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Photoremovable Protecting Groups in Chemistry and Biology: Reaction Mechanisms and Efficacy

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1 INTRODUCTION

Photoremovable protecting groups (PPGs) provide spatial and temporal control over the release of various chemicals such as bioagents (neurotransmitters, cell signaling molecules), acids, bases, Ca^{2+} ions, oxidants, insecticides, pheromones, fragrances, etc. Following early reports on PPGs for use in organic synthesis by Barltrop,[1] Barton,[2] Woodward,[3] Sheehan[4] and their coworkers, applications to biology were sparked off by Engels and Schlaeger[5] and Kaplan and coworkers,[6] who first achieved the photorelease of cyclic adenosine monophosphate (cAMP) and ATP, respectively. The latter authors introduced the convenient, if somewhat misleading term “caged” to designate a compound protected by a PPG. Two general perspectives[7] and many more specialized reviews covering applications of PPGs in synthesis,[8] biochemistry and neurobiology,[9] biomedicine,[10] volatiles release,[11] polymerization,[12] and fluorescence activation[13] have been published during the last decade, and a journal issue themed on these topics has recently been published.[14] The present review covers recent developments in the field, focusing on the scope, limitations and applications of PPGs, which are used to release organic molecules. Photoactivation of small inorganic species and ions, such as NO,[15] CO,[16] Ca^{2+},[9h,17] Zn^{2+},[18] Cd^{2+},[19] or Cu^{+}[20] is not covered. Simplified basic structures of the photoremovable protecting groups discussed in this review are listed in Table 1 (the leaving groups are shown in red).

The criteria for the design of a good PPG will depend on the application. No single system needs to fulfill all of the following requirements:

i. In general, the PPG should have strong absorption at wavelengths well above 300 nm, where irradiation is less likely to be absorbed by (and possibly cause damage to) the biological entity.[21] Moreover, the photoreaction should be clean and occur with a high *quantum yield* or efficiency for release, Φ_{rel}. The quantum yield Φ_{rel} is

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equal to the amount of released substrate, n_{rel}/mol, divided by the amount of photons at the irradiation wavelength λ, n_p/mol = n_p/einstein, that were absorbed by the caged compound: $\Phi_{rel} = n_{rel}/n_p$. An important measure for the efficacy of a PPG is the product of the quantum yield and the molar decadic absorption coefficient ε of the PPG, $\Phi_{rel}\varepsilon(\lambda_{irr})$, which is proportional to the amount of release at the given excitation wavelength.[22]

ii. Sensitive detection of the response under study often depends not only on the product $\Phi_{rel}\varepsilon(\lambda_{irr})$, but also on the background level of activity of the caged compound prior to irradiation. Hence, the PPGs must be pure, exhibit low intrinsic activity, and be stable in the media prior to and during photolysis.

iii. The PPGs should be soluble in the targeted media; they may further be required to pass through biological barriers such as cell membranes, and show affinity to specific target components, for example, binding sites on cancer cells or the active site of an enzyme.

iv. The photochemical by-products accompanying the released bioactive reagent should ideally be transparent at the irradiation wavelength to avoid competitive absorption of the excitation wavelengths. Moreover, they must be biocompatible, i.e., they should not react with the system investigated.

v. To study the kinetics of rapid responses to a released agent in samples such as brain tissue or single live cells, the PPG must be excited by a short light pulse and the *appearance rate constant* k_{app} of the desired free substrate must exceed the rate constant of the response under investigation. Commonly, there are several reaction steps involving ground- and excited-state intermediates that precede the actual release of the free substrate. Therefore, detailed knowledge of the reaction mechanism is needed, in particular, the rate-determining step in the reaction path and its lifetime τ_{rd} or k_{app} must be known, unless the appearance of the free substrate (k_{app}) can be monitored directly by time-resolved techniques.

Nitrobenzyl, nitrophenethyl compounds and their dimethoxy derivatives (nitroveratryl) (Section 3) are by far the most commonly used PPGs. The decay of their primary quinonoid intermediates on the microsecond time scale does not generally correspond to the rate-determining step of the overall reaction, and the release of the free substrate may be orders of magnitude slower. Moreover, photolysis of these compounds forms potentially toxic and strongly absorbing by-products such as *o*-nitrosobenzaldehyde. Quite a number of alternative PPGs have been developed that do not suffer from these disadvantages.

The appearance rate constant k_{app} of the desired product is equal to the inverse of the rate-determining intermediate's lifetime τ_{rd}, $k_{app} = 1/\tau_{rd}$, that often depends on the solvent as well as on the concentrations of acids and bases including those of the general acids and bases contained in buffers. *Release rate constants*, $k_r = \eta_r/\tau_r$, are sometimes quoted, where η_r is the efficiency of the releasing reaction step, $\eta_r = k_r/\Sigma k$, and $\tau_r = 1/\Sigma k$ is the lifetime of the intermediate that is assumed to release the substrate; Σk includes k_r and the rate constant of all competing reactions occurring from that intermediate. Note that the release rate constant k_r may be slower or faster than the more relevant appearance rate constant k_{app} of the desired substrate; a) $k_r < k_{app}$ if $\Sigma k > k_r$, i.e., if reactions other than substrate release contribute to the decay rate of the releasing intermediate. A trivial example of case a) is shown in Scheme 1; b) $k_r > k_{app}$ if the actual release is preceded by a slower, rate-determining step of the reaction sequence.

The *speed of release* is an ambivalent expression; it may refer to the efficiency of a PPG, $\Phi_{rel}\varepsilon(\lambda_{irr})$, the amount released by a given irradiation dose, or to the appearance rate constant in time-resolved work.

The absorption spectra of a number of chromophores frequently encountered as PPGs are shown in Figure 1.

2 ARYLCARBONYLMETHYL GROUPS

Aromatic ketones are readily accessible synthetically, thermally stable and their photophysical and photochemical properties well understood. The lowest energy transition of simple carbonyl compounds is typically a weak n,π* band ($\varepsilon \sim 10–100\ M^{-1}\ cm^{-1}$).[27] The higher energy π,π* absorption bands are strong, and internal conversion to the S_1 state is very fast (e.g., ~100–260 fs for acetophenone).[28] The electronic transitions of aromatic ketones are sensitive to solvent polarity and to substitution on the phenyl ring. Hydrogen bonding of protic solvents to the carbonyl oxygen stabilizes the oxygen non-bonding orbital giving rise to a hypsochromic shift of the n,π* absorption band. Both electron-donating groups and polar solvents tend to stabilize the π,π* states. The strong bathochromic shift induced by *para* amino substituents is attributed to a CT interaction[29] (for example, λ_{max} for *p*-aminobenzaldehyde is ~325 nm (π,π*) in cyclohexane).[24] Aromatic ketones are highly phosphorescent and only weakly fluorescent[30] due to their fast ($>10^{10}\ s^{-1}$), very efficient intersystem crossing to the triplet state, for which two energetically close lying states (n,π* and π,π*) seem to play a crucial role, possibly due to a $S_1/T_2/T_1$ intersection.[31] The singlet–triplet energy gap is much larger for π,π* than for n,π* states. The lowest π,π* and n,π* triplet states are nearly degenerate and substitution on the phenyl ring as well as polar solvents may lead to triplet state inversion.[27,32] Some of the important photophysical properties of acetophenone, the parent aryl ketone, are summarized in Table 2. Examples of the absorption spectra of other representative PPG aryl ketones are provided in Figure 1.

The carbonyl group of aromatic ketones is usually the center of the photochemical reactivity. Scheme 2 shows the most important photoreactions that lead to the liberation of a leaving group (X) and which are discussed in the following paragraphs. Ketones with n,π* lowest triplets, possessing a half vacant n orbital localized on the carbonyl oxygen, are far more reactive than those with π,π* lowest triplets with spins delocalized on the aromatic ring. The singlet or triplet n,π* states thus readily abstract hydrogen atoms from suitable donors (entry 1), whereas both n,π* and π,π* states can be reduced in the presence of good electron donors (entry 2). The reaction intermediates hereby formed may subsequently release X^- from the α-position. Intramolecular H-transfer reactions in *o*-alkylacetophenones result in the formation of ground state photoenols that liberate X^- from the α- (entry 3) or *o*-ethyl (entry 4) positions. Entry 5 shows the *p*-hydroxyphenacyl moiety, which undergoes a photo-Favorskii rearrangement to release X^-. Finally, the benzoin derivative in entry 6 releases X^- to form 2-phenylbenzofuran.

2.1 Phenacyl and Other Related Arylcarbonylmethyl Groups

Employing phenacyl compounds as PPGs has been the subject of interest for several decades.[39] α-Substituted esters of the phenacyl chromophore are typical of the PPG framework for release of carboxylic acids, for example. Homolytic scission of the ester C–O bond, that would result in the formation of phenacyl and acyloxy radicals, has not been confirmed. Instead, a mechanism that involves hydrogen abstraction from a hydrogen-atom donor by the excited carbonyl group (photoreduction[27]) of phenacyl ester via a ketyl ester intermediate (entry 1, Scheme 2) has been established by laser flash photolysis.[40]

Excited phenacyl and 3-pyridacyl esters of benzoic acid were reported to react with an excess of aliphatic alcohols in a chain reaction process to give benzoic acid in addition to acetophenone and 3-acetylpyridine, respectively, as the by-products.[41] Singh and coworkers have reported that arylcarbonylmethyl groups, i.e., naphth-2-ylcarbonylmethyl[42] and pyren-1-ylcarbonylmethyl,[43] can release various carboxylic acids upon irradiation. The photochemistry of the 4-methoxyphenacyl moiety is discussed in Section 2.3.

In the presence of an electron donor, a mechanism involving electron transfer from the donor to the carbonyl group, followed by release of the leaving group, can also be accommodated (entry 2, Scheme 2). This PPG strategy will be discussed in Section 8.2.

When a relatively stable radical can be released from the α-carbon of the phenacyl group, phenacyl radicals are produced in the primary homolytic step. This has been demonstrated in the reactions of phenacyl halogenides[44] or azides.[45] An alternative mechanism, formation of the phenacylium cation from phenacyl ammonium salts, which are used as photoinitiators for cationic polymerization reactions, upon irradiation via a heterolytic cleavage of the C–N bond, has been proposed.[46] Recently Klán and coworkers demonstrated that readily accessible *S*-phenacyl xanthates undergo photoinitiated homolytic scission of the C–S bond in the primary step, opening their use as PPGs for alcohols in the presence of H-atom donating solvents, where the xanthate moiety represents a photolabile linker.[47]

The 4-acetyl-2-nitrobenzyl (ANB, **1**) moiety, substituted in both the benzylic and the phenacyl positions with leaving groups, has recently been proposed as a monochromophoric photocleavable linker (Scheme 3).[48] This linker thus combines the properties of two well-known photoremovable groups, 2-nitrobenzyl (Section 3.1) and phenacyl moieties, in a single chromophore. Liberation of R'CO_2H from the intermediate **2** requires the presence of an H-atom donor. Depending on the presence or absence of H-atom donors, the attached groups can be disconnected selectively and orthogonally upon irradiation in high chemical yields (88–97%).

2.2 *o*-Alkylphenacyl Groups

2-Alkylphenyl ketones readily photoenolize to the corresponding dienols (photoenols, *o*-xylylenols). For example, 2-methylacetophenone (**3**) undergoes intramolecular 1,5-hydrogen abstraction via the triplet state to form a triplet 1,4-biradical (enol, ^{3}**E**) that yields two isomeric, (*E*)- and (*Z*)-, photoenols, whereas fast direct enolization from the lowest excited singlet state produces only the (*Z*)-isomer (Scheme 4).[49] This scheme may serve as a blueprint for the reactions of related 2-alkylphenacyl compounds. The (*Z*)-isomer, having a lifetime similar to that of the triplet biradical, is generally converted efficiently back to the starting molecule via a 1,5-sigmatropic hydrogen transfer. Its lifetime is solvent-dependent because hydrogen bonding of the hydroxyl group to a polar solvent strongly retards intramolecular hydrogen back transfer.[49a] In contrast, reketonization of the (*E*)-dienols requires intermolecular proton transfer that may occur either by protonation of the methylene group by a general acid or by proton transfer from the enol to the solvent or a general base, followed by carbon protonation of the dienol anion.[49a] The resulting long lifetime of the (*E*)-isomers in dry solvents allows for thermal conrotatory ring closure to give benzocyclobutenols, or trapping by diverse dienophiles such as alkenes, alkynes, or carbonyl compounds in a stereospecific [4+2] cycloaddition reaction.[50] However, they may persist up to seconds in the absence of trapping agents. Photoenolization reactions have been thoroughly reviewed by Sammes in the 1970s,[51] recently by Klán et al.[52] and, to a modest extent, in several other reviews and book chapters.[8d,27,32,50,53]

When leaving groups are present on the α-carbon of 2-alkylphenacyl derivatives (**4**), they are released from the photoenol intermediates (Scheme 5). In general, the indanone[54] (**5**)

and benzocyclobutenol[55] (**6**) side-products are formed in non-nucleophilic solvents, while acetophenone derivatives substituted on the *o*-methyl group **7** are produced in the presence of a nucleophile, such as methanol.

This reaction, reported for the first time on phenacyl chlorides and bromides by Bergmark,[56] was shown by Klán and coworkers to be useful for PPG applications.[54b] Klán and Wirz later demonstrated that 2,5-dimethylphenacyl (DMP) can serve as a PPG for carboxylic acids,[57] phosphates, sulfonates,[54a] alcohols (as carbonates),[58] and amines (as carbamates).[59] It was recognized that only moderately good or excellent leaving groups are released efficiently within the photoenol lifetime. Studies by laser flash photolysis showed that photolysis produces the anticipated reaction intermediates, the short-lived triplet enol ^{3}**E** and two longer-lived, ground state photoenols assigned to the corresponding (*Z*)- and (*E*)-photoenols.[54a,57b,58] For example, the (*E*)-photoenol was found to have a sufficient lifetime (1–100 ms) to release carboxylic acids and carbonates, while the (*Z*)-photoenol (τ = 0.5–10 μs) regenerated the starting ketone.[57b,58] Irradiation of DMP esters in methanol efficiently releases the corresponding free acid (HX) along with indanone and 2-(methoxymethyl)-5-methylacetophenone as the major co-products, as shown in Scheme 5. The mechanism of DMP benzoate (**8**) photolysis, determined by LFP in degassed methanol, is displayed in Scheme 6.[57b] Three intermediates, a short-lived one, $\lambda_{max} \approx 340$ nm (triplet enol ^{3}**E**), and two longer-lived ones, $\lambda_{max} \approx 390$ nm (photoenols), were formed. In this case, only the longer-lived (*E*)-photoenol released benzoic acid via the triplet pathway with an appearance rate constant for benzoate of $k_{app} = 1/\tau(E\text{-enol}) = 4.5 \times 10^2\ s^{-1}$.

Structurally constrained phenyl ketones, such as 1-oxoindan-2-yl and 1,3-dioxoindan-2-yl derivatives, which can form only the short-lived (*Z*)-xylylenols, do not release carboxylic acids upon irradiation.[60] Only the chloride anion was found to be eliminated from the (*Z*)-xylylenol (τ = 23 μs in methanol) obtained from 2,5-dimethylphenacyl chloride via the singlet pathway.[61] To overcome the obstacle of leaving groups poor to escape from the short-lived photoenol intermediates, alcohols and amines were attached through a carbonate[58] or carbamate[59] linkage, respectively, which have similar leaving group properties to that of a carboxylate. For example, the galactopyranosyl carbonate **9** releases a carbonate monoester in a high chemical yield that disintegrates thermally into the corresponding alcohol **10** and CO_2 (Scheme 7)[58] on the millisecond time scale.[62] Table 3 summarizes the photochemical data for the DMP chromophore substituted by various leaving groups.

Until now, only a few applications of the *o*-methylphenacyl moiety as a photoremovable protecting group have been reported. Wang and coworkers used the DMP photoremovable group in polymer-supported synthesis,[63] and Park and Lee showed that this moiety can be part of new photoresponsive polymers.[64]

On the other hand, the photochemistry of α-substituted *o*-alkylphenacyl derivatives was utilized for the photochemical synthesis of interesting functionalized indan-1-ones. In such cases, releasing the leaving group is not of primary interest; it is designed to be a good leaving group and not to interfere with the course of the synthesis. Wessig and coworkers used this concept to prepare various synthetically interesting 1-indanone model derivatives[65] and later two sesquiterpene indane derivatives, pterosine B or C (e.g., **11**, Scheme 8), in which the key step is the photoenolization reaction of **12**.[66] Klán and coworkers showed that photolysis of 4,5-dimethoxy-2-methylphenacyl benzoate can lead to the corresponding indanone derivative that is a precursor for the subsequent synthesis of donepezil, a centrally acting reversible acetylcholinesterase inhibitor used to treat Alzheimer's disease.[67] Park and collaborators have recently shown that photolysis of 2,4,6-trialkylphenacyl benzoates can also lead to the corresponding benzocyclobutenols (**6** in Scheme 5) in addition to

indanones,[55] while irradiation of α-dichloro-2-acetophenone yields a mixture of various photoproducts.[68] Berkessel and coworkers used the photoenolization reaction as a tool to study the cyclization of 4'-benzophenone-substituted nucleoside derivatives as models for ribonucleotide reductases.[69]

Klán and coworkers reported that the photolysis of 2-(alkoxymethyl)-5-methyl-α-chloroacetophenones (**13**) is very sensitive to traces of water in the solvent (Scheme 9).[70] While 3-methoxy-6-methylindan-1-one (**14**) was a major product in dry, non-nucleophilic solvents, the isobenzofuran-1(3*H*)-one **15** was obtained in the presence of trace amounts of water. The authors demonstrated that the photoenols produced by photolysis of **13** add water as a nucleophile to yield 2-acetyl-4-methylbenzaldehyde (**16**), which subsequently forms **17** via a second, singlet state photoenolization reaction. The same research group also reported that irradiation of the 2,5-dimethylbenzoyl oxiranes **18** results in a relatively efficient and high-yield formation of β-hydroxy functionalized indanones that structurally resemble biologically active pterosines (Scheme 10).[71] In this case, a ring opening process, rather than release of a leaving group, follows the photoenolization step. An electronic excited-state switching strategy has been utilized to control the selectivity of this reaction in the total synthesis of indanorine.[72] The excited-state character of the parent compound was changed to create a productive ^{3}n,π* state by a temporary structural modification selected on the basis of quantum chemical calculations prior to the synthesis. In addition, competition of a triplet state photoenolization reaction with a photo-Favorskii rearrangement for (*o*/*p*)-hydroxy-*o*-methylphenacyl esters was shown to depend on the water content of the solvent.[73]

In the 1970s, Ullman and Tseng proposed a new PPG based on (2-hydroxyethyl)benzophenone derivatives (**19**, R = Ph, Scheme 11), having a leaving group attached in the benzophenone *ortho* position via an ethylene linker.[74] A recent methodical investigation by Pirrung and his coworkers was carried out in order to elucidate the scope and limitations of the deprotection reaction.[75] Alternatively, Wirz[7a] and later Banerjee and their coworkers[76] proposed a similar photoremovable protecting group based on the 1-[2-(2-hydroxyalkyl)phenyl]ethanone **19** (R = alkyl, Scheme 11). The leaving group was reported to be released with a low photochemical efficiency.[76] Interestingly, irradiation of 2-acetylphenyl- or 2-benzoylphenylacetic acid results in efficient release of CO_2.[77]

The same mechanism, photoenolization followed by heterolytic elimination of HX, was shown to operate in substituted 5-(ethylen-2-yl)-1,4-naphthoquinone (**20**, X = Br, dialkyl phosphate, carboxylate), a photoremovable protecting group that absorbs up to 405 nm and provides fast and efficient release of bromide or diethyl phosphate (Φ = 0.7 in aqueous solution) (Scheme 12).[78] The blue photoenol forms in the ground state within 2 ps of excitation and with a quantum yield of unity.[79]

Photoenolization reactions can also be used for releasing protected alcohols through intramolecular lactonization. Gudmundsdottir and her collaborators reported that the corresponding (*Z*)- and (*E*)-photoenols are produced by irradiation of the 2-(2-isopropylbenzoyl)benzoate ester **21** via the triplet excited state (Scheme 13).[8d,80] An alcohol, such as geraniol (in up to 90% chemical yield), and the side product **22** are formed in various solvents as well as in thin films. 2-(2-Methylbenzoyl)benzoate esters are not reactive under the same conditions.[80a] In addition, the 4-oxo-4-*o*-tolylbutanoate **23** releases methanol by a photoenolization-induced lactonization process (Scheme 14).[81]

2.3 *p*-Hydroxyphenacyl Groups

Among the known photoremovable protecting groups, *p*-hydroxyphenacyl (**24**, pHP, Scheme 2e, Scheme 15) has emerged as a promising candidate.[82] Since debuting a little over

a decade ago, the pHP chromophore has found application as a photoremovable protecting group in neurobiology,[7,83] enzyme catalysis,[7b,9u,83b,c] and synthetic organic chemistry.[84] The intriguing features of this protecting group are the skeletal rearrangement that accompanies the release of a substrate, the quantitative chemical yield of released product and the necessary role of water.[7,9u,82–83,85] Advantageous properties are the hydrophilicity of the pHP ligand, the high quantum yields, and the unusually clean reaction which yields only one significant byproduct.

The absorption spectrum changes drastically as the reaction progresses from a conjugated phenyl ketone (Figure 1) to a nonconjugated phenol, 4-hydroxyphenyl acetate (**25**, R = H, Figure 2). The purported intermediate (**26**) shown in Scheme 15 is reminiscent of the cyclopropanone intermediates proposed for the Favorskii rearrangement;[86] thus this transformation has been termed the photo-Favorskii rearrangement.[87]

p-Hydroxyacetophenone (pHA, **24**: X = H) serves as a model for the pHP chromophore. Figure 3 displays the absorption spectra of pHA in neutral water, of pHA^- in aqueous NaOH, and of protonated $HpHA^+$ in aqueous $HClO_4$.[89]

pHA (**24**, X = H) is also the basic framework for the synthesis of the parent pHP protecting group that accommodates an expanding number of leaving groups (HX).[7,9u,82–83,85d,e] Most of the leaving groups have been introduced through a sequence of bromination of pHA followed by its S_N2 displacement with the conjugate base of the leaving group (X^-) under basic conditions[82,83c,85a–c] (Scheme 16a–c). In some instances, protection of the phenol group by benzylation, silylation, or acetylation is required.

More complex syntheses are required for more reactive or highly functionalized leaving groups, such as protected nucleotides, i.e., pHP ATP (**24**, X = ATP),[82,83c,84,90] pHP GTP,[91] and ^{18}O-labeled isotopomers of pHP GTP.[91–92] *p*-Hydroxyphenacyl monophosphates are available either through displacement of pHP Br (**24**, X = Br) or through esterification of 2,4'-dihydroxyacetophenone.[85b] Dibenzyl, diphenyl and diethyl phosphates, for example, are sufficiently nucleophilic to undergo S_N2 replacement when the reagents and solvents are rigorously dried. The benzyl groups can be removed by hydrogenolysis with H_2/Pd after ketal protection of the phenacyl carbonyl.[82,83c] *p*-Hydroxyphenacyl phosphoric acid then can be coupled with ADP or GDP through their imidazolium salts to provide the protected nucleotides pHP ATP[82,83c,90] and pHP GTP,[90–91] respectively (Scheme 16d). These protected nucleosides have found several applications in studies on enzyme catalysis. An advantage of this sequence is the ability to introduce site-specific ^{18}O-labeled isotopomers of GTP[90–91] that are employed as probes for functional group assignment and dynamic changes in time-resolved Fourier transform infrared (TR-FTIR) studies. Of the leaving groups thus far explored, sulfonates,[9u,85d,93] phosphates,[7,9u,82–83,85a–d,90–93] and carboxylates,[7,9u,83,85a–c,93] are the most efficacious and therefore most commonly encountered.

Another, less frequently encountered synthetic method employs addition of α-diazo-*p*-hydroxyacetophenone (**27**) to the conjugate acid of the leaving group (HX) under acidic conditions (Scheme 17).[93] This approach is particularly useful for protection of highly reactive or base sensitive leaving groups. Advantages of the diazoketone approach include the ease of synthesis of a variety of substituted diazoacetophenones and the mild conditions for the coupling reaction. The yields are generally good and the only byproduct is N_2. Furthermore, protection of the phenolic OH group or other, less acidic functional groups on the leaving group is normally unnecessary. When the phenolic OH does require protection, the acetate ester is either retained or otherwise readily prepared and is later removed by mild hydrolysis.

The excited state equilibria of *p*-hydroxyacetophenone (**24**, X = H; pHA) reflect the important nonproductive reactions and the photophysical properties of pHP. A recent, detailed study[89] of the primary photophysical processes of pHA and the ensuing proton transfer reactions in aqueous solution by picosecond pump–probe spectroscopy and nanosecond laser flash photolysis has provided a comprehensive reaction scheme (Scheme 18): Following fast and quantitative ISC of excited pHA, $\tau(^1\text{pHA}^*) = 3.4$ ps, to the triplet state, ^{3}pHA*, spontaneous adiabatic ionization of ^{3}pHA* in aqueous solution occurs with a rate constant $k_{H^+} \approx 1 \times 10^8\ s^{-1}$ yielding the triplet of the conjugate base anion $^3\text{pHA}^{-}$* and, simultaneously, the quinoid triplet enol tautomer ^{3}pQ*. The latter is formed by *in-cage* capture of a proton at the more basic carbonyl oxygen of $^3\text{pHA}^{-}$*. The equilibrium ^{3}pQ* $\leftrightarrows$ $^3\text{pHA}^{-}$* + H^+ is established subsequently by diffusional processes on the nanosecond time scale. The formation of ^{3}pQ* from ^{3}pHA* is accelerated by strong acids (via the protonated species $^3\text{HpHA}^{+}$*) and is suppressed by buffer bases, which form $^3\text{pHA}^{-}$* upon encounter with ^{3}pHA*. The triplet state proton transfer equilibria of ^{3}pHA* are summarized in Scheme 18.[89]

It has been suggested[89] that similar proton transfer processes may account for the lower-than-unity quantum yields found for most pHP PPGs, especially those carrying poor leaving groups, as formation of the less reactive pHP triplet anion and the nonreactive triplet quinone enol represent energy-wasting pathways.[85d,e,94] Furthermore, earlier studies on pHP phosphate and carboxylate esters had documented the importance of aqueous solvents for the photochemical release of the leaving group, the rearrangement of the chromophore, and the role of the triplet state as the reactive excited state, i.e., a short-lived, quenchable triplet (E_T = 71.2 kcal mol^{-1}).[82,83c] Subsequent work by Wan and Corrie,[95] Phillips[85a,b,96] and Givens, Wirz, and coworkers[7,9u,83b,c,85d,94,97] added a rich compilation of spectroscopic and kinetic information. Recently, the effect of ring size on the photo-Favorskii induced ring-contraction reaction of various hydroxybenzocycloalkanonyl acetate and mesylate esters has provided new insight into the mechanism of the rearrangement.[98]

The Phillips group assigned electronic configurations of the key excited states, confirming the triplet state as the reactive excited state, using a combination of time-resolved transient absorption, fluorescence, and Resonance Raman spectroscopy, and femtosecond and picosecond Kerr-gated Resonance Raman spectroscopy (KTRF). An examination of the weak fluorescence from *p*-hydroxyphenacyl acetate (pHP OAc; **24**, X = OAc) in anhydrous CH_3CN revealed that the excited singlet manifold of the pHP chromophore is composed of two fluorescing states, a $^1\boldsymbol{\pi},\boldsymbol{\pi}^*$ (334 nm) state and a lower lying $^1\text{n},\boldsymbol{\pi}^*$ (427 nm).[96a] The positions of the two emission bands are influenced by the solvent: in more polar, aqueous media (e.g., 90% aq. CH_3CN), the two bands are shifted toward one another to 356 nm and 392 nm, respectively, or to an energy difference between the $^1\boldsymbol{\pi},\boldsymbol{\pi}^*$ and $^1\text{n},\boldsymbol{\pi}^*$ states of 7.4 kcal mol^{-1} from an energy difference of 18.7 kcal mol–^{1} in anhydrous CH_3CN. The shift enhances the overlap of the two states resulting in increased vibronic coupling and consequently more efficient internal conversion to the lower $^1\text{n},\boldsymbol{\pi}^*$ state. DFT calculations of the electronic states of pHP OAc further suggest that the $^3\boldsymbol{\pi},\boldsymbol{\pi}^*$ state (E_T = 72.9 kcal mol^{-1}) lies just below the $^1\text{n},\boldsymbol{\pi}^*$ state (E_S = 75 kcal mol^{-1}) and is sandwiched between the $^1\text{n},\boldsymbol{\pi}^*$ singlet and the nearby $^3\text{n},\boldsymbol{\pi}^*$ state (71.5 kcal mol^{-1}).[85a,95–96,99] The authors suggest that the surfaces of these three states[31] merge resulting in enhanced intersystem crossing (Φ_{ST} = 1.0) with a rate of $k_{isc} = 5 \times 10^{11}\ s^{-1}$ to a nearly degenerate, "mixed $^3\text{n},\boldsymbol{\pi}^{*-}\ ^3\boldsymbol{\pi},\boldsymbol{\pi}^*$" state. Their findings reaffirmed the important role of water on the photophysical and photochemical processes of pHP.[96a]

For instance, the ps-KTRF studies showed that added water made only a small difference in the growth rate of the triplet (from 7 to 12 ps), but greatly influenced its decay rate, resulting in second-order quenching of the triplet.[96a] A solvent change from anhydrous to 50%

aqueous CH_3CN caused a 100-fold diminution in the $^3\pi,\pi^*$ triplet lifetime. Phillips attributed the large decrease in the lifetime to a leaving group effect: pHP OAc, with the poorer leaving group, had nearly the same triplet time constant in neat, air-saturated CH_3CN as that of pHP diethyl phosphate (pHP DEP, 150 ns). In the aqueous media, both triplet lifetimes decreased, but the pHP OAc lifetime ($^3\tau$ = 2.13 ns) was five times longer than the lifetime of the more reactive pHP DEP ($^3\tau$ ~ 420 ps; 70% CH_3CN).[96a]

The most important mechanistic information obtained by Phillips' group was from the picosecond time-resolved resonance Raman (ps-TR-RR) results of the 600–1600 cm^{-1} spectral region measured during photolysis of pHP DEP (Figure 4). Scans taken in the first few ps show only diffuse, weak absorption signals attributable to the excited singlet and triplet states of pHP DEP. At approximately 300 ps, the scans show the emergence of four new bands that become prominent after 0.7 to 1.0 ns and by 6 ns are the only bands remaining. These four peaks precisely match those obtained with an authentic sample of the photoproduct, *p*-hydroxyphenylacetic acid (**25**, R = H). This TR-RR profile sets the reaction time-constant for the rearrangement and, therefore, encompasses the period for both the release of the leaving group and the rearrangement of the chromophore. In fact, the rearrangement product is in full bloom within just one or two ns, demonstrating both that the leaving group has departed and, more strikingly, that the complex rearrangement including any intermediates that may intervene between the excited triplet state and **25** had silently formed and then expired completely escaping ps-TR-RR detection. Based on a kinetic analysis of the appearance of **25**, Phillips showed that such a silent intermediate or intermediates were necessary. He assigned a candidate for the intermediate to 'M' to a *p*-quinone methide cation that was formed by direct heterolysis of the leaving group from triplet pHP DEP. This assignment was corrected in a later study (vide infra).[100]

Another significant result came from the analyses of the photolysis products from a series of pHP substituted acetate esters in Corrie and Wan's study.[95] The acetates were chosen for their increasing propensity toward decarboxylation when converted to carboxy radicals by photoinduced homolysis of the corresponding arylmethyl esters. Photolysis of the pHP esters, i.e., acetate, phenylacetate, pivalate, and diphenylhydroxyacetate, however, produced only carboxylic acids in >90% yield, free of any radical derived decarboxylation products.[101] This confirmed the heterolytic pathway suggested by Givens,[85d,e] Falvey,[40] and Phillips.[99–100]

The next layer of evidence on the photo-Favorskii mechanism arose from time-resolved transient absorption (TR-TA) studies[85d] which revealed two additional reactive intermediates, an early, very short-lived transient appearing on the tail of the triplet decay (Figure 5) and a later, long-lived species. The critical evidence for the first transient was obtained using pHP OTs (**24**, X = OTs), OMs, and DEP, all excellent leaving groups that depart efficiently and rapidly. For example, the transient formed from ^{3}pHP DEP (lifetime, $^3\tau$ = 63 ps; in water) appears as a weak set of absorptions on the tail of the pHP triplet. These three maxima were assigned to an allyloxy-phenoxy triplet biradical (^{3} **28**, Scheme 19): the decay profile of ^{3} **24** ($^3\tau$ = 100 ps in 87% aqueous CH_3CN) transforms into the profile of the slightly longer-lived transient ^{3} **28** (τ_{birad} = 500 ps).

The three weak absorptions of **28** were detected[85d] only with the best leaving groups. The bands at 340, 430 and 440 nm were taken as evidence of a phenoxy radical intermediate and thus assigned to the biradical **28**. As noted earlier, kinetic analysis of the ps-TR-RR spectra by Phillips[85a,b] had suggested the intervention of an intermediate "M", formed from the triplet state that proceeded to the final product **25**. The intermediate "M" is now attributed[85d] to the triplet biradical ^{3}**28** that is assumed to be formed adiabatically. The formation of ^{3}**28** can be viewed as being extruded from ^{3}**24** leaving behind the leaving

group X^- and a proton in the ground state, thus obeying the Wigner spin rule. The fate of ^{3}**28** is ISC and closure to an as yet undetected spirodienedione **26**. The resulting traditional Favorskii-like intermediate very rapidly hydrolyzes to *p*-hydroxyphenylacetic acid completing the formal ground state events normally proposed for the Favorskii rearrangement.[102]

A further, long-lived intermediate was identified as the known *p*-quinone methide[103] **29** (τ = 0.3 s) which hydrates yielding *p*-hydroxybenzyl alcohol (**30**).[85d] The formation of small amounts of **30** is also a signature of the elusive spirodione intermediate **26**, the lifetime of which appears to be shorter than its rate of formation under the reaction conditions. Thus, the validation of **26** is based solely on a requirement for the carbon skeleton reorganization and a very facile CO extrusion from **26** due to its strained bicyclic structure, and complemented by DFT calculations.

The full photo-Favorskii mechanism, as currently understood, is outlined in Scheme 19. The main course of the reaction proceeds through a concerted elimination of the leaving group and a proton to generate ^{3}**28**. It is suggested that ^{3}**28** relaxes to hypothetical intermediate **26** that yields the products of rearrangement and decarbonylation. However, alternative concerted loss of HX with intersystem crossing to form **26** directly has not been entirely ruled out. Yet further studies will be necessary to unravel this conundrum.[104]

The Position and Requirement for a *p*-Hydroxy Group—Unsubstituted phenacyl, which is also a PPG (Section 2.1), does not undergo a photo-Favorskii rearrangement but rather reacts through a photoreduction mechanism. The *p*-OH modification of the phenacyl chromophore causes a profound change in the photochemical behavior. The search for alternative functional groups or other locations of the OH group on the phenacyl chromophore that would accommodate a Favorskii rearrangement pathway has met with very little success and only in the case of the *o*-hydroxyphenacyl analog.[73] *m*-Hydroxyphenacyl acetate and a 5-hydroxy-1-naphthacyl analog were unreactive under photo-Favorskii conditions.[105]

Electron donors such as *p*-methoxy and *o*-methoxyphenacyl have been tested as early as the seminal report of the photo-Favorskii rearrangement by Anderson and Reese.[87] For these examples, the photo-Favorskii rearrangement competes with photoreduction, forming mixtures of the corresponding methoxyacetophenones and phenyl acetates. In the early 1970's Sheehan developed the *p*-methoxyphenacyl derivatives as a PPG for photolysis in dioxane or ethanol, producing reduction products.[39,106] Givens later showed that the reaction in methanol or *t*-butanol (hydroxylic solvents) did undergo the Favorskii rearrangement as the major pathway yielding *p*-methoxyphenylacetates. The competing photoreduction pathway was also evident from the significant proportion of reduction to *p*-methoxyacetophenone. [107] Phillips and coworkers showed that *p*-methoxyphenacyl diethyl phosphate undergoes a rapid heterolytic cleavage that results in deprotection and formation of a solvolytic rearrangement product.[108]

Other electron donating substituents have met with even less success toward the rearrangement of the chromophore.[82] While several *p*-methoxy and other *p*-alkoxy analogs have been successfully employed as PPG's for the release of carboxylates,[39,106,109] phosphates,[82,107] carbonates and carbamates,[110] they do not lead to rearrangement of the chromophore.

The Nature of the Leaving Group—The most efficacious leaving groups are conjugate bases of moderate to strong acids, e.g., sulfates,[85d,93] phosphates[7,9u,82–85,99] (thiophosphate),[100,111] carboxylates[7b,9u,85a–c,93–95,97b,c,112] phenolates[9u,93] and

thiolates.[111,113] In general, quantum yields monotonically decrease with an increase in the acid leaving group's pK_a (Table 4), conforming to a Brøsted leaving group relationship (β_{LG}) which correlates the pHP release rate constant with the K_a of the leaving group. A correlation of the log of the rate constants (log k_r), derived from the quantum yields and the triplet lifetimes as $k_r = \Phi/^3\tau$ (see Table 4[b] for details) with the pK_a of the leaving groups gave ($\beta_{LG} = -0.24 \pm 0.03$).[9u,114]

The good quantum efficiencies and high appearance rate constants of the free substrates ($k_{app} = 1/^3\tau$) make the pHP protecting group attractive for quantitative and mechanistic studies in biology and physiology.[9u] Other beneficial features include good aqueous solubility and stability, ease of synthesis, the biologically benign quality of the pHP group and its photoproducts, and the lack of quenching by adventitious O_2 in aqueous solvents.

ATP and GTP release from the pHP protected nucleotides has been extensively investigated resulting in pHP becoming the "phototrigger" of choice for fast kinetic studies of the enzyme catalyzed hydrolysis by Ras and Rap GTPase Activating Proteins (GAP proteins).[90–92] The phototrigger methodology for activating hydrolysis by photodeprotection of GTP or ATP is rapid (an appearance rate constant $k_{app} = 1/^3\tau = 1.6 \times 10^{10}$ s^- as measured for pHP diethyl phosphate in water[99]) and was assumed by the authors to be sufficient for measuring the kinetic rate constants for most subsequent binding and hydrolysis steps for the nucleotide.[116] Thus, the pHP protecting group provides researchers with a powerful arsenal for fast-kinetic mechanistic investigations.

Köting and Gerwert, for example, compared the release rates for pHP versus NPE (1-(2-nitrophenyl)ethyl; Section 3.2) GTP esters (Figure 6).[116] The rise time for photorelease of GTP from pHP GTP was too fast to record by their TR-FTIR instrument (τ_{rise} = 10 ms), whereas they were able to monitor the NPE GTP appearance rate constant ($k_{app} = 2 \pm 1$ s^{-1}, Figure 6). They then exploited the rate advantage of pHP GTP to study the catalytic GTP hydrolysis by Ras GTPase and other GAP-based catalytic hydrolysis mechanisms.

In pursuing the mechanistic pathway for Ras GTPase catalysis, comparisons of the FTIR spectra of individual α, β and γ-^{18}O-labeled and unlabeled phosphates of GTP, inorganic phosphate (P_i), and GDP hydrolysis products as well as ^{13}C and ^{14}N-labeled site-specific amino acids provided detailed information on both bonding and environmental changes at the enzyme active site. TR-FTIR was then employed to monitor the changes in binding and the evolution and decay of the intermediates during hydrolysis as well as the product release step and to determine the rate constants.[92] Figure 7 illustrates the power of TR-FTIR to resolve the changes in structure and binding at the labeled sites as a function of reaction time. Scheme 20 summarizes the key steps for the hydrolysis, beginning with initial binding of free GTP and ending with the release of inorganic phosphate (P_i) from the enzyme 'pocket', in the rate limiting step that controls signal transduction. In contrast, with NPE GTP as the phototrigger, only the (last) rate limiting step could be determined.[92]

For thiolates, the nucleophilicity of leaving group is especially noteworthy because leaving groups can readily be protected through *in situ* derivatization. pHP Br can be added directly to thiols and thiophosphates, even in the presence of other nucleophilic groups on the substrate or in the media. Direct derivatization of thiols and thiophosphates has been exploited for peptides and proteins that possess exposed cysteine and thiophosphate residues, an especially useful feature when the thiol group is an integral part of the catalytic center.[115] Model reactions where pHP Br was reacted directly with 3'-thio-deoxythymidine, cysteine, and glutathione produced the corresponding pHP thioethers in 80–90% yields in buffered solutions (Scheme 21). Deprotection by irradiation at 300–365 nm releases the thiol in 60–70% yield, performing essentially as a protection-deprotection switch.

The switch sequence was employed by Pei[113] and by Bayley.[111] Pei inhibited the phosphorylation of a cysteine located at the active site of protein tyrosine phosphatases (PTK) by direct addition of pHP Br. The phosphorylated cysteine turned "OFF" PTK, a common type of suicide inhibition employed with other phenacyl halides. However, photolysis of the pHP thiolates freed the catalytic cysteine unit turning PTK back "ON". Interestingly, the protection step was regioselective for blocking only Cys 453, the cysteine at the catalytic site, and none of the other three available cysteine residues.

The protection-deprotection sequence was also reported for the C subunit of protein kinase A (PKA) at Thr-197 and for a thiophosphorylated tyrosine (Y) on a model 11-aa peptide, EPQ**Y**EEIPILG by Bayley's group.[111] Two PPG's were compared: reacting thiophosphate with *o*-nitrobenzyl bromide (75%) and protection with pHP Br (90%). Deprotection proved more difficult with the *o*-nitrobenzyl (oNB, Section 3.1) thioether because the nitrosobenzaldehyde as a side-product reacted with the newly exposed thiol causing inhibition. The quantum yield for the reaction was modest (0.37). pHP deprotection was more efficient ($\Phi = 0.56$ to 0.65) and the 70% recovery of the activity was higher because there were no competing reactions of the byproducts with the exposed thiophosphate. This methodology was transferrable into *in vitro* cell machinery by simply importing the pHP Br into human B cells.[111]

Substituent effects on the chromophore—Very recently, a number of new *ortho* and *meta* substituted *p*-hydroxyphenacyl PPGs were introduced to extend the versatility by absorbing at longer wavelengths and by altering the solubility properties. The influence of substituents on the chromophore's physical, spectral and mechanistic capabilities, by necessity, became the target of several studies. GABA was selected as the common leaving group because it imparted good aqueous solubility and is biologically significant. Quantum yields of a representative collection of 2- and 3-substituted pHP GABA's (Table 5) vary only modestly for these substituents. *meta*-Electron donors such as 3-OCH_3 generally display lowered quantum yields whereas electron withdrawing groups such as 3-CF_3 and 3-CN often give rise to slightly increased yields. The rate constants for release are consistently high, in the range of 10^9 s^{-1}.[94]

Certain groups quench the reactivity completely. Among these are the *meta*-attached NO_2, OH, and $COCH_3$ and the *ortho*-OH under normal photo-Favorskii photolysis conditions.

In addition to GABA, there are many other small molecule and amino acid neuroactive agonists and antagonist with carboxylic acid end groups. Although carboxylate release is generally less efficient than those of phosphates and tosylates, caged carboxylates find useful applications in neurobiology and neurophysiology, taking advantage of the rapid rate of release and the unreactive, benign qualities of **25** photoproduct vis-à-vis *o*-nitrobenzyl-based PPG's (Section 3.1).[92,97b,c,117] Substituent modification of the pHP derivative **32**, such as the 3-CF_3 and 3-OCH_3 pHP GABA compounds shown in Scheme 22, expand and extend the versatility of the PPG methodology. Here, the relative efficacy of modified pHP GABA to stimulate the $GABA_A$ receptor is documented in Figure 8.

The effect of *m*-methoxy, trifluoromethoxy and trifluoromethyl groups on pHP caged GABA's were tested for their efficacy to release GABA in whole-cell patch clamp studies on neurons in cortical slices. Local photolysis with short UV light pulses (10–50 ms) delivered through a small-diameter optical fiber produced transient whole-cell inward currents from released GABA.[97b]

Effect of Media pH and pHP pK_a—Because the ionization of substituted pHP derivatives to their conjugate bases change during irradiation in unbuffered media (Figure

3), the pH effects on the pHP photochemistry were examined (Table 6). The extent of quinone methide formation is altered also by the pH and the substituents on the chromophore (Scheme 18).

Raising the pH above 8 lowers the quantum yields, reflecting the lower reactivities of the conjugate bases (Table 6). In all cases, the quantum yields were maximal in neutral or slightly acidic conditions but dropped at higher pH. As shown for the pK_a's of the corresponding acetophenones, there is a substantial substituent effect on the pK_a which is manifested in a pronounced UV-vis spectral change (see Figure 3). The prominent π,π^* transition at 260–280 nm for neutral *p*-hydroxyacetophenone is shifted to 320–340 nm, the π,π^* transition for the conjugate base, and the absorptivity nearly doubles.

The resultant interplay of pK_a of the substituted pHP derivative and the pH of the solution influence the quantum yield as illustrated with 3-CF_3 pHP GABA. The quantum yields at pH 5 (Φ = 0.24) decrease to half of their value when the pH is 7.3 (Φ = 0.12) and a third at pH 9.2 (Φ = 0.08). Product yields remain the same at all three pH values demonstrating that the photo-Favorskii rearrangement is still the major reaction pathway for the conjugate base.

These initial results on substituted pHP protecting groups show promise for extending their use in chemistry, physiology and biochemistry.

2.4 Benzoin Groups

In the course of their groundbreaking studies on benzoin (desyl alcohol; Figure 1; Scheme 2, entry 6) acetates, Sheehan and Wilson determined that the 3',5'-dimethoxybenzoin (DMB, **33**, X = OAc) derivative performed best as a PPG of acetate.[4,118] The reaction proceeded in an extraordinarily smooth fashion as illustrated by the spectra shown in Figure 9. The expected product 2-phenyl-5,7-dimethoxybenzofuran (**34**, DMBF, Scheme 23) was formed in quantitative yield and the quantum yield was determined as 0.64 ± 0.03. The authors noted that the photocyclization of DMB acetate was not quenched by either naphthalene or neat piperylene, and they concluded that the reaction proceeds from the excited singlet state or an extremely short-lived triplet state.

It has taken substantial efforts to elucidate the detailed mechanism of this reaction, and a clear picture (Scheme 24) has emerged only in recent years. Time-resolved work on DMB-derivatives was performed by the groups of Trentham,[119] Wan,[120] Simon,[121] Wirz,[122] and Phillips.[123] By ns-LFP of several DMB carboxylate esters (**33**, X = OCOR) in dry acetonitrile, Corrie and Wan[120] observed a strong transient absorption at 485 nm that was formed within the lifetime of their laser pulse (~10 ns) and decayed with a lifetime of 1 μs. This transient was assigned to the cyclohexadienyl cation (**35**, Scheme 24). An additional transient absorption with μs-lifetime was observed at λ_{max} = 330 and 420 nm. Introduction of air resulted in a faster decay of this transient, but did not affect the lifetime of the 485-nm transient or the yield of the final product **34** (DMBF). The (330, 420)-nm transient was therefore assigned to the (non-reactive) triplet state of the DMB esters (^{3}**33**). These assignments have stood the test of time. However, subsequent studies with better time resolution showed that heterolytic cleavage of the excited singlet state is not, as claimed,[120] the primary photochemical step of DMB esters, and that the cyclohexadienyl cation is not even an intermediate along the predominant reaction path releasing the substrate HX.[122,123b]

Pump–probe experiments of DMB acetate and fluoride (**33**, X = OCOMe, F) with picosecond time resolution revealed a preoxetane biradical intermediate **36**, λ_{max} = 355 nm, that was formed from the singlet state, τ = 17 ps, and decayed with a lifetime of 1–2 ns.[122] The biradical **36** was shown to be the precursor of the cyclohexadienyl cation **35**, λ_{max} = 485 nm, the lifetime of which was found to be strongly reduced by the addition of water to

the acetonitrile solution, $k_w = 6 \times 10^6\ M^{-1}\ s^{-1}$. This work proved that the reactive intermediate is the biradical **36**, which releases the DMB-caged ligands HX on a time scale of 1–2 ns, largely independent of the leaving group ability of X. Thus, DMB is an excellent PPG for the kinetic investigation of fast processes such as protein folding.[124] The existence of a biradical intermediate **36** had been proposed earlier on the basis of preparative work by Rock and Chan, who also showed that a benzoin side-product (**37**) is formed in aqueous solution.[125] Otherwise, the reaction proceeds cleanly and efficiently in both polar and apolar solvents.

In the most recent time-resolved study of DMB phosphate (X = $OPO(OEt_2)$ Phillips and co-workers[123b] investigated the ultrafast primary photophysical processes by absorption spectroscopy and provided evidence for the formation of an intramolecular charge-transfer singlet state (S_1, τ = 14 ps) as had been proposed earlier.[120] Moreover, using nanosecond time-resolved resonance Raman spectroscopy, they proved that the final product **34** (DMBF) is largely formed within the time resolution (~10 ns) of their setup. It was postulated that DMBF is formed by concerted HX elimination directly from the biradical **36**, largely independent of the solvent, and that the cyclohexadienyl cation is not a precursor of DMBF. Nevertheless, earlier ns-LFP experiments had shown that a second, minor wave of DMBF is also released from the cyclohexadienyl cation on a time scale of 1 μs in dry acetonitrile.[122,126] Finally, Phillips and co-workers[127] reported extensive CASPT2 calculations in support of the ultrafast primary processes that they had observed by transient absorption.[123b]

The photoreaction of parent benzoin derivatives follows an entirely different course (Scheme 25). Givens and Matuszewski reported that irradiation of benzoin diethyl phosphate (**38**, X = $OPO(OEt)_2$; BDP) in acetonitrile proceeds cleanly and quantitatively with a quantum yield of 0.28.[128] Stern–Volmer quenching studies with either piperylene or naphthalene indicated that the reaction proceeds via the triplet state with a lifetime of a few nanoseconds. A study using ps-pump–probe and ns-LFP of BDP was reported by Rajesh et al.[129] The assignment of the observed transient intermediates was assisted by DFT calculations. Two competing reaction paths of diethyl phosphate elimination proceed from the triplet state of BDP: Reaction via path a) yielding **39** (R = H or CH_2CF_3) predominates in water and 2,2,2-trifluoroethanol (TFE), while exclusively path b) yielding 2-phenylbenzofuran (**40**) is followed in acetonitrile. Path a) proceeds via a transient intermediate, λ_{max} = 570 nm, that was attributed to the triplet state of the carbocation formed adiabatically from ^{3}**38** by heterolytic release of the phosphate anion. A triplet multiplicity of the cation ^{3}**41** was indicated by the observation of oxygen quenching, $k_q \approx 1 \times 10^9\ M^{-1}\ s^{-1}$, and by the fact that its lifetime in water (430 ns) is similar to that in the much less nucleophilic solvent TFE (660 ns). This indicated that the rate-determining step for hydrolysis of the triplet cation is ISC to the singlet ground state. For both pathways, the reactive intermediate releasing diethyl phosphate is thus the excited triplet state with a lifetime of about 10 ns.

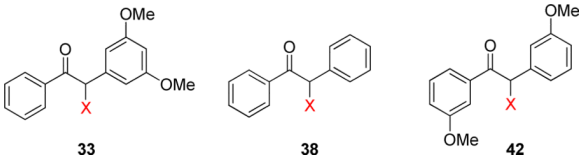
The assignments of the observed transients have been largely confirmed and corroborated by Phillips and coworkers using fs-pump–probe and ns-resonance Raman spectroscopies as well as DFT calculations.[130–131] The formation and decay of the cation intermediate in 75% aqueous acetonitrile solution was measured by ns-time resolved resonance Raman spectroscopy. An essential difference from the previous study[129] is that two cationic species appeared in sequence: The first of these (main feature at 1560 cm^{-1}), which was formed within the rise time of the instrument (~10 ns), was attributed to the triplet cation ^{3}**41** with optical absorption at 570 nm. The 1560-cm^{-1} signal decayed with a lifetime of 100 ns forming another transient species (main feature 1626 cm^{-1}), which decayed with a lifetime of 200 ns and was attributed to the singlet ground state of the cation (**41**). The lifetime of the

short-lived species (100 ns, 1560 cm^{-1}) was reduced by purging the solution with oxygen. It is hard to reconcile the observations by optical LFP[129] and Raman spectroscopy[130] and more work may be required to settle this point.

Very soon after the initial reports on PPG's, Sheehan published the photoconversion of substituted benzoin esters into benzofurans with the concomitant loss of acetate (**38**, X = OAc, Scheme 23).[4,132] Several years later he exploited this reaction as a PPG for carboxylic acids.[118]

The benzoin group remained remarkably underutilized for two decades, until Baldwin and coworkers used it for the photorelease of phosphates. Thus, phosphate derivatives of **33**, **38**, and **42** (X = OPO_3^{2-}) were investigated, and all three released inorganic phosphate upon irradiation with a laser at 308 nm or 355 nm with appreciable yields (35–55% under continuous irradiation).[106a]

Although, as Sheehan had already pointed out in his initial studies, the 3',5'-dimethoxybenzoin derivative **33** was the most reactive, easier synthesis of the symmetrical benzoin derivative **38** made it equally attractive. Doubts on the purity of the substrates prompted another study, which provided a reliable preparative method for the phosphate (X = OPO_3^{2-}) and esters (X = OAc), rendering **33** an ideal candidate for a fast and clean release of phosphates.[119] The same PPG was used to protect the 3'-phosphate of nucleotides.[133]



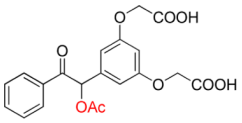
DMB phototriggers have been extensively used for applications in drug delivery,[134] muscle relaxation studies,[119] lithography,[135] biochip fabrication,[133,136] protein folding and unfolding,[124] or for masking a photochemical switch.[137] cAMP derivatives of **38** were also able to release cAMP upon photolysis.[107b,107c,138] Likewise, glutamate and GABA were released from **38**, with the PPG at the γ-carboxyl group (Scheme 26). However, neither the α- nor the *N*-protected derivatives of **38** led to a clean photolysis.[139]

Various types of leaving groups, such as amines, can be released from derivatives of 3',5'-dimethoxybenzoin (**33**).[140] While there are no photochemical reasons preventing the use of a whole array of leaving groups, the sometimes delicate preparation of certain derivatives has to be considered. α-Ketol rearrangement can scramble the position of the methoxy groups on *both* arenes, and an activated ester precursor can react intramolecularly into an inert cyclic product. However, carbamates could be prepared by the reaction of **33** (X = OH) with cyclohexylisocyanate or by preparing the *p*-nitrophenyl mixed carbonate.[140c,141] They were utilized for the photogeneration of bases in films.[142] In the solid state, **33** released cyclohexylamine with Φ = 0.067 (254 nm), 0.08 (313 nm), 0.054 (336 nm), and 0.028 (365 nm). The liberated benzofuran side product absorbs at shorter wavelengths; this photobleaching is crucial for applications in thick films, allowing light to reach deeper layers. Again, the methoxy groups on the benzylic side were found to be important for the reactivity; other substituents on the benzoyl side also had an impact, but less significant. An alternative preparative method was devised by Pirrung, where the benzoin is allowed to react with carbonyl diimidazole (preactivated by methyl triflate), followed by the amine.[140b] Primary amines, however, failed to give the desired carbamate and gave instead the cyclic product mentioned above.

The activation procedure with carbonyldiimidazole proved efficient also for the preparation of carbonates, thus allowing **33** to release alcohols (X = OCOOR). It was used to protect the 5' primary alcohol of nucleotides,[135b] various kinds of alcohols, or benzylthiol.[136]

The protection of chiral molecules (such as nucleotides) can be problematic with DMB, because it also bears a stereogenic center. Access to an enantiopure derivative of **33** would therefore be highly desirable. Enantioselective syntheses of **33** have been published, using enantiopure TMS-protected cyanohydrins generated either by asymmetric catalysis or enzymatic resolution (Scheme 27).[143] Addition of an aryl-Grignard reagent to the nitrile, followed by acidic hydrolysis, leads to chiral unsymmetrical benzoin. When asymmetry is not required, more straightforward routes are available, in particular by using a dithiane as a benzoyl anion equivalent.[144] This method was used to prepare derivatives of DMB that could release a phenol (ubiquinol),[145] or as a linker for peptides.[144] This dithiane route was cleverly exploited in a safety-catch strategy, where keeping the carbonyl function masked prevented any photolytic activity, whereas hydrolysis restored the initial sensitivity.[146] A related strategy was recently proposed, where the carbonyl group is masked as a dimethyl ketal, which can be smoothly hydrolyzed into the photolabile benzoin derivative (3% TFA in CH_2Cl_2, 5 minutes).[147]

As will be mentioned in the next chapter on nitrobenzyl derivatives (Section 3.1), water-insolubility is a major issue when the release of bioactive material is sought under physiologic conditions. Thus, the water-soluble derivative **43** was prepared. The possibility of carrying out the photolysis in aqueous solution gave an additional hint in favor of the cationic mechanism (Scheme 24), as the free DMB alcohol was also observed as a side product, in addition to the expected benzofuran.[125]



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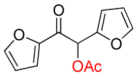

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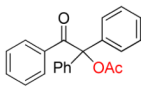


45

Attempts to improve the reactivity by further modification of the main core were proposed, such as the replacement of both aromatic groups by the 2-furyl moiety. Dipeptide esters of this "furoin" analogue **44** indeed could be deprotected, but in lower yields than the parent structure.[148] On the other hand, esters of the achiral 1,2,2-triphenylethanone **45** proved to be as reactive as **33** (DMB) (Scheme 28).[149] The diphenylbenzofuran side product continues to react under irradiation to form a more conjugated heterocycle.

Chirality in the PPG is not necessarily a problem, and can actually be exploited. Klán et al. used enantiopure acrylate derivatives as a *photoremovable chiral auxiliary* (PCA). Thus, the acrylate **46** reacted in a highly enantioselective manner with cylclopentadiene in the presence of a Lewis acid, and the cycloadduct was photolyzed ($\Phi = 0.43$) at 313 nm to give the Diels-Alder *exo* product as the main diasteroisomer, with *ee*'s up to 96% (Scheme 29).[150]

The photochemistry of several benzoin derivatives is summarized in Table 7.

3 NITROARYL GROUPS

3.1 *o*-Nitrobenzyl Groups

o-Nitrobenzylic derivatives have been widely used despite their disadvantages. They were proposed as general PPGs in 1970,[3] but there were earlier reports on their

photochemistry,[151] including the one on the photoisomerization of *o*-nitrobenzaldehyde into the corresponding nitrosobenzoic acid.[152]

Hydrogen transfer from the *o*-alkyl substituent to the nitro group forming an *aci*-nitro tautomer in the ground state is commonly taken to be the primary photoreaction of *o*-alkylnitroarenes. Parent *o*-nitrotoluene (**47**, oNT, Scheme 30) and several derivatives have been studied by time resolved spectroscopy.[153] The most recent investigation of oNT and the analogous *o*-nitrobenzaldehyde by Gilch and co-workers,[154] who used femtosecond transient absorption and stimulated Raman spectroscopy, has finally provided a convincing and complete picture of the early events. The results reported by these authors about oNT[154a] are summarized in Scheme 30, which bears a striking similarity to that for the photoenolization of *o*-methylacetophenone (Scheme 4 in Section 2.2).

In aqueous solution, equilibration between the (*Z*)- and (*E*)-*aci*-isomers by proton exchange between the oxygen atoms through solvent water is faster than the intramolecular back reaction (*Z*)-*aci* → oNT and the *aci*-decay obeys a single exponential rate law.[153f] A detailed investigation of the pH–rate profile provided the acidity constant of the equilibrated *aci*-tautomers of oNT, $pK_a = 3.57 \pm 0.02$, and kinetic isotope effects on the *aci*-decay kinetics indicated that the dominant rate-determing step for *aci*-decay switches from carbon protonation by H^+ below pH 6, to carbon protonation by water above pH 6. In strongly acidic solutions, acid-catalyzed addition of water to the methylene carbon followed by dehydration of the resulting nitroso hydrate yields *o*-nitrosobenzyl alcohol.[153f]

A total quantum yield ($\Phi_{aci} = 0.08$) for the formation of *aci*-nitro tautomers from oNT in THF was estimated on the basis of transient absorbance intensities;[154a] this value is an order of magnitude larger than previous estimates that were obtained with aqueous solutions of oNT by photoinduced H/D exchange[153f] and by another comparison of transient absorbance intensities.[155] The discrepancy was attributed to fast retautomerization of the (*Z*)-*aci*-nitro isomer to oNT.[154a] However, this explanation cannot hold as the (*Z*)- and (*E*)-isomers are rapidly equilibrated in aqueous solution.[153f] An independent value of Φ_{aci} for oNT might be obtained by measuring the quantum yield of the irreversible reaction in strongly acidic solutions.[153f] Fortunately, many derivatives of oNT show much higher quantum yields Φ_{aci} (vide infra).

o-Nitrobenzyl (oNB) and 1-(2-nitrophenyl)ethyl (NPE; see Section 3.2) derivatives that carry a leaving group at the benzylic position release the protected substrate upon irradiation. The reaction proceeds via *aci*-nitro intermediates that are readily observed by flash photolysis at $\lambda_{max} \approx 400$ nm. The decay of these *aci*-transients frequently follows a biexponential rate law (due, presumably, to the formation of both geometrical isomers at the methylene group); the *aci*-decay rate constants are on the order of 10^2–10^4 s^{-1} and vary strongly with substitution, solvent, and with pH in aqueous solution.

A detailed mechanistic study of the release of ATP from 'caged ATP',[6] P^3-1-(2-nitrophenyl)ethyl ester of adenosine triphosphate **48** (Scheme 31), was reported in 1988 by Trentham and coworkers.[156]

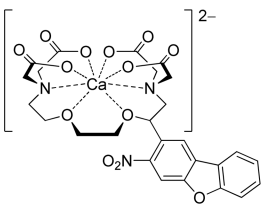
The appearance rates of the three products formed by irradiation of caged ATP, namely ATP^{2-} (bioassay), 2-nitrosoacetophenone (**49**, absorption at 740 nm), and H^+ (using an indicator dye), were each monitored, and found to coincide with the decay of the *aci*-nitro intermediate. Later work using time-resolved infrared detection and isotopic labeling further established that the release of ATP occurs in a first-order reaction that is synchronous with the decay of the *aci*-anion ($k = 52$ s^{-1} at pH 7, 10 °C).[157] The reaction mechanism proposed by Trentham[156] was unchallenged for many years and it was frequently taken for granted

that *aci*-decays were synchronous with substrate release. That assumption is not warranted in general, however, especially with more nucleophilic leaving groups.

Subsequent LFP and time-resolved IR studies were used to study the release of alcohols from oNB[158] and NPE[159] (Section 3.2) ethers at near neutral pH. Detailed kinetic studies covering a wide pH-range (Figure 10)[158] indicated that the mechanism proposed by Trentham and coworkers,[156] though it had been fully consistent with their results, needed to be revised on several counts (Scheme 32): a) Cyclization to the 1,3-dihydrobenz[*c*]isoxazol-1-ol intermediate (**50**) occurs from the *neutral aci*-compounds (**51**), as predicted by DFT calculations,[160] not from the conjugate bases (**51**$^-$). This accounts for the specific acid catalysis often observed for the decay rates the *aci*-intermediates. b) The cyclization **51** → **50** is irreversible. c) At pH values below 8, hydrolysis of the hemiacetal intermediate **52** formed by ring opening of **50** is rate-determining for the release of methanol and may be rate-determining with other poor leaving groups. The intermediates **50** and **51** have also been identified by IR analysis following irradiation of oNB methyl ether in Ar and N_2 matrices at 12 K.[161]

As can be seen from Figure 10, the release of methanol from oNB methyl ether in the final reaction step **52** → **53** is many orders of magnitude slower than the decay of the *aci*-intermediates **51/51**$^-$ at pH values near neutral. A faster reaction path bypassing intermediates **50** that was proposed by Corrie et al.[159] was subsequently shown not to be operative.[158] The same holds for the release of glycolic acid from oNB glycolic acid ether, which also proceeds via a long-lived hemiacetal with a lifetime of 4 s at 20 °C in wholly aqueous solution at pH 7.[162] Moreover, buffers were found to intercept the *aci*-intermediates when used in high concentrations, thereby further retarding the desired release of alcohols from oNB ethers.[162]

Nevertheless, Ellis-Davies and coworkers reported fast release of Ca^{2+} ions from the EGTA chelator complexes that are attached through an ether linkage to 3-nitrodibenzofuran-2-yl (**54**, NDBF EGTA) and several 6-nitroveratryl (**55**, NV EGTA)[163] derivatives. Rate constants of Ca^{2+} ion release on the order of 10^4 to 10^5 s^{-1} were observed by monitoring the fluorescence signal arising from the Ca^{2+}-dyes Ca-Green-5N[164] or Ca-Orange-5N.[163] This enables relatively fast mobilisation of intracellular Ca^{2+} by photolysis of NV- and NDBF-caged IP_3 (inositol 1,4,5-trisphosphate).[165] The authors assumed that cleavage of the benzylic carbon–ether linkage is much faster in derivatives of NDBF and NV than of oNB, possibly bypassing a hemiacetal intermediate. In our view, a more likely interpretation of these observations is that the formation of the cyclic intermediates of type **50** already reduces the binding constants of the chelator complexes sufficiently to afford substantial Ca^{2+} ion release with rates corresponding to the *aci*-decay rates. Indeed, biphasic release of Ca^{2+} from compound **55** (NV EGTA) with rate constants of 5×10^4 and 1.5 s^{-1} has been observed.[163]



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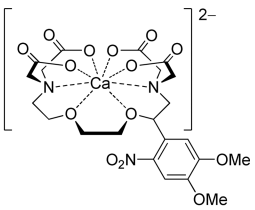


55

The formation of the reactive *aci*-nitro intermediates may proceed from both the excited singlet and triplet states. Steiner and coworkers have shown that the 2-(2-nitrophenyl)prop-1-oxycarbonyl (NPPOC, Section 3.2) PPGs used in photolithographic

DNA chip synthesis can be considerably enhanced by covalently linked triplet sensitizers (Section 8.1) such as thioxanthone.[166] Moreover, the same group recently reported that sensitization by diffusion in a thin film can be more effective than intramolecular sensitization for sensitizer concentrations higher than 5 mM.[167] On the other hand, Göner showed that triplet states of CT-character are formed by direct excitation of NV derivatives and related compounds that, however, do not participate in *aci*-nitro formation or the release of the substrate.[168]

Various substituents at the benzylic position of oNB were found to increase their perfomance as PPGs. For example, Hess and coworkers discovered that addition of a carboxylate to the benzylic carbon atom of the oNB caging chromophore increased release rates.[169] However, decarboxylation is a significant reaction pathway for photolabile calcium chelator derivatives of EDTA and EGTA.[170] Radical stabilization energies computed by DFT methods were shown to be a useful predictor of the relative efficiency with which LGs are photoreleased from oNB protecting groups.[171]

The presence of a hydroxy group at the benzylic carbon in **56** opens a new pathway for the decay of *aci*-nitro intermediates via a nitroso hydrate (Scheme 33, path b).[168a,172] pH–Rate profiles for the reaction steps involved in paths a) and b) in aqueous solution have been determined.[172] The caged Ca^{2+} chelator 'nitr-5' is a BAPTA (1,2-bis(o-aminophenoxy)ethane-*N,N,N',N'*-tetraacetic acid) derivative of an *o*-nitrobenzyl alcohol reported by Tsien and coworkers[173] who proposed that the relatively fast Ca^{2+} release (3000 s^{-1}) from 'nitr-5' may be attributable to proton shuffling, i.e., path b of Scheme 33.

The parent oNB structure **57**, although not the most widely used, represents the generic form of this family of PPGs. The leaving group can be directly attached to the benzylic site, as in **57** and this is the typical mode for the release of carboxylic acids,[3] thiols[174], histidine[175] and phosphates (Scheme 34, several examples shown).[5,107b] Although it is possible to directly attach alcohols and amines, they are most frequently linked as carbonic acid derivatives **58** (X = OCO–X'), which are better leaving groups and make the synthesis more convenient, i.e., by the direct reaction of the alcohol or amine with the readily available *o*-nitrobenzyl chloroformate. These strategies are, however, inappropriate when rapid release is needed (e.g., for electrophysiological applications), as the post-photolytic fragmentation is the rate-limiting step for release.[140a,159] This also does not prevent other major drawbacks of this PPG for the release of alcohols, which is slow (vide supra), and of amines, which undergo condensation with the nitroso-aldehyde side product leading to a stable imine; however, the latter reaction can be avoided by the addition of carbonyl scavengers, such as semicarbazide hydrochloride.[3] Another, more serious, problem is the formation of nitrosoaldehyde that yields brown-colored degradation products that absorb the incident light, thus create an internal filter.

o-Nitrobenzylic PPGs have naturally led to various synthetic and biological applications, especially for caged-biomolecules, and only selected examples will be discussed here as many reviews have been published on the field during the last decade.[9c,9f,9l,m,12b,176]

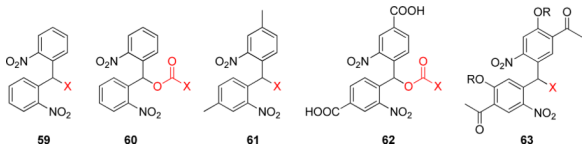
For example, photolytic deprotection of PPGs under very mild conditions provides a great advantage for automated DNA or RNA synthesis compared to the traditionally acyl-protecting group used. In this aim, a pioneer application was developed by Pitsch using oNB (**57**) as a protecting group for the 2'-oxygen of the four different bases for oligoribonucleotide synthesis (Scheme 35).[177] Interestingly, whereas nucleobases were protected via the usual carbamate function, the 2'-oxygen and the 2-nitrobenzyl group were linked together via an oxymethyl acetal.

2,4-Dinitrophenol was released in mitochondria, by first linking it to a cationic phosphonium targeting group via an *o*-nitrobenzyl ether. Incubation in the cytoplasm allowed migration of the assembly into the mitochondria, and was followed by subsequent photolysis (λ = 355 nm).[178] Ingenious inclusion of nitrobenzylic units in vesicles allowed a dose-controlled release of the encapsulated hydrophobic guests upon irradiation (λ > 315 nm).[179] Other interesting applications were developed in the preparation of otherwise inaccessible metal-organic frameworks, by inclusion of *o*-nitrobenzyl ethers and subsequent photolysis.[180]

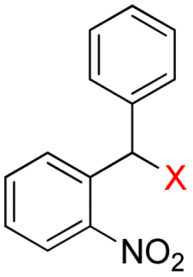
o-Nitrobenzylic PPGs have also been employed in natural product syntheses. One well-known and impressive application was reported by Nicolaou and coworkers in the total synthesis of the Calicheamicin γ1 where the high compatibility of **57** with other classical PGs and functions was demonstrated.[181] Another smart example is the use of **57** in the synthesis of an analog of Leukotriene C4 (LTC4, Scheme 36).[182] In the final steps, deprotection by irradiation at 350 nm of the nitrobenzyl derivative affords the secondary amine in 74% yield. It is noteworthy that no isomerization of the triene part and no racemization were induced by photolysis.

Over the years, multiple modifications have been developed in order to tune the properties, mostly towards an increase in quantum yield, an increase in the rate of release and increasing absorbance at longer wavelengths. Substitution at the benzylic site mainly affects quantum yields, whereas modification on the aromatic moiety affects the absorbance.

Substitution at the Benzylic Position—In addition to providing an electronic effect at the benzylic site, a second hydrogen-abstracting unit could, in principle, increase the efficiency. Already in the 1970's, Patchornik and Woodward proposed this modification, which worked up to a certain point.[3] It should be kept in mind that most substitutions at this site create a chiral center, which can become a drawback if chiral molecules have to be protected (and that is the case for most of the relevant applications, such as amino acids, carbohydrates and oligonucleotides), unless the added subsituent is identical to the aromatic core. A second *o*-nitrophenyl would fit in this category. However, an increase in photolysis quantum yields was not explicitly mentioned, and the increase in chemical yield might just be the consequence of the formation of a ketone instead of an aldehyde side-product, which is less prone to the parasitic imine formation. Thus, **59** was able to release carboxylic acids quantitatively and inorganic phosphate with 85% yield,[106a] whereas **60** released amino acids in yields between 70% and 95% in the absence of a carbonyl scavenger. Various derivatives have been prepared since, among them **61** and **62**, which liberated acetic acid in good quantum yields (Φ = 0.2 for **61**),[168b] or **63**.[183]



Despite the problem of chirality, a phenyl group can have a beneficial effect, as had been shown much earlier by Barltrop and coworkers with esters of **64** and carbamates of **65**,[151] and was later used in linkers for solid-phase synthesis.[184]



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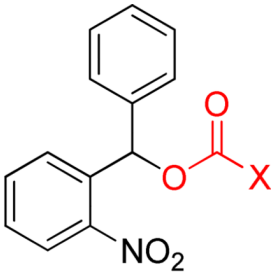
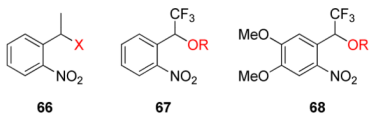


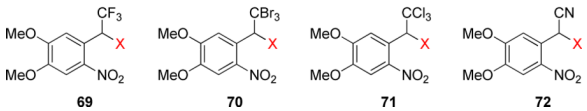
65

Simpler substituents, such as a methyl group, have a beneficial impact on the quantum yield. Thus, pivalate esters of **57** have release quantum yields in a polymeric matrix of 0.04 and 0.13 in acetonitrile solution, whereas they are much higher for pivalate ester **66** (Φ = 0.09 in polymer and 0.64 in acetonitrile).[185] Solution-phase quantum yields cannot be directly extrapolated to those of the solid-phase, as the available conformations can be quite different.[186] Derivatives of **66** have many other uses, such as the release of biologically active carboxylic acids in plant cells,[187] or on solid support.[188] Goeldner and coworkers proposed the introduction of a strongly electron-withdrawing group at the benzylic carbon, which had a massive effect on the quantum efficiency on choline and arseniocholine ether derivatives (Φ = 0.7 for **67**, and Φ = 0.43 for **68**) and sugar ethers (Φ = 0.62 for **67**, and Φ = 0.52 for **68**). Such derivatives were, however, not widely used in organic synthesis, as they were assembled by Mistunobu reactions, which were sluggish for secondary alcohols. Nevertheless, interesting applications, such as the release of choline or arsenocholine, were used as examples.[189]

Jullien and coworkers prepared and evaluated the 6-nitroveratryl (NV, or 4,5-dimethoxy-2-nitrobenzyl, DMNB) derivatives **69, 70, 71**, and **72** with electron-withdrawing substituents at the benzylic site; despite earlier claims, it was found that the substituents at the benzylic site, while having an unambiguously observable effect (up to a factor 3 between the most and least efficient), did not increase the quantum efficiency by orders of magnitude (Φ = 0.013 for −Br and Φ = 0.003 for −CN).[190] Interestingly, the cyano compound had been independently identified by a clever combinatorial technique by Pirrung and coworkers as being quite efficient.[191] Such apparent contradictions have been reported in the field of PPGs for decades and could potentially slow down future development of new or modified PPGs, since no clear trend emerges from the huge amount of sometimes unreliable data accumulated. The determination of quantum yields remains a delicate operation subject to significant experimental error; furthermore, all these different groups are frequently tested for the release of different leaving groups (phenols, carboxylic acids, amine, aliphatic alcohols, carbamates) under different irradiation wavelengths, in different solvents and buffers, and each with a different photochemical apparatus. We have seen above the enormous importance that the effects of solvation and proton transfer play on the reaction mechanism.

