JOC Article
pubs.acs.org/joc

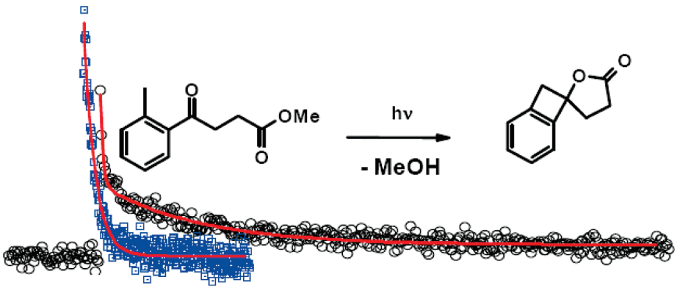
Effect of Alkyl Substituents on Photorelease from Butyrophenone Derivatives

Sivaramakrishnan Muthukrishnan,[†] Jagadis Sankaranarayanan,[†] Tamara C. S. Pace,[‡] Armands Konosonoks,[†] Mariel E. DeMichiei,[†] Michael J. Meese,[†] Cornelia Bohne,[‡] and Anna D. Gudmundsdottir*

[†]*Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221, and* [‡]*Department of Chemistry, University of Victoria, Victoria, BC, Canada V8W 3 V6*

anna.gudmundsdottir@uc.edu

Received September 30, 2009



Photolysis of **1a** yields **4a** in argon-saturated methanol, whereas **1b** is photostable. Laser flash photolysis of **1a** in acetonitrile shows formation of biradical **2a** (λ_{max} = 340 nm, τ = ~60 ns), which undergoes intersystem crossing to form **Z-3a** (λ_{max} = 380 nm, τ = 270 ns) and **E-3a** (λ_{max} = 380 nm, τ = 300 ms). **Z-3a** regenerates the starting material, whereas **E-3b** undergoes intramolecular lactonization to release the alcohol moiety and form **4a**. Similar laser flash photolysis of **1b** shows formation of biradical **2b** (λ_{max} = 340 nm, τ = 1.9 μs in acetonitrile), which is longer-lived than **2a** is. However, **2b** only undergoes intersystem crossing to form **Z-3b** (λ_{max} = 380 nm, τ = 4.3 μs). Calculations demonstrate that intramolecular pseudo hydrogen bonding between the OH moiety and the radical centered on the isopropyl carbon in **2b** and the bulkiness of the isopropyl group prevent the necessary rotation to form **E-3b**. In comparison, **2a** does not form an intramolecular pseudo hydrogen bond between the methylene radical center and the OH group, and as a consequence, it undergoes intersystem crossing to form both **E-** and **Z-3a**.

Introduction

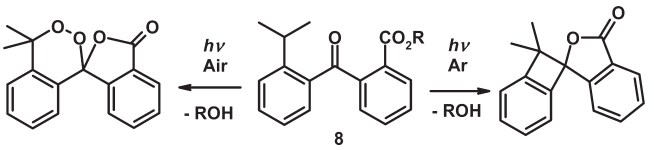
Phototriggers, photocaging groups, or photoremovable protecting groups (PRPGs) have been used to release molecules with specific properties in a wide variety of applications.[1−5] For example, PRPGs have been used as aids in multistep syntheses and to deliver fragrance in household goods. Furthermore, PRPGs have been used to study various physiological events, such as enzyme activities, ion channel permeability, protein folding, and muscle contraction by ATP hydrolysis.[6] PRPGs are particularly useful in physiological studies because bioactive molecules can be delivered with high spatial and temporal control within living cells. Because photoremovable protecting groups have potential use in such a wide diversity of applications, there is a need for PRPGs with different physical properties that can specifically be tailored to each application.

The most common PRPGs are nitrobenzene derivatives, which have been studied extensively.[7−9] The photorelease from nitrobenzene derivatives is initiated by intramolecular

(1) Sankaranarayanan, J.; Muthukrishnan, S.; Gudmundsdottir, A. D. In *Advances in Physical Organic Chemistry*; Richard, J., Ed.; Academic Press: New York, 2009; Vol. 43, p 39.
(2) Klan, P.; Paola Pelliccioli, A.; Pospisil, T.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, *1*, 920–923.
(3) Ellis-Davies, G. C. R. *Nat. Methods* **2007**, *4*, 619–628.
(4) Mayer, G.; Heckel, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4900–4921.
(5) Givens, R. S.; Kotala, M. B.; Lee, J.-I. In *Dynamic Studies in Biology*; Goeldner, M., Givens, R., Eds.; Wiley-VCH: Weinheim, 2005; pp 95−129.
(6) *Dynamic Studies in Biology*; Goeldner, M., Givens, R., Eds.; Wiley-VCH: Weinheim, 2005.
(7) Pelliccioli, A. P.; Wirz, J. *Photochem. Photobiol. Sci.* **2002**, *1*, 441–458.
(8) Mayer, G.; Heckel, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4900–4921.
(9) Corrie, J. E. T. In *Dynamic Studies in Biology*; Goeldner, M., Givens, R., Eds.; Wiley-VCH: Weinheim, 2005; pp 1−28.

DOI: 10.1021/jo9021088 Published on Web 01/29/2010

SCHEME 1

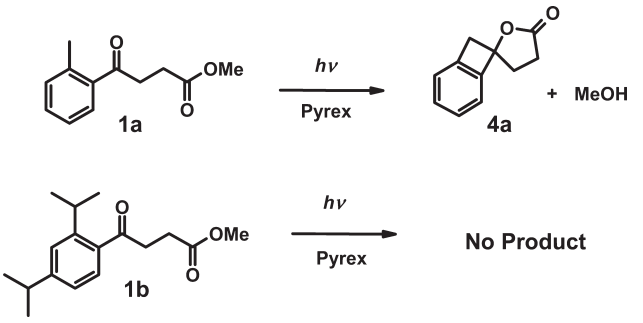


H-atom abstraction to yield photoenols that react further to release the protected molecules. Several other PRPGs have been reported that also rely on intramolecular H-atom abstraction and photoenolization to initiate photorelease.[10−14] We have made PRPGs that are benzophenone ester derivatives and release their alcohols upon exposure to light via photoenolization.[15−17] The benzophenone derivative shown in Scheme 1 releases its alcohol moiety upon exposure to light via photoenolization.[16] The release is independent of the reaction medium and takes place in argon- and oxygen-saturated solutions. Furthermore, the photorelease takes place efficiently in thin films of the PRPGs. The rate of release is slow on the order of seconds. The chemical yields for release are quantitative, whereas the quantum yield for the release is ~0.17. In our continuing effort to design new photoremovable protecting groups with unique properties, we synthesized esters **1a** and **1b**, which differ from the benzophenone-based PRGPs we studied previously, because **1a** and **1b** are more flexible. Esters **1a** and **1b** are butyrophenone derivatives and thus have a flexible alkyl chain. We investigated the photoreactivity of **1a** and **1b** and how their flexibility affects the mechanisms for photorelease.

