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Copper Reactivity Can Be Tuned to Catalyze the Stereoselective Synthesis of 2-Deoxyglycosides from Glycals

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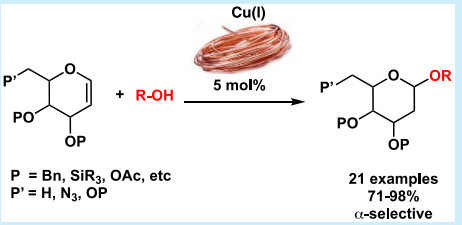
ABSTRACT: We demonstrate that tuning the reactivity of Cu by the choice of oxidation state and counterion leads to the activation of both "armed" and "disarmed" type glycals toward direct glycosylation leading to the α-stereoselective synthesis of deoxyglycosides in good to excellent yields. Mechanistic 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]

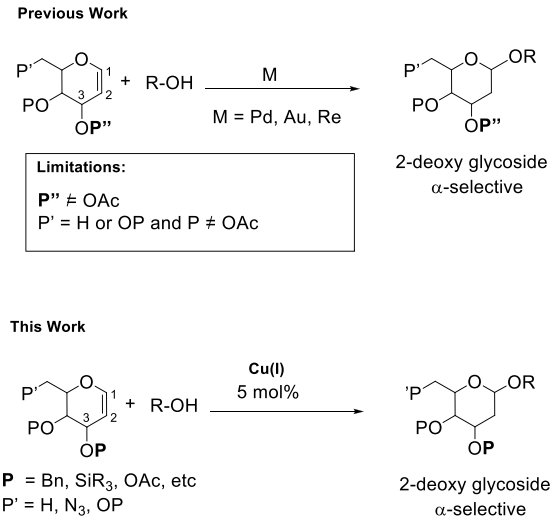
First row transition metals have recently attracted attention as alternatives to precious metals in catalysis.[4] Among those, copper is a cost-effective, earth-abundant, and sustainable metal and Cu-complexes can display unique and versatile reactivity and good functional group tolerance.[4] The chemistry exhibited by Cu can be very diverse depending on its oxidation state, as this metal can efficiently catalyze 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-Deoxyhexoses 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 stereoselective protocols for their assembly have been of great interest.[5,18,22−38]

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),[39,40] Au(I),[41] or Re(V)[42] 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]

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) [$Cu(MeCN)_4(NTf_2)$ and $(CuOTf)_2 \cdot C_6H_6$] and Cu(II) [$Cu(NTf)_2 \cdot H_2O$ and $Cu(OTf)_2$] salts at different catalyst loadings, reaction temperatures, and solvents

Scheme 1. Cu^{I}-Catalyzed Direct Synthesis of Deoxyglycosides from Glycals



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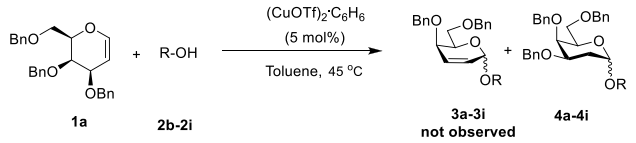
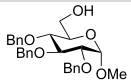
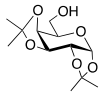
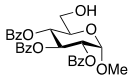
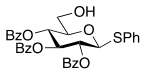
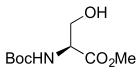
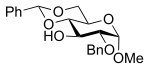
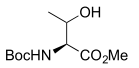
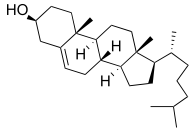
were initially screened as promoters in the glycosylation of perbenzylated galactal **1a** and glucoside acceptor **2a**[6] (See Table S1 in the Supporting Information (SI)). It was found that 5 mol % $(Cu^{I}OTf)_2{\cdot}C_6H_6$ in toluene at 45 °C gave the best results (Table 1, entry 1). The substrate scope was thus

Table 1. Reaction of Glycal 1a with Glycoside Acceptors 2b−2i



1a 2b-2i 3a-3i not observed 4a-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.

investigated, and galactal **1a** was reacted with a range of primary and secondary OH nucleophiles **2b−2i**[43] 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 1, 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).

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 as 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[18,19,40] as we also observe when using Cu(II) (Table 2, entry 1). The reaction was also amenable to glycosylations with glucal substrates, and reactions with 3,4-*O*-siloxane-protected **5a**[44] or **5b**[44] 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-catalyzed 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).[45] 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).

