Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

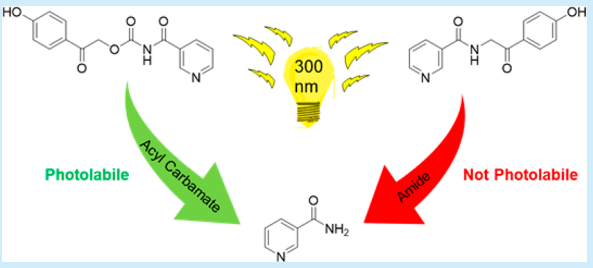
pHP-Tethered *N*-Acyl Carbamate: A Photocage for Nicotinamide

Farbod Salahi,[†] Vatsal Purohit,[§] Guillermo Ferraudi,[‡] Cynthia Stauffacher,[§] Olaf Wiest,*[,†,∥] and Paul Helquist*[,†]

[†]Department of Chemistry and Biochemistry, University of Notre Dame, Notre Dame, Indiana 46556, United States
[‡]Notre Dame Radiation Research Laboratory, Notre Dame, Indiana 46556, United States
[§]Department of Biological Sciences, Purdue University, 915 West State Street, West Lafayette, Indiana 47907, United States
[∥]Laboratory of Computational Chemistry and Drug Design, School of Chemical Biology and Biotechnology, Peking University, Shenzhen Graduate School, Shenzhen 518055, China

Supporting Information

ABSTRACT: The synthesis of a new photocaged nicotinamide having an *N*-acyl carbamate linker and a *p*-hydroxyphenacyl (pHP) chromophore is described. The photophysical and photochemical studies showed an absorption maximum at λ = 330 nm and a quantum yield for release of 11% that are dependent upon both pH and solvent. While the acyl carbamate releases nicotinamide efficiently, a simpler amide linker was inert to photocleavage. This photocaged nicotinamide has significant advantages with respect to quantum yield, absorbance wavelength, rate of release, and solubility that make it the first practical example of a photocaged amide.



The nicotinamide moiety of NAD^+ (Figure 1), the most abundant cofactor in eukaryotic cells, is responsible for oxidoreduction chemistry in many enzymes. NAD(P)/NAD(P)H-dependent enzymes, such as sirtuins, CD38, or HMG-CoA reductase, are involved in many redox pathways in living cells. Understanding the mechanisms of these enzymes, the malfunctions of which cause various diseases, is an important goal in enzymology and could enable the design and development of more efficient drugs for these important pathways.[1]

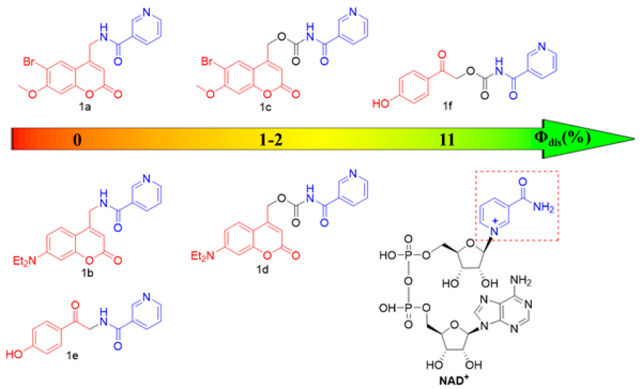


Figure 1. Photocaged nicotinamides.

One approach that provides control over both the time and location of initiation of a reaction is the interruption of the binding of this coenzyme in a reactive position. Activation by an external trigger enables the study of the associated enzymes and elucidation of their mechanisms in microsecond to nanosecond time scales. One tool that can be employed for this purpose is a photoremovable chromophore, which while chemically bound to NAD^+ can block its normal activity.[2] Such chromophores, known as photocaging groups, can be cleaved from the cofactor upon light irradiation to effect release of NAD^+ and initiation of a reaction at a precisely controlled time and location. This type of spatiotemporal control is a powerful means to manipulate enzymes and release of a range of bioactive molecules, such as neurotransmitters and cell-signaling molecules.[3−5] Although there are many examples of photocaged phosphates or carboxylic acids,[3,4] the photocaging of poor leaving groups such as amides or amines is still a topic of intense research.[5e]

Photocaging groups must have certain properties to be useful in cellular studies.[4c] They should have a large molar extinction coefficient above 300 nm to avoid absorption interference by aromatic amino acids. Photocaged molecules should efficiently undergo primary photocleavage with a quantum yield of at least 10% and be stable and soluble under physiological conditions. The released caging group should be inert and not absorb at a wavelength that interferes with the cleavage process. Finally, its synthesis should be amenable to modifications for improvement of these properties and caging of a variety of functional groups.

