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DOI
10.1002/anie.202403271
10.1002/ange.202403271

Publication date
2024

Document Version
Final published version

Published in
Angewandte Chemie, International Edition

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Link to publication

Citation for published version (APA):
Kaplaneris, N., Akdeniz, M., Fillols, M., Arrighi, F., Raymenants, F., .Sanil, G., Gryko, D. T., & Noël, T. (2024). Photocatalytic Functionalization of Dehydroalanine-Derived Peptides in Batch and Flow. *Angewandte Chemie, International Edition*, *63*(19), Article e202403271. https://doi.org/10.1002/anie.202403271, https://doi.org/10.1002/ange.202403271

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How to cite: *Angew. Chem. Int. Ed.* **2024**, *63*, e202403271
doi.org/10.1002/anie.202403271

Hydroarylation

Photocatalytic Functionalization of Dehydroalanine-Derived Peptides in Batch and Flow

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Abstract: Unnatural amino acids, and their synthesis by the late-stage functionalization (LSF) of peptides, play a crucial role in areas such as drug design and discovery. Historically, the LSF of biomolecules has predominantly utilized traditional synthetic methodologies that exploit nucleophilic residues, such as cysteine, lysine or tyrosine. Herein, we present a photocatalytic hydroarylation process targeting the electrophilic residue dehydroalanine (Dha). This residue possesses an α,β-unsaturated moiety and can be combined with various arylthianthrenium salts, both in batch and flow reactors. Notably, the flow setup proved instrumental for efficient scale-up, paving the way for the synthesis of unnatural amino acids and peptides in substantial quantities. Our photocatalytic approach, being inherently mild, permits the diversification of peptides even when they contain sensitive functional groups. The readily available arylthianthrenium salts facilitate the seamless integration of Dha-containing peptides with a wide range of arenes, drug blueprints, and natural products, culminating in the creation of unconventional phenylalanine derivatives. The synergistic effect of the high functional group tolerance and the modular characteristic of the aryl electrophile enables efficient peptide conjugation and ligation in both batch and flow conditions.

Peptide and protein therapeutics are currently experiencing a significant breakthrough, setting them on par with small molecules as potential drug candidates.[1] Late-stage functionalization (LSF) of biomolecules and drug scaffolds has proven to be a powerful strategy for efficiently exploring the chemical landscape, eliminating the need for expensive and resource-intensive de novo methodologies.[2] Consequently, the site- and chemoselective LSF of peptides has garnered substantial interest from both academic researchers and the pharmaceutical industry.

Within this context, the incorporation of unnatural amino acids into peptides can significantly modify their bioactivity and enhance proteolytic stability.[3] For the LSF of peptides to be effective, it necessitates highly selective and mild reaction conditions capable of forging bonds with high precision amidst the complex array of functional groups inherent to peptides. To overcome this challenge, a diverse array of synthetic strategies has been utilized, encompassing classical condensations and (cyclo)additions,[4] transition-metal catalysis,[5] click chemistry,[6] photochemistry,[7] and more recently electrochemistry.[8] Notably, among the proteinogenic amino acids, those with nucleophilic side chains have been most extensively investigated for photochemical LSF.[9] Key examples include cysteine,[10] tryptophan,[11] methionine,[12] and tyrosine.[13]

In contrast, dehydroalanine (Dha) represents an electrophilic residue that, although not proteinogenic, occurs naturally and is prevalent in a host of antimicrobial peptides.[14] It presents an alternative avenue for functionalization, as depicted in Figure 1a.[15] The recent advancement in photochemical LSF of Dha-enriched peptides[16] has facilitated targeted and chemoselective processes such as alkylation,[17] fluoroalkylation,[18] acylation,[19] and to a more limited degree, arylation.[20] Prior arylation approaches typically demanded aryl bromides as coupling agents, necessitating complex and laborious de novo synthesis to produce a variety of functionalized partners. However, recent studies by the groups of Ritter,[21] Procter,[22] and Alcarazo[23] has highlighted the utility of arylsulfonium salts. These salts enable straightforward preparation routes leading to intricate aryl electrophiles,[24] which are instrumental for both transition metal-catalyzed cross-coupling chemistry[25] and photochemical applications.[26] Building on this, vinyl-sulfonium salts have recently been employed for various polar transformations.[27]

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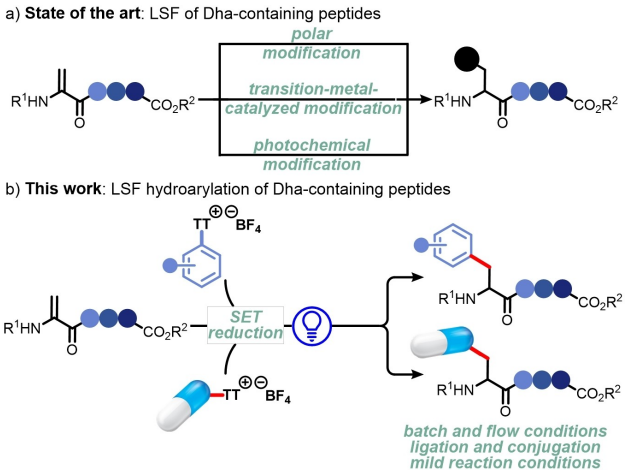


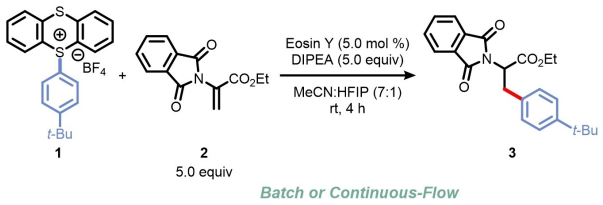
Figure 1. a) Dha diversification. b) Photocatalytic LSF of Dha-containing peptides with arylthianthrenium salts.

