Environment-friendly organic synthesis. The photochemical approach*

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Abstract: Photochemical reactions are expected to have an increasing role in organic synthesis with the drive towards environment-friendly reactions. Some examples illustrating the scope and versatility of radical alkylation of electrophilic alkenes via photoinduced electron transfer are presented. A few applications in special fields are mentioned.

PHOTOCHEMISTRY FOR ORGANIC SYNTHESIS

Photoinitiated reactions are promising candidates for environment-friendly organic synthesis. The central issue of organic chemistry is to make quite stable organic molecules susceptible to reactions. This is obtained either by weakening a covalent bond (e.g., by complexation or adsorption on a catalyst surface) or by polarizing it (e.g., again by complexation or by forming a hydrogen bond) or by cleaving a covalent bond. The last choice is the one requiring more energy and more control of the medium, as typified by the deprotonation of a carbonyl or carboxyl derivative to form an enolate, probably the most largely used strategy for the formation of the carbon–carbon bond.

Photochemistry is different, since electronically excited states (see eq. 1) differ from ground states not only for the high energy level, but also, and perhaps more importantly, for the dramatic change in the electronic distribution by which they are characterized as well as by the fact that such a change does not require the addition of a chemical reagent or—at least in principle—a special care of the medium. To take a simple example, a ketone is a weak electrophile, due to the polarization of the π C–O bond. As such, it reacts only with quite active (usually charged) nucleophiles. The electrophilicity can be increased by increasing the polarization (e.g., by complexation by means of a Lewis acid), and under these conditions weaker electrophiles add. However, electronic excitation brings about a more deep-seated change. The $n\pi^*$ excited state is no more a C-electrophile (3 electrons now crowd in the π space) but the single electron remaining in the n_O orbital gives to this species a strong radical reactivity centerd at the oxygen atom (see Scheme 1). Indeed, the typical reactions are fast (typical rates $\geq 1 \times 10^6$ M^{-1}s^{-1}) H-abstractions from a C–H bond or addition to an alkene, i.e., the same reactions that an alkoxy radical would give.
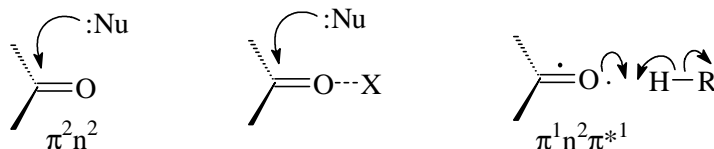
$$A + h\upsilon \rightarrow A^* \rightarrow \text{Products} \tag{1}$$

Scheme 1

Importantly, such a change is obtained by the absorption of a photon, not by adding a reagent, and is relatively independent from the experimental parameters (temperature, medium characteristics, other reagents present). Therefore, the judicious choice of such parameters allows the direction of the reaction toward the desired target and gives to photochemical reactions an unparalleled versatility in every direction. This certainly includes a further control of the environmental compatibility and this must be added to the intrinsic advantage of such reactions, in which the maximum change of the reactivity is obtained through the minimum addition of reagents (in fact, none).

The reactivity of every excited state depends on its electronic structure and offers a real variety of novel chemical processes that can be used for synthesis (e.g., the above-mentioned radical reactions of the $n\pi^*$ state of ketones, the geometric isomerization of alkenes, the rearrangement of some aromatics) [1]. The utility of photochemistry in key steps of organic synthesis has been demonstrated through many examples, including scaling up to reasonable amounts [2] and industrial applications [3].

Furthermore, there is a property that all excited states share independently from the structure, and this is the fact that they are much more easily both reduced and oxidized than the corresponding ground states. The excitation energy, E_{exc}, must be added to the values of the redox potentials, E_{ox} and E_{red}, in the ground state, and since E_{exc} is large (2 to 4 eV) single electron transfer processes, a rarity in the ground state, are quite common in photochemistry [4]. This property makes another option available, since it offers a peculiarly mild —and again versatile—access to the radical ions of organic molecules and their chemistry.

$$A + h\nu \rightarrow A^* + D \rightarrow A^{-\cdot} + D^{+\cdot} \rightarrow Products \qquad (2)$$

Without attempting to extensively survey the perspective of photochemistry in the frame of the development of sustainable chemistry, we wish to report here some examples of C–C bond forming reactions via photoinduced electron transfer that we have helped to develop, as well as to give some indications about the broad field of application of photochemical methods.

