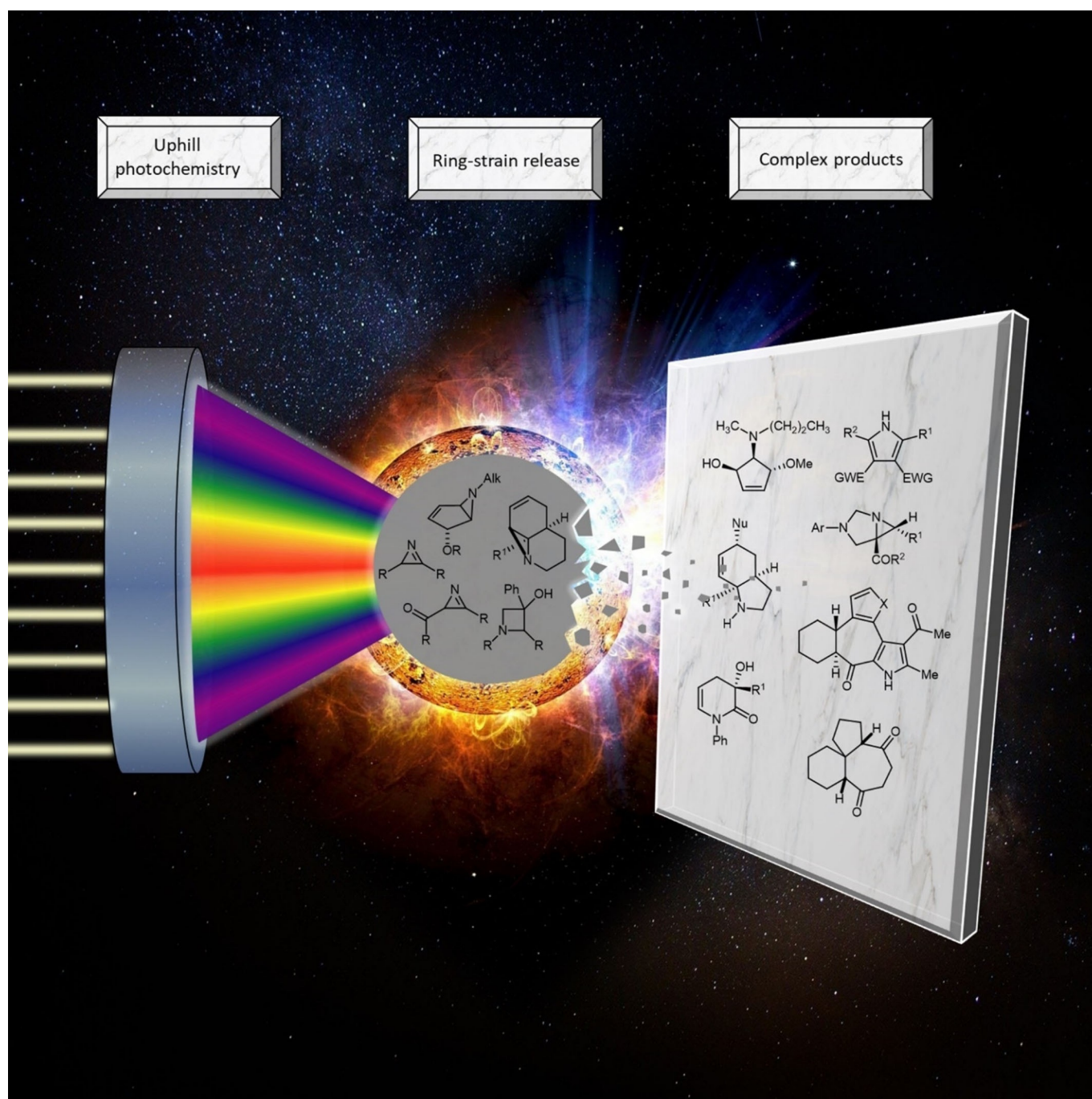▌**Photochemistry** |*Reviews Showcase*|

🏅 Strain Release Chemistry of Photogenerated Small-Ring Intermediates

Adriana Luque[+], Jan Paternoga[+], and Till Opatz*[a]

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Abstract: Photochemical processes, such as isomerizations and cycloadditions, have proven to be very useful in the construction of highly strained molecular frameworks. Photoinduced ring strain enables subsequent exergonic reactions which do not require the input of additional chemical energy and provides a variety of attractive synthetic options leading to complex structures. This review covers the progress achieved in the application of sequences combining excitation by ultraviolet light to form strained intermediates, which are further transformed to lower energy products in strain-release reactions. As ring strain is considerable in small ring systems, photogenerated three- and four-membered rings will be covered, mainly focusing on examples from 2000 to May 2020.

Introduction

The concept of ring strain, first described and intensely investigated by Adolf von Baeyer in 1885, has found broad application in organic synthesis.[1] In addition, a large number of natural products contain strained substructures.[2] Starting from the almost unstrained cyclohexane, contraction of the ring size builds ring strain energy dominated by angular (Baeyer) strain and torsional (Pitzer) strain (Figure 1), making three- and four-membered rings ideal substrates for strain-releasing chemistry.[3]

Although many of these small-ring systems are commonly synthesized in thermal reactions, the shape of the energy hypersurface of electronically excited states offers unique possibilities in terms of both selectivity of the reaction and structural complexity of the accessible strained compounds. Numerous excellent reviews on light-induced rearrangements and cyclo-

additions in the synthesis of small-ring carbocycles, heterocyclic analogues as well as natural products, have been published recently, pointing out the high potential of these transformations.[4]

Under the premise of sufficiently high quantum yields, photochemistry can also be preferable over classical reactions in view of the concept of green chemistry. Photon-absorption of UV-B irradiation ($\lambda \approx 300$ nm) for example corresponds to an energy equivalent of 95 kcal mol^{-1} and therefore gives access to traceless valence isomerizations or photoinduced cycloadditions resulting in products that energetically are clearly located uphill of the starting materials. The use of energy-transfer from photocatalysts excited by visible light to circumvent the use of UV radiation was also reviewed lately. It can also result in eco-friendly transformations, although the amount of energy that can be transferred to the substrate during these processes is lower than in the case of direct excitation.[6] Although other examples also exist, the light energy is often transformed into a certain ring strain of the photoproducts, which can be used in (catalyzed) follow-up reactions. As a potential drawback, high-energy intermediates are frequently also prone to undergo thermal or photochemical secondary reactions, making it often necessary to directly transform them into thermodynamically stable products to obtain high yields.

Depending on the reactivity of the strained intermediate and the nature of the reaction partner, the intended follow-up reactions can be performed without any added catalyst as well as under catalysis of Brønsted acids or bases or under Lewis acid catalysis. Recently, several groups also described (transition-)metal and photoredox catalysis in follow-up transformations of strained photoproducts. In all these examples, the inherent ring strain of the photogenerated intermediate serves as the driving force for the subsequent step(s). Surprisingly, in contrast to the rapidly growing number of transition metal-[7] as well as photoredox-catalyzed[8] transformations of strained substrates in terms of C–H and C–C bond activations, only few of the examples incorporate strained photoproducts. The combination of photoinduced generation of strained intermediates with fast (catalyzed) follow-up reactions could nevertheless be an advantageous general concept. The activation energy is injected into the molecule by photon absorption and circumvents the generation of low-energy co-products that for example drive classical C–C-cross coupling reactions. Additionally, the photochemical generation of the high-energy intermediates enables formal endergonic reactions between starting materials and follow-up products to proceed (Figure 2).
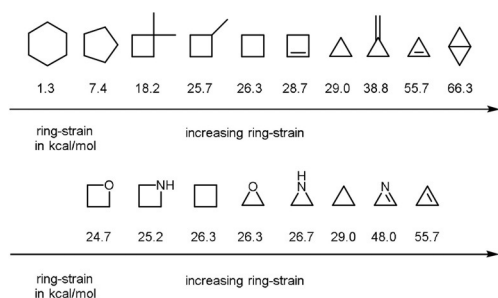

Figure 1. Ring strain energies of different (substituted) small-ring-systems and their hetero-analogues.[5]

[a] A. Luque,[+] J. Paternoga,[+] Prof. Dr. T. Opatz
Department of Chemistry
Johannes Gutenberg University
Duesbergweg 10–14, 55128 Mainz (Germany)
E-mail: opatz@uni-mainz.de

[+] These authors contributed equally to this work.

The ORCID identification number(s) for the author(s) of this article can be found under:
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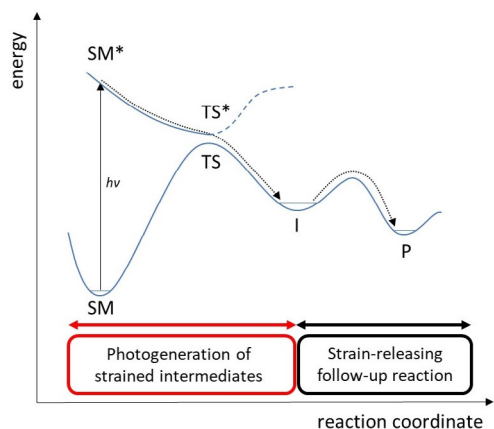Europe
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Figure 2. Feasible energy profile of a formal endergonic strain-releasing reaction via a photogenerated high-energy intermediate (I). (SM = starting material; TS = transition state; P = product).

Finally, the use of fast trapping reactions allows for the use of highly reactive intermediates in one-pot procedures which cannot be isolated in acceptable yields as they readily react in secondary photochemically or thermally induced side reactions. Based on these considerations, this review will cover strain-releasing follow-up reactions of photogenerated small-ring intermediates focusing on recent (2000–2020) examples from the literature, including our own work.

Three-Membered Ring Systems

Examples of photogenerated three-membered carbocycles in strain-releasing chemistry are still rare. The picture changes drastically when it comes to the hetero-analogues and especially to the nitrogen containing three-membered ring-systems. Both aziridines, in terms of highly reactive vinyl aziridines, and azirines are frequently used in such reaction sequences.

Aziridines

Aziridines are the simplest aza-heterocycles and feature a significant ring strain as well as polarized carbon-heteroatom bonds, which makes them very reactive in various kinds of transformations such as cycloadditions, rearrangements and isomerizations as well as ring-opening reactions induced by a broad range of nucleophiles.[9]

Vinyl aziridines starting from pyridinium salts

Among the variously functionalized aziridines, vinyl aziridines have shown to be particularly versatile building blocks in organic synthesis. One of the first reports on the photogeneration of such compounds was published by the group of Kaplan in 1972, who described a photoinduced cyclization of N-alkylpyridinium chloride **1** in aqueous solution to intermediately furnish the 6-azabicyclo[3.1.0]hexenyl cation **4**, which is readily transformed into an 6-azabicyclo[3.1.0]hex-3-en-2-exo-ol with the same structure as **5** upon spontaneous addition of

water.[10] The addition was found to proceed stereoselectively via an attack from the convex face. The synthetic potential of pyridinium salt photochemistry was not recognized until the late 1990s, when Mariano and others developed numerous reaction sequences involving the highly strained bicyclic vinyl aziridinols or ethers (obtained by replacing water with alcohols as the nucleophiles) to several ring strain-releasing follow-up reactions in order to stereoselectively synthesize 3,4,5-trisubstituted cyclopentenes in simple photoirradiation-nucleophilic ring-opening sequences.[11] The advantages of this reaction sequence could impressively be demonstrated in the total synthesis of several natural products as (+)-castanospermine,[12] (+)-mannostatin A,[13] (−)-swainsonine[14] and (−)-cephalotaxine.[15]

A representative example of such a sequence is the conversion of the photogenerated 4-methoxy-6-propyl-6-azabicyclo[3.1.0]hex-2-ene **5** to the (3,4-cis)(3,5-trans)-aminocyclopentenyl alcohol **3**, reported by Mariano and co-workers in 1996

Adriana Luque received her bachelor's degree in chemistry at UIS (Colombia) in 2013. After obtaining her master's degree at UNAM (Mexico) in 2016, she started working as a graduate student in the Opatz lab at JGU Mainz. Her current research interests focus on catalyzed ring-opening reactions of stable photoproducts.

