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Direct Formation of Amide-Linked *C*-Glycosyl Amino Acids and Peptides via Photoredox/Nickel Dual Catalysis

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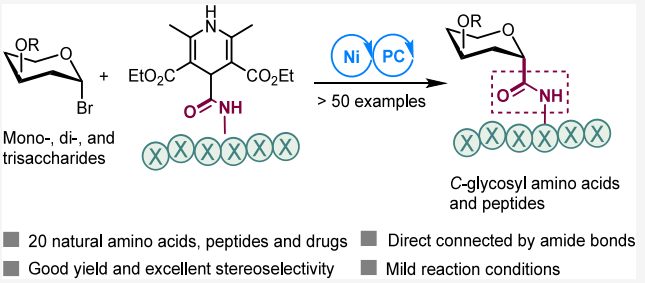
ABSTRACT: Glycoproteins account for numerous biological processes including those associated with diseases and infections. The advancement of glycopeptides has emerged as a promising strategy for unraveling biological pathways and discovering novel medicines. In this arena, a key challenge arises from the absence of efficient synthetic strategies to access glycopeptides and glycoproteins. Here, we present a highly concise approach to bridging saccharides with amino acids and peptides through an amide linkage. Our amide-linked *C*-glycosyl amino acids and peptides are synthesized through cooperative Ni-catalyzed and photoredox processes. The catalytic process generates a glycosyl radical and an amide carbonyl radical, which subsequently combine to yield the *C*-glycosyl products. The saccharide reaction partners encompass mono-, di-, and trisaccharides. All 20 natural amino acids, peptides, and their derivatives can efficiently undergo glycosylations with yields ranging from acceptable to high, demonstrating excellent stereoselectivities. As a substantial expansion of applications, we have shown that simple *C*-glycosyl amino acids can function as versatile building units for constructing *C*-glycopeptides with intricate spatial complexities.



INTRODUCTION

Protein glycosylation, occurring in approximately 50% of human proteins,[1] significantly influences protein properties and functions, including intercellular communication, as well as alterations in protein thermal stability and folding.[2−4] In molecular biology and medicine, the increasing demand for glycopeptides and glycoproteins has spurred efforts to develop efficient methods for linking sugar units and peptides.[5,6] Naturally occurring glycopeptides and glycoproteins possess labile *O*- or *N*-glycosidic bonds, presenting a significant challenge in research.[7−10] One solution involves replacing these unstable bonds with robust C−C bonds, creating *C*-glycoside analogs that remain functional under biological conditions. This strategic substitution has led to the development of numerous drug-related *C*-glycopeptides (Figure 1A).[11−14]

Current methods for synthesizing *C*-glycopeptides involve the implementation of Giese-type reactions,[15−19] where sugar radicals are trapped by electron-deficient alkenes, forming *C*-glycopeptides with saturated sp^3 carbon linkages. The Yu group disclosed Ni-catalyzed reductive hydroglycosylation to prepare vinyl *C*-glycosyl amino acids and peptides.[20] The Koh group pioneered a multicomponent synthesis of *C*-glycopeptides with keto-glycosidic bonds using a nickel catalyst.[21] As a continued endeavor, they subsequently reported the direct cross-coupling of sugar halide with amino acid-derived redox-active electrophiles to assemble glycopeptides with alkyl glycosidic linkages.[22] In 2021, the Goddard-Borger group reported the *C*-mannosylation of tryptophan through Ni-catalyzed photoreductive cross-coupling of glycosyl and aryl bromides.[23] Noteworthy, tryptophan *C*-mannosylation represents the recognized natural form of protein *C*-glycosylation. In many of these cases, functional groups with reactivity need to be installed onto amino acids and peptides in advance to provide reaction sites for the formation of C−C bonds. As a result, the resulting glycopeptides often contain unnecessary specific linker residues (e.g., repeated sp^3 carbon atoms and aryl, alkenyl, or ketone groups, as shown in Figure 1B, right). These contrived events could potentially create further complications in the assessment of the activity and applications of *C*-glycopeptides.

