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Stereoselective alkyl *C*-glycosylation of glycosyl esters *via* anomeric C–O bond homolysis: efficient access to *C*-glycosyl amino acids and *C*-glycosyl peptides†

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C-Glycosyl peptides possess excellent metabolic stability and therapeutic properties and thus play critical roles in biological studies as well as drug discoveries. However, the limited accessibility of *C*-glycosyl amino acids has significantly hindered the broader research of their structural features and mode of action. Herein, for the first time we disclose a novel visible-light-driven radical conjugate addition of 1,4-dihydropyridine (DHP)-derived glycosyl esters with dehydroalanine derivatives, generating *C*-glycosyl amino acids and *C*-glycosyl peptides in good yields with excellent stereoselectivities. Redox-active glycosyl esters, as readily accessible and bench-stable radical precursors, could be easily converted to glycosyl radicals *via* anomeric C(sp^3)–O bond homolysis under mild conditions. Importantly, the generality and practicality of this transformation were fully demonstrated in >40 examples including 2-dexosugars, oligosaccharides, oligopeptides, and complex drug molecules. Given its mild reaction conditions, robust sugar scope, and high anomeric control and diastereoselectivity, the method presented herein could find widespread utility in the preparation of C(sp^3)-linked sugar-based peptidomimetics.

Introduction

Glycoproteins are widely present on the cell surface and play irreplaceable roles in a wide range of biological processes, such as immune response, signal transduction, and cell adhesion.[1,2] In nature, most of the glycopeptides/proteins bear *O*/*N*-glycosidic linkages, and the only known form of *C*-glycosidic linkage is found to be the Manα1-C2-Trp motif.[3] While glycopeptides/proteins hold promise as novel therapeutic and diagnostic tools, the labile *O*/*N*-glycosidic bonds are susceptible to hydrolysis and enzymatic cleavage potentially hindering their widespread utility in drug discovery.[4] As a result, it is of great interest to replace the hydrolysable *O*/*N*-glycosidic linkage with a more stable C-, S- or Se-linked analogue.[5,6] Given their remarkable resistance to hydrolysis and enzymatic degradation and innate drug-like properties, *C*-glycosides have emerged as a robust surrogate of the native *O*/*N*-glycoconjugate with enhanced pharmacokinetic properties.[7] Within this class, *C*-alkyl glycoamino acids and glycopeptides are becoming the focus of various studies of biological functions and disease models, as well as in the design of therapeutic peptides.[8] For example, peptidyl nucleoside antibiotics, including Nikkomycin Z **1**[9] and Amipurimycin **2**,[10] show excellent antimycotic activities. Furthermore, glycosylation as an effective synthetic strategy can significantly improve the bioavailability of endogenous peptides,[11] for instance, *C*-linked glycosyl decapeptide **3**,[12] [(αGal)Ala^7]dermorphin **4**,[13] and galactosylated-NAPamide **5** (ref. 14) (Fig. 1a).

In comparison to the well-developed *O*/*N*-glycosylation[2,3,15] or *S*/*Se*-glycosylation[16–19] of amino acids or peptides, *C*-glycosylation of amino acids or peptides is much more challenging and has lagged far behind.[20] Although outstanding progress has been recently made in the synthesis of C(sp^2)-linked glycoamino acids and glycopeptides,[21–23] the precise preparation of *C*-alkyl analogues remains a longstanding challenge.[20] Given the high-density functionalization of peptides and acidic nature of the α-position of amino acids, the conventional methods to prepare *C*-alkyl glycosides become frequently futile for *C*-alkyl glycoamino acids or glycopeptides.[24,25] Gagné and co-workers reported an indirect approach to *C*-alkyl glycoamino acids using

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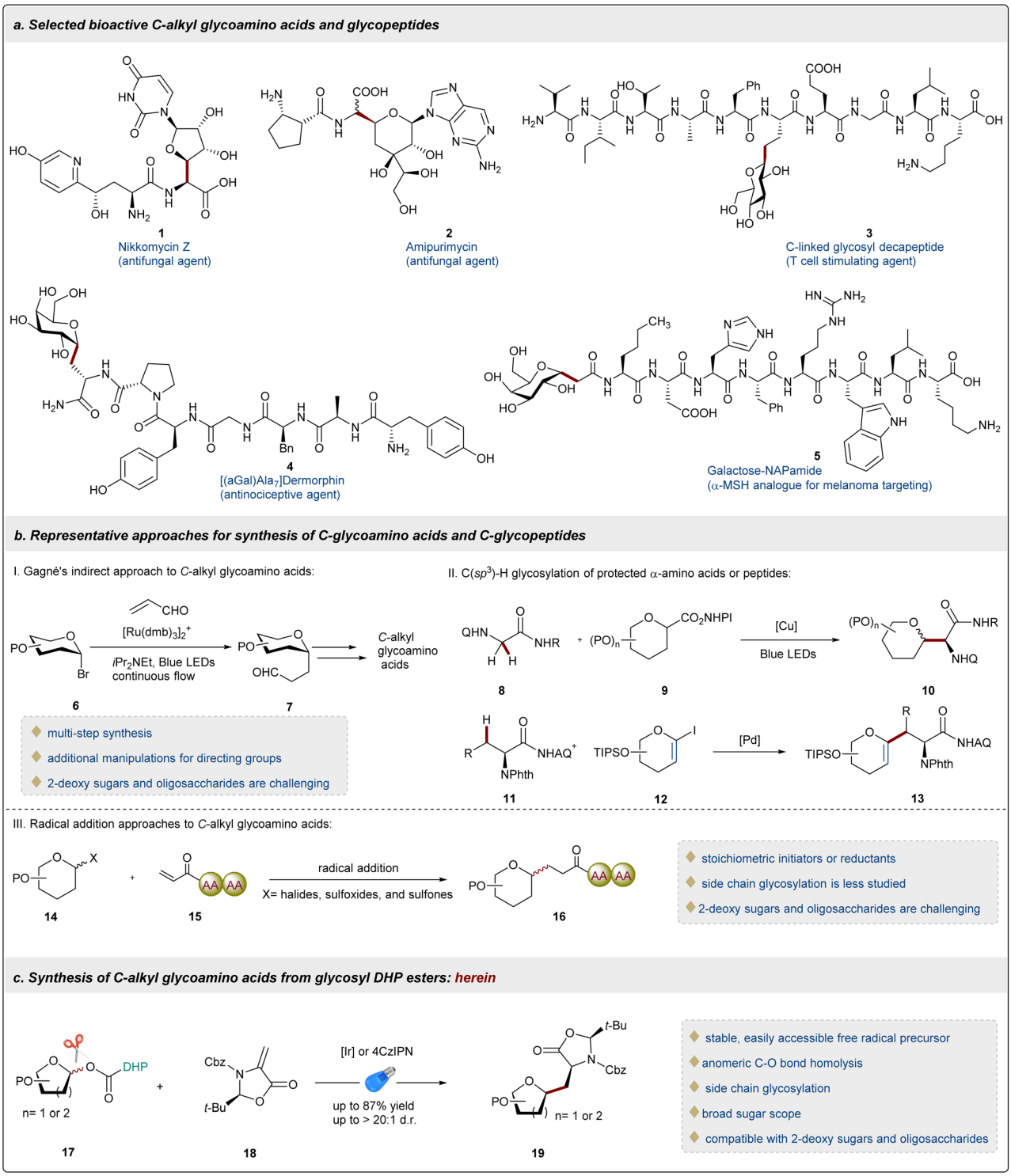


Fig. 1 Selected bioactive *C*-alkyl glycopeptides and their synthetic strategies.

