Diastereoselective Decarboxylative Alkynylation of Anomeric Carboxylic Acids Using Cu/Photoredox Dual Catalysis

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ABSTRACT: Alkynyl *C*-nucleosides are of high value for various applications; however, their synthesis remain underexplored. Here we report a simple route towards the synthesis of alkynyl *C*-nucleosides from simple and stable furanosyl carboxylic acids and terminal alkynes under low-cost and non-toxic copper catalysis. The approach that we report here demonstrates the power of Cu/photoredox dual catalysis to access highly complex glycosides under mild conditions.

C-Nucleosides has emerged as a promising class of bioactive glycosides most notably in the fields of virology and cancer therapy.[1] These derivatives in which the anomeric C–N nucleosidic bond is replaced by a C–C bond, are considered as glycomimetics of natural nucleosides as they are known to be more resistant towards hydrolysis under biological conditions.[2] Representative natural and synthetic *C*-nucleosides are disclosed in Figure 1a, including varitriol[3] and showdomycin[4] (natural nucleosides), ribavirin analogs[5] such as pyrazomycin[6] or SO91[7] (antitumor agent), and benzamide ribonucleotide[8] (BAR, IMP dehydrogenase inhibitor). Recently, the remdesivir *C*-nucleoside metabolite GS-441524 (Figure **1a**) was reported as a potential inhibitor of SARS-CoV-2 by binding to the nsP3 macrodomain of the virus.[9] Moreover, *C*-nucleosides have been used to study RNA and DNA processing enzymes with the aim to extend the genetic alphabet and designing new therapeutic proteins.[10]

Because of their key role in many biological processes, the development of methods towards an efficient and stereoselective synthesis of *C*-nucleosides is considered to be of great importance.[11] Various chemical scaffolds such as aromatics, heteroaromatics, alkyls, alkenyls and alkynyls were introduced at the anomeric pentose sugar position. Among all these architectures, alkynylated nucleosides (called also sugar acetylene) are particularly important as they offer a unique opportunity to increase the complexity of the targeted *C*-nucleoside, due to the numerous possible transformations of the C–C triple bond (Figure **1b**).[12] For instance, the alkyne function may be subjected to partial or total reduction, hydrometallation[13] followed by a selective functionalization or (4+2) cycloaddition with azides to produce triazoles[14] or with dienes[15] to access to aromatic nucleosides (Figure **1b**). Besides, *C*-alkynyl nucleosides may be used as partners in a C–H activation/annulation process with anilines to afford a variety of substituted *C*-furanosyl indoles.[16] Otherwise, *C*-ethynyl furanosides are also reported as a promising antibiotic by acting against Zn^{2+}-dependent enzyme LpxC[17] (Figure 2a). Despite these possibilities, their use is underdeveloped, and only few methods for their synthesis are reported (Figure 2a).[11] Among them, the introduction of the alkynyl function at the anomeric position involves the reaction of furanosyl halides or acetates with alkyne iodides mediated by indium.[18] Organometallic alkynes such as alkynyl trifluoroborates[19] or alkynyltin species[20] are well known to be good partners in the

