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Highly stereoselective synthesis of aryl/heteroaryl-*C*-nucleosides *via* the merger of photoredox and nickel catalysis†

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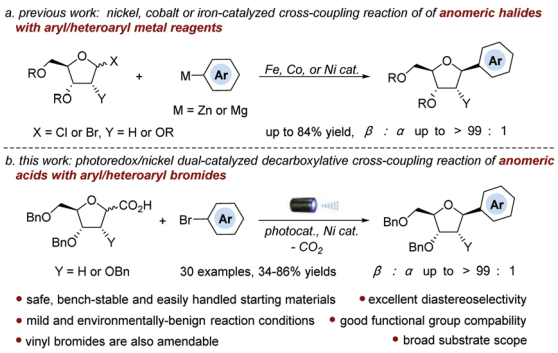
A photoredox/nickel dual-catalyzed decarboxylative cross-coupling reaction of anomeric ribosyl/deoxyribosyl acids with aryl/heteroaryl bromides has been developed. The reaction proceeds smoothly under visible-light irradiation and features the using of cost-effective and easily handled catalysts and starting materials, which allows the highly stereoselective synthesis of diverse aryl/heteroaryl-*C*-nucleosides in moderate to high yields.

C-Nucleosides with aryl and heteroaryl groups as nucleobase surrogates represent a class of promising antiviral and anticancer agents and are extensively applied in chemical biology to extend the genetic alphabet (see representative examples shown in Fig. S1, ESI†).[1,2]

The cross-coupling reaction enabled by low-cost and relatively non-toxic transition-metal catalysts, such as nickel, cobalt or iron catalyst, offers a powerful tool to access this class of valuable targets (Scheme 1a). The transformations typically proceed *via* anomeric radical intermediates and exhibit many advantages over the conventional methods based on the corresponding anions and cations: the reaction conditions are generally mild so that varied functional and protecting groups are tolerated and undesired elimination and/or epimerization reactions are suppressed.[3] For example, the nickel- and cobalt-catalyzed procedures have been reported for the synthesis of phenyl-*C*-nucleosides albeit with variable yields (20–88% yields) and limited substrate scope.[4,5] Recently, a highly stereoselective cross-coupling reaction catalyzed by a well-defined iron complex has been developed by Nakamura's group, providing aryl/heteroaryl-*C*-nucleosides in moderate to high yields and excellent β-selectivity (64–84%, $\beta:\alpha > 99:1$).[6] Nonetheless, this method suffers from the use of hazardous organometallic reagents and moisture-sensitive anomeric halides as the coupling partners. Moreover, low reaction efficiency was typically observed in the synthesis of the medicinally valuable electron-deficient aryl/heteroaryl-*C*-nucleosides.



Scheme 1 Synthesis of *C*-nucleosides *via* nickel, cobalt or iron-catalyzed radical cross-coupling approach.

To overcome these limitations, herein, we wish to report a novel photoredox/nickel dual-catalyzed cross-coupling approach for the highly stereoselective synthesis of both electron-rich and -deficient aryl/heteroaryl-*C*-nucleosides in moderate to high yields (Scheme 1b). By utilizing an organic photocatalyst (4CzIPN) in the presence of visible light, anomeric radicals are *in situ* generated *via* the decarboxylation process and efficiently coupled with a variety of aryl and heteroaryl bromides. In addition to the mild reaction conditions, broad substrate scope and good functional group compatibility, the most significant advantage of this transformation is the using of safe, bench-stable and easily handled starting materials. The powerful synthetic capacity of this method was further demonstrated by its application in the synthesis of various vinyl-*C*-nucleosides.