C-glycosyl aldehydes **6** as key intermediates (Fig. 1b),[26] which promoted the research on the photoredox-mediated synthesis of *C*-glycoamino acids. Recently, significant efforts have been directed toward the preparation of *C*-glycosyl glycines **10**, with key contributions from Wang,[27] Wang,[28] Xu,[29] and Liang.[30] Of particular note, these elegant approaches are applicable to *C*-glycosyl alanines **13**. Notable advances have been achieved in Pd-catalyzed β-C(sp^3)–H glycosylation of amino acids and peptides with 1-iodoglycals **12**, as reported independently by Liu[31] and Ackermann[32] using triazolyldimethylmethyl triazole and aminoquinoline as directing groups, respectively (Fig. 1b). This powerful strategy may not be compatible with oligosaccharides due to the intrinsic instability of 1-iodoglycals **12**, and the further hydroboration/oxidation reaction of *C*-alkyl-

substituted glycals **13** obtaining sugars in a mixture of diastereomers.[31] Recently, Niu[33] and Koh[34,35] have developed novel methods for the synthesis of *C*-alkyl glycopeptides through the Giese reaction of glycosyl radicals to peptides **15** on the N-terminus, utilizing novel glycosyl sulfoxides, sulfones and common glycosyl chlorides as glycosyl precursors **14**, respectively. However, the use of stoichiometric amounts of radical initiators or reductants and the synthesis of 2-deoxy saccharides and oligosaccharides remain crucial issues. Therefore, a general and concise method to attain alkyl *C*-amino acids or glycopeptides from readily available starting materials under mild conditions is still a formidable challenge. Radical glycosylation has become a highly active area of research, owing to its excellent chemoselectivity and good anomeric control.[5,36] Various unnatural glycosyl derivatives are extensively explored as glycosyl radical precursors, including glycosyl halides,[37] xanthates,[38] sulfones,[39] glycosyl-based DHPs,[40,41] glycosyl carboxylic acids,[42,43] redox-active esters,[27,44] and anomeric nucleophiles.[45,46] It is worth noting that multi-step synthesis, inherent instability, special reaction conditions and narrow sugar scope remain as several of the key obstacles reducing the practical value of these unnatural glycosyl derivatives. Undoubtedly, the ideal generation of glycosyl radicals is the direct homolytic cleavage of anomeric C(sp^3)–OH bonds of native carbohydrates. However, anomeric C(sp^3)–O bond homolysis poses a significant challenge because the BDE of the anomeric C(sp^3)–OH (~99 kcal mol^{-1} for furanose and ~101 kcal mol^{-1} for pyranose) is even higher than that of an alcohol (~96 kcal mol^{-1}).[47] In general, various redox auxiliaries that include xanthates,[48,49] phosphites,[50] oxalates,[51,52] carboxylates,[53,54] and ethers[55] have been employed to transform hydroxyl groups into activating groups to generate *C*-radical intermediates under electron transfer or light irradiation. Unfortunately, most of the above redox auxiliaries are not suitable for carbohydrate substrates, possibly due to the instability of the corresponding glycosyl esters at the anomeric position.[33,45,46,56] Recently, dihydropyridine (DHP) as a versatile activating group has been successively applied in various radical glycosylation reactions *via* C–C bond cleavage at the C4 or C5 position of sugars.[40,41,57] To homolytically cleave challenging anomeric C(sp^3)–O bonds, DHPs were used as redox auxiliaries to obtain stable glycosyl esters and then *C*-aryl and *C*-acyl glycosides *via* sequential C–C and C–O bond cleavage under nickel/photoredox dual catalysis were successfully achieved.[53,54] In comparison to most of the glycosyl radical precursors, the redox glycosyl DHP esters are very impressive because of their easy accessibility, stability, and compatibility with 2-deoxysugars. However, studies on C(sp^3)-glycosylation of DHP-derived glycosyl esters and the reactivity and compatibility of DHP groups in complex oligosaccharides remain unexplored.

In order to provide a meaningful solution to these fundamental issues and in line with our interest on the precise preparation of carbohydrates and modification of complex peptides,[36,58] we herein disclose the first example of photoredox-catalyzed radical conjugated addition of DHP-derived glycosyl esters **17** with highly reactive dehydroalanine (Dha) **18** for the synthesis of C(sp^3)-glycosyl amino acids and peptides *via* anomeric C–O bond homolysis (Fig. 1c). This novel glycosylation method advances the development of catalytic methods applicable to complex and challenging carbohydrate substrates and complements the current state-of-the art methodologies.