Therefore, we were intrigued by the prospect of developing a photocatalytic LSF approach for Dha-containing peptides using the highly versatile and modular arylthianthrenium salts, as illustrated in Figure 1b. This transformation was accomplished by the single electron transfer (SET) reduction of these salts, which generates an exceptionally reactive aryl radical. This radical readily adds to the α,β-unsaturated moiety within the Dha backbone. To guarantee gentle reaction conditions and minimize reaction times–key factors for ensuring broad functional group compatibility and scalability—we also devised a continuous-flow protocol.[28] Notably, our method facilitates the efficient ligation of peptides and their conjugation with various drug scaffolds.

Our initial efforts in achieving regioselective arylation of Dha derivative **2** focused on the use of arylthianthrenium salt **1** (For detailed optimization, see Supporting Information). We employed DIPEA as the stoichiometric reductant and eosin Y as a photocatalyst, with the reaction driven by visible light irradiation at a wavelength of 456 nm (Table 1). The reaction proceeded efficiently (72 % isolated yield) in a solvent mixture of MeCN:HFIP (7:1) at room temperature over 4 hours (Table 1, Entry 1). Other protic or aprotic polar solvents failed to provide satisfactory conversions (Table 1, Entries 2 and 3). It became evident that the choice of solvent was critical; variations in the solvent system composition, containing different ratios between MeCN and HFIP, resulted in decreased yields (Table 1, Entry 4). A control experiment demonstrated the essential role of DIPEA (entry 5). Other potential reductants, including various amines and dihydropyridines, were also tested but failed to effectively produce the target product **3** (Table 1, Entries 6 and 7). Furthermore, we explored a range of photo-organocatalysts and metal-based photocatalysts, which unfortunately led to less efficient processes (Table 1, Entries 8 and 9). Gratifyingly, the synthesis of the unnatural amino acid **3** could be smoothly performed in a continuous-flow photoreactor in a significantly reduced reaction time ($t_R = 20$ min) with comparable efficiency (Table 1, Entry 10).

Building upon the established optimal conditions for the photocatalytic arylation of Dha **2**, both in batch and flow (Table 1, Entries 1 and 10), we sought to evaluate the versatility and scope of our method. Hereto, we applied various arylthianthrenium salts **4** to the established protocol, as delineated in Scheme 1. Scaling up our model reaction using arylthianthrenium salt **1** and Dha derivative **2** by flow technology was successful, achieving a 71 % isolated yield at a 1.0 mmol scale under our standard conditions.

Table 1: Optimization of the photocatalytic arylation of the Dha derivative **2** with arylthianthrenium salt **1**.[a]



1 **2** 5.0 equiv **3**

Entry	Deviation from the standard conditions	Yield [%][b]
1	None	72
2	MeOH/*i*-PrOH/HFIP/DMF/DMSO as solvent	40/38/nd/nd/nd
3	MeCN as solvent	45
4	MeCN:HFIP (1:1)/(3:1)/(19:1) as solvent	36/63/49
5	without DIPEA	nd
6	TEA/TBA/DABCO/TEOA instead of DIPEA	37/29/nd/55
7	hantzsch ester (2.0 equiv) instead of DIPEA	23
8	eosin Y-Na_2/fluorescein/rhodamine B/Ru(bpy)$_3$$Cl_2$ as photocatalyst	68/47/52/45
9	Ir(ppy)$_3$/10-phenylphenothiazine as photocatalyst	nd/10[c]
10	under flow conditions $t_R = 20$ min	69

[a] Reaction conditions: **1** (0.20 mmol), **2** (1.0 mmol), eosin Y (5.0 mol %), DIPEA (1.0 mmol), MeCN:HFIP (7:1, 4.0 mL), at room temperature, 456 nm for 4 h. [b] Yield of isolated product. [c] Yield determined by ^{1}H NMR spectroscopy using trichloroethylene as an external standard. HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol, DMF: *N*,*N*-dimethylformamide, DMSO: dimethyl sulfoxide, DIPEA: *N*,*N*-diisopropylethylamine, TEA: triethylamine, TBA: tributylamine, DABCO: 1,4-diazabicyclo[2.2.2]octane, TEOA: 2-(bis(2-hydroxyethyl)amino)ethanol, bpy: 2,2′-bipyridine, ppy: 2-phenylpyridine.

