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Research Article

Diastereoselective sp^3 C−O Bond Formation via Visible Light-Induced, Copper-Catalyzed Cross-Couplings of Glycosyl Bromides with Aliphatic Alcohols

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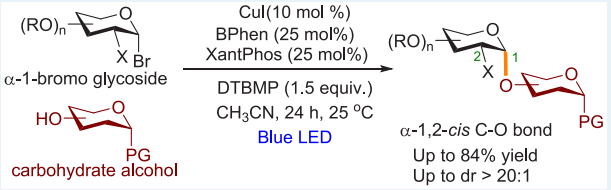
ABSTRACT: Copper-catalyzed cross-coupling reactions have become one of the most powerful methods for generating carbon−heteroatom bonds, an important framework of many organic molecules. However, copper-catalyzed C(sp^3)−O cross-coupling of alkyl halides with alkyl alcohols remains elusive because of the sluggish nature of oxidative addition to copper. To address this challenge, we have developed a catalytic copper system, which overcomes the copper oxidative addition barrier with the aid of visible light and effectively facilitates the cross-couplings of glycosyl bromides with aliphatic alcohols to afford C(sp^3)−O bonds with high levels of diastereoselectivity. Importantly, this catalytic system leads to a mild and efficient method for stereoselective construction of α-1,2-*cis* glycosides, which are of paramount importance, but challenging. In general, stereochemical outcomes in α-1,2-*cis* glycosidic C−O bond-forming processes are unpredictable and dependent on the steric and electronic nature of protecting groups bound to carbohydrate coupling partners. Currently, the most reliable approaches rely on the use of a chiral auxiliary or hydrogen-bond directing group at the C2- and C4-position of carbohydrate electrophiles to control α-1,2-*cis* selectivity. In our approach, earth-abundant copper not only acts as a photocatalyst and a bond-forming catalyst, but also enforces the stereocontrolled formation of anomeric C−O bonds. This cross-coupling protocol enables highly diastereoselective access to a wide variety of α-1,2-*cis*-glycosides and biologically relevant α-glycan oligosaccharides. Our work provides a foundation for developing new methods for the stereoselective construction of natural and unnatural anomeric carbon(sp^3)−heteroatom bonds.



KEYWORDS: *copper catalysis, visible light, C(sp^3)−O bond, cross-coupling, stereoselective*

INTRODUCTION

Copper has been considered a privileged metal because it is nontoxic and abundant. In addition, high-valent Cu(III) complexes have the propensity to undergo facile reductive elimination with a variety of coupling partners.[1] As a result, copper-catalyzed cross-coupling reactions have become one of the most versatile carbon−heteroatom bond-forming methodologies[2] for constructing pharmaceutical targets, agrochemicals, and polymers.[3] For instance, Buchwald and others illustrated the utility of copper catalysis in the cross-couplings of aryl halides with alkyl alcohols (Scheme 1A) as a powerful method for C(sp^2)−O bond formation.[4] However, the incorporation of alkyl halides to generate C(sp^3)−O bonds remains elusive. The limited capacity of copper to promote C(sp^3)−O bond formation could be attributed to its relatively slow rate of oxidative addition to alkyl halide to generate the alkylcopper(III) intermediate, which has been determined to be the rate-determining step in such catalytic cycles.[5] Although studies in ligand design have improved the rates of the copper oxidative addition, the scope of copper-catalyzed carbon−oxygen cross-coupling has remained largely restricted to aryl halides.[6]

Recently, Fu and co-workers reported the photoinduced copper-catalyzed cross-couplings of alkyl halides with nitrogen nucleophiles to form C(sp^3)−N bonds.[7] Their method effectively overcomes the copper oxidative addition problem with a copper(II) species capturing alkyl radicals, which are generated from carbon−halide bond cleavage in the presence of light and copper. Realizing that this concept could be adapted to afford C(sp^3)−O bonds, we sought to design a copper-catalyzed cross-coupling of a glycosyl bromide with an aliphatic alcohol under excitation by a blue light-emitting diode (LED) (Scheme 1B). We recognized that this light-driven copper catalysis process could lead to a mild and efficient

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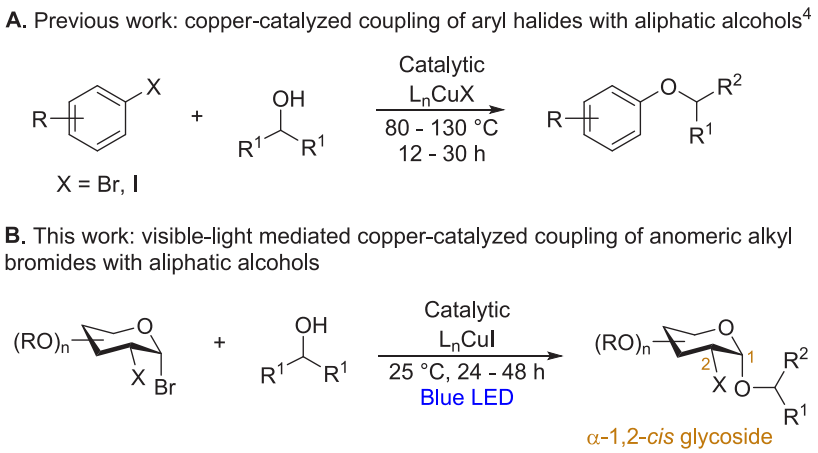
Scheme 1. Copper-Catalyzed C−O Bond Formation



method for the diastereoselective construction of α-1,2-*cis* glycosides via a glycosyl radical, which tends to favor α-substitution.[8] Despite extraordinary efforts and significant advances over the past several decades, the translation of most modern organic methodologies to diastereoselectively construct anomeric α-1,2-*cis* carbon−oxygen bonds remains challenging.[9] Most current coupling methods rely on the nature of the protecting groups bound to the carbohydrate substrates to effect stereoselectivity.[10] However, there are only a few catalyst and reagent controlled approaches reported for the construction of challenging α-1,2-*cis* glycosides without relying on protecting groups to direct selectivity at the newly formed glycosidic bond.[11]

In the field of photoredox catalysis, utilization of glycosyl halides in cross-coupling reactions with aliphatic alcohols to form C(sp^3)−O bonds has never been achieved.[12] Therefore, it was apparent at the outset of our investigations that the adaptation of the visible-light-mediated copper catalysis system to anomeric C−O bond formation would present several obstacles. First, although it has been reported that copper−nucleophile complexes can undergo excitation in the photo-induced process,[13] it was unclear if a complex formed between a copper catalyst and carbohydrate alkyl alcohol would have the necessary absorption and reactivity profile to engage in a copper-catalyzed C−O bond formation. Another issue is whether the coupling proceeds via a radical mechanism,[13] wherein the anomeric carbon−halide bond is cleaved in the presence of copper and light to form glycosyl radical. Finally, questions still remain concerning how this approach could provide catalyst control of the selectivity for α-1,2-*cis* C−O bond formation. As a consequence, the development of methods that simultaneously construct anomeric C(sp^3)−O bonds and control α-1,2-*cis* stereochemistry is of paramount importance, although challenging. Here, we describe a distinct approach for stereocontrolled formation of α-1,2-*cis* glycosides, through the action of a visible-light-mediated copper catalyst. Many of the synthetic limitations for the synthesis of these anomeric C−O linkages are overcome by this method.

RESULTS AND DISCUSSION

In our pursuit of photoinduced copper-catalyzed anomeric C(sp^3)−O bond formation, we initially evaluated various combinations of ligands, copper sources, acid scavenger, solvents, and reaction time (Figures S1−S6). This search revealed that blue LED irradiation of α-1-bromo-D-glucoside **1** (0.2 mmol, 1 equiv)[14] and primary alcohol **2** (0.3 mmol, 1.5 equiv) as model substrates with CuI (10 mol %), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XantPhos, 25 mol %), 4,7-diphenyl-1,10-phennathroline (BPhen 25 mol %), and acid scavenger di-*tert*-butylmethylpyridine (DTBMP) in acetonitrile at 25 °C for 24 h afforded the coupling product **3** in good yield with excellent levels of diastereoselectivity (70%, α:β = 13:1, Table 1, entry 1).[15,16] Control experiments established that copper, both ligands (XantPhos and BPhen), acid scavenger (DTBMP), and blue LED irradiation are essential to achieve anomeric C(sp^3)−O bond formation (entries 2−10). Interestingly, the coupling proceeded in a simple 10 mol % CuI solution to provide **3** in only 9% yield as a 9:1 mixture of α- and β-diastereomers (entry 11), suggesting that CuI acts as a Lewis acid. Employing a stoichiometric amount of CuI only provided 31% of the desired product **3** with a similar selectivity (entry 12).

