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 varitriol³ and showdomycin⁴ (natural nucleosides), ribavirin analogs⁵ such as pyrazomycin⁶ or SO91⁷ (antitumor agent), and benzamide ribonucleotide⁸ (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, hydrometallation¹³ followed by a selective functionalization or (4+2) cycloaddition with azides to produce triazoles¹⁴ or with dienes¹⁵ 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 Zn²⁺-dependent enzyme LpxC¹⁷ (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 Organome-

tallic alkynes such as alkynyl trifluoroborates¹⁹ or alkynyltin species²⁰ are well known to be good partners in the

(a) Example of natural and bioactive C-Nucleosides

(b) Possible further functionalizations of alkyne C-Nucleosides

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

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 acid used. These issues often limit the practicability of the

Figure 2. (a) strategies for the synthesis of alkynyl C-nucleosides, (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 photoredox²² 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-workers²⁸ 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, $E_{1/2\text{furanose}(\text{OBn})_3} = +1.15$ 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 ($E_{1/2(\text{PC}^+/\text{PC}^-)} = +1.35$ 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 1 mol%	50
4	CuOAc 10 mol%	61
5	L1 or L2 or L3 or L4 instead of L5	traces
6	L6 instead 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 alkynyl (**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)³–C(sp³) 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 O₂ 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-methoxyphenylacetylene **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(CF₃) ppy]₂(dtbbpy) PF₆ photocatalyst (**PC2**, $E_{1/2(PC^+/PC^-)} = +1.21$ 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-CF₃-ppy)₃, IrMe(Me)ppy₂(dtbpy)PF₆ 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, –CF₃, –COMe and –CO₂Me) 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(sp³)–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 ($E_{1/2(furanose(OBn)3} = +1.15$ V, $E_{1/2(pyranose(OBn)4} = +1.32$ V, respectively)³³. Thus, we attempted to perform the coupling of **1a** and **2a** by using a photocatalyst having a higher oxidative potential than **PC2** ($E_{1/2(PC^+/PC^-)} = +1.21$ V vs SCE in MeCN) such as 4CzIPN ($E_{1/2(PC^+/PC^-)} = +1.35$ 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 C≡C 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 PTSA³⁵ 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. Further 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 middle^{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 alkylation of anomeric radicals

In summary, we described here the first catalytic approach for the alkylation 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 alkylation 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

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ABBREVIATIONS

REFERENCES

- (1) (a) Jordheim, L. P.; Durantel, D.; Zoulim, F.; Dumontet, C. Advances in the development of nucleoside and nucleotide analogues for cancer and viral diseases. *Nat. Rev. Drug Discovery* **2013**, *12*, 447–464. (b) Coats, S. J.; Garnier-Amblard, E. C.; Amblard, F.; Ehteshami, M.; Amiralaei, S.; Zhang, H.; Zhou, L.; Boucle, S. R. L.; Lu, X.; Bondada, L.; Shelton, J. R.; Li, H.; Liu, P.; Li, C.; Cho, J. H.; Chavre, S. N.; Zhou, S.; Mathew, J.; Schinazi, R. F. Chutes and ladders in hepatitis C nucleoside drug development. *Antiviral Res.* **2014**, *102*, 119–147. (c) Pradere, U.; Garnier-Amblard, E. C.; Coats, S. J.; Amblard, F.; Schinazi, R. F. Synthesis of nucleoside phosphate and phosphonate prodrugs. *Chem. Rev.* **2014**, *114*, 9154–9218. (d) DeClercq, E. C-Nucleosides to be revisited: Miniperspective. *J. Med. Chem.