Since the pioneering work by MacMillan group,[7] photoredox/nickel dual-catalyzed decarboxylative cross-coupling reaction has emerged as a versatile method for the synthesis of valuable targets.[8] Our group has also reported a visible-light-promoted

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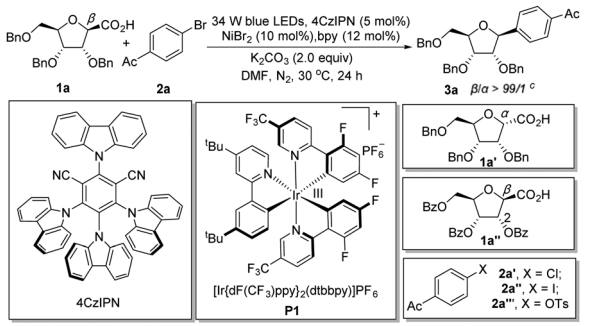
nickel- and organic-dye-cocatalyzed formylation reaction of aryl halides using diethoxyacetic acid as a formyl equivalent.[9] We envisaged that this state-of-the-art coupling technology might be extended for the synthesis of aryl/heteroaryl-*C*-nucleosides.

The initial investigation of the proposed reaction started with subjecting the readily accessible *O*-benzyl protected β-ribosyl acid **1a** and 1-(4-bromophenyl)ethan-1-one **2a** to the standard reaction conditions established in our previous study using 4CzIPN and $NiCl_2{\cdot}6H_2O$ as the catalysts and 34 W blue-light-emitting diodes (LEDs) as the light source.[9] To our delight the desired product **3a** was obtained in a tractable yield and excellent diastereoselectivity (32% yield, β:α > 99:1, entry 1, Table S1, ESI†). This outcome inspired us to systematically investigate the interesting reaction. Extensive reaction condition screening (Tables S1–S5, ESI†) identified the optimal conditions as follow: in the presence of 34W LEDs, 5 mol% of 4CzIPN, 10 mol% of $NiBr_2$, 12 mol% of 2,2′-bipyridine (bpy) and 2 equiv. of K_2CO_3, the reaction of **1a** with 2 equiv. of **2a** is conducted in DMF for 24 h at 30 °C. Under this reaction conditions, the *O*-benzyl protected *C*-nucleoside **3a** was produced in high yield and excellent β-selectivity (82%, β:α > 99:1, entry 1, Table 1). The variation of the standard reaction conditions by using $Ir[dF(CF_3)ppy]_2$-(dtbbpy)PF_6 as an alternative photocatalyst resulted in slightly diminished yield, while the diastereoselectivity remained unaffected (71% yield, β:α > 99:1, entry 2, Table 1).[7] The use of reduced amount of $NiBr_2$ (5 mol%) and bpy (6 mol%) in the reaction also led to a decreased reaction efficiency (entry 3, Table 1). Interestingly, the use of *O*-benzyl protected α-ribosyl acid **1a′** as the substrate has little effect on the reaction outcome (80% yield, β:α > 99:1, entry 4, Table 1). However, switching the protecting group of **1a** from benzyl (Bn) to benzoyl (Bz) completely suppressed the reaction (entry 5, Table 1). The extra coordination interaction induced by the Bz group at C2 position might interfere with the nickel catalysis (Scheme S1, ESI†), which is expected to explain these results. With respect to the electrophilic coupling partner, we found that aryl bromides were preferred (entries 6–8, Table 1). Control experiments established the importance of visible light, photocatalyst, nickel catalyst, ligand, and base, as no formation of the desired cross-coupled product was observed in the absence of these reaction promoters (entries 9–13, Table 1). Furthermore, the inhibition of the reactivity was also observed by the presence of molecular oxygen and TEMPO (23–25% yields, entries 14 and 15, Table 1), again suggesting the radical nature of the reaction.

Having established the optimal reaction conditions (entry 1, Table 1), the scope of the transformation with respect to the aryl/heteroaryl bromides was explored (Scheme 2). The aryl and electron-rich heteroaryl bromides were found to readily couple with **1a**, providing the desired products in moderate to high yields and excellent β-selectivity (34–86%, β:α > 99:1). The reactions of the aryl bromides bearing electron-withdrawing groups at the *para*-position proceeded well (**3b–3f**, 61–85% yields), while the introduction of strong electron-donating group at this position was detrimental to the reaction efficiency (**3g**, 51% yield). A variety of functional groups, such as ester, cyano, sulphonate and alkynyl, were well tolerated, providing handles for further synthetic elaboration. The introduction of

Table 1 The optimization and validation of the reaction conditions[a]

