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# Late-stage peptide modification and macrocyclization enabled by tertiary amine catalyzed tryptophan allylation†

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Late-stage modification of peptides could potentially endow peptides with significant bioactivity and physicochemical properties, and thereby provide novel opportunities for peptide pharmaceutical studies. Since tryptophan (Trp) bears a unique indole ring residue and plays various critical functional roles in peptides, the modification methods for tryptophan were preliminarily developed with considerable progress via transition-metal mediated C–H activation. Herein, we report an unprecedented tertiary amine catalyzed peptide allylation via the  $S_{N2'}-S_{N2'}$  pathway between the N1 position of the indole ring of Trp and Morita–Baylis–Hillman (MBH) carbonates. Using this method that proceeds under mild conditions, we demonstrated an extremely broad scope of Trp-containing peptides and MBH carbonates to prepare a series of peptide conjugates and cyclic peptides. The reaction is amenable to either solid-phase (on resin) or solution-phase conditions. In addition, the modified peptides can be further conjugated with other biomolecules at Trp, providing a new handle for bioconjugation.

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## Introduction

Peptides are highly promising bioactive molecules that have been extensively studied in recent decades as important potential therapeutic agents and biomaterials,<sup>1–3</sup> chemical biology probes,<sup>4</sup> and a platform for targeted therapeutics.<sup>5</sup> In contrast to their flourishing successes in academics, however, native peptides that can often suffer from innate limitations such as poor proteolytic stability and low membrane permeability,<sup>3</sup> are hindered from further application and transformation as clinical drugs, which can be mitigated by introducing structural modifications and cyclizations.<sup>6–9</sup> In addition, the introduction of electrophilic “warheads” that are beyond canonical amino acids into peptides enables them to covalently bind to their target of interest to further increase their potency, which has been demonstrated by the success of proteasome inhibitor carfilzomib.<sup>10,11</sup> In this context, chemical manipulation of peptides has been in urgent demand and emerged as a major tool for structurally sound arrangement of

peptides, leading to an arsenal of late-stage peptide bioconjugation and modification.<sup>12–18</sup> Despite the fruitful progress, alternatives for peptide late-stage chemical manipulation are still highly desired and attracted intensive attention from the chemical community.

Tryptophan (Trp), the rarest native proteinogenic amino acid accounting for only ~1% abundance while existing in approximately 90% of all proteins,<sup>19</sup> is an ideal site of interest for peptide and protein modification. The side chain of Trp, in particular, bears a unique indole ring that showcases a huge potential in late-stage modification due to its variable chemical reactivity. As a consequence, a variety of methods leveraging Trp modification have been developed and applied to peptides and proteins (Scheme 1a).<sup>20,21</sup> Take the last 3 years for instance, transition-metal-catalyzed C–H activation provides distinct peptide late-stage modification with good chemoselectivity, which has been explored by several groups.<sup>22–30</sup> However, the reported methods require harsh reaction conditions, such as high temperatures, oxidant additives, auxiliary directing groups, and complex reaction conditions, which restrict their application prospects in bioactive peptide research. With the development of photochemistry in recent years, radical-mediated C2 amination,<sup>31–33</sup> fluoroalkylation,<sup>34,35</sup> alkylation,<sup>36,37</sup> and thiation<sup>38,39</sup> on the indole ring of tryptophan have been explored for the functionalization of peptides. In sharp contrast, modification on the NH position of the indole ring of Trp is much less explored due to the lower nucleophilicity and basicity of indole N–H of Trp among the multiple nucleophilic sites in peptide. A copper-promoted  $N_{(in)}$ -arylation of the indole

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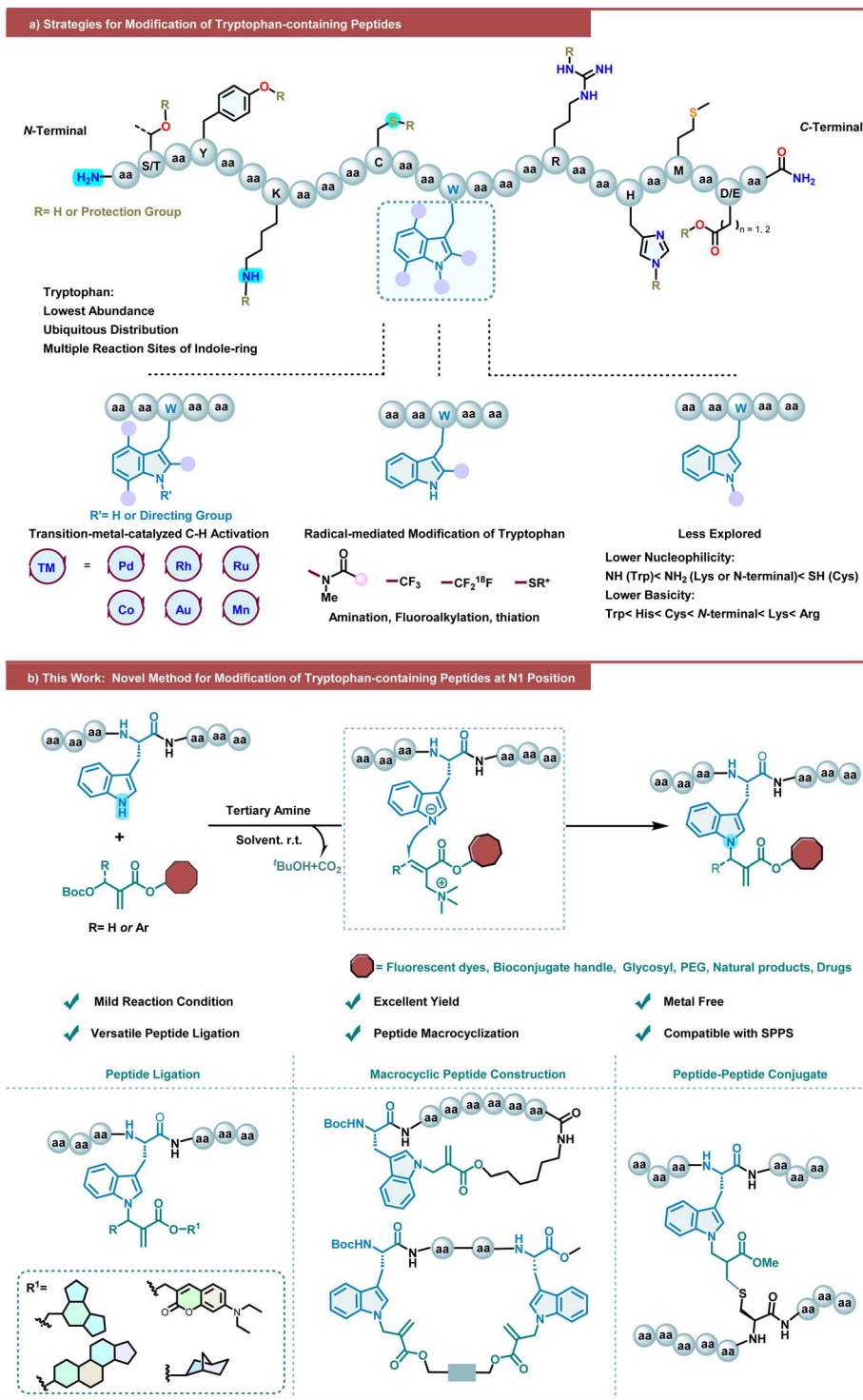
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Scheme 1 Late-stage modification of peptides containing the Trp side chain.

