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Photochemical rearrangements in organic synthesis and the concept of the photon as a traceless reagent.

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Abstract

Many photochemical reactions are carried out under particular sustainable conditions. Often no chemical activation is necessary and the photon is considered as a traceless reagent. These reactions give access to unusual molecular structures and therefore are highly appreciated for application to organic synthesis, especially in heterocyclic chemistry. In this context, photochemical position isomerizations of heterocyclic compounds are discussed. Photochemical rearrangements induced by electron and hydrogen atom transfer (HAT) are also used for the preparation of heterocyclic compounds. Photochemical electrocyclization is discussed with six-membered heterocycles such as pyridine derivatives. Finally, photochemically induced cyclization are presented as a very suitable method for the construction of heterocycles. The synthesis of biologically active compounds is particularly focused. Thus perspectives of sustainable chemistry are presented for the pharmaceutical and agrochemical industry.

Key Words

Heterocycles – Industrial Photochemistry – Sustainable Chemistry – Organic Chemistry – Photochemical Isomerization – Hydrogen Atom Transfer – Cyclization – Natural Products – Scaffolds – Bioactive Compounds

Introduction

In 1912, the famous Italian chemist Giacomo Ciamician (1857 – 1922) published his vision on a sustainable nonpolluting, a clean chemical industry in which chemical transformations are mainly carried out with light as it is done by green plants.¹ Four years before, he exposed even more precise ideas on sustainable chemistry. In a lecture before the French Chemical Society, he stated:

*Mais, outre les ferments, il y a un autre agent qui est de la plus grande importance, pour les plantes du moins, et dont l'influence sur les processus organiques mérite une étude profonde : c'est la lumière.*²

In this way, he established a link between enzymatic (catalytic) and photochemical reactions. This event is considered as the beginning of green chemistry.³ Almost in the same time Emanuele Paternò also recognized the interest of reactions induced by light absorption for organic synthesis.⁴ The interest of photochemical reactions in connection with sustainable chemistry and organic synthesis has then been neglected for a long time. However, since about ten years in the academic research and since about three years in industrial research⁵, we observe a bright renaissance of this research domain. Photocatalytic reactions with visible light play an important role in this development.⁶

Photochemical reactions of organic compounds are characterized by the fact that these compounds change their electronic configuration when they are excited by light absorption.^{7,8} Consequently, their chemical reactivity is considerably modified and compounds or compound families become available which cannot or difficultly be synthesized using classical organic reactions.^{9,10} Thus the photon has to be considered as a reagent which does not only increase the reactivity but which also modifies it.⁸ The traditional strong links between organic and physical photochemistry permits a profound understanding of such reactions which also facilitates their

optimization.¹¹ Photochemical reactivity of a functional group is often complementary to the corresponding ground state reactivity.

In connection with sustainable chemistry, it is important to note that the photon is a traceless reagent.^{12,13} Its application reduces the formation of side products and waste. The impact for green chemistry is particularly high when these reactions are carried out with sunlight as renewable energy resource.^{13,14}

Photochemical reactions can also be induced using different kinds of photosensitization.¹⁵ In such cases, the light absorbing compound transfers its excitation energy onto the substrate which **reacts** at its excited state. Other forms of sensitization such as processes involving electron or hydrogen transfer between the sensitizer and the substrate or reaction intermediates are also observed and frequently applied.

In this chapter we mainly focus on photochemical rearrangements resulting from direct light absorption. Owing their interest in many domains such as the synthesis of biological active compounds or material science, mainly transformations with heterocyclic compounds will be discussed. Nevertheless, it should be mentioned that a lot of photochemical rearrangements leading to complex isocyclic compounds have been and are currently studied.¹⁶ As in the case of many photochemical reactions, the concept of the photon as traceless reaction is particularly well applied in such rearrangements.¹²

Photochemical position isomerization of heterocycles

Five membered heterocyclic compounds are encountered in many biologically active compounds. Especially in the case of two or more heteroatoms, the position of these atoms as well as the substitution pattern significantly affect their properties. This can nicely be showed for the case of the heteroaromatic compounds imidazoles and pyrazoles possessing two nitrogen atoms. In the first case, both nitrogens are in positions 1 and 3 while in the second case, they are in positions 1 and 2. Typical examples of different biological activity of both position isomers are depicted in Figure 1. The phosphodiesterase 5 (PDE) inhibition is increased when the pyrazole ring in **1** is replaced by an imidazole ring in **2**.¹⁷ Different activities have been observed for purine (**3**) and corresponding pyrazole (**4**) derivatives as inhibitors of RNA or DNA glycosylase activity of shiga toxin 1.¹⁸

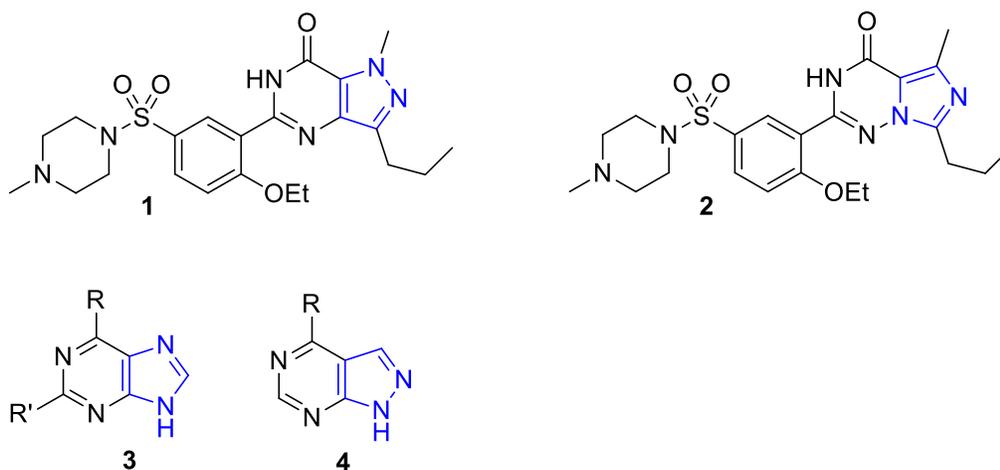
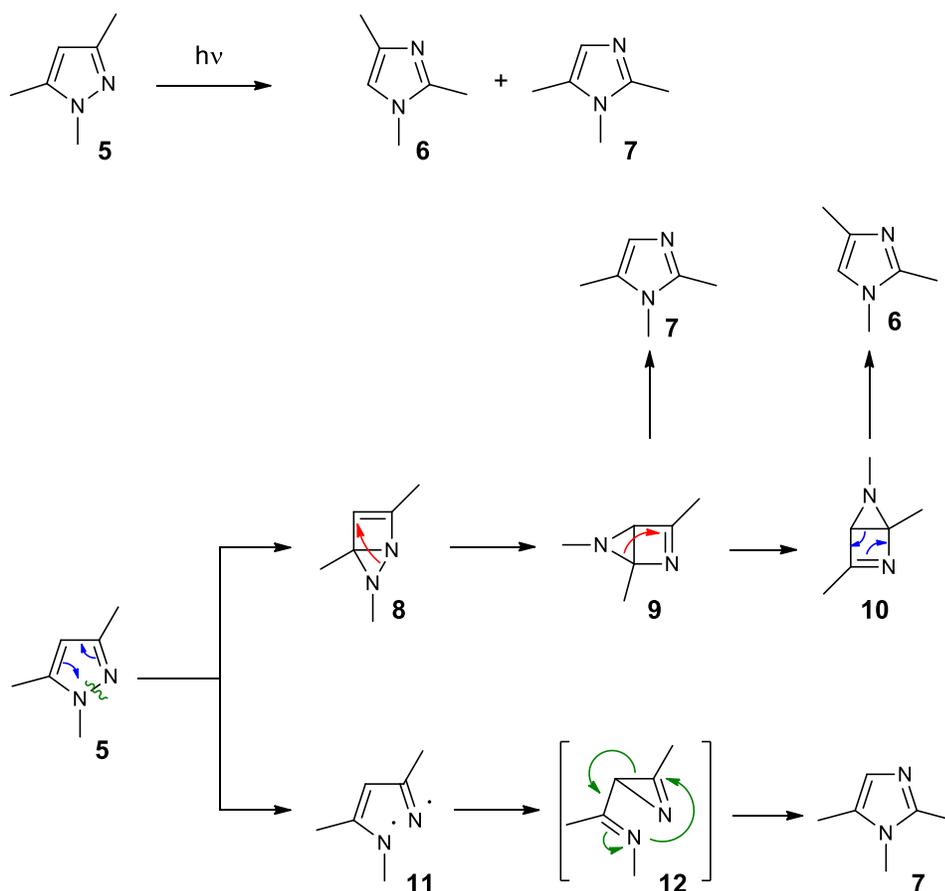


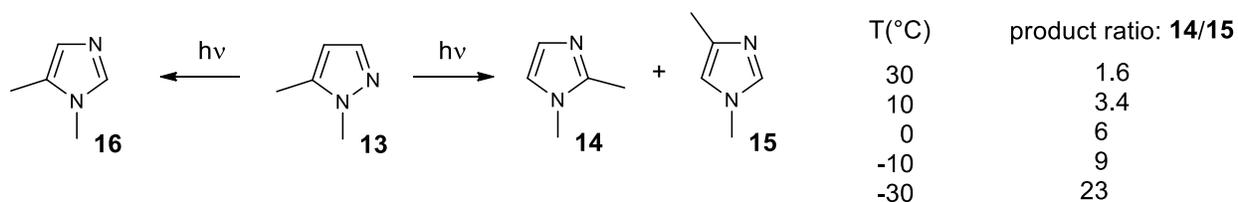
Figure 1. The pyrazole derivative **1** possesses a higher activity than the corresponding imidazole derivative **2**. Similar effects are observed when replacing a purine compound **3** by its pyrazole position isomer **4**.

Various synthesis methods have been developed to prepare imidazoles, pyrazoles or similar heterocyclic compound families.¹⁹ Of course, the scope of each of these methods is limited.

Photochemical rearrangements, in particular the transformation of one family into the other could significantly extend the structural diversity. Pyrazole derivatives can be easily transformed into corresponding imidazoles (Scheme 1).²⁰ In a sequence of photochemical electrocyclization steps, bicyclic intermediates **8**, **9** and **10** are generated from **5** involving $[\pi 2+\sigma 2]$ electrocyclic reactions (blue arrows) and 1,3-sigmatropic shifts (red arrows). In a 1,3-sigmatropic shift, final compounds **6** and **7** are formed. The product ratio strongly depends on the reaction temperature. Thus the pyrazole **13** was transformed into compounds **14**, **15** and **16** in different ratios (Scheme 2).²¹ Intermediates such as **8**, **9** or **10** (compare Scheme 1) are involved in the formation of **14** and **15** while intermediates such as **11** or **12** are involved in the formation **16**. More generally in such reactions, a competition between both mechanisms is discussed.²² All these reactions are part of the larger family of circumambulatory rearrangements.²³



Scheme 1. Photochemical rearrangements of the pyrazole and imidazoles derivatives.

Scheme 2. Temperature dependence of the product ratio **14/15**.

Similar reactions have been carried out with benzopyrazoles such as **17** (Scheme 3).²⁴

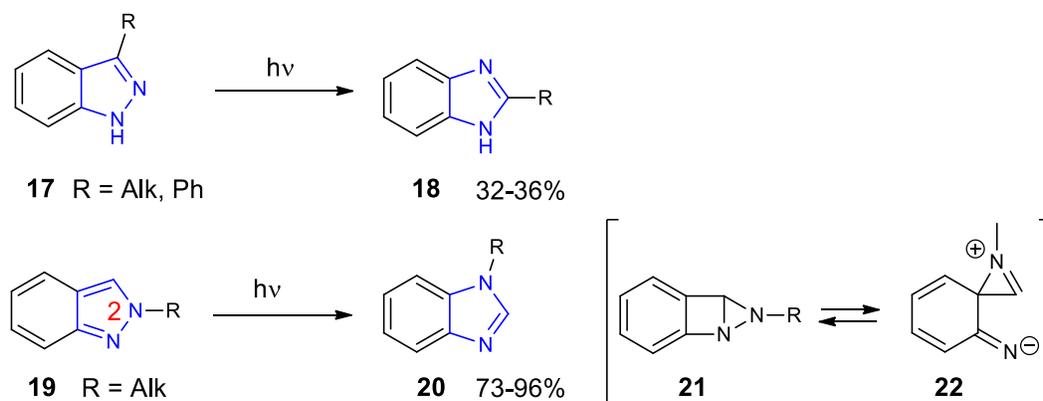
Photochemical position isomerization yields the corresponding benzo imidazole derivatives **18**.

Much better yields were obtained in the corresponding reaction of isomers **19** carrying an alkyl substituent on the nitrogen atom in 2 position. This compound can also be considered as being derived from ortho-benzoquinone. Compounds **19** were efficiently transformed into the

benzoimidazoles **20**. In this reaction, intermediates **21** and **22** are most probably involved.²⁵ In a

reaction at low temperature (-60°C), the formation of compound **21** was observed. Upon warmup, **21** yielded again the starting product **19**. For this reason, the formation of an additional

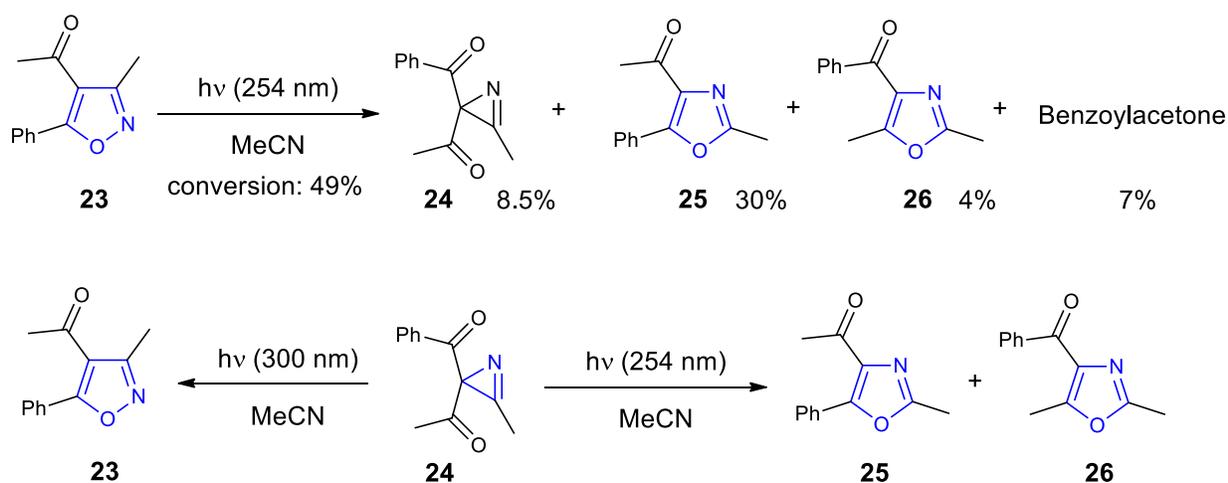
intermediate (**22**) was discussed.



Scheme 3. Photochemical transformation of benzopyrazoles into corresponding

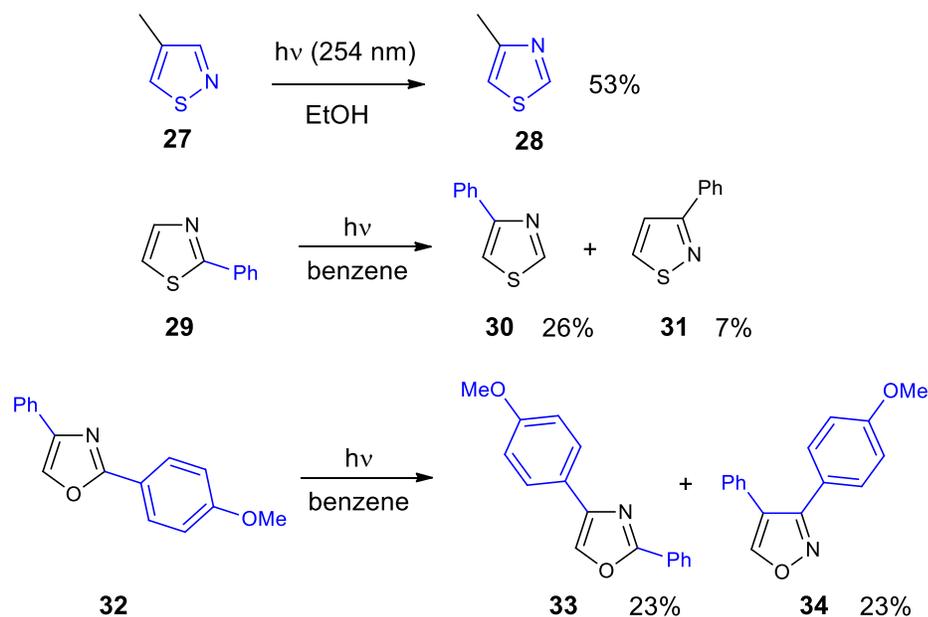
benzoimidazoles. The irradiation has been carried out with high pressure Hg-vapor lamps.

Isoxazoles possess a similar structure than pyrazoles in which one nitrogen is replaced by an oxygen atom. Consequently, similar position isomerizations are observed with this compound family. Upon irradiation, compound **23** was transformed into compounds **24**, **25** and **26** along with small amounts of benzoylacetone (Scheme 4).²⁶ In an extended mechanistic study, the azirine compound **24** was irradiated at $\lambda = 300$ nm, yielding the isoxazole **23**. When the same compound was irradiated at $\lambda = 254$ nm, oxazoles **25** and **26** were formed. It was suggested that in the first case, a zwitterion intermediate is involved while in the second case, a diradical intermediate at the triplet state should be formed. This is an example which infringes the general accepted principle that a photochemical reaction always occurs from the lowest excited singlet or triplet state as it was formulated in analogy with the Kasha and Vavilov rules (see page 40 in ref. 7). Especially in cases of intramolecular reactions which are faster than inter conversion processes, such infringes are observed. Similar reactions has been carried out with corresponding benz- or naphthisoaxazoles.²⁷ Azirines are interesting synthesis intermediates. For example, in situ addition of β -dicarbonyl compounds leads to highly substituted pyrroles.²⁸



Scheme 4. Photochemical rearrangement of an acylisoxazole compound.

