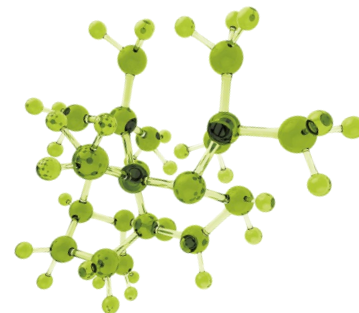


# A selection and comments on publications reporting significant advances concerning production and use of peptides.



Selection by Jan Pawlas, Ph.D. Scientist, Global Development, PolyPeptide Group  
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- 1) F. Albericio, O. Al Musaimi and B. G. de la Torre, Greening Fmoc/tBu Solid-Phase Peptide Synthesis, *Green Chem.*, 2020, **22**, 996. DOI: [10.1039/C9GC03982A](https://doi.org/10.1039/C9GC03982A). Albericio et al. deliver a tour de force account covering all facets of greening the most widespread peptide synthesis methodology: Fmoc/tBu SPPS. A must read for anyone interested in rendering peptide chemistry greener.
- 2) T. Nuijens, A. Toplak, M. Schmidt, A. Ricci and W. Cabri, Natural Occurring and Engineered Enzymes for Peptide Ligation and Cyclization, *Front. Chem.*, 2019, **7**, article 829. DOI: [10.3389/fchem.2019.00829](https://doi.org/10.3389/fchem.2019.00829). Nuijens and co-workers review contemporary state-of-the-art enzymes available for inter and intramolecular amide bond formations involving unprotected peptide and protein frameworks. Adopting these biocatalysts can potentially enable construction of previously inaccessible peptide based architectures as well as allow for the synthesis of various classes of therapeutic peptides in a more sustainable manner.
- 3) Handoko, S. Satishkumar, N. R. Panigrahi and P. S. Arora, Rational Design of an Organocatalyst for Peptide Bond Formation, *J. Am. Chem. Soc.*, 2019, **141**, 15977. DOI: [10.1021/jacs.9b07742](https://doi.org/10.1021/jacs.9b07742). While use of catalysts for formation of amide bonds in solution has been the subject of numerous studies making amide bonds catalytically in the context of SPPS has thus far been more difficult. The team of Arora demonstrates the feasibility of diselenide catalyzed, phosphine mediated construction of amide bonds on solid supports. This discovery paves the way for the advancement of chemoselective, cost efficient catalysts which may obviate the use of stoichiometric reagents for making peptides within the realms of SPPS.
- 4) B. J. Cafferty, A. S. Ten, M. J. Fink, S. Morey, D. J. Preston, M. Mrksich and G. M. Whitesides, Storage of Information Using Small Organic Molecules, *ACS Cent. Sci.*, 2019, **5**, 911. DOI: [10.1021/acscentsci.9b00210](https://doi.org/10.1021/acscentsci.9b00210). Whitesides et al. demonstrate that a set of 32 short oligopeptides can be used as high fidelity molecular devices for storing information. Taking into account the efficiency and versatility of current synthetic peptide methods, this study outlines potentially vast applications of peptide based architectures within information technologies.
- 5) K. Y. K. Kumar, V. R. Dama, C. Suchitraa and T. C. Maringanti, A simple, sensitive, high-resolution, customized, reverse phase ultra-high performance liquid chromatographic method for related substances of a therapeutic peptide (bivalirudin trifluoroacetate) using the quality by design approach, *Anal. Methods*, 2020, **12**, 304. DOI: [10.1039/c9ay01998g](https://doi.org/10.1039/c9ay01998g). The study detailing the development of UPLC methodologies suitable for resolution of substances closely related to the 20-mer bivalirudin underscores the utmost importance of advancing adequate analytical tools in contemporary manufacturing of peptide therapeutics.
- 6) R. Egbua, C. F. van der Walleb, S. Brocchinia, G. R. Williams, Inhibiting the fibrillation of a GLP-1-like peptide, *Int. J. Pharm.*, 2020, **574**, 118923. DOI: <https://www.sciencedirect.com/science/article/pii/S0378517319309688?via%3Dihub>. Aggregation is a phenomena that hampers the development of a wide range of peptide drugs. The study by Williams et al. in which the use of the non-ionic surfactant polysorbate 80 completely prevents fibril formation in a GLP peptide illustrates that use of suitable excipients provides a useful avenue in combatting aggregation during the development of peptide therapeutics.