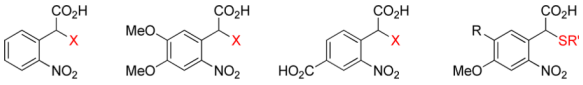


66 **67** **68**



69 **70** **71** **72**

As mentioned for the benzoin PPG (see Section 2.4), water-solubility is a crucial point for biological applications and this property can be achieved by the introduction of a CO_2H substituent. Hess and coworkers designed the α-carboxynitrobenzyl (α-CNB) derivative **73** for the release of phenolic OH groups; there was a significant increase in the release rate, but this was observed only at shorter wavelengths.[169,192] Bassani and coworkers recently reported that the α-carboxy-6-nitroveratryl (α-CNV) analogue **74** released carboxylic acids in quantitative chemical yields with Φ = 0.17 and a rate of release 2–3 orders of magnitude larger than the parent compound,[193] and capsaicin through an ether bond.[194] A related strategy (based on **75**) had been devised by Schaper and coworkers.[195] Thiols could also be released with the derivative **76**.[196] A time-resolved infrared study of the photoreactivity of α-CNB **74** was performed by Corrie and coworkers.[197] Related groups were studied computationally by Schaper and coworkers.[198]



73 **74** **75** **76**: R = OMe or H

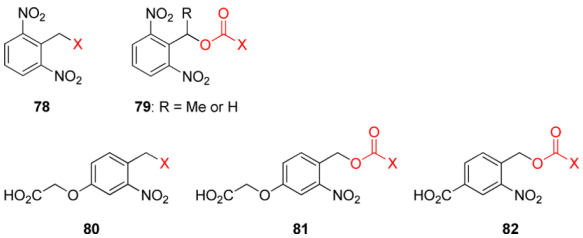
Pirrung and coworkers designed a clever way of dealing with the nitroso side-product, responsible for the internal filter effect. It was trapped in situ by a Diels-Alder reaction with a diene function included at the benzylic site (Scheme 37).[199] These pentadienylnitrobenzyl PPG esters, ethers and carbamates **77** were used to release carboxylic acids, alcohols and amines (Φ = 0.22, 0.41 and 0.38, respectively); an analogue with a methylenedioxy group on the aromatic ring was also discussed, with improved properties (in this case, the increase in absorbance more than compensated for the usual decrease in quantum yields).

Substituents on the Aromatic Ring of the *o*-Nitrobenzyl Chromophore—

Because of the problems of chirality, the synthetic issues and the limited impact on the absorbance, considerably less work was devoted on substitution at the benzylic site than the very numerous modifications on the aromatic ring. Such modifications bring three features: a) the tuning of the absorbance with concomitant effects on the quantum yield, b) the possibility to anchor the group on a solid support or on a linker; this will not be discussed here, as a book chapter reviewed the field recently,[200] and c) the possibility to modulate the solubility properties of the group.

A second electron-withdrawing nitro group was added to increase the hydrogen-abstraction capacity (reminiscent of **59** and **60**), and the release of amines from carbamates **78** was much more efficient than for **58** (Φ = 0.62 *vs.* Φ = 0.13 in the solid state).[186] Interestingly, in the same study, the carbamate derivative of **66** showed a quantum yield of release of 0.11, which differs from earlier data. This was attributed to the influence of the matrix. The analog **79** was also exploited a few years later.[187]

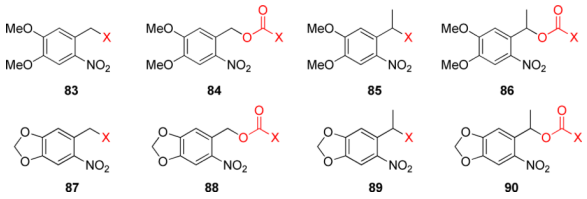
Various groups have been added to increase the hydrophilicity of the cage again to address the water-solubility issue. As an example, the carboxylic acid **80** with a one-carbon spacer was reported by Allan.[187] Similarly, **81** and **82** were also exploited.[169b,201]



78 **79**: R = Me or H

80 **81** **82**

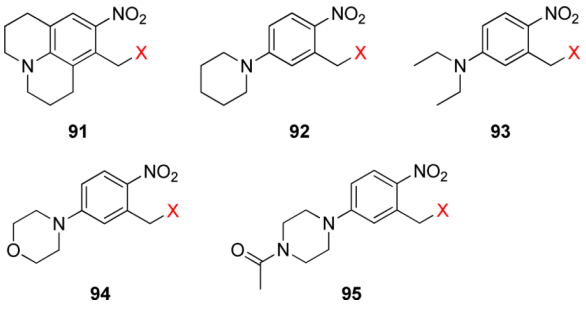
Early on, two methoxy groups were added to increase the absorbance at longer wavelengths (λ >350 nm, and Rayonet® lamps at 420 nm still provide photolysis at reasonable rates), leading to the 6-nitroveratryl (NV, **83**) and 6-nitroveratryloxycarbonyl (NVOC, **84**) moieties. These are undoubtedly the most frequently used groups to date both in solution[3] and in the solid-phase (for two recent, among many other examples, see[202]). Multiple variants have been evaluated, such as the introduction of an α-methyl group at the benzylic site: the methyl-6-nitroveratryl (MeNV, **85**) and methyl-6-nitroveratryloxycarbonyl (MeNVOC, **86**) groups. Very close analogs, but with slightly altered properties, presumably due to a restriction in the freedom in aligning the non-bonding orbitals of the oxygen with the aromatic π system, are the methylenedioxy derivatives **87** and **88**. Further addition of an α-methyl group led to α-methyl-(6-nitropiperonyloxymethyl) (MeNPOM, **89**) and the now famous analogous 3,4-(methylenedioxy)-6-nitrophenylethoxycarbonyl (MeNPOC **90**) groups. The latter moiety was used in the automated synthesis of DNA chips.[203] A solution-phase comparison of the quantum yield of release of thymidine derivatives of NVOC (Φ = 0.0013) and MeNPOC (Φ = 0.0075) was performed.[204]



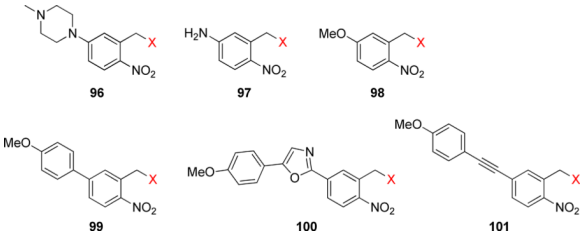
Caged nucleobases were used for the transient disruption of DNA hybridization to photochemically control DNAzyme activity.[205] This strategy is illustrated in Scheme 38 where the **89** (MeNPOM)-protected thymidine phosphoramidite is incorporated into DNA using classical synthetic procedures. The caged-DNAzyme thus obtained can be quantitatively reactivated by irradiation at higher wavelengths. MeNPOM presents several advantages compared to the parent compounds **73, 87** and **90**: the very efficient conversion upon irradiation at 365 nm, the high stability of the caged molecules in aqueous media, the less toxic acetophenone byproduct and its easy incorporation via the chloromethyl ether derivative.[206]

Inactivation of fluorophores (see Section 11) was effected by similar caging, for example by binding nitroveratryl groups to rhodamines and fluoresceins.[207]

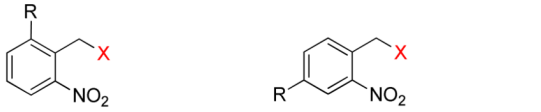
A recent computational study[198] was complemented by an experimental systematic evaluation of substiuents on the aromatic ring and at the benzylic site,[168b] and showed surprisingly low influence of these groups (except for the strongly electron-releasing amine of **91**, an effect that was reported earlier). Indeed, one of us reported a very significant lowering of the deprotection efficiency by having electron releasing groups *para* to the nitro group, a manifestation of the CT-character of the excitation as mentioned above.[208] This was exploited in a so-called *safety-catch* approach, where esters of **92, 93, 94**, and **95** were protected against photolysis in normal conditions. Upon protonation with a strong acid, the reactivity was restored, thus allowing normal photolysis.[209]



Similarly, the reactions of the compounds **96, 97**, and **98**, evaluated by Jullien and coworkers, were found to be less efficient than those of the non-substituted congeners (in fact, they were too slow to be measured in the case of **96** and **97**).[190]

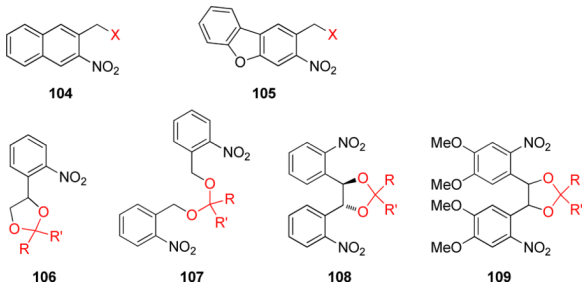


The same authors also examined the effect of other groups, in *para* position to the nitro group, with or without additional conjugation (**99, 100**, and **101**).[190] As was the case for the benzylic substituent, these extra groups had a limited impact on the quantum yield, although the highly conjugated group in **101** decreased the reaction efficiency. The authors also explicitly pointed out an inverse correlation between the quantum yield and longer absorption wavelengths. Various other *o*-nitrobenzyl alcohol (e.g., **102** and **103**) derivatives substituted in the *ortho*-position to the benzylic group, or *meta*-position to the nitro group, have been reported.[12b,185,208] The reaction efficiency of their ethers was tested in terms of kinetics of release, quantum yields in solution or in the solid state as a function of the irradiation wavelength for some of them.



102: R = Me, OMe, CN **103**: R = Cl, Br, NO_2, OMe, CO_2Me, Ph

In an effort to increase the absorbance at longer wavelength, Singh and coworkers extended the aromatic core as a naphthalene[210] or 7-methoxynaphthalene.[211] The corresponding esters **104** were able to release aromatic rings containing carboxylic acids at 380 nm, with Φ ranging between 0.08 and 0.16 (in acetonitrile-water).[210] The nitrodibenzofuran **105** also had very interesting properties (such as efficient deprotection), which were applied in recent examples.[164–165]



The carbonyl group is among the groups most frequently in need of facile protection-deprotection protocols, so it is surprising that very few PPGs have been developed for it. Gravel and coworkers were among the first to address this issue, by first introducing the ketal **106** in 1974.[212] One issue was the generation of a mixture of diastereoisomers if the ketone to be protected was nonsymmetrical. The same group found later that the even simpler ketal **107** could circumvent the problem.[213] A solid-support version of **106** was developed.[214]

Another way of dealing with the issue of chirality was proposed by one of us, with the ketal 108, derived from the very easily prepared enantiopure (1*R*,2*R*)-bis(*o*-nitrophenyl)ethanediol,[215] which was used by Walsh and coworkers for the preparation of the otherwise too sensitive intermediate.[216] The substituted version **109** with a red-shifted absorption was proposed later.[217] On the other hand, for the release of simple aldehydes, it is not necessary to consume two aromatic releasing units, and α-acetyl acetals have been shown to release aldehydes efficiently upon irradiation (Scheme 39).[218]

In a similar strategy, the *o*-nitrobenzaldehyde derived acetals **110** or **111** were used to protect 1,2- or 1,3-diols, principally for protection of saccharides.[219] However, in this case, only one alcohol can be deprotected leading to photostable 2-nitrosobenzoic acid derivatives. Moderate to high regioselectivities were obtained during the deprotection mostly determined by steric and electronic effects of the nonsymmetrical substrates (Scheme 40).[219a] The final deprotection of diols could be achieved under basic conditions or by intracellular hydrolysis. A reverse strategy was developed by Iwamura et al. with the treatment of **111** by boron trifluoride in the first step to release an ether of **57**, which was subsequently cleaved photochemically.

Two-Photon Absorption—The two-photon irradiation technique (see also Section 9) enhances the efficient temporal and spatial control of biomolecule delivery. Taking advantage of this for a biological application, Kao and coworkers reported that vanilloid derivatives of oNB (**57**) and NV (**83**) can be photoreleased in situ to activate TRPV1 receptors on nociceptive neurons with one-photon quantum efficiencies of 0.13 and 0.041 (Scheme 41).[220] In another example, retinoic acid derivatives of **72** and **83** were prepared and photolyzed, first at 365 nm.[221] The presence of a long-wavelength tail in the absorption spectrum does not prevent liberation, although isomerization of double bonds did occur. In the two-photon mode (excitation at 750 nm; 25 mGM) retinoic acid was also liberated from cage **57**, and dynamic studies on zebrafish embryogenesis were carried out (vide infra).

An interesting alternative to the simultaneous absorption of two photons is the use of lanthanide-containing upconverting nanoparticles (UCNPs; see Section 8.3). In this case, two near-infrared (NIR) photons are absorbed sequentially, and the nanoparticle re-emits one higher energy photon, in a spectral range that can be exploited by PPGs. Such an example was recently shown by Branda, Zhao et al., where nitroveratrylester-containing

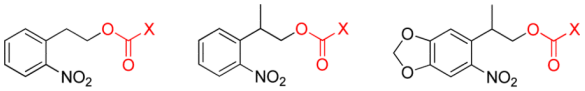
micelles were dissociated upon irradiation with a continuous-wave NIR laser.[222] A similar strategy was also used to photolyze benzoin esters.[223]

Isotopic Substitution—As the transfer of hydrogen from the benzylic site to the nitro group is involved in the primary photochemical step, it was found that the rupture of the stronger C–D bond was less efficient.[224] The photolysis of the esters **57** bearing a perdeuterated benzylic position was 3.8–8.3-times less efficient (depending on the irradiation wavelength). The substituents on the aromatic ring in the analogous esters **83** diminished this isotope effect. The origin of these observations has not yet been fully elucidated; so far the phenomenon was utilized in the selective removal of two photolabile (oNB and NV) groups (Scheme 42; a, b depicts two different isotopically labeled derivatives).[225]

The photochemistry of the oNB derivatives is summarized in Table 8.

3.2 *o*-Nitro-2-phenethyloxycarbonyl Groups

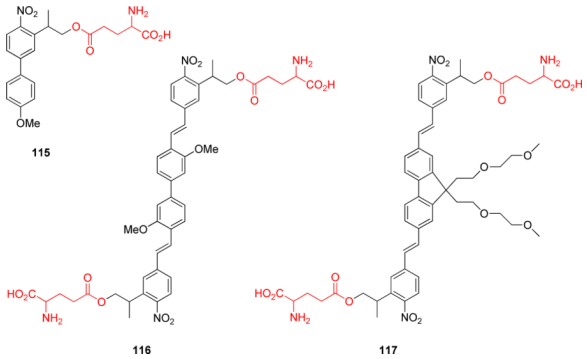
In the late 1990's, Hasan and coworkers designed the oNB one-carbon homolog **112** (1-(2-nitrophenyl)ethyloxycarbonyl, NPEOC; "OC" stands for the −C(=O)− group), and its α-methylated analog **113** (NPPOC).[226]



112 **113** **114**

Interestingly, despite the structural similarity between **112/113** and **57**, the release mechanism differs markedly, and the observation of a nitrostyrene side product is compatible with a photoinduced elimination (Scheme 43),[226] reminiscent to the photoelimination from ketones by photoenolization mentioned earlier (Scheme 5). It turned out that **112** eliminated a 5'-O nucleoside carbonate (Φ = 0.042) with a higher quantum yield than that of its oNB analog **57** (Φ = 0.033). The substitution of the benzylic center with a methyl considerably added to the efficiency (Φ = 0.35), which made **113** a candidate of choice for oligonucleotide synthesis.[227] This group was further modified in order to increase the absorbance, such as in the 2-(3,4-methylenedioxy-6-nitrophenyl)propoxycarbonyl (MNPPOC; **114**)[204,228] or analogous 3-(4,5-dimethoxy-2-nitrophenyl)-2-butyl (DMNPB, Section 9)[229] derivatives, but **113** was applied in automated light-directed olgonucleotide synthesis (DNA-chips).[230] Amino acids[231] and carbohydrates were protected with NPPOC at the 6-position, including thiophenyl glycoside donors.[232] NPPOC derivatives are themselves relatively inefficient in two-photon deprotections; however, in the presence of sensitizers (Section 8) (it has been shown by Wöll and coworkers that NPPOC can be sensitized),[166,233] the cross-section can reach useful levels for several applications.[234] This is discussed in more detail in Section 9. A very recent example of sensitization was shown by Winssinger and coworkers, where a thioxanthenone sensitizer is bound to a nucleic acid sequence, which is able to promote the photolysis only when hybridized with a NPPOC-containing sequence with the matching complementary bases.[235]

Further modification of the backbone may increase the two-photon absorption cross section (Section 9), such as in the biphenyl derivative **115**,[236] or highly conjugated systems **116** and **117**.[237] This has also been recently demonstrated by Goeldner and coworkers who studied the photochemical properties of biphenyl-containing photoremovable protecting groups possesing the *o*-nitrobenzyl, phenacyl, and 2-(*o*-nitrophenyl) propyl functionalities.[238]



Replacement of the methoxy substituent of **115** by an amino group increased significantly the two-photon cross section (Section 9).[239] The high efficiency of NPPOC was exploited in many applications.[166,204,228,230–234,236,240]

3.3 *o*-Nitroanilides

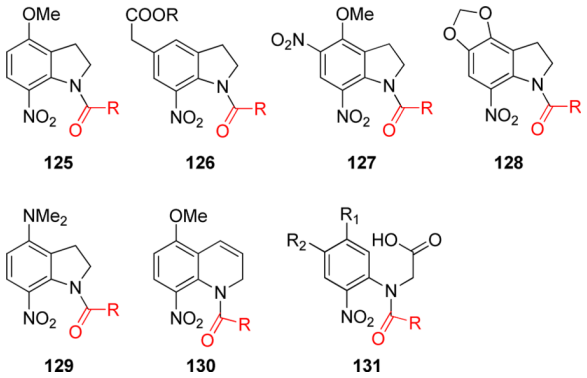
Nitroanilide derivatives, such as **118**, were shown in the 1970's to be photolabile and to release carboxylic acids (Scheme 44) and various by-products depending on the conditions.[241] The early works concluded that the reaction is a rearrangement and not a solvolysis, as no isotopic incorporation was observed when the photolysis was carried out in $H_2{}^{18}O$. Likewise, derivatives of **119** are also photolabile, but their cyclic nature prevents a direct H-abstraction on the amide alkyl substituent.[242] Failure to provide esters when the reaction is carried out in alcoholic solvents was an additional argument against a simple solvolysis.

Neither **118** nor **119** were widely exploited in synthesis, to the exception of the carbamate derivatives of **118** (R = O−alkyl, R^1 = Me, R^2 = H) that were used as a PPG for alcohols (Scheme 45).[243]

The size of the fused nitrogen heterocycle proved to be crucial for the reactivity, and the 5-membered analogues of **119** (Scheme 44), such as **120** and **121** (R = alkyl) released carboxylic acids very efficiently upon photolysis.[244] Most remarkably, when the reaction was carried out in nucleophilic solvents, such as methanol or ammonia-containing dichloromethane, the primary amide was obtained. Corrie, Bochet, Toscano and coworkers succeeded in providing a comprehensive picture of the reaction mechanism.[245] The mechanistic studies concluded that a photoinduced acyl migration from the indoline nitrogen atom of **122** to one of the nitro group oxygen's occurs, leading to a highly electrophilic N–O-acyl intermediate **123** (Scheme 46).[245a,b]

Interestingly, this intermediate further reacts via two distinct pathways depending on the solvent. In water, deprotonation releases a carboxylic acid, with the concomitant formation of a nitrosoindole **124** (pathway b, Scheme 46), whereas in moist organic solvents, the acyl moiety undergoes a nucleophilic attack either by the solvent (water, alcohol) or by an external nucleophile (pathway a). Variation in the substitution pattern on the indoline aromatic ring can to a certain extent influence the ratio of the side products.[246] These 7-nitroindolines release their protected function efficiently,[247] and tuning of the aromatic substituents at the C-4 and C-5 position has an impact on their reactivity. Thus, the acetamide **120** (R = Me) releases acetic acid with quantum yields of 0.06 and 0.12 in water and MeCN/H_2O 99:1, respectively.[245a] On the other hand, the reaction of **125** was about 2.5 times more efficient than that of **121** or **126**, and 5 times more efficient than that of **127**; **128** and **129** were totally photochemically inert, possibly due to a low-lying charge transfer excited state.[246,248] Corrie and coworkers also designed a clever combination of a

nitroindoline core and an absorbing “antenna”, which will be discussed later (Section 8.1).[249] The compounds **130**[250] and **131**[251] have recently been proposed as PPGs.



The bromonitroindoline **120** was used in an early example of peptide synthesis as a protecting group for the C-terminus.[252] The solvolysis pathway was used to give the carboxamide by using an ammonia-containing solvent, a feature frequently sought in peptide synthesis. A few years later, a spectacular exploitation of this nucleophilic attack of the reactive intermediate was published by Pass, Amit and Patchornik, with the use of a *N*-nucleophilic peptide fragment (Scheme 47).[253] Otherwise sensitive glycopeptides were assembled using this strategy.[254]

More recently, the derivatives **121** were used in regular organic synthesis for preparing amides from amines,[255] but also by using weaker nucleophiles in the formation of thioesters from thiols,[256] and esters from alcohols.[257] The preparation of more complex derivatives of **121** can be difficult, as the nucleophilicity of the indoline nitrogen is greatly reduced by delocalization through the two strong electron-withdrawing groups, but indirect routes were designed, and the synthesis of a series of amino acids was recently published.[258] The availability of such photoactivable amino acids allowed the allphotochemical synthesis of peptides, by exploiting the different-wavelengths sensitivity of the indoline protecting group on the *N*-terminus.[259] For other application of this chromatic orthogonality, see **Section 10**.

Carbamates can also be prepared by photoinduced transfer of fluorenylmethyloxycarbonyl (Fmoc) **132** or benzyloxycarbonyl (Cbz) **133** derivatives. So far, the Boc analogues were significantly inferior (Scheme 48).[260]

Other functional groups were released from nitroindoline derivatives; Hassner published the release of alcohols from carbamates of **120** (R = OR), or amines from ureas of **120** (R = NR^1R^2).[261] The 7-nitroindolines found the applications in neuronal studies[262] and other physiological sciences. For example, derivatives of **125** were found to be active in releasing glutamate or GABA in two-photon absorption mode.[249e,263] In some instances, 7-nitroindolines proved to be inferior compared to nitrobenzyl cages.[264]

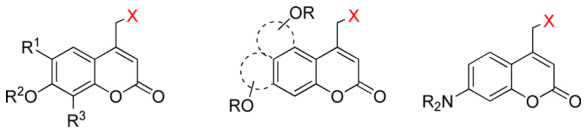
In general, photoinduced acyl transfers are relatively rare,[255c] and recent attempts to design groups with similar properties were only moderately successful.[265]

4 COUMARIN-4-YLMETHYL GROUPS

Photolysis of 7-methoxycoumarinyl-4-methyl derivatives, which established coumarins as a photoactivatable phosphate releasing group, was first demonstrated by Givens with diethyl phosphate ester **134** (Scheme 49).[266]

This discovery set the stage for the development of a new class of (coumarin-4-yl)methyl cages (Table 9). The attractive features of the coumarin phototriggers, such as large molar absorption coefficients at longer wavelength, high propensity toward two-photon activation (see Section 9), and fast release rates, taken together with improved stability and fluorescent properties that provide a tag for convenient monitoring of the reaction course, have raised researchers' awareness to this relatively new class of PPG's.[9f,9u,267] Clever modifications of the substituents at C6 and C7 in the coumaryl group addressed low water solubility, typical of the first-generation 7-alkoxycoumaryl PPG (types **135** and **136**; Table 9), and also helped extend the absorption maximum of the group into the biologically benign range (≥350 nm to 700 nm for 2-photon (Section 9) activation[10d]). Thus, installation of an additional alkoxy group at C6 in the structure of parent 7-alkoxycoumarinylmethanol produced a shift of the absorption maximum by 30 nm. The 6-bromo-derivative was designed to lower the pK_a of the 7-hydroxy group by two units to effect a complete deprotonation at physiological pH thereby enhancing water solubility and causing a λ_{max} shift of 60 nm. Introduction of the second-generation of coumarinylmethyl PPGs with 7-amino substituents (type **137**; Table 9) further improved the spectroscopic and photochemical properties of the cage, moving the absorption maxima to 350–400 nm and recording the highest quantum yields (0.21–0.28) among the analogs. Furthermore, the problem of water solubility, which can be an obstacle to biological application, has been addressed by appending polar groups such as carboxylates to the aniline moiety. Polyaromatic analogs were also synthesized to improve fluorophoric properties of the cage for use both as a fluorescent tags and as PPGs (type **136**; Table 9).

Comprehensive reviews by Furuta,[268] Dore,[269] Loudwig and Bayley,[270] and more recently one by Givens and Rubina[9u] encompass much of the ground work on the photochemistry of coumarylmethyl PPG's with an emphasis on biological applications. Important mechanistic aspects, synthesis and several selected recent applications are given below.



135 **136** **137**

λ_{max} 320–330 (R^1 = H, OR) λ_{max} 340–360 λ_{max} 350–400
λ_{max} 330–380 (R^1 = Br)

Synthetic Approaches to Coumarin-Caged Compounds

Coumarin-4-ylmethanol **138**, easily available from the corresponding halides, is the common precursor of coumarin-caged esters, including phosphates, carboxylates, sulfonates as well as carbonate, carbamate and anhydride derivatives (Scheme 50).[9a] Carboxylic acids, including amino acids, can also be efficiently caged via SN2 substitution of coumarinylmethyl bromide **139**. Likewise, coumarin-4-methylamines and -thiols can be directly obtained from bromides **139** by standard alkylation. Coumarin-caged diols, e. g., acetals **140**, were prepared in two steps from aldehyde **141**, which in turn is available from the corresponding alcohol **138** by oxidation with manganese dioxide (Scheme 50).[295] Aldehyde **141** is also a convenient precursor to 4-diazomethylcoumarin **142**, which has proven to be effective in protecting complex phosphates, particularly cyclic adenosine nucleotides, when standard approaches employing coumarin-4-ylmethanol **138** or coumarin-4-yl bromide **139** frequently fail to provide the desired product.[271a,279a]

The Mechanism of Photorelease and Selected Applications

A general mechanism of photorelease of phosphates, sulfonates and carboxylic acids, the most successfully applied leaving groups, is summarized in Scheme 51.[276,296] After initial light absorption, relaxation takes place to the lowest $^1(\pi,\pi^*)$ excited singlet state which partitions between unproductive radiationless decay and fluorescence, and heterolytic C–X bond cleavage. The initially formed tight ion pair (coumarinylmethyl cation and leaving group conjugate base) is the key intermediate. The coumarinylmethyl cation either reacts directly with adventitious nucleophiles or solvent to generate a new stable coumarylmethyl product. Alternatively, the tight ion pair escapes the solvent cage and reacts with available nucleophiles. Although there is evidence of intersystem crossing occurring with 7-aminocoumarins,[284c] there are no indications of triplet reactivity. Recombination of the tight ion pair regenerates the ground state caged derivative, an additional non-productive pathway.

Time-resolved absorption studies have demonstrated that the heterolytic bond cleavage is very fast with rate constants reaching 2×10^{10} s^{-1} (measured for phosphate esters), among the most rapid photorelease rates for any caged compounds.[297] However, ion pair recombination dominates the subsequent reactions and is about 10 times faster than nucleophilic trapping of the coumarinylmethyl cation by solvent.[276,296] Evidence in support of SN1 cleavage at carbon, vis-a-vis a photosolvolysis pathway, was obtained using ^{18}O-labeled water, which afforded labeled coumarinylmethanol and label-free phosphoric acid (Scheme 51).[297] Installation of electron-donating substituents on the coumaryl moiety and choice of a leaving group with low pK_a values facilitate the reaction and, at the same time, impede ion pair recombination.[276]

Poor leaving groups such as alcohols, phenols, and thiols render (coumarin-4-yl)methyl derivatives resistant to heterolysis. Such groups can be more efficiently released when caged through a carbonate linkage with the (6-bromo-7-hydroxy/alkoxycoumarin-4-yl)methyl moiety **143** (X = O, S, Scheme 52). As noted earlier, the initially liberated carbonic or thiocarbonic acid is unstable and undergoes decarboxylation to give free alcohol or thiol.[196,272,275,289] The rates of these decarboxylation reactions are usually quite slow, $k_{-CO_2} = 10^{-3}$ s^{-1},[298] but subject to both acid and base catalysis.

Analogous to alcohols, release of amines from coumarin-4-ylmethyl carbamates **143** (X = NR") proceeds uneventfully, although at a slower rate of decarboxylation (Scheme 52).[272,288,290,299] As in the case of carbonates, the rate-limiting step is decarboxylation of the released carbamate anion, which is more strongly dependent on the pH and on the nature of the released amine or amino acid.[62,300] This could become a limitation for applications requiring a very rapid substrate release.

Carbamate-linked coumaryl PPG was used by Hayashi and Kiso to mask the benzylamine moiety and suppress the pharmacophore activity in isotaxel (Scheme 53).[283] The resulting photoresponsive prodrug phototaxel (**144**), was selectively activated using visible light (430 nm) to release isotaxel (**145**), which converted into paclitaxel (**146**) by a spontaneous intramolecular *O*- to *N*-acyl migration.[283] To improve water solubility of the phototaxel prodrug, the *N*-ethyl groups of the coumarin cage were replaced with *N*-(2-(dimethylamino)ethyl)acetamide groups.[301] It should be mentioned that an alternative *O*-protected paclitaxel prodrug with a carbonate linked coumarin was unstable in aqueous solutions.

Among the most significant advances in the photochemistry of coumarin-based protecting groups has been the discovery and development of two-photon activation (see Section 9).[9h,302] Initially reported for the two-photon release from coumarin-caged substrates by

Furuta, Dore, Tsien, and coworkers[303] this approach for decaging has developed into a major area of research and discovery.[9a,269]

Block methylmethacrylate copolymer **147** esterified with the (7-diethylaminocoumarin-4-yl)methyl group exhibiting a large two-photon absorption cross-section was used by Morris and Zhao to study light-responsive micelle disruption (Scheme 54).[304] UV irradiation of the micelles loaded with the hydrophobic nile red dye revealed nonradiative energy transfer between the coumarin chromophore and the dye. Micelles without dye showed significant fluorescence self-quenching due to tight packing of the coumarin groups within confined space; however, photorelease of the chromophore was accompanied by micelle disruption which caused a dramatic increase in its fluorescence. Experiments with dye-loaded micelles placed in a dialysis cap immersed in water showed efficient diffusion of photoreleased coumarin into water (measured by fluorescence emission), while hydrophobic guest dye molecules remained within the cap. Multiphoton irradiation using near infra-red light was less disruptive for micelles, yet sufficient to release loaded dye.[304]

An efficient multiphoton uncaging permitted exposure of the functional groups (primary amines and sulfides) buried within modified aragose gel **148**, creating complex 3D sites ready for selective immobilization of biologically relevant entities without affecting the mechanical properties of the patterned material (Scheme 55).[299,305]

A single example of photodeprotection of a coumarinylmethylamine through a C–N bond cleavage has been reported. This reaction proceeded efficiently only in the presence of an excess of a hydrogen-atom donor, such as *n*-decanethiol or 1,4-cyclohexadiene (Scheme 56).[306] Thus, a radical mechanism has been proposed that involved electron-transfer between the amine and coumaryl moieties forming the intramolecular radical ion pair **149**. Subsequent cleavage of the C–N bond generated an aminyl radical and the resonance stabilized coumarinylmethyl radical **150**, both of which were trapped by hydrogen-atom donors.

When the released group is the conjugate base of a very strong acid, the caged substrate becomes a “caged proton source” that permits the spatial and temporal control of rapid change in pH. Thus, the release of phosphoric acid, methanesulfonic acid or sulfuric acid derivatives from their coumarin-caged precursors **151** has been employed as a proton trigger in studies of proton-dependent cellular signal transduction (Scheme 57).[307] The release occurred within two nanoseconds giving a significant drop in the pH of up to three units. It was also noted that hydrophobic phosphate derivatives penetrate cell membranes whereas charged sulfate was membrane-impermeant.

Photorelease of diols from cyclic (coumarin-4-yl)methyl acetals **152** proceeds via an ion-pair intermediate **153**, which then reacts with water to produce the hemiacetal **154**. The latter decomposes to give free diol and coumaryl aldehyde **155** (Scheme 58).[308] Interestingly, the photodegradation of coumaryl-caged diols was found to be dependent on the size of the cyclic acetal. Thus, 1,2- and 1,4-diols were released equally efficiently (Φ = 0.005–0.03), whereas the corresponding 1,3-diols appeared to be completely inert to photolysis. Although different stereoelectronic properties of the three acetals precluded direct comparison of the propensity toward ring opening,[308] it is probable that the divergent quantum yields result from lack of recyclization because of the increasing ring strain for 5- and 7-membered acetals (by ca. 6 kcal mol^{-1}) compared with recyclization to the “strainless” 6-membered analog.[309]

A complementary approach for protecting carbonyl compounds in a form of a photolabile cyclic coumaryl acetal has also been demonstrated (Scheme 59).[287,291] Remarkably, both

single- and two-photon uncaging (Section 9) of 4-coumarin-4-yl-1,3-dioxolanes **156** were successfully achieved under physiological conditions. In line with the above example, the proposed mechanism involved photoinitiated heterolysis and subsequent solvolysis of the zwitterionic species **157**.

Caged carbonyl compounds **158** were obtained from (coumarin-4-yl)methyl chloride (**159**) by Wittig olefination followed by dihydroxylation of the resulting alkene with OsO_4 and subsequent acetalization or ketalization under standard conditions (Scheme 60).[291]

Alternatively, caged progesterone **160** was synthesized by Hagen, and coworkersvia ketalization of the commercially available pregnenolone **161**, followed by Oppenauer oxidation of intermediate **162** (Scheme 61).[310] Photoactivation of coumaryl-caged progesterone produced **163** in only 30% yield, which, however, was sufficient to initiate progesterone-mediated response in sperm. Two-photon excitation of **160** (755 nm) also caused release of progesterone, albeit with ca. 5 times lower efficiency as compared to photolysis of the analogous glutamate derivative.[301]

5 ARYLMETHYL GROUPS

5.1 Simple Arylmethyl Groups

A large family of photolabile protecting groups is based on photochemically induced hydrolysis (or less commonly alcoholysis) of benzyl or heterobenzyl esters or ethers **164** (Scheme 62).

In fact, photochemical release of glycine from its benzyloxycarbonyl derivative was the first application of a “photosensitive protecting group” in organic chemistry.[1] Barltrop and Schofield reported that irradiation of *N*-benzyloxycarbonylglycine **165** with 254 nm light resulted in the release of glycine in 75% yield and a quantum yield of 0.15 (Scheme 63). Photolabile protection of amino acids and dipeptides was further demonstrated by Chamberlin, who employed the 3,5-dimethoxybenzyloxycarbonyl protecting group (**166**).[311] Substrates were released in up to 85% yield upon illumination with a high-pressure mercury lamp for 1.5 h.

From a mechanistic point of view, this photosolvolysis can proceed via initial light-induced homolysis of the C–O bond, followed by rapid electron transfer to give an ion pair (Scheme 64). The latter is then trapped by solvent to give the final products. Pincock and coworkers have shown that this mechanism is predominant in the photolysis of simple benzyl derivatives.[101] In fact, photosolvolysis of benzyl esters is often accompanied by the formation of radical products.[312]

Calculations by Zimmerman and coworkers[312a,313] suggested that heterolysis of the C–O bond is energetically preferred over the homolysis, especially in the presence of *ortho* and *meta* substituents stabilizing the cation. While studying the photochemical solvolysis of benzyl acetates, Zimmerman has observed the now famous “*meta*-effect”: a higher efficiency of photocleavage for *meta*-methoxy-substituted benzyl esters.

Structural features that help to delocalize positive charge in the ground state enhance the efficiency of the electron transfer step (Scheme 64), while excited state cation-stabilizing moieties promote the direct photoheterolysis of the C–O bond. The efficiency of the uncaging reaction depicted in the Scheme 64 is defined by the competition between solvent capture of the ion pair to give the liberated hydroxyl compound ROH and recombination leading to the starting material (polar protic solvents enhance both the heterolytic cleavage and electron transfer). Therefore, photodeprotection of carboxylates, carbonates, carbamates,

phosphates, and other good leaving groups is usually quite efficient, while uncaging of alcohols is more challenging. Enhanced stability of the benzyl cation and increased steric hindrance around the cationic center also help to slow down the ion recombination. Thus, the design of new PPGs of this class was mostly focused on the incorporation of features helping to delocalize positive charge. However, there is a pitfall associated with this approach: a very stable cation makes the PPG susceptible to acid-catalyzed hydrolysis. In fact, the conventional acid-labile trityl protecting group can be removed from caged nucleosides (**167**) in 71–99% yield upon 254 nm irradiation with ca. 10% quantum efficiency (Scheme 65).[314]

Wang and coworkers systematically explored various trityl derivatives and found that the 3-(dimethylamino)trityl group (**168**, DMATr, Scheme 65) is the most efficient alcohol caging group in the trityl series ($\Phi = 0.2$).[315] Introduction of a strong electron-donating *meta*-substituent in one of the trityl rings improves the photochemical reactivity due to the *meta*-effect, stabilizing the PPG derivative to hydrolysis in the dark. This PPG has a relatively long absorption wavelength ($\lambda_{max} = 309$ nm), is stable in acidic media, and releases alcohols with 0.12–0.20 quantum yield efficiency. DMATr can be easily installed by simple solvent-free heating of the DMATr acetate with the alcohol. Several alcohols, including sugars and thymidine have been protected and released upon irradiation with a medium-pressure mercury lamp in methanol with 80–90% yields. DMATr is also orthogonal to conventional methoxytrityl protecting groups, as it can be removed by irradiation in methanol, whereas the methoxytrityl protection is cleaved upon treatment with 80% acetic acid.

A similar α,α-dimethyl-3,5-dimethoxybenzyloxycarbonyl PPG (**169**, Ddz, Scheme 66) was employed by Cameron and Frechet for caging of amines.[316] Irradiation of these thermally stable carbamates with a medium-pressure mercury lamp results in liberation of free amines both in THF solution and in the solid state.

The stability of 9-phenylxanthylium cation prompted the development of the 9-phenylxanthyl (**170**, pixyl, Px) PPG for primary alcohols (Scheme 67).[317]

The pixyl PPG is readily introduced in 65–74% yield by treating alcohols with commercially available pixyl chloride in the presence of pyridine. Irradiation of the pixyl ethers at 254 or 300 nm results in the release of the alcohol in 78–97% yield. Based on deprotection of the nucleoside thymidine, the authors suggested that Px could be an effective protecting group for the combinatorial synthesis of oligoribonucleotides.

The 9-phenylthioxanthyl group (**171**, *S*-pixyl, S-Px, Scheme 68) was found to be an even more efficient cage for primary alcohols, as it absorbs at longer wavelengths and has a higher quantum yield of deprotection.[318] It was also shown that *i*-butyryl and benzoyl protection of amino groups in nucleobases is not affected by the photolysis. The chemical yield of deprotection varied from 75% for cytidine to 97% for thymidine.

Further studies of the substituent effects on the photochemical release of thymidine from the S-Px cage showed that an electron-donating group in the 3-position enhances the efficiency of the photolysis by a factor of three.[319] Moreover, some of these compounds proved to be suitable for deprotection under irradiation with 350 nm light. For example, 5'-*O*-(3-methoxy-9-phenylthioxanthyl)-2'-deoxythymidine (**172**, Scheme 68) quantitatively releases thymidine by irradiation at 300 or 350 nm.

Direct photosolvolysis of ethers, such as **167**, **168**, **170–172**, has great advantage for alcohol caging over the use of photolabile carbonates. Substrates are released directly from the excited state of the photocage within few microseconds in the former case, while

decarboxylation of photochemically generated mono-carbonate in the latter case is a much slower process.

Photosolvolysis of arylmethanol derivatives has also been employed for the deprotection of carbonyl compounds components of photolabile acetals. Wang and co-workers developed a photoremovable protecting group for carbonyl compounds based on trityl photochemistry.[320] Ketones and aldehydes are converted into cyclic acetals (**173**) by treatment with 5-methoxysalicylic alcohol derivatives (Scheme 69). Upon irradiation, the carbonyl compounds are released in 75–90% yield and good quantum efficiency ($\Phi = 0.11$). The authors proposed that this reaction proceeds via a two-step mechanism involving a zwitterionic intermediate. However, it is also possible that initial photocleavage of the benzylic C–O bond produces a hemiacetal, which undergoes further hydrolysis. This cage is remarkably stable to a variety of reagents including metalloorganic (PhLi, $LiAlH_4$, *t*-BuOK), strong acids (AcOH, TFA, conc HCl), and mild oxidants (DDQ). Besides, Thevenet and Neier have recently studied photorelease of alcohols from the corresponding naphthalen-2-ylmethylidene and arylethynylmethylidene acetals.[321]

The methoxy substituent in **173** was strategically positioned to exploit Zimmerman's *meta*-effect.[312a,313] The second methoxy group in **174** makes photoheterolysis of benzylic C–O even more efficient as noted earlier. A series of carbonyl compounds were protected in the presence of *p*-toluenesulfonic acid[322] or in the neat state and with no added catalysts at 140 °C[323] and then released ($\Phi = 0.17–0.23$)[320c,320e] from the photocage **174** upon irradiation with a 450 W medium-pressure mercury lamp in aqueous acetonitrile. Both protection and uncaging proceeded in 74–99% yields. Introduction of electron-donating or withdrawing substituents in *para*-position of the phenyl substituents in **174** allows for the adjustment of λ_{max} of the chromophore.[320c]

The majority of trityl and benzyl-based PPGs requires irradiation with light of rather short wavelength to achieve efficient substrate release. In order to shift the caging chromophore absorbance to longer wavelengths the photocleavage of several polyaromatic analogs of the benzyl protecting group, including (2-naphthyl)methyl,[324] (anthracen-9-yl)methyl,[325] (pyren-1-yl)methyl (**175**, Scheme 70),[326] (perylen-3-yl)methyl,[327] and (phenanthren-9-yl)methyl[326a–c] was explored.

These cages have significant absorbance at 350 nm and show weak to moderate fluorescence ($\Phi_{fl} = 0.01–0.2$). Polyaromatic PPGs are well suited for release of very good leaving groups, such as phosphates (**175a**). Uncaging of carboxylic acids, on the other hand, is less reliable, and alcohols are released with less than 0.005 quantum efficiency. The common drawback of polyaromatic PPGs is their poor aqueous solubility. Addressing this problem, Furuta and co-workers have developed the anthraquinon-2-ylmethoxycarbonyl cage (**176**, Aqmoc),[324,326d] which undergoes fairly efficient photocleavage at 350 nm ($\Phi_{350\ nm} = 0.10$) and has good aqueous solubility (Scheme 71). The utility of Aqmoc group for photoremovable protection of carbohydrates and nucleosides has been demonstrated with 68% and 91% chemical yields, respectively. 1,3-Pentadiene efficiently quenches the photosolvolysis reaction suggesting that cleavage of Aqmoc protection proceeds via the triplet state of the chromophore.

A variation of the anthraquinon-2-ylmethoxy group with a methyl substituent in the benzylic position (**177**, anthraquinon-2-yleth-2-yl, Aqe) was tested for caging of carboxylic acids (Scheme 72).[328]

This chromophore has a λ_{max} at 325 nm and significant absorbance at 350 nm. Irradiation of 2-(1′-hydroxyethyl)-anthraquinone carboxylates **177a–c** at the latter wavelength resulted in

relatively efficient (Φ ~ 0.12) release of the corresponding carboxylic acids in good yields. Uncaging of *p*-nitrobenzoic acid and *N*-acetyl-*L*-tryptophan proceeds with a low quantum (Φ < 0.01) and poor chemical yield, apparently due to intramolecular energy transfer from anthraquinone to the caged acids.[328] Based on quenching studies and product analysis, the authors proposed a two-step mechanism for the photocleavage of esters **177** (Scheme 73). The initial photoreduction of anthraquinone, which proceeds via the triplet state, produces hydroquinone **178**. For this step to work the reaction media must contain hydrogen donors (e.g., methanol or THF). The second photochemical step resembles the cleavage of *o*-hydroxybenzyl esters (Section 5.2).

The (anthraquinon-2-yl)methyl chromophore has been employed in the development of photolabile acetals **179** (Scheme 74).[329]

The caged carbonyl compounds **179a–d** were prepared in 40–60% yield by the reaction of anthraquinon-2-ylethyl-1',2'-diol (Aqe-diol, **180**) with ketones or aldehydes in the presence PPTS and a dehydrating agent. Acetals **179a–d** are stable in the dark in neutral solution. Upon 350-nm irradiation in MeCN/aqueous buffer (1:1) carbonyl compounds are liberated with 0.03–0.09 quantum efficiency in 60–90% chemical yield. Under these reaction conditions, Aqe-diol **180** undergoes further decomposition producing undetermined byproducts.[329]

Dore and co-workers developed heteroaryl-based PPG for carboxylic acids, (8-bromo-7-hydroxyquinoline-2-yl)methyl (BHQ), which has a strong band with λ_{max}= 370 nm.[330] Photodeprotection of acetic acid from the hydroxyquinoline **181a** (Scheme 75) was found to be more efficient compared to 4,5-dimethoxy-2-nitrobenzyl (DMNB, Section 3.1) and (6-bromo-7-hydroxycoumarin-4-yl)methyl (BHCM, Section 4) acetates.[331] Noteworthy, this group can be removed under two-photon excitation conditions[332] (see also Section 9). BHQ-caged carboxylates (**181b**), phosphates (**181c**), and diols (**182**) are efficiently released under simulated physiological conditions using single photon and two-photon activation.[331] In addition, a (2-phenylquinolin-4-yl)methyl group[333] and the corresponding arylmethylsulfonyl analogue[334] have been proposed as PPGs for alcohols and amines, respectively.

Photochemical properties of the quinoline-based PPGs could be further adjusted by varying the substituent in the aromatic ring.[335] For example, replacing the bromine substituent in BHQ with a cyano group (8-cyano-7-hydroxyquinoline-2-yl)methyl, CyHQ) results in a significant red shift of the chromophore. However, none of the (quinoline-2-yl)methyl derivatives had higher sensitivity towards two-photon absorption than the parent BHQ group.

Another heterocyclic analog of benzyl PPG, (benzoxazol-2-yl)methyl and its derivatives, were tested for photolabile protection of the carboxyl group in amino acids.[336] *N*-(Phenylmethoxy)carbonyl-*D*-alanine was released in moderate to quantitative yield upon rather lengthy irradiation at 350 nm.

5.2 *o*-Hydroxyarylmethyl Groups

Introduction of the hydroxy substituent *ortho* to the benzylic position dramatically changes the mechanism of C–O bond cleavage and enhances the overall efficiency of the process. Irradiation of *o*-hydroxybenzyl ethers (**183**) or their naphthyl analogs (**184**, (3-hydroxynaphthalen-2-yl)methyl, NQMP) results in the quantitative release of an alcohol and the formation of *o*-quinonemethide (**185**) (Scheme 76).[337] In the presence of water, the latter undergoes very rapid hydration to give the parent diol or can be trapped with vinyl ether to give photostable chroman.

The release of the substrate proceeds within 12 μs after excitation with 0.20 to 0.40 quantum efficiency and in high to quantitative yield. The quantum and chemical yields of the uncaging reaction show little dependence on the nature of the hydroxy compound. Thus, alcohols, phenols, and carboxylic acids caged with the (3-hydroxy-2-naphthalenyl)methyl group (**184**) are released in 91–98% yield upon 300 or 350 nm irradiation (Scheme 77).[338]

The common drawback of photolabile protecting groups described in this section is that the chromophore of the cage is usually preserved in the photoreaction, reducing the efficiency of the photolysis at higher concentration of caged compounds due to the internal filter effect. The 2,5-dihydroxybenzyl (**186**, DHB) cage alleviates this problem. The quinone methide **187** formed upon the release of a substrate undergoes tautomerization into methyl-*p*-quinone **188** (Scheme 78).[339] UV spectra of the caged compounds **186a–d** show a characteristic absorption band at 297 nm, while **188** has no absorbance at this wavelength. The compound **189** incorporates a safety-catch feature: *p*-quinone precursor is photochemically inert, but mild in situ reduction (sodium dithionite, NADH, etc.) of this compound produces the photoreactive hydroquinone **186**.[339]

A variation of the DHB group was adapted for caging 1,2- and 1,3-glycols, as well as for photolabile benzylidene protection of carbohydrates. Thus glucose was released with 0.30 quantum yield and 97% chemical yield upon irradiation of **190** (Scheme 79).[340]

o-Hydroxybenzylidene acetals, such as **190** or **191** (Scheme 80) undergo slow dark hydrolysis in aqueous solutions with a half-life from two days to several weeks, while *p*-quinone precursors are stable both in solution and in solid state. When hydrolytic stability and bleaching of the caging chromophore are not important, glycols can be efficiently caged as photolabile acetals of 5-methoxysalicyl aldehyde (Scheme 80).[339]

A dihydroxybenzyl-based group (**192**) was also developed for the protection of carbonyl compounds (Scheme 81).[341] Ketones and aldehydes are converted into 2-(1,2-dihydroxyethyl)-1,2-benzoquinone acetals **193**. The latter compounds are stable in the dark, but are quantitatively converted to the corresponding photolabile acetals **192** using mild reducing agents. Irradiation of the latter with 300 nm light results in the efficient photocleavage of the acetals, releasing carbonyl compounds in 88–100% chemical yields.[341]

In addition, a novel bichromophoric fluorescent photolabile protecting group, based on (3-hydroxynaphthalene-2-yl)methyl and dansyl moieties, was recently shown to combine the photochemical release with fluorescent imaging by the caged substrates.[342]

Falvey and coworkers have employed an entirely different strategy for the photocleavage of benzyl analogues, such as 4-picolyl and *N*-methyl-4-picolinium esters using photosensitizers (see Section 8.2).[8b,343] In addition, visible-light photoredox catalysts have also been used to trigger deprotection of benzyl ethers[344] or benzyl amines.[345]

The properties of the most useful arylmethyl-based PPGs from Section 5 are summarized in Table 10.

6 METAL-CONTAINING GROUPS

Metal-containing photoremovable protecting groups upon irradiation have been shown to release coordinated metal ions, gaseous inorganic molecules, such as NO or CO, or organic molecules, often of biological interest. This innovative research topic has recently been reviewed by Haas and Franz,[347] Schatzschneider,[9o] Ciesienski and Franz,[9t] and Schiller and his coworkers;[10b] thus it is not covered comprehensively here.

These cages are metal complexes which undergo a change in the metal coordination environment upon single- or multi-photon excitation. Several types of organic ligands, such as amines, nitriles, azides, or thioethers, have been shown to be released. Upon irradiation with visible light above 480 nm, the most common $[Ru^{2+}(bpy)_2]^{2+}$ core (**195**; an amine is a leaving group in this case) liberates various nitrogen atom-containing ligands (Scheme 82), such as 4-aminopyridine, serotonin, butylamine, tryptamine, tyramine,[348] γ-amino butyric acid,[349] glutamate,[350] or azide.[351] One of the amino group-containing ligands has also been replaced by triphenylphosphine to increase the release quantum yield.[349b] Etchenique and collaborators have reported that ruthenium–bipyridine-based caged nicotine ($[Ru(bpy)_2(nic)_2]^{2+}$ where nic = nicotine) is released with the quantum yield $\Phi = 0.23$ upon irradiation with blue (473 nm) or green (532 nm) light.[352] Gobetto, Sadler and coworkers have used spectroscopic and DFT computational methods to study the release mechanism.[353] They showed that the photochemical activity is related to the presence of singlet and triplet transitions involving σ-antibonding orbitals, and identified and characterized the triplet state responsible for the photodissociation process.[353a] Excitation of the metal-ligand-to-ligand charge-transfer (MLLCT) band of the $[Ru(bpy)(4AP)4]^{2+}$ complex (4AP = 4-aminopyridine) was found to provide selective photodissociation of two 4AP moieties in two consecutive steps with quantum yields of approximately 6×10^{-3} and 2×10^{-4}, respectively.[353c] The photorelease of an aliphatic amine from a ruthenium–bipyridine-based PPG attached to silica surfaces has recently been shown to occur upon single- (460 nm) and two-photon (900 nm) excitation (Section 9).[354] A caged glutamate can also be liberated upon single- and two-photon activation from a Ru complex.[355] In addition, a photoactivatable fluorescent probe[356] as well as caging peptidomimetic inhibitors[357] are recent examples in which a ruthenium–bipyridine-based PPG releases a nitrile ligand. Thioether ligands, such as thioether-cholestanol hybrid,[358] *N*-acetylmethionine,[359] or biotin[359] can also be liberated from the $[Ru^{2+}(bpy)_2]^{2+}$ core upon irradiation with visible light.

7 MISCELLANEOUS Groups

7.1 Pivaloyl Group

Initially used as part of a photolabile linker for solid-phase synthesis, pivaloyl derivatives such as **196** fragment by a Norrish-type I mechanism equally well in solution phase, releasing carboxylic acids or alcohols (Scheme 83).[360] The carbonyl group might seem to be a nuisance due to cross reactivity, but these pivaloyl esters show remarkable stability under typical synthetic conditions (such as acids, bases or transition-metal catalysts). The side products are all volatile: carbon monoxide, isobutene, and acetone), and the quantum yield of release is quite high ($\Phi = 0.56$). They require, however, the use of a relatively short wavelength source (280–340 nm), which can be problematic when dealing with biomolecules.

7.2 Esters of Carboxylic Acids

The 2-benzoylbenzoic acid moiety (**197**) has been utilized as a PPG for primary and secondary alcohols, or thiols (Scheme 84).[361] This chromophore exhibits photochemical reactivity typical for benzophenone, such as photoinitiated H-atom or electron transfer to the excited carbonyl group. Alcohol release is accompanied by the formation of a dimeric side-product **198** in the presence of an H-atom donor, whereas the isobenzofuranone derivative **199** is obtained by photoreduction with, for example, amines.

2-Benzoylbenzoic acid derivatives were utilized as photoreversible inhibitors of serine proteases by Porter and Jones.[362] Various esters **200** served as efficient chymotrypsin (a digestive enzyme) inhibitors (Scheme 85). The synthesized acyl-chymotrypsins were found

to be stable to hydrolysis from hours to months; a sharp increase of enzyme activity was then observed upon irradiation at 366 nm: up to 80% of the preinhibition activity was recovered. The corresponding 2-aroylbenzoic acid was formed as a side-product; Scheme 85 shows one of the proposed reaction mechanisms.

A photofragmentation reaction of xanthenoic esters has been shown to give lactones of various ring sizes.[363] The initial homolytic O–C bond cleavage of the esters **201** leads to xanthene and formyl radicals which rearrange to lactones **202** and **203** in moderate to low chemical yields (10–55%; Scheme 86). The corresponding alcohols **204** and formates **205** were isolated as side-products.

A water-soluble visible-light absorbing ($\varepsilon_{400} > 9000\ M^{-1}\ cm^{-1}$) PPG for carboxylic acids based on the aminonitrophenyl chromophore **206** has been demonstrated to photorelease β-alanine (**207**), which then activates the inhibitory glycine receptor in the mammalian central nervous system (Scheme 87).[364] β-Alanine was found to be released in 5 μs with rather low quantum yields of $\Phi = 0.03$ and 0.002, when irradiated at $\lambda = 360$ or 450 nm, respectively.

7.3 Arylsulfonyl Group

The photochemical generation of acids (photoacids) is an important strategy in the development of coating and imaging technologies as well as the synthesis of polymers.[365] In such a process, the acids are typically photochemically produced from relatively small amounts of an excited initiator to start a chain reaction. However, this topic is beyond the scope of this review; here we only cite a few recent reports[366] as examples.

Arylsulfonyl ester (Scheme 88) or amide photoacids are also frequently used as PPGs (e.g.,[367]). For example, this strategy was utilized for dopamine release from a photocleavable biotin-linker[368] or for reactivation of a benzenesulfonyl-caged Zn^{2+} tetraazacyclododecane complex.[369] Acid (proton) photorelease has been used to study proton binding in the sarcoplasmic reticulum.[370]

7.4 Ketones: 1,5- and 1,6-Hydrogen Abstraction

A considerable focus has been devoted to the development of photochemically releasable volatile odoriferous compounds – fragrances. Such applications have been a subject of several recent reviews.[11,371] Aldehydes and ketones are important classes of fragrance molecules. Hermann and coworkers have shown that protected carbonyl compounds can be photoreleased from α-keto esters (**208**) via the Norrish Type II photofragmentation under mild conditions in the presence of air (Scheme 89).[372] The initially formed 1,4-biradical reacts with air oxygen followed by the release of the aldehyde or ketone **209**, carbon dioxide, and the corresponding carboxylic acid. In the absence of oxygen, **208** can also undergo β-cleavage to give **209** and a ketene intermediate.

Photochemically triggered hydrolysis of protected volatile aldehydes or ketones has also been demonstrated employing 1,5-diketones with abstractable γ-hydrogen[373] or 1-alkoxy-9,10-anthraquinones, e.g., **210** (Scheme 90).[374] The reaction starts with 1,6-hydrogen atom abstraction followed by electron transfer to form the zwitterion **211**, which is trapped by an alcohol. The final fast hydrolytic step liberates the protected compound **212**.

7.5 Carbanion-Mediated Groups

Another type of PPGs relies on the photochemical formation of a carbon-centered anion, which drives the subsequent release of a leaving group via β-elimination (Scheme 91). This strategy, developed by Scaiano and coworkers,[375] is often based on the photochemical decarboxylation in the side chain of a chromophore and is compatible with an aqueous

environment. Benzophenone (LG = carboxylate; $\Phi < 0.7$),[375a] xanthone (LG = carboxylate; $\Phi < 0.7$[376]),[377] and phthalimide[378] moieties have been employed as the chromophores. In this context, a stereodifferentiation process involving the release of the caged molecule has been demonstrated on photoinduced decarboxylation of 2-phthalimido-3-hydroxy-propionate derivatives in which different reaction efficiencies were found for cages with threo or erythro configurations.[379] Griesbeck and coworkers have shown that methylthiomethyl esters of ω-phthalimido carboxylic acids can liberate the carboxylic acids upon irradiation.[380]

7.6 Sisyl and Other Silicon-Based Groups

Silicon-based protecting groups are often used in organic synthesis to protect alcohols as silyl ethers due to their predictable and selective deprotection and tolerance to many organic reagents. A bulky sisyl (tris(trimethylsilyl)) group, has been introduced as a photocleavable protecting group for primary and secondary alcohols.[381] It was shown that it is stable to aqueous bases, Grignard and Wittig reagents, and resistant to selected fluoride salts. Irradiation of sisyl ethers at 254 nm leads to the deprotection of the alcohols in good chemical yields (62–95%)[382] by a radical mechanism.[383]

The Si–O bond of various trialkylsilyl esters can also be photocleaved by in situ generation of HBr from a catalytic amount of CBr_4.[384] Such an approach has been employed for the deprotection of *t*-butyldimethylsilyl and β-(trimethylsilyl)ethoxy methyl ethers.[385] It was shown that the primary silyl ethers on carbohydrate molecules can be selectively liberated in the presence of secondary silyl ethers.

Photochemical protodesilylation of **213** in the presence of hexafluoroisopropanol (HFIP) or isopropanol (IPA) was reported to form an alkoxy intermediate, in which the C–Si bond is oxidized in a subsequent step to release a triol (Scheme 92).[386]

7.7 2-Hydroxycinnamyl Groups

Porter and coworkers have been first to utilize a 2-hydroxycinnamyl moiety (**214**, Scheme 93) as a PPG in 1987, in this particular case, for the photochemical activation of thrombin, a serine proteinase.[387] In general, this system undergoes initial photoinitiated isomerization followed by cyclization which facilitates the release of caged substrates such as alcohols. Hiramatsu and coworkers utilized a caged reagent for a fluorimetric assay of peroxidase that led to uniform addition of a reagent without stirring.[388] A trihydroxycinnamyl ester-based photocleavable detergent was applied for enhancing the water solubility of cell proteins followed by their MALDI-MS determination.[389] The 3,5-dibromo-2,4-dihydroxycinnamic caging group was synthesized and used for 2-photon release of a biologically active substrate in a specific region within the cell.[390] The fluorescence emission of the photocyclization byproduct, 6,8-dibromo-7-hydroxycoumarin, then provided the information about the concentration of the released species. Applications of this chemistry to release of a fluorescent reporter and the desired caged substrate[391] or mask bioactivity of complex enzymes, such as thrombin, factor Xa, and trypsin, have been demonstrated.[392] A small library of the *o*-hydroxycinnamic derivatives was recently synthesized to study and improve one- and two-photon release.[393] Cinnamate esters were also successfully coupled with a CdSe nanocrystal surface.[394] The corresponding coumarins were then released upon irradiation of the CdSe nanocrystal by visible light. This protocol also aided the understanding of fundamental nanocrystal-ligand interactions.

Silyl analogues of 2-hydroxycinnamyl derivatives (**215**) as PPGs have been introduced by Pirrung and coworkers (Scheme 94).[395] A clean and high-yield (< 92%) deprotection of primary and secondary alcohols was reported.

7.8 α-Keto Amides, α,β-Unsaturated Anilides, and Methyl(phenyl)thiocarbamic Acid

Steinmetz and coworkers reported that the carboxylates (including GABA, BocAla, and Glu) attached to the α-carbon of α-ketoamides (**216**) could be photochemically released, possibly through a zwitterionic intermediate **217**, in very good chemical (<93%) and quantum (0.28–0.37) yields, along with the formation of a mixture of two diastereomeric hemiacetals **218** and a small amount of oxazolidinone **219** as by-products (Scheme 95).[396] The yield of **219** was found to depend strongly on the type of the alkyl substituents on the carbon adjacent to the amide nitrogen.[397] Time-resolved pH-jump experiments showed that the reaction rate is on the microsecond time scale and that carboxylate release occurs in the rate-determining step.[398] Phenolates can also be liberated from **216**.[399] Laser flash photolysis experiments demonstrated that *p*-substituted phenolic substituents undergo photocleavage to give the corresponding phenol with good quantum yields (0.2–0.3).[400] The authors proposed a mechanism that involves H-atom transfer from an *N*-alkyl group to the carbonyl to produce a zwitterionic intermediate that eliminates the phenolate.

α,β-Unsaturated anilides (**220**) have been utilized as PPGs for carboxylates or phenolates (Scheme 96).[401] The chemical (<71%) and quantum (<0.083) yields of LG release were reported. A zwitterionic intermediate analogous to **217**, responsible for LG extrusion, is assumed to form.

The cysteinyl radical was shown to be photochemically released from the methyl(phenyl)thiocarbamic acid chromophore **221** (Scheme 97).[402] The S–S bond cleavage and the cysteinyl radicals' recombination was studied by time-resolved IR spectroscopic techniques.

7.9 Thiochromone *S*,*S*-Dioxide

Kakiuchi and coworkers recently introduced a novel PPG based on the thiochromone *S*,*S*-dioxide chromophore **222** (Scheme 98).[403] The alcohols (as carbonates), amines (as carbamates), and carboxylic acids were released in excellent chemical yields (up to 99%) upon irradiation at λ = 280 nm in methanol. The reaction progress was monitored by fluorescence spectroscopy.

7.10 2-Pyrrolidino-1,4-Benzoquinone Group

Steinmetz and coworkers have demonstrated that 2-pyrrolidino-1,4-benzoquinone **223** gives, upon irradiation with visible light (below ~700 nm), an unstable benzoxazoline photoproduct, which expels a leaving group, such as carboxylate or phenolate, in a subsequent dark elimination reaction (Scheme 99).[404] The reaction proceeds with quantitative chemical but modest quantum (Φ = 0.03–0.10) yields.

7.11 Triazine and Arylmethyleneimino Groups

A triazine moiety can be used as a (thermally) labile linker in solid-phase synthesis.[405] Its applicability as a photocleavable linker has also been reported.[406] Laser irradiation of **224** at 355 nm leads to liberation of the protected amines or amino acid derivatives in moderate to high chemical yields (77–100%; Scheme 100). A triazine linker has also been employed as part of a homopolymer backbone to yield photoinduced backbone fragmentation.[407]

It has been shown that the naphthylmethyleneimino group (Ar–C=N–OCO–NHR; Ar = 1-naphthyl) releases aliphatic or aromatic primary amines as well as α-amino acids (NH_2R) in good to excellent chemical yields (51–96%) upon irradiation at 280 or 340 nm. The reaction proceeds via a hemolytic cleavage of the N–O(CO) bond. Such strategies are similar to those utilized in the field of photobase generation, which is not covered by this review.[12a]

7.12 Xanthene and Pyronin Groups

Wirz and coworkers have recently demonstrated that the 6-hydroxy-3-oxo-3*H*-xanthen-9-yl)methyl derivatives **225** release diethyl phosphate or carboxylic acid upon irradiation with visible light (over 500 nm) with quantum yields of 0.005–0.04 (Scheme 101).[408] This reaction is the subject of further investigation.

A novel class of pyronin analogues **226**, which undergo a photochemical cleavage of the C–C bond in the presence of water both in solution and on a silica gel surface upon direct irradiation with yellow light (Scheme 102), has been reported by Klan and coworkers.[409] The final chromophoric photoproduct was shown to be a stable compound absorbing below 430 nm. The course of the reaction was monitored by the characteristic fluorescence emissions of both the starting compound (λ_{max} = 607 nm) and the final product (λ_{max} = 448 nm). As one of the rare examples of visible-light triggered caged systems, it was suggested that the moiety could be used in the field of photoremovable protecting groups or caged fluorophores (Section 11).

7.13 Retro-Cycloaddition Reactions

A photocleavable linker based on 7-hydroxy-1,1-dimethylnaphthalenone (**227**) for drug attachment to a polymer support has recently been introduced.[410] It undergoes a photochemical [2+2] cycloaddition with 5-fluoro-1-heptanoyl uracil (**228**), a well-known cytotoxic agent derivative, to form a heterodimers (**229**; Scheme 103). The linker–drug conjugate is then photochemically polymerized at 470 nm with methyl methacrylate (**230**) yielding a HEMA/MMA copolymer. Photoinduced release of **228** from the polymer via single (Φ = 0.01 at λ = 331 nm) or two-photon absorption was observed.

A different strategy – photosensitizer drug delivery via an optical fiber – has recently been designed by Greer and coworkers.[411] A singlet oxygen sensitizer (pheophorbide) bound to a porous silica cap of a hollow optical fiber via an alkene spacer (**231**) was shown to be released in an oxygen stream (Scheme 104). A (*Z*)-enol ether bridge of **231** reacts with $^1O_2$ to give the dioxetane intermediate **232**, which cleaves to liberate the photosensitizer at the probe tip in the proximity of a tumor cell. Such a sensitizer delivery has the potential for photodynamic therapy. In a different study, Wilson and coworkers described the photorelease of *o*-quinones from pyrene dihydrodioxin (**233**, Scheme 105).[412]

Utilization of a dithienylethene photochemical switch[413] for the thermal release of an electrondeficient alkene has been reported.[414] The thermally stable derivative **234** undergoes photochemically reversible ring-opening reaction to give **235**, which liberates ethylene via reverse Diels–Alder reaction (Scheme 106). The reaction can be controlled by selection of the irradiation wavelength.

Triggering of a retro Diels-Alder reaction through a photothermal effect was demonstrated by Gates and coworkers for the first time.[415] A nanoparticle attached to the caged compound through a linker absorbs the incident light at a specific frequency (of a plasmon resonance) and converts it into heat which then promotes the chemical reaction to liberate the attached chemical species.[415]

An alternative approach that utilizes coumarin dimers as photocleavable linkers between the substrate and the polymeric carrier was investigated by Hampp.[416] The core dimeric coumarin cage **236** was constructed by [2+2] photocycloaddition (Scheme 107). Deprotection of a *t*-butyldimethylsilyl (TBS) group, followed by esterification, was used to successively install a polymer tether (**237**) and chlorambucil (**238**).[416b]

This type of caging presumes linking through the 7-hydroxy group of one coumarin moiety to the active substance while the other coumarin is attached to a polymer support. The cleavage of the dimer occurs via [2+2] cycloreversion, which can be triggered both by single- and two-photon absorption (Scheme 108).[417]

8 SENSITIZED RELEASE

In most cases, a PPG is the chromophore which is responsible for both the light absorption and the primary photochemical step, resulting in a specific bond breaking process. There have been more or less successful attempts to modify the structure of a PPG in order to enhance its absorption properties and chemical reactivity. Recent research efforts have focused on the development of the systems composed of two, separated or linked, molecular components, in which the photorelease occurs from the moiety that is indirectly activated by energy transfer from or electron transfer from/to the excited auxiliary chromophore (photosensitizer).[27] Such a sensitizer moiety should absorb strongly in the region of interest.

8.1 Sensitized Release: Photoinduced Energy Transfer

Energy transfer is a process by which the excitation energy of an excited molecule (donor; sensitizer, S) is transferred (k_{ET}) to a neighboring molecule (acceptor; quencher, Q, Scheme 109).[27] Photosensitization via energy transfer is one of the most common and practical ways to generate excited states, particularly triplet states, especially when direct excitation at a desired wavelength cannot be achieved or when it does not lead to the desired excited state. For efficient triplet–triplet transfer, the process should be exergonic to prevent reverse transfer (k_d); the donor molecule has to undergo efficient intersystem crossing, and have a high molar absorption coefficient at the irradiation wavelength as well as a sufficiently long triplet lifetime to enable quantitative energy transfer.[27,418] If the acceptor molecule is a PPG, the reaction (k_r) then leads to release of a leaving group. Bimolecular sensitization is achieved through diffusive encounters. When the donor is covalently bound to the acceptor molecule, intramolecular energy transfer enables a more specific control of the transfer;[419] in such a case, only “equimolar” amounts (or less) of a sensitizer are needed. This strategy, benefiting from an increased “uncaging cross-section” ($\Phi_{rel}\varepsilon(\lambda_{irr})$; see the footnote in Section 1 for discussion) of release using triplet sensitization, has already been demonstrated on several examples.

In 2004, Steiner, Green and coworkers demonstrated that triplet sensitization of a known photoremovable protecting 2-(2-nitrophenyl)propyl moiety (**239**, Scheme 110; see also Section 3.2) in homogeneous solutions or on glass substrates (microarray chips) enhances its uncaging cross-section.[418] The leaving group (alcohol), attached as a carbonate, is liberated in the course of the reaction as a carbonate monoester that disintegrates thermally into the corresponding alcohol and CO_2. Acridin-9(10*H*)-one (**240**) and 9*H*-thioxanthen-9-one (**241**) were used as sensitizers (sens) that were excited by both continuous illumination and laser flash photolysis to study the reaction mechanism. Transient absorption observed at ~400 nm was assigned to the *aci*-nitro intermediate **242** (see Section 3.1). The sensitization kinetics of this bimolecular process were found to be nearly diffusion-controlled both in solution (k_q = $1–4 \times 10^9$ M^{-1} s^{-1}; in acetonitrile or methanol) and on the chip. Four photolabile phosphoramidites were synthesized for testing high-density oligonucleotide microarrays; the average chemical yield for release of the bases by using **241** was 97%. The kinetic analysis of the photosensitized cleavage reaction of surface-bound photolabile chromophores with free diffusion of sensitizer molecules from the bulk of a solution to the surface has recently been reported.[167]

In addition, Pirrung, Dore, and coworkers have recently demonstrated that, while the 2-(2-nitrophenyl)propyl group has a low sensitivity to two-photon excitation (see also Section 9),

the presence of a sensitizer with a large two-photon absorption cross-section, such as **241**, in the solution improves it considerably.[234]

Steiner and coworkers have also designed and studied covalently linked 9*H*-thioxanthen-9-one (the sensitizer) and 2-(2-nitrophenyl)-propoxycarbonyl chromophores.166,233,240b, 240g Scheme 111 shows an example of such a compound (**243**), in which the sensitizer is attached to the chromophore via a saturated four-bond aliphatic tether. After the sensitizer is excited and intersystem crosses to the triplet state, the energy is transferred through space to the 2-(2-nitrophenyl)propyl group, which liberates thymidine.

A variety of other covalently linked 9*H*-thioxanthen-9-one derivatives, including **244** (Scheme 111), in which the sensitizer is directly attached to the photoactive chromophore, were also prepared and studied to compare their photophysical and photochemical properties using stationary fluorescence and nanosecond and femtosecond time-resolved laser spectroscopy.[166] The authors proposed a dual mechanism of triplet–triplet energy transfer. It was suggested that a slower transfer involves the lowest triplet (T_1; π,π^*) state of 9*H*-thioxanthen-9-one in the case of long-tether bichromophores. When bichromophores are connected through a short linker, the energy is believed to be transferred from the T_2 (n,π^*) state. These protecting groups were tested under conditions for lithographic DNA-chip synthesis.[233] Their speed of release was found to be ten times higher than that of the non-modified 2-(2-nitrophenyl)propyl moiety.

Corrie and coworkers have designed the benzophenone antenna-sensitized 1-acyl-7-nitroindolines **245**,[249a–d] which display a significantly enhanced extent of photochemical cleavage in solution compared to their non-sensitized analogues[247–248] (Scheme 112; see also Section 3.3). The 4,4'-dialkoxybenzophenone chromophore (sens), which has substantially higher molar absorption coefficients in the region 270–320 nm than those of the nitroindoline moiety,[249d] serves as a light-harvesting antenna that transfers its triplet energy to form the reactive triplet state of the acceptor (PPG). It subsequently undergoes rapid photocleavage to liberate the 1-acyl substituent as the carboxylate in aqueous media. The triplet energy of 4,4'-dialkoxybenzophenone (E_T = 70 kcal mol^{-1}) is about 10 kcal mol^{-1} higher than the estimated E_T of nitroindoline, which is one of the key conditions for efficient transfer.[249d] The authors then evaluated biological effects of released L-glutamate from **245** (R = $CH_2CH_2CH(NH_3^+)COO^-$) using hippocampal neurons in primary culture and cerebellar granule cells in an acute brain slice preparation.[249c] The data suggested that glutamate was completely released in the irradiated samples. Recently, a more water-soluble analogue of **245** was synthesized and tested.[249a]

8.2 Sensitized Release: Photoinduced Electron Transfer

The release of a leaving group can also be induced by photoinduced electron transfer (PET). In general, the excited state of a sensitizer (S) is quenched due to electron transfer to a quencher (Q; k_{eT}; Scheme 113). S and Q can be either separated or interconnected via a tether. As a result, a radical ion pair is formed provided that both S and Q are neutral prior the reaction. The radical ion pair can undergo a chemical reaction[420] to give the products (here, the leaving group is released from one of the radical ions, k_r) or a reverse electron transfer to regenerate S and Q (k_{-eT}). This represents an important fork in the reaction seqeunce which determines the overall release quantum yields. The strategy allows the light absorption step to be studied separately from the release step; therefore, both processes can be independently optimized. In principle, two major mechanistic strategies can be designed because either of the S or Q moieties can represent a PPG bearing the leaving group. As a result, the PPG can either be oxidized by loss of an electron or reduced by accepting an electron in a direct (the protecting group is a chromophore) or sensitized manner. Obviously,

only the latter method has the benefits of a tunable chromophore. Some of the PET-based PPGs and their applications have been reviewed by Falvey and Sundararajan.[8b]

The Gibbs free energy of photoinduced electron transfer $\Delta_{eT}G^{\circ}$ in an excited encounter complex (D··A)* can be calculated from Eq 1, where $E^{\circ}(D^{\bullet+}/D)$ is the standard electrode potential of the donor radical cation, $E^{\circ}(A/A^{\bullet-})$ that of the acceptor A, ΔE_{0-0} is the 0–0' excitation energy of the corresponding excited molecule (D* or A*), and w are the electrostatic work terms.[27,421]

$$\Delta_{eT}G^{\circ}=N_A\{e[E^{\circ}(D^{\bullet+}/D)-E^{\circ}(A/A^{\bullet-})]+w(D^{\bullet+},A^{\bullet-})-w(D,A)\}-\Delta E_{0-0} \quad \text{Eq 1}$$

Photofragmentation of tosylamides (**246**) in the presence of an electron donor (sensitizer), such as 1,4-dimethoxybenzene, and a reducing agent, such as ascorbic acid or sodium borohydride, resulting in the release of a free amine, was demonstrated by Yonemitsu and coworkers (Scheme 114) as the first example of a PET-based deprotection.[422] The reductant acts as the source of the hydrogen atom and an electron (thus restoring the sensitizer). The release of simple amines occurs in high chemical (75–91%) and quantum (<0.65) yields. A covalently linked sensitizer approach was also explored.[423]

More recently, Corrie and coworkers reported on the photochemistry of sulfonamide derivatives of amino acids.[424] Glycine was released from the parent compound in rather low chemical yields unless a large excess of ascorbate was present in the solution. The best yields for the amino acid derivatives were found to be below 30%.[425] The concurrent decarboxylation, triggered by intramolecular hydrogen-atom or electron transfer from the peptide bond, was believed to represent the major competing reaction.[426] The tosyl group has also been used as a protecting group for near-quantitative thymidine liberation in the presence of 1,5-dimethoxynaphthalene as an electron donor in the synthesis of 5'-amino analogues of 3'-azido-3'-deoxythymidine (AZT).[427] In contrast, methanesulfonyl and pentafluorosulfonyl esters were shown to be less suitable PET-based protection moieties.[428]

In addition to their intrinsic photoreactivity, phenacyl derivatives (Section 2.1) can also release the leaving groups from the α-position upon one-electron reduction to the corresponding phenacyl anion radicals (Scheme 115). The carboxylates, for example, are liberated with a rate constant of ~10^8 s^{-1}.[429] Falvey and coworkers demonstrated that these leaving groups are readily released from phenacyl esters (**247**) upon photosensitized electron reduction by light-absorbing amines (sens), provided they possess excited state oxidation potentials below or equal to −2.2 V.[430] Quantitative yields were reported for various derivatives. This approach was later extended for sensitizers which absorb at wavelengths in the near UV region (<400 nm).[430b] Similarly, irradiation of phenacyl esters in micelles,[57a] or 1-oxoindan-2-yl and 1,3-dioxoindan-2-yl esters in acetonitrile solutions[60] was shown to liberate the carboxylic acids in high chemical yields. The release of other leaving groups has also been examined. A high-yielding (68–100%) liberation of phosphates, diacids, and alcohols (protected via carbonate linker) was reported.[431]

The electron-donor sensitizers can also be covalently attached to the phenacyl moiety. Laser flash photolysis studies revealed that a charge transfer state (τ ~500 ns) between *N,N*-dimethylaniline and the phenacyl chromophores of **248** is formed upon irradiation (Scheme 116).[343a] The phenacyl anion radical subsequently releases the leaving group (carboxylate) or regenerates the ground state of the parent compound.

