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Photochemically induced radical addition of tertiary amines to C=C and C=O double bonds: A green chemistry contribution to organic synthesis*

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Abstract: Photochemically induced electron transfer considerably enriches the redox chemistry of organic molecules. This primary step has been used to produce α-amino alkyl radicals that can be added to various double bonds. The addition to olefinic and carbonyl bonds is discussed. Homogeneous and heterogeneous photocatalysis methods with various electron-transfer sensitizers are described.

Keywords: photochemistry; catalysis; radical reactions; heterocycles; sustainable processes.

INTRODUCTION

In organic synthesis, chemical transformations are generally performed using heat or reagent activation, which then induce substrate reactivity. Very often, reagent transformation leads to undesired but inevitable by-products. In the case of catalytic reactions, the reagent (catalyst) is regenerated, considerably diminishing the problem of by-products.

Absorbing light, molecules reach an electronically excited state in which the distribution of electrons is significantly different from the ground state. Consequently, the chemical properties and in particular the chemical reactivity changes [1]. For example, redox potentials alter in the way that electron transfer becomes possible. Such a photochemical electron transfer considerably broadens the redox chemistry of organic compounds [2]. It has been applied to the generation of reactive intermediates of radical reactions. The latter reactions, although highly interesting for application in organic synthesis, frequently suffer from toxic reagents such as tin derivatives [3]. In many cases, photochemically induced electron-transfer reactions avoid such compounds and make the transformations safe and environmentally friendly.

The addition of α-amino alkyl radicals to double bonds is particularly interesting because the resulting products frequently possess interesting biological activity. These radicals are most frequently generated via photochemical electron transfer (Fig. 1) [4]. An acceptor molecule is photochemically excited. A single electron transfer from the tertiary amine to the acceptor molecule leads to a radical ion pair. After proton exchange, neutral radicals are obtained, among them α-amino alkyl radicals. Various radical reactions are then possible.

In this article, several addition reactions of α-amino alkyl radicals to carbonyl and olefinic double bonds will be presented.

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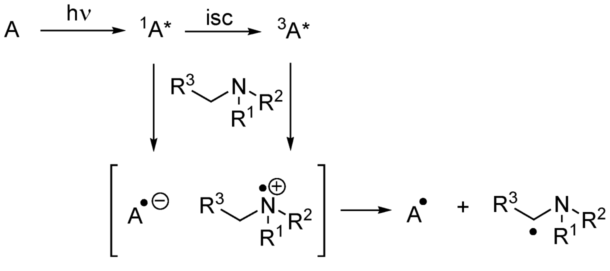


Fig. 1 Generation of α-amino alkyl radicals via photochemical electron transfer.

ADDITION TO CARBONYL FUNCTIONS

The intramolecular addition of photochemically produced α-amino alkyl radicals has been applied to the preparation of a variety of cyclic compounds. Small cycles such as **1** [5] as well as medium-sized cycles such as **2a,b** [6] can be built (Fig. 2). In both cases, the carbonyl function is photochemically excited and the reaction starts with intramolecular electron transfer. For similar reactions, see ref. [7].

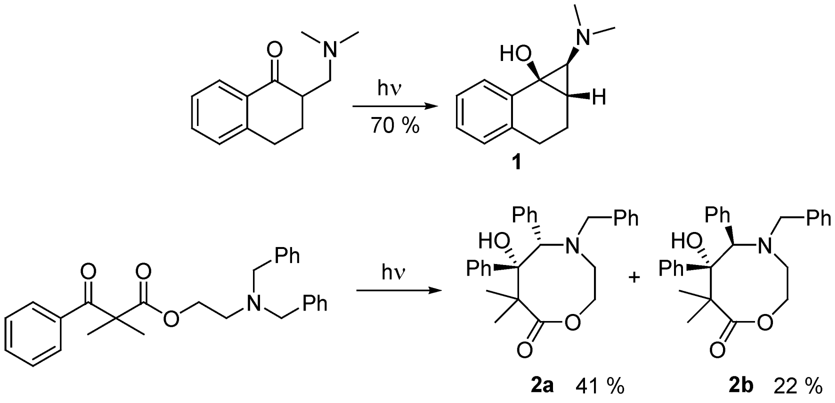


Fig. 2 Photochemical electron transfer-induced cyclization.