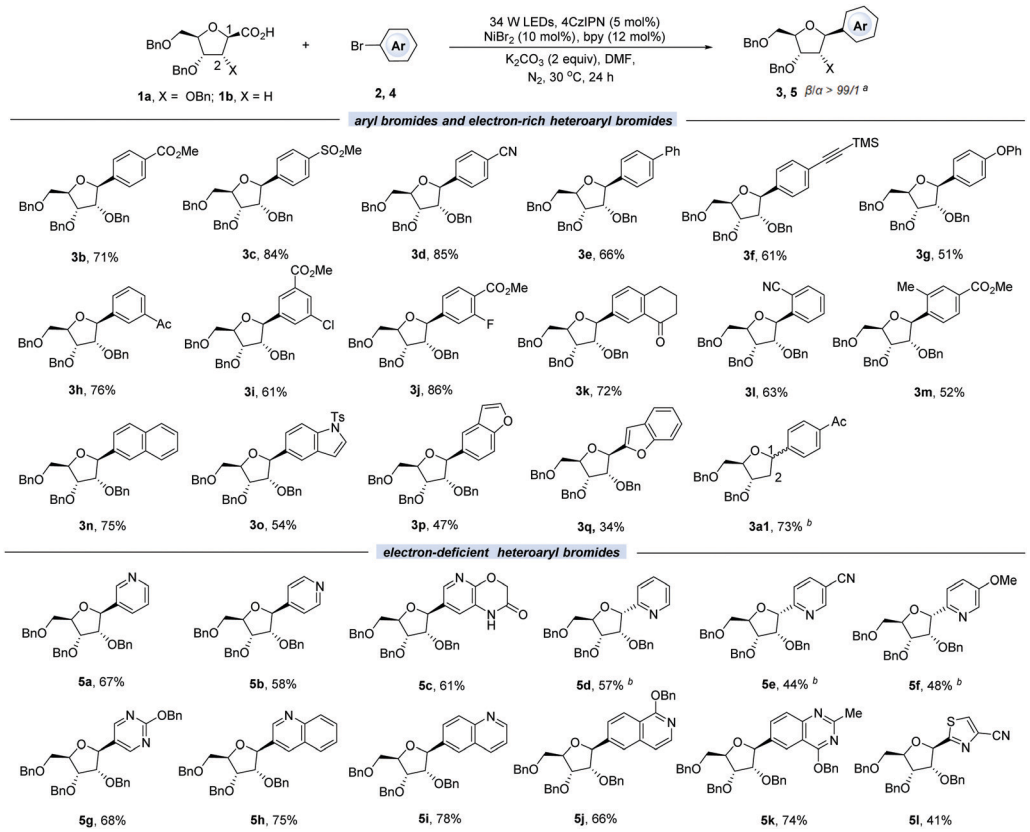


Entry	Reaction conditions	Yield[b]
1	Standard conditions	82%
2	**P1** instead of 4CzIPN	71%[d]
3	Using reduced amount of $NiBr_2$ and bpy	57%[e]
4	**1a′** instead of **1a**	80%
5	**1a″** instead of **1a**	Trace[f]
6	**2a′** instead of **2a**	65%
7	**2a″** instead of **2a**	23%
8	**2a‴** instead of **2a**	70%
9	In darkness	n.d[g]
10	No photocatalyst	n.d[g]
11	No Ni catalyst	n.d[g]
12	No ligand	n.d[g]
13	No base	n.d[g]
14	Under air	25%
15	In the presence of TEMPO	23%[h]

[a] Standard reaction conditions: a mixture of **1a** (0.2 mmol), **2a** (0.4 mmol), $NiBr_2$ (0.02 mmol), bpy (0.024 mmol), 4CzIPN (0.01 mmol), and K_2CO_3 (0.4 mmol) in DMF (10 mL) was irradiated with 34 W blue LEDs at 30 °C under N_2 for 24 h, unless otherwise noted. [b] Isolated yields were reported. [c] Determined using ^1H NMR spectroscopy. [d] 1 mol% of **P1** was used. [e] 5 mol% of $NiBr_2$ and 6 mol% of bpy were used. [f] The target product should be *O*-benzoyl protected *C*-nucleoside. [g] Not detected. [h] 1.0 equiv. of TEMPO was employed in the reaction.