Results

1. Product Studies. Photolysis of **1a** in argon-saturated methanol resulted in the formation of **4**, whereas irradiation of **1b** under similar conditions did not yield any photoproducts (Scheme 2). We theorize that photolysis of **1a** results in **2** by intramolecular H-atom abstraction and formation of photoenols, as shown in Scheme 3. In more detail, irradiation of **1a** results in formation of the triplet ketone (T_{1K}) of **1a**, which undergoes intramolecular H-atom abstraction to form biradical **2a**. Intersystem crossing of **2a** yields photoenols **E-3a** and **Z-3a**. Presumably, **Z-3a** is short-lived and decays back to the starting material via 1,5 H-atom shift, whereas **E-3a** lactonizes to form **4**. It is also possible that the singlet excited state of the ketones (S_{1K}) of **1a** and **1b** form **Z-3** directly; however, the S_{1K} of **1a** and **1b** is not expected to result in **E-3**.[18]

SCHEME 2. Photolysis of 1a,b in Argon-Saturated Methanol



In oxygen-saturated solution, photolysis of **1a** primarily yielded **5** and a smaller amount of **6**, whereas **1b** yielded **7** (Scheme 4). Products **5** and **7** can all be attributed to trapping biradicals **2a,b** with oxygen to form peroxides, which hydrolyze to form **5** and **7** (Scheme 5). Presumably, **6** is formed by secondary photolysis of **5**. Similar photoproducts in oxygen-saturated solutions have been obtained from photolysis of *o*-methyl benzophenone derivatives that undergo intramolecular H-atom abstraction to form photoenols.[15,19] The peroxides shown in Scheme 5 must form **5** and **7** faster than they undergo intramolecular lactonization, and thus release of the alcohol moiety from **1a,b** is not observed in oxygen-saturated solutions.

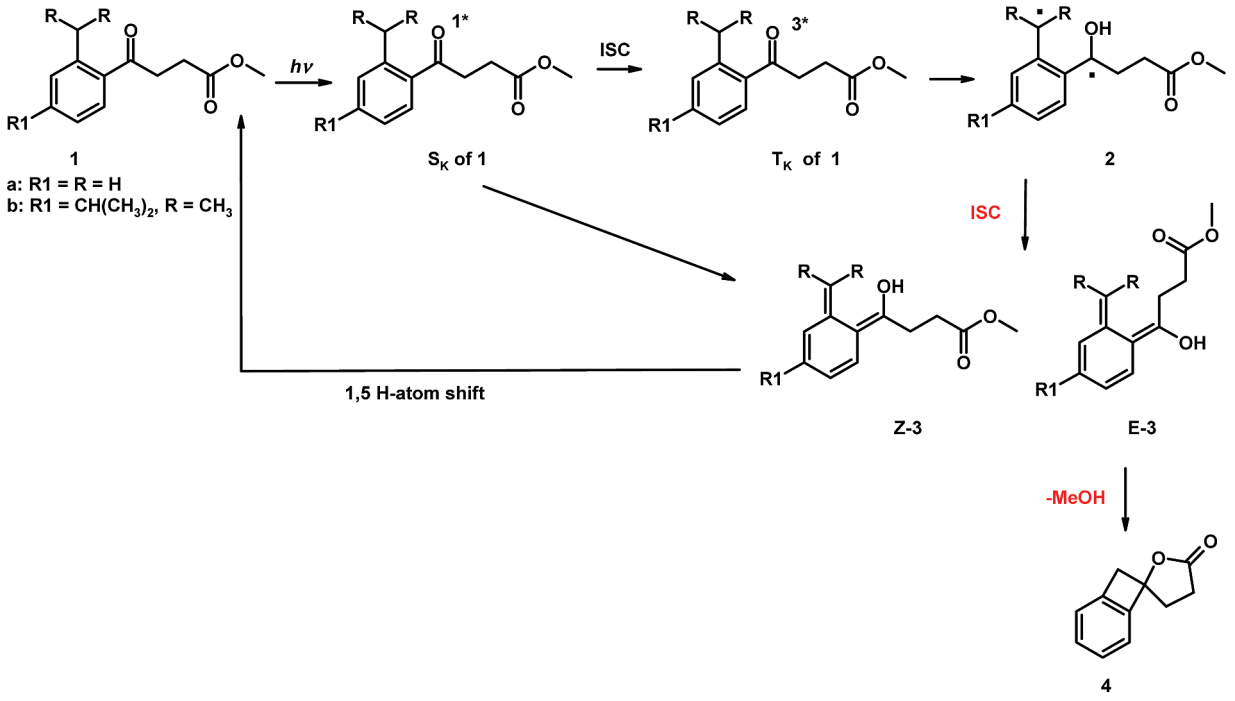
Quantum Yields. The quantum yields for depleting **1a** and forming **4** in argon-saturated methanol were measured (Table 1). We also measured the quantum yields for depleting **1a** and forming **5** and **6** in oxygen-saturated methanol. Thus, the quantum yield for release from **1a** in argon-saturated solution is lower than what we observed for **8**, which has a quantum yield of 0.14 for photorelease in 2-propanol.[16]

Laser Flash Photolysis. We performed laser flash photolysis to support the proposed mechanism for photorelease from **1a** (Scheme 3). Laser flash photolysis of **1a** in nitrogen-saturated methanol at short delays resulted in a transient absorption with λ_{max} at ~340 nm and at ~380 nm (Figure 1). In oxygen-saturated methanol, the ~340 nm absorption was quenched, indicating that it is due to an oxygen-labile intermediate, which we assign to **2a** on the basis of the similarity of this transient spectrum to the absorption of an analogous biradical formed from intramolecular H-atom abstraction in *o*-methyl-acetophenone derivatives.[10,18] For example, Klan and co-workers demonstrated that the triplet ketone in **1c** has a short lifetime (~3 ns) because it undergoes efficient intramolecular H-atom abstraction to form biradical **2c**, which has λ_{max} at 340 nm and a lifetime of ~300 ns in methanol (Scheme 6).

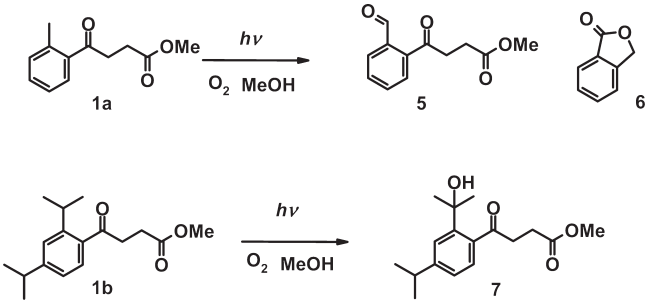
At longer delays, laser flash photolysis of **1a** resulted in a transient absorption with λ_{max} at ~380 nm, which is not quenched by molecular oxygen and which we assigned to **E-3a** and **Z-3a** on the basis of comparison to the transient spectra of similar photoenols.[10,15,16,18] We were not able to measure the rate constant for the formation of **E-3a** and **Z-3a** at 380 nm as a growth kinetics because the absorption bands for **2a** and **3a** overlap. Biradical **2a** must have a higher molar absorptivity than **E-3a** and **Z-3a**, and the kinetics