Also sulfur analogue isothiazoles were transformed in the same way. Upon irradiation 4-methylisothiazole **27** yielded 4-methylthiazole **28** (Scheme 5).^{29,30} In an acidic medium protonation may occur at the nitrogen atom. Under these conditions, the reaction is reversible. Under similar reaction conditions, a migration of the phenyl substituent in the thiazole **29** took place leading to the regioisomer **30** along with small amounts of the isothiazole **31**.³¹ As shown by a computational study bicyclic intermediates (compare **8**, **9** and **10** in Scheme 1) are involved in the main reaction.³² Such migrations of substituents are also observed in photochemical rearrangements of oxazoles. Thus the positions of the aryl substituents in **32** have been exchanged leading to the formation of **33** (Scheme 5).³³ In this case, substantial amounts of the isoxazole **34** were also obtained.

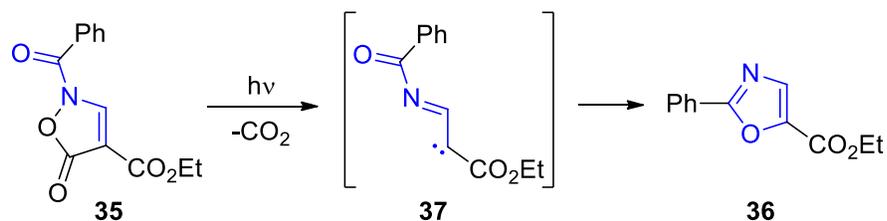


Scheme 5. Photochemical rearrangement of heteroatoms and migration of a substituent in isothiazole, thiazole and oxazole derivatives.

More complex isoxazolone compounds such as **35** also provide an access to oxazole derivatives.

The irradiation ($\lambda = 300 \text{ nm}$) of this compound efficiently yielded the oxazole **36** (Scheme 6).³⁴

The reaction can be carried out either in acetonitrile or acetone as solvent. In the latter case, triplet sensitization should be considered. After photochemical excitation, decarboxylation takes place and the intermediate **37** is formed. Cyclization leads to the final product **36**. Similar transformations have been performed using pyrolysis conditions.



Scheme 6. Photolysis of an isoxazolone compound leading to an oxazole derivative.

Oxazoles or thiazoles play a key role in many biologically active compounds. For example, they are encountered in cyclopeptides such as bistratamide C or complex molecules such as theonezolidine A (Figure 2).^{35,36} Reactions depicted in Scheme 5 may be applied to isomerization of partial structures in such compounds or to the synthesis of them or similar active compounds.³⁷

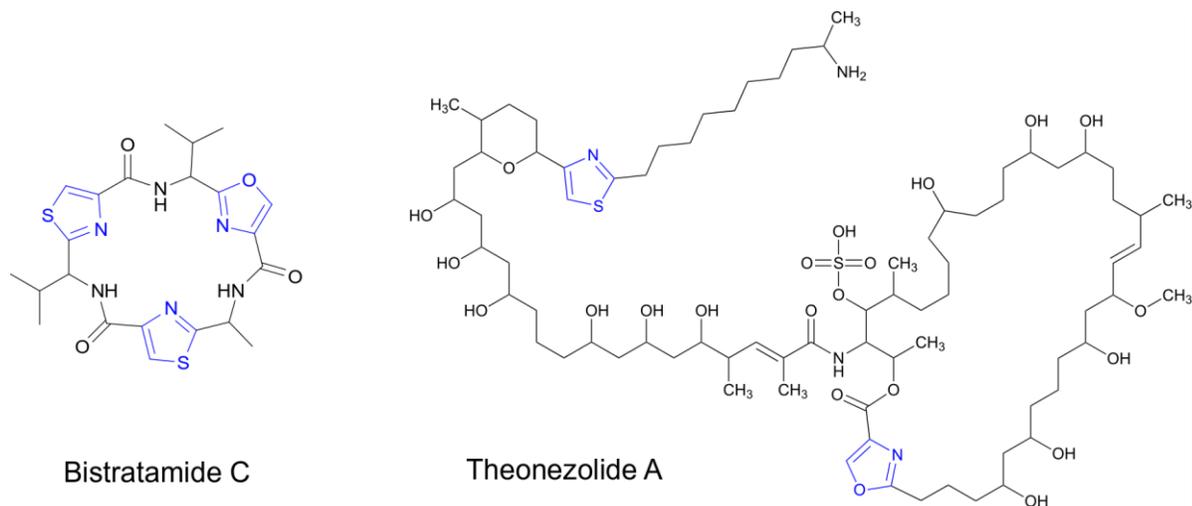
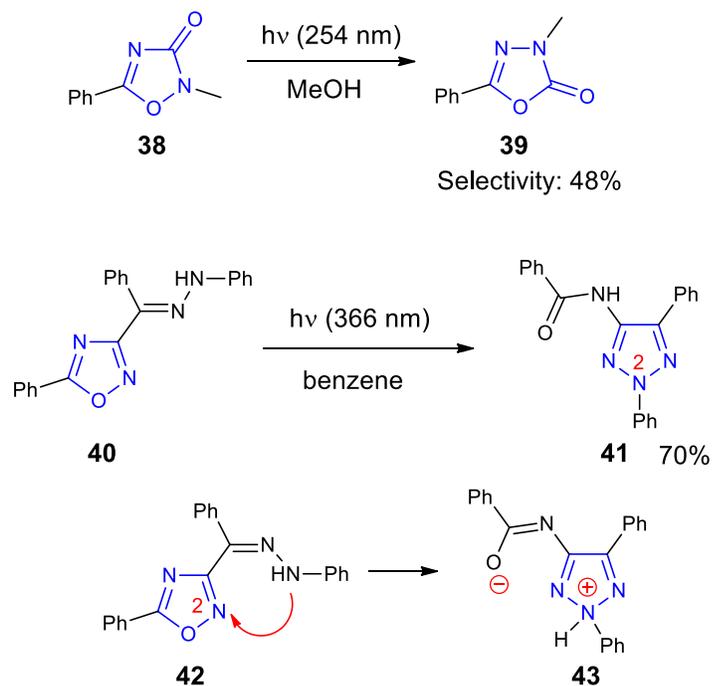


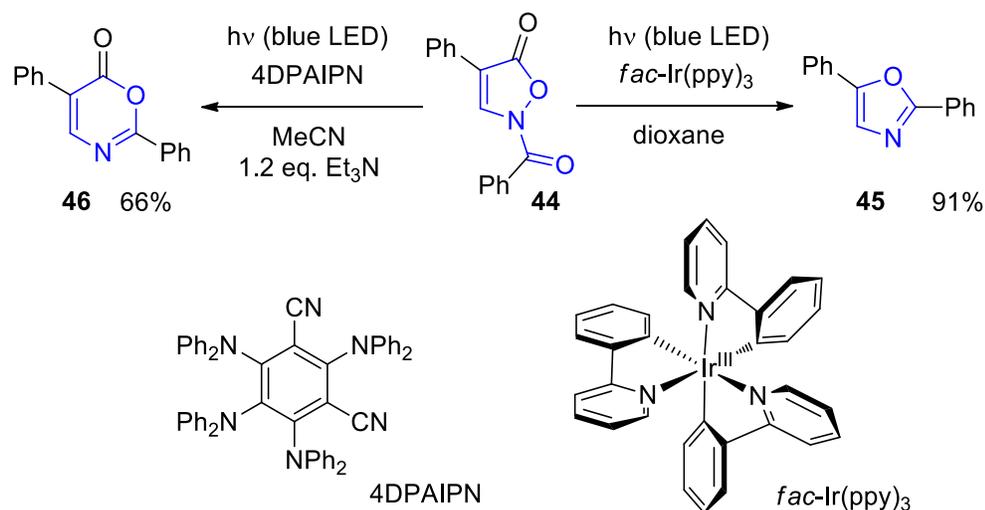
Figure 2. Examples of natural products possessing oxazole and thiazole moieties.

Five-membered aromatics with three heteroatoms also play an important role in the domains of bioactive compounds or the preparation of new materials.³⁸ Photochemical reactions similar to those previously discussed have been performed with such compounds.³⁹ Often the cleavage of N-O bonds play a key role in such transformations.⁴⁰ The heteroatoms as well as the substituents change their places. Under photochemical conditions, the heteroatoms in compound **38** rearrange leading to the position isomer **39** (Scheme 7).⁴¹ A urea function is transformed into a carbamate. When irradiated at longer wavelengths, the isoxadiazole derivative **40** was efficiently transformed into triazole derivative **41**.⁴² Possessing a substituent at the middle nitrogen (position 2), it is a rather unusual triazole isomer. An attack of amine nitrogen atom of the side chain hydrazone on the nitrogen in 2 position (**42**) with formation of intermediate **43** was discussed as key step in this photochemical reaction.



Scheme 7. Photochemical rearrangements with isoxadiazole derivatives.

Currently, photoredox catalysis and its application to organic synthesis considerably contributes to the renaissance of organic photochemistry.⁴³ Rearrangement reactions of heterocyclic compounds have also been carried out under these conditions.⁴⁴ When the isoxazolone derivative **44** is irradiated in the presence of the photoredox catalyst *fac*-Ir(ppy)₃, the oxazole derivative **45** is obtained in high yield (Scheme 8).⁴⁵ Also in this case (compare Scheme 6), decarboxylation is involved. When the organic photoredox catalyst 4DPAIPN is used and in the presence of trimethylamine, the ring-extension product **46** is obtained. In this case, it has been suggested that decarboxylation is avoided by electron transfer from the amine to a corresponding carboxyl radical intermediate. The reactions have been carried out with a large variety of substrates. Numerous corresponding thiocarbonyl derivatives have been transformed in the same way, however by direct light absorption.⁴⁶ No photocatalysis was necessary in this case.

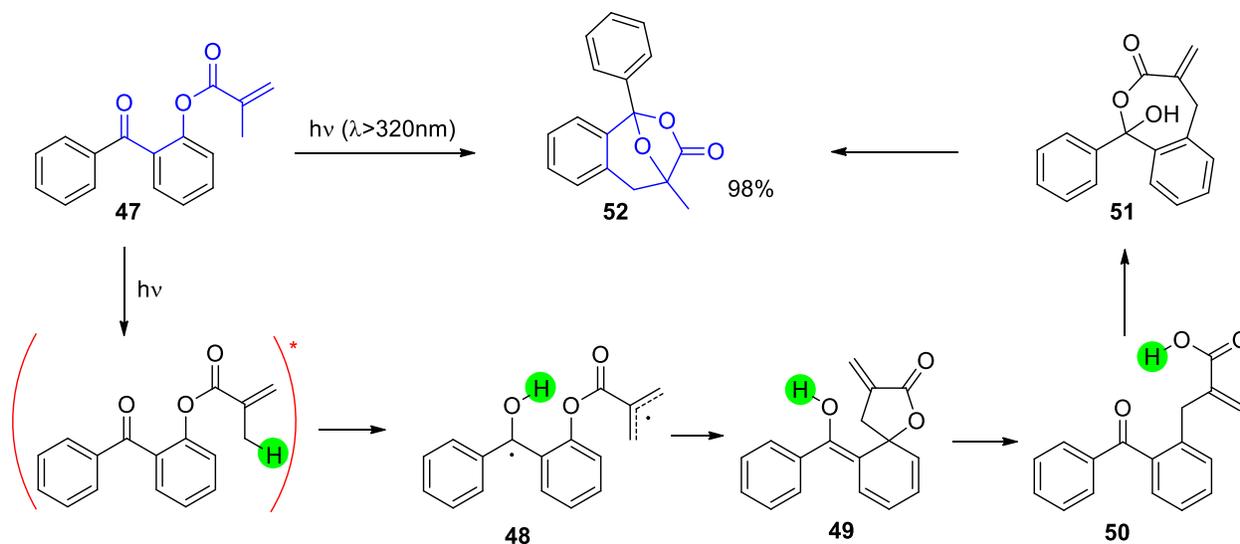


Scheme 8. Photoredox catalytic rearrangements of an isoxazolone derivative.

Photochemical rearrangements induced by electron and hydrogen atom transfer (HAT).

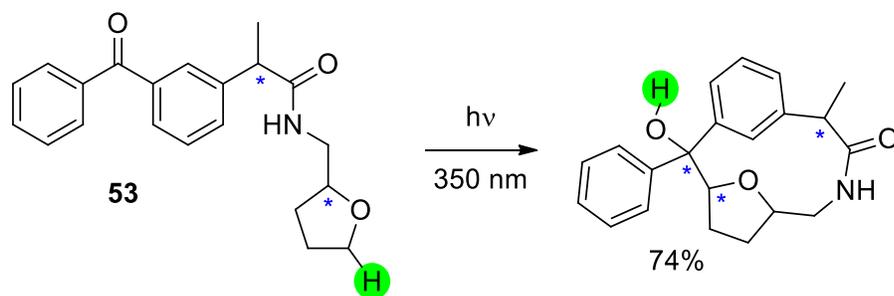
Hydrogen transfer play a key role in many chemical⁴⁷ and biochemical processes.⁴⁸ Radical intermediates are generated which can rearrange or react with other compounds leading to final products. Photochemical conditions provide sustainable methods to generate such intermediates.

For example, utilization of toxic reagents still frequently used in radical chemistry is thus avoided.⁴⁹ In the context of organic photochemistry often two mechanisms are generally discussed for the hydrogen atom transfer (HAT) from a donor to an electronically excited acceptor: (1) The transfer occurs in one step which means that the electron and the proton are transferred simultaneously. (2) The electron is transferred first and the proton follows.⁵⁰ In both cases, neutral radical intermediates are generated. In a more general context, these mechanisms are part of a large number of processes involving proton coupled electron transfer (PCET).⁵¹ In connection with investigations of photochemical cycloadditions aromatic compounds⁵² also aromatic ketones have been investigated. A one-step hydrogen atom transfer is involved in the photochemical transformation **47** (Scheme 9).⁵³ After photochemical excitation, hydrogen abstraction to the carbonyl function occurs leading to the intermediate **48** possessing a ketyl radical and an allyl radical moiety. After a rearrangement via intermediate **49**, compound **50** is formed. Formation of the hemiacetal **51** and addition of the resulting hydroxyl function to the olefinic double bond leads to the final product **52** in high yield.



Scheme 9. A one-step hydrogen atom transfer (HAT) is involved in the photochemical reaction of the benzophenone derivative **47**.

Many hydrogen abstraction reactions have been reported with electronically excited aromatic ketones.⁵⁴ A typical example is depicted in Scheme 10. Upon irradiation, the anti-inflammatory drug ketoprofen **53** undergoes macrocyclization.⁵⁵ The efficiency of this reaction and the reaction of similar compounds depends on the relative configuration in the substrate. Such reactions may cause undesired side effects such as phototoxicity or photoallergy. The present study focus on the stereoselectivity and thus on a more profound understanding of the interaction between the drug and a biochemical structure, for example an enzyme. Such interactions also significantly determine the extent of the adverse effects such as phototoxicity.

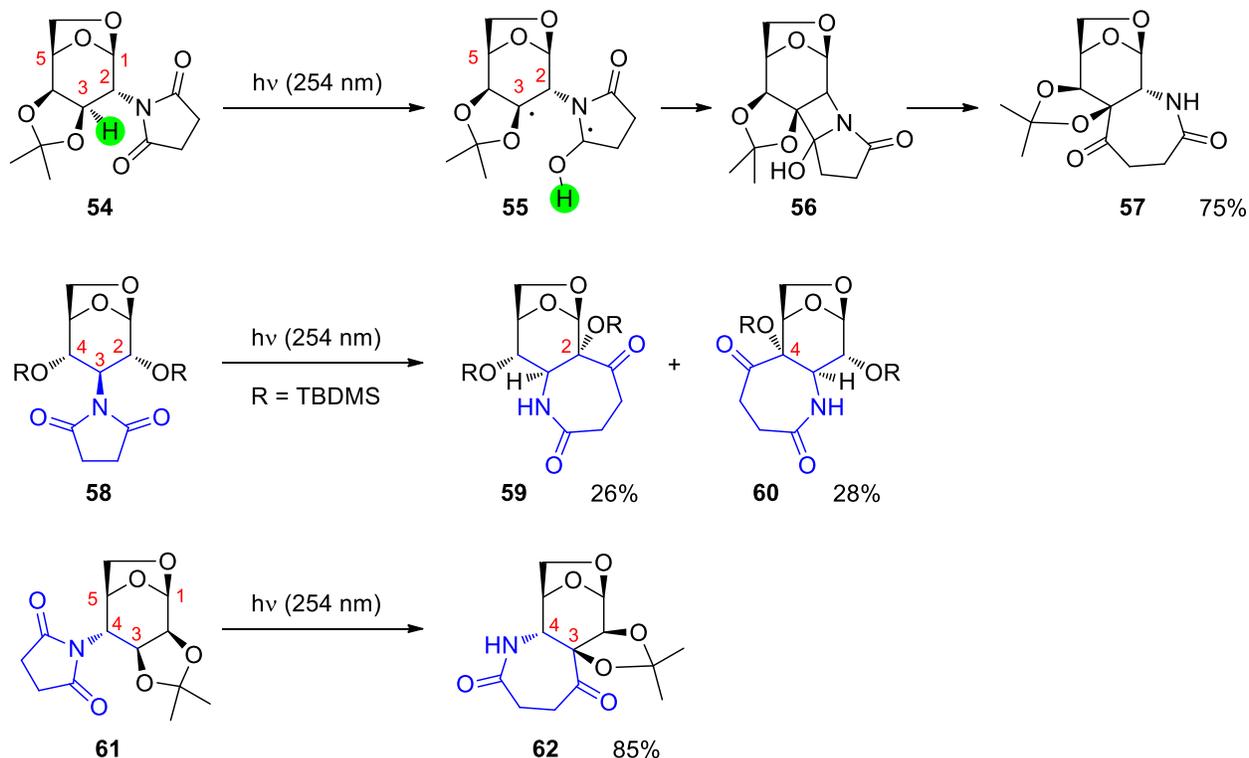


Scheme 10. Long distant 1,12–hydrogen atom transfer leading to macrocyclization.