SYNTHETIC PATHS VIA PHOTOINDUCED ELECTRON TRANSFER

Radical ions are intermediates in some important reactions [5] and are typically generated by electrochemistry or by the action of a strong reducing or oxidizing inorganic reagent, (e.g., eqs 3 and 4).

$$D - e^- (anode) \rightarrow D^{+\cdot} \qquad (3)$$

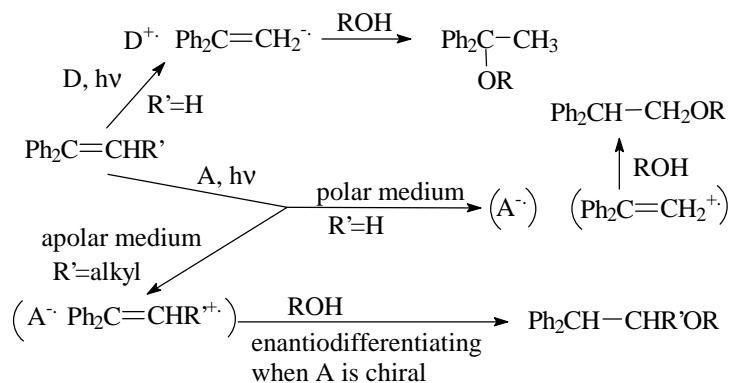$$D + M^{n+} \rightarrow D^{+\cdot} + M^{(n-1)+} \qquad (4)$$

Photoinduced electron transfer (PET) [4], however, offers a totally alternative approach with respect to these methods, since in this case single electron transfer involving two organic molecules is obtained (eq. 2). This is a double advantage. First, the photochemical process can be carried out in a neat organic solvent, not requiring the use of a conducting salt as in electrochemistry and avoiding limitations in the choice of the solvent and any possible interference related to the use of an inorganic reagent. Second, the oxidizing or reducing species is the excited state, present in solution at a very low steady state concentration due to the low lifetime. Therefore, the chemistry of the first formed radical ion can be better controlled, avoiding over oxidation or reduction (e.g., see eq. 5) quite often observed in other cases.

$$D^{+\cdot} - e^- (or + M^{n+}) \rightarrow D^{++} (+ M^{(n-1)+}) \qquad (5)$$

The above characteristics make photoinduced electron transfer an attractive choice for the generation of radical ions and the exploration of the chemistry of these little-known intermediates. The observed processes generally involve either addition to multiple bond or σ bond fragmentation. A typical example of the first group is polar addition to styrene and derivatives. In the case of an oxidative PET process (via a photoexcited sensitizer S), the radical cation is formed and addition occurs in the

anti-Markovnikov sense, whereas a reductive PET step leads to the radical anion and hence to Markovnikov addition (Scheme 2) [6]. A further appealing possibility is given by retaining the radical ions in close proximity rather than allowing them to diffuse in solution, for example, by carrying out the reaction in an apolar medium. Under these conditions an enantiodifferentiating addition occurs when a chiral sensitizer is used [7].
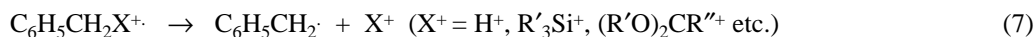
Fragmentation processes, on the other hand, represent a mild way for generating radicals from unconventional precursors as shown, for the oxidative path, in eq. 6.

$$D^{+\cdot} \; Ph_2C{=}CH_2^{-\cdot} \xrightarrow{\;ROH\;} \; Ph_2C{-}CH_3 \atop \qquad\qquad\qquad\quad OR$$

$$Ph_2CH{-}CH_2OR$$

D, hν R'=H

$Ph_2C{=}CHR'$

A, hν polar medium R'=H $\left(A^{-\cdot}\right)$ $\left(Ph_2C{=}CH_2^{+\cdot}\right)$ ↑ ROH

apolar medium R'=alkyl

$\left(A^{-\cdot} \; Ph_2C{=}CHR'^{+\cdot}\right) \xrightarrow[\text{enantiodifferentiating}]{\;ROH\;} Ph_2CH{-}CHR'OR$ when A is chiral