When the amine function is transformed into an amide or peptide, photoinduced electron transfer from the nitrogen atom is no longer possible. Nevertheless, hydrogen transfer via abstraction is possible (Norrish–Yang reaction) [8]. The α-ketoester **3** yields the γ-lactams **4a,b** in high yield (Fig. 3) [9]. The reaction was used to establish the structure of the pyrrolizidine alkaloid curassanecine. In this example, the stereoselectivity is rather low. In many other cases, the reaction can be carried out with higher stereoselectivity [8,10]. This transformation is also part of a strategy using radical reactions for the synthesis of α-amino acids and derivatives [11].

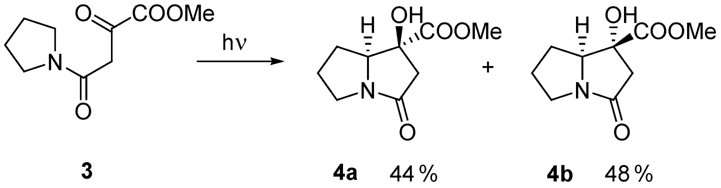
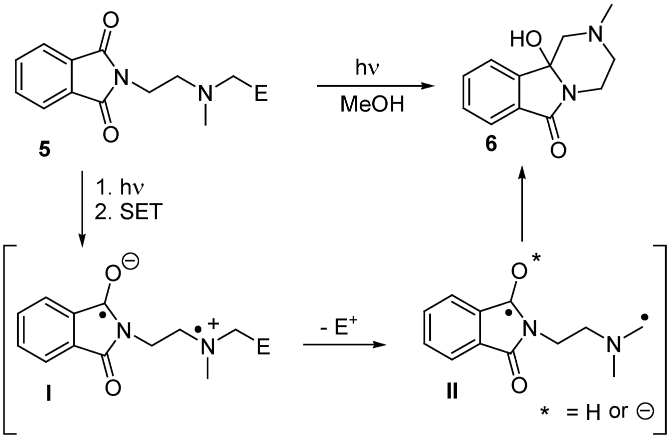


Fig. 3 Application of the Norrish–Yang reaction to the synthesis of pyrrolicidine alkaloids.

A large variety of reactions have been performed with phthalimides as electron acceptors [12]. After excitation of the phthalimide moiety in **5**, electron transfer (SET) occurs from the tertiary amine leading to a distonic diradical **I** (Fig. 4) [13]. Proton exchange is not always the best way to generate the neutral diradical **II** (see also Fig. 1). In these cases, back electron transfer becomes competitive and can significantly diminish the overall reaction efficiency. This relationship is well illustrated by the corresponding quantum yields Φ. As shown in the Fig. 4 table, the trimethylsilyl group is a better leaving group. The difference between the proton and the trimethylsilyl substituent is increased when alcohols such as methanol are used as solvent or cosolvent. Among the investigated leaving groups, carboxylate is the best one. In this case, carbon dioxide is released, which is an entropically favored reaction step. Furthermore, this leaving group does not produce any side products remaining in the reaction mixture. The final product **6** is obtained by radical combination. The reaction has been applied to the synthesis of macrocyclic compounds. The phthalimide derivative **7** was irradiated in the presence of acetone as sensitizer (Fig. 5) [14]. The 18-membered ring (**8**) was isolated in good yields. A large variety of cyclic polypeptides have been synthesized in the same way [15]. Chiral memory effects have been observed with these reactions. The L-proline derivative **9** was transformed into the bislactam **10**, and 86 % of the chiral information was preserved in the final product **10** [16]. As in the previous case, electron transfer occurred between the carboxylate function and the phthalimide moiety which was directly excited to its triplet state (T_1) via acetone sensitization. The configuration of the pyrrolidine moiety in **10** has been inverted with respect to the substrate **9**. This result was explained by an enhanced rotation barrier around the central C–N bond of an atropisomer of intermediate **III** before cyclization. The biradical also possesses triplet character. For various other examples of the intramolecular addition of tertiary amines to phthalimides, see ref. [17].



Leaving group E	Φ
H	0.003
$SiMe_3$	0.038
CO_2^-	0.32

Fig. 4 Cyclization of an amino phthamimido derivative induced by photochemical electron transfer, influence of the leaving group on the quantum yield.

