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Biocompatible Photoinduced Alkylation of Dehydroalanine for the Synthesis of Unnatural α-Amino Acids

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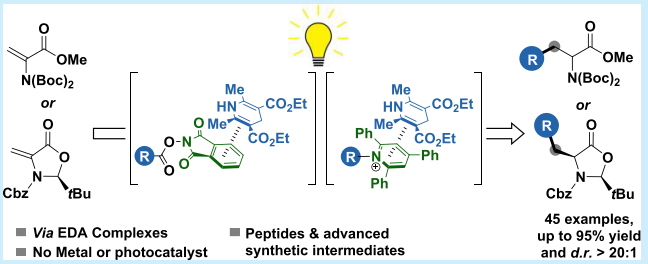
ABSTRACT: A site-selective alkylation of dehydroalanine to access protected unnatural amino acids is described. The protocol is characterized by the wide nature of alkyl radicals employed, mild conditions, and functional group compatibility. This protocol is further extended to access peptides, late-stage functionalization of pharmaceuticals, and enantioenriched amino acids.



New synthetic methodologies to access derivatized amino acids offer medicinal and biological chemists an expanded toolbox toward the synthesis of biologically relevant molecules.[1] These privileged motifs have been found as building blocks in drug development[2] and are used as a chiral pool for ligand preparation and catalyst design owing to their wide structural diversity (Scheme 1A).[3] In the context of drug design, the straightforward synthesis of non-natural amino acids through amino acid side chain modification can remarkably improve the drug absorption−distribution−metabolism−excretion−toxicity (ADMET) properties.[4] As such, methods that provide site-selective or site-specific amino acid/peptide modifications under biocompatible conditions are essential for drug development, especially for those drug programs based on the modification of proteins, antibodies, and DNA.[5] Nowadays, classical synthetic methodologies generally rely on higher-energy systems, either through highly reactive organometallic reagents[6] or UV-irradiation,[7] to reach the desired reaction outcome. On the other hand, contemporary synthetic methodologies have focused on selective and mild conditions. Visible-light mediated catalytic methodologies have offered an innovative solution to forge similar bonds as enabled by classical methodologies but with the advantages of using a low-energy source, which allows for selective and controlled reactions.[8]

Of the synthetic precursors to amino acids, dehydroalanine (Dha) offers tremendous opportunities as it contains a double bond, which behaves as a nucleophile or electrophile. This reactivity has found particular success in reactions with nucleophiles and allows stereoselective transformations (*i.e.*, employing a modified Dha called Karady−Beckwith alkene).[9]

These features have made Dha an excellent synthon for the selective synthesis of noncanonical amino acids and the late-stage decoration of biologically relevant peptides; consequently, new strategies for Dha's modification have been significantly investigated.[10]

Among the recent reports, photocatalytic transformations have taken advantage of radical addition to Dha species, employing a variety of precursors.[11] In this regard, the use of abundant and cheap radical feedstocks, such as carboxylic acids and their derivatives, *e.g.*, *N*-hydroxyphthalimides (NHPI) esters and oxalates, for radical generation opened a new perspective for the development of sustainable methodologies (Scheme 1B).[12] Moreover, the replacement of highly reactive organometallic reagents is one of the important advantages of these strategies.[13]

Recently, our group has been involved in developing photoinduced processes enabled by EDA complexation.[14,15a] Inspired by these studies, we have now developed a simple, mild, biocompatible, and scalable protocol for the alkylation of Dha's through the implementation of aliphatic amines[16] and carboxylic acid redox-active derivatives[17] (Scheme 1C). Complementary to previous photoredox protocols, this approach is metal- and catalyst-free, and it demonstrates high functional group tolerance to afford a large family of unnatural amino acids in moderate to good yields.

