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Glycosylation |*Hot Paper*|

Highly Stereoselective β-Mannopyranosylation via the 1-α-Glycosyloxy-isochromenylium-4-gold(I) Intermediates

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Abstract: While the gold(I)-catalyzed glycosylation reaction with 4,6-*O*-benzylidene tethered mannosyl *ortho*-alkynylbenzoates as donors falls squarely into the category of the Crich-type β-selective mannosylation when $Ph_3PAuOTf$ is used as the catalyst, in that the mannosyl α-triflates are invoked, replacement of the ^-OTf in the gold(I) complex with less nucleophilic counter anions (i.e., $^-NTf_2$, $^-SbF_6$, $^-BF_4$, and $^-BAr_4^F$) leads to complete loss of β-selectivity with the mannosyl *ortho*-alkynylbenzoate β-donors. Nevertheless, with the α-donors, the mannosylation reactions under the catalysis of $Ph_3PAuBAr_4^F$ (BAr_4^F = tetrakis[3,5-bis(trifluoromethyl)phenyl]-borate) are especially highly β-selective and accommodate a broad scope of substrates; these include glycosylation with mannosyl donors installed with a bulky TBS group at O3, donors bearing 4,6-di-*O*-benzoyl groups, and acceptors known as sterically unmatched or hindered. For the *ortho*-alkynylbenzoate β-donors, an anomerization and glycosylation sequence can also ensure the highly β-selective mannosylation. The 1-α-mannosyloxy-isochromenylium-4-gold(I) complex (**Cα**), readily generated upon activation of the α-mannosyl *ortho*-alkynylbenzoate (**1α**) with $Ph_3PAuBAr_4^F$ at −35 °C, was well characterized by NMR spectroscopy; the occurrence of this species accounts for the high β-selectivity in the present mannosylation.

Introduction

The β-*O*-D-mannopyranoside linkage occurs prominently in the common pentasaccharide core of the N-linked glycoproteins, and also in various mannans, glycosphingolipids, and lipopolysaccharides as well.[1] This glycosidic bond was recognized as one of the most difficult types of glycosidic linkages for chemical synthesis, owing to the superimposed influence of the anomeric effect and the steric effect of the axial C2 substituents that favor strong formation of the 1,2-*trans*-α-mannosides.[2] Therefore, indirect approaches have been implemented to synthesize β-mannosides,[3–5] with the most reliable one being the inversion of the C2 configuration of β-glucopyranosides[4] or glycosylation by intramolecular aglycone delivery (IAD).[5,6] Direct β-selective mannosylation has been realized with mannosyl bromides as donors and insoluble silver salts as promoter, relying on shielding of the α-face of the mannosyl α-bromides by the heterogeneous promoter,[2,7] or with mannosyl tosylates equipped with a highly electron-withdrawing substituent at O2 to provide an opposing dipole to facilitate the S_N2-like substitution.[8] Direct alkylation of 1-O-metallated mannopyranoses could also lead to β-mannosides.[9] However, these early direct methods suffer from narrow substrate scope and difficulty in controlling the reaction conditions. A groundbreaking discovery was made, accidently, by Crich and Sun in 1996; the preactivation of 4,6-*O*-benzylidene-2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl-D-mannopyranosyl sulfoxide with Tf_2O/DTBMP (2,6-di-*tert*-butyl-4-methylpyridine) at low temperature (−78 °C) followed by addition of acceptors led to highly β-selective mannosylation.[10] Tremendous efforts have since been devoted to the studies on the scope and mechanism of this unexpected reversal of stereoselectivity in mannosylation (Figure 1).

The important results and rationale include:

- Themannopyranosyl α-triflates are characterized as important intermediates for the β-mannosylation.[11–17] Thus, donors with a variety of leaving groups including thiomannosides,[12] mannosyl trichloroacetimidates,[13] *N*-phenyltrifluoroacetimidates,[14] diethyl phosphites,[15] 1-hydroxy derivatives,[16] and 2-(hydroxycarbonyl)benzyl mannosides[17] could also be employed for β-mannosylation under conditions invoking formation of the mannopyranosyl α-triflates.
- Catalytic activation of the mannopyranosyl donors, thus leading to in situ formation of the mannopyranosyl α-triflates, could also effect β-selective mannosylation.[13–15]
- Nevertheless, the β-mannosylation does not proceed via an S_N2 substitution of the α-triflates, rather an S_N1 substitution on a transient contact ion pair (CIP) developed from the α-triflates,[18] or an oxocarbenium ion in a $B_{2,5}$ conformation is involved.[13a,19]
- Tethering the 4- and 6-OH groups (mostly with a 4,6-*O*-benzylidene acetal) in the donors is critically important which

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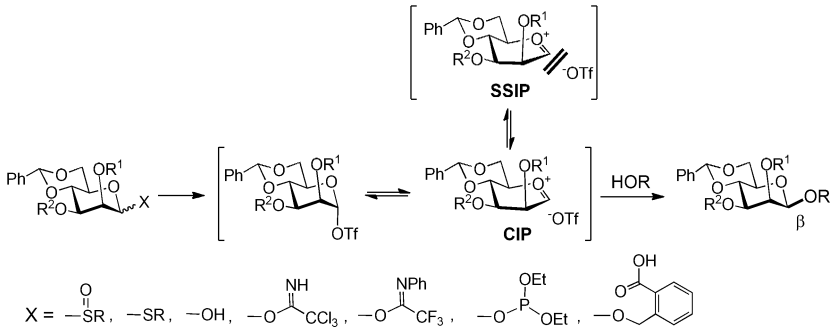


Figure 1. Direct β-selective mannosylation based on the formation of α-mannosyl triflate intermediates.

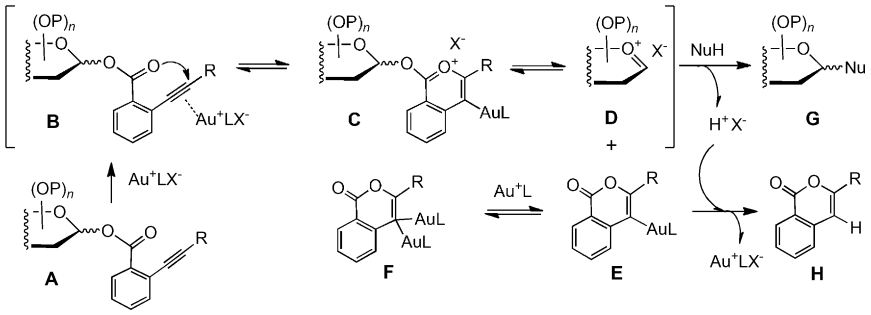


Figure 2. The gold(I)-catalyzed glycosylation reaction with glycosyl *ortho*-alkynylbenzoates (**A**) as donors.

retards the equilibrium of the glycosylation intermediates from the α-triflates and the CIP to the solvent-separated ion pair (SSIP), so as to ensure the β-mannosylation.[19,20] Such an effect is attributable to the torsional strain encountered as the chair–chair donor undergoes a conformational change to a chair–half-chair oxocarbenium ion;[21] the fixed *trans-gauche* (*tg*) conformation of the C5–C6 bond that maximizes the electron-withdrawing effect of O6, so as to disfavor the formation of the dissociative glycosyl oxocarbenium ion (SSIP), is well documented.[22]