Also α,β -unsaturated carbonyl compounds or α,β -unsaturated lactones are efficient hydrogen atom acceptors when excited to the triplet state. Such reactions are particularly interesting for application to the synthesis of complex heterocyclic compounds.⁵⁶

Various imides undergo similar hydrogen abstraction reactions.^{57,58} When the anhydrogalactopyranose derivative **54** is irradiated, hydrogen abstraction occurs selectively in position 3 leading to the diradical intermediate **55** (Scheme 11).⁵⁹ The succinimide moiety is the hydrogen acceptor. Radical combination yields the hydroxyl azetidine **56** which rearranges to yield the final product **57**. This reaction sequence is a heterocyclic analogue of the Norrish Yang

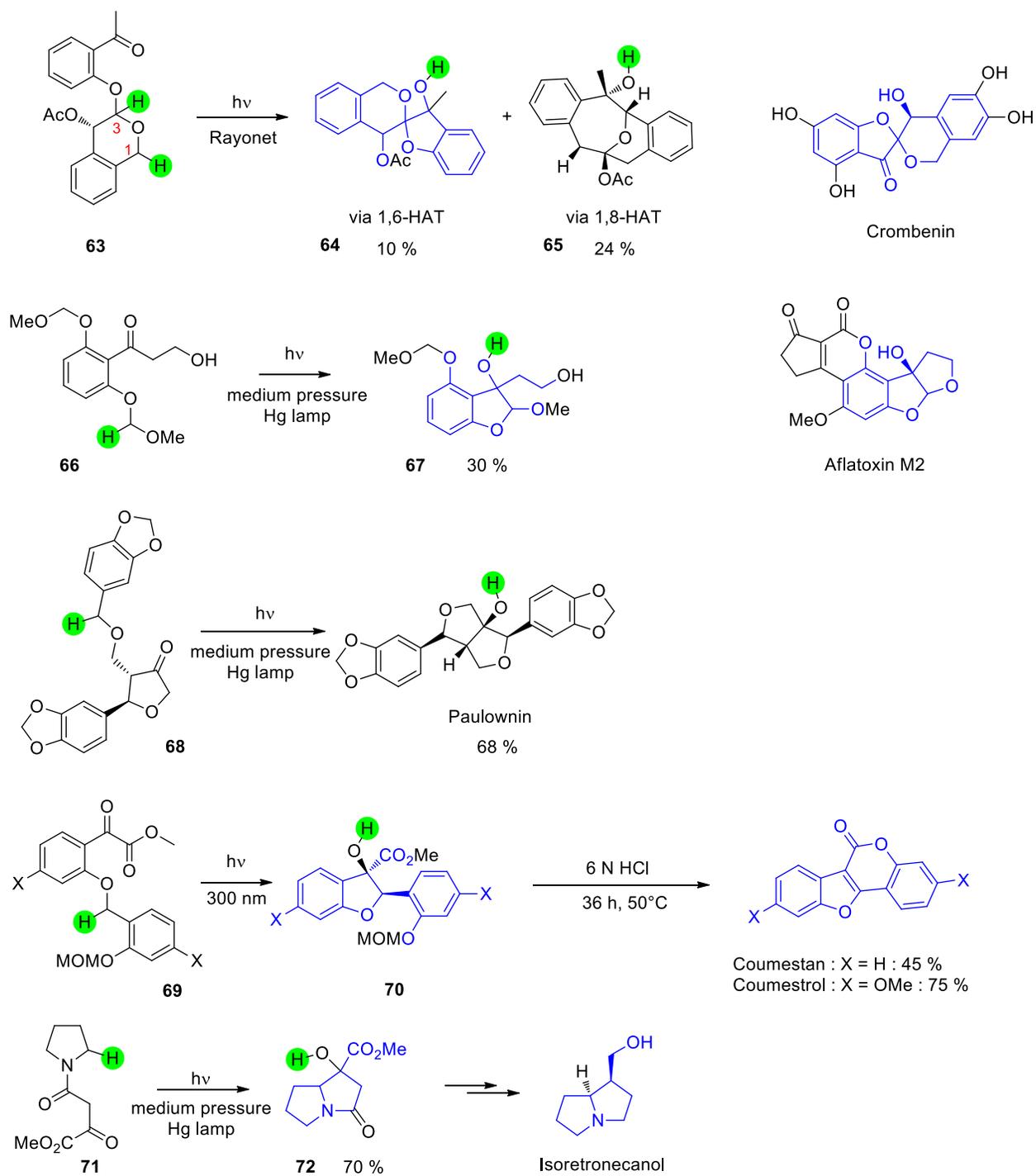
reaction.⁵⁷ The reaction has also been carried out with anhydropyranose derivative carrying the succinimide substituent in other positions. In the case compound **58**, hydrogen abstraction occurs in position 2 and 4 leading to the caprolactams **59** and **60** respectively.⁶⁰ In corresponding diastereoisomers Norrish-Type II elimination products were also isolated. In the case of the isomer **61**, again a regioselective reaction was observed.⁵⁹ Compound **62** was obtained in high yields. Concerning the reactions of compounds **54** and **61**, it must be noted that in any case, hydrogen abstraction in positions 1 or 5 does not occur. C-H bond dissociation energies at such bridge points are high because particularly unstable σ -type radicals are formed. The same reaction has been carried out with corresponding glutarimide derivatives. A lot of such reactions have been carried out with phthalimides.^{61,62}



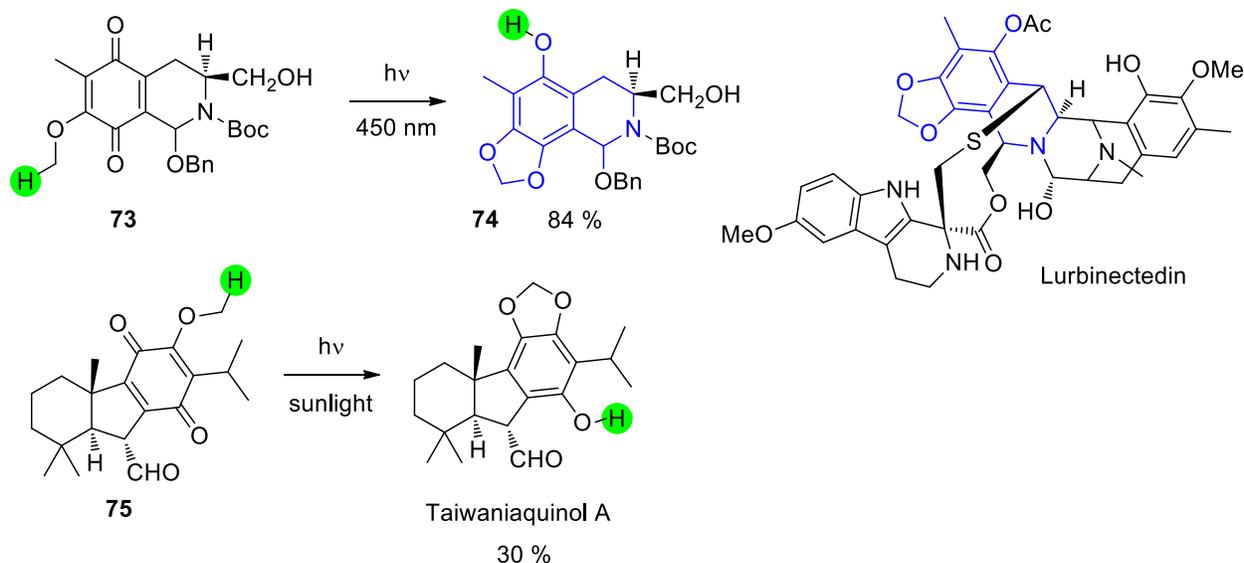
Scheme 11. Photochemical transformations of succinimide substituted anhydropyranose compounds leading to annulated ketocaprolactams.

The reaction has efficiently been applied to the synthesis of benzofuran or tetrahydrofuran compounds. Such moieties are found as core structure in many natural products. Upon UV irradiation of compound **63**, a hydrogen atom is transferred to the ketofunction from the benzo tetrahydropyrene moiety either from the acetale position 3 (1,6-HAT) leading to compound **64** or the benzyl position 1 (1,8-HAT) leading to compound **65** (Scheme 12). The photochemical product **64** is a partial structure of the natural product crombenin.⁶³ Starting from the simple symmetrical trihydroxypropiophenone derivative **66**, aflatoxin M2 core structure **67** is obtained in only one step via photochemical HAT.⁶⁴ In the cyclic ketone **68** hydrogen is abstracted from a benzyl position. Radical combination yields the furo[3,4-c]furan lignane paulownin.⁶⁵ It should be pointed out that this reaction is highly diastereoselective. The ketone function in α -keto esters are efficient hydrogen acceptors.⁶⁶ Photochemical HAT in compounds **69** yields **70** in high diastereoselectivity.⁶⁷ The photoadducts were transformed into the natural products coumestan and coumestrol. The reaction was also applied to the synthesis of alkaloids. In compound **71** the pyrrolidine amid moiety was added to the α -keto ester function.⁶⁸ The resulting bicyclic lactam **72** was transformed into the pyrrolizidine alkaloid isoretronecanol.

Benzoquinone or benzoquinone structures play a key role in many syntheses (chemical or bio) of alkaloids possessing alkoxy benzene moieties such as benzo[d][1,3]dioxoles.^{69,70} After light absorption by the quinone compound **73**, hydrogen is abstracted from the methoxy group occurs (Scheme 13).⁷¹ Tautomerization and radical coupling steps lead to the formation of the benzo[d][1,3]dioxole structure **74**. Such tetrahydroisoquinolines are partial structures in the very big family of isoquinoline alkaloids. In particular **74** is part of lubrinectidin. The same reaction was applied to the synthesis of tawaniaquinol A.⁷² The transformation of **75** (tawaniaquinone F) can be carried out with sunlight.



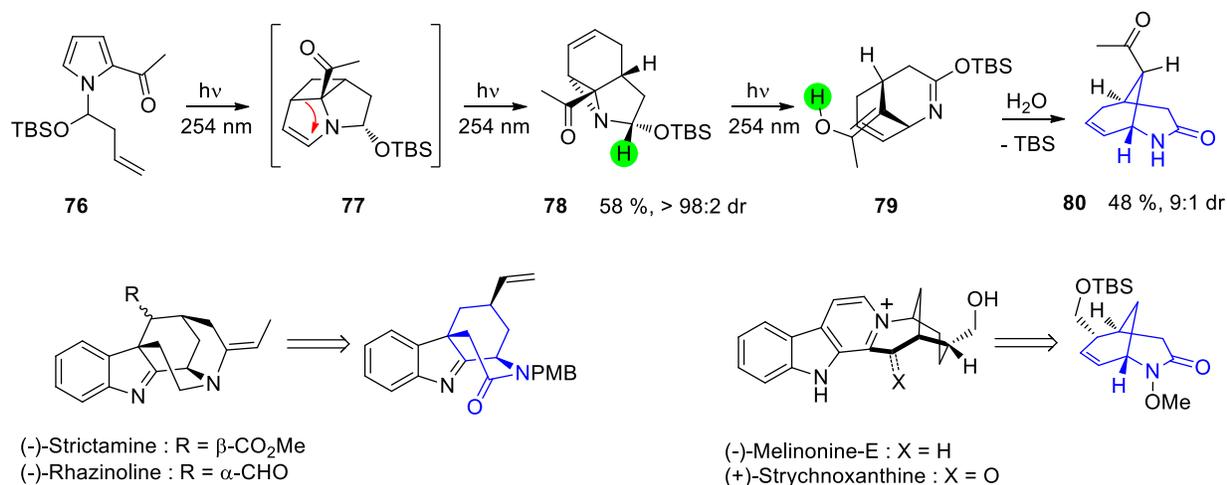
Scheme 12. Photochemical 1,6-HAT and its application natural product synthesis.



Scheme 13. Intramolecular HAT in quinone compounds and its application to the synthesis of natural products.

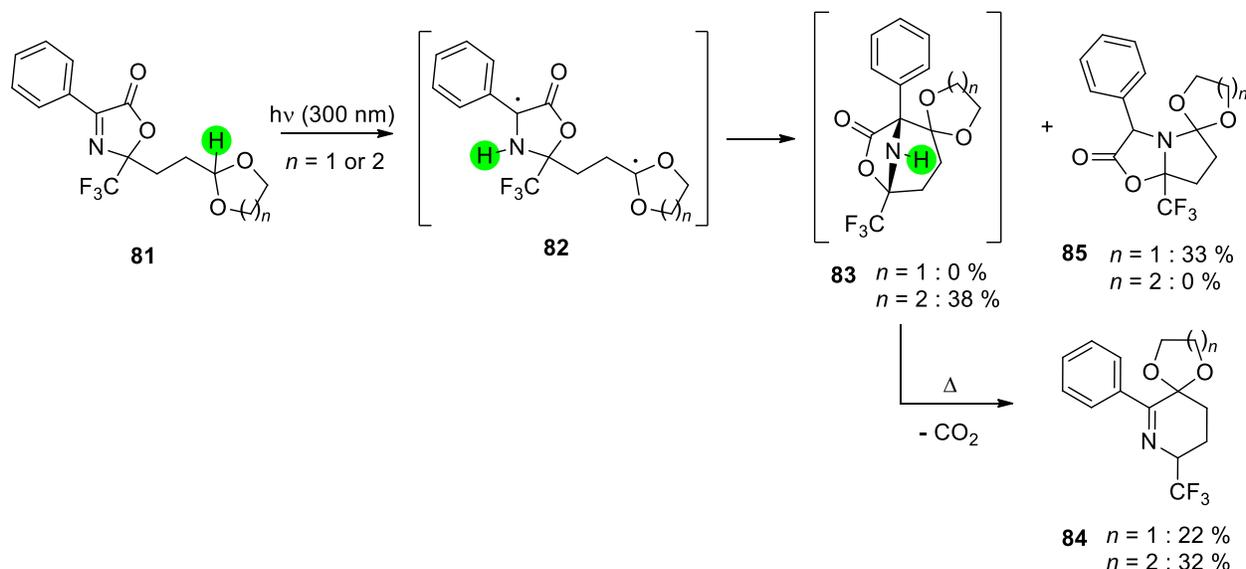
HAT is also applied to the synthesis of complex nitrogen containing polycyclic compounds in which more than one photochemical key step involved. Upon irradiation the pyrrole derivative **76** first undergoes [2+2] photocycloaddition (**77**) (Scheme 14).⁷³ In a 1,3 sigmatropic shift, the azirine compound **78** is formed. This reaction occurs in a stereospecific way. Photochemical hydrogen abstraction from the hemiaminal position to the keto function leads to **79**. This transformation which is observed after a longer irradiation time resembles to a Norrish-type II reaction. After tautomerization (enol) and hydrolysis, the bridged lactam **80** (azocanone) is obtained. It is a substructure of synthesis intermediates of alkaloids such as strictamine, rhazoline, melinonine or strychnoxanthine.⁷⁴

Similar reactions have been carried out in flow reactors.⁷⁵ This technology is now often used for photochemical transformations.⁷⁶ It accounts for the particular challenges of chemical engineering in connection with the Lambert-Beer law. Furthermore, aspects of process safety and efficiency in connection with continuous production are addressed.



Scheme 14. Synthesis of bridged azocanone, a useful synthesis intermediate for alkaloids.

In some regards, the photochemistry of imines resembles to that of carbonyl compounds. Under photochemical reaction conditions, the oxazolone derivatives **81** abstracts hydrogen from the acetale moiety leading to the diradicals **82** (Scheme 15).⁷⁷ Radical combination yields the azaspirobicyclooctanedioxolan and -dioxan derivatives **83**. Especially in the case of the dioxolan compound (n=1), thermal decarboxylation occurs yielding the cyclic imines **84**. In the same case, compound **85** with a newly formed C-N bond is also obtained. It was shown that this product results from the same intermediate **82** which was explained by the zwitterionic nature of the singlet state of **82**. Compound **85** possesses a core structure of molecules used for the treatment of diabetes.⁷⁸ Similar photochemical cyclization reactions have been carried out with α,β -unsaturated butyrolactone derivatives carrying an acetale or sugar substituent on the side chain.^{56,79}



Scheme 15. Photochemical cyclization with oxazolone derivatives involving HAT.

All previously discussed photo-induced HATs are one-step processes which means that the proton and the electron are transferred simultaneously. As mentioned above in such photochemical reactions, also a two-step HAT is often discussed.^{50,51} The one-step transfer takes place when the photochemical electron transfer is endergonic (Figure 3a). However, the formation of the neutral radical intermediates is exergonic. In the case of an electronically excited species, for example the hydrogen acceptor, this step enables a dissipation of the excitation energy. When the photochemical electron transfer is also exergonic, a two-step process becomes possible and the electron is transferred first and radical ion pair is formed (Figure 3b). The proton follows and the same neutral radical intermediates are formed. The exergonicity of the photochemical electron transfer can be estimated with the Rehm-Weller relationship.⁸⁰ In the context of application to organic synthesis, it should be pointed out that the outcome of such reactions often significantly depends on the mechanism of the hydrogen atom transfer.

