4-π-Photocyclization: Scope and Synthetic Applications

Susannah C. Coote[a]

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-dihydropyrazines. 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, 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, asymmetric electrocyclic reactions, and the application of electrocyclic reactions in complex natural product synthesis.[4-π-Electrocyclizations (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]

Susannah C. Coote was born in Bristol in 1981. She received her MChem degree from the University of York (UK) in 2003, after spending her final year at the Université Joseph Fourier (France). Susannah remained at the University of York for her graduate studies, working with Prof. Peter O’Brien on aziridine chemistry. After the award of her PhD degree in 2007, Susannah undertook postdoctoral positions at the Université Paris-Sud in France (2007-2008, working with Prof. Cyrille Kouklevsky on nitroso-Diels-Alder reactions), and the University of Manchester (2009-2012, working with Prof. David Procter on new samarium diiodide-mediated methodology). In 2012, she was awarded an Alexander von Humboldt fellowship and moved to the Technische Universität München in Germany to work with Prof. Thorsten Bach on enantioselective photochemistry. Susannah was appointed to a lectureship at Lancaster University (UK) in 2014. Her research group focuses on the development of new photochemical methodology, in particular on the synthesis of four-membered rings.

[a] Dr S. C. Coote
Department of Chemistry
Lancaster University
Bailrigg, Lancaster, LA1 4YB
E-mail: s.coote@lancaster.ac.uk
Homepage: susannahcoote.wordpress.com
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.\(^10\)

\[\text{hv} \quad \text{H}_2\text{SO}_4 (aq) \quad \xrightarrow{HBF_4^\text{-}} \quad \text{H}_2\text{O} \quad \text{BF}_4^- \quad \xrightarrow{\text{FSO}_2\text{H} \ -60 \ ^\circ\text{C}} \quad \xrightarrow{47 \ ^\circ\text{C}} \quad \text{4} \]

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).\(^13\)

\[\text{hv (254 nm)} \quad \text{pentane} \quad \xrightarrow{5} \quad \text{6} \]

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).\(^14\)

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.\(^18\)

\[\text{hv} \quad \text{9} \quad \xrightarrow{[6+4]} \quad \text{[6+2]} \quad \text{[4+2]} \quad \text{[6+6]} \]

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).\(^19\)
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).\(^\text{19}\) 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.\(^\text{20}\) Thus, irradiation of BF\(_3\)-9 in acetonitrile for 30 minutes resulted in 80% conversion, and the photocycloadduct 12 was isolated in 59% yield (Scheme 6).\(^\text{21}\) Similar results were also observed through adding one equivalent of BF\(_3\)-EtO\(_2\) (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 BF\(_3\)-9 complex is more intense than that of uncomplexed 9, although no significant absorption shift was observed upon complexation with BF\(_3\).

**Scheme 6.** 4-π-Photocyclization of tropone in acidic organic solutions.

The photochemistry of annelated tropones was investigated by Jones and co-workers.\(^\text{22}\) Thus, benzo-fused tropones 13 underwent 4-π-photocyclization upon irradiation when R\(^1\) and/or R\(^2\) was an electron-donating group, generating tricyclic cyclobutenes 14 in low-moderate yields (Scheme 7). Interestingly, other benzotropones (bearing OH, NO\(_2\), NH\(_2\), Br substituents) gave only polymeric material upon irradiation.

**Scheme 7.** 4-π-photocyclization of benzotropones 13 to give cyclobutenes 14.

Heterocyclic analogues of benztropones 13 were also studied\(^\text{23}\) and in the case of thiophene-fused 15 tropones, the substitution pattern on the tropone was found to strongly influence the reactivity. Hence, thienotropane 15 did not undergo 4-π-photocyclization; instead, dimerization took place, forming photodimer 16 in low yield (Scheme 8). In contrast, thienotropane 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.