We started our investigation by studying the reaction between the proline NHPI ester derivative **1a** and dehydroalanine **2a**, in the presence of Hantzsch ester **3a**, under blue LED irradiation. After a set of preliminary experiments (see SI for details), we have found that the

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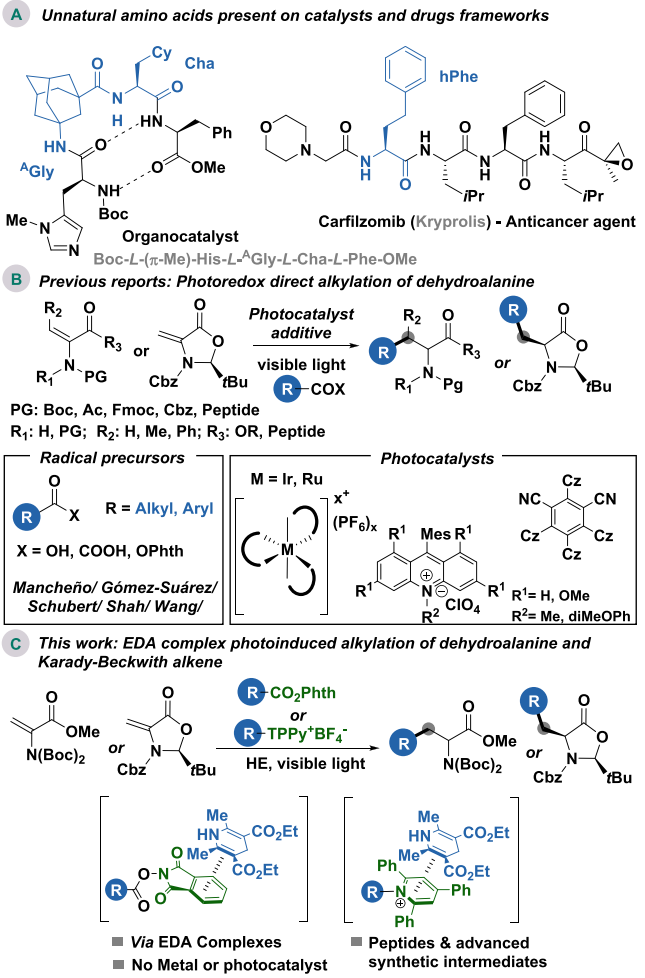
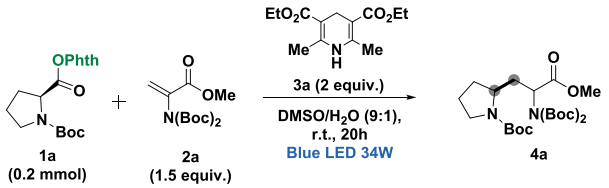
Scheme 1. Photocatalytic Hydroalkylation of Dehydroalanine[a]



[a]EDA = R-CO_2Phth + HE and R-$TPPy^+BF_4^-$ + HE.

optimum conditions involving 1.0 equiv of **1a**, 1.5 equiv of **2a**, and 2.1 equiv of **3a** in DMSO/H_2O (9:1) afforded the desired product (**4a**) in excellent yield, after 20h of irradiation (Table 1, entry 1).

Table 1. Optimization of Reaction Parameters



entry	deviation from optimum conditions	yield of **4a**[a]
1	none	90%
2	without **3a**	0%
3	1.5 equiv of **3a**	75%
4	addition of 1.5 equiv of DIPEA	85%
5	1.5 equiv of DIPEA instead of **3a**	32%
6	1 mol % of $[Ru(bpy)_3](PF_6)_2$	70%
7	without light	0%

[a]Isolated yields. Diastereoselectivities were determined by NMR and corresponded to 1:1 in all cases.

Entries 2−6 summarize some deviations from the optimized conditions. The absence or the use of a smaller amount of **3a** was shown to be detrimental to the reaction outcome (entries 2 and 3). A slight erosion in the reaction efficiency was further observed when DIPEA was used as a second additive (entry 4). A control experiment in the absence of **3a** but with 1.5 equiv of DIPEA afforded **4a** in a very low yield (entry 5). Moreover, the presence of 1 mol % of commercially available $[Ru(bpy)_3](PF_6)_2$ as a photoredox catalyst did not alter the reaction performance (entry 6). As a control experiment, we performed the reaction in the dark, and no formation of desired product was observed (entry 7).