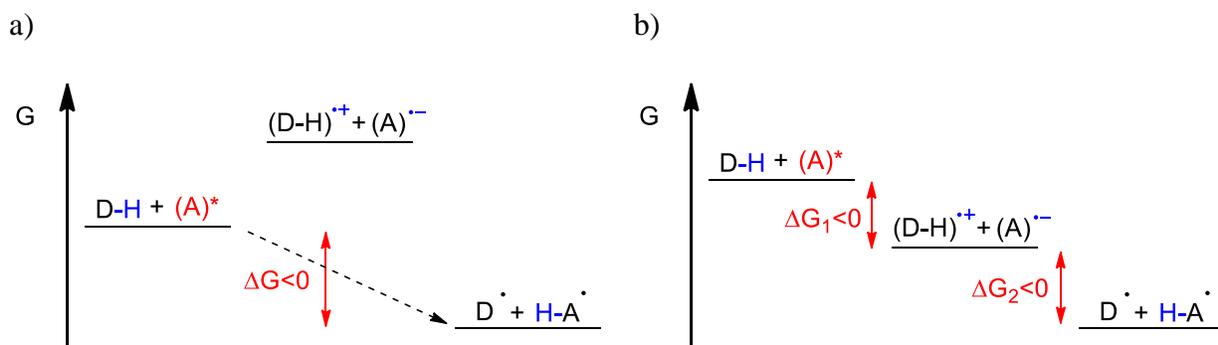
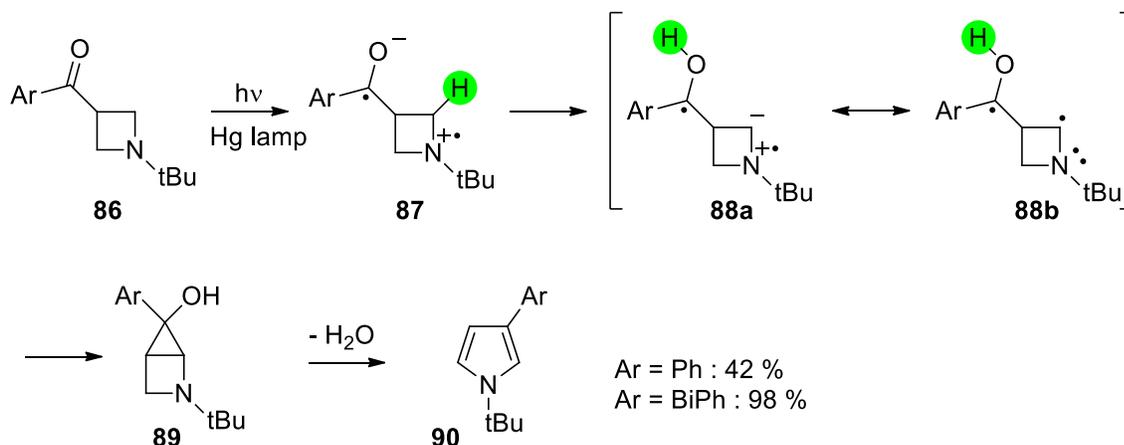


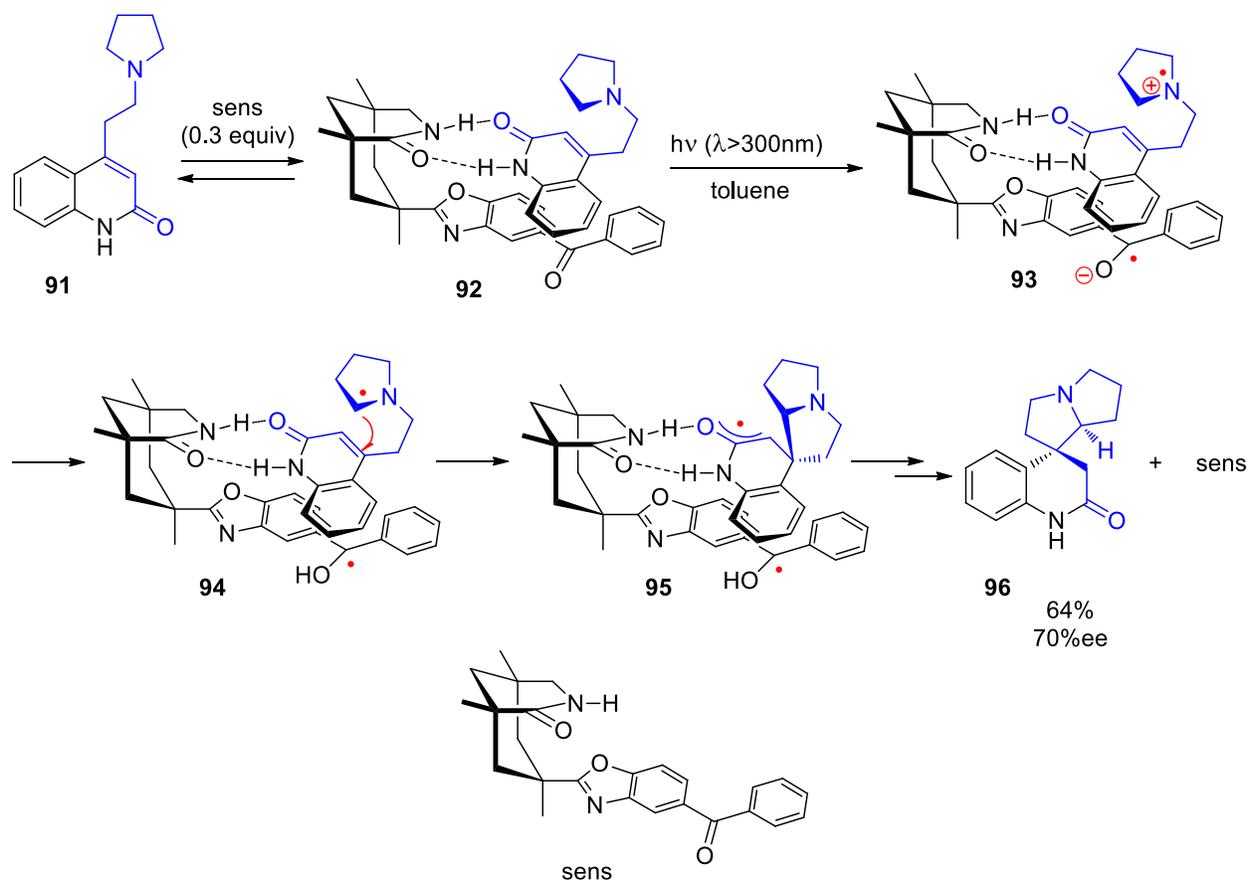
Figure 3. Photochemical induced hydrogen transfer from a donor to an electronically excited acceptor. a) One-step process, b) two-step process.

Amines are efficient electron donors and a two-step process often takes place. After photochemical excitation of the azetidiny aryl ketone **86**, an electron transfer occurs from the acetidine nitrogen to the aromatic carbonyl group leading to the intramolecular radical ion pair **87** (Scheme 16).⁸¹ After proton transfer in the same direction, neutral diradical **88a,b** is generated. Radical combination yields the bicyclic compound **89**. Dehydration and a rearrangement yield the pyrrole derivative **90**. Photocatalysis (triplet sensitization) was also applied to perform similar pyrrole syntheses.⁸²



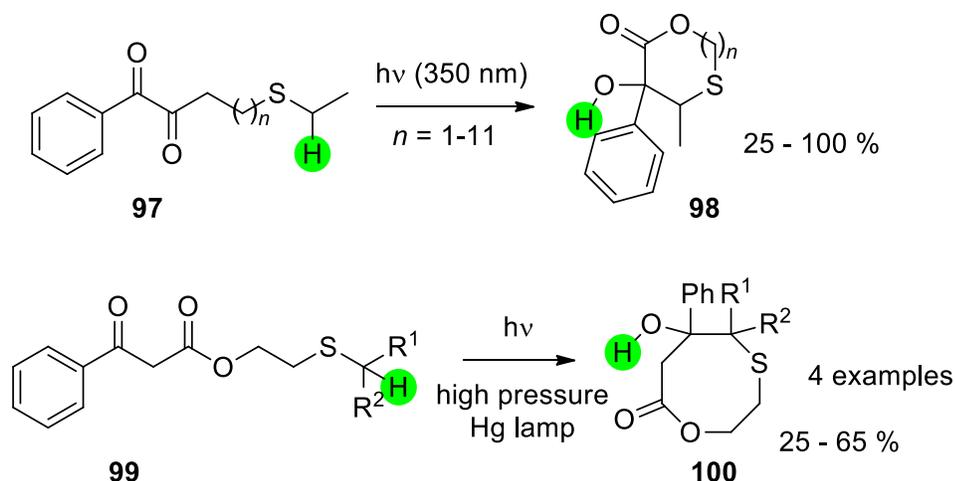
Scheme 16. Synthesis of pyrroles from azetidiny aryl ketone using two-step HAT transfer.

As photochemical electron transfer is involved, photoredox catalysis can be used to perform such reactions. Photoinduced intramolecular addition of tertiary amines can also be carried out on numerous other unsaturated functional groups such as α,β -unsaturated lactams. In the case of quinolone compound **91** however, the electron is not transferred to the electron poor alkene of the lactam function but on the photochemical excited sensitizer (Scheme 17).⁸³ The radical ion pair **93** is formed. The neutral radicals **94** are then formed by proton transfer. Intra molecular addition of the nucleophilic α -aminoalkyl radical to the electron poor double bond occurs (**95**). In the last step, a hydrogen atom is transferred from the ketyl radical to the oxoallyl radical which leads to the final spirocyclic pyrrolizidine compound **96**. Details of the mechanism have also been discussed for the intermolecular addition of simple tertiary amines to α,β -unsaturated lactones.^{84,85} For some time now, such reactions are also carried out using photoredox catalysis with visible light.⁸⁶ A further issue of the reaction depicted in Scheme 17 is asymmetric synthesis. In this reaction chirality is induced by complexation of the substrate **92** with a chiral ligand which carries the aromatic ketone as sensitizing group. Complexation occurs via two hydrogen bonds. In this regard, the ketone also acts as shielding group in order to favor the approach of the α -aminoalkyl radical in one diastereotopic half space. The approach of the sensitizer to the substrates also facilitates the reaction steps of electron and hydrogen transfer. A lot of different photochemical reactions can be stereoselectively performed under these conditions.⁸⁷



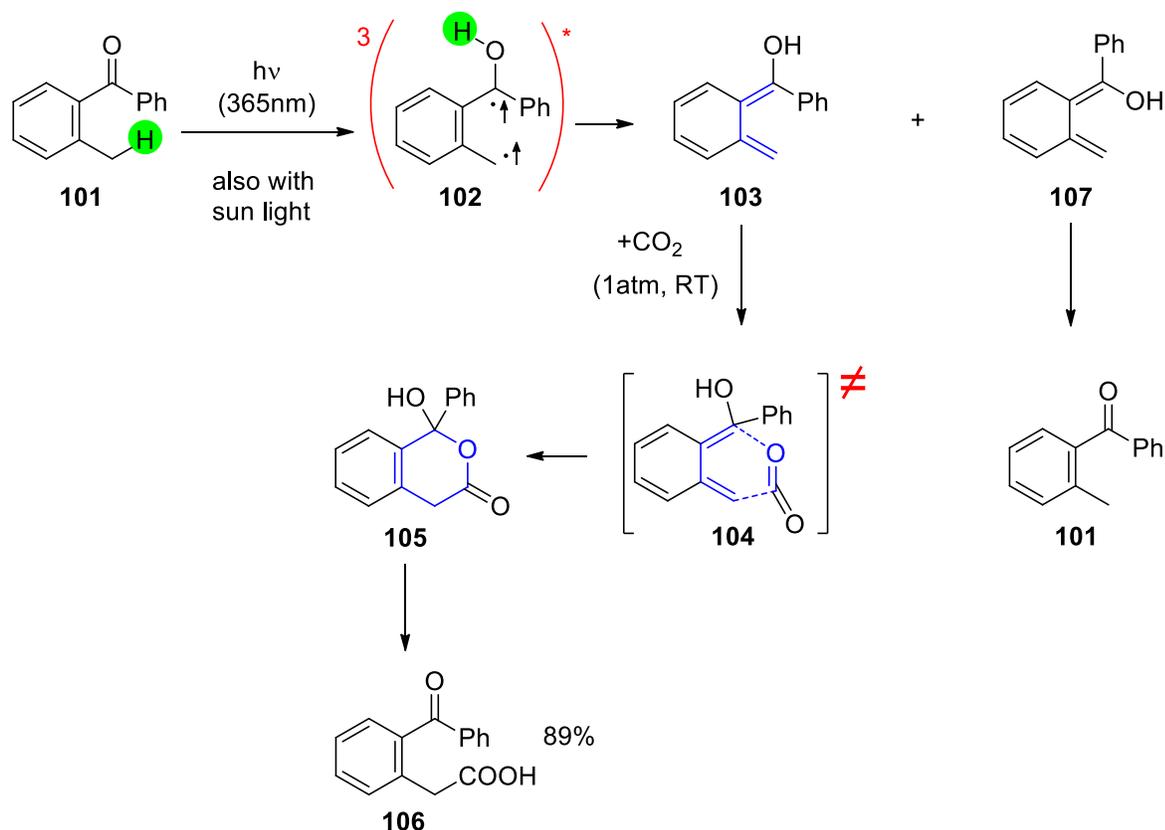
Scheme 17. Intramolecular photoinduced asymmetric addition of a tertiary amine group to a quinolone moiety.

Macrocyclizations have also been carried out successfully with these reaction.^{61,62} The α -ketoester **97** carrying thioether containing side chains of different lengths undergoes easily macrocyclization (**98**) (Scheme 18).⁸⁸ Likewise tertiary amines, thioethers are efficient one-electron donors and a two-step hydrogen transfer process is involved. The efficiency in macrocyclizations might be linked to the formation of radical ion pairs. In some cases, photopinacolization products are observed. Also β -ketoesters undergo similar reactions. Starting from **99**, various oxathiocanone derivatives **100** have been obtained.⁸⁹



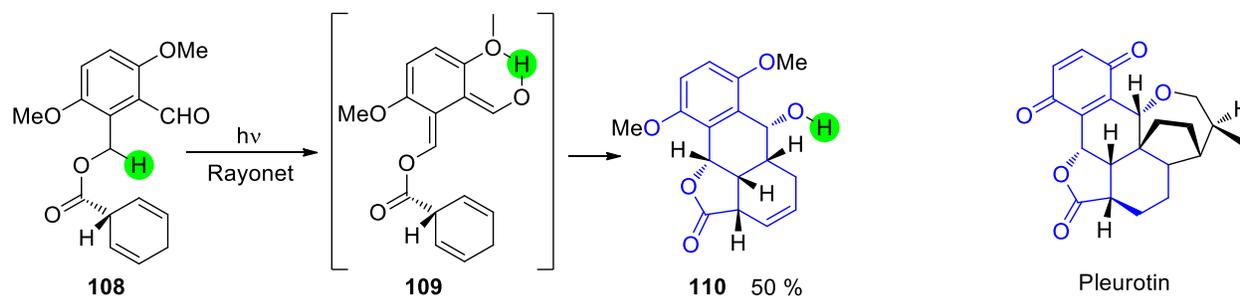
Scheme 18. Photoinduced macrocyclization with thioethers involving a two-step hydrogen atom transfer process.

Intramolecular photochemical hydrogen atom transfer (HAT) is also observed with aromatic carbonyl compounds. In such reactions, hydroxylquinodimethane intermediates are formed. They can also be considered as phototautomers. A spectacular example is shown in Scheme 19.⁹⁰ After photochemical excitation of **101** to the triplet state, hydrogen is transferred from the methyl group to the carbonyl oxygen (**102**). The corresponding singlet ground state **103** possesses a dienol moiety. Such intermediates can also be trapped by electron poor alkenes in a Diels-Alder reaction.⁹¹ In the present case, CO₂ was added leading to the lactone intermediate **105** which after ring opening yielded the keto-carboxylic acid **106**. A theoretical investigation provided evidence for the formation of the typical transition state **104** of a [4+2] cycloaddition. Two stereoisomers **103** and **107** of the dienol intermediate are formed in such reaction. While **103** undergoes cycloaddition, **107** gave the starting compound **101** by tautomerization.



Scheme 19. Photochemical carboxylation of o-alkylphenyl ketones with CO₂.

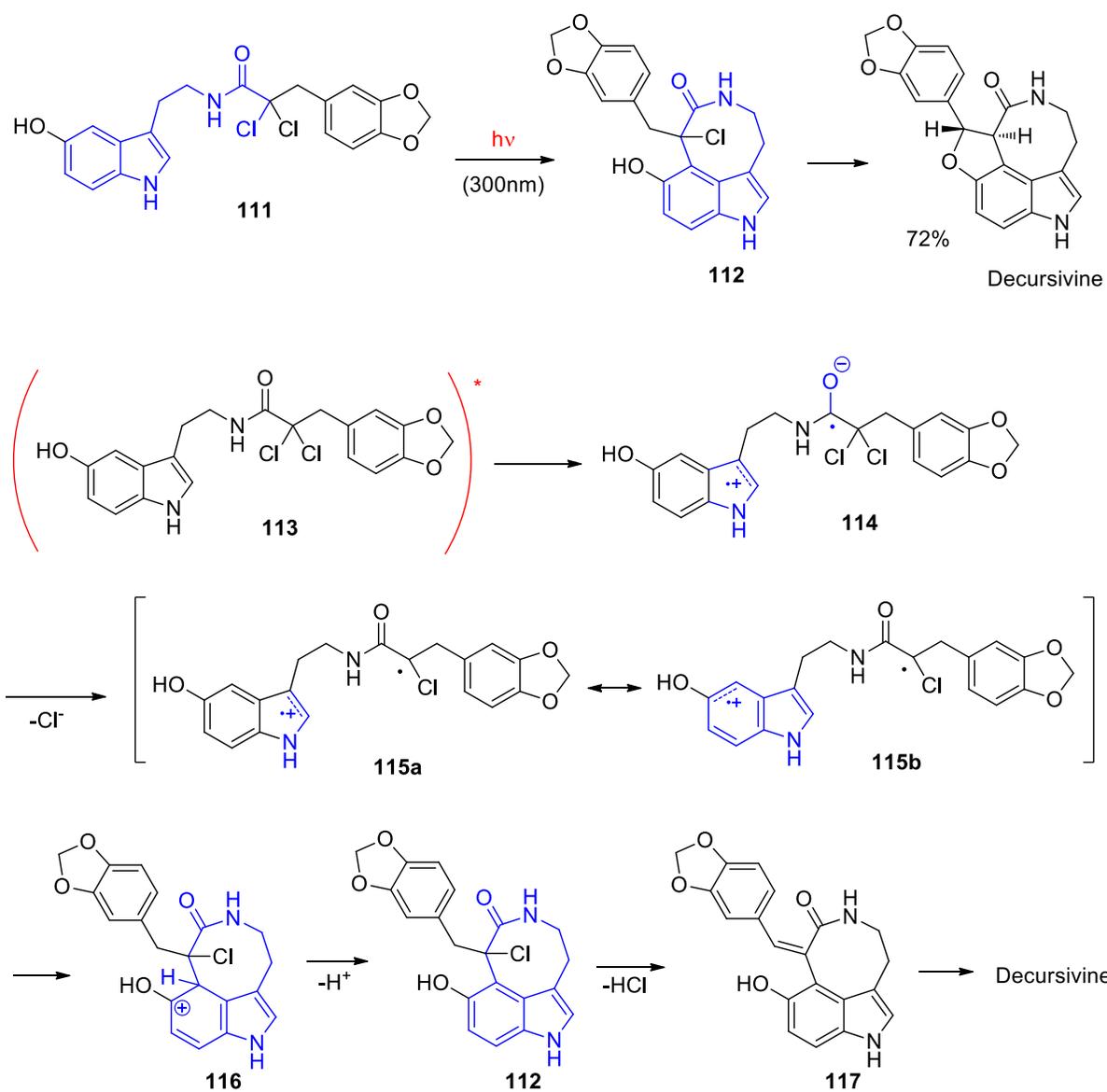
Numerous applications of this reaction to the synthesis of natural products and heterocyclic compounds have been reported.⁹² The o-hydroxymethyl benzaldehyde derivative **108** undergoes intramolecular hydrogen abstraction at the ortho side chain yielding the dienol intermediate **109** (Scheme 20).⁹³ This step is favored by the presence of the o-methoxy group enabling the formation of a hydrogen bond. The dienol is trapped by an intramolecular Diels-Alder reaction leading to the final product **110** which is a key intermediate in the synthesis of pleurotin. This compound was isolated from the mushroom *Pleurotis grieseus* and possesses activity against Ehrlich ascites carcinoma, L-1210 lymphoid leukemia and mammary tumors.