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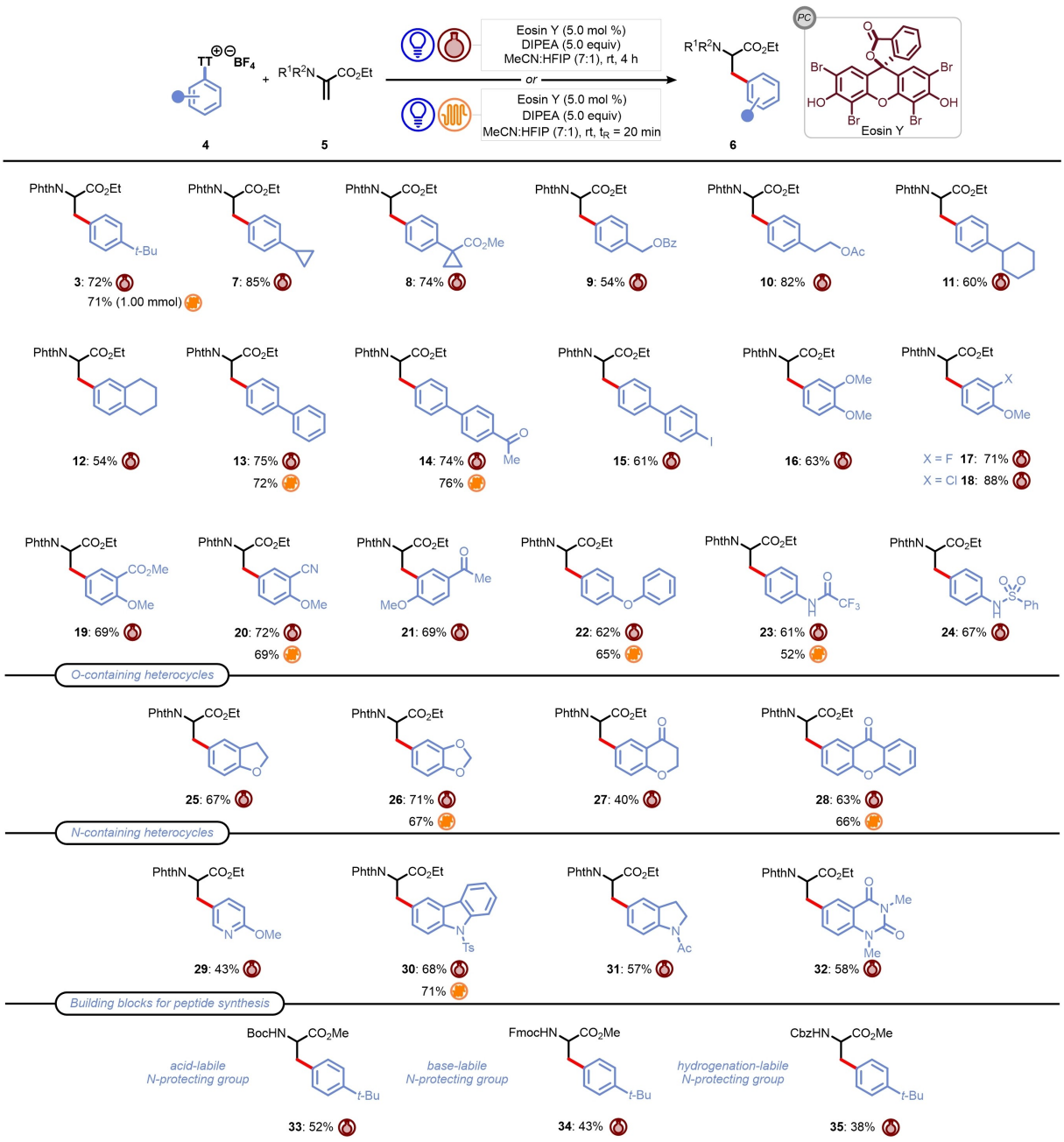

Scheme 1. Synthesis of unnatural amino acids through radical addition to Dha derivative **5** using various arylthianthrenium salts. For further experimental details see the Supporting Information.

We then extended our approach to include alkyl-substituted arylthianthrenium salts **4**, which served as competent reaction partners into our protocol, yielding the anticipated products **7**–**12** in good to excellent isolated yields. Notably, the synthesis of biaryl unnatural amino acids **13**–**15** was achieved in excellent yields. These amino acids bear functional groups amenable to subsequent synthetic manipulations, such as condensations and transition-metal catalyzed cross-couplings. Impressively, the aryl iodide bond, typically sensitive to reduction under photocatalytic conditions, proved to be compatible with our process. The method's adaptability was further underscored by its application to heteroatom-containing arylthianthrenium salts **4**, leading to an array of phenylalanine derivatives (**16**–**24**). The yields were moderate to excellent, maintaining both high chemo- and regioselectivity. Additionally, our methodology demonstrated its robust functional group tolerance by facilitating access to a diverse set of heterocycle-containing amino acids. This collection of compounds included structures with dihydrobenzofuran, benzodioxole, chromanone, xanthone, pyridine, carbazole, indoline, and quinazoline-dione, showcasing the broad applicability and robustness of the synthetic strategy. In addition, our methodology enabled the synthesis of diverse amino acid