* **2016**, *59*, 2301–2311. (e) Draffan, A. G.; Frey, B.; Pool, B.; Gannon, C.; Tyndall, E. M.; Lilly, M.; Francom, P.; Hufton, R.; Halim, R.; Jahangiri, S.; Bond, S.; Nguyen, V. T. T.; Jeynes, T. P.; Wirth, V.; Luttkick, A.; Tilmanis, D.; Thomas, J. D.; Pryor, M.; Porter, K.; Morton, C. J.; Lin, B.; Duan, J.; Kulolj, G.; Simoneau, B.; McKercher, G.; Lagacé, L.; Amad, M.; Bethell, R. C.; Tucker, S. P. Discovery and Synthesis of C-Nucleosides as Potential New Anti-HCV Agents. *ACS Med. Chem. Lett.* **2014**, *5*, 679–684. (f) Wang, G.; Wan, J.; Hu, Y.; Wu, X.; Prhac, M.; Dyatkina, N.; Rajwanshi, V. K.; Smith, D. B.; Jekle, A.; Kinkade, A.; Symons, J. A.; Jin, Z.; Deval, J.; Zhang, Q.; Tam, Y.; Chanda, S.; Blattand, L.; Beigelman, L. Synthesis and Anti-Influenza Activity of Pyridine, Pyridazine, and Pyrimidine C-Nucleosides as Favipiravir (T-705) Analogues. *J. Med. Chem.* **2016**, *59*, 4611–4624. (g) Franchetti, P.; Cappellacci, L.; Grifantini, M.; Barzi, A.; Nocentini, G.; Yang, H.; O'Connor, A.; Jayaram, H. N.; Carrell, C.; Goldstein, B. M. Furanfuran and Thiophenfuran: Two Novel Tiazofuran Analogs. Synthesis, Structure, Antitumor Activity, and Interactions with Inosine Monophosphate Dehydrogenase. *J. Med. Chem.* **1995**, *38*, 3829–3837. (h) Krohn, K.; Heinsand, H.; Wielckens, K. Synthesis and cytotoxic activity of C-glycosidic nicotinamide riboside analogs. *J. Med. Chem.* **1992**, *35*,

- 511–517. (i) Feldman, A. W.; Romesberg, F. E.; Expansion of the Genetic Alphabet: A Chemist's Approach to Synthetic Biology. *Acc. Chem. Res.*, **2018**, *51*, 394–403. (j) Subadolknik, R. J. *Nucleoside Antibiotics*, Wiley Interscience, New York, **1970**. (k) Marquez, V. E.; Lim, M. I.; Carbocyclic Nucleosides. *Med. Res. Rev.* **1986**, *6*, 1–40. (l) Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*, Pergamon, Oxford, **1995**. (m) Ritchie, G. E.; Moffatt, B. E.; Sim, R. B.; Morgan, B. P.; Dwek, R. A.; Rudd, P. M. Glycosylation and the Complement System. *Chem. Rev.* **2002**, *102*, 305–320. (n) Hanessian, S.; Lou, B. Synthesis of Glycopeptides Containing Carbohydrate and Peptide Recognition Motifs. *Chem. Rev.* **2000**, *100*, 4495–4538.
- (2) (a) Dwek, R. A. Glycobiology: Toward Understanding the Function of Sugars. *Chem. Rev.* **1996**, *96*, 683–720. (b) Nicotra, F. Synthesis of C-glycosides of biological interest. *Top. Curr. Chem.* **1997**, *187*, 55–83. (c) Weatherman, R. V.; Mortell, K. H.; Chervenak, M.; Kiessling, L. L.; Toone, E. J. Specificity of C-Glycoside Complexation by Mannose/Glucose Specific Lectins. *Biochemistry* **1996**, *35*, 3619–3624. (d) Davis, F. F.; Allen, F. W. Utilization of purines and their derivatives by Gaffkya Homari. *J. Biol. Chem.* **1957**, *227*, 807–810. (e) Michelson, A. M.; Cohn, W. E. Cyclopseudouridine and the configuration of pseudouridine. *Biochemistry* **1962**, *1*, 490–495. (f) Cortese, R.; Kammen, H. O.; Spengler, S. J.; Ames, B. N. Biosynthesis of Pseudouridine in Transfer Ribonucleic Acid. *J. Biol. Chem.* **1974**, *249*, 1103–1108. (g) Daves, G. D.; Cheng, C. C. The Chemistry and Biochemistry of C-Nucleosides. *Prog. Med. Chem.* **1976**, *13*, 303–349. (h) Hacksell, U.; Daves, G. D. The Chemistry and Biochemistry of C-Nucleosides and C-Arylglycosides. *Prog. Med. Chem.* **1985**, *22*, 1–65. (i) Samuelsson, T.; Boren, T.; Johansen, T. I.; Lustig, F. Properties of a transfer RNA lacking modified nucleosides. *J. Biol. Chem.* **1988**, *263*, 13692–13699. (j) Townsend L. B. Chemistry of Nucleosides and Nucleotides; **1994**; Vol. 3.
- (3) Kumar, V.; Shaw, A. K. First Total Synthesis of (+)-Varitriol. *J. Org. Chem.* **2008**, *73*, 7526–7531.
- (4) (a) Roy-Burman, S.; Roy-Burman, P.; Visser, D. W. Showdomycin, A New Nucleoside Antibiotic. *Cancer Res.* **1968**, *28*, 1605–1610. (b) Palmu, K.; Rosenqvist, P.; Thapa, K.; Ilina, Y.; Siitonen, V.; Baral, B.; Mäkinen, J.; Belogurov, G.; Virta, P.; Niemi, J.; Metsä-Ketelä, M. Discovery of the Showdomycin Gene Cluster from Streptomyces showdoensis ATCC 15227 Yields Insight into the Biosynthetic Logic of C-Nucleoside Antibiotics. *ACS Chem Biol.* **2017**, *16*, 1472–1477. (c) Böttcher, T.; Sieber, S. A. Showdomycin as a Versatile Chemical Tool for the Detection of Pathogenesis-Associated Enzymes in Bacteria. *J. Am. Chem. Soc.* **2010**, *132*, 6964–6972.
