Light-Mediated Cross-Coupling of Anomeric Trifluoroborates

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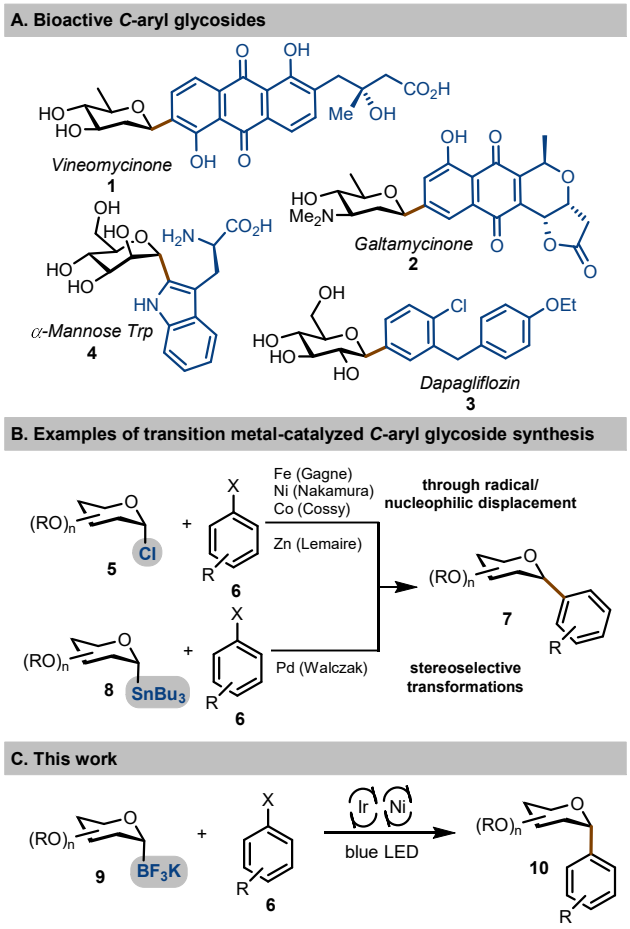
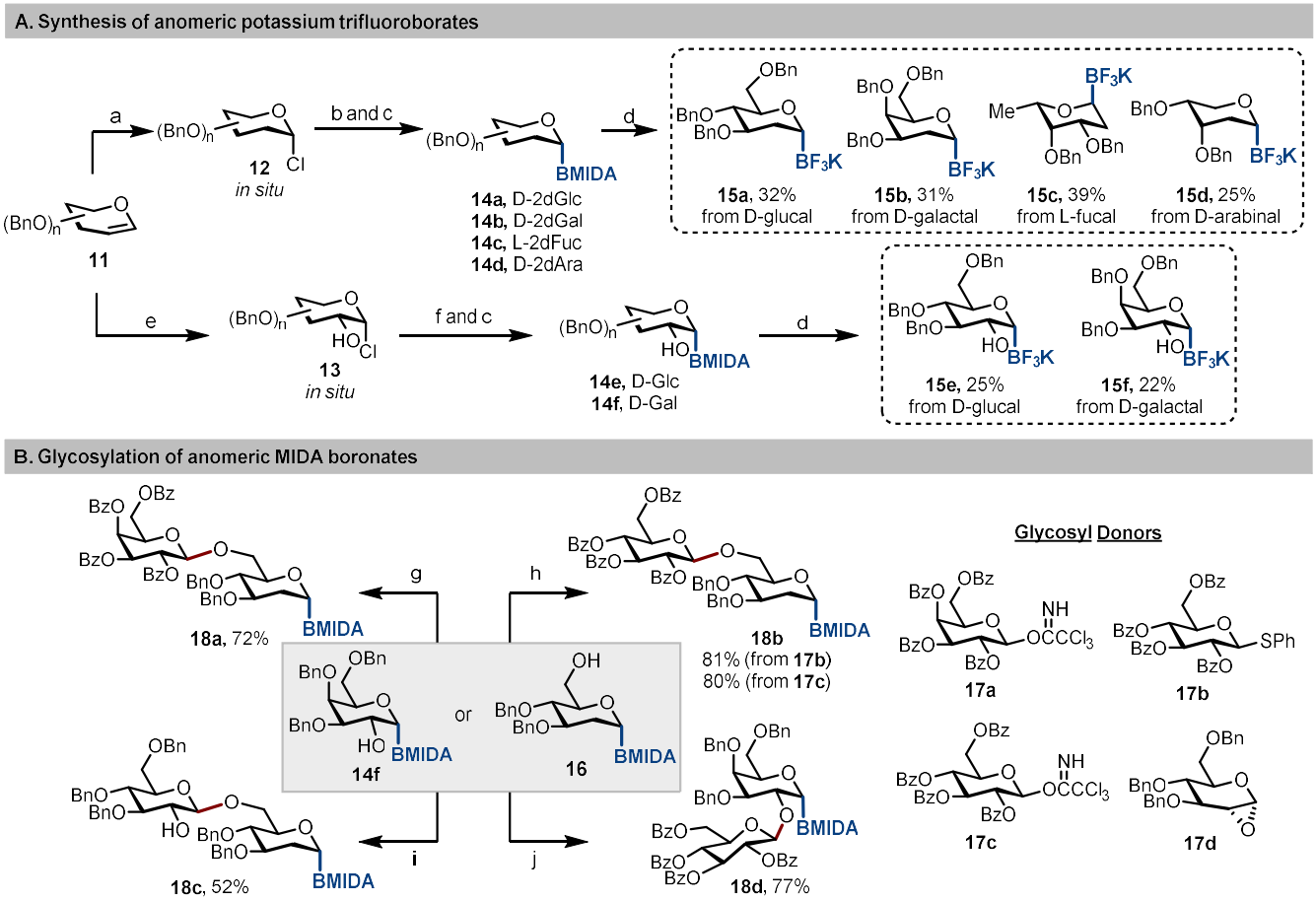
ABSTRACT: Stereoselective reactions at the anomeric carbon constitute the cornerstone of preparative carbohydrate chemistry. Here, we report the synthesis of axial C1 trifluoroborates and stereoselective C-arylation and etherification reactions under photoredox conditions. These reactions are characterized by high anomeric selectivities for 2-deoxysugars and broad substrate scope (24 examples), including disaccharides and trifluoroborates with free hydroxyl groups. Computational studies show that high axial selectivities for these reactions originate from a combination of kinetic anomeric effect of the intermediate C1 radical and stereoelectronic stabilization of Ni(III) through the metallo-anomeric effect. Taken together, this new class of carbohydrate reagents adds the palette of anomeric nucleophile reagents suitable for efficient installation C-C and C-heteroatom bonds.