(10) Zabadal, M.; Pelliccioli, A. P.; Klan, P.; Wirz, J. *J. Phys. Chem. A* **2001**, *105*, 10329–10333.
(11) Atemnkeng, W. N.; Louisiana, L. D.; Yong, P. K.; Vottero, B.; Banerjee, A. *Org. Lett.* **2003**, *5*, 4469–4471.
(12) Bergmark, W. R.; Barnes, C.; Clark, J.; Paparian, S.; Marynowski, S. *J. Org. Chem.* **1985**, *50*, 5612–5615.
(13) Bergmark, W. R. *J. Chem. Soc., Chem. Commun.* **1978**, 61–62.
(14) Jones, P. B.; Brinson, R. G.; Sarma, S. J.; Elkazaz, S. *Org. Biomol. Chem.* **2008**, *6*, 4204–4211.
(15) Konosonoks, A.; Wright, P. J.; Tsao, M.-L.; Pika, J.; Novak, K.; Mandel, S. M.; Krause Bauer, J. A.; Bohne, C.; Gudmundsdottir, A. D. *J. Org. Chem.* **2005**, *70*, 2763–2770.
(16) Pika, J.; Konosonoks, A.; Robinson, R. M.; Singh, P. N. D.; Gudmundsdottir, A. D. *J. Org. Chem.* **2003**, *68*, 1964–1972.
(17) Pika, J.; Konosonoks, A.; Singh, P.; Gudmundsdottir, A. D. *Spectrum* **2003**, *16*, 12–17.
(18) Pelliccioli, A. P.; Klan, P.; Zabadal, M.; Wirz, J. *J. Am. Chem. Soc.* **2001**, *123*, 7931–7932.
(19) Pfau, M.; Molnar, J.; Heindel, N. D. *Bull. Soc. Chim. Fr.* **1983**, 164–169.

SCHEME 3. Proposed Mechanism for Photorelease from 1



SCHEME 4. Photolysis of 1a,b in Oxygen-Saturated Methanol



corresponds to the sum of the absorption changes for **2a** and **E-3a** and **Z-3a** where the observed rate constant is the same for the two processes.[20] However, the rate for forming photoenols has been measured for similar compounds where the molar absorptivity of the photoenols is higher than that for the biradical precursors or the absorption of these intermediates is better resolved.[10,15,18]

We analyzed the kinetics for the absorption for **2a** at 340 nm and found that it was formed immediately during the laser pulse and the lifetime, as determined by its monoexponential decay, was ~580 ns in methanol and ~60 ns acetonitrile, respectively (Table 2). The transient absorption at 340 nm does not decay to the baseline, and the residual absorption decays on longer time scales. We assigned the residual absorption to **E-** and **Z-3a**, and we analyzed the kinetics for **E-** and **Z-3a** at 390 nm where these transients absorb more strongly. The kinetics at 390 nm showed a very rapid decay followed by a decay on the millisecond time scale (Figure 2). The fast decay corresponds to **2a**. The fit of the slow decay at 390 nm began 20 μs after the laser pulse, when the contribution from **2a** became negligible. The kinetics 20 μs after the laser pulse could not be fit to a monoexponential function, confirming the presence of both **Z-** and **E-3a**, which have different lifetimes. The recovered lifetimes of 80 ± 20 μs and 500 ± 70 μs were assigned to **Z-** and **E-3a**, respectively. The large uncertainties for these two lifetimes are a consequence of the poor definition of the final absorbance value after all transients decayed. As expected, the decay rate for **Z-** and **E-3a** is not affected by oxygen.

The kinetics for **1a** in acetonitrile were similar to the kinetics in methanol, but the lifetimes were different (Table 2). A fast decay was observed at 340 and 390 nm (Figures S1 and S2 in Supporting Information) At 390 nm, the decay levels off on the tenths of a microsecond time scale, indicating that **E-3a** is very long-lived; a lifetime of 300 ms was determined when the kinetics were measured for longer times (Figure S3 in Supporting Information). The lifetimes for the triplet biradical **2a** and the Z-enol **Z-3a** were similar, and therefore the decay at 340 nm could be fit to a monoexponential function (τ = 120 ns) or to the sum of two exponentials (τ = 50−70 ns, τ_2 = 240 ns−1 μs) leading to equally acceptable residuals. The fit of the kinetics collected at 390 nm for short time ranges (not shown) recovered only one lifetime of 270 ns when the kinetics were fit to a monoexponential function or to a sum of two exponential function (i.e., the two lifetimes had the same value). The latter result is consistent with the fact that the molar absorptivity of the enol is higher at 390 nm than at 340 nm. Therefore, we assign the lifetime of 270 ns to the Z-enol and 50−70 ns to the triplet biradical.

The transient absorption obtained from laser flash photolysis of **1b** in nitrogen-saturated methanol gave similar results as for **1a** (Figure 3); thus, we assigned the transients with λ_{max} at 340 nm to **2b** and λ_{max} at 380 nm to **3b**. The kinetics for **2b** were measured at 330 nm and showed a

(20) Encinas, M. V.; Wagner, P. J.; Scaiano, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 1357–1360.

SCHEME 5

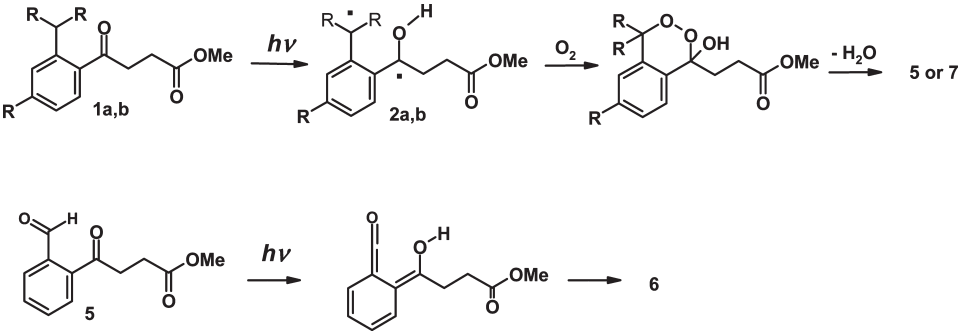


TABLE 1. Quantum Yields for Depletion of 1a and Formation of 4, 5, and 6

	quantum yields (Φ)			
	depleting	forming		
	1a	**4**	**5**	**6**
Ar	0.016 ± 0.002	0.013 ± 0.002		
O_2	0.007 ± 0.001		0.004 ± 0.0004	0.001 ± 0.0001

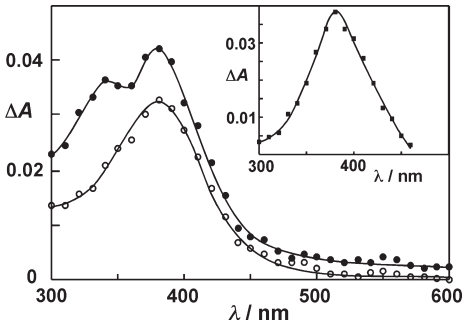


FIGURE 1. Transient spectra (λ_{ex} = 266 nm) for **1a** in methanol purged with nitrogen after a laser pulse at delays of (●) 186 ns and (○) 631 ns. The inset shows the transient spectrum for **1a** in methanol purged with oxygen at a delay of 178 ns after the laser pulse. The lines are included to guide the eye.

monoexponential decay, which had a lifetime of 1.9 μs in methanol and 2.9 μs in acetonitrile. This absorption did not decay to the baseline due to the overlap of the absorption of **3b**, and as expected, the transient absorption for **2b** was quenched in oxygen-saturated solutions. The kinetics for **3b** were analyzed at 390 nm (Figure 4) and showed that this transient absorption decays to the baseline within 100 μs, indicating that no long-lived photoenol was formed. Thus, we assigned this transient to **Z-3b**. The lifetime of **Z-3b** was 6 μs in methanol and 4.3 μs in acetonitrile, and these lifetimes were not affected by oxygen.

