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Visible-Light-Mediated, Chemo- and Stereoselective Radical Process for the Synthesis of *C*-Glycoamino Acids

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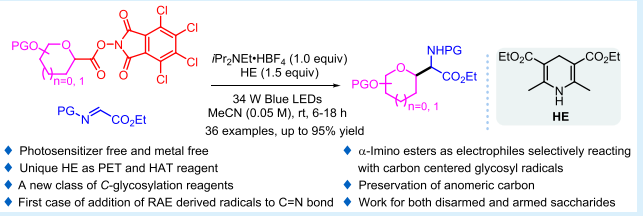
Supporting Information

ABSTRACT: An approach for efficient synthesis of *C*-glycosyl amino acids is described. Different from typical photoredox-catalyzed reactions of imines, the new process follows a pathway in which α-imino esters serve as electrophiles in chemoselective addition reactions with nucleophilic glycosyl radicals. The process is highlighted by the mild nature of the reaction conditions, the highly stereoselectivity attending C−C bond formation, and its applicability to *C*-glycosylations using both armed and disarmed pentose and hexose derivatives.

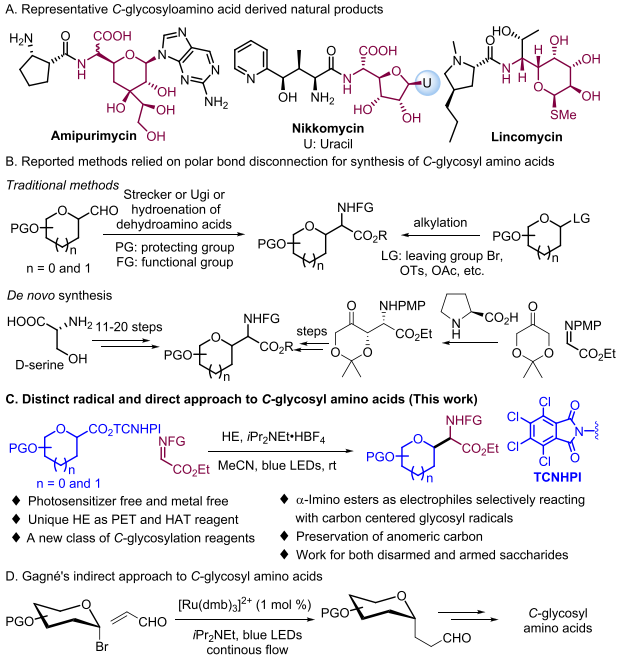


C-Glycosyl amino acids are a unique class of compounds widely present in nature that have an enormously diverse array of biological properties.[1] Notable examples of substances in this family include the peptidyl nucleoside antibiotics amipurimycin, polyoxins, and nikkomycin, which have potent antimycotic activities against various human pathogenic fungi and bacteria (Scheme 1A).[2,3] More pronounced impacts of *C*-glycosyl amino acids arise from their broad application in biomedical and drug discovery studies of glycopeptides and proteins.[4,5] Finally, the presence of C−C linkages to anomeric centers gives members of this family higher metabolic stabilities and lipophilicities than those of O−C bond-containing counterparts. In many instances, this feature leads to improved biological activities, membrane permeabilities, and bioavailabilities.[4,5]

In routes developed to date for the synthesis of *C*-glycosyl amino acids, installation of an amino acid moiety onto a glycosyl framework has relied on the use of well-established α-amino acid synthesis strategies, such as alkylation of α-amino acid equivalents, Strecker reactions, hydrogenation of dehydroamino acids, and multicomponent Ugi reactions with sugar derivatives (Scheme 1B).[6] In addition, de novo synthesis of *C*-glycosyl amino acids has been shown to be a viable approach to access unnatural substances in this family. Although often reliable, these polar bond disconnection based methods are inherently limited by a number of factors including the need for lengthy synthetic sequences, harsh reaction conditions, and/or a limited substrate scope.[7]

As part of a recent program to develop radical-based cross-coupling processes for selective C−C bond formation,[8] we envisaged that an open-shell pathway might be applicable to the concise synthesis of *C*-glycosyl amino acids under mild conditions.[9,10] Specifically, we believed that addition of glycosyl radicals, generated from appropriate glycosyl precursors, to readily available α-imino esters would constitute a viable approach to the preparation of these substances (Scheme 1C). To our knowledge, a strategy of this type has