Carbohydrates are critical encoders of biological information due to their extensive structural complexity.[1] Saccharides are also involved in a number of important biological processes.[2,3,4] Among bioactive glycoconjugates, *C*-aryl glycosides have recently been targeted due to anti-tumor[5] (e.g., antibiotics **1**[6] and **2**) and anti-diabetic activities exemplified by dapagliflozin **3**[7] and *C*-mannosyl proteins (**4**)[8] (Scheme 1A). Recent progress in the chemical synthesis of *C*-glycosides revealed an array of new transformations in order to rapidly assemble diverse structures.[9] Current methods featuring transition metal-catalyzed synthesis of *C*-aryl glycosides use Co,[10] Fe,[11] Ni,[12] and Zn[13] complexes (Scheme 1B) engaging anomeric halides as viable coupling partners. Alternatively, redox-active esters emerged as the source of anomeric radicals[14] and, when coupled with a Ni catalyst, can produce *C*-aryl glycosides.[15] These methods are characterized by variable selectivities, poor functional group tolerance, and a narrow scope. In an effort to address these obstacles, we recently showed high control of selectivity through a stereoretentive oxidative addition/reductive elimination Pd-catalyzed processes allowing for a complete control of stereochemistry using C1 stannanes.[9b, 16] To further expand the scope of anomeric nucleophiles, we hypothesized that C1 trifluoroborates could give rise to air-stable glycosyl donors and could be engaged in C(sp^3)-C(sp^2) cross-coupling reactions. Trifluoroborates have found widespread use as a nucleophilic component in various cross-couplings due to their stability, low toxicity, and compatibility with numerous functional groups.[17] These reagents have been shown to partake in light-mediated reactions with aryl halides using nickel and photoredox

Scheme 1. C-glycosides and selected synthetic



Scheme 2. Synthesis and glycosylation of anomeric boron compounds

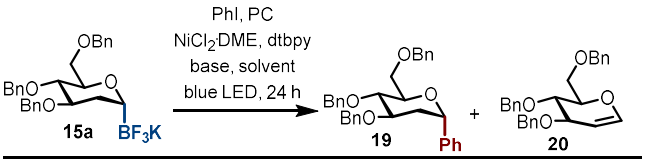


Reagents and conditions: (a) **11**, HCl (2.0 equiv.), THF, 23 °C, 1 h. (b) Li/naphthalene, THF, -78 °C, then $B(OMe)_3$ (3.0 equiv.), -78 °C, 2 h. (c) MIDA (3.0 equiv.), PhMe/DMSO (5:1), 115 °C, 3 h. (d) KHF_2 (5.0 equiv.), MeOH, 70 °C, 24 h. (e) **11**, Oxone (4.0 equiv.), $NaHCO_3$ (sat.), acetone, 0 °C to 23 °C, 3 h then HCl (2.0 equiv.), THF, 23 °C, 1 h. (f) *n*-BuLi (1.1 equiv.), THF, -78 °C, then Li/naphthalene, -78 °C, then $B(OMe)_3$ (3.0 equiv.), -78 °C, 2 h. (g) **17a** (1.2 equiv.), **16** (1.0 equiv.), TMSOTf (0.05 equiv.), 4 Å MS, CH_2Cl_2, -20 °C, 2 h. (h) **17b** (1.2 equiv.), **16** (1.0 equiv.), NIS (1.2 equiv.), AgOTf (0.2 equiv.), 4 Å MS, CH_2Cl_2, -45 °C, 2 h. (i) AgOTf (0.01 equiv.), **16** (1.0 equiv.), **17d** (1.5 equiv.), $Au(PPh_3)Cl$ (0.01 equiv.), 4 Å MS, CH_2Cl_2, -78 °C to 23 °C, 30 h (j) **17b** (1.2 equiv.), **14e** (1.0 equiv.), TMSOTf (0.05 equiv.), 4 Å MS, CH_2Cl_2, -20 °C, 2 h.

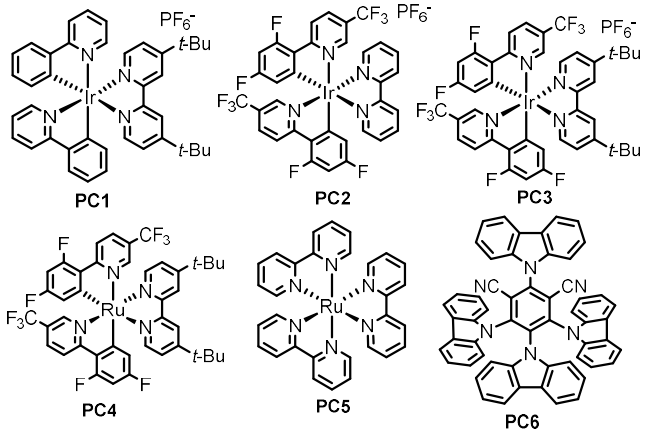
catalysts engaged in a dual catalytic system.[17c, 18] Based on this literature precedent, we further hypothesized that with a proper control of the electronic effects either through the modulation of the protective groups or ligands on the high-valent nickel center, axial trifluoroborates could effectively undergo a stereoretentive coupling with electrophilic partners. This proposal was supported by a recent study from the Hirai group[19] featuring the synthesis of stable silicon-protected potassium trifluoroborates of 2-deoxy-β-D-glucose and β-D-galactose. Here, we report the synthesis and stereoretentive C-C cross-coupling reactions of α-anomeric trifluoroborates **9** of common mono- and disaccharides under the photoredox conditions (Scheme 1C). These reagents are a reliable source of anomeric radicals and can be merged with Ni(II) co-catalyst to form *C*-glycosides in excellent anomeric selectivities.

Based on the perceived stability of methyliminodiacetic acid boronate (BMIDA) esters,[20] we first attempted the synthesis of C1 boronates derived from 2-deoxysugars and fully oxygenated monosaccharides (Scheme 2A) as potential precursors of trifluoroborates. Protected glycals **11** were used as the staring materials for both pathways and were converted into α-glycosyl chlorides **12** followed by a retentive transmetalation with lithium naphthalenide and quenching with $B(OMe)_3$ at -78 °C.[21] The crude boronic esters were then converted into BMIDA esters **14** in a reaction with MIDA at 115 °C. Furthermore, we were able to convert **14** into trifluoroborates **15** using aqueous KHF_2[22] and salts **15** were purified by simple filtration or flash column chromatography on silica gel. This protocol allowed for the preparation of trifluoroborates derived from D-glucal (**15a**), D-galactal (**15b**), L-fucal (**15c**), D-arabinal (**15d**) in 25-39% (yields over four steps) as well as D-glucose **15e** and D-galactose **15f** in 22-25% yield.

