Published in final edited form as:
Photochem Photobiol Sci. 2014 February ; 13(2): 324–341. doi:10.1039/c3pp50305d.

2-Diazo-1-(4-hydroxyphenyl)ethanone: A Versatile Photochemical and Synthetic Reagent[a]

Sanjeewa N. Senadheera[b], **Anthony S. Evans**[c], **John P. Toscano**[c], and **Richard S. Givens**[b,*]

[b]Department of Chemistry, University of Kansas, Lawrence, Kansas 66045, U.S.A

[c]Department of Chemistry, Johns Hopkins University, Baltimore, Maryland 21218, U.S.A

Abstract

α-Diazo arylketones are well-known substrates for Wolff rearrangement to phenylacetic acids through a ketene intermediate by either thermal or photochemical activation. Likewise, α-substituted *p*-hydroxyphenacyl (pHP) esters are substrates for photo-Favorskii rerrangements to phenylacetic acids by a different pathway that purportedly involves a cyclopropanone intermediate. In this paper, we show that the photolysis of a series of α-diazo-*p*-hydroxyacetophenones and *p*-hydroxyphenacyl (pHP) α-esters both generate the identical rearranged phenylacetates as major products. Since α-diazo-*p*-hydroxyacetophenone (**1a**, pHP N_2) contains all the necessary functionalities for either Wolff or Favorskii rearrangement, we were prompted to probe this intriguing mechanistic dichotomy under conditions favorable to the photo-Favorskii reangement, i.e., photolysis in hydroxylic media. An investigation of the mechanism for conversion of **1a** to *p*-hydroxyphenyl acetic acid (**4a)** using time-resolved infrared (TRIR) spectroscopy clearly demonstrates the formation of a ketene intermediate that is subsequently trapped by solvent or nucleophiles. The photoreaction of **1a** is quenched by oxygen and sensitized by triplet sensitizers and the quantum yields for **1a**–**c** range from 0.19 to a robust 0.25. The lifetime of the triplet, determined by Stern-Volmer quenching, is 15 ns with a rate for appearance of **4a** of $k = 7{,}1 \times 10^6\ s^{-1}$ in aq. acetonitrile (1:1 v:v). These studies establish that the primary rearrangement pathway for **1a** involves ketene formation in accordance with the photo-Wolff rearrangement. Furthermore we have also demonstrated the synthetic utility of **1a** as an esterification and etherification reagent with a variety of substituted α-diazo-*p*-hydroxyacetophenones, using them as synthons for efficiently coupling it to acids and phenols to produce pHP protect substrates.

Keywords

Photoremovable protecting groups; photorelease; substituents. photo Favorskii rearrangement; Wolff rearrangement

[a]This article is dedicated to the memory of Professor Nicholas J. Turro (1938-2012)), one of the giants of physical-organic photochemistry upon whose shoulders many of us stood.

[*]corresponding author: givensr@ku.edu.

Introduction

Two well-known and closely related ground state rearrangements, the Wolff (WR) and Favorskii (FR) rearrangements, have a common signature for their reorganizational behavior.[1] Both proceed by elimination reactions coupled with a 1,2-carbon migration before reacting with a nucleophilic trapping reagent that, overall, converts an α-substituted ketone to a carboxylic acid. Photochemical versions of these rearrangements, the photo-Wolff (pWR)[2] and photo-Favorskii (pFR)[3] rearrangements, are well-known variations of these rearrangements (Scheme 1). Of these two, the photo-Favorskii rearrangement is the more recent[3,4] and less well-studied. Increased interest in the pFR is due, in part, to its emergence in the mechanistic studies of the p-hydroxyphenacyl (pHP) group as a photoremovable protecting group (PPG) for several key functional groups that are important in chemical and biological studies.[5,6] Furthermore, recent applications of pFR for ring-contraction reactions by photolysis of 4-hydroxybenzocycloalkanone esters have been demonstrated.[7] Similar photoinduced ring contraction reactions have been hallmarks of FR, WR, and pWR reactions, particularly α-diazocycloalkanones.[8] These similarities plus recent mechanism studies of the photo-Favorskii reaction[3c,7b,9,10] have added significantly to our understanding of the rearrangement reaction, inviting a more in depth comparison between the pFR and the more well-established pWR.[2,11]

Based on literature precedence, the pWR and pFR rearrangements follow two completely different pathways, yet arrive at one common major product, carboxylic acid **4**. One common feature of both the pWR[12] and pFR[1–3,13] for aryl ketones is that they commence by heterolytic departure of a leaving group from an excited state of the α-substituted phenacyl ketone (e.g., **1**) followed by 1,2-aryl migration. For the pFR, a required *p*-hydroxylphenacyl group assists the leaving group heterolysis in aqueous solvents through concomitant loss of the phenolic proton, whereas the pWR should not be limited by nor require any special assistance from the aryl substituent.[2c,2d,14] However, since the *p*-hydroxy group has not been among the substituents that have been reported for pWR rearrangements of aryl ketones, its role and the effect of aqueous solvents on the pWR are not known. 2-Diazo-1-(4-hydroxyphenyl)ethanones (α-diazo-*p*-hydroxyphenacyl analogs, **1a**–**e** (LG = N_2) represent potential cross-over substrates that may be employed to probe for either (or both) the photo-Wolff carbene-ketene or the photo-Favorskii diradical-cyclopropanone sequences as depicted in Scheme 2.

To test for this dichotomous behavior, we have explored the photochemistry of **1a** and several other α-diazo-*p*-acetophenones, tracking the mechanistic questions raised here, while also exploiting the synthetic utility of these α-diazoketones as synthons for general routes to direct installation of the *p*-hydroxyphenacyl (pHP) protecting group for important acidic functional groups in chemistry and biology.[6a,15]

Results

The potential synthetic utility of **1a** is based on the well-established applications of diazomethane and its derivatives[16] as esterification reagents. This methodology is especially appealing because of the rapid, clean installation of a phenacyl protecting group on acidic

functional groups which should require fewer steps and expand pHP protection to other functional groups.[17] In exploring these purposes, we chose a series of α-diazo-*p*-hydroxyacetophenones as models that would serve as common reagents for the photo-Wolff rearrangement studies and that could be compared with our previous studies using pHP analogs.[9a–b,18]

The diazo ketones were synthesized from the acylated substituted 4-hydroxybenzoic acids **6** by treatment with $SOCl_2$ to give the acid chlorides (Scheme 3). Conversion to acetyl-protected diazo-*p*-hydroxyacetophenones **7** in 65–69 % yield occurred with addition of excess diazomethane.[17,19,20] Deacetylative deprotection of the phenol with NH_4OAc in aqueous methanol occurred in the workup step and gave quantitative yields of **1a–d**. The acetyl analog **1d**[21] was synthesized by first converting *p*-acetoxybenzoic acid **6a** to 3-acetyl-4-hydroxybenzoic acid through a Fries rearrangement followed by re-acetylation of the phenolic group to give **6d**.[22] Conversion to the acid chloride and addition of diazomethane gave 3-acetyl derivative **7d** in low yield (38%), however.

The α-diazoketones **1a**–**d** were converted to their diethyl phosphate esters **9a–d** in 75–79% yield by treatment with diethyl phosphoric acid.[21] The ortho methoxy substituted analog 2-diazo-1-(4-hydroxy-2-methoxyphenyl)ethan-1-one (**1e**) could not be synthesized by this route due to instability of **1e** to the reaction conditions. However, treatment of **6e** with $SOCl_2$ and then excess diazomethane gave 2-methoxy diazoketone **7e** in good yield (69%). Exposure of **7e** to silica gel, acids, aqueous bases, or unbuffered H_2O resulted in the formation of 6-hydroxybenzofuran-3(2H)-one (**8e**). A similar neighboring group cyclization had been reported by Gefflaut and Périé[23] for *o*-benzyloxy α-diazoacetophenone upon treatment with dibenzyl phosphoric acid (Scheme 4). Therefore, acetate **7e** was used as its protected phenol for photochemical studies. Likewise, the instability of **7e** to acid precluded its conversion to 2-methoxy-pHP diethyl phosphate which, instead, was obtained by the Sn2 bromide displacement from α-bromo-2-methoxy-4-hydroxyacetophenone, the method previously reported for most pHP phosphates.[10b]

To further demonstrate the utility of **1a**, it was employed as a synthon to cage several other functional groups (Scheme 5), i. e., as a general entrée for the synthesis of pHP esters of dibenzyl phosphate,[10b,21] three examples of sulfonates esters,[17,21] two phenol ethers,[21] and several carboxylate esters[9,17] including the pHP protected, neuro active agents glutamate[9,18a] and GABA.[9] Previous syntheses of these pHP derivatives employed Sn2 strategies using protected bromoacetophenones (pHP Br), a more cumbersome route.

Properties of 2-diazo-4-hydroxyphenylethanones

The X-ray crystallographic data is provided in the Supporting Information in Table SI1 and Figures SI1 and SI2. The p*K*a's and UV-vis spectra of **1a**–**d** in aqueous CH_3CN (unbuffered) and buffered media are given in Table 1 and in Figures SI3 and SI4.

UV-vis spectra for **1a** in H_2O/CH_3CN (Figure SI3 and SI4) and in buffer solutions show absorption maxima at λ_{max} =306 nm at pH 4 to 7 giving no hint of the presence of its conjugate base. This indicates that the absorption spectra at pH 4 – 7 are for the neutral form of **1a** as expected from its pK_a of 9.1. Although the conjugate base is not present in this pH

range, it is prominent at pH 10 as evidenced by the 40 nm red-shifted λ_{max} at 346 nm (Figure SI4). The solution's color changes from a light yellow at pH 7 to a bright yellow at pH 10. In general, all of the maxima of **1a** – **d** are red shifted relative to their *p*-hydroxyacetophenones (pHA) and pHP esters due to the extended cross-conjugation of the α–diazo group.

The pKa's for *p*-hydroxyacetophenone and pHP esters are generally an order of magnitude lower than **1a–d.** For example, **1a** (p*K*a 9.1) is much less acidic than 4-hydroxyacetophenone (pHA, p*K*a 7.9)[21,24] or any of the pHP esters (p*K*a range from 3.9 to 8.2).[21] The complex acid-base equilibria for **1a** are profiled in Scheme 6. UV-vis spectra confirm that structure **1a** predominates at pH 4 – 7 and that the conjugate base **1a**$^{-}$predominates at pH 10. There is no UV, transient UV, or transient IR (*vide infra*) evidence for either the quinone methide enol alcohol (**QEA**) or the diazoquinone methide enolate zwitterion (**QEZ**) that have been reported for *p*-hydroxyacetophenone.[5] Likewise, the complete absence of any hydrogen-deuterium exchange of the α-proton of **1a** for samples dissolved and then photolyzed in D_2O (^{1}H NMR). This precludes any equilibrium between **1a** and the quinone enolate form (**QEZ**). Therefore, structures like **1a′H$^+$, 1a″H$^+$,** and **QEZ** (Scheme 6) are not contributing to the equilibria of **1a** within the pH range of 4 – 7.

The X-ray crystallographic structure of **1a** (Figure SI1 and SI2, Table SI1) confirm that the molecule is indeed nearly planar, only slightly twisted by approximately 12 – 14° out of the aryl plane, with the diazo functional group anti-periplanar to the aryl ring. The C1–C2 ethanone bond is shortened to 1.43 Å from 1.46 Å for other diazo acetophenones,[25] suggesting a small degree of conjugation between the diazo group and the carbonyl.

^{1}H NMR of **1a** displays one singlet at δ 6.30 (D_2O:CD_3CN, 1H, s) for the α–methine proton consistent with a single s-Z configuration deduced from the crystallographic data (SI1) and consistent with several other diazoacetophenones[25,26,27,28,29,30,31] and semi empirical (AM1) and *ab initio* (HF/6-31G(d)) determinations.[32,33]

Photochemistry

Irradiation of **1a** at 300 or 350 nm in Pyrex vessels under ambient conditions either in unbuffered or buffered (pH 4, 7, or 10) aqueous acetonitrile (D_2O/CD_3CN, 1:1) produced nitrogen effervescence. Disappearance of **1a** and appearance of 4-hydroxyphenylacetic acid (**4a)** were determined by the changes in their ^{1}H NMR signals at 6.23 and 3.49 ppm, respectively or by reverse-phase HPLC (RP-HPLC) analysis. The total areas of the 3.49 and 6.23 ppm signals remained constant while the ratio of the two areas changed throughout the reaction indicating that there was no exchange with D_2O before, during, or after the rearrangement.

Several unidentified minor products were detected by NMR, HPLC and LC-MS. Attempts were nade to probe the reaction mixture for other photoproducts analogous to those expected in either the pWR or pFR reactions including ^{1}H NMR and co-injection of the photolyzate mixtures of **1a** with authentic samples, 4-hydroxyacetophenone (by photoreduction), 4-(1-hydroxyethyl)phenol (by photohydrolysis),[10c, 34] or 4-hydroxybenzyl alcohol (the

ubiquitous byproduct of pFR photorearrangment)[3c] and analyzed by RP-HPLC and GC/MS. None of these compounds were present. Similarly, photolysis in aqueous CH_3CN at pH 10 and in dry CH_3CN gave only complex mixtures of photoproducts, none of which were the expected rearrangement or hydrolysis photoproducts. These results are in contrast with photolysis in >5% H_2O:CH_3CN at a pH of 4.0–7.0 where **4a** was the product.

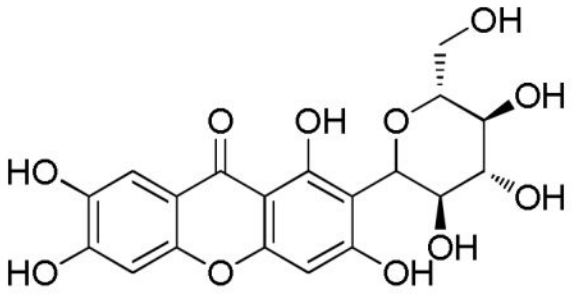
Photolysis of **1a** in the presence of Lewis acid (HBF_4) in 1:1 CD_3OD:CD_3CN and in H_2O:CH_3CN at −10 °C, conditions similar to those for ground state esterification reactions were performed. At this temperature, **1a** is stable and no N_2 effervescence is observed. After photolysis for 1 hr with 16 × 300 nm lamps in HBF_4 (1:1 CD_3OD:CD_3CN), the sample was warmed to room temperature. Some effervescence due to unreacted **1a** was noted. ^{1}H NMR indicated two products, methyl *p*-hydroxyphenylacetate and 2-methoxy -1-(4-hydroxyphenyl)ethanone, the latter from the workup (Scheme 7). A control run without irradiation indicated no exchange of the α-H for D in **1a** and no indication exchange in this product.

Quantum yields for the disappearance of diazo pHP **1a** and appearance of **4a** were determined by RP-HPLC in unbuffered aqueous acetonitrile (1:1) at 300 nm. The disappearance quantum yield for **1a** and the three substituted derivatives **1b** – **d** are comparable to other diazo 4-substituted acetophenones photolyzed at 300 nm as indicated in Table 2.[35]

Quantum yield measurements and the photorearrangement products for **1b–d** and **7b**,**e** were determined. The acetyl protected 3-methoxy diazo *p*HP **7b** produced rearranged acid **4b** in good yield, whereas the acetyl-protected 2-methoxy diazo *p*HP **7e** gave a 1:1 mixture of 3-oxo-2,3-dihydrobenzofuran-6-yl acetate (**8g**) and rearranged acid **4e**. The formation of **4e** follows the same rearrangement pathway as the unsubstituted and *meta* substituted diazo pHP derivatives **1a–d** and is also responsible for the formation of **4b** independent of the added acetyl protecting group. In contrast, formation of acetate **8g** must arise by another pathway, possibly involving a carbene, but does not involve the pWR rearrangement.

