6-π-ring-opening to give a diimine, followed by cyclisation. Warrener and co-workers later reported that they could only obtain yields of **186a** of around 20% using this approach,[115] but Stearns and Ortiz de Montellano reported a similar yield for the 4-π-photocyclization of dihydropyridazine **185b** to give **186b**, again accompanied by the corresponding pyrrole product.[116]

185a (R = Me)   **186a** (61%)   **187a** (14%)
185b (R = Et)   **186b** (~60%)   **187b** (yield n.r.)
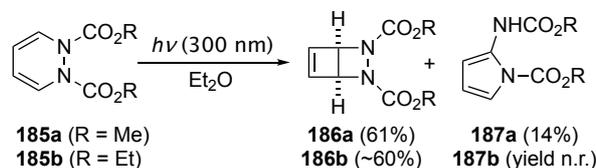
Scheme 63. Photochemistry of 1,2-dihydropyridazines.

For applications in solar energy storage, the groups of Liu and Bettinger studied the 4-π-photocyclization of 1,2-dihydro-1,2-azaborinine derivatives such as **188**, first under matrix isolation conditions,[117] then in solution.[118] Upon irradiation in deuterated cyclohexane, **188** underwent clean photocyclization to **189** (Scheme 64). The product could be isolated, and was reported to

be stable for weeks under inert atmosphere, but no yield was reported. Further irradiation at 254 nm was reported to lead to cycloreversion to cyclobutadiene and iminoborane **190**, with the latter being isolated after dimerization to a diazadiboretidine.
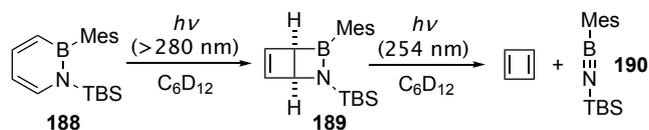
Scheme 64. 4-π-Photocyclization of 1,2-dihydro-1,2-azaborinine **188**.

5. Conclusions

The 4-π-photocyclization of a wide range of cyclic 1,3-diene systems leads to interesting bicyclic cyclobutene products, often in good yields. Various different photoprocesses may compete with the 4-π-photocyclization, depending on the structure of the substrate, although in some cases these side reactions can be minimized by careful control of the irradiation conditions. In general, earlier reports of 4-π-photocyclizations focused on the feasibility of the cyclization, as well as mechanistic studies, which has greatly enriched our understanding of the reactivity of these systems upon irradiation. However, in many cases the isolated yields of products are not reported, and irradiation conditions may not be described in detail, which often makes the preparative utility of these reactions difficult to estimate. Nevertheless, recent creative applications of 4-π-photocyclizations in total synthesis as well as medicinal chemistry and materials chemistry have highlighted the synthetic potential of these processes. With the plethora of photochemical equipment now available to the synthetic chemist (and the recent focus on photochemistry in flow as an enabling technique), further work will no doubt optimize those processes that have already been described, and enable the discovery of new 4-π-photocyclizations as well as the application of this methodology in other areas of research. Like cycloaddition reactions, such as the ubiquitous Diels-Alder reaction, 4-π-photocyclizations offer total atom economy, and deliver products that are primed for further functionalization. Nevertheless, 4-π-photocyclizations have been particularly underexploited in synthesis compared to the Diels-Alder reaction. The examples discussed in this minireview serve to highlight the synthetic potential of these intriguing reactions and their versatile bicyclic products, and it is hoped that in the future a more widespread appreciation of the 4-π-photocyclization as well as the versatility of their bicyclic products will inspire further innovations in this exciting area of synthetic photochemistry.

Keywords: cyclization • electrocyclic reaction • photochemistry • cyclobutene • pericyclic reaction

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Entry for the Table of Contents

Layout 2:

MINIREVIEW

Photocyclization

Susannah C. Coote*

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4-π-Photocyclization: Scope and Synthetic Applications
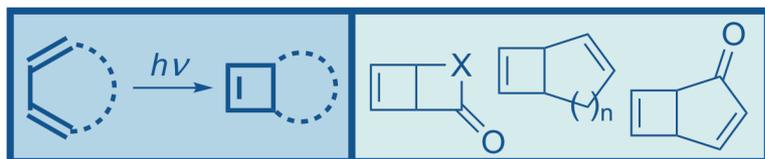
4-π-Photocyclizations (also referred to a valence isomerizations) allow the generation of versatile bicyclic cyclobutenes building blocks from a range of 1,3-dienes in a totally atom-economical process. Herein, the historical developments and recent innovations in 4-π-photocyclizations are reviewed, illustrated by applications of these intriguing reactions in total synthesis, medicinal chemistry and materials chemistry.