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Copper Reactivity can be Tuned to Catalyse the Stereoselective Synthesis of 2-deoxy Glycosides from Glycals

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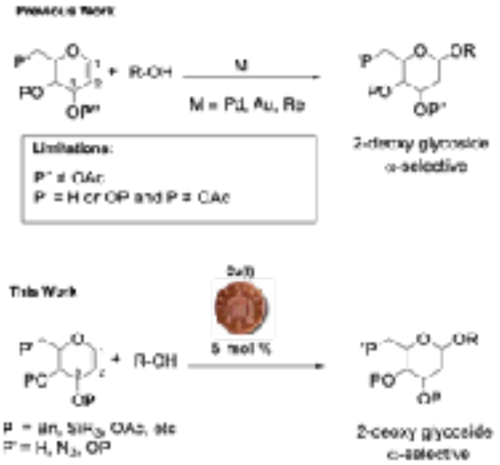
Abstract: We demonstrate that tuning the reactivity of Cu by the choice of oxidation state and counterion leads to the activation of both "armed" and "disarmed" type glycals towards direct glycosylation leading to the α-stereoselective synthesis of deoxyglycosides in good to excellent yields. Mechanistic studies show that Cu^{I} is essential for effective catalysis and stereocontrol and that the reaction proceeds through dual activation of both the enol ether as well as the OH nucleophile.

Carbohydrates play significant roles in a wide range of biological events[1] and efficient catalytic and asymmetric methods to access this class of chiral molecules are needed to further our understanding of their various roles and functions in health and disease.[2, 3]

First row transition metals have recently attracted attention as alternatives to precious metals in catalysis.[4] Among those, copper is a cost-effective, earth-abundant and sustainable metal and Cu-complexes can display unique and versatile reactivity and good functional group tolerance.[4] The chemistry exhibited by Cu can be very diverse depending on its oxidation state, as this metal can efficiently catalyse reactions involving one or two-electron mechanisms.[4-7] In the context of *O*-linked glycosylation reactions, a few examples of Cu(II) as a mild oxophilic Lewis acid catalyst for the activation of oxygen-containing leaving groups have been reported.[8-11] More recently, the use of $Cu^{II}(OTf)_2$ as an *in situ* oxidant in the photoinduced-activation of thioglycosides was also exemplified.[12] However, despite copper catalysts being relatively cheap and widely available, we were surprised by the overall under exploration of this metal in glycosylation chemistry[13-17].

Our group is interested in the development of sustainable and catalytic methods for the synthesis of oligosaccharides.[18-21] 2-deoxy-hexoses are prominent components of natural products which due to the lack of substituents at *C*-2 to direct the nucleophile approach present significant synthetic challenges and their improved and stereoselective protocols for their assembly has been of great intetest.[5, 18, 22-37]

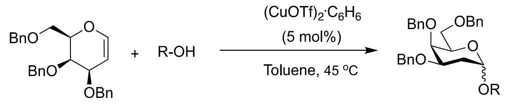
Previous work from our group and others has shown that activation of glycals to yield glycosides can be achieved using transition metals such as Pd(II)[38, 39], Au(I)[40] or Re(V)[41] catalysts, however activation of sensitive enol ethers bearing electron-withdrawing groups at the *C*-3 position of the glycal was not possible under those conditions (Scheme 1) and in general harsher conditions used to activate such glycals often lead to donor hydrolysis and/or Ferrier type products.[26]



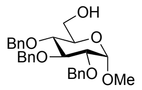
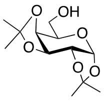
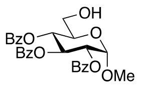
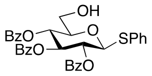
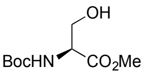
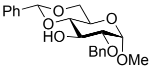
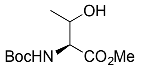
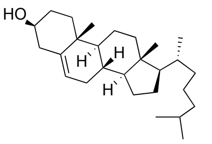
Scheme 1: Cu^{I}-catalysed direct synthesis of deoxyglycosides from glycals