Next, we turned our attention to exploring the scope and limitations of this metal-free hydroalkylation protocol (Scheme 2). A variety of cyclic and acyclic amino acid NHPI esters (**4a**−**4g**) were successfully employed, showing a remarkable tolerance to both protected alcohols and amines as well as aromatic and steric encumbrance. Moreover, cycloalkyl NHPI esters (**4h**−**4k**) were successfully applied under the reaction conditions, where a minor relationship between the ring size and chemical yield could be observed. Consistent with this relationship, the highest yielding substrate of this series is **4k** (70%), which comes from the most stable cyclohexyl radical. In addition, the 4-carboxyl-piperidine derivative afforded the corresponding amino acid **4l** in 47% yield. Next, acyclic secondary NHPI esters were also evaluated, affording the silylated **4m** and lipidic **4n** derivatives in 70% and 48% yields, respectively. Moving to tertiary alkyl NHPI esters (**4o**−**4u**), the reaction also tolerated sterically hindered quaternary carbon centers with good generality. As previously observed, radical stability had an appreciable effect on chemical yields, with adamantyl NHPI ester affording **4q** in 95% yield. The generation of the tertiary radical through a radical-relay process, starting from the citronellic acid NHPI ester, efficiently gave access to the amino acid **4u** in 61% yield. Primary alkyl and benzylic NHPI esters were also successfully employed under the optimized reaction conditions, albeit in lower yields, affording the respective homoallylic, homobenzylic, and benzylic unnatural amino acids **4v**−**4z** (Scheme 2).

Envisioning applications in bioconjugation, the incorporation of pharmaceutically active ingredients was also investigated. While gemfibrozil (used for dyslipidemia treatment) residue could be efficiently coupled, affording the modified amino acid **4aa** in good chemical yield (77%), the use of the nonsteroidal anti-inflammatory etodolac's NHPI ester afforded **4ab** in 15%. The lower yield observed for **4ab** is probably due to the steric hindrance of the neopentylic radical involved in the process. Gratifyingly, peptide residues were also successfully incorporated into the Dha, with the unnatural dipeptide **4ac** and tripeptide **4ad** being afforded in 65% and 76% yields, respectively. To summarize, the results described in Scheme 2 demonstrate the generality of our method, showing its applicability toward the preparation of a wide range of unnatural amino acids, including derivatives decorated with bioactive molecules, and its great potential for peptide functionalization.

We then decided to evaluate the scalability of this new metal-free photochemical protocol. By using conditions similar to those previously applied, a 2 mmol scale experiment employing the *N*-Boc-amino isobutyric acid NHPI ester successfully afforded the amino acid **4c** in 82% yield (see SI for further information).