The transient kinetics of **1b** were studied in argon-, air-, and oxygen-saturated solutions. The transient absorption of **2b** is expected to be quenched by oxygen but not the transient absorption due to **Z-3b**, leading to a better separation of the kinetics for these two species in the presence of oxygen. In air-saturated solutions, a fast transient was observed indicating that the lifetime **2b** was shortened by oxygen (Figure 4). In addition, a decrease in the initial ΔA values was observed consistent with the quenching of the precursor to **3b**, which is **2b**. In oxygen-saturated solution the transient with short lifetime is not apparent, indicating that the lifetime for **2b** is shorter than the time resolution of the kinetic experiment (~20 ns), in line with a diffusion-controlled quenching rate constant of **2b** by oxygen.[10,21] These results indicate that the lifetime of **2b** was shortened by at least a factor of 100 for the oxygen-saturated solution, leading to a decrease in the yield for **Z-3b**, as indicated by the ΔA value right after the laser pulse. This result indicates that some of the **Z-3b** is formed from the triplet biradical. However, complete quenching of the absorption due to **Z-3b** would have been expected if all of **Z-3b** was formed from **2b**. The fact that a significant amount of **Z-3b** is present in oxygen-saturated solutions suggests that **3b** is also formed from the excited singlet state of **1b**. Quantification of the parallel reaction from the triplet and the singlet excited state of the ketone in **1b** by analyzing the dependence of the ΔA values right after the laser pulse with the oxygen concentration is not possible because of the overlapping absorption of **2b** and **Z-3b**. However, since hydrogen abstraction by the singlet ketone in **1b** can only yield **Z-3b**, it further supports the assignment of the transient signal for the photoenol **3b** to its *Z*-conformer.

The transient spectroscopy demonstrated that **1a** and **1b** undergo intramolecular H-atom abstraction to form biradicals **2a** and **2b**, respectively. Biradical **2b** is longer-lived than **2a**; however, the major difference between **2a** and **2b** is that **2a** undergoes intersystem crossing to form both **Z-** and **E-3a**, whereas **2b** only yields **Z-3b**. Furthermore, **Z-3a** is much longer-lived in methanol than in acetonitrile, suggesting that the 1,5-hydrogen shift for **Z-3a** is retarded by hydrogen bonding of the alcohol moiety. Haag et al. initially demonstrated that *Z*-photoenols are longer-lived in protic solvents.[22] For example, they showed that the *Z*-photoenol from *o*-methyl acetophenone has a lifetime of less than 20 ns in cyclohexane but a lifetime of 160 μs in hexamethyl phosphoramide. Haag et al. theorized that *Z*-photoenols are stabilized by intermolecular H-atom bonding with the solvent which impedes the 1,5-hydrogen shift to regenerate the starting material. In comparison, the lifetime of **Z-3b** is not affected significantly by the solvent. Since the lifetime of **Z-3b** it is not significantly shortened in nonprotic solvents, we hypothesize that steric bulkiness of the isopropyl group in **Z-3b** limits the solvation of the hydroxyl group and thus the

(21) Plistil, L.; Solomek, T.; Wirz, J.; Heger, D.; Klan, P. *J. Org. Chem.* **2006**, *71*, 8050–8058.
(22) Haag, R.; Wirz, J.; Wagner, P. J. *Helv. Chim. Acta* **1977**, *60*, 2595–2607.

SCHEME 6

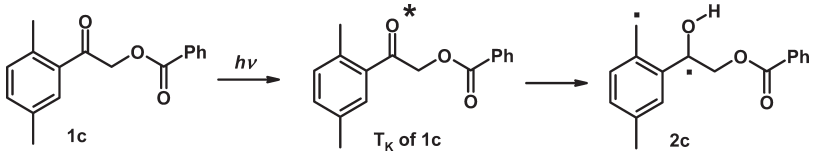


TABLE 2. Lifetimes of 2 and 3 in Methanol and Acetonitrile

	τ	
transient	methanol	acetonitrile
2a	580 ns	50−70 ns
Z-3a	60−100 μs	270 ns
E-3a	430−570 μs	300 ms
2b	1.9 μs	2.9 μs
Z-3b	6 μs	4.3 μs

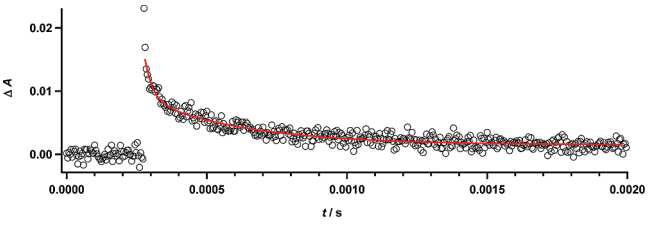


FIGURE 2. Laser flash photolysis of **1a**, monitored at 390 nm in nitrogen-saturated methanol.

intramolecular H-atom bonding retards the 1,5-hydrogen shift, similarly in protic and nonprotic solvents. The lifetime of **E-3a** is considerably shorter in methanol than in acetonitrile presumably because both lactonization and reketonization[23] are more efficient in protic solvents.

2. Calculations. We performed calculations to explain the difference in the reactivities of **1a** and **1b**. The calculations were done using Gaussian03 at the B3LYP level of theory with 6-31+G(d) as the basis set.[24−26] We optimized the structures of **1a,b** and the triplet excited states of the ketones (T_{1K}) of **1a,b** and calculated their IR spectra. We found that the T_{1K} of **1a** and **1b** are 68 and 66 kcal/mol above their ground states (S_0), respectively, which is considerably lower than the values observed for T_K of analogous acetophenone derivates.[27] However, we have previously shown that density

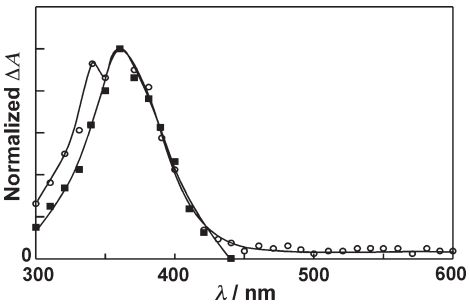


FIGURE 3. Normalized transient spectra (λ_{ex} = 266 nm) for **1b** in methanol purged with nitrogen (○, delay of 296 ns) and oxygen (■, delay of 463 ns). The lines are included to guide the eye.