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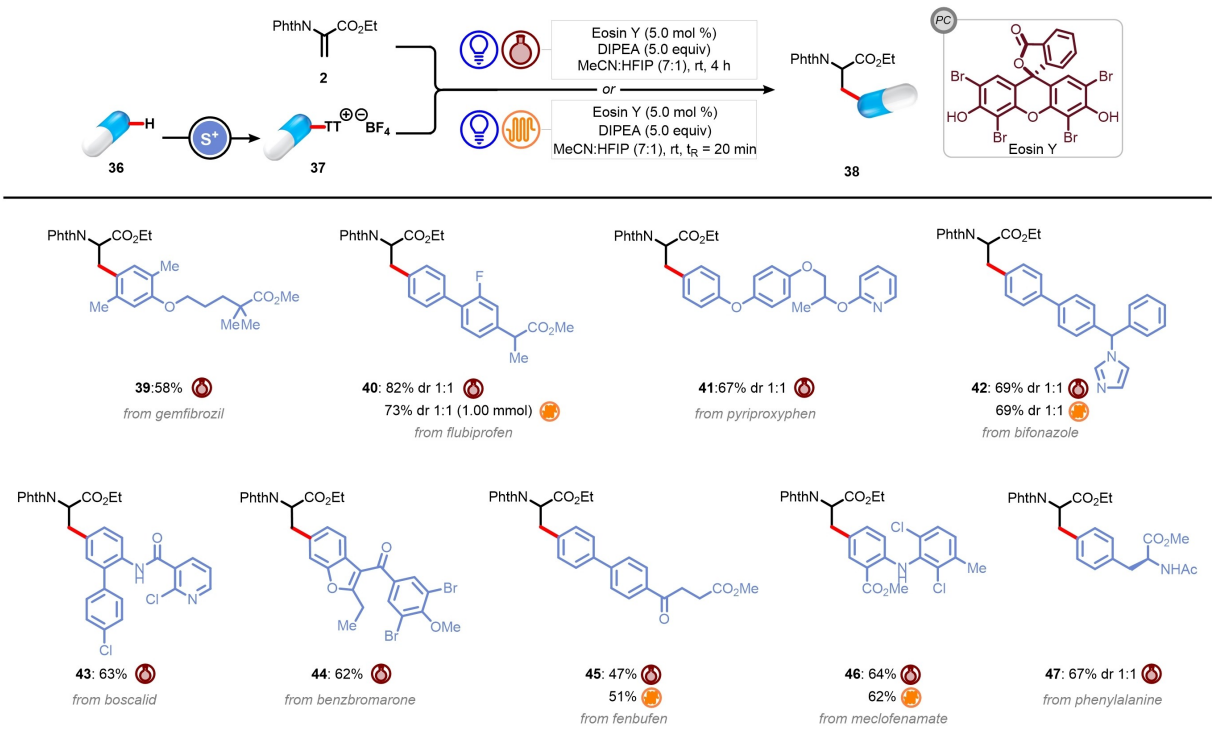

Scheme 2. Synthesis of conjugated and ligated unnatural amino acids by radical addition to Dha derivative **2** using arylthianthrenium salts **37** derived from biologically active molecules **36**. For further experimental details see the Supporting Information.

derivatives for peptide synthesis, incorporating orthogonal protecting groups, requiring only minor adjustments to reaction conditions. We evaluated acid-, base- and hydrogenation-labile protecting groups, including *tert* -butyloxycarbonyl (Boc), fluorenylmethyloxycarbonyl (Fmoc), and benzyloxycarbonyl (Cbz) resulting in the successful preparation of the desired building blocks **33**–**35**.

The streamlined and selective synthesis of arylthianthrenium salts prompted us to investigate their application with drug scaffolds and natural product derivatives, numbered as **36**, within our photocatalytic protocol, aiming to create distinctive conjugates as depicted in Scheme 2. The process proved to be of high value, allowing for the seamless integration of a variety of drugs onto the Dha backbone, yielding an array of novel amino acid/drug conjugates **38**. The mild conditions of our photocatalytic hydroarylation were evidenced by the complete preservation of vulnerable heterocyclic structures, such as those found in pyriproxyphen, bifonazole, boscalid, and benzbromarone. The successful incorporation of drug scaffolds onto amino acid backbones led us to extend our strategy to the chemical ligation of peptides. We utilized an arylthianthrenium salt derivative of phenylalanine under our standard conditions, which afforded the targeted unnatural dipeptide **47** with excellent chemo- and regioselectivity. Furthermore, we synthesized a series of conjugates employing continuous-flow conditions, achieving similar success even when scaling up the reactions, which underscores the practicality and scalability of our synthetic approach.

We then advanced to the late-stage functionalization of more complex peptide structures **48**, applying our photocatalytic conditions detailed in Scheme 3. We were able to precisely and selectively functionalize a variety of di-,tri-, penta- and hexapeptides, decorating them with a multitude of functional groups derived from the aromatic core. Notably, peptides containing residues with sensitive functionalities like thioether, phenol, and indole groups were tolerated without any interference from photocatalytic single electron transfer (SET) processes or hydrogen atom transfer reactions, which typically present significant deleterious side pathways. In addition, our protocol was not hindered by the position of the Dha residue in the peptide, as the functionalization at *N*-, *C*-terminus as well as inside the peptide sequence was accomplished. Furthermore, our methodology facilitated the rapid synthesis of a tripeptide **66**, which showcased an atypical linkage, demonstrating the applicability of our ligation techniques. This process also proved to be highly capable at integrating drug scaffolds with peptides, further emphasizing the remarkable functional group compatibility of our system, even within the intricate context of peptide conjugation.

In conclusion, we have successfully developed a photocatalytic hydroarylation protocol that efficiently targets the Dha backbone utilizing versatile arylthianthrenium salts. This novel strategy has demonstrated its versatility in the synthesis of a diverse array of unnatural amino acids, with the potential for straightforward scale-up under a continuous-flow regime. The remarkable functional group tolerance of our methodology enables the preservation of delicate