Falvey and coworkers demonstrated that the 4-pyridylmethyl (picolyl) group, previously used as a conventional protecting group for carboxylates in peptide synthesis, could be photochemically reduced in the presence of *N,N,N',N'*-tetramethylbenzidine.[343b] The low

reduction potential of the picolyl group (E[pyridine/pyridine$^{-\bullet}$]= −2.62 V vs SCE)[38] precludes this group from being reduced by most sensitizers; therefore, alkylation on the nitrogen (**249**, Scheme 117) was chosen to increase its reduction potential. Irradiation of a perchlorate salt of **249**, in the presence of, for example, the carbazole **250** as an electron donor, liberates a leaving group, such as a carboxylate.[343b] The addition of 1,4-cyclohexadiene as a hydrogen atom donor (to suppress back electron transfer) was found to result in increased chemical (86%) and quantum (0.39) yields of carboxylic acid release. The *N*-methylpicolinium esters can also serve as protecting moieties in the absence of any external photosensitizer when the iodide counterion (an electron donor) is exchanged for perchlorate.[343b]

Deprotection of carboxylic acids, amino acids, and phosphates from **249** in the presence of visible-light absorbing photosensitizers and 1,4-cyclohexadiene has been reported to take place in high chemical yields (87–100%).[432] The pyrromethene photosensitizers (PM 546 and 597) employed in this work are dyes originally developed for use in lasers. Mediated electron transfer with benzophenone or xanthone tethered to the picolinium moiety in the presence of a photosensitizer was used to increase the quantum yield of carboxylic or amino acids release to $\Phi = 0.72$ at $\lambda = 380$ (Scheme 118).[343c,433] Gold nanoparticles absorbing the visible light (>500 nm) were shown to mediate electron transfer between dithiothreitol, a good electron donor, and an *N*-methylpicolinium ester in aqueous solution with quantum yields in the range between 0.5 and 4.5, suggesting involvement of a radical chain mechanism.[434] Ketocoumarin dyes were also used in a similar application.[435] Tris(bipyridyl)ruthenium(II) as both a photosensitizer and a mediator for electron transfer between a good electron donor and the newly synthesized water-soluble 2-cyanopicolinium protecting group was recently demonstrated to result in the release of various carboxylic acids.[436]

Falvey and coworkers then exercised the same principle to control the viscosity of aqueous solutions of **251** and cetyl trimethylammonium bromide by using visible light to initiate sensitized photorelease from the picolinium group and UV light to control photoisomerization of the attached cinnamic acid (Rubpy = tris(bipyridyl)ruthenium(II) as a sensitizer; Scheme 119).[437] The irradiation protocols are thus conveniently orthogonal to one another.

Visible-light-absorbing tris(bipyridyl)ruthenium(II) has also been recently used to mediate electron transfer to *N*-methylpicolinium carbamates (**252**) to give free amines in several steps (Scheme 120).[438] Another application of a visible-light photoredox catalyst, such as Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6), in the oxidation of electron-rich arenes resulting in the selective deprotection of *p*-methoxybenzyl ethers in 69–91% yields has been demonstrated by Stephenson and collaborators.[344a] 2,3-Dichloro-5,6-dicyano-*p*-benzoquinone as an electron acceptor has been used for deprotection of various benzyl ethers by Toshima and collaborators.[344b] In addition, Lechner and Konig have shown that flavin photocatalysis can be used as visible-light-absorbing sensitizers in the deprotection of benzyl amines.[345]

Benzyl ethers can release alcohols through oxidatively sensitized irradiation;[439] however, no additional reports have been published in the past decade. In a different strategy, Floreancig and Tu demonstrated the protection of carbonyl and carboxyl compounds, which can be released by intramolecular photoinduced electron transfer from a phenethyl alcohol/ether group to covalently tethered anthraquinone (as a sensitizer) in **253** according to Scheme 121.[440] The reported chemical yields of the deprotection were between 6 and 97%.

Cossy and Rakotoarisoa have discovered that the 2-acetoxyethyl group can be used to protect secondary amines.[441] The deprotection is facilitated by photoinduced electron

transfer from the acetoxyethyl derivative **254** to the dimethoxybenzophenone sensitizer **255** via a cation radical intermediate and the iminium salt **256**, which subsequently hydrolyzes to release the secondary amine **257** in 60–80% chemical yields (Scheme 122).

A blue-light triggered photorelease system based on the riboflavin binding protein dodecin (a dodecameric hollow-spherical flavoprotein with six flavin binding sites) has recently been developed by Noll and coworkers.[442] The release of the reduced flavin derivatives is reported to be triggered by irradiation with blue light of the dodecin-bound flavin anchor.

Kutateladze and coworkers have developed a novel strategy of aldehyde and ketone (**258**) protection using the dithiane moiety, which can be efficiently removed via oxidative photoinduced electron transfer in the presence of a sensitizer (sens), such as benzophenone (Scheme 123).[443] The starting compounds **259** are easily synthesized from the lithium salts of 1,3-dithianes and the corresponding carbonyl compounds. Upon irradiation, the carbonyl compounds are released in excellent to mediocre chemical yields (e.g., 35–97%)[443] and with reasonable efficiency (Φ = 0.06–0.17).[444]

A simplified mechanism of the oxidative deprotection is shown in Scheme 124. The reaction of **260** is facilitated by electron transfer to the excited state of benzophenone, resulting in formation of the cation radical **261** and the benzophenone radical anion **262**. Depending on the solvent polarity, **262** deprotonates **261** in the solvent cage, or both species escape the solvent cage and form the same compounds through the reaction with water. It was evident from LFP studies that in-cage deprotonation occurs in dry acetonitrile while the latter process is dominant in more polar acetonitrile/water mixtures.[445] Deprotonation of the radical cation of an adduct of dithiane and, for example a *t*-butyl-substituted carbonyl compound, gives the zwitterionic intermediate **263** which may, following intramolecular electron transfer, lead to an alternative C–C bond scission to give a stable *t*-butyl radical.[446] However, the detailed mechanism is still not completely clear.[447] Adducts of trithianes and trithiabicyclo[2.2.2]octanes, analogous to those of 1,3-dithianes, have also been studied as protection moieties.[448] In addition, the dithiane moiety was successfully coupled with amino acids to form novel dithiazane photocleavable linkers.[449] 9*H*-Thioxanthen-9-one has also been introduced as a sensitizer in the dithiane, trithiane, and dithiazane-based photolabile scaffolds.[450]

The dithiane-based linkers were explored for various applications, such as photolabile phospholipids and amphiphiles,[451] calixarene-based rosette,[452] or barbiturate receptors.[453] Dithiane-spiro-crown ethers (e.g., **264**; Scheme 125) were used as photolabile moieties that allowed photochemical interruption of transport through liquid membranes,[448a] or as photolabile linkers.[454]

Triggering of two-photon fluorescence (see also Section 9) as a reporting function has been developed.[455] Kutateladze and coworkers used dithianes to mask the sensitizer molecules immobilized on beads, dendrimers, or peptides to demonstrate that excitation of a single free sensitizer leads to liberation of its own copy, thus leading to signal amplification.[456] Events, which occur on an attomolar concentration scale, can now be detected via molecular recognition-triggered photo-amplified fluorescence quenching.[457] Dithiane-based photolabile tags have also been used for encoding and direct screening of solution phase combinatorial libraries.[458]

Dalko and coworkers have recently reported on a very interesting bichromophoric system composed from hydroxymethyl quinolene-derived probes which are activated through interactions of X-ray or γ irradiation with gadolinium (III) complexes (Scheme 126).[459]

These metal complexes act as intramolecular antennae and convert part of the energy resulting in electron transfer and subsequent fragmentation of the quinolines.

8.3 Sensitized Release: Light Upconverting Nanoparticles

In contrast to multi-photon excitation which comprises the simultaneous absorption of two or more photons using pulses with femtosecond duration (Section 9), photon upconversion is a sequential absorption of two or more photons.[460] Light upconverting nanoparticles (UCNPs) have attracted considerable attention as visible or near-IR (NIR) harvesting light antennae which, upon energy or heat transfer (photothermal effect), can trigger a release of species, such as drugs.[461]

Branda and co-workers used a dimethoxybenzoin PPG coupled to monodispersed core-shell nanoparticles (NPs) composed of $NaYF_4$ nanocrystals doped with lanthanides to release carboxylates upon NIR light activation (980 nm) followed by NP fluorescence exciting the benzoin chromophore.[223] The wavelength of emission may be controlled by the power density of lasers used for NPs excitation.[462] The same principle has also been demonstrated on photoswitches.[463]

Remotely triggered release was achieved by heat transfer from gold nanoparticles which can be tethered to, encapsulated within, or suspended freely outside liposomes or micelles that can serve as drug carriers.[222,464] In a similar study, gold NPs were enclosed in biodegradable and biocompatible microspheres (1–15 μm) containing the antitumor drug paclitaxel.[465] The NIR-activated photothermal effect leads to efficient paclitaxel release.

A variety of target compounds, such as oligonucleotides or *si*-RNA, can also be adsorbed on the modified surface of a gold NP[466] or coupled to the NP surface via gold-thiol conjugation.[467] For example, a high payload of doxorubicin was coated and successfully released from both the outer and inner shells of polyethylene glycol (PEG) hollow gold nanoparticles.[468] Chromatic orthogonality (see also Section 10) to release two different DNA oligonucleotides has been demostrated on gold nanorods differing in their aspect ratio,[469] which is promising for future applications in cancer theranostics.[470]

9 TWO-PHOTON EXCITATION-INDUCED PHOTORELEASE

The removal of the photolabile protecting groups discussed in this review usually requires UV irradiation. These conditions, however, are not compatible with many biomedical applications, as UV-Vis light is efficiently absorbed by the tissue.[471] The major absorbing species in vertebrate tissues is oxyhemoglobin, which filters practically all the light of wavelengths shorter than 650 nm.[471] On the other hand, water becomes increasingly absorbant at wavelengths longer than 950 nm. These two factors define the “phototherapeutic window”, the region of relative tissue transparency between 650 and 950 nm.[472] The increased depth of tissue penetration of radiation in this region is accompanied by additional advantages: lower scattering and reduced phototoxic effects. However, red and NIR photons have relatively low energy, limiting the range of processes they can initiate. In addition, the majority of chromophores with useful single-photon absorbance in the “phototherapeutic window” are also sensitive to visible light, complicating the handling of the caged substrates. One of the approaches that overcomes most of these problems is to employ nonresonant two-photon excitation (2PE). At high light intensity, chromophores may simultaneously absorb two red/NIR photons producing higher energy excited states, the same as or similar to those accessible by direct excitation with UV photons of about twice the frequency.[473] Additionally, by focusing the irradtiation of 2PE on UV-chromophores within UV-absorbing materials provides an opportunity to control substrate release in three dimensions. The probability of 2PE is proportional to radiant intensity squared, which is

many orders of magnitude higher in the λ^3 volume around the focal point than in other areas of the laser beam.[474] This phenomenon has made possible the development of 3-D applications in fluorescent imaging,[473a,474b,475] microscopy,[474b,476] photonics,[477] 3-D fabrication,[478] and potentially even in drug delivery[304,479] and photodynamic therapy.[480] Substantially less data are available on two-photon induced photochemical reactions[473c,481] and their use in biochemistry.[164,476b,482] The 3-D capabilities of two-photon-induced uncaging were successfully employed in neuron mapping,[10d,483] investigation of intracellular processes,[484] regulation of protein activity *in vitro*[221,485] and *in vivo*,[221,485b] as well as in the development of 2PE-uncaging microscopy.[486]

2PE requires very high light intensities, which can be achieved only using ultrafast pulsed lasers. Thus, a commercially available mode-locked Ti:sapphire laser can provide a photon irradiance (E_p) of 10^{25} photons cm^{-2} s^{-1} (3 mm beam at 100 fs pulse duration, and repetition frequency ν = 90 MHz) or more. The principal emission of the most common Ti:sapphire lasers is at 800 nm, which almost perfectly corresponds to the minimum of mammalian tissues absorbance. Lasers that can be tuned to shorter wavelengths are usually more expensive. The differential form of the Beer's law for two-photon excitation[487] is shown below (Eq 2), where E_p is the photon irradiance (photons cm^{-2} s^{-1}), δ is the two-photon cross section (cm^4 s $photon^{-1}$ $molecule^{-1}$), N is the concentration (molecules cm^{-3}), and x is the sample thickness (cm).

$$-\partial E_p = 2\delta E_p^2 N \partial x \quad \text{Eq 2}$$

$$-\Delta E_p = 2\delta E_p^2 N \Delta x \quad \text{Eq 3}$$

As light intensity virtually does not change when passing through the sample due to low two-photon absorption, we can write Eq 2 in a simplified form (Eq 3). The rate of photoreaction with quantum yield Φ (molecule $photon^{-1}$) is proportional to photon irradiance absorbed by the sample, which is in turn proportional to squared photon irradiance (Eq 4).[481f] The coefficient ½ in Eq 4 reflects the two-photon nature of the process.

$$-\frac{dN}{dt} = \frac{\Phi \Delta E_p}{2x} = \Phi \delta E_p^2 N \quad \text{Eq 4}$$

$$N_t = N_0 \left(1 - e^{\Phi \delta E_p^2 t_{pulse} \nu t_{irr}}\right) \quad \text{Eq 5}$$

Integration of Eq 4 and taking into account the pulsed nature of the irradiation gives Eq 5.[481f] N_0 and N_t represent starting and current concentration of a substrate; E_p represents the averaged photon irradiance during the pulse, t_{pulse} is pulse duration, ν is laser repetition rate, and t_{irr} the time of exposure. Strictly speaking, E_p^2 should be integrated for the duration of the pulse but this approximation introduces insignificant error. For low conversion experiments that employ the Ti:sapphire laser discussed above we can write a simplified Eq 6, where δ is expressed in Goeppert-Mayer units (1 GM = 10^{-50} cm^4 s $photon^{-1}$ $molecule^{-1}$).

$$\frac{N_0 - N_t}{N_0} \approx (\Phi \delta \tau) \times 10^{-5} \text{photon molecule}^{-1}\ \text{GM}^{-1}\text{s}^{-1} \quad \text{Eq 6}$$

Thus, to achieve 1% release of a substrate within the focal volume of a laser beam using a PPG with a quantum yield of uncaging $\Phi = 0.5$ and a 2PE cross-section of $\delta = 1$ GM, the sample has to be irradiated for about 30 min. One should also take into account the background one-photon absorbance of tissue materials, which is about 10^{-3} per 1 cm at 750 nm,[476b,488] and the broadening of ultra-short pulses in dense media. For an efficient two-photon photochemistry in tissues, the product δE_p should be at least 10^{-25} cm^2 molecule^{-1}.[487] This means that at light intensities produced by a Ti:sapphire laser, the two-photon absorption cross-section δ of the PPG should be around 1 GM or higher.

The cross section of two-photon absorption for most organic chromophores is rather low (δ < 1 GM); however, some recently synthesized fluorophores, which usually contain D-**π**-A-**π**-D (D = donor, A = acceptor) or a similar structural motif, have δ over 1000 GM.[477b,c] Unfortunately, these advances in the design of two-photon chromophores have not yet been applied to photolabile protecting groups. The suitability of several conventional (single photon) PPGs for 2PE-induced substrate release has been explored instead (Table 11). The efficiency of this process is better characterized by the two-photon cross section of uncaging (δ_{unc}), which is a product of the two-photon absorption cross section (δ) and the 2PE quantum efficiency (Φ_{2PE}),[489] $\delta_{unc} = \Phi_{2PE}\delta$. It should be noted that the value of δ_{unc} is strongly dependent on the wavelength of irradiation. Many cages that show decent efficiency of substrate release at 740–750 nm have very low δ_{unc} at 800 nm.

The most widely used *o*-nitrobenzyl-based PPGs have a rather low two-photon uncaging cross section, which varies, depending on the substitution in the ring and the wavelength of excitation, from 0.01 to 0.035 GM (Table 11). The NV cage (**83**) shows the highest sensitivity to 2PE in this family, with $\delta_{unc} = 0.035$ GM at 730 nm.[490] When *o*-nitrobenzyl (oNB) PPGs are used for caging of fluorescent dyes (Section 11), the quantum yield and two-photon cross section of uncaging is often improved apparently due to the energy transfer from the dye to the caging chromophore. Thus, coumarin is released from the oNB-cage (**57**) with 53% quantum efficiency in single-photon excitation at 365 nm and with 2PE δ = 0.37–0.68 GM at 740 nm.[491] The analogous 2-(2-nitrophenyl)prop-1-yl-based PPGs, such as NPPOC, NPEOC, (Section 3.2) or DMNPB (**265**), possess the same *o*-nitrophenyl chromophore but have 5–12 times higher δ_{unc} due to more efficient photochemistry.[492] The two-photon uncaging cross-section of these groups can be also improved by sensitization. Thus, in the presence of a triplet sensitizer with a large 2PE cross-section (i.e., thioxanthone), the two-photon uncaging action cross-section of NPEOC (Section 3.2) is enhanced to 0.86 from 0.12 GM.[234] Extension of the conjugated **π**-system of the chromophore ((4'-methoxy-4-nitrobiphenyl-3-yleth-2-yl)methyl, PMNB, **115**; (4'-tris-ethoxymethoxy-4-nitrobiphenyl-3-yleth-2-yl)methyl, PENB, **266**),[236–237,493] especially when combined with a symmetrical structure (BNSF, **117**),[237] brings the two-photon uncaging cross-sections into a respectable 3–5 GM range. However, these groups are rather bulky and suffer from poor solubility.

(Coumarin-4-yl)methyl-based (Section 4) PPGs **267**, **268**, **269**, **270**, and **143** are usually more efficient two-photon cages than simple NPE and NPP (Section 3.2) analogs (Table 11). The uncaging cross sections of the popular BHCM group (**143**, Section 4) range from 0.35 to 2 GM at 740 nm depending on the caged substrate.[288,294] Incorporation of two additional bromine atoms in the benzene ring of BHCM (**271**) results in a red shift of the 2PE maximum and further enhancement of the two-photon uncaging efficiency (Table 11).[303]

Dore and co-workers have systematically studied the effects of electron-donating and electronwithdrawing substituents on the two-photon uncaging cross sections of (quinoline-4-yl)methyl PPGs (Section 5).[331] The most efficient two-photon induced substrate release in this family was reported for the BHQ cage (**181**, $\delta_{unc} = 0.6$–0.9 GM at 740 nm).[330a]

Replacement of the bromo substituent for the cyano- (**272**) or chloro- (**273**) groups resulted in a reduced δ_{unc}, nitro group largely suppressed the two-photon sensitivity.[335a] The 7-dimethylamino- (**274** and **275**) and mercapto- (**276**) (quinoline-4-yl)methyl derivatives are also presented in the table.

The 2-hydroxycinnamyl cage (Section 7.7) developed by Porter's group[387a] was also found to be amenable to 2PE-triggered substrate release. Jullien and coworkers have demonstrated that with the appropriate choice of substituents in the aromatic ring (**277**, **278**, **279**, **280**), the photochemical step of the uncaging process, *trans–cis* isomerization of the (*E*)-cinnamate moiety, can be induced under two-photon photolysis conditions.[393b] 4-Amino substituted (*E*)-(*o*-hydroxyphenyl)acrylates possess the highest two-photon activation cross section (**281**, δ_{unc} = 2.0 GM; **282**, δ_{unc} = 4.7 GM at 740 nm).[393a] While the substrate release from these cages is relatively slow at a biological pH (Section 7.7), the 2PE-sensitive (*E*)-cinnamates are remarkably easy to synthesize.

Despite the rather low two-photon cross-sections of nitroindolyl cages (**125**, **127**, **283**, and **130**, Table 11; see also Section 3.3), they have been successfully employed in several biochemical applications.[10d,250,483,494]

Ruthenium complexes that contain amino compounds in their coordination sphere can release these substrates (Section 6) under two-photon irradiation in aqueous solution. Thus, 800-nm irradiation of $Ru(bipy)_2(4\text{-aminopyridine})_2^{2+}$ or $Ru(bpy)_2(PMe_3)(GluH_2)^{2+}$ was found to result in the release 4-aminopyridine or glutamine with 0.01 to 0.1 GM cross-sections.[495]

10 CHROMATIC ORTHOGONALITY

The diversity of different PPGs, operating by different mechanisms and bearing different types of chromophores opens the door for wavelength-selective deprotection. Indeed, the possibility of releasing on demand various types of molecules (e.g. in a cell, or wherever access by conventional injection techniques is not possible) is a very appealing prospect. A first-order approximation would suggest that absorption maxima sufficiently distant could work; however, fast energy transfer may thwart such a strategy, in particular for cases where both chromophores are part of the same molecular entity. Careful choice of PPG pairs made such a wavelength discrimination possible, allowing for the selective release of two different carboxylic acids, in what was an early example of chromatic orthogonality (Scheme 127).[208,498]

The same benzoin (Section 2.4)/nitroveratryl (Section 3.3) pair was then shown to be equally orthogonal in the intramolecular case, where spatial proximity is more critical than in separate molecules (Scheme 128).[499] Reactivity tuning by way of a kinetic isotope effect was also exploited to make two derivatives of *o*-nitrobenzylic esters (Section 3.1) chromatically orthogonal.[225]

Examples of this principle were shown soon after in the solid phase synthesis of peptides[360c] and in the selective release from resins by using the nitroveratry/pivaloylglycol pair.[500] del Campo and coworkers investigated a more complex version of the wavelength-selective cleavage by putting seven photolabile protecting groups on various functionalities immobilized through an organosilane tether on a glass surface against each other.[240e,501] Systematic analysis of photolytic characteristics of common photolabile groups helped establish several protecting strategies that permit the simultaneous use of up to four orthogonal photoactivated groups, such as: benzoin (λ_{ex} = 255 nm, Section 2.4), *p*-hydroxyphenacyl (pHP, λ_{ex} = 275 nm, Section 2.3), 5,7-dinitroindolinyl (DNI, λ_{ex} = 360 nm, Section 3.3) and [7-(diethylamino)coumarin-4-yl]methyl (DEACM, λ_{ex} = 435 nm,

Section 4) that can be cleaved sequentially from the same solid support under different irradiation conditions.[240e] It was also noted that two-photon excitation can potentially expand the spectral window and increase the number of possible functional levels for selective spatiotemporal activation.

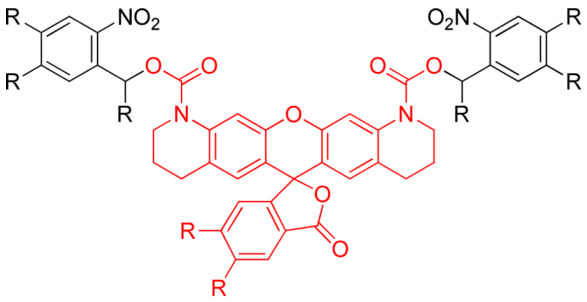
Applications in biochemistry are appearing more and more frequently, such as the protection of cysteines (using variously substituted coumarins),[196] nucleotides (using a coumarin/nitrophenethyl pair),[502] or both,[503] and the release of both substrates and inhibitors (also using a coumarin/nitrophenethyl pair),[504] or the selective release of glutamate or GABA by two-colors/twophoton excitation.[263b] The latter strategy was also applied very recently with a NV/*p*-MeO-phenacyl pair by Emptage, Conway and coworkers.[106c] The same concept was shown to be valid in the solid phase, where the wavelength-selective modification of surfaces was performed with orthogonal pairs [135a,501] or quartets.[240e]

11 PHOTOACTIVATABLE FLUORESCENT DYES

Photoactivatable (caged) fluorophores[13b] are fluorogenic and release a fluorescent molecule upon irradiation. They are obtained by coupling a fluorescent dye to a PPG that prevents it from displaying fluorescence. Caged fluorescent dyes provide a highly sensitive tool to monitor the flow of liquids (rheology) and to follow the movements and the distribution of particular species of interest at the single molecule level and with a spatial resolution at the nanometer scale, i.e., beyond the diffraction limit of optical microscopy (~250 nm). Fluorescence imaging microscopy is among the most powerful techniques for observing dynamic processes in living cells. To monitor the movement of target molecules or species in real time, it is necessary to create a local region within the cell where the fluorescence intensity is higher than in the bulk. Imaging with high target-to-background contrast requires a high activation ratio, i.e., a high ratio of postactivation to preactivation signal intensity. Thus, the signal intensity arising from the caged fluorophore should be close to zero.

The classic method for creating a differentially labeled region has been fluorescence photobleaching, i.e, reducing fluorescence intensity by irradiation, usually by reaction of a fluorescent dye with singlet oxygen. Alternatively, photochemically labile fluorophores such as the aminophthalimide–serine shown in Scheme 129 can be used.[378] Disadvantages of photobleaching through singlet oxygen are that it may cause local damage to proteins and membranes and that it is difficult to track a region of reduced fluorescence within a background of higher fluorescence. The use of a non-bleachable reference fluorophore has been proposed to track the distribution of the bleached molecules by image differencing.[505]

To overcome these limitations, numerous photoactivatable fluorophores have been developed. The design and use of caged fluorophores have been reviewed.[9n,13a,b,506] Desiderata for an effective caged fluorescent probe are: biostability and -compatibility, a high affinity to or, preferentially, specificity for the target (e.g., cancer cells),[507] rapid and efficient photoactivation providing a high ratio of pre- and postirradiation fluorescence, a high fluorescence quantum yield, photostability of the uncaged fluorophore, and practicable synthesis. Up to 1998,[506] caged fluorophores have all employed variants of oNB (Section 3) caging group (e.g., **284**).



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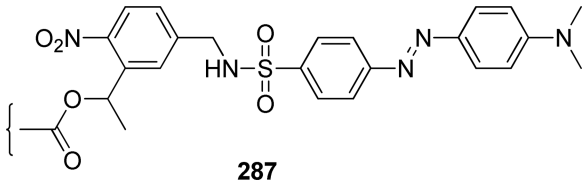
The full activation of such bis-caged lactovne (leuco) forms of rhodamine or fluorescein requires the removal of both PPGs. Removal of one PPG is sufficient to restore the chromophore, but the remaining nitroaromatic group often largely quenches the fluorescence emission of the mono-caged dye. Full deprotection therefore requires high doses of UV irradiation. On the other hand, the non-negligible fluorescence quantum yield of mono-protected fluorescein hampers its use as a caged fluorophore, because the activation ratio upon deprotection is usually insufficient. A monoprotected variant of fluorescein (TokyoGreen, **285**, Scheme 130) has, however, been developed that exhibits very little fluorescence.[508] The fluorescence quantum yield of singly 2-(2-nitrophenyl)prop-1-yl (NPP) (Section 3.1) protected TokyoGreen (**286**) is less than 1/100th that of protected fluorescein. It liberates the highly fluorescent free form (Φ_{fl} = 0.96) by removal of the PPG with a quantum yield of 0.03.[509]

Several other examples of fluorescence activation by photochemical removal of a quencher moiety attached near the fluorophore have been reported. Other than by electron transfer, fluorescent singlet states can be quenched by Forster resonance energy transfer (FRET, somewhat inadequately called “fluorescence resonance energy transfer” by most biochemists)[510] to an adjacent, nonfluorescent, but photoremovable chromophore. For example, a synthetic route to incorporate a photocleavable 4-dimethylaminoazobenzene-4'-sulfonyl (**287**, dabsyl)[511] moiety and fluorescein at adjacent cytidines in the middle of a 25-mer oligodeoxynucleotide has been reported.[512] UV irradiation removed the dabsyl moiety, which increased the fluorescence intensity 51-fold and restored the melting temperature of the nucleotide. Such caged fluorescent oligodeoxynucleotides will allow many DNA processes to be controlled with light.



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The same principle was used to regulate the DNA polymerase reaction by the Klenow fragment of polymerase I with UV light. A 25-mer caged fluorescent oligodeoxynucleotide as the template was functionalized with a fluorescein reporter and the photoremovable dabsyl quencher moiety (**287**). With this template, the Klenow fragment was blocked from extending a complementary 12-mer primer. Removal of the quencher by short UV photolysis partly restored the activity of the Klenow fragment and the reactivation could be monitored by fluorescence.[511]

A related approach was used to provide for real-time monitoring of Smad2, a key protein involved in the transforming growth factor β (TGF-β) signaling pathway, spatial and

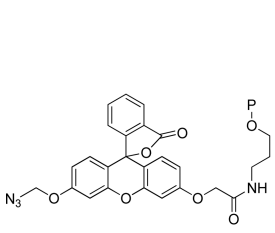
temporal control of its activity, and differentiation between its active and inactive state.[513] The protein was labeled at neighboring sites with a fluorescein chromophore and with a 4-dimethylaminoazobenzene-4'-carboxylic (dabcyl) acid quencher through a photocleavable 4-[4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy] butanoic acid linker. This both suppressed the protein activity and quenched its fluorescence. Photocleavage of the caging group resulted in the simultaneous restoration of protein activity and luminescence of the fluorescent tag.

Numerous photocleavable (coumarin-4-yl)methyl esters with fast release have been described (Section 4).[276,289,296] NPP-caged coumarins that display more than 200-fold fluorescence enhancement upon UV irradiation were developed (Scheme 131).[491] The combined advantages of robust fluorescence contrast enhancement, high uncaging efficiency, noninvasive cellular delivery, and flexible chemistry for bioconjugations are promising for the use of these caged coumarins in biochemical and biological research. The high uncaging efficiency is attributed to the antenna function of the coumarin, i.e., light absorbed by the coumarin chromophore is utilized to cleave the NPP cage. It should, however, be noted that NPE-caged fluorophores are subject to the known disadvantages of *o*-nitrobenzyl photochemistry (see Section 3.1).

To prepare a caged coumarin emitting a different color, the *o*-nitrobenzyl-caged coumarin was linked to a water-soluble fluorescein dye emitting at 520 nm.[514] The caged dye can be localized in the sample prior to photolysis by directly exciting the fluorescein moiety at 490 nm. After uncaging the coumarin chromophore, the green emission can be excited at 410 nm due to efficient FRET from the coumarin moiety to the fluorescein dye. This is especially desirable for experiments demanding highly localized photoactivation by two-photon uncaging, which requires knowing the distribution of the label in three dimensions. These probes thus offer new opportunities to image molecular and cellular dynamics.

A light-activated fluorescent reporter of intracellular protein kinase activity has been designed (Scheme 132) that furnishes a fluorescent readout.[515] The photolytically labile appendage affords control over both the timing and the amount of active sensor release. The quantum yield for photolytic conversion is 0.06. The caged fluorescent substrate was introduced into HeLa cells via microinjection. Following in situ illumination of the caged peptide, time-dependent changes of the fluorescence intensity due to phosphorylation of the released hydroxyl function provided a measure of protein kinase activity in the cells.

Azidomethyl-caged fluorescein derivatives (**288** and **289**) were utilized to monitor the dynamics of oligonucleotides in living human cells. Both compounds were rapidly activated upon brief irradiation and showed a strong increase in fluorescence intensity.[516]



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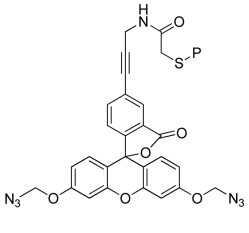

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The addition of lithiated dithianes to 2-amidothioxanthones disrupts conjugation, resulting in a blue shift of the absorption and a dramatic decrease in fluorescence intensity. The product represents a new caging system capable of fast quantification of released payloads such as TentaGel beads by single- or two-photon fluorescence.[455] Irradiation induces homolytic C–

C fragmentation followed by disproportionation of the two radicals (Scheme 133). The half-life of the radical intermediates was 1.7 μs.

Rhodamine dyes having a 2-diazo caging group incorporated into a spiro-9*H*-xanthene fragment have been synthesized by reaction of diazomethane with the acid chloride of rhodamine B.[517] The yellow crystalline diazoketone **290** was obtained in high yield (Scheme 134). Caged rhodamines with an additional carboxy group in the benzoyl fragment of the diazoketone that may be linked to an amino or a thiol reactive site were also made. Application of a related system featuring a high contrast ratio (1 : 140) and activation by visible light (λ < 420 nm) to high-resolution microscopy was recently reported.[518]

A ruthenium-rhodamine complex **291** (see Section 6) has been evaluated as an activatable fluorescent probe (Scheme 135).[356]

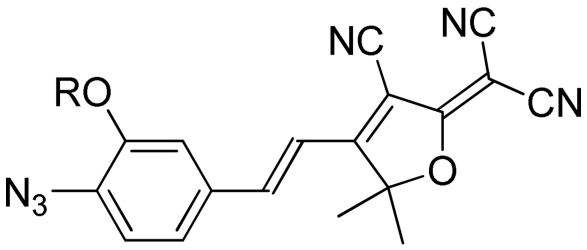
A photoactivatable nitrobenzyl-caged (Section 3.1) green fluorescent protein (**292**, GFP) that is practically non-fluorescent prior to irradiation was synthesized recently (Scheme 136).[519] The relative brightness at the wavelength of maximum emission (486 nm) increased by at least 4 orders of magnitude during photoactivation at 365 nm.

Photoactivatable fluorescent proteins have become an important addition to the set of molecular probes used to understand cellular function. Wild-type GFP[520] is in fact already a caged fluorophore of sorts. The protein can adopt two conformations with different absorption maxima, and irradiation shifts the molecules towards the longer-wavelength absorbing form. Photoconversion in wild-type GFP is thought to involve rotation of threonine 203 and decarboxylation of glutamic acid 222. A mutant of wild-type GFP, in which the threonine 203 position is replaced by histidine, was shown to increase its fluorescence intensity (λ_{ex} = 488 nm, λ_{em} = 520 nm) 100 times upon intense irradiation at 413 nm.[521] The activated protein remains stable for days under aerobic conditions. This photoactivatable variant of the *Aequorea victoria* GFP was used both as a free protein to measure protein diffusion across the nuclear envelope and as a chimera with a lysosomal membrane protein to demonstrate rapid interlysosomal membrane exchange.

Optical microscopy provides spatial resolution down to the diffraction limit of ~250 nm, but single fluorescent particles can now be localized down to ~1 nm precision, and spectroscopic techniques, such as Forster resonance energy transfer (FRET), can offer yet smaller distance changes. Super-resolution (subdiffraction) imaging techniques based on sequential imaging of sparse subsets of single molecules have employed fluorophores whose emission can be photoactivated or photoswitched.[522] The common principle is that only one point-like light source is active in a diffraction-limited area at any time. Imaging with a sensitive camera localizes this fluorophore. Its exact location can then be determined to well below the diffraction limit by fitting a point-spread function. In the beginning of data acquisition, all except a few fluorophores are prepared in the off-state and the number of active fluorophores is kept constant by applying an activating light source that compensates for the loss of fluorophores by photobleaching or switching off. A super-resolution image of a labeled complex structure can then be reconstructed from many successive rounds of weak photoactivation and fitting. This method has been used to image intracellular proteins at nanometer spatial resolution. As an alternative to caged fluorophores for super-resolution microscopy, on- and off-states have been engineered by controlling the photophysics of fluorophores by electron transfer reactions.[523]

Because good organic fluorophores are more photochemically stable than most fluorescent proteins, organic fluorophores have a potential benefit in super-resolution imaging schemes, but targeting to specific cellular proteins must be provided. The design and application of

target-specific azido 2-dicyanomethylene-3-cyano-2,5-dihydrofuran, a photoactivatable push–pull fluorogen which produces bright fluorescent labels suitable for single-molecule super-resolution imaging in live bacterial and fixed mammalian cells were reported (**293**).[524]



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The same authors subsequently demonstrated that the azide-to-amine photoactivation process is generally applicable to a variety of push-pull chromophores, which provide a new class of photoactivatable single-molecule probes for fluorescent labeling and super-resolution microscopy.[525] Moreover, these photoactivated push-pull dyes can insert into bonds of nearby biomolecules, simultaneously forming a covalent bond and becoming fluorescent (fluorogenic photoaffinity labeling).

The design, synthesis, and photophysical characterization of a class of ligand-directed, photoactivatable, turn-on fluorescent probes for the spatially controlled imaging of microtubules in live mammalian cells was reported.[526] A series of taxoid–tetrazoles, in which 7-β-alanyltaxol L was attached to a water-soluble tetrazole bearing an *o*-allyloxy group at the *N*-phenyl ring via a flexible linker. Upon irradiation at 302, 365 or even 405 nm, the tetrazoles **294** undergo deazotization generating reactive nitrile imine dipoles that spontaneously react with the prealigned allyl group to form pyrazoline fluorophores (Scheme 137). Whereas none of the taxoid–tetrazoles was fluorescent, the taxoid–pyrazolines exhibited strong fluorescence emission in the range of 500–800 nm. With this photoactivatable fluorescent probe, it should be possible to label microtubules asymmetrically within a single cell and identify factors that break cellular symmetry during cell division.

12 CONCLUSION

Photoremovable protecting groups (PPGs) release molecules such as enzymes, neurotransmitters, signalling molecules, fluorophores, insecticides, pheromones, and fragrances that thereby exhibit desirable physical, chemical, or biological qualities upon photoactivation. They are synthetically malleable and accessible, offering a wide range of structures for designed applications. They offer excellent spatial and temporal control for the substrate release. Their applications span many scientific fields, from DNA chip technology, drug delivery, and photoregulation of proteins, to rheology, solid-phase synthesis, surface chemistry, and nanotechnology. PPGs are excellent, versatile tools for time-resolved studies of chemical processes in living cells. Multiphoton excitation can provide superior spatial resolution and the new chromophores included herein offer more precise temporal control for addressing the dynamics of *in vivo* events in living organisms.

There has been an upsurge in interest in PPGs over the past decade that has resulted in a dramatic increase in the number of new designs and the development of both new and known PPGs to fulfill the demands for better sensitivity, faster kinetics, and more demanding bioanalytical applications. The many new discoveries have brought substantial

improvements and versatility to the synthesis, thermal stability, solubility, and absorption properties of PPGs, as well as improved efficiencies and rates of release. Nonetheless, there still remain many important research goals, such as extending the wavelength coverage for activation of PPGs with visible and infrared light and improving the absorption properties for wavelength-selective, orthogonal activation, and melding these features with the inherent advantages of photoactivation that PPG posess as outlined at the beginning of this review.

Our goal has been to aid and assist researchers in applying these tools and to attract and encourage their participation in this rapidly developing field.

Acknowledgments

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LIST OF ABBREVIATIONS

2PE	two-photon excitation
Ac	acetyl
ACM	(7-aminocoumarin-4-yl)methyl
α-CNB	α-carboxynitrobenzyl
α-CNV	α-carboxy-6-nitroveratryl
ADP	adenosine diphosphate
Ala	alanine
ANB	4-acetyl-2-nitrobenzyl
Aqe	anthraquinon-2-yleth-2-yl
Aqm	anthraquinon-2-ylmethoxy
Aqmoc	anthraquinon-2-ylmethoxycarbonyl
ATP	adenosine-5'-triphosphate
ATP	adenosine triphosphate
BCMACM	{7[bis(carboxymethyl)-amino]coumarin-4-yl}methyl
BCMCM	[6,7-bis(carboxymethoxy)coumarin-4-yl]methyl
BDP	benzoin diethyl phosphate
BHCM	(6-bromo-7-hydroxycoumarin-4-yl)methyl
BHQ	(8-bromo-7-hydroxyquinoline-2-yl)methyl
Bni	5-bromo-7-nitroindolinyl
BNSF	2,7-bis-{4-nitro-8-[3-(2-propyl)-styryl]}-9,9-bis-[1-(3,6-dioxaheptyl)]-fluorine
Boc	*N*-(*t*-butoxycarbonyl)
cAMP	cyclic adenosine monophosphate

Cbz	benzyloxycarbonyl
CDNI	4-carboxymethoxy-5,7-dinitroindolinyl
CM	(coumarin-4-yl)methyl
CMCM	[7-(carboxymethoxy)coumarin-4-yl]methyl
CT	charge transfer
CyHQ	(8-cyano-7-hydroxyquinoline-2-yl)methyl
dabsyl	dimethylaminoazobenzene-4'-sulfonyl
dabcyl	4-dimethylaminoazobenzene-4'-carboxylic
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
Ddz	α, α-dimethyl-3,5-dimethoxybenzyloxycarbonyl
DEACM	[7-(diethylamino)coumarin-4-yl]methyl
DEP	diethyl phosphate
DFT	density functional theory
DHB	2,5-dihydroxybenzyl
DMACM	[7-(dimethylamino)coumarin-4-yl]methyl
DMAQ	[7-(dimethylamino)quinoline-2-yl]methyl
DMAQ-Cl	[7-(dimethylamino)-4-chloroquinoline-2-yl]methyl
DMATr	3-(dimethylamino)trityl
DMB	3’,5’ dimethoxybenzoin
DMBF	2-phenyl-5,7-dimethoxybenzofuran
DMCM	6,7-dimethoxy(coumarin-4-yl)methyl
DMNB	4,5-dimethoxy-2-nitrobenzyl
DMNPB	3-(4,5-dimethoxy-2-nitrophenyl)-2-butyl
DMP	2,5-dimethylphenacyl
DNI	5,7dinitroindolinyl
EDTA	ethylenediaminetetraacetic acid
EGTA	ethylene glycol tetraacetic acid
E_S	energy of the lowest excited singlet state
E_T	energy of the lowest excited triplet state
Fmoc	fluorenylmethyloxycarbonyl
FRET	Förster resonance energy transfer
GABA	γ-aminobutyric acid
GAP	GTPase activating protein
GDP	guanosine diphosphate
GFP	green fluorescent protein
GTP	guanosine triphosphate

HCM	(7-hydroxycoumarin-4-yl)methyl
HEMA	(hydroxyethyl)methacrylate
HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
HFIP	hexafluoroisopropanol
CHQ	(8-chloro-7-hydroxyquinoline-2-yl)methyl
IPA	isopropanol
ISC	intersystem crossing
KMOPS	potassium 3-(*N*-morpholino)propanesulfonate
KTRF	Kerr-gated time-resolved fluorescence
LFP	laser flash spectroscopy
LG	leaving group
LTC4	Leukotriene C4
MCM	(methoxycoumarin-4-yl)methyl
MDNI	4-methoxy-5,7-dinitroindolinyl
MeNPOC	3,4-(methylenedioxy)-6-nitrophenylethoxycarbonyl
MeNV	α-methyl-6-nitroveratryl
MeNVOC	α-methyl-6-nitroveratryloxycarbonyl
MeNPOM	α-methyl-(6-nitropiperonyloxymethyl)
MLLCT	metal-ligand-to-ligand charge-transfer
MMA	methyl methacrylate
MNDQ	5-methoxy-8-nitro-1,2-dihydroquinolinyl
MNI	4-methoxy-7-nitroindolinyl
MNPPOC	2-(3,4-methylenedioxy-6-nitrophenyl) propoxycarbonyl
NDBF	3-nitrodibenzofuran-2-yl
NIR	near-infrared
NOPA	noncollinear optical parametric amplifier
NP	nanoparticle
NPE	1-(2-nitrophenyl)ethyl
NPEOC	1-(2-nitrophenyl)ethyloxycarbonyl
NPP	2-(2-nitrophenyl)prop-1-yl
NPPOC	2-(2-nitrophenyl)prop-1-oxycarbonyl
NQMP	(3-hydroxynaphthalen-2-yl)methyl
NV	6-nitroveratryl; (3,4-dimethoxy-6-nitrophenyl)methyl
NVOC	6-nitroveratryloxycarbonyl
oNB	2-nitrobenzyl
oNT	2-nitrotoluene

PAK	protein kinase A
PB	phosphate buffer
PBS	phosphate buffered saline
PCA	photoremovable chiral auxiliary
PEG	polyethylene glycol
PENB	(4'-trisethoxymethoxy-4-nitrobiphenyl-3-yleth-2-yl)methyl
PET	photoinduced electron transfer
pHA	4-hydroxyacetophenone
pHP	4-hydroxyphenacyl
PMNB	(4'-methoxy-4-nitrobiphenyl-3-yleth-2-yl)methyl
PPG	photoremovable protecting group
PPTS	pyridinium *p*-toluenesulfonate
PTK	protein tyrosine phosphatase
Px	9-phenylxanthyl, pixyl
SCE	saturated calomel electrode
S-Px	9-phenylthioxanthyl, *S*-pixyl
TBS	*t*-butyldimethylsilyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
TGF	transforming growth factor
TMS	tetramethylsilyl
TQ	(7-mercaptoquinoline-2-yl)methyl
TR-FTIR	time-resolved Fourier transform infrared
TR-RR	time-resolved resonance Raman
TR-TA	time-resolved transient absorption
Ts	tosyl
UCNP	upconverting nanoparticle
X	leaving group

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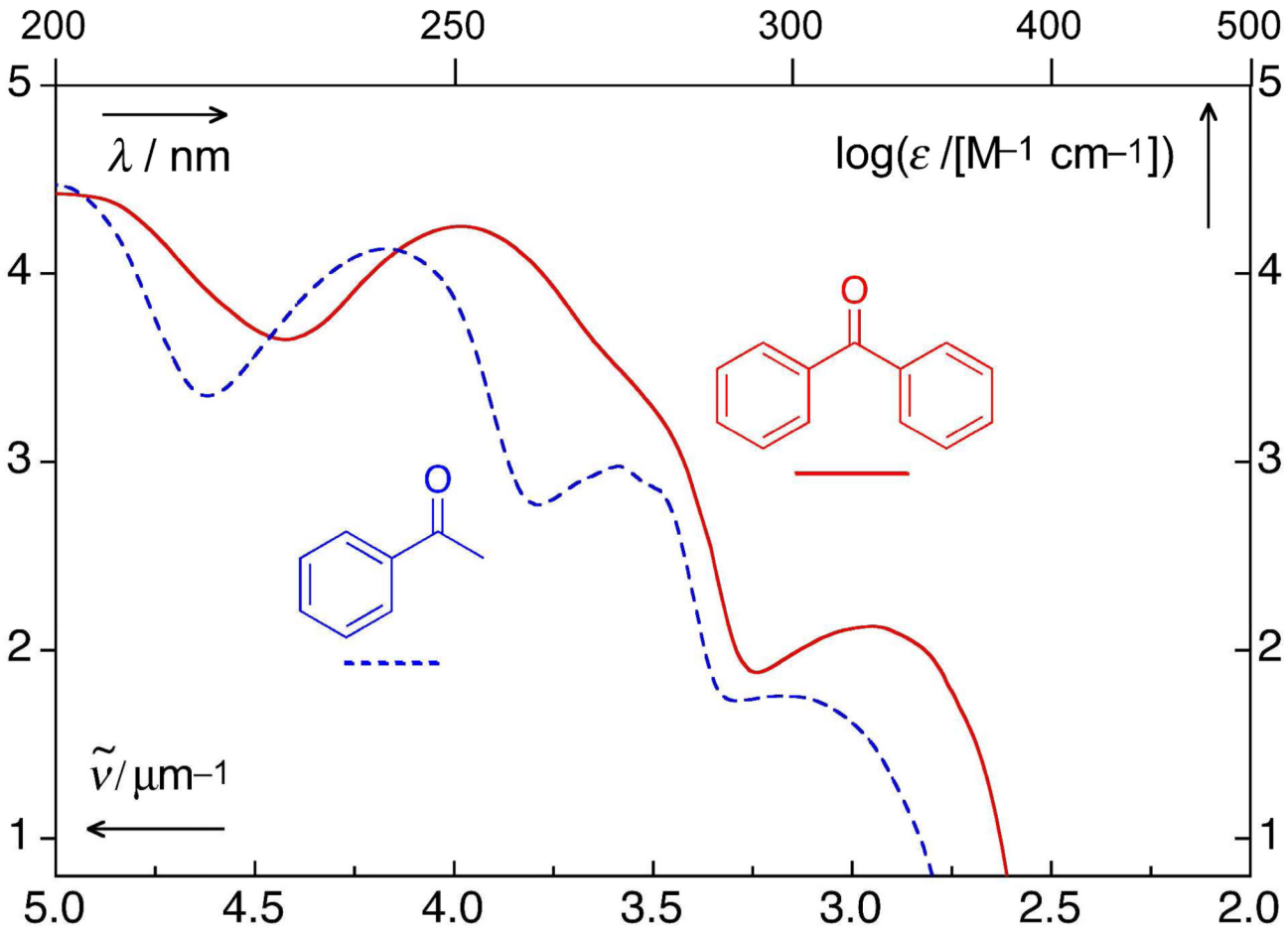

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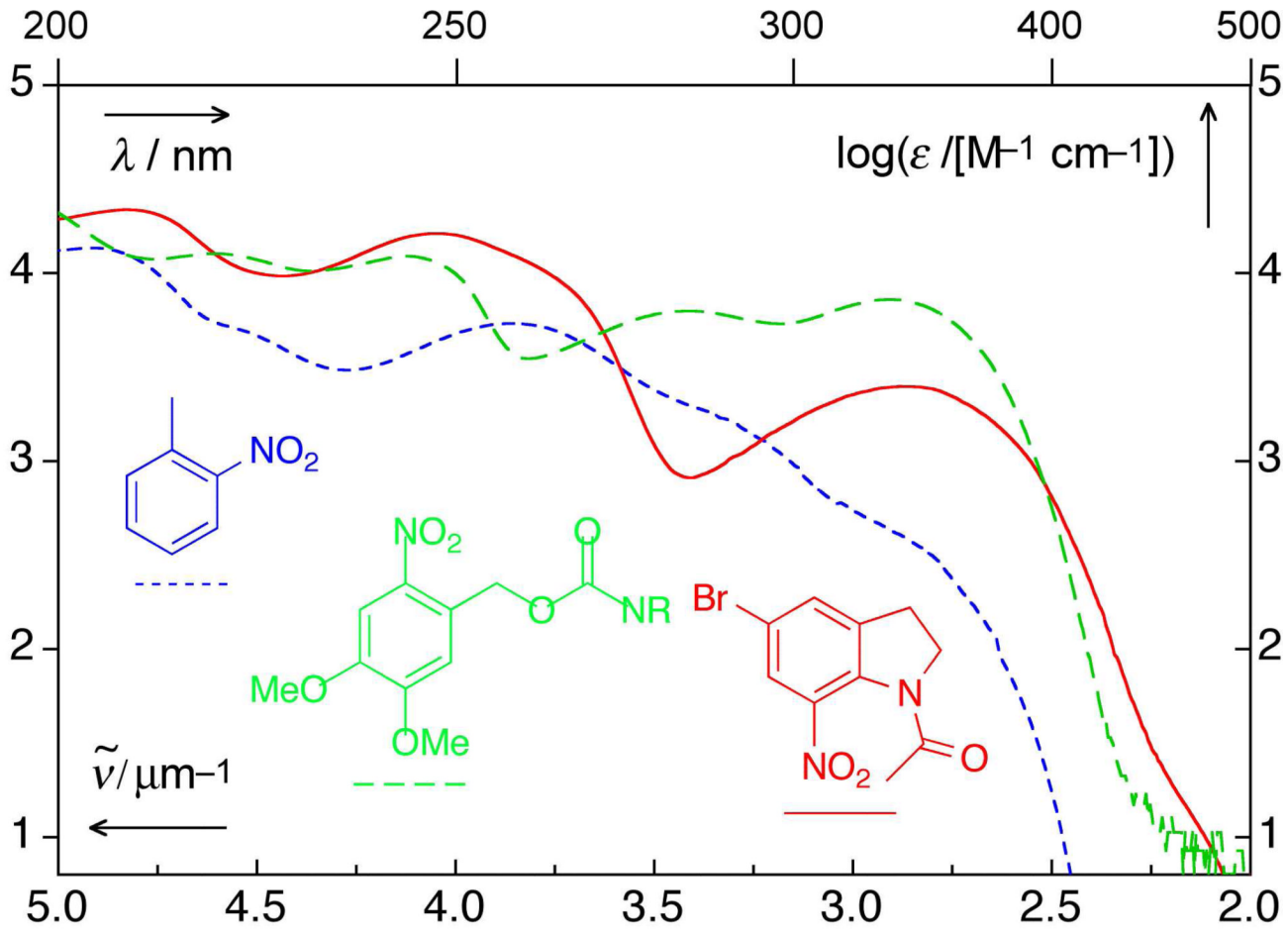
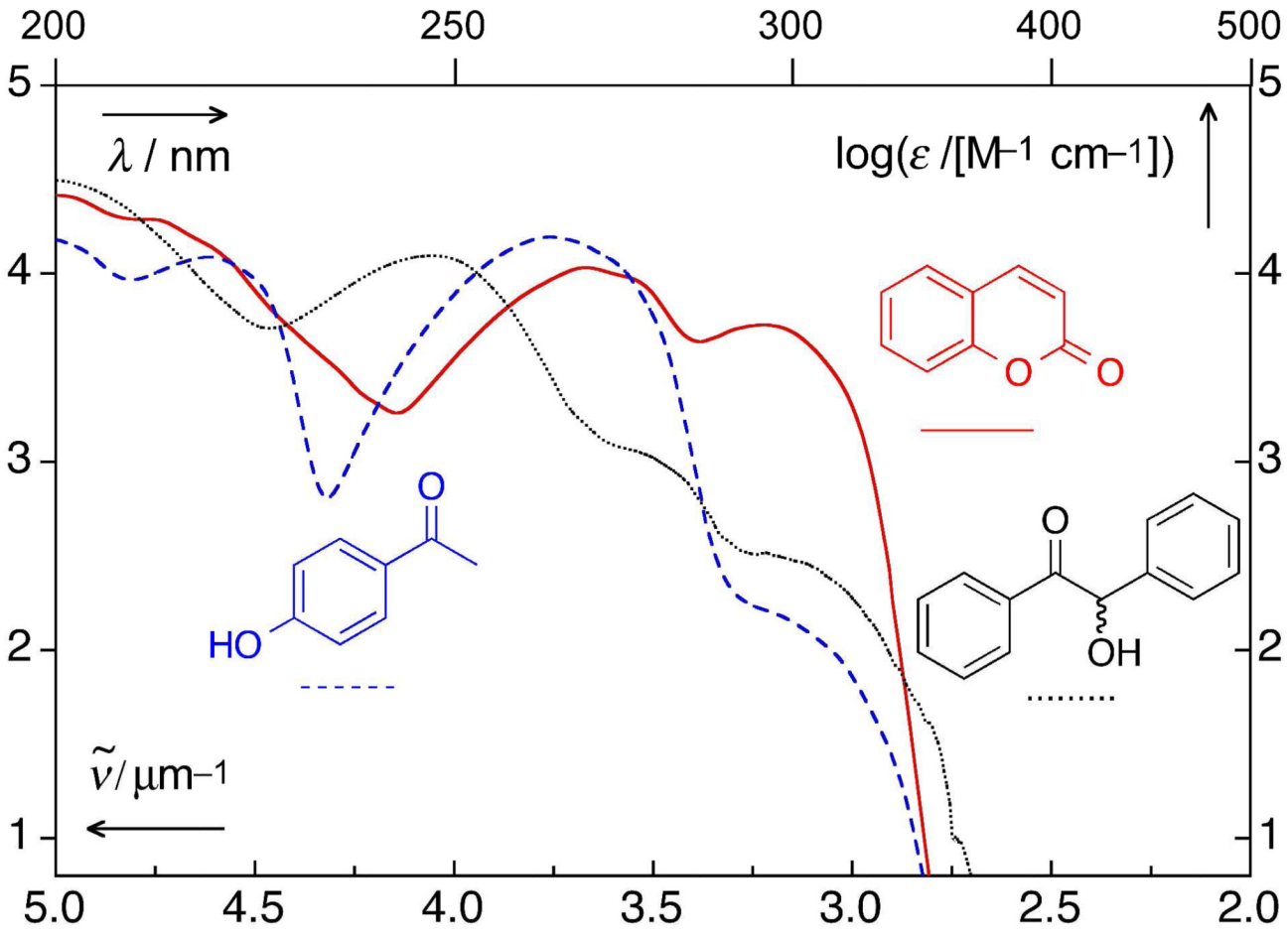


(c)



(d)

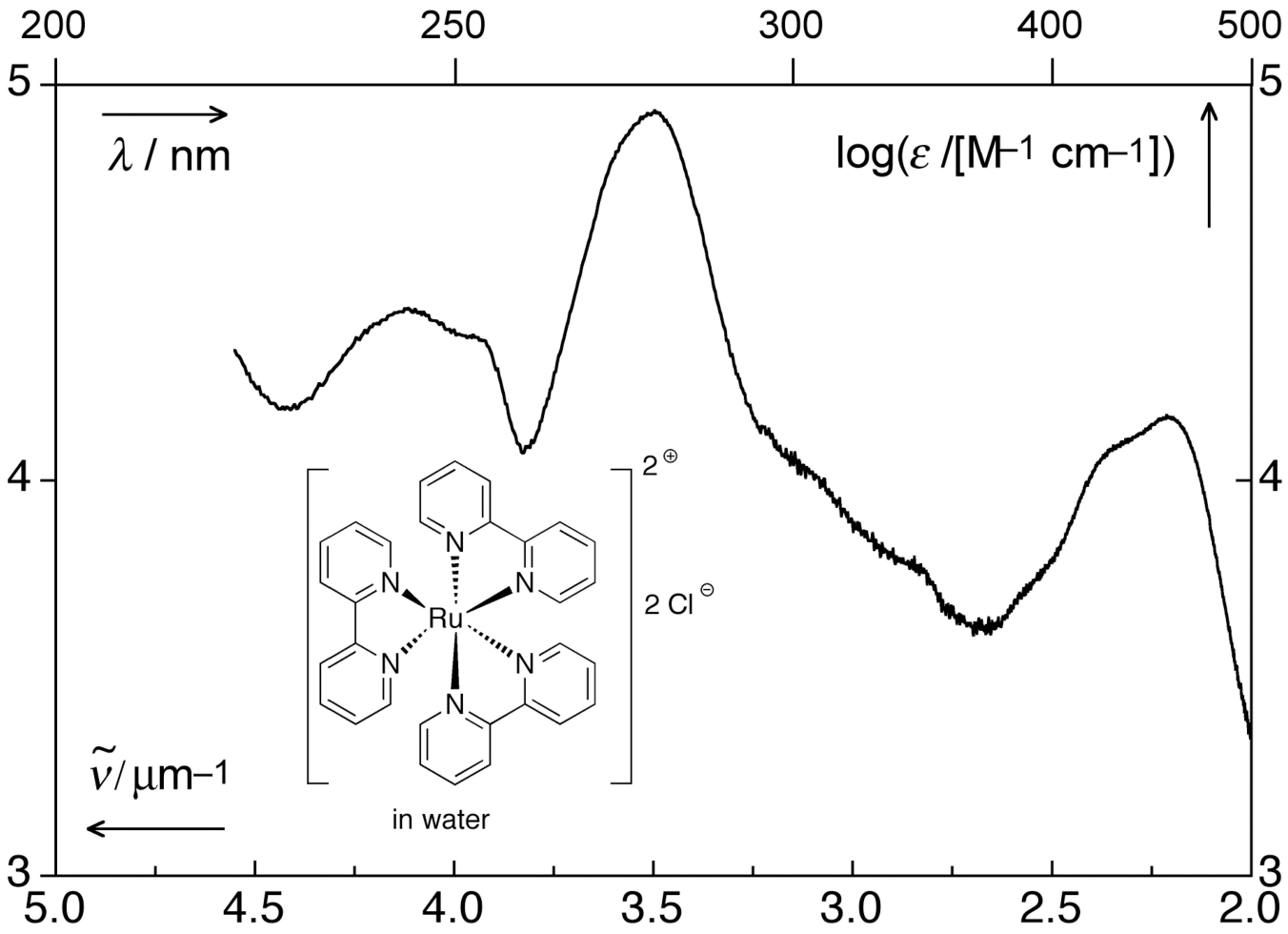


Figure 1.

UV-Spectra of selected chromophores.[23] (a) Benzophenone (ethanol; solid, red),[24] acetophenone (ethanol; dashed, blue);[24] (b) 1-acetyl-5-bromo-7-nitroindoline (acetonitrile; solid, red), 2-nitrotoluene (dashed, blue); (3,4-dimethoxy-6-nitrophenyl)methyl (nitroveratryl) derivative (acetonitrile, dashed, green);[25] (c) coumarin (acetonitrile, solid, red), *p*-hydroxyacetophenone (acetonitrile, dashed, blue), and benzoin (acetonitrile, dotted, black); (d) tris(bipyridyl)ruthenium(II) chloride (water).[26]

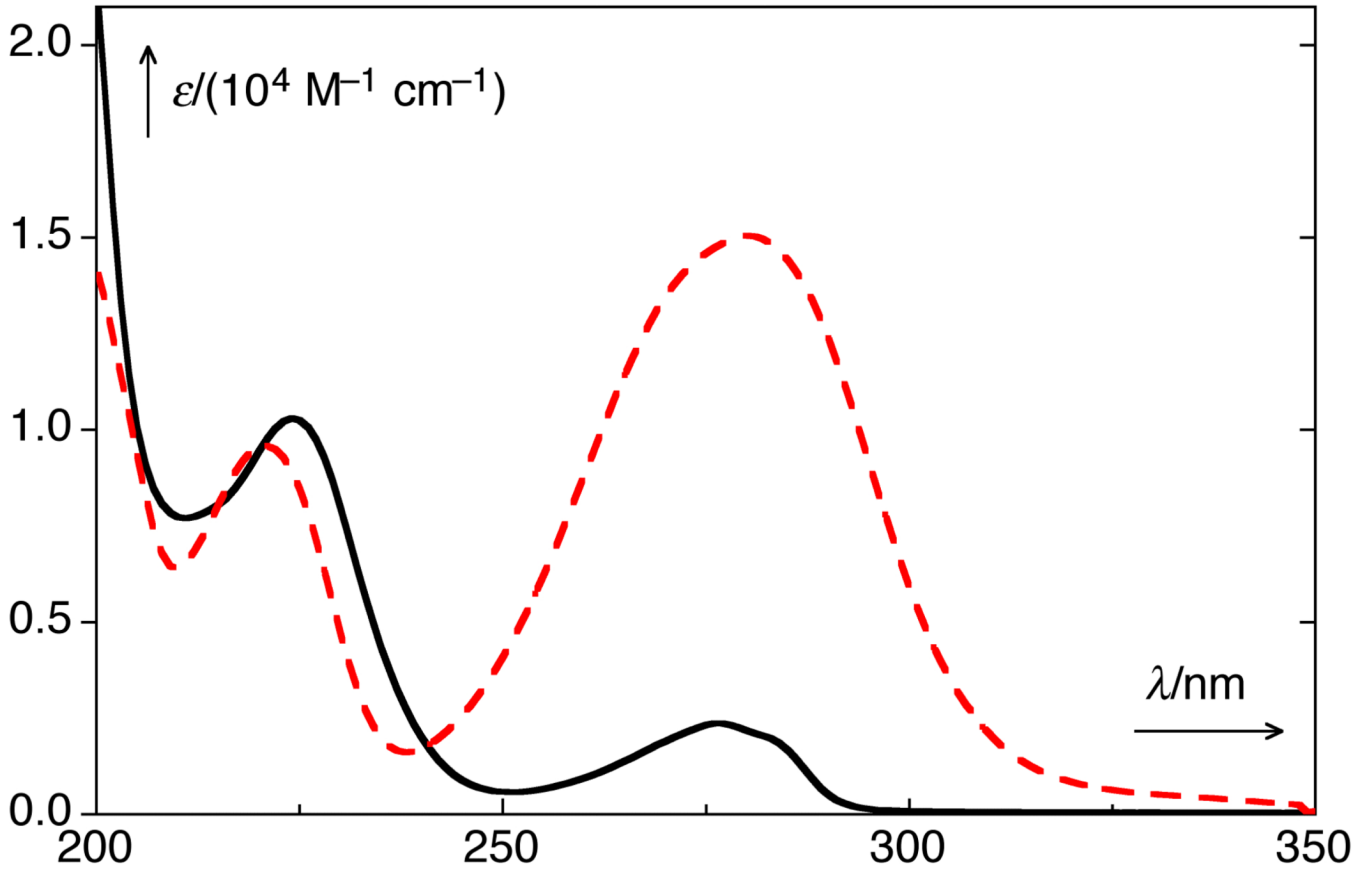


Figure 2.
UV-vis absorption spectra of *p*-hydroxyphenacyl diethyl phosphate (**24**, X = $OPO(OEt)_2$; pHP DEP; dashed, red) and *p*-hydroxyphenylacetic acid (**25**, R = H; black) in H_2O/MeCN (1:1).[88]

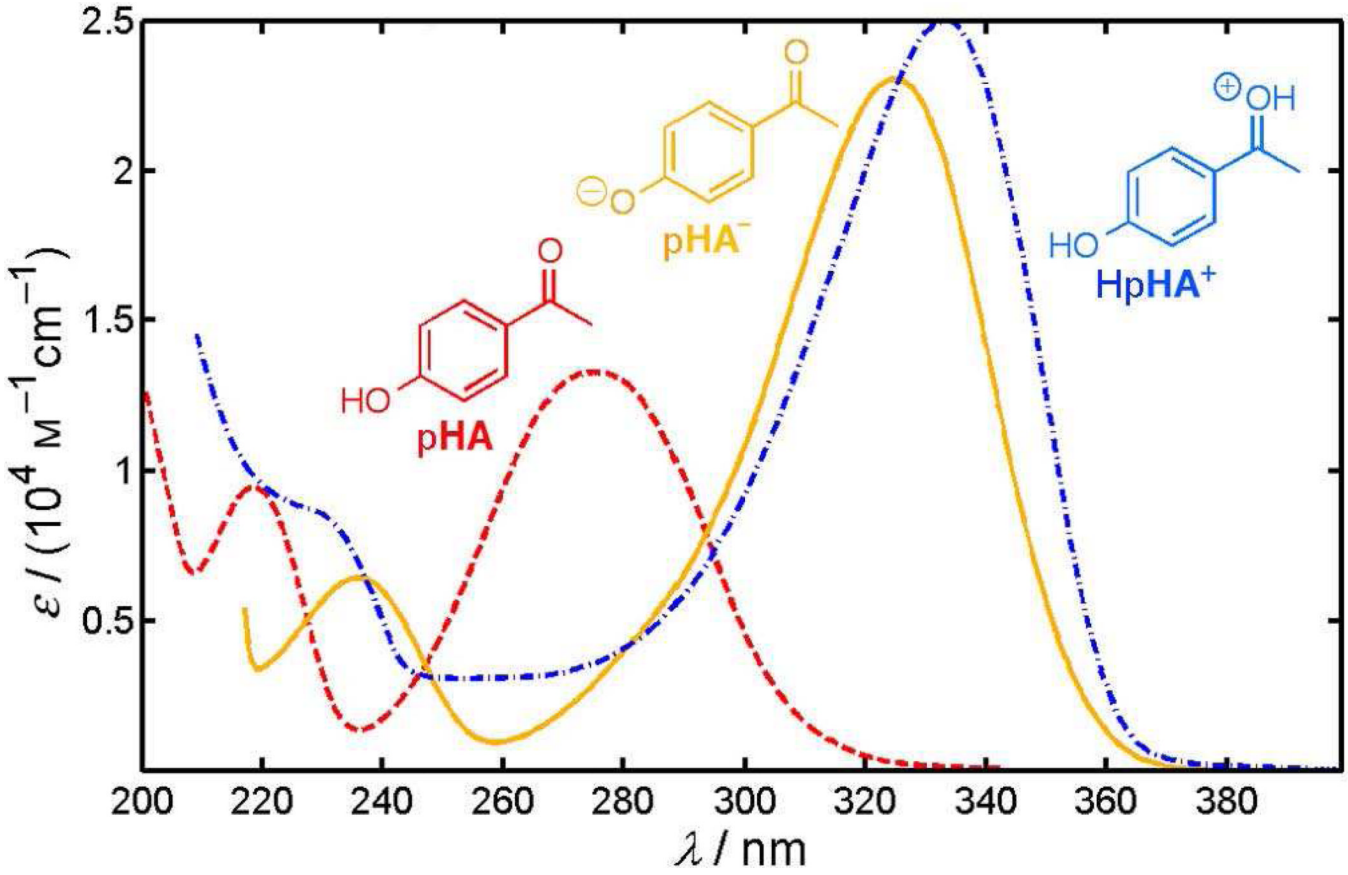


Figure 3.

Absorption spectra of pHA (**24**, X = H; dashed, in red) in neutral water (λ_{max} = 278 nm), of pHA^- in 0.05 M aqueous NaOH (λ_{max} = 325 nm; solid, in yellow), and of $HpHA^+$ in 70% aqueous $HClO_4$ (λ_{max} = 333 nm; dash–dot, in blue). The triplet excited state equilibria are shown in Scheme 18 below. The pK_a of ground state pHA is 7.9 ± 0.1 (the concentration quotient at ionic strength I = 0.1 M, 25 °C). Adapted with permission from ref.[89] Copyright 2012 American Chemical Society.

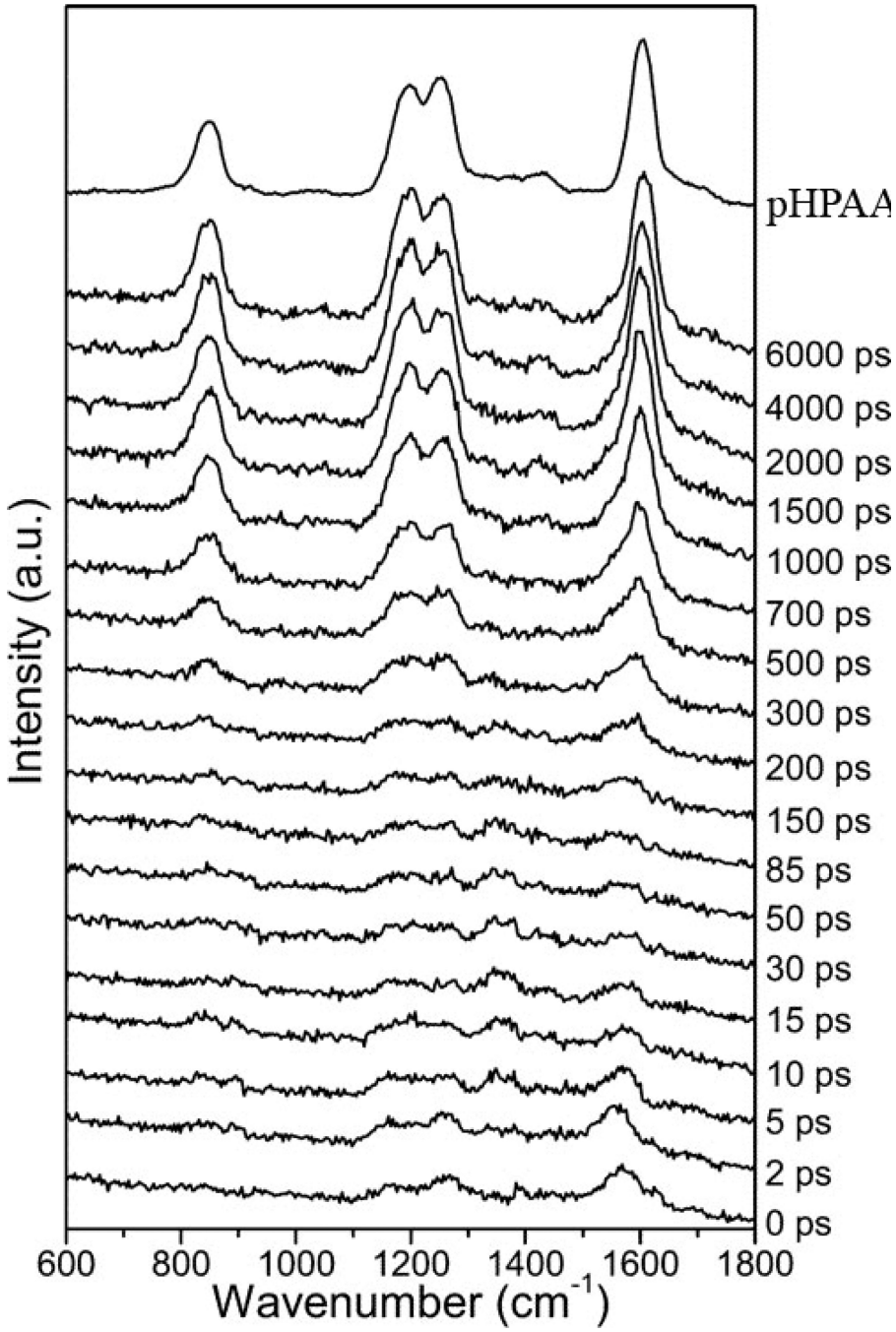


Figure 4.

Picosecond time-resolved resonance Raman spectra of pHP DEP (**24**, X = diethyl phosphate) obtained with a 267 nm pump and 200 nm probe wavelengths in a H_2O/CH_3CN (1:1) mixed solvent. The resonance Raman spectrum of an authentic sample of *p*-hydroxyphenylacetic acid recorded with 200 nm excitation is displayed at the top. Reprinted with permission from ref.[96a] Copyright 2005 American Chemical Society.

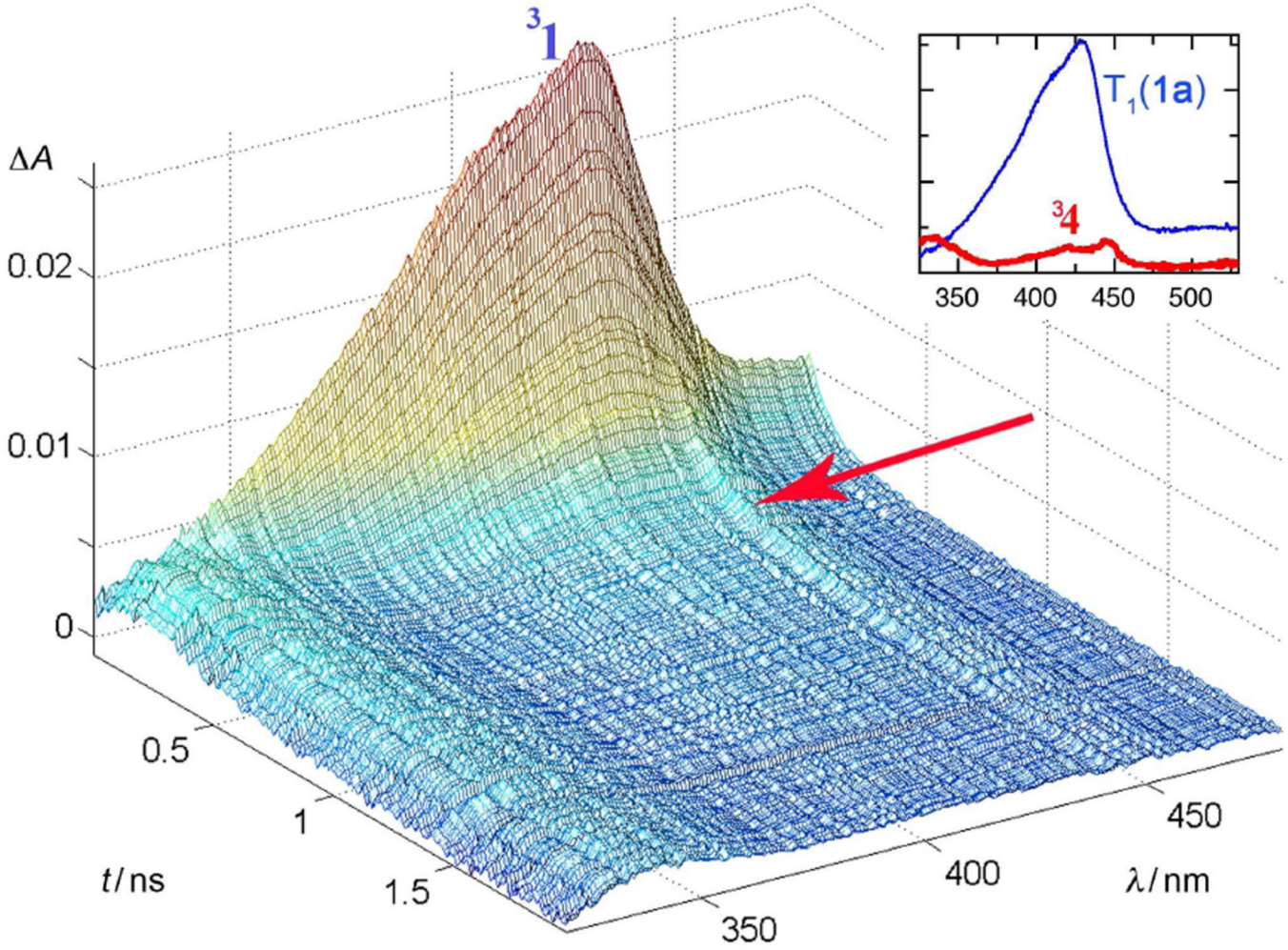


Figure 5.