Carreno and co-workers described the 4-π-photocyclization 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.\(^\text{24}\) 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\(^\text{25}\) and perfluorinated\(^\text{26}\) 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 tropolones that bear a hydroxy substituent at any point around the ring. Whilst their structure is very similar to tropolones, their photochemistry is markedly different. Three isomers of tropolone are possible, depending on the position of the hydroxy group: the \( \alpha \), \( \beta \) and \( \gamma \)-tropolones (Figure 1).

![Figure 1. The \( \alpha \), \( \beta \) and \( \gamma \)-tropolones.](image)

Chapman and Pasto outlined three possibilities for the electrocromerization of tropolone systems, namely the Type A, Type B and Type C cyclizations (Scheme 10). Type A (a \( 6 \pi \)-electroclysis 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 \( 4 \pi \)-cyclizations, and differ in the choice of the \( 4 \pi \)-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 \( \alpha \)-tropolone derivatives: Types B and C.](image)

The first example of the \( 4 \pi \)-photocyclization of a simple tropolone derivative was reported by Chapman and Pasto in 1960.\(^{27} \) An aqueous solution of \( \gamma \)-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 \( \gamma \)-tropolone methyl ether.](image)

The following year, the groups of Daub and Chapman disclosed the results of their study on the photochemistry of \( \alpha \)-tropolone methyl ether 23, which turned out to be quite complex.\(^{28} \) Although 23 initially underwent a Type B \( 4 \pi \)-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 \( \alpha \)-tropolone methyl ether.](image)

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 wurtzite 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 methoxo group. The collapse of 28 results in the re-formation of 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.](image)

The remarkable transformation of 24 into 25 has been exploited by Winter and Trauner in the first step of their synthesis of \((\pm)\) hippolachnin A, in which the central carbon skeleton of the target molecule is formed in just one step (Scheme 14).\(^{30} \)

![Scheme 14. Synthesis of \((\pm)\) hippolachnin A.](image)
In common with its methyl ether, \( \alpha \)-tropolone itself (29) undergoes 4-\( \pi \)-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, Wulf and co-workers obtained bicycle 30 in 83\% yield through irradiation of a thin-layer solution of \( \alpha \)-tropolone at 300 nm in dichloromethane. \(^{32}\)

The bicyclic product formed upon irradiation of tropolone has wide synthetic potential. For example, Wulf 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). \(^{32}\)

Mukai and Miyoshi studied the photochemistry of 5-phenyl-\( \alpha \)-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 \( \alpha \)-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-\( \alpha \)-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.

The photochemistry of a limited range of benzo-fused tropolones has also been described. Forbes and co-workers reported that whilst benzotropolone 43 underwent 4-\( \pi \)-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\textsuperscript{36b} 3,4-Benzotropolone (47) underwent cyclization to give tricycle 49 in “good yield”, with 48 proposed as a key intermediate (Scheme 19).

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

Scheme 19. Photochemistry of benzo-fused tropolones.

Colchicine (50) is an interesting tropolone-containing alkaloid that can be isolated from Colchicum autumnale, the autumn crocus.\textsuperscript{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.\textsuperscript{38} Subsequently, Forbes repeated the experiment, obtaining the same three products, although this time β-lumicolchicine was obtained as the major product.\textsuperscript{39} The structures of the β- and γ-lumicolchicines (51a and 51b) were elucidated by Forbes,\textsuperscript{39} by Gardner and co-workers,\textsuperscript{40} and by Chapman and co-workers,\textsuperscript{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.\textsuperscript{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 diradical cyclization of colchicine from its first excited singlet state.\textsuperscript{43} The photochemistry of thiocolchicine (53, Scheme 20) was also investigated,\textsuperscript{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 acetylenicolchinol-O-methyl ether (NCME),\textsuperscript{44} which is active against several cancer cell lines and exhibits greater inhibition of tubulin assembly than colchicine itself.\textsuperscript{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 \textit{retro}-4-π-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/\textit{retro}-cyclization step, with the two-step procedure (involving purification of 51a) giving superior results.
A number of approaches to enantioselective 4-π-photocyclizations of tropolones have also appeared, but are beyond the scope of this review. So far, only moderate enantioselectivities have been obtained, using methods based on polymer microcapsules, liquid crystals, cyclodextrins, and inclusion complexes. In summary, the photochemistry of cycloheptatriene systems (including tropolones 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. Carboxyclic 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 pyrociferol 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 for a near-planar arrangement of the two double bonds.