Sensitization and quenching studies

The singlet and triplet energies of the diazo pHP **1a** are estimated to be E_S = 85 kcal/mol (λ_{fluor} 338 nm) and E_T 69 = kcal/mol (λ_{phos} 410 nm), respectively. Two sensitizers were chosen based on their E_T values and their hydrophilicity: benzophenone-4,4′-dicarboxylic acid (**20**, E_T = 69 kcal mol^{-1})[31,36,37,38,39,40] and mangiferin (**21**, a xanthone derivative, E_T = 71–74 kcal mol^{-1}(ethanol-ether)[41,42,43,44]. The results demonstrate that there is a significant triplet contribution to the rearrangement (Table 3).



21, mangiferin

Likewise, oxygen quenched the reaction, decreasing the quantum yields by 30% to 55%. When samples were purged for 30 min either with argon or with 100% O_2 before photolysis, the Stern-Volmer dependence on the quencher concentration was used to determine the triplet lifetime ($\tau = 1.5 \times 10^{-10}$ s) and the rate of appearance of **4a** of 6.6×10^9 s^{-1}using an estimated rate constant for O_2 diffusion of $k_{diff} = 1.37 \times 10^{10}$ M^{-1} s^{-1} in 50% aqueous acetonitrile (Table 4 and Figure SI5). [24,45,46,47,48]

Time-Resolved Infrared Studies

Nanosecond time-resolved infrared (TRIR) experiments[49,50,51] were performed using a 266 nm (5 ns, 1.5 mJ) laser for the photolysis of **1a** in argon-saturated 5% aqueous acetonitrile (v:v) and monitored in the spectral region 2200 – 2000 cm^{-1} (Figure 1). The strong band observed at 2110 cm^{-1} is assigned to ketene **3a** in good agreement with previous studies on α-diazo ketones[52,53,54,55] such as α-diazo-*p*-methoxyacetophenone (2115 cm^{-1}) and α-diazoacetophenone (2118 cm^{-1}).[52]

To confirm our assignment of the 2110 cm^{-1} signal to ketene **3a**, we examined its reactivity with diethylamine (DEA) to form *N*,*N*-diethyl-*p*-hydroxyphenyl acetamide (**24**, Scheme 9). TRIR data observed following photolysis of **1a** in argon-saturated acetonitrile with 2 mM added DEA are shown in Figure 2. Under these conditions the 2110 cm^{-1} ketene signal is quenched and a transient intermediate is observed at 1685 cm^{-1}. This intermediate is assigned to either zwitterion **23** or its tautomer, enol **22**, the addition product of DEA to **3a**, which collapses to amide **24** as indicated by the growth of the band at 1640 cm^{-1}.

Measurements of the rate of decay of the 2110 cm^{-1} ketene signal and the rate of growth of the 1685 cm^{-1} signal with varying concentrations of DEA were used to obtain the second-order rate constant for the addition of DEA to ketene **3a**, $k_{DEA} = 6 \times 10^6$ $M^{-1}s^{-1}$. The observed rate of the relevant intermediate decay or formation (k_{obs}) as a function of added DEA is given by $k_{obs} = k_0 + k_{DEA}[DEA]$, where k_0 is the observed first-order decay rate constant in the absence of DEA and k_{DEA} is the second-order rate constant for reaction with DEA (see Figure SI6). This derived rate constant is approximately two orders of magnitude slower than other closely related DEA-ketene addition rates.[52] The sluggishness of the reaction may be attributed to the lower electrophilicity of the ketene caused by the *p*-hydroxyphenyl group or its conjugate base. Protonation of DEA by the phenol may further influence the rate by diminishing its concentration.

Attempts to detect the cyclopropanone C=O stretch the IR region of 1950 – 1800 cm^{-1}, which would be characteristic of the spirodienedione intermediate **2**, the intermediate expected from the pFR reaction, were unsuccessful. No transient signals were observed in this region.

Discussion

The TRIR evidence clearly demonstrates that the major if not exclusive pathway for α-diazo-*p*-hydroxyacetophenone photochemistry is through a ketene intermediate. At room temperature when performed at a pH less than 4 (HBF_4/CD_3OD), **1a** is unstable and spontaneously expels N_2 to form α-methoxy-*p*-hydroxyacetophenone, the solvolysis product. At −10 °C with HBF_4 (in 1:1CD_3OD: CD_3CN), a temperature low enough that N_2 is not released thermally, photolysis of **1a** gives Wolff rearrangement product, i.e., *p*-hydroxyphenylacetate methyl ester (d_5), through its ketene precursor (and the corresponding solvolysis product from workup). Neither *p*-hydroxybenzyl alcohol (**5**) nor its methyl ether was detected. Furthermore, ^1H NMR of the photoreaction mixture gave no evidence for exchange of the original α-proton on **1a** in the deuterated solvents, i.e., the α–proton remaining intact throughout the conversion to the rearrangement and photosolvolysis products. These results along with the studies of buffered D_2O:CD_3CN (1:1) solutions from pH 4 – 7 rule out any reversible protonation or deuteration of **1a** at the α-carbon expected form intermediate species such as $\mathbf{1a'H^+}$, $\mathbf{1a''H^+}$ or the quinone methide **QEZ** (Scheme 6) which may be crucial for onset of a pFR pathway.

The photochemistry at pH 10, on the other hand, produces only a complex mixture of unidentified product and none of the signature products from either the pFR or pWR pathways. While this is not an exhaustive, all-inclusive investigation of possible variables that might divert the pathway of **1a** away from the Wolf rearrangement, the dominance of the pWR pathway is clearly evident under conditions examined here.

TRIR spectroscopy provides the spectral evidence, demonstrating ketene **3a** as the exclusive intermediate. No evidence for a cyclopropanone carbonyl stretch in the region of 1800 – 1850 cm^{-1} as anticipated for **2a** was found.

Quantum yield studies demonstrate that the *p*-hydroxy group does not impact the overall efficiency of the photo-Wolff rearrangement reaction when compared with other substituted phenacyl derivatives (Table 2). However, the TRIR studies do reveal that nucleophilic addition by diethylamine to the intermediate ketene **3a** proceeds much more slowly, i.e., by over two orders of magnitude, than reported for DEA additions to similarly substituted phenylketenes ($k_{nuc} = 9 \times 10^6$ M^{-1} $s^{-1}$for *p*-OH vs. $k_{nuc} = 3.30 \times 10^4$ M^{-1} s^{-1} for *p*-OCH_3).[52] The greater electron-donating character of the *p*-hydroxy substituent or possibly its conjugate base reduces the ketene's nucleophilicity thus slowing the rate of attack at the carbonyl carbon. (Scheme 9, Figure 2).

Sensitization and quenching studies indicate that there is a prominent triplet component to the rearrangement. Both hydrophilic triplet sensitizers, benzophenone (**20**) and 9H-xanthen-9-one (**21**), promote the rearrangement with sensitization quantum yields by **20**

occurring at very nearly the same efficiencies as found for direct excitation of **1a**. Likewise, oxygen quenching decreases the quantum efficiency by >40%. The concentration dependence of the oxygen quenching provides a Stern-Volmer estimate of quenching rate of $k_q = 6.6 \times 10^9\ M^{-1}\ s^{-1}$ and a lifetime for ^{3}**1a** of $\tau^3 = 1.5 \times 10^{-10}$ s, sufficiently long that proton transfer is possible on the excited state surface. However, there is no evidence for changes in the product distribution or the isotopic integrity of the reactant or product that would be expected if a Favorskii pathway intervened. The byproduct characteristic of the pFR pathway was not detected under direct or sensitization conditions; specifically absent was the benzyl alcohol **5a**, the ubiquitous side product of the photo Favorskii reaction (Scheme 1).

Nonetheless, these results are perplexing when one considers the ground state reactions and chemistry of **1a** and its analogs. For example, the most common ground state reactions of **1a** in the absence of light or catalysts but in the presence of mild to strong acids in hydroxylic solvents, such as H_2O or CH_3OH, is either esterification or etherifcation *without skeletal rearrangement*, a very advantageous feature for our general synthetic methodology for the synthesis of pHP protected derivatives.

General consideration of the mechanistic pathway for these synthetically valuable esterification reactions for **1a** and its derivatives with diazo alkanes begins with protonation of the diazo derivative by acid followed by nucleophilic displacement of N_2[56] (Scheme 10). For diazomethane, the protonation at carbon has been shown to be reversible using deuterium exchange conditions.[16] However, in our case for **1a**, exchange does not occur, suggesting that alternative mechanistic pathways or irreversible protonation are occurring. It is also apparent that intermolecular nucleophilic pathways prevail over any intramolecular participation of the electron rich phenol ring, which, of course, would lead to Favorskii products.

Since pHP has become an important photoremovable protecting group (PPG) for biological studies[6] by providing rapid rates (fsec to nsec) for heterolysis with little or no byproduct damage or deleterious biological interference to proteins and by very efficiently releasing many functional groups ($\Phi = 0.1 – 1.0$), a general synthetic entrée to pHP and its congeners is now possible by employing substituted α-diazo-p-hydroxyacetophenones (**1a–d**) to afford pHP photoprotection. Synthesizing a range of substituted 2-diazo-1-(4-hydroxyphenyl)ethanones has value in its utility for protecting important acid and phenol functionalities under very mild conditions in quantitative yield.

Conclusions

With the array of substituted diazoketones **1a**–**d**, we have explored the concept of dual mechanisms for the photo-Wolff and photo-Favorskii rearrangements. Although two excited state pathways for α-diazo-p-hydroxyacetophenone (**1a**) might include a traditional photo-Wolff ketene mechanism[57] or a photo-Favorskii cyclopropanone pathway (or both), **1a** and its congeners exclusively follow the photo Wolff pathway. These reactions were shown to be triplet processes through sensitization and quenching studies. Subtle changes in the excited state p*K*a's, substituents on the chromophore, solvent, or the pH of the solvent do

not alter or divert the reaction pathway of **1** from ketene formation, i.e., from the Wolff rearrangement pathway.

It is both significant and utilitarian that α-diazo-p-hydroxyacetophenones (**1a**–**d**) function as excellent synthons for pHP protection reactions. Synthetic yields of pHP protected functional groups using α-diazo-*p*-hydroxyacetophenones give better yields and avoid the necessity for masking the phenolic group of pHP during installation of the protecting group.

Experimental

General Methods

All compounds were prepared by literature procedures unless indicated otherwise. All reagents were purchased from commercial sources and used without further purification unless otherwise noted. Nitrobenzene and dichloromethane (DCM) were distilled prior to use. ^{1}H NMR spectra were recorded on a Bruker 400 MHz instrument unless otherwise noted. IR spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer; results are reported in cm^{-1}. UV/vis spectra were recorded on a Cary 100 spectrophotometer. HPLC analyses were performed with a C18 Econosphere 250 × 4.6 mm analytical column connected to a dual pump system for preliminary studies. Mass spectrometry was performed on a Sciex API-1 Plus quadrupole mass spectrometer with an electrospray ionization (ESI) source. pH values of solutions were measured using a pH 510 meter calibrated with certified buffer solutions of pH 4, 7, and 10. A freeze drier was used for lyophilization (at −52 °C and 0.04 mbar). Thin layer and column chromatography were performed on precoated silica gel plates and standard grade (32–63 μm) silica gel, respectively. Melting points are uncorrected.

The following compounds were synthesized as described previously: 2-hydroxy-1-(4-hydroxyphenyl)ethan-1-one,[58] 4-Acetoxy-3-methoxybenzoic acid **(6b)**,[59] 4-Acetoxy-3,5-dimethoxybenzoic acid **(6c)**, [60] 4-acetoxy-3-acetylbenzoic acid **(6d)**,[21] 1-(3-Acetyl-4-hydroxyphenyl)-2-diazoethanone **(1d)**,[21] diethyl 2-(3-acetyl-4-hydroxyphenyl)-2-oxoethyl phosphate **(7d)**,[21] 2-(4-hydroxyphenyl)-2-oxoethyl 2,2,2-trifluoroacetate **(12)**,[21] 2-(4-hydroxyphenyl)-2-oxoethyl 4-methylbenzenesulfonate **(15)**.[17] 2-(4-hydroxyphenyl)-2-oxoethyl methanesulfonate **(17)**.[17]

4-(2-Diazoacetyl)-3-methoxyphenyl acetate, 7a (α-Diazo-*p*-acetoxyacetophenone)—The general methods of Arndt[61] and Beams and Mander[62] were applied with modifications. To a solution of KOH (678 mg, 12.1 mmol) in 2-methoxyethanol (5 mL) and water (5 mL), diazold (1.17 g, 5.4 mmol) in diethylether (50 mL) was added carefully. The resulting mixture was gently heated to reflux temperatures (40–50 °C). The ether layer was distilled into a collection flask that was kept in an ice bath at 0 °C. The ether distillate was sequentially dried over KOH pellets for 1 h at 0 °C and with Na pieces for 1 h at 0 °C. Then a solution of the acid chloride (200 mg, 1.00 mmol) in dry ether (10 mL) was added to the distillate with vigorous stirring at −5 °C. The reaction mixture was allowed to come to 0 °C and stirred for 4 h. The solvent was evaporated, and the yellow colored crude residue was purified by flash chromatography using a gradient solvent system-EtOAc/hexane (1:4), EtOAc/hexane (1:3), and EtOAc/hexane (1:2) to afford

α-diazo-*p*-acetoxyacetophenone (**7a**) as yellow needles (112 mg, 0.55 mmol, 55% yield): mp 105–107 °C; ^{1}H NMR ($CDCl_3$) δ ppm 7.81-7.79 (1H, dd, *J* = 6.8 Hz, 1.8 Hz), 7.20-7.18 (1H, dd, *J* = 6.8 Hz, 1.8 Hz), 5.88 (1H, s), 2.33 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 185.3, 169.1, 154.2, 134.4, 128.4, 122.1, 54.4, 21.4; IR (KBr, cm^{-1}) 3067, 2114, 1757, 1609, 1574, 1417, 1392, 1369, 1103, 1167, 916, 860; MS (ESI (+)) *m*/*z* calcd for $(C_{10}H_8N_2O_3 + H)^+$ 205.0613, found 205.0624.

4-(2-Diazoacetyl)-2-methoxyphenyl acetate (7b)—The general methods of Adams and Binder[63] and Arndt[61] were followed with modifications. A flame dried 50 mL round bottomed flask was charged with 4-acetoxy-3-methoxybenzoic acid (**6b**, 0.840 g, 2.8 mmol) and freshly distilled $SOCl_2$ (20 mL) was added under Ar. The resulting mixture was refluxed at 80 °C for 8 h and concentrated under reduced pressure to afford 4-acetoxy-3-methoxy-benzoyl chloride as colorless oil. This acid chloride was used in the next step without any purification.