^{31}P NMR was conducted on the in situ generated complex to probe the active catalyst in the reaction. The chemical shift was determined to be δ = −11.99 ppm, generated from the combination of CuI, BPhen, and Xantphos, and this chemical shift matched that of the isolated complex, [Cu(BPhen)(Xantphos)]BF_4 (δ = −11.87 ppm). As such, we conducted the cross-coupling of **1** with **2** in the presence of [Cu(BPhen)(Xantphos)]BF_4 (Table 1, entry 13), and the 1,2-*cis* product **3** was obtained in a yield and α-selectivity (60%, α:β = 9:1) similar to that promoted by in situ generated copper catalyst from the combination of CuI, BPhen, and Xantphos. This result suggests that the [Cu(BPhen)(Xantphos)]$^+$ complex is likely to be active in catalysis. We recently reported the use of BPhen as the organocatalyst to promote the coupling of glycosyl bromide **1** with carbohydrate alcohol **2** at 50 °C.[17] To validate that the cross-coupling is promoted by the copper complex, we conducted the reaction of **1** with **2** in the presence of 25 mol % BPhen (Table 1, entry 14), and the desired disaccharide **3** was isolated in less than 5% yield. For comparison, we also conducted the coupling reaction using traditional Lewis acid, silver triflate (entry 15), wherein an oxocarbenium ion is likely to be the key intermediate in the reaction. An alcohol is then approached on either the α- or the β-face of the oxocarbenium intermediate to provide a mixture of α-1,2-*cis*- and β-1,2-*trans* products. As expected, the use of a stoichiometric amount of silver triflate provided the coupling product **3** as a 4:1 mixture of α- and β-diastereomers (entry 15).

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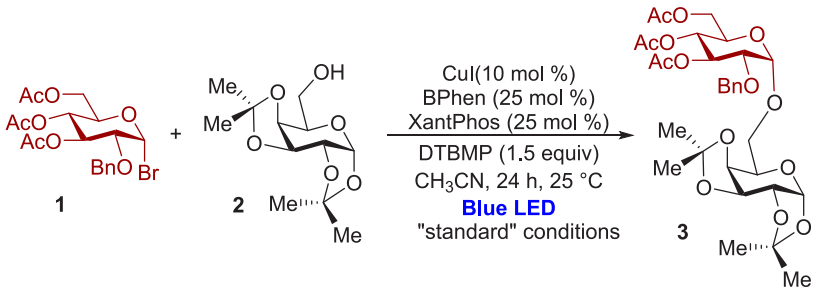
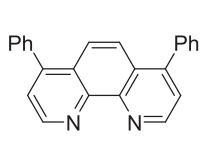
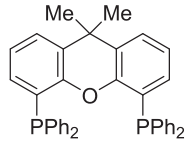
Table 1. Effect of Reaction Parameters[a]



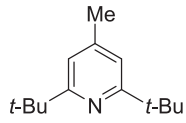
entry	variation from the "standard" condtions	yield[b] (%)	α:β ratio[c]
1	none	70	13:1
2	no light	10	10:1
3	no BPhen	34	13:1
4	no XantPhos	46	13:1
5	no DTBMP	27	13:1
6	no CuI	<1	n/a
7	no BPhen and no DTBMP	10	10:1
8	no CuI and no DTBMP	<1	n/a
9	no CuI and no XantPhos	<1	n/a
10	no CuI and no BPhen	<1	n/a
11	10 mol % CuI, 1.5 equiv of DTBMP only	9	9:1
12	100 mol % CuI, 1.5 equiv of DTBMP only	31	9:1
13	10 mol % Cu(XantPhos)(BPhen)BF_4, DTBMP, blue LED	60	9:1
14	25 mol % BPhen and 1.5 equiv of DTBMP only	5	10:1
15	100 mol% AgOTf, 1.5 equiv of DTBMP only	55	4:1



BPhen



XantPhos



DTBMP

[a]The reaction was conduct with **1** (0.2 mmol, 1 equiv) and **2** (0.3 mmol, 1.5 equiv). [b]Isolated yield. [c]Diastereoselective (α:β) ratio of the isolated product determined by ^{1}H NMR.

Having established the ability of the photoinduced copper catalyst to promote the formation of the anomeric C(sp^3)−O bond with high levels of selectivity, we studied the current system in comparison to our previously developed phenanthroline-catalyzed stereoretentive glycosylation method (Table 2).[17] There are two major limitations associated with the phenanthroline-catalyzed method. First, the reaction must be conducted at 50 °C to achieve high conversion. Second, the diastereoselectivity of the coupling products decreases when sterically hindered alcohols are coupled to the electron-rich glycosyl bromides. Our computational and experimental studies indicate a double S_N2 pathway involving a phenanthroline-catalyzed reaction with α-glycosyl bromide wherein a covalent β-glycosyl phenanthrolium ion is the key intermediate, and the S_N1−S_N2 reaction paradigm was slightly shifted in the presence of the hindered alcohols. Because the visible-light-mediated copper catalysis is unlikely to proceed through the traditional S_N2−S_N1 pathway and the stereochemical outcome of the coupling product is likely to be controlled by the [Cu(BPhen)(Xantphos)]$^+$ complex, we hypothesize that this catalytic copper system could overcome the limitations previously associated with the phenanthroline system. To validate our hypothesis, the coupling of α-glycosyl bromide **4** with the C4-hydroxy of L-rhamnoside **5** was conducted to afford the desired product **6** (Table 2, entry 1) in good yield and excellent levels of diastereoselectivity (74%, α:β > 20:1). In contrast, our previous phenanthroline-catalyzed method provided **6** in 42% yield with α:β = 7:1. A similar outcome was observed with the coupling of α-fucosyl bromide **7** with the secondary alcohol **5** (entry 2). To our excitement, the photoinduced copper system is also applicable with the challenging glucuronic acid electrophile **9** to provide the

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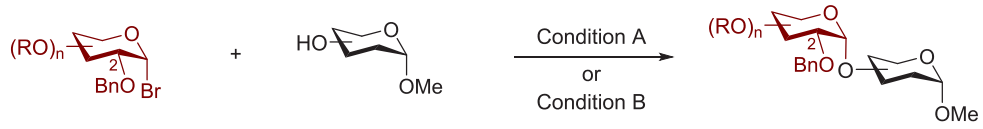
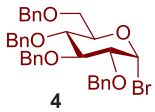
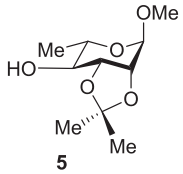
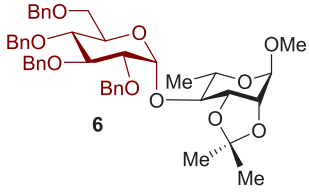
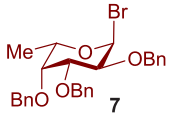
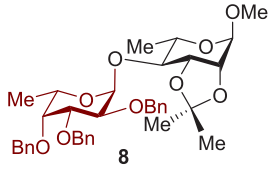
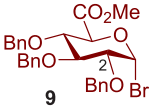
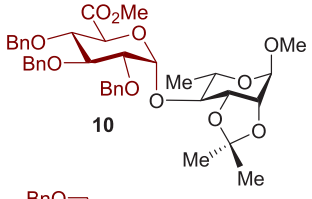
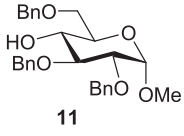
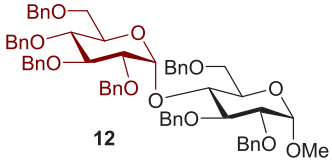
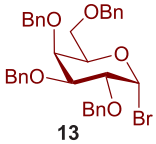
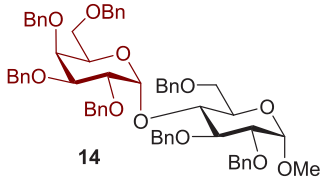
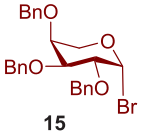
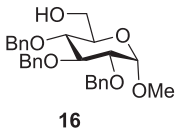
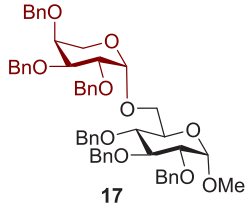
Table 2. Comparative Studies between Photoinduced Copper Catalysis and Organocatalysis



Conditions A: CuI(10 mol %), BPhen (25 mol %), XantPhos (25 mol %), DTBMP (1.5 equiv), CH_3CN, 24 h, 25 °C, Blue LED

Conditions B: BPhen (30 mol %), IBO (2 equiv), MTBE, 48 h, 50 °C

entry	electrophiles	nucleophiles	products	conditions **A** yield[b] (α:β)[c]	conditions **B** yield[b] (α:β)[c]
1	 **4**	 **5**	 **6**	74% (α:β > 20:1)	42% (α:β = 7:1)
2	 **7**	**5**	 **8**	57% (α:β > 20:1)	58% (α:β = 4:1)
3	 **9**	**5**	 **10**	53% (α:β > 20:1)	11% (α:β = 5:1)
4	**4**	 **11**	 **12**	60% (α:β > 20:1)	55% (α:β = 7:1)
5	 **13**	**11**	 **14**	61% (α:β > 20:1)	43% (α:β = 5:1)
6	 **15**	 **16**	 **17**	79% (α:β > 20:1)	47% (α:β > 20:1)