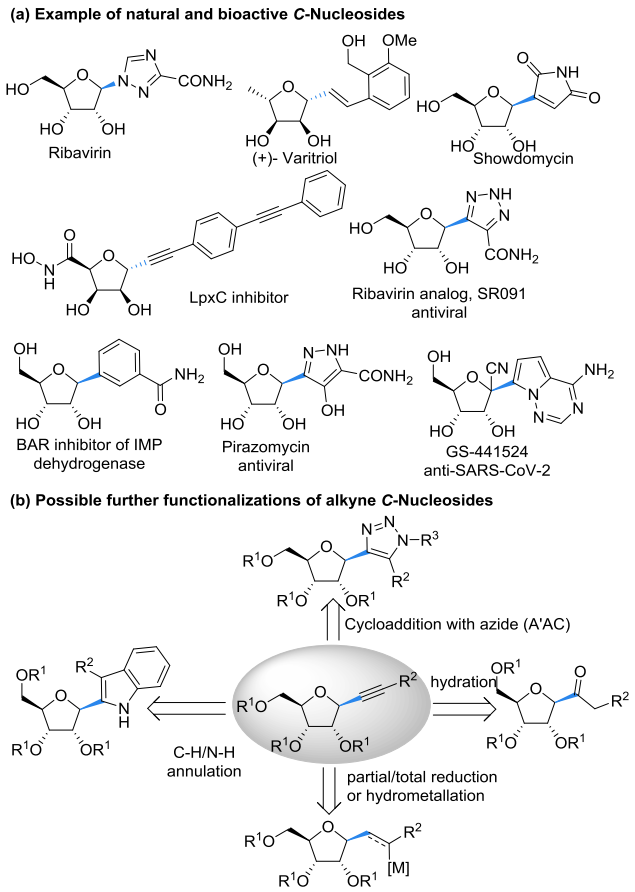


Figure 1. (a) natural and bioactive C-nuleosides, (b) examples of possible transformations of alkynyl C-nuleosides

glycosylation of furanosyl fluorides and bromides in the presence of Lewis acids such as boron trifluoride or zinc chloride. Grignard alkynyl reagents are also used as nucleophiles in the coupling with acetals.[21] Although their high interest, these methods require the use of harsh conditions (high temperature and excess of the metal in the case of indium coupling) and overstoichiometric amounts of air and moisture sensitive alkynyl organometallics as well as the nature of the used Lewis acidic used. These issues often limit the practicability of the

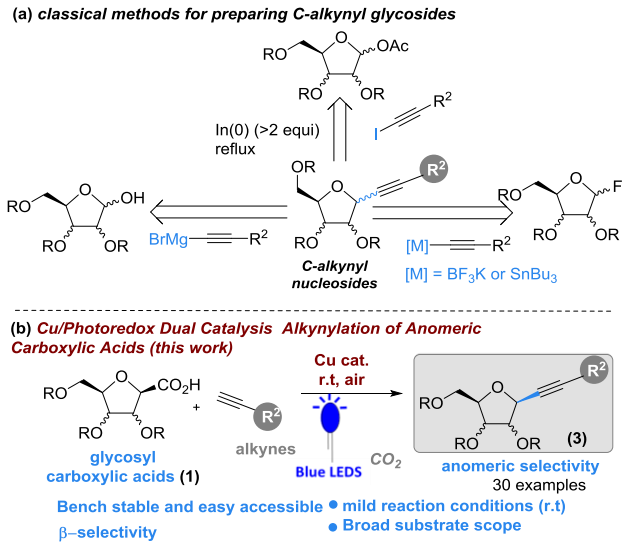
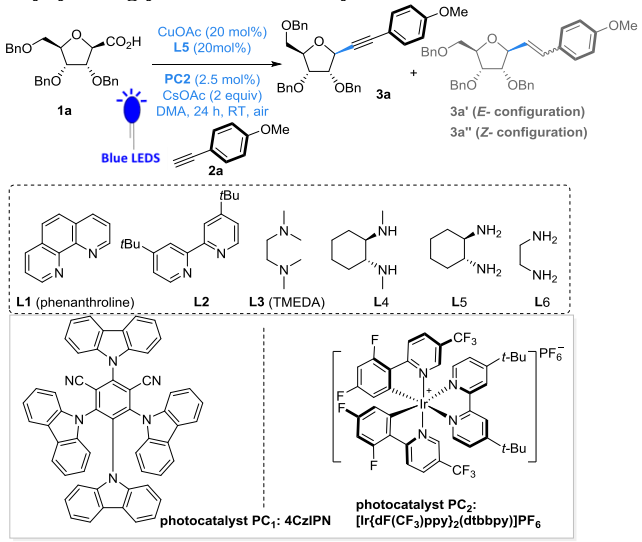


Figure 2. (a) strategies for the synthesis of alkynyl *C*-nuleosides, (b) Cu/photoredox approach developed herein

