Enantioselective synthesis of heterocyclic compounds using photochemical reactions

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Abstract

Different methods for the direct enantioselective photochemical synthesis of heterocycles are presented. Currently, asymmetric catalysis with templates involving hydrogen bonds or metal complexes is intensively investigated. Enzyme catalysis can be simplified under photochemical conditions. For example, in multi enzyme systems, one or more enzyme catalytic steps can be replaced by simple photochemical reactions. Chiral induction in photochemical reactions performed with homo-chiral crystals is highly efficient. Such reactions can also be carried out with crystalline inclusion complexes. Inclusion of a photochemical substrate and an enantiopure compound in zeolites also leads to enantioselective compounds. In all these methods, the conformational mobility of the photochemical substrates is reduced or controlled. Memory of chirality is a particular case in which a chiral information is temporally lost but the rigid conformations stabilize the molecular structure which leads to the formation of enantiopure compounds. Such studies allows a profound understanding on how particular conformations determine the configuration of the final products.

Graphical abstract

1 Introduction

Photochemical reactions play a key role in organic synthesis methodology [1–3]. In this regard, the reactions are particularly interesting because new compounds or compound families become available or more easily available. This significant extension of the chemical structure space or the molecular diversity [4–7] is due to the fact that photochemical excitation considerably modify the reactivity of chemical compounds [8–10]. High molecular diversity and complexity is of high interest in the pharmaceutical chemistry and agrochemistry where new biologically active compounds are searched [11–13]. Many other domains such as material science, for example organic semiconducting materials [14] are also concerned. Heterocyclic compounds play an important role in all these domains [1–3, 15–18]. Many heterocycles are aromatic and possess a "flat" structure and they are easily synthesized by many coupling reactions. A particular interest is

in access to tridimensional ring structures. [18–20] In this regard, stereoselectivity becomes an important topic. In the past, photochemical reactions were often considered as inherently unselective because the energy uptake in such transformations is high and the dispersion of the excitation energy can only occur without any control. In fact, the dispersion of this energy can be controlled [21] and selective, also stereoselective or stereospecific reactions are observed. In the literature numerous of such reactions are reported [22–30]. Often supramolecular structures in the broadest sense are frequently involved [31–35]. Recently in connection with different types of photocatalysis, the application of photochemical reactions to organic synthesis has gained enormous interest [36–39].

It should further be pointed out that organic photochemical reactions play a key role in the context of sustainable chemistry. This was recognized more than 100 years ago when comparing organic photochemical reactions to photosynthesis of green plants [40–42]. It is the beginning of

"Green Chemistry" [43–45]. In fact, many of these reactions fulfill requirements of sustainable chemistry [46, 47].

Various methods of chemical engineering are developed for photochemical reactions. Micro-reactor systems are constructed to optimize these reactions with respect to problems in connection to optical density of the reaction mixtures and also to face safety problems. A continuous production is of general interest in chemical industry [48–53]. In this context, flow reactors are developed. It should also be pointed out that sunlight is an abundantly available light source free of charge. Optimized reactors have been constructed for solar photochemical transformations [54].

In the present article, methods will be presented which lead directly to enantiopure or enantioenriched compounds. Heteroatoms of the newly formed heterocycle may be involved as essential part of the chromophore or the reaction center. A large number of examples are reported in which the heteroatom acts as a linker in a side chain. The review is not comprehensive. Characteristic examples from different domains are discussed.

2 Chiral induction with template structures

The transformation of substrates which are complexed to enantiopure compounds leads to enantiopure or enantioenriched products [34]. This strategy was applied to the intramolecular addition of a tertiary amine to an α,β -unsaturated lactam (Scheme 1) [55]. In this reaction, photochemical electron transfer plays a key role. The lactam **1** is complexed