A solution of acid chloride (910 mg, 3.9 mmol) in dry ether (10 mL) was added dropwise to the dried ether distillate containing the diazomethane with vigorous stirring at −5 °C. The reaction mixture was allowed to come to 0 °C and stirred overnight. The solvent was evaporated, and the yellow residue was purified by flash chromatography with a gradient solvent system. [EtOAc/hexane (1:4), EtOAc/hexane (1:3), and EtOAc/hexane (1:2)] to afford 4-(2-diazoacetyl)-2-methoxyphenyl acetate (**7b**) as a yellow crystalline solid (645 mg, 69% yield): mp = 96–99 °C; ^{1}H NMR (500 MHz, CD_3COCD_3) δ ppm 7.56 (1H, d, *J* = 2 Hz), 7.47-7.45 (1H, d, *J* = 8.2 Hz), 7.18-7.16 (1H, d, *J* = 8.2 Hz), 6.63 (1H, s), 3.90 (3H, s), 2.26 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm 185.6, 168.8, 152.6, 144.5, 136.5, 124, 120.4, 111.6, 56.5, 54.4, 20.5; IR (KBr, cm^{-1}) 3078, 2112, 1765, 1582, 1508, 1420, 1367, 1192, 904, 785; MS (ESI (−)) calcd for $(C_{11}H_9N_2O_4 - H)^-$ 233.0562, found 233.0553.

2-Diazo-1-(4-hydroxyphenyl)ethan-1-one, 1a. (α-diazo-p-hydroxyacetophenone)—The general method of Das et al.[64] was followed with modifications. To a stirred solution of α-diazo-*p*-acetoxyacetophenone (**7a**, 60 mg, 0.29 mmol) in aqueous MeOH (H_2O:MeOH, 1:4, 10 mL), NH_4OAc (181 mg, 2.4 mmol) was added. The resulting mixture was warmed to 50 °C and the progress of the reaction was monitored by TLC. After 4 h, the reaction mixture was concentrated and the residue was extracted with EtOAc (10 mL × 5). Combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated to afford α-diazo-p-hydroxyacetophenone (**1a**) as a yellowish orange colored crystalline solid that was further purified on silica gel (hexane:EtOAc, 1:1) to generate the pure compound as yellow colored crystals (48 mg, 0.30 mmol, 100% yield), mp = 144–150 °C (dec.): ^{1}H NMR (CD_3COCD_3) δ ppm 9.20 (1H, s), 7.77-7.75 (2H, d, *J* = 8.8 Hz), 6.92-6.90 (2H, d, *J* = 8.8 Hz), 6.47 (1H, s); ^{13}C NMR (100 MHz, CD_3COCD_3) δ (ppm) 185.4, 162.7, 129.9, 129.7, 116.2, 53.2; IR (KBr, cm^{-1}) 3263, 2170, 2123, 1605, 1560, 1508, 1261, 1230, 1173, 1099, 1028, 802; UV/Vis (CH_3CN/H_2O), λ_{max} (ε $Lmol^{-1}cm^{-1}$) 306 (14165); MS (ESI (+)) m/z calcd for $(C_8H_6N_2O_2 + H)^+$ 163.0507, found 163.1299; *m*/*z* calcd for $(C_8H_6N_2O_2 + Na)^+$ 185.1118, found 185.1129.

2-Diazo-1-(4-hydroxy-3-methoxyphenyl)ethanone (1b)—The general method of Das et al.[64] was applied with modifications. To a stirred solution of 4-(2-diazoacetyl)-2-methoxyphenyl acetate (**7b**, 600 mg, 2.56 mmol) in aqueous MeOH (H_2O:MeOH, 1:4, 20 mL), was added NH_4OAc (1.578 g, 20.49 mmol). The resulting mixture was warmed at 50 °C and the progress of the reaction was monitored by TLC. After 8 h, the reaction mixture was concentrated and the residue was extracted with acetone (10 mL × 5). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated to afford 2-diazo-1-(4-hydroxy-3-methoxyphenyl)ethanone (**1b**) as a yellow-orange oil which was further purified on silica gel (hexane: EtOAc, 1:1) to generate the pure compound as a yellow oil (473 mg, 96% yield): ^{1}H NMR (500 MHz, CD_3COCD_3) δ ppm 8.45 (1H, s), 7.40-7.38 (1H, d, J = 2.1 Hz), 6.88-6.86 (2H, d, J = 8.4 Hz), 6.53 (1H, s), 3.90 (3H, s); ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm) 185.4, 152.1, 148.5, 130, 122, 115.6, 110.8, 56.4, 53.3; IR (Teflon film, cm^{-1}) 3279, 3008-2839, 2106, 1688, 1591, 1516, 1356, 1277, 1200, 1028, 777; MS (ESI (−)) calcd for $(C_9H_8N_2O_3 - H)^-$ 191.0457, found 191.0438.

2-Diazo-1-(4-hydroxy-3,5-dimethoxyphenyl)ethanone (7c)—A flame dried 50 mL round bottomed flask was charged with 4-acetoxy-3,5-dimethoxybenzoic acid (**6c**, 1.085 g, 4.5 mmol) and freshly distilled $SOCl_2$ (20 mL) was added under Ar. The resulting mixture was refluxed at 80 °C for 8 h and concentrated under reduced pressure to afford 3,5-dimethoxy-4-acetoxybenzoyl chloride as a colorless oil. This acid chloride was used in the next step without any further purification. General method A was used to generate diazomethane in excess by distillation in dry ether. Then a solution of acid chloride (1.165 g, 4.5 mmol) in dry ether (10 mL) was added dropwise to the distillate (diazomethane) with vigorous stirring at −5 °C. The reaction mixture was allowed to come to 0 °C and stirred overnight. The solvent was evaporated, and the dark yellow colored residue was used in the next step without purification. To a stirred solution of crude 4-(2-diazoacetyl)-2,6-dimethoxyphenyl acetate (690 mg, 2.61 mmol) in aqueous MeOH (H_2O:MeOH, 1:4, 20 mL), NH_4OAc (1.61 g, 20.89 mmol) was added. The resulting mixture was warmed at 50 °C and the progress of the reaction was monitored by TLC. After 8 h, the reaction mixture was concentrated and the residue was extracted with acetone (10 mL × 5). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated to afford 2-diazo-1-(4-hydroxy-3,5-dimethoxyphenyl)ethanone (**7c**) as a yellow-brown oil which was further purified on silica gel (hexane:EtOAc, 1:1) to generate the pure compound as a thick yellow oil (545 mg, 94% yield): ^{1}H NMR (400 MHz, CD_3COCD_3) δ ppm 8.03 (1H, s), 7.20 (2H, s), 3.88 (6H, s); ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm) 185.5, 148.6, 128.6, 105.5, 56.8, 53.3; IR (KBr, cm^{-1}) 3313, 2115, 1601, 1564, 1518, 1456, 1371, 1194, 1114, 762, 733, 669; MS (ESI (−)) *m/z* calcd for $(C_{10}H_{10}N_2O_4 - H)^-$221.0562, found 221.0558.

4-(2-Diazoacetyl)-3-methoxyphenyl acetate (7e)—A flame dried 50 mL round bottomed flask was charged with 4-acetoxy-2-methoxybenzoic acid (**7e**, 840 mg, 4.0 mmol) and freshly distilled $SOCl_2$ (20 mL) was added under Ar. The resulting mixture was refluxed at 80 °C for 8 h and concentrated under reduced pressure to afford 4-acetoxy-2-methoxybenzoyl chloride as colorless oil. This acid chloride was used in the next step without further purification. General method A was used to generate diazomethane in excess by distillation in dry ether. Then a solution of acid chloride (913 mg, 4.0 mmol) in dry ether

(10 mL) was added dropwise to the distillate containing the diazomethane in ether with vigorous stirring at −5 °C. The reaction mixture was allowed to come to 0 °C and stirred overnight. The solvent was evaporated, and the yellow solid was purified by flash chromatography on triethylamine saturated silica gel with a gradient solvent system [EtOAc/hexane (1:4), EtOAc/hexane (1:3), and EtOAc/hexane (1:2)] to afford 4-(2-diazoacetyl)-3-methoxyphenyl acetate (**7e**) as a yellow solid (645 mg, 69% yield): mp 87–90 °C; ^{1}H NMR (500 MHz, CD_3COCD_3) δ ppm 7.90-7.88 (1H, d, *J* = 7.8 Hz), 6.94 (1H, d, *J* = 2 Hz), 6.84-6.82 (1H, d, *J* = 8.5), 6.63 (1H, s), 3.95 (3H, s), 2.27 (3H, s); ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm) 169.3, 156.1, 131.8, 115, 107.1, 58.1, 56.6, 21.1; IR (KBr, cm^{-1}) 3126-3032, 2102, 1765, 1618, 1601, 1418, 1358, 1261, 1207, 1016, 962, 906, 690; MS (ESI (+)) *m*/*z* calcd for $(C_{11}H_{10}N_2O_4 + H)^+$ 235.0719, found 235.0728.

Conversion of 2-diazo-1-(4-hydroxyphenyl)ethanones 1a–d to the corresponding pHP phosphate and carboxylate esters

Diethyl 2-(4-hydroxyphenyl)-2-oxoethyl phosphate (9a)—To a stirred solution of α-diazo-*p*-hydroxyacetophenone (**1a**, 100 mg, 0.62 mmol) in benzene (5 mL), diethyl phosphate (190 mg, 1.23 mmol) in benzene (5 mL) was added dropwise. The resulting mixture was stirred at 60 °C and the progress of the reaction was monitored by TLC. After 24 h the benzene layer was washed sequentially with saturated $NaHCO_3$ (20 mL) and water (20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to afford diethyl 2-(4-hydroxyphenyl)-2-oxoethyl phosphate (**9a**) as yellowish white solid that was chromatographed on silica gel (hexane:EtOAC, 1:1) to produce the pure compound as a white solid (149 mg, 84% yield). The spectroscopic data agree with literature values.[4] Likewise, diethyl phosphate esters of **9a′–d** were synthesized by the same procedure.

Diethyl 2-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl phosphate (9b)—A dark yellow crude product of **9b** was further purified on silica gel using a gradient solvent system [EtOAc/hexane (3:1), and EtOAc/MeOH (19:1)] to isolate the pure compound as a white crystalline solid (340 mg, 92% yield): mp 95–98 °C: ^{1}H NMR (400 MHz, CD_3COCD_3) δ ppm 9.40 (1H, s) 7.83-7.7.81 (2H, d, *J* = 8.8 Hz), 6.56 (2H, m, including a doublet), 5.12-5.09 (2H, d, *J* = 11.2 Hz); 4.20-4.13 (4H, m), 3.94 (3H, s), 1.33-1.29 (6H, m); ^{31}P NMR (162 MHz, CD_3COCD_3) δ ppm −0.37; ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm) 191.5, 164.97, 162.9, 133.4, 117.3, 109.4, 99.7, 73.1-73.0, 64.4, 56.1, 16.5; IR (KBr, cm^{-1}) 3134, 1672, 1602, 1473, 1383, 1337, 1231, 1032, 984, 849; UV/vis [H_2O/CH_3CN (1:1)], λ_{max} (ε $M^{-1}cm^{-1}$) 307 (8498), 278 (9465); MS (ESI (+)) *m*/*z* calcd for $(C_{13}H_{19}O_7P - H)^-$ 317.0790, found 317.0795.

Diethyl 2-(4-hydroxy-3,5-dimethoxyphenyl)-2-oxoethyl phosphate (9c)—A brown-yellow oil crude product was chromatographed on silica gel with a gradient solvent system; EtOAc/hexane (1:2), EtOAc/hexane (1:1), EtOAc/hexane (2:1), and EtOAc/hexane (3:1)) to produce the pure diethyl 2-(4-hydroxy-3-methoxyphenyl)-2-oxoethyl phosphate (**9c**) as a thick yellow oil (588 mg, 75% yield): ^{1}H NMR (400 MHz, CD_3COCD_3) δ ppm 8.26 (1H, s) 7.32 (2H, s), 5.37-5.34 (2H, d, *J* = 10.8 Hz); 4.20-4.13 (2H, m), 3.91 (3H, s), 1.33-1.29 (6H, m); ^{31}P NMR (162 MHz, CD_3COCD_3) δ ppm −0.12; ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm) 191.8-191.7, 148.7, 142.6, 106.6, 69.5, 64.5-64.4, 56.8, 16.50; IR

(Teflon film, cm^{-1}) 3242, 2982-2848, 1693, 1605, 1518, 1460, 1327, 1194, 1115, 1045, 802; UV/vis [H_2O/CH_3CN (1:1)], λ_{max} (ε $M^{-1}cm^{-1}$) 305 (1617); MS (ESI (−)) *m*/*z* calcd for $(C_{14}H_{21}O_8P - H)^-$347.0896, found 347.0889.

2-(4-Hydroxyphenyl)-2-oxoethyl diphenyl phosphate (9a′): The general methods of Epstein and Garrossian[65] and Périé and Gefflaut[23] were used with modifications. To a stirred solution of α-diazo-*p*-hydroxyacetophenone (**1a**, 11 mg, 0.068 mmol) in benzene (5 mL), diphenyl phosphate (34 mg, 0.14 mmol) in benzene (5 mL) was added dropwise. The resulting mixture was stirred at rt and the progress of the reaction was monitored by TLC. After 30 min, the benzene layer was washed sequentially with saturated $NaHCO_3$ (20 mL) and water (20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to afford 2-(4-hydroxyphenyl)-2-oxoethyl diphenyl phosphate **9a′**, as a yellowish white solid that was chromatographed on silica gel (hexane:EtOAC, 1:1) to produce the pure compound (24 mg, 92% yield). The spectroscopic data are in agreement with reported data.[10b]

2-(4-Hydroxyphenyl)-2-oxoethyl benzoate (10): To a stirred solution of α-diazo-*p*-acetoxyacetophenone (**1a**, 20 mg, 0.098 mmol) in benzene (5 mL), benzoic acid (24 mg, 0.20 mmol) in benzene (5 mL) was added dropwise. The resulting mixture was refluxed at 70 °C. The progress of the reaction was monitored by TLC. After 42 h the benzene layer was washed sequentially with saturated $NaHCO_3$ (40 mL) and water (40 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to afford a mixture of acetoxy benzoate and unprotected benzoate as a yellowish brown colored solid. (30 mg, 0.10 mmol, 100% yield). To a solution of the above mixture (30 mg, 0.147 mmol) in aqueous MeOH (1:4, 10 mL), NH_4OAc (92 mg, 1.19 mmol) was added. The resulting mixture was warmed at 50 °C and the progress of the reaction was monitored by TLC. After 4 h, the reaction mixtuture was concentrated and the residue was extracted with EtOAc (10 mL × 5). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated to afford the crude benzoate ester as a yellowish orange colored crystalline solid. The crude compound was further purified on silica gel (EtOAc/hexane 1:1) to give pure 2-(4-hydroxyphenyl)-2-oxoethyl benzoate (**10**) as a white solid (25 mg, 0.098 mmol, 97% yield), ^1H NMR (CD_3COCD_3) δ ppm 9.33 (1H, s), 8.12-8.09 (2H, m), 7.98-7.95 (2H, m), 7.70-7.66 (1H, m), 7.57-7.53 (2H, m), 7.00-6.97 (2H, m), 5.65 (2H, s); ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm) 191.12, 166.47, 163.31, 134.20, 131.27, 131.07, 130.55, 129.54, 127.66, 116.44, 116.36, 67.34; IR (KBr, cm^{-1}) 3350, 1685, 1600, 1500, 840, 720, 690; MS (ESI (+)) m/z calcd for $(C_{15}H_{13}O_4 + H)^+$ 256.0798, found 256. 0814.