scope of substrates. Moreover, a mixture of both anomers is mainly observed in numerous reported methods. Then, developing new, mild and catalytic conditions to access diastereoselectively alkynyl *C*-nucleosides is still one of the highly challenging topics in glycochemistry. In light of the aforementioned challenges, we were intrigued to develop an efficient catalytic method to perform a decarboxylative alkynylation of ribosyl radicals under dual photoredox[22] catalysis conditions (Figure **2**). In this context, anomeric radicals have recently been manipulated in conjunction with Ni/Ru or Ir photoredox dual catalysis for the synthesis of alkyl-, (hetero)aryl- and acyl-*C*-glycosides.[23] Gagnée and co-workers used this approach to generate anomeric radicals from pyranosyl bromides which react with alkenes to produce exclusively alkyl α-*C*-glycopyranosides.[24] Molander group reported a range of glycosyl-based radicals generated from dihydropyridyl glycoside precursors and coupled with activated carboxylic acids to synthesize non-anomeric *C*-acyl glycosides.[25] This approach was applied recently to carbohydrate substrates bearing the dihydropyridine (DHP) as an activating anomeric group to prepare C-aryl glycosides, including nucleosides and 2-deoxysugars.[26] Very recently, 2-deoxyglycosyl boronic acid derivatives were used as radical sources to synthesize a series α-*C*-glycosides mediated by a photoredox/nickel dual catalytic system.[27] Finally, Wang, Zhang and co-workers[28] demonstrated for the first time, that ribosyl acids are valuable partners in the photoredox/nickel dual-catalyzed cross-coupling with heteroaryl and vinyl bromides, furnishing various β-selective heteroaryl-*C*-nucleosides in good yields. Based on this exceptional reactivity of anomeric radicals, we considered them to be well-suited for the development of an alkynylation photoredox cross-coupling process with terminal alkynes. Indeed, pioneer studies demonstrated recently that copper acetylide which could be formed from terminal alkyne and copper salt under mild conditions, were compatible with a photoredox process in the alkynylation of *N*-hydroxy phthalimide esters.[29] Based on all these observations and our ongoing interests in metal-catalyzed functionalization of sugar motifs,[30] we propose herein a catalytic method for the decarboxylative alkynylation of ribosyl carboxylic acids with terminal alkynes under copper/photoredox dual catalysis (Figure **2b**). This approach which proceeds *via* anomeric radical intermediate, exhibits many advantages over the conventional methods: (*i*) the use of bench-stable and easily handled sugar carboxylic acids, (*ii*) the use of earth-abundant and low cost- transition metal copper catalyst, (*iii*) mild reaction conditions (RT) and (*iv*) large functional groups tolerance. If successful, this approach would provide not only an excellent complementary pathway to the established alkynylation methods but also immediate access to a reactive platform that can be engaged in numerous postfunctionalization.

To initiate this study, we chose the coupling of tri-*O*-benzylated 1-β-D-glucofuranose **1a** with 4-methoxyphenylacetylene **2a** as a model study under various reaction conditions. Representative results from this optimization study are summarized in Table 1. The reaction of *O*-Benzylated-furanose **1a** (1 equiv, $E_{1/2\text{furanose(OBn)3}}$ = +1.15 V *vs* SCE in MeCN) with **2a** (3 equiv) was first investigated by using 20 mol% of CuOAc, 2.5 mol% of a commercially available 4CzIPN photocatalyst ($E_{1/2(PC^*/PC^{\cdot-})}$ = +1.35 V *vs* SCE in MeCN) in the presence of CsOAc (2 equiv) as a base in DMA under blue light emitting diode (LED) irradiation (Table S1, entry 1, ESI). Surprisingly, performing the reaction under argon led to the formation of a mixture of three products: the alkynylated glycoside **3a** in 50% yield



Entry	Deviation from the standard conditions	Yield **3a** (%)[b]
1	none	96
2	**PC1** instead **PC2**	78
3	**PC2** 1mol%	50
4	CuOAc 10 mol%	61
5	**L1** or **L2** or **L3** or **L4** instead of **L5**	traces
6	**L6** insteadn of **L5**	48
7	**1a** (1equiv) and **2a** (5 equiv)	40
8	No photocatalyst **PC**	0
9	No Cu-catalyst	0
10	dark	0

[a] Reactions conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), CsOAc (0.4 mmol), DMA (2.0 mL), blue LEDs (4.5 W, irradiation). [b]Isolated yield.

Table 1. Optimization of the coupling reaction of **1a** with **2a**[a]