substituents at the *meta*-position of aryl bromides has little effect on the reaction outcome (**3h–3k**, 61–86% yields), while inferior reaction efficiency was typically observed for the aryl bromides with *ortho*-substituents (**3l–3m**, 52–63% yields). Notably, a number of *C*-nucleosides bearing large π-stacking moieties, which serve as artificial nucleobases to extend the genetic alphabet,[2] could also be readily accessible with our method (**3n–3q**, 34–75% yields). Furthermore, low diastereoselectivity was observed in the reaction of *O*-benzyl protected β-deoxyribosyl acid **1b** with **2a** (**3a1**, 61% yield, β:α = 1:4), suggesting that the substituent at the C2 position of anomeric acids plays a crucial role in controlling the anomeric configuration.

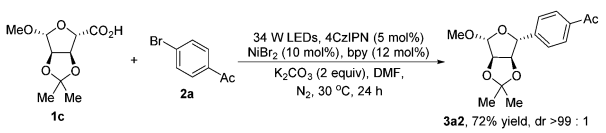
The *C*-nucleosides bearing electron-deficient heteroaryl groups exhibit attractive pharmaceutical profiles and have become an important target of synthetic efforts in recent decades.[1] Therefore, we next turned our attention to the scope of electron-deficient heteroaryl bromides. Various pyridyl bromides were proved competent substrates (**5a–5f**, 44–67% yields). As expected, β-*C*-nucleoside products were mainly detected in the reaction of 3-Br- and 4-Br-pyridines with **1a** (**5a–5c**, β:α > 99:1). Surprisingly, varying the position of Br at pyridine from C3 or C4 to C2 resulted in completely opposite diastereoselectivity (**5d–5f**, β:α < 1:99). Further investigation of this abnormal



Scheme 2 Photoredox/Ni dual-catalyzed decarboxylative cross-coupling reactions of anomeric ribosyl/deoxyribosyl acids with aryl/heteroaryl bromides. For the experimental details, see general procedure in ESI† for the experimental details unless otherwise noted, isolated yields were reported. [a]Stereomeric ratio was determined using ^{1}H NMR spectroscopy. [b]Stereomeric ratio: **3a1**, β : α = 1 : 4; **5d–5f**, β : α < 1 : 99.

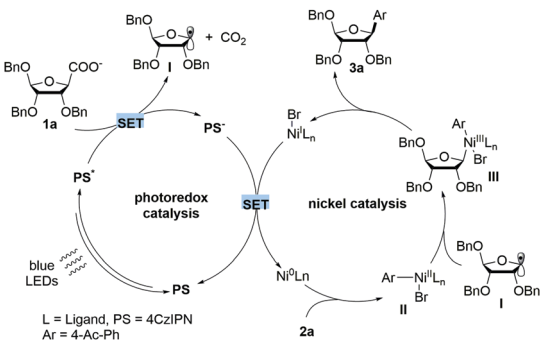
control of anomeric configuration is still ongoing in our laboratory. Remarkably, it was found that pyrimidyl, quinolyl, isoquinolyl and benzopyrimidyl bromides could also readily undergo the coupling reaction with **1a** (**5j–5k**, 66–78%, β : α > 99 : 1). Interestingly, this metallaphotoredox protocol is also suitable for cyan-substituted thiazolyl bromide (**5l**, 41% yield, β : α > 99 : 1), providing a potential alternative approach for the synthesis of the anti-tumor *C*-nucleoside tiazofurin[1a] in combination with the following hydrolysis of cyan group and debenzylation reaction (Scheme S3, ESI†).

Recently, the impressive compatibility of photoredox/nickel dual-catalysis with non-anomeric glycosyl 1,4-dihydropyridine derivatives (DHPs) has been demonstrated in the synthesis of reversed aryl *C*-glycosides.[10] Inspired by this work, non-anomeric glycosyl acids were investigated. To our delight, the non-anomeric furanosyl acids **1c** was proved effective reactant (**3a2**, 79% yield, dr > 99 : 1, Scheme 3), while the non-anomeric pyranosyl acid failed to give the desired product.