Pump–probe spectra of pHP DEP (**24**, X = diethyl phosphate) in 87% aqueous CH_3CN. The sample was excited with a pulse from a Ti/Sa–NOPA laser system (266 nm, 150 fs pulse width, pulse energy 1 μJ). The inset shows the species spectra of ^{3}pHP DEP and biradical ^{3}**28** that were determined by global analysis of the spectra taken with delays of 10–1800 ps using a biexponential fit. Reprinted with permission from ref.[85d] Copyright 2008 American Chemical Society.

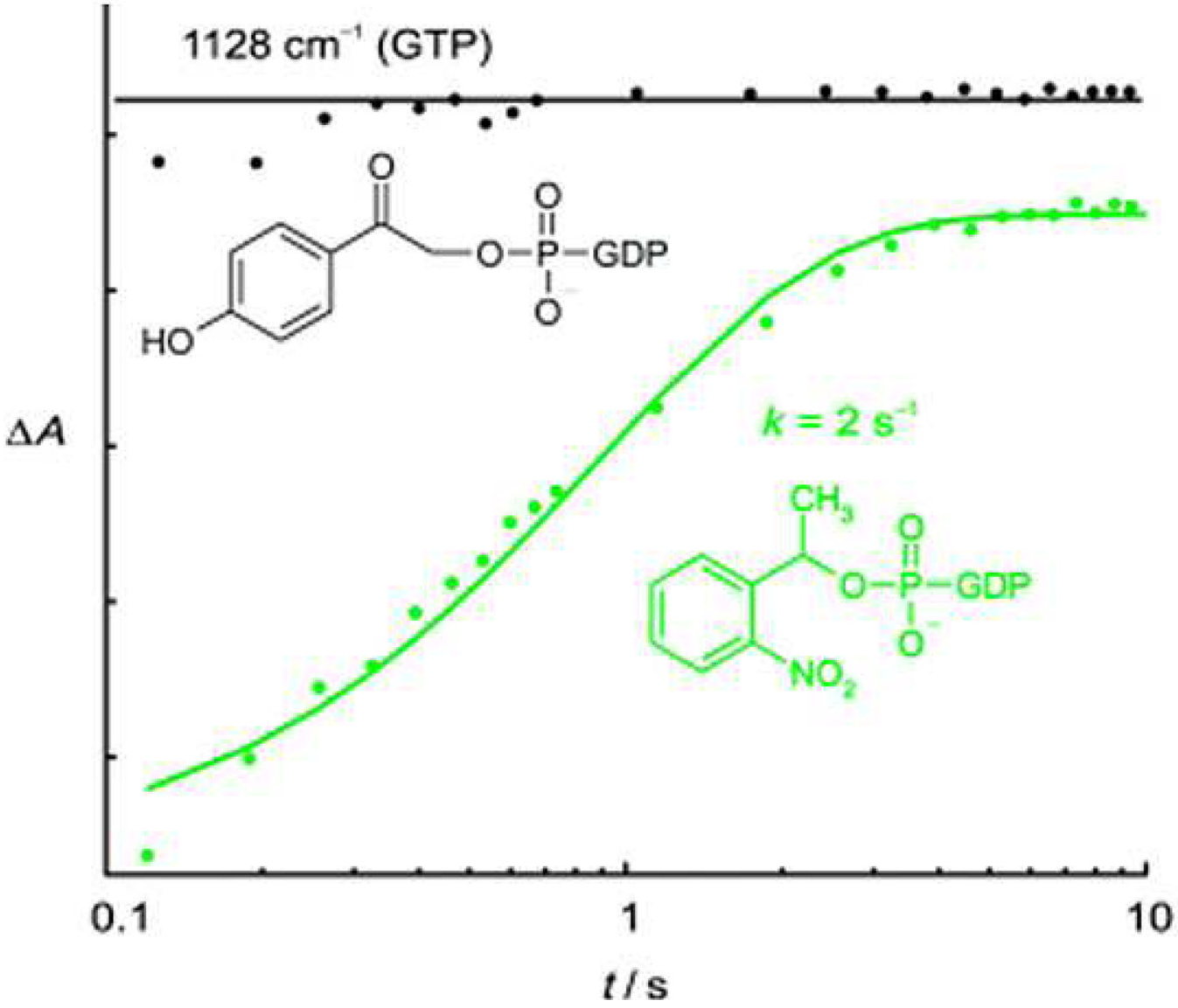


Figure 6.

Formation of GTP measured as its Mg^{+2} complex at 1128 cm^{-1} from pHP caged GTP (black) is already complete at the first data point. Formation of GTP from NPE caged GTP (green) takes place more slowly with a rate constant of 2 s^{-1} since the rate limiting step is release from a ground state hemiacetal intermediate (Section 3.2), an inherently slow process on the timescale necessary for the kinetic measurements reported here.[116] Reprinted with permission from ref.[116] Copyright 2007 Wiley and Sons.

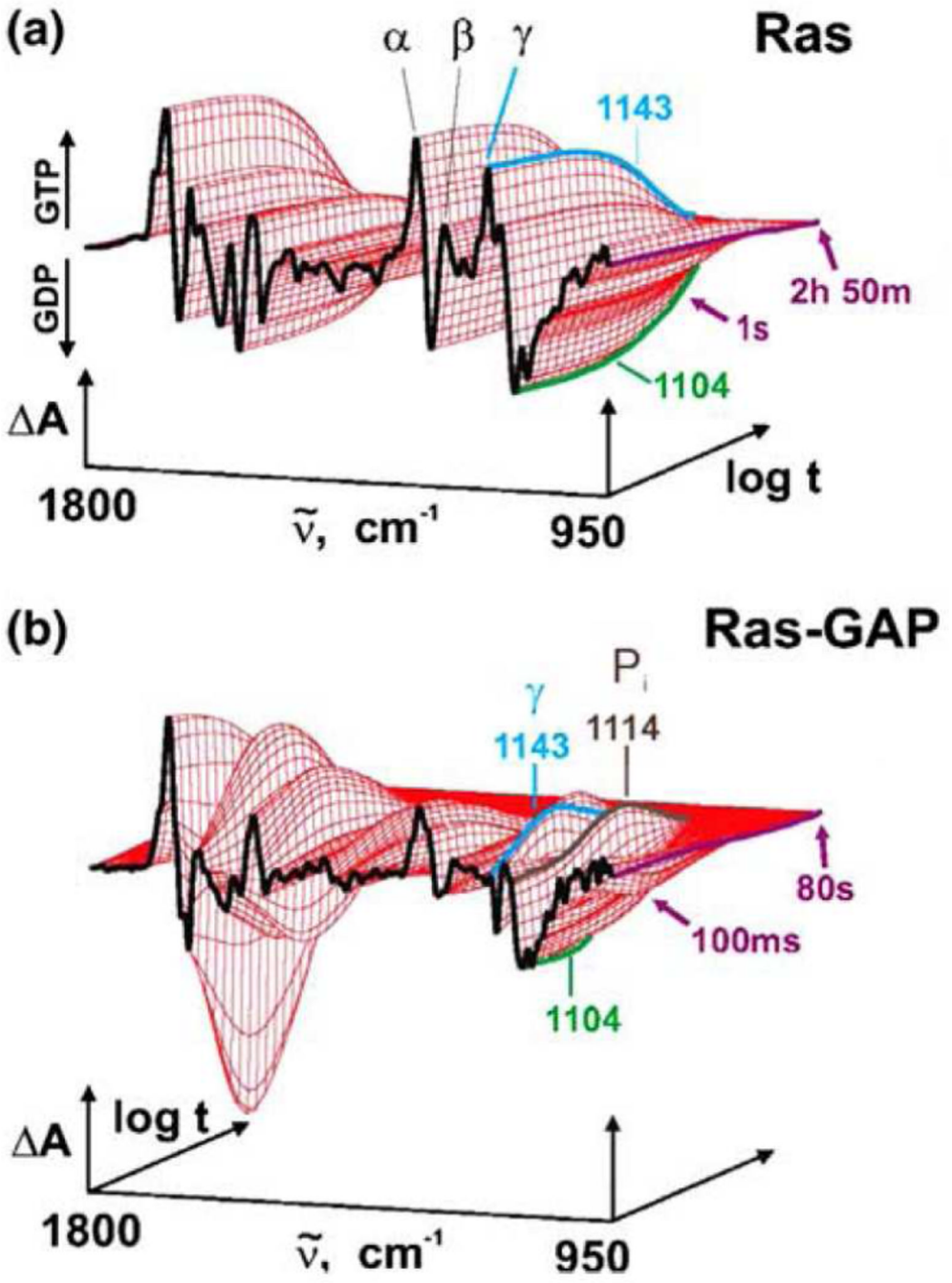


Figure 7.

(a) Difference spectra by TRIR absorption of the intrinsic Ras-catalyzed GTPase reaction. A single exponential function by global fit analysis shows the change from Ras GTP to Ras GDP at 1143 cm^{-1}. (b) TRIR absorbance difference spectra for the GAP-catalyzed GTPase by Ras. Two intermediates are seen by the fit of three exponential functions at 1143 and 1114 cm^{-1}. The appearance of GTP at 1143 cm^{-1} arises from pHP caged-GTP followed by GTP hydrolysis. Protein bound P*i* appears at 1114 cm^{-1} which is subsequently released as the rate limiting step (Scheme 20). Reprinted with permission from ref. [92a] Copyright 2004 Elsevier B. V.

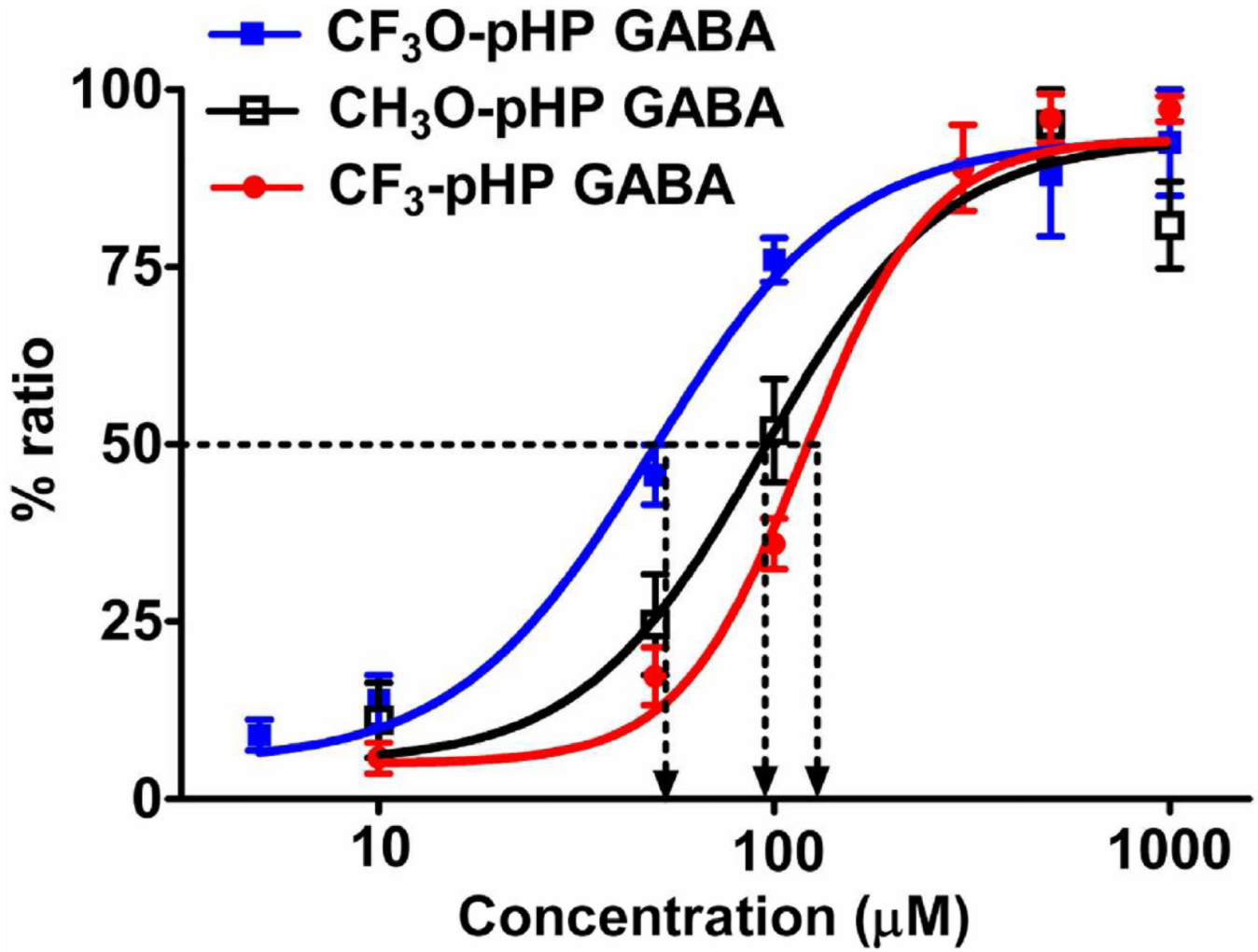


Figure 8.

Comparison of EC_{50}'s for GABAA receptor activation by rapid photolysis of pHP (**24**) GABA. Dose-response curves for 3-CF_3O-pHP GABA (blue, n = 7 neurons), 3-CF_3-pHP GABA (red, n = 6 neurons), and 3-CH_3O-pHP GABA (black, n = 6 neurons) with population data of peak currents normalized to the maximum peak response. EC_{50} and Hill's coefficient values were: 3-CF_3O-pHP GABA, 49.2 μM, 1.8, n = 7 neurons; 3-CH_3O-pHP GABA, 93.4 μM, 1.9, n = 6 and 3-CF_3-pHP GABA 119.8 μM, 2.73 n = 6. Reprinted with permission from ref.[97b] Copyright 2009 American Chemical Society.

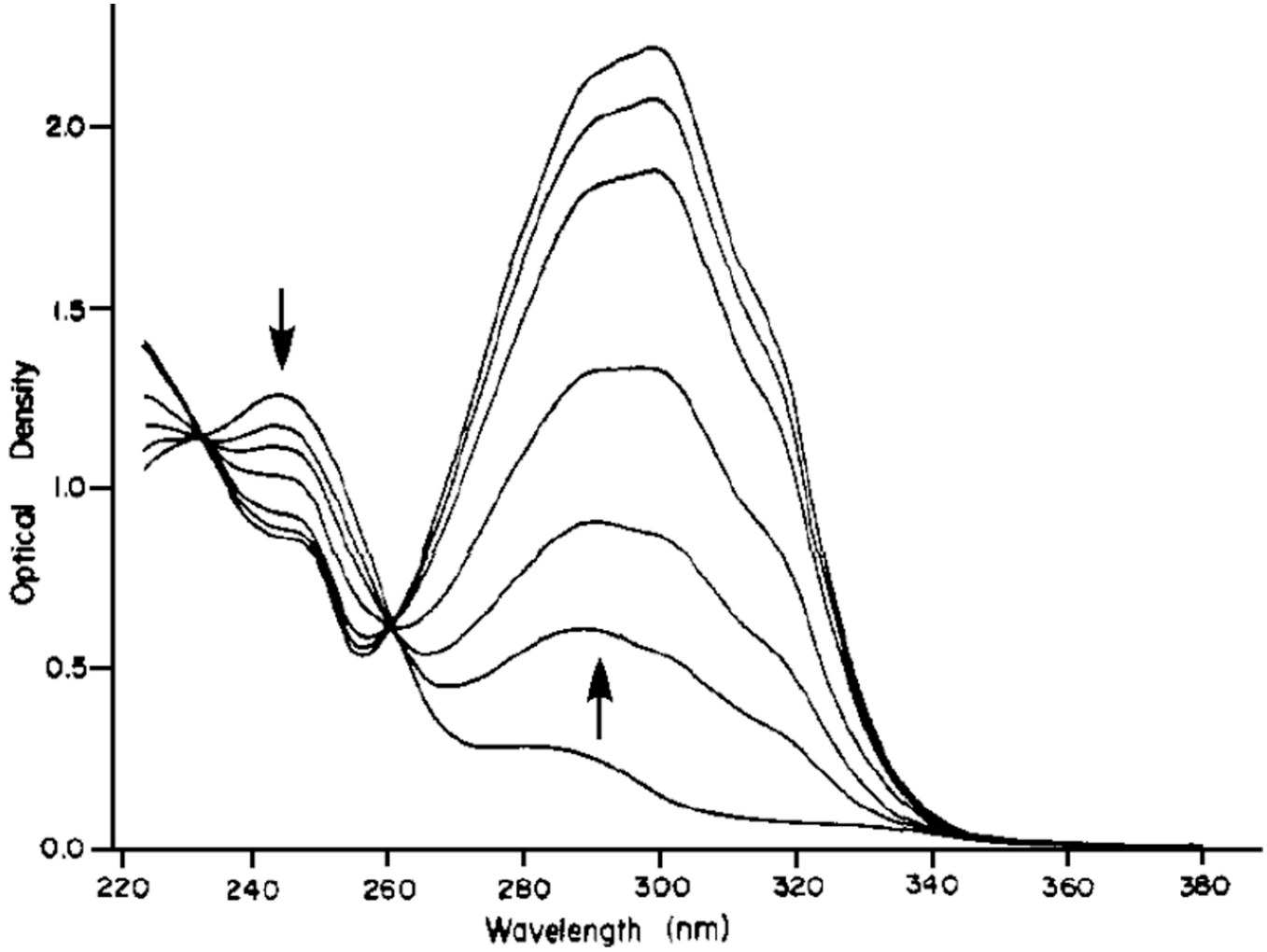


Figure 9.

Course of the photolysis of DMB (**33**) acetate to DMBF (**34**) in acetonitrile (Scheme 23); irradiated in a photochemical reactor at 360 nm. Reprinted with permission from ref.[118] Copyright 1971 American Chemical Society.

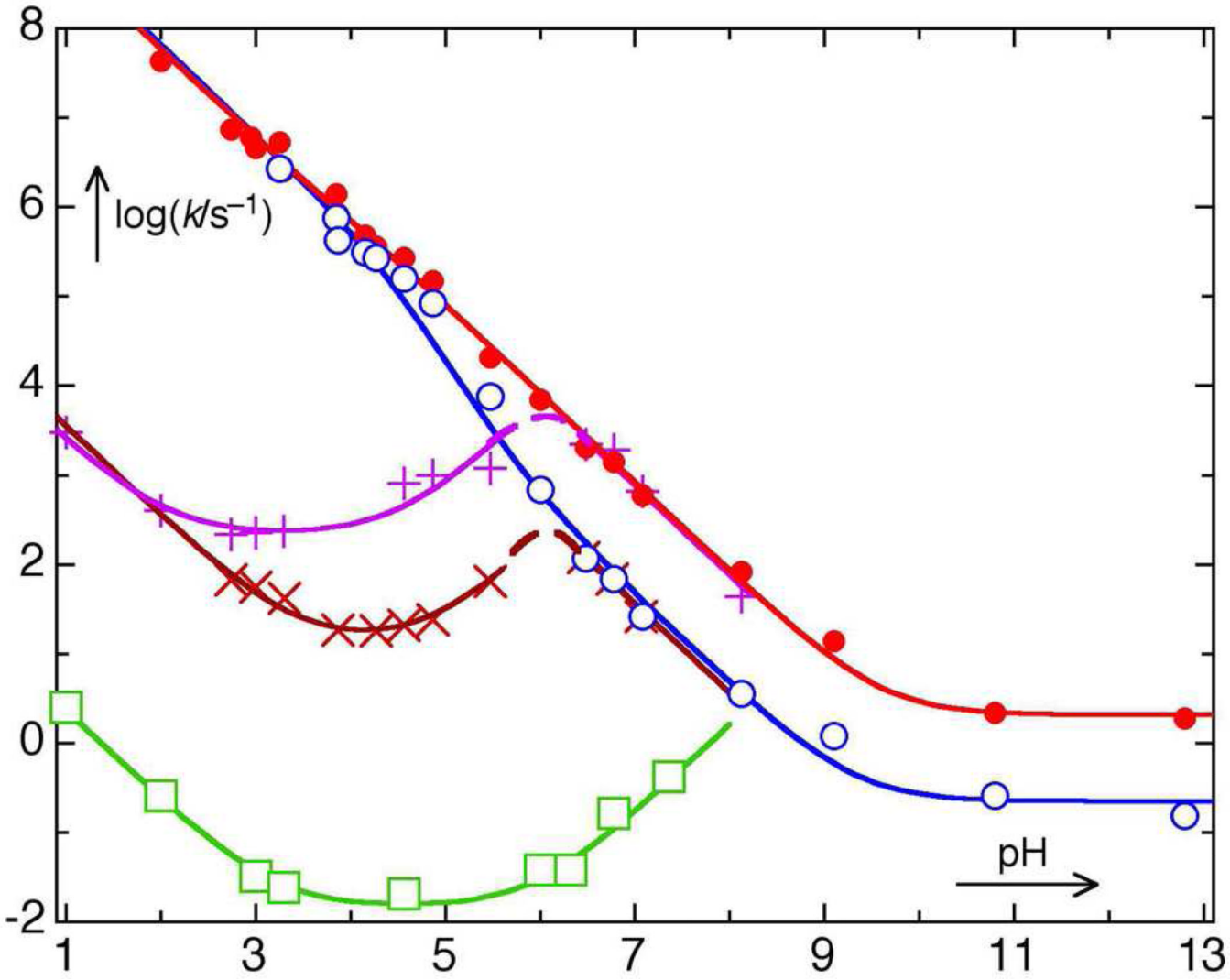
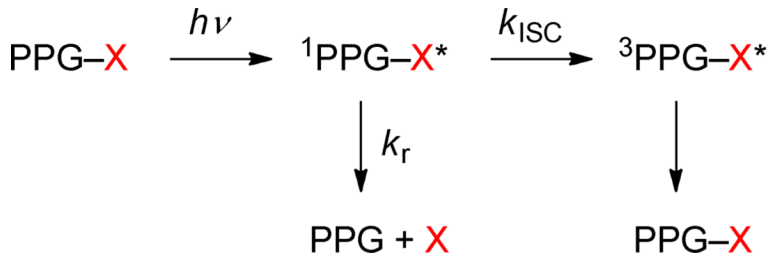


Figure 10.

pH–Rate profiles for the reaction steps **51**/**51**$^{-}$ → **50** (• and o), **50** → **52** (+ and × and **52** → **53** (□) of *o*NB methyl ether in aqueous solution. Reprinted with permission from ref.[158] Copyright 2004 American Chemical Society.

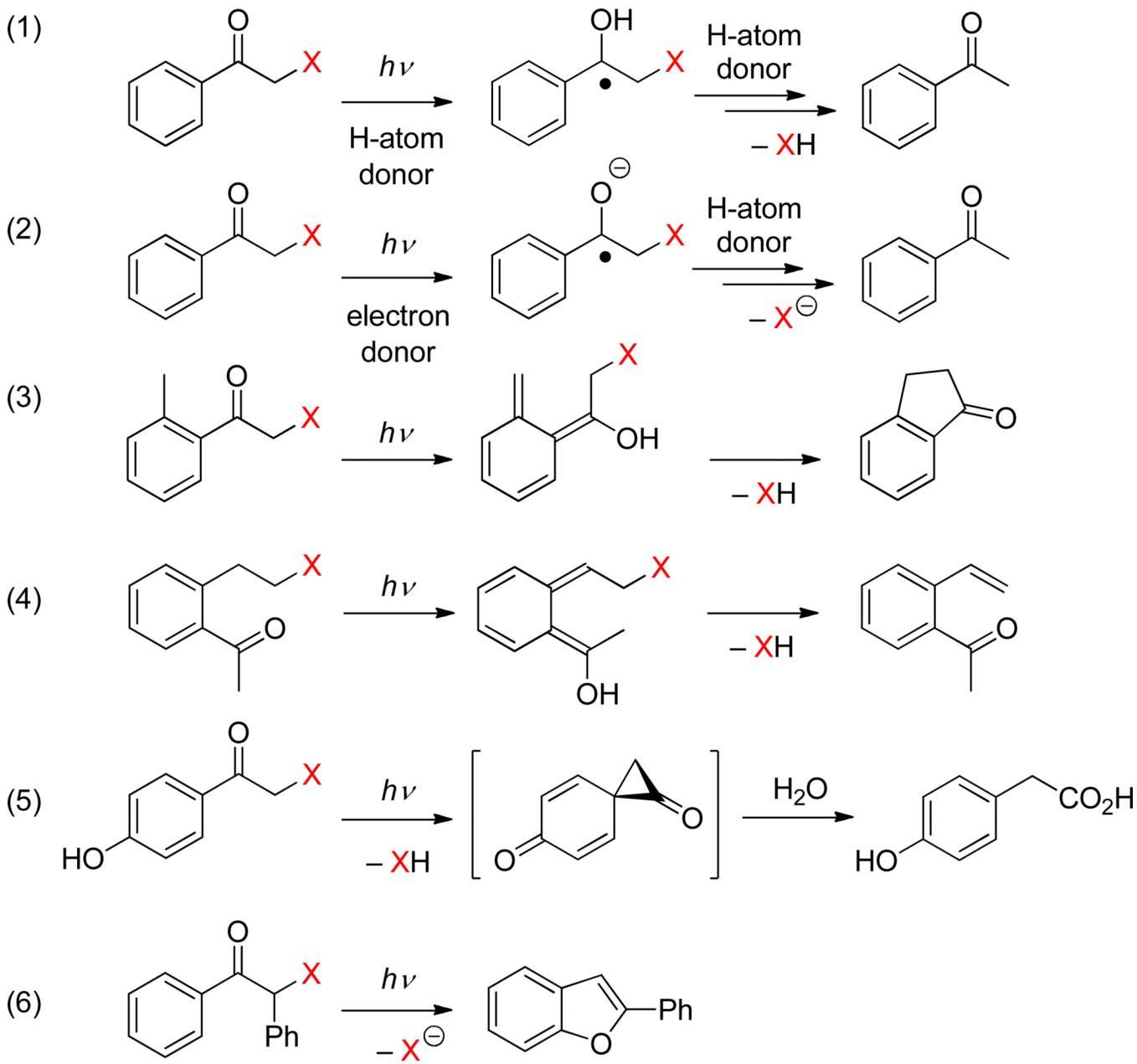


$$\Phi_r = \eta_r = k_r/(k_r + k_{ISC}) = k_r\tau_r$$

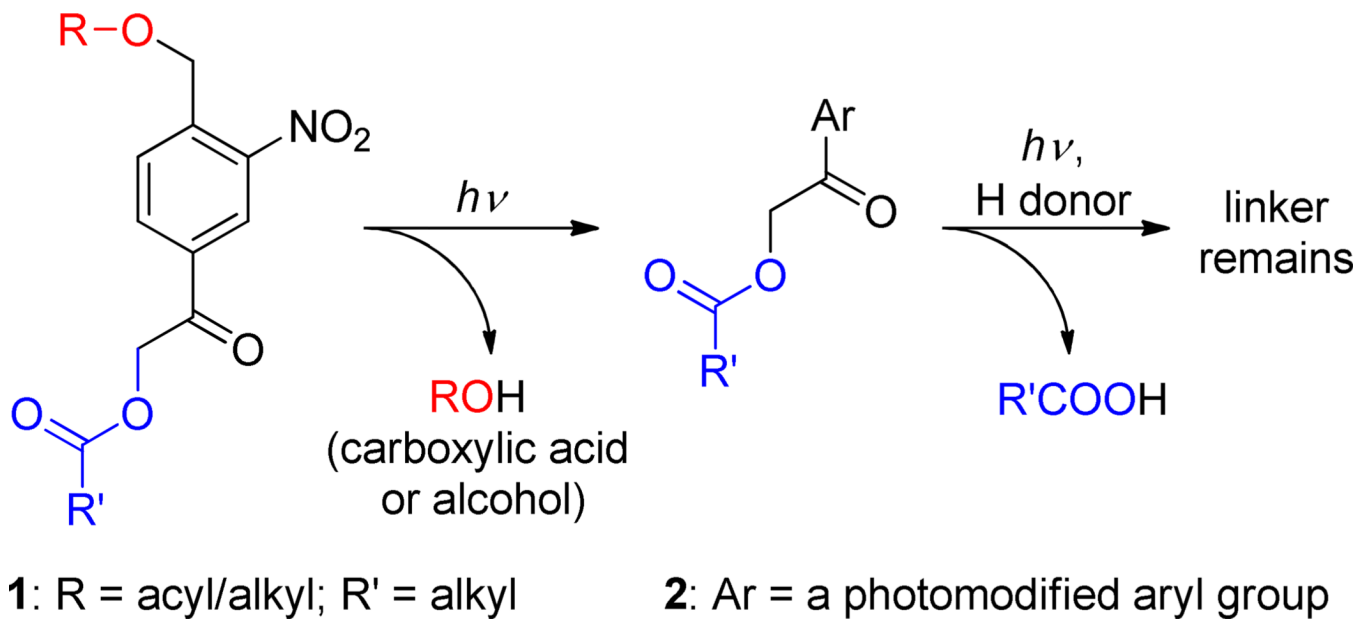
$$k_r < k_{app} = k_r + k_{ISC}$$

Scheme 1.

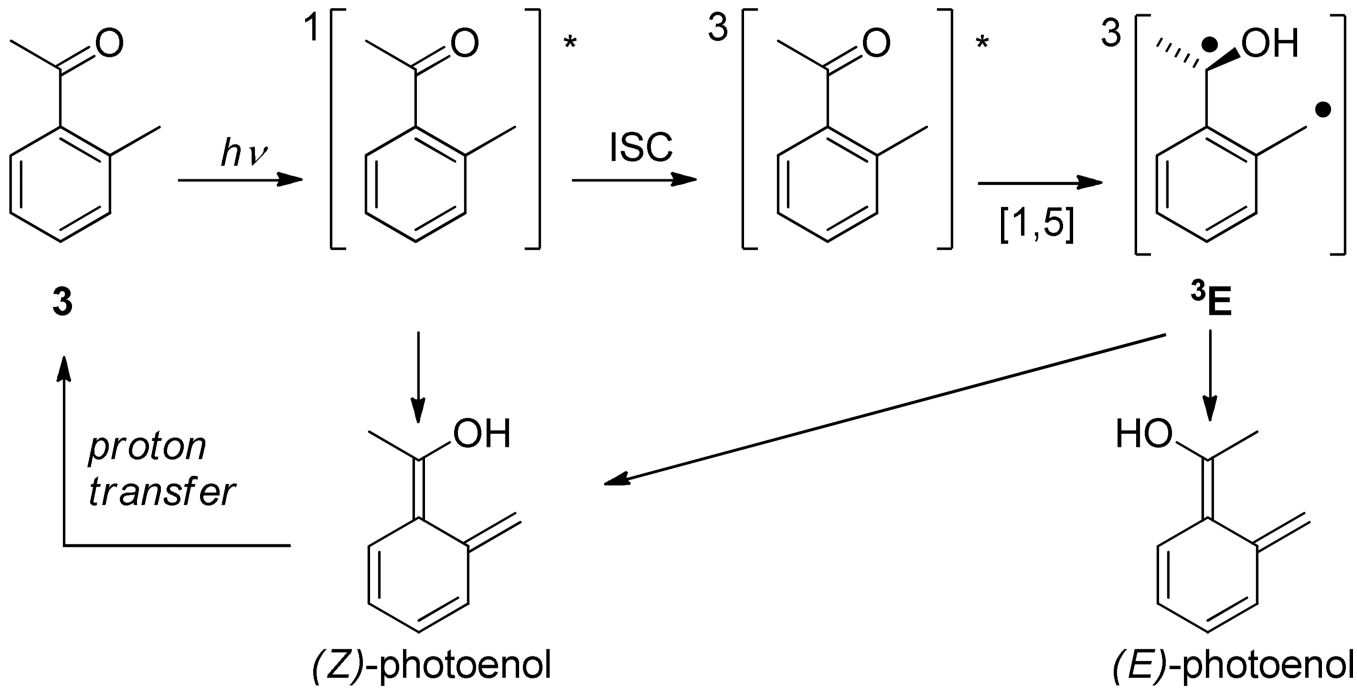
A simple case where the release rate constant of the free substrate (leaving group) X, k_r, is smaller than its appearance rate constant, k_{app}



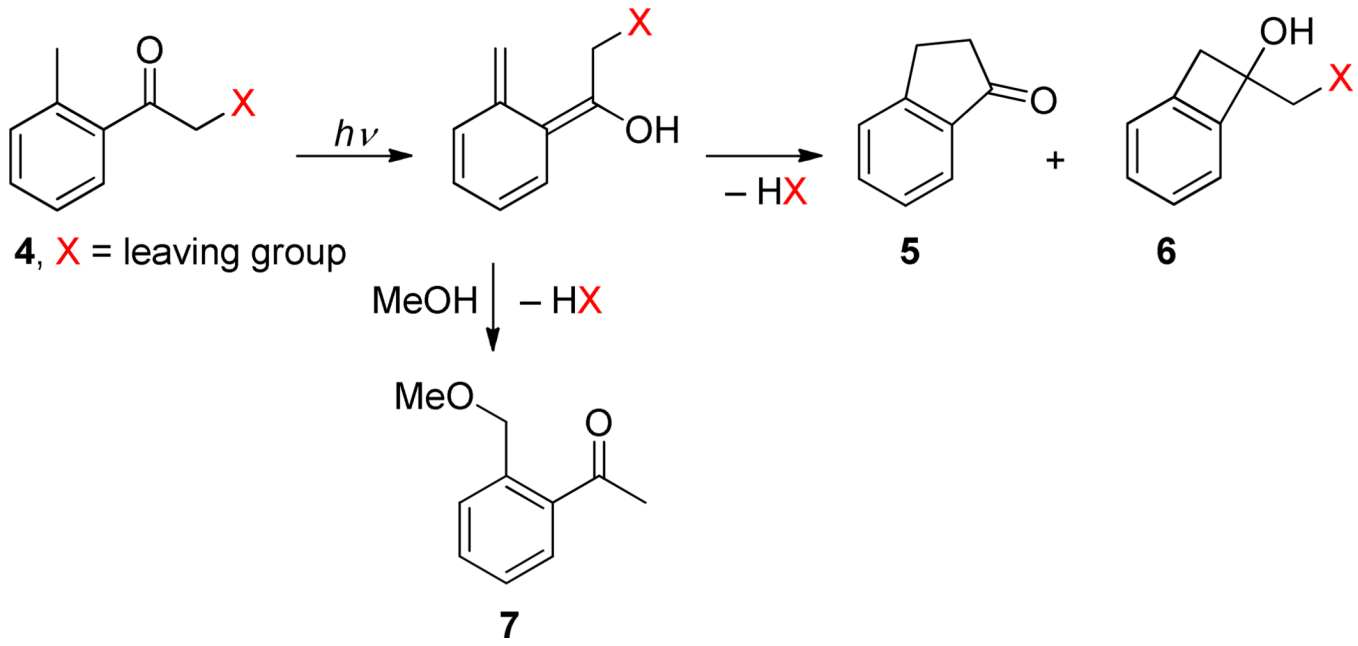
Scheme 2.
Photochemistry of Aromatic Ketones that Release a Leaving Group (X)



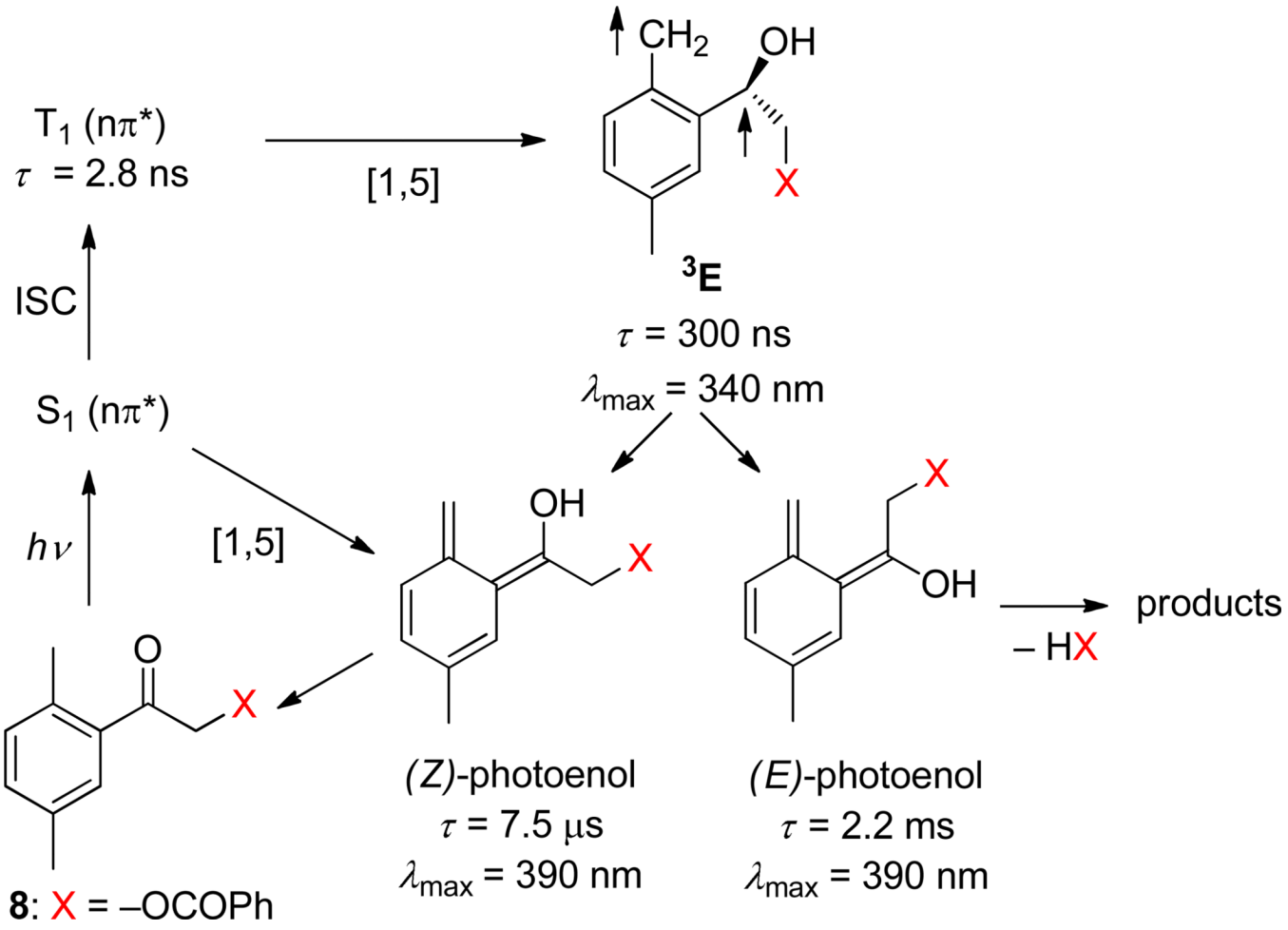
Scheme 3.
Monochromophoric Photocleavable Linker[48]



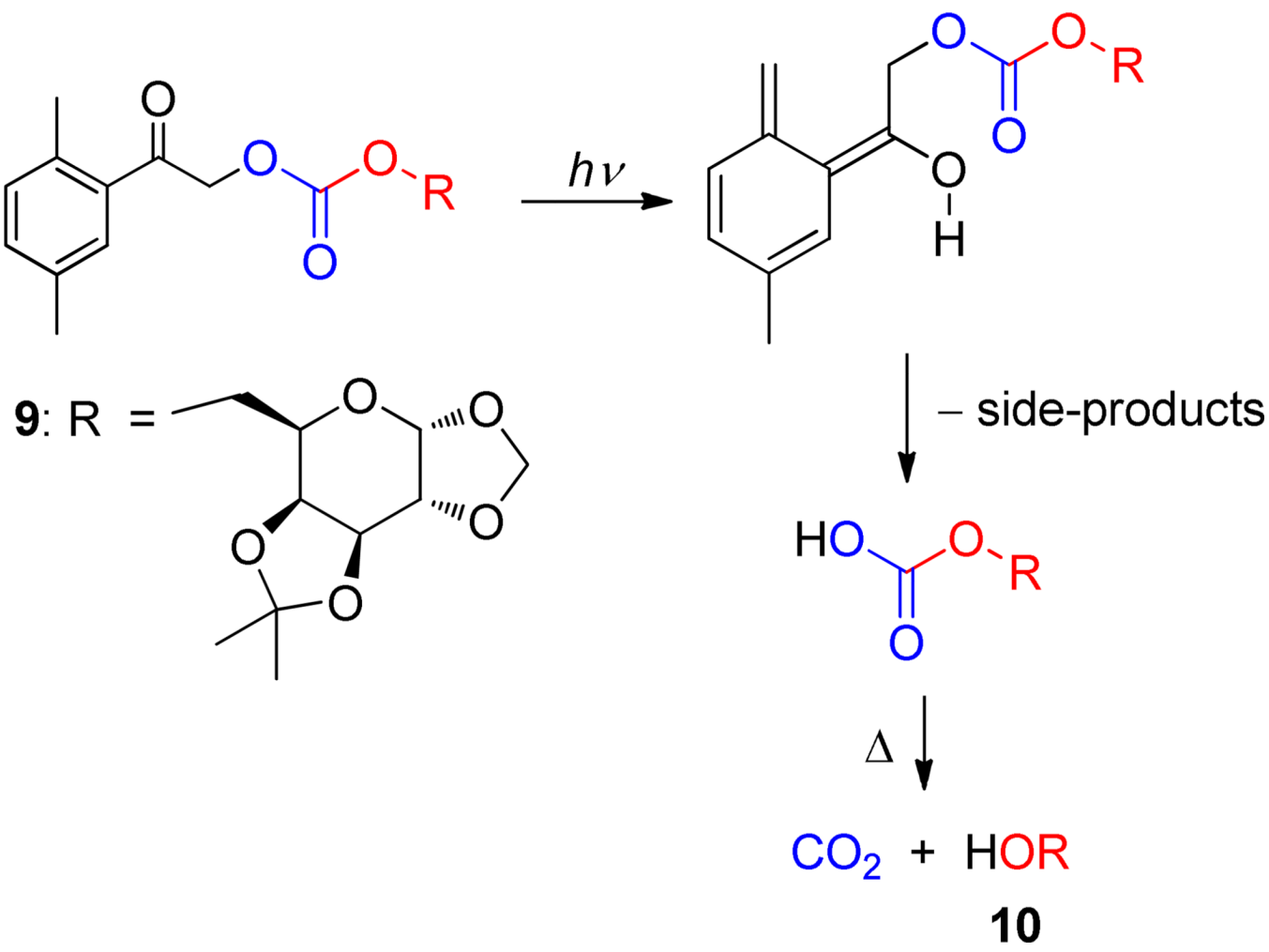
Scheme 4.
Photoenolization of 2-Methylacetophenone[49]



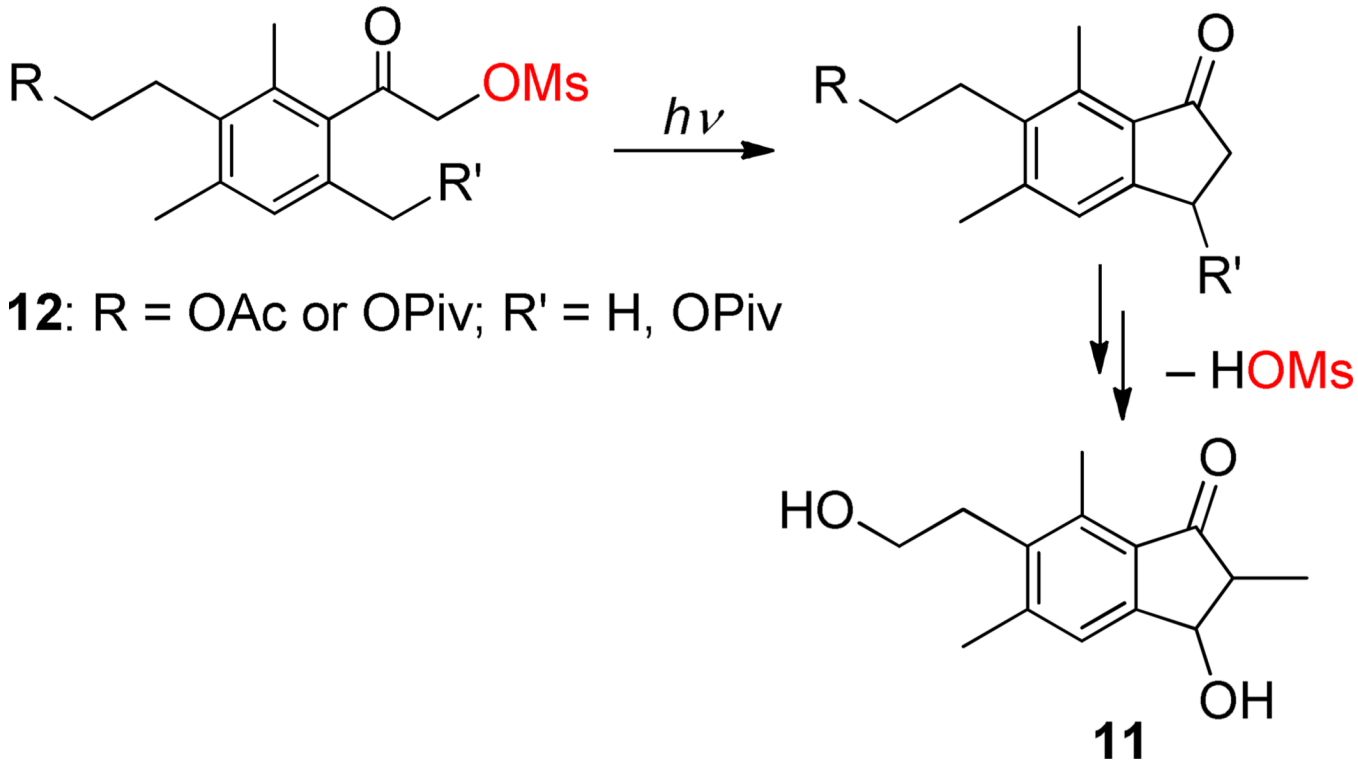
Scheme 5.
Photochemistry of 2-Alkylphenacyl Compounds[54]



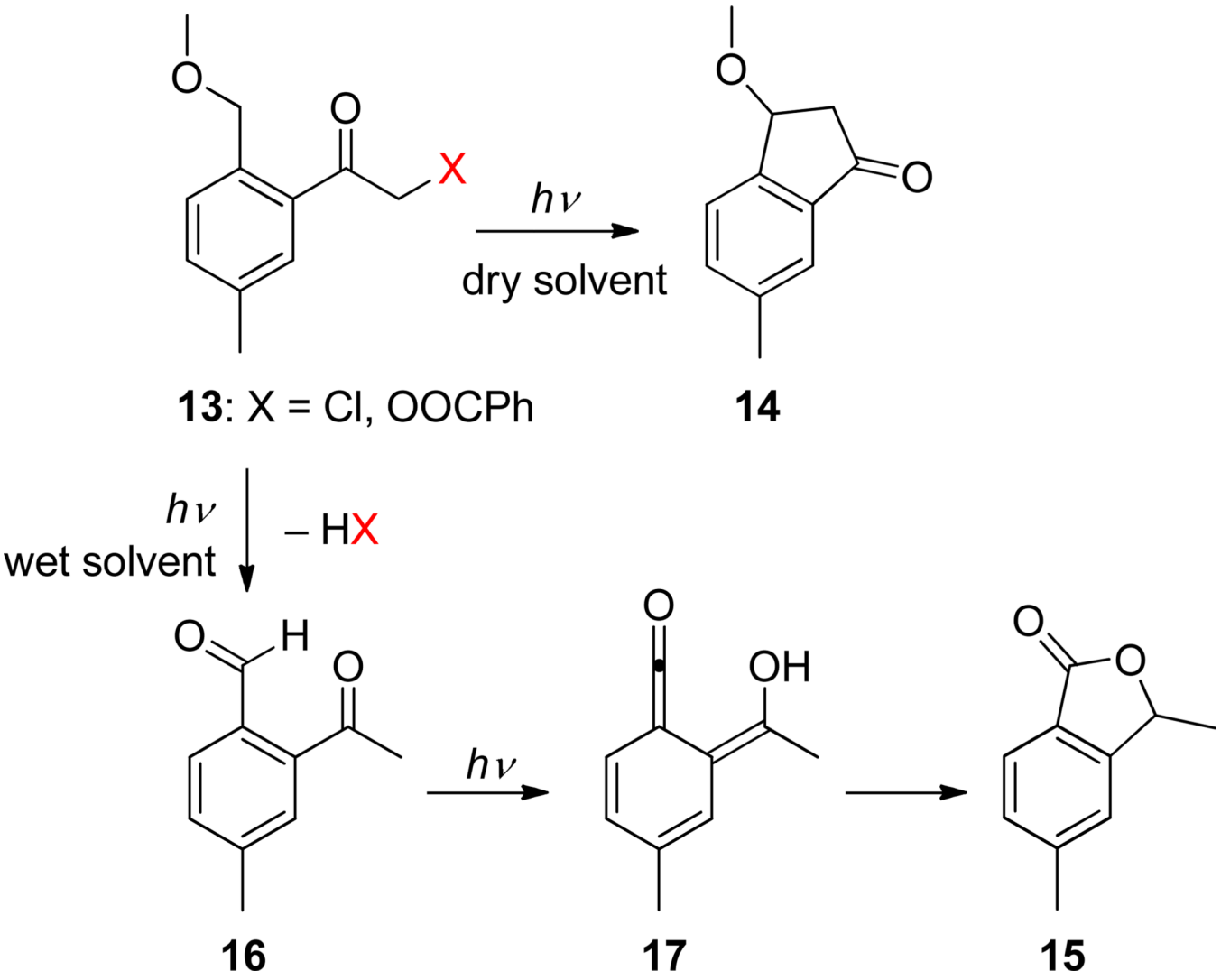
Scheme 6.
Photochemistry of DMP Esters[57b]



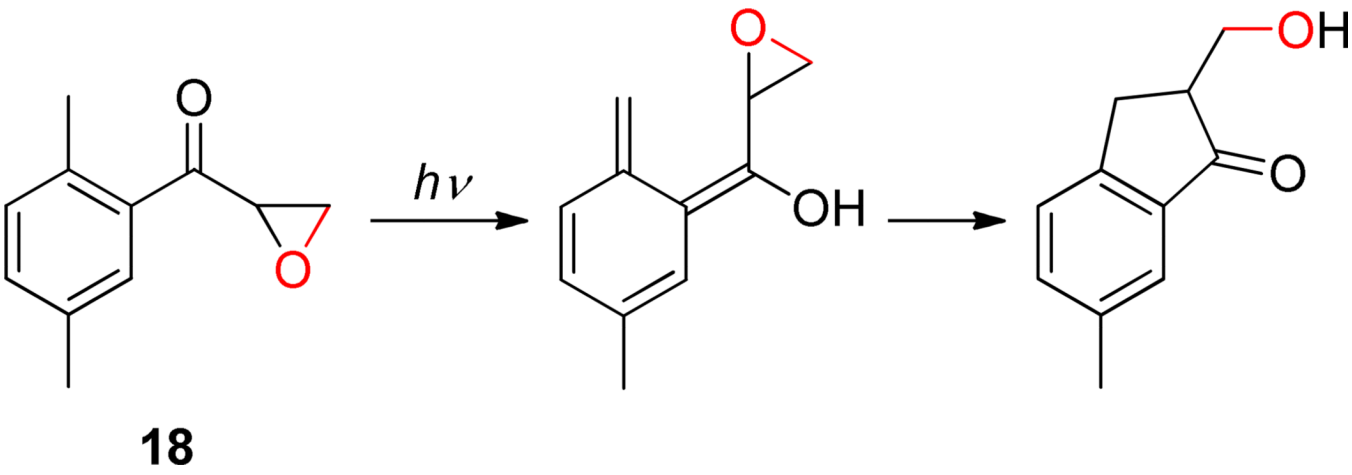
Scheme 7.
Photochemistry of a DMP Galactopyranosyl Carbonate[58]



Scheme 8.
Photochemical Synthesis of Pterosines[66]

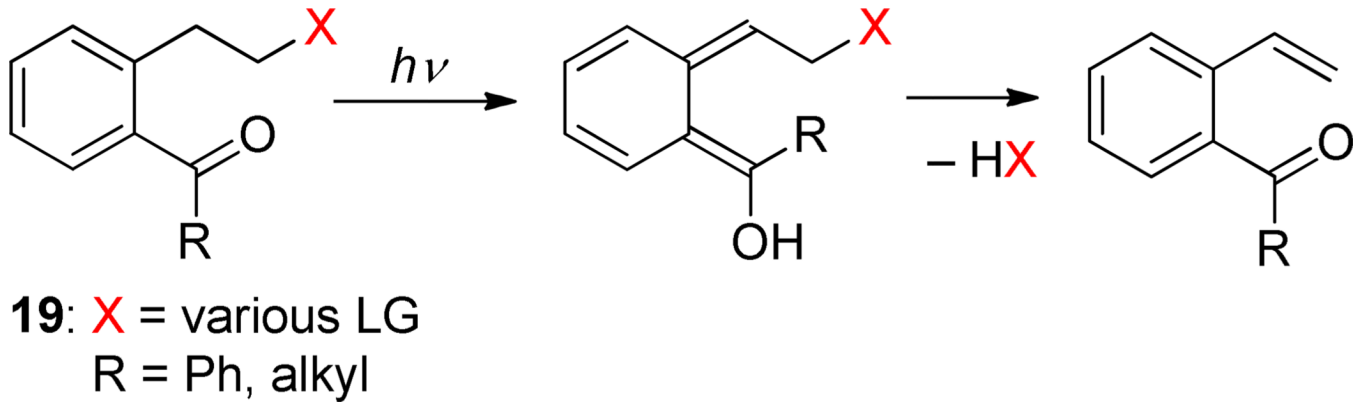


Scheme 9.
Photochemistry of 2-(Alkoxymethyl)-5-methyl-α-chloroacetophenones[70]

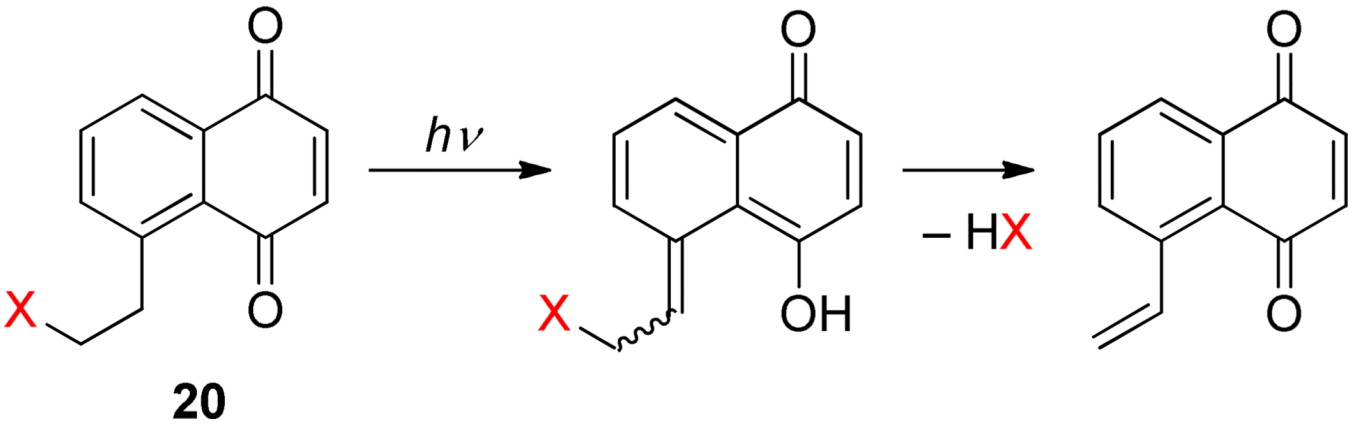


18

Scheme 10.
Photochemistry of 2,5-Dimethylbenzoyl Oxiranes[71]

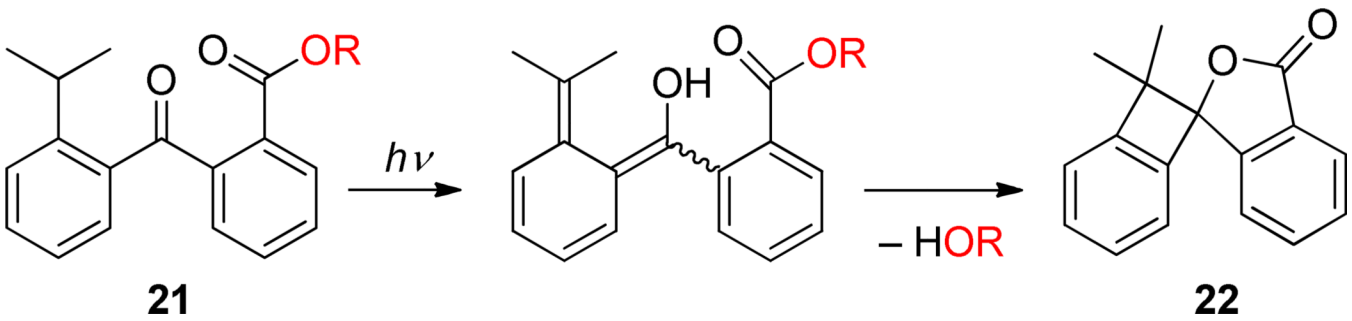


Scheme 11.
Photochemistry of 1-[2-(2-Hydroxyalkyl)phenyl]ethanones[74]

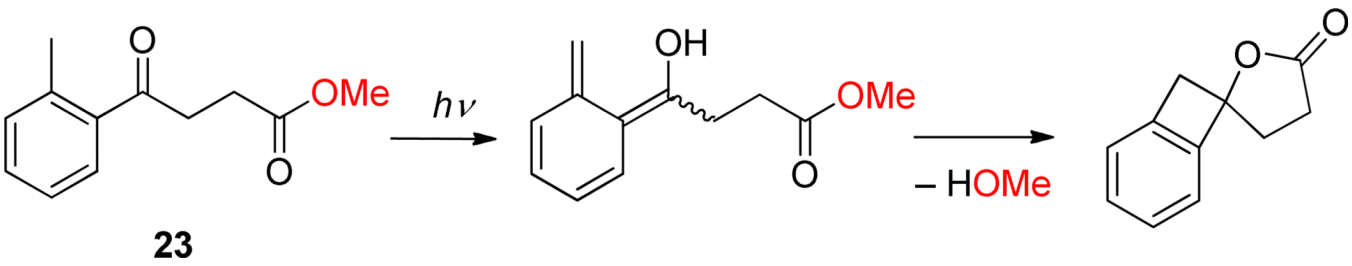


20

Scheme 12.
Photochemistry of 5-(Ethylen-2-yl)-1,4-naphthoquinones[78]

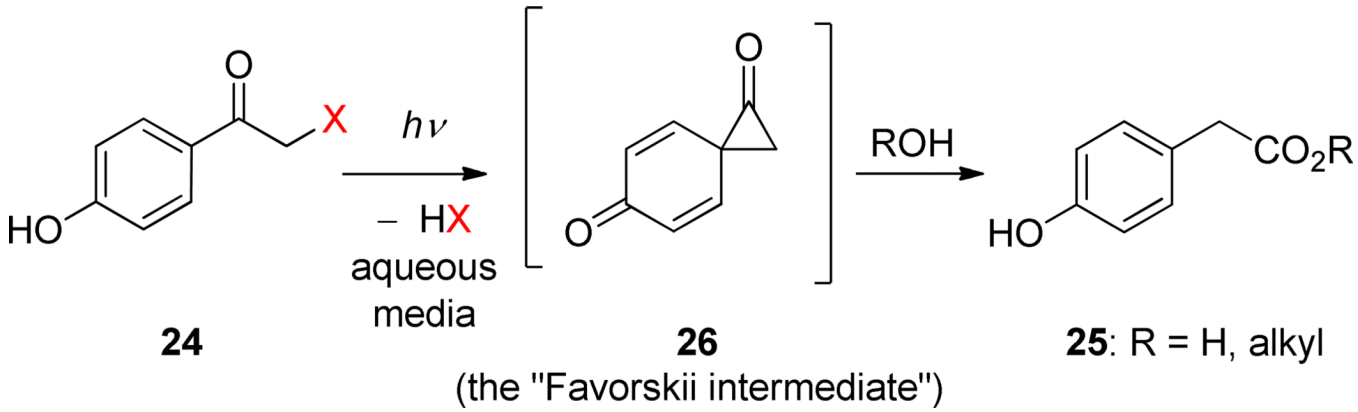


Scheme 13.
Photochemistry of 2-(2-Isopropylbenzoyl)benzoate Esters[8d,80]

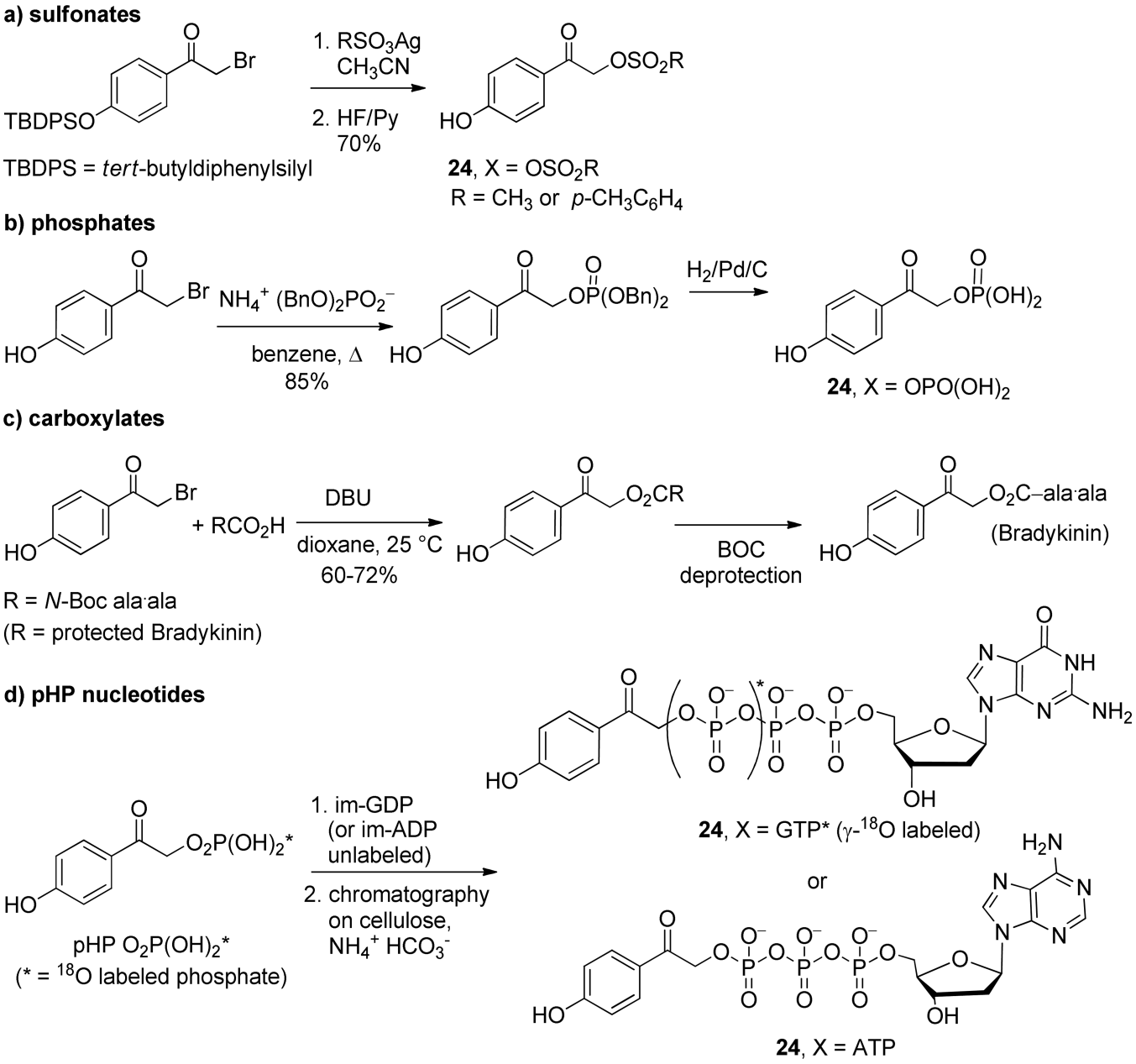


23

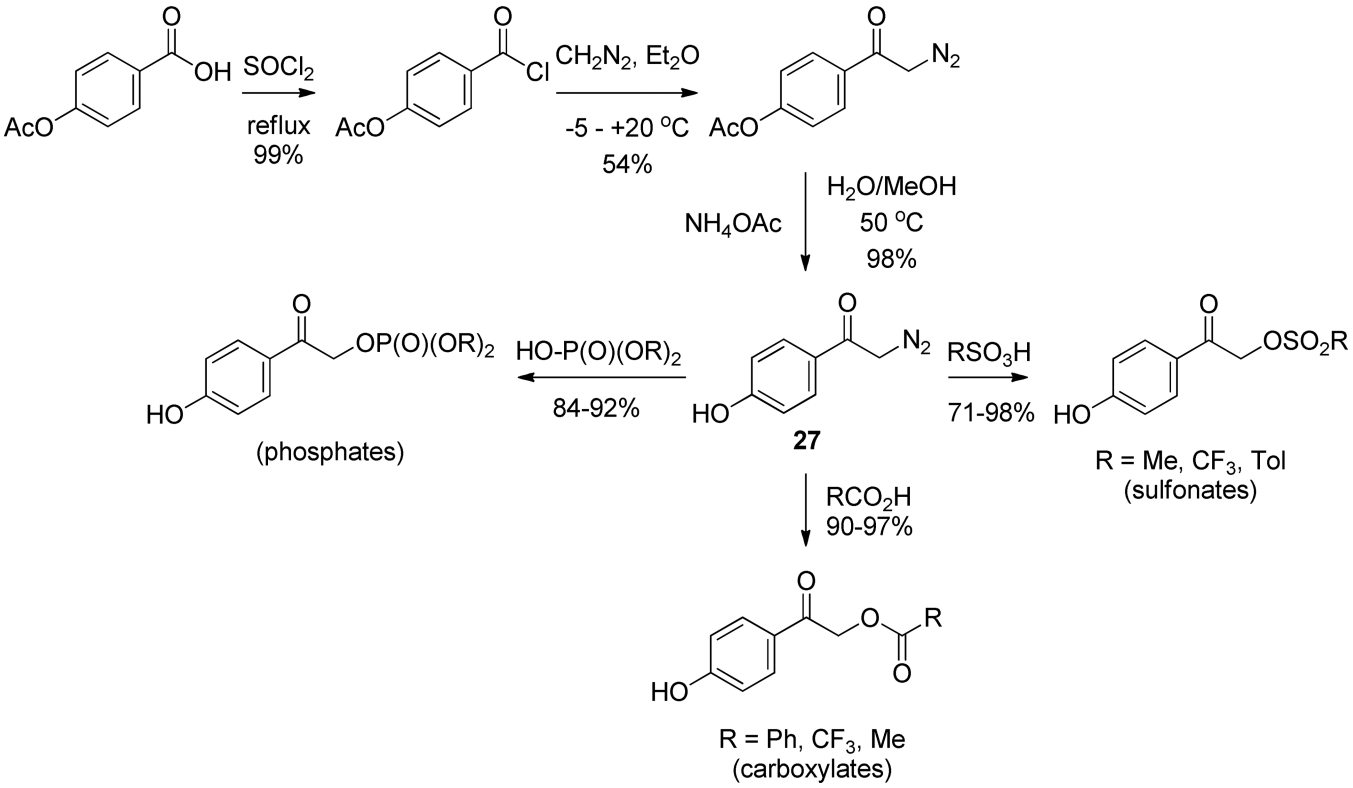
Scheme 14.
Photochemistry of 4-Oxo-4-*o*-tolylbutanoate[81]



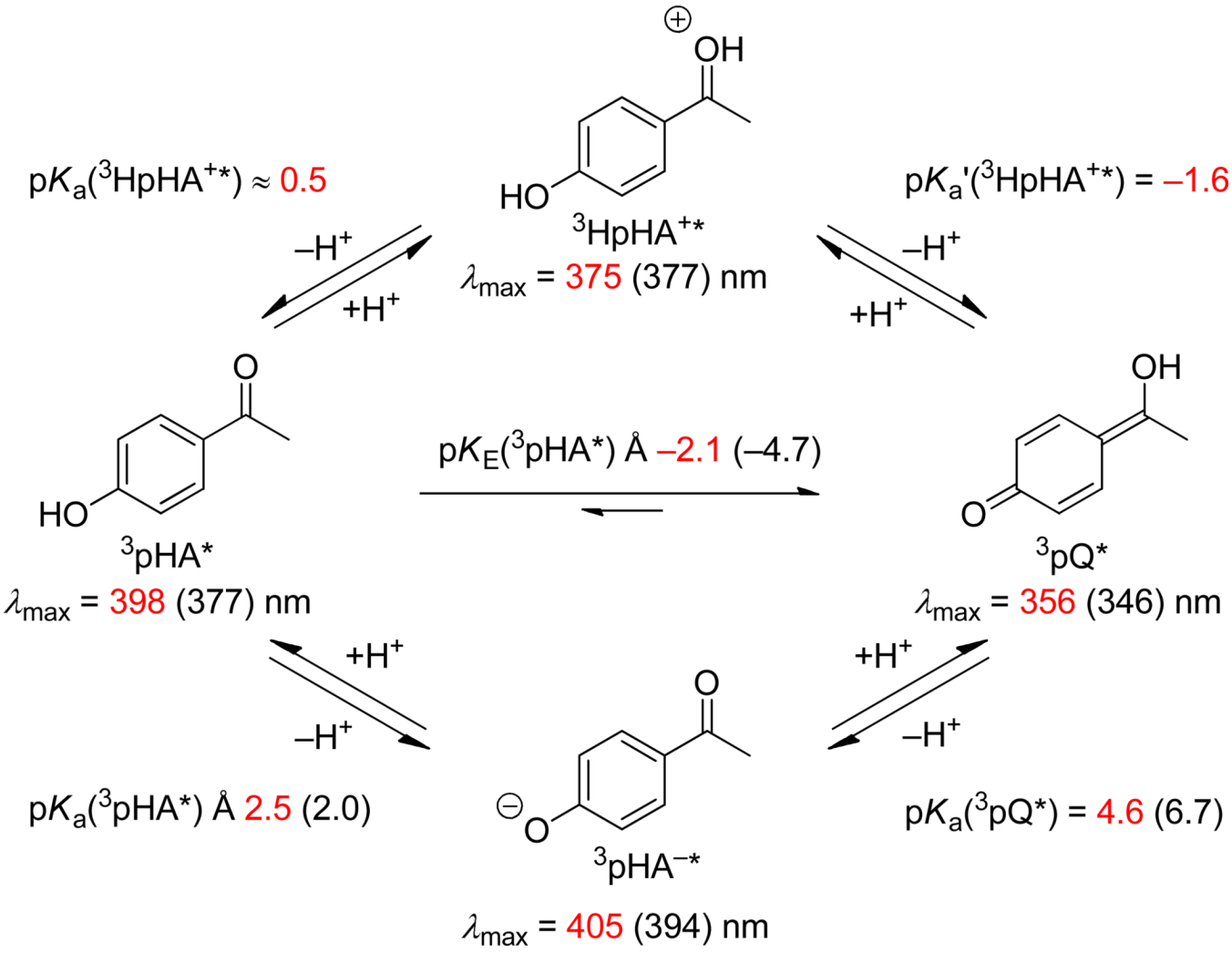
Scheme 15.
Photochemistry of pHP as a Protecting Group[82]



Scheme 16.
Nucleophilic Substitution Routes for pHP (**24**) Functional Group Protection

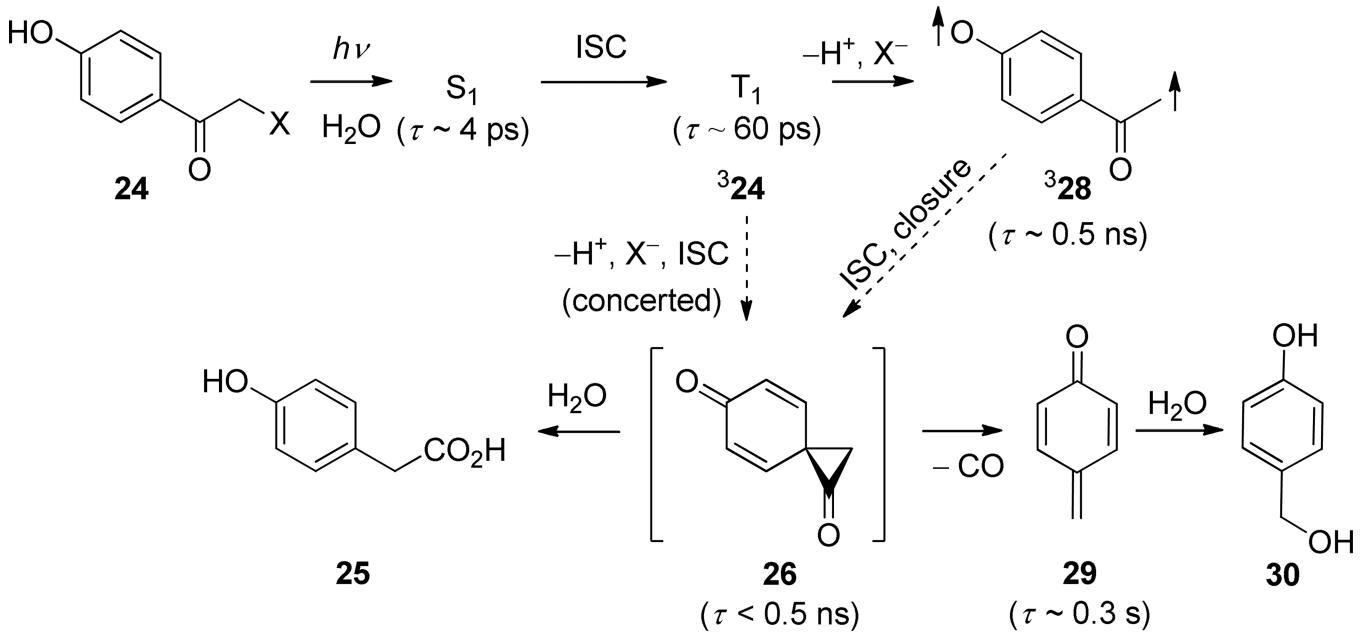


Scheme 17.
Strategies for α-Diazo-*p*-Hydroxyacetophenone Coupling to Protect Acidic Leaving Groups[93]

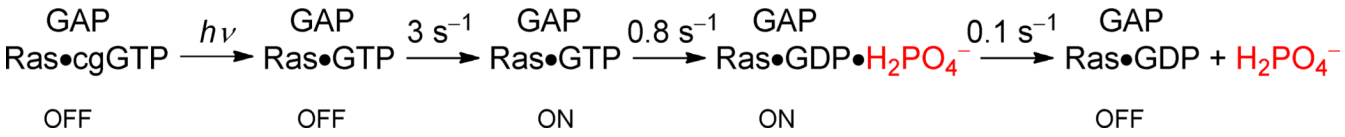


Scheme 18.

Triplet State Proton Transfer Equilibria of pHA (**24**, X = H) in Aqueous Solution (the experimental values for the pK_as and absorption maxima are in black and calculated values in red). Adapted with permission from ref.[89] Copyright 2012 American Chemical Society.

