JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/JACS

Article

Decarboxylative Alkyl Coupling Promoted by NADH and Blue Light

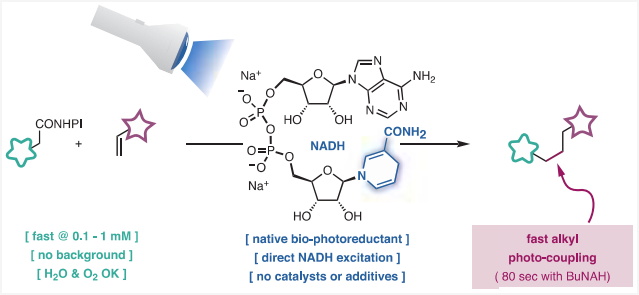
Rajdip Chowdhury,[$] Zhunzhun Yu,[$] My Linh Tong, Stefanie V. Kohlhepp, Xiang Yin, and Abraham Mendoza*

Cite This: J. Am. Chem. Soc. 2020, 142, 20143−20151

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Photoexcited dihydronicotinamides like NADH and analogues have been found to generate alkyl radicals upon reductive decarboxylation of redox-active esters without auxiliary photocatalysts. This principle allowed aliphatic photocoupling between redox-active carboxylate derivatives and electron-poor olefins, displaying surprising water and air-tolerance and unusually high coupling rates in dilute conditions. The orthogonality of the reaction in the presence of other carboxylic acids and its utility in the functionalization of DNA is presented, notably using visible light in combination with NADH, the ubiquitous reductant of life.



INTRODUCTION

Visible light is a prime stimulus to control the conformation of chemical bonds,[1] or their cleavage.[1a,2] The phototriggered formation of chemical bonds can enable frontier research in medicine and biology,[3] but their development is still a challenge in comparison to thermal click reactions[4] due to the slower rate and the need for UV-light and/or photocatalysts.[5] On one hand, photo-cross-linking methods still rely on unstable precursors like azirines or cyclopropanones.[5a,6] On the other hand, recent C−C coupling reactions using photobiocatalytic systems have shown great promise but these are still limited to activated substrates with auxiliary photosensitizers and electron donors.[7] As such, developments in self-sensitized, phototriggered, and fast C−C photocoupling between simple functionalities are still highly sought after (Scheme 1A).[8,9] Aliphatic linkages are particularly attractive due to their small size, robustness, and flexibility, which maximize the chances to obtain functional and metabolically stable conjugates.[8]

Decarboxylative radical addition reactions (Scheme 1A) have recently emerged as prime tools to create aliphatic ligations in biomolecules.[8,9] These methods take advantage of the abundance of carboxylic acids[8,10] and the various technologies developed with Michael acceptors.[1b,11] Despite their success, radical addition reactions are slow (6−12 h) and require additional catalysts, inorganic reducing suspensions, and/or additives that are not native to biological systems.[8] The abundance of endogenous carboxylic acids in biomolecules or biomatrices poses a selectivity challenge for carboxylic acid substrates (**1**), due to their similar oxidation potentials.[8c−e] In contrast, the *N*-hydroxyphthalimide (NHPI) esters (**2**) can be orthogonally activated in the presence of other carboxylates via single-electron reduction.[8a,b,f−l] Recent methods based on desymmetrization[8n] and late-stage carbene transfer[12] illustrate the potential of redox-active esters to be introduced through strategies unavailable to the parent carboxylic acids.

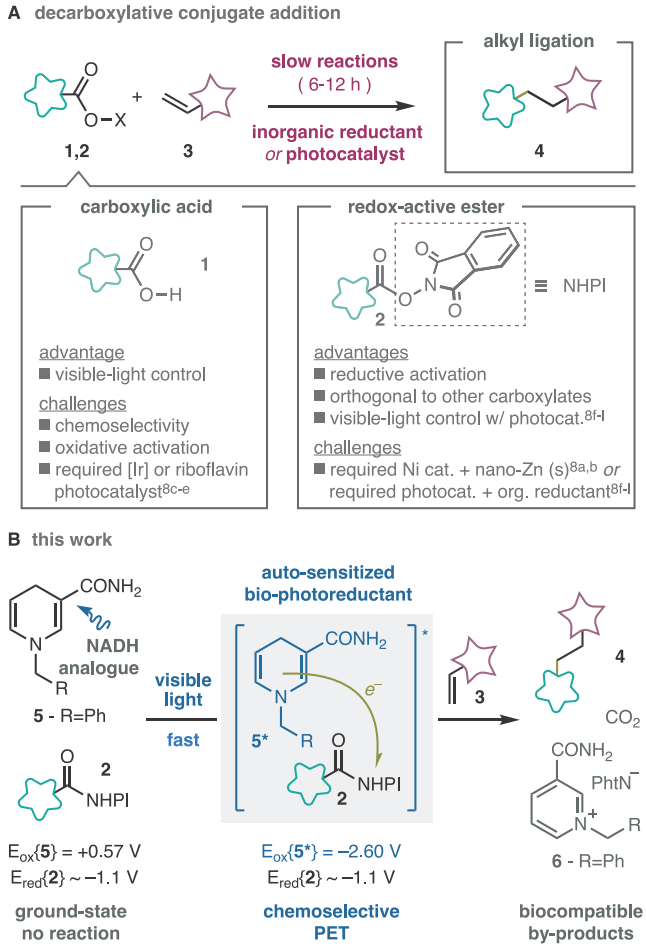
During our synthetic studies with redox-active carbenes,[12] we recognized that the coupling of redox-active esters and Michael acceptors[8a,b,f−l] could significantly expand its capabilities with a suitable biocompatible reductant (Scheme 1B). The reduced nicotinamide adenine dinucleotide (NADH) would be ideal because it is a native component of biological systems.

The redox potential of NADH and its analogs (E_{ox}{**5**} = 0.57 V vs Ag/Ag$^+$) is insufficient to activate redox-active esters (E_{red}{**2**} ∼ − 1.1 ± 0.1 V vs Ag/Ag$^+$).[13] These dihydronicotinamides are potent single-electron reductants in the excited state (E_{ox}*{**5**} = −2.60 V vs Ag/Ag$^+$),[14,15] but their short lifetimes in solution (τ{**5***} ∼ 0.7 ns)[16] have limited their application as autonomous photoreductants.[14,17,18] At the onset of our work, these reagents required additional (photo)catalysts[8f−l,18,19] or enzymes[20] under rigorously anhydrous and degassed conditions to drive reductive couplings. We reasoned that the short-lived excited states of these systems would have a minimal impact in photoinitiated reactions[21] and would avoid side-reactions in the presence of dioxygen derived from triplet-sensitization. The transient generation of the powerful photoreductant **5*** would effectively circumvent the incompatibility with oxygen and moisture of other ground state super electron donors.[22] Importantly, the expected byproducts of the reaction would be biocompatible: the cofactor NAD$^+$

Received: September 15, 2020
Published: October 30, 2020

https://dx.doi.org/10.1021/jacs.0c09678
J. Am. Chem. Soc. 2020, 142, 20143−20151

Scheme 1. Approach Towards Aliphatic Photo-Coupling with Native NADH Bio-Photoreductant[a]



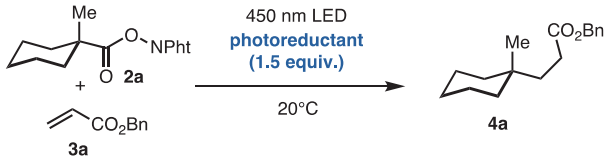
[a]NAD, Nicotinamide Adenine Dinucleotide; PET, Photoinduced Electron Transfer; **5** − R = Ph, R'= H.