Scheme 1. Representative Natural Products Containing *C*-Glycoamino Acids and Traditional and New Approaches for Synthesis of *C*-Glycosyl Amino Acids



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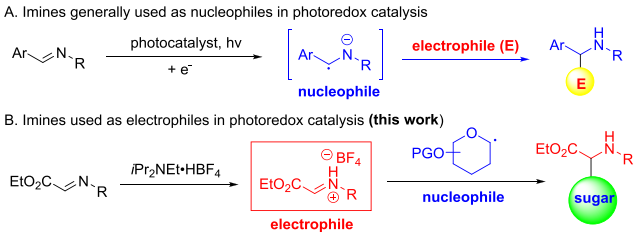
not been documented previously. However, we were aware that Gagné had developed a related yet indirect approach to *C*-glycosyl amino acids (Scheme 1D)[10] in which *C*-glycosyl aldehydes, serving as key intermediates, are generated by using $[Ru(dmb)_3]^{2+}$-photocatalyzed radical addition reactions of glycosyl bromide derived radicals to acrolein. It is noteworthy that a non-photochemical process mediated by Et_3B/O_2 was developed using α-alkoxyacyl tellurides and glyoxylic oxime ether as the key reagents.[9b]

The role of imines in photoredox-catalyzed reactions[11,12] has typically been in the context of their single-electron transfer (SET) promoted conversion to nucleophilic radical anions that react with electrophiles (Scheme 2A). In contrast, photo-

Scheme 2. Roles of Imines in Photoredox Catalysis



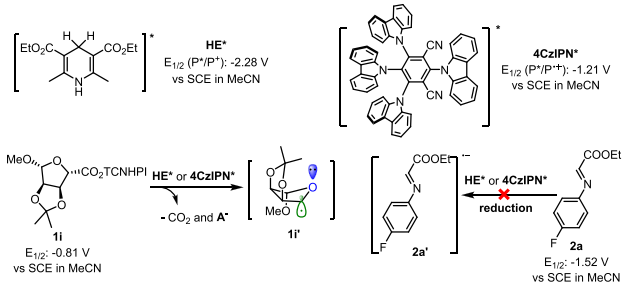
catalyzed processes, in which imines act as electrophiles in reactions with nucleophilic radicals, are very rare.[12] This is likely a consequence of the occurrence of competitive reactions of intermediate radicals and SET-mediated imine reduction. Furthermore, *N*-hydroxyphthalimide-derived redox-active esters (RAEs) have been demonstrated as effective radical precursors in transition-metal and photoredox-catalyzed C−C bond-forming processes.[13] Nonetheless, to the best of our knowledge, such radicals have not been reported in the reaction with a C═N bond.[14]

In the investigation described below, we developed a direct photochemical process for preparation of *C*-glycosyl amino acid derivatives that utilizes readily available α-imino esters (Scheme 1C). Differing from the role played by imines in typical photoredox-catalyzed reactions, α-imino esters in the new process serve as electrophiles in reactions with in situ generated nucleophilic glycosyl radicals (Scheme 2B). Moreover, in this effort, we demonstrated that glycosyl radicals can be generated using RAE of saccharides, a new class of bench-stable and readily prepared *C*-glycosylation reagents. Moreover, in this effort, we demonstrated that glycosyl radicals can be generated using RAEs of saccharides, a new class of bench-stable and readily prepared *C*-glycosylation reagents. As far as we are aware, this study represents the first case of the addition of RAE-derived radicals to a C═N rather than a C═C bond. In addition, we showed that the process does not require the use of an often expensive photosensitizer (PS), consistent with Melchiorre's work.[15] Instead, inexpensive Hantzsch ester (HE, ca. $0.071/mmol) can play the role of both a PS and hydrogen atom transfer donor in the new process. Finally, the preparative power of the new PS and metal-free strategy is a consequence of the mildness of the conditions employed and its application to reactions of both armed and disarmed pentoses and hexoses, in which the integrities of preexisting anomeric carbons are preserved.

In exploratory studies designed to assess the new approach to the preparation of *C*-glycosyl amino acids, we found that commonly used glycosyl bromides,[10] carboxylic acids,[16] and oxalates[17] do not serve as efficient glycosyl radical precursors in visible-light and PS-promoted reactions with α-imino ethyl ester **2a** (see Table S1). As expected, direct reduction of glycosyl derivatives and/or the imine occurs in these cases.