- Although less prominently, electron-withdrawing groups at O4 and O6 in the donors could also facilitate the β-selectivity in mannosylation.[23]
- While the non-participating substituent at O2 has a minor effect on the β-mannosylation,[19,24] the bulkiness of the protecting group at O3, which could force the O2 substituent to shield the β-face of the donor, remarkably affect the β-selectivity in mannosylation.[25]

Recently, we developed a new glycosylation protocol that uses glycosyl *ortho*-alkynylbenzoates (**A**) as donors and a gold(I) complex as catalyst (Figure 2).[26] With the avoidance of strong acidic, nucleophilic, or electrophilic species (usually derived from the leaving groups and promoters in the classical glycosylation reactions), this glycosylation method has found wide application in the synthesis of complex glycoconjugates.[27] Mechanistic studies show that activation of the C≡C triple bond in donor **A** by the gold(I) species (preferably Ph_3PAu^+) leads to formation of a glycosyloxypyrylium gold(I) intermediate **C**,[28] which might collapse to sugar oxocarbenium ion **D** and isochromen-4-yl-gold(I) complex **E**.[29] Gold(I) complex **E** and bis-gold(I) complex **F**, which are in equilibrium,[28] are unable to catalyze the glycosylation, but consumption of a proton derived from the glycosidic coupling of **D** and acceptor (NuH) regenerates the active gold(I) cation. The occurrence of intermediate **C** is supported by a trapping reaction, however, under conditions not exactly identical to those for the glycosylation.[28] That the glycosylation might proceed via a S_N2-type substitution on intermediate **C** has been implied by the observation of dependence of the β/α selectivity on the starting anomeric configuration of the donors in some circumstance.[28]

Applying the gold(I)-catalyzed glycosylation with the relevant mannosyl *ortho*-alkynylbenzoates as donors to the Crich-type β-mannosylation would lead to new insights into the glycosylation reactions. Whereupon, the pertinent questions to address include: 1) Does the glycosyloxypyrylium gold(I) intermediate **C** occur and play a role in the glycosylation reaction or does the glycosyl α-triflate dominate (when $X^- = {}^-OTf$)? 2) Could other non-coordinating counter anions play a similar role as ^-OTf does? 3) Could the scope of the Crich-type β-mannosylation be further expanded? Here we report results relevant to these questions.

Results and Discussion

Mannosylation with 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α/β-D-mannopyranosyl *ortho*-hexynylbenzoates (1α/1β) under the catalysis of gold(I) complexes

We started the present study with 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-D-mannopyranosyl *ortho*-hexynylbenzoate **1α** and **1β** as donors (Figure 3), which are installed with the prototypical pattern of protecting groups enabling the Crich-type β-mannosylation.

Adamantanol **6b**, which represents an achiral and modest nucleophile, was firstly chosen as the acceptor, and $Ph_3PAuOTf$, which contains the critically important counter anion ^-OTf for the Crich-type β-mannosylation, was selected as the catalyst. Under the conventional conditions, wherein 0.2 equiv of $Ph_3PAuOTf$ was added to a solution of the donor and acceptor in CH_2Cl_2 in the presence of 4 Å MS at 0 °C, the condensation of **1α** and **1β** with **6b** led to the desired glycoside **7** in excellent yields and with good β-selectivity (β/α = ~6.5:1; Table 1,

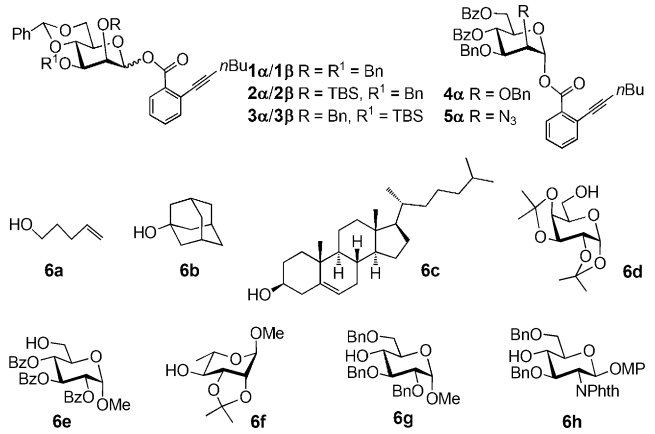
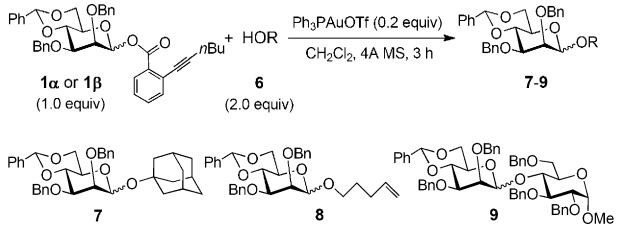


Figure 3. Mannosyl *ortho*-hexynylbenzoate donors **1**–**5** and acceptors **6a**–**6h**.

Table 1. $Ph_3PAuOTf$-catalyzed glycosylation of 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α/β-D-mannopyranosyl *ortho*-hexynylbenzoates (**1α**/**1β**).



Entry	Donor	Acceptor	*T* [°C]	Product (yield [%])	β/α ratio[a]
1	**1α**	**6b**	0	**7** (95)	6.5:1
2	**1β**	**6b**	0	**7** (99)	6.4:1
3	**1β**	**6b**	−30	**7** (99)	6.6:1
4[b]	**1β**	**6b**	−72 to 0	**7** (99)	9.0:1
5	**1α**	**6a**	0	**8** (92)	6.7:1
6	**1β**	**6a**	0	8 (99)	5.1:1
7	**1α**	**6g**	0	**9** (89)	4.3:1
8	**1β**	**6g**	0	**9** (89)	4.5:1

[a] The β/α ratio was determined by HPLC. [b] $Ph_3PAuOTf$ (1.0 equiv) was added before addition of the acceptor.

entries 1 and 2). The reaction could proceed effectively at −30 °C, however, the β-selectivity remained unchanged (entry 3). Preactivation of the donor (**1β**) with 1.0 equivalent of $Ph_3PAuOTf$ at −72 °C, followed by addition of **6b** and then warming to room temperature led to a slightly increased β-selectivity (β/α = 9:1; entry 4). With primary alcohol **6a** and the hindered sugar alcohol **6g** as acceptors, the condensation (at 0 °C) with donors **1α** and **1β** also led to effective β-selective mannosylation (entries 5–8). That the yield and β/α selectivity are virtually independent of the anomeric configuration of the starting donors (cf. entry 1/2, 5/6, and 7/8) indicates that a common intermediate is derived from donor **1α** and **1β**. In fact, the signals corresponding to the well-documented mannosyl α-triflate were detected by NMR spectroscopy after addition of $Ph_3PAuOTf$ (1.0 equiv) to a CD_2Cl_2 solution of **1β** at −72 °C (Supporting Information Figure S2).[16b] Thus, the present results fall squarely into the scope of the Crich-type β-mannoslyation.