Given the essential role of amide bonds in peptides and proteins, we propose that the direct linkage of amino acids or peptides with carbohydrates through amide bonds, to create *C*-glycopeptides, presents an attractive yet challenging under-

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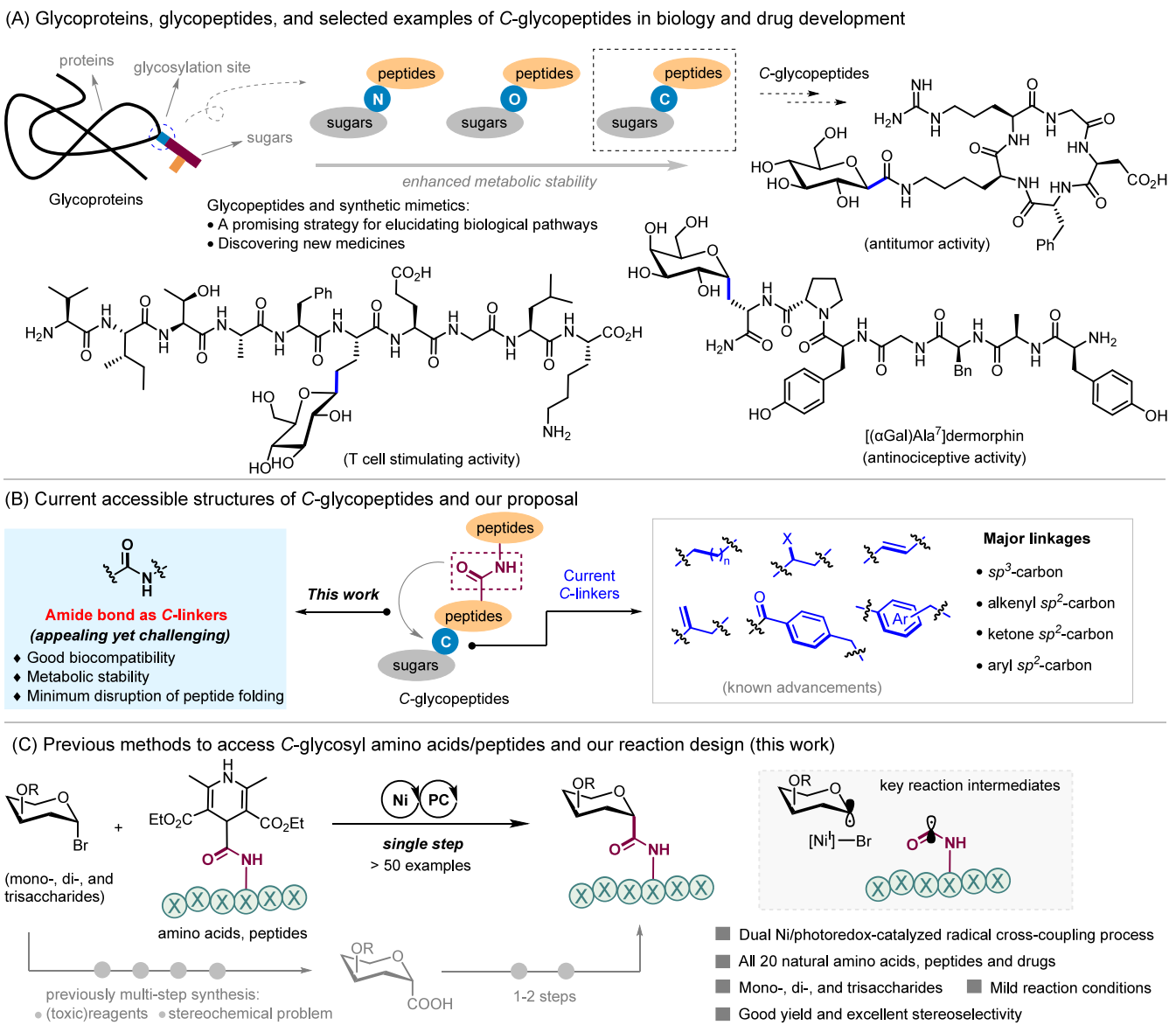

Figure 1. Significance of *C*-glycopeptides, challenges in their synthesis, and our protocol.

taking (Figure 1B, left). The traditional approach primarily relies on the direct condensation of sugar acids and amino acid fragments. However, the synthesis of sugar acids is not straightforward, involving the use of toxic reagents, challenging stereoselectivity control, and relatively low efficiency in multistep synthesis (Figure 1C).[13,24−30] Recent studies have demonstrated the efficiency of metallaphotoredox catalysis in promoting the cross-coupling of glycosyl donors with various electrophiles.[22,23,31−37] Here, we disclosed that photoredox/nickel dual catalysis enables the direct linkage of amino acids and peptides with glycosyl bromide donors via amide bonds, thereby accessing a diverse array of *C*-glycosyl amino acids and peptides in a stereoselective manner. Technically, this method involves the native NH_2 functional group in amino acids reacting with dihydropyridine (DHP) acid to generate redox-active substrates (e.g., compound **2a**).[38] We have presented an effective strategy for *C*-glycosylation modifications of amino acids, peptides, and potentially proteins.