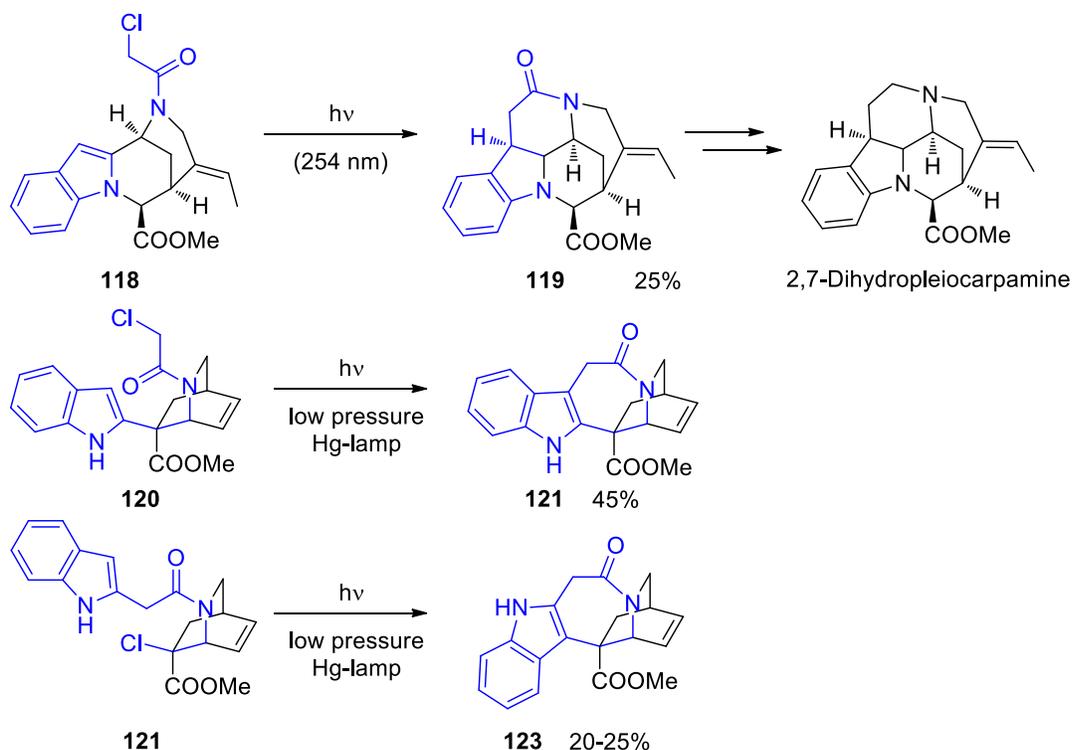
Scheme 20. Photoenolization of o-hydroxymethyl benzaldehyde derivative **108** via photochemical HAT. Synthesis of a core structure of pleurotin.

The Witkop reaction permits the synthesis of a variety of heterocyclic compounds possessing a lactam moiety.^{94,95} It is mainly carried out with indole derivatives such as **111** (Scheme 21).⁹⁶ In a photochemical reaction of this compound the product **112** is generated. Further intermolecular reactions lead to the natural product decursivine which possesses antimalarial activity. After electronic excitation (**113**), an electron transfer from the indole moiety to the α,α -dichloroamide function occurs leading to the intramolecular radical ion pair **114**. After release of a chloride ion, the diradical cation **115a,b** is formed. Cyclization occurs via radical combination and the intermediate **116** is generated which is a typical Wheland intermediate of the electrophilic aromatic substitution. Consequently deprotonation yields the final product **112** of the Witkop reaction. In the present case, elimination of HCl (**117**) and intramolecular Michael addition leads to decursivine in a very concise synthesis.

The Witkop reaction was also applied to the transformation of more complex compounds such as **118** in Scheme 22.⁹⁷ Only few more steps were necessary to obtain the synthesis target 2,7-dihydropleiocarpamine from the photochemical product **119**. The reliability of the reaction for the synthesis of particular isomers is nicely shown for the transformation of **120** into **121**⁹⁸ and in the corresponding transformation of the regio isomer **122** into **123**.^{98,99} A large variety of catharanthine derivatives has thus become available by the same photochemical key step.

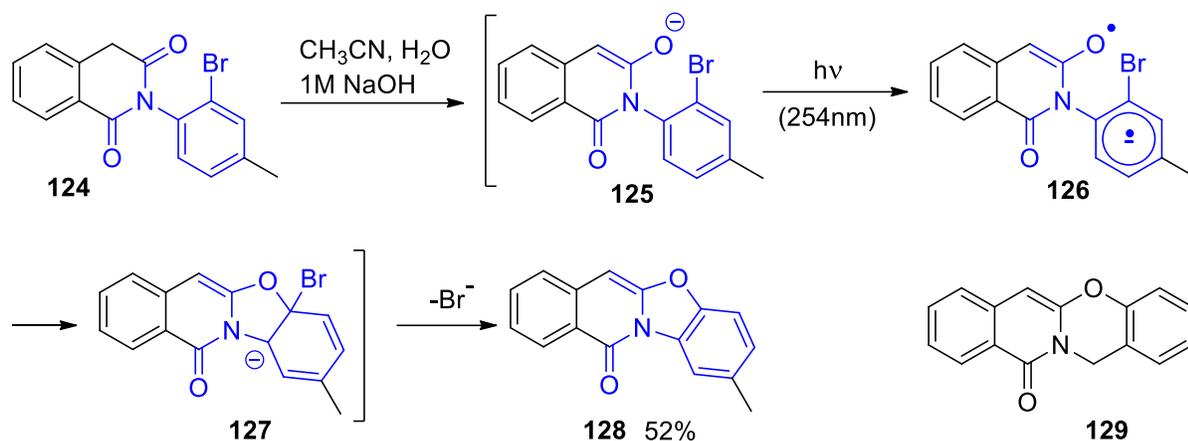


Scheme 21. Mechanism and application to the concise synthesis of decursivine of the Witkop reaction.



Scheme 22. Application of the Witkop reaction to the synthesis of 2,7-dihydropleiocarpamine and catharanthine derivatives.

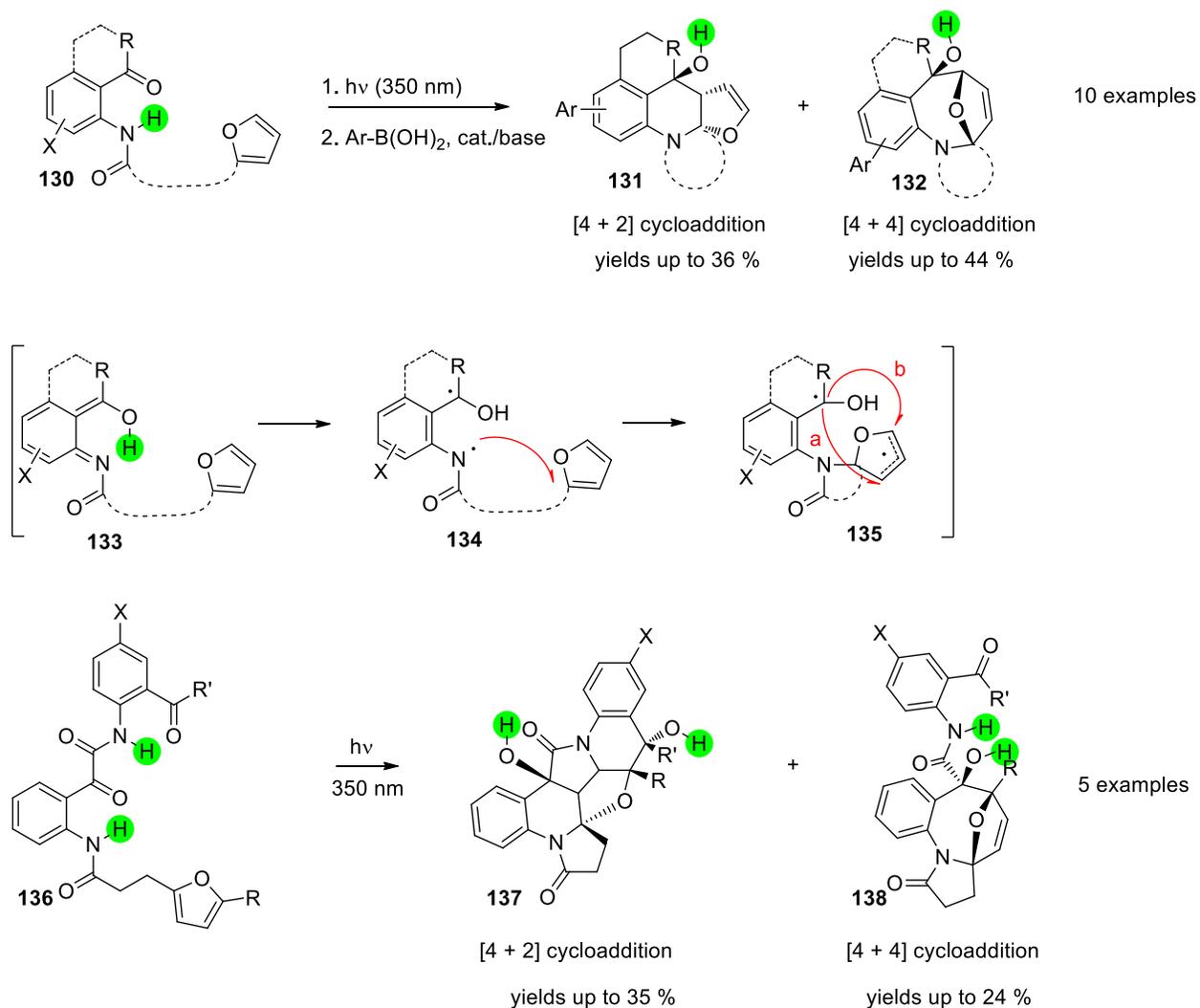
A similar reaction mechanism is involved in the nucleophilic aromatic substitution under photochemical conditions (photochemical $S_{RN}1$ reaction).¹⁰⁰ Such an intramolecular reaction is observed in a basic reaction medium with the imide **124** carrying an arylbromide substituent (Scheme 23).¹⁰¹ The following mechanism has been suggested. After photochemical excitation, intramolecular electron transfer occurs from the enolate moiety in **125** to the aryl bromide substituent (**126**). Radical combination leads to the anion intermediate **127**. The final product **128** is obtained by release of bromide. A corresponding isoquinoline derivative **129** was also obtained. Due to the reduced reactivity of the corresponding substrate, a more basic reaction medium (3M NaOH) was necessary. A large variety of complex heterocyclic compounds have been synthesized with this reaction.¹⁰²



Scheme 23. Intramolecular photochemical $\text{S}_{\text{RN}}1$ reaction.

Photochemically induced hydrogen atom transfer also occurs from heteroatoms such as amide nitrogen to an electronically excited carbonyl function. A large variety of anthranilic acid derivatives such as **130** undergo such an intramolecular hydrogen atom transfer (Scheme 24).¹⁰³ Iminenol intermediates **133** are generated. It has been shown that such structures correspond to an excited singlet state S_1 . A corresponding triplet ground state T_0 **134** may undergo further chemical transformation.¹⁰⁴ The particular reactive nitrogen centered radical will add to the furan moiety leading to the spirocyclic intermediate **135**. Radical combination can occur in two different positions leading either to formal [2+4] adducts (compare **131**) via pathway a or to formal [4+4] adducts (compare **132**) via pathway b. Such reactions are particularly interesting since they generate a high degree of molecular diversity and complexity which is very much appreciated in the search of new biologically active compounds. In the present case, this diversity is further increased by the combination with the Suzuki reaction (**131** and **132**). Especially, the molecular complexity can further be increased when the reaction is carried out with compounds possessing two formal anthranilic acid moieties such as in **136**.¹⁰⁵ In the case of an initial [4+2] cycloaddition, a second one takes place and compound **137** is isolated. A corresponding reaction

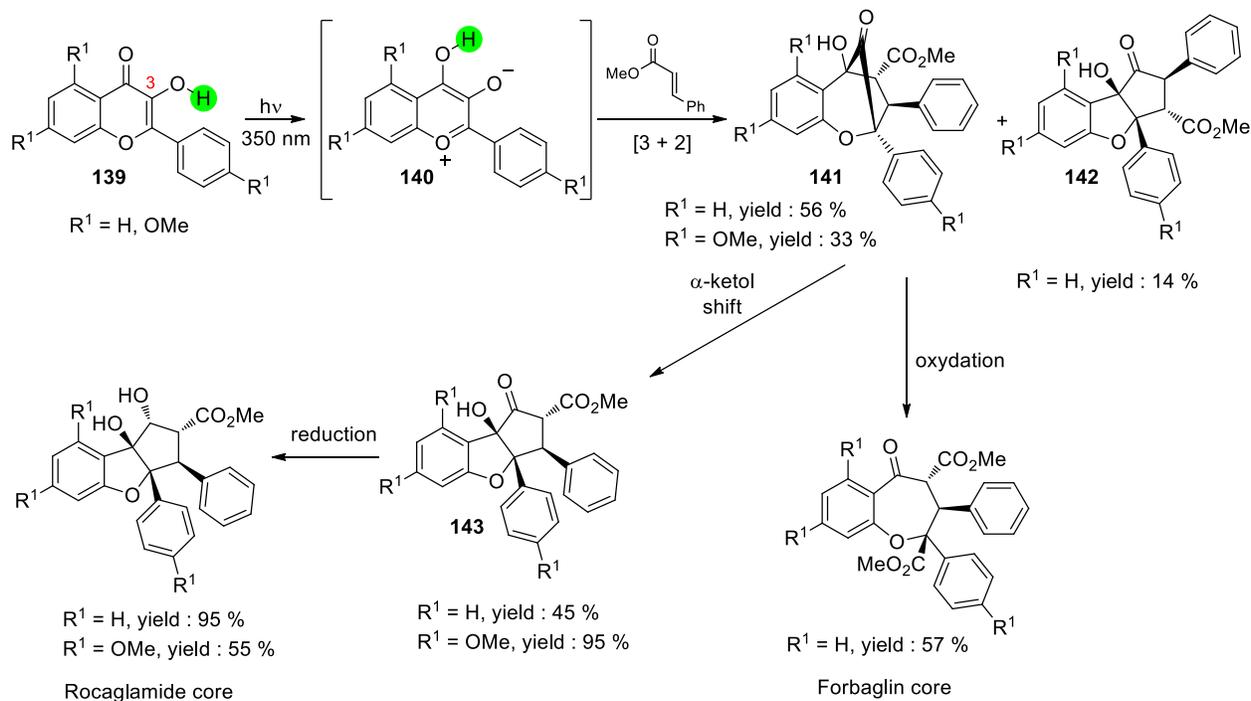
of the [4+4] adduct **138** is not possible. Such photochemical hydrogen atom or proton transfers between heteroatoms such as nitrogen or oxygen, are also discussed in the context of excited state intramolecular proton transfer (ESIPT).¹⁰⁶



Scheme 24. Formation of complex polyheterocyclic compounds by photochemical transformation of anthranilic acid derivatives involving intramolecular hydrogen atom transfer.

An ESIPT is also involved in the photochemical transformations of 3-hydroxyl flavone compounds¹⁰⁷ such as **139** (Scheme 25). Upon irradiation in the presence of cinnamic esters, compounds **141** and **142** are obtained.¹⁰⁸ At the excited state, an intramolecular proton transfer

takes place leading to the intermediate dipolar pyrylium structure **140** which undergo cycloaddition. Further transformations lead to the rocaglamide and forbaglin cores. Such compounds possess potent anticancer and antileukemic activity. In such reactions often, a α -ketol shift is observed. In the present case, this reaction leads to the formation of compound **143** which was transformed into a rocaglamide core.

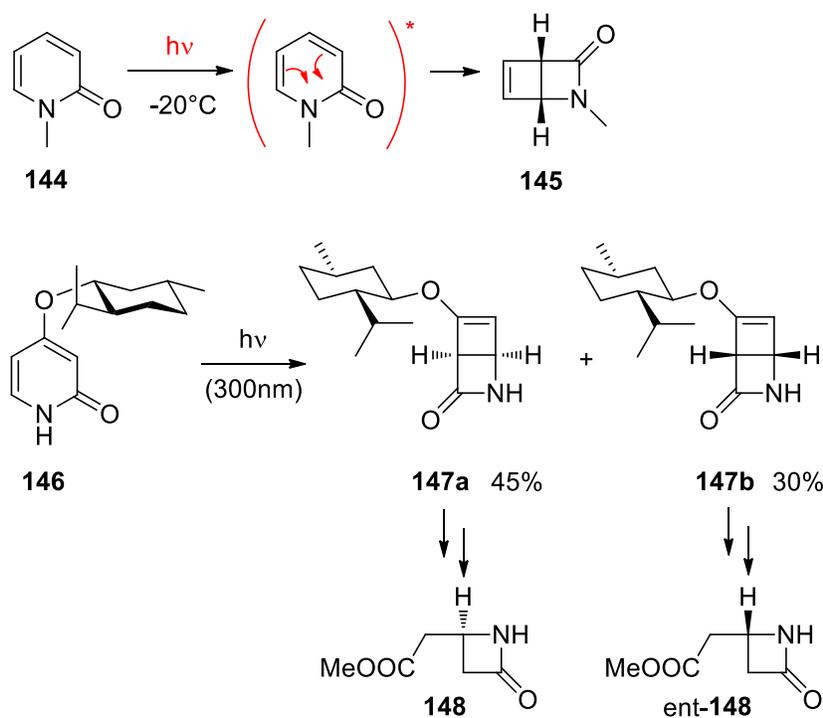


Scheme 25. ESIP in photochemical transformations of 3-hydroxyl flavone compounds.

