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Silver-Catalyzed Stereoselective Formation of Glucosides Using Glucosyl Ynenoates as Donors

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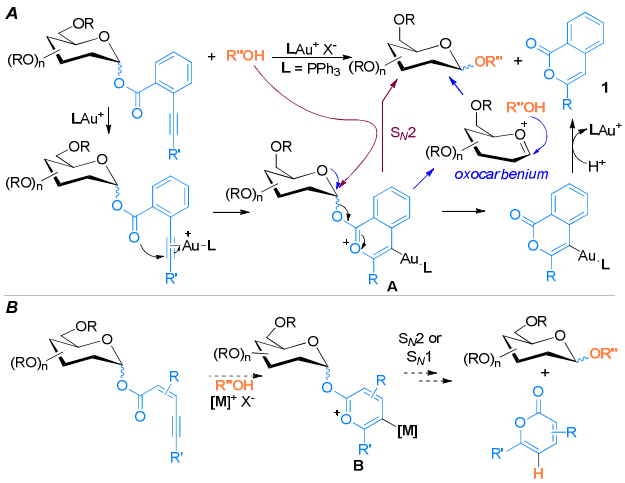
Abstract. A silver-catalyzed glycosylation reaction employing readily accessible and stable glucosyl ynenoates is developed. The reactions are mostly high yielding and exhibit varying levels of stereoinversion at the anomeric position. Comparing to the established and versatile Yu's gold catalysis, this chemistry features the use of substantially cheaper $AgNTf_2$.

Yu's *o*-alkynylbenzoate strategy (Scheme 1A)[1] enables highly efficient glycosylation under exceptionally mild gold catalysis conditions and has served as an enabling technology in the synthesis of polysaccharides and glycoconjugates including trioxacarcin D,[2] (-)-spinosyn A,[3] and mannopeptimycin α[4] due to the avoidance of harsh acidic conditions and the use of shelf stable glycosyl carboxylates. Conventional glycosylation strategies do not work well in these circumstances.[3-4]

Despite the remarkable success with Yu's method and other related developments,[5] there are still potential issues, which are: a) the often high loadings (typically 10 mol% or more) of gold catalysts. While the addition of HOTf (10 mol%) can decrease catalyst loadings down to 0.1 mol%,[6] it would likely be incompatible with acid labile functional groups;[2] b) due to the high price of the metal, this gold catalysis is expensive to scale up; c) due to the acidic nature of the gold catalysts, basic functional groups will in general require higher catalyst loadings (as in the case of spinosyn A[3] where 2 equiv. of Ph_3PAuCl are used due to the presence of a basic NMe_2), making the chemistry cost prohibitive; d) the anomeric selectivity mostly relies on substrate structures, and the S_N2 mode achieved so far is limited.[1c,7]

Outside the extensive work by Yu on the glycosyl *o*-alkynylbenzoate donors,[1c,6,8] there is no report on their ynenoate counterparts, which is void of the fused benzene ring.

As shown in Scheme 1B, we anticipated that these new donors could likewise undergo cyclization in the presence of a soft Lewis acid to afford the pyrylium intermediate **B**. In line with that benzene enjoys more aromaticity (36 kcal/mol resonance energy) than the second benzene ring in naphthalene (61-36 = 25 kcal/mol resonance energy), the pyrylium ring in **B** should enjoy more aromaticity than that in the Yu's intermediate **A**. DFT calculations[9] at the B3LYP/6-311++g(d,p) level give the difference of aromatic stabilization energies of the pyrylium ring of 2-methoxypyrylium over that of 1-methoxyisochromenylium to be around 3 kcal/mol. To this end, it is reasoned that **B** could be formed more readily and is a less activated donor, which might offer the following advantages: a) the use of less soft-acidic and cheaper metal catalyst; b) increased preference of S_N2 over S_N1 in the glycosidic bond formation process. Herein we disclose our initial studies with such glycosyl ynenoate substrates.



Scheme 1: π-acidic metal-catalyzed glycosidic bond formation. A) Yu's approach using *o*-alkynylbenzoates. B) Our design using ynenoates.