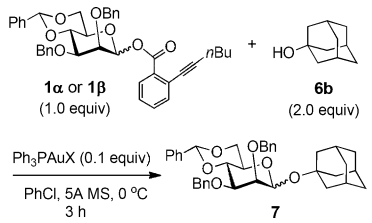
We then explored the model condensation of **1α**/**1β** and **6b** in the presence of Ph_3PAu^I complexes bearing a variety of counter anions other than ^-OTf; these included $Ph_3PAuNTf_2$, $Ph_3PAuSbF_6$, Ph_3PAuBF_4, and $Ph_3PAuBAr_4^F$ (BAr_4^F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate). PhCl was chosen as the solvent to accommodate well all these gold(I) complexes.[30] The comparative results of the glycosylation reactions catalyzed by 0.1 equivalents of the gold(I) complex in the presence of 5 Å MS at 0 °C are listed in Table 2. The present $Ph_3PAuOTf$-catalyzed reactions of **1α** and **1β** both led to β-selective mannosylation, although the β/α selectivity is moderate and slightly different (β/α = 3.7:1 from **1α** vs. 4.7:1 from **1β**; entries 1 and 2). In great contrast, when $Ph_3PAuNTf_2$ was used as the catalyst, the glycosylation of **1α** underwent β-selective mannosylation (β/α = 5.4:1; entry 3), however, the reaction of **1β** favored the formation of the α-glycoside (β/α = 1:1.6; entry 4). Similar results were attained with $Ph_3PAuSbF_6$ as the catalyst, and the β/α ratio further decreased to 1:3.2 when starting with **1β** (entries 5 and 6). Ph_3PAuBF_4 was found to be not effective as catalyst for the present glycosylation reaction; the coupled glycoside **7** was isolated in low yields due to either recovery of the starting **1α** or formation of the corresponding mannosyl fluoride (entries 7 and 8). Nevertheless, the reaction of **1α** was still β-selective while the reaction of **1β** favored formation of the α-glycoside (β/α = 1:2). With $Ph_3PAuBAr_4^F$ as the catalyst, the condensation of **1α** and **6b** furnished glycoside **7** in a high 95% yield and with a remarkable β/α ratio of 49:1 (entry 9). The α-anomer was completely undetectable on HPLC when the reaction temperature was lowered to −20 °C (entry 10). Under identical conditions, the reaction of **1β** had no β/α selectivity (entry 11).

The nucleophilicity of $^-NTf_2$, $^-SbF_6$, $^-BF_4$, and $^-BAr_4^F$ is significantly poorer than ^-OTf,[31] thus formation of the corresponding covalent mannosyl species relevant to the mannosyl α-triflates is not likely at least under the present glycosylation conditions, this is evidenced by the present outcomes. In fact, we conducted an NMR measurement of a mixture of **1β** and $Ph_3PAuNTf_2$ (1.0 equiv) in CD_2Cl_2 at −72 °C, and failed to detect any signals assignable to the purported glycosyl triflimide.[32] The β-selective mannosylation with **1α** as donors, especially when $Ph_3PAuBAr_4^F$ was used as the catalyst, should involve a new mannosyl α-species, either a covalent one or a CIP.

$Ph_3PAuBAr_4^F$-catalyzed β-selective mannosylation with α-mannosyl *ortho*-hexynylbenzoates as donors

The surprisingly high β-selectivity found in the condensation of α-mannosyl *ortho*-hexynylbenzoate **1α** and adamantanol **6b** under the catalysis of $Ph_3PAuBAr_4^F$ prompted us to explore the scope of this reaction carefully. We first selected diacetone galactose **6d** as the acceptor, which was known to be a less matching partner in the Crich-type β-mannosylation.[33] The reaction of **1α** (1.0 equiv) and **6d** (2.0 equiv) proceeded smoothly in the presence of $Ph_3PAuBAr_4^F$ (0.2 equiv) in PhCl at 25 °C to provide the coupled disaccharide **10** in 95% yield and a β/

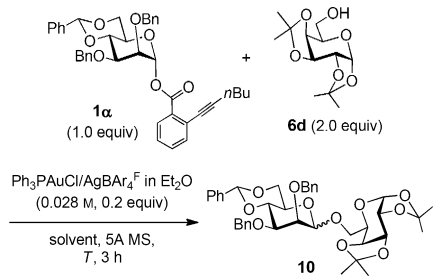
Table 2. Glycosylation of mannopyranosyl *ortho*-hexynylbenzoates (**1α**/**1β**) with alcohol **6b** under the catalysis of Ph_3PAu^I complexes bearing a variety of the counter anions.



Entry	Donor	Catalyst	Yield [%]	β/α ratio[a]
1	**1α**	$Ph_3PAuOTf$	90	3.7:1
2	**1β**	$Ph_3PAuOTf$	90	4.7:1
3	**1α**	$Ph_3PAuNTf_2$	90	5.4:1
4	**1β**	$Ph_3PAuNTf_2$	90	1:1.6
5	**1α**	$Ph_3PAuSbF_6$	90	5.3:1
6	**1β**	$Ph_3PAuSbF_6$	90	1:3.2
7	**1α**	Ph_3PAuBF_4	23[b]	1:0
8	**1β**	Ph_3PAuBF_4	61[c]	1:2.0
9	**1α**	$Ph_3PAuBAr_4^F$	95	49.0:1
10[d]	**1α**	$Ph_3PAuBAr_4^F$	90	1:0
11[d]	**1β**	$Ph_3PAuBAr_4^F$	90	1.2:1

[a] The β/α ratio was determined by HPLC; [b] 69% **1α** was recovered; [c] 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-mannopyranosyl fluoride (**S17**) was isolated (~27%) as a byproduct. [d] The reaction was performed at −20 °C.

Table 3. Optimization of the reaction conditions for the β-selective mannosylation of galactose acceptor **6d** with mannosyl *ortho*-hexynylbenzoate **1α** catalyzed by $Ph_3PAuBAr_4^F$.



Entry	Solvent	*T* [°C]	Yield [%]	β/α ratio[a]
1	PhCl	25	95	5.7:1
2	PhCl	0	99	7.4:1
3	PhCl	−20	99	9.6:1
4[b]	PhCl	−20	99	13.0:1
5	CH_2Cl_2	0	90	4.5:1
6	Et_2O	0	99	2.3:1
7[c]	PhCl	−20	99	21.0:1

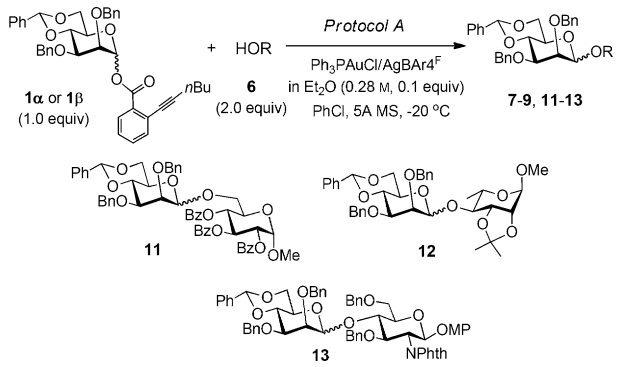
[a] The β/α ratio was determined by HPLC. [b] The catalyst loading was reduced to 0.1 equiv; [c] 0.1 equiv of the catalyst with a concentration of 0.28 M (in Et_2O) was used.

