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Gold(I)-Catalysed Direct Stereoselective Synthesis of Deoxyglycosides from Glycals.

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Supporting Information Placeholder

ABSTRACT: Au(I) in combination with AgOTf enables the unprecedented direct and α-stereoselective catalytic synthesis of deoxyglycosides from glycals. Mechanistic investigations suggest that the reaction proceeds via Au(I)-catalysed hydrofunctionalization of the enol ether glycoside. The room temperature reaction is high yielding and amenable to a wide range of glycal donors and OH nucleophiles.

Selective activation of alkyne and alkene bonds by gold catalysis has been extensively explored in organic synthesis to produce highly complex chemical architectures under mild conditions.[1] Extension of these studies to oligosaccharide synthesis has resulted in the development of Au(III) and Au(I) catalysed *O*-glycosylations.[2] Most reports proceed via the Au-activation of an anomeric alkynyl in the glycosyl donor to furnish the corresponding oxonium ion which then reacts with the incoming OH nucleophile.[3]

Deoxyhexoses are often found as components of a wide range of natural products and the chiral acetal is often instrumental for their biological activity.[4] Unlike fully oxygenated glycosides, the lack of substituents at C-2 to direct the nucleophile approach presents an additional synthetic challenge which has piqued the interest of many research groups.[2e, 2f, 5] Stemming from our interest in the development of catalytic methods for the direct stereoselective synthesis of deoxyglycosides[6] and in particular the application of transition metal catalysis for the activation of glycals.[7] We proposed that the ability of Au to effect the addition of oxygen nucleophiles across C=C bonds[1] would be ideally suited for the activation of glycal enol ethers.
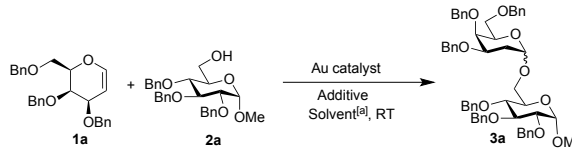

P = protecting group
R = OP, H
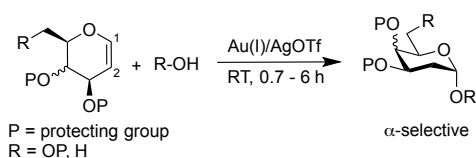
Scheme 1. Au-catalysed direct synthesis of deoxyglycosides from glycals.

Herein we describe the unprecedented Au(I) direct activation of glycals to yield α-deoxyglycosides. Products resulting from the *syn* addition of a proton and oxygen from the nucleophile across the carbon-carbon double bond are formed when [(pCF₃Ph)₃P)AuCl] and AgOTf are used as the glycosylation promoter (Scheme 1). Mechanistic studies suggest that the reaction proceeds via Au(I)-catalysed hydrofunctionalization of the enol ether to yield the desired glycoside with high stereocontrol.

Initial experiments began with the screening of a series of commercial Au catalysts: gold(III) trichloride (AuCl₃), (triphenylphosphine)gold(I) chloride [(Ph₃P)AuCl] and [tris(*p*-trifluoromethylphenyl)phosphine]gold(I) chloride [(pCF₃Ph)₃P)AuCl], for their ability to promote the stereoselective glycosylation of perbenzylated galactal **1a** with glucoside acceptor **2a**[6a] in CH₂Cl₂ at room temperature in the absence and presence of AgOTf as additive. As summarized in Table 1, reactions with any of the Au catalysts in the absence of AgOTf yielded little or no product after 16 h (entries 1, 4 and 7). Moreover, the combination of 5 mol% Au(III) and 10 mol% AgOTf could not efficiently activate **1a** and disaccharide **3a** was obtained in a 32% yield and a 9:1 α:β ratio within 1 h (entry 2). It is noteworthy that similar low yields were observed in reactions with only AgOTf after 16h (entry 3). Excitingly, activation with Au(I) proved to be more efficient and reactions in the presence of 5 mol% (Ph₃P)AuCl and 10 mol% AgOTf, afforded **3a** in 60% yield and 12:1 α:β ratio within 1h (entry 5), while combinations of [(pCF₃Ph)₃P)AuCl] and AgOTf gave **3a** within 45 min and 77% yield and >30:1 α:β stereocontrol (entry 8). Next, we decided to explore the effect of catalyst and additive loading in the model reaction. It was found that 3 mol% of [(pCF₃Ph)₃P)AuCl] in combination with 6 mol% of AgOTf was optimal (entry 11, 89% and >30:1 α:β *vs* entry 6), with lower loadings of both components being detrimental to reaction rate (entries 9 and 10). Replacing AgOTf for either AgSbF₆, AgBF₄, Ag₂CO₃ or BF₄K had also a negative effect leading to either no reaction (entries 14 and 15) or intractable mixture of products (entries 12 and 13). Solvent and temperature effects were then evaluated; reactions in acetonitrile did not proceed, while reactions in toluene afforded **3a** with a slight decrease in yield and stereocontrol when compared to CH₂Cl₂ (entries 16 and 17 vs 11). Finally, reactions carried out at 0 °C and allowed to warm to RT were slower leading to lower yields and stereocontrol (entry 18: 16 h, 68% and >20:1 α:β).