(or analogues thereof), CO_2, and phthalimide (LD_{50}{rat oral} > 5 g/kg).[23]

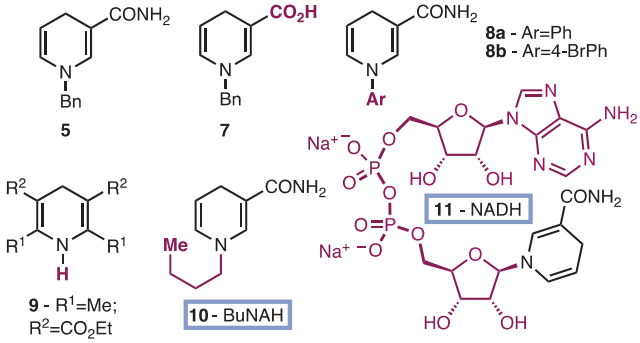
RESULTS AND DISCUSSION

Toward this end, the reaction of the NADH model BNAH (**5**) with the redox-active ester **2a** and the acrylate acceptor **3a** was studied under blue light illumination (λ = 450 nm) without photocatalysts or additives (Scheme 2).[8f−l] To our delight, the desired decarboxylative coupling product **4a** was obtained in high yield using DMSO as solvent (entry 1). The reaction was found to be surprisingly fast, reaching 66% yield after 5 min of illumination (entry 2). Given the importance of maximizing the reaction rate for its implementation at higher dilution,[3,4,4c−i] we explored related photoreductants. It was found that the dihydronicotinamide moiety is essential for high activity (entry 3) as well as the appropriate substitution at the heterocyclic nitrogen (entries 4,5). In line with seminal studies by Overman[8h] and recent work by Shang,[24] the dihydropyridine **9** was found to promote the reaction, but it was slower and less efficient than the more biocompatible dihydronicotinamides (entry 6).[25] Interestingly, the *N*-butyl dihydronicotinamide BuNAH (**10**), which is the closest structural homologue to NADH among the photoreductants explored, was optimal both in terms of yield and rate (entry 7).

Scheme 2. Discovery of the Photo-Coupling Promoted by BuNAH (10) and NADH (11)



entry	solvent	$[2a]_0$ (mM)	photoreductant	t	4a yield (%)[a]
1	DMSO	100	**5**	19 h	92
2	DMSO	100	**5**	5 min	66
3	DMSO	100	**7**	2 h	<5
4	DMSO	100	**8a**	36 h	36
5	DMSO	100	**8b**	36 h	26
6	DMSO	100	**9**	30 min	84
7	DMSO	100	**10**	5 min	99
8	DMSO	1	**10**	20 min	87
9	50% H_2O/DMSO	1	**10**	60 min	72
10	50% H_2O/DMSO (Air)	1	**10**[b]	60 min	79
11	DMSO	10	**11**	60 min	63
12	50% H_2O/DMSO	1	**11**[c]	60 min	69



[a]Determined by ^{1}H NMR using 1,1,2,2- tetrachloroethane as internal standard. [b]3 equiv used. [c]10 equiv used.

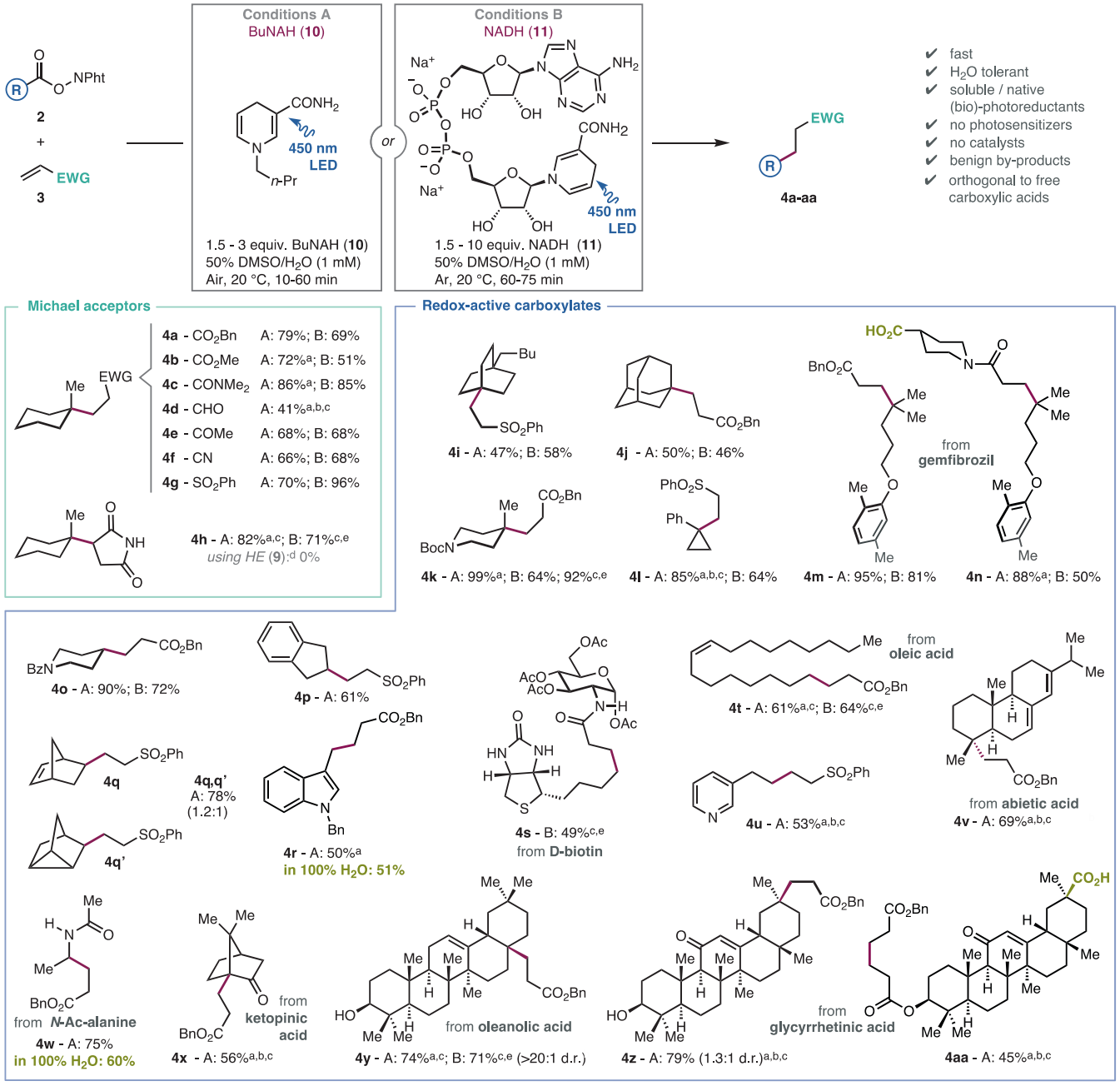
This result can be rationalized by the slightly more reductive character of BuNAH (**10**)[26] than the *N*-benzyl- and *N*-aryl-dihydronicotinamides **5**,**8**. Moreover, the performance of BuNAH (**10**) is only marginally affected by concentrations as low as 1 mM (entry 8). The system tolerates water as cosolvent (50% v/v; entry 9) and air atmosphere (entry 10). These are unique features that contrast with sensitive ground-state organic reductants[22a,4b,c,24,25] and other photocatalyzed reactions.[8f,h,18,19c,d] Interestingly, BuNAH (**10**) can be prepared in multigram amounts, stored indefinitely as a solid, and handled for more than a week as a DMSO stock solution (see SI), thus enabling microdosing in high-throughput studies.

These results led us to explore the performance of NADH (**11**) due to its relevance as the native reductant in biological systems. The photophysics of NADH (**11**) have additional challenges due to its shorter excited state lifetime (τ{NADH} ~ 0.4 ns) and the interaction between its dihydronicotinamide and adenine moieties.[27] To our delight, the commercial NADH disodium salt (**11**) promoted the coupling reaction in a dilute mixture of water and DMSO (1−10 mM; entries 11,12). Unlike that of BuNAH (**10**), it was found that the use of NADH (**11**) required inert atmosphere and larger amounts for optimal results, probably due to its higher sensitivity and/or less favorable photophysic properties.