To probe the mechanism of our reaction, a 3:1 α/β-anomeric disaccharide mixture (**4j**; see the SI 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 (Figure S1 in the SI). 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 Figure S2). In the presence of 20 mol % DIPEA, the reaction between galactal **1a** and **2d** using either $Cu(NTf)_2{\cdot}H_2O$ or $Cu(OTf)_2$ was inhibited, which suggests that the presence of a Brønsted 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 % TfOH were carried out in toluene (Table S2 in the SI). 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 the SI 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 (Figure S3). NMR mixtures of 1 equiv of $(Cu^{I}OTf)_2{\cdot}C_6H_6$ 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 equiv of $Cu^{II}(OTf)_2$ and **1a** led to quick glycal activation and formation of degradation products (see Figures S4−S6 in the SI). On the other hand, no interactions between deactivated peracetylated 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 (Figure S7 and S8). Moreover, reaction between **1a** and **2c** using 5 mol % $Cu^{II}(OTf)_2$ and 10 mol % sodium ascorbate (to generate

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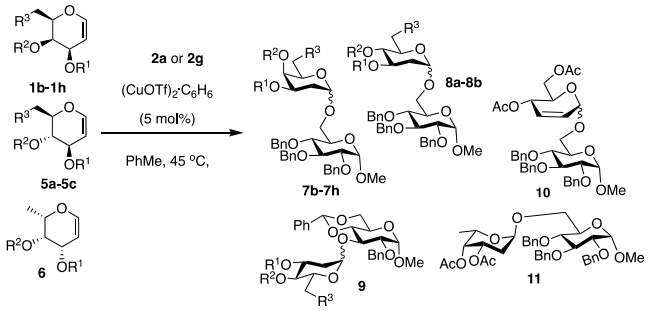
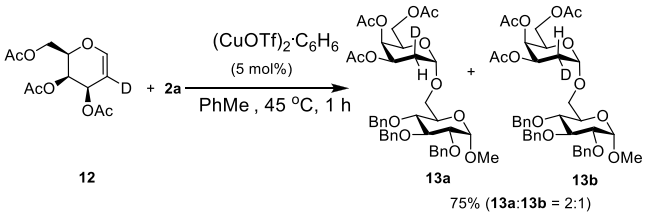
Table 2. Reaction Scope between Glycals 1b−1h, 5a−5c, and 6 with Acceptors 2a or 2g



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	N_3	**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**	$O[Si(iPr)_2]_2$		OTIPS	**8a**	3	72[c]	30:1
9	**5b**	$O[Si(iPr)_2]_2$		OBn	**8b**	4	79[c]	30:1
10	**5b**	$O[Si(iPr)_2]_2$		OBn	**9**	1	75[c]	30:1
11	**5c**	Ac	Ac	OAc	**10**	5	67[e]	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 $Cu(NTf_2)_2·H_2O$ or $Cu(OTf)_2$ afforded inseparable anomeric mixtures of Ferrier and glycoside products (13:87 (79%) and 25:75 (67%), respectively). [e]The reaction favored the Ferrier product over the 2-deoxyglycoside product (the latter obtained in 15%).

Scheme 2. Glycosylation of Deuterated Glycal Donor 12 with 2a



Cu(I) *in situ*) also afforded **4c** in 89% yield and >30:1 *α*:*β* (Table 1, entry 3). This result further indicates that Cu(I) is important for effective catalysis toward stereoselective glycosylation.

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).[46] The reduction of Cu(II) to Cu(I) is a quasi-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 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, suggesting that the complexation of one DHP to Cu^I through the *π* system is possible.[47−49]

The interaction of Cu(II) and Cu(I) with deactivated triacetyl galactal **1b** was next considered (see SI Figure S14). Interestingly, the pattern observed is somehow different with

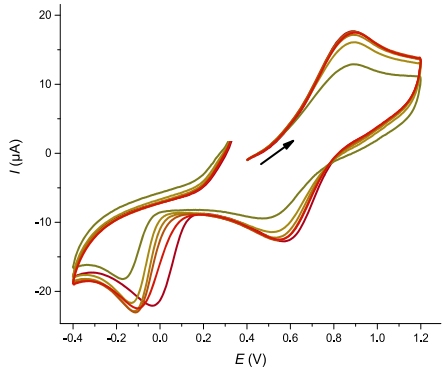


Figure 1. CV toward oxidation potentials of $[Cu^I(OTf)]$ (2 mM) in the presence of benzyl alcohol (158 equiv) with increasing amounts of **1b** (0, 1, 2, 5, 14, 50 equiv), recorded at a steady glassy carbon disk electrode (d = 3 mm) in nitromethane containing *n*-Bu_4NBF_4 (0.3 M) at 20 °C with a scan rate of 0.5 V s^{-1}.

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 toward 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 (see SI Figures S9−S12). However, Cu(I)-**1b** has a lower stoichiometry than the Cu(I)-cyclohexene one, in agreement with the formation of aggregates (see SI Figure S15).