ring of Trp with triarylbismuthine species has been reported by Gagnon and coworkers.<sup>40</sup> More recently, Paixão and coworkers have disclosed the dual photoredox/metal catalysis mediated *N*<sub>(in)</sub>-arylation of tryptophan-containing peptide on resin.<sup>41</sup> Our group has developed a chiral phosphoric acid-catalyzed chemoselective enantioselective functionalization of tryptophan at

the N1 position, enabling direct access to chiral propargyl amination derivatives with good yields and stereoselectivities.<sup>42</sup> Studer and coworker have reported the visible-light-mediated N1 position hemiaminal modification of Trp-containing peptides through the N-H insertion of siloxycarbenes photochemically generated from acylsilanes.<sup>43</sup> Very recently, Spring



and coworkers reported a tryptophan-mediated multicomponent Petasis reaction for peptide stapling and late-stage functionalization.<sup>44</sup> Nevertheless, the development of Trp modification on its N1 position of the indole ring is still in its infancy. Thus, it is essential to introduce novel strategies to enrich the toolbox for peptide modification.

In line with our ongoing interest in peptide chemistry, including those Trp modifications,<sup>33,39,42,45–49</sup> we have been trying to explore more mild, easy-to-manipulate alternatives for peptide modification/functionalization to enrich the scenario. Promoted by our previous work on organocatalytic indole functionalization<sup>50,51</sup> and Morita–Baylis–Hillman (MBH) carbonate based allylation,<sup>52–54</sup> and inspired by Chen's *N*-allylic alkylation of indoles with MBH carbonates,<sup>55</sup> we sought to explore the reaction between Trp and MBH carbonates to develop a novel strategy for peptide functionalization. Interestingly, in 2018, Ackermann and coworkers accomplished MnBr(CO)<sub>5</sub>-catalyzed C2–H activation allylation of the indole ring of Trp with an auxiliary pyridyl directing group using MBH carbonates for oligopeptide modification and cyclization.<sup>56</sup> Herein, we envisioned that MBH carbonates could be utilized to achieve the indole *N*1-allylation of Trp *via* the S<sub>N</sub>2'–S<sub>N</sub>2' pathway under tertiary amine catalysis, ultimately enabling the metal-free late-stage functionalization and macrocyclization of peptides under mild conditions, with electrophilic acrylate “warheads” introduced into peptides of interest (Scheme 1b). However, several challenges must be taken into account from the precision perspective: (1) the existence of various competitive nucleophilic functional groups in peptides, such as –SH (Cys), –NH<sub>2</sub> (Lys), –OH (Tyr, Ser, and Thr) and others, makes it a daunting task to control the chemoselectivity; (2) the multiple competitive reactive sites, particularly the very electron-rich C2=C3 region, on the indole ring of Trp make its regioselective control extremely challenging; (3) potential stereoselectivity control is also a challenge.

## Results and discussion

To verify our hypothesis, we initiated our investigation using the model reaction of Boc–Trp–OMe (**1a**) with an MBH carbonate (**2a**) catalyzed by different tertiary amines (10 mol%) in DCE at room temperature overnight (Table S1, entries 1–4†). Fortunately, the DABCO-catalyzed reaction afforded only one product, an *N*-allylation product, in excellent yields (Table S1, entry 1,† 96% yield). Encouraged by this result, we further investigated different inorganic bases and tertiary phosphine catalysts (Table S1, entries 5–9†) and found that DABCO exhibited the highest catalytic activity. Further parameters were then screened to optimize the reaction. The choice of solvent had a significant effect on the yield (Table S1, entries 10–17†), with DCM proving to be the optimal solvent. Pleasingly, when the catalyst loading was increased to 20 mol%, the reaction time was reduced to 1 h without any loss of yield. Furthermore, we conducted an investigation of the chemoselectivity between tryptophan and other natural amino acids with nucleophilic residues (see the ESI†). This reaction demonstrated exclusive

chemoselectivity with Trp, Tyr, and His, but unsatisfactory selectivity with Lys, Arg, Ser and Cys.

With the optimized conditions in hand, we explored the scope of the proposed method. First, we investigated the generality of our allylation regime for a broad range of Trp-containing peptides (Fig. 1). Gratifyingly, all the peptides with Trp residues reacted readily with **2a**, affording the corresponding products in high isolated yields (up to 99%). All di- and tripeptides with protected residues, such as lysine and tyrosine, were converted to produce allylation products in excellent yields (**3b–3i**). This successful application encouraged the exploration of more complex peptide structures. To our delight, this approach proved to be robust for the conversion of tetrapeptides, pentapeptides, and heptapeptides (**3j–3n**). In addition, the position of the Trp residue in the peptide sequence can be divided into an N-terminus, an internal segment, and a C-terminus; however, the results suggest that positioning has a negligible effect on conversion (**3d**, **3f**, and **3h**). In contrast, the composition of amino acids in peptide sequences has a more significant effect on conversion, presumably because these peptides have low solubility in DCM (**3j**, **3l**, and **3m**). More importantly, these findings demonstrate the utility of our approach in directly accessing the modification of bioactive peptides (endomorphin-1, **3k**, and spinorphin, **3n**) without relying on long *de novo* syntheses based on prefunctionalized building blocks.