with a Kemp's acid derivative via hydrogen bonds (**2**). In this complex, the benzophenone derived sensitizer is placed close to the substrate. After excitation of the former, electron transfer occurs from the tertiary amine (pyrrolidine moiety) to the sensitizer leading to the radical ion pair **3**. Transfer of a proton yields the neutral radical intermediates in structure **4**. In a Michael type reaction, the nucleophilic α -aminoalkyl radical adds to the lactam moiety. The resulting neutral intermediate **5** possesses an electrophilic oxoallyl radical and a nucleophilic ketyl radical. Electron transfer (**6**) followed by a proton transfer yields the spirocyclic final product **7**. In these radical addition and hydrogen atom transfer steps, polar effects play an important role [56–58]. In reactions like the ones discussed here, mainly two different mechanisms of the hydrogen atom transfer (HAT) are frequently discussed [59, 60]. In the present case, a two-step process takes place. The electron transfer occurs first and the proton follows [61–64]. In cases, where the photochemical electron transfer is endergonic, the formation of neutral radicals however is exergonic, the HAT occurs in one step. In a more general context, such processes are discussed as proton coupled electron transfer (PCET) processes [65–67]. In the case of the reaction depicted in Scheme 1, hydrogen bonds are also involved which further favors such processes. The aromatic ketone in the Kemp's acid derivative acts not only as photochemical sensitizer but also as diastereo-differentiating shielding group.

Using the very similar template **10**, an intramolecular [2 + 2] photocycloaddition was carried out with the α,β -unsaturated lactam derivative **8** (Scheme 2) [68]. In this

Scheme 1 Enantioselective cyclization involving photochemical electron transfer

Scheme 2 Enantioselective synthesis of a polycyclic pyrrolidine derivative using a [2+2] photocycloaddition

reaction the pyrrolidine derivative **9** was formed with a high enantioselectivity. The irradiation was performed with visible light. Under these conditions, the photocycloaddition can take place almost only in the template structure **11** where the thioxanthone group absorbs visible light (Fig. 1). The triplet energy of the sensitizer is transferred to the lactam which undergoes [2+2] photocycloaddition at its T_1 state. The non-complexed lactam undergoes the same reaction, when irradiated with UV light. As in the previous case, the sensitizer also acts as diastereo-differentiating shielding group. In a similar way, tetrahydrofuran derivatives can be synthesized [69–71].

Using almost the same reaction conditions as the transformation of the quinolinone derivative **8** (compare Scheme 2), the quinoxalinone derivative **12** was transformed into corresponding azetidine **13** was obtained in high yield and high enantioselectivity (Scheme 3) [72]. The reaction was also successfully carried out in an intermolecular way.

Fig. 1 UV/Vis spectra of a similar quinolin-2(1*H*)-one derivative **A** ($c=0.5$ mM) and **10** ($c=0.5$ mM) in trifluoromethyl benzene

Scheme 3 Enantioselective intramolecular synthesis of an azetidine using the aza analogue Paternò-Büchi reaction

Complexation with Lewis acids often induces a bathochromic shift of a chromophore absorption. This property was applied to the enantioselective synthesis of polycyclic valerolactam derivatives such as **17**. The complexation of dihydropyridinone derivative **14** with the chiral borane derivative **15** yields structure **16** (Scheme 4) [73]. The absorption of the chromophore is thus shifted to longer wavelengths (Fig. 2). When a corresponding reaction mixture is irradiated at 366 nm, only the complex **16** is excited and chiral induction by the proline derived borate is efficient.

Chiral induction also occurs in the chiral ligand sphere of a metal. This strategy was applied to the transformation of benzaldehyde derivatives such as **18** into the tricyclic isochromanones **19** (Scheme 5) [74]. The substrate forms complexes **20** with enantiopure Δ -RhS. Complexation occurs via the carbonyl function of the α,β unsaturated carbonyl moiety and a pyrazole nitrogen atom. After photochemical excitation, intramolecular hydrogen atom transfer (HAT) occurs and the diradical intermediate **21** is generated [75]. A corresponding singlet species **22** is formed by an intersystem crossing step. In a rhodium catalyzed step, the cyclopropane complex **23** is formed. Ligand exchange yields the final product and enables complexation with the starting

Scheme 4 Enantioselective acid catalyzed construction of a polycyclic valerolactam derivative via intramolecular [2+2] photocycloaddition

Fig. 2 Bathochromic shift of the absorption maximum of compound **14** by Lewis acid complexation. UV/vis spectra of **14** ($c = 0.5$ mM in CH_2Cl_2) in the absence and in the presence of 20 equivalents of a Lewis acid

compound. The same strategy with a similar rhodium complex was applied to the synthesis of cyclic imines via [2 + 3] photocycloaddition [76]. Complexation of a substrate to copper carrying a chiral bisdihydrooxazolylmethane ligand was used for the asymmetric synthesis of dihydrooxazole [77].