2-(4-Hydroxyphenyl)-2-oxoethyl acetate (11): To a stirred solution of α-diazo-*p*-hydroxyacetophenone (**1a**, 10 mg, 0.062 mmol) in acetonitrile and water (10 mL, 4:1), glacial acetic acid (1 mL, 16 mmol) was added dropwise at rt. The resulting mixture was stirred at rt and the progress of the reaction was monitored by TLC. After 16 h the reaction mixture was concentrated and ethyl acetate (10 mL) was added. The organic layer was washed sequentially with saturated $NaHCO_3$ (20 mL) and water (20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to afford crude acetate ester as a yellowish brown solid that was chromatographed on silica gel (EtOAc/hexane 1:1) to give the pure 2-

(4-hydroxyphenyl)-2-oxoethyl acetate, **11**, as a white solid (11.8 mg, 0.061 mmol, 98% yield). The spectroscopic data are in agreement with reported data.[21]

2-amino-5-(2-(4-hydroxyphenyl)-2-oxoethoxy)-5-oxopentanoic acid (13): The general method of Shinada et al.[66] was followed with modifications. To a stirred solution of α-diazo-*p*-hydroxyacetophenone (20 mg, 0.12 mmol) in toluene (10 mL), 5-tert-butoxy-2-(tert-butoxycarbonylamino)-5-oxopentanoic acid (Boc-Glu(O*t*Bu)-OH - 56 mg, 0.18 mmol) in toluene (2 mL) was added dropwise at rt. A catalytic amount of copper acetoacetonate (3 mg, 0.012 mmol) was added. The resulting mixture was stirred at 60 °C and the progress of the reaction was monitored by TLC. After 2 h ethyl acetate (10 mL) was added. The organic layer was washed sequentially with saturated $NaHCO_3$ (20 mL) and water (20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to afford the crude protected glutamate ester that was chromatographed on silica gel (hexane:EtOAc, 1:1) to produce protected glutamate ester as a yellowish brown solid that was then used in the deprotection step. To a stirred solution of the above compound in CH_2Cl_2 (1 mL), freshly distilled TFA (9 mL) was added. The reaction mixture was allowed to stir for 15 min and concentrated under reduced pressure. Then residue was dissolved in water and CH_2Cl_2 (20 mL, 1:1). The water layer was extracted, frozen, and then lyophilized to afford *p*HP-glutamate, **13,** as a white solid (35 mg, 71% overall yield). The spectroscopic data are in agreement with reported data.[67]

2-(4-hydroxyphenyl)-2-oxoethyl 4-aminobutanoate (14): The general method of Shinada et al.[66] was followed with modifications. To a stirred solution of α-diazo-*p*-hydroxyacetophenone (**1a**, 50 mg, 0.31 mmol) in toluene (10 mL), 4-(tert-butoxycarbonylamino) butanoic acid (Boc-GABA, 75 mg, 37 mmol) in toluene (2 mL) was added dropwise at rt. A catalytic amount of copper acetylacetonate (8 mg, 0.031 mmol) was added to the reaction mixture. The resulting mixture was stirred at 60 °C and the progress of the reaction was monitored by TLC. After 2 h ethyl acetate (10 mL) was added. The organic layer was washed sequentially with saturated $NaHCO_3$ (20 mL) and water (20 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to afford crude Boc-GABA ester as a yellowish brown solid which was chromatographed on silica gel (hexane:EtOAc, 1:1) to give the *p*HP Boc-GABA as a yellowish brown solid. To a stirred solution of the above compound in CH_2Cl_2 (5mL), freshly distilled TFA (5 mL) was added. The reaction mixture was allowed to stir for 15 min and concentrated under reduced pressure. The residue was dissolved in water and CH_2Cl_2 (20 mL, 1:1). The water layer was extracted, frozen, and then lyophilized to afford *p*HP GABA, **14**, as a white solid (81 mg, 75% overall yield). The spectroscopic data are in strong agreement with literature.[9b]

2-(4-hydroxyphenyl)-2-oxoethyl trifluoromethanesulfonate (16): To a stirred solution of α-diazo-*p*-hydroxyacetophenone (**1a**, 10 mg, 0.062 mmol) in anhydrous benzene (6 mL), triflic acid (10 mg, 0.068 mmol) in benzene (4 mL) was added dropwise at 0 °C under Ar. The reaction mixture was allowed to stir for 30 min at 0 °C, and then brought to room temperature. At that point, ethyl acetate (10 mL) was added to the reaction mixture and the organic phase was washed with saturated $NaHCO_3$ solution (15 mL × 3) and water (20 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and filtered. The solvent was

evaporated to afford 2-(4-hydroxyphenyl)-2-oxoethyl trifluoromethanesulfonate as a yellowish brown solid which was run through a small pad of silica gel (hexane/EtOAc, 1:1) to afford the 2-(4-hydroxyphenyl)-2-oxoethyl trifluoromethanesulfonate (**16**, R = CF_3SO_3) as a white solid which decomposed with time at room temperature (16 mg, 0.056 mmol, 91% yield)], ^{1}H NMR (400 MHz, CD_3COCD_3) δ ppm 9.48 (1H, s), 7.96-7.94 (2H, dd, *J* = 6.8 Hz, 2 Hz), 7.00-6.98 (2H, dd, *J* = 6.8 Hz, 1.96 Hz), 5.81 (2H, s); ^{19}F NMR (376 MHz, CD_3COCD_3) δ (ppm) −76.47 (3F, s). Product was really unstable and decomposed slowly at room temperature. Thus, the other spectroscopic data was not obtained on the target compound.

1-(4-hydroxyphenyl)-2-(4-methoxyphenoxy)ethan-1-one (18): The general method of Shinada et al.[66] was followed with modifications. To a stirred solution of α-diazo-*p*-acetoxyacetophenone (**1a**, 20 mg, 0.098 mmol) in anhydrous toluene (10 mL), and 4-methoxyphenol (24 mg, 0.19 mmol) in toluene (2 mL) was added dropwise at rt. A catalytic amount of rhodium(II) acetate dimer (4 mg, 0.01 mmol) was added to the reaction mixture. The resulting mixture was stirred at 60 °C overnight under inert atmosphere. The reaction mixture was concentrated and the yellow colored crude product was used for the deprotection step without further purification. To a stirred solution of the crude acetate in aqueous MeOH (1:4, 10 mL), NH_4OAc (60 mg, 0.78 mmol) was added. The resulting mixture was warmed at 50 °C and the progress of the reaction was monitored by TLC. After 8 h, the reaction mixture was concentrated and the residue was extracted with EtOAc (10 mL × 5). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated to afford 2-(4-methoxyphenoxy)-4-hydroxyacetophenone, **18**, as a brownish white solid which was further purified on silica gel (hexane:EtOAc, 1:1) to generate the pure compound as a white solid (18 mg, 56% overall yield). The spectroscopic data are in strong agreement with reported data.[21]

1-(4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenoxy)ethan-1-one (19): To a stirred solution of α-diazo-*p*-acetoxyacetophenone (**1a**, 40 mg, 0.20 mmol) in anhydrous toluene (10 mL), and *p*-trifluoromethyl phenol (64 mg, 0.39 mmol) in toluene (2 mL) was added dropwise at rt. A catalytic amount of rhodium(II) acetate dimer (9 mg, 0.02 mmol) was added to the reaction mixture. The resulting mixture was stirred at 60 °C overnight under inert atmosphere. The reaction mixture was concentrated and the yellow colored crude product was used for the deprotection step without any purification. To a stirred solution of the crude 1-(4-acetoxyphenyl)-2-(4-(trifluoromethyl)phenoxy)ethanone in aqueous MeOH (1:4, 10 mL), NH_4OAc (120 mg, 1.6 mmol) was added. The resulting mixture was warmed to 50 °C and the progress of the reaction was monitored by TLC. After 8 h, the reaction mixture was concentrated and the residue was extracted with EtOAc (10 mL × 5). The combined organic layers were dried over anhydrous $MgSO_4$ and the solvent was evaporated to afford the 1-(4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenoxy)ethanone as a brownish white solid which was further purified on silica gel (hexane:EtOAc, 1:1) to generate the pure 1-(4-hydroxyphenyl)-2-(4-(trifluoromethyl)phenoxy)ethanone, **19**, as a brownish white solid (49 mg, 68% overall yield. The spectroscopic data are in strong agreement with reported data.[21]

Physical and spectral properties of 2-diazo-1-(4-hydroxyphenyl)ethan-1-one

X-Ray Crystallographic structure for the 2-diazo-1-(4-hydroxyphenyl)ethan-1-one (1a)—The needle shaped light yellow color crystals of diazo *p*HP **1a** were produced from hexane/EtOAc solvent system. Colorless rectangular parallelepiped-shaped crystals of $C_8H_6N_2O_2$ are, at 100(2) K, orthorhombic, space group Pbca – D_{2h}^{15} (No. 61)[68] with **a** = 13.729(2) Å, **b** = 6.795(1) Å, **c** = 16.111(2) Å, V = 1503.1(3) Å^3 and Z = 8 molecules [d_{calcd} = 1.433 g/cm^3; μ_a(MoKα) = 0.106 mm^{-1}] A full hemisphere of diffracted intensities (1850 40-second frames with a ω scan width of 0.30°) was measured for a single-domain specimen using graphite-monochromated MoKα radiation (λ= 0.71073 Å) on a Bruker SMART APEX CCD Single Crystal Diffraction System.[69] X-rays were provided by a fine-focus sealed X-ray tube operated at 50kV and 30mA. Lattice constants were determined with the Bruker SAINT software package using peak centers for 5566 reflections. A total of 12759 integrated reflection intensities having 2θ((MoKα)< 58.23° were produced using the Bruker program SAINT[70]; 1932 of these were unique and gave R_{int} = 0.063 with a coverage which was 95.5% complete. The data were corrected empirically for variable absorption effects using equivalent reflections; the relative transmission factors ranged from 0.722 to 1.000. The Bruker software package SHELXTL was used to solve the structure using “direct methods” techniques. All stages of weighted full-matrix least-squares refinement were conducted using F_o^2 data with the SHELXTL Version 6.10 software package.[71]

The final structural model incorporated anisotropic thermal parameters for all nonhydrogen atoms and isotropic thermal parameters for all hydrogen atoms. All hydrogen atoms were located in a difference Fourier and included in the structural model as independent isotropic atoms whose parameters were allowed to vary in least-squares refinement cycles. A total of 133 parameters were refined using no restraints, 1932 data and weights of w = 1/ [$\sigma^2(F^2)$ + (0.0870 P)^2+ 0.7647 P], where P = [F_o^2 + 2F_c^2] / 3. Final agreement factors at convergence are: R_1(unweighted, based on F) = 0.064 for 1835 independent absorption-corrected “observed” reflections having 2θ(MoKα)< 58.23° and I>2σ(I); R_1(unweighted, based on F) = 0.067 and wR_2(weighted, based on F^2) = 0.165 for all 1932 independent absorption-corrected reflections having 2θ(MoKα)< 58.23°. The largest shift/s.u. was 0.000 in the final refinement cycle. The final difference map had maxima and minima of 0.42 and −0.35 e$^-$/Å^3, respectively.

UV/Vis study of 2-diazo-1-(4-hydroxyphenyl)ethan-1-one (1a) at different pH values—A 10 mL volumertric flask was charged with 2-diazo-1-(4-hydroxyphenyl)ethan-1-one (**1a**, 10 mg, 0.062 mmol) and dissolved in CH_3CN (5.0 mL) and H_2O (5.0 mL). The pH was adjusted by changing the pH of H_2O (5.0 mL) before mixing it with CH_3CN (5.0 mL). A buffer solution of sodium acetate/acetic acid in water was used to obtain pH 4. A buffer solution of ammonium acetate/ammonia was used to achieve pH 7 and 10, respectively. The UV-Vis scans were performed under ambient conditions with suitable dilutions at each pH value.

General procedure for p*K*a determination

A sample of the 2-diazo-1-(4-hydroxyphenyl)ethan-1-one **1a–d** (~ 10 mg, ~ 0.05 mmol) was dissolved in H_2O/CH_3CN (20 mL) in a beaker and was titrated with 0.005M NaOH solution

(prepared in H_2O/CH_3CN) while stirring the contents vigorously after each addition. pH measurements were taken for each 0.4 mL addition of NaOH solution. Scatter plots were created by plotting pH vs. volume of NaOH solution for each compound. p*K*a for compounds **1a–d** was determined at the half equivalence point using these plots.

General procedure for photolysis—A sample of the 2-diazo-1-(4-hydroxyphenyl)ethan-1-one **1a** – **d**, **7b**,**e** (~ 6 mg. ~0.05 mmol) dissolved in 1.0 mL of $CD_3CN:D_2O$ was placed in an NMR tube (or Pyrex test tubes) and irradiated in a Rayonet RPR-100 photochemical reactor fitted with a merry-go-round apparatus and with 16–350 nm (RPR 3500 Å) or 2–300 nm (RPR 3000 Å) lamps. The tubes were placed in a RPR merry-go-round apparatus and a counter was started at the onset of exposure to record the time of irradiation. The samples were irradiated at 40–45 °C in the presence or absence of oxygen as indicated in Table 3 and 4. Exposure times were controlled by manual removal of the sample from the reactor or alternately by turning the lamps on or off.

For the NMR tubes, the reaction course was monitored by ^1H NMR. The NMR yields of the major products **4a** – **d**, or **8g** and the disappearance of the diazo pHP derivative (**1a** – **d**, **7b,e**,) were monitored until the diazo pHP had disappeared. For the Pyrex tubes, the crude mixture was concentrated and the main products were isolated by base extraction. The product identities were confirmed by comparison of their ^1H and ^{13}C NMR spectra with those of authentic samples available from earlier pHP photochemical studies. The presence or absence of minor side products were established by spiking the reaction mixture with authentic samples and analysis by NMR or HPLC.

Quantum yield measurements

By RP-HPLC—A stock solution was prepared by dissolving biphenyl (160 mg, 1.04 mmol, standard) in CH_3CN (90 mL) in a 100 mL volumetric flask and diluting it to the mark with H_2O (10 mL). A quartz tube was charged with 2-diazo-1-(4-hydroxyphenyl)ethan-1-one (**1a**, 10 mg, 0.062 mmol) CH_3CN (1.0 mL) and H_2O (1.0 mL) and 2.0 ml of the biphenyl internal standard solution (3.2 mg, 0.021 mmol) was added. The sample was irradiated at 300 or 350 nm with 2–300 or 16–350 nm lamps, aliquots (100 μL) were collected after 0, 2, 4, 6, and 8 min and diluted with 950 μL of $CH_3CN:H_2O$ (1:1), then analyzed by HPLC using a Waters XTerra MS-C18 analytical column. Average peak areas from three injections of each aliquot corrected for the internal standard were used to obtain vs. irradiation time (in min) to obtain slope (*m*) for the best fit by linear regression analysis. The light output (*L*) in units of millieinsteins per minute of 300 and or350 nm irradiation. The quantum yields (Φ) for the disappearance of 2-diazo-1-(4-hydroxyphenyl)ethan-1-one and appearance of PAA (**4**) are given in Table 2 and 3.

Photolysis samples were also analyzed bu RP-HPLC performed with a Waters XTerra MS-C18 analytical column (column size: 2.1 × 150 mm, particle size: 5 μm) connected to a Waters Alliance HT 2795 or a Waters Aquity UPLC. The solvent system was 99% CH_3CN, 1% H_2O, 0.06% formic acid and 99% H_2O, 1% CH_3CN, 0.08% formic acid. Detection was at 250 nm and 280 nm. The flow rate was 0.2 mL/min and the injection volume was 5 μL. Each sample was run three times. The light output for the determination of quantum

efficiencies was measured by using the potassium ferrioxalate method.[72] The results are [given in Table 2 and 3.