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). Tricyclic 61 has very recently been employed in approaches to trans-poly(acetylene), as well as to benzoladderane mechanophores.
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.\(^{66}\)

**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,\(^{68,69}\) 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).\(^ {70}\) The latter reaction is thought to be initiated via \(n \rightarrow \pi^*\) 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).\(^{66}\) 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-pyrene 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-pyrene.
Subsequent studies by a range of research groups focused on the irradiation of 2-pyrene at very low temperatures (8-20 K) in argon matrices. 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.

The outcome of irradiation of 2-pyrene 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-butenolate (78) essentially quantitatively. 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-pyrene, resulting in constant consumption of ketene (Scheme 29). Interestingly, acetophenone-sensitized irradiation of 2-pyrene does not give 76, but rather two Diels-Alder-like dimers. Since the rate of reaction of 2-pyrene 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. 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). 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 diastereodivergent 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.

The relatively facile ring-opening of cyclobutenes through a thermal 4-π-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). This approach has been applied to the synthesis of several natural products, including (-)-heodomycin (Scheme 32), piperine and thionymycin C. Alternatively, the addition of phenols to bicyclic lactone 76 leads directly to diene products, via the corresponding cyclobutenyl intermediates. Here, 4-π-retro-cyclization occurs readily at room temperature – no heating is necessary.

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-pyrene itself, producing bicyclic lactones 86 in quantitative yield upon irradiation in diethyl ether –15 °C (Scheme 32).

![Scheme 30](image-url)

Scheme 30. Irradiation of 2-pyrene generates bicyclic lactone and ketene.

![Scheme 31](image-url)

Scheme 31. Alkylation of bicyclic lactone 76 to give substituted cyclobutenes.

![Scheme 32](image-url)

Scheme 32. Alkylation of bicyclic lactone 76 in the synthesis of (-)-heodomycin.
The photochemistry of 4,6-dimethyl-2-pyrene (87) was first studied by de Mayo.° Irradiation in methanol gave an alkene product derived from a ketene, in line with the behavior of 2-pyrene 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. 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-pyrene 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-pyrene.

The same authors also studied 3,4,5,6-tetramethyl-2-pyrene (92), expecting very similar reactivity to that of 87.° 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 keteketene 94) is also observed, whereas the analogous keteketene 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-pyrene.

De Mayo and co-workers investigated the photochemistry of 4-methoxy-6-methyl-2-pyrene (95a), reporting that upon irradiation in benzene, both the ketene 96a and the lactone 98a were formed (from inspection of infrared data).° 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-pyrene 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-pyrene 95b.° 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-pyrenes bearing oxygen substituents.

Javaheiripour and Neckers investigated the photochemistry of coumalic acid and several of its ester derivatives, both in solution and in the solid state.° 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-pyrene 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.

$$\text{MeO}_2\text{C} - \text{O} - \text{O} \quad \text{hv} (300 \text{ nm}) \quad \text{EtO} \quad \text{MeO}_2\text{C} - \text{H}$$

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 solvent diethyl ether, under conditions 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.

$$\text{MeO}_2\text{C} - \text{O} - \text{H} \quad \text{hv} (300 \text{ nm}) \quad \text{CHCl}_3 \quad 15^\circ \quad \text{MeO}_2\text{C} - \text{O} - \text{CO}_2\text{Me}$$

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-pyrene 105 could be converted to 11.1 grams of cyclobutane 107 (Scheme 37; 81% yield over two steps).

