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

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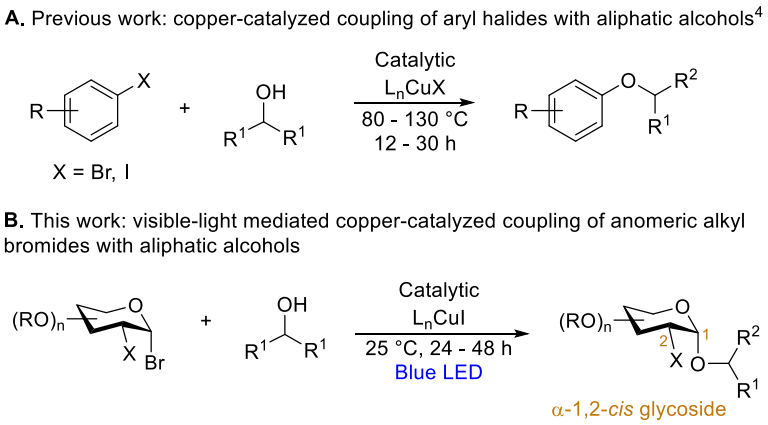
ABSTRACT

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 remain 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 anomeric alkyl bromides with aliphatic alcohols to afford C(sp^3)-O bonds with excellent levels of α-1,2-*cis* diastereoselectivity. Importantly, this catalytic system leads to a general method for stereoselective construction of the biologically relevant α-1,2-*cis* oligosaccharides, which are of paramount importance, but challenging. In general, stereochemical outcomes in α-1,2-*cis* glycosidic bond-forming processes are unpredictable and dependent on the steric and electronic nature of protecting groups bound on carbohydrate coupling partners. In our approach, earth-abundant copper not only acts as a photocatalyst and a bond-forming catalyst, but also enforces stereocontrolled formation of anomeric C-O bonds. This cross-coupling protocol is not confined to highly specific substrates and enables diastereoselective access to a variety of α-1,2-*cis* and α-2-deoxy-2-fluoro-glycosides as well as biologically relevant α-glycan oligosaccharides. Our work provides a foundation

for developing novel methods for the stereoselective construction of natural and unnatural anomeric carbon(sp^3)-heteroatom bonds.

INTRODUCTION

Copper has been considered a privileged metal because it is non-toxic 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]



Scheme 1. Copper-Catalyzed C-O Bond Formation

Recently, Fu and coworkers 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 the anomeric alkyl carbon 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 general method for diastereoselective construction of α-1,2-*cis* linkages 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] thereby, requiring highly specialized coupling partners. Catalyst controlled approaches have been examined to generate challenging α-1,2-*cis* linkages without protecting groups to direct selectivity, though these methods are still limited.[11]

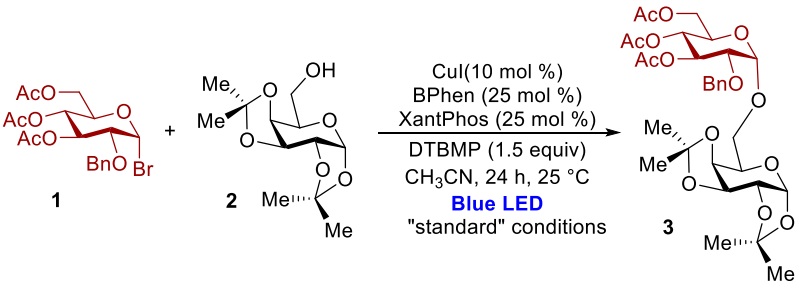
In the field of photoredox catalysis, utilization of anomeric alkyl halides in cross coupling reactions with aliphatic alcohols to form C(sp^3)-O bonds has never been achieved.[12] Therefore, it was apparent at the outset of our investigations that the adaptation of the visible-light mediated copper 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 photoinduced process,[7] 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,[7] wherein the anomeric carbon-halide bond is cleaved in the presence of copper and light to form alkyl 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 method 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* anomeric carbon-oxygen bonds, 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

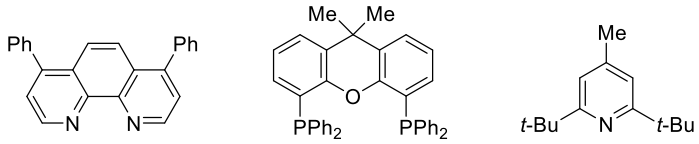
In our pursuit of photoinduced copper-catalyzed anomeric C(sp^3)-O bond formation, we initially evaluated various combinations of ligands, copper sources, acid scavenger, solvents, and reaction time (Figure S1-S7). This search revealed that blue LED irradiation of α-1-bromo-D-glucoside (alkyl bromide) **1**[13] and primary alcohol **2** of D-galactoside nucleophile 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*-butylmethyl pyridine (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).[14,15] 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, coupling proceeded in a simple 10 mol% CuI solution to provide **3** in 9% yield as a 9:1 mixture of α and β-diastereomers (entry 11), suggesting that the coupling proceeds through a conventional oxocarbenium intermediate,[9] wherein CuI serves as a Lewis acid and the selectivity is a result of thermodynamic control. Employing stoichiometric amount of CuI only provided 31% of the desired product **3** with a similar selectivity (entry 12).