- (5) (a) Witkowski, J. T.; Robins, R. K.; Sidwell, R. W.; Simon, L. N. Design, Synthesis, and Broad Spectrum Antiviral Activity of 1-β-D-Ribofuranosyl-1, 2, 4-triazole-3-carboxamide and Related Nucleosides. *J. Med. Chem.* **1972**, *15*, 1150–1154. (b) Sidwell, R. W.; Huffman, J. H.; Khare, G. P.; Allen, L. B.; Witkowski, J. T.; Robins, R. K. Broad-Spectrum Antiviral Activity of Virazole: 1-β-D-Ribofuranosyl-1, 2, 4-triazole-3-carboxamide. *Science* **1972**, *177*, 705–706. (c) Choo, Q. L.; Kuo, G.; Weiner, A. J.; Overby, L. R.; Bradley, D. W.; Houghton, M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* **1989**, *244*, 359–362.
- (6) (a) Sweeney, M. J.; Davis, F. A.; Gutowski, G. E.; Marnili, R. L.; Hoffman, D. H.; Poore, G. A. Experimental Antitumor Activity of Pyrazomycin. *Cancer Res.* **1973**, *33*, 2619–2623. (b) Gutowski, G. E.; Chaney, M. O.; Jones, N. D.; Hamill, R. L.; Davis, F. A.; Miller, R. D. Pyrazomycin B: Isolation and characterization of an α-C-nucleoside antibiotic related to pyrazomycin. *Biochem. and Biophys. Res. Commun.* **1973**, *51*, 312–317.
- (7) (a) Sabat, N.; Migianu-Griffoni, E.; Tudela, T.; Lecouvey, M.; Kellouche, S.; Carreiras, F.; Gallier, F.; Uziel, J.; Lubin-Germain, N. Synthesis and antitumor activities investigation of a C-nucleoside analogue of ribavirin. *Eur. J. Med. Chem.* **2020**, *188*, 112009–11016. (b) Solarte, C.; Dos Santos, M.; Gonzalez, S.; Miranda, L. S. M.; Guillot, R.; Ferry, A.; Gallier, F.; Uziel, J.; Lubin-Germain, N. Synthesis of C-Ribosyl-1, 2, 3-triazolyl Carboxamides. *Synthesis* **2017**, *49*, 1993–2002. (c) Youcef, R.; Santos, M.; Roussel, S.; Baltaze, J.; Lubin-Germain, N.; Uziel, J. Huisgen Cycloaddition Reaction of C-Alkynyl Ribosides under Micellar Catalysis: Synthesis of Ribavirin Analogues. *J. Org. Chem.* **2009**, *74*, 4318–4323.
- (8) (a) Krohn, K.; Heins, H.; Wielckens, K. Synthesis and Cytotoxic Activity of C-Glycosidic Nicotinamide Riboside Analogues. *J. Med. Chem.* **1992**, *35*, 511–517. (b) Jayaram, H. N.; Gharehbaghi, K.; Jayaram, N. H.; Rieser, J.; Krohn, K.; Paull, K. D. Cytotoxicity of a new IMP dehydrogenase inhibitor, benzamide riboside, to human myelogenous leukemia K562 cells. *Biochem. Biophys. Res. Commun.* **1992**, *186*, 1600–1606. (c) Gharehbaghi, K.; Paull, K. D.; Kelley, J. A.; Barchi, J. J.; Marquez, V. E.; Cooney, D. A.; Monks, A.; Scudiero, D.; Krohn, K.; Jayaram, H. N. Cytotoxicity and characterization of an active metabolite of benzamide riboside, a novel inhibitor of IMP dehydrogenase. *Int. J. Cancer* **1994**, *56*, 892–899. (d) Saunders, P. P.; Arimilli, S.; Krohn, K.; Muhs, M. A.; Alvarez, E.; Surveler, R. Metabolism and action of benzamide riboside in Chinese hamster ovary cells. *AntiCancer Drugs* **1996**, *7*, 93–99. (e) Grush, M.; Rosenberger, G.; Fuhrman, G.; Braun, K.; Titscher, B.; Szekeres, T.; Fritzer-Szekeres, M.; Oberhuber, G.; Krohn, K.; Hengstschlaeger, M.; Krupitza, G.; Jayaram, H. N. Benzamide riboside induces apoptosis independent of Cdc25A expression in human ovarian carcinoma N.1 cells. *Cell Death Differ.* **1999**, *8*, 736–744. (f) Krohn, K.; Dorner, H.; Zukowski, M. Chemical Synthesis of Benzamide Riboside. *Curr. Med. Chem.* **2002**, *9*, 727–731. (g) Gharehbaghi, K.; Grunberger, W.; Jayaram, H. N. Studies on the Mechanism of Action of Benzamide Riboside: A Novel Inhibitor of IMP Dehydrogenase. *Curr. Med. Chem.* **2002**, *9*, 743–748.