contaminated with *Z*- and *E*- alkenyl glycosides **3a'** and **3a''**. The formation of the undesired alkenyl *C*-nucleosides is in total agreement with the recently reported study of Pericas *et al*. on the decarboxylative hydroalkylation of alkynes *via* dual copper-photoredox catalysis.[31] This first result indicates clearly that under these conditions, two possible pathways are running concomitantly leading to the formation of akynyl (**3a**) and alkenyl (**3a'**, **3a"**) products. Importantly, conducting the same reaction under air instead of argon produces exclusively the β-*C*-alkynyl nucleoside **3a** in 60% yield (Table S4, entry 1, ESI). This second observation demonstrates that the presence of oxygen inhibits the alkenylation pathway in favor of the C(sp)–C(sp^3) bond formation. Nevertheless, a subtle amount of oxygen is necessary for the efficiency of the coupling since running the reaction under pure oxygen did not produce **3a** (Table S4, entry 2, ESI). Although at this stage we don't have any explanation, we can speculate that the high concentration of O_2 may induce side reactions involving radical oxygen species. This outcome inspired us to explore this alkynylation reaction under air. Thus, increasing the amount of the 4-methoxyphenylacytelene **2a** up to 5 equiv furnished **3a** in only 37% yield (Table S5, entry 2, ESI). Fine adjusting the ratio between **1a**/**2a** to 2:1 under otherwise the same conditions produces selectively **3a** in an excellent 78% yield (entry 2, Table 1). Also, reaction with Ir[dF(CF_3) ppy]$_2$(dtbbpy) PF_6 photocatalyst (**PC2**, $E_{1/2(PC^*/PC^{-\cdot})}$ = +1.21 V *vs* SCE in MeCN) instead of 4CzIPN was more efficient and gave the product **3a** in an excellent 96% yield (entry 1). Tentative to decrease amounts of the photocatalyst to 1 mol% or the copper-catalyst to 10 mol% led to low yields (50% and 61% yields respectively, entries 3 and 4). Using other photocatalysts such as Ir(p-CF_3-ppy)$_3$, IrMe(Me)ppy$_2$(dtbpy))PF_6 or tris$_2$-phenylpyridinato-C_2-Niridium(III) failed (Table S6, entries 3-5, ESI). The influence of the copper *N*,*N*-ligands was also examined by a screening of different ligands, but only L5 revealed to be efficient since the other ligands were less reactive (L6-8, entries 6-8) or completely inactive (L1-4, entries 2-5). Negative controlling experiments demonstrated the Cu-catalyst, the Ir-photocatalyst and the light are necessary (entries 8−10) anticipating the cooperative Cu/Ir dual photocatalysis mechanism rather than a photoinduced Cu-catalysis one. Of note, the anomeric configuration of β-*C*-alkynyl nucleoside **3a** was unambiguously assigned by the coupling constant $J_{1,2}$ = 4.5 Hz and confirmed for **3b** ($J_{1,2}$ = 4.3 Hz) by comparison with literature NMR data.[32]

Encouraged by these results, we investigated next the scope and limitations of this dual Cu/photocatalysis process by systematically varying the nature of the alkyne **2** and the sugar **1**. The substrate scope for alkynes was first explored keeping furanosyl acid **1a** as the substrate (Scheme 1). Aryl-substituted alkynes bearing electron-withdrawing and electron-donating groups in *ortho*, *meta* or *para* positions (–OMe, –Cl, –F, –CF_3, –COMe and –CO_2Me) were successfully reacted under our conditions to afford the corresponding alkynyl *C*-nucleosides (**3a-p**) in yields up to 96%. In addition, the enyne substrate **2q** was employed successfully in the reaction to produce **3q** in 64% yield. Moreover, challenging heteroaromatic alkynes could be used in the coupling as compounds **3r** and **3s** obtained in 70% and 56% yields, respectively. More interestingly, aliphatic alkynes which are known to be less reactive such as 1-pentyne, 1-hexyne, cyclohexyne, cyclopropyne as well as but-3-yn-1-yl benzene were also successful, furnishing **3t-x** in yields ranging from 52% to 93%. Finally, the substituted 5-chloropent-1-yne was employed successfully in this reaction and its C(sp^3)–Cl survived during the process (*C*-nucleoside **3y**).

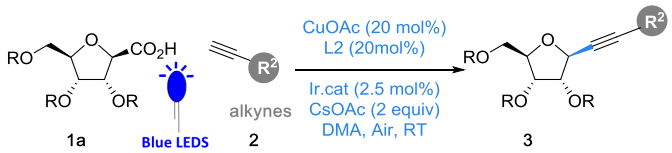
Next, we investigated the reactivity of a series of sugar carboxylic acids (Scheme 1). At first, we studied the scope of the coupling of ribofuranoses bearing various common protecting groups. Thus, substrate **1b** bearing benzoyl and acetonide protecting groups underwent an efficient alkynylation to produce *C*-nucleoside **3z** in 54% yield and in an anticipated α/β ratio of 4:1 as reported recently.[26] Otherwise, using the disarming OAc-protecting groups did not provide the desired product **3aa** under our optimized conditions.

