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Mechanistic Insights into the Gold(I)-Catalyzed Activation of Glycosyl *ortho*-Alkynylbenzoates for Glycosidation

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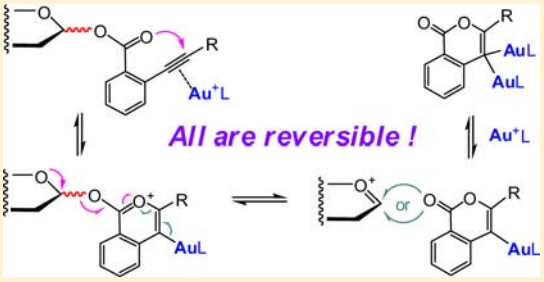
Supporting Information

ABSTRACT: Anomerization, which involves cleavage and formation of the anomeric C−O bond, is of fundamental importance in the carbohydrate chemistry. Herein, the unexpected gold(I)-catalyzed anomerization of glycosyl *ortho*-alkynylbenzoates has been studied in detail. Especially, crossover experiments in the presence of an exogenous isochromen-4-yl gold(I) complex confirm that the anomerization proceeds via the exocleavage mechanism, involving (surprisingly) the addition of the isochromen-4-yl gold(I) complex onto a sugar oxocarbenium (or dioxolenium) and an elimination of LAu^+ from the vinyl gold(I) complex. The inhibitory effect of the exogenous isochromen-4-yl gold(I) complex when in stoichiometric amount on the anomerization has guided us to disclose an isochromen-4-yl *gem*-gold(I) complex, which is inactive in catalysis but in equilibrium with the monogold(I) complex and the LAu^+ catalyst. The proposed key intermediate in the anomerization, a transient glycosyloxypyrylium species, is successfully trapped via a cycloaddition reaction with *n*-butyl vinyl ether as a dienophile. S_N2-like substitution of the initially formed glycosyloxypyrylium intermediate has then been achieved to a large extent via charging with acceptors in an excess amount to lead to the corresponding glycosides in a stereoselective manner.



INTRODUCTION

Homogenous gold(I)-catalyzed organic reactions have attracted tremendous attention in recent years.[1] Most of these transformations are initiated by the addition of heteroatom nucleophiles onto LAu^+ activated C−C π-bonds. A generic mechanism for the gold(I)-catalyzed nucleophilic addition onto alkynes is outlined in Figure 1. In that, the coordination of the

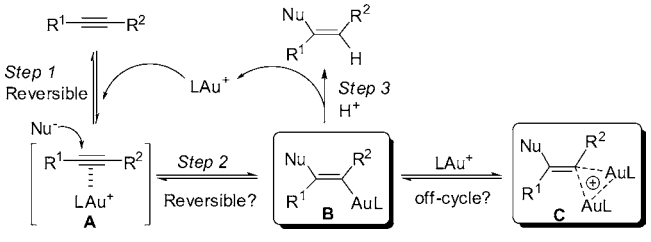


Figure 1. A generic mechanism for the gold(I)-catalyzed nucleophilic addition onto alkynes.

gold(I) cation to C−C triple bond is a reversible process (step 1), leading to the π-complex **A** as a transient intermediate.[2] Addition of a nucleophile onto the π-complex provides vinylgold(I) compound **B**. This key intermediate and the like have been isolated and characterized from a number of the gold(I)-catalyzed transformations since 2008.[3,4] In a few of the reactions the formation of the vinylgold(I) **B** (step 2) is also found to be reversible.[5−8] Protodeauration of **B** completes the nucleophilic addition reaction with regeneration of the gold(I) catalyst (step 3).[9] The three-center two-electron *gem*-diaurated complex **C** has recently been characterized experimentally.[8,10−19] Gagné, Fürstner, and co-workers proposed that the formation of the *gem*-diaurated species might compete with protodeauration and hence have an impact on the catalytic efficiency.[10,11] Nevertheless, in the gold(I)-catalyzed intramolecular allene hydroalkoxylation reaction, the bis(gold)vinyl species was found to be an off-cycle intermediate.[8,17] The occurrence of the *gem*-diaurated species and their roles in many other gold(I)-catalyzed transformations remains to be disclosed.[19b,20]