RESULTS AND DISCUSSION

Reaction Development. Our study began by utilizing tetraacetyl-protected α-mannosyl bromide **1a** and amino acid-derived redox-active dihydropyridine **2a** as model substrates to establish a method for the direct synthesis of amide-linked *C*-glycosyl amino acids and peptides (Table 1). After extensive optimization, we determined that the coupling between **1a** and **2a** proceeded smoothly under blue light irradiation (40 W, 467 nm), with 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) serving as the photocatalyst, nickel(II) bis(acetylacetonate) ($Ni(acac)_2$) as the metalcatalyst, (*S*,*S*)-2,2-bis(4-phenyl-2-oxazolin-2-yl)propane (**L7**) as the ligand, Na_2CO_3 as the base, and 1,4-dioxane as the solvent. Under optimal conditions, the reaction produced the desired *C*-glycosyl amino acids **3** in 81% yield with excellent stereoselectivity (α-anomer, see Supporting Information for structural assignment) (entry 1). When the experiments were conducted in tetrahydrofuran (THF) (entry 2), the cross-coupling product **3** was obtained in a slightly lower yield compared to the use of 1,4-dioxane. The use of acetonitrile

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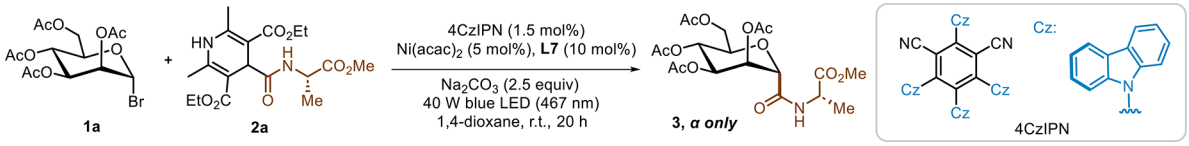
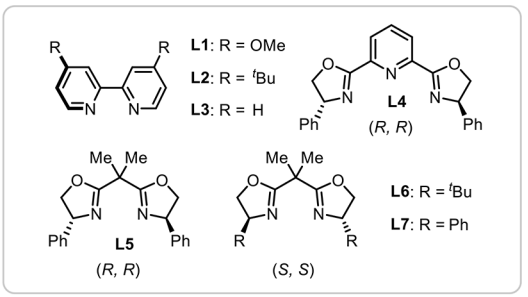
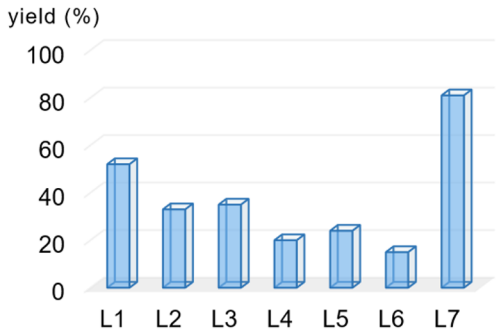
Table 1. Reaction Optimization



entry[a]	deviation from standard conditions	yield (%)[b]
1	none	81
2	THF as solvent	76
3	MeCN as solvent	17
4	**L1** instead of **L7**	52
5	**L2** instead of **L7**	33
6	**L3** instead of **L7**	35
7	**L4** instead of **L7**	20
8	**L5** instead of **L7**	24
9	**L6** instead of **L7**	15
10	$NiBr_2$·DME instead of $Ni(acac)_2$	72
11	$Ni(cod)_2$ instead of $Ni(acac)_2$	60
12	without Na_2CO_3	13
13	without 4CzIPN or in the darkness	N.D.
14	addition of TEMPO	N.D.





[a]Standard reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.15 mmol, 1.5 equiv), 4CzIPN (1.5 mol %), Ni source (5 mol %), ligand (10 mol %), base (0.25 mmol, 2.5 equiv), solvent (2.0 mL, 0.05 M) and irradiated with a 40 W blue LED (467 nm) at room temperature for 20 h. [b]Determined by ^{1}H NMR using 4-chlorobenzaldehyde as an internal standard. See Supplementary Section 3 for more details of optimization studies and control experiments.