α ratio of 5.7:1 (Table 3, entry 1). This outcome is comparable to those with the corresponding mannosyl sulfoxide as donor (β/α = 5.6:1).[33] Lowering the reaction temperature to 0 °C and −20 °C improved considerably the β-selectivity to 7.4:1 and 9.6:1, respectively (entries 2 and 3). Surprisingly, when the catalyst loading was reduced to 0.1 equivalent, the reaction at 0 °C led to a remarkably higher β-selectivity (β/α = 13:1; entry 4). It was noted that the catalyst $Ph_3PAuBAr_4^F$ was freshly prepared by mixing Ph_3PAuCl and $AgBAr_4^F$ in Et_2O (0.028 M).[34] Thus, the present increase of the β-selectivity upon lowering the amount of the catalyst might be attributable to the reduction of the volume of Et_2O in the reaction mixture (from 340 to 170 μL Et_2O in 2 mL PhCl). This rational was supported by the next experiment conducted in Et_2O, wherein the β/α ratio of the product was only 2.3:1 (entry 6). CH_2Cl_2 was also found to be less effective than PhCl as the solvent with the 0.028 M concentration of $AgBAr_4^F$ in Et_2O was used as the catalyst (entry 5). Taken together, we came up with the optimal conditions for the condensation of **1α** and **6d**, and a concentrated solution of $Ph_3PAuBAr_4^F$ in Et_2O (0.1 equiv, 0.28 M) was used as the catalyst, PhCl as the solvent, and −20 °C as the working temperature (Protocol A); the coupled disaccharide **10** was furnished in an excellent 99% yield and a β/α ratio of 21:1 (entry 7).

We then applied the optimized conditions (Protocol A) to examine the scope of the acceptors in the $Ph_3PAuBAr_4^F$-catalyzed mannosylation of **1α** (Table 4). With the simple alcohols **6a**, **6b**, and the primary sugar alcohol **6e** as acceptors, the glycosylation of **1α** proceeded smoothly, providing the coupled β-mannosides **8**, **7**, and **11**, respectively, in nearly quantitative yields and with complete β-selectivity (β/α > 50:1) within 3 h (entries 1–3). The condensation with sugar secondary alcohol **6f** required 12 h for completion, nevertheless, the coupled disaccharide **12** was also isolated in excellent yield (95%) and β-selectivity (β/α = 20:1; entry 4). The condensation with the hindered sugar alcohol **6g** was thus conducted at a higher 0 °C; the reaction was complete within 3 h without erosion of the coupling yield and β-selectivity (96%, β/α = 20:1; entry 5). The coupling of **1α** with the hindered glucosamine derivative **6h** was even more challenging, but could provide a valuable building block for the synthesis of the core pentasaccharide of the N-linked glycoproteins.[35] Gratifyingly, a slight enhancement of the reaction conditions (by increasing the catalyst loading to 0.2 equiv and the reaction temperature to −10 °C) was able to drive the reaction to completion within 12 h, wherein the coupled disaccharide **13** was isolated in a satisfactory 88% yield and a practically useful β/α ratio of 12:1 (entry 6).

The *ortho*-hexynylbenzoate **1β** could condense with the simple or hindered alcohols effectively under conditions similar to that for the glycosylation of its α-counterpart **1α**, leading to the corresponding coupled glycosides in excellent yields (>90%; entries 7–10). In contrast, however, the mannosylation of **1β** showed no β/α selectivity with active acceptors (β/α = 1.2:1 for **6b** and 1:1.6 for **6e**) or moderate β-selectivity with poor acceptors (β/α = 4.4:1 for **6f** and 5.6:1 for **6g**). The reactions of **1β** with the poor acceptors **6f** and **6g** were conducted at a higher 0 °C, and **1β** could undergo anomerization to give **1α**; thus, the moderate β-selectivity observed here might be caused by the glycosylation of the resultant **1α** (Figure 4).

Table 4. The scope of acceptors in the $Ph_3PAuBAr_4^F$-catalyzed β-selective mannosylation of mannosyl *ortho*-hexynylbenzoate **1α** and comparison to the glycosylation of **1β**.



Entry	Donor	Acceptor	*t* [h]	Product (yield [%])	β/α ratio[a]
1	**1α**	**6a**	3	**8** (99)	>50:1
2	**1α**	**6b**	3	**7** (99)	1:0
3	**1α**	**6e**	3	**11** (99)	>50:1
4	**1α**	**6f**	12	**12** (95)	20.0:1[b]
5[c]	**1α**	**6g**	3	**9** (96)	20.0:1
6[d]	**1α**	**6h**	12	**13** (88)	12.0:1
7	**1β**	**6b**	3	**7** (90)	1.2:1
8	**1β**	**6e**	3	**11** (99)	1:1.6
9[c]	**1β**	**6f**	3	**12** (93)	4.4:1[b]
10[c]	**1β**	**6g**	3	**9** (96)	5.6:1

[a] The β/α ratio was determined by HPLC. [b] The β/α ratio was determined by NMR spectroscopy. [c] The reaction was performed at 0 °C. [d] The reaction was performed at −10 °C with 0.2 equiv catalyst for 12 h.

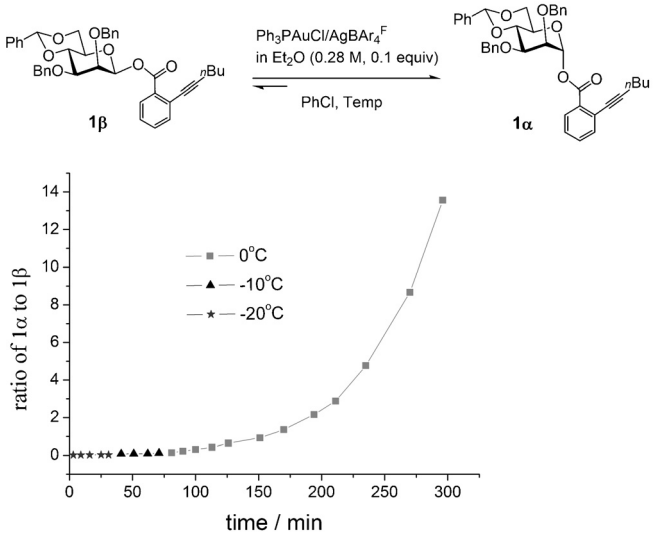


Figure 4. Anomerization of **1β** to **1α** under the catalysis of $Ph_3PAuBAr_4^F$.

Ph_3PAu^I-catalyzed anomerization of β-mannosyl *ortho*-hexynylbenzoate to its α-anomer and the subsequent β-selective mannosylation

The anomerization process from mannosyl *ortho*-hexynylbenzoate **1β** to **1α** under the $Ph_3PAuBAr_4^F$-catalyzed glycosylation conditions in the absence of acceptor was monitored by HPLC (see the Supporting Information). Thus, **1β** was treated with 0.1 equivalents $Ph_3PAuBAr_4^F$ (in Et_2O, 0.28 M) in PhCl at −20 °C, and **1α** was not detectable. Raising the temperature to −10 °C, **1β** stayed nearly intact. Nevertheless, at 0 °C, the anomerization took place smoothly, an equilibrium of **1α**/**1β** = 14:1 was reached within approximately 4 h (Figure 4). It should be noted that no side reaction, such as the 1,2-elimination to give the glucal derivative (i.e., **S16**), was observed under these conditions.