[a]The reaction was conduct with 1 equiv (0.2 mmol) of glycosyl bromides and 1.5 equiv (0.3 mmol) of aliphatic alcohols. [b]Isolated yield. [c]Diastereoselective (α:β) ratio determined by ^{1}H NMR analysis.

coupling product **10** in 53% yield with α:β > 20:1 (entry 3). To compare, the phenanthroline-catalyzed method provided **10** in 11% yield with moderate selectivity (α:β = 5:1). To further demonstrate the broad applicability of the visible-light-mediated copper method, we investigated the coupling of α-glycosyl bromides **4** and **13** with the hindered C4-hydroxy of

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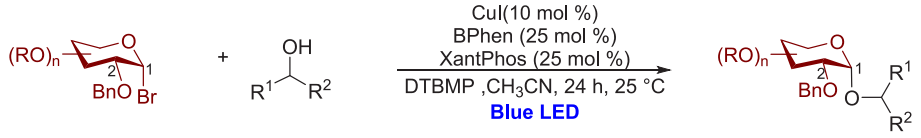
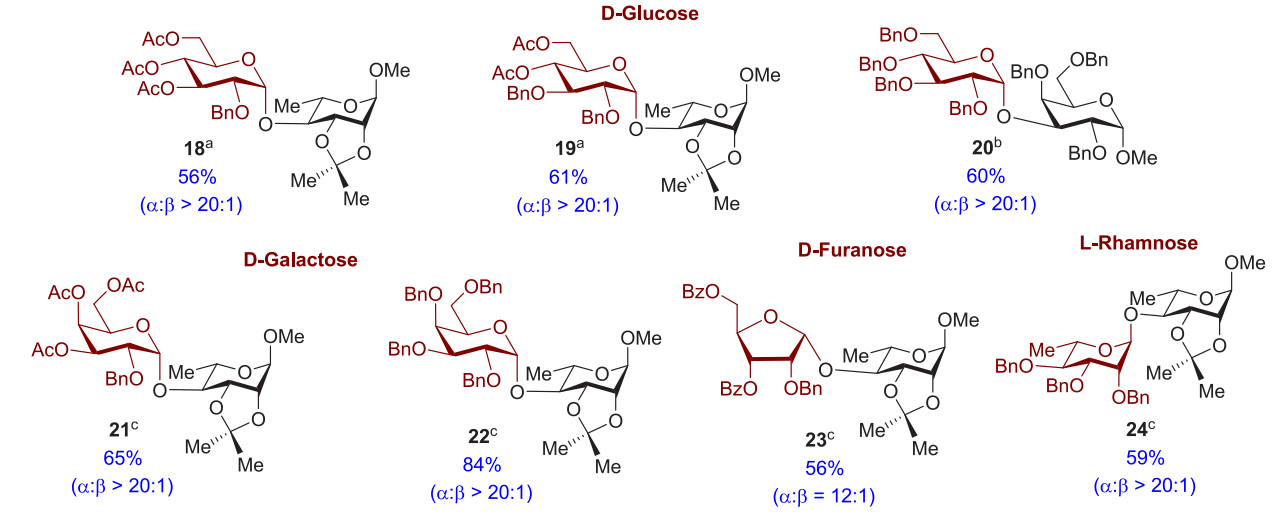
Table 3. Coupling of Secondary Alcohols with Various Glycosyl Bromides[a]





[a]Reactions performed with R−Br (0.2 mmol, 1.0 equiv) and R−OH (0.3 mmol, 1.5 equiv). Yields isolated. The diastereomeric ratios (α:β) were determined by ^{1}H NMR. [b]R−Br (0.3 mmol, 1.5 equiv), R−OH (0.2 mmol, 1.0 equiv). [c]R−Br (0.4 mmol, 2.0 equiv), R−OH (0.2 mmol, 1 equiv).

glucoside **11** (entries 4 and 5). As expected, the photoinduced copper catalysis (**12** and **14**, α:β > 20:1) is more α-selective than the phenanthroline catalysis (**12**, α:β = 7:1 and **14**, α:β = 5:1). We previously observed that α-1-bromo L-arabinoside **15** (entry 6) decomposed during the course of the reaction under phenanthroline-catalyzed conditions (**17**, 47%).[17] We questioned whether this electrophile **15** could be a suitable substrate under photoinduced copper-catalyzed conditions. To our excitement, the coupling of **15** with primary alcohol **16** proceeded smoothly to provide disaccharide **17** in much higher yield (79%, entry 6). Overall, the results in Table 2 highlight that the visible-light-mediated copper system is efficient and highly selective for the cross-couplings of the electron-rich α-glycosyl bromides with the hindered alcohols of carbohydrates. More importantly, this copper method is conducted at room temperature and effective for constructing an anomeric C(sp^3)−O bond with reduced levels of waste through the use of substoichiometric amounts of metal and a high reaction concentration (0.5 M).

The α-1,2-*cis* glycosidic C−O bonds have also been reported by Boons and Demchenko using the chiral auxiliary and hydrogen-bond directing group at the C2- and C4-positions of carbohydrate electrophiles, respectively.[10] For instance, the Boons approach is based on neighboring participation of a (1*S*)-phenyl-2-sulfanyl)ethyl auxiliary at the C2-position of glycosyl electrophiles to control the formation of the α-1,2-*cis* products.[10a] The Demchenko approach utilizes the picolinyl and picoloyl groups at the C4-position of electrophiles to control the α-1,2-*cis* selectivity through intermolecular hydrogen bonding between a nitrogen atom of picolinyl and picoloyl groups and a hydroxyl group of a nucleophile. In contrast, our method utilizes the commonly used benzyl ether protecting group whose nonassisting functionality often leads to a mixture of α- and β-diastereomeric products. Because our system relies on a copper complex to act as a photocatalyst and a C−O bond-forming catalyst as well as to enforce stereocontrolled formation of α-diastereomer, the coupling products are likely to form with high levels of selectivity. For instance, cross-coupling of α-glycosyl bromide **4** with sterically hindered secondary alcohol **11** under photoinduced, copper-catalyzed conditions provided the desired disaccharide **12** in 60% yield with high levels of α-selectivity (α:β > 20:1, Table 2, entry 5). To compare, use of a stoichiometric amount of silver triflate as Lewis acid afforded **12** (Figure S7) as a 2:1 mixture of α- and β-diastereomers. Recently, Mong and co-workers reported the use of *N*,*N*-dimethylformamide (DMF) as an α-modulating additive to direct the selectivity.[11c] In their seminal work, glycosylation of alcohol **11** with a phenylthiol derivative of **4** using a reagent combination of NIS (1.5 equiv) and TMSOTf (1.5 equiv) in −10 °C as a promoter and DMF (6 equiv) as α-modulator provided **12** in 75% yield with α:β = 9:1.[11c]

Moving forward, we evaluated the scope of the electron-withdrawing α-glycosyl bromides with respect to various secondary alcohols (Table 3). In our study, we chose to investigate the couplings with hindered secondary alcohols as they have been reported to provide the carbohydrate products with poor to moderate levels of diastereoselectivities.[18] Accordingly, α-1-bromo-D-glucosides bearing acetyl and benzyl protecting groups were examined in the coupling to C4- and C3-hydroxys. In all cases, the reactions proceeded at room temperature to provide the desired disaccharide products (**18**−**20**) in good yields (56−61%) and excellent stereocontrol (α:β > 20:1). To determine whether the selectivity of the coupling products obtained under copper-catalyzed conditions depends on a reaction concentration, the cross-coupling of α-glycosyl bromide **4** with C3-hydroxy of galactoside was conducted at