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 only	9	9:1
12	100 mol % CuI 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



BPhen XantPhos DTBMP

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

^{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

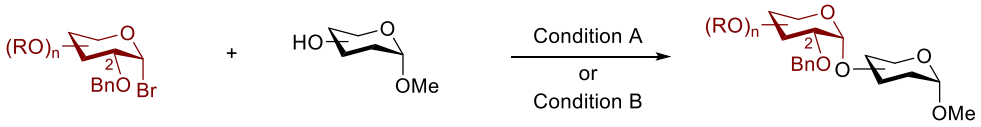
CuI, BPhen, and Xantphos, and this chemical shift matched with that of the isolated complex, [Cu(BPhen)(Xantphos)]BF_4, (δ = -11.87 ppm). As such, we conducted the cross coupling of **1** with **2** in the presence of [Cu(BPhen)(Xantphos)]BF_4 (Table 1, entry 13), and the 1,2-*cis* product **3** was obtained in similar yield and α-selectivity (60%, α:β = 9:1) to that promoted by *in situ* generated copper catalyst from the combination of CuI, BPhen, and Xantphos. This result suggest 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 **1** with **2** at 50 °C.[11b] 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 product **3** was isolated in less than 5% yield.

Having established the ability of the photoinduced copper catalyst to promote the formation of anomeric C(sp^3)-O bond with high levels of diastereoseletivity, we set out investigating the advantage of the current system over our previously developed phenanthroline-catalyzed stereoselective glycosylation method.[11b] There are two major limitations associated with the phenanthroline-catalyzed method.[11a] First, the reaction must be conducted at 50 °C to achieve high conversion.[11a] Second, the diastereoselectivity of the coupling products decreases when sterically hindered alcohols are coupled to the electron-rich alkyl bromides.[11a] Our computational and experimental studies indicate a double S_N2 pathway involving phenanthroline-catalyzed reaction with α-alkyl 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.[11a] Since the visible light-mediate 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-alkyl bromide of glucoside **4**[13] with the hindered C4-hydroxy of L-rhamnoside **5** was conducted under standard photoinduced copper conditions to afford the coupling 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 stereoselective method provided **6** in only 42% yield with α:β = 7:1. 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 more suited with the challenging α-alkyl bromide of glucuronic acid **9** (entry 3). While copper catalysis provided the coupling product **10** in 53% yield with α:β >20:1 (entry 3), phenanthroline catalysis 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 both α-alkyl bromides of glucoside **4** and galactoside **11** with the most hindered C4-hydroxyl of glucoside **11** (entries 4 and 5). As expect, the copper

catalysis (**12** and **14**, α:β >20:1) is much more α-selective than the phenanthroline catalysis (**12**, α:β = 7:1 and **14**, α:β = 5:1). We previously observed that α-alkyl bromide of tribenzyl L-arabinoside **15** (entry 6) decomposed during the course of the reaction under phenanthroline-catalyzed conditions (**17**, 47%).[11a] As such, we questioned whether α-alkyl bromide **15** is a suitable substrate under photoinduced copper-catalyzed conditions Accordingly, the coupling of **15** with **16** proceeded smoothly to provide product **17** in much higher yield (79%, entry 6)). Overall, these results in Table 2 highlights that the visible-light-mediated copper system is more efficient and highly selective than the phananthroline method for the cross couplings of the electron-rich α-alkyl bromides with the hindered alcohols of carbohydrates. More importantly, this photoinduced copper method is conducted at room temperature and highly effective for constructing anomeric C(sp^3)-O bond with reduced levels of waste through use of sub-stoichiometric amounts of metal and a high reaction concentration (0.5 M).