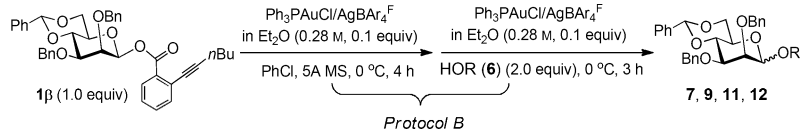
Given enough time for anomerization, β-selective mannosylation should be realized starting with **1β** (or a mixture of **1β** and **1α**). In fact, treatment of **1β** with $Ph_3PAuBAr_4^F$ (in Et_2O, 0.28 M, 0.1 equiv) in PhCl at 0 °C for 4 h, followed by addition of acceptor **6b** and then a second portion of the catalyst, led to the coupled glycoside **7** in a high 90% yield and an excellent β/α ratio of 50:1 (Table 5, entry 1). Appling this procedure (Protocol B) to the condensation of **1β** with sugar alcohols **6e**, **6f**, and **6g** provided the corresponding coupled disaccharides **11**, **12**, and **9**, respectively, in satisfactory yields (>85%) and β-selectivity (>10:1; entries 2–4).

$Ph_3PAuBAr_4^F$-catalyzed β-selective mannosylation with 4,6-*O*-benzylidene-2-*O*-*tert*-butyldimethylsilyl-3-*O*-benzyl- or 3-*O*-*tert*-butyldimethylsilyl-2-*O*-benzyl-mannosyl *ortho*-hexynylbenzoates (2α/2β or 3α/3β) as donors

Replacement of the benzyl group at O2 with a bulkier *tert*-butyldimethylsilyl (TBS) group in the donors did not affect much of the β-selectivity in the Crich-type β-mannosylation.[33] Thus, the glycosylation of 4,6-*O*-benzylidene-2-*O*-TBS-3-*O*-benzyl-mannosyl *ortho*-hexynylbenzoate donor **2α**/**2β** following the present Protocol A or Protocol B was expected to be highly β-selective. In fact, coupling of **2α** with sugar alcohol **6f** following Protocol A gave the coupled disaccharide **14** (93%) in a β/α ratio of 12:1 (Table 6, entry 1). Similar coupling with the hindered acceptor **6g** led to the coupled disaccharide **15** in a similar β/α ratio (15:1), however in a lower yield of 67% (entry 2). Starting with **2β** (Protocol B), disaccharide **15** was isolated in a better 78% yield with a slightly lower β-selectivity (β/α = 12:1; entry 3). These results prove the usefulness of **2α**/**2β** as β-mannosylation donors, although both the yields and β-selectivity are lower compared to those attained with the 2-*O*-benzyl donors **1α**/**1β**.

A more challenging issue in the Crich-type β-selective mannosylation was the use of a donor with the bulky TBS group at O3.[24b,25] Surprisingly, this was found not to be a problem with mannosyl *ortho*-hexynylbenzoates **3α**/**3β** as donors under the catalysis of $Ph_3PAuBAr_4^F$ (Table 6, entries 4–8). Thus, condensation of **3α** with adamantanol **6b** following Protocol A led to glycoside **16** (98%) in an astonishing β/α ratio of 38:1 (entry 4). Starting with **3β**, anomerization/glycosidation (Protocol B) led to **16** in 85% yield with β/α = 23:1 (entry 5). With primary sugar alcohol **6e** as accepter, the glycosylation of **3α** was still efficient (83%, β/α = 18:1); whereas compound **20** was isolated in 16% yield (based on **3α**), indicating the migration of the TBS group from O3 in the donor to the alcoholic

Table 5. β-Selective mannosylation with β-mannosyl *ortho*-hexynylbenzoate **1β** as donor under the catalysis of $Ph_3PAuBAr_4^F$.

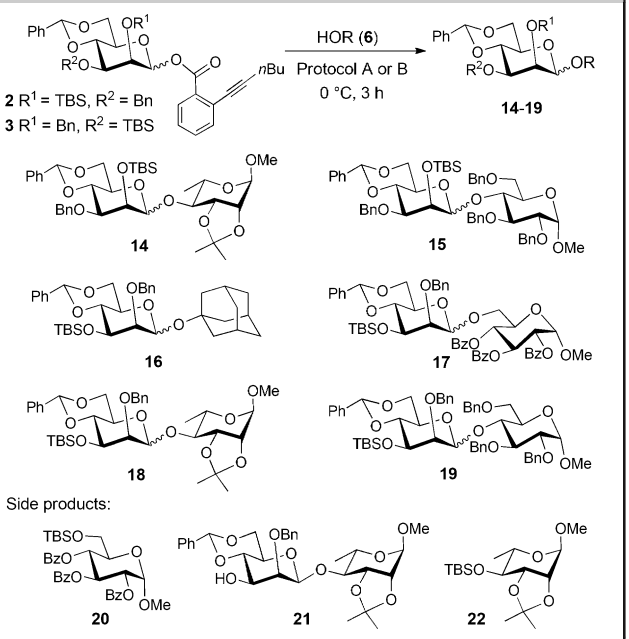


Entry	Acceptor	Product (yield [%])	β/α ratio[a]
1	**6b**	**7** (90)	50.0:1
2	**6e**	**11** (95)	19.0:1
3	**6f**	**12** (89)	10.0:1
4[b]	**6g**	**9** (85)	16.0:1

[a] The β/α ratio was determined by HPLC. [b] The β/α ratio was determined by NMR spectroscopy.

yield, together with the desilylated disaccharide **21** (20%) and silylated acceptor **22** (14%). The β-selectivity was still satisfactory (β/α = 12:1). The condensation of **3α** with the hindered sugar alcohol **6g** was conducted in the presence of 0.2 equivalents of the gold(I) catalyst at −20 °C, providing disaccharide **19** in a still satisfactory yield of 79% and β/α ratio of 7:1 (entry 8).

Table 6. The $Ph_3PAuBAr_4^F$-catalyzed β-selective mannosylation of mannosyl *ortho*-hexynylbenzoates **2α/β** and **3α/β**.



Entry	Donor	Acceptor	Protocol	Product (yield [%])	β/α ratio[a]
1	**2α**	**6f**	A	**14** (93)	12.0:1[b]
2	**2α**	**6g**	A[c]	**15** (67)	15.0:1
3	**2β**	**6g**	B	**15** (78)	12.0:1
4	**3α**	**6b**	A	**16** (98)	38.0:1
5	**3β**	**6b**	B	**16** (85)	23.0:1
6	**3α**	**6e**	A	**17** (83)[d]	18.0:1
7	**3α**	**6f**	A	**18** (66)[e]	12.0:1[b]
8	**3α**	**6g**	A[f]	**19** (79)	7.0:1

[a] The β/α ratio was determined by HPLC. [b] The β/α ratio was determined by NMR spectroscopy; [c] 0.2 equiv of the gold(I) catalyst was used. [d] Compound **20** (16%) was isolated as a byproduct. [e] Compounds **21** (20%) and **22** (14%) were isolated as byproducts. [f] The reaction was conducted at −20 °C for 6 h in the presence of 0.2 equiv of the gold(I) catalyst.

acceptor (entry 6). The silyl group migration became more serious when rhamnose derivative **2f** was used as acceptor (entry 7); the coupled disaccharide **18** was isolated in 66% yield, together with the desilylated disaccharide **21** (20%) and silylated acceptor **22** (14%). The β-selectivity was still satisfactory (β/α = 12:1). The condensation of **3α** with the hindered sugar alcohol **6g** was conducted in the presence of 0.2 equivalents of the gold(I) catalyst at −20 °C, providing disaccharide **19** in a still satisfactory yield of 79% and β/α ratio of 7:1 (entry 8).