Results and discussion

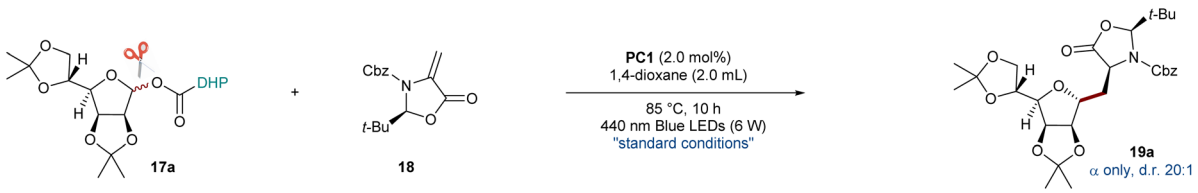
Reaction development

The visible-light-driven radical conjugate addition (RAC) of Dhas is a powerful tool to access nonproteinogenic amino acids, peptides, and proteins.[59] In particular, diastereoselective radical addition to chiral Karady–Beckwith Dhas is becoming an attractive method for the precise preparation of α-amino acid derivatives.[60] Based on the high diastereocontrol, the model reaction of *O*-mannofuranosyl ester **17a** (1.5 equiv) with Karady–Beckwith Dha **18** (1.0 equiv) to afford *C*-alkyl glycoamino acid **19a** was used to optimize reaction conditions (Table 1). To our delight, the desired *C*-alkyl glycoamino acid **19a** was isolated in 69% yield with excellent anomeric control (only α isomer) and diastereoselectivity around the oxazolidinone auxiliary (d.r.>20 : 1) after 10 h of irradiation with blue light emitting diodes (LEDs, 6 W) in the presence of a common photocatalyst Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 **PC1** in 1,4-dioxane (entry 1). When MeCN or THF was used as an alternative solvent, the isolated yields were reduced to 52% and 33%, respectively (entries 2–3). Further modifications of the reaction conditions, such as the modified ratio of **17a : 18** (entry 4), had only negative effects on the reaction yields. Similarly, reduced or elevated temperatures reduced the yield of **19a** (entry 5). We hypothesize that lower temperature might not provide sufficient driving force for the sequential C–C and C–O bond cleavage of glycosyl DHP esters (confirmed by the recovery of **17a**), whereas higher temperatures result in the oxidation of the glycosyl donor to **19a**[ox] bearing a pyridine motif. We further probed the reaction conditions with different photocatalysts under blue LED irradiation (entries 6–8). While no reaction was observed using Ir(ppy)$_3$ (**PC2**) and Ru(bpy)$_3$$Cl_2$ (**PC3**), about 7% of **19a** was isolated when inexpensive 4CzIPN (**PC4**) was employed. To our delight, simply changing the solvent to MeCN led to a 64% yield of the desired product using **PC4** as the photocatalyst (entry 9). Subsequently, increasing the amount of **PC4** and extending the reaction time further improved the yields to 70% and 82%, respectively (entries 10 and 11). Extended exposure of the reaction to light radiation and changing the concentration to 0.67 M led to further improvement of the isolated yield of **19a** to 85% (entry 12). Using the same strategy, the desired glycosyl amino acid **19a** was obtained in an 80% yield using **PC1** as a photocatalyst after 10 h of irradiation (entry 13). Notably, the radical addition reaction can also be conducted in a 3 : 1 mixture of MeCN and H_2O with 78% isolated yield of **19a** (for details, see the ESI†). Finally, control experiments demonstrated the necessity of a photocatalyst and visible light for the alkyl *C*-glycosylation reaction to take place (entry 14).

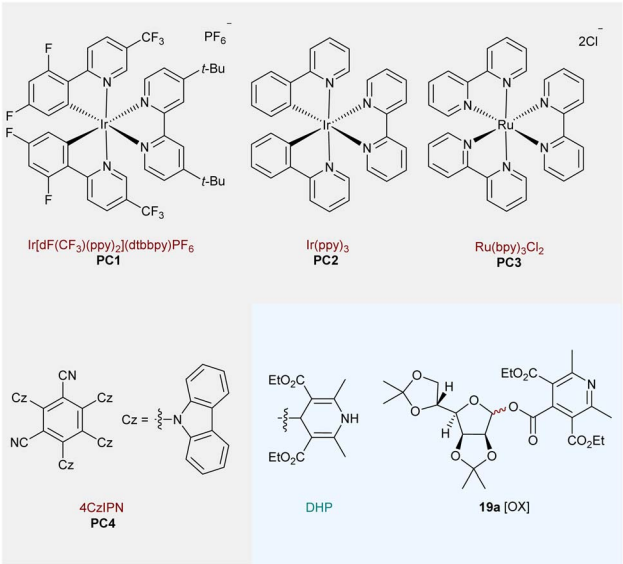
Scope of monosaccharides

With the optimal reaction conditions established, we next focused on testing the scope of DHP-derived glycosyl esters. As shown in Fig. 2, a broad range of structurally diverse glycosyl

Table 1 Optimization of the reaction conditions[a]



Entry	Variation from standard conditions	Yield
1	None	69
2	MeCN instead of 1,4-dioxane	52
3	THF instead of 1,4-dioxane	33
4	A ratio of **17a** : **18** (1 : 15) was used	36
5	60 °C, 70 °C or 100 °C instead of 85 °C	35–63
6	**PC2** instead of **PC1**	n.d.
7	**PC3** instead of **PC1**	n.d.
8	**PC4** instead of **PC1**	7
9	**PC4** and MeCN were used	64
10	**PC4** and MeCN were used	70[b]
11	**PC4**, MeCN and 20 h were used	82[b]
12	**PC4**, MeCN and 20 h were used	85[b,c]
13	3.0 mL of 1,4-dioxane instead of 2.0 mL	80
14	No PC or light	0



[a] Standard reaction conditions: **17a** (0.30 mmol), **18** (0.20 mmol), Ir[dF(CF$_3$)(ppy)$_2$](dtbbpy)PF$_6$ **PC1** (2.0 mol%), 1,4-dioxane (3.0 mL), 440 nm blue LEDs (6 W), 85 °C, 10 h, N_2, and isolated yields. [b] **PC4** (2.5 mol%) was used. [c] MeCN (3.0 mL) was used; d.r. was determined by ^{1}H NMR analysis of crude reaction mixtures.

DHP esters derived from various monosaccharides and oligosaccharides underwent the radical addition smoothly and produced the corresponding alkyl *C*-glycosylamino acids **19b–19w** in moderate to good yields and excellent diastereoselectivity around the oxazolidinone auxiliary. D-Ribofuranoses with various common protecting groups, such as benzoyl (**19b**), acetyl (**19c**), silyl (**19d**), and benzyl (**19e** and **19f**), readily underwent the alkyl *C*-glycosylation, affording **19b–19f** in 57–87% isolated yields. Other glycosyl NHP esters derived from common furanoses, including D-xylofuranose (**19g**), D-arabinofuranose (**19h**), and 2-deoxy-D-ribofuranose (**19i**), produced the corresponding radical addition products (**19g–19i**) in good yields. The opposite anomeric stereoselectivity between D-arabinofuranose **19h** and 2-deoxy-D-ribofuranose **19i** reflects a dominating effect of the C2 substituent group on the stereochemical outcome because of the steric hindrance.[34,54] These results stand in contrast to the reported methods on radical addition of glycosyl radicals,[33–35] and 2-deoxy-D-ribofuranosyl NHP esters show good reactivity and selectivity under the standard conditions due to their excellent stability and generation of glycosyl radicals under mild photoredox conditions. Subsequently, a variety of common pyranoses, such as D-mannopyranose, D-mannosamine, D-galactopyranose, L-rhamnopyranose, and 2-deoxy-D-glucopyranose, were readily transformed into alkyl *C*-glycoamino acids **19j–19r** with good to excellent stereoselectivities (Fig. 2b). The suboptimal yields of fully protected monosaccharides with disarmed protected groups, such as **19l**, **19m** and **19q**, could be attributed to the low nucleophilicity of the corresponding glycosyl radicals. Importantly, 2-deoxy-D-glucopyranose, proved to be a competent substrate for the radical addition with high α-selectivity despite the lack of the controlling C2 substituent. The stereochemistry of all cross-coupling products was further confirmed by 2D COSY and HSQC analyses (see the ESI† for details). In general, the stereochemical outcome of desired products could be explained by a combination of the anomeric and steric effects.[61,62]