Jan Paternoga graduated at the University of Mainz (B.Sc in 2015 and honoured M.Sc in 2017). During his studies he received a DAAD scholarship for visiting the lab of Prof. Winnik at the University of Toronto. Currently, he is working on his PhD in the group of Prof. Opatz. His research interests focus on telescoping or one-pot strain-releasing sequences of photoproducts.

Till Opatz graduated from Frankfurt University in 1997 and completed his PhD at JGU Mainz with Prof. Horst Kunz in 2001. After a post-doctoral stay in Utrecht, he returned to JGU for his habilitation. In 2007, he was appointed professor at Hamburg University and returned again to JGU as a full professor in 2010. His research focuses on new synthetic methods, bioactive compounds, natural products and sustainable chemistry.
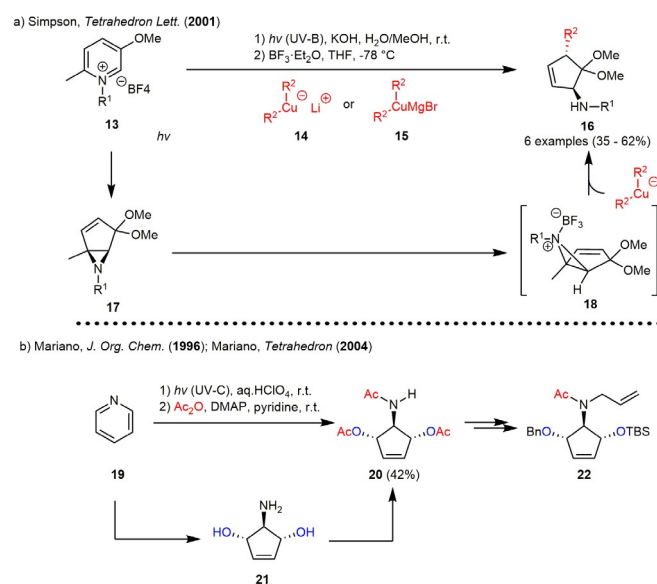
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(Scheme 1a). Photoirradiation of *N*-propylpyridinium chloride **1** in methanol followed by addition of sodium hydrogen carbonate furnished the bicyclic aziridine **5** as a single diastereomer. The subsequent ring-opening of **5** with ethyl chloroformate stereoselectively generated the (3,4-*trans*)(3,5-*cis*)-chlorocarbamate **6**, which underwent azlactonization upon heating. The oxazolidone **7** was afterwards reduced to afford the (3,4-*cis*)(3,5-*trans*)-cyclopentene **3**. This lactonization-reduction sequence enabled the stereoinversion at C-3.[11a] In 1997, the Burger group reacted the photogenerated 6-azabicyclo[3.1.0]-hex-3-en-2-ol derivatives **11** with diiron nonacarbonyl followed by oxidative decomplexation to generate *cis*-fused cyclopentene-β-lactams **9** (Scheme 1b). Irradiation of N-alkylpyridinium salt **8** under basic conditions again afforded the bicyclic aziridines **11** that were subsequently treated with diiron nonacarbonyl in THF to form the iron complex **12**, which could be isolated in good yields. The authors expected [Fe(CO)$_4$(THF)] to be the active carbonylation reagent, which was assumed to be in equilibrium with dinuclear starting material under the reaction conditions. The attack itself was found to stereoselectively occur from the *endo*-face of the bicyclic vinyl aziridines **11**. Subsequent CO insertion into the metal-nitrogen bond and oxidative decomplexation with ceric ammonium nitrate (CAN) furnished the β-lactams **9**.[11b]
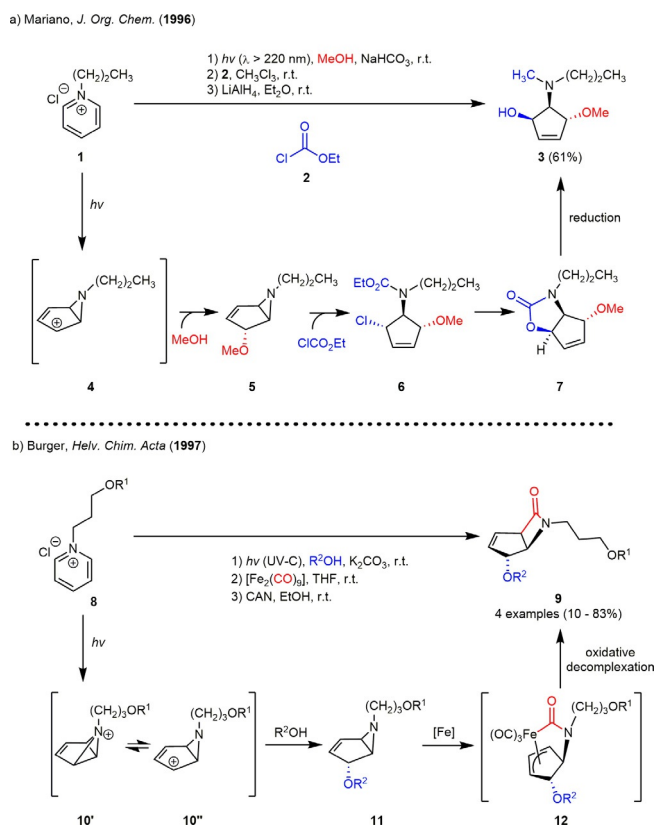
In 2001, the group of Simpson was able to extend the photoisomerization to 3-alkoxypyridinium salt **13**, which generated the 6-alkyl-4,4-dimethoxy-1-methyl-6-azabicyclo[3.1.0]hex-2-enes **17** upon irradiation in aqueous methanol. The photogenerated intermediates **17** were subsequently reacted with the organocuprates **14** or **15** under Lewis acid catalysis (BF$_3$·OEt$_2$) to afford the (3,5-*trans*)aminocyclopentenes **16** in moderate yields (Scheme 2a).[16] The authors assumed the stereoselective generation of the *trans*-isomer during this S$_N$2′ reaction to be based on the steric bulk introduced by the Lewis acid coordinated to the nitrogen lone pair. An alternative explanation was proposed by Corey in 1984, who suggested that S$_N$2′-reactions of cuprates generally show predominantly anti-stereoselectivity due to the fact that filled *d*-orbitals on the copper can interact with both the π* antibonding orbital of the olefin and the σ* orbital of the carbon-leaving group bond.[17] As already mentioned, the Mariano group used the latter concept in the synthesis of several natural products. The enantiopure starting material in all of these cases was synthesized starting from pyridine **19**, which was incorporated in the photoisomerization-ring-opening sequence with subsequent acetylation of 3,5-dihydroxy-4-aminocyclopentene **21**. (Scheme 2b). The extension of the sequence on unsubstituted pyridines required the use of aqueous perchloric acid solution as a solvent to generate the protonated pyridinium salt in situ during irradiation. The *meso*-configurated triacetylated 3,4,5-trisubstituted cyclopentene **20** could be enzymatically desymmetrized and directly used for the total synthesis of (+)-mannostatin A.[13] Subsequent blocking of the hydroxy groups with different protecting groups and allylation of the Boc-protected nitrogen led to precursor **22**, which was for example successfully incorporated in an olefin metathesis for the total synthesis of (−)-swainsonine.[14]

a) Mariano, *J. Org. Chem.* (**1996**)

b) Burger, *Helv. Chim. Acta* (**1997**)

Scheme 1. (a) Photocyclization-aziridine ring-opening sequences to construct the 3,4,5-trisubstituted cyclopentene **3**. (b) Photolysis of N-alkylpyridinium salts to construct 6-azabicyclo[3.1.0]hex-3-en-2-ol derivatives **11** as building blocks in the synthesis of bicyclic β-lactams **9**.

a) Simpson, *Tetrahedron Lett.* (**2001**)

b) Mariano, *J. Org. Chem.* (**1996**); Mariano, *Tetrahedron* (**2004**)

Scheme 2. (a) Stereoselective addition of organocuprates to 6-alkyl-4,4-dimethoxy-1-methyl-6-azabicyclo[3.1.0]hex-2-enes. (b) Photoisomerization-ring-opening sequence to generate enantiopure 3,4,5-trisubstituted cyclopentene as starting material for the total synthesis of several natural products.

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In 2005, Mariano also reported the extension of the shown methodology to 1,2-fused pyridinium salts in order to enable an S_N2'-type ring-opening reaction of the highly strained intermediates **27**, **28** and **30** (Scheme 3a). Irradiation of the tetrahydroquinolizinium salt **23** in aqueous perchloric acid solution furnished a mixture of the tricycles **27** and **28** (7:1). Subsequent S_N2' ring-opening and peracetylation led to the formation of the [5.3.0]bicycle **24** and spiro-bicycle **25** in low yield. When basic conditions were applied to the dihydroindolizinium salt **29** during irradiation, a remarkably regioselective photoisomerization yielded in the exclusive formation of the tricyclic allylic alcohol **30**, which could be converted into the *meso*-diester **31** in high yield (Scheme 3b).[18]

The group of Afonso also contributed to the photochemistry of pyridinium salts in the past years by applying flow-conditions to the synthesis of the fused vinyl aziridines and the ring-opened trisubstituted cyclopentenes. While the first reports basically focused on the transfer of the known procedures into flow-conditions and the investigation of the nucleophile substrate scope for the subsequent ring-opening of the 6-alkyl-6-azabicyclo[3.1.0]hex-2-en-4-yl alcohols and ethers, the group was very recently able to demonstrate a palladium-mediated ring-opening reaction of the photogenerated 6-alkyl-6-azabicyclo[3.1.0]hex-2-en-4-yl alcohols or ethers (**36**). By applying these conditions, the substrate scope of nucleophiles capable of the latter ring-opening could be extended to 1,3-dicarbonyls and analogues (**33** and **34**) in moderate to high yield. Additionally, the authors reported the structure of the products to indicate the nucleophilic attack to formally occur from the *endo*-face of the vinyl aziridines **36** affording the *syn*-S_N2'-products. Mechanistically, the palladium(0) catalyst was assumed to oxidatively add into the aziridine's C–N bond initially forming a palladium-stabilized allylic zwitterion, in which the negative charge is located on nitrogen. The basicity of the anionic nitrogen was assumed to be high enough for the deprotonation of cyclic 1,3-diketones **34**, while a stronger external base (NaH)

must be added for the acyclic analogues **33**. The palladium catalyst is assumed to attack from the *exo*-face forcing the deprotonated nucleophile to attack the allyl-palladium complex **37** via an outer sphere C-allylation from the former *endo*-face. Ligand exchange liberates the 3,4,5-trisubstituted cyclopentenes **35** in low to high yield (Scheme 4).[19]
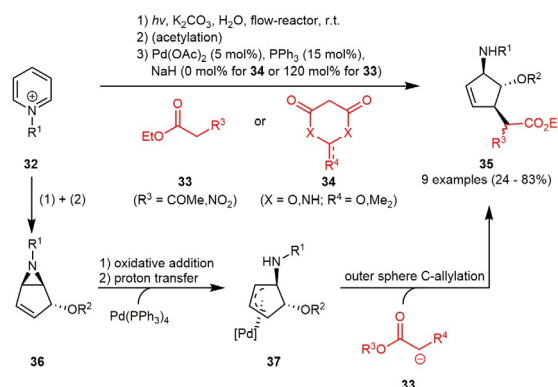
Scheme 4. Palladium-catalyzed nucleophilic ring-opening of photogenerated vinylaziridines with 1,3-dicarbonyl compounds leading to *syn*-S_N2' products.