- (9) Ni, X.; Schröder, M.; Olieric, V.; Sharpe, M. E.; Hernandez-Olmos, V.; Proschak, E.; Merk, D.; Knapp, S.; Chaikuad, A. Structural Insights into Plasticity and Discovery of Remdesivir Metabolite GS-441524 Binding in SARS-CoV-2 Macromolecule. *ACS Med. Chem. Lett.* **2021**, *12*, 603–609.
- (10) (a) Dhami, K.; Malyshev, D. A.; Ordoukhanian, P.; Kubelka, T.; Hocke, M.; Romesberg, F. E. Systematic exploration of a class of hydrophobic unnatural base pairs yields multiple new candidates for the expansion of the genetic alphabet. *Nucleic Acids Res.* **2014**, *42*, 10235–10244. (b) Feldman, A. W.; Dien, V. T.; Karadeema, R. J.; Fischer, E. C.; You, Y.; Anderson, B. A.; Krishnamurthy, R.; Chen, J. S.; Li, L.; Romesberg, F. E. Optimization of Replication, Transcription, and Translation in a Semi-Synthetic Organism. *J. Am. Chem. Soc.* **2019**, *141*, 10644–10653. (c) Laverne, T.; Degardin, M.; Malyshev, D. A.; Quach, H. T.; Dhami, K.; Ordoukhanian, P.; Romesberg, F. E. Expanding the Scope of Replicable Unnatural DNA: Stepwise Optimization of a Predominantly Hydrophobic Base Pair. *J. Am. Chem. Soc.* **2013**, *135*, 5408–5419. (d) Malyshev, D. A.; Dhami, K.; Laverne, T.; Chen, T.; Dai, N.; Foster, J. M.; Corrêa, I. R.; Romesberg, F. E. A semi-synthetic organism with an expanded genetic alphabet. *Nature* **2014**, *509*, 385–388. (e) Guo, J.; Wang, S.; Dai, N.; Teo, Y. N.; Kool, E. T. Multispectral labeling of antibodies with polyfluorophores on a DNA backbone and application in cellular imaging. *Proc. Natl. Acad. Sci.* **2011**, *108*, 3493–3498.
- (11) (a) Temburnikar, K.; Seley-Radtke, K. L. Recent advances in synthetic approaches for medicinal chemistry of C-nucleosides. *Beilstein J. Org. Chem.* **2018**, *14*, 772–785. (b) Tatina, M. B.; Hussain, A.; Dhas, A. K.; Mukherjee, D. Advances in C-alkynylation of sugars and its application in organic synthesis. *RSC Adv.* **2016**, *6*, 75960–75972.
- (12) Selected review: (a) Song, G.; Fen, W.; Li, X. C-C, C-O and C-N bond formation via rhodium(III)-catalyzed oxidative C-H activation. *Chem. Soc. Rev.* **2012**, *41*, 3651–3678. (b) Song, X.; Qiu, Y.; Liu, X.

- Liang, Y. Recent advances in the tandem reaction of azides with alkynes or alkynols. *Org. Biomol. Chem.* **2016**, *14*, 11317–11331. (c) Severin, R.; Doye, S. The catalytic hydroamination of alkynes. *Chem. Soc. Rev.* **2007**, *36*, 1407–1420. (d) Pohlki, F.; Doye, S. The catalytic hydroamination of alkynes. *Chem. Soc. Rev.* **2003**, *32*, 104–114. (e) Alonso, F.; Beletskaya, I. P.; Yus, M. Transition-Metal-Catalyzed Addition of Heteroatom–Hydrogen Bonds to Alkynes. *Chem. Rev.* **2004**, *104*, 3079–3160. (e) Müller, T. E.; Beller, M. Metal-Initiated Amination of Alkenes and Alkynes. *Chem. Rev.* **1998**, *98*, 675–704.
- (13) Alami, M.; Hamze, A.; Provot, O. Hydrostannylation of Alkynes. *ACS Catalysis* **2019**, *9*, 3437–3466.
- (14) Ma, J.; Ding, S. Transition Metal-Catalyzed Cycloaddition of Azides with Internal Alkynes. *Asian J. Org. Chem.* **2020**, *9*, 1872–1888.