Table 1. Optimization of C-C cross-coupling



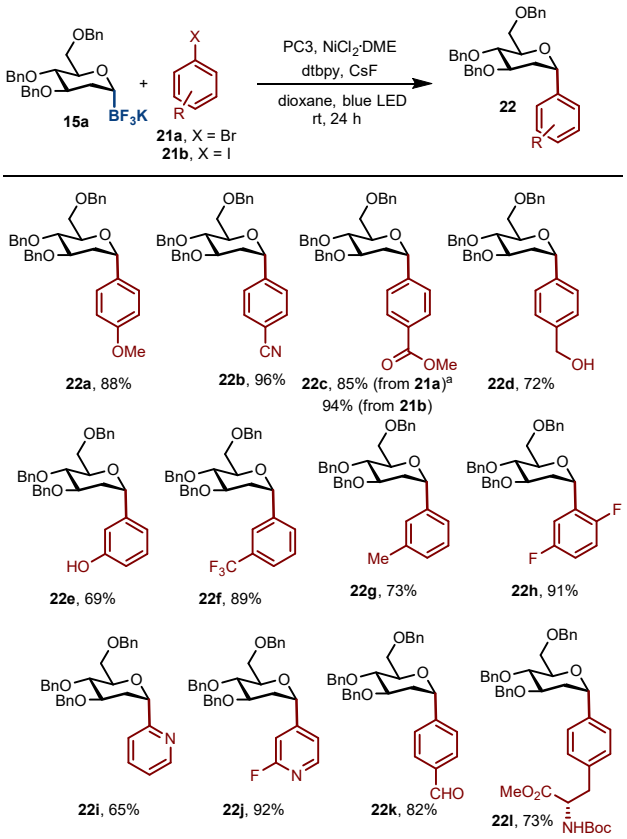
Entry	Catalyst	Base	Solvent	19 [%]	20 [%]
1	PC1	Cs_2CO_3	dioxane	20	2
2	PC2	Cs_2CO_3	dioxane	57	14
3	PC3	Cs_2CO_3	dioxane	67	12
4	PC4	Cs_2CO_3	dioxane	26	5
5	PC5	Cs_2CO_3	dioxane	-	-
6	PC3	CsF	dioxane	83	3
7	PC6	CsF	dioxane	69	6
8	PC3	Na_2CO_3	dioxane	15	20
9	PC3	*t*BuOK	dioxane	-	-
10	PC3	K_3PO_4	dioxane	22	20
11	PC3	KF	dioxane	10	15
12	PC3	LiF	dioxane	9	19
13	PC3	CsF	acetone	73	28
14	PC3	CsF	THF	72	18



General conditions: **15a** (0.15 mmol), (Ph-I) (0.10 mmol), PC3 (0.025 equiv.), $NiCl_2$·DME (0.05 equiv.), dtbpy (0.05 equiv.), CsF (1.5 equiv.), 1,4-dioxane (2.0 mL), blue LED (40W), 23 °C, 24 h, N_2.

The structural diversity of anomeric MIDA boronates was expanded by chemical glycosylation with commonly used glycosyl donors (Scheme 2B). To this end, two BMIDA glycosyl acceptors **14f** and **16** were tested. We found that trichloroacetimidates such as **17a** and **17c** could be activated with TMSOTf (5 mol%) and produced disaccharides **18a** and **18b** excellent yields. To test more electrophilic conditions, we employed thioglycoside **17b** and prepared BMIDA disaccharide **18b** in 81% using NIS as the activator. We were also interested to test milder, transition metal-catalyzed reactions in order to expand the scope of glycosyl donors. To this end, congested acceptor **14a** was treated with 1,2-*anhydro* sugar **17d** in the presence of a gold catalyst previously reported by Yu.[23] Although this reaction was slow (~30 h at 23 °C), we were able to produce disaccharide **18c** in 52% yield with exclusive β-selectivity. Based on these preliminary studies we conclude that BMIDA esters are compatible with Lewis acid activators and can be considered as a mildly deactivating group when located at the anomeric carbon in a glycosyl acceptor. These

Scheme 3. Scope of C-arylation



For all compounds tested only one anomer (α:β >99:1) was observed by ^{1}H NMR in crude reaction mixtures. Reagents and conditions taken from Table 1, entry 6. [a]87% isolated yield with 0.15 mmol of **15a**.

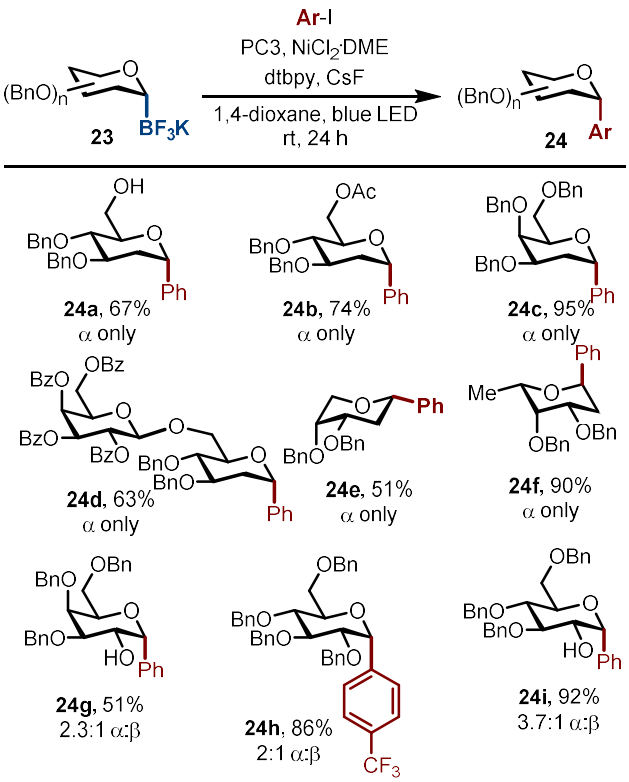
results also highlight the utility of BMIDA esters as convenient surrogates of more active boron donors such as boronic acids and trifluoroborates that may not survive electrophilic activation.

Next, we enagaged anomeric boronates in C-C cross-coupling reactions. Initially we tested reactions with MIDA boronates **14** but these reagents proved to be too stable under slow-release Pd-catalyzed cross-coupling conditions.[20a] To overcome this problem, potassium trifluoroborates **15** were studied and 2-deoxy-α-D-glucose **15a** and iodobenzene were selected as the model system (Table 1). Evaluation of several established photocatalyst revealed that PC3 significantly outperformed other Ir- and Ru-based complexes (entries 1-7). Inspired by the prior work for the Molander group, we focused on PC3 as our initial photocatalyst, Cs_2CO_3 (1.5 equiv.) as a base in 1,4-dioxane and combination of 5 mol% $NiCl_2$·DME (DME=dimethoxyethane) with 5 mol% dtbpy (dtbpy=4,4′-di-*tert*-butyl-2,2′-bipyridine).[18d] After stirring for 24 h, we isolated 67% of **19** with only α-selectivity and 12% of β-hydride elimination glucal **20** (entry 3). Interestingly, PC6 (entry 6) showed encouraging yield of **19** (69%) but significantly suppressed elimination.