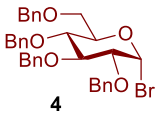
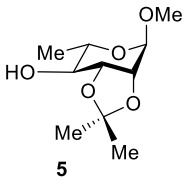
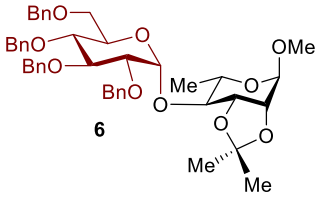
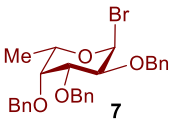
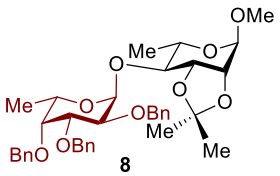
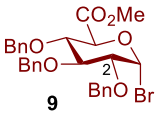
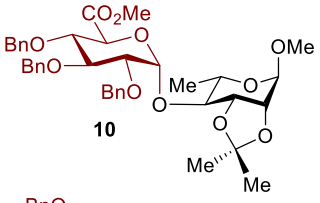
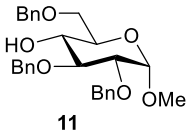
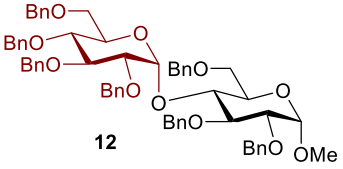
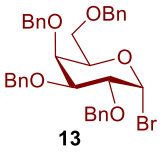
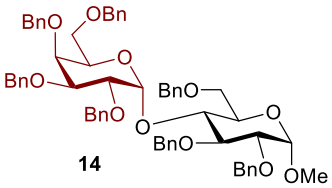
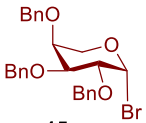
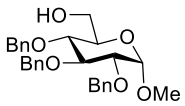
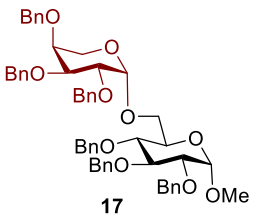
Moving forward, we evaluated the scope of the electron-withdrawing α-alkyl bromides with respect to aliphatic alcohols. In contrast to the previous phenanthroline-catalyzed reactions, the electron-withdrawing α-alkyl bromides proceeded can proceed efficiently at room temperature under visible-light-mediated copper conditions. (Table 3). We first chose to explore couplings with hindered secondary alcohols as they have been reported to provide the anomeric C-O bond products with poor to moderate levels of diastereoselectivities.[16] Accordingly, α-alkyl bromides of D-glucose substrates bearing acetyl and benzyl protecting groups were examined with C4- and C3-hydroxys of carbohydrates. In all cases, the reactions proceeded at room temperature to provide the desired coupling products (**18** to **20**) in good yields (50% to 60%) and excellent stereocontrol (α:β > 20:1), highlighting the advantage of the copper system over the phenanthroline system. For instance, while both systems produced the coupling product **19** in comparable yield and selectivity, the phenanthroline-catalyzed reaction was conducted at 50 °C for 48 h.[11a] In addition, this photoinduced catalytic copper method is much more α-selective in the coupling with the hindered alcohols than the traditional sulfide-mediated glycosylation approach.[16] A similar trend was also observed when variation in the structure of α-alkyl bromides of carbohydrate substrates was tested, delivering the C-O bond products containing D-galactose (**21** and **22**) and L-rhamonose (**24**) with excellent α-diastereoselectivity (α:β > 20:1). Interestingly, this visible-light-mediated copper system is also effective at promoting the coupling with five-membered ring alkyl bromide to provide the desired product **23** with high 1,2-*cis* selectivity (α:β = 12:1).

Table 2. Comparative Studies Between Photoinduced Copper Catalysis and Organocatalysis



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

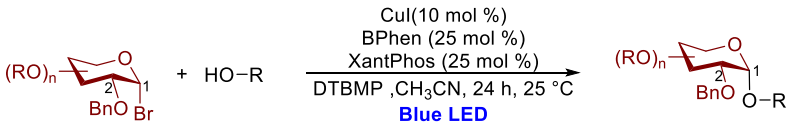
Condition B: BPhen (30 mol %), IBO (2 equiv), MTBE, 48 h, 50 °C

entry	electrophiles	nucleophiles	products	condition **A** yield[b] (α:β)[c]	condition **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 of electrophiles and 1.5 equiv of nucleophiles. [b] Isolated yield. [c] Diastereoselective (α:β) ratio determined by ^{1}H NMR analysis.