The synthesis of a NAD^+ derivative having the nicotinamide moiety photocaged with an *o*-nitrobenzyl group was previously reported by Salerno for use in time-resolved mechanistic

Received: March 1, 2018

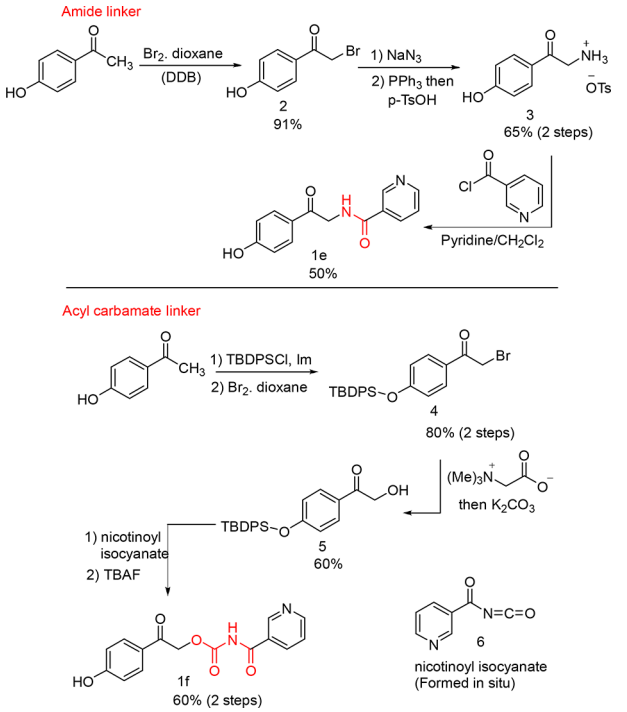
DOI: 10.1021/acs.orglett.8b00697
Org. Lett. XXXX, XXX, XXX−XXX

studies of NAD$^+$-dependent enzymes[2b,6] and was employed by Koshland in a study of isocitrate dehydrogenase.[2a] The main drawbacks of this type of caging group are poor solubility, absorption at an undesirably low wavelength of 260 nm, a slow rate and low yield of photorelease, and the formation of a reactive byproduct, *o*-nitrosobenzaldehyde.

Recently, our group reported the synthesis of caged nicotinamides **1a−d** (Figure 1) tethered to a coumarin chromophore. The numerical values in the colored, horizontal arrow show quantum yields (Φ_{dis}) over the range of photocaged nicotinamides studied in the previous and current work. The amides **1a,b** did not undergo uncaging upon irradiation (Φ_{dis} = 0). Redesign of the amide moiety to a carbamate linkage based on an orbital analysis led to photocages with low yields of cleavage.[7] While coumarin chromophores **1c,d** have absorption wavelengths above 300 nm and are thus an improvement over the *o*-nitrobenzyl group, their main drawbacks were slow release, low quantum yields of 1−2% for photocleavage, and poor solubility in aqueous media. These results indicate the need for new nicotinamide caging groups that undergo faster release with better photolytic efficiency and solubility. To address these problems, we designed a new photocaged nicotinamide based on an *N*-acyl carbamate-tethered *p*-hydroxyphenacyl (pHP) group. The pHP chromophore has been employed for caging of carboxylate, phosphate, alcohol, and ammonium leaving groups.[8]

The syntheses of pHP nicotinamide derivatives with either an amide (**1e**) or an *N*-acyl carbamate linker (**1f**) are shown in Scheme 1. The synthesis of the amide-linked pHP starts with

Scheme 1. Synthesis of Caged Nicotinamides



bromination of commercially available *p*-hydroxyacetophenone with a dioxane dibromide complex[9] (DDB) to give *α*-bromo-pHP **2**. *α*-Amino-pHP **3** was obtained by nucleophilic substitution of **2** with sodium azide,[10] followed by reduction of the resulting azide to the amine. This conversion was attempted with hydrogen and Pd/C (54%) and with $SnCl_2$ (37%), but the best result was obtained using the Staudinger reduction with PPh_3 and p-TsOH, yielding **3** in 65% over two steps. Subsequent amide bond formation by reaction of **3** with nicotinoyl chloride failed when using triethylamine (TEA) as base and DMF as solvent. Changing the solvent to a mixture of DCM and pyridine gave the desired amide **1e** in 50% yield.