By ^{1}H-NMR—A Pyrex NMR tube was charged with **1b–d** (~ 6 mg, ~ 0.05 mmol, 2 mg in the case of **1d**) and dissolved in CD_3CN (400 μL) and D_2O (400 μL). DMF (2 μL) was added as an internal standard. The contents were mixed thoroughly. The resulting sample was photolyzed without degassing at 300 nm with 4–3000 Å lamps, and the ^{1}H NMR spectra were collected after 0, 2, 4, 6 and 8 min. The depletion of **1b–d** and appearance of **4b–c** was determined by integration of the ^{1}H NMR signals at δ ~ 6.2 ppm and ~ 3.50 ppm compared to the DMF peaks which gave the disappearance of starting material and appearance of the corresponding phenylacetic acid respectively. Scatter plots were created by plotting the number of mmol of **1b–d** or **4b–c** vs. irradiation time. The slope (*m*) of the best fit line from the linear regression analysis was determined. The light output (*L*) of the 4–3000 Å lamps in the photoreactor was determined separately using the potassium ferrioxalate method in units of millieinsteins per min. The quantum yield (Φ) for the disappearance of **1b–d** and the appearance of **4b–c** was then calculated ($\Phi = |m|/L$). The results are given in Table 2.

Photolysis of 1a under acidic conditions at −10 °C—General procedure for photolysis was performed on **1a** as mentioned above under following specific conditions in an NMR tube. Dry ice in isopropanol was utilized to maintain the temperature at −10 °C in a dewar during the photolysis. A Pyrex NMR tube was charged with MeOH-d_4 (380 μL) and HBF_4 [48% (w/w) in H_2O (20 μL)] was added to it. Small amount of anhydrous $MgSO_4$ was used to dry MeOH-d_4 and the content was cooled at −10 °C in a beaker. A separate scintillation vial was charged with **1a** (~ 6 mg, ~ 0.05 mmol) and dissolved in MeOH-d_4 (400 μL) and transferred to the NMR tube after lowering the temperature to −10 °C. The contents were mixed thoroughly at −10 °C. The resulting sample was photolyzed in the dewar at −10 °C without degassing at 300 nm with 16–3000 Å lamps, and the ^{1}H NMR spectrum was collected after 80 min. (the content from the NMR tube was filtered through a fluted filter paper followed by plug of cotton wool and sea sand to remove $MgSO_4$ before running the NMR). The same experiment was repeated at room temperature to compare the effect of temperature on photolysis under very acidic conditions. The product identities were confirmed by comparison of their ^{1}H NMR spectra with those of authentic samples available from earlier pHP photochemical studies. The presence or absence of minor side products were established by spiking the reaction mixture with authentic samples and analysis by NMR.

Sensitization Experiments

Photolysis of α-diazo-*p*-hydroxyacetophenone with benzophenone-4,4-dicarboxylic acid (3.70×10^{-3} M and 9.25×10^{-3} M)—A quartz tube charged with 1-diazo-2-(4-hydroxyphenyl)ethanone (**1a**, 10 mg, 0.062 mmol) dissolved in CH_3CN:H_2O (1:1. 1.0 mL) and biphenyl (2.0 mL from the internal standard stock solution, (3.2 mg, 0.021 mmol) and benzophenone-4,4-dicarboxylic acid (4 mg, 0.015 mmol, sensitizer) were placed in a quartz test tube. The resulting mixture was thoroughly mixed to givel a clear solution then irradiated at 300 or 350 nm and aliquots (100 μL) collected after 0, 2, 4, 6, and 8 min of

photolysis. Each aliquot was diluted with 950 μL of CH_3CN/H_2O, 1:1 and analyzed by HPLC. The quantum yields of the disappearance of **1a** and appearance of **4** were determined. The experiment was repeated with a sensitizer concentration of 9.25×10^{-3} M. Results are in Table 3.

Photolysis of 1a with a xanthone sensitizer, Mangiferin, 21 (4.76×10^{-3} M and 1.19×10^{-2}M)—A quartz tube charged with **1a** (10 mg, 0.062 mmol) dissolved in $CH_3CN:H_2O$ (1:1. 1.0 mL) and biphenyl (2.0 mL from the internal standard stock solution, and mangiferin, **21** (8 mg, 0.019 mmol, sensitizer) were placed in a quartz test tube. After thorough mixing, the sample was irradiated at 300 or 350 nm and aliquots (100 μL) collected after 0, 2, 4, 6, and 8 min. Aliquots were diluted with 950 μL of CH_3CN/H_2O, 1:1 and analyzed by HPLC. The experiment was repeated with the sensitizer concentration of 1.19×10^{-2} M. The quantum yields for disappearance of **1a** and appearance of **4** in Table 3.

Photolysis of 1a under Ar—A quartz tube was charged with **1a** (10 mg, 0.062 mmol) dissolved in $CH_3CN:H_2O$ (1:1. 1.0 mL) and biphenyl (2.0 mL from the internal standard stock solution, and mangiferin (8 mg, 0.019 mmol, sensitizer) were placed in a quartz test tube. The tube, fitted with a rubber septum, was cooled in an ice bath, purged with Ar for 30 min and irradiated at 300 nm. Aliquots (100 μL) were collected after 0, 2, 4, 6, and 8 min of photolysis. Aliquots were diluted with 950 μL of CH_3CN/H_2O (1:1) and analyzed by HPLC. The quantum yields of the disappearance of **1a** and appearance of **4** are given in Table 3.

Quenching Experiments

Photolysis of 1a outgassed with oxygen—A quartz tube was charged with **1a** (10 mg, 0.062 mmol) dissolved in $CH_3CN:H_2O$ (1:1. 1.0 mL) and biphenyl (2.0 mL from the internal standard stock solution, and the contents mixed thoroughly. The tube was fitted with a rubber septum and sealed, cooled in an ice bath, and purged with pure oxygen for 30 min. The sample was irradiated at 300 nm, and aliquots (100 μL) collected after 0, 2, 4, 6, and 8 min of photolysis. Aliquots were diluted with 950 μL of CH_3CN/H_2O, 1:1 and analyzed by HPLC. The same procedure was repeated three times. The quantum yields of the disappearance of **1a** and appearance of **4** are given in Table 3. Stern-Volmer quenching determined using the values from literature determinations of the oxygen concentrations for degassing with Argon, ambient air concentrations and purging with pure O_2. The Stern-Volmer results are given in Table 4.

Time-Resolved Infrared Experiments

Nanosecond time-resolved infrared (TRIR) experiments were conducted (with 16 cm^{-1}spectral resolution) following the method of Hamaguchi[49,50] and co-workersas has been described previously.[51] Briefly, the broadband output of a $MoSi_2$ IR source (JASCO) is crossed with excitation pulses from a Continuum Minilite II Nd:YAG laser (266 nm, 5 ns, 1.5 mJ) operating at 15 Hz. Changes in IR intensity are monitored using an AC-coupled mercury/cadmium/tellurium (MCT) photovoltaic IR detector (Kolmar Technologies, KMPV11-J1/AC), amplified, digitized with a Tektronix TDS520A oscilloscope, and collected for data processing. The experiment is conducted in dispersive mode with a JASCO TRIR 1000 spectrometer.

Control Experiments with the 2-diazo-1-(4-hydroxyphenyl)ethan-1-one (1a); Dark Reaction

An NMR tube was charged with 2-diazo-1-(4-hydroxyphenyl)ethan-1-one (**1a**, 10 mg, 0.062 mmol) dissolved in CD_3CN (1 mL) and D_2O (1 mL). The contents were mixed thoroughly and warmed in a water bath at 40 °C in the dark for 2 h. ^1H NMR spectra were recorded before and after heating. There was no significant change before and after the heating. The sample was kept another 48 h in the dark and the ^1H NMR spectrum was recorded. No significant difference was observed.

Characterization of photoproducts

6-Hydroxybenzofuran-3(2H)-one (8e)—6-Hydroxybenzofuran-3(2H)-one (**8e**) was a product of the deprotection of 4-(2-diazoacetyl)-3-methoxyphenyl acetate (**7e**, 280 mg, 1.47 mmol) with NH_4OAc (898 mg, 11.65 mmol) in H_2O/MeOH, 1:4 (20 mL) at 50 °C for 8 h. The off-white compound was characterized by NMR and mass spectroscopy as 6-hydroxybenzofuran-3(2H)-one [**8e**, (218 mg, 100% yield). The spectroscopic data are in agreement with reported data.[73]

3-Oxo-2,3-dihydrobenzofuran-6-yl acetate (8g). Method A—The general method of Wuennemann was followed.[74] **Method B**; 3-Oxo-2,3-dihydrobenzofuran-6-yl acetate (**8g**) was also formed in the photolysis of 4-(2-diazoacetyl)-3-methoxyphenyl acetate (**7e**, 40.0 mg, 0.17 mmol) in CH_3CN/H_2O (1:1) using 2–300 nm lamps under ambient conditions. After 10 min, the photolysis mixture was concentrated and the resulting residue was chromatographed on silica gel (EtOAc/hexane (1:3), EtOAc/hexane (1:2), and EtOAc/hexane (1:1)) to afford 3-oxo-2,3-dihydrobenzofuran-6-yl acetate (**8g**) as white crystalline solid (12 mg, 0.062 mmol, 36% yield), mp 122–124 °C: ^1H NMR (500 MHz, CD_3COCD_3) δ ppm 7.65-7.64 (1H, d, J = 8.3 Hz), 7.02 (1H, d, J = 1.8 Hz), 6.92-6.90 (1H, d, J = 8.3 Hz), 4.75 (2H, s), 2.30 (3H, s); ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm) 198.6, 175.4, 169.2, 159.5, 125.3, 119.9, 117.4, 108.1, 76.3, 21.1; IR (KBr, cm^{-1}) 3113-2943, 1759, 1707, 1618, 1454, 1194, 1015, 906, 829, 688; MS (ESI (−)) *m*/*z* calcd for $(C_{10}H_8O_4 - H)^-$ 191.0344, found 191.0359.

2-(4-Acetoxy-2-methoxyphenyl)acetic acid (4e)—The 2-(4-acetoxy-2-methoxyphenyl)acetic acid, **4e** was obtained from photolysis of 4-(2-diazoacetyl)-3-methoxyphenyl acetate (**7e**, 40.0 mg, 0.17 mmol) in CH_3CN/H_2O, 1:1 at 300 nm under ambient conditions. After 10 min, the photolysis mixture was concentrated and the resulting residue was chromatographed on silica gel (EtOAc:hexane (1:3), EtOAc:hexane (1:2), EtOAc:hexane (1:1), and EtOAc:hexane (2:1)) to afford 2-(4-acetoxy-2-methoxyphenyl)acetic acid as a yellow solid (**4e**, 10 mg, 0.045 mmol, 26% yield): mp 94–104 °C (dec.); ^1H NMR (500 MHz, CD_3COCD_3) δ ppm 7.22-7.20 (1H, d, J = 8 Hz), 6.70 (1H, s), 6.61-6.60 (1H, d, J = 7.2 Hz), 3.75 (3H, s), 3.54 (2H, s), 2.23 (3H, s); ^{13}C NMR (125 MHz, CD_3COCD_3) δ (ppm) 169.7, 159.1, 151.8, 132, 117.7, 114.7, 114.1, 105.8, 56.2, 27.4, 21.1; IR (KBr, cm^{-1}) 3396-2554 (br), 1763, 1705, 1608, 1506, 1419, 1209, 1146, 1016, 960, 899, 804; MS (ESI (+)) *m*/*z* calcd for $(C_{11}H_{12}O_5 + Na)^+$ 247.0583, found 247.0575.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support for this work was provided by NIH grant R01 GM72910 (RSG) and NSF grant CHE-1213438 (JPT). We thank Anuranga I. Bandara for assistance with the p*K*a determinations and the quantum yield measurements for compounds **1a–d**. We wish to thank Dr. Victor Day of the University of Kansas X-ray Crystallography Laboratory for his efforts in acquiring the X-ray crystallographic data of **1a**.

Notes and References

1. (a) Favorskii AE. J Russ Phys Chem Soc. 1894; 26:590.(b) Kende AS. Or React. 1960; 11:261–316.
2. (a) Kirmse W. Eur J Org Chem. 2002; 14:2193–2256.(b) Celius, TC.; Wang, Y.; Toscano, JP. CRC Handbook of Organic Photochemistry and Photobiology. 2. Horspool, WM.; Lenci, F., editors. CRC Press; Boca Raton, FL: 2004. p. 90/1-90/16.(b) Burdzinski G, Platz MS. J Phys Org Chem. 2010; 23:308–314.(d) Wang J, Burdzinski G, Kubicki J, Platz MS. J Am Chem Soc. 2008; 130:11195–11209. [PubMed: 18656918]
3. (a) Anderson JC, Reese CB. Tetrahedron Lett. 1962; 1:1–4.(b) Givens RS, Park CH. Tetrahedron Lett. 1996; 35:6259–6266.(c) Givens RS, Heger D, Hellrung B, Kamdzhilov Y, Mac M, Conrad PG, Cope E, Lee JI, Mata-Segreda JF, Schowen RL, Wirz J. J Am Chem Soc. 2008; 130:3307–3309. [PubMed: 18290649]
4. Park TC-H, Givens RS. J Am Chem Soc. 1997; 119:2453–2463.
5. Klán P, Šolomek T, Bochet CG, Blanc A, Givens RS, Rubina M, Popik V, Kostikov A, Wirz J. Chem Rev. 2013; 113:119–191. [PubMed: 23256727]
6. (a) Goeldner, M.; Givens, RS. Dynamic Studies in Biology. Wiley-VCH; Weinheim, Germany: 2005. (b) Mayer G, Heckel A. Angew Chem, Int Ed. 2006; 45:4900–4921.(c) Lee HM, Larson DR, Lawrence DS. ACS Chem Biol. 2009; 4:409–427. [PubMed: 19298086] (d) Givens RS, Rubina M, Wirz J. Photochem Photobiol Sci. 2012; 11:472–488. [PubMed: 22344608]
7. (a) Kammath VB, Solomek T, Ngoy BP, Heger D, Klán P, Rubina M, Givens RS. J Org Chem. 2013; 78:1718–1729. [PubMed: 22686289] (b) Solomek T, Ngoy BP, Heger D, Givens R, Klan PJ. Am Chem Soc. 2013 (in press).
8. Blancafort L, Migani A, Li Q. J Phys Chem Lett. 2012; 3:1056–1061.
9. (a) Stensrud KF, Heger D, Sebej P, Wirz J, Givens RS. Photochem Photobiol Sci. 2008; 7:614–624. [PubMed: 18465018] (b) Stensrud K, Noh J, Kandler K, Wirz J, Heger D, Givens RS. J Org Chem. 2009; 74:5219–5227. [PubMed: 19572582]
10. (a) Ma C, Zuo P, Kwok WM, Chan WS, Kan JTZ, Toy PH, Phillips DL. J Org Chem. 2004; 69:6641–6657. [PubMed: 15387586] (b) Ma C, Kwok WM, Chan WS, Zuo P, Kan JTW, Toy PH, Phillips DL. J Am Chem Soc. 2005; 127:1463–1472. [PubMed: 15686379] (c) Chan WS, Kwok WM, Phillips DL. J Phys Chem A. 2005; 109:3454–3469. [PubMed: 16833683] (d) Ma C, Kwok WM, Chan WS, Du Y, Kan JTW, Phillips DL. J Am Chem Soc. 2006; 128:2558–2570. [PubMed: 16492039] (e) Zuo P, Ma C, Kwok WM, Chan W, Phillips DL. J Org Chem. 2005; 70:8661–8675. [PubMed: 16238294] (f) Chen XB, Ma C, Kwok WM, Guan X, Du Y, Phillips DL. Phys Chem A. 2006; 110:12406–12413.
11. Burdzinski G, Kubicki J, Sliwa M, Réhault J, Zhang Y, Vyas B, Luk HL, Hadad CM, Platz MS. J Org Chem. 2013; 78:2026–2032. [PubMed: 23190449]
12. (a) Horner L, Kirmse W, Muth K. Chem Ber. 1958; 91:430–437.(b) Meinwald J, Lewis A, Gassman PG. J Am Chem Soc. 1962; 84:977–983.(c) Cookson RC, Hudec J, Knight SA, Whitear BRD. Tetrahedron. 1963; 19:1995–2007.
13. Givens RS, Rubina M, Stensrud KL. J Org Chem. 2013; 78:1709–1717. [PubMed: 23057737]
14. (a) Kirmse W, Horner L. Liebigs Ann Chem. 1959; 625:34–43.(c) Wang J, Burdzinski G, Kubicki J, Gustafson TL, Platz MS. J Am Chem Soc. 2008; 130:5418–5419. [PubMed: 18366167] (d) Tomioka H, Okuno H, Izawa Y. J Org Chem. 1980; 45:5278–5283.