β-Selective mannosylation with 4,6-di-*O*-benzoyl-mannosyl *ortho*-hexynylbenzoates (4α and 5α) as donors

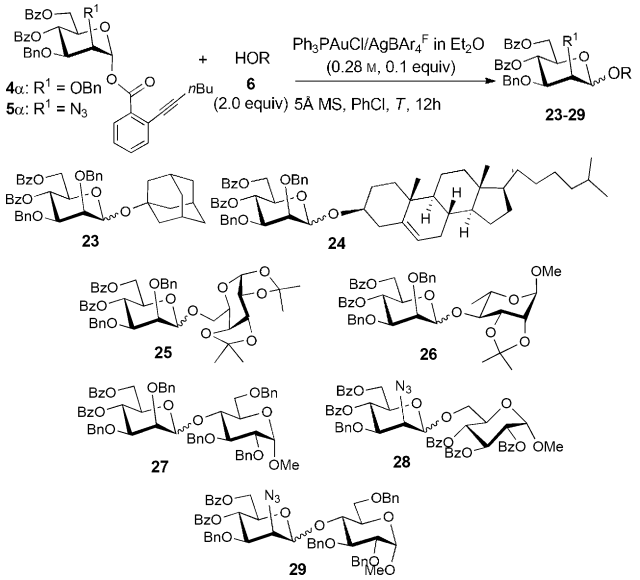
Tethering the 4- and 6-OH groups in donors is found to be critically important in the Crich-type β-mannosylation,[20,36] nevertheless, strongly electron-withdrawing groups, such as the sulfonyl group at O4/O6 or the carboxyl function at C6, could also facilitate the mannosylation with β-selectivity, especially upon condensation with active acceptors.[23,37] We examined the glycosylation of mannosyl donor **4α**, which was installed with two easily removable benzoyl groups at the O4 and O6, under the present gold(I)-catalyzed conditions (Table 7). Gratifyingly, the condensation of **4α** with a range of the acceptors (**6b**, **6c**, **6d**, **6f**, and **6g**) in the presence of 0.1 equivalents of $Ph_3PAuBAr_4^F$ in PhCl led to the coupled glycosides (**23**–**27**) in high yields (>88%) and β-selectivity (β/α > 8.1:1; entries 1–5). It should be noted that the 4,6-di-*O*-benzoyl donor **4α** was slightly more active than the 4,6-*O*-benzylidene counterpart **1α**, therefore the glycosylations could be conducted at lower temperatures (≤ −20 °C) to allow completion of the reactions within 12 h.

4,6-Di-*O*-benzoyl-3-*O*-benzyl-2-deoxy-2-azido-mannosyl *ortho*-hexynylbenzoate **5α** was also briefly examined in the present glycosylation with two representative sugar alcohols **6e** and **6g** (entries 6 and 7). It is known that the 2-azido-mannosyl donors are much less active than the corresponding 2-benzyloxy donors and are less β-selective in mannosylation.[38] The condensation of **5α** with primary alcohol **6e** at −10 °C led to the coupled disaccharide **28** nearly quantitatively with a β/α ratio of 7:1 (entry 6); whereas condensation with hindered alcohol **6g** gave disaccharide **29** in a satisfactory 85% yield, albeit with a lower β-selectivity (β/α = 4.9:1; entry 7).

Characterization of the 1-α-glycosyloxy-isochromenylium-4-gold(I) intermediate in the β-mannosylation

The formation of mannosyl α-triflates has been proven to be critically important in the Crich-type β-mannosylation. To characterize the corresponding intermediate in the present $Ph_3PAuBAr_4^F$-catalyzed β-mannosylation, we carried out careful NMR analysis on the activation of *ortho*-hexynylbenzoate **1α** with $Ph_3PAuBAr_4^F$ in [D_5]PhCl at −35 °C (Figure 5; see the Supporting Information).

Table 7. β-Selective mannosylation with 4,6-di-*O*-benzoyl-α-mannosyl *ortho*-hexynylbenzoates **4α** and **5α** as donors.



Entry	Donor	Acceptor	*T* [°C]	Product (yield [%])	β/α ratio[a]
1	**4α**	**6b**	−20	**23** (99)	12.0:1
2	**4α**	**6c**	−42	**24** (90)	20.0:1[b]
3	**4α**	**6d**	−42	**25** (99)	8.8:1
4	**4α**	**6f**	−42	**26** (91)	8.1:1
5	**4α**	**6g**	−30	**27** (88)	10.0:1
6	**5α**	**6e**	−10	**28** (99)	7.0:1
7	**5α**	**6g**	−10	**29** (85)	4.9:1

[a] The β/α ratio was determined by HPLC. [b] The β/α ratio was determined by NMR spectroscopy.

The ^{1}H NMR spectra were recorded before and after addition of 0.4, 1.0, or 1.4 equiv of $AgBAr_4^F$ into a [D_5]PhCl solution of **1α** and Ph_3PAuCl at −35 °C, respectively. As shown in Figure 6 (and Supporting Information Figures S3–S6), a new set of signals appeared cleanly after addition of $AgBAr_4^F$, thus the presence of $Ph_3PAuBAr_4^F$. The intensity of these signals increased along with the increase of the equivalent of $AgBAr_4^F$, while the signals of the starting **1α** decreased accordingly, with the intensity ratio (those new/those from **1α**) being 0.3:1, 1.8:1, and 4.4:1 at 0.4, 1.0, and 1.4 equivalents of $AgBAr_4^F$ being introduced, respectively. These results indicate the clean formation of a new species upon activation of **1α** with $Ph_3PAuBAr_4^F$, which is stable at least in PhCl at −35 °C.

To elucidate the structure of the evolved species, the mixture, upon addition of 1.4 equivalents of $AgBAr_4^F$, was further subjected to HSQC (heteronuclear singular quantum correlation) and HMBC (heteronuclear multiple bond coherence) measurements (see Supporting Information Figures S5 and S6). As shown in Table 8, all the diagnostic signals were assignable to the glycosyl 1-α-glycosyloxy-isochromenylium-4-gold(I) complex **Cα**. The anomeric H1 appeared as a singlet at 6.61 ppm, which showed HSQC correlation to C1 at 102.4 ppm and HMBC correlation to C2, C2′, C3′, and C5′. The signal at 168.0 ppm was thus assigned to carbonyl C2, that was further supported by its HMBC correlation to the aromatic H4 (at 7.85 ppm). The two allylic H11 signals were well diagnostic, which appeared as a pair of board peaks (due to the chirality of the molecule), at 3.04 and 3.21 ppm, respectively. The HMBC correlation of H11 led to the assignment of C9 (at 152.7 ppm), C10 (at 163.0 ppm), as well as C12 (at 31.8 ppm). The HMBC correlation found between C9 to H7 and H11 and C10 to H11 and H12 further proved the assignment. The splitting of the ^{13}C signal of C9 with a coupling constant of 110.5 Hz, which is caused by the phosphorus atom in the Ph_3P moiety, confirmed that the Ph_3PAu was attached at C9 rather than at C10. In addition, ^{31}P NMR spectra displayed a single sharp resonance at $\delta p = 42.5$ ppm (Supporting Information Figure S4), in accordance with that of a vinyl-$AuPPh_3$ species, such as **E** ($\delta p = 45.6$ ppm).[29]