(MeCN) dramatically decreased the efficiency (entry 3). Ligand screening revealed that (*S*,*S*)-2,2-bis(4-phenyl-2-oxazolin-2-yl)propane (**L7**) was optimal for promoting this photoredox/Ni-catalyzed cross-coupling. Notably, the use of ligand **L5**, the enantiomer of **L7**, resulted in a significantly lower yield, possibly due to the chirality mismatch between the nickel complex and substrates (entry 8).[39] Among all of the metal catalysts tested, $Ni(acac)_2$ outperformed the others. Attempts to replace it with $NiBr_2$·DME or $Ni(cod)_2$ resulted in lower yields (entries 10 and 11). In the absence of the inorganic base Na_2CO_3, the yield significantly decreased (entry 12; for more details see Supporting Information). Control experiments demonstrated that both the photocatalyst and light irradiation were indispensable for the reaction (entry 13). It is worth noting that the addition of TEMPO as a radical scavenger completely inhibited the reaction (entry 14).

Reaction Scope. With the established optimal reaction conditions, we proceeded to explore the generality of this cross-coupling reaction. The scope of DHP-tagged amino acids and peptides **2** was initially explored using α-mannosyl bromide **1a** as a model substrate (Figure 2). Remarkably, all 20 common L-amino acids were compatible with the reaction, with 17 of them exclusively yielding the desired *C*-glycosyl amino acids in the α-anomer form in moderate to high yields, despite their varying side chain electronic and steric properties (**3**−**23**).

It is noteworthy that sulfur-containing amino acids exhibited significantly reduced yields (e.g., **20** and **21**), likely due to the deactivating effect of the sulfur atom on the nickel catalyst through a coordination process.[40] The use of DHP-tagged L-histidine as a substrate produced the desired *C*-glycosyl amino acid in low yield (**22**). Possible unproductive pathways involve the Minisci-type reactions[41] and Ni-catalyzed C−H activation transformations[42] at the imidazole side chain of histidine. Noteworthy, the absolute configuration of the chiral center of the amino acid and the protecting group of the carboxylic acid has a slight effect on the reaction. Specifically, DHP-tagged D-alanine smoothly underwent the reaction albeit in slightly lower yield compared to L-alanine (**3** vs **24**). Switching the protecting group of carboxylic acids to *tert*-butyl (^{t}Bu) resulted in *C*-glycosyl amino acids **25** and **26**. These two products were further utilized as building blocks for the synthesis of more intricate *C*-glycopeptides (vide infra). Furthermore, a series of DHP-tagged peptides have been proven to be effective substrates, yielding the desired *C*-glycopeptides in moderate yields (**27**−**33**). Remarkably, the captivating disaccharide **34** could be efficiently constructed, utilizing amide bonds as distinctive glycosidic linkages.

The practicality of this mild and straightforward approach is further demonstrated in the late-stage glycosylation modification of commercially available amino acids and peptide drug molecules, showcasing its advantages and potential in constructing glycoconjugate drugs (Figure 3A). For instance, γ-amino acid drug molecules such as pregabalin, gabapentin, and baclofen, utilized as antiepileptic agents[43,44] and muscle relaxants,[45] respectively, were employed. Their corresponding DHP derivatives were found to be compatible with the reaction conditions, yielding the target glycosylated molecules