$$\text{MeO}_2\text{C} - \text{O} - \text{H} \quad \text{hv} (300 \text{ nm}) \quad \text{PhMe} (50 \text{ mM}) \quad 0.3 \text{ mL/min, 76 h} \quad 6-8^\circ \quad \text{H}_2 \quad \text{Pt/C} \quad \text{CO}_2\text{Bu} \quad \text{H}_2$$

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.76 Thus, 3-pyrene-2-pyrene 108 underwent photocyclization upon irradiation at 300 nm in benzene, producing bicyclic lactone 109 in 83% yield (yield determined by 1H NMR spectroscopy; Scheme 40). Next, rhodium-catalyzed cyclopropanation of 109 delivered usnus 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.

$$\text{hv} (300 \text{ nm}) \quad \text{Me}_2\text{C}_2 \quad \text{Rho(esp)}_2 \quad \text{CO}_2\text{DCE} \quad \text{EtO}_2\text{C} - \text{N}_2 \quad \text{H}_2\text{Pt/C} \quad \text{EtO}_2\text{C} - \text{H}$$

Scheme 40. Total synthesis of (±)-vibralactone (112).

In summary, the photochemistry of a range of different 2-pyrene 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 sensitizers (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-pyriones have been treated under exactly the same conditions. Therefore, it is difficult to predict the outcomes of irradiation of other 2-pyriones, 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-pyriones 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-pyrene, generating bicyclic lactam 114 in 20% yield upon irradiation (Scheme 41).

![Scheme 41. 4-π-photocyclization of N-methyl-2-pyridone.](image)

Interestingly, Corey and Streith made no mention of the formation of dimeric products, which several groups had previously obtained from the irradiation of 2-pyriones. 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. The dimers were initially incorrectly identified as 116, but subsequent reports confirmed the correct structure as 117 (Scheme 42).

![Scheme 42. Photochemical dimerization of 2-pyridones.](image)

Subsequently, Paquette and Slomp investigated the photochemistry of a range of 2-pyriones (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-Pyriones investigated by Paquette and Slomp.](image)

On the other hand, De Selms and Schleigh reported that upon irradiation in methanol, a range of substituted 2-pyriones (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. Lactams 118 were reported to be stable indefinitely at room temperature, but to revert to 2-pyriones 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.](image)

Furrer carried out similar studies on a range of substituted 2-pyriones 120, and in most cases bicyclic lactams were obtained in good yields (selected examples are shown in Table 1). 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).

<table>
<thead>
<tr>
<th>entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Time (h)</th>
<th>Yield 120 (%)</th>
<th>Yield dimer (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>vinyl</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>n.r.</td>
<td>85</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>88</td>
<td>90</td>
<td>n.r.</td>
</tr>
</tbody>
</table>
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).

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).

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. As expected, lower concentration favors 4-π-photocyclization, whilst higher concentrations favor dimerization. Figure 3. 2-Pyridones investigated by Matsushima and Terada.

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. Matsushima and Terada also studied the ground-state association equilibria in 2-pyridones 132a-d, which were postulated to play an important role in the selectivity for unimolecular or bimolecular reaction of 132. In general, NH-2-pyridines 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-pyridines 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-pyridines 133 and 135 (Scheme 48). Interestingly, whilst 133 gave the expected bicycle 134 in 52% yield, 135 did not give the expected 4-π-photocyclization – in fact, 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 photoproduce was reported to be unstable (undergoing thermal reversion to 137), but the cyclobutene ring could be hydrogenated to produce a more stable derivative.

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, whilst Brennan reported the production of cis-azetidinone 142 from bicycle 141 through ozonolysis with in-situ reduction of the intermediate molezonide (Scheme 50). 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). This approach was later extended to more substituted 2-pyridones, then further expanded by replacing the oxygen substituent with a chiral auxiliary, to enable access to enantiopure azetidinones.
Adam and co-workers prepared functionalized azetidinones from bicyclic lactams through ring-opening/cross metathesis sequences. 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).

In a complementary application, (π-opening the azetidinone ring in Scheme 89% yield (example, bicycle higher yields were obtained with silyl catalyst in the presence of ethylene led to divinylazetidinone 150% 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).