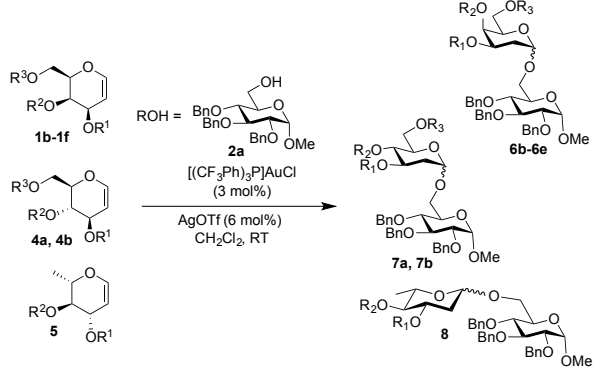**Table 1. Initial catalyst screen in the glycosylation of galactal 1a.**

Entry	Au catalyst (mol%)	Additive	Time (h)	Yield (%)[b]	α:β[b]
1	AuCl$_3$ (5)	-	1	_[f]	N/A
2	AuCl$_3$ (5)	AgOTf (10)	1	32	9:1
3	-	AgOTf (10)	16	32	8:1
4	(Ph$_3$P)AuCl (5)	-	16	<5	N/A
5	(Ph$_3$P)AuCl (5)	AgOTf (10)	1	60	12:1
6	(Ph$_3$P)AuCl (3)	AgOTf (6)	1	62	10:1
7	[(pCF$_3$Ph)$_3$P]AuCl (5)	-	16	11	N/A
8	[(pCF$_3$Ph)$_3$P]AuCl (5)	AgOTf (10)	0.7	77	>30:1
9	[(pCF$_3$Ph)$_3$P]AuCl (1)	AgOTf (2)	3	73	>20:1
10	[(pCF$_3$Ph)$_3$P]AuCl (3)	AgOTf (3)	2	75	>30:1
11	[(pCF$_3$Ph)$_3$P]AuCl (3)	AgOTf (6)	0.7	89	>30:1
12	[(pCF$_3$Ph)$_3$P]AuCl (3)	AgSbF$_6$ (6)	16	24[f]	>30:1
13	[(pCF$_3$Ph)$_3$P]AuCl (3)	AgBF$_4$ (6)	16	31[f]	>30:1
14	[(pCF$_3$Ph)$_3$P]AuCl (3)	Ag$_2$CO$_3$ (6)	16	s.m.	N/A
15	[(pCF$_3$Ph)$_3$P]AuCl (3)	BF$_4$K (6)	16	s.m.	N/A
16	[(pCF$_3$Ph)$_3$P]AuCl (3)	AgOTf (6)	16[c]	s.m.	N/A
17	[(pCF$_3$Ph)$_3$P]AuCl (3)	AgOTf (6)	0.7[d]	75	>20:1
18	[(pCF$_3$Ph)$_3$P]AuCl (3)	AgOTf (6)	16[e]	68	>20:1

[a] Reactions carried out in CH$_2$Cl$_2$ unless highlighted otherwise; [b] Determined by crude ^{1}H-NMR. [c] Reaction in MeCN as solvent RT. [d] Reaction in Toluene as solvent. [e] Reaction carried out at -40 °C to RT. [f] Inseparable mixture of products including ferrier products. s.m. = starting material. N/A = not applicable.

Having established the optimum reaction conditions, our attention then turned to investigating the scope of the glycal donor. To that end, a series of differentially protected galactals **1b-1f**, glucals **4a** and **4b** and L-rhamnal **5** bearing benzyl, acetate, methoxymethyl acetal, silyl ether and siloxane protecting groups were prepared and subjected to the reaction conditions with **2a** as the nucleophile (Table 2). Pleasingly, reactions involving galactal donors **1b-1f** were complete within 0.7 - 6h and in good to excellent yields (65-91%) and α-selectivities (6:1 to >30:1 α:β ratio) (entries 1-4), with the exception of peracetylated galactal **1f** which gave no product (entry 5).[8] Encouragingly, the reaction was also amenable to glycosylations with glucal substrates, and reactions between 3,4-*O*-siloxane protected **4a**[2c] and **4b**[2c] afforded the corresponding glycosides **7a** and

7b with high α-stereocontrol (>30:1 α:β) and yields (78-83 %) within 2-3h (entries 6 and 7). Moreover, activation of 3,4-*O*-siloxane protected L-rhamnal **5**,[6b] afforded 2,6-dideoxyglycoside **8** in 91% yield within 1 h and in a 5:1 α:β ratio (entry 9).