Next, we turned our attention to investigating the applicability of this allylation strategy through the smooth ligation of a tripeptide with a wide variety of MBH carbonates (Fig. 2). To our delight, all the MBH carbonate derivatives reacted smoothly with the Boc–Leu–Trp–Phe–OMe tripeptide, furnishing the desired products in good-to-excellent yields (up to 94%). As shown in Fig. 2, the reaction with different acrylates, including ethyl, *tert*-butyl, and benzyl esters, proceeded efficiently, producing the corresponding allylation products in good yields (**4a–4c**). This success indicates that allylation provides a unique opportunity to regulate the physical and biological properties of peptides by introducing various substituents with different characteristics. The lipidated and PEGylated motifs can assemble with the tripeptide to regulate the hydrophilic and hydrophobic properties in good yields (**4d** and **4e**). The PEGylation of peptides is also attractive for enhancing their pharmacological properties for application in drug delivery. Similarly, the biorthogonal alkyne handle was ligated with a peptide for further click chemistry, resulting in excellent yields (**4f**, 94%). This allylation strategy enabled position-specific fluorescent labelling of peptides by assembling them with a coumarin fluorescent dye (**4g**, 68%). The versatile *N*-allylation of Trp-containing peptide manifolds has also proved amenable to the ligation of bioactive molecules. Glycosylation can modulate the properties and functions of the peptides and proteins involved in various biological processes. Under our experimental conditions, the masked galactose efficiently conjugated to the Trp residue to produce glycosylated peptides in good yields (**4h**, 83%). Furthermore, several natural products and drugs, such as piperonyl alcohol, (1)-menthol, (1)-borneol, epiandrosterone, and cholesterol,



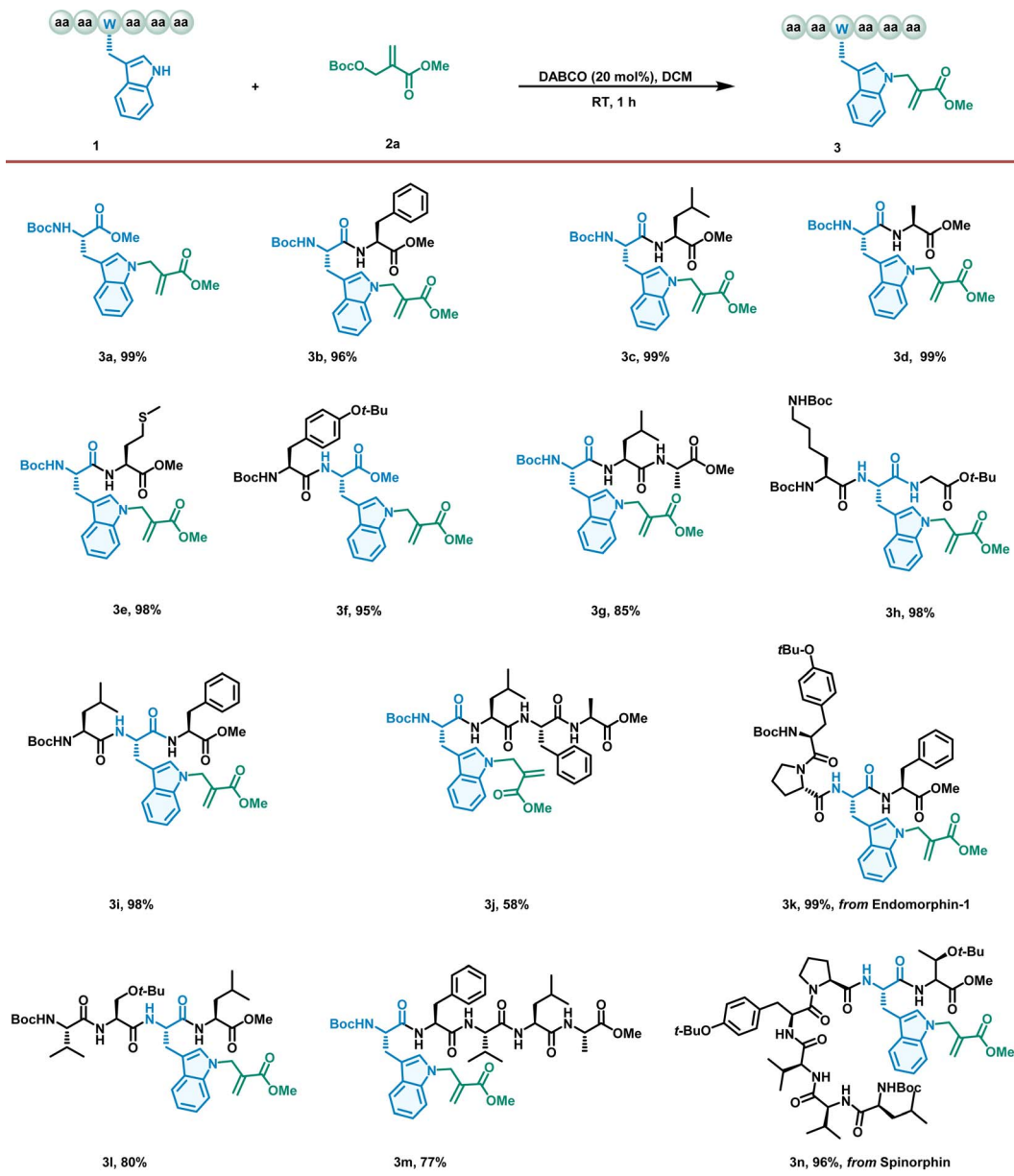


Fig. 1 Alkylation of tryptophan-containing peptides with MBH carbonate. Unless otherwise stated, the reaction was carried out with **1** (0.1 mmol), **2a** (0.2 mmol, 2 eq.), catalyst (0.02 mmol, 20 mol%) in 1 mL DCM at room temperature for 1 hour. Yields are isolated yields after column chromatography.