We synthesized the corresponding *N*-acyl carbamate-linked pHP derivative **1f** to compare the efficiency of releasing the two differently caged nicotinamides. Compound **1f** was prepared in five steps, starting with *p*-hydroxyacetophenone, which was first protected as the TBDPS ether. Different methods for the bromination to obtain *α*-bromo pHP **4** were explored, including use of $CuBr_2$,[11] bromine,[12] benzyltrimethylammonium tribromide[13] ($BTMABr_3$), and DDB.[9] While bromine gave a low yield of monobrominated product (30%), the use of $CuBr_2$ improved the yield (58%) but gave a mixture of mono- and dibrominated products. Changing to $BTMABr_3$ decreased the amount of dibrominated compound and increased the yield of the monobrominated product (78%). The highest yield of **4** was obtained by applying DDB. For conversion of bromide **4** to *α*-hydroxy ketone **5**, different reagents such as sodium formate[14a] and cesium formate[14b] were tested, but the yields were not satisfactory. Utilizing trimethyl glycine[14c] in refluxing ethanol afforded **5** in 60% yield. The multicomponent carbonylative cross coupling of **5** with 3-bromopyridine and an isocyanate salt to install the acyl carbamate linker[15] yielded only the recovered starting material. Thus, we chose to generate nicotinoyl acyl isocyanate *in situ* by addition of oxalyl chloride[16] to a solution of nicotinamide in 1,2-dichloroethane (DCE) and trapping with **5** to form the desired *N*-acyl carbamate. Removal of the TBDPS protecting group with TBAF afforded the desired **1f** in 60% yield over two steps.

Because the same pHP chromophore is in both **1e** and **1f**, the compounds should have similar photophysical characteristics. Compound **1f** was selected to study solvent and pH dependence of the photophysical properties (Figure 2). An

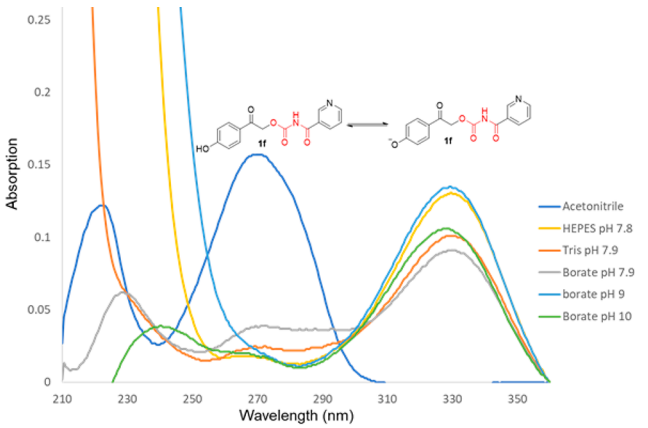


Figure 2. UV−vis spectra of caged nicotinamide **1f** at different pH values.

absorption maximum with λ_{max} = 273 nm was determined for the neutral form of **1f** in acetonitrile. A large red shift to 330 nm was observed as the pH was increased to 7.9 and above, which is attributed to deprotonated pHP. The pK_a of **1f** was determined to be 7.9 by pH screening (see Supporting Information, SI). It was also observed that **1f** is stable in wet acetonitrile at ambient temperature in the dark over 24 h,

DOI: 10.1021/acs.orglett.8b00697
Org. Lett. XXXX, XXX, XXX−XXX

demonstrating the stability toward hydrolysis, which is an important property for biological studies.