Table 2. Reaction of glycals 1b-1f, 4a, 4b and 5 with model glycoside acceptor 2a.

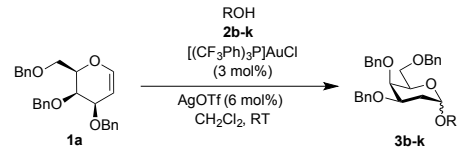| Entry		R^1	R^2	R^3	Product (time (h))	Yield (%)[a]	α:β[b]
1	1b	Bn	Bn	Ac	6b (0.7)	94	>30:1
2	1c	Bn	Bn	TIPS	6c (3)	65	6:1
3	1d	MOM	MOM	MOM	6d (6)	76	>30:1
4	1e	TBS	TBS	TBS	6e (2)	78	>30:1
5	1f	Ac	Ac	Ac	6f (-)	-	N/A
6	4a	O[Si(i-Pr)$_2$]$_2$		Bn	7a (3)	78	>30:1
7	4b	O[Si(i-Pr)$_2$]$_2$		TIPS	7b (2)	83	>30:1
9	5	O[Si(i-Pr)$_2$]$_2$		-	8 (1)	91	5:1

[a] Isolated yield. [b] Determined by ^{1}H-NMR. N/A = not applicable.

To explore the substrate scope of the glycosylation, galactal **1a** was reacted with a range of primary and secondary OH nucleophiles **2b-2k** under the optimized reaction conditions at RT (Table 3). 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 **2e**, thioglycoside **2d** and Boc-protected serine **2f** afforded the corresponding glycoside products in 77-85% yield within 0.7 h and with an >30:1 α:β ratio (Table 3, entries 1-5). Similarly, reactions with secondary alcohols such as Boc-protected threonine **2g**, glycoside **2h**, (R)-(-)-1-(2-naphtyl)ethanol **2i**, cholesterol **2j** or N-hydroxysuccinimide **2i** also afforded the desired products in good yields (65-85%) and with high α-selectivity (>30:1 α:β ratio to only α) (entries 6-10). These results further highlight that the catalytic system works well across a range of reactivity profiles in both the glycal moiety and nucleophile acceptor.

**Table 3. Acceptor scope in glycosylation reactions with galactal 2a.**

ROH
2b-k
[(CF$_3$Ph)$_3$P]AuCl
(3 mol%)
AgOTf (6 mol%)
CH$_2$Cl$_2$, RT

1a → **3b-k**

Entry	ROH		Time (h)	Yield (%)[a]	α:β[b]
1	BnOH	**2b**	0.7	85	>30:1
2		**2c**	0.7	81	>30:1
3		**2d**	0.7	77	>30:1
4		**2e**	0.7	79	>30:1
5		**2f**	0.7	83	>30:1
6		**2g**	2	69	>30:1
7		**2h**	4	65	>20:1
8		**2i**	1.5	81	>30:1
9		**2j**	2	76	>30:1
10		**2k**	6	85	α only

[a]Yield of isolated product. [b] Determined by crude ^{1}H-NMR.

The synthetic utility of the Au(I)-catalysed glycosylation was demonstrated in the sequential synthesis of oligosaccharides **9-11** (Scheme 2). Thus, galactal **1a** was reacted with **2a** under the optimised Au(I) conditions, which after selective deacetylation using NaOMe in MeOH afforded acceptor **9** in 70% yield after the 2 steps, with a >30:1 α:β selectivity. Coupling of **9** with **1a** followed by ester deprotection as before, gave trisaccharide **10** in 49% yield (>30:1 α:β). The coupling process was repeated once more and tetrasaccharide **11** was thus obtain in 52% yield and with the same high levels of α-stereocontrol as before. While the coupling yields decreased with each glycosylation, likely due to the bulk of the glycosyl acceptor, remarkably the high diastereoselectivity is maintained.
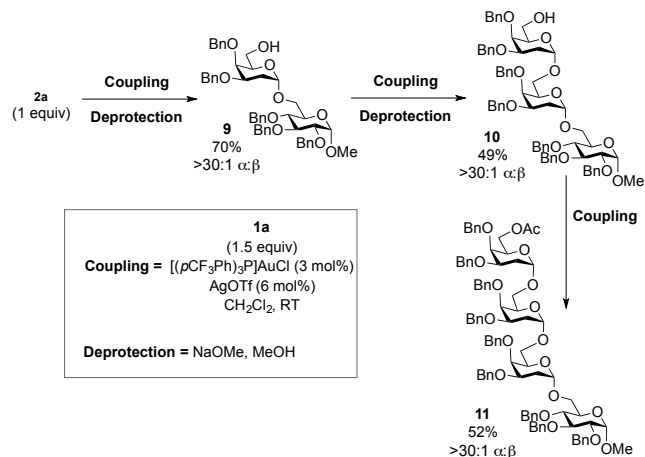
**Scheme 2. Au(I)-catalysed synthesis of di-tri and tetrasaccharides 9-11.**
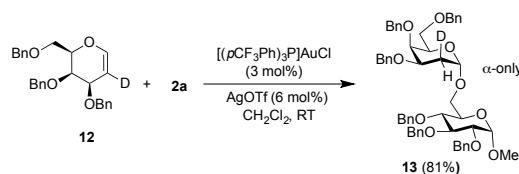
Scheme 3. Mechanistic studies with deuterated glycal donor 12 and 2a.