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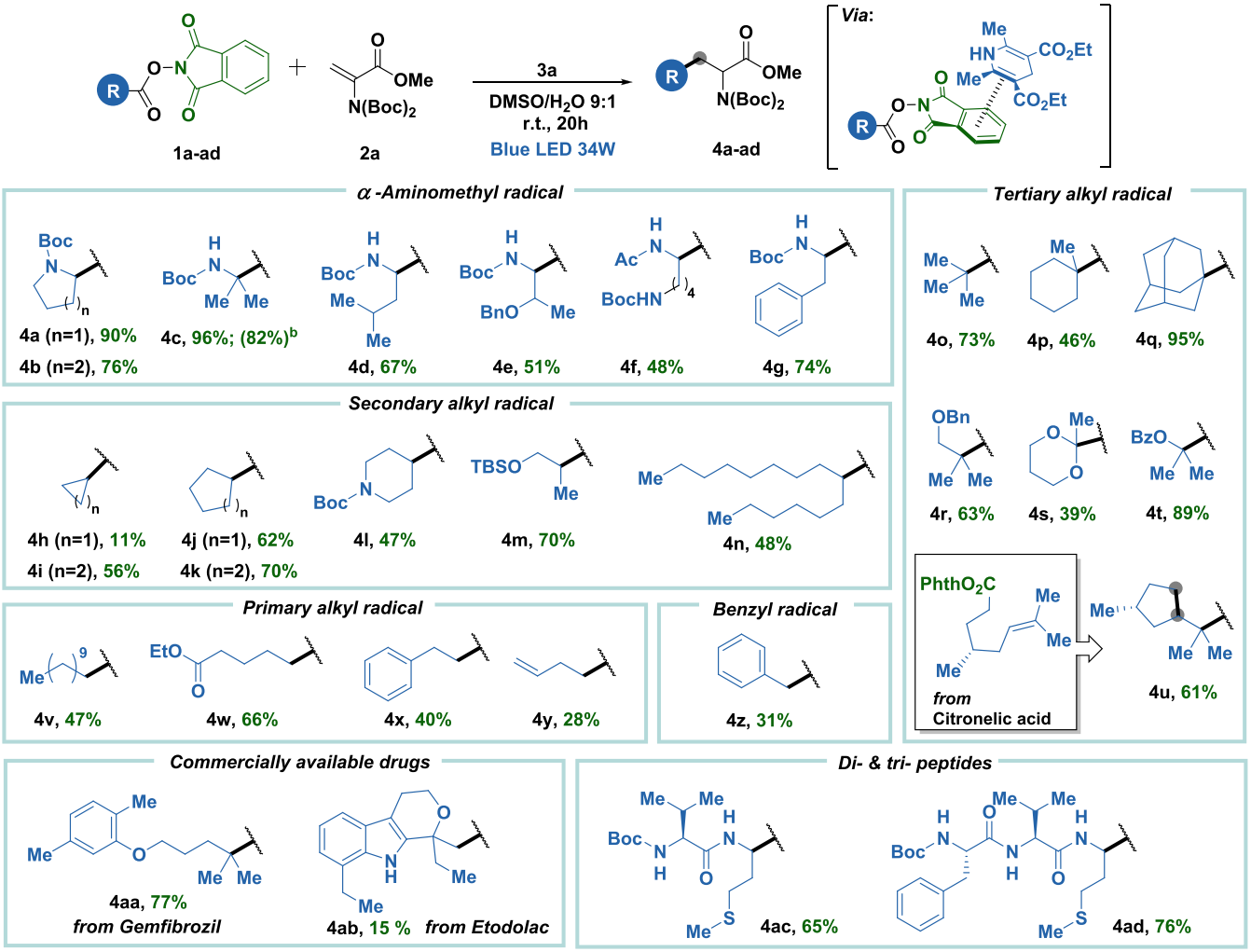
Scheme 2. Scope of NHPI Esters[a]



[a]Reaction conditions: **1a−ad** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.42 mmol) in DMSO/H_2O (9:1) (0.15 M). Yields of isolated products. Diastereomeric ratios were determined by ^{1}H NMR analysis from the crude reaction mixture and corresponded to 1:1 in all cases where diastereomers were formed. [b]2 mmol scale experiment.

Aiming at expanding the scope and the generality of these reactions to other radical precursors, we envisioned that functionalized alkylpyridinium salts would be compatible to the conditions previously optimized for the achieved NHPI esters.[16b] Pleasingly, this reactivity enabled the direct construction of a range of non-natural α-amino acids **4k**, **4z**, and **6a−f** in good chemical yields (Scheme 3).

We further examined pyridinium salts derived from cyclic secondary alkyl amines, which afforded the respective desired products **4k** and **6a**, in 80% and 67% yields, respectively. The acyclic secondary pyridinium salts containing the *O*-acetylated-phenol moiety furnished hydrolyzed product **6b** in 68% yield. In addition, *O*-acylated pyridinium salts prepared from amino alcohols could also be successfully employed (**6c−6e**). It is noteworthy that this reaction has also enabled the installation of a modified pharmaceutical ingredient (**5g**) onto the α-amino acid side chain, affording the bioconjugated α-amino acid **6e** in 78% yield. Next, a benzylic pyridinium salt was subjected to the optimal conditions, delivering the homo-phenylalanine **4z** in 74% yield. A primary alkylpyridinium salt derived from β-alanine **5h** has also been tested, affording the protected glutamic ester **6f** in 25% yield.