Scope of oligosaccharides

To further expand the scope of the alkyl *C*-glycosylation reaction, we then investigated the reactions of DHP esters derived from complex oligosaccharides (Fig. 2c). As mentioned above, most of the current methods for the formation of alkyl *C*-glycosides are limited to the reactions with monosaccharides, and the direct stereoselective *C*-glycosylation with free radical

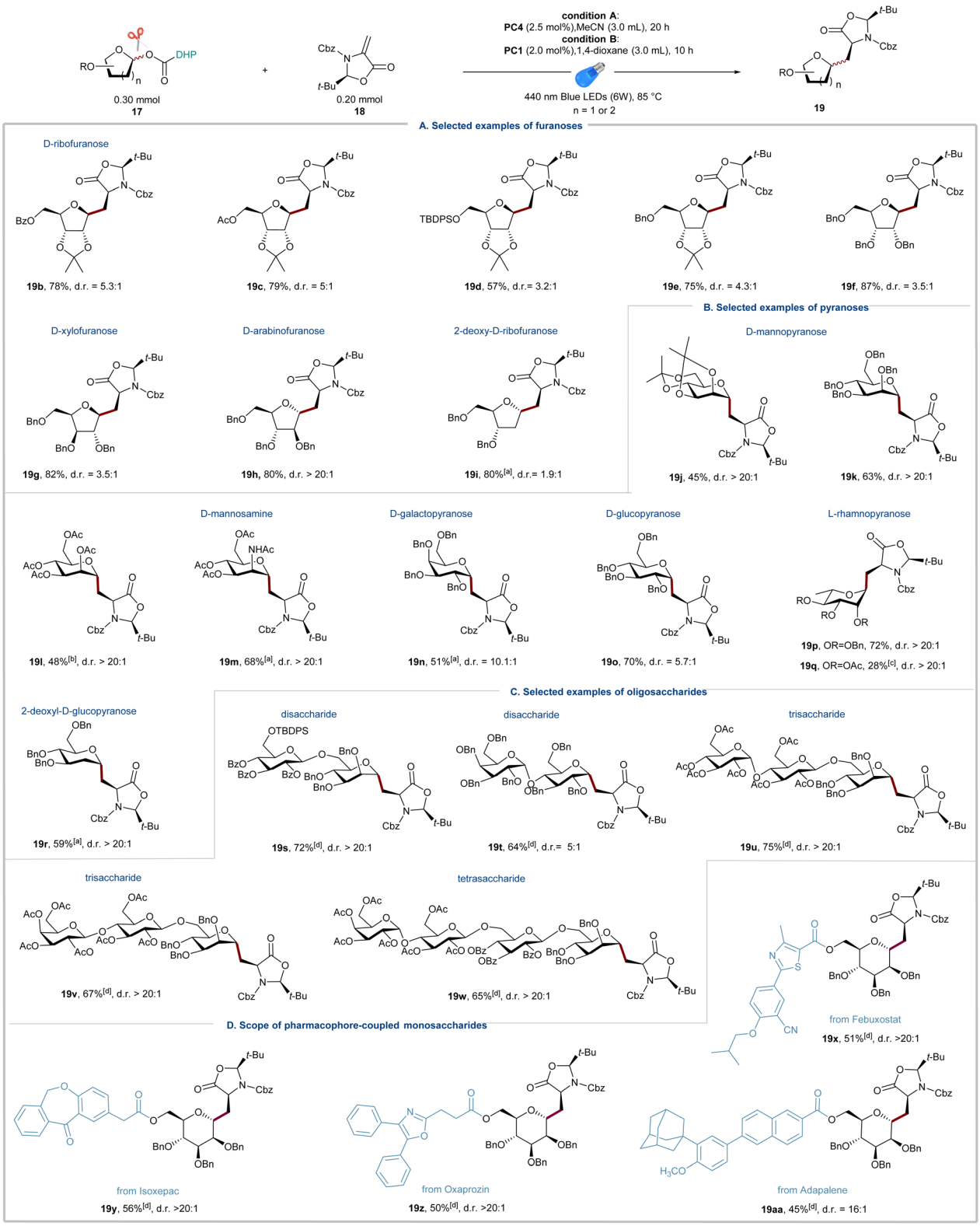


Fig. 2 Scope of *C*-alkyl glycosylation with DHP-derived glycosyl esters. (a) Scope of furanoses. (b) Scope of pyranoses. (c) Scope of oligosaccharides. (d) Scope of pharmacophore-coupled monosaccharides. **19b–19f**, **19h**, **19o**, and **19p** used conditions A; **19g**, **19i–19n**, and **19q–19aa** used conditions B; [a]20 h was used; [b]24 h was used; [c]**17** (0.15 mmol), **18** (0.10 mmol), 1,4-dioxane (1.5 mL), and 20 h was used; [d]**17** (0.15 mmol), **18** (0.10 mmol), 1,4-dioxane (3.0 mL), and 24 h. d.r. was determined by ^{1}H NMR analysis of crude reaction mixtures.

precursors of oligosaccharides and Michael acceptors is rare. These limitations could be attributed to the incompatibility of free radical precursors with oligosaccharide synthesis and the lack of effective methods to generate and stabilize oligosaccharide radicals. We found that oligosaccharide DHP esters could be easily prepared on a gram scale by simple coupling of DHP acids and C1-hemiacetals (24–53%) and remain bench stable for several months. To our delight, disaccharide DHP esters could be engaged in cross-coupling reactions without any significant modifications of the standard conditions, allowing for the formation of alkyl *C*-disaccharides **19s** and **19t** in 72% and 64% isolated yields with good to excellent stereoselectivity. The scope of the radical glycosylation could be further extended to more complex oligosaccharides and the radical *C*-glycosylation reactions forming alkyl *C*-trisaccharides (**19u** and **19v**) and a tetrasaccharide (**19w**) produced the corresponding products in yields exceeding 65% with d.r. >20 : 1.