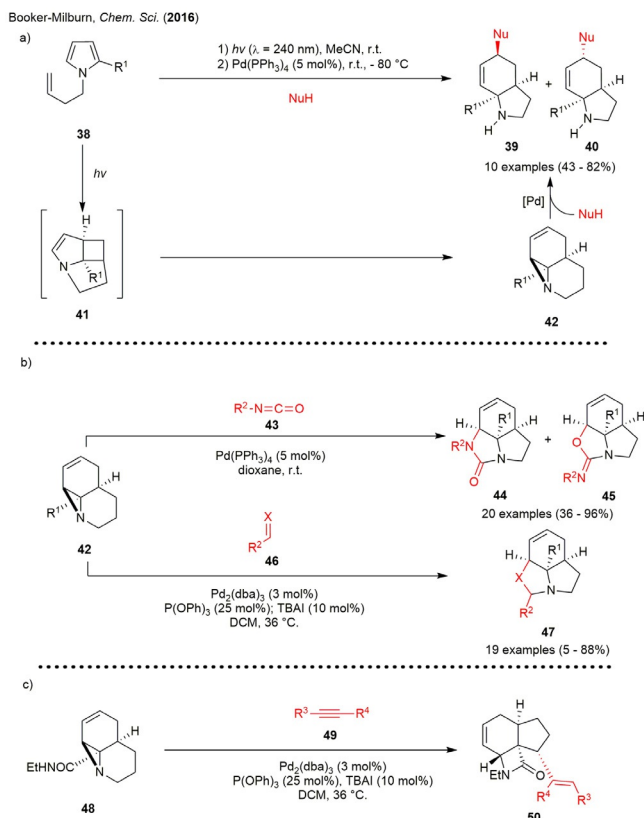### Terminal alkenyl tethered pyrroles as substrates

Another photochemical reaction leading to highly reactive polycyclic vinyl aziridines was described by the group of Booker-Milburn in 2013. Irradiation of N-butenyl substituted pyrroles **38** furnished the tricyclic aziridines **42** via two subsequent photoinduced isomerizations. The developed methodology could also be transferred to photoflow conditions providing the highly strained aziridines **42** in multi-gram quantities (up to 22 gram per day). Mechanistically, excitation with a 254 nm low pressure Hg lamp results in an initial [2+2] cycloaddition of the terminal alkene with the C2–C3 bond of the pyrrole to give cyclobutane **41**, which undergoes a second photoinduced fragmentation-rearrangement reaction leading to tricycle **42**.[20] The proximity of functional groups within the tricycle enables the cycloaddition and ring-opening reactions. Treatment of vinyl aziridine **42** with a range of carbon-nucleophiles and Pd(PPh$_3$)$_4$ via a Tsuji–Trost-type S_N2' ring-opening yielded in an inseparable mixture of diastereomers **39** and **40** (Scheme 5a). The *anti/syn* ratio was reported to be highly dependent on the polarity of the solvent. Less polar solvents such as 1,4-dioxane favored formation of the bicycle **39**, while more polar solvents like acetonitrile or *N,N*-dimethylformamide favored the formation of **40**. The observation was explained by the change from an outer sphere mechanism (direct attack of the nucleophile on carbon—overall retention) to an inner sphere process (initial attack on metal—overall inversion) upon increasing the polarity of the solvent.

The second part of the study involved [3+2] cycloadditions between the photogenerated aziridines **42** and a wide variety of aryl and sulfonyl isocyanates (**43**) under Pd^0 catalysis to form the vinyl substituted cyclic urea compounds **44**. Surpris-
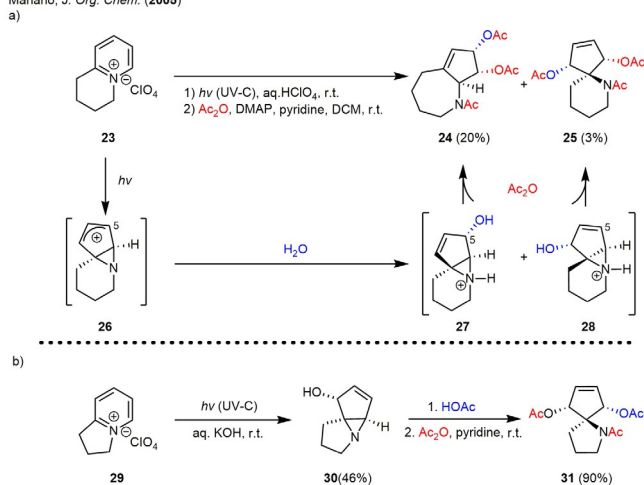
Scheme 3. (a) Photoirradiation-ring-opening sequence of the tetrahydroquinolizinium salt **23** under acidic conditions. (b) Photoirradiation-ring-opening sequence of dihydroindolizinium salt **29** under basic conditions.

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Scheme 5. (a) Pd-catalyzed ring-opening of photogenerated tricyclic aziridines. (b) Pd-catalyzed [3+2] cycloadditions of aziridines with isocyanates as well as aldehydes and imines. (c) Pd-catalyzed addition/cyclisation sequence of photogenerated aziridine with internal alkynes.

ingly, lower (1 mol%) catalyst loadings and catalyst-free conditions led to a change in chemoselectivity, furnishing the cyclic imidates **45**. The cycloaddition could also be extended to other dipolarophiles like alkenes, aldehydes, and imines to generate the tricyclic compounds **47** with high diastereoselectivity. For these sets of reactions, the use of triphenyl phosphite as a ligand was found to be crucial (Scheme 5 b). Finally, this approach was extended to generate the tricyclic fused β-lactams **50** as a single diastereomer by palladium-mediated reaction of amide **48** with the internal alkynes **49**. The high reactivity of the photogenerated aziridines in this reaction could be impressively demonstrated by the generation of the products under catalyst-free conditions at room temperature, although reaction times were long (Scheme 5 c).[21]

In 2017, the developed methodologies were successfully incorporated into the total synthesis of (±)-3-demethoxyerythratidinone in five steps starting from a simple pyrrole derivative.[22] Irradiation of pyrrole carboxylate **51** using the already introduced flow reactor produced gram quantities of the aziridine (±)-**55**. The following Pd-catalyzed Tsuji–Trost-type reaction with acetic acid gave the S_N2' ring-opened hexahydroindole (±)-**52** in excellent yield and as single diastereomer. Further manipulations resulted in (±)-3-demethoxyerythratidinone **53** (Scheme 6).
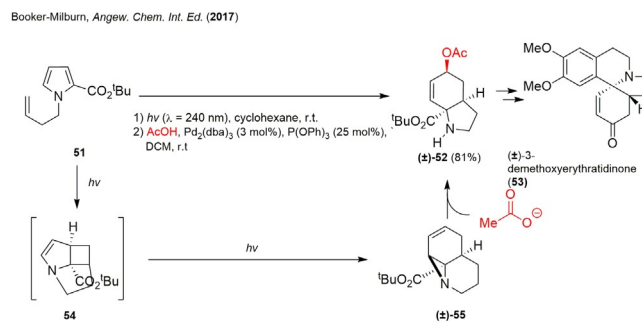
Scheme 6. Pd-catalyzed ring-opening of photogenerated tricyclic aziridines in the total synthesis of (±)-3-demethoxyerythratidinone.
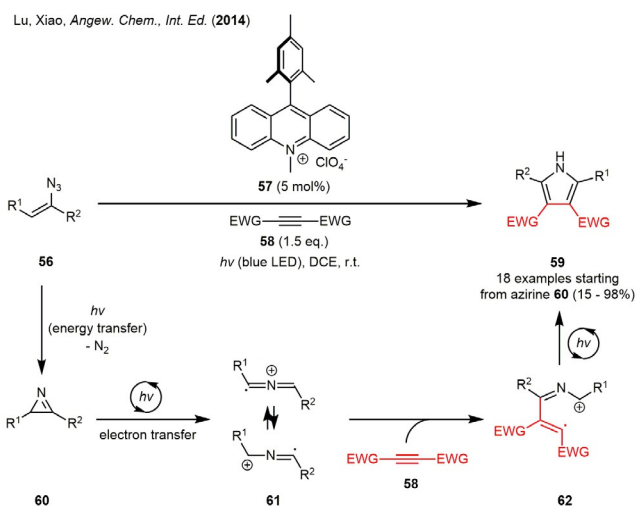
2H-Azirines

2H-Azirines are commonly used in strain-release chemistry as they occupy both high ring strain (vide supra) as well as a polarized internal imine function that serves as reaction center for most of the follow-up reactions. 2H-Azirines are commonly synthesized using the Neber rearrangement as well as the thermal or photochemical decomposition of vinyl azides, which proceeds via a highly reactive nitrene intermediate.[23]

2H-Azirines starting from vinylnitrenes

The photochemical synthesis of 2H-azirines from vinyl azides in those cases are carried out using UV- or visible-light irradiation depending on the substitution pattern of the starting material. In 2014, the Yoon group reported a general visible-light photosensitization approach to form 2H-azirines from vinyl azides under very mild conditions. Catalytic amounts (1 mol%) of [Ru(dtbbpy)$_3$](PF$_6$)$_2$ were used as energy transfer agent enabling UV-absorbing substrates to be formed using visible light as well as generally accelerating the 2H-azirine formation from all kinds of substrates.[24] Based on this fast and scalable isomerization, several procedures were developed that are incorporating the photogenerated 2H-azirines in strain-releasing chemistry.