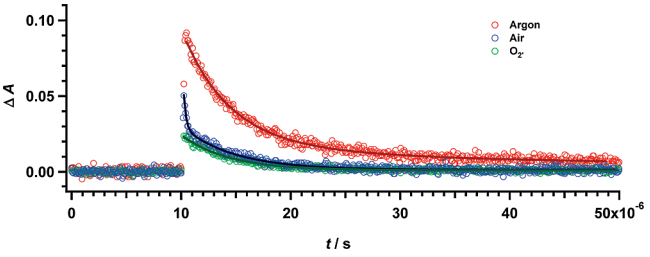


FIGURE 4. Laser flash photolysis of **1b**, monitored at 390 nm in argon-, air-, and oxygen-saturated methanol. The solutions had same concentration (0.5 mM) and equal absorption at the laser excitation wavelength of 308 nm.

functional calculations underestimate the energy of triplet ketones with (n,π*) configurations.[28] In comparison, time-dependent density theory (TD-DFT)[29−33] estimates T_K of **1a,b** to be 74 kcal/mol above their S_0, which fits well with the measured energies of T_K of analogous acetophenone derivates.

We calculated the transition states for the intramolecular H-atom abstraction to form **2a** and **2b.** These transition states were located a few kcal/mol above T_K of **1**, indicating that the hydrogen abstraction is feasible for both **1a** and **1b**.

The calculations show that the lowest-energy conformers **A** and **B** of **2a**,**b** have an intramolecular H-atom bond between the C=O and the OH moieties (Figure 5). In addition, **2b** has a low-energy conformer **C** that has a pseudo

(23) Literak, J.; Dostalova, A.; Klan, P. *J. Org. Chem.* **2006**, *71*, 713–723.
(24) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian Inc.: Wallingford CT, 2003.
(25) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
(26) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B: Condens. Matter* **1988**, *37*, 785–789.
(27) Murov, S. L. C., I.; Hug, G. L.; *Handbook of Photochemistry*, 2nd ed.; Marcel Dekker, Inc.: New York, 1993.
(28) Muthukrishnan, S.; Mandel, S. M.; Hackett, J. C.; Singh, P. N. D.; Hadad, C. M.; Krause, J. A.; Gudmundsdottir, A. D. *J. Org. Chem.* **2007**, *72*, 2757–2768.
(29) Parr, R. G.; Weitao, Y. *Density Functional Theory in Atoms and Molecules*; Oxford University Press: Oxford, 1989.
(30) *Density Functional Methods in Chemistry*; Labanowksi, J. K., Andzelm, J. W., Eds.; Springer-Verlag: New York, 1991.
(31) Bauernschmitt, R.; Ahlrichs, R. *Chem. Phys. Lett.* **1996**, *256*, 454–464.
(32) Stratmann, R. E.; Scuseria, G. E.; Frisch, M. J. *J. Chem. Phys.* **1998**, *109*, 8218–8224.
(33) Foresman, J. B.; Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *J. Phys. Chem.* **1992**, *96*, 135–149.

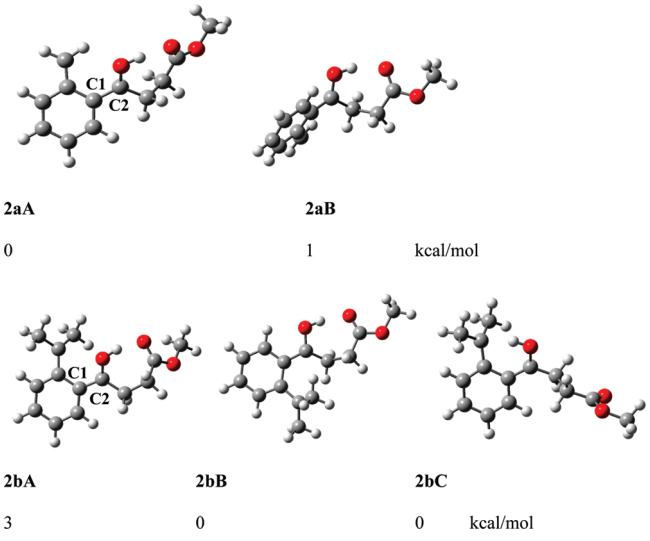


FIGURE 5. Low-energy conformers of **2a,b**.

hydrogen bond between the isopropyl radical center and the OH group. It should be pointed out that in the literature, there are several reports of hydrogen bonding that involve alkyl radicals.[34−37] The distance between the isopropyl radical center and the OH hydrogen is only 1.9 Å and supports formation of pseudo hydrogen bonding along with the calculated frequency of the O−H stretch at 3400 cm^{-1}. In comparison, the O−H stretch in **2b** that does not have intramolecular hydrogen bonding is calculated to be at 3726 cm^{-1}. Because the isopropyl radical center in **2b** is stabilized by the two methyl groups, it is feasible for the radical center to rotate out of the conjugation with the phenyl ring and to form the pseudo hydrogen bond with the OH moiety. In comparison, the methylene radical center in **2a** is mainly stabilized by conjugation with the phenyl ring; thus, the methylene radical does not rotate to form a pseudo hydrogen bond with the OH group.

We hypothesize that the bulkiness of the isopropyl group and the intramolecular pseudo hydrogen bond in **2bC** prevent rotation around the carbon−carbon bond between the phenyl and the ketyl groups. To support this hypothesis, we calculated the barrier for **2a** and **2b** to rotate around the C1−C2 bond (Figure 6). The torsion rotation around C1−C2 is ∼4 kcal/mol more restricted for biradical **2b** than for **2a** due to both the intramolecular pseudo hydrogen bonding and the bulkiness of the isopropyl group. Similarly, the rotation scans around the C1−C2 bond for conformers **2aA** and **2bA** give similar results (Supporting Information). The restricted torsion rotation around the C1−C2 bond explains why **2b** yields only **Z-3b**, as the rotation restriction prevents **2b** from forming conformers similar to **2bB**, which can undergo intersystem crossing to form **E-3b**.