Recently, we developed a new glycosylation protocol with glycosyl *ortho*-alkynylbenzoates as donors and a gold(I) complex as catalyst (Figure 2).[21] The activation mechanism via an gold(I)-catalyzed intramolecular nucleophilic addition of alkynes is unprecedented in the glycosylation reactions.[22] Due to the avoidance of strong acidic, nucleophilic, or electrophilic species (compared to the classical glycosylation reactions), this new protocol shows a broad applicability in the synthesis of glycans and glycoconjugates.[21e] Especially, substrates vulnerable to acidic conditions have been glycosylated effectively with this method.[23] This new reaction also opens a new window to look into the mechanisms of both the gold(I) catalysis and the

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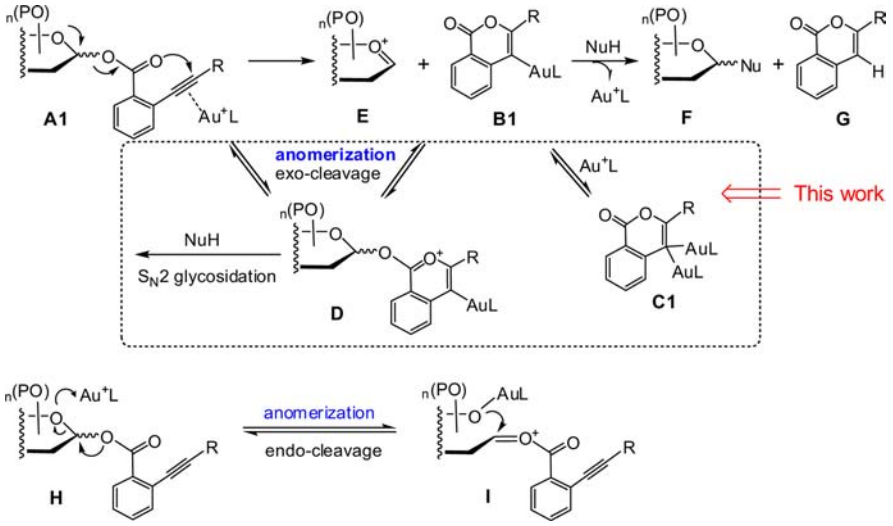

Figure 2. Gold(I)-catalyzed glycosylation reaction with glycosyl *ortho*-alkynylbenzoates as donors, the present findings, and the alternative endocleavage pathway for anomerization.

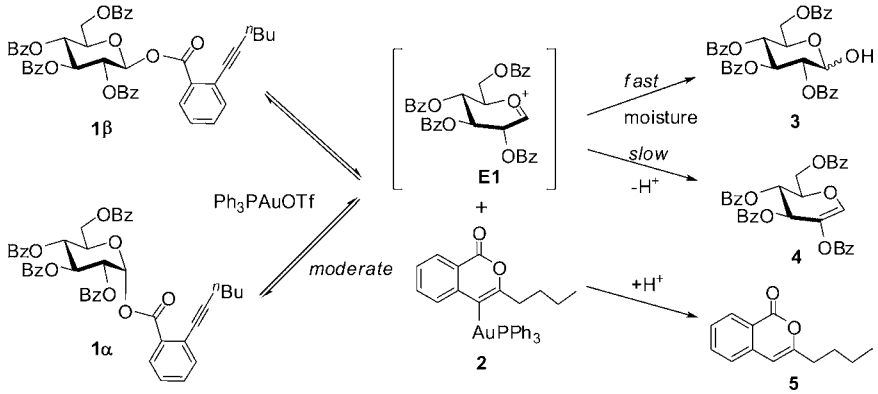

Figure 3. Major transformations of perbenzoyl glucopyranosyl *ortho*-hexynylbenzoates **1*β*** and **1*α*** in the presence of $Ph_3PAuOTf$.