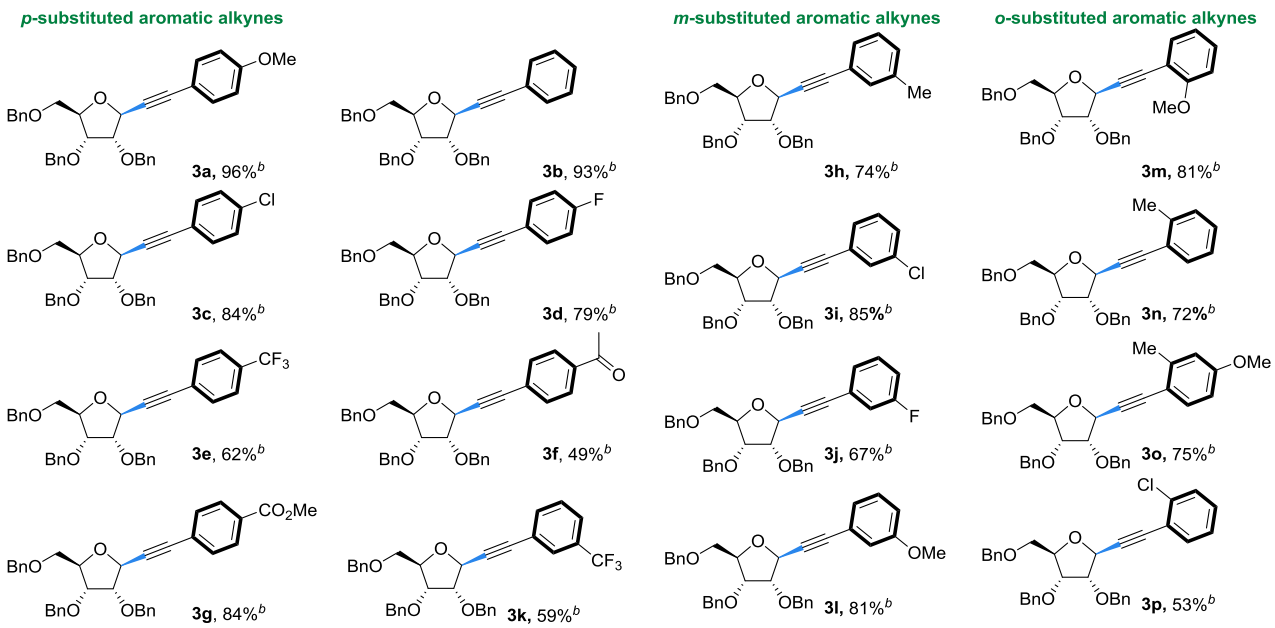
It is well established that the substituent at the C2 position of anomeric ribofuranoses plays a critical role in controlling the anomeric configuration. Thus, under our conditions the coupling of **2a** with benzyl protected 2-deoxy-D-ribose **β-1d** furnished **3ab** in 45 % yield and a ratio α/β of 6:1 in favor of the α–anomer. The same reactivity was recently observed on the arylation of furanosyl radicals under photoredox Ni-catalysis.[27,28] Of note, both α- and β-anomers were separated through a simple column chromatography. Interestingly, the anomeric configuration does not play any important role in the stereoselectivity of the reaction since running the same reaction starting from the **α-1d** anomer led to the same ratio of α/β (7:1). Interestingly, alkynylation of the non-anomeric furanosyl acid **1e** was proved to be effective furnishing the reversed alkynyl *C*-nucleoside **3ac** in good yield and excellent diastereoselectivity. Finally, decarboxylative alkynylation of tetrahydrofuran was less efficient under our conditions and provided the desired alkynylated product **3ae** in only 10% yield. Furthermore OBn-protected glucopyranosyl acid **1h** (see ESI, page S7) turned out to be an unsuitable substrate for this reaction as it failed to produce the corresponding alkynylated *C*-pyranoside. This finding demonstrates clearly that generation and reactivities of furanosyl and pyranosyl radicals are different under these photoredox conditions. This may be explained partially, by the significant difference of the reduction potential ($E_{1/2}$) between the furanosyl and pyranosyl carboxylate salts ($E_{1/2furanose(OBn)3}$ = +1.15 V, $E_{1/2pyranose(OBn)4}$ = +1.32 V, respectively)[28]. Thus, we attempted to perform the coupling of **1a** and **2a** by using a photocatalyst having a higher oxidative potential than **PC2** ($E_{1/2(PC^*/PC^{-\cdot})}$ = +1.21 V *vs* SCE in MeCN) such as 4CzIPN ($E_{1/2(PC^*/PC^{-\cdot})}$ = +1.35 V *vs* SCE in MeCN). However, under these conditions, the reaction failed.