Next, the photochemistry of the pHP nicotinamides was investigated. Previous studies showed that caged nicotinamides **1a**–**1d**, linked to a coumarin by an amide or an *N*-acyl carbamate linker, do not undergo efficient photorelease of nicotinamide, as shown by low quantum yields in the 1% range for the acyl carbamates and no detectable cleavage of the amides (Table 1, entries 1–4). The first attempt at photo-

Table 1. Comparative Studies of Caged Nicotinamide

entry	compound	$\lambda_{max(nm)}$	pH	ε (M^{-1} cm^{-1})	Φ_{dis}
1	**1a**[8]	370	8.1	22731	-
2	**1b**[8]	380	7	24375	-
3	**1c**[8]	330	7	11442	1%
4	**1d**[8]	379	7	14027	1.6%
5	**1f**	330	8.5	11730	1%

cleavage of the new acyl carbamate-tethered pHP derivative **1f** at 330 nm in a mixture of phosphate buffer and acetonitrile at pH 8.5 also showed a low quantum yield (entry 5). This result can be attributed to the lower reactivity of the conjugate base of the phenolic group of the pHP chromophore in comparison with its neutral form.[17]

Therefore, the need to study solvent and pH effects became apparent (Table 2). Changing the solvent to a nonaqueous,

Table 2. pH and Solvent Studies of the Photochemical Reaction of 1e and 1f

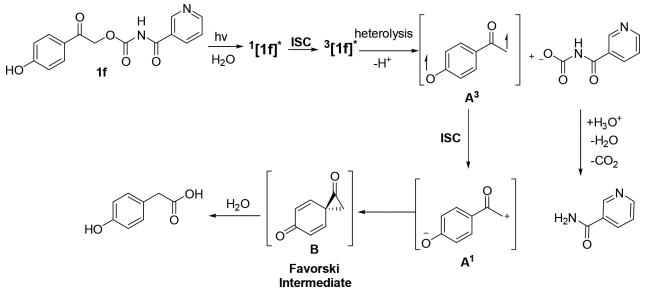
entry	compound	solvent[c]	$\lambda_{(nm)}$[d]	$\lambda_{irr(nm)}$[e]	pH	Φ_{dis}[f]
1	**1f**	CH_3CN[a]	330	330	8.5	1%
2	**1f**	CH_3CN	273	300	7	-
3	**1f**	CH_3CN_{aq}[b]	273	300	7	11%
4	**1e**	CH_3CN_{aq}[b]	273	300	7	-

[a]CH_3CN 20% 50 mM phosphate buffer, pH: 8.5. [b]20% water in CH_3CN. [c]Other organic cosolvents, such as MeOH and DMSO, in combination with water gave rise to solubility issues. [d]Maximum wavelength. [e]Wavelength of radiation. [f]Quantum yield of cleavage

organic medium completely inhibits the photochemical pathway, even at pH 7 with the pHP group in its neutral form (entry 2). This result suggests that water plays a crucial role in the release of nicotinamide. The use of an organic solvent/water mixture at pH 7 provided an increase of the quantum yield to a useful value of 11% (entry 3). To the best of our knowledge, this is the highest quantum yield that has been reported for releasing such an amide, and consequently the first time that a practical method for photocaging of an amide has been achieved. Consistent with our earlier results,[7] photocleavage of the amide-linked **1e**, which was used as a control experiment, did not occur (entry 4) under the most favorable conditions for **1f**.

A possible mechanism[14a,18] for photocleavage of the acyl carbamate-linked pHP nicotinamide **1f** is shown in Scheme 2. Absorption of light by **1f** leads to a singlet excited state, ^{1}[**1f**], which undergoes an intersystem crossing to the triplet state ^{3}[**1f**]. Heterolysis of ^{3}[**1f**] gives rise to short-lived triplet biradical ^{3}**A** and nicotinoyl carbamate conjugate base, which upon decarboxylation generates the desired uncaged nicotinamide.[7b] Product ^{3}**A** undergoes a second ISC leading to ^{1}**A**, which upon photo-Favorskii rearrangement generates the spiro

Scheme 2. Proposed Mechanism for Uncaging Nicotinamide



intermediate **B**. Finally, nucleophilic attack of water on **B** leads to formation of arylacetic acid.