were also efficiently conjugated to the Trp residue of the tripeptide in moderate-to-good yields under standard conditions (**4i–4m**). These results demonstrate the potential of this chemistry for the construction of peptide conjugates. We further explored the scope of sterically hindered MBH carbonates bearing benzene rings (Fig. 2). After meticulous screening of chiral tertiary amine catalysts, we found that the bifunctional catalyst beta-isocupreidine ( $\beta$ -ICD) readily catalyzed the allylation of Boc-Trp-OMe and afforded the product in excellent yields (98%) with 7.1:1 d.r., indicating that properly distributed H-bonds in the transition state may play an essential role in conveying stereochemical information (see

the ESI<sup>†</sup>). In addition, the reaction with the Boc-Leu-Trp-Phe-OMe tripeptide proceeded smoothly, affording the allylation product in 99% yield and 5.3:1 d.r. (**4n**). We then investigated a series of MBH carbonates bearing halogen substituents on the benzene rings. All MBH carbonates provided the corresponding products in good yields and moderate diastereoselectivities (**4o–4q**). When an MBH carbonate containing strong electron-withdrawing groups (such as NO<sub>2</sub>) was employed, the reaction proceeded smoothly and afforded **4r** in moderate yields (53%). The allylation also proceeded smoothly using the MBH carbonate with an aliphatic benzene and a naphthyl substituent (**4s** and **4t**).





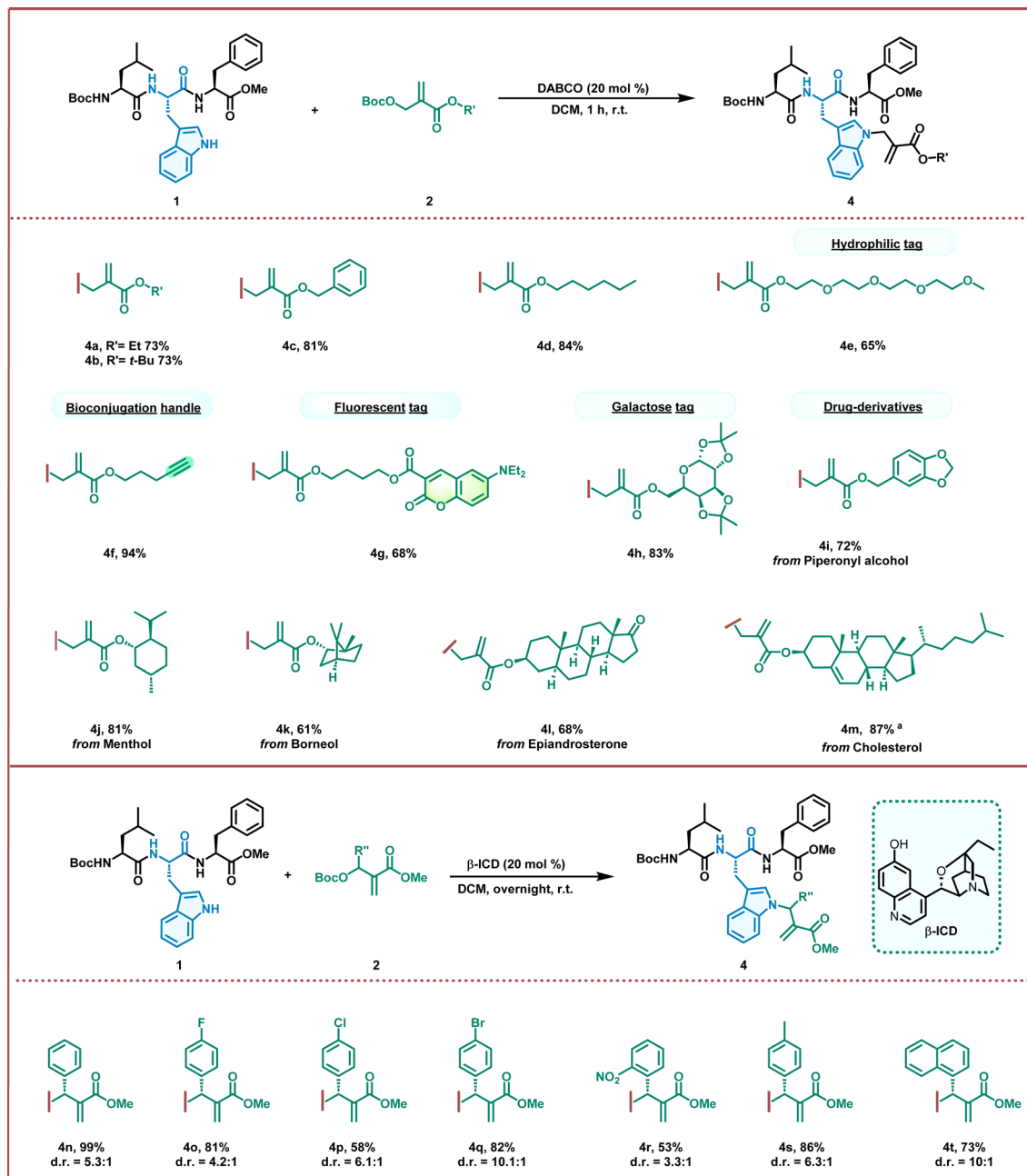


Fig. 2 Allylation of tryptophan-containing peptides with MBH carbonates. Unless otherwise stated, the reaction was carried out with **1** (0.1 mmol, 1.0 eq.), **2** (0.2 mmol, 2.0 eq.), and DABCO or  $\beta$ -ICD (0.01 mmol, 20 mol%) in 1 mL DCM at room temperature for 1 hour or overnight. Yields are isolated yields after column chromatography. d.r. was determined by  $^1\text{H}$  NMR. <sup>a</sup>The reaction was carried out for 24 h.

These results demonstrate the great application potential of organic asymmetric catalysis for late-stage modification of peptides.

As macrocyclic peptides can significantly enhance the cellular uptake, metabolic stability, and binding affinity of targets, it is essential to develop strategies to construct macrocyclic peptides.<sup>8,9,57</sup> We investigated the practicality of the intramolecular Trp allylation method for preparing macrocyclic peptides (Fig. 3A). Allylation-modified macrocyclic peptides were obtained in moderate-to-good yields by intramolecular methods

using alkyl MBH carbonate cross-linkers. To improve the yield of such intramolecular macrocyclic peptides and avoid detrimental di- and oligomerization, we diluted the reaction mixture after a simple screening of the reaction concentration. Gratifyingly, under the dilute conditions, a series of linear peptides were smoothly cyclized with excellent chemoselectivity and good yields, furnishing 17- to 35-membered macrocycles (**5a–5f**). Various amino acids (such as Asp and Ser) can be tolerated under these conditions. The functional side chain of the natural amino acid (Glu) can also be used to tether the MBH carbonate moiety.