A large variety of TADDOLs ($\alpha, \alpha, \alpha', \alpha'$ -tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol) can be synthesized from tartaric acid. They are capable of complexing numerous substrates via hydrogen bonds [78]. Such complexes are formed either in solution or in the solid state. When complexed with the TADDOL **31**, the flavon derivative **24** undergoes photocycloaddition with the

diphenylbutadiene **25** leading to compounds **26** and **27** (Scheme 6) [79]. After reduction the diastereoisomeric polycyclic compounds **28** and **29** are isolated. The major isomer **28** was obtained in high enantioselectivity. It has been suggested that a chromenylium structure is formed (**30**). This involves excited state intramolecular proton transfer (ESIPT) [80–82]. The alkene **25** reacts in a highly stereoselective [2 + 3] cycloaddition. The reaction occurs at the triplet state and electron transfer may be involved. The enantiomeric purity was further increased by recrystallization. Compound **28** is an intermediate of the synthesis of (+)-foveoglin A.

Scheme 5 Asymmetric photocatalyzed synthesis of isochromanone compounds

Scheme 6 Asymmetric synthesis of (+)-foveoglin A using ESIPT promoted [2 + 3] cycloaddition

The latter belongs to a compound family possessing anti-cancer and antiviral activities.

As already mentioned, proton coupled electron transfer (PCET) can be involved when substrates are complexed with templates via hydrogen bonds [65–67]. This interaction was used to efficiently induce chirality [83, 84]. Thus the photocatalytically induced cyclization of sulfonamides **32** to the corresponding pyrrolidines **33** was carried out with high enantioselectivity (Scheme 7) [85]. The nitrogen centered radical species **34** is generated by electron transfer to the

electronically excited iridium photocatalyst and a proton transfer to the chiral phosphate **P1**. Radical cyclization leads to the intermediate **35**. In this step efficient chiral induction takes place. It occurs in close connection with **P1**.

Pyridines are important heterocycles and play a key role in many domains. The Vollhardt reaction provides an elegant access to these compounds. Two alkynes react with a nitrile derivative in a [2 + 2 + 2] cycloaddition [86]. It has been shown that this reaction can be carried out under mild conditions with inexpensive cobalt catalysts

Scheme 7 Enantioselective radical cyclization involving PCET **Scheme 8** Synthesis of pyridines with the cobalt catalyzed [2 + 2 + 2] cycloaddition. The reaction is performed under mild conditions using visible light irradiation

when the reaction solutions are irradiated with visible light (Scheme 8) [87, 88]. Under these conditions, the formation of the catalytically active species CpCo^{I} from the precursor **36** is accelerated. It has been observed that the formation of the cobaltacyclopentadiene intermediate **37** is also accelerated since the formation of the intermediates **38** and **39** becomes the rate limiting. The overall reaction becomes first order concerning the consumption of the nitrile. A large number of pyridine derivatives has been obtained with this method [89, 90]. Due to the mild reaction conditions, asymmetric catalysis with corresponding cobalt complexes was successfully performed. The chiral cobalt catalyst **40** was used to induce chirality

in the reaction of the diene compound **41** with acetonitrile (Scheme 9) [91]. In this reaction, axial chirality in the pyridine compound **42** is induced. The enantiomers of **42** are also atropisomers. Under similar conditions, the cyanonaphthalene derivative **43** was transformed either with dienes or with two equivalents of monoalkynes yielding tetracyclic (**44**) or tricyclic pyridines (**45**) respectively. In this context, it should be pointed out that atropisomerism in stereoselective photochemical reactions play an important role again [92].