We turned our attention on *N*-hydroxyphthalimide-derived RAEs.[13,14] Based on these earlier observations, we envisioned that incorporation of *N*-hydroxytetrachlorophthalimide esters into sugars would give rise to glycosyl RAEs (**1**) that might serve as a new class of glycosyl radical progenitors (Scheme 3).

Scheme 3. Design of Glycosyl RAEs as Radical Progenitor for Direct Coupling with α-Imino Esters



Accordingly, we reasoned that it would be possible to generate glycosyl radicals by photoredox processes using visible light and PSs. A consideration of the reduction potential of RAE **1** ($E_{1/2}$ = −0.81 V vs SCE in MeCN, Figure 2S) suggests that its SET-promoted reduction would be thermodynamically favorable. We reasoned that the formed radical anion of **1i** would be capable of producing glycosyl radical **1i′** by loss of CO_2 and tetrachlorophthalimide anion. In contrast, the imino ester substrate would be less prone to reduction because of its more negative reduction potential (for example, **2a** = −1.52 V vs SCE in MeCN, Figures 2S and 3S).

In initial experiments designed to evaluate the feasibility of the new radical process for producing *C*-glycosyl amino acid derivatives, we explored the reaction of the RAE of α-D-glycopyranosiduronic acid **1a** with ethyl 2-[(4-fluorophenyl)-imino]acetate (**2a**) (Table 1 and S1). The results showed that irradiation of a solution of **1a** (0.1 mmol), **2a** (0.15 mmol), the PS 4CzIPN (0.002 mmol), HE (0.15 mmol), and $iPr_2NEt\cdot HBF_4$ (0.1 mmol) in MeCN (0.05 M **1a**) using 34 W Kessil blue LEDs leads to formation of the glucosyl amino ester **3a** in 83% yield (entry 2, Table 1). It should be noted that in this reaction the configuration of the anomeric carbon (C-1) is conserved. Moreover, in the reaction, the new C−C bond is installed in an α-stereoselective manner as a likely consequence of a combination of stereoelectronic and steric factors (Figure 9S).[9a,b] Moreover, a nearly 1:1 mixture of diastereomers is formed as a consequence of the lack of stereocontrol at C-6, a finding that is consistent with those made in a previous investigation.[9b]

Other PSs including $Ir[dF(CF_3)ppy]_2(dtbpy)PF_6$, $(Ru(bpy)_3(BF_4)_2$, $Ir(ppy)_2(dtbpy)PF_6$, and $Ir(ppy)_3$ also promote similarly efficient coupling reactions (entries 3 and 4 in Table 1 and Table S1), but a change in solvent to DCM causes a significant decrease in the yield of the process (27%, entry 5). At first surprising, we observed that irradiation of a solution of **1a** and **2a** not containing a PS under otherwise identical conditions leads to generation of **3a** in an excellent yield (93%, dr = 1.1:1, entry 1).

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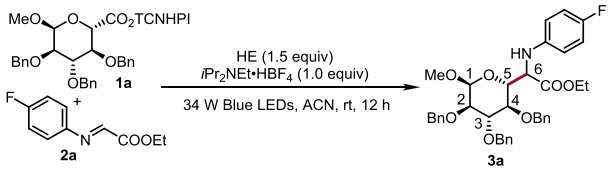
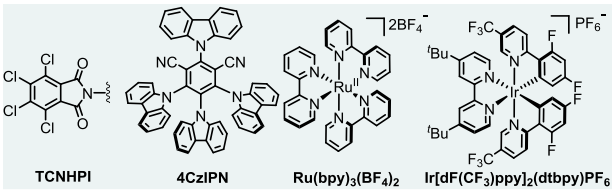
Table 1. Optimization of Reaction Conditions[a]



entry	deviation from standard conditions	yield (%)[b]
1	none	93 (90)[c]
2	4CzIPN as PS	83 (81)[c]
3	$Ru(bpy)_3(BF_4)_2$ as PS	81
4	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ as PS	76
5	DCM as solvent, 4CzIPN as PS	27
6	without $iPr_2NEt•HBF_4$, 4CzIPN as PS	69
7	without HE, 4CzIPN as PS	27
8	no light	0
9	no HE	0
10	no $iPr_2NEt•HBF_4$	0



[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), HE (0.15 mmol), $iPr_2NEt·HBF_4$ (0.1 mmol), ACN (2 mL), rt, 34 W Kessil Blue LEDs, 12 h. [b]Yield is determined by ^1H NMR spectroscopy with 1,1,2,2-tetrachloroethane as an internal standard. [c]Isolated yield.