Scope of pharmacophore-coupled monosaccharides

Besides the well-known antibody–drug conjugates (ADCs), peptide–drug conjugates (PDCs) are gaining recognition as a novel modality for targeted drug delivery with improved efficacy and reduced side effects for cancer therapy.[63] The linker between the peptide and drug plays a critical role in the circulation time of the conjugate and release of the drug for full activity at the target site. Therefore, the research to develop effective linkers for the design of PDCs is important and promising. Herein, we were intrigued by the viability of the visible-light driven radical *C*-glycosylation of pharmacophore-coupled glycosyl DHP esters and substrate **18** (Fig. 2d). To our delight, the bioconjugation reactions using sugars as linkers proved reliable and a series of glycosyl DHP esters derived from D-ribofuranose and D-mannopyranose could be coupled with commercial drugs, including Febuxostat, Isoxepac, Oxaprozin, and Adapalene, affording the corresponding products **19x–19aa** in 45–56% yield. The above results revealed that our method exhibits remarkable potential application in rapid assembly of glycopeptide drug molecules.

Scope of Dha amino acids and peptides

Encouraged by the above results, we next investigated the radical addition of *O*-mannofuranosyl esters **17a** to various amino acids and Dha peptides (Fig. 3). We hypothesized that the efficiency of radical addition will be correlated with different protecting groups located on the nitrogen atom with the electron-withdrawing group promoting the addition of a nucleophilic radical. In addition to chiral Dha **18**, bis-*N*-Boc-protected, bis-*N*-Ac-protected, Boc-*N*-methyl protected and bis-*N*-phthalimide protected Dha were all effectively transformed into the desired product in 49–86% isolated yields; however, trace product was detected when *N*-Boc-protected or *N*-Ac-protected Dha was used. This observation is consistent with the prior studies highlighting the importance of the torsional angle [ω(C=C–N–C)] between the plane of the olefin and the

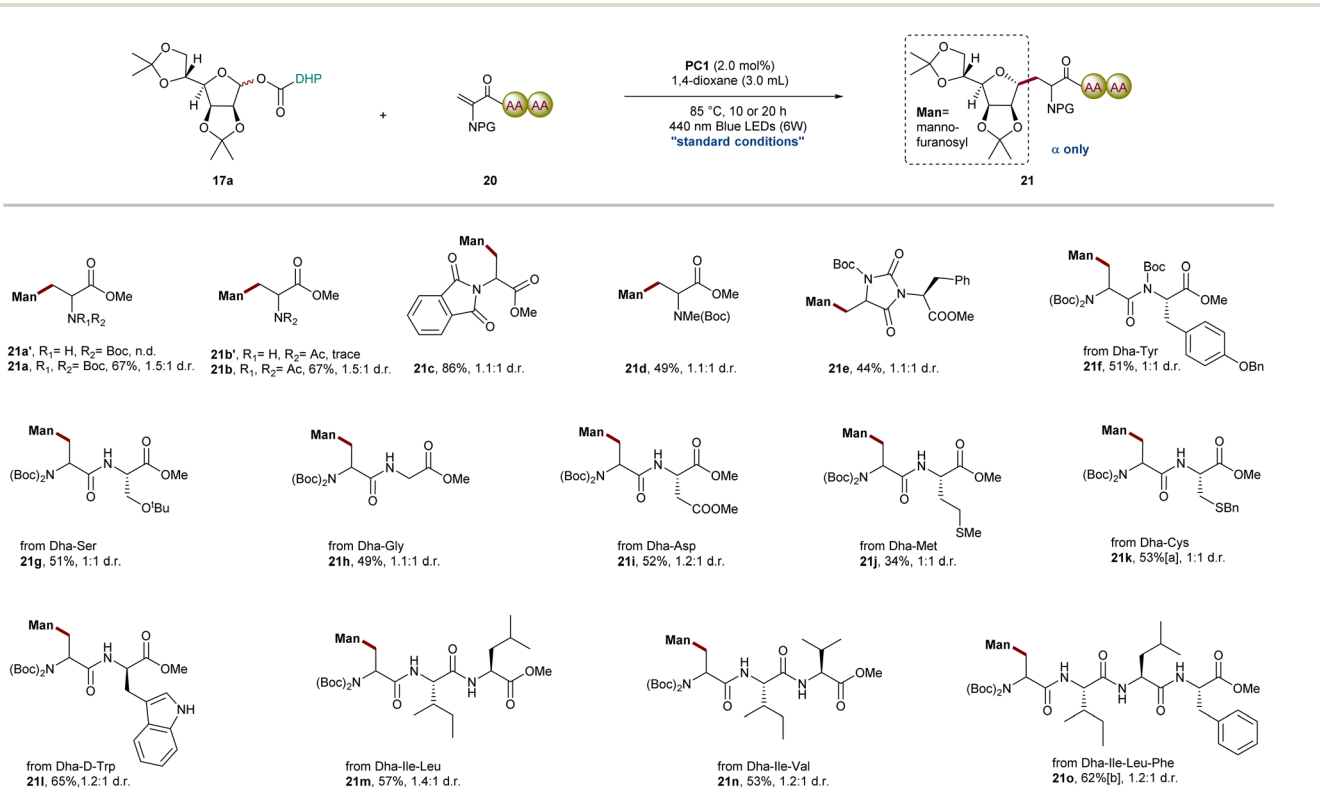


Fig. 3 Scope of Dha amino acids and peptides. General reaction conditions: **17a** (0.30 mmol), **20** (0.20 mmol), **PC1** (2.0 mol%), 1,4-dioxane (3.0 mL), blue LEDs (6 W), 85 °C, 10 h, N_2, and isolated yields; [a]**20h**; [b]**20o** (0.10 mmol) and 24 h. d.r. was determined by ^{1}H NMR analysis of crude reaction mixture.