3 Photochemically supported enzymatic reactions

Enzyme catalysis is an efficient method for the preparation of enantiomerically pure compounds [93]. Often multi enzyme systems are used for such transformations which complicates the application to organic synthesis. Photochemical transformations can simplify such transformations. Especially in the case of redox catalysis, photochemical reactions can replace one or more of enzyme activities in multi-enzyme systems. Mild photochemical conditions were applied to a large number of organic syntheses with enzymes [94–96].

The Baeyer–Villiger monooxygenase (BVMO) was efficiently applied to the asymmetric synthesis of lactones and esters (Scheme 10) [97–100]. Under normal conditions, the BVMO catalyzes the transformation of a ketone into an ester function (Scheme 10a). Molecular oxygen is used as oxidant which is first reduced to hydrogen peroxide by enzyme linked Flavin adenine dinucleotide ($\text{E-FAD}_{\text{red}}$). The hydrogen peroxide undergoes the Baeyer–Villiger

Scheme 9 Asymmetric catalysis of pyridines supported by irradiation with visible light

Scheme 10 **a** Baeyer–Villiger reaction under normal conditions using a two enzyme-system. **b** Replacement of the glucose dehydrogenase by a simple photoredox catalytic system based on non-linked FAD

reaction with the ketone substrate. The oxidized flavin species is reduced by NADPH leading to E-FAD_{red} and NADP⁺. NADPH is regenerated by glucose dehydrogenase. This second enzyme activity was efficiently replaced by a simple photocatalytic reaction involving non linked

FAD (Scheme 10b). The enzyme-linked E-FAD_{ox} is reduced by free FAD_{red}. The resulting FAD_{ox} is reduced in a photoredox catalytic reaction using visible light irradiation. Various electron donors such as EDTA can be used for this step.

Scheme 11 Photochemically supported enzyme catalyzed Baeyer–Villiger of a racemic ketones

Under these mild reaction conditions the racemic ketone **46** is partially transformed into the corresponding lactone (Scheme 11) [101]. Only the *R* enantiomer of **46** is transformed and **47** is obtained in high enantio-purity. The *S* enantiomer of **46** can also be isolated. In the case, of the bicyclic ketone **48**, both enantiomers are transformed. However, depending on the absolute configuration, two different regioisomers of the resulting lactones are formed in high enantioselectivity. The α -*R* enantiomer is transformed into the untypical [102, 103] Baeyer–Villiger product **50** while the reaction of the α -*S* enantiomer yields the bicyclic lactone **49**.

Photoredox catalysis was also combined with alcohol dehydrogenase (ADH) catalysis [104]. These enzymes use the NAD(P)H/NAD(P)⁺ system as cofactor [105]. The achiral diol **51** was enantioselectively oxidized to the lactol **52** by dehydrogenation of one alcohol function using horse liver alcohol dehydrogenase (HLADH) (Scheme 12) [106]. In this reaction step, one equivalent of NADH is formed. The corresponding NAD⁺ form is regenerated in a photoredox catalytic reaction with flavin mononucleotide (FMN). In this step, molecular oxygen is used as electron acceptor yielding hydrogen peroxide. In a second reaction sequence, the lactol

Scheme 12 Enantioselective synthesis of a lactone using photochemically supported enzyme catalysis

Scheme 13 Asymmetric radical cyclization induced by a photobiocatalytic step

52 is transformed into the (*S*)-4-methylvalerolactone **53**. The irradiation was carried out with blue LED ($\lambda_{\text{max}} = 465 \text{ nm}$).