15. Greene, TW.; Wutts, PGM. Greene's Protective Groups in Organic Synthesis. 4. John Wiley & Sons; New Jersey, United States: 2007.
16. (a) Gassman PG, Greenlee WJ. Org Syn. 1973; 53:38–43.(b) Pizey, JS. In Synthetic Reagent. Ellis Horwwd, Ltd; Chichester, England: 1977. (c) More O'Ferrall RA. Adv Phys Org Chem. 1967; 5:331–399.(d) Hassid AI, Kreevoy MM, Liang TM. Faraday Symp Chem Soc. 1975; 10:69.(e) Albery WJ, Conway CW, Hall JA. J Chem Soc, Perkin Trans 2: Phys Org Chem. 1976; 4:473–477.(f) Kuehnel E, Laffan DDP, Lloyd-Jones GC, Del Campo TM, Shepperson IR, Slaughter JL. Angew Chem Int Ed. 2007; 46:7075–7078.
17. Remeš M, Roithová J, Schröder D, Cope E, Perera C, Senadheera SN, Stensrud K, Ma CC, Givens RS. J Org Chem. 2011; 76:2180–2186. [PubMed: 21384805]
18. (a) Park C-H, Givens RS. J Am Chem Soc. 1997; 119:2453–2463.(b) Conrad PG II, Givens RS, Weber JFW, Kandler K. Org Lett. 2000; 2:1545–1547. [PubMed: 10841475]
19. Curtius T. Ber. 1883; 16:2230–2231.
20. (a) An earlier use of diazo pHP for the synthesis of pHP O_2CCF_3 (12) has been reported in reference 17 see also Doyle MP, McKervey MA, Ye T. Modern Catalytic Methods for Organic Synthesis with Diazo Compounds. John Wiley & SonsNew York1998:433–486.
21. Givens RS, Stensrud K, Conrad PG II, Yousef AL, Perera C, Senadheera SN, Domink H, Wirz J. Can J Chem. 2011; 89:364–384. [PubMed: 24436496]
22. Nagano T, Matsumura K. J Am Chem Soc. 1953; 75:6237–6238.
23. Périé J, Gefflaut T. Synth commun. 1994; 24:29–33.
24. (a) Conrad PG II, Givens RS, Hellrung B, Rajesh CS, Ramseir M. J Am Chem Soc. 2000; 122:9346–9347.(b) Sebej P, Lim BH, Park BS, Givens RS, Klan P. Org Lett. 2011; 13:644–647. [PubMed: 21235252]
25. (a) Goodman JM, Jmes JJ, Whiting A. J Chem Soc Perkin Trans 2. 1994:109–16.(b) March, J. Advanced Organic Chemistry. 4. Wiley; New York: 1992.
26. Kaplan F, Meloy GK. Tetrahedron Lett. 1964:2427–2430.
27. Kaplan F, Meloy GK. J Am Chem Soc. 1966; 88:950–956.
28. Tomioka H, Kitagawa H, Izawa Y. J Org Chem. 1979; 44:3072–3075.
29. Tomioka H, Okuno H, Izawa Y. J Org Chem. 1980; 45:5278–5283.
30. Paliani G, Sorriso S, Cataliotti R. J Chem Soc, Perkin Trans 2: Phys Org Chem. 1976:707–710.
31. Sorriso S, Piazza G, Foffani A. J Chem Soc B. 1971:805–809.
32. Werstiuk NH, Muchall HM, Ma J, Liu MTH. Can J Chem. 1998; 76:1162–1173.
33. Muchall NH, Pitters MS, Workentin MS. Tetrahedron. 1999; 55:3767–3778.
34. Zhang K, Corrie JET, Munasinghe VRN, Wan P. J Am Chem Soc. 1999; 121:5625–5632.
35. Mazzucato U, Cauzzo G, Foffani A. Tetrahedron Lett. 1963; 23:1525–1529.
36. Scaiano JC. J Am Chem Soc. 1980; 102:7747–7753.
37. Herkstroeter WG, Lamola AA, Hammond GS. J Am Chem Soc. 1964; 86:4537–4540.
38. Turro, NJ. Modern Molecular Photochemistry. Benjamin/Cummings Publishing Co. Inc; Menlo Park: 1978.
39. Pastor-Pérez L, Wiebe C, Pérez-Prietto J, Stiriba S–E. J Org Chem. 2007; 72:1541–1544. [PubMed: 17288402]
40. Klan, P.; Wirz, J. Photochemistry of Organic Compounds From Concepts to Practice. Wiley; 2009.
41. Murov, SL.; Carmichael, I.; Hug, GL. Handbook of Photochemistry. Marcel Dekker Inc; New York: 1993.
42. Calvert, JG.; Pitts, JN. Photochemistry. Wiley & Sons; New York: 1966.
43. Andreu GL, Delgado R, Velho JA, Curti C, Vercesi AE. Arch Biochem Biophys. 2005; 439:184–193. [PubMed: 15979560]
44. Gut IG, Wood PD, Redmond RW. J Am Chem Soc. 1996; 118:2366–2373.
45. Rajesh CS, Givens RS, Wirz J. J Am Chem Soc. 2000; 122:611–618.
46. Givens RS, Lee J-I. J Photosci. 2003; 10:37–48.
47. Candeias NR, Afonso CAM. Curr Org Chem. 2009; 13:763–787.

48. Scaiano JC. J Am Chem Soc. 1980; 102:7747–7753.
49. Iwata K, Hamaguchi H. Appl Spectrosc. 1990; 44:1431–1437.
50. Yuzawa T, Kato C, George MW, Hamaguchi H. Appl Spectrosc. 1994; 48:684–690.
51. Wang Y, Yuzawa T, Hamaguchi H, Toscano JP. J Am Chem Soc. 1999; 121:2875–2882.
52. Wagner BD, Arnold BR, Brown GS, Lusztyk J. J Am Chem Soc. 1998; 120:1827–1834.
53. Allen AD, Colomvakos JD, Diederich F, Eagle I, Hao X, Liu R, Lusztyk J, Ma J, McAllister MA, Rubin Y, Sung K, Tidwell TT, Wagner BD. J Am Chem Soc. 1997; 119:12125–12130.
54. Camara de Lucas N, Netto-Ferreira JC, Andraos J, Lusztyk J, Wagner BD, Scaiano JC. Tetrahedron Lett. 1997; 38:5147–5150.
55. Wagner BD, Zgierski MZ, Lusztyk J. J Am Chem Soc. 1994; 116:6433–6434.
56. (a) Andraos J, Chiang Y, Kresge AJ, Pojarlieff IG, Schepp NP, Wirz J. J Am Chem SOC. 1994; 116:73–81.(b) McGarrity JF, Smyth T. J Am Chem SOC. 1980; 102:7303–7308.
57. Wolff L. Justus Liebigs Ann Chem. 1902; 325:129–195.
58. Park C-H, Givens RS. J Am Chem Soc. 1997; 119:2453–2463.
59. Qin J, Xie M, Hu Z, Zhao H. Synth Commun. 1992; 22:2253–2258.
60. Liu C, Gou W, Shi X, Kaium MA, Gu X, Zhu YZ. Eur J Med Chem. 2011; 46:3996–4009. [PubMed: 21723646]
61. Arndt, F. Organic Synthesis, Collective. Vol. II. Wiley & Sons; New York: 1943. p. 165-167.
62. Mander LN, Beames D. J Aust Chem. 1974; 27:1257–1268.
63. Adams R, Binder LO. J Am Chem Soc. 1941; 63:2773–2776.
64. Das B, Ravindranath N, Mahender G, Ramesh C. Tetrahedron. 2003; 59:1049–1054.
65. Epstein WW, Garrossian M. J Chem Soc, Chem Commun. 1987; 8:532–533.
66. Shinada T, Kawakami T, Sakai H, Takada I, Ohfune Y. Tetrahedron Lett. 1998; 39:3757–3760.
67. Givens RS, Jung A, Park C-H, Weber J, Bartlett W. J Am Chem Soc. 1997; 119:8369–8370.
68. International Tables for Crystallography. 4. Vol. A. Kluwer; Boston: 1996.
69. Data Collection: SMART Software Reference Manual. Bruker-AXS; Madison, WI, USA: 1998.
70. Data Reduction: SAINT Software Reference Manual. Bruker-AXS; Madison, WI, USA: 1998.
71. Sheldrick, GM. SHELXTL Version 6.10 Reference Manual. Bruker-AXS; Madison, WI, USA: 2000.
72. Hatchard CG, Parker CA. Proc R Soc London A. 1956; A220:518–536.
73. Lee CY, Chew EH, Go ML. Eur J Med Chem. 2010; 45:2957–2971. [PubMed: 20392544]
74. Wuennemann S, Froehlich R, Hoppe D. Organic Lett. 2006; 8:2455–2458.

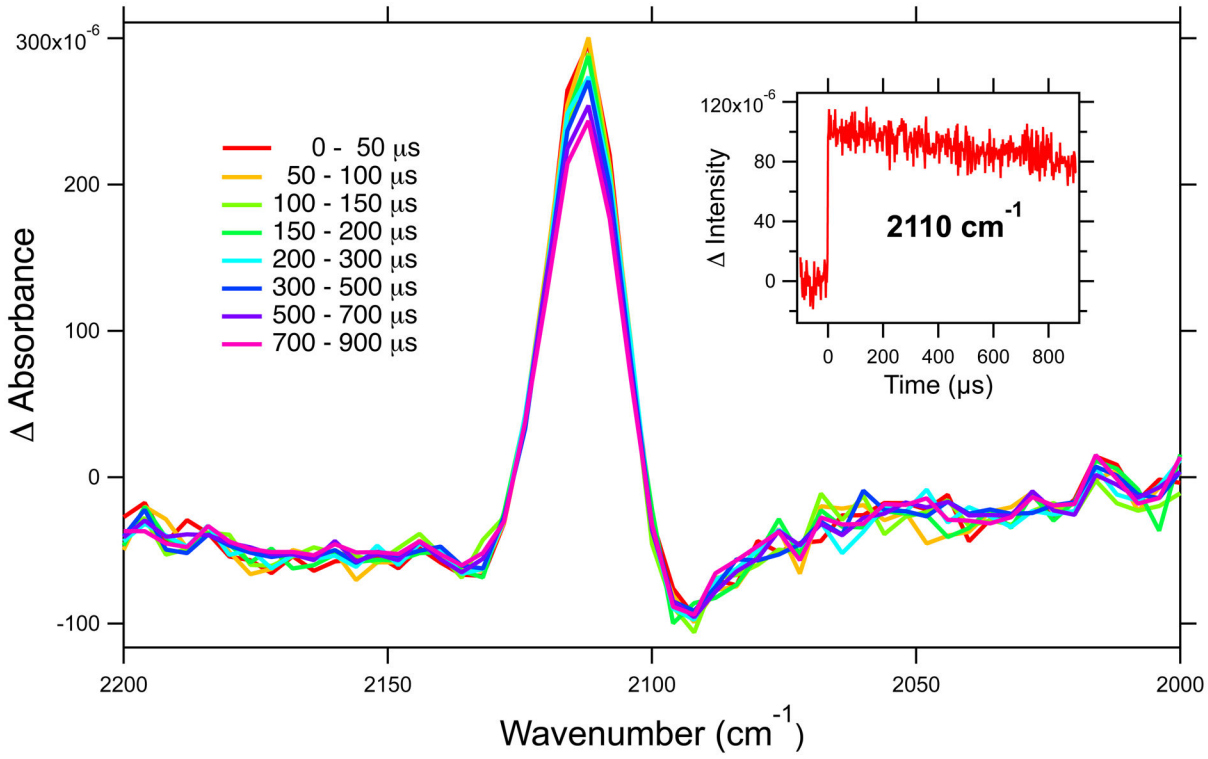


Figure 1.

TRIR difference spectra averaged over the timescales indicated following 266 nm laser photolysis of a solution of **1a** prepared in argon-saturated 5% aqueous acetonitrile with an O.D. of 0.99 at 266 nm (0.5 mm path length). The inset shows the corresponding kinetic trace observed at 2110 cm^{-1}.