Scheme 2

$$A^* \; + \; RX \; \rightarrow \; A^{-\cdot} \; + \; RX^{+\cdot} \; \rightarrow \; R\cdot \; + \; X^+ \tag{6}$$

This is relevant in view of the constantly increasing contribution of radical processes to the development of C–C bond forming synthetic procedures. Oxidative fragmentation by ground-state oxidants such as Mn(III) and Ce(IV) derivatives [8] is rather limited in scope, in practice applying only to tautomeric enols. However, the excited states of organic molecules are much stronger oxidants, and under PET conditions a large variety of weak donors undergo single electron oxidation and ensuing fragmentation according to eq. 6 [9,10]. These include alkenes [11], aromatic hydrocarbons [12], aliphatic stannanes and silanes [13], ketals [14], carboxylic acids [15], and even aliphatic hydrocarbons [16]. The high energy of these radical cations makes fragmentation a fast process able to compete with back electron transfer and thus leads to a photoinduced reaction with a reasonable quantum yield. Importantly, different bonds fragment at different rates [17], and the generation of radicals through this path is quite selective. By choosing an appropriate precursor one can obtain both a stabilized radical, for example, a benzyl radical (see eq. 7), and a non-stabilized alkyl radical when the electron-donating moiety is lost with the electrofugal group, for example, in the case of an aliphatic ketal, eq. 8).

$$C_6H_5CH_2X^{+\cdot} \; \rightarrow \; C_6H_5CH_2\cdot \; + \; X^+ \; (X^+ = H^+, R'_3Si^+, (R'O)_2CR''^+ \text{ etc.}) \tag{7}$$

$$RR'C(OR'')_2^{+\cdot} \; \rightarrow \; R\cdot \; + \; R'C(OR'')_2^+ \tag{8}$$

Radicals are thus generated under mild conditions and are added to the appropriate trap. A typical application is radical substitution of a cyano by an alkyl group in an aromatic nitrile ArCN (which also serves as the excited acceptor, thus being reduced to the radical anion, eq. 9) [18].

$$ArCN^* \; + \; RX \; \rightarrow \; ArCN^{-\cdot} \; + \; R\cdot \; + \; X^+ \; \rightarrow \; ArR \; + \; CN^- \tag{9}$$

A more important and general reaction, however, is the radical conjugate alkylation of electrophilic alkenes. The latter method has been found to occur satisfactorily under PET conditions [19,20].
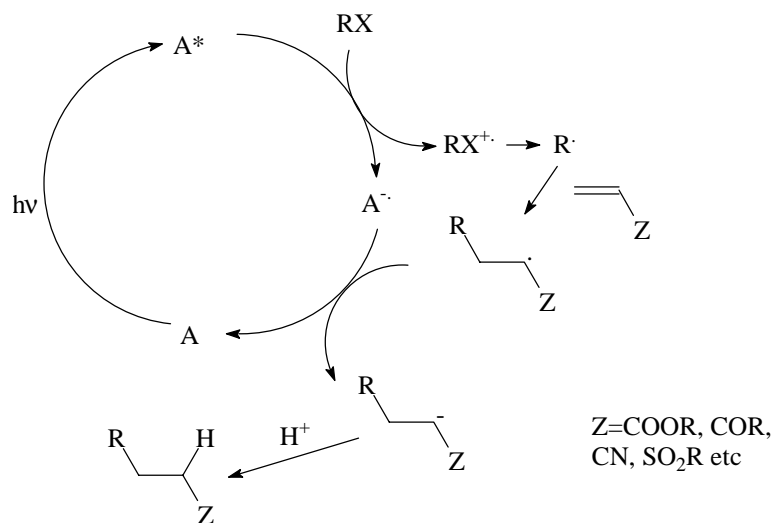
Scheme 3

In this case, the excited acceptor functions as a non-consumed sensitizer, since it is regenerated by back electron transfer to the radical adduct (see Scheme 3).