Under similar reaction conditions using an ene-reductase, lactams have been enantioselectively synthesized (Scheme 13) [107]. α -Halogenoacetamides such as **54** are transformed into lactams **55**. In most cases, the products have been obtained in high yields with high enantioselectivities. An ene-reductase from *Gluconobacter oxydans* (GluER-T36A) was used which contains a flavin cofactor (FMN). The regeneration of NADP is catalyzed by a glucose dehydrogenase (GDH-105). The reaction starts with a photochemical electron transfer from the FMN of the enzyme to the substrate **54**. It has been shown that the substrate **54** forms an electron donor acceptor complex with the reduced form of flavin compounds which is a precursor of the electron transfer. After release of chloride, the radical intermediate **56** is generated. Cyclization yields the intermediate **57**. The final product **55** is obtained by hydrogen atom transfer (HAT). Very similar transformations have been carried out with anilides. In this case the α -acyl radical adds to the aryl substituent which leads to oxindoles [108]. It should be mentioned that this reaction is a photocatalytic variant of the Witkop reaction [109].

The combination of enzymatic catalysis and photochemistry provides numerous perspectives for organic synthesis [110–113]. This strategy is also an important element of sustainable (green) chemistry. Enzymatic and

photochemical reactions are key processes of the photosynthesis of green plants. For this reason, they have already been considered as perspectives for a clean, non-polluting chemical industry by G. Ciamician more than 100 years ago. [40–42] It is the beginning of green chemistry [43–45] although it has been forgotten over decades.

4 Chiral induction in crystals

Stereoselective synthesis is often linked to efficient conformation selection. The conformational rigidity in crystal is an efficient way to control conformational equilibria and to select a particular conformation. Packing in crystals may also orientate substrates in a particular way that is unfavorable in solution with the consequence to induce a particular photoreactivity. Molecular and crystal symmetry are connected [114]. Depending on the molecular symmetry, particular space groups are realized in crystal. Spectacular asymmetric reactions have been performed

in crystals with achiral substrates which crystallize in Sohncke space groups [115, 116]. Pure enantiomers can only crystallize in such symmetry groups. Achiral compounds may crystallize these groups. When they do so, most frequently, one enantiopure conformer is present in the homochiral crystals [117, 118]. When chemical reactions are performed with such crystals, the products are most frequently formed in high enantiomeric excess. Such reactions are also discussed in the context of "absolute asymmetric synthesis" [119].

The α -ketoamides **58** crystallize in Sohncke space groups and thus form enantiopure entities (Scheme 14) [120, 121]. Irradiation of such crystals leads to diradical intermediates **60**. Radical combination yields enantioselectively the hydroxy- β -lactams **59**. These reactions steps take place under strict conformation control by the crystal environment and high enantioselectivity is observed in most cases. For Ar=Ph, the substrate crystallized in the space group $P2_12_12_1$. [122] Irradiation of corresponding homochiral crystals yields the corresponding photoproduct **59** (Ar=Ph) with

Scheme 14 Enantioselective synthesis of β -lactams using absolute asymmetric synthesis with homochiral crystals

Scheme 15 Synthesis of β -lactams by photochemical transformation of chiral ammonium salts in the solid state

Scheme 16 Enantioselective photo-Claisen rearrangement in the solid state

Scheme 17 Photochemical electrocyclicization in TADDOL host-guest structures yielding quinolones in high enantioselectivity

93% ee. The product crystallizes in the same space group $P2_12_12_1$. In the present study, both enantiomers have been selectively prepared from the corresponding homochiral crystals. Under similar conditions the β -thiolactam **62** was enantioselectively prepared from the thioamide **61** [123]. The starting product **61** crystallizes in the space group $P2_1$. After photochemical excitation and intramolecular hydrogen atom transfer (HAT), the diradical intermediate **63** is formed. Radical combination yields the final product **62** in high enantioselectivity. When **61** is irradiated in solution the β -thiolactam **62** is formed as a racemate along with side products [124]. Further similar stereoselective reactions have been reported [125].

When particular crystallization methods, e.g. seeding crystallization with the desired homochiral crystal, the achiral starting compound can be selectively transformed into only one of the enantiomorphous crystals [126]. This method enables the controlled preparation of one desired enantiomer. It should further be pointed out that such solid-state photochemical reactions can also be carried out on larger scale when suspensions are irradiated [127]. This opens perspectives for an industrial production.