To gain information about the functions of HE and $iPr_2NEt·HBF_4$ in the photoinduced process, we explored reactions carried out in the absence of either substance using 4CzIPN as the photocatalyst (entries 6 and 7). The results show that these processes take place in a dramatically lower or only moderate yield, respectively. However, no *C*-glycosyl amino ester product is formed when neither HE nor $iPr_2NEt·HBF_4$ is present (entries 9 and 10). The observations indicate that both substances play essential roles in the reaction (see below). Finally, **3a** is not formed when visible-light irradiation is absent (entry 8) or when TEMPO is present (Table S1).

We next evaluated the scope of the C−C coupling reaction utilizing imine **2a** and RAEs derived from various saccharides. As can be seen by viewing the data in Scheme 4, coupling reaction occurs efficiently (72−95%) with RAEs containing both electron-donating (benzyl, acetonide, methyl, i.e., armed sugars) and electron-deficient (benzoyl, acyl, i.e., disarmed sugars) substituents on the saccharide scaffold, as well as with pentoses (ribose, xylose) as well as hexoses (glucose, galactose, mannose, trehalose). In most cases, reactions of saccharide substrates bearing electron-rich and small protecting groups are higher yielding (i.e., forming **3a** (90%) > **3c** (86%) > **3a** (81%), **3d** (77%) > **3e** (72%), **3g** (95%) > **3f** (86%), **3i** (95%) > **3h** (93%)). Notably, the RAE of trehalose **2l**, a biologically important disaccharide, is efficiently converted to the corresponding *C*-glycoamino ester **3l** in 83% yield.

We next examined the imine scope of the process using a variety of structurally diverse imines, including those containing *N*-aryl (**2m**-**2ag**), sulfonyl (**2ah**), sulfinyl (**2ai**), and even benzyl (**2aj**) groups, and those that lack the ester group (i.e., simple benzaldimines **3t**−**ai**). The observations show that the aldimines participate in coupling reactions that take place in moderate to excellent yields (40−96%). Except for that of **3s**, reactions of *N*-arylimines containing electron-attracting groups (**2a**, **2p**, **2q**, and **2s**) are higher yielding (89−93%) than those of electron-donating substituted analogues (**2n**, **2o**, 70−87%), and the efficiency of the reaction of *ortho*-substituted *N*-arylimine **2r** (49%) is lower than that of its *meta*-analogue **3q** (94%). Additionally, reactions of the benzaldimine substrates tolerate a diverse range of functional groups, including halogen (**2u**−**x**), nitrile (**2z**−**ab**), amide (**2ac**), pyridyl (**2y**), methoxyl (**2ad**), allyloxy (**2ae**), methyl (**2af**), and phenyl (**2ag**). Moreover, the position of the substituent on the aromatic ring of these aldimines has a definite but small effect on reaction efficiencies (e.g., *para* (**2z**, 87%) > *meta* (**2aa**, 70%) > *ortho* (**2ab**, 62%)). Of particular note is the fact that the reaction of **2aj**, which exemplifies *N*-alkylaldimine substrates that are traditionally problematic in radical addition reactions,[12] reacts to form the corresponding adduct **3aj** in a modest 44% yield. Finally, the preparation of the *N*-protected glycoamino acid derivatives, *N*-sulfonyl (**3ah**, 66%) and sulfinyl (**3ai**, 40%), is readily accomplished using this approach.

To assess the potential synthetic value of this protocol, we applied it to the synthesis of glycopeptide **4** using the amino ester adduct **3o** as the building block (Scheme 5). We found that the *N*-methoxyphenyl group in **3o** is easily removed by oxidation with CAN (cerium ammonium nitrate)[18] and that the resulting amine reacts with the dipeptide (2-benzyloxycarbonylaminoacetylamino)acetic acid to produce the glycopeptide **4** in a yield of 69% for the two steps.

A few preliminary experiments were carried out to gain insight into the role that HE plays in the process when no PS is present. As can be seen by viewing Figure 1A, the absorption spectrum of HE in acetonitrile extends into the visible region (up to 430 nm). This observation suggests that the pathway followed in the absence of a PS likely involves direct photoexcitation of HE to form the corresponding excited-state HE*, which then serves as the SET donor to the RAE. To determine the effective roles played by HE and the PS in promoting this process, time courses of reactions of **1i** with **2a** and of **1a** with **2d**, carried out in the absence and presence of the PS 4CzIPN, were elucidated. The results, displayed in Figure 1B,C, show that the presence of 4CzIPN leads to a significant enhancement in the observed rates of the radical coupling reactions and that in some cases (but not all cases) it has an effect on overall chemical yields. Although a more detailed mechanistic study is required, we believe that the greater observed rates and possibly efficiencies of reactions carried out in the presence of a PS are associated with a broader wavelength range of visible-light absorption by PS vs HE.