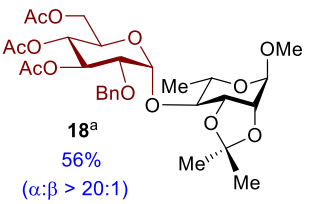
Motivated by the high efficiency of the photoinduced copper system, we next examined the cross couplings of a variety of electron-withdrawing and electron-donating α-alkyl bromides with primary alcohols. As can be seen in Table 3, the reactions were highly diastereoselective to produce the coupling C-O 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. For instance, α-alkyl bromide of D-galactose whose axial C4-benzyl protecting group has been recently reported[17] to favor the β-1,2-*tran*s product[14] provided the desired α-1,2-*cis* product **30** with excellent stereocontrol (α:β = 13:1). Although these results are comparable to those obtained under phenanthroline-catalyzed conditions,[11a] these reactions can be conducted at room temperature to achieve high conversion. 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.[18] To compare, the phenanthroline-catalyzed method provide **32** in 80% yield with α:β = 6:1.[11a] Next, we explored the effect of the C2 substituents of α-alkyl bromides on the selectivity (Table 3). The ability of a C2-F bond to have an impact on the diastereoselectivity of anomeric C-O bond formation has been reported.[19] The tetrabenzylated D-glucose and D-galactose substrates, having the C2-fluoro group, are highly β-selective under Lewis acid-mediated conditions.[19] In contrast, the copper-catalyzed approach provided the 1,2-*cis* C-O bond products containing D-glucose (**33**) and D-galactose (**34**) with excellent α-diastereoselectivity (Table 2). Because of conformational flexibility of 2-deoxy-D-glucose, α-alkyl bromide of this substrate lacking C2-oxygen still exhibited moderate selectivity (**35**, α:β = 4:1). In contrast, **35** was isolated as a 1.5:1 mixture of α- and β-diastereomers under phenanthroline-catalyzed conditions (Figure S8).

Table 3: Scope of Aliphatic Alcohols and Glycosyl Bromides.[a]

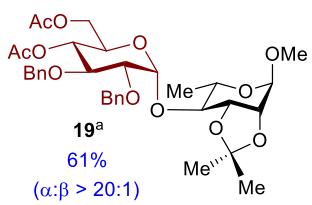


Secondary Alcohols

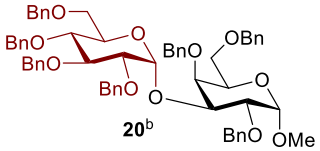
D-Glucose



18[a] 56% (α:β > 20:1)

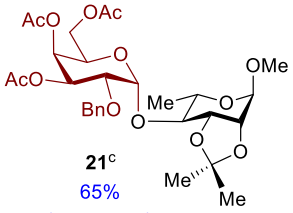


19[a] 61% (α:β > 20:1)

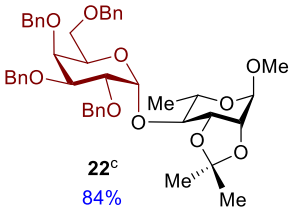


20[b] 50% (α:β > 20:1)

D-Galactose

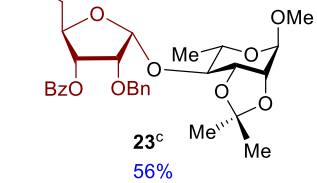


21[c] 65% (α:β > 20:1)



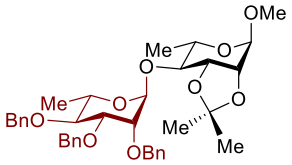
22[c] 84% (α:β > 20:1)

D-Furanose



23[c] 56% (α:β = 12:1)

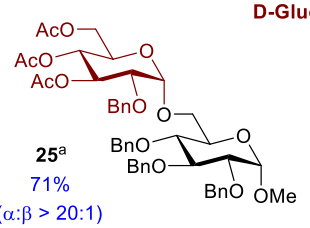
L-Rhamnose



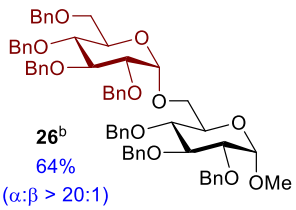
24[c] 59% (α:β > 20:1)

Primary Alcohols

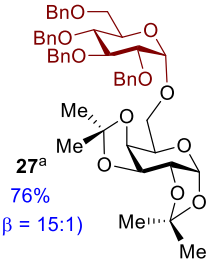
D-Glucose



25[a] 71% (α:β > 20:1)

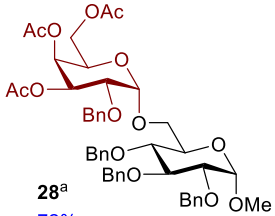


26[b] 64% (α:β > 20:1)

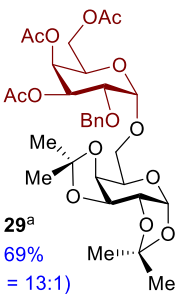


27[a] 76% (α:β = 15:1)