We set out to explore the scope of the photocoupling using artificial BuNAH (**10**; conditions A) or natural NADH (**11**; conditions B) as photoreductants in aqueous (50% H_2O in

https://dx.doi.org/10.1021/jacs.0c09678
J. Am. Chem. Soc. 2020, 142, 20143−20151

Scheme 3. Scope Study[‡]



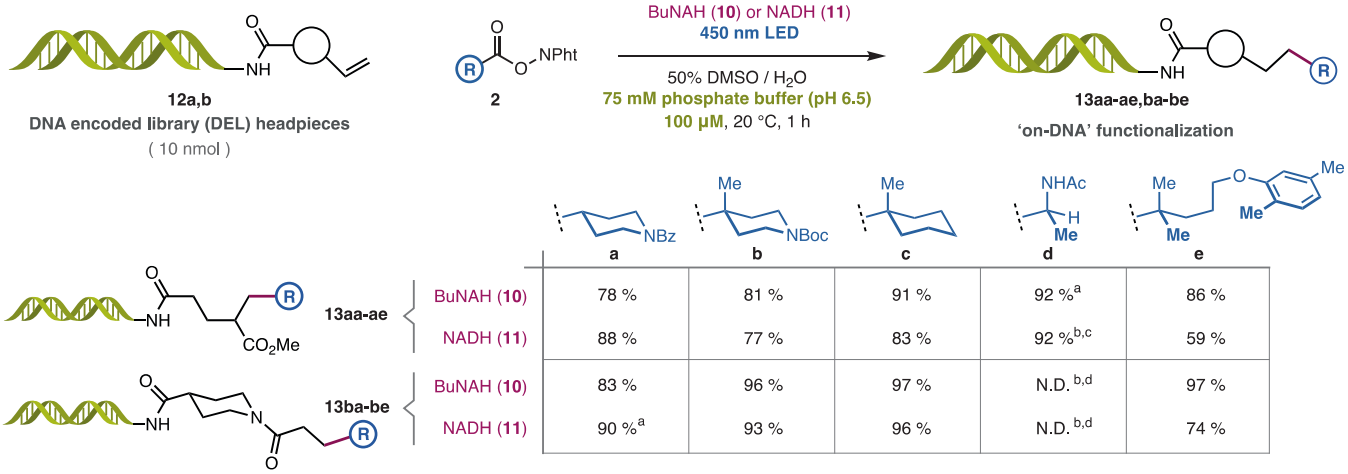
‡Yields were determined by ^{1}H NMR using an appropriate internal standard; for isolated yields at preparative concentrations, see SI. HE; Hantzsch ester (**9**). [a]Ar atmosphere. [b]100 mM concentration. [c]DMSO was used as solvent. [d]Dihydropyridine **9** was used instead of BuNAH (**10**) for comparison. [e]20 mM concentration.

DMSO) and dilute conditions (1 mM; Scheme 3) most relevant in Chemical Biology. Alternatively, preparative scale reactions can be undertaken at higher concentrations in DMSO (see SI for details). Various Michael acceptors bearing electron-withdrawing groups such as ester (**4a,b**), amide (**4c**),[11c] aldehyde (**4d**), ketone (**4e**), nitrile (**4f**), or sulfone (**4g**) were accommodated. Among these, acrolein was significantly less efficient as an acceptor, probably due to degradation of the sensitive aliphatic aldehyde product **4c**. The maleimide scaffold (**4h**) that is common in bioconjugation reactions[1b,5e,11a,b] was found to be very efficient. In stark contrast, no coupling product was obtained using the dihydropyridine **9**,[24,25] thus illustrating the superior reactivity of BuNAH (**10**) or NADH (**11**) as photoreductants.[24,25] High yields and fast reactions also occur across a wide range of redox-active esters. Tertiary sites are coupled efficiently, thus allowing interesting structures to be functionalized, including bicyclic (**4i**), adamantyl (**4j**), piperidine (**4k**), cyclopropane (**4l**), and more complex scaffolds such as the drug gemfibrozil (**4m,n**). Secondary radical precursors are equally effective in the reaction (**4o,q**).

Interestingly, the products **4q,q'** demonstrate that the norbornenyl−nortricyclyl radical equilibrium[28] can be established before their capture by the Michael acceptor. Primary

https://dx.doi.org/10.1021/jacs.0c09678
J. Am. Chem. Soc. 2020, 142, 20143−20151

Scheme 4. Alkyl Photo-Coupling on DNA



		a	b	c	d	e
13aa-ae	BuNAH (**10**)	78 %	81 %	91 %	92 %[a]	86 %
	NADH (**11**)	88 %	77 %	83 %	92 %[b,c]	59 %
13ba-be	BuNAH (**10**)	83 %	96 %	97 %	N.D.[b,d]	97 %
	NADH (**11**)	90 %[a]	93 %	96 %	N.D.[b,d]	74 %

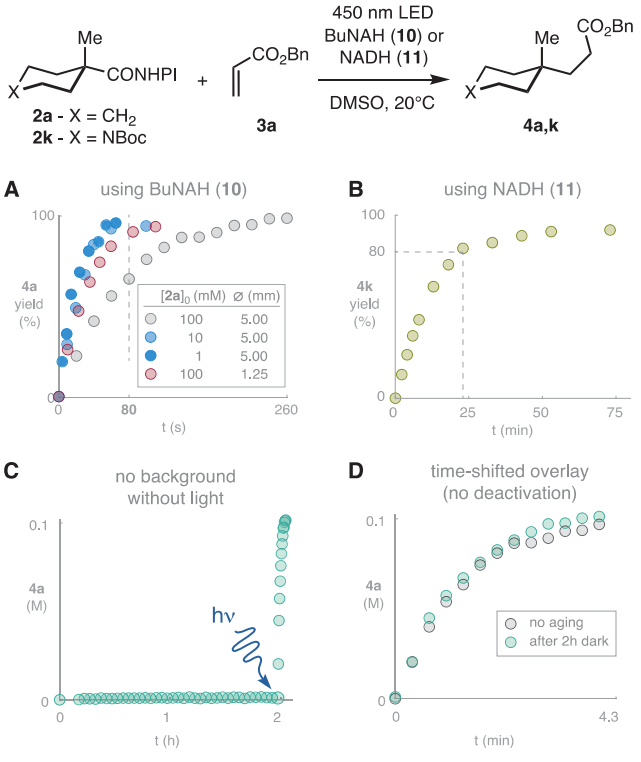
[a]Reaction time 2 h. [b]Reaction time 4 h. [c]Buffer pH 5.5. [d]Coupling product was detected by MS but could not be quantified due to insufficient chromatographic resolution. ND, Not Determined.

carboxylate derivatives led to the products (**4r−u**) featuring robust and flexible alkyl-ligations. These include the cross-coupling of indole (**4r**), *D*-biotin (**4s**), a fatty acid (**4t**), and pyridine (**4u**) derivatives. Among those, the biotinylated product **4s** displays an easily oxidizable thioether, a polar urea, a secondary amide, and an anomerically activated sugar.[29] Moreover, the reaction was proven to be useful in the late-stage functionalization of natural products, including the peptide model derived from alanine (**4w**), and various densely functionalized terpenes with unprotected ketone, enone, olefin, diene, alcohol, and ester functions (**4v,x-aa**). The orthogonality between redox-active esters and unprotected carboxylic acids is demonstrated on the products **4n,aa**. These substrates would lead to mixtures of products and/or polymers through existing coupling reactions based on oxidative decarboxylation.[8c−e] Furthermore, the coupling reactions were complete in 10−75 min. This is substantially faster than previous methods despite the dilute conditions. Particularly sensitive or apolar substrates were understandably less efficient in the standard dilute aqueous media of the reaction (i.e., **4d,s,u,v,y,z,aa**). In these cases, coupling efficiencies are enhanced simply by using higher concentration, inert atmosphere, and DMSO as solvent. However, in more favorable substrates, the reaction could operate even in pure water as solvent with similar results (**4r,w**).

The features of this system in terms of rate, concentration, water tolerance, and solubility of its components made it an ideal candidate for the *in vitro* alkyl photocoupling on polar biomacromolecules. To benchmark the performances of BuNAH (**10**) and NADH (**11**) in this context against comparable decarboxylative coupling methods, we set out to explore coupling reactions on DNA.[8b,d] These are important in the synthesis of DNA-encoded libraries (DEL)[8b,d,9e] yet challenging due to the complex functionality of the substrates and low scale at which these reactions need to occur. To our delight, DEL headpieces **12a,b** were coupled efficiently using either BuNAH (**10**) or NADH (**11**) and blue light at 10 nmol-scale to deliver "on-DNA"-functionalized products **13aa-ae,ba-be** (Scheme 4). These reactions are generally completed in 1 h with excellent yields despite the micromolar concentrations (100 μM) in buffered media. Importantly, all the components in this system can be handled as dilute solutions, thus facilitating mixing in small reaction volumes (<300 μL). These features are characteristic of this system and can facilitate the future implementation of this reaction in automatic platforms.