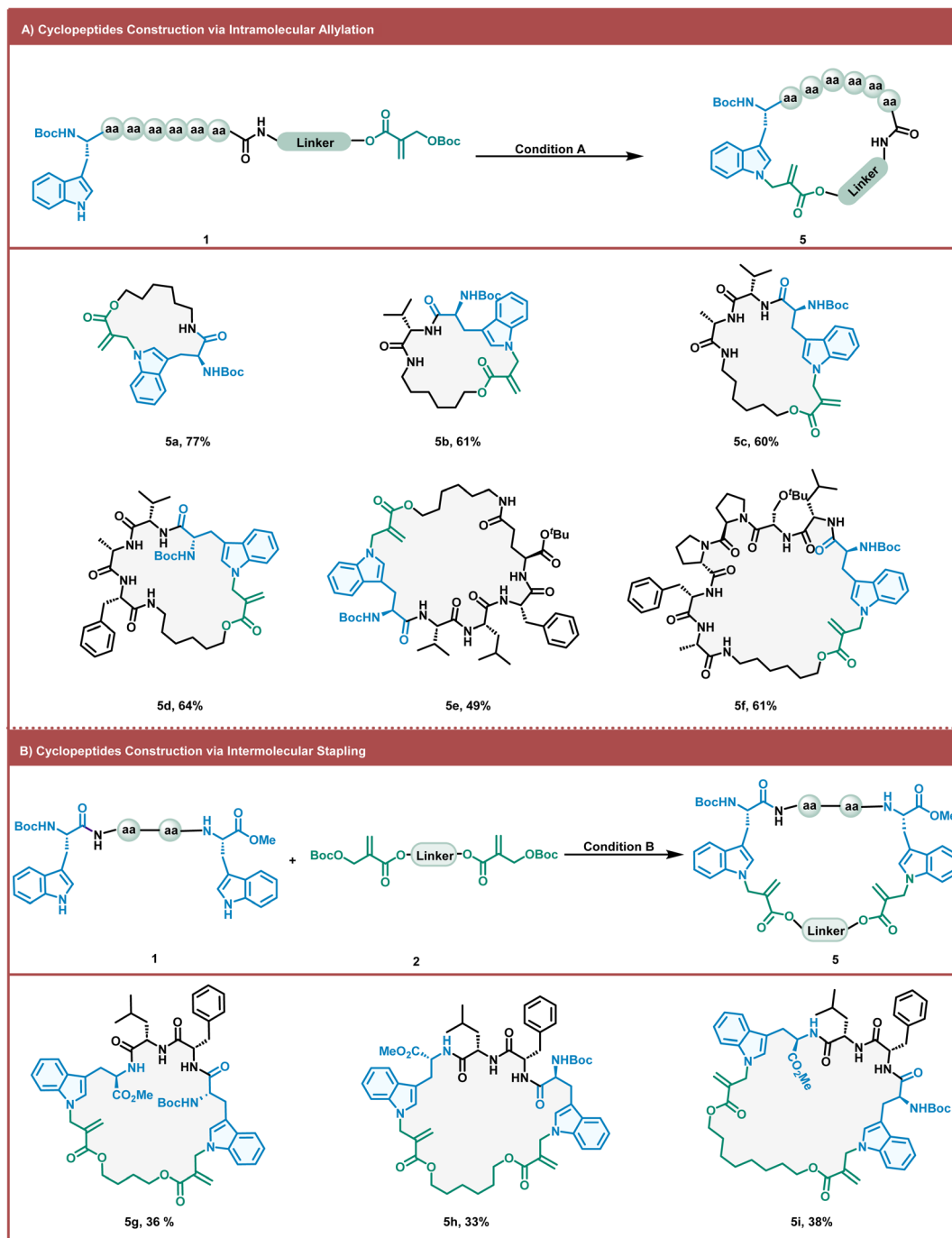


Fig. 3 Macrocyclic peptide construction *via* intramolecular or intermolecular allylation of Trp. Reaction conditions (A) 0.1 mmol **1**, DABCO (0.02 mmol, 20 mol%) in 10 mL DCM at room temperature for 1 h. Yields are isolated yields after column chromatography. Reaction conditions (B) 0.1 mmol **1**, 0.12 mmol **2**, DABCO (0.02 mmol, 20 mol%) in 10 mL DCM at room temperature for 1 h. Yields are isolated yields after column chromatography.

Thus, cyclic peptide (**5e**) was readily obtained in moderate yields (49%). The yield did not decrease with increasing linear peptide length. When the linear peptide sequence contained a  $\beta$ -hairpin motif sequence, the cyclization yield becomes slightly higher than that without  $\beta$ -hairpin motif sequences (**5f**). Peptide stapling is an important strategy for the synthesis of macrocyclic peptides

with  $\alpha$ -helical conformations.<sup>58,59</sup> We further investigated the practicality of the intermolecular Trp allylation method for the construction of stapling peptides (Fig. 3B). Three macrocyclic peptides containing 30–34 members were obtained by stapling different lengths of alkyl MBH carbonates with tetrapeptides *via* intermolecular allylation (**5g–5i**). This stapling method can