Thereafter, we turned our attention to the hydroalkylation of the Karady−Beckwith alkene (Scheme 4). This chiral Dha comprises an efficient entry for the preparation of enantioenriched nonproteinogenic amino acids. A set of NHPI redox-active esters and the benzylic pyridinium salt were evaluated under previously reported conditions and gave access to another family of amino acids in good yields and excellent diastereoselectivities (**8a−f**). In order to evaluate our protocol against other Dha residues, experiments using *N*-Boc-, *N*-acetyl-, and *N*-Boc,Cbz-Dha residues have been performed. From these studies, no reactivity could be observed for the two first ones, while the last one afforded the expected product in 82% yield (see Supporting Information for more details). A plausible explanation for lack of reactivity of the monoprotected Dha residues has been previously addressed by Molander and relies on the conformation of those species, which dramatically affects their reactivity.[11d]

Finally, to better understand the reaction mechanism of this new protocol, additional control experiments were performed. In consonance with previous studies by Chen,[18a] Aggarwal,[18b] Glorius,[18c] and our group,[14] UV−vis and NMR analysis of solutions containing **3a** combined with different amounts of

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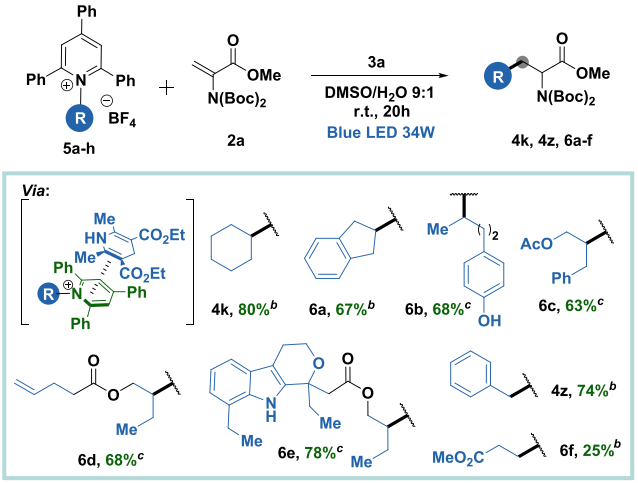
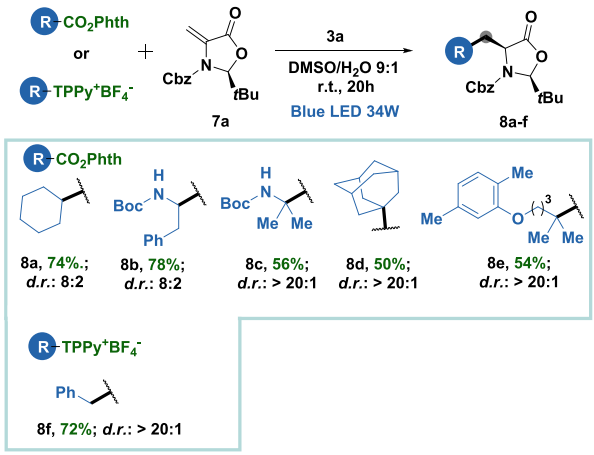
Scheme 3. Scope Study of Pyridinium Salts[a]



[a]Reaction conditions follow in subsequent notes. [b]**5** (0.2 mmol), **2a** (0.3 mmol), **3a** (0.42 mmol) in DMSO/H_2O (9:1) (0.15 M). [c]**5** (0.1 mmol), **2a** (0.15 mmol), **3a** (0.21 mmol) in DMSO/H_2O (9:1) (0.15 M). Yields of isolated products. Diastereomeric ratios were determined by ^{1}H NMR analysis from the crude reaction mixture and corresponded to 1:1 in all cases where diastereomers were formed.