We also optimized the structure of **E-** and **Z-3a,b** and found that **Z-3a** is more stable than **E-3b** by a few kcal/mol. In comparison, **E-3b** and **Z-3b** are of similar stability; presumably,

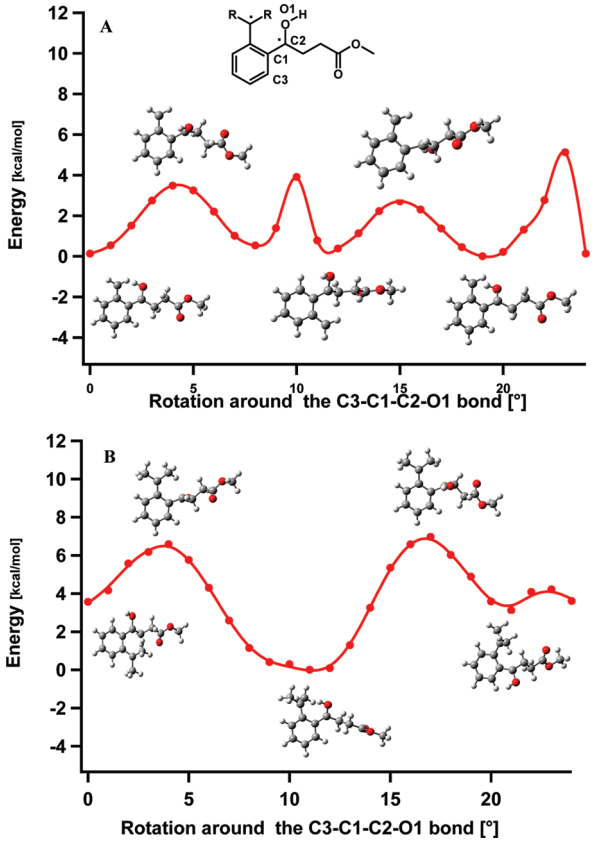


FIGURE 6. Energy as a function of rotation around the C3−C2−C1−O1 bond in (A) **2a** and (B) **2b**.

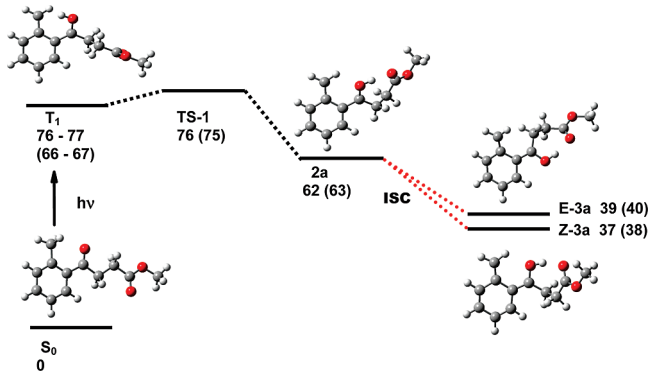


FIGURE 7. Calculated stationary points on the energy surface of **1a**. The calculated energies are in kcal/mol. Numbers in parentheses are the calculated energies in methanol.

the steric demand of the isopropyl group and the intramolecular H-atom bond destabilize **Z-3b** in comparison to **E-3b**.

Finally, we calculated the transition states for **Z-3a,b** undergoing a 1,5-hydrogen shift to regenerate **1a,b**. The transition state for **Z-3a** to form **1a** is located 7 kcal/mol above **Z-3a**; similarly, the transition state for **Z-3b** forming **1b** is 8 kcal/mol above **Z-3b**. Thus, **Z-3a** is somewhat better aligned for 1,5-hydrogen shifts than **Z-3b**, which explains the short lifetime of **Z-3a** in acetonitrile (Table 1). However, it is difficult to predict what effect steric hindrance will have on the lifetimes of **Z-3a,b** because hydrogen bonding of their alcohol moiety will also retard 1,5-hydrogen shifts.

(34) Hammerum, S. *J. Am. Chem. Soc.* **2009**, *131*, 8627–8635.
(35) Jacox, M. E. *Chem. Phys.* **1979**, *42*, 133–148.
(36) Merritt, J. M.; Rudic, S.; Miller, R. E. *J. Chem. Phys.* **2006**, *124*, 084301/1–084301/12.
(37) Misochko, E. Y.; Benderskii, V. A.; Goldschleger, A. U.; Akimov, A. V.; Shestakov, A. F. *J. Am. Chem. Soc.* **1995**, *117*, 11997–11998.

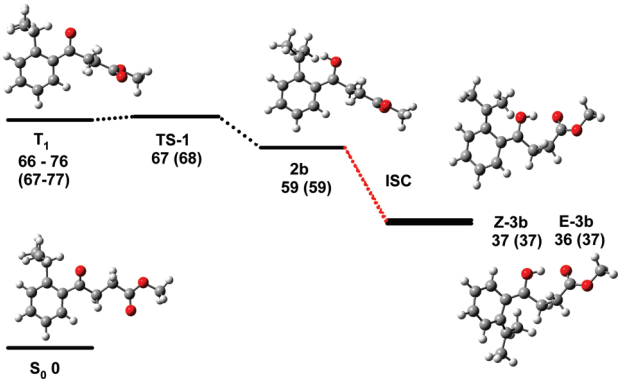


FIGURE 8. Calculated stationary points on the energy surface of **1b**. The calculated energies are in kcal/mol. Numbers in parentheses are the calculated energies in methanol.

The calculations support that both **1a** and **1b** undergo efficient H-atom abstraction to form **2a** and **2b**, respectively. However, **2a** undergoes intersystem crossing to form both **E-** and **Z-3a**, whereas **2b** only yields **Z-3b** due to restricted rotation about the C1−C2 bond. Both an intramolecular pseudo hydrogen bond and the bulkiness of the of the isopropyl group restrict this rotation.

Discussion

Both esters **1a** and **1b** undergo efficient intramolecular hydrogen abstraction to form **2a** and **2b**, respectively. Biradical **2b** is considerably longer-lived than **2a**, presumably because it is better stabilized by intramolecular pseudo hydrogen bonding between the radical center on the isopropyl group and the hydroxyl moiety. Additionally, the two methyl groups also stabilize the electron-deficient isopropyl radical in **2b**. The steric demand of the isopropyl substituent and the intramolecular pseudo hydrogen bond prevents **2b** from rotating around the C1−C2 bond and thus undergo intersystem crossing to form **E-3b**. In comparison, the rotation around the C1−C2 groups is less hindered in **2a**, and it undergoes intersystem crossing to form both **Z-** and **E-3a**. Both photoenols **Z-3a,b** reform their starting materials via 1,5 H-atom shifts. The lifetime of **Z-3a** is somewhat shorter than that of **Z-3b**. Calculations show that **Z-3a** is better aligned for 1,5-hydrogen shift explaining why **Z-3a** decays faster than **Z-3b** does. In contrast, **E-3a** undergoes electrocyclic ring closure and intramolecular lactonization to form **4a** and release methanol.

As mentioned earlier, we have previously shown that ester **8** releases its alcohol moiety by photoenolization (Scheme 7).[16] The E-photoenol (**E-10**) from **8** has a lifetime on the order of seconds; thus, the decay of **E-10** is much slower than that observed for **E-3a**. We hypothesize that **E-3a** is more flexible than **E-10** and thus it undergoes lactonization more rapidly. However, we cannot determine whether the lactonization precedes the electroscyclic ring closure in **E-10** and **E-3a**, and thus it possible that **E-3a** undergoes electrocyclic ring closure faster than **E-10**, rather than lactonization. Interestingly, the isopropyl group in **9** does not prevent the formation of **E-10** as it does for **2b**; presumably, the intramolecular pseudo hydrogen bonding in **9** is not as important as in **2a** because each radical center in **9** is stabilized by their adjacent phenyl rings.