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). 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).

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, allowing relatively low yields (3-34%) of highly enantioenriched bicyclic lactams to be obtained (enantioenic 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, cyclodextrin inclusion complexes, chiral auxiliaries within zeolites, and direct irradiation of crystals or inclusion complexes in the solid state.

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 enantioemic excesses of up to 95%. 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.

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-oxyg enated 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. 159 was prepared directly from pyridine in approximately 60% yield, and could be converted to bicyclic azetidinone 160 either by irradiating at 300 nm in dichloromethane, or at 350 nm in acetone (Scheme 55). The corresponding azetidinone 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).
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 methylolithium (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

\[
\begin{align*}
\text{Bn} \quad \text{N} \quad \text{H} \quad \text{MeLi; H}_2\text{O} \\
\text{160} \quad \text{MeOTf} \\
\text{163} \quad \text{LiAlH}_4 \\
\text{161} \quad \text{quant.}
\end{align*}
\]

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 chlorofomate, and irradiation of 164 in dichloromethane for 10-18 hours gave the bicyclic azetidines 165, albeit in low yields.

\[
\begin{align*}
\text{R}^1 = \text{H/Me, R}^2 = \text{H/Me/Ph, R}^3 = \text{H/Ph, R}^4 = \text{Me/Bn} \\
\text{164} \quad \text{hv} (> 280 \text{ nm}) \quad \text{CH}_2\text{Cl}_2 \\
\text{165} \quad (15-26%)
\end{align*}
\]

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, thirane 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 azidination and cyclopropanation of 165a proceeded in low yields, resulting in lower isolated yields of 167 when X = N-CO2Et or CH2 (Scheme 58).

\[
\begin{align*}
\text{X} = \text{O, N-CO}_2\text{Et, S or CH}_2 \\
\text{165a} \quad \text{heat} \\
\text{166} \quad \text{167}
\end{align*}
\]

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 RuO4-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).

\[
\begin{align*}
\text{hv} (> 280 \text{ nm}) \quad \text{MeO} \quad \text{OR}^4 \\
\text{169} \quad \text{hv} (300 \text{ nm}) \quad \text{acetone} \\
\text{170} \quad \text{R}^1 \quad \text{R}^2 \quad \text{R}^3 \quad \text{R}^4 \quad \text{Yield 170 (\%)}
\end{align*}
\]

Table 2. Two-step conversion of bicyclic azetidines to azepine derivatives.

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 R3 ≠ H, the photocyclization is torqueselective, placing the R3 substituent in the endo position.
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). 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-dihydropyridines 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. 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). Bicycles 176 could be transformed into substituted quinolines 177 simply by heating (Scheme 61). In contrast, less substituted pyrimidinones underwent ring opening to \( N \)-aryl imines rather than photocyclization.

Scheme 61. Photochemistry of substituted 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). 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, 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.

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-diazaborinine derivatives such as 188, first under matrix isolation conditions, then in solution. 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 diazadiaboretidine.

Scheme 64. 4-π-Phtocyclization of 1,2-dihydro-1,2-azaborinine 188.

5. Conclusions

The 4-π-ph tocyclization 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-ph tocyclization, 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-ph tocyclizations 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-ph tocyclizations in total synthesis as well as medicinal chemistry and materials chemistry have highlighted the synthetic potential of these processes. With the plethora of photochemical tool available now 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-ph tocyclizations 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-ph tocyclizations offer total atom economy, and deliver products that are primed for further functionalization. Nevertheless, 4-π-ph tocyclizations 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-ph tocyclization as well as the versatility of their bicyclic products will inspire further innovations in this exciting area of synthetic photochemistry.

Keywords: cyclization • electron-cyclic reaction • photochemistry • cyclobutene • pericyclic reaction

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MINIREVIEW

Entry for the Table of Contents

Layout 2:

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4-π-Photocyclizations (also referred to as 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.