These findings prompted us to explore the utility of copper in the activation of glycals to yield 2-deoxyglycosides. To that end, a series of Cu(I) and Cu(II) salts at different catalyst loadings, reaction temperatures and solvents were initially screened as promoters in the glycosylation of perbenzylated galactal **1a** and glucoside acceptor **2a**[6a] (See Table S1 in ESI). It was found that 5 mol% $(Cu^{I}OTf)_2\cdot C_6H_6$ in toluene at 45 °C gave the best results (Table 1, entry 1). The substrate scope was thus investigated and Galactal **1a** was reacted with a range of primary and secondary OH nucleophiles **2b-2i**[42] under the optimized reaction conditions (Table 1). In all cases, reactions proceeded smoothly and in good to excellent yields and α-selectivity, demonstrating that the catalytic system tolerates the presence of common alcohol and amine protecting groups such as acetals, ethers, esters and carbamates. Glycosylations with primary alcohols such as simple benzyl alcohol **2b**, glycosides **2c** and **2d**, thioglycoside **2e** and Boc-protected serine **2f** afforded the corresponding glycoside products in 79–88% yield within 2 h and with an >30:1 α:β ratio (Table 2, entries 2–6). Similarly, reactions with secondary alcohols such as, glycoside **2g**, Boc-protected threonine **2h** and cholesterol **2i** also afforded the desired products in good yields (72–75%) and with high α-selectivity (>30:1 α:β ratio, entries 7–9).

Table 1. Reaction of glycal **1a** with glycoside acceptors **2b**-**2i.**



1a **2b-2i** **4b-4i**

Entry	ROH		Time (h)	Yield (%)[a]	α:β[b]
1		**2a**	1.5	87	>30:1
2	BnOH	**2b**	1	82	>30:1
3		**2c**[c	1.5	80	>30:1
4		**2d**	1.5	88	>30:1
5		**2e**	1.5	82	>30:1
6		**2f**	2	79	>30:1
7		**2g**	1.5	72	>30:1
8		**2h**	2	75	>30:1
9		**2i**	4.5	72	>30:1

[a] Isolated yield. [b] Determined by ^{1}H-NMR. [c] Reaction using Cu(II)(OTf)$_2$ (5 mol%) and sodium ascorbate (10 mol%) to generate Cu(I) in situ also afforded **4c** in 89% yield and >30:1 α:β.

Next, the scope of the reaction with respect to the glycal donor was investigated. A series of differentially protected galactals **1b**-**1h**, glucals **5a** and **5b** and fucal **6** bearing benzyl, acetate, methoxymethyl acetal, silyl ether and siloxane protecting groups were prepared and subjected to the glycosylation conditions with **2a** or **2g** as the acceptors (Table 2). Pleasingly, reactions involving galactal donors **1c**-**1h** were complete within 2–4 h and in yields of 72–98% and high α-selectivities (15:1 to 30:1) (entries 2–6). Excitingly, Cu^{I}-activation of galactals bearing acetyl groups at *C*-3 such peracetylated galactal **1b** and silyl acetal **1h** with **2a** gave glycosylation products **7b** and **7h**, in 63% and 84% yield respectively, with high α-stereocontrol (entries 1 and 7). This is noteworthy, as most protocols used to activate 'disarmed' glycals tend to give mixtures of glycoside and Ferrier-type products [18, 19, 39] as we also observe when using Cu(II) (Table 2, entry 1[d]). The reaction was also amenable to glycosylations with glucal substrates, and reactions with 3,4-*O*-siloxane-protected **5a**[43] or **5b**[43] afforded the corresponding glycosides **8a**, **8b** and **9** in high α-stereocontrol (>30:1α:β) and yields (72–79%) within 1–4 h (entries 8–10). Under the Cu-catalysed reaction, peracetylated glucal **5c** could also be activated, however it afforded Ferrier type glycoside **10** as the major product (67%, 78:22 α:β, entry 11).[44] Conversely, activation of peracetylated L-fucal **6**[18] afforded 2,6-dideoxyglycoside **10** in 71% yield within 2 h and in a >30:1 α:β ratio (entry 12).

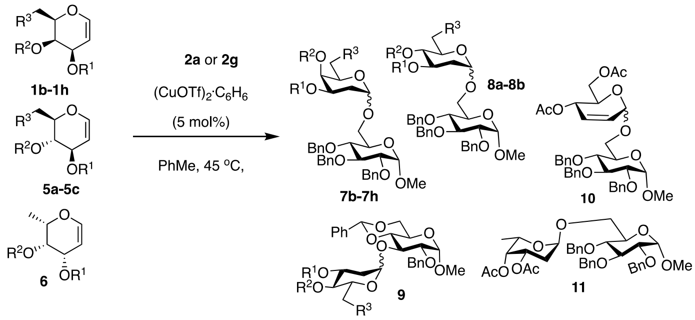


Table 2. Reaction scope between glycals **1b**-**1h**, **5a**-**5c** and **6** with acceptors **2a**
or **2g**.