A scheme outlining the various mechanistic scenarios possible for this photoinduced coupling reactions is displayed in Scheme 6. The scheme shows the potential roles played by HE and the PS as light-absorbing activating agents, the catalytic function of the PS, the role played by HE as a hydrogen atom donor, and the acid-catalysis function of $iPr_2NEt·HBF_4$.

In the investigation described above, we developed a new strategy for the synthesis of *C*-glycosyl amino acids that relies on the photocatalyzed generation of *C*-glycosyl radicals from redox-active esters of saccharides and their addition to aldimines. Different from typical photoredox- catalyzed

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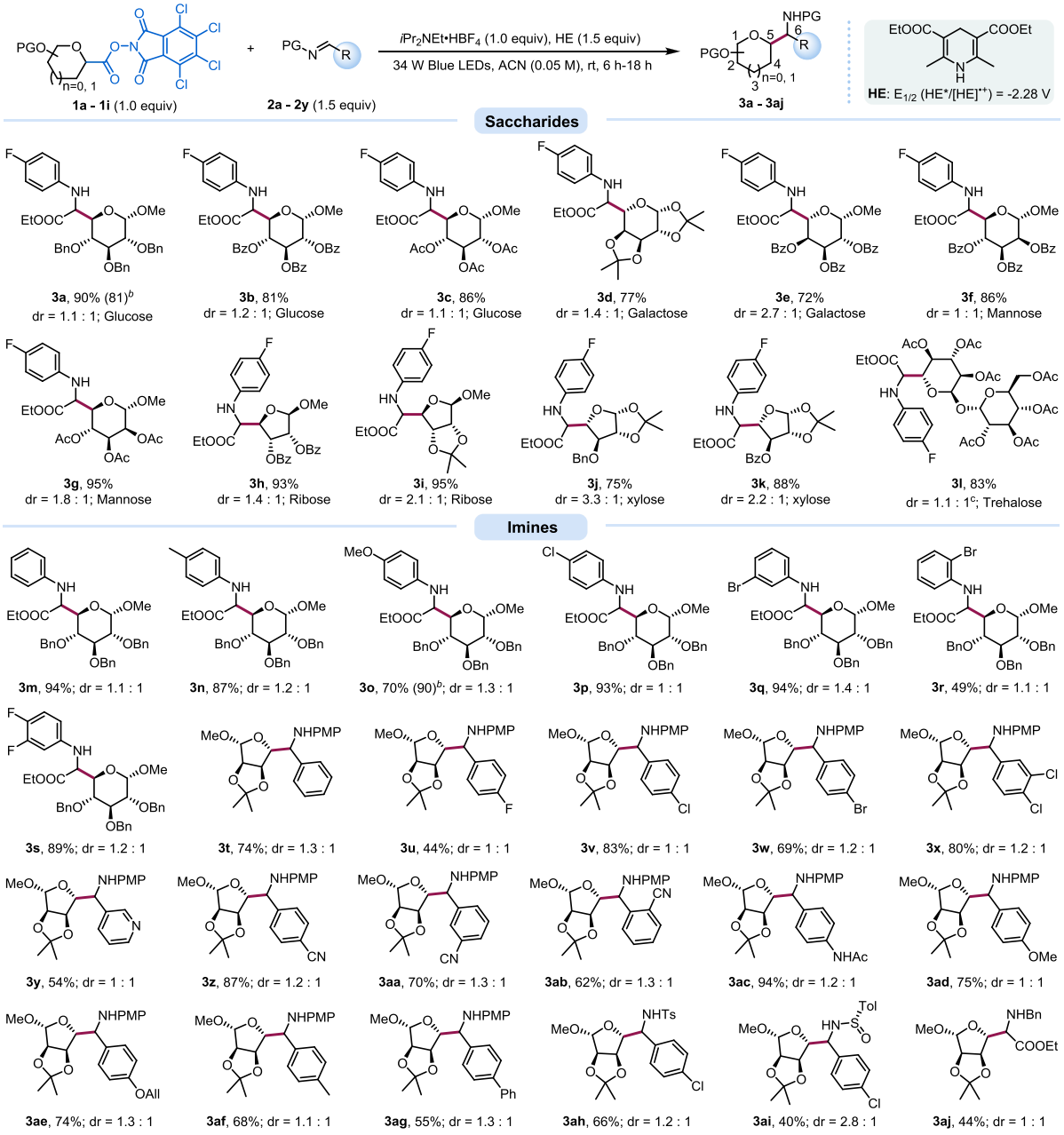
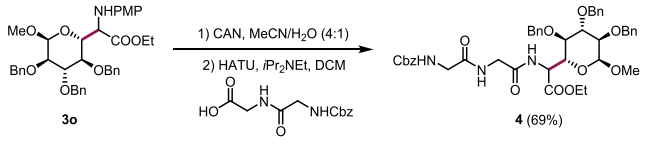
Scheme 4. Scope of the *C*-Glycosylation Reaction[a]