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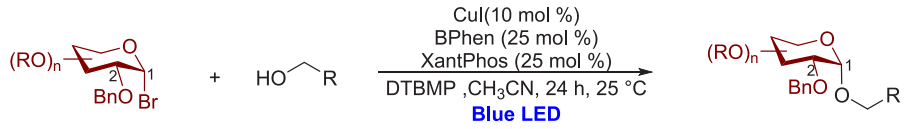
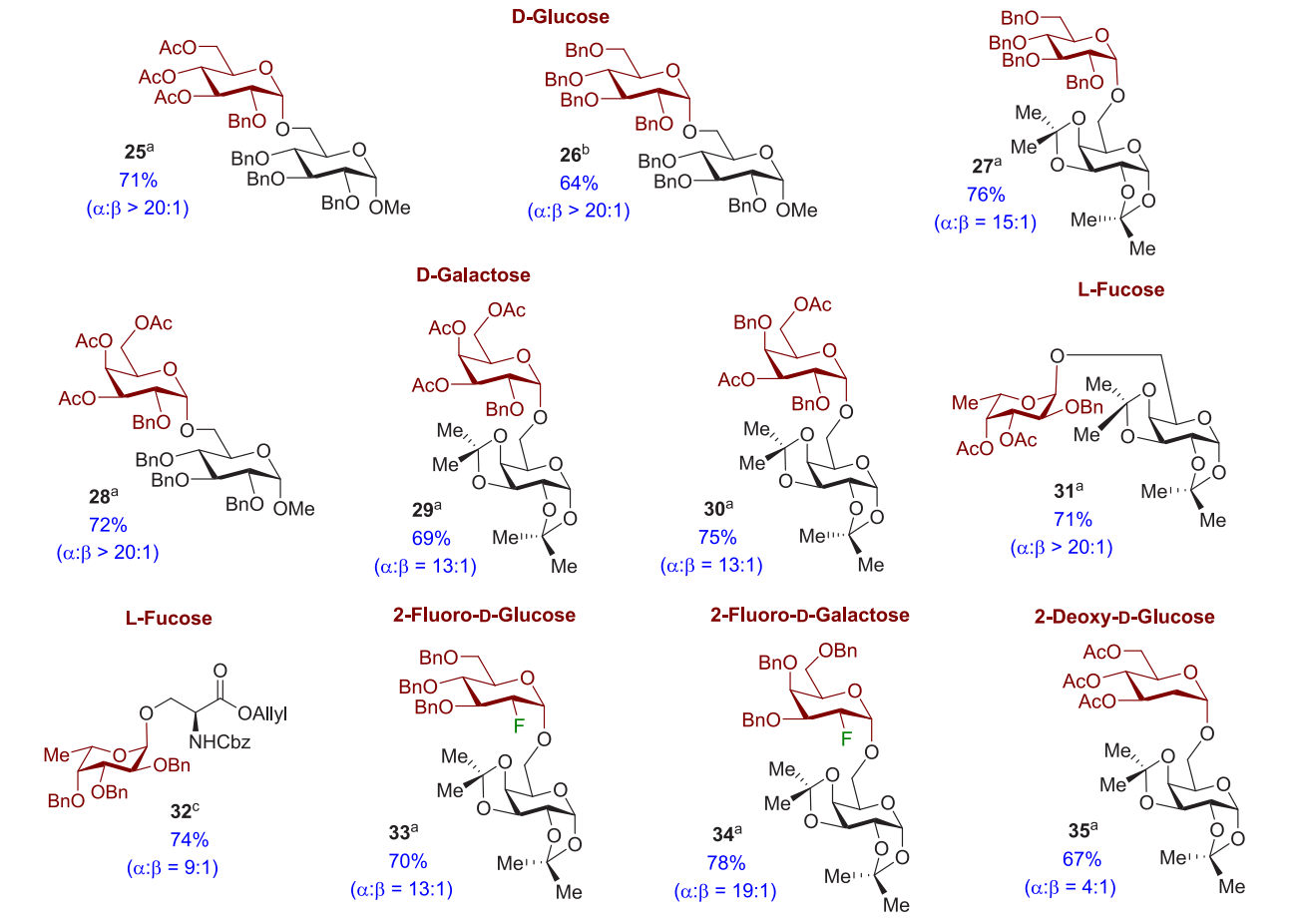
ACS Catal. 2020, 10, 5990−6001

Table 4. Scope of Primary Alcohols and Glycosyl Bromides[a]





[a]Reactions performed with R−Br (0.2 mmol, 1.0 equiv) and R−OH (0.3 mmol, 1.5 equiv). Yields isolated. The diastereomeric ratios (α:β) were determined by ^{1}H NMR. [b]R−Br (0.3 mmol, 1.5 equiv), R−OH (0.2 mmol, 1.0 equiv). [c]R−Br (0.4 mmol, 2.0 equiv), R−OH (0.2 mmol, 1 equiv).

three different concentrations (0.25, 0.5, and 1 M). The selectivity of the coupling product **20** remained the same (α:β > 20:1) for the three reaction concentrations. The standard 0.5 M reaction concentration provided **20** in 60% yield, while a slightly higher yield (64%) was obtained at a higher (1 M) concentration (Figure S8). On the other hand, the reaction was sluggish at a lower (0.25 M) concentration (Figure S8). To compare to the current method for the highly diastereoselective synthesis of α-1,2-*cis* glycosides, the selectivity of the Demchenko approach using the C4-picoloyl functionality as the hydrogen-bond directing group appears to depend on the reaction concentration.[10b] For instance, while a low reaction concentration (5 mM) provided the coupling derivative of product **20** with excellent selectivity (α:β > 20:1), the reaction was less selective at a high concentration (50 mM, α:β = 10:1).[10b] We observed that while the electron-withdrawing glycosyl bromides can proceed efficiently at room temperature under visible-light-mediated copper conditions, the yields of the coupling products are lower than those obtained under phenanthroline-catalyzed conditions.[17] For instance, the copper system provided the product **19** in 61% yield, while the phenanthroline system afforded **19** in 73% yield.[17] Variation in the structure of α-glycosyl bromides was also tested, delivering the products containing D-galactose (**21** and **22**) and L-rhamnose (**24**) with high α-diastereoselectivity (α:β > 20:1). Interestingly, the visible-light-mediated copper system is also effective at promoting the coupling with electron-withdrawing five-member ring ribosyl bromide to provide the desired product **23** with high α-1,2-*cis* selectivity (α:β = 12:1).

Motivated by the high efficiency of the photoinduced copper system to promote the reaction of α-glycosyl bromides with secondary alcohols, we next examined the cross-couplings of a variety of electron-withdrawing and electron-donating glycosyl bromides with primary alcohols (Table 4). The reactions were highly diastereoselective to produce the coupling products (**25** to **31**) in good yields and excellent selectivity, underscoring broad applications of the visible-light-mediated copper-catalyzed anomeric C(sp^3)−O bond formation. To compare, the reaction of the thioglycoside derivative of α-glycosyl bromide **4** with primary alcohol **16** under traditional glycosylation conditions provided the desired product **26** as

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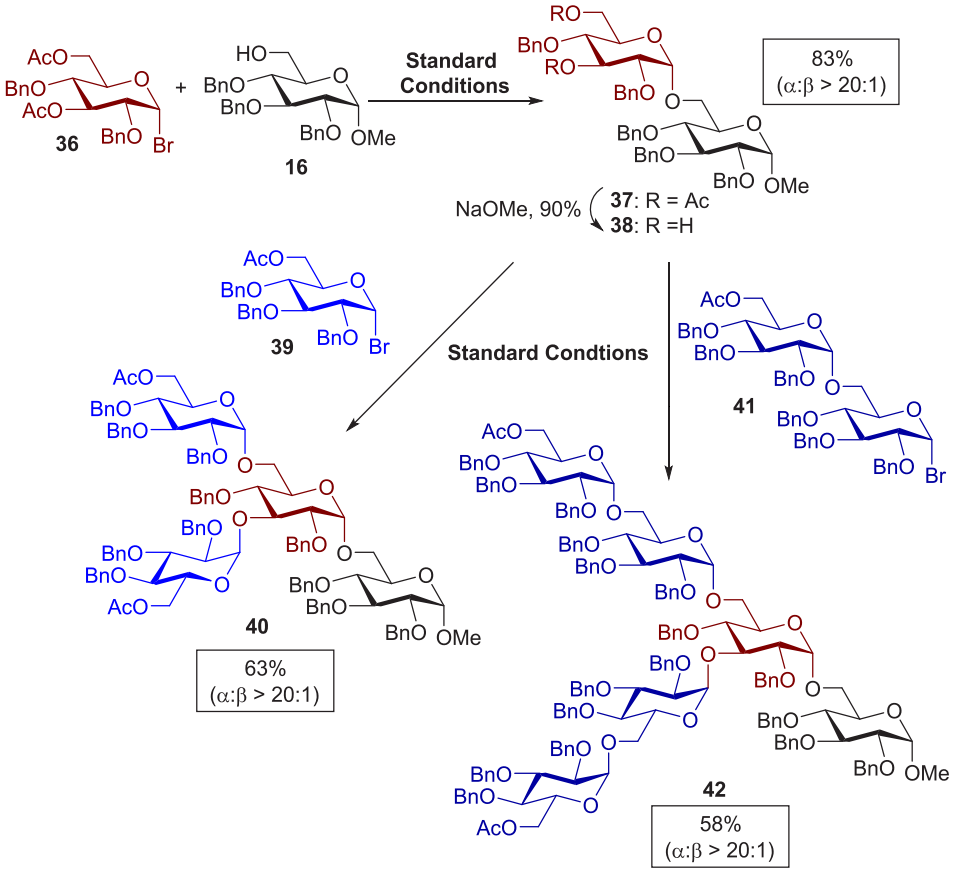
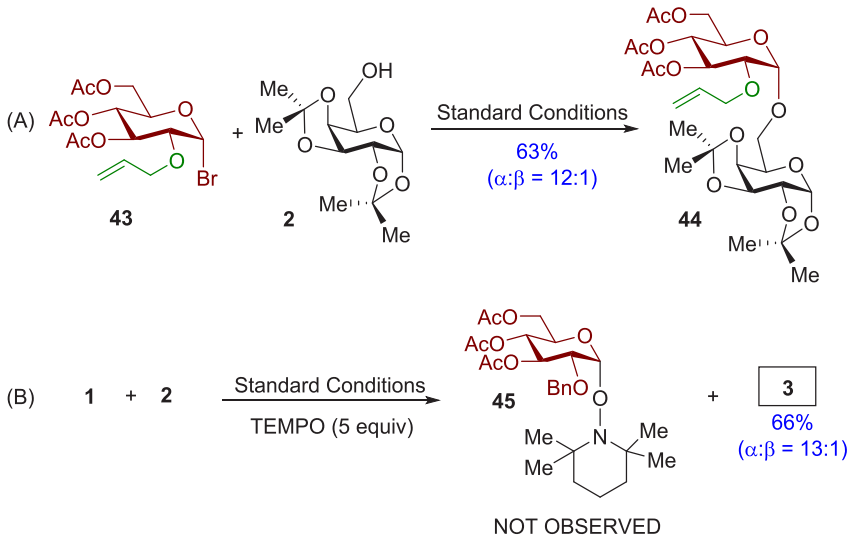
Scheme 2. Copper-Catalyzed Oligosaccharide Synthesis