The interaction between the OH nucleophile and copper was also studied and BnOH was chosen as a model substrate,

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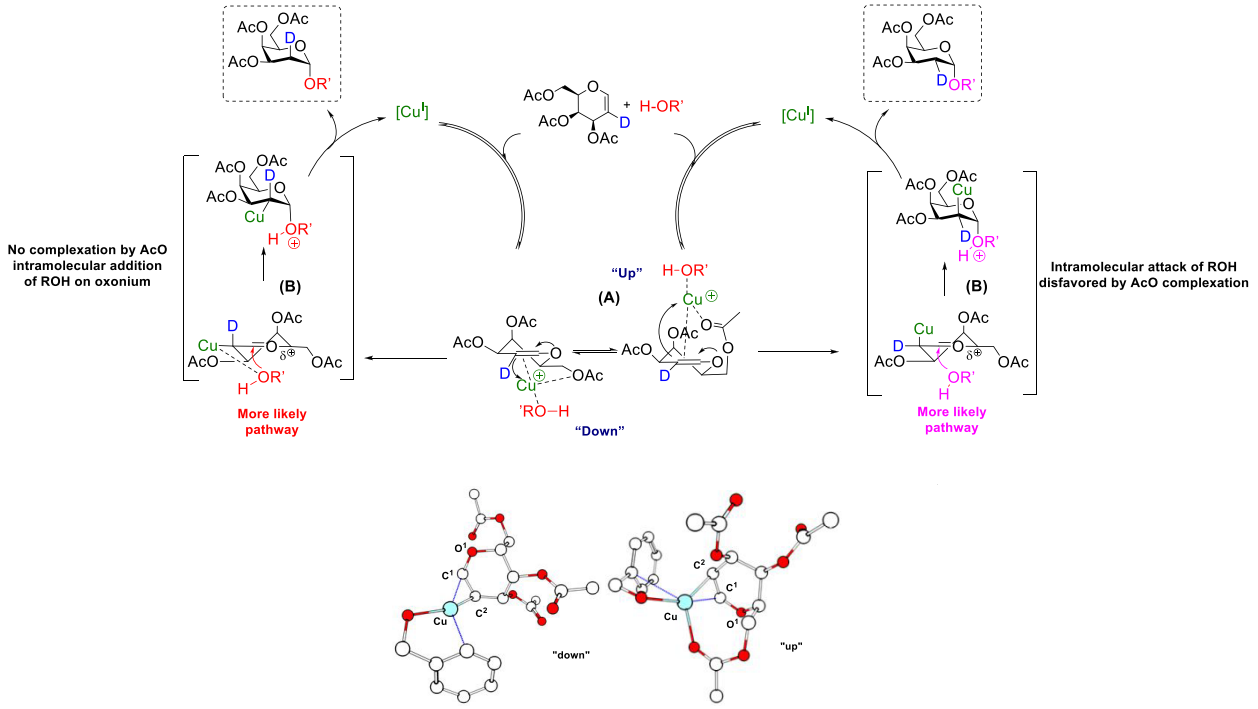
Scheme 3. Proposed Mechanism and 3D Structures of Mixed Complexes $[Cu^{I}(1b)(ROH)]^{+}$ Optimized at the DFT B3LYP/def2-SVP Level



as it was the simplest alcohol used in our scope. In the presence of BnOH, the reduction peak of Cu(II) was shifted toward lower potentials, as was the reduction peak of Cu(I) (see SI 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 (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 $Cu^{I}(OTf)$ in the presence of an excess of BnOH (158 equiv).[50] The reduction peak of Cu(I) was shifted toward lower potentials (Figures 1, S20, and S21). This is consistent with the formation of a complex between Cu(I) and **1b** even in the presence of a large excess of BnOH.

From our initial mechanistic studies, we concluded that (i) Cu(I)OTf leads to activation of the glycal double bond and that in the case of electron-deficient enol ethers Cu(I) interactions with the acyl groups facilitate the activation;[51] (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 $[Cu(\mathbf{1b})(ROH)]^{+}$ were optimized using DFT at the B3LYP/def2-SVP level to help us provide some insights with regard 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 S22 and Table S3, SI). 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. A mechanism can thus be proposed involving two $[Cu(\mathbf{1b})(ROH)]^{+}$ 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, 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 counterion 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.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04525.

Experimental procedures, full characterization data and copies of NMR data (PDF)

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Author Contributions

‖C.P.-N. and A.S.: Equal contribution.

Notes

The authors declare no competing financial interest.

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(46) 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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(50) The model competition of BnOH with cyclohexene was also studied see the SI for details.
(51) A parallel mechanism of glycal activation in which traces of triflic acid or another proton donor species are involved cannot be completely discarded.

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