Furthermore, we looked at the role of base focusing on PC3 as the catalyst of choice. We found that the base proved to be essential in increasing the overall yield and reducing the extent of elimination product with CsF as the best additive furnishing **19** in 83% (entry 7). Sodium carbonate (entry 8), potassium *tert*-butoxide (entry 9), and potassium phosphate (entry 10) showed reduced yields with an increase in elimination. Although additional studies on the role of the base in photoredox reactions is needed, we also established that the counterion combination is essential, and fluoride ion itself is not sufficient to suppress elimination, as demonstrated by the results with KF and LiF (entry 11 and 12, respectively). Finally, we explored solvents other than 1,4-dioxane – acetone (entry 13) and tetrahydrofuran (entry 14) produced comparable although slightly diminished yields. For all conditions shown in Table 1, single anomer (α) was observed.

With suitable conditions in hand (Table 1, entry 6), our focus was to determine the extent of functional group tolerance (Scheme 3). Electron-rich 4-iodoanisole afforded **22a** in 88% with no loss of stereoselectivity. Electron-deficient cyano (**22b**) and ester (**22c**) groups gave almost quantitative yields (96% and 94%, respectively). These results suggest that electron withdrawing groups furnish better yields

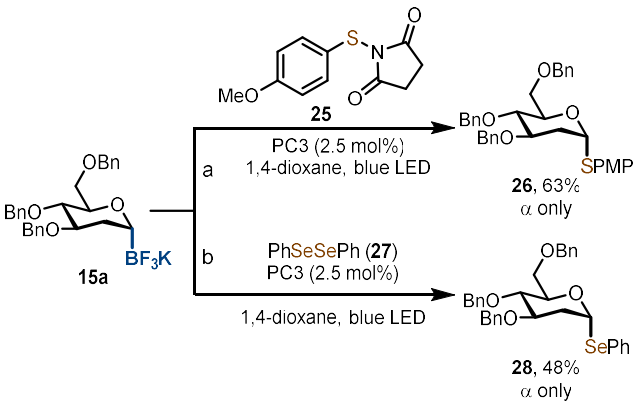
Scheme 4. Scope of photoredox *C*-arylation with pyranosyl trifluoroborates.



likely due to increasing the rate of reductive elimination and the ability to stabilize generated aryl radical.[24] Unprotected

Anomeric selectivities were determined by analysis of crude reaction mixtures (^{1}H NMR). Reagents and conditions taken from Table 1, entry 6.

Scheme 5. Scope of photoredox etherification of 2-deoxy-D-glucose trifluoroborate 15a

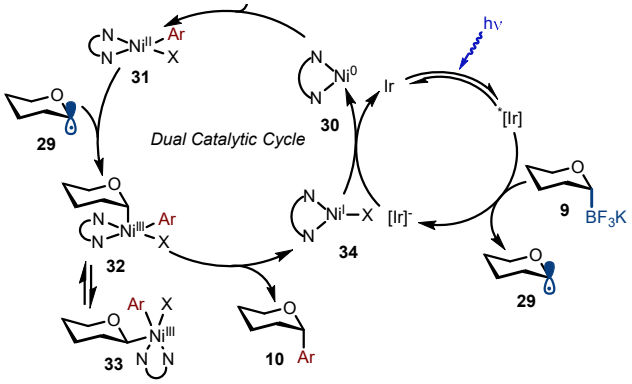


For all compounds shown, only one anomer (α:β >99:1) was observed by ^{1}H NMR in crude reaction mixtures. *Reagents and conditions:* (a) **15a** (0.15 mmol), **25** (0.10 mmol), **PC3** (.025 equiv.), 1,4-dioxane (2.0 mL), 23 °C, 24 h, N_2. (b) **15a** (0.10 mmol), **28** (0.10 mmol), **PC3** (.025 equiv.), 1,4-dioxane (2.0 mL), 23 °C, 24 h, N2.

4-iodobenzyl alcohol produced **22d** cleanly in 72% yield signifying that fully deprotected saccharides could be tolerated with these reaction conditions (*vide infra*). *meta*-Substituted phenol gave the corresponding glycoside **22e** in an acceptable 69% yield similar to electron-poor (**22f**, **22h**) and electron-rich (**22g**) *meta*-substituted functional groups, which provided clean conversion into products in 73-91%. These results led us to the investigate more difficult pyridine-based couplings such as 2-iodopyridine (**22i**) and 2-fluoro-4-iodopyridine (**22j**), which gave the expected products establishing a simple one-step protocol for the synthesis of pyridine glycals. Following these results, we focused on more challenging substrates such as the ones with a formyl group (**22k**, 82%) and 4-iodophenyalanine (**22l**, 73%). For all compounds shown in Scheme 3, exclusive α selectivity was observed (>99:1 α:β, ^{1}H NMR).

After uncovering the broad functional-group tolerance of an assortment of iodoarenes, we proceeded to apply our conditions to incorporate other sugars (Scheme 4). D-glucose with a free hydroxyl group (**24a**) or protected as an acetate (**24b**) is a viable substrate for ptororedox C(sp^2)-C(sp^3) cross-coupling. Similarly, 2-deoxy-D-galactose (**24c**) and di-deoxysugars derived from D-arabinose (**24e**) and L-fucose (**24f**) furnished high axial selectivities in modest to high yields. To our delight, disaccharides are also competent reagents in photocatalytic *C*-arylation and afforded **24d** in 63%. Both, D-galactose (**24g**) and D-glucose (**24h**, **24i**) regardless of the nature of the protective group located at C2 resulted in a mixture of α:β products, with the smaller hydroxyl groups resuling in slightly improved axial preference (2.3-3.7:1). Because the proposed activation method proceeds through a radical species, we also wondered if C1 trifluoroborates can be enaged in C-S[21c] and C-Se[25] bond-forming reactions (Scheme 5). To our delight, the formation of both ethers **26** and **28** proceeded smoothly from **15a** and eletrophilic sulfur (**25**) or selenium (**27**) sources without a nickel co-catalyst.