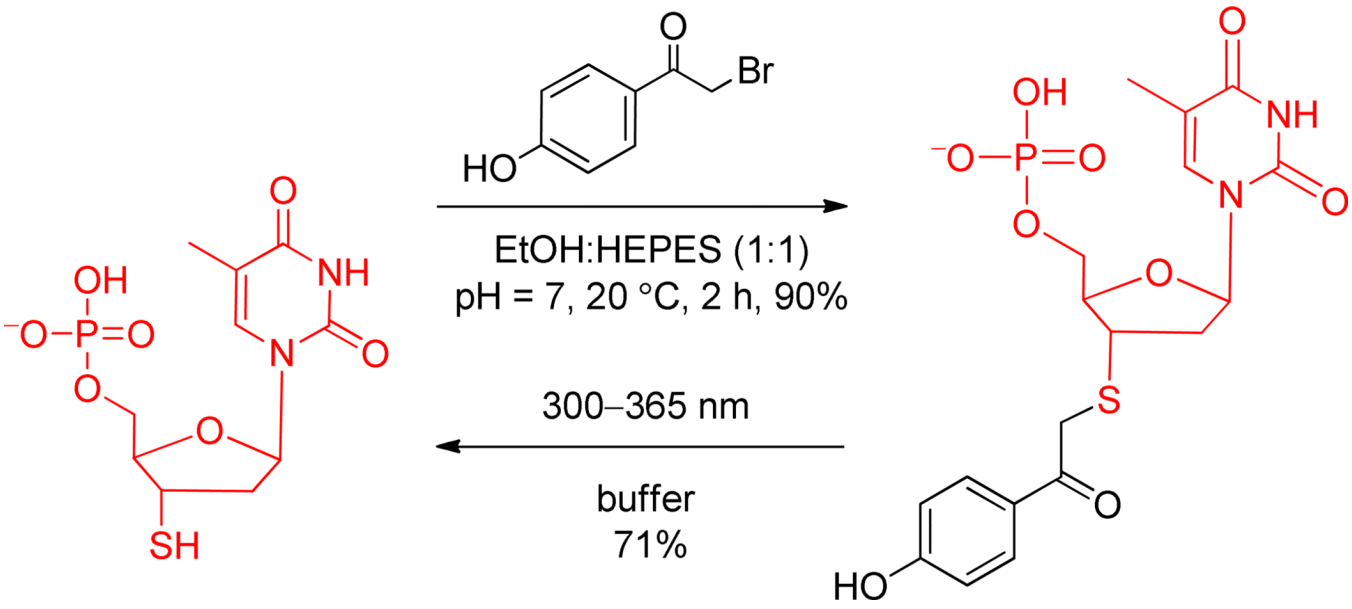


Scheme 19.
Refined Mechanism Based on Time-Resolved Transient Absorption (TR-TA) Analysis.[85d]

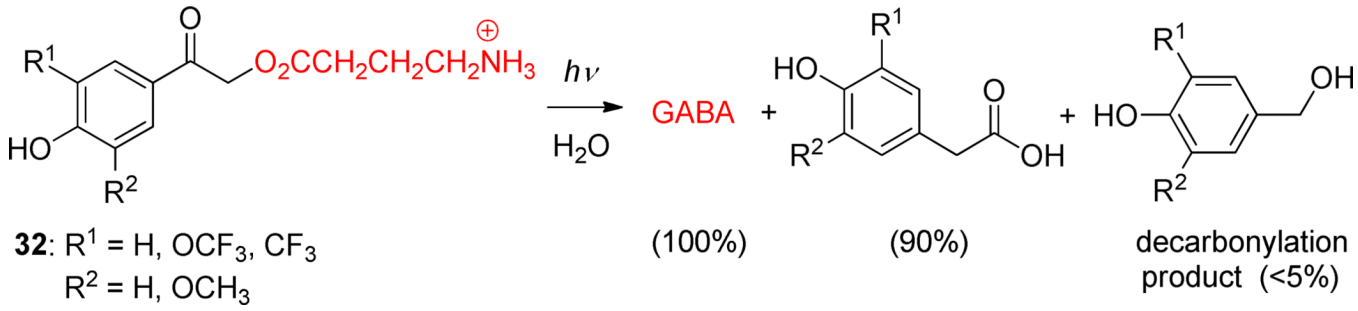


Scheme 20.

The Rate Constants and Mechanism for Ras GTPase (GAP) Hydrolysis of GTP derived from the initial photorelease of GTP from pHP caged GTP (the nonsignaling "OFF" to the signaling "ON" states are shown).[92b]

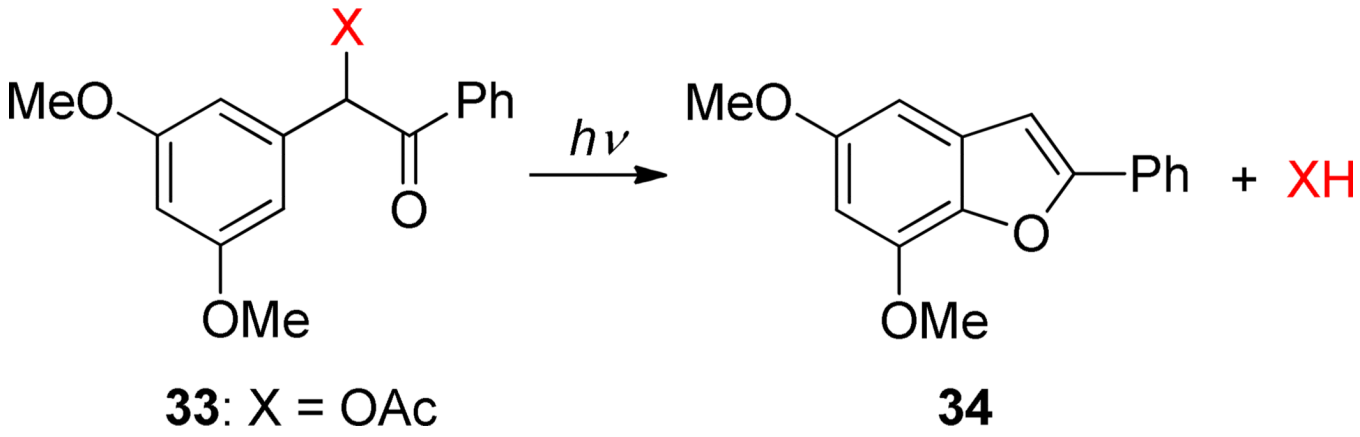


Scheme 21.
The Reversible Protection-deprotection of a Thiol on 3'-Thiodeoxythymidine with pHP Br.[115]



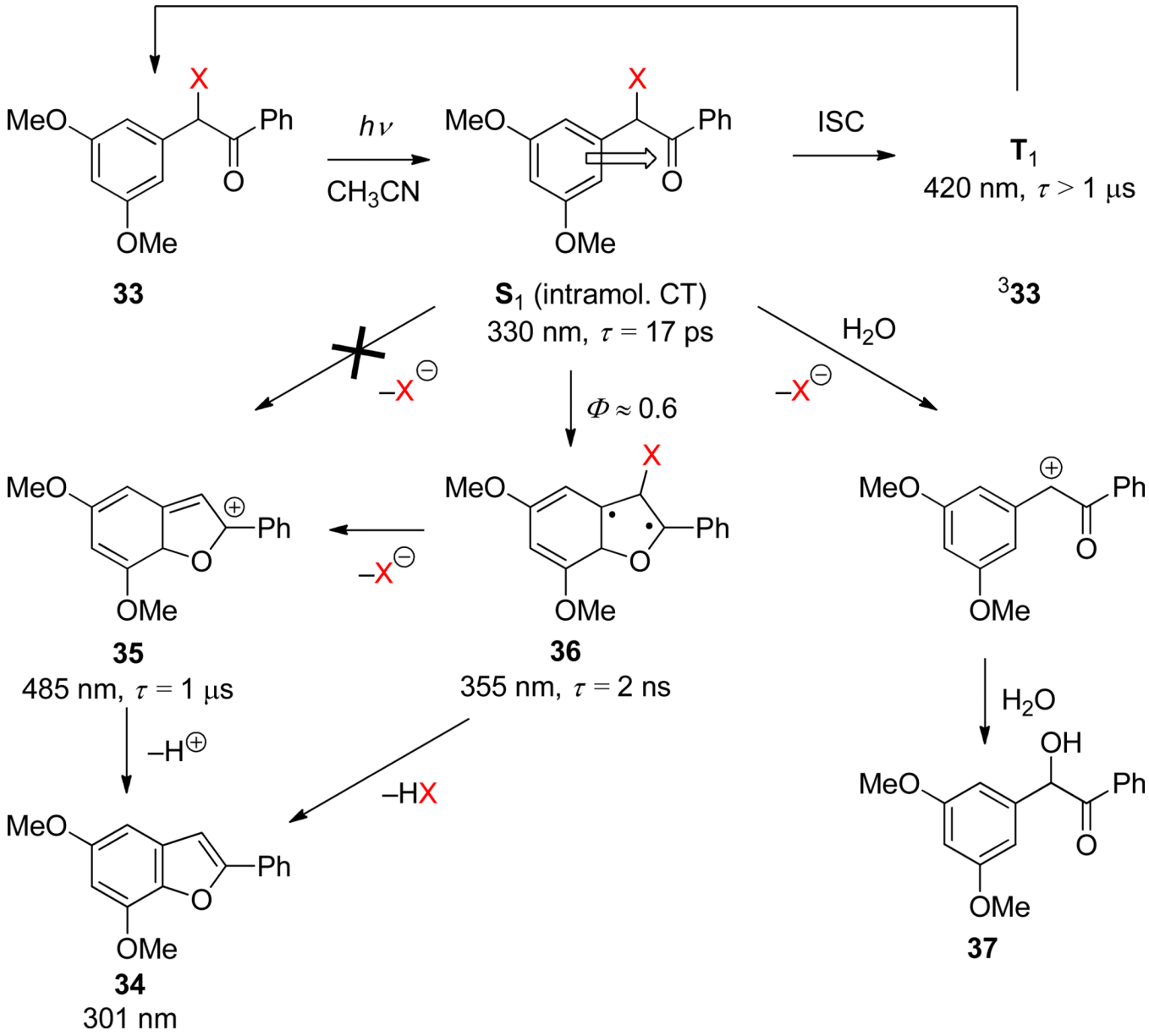
Scheme 22.

m-Electron Donor and Acceptor Group Compatibility for Photorelease of GABA from *m*-Substituted pHP GABA.[97b]

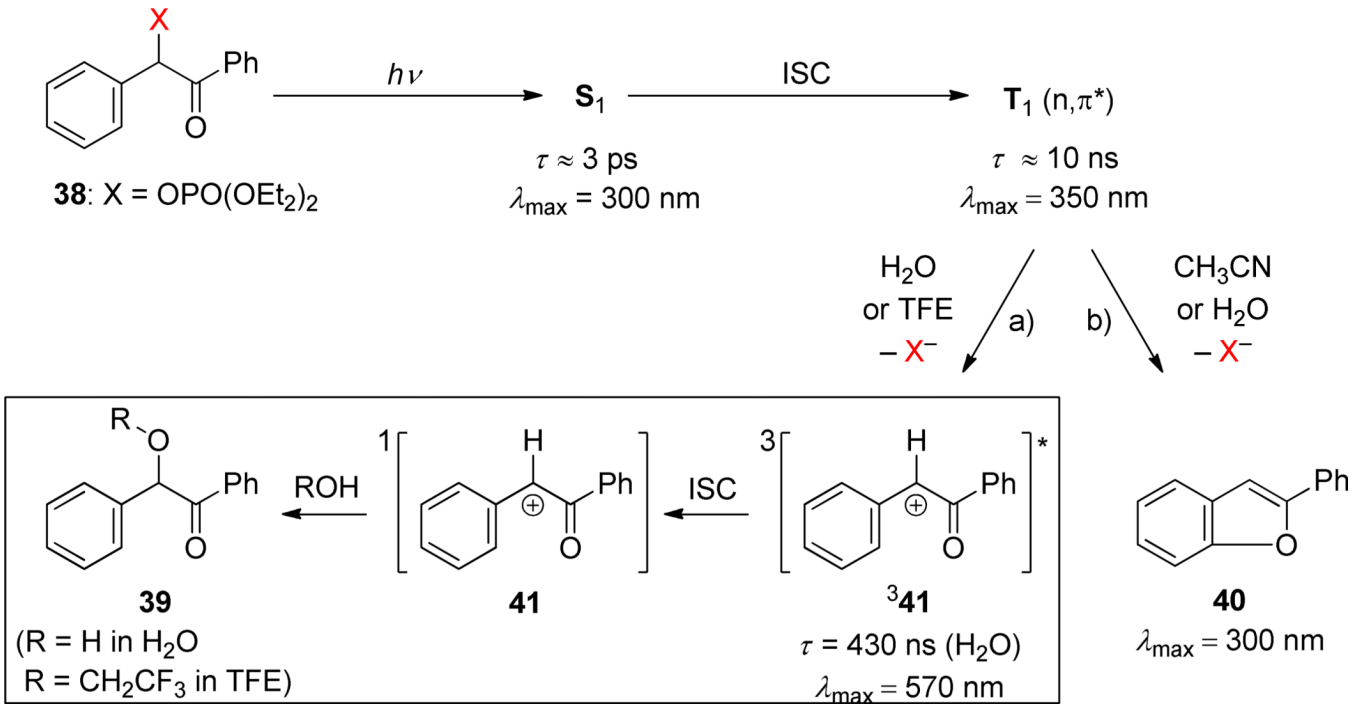


33: X = OAc **34**

Scheme 23.
Photocyclization of DMB Acetate[4,118]

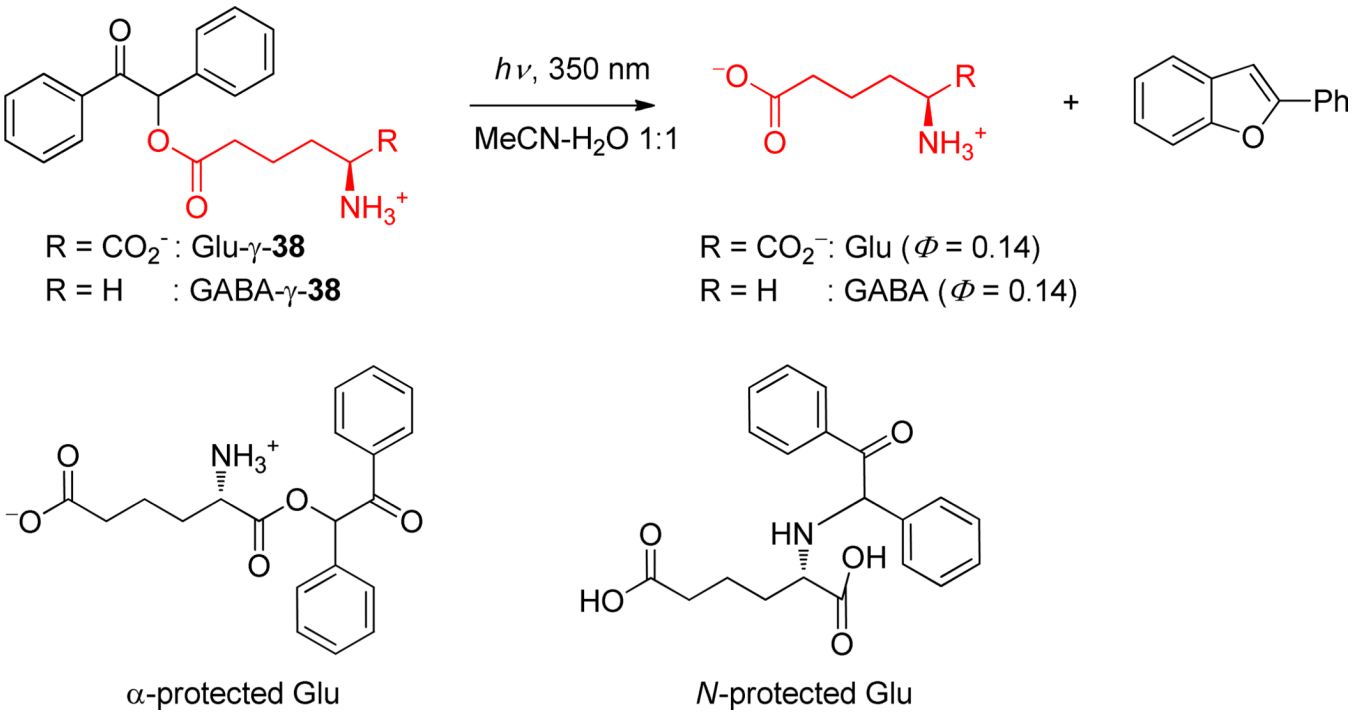


Scheme 24.
Mechanism of the Photocyclization of 3',5'-Dimethoxybenzoin (DMB) Derivatives (X = OCOR, $OPO(OEt)_2$, F).[122,123b]

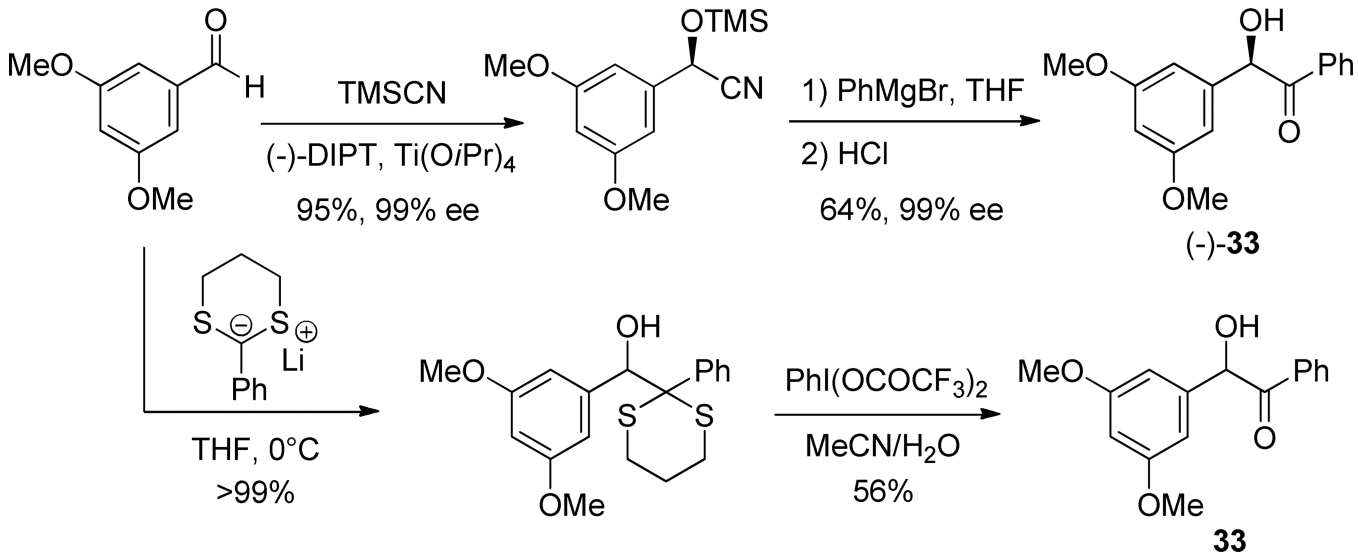


Scheme 25.

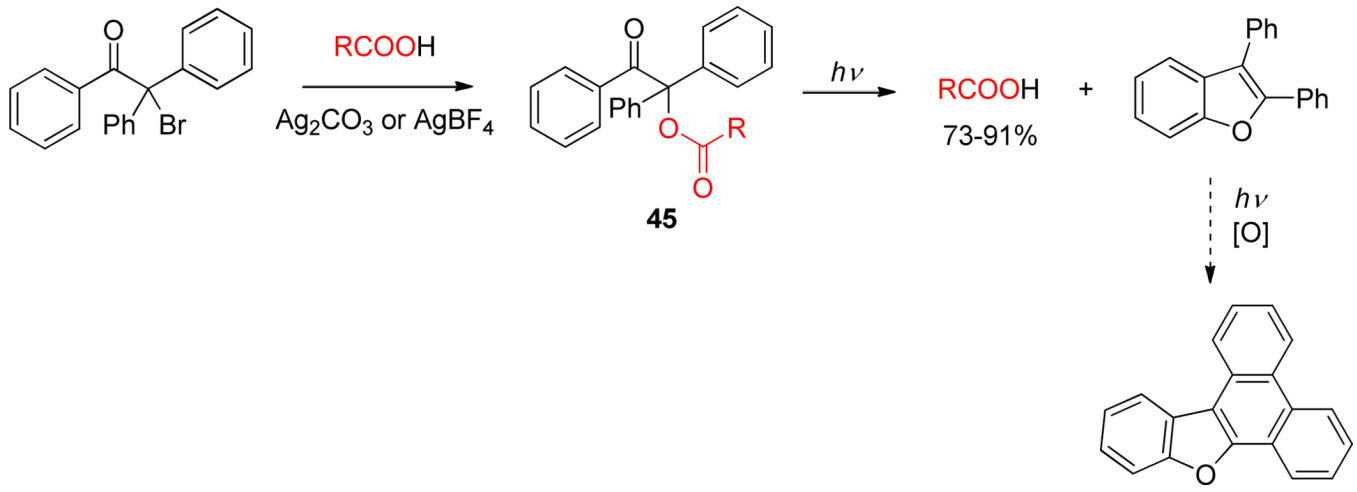
Mechanism of the Photorelease of Diethylphosphate from **38** (X = $OPO(OEt)_2$) in Various Solvents.[129–130]



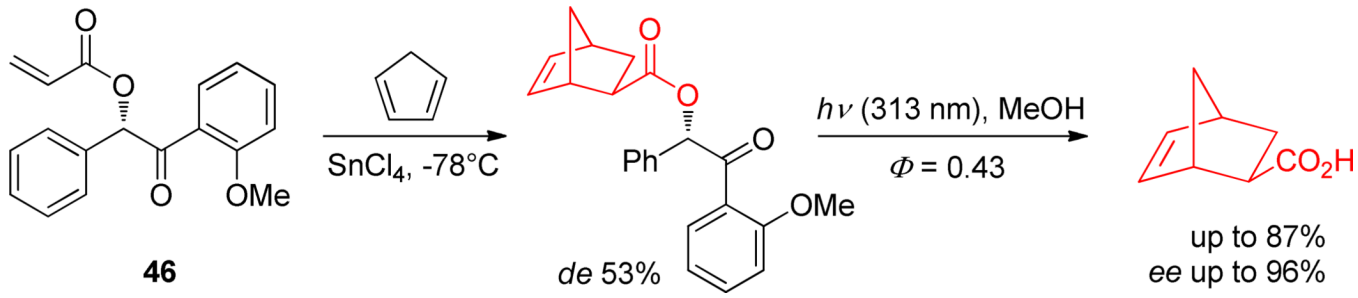
Scheme 26.
Release of Glutamate and GABA from Benzoin Derivatives[107b,107c,138]



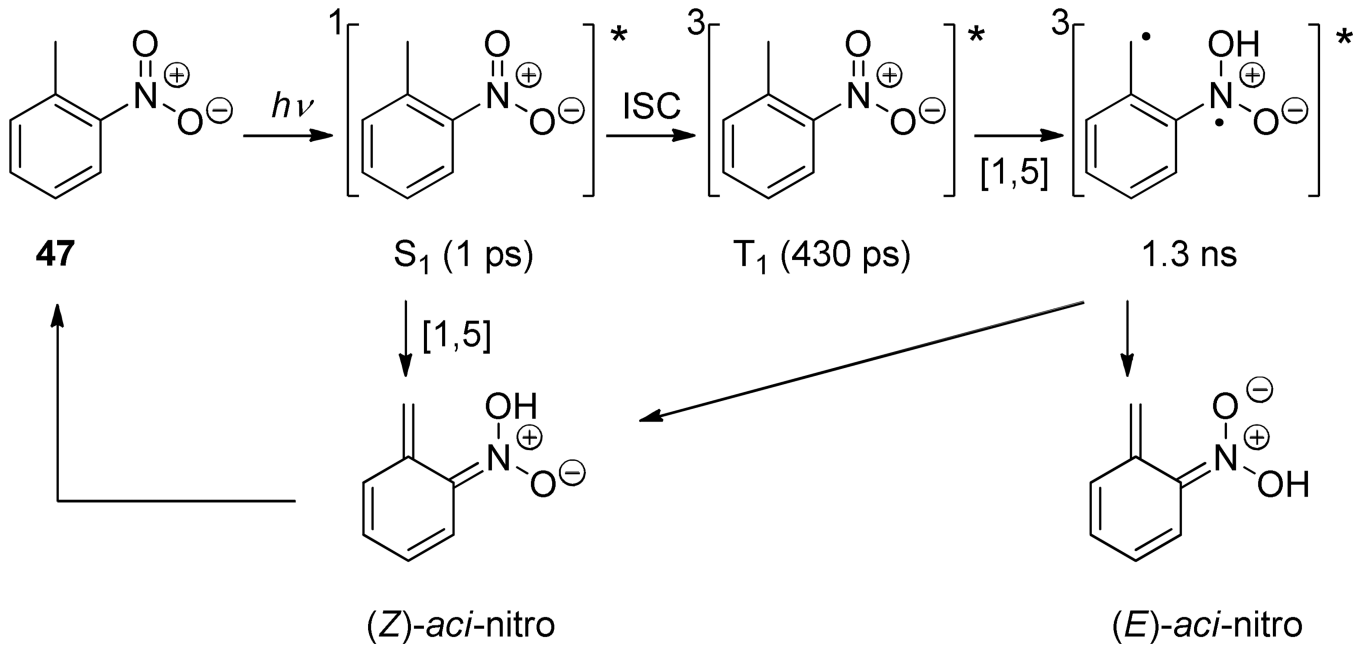
Scheme 27.
Preparation of Racemic and Enantiopure 3',5'-Dimethoxybenzoin (DMB; **33**, X = OH)[143]



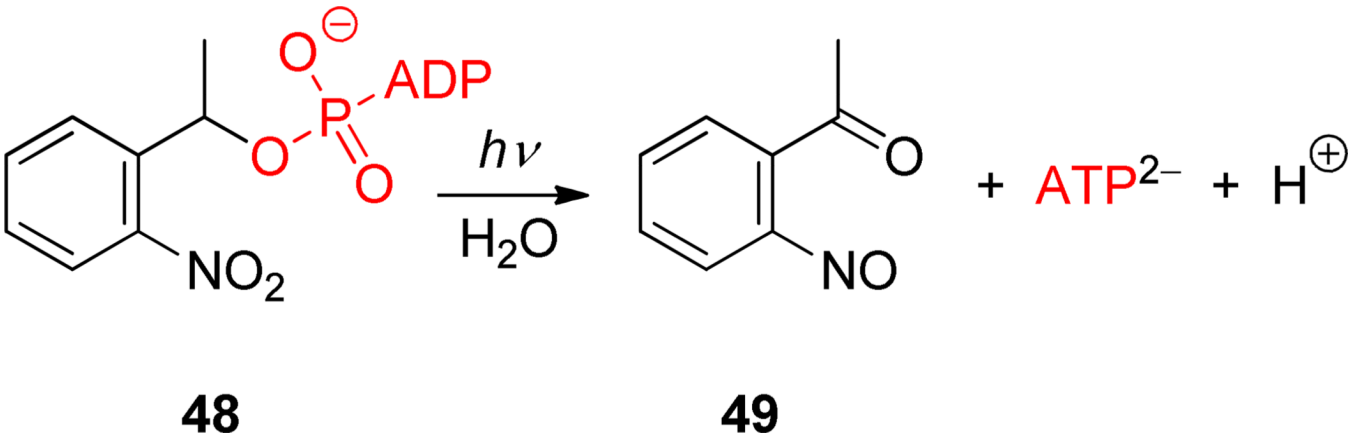
Scheme 28.
Photolysis of 1,2,2-Triphenylethanone Esters[149]



Scheme 29.
Use of a Chiral Benzoin as a Photoremovable Chiral Auxiliary[150]

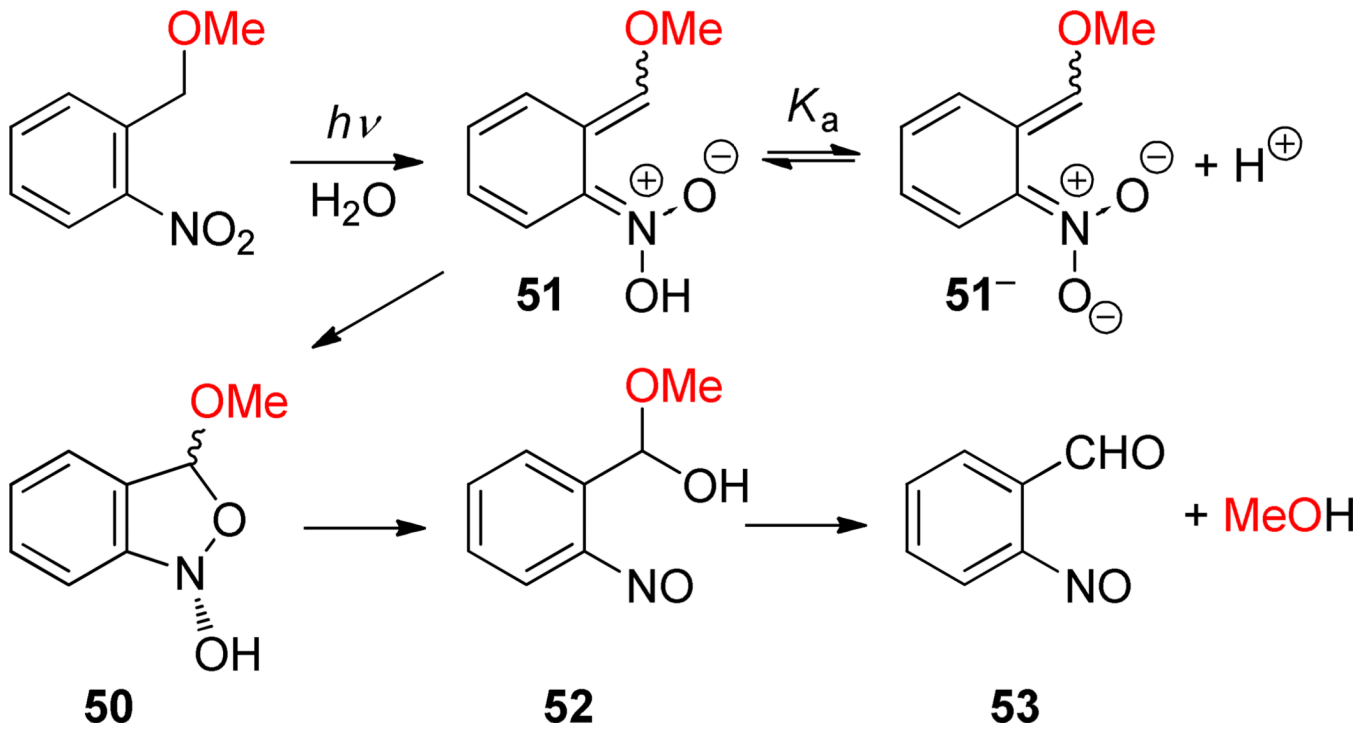


Scheme 30.
Reaction Mechanism for the Phototautomerization of *o*NT in THF.[154a]

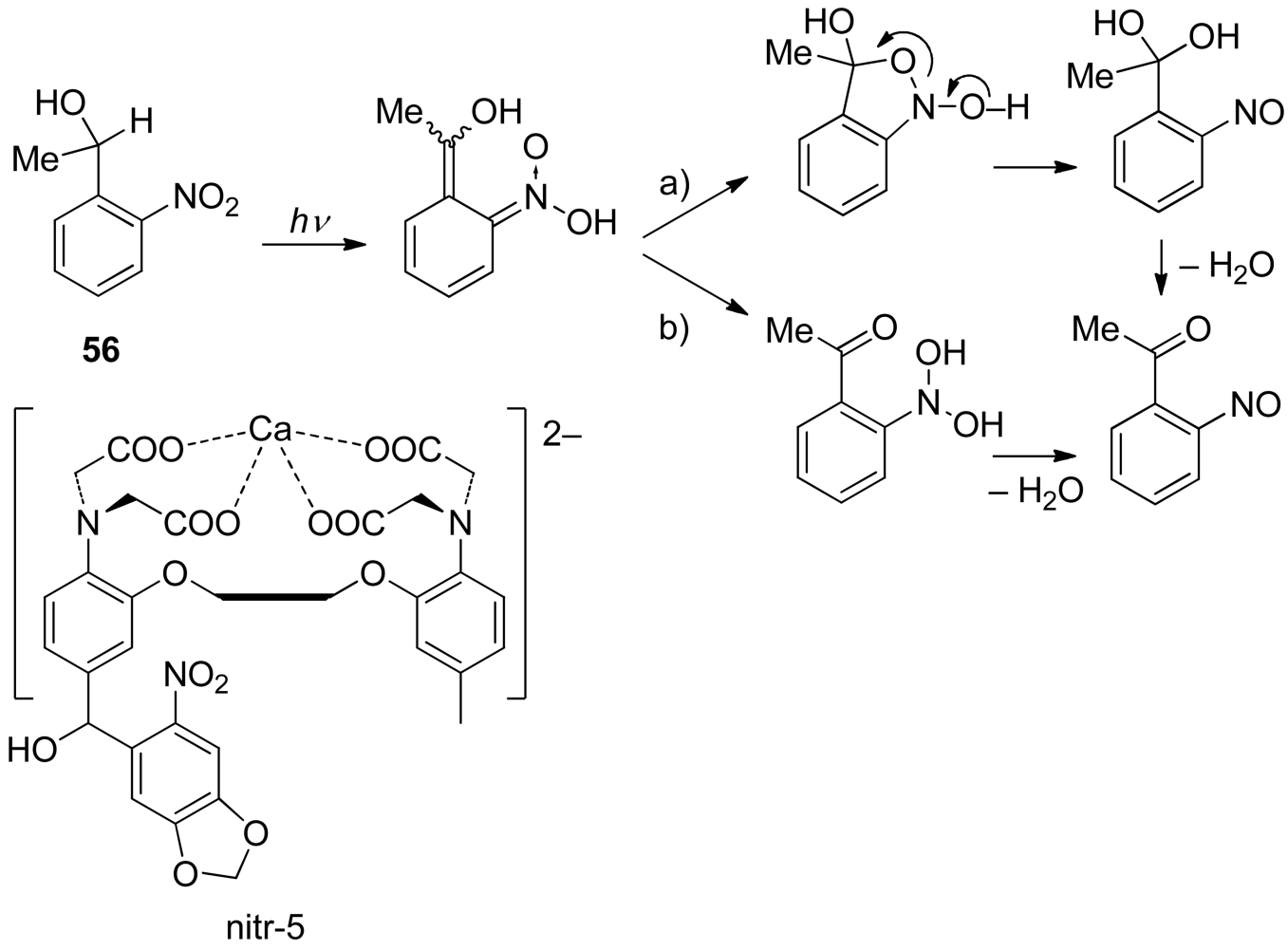


48 **49**

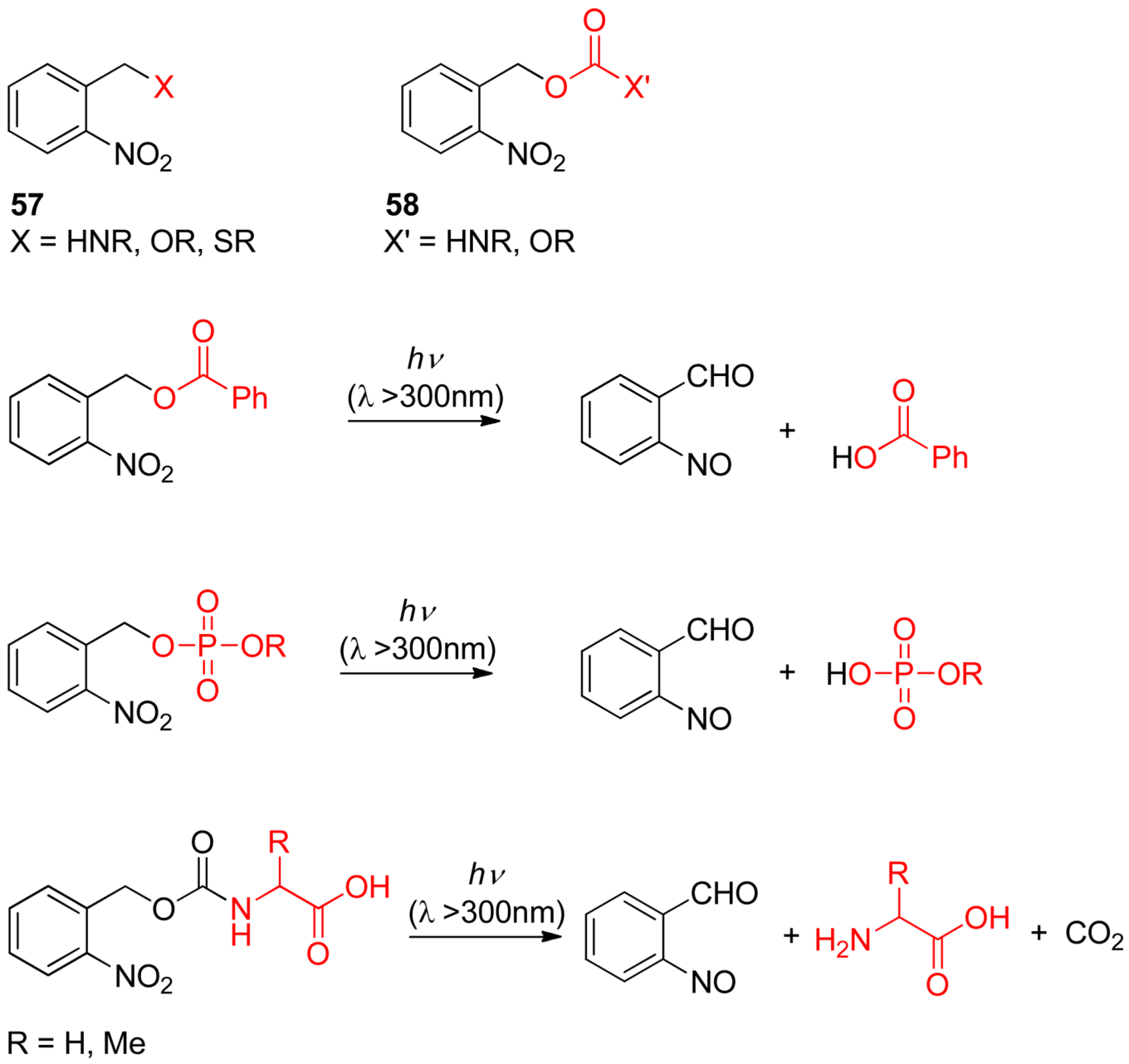
Scheme 31.
Photochemistry of P^3-1-(2-Nitrophenyl)ethyl Ester of Adenosine Triphosphate[156]



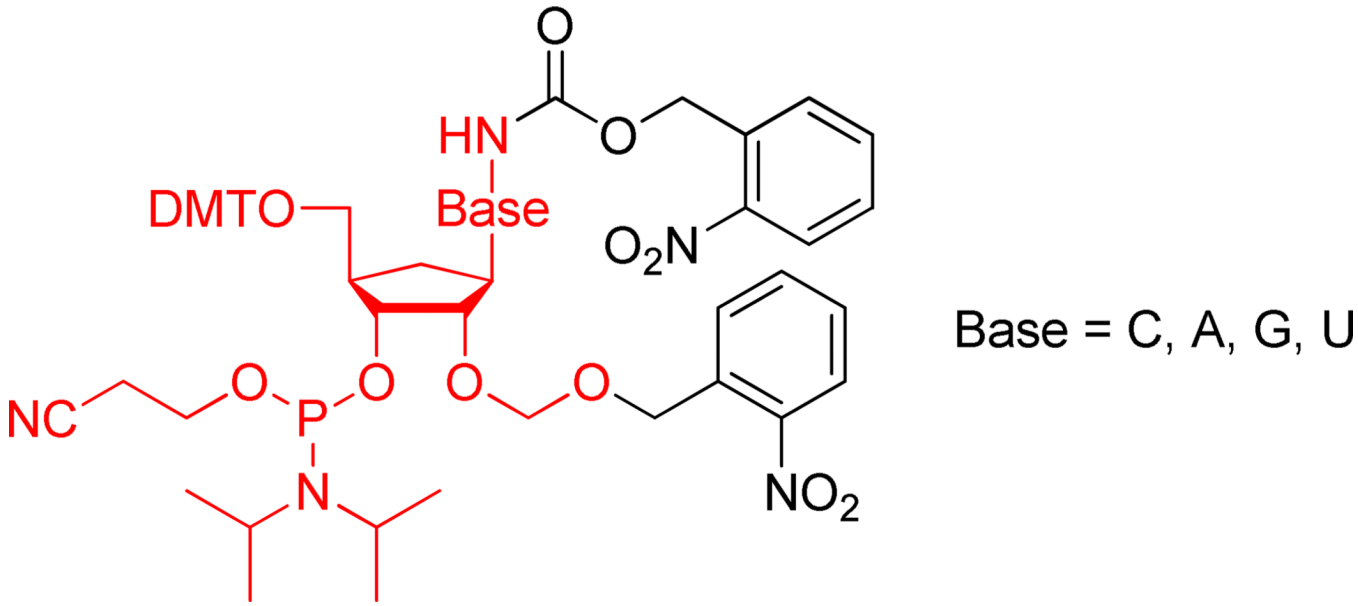
Scheme 32.
The Mechanism of 1-(Methoxymethyl)-2-nitrobenzene Photoreaction[160]



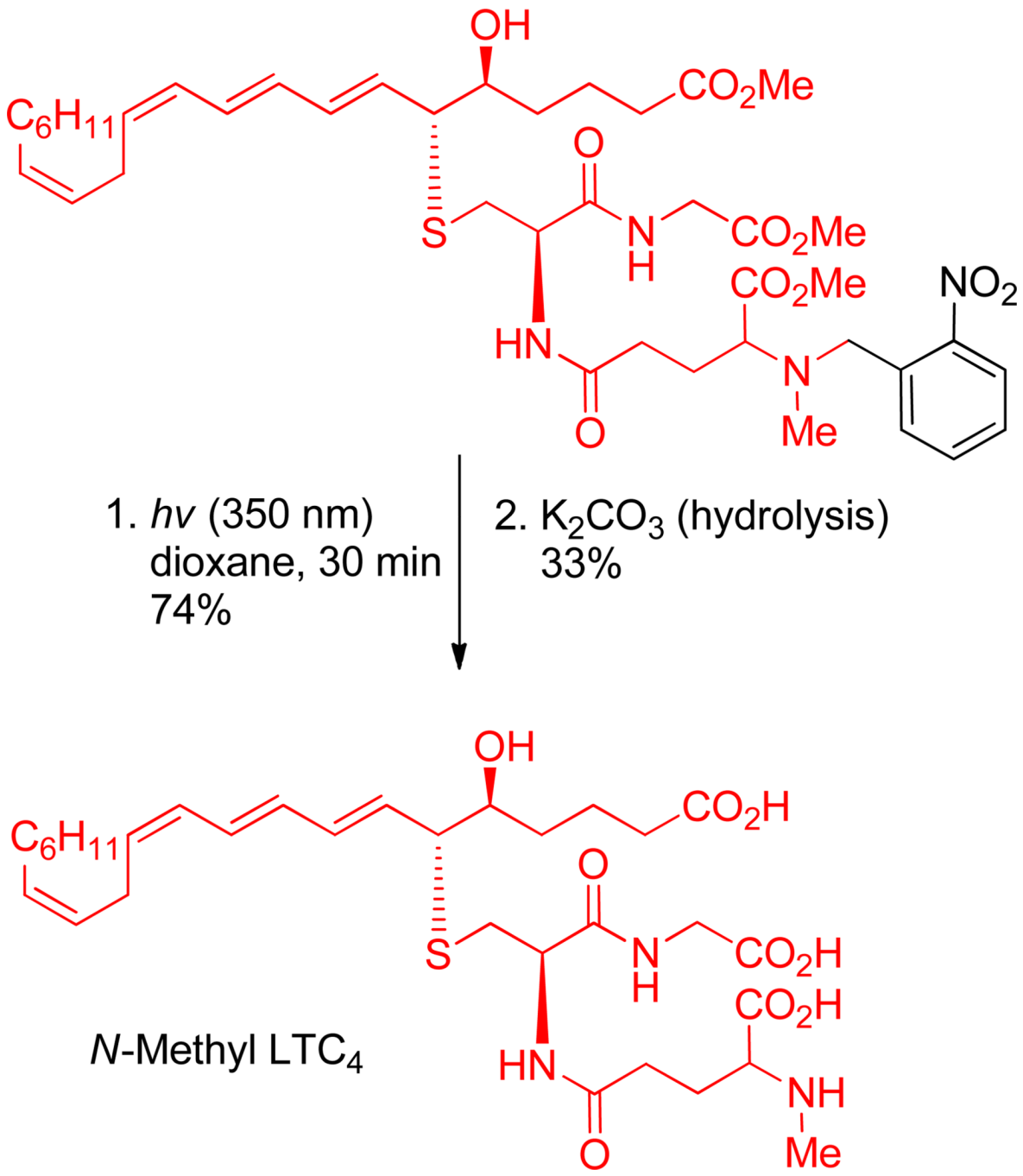
Scheme 33.
Photochemistry of the Hydroxy Derivative **56**[168a,172]



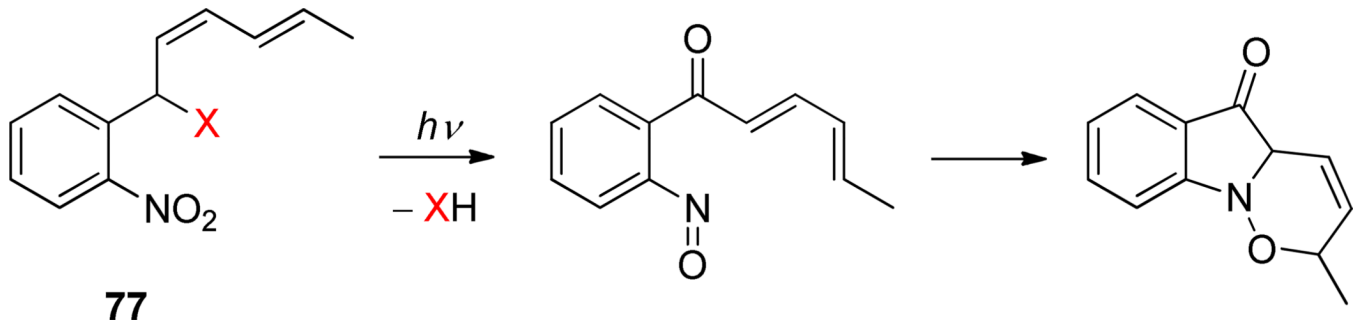
Scheme 34.
Photolysis of Some *o*-Nitrobenzyl Derivatives



Scheme 35.
Protected Phosphoramidite Building Blocks for Automated RNA Synthesis[177]

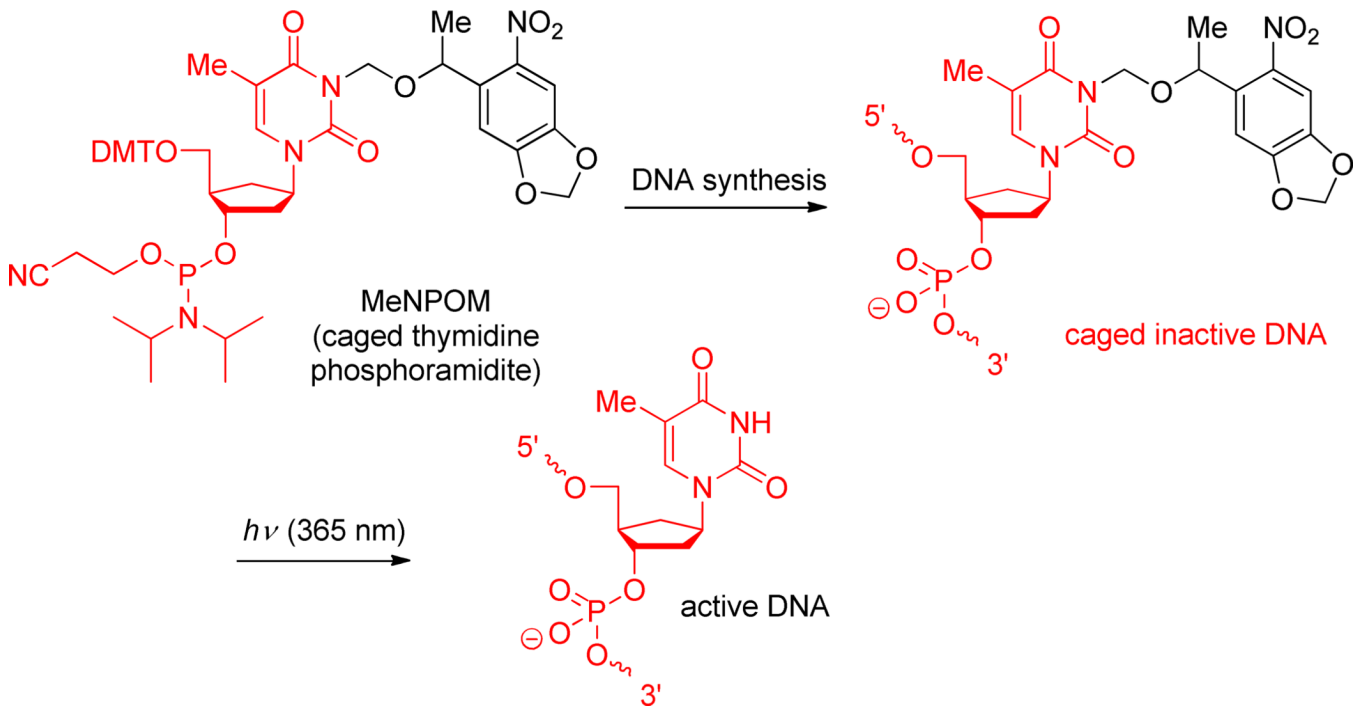


Scheme 36.
Final Steps in the Total Synthesis of *N*-Methyl LTC4[182]

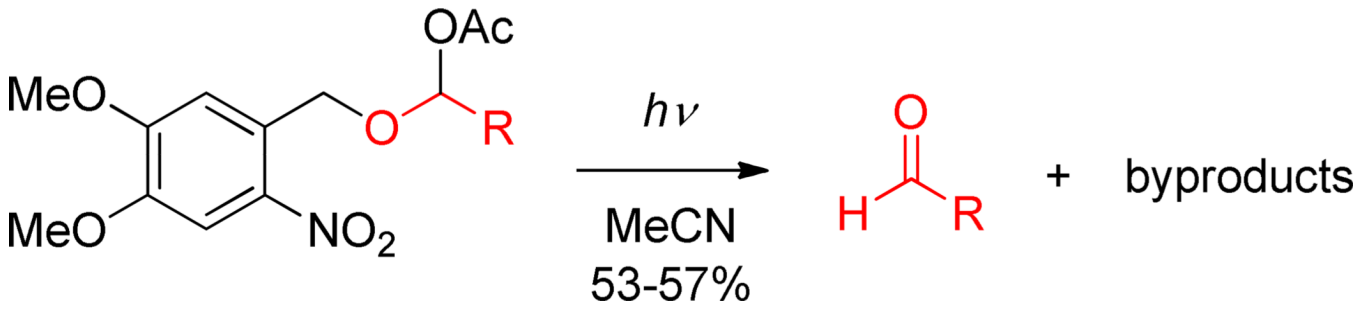


77

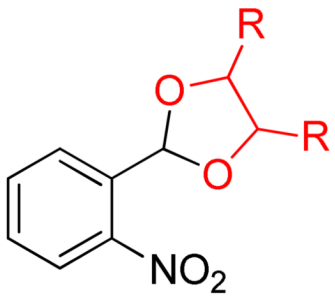
Scheme 37.
Trapping of the Nitroso Byproduct in a Diels-Alder Cycloaddition[199]



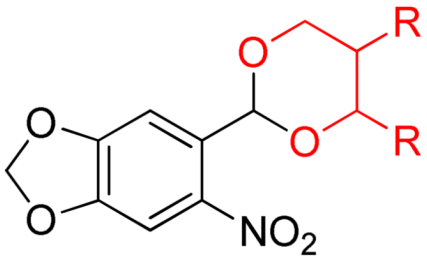
Scheme 38.
Preparation of Caged-DNAzyme and Activation by Nonphotodamaging UV Light[205]



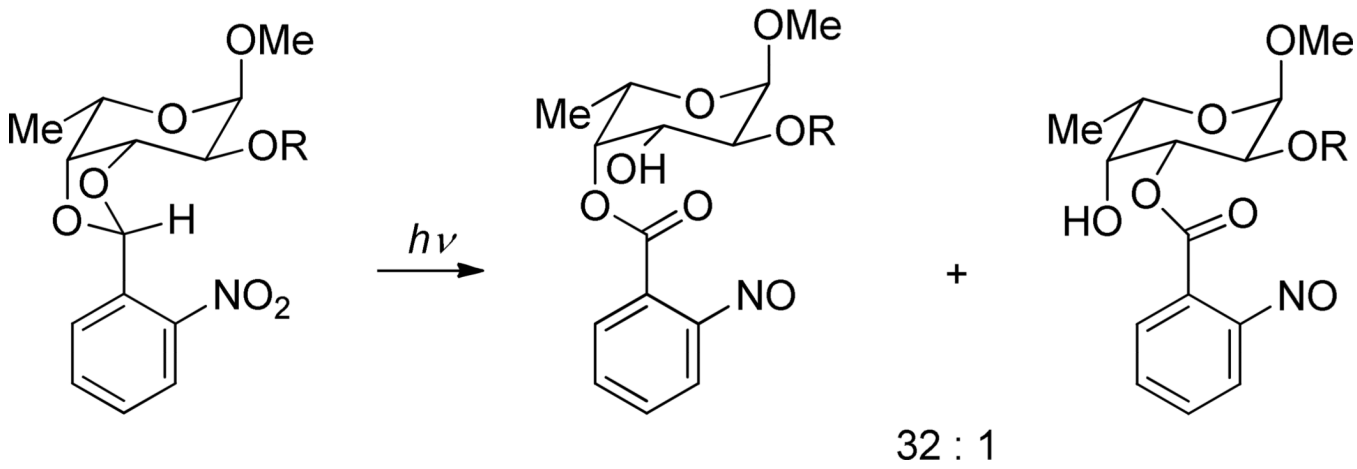
Scheme 39.
hotolysis of α-Acetyl Acetals[218]



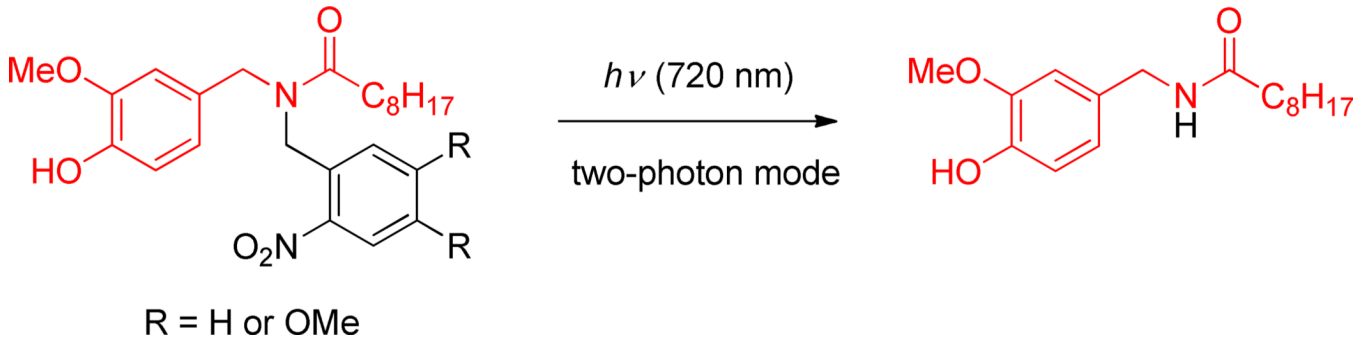
110



111

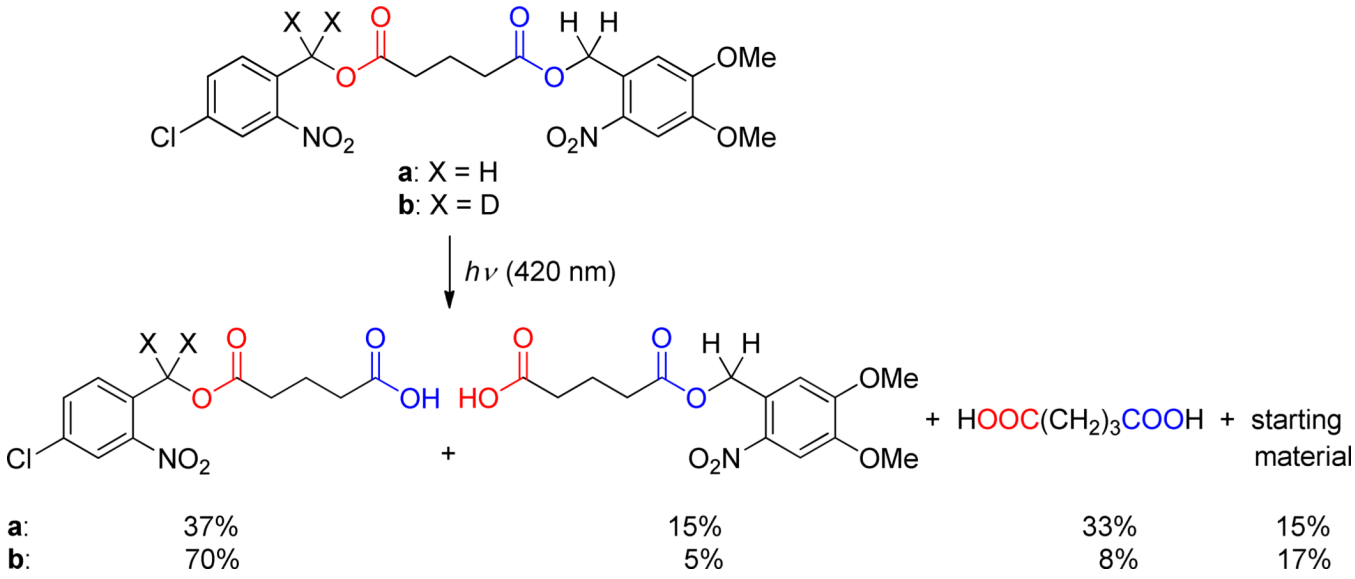


Scheme 40.
Selectivity in the Deprotection of **110**-Protected 1,2-Diol[219a]

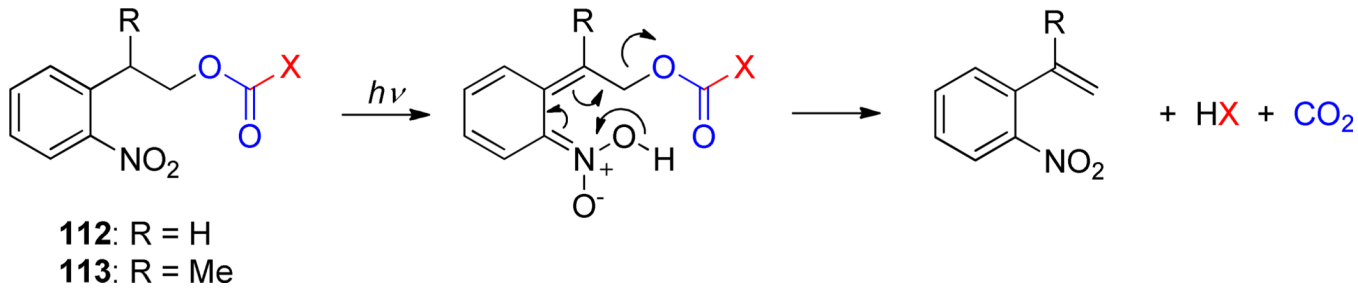


R = H or OMe

Scheme 41.
Two-Photon Activation of Vanilloid Derivatives[220]

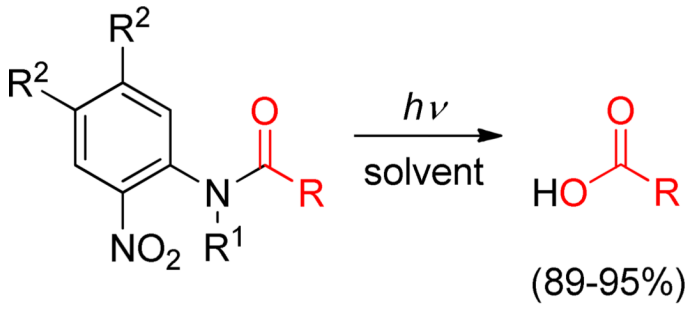


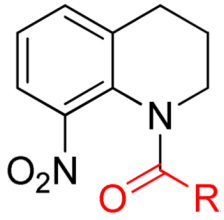
Scheme 42.
Impact of Isotopic Substitution on the Photoreactivity[225]



112: R = H
113: R = Me

Scheme 43.
Photolysis of 2-Nitro-2-Phenethyl Derivatives[226]





118:

R = Me, Ph, 2-naphthyl

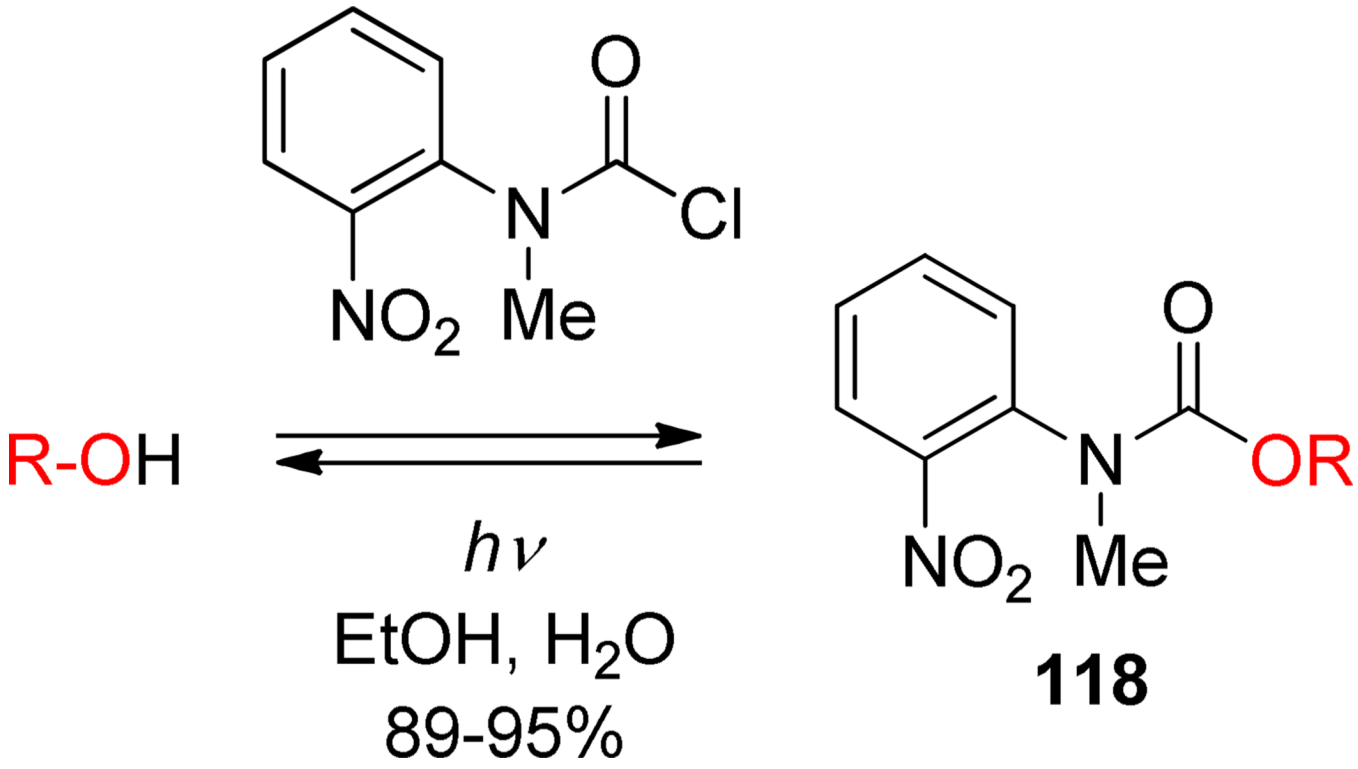
R^1 = alkyl, aryl

R^2 = H, OMe

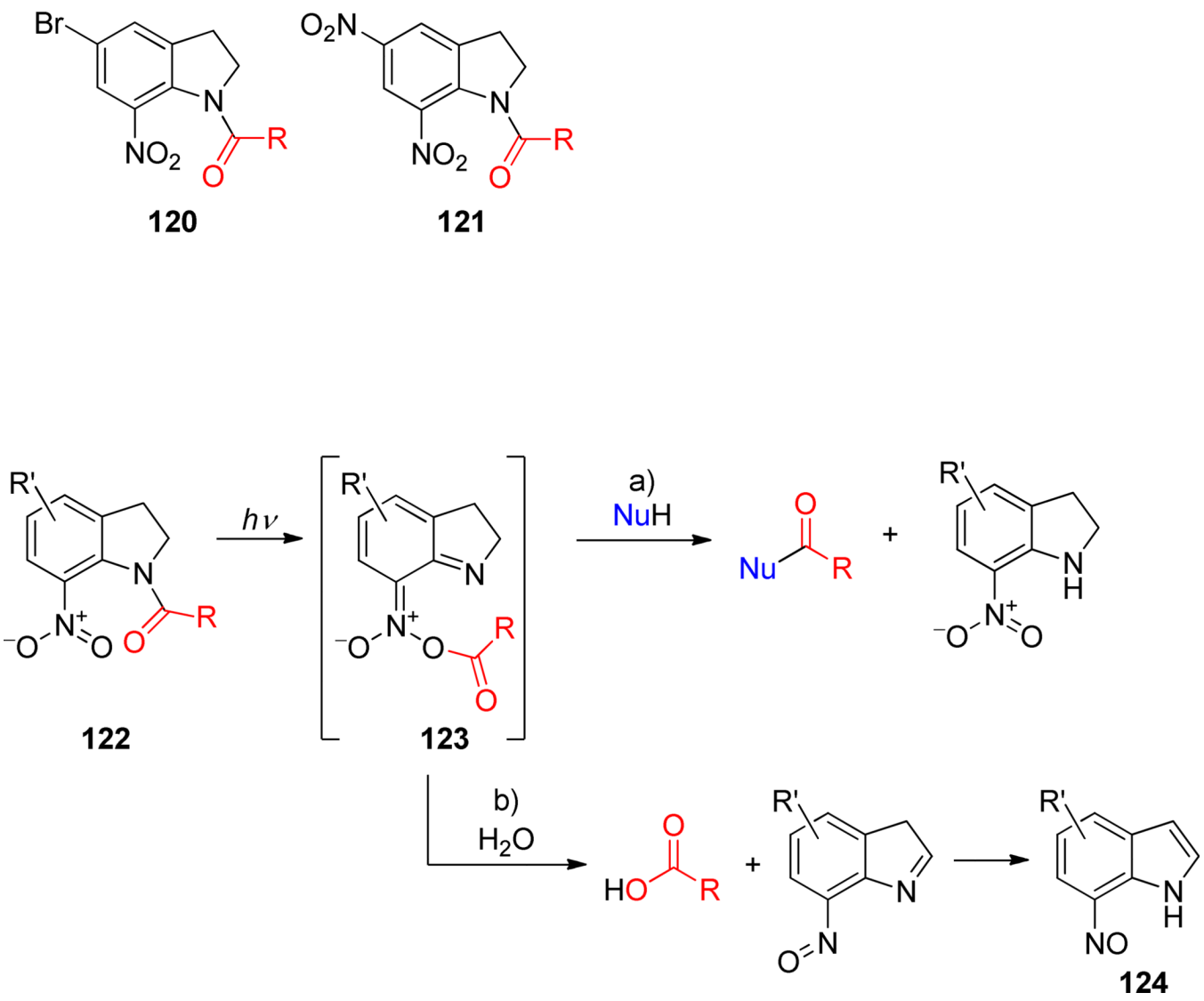
solvent = $MeOH/H_2O$, $EtOH/H_2O$, *i*PrOH, benzene

119

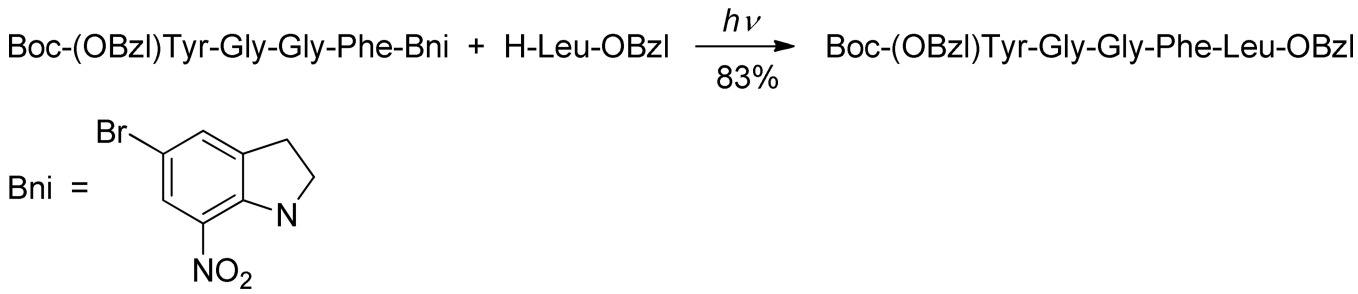
Scheme 44.
Photoactive *o*-Nitroanilide Derivatives[241]



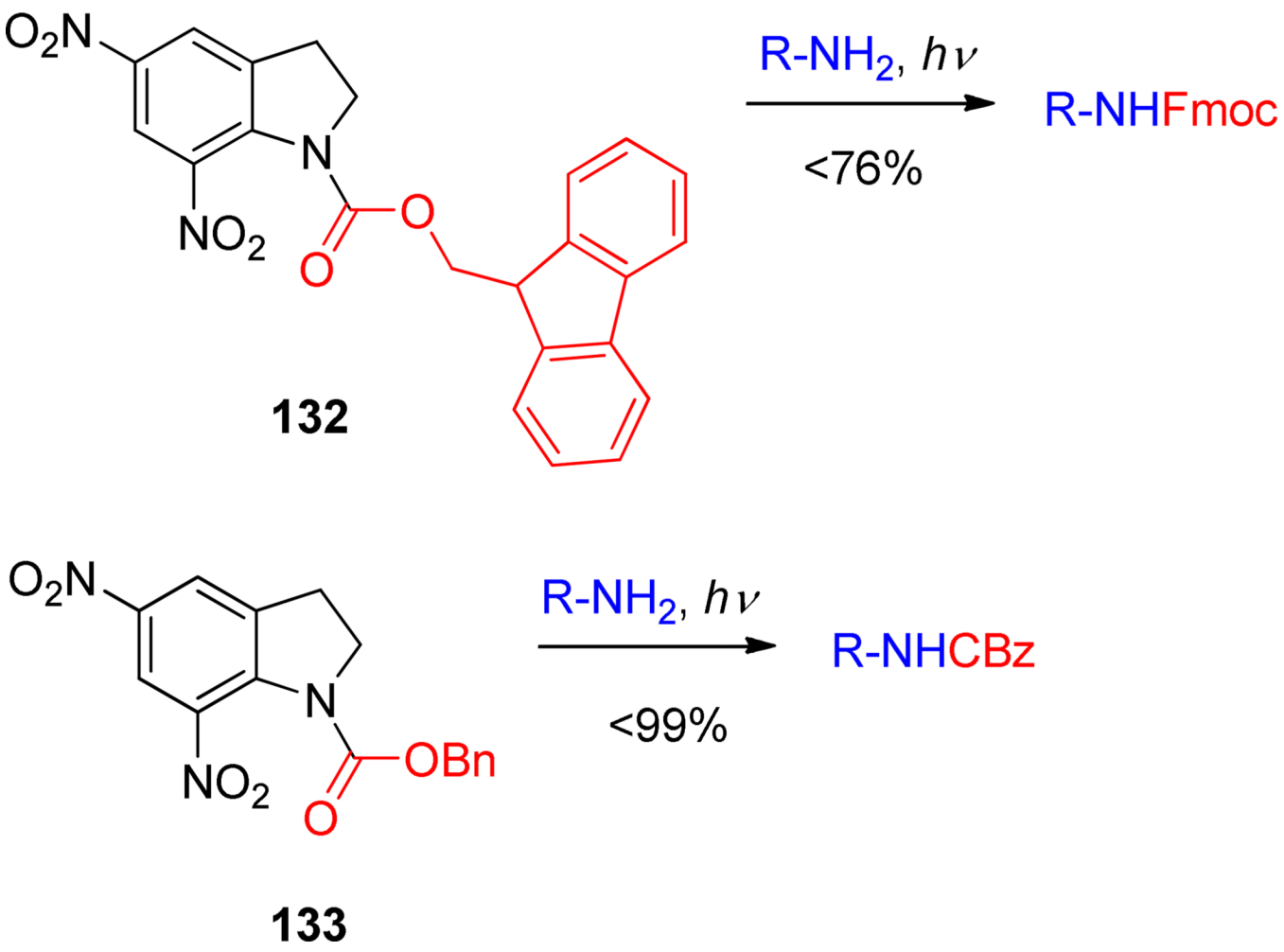
Scheme 45.
Use of *o*-Nitroanilide Carbamates as PPGs for Alcohols[243]



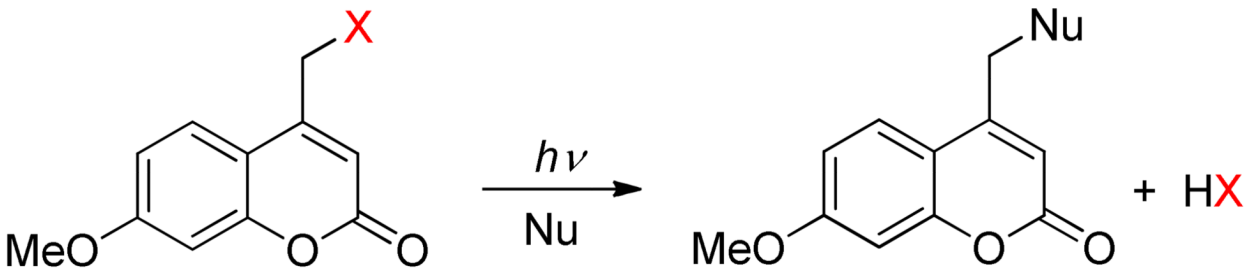
Scheme 46.
Diverging Reaction Pathways in Organic Solvents and in Water[245a,b]



Scheme 47.
Peptide Coupling Using Acylated 5-Bromo-7-Nitroindolines (Bni)[253]



Scheme 48.
Photochemical Introduction of the Fmoc and Cbz Groups[260]

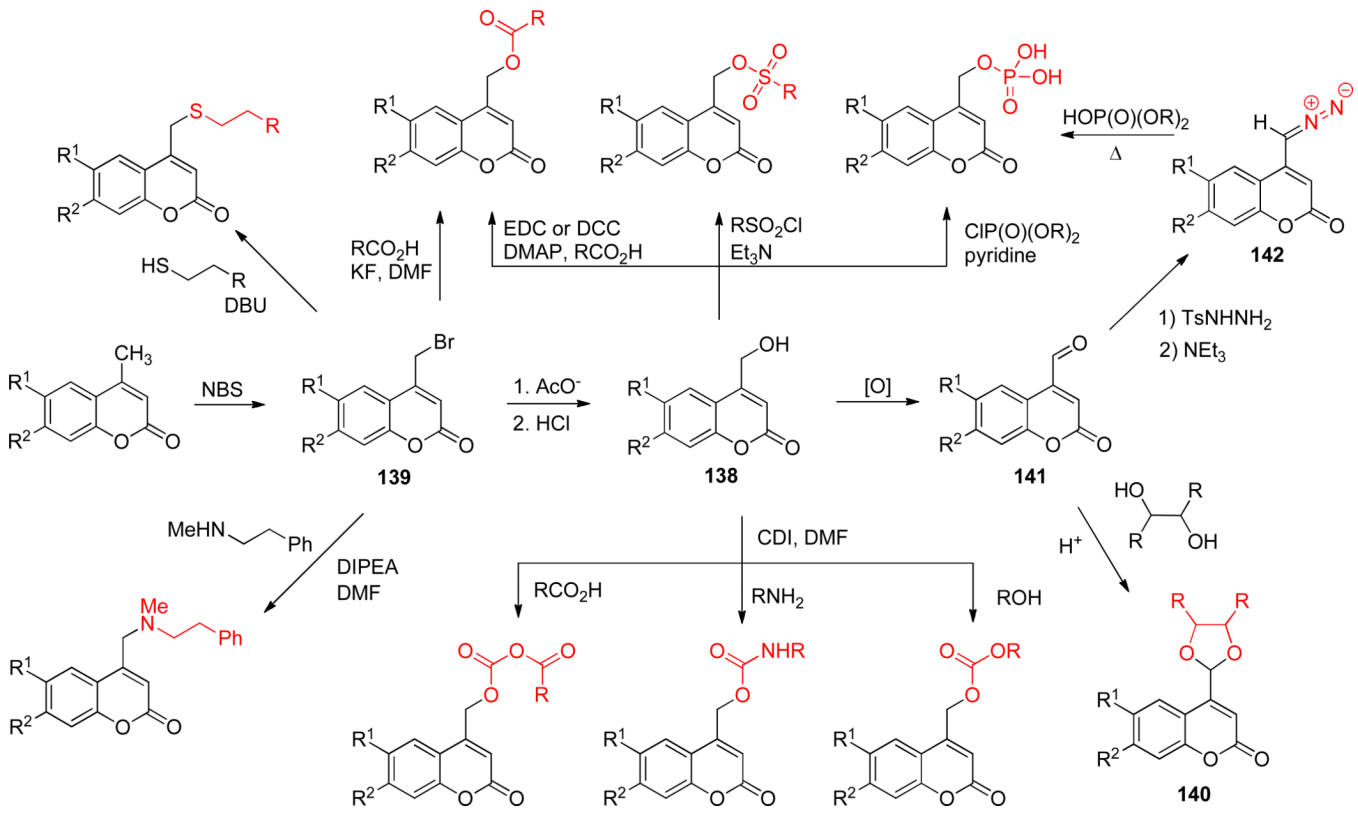


134: X = $OP(O)(OEt)_2$

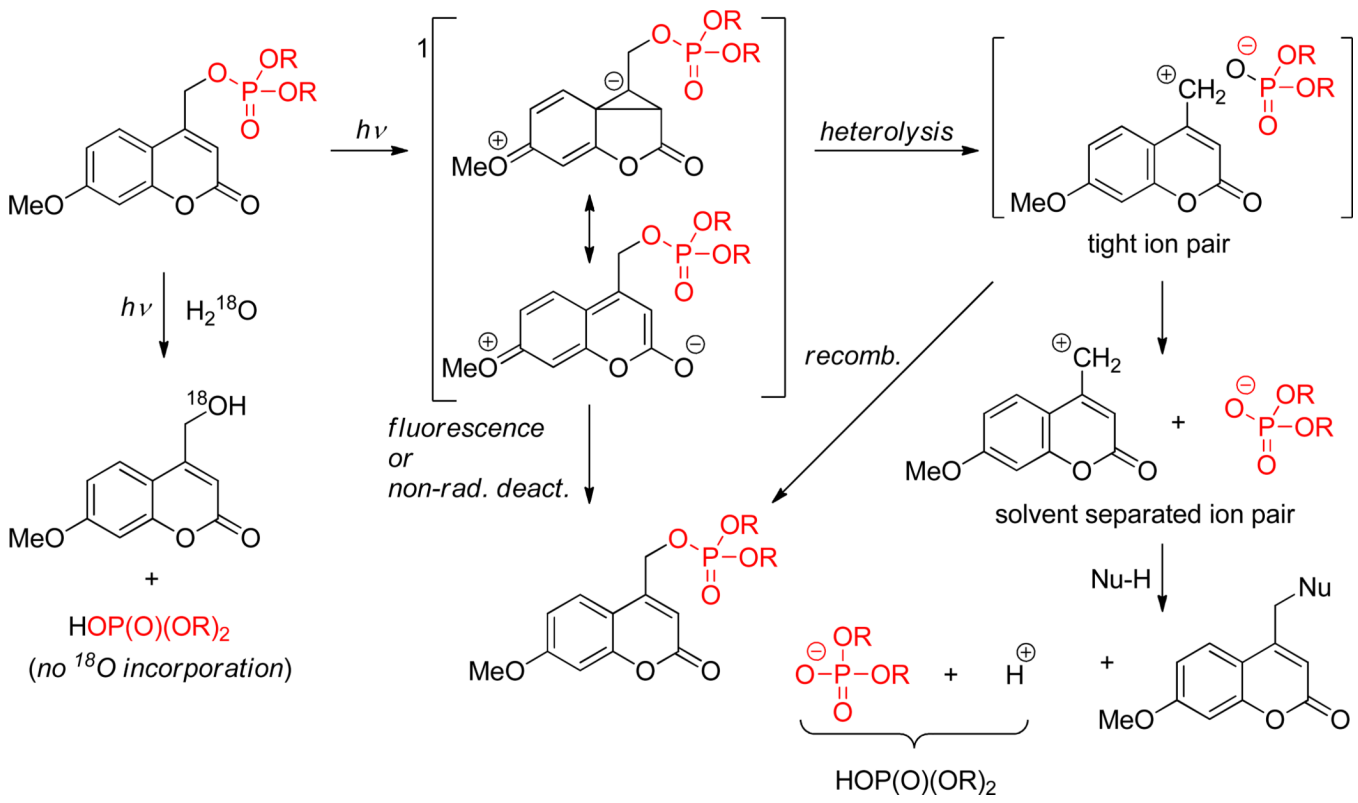
Nu = MeOH, piperidine, cysteine, tyrosine, α-chymotrypsin, HMT

Scheme 49.