In the same year, the groups of Lu and Xiao described a photoredox-catalyzed formal [3+2] cycloaddition of 2H-azirines bearing alkyl and aryl substituents with electron-poor alkynes forming highly substituted pyrroles in an overall redox-neutral process (Scheme 7).[25] The authors were able to demonstrate the replacement of the azirine starting material with the corresponding vinyl azides furnishing pyrroles **59** in similar yield. Further control experiments pointed towards the high potential of Fukuzumi's acridinium-based photocatalyst **57** both in terms of energy as well as of electron transfer. Mechanistically, the 2H-azirine **60** is generated by means of an energy transfer from the excited photocatalyst. Afterwards, the 2H-azirines **60** are oxidized by the strongly oxidizing photocatalyst leading to a ring opening under scission of the C—C bond. Addition of the resulting azaallenyl radical cation **61** to an alkyne results in intermediate **62**. The catalytic cycle is closed by the single-electron-reduction of the radical cation

Lu, Xiao, *Angew. Chem., Int. Ed.* (2014)

Scheme 7. Photogenerated 2*H*-azirines in the photoredox-mediated formal [3+2] cycloaddition with alkynes forming highly substituted pyrroles.

a) Maurya, *Org. Lett.* (2016)

b) Maurya, *J. Org. Chem.* (2017)

Scheme 8. Photogenerated 2*H*-azirines as dipolarophiles in [3+2] cycloadditions with photoredox-generated 1,3-dipoles forming (a) fused β carboline derivatives and (b) 1,3 diazabicyclo[3.1.0]hexanes.

62, which finally leads to the formation of pyrrole **59** by cyclization and aromatization (Scheme 7).

Although the authors did not incorporate the photogeneration of azirine **60** in succeeding studies, several other groups were able to extend the demonstrated methodology to other reaction partners furnishing oxazoles,[26] 2-acyloxazoles,[27] 2,5-dihydro imidazoles,[26] 2,5-dihydroisoxazoles,[28] 1,2,4-triazoles[29] and 2,4,5-trisubstituted pyrroles.[30]

In the following years, the Maurya group described several examples which combined the sensitized generation of 2*H*-azirines with further follow-up reactions. The first examples were published in 2016 and 2017, where the photocatalyst [Ru(bpy)₃](PF₆)₂ was employed both as energy and electron transfer catalyst furnishing 1,3-diazabicyclo[3.1.0]hexanes in moderate to good yields and excellent diastereoselectivity (Scheme 8).[31]

The dual catalysis enabled by a single photocatalyst gives access to [3+2] cycloadditions of the photoredox-/*tert*-butylhydroperoxide (TBHP) generated dipoles **66** and **70** to 2*H*-azirines as the dipolarophiles. The dipole formation was proposed to involve two subsequent SET-oxidations of the tertiary amine alternating with hydroxide-induced deprotonation. TBHP was assumed to serve as the terminal oxidant in this process, liberating the required hydroxide ions upon reductive O–O-bond scission. The photogenerated 2*H*-azirine on the other hand acts as a dipolarophile and is again produced in situ by energy transfer from the excited photocatalyst.
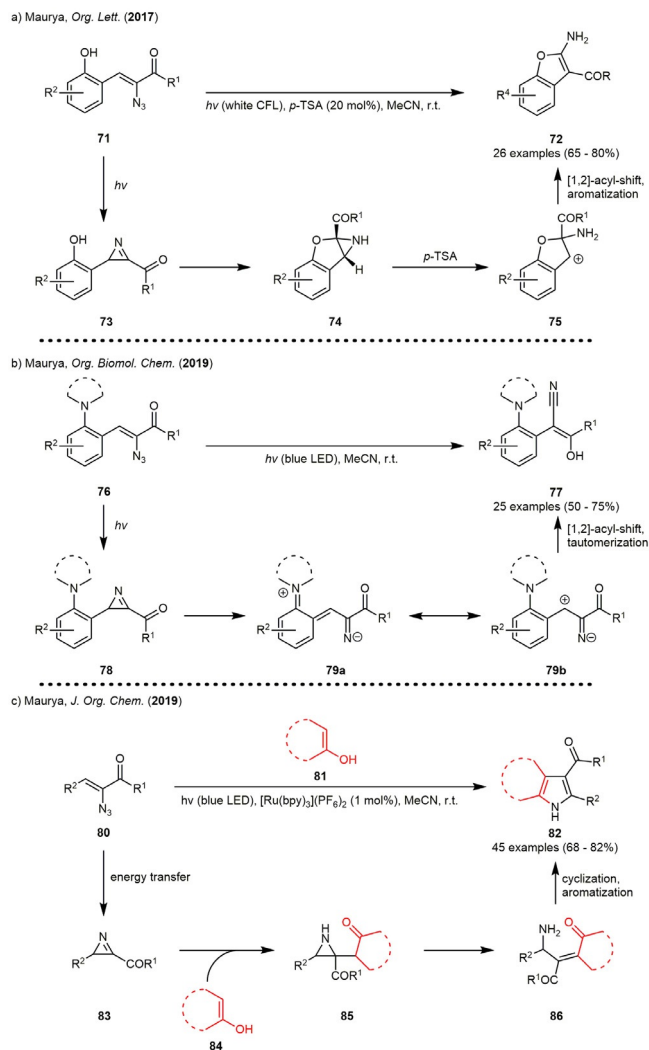
In the first example, 1,2,3,4-tetrahydro-β-carboline derivatives (**63**) were incorporated into the previously described [3+2] cycloaddition yielding in highly complex 1,3-diazabicyclo[3.1.0]hexanes **65** as single diastereomers. The authors were also able to transfer the reaction into a flow microreactor in order to decrease the reaction time while simultaneously increasing the yield by 16% absolute.[31a] Basically the same reaction conditions could be used for [3+2] cycloadditions between photogenerated 2*H*-azirines and azomethine ylides, which are generated from *N,N*-dimethylanilines **67** with the
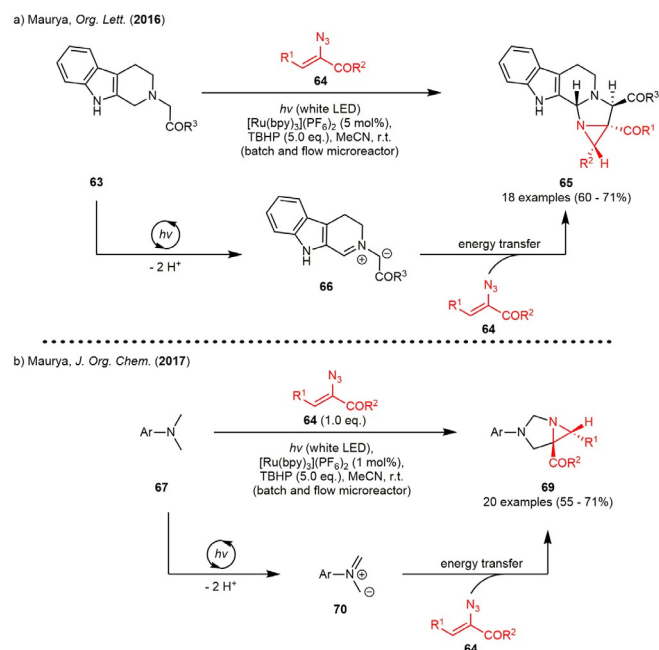
photoredox/TBHP system described above. Again, a large variety of aromatic substituents on the vinyl azide substrate as well as halogen and alkyl substituents on the aniline starting materials furnished the 1,3-diazabicyclo[3.1.0]hexanes **69** in moderate to good yield. The authors were again able to increase the yield by 19% absolute through application of photoflow conditions.[31b]

The group also described intra- and intermolecular reactions of the photogenerated 2*H*-azirines with phenolic hydroxy groups (Scheme 9). In 2017, an intramolecular approach was described starting from α-azido-γ-(2-hydroxyaryl)chalcones **71** and yielding 2-aminobenzofuran **72** (Scheme 9a) in moderate to high yields through action of *p*-toluenesulfonic acid (*p*-TSA). In these examples, the authors were able to induce the azirine formation without sensitization, although reaction times increased using the uncatalyzed approach. The mechanism proceeds via the intramolecular addition of the phenolic hydroxy group to the C=N bond of the photogenerated azirine **73** forming the [3.1.0]bicycle **74**. This bicycle was sometimes found to be the main product when no acid was added to the reaction mixture. The product formation was presumed to be induced by an [1,2]-acyl-shift after acid-catalyzed ring-opening of the aziridine **74**.[32] When the phenolic hydroxy group was replaced by a cyclic tertiary amine, the chemoselectivity changed and β-stilbenes **77** were formed as the major products in moderate to good yields (Scheme 9b). Moreover, no C=N addition products were observed. Instead, an intramolecular ring opening of the photogenerated azirine was proposed, forming zwitterion **79**. The zwitterion was presumed to undergo a [1,2]-acyl-shift leading to the β-stilbene **77** after tautomerization.[33] In 2019, an intermolecular acid-free approach using

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Scheme 9. Photogenerated 2*H*-azirines in (un)catalyzed strain-releasing chemistry forming heterocycles and other rearrangement products.

phenols was described forming (fused) indoles in good yields (Scheme 9 c). The photocatalyst [Ru(bpy)$_3$](PF$_6$)$_2$ was again used in the transformation in order to accelerate the 2*H*-azirine formation. The reaction was reported to involve an initial proton transfer to the azirine enabling a nucleophilic attack of the enolate fragment inducing a dearomatization of the former phenol moiety. The formed β-ketoaziridines **83** furnish the indole derivative **82** by ring-opening and subsequent cyclization.[34] The latter concept was also adopted by other groups. In 2019, the Handlon group developed a metal-free base-induced imidazole synthesis starting from vinyl azides and cyanamides in moderate to excellent yields (Scheme 10 a). During the optimization, the authors also compared thermal and photochemical conditions for the generation of the 2*H*-azirine intermediates. While the yields were slightly lower for most of the photoinduced examples, the photochemical reactions could expectably be carried out at room temperature.[35]

Mechanistically, the authors proposed a nucleophilic attack of the deprotonated cyanamide on C-2 of the 2*H*-azirine producing the iminyl anion **91**. The anion **91** is assumed to cyclize,
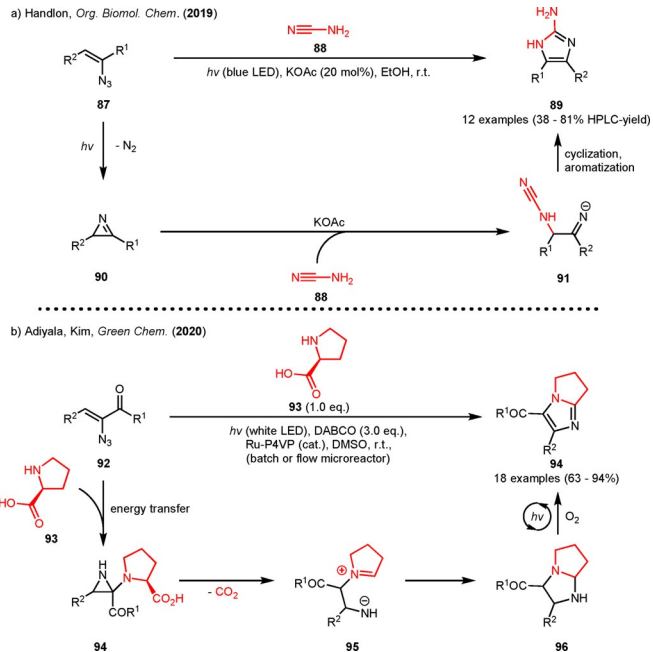
Scheme 10. Photogenerated 2*H*-azirines as intermediates in the strain-releasing synthesis of (fused) imidazoles.