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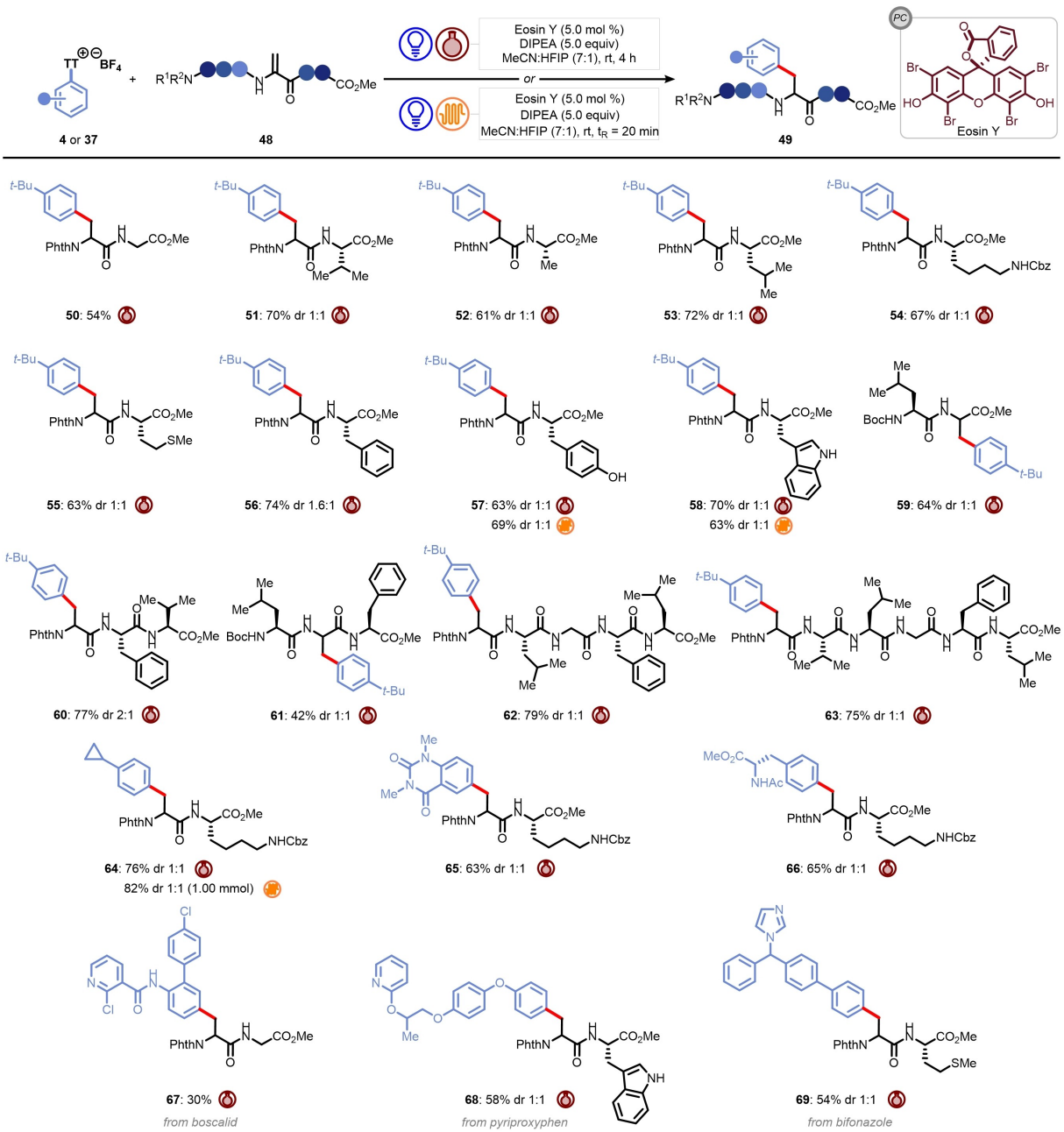

Scheme 3. LSF of Dha-containing peptides **48** leading to conjugation and ligation. For further experimental details see the Supporting Information.

chemical structures during synthesis, broadening the scope of compatible coupling partners. Furthermore, the precise site- and chemoselectivity of this technique showcase its utility in the modification of peptides bearing a variety of sensitive residues. Looking forward, this mild photocatalytic approach is poised to impact the late-stage functionalization of complex peptides and proteins, offering new avenues for biochemical research and therapeutic development.

Supporting Information

The authors have cited additional references within the Supporting Information (Ref. [12c,21,25e,26b,26h,29]).

Acknowledgements

We are grateful to have received generous funding from the European Union H2020 under the call HORIZON-HLTH-2021-IND-07 (SusPharma, 101057430, T.N., N.K.), under the Marie S. Curie Grant Agreement (CHAIR, No 860762, S.G., D.T.G., T.N.), the ERC CoG grant for T.N. (Flow-

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HAT, No. 101044355, T.N., M.A.) and FETopen (FLIX, No. 862179, F.R., T.N.).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: late-stage diversification · photocatalysis · flow chemistry · unnatural amino acids · peptides

[1] a) L. Wang, N. Wang, W. Zhang, X. Cheng, Z. Yan, G. Shao, X. Wang, R. Wang, C. Fu, *Signal Transduct. Target. Ther.* **2022**, *7*; b) M. Muttenthaler, G. F. King, D. J. Adams, P. F. Alewood, *Nat. Rev. Drug Discovery* **2021**, *20*, 309–325; c) E. Valeur, S. M. Guéret, H. Adihou, R. Gopalakrishnan, M. Lemurell, H. Waldmann, T. N. Grossmann, A. T. Plowright, *Angew. Chem. Int. Ed.* **2017**, *56*, 10294–10323.

[2] a) L. Guillemard, N. Kaplaneris, L. Ackermann, M. J. Johansson, *Nat. Chem. Rev.* **2021**, *5*, 522–545; b) L. Zhang, T. Ritter, *J. Am. Chem. Soc.* **2022**, *144*, 2399–2414; c) P. Bellotti, H.-M. Huang, T. Faber, F. Glorius, *Chem. Rev.* **2023**, *123*, 4237–4352; d) N. J. Castellino, A. P. Montgomery, J. J. Danon, M. Kassiou, *Chem. Rev.* **2023**, *123*, 8127–8153.

[3] a) M. A. T. Blaskovich, *J. Med. Chem.* **2016**, *59*, 10807–10836; b) E. Lenci, A. Trabocchi, *Chem. Soc. Rev.* **2020**, *49*, 3262–3277.