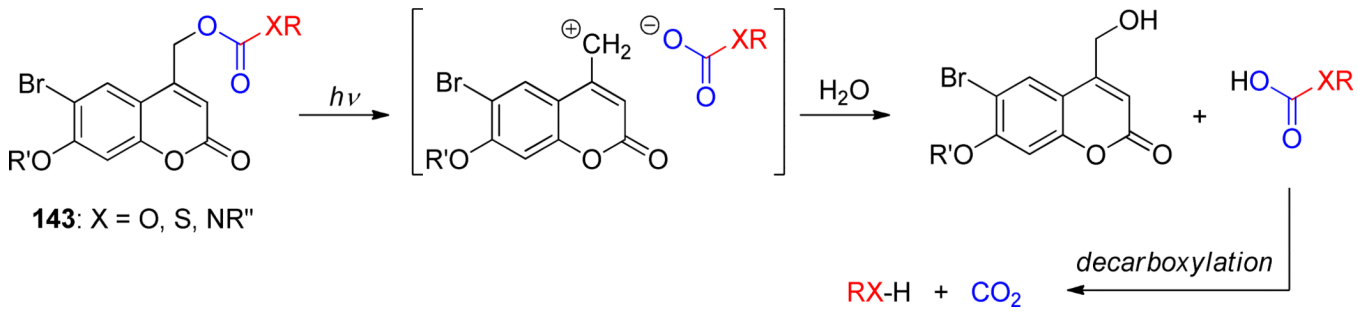
Release of Phosphates from 7-Methoxycoumarin Derivatives[266]



Scheme 50.
Synthetic Approaches to Coumarin-Caged Compounds

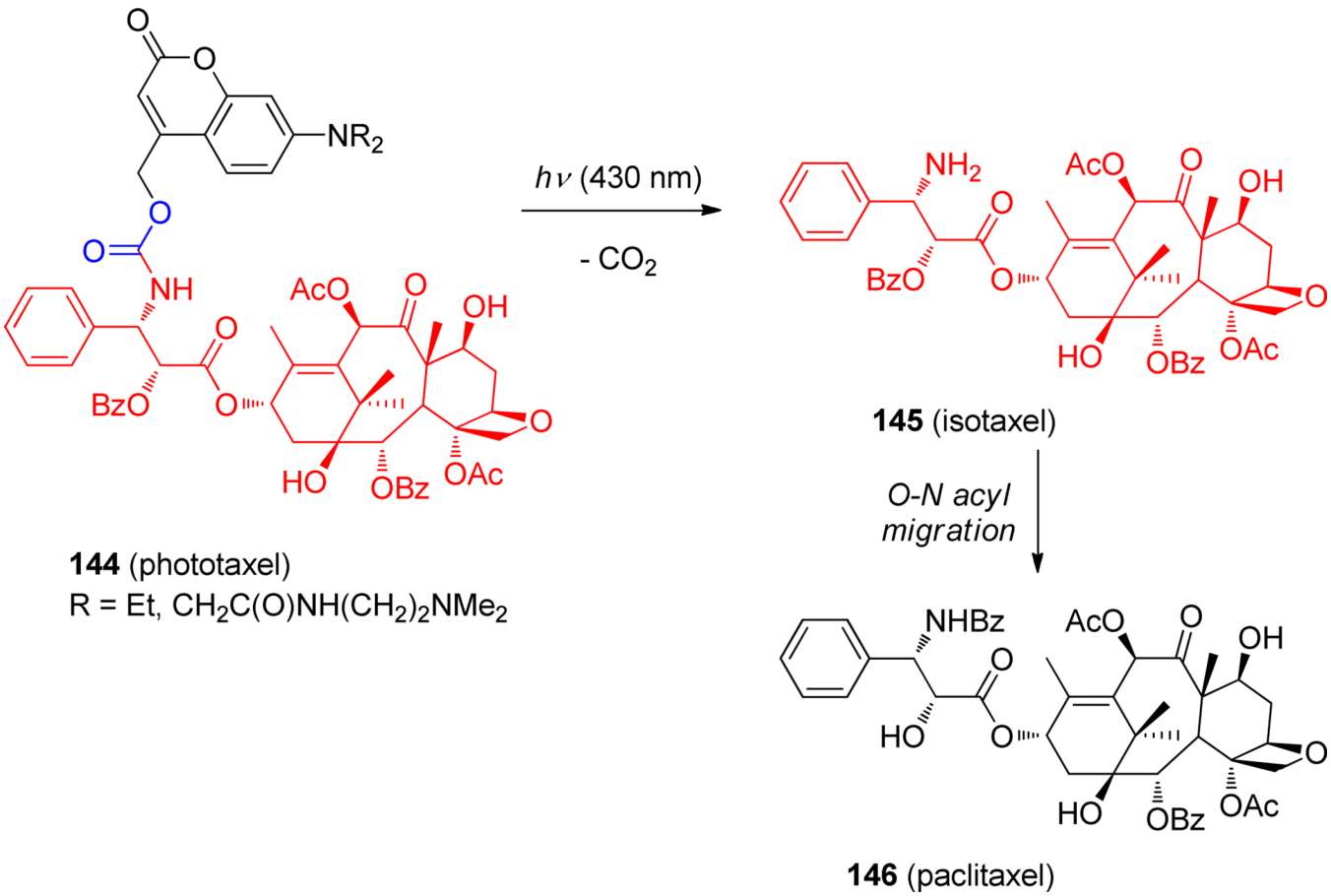


Scheme 51.
The Mechanism of Photorelease of Coumarin-Caged Compounds[297]

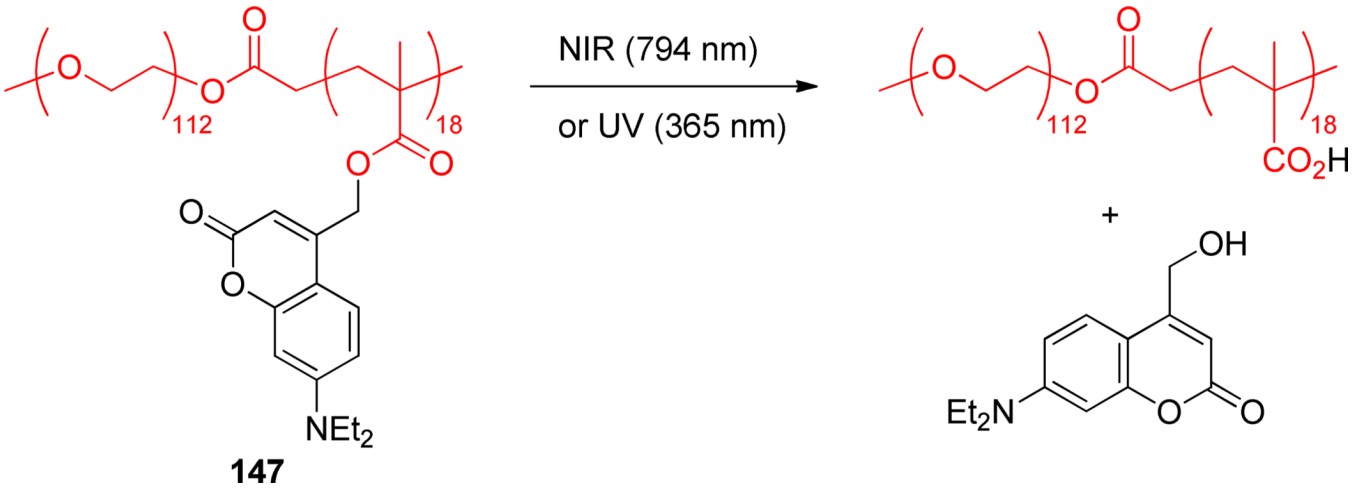


143: X = O, S, NR"

Scheme 52.
Decarboxylative Photorelease of Alcohols, Thiols and Amines

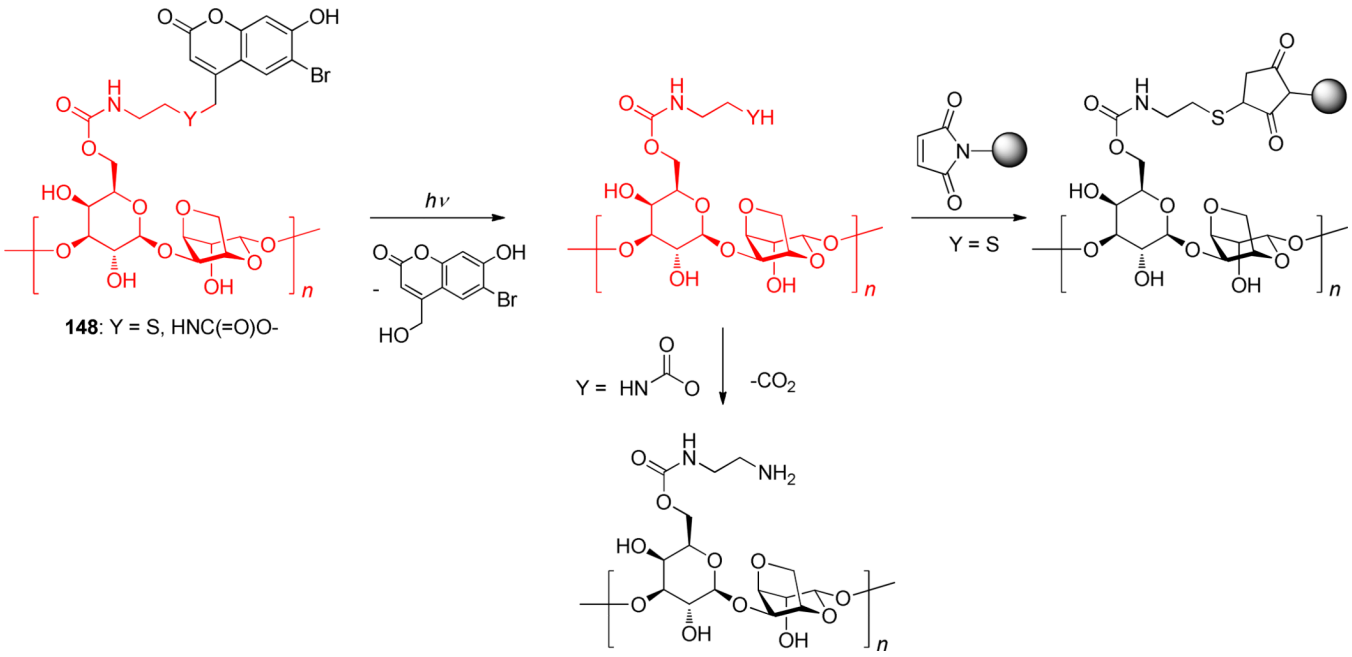


Scheme 53.
Activation of Paclitaxel by Visible Light[283]

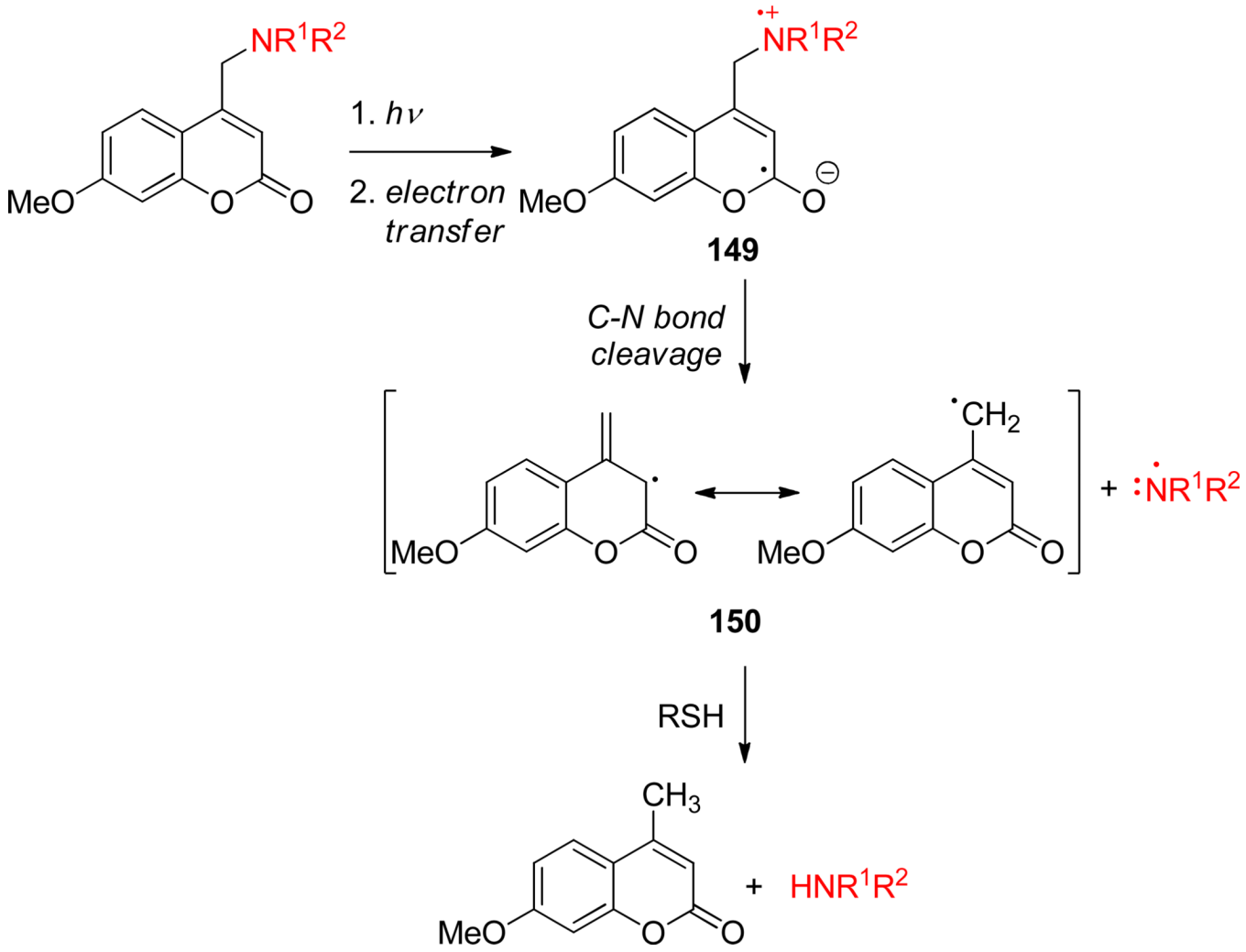


147

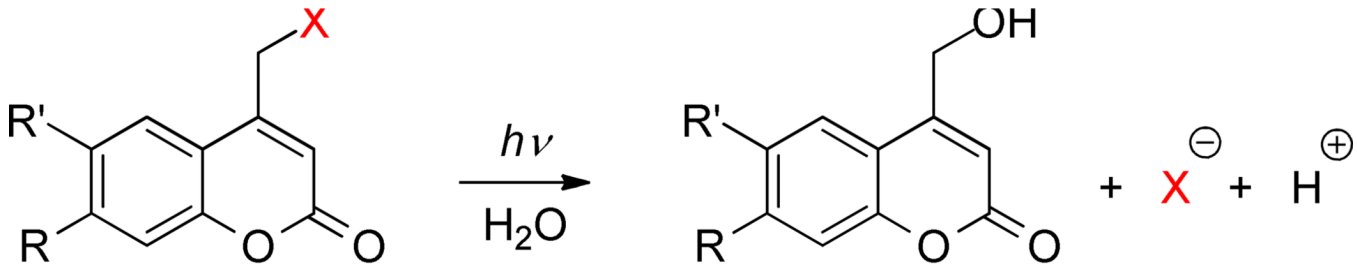
Scheme 54.
Light-Responsive Micelle Disruption[304]



Scheme 55.
Selective Photoactivation of Functional Groups within Aragose Gel[299,305]

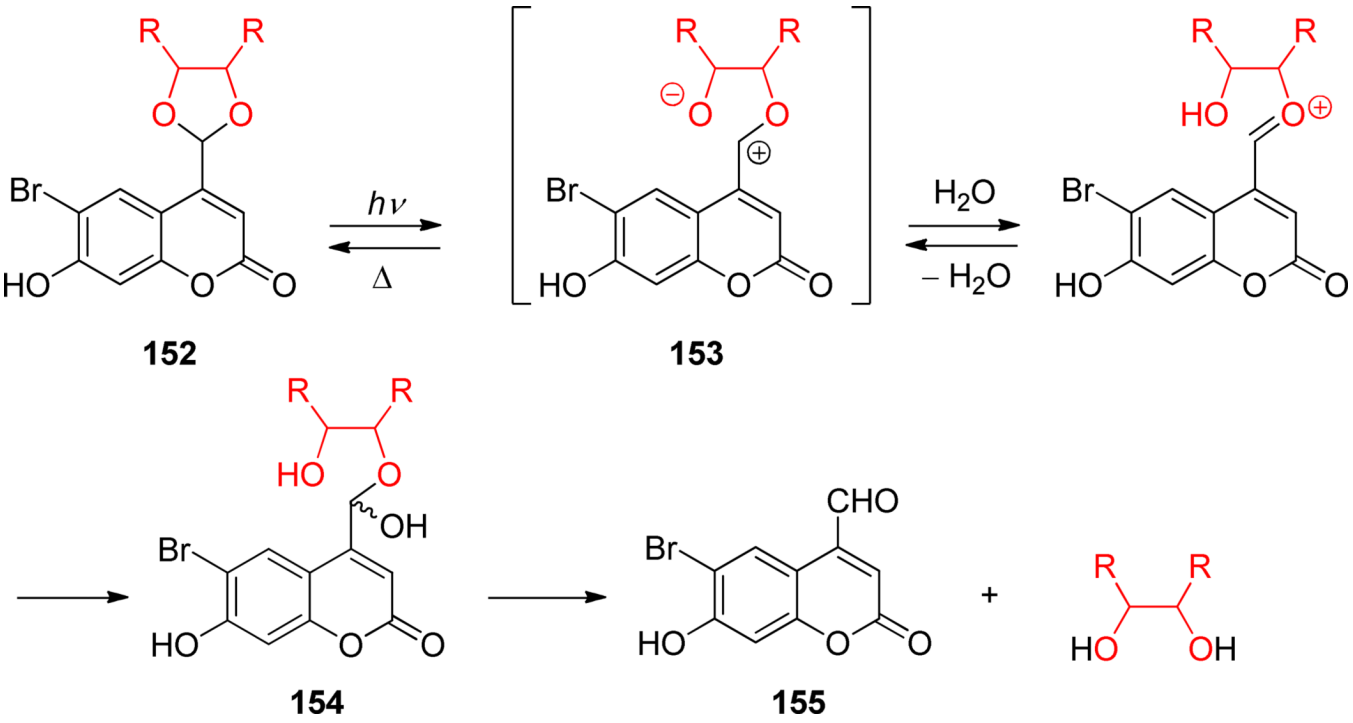


Scheme 56.
Uncaging of Amines via Direct C–N Bond Cleavage[306]

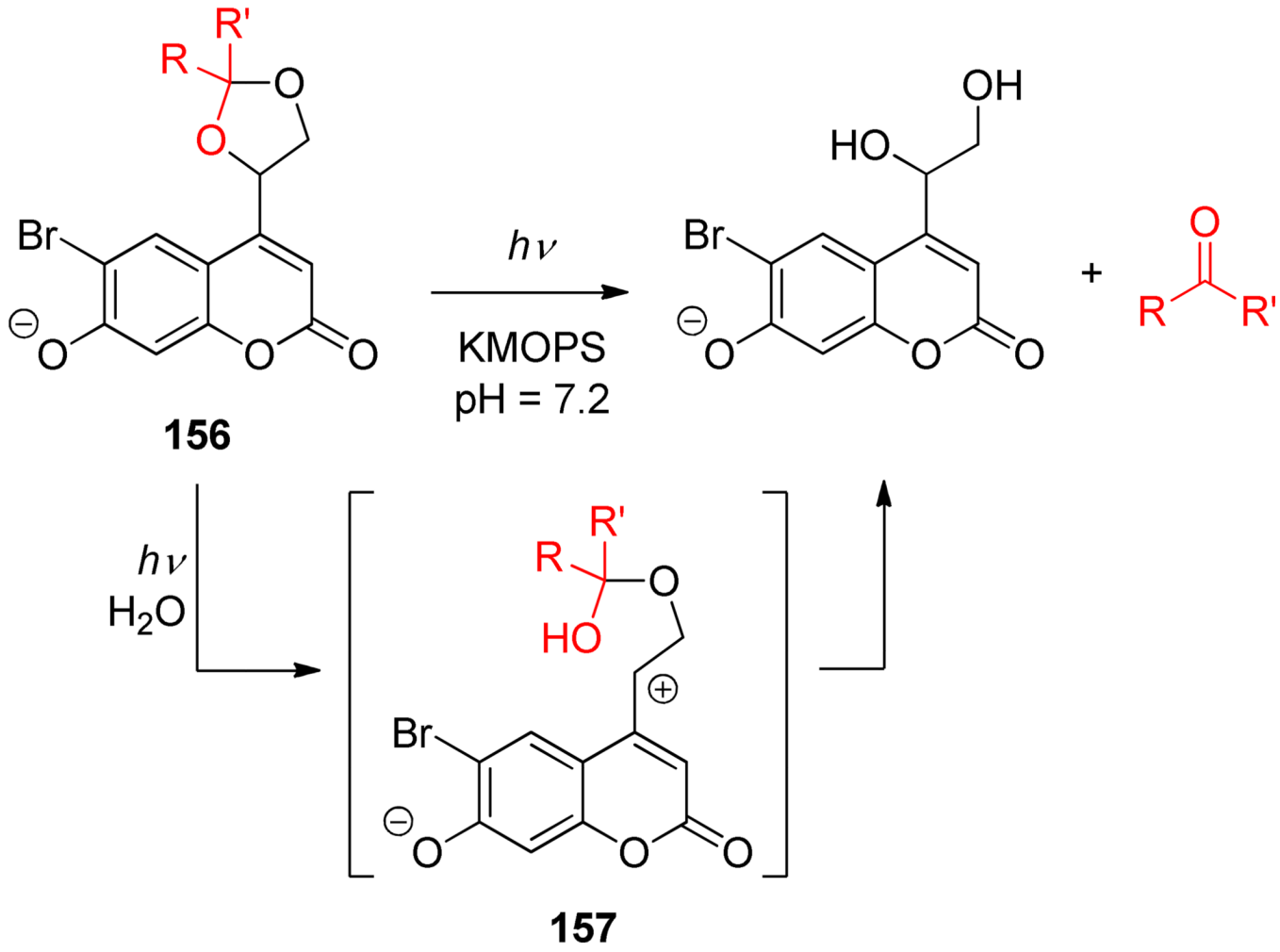


151:
R = OMe, NMe_2
R' = OMe, H
X = $OPO(OEt)_2$, OSO_2Me, OSO_3^-

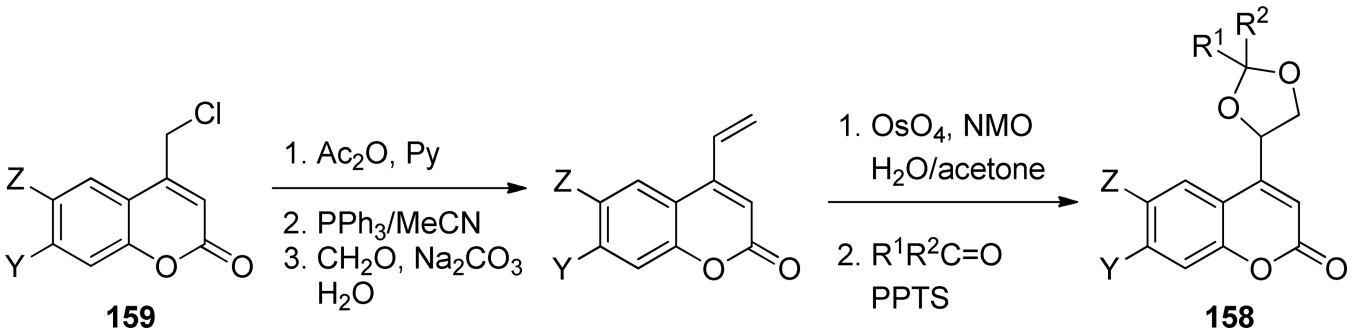
Scheme 57.
Caged Proton Source: Photorelease of Strong Acids[307]



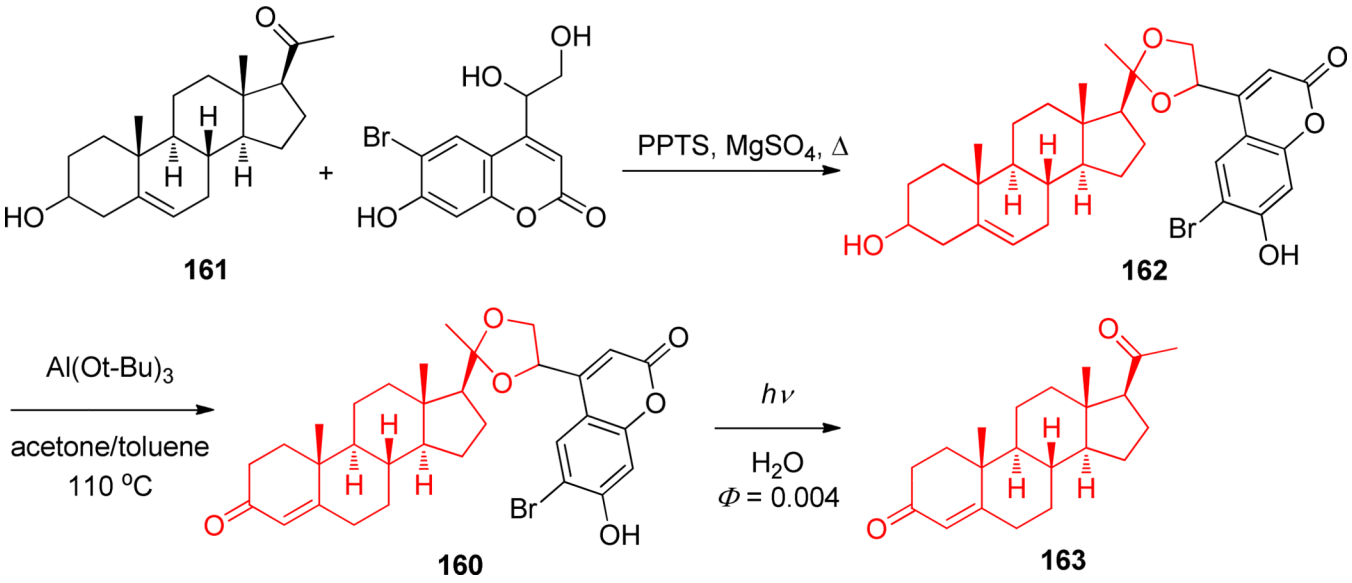
Scheme 58.
Photorelease of Coumarin-Caged Diols[308]



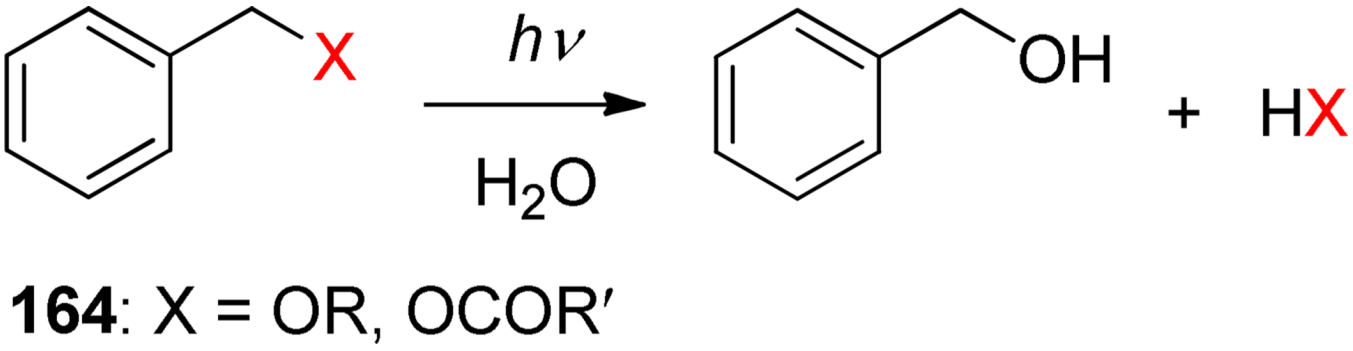
Scheme 59.
Photorelease of Coumarin-Caged Carbonyl Compounds[287,291]



Scheme 60.
Synthesis of Coumarin-Caged Carbonyl Compounds[291]

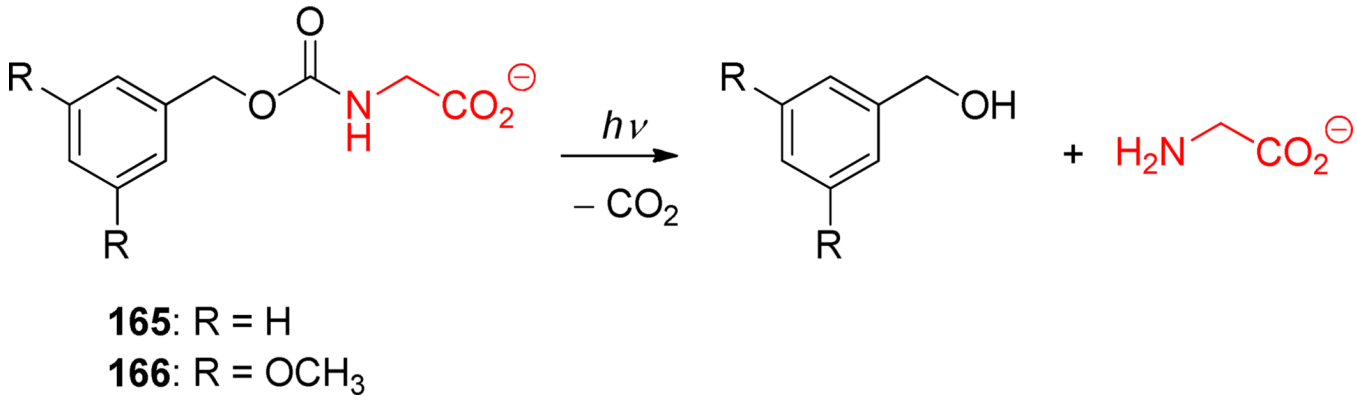


Scheme 61.
Photoactivation of Coumaryl-Caged Progesterone[310]



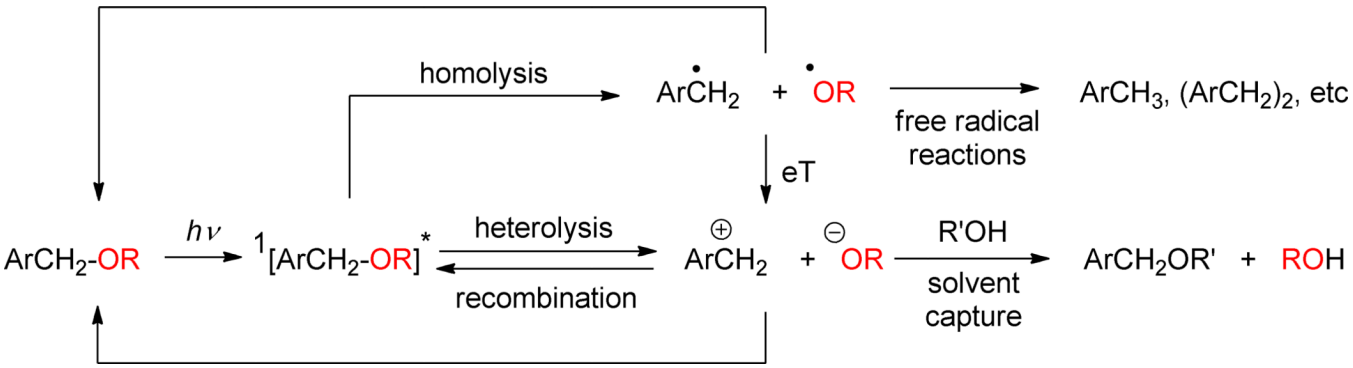
164: X = OR, OCOR′

Scheme 62.
Photochemical Cleavage of Benzyl Protection

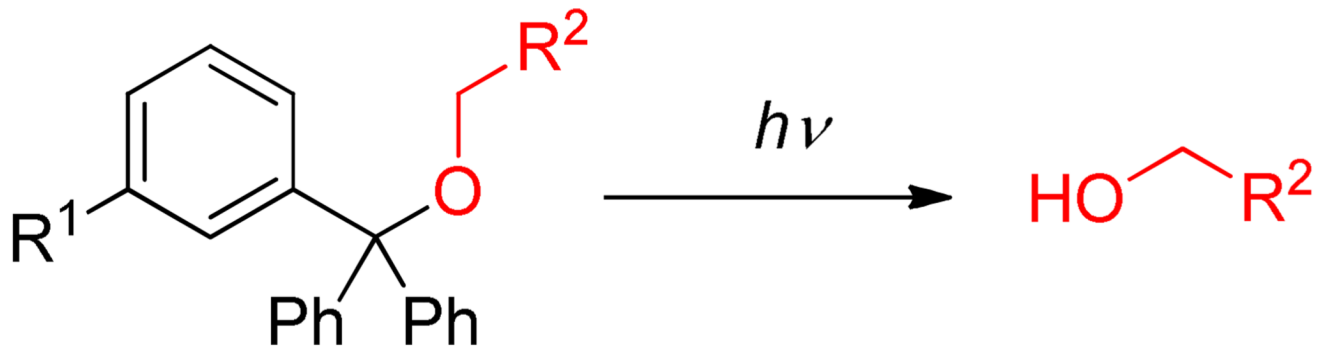


165: R = H
166: R = OCH_3

Scheme 63.
Uncaging of Glycine[1,311]



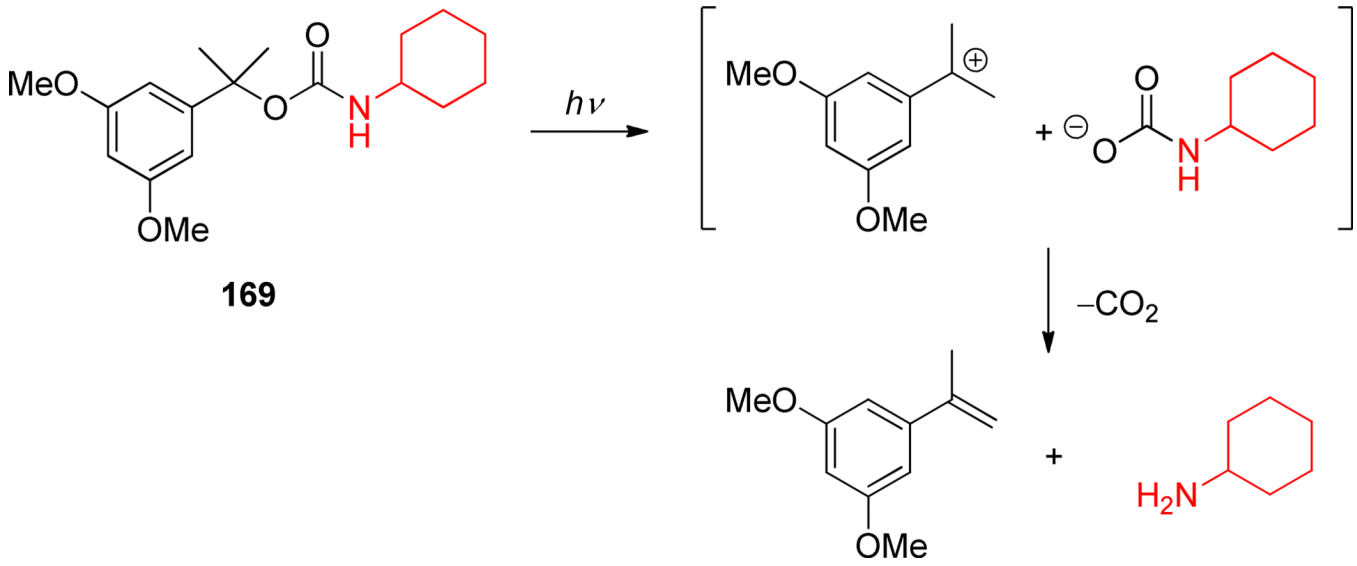
Scheme 64.
Photochemistry of Arylmethyl Ethers



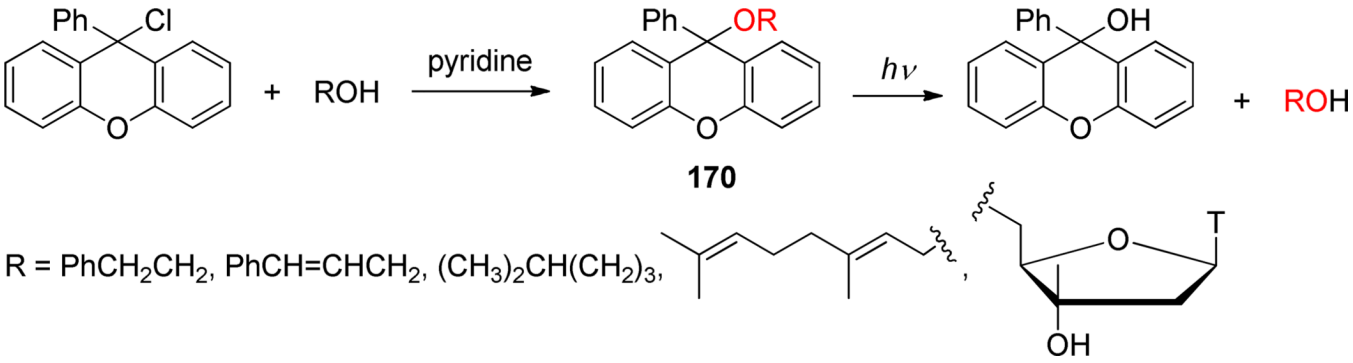
167: R^1= OMe; R^2= nucleoside

168: R^1= Me_2N; R^2= various alkyl substituents

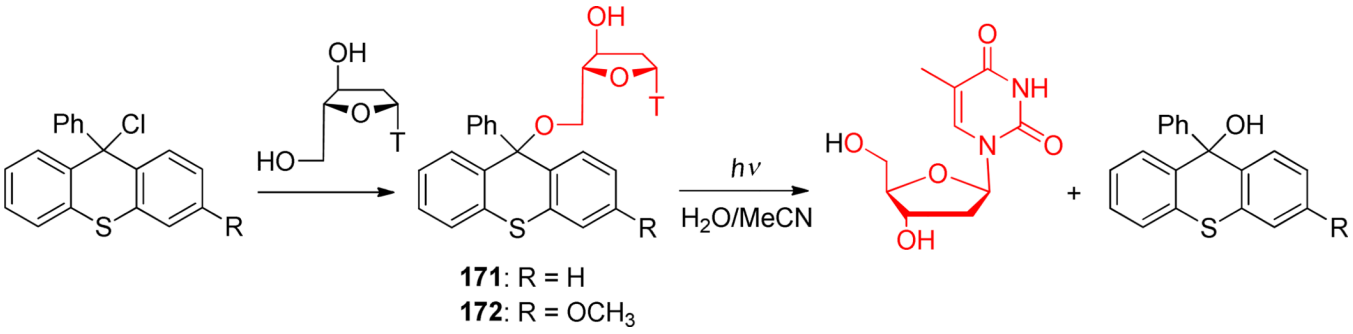
Scheme 65.
Photocleavage of the Trityl PPG[314]



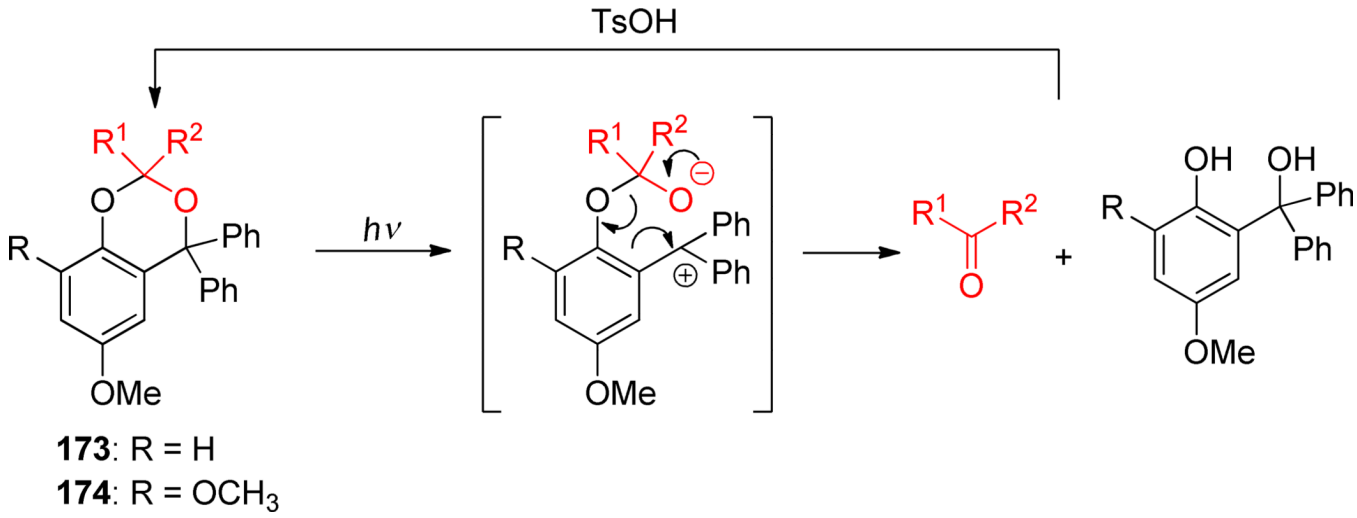
Scheme 66.
Uncaging of Amines[316]



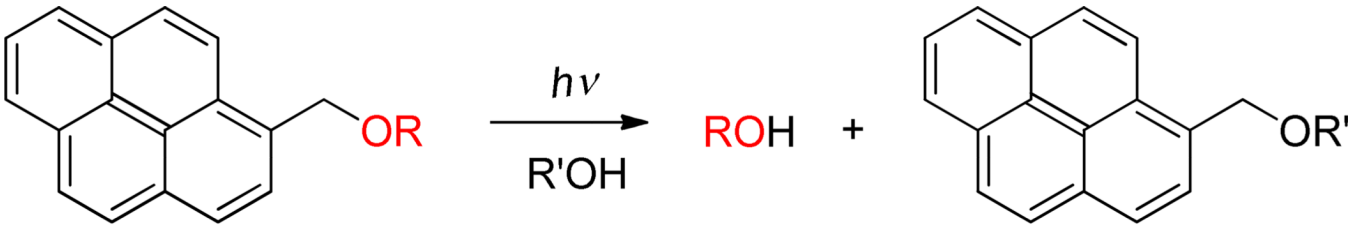
Scheme 67.
Protection and Photochemical Release of Primary Alcohols[317]



Scheme 68.
Use of the *S*-Pixyl PPG for Caging and Release of Nucleosides[318]

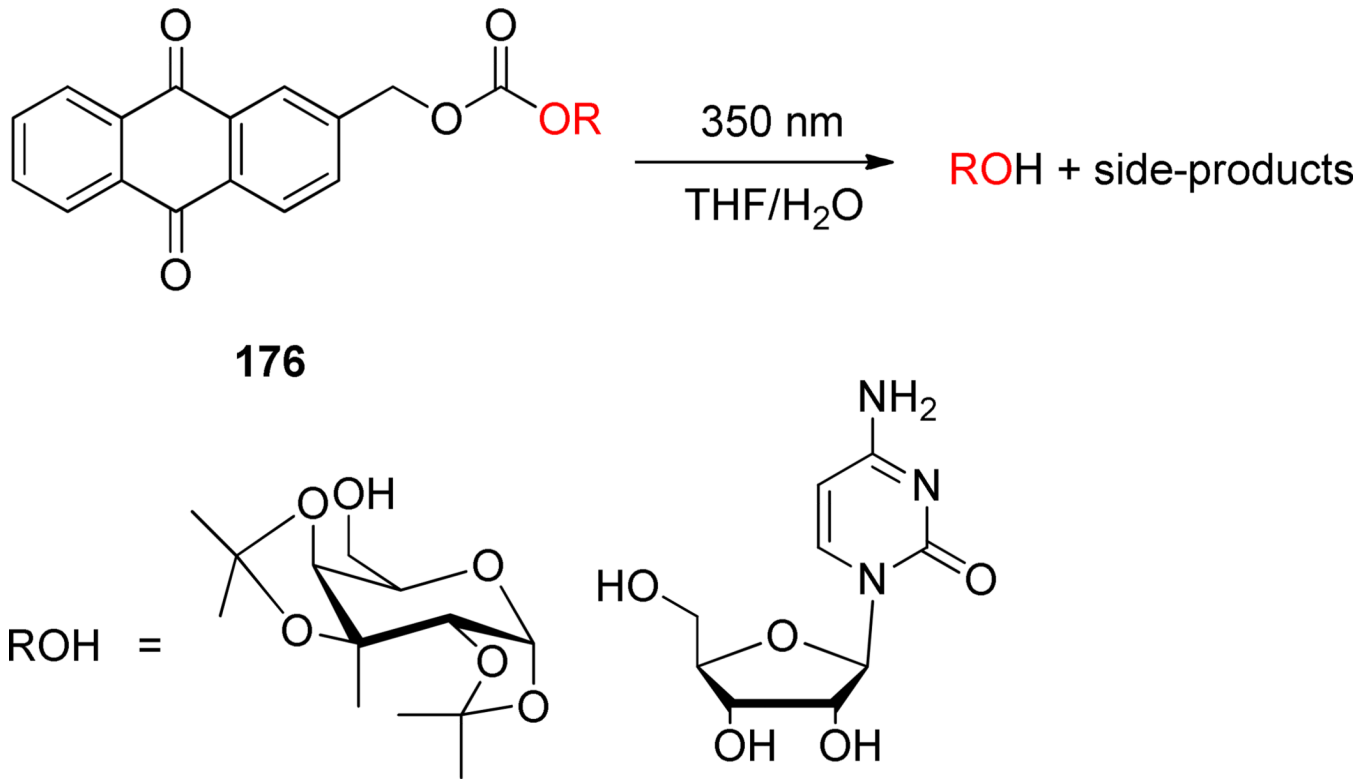


Scheme 69.
Photolabile Acetals for the Protection of Ketones and Aldehydes[320]

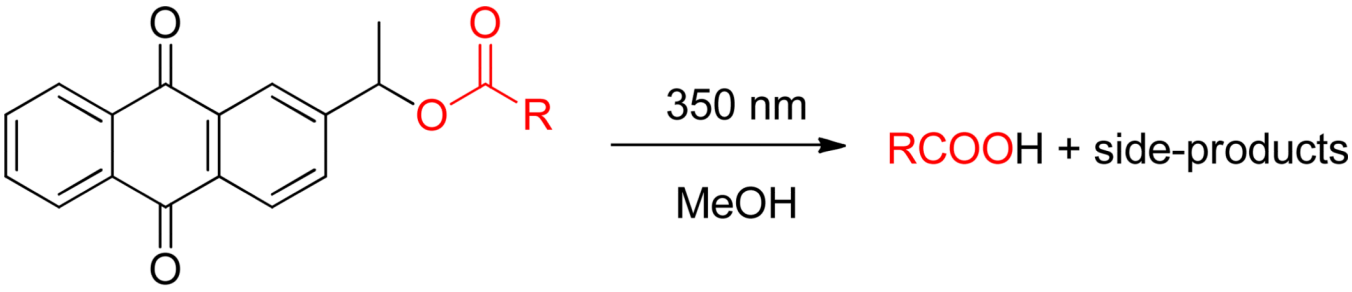


175a: R = PO(OR'')
b: R = COR''
c: R = alkyl

Scheme 70.
Photocleavage of the Fluorescent (Pyren-1-yl)methyl Protecting Group[326]

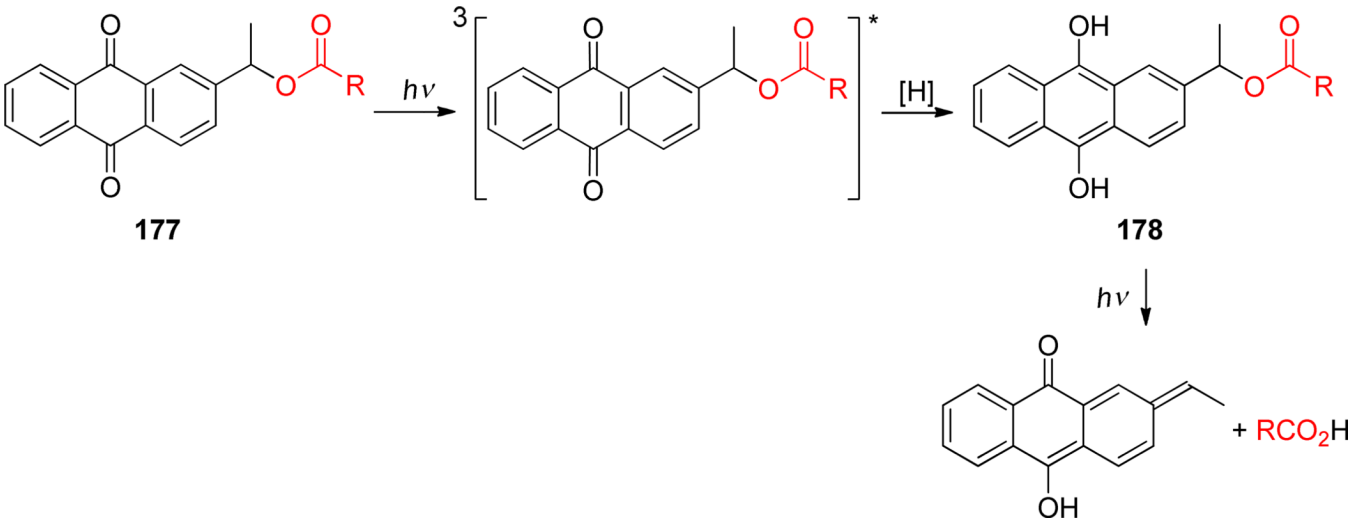


Scheme 71.
Aqmoc Caging of Primary Alcohols[324,326d]

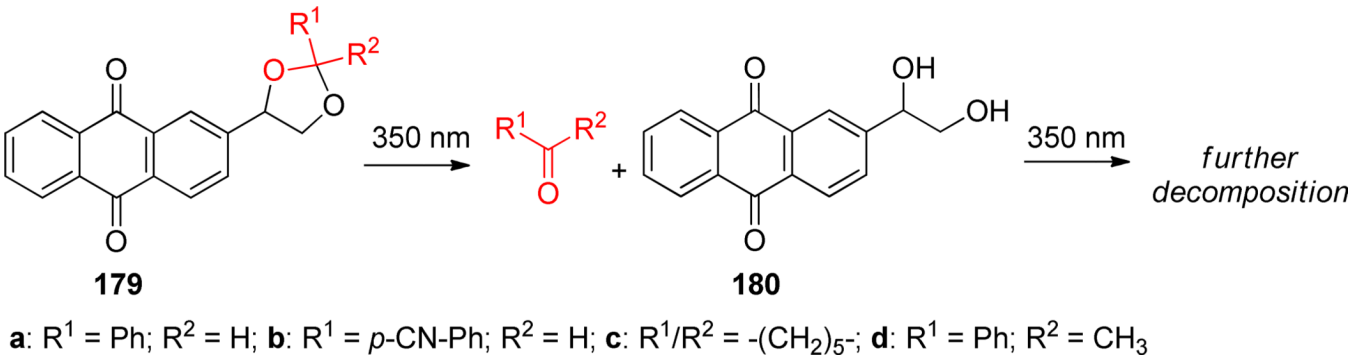


177a: R = *p*-MeO-C_6H_4
b: R = *o*-Me-C_6H_4
c: R = Ph
d: R = *p*-NO_2-C_6H_4
e: RCOOH = *N*-acetyl-L-tryptophan

Scheme 72.
Aqe Cage for Carboxylic Acids[328]



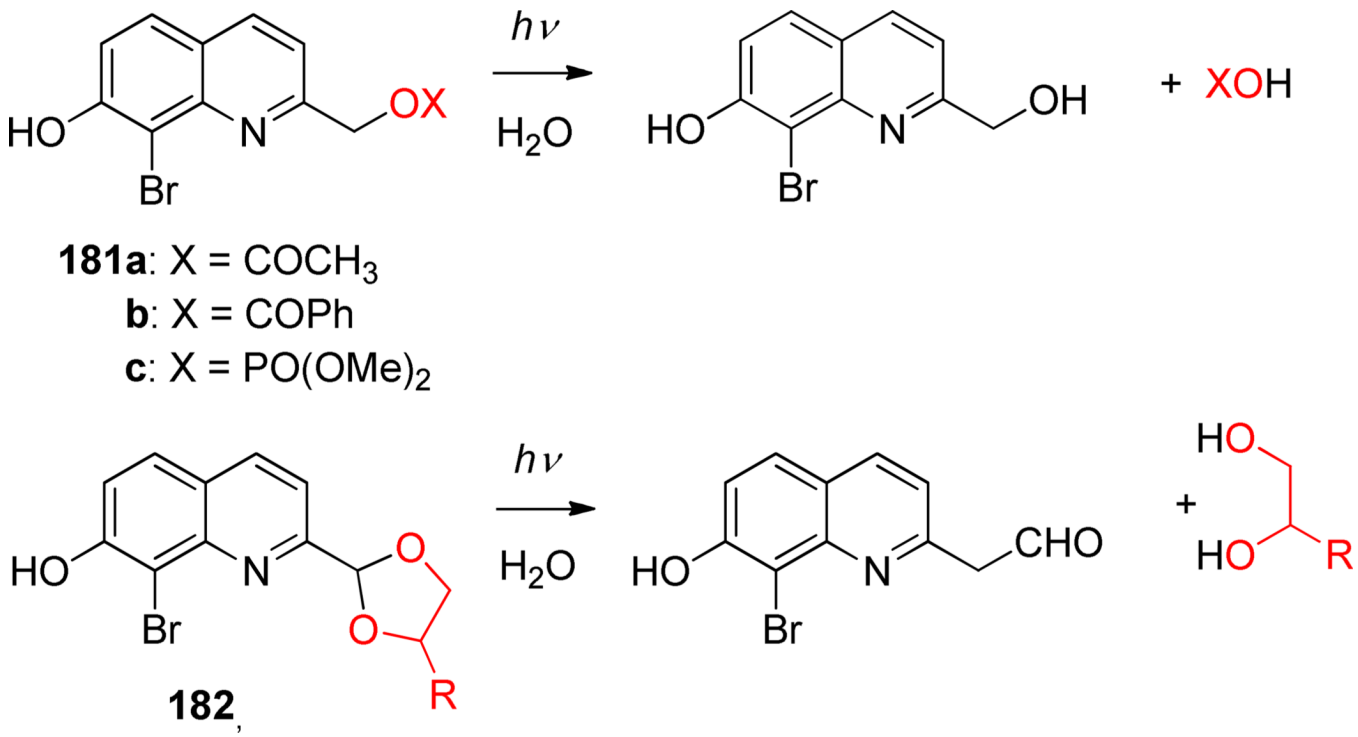
Scheme 73.
The Mechanism of Carboxylic Acid Release from the Aqe Cage[328]



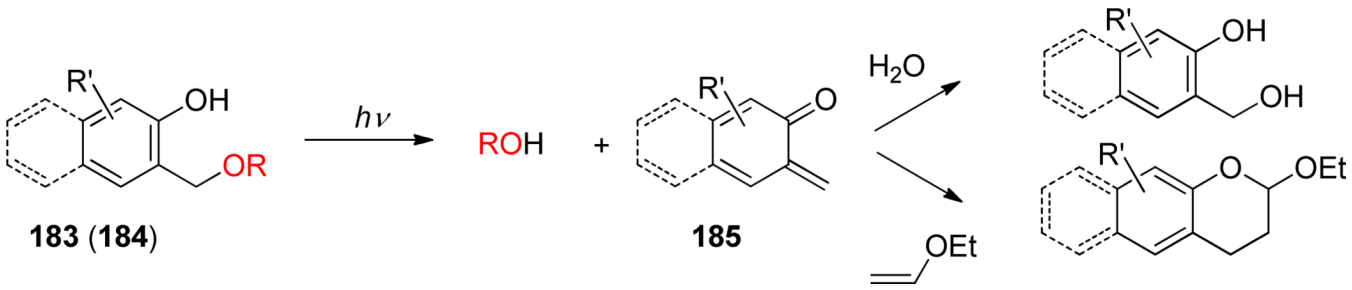
179 **180**

a: R^1 = Ph; R^2 = H; **b**: R^1 = *p*-CN-Ph; R^2 = H; **c**: R^1/R^2 = -$(CH_2)_5$-; **d**: R^1 = Ph; R^2 = CH_3

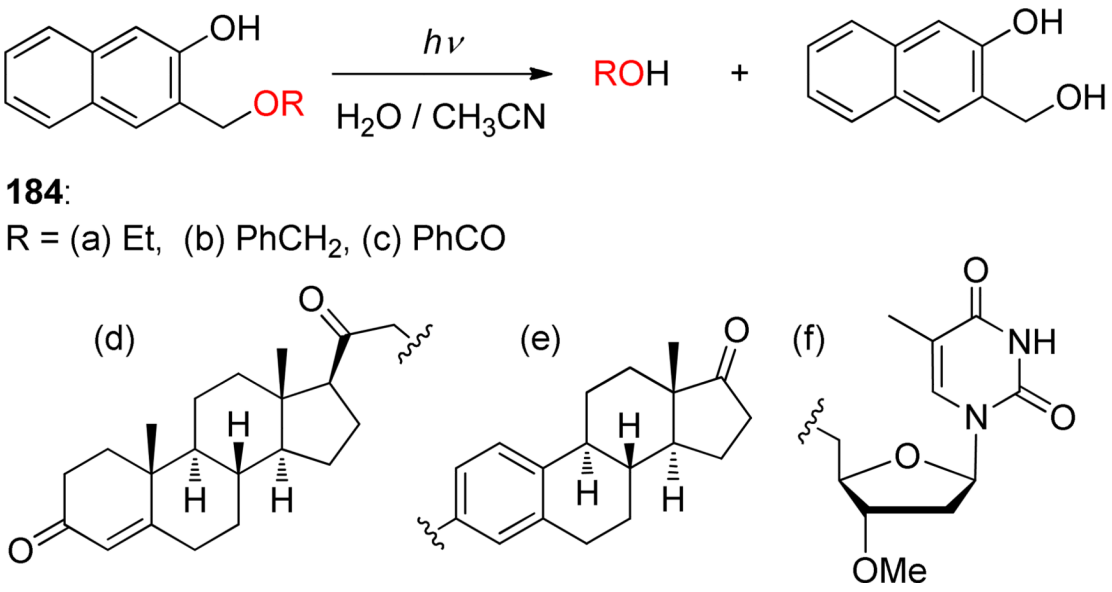
Scheme 74.
(Anthraquinon-2-yl)methyl-based Photolabile Acetals[329]



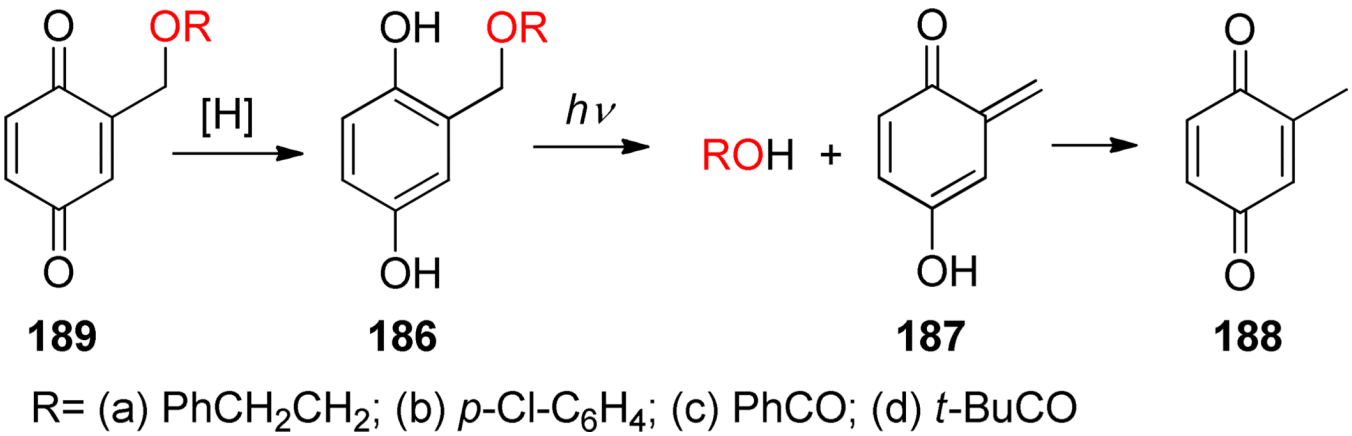
Scheme 75.
(8-Bromo-7-hydroxyquinoline-2-yl)methyl (BHQ)-based PPGs[331]



Scheme 76.
The Mechanism of Substrate Release from the *o*-Hydroxybenzyl/naphthyl Cage[337a,b]

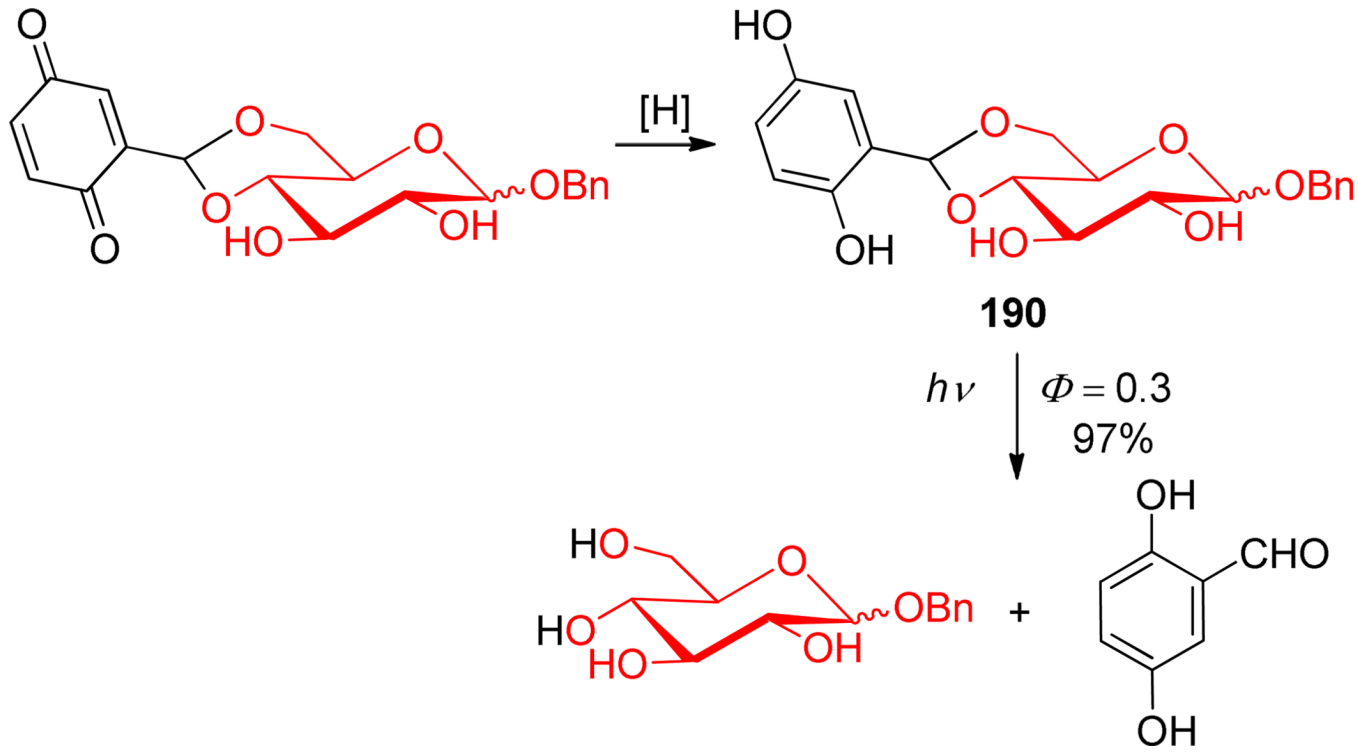


Scheme 77.
Photochemical Release of Alcohols, Phenols, and Carboxylic Acid from NQMP Cage[338]

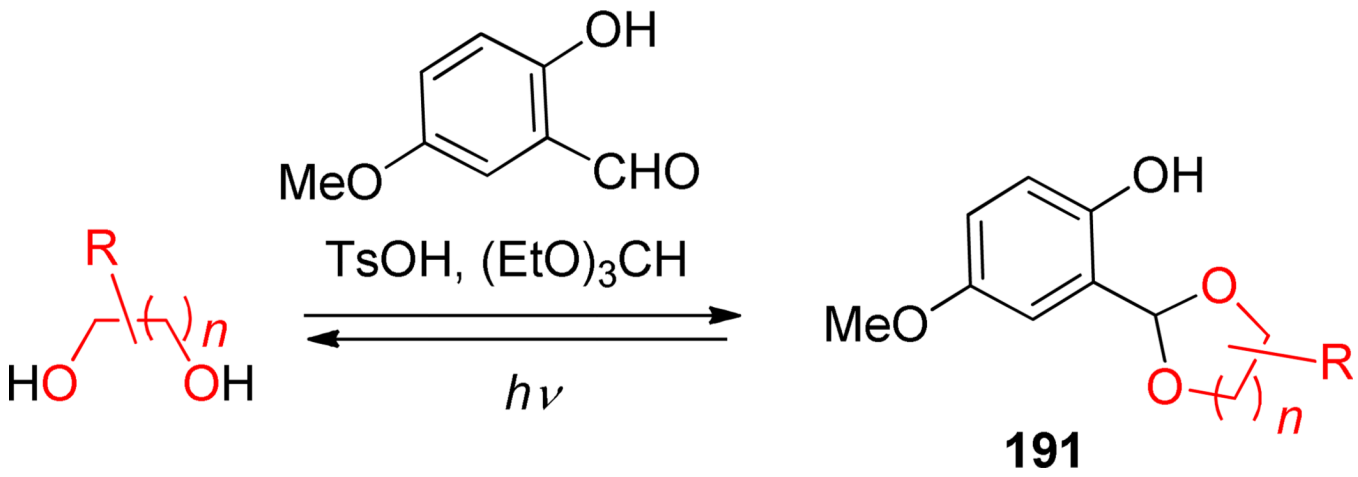


R= (a) $PhCH_2CH_2$; (b) *p*-Cl-C_6H_4; (c) PhCO; (d) *t*-BuCO

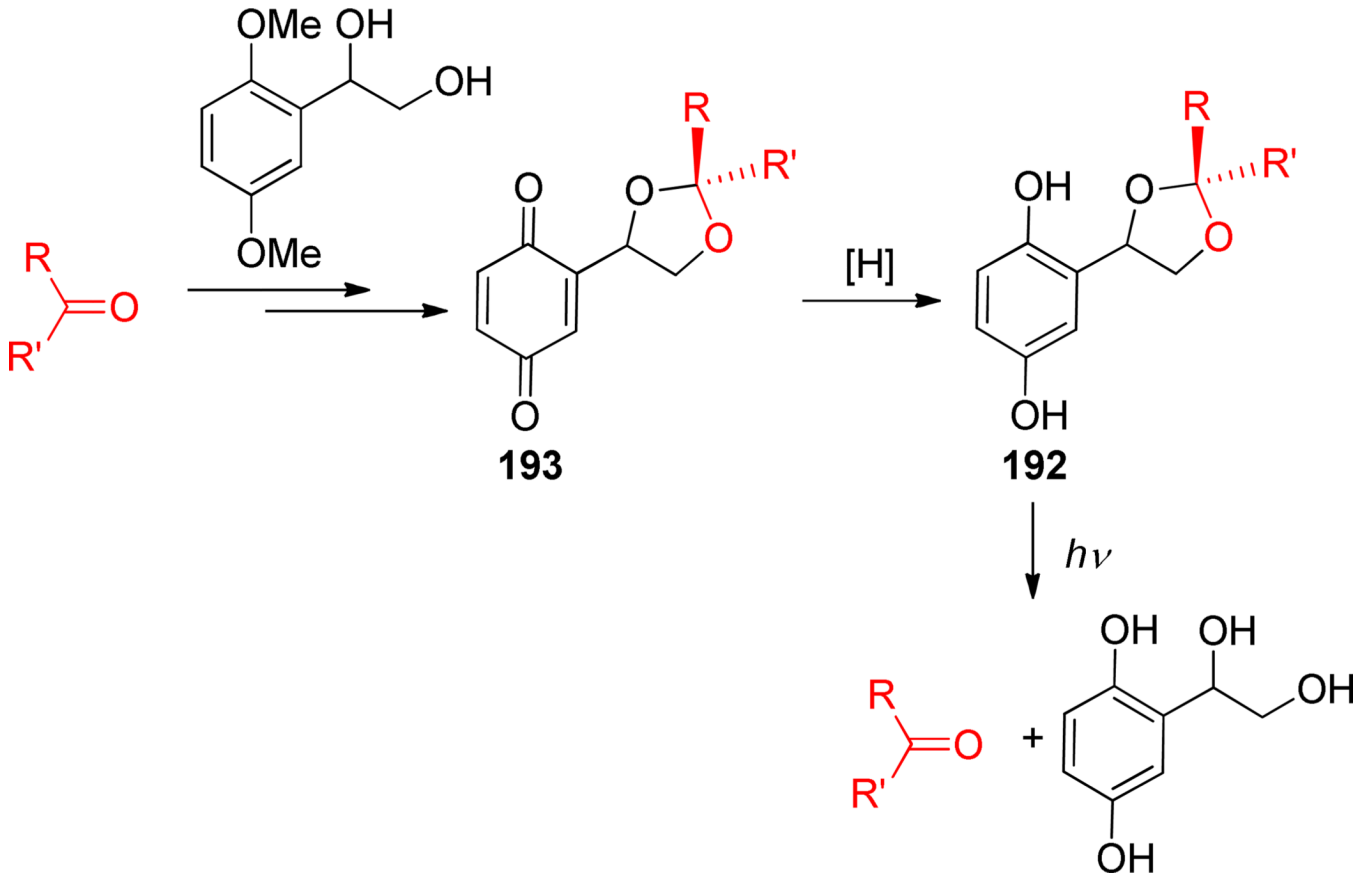
Scheme 78.
2,5-Dihydroxybenzyl Cage Incorporating a “Safety Catch” Feature[339]



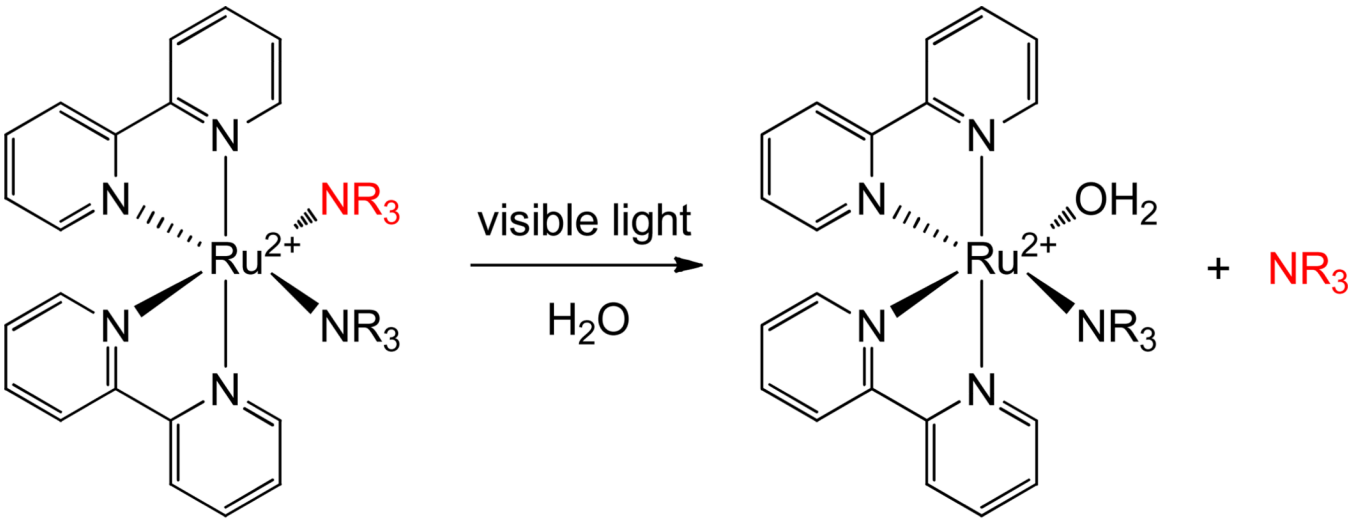
Scheme 79.
Photolabile Benzylidene Protection of Carbohydrates[340]