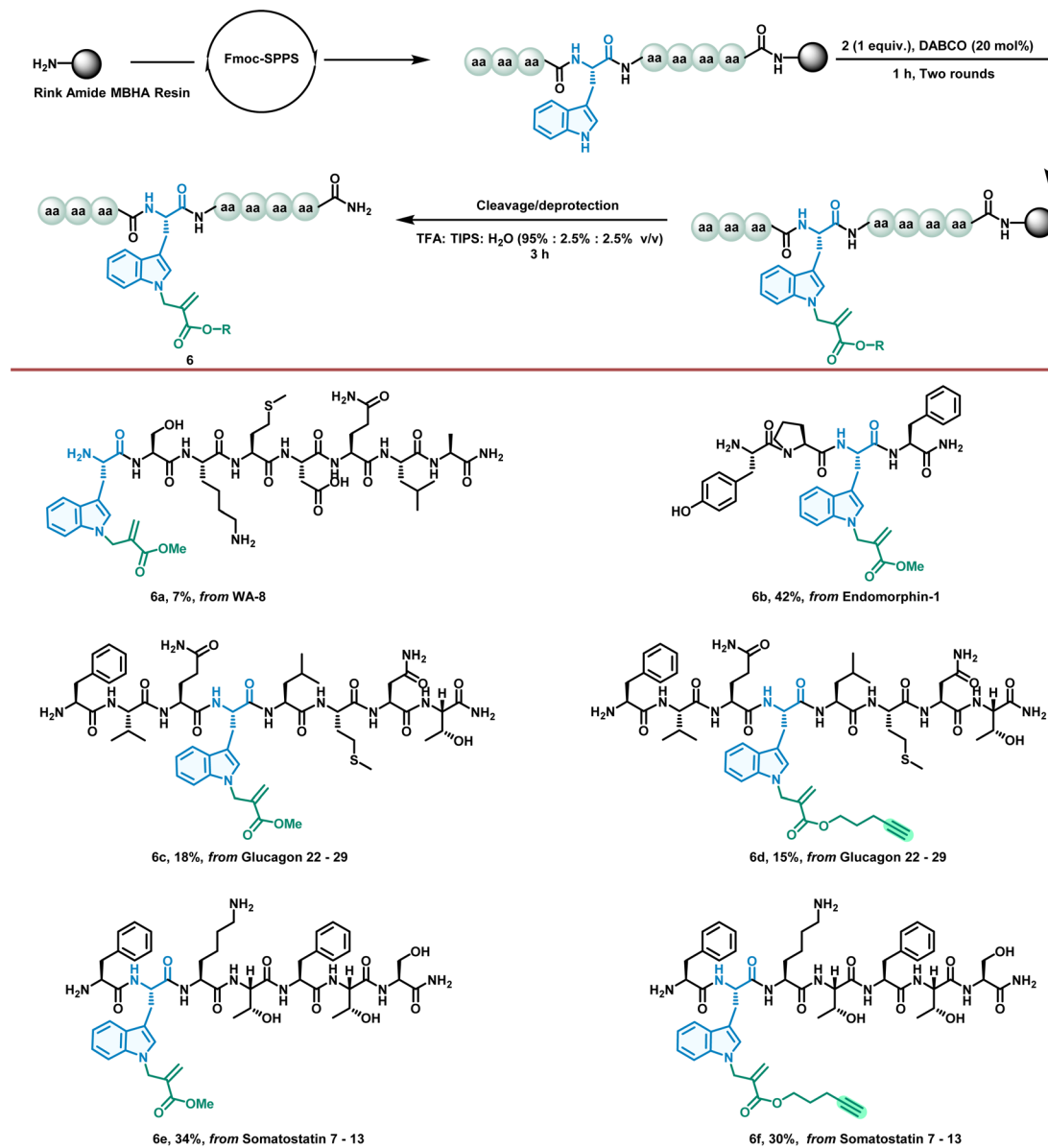


Fig. 4 Application of the allylation modification on SPPS.

introduce more diverse staple linkages with the inherent amino acids in peptides, avoiding unnatural amino acid synthesis and incorporation.

Encouraged by these outstanding results in the Trp residue allylation regime, we further investigated the peptide allylation to obtain the desired modified bioactive peptides and fragments with good chemoselectivity and yields. Notably, this powerful organocatalytic allylation successfully occurred on a solid support despite the limitations of heterogeneous reaction conditions (Fig. 4). For this purpose, we first incorporated unprotected Trp residues into the peptides during SPPS. After the synthesis of the resin-supported peptides, we explored allylation to obtain the desired modified bioactive peptides and fragments with good chemoselectivity and yields (**6a-f**). This

may provide a rapid and efficient alternative for the preparation of diverse peptide lead analogues.

To further extend the capabilities of this chemistry, we constructed peptide-peptide conjugates *via* the thia-Michael addition reaction utilizing the Michael receptor incorporated into the peptide and the thiol group of a cysteine residue in the peptide. Next, we performed peptide-peptide conjugation (Fig. 5). The modified peptide (**6e**) prepared by solid support allylation was reacted with the oligopeptide (P-10: AP02702; containing 13 amino acids within 1 cysteine) at 37 °C and pH 8.35 for 1 h, and the result was analysed by LC-MS/MS. To our delight, the peptide-peptide conjugate was readily constructed with high efficiency under mild conditions. The success of this peptide-peptide conjugate may support further applications of



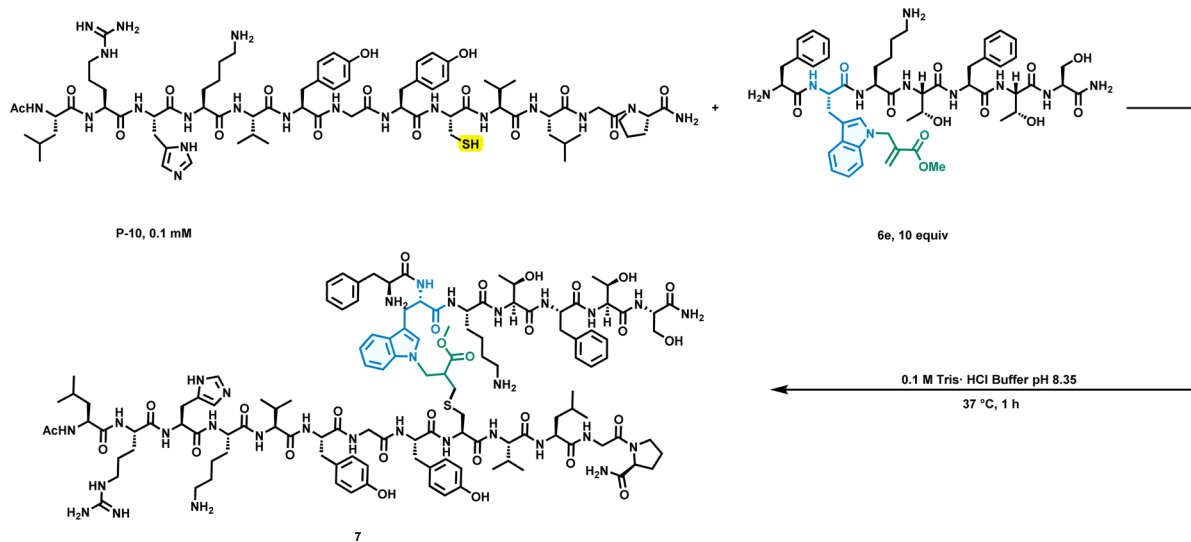


Fig. 5 Peptide-peptide conjugate by the thia-Michael addition reaction.

our work in the field of peptide-protein conjugates or peptide inhibitors.