furnishing the imidazole product **89** after protonation and tautomerization. Based on other reports, the reaction might be more likely to proceed via an addition to the C=N bond, trans-protonation, ring-opening/ring closure and tautomerization or through intermediate formation of a [2.1.0]bicycle.[35]

Recently, the groups of Adiyala and Kim were also able to combine photoredox catalysis with the sensitized generation of 2*H*-azirines in order to synthesize fused imidazoles **94** starting from α-azidochalcones **92** and proline (**93**) (Scheme 10 b).[36] An immobilized ruthenium(III)-polyvinylpyridine complex employed both under batch as well as under flow microreactor conditions afforded the fused imidazoles in good to excellent yields while tolerating a variety of mostly electron-rich aromatic substituents on the α-azidochalcones **92**. The authors assumed the reaction to proceed via an off-cycle addition of the amine moiety of proline into the C=N double bond of the photogenerated 2*H*-azirine followed by ring-opening, decarboxylation and cyclization giving the saturated analogue **96**. Photoredox catalysis with oxygen as terminal oxidant is presumed to subsequently enable aromatization to imidazole **94** via two SET-oxidations alternating with superoxide induced deprotonation.[36]

2-Acylazirines from arylated isoxazoles

In 1967, the group of Singh described the photoisomerization of isoxazoles under UV irradiation leading to thermodynamically stable oxazoles. The isomerization itself is known to proceed via the formation of the highly strained and metastable 2-acylazirines, that are further converted into the oxazoles upon continued irradiation.[37] Therefore, the Opatz group developed one-pot procedures to trap the photoproducts in fast thermal

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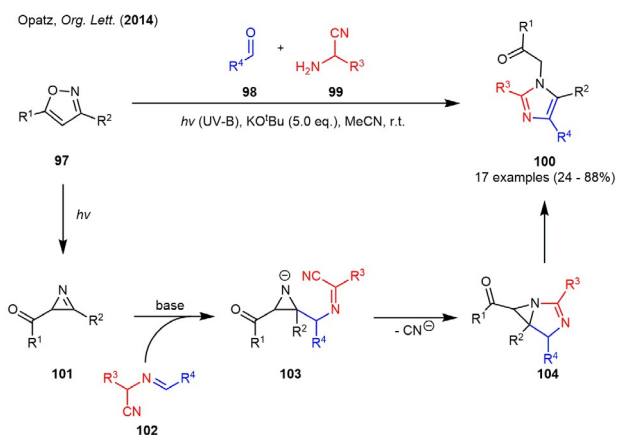**Chemistry Europe**
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follow-up reactions in order to suppress the yield-limiting oxazole formation.

In 2014, a metal-free three-component synthesis of tetrasubstituted imidazoles (**100**) was described which employs a base induced condensation of the photogenerated 2-acylazirines (**101**) with α-(alkylideneamino)-nitriles **102** (Scheme 11). The reaction partners were also generated in situ from the corresponding aldehydes **98** and α-aminonitriles **99** by means of a condensation reaction. Both aryl and alkyl substituents on all of the substrates could be incorporated in this transformation in moderate to high yield. Mechanistic studies and in-silico calculations suggested the reaction to proceed via an addition of the deprotonated α-(alkylideneamino)nitrile to the C=N double bond of the photogenerated 2-acylazirine **101**. A 5-endo-trig cyclization and cyanide elimination furnish the [3.1.0]bicycle **104**, which is converted to imidazole **100** via proton elimination, ring-opening and reprotonation of the formed enolate.[38] The Opatz group then focused on the use of metal-catalysis for the downstream reactions of the photogenerated 2-acylazirines. In 2016, a cobalt-catalyzed condensation reaction between 1,3-diketones **105** and photogenerated 2-acylazirines **101** was reported. Using this methodology, tetrasubstituted pyrroles could be synthesized in moderate to excellent yields depending on the nature of the alkyl- or aryl-substituents on the starting isoxazole (Scheme 12a).[39]
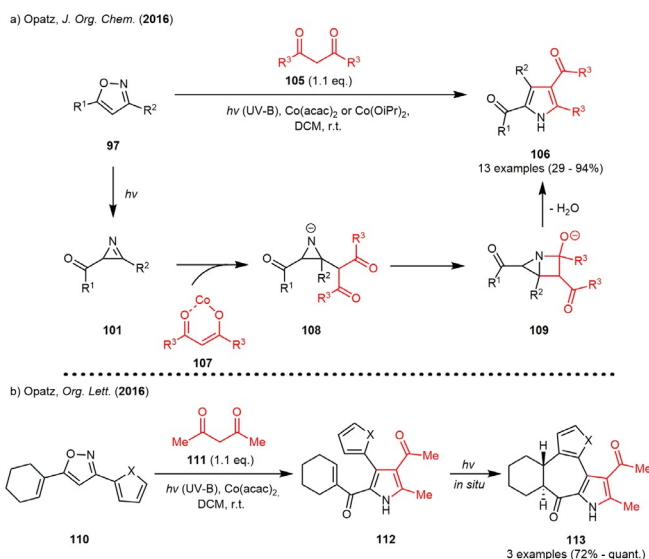
The mechanism was proposed to involve an addition of the 1,3-diketone-cobalt chelate **107** to the C=N bond of the 2-acylazirine followed by an 4-exo-trig cyclization forming the [2.1.0]bicycle **109**. Ring-opening and water elimination furnish the tetrasubstituted pyrrole **106**. The latter concept could also be extended to α,β-unsaturated isoxazoles. The resulting α,β-unsaturated pyrroles instantly underwent a unexpected electrocyclization upon irradiation furnishing the vinylogous Nazarov products **113** (Scheme 12b).[40]

In 2019, Opatz and co-workers were able to demonstrate a metal-catalyzed dimerization reaction of the photogenerated 2-acylazirines **101** (Scheme 13).
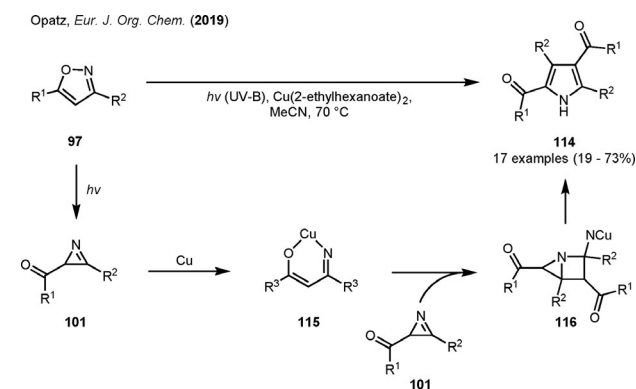
By employing a simple copper catalyst at elevated temperatures, aryl substituted isoxazoles were readily transformed into
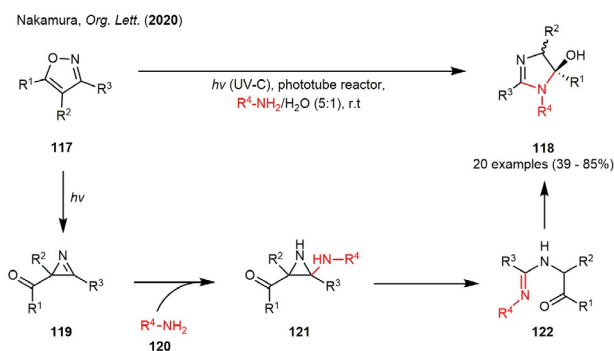
Scheme 12. Photogenerated 2-acylazirines in (a) metal-catalyzed synthesis of tetrasubstituted pyrroles and (b) photoinduced vinylogous Nazarov cyclization when α,β-unsaturated isoxazoles were incorporated.

Scheme 13. Photogenerated 2-acylazirines in the metal-catalyzed dimerization of tetrasubstituted imidazoles.

dimerized tetrasubstituted pyrroles (**114**) under UV-irradiation in moderate to high yield. Mechanistically, the copper catalyst was presumed to oxidatively add into the C–N single bond of a 2-acylazirine initially. Ring enlargement forms the copper chelate **115**, which adds to the C=N double bond of another 2H-azirine. The tetrasubstituted pyrrole **114** was assumed to be subsequently furnished by 4-exo-trig cyclization, ring opening of the formed [2.1.0]bicycle **116** to the corresponding 2H-pyrrole and a 1,5-sigmatropic H-shift.[41] Recently, the Nakamura group also adopted the isoxazole/oxazole photoisomerization for a catalyst-free synthesis of 5-hydroxyimidazolines **118** by reacting the photogenerated 2-acylazirines **119** with an excess of a primary amine under mediation of water (Scheme 14).

No further solvent was required in these examples. Additionally, the reaction times could be drastically reduced compared to the previous examples by performing the reactions in a thin FEP tubing wrapped around a UV-C lamp. The products were

Scheme 11. Photogenerated 2-acylazirines in the metal-free synthesis of tetrasubstituted imidazoles.

Nakamura, *Org. Lett.* (2020)

Scheme 14. Photogenerated 2-acylazirines in the catalyst-free synthesis of 5 hydroxyimidazolines.

isolated in moderate to excellent yields with the reaction tolerating several aromatic substituents on the isoxazole as well as the employment of various aliphatic amines. The authors were also able to further transform the synthesized imidazolines **118** into their unsaturated imidazole analogues with TFAA as a dehydrating agent. Mechanistically, the primary amine adds to the C≡N double bond of the photogenerated 2-acylazirine forming aziridine **121**, which readily undergoes ring-opening and isomerization to ketone **122**. Cyclization and tautomerization finally yield in the 5-hydroxyimidazoline derivatives **118**.[42]

Four-Membered Small-Ring Systems

As the ring strain energies of the four-membered cycloalkanes and heteroanalogues are very similar to those of their previously discussed three-membered analogues (see Figure 1), it is not very surprising that they are frequently used in ring strain releasing chemistry as well as natural product synthesis.[3e, 7a, c] Four-membered ring systems can be easily accessed using for example, photochemical [2+2] cycloadditions starting from readily available precursors and therefore making them versatile intermediates in the synthesis of complex frameworks.[43] In earlier years, these photogenerated intermediates were widely applied in strain-release methodologies under uncatalyzed as well as under Lewis- or Brønsted acidic conditions for natural product synthesis. Recently their unique properties and reactivities were also incorporated in more demanding transformations. The most prominent [2+2] photoproducts are cyclobutanes (derived from alkenes and enones), cyclobutenes (derived from alkenes and alkynes) and oxetanes (prepared in Paternò–Büchi reactions). Since the chemistry of oxetanes was recently reviewed elsewhere,[3b, c] this section will focus on ring strain releasing chemistry of photogenerated cyclobutanes and cyclobutenes. The described examples mainly focus on [2+2] photocycloaddition-fragmentation strategies using a wide variety of fragmentation conditions and therefore complement the well-known medium-ring annulation procedures.[44]