Scheme 3. Control Experiments



a 2:1 mixture of α- and β-diastereomers.[10b] In stark contrast, the photoinduced copper-catalyzed cross-coupling provided **26** with excellent α-1,2-*cis* selectivity (α:β > 20:1). As compared to the Demchenko approach with use of primary alcohol **16**, the picoloyl group at the C4-position is α-1,2-*cis* selective, while the picolinyl group at remote positions (C2, C3, C4, and C6) favors the β-1,2-*trans* selectivity.[10b] Next, we tested whether our catalytic copper system could override the substrate's inherent selectivity bias. We conducted the coupling with α-galactosyl bromide whose axial C4-benzyl, picolinyl, and picoloyl groups have been reported to favor the β-1,2-*trans* product.[10b,19] To our excitement, the visible-light-mediated copper-catalyzed cross-reaction favored the α-1,2-*cis* product (**30**, α:β = 13:1). An additional feature that highlights this system is the tolerance of the method to protected serine nucleophiles, delivering glycoconjugate **32** (74%, α:β = 9:1), which is a thrombospondin type 1 repeating unit associated with an autosomal recessive disorder.[20] Next, we explored the effect of the C2 substituents of α-glycosyl bromides on the selectivity (Table 4) to gain insight into the mechanism of the

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ACS Catal. 2020, 10, 5990−6001

copper system. The ability of a C2−F bond to have an impact on the diastereoselectivity of anomeric C−O bond formation has been reported.[21] The tetrabenzylated D-glucose and D-galactose substrates, having the C2-fluoro group, are highly β-selective under Lewis acid-mediated conditions.[21] In stark contrast, the photoinduced, copper-catalyzed approach is highly α-selective, providing the α-1,2-*cis* disaccharides containing D-glucose (**33**, α:β = 13:1) and D-galactose (**34**, α:β = 19:1). On the other hand, α-glycosyl bromide lacking C2-oxygen functionality exhibited moderate selectivity (**35**, α:β = 4:1)[22] due to its conformational flexibility.

We expect that the visible-light-induced copper approach will be particularly useful when applied to the synthesis of biologically relevant α-glycans. Well-defined construction of the oligosaccharide motifs of these natural α-glycans will allow one to study these bioactive fragments as potential prebiotics.[23] To illustrate this potential, the stereocontrolled synthesis of the branched dextran oligosaccharides **40** and **42** was investigated (Scheme 2). Accordingly, we subjected α-1-bromo D-glucoside **36** (2.48 g, 4.9 mmol, 1.2 equiv) and primary alcohol **16** (1.9 g, 4.1 mmol, 1.0 equiv) to the standard photoinduced copper conditions. In this case, 1,2-*cis* disaccharide **37** (3.028 g) was isolated in 83% yield with high levels of α-selectivity (α:β > 20:1). It is worth mentioning that this reaction was done on a gram scale and still maintained an excellent result, illustrating the scalability and reproducibility of our method. Subsequent hydrolysis of **37** provided the corresponding diol **38**, which serves as a nucleophilic coupling partner for another cross-coupling iteration with α-glycosyl bromides **39** and **41** to afford tetrasaccharide **40** (224 mg, 63%, α:β > 20:1) and hexasaccharide **42** (212 mg, 58%, α:β > 20:1), respectively, under standard coupling conditions.

Although reaction development is the major focus of this investigation, we performed preliminary mechanistic studies. It has been reported that an anomeric C1-radical generated in the coupling reaction would undergo a 5-*exo*-trig cyclization with a C2-pendant olefin to generate the bicyclic product.[24] As such, we conducted the coupling of α-glycosyl bromide **43** (Scheme 3A) bearing a C2-pendant olefin with primary alcohol **2**. The coupling product **44** was, however, observed in the reaction, and no cyclization product was isolated. Kochi and co-workers have previously demonstrated that carbon radicals can be oxidized rapidly by copper complex to generate alkyl copper intermediates;[25,26] therefore, it is possible that oxidation of anomeric C1-radical by a copper(II) complex to form alkylcopper(III) complex is faster than a radical 5-*exo*-trig cyclization.[25,27] Next, we hypothesize that if C−O bond formation occurs through out-of-cage, addition of TEMPO (5 equiv) to the reaction mixture would lead to the formation of a TEMPO adduct. As can be seen in Scheme 3B, the TEMPO-trapping product **45** was not detected in the coupling reaction, suggesting that electron transfer and subsequent interactions with anomeric radical intermediate are likely to take place within the same solvent cage.

In UV/vis absorption experiments, the in situ generated copper catalyst from the combination of CuI, BPhen, and Xantphos in the ratio of 1:2.5:2.5 shows broad absorption (Figure 1A) in the visible region (λ_{max} = 408 nm), whereas the mixture of CuI and BPhen or of CuI and Xantphos shows no absorption, suggesting the importance of these two ligands in forming the complex. The same absorption peak in the visible light region was also observed for the isolated copper complex, [Cu(BPhen)(Xantphos)]BF_4 (Figure S11). Furthermore, ^{31}P

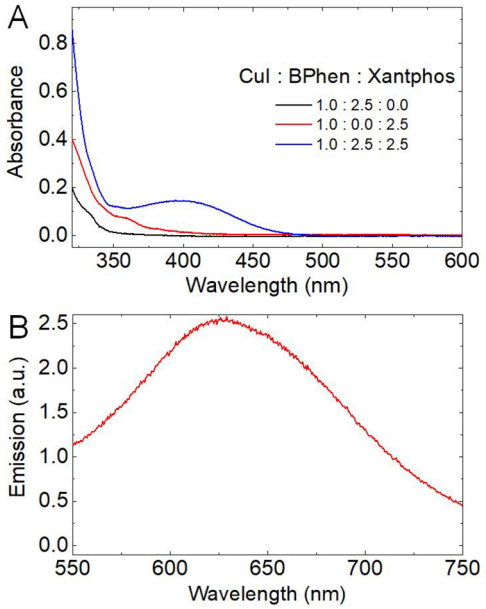

Figure 1. (A) UV/vis absorption spectra for CuI, BPhen, and Xantphos with different mole ratios. The spectra were acquired with a 0.5 nm interval. (B) Emission spectrum of the copper complex (CuI:BPhen:Xantphos = 1:2.5:2.5) at 0.1 mM concentration with an excitation wavelength of 450 nm.

NMR analysis showed that the in situ generated copper complex (δ = −11.99 pm) and the isolated copper complex (δ = −11.87 pm) have similar chemical shifts. The isolated copper catalyst was effective at promoting the coupling to provide the coupling product **3** (entry 13, Table 1) in yield and α-selectivity similar to that promoted by in situ generated copper catalyst (entry 1, Table 1). Collectively, these results suggest that the $[Cu(BPhen)(Xantphos)]^+$ complex is likely to be the primary photoreductant in the visible-light-mediated copper-catalyzed cross-coupling. In addition, we observed a clear peak at 630 nm in emission spectra of the in situ generated copper complex under the irradiation of 450 nm (Figure 1B), suggesting the existence of the excited-state copper species. The emission spectrum of [Cu(BPhen)(Xantphos)]BF_4 (Figure S12) shows a trend similar to that of the in situ generated copper catalyst (Figure 1B), further supporting that $[Cu(BPhen)(Xantphos)]^+$ is the active catalyst.

