Time-Resolved Decarboxylative Alkyl Coupling Promoted by NADH and Blue Light

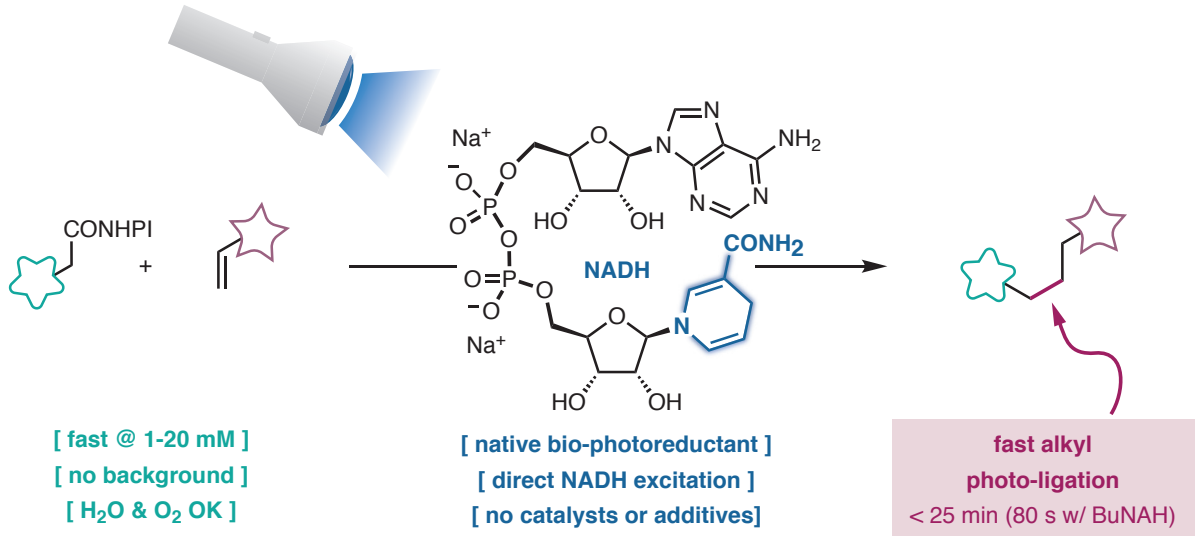
Rajdip Chowdhury,‡ Zhunzhun Yu,‡ Stefanie V. Kohlhepp, Xiang Yin,

and Abraham Mendoza*

‡*These authors contributed equally.*

Dept. of Organic Chemistry, Arrhenius laboratory, Stockholm University,

106 91 Stockholm (Sweden)