(Fused) cyclobutanes and cyclobutenes from enones

The use of photogenerated cyclobutanes (derived from two alkenes) and especially of α-ketocylobutanes (derived from an

α,β-unsaturated ketone and an alkene) in natural product synthesis is well-established. For example, Pirrung demonstrated a Cargill rearrangement[45] as a follow-up reaction on the photogenerated cyclobutane **127** in 1979. The addressed target (±)-isocomene (**126**) belongs to a family of tricyclic angular triquinane sesquiterpenes initially isolated from the plant *Isocoma wrigthii*.[46] The tricyclo[6.3.0.0^{1,6}]undecanone intermediate **127** was produced from an intramolecular [2+2] photocycloaddition of enone **123** and directly transformed into the tricyclic ketones **124** and **125** (Scheme 15). The Cargill reaction was afterwards induced by *para*-toluenesulfonic acid (*p*-TSA) to generate the cyclobutylcarbinyl cation **128** in situ, which readily underwent two [1,2]-alkyl-shifts furnishing the tricyclic ketones **124** (path a) and **125** (path b). The natural product **126** could afterwards be generated by methyl addition and elimination on ketone **125**.[47]

A more recent example of a (Lewis acid-promoted) skeletal rearrangement of photogenerated cyclobutanes in natural product synthesis was described by Kakiuchi and co-workers in 2004. Lewis acid-catalyzed ring expansion of the photogenerated fused α-keto-*exo*-methylencyclobutane **135** yields in the triquinane structure **133**,[48] which has previously been converted to the natural product (±)-pentalenene (**134**) by the group of Paquette.[49] Among a variety of Lewis- or Brønsted acids such as boron trifluoride etherate (BF$_3$·OEt$_2$) or triflic acid (TfOH), only titanium(IV)-chloride (TiCl$_4$) afforded the desired product **133** in excellent yield (Scheme 16). The carbonyl group of the photogenerated cyclobutane **135** was selectively addressed by the titanium catalyst in the presence of the highly reactive *exo*-methylene moiety, which is attacked by Brønsted acids instead. Under these conditions, ring-opening selectively occurs under C1-C6 scission furnishing cation **136**, which readily undergoes a [1,2]-hydride- shift and cyclization yielding in the tricyclic triquinane structure **133**.[48]

The combination of the ring strain of cyclobutanes with the reactivity of the α-keto group was also employed in radical reactions. In 1996, the group of Crimmins described a free radical ring-expansion reaction via fragmentation of fused α-ketocyclobutanes **140**, which were generated by means of a stereoselective intramolecular [2+2] cycloaddition of the enone and


Pirrung, *J. Am. Chem. Soc.* (1979)
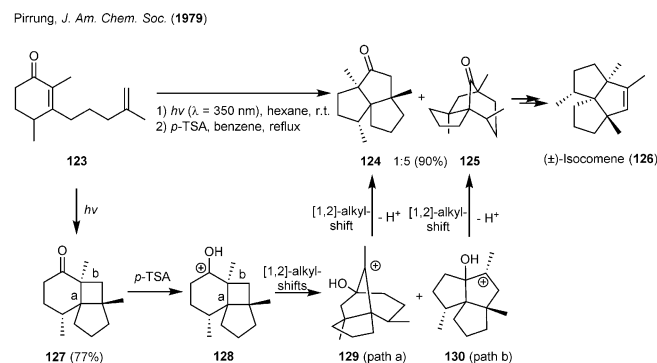
Scheme 15. Total synthesis of (±)-isocomene via a combination of intramolecular [2+2] photocycloaddition and subsequent Cargill rearrangement as the key step.

Kakiuchi, *Synthesis* (**2004**)
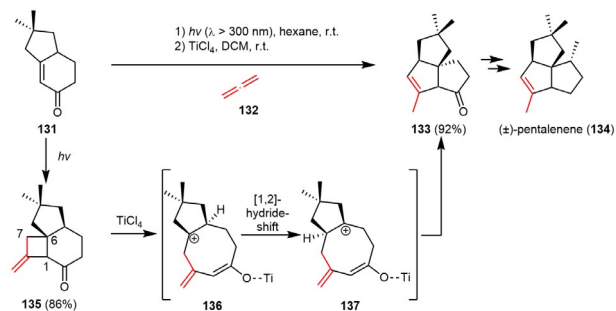
Scheme 16. Allene-enone [2+2] photocycloaddition and Lewis acid-catalyzed rearrangement towards in the formal total synthesis of (±)-pentalenene.

terminal alkene moiety of substrate **138**. Removal of the methoxymethyl ether (MOM) protecting group followed by the Barton-McCombie sequence (thioacylation and subsequent free radical reduction) afforded the ring-expanded carbocycles **139** in moderate to excellent yield. The regioselective bond scission was assumed to result from the stabilization of the radical intermediate by the two neighboring carbonyl groups. The authors were also able to extend the sequence to different medium-sized fused bicycles by introducing different ring sizes and tethered terminal alkene chains into the substrate (Scheme 17).[50]

Crimmins, *Tetrahedron Lett.* (**1996**)
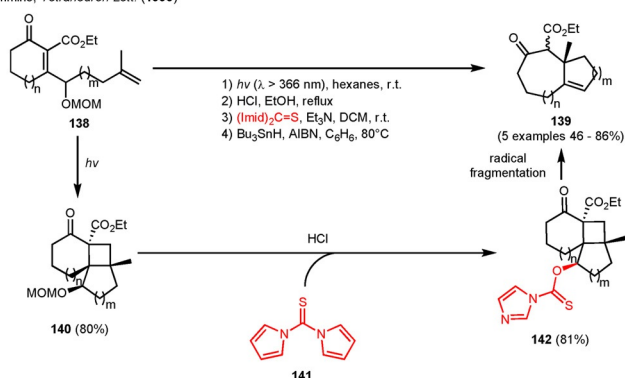
Scheme 17. Photocycloaddition-free radical fragmentation sequence in the synthesis of medium-sized bicycles.

In order to introduce an alkene moiety into the extended bicyclic ring system **144**, the groups of Shipe and Sorensen described a different approach in the enantioselective synthesis of the guanacastepene diterpenes A and E. Again, an intramolecular enone-olefin [2+2] photocycloaddition furnished the strained α-ketocyclobutane **145**. Ring opening of **145** was introduced using a remote single electron transfer reduction of the α-carbonyl by samarium diiodide. Subsequent ring-opening and trapping of the samarium enolate with phenylselenenyl bromide (**146**) afforded the organoselenide **147**. Elimination after oxidation with *meta*-chlorperbenzoic acid (*m*-CPBA) finally afforded the tricyclic compound **144** (Scheme 18).[51]
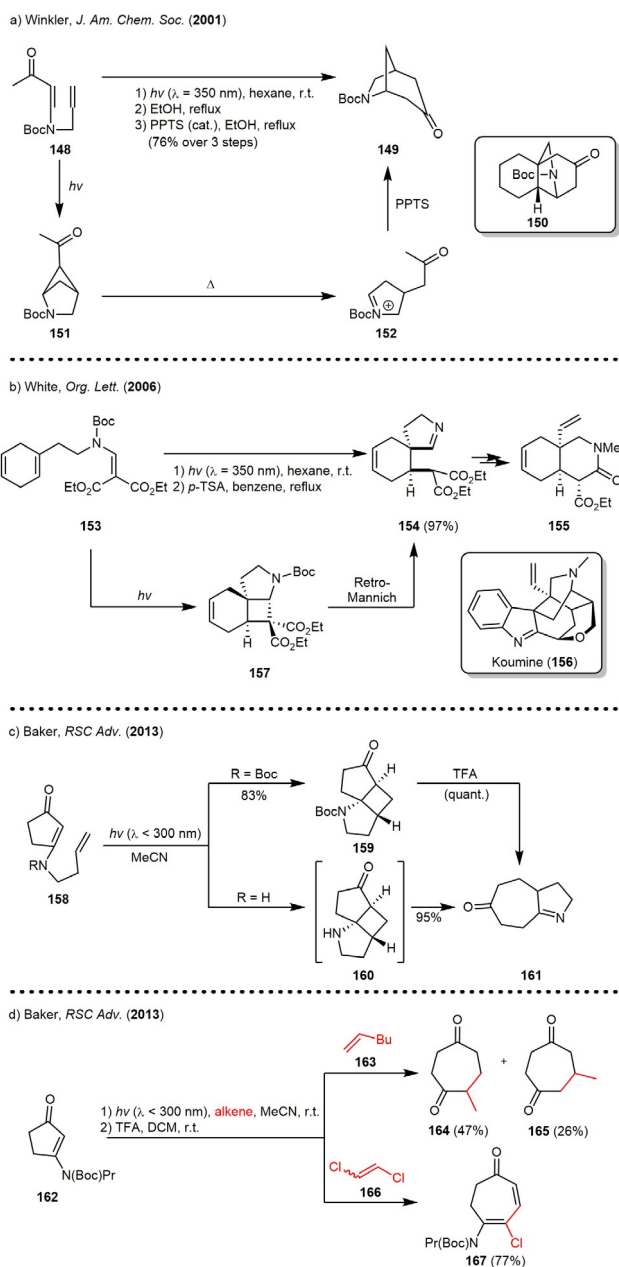
Sorensen, *Org. Lett.* (**2002**)
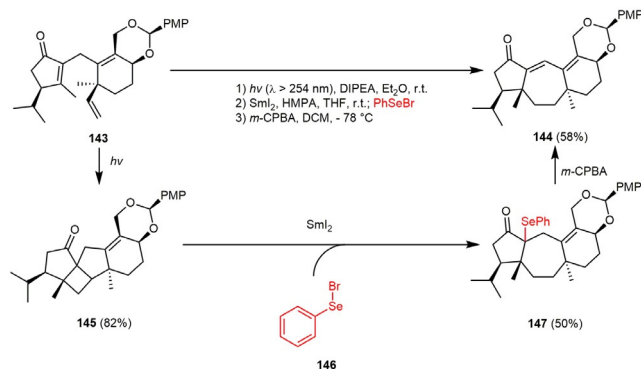
Scheme 18. Radical fragmentation of a photogenerated cyclobutane in the synthesis of (+) guanacastepene A and E.

(Fused) cyclobutanes from vinylogous amides

The extension of the previously discussed photocycloaddition/fragmentation sequence to vinylogous amides/enaminones leads to nitrogen-containing ring systems and is therefore frequently used in natural product synthesis for the construction of alkaloid structures. Based on the first contribution of Tamura and co-workers in 1975,[52] several groups adopted the photocycloaddition/retro-Mannich sequence in order to synthesize various natural products like sesquiterpenes,[53] taxane,[54] mesembrine,[55] vindorosine,[56] manzamine A,[57] koumine,[58] (±)-coerulescine,[59] and peduncularine.[60] As the sequence was also incorporated in several methodological publications,[59,61] only selected more recent examples of the topic will be described below in order to showcase the reactivity of the photoadducts.