Photochemical Electrocyclic Reactions

Numerous heterocyclic compounds undergo photochemically induced electrocyclic reactions leading to constrained bicyclic moieties which are hardly accessible by conventional methods of chemical synthesis.^{109,110} Pyridones such as **144** (Scheme 26) undergo photochemical $[\pi 2_s + \sigma 2_s]$ electrocyclization.¹¹¹ According to the Woodward-Hoffmann rules¹¹², this disrotatory cyclization is symmetry allowed at the excited state (Figure 4). For reasons of molecular constrain, a corresponding conrotatory process (at the ground state) in the pyridone system is not possible.

The photochemical reaction is therefore a privileged method for the preparation of bicyclic compounds such as **145** possessing a cyclobutene and a β -lactam moiety. The reaction was widely applied and especially substituted cyclization products where stable and proved to be interesting synthesis intermediates.¹¹³ An asymmetric version of the reaction has also been carried out (Scheme 26).¹¹⁴ Thus the menthyloxy derivative **146** was transformed into **147a** and **147b**. Both diastereoisomers were separated by fractional crystallization. They were transformed into the corresponding enantiomeric monocyclic β -lactam compounds **148** and ent-**148**.



Scheme 26. Photochemical electrocyclicization of pyridone derivatives.

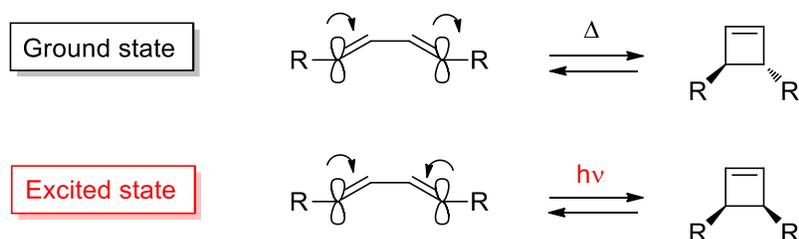
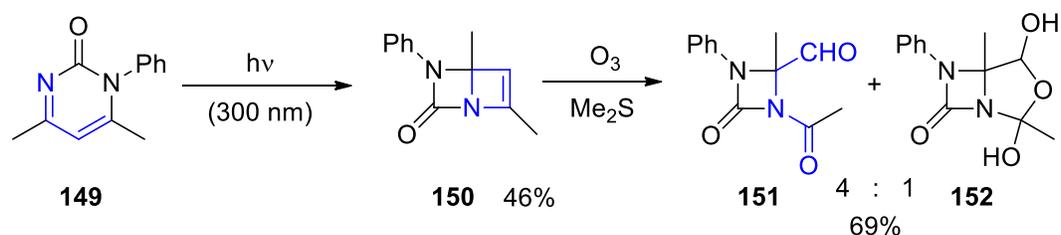


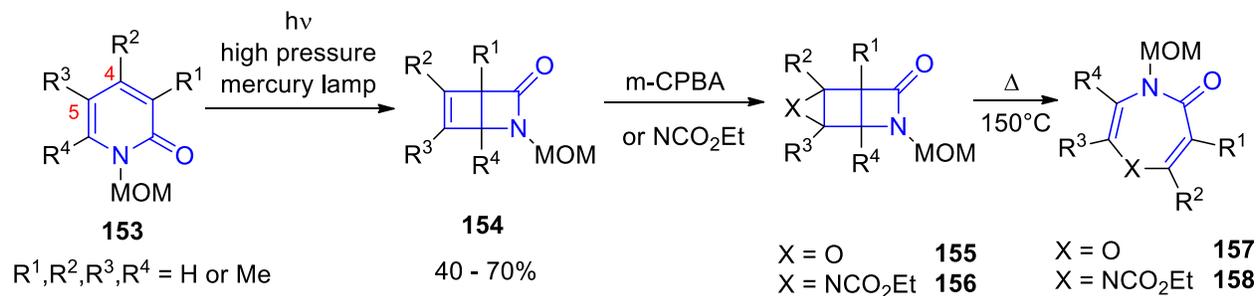
Figure 4. Thermal conrotatory and photochemical disrotatory electrocyclicization processes.

The electrocyclic reaction was also successfully performed with 4π systems containing an imine function such as in the pyrimidone derivative **149** (Scheme 27).¹¹⁵ The bicyclic compound **150** thus obtained containing a 4 membered cyclic urea function. An enamine function is incorporated in the second 4 membered ring moiety. Such compounds are interesting synthesis intermediates. For example, ozonolysis yields compound **151** and **152**. **152** is formed from **151** by addition of water.



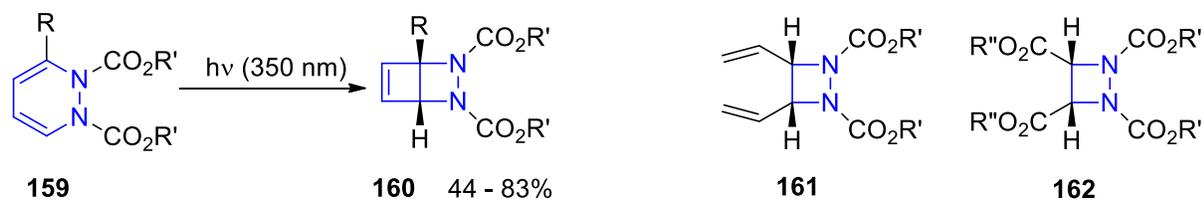
Scheme 27. Photochemical electrocyclic cyclization with a pyrimidone derivative.

The interest of this reaction for further application to organic synthesis of heterocyclic compounds has nicely been shown with the reaction of **153** (Scheme 28).¹¹⁶ A variety of bicyclic photoproducts **154** were obtained in good yields. Epoxidation or reaction with ethoxycarbonylnitrene (generated from N-ethoxycarbonyl-p-nitrobenzyltriethylammonium bromide) of the cyclobutene moiety yielded the tricyclic compounds **155** and **156** respectively. These compounds undergo thermal rearrangement leading to 1,4-Oxazepines **157** and 1,4-Diazepines **158**. Such compounds are hardly available by conventional methods of organic chemistry. The overall synthesis consists in an insertion of either an oxygen or a nitrogen atom in the C-C bond between positions 4 and 5 of the initial pyridone substrate **153**.



Scheme 28. Synthesis of 1,4-Oxazepines **157** and 1,4-Diazepines **158** starting from pyridines.

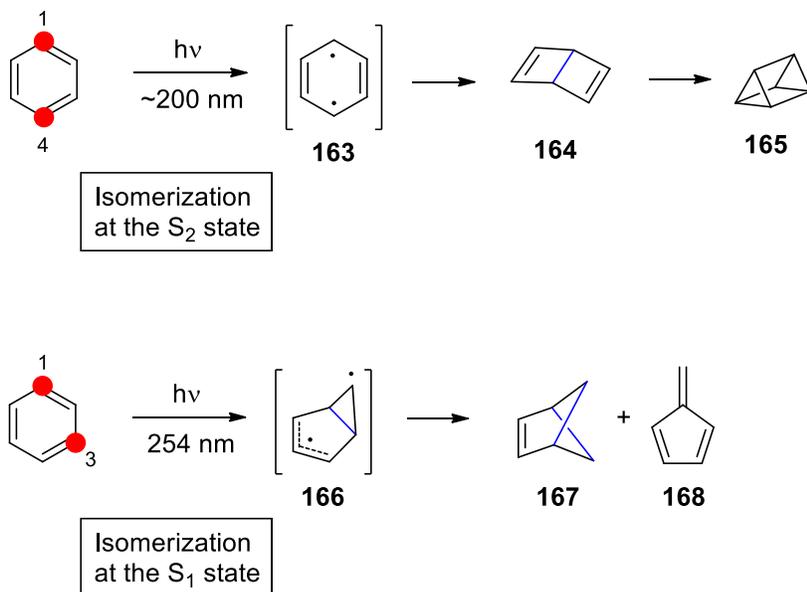
The reaction has also been carried out with dihydropyridazine such as **159** (Scheme 29).¹¹⁷ The resulting 1,2-diazetidines **160** has been obtained in good yields. Gram scale transformation have been successfully performed and various transformations of the photoproducts have been carried out. Thus ring opening metathesis with ethylene yielded the divinyl diazetidine **161** and RuO₂ catalyzed oxidation was used to synthesize tetracarboxylate derivatives **162**.



Scheme 29. Photocyclization of 1,2-dihydropyridazines.

In the previously discussed transformations of six membered heterocycles, the reaction centers are located in para positions. Similar reactions are also observed when the reaction centers are located in meta positions of the corresponding substrates. Topologically, both reactions are related to rearrangements of benzene (Scheme 30).^{118,119} At the S₂ state (**163**), a C-C σ-bond is formed between positions 1 and 4 yielding Dewar benzene **164**. Under the reaction conditions, this compound undergoes intramolecular [2+2] photocycloaddition yielding prismane **165**. In contrast, at the S₁ state, a C-C σ-bond is formed between positions 1 and 3 and a bicyclic

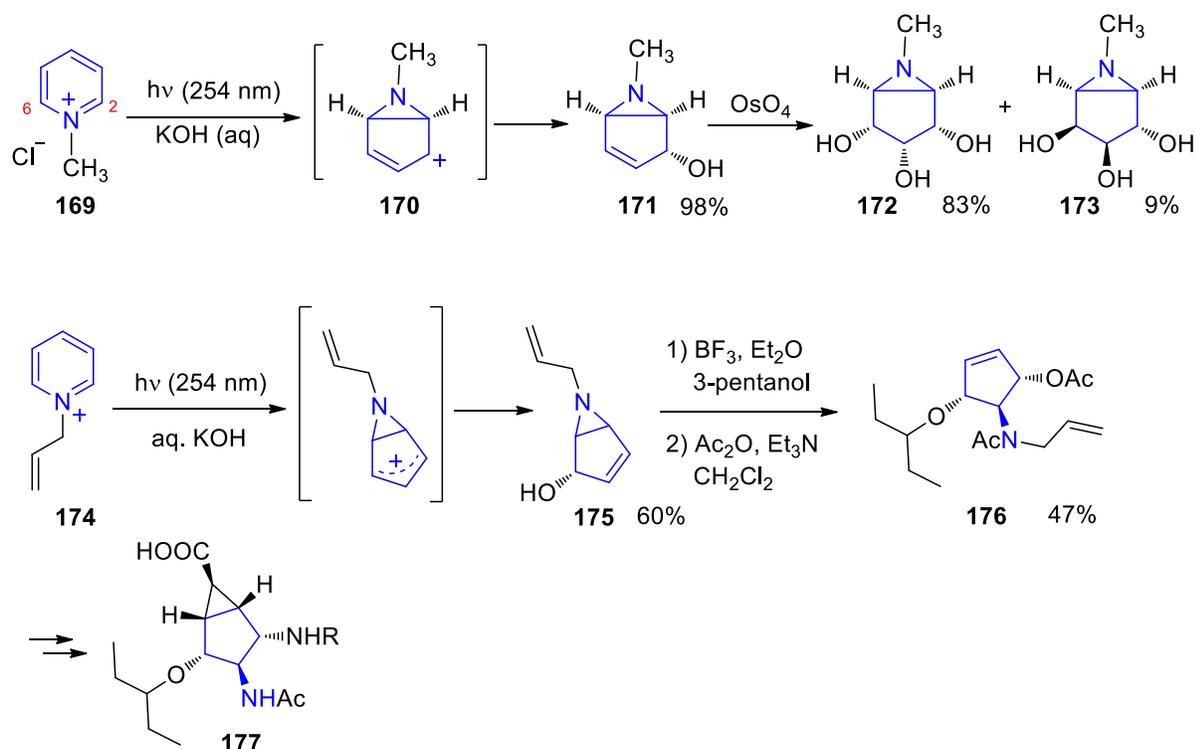
intermediate **166** can be formed. Further C-C bond formation leads to benzvalene **167**. The byproduct fulvene **168** is generated from **166** by fragmentation of a C-C bond of the cyclopropane moiety and hydrogen shift. The formation of bicyclo[3.1.0] intermediates like **166** are frequently discussed in photochemical reactions of pyridinium derivatives.¹²⁰ This reaction was frequently applied to the synthesis of biologically active compounds.¹²¹



Scheme 30. Photochemical isomerizations of benzene.

Upon irradiation, the pyridinium salt **169** undergoes photoisomerization by C-C bond formation in positions 6 and 2 (Scheme 31).^{122,123} In the basic reaction medium, a hydroxyl function is added to the resulting allyl carbenium ion **170**. This reaction was carried out in almost quantitative yield. Cis-hydroxylation of the photochemical product **171** yielded mainly the meso isomer **172** in good yield along with minor amounts of the racemic compound **173**. Such polyhydroxylated cyclic amine compounds are glycomimetics and consequently their glycosidase inhibitor activity is systematically investigated. The same photochemical reaction has been carried out with a corresponding N-allyl derivative **174**.¹²⁴ Treatment under acidic conditions and

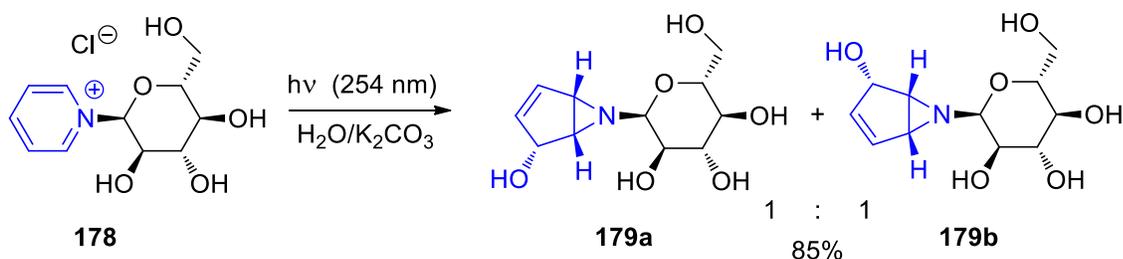
in the presence of 3-pentanol of the photochemical product led to the cyclopentenylamine derivative which is acetylated (**176**). Further transformations yielded compound **177**. This scaffold was studied as influenza neuraminidase inhibitor. Considering an industrial application, the photochemical transformation has also been carried out using a continuous flow photoreactor on multi gram scale with a productivity of $3.7 \text{ g L}^{-1} \text{ h}^{-1}$.¹²⁵ This technique is now widely applied to organic photochemistry in order of optimize these reactions^{76,126} also with a particular focus on heterocyclic chemistry.¹²⁷



Scheme 31. Photochemical electrocyclicization of pyridinium salts.

As in many cases of organic photochemical reactions, no particular protecting groups are necessary. This is nicely shown for the transformation of the glucosyl pyridinium salt **178** (Scheme 32).¹²⁸ The two diastereoisomers **179a,b** of the azabicyclo[3.1.0]hexenol derivative has been obtained in high yield from the photochemical electrocyclicization. The hydroxyl groups of the

glucosyl moiety were not protected. Peracetylation after the photochemical reaction was used to separate the diastereoisomers by crystallization.



Scheme 32. Photochemical electrocyclization of a glucosyl pyridinium salt.

Due to its efficiency and large scope, the photochemical electrocyclization of pyridinium salts is an ideal key step in the synthesis of many biological active compounds (in particular glycosidase inhibitors) and natural products, in particular cyclopentylamine derivatives of nitrogen containing heterocycles.¹²⁹ Some examples are shown in Figure 5: mannostatin A¹³⁰, trehazolin¹³¹, cephalotaxine¹³² or lactacystin.¹³³ Often complex carbon skeletons such as spirocyclic compounds are generated in the photochemical key step of these syntheses.

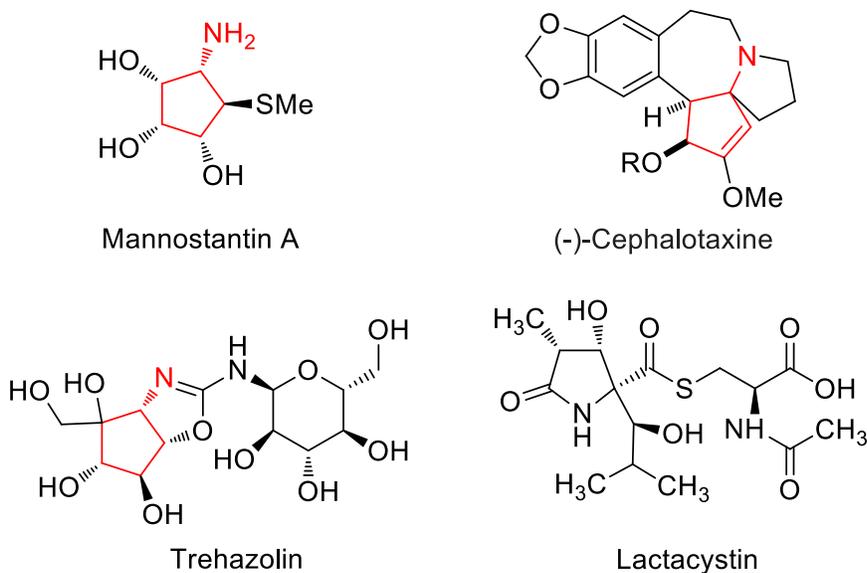
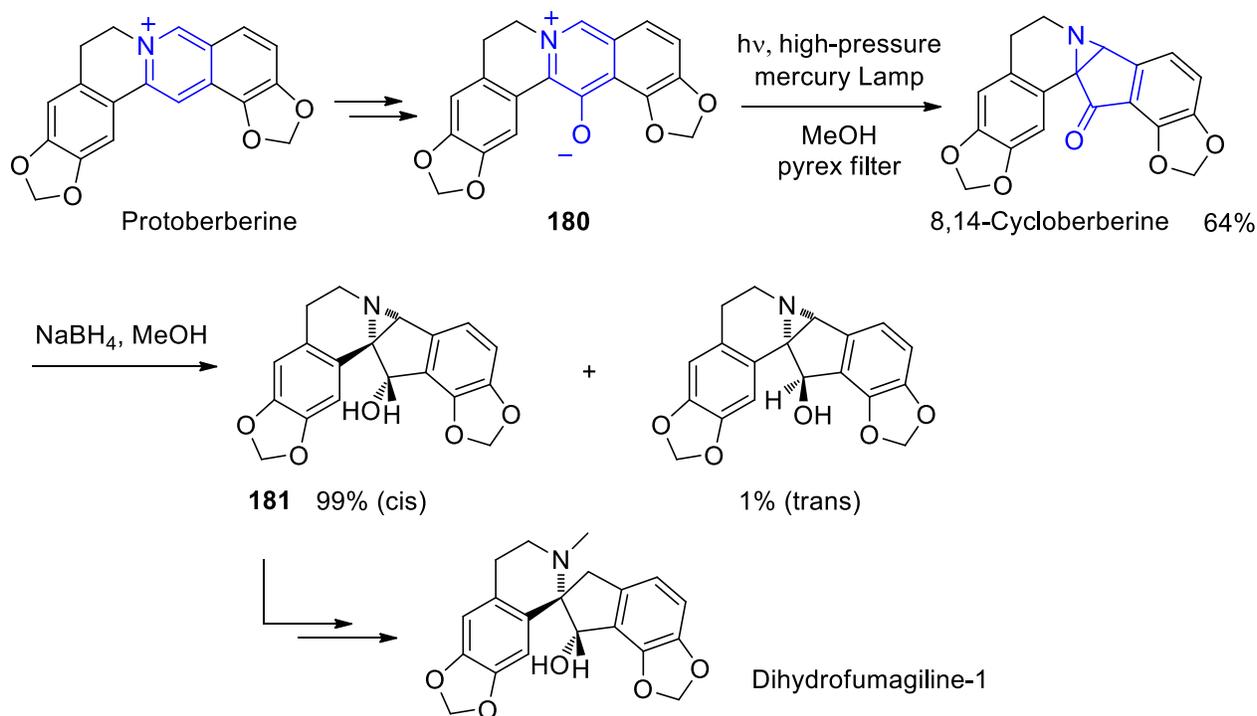


Figure 5. Natural products which are accessible by photochemical electrocyclization of pyridinium salts.