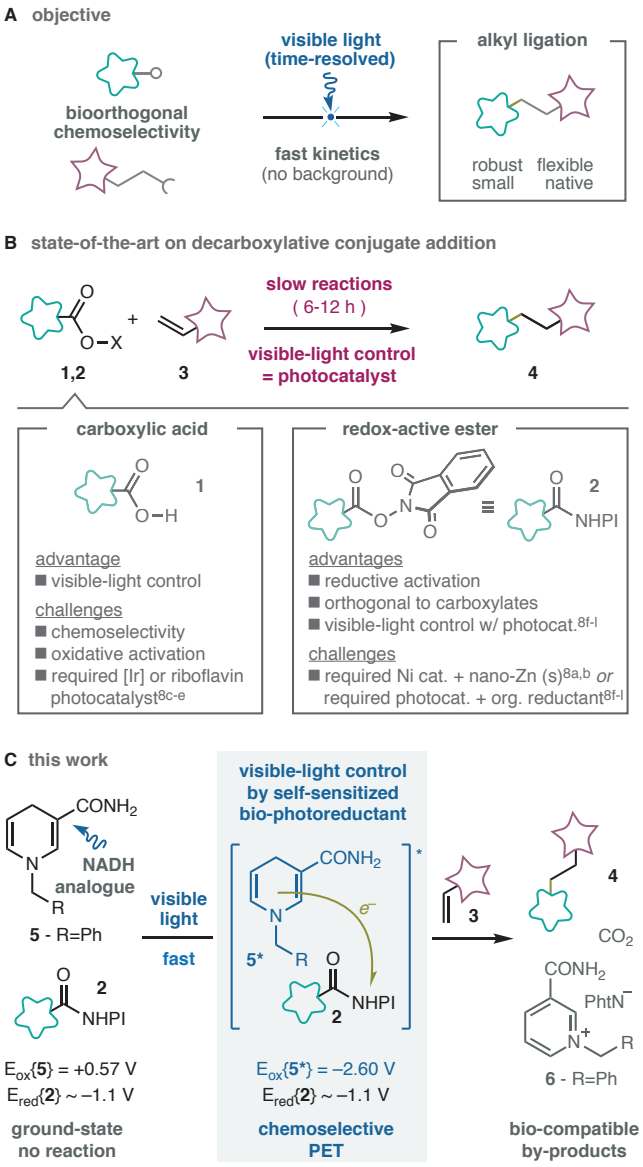


ABSTRACT: Flexible, small and strong alkyl ligations created upon external light stimuli can open new avenues for medicinal and biological research. Herein, we have found that NADH and analogues can drive photo-couplings without auxiliary photocatalysts. The time-resolved alkyl photo-ligation between redox-active carboxylate derivatives and electron-poor olefins displays a surprising moisture and air-tolerance, and unusually high coupling rates in dilute conditions. This work sets the conceptual basis for further biocompatible C-C coupling

reactions promoted by visible-light in combination with NADH, the ubiquitous reductant of biological systems.

Visible light is a prime stimulus to externally control complex systems. It can be used to unravel the mechanisms of life, for example, by altering the conformation of biomolecules (photo-switches),[1] or activating specific substances (photo-decaging).[1a,2] Photo-triggered coupling reactions can enable frontier research in medicine and biology,[3] but their development is still challenging due to the exogenous systems required for light absorption, and their slower rate. Fast bioorthogonal reactions are not regulated by light, and create substantial heterocyclic footprints that can affect function.[3-4] Current photo-regulated versions of these reactions are limited by UV irradiation, and the photocatalysts needed for visible light harvesting.[5] Photo-crosslinking methods still demand unstable precursors like azirines or cyclopropanones.[5a,6] Recent C–C coupling reactions using photo-biocatalytic systems are based in auxiliary photosensitizers and electron donors, which may be problematic in more complex settings.[7] As such, developments in self-sensitized, time-resolved, and fast C–C photo-coupling between simple functionalities are still highly sought after (Scheme 1, A).[8,9] Aliphatic ligations are particularly attractive due to their small size, robustness, and flexibility, which maximizes the chances to obtain functional and metabolically-stable conjugates.[8]

Scheme 1. Approach towards time-resolved alkyl ligation with native NADH bio-photoreductants.



Decarboxylative radical addition reactions (Scheme 1, B) have recently emerged as a prime tool to create aliphatic ligations in biomolecules.[8-9] These methods take advantage of the abundance of carboxylic acids,[8,10] and the various technologies available to install Michael acceptors.[1b,11] Despite their success, these mild reactions are too slow (6-12 h) to be suitable for time-resolved coupling using visible light, and require additional catalysts, inorganic reducing suspensions, and/or additives that are not native to biological systems.[8] The

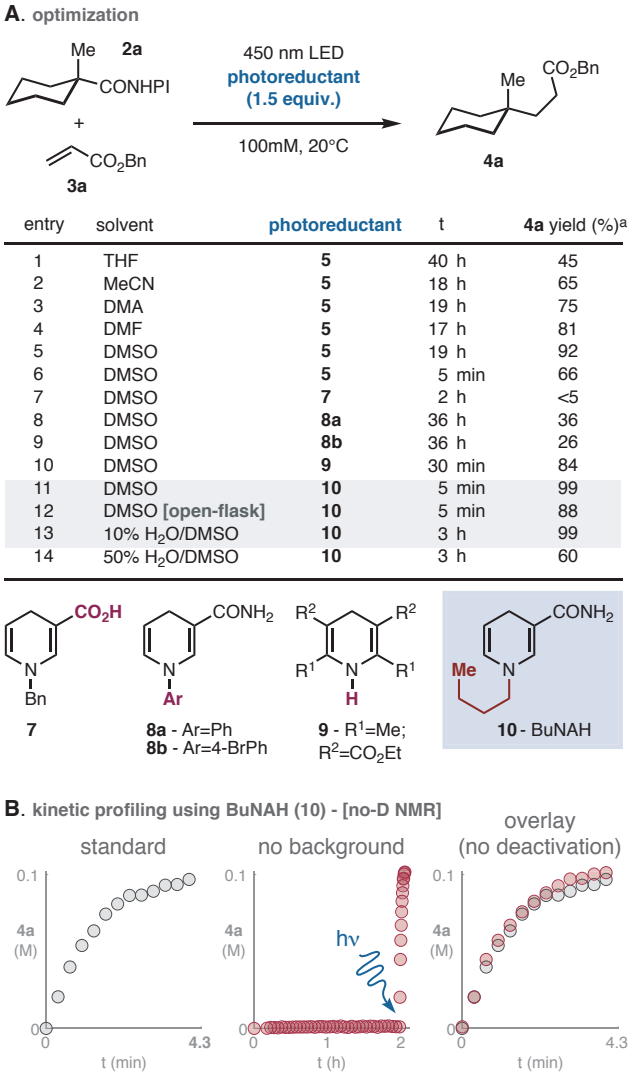
abundance of endogenous carboxylic acids in bio-molecules pose a selectivity challenge for carboxylic acid substrates (**1**), due to their similar oxidation potentials.[8c-e] In contrast, the *N*-hydroxyphthalimide (NHPI) esters (**2**) can be orthogonally activated in the presence of other carboxylates *via* single-electron reduction.[8a,b,f-l]