The combination of the photochemical substrate with a homochiral element also enables a control of the enantioselectivity. In this case, the compounds only crystallize in the 65 Sohncke space groups. A specific chiral environment is created around the substrate. [114–117] In the context of this topic, the chiral element is not covalently connected to the photochemical substrate [128]. In the case of ammonium

Fig. 3 X-ray structures of compound **70** (a) and **74** (b) in 1:1 cocrystals with a TADDOL (compare Scheme 17)

Scheme 18 Photochemical electrocyclicization of the dihydroazepinone **76** complexed with β -cyclodextrin

Scheme 19 Enantioselective photochemical electrocyclicization of pyridones **79** yielding bicyclic β -lactams **80**. The pyridones are co-absorbed with chiral aminoalcohols in Y zeolites

salts of chiral amines such as **64** (Scheme 15), both elements are combined by ionic interactions [129]. Irradiation of such salts with an aromatic α -ketoamide as chromophore in the solid state yields α -hydroxy- β -lactams **65**. In most cases, the products isolated as methyl benzoates (diazomethane workup) were obtained in high yield and enantioselectivity. Oxooxazolidines **66** were formed in minor amounts.

Under similar conditions the chiral ammonium salt of the norbornene derivative **67** undergoes an enantioselective photochemical Claisen rearrangement [130] leading to the bicyclic dihydrofuran compound **69** (Scheme 16) [131]. After photochemical excitation to the $n\pi^*$ state, the 1,4-diradical intermediate **68** is formed. Such intermediates are also formed in the Paternò-Büchi reaction [132–134] where they play a key role for the stereoselectivity [21, 135]. A typical reaction of such intermediates is the cleavage of the C–O bond (b) regenerating the substrate which diminishes the quantum yield of such reactions. In the present case, a C–C bond (a) of the norbornene fragment is cleaved yielding the final product **69**. As in the previous case, the products were isolated as methyl benzoates (diazomethane workup).

5 Inclusion structures

It has already been pointed out that TADDOLs (α, α', α' -tetraaryl-2,2-disubstituted 1,3-dioxolane-4,5-dimethanol) are efficient chiral auxiliaries that are not covalently bound to a reacting molecule. [78] These compounds are able to co-crystallize with numerous organic compounds. In these chiral host structures, the substrates react with high enantioselectivity [136–138]. Furoic acid amides easily co-crystallize with TADDOL (**70**) forming a 1:1 inclusion complex (Scheme 17) [139]. The interactions between host and guest are essentially established by hydrogen bonds (Fig. 3a). Due to the polar mesomeric structure **72**, irradiation of such crystals leads to a conrotatory electrocyclic reaction of the 6π

system with formation of intermediate **73**. Tautomerization yield the final product **71** in high enantioselectivity. Under similar conditions, the same reaction has been carried out with the acrylanilide **74**. In a 1:1 crystalline inclusion complex, the interactions between the host and guest structures are essentially based on van der Waals $\pi\pi$ -stacking or edge-to-face bonds (Fig. 3b) [140]. Irradiation of the inclusion complex again leads to the quinolone derivative **75** in high enantioselectivity.

Cyclodextrins are frequently studied as host structure for inclusion complexes [35, 141–143]. The unsaturated lactam **76** forms an inclusion complex with β -cyclodextrin (Scheme 18) [144]. The 1:1 complex is obtained as a water insoluble powder. A corresponding suspension was irradiated with UV light. Under these conditions, a disrotatory electrocyclic reaction takes place leading to the bicyclic butyrolactam **77**. Hydrogenation yields the corresponding cyclobutane derivative **78** in good yield and moderate enantioselectivity.