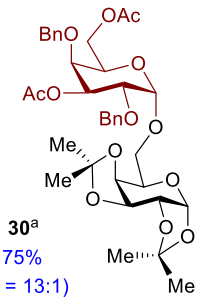
D-Galactose



28[a] 72% (α:β > 20:1)

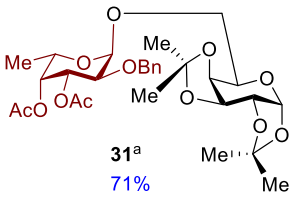


29[a] 69% (α:β = 13:1)



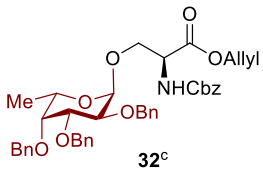
30[a] 75% (α:β = 13:1)

L-Fucose



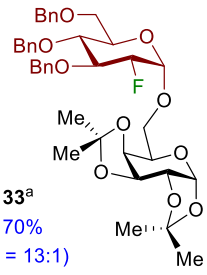
31[a] 71% (α:β > 20:1)

L-Fucose



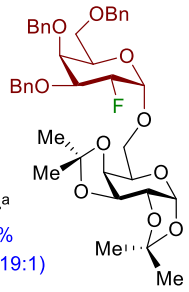
32[c] 74% (α:β = 9:1)

2-Fluoro-D-Glucose



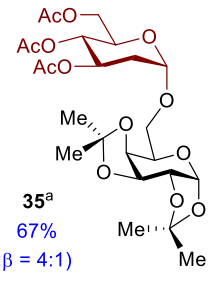
33[a] 70% (α:β = 13:1)

2-Fluoro-D-Galactose



34[a] 78% (α:β = 19:1)

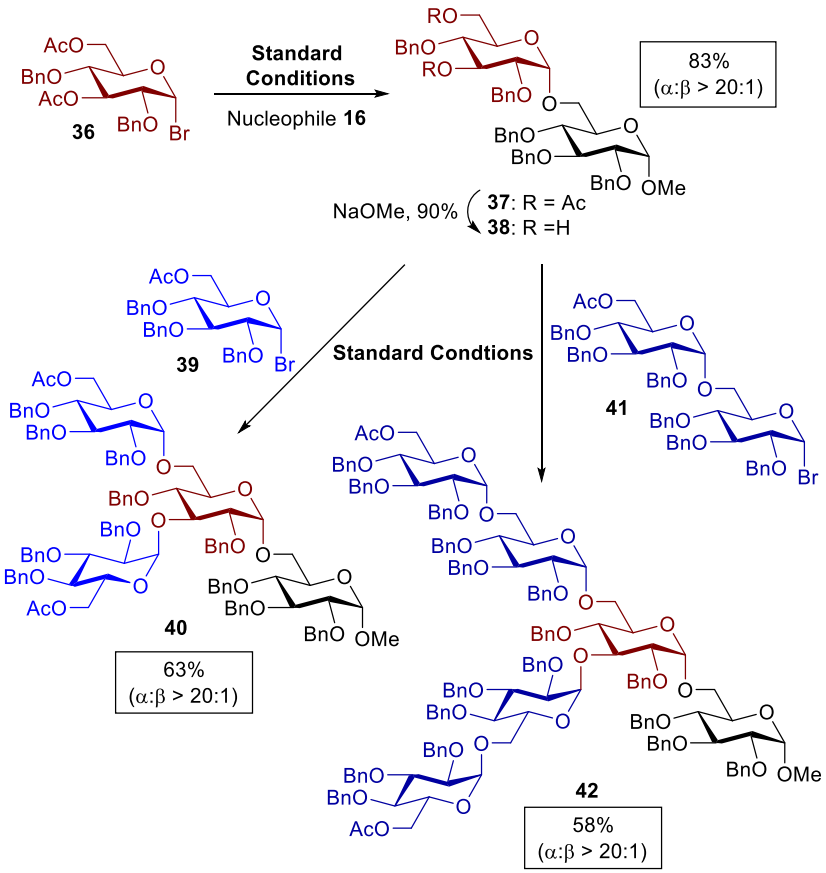
2-Deoxy-D-Glucose



35[a] 67% (α:β = 4:1)

[a] Reactions performed with R-Br (1 equiv.) and R-OH (2 equiv). Yields isolated. The diastereomeric ratios (α:β) were determined by ^{1}H NMR. [b] R-Br (1 equiv), R-OH (1.5 equiv). [c] R-Br (1.5 equiv), of R-OH (1 equiv). [c] R-Br (2 equiv), R-OH (1 equiv).