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 1, C). 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] However, they become potent single-electron reductants upon irradiation (E_{ox}*{**5**} = –2.60 V vs Ag/Ag^+),[14,15] but the short lifetimes of their excited states in solution (τ{**5***} ~ 0.7 ns)[16] has 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 their photoinitiation,[21] and would avoid triplet-sensitization side-reactions in the presence of dioxygen. The transient generation of the powerful photo-reductant **5*** would effectively circumvent the incompatibility with oxygen and moisture of other ground state super electron donors.[22] Importantly, the expected by-products of the reaction would be the native biological co-factor NAD^+ (or analogues thereof), CO_2, and benign phthalimide (LD_{50}{rat oral} > 5 g/kg).[23]

Towards 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, A).[8f-l] To our delight, the desired decarboxylative coupling product **4a** was observed, albeit only in moderate yield (entry 1). The solvent had a marked effect (entries 1-5), and DMSO proved optimal (entry 5), thus facilitating future applications in biological and medicinal research. The reaction was found to be surprisingly fast, reaching 66% yield after 5 minutes of illumination (entry 6). Given the importance of maximizing the reaction rate for its implementation at higher dilution,[3-4,4c-i] we explored related photo-reductants. It was found that the dihydronicotinamide moiety is essential for high activity (entry 7), as well as the appropriate substitution at the heterocyclic nitrogen (entries 8,9). The dihydropyridine **9** was found to promote the reaction, albeit it was slower and less efficient than the more biocompatible dihydronicotinamides (entry 10).[24,25] Interestingly, the *N*-alkyl dihydronicotineamide BuNAH (**10**), which is the closest structural homologue to NADH among the photoreductants **5,7-10**, was found to be optimal both in terms of yield and rate (entry 11). 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, BuNAH (**10**) is only marginally affected by the presence of oxygen and water, unlike other organic (photo)reductants.[22a-c,24-25] This is evidenced by the minimal erosion of efficiency under open-flask conditions (entry 12), and the identical performance in the presence of 10% v/v H_2O (entry 13), which is relevant in the synthesis of DNA-encoded libraries.[8b] Even with 50% v/v H_2O the reactivity is considerable (entry 14, unoptimized), despite the limited solubility of the model substrates **2a,3a** in this medium. Interestingly, BuNAH (**10**) can be prepared in multi-gram amounts, stored indefinitely as a solid, and handled for more than a week as a DMSO stock solution (see SI), thus enabling micro-dosing in high-throughput studies.