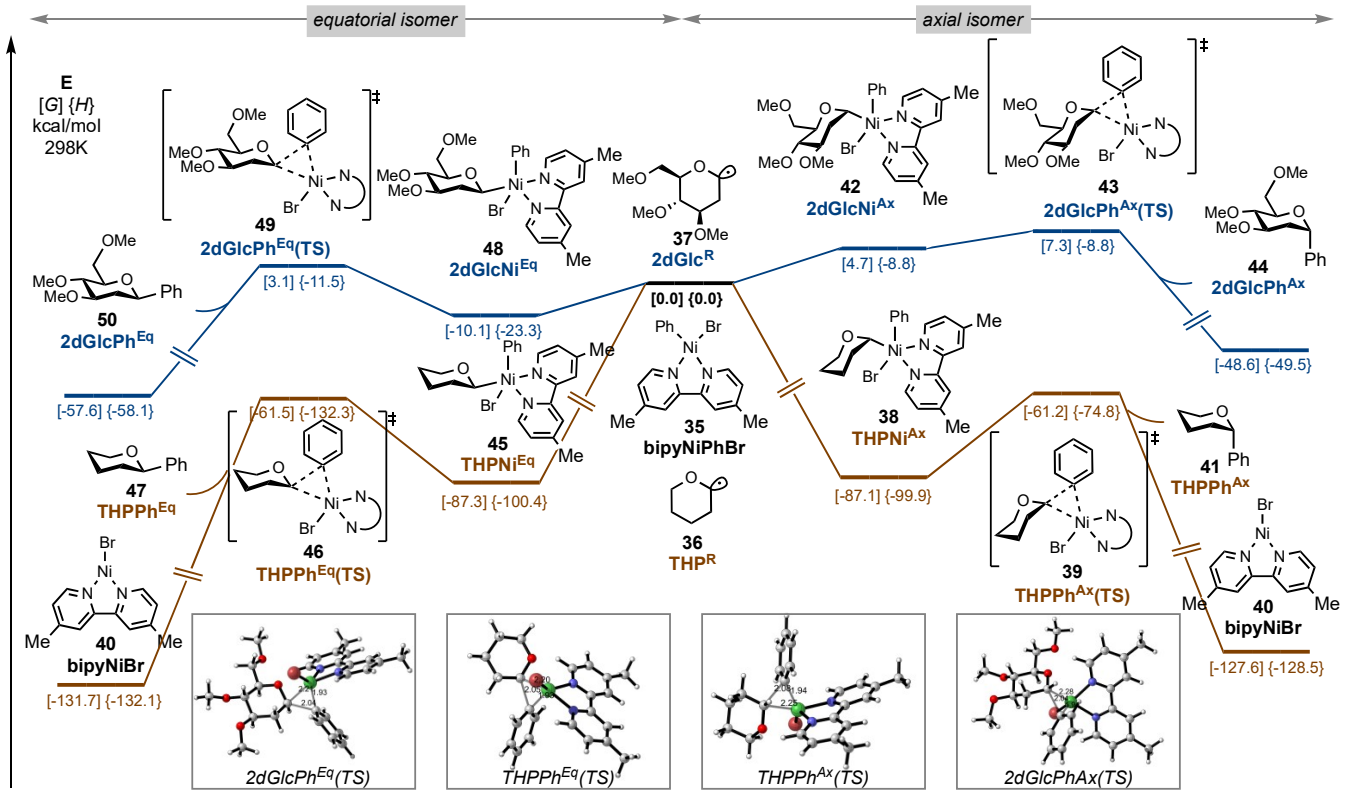
Scheme 6. Proposed dual catalytic cycle initiated by radical generation from C1 trifluoroborates.



The high axial selectivities in reactions with 2-deoxysaccharides (and a mixture of anomers in the case of "regular" saccharides) are consistent with the metallo-anomeric effect operational for high-oxidation state nickel complexes[26] combined with the kinetic preference of the C1 radicals.[27] To rationalize the high selectivities, we propose a mechanism of C-arylation shown in Scheme 6. The anomeric radical intermediate **29** generated from α-trifluoroborates **9** enters the catalytic cycle through a recombination with Ni(II) intermediate **31**. This hypothesis is supported by the previous studies with non-stabilized alkyl radicals that couple with aryl halides with low barriers for reductive elimination.[28] A direct C-C coupling between **29** and **31** leading to C-aryl glycosides is a possible pathway but this outer-sphere step is not supported by the prior computational studies. Intermediates **32** and **33** may undergo interconversion through a homolytic cleavage but the likelihood of this event is low if the barrier for reductive elimination *en route* to **10** is sufficiently shallow to prevent anomerization. The reductive elimination step from **32** and **33** is a stereoretentive process, and the overall stereochemical outcome is determined by the kinetic anomeric effect of radicals **29** augmented by the metallo-anomeric stabilization from Ni(III).

To shine more light on the origin of high selectivities in the reactions with C1-trifluoroborates, we performed DFT calculations focusing on the critical stereodetermining steps in the proposed cycle (Scheme 7).[29] The optimized structures of α- and β-trifluoroborates show that that the C1-B bond in the axial borate is slightly elongated (1.641 Å) compared to the equatorial isomer (1.637 Å) indicating that the homolytic cleavage may be more facile for the axial substrates (for details, see the SI). Furthermore, the radical **29** generated from axial trifluoroborates is already in the preferred axial configuration.[27] We next analyzed the reaction pathways for the axial and equatorial isomers for tetrahydropyran (THP) and 2-deoxy-D-glucose (2dGlc). Recombination of **bipyNiPhBr** with both radicals in either pathway is a highly favorable process with substantial gain in free energy regardless of the configuration of the intermediates. We note that the axial isomer **THPNi^{Ax}** is slightly more stable than the equatorial structure **THPNi^{Eq}** (0.5 kcal/mol), but the free energy for THP and 2-dGlc indicate that the

Scheme 7. Computational analysis of axial and equatorial reactions pathways



2-deoxy-D-glucose (blue) and tetrahydropyran (yellow) radicals calculated at the B3LYP-D3/def2-TZVPP-SDM(1,4-dioxane)//B3LYP-D3/def2-SV-SDM(1,4-dioxane) levels. Gibbs free energy (298K, 1 atm; in brackets) and enthalpy (in braces) are reported in kcal/mol.

steric factors responsible for destabilization of the axial isomer. Our prior work on the metallo-anomeric effect indicates that increasing the oxidation state of the metal center at the anomeric position leads to increased thermodynamic preference of the axial isomers due to maximization of the electronic overlap between $n_{(O)}$ and $\sigma^*_{(C\text{-}M)}$ orbitals.[26] We also note that the extent of metallo-anomeric stabilization in **THPNi^{Ax}** and **2dGlcNi^{Ax}** is diminished due to the presence of a donating ligand in the apical position resulting in a competition between $n_{(O)}$ and $n_{(N)}$ for the $\sigma^*_{(C\text{-}Ni)}$ orbitals. The subsequent reductive elimination in the axial isomer **2dGlc^{Ax}** is fast with $\Delta G^{\neq}$ ~1.6 kcal/mol. The barrier for the same step in the catalytic cycle in the equatorial isomer **2dGlc^{Eq}** is higher (~13.2 kcal/mol) but under the reaction conditions both steps are considered feasible. Interestingly, the energies of transition states for reductive elimination for THP are considerably higher (25.8 and 25.9 kcal/mol for **THPPh^{Eq}(TS)** and **THPPh^{Ax}(TS),** respectively), which can be attributed to a flexible structure of the THP ring that undergoes more substantial ring reorganization in the TS (this is also reflected in the entropic contributions for both TSs). The glucose ring with three equatorial groups is more rigid, and the extent of torsional changes to promote C-C bond formation in this case is less pronounced. As expected, the equatorial isomers for both products (**THPPh^{Eq}** and **2dGlcPh^{Eq}**) are more stable than the axial isomers **THPPh^{Ax}** and **2dGlcPh^{Ax}**. Anomeric selectivities for reactions shown in Scheme 5 can be rationalized by the kinetic anomeric effects of the putative radical **37**.[30]

In summary, we introduced here a new class of C1-trifluoroborates that are competent reagents for the formation of C-C and C-chalcogen bonds in 2-deoxy and fully substituted saccharides under the photoredox conditions. Although the overall transformation proceeds via single-electron transfer mechanism, the observed selectivities result in the net stereoretention and complement other C-C cross-coupling technologies with anomeric nucleophiles. Our results are also supportive of the growing importance of stereoelectronic effects such as the metallo-anomeric effect in designing stereoselective glycosylation reactions.