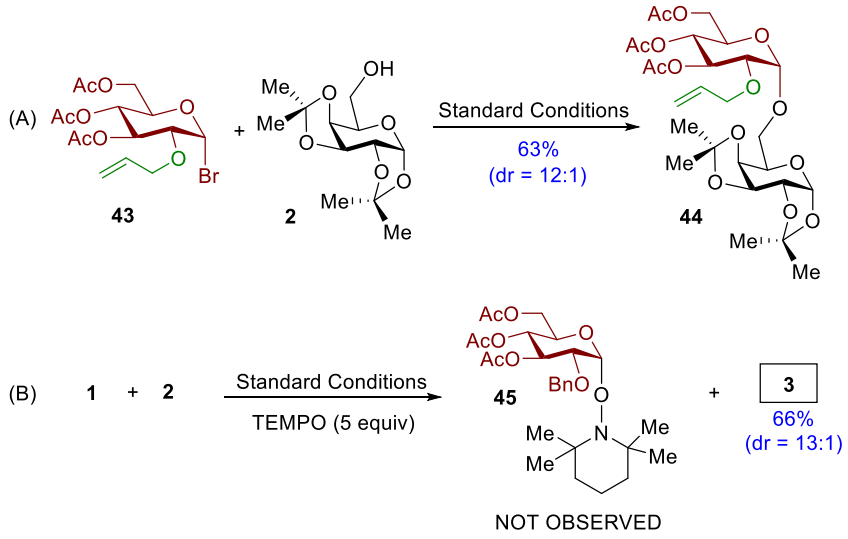
We expect that the visible-light-induced copper approach will be particularly useful when applied to the synthesis of biologically relevant α-glycans. Well-defined construction of the oligosaccharide motifs of these natural α-glycans will allow to study these bioactive fragments as potential prebiotics.[20] 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** and glucoside nucleophile **16** to the standard photoinduced copper conditions. In this case, 1,2-*cis* disaccharide **37** was isolated in 83% yield with excellent 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 reproduciblity 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-alkyl bromides **39** and **41** to afford tetrasaccharide **40** and hexasaccharide **42**, respectively, as α-products (α:β > 20:1) under standard conditions.



Scheme 2. Copper-Catalyzed Oligosaccharide Synthesis

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.[21] As

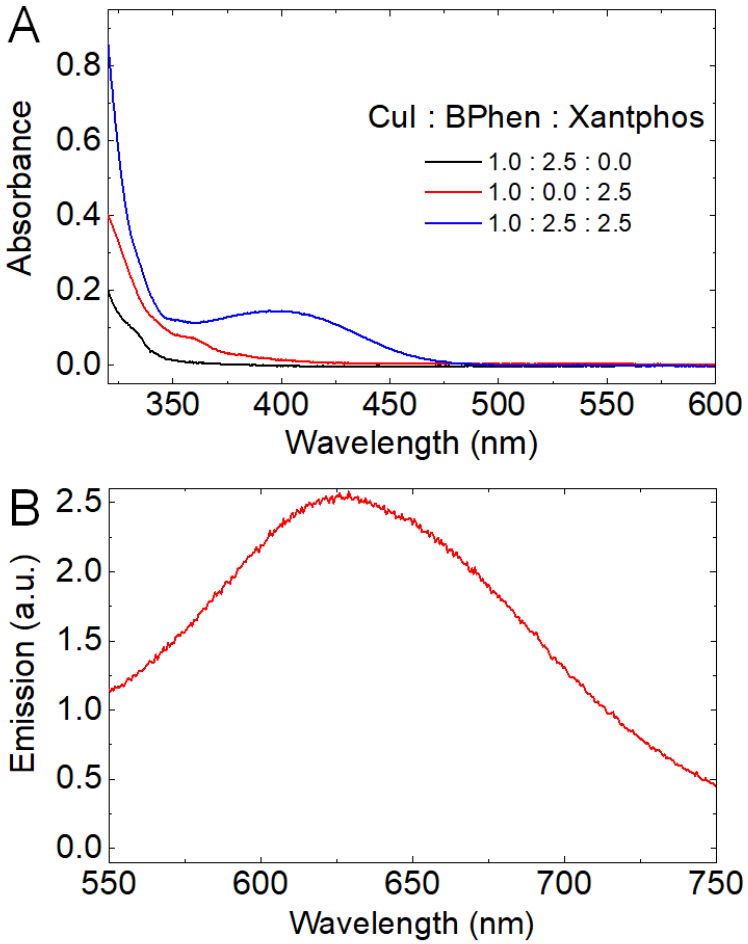
such, we conducted the cross coupling of α-alkyl bromide **34** (Scheme 3A) bearing a C2-pendant olefin with C6-hydroxy of galactoside **2**. The coupling product **36** was, however, observed in the reaction, and no cyclization product was isolated. Kochi and coworkers have previously demonstrated that carbon radicals can be oxidized rapidly by copper complex to generate alkyl copper intermediates.[26,27] Therrefore, it is possible that oxidation of anomeric C1-radical by a copper(II) complex to form alkylcopper(III) complex (*vide infra*, Scheme 5) is faster than a radical 5-*exo*-trig cyclization.[22] Next, we hypothesize that if C-O bond formation occurs through out-of-cage coupling of an anomeric radical with a copper(II) complex, addition of TEMPO (5 equiv.) to the reaction mixture would lead to 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.