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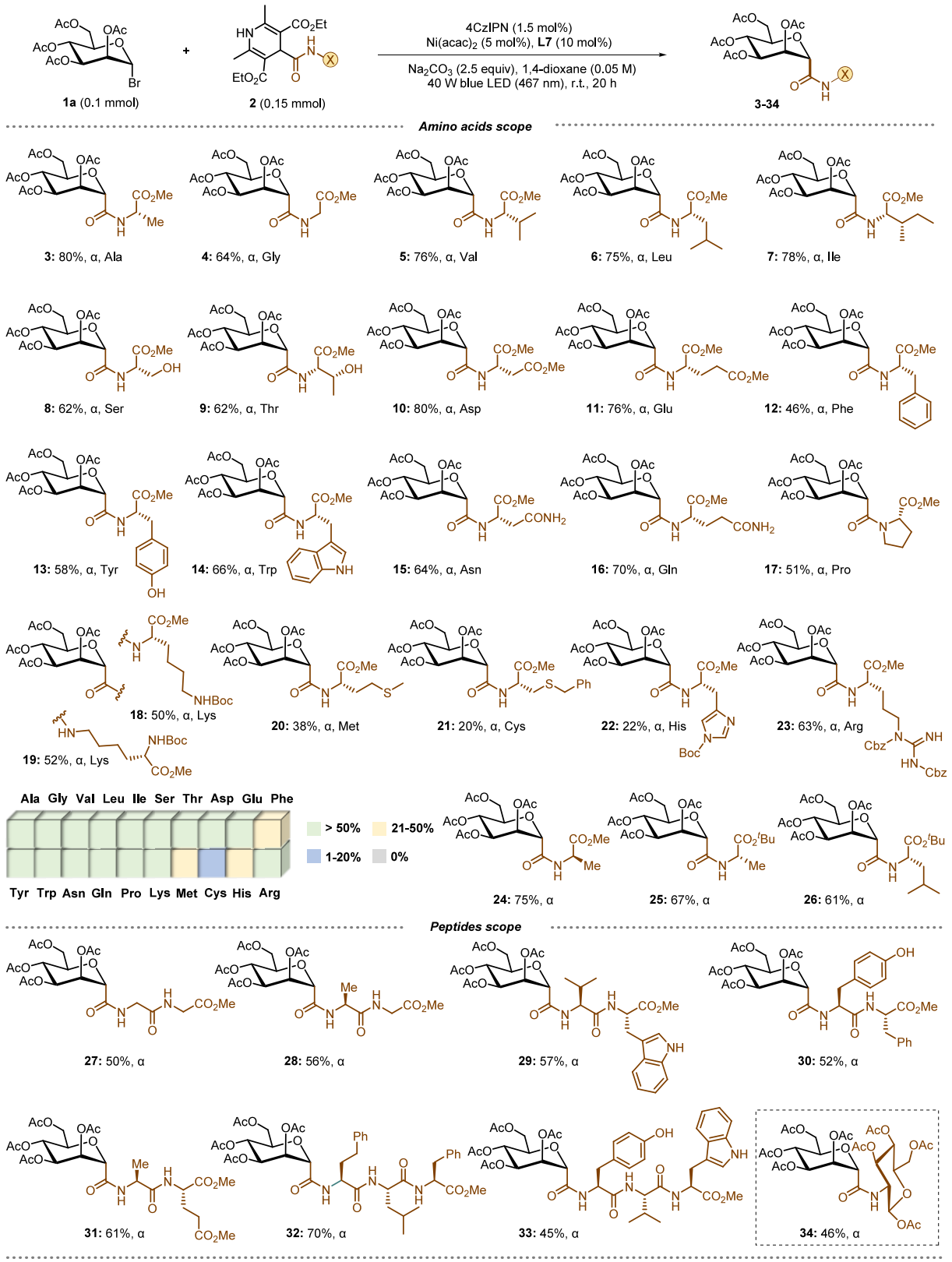

Figure 2. Substrate scope of amino acids and peptides. Isolated yields are reported. All products observed and isolated occur as a single anomer.

(**35**−**37**) in good yields. The diastereomeric ratio of compound **37** was determined from racemic baclofen as the starting material. Other drug-related non-natural amino acids, including selenocysteine,[46] levodopa,[47] and indoximod,[48] also proved to be suitable substrates. Under our optimal reaction conditions, they smoothly coupled with glycosyl bromide donors, yielding the desired products in useful yields (**38**−**40**). Bestatin, a dipeptide employed as a competitive and reversible protease inhibitor,[49] was efficiently glycosylated to yield compound **41** in 55% yield. Spinorphin is an endogenous,