- (15) (a) Ackermann, L. Carboxylate-Assisted Ruthenium-Catalyzed Alkyne Annulations by C–H/Het–H Bond Functionalizations. *Acc. Chem. Res.* **2014**, *47*, 281–295. (b) Guo, T. L.; Huang, F.; Yu, L. K.; Yu, Z. K. Indole synthesis through transition metal-catalyzed C–H activation. *Tetrahedron Lett.* **2015**, *56*, 296–302. (c) Kumar, I.; Kumar, R.; Sharma, U. Recent Advances in the Regioselective Synthesis of Indoles via C–H Activation/Functionalization. *Synthesis* **2018**, *50*, 2655–2677. (d) Mancuso, R.; Dalpozzo, R. Recent Progress in the Transition Metal Catalyzed Synthesis of Indoles. *Catalysts* **2018**, *8*, 458–464.
- (16) Hilt, G.; Danz, M. Regioselective Cobalt-Catalyzed Diels–Alder Reaction towards 1, 3-Disubstituted and 1, 2, 3-Trisubstituted Benzene Derivatives. *Synthesis* **2008**, *14*, 2257–2263.
- (17) Jana, K. S.; Löppenber, M.; Daniliuc, C. G.; Holl, R. Synthesis and biological evaluation of C-ethynyl furanosides as LpxC inhibitors. *Tetrahedron* **2015**, *71*, 956–966.
- (18) Germain, N. L.; Baltaze, J. P.; Coste, A.; Hallonet, A.; Lauréano, H.; Legrave, G.; Uziel, J.; Auge, Direct C-Glycosylation by Indium-Mediated Alkynylation on Sugar Anomeric Position. *J. Org. Lett.* **2008**, *10*, 725–728.
- (19) (a) Zeng, J.; Vedachalam, S.; Xiang S.; Liu, X.-W. Synthesis of Pillar[5]arene Dimers and Their Cooperative Binding toward Some Neutral Guests. *Org. Lett.* **2011**, *13*, 42–45. (b) Asano, N. Glycosidase inhibitors: update and perspectives on practical use. *Glycobiology* **2003**, *13*, 93R–104R. (c) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. Sugar-mimic glycosidase inhibitors: natural occurrence, biological activity and prospects for therapeutic application. *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.
- (20) Zhai, D.; Zhai, W.; Williams, R. M. Alkynylation of Mixed Acetals with Organotin Acetylides. *J. Am. Chem. Soc.* **1988**, *110*, 2501–2505.
- [21] Buchanan, J.G.; Edgar, A.R.; Power, M. J. C-nucleoside studies. Part I. Synthesis of [2, 3, 5-tri-O-benzyl- α (and β)-D-ribofuranosyl]ethyne. *J. Chem. Soc. Perkin Trans. I* **1974**, 1943–1949.
- (22) (a) Vaillant, F. L.; Waser, J. Alkynylation of radicals: spotlight on the “Third Way” to transfer triple bonds. *Chem. Sci.* **2019**, *10*, 8909–8923. (b) Vaillant, F. L.; Courant, T.; Waser, J. Room-Temperature Decarboxylative Alkynylation of Carboxylic Acids Using Photoredox Catalysis and EBX Reagents. *Angew. Chem. Int. Ed.* **2015**, *54*, 11200–11356.
- (23) (a) Xu, L.; Fana, N.; Hu, X. Recent development in the synthesis of C-glycosides involving glycosyl radicals. *Org. Biomol. Chem.* **2020**, *18*, 5095–5109. (b) Ghouilem, J.; Robichon, M. D.; Bideau, F. L.; Ferry, A.; Messaoudi, S. Emerging Organometallic Methods for the Synthesis of C-Branched (Hetero)aryl, Alkenyl, and Alkyl Glycosides: C–H Functionalization and Dual Photoredox Approaches. *Chem. Eur. J.* **2021**, *27*, 491–511.
- (24) (a) Andrews, R. S.; Becker J. J.; Gagné, M. R. Intermolecular Addition of Glycosyl Halides to Alkenes Mediated by Visible Light. *Angew. Chem. Int. Ed.* **2010**, *49*, 7274–7276. (b) Andrews, R. S.; Becker, J. J.; Gagné, M. R. A photoflow reactor for the continuous photoredox-mediated synthesis of C-glycoamino acids and C-glycolipids. *Angew. Chem. Int. Ed.* **2012**, *51*, 4140–4143.
- (25) Dumoulin, A.; Matsui, J. K.; Gutiérrez- Bonet, A.; Molander, G. A. Synthesis of Non-Classical Arylated C-Saccharides through Nickel/Photoredox Dual Catalysis. *Angew. Chem. Int. Ed.* **2018**, *57*, 6614–6728.
- (26) Wei, Y.; Benzvi, B.; Diao, T. Diastereoselective Synthesis of Aryl C-Glycosides from Glycosyl Esters via C–O Bond Homolysis. *Angew. Chem. Int. Ed.* **2021**, *60*, 9433–9438.