ASSOCIATED CONTENT

Supporting Information

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

Copies of NMR spectra, detailed experimental procedures, and computation data (PDF)

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Notes

The authors declare no competing financial interest

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REFERENCES

1. Varki, A.; Cummings, R. D.; Esko, J. D.; Freeze, H. H.; Stanley, P.; Bertozzi, C. R.; Hart, G. W.; Etzler, M. E., *Essentials of Glycobiology*. Cold Spring Harbor Laboratory Press: Cold Spring Harbor (NY), 2009.

2. Imberty, A.; Varrot, A., Microbial recognition of human cell surface glycoconjugates. *Curr. Opin. Struct. Biol.* **2008,** *18*, 567-76.

3. Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A., Glycosylation and the immune system. *Science* **2001,** *291*, 2370-6.

4. Ernst, B.; Magnani, J. L., From carbohydrate leads to glycomimetic drugs. *Nat. Rev. Drug Discov.* **2009,** *8*, 661.

5. Bililign, T.; Griffith, B. R.; Thorson, J. S., Structure, activity, synthesis and biosynthesis of aryl-C-glycosides. *Nat. Prod. Rep.* **2005,** *22*, 742.

6. (a) Ōmura, S.; Tanaka, H.; Ōiwa, R.; Awaya, J.; Masuma, R.; Tanaka, K., New antitumor antibiotics, OS-4742 A1, A2, B1, and B2 produced by a strain of *Streptomyces*. *J. Antibiot.* **1977,** *30*, 908; (b) Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H.; Ōmura, S., The structure of vineomycin B2. *J. Antibiot.* **1981,** *34*, 1517; (c) Danishefsky, S.; Uang, B. J.; Quallich, G., Total synthesis of vineomycinone B2 methyl ester. *J. Am. Chem. Soc.* **1985,** *107*, 1285-1293; (d) Tius, M. A.; Gu, X. Q.; Gomez-Galeno, J., Convergent synthesis of vineomycinone B2 methyl ester. *J. Am. Chem. Soc.* **1990,** *112*, 8188-8189; (e) Tius, M. A.; Gomez-Galeno, J.; Gu, X. Q.; Zaidi, J. H., C-Glycosylanthraquinone synthesis: total synthesis of vineomycinone B2 methyl ester. *J. Am. Chem. Soc.* **1991,** *113*, 5775-5783; (f) Bolitt, V.; Mioskowski, C.; Kollah, R. O.; Manna, S.; Rajapaksa, D.; Falck, J. R., Total synthesis of vineomycinone B2 methyl ester via double Bradsher cyclization. *J. Am. Chem. Soc.* **1991,** *113*, 6320-6321; (g) Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K., Convergent total synthesis of vineomycinone B2 methyl ester and its C(12)-epimer. *J. Am. Chem. Soc.* **1991,** *113*, 6982-6992; (h) Chen, C.-L.; Sparks, S. M.; Martin, S. F., C-Aryl Glycosides via Tandem Intramolecular Benzyne−Furan Cycloadditions. Total Synthesis of Vineomycinone B2 Methyl Ester. *J. Am. Chem. Soc.* **2006,** *128*, 13696-13697; (i) Kusumi, S.; Tomono, S.; Okuzawa, S.; Kaneko, E.; Ueda, T.; Sasaki, K.; Takahashi, D.; Toshima, K., Total Synthesis of Vineomycin B2. *J. Am. Chem. Soc.* **2013,** *135*, 15909-15912.

7. (a) Meng, W.; Ellsworth, B. A.; Nirschl, A. A.; McCann, P. J.; Patel, M.; Girotra, R. N.; Wu, G.; Sher, P. M.; Morrison, E. P.; Biller, S. A.; Zahler, R.; Deshpande, P. P.; Pullockaran, A.; Hagan, D. L.; Morgan, N.; Taylor, J. R.; Obermeier, M. T.; Humphreys, W. G.; Khanna, A.; Discenza, L.; Robertson, J. G.; Wang, A.; Han, S.; Wetterau, J. R.; Janovitz, E. B.; Flint, O. P.; Whaley, J. M.; Washburn, W. N., Discovery of Dapagliflozin: A Potent, Selective Renal Sodium-Dependent Glucose Cotransporter 2 (SGLT2) Inhibitor for the Treatment of Type 2 Diabetes. *J. Med. Chem.* **2008,** *51*, 1145-1149; (b) Dhillon, S., Dapagliflozin: A Review in Type 2 Diabetes. *Drugs* **2019,** *79*, 1135-1146.

8. (a) Hofsteenge, J.; Müller, D. R.; de Beer, T.; Löffler, A.; Richter, W. J.; Vliegenthart, J. F., New type of linkage between a carbohydrate and a protein: C-glycosylation of a specific tryptophan residue in human RNase Us. *Biochemistry* **1994,** *33*, 13524-30; (b) Niwa, Y.; Simizu, S., *C*-Mannosylation: Previous Studies and Future Research Perspectives. *Trends Glycosci. Glycotechnol.* **2018,** *30*, E231-E238.

9. (a) Yang, Y.; Yu, B., Recent Advances in the Chemical Synthesis of C-Glycosides. *Chem. Rev.* **2017,** *117*, 12281-12356; (b) Zhu, F.; Yang, T.; Walczak, M. A., Glycosyl Stille Cross-Coupling with Anomeric Nucleophiles – A General Solution to a Long-Standing Problem of Stereocontrolled Synthesis of C-Glycosides. *Synlett* **2017,** *28*, 1510-1516; (c) Kitamura, K.; Ando, Y.; Matsumoto, T.; Suzuki, K., Total Synthesis of Aryl C-Glycoside Natural Products: Strategies and Tactics. *Chem. Rev.* **2018,** *118*, 1495-1598; (d) K. L. M. Hoang, W.-L. Leng, Y.-J. Tan, X.-W. Liu, *Stereoselective C-glycosylation from Glycan Scaffolds* in *Selective Glycosylations: Synthetic Methods and Catalysts*, pp. 135-153, C. Bennett (Ed.), Wiley, **2017**

10. (a) Nicolas, L.; Izquierdo, E.; Angibaud, P.; Stansfield, I.; Meerpoel, L.; Reymond, S.; Cossy, J., Cobalt-catalyzed diastereoselective synthesis of C-furanosides. Total synthesis of (−)-isoaltholactone. *J. Org. Chem.* **2013,** *78*, 11807; (b) Nicolas, L.; Angibaud, P.; Stansfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J., Diastereoselective Metal-Catalyzed Synthesis of C-Aryl and C-Vinyl Glycosides. *Angew. Chem. Int. Ed.* **2012,** *51*, 11101-11104.