[4] E. A. Hoyt, P. M. S. D. Cal, B. L. Oliveira, G. J. L. Bernardes, *Nat. Chem. Rev.* **2019**, *3*, 147–171.

[5] a) M. Jbara, S. K. Maity, A. Brik, *Angew. Chem. Int. Ed.* **2017**, *56*, 10644–10655; b) J. Wang, H. Lundberg, S. Asai, P. Martín-Acosta, J. S. Chen, S. Brown, W. Farrell, R. G. Dushin, C. J. O'Donnell, A. S. Ratnayake, P. Richardson, Z. Liu, T. Qin, D. G. Blackmond, P. S. Baran, *Proc. Nat. Acad. Sci.* **2018**, *115*, E6404–E6410; c) W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 14700–14717; d) J. Ohata, S. C. Martin, Z. T. Ball, *Angew. Chem. Int. Ed.* **2019**, *58*, 6176–6199; e) C. Zhang, E. V. Vinogradova, A. M. Spokoyny, S. L. Buchwald, B. L. Pentelute, *Angew. Chem. Int. Ed.* **2019**, *58*, 4810–4839; f) H.-R. Tong, B. Li, G. Li, G. He, G. Chen, *CCS Chem.* **2021**, *3*, 1797–1820.

[6] a) M. Bernús, D. Mazzarella, J. Stanić, Z. Zhai, A. Yeste-Vázquez, O. Boutureira, A. F. G. Gargano, T. N. Grossmann, T. Noël, *Nat. Synth.* **2024**, *3*, 185–191; b) L. Markey, S. Giordani, E. M. Scanlan, *J. Org. Chem.* **2013**, *78*, 4270–4277.

[7] a) C. Bottecchia, T. Noël, *Chem. Eur. J.* **2019**, *25*, 26–42; b) J.-Q. Liu, A. Shatskiy, B. S. Matsuura, M. D. Kärkäs, *Synthesis* **2019**, *51*, 2759–2791; c) L. Raynal, N. C. Rose, J. R. Donald, C. D. Spicer, *Chem. Eur. J.* **2021**, *27*, 69–88; d) V. M. Lechner, M. Nappi, P. J. Deneny, S. Folliet, J. C. K. Chu, M. J. Gaunt, *Chem. Rev.* **2022**, *122*, 1752–1829.

[8] A. S. Mackay, R. J. Payne, L. R. Malins, *J. Am. Chem. Soc.* **2022**, *144*, 23–41.

[9] F. J. Aguilar Troyano, K. Merkens, K. Anwar, A. Gómez-Suárez, *Angew. Chem. Int. Ed.* **2021**, *60*, 1098–1115.

[10] a) E. L. Tyson, Z. L. Niemeyer, T. P. Yoon, *J. Org. Chem.* **2014**, *79*, 1427–1436; b) A. Talla, B. Driessen, N. J. W. Straathof, L. G. Milroy, L. Brunsveld, V. Hessel, T. Noël, *Adv. Synth. Catal.* **2015**, *357*, 2180–2186; c) C. Bottecchia, M. Rubens, S. B. Gunnoo, V. Hessel, A. Madder, T. Noël, *Angew. Chem. Int. Ed.* **2017**, *56*, 12702–12707; d) B. A. Vara, X. Li, S. Berritt, C. R. Walters, E. J. Petersson, G. A. Molander, *Chem. Sci.* **2018**, *9*, 336–344; e) H. Choi, M. Kim, J. Jang, S. Hong, *Angew. Chem. Int. Ed.* **2020**, *59*, 22514–22522; f) R. C. Griffiths, F. R. Smith, D. Li, J. Wyatt, D. M. Rogers, J. E. Long, L. M. L. Cusin, P. J. Tighe, R. Layfield, J. D. Hirst, M. M. Müller, N. J. Mitchell, *Chem. Eur. J.* **2023**, *29*, e202202503.

[11] a) Y. Wang, J. Wang, G.-X. Li, G. He, G. Chen, *Org. Lett.* **2017**, *19*, 1442–1445; b) Y. Yu, L.-K. Zhang, A. V. Buevich, G. Li, H. Tang, P. Vachal, S. L. Colletti, Z.-C. Shi, *J. Am. Chem. Soc.* **2018**, *140*, 6797–6800; c) B. Ding, Y. Weng, Y. Liu, C. Song, L. Yin, J. Yuan, Y. Ren, A. Lei, C. W. Chiang, *Eur. J. Org. Chem.* **2019**, 7596–7605; d) S. J. Tower, W. J. Hetcher, T. E. Myers, N. J. Kuehl, M. T. Taylor, *J. Am. Chem. Soc.* **2020**, *142*, 9112–9118; e) B. Laroche, X. Tang, G. Archer, R. Di Sanza, P. Melchiorre, *Org. Lett.* **2021**, *23*, 285–289; f) R. N. Lima, J. A. C. Delgado, D. I. Bernardi, R. G. S. Berlinck, N. Kaplaneris, L. Ackermann, M. W. Paixão, *Chem. Commun.* **2021**, *57*, 5758–5761; g) C. R. Hoopes, F. J. Garcia, A. M. Sarkar, N. J. Kuehl, D. T. Barkan, N. L. Collins, G. E. Meister, T. R. Bramhall, C.-H. Hsu, M. D. Jones, M. Schirle, M. T. Taylor, *J. Am. Chem. Soc.* **2022**, *144*, 6227–6236.