Scheme 2. Discovery and kinetic evaluation of the photo-coupling promoted by BuNAH (10).



entry	solvent	photoreductant	t	4a yield (%)[a]
1	THF	5	40 h	45
2	MeCN	5	18 h	65
3	DMA	5	19 h	75
4	DMF	5	17 h	81
5	DMSO	5	19 h	92
6	DMSO	5	5 min	66
7	DMSO	7	2 h	<5
8	DMSO	8a	36 h	36
9	DMSO	8b	36 h	26
10	DMSO	9	30 min	84
11	DMSO	10	5 min	99
12	DMSO [open-flask]	10	5 min	88
13	10% H_2O/DMSO	10	3 h	99
14	50% H_2O/DMSO	10	3 h	60

7 — **8a** - Ar=Ph; **8b** - Ar=4-BrPh — **9** - R^1=Me; R^2=CO_2Et — **10** - BuNAH

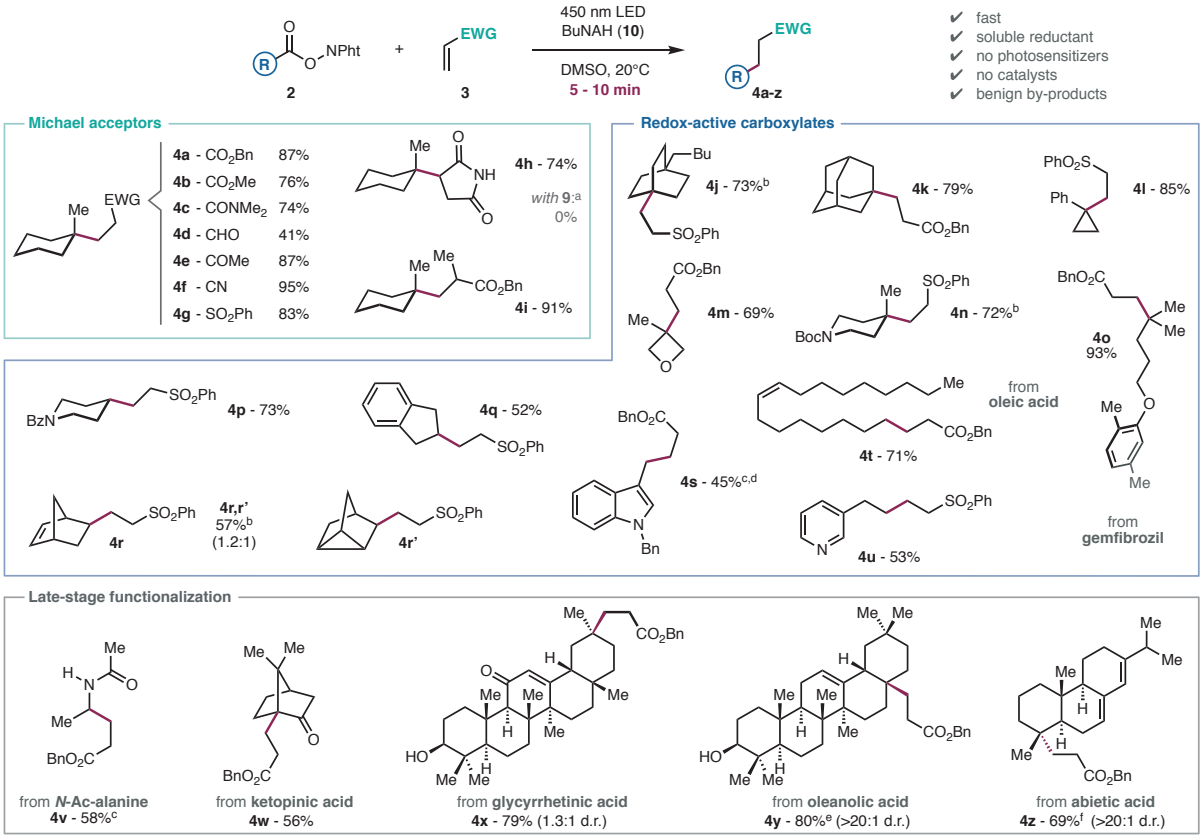
[a] Determined by ^{1}H-NMR using 1,1,2,2- tetrachloroethane as internal standard.

The kinetic time-profile of the reaction was obtained using *in situ* no-D NMR monitoring.[27] Non-deuterated 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 by-products (see SI). This way it was possible to confirm that the reaction is complete in 4.3 minutes using BuNAH (**10**) without additional photocatalysts (Scheme 2, B; left).[8f-l] The stability of system

in the absence of light is crucial in biology studies to develop equilibria before triggering the C–C coupling event.[3,5-6] Pleasingly, the reaction does not progress in dark, but is quickly completed upon illumination (Scheme 2, B; center). Importantly, the kinetic profile of the reaction after the long dark period is identical to the standard reaction (Scheme 2, B; right), thus evidencing the absence of static deactivation.

