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Editorial

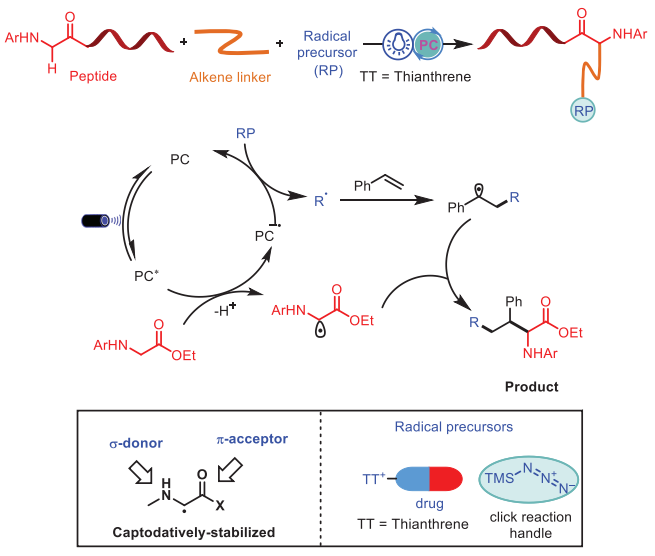
Stabilized carbon radical-mediated three-component functionalization of amino acid/peptide derivatives

Amino acids are the building blocks of proteins and play vital roles in both biological systems and drug development. In recent years, increasing attention has been given to the functionalization of amino acid derivatives. Since the introduction of therapeutic insulin in the early 20th century, the conjugation of drug molecules with amino acids and peptides has been pivotal in driving advancements in drug discovery and become an integral part of modern medical practice. Currently, over a hundred peptide-drug conjugates have received global approval and are widely used to treat diseases such as diabetes, cancer, chronic pain, and multiple sclerosis. Key technologies for conjugating peptides with bioactive molecules include antibody-drug conjugates (ADCs), peptide-drug conjugates (PDCs), and proteolysis targeting chimeras (PROTACs). Significant efforts have been dedicated to developing strategies for the modification of amino acids and peptides, with particular focus on site-selective C–H alkylation/arylation reactions. These reactions are crucial for synthesizing bioactive molecules, as they enable the precise introduction of functional groups at specific positions, thereby improving the pharmacological properties of the resulting compounds.

The photocatalytic difunctionalization of alkenes has garnered significant interest due to its ability to construct complex molecules in a single step. Considering the critical role of C(sp^3)-H alkylation in amino acid and peptide derivatives for integrating functional fragments in modern drug development, there is a pressing need for an efficient C–H functionalization strategy. Such a protocol should enable the modular incorporation of readily available compounds, such as alkenes, and functional fragments into amino acid and peptide derivatives under mild reaction conditions.

The research group of Lan-Gui Xie from Nanjing Normal University has conducted a series of studies, using *N*-aryl glycinate substrates which can produce captodatively-stabilized [1] carbon-centered radicals under photoredox catalytic conditions. The coupling between glycinate derived radical and transient carbon radical generated from the addition of functional fragment to alkene is enabled by the captodative stability of the former [2]. Building on these findings, they have previously developed a visible-light-induced carbosulfenylation of styrenes with *N*-aryl glycinates/peptides and disulfides [3]. Very recently, Xie's group further developed the photoredox-catalyzed three-component arylative/azido alkylation of amino acid and peptide derivatives using aryl thianthrenium salts/$TMSN_3$ and alkenes (Scheme 1) [4,5]. In these protocols, blue light irradiation initiates the generation of the excited state of the photocatalyst, which engages in electron transfer process-abstracting an electron from *N*-aryl glycinate to form a captodatively-stabilized carbon-centered radical under base conditions. An aryl radical is able to be generated through the single electron transfer between the aryl thianthrenium salt and the photocatalyst. While the other radical precursor $TMSN_3$ has the potential to be oxidized by SF_6 radical anion that is generated from the contact of electron scavenger SF_6 and the photocatalyst. These two types of radicals can be trapped by styrene/alkene to generate benzyl radical, which undergoes radical-radical coupling with the stabilized carbon radical to give products.

Through photoredox catalytic processes, the reaction enables the modular incorporation of functional groups under mild conditions, offering broad substrate scope and excellent functional group tolerance. The advantage of using aryl thianthrenium salt as the coupling partner is represented by the ability to integrate pharmacologically relevant fragments with amino acids/peptides, providing straightforward pathway for the synthesis of peptide-drug conjugates. While azide functionality is well known as the click handle for ligating two bio-relavant fragments. Considering the growing



Scheme 1. Stabilized carbon radical-mediated three-component functionalization of amino acid/peptide derivatives.

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importance of amino acid and peptide modifications in the pharmaceutical industry, the development of stabilized carbon radical-mediated reactions is anticipated to continue to thrive in the coming years.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] R. Sustmann, H.G. Korth, Adv. Phys. Org. Chem. 26 (1990) 131–178.
[2] D. Leifert, A. Studer, Angew. Chem. Int. Ed. 59 (2020) 74–108.
[3] Z. Yang, J. Liu, L.G. Xie, Adv. Sci. 11 (2024) 2402428.
[4] B. Dong, W. Qi, Y. Chen, et al., Adv. Sci. 11 (2024) 2411579.
[5] L. Zhang, S. Gu, Y. Zhao, et al., Cell Rep. Phys. Sci. 5 (2024) 102256.