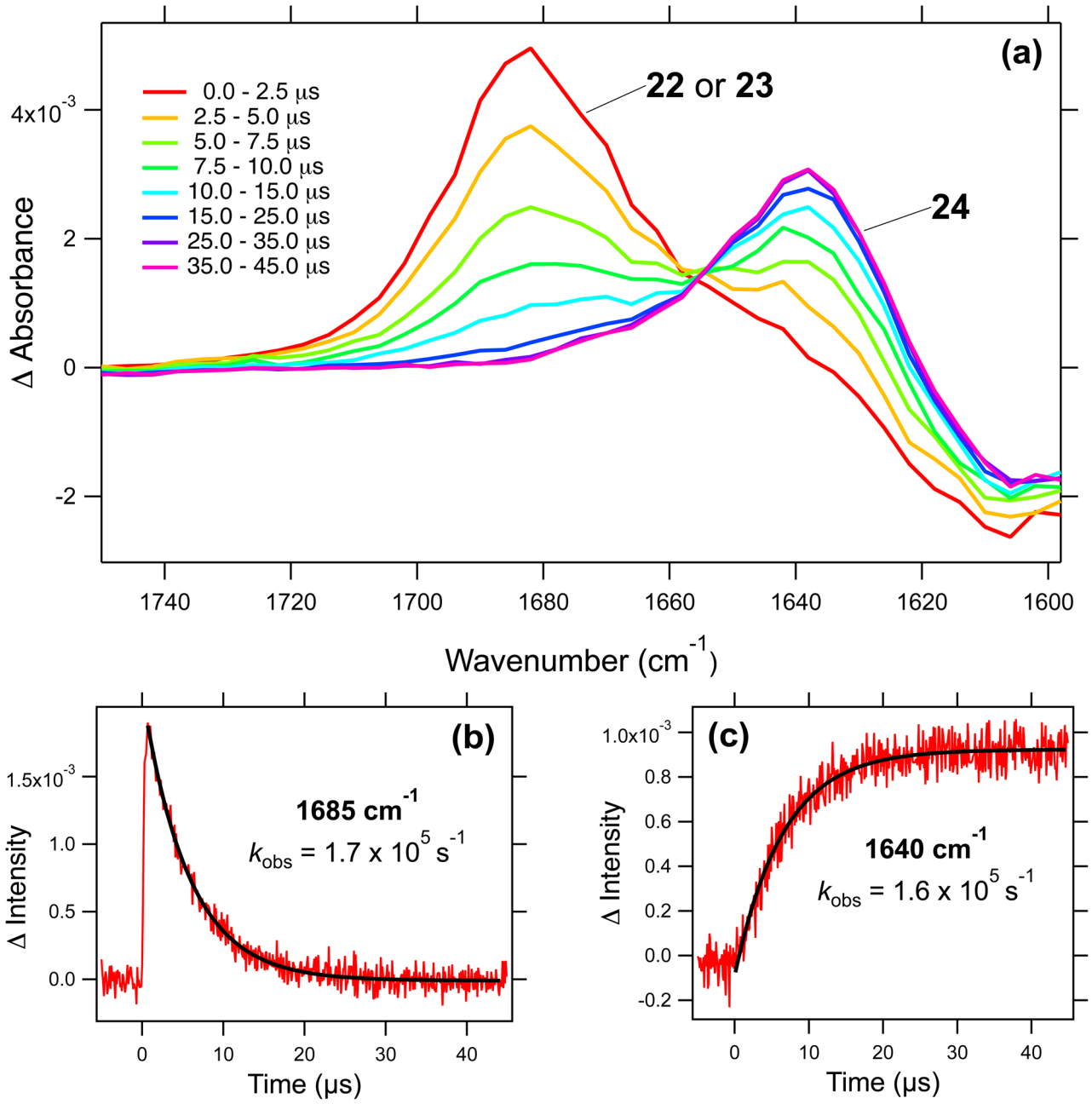
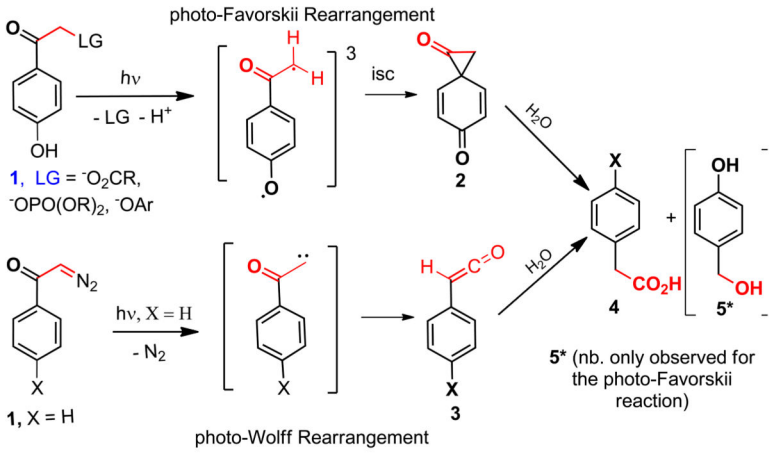


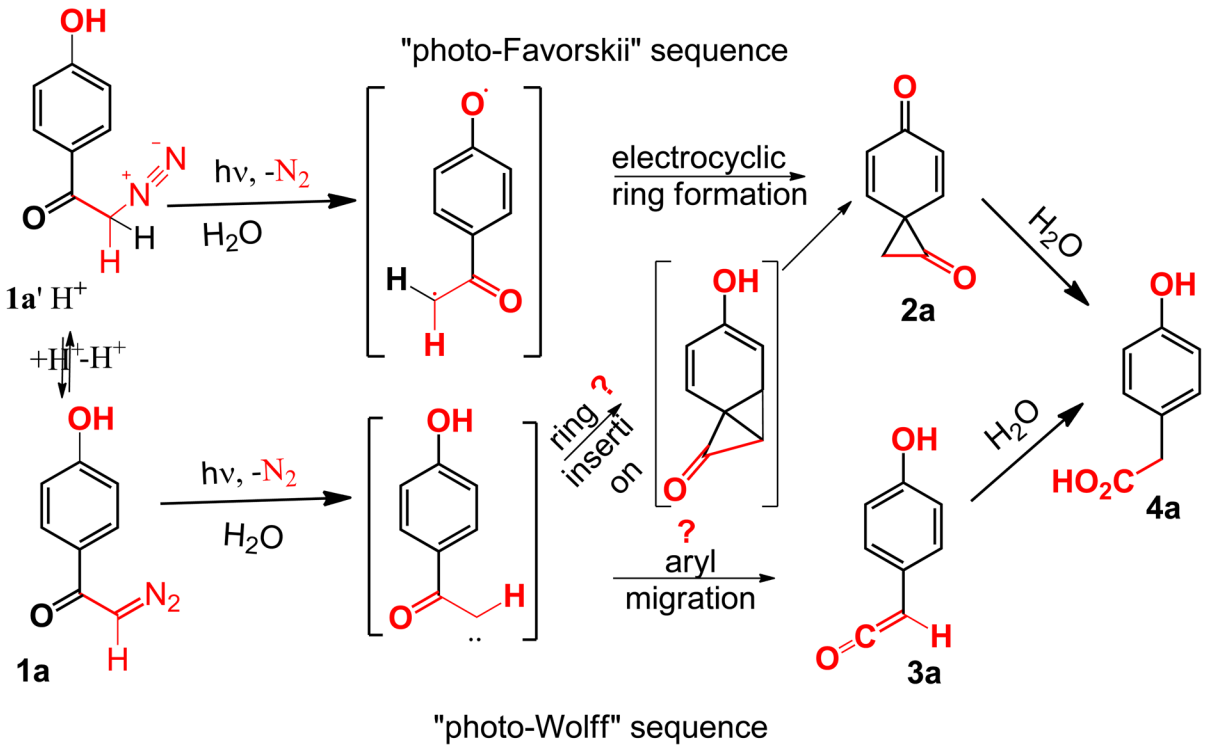
Figure 2.

(a) TRIR difference spectra averaged over the timescales indicated following 266 nm laser photolysis of a solution of **1a** with 2 mM diethylamine prepared in argon-saturated acetonitrile with an O.D. of 0.99 at 266 nm (0.5 mm path length). The corresponding kinetic traces observed at 1685 cm^{-1} and 1640 cm^{-1} are shown in (b) and (c), respectively. The red curves are experimental data; the black curves are best fits to a single-exponential function.



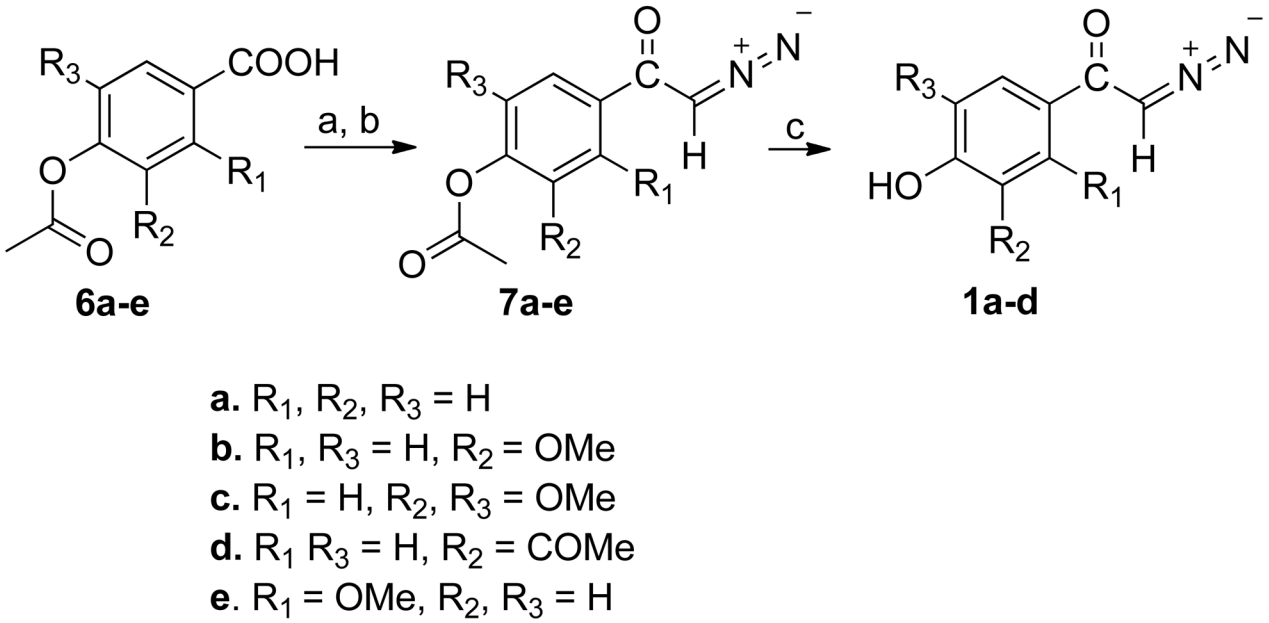
Scheme 1.

General rearrangement pathways for the photo-Wolff (pWR) and photo-Favorskii (pFR) reactions.



Scheme 2.

The divergent pathways available to 2-diazo-1-(4-hydroxyphenyl) ethanone (α-diazo-*p*-hydroxyacetophenone, **1a**).

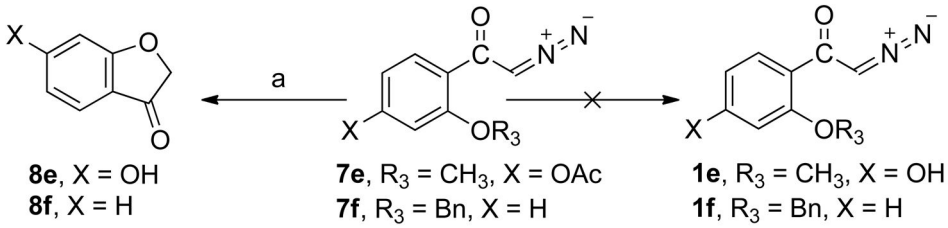


a. R_1, R_2, R_3 = H
b. R_1, R_3 = H, R_2 = OMe
c. R_1 = H, R_2, R_3 = OMe
d. R_1 R_3 = H, R_2 = COMe
e. R_1 = OMe, R_2, R_3 = H

Scheme 3.

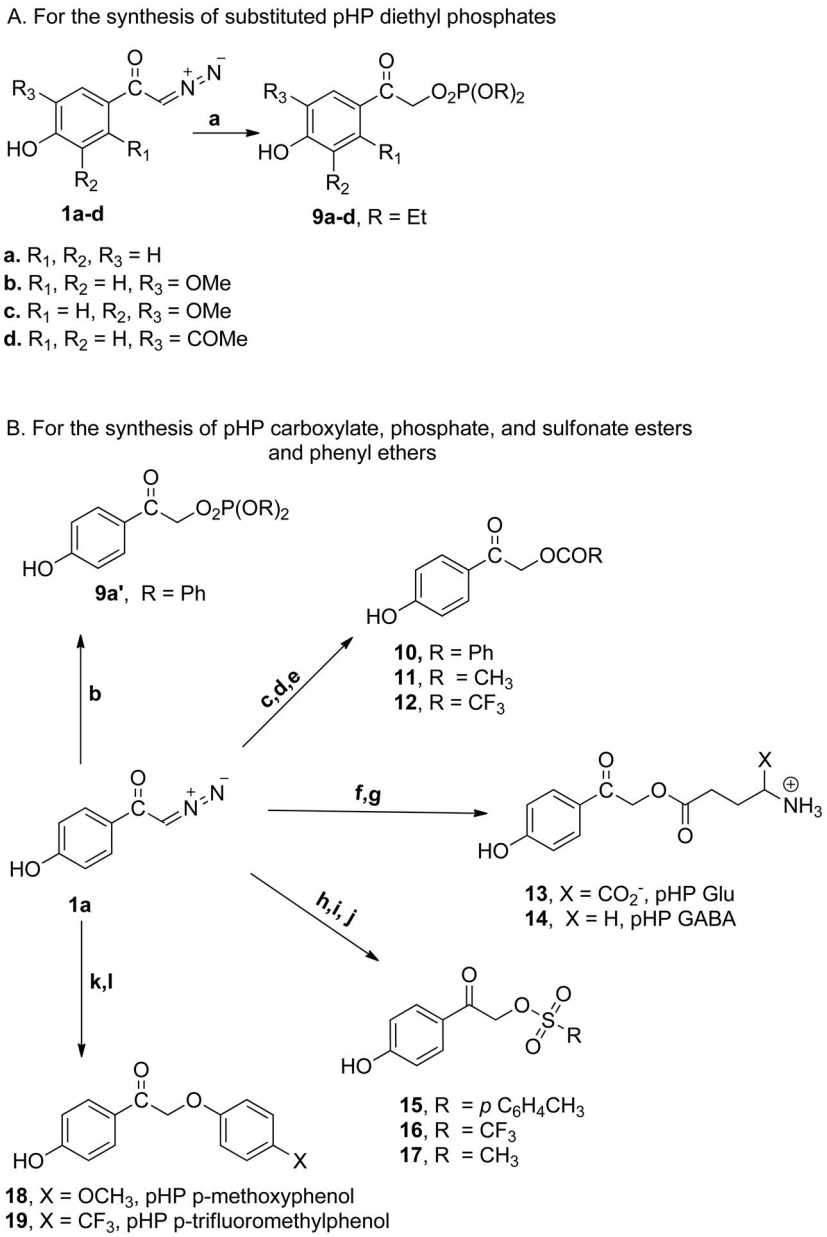
Synthesis of substituted 2-diazo-1-(4-hydroxyphenyl)ethanones (**1a–d**).

Reagents and conditions; (a) $SOCl_2$, reflux, 8 h, 95–99%; (b) CH_2N_2, Et_2O, 0 °C to rt, overnight, 38–69%; (c) NH_4OAc, H_2O/MeOH, 1:4, 50 °C, 8 h, 90–98%.



Scheme 4.

Cyclization reactions of 2-diazo-1-(2-methoxyphenyl)ethanones (**7e**,**f**) to furanones **8e**, f. Reagents and conditions; (a) NH_4OAc, H_2O/MeOH, 1:4, 50 °C, 8 h or H^+ or H_2O or OH^-, rt, 100%.