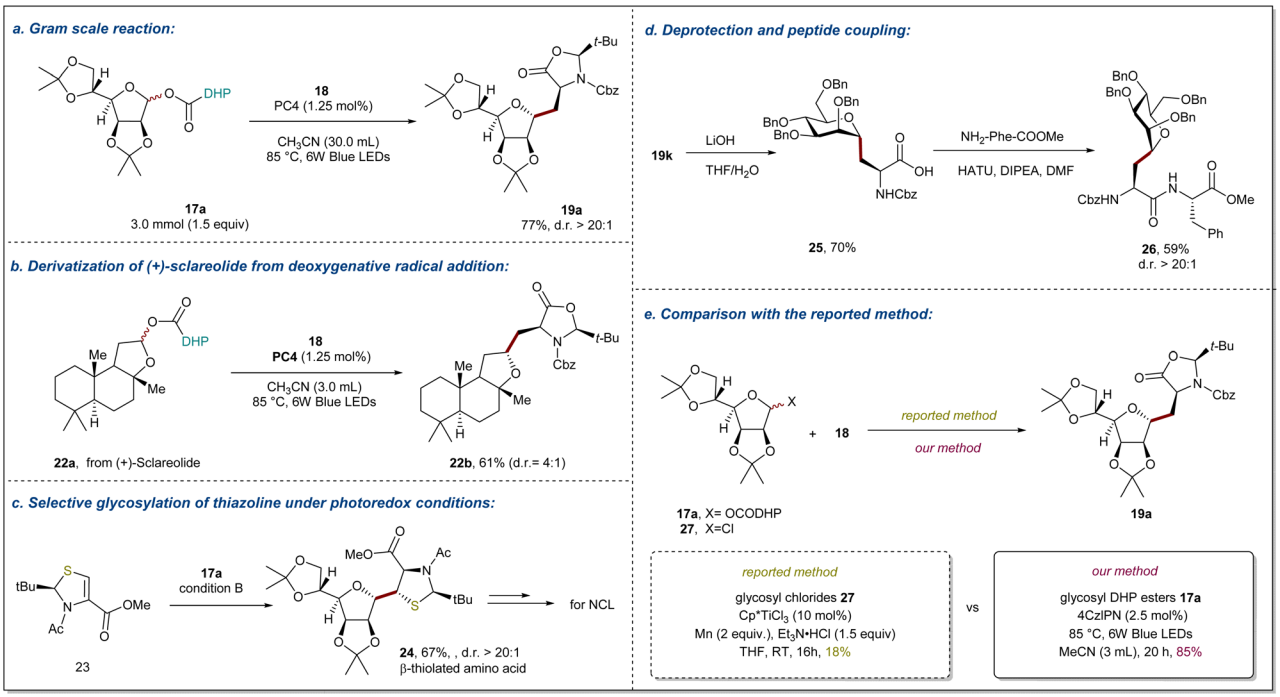


Fig. 4 Synthetic applications and downstream transformations. (a) Gram scale reaction of **17a**. (b) Derivatization of (+)-sclareolide. (c) Radical glycosylation of thiazolines for preparing β-thiolated amino acids. (d) Deprotection of glycosyl amino acids and preparation of glycopeptides *via* a peptide coupling reaction. (e) Comparison of glycosyl chlorides and glycosyl DHP esters. Reaction details are shown in ESI notes 7.†

carbamate that might contribute to the disparate reactivity.[64] The introduction of two bulky N-protected groups or a cyclic structure weakens the conjugation effect of the nitrogen lone pair into the adjoining π system and significantly decreases the electronic density of the terminus of the olefin to improve the efficiency of radical addition. Capitalizing on these results, we then studied a series of Dha-containing dipeptides and tripeptides, such as cyclic Dha–Phe **20e**, Dha–Tyr **20f**, Dha–Ser **20g**, Dha–Gly **20h**, Dha–Asp **20i**, Dha–Met **20j**, Dha–Cys **20k**, Dha–D-Trp **20l**, Dha–Ile-Leu **20m**, and Dha–Ile-Val **20n**, all of which smoothly deliver the corresponding mannofuranosyl peptides in acceptable yields (34–65%) with excellent anomeric selectivity and chemoselectivity. Importantly, this mild radical *C*-glycosylation between oligopeptides such as tetrapeptide(Dha–IIe-Leu–Phe) and sugar DHP ester was also conducted in 62% yield, which further highlighted the generality of this method in late-stage glycodiversification of complex oligopeptides.[19,33] As we all know, radical additions to Dha derivatives often result in mixtures of diastereomers, presenting a significant challenge in peptide modification. In contrast to the highly stereoselective outcomes observed with chiral Karady-Beckwith Dha **18**, peptides containing Dha exhibit moderate diastereoselectivity due to the limited steric hindrance and electronic effects. However, it is worth emphasizing that recent studies have demonstrated the potential of catalytic systems composed of transition metals and chiral ligands to achieve stereoselective radical additions to peptides containing Dha.[65]

Application

The practicality of this method was demonstrated by a gram-scale synthesis of **19a** (77% yield in a 3.0 mmol scale reaction) as shown in Fig. 4a. One of the objectives of this study is to provide an efficient method for the preparation of alkyl *C*-glycosyl amino acids/peptides and establish a general method for the late-stage functionalization of complex molecules. To demonstrate the generality of deoxygenative radical addition, we prepared DHP ester **22a** derived from natural product (+)-sclareolide and engaged it in visible-light photoredox-catalyzed radical addition to afford **22b** in 61% yield with 4 : 1 d.r (Fig. 4b). It is well known that β-thiolated amino acid derivatives not only play important roles in regulating the function and conformation of proteins, but also serve as important units for peptide design and bioconjugation. However, the difficulty in obtaining enantiopure β-thiolated amino acids with diverse structures is a major limitation to their widespread application. Recently, the Wang group developed an interesting photoredox-catalyzed Giese reaction of chiral thiazolidines to access enantiopure β-thiolated amino acids.[66] Inspired by this, we wondered whether our method could be applied to prepare β-thiolated amino acids containing sugar units, which are difficult to obtain using conventional methods. Gratifyingly, new chiral thiazolidines **23** could be smoothly transformed into β-thiolated amino acids containing sugar units **24** (67%) with excellent diastereoselectivity (Fig. 4c). As illustrated in Fig. 4d, the deprotection of the cyclic group on compound **19k** with LiOH provided glycosyl amino acids **25** in

70% yield, which can be easily converted into side chain *C*-glycosylated dipeptides **26** in 59% with >20 : 1 d.r. under standard peptide coupling conditions. Finally, to further illustrate the effective complementarity of our method to existing methods, the model reaction of glycosyl chlorides **27** using Ti-catalyzed conditions was conducted, providing the desired product in only 18% isolated yield (Fig. 4e).[34,35]

Mechanistic studies

To gain more insights into the reaction mechanism, several control experiments were conducted as outlined in Fig. 5. First, the model reactions were carried out in the presence of radical scavengers TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) and DPE (1,1-diphenylethylene), which reduced the yield of **19a** to <5% and 42%, respectively (Fig. 5a). In the radical trapping experiments with glycosyl radicals, Tempol glycosides were not detected due to their further decomposition under blue irradiation.[67] Gratefully, the radical addition products of glycosyl radicals with DPE **28** and alkoxycarbonyl radicals with DPE **29** are detected by HRMS. Thus, these results suggest that the reaction path of this process is a radical pathway. Next, deuterium labeling experiments to probe the origin of the hydrogen source were performed (Fig. 5b). The model reaction with d_3-MeCN as solvent was found to give product **19a** in 67% yield with no deuterium incorporation, suggesting that any hydrogen atom transfer with solvent MeCN is less likely. Additionally, in a mixture of MeCN and D_2O, *d*-**19a** was obtained in 82% yield with >99% deuterium incorporated at the α-site of the amino acid precursor, which indicates that a carbanion might be involved in the transformation. Furthermore, a light on-off experiment was carried out with **17a** and **18** (Fig. 5c). We found that **19a** was only obtained during the periods of constant irradiation.