The Winkler group described numerous reaction sequences building on the ring-opening of photogenerated ring systems as key steps and incorporated these reactions in the synthesis of several natural products. In 2001, the group reported a photocyclization of the Boc-prototected vinylamide **148** furnishing the [2.1.1]bicycle **151** (Scheme 19a). The preferred formation of the [2.1.1]- over the [2.2.0]bicyclic system was assumed to be based on kinetic reasons ("rule of five"). Subsequent thermal decomposition and acid-catalyzed cyclization furnished the [3.2.1]bicycle **149** in excellent yield. The transfer of the developed methodology to a cyclohexenyl derivative afforded tricycle **150**, which can be viewed as the core of the carbon skeleton of the hetisine alkaloids.[61b] In 2006, the methodology was further adopted in the total synthesis of the natural product peduncularine.[60]

In the same year, White employed β-phenethylamine **153** in the synthesis of the spiropyrroline **154**, which was used as key intermediate for the construction of the tetracyclic core of the indolenine alkaloid koumine (**156**) (Scheme 19b). An intramolecular photocycloaddition of β-aminoalkylidene malonate **153** furnished cyclobutane **157** in almost quantitative yield. Upon removal of the *Boc*-protecting group with trifluoroacetic acid (TFA), tricyclic cyclobutane **157** spontaneously underwent a retro-Mannich fragmentation forming spiroimine **154**. The

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Scheme 19. Photocyclization/retro-Mannich sequences in (a) the synthesis of the tricyclic core of the hetisine alkaloids, (b) the total synthesis of koumine (c) the comparison between unprototected (R=H) and protected (R=Boc) vinylamide precursors and (d) intermolecular sequences.

latter product was isolated as a single stereoisomer indicating both the concerted mechanism of the photocycloaddition as well as the stereospecificity of the retro-Mannich reaction.[58]

In 2013, the Baker group described a variety of both intra- and intermolecular [2+2] cycloadditions of alkenes with vinyl-amides **158** and **162** followed by retro-Mannich reactions lead-ing to fused 1-pyrrolines, diketones, ketoimines or conjugated enaminones (Scheme 19 c and d). In terms of intramolecular re-actions, the group was able to confirm earlier observa-tions[52,61a,62] of such sequences, which pointed out, that the tri-cyclic fused cyclobutanes **159/160** can only be isolated if the

amine was Boc-protected, whereas both deprotection as well as irradiation of the unprotected vinylamide resulted in spon-taneous retro-Mannich-type ring enlargement reactions of the fused cyclobutane **160** yielding in tricyclic 1-pyrroline **161**. In these examples, the authors were able to suppress the retro-Mannich reaction by sodium borohydride-induced reduction of the keto function of the tricyclic cyclobutane **159**. In the same publication, vinylogous amides **162** not tethered with terminal alkenes could be incorporated in intermolecular [2+2] cycload-dition-retro-Mannich sequences using different alkenes in order to synthesize 1,4-diketocycloheptanes **164/165** or conju-gated enaminone **167** depending on the alkene used.

de Mayo and related reactions

A significant contribution to the field of photochemistry was made by the de Mayo group in 1962, who described the syn-thesis of 1,5-diketones through a two-step process involving the [2+2] photocycloaddition of an enolizable 1,3-dicarbonyl compound with an olefin forming a cyclobutanol intermediate, which is readily fragmented via a retro-aldol reaction yielding in 1,5-dicarbonyl compounds.[63] The sequence is frequently in-corporated in organic chemistry and especially in natural prod-uct total synthesis. Some of the recent examples are shown in Scheme 20 and will be discussed below.

In 2002, Winkler and co-workers reported the first total syn-thesis of (±)-ingenol **170**, a complex diterpenoid originally iso-lated from *Euphorbia ingens*.[64] The authors were able to estab-lish the unusual C-8/C-10 „inside-outside" stereochemistry of **170** by using a dioxenone photocycloaddition/fragmentation sequence. An intramolecular [2+2] photocycloaddition of the allylic chloride **168** gave cyclobutane **171** together with its C-13-chloro-analogue **172** (**171/172** = 5:2). Fragmentation of cy-clobutane **171** with methanolic potassium carbonate finally yielded in the ring-enlarged tricycle **169** in 40% yield over two steps. Tricycle **169** could be subsequently converted to (±)-in-genol **170** (Scheme 20 a).[65]

In 2003, the group of Hong described a photochemical access towards the tricyclic core of fusoxysporone **177**,[66] a vis-cidane-type diterpene first isolated from liquid cultures of the fungus *Fusarium oxysporum* in 1992.[67] The authors irradiated the β-acetoxy-substituted enone **173** yielding in cyclobutane **177**. Treatment with aqueous KOH in methanol afforded a rac-emic mixture of the desired tricyclic diones **174** and **175** (Scheme 20 b). Another example was reported by Minter and Winslow, who used a de Mayo-approach towards the synthesis of the galanthan tetracyclic skeleton **182**.[68] To this end, isocar-bostyril **178** was irradiated in acetonitrile to give **181** in 72% yield. Mechanistically, a remarkable regioselective intramolecu-lar [2+2] photocycloaddition afforded the corresponding cyclo-butane **180**, which subsequently underwent a retro-aldol frag-mentation yielding in tricycle **181**. A piperidine-mediated aldol cyclization gave galanthan derivative **181** as single diastereo-mer, as the C1-carbonyl is selectively attacked from the *endo*-face (Scheme 20 c).
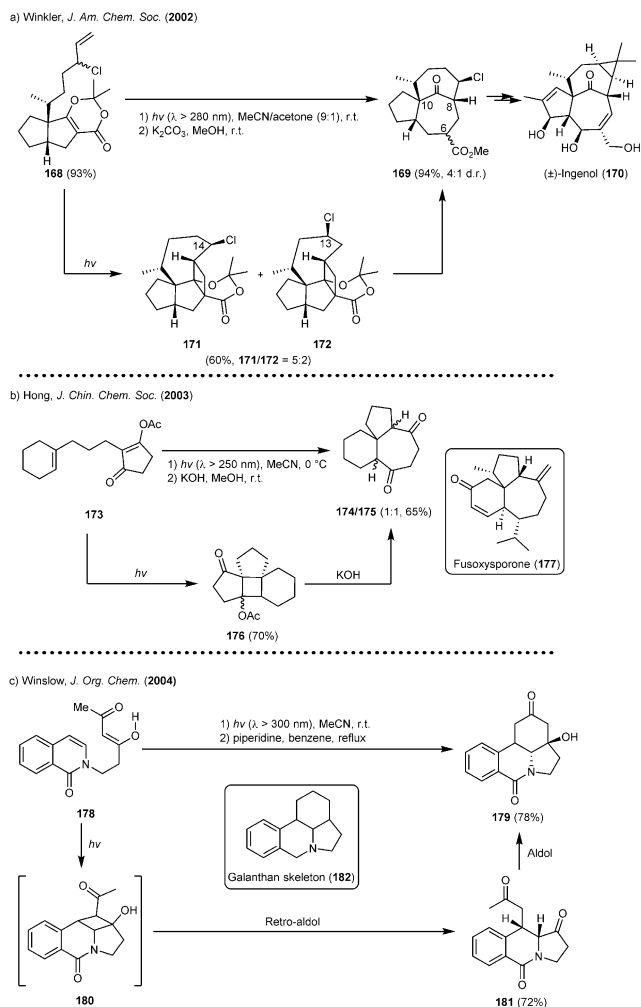
Scheme 20. de Mayo-type reactions in the natural product synthesis of (a) (±) ingenol (b) fusoxysporone and (c) the galanthan skeleton.

Cyclobutanes as Norrish–Yang products

A different approach for the synthesis of highly reactive cyclobutanes are the Norrish–Yang reactions, which proceed via an H-atom transfer (HAT) after excitation of a carbonyl compound containing abstractable γ-hydrogen atoms. The formed biradicals usually recombine to cyclobutanols. Although Norrish–Yang conditions are frequently used in photochemical reactions leading to cyclic compounds and natural products,[69] the use of these carbocyclic photoadducts as strain-releasing intermediates are rare. Nevertheless, in 2014 the Murakami group described a ring expansion reaction of orthocyclophanes **183** to the more strained metacyclophanes **184**. The described reaction combines a light-induced Norrish-Yang type cyclization yielding in cyclobutanol (±)-**185**, which was afterwards incorporated in a subsequent rhodium-mediated C–C activation reaction. The example demonstrates that the use of an initial endergonic photocyclization reaction enables a formal endergonic reaction sequence. Mechanistically, excitation of the carbonyl group using UV-irradiation formed the already mentioned 1,4-biradicals that readily generated o-quinodimethanes **184** as mixture of diastereomers. The cyclobutanol (±)-**185** was only

generated from the (Z)-isomer by means of a 8π-electrocyclization, whereas the (E)-isomer having an inward-oriented hydroxy group was more likely to undergo a 1,5-proton shift to regenerate **183**. Deprotonation and ligand exchange of the rhodium-hydroxide complex with the photogenerated cyclobutanol (±)-**185** generated rhodium benzocyclobutenolate **186**, in which the benzene ring likely π-coordinated to rhodium. The following β-carbon elimination of the C(ipso)–C(sp³) bond formed arylrhodium complex **187**. Finally, protonation furnished the metacyclophane **184** (Scheme 21 a). The arylrhodium intermediate could also be incorporated into a subsequent conjugated addition with methyl vinyl ketone **190** giving rise to the stereospecific synthesis of metacyclophanes (±)-**191**, when bulky substituents such as alkyltrimethylsilane, benzyl or phenoxymethyl were used as R^1. The authors were able to show that irradiation of precursor **188** gave tricyclic benzocyclobutenol (±)-**189** as only diastereomer because of steric and kinetic (vide supra) reasons (Scheme 21 b). The rhodium-mediated ring-opening was assumed to occur under central-to-planar chirality transfer as the coordinating benzene facilitates a site-selective migration of the ipso-sp²-carbon onto the rhodium center. The bulky COD-ligand was assumed to prohibit the ring flipping across the newly expanded ansa-chain afterwards.[70]
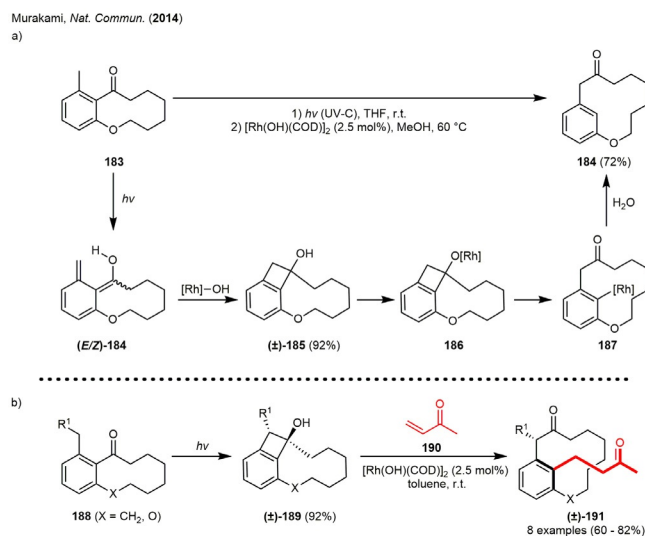
Scheme 21. Rhodium-catalyzed ring-enlargement reaction via a Norrish–Yang-cyclization/metal-catalyzed fragmentation sequence in the synthesis of (a) metacyclophane and (b) substituted metacyclophane generated by a subsequent C–H activation.