The kinetic time-profile of the reaction with BuNAH (**10**) was obtained using *in situ* no-D NMR monitoring.[30] Nondeuterated DMSO was used to prevent any potential artifacts due to solvent isotopic effects in the propagation of the radical chain. However, it was found that the reaction proceeds similarly in DMSO and DMSO-d_6, without any solvent-derived byproducts (see SI). This way it was possible to confirm that the reaction can be completed in 4.3 min at 100 mM concentration (Scheme 5A; gray).[8f−l] Moreover, 10-

Scheme 5. Kinetic Profiling of the Photo-Coupling by No-D ^{1}H NMR

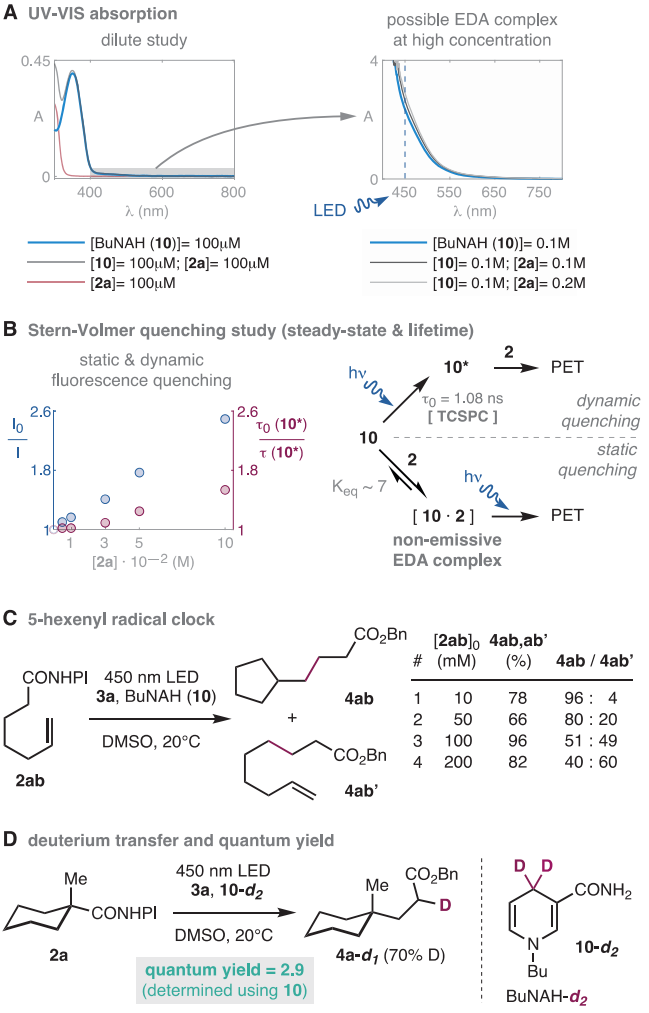


https://dx.doi.org/10.1021/jacs.0c09678
J. Am. Chem. Soc. 2020, 142, 20143−20151

fold (10 mM) and even 100-fold (1 mM) dilutions resulted in a surprising rate acceleration (Scheme 5A; blue traces). The reaction is completed in just 80 s of illumination at 1−10 mM with identical efficiency. To discern the origin of the acceleration, a control experiment was run in the least favorable concentration (100 mM) using a thinner reactor tube (1.25 mm diameter) to minimize the light path on the system. This resulted in significantly faster kinetics (Scheme 5A; red). This result demonstrates that the acceleration observed upon dilution stems from the attenuation of the inner filter effect.[31] With the usage of NADH (**11**) as photoreductant, the reaction is slower (Scheme 5B) but faster than previous decarboxylative coupling reactions.[8,24] The reaction is completed in 60 min (>80% in less than 25 min). These results are remarkable considering the dilute conditions (20 mM) in the presence of only 1.5 equiv of the acceptor **3a** and NADH (**11**). Importantly, the system is stable in the absence of light (Scheme 5C). After a long dark period, the system was illuminated obtaining an identical kinetic profile to that of a standard experiment, as evidenced by the time-shifted overlay (Scheme 5D). This demonstrates the absence of static deactivation in the dark, which may be relevant in cases where other equilibria need to be established before the C−C coupling event is phototriggered.[3,5,6]

Absorption spectroscopy revealed that the light absorption of BuNAH (**10**) is similar to those of other dihydronicotinamides,[16] featuring a strong band at 350 nm that extends into the visible region (Scheme 6A, left). In the presence of the redox-active ester **2a**, which only absorbs below 350 nm, the absorption increases marginally at 450 nm using concentrations as high as 0.1 M (12% increase; Scheme 6A, right), which may indicate the formation of a donor−acceptor complex (EDA).[32,33] Thus, we set out to study the relevance of this possible EDA interaction in the photoactivation of this reaction. Stern−Volmer studies evidenced a linear quenching of the steady-state fluorescence of BuNAH (**10**; Scheme 6B; blue) with increasing concentrations of the redox-active ester **2a**. Nevertheless, the linear decrease in luminescence intensity is not a definitive proof of the mechanism by which this phenomenon occurs.[34] Therefore, the fluorescence lifetime of the excited state **10*** (τ_0(**10***) = 1.08 ns) was measured using Time-Correlated Single Photon Counting (TCSPC). This study revealed a decrease in the lifetime of excited BuNAH (**10***, Scheme 6B; purple) upon increase of the concentration of redox-active ester **2a**. However, the significantly different slopes of the steady-state and lifetime Stern−Volmer plots were not consistent with a conventional dynamic quenching scenario.[34] Instead, the data supports the formation of a nonemissive EDA complex **10·2** in equilibrium with the free **10** (Scheme 6B; right). The corresponding equilibrium constant could be estimated through fitting of the steady-state and lifetime data (K_{eq} ∼ 7; see SI).[34] Consistently, no additional luminescence bands corresponding to the EDA complex **10·2** could be observed in either excitation or emission spectra (see SI). At this point, it is unclear which of these coexisting dynamic and static interactions between BuNAH (**10**) and the redox-active ester **2** are most important for the reactivity. However, it is known that the formation of EDA complexes is affected by changes in the substrate, solvent, concentration, and/or temperature.[32] The fact that the reaction is not inhibited in dilute conditions disfavors the EDA complex to be critical in the photoactivation of this system.[24] In this sense, the direct reduction by photoexcited

Scheme 6. Mechanistic Studies



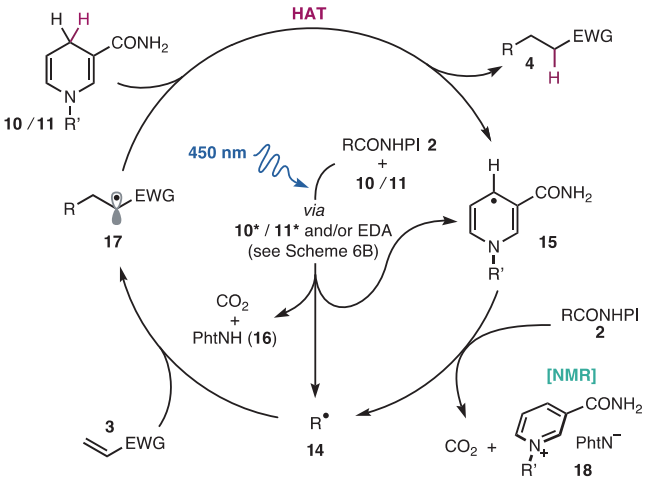
dihydronicotinamides without engagement in donor−acceptor complexes[32,33] has been documented but only in the context of more activated alkyl halide substrates.[17b]