Thus, **1a** can be used as a PRPG for alcohols. The release takes place via intramolecular hydrogen abstraction and photoenolization to form **Z-** and **E-3a.** In comparison, photolysis of **1b** also results in intramolecular hydrogen abstraction and formation of a photoenol **Z-3b**. However, **Z-3b** does not release the methanol moiety but rather regenerates **1b**. Consequently, **1a** has potential as a photoprotecting group for alcohols in applications, whereas **1b** can be used for control experiments, as it has similar structure and photochemistry as **1a** but does not release its alcohol moiety.

The major difference between benzophenone and butyrophenone based PRPGs **8** and **1** is flexibility. The increased flexibility presumably allows **E-3a** to release its alcohol moiety faster than **E-10**. However, with increased flexibility the rotation barrier becomes important and can inhibit access to some decay pathways. The increased flexibility of **1b** compared to **8**, prevents it from releasing its alcohol moiety because rotation prevents **2b** from forming **E-3b**. Thus, a general conclusion for designing PRPGs based on photoenolization and lactonization is that increased flexibility can make the lactonization faster, but potential rotational barriers can also allow other processes to compete with the photorelease.

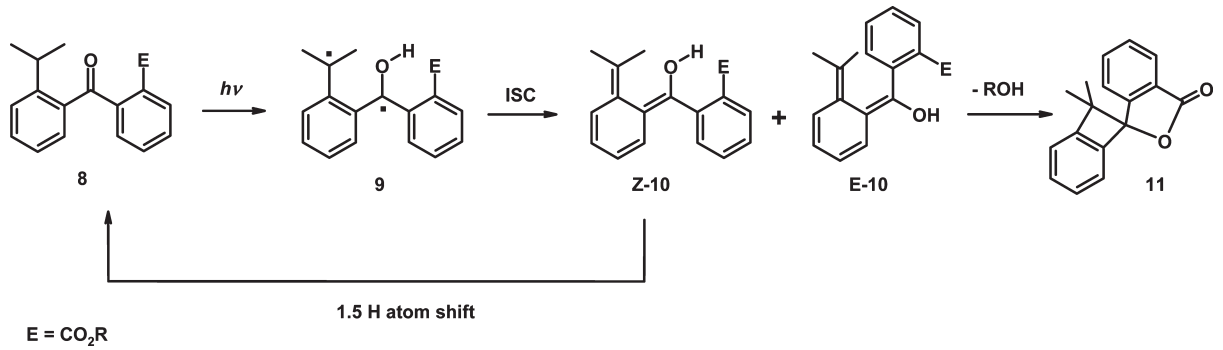
Experimental Section

1. Calculations. All geometries were optimized at the B3LYP level of theory and with the 6-31G+(d) basis set as implemented in the Gaussian03 programs.[25,26] All transition states were confirmed to have one imaginary vibrational frequency by analytical determination of the second derivatives of the energy with respect to internal coordinates. Intrinsic reaction coordinate[38] calculations were used to verify that the located transition states corresponded to the attributed reactant and product.[39,40] The absorption spectra were calculated using time-dependent density functional theory (TD-DFT).[29−33] The T_1 states of esters **1a** and **1b** were optimized using UB3LYP method with 6-31+G(d) basis set. The effect of solvation was calculated using the self-consistent reaction field (SCRF) method with the integral equation formalism polarization continuum model (IEFPCM) with methanol as the solvent.[41−45]

2. Laser Flash Photolysis. Laser flash photolysis was done with an Excimer laser (308 nm, 17 ns) and a YAG laser (266 nm, 15 ns).[46,47] Stock solutions of esters **1** in methanol and acetonitrile were prepared with spectroscopic grade solvents, such that the solutions had absorptions between 0.6 and 0.8 at 308 or 266 nm. Typically, ~2 mL of the stock solution was placed in a 10 mm × 10 mm cell in cross-section, 48-mm-long quartz cuvette and was purged with nitrogen or oxygen, as desired, for 5 min. The rates were obtained by fitting an average of 3−8 kinetic traces.

(38) Wilson, R. M.; Hannemann, K.; Heineman, W. R.; Kirchhoff, J. R. *J. Am. Chem. Soc.* **1987**, *109*, 4743–4745.
(39) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154–6211.
(40) Gonzalez, C.; Schlegel, H. B. *J. Phys. Chem.* **1990**, *94*, 5523–5527.
(41) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem Rev* **2005**, *105*, 2999–3093.
(42) Mennucci, B.; Cances, E.; Tomasi, J. *J. Phys. Chem. B* **1997**, *101*, 10506–10517.
(43) Cances, E.; Mennucci, B. *J. Chem. Phys.* **2001**, *114*, 4744–4745.
(44) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027–2094.
(45) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161–2200.
(46) Liao, Y.; Bohne, C. *J. Phys. Chem.* **1996**, *100*, 734–743.
(47) Muthukrishnan, S.; Sankaranarayanan, J.; Klima, R. F.; Pace, T. C. S.; Bohne, C.; Gudmundsdottir, A. D. *Org. Lett.* **2009**, *11*, 2345–2348.

SCHEME 7



3. Preparation of Starting Materials. Preparation of 1a. A solution of *o*-bromotoluene (7.4 g, 0.043 mol) in anhydrous tetrahydrofuran (THF) (50 mL) was added dropwise over 30 min to magnesium turnings (1.05 g, 0.043 mol) while stirring to form the Grignard reagent, which was grayish-yellow in color. Simultaneously, to a solution of anhydrous LiBr (7.36 g, 0.086 mol) in anhydrous THF (35 mL) was added anhydrous CuBr (6.15 g, 0.043 mol), which resulted in a green solution. The Grignard reagent was added to the green CuBr solution dropwise over 20 min. To the resulting slurry, a solution of β-carbomethoxypropionyl chloride (6.45 g, 0.043 mol; prepared from succinic anhydride according to the literature procedure in 90% yield[48]) in anhydrous THF (10 mL) was added over 15 min. A highly exothermic reaction ensued, and the resulting solution was stirred further for 20 min at room temperature. The reaction was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 40 mL). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated to obtain a red oil. Upon purification of the oil by column chromatography (silica gel 2.4 cm × 25 cm, 85:15 hexane/ethyl acetate), **1a** was obtained as a pale yellow oil (3.5 g, 0.017 mol, yield 40%). IR ($CHCl_3$) 3020, 1735, 1686, 1218 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.70−7.73 (m, 1H), 7.23−7.38 (m, 3H), 3.71 (s, 3H), 3.23 (t, 7.2 Hz, 2H), 2.75 (t, 7.2 Hz, 2H), 2.50 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 173.4, 138.3, 137.4, 132.0, 131.5, 128.6, 125.7, 51.8, 36.1, 28.2, 21.3 ppm; MS (EI) *m*/*z* (relative intensity) 206 (M^+, 5), 175 (10), 145 (5), 131 (5), 119 (100), 91 (100), 65 (50); HRMS *m*/*z* calcd for $C_{12}H_{14}O_3Na$, $[M + Na]^+$ 229.0841, found 229.0846.