On the basis of the aforementioned preliminary results (Scheme 3 and Figure 1) and the recent literature reports,[13] a proposed mechanism for the visible-light-mediated copper-catalyzed anomeric C(sp^3)−O bond formation is outlined in Scheme 4. The first step involves the coordination of the aliphatic oxygen nucleophile to the Cu(I) center to form the corresponding copper(I)−oxygen complex **A**.[13] Photoexcitation of copper(I) complex **A** could result in an excited-state copper(I) species **B** that potentially engages in electron transfer with α-glycosyl bromide **C**.[28] This irradiation step corresponds well to the broad absorption and emission observed experimentally (Figure 1). However, the results obtained with control experiments (Scheme 3) suggest that the coupling reaction may not proceed via a copper(II) complex **D** and a long-lived glycosyl radical **E**.[13] As such, the glycosyl radical **E** can either react with copper(II) complex **D** to form a copper(III) species **F** (path A)[25,26] or be oxidized by copper(II) complex **D** to generate oxocarbenium ion **G**

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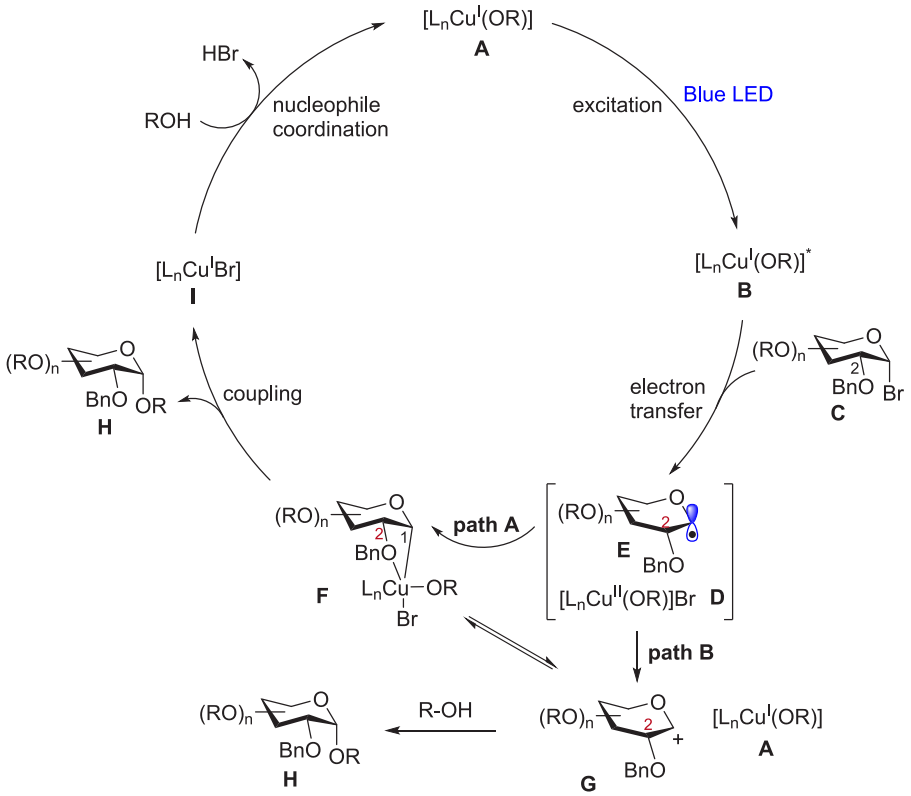
Scheme 4. Proposed Mechanism



(path B).[29] Dissociation of the alkylcopper(III) complex **F** could also provide the oxocarbenium ion intermediate **G**. If path A is operative, reductive elimination from complex **F** affords C(sp^3)–O bond **H** and a copper(I) species **I**. The copper(I) complex **A** is regenerated to reset the cycle. Alternatively, nucleophilic attack onto the oxocarbenium ion (path B) also results in the formation of the desired product **H**.

The onsite potential of the reduction of α-glycosyl bromide **1** to glycosyl radical (compound **E** in Scheme 4) was measured to be ~−0.5 V using an Ag electrode (Figure S13) as Ag is known to be an effective catalyst for reducing alkyl bromide.[30] Direct measurement of the oxidation potential of complex **B** is challenging because **B** is the unstable excited state of copper(I) complex **A** (Scheme 4). Common strategy to address this challenge is to estimate from the oxidation potential of **A** and the emission wavelength of **B** (Figure 2a). However, the preliminary attempt on the isolation of **A** was not successful. We then noticed that mixing [Cu(BPhen)(Xantphos)]BF_4 (equivalent to complex **I** in Scheme 4) and MeO^-, which presumably generated **A**, did not change the emission wavelength of copper complex **I** (Figure 2b), suggesting **A** and **I** as well as their corresponding excited states **B** and **I*** may be energetically similar. Therefore, we estimated the oxidation potential of complex **B** from the oxidation potential of **I***. To obtain the oxidation potential of complex **I***, we first measured the emission wavelength of **I** to be 630 nm (Figure 2c), equivalent to 1.97 eV. We then measured the onset potential for the oxidation of **I** to be ~0.9 V (Figure 2d). Collectively, the oxidation potential of **I*** is the difference between 0.9 and 1.97 V, equal to −1.07 V. Overall, the reduction potential of compound **C** was measured to be −0.5 V using catalytic Ag electrode (Scheme 5). The oxidation

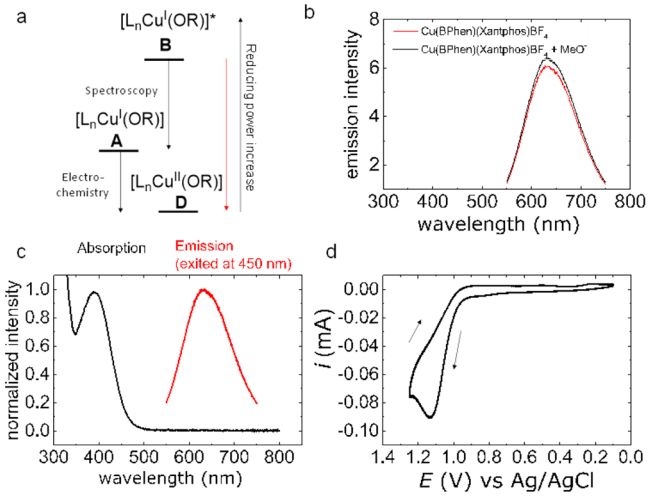


Figure 2. (a) Energy level diagram for estimating the oxidation potential of **B** to **D** from the spectroscopic measurement of the emission wavelength of **B** and the electrochemical measurement of the oxidation potential of the ground state **A**. (b) Emission spectra of [Cu(BPhen)(Xantphos)]$^+$ (equivalent to compound **I** in Scheme 4) with and without MeO^-, showing no noticeable difference in emission wavelength. (c) Absorption and emission spectra of compound **I**. (d) Cyclic voltammogram of compound **I** (2 mM) in acetonitrile containing 0.1 M tetrabutylammonium perchlorate as the electrolyte using GCE. Scan rate = 0.2 V.

potential of complex **B** was estimated to be ~−1.07 V from spectroscopic and electrochemical measurements (Scheme 5).

Finally, we hypothesize that the high levels of α-1,2-*cis* diastereoselectivity observed in the coupling products could be rationalized due to an interaction between the Cu center and C2-oxygen (complex **F**, Scheme 4).[31] Kochi and co-workers

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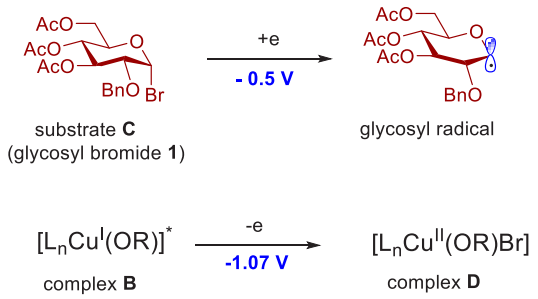
ACS Catal. 2020, 10, 5990−6001

Scheme 5. Summary of the Redox Potential of Excited-State Copper(I) Complex B and Substrate C (α-Glycosyl Bromide 1) Proposed in Scheme 4



have previously demonstrated that carbon radicals are oxidized by copper near a diffusion control to form the alkylcopper intermediate,[25,26] further supporting the proposed copper(III) complex **F**. To further validate that copper(III) species **F** is likely to form in the reaction, the C2-oxygen atom of α-glycosyl bromide was replaced with fluorine atom as fluorine has been proposed to coordinate to the Cu center.[32] The 2-fluoro-2-deoxy glycosyl bromides also favored the α-1,2-*cis* products (**33** and **34**, Table 4). On the other hand, if path B in Scheme 4 is operative, the coupling products should be obtained with low levels of selectivity as a nucleophile can attack on either face of the oxocarbenium intermediate **G**. Glycosyl radicals are more easily oxidized to cations than are the carbon radicals investigated by Kochi.[25,26] As such, we hypothesized that substitution of the C2-oxygen with hydrogen atom could further facilitate the formation of the 2-deoxy oxocarbenium ion that resulted either from dissociation from a copper(III) complex or from oxidation of the anomeric radical by copper(II) complex. If 2-deoxy cation is generated in the reaction, an alcohol nucleophile can approach on either its α- or its β-face to provide a mixture of 1,2-*cis* and 1,2-*trans* diastereomers, which was confirmed by an experimental result obtained with the coupling product **35** (Table 4).[33]