11. Adak, L.; Kawamura, S.; Toma, G.; Takenaka, T.; Isozaki, K.; Takaya, H.; Orita, A.; Li, H. C.; Shing, T. K. M.; Nakamura, M., Synthesis of Aryl C-Glycosides via Iron-Catalyzed Cross Coupling of Halosugars: Stereoselective Anomeric Arylation of Glycosyl Radicals. *J. Am. Chem. Soc.* **2017,** *139*, 10693-10701.

12. (a) Gong, H.; Sinisi, R.; Gagne, M. R., A room temperature Negishi cross-coupling approach to C-alkyl glycosides. *J. Am. Chem. Soc.* **2007,** *129*, 1908; (b) Gong, H.; Gagne, M. R., Diastereoselective Ni-catalyzed Negishi cross-coupling approach to saturated, fully oxygenated C-alkyl and C-aryl glycosides. *J. Am. Chem. Soc.* **2008,** *130*, 12177.

13. Lemaire, S.; Houpis, I. N.; Xiao, T.; Li, J.; Digard, E.; Gozlan, C.; Liu, R.; Gavryushin, A.; Diène, C.; Wang, Y.; Farina, V.; Knochel, P., Stereoselective C-Glycosylation Reactions with Arylzinc Reagents. *Org. Lett.* **2012,** *14*, 1480-1483.

14. Xu, L.-Y.; Fan, N.-L.; Hu, X.-G., Recent development in the synthesis of C-glycosides involving glycosyl radicals. *Org. Biomol. Chem.* **2020,** *18*, 5095-5109.

15. (a) Levy, D. E.; Tang, C., *The Chemistry of C-Glycosides*. 1995; (b) Bokor, É.; Kun, S.; Goyard, D.; Tóth, M.; Praly, J.-P.; Vidal, S.; Somsák, L., C-Glycopyranosyl Arenes and Hetarenes: Synthetic Methods and Bioactivity Focused on Antidiabetic Potential. *Chem. Rev.* **2017,** *117*, 1687-1764; (c) Dumoulin, A.; Matsui, J. K.; Gutiérrez-Bonet, Á.; Molander, G. A., Synthesis of Non-Classical Arylated C-Saccharides through Nickel/Photoredox Dual Catalysis. *Angew. Chem. Int. Ed.* **2018,** *57*, 6614-6618; (d) Badir, S. O.; Dumoulin, A.; Matsui, J. K.; Molander, G. A., Synthesis of Reversed C-Acyl Glycosides through Ni/Photoredox Dual Catalysis. *Angew. Chem. Int. Ed.* **2018,** *57*, 6610-6613; (e) 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; (f) Wei, Y.; Ben-zvi, B.; Diao, T., Diastereoselective Synthesis of Aryl C-Glycosides from Glycosyl Esters via C−O Bond Homolysis. *Angew. Chem. Int. Ed.* **2021,** DOI: 10.1002/anie.202014991.

16. (a) Zhu, F.; Rourke, M. J.; Yang, T.; Rodriguez, J.; Walczak, M. A., Highly stereospecific cross-coupling reactions of anomeric stannanes for the synthesis of C-aryl glycosides. *J. Am. Chem. Soc.* **2016,** *138*, 12049-12052; (b) Zhu, F.; Rodriguez, J.; Yang, T.; Kevlishvili, I.; Miller, E.; Yi, D.; O'Neill, S.; Rourke, M. J.; Liu, P.; Walczak, M. A., Glycosyl Cross-Coupling of Anomeric Nucleophiles: Scope, Mechanism, and Applications in the Synthesis of Aryl C-Glycosides. *J. Am. Chem. Soc.* **2017,** *139*, 17908-17922; (c) Yi, D.; Zhu, F.; Walczak, M. A., Stereoretentive Intramolecular Glycosyl Cross-Coupling: Development, Scope, and Kinetic Isotope Effect Study. *Org. Lett.* **2018,** *20*, 4627-4631; (d) Yi, D.; Zhu, F.; Walczak, M. A., Glycosyl Cross-Coupling with Diaryliodonium Salts: Access to Aryl C-Glycosides of Biomedical Relevance. *Org. Lett.* **2018,** *20*, 1936-1940.

17. (a) Yasu, Y.; Koike, T.; Akita, M., Visible Light-Induced Selective Generation of Radicals from Organoborates by Photoredox Catalysis. *Adv. Synth. Catal.* **2012,** *354*, 3414-3420; (b) Molander, G. A., Organotrifluoroborates: Another Branch of the Mighty Oak. *J. Org. Chem.* **2015,** *80*, 7837-7848; (c) Tellis, J. C.; Kelly, C. B.; Primer, D. N.; Jouffroy, M.; Patel, N. R.; Molander, G. A., Single-Electron Transmetalation via Photoredox/Nickel Dual Catalysis: Unlocking a New Paradigm for sp3–sp2 Cross-Coupling. *Acc. Chem. Res.* **2016,** *49*, 1429-1439; (d) Luo, J.; Zhang, J., Donor–Acceptor Fluorophores for Visible-Light-Promoted Organic Synthesis: Photoredox/Ni Dual Catalytic C(sp3)–C(sp2) Cross-Coupling. *ACS Catal.* **2016,** *6*, 873-877; (e) Primer, D. N.; Molander, G. A., Enabling the Cross-Coupling of Tertiary Organoboron Nucleophiles through Radical-Mediated Alkyl Transfer. *J. Am. Chem. Soc.* **2017,** *139*, 9847-9850.