Zeolites are porous aluminosilicates which absorb organic molecules of different sizes depending on the dimensions of the cavities [145–147]. They are used as catalysts in many domains of chemistry, also in chemical industry. Zeolites have also been used as host structure for photochemical reactions [148–150]. The photochemical electrocyclicization of pyridone derivatives such as **79** have been performed in super cages of MY zeolites (Scheme 19) [151]. M are different alkali metals. These cages are achiral. In order to induce enantioselectivity in a chiral environment, (–)-norephedrine or (–)-ephedrine were adsorbed together with the substrate **79**. A maximum of interaction with the chiral inductor was established by using a tenfold excess for the preparation of the host guest structure. Although not covalently bound and due to the confinement in the super cages, the pyridone substrate is placed close to the enantiopure aminoalcohol and a control of the conformer equilibrium becomes possible. The presence of larger substituents R on the pyridone leads to higher enantiomeric excesses (up to 53%) in the bicyclic β -lactams **80**. It should be pointed out that when the reaction was carried out in solution and in the presence of dissolved chiral aminoalcohols, no chiral induction was detected. When the pyridone carries a covalently bonded chiral auxiliary, the diastereo-selectivity is improved when the reaction is carried out in zeolites instead of solution.

6 Memory of chirality

In many stereoselective reactions, the chiral information is transferred from a center of chirality, for example an asymmetric carbon atom, to the reaction center [152]. The products are obtained with a certain diastereo-selectivity. In particular cases, the initial chiral information is destroyed

Scheme 20 Memory of chirality with inversion of configuration in a photochemical decarboxylation cyclization reaction (above). Memory of chirality with retention of configuration in an electrochemical reaction (bottom)

during the reaction and before the final products are formed. The chiral information is then conserved in more or less stable conformers or non-covalent interactions and the reactions remain stereoselective. This phenomenon is called "memory of chirality" [153–156].

The proline derivative **81** was irradiated in an acetone/water mixture (Scheme 20) [157]. Under these conditions acetone is electronically excited and transfers its triplet energy to **81**. Intramolecular electron transfer from the carboxylate function to the phthalimide moiety yields the intermediate **82**. Immediate decarboxylation leads to the α -aminoalkyl radical species **83**. In this step, the chiral information initially localized in an asymmetric carbon atom is lost. Radical cyclization yields the final product **84** in high enantioselectivity. It must be pointed out that the chiral information that is intermediately conserved in a conformationally rigid structure is transferred by inversion of

configuration. This observation is explained by the fact that the spin multiplicity changes from the triplet in the diradical intermediate **83**, **85** to the singlet state in the final product **86**. In such a process, intersystem crossing and radical combination concomitantly occurs when both radical carrying p orbitals are orthogonally orientated as depicted in structure **85** [158–160]. Such an arrangement increases spin orbit coupling. Among numerous conformations in such a structure that one of a minimum of steric hindrance is privileged which has a significant impact on the stereoselectivity of these reactions [161, 162]. It was shown for a similar electrochemical reaction that compound **87** was transformed into compound **88** with almost the same enantioselectivity but with retention of configuration [156, 163, 164]. This result was explained by the fact that the reaction step in which the center of chirality is created (**89**) takes place exclusively at the singlet state. Further examples of memory of chirality

effects have been reported for photochemical reactions involving radical intermediates [165–169].

7 Conclusion

Synthesis strategies giving systematic access to enantiopure heterocyclic compounds are appreciated and also provide perspectives for chemical industry. These compounds are needed in many domains such as new biologically active compounds for medicine and agriculture or for material science. As organic photochemical reactions in general, such transformation are also of high interest in the context of sustainable chemistry.

Templates or organometallic compounds currently play an important role when photoredox catalytic or photosensitized reactions are studied. [34, 36–39] Enzyme catalysis is an important tool in asymmetric synthesis. Using photochemical conditions and reactions can simplify and improve such reactions. [94–96] For example, co-catalytic steps may be replaced by simple photochemical reactions. Performing photochemical reactions in the crystalline state [117] is an efficient method for the enantioselective synthesis of heterocyclic compounds. It is certainly the most efficient method to freeze conformers and thus control the stereoselectivity. This provides also interesting perspectives for material science. Supramolecular structures, such as inclusion complexes provide numerous methods for enantioselective photochemical reactions [31–33, 170, 171]. With such reactions, many fundamental aspects of chemical reactivity can be studied. For example, the influence of the intersystem crossing on the stereoselectivity was studied in connection with memory of chirality effects.

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Declarations

Conflict of interest The author states that there is no conflict of interest.

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