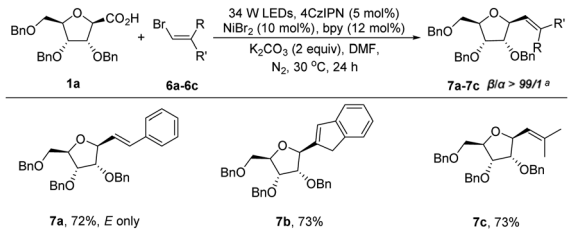


Scheme 3 Photoredox/Ni dual-catalyzed decarboxylative cross-coupling reactions of non-anomeric furanosyl acid.

Based on the established mechanism of photoredox/nickel dual-catalyzed decarboxylative coupling reaction,[7–9] as well as the observation that the formation of **3a** was inhibited by the presence of TEMPO (entry 15, Table 1), a plausible mechanism is proposed (Scheme 4). Initial excitation of the 4CzIPN (PS) would produce photoexcited state of 4CzIPN (PS*). The high reduction potential of the photoexcited state of 4CzIPN (PS*) (E^{*red} = +1.35 V *vs.* SCE, CH_3CN)[11] enables the following photooxidative decarboxylation reactions of **1a** (E^{ox} = +1.15 V *vs.* SCE, CH_3CN; Fig. S2, ESI†) and the formation of a sp^2-hybridized anomeric radical **I**. Concurrent with this photoredox



Scheme 4 Proposed mechanism.



Scheme 5 Photoredox/Ni dual-catalyzed decarboxylative cross-coupling of anomeric ribosyl acid with vinyl bromides. For the experimental details, see general procedure in ESI† unless otherwise noted, isolated yields were reported. [a]Stereomeric ratio was determined using ^{1}H NMR spectroscopy.

cycle, we assumed that the active Ni(0) species (Ni^0Ln) *in situ* generated *via* two SET reductions of (bpy)Ni(II)Br_2 by the photocatalyst PS- would undergo oxidative addition into the aryl bromides **2a**, forming the electrophilic Ni(II)-aryl intermediate **II**. This Ni(II) species would rapidly intercept anomeric ribosyl radical **I** to generate a Ni(III)-aryl-ribosyl complex **III**, which should undergo reductive elimination to produce the desired product **3a** accompanied with the formation of Ni(I) complex (bpy)Ni(I)Br. Reduction of (bpy)Ni(I)Br by PS-, would then reconstitute both Ni(0) species (Ni^0Ln) and ground state of 4CzIPN (PS).

Finally, the protocol was employed to transform vinyl bromides into vinyl-*C*-nucleosides (Scheme 5). As expected, various vinyl bromides were also proved effective reactants (**7a–7c**, 72–73%, $\beta:\alpha > 99:1$). Interestingly, only *trans*-**7a** was formed, even when a mixture of *trans* and *cis* styryl bromides (*trans* : *cis* = 1 : 1) was used as the substrate.

In conclusion, we have established a robust radial cross-coupling strategy for the highly stereoselective synthesis of biologically important aryl/heteroaryl-*C*-nucleosides from readily accessible anomeric ribosyl/deoxyribosyl acids and a variety of aryl/heteroaryl bromides. This new approach is enabled by the catalytic activation of both coupling partners through the synergistic merger of photoredox and nickel catalysis in the presence of visible light. The benign nature of the reaction conditions has been exemplified by the breadth of functional groups tolerated in this transformation. Furthermore, the reactions display broad substrate scope and feature the using of cost-effective and easily handled starting materials and catalysts. We believe that these advantages will enable the rapid access to diverse aryl/heteroaryl-*C*-nucleoside collections for drug discovery and chemical biology study.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) E. De Clercq, *J. Med. Chem.*, 2016, **59**, 2301–2311; (*b*) A. G. Draffan, B. Frey, B. Pool, C. Gannon, E. M. Tyndall, M. Lilly, P. Francom, R. Hufton, R. Halim, S. Jahangiri, S. Bond, V. T. T. Nguyen, T. P. Jeynes, V. Wirth, A. Luttick, D. Tilmanis, J. D. Thomas, M. Pryor, K. Porter, C. J. Morton, B. Lin, J. Duan, G. Kukolj, B. Simoneau, G. McKercher, L. Lagacé, M. a. Amad, R. C. Bethell and S. P. Tucker, *ACS Med. Chem. Lett.*, 2014, **5**, 679–684; (*c*) G. Wang, J. Wan, Y. Hu, X. Wu, M. Prhavc, N. Dyatkina, V. K. Rajwanshi, D. B. Smith, A. Jekle, A. Kinkade, J. A. Symons, Z. Jin, J. Deval, Q. Zhang, Y. Tam, S. Chanda, L. Blatt and L. Beigelman, *J. Med. Chem.*, 2016, **59**, 4611–4624; (*d*) P. Franchetti, L. Cappellacci, M. Grifantini, A. Barzi, G. Nocentini, H. Yang, A. O'Connor, H. N. Jayaram, C. Carrell and B. M. Goldstein, *J. Med. Chem.*, 1995, **38**, 3829–3837; (*e*) K. Krohn, H. Heins and K. Wielckens, *J. Med. Chem.*, 1992, **35**, 511–517.