CONCLUSIONS

Utilization of visible light to overcome the relatively slow rate of oxidative addition in copper catalysis has facilitated the development of the cross-couplings of α-glycosyl bromides with alkyl alcohols to stereoselectively generate the challenging anomeric C(sp^3)−O bonds of α-1,2-*cis* glycoside products, an important motif of many bioactive carbohydrate molecules. Unlike the substrate-controlled approaches that rely on the chiral auxiliary group or the directing group at C2 and C4-position of carbohydrate electrophiles to control the α-1,2-*cis* diastereoselectivity, our method relies on copper catalyst to enforce stereocontrol. Furthermore, in stark contrast to nearly all catalytic glycosylation reactions, which typically proceed via either the S_N1 or the S_N2 pathway, this method utilizes copper catalyst induced by visible light to engage in a C−O bond formation. We anticipate this method would be widely adopted for generating other types of anomeric bond formations and provide a foundation for investigating cross-couplings of noncarbohydrate alkyl halides with sp^3-hydridized nucleophiles. The detailed mechanism, using a combined experimental and computational study, of these visible-light-mediated copper-catalyzed cross-couplings of α-glycosyl bromides with alcohol nucleophiles is under investigation and will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c01470.

Detailed experimental procedure and characterization data of the new compounds, including the NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Casitas, A.; Ribas, X. The Role of Organometallic Copper(III) Complexes in Homogeneous Catalysis. *Chem. Sci.* **2013**, *4*, 2301. (b) Hickman, A. J.; Sanford, M. S. High-Valent Organometallic Copper and Palladium in Catalysis. *Nature* **2012**, *484*, 177−185.

(2) (a) Beletskaya, I. P.; Cheprakov, A. V. Copper in Cross-Coupling Reactions: The Post-Ullmann Chemistry. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Monnier, F.; Taillfer, M. Catalytic C-C, C-N, and C-O Ullmann-Type Coupling Reactions. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954.

(3) (a) Evano, G.; Blanchard, N.; Toumi, M. Copper-Mediated Coupling Reactions and Their Applications in Natural Products and Designed Biomolecules Synthesis. *Chem. Rev.* **2008**, *108*, 3054. (b) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev.* **2013**, *113*, 6234.

(4) (a) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. Copper-Catalyzed Coupling of Aryl Iodides with Aliphatic Alcohols.

Org. Lett. **2002**, *4*, 973. (b) Altman, R. A.; Shafir, A.; Choi, A.; Lichtor, P. A.; Buchwald, S. L. An Improved Cu-Based Catalyst System for the Reactions of Alcohols with Aryl Halides. *J. Org. Chem.* **2008**, *73*, 284. (c) Liu, Y.; Park, S. K.; Xiao, Y.; Chae, J. Copper(II)-Catalyzed C-O Coupling of Aryl Bromides with Aliphatic Diols: Synthesis of Ethers, Phenols, and Benzo-Fused Cyclic Ethers. *Org. Biomol. Chem.* **2014**, *12*, 4747. (d) Zheng, Y.; Zou, W.; Luo, L.; Chen, J.; Lin, S.; Sun, S. Ligand-Free Cu-Catalyzed O-Arylation of Aliphatic Diols. *RSC Adv.* **2015**, *5*, 66104.

(5) (a) Jones, G. O.; Liu, P.; Houk, K. N.; Buchwald, S. L. Computational Explorations of Mechanisms and Ligand-Directed Selectivities of Copper-Catalyzed Ullmann-Type Reactions. *J. Am. Chem. Soc.* **2010**, *132*, 6205. (b) Yu, H.-Z.; Jiang, Y.-Y.; Fu, Y.; Liu, L. Alternative Mechanistic Explanation for Ligand-Dependent Selectivities in Copper-Catalyzed *N*- and *O*-Arylation Reactions. *J. Am. Chem. Soc.* **2010**, *132*, 18078. (c) Giri, R.; Brusoe, A.; Troshin, K.; Wang, J. Y.; Font, M.; Hartwig, J. F. Mechanism of the Ullman Biaryl Ether Synthesis Catalyzed by Complexes of Anionic Ligands: Evidence for the Reaction of Iodoarenes with Ligated Anionic Cu^{I} Intermediates. *J. Am. Chem. Soc.* **2018**, *140*, 793.

(6) (a) Amal Joseph, P. J.; Priyadarshini, S. Copper-Mediated C-X Functionalization of Aryl Halides. *Org. Process Res. Dev.* **2017**, *21*, 1889. (b) Bhunia, S.; Pawar, G. G.; Kumar, S. V.Y.; Jiang, Y.; Ma, D. Selected Copper-Based Reactions for C-N, C-O, C-S, and C-C Bond Formation. *Angew. Chem., Int. Ed.* **2017**, *56*, 16136.

(7) For selected examples, see: (a) Bissember, A. C.; Lundgren, R. J.; Creutz, S. E.; Peters, J. C.; Fu, G. C. Transition-Metal-Catalyzed Alkylations of Amines with Alkyl Halides: Photoinduced, Copper-Catalyzed Couplings of Carbazoles. *Angew. Chem., Int. Ed.* **2013**, *52*, 5129. (b) Do, H.-Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. Photoinduced, Copper-Catalyzed Alkylation of Amides with Unactivated Secondary Alkyl Halides at Room Temperature. *J. Am. Chem. Soc.* **2014**, *136*, 2162. (c) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. Asymmetric Copper-Catalyzed C-N Cross-Coupling Induced By Visible Light. *Science* **2016**, *351*, 681. (d) Matier, C. D.; Schwaben, J.; Peters, J. C.; Fu, G. C. Copper-Catalyzed Alkylation of Aliphatic Amines Induced by Visible Light. *J. Am. Chem. Soc.* **2017**, *139*, 117707. (e) Zhao, W.; Wurz, R. P.; Peters, J. C.; Fu, G. C. Photoinduced, Copper-Catalyzed Decarboxylative C-N Coupling to Generate Protected Amines: An Alternative to the Curtius Rearrangement. *J. Am. Chem. Soc.* **2017**, *139*, 12153.

(8) Dupuis, J.; Giese, B.; Ruegge, D.; Fischer, H.; Korth, H.-G.; Sustmann, R. Conformation of Glycosyl Radicals: Radical Stabilization by β-CO Bonds. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 896.

(9) Nigudkar, S. S.; Demchenko, A. V. Stereocontrolled 1,2-*Cis* Glycosylation As the Driving Force of Progress in Synthetic Carbohydrate Chemistry. *Chem. Sci.* **2015**, *6*, 2687.

(10) (a) Kim, J. H.; Yang, H.; Park, J.; Boons, G. J. A General Strategy for Stereoselective Glycosylation. *J. Am. Chem. Soc.* **2005**, *127*, 12090. (b) Yasomanee, J. P.; Demchenko, A. V. Effect of Remote Picolinyl and Picoloyl Substituents on the Stereoselectivity of Chemical Glycosylation. *J. Am. Chem. Soc.* **2012**, *134*, 20097.