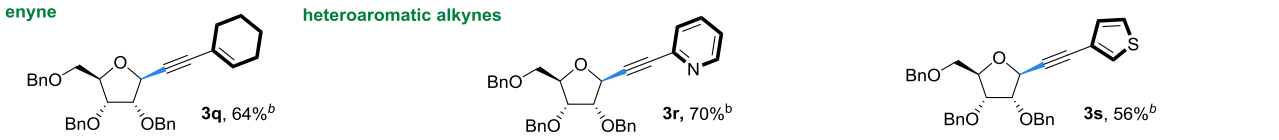
Alkynes are highly valuable intermediates in organic synthesis as they can be involved in a wide range of transformations at triple bonds. To further show the synthetic utility of our protocol, we evaluated whether the alkyne function of **3a** could be used as a platform to access more complex C-nucleosides through simple transformations of the CΞC bond (Scheme 2). To our delight, complete hydrogenation of **3a** afford a pure alkyl β-*C*-nucleoside **4a** in an excellent yield. In addition, **3a** was converted to pyridazine *C*-nucleosides **4b** in good yield through inverse demand hetero Diels–Alder reaction with dimethyl 1,2,4,5- tetrazine-3,6-dicarboxylate (Scheme 2).[33] This is an immediate application to the synthesis of pyrrole *C*-

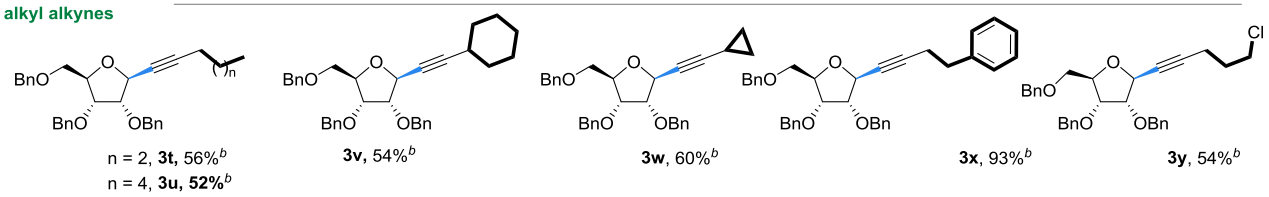
nucleoside analogs of biological interest.[34] Finally, hydration of the alkyne **3a** by PTSA[35] gave the corresponding ketone *C*-nucleosides **4c**/**4c'** in a 1:3 mixture of both regioisomers (73% yield, Scheme 2).

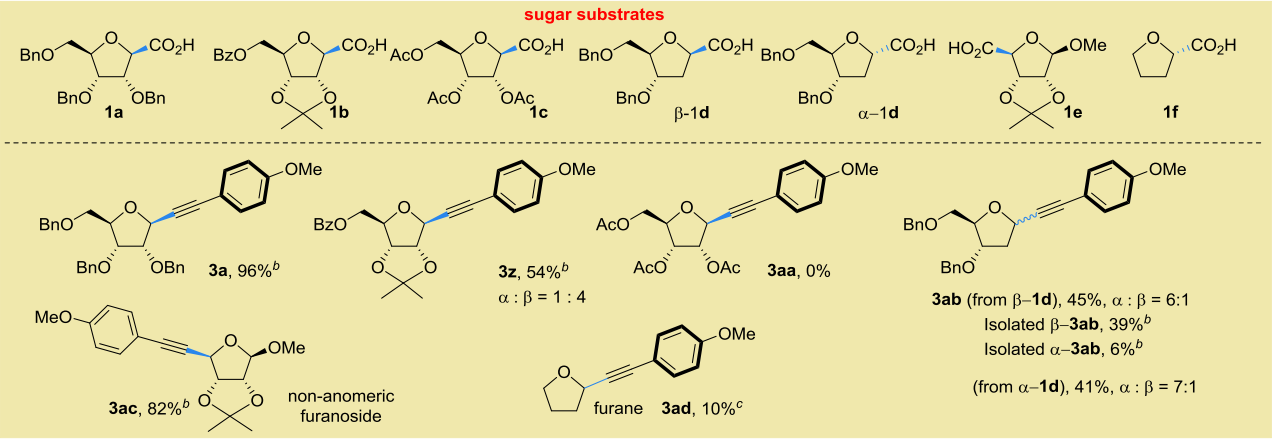
Scheme 1. Scope and limitation of the coupling of furanosyl carboxylic acids **1a-f** with alkynes **2**.[a]