In conclusion, we have developed a new photoremovable protecting group for caging an amide functionality by combining the *p*-hydroxyphenacyl chromophore with an acyl carbamate linker. It undergoes cleavage with a quantum yield of 11% upon irradiation at 300 nm and neutral pH in an aqueous medium. These conditions are favorable for studies of biological systems. This set of properties provides major improvements over previously reported caging of nicotinamide by coumarin and nitrobenzyl groups. The new photocage has a number of potential applications, including time-resolved studies of NAD(P)-dependent enzymes. The combination of an acyl carbamate linker with the pHP chromophore may be applicable for photocaging other amide moieties present in other important cofactors such as vitamin B_{12}, biotin, and coenzyme A.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00697.

Experimental procedures include ^{1}H and ^{13}C spectra and characterization data of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: owiest@nd.edu.
*E-mail: phelquis@nd.edu.

ORCID

Olaf Wiest: 0000-0001-9316-7720

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to acknowledge support of this research by the National Institutes of Health (1R01GM111645), valuable discussions with Professor R. S. Givens (University of Kansas), and technical assistance by Dr. Douglas Miller and Dr. William Boggess (Notre Dame).

■ REFERENCES

(1) (a) Istvan, E. S. Bacterial and mammalian HMG-CoA reductases: related enzymes with distinct architectures. *Curr. Opin. Struct. Biol.* **2001**, *11*, 746–751. (b) Magni, G.; Di Stefano, M.; Orsomando, G.; Raffaelli, N.; Ruggieri, S. NAD(P) Biosynthesis Enzymes as Potential Targets for Selective Drug Design. *Curr. Med. Chem.* **2009**, *16*, 1372–