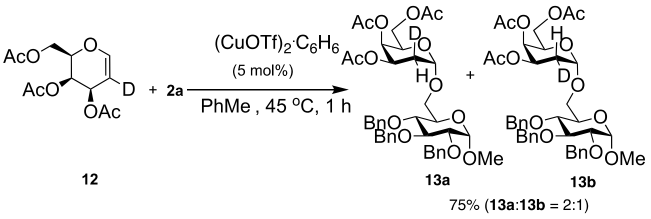
Entry	Donor	R1	R2	R3	Product	Time (h)	Yield (%)[a]	α:β[b]
1	**1b**	Ac	Ac	OAc	**7b**	2	63[c][d]	15:1
2	**1c**	Bn	Bn	OAc	**7c**	3	80	25:1
3	**1d**	TBS	TBS	OTBS	**7d**	4	78	30:1
4	**1e**	TBS	TBS	N3	**7e**	4	98	30:1
5	**1f**	MOM	MOM	OMOM	**7f**	3	75	30:1
6	**1g**	MOM	OSi(*tBu*)$_2$		**7g**	3	72	30:1
7	**1h**	Ac	OSi(*tBu*)$_2$		**7h**	3	84	21:1
8	**5a**	O[Si(*i*Pr)$_2$]$_2$ O[Si(*i*Pr)$_2$]$_2$ O[Si(*i*Pr)$_2$]$_2$		OTIPS	**8a**	3	72[c]	30:1
9	**5b**			OBn	**8b**	4	79[c]	30:1
10	**5b**			OBn	**9**	1	75[c]	30:1
11	**5c**	Ac	Ac	OAc	**10**	5	67[d]	78:22
12	**6**	Ac	Ac	-	**11**	2	71[c]	30:1

[a] Isolated yield. [b] Determined by ^{1}H-NMR. [c] Reaction was carried out at 70° C. [d] reactions using **Cu^{II}-a** or **Cu^{II}-b** afforded inseparable anomeric mixtures of Ferrier and glycoside products (13:87 (79%) and 25:75 (67%), respectively). [d] The reaction favoured the Ferrier product over the 2-deoxyglycoside product (15%)).

To probe the mechanism of our reaction, a 3:1 α/β-anomeric disaccharide mixture (**4j,** see ESI for details) was subjected to the reaction conditions in the absence and presence of the OH acceptor and gave no change in the anomeric ratio, indicating that the high α-selectivity is not the result of anomerization (Fig. S1 in ESI). Reaction with deuterated galactal **12** yielded disaccharides **13a** and **13b** in 70% yield as a 2:1 mixture of *cis*:*trans* products in favor of equatorial protonation and axial addition of the OH nucleophile across the double bond, (Scheme 2 and fig. S2). In the presence of 20 mol% of DIPEA the reaction between galactal **1a** and **2d** using either **Cu^{I}-b** or **Cu^{II}-b** was inhibited, which suggests that the presence of brøsted acid might be involved in the reaction.[15] To evaluate this, reactions between both **1a** and **1b** and **2a** in the presence of 0.1–2 mol% of TfOH were carried out in toluene (Table S2 in ESI). In general, lower conversions (20-60%) and selectivities (3:1 α:β ratios) were observed in all cases including inseparable mixtures of other side-products (see ESI for details). This suggests that although a catalytic amount of TfOH alone is able to activate both armed and disarmed glycals, Cu(I) is essential for effective and controlled catalysis.

^{1}H-NMR spectroscopy studies carried out at room temperature in toluene-d^{8} of equimolar mixtures of Cu(I) catalyst and glycoside acceptor **2a** showed signal broadening for **2a**, suggesting an interaction between Cu(I) and the alcohol (Fig. S3). NMR mixtures of 1 eq. (Cu^{I}OTf)$_2$.C$_6$H$_6$ and galactal **1a** also showed slight H-shifts and peak broadening associated with an interaction between the alkene protons in **1a** (from δ 6.22 to 6.21 ppm), while mixtures of 1 eq. Cu^{II}(OTf)$_2$ and **1a** led to quick glycal activation and formation of degradation products (See Figs. S4-S6 in ESI). On the other hand, no interactions between deactivated per-acetylated galactal **1b** and Cu(I) were observed by ^{1}H-NMR at room temperature, while slow degradation of **1b** in the presence of Cu(II)OTf$_2$ could be seen over time (Fig. S7 and S8). Moreover, reaction between **1a** and **2c** using 5 mol% Cu^{II}(OTf)$_2$ and 10 mol% sodium ascorbate (to generate Cu(I) *in situ*) also afforded **4c** in 89% yield and >30:1 α:β (Table 2, entry 2[d]). This result further indicates that Cu(I) is important for effective catalysis towards stereoselective glycosylation.