Scheme 3. Control Experiments

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 5A) 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 S9). This isolated copper catalyst was also effective at promoting the coupling to provide 1,2-*cis* product **3** (entry 13, Table 1) in similar yield and α-selectivity to that promoted by *in situ* generated copper catalyst (entry 1, Table 1) from the combination of CuI, BPhen, and Xantphos. These results suggest that the $[Cu(BPhen)(Xantphos)]^+$ complex is the primary photoreductant in the visible light-mediated copper-catalyzed cross-coupling. In addition, we observed the clear peak in 630 nm in emission spectra of the *in*

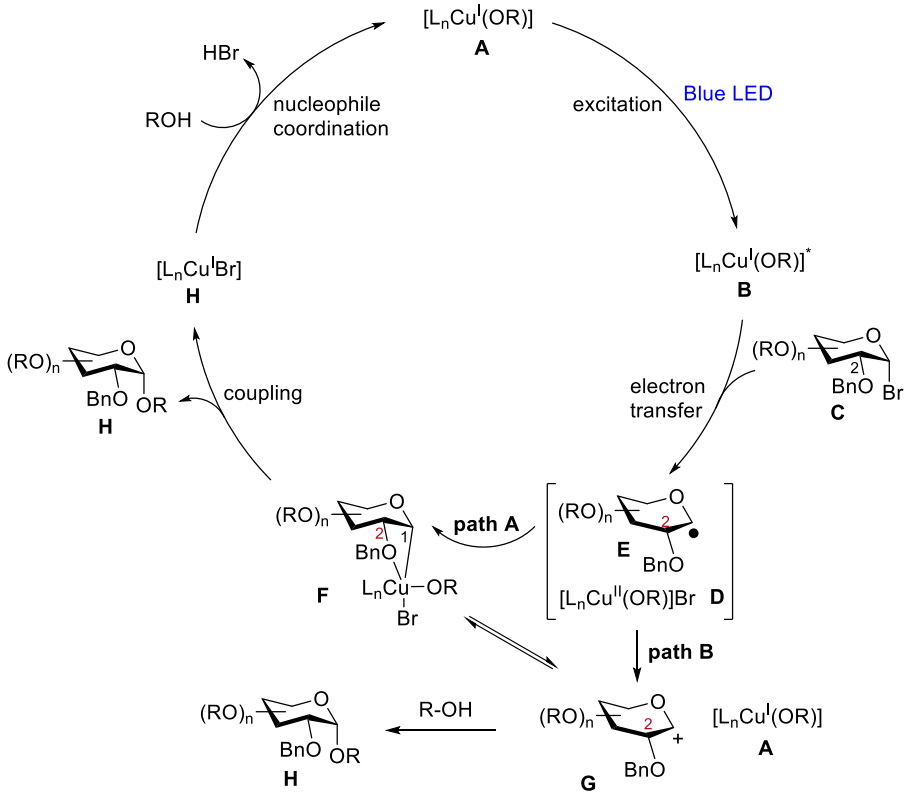
situ generated copper complex under the irradiation of 450 nm (Scheme 4B), suggesting the existence of the excited state copper species. The emission spectra of [Cu(BPhen)(Xantphos)]BF_4 (Figure S10) shows a similar trend to those of the *in situ* generated copper catalyst (Figure 4B), further supporting that $[Cu(BPhen)(Xantphos)]^+$ is the active catalyst.



Scheme 4. (**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 spectra of the copper complex (CuI:BPhen:Xantphos = 1:2.5:2.5) at 0.1 mM concentration with an excitation wavelength of 450 nm.