We set out to explore the scope of the photo-coupling with a series of model systems (Scheme 3). 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. The maleimide scaffold (**4h**) that is common in bioconjugation reactions[1b,5e,11a,b] was found to be very efficient using BuNAH (**10**), which is clearly superior to the artificial dihydropyridine **9**.[24-25] The branched methacrylate ester (**4i**) can also be used effectively. High yields and fast reactions also occur across a wide range of redox-active esters. Tertiary sites are coupled efficiently, thus allowing interesting cores to be derivatized, including bicyclic (**4j**), tricyclic (**4k**), cyclopropane (**4l**), oxetane (**4m**), piperidine (**4n**), and a pharmaceutical (**4o**). Secondary radical precursors are equally effective in the reaction (**4p-r**). Interestingly, the products **4r,r'** display that the norbornenyl-nortricyclyl radical equilibrium[28] can be established before capture by the Michael acceptor. Primary carboxylate derivatives led to the products (**4s-u**) featuring small and flexible alkyl-ligations. These include the cross-coupling of indole (**4s**), fatty acid (**4t**), and pyridine (**4u**) derivatives. Moreover, the reaction has proven useful in the late-stage functionalization of natural products, including the peptide model derived from alanine (**4v**), and various densely-functionalized terpenes (**4w-z**) with unprotected, ketone, enone, olefin, diene and alcohol functions.

Scheme 3. Scope study.



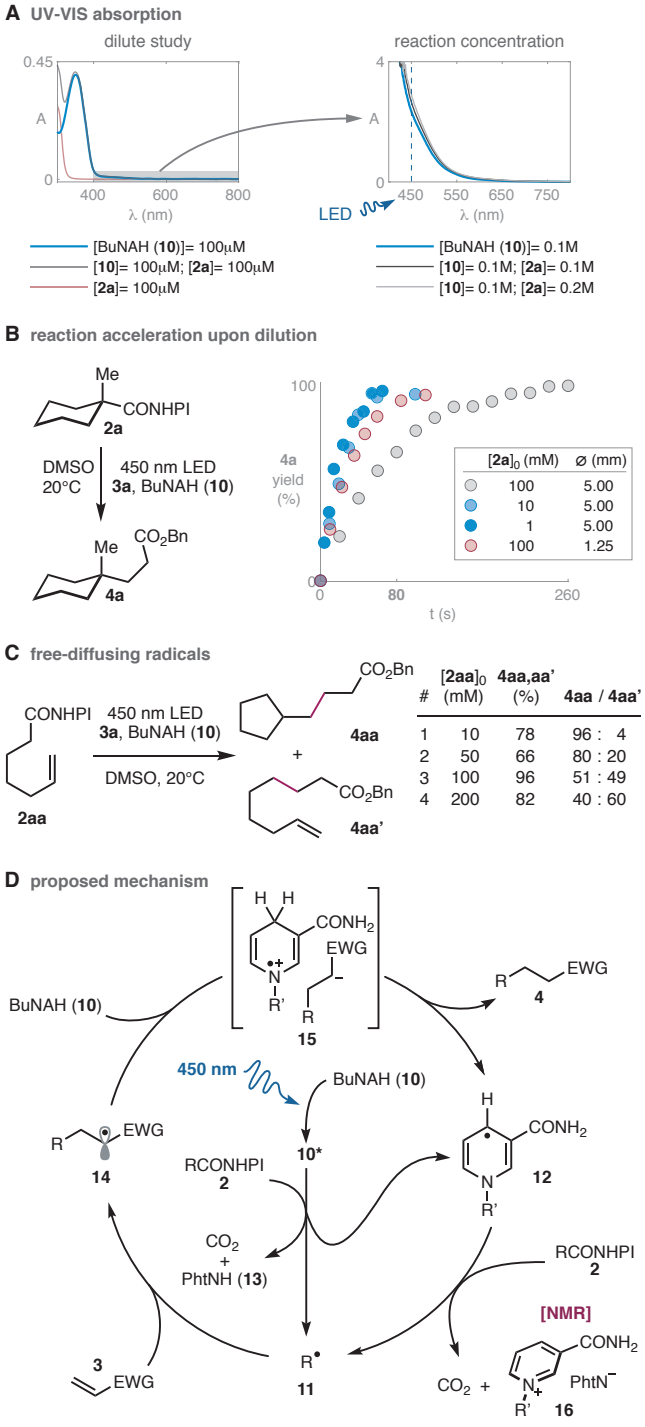
Conditions: **2** (0.1 mmol; 100 mM), **3** (150 mM), **10** (150 mM), 450 nm LED, DMSO, 20°C (thermostatic). [a] Dihydropyridine **9** was used instead of BuNAH (**10**) for comparison; [b] 15 min reaction time; [c] isolated yield **4s,v** is 30% and 36%, respectively; [d] 2 h reaction time; [e] 25 min reaction time; [f] 20 min reaction time.