These results indicate that the reaction underwent a catalytic radical process rather than a radical chain pathway. Taken together, these data support the proposal that the NH group of DHP ester serves as a hydrogen atom source. Additionally, a pair of NHP esters **30a** and **30b** that differ only by the O atom *vs.* a CH_2 group were prepared and subjected to the standard conditions (Fig. 5d). While **30a** was smoothly converted to **31a** in 48% isolated yield, the all-carbon analog **30b** failed to deliver the Giese addition product **31b** and was completely consumed due to decomposition. These findings demonstrate that α-oxygen atoms are significant to facilitate the C–O bond homolysis, and the resulting carbon radicals are stabilized by the adjacent ion pair of oxygen atoms.[68] These observations were further supported by the DFT calculations for **30a** and **30b** summarized in Fig. 6. To reduce the computational cost and complexity, we simplify the process of producing free radicals by homolysis of C–O bonds without PC. While the homolytic cleavage of the DHP esters results in cyclohexane and tetrahydropyran radicals **33** of almost identical energies, the fragmentation of **33** is strongly controlled by the presence of a heteroatom which facilitates the expulsion of CO_2 by 7.0 kcal mol^{-1}. The resultant radicals show differential NBO atomic

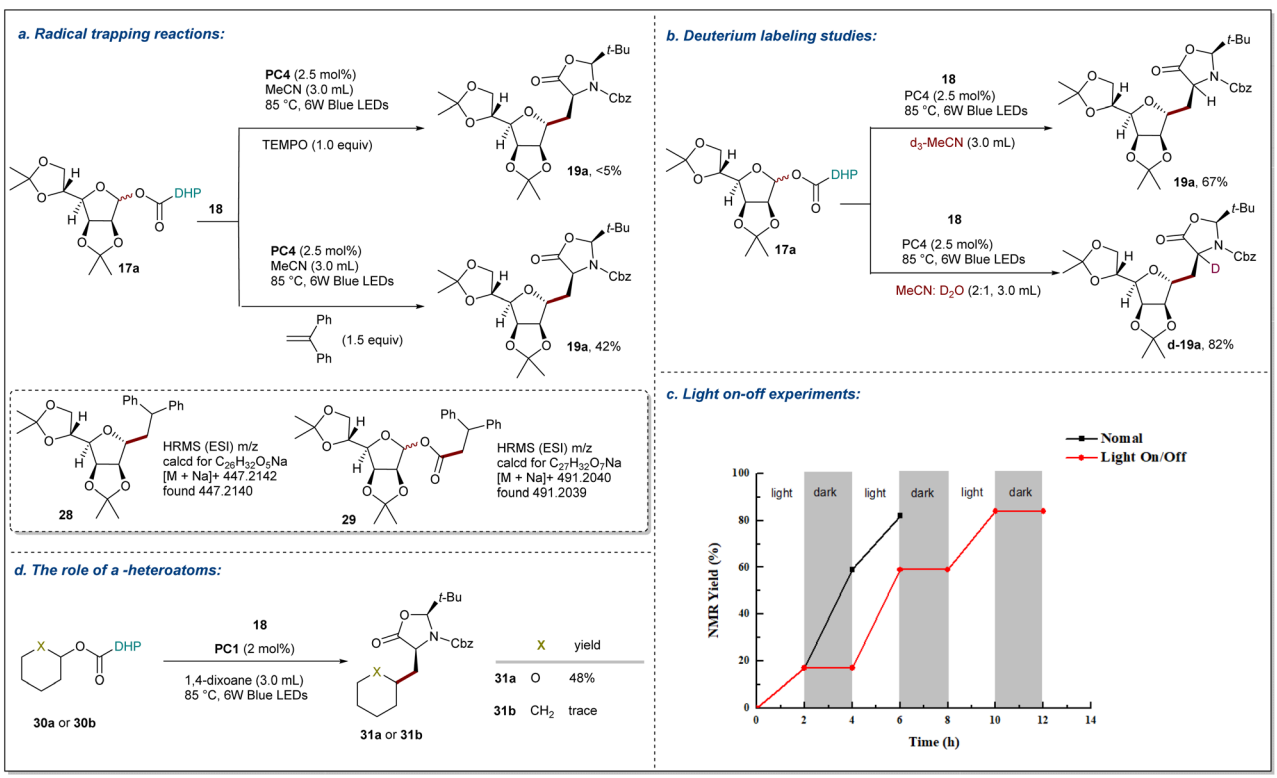


Fig. 5 Mechanistic studies. (a) Radical-trapping experiment. (b) Deuterium labeling studies. (c) Light on-off experiments. (d) Control experiment supporting the essential role of α-heteroatoms. Reaction details are shown in the ESI notes 8 Mechanistic studies.†

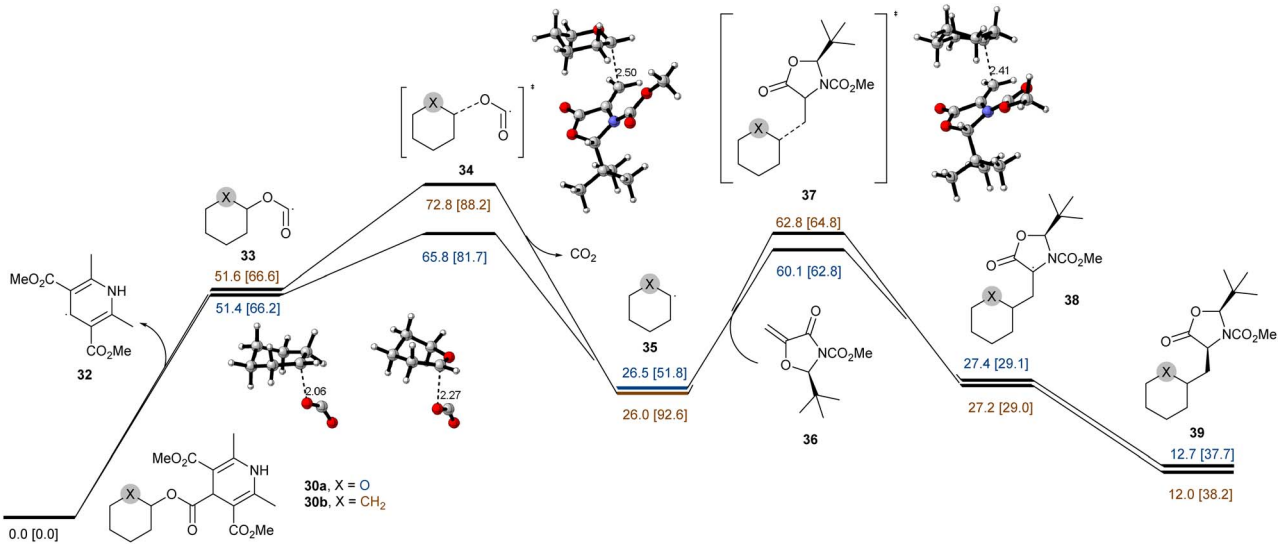


Fig. 6 Computational studies of the mechanistic aspects of the reaction. Computational analysis of addition reactions for cyclohexane (blue) and tetrahydropyran (yellow) DHP esters calculated at the ωB97XD/6-31+G(d,p)-SDM(dichloromethane)//ωB97XD/6-311+G(d,p)-SDM(dichloromethane) levels of theory. Gibbs free energy (298 K, 1 atm) and enthalpy (in brackets) are reported in kcal mol^{-1}.