To probe the mechanism of our reaction, a 6:1 α/β-anomeric mixture of **3a** was subjected to the reaction conditions in the absence and presence of acceptor **2a** and gave no change in the anomeric ratio, indicating that the high α-selectivity is not the result of anomerization (fig S2 in ESI). Reaction with deuterated galactal **12** yielded disaccharide **13** (81% yield) with the newly formed bonds *cis* to each other (Scheme 3). These results confirm that the addition of the OH nucleophile across the double bond is preferentially *syn*-diastereoselective. Moreover, ^{1}H-NMR spectroscopy studies in CD$_2$Cl$_2$ of mixtures of [(pCF$_3$Ph)$_3$P]AuOTf]and glycoside acceptor **2a** did not show any changes in the spectra, suggesting there is no interaction between the Au-catalyst and the OH nucleophile. NMR mixtures of [(pCF$_3$Ph)$_3$P]AuCl], AgOTf and glycal **1a** clearly showed H-shifts associated with the shift of alkene protons in **1a** (from δ 6.27 ppm to 6.67) which suggests the formation of a reactive Au carbene intermediate[1] (See figs. S3 and S4 in ESI for details). This interaction is also supported by the shift observed in the IR stretch associated to the alkene signals of **1a** when the Au-catalyst is present (from 1643 to 1608 cm^{-1}). Additionally, monitoring of the reaction between **12** and **2a** by ^{1}H-NMR only showed signals corresponding to starting material and products (fig S1 in ESI), suggesting the reaction proceeds via short-lived intermediates.

While a detailed mechanism awaits further examination, our initial findings suggest, as proposed in Scheme 4, that reversible coordination of the Au(I) cation to C=C double bond leads to π-complex (A),[10] which can lead to the formation of transient oxacarbenium ion (B), that is quickly

3

trapped by the OH nucleophile with concomitant protonolysis of the Au-C bond[10b, 11] to yield the glycoside products and regenerate the Au(I) catalyst.[12]
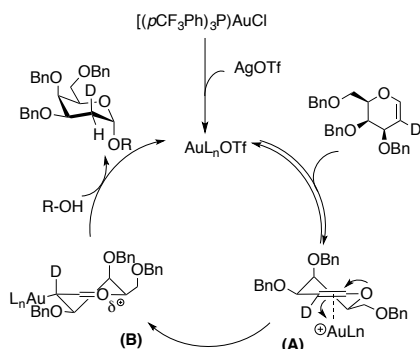
Scheme 4. Proposed mechanism.

In conclusion, we have described the first example of a Au(I)-catalysed direct and stereoselective glycosylation of glycal enol ethers. This mechanistically interesting reaction is mild and widely applicable to a range of glycal donors and nucleophile acceptors. The reaction proceeds with excellent yields and high selectivity for the α-anomer and is tolerant of most common protecting groups. We exemplify the generality and versatility of the approach in the stereoselective synthesis of a series of oligosaccharides, glycosyl-amino acids and other glycoconjugates. Given the abundance of chiral acetals in natural products, where enol ether functionalities are also featured, this method should find applications in and beyond the field of carbohydrates.

ASSOCIATED CONTENT

Supporting Information. Full experimental and characterization data for all compounds, including NMR spectra. The Supporting Information is available free of charge on the ACS Publications website.

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(8) Although we show that ester groups are tolerated elsewhere in the glycal donor (Table 3, entry 1), this result is not completely surprising, since the presence of a deactivating ester group at C-3 near the reacting double bond is known to significantly decrease the reactivity of the glycal donor.[6a]

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(12) when Na_2CO_3 is added, the proton is sequestered stopping the cycle. However, ^{1}H-NMR mixtures of 1a and 2a, Au-catalyst and the base still show the interaction with the alkene protons Fig S4 in ESI.

P = protecting group
R = H, OP

[(CF$_3$Ph)$_3$P]AuCl
(3 mol%)

AgOTf (6 mol%)
CH$_2$Cl$_2$, RT
0.7 - 6 h

23 examples
65-94%
α-selective