[12] a) M. T. Taylor, J. E. Nelson, M. G. Suero, M. J. Gaunt, *Nature* **2018**, *562*, 563–568; b) J. Kim, B. X. Li, R. Y.-C. Huang, J. X. Qiao, W. R. Ewing, D. W. C. Macmillan, *J. Am. Chem. Soc.* **2020**, *142*, 21260–21266; c) O. J. Knowles, L. O. Johannissen, G. E. M. Crisenza, S. Hay, D. Leys, D. J. Procter, *Angew. Chem. Int. Ed.* **2022**, *61*, e202212158.

[13] a) S. Sato, H. Nakamura, *Angew. Chem. Int. Ed.* **2013**, *52*, 8681–8684; b) N. Ichiishi, J. P. Caldwell, M. Lin, W. Zhong, X. Zhu, E. Streckfuss, H.-Y. Kim, C. A. Parish, S. W. Krska, *Chem. Sci.* **2018**, *9*, 4168–4175; c) B. X. Li, D. K. Kim, S. Bloom, R. Y.-C. Huang, J. X. Qiao, W. R. Ewing, D. G. Oblinsky, G. D. Scholes, D. W. C. Macmillan, *Nat. Chem.* **2021**, *13*, 902–908; d) T. Long, L. Liu, Y. Tao, W. Zhang, J. Quan, J. Zheng, J. D. Hegemann, M. Uesugi, W. Yao, H. Tian, H. Wang, *Angew. Chem. Int. Ed.* **2021**, *60*, 13414–13422.

[14] C. Bonauer, T. Walenzyk, B. König, *Synthesis* **2006**, 1–20.

[15] J. Dadová, S. R. G. Galan, B. G. Davis, *Curr. Opin. Chem. Biol.* **2018**, *46*, 71–81.

[16] X. Peng, K. Xu, Q. Zhang, L. Liu, J. Tan, *Trends Chem.* **2022**, *4*, 643–657.

[17] a) A. D. De Bruijn, G. Roelfes, *Chem. Eur. J.* **2018**, *24*, 11314–11318; b) T. Rossolini, J. A. Leitch, R. Grainger, D. J. Dixon, *Org. Lett.* **2018**, *20*, 6794–6798; c) T. Brandhofer, O. G. Mancheño, *ChemCatChem* **2019**, *11*, 3797–3801; d) P. Ji, Y. Zhang, Y. Dong, H. Huang, Y. Wei, W. Wang, *Org. Lett.* **2020**, *22*, 1557–1562; e) J. A. Leitch, T. Rossolini, T. Rogova, D. J. Dixon, *ACS Catal.* **2020**, *10*, 11430–11437; f) D. Reich, A. Trowbridge, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2020**, *59*, 2256–2261; g) R. C. W. Van Lier, A. D. De Bruijn, G. Roelfes, *Chem. Eur. J.* **2021**, *27*, 1430–1437.

[18] B. Josephson, C. Fehl, P. G. Isenegger, S. Nadal, T. H. Wright, A. W. J. Poh, B. J. Bower, A. M. Giltrap, L. Chen, C. Batchelor-Mcauley, G. Roper, O. Arisa, J. B. I. Sap, A. Kawamura, A. J. Baldwin, S. Mohammed, R. G. Compton, V. Gouverneur, B. G. Davis, *Nature* **2020**, *585*, 530–537.

[19] X. Wang, Y. Chen, H. Song, Y. Liu, Q. Wang, *Org. Lett.* **2021**, *23*, 2199–2204.

[20] a) R. A. Aycock, D. B. Vogt, N. T. Jui, *Chem. Sci.* **2017**, *8*, 7998–8003; b) T. Constantin, M. Zanini, A. Regni, N. S. Sheikh, F. Juliá, D. Leonori, *Science* **2020**, *367*, 1021–1026; c) J. R. Immel, M. Chilamari, S. Bloom, *Chem. Sci.* **2021**, *12*, 10083–