The expected intermediacy of free-diffusing alkyl radicals was demonstrated by the different ratios of the products **4ab,ab'** that were obtained using the 5-hexenyl radical clock precursor **2ab** at different initial concentrations (Scheme 6C). To discern the fate of the radical intermediate that would result from the addition of the alkyl radical into the electron-deficient olefin, we conducted a series of experiments with the dideuterated BuNAH derivative **10**-d_2 (Scheme 6D). These experiments revealed that hydrogen atom transfer (HAT) from BuNAH (**10**) is the main process to quench the putative radical addition product.[8g,h,19c−e] Further control experiments confirmed that the solvents (DMSO and H_2O) do not exchange with **10**-d_2 under the reaction conditions and do not have any relevant role in the HAT process (see SI). The involvement of a radical chain mechanism was studied measuring the average quantum yield. This was determined in triplicate at 20−25% conversion of **2a**, obtaining a value of 2.9 ± 0.5, which points to the propagation of a radical chain.[31]

The mechanistic proposal in Scheme 7 comprises the electron−proton−electron transfer manifold that is typical in radical reductions mediated by dihydronicotinamides[14,17,35] and our own experiments (Schemes 5 and 6). Photoinduced electron and proton transfer from dihydronicotinamide **10** to

https://dx.doi.org/10.1021/jacs.0c09678
J. Am. Chem. Soc. 2020, 142, 20143−20151

Scheme 7. Proposed Mechanism



the redox-active ester **2** through the dynamic and/or static mechanisms discussed above (Scheme 6B) produces the carbon centered radical **14**, a nicotinyl radical **15**, phthalimide (**16**), and CO_2. The radical **14** adds to the olefin **3** to produce the radical **17**, which after concerted[8g] or stepwise[3s] HAT yields the coupling product **4** and the nicotinyl radical **15**.[8g] The latter could reduce the redox-active ester **2** to produce the pyridinium salt **18**, CO_2, and the alkyl radical **14** that propagates the chain reaction (see Scheme 6C,D).[8g] The formation of the pyridinium salts **18** derived from BuNAH (**10**) and NADH (**11**) and their kinetic correlation with the formation of the product **4** has also been evidenced by *in situ* NMR monitoring (see SI).

CONCLUSIONS

Herein, we report that the dihydronicotinamides BuNAH (**10**) and NADH (**11**) promote the photocoupling of redox-active esters and Michael acceptors upon illumination with blue light. These reactions do not require external photocatalysts or additives, have no detectable background reactivity, can run in water, and have an unusually high rate even at low concentration. This system has demonstrated its utility in the functionalization of DNA macromolecules in extremely dilute conditions. The mechanistic experiments demonstrate the multifaceted role of these dihydropyridines as photoinitiators, reductants, and hydrogen-atom donors to drive this fast photocoupling using a minimal homogeneous system. This work introduces NADH (**11**) as an autonomous photoreductant and opens prospects for new artificial coupling reactions that our group is currently investigating.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c09678.

Experimental procedures, characterization, and other data (PDF)

AUTHOR INFORMATION

Corresponding Author

Abraham Mendoza − *Department of Organic Chemistry, Arrhenius laboratory, Stockholm University, 10691 Stockholm, Sweden;* orcid.org/0000-0001-9199-6736; Email: abraham.mendoza@su.se

Authors

Rajdip Chowdhury − *Department of Organic Chemistry, Arrhenius laboratory, Stockholm University, 10691 Stockholm, Sweden;* orcid.org/0000-0001-5515-4371

Zhunzhun Yu − *Department of Organic Chemistry, Arrhenius laboratory, Stockholm University, 10691 Stockholm, Sweden*

My Linh Tong − *Department of Organic Chemistry, Arrhenius laboratory, Stockholm University, 10691 Stockholm, Sweden;* orcid.org/0000-0003-4305-3295

Stefanie V. Kohlhepp − *Department of Organic Chemistry, Arrhenius laboratory, Stockholm University, 10691 Stockholm, Sweden;* orcid.org/0000-0003-3433-4642

Xiang Yin − *Department of Organic Chemistry, Arrhenius laboratory, Stockholm University, 10691 Stockholm, Sweden*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.0c09678

Author Contributions

[$]These authors contributed equally.

Funding

Financial support from the Knut and Alice Wallenberg Foundation (KAW2016.0153), and the European Research Council (714737) is gratefully acknowledged.

Notes

The authors declare no competing financial interest.

Raw data for this article can be downloaded from Zenodo DOI: 10.5281/zenodo.4106400.

ACKNOWLEDGMENTS

We are indebted to the personnel of AstraZeneca Gothenburg and the Dept. of Organic Chemistry at Stockholm University for unrestricted support. The authors particularly thank Dr F. Juliá-Hernández for fruitful discussions, and Prof. E. Borbas and S. Kiraev (Uppsala U.) for assistance with early stage fluorescence measurements.

REFERENCES

(1) (a) Ankenbruck, N.; Courtney, T.; Naro, Y.; Deiters, A. Optochemical Control of Biological Processes in Cells and Animals. *Angew. Chem., Int. Ed.* **2018**, *57* (11), 2768−2798. (b) Fehrentz, T.; Schönberger, M.; Trauner, D. Optochemical Genetics. *Angew. Chem., Int. Ed.* **2011**, *50* (51), 12156−12182. (c) Albert, L.; Vázquez, O. Photoswitchable Peptides for Spatiotemporal Control of Biological Functions. *Chem. Commun.* **2019**, *55* (69), 10192−10213. (d) Szymański, W.; Beierle, J. M.; Kistemaker, H. A. V.; Velema, W. A.; Feringa, B. L. Reversible Photocontrol of Biological Systems by the Incorporation of Molecular Photoswitches. *Chem. Rev.* **2013**, *113* (8), 6114−6178. (e) Heinrich, B.; Bouazoune, K.; Wojcik, M.; Bakowsky, U.; Vázquez, O. *ortho*-Fluoroazobenzene Derivatives as DNA Intercalators for Photocontrol of DNA and Nucleosome Binding by Visible Light. *Org. Biomol. Chem.* **2019**, *17* (7), 1827−1833. (f) Broichhagen, J.; Trauner, D. The in vivo Chemistry of Photoswitched Tethered Ligands. *Curr. Opin. Chem. Biol.* **2014**, *21*, 121−127.

(2) (a) 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* (1), 119−191. (b) Kolarski, D.; Sugiyama, A.; Breton, G.; Rakers, C.; Ono, D.; Schulte, A.; Tama, F.; Itami, K.; Szymanski, W.; Hirota, T.; Feringa, B. L. Controlling the