glycosylation reaction. In this respect, we have disclosed that isochromen-4-yl gold(I) compound **B1** is a stable intermediate requiring H^+ to regenerate the LAu^+ catalyst,[24] and the gold(I) precatalysts, such as $Ph_3PAuOTf$, undergo hydration easily to form a series of the gold(I) oxo species.[25a] We have also disclosed the first experimental evidence for the remote participation of the 4-*O*-acyl group on the glycosidation of glucopyranosyl donors[26a] and a concentration effect on the remote participation of the 3-*O*-acyl group in the N-glycosidation of 2-deoxyfuranosyl donors.[26b]

During experimentation with the gold(I)-catalyzed glycosylation, we observed frequently the occurrence of anomerization of the glycosyl *ortho*-alkynylbenzoates. The anomerization of glycosides is well-known,[27,28] which proceeds via two alternative pathways with only a few exceptions.[29] In the presence of a protic or Lewis acid, glycosides undergo either a endo- or exocyclic cleavage pathway.[27,28] Either pathway if catalyzed by a gold(I) cation would be unusual, with the former (**H↔I**) involving (unlikely) an activation of the ring oxygen (instead of the alkyne) by gold(I) cation and the latter an nucleophilic addition of the isocoumarin (i.e., **E**+**B1**→**D**) and an elimination of the vinylgold(I) complex to alkyne (**D**→**A1**). This puzzle prompts us to make an intensive investigation of the gold(I)-catalyzed anomerization of glycosyl *ortho*-alkynylbenzoates. Herein we report the interesting findings.

RESULTS AND DISCUSSION

Transformation of Perbenzoyl Glucopyranosyl *ortho*-Hexynylbenzoates (1*β*/1*α*) in the Presence of $Ph_3PAuOTf$. A commonly used donor, perbenzoyl glucopyranosyl *ortho*-hexynylbenzoate (**1*β*/1*α***)[21] was first examined for its transformations under the typical gold(I)-catalyzed glycosylation reaction conditions (0.05 equiv $Ph_3PAuOTf$, CH_2Cl_2, rt) in the absence of an acceptor (Figure 3). Starting with either **1*β*** or **1*α***, a mixture of **1*α*/1*β*** resulted, in addition, lactol **3**, glycal **4**, and isocoumarin **5** were isolated. NMR monitoring of the reaction processes (0.015 equiv $Ph_3PAuOTf$, $CDCl_3$, 25 °C) revealed that the hydrolysis product **3** was formed within 5 min; the anomerization reached at a equilibrium (**1*α*/1*β*** = ~13:1) at about 1 h; the elimination reaction (leading to **4**) completed slowly in ~6 h; and isocoumarin **5** was formed in a similar rate as that of the formation of **4** and was obtained in nearly quantitative yield at last (Figure S4). The yield of the hydrolysis product (**3**) was dependent on the amount of moisture occurring in the reaction; exclusion of moisture (with freshly dried molecular sieves) could avoid largely the hydrolysis.

An HPLC approach was then set up to analyze accurately the processes of these gold(I)-catalyzed transformations. Thus, a small amount of the reaction mixture (~10 μL) was taken by syringe into a solution of acetonitrile containing (*p*-MeOPh)$_3$P

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(for quenching the reaction)[30] at intervals, and the resulting solution was directly subjected to HPLC analysis.[31] The yield and relative ratio of **1β** and **1α** together with the yields of glycal **4** and isocoumarin **5** as a function of time could then be recorded. To examine factors (including the gold(I) catalyst and its amount and the reaction solvent and temperature) that affect the reaction rate and equilibrium position, reactions (all started with **1β** at 0.10 mmol scale) under varied conditions were analyzed (Figure 4).