2 (*a*) K. Dhami, D. A. Malyshev, P. Ordoukhanian, T. Kubelka, M. Hocek and F. E. Romesberg, *Nucleic Acids Res.*, 2014, **42**, 10235–10244; (*b*) A. W. Feldman, V. T. Dien, R. J. Karadeema, E. C. Fischer, Y. You, B. A. Anderson, R. Krishnamurthy, J.-S. Chen, L. Li and F. E. Romesberg, *J. Am. Chem. Soc.*, 2019, **141**, 10644; (*c*) A. W. Feldman and F. E. Romesberg, *Acc. Chem. Res.*, 2018, **51**, 394–403.

3 (*a*) J. Štambaský, M. Hocek and P. Kočovský, *Chem. Rev.*, 2009, **109**, 6729–6764; (*b*) K. Temburnikar and K. L. Seley-Radtke, *Beilstein J. Org. Chem.*, 2018, **14**, 772–785; (*c*) J.-D. Liu and H.-H. Gong, *Org. Lett.*, 2018, **20**, 7991–7995; (*d*) J.-D. Liu, C.-H. Lei and H.-H. Gong, *Sci. China Chem.*, 2019, **62**, 1–5.

4 H.-G. Gong and M. R. Gagné, *J. Am. Chem. Soc.*, 2008, **130**, 12177–12183.

5 L. Nicolas, E. Izquierdo, P. Angibaud, I. Stansfield, L. Meerpoel, S. Reymond and J. Cossy, *J. Org. Chem.*, 2013, **78**, 11807–11814.

6 L. Adak, S. Kawamura, G. Toma, T. Takenaka, K. Isozaki, H. Takaya, A. Orita, H.-C. Li, T. K. M. Shing and M. Nakamura, *J. Am. Chem. Soc.*, 2017, **139**, 10693–10701.

7 (*a*) Z.-W. Zuo, H. Cong, W. Li, J. Choi, G.-C. Fu and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2016, **138**, 1832–1835; (*b*) Z.-W. Zuo, D. T. Ahneman, L.-L. Chu, J. A. Terrett, A. G. Doyle and D. W. C. MacMillan, *Science*, 2014, **345**, 437–440.

8 (*a*) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans and D. W. C. MacMillan, *Nat. Rev. Chem.*, 2017, **1**, 0052; (*b*) Y.-Y. Gui, L. Sun, Z.-P. Lu and D.-G. Yu, *Org. Chem. Front.*, 2016, **3**, 522–526; (*c*) M. N. Hopkinson, B. Sahoo, J.-L. Li and F. Glorius, *Chem. – Eur. J.*, 2014, **20**, 3874–3886.

9 H. Huang, X. Li, C. Yu, Y.-T. Zhang, P. S. Mariano and W. Wang, *Angew. Chem., Int. Ed.*, 2017, **56**, 1500–1505.

10 A. Dumoulin, J. K. Matsui, L. Gutiérrez-Bonet and G. A. Molander, *Angew. Chem., Int. Ed.*, 2018, **57**, 6614–6618.

11 J. Luo and J. Zhang, *ACS Catal.*, 2016, **6**, 873–877.