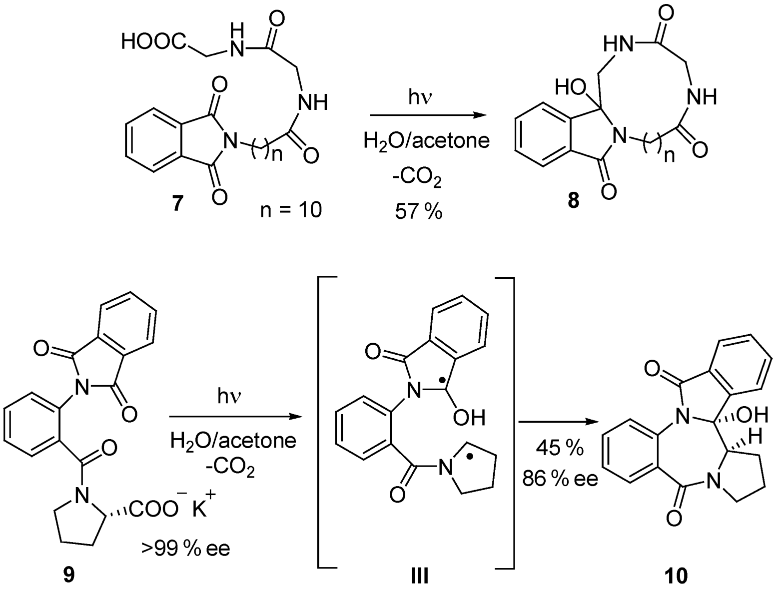


Fig. 5 Cyclization of a phthalimido derivative in a photosensitized reaction.

Most frequently, C–C bonds are generated in these reactions. However, an interesting example of a C–O bond formation has been published (Fig. 6) [18]. The photochemical cyclization of the linear peptide **11** containing an anthracenequinone moiety leads to the 18-membered cyclopeptide **12**. The driving force of this rather unusual regioselectivity is the aromatic character in the final product **12**.

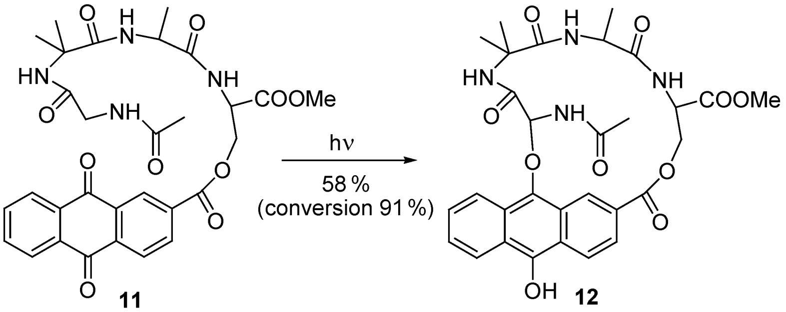


Fig. 6 Intramolecular C–O bond formation via addition of an α-amino alkyl radical to a carbonyl function.

ADDITION TO ALKENES

α-Amino alkyl radicals are nucleophilic and therefore readily add to electron-deficient alkenes. The reaction has been known for a long time, but this transformation has only recently been efficiently performed. *N*-Methylpyrrolidine **13** was added to furanones such as **14** with yields higher than 90 % and a quantum yield of 4 (Fig. 7) [19]. The facial diastereoselectivity was almost quantitative. The configuration of the second chiral center in the α-position of the nitrogen atom was not controlled, and the two diastereoisomers **15a,b** were isolated. The efficiency of the reaction is due to the sensitization with electron donor-substituted aromatic ketones such as **16**, **17**, or **18**. When compared to more conventional sensitizers such as benzophenone or acetophenone, it can be concluded that in the case of the new sensitizers:

- yields are particular high;
- the reactions are significantly faster, which facilitates large-scale transformations; and
- the new sensitizers are used only in catalytic amounts and can be recovered up to 80 % after the reaction.

It should be underlined that in many sensitized photochemical electron-transfer reactions, the sensitizer such as benzophenone or acetophenone is consumed [20]. High recovery as well as the considerable reaction acceleration in the present case make these new sensitizers efficient homogenous photocatalysts. The relatively low quantum yield indicates that the radical chain process is rather inefficient when compared to other photochemically induced radical chain reactions. This has been explained by an efficient termination step enabling the regeneration of the sensitizer or catalyst. For more mechanistic details, see also refs. [21,22].