Scheme 2. Glycosylation of deuterated glycal donor **12** with **2a**.



To better understand the interactions between the Cu catalysts and both donor **1b** and the OH nucleophile, cyclic voltammetry experiments were undertaken. The electrochemical behaviors of both Cu (I) and Cu(II) were studied (Figure 1, [Cu^{I}(OTf)]$_2$ data shown).[45] The reduction of Cu(II) to Cu(I) is a reversible transfer occurring around $E_{1/2}$ = +0.8 V *vs* SCE, while the electrodeposition and oxidative dissolution of Cu(0) occurred at +0.1 V and +0.6 V, respectively. The interaction with dihydropyran (DHP), as a model, was first investigated (Figure S13). Based on the shift of potentials observed for the reduction peak of Cu^{I}, we can conclude that Cu^{I} is stabilized compared to Cu^{0} due to the formation of a Cu^{I}-DHP complex,[44-46] suggesting that the complexation of one DHP to Cu^{I} through the π system is possible.

The interaction of Cu(II) and Cu(I) with tri-acetyl galactal **1b** was next considered (see ESI, Figure S14), since previous reported methods failed to activate electron-poor glycals towards direct glycosylation[18, 19, 39], we wanted to better understand the interaction of this substrate with the metal. Interestingly, the pattern observed is somehow different with galactal than with DHP due to the possible complexation of copper by acetates. In the presence of **1b**, the reduction peaks of both Cu(I) and Cu(II) were shifted towards lower potentials.. These observations are consistent with the formation of different Cu(I)-**1b** complexes and Cu(II)-**1b**. The latter is likely the result from an interaction between Cu(II) and acetates as expected from the oxophilicity of Cu(II) and also since no interaction with C=C bond was observed in the CV experiment with cyclohexene. However, the Cu(I)-**1b** has a lower stoichiometry than the Cu(I)-cyclohexene one, in agreement with the formation of aggregates (see ESI Figure S15).

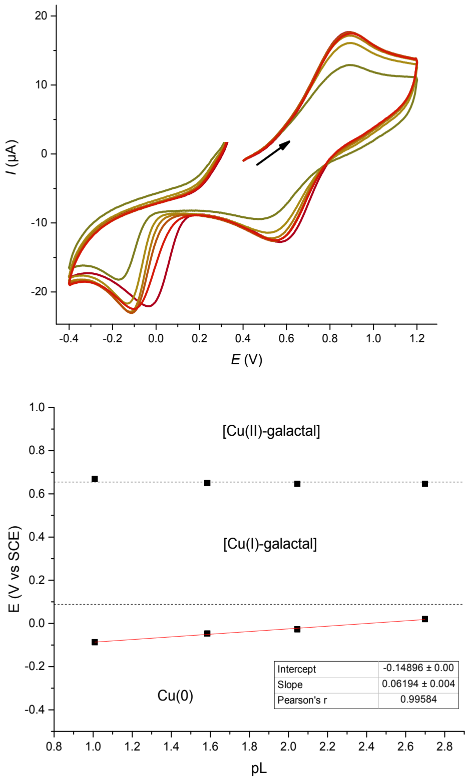


Figure 1. top: CV towards oxidation potentials of [Cu^{I}(OTf)] (2 mM) in the presence of benzyl alcohol (158 equiv) with increasing amounts of **1b** (0, 1, 2, 5, 14, 50 equiv), recorded at a steady glassy carbon disk electrode (d = 3 mm) in nitromethane containing *n*-Bu$_4$NBF$_4$ (0.3 M) at 20 °C with a scan rate of 0.5 V s^{-1}.. bottom: Potential-pL (L = tri-acetyl-galactal, pL = -log(L)) plot constructed using the E(1/2) values extracted from the CV plots in the presence of excess BnOH (158 equiv). SCE = saturated calomel Electrode

The interaction between the OH nucleophile and copper was also studied and BnOH was chosen as a model substrate, as it was the simplest alcohol used in our scope. In the presence of BnOH, the reduction peak of Cu(II) was shifted towards lower potentials, as was the reduction peak of Cu(I) (See Supporting

Information, Figure S16). These observations are consistent with the formation of complexes between BnOH and both Cu(I) and Cu(II) with a higher stoichiometry for the Cu(II) complex (see Supporting Information, Figure S17). Finally, in order to study the nature of the catalyst under conditions close to the catalytic ones, increasing amounts of galactal **1b** were added to a mixture of Cu^{I}(OTf) (**Cu^{I}-b**) in the presence of an excess of BnOH (158 equiv).[49] The reduction peak of Cu(I) was shifted towards lower potentials (Figure 1 and Figure S20). This is consistent with the formation of a complex between Cu(I) and **1b** even in the presence of a large excess of BnOH.