Scheme 4. Diastereoselective Amino Acid Synthesis Using the Karady–Beckwith Alkene[a]



[a]Radical precursor (0.1 mmol), **7a** (0.15 mmol), **3a** (0.21 mmol) in DMSO/H_2O (9:1) (0.15 M). Yields of isolated products. The dr values were calculated from crude ^{1}H NMR.

the NHPI ester **1a** and the pyridinium salt **5d** strongly support the formation of the EDA complex during those processes. We also observed that the addition of **2a** to those reaction mixtures disrupts the formation of such complexes, ruling out the possibility of a ternary complexation system (see SI, Figures S2, S4 and S5, for more details). By carrying out experiments with deuterium-labeled solvents, product **4a** did not afford high levels of deuterium incorporation, indicating that the Hantzsch ester should act as the main proton source (see SI, Scheme S1, for further information). On the basis of these observations and previous literature reports,[18] a plausible reaction mechanism could be outlined (see SI, Scheme S2, for further information).

In summary, a biocompatible metal-free photoinduced approach for the hydroalkylation of dehydroalanine has been reported. This strategy features a good functional group tolerance, experimental simplicity, and scalability, being a straightforward and efficient strategy for the incorporation of biologically relevant scaffolds to α-amino acid side chains. The protocol is also applicable to the Karady–Beckwith alkene, opening a new opportunity for the preparation of enantioenriched nonproteinogenic amino acids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01781.

Experimental details (procedures for starting materials preparation, general procedures for the preparation, as well as full characterization of all new compounds) (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) de Graaf, A. J.; Kooijman, M.; Hennink, W. E.; Mastrobattista, E. Nonnatural Amino Acids for Site-Specific Protein Conjugation. *Bioconjugate Chem.* **2009**, *20*, 1281−1295. (b) Blaskovich, M. A. T. Unusual Amino Acids in Medicinal Chemistry. *J. Med. Chem.* **2016**, *59*, 10807−10836.

(2) (a) Henninot, A.; Collins, J. C.; Nuss, J. M. The Current State of Peptide Drug Discovery: Back to the Future? *J. Med. Chem.* **2018**, *61*, 1382−1414. (b) Purcell, A. W.; McCluskey, J.; Rossjohn, J. More than