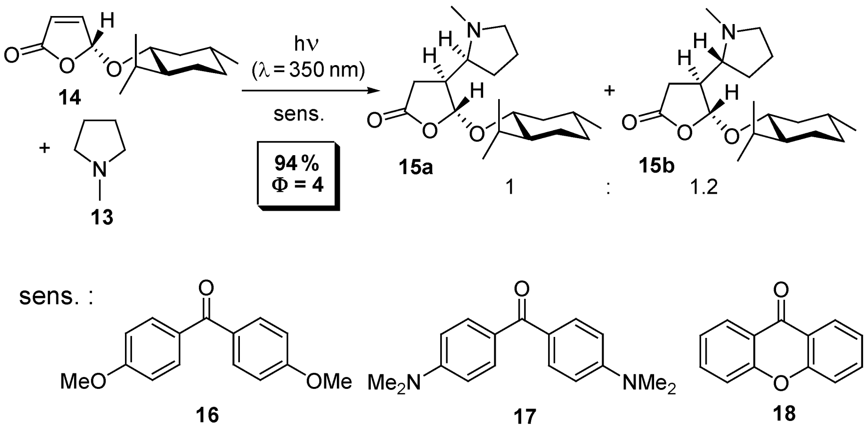


Fig. 7 Intermolecular photosensitized addition of *N*-methylpyrrolidine **13** to the furanone **14**.

Using inorganic semiconductors such as TiO_2 or ZnS, the addition of **13** to furanones such as **19** was performed with yields up to 98 % (Fig. 8) [23]. After light absorption, an electron is transferred from the valence band to the conduction band and the particle can now oxidize the tertiary amine **13**. Deprotonation of the resulting radical cation then leads to the α-amino alkyl radical **IV**. The addition of this intermediate to furanone **19** leads to the electrophilic radical **V**. The electron in the conduction band of the semiconductor particle reduces the intermediate **V** and after protonation, the final product **20** is obtained.

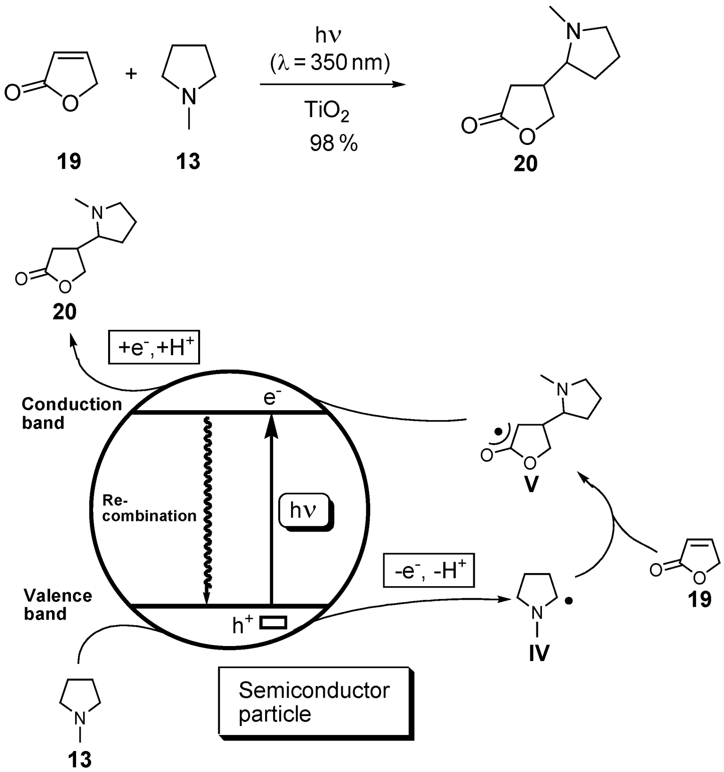


Fig. 8 Semiconductor-sensitized addition of *N*-methylpyrrolidine **13** to the furanone **19**.

It is clear that the use of homogeneous or heterogeneous photocatalysis with no need for chemical activation of the substrates for C–C bond formation avoids the formation of polluting side products.