[a]Reaction conditions: redox-active ester **1a−i** (0.1 mmol), imines **2a−y** (0.15 mmol), HE (0.15 mmol), iPr$_2$NEt·HBF$_4$ (0.1 mmol), ACN (2 mL), rt, 34 W Kessil Blue LEDs, 6−18 h. [b]Experiment is carried out in the presence of 4CzIPN (1 mol %). The dr values were determined by ^{1}H NMR.

Scheme 5. Synthetic Application of the New Radical-Coupling Reaction



reactions of imines, which generate polarity reversed nucleophilic imine radical anions, imines in the newly developed process serve as electrophiles in chemoselective C−C bond-forming reactions with nucleophilic in situ generated glycosyl radicals. An important feature of this effort is found in the development of a new class of glycosyl radical progenitors in the form of redox-active esters of saccharides. The new method is both straightforward and mild, and it can be utilized for the efficient production of synthetically and biologically valued *C*-glycosyl amino acid derivatives. Furthermore, the process proceeds in the presence or absence of single-electron-donating photosensitizers that are generally required to promote photoredox-catalyzed processes. In the absence of PSs, the Hantzsch ester plays a unique dual role as both as a light-activated electron donor to the redox-active esters and a hydrogen atom source. The broad substrate scope of the process encompassing both armed and disarmed pentoses and hexoses and the preservation of the integrities of the anomeric carbons in these substrates are advantageous

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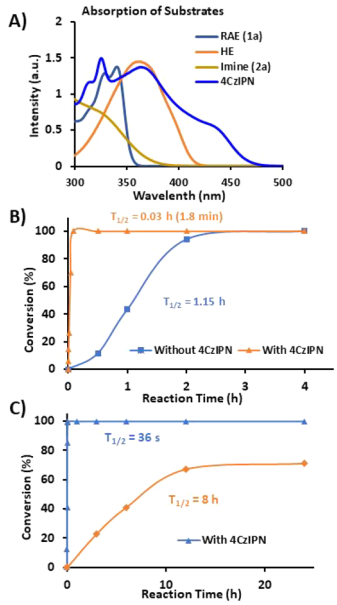
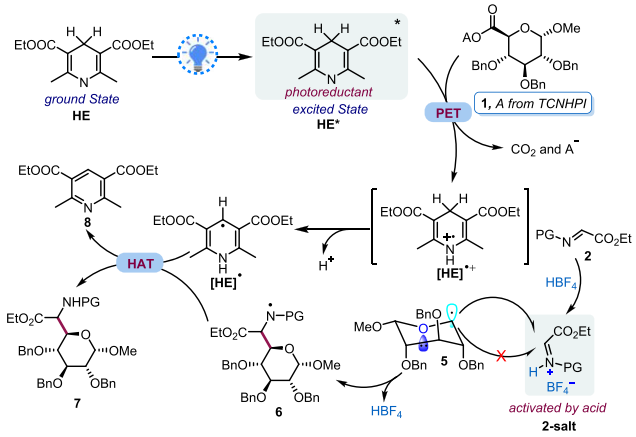


Figure 1. (A) UV−vis absorption spectra of **1a**, HE, **2a**, and 4CzIPN in MeCN. Reactions between (B) **1i** and imine **2a** and (C) **1a** and imine **2d** in the presence and absence of 4CzIPN.

Scheme 6. Possible Mechanistic Scenarios



features that should make the new method applicable to the synthesis of a broad range of biologically valued *C*-glycosyl amino acids and peptides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00724.

Experimental details and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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