On the basis of the aforementioned preliminary results (Schemes 3 and 4), an outline of a proposed mechanism for the visible-light-mediated copper-catalyzed anomeric C(sp^3)-O bond formation is outlined in Scheme 5. 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**. Photoexcitation of **A** could result in an excited-state copper(I) species **B** that could engage in electron transfer with the anomeric α-alkyl bromide **C**. This irradiation step corresponds well to the broad absorption and emission observed experimentally (Scheme 4). However, the results obtained with control experiments (Scheme 4) suggest that the coupling

reaction may not proceed via a copper(II) complex **D** and a long-lived anomeric radical **E**.[7] As such, the anomeric radical can either react with copper(II) complex **D** to form a copper(III) species **F** (path A)[27] or be oxidized by copper(II) complex **D** to generate oxocarbenium ion **G** (path B).[28] Dissociation of the alkylcopper(III) complex **F** could also provide the oxocarbenium ion intermediate **G** in path B. If path A is operative, reduction elimination from complex **F** affords C(sp^3)-O bond **H** and a copper(I) species **H**. 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**.



Scheme 5. Proposed Mechanism

The results from the radical trap experiments in Scheme 4 indicate that the photoreduced copper-catalyzed C-O cross-coupling may not proceed via a long-lived radical intermediate such as complex **E** (Scheme 5). As such, 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 5).[23] Kochi and coworkers have previously demonstrated that carbon radicals are oxidized by copper near a diffusion control to form the alkylcopper intermediate,[26,27] further supporting the proposed copper(III) complex **F**. To further support that copper(III) species **F** is likely to form in the reaction, the C2-oxygen atom of alkyl bromide was replaced with fluorine atom as fluorine has been proposed to coordinate to the Cu center.[24] The 2-fluro-2-deoxy alkyl bromides also favored the α-1,2-*cis* products (**33** and **34**, Table 3).

On the other hand, if path B in Scheme 5 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**.[25] Anomeric radicals are more easily oxidized to cations than the carbon radicals investigated by Kochi.[28] As such, we hypothesized that substitution of the C2-oxygen with H atom could further facilitate the formation of the 2-deoxy oxocarbenium ion 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 β-face to provide a mixture of 1,2-*cis* and 1,2-*trans* diastereomers,[25] which was confirmed by an experimental result obtained with the coupling product **35** (Table 3).

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 anomeric α-alkyl bromides with alkyl alcohols to stereoselectively generate the challenging anomeric C(sp^3)-O bonds of α-1,2-*cis* glycoside products, the important framework of many bioactive carbohydrate molecules. In contrast to nearly all catalytic glycosylation reactions which typically proceeds via either S_N1 or S_N2 pathway, this method utilizes copper catalyst induced by visible light to effect diastereoselective sp^3 C-O glycosidic linkage 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 non-carbohydrate alkyl halides with sp^3-hydridized nucleophiles. The detailed mechanism of this visible-light-mediated copper-catalyzed cross couplings of α-alkyl bromides of carbohydrates with alcohol nucleophiles is under investigation and will be reported in due course.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Experimental details, characterization, and spectral data (PDF)

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Author Contributions

† Equal contributions

Notes

The authors declare no competing financial interests.

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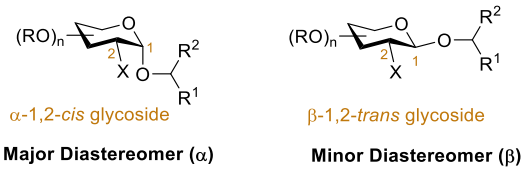
(13) We choose to test the scope with benzyl and acetyl protected substrates so that we can compare our method with others based on the agreement with several groups funded by NIH Glycoscience.
(14) Two possible diastereomers could be generated from the visible-light mediated copper-catalyzed C(sp^3)-O cross coupling:



(15) Coupling of anomeric alkyl bromides with alkyl alcohols has been reported to proceed in the presence of stoichiometric amount of tetraethylammonium bromide under reflux conditions, see: R. U. Lemiexu, K. B. Hendriks, R. V. Stick, K. James, *J. Am. Chem. Soc.* **1975**, *97*, 4056.
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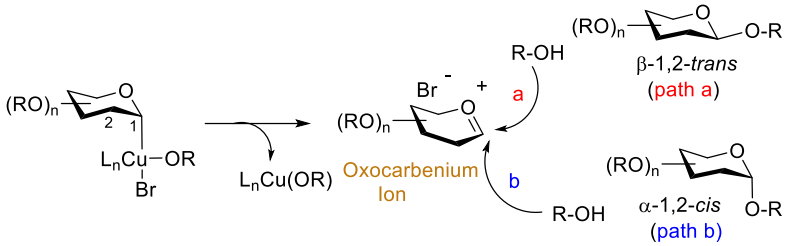
(25) Competing pathway for use of alkyl bromide lacking C2-oxygen:



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