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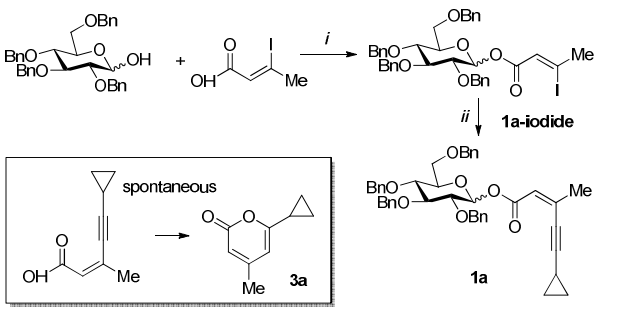
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

At the beginning, we chose the ynenoate donor **1a** as the substrate. It was initially prepared from (*Z*)-3-iodobutenoic acid and 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose in two steps, i.e., a) DCC-promoted formation of the glycosyl ester **1a-iodide**, and b) its Sonogashira coupling with cyclopropyl acetylene. Later, the DCC-promoted coupling was replaced by the reaction of the carboxylic acid with the corresponding glucosyl trichloroacetimidate[10] in order to selectively access either α- or β-**1a-iodide**. These approaches can permit an 'active-latent' strategy.[11] The alternative one-step preparation of **1a** from the tetra-*O*-benzylated glucose was thwarted by the unstable nature of the ynenoic acid, which undergoes spontaneous cyclization during preparation to form the 2H-pyran-2-one **3a**. This phenomenon is not observed in Yu's system,[12] which is consistent with our reasoning that pyrylium has more aromatic stabilization than benzopyrylium.

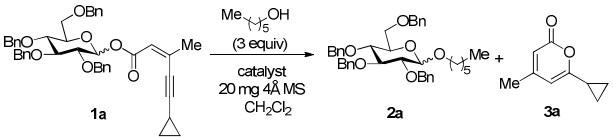


Scheme 2: Synthesis of glucosyl ynenoate **1a**. Reaction conditions: i) DMAP (0.1 equiv) DCC (1.1 equiv), DCM, rt, 94% yield, α/β = 1:1; ii) 0.03 equiv $PdCl_2(PPh_3)_2$, 0.1 equiv CuI in Et_3N, rt, 95% yield.

We first examined the reaction of α-**1a** with *n*-hexanol (3 equiv) under different reaction conditions (Table 1, entries 1-8). With $Ph_3PAuNTf_2$ as catalyst, despite a reasonable conversion (i.e., 38%) at -35 ◦C in 1 h and the quantitative formation of the pyranone byproduct **3a** based on conversion, little desired glucoside **2a** was formed, while hydrolysis dominated (entry 1). Mindful of the potential ease of activation (vide supra), we conducted the reaction with $AgNTf_2$ under otherwise identical conditions, a similar conversion (i.e., 36%, entry 2) was observed, and again **3a** was formed quantitatively based on consumed **1a**. Moreover, **2a** was formed in 15% yield along with 17% yield of the glucose due to hydrolysis. The fact that Ag is superior to Au in the reaction of **1a** was pleasantly surprising and directed our screening toward Ag catalysis. With 4Å MS added to keep the reaction media dry, the reaction was substantially impeded, likely due to catalyst inhibition by impurities from the dehydrant. The same is observed with gold catalysis. With 1.5 equiv. of $AgNTf_2$, the reaction went to completion after 5 h at -35 ◦C (entry 3). Little hydrolysis was detected, and **2a** was formed nearly quantitatively. Moreover, the α/β ratio is 1:8.4, favouring the β-anomer. This outcome reflects a partial S_N2 process in the glycosylation reaction. By switching the counter anion from NTf_2^- to OTf^-, the preference for β-**2a** was decreased to 5.6/1, likely due to the participation of the counter anion as a nucleophilic species (entry 4). On the other hand, SbF_6^- had little impact (entry 5). While no reaction could be detected at -72 ◦C (entry 6), the switch of reaction solvent led to drastic decrease of anomeric selectivity in the case of ^{t}BuOMe (entry 7) or slight decrease in the case of DCE (entry 8).

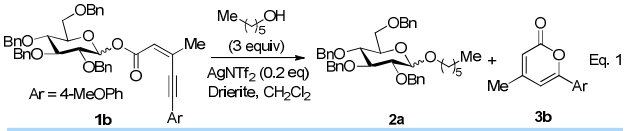
As expected, when β-**1a** was employed, the apparent inversion of anomeric stereochemistry (i.e., the S_N2 process) is less remarkable than in the case of its α-anomer (entries 9-11). However, when the reaction was run at -72 ˚C, instead of no conversion of α-**1a**, the reaction of β-**1a** did occur, albeit slowly, and was exclusively S_N2 (entry 12). To lower down the catalyst loading, we explored other desiccates and found out that Drierite (anhydrous $CaSO_4$) did not notably impede the catalysis, and 0.2 equivalent of $AgNTf_2$ was enough to drive the reaction to completion in 15 h with α-**1a** (entry 13) and in 5 h with β-**1a** (entry 14) while the anomeric selectivities remain more or less the same.