DOI: 10.1021/acs.orglett.8b00697
Org. Lett. XXXX, XXX, XXX–XXX

1390. (c) North, B.; Verdin, J.; Sirtuins, E. Sir2-related NAD-dependent protein deacetylases. *Genome Biol.* **2004**, *5*, 224.
(2) (a) Cohen, B. E.; Stoddard, B. L.; Koshland, D. E., Jr. Caged NADP and NAD. Synthesis and Characterization of Functionally Distinct Caged Compounds. *Biochemistry* **1997**, *36*, 9035−9044. (b) Salerno, C. P.; Magde, D.; Patron, A. P. Enzymatic Synthesis of Caged NADP Cofactors: Aqueous NADP Photorelease and Optical Properties. *J. Org. Chem.* **2000**, *65*, 3971−3981.
(3) (a) Goeldner, M.; Givens, R. S. *Dynamic Studies in Biology: Phototriggers, Photoswitches and Caged Biomolecules*; Wiley-VCH: Weinheim, Germany, 2005. For reviews, see: (b) Klán, P.; Šolomek, T.; Bochet, C. G.; Blanc, A.; Givens, R.; Rubina, M.; Popik, V.; Kostikov, A.; Wirz, J. Photoremovable Protecting Groups in Chemistry and Biology: Reaction Mechanisms and Efficacy. *Chem. Rev.* **2013**, *113*, 119−191. (c) Deiters, A. Principles and Applications of the Photochemical Control of Cellular Processes. *ChemBioChem* **2010**, *11*, 47−53. (d) Brieke, C.; Rohrbach, F.; Gottschalk, A.; Mayer, G.; Heckel, A. Light-Controlled Tools. *Angew. Chem., Int. Ed.* **2012**, *51*, 8446−8476. (e) Givens, R. S.; Rubina, M.; Wirz, J. Applications of p-hydroxyphenacyl (pHP) and coumarin-4-ylmethyl photoremovable protecting groups. *Photochem. Photobiol. Sci.* **2012**, *11*, 472−488.
(4) (a) Agarwal, H.; Zhai, S.; Surmeier, D. J.; Ellis-Davies, G. C. R. Intracellular Uncaging of cGMP with Blue Light. *ACS Chem. Neurosci.* **2017**, *8*, 2139−2144. (b) Olson, J. P.; Kwon, H.; Takasaki, K.; Chiu, C.; Higley, M.; Sabatini, B.; Ellis-Davies, G. C. R. Optically Selective Two-Photon Uncaging of Glutamate at 900 nm. *J. Am. Chem. Soc.* **2013**, *135*, 5954−5957. (c) Ellis-Davies, G. J. Caged compounds: photorelease technology for control of cellular chemistry and physiology. *Nat. Methods* **2007**, *4*, 619−628. (d) Kaplan, J. H.; Forbush, B., III; Hoffman, J. F. Rapid photolytic release of adenosine 5′-triphosphate from a protected analog: utilization by the sodium: potassium pump of human red blood cell ghosts. *Biochemistry* **1978**, *17* (10), 1929−1935.
(5) (a) Slanina, T.; Shrestha, P.; Palao, E.; Kand, D.; Peterson, J. A.; Dutton, A. S.; Rubinstein, N.; Weinstain, R.; Winter, A. H.; Klán, P. In Search of the Perfect Photocage: Structure−Reactivity Relationships in meso-Methyl BODIPY Photoremovable Protecting Groups. *J. Am. Chem. Soc.* **2017**, *139*, 15168−15175. (b) Conrad, P. G., II; Givens, R. S.; Weber, J. F. W.; Kandler, K. New Phototriggers: Extending the p-Hydroxyphenacyl $\pi-\pi^*$ Absorption Range. *Org. Lett.* **2000**, *2*, 1545−1547. (c) Narumi, T.; Takano, H.; Ohashi, N.; Suzuki, A.; Furuta, T.; Tamamura, H. Isostere-Based Design of 8-Azacoumarin-Type Photolabile Protecting Groups: A Hydrophilicity-Increasing Strategy for Coumarin-4-ylmethyls. *Org. Lett.* **2014**, *16*, 1184−1187. (d) Takano, H.; Narumi, T.; Nomura, W.; Furuta, T.; Tamamura, H. Utilization of the Heavy Atom Effect for the Development of a Photosensitive 8-Azacoumarin-Type Photolabile Protecting Group. *Org. Lett.* **2015**, *17*, 5372−5375. (e) Sitkowska, K.; Feringa, B. L. Szymaski Green-Light-Sensitive BODIPY Photoprotecting Groups for Amines. *J. Org. Chem.* **2018**, *83*, 1819−1827.
(6) Salerno, C. P.; Resat, M.; Magde, D.; Kraut, J. Synthesis of Caged NAD(P)$^+$ Coenzymes: Photorelease of NADP$^+$. *J. Am. Chem. Soc.* **1997**, *119*, 3403−3404.
(7) (a) Bourbon, P.; Peng, Q.; Ferraudi, G.; Stauffacher, C.; Wiest, O.; Helquist, P. Synthesis, Photophysical, Photochemical, and Computational Studies of Coumarin-Labeled Nicotinamide Derivatives. *J. Org. Chem.* **2012**, *77*, 2756−2762. (b) Bourbon, P.; Peng, Q.; Ferraudi, G.; Stauffacher, C.; Wiest, O.; Helquist, P. Development of carbamate-tethered coumarins as phototriggers for caged nicotinamide. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 6321−6324.