Scheme 80.
Photolabile Protection of Glycols[339]



Scheme 81.
Safety-Catch Photolabile Acetal for Carbonyl Group Protection[341]



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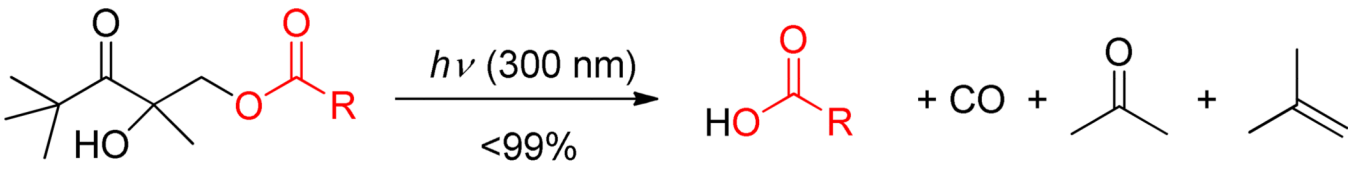
$[Ru(bpy)_2(NR_2)_2]^{2+}$

Scheme 82.
Photorelease from the $[Ru^{2+}(bpy)_2]^{2+}$ Cage



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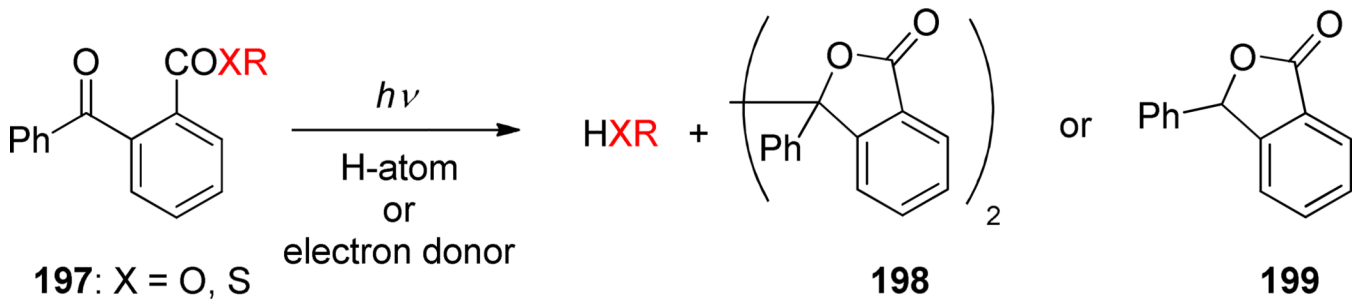
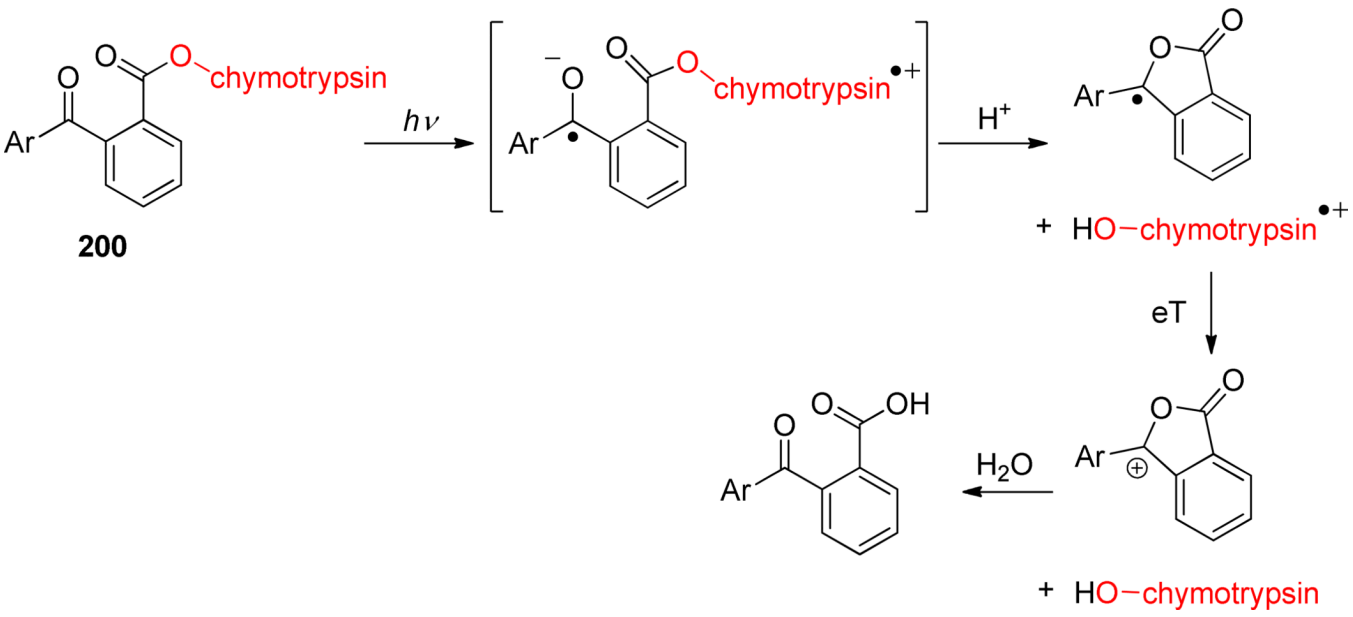
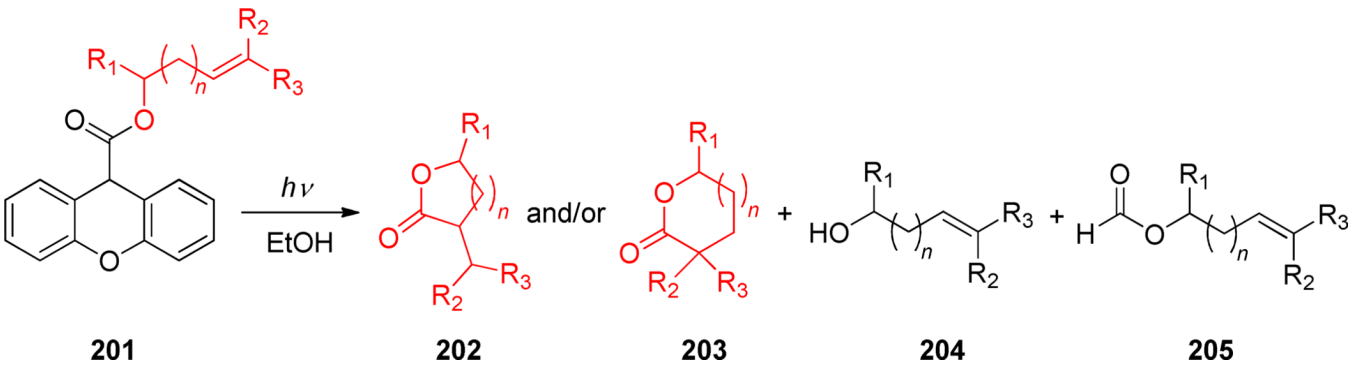
Scheme 83.
Photolysis of Pivaloylglycol Derivatives[360]



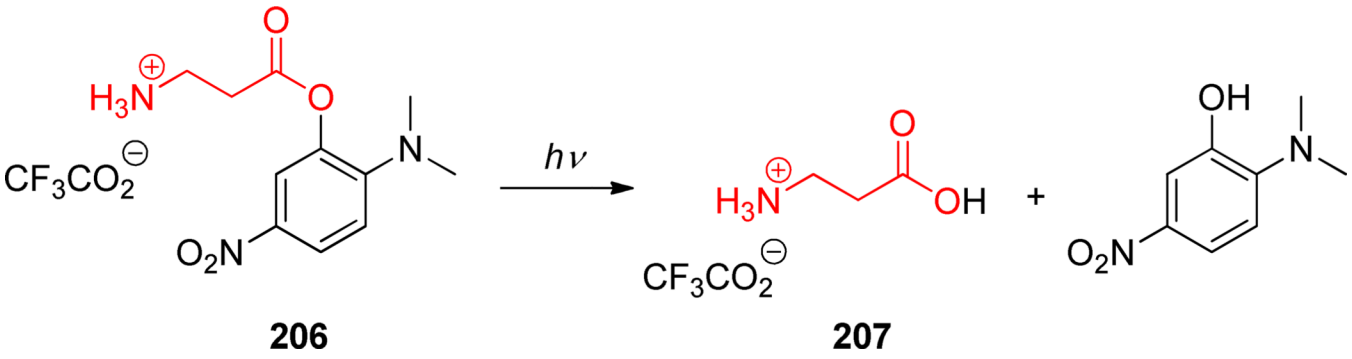
Scheme 84.
Photochemistry of 2-Benzoylbenzoic Acid Esters[361]



Scheme 85.
Chymotrypsin Photorelease[362]

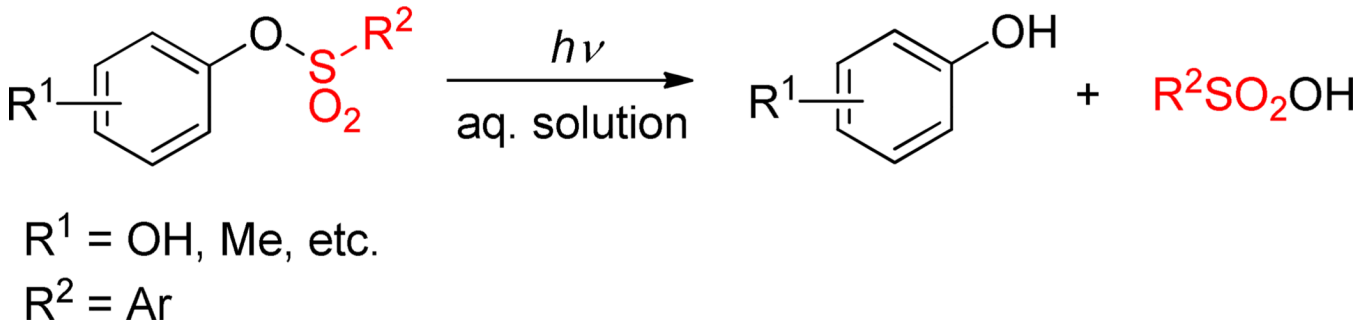


Scheme 86.
Photofragmentation of Xanthenoic Esters[363]



206 **207**

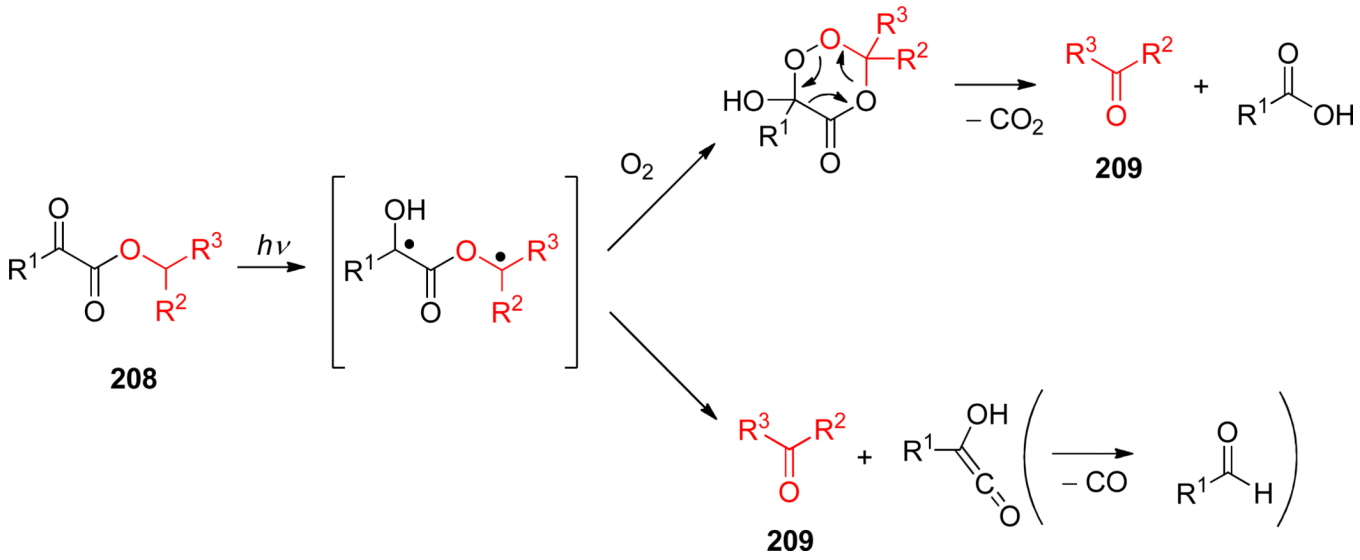
Scheme 87.
Liberation of β-Alanine from the Aminonitrophenyl Chromophore[364]



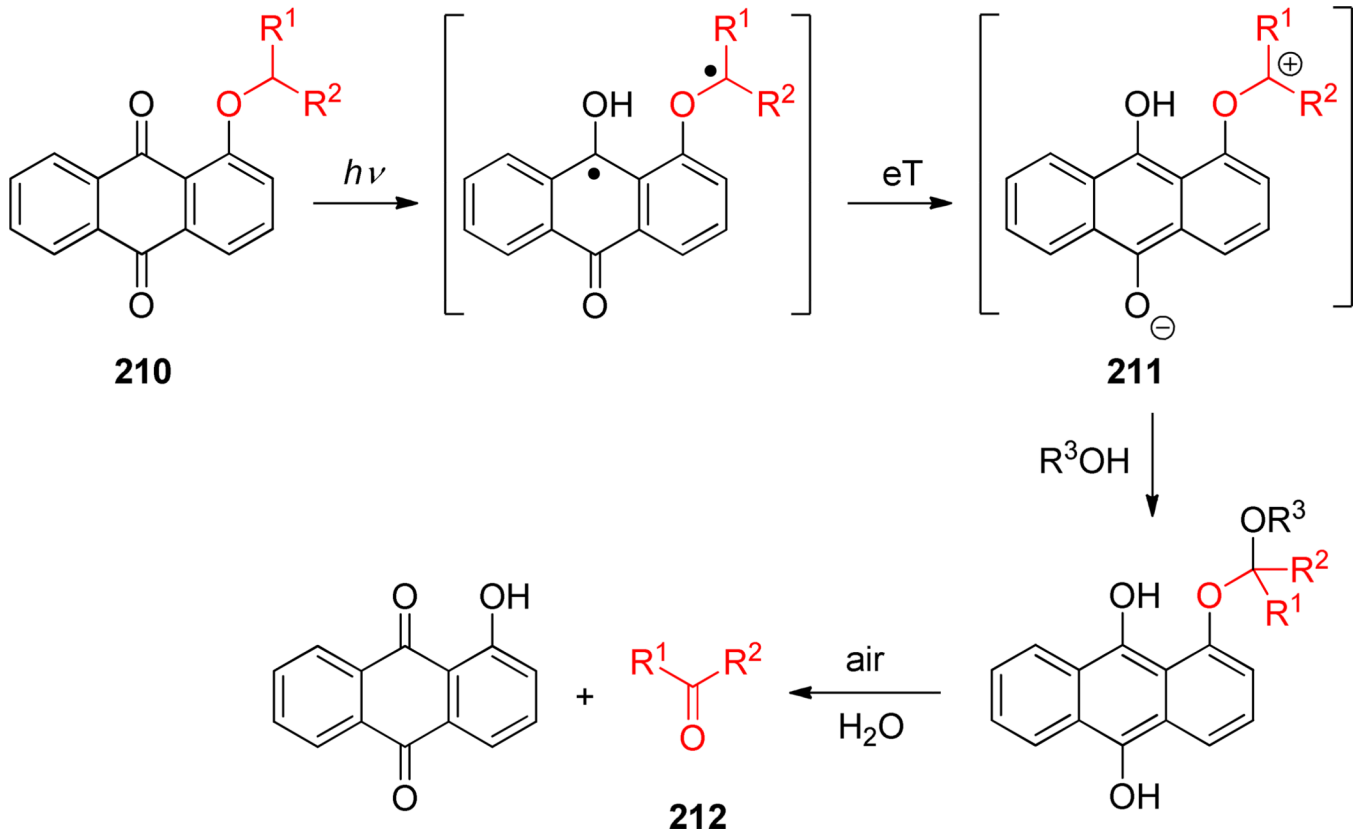
R^1 = OH, Me, etc.

R^2 = Ar

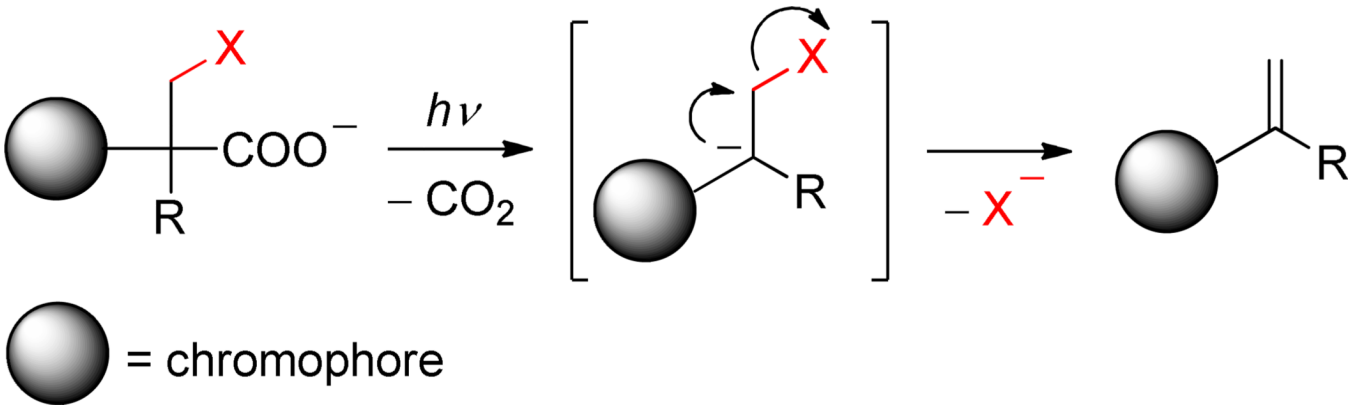
Scheme 88.
Photochemistry of Arylsulfonyl Esters



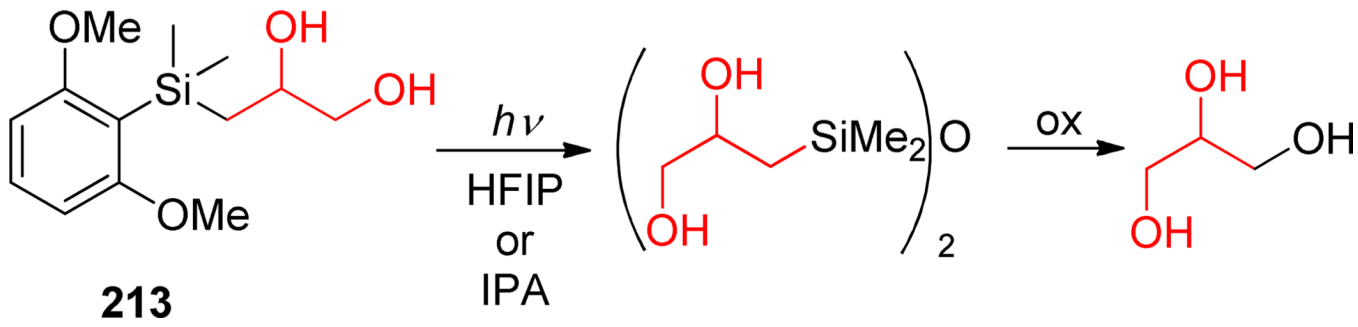
Scheme 89.
Photochemistry of α-Keto Esters[372]



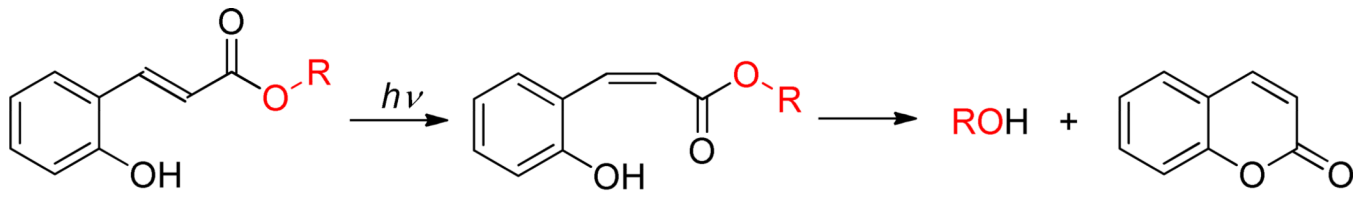
Scheme 90.
Photochemistry of 1-Alkoxy-9,10-anthraquinones[374]



Scheme 91.
Carbanion-Mediated Photocleavage



Scheme 92.
Photochemistry of Trialkylsilyl Esters[386]



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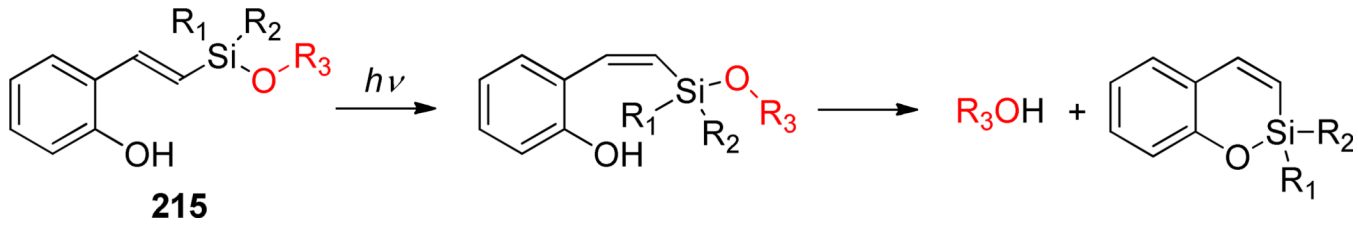
Scheme 93.
Photochemistry of *o*-Hydroxycinnamic Derivatives



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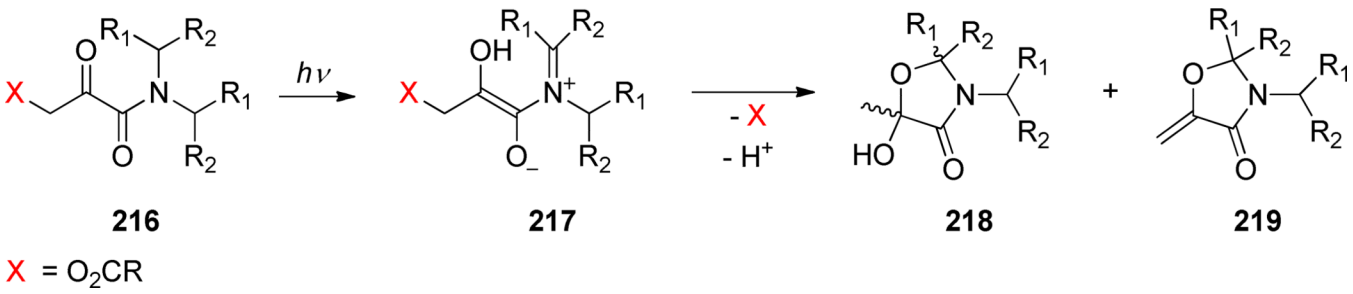
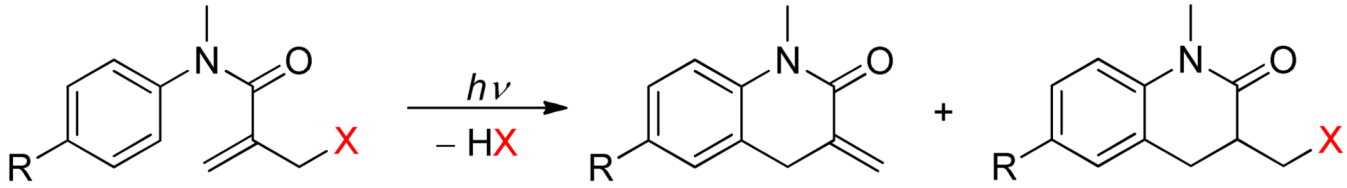
Scheme 94.
Photochemistry of Silyl Analogues of 2-Hydroxycinnamyl Derivatives[395]



216 **217** **218** **219**

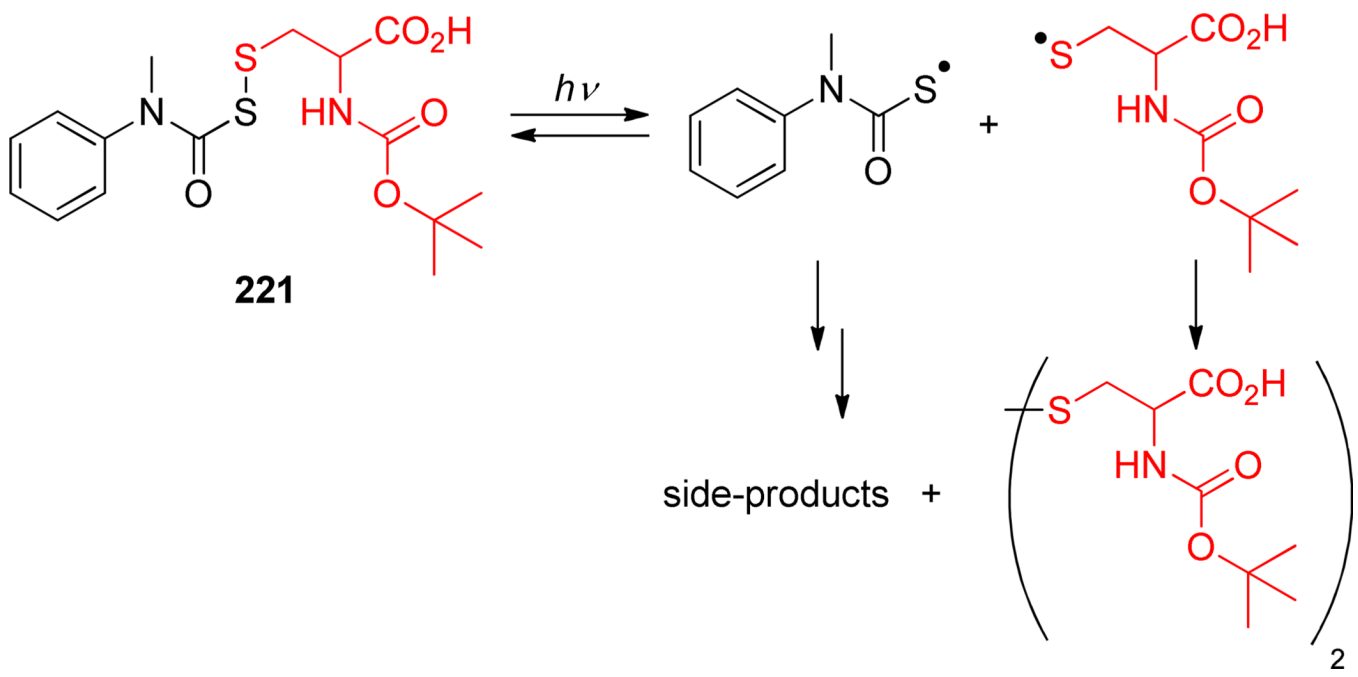
X = O_2CR

Scheme 95.
α-Ketoamides as PPGs[396]

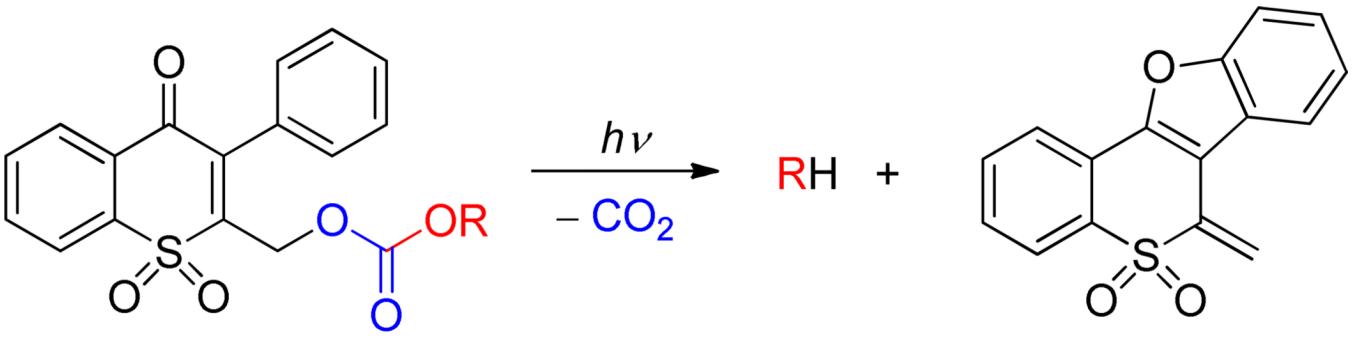


220: R = CO_2CH_3 or COPh
X = carboxylate or phenolate

Scheme 96.
α,β-Unsaturated Anilides as PPGs[401]

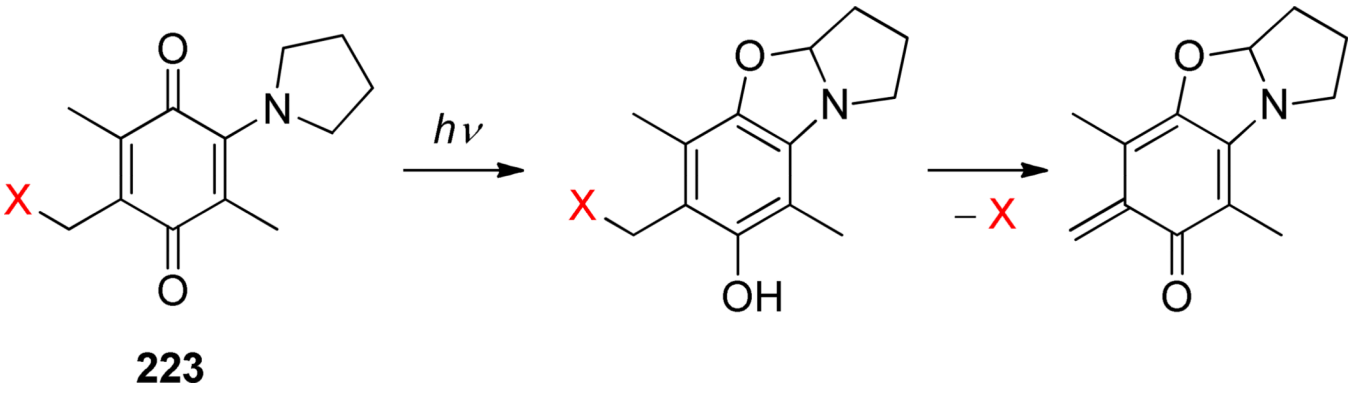


Scheme 97.
Photochemistry of a Methyl(phenyl)thiocarbamic Acid Chromophore[402]



222

Scheme 98.
Photochemistry of a Thiochromone *S,S*-Dioxide Derivative[403]



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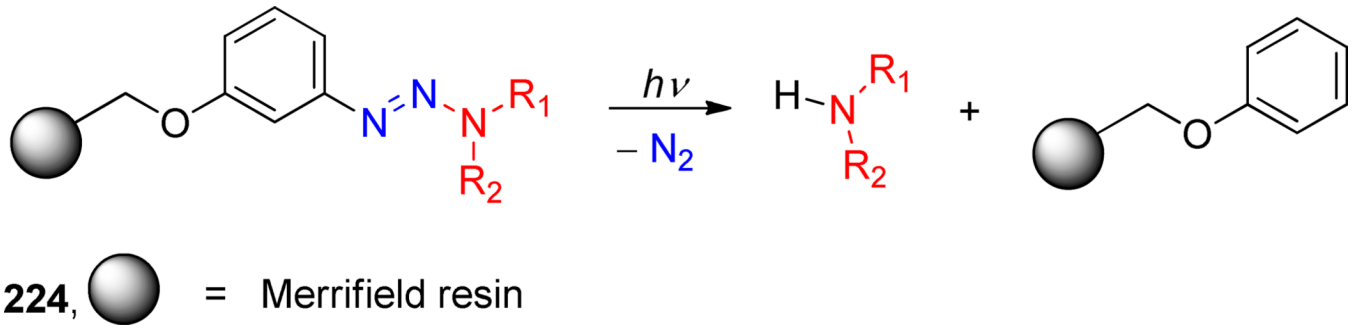
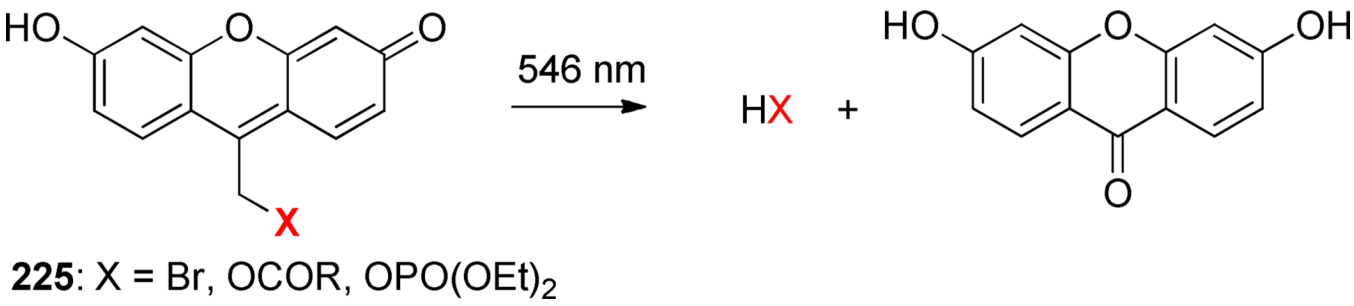
Scheme 99.
Photochemistry of 2-Pyrrolidino-1,4-Benzoquinone Derivatives[404]



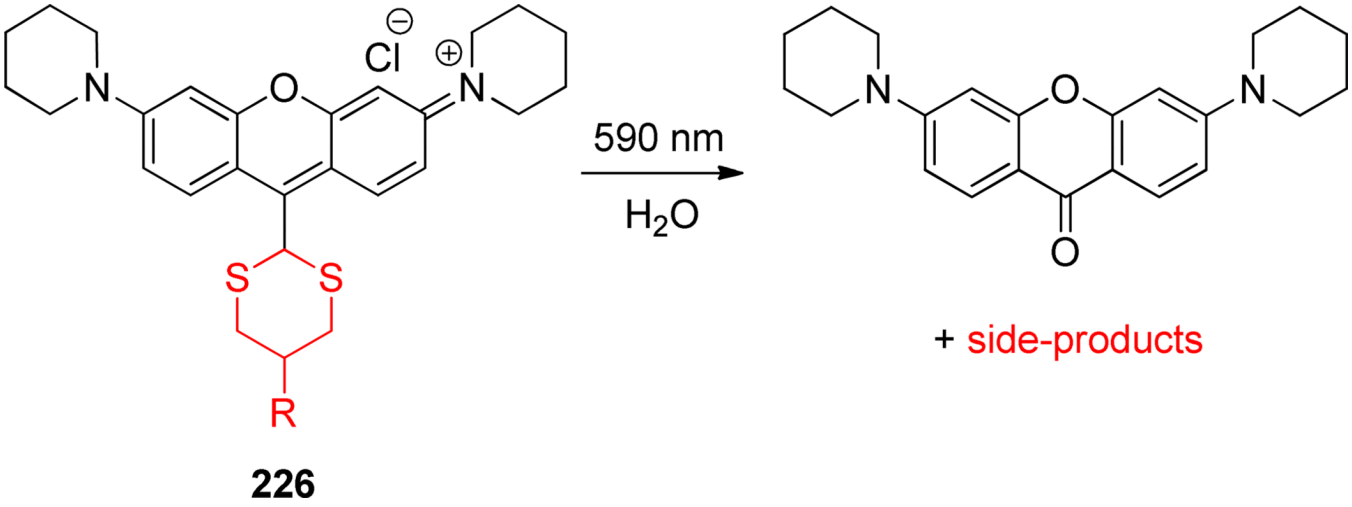
224, = Merrifield resin

Scheme 100.
A Triazine Moiety as a Photolabile Linker[406]



225: X = Br, OCOR, $OPO(OEt)_2$

Scheme 101.
Photorelease from the Xanthene Derivatives[408]



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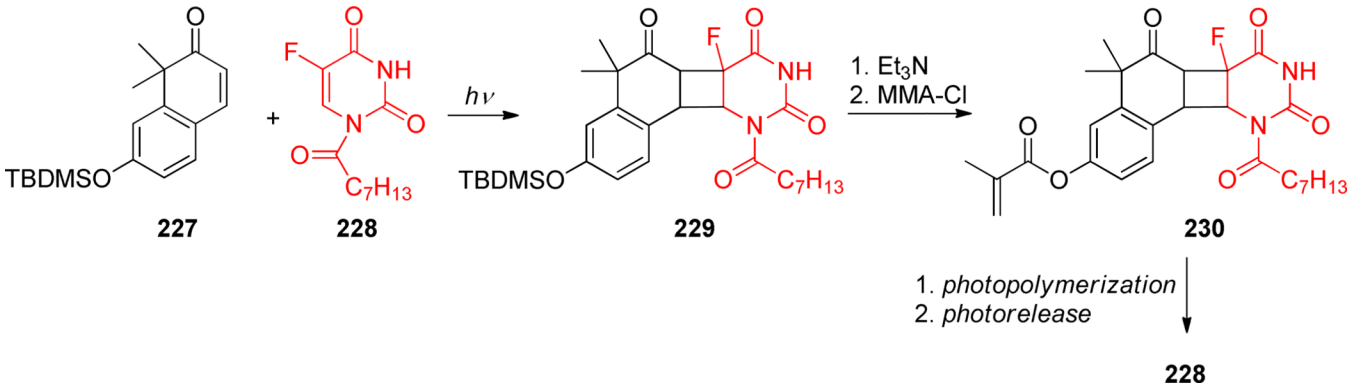
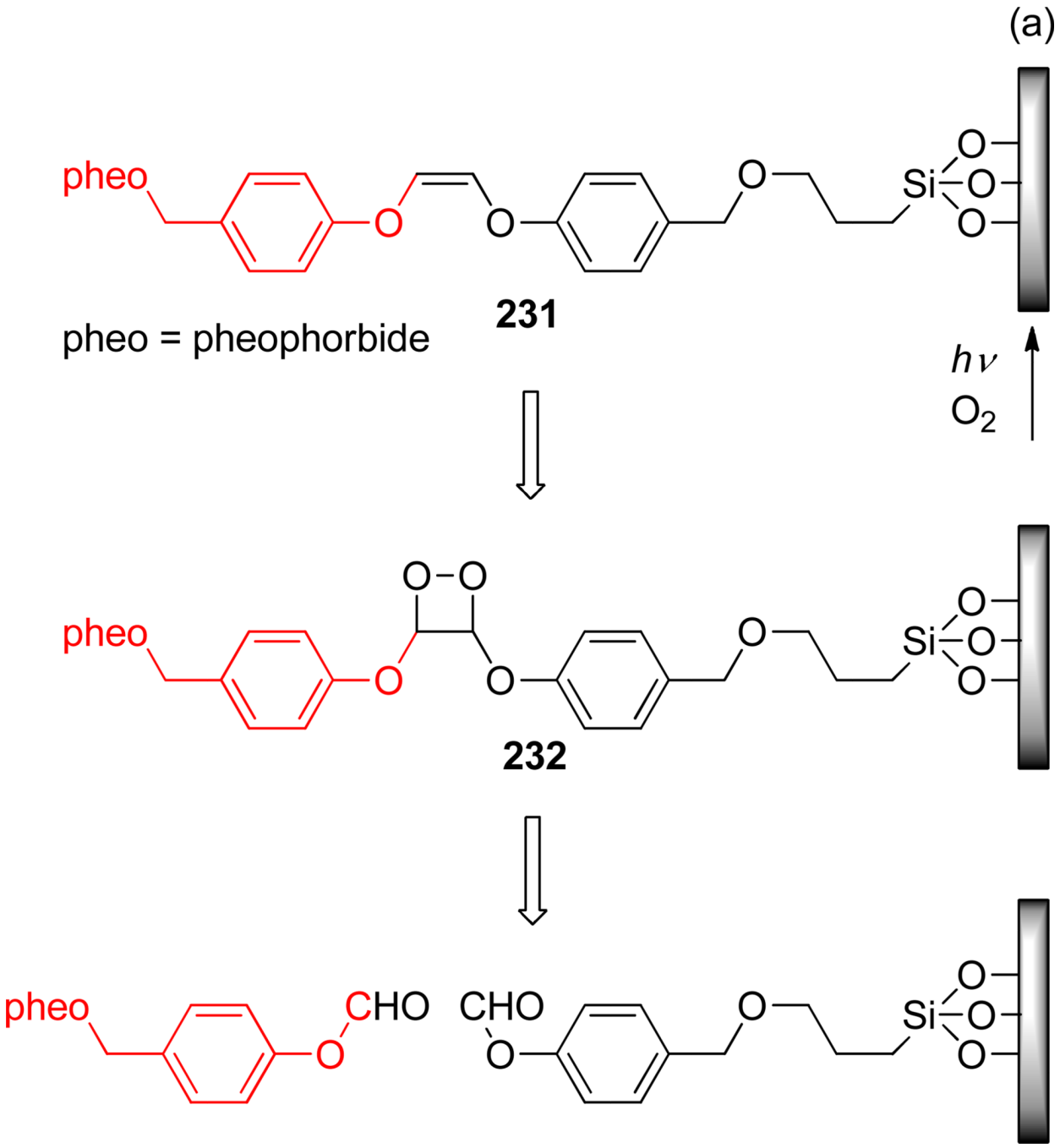
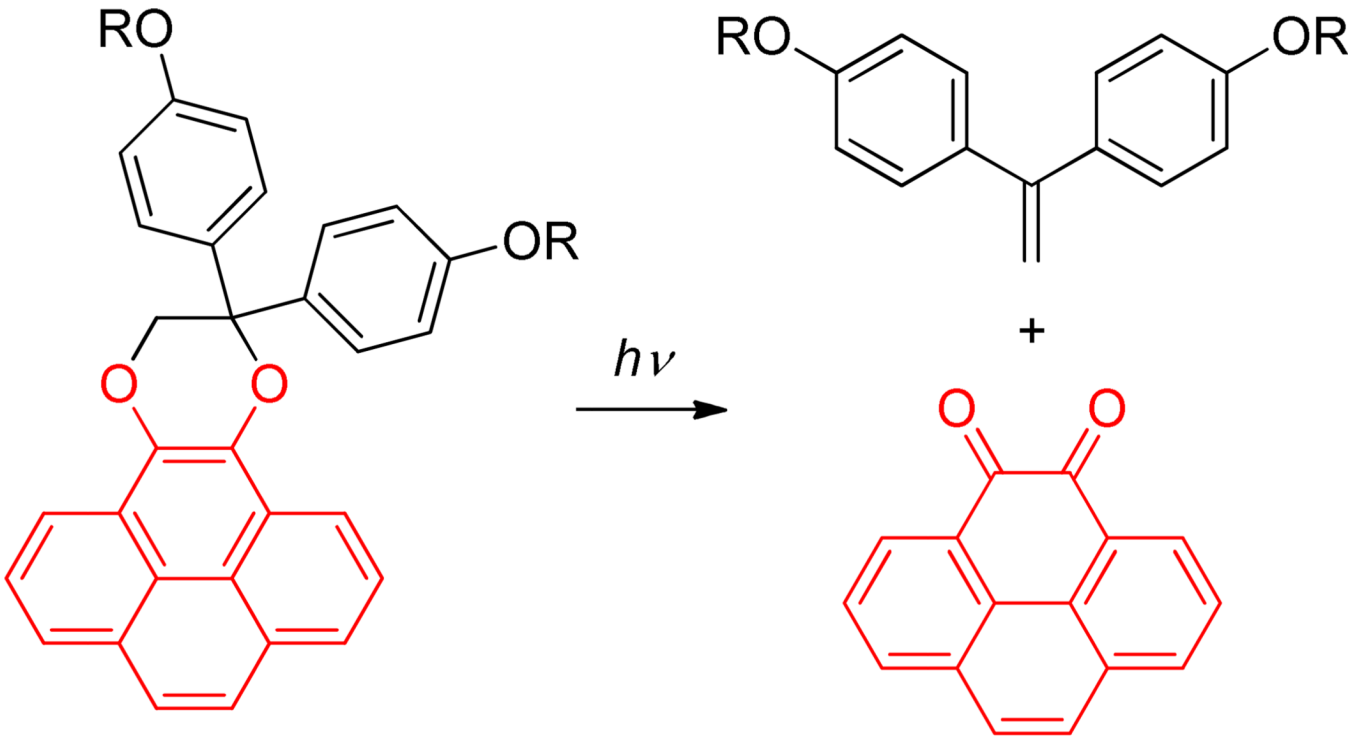
Scheme 102.
Photochemistry of Pyronine[409]



Scheme 103.
[2+2] Photocycloaddition of 7-Hydroxy-1,1-dimethylnaphthalenone[410]



Scheme 104.
Photosensitizer Drug Delivery (a: optical fiber equipped with porous Vycor glass)[411]



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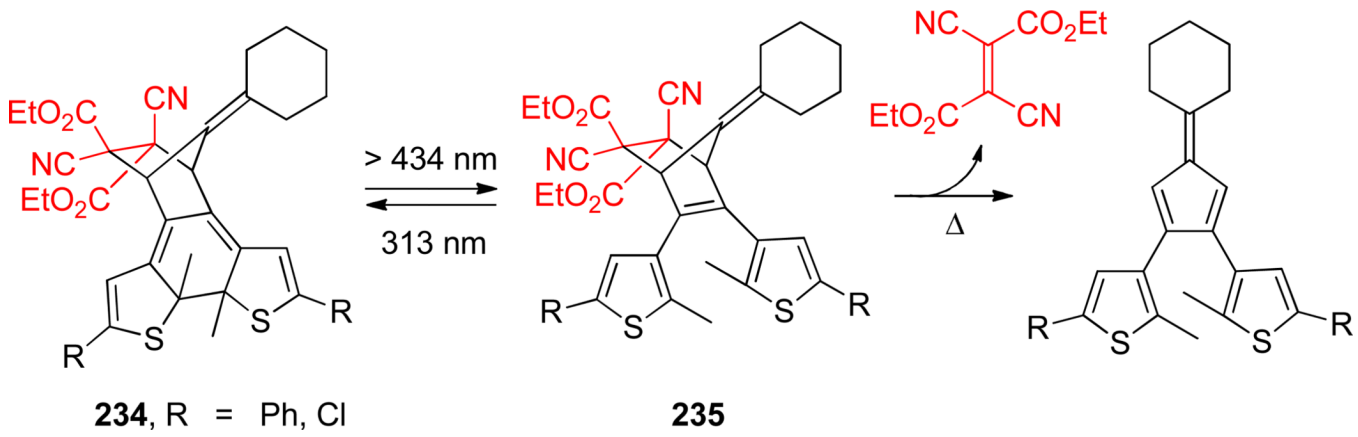
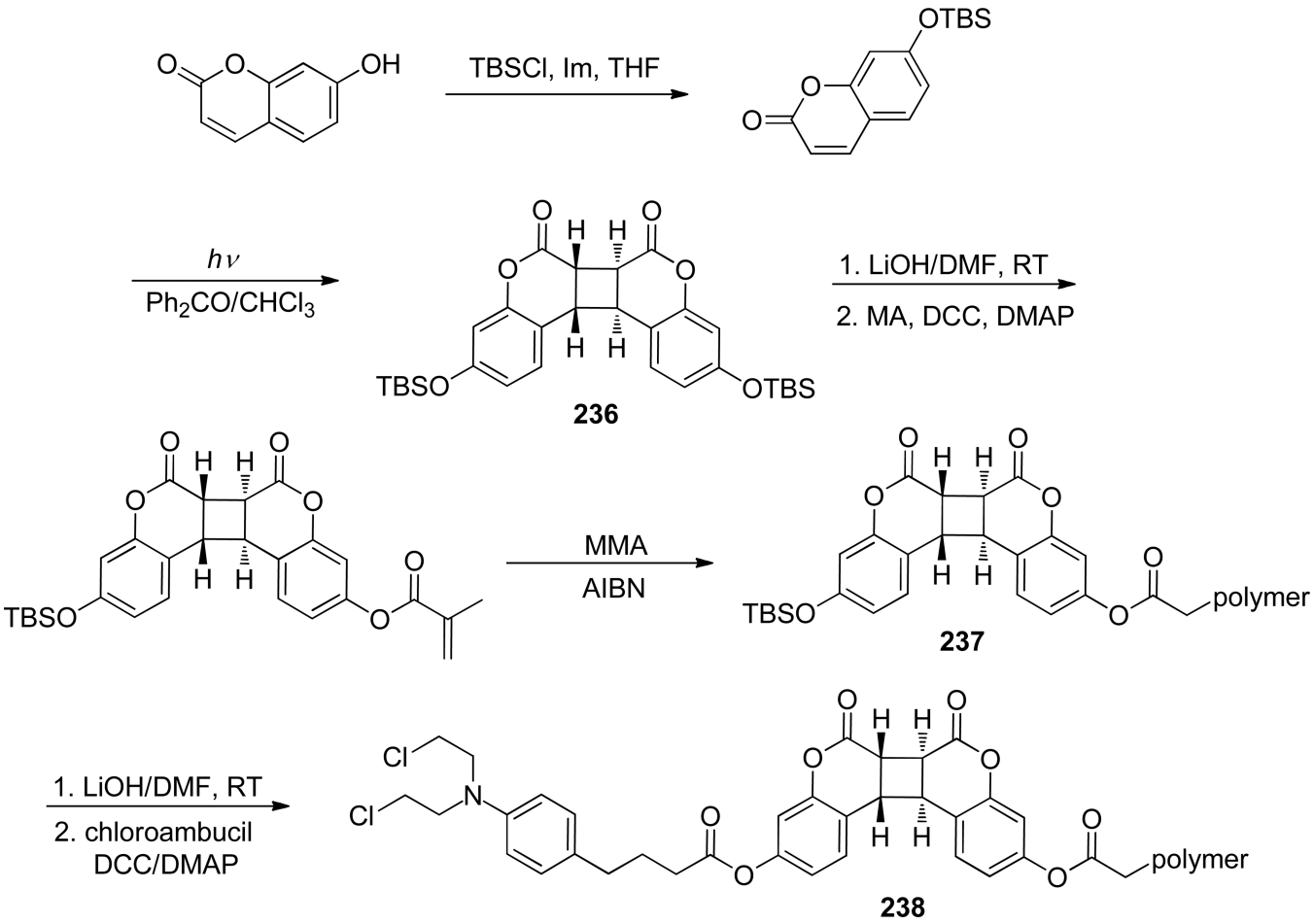
Scheme 105.
Photorelease of *o*-Quinones from Pyrene Dihydrodioxin[412a]

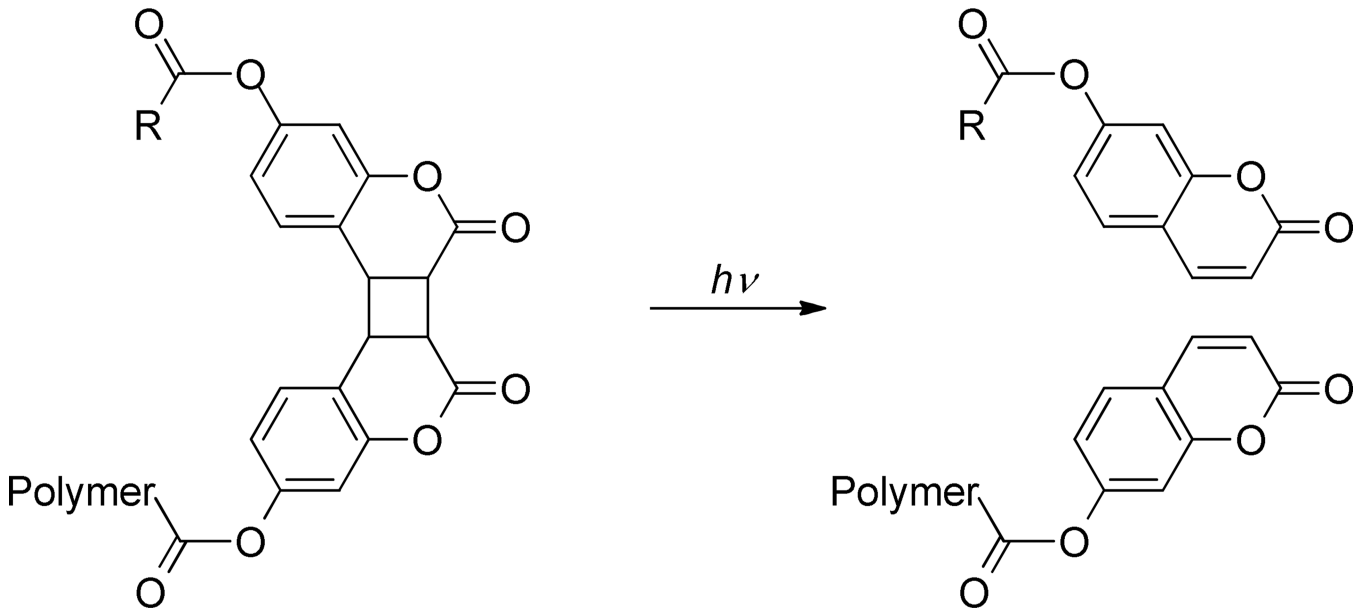


234, R = Ph, Cl **235**

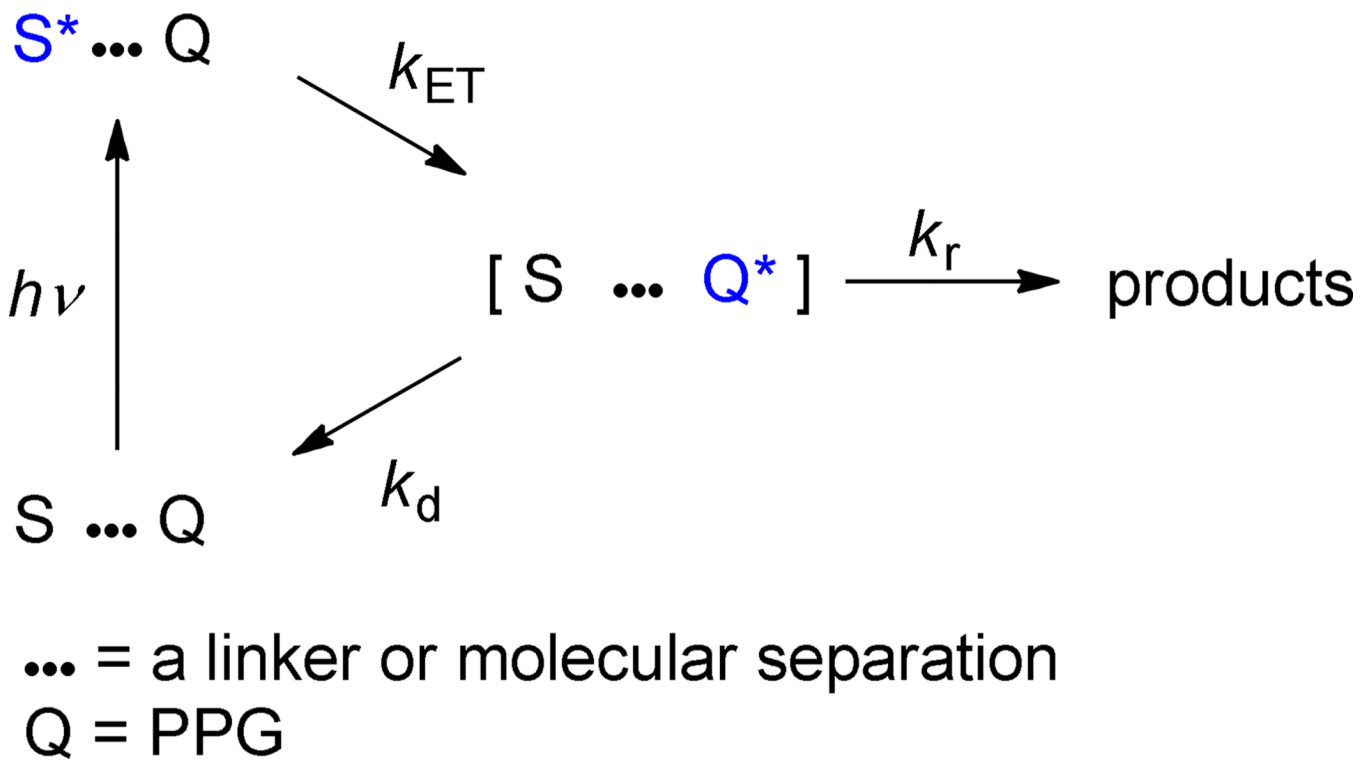
Scheme 106.
Sequential Photorelease Using a Molecular Switch[414]



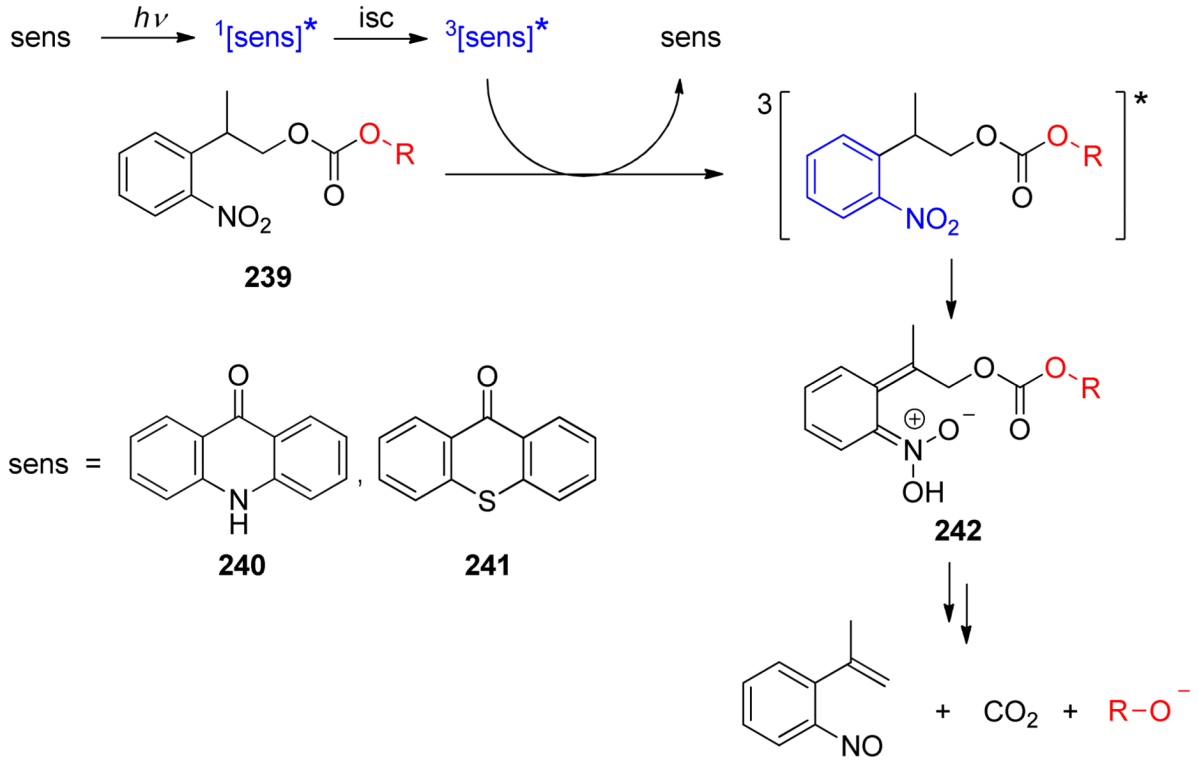
Scheme 107.
Immobilization of Chloroambucil on Polymer Support via a Photolabile Linker[416]



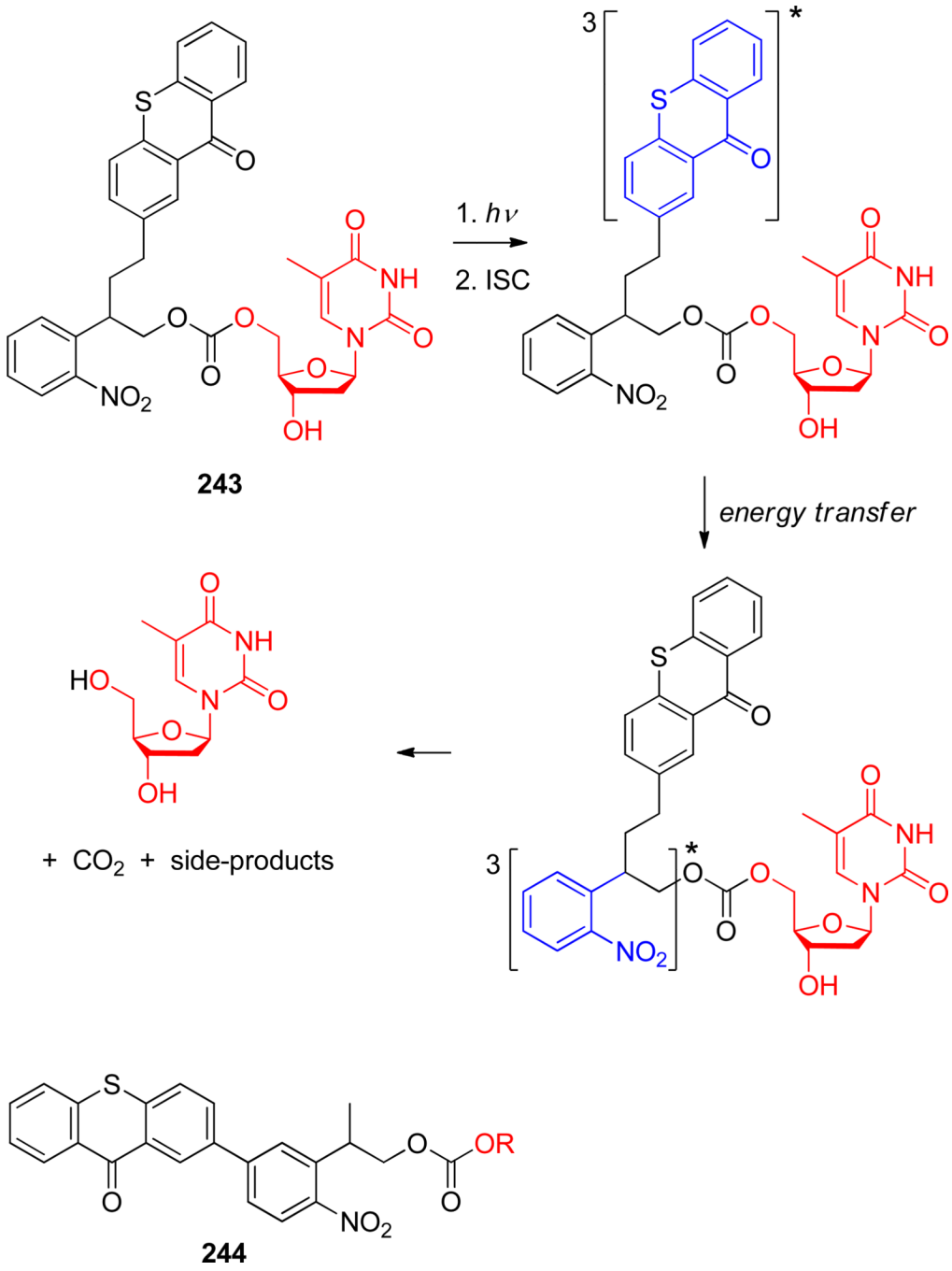
Scheme 108.
Photorelease via [2+2] Cycloreversion[417]



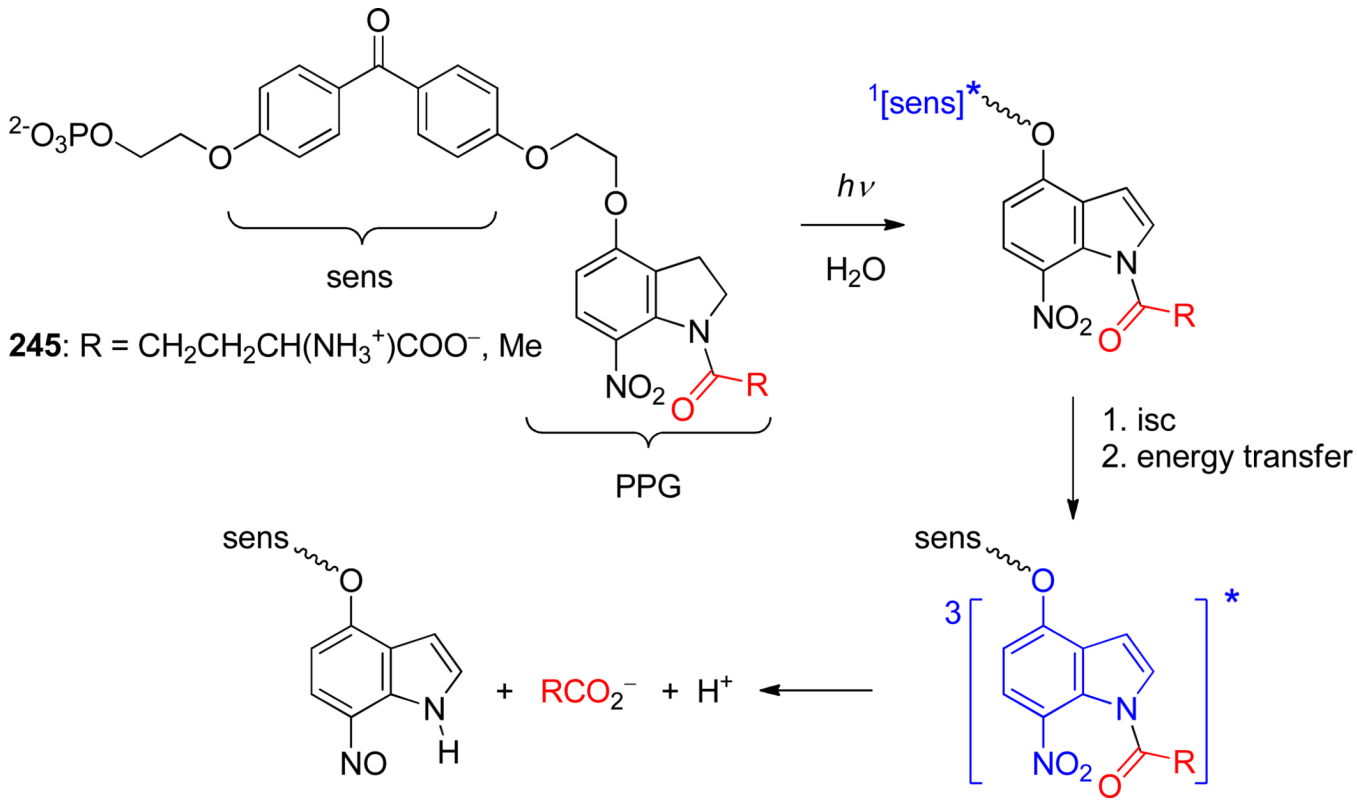
Scheme 109.
Photoinduced Energy Transfer (Blue color depicts an electronic excitation).