Circadian Clock with High Temporal Resolution through Photodosing. *J. Am. Chem. Soc.* **2019**, *141* (40), 15784−15791.
(3) Devaraj, N. K. The Future of Bioorthogonal Chemistry. *ACS Cent. Sci.* **2018**, *4* (8), 952−959.
(4) For examples of nonlight regulated bioorthogonal reactions, see: (a) Sletten, E. M.; Bertozzi, C. R. Bioorthogonal Chemistry: Fishing for Selectivity in a Sea of Functionality. *Angew. Chem., Int. Ed.* **2009**, *48* (38), 6974−6998. (b) Patterson, D. M.; Nazarova, L. A.; Prescher, J. A. Finding the Right (Bioorthogonal) Chemistry. *ACS Chem. Biol.* **2014**, *9* (3), 592−605. (c) Whiting, M.; Muldoon, J.; Lin, Y.-C.; Silverman, S. M.; Lindstrom, W.; Olson, A. J.; Kolb, H. C.; Finn, M. G.; Sharpless, K. B.; Elder, J. H.; Fokin, V. V. Inhibitors of HIV-1 Protease by Using In Situ Click Chemistry. *Angew. Chem., Int. Ed.* **2006**, *45* (9), 1435−1439. (d) Fang, Y.; Zhang, H.; Huang, Z.; Scinto, S. L.; Yang, J. C.; Am Ende, C. W.; Dmitrenko, O.; Johnson, D. S.; Fox, J. M. Photochemical Syntheses, Transformations, and Bioorthogonal Chemistry of *Trans*-Cycloheptene and Sila *Trans*-Cycloheptene Ag(I) complexes. *Chem. Sci.* **2018**, *9* (7), 1953−1963. (e) An, P.; Lewandowski, T. M.; Erbay, T. G.; Liu, P.; Lin, Q. Sterically Shielded, Stabilized Nitrile Imine for Rapid Bioorthogonal Protein Labeling in Live Cells. *J. Am. Chem. Soc.* **2018**, *140* (14), 4860−4868. (f) Blackman, M. L.; Royzen, M.; Fox, J. M. Tetrazine Ligation: Fast Bioconjugation Based on Inverse-Electron-Demand Diels−Alder Reactivity. *J. Am. Chem. Soc.* **2008**, *130* (41), 13518−13519. (g) Patterson, D. M.; Nazarova, L. A.; Xie, B.; Kamber, D. N.; Prescher, J. A. Functionalized Cyclopropenes As Bioorthogonal Chemical Reporters. *J. Am. Chem. Soc.* **2012**, *134* (45), 18638−18643. (h) Sachdeva, A.; Wang, K.; Elliott, T.; Chin, J. W. Concerted, Rapid, Quantitative, and Site-Specific Dual Labeling of Proteins. *J. Am. Chem. Soc.* **2014**, *136* (22), 7785−7788. (i) Laughlin, S. T.; Baskin, J. M.; Amacher, S. L.; Bertozzi, C. R. In Vivo Imaging of Membrane-Associated Glycans in Developing Zebrafish. *Science* **2008**, *320* (5876), 664−667.
(5) For examples of light-regulated bioorthogonal reactions: (a) Tasdelen, M. A.; Yagci, Y. Light-Induced Click Reactions. *Angew. Chem., Int. Ed.* **2013**, *52* (23), 5930−5938. (b) Chen, R. T.; Marchesan, S.; Evans, R. A.; Styan, K. E.; Such, G. K.; Postma, A.; McLean, K. M.; Muir, B. W.; Caruso, F. Photoinitiated Alkyne−Azide Click and Radical Cross-Linking Reactions for the Patterning of PEG Hydrogels. *Biomacromolecules* **2012**, *13* (3), 889−895. (c) Singh, K.; Fennell, C. J.; Coutsias, E. A.; Latifi, R.; Hartson, S.; Weaver, J. D. Light Harvesting for Rapid and Selective Reactions: Click Chemistry with Strain-Loadable Alkenes. *Chem.* **2018**, *4* (1), 124−137. (d) Kaur, G.; Singh, G.; Singh, J. Photochemical Tuning of Materials: A Click Chemistry Perspective. *Mater. Today Chem.* **2018**, *8*, 56−84. (e) Bordoni, A. V.; Lombardo, M. V.; Wolosiuk, A. Photochemical radical thiol−ene click-based methodologies for silica and transition metal oxides materials chemical modification: a mini-review. *RSC Adv.* **2016**, *6* (81), 77410−77426. (f) Ramil, C. P.; Lin, Q. Photoclick chemistry: a fluorogenic light-triggered in vivo ligation reaction. *Curr. Opin. Chem. Biol.* **2014**, *21*, 89−95.
(6) (a) Li, G.; Liu, Y.; Liu, Y.; Chen, L.; Wu, S.; Liu, Y.; Li, X. Photoaffinity Labeling of Small-Molecule-Binding Proteins by DNA-Templated Chemistry. *Angew. Chem., Int. Ed.* **2013**, *52* (36), 9544−9549. (b) Herner, A.; Lin, Q. Photo-Triggered Click Chemistry for Biological Applications. *Top. Curr. Chem.* **2016**, *374* (1), 1.
(7) Lee, S. H.; Choi, D. S.; Kuk, S. K.; Park, C. B. Photobiocatalysis: Activating Redox Enzymes by Direct or Indirect Transfer of Photoinduced Electrons. *Angew. Chem., Int. Ed.* **2018**, *57* (27), 7958−7985.
(8) For decarboxylative radical additions with redox-active esters in biomolecules, see: (a) Qin, T.; Malins, L. R.; Edwards, J. T.; Merchant, R. R.; Novak, A. J. E.; Zhong, J. Z.; Mills, R. B.; Yan, M.; Yuan, C.; Eastgate, M. D.; Baran, P. S. Nickel-Catalyzed Barton Decarboxylation and Giese Reactions: A Practical Take on Classic Transforms. *Angew. Chem., Int. Ed.* **2017**, *56* (1), 260−265. (b) Wang, J.; Lundberg, H.; Asai, S.; Martín-Acosta, P.; Chen, J. S.; Brown, S.; Farrell, W.; Dushin, R. G.; O'Donnell, C. J.; Ratnayake, A. S.; Richardson, P.; Liu, Z.; Qin, T.; Blackmond, D. G.; Baran, P. S. Kinetically guided radical-based synthesis of C(sp3)−C(sp3) linkages on DNA. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115* (28), E6404−E6410. For decarboxylative radical additions with carboxylic acids in biomolecules, see: (c) McCarver, S. J.; Qiao, J. X.; Carpenter, J.; Borzilleri, R. M.; Poss, M. A.; Eastgate, M. D.; Miller, M. M.; MacMillan, D. W. C. Decarboxylative Peptide Macrocyclization through Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56* (3), 728−732. (d) Kölmel, D. K.; Loach, R. P.; Knauber, T.; Flanagan, M. E. Employing Photoredox Catalysis for DNA-Encoded Chemistry: Decarboxylative Alkylation of α-Amino Acids. *ChemMedChem* **2018**, *13* (20), 2159−2165. (e) Bloom, S.; Liu, C.; Kölmel, D. K.; Qiao, J. X.; Zhang, Y.; Poss, M. A.; Ewing, W. R.; MacMillan, D. W. C. Decarboxylative alkylation for site-selective bioconjugation of native proteins via oxidation potentials. *Nat. Chem.* **2018**, *10*, 205−211. For photocatalyzed coupling of redox-active esters and Michael acceptors, see: (f) Brandhofer, T.; Mancheño, O. G. Versatile Ru-Photoredox-Catalyzed Functionalization of Dehydro-Amino Acids and Peptides. *ChemCatChem* **2019**, *11* (16), 3797−3801. (g) Okada, K.; Okamoto, K.; Morita, N.; Okubo, K.; Oda, M. Photosensitized decarboxylative Michael addition through N-(acyloxy)phthalimides via an electron-transfer mechanism. *J. Am. Chem. Soc.* **1991**, *113* (24), 9401−9402. (h) Pratsch, G.; Lackner, G. L.; Overman, L. E. Constructing Quaternary Carbons from N-(Acyloxy)phthalimide Precursors of Tertiary Radicals Using Visible-Light Photocatalysis. *J. Org. Chem.* **2015**, *80* (12), 6025−6036. (i) Schnermann, M. J.; Overman, L. E. A Concise Synthesis of (−)-Aplyviolene Facilitated by a Strategic Tertiary Radical Conjugate Addition. *Angew. Chem., Int. Ed.* **2012**, *51* (38), 9576−9580. (j) Schwarz, J.; König, B. Metal-free, visible-light-mediated, decarboxylative alkylation of biomass-derived compounds. *Green Chem.* **2016**, *18* (17), 4743−4749. (k) Müller, D. S.; Untiedt, N. L.; Dieskau, A. P.; Lackner, G. L.; Overman, L. E. Constructing Quaternary Stereogenic Centers Using Tertiary Organocuprates and Tertiary Radicals. Total Synthesis of trans-Clerodane Natural Products. *J. Am. Chem. Soc.* **2015**, *137* (2), 660−663. (l) Jamison, C. R.; Overman, L. E. Fragment Coupling with Tertiary Radicals Generated by Visible-Light Photocatalysis. *Acc. Chem. Res.* **2016**, *49* (8), 1578−1586. for a related decarboxylative alkynylation, see: (m) Yang, J.; Zhang, J.; Qi, L.; Hu, C.; Chen, Y. Visible-light-induced Chemoselective Reductive Decarboxylative Alkynylation under Biomolecule-compatible Conditions. *Chem. Commun.* **2015**, *51*, 5275−5278. (n) Chen, T. − G.; Barton, L. M.; Lin, Y.; Tsien, J.; Kossler, D.; Bastida, I.; Asai, S.; Bi, C.; Chen, J. S.; Shan, M.; Fang, H.; Fang, F. G.; Choi, H. − W.; Hawkins, L.; Qin, T.; Baran, P. S. Building C(sp3)-rich complexity by combining cycloaddition and C−C cross-coupling reactions. *Nature* **2018**, *560*, 350−354.
(9) For other types of photochemical radical couplings in biomolecules, see: (a) Aycock, R. A.; Pratt, C. J.; Jui, N. T. Aminoalkyl Radicals as Powerful Intermediates for the Synthesis of Unnatural Amino Acids and Peptides. *ACS Catal.* **2018**, *8* (10), 9115−9119. (b) Kölmel, D. K.; Meng, J.; Tsai, M.-H.; Que, J.; Loach, R. P.; Knauber, T.; Wan, J.; Flanagan, M. E. On-DNA Decarboxylative Arylation: Merging Photoredox with Nickel Catalysis in Water. *ACS Comb. Sci.* **2019**, *21* (8), 588−597. (c) Garreau, M.; Le Vaillant, F.; Waser, J. C-Terminal Bioconjugation of Peptides through Photoredox Catalyzed Decarboxylative Alkynylation. *Angew. Chem., Int. Ed.* **2019**, *58* (24), 8182−8186. (d) Bottecchia, C.; Noël, T. Photocatalytic Modification of Amino Acids, Peptides, and Proteins. *Chem. - Eur. J.* **2019**, *25* (1), 26−42. (e) Phelan, J. P.; Lang, S. B.; Sim, J.; Berritt, S.; Peat, A. J.; Billings, K.; Fan, L.; Molander, G. A. Open-Air Alkylation Reactions in Photoredox-Catalyzed DNA-Encoded Library Synthesis. *J. Am. Chem. Soc.* **2019**, *141* (8), 3723−3732.
(10) (a) Bratt, E.; Suárez-Pantiga, S.; Johansson, M. J.; Mendoza, A. Mechanism and regioselectivity of the anionic oxidative rearrangement of 1,3-diketones towards all-carbon quaternary carboxylates. *Chem. Commun.* **2019**, *55* (60), 8844−8847. (b) Colas, K.; dos Santos, A. C. V. D.; Mendoza, A. *i*-Pr_2NMgCl·LiCl Enables the Synthesis of Ketones by Direct Addition of Grignard Reagents to Carboxylate Anions. *Org. Lett.* **2019**, *21* (19), 7908−7913.