The reaction is stoichiometric in light (the quantum yield ranges from 0.1 to 0.4 in satisfactory cases) but catalytic as far as the amount of the sensitizer (chosen among aromatic nitriles—DCN, dicyanonaphthalene, TCB, tetracyanobenzene—esters, ketones or quinones, see Scheme 4) is concerned. The PET-induced alkylation is complementary to established radical-chain or redox methods, for example, being effective also in cases where the stabilization of the radical adduct makes chain propaga-
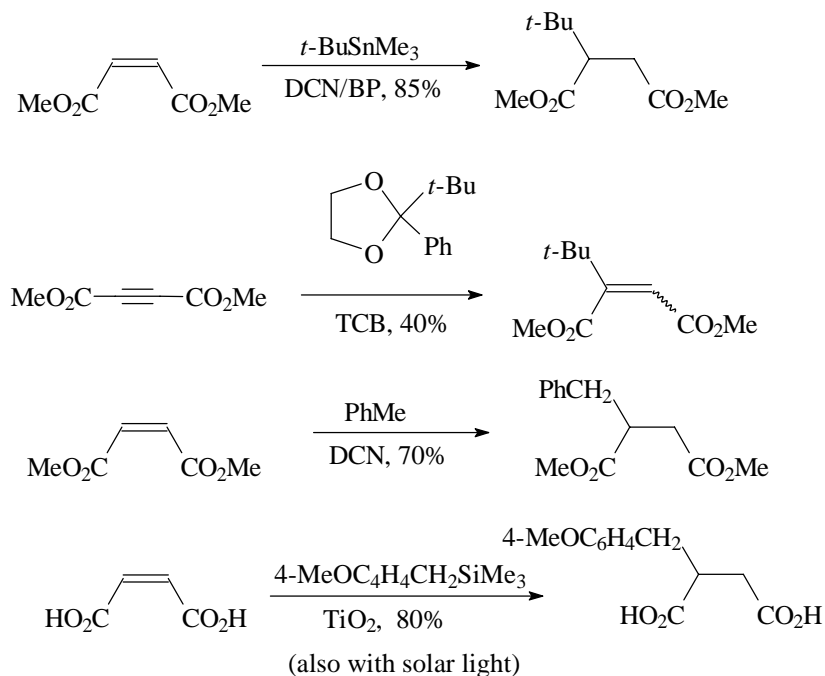
Scheme 4

tion too slow to sustain the process, as is the case for capto-dative alkenes. Furthermore, the large choice of radical precursors (including many classes of tin-free derivatives, see above) and of the experimental conditions make the method attractive for more environment-friendly syntheses.

A further advantage is the possibility of carrying out such alkylations by using a robust and reusable solid sensitizer such as titanium dioxide, a procedure that can be easily scaled up and can be adapted to the use of solar light (see the last example in Scheme 4) [21].

FURTHER SYNTHETICALLY USEFUL PHOTOCHEMICAL REACTIONS

The peculiar versatility of photochemical reactions forming covalent bonds is expected to be usefully applied in special fields of organic synthesis which are rapidly developing. A few examples are indicated below, in order to give an idea of the variety of the scope.

The scarce medium-dependence of excited state reactions may be exploited, for example, for switching to water as the solvent [22]. The mild conditions are useful for the mild cleavage of protective groups [23] or in supramolecular chemistry (e.g., for controlling the molecular weight of polymers formed from self-assembling units) [24]. On the other hand, other applications form a covalent bond in a predetermined way by exploiting the arrangement of the molecule in the environment (e.g., by carrying out one- or two-component syntheses in the crystal state, with the further option of exploiting the crystal chirality of achiral compounds for the stereoselective formation of covalent bonds) [25]. A targeted interstrand DNA cross-linking has also been achieved by photochemical means [26]. The possibility of local irradiation can be useful in solid-phase synthesis, both for bond formation and for the mild cleavage of the product from the resin [27] or for the preparation and patterning of self-assembled monolayers [28].

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