## Conclusions

We have developed a practical and efficient strategy for the late-stage functionalization of Trp-containing peptides *via* organocatalysis. This is the first example of organocatalyzed allylation of peptides at the indole NH site of the Trp residue with various acrylate substituents, using MBH carbonates as reaction counterparts. To further demonstrate the application of this strategy, various functional molecules, including fluorophores, lipids, hydrophilic tags, saccharides, and natural products, were incorporated into the peptides. Significantly, this allylation enables the construction of cyclopeptides *via* intramolecular cyclization and intermolecular stapling under mild conditions. In addition, this reaction allows the peptide allylation on resin by solid-phase peptide synthesis (SPPS), granting access to structurally intricate peptide molecules. Ultimately, the modified peptides can be conjugated to other biomolecules *via* an electrophilic warhead generated by the reaction. Hence, this strategy provides an important toolkit for peptide modification and peptide-drug conjugate design. We anticipate that this toolkit will have broad applications in peptide chemical biology and peptide drug discovery.

## Data availability

The data that support the findings of this study are available in the ESI† of this article.

## Author contributions

W. S. and R. W. conceived the project and designed the experiments. Y. L., W. M. and Z. H. conducted the experiments. Y. L., G. L., G. B., Y. L., and W. S. conducted the data analysis and

wrote the manuscript. All authors discussed the results and commented on and edited the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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## Notes and references

- 1 I. W. Hamley, *Chem. Rev.*, 2017, **117**, 14015–14041.
- 2 M. Muttenthaler, G. F. King, D. J. Adams and P. F. Alewood, *Nat. Rev. Drug Discovery*, 2021, **20**, 309–325.
- 3 L. Wang, N. Wang, W. Zhang, X. Cheng, Z. Yan, G. Shao, X. Wang, R. Wang and C. Fu, *Signal Transduction Targeted Ther.*, 2022, **7**, 48.
- 4 C. L. Charron, J. L. Hickey, T. K. Nsiama, D. R. Cruickshank, W. L. Luyt and L. G. Turnbull, *Nat. Prod. Rep.*, 2016, **33**, 761–800.
- 5 B. M. Cooper, J. Iegre, D. H. O’Donovan, M. Ö. Halvarsson and D. R. Spring, *Chem. Soc. Rev.*, 2021, **50**, 1480–1494.
- 6 A. Henninot, J. C. Collins and J. M. Nuss, *J. Med. Chem.*, 2018, **61**, 1382–1414.
- 7 M. Erak, B. Bellmann-Sickert, S. Els-Heindl and A. G. Beck-Sickinger, *Bioorg. Med. Chem.*, 2018, **26**, 2759–2765.
- 8 L. Reguera and D. G. Rivera, *Chem. Rev.*, 2019, **119**, 9836–9860.
- 9 A. A. Vinogradov, Y. Yin and H. Suga, *J. Am. Chem. Soc.*, 2019, **141**, 4167–4181.