https://dx.doi.org/10.1021/jacs.0c09678
J. Am. Chem. Soc. 2020, 142, 20143−20151

(11) (a) Renault, K.; Fredy, J. W.; Renard, P.-Y.; Sabot, C. Covalent Modification of Biomolecules through Maleimide-Based Labeling Strategies. *Bioconjugate Chem.* **2018**, *29* (8), 2497−2513. (b) Spicer, C. D.; Pashuck, E. T.; Stevens, M. M. Achieving Controlled Biomolecule−Biomaterial Conjugation. *Chem. Rev.* **2018**, *118* (16), 7702−7743. (c) Lee, Y.-J.; Wu, B.; Raymond, J. E.; Zeng, Y.; Fang, X.; Wooley, K. L.; Liu, W. R. A Genetically Encoded Acrylamide Functionality. *ACS Chem. Biol.* **2013**, *8* (8), 1664−1670.

(12) (a) Yu, Z.; Mendoza, A. Enantioselective Assembly of Congested Cyclopropanes using Redox-Active Aryldiazoacetates. *ACS Catal.* **2019**, *9* (9), 7870−7875. (b) Montesinos-Magraner, M.; Costantini, M.; Ramírez-Contreras, R.; Muratore, M. E.; Johansson, M. J.; Mendoza, A. General Cyclopropane Assembly by Enantioselective Transfer of a Redox-Active Carbene to Aliphatic Olefins. *Angew. Chem., Int. Ed.* **2019**, *58* (18), 5930−5935.

(13) (a) Horner, L.; Jordan, M. Studien zum Vorgang der Wasserstoffübertragung, 53. Beitrag zur Kenntnis der elektroreduktiven Spaltung von Hydroxylaminderivaten. *Justus Liebigs Ann. Chem.* **1978**, *1978* (9), 1518−1525. (b) Li, H.; Breen, C. P.; Seo, H.; Jamison, T. F.; Fang, Y.-Q.; Bio, M. M. Ni-Catalyzed Electrochemical Decarboxylative C−C Couplings in Batch and Continuous Flow. *Org. Lett.* **2018**, *20* (5), 1338−1341.

(14) Fukuzumi, S.; Inada, O.; Suenobu, T. Mechanisms of Electron-Transfer Oxidation of NADH Analogues and Chemiluminescence. Detection of the Keto and Enol Radical Cations. *J. Am. Chem. Soc.* **2003**, *125* (16), 4808−4816.

(15) For photocatalysis based on NAD^+ excitation, using UV light and sacrificial electron donors, see: Kim, J.; Lee, S. H.; Tieves, F.; Paul, C. E.; Hollmann, F.; Park, C. B. Nicotinamide adenine dinucleotide as a photocatalyst. *Sci. Adv.* **2019**, *5* (7), eaax0501.

(16) Martens, F. M.; Verhoeven, J. W.; Gase, R. A.; Pandit, U. K.; de Boer, T. J. On the question of one-electron transfer in the mechanism of reduction by NADH-models. *Tetrahedron* **1978**, *34* (4), 443−446.

(17) For seminal work on the photochemistry of NADH analogues, see: (a) Fukuzumi, S.; Mochizuki, S.; Tanaka, T. Photoreduction of phenacyl halides by NADH analogues. Origins of different mechanistic pathways. *J. Chem. Soc., Perkin Trans. 2* **1989**, *2* (10), 1583−1589. (b) Fukuzumi, S.; Hironaka, K.; Tanaka, T. Photoreduction of alkyl halides by an NADH model compound. An electron-transfer chain mechanism. *J. Am. Chem. Soc.* **1983**, *105* (14), 4722−4727. (c) Fukuzumi, S.; Koumitsu, S.; Hironaka, K.; Tanaka, T. Energetic comparison between photoinduced electron-transfer reactions from NADH model compounds to organic and inorganic oxidants and hydride-transfer reactions from NADH model compounds to *p*-benzoquinone derivatives. *J. Am. Chem. Soc.* **1987**, *109* (2), 305−316.

(18) For a related radical fragmentation of photoexcited 4-alkyl-dihydropyridines, see: (a) van Leeuwen, T.; Buzzetti, L.; Perego, L. A.; Melchiorre, P. A Redox-Active Nickel Complex that Acts as an Electron Mediator in Photochemical Giese Reactions. *Angew. Chem., Int. Ed.* **2019**, *58* (15), 4953−4957. (b) Buzzetti, L.; Prieto, A.; Roy, S. R.; Melchiorre, P. Radical-based C-C Bond-Forming Processes Enabled by the Photoexcitation of 4-Alkyl-1,4-dihydropyridines. *Angew. Chem., Int. Ed.* **2017**, *56* (47), 15039−15043. (c) Bonet, A. G.; Tellis, J. C.; Matsui, J. K.; Vara, B. A.; Molander, G. A. 1,4-Dihydropyridines as Alkyl Radical Precursors: Introducing the Aldehyde Feedstock to Nickel/Photoredox Dual Catalysis. *ACS Catal.* **2016**, *6*, 8004−8008.

(19) For related photocatalyzed reactions of redox-active esters, see: (a) Okada, K.; Okamoto, K.; Oda, M. A new and practical method of decarboxylation: photosensitized decarboxylation of N-acyloxyphthalimides via electron-transfer mechanism. *J. Am. Chem. Soc.* **1988**, *110* (26), 8736−8738. (b) Okada, K.; Okubo, K.; Morita, N.; Oda, M. Reductive decarboxylation of N-(acyloxy)phthalimides via redox-initiated radical chain mechanism. *Tetrahedron Lett.* **1992**, *33* (48), 7377−7380. (c) Pac, C.; Ihama, M.; Yasuda, M.; Miyauchi, Y.; Sakurai, H. Tris(2,2'-bipyridine)ruthenium(2+)-mediated photoreduction of olefins with 1-benzyl-1,4-dihydronicotinamide: a mechanistic probe for electron-transfer reactions of NAD(P)H-model compounds. *J. Am. Chem. Soc.* **1981**, *103* (21), 6495−6497. (d) Lackner, G. L.; Quasdorf, K. W.; Overman, L. E. Direct Construction of Quaternary Carbons from Tertiary Alcohols via Photoredox-Catalyzed Fragmentation of tert-Alkyl N-Phthalimidoyl Oxalates. *J. Am. Chem. Soc.* **2013**, *135* (41), 15342−15345. For radical couplings using nonredox-ester phthalimide derivatives, see: (e) Ito, Y.; Kimura, A.; Osawa, T.; Hari, Y. Photoredox-Catalyzed Deformylative 1,4-Addition of 2′-Deoxy-5′-O-phthalimidonucleosides for Synthesis of 5′-Carba Analogs of Nucleoside 5′-Phosphates. *J. Org. Chem.* **2018**, *83* (18), 10701−10708. (f) Deng, Y.; Nguyen, M. D.; Zou, Y.; Houk, K. N.; Smith, A. B. Generation of Dithianyl and Dioxolanyl Radicals Using Photoredox Catalysis: Application in the Total Synthesis of the Danshenspiroketallactones via Radical Relay Chemistry. *Org. Lett.* **2019**, *21* (6), 1708−1712. (g) Zhang, J.; Li, Y.; Zhang, F.; Hu, C.; Chen, Y. Generation of Alkoxyl Radicals by Photoredox Catalysis Enables Selective C(sp3)−H Functionalization under Mild Reaction Conditions. *Angew. Chem., Int. Ed.* **2016**, *55* (5), 1872−1875.