Table 1. Condition studies with the ynenoate **1a**[a]



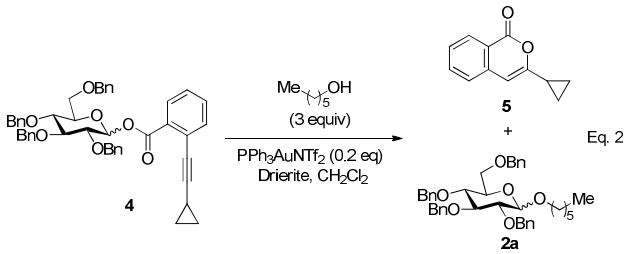
en-try	Catalyst (equiv)/solvent	1a	Temp (˚C)	Time (h)	Conv. (%)	2a α:β	2a Yield (%)
1[c]	$Ph_3PAuNTf_2$ (0.1)	α	-35	1	38	-	<5 (21[b])
2[c]	$AgNTf_2$ (0.1)	α	-35	1	36	-	15(17[b])
3	$AgNTf_2$ (1.5)/DCM	α	-35	5	100	1:8.4	>95
4	AgOTf(1.5)/DCM	α	-35	5	100	1:5.6	>95
5	$AgSbF_6$ (1.5)/DCM	α	-35	5	100	1:8.2	>95
6	$AgNTf_2$ (1.5)/DCM	α	-72	30	30	-	0
7	$AgNTf_2$ (1.5)/^{t}BuOMe	α	-35	15	100	1:1.7	>95
8	$AgNTf_2$ (1.5)/DCE	α	-35	5	100	1:7.4	>95
9	$AgNTf_2$ (1.5)/DCM	β	-35	5	100	4.2:1	>95
10	AgOTf(1.5)/DCM	β	-35	5	100	1:1	>95
11	$AgSbF_6$ (1.5)/DCM	β	-35	5	100	3.8:1	>95
12	$AgNTf_2$ (1.5)/DCM	β	-72	48	30	1:0	30%
13[d]	$AgNTf_2$ (0.2)/DCM	α	-35	15	100	1:8.0	>95
14[d]	$AgNTf_2$ (0.2)/DCM	β	-35	5	100	5.2:1	>95

[a] Reactions were performed in sealed vials with 10 mg of **1a**. Yield estimated by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal reference, and the α:β ratio determined by ^{1}H NMR. [b] The amount of 2,3,4,6-tetra-*O*-benzylglucose due to hydrolysis. [c] No MS added, and the reaction quenched with ^{n}Bu$_4$NCl. [d] Drierite (20 mg) used instead of 4 Å MS.



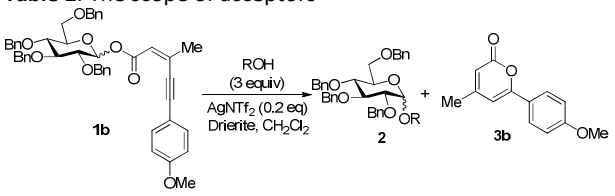
	reaction conditions	2a
α-**1b**	-40 → -30 °C, 48 h	α/β = 1:20; 90% isolated yield
β-**1b**	-30 °C, 5 h	α/β = 8:1; 95% isolated yield

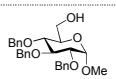
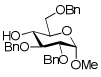
We also explored varying the ynenoate part by changing the substituents and found out that the reactions of **1b**, which differs from **1a** by a *p*-methoxyphenyl group at the alkyne terminus, result in higher levels of anomeric configuration inversion with either of its anomers (Scheme 3). Notably, in the case of α-**1b**, the β-glucoside **2a** was formed with an excellent 20:1 β-selectivity.



	reaction conditions	2a
α-**4**	-35 °C, 5 h	α/β = 1:15; >95% yield
β-**4**	-35 °C, 5 h	α/β = 13:1; >95% yield

Table 2. The scope of acceptors[a]