In comparison to the NMR signals in **1α** (Table 8), the anomeric H1 of **Cα** shifted upfield only by 0.25 ppm while C1 downfield by 9.0 ppm. In fact, the chemical shift of C1 in the corresponding 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-mannopyranosyl triflate is at a slightly lower field of 105.4 ppm,[16b] whereas the C1 of a oxocarbenium species would exceed 220 ppm.[18d,39] The carbonyl C2 (at 168.0 ppm) of **Cα** shifted slightly downfield by 3.8 ppm, indicating the delocalization of positive charge to the two oxygen atoms. It is noted that the chemical shift of a related α,α-dialkoxybenzyl cationic carbon is at approximately 180 ppm.[40] The biggest change came from those of C9 and C10, which moved downfield by 72.1 and 66.1 ppm, respectively, corresponding to the change from

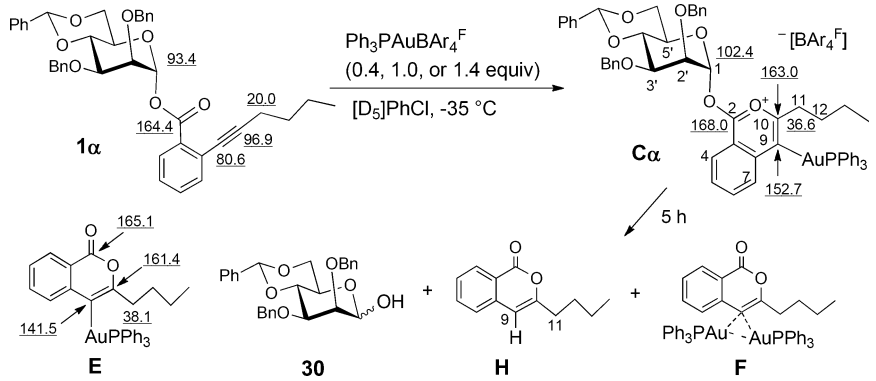


Figure 5. NMR monitoring of donor **1α** in the presence of $Ph_3PAuBAr_4^F$ (0.4, 1.0, or 1.4 equiv) in [D_5]PhCl at −35 °C (the underscored numbers are the ^{13}C NMR chemical shifts).

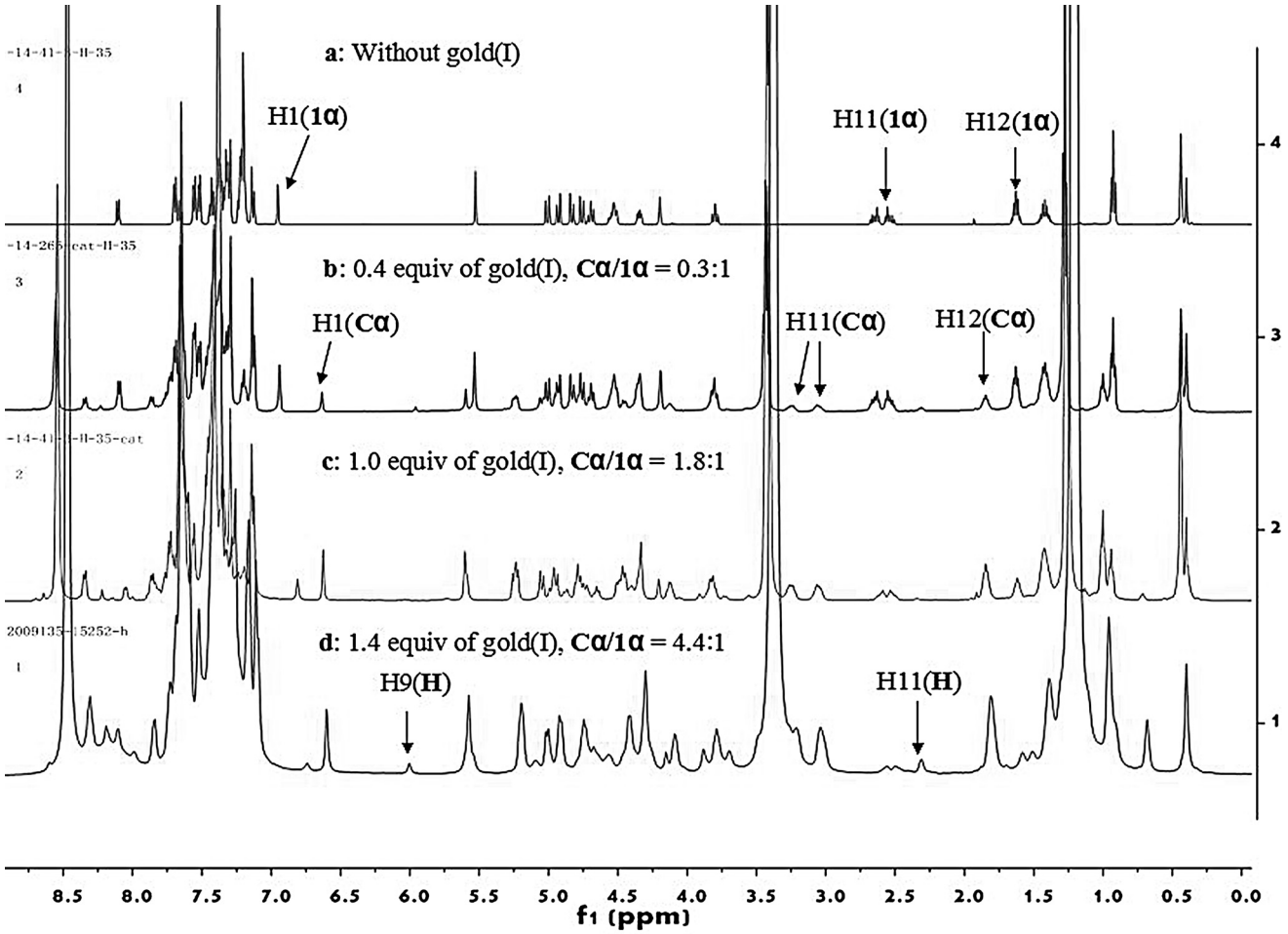


Figure 6. ^{1}H NMR spectra of donor **1α** and the mixtures of **1α** and $Ph_3PAuBAr_4^F$ (0.4, 1.0, and 1.4 equiv, respectively) in [D_5]PhCl at −35 °C. The intense signals at 1.20 and 3.37 ppm arise from residual Et_2O that was used in the preparation of $Ph_3PAuBAr_4^F$ (see the Supporting Information).

Table 8. ^{1}H (600 MHz), ^{13}C (150 MHz), HSQC, and HMBC NMR data assigned for compounds **Cα** and **1α** in [D_5]PhCl (and [D_5]PhCl/$CDCl_3$, 10:1)[a] at −35 °C.