Azetidines as Norrish–Yang products

In recent years, Norrish–Yang reactions were also incorporated into the synthesis of azetidines as highly reactive photogenerated intermediates. As azetidines almost possess the same ring strain energy as their lighter aziridine homologues, it is not surprising that they are also suitable as synthetically valuable intermediates capable of undergoing various ring opening transformations.[71]

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In 2013, the Murakami group reported the synthesis of substituted indoles in moderate to high yield by combination of a sunlight-induced Norrish–Yang reaction with a subsequent rhodium-catalyzed ring-opening-cyclization sequence (Scheme 22). The 2-(*N*-aryl-*N*-methylamino) acetophenones **192** were irradiated in a Pyrex flask equipped with a previously exposed sunlight collector for 8 h on a sunny day. The subsequent addition of the rhodium catalyst followed by treatment with aqueous HCl led to the formation of indoles **193** in moderate to good yields. Irradiation of α-aminoketone **192** resulted in the expected Norrish–Yang photoproduct **195**. Rhodium-mediated ring-opening of the 3-azetidinol **195** and subsequent 1,4-rhodium shift furnished intermediate **197**, which underwent an intramolecular addition to the carbonyl group. The generated hydroxyindoline **198** was aromatized using acidic conditions yielding in a variety of indoles **193** in moderate to good yield (Scheme 22 a). The authors reported the sequence to be highly regioselective when unsymmetrically substituted α-aminoketones **192** were used.[72]

In 2015, the Murakami group described a related approach starting from N-allylglyoxylamides **199** to construct (3*R*)-3-hydroxy-1,4-dihydropyridin-2-ones (**200**) in moderate yield but excellent enantioselectivity. The sequence was again based on the combination of a Norrish–Yang photogeneration of azetidinol (±)-**201** with a rhodium-catalyzed ring-opening-cyclization follow-up reaction. The group was able to perform the reaction

in an enantioselective fashion by using the chiral (*R*)-(*S*)-JOSIPHOS ligand (Scheme 22 b). The irradiation of the glyoxylamides **199** with a blue LED lamp generated the four-membered lactam (±)-**201** as a mixture of diastereomers. The subsequent rhodium-mediated reaction using a combination of [Rh(OH)(COD)]₂ and chiral (*R*)-(*S*)-JOSIPHOS ligand furnished 1,4-dihydropyridin-2-ones (*R*)-**200** with excellent *ee*. Mechanistically, deprotonation and ligand exchange of the rhodium catalyst followed by ring-opening afforded the metal-allyl-complex **202**. Rhodium-catalyzed nucleophilic addition to the α-carbonyl furnished the six-membered metal-bound-lactam **203**. Addition of water gave (3*R*)-3-hydroxy-1,4-dihydropyridin-2-ones (*R*)-**200**.[72]

In 2019, the Baxendale group began to contribute to the field of photogenerated azetidinol intermediates by applying photoflow conditions in their synthesis.[73] The group was able to incorporate the photogenerated azetidinols **207** in a Ritter-type-reaction with several aliphatic and aromatic nitriles followed by an acid-catalyzed rearrangement reaction furnishing oxazolines **206** in moderate to excellent yield (Scheme 23). Mechanistically, irradiation of sulfonamides **204** under photoflow conditions furnished the Norrish–Yang products **207**. Acid-induced elimination of water followed by addition to the nitrile and hydrolysis of the nitrilium-ion gave amide **208** that undergoes a strain-releasing ring-enlargement rearrangement furnishing oxazolines **206** via nucleophilic attack of the carbonyl at the polarized proximal C—N bond. Applying the same reaction conditions, the authors were also able to introduce oxygen and sulfur-based nucleophiles in order to synthesize 2,3-dihydrobenzofurans and sulfur-substituted azetidines.[74]

Very recently, the groups of Musaev, Yeung, and Sarpong reported the use of photogenerated azetidinol **212** in a hitherto unknown palladium-catalyzed C—C cross coupling reaction with aryl and alkenyl bromides as well as triflates to generate α-functionalized piperidines **211** (Scheme 24).

Irradiation of the phenylglyoxylamides **209** in the solid state with blue LEDs lead the formation of N-fused bicyclo-β-lactams (±)-**212** through a Norrish-Yang reaction. The azetidinols (±)-**212** were subsequently incorporated in the palladium-mediated α-functionalization reaction as masked nucleophiles using aryl and alkenyl bromides and triflates as cross-coupling

a) Murakami, *Chem. Lett.* (**2013**)
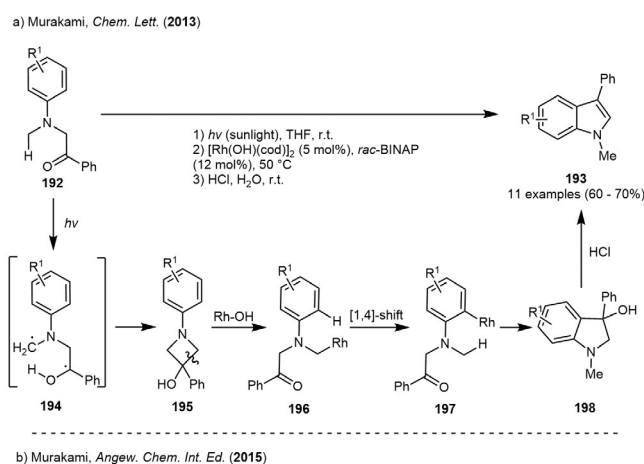
Scheme 22. Photogenerated azetidinols as intermediates in the rhodium-mediated (a) synthesis of indole derivatives and (b) enantioselective preparation of 1,4-dihydropyridin-2-ones.

Baxendale, *J. Org. Chem.* (**2020**)
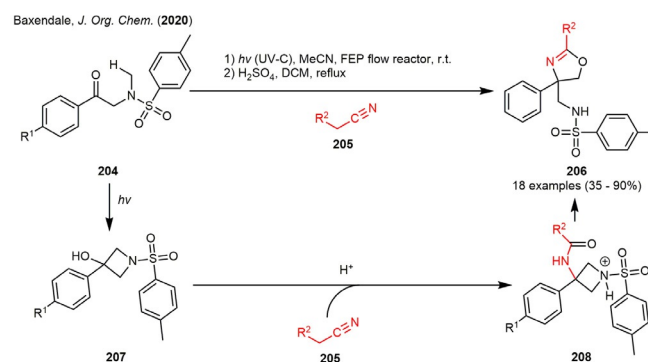
Scheme 23. Photogenerated N-tosylated azetidinols in a Ritter-type reaction furnishing oxazolines.
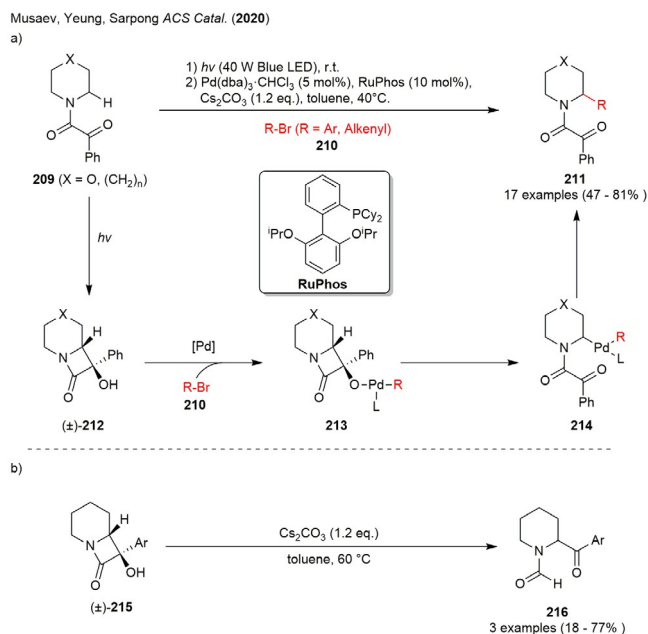
Scheme 24. Photogenerated N-fused bicyclo-β-lactams in (a) the palladium-mediated α-functionalization of piperidines and analogues as well as (b) base-mediated α-acetylation of piperidines.

partners. Optimization studies showed the use of RuPhos as a ligand to be crucial for obtaining decent yields of the desired product **211**. The authors reported a plausible rection mechanism consistent with the proposal by Uemura in 1999.[75] Oxidative addition of the palladium(0)-catalyst in the aryl bromide formed a palladium(II) complex. Deprotonation and ligand exchange furnished intermediate **213**, which underwent β-C–C cleavage in order to generate α-palladated piperidine **214**. The catalytic cycle was closed by reductive elimination liberating the α-arylated product **211** and the active catalyst (Scheme 24 a). The phenylglyoxyl directing group could be removed after the reaction under basic conditions.[76]

Additionally, a control experiment without the palladium catalyst starting from azetidinols (±)-**215** revealed a Cs_2CO_3-promoted rearrangement yielding in α-acylated piperidines **216**. Product formation was assumed to be the result of base-induced cleavage of the distal bond of the azetidinols (±)-**215**. Both experimental as also computational evidence pointed towards the importance of the cesium counterion for this transformation (Scheme 24 b).[76]

Conclusions and Outlook

Photochemical reactions contribute to the emerging field of sustainable chemistry, since the driving force of these transformations is introduced into the molecule by photon absorption and therefore can provide very mild and potentially eco-friendly reaction conditions. The high excitation energy transferred in particular by UV irradiation leads to high energy intermediates and products. Accordingly, the so called uphill-photochemistry enables photoinduced isomerizations and cycloadditions leading to a versatile toolbox of strained three- and four-

membered photoproducts. Impressive progress in this field was made by developing efficient photoflow conditions for the synthesis of such strained photoproducts. The latter can subsequently be subjected to numerous strain-releasing reactions, in which their inherent ring strain energy serves as a driving force facilitating very mild and sustainable conditions for the overall sequences compared to the generation of low-energy co-products in classical bond activation procedures. This review features recent contributions to the field of photo-generated strained intermediates. While earlier reports clearly focused on acid- or uncatalyzed approaches, recent contributions open the field to metal-catalyzed C–C activations in order to access structurally complex products. The use of very potent photocatalysts in terms of both energy transfer as well as photoinduced electron transfer (PET) might provide further innovations with respect to sustainability by applying visible light for such transformations. The progress made in this area has so far led to powerful methodologies suitable for the construction of natural products or biologically active molecules. The exceptional reactivity and structural features of photogenerated strained ring systems will likely lead to broader applications in various areas of the chemical sciences. In strained photoproducts, single bonds which are difficult to activate in other settings can be broken and suitable catalysts can take control over these processes. Classical synthetic methods often achieve bond activations or bond forming processes through the generation of low-energy co-products (e.g. metal halides or other salts as in classical cross-couplings) which must either be recycled or disposed of. In contrast, photoactivation/strain-release can even produce final products of higher energy content than the starting materials without the generation of any other potentially undesired molecular entities. Its inherent sustainable nature holds promises for more environmentally benign synthetic approaches and thus fits well into the general context of current research activities worldwide.

Conflict of interest

The authors declare no conflict of interest.

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