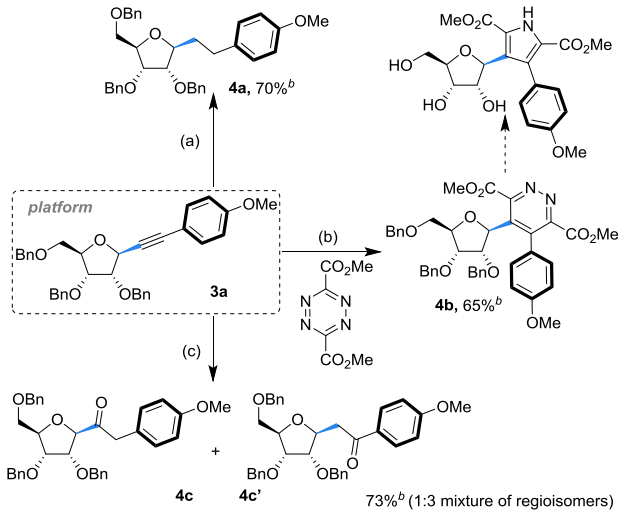






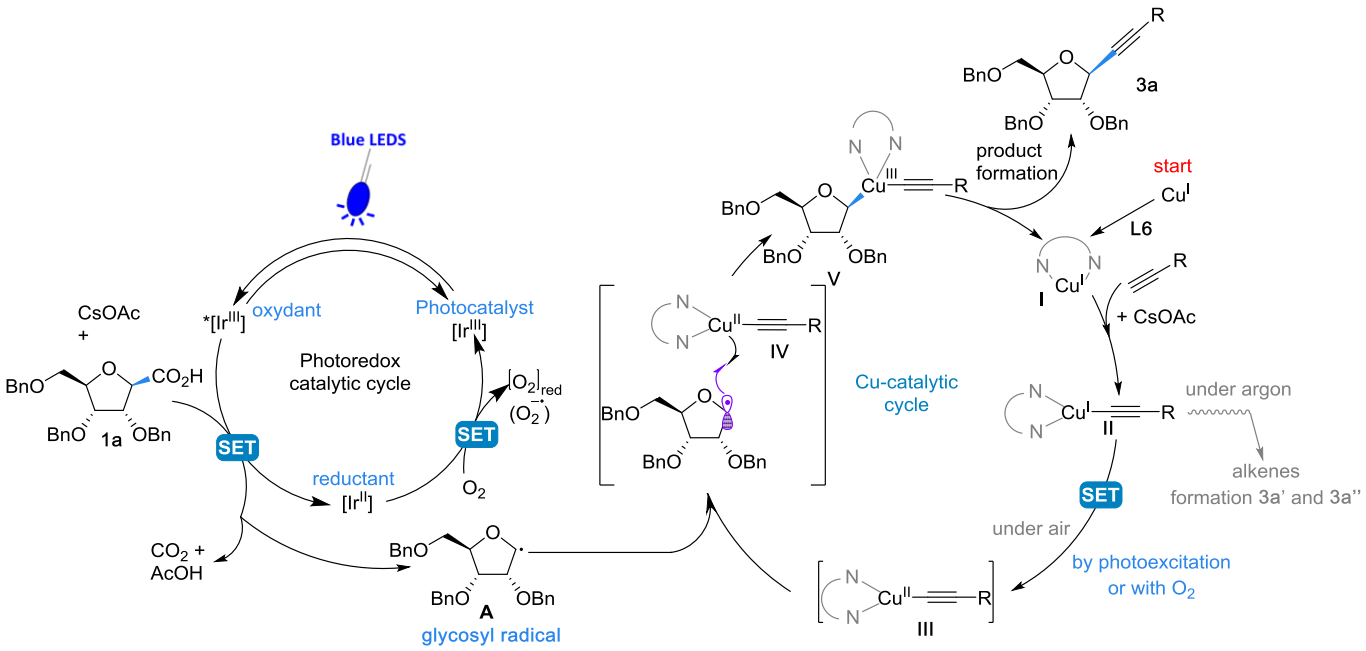
[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), CuOAc (20 mol%), L5 (20 mol%), PC2 (2.5 mol%) and CsOAc (0.4 mmol) in DMA (2.0 mL) under air and blue LEDs (4.5 W, irradiation) for 24 h. [b]Isolated yield. [c]estimated by LCMS.