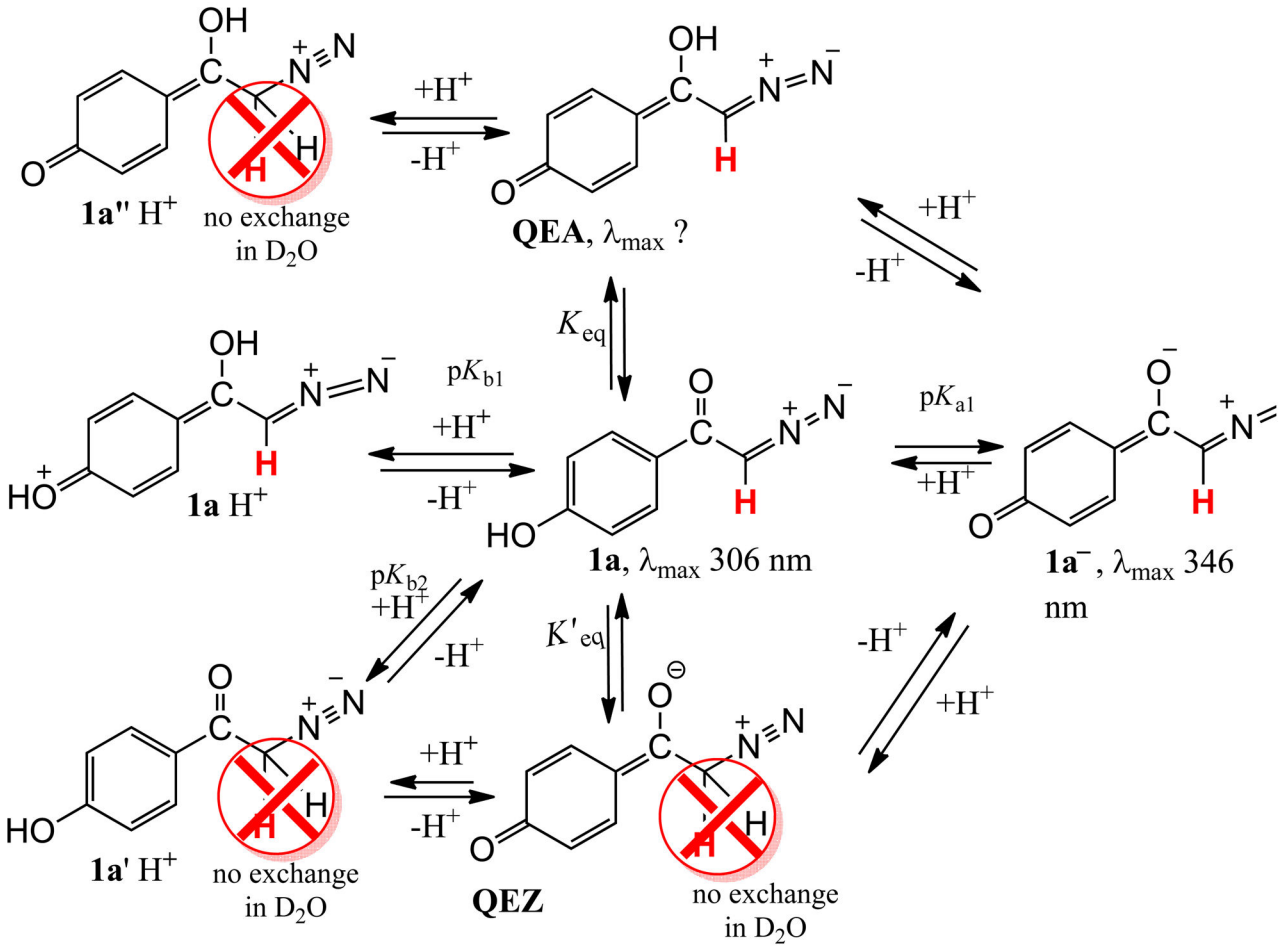


Scheme 5.

Substituted 2-diazo-4-hydroxyphenylethanones as synthons for pHP caging.

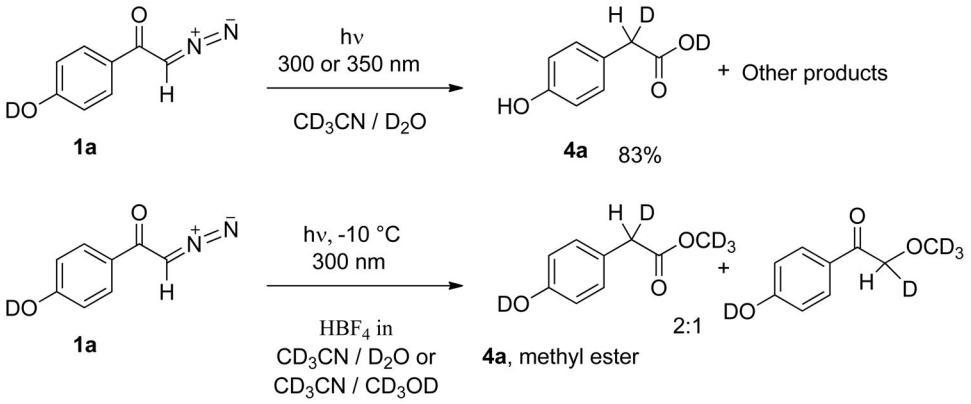
Reagents and conditions; (a) $HOP(O)(OEt)_2$, benzene, 60 °C, 24 h, 75–79%, (b) $HOP(O)(OPh)_2$, benzene, 60 °C, 24 h, 92%, (c) $PhCO_2H$, benzene, 70 °C, 42 h, 97%; (d) CH_3COOH, H_2O/CH_3CN, 1:1, 16 h, rt, 98%; (e) CF_3COOH, benzene, 0 °C - rt, 1 h, 94%; (f) Boc-Glu(O^{t}Bu)-OH, cat. $Cu(acac)_2$, toluene, 60 °C, 2 h, followed by TFA/CH_2Cl_2, 1:1, 15 min, rt, 71% overall yield (g) Boc-GABA, cat. $Cu(acac)_2$, toluene, 60 °C, 2 h followed by TFA/CH_2Cl_2, 1:1, 15 min, rt, 75% overall yield, (h) *p*-TsOH.H_2O, CH_3CN, 0 °C – rt, 1 h, 71%; (i) CF_3SO_3H, benzene, 0 °C – rt, 30 min, 91% (crude); (j) MsOH, benzene, 0 °C – rt, 1.5 h, 98%, (k) as the acetate **7a**, *p*-$CH_3OC_6H_4OH$, 50 °C, 8 h, then NH_4OAc, H_2O/

MeOH, (1:4), 50 °C, 8 h, 56–68% overall yield (l) as the acetate **7a**, *p*-$CF_3C_6H_4OH$, 50 °C, 8 h, then NH_4OAc, H_2O/ MeOH, (1:4), 50 °C, 8 h, 56–68% overall yield.



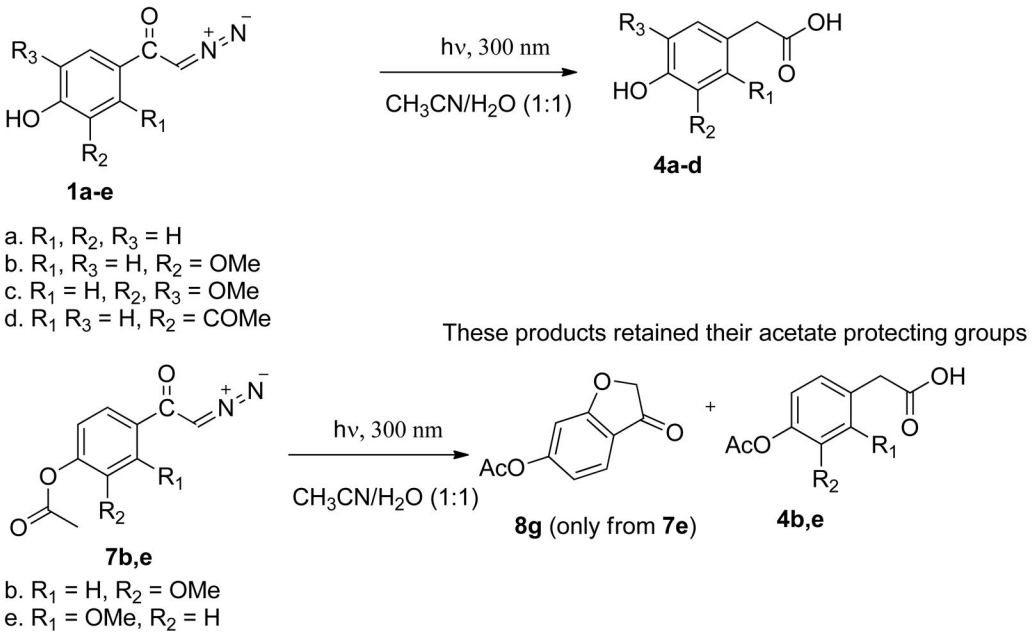
Scheme 6.

Single proton acid-base equilibria of 2-diazo-1-(4-hydroxyphenyl)ethanone **1a**.



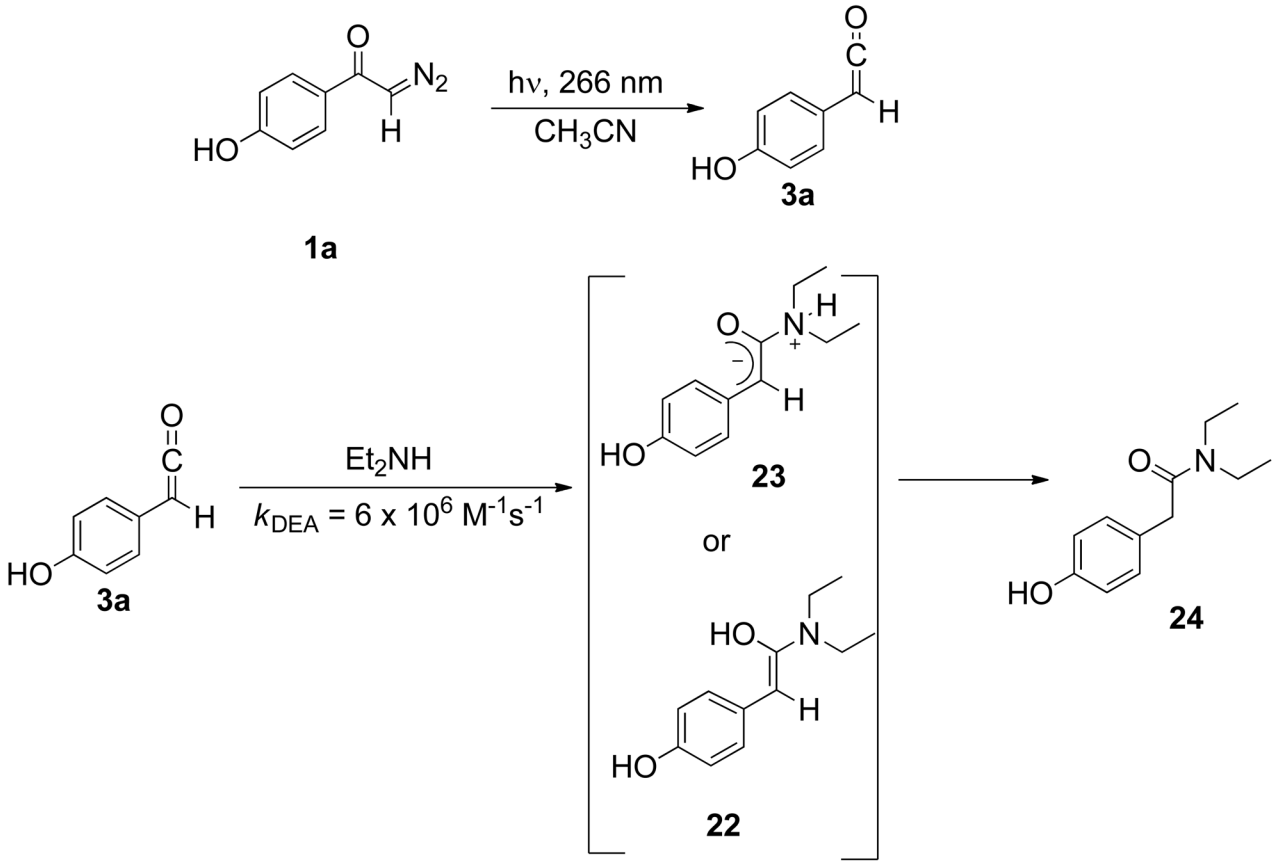
Scheme 7.

The photorearrangements of **1a** in neutral and acidic aqueous acetonitrile.



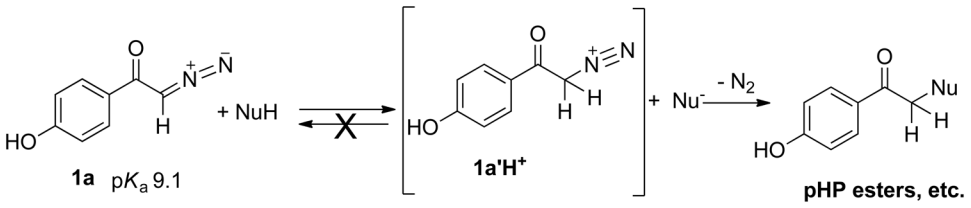
Scheme 8.

Photochemistry of **1a** – **d, 7b** and **7e**.



Scheme 9.

The photochemistry of **1a** in acetonitrile with added diethylamine to form *N*,*N*-diethyl amide **24**.



Scheme 10.

Mechanism for irreversible protonation yielding esterification of acids.

Table 1

pKa's and UV-vis maxima and extinction coefficients for **1a**–**d**.

Substituted α-diazo acetophenones	pKa	pH/buffer	λ_{max} (log ε_{max})
1a	9.1	4.0[a]	306 (4.23)
		7.0[b]	306 (4.15)
		10.0[c]	346 (4.13)
1b, 3-OMe	8.9	H_2O	315 (4.15)
1c, 3,5-$(OMe)_2$	9.0	H_2O	318 (4.27)
1d, 3-$COCH_3$	7.7	H_2O	295 (3.90)

[a] sodium acetate/acetic acid buffer (0.1M);

[b] ammonium acetate/ammonia (0.1M);

[c] ammonium acetate/ammonia (0.1M).

Table 2

Substituent and solvent effects on the photorearrangement of 4-substituted α-diazo acetophenones **1** to arylacetates **4** at 300 nm.

Substituted α-diazo acetophenones	λ_{max}[a]/nm	Φ_{dis}[b]	Φ_{app}[b]	Ref.
1, H-C_6H_4-$COCHN_2$	294[c]	0.46[c], 0.40[c]		35
1a, 4-OH	306	0.25	0.23	This work
1b, 4-OH, 3-OMe	315	0.21	0.19	This work
1c, 4-OH, 3,5-$(OMe)_2$	318	0.19	0.18	This work
1d, 4-OH, 3-$COCH_3$	295	0.10	nd	This work
1f, 4-CH_3O-C_6H_4-$COCHN_2$	304[c]	0.34[c]		35
1g, 4-NO_2-C_6H_4-$COCHN_2$	307[c]	0.18[c]		35

[a] H_2O:CH_3CN (1:1);

[b] D_2O:CD_3CN (1:1);

[c] Methanol

Table 3

Sensitization and Quenching Quantum Yields for **1a.**

Conditions[a]	Excitation Wavelength (nm)	$\Phi^{b}_{dis.}$	$\Phi^{b}_{app.}$
Direct Irradiation[c]	300	0.25	0.22
Sensitization with **21**[d]	300	0.13	0.11
Sensitization with **20**[e]	300	0.19	0.13
Purged with 100% O_2	300	0.17	0.12
Purged with Ar	300	0.28[f]	0.24

[a] Solvents were 1:1 H_2O:CH_3CN. Each sample was irradiated for 8 min using the conditions given in the Table 3 with 2–300 nm lamps.

[b] Analysis of the samples was by RP-HPLC, error limits were ± 0.01.

[c] Not degassed.

[d] Sensitization with **21** using 16–350 nm lamps, concentration of **21** was 4.76×10^{-3} M.

[e] Concentration of **20** was 3.70×10^{-3} M.

[f] Error limit was ± 0.02.

Table 4

O_2 quenching of **1a** in 1:1 H_2O:CH_3CN.

Experimental condition	$[O_2]$, M	Φ_{dis}	Φ_{app}	$(\Phi_0/\Phi)_{dis}$	$(\Phi_0/\Phi)_{app}$
Purged with Ar	2.7×10^{-6}	0.28	0.24	1.00	1.00
Ambient conditions, not purged	2.7×10^{-4}	0.25	0.22	1.12	1.09
Purged with O_2	2.0×10^{-3}	0.17	0.12	1.65	2.00

[a]The oxygen concentration was reduced to approximately 10^{-6} M by degassing the photolysis solution with Ar.[38]