Photochemical electrocyclization of pyridine derivatives was also applied to interconversions of compounds belonging to a natural product family. Peroxidation of protoberberine yielded the zwitterion compound **180** which is an ideal precursor for a photochemical electrocyclization (Scheme 33).¹³⁴ The photochemical reaction directly led to 8,14-cycloberberine with its cyclopentanone moiety. The photochemical reaction was carried out with a variety of substrates. Opening of the aziridine ring led to spirocyclic compounds which can be further transformed into corresponding alkaloids such as sibiricine. Stereoselective reduction of 8,14-cycloberberine with NaBH_4 yields mainly the cis alcohol **181** which is a precursor of dihydrofumagiline-1.¹³⁵



Scheme 33. Application of the photochemical electrocyclization to the chemistry of berberine alkaloids.

Instead of protonation of the pyridine nitrogen, the photochemical cyclization can also be favored by N-oxidation. Such a reaction was applied to the synthesis of DNA topoisomerase I inhibitors as they are used for cancer therapy. This pharmaceutical activity was observed with camptothecin, a product from traditional Chinese medicine and isolated from *Camptotheca acuminata* (Figure 6).¹³⁶ In order to increase the activity, derivatives such as topotecan or irinotecan had to be synthesized. An important step of many of these syntheses is the selective oxidation in position 10 of camptothecin. Camptothecin is easily oxidized at the pyridine nitrogen leading to the N-oxide **182** (Scheme 34).¹³⁷ This oxidation state should be transferred into the 10 position. When **182** is irradiated in an acidic medium, electrocyclization in positions 2 and 13 takes place leading to intermediate **183**. When compared to the previously discussed reactions of pyridinium salts, it can be stated that in the present case, the activation of the pyridine ring by N-protonation is replaced by an N-oxidation. Addition of a hydroxyl group is now favored in the 10 position yielding the intermediate **184**. Acid catalyzed dehydration and rearomatization in rings A and B lead to the final product **186**. The process has been optimized for the industrial production using a series of flat-bed reactors enabling a continuous flow production.¹³⁸ This technology permits a more economic and ecologically friendly production.¹²⁶ More precisely, a higher concentrated solution of the substrate can be irradiated due to the reduced optical trajectory in flat-bed reactors. Thus the solvent quantity is significantly reduced. Also conversion and yields, especially the space-time-yield (2 kg per day in 330 L in an industrial photoreactor system) are increased. Furthermore, processes conducted in micro-flow reactors are generally more safety.

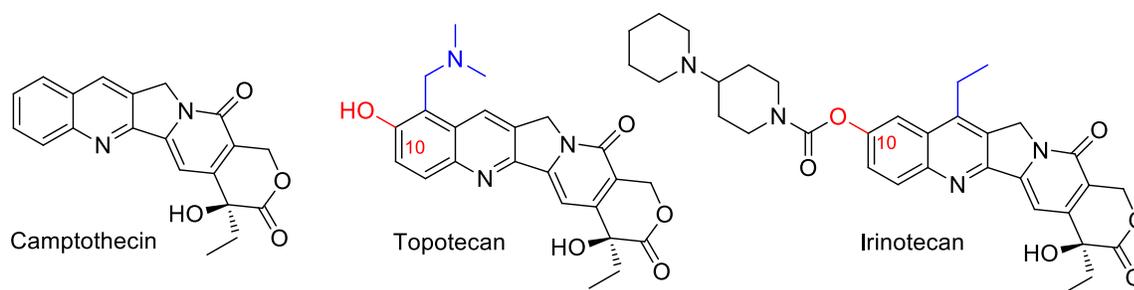
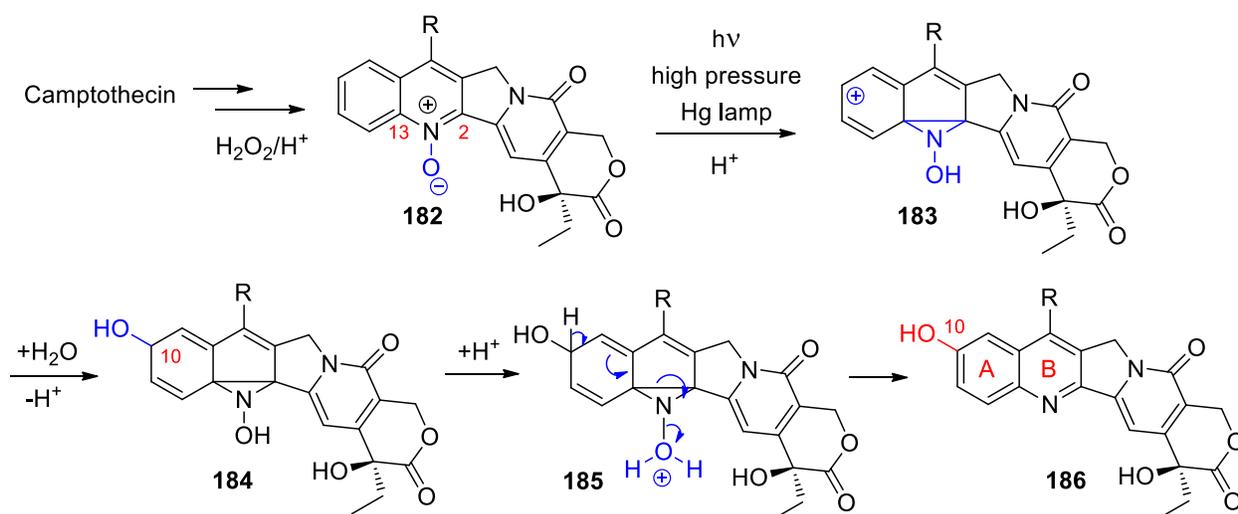
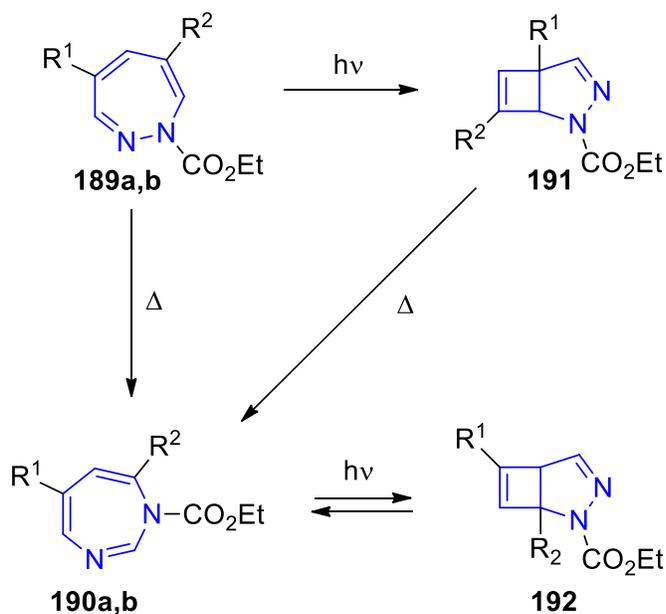
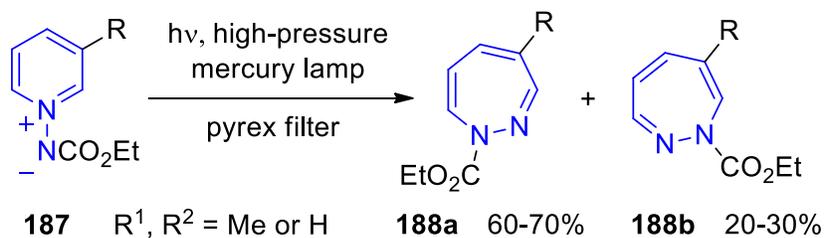


Figure 6. DNA topoisomerase inhibitors. Derivatives of camptothecin.



Scheme 34. Hydroxylation of camptothecin derivatives in position 10.

In a similar way, the pyridine system is activated by a N-carbamylfunction for a photochemical rearrangement. Compounds **187** undergo rearrangement to the corresponding two regioisomeric **188a,b** (Scheme 35).¹³⁹ Further irradiation leads to bicyclic compounds such as **191**. The combination of this system with thermal rearrangements extends the molecular diversity. Thus compounds **190a,b** are obtained which themselves undergo photochemical rearrangements to **192**, a regioisomer of **191**. It should be pointed out that these transformations can be performed under controlled conditions so that the formation of each compound family can be addressed.



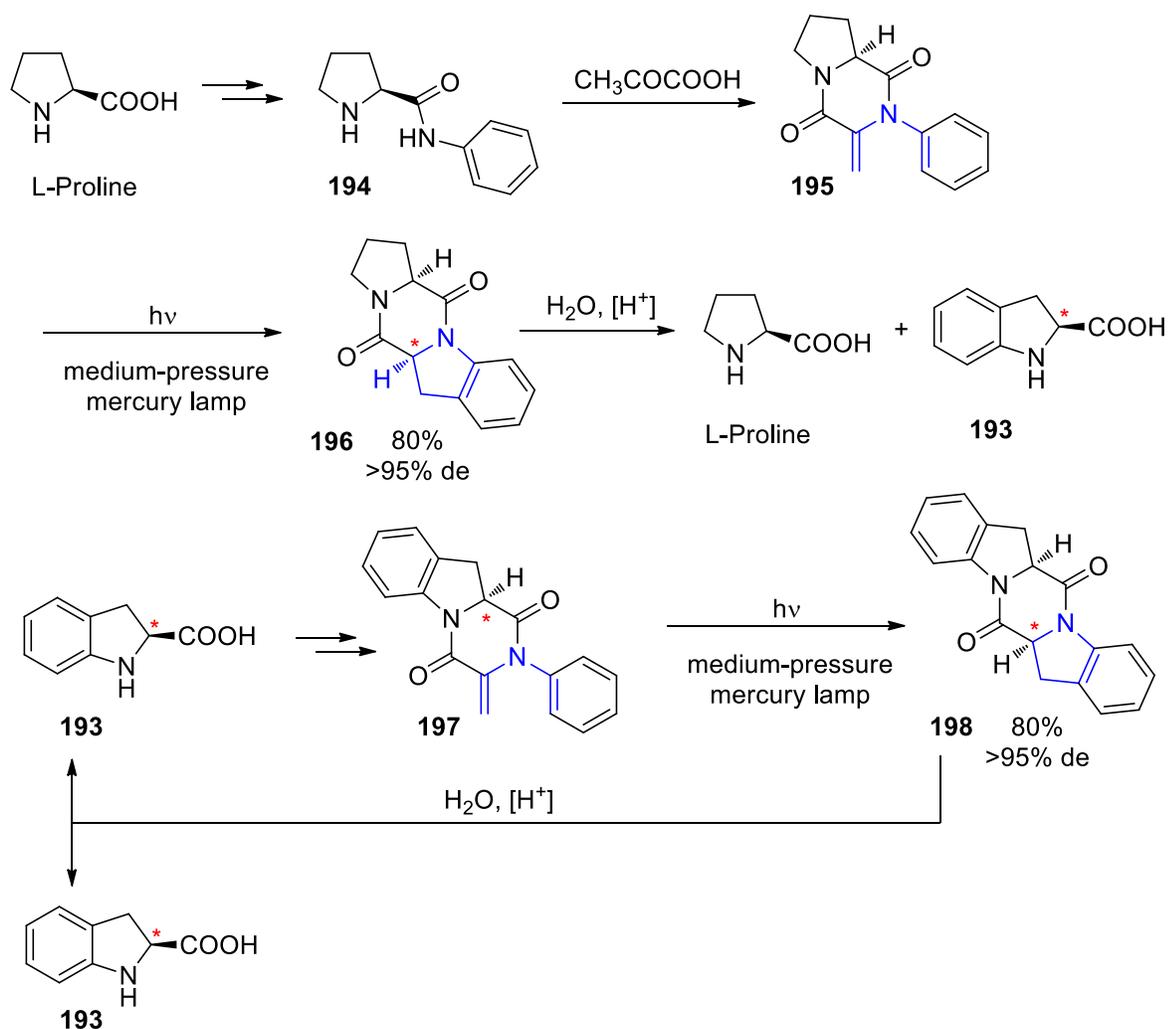
Scheme 35 Photochemical and thermal rearrangements of N-carbamylpyridines.

Photochemical cyclizations

Photochemical cyclizations involving at least two unsaturated moieties play an important role in heterocyclic chemistry.^{109,140,141,142} These reactions have also been applied to the synthesis of photoswitches and photochromic compounds with various heterocyclic moieties.¹⁴³

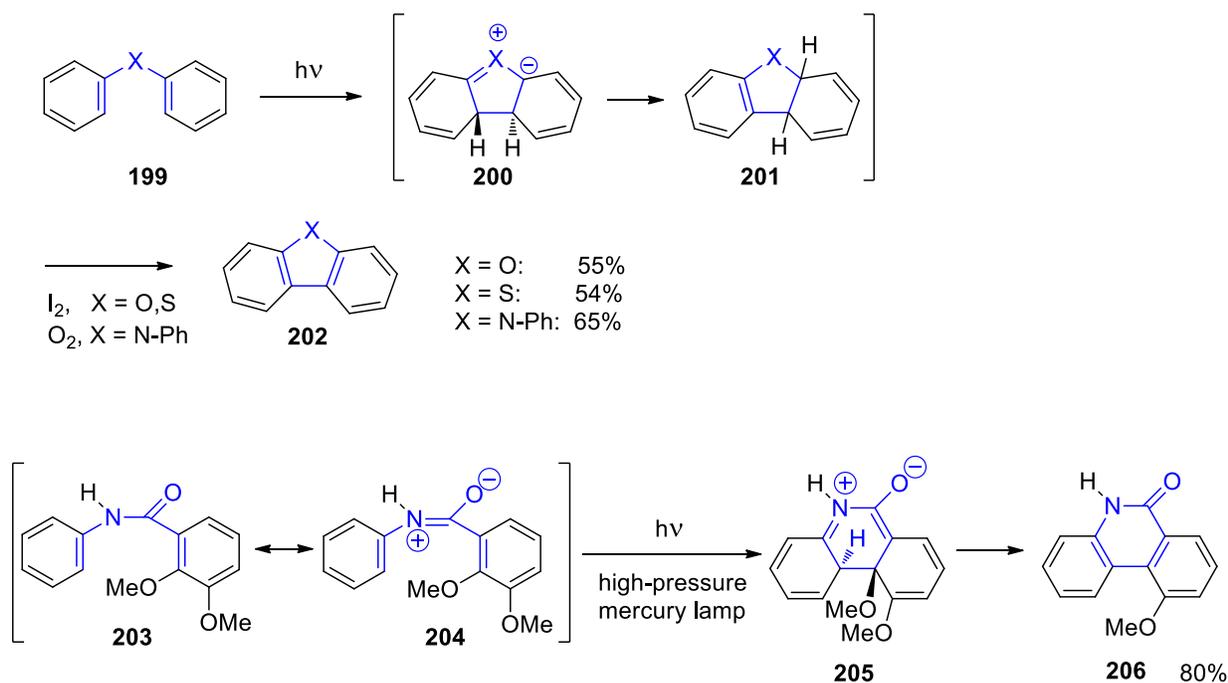
Such a reaction can be applied to the industrial production of (S)-indoline carboxylic acid **193** (Scheme 36).¹⁴⁴ The process starts with the synthesis of L-Proline anilide **194**. In a very convenient step, the precursor **195** for the photochemical cyclization is obtained. This efficient step leads to **196** in a stereospecific way. After hydrolysis of the photochemical product L-proline and the target compound **193** are isolated. They need to be separated. For the further production

of (S)-indoline carboxylic acid **193**, the latter was used as template. Thus the corresponding precursor **197** is synthesized in the same way than **195**. The photocyclization of **197** is also highly efficient and the photochemical product is obtained in a stereospecific way. After hydrolysis two equivalents of (S)-indoline carboxylic acid **193** are obtained and no separation is necessary. A part of the compound is recycled in the production process. In terms of chiral induction, the present process is a case of chiral amplification as it is frequently discussed in catalytic reactions.¹⁴⁵ Concerning chiral induction, many of such photochemical cyclizations have been carried out using asymmetric catalysis⁸⁷ or they have been carried out in a chiral crystal matrix.¹⁴⁶



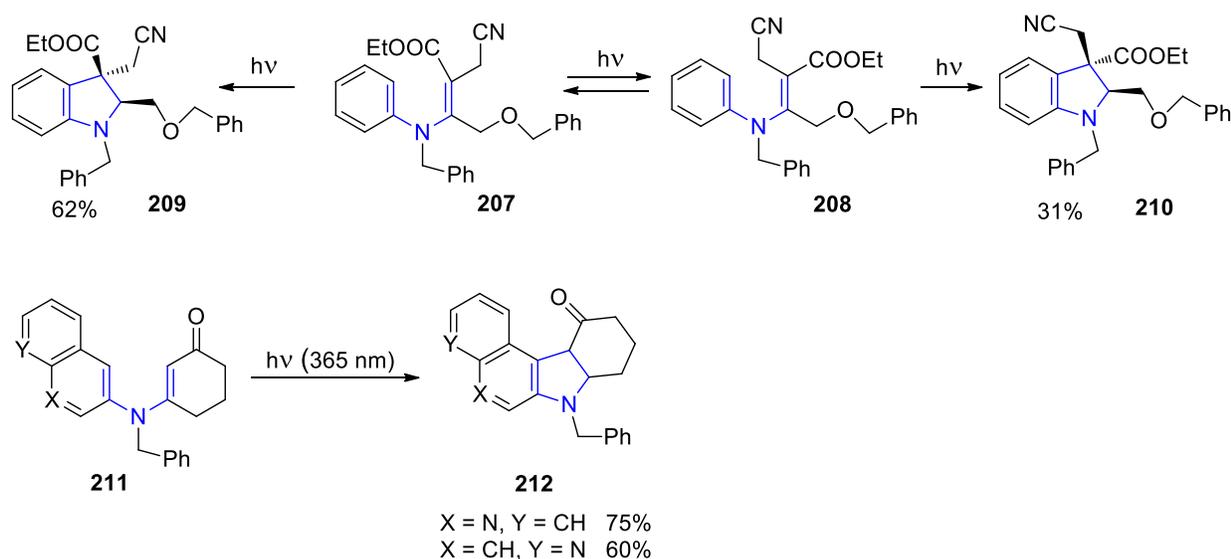
Scheme 36. Industrial process for the production of (S)-Indoline carboxylic acid **193**.