More complex reactions (in particular, radical addition cyclization processes) have also been performed using photochemical electron transfer. Aromatic amines such as *N*,*N*-dimethylaniline **21** were added to menthyloxyfuranone **14** (Fig. 9) [21]. The reaction is sensitized by Michler's ketone **17** (also compare Fig. 7). The resulting tetrahydroquinoline derivatives **22a,b** have been isolated with 90 % d.e. The presence of acetone as a mild oxidant is necessary to inhibit by-product formation via reduction of the furanone **14** [21,22]. Applying the optimized reaction conditions, a variety of nitrogen-containing heterocycles have been obtained. The transformation of the tetrahydronaphthyl amine derivative **23** lead to **24**, which resembles an azasteroid. Benzoquinolizidine derivatives such as **26a,b** have been obtained from the reaction of *N*-phenylpiperidine **25**. In this case, the radical addition to **14** occurred stereospecifically *anti* with respect to the alkoxy substituent. The configuration of the chiral center in the α-position of the nitrogen atom was not controlled, and two diastereoisomers were formed in comparable yields. The same reaction was also performed using various inorganic semiconductors as heterogeneous photocatalysts [24]. These transformations are particular interesting since tetrahydroquinolizidine derivatives possess a variety of biological activities [25].

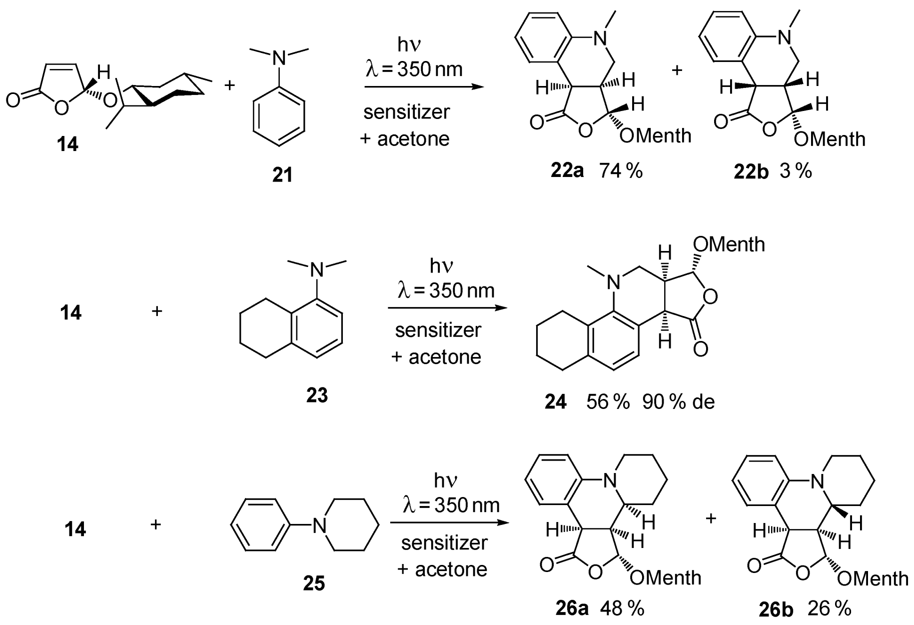
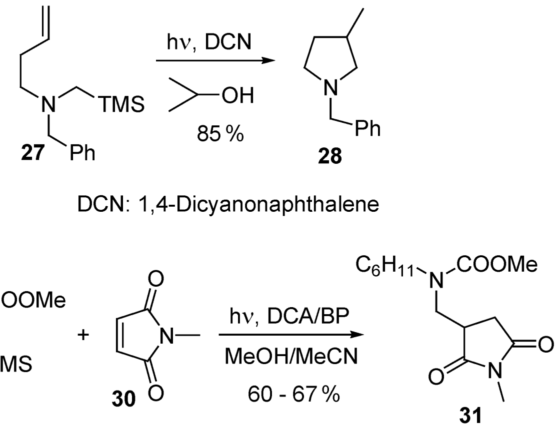


Fig. 9 Photoinduced radical tandem addition cyclization reactions with aromatic tertiary amines.