(11) For representative examples, see: (a) Park, J.; Kawatkar, S.; Kim, J.-H.; Boons, G.-J. Stereoselective Glycosylations of 2-Azido-2-deoxy-glucosides Using Intermediate Sulfonium Ions. *Org. Lett.* **2007**, *9*, 1959. (b) Mensah, E. A.; Nguyen, H. M. Nickel-Catalyzed Stereoselective Formation of α-2-Deoxy-2-Amino Glycosides. *J. Am. Chem. Soc.* **2009**, *131*, 8778. (c) Mensah, E. A.; Yu, F.; Nguyen, H. M. Nickel-Catalyzed Stereoselective Glycosylation with C(2)-*N*-Substituted Benzylidene D-Glucosamine and Galactosamine Trichloroacetimidates for the Formation of 1,2-*Cis*-2-Amino Glycosides. Applications to the Synthesis of Heparin Disaccharides, GPI Anchor Psuedodisaccharides, and α-GalNAc. *J. Am. Chem. Soc.* **2010**, *132*, 14288. (d) Lu, S.; Lai, Y.; Chen, J.; Liu, C.; Mong, K. Dimethylformamide: An Unusual Glycosylation Modular. *Angew. Chem., Int. Ed.* **2011**, *50*, 7315. (e) Ingle, A. B.; Chao, C.-S.; Hung, W.-C.; Mong, K.-K. T. Tuning Reactivity of Glycosyl Imidinium Intermediate for 2-Azido-2-deoxyglycosyl Donors in α-Glycosidic Bond Formation. *Org. Lett.* **2013**, *15*, 5290. (f) Sun, L.; Wu, X.; Xiong, D.; Ye, X. Stereoselective Koenigs-Knorr Glycosylation Catalyzed by Urea. *Angew. Chem., Int. Ed.* **2016**, *55*, 8041. (g) Wang, L.; Overkleeft, H. S.; van der Marel, G. A.; Codee, J. D. C. Reagent Controlled Stereoselective Synthesis of R-Glucans. *J. Am. Chem. Soc.* **2018**, *140*, 4632. (h) Singh, Y.; Wang, T.; Geringer, S. A.; Stine, K. J.; Demchenko, A. V. Regenerative Glycosylation. *J. Org. Chem.* **2018**, *83*, 374. (i) Zhang, Y.; Zhou, S.; Wang, X.; Zhang, H.; Guo, Z.; Gao, J. A New Method for e-Specific Glucosylation and Its Application to the One-Pot Synthesis of a Branched r-Glucan. *Org. Chem. Front.* **2019**, *6*, 762. (j) Sletten, E. R.; Tu, Y.-J.; Schlegel, H. B.; Nguyen, H. M. Are Bronsted Acids the True Promoter of Metal-Triflate-Catalyzed Glycosylations? A Mechanistic Probe into 1,2-*cis*-Aminoglycoside Formation by Nickel Triflate? *ACS Catal.* **2019**, *9*, 2110.

(12) Terrett, J. A.; Cuthbertson, J. D.; Shurtleff, V. W.; MacMillan, D. W. C. Switching on Elusive Organometallic Mechanisms with Photoredox Catalysis. *Nature* **2015**, *524*, 330.

(13) (a) Creutz, S. E.; Lotito, K. J.; Fu, G. C.; Peters, J. C. Photoinduced Ullman C-N Coupling: Demonstrating the Viability of a Radical Pathways. *Science* **2012**, *338*, 647. (b) Ahn, J. M.; Ratani, T. S.; Hannoun, K. I.; Fu, G. C.; Peters, J. C. Photoinduced, Copper-Catalyzed Alkylation of Amines: A Mechanistic Study of the Cross-Coupling of Carbazole with Alkyl Bromide. *J. Am. Chem. Soc.* **2017**, *139*, 12716.

(14) We choose to test the scope with benzyl and acetyl protected substrates so that we can compare our method with others on the basis of the agreement with several groups funded by NIH Glycoscience.

(15) Two diastereomers that differ in the configuration of the anomeric center, α-1,2-*cis* glycoside (major) and β-1,2-*trans*-glycoside (minor), could be generated from the visible-light-mediated copper-catalyzed $C(sp^3)$−O cross-coupling.

(16) Glycosylation of glycosyl bromides with carbohydrate alcohols has been reported under a variety of reaction conditions; see the selected examples: (a) Lemiexu, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. Halide Ion Catalyzed Glycosidation Reactions. Syntheses of Alpha-Linked Disaccharides. *J. Am. Chem. Soc.* **1975**, *97*, 4056. (b) Singh, Y.; Demchenko, A. V. Koenigs-Knorr Glycosylation Reaction Catalyzed by Trimethylsilyl Trifluoromethanesulfonate. *Chem. - Eur. J.* **2019**, *25*, 1461. (c) Singh, Y.; Demchenko, A. V. Defining the Scope of the Acid-Catalyzed Glycosidation of Glycosyl Bromides. *Chem. - Eur. J.* **2020**, *26*, 1042.

(17) Yu, F.; Li, J.; DeMent, P. M.; Tu, Y.-T.; Schlegel, H. B.; Nguyen, H. M. Phenanthroline-Catalyzed Stereoretentive Glycosylations. *Angew. Chem., Int. Ed.* **2019**, *58*, 6957.

(18) Nguyen, H. M.; Chen, Y.; Duron, S. G.; Gin, D. Y. Sulfide-Mediated Dehydrative Glycosylation. *J. Am. Chem. Soc.* **2001**, *123*, 8766.

(19) Chatterjee, S.; Moon, S.; Hentschel, F.; Gilmore, K.; Seeberger, P. H. An Empirical Understanding of the Glycosylation Reaction. *J. Am. Chem. Soc.* **2018**, *140*, 11942.

(20) Vasudevan, D.; Takeuchi, H.; Johar, S. S.; Majerus, E.; Haltiwanger, R. S. Peters Plus Syndrome Mutations Disrupt a Noncanonical ER Quality-Control Mechanism. *Curr. Biol.* **2015**, *25*, 286.

(21) (a) Bucher, C.; Gilmour, R. Fluorine-Directed Glycosylation. *Angew. Chem., Int. Ed.* **2010**, *49*, 8724. (b) Durantie, E.; Bucher, C.; Gilmour, R. Fluorine-Directed beta-Galactosylation: Chemical Glycosylation Development by Molecular Editing. *Chem. - Eur. J.* **2012**, *18*, 8208.

(22) The product **35** was isolated as a 1.5:1 mixture of α- and β-diastereomers under phenanthroline-catalyzed conditions (Figure S9).

(23) Sarbini, S. R.; Kolida, S.; Deaville, E. R.; Gibson, G. R.; Rastall, R. A. Potential of Novel Dextran Oligosaccharides as Prebiotics for Obesity Management through *in vitro* Experimentation. *Br. J. Nutr.* **2014**, *112*, 1303.

(24) (a) Nicolas, L.; Angibaud, P.; Stansfield, I.; Bonnet, P.; Meerpoel, L.; Reymond, S.; Cossy, J. Diastereoselective Metal-

https://dx.doi.org/10.1021/acscatal.0c01470
ACS Catal. 2020, 10, 5990−6001

Catalyzed Synthesis of *C*-Aryl and *C*-Vinyl Glycosides. *Angew. Chem., Int. Ed.* **2012**, *51*, 11101. (b) Adak, L.; Kawamura, S.; Toma, G.; Takenaka, T.; Osozaki, 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.

(25) (a) Kochi, J. K.; Subramanian, R. Kinetics of Electron-Transfer Oxidation of Alkyl Radicals by Copper(II) Complexes. *J. Am. Chem. Soc.* **1965**, *87*, 4855. (b) Kochi, J. K. Mechanism of Organic Oxidation and Reduction by Metal Complexes. *Science* **1967**, *155*, 415. (c) Kochi, J. K.; Bemis, A.; Jenkins, C. L. Mechanism of Electron Transfer Oxidation of Alkyl Radicals by Copper(II) complexes. *J. Am. Chem. Soc.* **1968**, *90*, 4616.

(26) De La Mare, H. E.; Kochi, J. K.; Rust, F. F. On a Transannular Photodesmotic Transition. *J. Am. Chem. Soc.* **1961**, *83*, 2013.

(27) Lakhani, C.; Mathew, L.; Warkentin, J. Rate Constant for Hydroxylation of a Primary Alkyl Radical by Induced Decomposition of an Alpha Hydroperoxyalkyl Diazene. *Can. J. Chem.* **1987**, *65*, 1748.

(28) We observed that β-glycosyl bromide rapidly converted into α-glycosyl bromide in the presence of 25 mol % of bathophenanthroline (BPhen) ligand within an hour at room temperature.

(29) Wayner, D. D. W.; McPhee, D. J.; Griller, D. Oxidation and Reduction Potentials of Transient Free Radicals. *J. Am. Chem. Soc.* **1988**, *110*, 132.

(30) Isse, A. A.; Giusti, A. D.; Gennaro, A.; Falciola, L.; Patrizia, R.; Mussini, P. R. Electrochemical Reduction of Benzyl Halides at a Silver Electrode. *Electrochim. Acta* **2006**, *51*, 4956.

(31) Karyakarte, S. D.; Um, C.; Berhane, I. A.; Chemler, S. R. Synthesis of Spirocyclic Ethers by Enantioselective Copper-Catalyzed Carboetherification of Alkenols. *Angew. Chem., Int. Ed.* **2018**, *57*, 12921.

(32) Zhang, Z.; Wang, F.; Mu, X.; Chen, P.; Liu, G. Copper-Catalyzed Regioselective Fluorination of Allylic Halides. *Angew. Chem., Int. Ed.* **2013**, *52*, 7549.

(33) We also investigated glycosyl bromide having a C2-*N*-acetyl functionality. Under the traditional glycosylation protocol, a neighboring group participation of the C2-acetyl protecting group provides β-1,2-*trans*-glycoside product almost exclusively. In stark contrast, a mixture of α-1,2-*cis*- and β-1,2-*trans*-glycosides was obtained under our photoinduced, copper-catalyzed cross-coupling conditions.

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