One Reason to Rethink the Use of Peptides in Vaccine Design. *Nat. Rev. Drug Discovery* **2007**, *6*, 404−414.
(3) (a) Metrano, A. J.; Chinn, A. J.; Shugrue, C. R.; Stone, E. A.; Kim, B.; Miller, S. J. Asymmetric Catalysis Mediated by Synthetic Peptides, Version 2.0: Expansion of Scope and Mechanisms. *Chem. Rev.* **2020**, *120*, 11479−11615. (b) Gnas, Y.; Glorius, F. Chiral Auxiliaries - Principles and Recent Applications. *Synthesis* **2006**, *2006*, 1899−1930.
(4) (a) deGruyter, J. N.; Malins, L. R.; Baran, P. S. Residue-Specific Peptide Modification: A Chemist's Guide. *Biochemistry* **2017**, *56*, 3863−3873. (b) Hoyt, E. A.; Cal, P. M. S. D.; Oliveira, B. L.; Bernardes, G. J. L. Contemporary Approaches to Site-Selective Protein Modification. *Nat. Rev. Chem.* **2019**, *3*, 147−171. (c) Krall, N.; da Cruz, F. P.; Boutureira, O.; Bernardes, G. J. L. Site-Selective Protein-Modification Chemistry for Basic Biology and Drug Development. *Nat. Chem.* **2016**, *8*, 103−113. (d) Spicer, C. D.; Davis, B. G. Selective Chemical Protein Modification. *Nat. Commun.* **2014**, *5*, 4740.
(5) Selected reviews: (a) Bottecchia, C.; Noël, T. Photocatalytic Modification of Amino Acids, Peptides, and Proteins. *Chem. - Eur. J.* **2019**, *25*, 26−42. (b) King, T. A.; Mandrup Kandemir, J.; Walsh, S. J.; Spring, D. R. Photocatalytic Methods for Amino Acid Modification. *Chem. Soc. Rev.* **2021**, *50*, 39−57. (c) Patel, S.; Badir, S. O.; Molander, G. A. Developments in Photoredox-Mediated Alkylation for DNA-Encoded Libraries. *Trends Chem.* **2021**, *3*, 161−175.
(6) (a) Rilatt, I.; Caggiano, L.; Jackson, R. F. W. Development and Applications of Amino Acid Derived Organometallics. *Synlett* **2005**, 2701−2719. (b) Perdih, A.; Sollner Dolenc, M. Recent Advances in the Synthesis of Unnatural α-Amino Acids - An Updated Version. *Curr. Org. Chem.* **2011**, *15*, 3750−3799.
(7) (a) Massi, A.; Nanni, D. Thiol−Yne Coupling: Revisiting Old Concepts as a Breakthrough for up-to-Date Applications. *Org. Biomol. Chem.* **2012**, *10*, 3791. (b) Hoyle, C. E.; Bowman, C. N. Thiol-Ene Click Chemistry. *Angew. Chem., Int. Ed.* **2010**, *49*, 1540−1573.
(8) Selected reviews: (a) Marzo, L.; Pagire, S. K.; Reiser, O.; König, B. Visible-Light Photocatalysis: Does It Make a Difference in Organic Synthesis? *Angew. Chem., Int. Ed.* **2018**, *57*, 10034−10072. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322−5363.
(9) (a) Hargrave, J. D.; Bish, G.; Köhn, G. K.; Frost, C. G. Rhodium-Catalysed Conjugate Addition of Arylboronic Acids to Enantiopure Dehydroamino Acid Derivatives. *Org. Biomol. Chem.* **2010**, *8* (22), 5120−5125.
(10) (a) Dadová, J.; Galan, S. R.; Davis, B. G. Synthesis of Modified Proteins via Functionalization of Dehydroalanine. *Curr. Opin. Chem. Biol.* **2018**, *46*, 71−81. (b) Josephson, B.; Fehl, C.; Isenegger, P. G.; Nadal, S.; Wright, T. H.; Poh, A. W. J.; Bower, B. J.; Giltrap, A. M.; Chen, L.; Batchelor-McAuley, C.; et al. Light-Driven Post-Translational Installation of Reactive Protein Side Chains. *Nature* **2020**, *585*, 530−537. (c) Bogart, J. W.; Bowers, A. A. Dehydroamino Acids: Chemical Multi-Tools for Late-Stage Diversification. *Org. Biomol. Chem.* **2019**, *17*, 3653−3669.
(11) (a) Aycock, R. A.; Vogt, D. B.; Jui, N. T. A Practical and Scalable System for Heteroaryl Amino Acid Synthesis. *Chem. Sci.* **2017**, *8*, 7998−8003. (b) Rossolini, T.; Leitch, J. A.; Grainger, R.; Dixon, D. J. Photocatalytic Three-Component Umpolung Synthesis of 1,3-Diamines. *Org. Lett.* **2018**, *20*, 6794−6798. (c) 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*, 9115−9119. (d) Sim, J.; Campbell, M. W.; Molander, G. A. Synthesis of α-Fluoro-α-Amino Acid Derivatives via Photoredox-Catalyzed Carbofluorination. *ACS Catal.* **2019**, *9*, 1558−1563. (e) de Bruijn, A. D.; Roelfes, G. Chemical Modification of Dehydrated Amino Acids in Natural Antimicrobial Peptides by Photoredox Catalysis. *Chem. - Eur. J.* **2018**, *24*, 11314−11318.