Photochemical cyclization was used for the synthesis of carbazols¹⁴⁷, dibenzofurans¹⁴⁸ and dibenzothiophenes¹⁴⁸ **199** (Scheme 37). In these reactions involving 6 electrons in the π -system, a dipolar intermediate such as **200** is generated. Such an intermediate has been trapped with 1,3-dipolar cycloaddition.¹⁴⁹ Further intermediates such as **201** are formed by a tautomerization step. The final product in which aromaticity is reestablished is generated under mild oxidation conditions. The heteroatom between the two aromatic moieties can be replaced by an amide function such as in **203**. Such functions possess two main mesomeric structures. In **204**, a π -system with 6 electrons undergoes photocyclization.¹⁵⁰ According to the Woodward-Hoffmann rules, the cyclization occurs in a conrotatory way.¹¹² In the present case, this leads to the intermediate **205**. The final product **206** is obtained by elimination of methanol.



Scheme 37. Photocyclizations leading to carbazoles, dibenzofurans, dibenzothiophene and dibenzopyridinones.

Compounds carrying α,β -unsaturated carboxyl or carbonyl groups and an aromatic substituent such as in **207** are also suitable substrates for photochemical cyclizations. Compounds **207** and **208** are in photostationary equilibrium (Scheme 38).¹⁵¹ Both isomers undergo photocyclization yielding **209** and **210** respectively. Quinoline derivatives **211** carrying a α,β -unsaturated ketone moiety have been transferred under similar conditions¹⁵². The corresponding photochemical products **212** have been obtained in good yields. In this case, the irradiation was carried out with "black light" ($\lambda = 365$ nm). Irradiation with lower wavelength light led to fragmentation of the substrates.



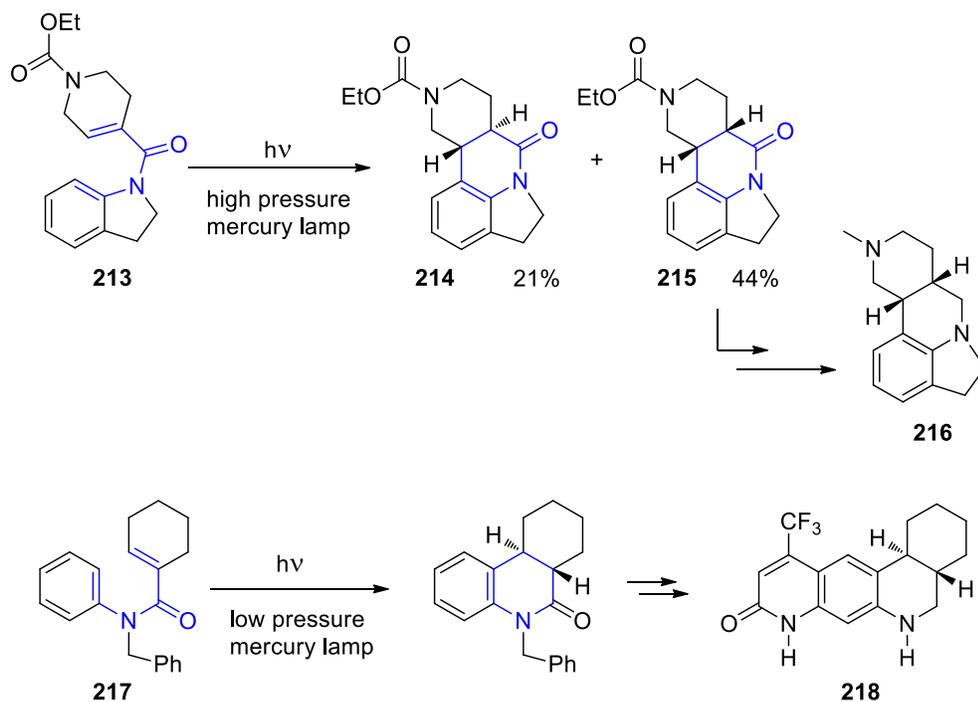
Scheme 38. Irradiation of compounds **207** and **208** (medium pressure mercury vapor lamp) yields indolines. Quinoline derivatives **212** have been obtained under similar conditions.

As it has already been pointed out, nitrogen containing heterocycles play an important role as biologically active compounds. Consequently, the herein discussed reactions have been applied to the synthesis of a large number of such compounds. Two examples are shown Scheme 39.

Compound **213** undergoes photocyclization yielding the tetracyclic compounds **214** and **215**.¹⁵³

This transformation is a nice example of photochemical reactions that, starting from a relatively

simple compound, in one step a complex compound is obtained. In the present case, especially the major photoproduct **215** contains already all structural elements of the target molecule **216** which is a 5-HT_{2C/2B} receptor antagonist. Such a pharmaceutical activity may be interesting for the therapy of diseases like eating disorders, migraine, obsessive compulsive disorders, and anxiety. The photocyclization of the cyclohexene carbanilide derivative **217** was used as key step in the synthesis of **218** which is a non-steroidal androgen receptor agonist.¹⁵⁴



Scheme 39. Application of photochemical cyclizations of α,β -unsaturated anilids as key steps in the synthesis of pharmaceutically active compounds.

The previously discussed reactions are a valuable tool for the synthesis of alkaloids. Some examples are depicted in Figure 7. The cyclization of anilides was used for the synthesis of yohimbine¹⁵⁵ and xylopinine¹⁵⁶. In the case of aspidospermidine¹⁵⁷, a α,β -unsaturated carbonyl moiety was cyclized. Lysergic acid¹⁵⁸ and a large variety of similar compounds such as chanoclavine-1¹⁵⁹ have been obtained from photocyclization products of the same furan

carboxamide precursor. The photocyclization with more complex heterocyclic amides has been used to contribute to structure determination of pseudodistonin A and B.¹⁶⁰

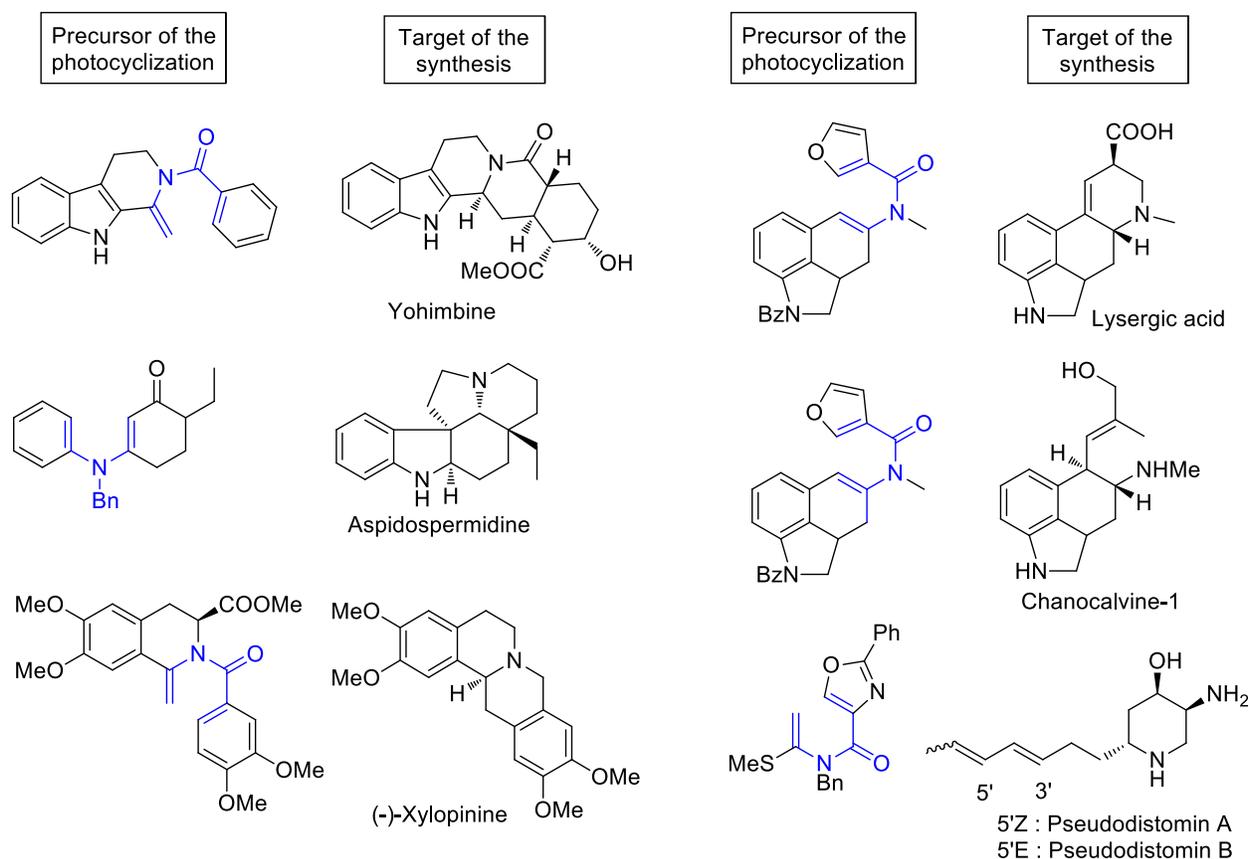
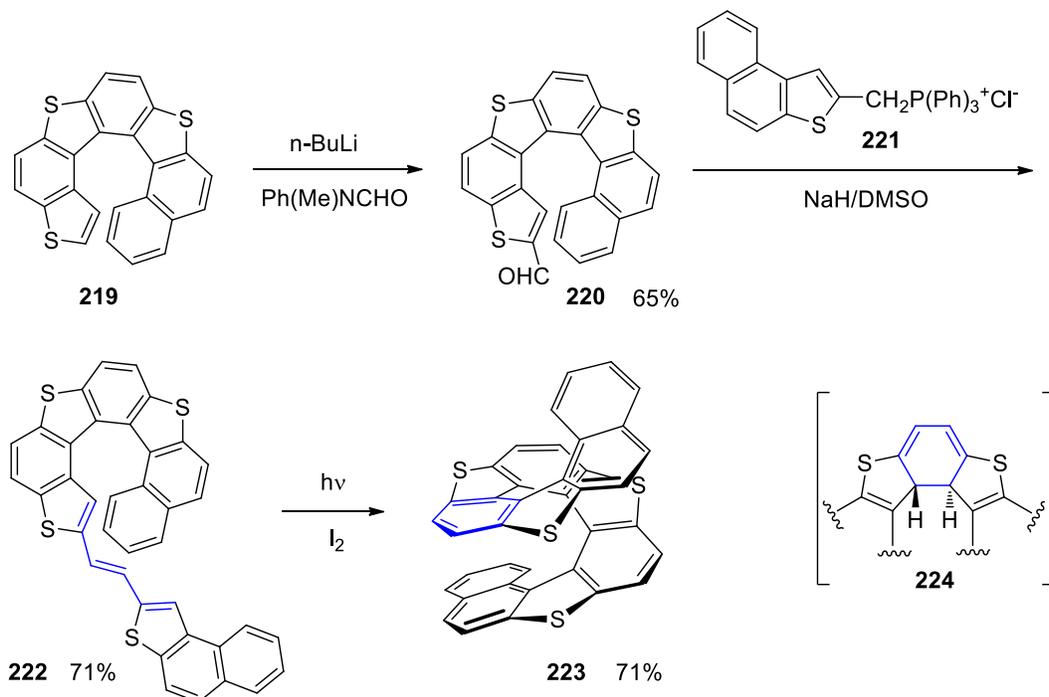


Figure 7. Examples of the application of photocyclization reactions to the synthesis of alkaloids.

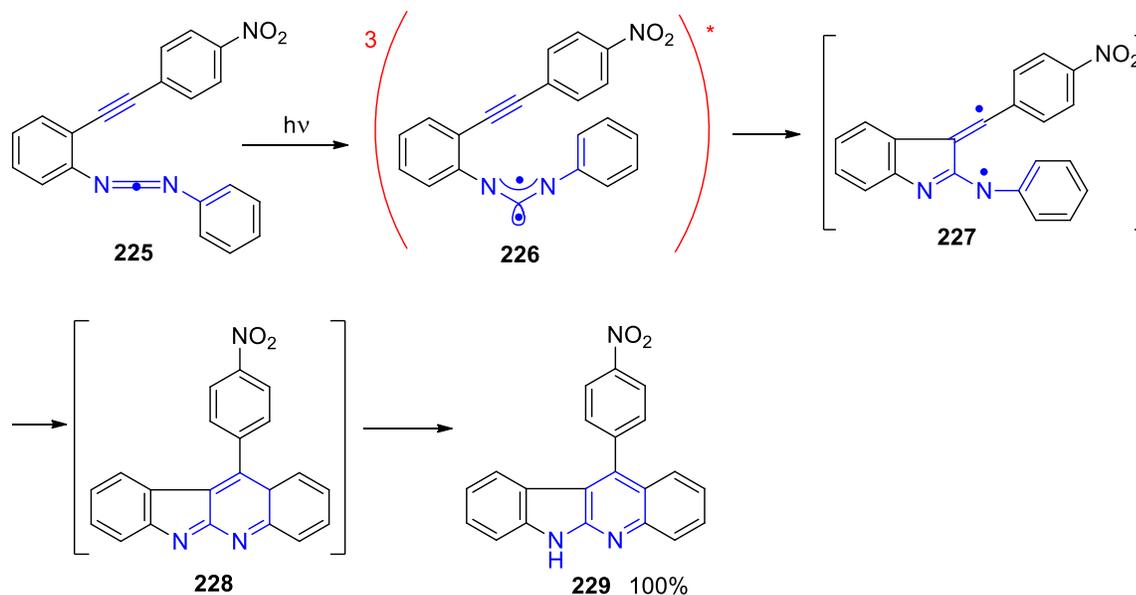
Photocyclization is a very suitable tool for the synthesis of helicenes.¹⁶¹ A subfamily of these compounds contains heterocyclic moieties such as thiophenes. Heterohelicenes such as **219** (Scheme 40) have been obtained in this way.¹⁶² A systematic synthesis strategy has been developed for the preparation of homologues. Thus lithiation followed by carbonylation yielded **220**. Wittig reaction with **221** was used to prepare the substrate **222** for a photocyclization. The latter occurs in a conrotatory sense leading to intermediate **224**. Under mild oxidation conditions,

in the presence of iodine, oxidation (aromatization) takes place and the final product **223** is obtained. A large variety of helicenes have been prepared using this strategy.



Scheme 40. Synthesis of heterohelicenes with thiophene moieties. Irradiations have been carried out with high pressure mercury vapor lamp.

Complex polyheterocyclic systems can also be synthesized by highly efficient cyclization of carbodiimides such as **225** (Scheme 41).¹⁶³ After photochemical excitation, the triplet species **226** is generated. Electronic excitation is achieved either by light absorption or by triplet sensitization of **225**. Radical addition to the alkyne function yields the diradical indol intermediate **227**. Radical combination occurs via addition to the phenyl substituent leading to the formation of intermediate **228**. The final product **229** is an indoloquinoline system which is formed by tautomerization in the last step.



Scheme 41. Photochemical cyclization of carbodiimides leading to indoloquinolines. The irradiations were carried out with various wavelengths between 254 and 419 nm.

Conclusion

Photochemical rearrangements provide a convenient access to a large variety of organic compounds. Often photochemical products possess an unusual structure and can therefore be conceived as interesting synthesis intermediates. Although reported in the literature for a long time, the application of such photochemical rearrangements to the synthesis of heterocyclic compounds was rarely studied in a systematic way in order to determine their scope and limitations for application to organic synthesis.

Heterocyclic compounds play a key role in many domains, for example, in the search of biologically active compounds for medicine or agriculture. Also in material science, such compounds are systematically studied, for example, when they possess electronic semi-conducting properties. It is therefore highly demanded to study photochemical reactions in connection with heterocyclic chemistry.

It must be particularly pointed out that most of the herein discussed reactions don't need any chemical activation. The photon is then the only reagent. It doesn't leave traces. Most of these photoreactions even don't need any photochemical sensitization. For many domains of chemistry, photochemical reactions represent an important tool of sustainability. In combination with other approaches such as catalysis or the use of products from renewable feedstock, numerous additional perspectives for sustainable chemistry can be developed.

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