- 10 V. Y. Berdan, P. C. Klauser and L. Wang, *Bioorg. Med. Chem.*, 2021, **29**, 115896.
- 11 M. Gehringer and S. A. Laufer, *J. Med. Chem.*, 2019, **62**, 5673–5724.
- 12 A. F. M. Noisier and M. A. Brimble, *Chem. Rev.*, 2014, **114**, 8775–8806.
- 13 J. N. deGruyter, L. R. Malins and P. S. Baran, *Biochemistry*, 2017, **56**, 3863–3873.
- 14 C. Zhang, E. V. Vinogradova, A. M. Spokoyny, S. L. Buchwald and B. L. Pentelute, *Angew. Chem., Int. Ed.*, 2019, **58**, 4810–4839.
- 15 H.-R. Tong, B. Li, G. Li, G. He and G. Chen, *CCS Chem.*, 2020, **2**, 1797–1820.
- 16 A. S. Mackay, R. J. Payne and L. R. Malins, *J. Am. Chem. Soc.*, 2022, **144**, 23–41.
- 17 V. M. Lechner, M. Nappi, P. J. Deneny, S. Folliet, J. C. K. Chu and M. J. Gaunt, *Chem. Rev.*, 2022, **122**, 1752–1829.
- 18 C. Wang, R. Qi, R. Wang and Z. Xu, *Acc. Chem. Res.*, 2023, **56**, 2110–2125.
- 19 D. Gilis, S. Massar, N. J. Cerf and M. Rooman, *Genome Biol.*, 2001, **2**, research0049.1.
- 20 J.-J. Hu, P.-Y. He and Y.-M. Li, *J. Pept. Sci.*, 2021, **27**, e3286.
- 21 H. Größ and N. Sewald, *Chem.-Eur. J.*, 2020, **26**, 5328–5340.
- 22 W. Wang, J. Wu, R. Kuniyil, A. Kopp, R. N. Lima and L. Ackermann, *Chem*, 2020, **6**, 3428–3439.
- 23 N. Kaplaneris, F. Kaltenhäuser, G. Sirvinskaite, S. Fan, T. D. Oliveira, L.-C. Conradi and L. Ackermann, *Sci. Adv.*, 2021, **7**, eabe6202.
- 24 N. Kaplaneris, A. Puet, F. Kallert, J. Pöhlmann and L. Ackermann, *Angew. Chem., Int. Ed.*, 2023, **62**, e202216661.
- 25 Z. Bai, C. Cai, W. Sheng, Y. Ren and H. Wang, *Angew. Chem., Int. Ed.*, 2020, **59**, 14686–14692.
- 26 L. Liu, X. Fan, B. Wang, H. Deng, T. Wang, J. Zheng, J. Chen, Z. Shi and H. Wang, *Angew. Chem., Int. Ed.*, 2022, **61**, e202206177.
- 27 J. Liu, P. Wang, W. Zeng, Q. Lu and Q. Zhu, *Chem. Commun.*, 2021, **57**, 11661–11664.
- 28 P. Wang, J. Liu, X. Zhu, Kenry, Z. Yan, J. Yan, J. Jiang, M. Fu, J. Ge, Q. Zhu and Y. Zheng, *Nat. Commun.*, 2023, **14**, 3973.
- 29 J. Li, J. Sun, X. Zhang, R. Zhang, Q. Wang, L. Zhang, L. Xie, C. Li, Y. Zhou, J. Wang, G. Xiao, F. Bai and H. Liu, *Chem. Commun.*, 2023, **59**, 868–871.
- 30 M. Nuruzzaman, B. M. Colella, C. P. Uzoewulu, A. E. Meo, E. J. Gross, S. Ishizawa, S. Sana, H. Zhang, M. E. Hoff, B. T. W. Medlock, E. C. Joyner, S. Sato, E. A. Ison, Z. Li and J. Ohata, *J. Am. Chem. Soc.*, 2024, **146**, 6773–6783.
- 31 S. T. Tower, W. J. Hetcher, T. E. Myers, N. J. Kuehl and M. T. Taylor, *J. Am. Chem. Soc.*, 2020, **142**, 9112–9118.
- 32 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 and M. D. Jones, *J. Am. Chem. Soc.*, 2022, **144**, 6227–6236.
- 33 C. Yu, R. E, X.-W. Zhang, W.-Q. Hu, G. Bao, Y. Li, Y. Liu, Z. He, J. Li, W. Ma, L.-Y. Mou, R. Wang and W. Sun, *ChemMedChem*, 2023, **18**, e2022006.
- 34 C. W. Kee, O. Tack, F. Guibbal, C. Wilson, P. G. Isenegger, M. Imiolek, S. Verhoog, M. Tilby, G. Boscutti, S. Ashworth, J. Chupin, R. Kashani, A. W. J. Poh, J. K. Sosabowski, S. Machooll, C. Plisson, B. Cornelissen, M. C. Willis, J. Passchier, B. G. Davis and V. Gouverneur, *J. Am. Chem. Soc.*, 2020, **142**, 1180–1185.
- 35 N. J. Kuehl and M. T. Taylor, *J. Am. Chem. Soc.*, 2023, **145**, 22878–22884.
- 36 B. Laroche, X. Tang, G. Archer, R. D. Sanza and P. Melchiorre, *Org. Lett.*, 2021, **23**, 285–289.
- 37 R. N. Lima, J. A. C. Delgado, D. I. Bernardi, R. G. S. Berlinck, N. Kaplaneris, L. Ackermann and M. W. Paixão, *Chem. Commun.*, 2021, **57**, 5758–5761.
- 38 L. R. Malins, K. M. Cergol and R. J. Payne, *Chem. Sci.*, 2014, **5**, 260–266.
- 39 G. Bao, P. Wang, J. Li, X. Song, T. Yu, J. Zhang, Y. Li, Z. He, R. E, X. Miao, J. Xie, J. Ni, R. Wang and W. Sun, *CCS Chem.*, 2024, **6**, 1547–1556.
- 40 A. Le Roch, H.-C. Chan and A. Gagnon, *Eur. J. Org. Chem.*, 2020, 5815–5819.
- 41 J. A. C. Dolgado, Y.-M. Tian, M. Marcon, B. König and M. W. Paixão, *J. Am. Chem. Soc.*, 2023, **145**, 26452–26462.
- 42 J. Yang, Z. He, L. Hong, W. Sun and R. Wang, *Org. Biomol. Chem.*, 2020, **18**, 4169–4173.
- 43 J. Reimler and A. Studer, *Chem.-Eur. J.*, 2021, **27**, 15392–15395.
- 44 S. Krajcovicova and D. R. Spring, *Angew. Chem., Int. Ed.*, 2023, **62**, e202307782.
- 45 G. Bao, P. Wang, G. Li, C. Yu, Y. Li, Y. Liu, Z. He, T. Zhao, J. Rao, J. Xie, L. Hong, W. Sun and R. Wang, *Angew. Chem., Int. Ed.*, 2021, **60**, 5331–5338.
- 46 Y. Liu, Z. He, W. Ma, G. Bao, Y. Li, C. Yu, J. Li, R. E, Z. Xu, R. Wang and W. Sun, *Org. Lett.*, 2022, **24**, 9248–9253.
- 47 G. Bao, P. Wang, X. Guo, Y. Li, Z. He, X. Song, R. E, T. Yu, J. Xie and W. Sun, *Org. Lett.*, 2023, **25**, 8338–8343.
- 48 Q. Zuo, Y. Li, X. Lai, G. Bao, L. Chen, Z. He, X. Song, R. E, P. Wang, Y. Shi, H. Luo, W. Sun and R. Wang, *Adv. Sci.*, 2024, **11**, 2308491.
- 49 C. Yu, R. E, Y. An, X. Guo, G. Bao, Y. Li, J. Xie and W. Sun, *Org. Lett.*, 2024, **26**, 4767–4772.
- 50 G. Zhu, G. Bao, Y. Li, W. Sun, J. Li, L. Hong and R. Wang, *Angew. Chem., Int. Ed.*, 2017, **56**, 5332–5335.
- 51 J. Yang, Z. Wang, Z. He, G. Li, L. Hong, W. Sun and R. Wang, *Angew. Chem., Int. Ed.*, 2020, **59**, 642–647.
- 52 W. Sun, L. Hong, C. Liu and R. Wang, *Org. Lett.*, 2010, **12**, 3914–3917.
- 53 W. Sun, X. Ma, L. Hong and R. Wang, *J. Org. Chem.*, 2011, **76**, 7826–7833.
- 54 G. Zhu, J. Yang, G. Bao, M. Zhang, J. Li, W. Sun, L. Hong and R. Wang, *Chem. Commun.*, 2016, **52**, 7882–7885.
- 55 H.-L. Cui, X. Feng, J. Peng, J. Lei, K. Jiang and Y.-C. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 5737–5740.
- 56 N. Kaplaneris, T. Rogge, R. Yin, H. Wang, G. Sirvinskaite and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **58**, 3476–3480.
- 57 P. G. Dougherty, A. Sahni and D. Pei, *Chem. Rev.*, 2019, **119**, 10241–10287.
- 58 Y. H. Lau, P. de Andrade, Y. Wu and D. R. Spring, *Chem. Soc. Rev.*, 2015, **44**, 91–102.
- 59 X. Li, S. Chen, W.-D. Zhang and H.-G. Hu, *Chem. Rev.*, 2020, **120**, 10079–10144.