charges (0.132 and −0.100 for O and CH_2 substituents, respectively) but comparable spin distributions (0.850 and 0.950, respectively), which translate into the fate of the subsequent reactions with a Michael acceptor. The conjugate addition with **36** shows ∼2.7 kcal mol^{-1} acceleration for the heteroatom-stabilized radicals, whereas the following steps yield structures **38** and **39** with comparable energies slightly favoring the carbocycle over the oxygen-substituted derivative. We attribute the overall efficiency of the Giese addition to the efficiency of the initial radial generation, which can then be engaged in a productive reaction with a competent acceptor.

Based on the above-mentioned preliminary and literature reports,[54] the following mechanism for this radical reaction mechanism is proposed (Fig. 7). Under blue LED irradiation, the photocatalyst [PC] is excited to its triple state [PC]*, which promotes the SET oxidation of **A** to **B** followed by deprotonation and radical fragmentation to generate the corresponding alkoxycarbonyl radical **C** and Hantzsch pyridine **D.** The subsequent decarboxylation is driven by the ejection of CO_2 and generates the active glycosyl radical **E.** The addition of **E** to chiral Dha gives rise to the radical intermediate **F.** Finally, the resulting radical **F** undergoes SET with the reduced

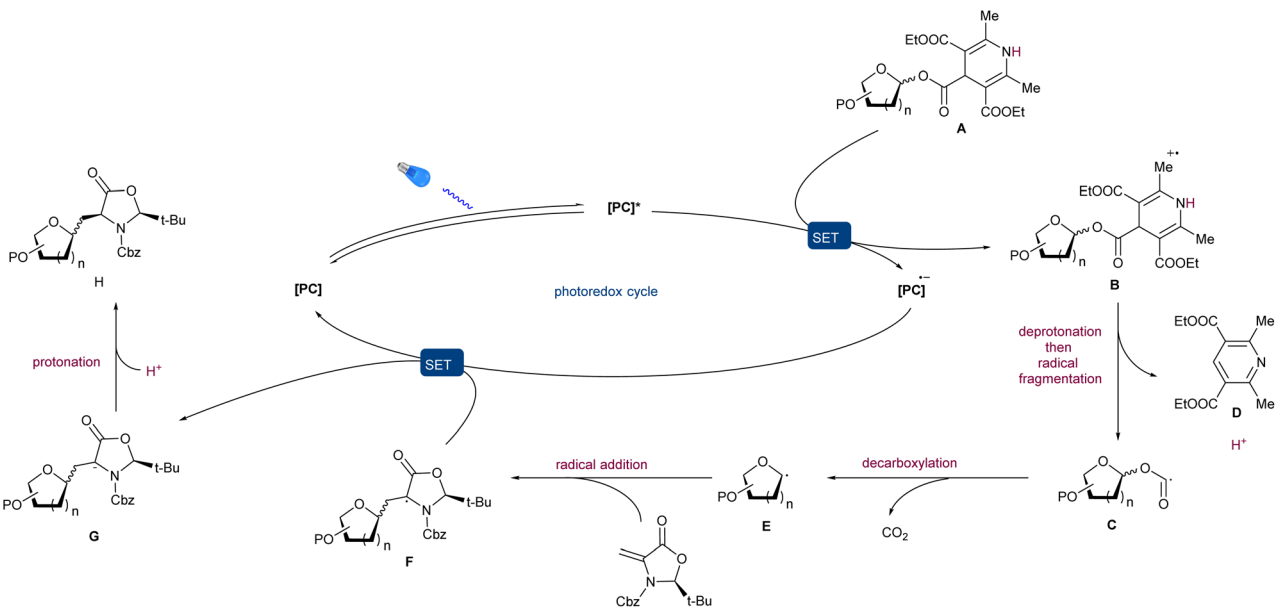


Fig. 7 Proposed reaction mechanism for alkyl *C*-glycosylation *via* C–O bond homolysis.

photocatalyst $[PC]^{\bullet -}$ to provide, after protonation, the desired product **H** and close the catalytic cycle.

Conclusions

In summary, we have developed the first visible-light photoredox catalyzed C(sp^3)-glycosylation of redox-active glycosyl DHP esters with dehydroalanine (Dha) derivatives *via* anomeric C–O bond homolysis for the concise synthesis of alkyl *C*-glycoamino acids and *C*-glycosyl peptides. By taking advantage of mild photocatalytic conditions, the novel alkyl *C*-glycosylation is compatible with a wide variety of carbohydrate substrates and Dha peptides, providing various *C*-glycoamino acids and *C*-glycopeptides in good yields with excellent anomeric control and good diastereoselectivity. Importantly, readily accessible and bench-stable glycosyl DHP esters smoothly participate in the radical glycosylation, allowing for efficient access to *C*-glycosyl alanine moieties involving challenging sugars, such as 2-deoxysugars and oligosaccharides. Therefore, this alkyl *C*-glycosylation of glycosyl esters *via* anomeric C–O bond homolysis not only promotes the development of radical glycosylation, but also provides a powerful tool for glycopeptide therapeutic discoveries. Furthermore, the integration of our method with the emerging technologies in peptide and protein chemistry, such as encoded libraries and direct bioconjugation, is currently ongoing in our laboratory.

Data availability

The authors declare that the data supporting the findings of this study, including experimental details and compound characterization, are available within the article and its ESI† file. All data are available from the corresponding author upon request.

Author contributions

F. Z. conceived and directed the project. A. C., S. Z., Y. H., and Z. Z. performed the experiments and analyzed the data. M. W. carried out computational studies. F. Z. and B. Y. wrote the manuscript with input from all the authors. All authors have read and approved the final version of the manuscript.

Conflicts of interest

A patent application by S. Z., L.-G. X., F. Z., A. C., and Y. H. detailing part of this research was filed through the Patent Office of the People's Republic of China (November 2022). S. Z., L.-G. X., F. Z., A. C., and Y. H. declare no other competing interests. The other authors declare no competing interests.

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