As previously mentioned, in cation of a tertiary amine radical, a silyl substituent is often a better leaving group than a proton, especially when the reaction is carried out in the presence of an alcohol as solvent or cosolvent. This tendency was also applied of to the addition of tertiary amines to alkenes to enhance the reactivity [26]. The unsaturated trimethylsilyl derivative **27** underwent efficient radical cyclization, yielding the pyrrolidine derivative **28** when dicyanonaphthalene was used as sensitizer in isopropanol as solvent (Fig. 10) [27]. Less-reactive carbamates could also be transformed. Using the two-component sensitizing system 9,10-dicyanoanthracene/biphenyl (DCA/BP) in catalytic amounts, the trimethylsilyl-substituted carbamate **29** was added to the maleiimide **30** [28]. In this case, the sensitization was performed in two steps (Fig. 11). First, electron transfer occurs from biphenyl to the photochemically excited dicyanoanthracene leading to the radical anion **VI** of the dinitrile and the radical cation **VII** of biphenyl. The radical cation can now oxidize the carbamate **29**. After desilylation and addition to **30**, the adduct **31** is formed via back electron transfer from the radical anion **VI** of dicyanoanthracene to the electrophilic radical **VIII**. The mechanistic scheme clearly explains the regeneration of the whole catalytic system. The same reaction conditions have been applied to corresponding intramolecular radical additions [29].



DCN: 1,4-Dicyanonaphthalene

DCA/BP: 9,10-Dicyanoanthracene/Biphenyl

Fig. 10 Radical addition of silylalkylamine derivatives to C=C double bonds using photochemical electron transfer.

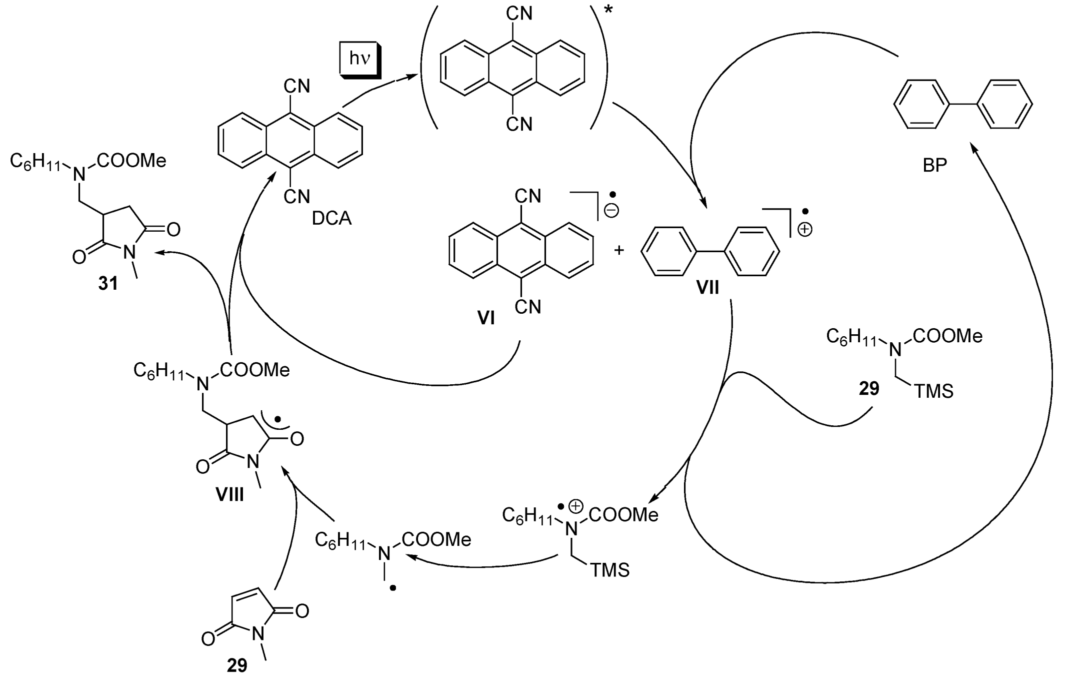


Fig. 11 Sensitization mechanism of the two-component system DCA/BP.

CONCLUSION

Photochemical reactions frequently enable transformations that are not possible with ground-state reactions, even when they are catalyzed. In cases where a redox reaction at the ground state is not possible, electron transfer may occur when one molecule is photochemically excited. In a first step, a radical ion pair is generated. The process is mainly performed with homogeneous and heterogeneous photocatalysts. Neutral radicals are obtained from radical cations through departure of a positively charged group, for instance, a proton. These radicals have been added to various double bonds, and the process has often been applied to synthesis. Compared to ground-state reactions, these photochemical transformations do not need any chemical activation of the substrates for C–C bond formation, which could lead to side products. These reactions should, therefore, be considered in the context of sustainable processes.

Years ago, G. Ciamician stated: "On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extent over the plains and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry and mankind is" [30].

Let us hope that at least a part of this vision can soon become reality.

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