7) S. Baldauf, D. Schauenburg and J. W. Bode, A Threonine-Forming Oxazetidine Amino Acid for the Chemical Synthesis of Proteins through KAHA Ligation, *Angew. Chem. Int. Ed.*, 2019, **58**, 12599. DOI: [10.1002/anie.201906486](https://doi.org/10.1002/anie.201906486). *Expanding the KAHA ligation methodology to encompass Thr is valuable as the preceding approaches employing ligations at HSer and Ser respectively suffer from the lack of the presence of HSer in most peptides for the former and limited stability of the requisite Ser building block for the latter. Ready commercial availability of the pertinent threonine oxazetidine building block will be crucial for the adoption of Thr KAHA based ligations by peptide synthesis practitioners.*

8) A. F. M. Noisier, M. J. Johansson, L. Knerr, M. A. Hayes, W. J. Drury III, E. Valeur, Lara R. Malins and R. Gopalakrishnan, Late-Stage Functionalization of Histidine in Unprotected Peptides, *Angew. Chem., Int. Ed.* 2019, **58**, 19096, DOI: [10.1002/anie.201910888](https://doi.org/10.1002/anie.201910888). *Interest in C-H functionalization of unprotected peptides as the means to access new molecular scaffolds has been increasing as of late. The report by Noisier et al. who expanded this methodology to C2 position of histidine by use of aliphatic sulfinic acid salts as radical precursors provides an entry to potential new classes of peptide medicines diversified at His.*

9) N. Hartrampf, A. Saebi, M. Poskus, Z. P. Gates, A. J. Callahan, A. E. Cowfer, S. Hanna, S. Antilla, C. K. Schissel, A. J. Quartararo, X. Ye, A. J. Mijalis, M. D. Simon, A. Loas, S. Liu, C. Jessen, T. E. Nielsen and B. L. Pentelute, Synthesis of Proteins by Automated Flow Chemistry, *ChemRxiv. Preprint.*, 2020, Feb. 11<sup>th</sup>, 12:57:08 (GMT). DOI: [10.26434/chemrxiv.11833503.v1](https://doi.org/10.26434/chemrxiv.11833503.v1). *Pentelute et al. report remarkably rapid flow syntheses of a range of proteins employing straight through Fmoc/t-Bu SPPS tactics. If the therapeutic molecules accessed in the aforementioned manner can adhere to the stringent requirements of regulatory agencies this methodology has the potential to alter the perception of SPPS as not being well suited for the production of very long peptide APIs.*

10) K. Torikai, R. Yanagimoto and L. A. Watanabe,  $N(\pi)-2$ -Naphthylmethoxymethyl-Protected Histidines: Scalable, Racemization-Free Building Blocks for Peptide Synthesis, *Org. Process Res. Dev.*, 2020, **XX**, XXXX. DOI: [10.1021/acs.oprd.9b00538](https://doi.org/10.1021/acs.oprd.9b00538). *The scalable synthesis of the  $\pi$ -nitrogen substituted Fmoc/Boc-His( $\pi$ -NAPOM)-OH as synthons for racemization free His couplings obviates the use of the preceding  $\pi$ -PMBOM functionalized His derivatives. The  $\pi$ -NAPOM moiety thus represents a valuable addition to the arsenal of available His protection groups albeit the fact that elevated temperature is needed for NAPOM removal means that further tinkering of the structure of this functional group may be needed to render the deprotection process milder.*

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