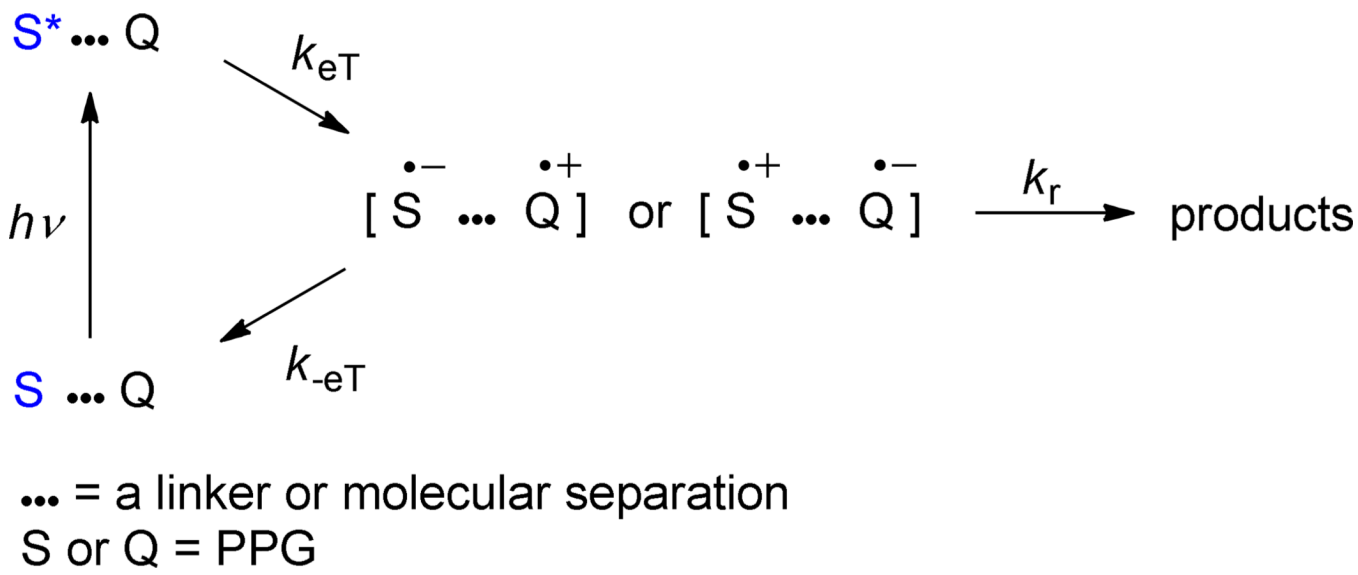
Scheme 110.
Intermolecular Triplet Sensitization of the 2-(2-Nitrophenyl)propyl Chromophore[418]



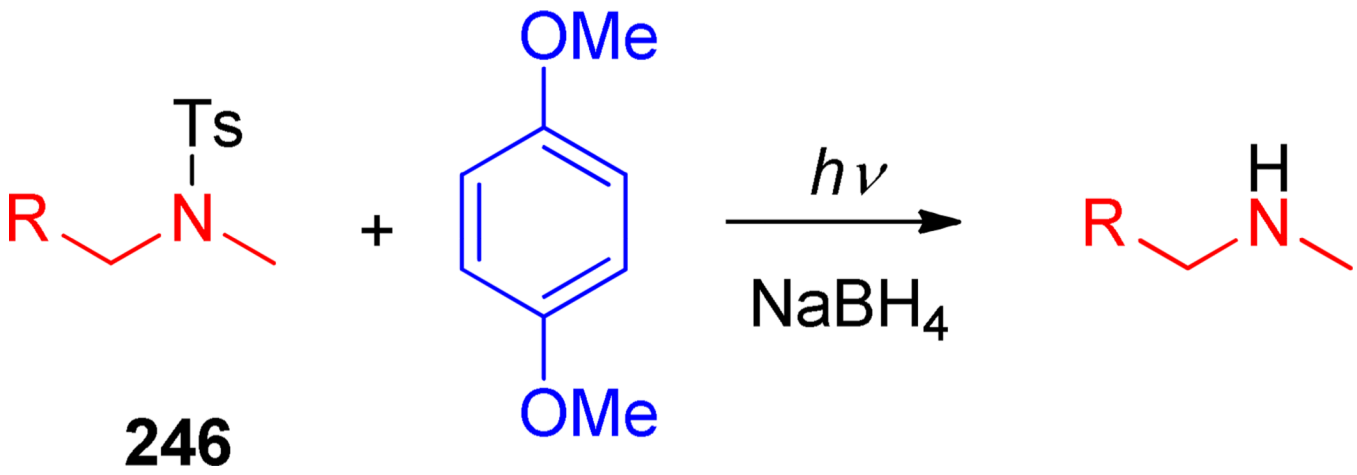
Scheme 111.
Intramolecular Triplet Sensitization of the 2-(2-Nitrophenyl)propyl Chromophore



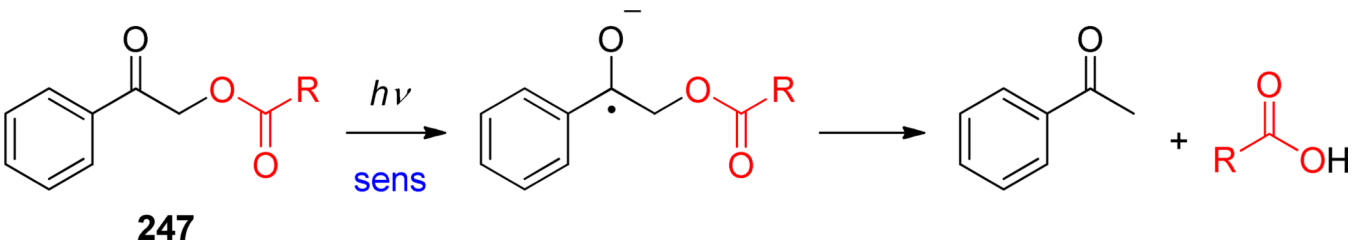
Scheme 112.
Antenna-Sensitized 1-Acyl-7-nitroindoline System[247–248]



Scheme 113.
Photoinduced Electron Transfer (blue color depicts a sensitizer)



Scheme 114.
Photosensitized Fragmentation of Tosylamides[422]



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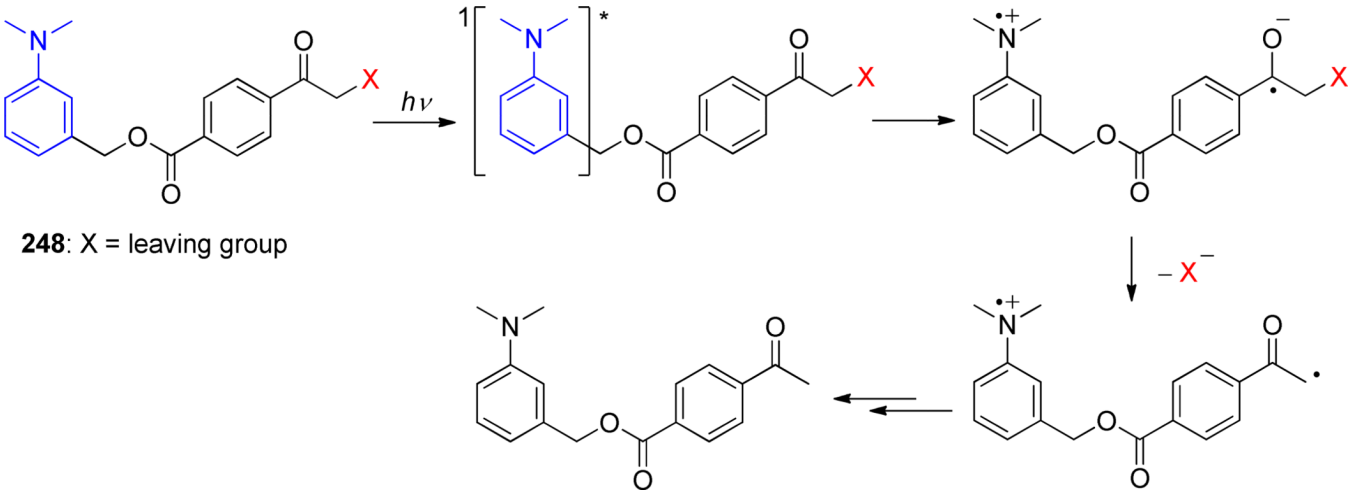
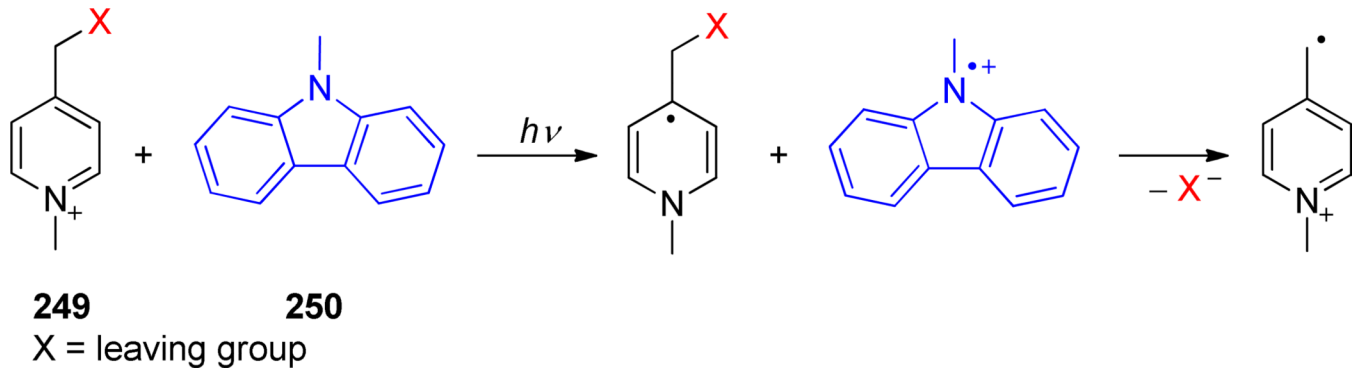
Scheme 115.
Photosensitized Release of Carboxylic Acids from Phenacyl Esters[430]



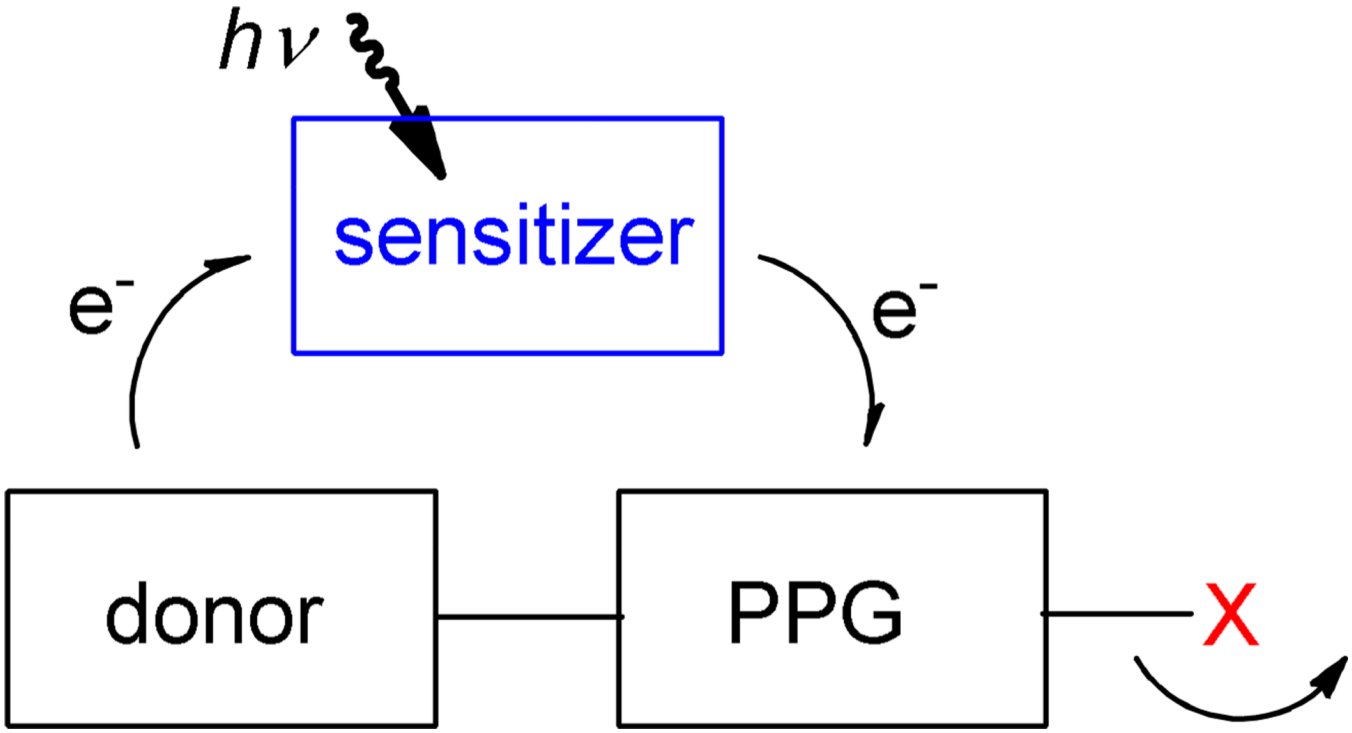
Scheme 116.
Bimolecular Sensitization of Phenacyl Esters[343a]



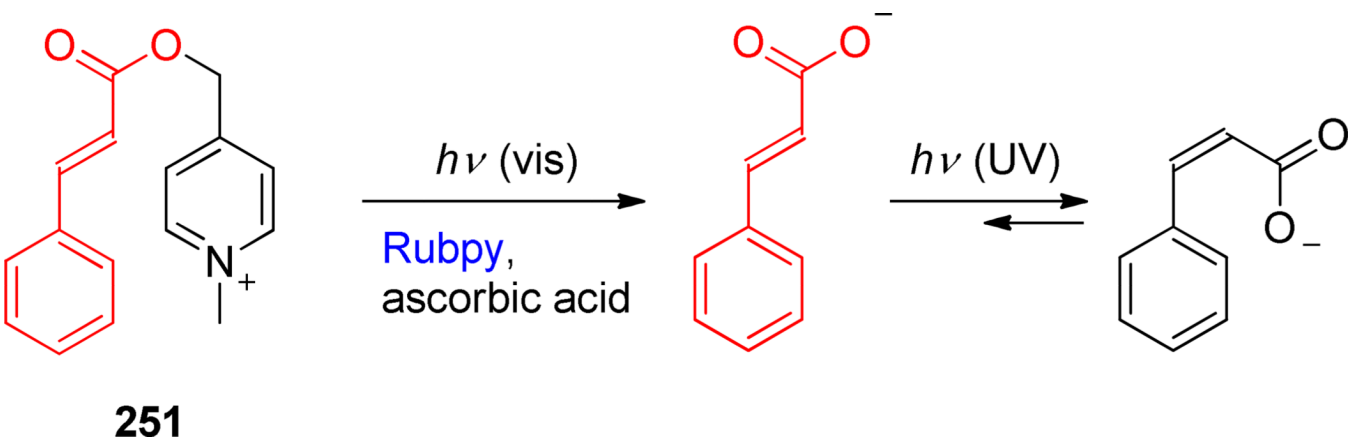
249 **250**

X = leaving group

Scheme 117.
The 4-Pyridylmethyl Group[343b]



Scheme 118.
Photorelease via Mediated Electron Transfer



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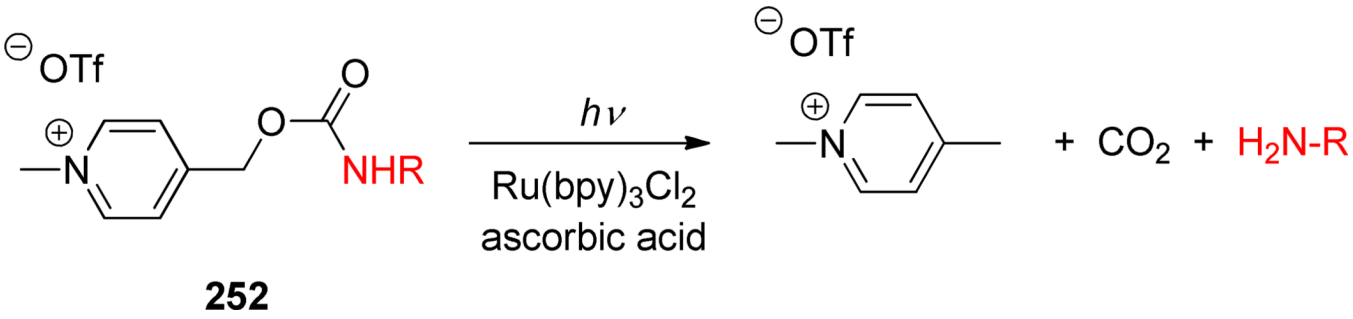
Scheme 119.
Orthogonal Photorelease and Photoisomerization[437]



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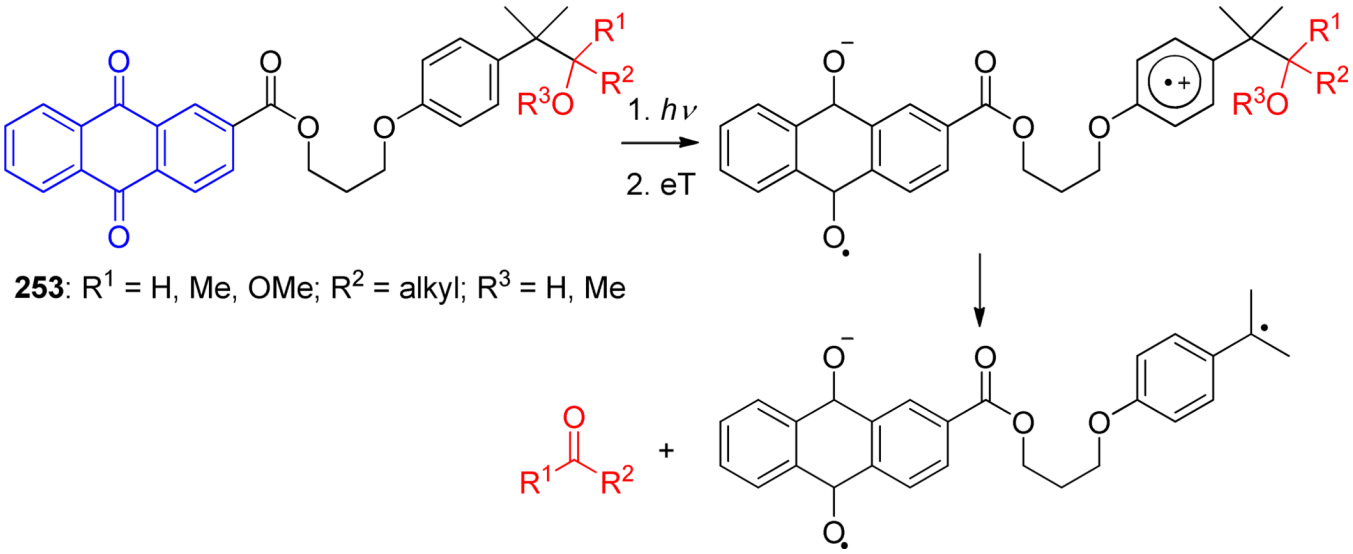
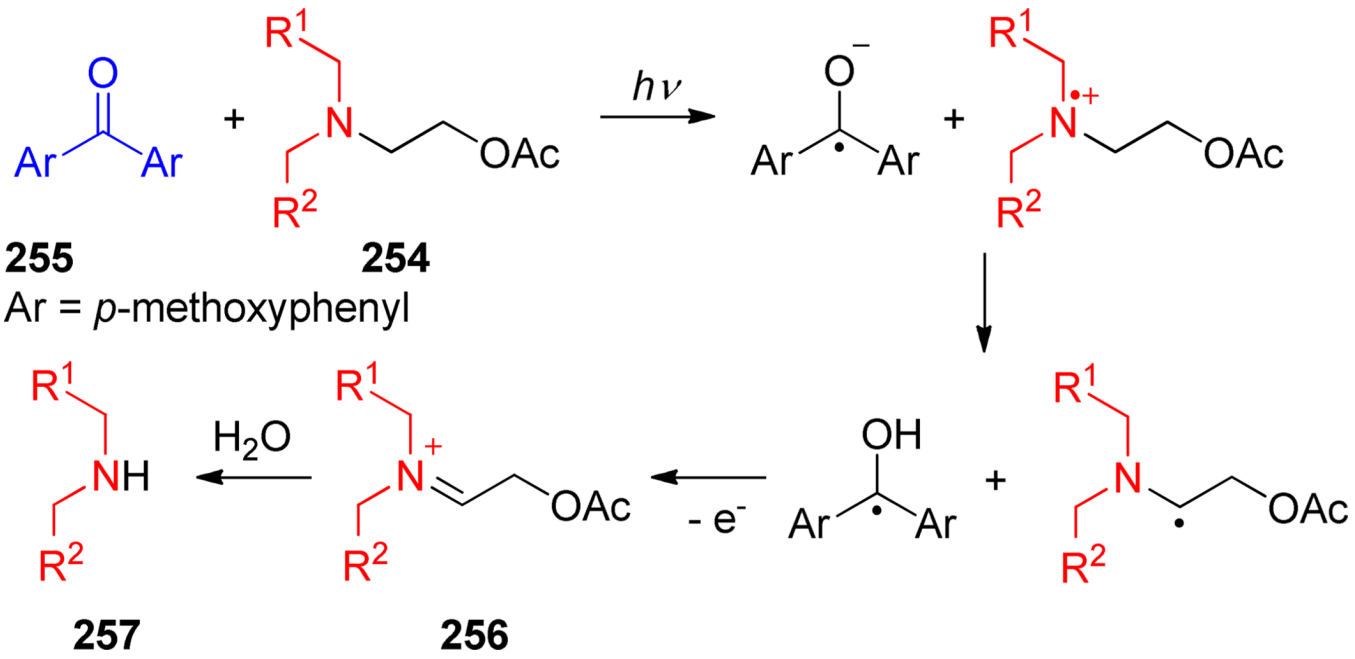
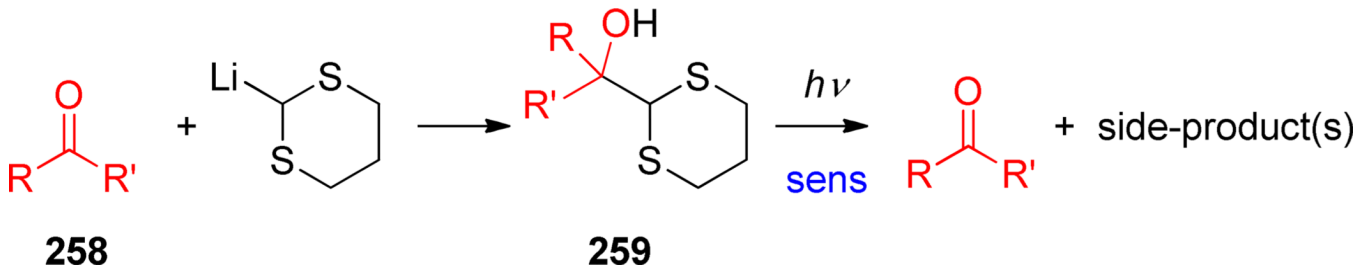
Scheme 120.
Visible-Light Deprotection of *N*-Methylpicolinium Carbamates[438]



Scheme 121.
Intramolecular Sensitization of the Phenethyl Alcohol/Ether Group[440]

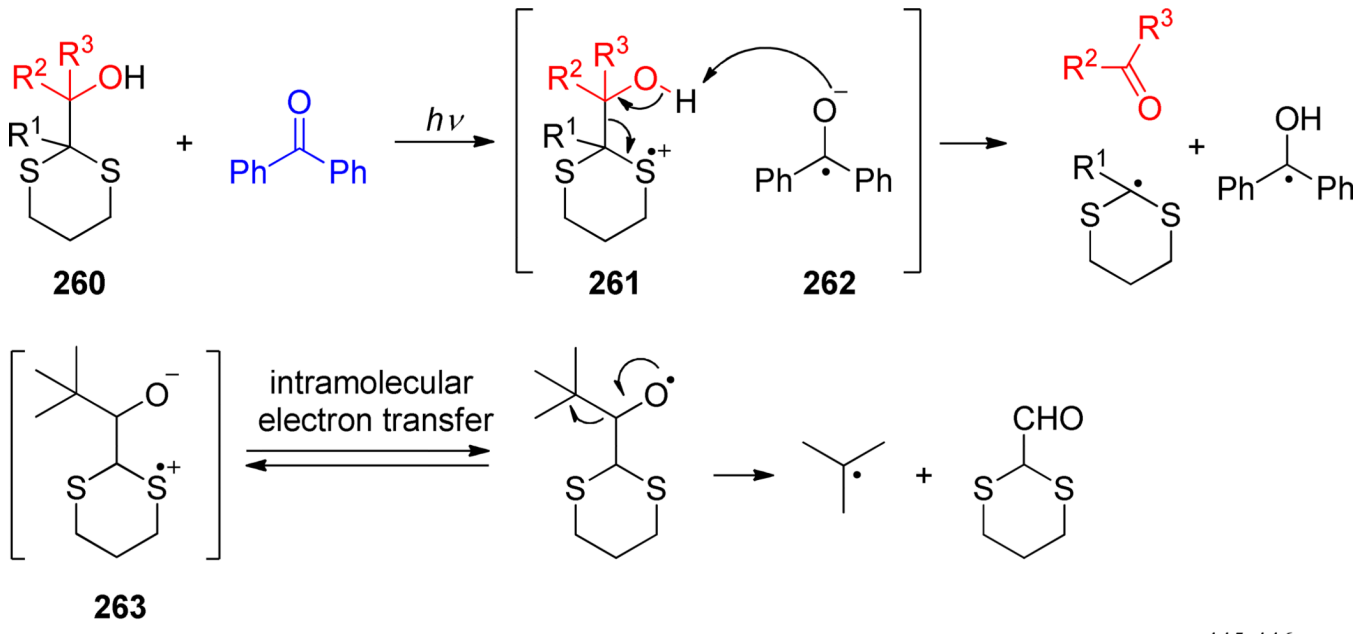


Scheme 122.
Sensitization of Acetoxyethyl Derivatives[441]

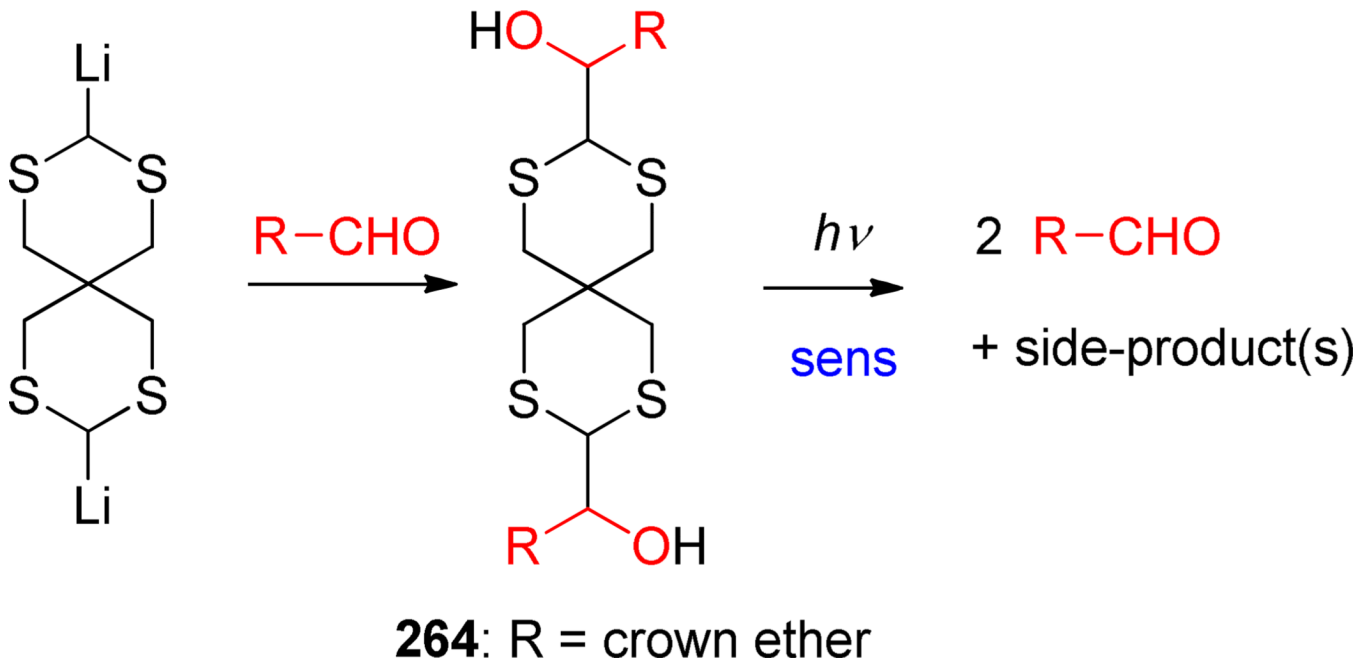


258 **259**

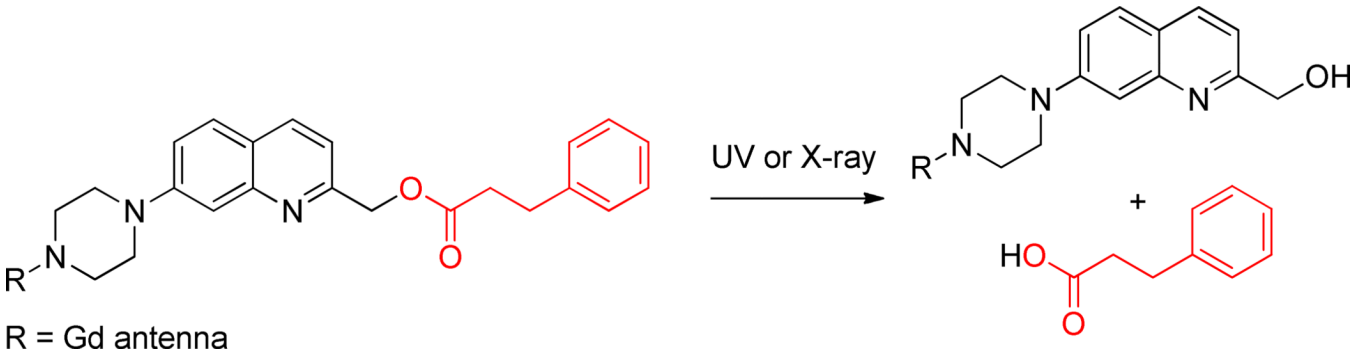
Scheme 123.
Photochemistry of Dithiane Moiety[443]



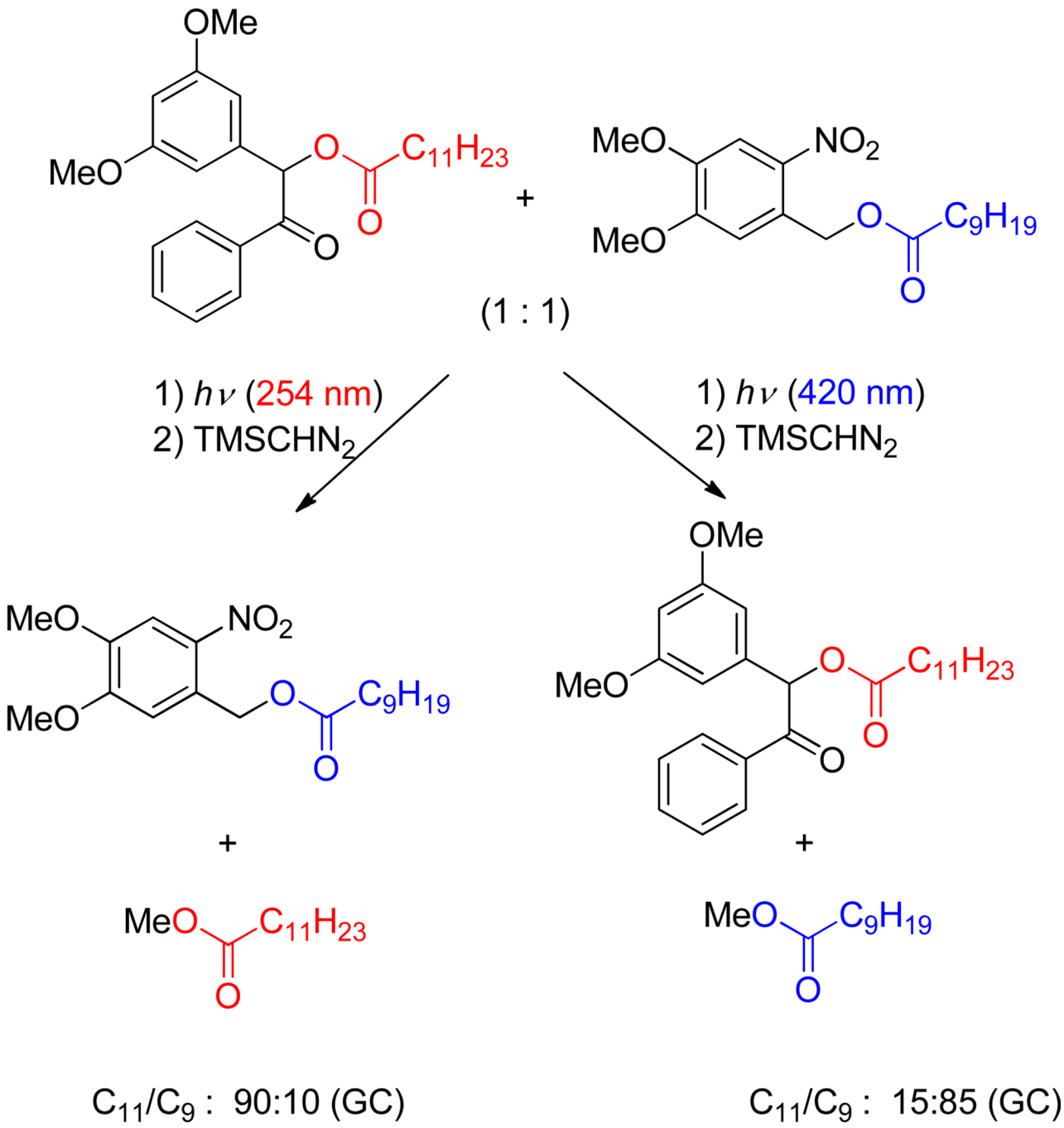
Scheme 124.
The Mechanism of Oxidative Deprotection of Dithiane Moiety[445–446]



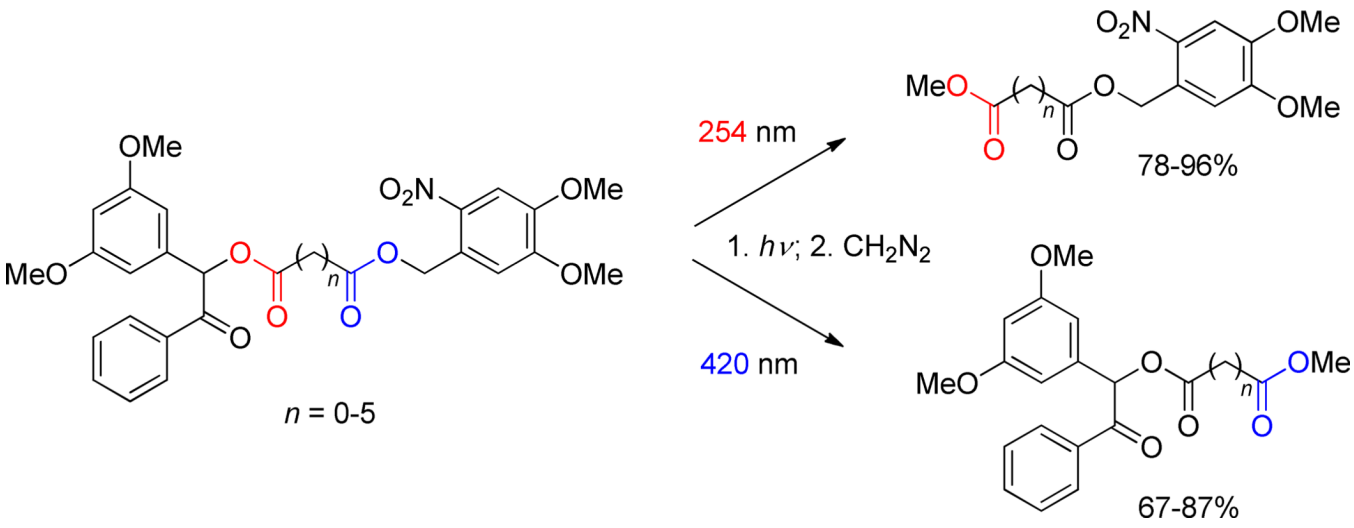
Scheme 125.
Photochemistry of Dithiane-spiro-crown Ethers[448a]



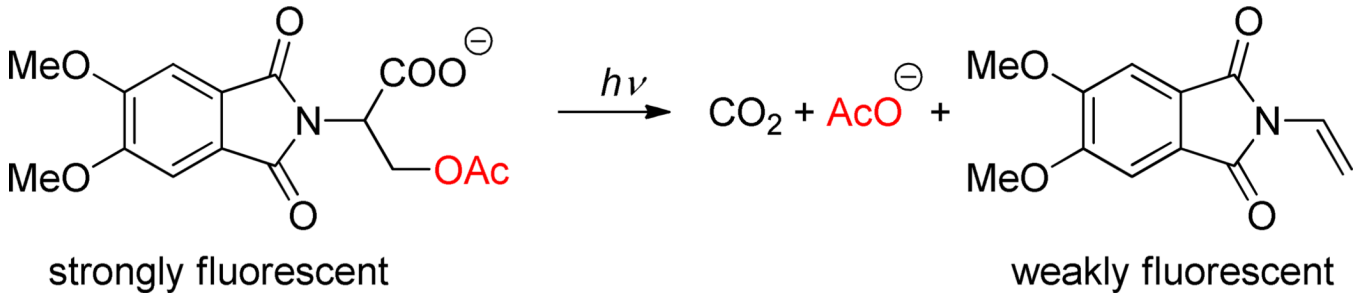
Scheme 126.
Photo- and Radiolysis of Caged Hydroxymethyl Quinolone Derivatives[459]



Scheme 127.
Example of Intermolecular Chromatic Orthogonality[208,498]

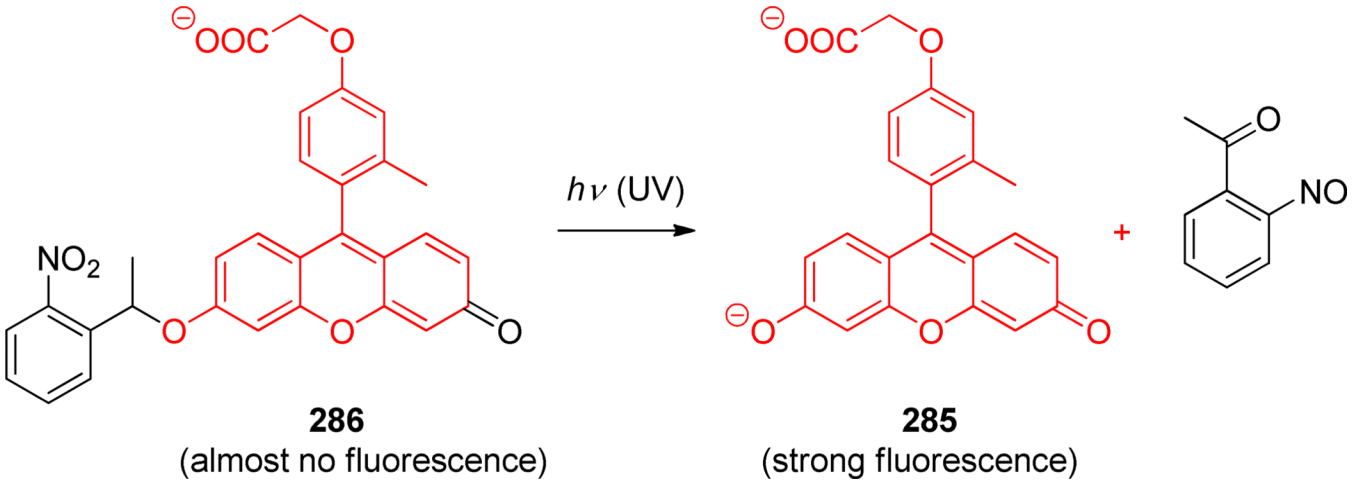


Scheme 128.
Example of Intramolecular Chromatic Orthogonality[499]

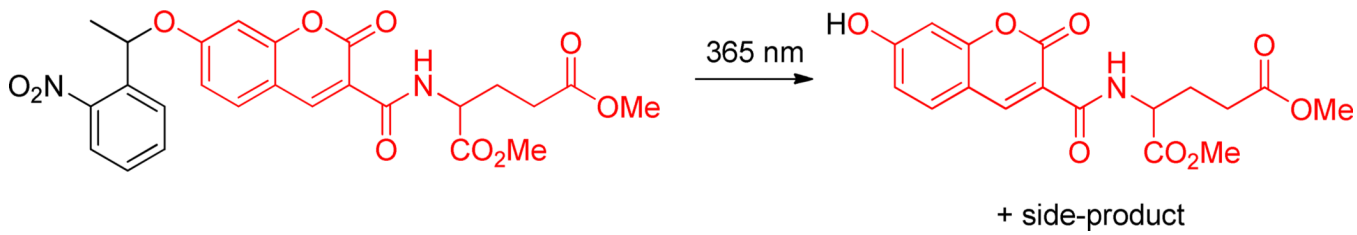


Scheme 129.

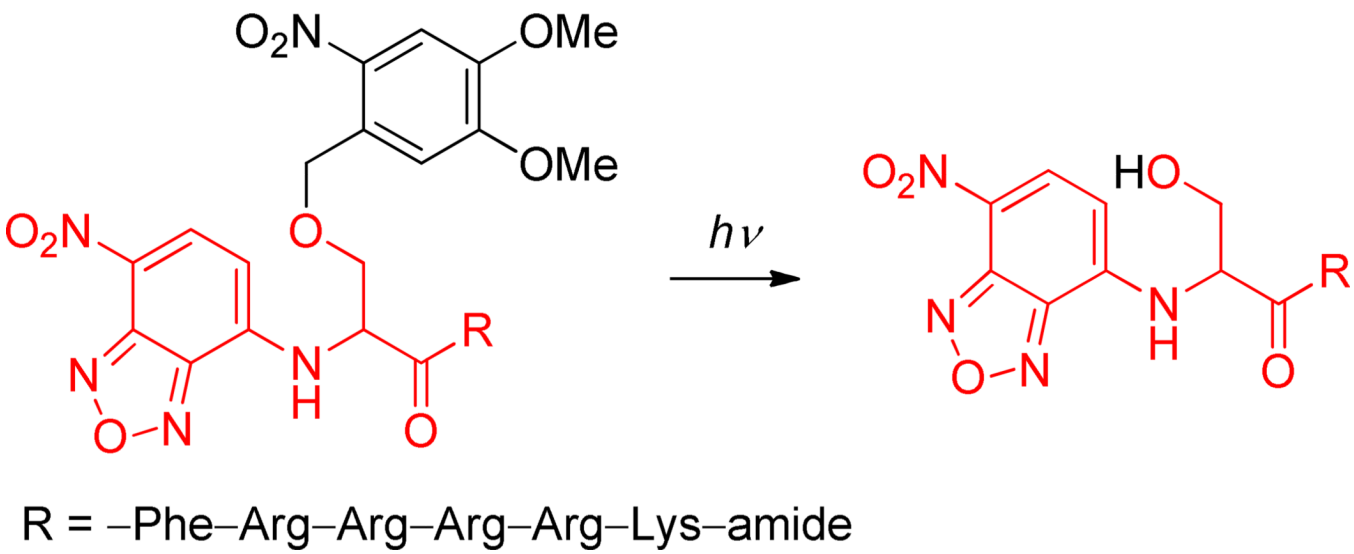
The "Armed" Phthalimide (λ_{max} = 340 nm, exhibits strong fluorescence, λ_{max} = 513 nm, in aqueous media at pH = 7. Irradiation liberates acetate and CO_2, and the fluorescence decreases)[378]



Scheme 130.
Deprotection of Mono-Caged Tokyo Green (its fluorescence is quenched by intramolecular electron transfer in the excited singlet state)[508]

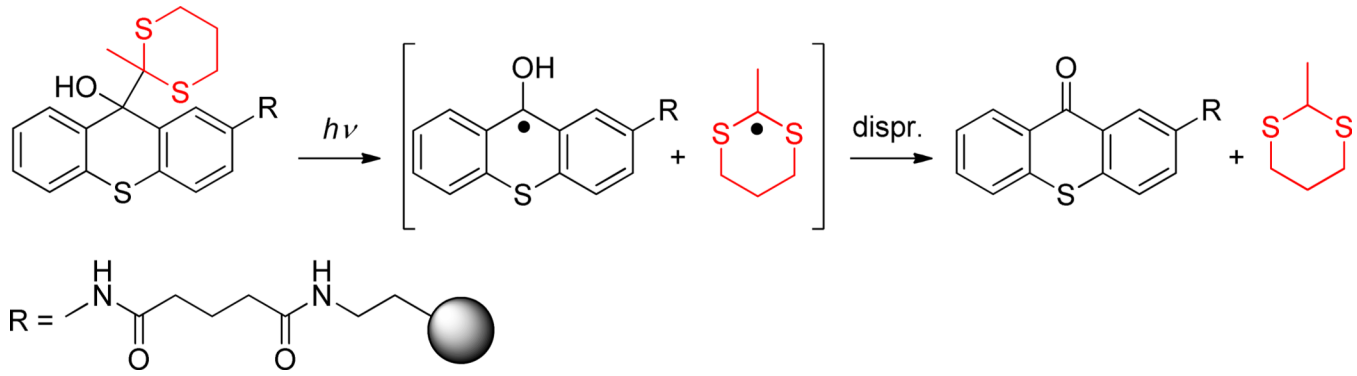


Scheme 131.
Caged Coumarin[491]

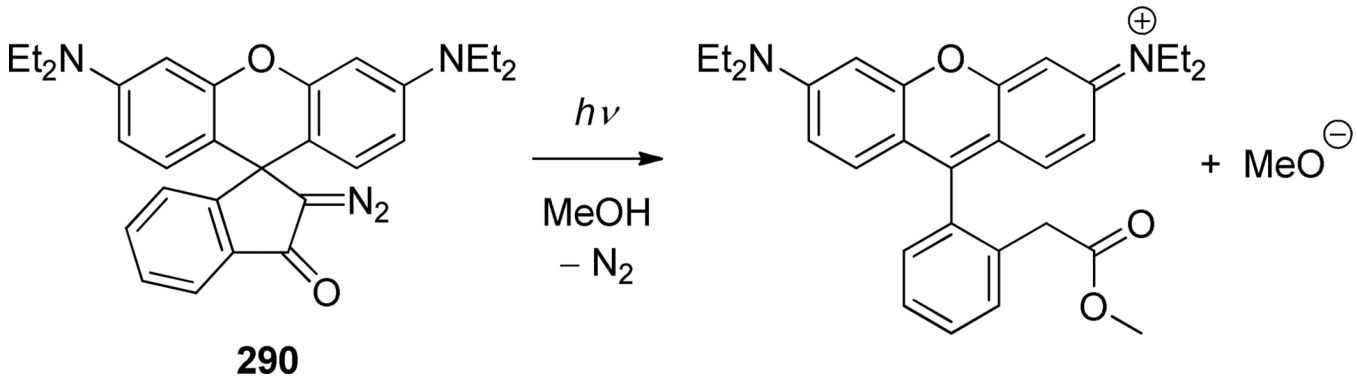


R = –Phe–Arg–Arg–Arg–Arg–Lys–amide

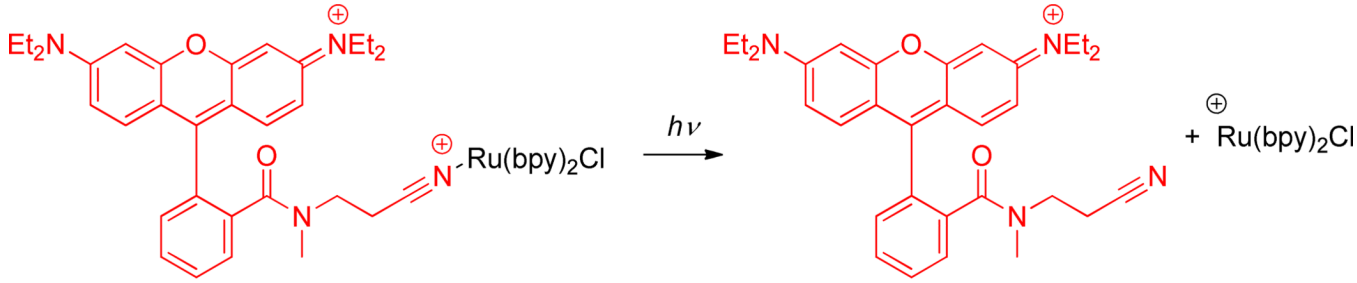
Scheme 132.
Fluorescent Reporter of Protein Kinase Activity[515]



Scheme 133.
Caged Thioxanthone[455]



Scheme 134.
Photochemistry of Caged Rhodamine (a Wolff Rearrangement)[517]



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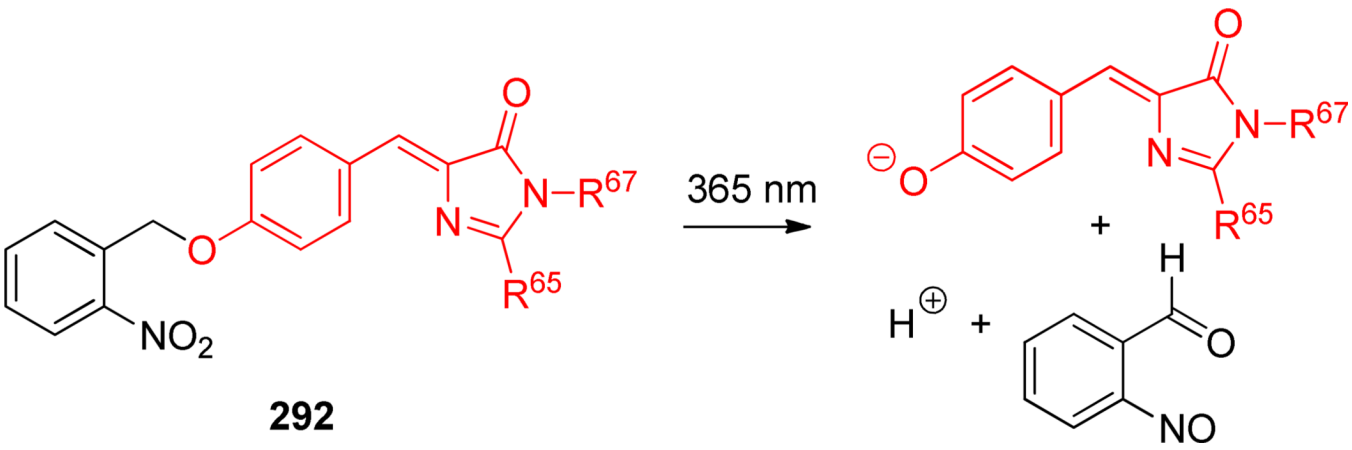
Scheme 135.
Photochemistry of Caged Rhodamine[356]



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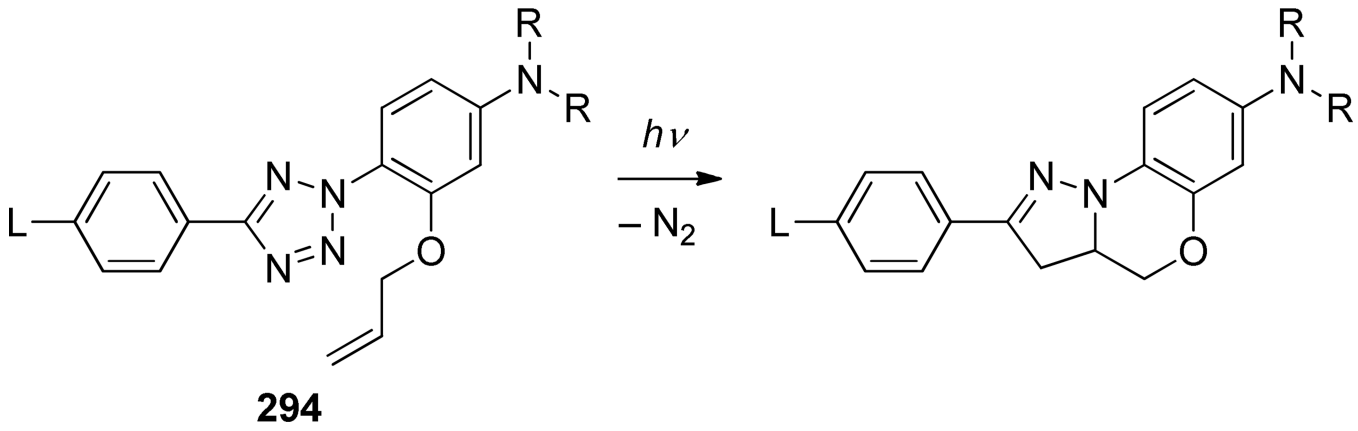
Scheme 136.
o-Nitrobenzyl-Caged GFP[519]



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Scheme 137.
Intramolecular Photoclick Reaction[526]

Table 1

Photoremovable Protecting Groups

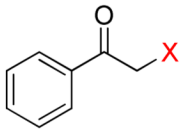
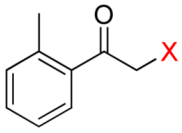
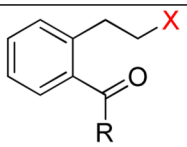
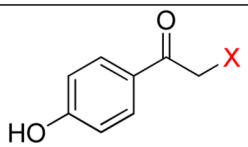
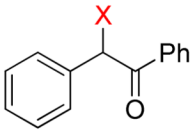
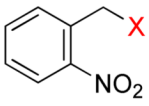
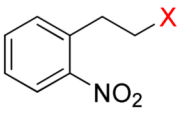
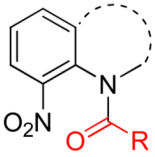
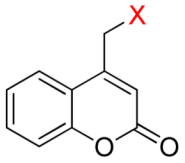
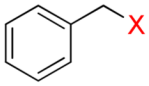
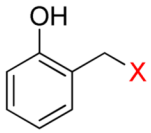
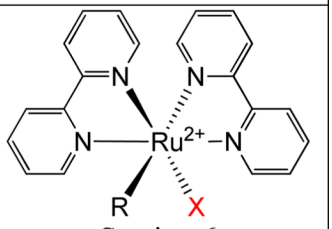
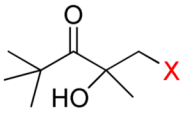
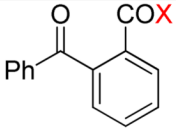
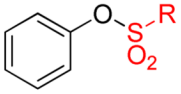
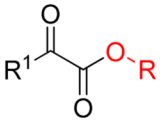
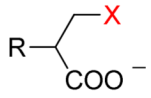
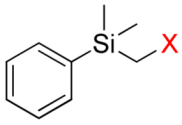
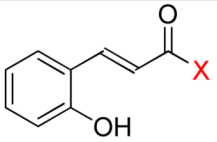
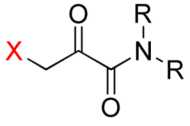
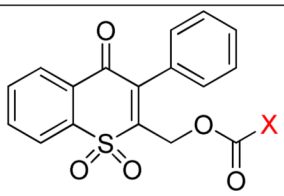
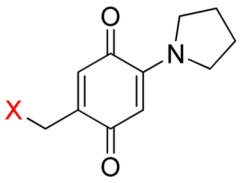
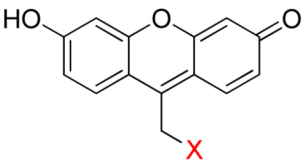
 Section 2.1	 Section 2.2	 Section 2.2	 Section 2.3
 Section 2.4	 Section 3.1	 Section 3.2	 Section 3.3
 Section 4	 Section 5.1	 Section 5.2	 Section 6
 Section 7.1	 Section 7.2	 Section 7.3	 Section 7.4
 Section 7.5	 Section 7.6	 Section 7.7	 Section 7.8
 Section 7.9	 Section 7.10	 Section 7.11	 Section 7.12

Table 2

Photophysical Properties of Acetophenone[a]

solvent	E_S / kJ mol^{-1} [b]	τ_S / ps [c]	Φ_f [d]	Φ_T [e]	E_T / kJ mol^{-1} [f]	Φ_p [g]
non-polar	330 [30b]	25 [33]	<1×10^{-6} [34]	1 [35]	310 [36]	4 × 10^{-4} [37]
polar	338 [36]	39 [33]	–	1 [35]	311 [36]	–

[a] Photophysical properties of many other aromatic ketones can be found in the Handbook of Photochemistry.[38]

[b] Lowest excited singlet state (S_1) energy.

[c] The lifetime of S_1

[d] Fluorescence quantum yield.

[e] ISC quantum yield.

[f] Lowest triplet state (T_1) energy.

[g] Phosphorescence quantum yield (23 °C isooctane).

Table 3

2,5-Dimethylphenacyl (**8**, DMP) Photoremovable Group

leaving group, X (protected species)	solvent	Quantum yield, Φ	chemical yield of HX release / %	k_{app}/s^{-1} [a]
Cl	benzene	0.11[56a] (0.12)[54a]		4.4×10^{6} [61]
	methanol	0.76[56a] (0.78)[54a]		4.4×10^{4} [61]
OC(=O)R (carboxylic acids)	benzene	0.18–0.25[54b,57b]	85–95[54b]	~2 [57b]
	methanol	0.09–0.14[57b]	92[54b]	4.5×10^{2} [57b]
$OP(=O)(OR)_2$ (phosphates)	benzene	0.09[54a]		~2 [54a]
	methanol	0.71[54a]	94[54a]	5×10^{4} [54a]
$OS(=O)_2R$ (sulfonic acids)	benzene	0.16–0.19[54a]		
	methanol	0.68[54a]	90–93[54a]	4×10^{4} [54a]
OC(=O)OR (alcohols)	cyclohexane	0.36–0.51[58]	>70[58]	*b*
	methanol	0.09–0.20[58]		*b*
$OC(=O)NR_2$ (amines)	cyclohexane	0.054–0.089[59]		*b*
	acetonitrile	0.035–0.070[59]	97[59]	*b*
	methanol	0.027–0.061[59]		*b*

[a] Appearance rate constant of the leaving group, calculated as $k_{app} = 1/\tau_{enol}$.

[b] Slow, presumably <1 ms^{-1}.

Table 4

Disappearance quantum yields, pK_a's, and rates of release for different leaving groups (X) for pHP X (**24**) arranged according to the pK_a of HX.

X (released substrate)	λ_{max} (log ε)[a] (pHP X)	pK_a (HX)	Φ_{-X}[b]	$k_r/10^8$ s^{-1}[c]	ref.
mesylate		−1.54	0.93	50	85d, 93,114
tosylate		−0.43	1.00	100	85d,93,114
OPO_3Et_2	271 (4.18)	2.12	0.4	12.	82,85a-c,96a,99,114
Glu	273 (3.94)	4.33	0.14	1.9	83c,97b,c
Ala·Ala	282 (4.12)	3.4	0.27	1.8	83c,112a
bradykinin	282 (4.07)	3.4	0.22	1.8[e]	83c,112a
p-$CF_3C_6H_4CO_2^-$		3.69	0.2	3.2	9u,93,114
formate		3.75	0.94	14.	9u1c
benzoate		4.21	0.32	2.8	9u,73,85c,93,114
acetate	279 (4.09)	4.76	0.4	N/A[f]	85a-c,95–96
GABA	282 (4.16); 325	4.76	0.2	6.2	83c,85e,94,97b,c
RPO_3S^-[d]		5.3	0.21	N/A	111
OPO_3^{-2}	280 (4.48)	7.19	0.38	N/A	82
GTP		7.4	N/A	N/A	91–92
ATP	253 (4.3); 320 (2.70)	7.4	0.37	68	82,83c,90
p-$CNC_6H_4O^-$		7.8	0.11	0.76	9u,93
RS^- [d]		8.4	0.085	N/A	111,113,115
$C_6H_5O^-$		9.89	0.04	1.0	9u,93
HO^-		15.7	<0.01	N/A	95

[a] In H_2O unless otherwise noted.

[b] Appearance efficiencies were identical within experimental error (± 5%). See Table 5 for examples.

[c] The rates are derived from several sources and conditions vary. The H_2O content was between 10% and 50% causing small variations in the quantum yields/rates (see text).

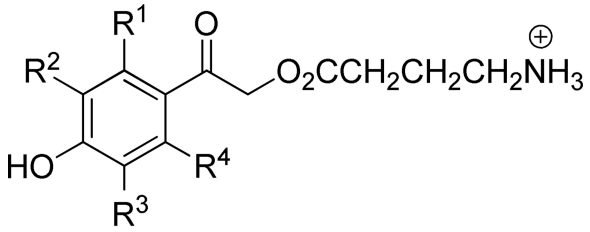
[d] Decaging of the catalytic subunit C199A/C343A of PKA (Protein Kinase A) at Thr-197.[111]

[e] Assumed to be the same as the model, Ala·Ala.

[f] N/A = not available.

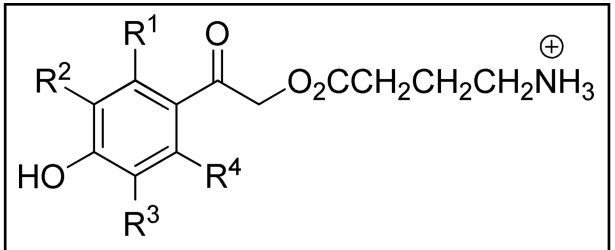
Table 5

The effects of substituents and pK_a on quantum yields[a] for the substituted pHP GABA **31** in unbuffered H_2O.[b] Entries are arranged in the order of decreasing pK_a of the substituted pHP chromophore. [94]



31

31	pK_a	Φ_{dis}[c]	Φ_{GABA}	$\Phi(25)$[d]	Φ_{dis} (Ac or DEP)[e]
3,5-CH_3	8.2	0.15	0.14	0.13	
3-CH_3	8.1	0.15	0.14	0.13	
2-CH_3	8.0	0.11	0.1	0.1	
3-OCH_3	7.9	0.07	0.06	ND[e]	0.39 (DEP)
R^1–R^4 = H	7.8	0.20	0.19	0.16	0.30 (Ac) 0.40 (DEP)
3,5-OCH_3	7.8	0.03	0.03	ND	0.44 (DEP)
2-F	7.2	0.28	0.27	0.26	
2,6-F	6.8	0.16	0.16	0.15	
3-F	6.7	0.16	0.15	0.15	
3-OCF_3	6.5	0.09	0.09	0.07	
2,3-diF	5.9	0.24	0.24	0.22	
2,5-diF	5.7	0.22	0.21	0.2	
3-CF_3	5.5	0.17	0.16	0.14	
3,5-F	5.3	0.11	0.11	0.1	
3-CN	5.2	0.42	0.35	0.39	0.17 (Ac)
2,3,5-triF	4.5	0.08	0.07	0.06	



31

31	pK_a	Φ_{dis} [c]	Φ_{GABA}	Φ(25) [d]	Φ_{dis} (Ac or DEP) [e]
tetra-F	3.9	0.11	0.1	0.1	

[a] All runs were low conversions to products (<5%); standard deviations were < ± 0.02.

[b] Unbuffered 18 MΩ ultrapure H_2O.

[c] Disappearance quantum yield when GABA is the leaving group.

[d] Quantum yield for the substituted phenylacetic acid (**25**).

[e] Disappearance quantum yield when Ac (acetate) or DEP (diethyl phosphate) is the leaving group.

[e] ND = not determined.[94]

Table 6

Substituent effects on the quantum yields[a] as a function of pH for GABA release from **31** at 300 nm in buffered $CH_3CN–H_2O$. Entries are arranged according to decreasing pK_a of the substituted pHP GABA.[94]

pHP GABA	pK_a	Φ_{dis} pH 5.0[b]	Φ_{dis} pH 7.3[c]	Φ_{dis} pH 8.2[c]
3,5-$(CH_3)_2$	8.2	N/A	0.17	0.11
3-CH_3	8.1	N/A	0.15	0.08
parent	8.0	0.21	0.21	0.09
2-F	7.2	0.24	0.21	0.06
3-F	6.7	0.15	0.12	0.02
3-OCF_3	6.5	0.07	0.06	0.02
3-CF_3	5.5	0.24	0.12	0.08
3,5-F_2	5.3	0.08	0.05	0.02
3-CN	5.2	0.21	0.33[d]	0.19[e]
2,3,5,6-F_4	3.9	0.08	0.10	0.09

[a] Standard deviations were < ± 0.02.

[b] 0.01 M Ammonium acetate.

[c] 0.01 M HEPES, 0.1 M $LiClO_4$, pH 7.3.

[d] 0.01 M Ammonium acetate, pH 7.

[e] 0.01 M Ammonium acetate, pH 9.

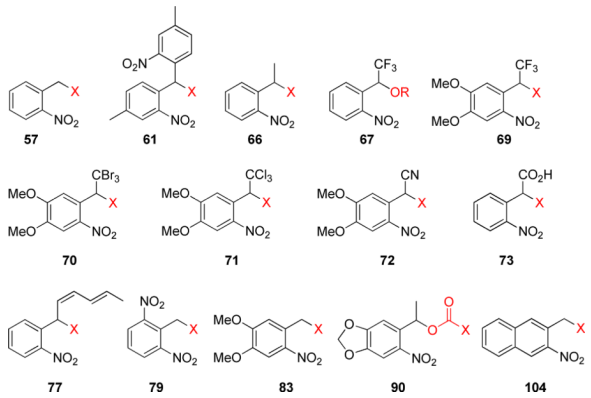
Table 7

Photolysis quantum yields for benzoin derivatives

PPG	X (leaving group)	medium (λ_{irr} / nm)	Φ	ref.
33	RCO_2	MeCN (366)	0.64	118
33	*c*-HexNHC(O)O	film (365)	0.028	142
38	RCO_2	MeCN-H_2O (350)	0.14	139
46	RCO_2	MeOH (313)	0.43	150

Table 8

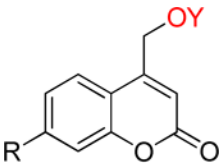
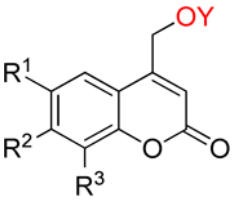
Photolysis Quantum Yields for Nitrobenzylic Derivatives

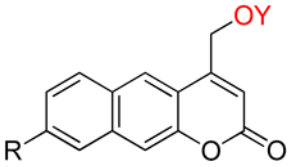
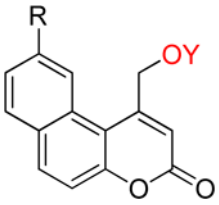
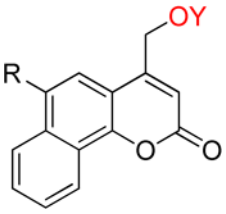
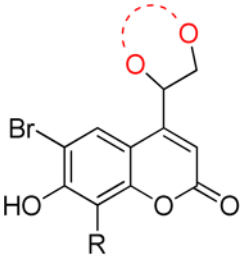


PPG	X (leaving group)	solvent (λ_{irr} / nm)	Φ	ref.
57 (oNB)	Thymidine-OCO_2	MeOH/H_2O, 1:1 (365)	0.033	226
57 (oNB)	*t*-BuCO_2	MeCN (254)	0.13	185
61	CH_3CO_2	MeCN (254)	0.2	168b
66	*t*-BuCO_2	polymer (254)	0.09	185
66	*t*-BuCO_2	MeCN (254)	0.64	185
66	*c*-Hex-$NHCO_2$	polymer (254)	0.11	186
67	choline-O	buffer, pH 7 (364)	0.7	189
67	sugar-O	buffer, pH 7 (364)	0.62	189
69	arsenocholine-O	buffer, pH 7 (364)	0.43	189
69	sugar-O	buffer, pH 7 (364)	0.52	189
70	coumarin-CO_2	MeCN/buffer, pH 7, 1:1 (325)	0.013	190
71	coumarin-CO_2	MeCN/buffer, pH 7, 1:1 (325)	0.011	190
72	coumarin-CO_2	MeCN/buffer, pH 7, 1:1 (325)	0.003	190
73	$PhCO_2$	EtOH/H_2O, 1:1 (355)	0.17	193
77	$PhCO_2$	$CDCl_3$ (350)	0.22	199
77	BnO	$CDCl_3$ (350)	0.41	199
77	*c*-Hex-$NHCO_2$	$CDCl_3$ (350)	0.38	199
79	*c*-Hex-$NHCO_2$	THF (254)	0.62	186
79	*c*-Hex-$NHCO_2$	polymer (254)	0.13	186
83 (NV)	thymidine-OCO_2	MeOH/H_2O, 1:1 (365)	0.0013	204
83	coumarin-CO_2	MeCN/buffer, pH 7, 1:1 (325)	0.006	190
90 (MeNPOC)	thymidine-OCO_2	MeOH/H_2O, 1:1 (365)	0.0075	204
104	RCO_2	MeCN/H_2O, 3:2 (>370)	0.08–0.16	210

Table 9

Typical Coumarin Chromophores Applied as PPGs

PPG[a]	substituents (chemical name, abbreviation)	λ_{max} / nm	solvent[b]	ref.
	R = H ((coumarin-4-yl)methyl, CM)	310–314	i	271
	R = OH (7-hydroxycoumarin-4-yl)methyl (HCM;)	324–325	iii	272
		326	iv	273
	R = OMe ((7-methoxycoumarin-4-yl)methyl, 7-MCM)	320	iii	274
		322–323	vi	275
		323	iii	272
		324	i, iv	273,276
		325–328	i	271a,276
	R = $O(CH_2)_2N$-peptide	330	v	277
	R = OCH_2CO_2H ([7-(carboxymethoxy)coumarin-4-yl]methyl, CMCM)	322	iv	278
	R = NH_2 ((7-aminocoumaryl)methyl, ACM)	348	iv	273
	R = NMe_2 ([7-(dimethylamino)coumarin-4-yl]methyl, DMACM)	385	ii	279
		387–394	I	271a,276
	R = NEt_2 ([7-(diethylamino)coumarin-4-yl]methyl, DEACM)	390	viii, ii	280, 281
		392	ii	282
		393	iv	283
		396	v	275
		396–402	I	276
	R = $N(CH_2CO_2H)_2$ ({7-[bis(carboxymethyl)-amino]coumarin-4-yl}methyl, BCMACM)	379–381	ii, vii	284
		380	iv	285
		382–386	ii	194,286
	R = $N(CH_2CO_2Bu^t)_2$	383	vii	196
	(R^1 = Me, R^2 = R^3 = H) ((6-methoxycoumarin-4-yl)methyl, 6-MCM)	345–346	i	276,284c
	R^1 = R^2 = OMe, R^3 = H (6,7-dimethoxy(coumarin-4-yl)methyl, DMCM)	344	vi	275
		346–349	i	276,284c
	R^1 = R^2 = OCH_2CO_2H, R^3 = H ([6,7-bis(carboxymethoxy)coumarin-4-yl]methyl, BCMCM)	340–342	iv	278
		436–441	ii	287

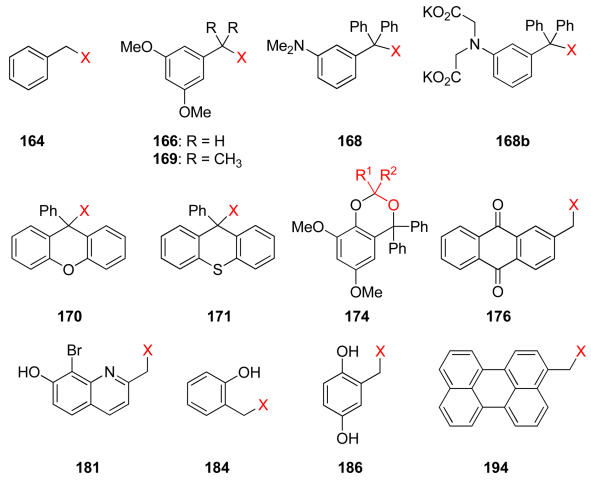
PPG[a]	substituents (chemical name, abbreviation)	λ_{max} / nm	solvent[b]	ref.
	R^1 = H, R^2 = R^3 = OCH_2CO_2H (7,8-BCMCM)	324	vii	196
	R^1 = Br, R^2 = OH, R^3 = H ((6-bromo-7-hydroxycoumarin-4-yl)methyl, BHCM)	370	v	275,288
		372–375	vii	289
		374–376	vi	275
	R^1 = Br, R^2 = OMe, R^3 = H	330	v	275,288
	R^1 = Br, R^2 = OH, R^3 = $N(CH_2CO_2Bu^t)_2$	372–376	vii	289
	R^1 = Br, R^2 = *n*-$C17H35CO_2$, R^3 = H	490	ii	290
	R = MeO	345	iii	274
	R = H	345	iii	291
	R = OH	360	iii	291
	R = OMe	347	iii	291–292
	R = OMe	373	i	293
	R = H	370	v	288,294
		371	vii	289
	R = $N(CH_2CO_2H)_2$	372	vii	289

[a]Leaving groups are in red.

[b] Solvent: HEPES/MeOH (i); HEPES buffer (ii); EtOH (iii); PB or PBS buffer (iv); KMOPS buffer (v); KMOPS/MeOH (vi); HEPES/MeCN (vii); water (viii).

Table 10

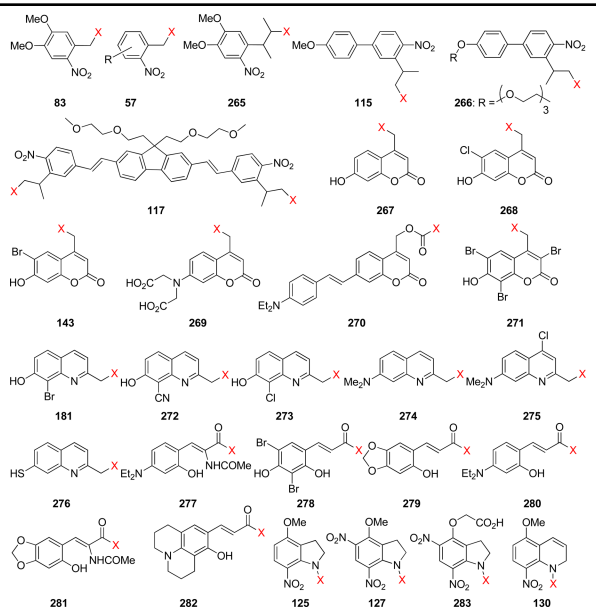
Arylmethyl- and Heteroarylmethyl-Based Photoremovable Protecting Groups



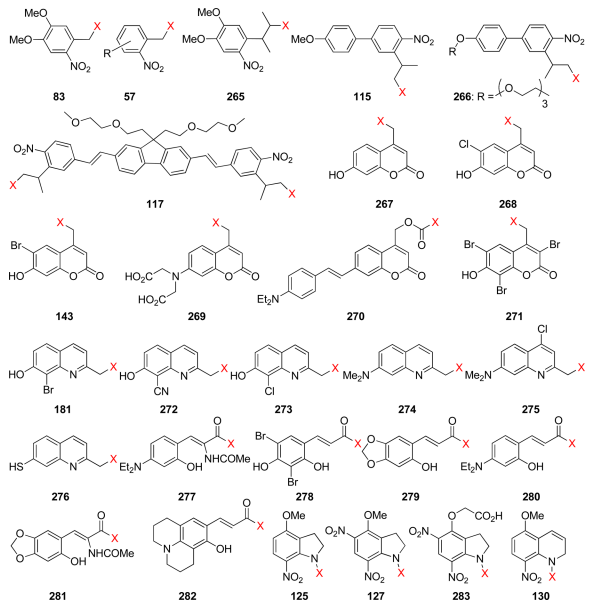
PPG	protected group	λ_{max} /nm	λ_{irr} /nm	release yield / %	Φ	ref.
164 (benzyl)	amine (as a carbamate)		254	75	0.15	1
166 (DMB)	amine (as a carbamate)	280	263–312	85		311
168 (DMATr)	alcohol	309	broadband	~ 85	0.12	315
168b	alcohol			92–100	0.23	346
169 (Ddz)	amines (as a carbamate)	276, 282	broadband			316
170 (Px)	alcohol		254 or 300	~ 90		317
171 (SPx)	alcohol		300 or 350	~ 90		318–319
174	carbonyl	297	> 280	92	0.17	315
176 (Aqm)	carboxylate, alcohol (as a carbonate), Carbonyl	330	350	~ 80	~ 0.1	324,326d
181 (BHQ)	carboxylate, phosphate, carbonyl	369	365	~ 90	0.04	330a,331,335
184 (NQMP)	alcohol, phenol, carboxylate	307	300 or 350	72–100	0.1–0.3	338
186 DHB)	alcohol, phenol, carboxylate, carbonyl, glycol	297	300	60–100	0.1–0.3	339–340
194	carboxylate, alcohol	438	>410	94–97	0.072–0.093	327

Table 11

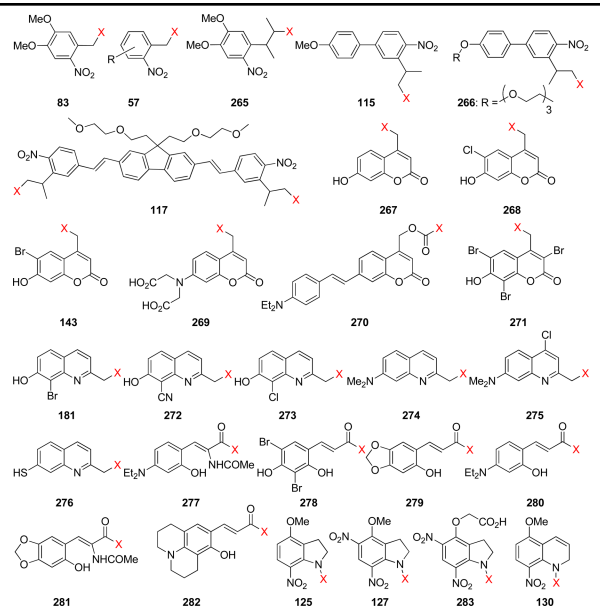
Single-Photon and Two-Photon Uncaging Quantum Efficiencies of Photolabile Protecting Groups



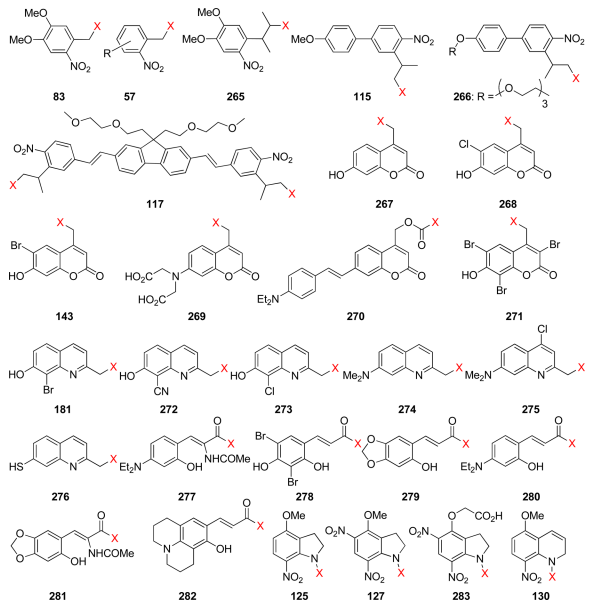
PPG	Φ[a]	λ / nm	δ_{unc} / GM[b]	λ / nm	ref.
83 (4,5-dimethoxy-2-nitrobenzyl, NV)	0.16	305	0.035 [c]	730	490
	0.006	365	0.03	740	303
	0.08	>365	0.01	800	496
			0.23 [c]	740	221,485b
			0.004 [c]–0.025	750	221,485b
57 (*o*-nitrobenzyl, oNB; R = Cl, OH, MeO, NH_2,*p*-$MeOC_6H_4$, etc.)	0.001–0.1	325	0.015–0.065	750	190
265(3-(4,5-dimethoxy-2-nitrophenyl)-2-butyl, DMNPB)	0.26	365	0.17	720	492
115 ((4'-methoxy-4-nitrobiphenyl-3-yleth-2-yl)methyl, PMNB)	0.1	315	0.45	800	236



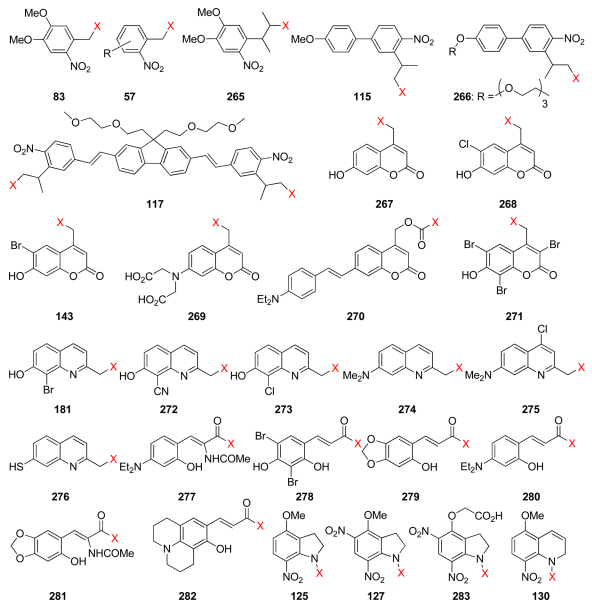
PPG	Φ^a	λ / nm	δ_{unc} / GM^b	λ / nm	ref.
			3.1	740	237
266 ((4'-tris-ethoxymethoxy-4-nitrobiphenyl-3-yleth-2-yl)methyl, PENB)	0.1	315	3.7	740	493
117 (2,7-bis-{4-nitro-8-[3-(2-propyl)-styryl]}-9,9-bis-[1-(3,6-dioxaheptyl)]-fluorene, BNSF)	0.25	354	5.0	800	237
267 ((7-hydroxycoumarin-4-yl)methyl)	0.025	365	1.07 0.13	740 800	331 303
268 ((6-chloro-7-hydroxycoumarin-4-yl)methyl)	0.01	365	1.07 0.34	740 800	303 303
143 ((6-bromo-7-hydroxycoumarin-4-yl)methyl, BHCM)	0.084 0.019–0.037	350 365	0.35 0.51–1.99 0.21	740 740 780	288 294,303 330a



PPG	Φ^a	λ / nm	δ_{unc} / GM^b	λ / nm	ref.
			0.37–0.42	800	303
269 ({7-[bis(carboxymethyl)-amino] coumarin-4-yl}methyl, BCMACM)	0.29	330–430	ca. 1 *c*	800	286
270 ({7-[(4-(dimethylamino)styryl]coumarin-4-yl}$^{1-2}$methoxycarbonyl)	0.83 × 10^{-3}	407	0.26	800	497
271 ((3,6,8-tribromo-7-hydroxycoumarin-4-yl)methyl)	0.065	365	0.96 3.1	740 800	303 303
181 ((8-bromo-7-hydroxyquinoline-2-yl)methyl, BHQ)	0.29–0.39	365	0.59–0.90 0.087	740 780	331 330a
272 ((8-cyano-7-hydroxyquinoline-2-yl)methyl, CyHQ)	0.31	365	0.32	740	335a
273 ((8-chloro-7-hydroxyquinoline-2-yl)methyl, CHQ)	0.10	365	0.12	740	335a



PPG	Φ^a	λ / nm	δ_{unc} / GM^b	λ / nm	ref.
274 ([7-(dimethylamino)quinoline-2-yl]methyl, DMAQ)	0.046	365	0.13	740	335a
275 ([7-(dimethylamino)-4-chloroquinoline-2-yl]methyl, DMAQ-Cl)	0.09	365	0.47	740	335a
276 ((7-mercaptoquinoline-2-yl)methyl, TQ)	0.063	365	0.42	740	335a
277 ((*Z*)-butyl 3-(4-(diethylamino)-2-hydroxyphenyl)-2-acetamidoacrylate)	0.05	300–400	0.3	750	393b
278 (3,5-dibromo-2,4-dihydroxycinnamate)	0.05 0.05	369 300–400	1.6 0.6	750 750	390 393a
279 ((*E*)-3-(6-hydroxy-benzo(1,3)dioxo-5-yl)acrylate)	0.03	300–400	3.8	750	393a
280((*E*)-3-(4-diethylamino-2-hydroxy-phenyl)acrylate)	0.02	300–400	2.0	750	393a
281 ((*Z*)-butyl 2-acetamido-3-(5-hydroxybenzo[d] [1,3]dioxol-6-yl)acrylate)	0.07	300–400	2.0	750	393b



PPG	Φ[a]	λ / nm	δ_{unc} / GM[b]	λ / nm	ref.
282((*E*)-3-(8-hydroxy-2,3,6,7-tetrahydro-*1H, 5H*-pyrido(3,2,1 -ij)quinolin-9-yl)acrylate)	0.03	300–400	4.7	750	393a
125 (4-methoxy-7-nitroindolinyl, MNI)	0.085	350	0.006	730	10d,483
127 (4-methoxy-5,7-dinitroindolinyl, MDNI)	0.47	350	0.06 [c]	730	494
283 (4-carboxymethoxy-5,7-dinitroindolinyl, CDNI)	0.5 [c]	334–364	0.06	720	483a
130 (5-methoxy-8-nitro-1,2-dihydroquinolinyl, MNDQ)	0.05	365	<0.06 [c]	720	250

[a]The single-photon quantum yield of substrate release;

[b]the two-photon cross-section of uncaging;

[c]by comparison with the literature data.