The shifts of both reduction and oxidation peaks associated with the Cu(II) and Cu(I) redox couple measured are not trivial, but the addition of **1b** seems to poorly impact them, which is consistent with the formation of a Cu(II)-**1b** complex of stoichiometry similar to that of the Cu(I)-**1b** complex. The slope of the *E vs* pL plot for the potential associated to Cu(I)/Cu(0) is close to 0.06 (Figure 1), indicating a 1:1 stoichiometry for Cu(I) and **1b**. When comparing with the slope observed in the absence of BnOH (0.02, Figure S14) it appears that BnOH is able to dissociate the metallic clusters formed between Cu(I) and **1b**. Indeed, the slope associated to Cu(II)/Cu(I) is close to 0 indicating that the complexes formed between Cu(II) and **1b** also have a 1:1 stoichiometry (as observed in the absence of BnOH).

From our initial mechanistic studies one can conclude that (i) Cu(I)OTf leads to activation of the carbon-carbon double bond of glycals and that in the case of electron-deficient enol ethers, Cu(I)-interactions with the acyl groups facilitate the activation of the "disarmed" glycal;[50] (ii) the active form of the catalyst is likely a complex involving both the glycal and the OH nucleophile [Cu(Glycal)(ROH)]$^+$. Two possible isomers of [Cu(**1b**)(ROH)]$^+$ were optimized using DFT at the B3LYP/def2-SVP level to help us provide some insights with regards to the active species (see the SI for computational details): one featuring a copper-acetate interaction ("up") and one with the copper in the position opposite to the acetate moieties ("down"). Upon coordination to the C=C bond, copper induces a modification of the electronic structure (Figure S21 and Table S3, ESI). The electronic density on the carbon C^2 increases (0.063 for up and -0.161 for down) while the one on O^1 and C^1 (+0.075 for up and +0.104 for down) decreases. In the meantime, the C=C bond length increases (+0.032 for up and +0.040 for down) while the C=O bond shortens (-0.008 for up and -0.019 for down). All these observations suggest that these complexes have a carbocation-like behavior. Based on these observations, a mechanism can be proposed involving two [Cu(**1b**)(ROH)]$^+$ complexes "up" or "down" (A) which can form two different oxocarbenium intermediates (B) that are quickly trapped by the OH nucleophile to yield the glycoside products (Scheme 3). Two alternative pathways can be invoked for the nucleophile addition, one involving an outer sphere attack of the OH nucleophile (not coordinated to Cu) on the carbocation ((B) pink arrow) and a second one with an inner sphere addition involving the ROH coordinated to Cu ((B) red arrow). Based on the labelling experiments (Scheme 2), it seems that a bottom face attack of the nucleophile is preferred.

In summary, we have shown that adjusting the oxidation state and counter ion of Cu can be exploited to control its reactivity profile. We demonstrate for the first time the Cu^{I}-catalyzed direct α-stereoselective glycosylation of glycals to give 2-deoxyglycosides in high yields and α-stereocontrol. The reaction is tolerant of most common protecting groups in both the glycal donor and nucleophile acceptor, including electron-deficient galactals. Initital investigations indicate that the Cu-catalyzed enol ether activation/functionalization may proceed through dual activation of both the enol ether and nucleophile, whereby the Cu catalyst plays a key role in effective glycosylation and stereocontrol. Understanding the reactivity of these type of catalytic systems is of fundamental importance to be able to exploit the repertoire of transition metal catalysis in synthesis.

Scheme 3. Proposed mechanism and 3D structures of mixed complexes [Cu^{I}(**1b**)(ROH)]$^+$ optimized at the DFT B3LYP/def2-SVP level.

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Keywords: Stereoselectivity • Copper catalysis • Glycosylation • Enol ether • Glycals

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44. This result is not completely unexpected for glucal substrates bearing a leaving group (e.g. acetate) at C-3, since glucals substrates favour a bigger shift toward $^5H_4$ conformations and undergo rearrangement/substitution more readily than their corresponding galactal counterparts.[10, 39]
45. The use of a poorly coordinating solvent such as nitromethane allowed us to investigate the interaction of both Cu(II) and Cu(I) with a ligand, while neutral ligands triflimide or triflate anions were used indiscriminately (as they exhibited the same electrochemical behavior in this instance) to avoid any binding competition issues.
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49. The model competition of BnOH with cyclohexene was also studied see SI for details.
50. A parallel mechanism of glycal activation in which traces of triflic acid or another proton donor species are involved can not be completely discarded.