- (27) Takeda, D.; Yoritake, M.; Yasutomi, H.; Chiba, S.; Moriyama, T.; Yokoo, A.; Usui, K.; Hirai, G. β -Glycosyl Trifluoroborates as Precursors for Direct α -C-Glycosylation: Synthesis of 2-Deoxy- α -C-glycosides. *Org. Lett.* **2021**, *23*, 1940–1944.
- (28) Ma, Y.; Liu, S.; Xi, Y.; Li, H.; Yang, K.; Cheng, Z.; Wang, W.; Zhang, Y. Highly stereoselective synthesis of aryl/heteroaryl-C-nucleosides via the merger of photoredox and nickel catalysis. *Chem. Commun.* **2019**, *55*, 14657–14660.
- (29) (a) Xia, H.-D.; Li, Z.; Gu, Q.; Dong, X.-Y.; Fang, J.; Du, X.; Wang, L.; Liu, X. Photoinduced Copper-Catalyzed Asymmetric Decarboxylative Alkynylation with Terminal Alkynes. *Angew. Chem. Int. Ed.* **2020**, *59*, 16926–16932; (b) Mao, Y.; Zhao, W.; Lu, S.; Yu, L.; Wang, Y.; Liang, Y.; Ni, S.; Pan, Y. Copper-catalysed photoinduced decarboxylative alkynylation: a combined experimental and computational study. *Chem. Sci.*, **2020**, *11*, 4939–4947
- (30) Selected articles: (a) Ghouilem, J.; Tran, C.; Grimblat, N.; Retailleau, P.; Alami, M.; Gandon, V.; Messaoudi, S. Diastereoselective Pd-Catalyzed Anomeric C(sp³)-H Activation: Synthesis of α -(Hetero)aryl C-Glycosides. *ACS Catal.* **2021**, *11*, 1818–1826. (b) Zhu, M.; Alami, M.; Messaoudi, S. Electrochemical nickel-catalyzed Migita cross-coupling of 1-thiosugars with aryl, alkenyl and alkynyl bromides. *Chem. Commun.* **2020**, *56*, 4464–4467. (c) Ghouilem, J.; Franco, R.; Retailleau, P.; Alami, M.; Gandon, V.; Messaoudi, S. Regio- and diastereoselective Pd-catalyzed synthesis of C2-aryl glycosides. *Chem. Commun.* **2020**, *56*, 7175–7178. (d) Zhu, M.; Dagousset, G.; Alami, M.; Magnier, E.; Messaoudi, S. Ni/Photoredox-Dual-Catalyzed Functionalization of 1-Thiosugars. *Org. Lett.* **2019**, *21*, 5132–5137. (e) Montoir, D.; Amoura, M.; Ababsa, Z. E. -A.; Vishwanath, T. M.; Yen-Pon, E.; Robert, V.; Beltramo, M.; Piller, V.; Alami, M.; Aucagne, A.; Messaoudi, S. Synthesis of aryl-thioglycopeptides through chemoselective Pd-mediated conjugation. *Chem. Sci.* **2018**, *9*, 8753–8759. (f) Probst, N.; Grelier, G.; Dhaoui, S.; Alami, M.; Gandon, V.; Messaoudi, S. Palladium(II)-Catalyzed Diastereoselective 2, 3-Trans C(sp³)-H Arylation of Glycosides. *ACS Catal.* **2018**, *8*, 7781–7786. (g) Probst, N.; Grelier, G.; Ghermani, N.; Gandon, V.; Alami, M.; Messaoudi, S. Intramolecular Pd-Catalyzed Anomeric C(sp³)-H Activation of Glycosyl Carboxamides. *Org. Lett.* **2017**, *19*, 5038–5041. (h) Bruneau, A.; Roche, M.; Hamze, A.; Brion, J. D.; Alami, M.; Messaoudi, S. Stereoretentive Palladium-Catalyzed Arylation, Alkenylation, and Alkynylation of 1-Thiosugars and Thiols Using Aminobiphenyl Palladacycle Precatalyst at Room Temperature. *Chem. Eur. J.* **2015**, *21*, 8375–8379.
- (31) Mastandrea, M. M.; Cañellas, S.; Caldentey, X.; Pericàs, M. A. Decarboxylative Hydroalkylation of Alkynes via Dual Copper-Photoredox Catalysis. *ACS Catal.* **2020**, *10*, 6402–6408.