Position	Complex **Cα**			Donor **1α**		ΔδH (**Cα**–**1α**)	ΔδC (**Cα**–**1α**)
	δH, *J* [Hz]	δC, *J* [Hz]	HMBC	δH, *J* [Hz]	δC, *J* [Hz]		
1	6.61 (bs)	102.4	H1 to C2, C2′, C3′, C5′	6.86 (bs)	93.4	−0.25	9.0
2′	4.32 (bs)	75.0	C2′ to H1, H2′ to C1	4.19 (bs)	76.6	0.13	−1.6
3′	4.44 (dd, *J* = 9.9, 3.2)	75.0	C3′ to H1, H3′ to C1	4.47	76.4	−0.03	−1.4
4′	4.76 (t, *J* = 9.7)	78.2	H4′ to C3′, C2′	4.64 (t, *J* = 9.8)	79.2	0.12	−1.0
5′	4.10 (td, *J* = 9.7, 5.1)	68.5	C5′ to H1	4.47	67.2	−0.37	1.3
6′a	3.84 (t, *J* = 10.4)	68.2		3.83 (t, *J* = 10.3)	68.7	0.01	−0.5
6′b	4.33	68.2		4.35 (dd, *J* = 10.3, 4.8)	68.7	−0.02	−0.5
2		168.0	C2 to H1, H4		164.4		3.8
4	7.85		H4 to C2	8.06		−0.21	
7	8.30		H7 to C9	7.62		0.68	
9		152.7 (d, *J* = 110.5)	C9 to H7, H11		80.6		72.1
10		163.0	C10 to H11, H12		96.9		66.1
11	3.12	36.6	H11 to C9, C10, C12	2.50	20.0	0.62	16.6
12	1.81	31.8	H12 to C10	1.65	30.8	0.16	1.0

[a] The ^{1}H NMR spectra showed better resolution in a mixed solvent of [D_5]PhCl/$CDCl_3$ (v/v = 10:1) than those in [D_5]PhCl, while the chemical shifts were nearly not changed (see Supporting Information Figure S7).

the C9≡C10 triple bond in (**1α**) to double bond in (**Cα**). Accordingly, the signal of C11 shifts from 20.0 to 36.6 ppm on going from a propargylic carbon to an allylic carbon. On the other hand, the diagnostic coupling constants of the sugar ring protons in **Cα** indicate the retention of the chair conformation from that of **1α** (Table 8).

It was noted that the mixture of **Cα** in the NMR tube at −35 °C finally underwent decomposition completely (> 5 h),

leading to mainly the hydrolyzed product **30**, together with isocoumarin **H**, and the bis-gold complex **F** (see the Supporting Information). Upon raising the temperature from −35 °C to RT, however, the mixture decomposed quickly, as indicated by the change of color from yellow to black within 5 min.

We also conducted the NMR analysis on the glycosylation process of donor **1α** and adamantanol **2b**, and **2b** (1.0 equiv) was introduced into the $[D_5]$PhCl solution of **1α** and Ph_3PAuCl in the NMR tube at −20 °C before addition of $AgBAr_4^F$ (0.2 equiv). Interestingly, the 1-α-mannosyloxy-isochromenylium-4-gold(I) complex **Cα** was detectable throughout the glycosylation reaction (~46 min, at −35 °C), whereas the starting **1α** was nearly completely converted into glycoside **7** and isocoumarin **H** (Supporting Information Figure S10).

It is noteworthy that the corresponding 1-β-mannosyloxy-isochromenylium-4-gold(I) complex (**Cβ**) could not be detected upon activation of **1β** under similar conditions used for the characterization of **Cα** from **1α**. Whereas, the detectable species included only the hydrolyzed product **30**, isocoumarin **H**, and the bis-gold(I) complex **F** (Supporting Information Figures S8 and S9). This indicates that the 1-β-mannosyloxy-isochromenylium-4-gold(I) complex **Cβ** is not stable, at least under the present conditions in that the glycosidation could proceed. In the presence of a hindered base di-*tert*-butylmethylpyridine, a small portion of the **Cβ** (6%) could be trapped by vinyl ether via a [3+2]-cycloaddition-migration-elimination sequence (see the Supporting Information).[28] Thus, S_N2-like substitution on **Cβ** could take place, although it might undergo decomposition more favorably to arrive at the sugar oxocarbenium (SSIP in Figure 1). This rational explains the modest β/α ratio attained in the glycosylation reaction of **1β**; glycosylation solely via the SSIP intermediate would lead to a much lower β/α ratio (compared to those attained in the present studies) for the mannosylation.

Conclusion

The gold(I)-catalyzed glycosylation reaction with 4,6-*O*-benzylidene-protected mannosyl *ortho*-alkynylbenzoates as donors falls squarely into the category of the Crich-type β-selective mannosylation when $Ph_3PAuOTf$ is used as the catalyst, wherein the mannosyl α-triflates are invoked. Replacement of the $^-$OTf in the Ph_3PAu^I catalyst with less nucleophilic counter anions, such as $^-NTf_2$, $^-SbF_6$, $^-BF_4$, and $^-BAr_4^F$, however, leads to the β-selective mannosylation with only the α-donors but a complete loss of β/α selectivity with the β-donors. It is found, unexpectedly, that the reactions with *ortho*-alkynylbenzoate α-donors under the catalysis of $Ph_3PAuBAr_4^F$ provide the coupled glycosides in significantly higher β/α selectivity compared to those with other Ph_3PAu^I complexes as catalyst. Under optimized conditions (Protocol A: $Ph_3PAuCl/AgBAr_4^F$ (0.28 M in Et_2O, 0.1 equiv), PhCl, 5 Å MS, −20 °C), the broad scope of the present reaction is testified by highly β-selective mannosylation with a range of donors and acceptors, including condensation with mannosyl donors bearing 4,6-di-*O*-benzoyl groups (**4α**) and sterically unmatched or hindered sugar acceptors (**6d** and **6g**). Especially surprising is that the β-selectivity remains satisfactory when the bulky TBS is installed at O3 in the *ortho*-alkynylbenzoate donor (**3α/β**), which is well documented to be detrimental in the Crich-type β-mannosylation. The *ortho*-alkynylbenzoate β-donors are readily anomerizable in the presence of the gold(I) catalyst into the α-counterparts, therefore given a period for anomerization before addition of acceptor (Protocol B) enables the highly β-selective mannosylation of the β-donors in the presence of $Ph_3PAuBAr_4^F$. In a practical manner, thus, the present β-selective mannosylation could be realized using anomeric mixtures of the *ortho*-alkynylbenzoates.

The 1-α-mannosyloxy-isochromenylium-4-gold(I) complex (**Cα**) is readily generated upon activation of the α-mannosyl *ortho*-alkynylbenzoate (**1α**) with $Ph_3PAuBAr_4^F$ at −35 °C, which has been well characterized by NMR spectroscopy for the first time. The occurrence of this species accounts for the high β-selectivity in the mannosylation. In the relevant reactions with poorer β/α selectivity, including those with β-mannosyl *ortho*-alkynylbenzoates (such as **1β**) as donors and with $^-NTf_2$, $^-SbF_6$, or $^-BF_4$ as the counter anion in the gold(I) catalyst, intermediates similar to **Cα** (or the α-triflate) are not detectable. Nevertheless, whether the β-mannosylation proceeds via an S_N2 substitution of the 1-α-mannosyloxy-isochromenylium-4-gold(I) complex (e.g., **Cα**) or via an S_N1 reaction via a CIP developed from the former, as in the Crich-type mannosylation, is yet to be clarified.

Acknowledgements

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Keywords: beta-mannopyranoside · glycosyl *ortho*-alkynylbenzoate · glycosylation · gold · non-coordinating counter anion

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