(20) Emmanuel, M. A.; Greenberg, N. R.; Oblinsky, D. G.; Hyster, T. K. Accessing non-natural reactivity by irradiating nicotinamide-dependent enzymes with light. *Nature* **2016**, *540*, 414−417.

(21) Studer, A.; Curran, D. P. Catalysis of Radical Reactions: A Radical Chemistry Perspective. *Angew. Chem., Int. Ed.* **2016**, *55* (1), 58−102.

(22) (a) Tsurugi, H.; Mashima, K. Salt-Free Reduction of Transition Metal Complexes by Bis(trimethylsilyl)cyclohexadiene, -dihydropyrazine, and −4,4′-bipyridinylidene Derivatives. *Acc. Chem. Res.* **2019**, *52* (3), 769−779. (b) Tsurugi, H.; Mashima, K. A New Protocol to Generate Catalytically Active Species of Group 4−6 Metals by Organosilicon-Based Salt-Free Reductants. *Chem. - Eur. J.* **2019**, *25* (4), 913−919. (c) Broggi, J.; Terme, T.; Vanelle, P. Organic Electron Donors as Powerful Single-Electron Reducing Agents in Organic Synthesis. *Angew. Chem., Int. Ed.* **2014**, *53* (2), 384−413. (d) Murphy, J. A.; Khan, T. A.; Zhou, S.-z.; Thomson, D. W.; Mahesh, M. Highly Efficient Reduction of Unactivated Aryl and Alkyl Iodides by a Ground-State Neutral Organic Electron Donor. *Angew. Chem., Int. Ed.* **2005**, *44* (9), 1356−1360. (e) Murphy, J. A.; Garnier, J.; Park, S. R.; Schoenebeck, F.; Zhou, S.-z.; Turner, A. T. Super-Electron Donors: Bis-pyridinylidene Formation by Base Treatment of Pyridinium Salts. *Org. Lett.* **2008**, *10* (6), 1227−1230.

(23) Lorz, P. M.; Towae, F. K.; Enke, W.; Jäckh, R.; Bhargava, N.; Hillesheim, W., Phthalic Acid and Derivatives. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley: New York, 2007.

(24) Zheng, C.; Wang, G.-Z.; Shang, R. Catalyst-free Decarboxylation and Decarboxylative Giese Additions of Alkyl Carboxylates through Photoactivation of Electron Donor-Acceptor Complex. *Adv. Synth. Catal.* **2019**, *361* (19), 4500−4505.

(25) During our scope studies, it has been independently disclosed[24] similar reactions promoted by the dihydropyridine **9**, albeit only under strictly deoxygenated and anhydrous conditions, and with lower efficiency and rate. The dihydronicotinamide BNAH (**5**) was declared unsuitable for this reaction,[24] in clear contrast with our results (Scheme 2, A; entry 5).

(26) (a) Brewster, M. E.; Simay, A.; Czako, K.; Winwood, D.; Farag, H.; Bodor, N. Reactivity of biologically important reduced pyridines. IV. Effect of substitution on ferricyanide-mediated oxidation rates of various 1,4-dihydropyridines. *J. Org. Chem.* **1989**, *54* (15), 3721−3726. (b) Paul, C. E.; Gargiulo, S.; Opperman, D. J.; Lavandera, I.; Gotor-Fernández, V.; Gotor, V.; Taglieber, A.; Arends, I. W. C. E.; Hollmann, F. Mimicking Nature: Synthetic Nicotinamide Cofactors for C=C Bioreduction Using Enoate Reductases. *Org. Lett.* **2013**, *15* (1), 180−183.

(27) Scott, T. G.; Spencer, R. D.; Leonard, N. J.; Weber, G. Synthetic spectroscopic models related to coenzymes and base pairs. V. Emission properties of NADH. Studies of fluorescence lifetimes and quantum efficiencies of NADH, AcPyADH, [reduced acetylpyridineadenine dinucleotide] and simplified synthetic models. *J. Am. Chem. Soc.* **1970**, *92* (3), 687−695.

https://dx.doi.org/10.1021/jacs.0c09678
J. Am. Chem. Soc. 2020, 142, 20143−20151

(28) (a) Alnajjar, M. S.; Kuivila, H. G. Free-radical and anion intermediates in the reactions of 5-halo-2-norbornenes and 3-halonortricyclenes with (trimethyltin)sodium. *J. Org. Chem.* **1981**, *46* (6), 1053−1057. (b) Walborsky, H. M.; Topolski, M. The surface nature of Grignard reagent formation. *J. Am. Chem. Soc.* **1992**, *114* (9), 3455−3459. (c) Wong, P. C.; Griller, D. A kinetic EPR study of the norbornenyl-nortricyclyl radical rearrangement. *J. Org. Chem.* **1981**, *46* (11), 2327−2329.

(29) We have also detected the successful coupling of the fully unprotected sugar, but only trace amounts could be isolated.

(30) Hoye, T. R.; Eklov, B. M.; Ryba, T. D.; Voloshin, M.; Yao, L. J. No-D NMR (No-Deuterium Proton NMR) Spectroscopy: A Simple Yet Powerful Method for Analyzing Reaction and Reagent Solutions. *Org. Lett.* **2004**, *6* (6), 953−956.

(31) Buzzetti, L.; Crisenza, G. E. M.; Melchiorre, P. Mechanistic Studies in Photocatalysis. *Angew. Chem., Int. Ed.* **2019**, *58* (12), 3730−3747.

(32) (a) Rosokha, S. V.; Kochi, J. K. Fresh Look at Electron-Transfer Mechanisms via the Donor/Acceptor Bindings in the Critical Encounter Complex. *Acc. Chem. Res.* **2008**, *41* (5), 641−653. (b) Lima, C. G. S.; Lima, T. M.; Duarte, M.; Jurberg, I. D.; Paixao, M. W. Organic Synthesis Enabled by Light-Irradiation of EDA Complexes: Theoretical Background and Synthetic Applications. *ACS Catal.* **2016**, *6* (3), 1389−1407. (c) Foster, R. Electron donor-acceptor complexes. *J. Phys. Chem.* **1980**, *84* (17), 2135−2141.

(33) Cao, Z.-Y.; Ghosh, T.; Melchiorre, P. Enantioselective radical conjugate additions driven by a photoactive intramolecular iminium-ion-based EDA complex. *Nat. Commun.* **2018**, *9* (1), 3274.

(34) (a) Lakowicz, J. R. *Principles of Fluorescence Spectroscopy, Plenum:* New York, 1983, ch. 9;. (b) Fraiji, L. K.; Hayes, D. M.; Werner, T. C. Static and Dynamic Fluorescence Quenching Experiments for the Physical Chemistry Laboratory *J. J. Chem. Educ.* **1992**, *69*, 424−428.

(35) Martens, F. M.; Verhoeven, J. W.; Varma, C. A. G. O.; Bergwerf, P. Photo-oxidation of 1,4-dihydropyridines by various electron acceptors: a laser flash photolysis study. *J. Photochem.* **1983**, *22* (2), 99−113.

https://dx.doi.org/10.1021/jacs.0c09678
J. Am. Chem. Soc. 2020, 142, 20143−20151