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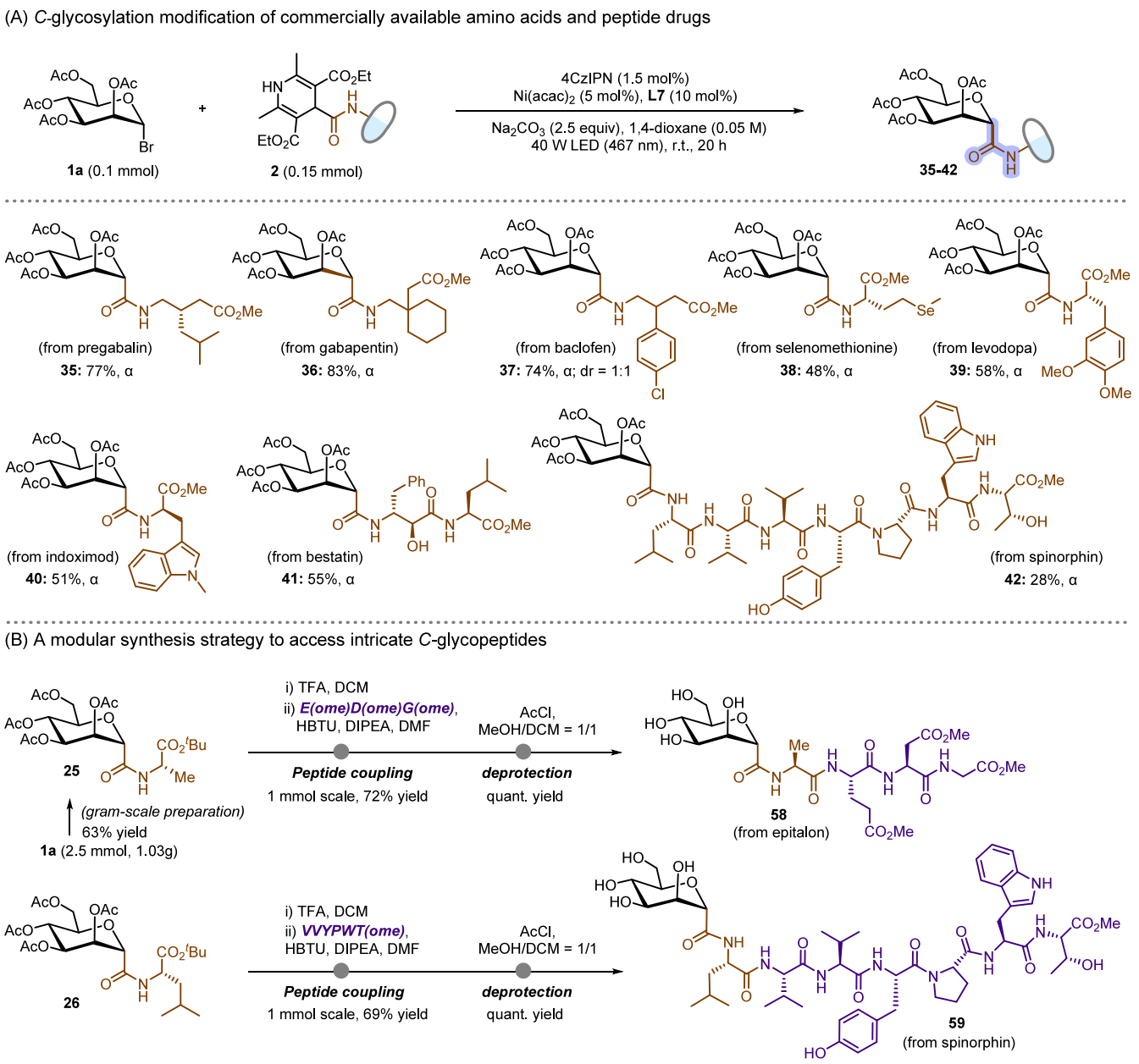

Figure 3. Substrate scope of drug-related amino acids and peptides. Isolated yields are reported. All products observed and isolated occur as a single anomer. Diastereomeric ratios (dr) of compound **37** were determined by NMR analysis of the crude reaction mixture.

nonclassical opioid peptide belonging to the hemorphin family.[50] Despite its relatively complex structure, effective late-stage glycosylation modification of this compound was achievable under our standard reaction conditions, albeit in a slightly lower yield. In addressing the lower efficiency faced by our developed photoredox/nickel dual catalysis in the *C*-glycosylation modification of more complex peptides, we have devised an alternative modular strategy (Figure 3B). Specifically, our method involves utilizing the synthesized uncomplicated glycosyl amino acids as foundational motifs. By employing a modular process that includes peptide deprotection, peptide coupling, and sugar deprotection, we are able to construct the desired intricate *C*-glycopeptide mimetics. A gram-scale preparation of *C*-glycosyl amino acids **25** was first conducted with a 63% yield. The feasibility of this strategy has been validated through the successful synthesis of *C*-glycopeptides **58** and **59**. Undoubtedly, this method provides exceptional flexibility and precision, allowing for significant expansion of the synthesized *C*-glycopeptide library.

Finally, we explored the generality with respect to glycosyl donors (Figure 4). Glycosyl bromide donors with various hydroxyl protecting groups, such as Bz, Piv, and TBDPS, were compatible with the reaction conditions, affording the desired products in good yields (e.g., **43**−**45**). In addition, rhamnose was demonstrated as a suitable substrate for glycosylation modifications of amino acids (e.g., **46**). Encouragingly, various disaccharides, and even trisaccharides, underwent smooth cross-couplings enabled by photoredox/nickel dual catalysis, yielding the desired *C*-glycopeptides in acceptable yields (e.g., **47**−**52**). Beyond pyranoses, we subjected an array of furanoses to our *C*-glycosylation coupling via an amide bond to afford various *C*-glycosyl amino acids. All of these reactions proceed smoothly, affording the corresponding products in moderate to good yields with a single anomer (e.g., **53**−**56**, see Supporting