(8) (a) Corrie, J. E.T.; Furuta, T.; Givens, R.; Yousef, A. L.; Goeldner, M. *Photoremovable Protecting Groups Used for the Caging of Biomolecules, in Dynamic Studies in Biology: Phototriggers, Photoswitches and Caged Biomolecules*; Goeldner, M., Givens, R. S., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, FRG, 2005. (b) Givens, R. S.; Stensrud, K.; Conrad, P. G.; Yousef, A. L.; Perera, C.; Senadheera, S. N.; Heger, D.; Wirz, J. *Can. J. Chem.* **2011**, *89*, 364−384.
(9) Pasaribu, S. J.; Williams, L. R. Selective bromination of substituted acetophenones with dioxan dibromide. *Aust. J. Chem.* **1973**, *26*, 1327−1331.
(10) Madea, D.; Slanina, T.; Klan, P. A photorelease, catch and photorelease strategy for bioconjugation utilizing a p-hydroxyphenacyl group. *Chem. Commun.* **2016**, *52*, 12901−12904.
(11) Huang, L.; Su, T.; Shan, W.; Luo, Z.; Sun, Y.; He, F.; Li, X. Inhibition of cholinesterase activity and amyloid aggregation by berberine-phenyl-benzoheterocyclic and tacrine-phenyl-benzoheterocyclic hybrids. *Bioorg. Med. Chem.* **2012**, *20*, 3038−3048.
(12) Kishimoto, T.; Uraki, Y.; Ubukata, M. Easy synthesis of β-O-4 type lignin related polymers. *Org. Biomol. Chem.* **2005**, *3*, 1067−1073.
(13) Ma, C.; Kwok, W. M.; Chan, W. S.; Zuo, P.; Kan, J. T.W.; Toy, P. H.; Phillips, D. L. Ultrafast Time-Resolved Study of Photophysical Processes Involved in the Photodeprotection of p-Hydroxyphenacyl Caged Phototrigger Compounds. *J. Am. Chem. Soc.* **2005**, *127*, 1463−1472.
(14) (a) Givens, R. S.; Rubina, M.; Stensrud, K. F. Stereochemically Probing the Photo-Favorskii Rearrangement: A Mechanistic Investigation. *J. Org. Chem.* **2013**, *78*, 1709−1717. (b) Wong, F. F.; Chang, P. W.; Lin, H. C.; You, B. J.; Huang, J. J.; Lin, S. K. An efficient and convenient transformation of α-haloketones to α-hydroxyketones using cesium formate. *J. Organomet. Chem.* **2009**, *694*, 3452−3455. (c) Rodriguez-Correia, A.; Knapp-Bühle, D.; Engels, J. W.; Heckel, A. *Org. Lett.* **2014**, *16*, 5128−5131.
(15) Yin, H.; de Almeida, A. M.; de Almeida, M. V.; Lindhardt, A. T.; Skrydstrup, T. Synthesis of Acyl Carbamates via Four Component Pd-Catalyzed Carbonylative Coupling of Aryl Halides, Potassium Cyanate, and Alcohols. *Org. Lett.* **2015**, *17*, 1248−1251.
(16) Yeung, Y. Y.; Corey, E. J. An efficient process for the bromolactamization of unsaturated acids. *Tetrahedron Lett.* **2007**, *48*, 7567−7570.
(17) (a) Slanina, T.; Šebej, P.; Heckel, A.; Givens, R. S.; Klán, P. Caged Fluoride: Photochemistry and Applications of 4-Hydroxyphenacyl Fluoride. *Org. Lett.* **2015**, *17*, 4814−4817. (b) Givens, R. S.; Heger, D.; Hellrung, B.; Kamdzhilov, Y.; Mac, M.; Conrad, P. G.; Cope, E.; Lee, J. I.; Mata-Segreda, J. F.; Schowen, R. L.; Wirz, J. The Photo-Favorskii Reaction of p-Hydroxyphenacyl Compounds Is Initiated by Water-Assisted, Adiabatic Extrusion of a Triplet Biradical. *J. Am. Chem. Soc.* **2008**, *130*, 3307−3309. (c) Conrad, P. G.; Givens, R. S.; Hellrung, B.; Rajesh, C. S.; Ramseier, M.; Wirz, J. *p*-Hydroxyphenacyl Phototriggers: The Reactive Excited State of Phosphate Photorelease. *J. Am. Chem. Soc.* **2000**, *122*, 9346−9347.
(18) (a) Jagadesan, P.; Da Silva, J. P.; Givens, R. S.; Ramamurthy, V. Photorelease of Incarcerated Guests in Aqueous Solution with Phenacyl Esters as the Trigger. *Org. Lett.* **2015**, *17*, 1276−1279. (b) Ma, C.; Kwok, W. M.; Chan, W. S.; Du, Y.; Kan, J. T. W.; Toy, P. H.; Phillips, D. L. Ultrafast Time-Resolved Transient Absorption and Resonance Raman Spectroscopy Study of the Photodeprotection and Rearrangement Reactions of p-Hydroxyphenacyl Caged Phosphates. *J. Am. Chem. Soc.* **2006**, *128*, 2558−2570. (c) Stensrud, K.; Noh, J.; Kandler, K.; Wirz, J.; Heger, D.; Givens, R. S. Competing Pathways in the Photo-Favorskii Rearrangement and Release of Esters: Studies on Fluorinated p-Hydroxyphenacyl-Caged GABA and Glutamate Phototriggers. *J. Org. Chem.* **2009**, *74*, 5219−5227.

DOI: 10.1021/acs.orglett.8b00697
Org. Lett. XXXX, XXX, XXX−XXX