- (32) (a) Zhai, D.; Zhai, W.; Williams, R. M. Alkynylation of Mixed Acetals with Organotin Acetylides, *J. Am. Chem. Soc.* **1988**, *110*, 2501–2505; (b) Naud, S.; Pipelier, M.; Viault, G.; Adjou, A.; Huet, F.; Legoupy, S.; Aubertin, A.; Evain, M.; Dubreuil, D. Synthesis of Polyhydroxylated Pyrano-Pyrrole Derivatives from Carbohydrate

- Precursors, *Eur. J. Org. Chem.*, **2007**, 20, 3296–3310; (c) Naud, S.; Pipelier, M.; Chaumette, C.; Viault, G.; Huet, F.; Legoupy, S.; Dubreuil, D. Synthesis of Novel Polyhydroxylated Tetrahydropyranopyrroles, *Synlett*, **2007**, 3, 403–406.
- (33) Joshi, U.; Josse, S.; Pipelier, M.; Chevallier, F.; Pradère, J. -P.; Hazard, R.; Legoupy, S.; Huet, F.; Dubreuil, D. Novel pyrrole C-nucleosides by nitrogen extrusion from pyridazine C-nucleosides. *Tetrahedron Lett.* **2004**, 45, 1031–1033.
- (34) (a) Lam, K. S.; Glersaye, S.; Patel, K.; Najmi, S.; Burnham, B. S. Abstracts of Papers, 225th ACS National Meeting, New Orleans, LA, United States, March 23–27, **2003**. (b) Krishna, P. R.; Reddy, V. V. Reddy, Srinivas, R. A new synthetic route to oxazole and pyrrole 2-deoxy-C-ribosides. *Tetrahedron* **2007**, 63, 9871–9888. (c) Nichols, R.; Andrews, P. C.; Zhang, P.; Bergstrom, D. E. A universal nucleoside for use at ambiguous sites in DNA primers, *Nature* **1994**, 369, 492–493. (d) Bergstrom, D. E.; Zhang, P.; Toma, P. H.; Andrews, P. C.; Nichols, R. Synthesis, Structure, and Deoxyribonucleic Acid Sequencing with a Universal Nucleoside: 1-(2'-Deoxy- β -D-ribofuranosyl)-3-nitropyrrole, *J. Am. Chem. Soc.* **1995**, 117, 1201–1209. (e) Klewler, D. A.; Hoskins, A.; Zhang, P.; Davisson, V. J.; Bergstrom, D. E.; LiWang, A. C. NMR structure of a DNA duplex containing nucleoside analog 1-(2'-deoxy- β -D-ribofuranosyl)-3-nitropyrrole and the structure of the unmodified control, *Nucleic Acids Res.* **2000**, 28, 4514–4522. (f) Harki, D. A.; Graci, J. D.; Korneeva, V. S.; Ghosh, S. K. B.; Hong, Z.; Cameron, C. E.; Peterson, B. R. Synthesis and Antiviral Evaluation of a Mutagenic and Non-Hydrogen Bonding Ribonucleoside Analogue: 1- β -D-Ribofuranosyl-3-nitropyrrole, *Biochemistry* **2002**, 41, 9026–9033.
- (35) Jacubert, M.; Provot, O.; Peyrat, J. F.; Hamze, A.; Brion, J. D.; Alami, M. p-Toluenesulfonic acid-promoted selective functionalization of unsymmetrical arylalkynes: a regioselective access to various arylketones and heterocycles. *Tetrahedron* **2010**, 66, 3775–3787.
- (36) (a) Dong, X.-Y.; Cheng, J.-T.; Zhang, Y.-F.; Li, Z.-L.; Zhan, T.-Y.; Chen, J.-J.; Wang, F.-L.; Yang, N.-Y.; Ye, L.; Gu, Q.-S.; Liu, X.-Y. Copper-Catalyzed Asymmetric Radical 1, 2-Carboalkynylation of Alkenes with Alkyl Halides and Terminal Alkynes. *J. Am. Chem. Soc.* **2020**, 142, 9501–9509. (b) Zhao, X.; MacMillan, D. W. C. Metallaphotoredox Perfluoroalkylation of Organobromides. *J. Am. Chem. Soc.* **2020**, 142, 19480–19486. (c) Cao, Z.; Li, J.; Sun, Y.; Zhang, H.; Mo, X.; Cao, X.; Zhang, G. Photo-induced copper-catalyzed alkynylation and amination of remote unactivated C(sp³)-H bonds, *Chem.Sci.* **2021**, 12, 4836–4840.