UV/VIS spectroscopic studies (Scheme 4, A) revealed that the light absorption of BuNAH (**10**) is analogous to BNAH (**5**),[16] featuring a strong band at 350 nm that extends into the visible region with low molar extinction (Scheme 4, A, left). In the presence of the redox-active ester **2a**, which only absorbs below 350 nm, the absorption increases marginally at the reaction concentration (12% increase at 450 nm and 0.1M; Scheme 4, A, right), which may indicate the formation of a donor-acceptor complex (EDA).[29,30] While EDA complexes are known to be affected by changes in the substrate, solvent, dilution and/or temperature,[29]

molecular chromophores are robust, and independent of these factors. Photo-excited dihydronicotinamides are known to reduce simple alkyl halides,[17b] without the π-acceptor moiety that is common in EDA interactions.[29,30] Moreover, diluting 10-fold (10 mM) and even 100-fold (1 mM), which should disfavor EDA formation, results in a surprising rate acceleration (Scheme 4, B). These facts and the marginal absorption of the EDA complex seems to disfavour its implication in the photoactivation of this system.[24] Remarkably, the reaction is completed in just 80 seconds at 1-10 mM with identical efficiency. Fast kinetics are also obtained at high concentration (100 mM) using a thinner reactor (1.25 mm diameter), thus demonstrating that the acceleration stems from the attenuation of the inner filter effect.[31] Lastly, the expected intermediacy of free-diffusing alkyl radicals is evidenced by the different ratios of the products **4aa,aa'** that were obtained using the 5-hexenyl radical clock precursor **2aa** at different initial concentrations (Scheme 4, C).

The mechanistic proposal for this reaction (Scheme 4, D) comprises the electron-proton-electron transfer manifold that is typical in radical reductions mediated by dihydronicotinamides,[14,17,32] and the mechanistic experiments discussed above (Scheme 4, A-C). Photo-induced electron and proton transfer from dihydronicotinamide **10** to the redox-active ester (**2**) produces the carbon centered radical **11**, a nicotinyl radical **12**, phthalimide (**13**) and CO_2. The radical **11** adds to the olefin **3** to produce the radical **14**, which after concerted[8g] or step-wise (*via* **15**)[32] hydrogen atom transfer yields the coupling product **4** and the nicotinyl radical **12**.[8g] The latter could reduce the redox-active ester (**2**) to produce the pyridinium salt **16**, CO_2, and a propagating alkyl radical chain (see **11**).[8g] The formation of the pyridinium salt **16** and their kinetic correlation with the formation of the product **4** has been evidenced by *in situ* NMR studies (see SI).

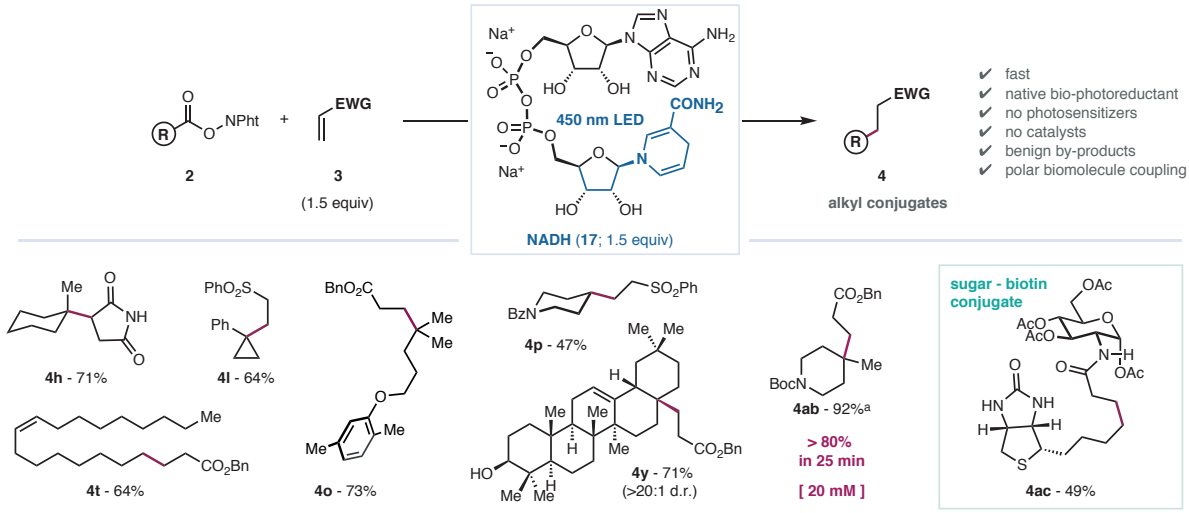
Scheme 4. Mechanistic studies.