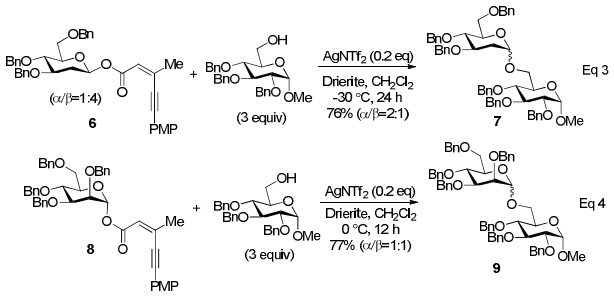


En-try	Sub-strate	Acceptor	Temp (˚C)	Time (h)	2	Yield[b]	α:β[c]
1	α-**1b**	isopropanol	-30 → -20	50	**2b**	92%	1:7.5
2	β-**1b**		-40	48	**2b**	91%	9:1
3	α-**1b**		-40 → -30	48	**2c**	88%	1:4
4	β-**1b**		-40 → -30	36	**2c**	87%	23:1
5	α-**1b**	BnOH	-40 → -30	48	**2d**	93%	1:6.7
6	β-**1b**		-40	48	**2d**	95%	10:1
7	α-**1b**	t-BuOH	-40 → -30	48	**2e**	91%	1:6.5
8	β-**1b**		-30	36	**2e**	92%	6.7:1
9	α-**1b**		-40 → -30	48	**2f**	87%	1:11
10	β-**1b**		-30	36	**2f**	89%	10:1
11	α-**1b**	cholesterol	-20	36	**2g**	85%	1:8
12	β-**1b**		-30	36	**2g**	86%	8:1
13	α-**1b**		-20	36	**2h**	60%	1:2
14	β-**1b**		-30	36	**2h**	85%	2.2:1
15	β-**1b**		rt	8	**2i**	58%	1.6:1
16	β-**1b**		0	8	**2j**	83%	2:1

[a] Reactions were performed in sealed vials or Schlenk tube. [b] Isolate yields. [c] α:β ratio determined by crude ^{1}H NMR.

To compare with Yu's system, we subjected the benzoate **4** under the similar conditions with $Ph_3PAuNTf_2$ as catalyst. As shown in Eq. 2, the reactions exhibit more S_N2 characteristics than those of **1a**, which shares the same cyclopropyl group at the alkyne end, but comparable to those of **1b**, although the gold catalysis appears to be faster. At this point, it is not clear why the anticipated enhancement of S_N2 process by this Ag catalysis does not occur.

With **1b** as the optimal glucosyl donor in the silver catalysis, we examined the scope of alcohol acceptors. As shown in Table 2, entries 1-12, a range of non-sugar alcohols are allowed, and the reaction yields are consistently high. Of note is that sterically demanding *tert*-butyl alcohol (entries 7 and 8) and menthol (entries 9 and 10) react smoothly to yield corresponding products with decent level of stereochemical inversion at the anomeric position. Interestingly, with (*R*)-1-phenylethanol (entries 3 and 4) as acceptor, its reaction with β-**1b** is highly stereo inverting, while its α-anomer exhibits moderate S_N2 character. The reactions with methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside, however, are only moderately stereoselective, although the stereoinversion trend remains (entries 13 and 14). This glycosylation approach was also tested against other glycosyl acceptors by using β-**1b** as the donor. With sterically more hindered and hence less reactive methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside as the acceptor, the reaction was exceedingly slow at -30 ˚C but proceeded smoothly at ambient temperature in 8 h. The disaccharide product **2i** was afforded in a fair yield and a low anomeric ratio (entry 15). The reaction of 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose could occur smoothly at 0 ˚C with good efficiency but again exhibited a low α/β ratio (entry 16).



We also examined the glycosyl ynenoates based on other monosaccharides. As shown in Eq. 3, **6** based on deoxy glucose reacted smoothly at -30 ˚C to afford the disaccharide **7** in 76% yield. The product anomeric ratio (α:β = 2:1) is comparable to that in Table 2, entry 14, but due to the existence of α-**6** (20%), this reaction most likely exhibited more characteristics of S_N2. On the other hand, 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl ynenoate **8** reacted slower and at 0 ˚C afforded the disaccharide **9** in a good yield despite without anomeric selectivity (Eq. 4). This silver catalysis, however, does not work with disarmed 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl ynenoate donors at room temperature due to the lack of activation, which in principle offers opportunities for chemoselective glycosylation.

Conclusions

We have developed a silver-catalyzed glycosylation reaction employing readily accessible and stable glucosyl ynenoates. The reactions result in mostly excellent yields and exhibit good levels of stereoinversion at the anomeric position when sufficiently nucleophilic non-sugar alcohols, despite varying steric hindrance, are employed. With sugar-based acceptors, however, moderate stereoinversions are detected with either a donor α- or β-anomer. Applications of this silver catalysis to other types of sugar donors are also examined. Comparing to the established and versatile Yu's gold catalysis, this chemistry features the use of substantially cheaper $AgNTf_2$ as catalyst and, as a mild alkyne-based glycosylation strategy, shall find general use in scenarios where excessive Au is needed due to large-scale transformations and/or the presence of basic and/or acid-labile residues.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

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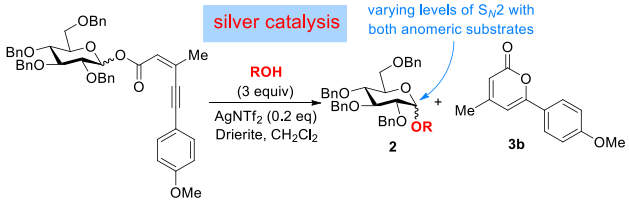

Developed is a silver-catalyzed glycosylation reaction employing readily accessible and stable glucosyl ynenoates and exhibiting mostly highly yielding.