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10091; d) J. R. Immel, S. Bloom, *Angew. Chem. Int. Ed.* **2022**, *61*, e202205606.
[21] F. Berger, M. B. Plutschack, J. Riegger, W. Yu, S. Speicher, M. Ho, N. Frank, T. Ritter, *Nature* **2019**, *567*, 223–228.
[22] M. H. Aukland, M. Šiaučiulis, A. West, G. J. P. Perry, D. J. Procter, *Nat. Catal.* **2020**, *3*, 163–169.
[23] K. Kafuta, A. Korzun, M. Böhm, C. Golz, M. Alcarazo, *Angew. Chem. Int. Ed.* **2020**, *59*, 1950–1955.
[24] H. Meng, M.-S. Liu, W. Shu, *Chem. Sci.* **2022**, *13*, 13690–13707.
[25] a) E. M. Alvarez, M. B. Plutschack, F. Berger, T. Ritter, *Org. Lett.* **2020**, *22*, 4593–4596; b) Y. Wu, Y.-H. Huang, X.-Y. Chen, P. Wang, *Org. Lett.* **2020**, *22*, 6657–6661; c) B. Lansbergen, P. Granatino, T. Ritter, *J. Am. Chem. Soc.* **2021**, *143*, 7909–7914; d) D. Zhao, R. Petzold, J. Yan, D. Muri, T. Ritter, *Nature* **2021**, *600*, 444–449; e) M. Wang, X. Zhang, M. Ma, B. Zhao, *Org. Lett.* **2022**, *24*, 6031–6036; f) N. Kaplaneris, A. Puet, F. Kallert, J. Pöhlmann, L. Ackermann, *Angew. Chem. Int. Ed.* **2023**, *62*, e202216661.
[26] a) R. Sang, S. E. Korkis, W. Su, F. Ye, P. S. Engl, F. Berger, T. Ritter, *Angew. Chem. Int. Ed.* **2019**, *58*, 16161–16166; b) F. Ye, F. Berger, H. Jia, J. Ford, A. Wortman, J. Börgel, C. Genicot, T. Ritter, *Angew. Chem. Int. Ed.* **2019**, *58*, 14615–14619; c) J. Li, J. Chen, R. Sang, W.-S. Ham, M. B. Plutschack, F. Berger, S. Chabbra, A. Schnegg, C. Genicot, T. Ritter, *Nat. Chem.* **2020**, *12*, 56–62; d) Y.-L. Zhang, G.-H. Wang, Y. Wu, C.-Y. Zhu, P. Wang, *Org. Lett.* **2021**, *23*, 8522–8526; e) M. J. Cabrera-Afonso, A. Granados, G. A. Molander, *Angew. Chem. Int. Ed.* **2022**, *61*, e202202706; f) A. Granados, M. J. Cabrera-Afonso, M. Escolano, S. O. Badir, G. A. Molander, *Chem Catal.* **2022**, *2*, 898–907; g) F.-S. He, P. Bao, Z. Tang, F. Yu, W.-P. Deng, J. Wu, *Org. Lett.* **2022**, *24*, 2955–2960; h) Y. Cai, S. Chatterjee, T. Ritter, *J. Am. Chem. Soc.* **2023**, *145*, 13542–13548; i) W. Zhang, T. Liu, H. T. Ang, P. Luo, Z. Lei, X. Luo, M. J. Koh, J. Wu, *Angew. Chem. Int. Ed.* **2023**, e202310978.
[27] a) M.-S. Liu, H.-W. Du, H. Meng, Y. Xie, W. Shu, *Nat. Commun.* **2024**, *15*, 529; b) M. J. Kim, D. J. Wang, K. Targos, U. A. Garcia, A. F. Harris, I. A. Guzei, Z. K. Wickens, *Angew. Chem. Int. Ed.* **2023**, *62*, e202303032; c) D. E. Holst, C. Dorval, C. K. Winter, I. A. Guzei, Z. K. Wickens, *J. Am. Chem. Soc.* **2023**, *145*, 8299–8307; d) M. S. Liu, H. W. Du, J. F. Cui, W. Shu, *Angew. Chem. Int. Ed.* **2022**, *61*, e202209929; e) M.-S. Liu, H.-W. Du, W. Shu, *Chem. Sci.* **2022**, *13*, 1003–1008; f) F. Juliá, J. Yan, F. Paulus, T. Ritter, *J. Am. Chem. Soc.* **2021**, *143*, 12992–12998.
[28] a) L. Buglioni, F. Raymenants, A. Slattery, S. D. A. Zondag, T. Noël, *Chem. Rev.* **2022**, *122*, 2752–2906; b) L. Capaldo, Z. Wen, T. Noël, *Chem. Sci.* **2023**, *14*, 4230–4247; c) S. D. A. Zondag, D. Mazzarella, T. Noël, *Annu. Rev. Chem. Biomol. Eng.* **2023**, *14*, 283–300.
[29] a) M. R. Paleo, D. Domínguez, L. Castedo, *Tetrahedron* **1994**, *50*, 3627–3638; b) C. J. Chapman, C. G. Frost, *Adv. Synth. Catal.* **2003**, *345*, 353–355; c) L. Navarre, R. Martinez, J.-P. Genet, S. Darses, *J. Am. Chem. Soc.* **2008**, *130*, 6159–6169; d) S. Koch, D. Schollmeyer, H. Löwe, H. Kunz, *Chem. Eur. J.* **2013**, *19*, 7020–7041; e) P. S. Engl, A. P. Häring, F. Berger, G. Berger, A. Pérez-Bitrián, T. Ritter, *J. Am. Chem. Soc.* **2019**, *141*, 13346–13351; f) X. Y. Chen, Y. H. Huang, J. Zhou, P. Wang, *Chin. J. Chem.* **2020**, *38*, 1269–1272; g) E. M. Alvarez, T. Karl, F. Berger, L. Torkowski, T. Ritter, *Angew. Chem. Int. Ed.* **2021**, *60*, 13609–13613; h) T. M. Faraggi, C. Rouget-Virbel, J. A. Rincón, M. Barberis, C. Mateos, S. García-Cerrada, J. Agejas, O. De Frutos, D. W. C. MacMillan, *Org. Process Res. Dev.* **2021**, *25*, 1966–1973; i) Y. Zhao, C. Yu, W. Liang, F. W. Patureau, *Org. Lett.* **2021**, *23*, 6232–6236; j) S. Tang, X. Zhao, L. Yang, B. Li, B. Wang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202212975; k) Y. Zhao, C. Empel, W. Liang, R. M. Koenigs, F. W. Patureau, *Org. Lett.* **2022**, *24*, 8753–8758; l) Y. Guo, L. Wei, Z. Wen, H. Jiang, C. Qi, *Chem. Commun.* **2023**, *59*, 764–767; m) S. Ni, J. Yan, S. Tewari, E. J. Reijerse, T. Ritter, J. Cornella, *J. Am. Chem. Soc.* **2023**, *145*, 9988–9993; n) Q. Wang, W. Xiao, H. He, J. Guo, M. Wang, M. Ma, B. Zhao, *J. Org. Chem.* **2023**, *88*, 10818–10827; o) J. Zhang, X.-F. Wu, *Org. Lett.* **2023**, *25*, 2162–2166.

Manuscript received: February 16, 2024
Accepted manuscript online: March 18, 2024
Version of record online: April 8, 2024

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