(12) (a) Brandhofer, T.; Mancheño, O. G. Versatile Ru-Photoredox-Catalyzed Functionalization of Dehydro-Amino Acids and Peptides. *ChemCatChem* **2019**, *11*, 3797−3801. (b) Zhang, O.; Schubert, J. W. Derivatization of Amino Acids and Peptides via Photoredox-Mediated Conjugate Addition. *J. Org. Chem.* **2020**, *85*, 6225−6232. (c) Shah, A. A.; Kelly, M. J.; Perkins, J. J. Access to Unnatural α-Amino Acids via Visible-Light-Mediated Decarboxylative Conjugate Addition to Dehydroalanine. *Org. Lett.* **2020**, *22*, 2196−2200. (d) Ji, P.; Zhang, Y.; Dong, Y.; Huang, H.; Wei, Y.; Wang, W. Synthesis of Enantioenriched α-Deuterated α-Amino Acids Enabled by an Organophotocatalytic Radical Approach. *Org. Lett.* **2020**, *22*, 1557−1562. (e) Merkens, K.; Aguilar Troyano, F. J.; Djossou, J.; Gómez-Suárez, A. Synthesis of Unnatural α-Amino Acid Derivatives via Light-Mediated Radical Decarboxylative Processes. *Adv. Synth. Catal.* **2020**, *362*, 2354−2359.
(13) 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.; et al. Kinetically Guided Radical-Based Synthesis of $C(Sp^3)$−$C(Sp^3)$ Linkages on DNA. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, E6404−E6410.
(14) Correia, J. T. M.; Piva da Silva, G. P.; Kisukuri, C. M.; André, E.; Pires, B.; Carneiro, P. S.; Paixão, M. W. Metal-Free Photoinduced Hydroalkylation Cascade Enabled by an Electron-Donor−Acceptor Complex. *J. Org. Chem.* **2020**, *85*, 9820−9834.
(15) Some recent reviews on photoinduced processes enabled by EDA complexes: (a) 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*, 1389−1407. (b) Crisenza, G. E. M.; Mazzarella, D.; Melchiorre, P. Synthetic Methods Driven by the Photoactivity of Electron Donor−Acceptor Complexes. *J. Am. Chem. Soc.* **2020**, *142*, 5461−5476.
(16) Selected reviews on photocatalytic deaminative processes: (a) M. Correia, J. T.; A. Fernandes, V.; Matsuo, B. T.; C. Delgado, J. A.; de Souza, W. C.; Paixão, M. W. Photoinduced Deaminative Strategies: Katritzky Salts as Alkyl Radical Precursors. *Chem. Commun.* **2020**, *56*, 503−514. (b) He, F.; Ye, S.; Wu, J. Recent Advances in Pyridinium Salts as Radical Reservoirs in Organic Synthesis. *ACS Catal.* **2019**, *9*, 8943−8960.
(17) Selected reviews on photocatalytic decarboxylative processes: (a) Murarka, S. *N*-(Acyloxy)Phthalimides as Redox-Active Esters in Cross-Coupling Reactions. *Adv. Synth. Catal.* **2018**, *360*, 1735−1753. (b) Jin, Y.; Fu, H. Visible-Light Photoredox Decarboxylative Couplings. *Asian J. Org. Chem.* **2017**, *6*, 368−385.
(18) (a) Zhang, J.; Li, Y.; Xu, R.; Chen, Y. Donor−Acceptor Complex Enables Alkoxyl Radical Generation for Metal-Free $C(Sp^3)$−$C(Sp^3)$ Cleavage and Allylation/Alkenylation. *Angew. Chem., Int. Ed.* **2017**, *56*, 12619−12623. (b) Wu, J.; Grant, P. S.; Li, X.; Noble, A.; Aggarwal, V. K. Catalyst-Free Deaminative Functionalizations of Primary Amines by Photoinduced Single-Electron Transfer. *Angew. Chem., Int. Ed.* **2019**, *58*, 5697−5701. (c) James, M. J.; Strieth-Kalthoff, F.; Sandfort, F.; Klauck, F. J. R.; Wagener, F.; Glorius, F. Visible-Light-Mediated Charge Transfer Enables C−C Bond Formation with Traceless Acceptor Groups. *Chem. - Eur. J.* **2019**, *25*, 8240−8244.

https://doi.org/10.1021/acs.orglett.1c01781
Org. Lett. 2021, 23, 5251−5255