4. Product Studies. Photolysis of 1a in Argon-Saturated Methanol. A degassed solution of **1a** (84 mg, 0.41 mmol) in methanol (20 mL) was irradiated through a Pyrex filter (> 300 nm) for 72 h using a medium-pressure mercury arc lamp. After the majority of the starting material was depleted (TLC, ethyl acetate/hexane, 1:4), the solvent was evaporated, and the photoproducts were separated by column chromatography (ethyl acetate/hexane) to give recovered **1** (5 mg, 0.024 mmol, 6% yield) and **4** (42 mg, 0.24 mmol, 59% yield) as an oil. The spectroscopic data for **4** is similar to those of an analogous lactone.[49] IR ($CHCl_3$) 3020, 1772, 1215 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37−7.18 (m, 4H), 3.64 (d, 14 Hz, 1H), 3.46 (d, 14 Hz, 1H), 2.75−2.71 (m, 2H); 2.80−2.50 (m, 2H) ppm; ^{13}C NMR (60 MHz, $CDCl_3$) δ 176.5, 145.6, 141.0, 130.8, 128.1, 123.8, 121.3, 88.0, 45.6, 32.1, 29.4 ppm; MS (EI) *m*/*z* (relative intensity) 173 ($[M - H]^+$, 50), 158 (10), 145 (100), 131 (80), 118 (80), 102 (15), 89 (80), 77 (15); HRMS *m*/*z* calcd for $C_{11}H_{11}O_2$, $[M + H]^+$ calcd 175.0759, found 175.0736.

Photolysis of 1a in Oxygen-Saturated Methanol. Ester **1a** (84 mg, 0.41 mmol) was dissolved in methanol (20 mL), and the solution was purged with oxygen for 20 min. Hexadecane (10 μL) was added as an internal standard. The resulting solution was irradiated through a Pyrex filter for 28 h using a medium-pressure mercury arc lamp. The reaction mixture was analyzed with GC−MS, which showed formation of two products, **5** (58%) and **6** (12%), as well as the remaining starting material (~30%). Comparison of GC−MS and ^1H NMR spectra of commercially available **6** verified its structure.

Because **5** decomposes on silica column, we derivatized it to form acetal **12** following the procedure described in the literature.[50] In this procedure, we selectively protected the aldehyde without affecting the ketone or the ester moieties. A product mixture (80 mg containing 58% of the aldehyde **5**, 46 mg, 0.21 mmol based on GC−MS) was dissolved in dry CCl_4 (5 mL), added to a stirred suspension of anhydrous acidic alumina (100 mg, 2 mmol) and dry ethylene glycol (15 mg, 0.24 mmol) in 5 mL of anhydrous CCl_4, and refluxed for 8 h under argon. The resulting mixture was filtered, evaporated, and purified by preparative silica gel plate with ethyl acetate/hexane/dichloromethane as the eluent (1:2:2) to obtain **12** as a colorless liquid (34 mg, 0.13 mmol, 66% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.72−7.43 (m, 4H), 6.23 (s, 1H), 4.01 (pseudo d, 4H, 2.8 Hz), 3.70 (s, 3H), 3.21 (t, 4 Hz, 2H), 2.76 (t, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 173.3, 136.6, 130.9, 128.8, 127.4, 126.9, 100.9, 72.2, 65.3 (2C), 51.7, 37.1, 28.4. HRMS *m*/*z* calcd 287.0895 for $C_{14}H_{16}O_5Na$, found 287.0905.

Photolysis of 1b in Argon-Saturated Solutions. Photolysis of **1b** (0.02 M) in dichloromethane for 7 days did not result in any new products.

Photolysis of 1b in Oxygen-Saturated Dichloromethane. Ester **1b** (110 mg, 0.4 mmol) was dissolved in dichloromethane (20 mL), and the solution was purged with oxygen for 20 min. The resulting solution was irradiated through Pyrex filter for 48 h using a medium pressure mercury arc lamp. The reaction mixture was analyzed with GC−MS that showed formation of a trace amount (~1−2%) of 4-[2-(1-hydroxy-1-methyl-ethyl)-4-isopropyl-phenyl]-4-oxo-butyric acid, methyl ester. The product was isolated on a silica column using 20% ethyl acetate in hexane to give 1.5 mg (0.004 mmol) of the product: ^1H NMR δ 7.56−7.50 (m, 2H), 7.34 (m, 1H), 3.71 (s, 3H), 3.44−3.34 (m, 1H), 3.18 (t, J = 7 Hz, 2H), 2.75 (t, J = 7 Hz, 2H), 1.59 (s, 6H), 1.24 (d, J = 7 Hz, 6H) ppm; ^{13}C NMR δ 203.5, 173.3, 152.1, 148.0, 136.7, 127.5, 122.4, 121.6, 72.6, 51.8, 37.2, 31.7, 29.7, 28.2, 24.2 ppm; IR 3401, 2917, 2848, 1738, 1689, 1603, 1460, 1403 cm^{-1}; HRMS $C_{17}H_{24}O_4Na$ $[M + Na]^+$ calcd 315.1572, exptl 315.1578

(48) Cason, J. *Org. Synth.* **1945**, 25.

(49) Sankaranarayanan, J.; Mandel, S. M.; Krause, J. A.; Gudmundsdottir, A. D. *Acta Crystallogr., Sect. E: Struct. Rep. Online* **2007**, *E63*, o721–o723.

(50) Kamitori, Y.; Hojo, M.; Masuda, R.; Yoshida, T. *Tetrahedron Lett.* **1985**, *26*, 4767–4770.

Quantum Yields. Methanol was dried and distilled prior to use. We used 4-methoxy butyrophenone as the actinometer. The quantum yield for forming 4-methoxyacetophenone (Φ = 0.095) from 4-methoxybutyrophenone in benzene has been reported by Lewis and Turro.[51] The mole to area ratio response of the GC traces was calibrated for **1a**, **4**, **5**, **6**, 4-methoxybutyrophenone, and 4-methoxyacetophenone. Irradiations of **1a** were carried out to ~5% conversion in argon- and oxygen-saturated methanol. Argon- or oxygen-saturated 2-propanol solutions (three replicates of each) containing 0.1 M of **1a** was irradiated on a merry-go-round apparatus using a 450-W medium pressure mercury arc lamp and potassium chromate filter to isolate the 3130-Å line.[52,53] The irradiated samples were analyzed with a GC chromatography equipped with an FID detector. The results from all three replicates were similar, and hence they were averaged and listed in Table 1.

(51) Lewis, F. D.; Turro, N. J. *J. Am. Chem. Soc.* **1970**, *92*, 311–320.
(52) Wagner, P. J.; Kemppainen, A. E. *J. Am. Chem. Soc.* **1968**, *90*, 5898–5899.
(53) Coulson, D. R.; Yang, N. C. *J. Am. Chem. Soc.* **1966**, *88*, 4511.

Acknowledgment. This work was supported by Petroleum Research Fund administrated by the American Chemical Society and the Ohio Supercomputer Center. C.B. and T.C. S.P. thank the Natural Science and Engineering Research Council (NSERC) for funding at Victoria, and T.C.S.P. thanks NSERC for a CGS-D scholarship.

Supporting Information Available: LFP of **1a**; synthesis and characterization of **1b**; Cartesian coordinates, energies, and vibrational frequencies of **1**−**3**; NMR spectra of **1a**, **4a**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.