The results on the photo-coupling using the model dihydronicotinamide BuNAH (**10**), allowed to evaluate the performance of NADH, the native reductant in biological systems (Scheme 5). This compound has additional challenges due to its shorter excited state lifetime (τ{NADH} ~ 0.4 ns), and more complex photophysics given the interaction between its

dihydronicotinamide and adenine moieties.[33] To our delight, the redox-active esters **2** were coupled with Michael acceptors **3** using commercial NADH disodium salt (**17**) under blue light illumination. The product **4ab** was obtained in 92% yield with fast initial rate (see SI; >80% yield in less than 25 minutes). These results are remarkable considering the dilute conditions (20 mM), and that only 1.5 equivalents of the acceptor **3a**, and natural NADH (**17**) were used. In analogy with the model system, it was confirmed the expected formation of NAD^+ and phthalimide as by-products by *in situ* NMR analysis (see SI). Moreover, the reaction is general across a variety of primary, secondary and tertiary redox-active esters, including imide (**4h**), alkene (**4t,y**), cyclopropane (**4l**), alcohol (**4y**) and heterocyclic functions (**4p,ab**), which were incorporated in good yields. The variety of Michael acceptors that can be used in this coupling compares well with our findings in the model system, and include acrylate (**4t,o,y,ab**), vinylsulfone (**4l,p**) and maleimide (**4h**) alike. This reaction is suitable for the coupling of polar biomolecules, as evidenced by the successful photo-biotinylation of a sugar derivative (**4ac**).[34] As far as we are aware, these are the first C–C coupling reactions driven by direct photo-excitation of NADH (**17**), they prove its autonomy to drive fast and efficient electron transfer,[20] and set the stage for future biocompatible photo-ligation protocols.

Scheme 5. Alkyl photo-ligation with NADH.



Conditions: **2** (0.05 mmol; 100 mM), **3** (1.5 equiv.), NADH (**17**; 1.5 equiv.), 450 nm LED, DMSO, 20°C, 75 min. Yields determined by ^{1}H-NMR using 1,1,2,2-tetrachloroethane as internal standard. [a] Reaction concentration 20 mM.

In summary, herein we report that NADH and other dihydronicotinamides promote time-resolved C–C coupling of redox-active esters and Michael acceptors upon illumination with blue light. These reactions do not require external photocatalysts or additives, has no detectable background reactivity, tolerates air and moisture, and has an unusually high rate even at low concentration. The system is driven by the robust excitation of the native reductant that is present in all biochemical systems, NADH. These results pave the way for future development of space- and time-resolved biocompatible alkyl photo-ligation protocols, which our group is currently developing.

Acknowledgement

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

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 non-light 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.* **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 photo-catalyzed 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.

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*-$Pr_2NMgCl{\cdot}LiCl$ Enables the Synthesis of Ketones by Direct Addition of Grignard Reagents to Carboxylate Anions. *Org. Lett.* **2019,** *21* (19), 7908-7913.

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,** (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.

19. For related photo-catalyzed 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 non-redox-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. 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.

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. (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.; de M. Lima, T.; Duarte, M.; Jurberg, I. D.; Paixão, 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.

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

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

32. 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.

33. Gordon Scott, T.; 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.

34. We have also detected the successful coupling of the fully unprotected sugar, but the product could only be isolated in trace amounts.