Scheme 2. Furthers functionalization of the triple bond.[a]



[a] Reactions conditions: (a) **3a** (0.1 mmol) and Pd/C 10 wt% in MeOH (0.1 M) at rt for overnight. (b) **3a** (0.2 mmol), Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (0.3 mmol, 1.5 equiv) in toluene (0.1 M), reflux. (c) **3a** (0.1 mmol) and PTSA (0.2 eq) in EtOH (0.4 M) at 120 °C, (MW) for 30 min. [b]Isolated yield.

Based on recent literature reports,[22a,28,29] a reasonable mechanism is proposed in Scheme 3. The photocatalytic cycle would start by the activation of the iridium catalyst to the excited state Ir* by the means of visible light followed by the oxidation of carboxylic acid (or cesium carboxylate) leading to the formation of the anomeric radical **A** and reduced iridium(II) complex. Simultaneously, the reaction of the Cu(I) catalyst and alkyne **2a** in the presence of the base generates the monomeric Cu(I)-acetylene complex **II**.[29,36] Then, single electron transfer (SET) of this later led to the Cu(II) complex **III**.[36] At this stage, two pathways may be involved (*i*) oxidation of the Cu(I) complex by oxygen as a terminal niddle[36b] or (*ii*) by the means of photoexcitation of [LCu(I)] to [LCu(I)*][37] followed by and electron transfer mechanism.[29,36b] Later, the anomeric radical **A**, can be captured by LCu(II)-acetylene **III** to form the high-valent transient Cu(III) species **IV** through the radical relay mechanism.[38] Reductive elimination would deliver the final β-alkynyl nucleoside **3a** and regenerate the Cu(I) catalyst for the next catalytic cycle. The final key step cycle would be then the reoxidation of iridium(II) complex by a molecule of dioxygen[36b, 39] to generate the ground-state Ir-photocatalyst and close the catalytic cycle.



Scheme 3. Proposed mechanism for the dual copper-photoredox catalyzed alkynylation of anomeric radicals

In summary, we described here the first catalytic approach for the alkynylation of anomeric furanosyls with various terminal alkynes *via* a cooperative photoredox/copper catalysis strategy. This method provides an unprecedented access to alkynyl *C*-nucleosides under mild conditions with high efficiency and diastereoselectivity. Further mechanistic investigations of this reaction are currently underway. We believe that this method not

only opens a new way for catalytic alkynylation of furanosides, but also provides a versatile and convergent approach for the synthesis of complex *C*-nucleosides through further functionalizations of the tripe bond.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Full optimization table, NMR spectra of all synthesized compounds and HPLC chromatograms.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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Notes

The authors declare no competing financial interest

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ABBREVIATIONS

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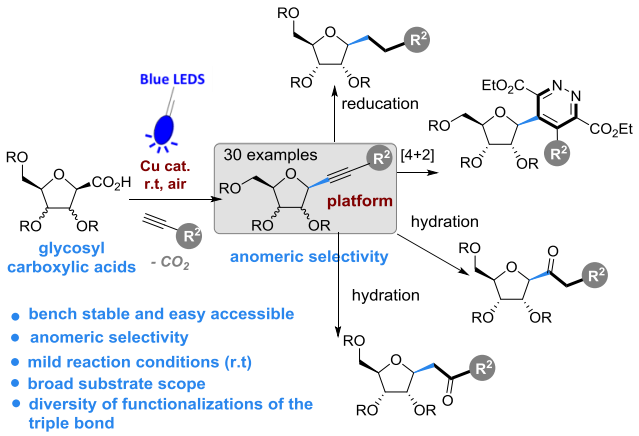
Blue LEDS
Cu cat.
r.t, air
glycosyl
carboxylic acids
- CO2
30 examples
platform
anomeric selectivity
reducation
[4+2]
hydration
hydration
bench stable and easy accessible
anomeric selectivity
mild reaction conditions (r.t)
broad substrate scope
diversity of functionalizations of the triple bond