18. (a) Tellis, J. C.; Primer, D. N.; Molander, G. A., Single-electron transmetalation in organoboron cross-coupling by photoredox/nickel dual catalysis. *Science* **2014,** *345*, 433-436; (b) Karakaya, I.; Primer, D. N.; Molander, G. A., Photoredox Cross-Coupling: Ir/Ni Dual Catalysis for the Synthesis of Benzylic Ethers. *Org. Lett.* **2015,** *17*, 3294-3297; (c) Yamashita, Y.; Tellis, J. C.; Molander, G. A., Protecting group-free, selective cross-coupling of alkyltrifluoroborates with borylated aryl bromides via photoredox/nickel dual catalysis. *Proc. Natl. Acad. Sci. U. S. A.* **2015,** *112*, 12026-12029; (d) Primer, D. N.; Karakaya, I.; Tellis, J. C.; Molander, G. A., Single-Electron Transmetalation: An Enabling Technology for Secondary Alkylboron Cross-Coupling. *J. Am. Chem. Soc.* **2015,** *137*, 2195-2198; (e) Skubi, K. L.; Blum, T. R.; Yoon, T. P., Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev.* **2016,** *116*, 10035-10074; (f) Kariofillis, S. K.; Shields, B. J.; Tekle-Smith, M. A.; Zacuto, M. J.; Doyle, A. G., Nickel/Photoredox-Catalyzed Methylation of (Hetero)aryl Chlorides Using Trimethyl Orthoformate as a Methyl Radical Source. *J. Am. Chem. Soc.* **2020,** *142*, 7683-7689; (g) Kariofillis, S. K.; Doyle, A. G., Synthetic and Mechanistic Implications of Chlorine Photoelimination in Nickel/Photoredox C(sp(3))-H Cross-Coupling. *Acc. Chem. Res.* **2021,** *54*, 988-1000.

19. Takeda, D.; Yoritate, 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.

20. (a) Knapp, D. M.; Gillis, E. P.; Burke, M. D., A General Solution for Unstable Boronic Acids: Slow-Release Cross-Coupling from Air-Stable MIDA Boronates. *J. Am. Chem. Soc.* **2009,** *131*, 6961-6963; (b) Struble, J. R.; Lee, S. J.; Burke, M. D., Ethynyl MIDA boronate: a readily accessible and highly versatile building block for small molecule synthesis. *Tetrahedron* **2010,** *66*, 4710-4718; (c) Dick, G. R.; Knapp, D. M.; Gillis, E. P.; Burke, M. D., General Method for Synthesis of 2-Heterocyclic N-Methyliminodiacetic Acid Boronates. *Org. Lett.* **2010,** *12*, 2314-2317; (d) Lennox, A. J. J.; Lloyd-Jones, G. C., Selection of boron reagents for Suzuki–Miyaura coupling. *Chem. Soc. Rev.* **2014,** *43*, 412-443.

21. (a) Wittmann, V.; Kessler, H., Stereoselective Synthesis of C-Glycoside with a Glycosyl Dianion. *Angew. Chem. Int. Ed.* **1993,** *32*, 1091-1093; (b) Burkhart, F.; Hoffmann, M.; Kessler, H., C-glycosides: A stereoselective synthesis of α- and β-C-galactosides with glycosyl dianions. *Tetrahedron Lett.* **1998,** *39*, 7699-7702; (c) Zhu, F.; Miller, E.; Zhang, S.-q.; Yi, D.; O'Neill, S.; Hong, X.; Walczak, M. A., Stereoretentive C(sp^3)–S Cross-Coupling. *J. Am. Chem. Soc.* **2018,** *140*, 18140-18150.

22. (a) Gillis, E. P.; Burke, M. D., Multistep Synthesis of Complex Boronic Acids from Simple MIDA Boronates. *J. Am. Chem. Soc.* **2008,** *130*, 14084-14085; (b) Churches, Q. I.; Hooper, J. F.; Hutton, C. A., A

General Method for Interconversion of Boronic Acid Protecting Groups: Trifluoroborates as Common Intermediates. *J. Org. Chem.* **2015,** *80*, 5428-5435.

23. Li, Y.; Tang, P.; Chen, Y.; Yu, B., Gold(I)-Catalyzed Glycosidation of 1,2-Anhydrosugars. *J. Org. Chem.* **2008,** *73*, 4323-4325.

24. Shields, B. J.; Kudisch, B.; Scholes, G. D.; Doyle, A. G., Long-Lived Charge-Transfer States of Nickel(II) Aryl Halide Complexes Facilitate Bimolecular Photoinduced Electron Transfer. *J. Am. Chem. Soc.* **2018,** *140*, 3035-3039.

25. Zhu, F.; O'Neill, S.; Rodriguez, J.; Walczak, M. A., Stereoretentive Manipulations of Anomeric Nucleophiles: Applications in the Synthesis of Selenoglycosides. *Angew. Chem. Int. Ed.* **2018,** *57*, 7091-7095.

26. Zhu, F.; Walczak, M. A., Stereochemistry of transition metal complexes controlled by the metallo-anomeric effect. *J. Am. Chem. Soc.* **2020,** *142*, 15127–15136.

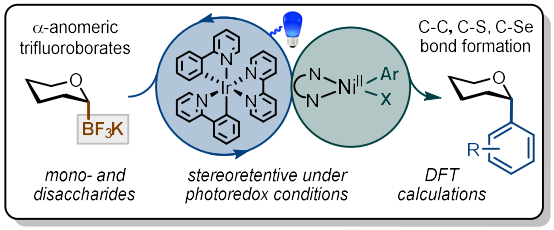
27. Abe, H.; Shuto, S.; Matsuda, A., Highly α- and β-selective radical C-glycosylation reactions using a controlling anomeric effect based on the conformational restriction strategy. A study on the conformation-anomeric effect-stereoselectivity relationship in anomeric radical reactions. *J. Am. Chem. Soc.* **2001,** *123*, 11870.

28. (a) Gutierrez, O.; Tellis, J. C.; Primer, D. N.; Molander, G. A.; Kozlowski, M. C., Nickel-Catalyzed Cross-Coupling of Photoredox-Generated Radicals: Uncovering a General Manifold for Stereoconvergence in Nickel-Catalyzed Cross-Couplings. *J. Am. Chem. Soc.* **2015,** *137*, 4896-4899; (b) Yuan, M.; Song, Z.; Badir, S. O.; Molander, G. A.; Gutierrez, O., On the Nature of C(sp3)–C(sp2) Bond Formation in Nickel-Catalyzed Tertiary Radical Cross-Couplings: A Case Study of Ni/Photoredox Catalytic Cross-Coupling of Alkyl Radicals and Aryl Halides. *J. Am. Chem. Soc.* **2020,** *142*, 7225-7234; (c) Campbell, M. W.; Yuan, M.; Polites, V. C.; Gutierrez, O.; Molander, G. A., Photochemical C–H Activation Enables Nickel-Catalyzed Olefin Dicarbofunctionalization. *J. Am. Chem. Soc.* **2021**, DOI: 10.1021/jacs.0c13077

29. Vogiatzis, K. D.; Polynski, M. V.; Kirkland, J. K.; Townsend, J.; Hashemi, A.; Liu, C.; Pidko, E. A., Computational Approach to Molecular Catalysis by 3d Transition Metals: Challenges and Opportunities. *Chem. Rev.* **2019,** *119*, 2453-2523.

30. Zhu, F.; Zhang, S.-q.; Chen, Z.; Rui, J.; Hong, X.; Walczak, M. A., Catalytic and Photochemical Strategies to Stabilized Radicals Based on Anomeric Nucleophiles. *J. Am. Chem. Soc.* **2020,** *142*, 11102-11113.

TOC Graphic


α-anomeric
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