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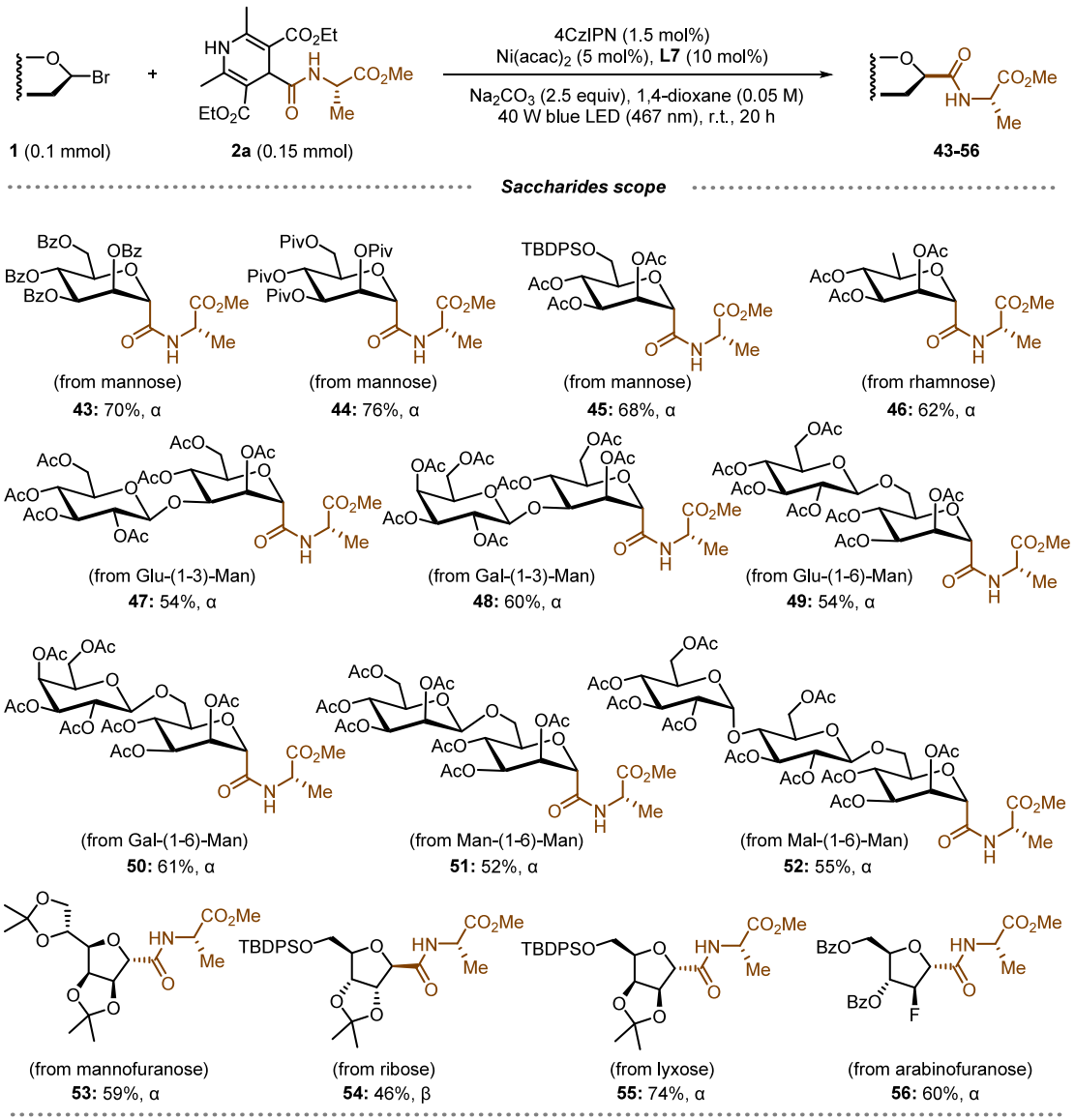

Figure 4. Substrate scope of saccharides. Isolated yields are reported. All products observed and isolated occur as a single anomer.

Information for structural assignment). The distinct anomeric selectivity observed in the product of ribose derivatives (**54**) can be attributed to the steric hindrance at the α-face of ribose created by the C2 and C3 substituents.[51]