- (37) Representative examples: (a) Sagadevan, A.; Pampana, V. K. K.; Hwang, K. C. Copper Photoredox Catalyzed A3' Coupling of Arylamines, Terminal Alkynes, and Alcohols through a Hydrogen Atom Transfer Process. *Angew.Chem. Int. Ed.* **2019**, 58, 3838–3842. (b) Hazra, A.; Lee, M. T.; Chiu, J. F.; Lalic, G. Photoinduced Copper - Catalyzed Coupling of Terminal Alkynes and Alkyl Iodides. *Angew. Chem. Int. Ed.* **2018**, 57, 5492–5496. (c) Sagadevan, A.; Charpe, V. P.; Ragupathi, A.; Hwang, K. C. Visible Light Copper Photoredox-Catalyzed Aerobic Oxidative Coupling of Phenols and Terminal Alkynes: Regioselective Synthesis of Functionalized Ketones via C $\equiv$ C Triple Bond Cleavage. *J. Am. Chem. Soc.* **2017**, 139, 2896–2899. (d) Sagadevan, A.; Ragupathi, A.; Hwang, K. C. Photoinduced Copper-Catalyzed Regioselective Synthesis of Indoles: Three-Component Coupling of Arylamines, Terminal Alkynes, and Quinones. *Angew.Chem. Int. Ed.* **2015**, 54, 13896–13901. (e) Sagadevan, A.; Ragupathi, A.; Lin, C. C.; Hwu, J. R.; Hwang, K. C. Visible-light initiated copper(i)-catalysed oxidative C-N coupling of anilines with terminal alkynes: one-step synthesis of α -ketoamides. *Green Chem.* **2015**, 17, 1113–1119. (f) Sagadevan, A.; Hwang, K. C. Photo-Induced Sonogashira C-C Coupling Reaction Catalyzed by Simple Copper(I) Chloride Salt at Room Temperature. *Adv. Synth. Catal.* **2012**, 354, 3421–3427.
- (38) (a) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. Enantioselective cyanation of benzylic C-H bonds via copper-catalyzed radical relay. *Science*, **2016**, 353, 1014–1018. (b) Lu, F.; Liu, D.; Zhu, L.; Lu, L.; Yang, Q.; Zhou, Q.; Wei, Y.; Lan, Y.; Xiao, W. Asymmetric Propargylic Radical Cyanation Enabled by Dual Organophotoredox and Copper Catalysis. *J. Am. Chem. Soc.* **2019**, 141, 6167–6172. (c) Lin, J.-S.; Wang, F.-L.; Dong, X.-Y.; He, W.-W.; Yuan, Y.; Chen, S.; Liu, X.-Y. Catalytic asymmetric radical aminoperfluoroalkylation and aminodifluoromethylation of alkenes to versatile enantioenriched-fluoroalkyl amines. *Nat. Commun.* **2017**, 8, 14841–14851. (d) Cao, Y.-X.; Dong, X.-Y.; Yang, J.; Jiang, S.-P.; Zhou, S.; Li, Z.-L.; Chen, G.-Q.; Liu, X.-Y. A Copper-Catalyzed Sonogashira Coupling Reaction of Diverse Activated Alkyl Halides with Terminal Alkynes Under Ambient Conditions. *Adv. Synth.Catal.* **2020**, 362, 2280–2284.
- (39) Selected references for the oxygen oxidation of Ir-photocatalysts, see (a) Condie, A. G.; Gonzalez-Gomez, J. C.; Stephenson, C. R. J. Visible-Light Photoredox Catalysis: Aza-Henry Reactions via C-H Functionalization. *J. Am. Chem. Soc.* **2010**, 132, 1464–1465. Related article on singlet O₂ sensitization by Ir photocatalyst, see: (b) Demas, J. N.; Harris, J. E. W.; McBride, R. P. Energy Transfer from Luminescent Transition Metal Complexes to Oxygen. *J. Am. Chem. Soc.* **1977**, 99, 3547–3551. (c) Gao, R.; Ho, D. G.; Hernandez, B.; Selke, M.; Murphy, D.; Djurovich, P. I.; Thompson, M. E. Bis-cyclometalated Ir(III) Complexes as Efficient Singlet Oxygen Sensitizers. *J. Am. Chem. Soc.* **2002**, 124, 14828–14829. (d) Huang, C.; Liang, C.; Sadhukhan, T.; Banerjee, S.; Fan, Z.; Li, T.; Zhu, Z.; Zhang, P.; Raghavachari, K.; Huang, H. In-vitro and In-vivo Photocatalytic Cancer Therapy with Biocompatible Iridium(III) Photocatalysts. *Angew. Chem. Int. Ed.* **2021**, 60, 9474–9479. Related article on oxygen oxidation of Ru photocatalysts, see: (e) Tyson, E. L.; Ament, M. S.; Yoon, T. P. Transition Metal Photoredox Catalysis of Radical Thiol-Ene Reactions. *J. Org. Chem.* **2013**, 78, 2046–2050. (f) Ischay, M. A.; Ament, M. S.; Yoon, T. P. Crossed intermolecular [2 + 2] cycloaddition of styrenes by visible light photocatalysis. *Chem. Sci.*, **2012**, 3, 2807–2811.