On the basis of the known research[38,52,53] and our radical trapping experiments (see Supporting Information), we proposed a plausible mechanism (Figure 5). Photoexcitation of the organic photocatalyst 4CzIPN ($E_{1/2}$(4CzIPN*/4CzIPN$^{\bullet-}$) = +1.43 V vs SCE in CH_3CN)[54] enables the single-electron oxidation of dihydropyridine substrates **2**. After the reaction undergoes deprotonation and the removal of aromatized pyridine byproducts, the carbamoyl radical **II** is generated. Simultaneously, the Ni^0 complex undergoes radical oxidative addition with 1-bromo sugar **1**, generating the hybrid 1-glycosyl-Ni-Br complexes **III** and **IV**.[52] The high stereoselectivity in our *C*-glycosylation could be attributed to the predominant $^4C_1$ conformation of the mannosyl radical **III**, which is effectively stabilized through the anomeric interaction involving the singly occupied molecular orbital (SOMO), σ^*_{C-O} orbital of the C2−O2 bond, and the lone pair electron η_O of the endocyclic-O.[55−58] Bonding with glycosyl radical intermediate **III** in an axial orientation (leading to the generation of α-products) ensures that the stabilizing factors related to orbital overlap are minimally affected. The carbamoyl radical **II** was subsequently captured by intermediate **IV** to form intermediate **V**, which, after reductive elimination, affords the desired glycopeptide product. Finally, the resulting intermediate **VI** undergoes SET reduction by the reduced photoredox catalyst, thereby completing the catalytic cycle.

CONCLUSIONS

In summary, we have disclosed a dual Ni/photoredox-catalyzed radical cross-coupling between easily available glycosyl bromides and amino acid/peptide-derived redox-active substrates. Our approach first leverages the intrinsic structural unit of the amide bond within peptides as the glycosidic linkage. By overcoming the obstacle of direct C−C bond formation between sugars, amino acids, and peptides, this method significantly expands the structural diversity of synthesized *C*-glycosyl amide acids and peptides. The practicality of this connection protocol has been repeatedly

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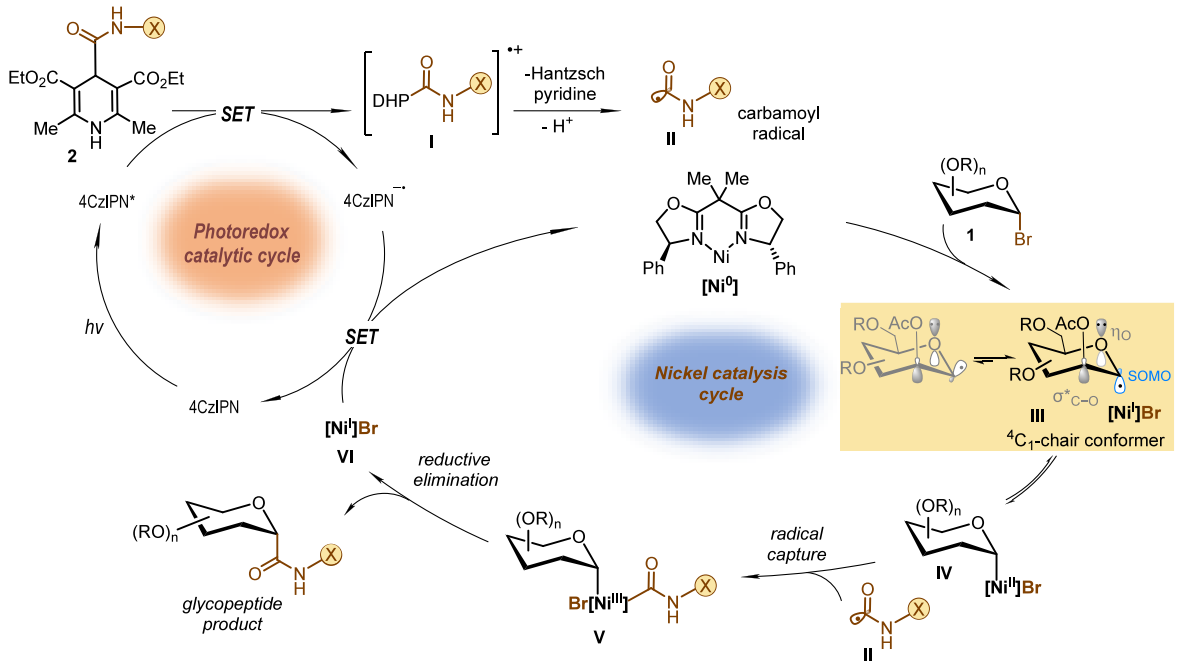

Figure 5. Proposed mechanism for cooperative Ni-catalyzed and photoredox processes.

evidenced in the synthesis of a wide variety of *C*-glycoamino acids and complex glycopeptides and the late-stage glycosylation modification of drug-related molecules. The reaction proceeds under mild conditions and is readily scaled up. From a practical perspective, our method will play a crucial role in various research fields related to synthetic glycopeptide mimetics, such as molecular biology and medicinal research.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c13456.

Full experimental details for the preparation of all new compounds and their spectroscopic and chromatographic data (PDF)

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X.-Y.Y. and G.W. contributed equally.

Notes

The authors declare no competing financial interest.

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