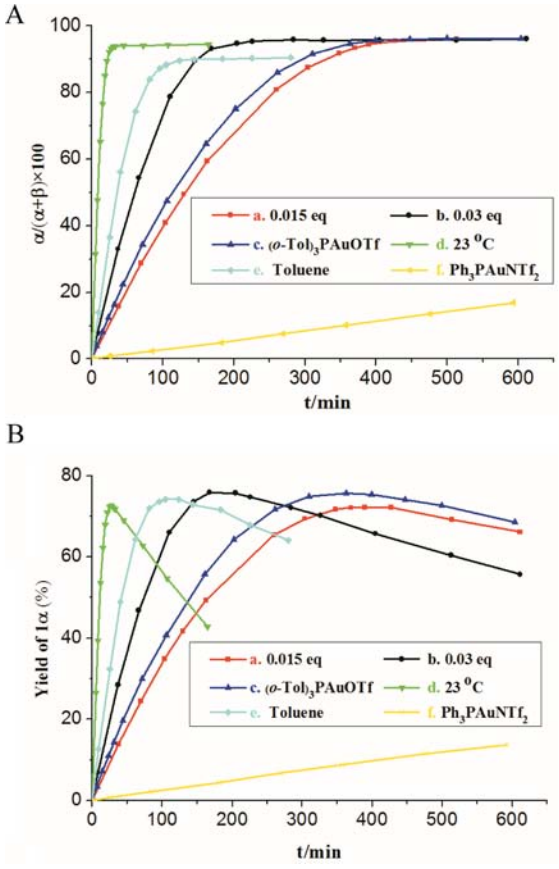


Figure 4. Kinetics of the transformations of glycosyl *ortho*-hexynylbenzoate **1β** in the presence of $R_3PAuOTf$ (or $Ph_3PAuNTf_2$) under varied conditions. (A) The percentage of **1α**/**1α** + **1β**; (B) the yield of **1α**, shown as a function of time. All the experiments were performed at 0.10 mmol scale in 0.55 mL solvent under conditions in contrast to $Ph_3PAuOTf$ (0.03 equiv)/CH_2Cl_2/0 °C (line b).

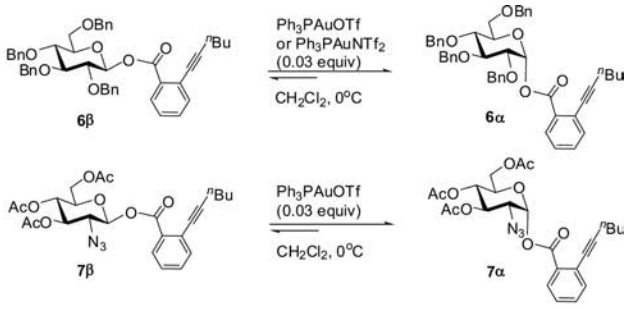
The anomerization proceeded smoothly, reaching equilibrium with **1α**/**1β** = 24:1 at ∼2.5 h, under the action of $Ph_3PAuOTf$ (0.03 equiv) in CH_2Cl_2 at 0 °C (Figure 4A, line b). As the percentage of **1α** increased, the rate of the anomerization decreased gradually. It was noted that the yield of **1α** decreased gradually after the equilibrium was reached (Figure 4B, line b), in accordance with the increased yield of the elimination product (Figure S2). When the loading of $Ph_3PAuOTf$ was decreased to 0.015 equiv, the anomerization reached equilibrium at ∼6.0 h, with the equilibrium position being unchanged (Figure 4A, line a). Switching the ligand in $Ph_3PAuOTf$ to the sterically hindered $(o\text{-Tol})_3P$ led to a much slower rate for the anomerization (Figure 4A, line c), nevertheless, the position of the equilibrium remained unchanged. Raising the reaction temperature from 0 to 23 °C resulted in a big increase of the anomerization rate and a slight shift of the equilibrium position from **1α**/**1β** = 24:1 to 16.5:1 (Figure 4A, line d). When the solvent was changed from CH_2Cl_2 to toluene, the anomerization also speeded up considerably, reaching the equilibrium at ∼1.5 h with the position of the equilibrium being shifted to **1α**/**1β** = 9.5:1 (Figure 4A, line e). These results show clearly that the rate of the anomerization is sensitive to all the reaction parameters, while the position of the equilibrium is only affected by the reaction solvent and temperature but not by the nature of the gold(I) catalyst and its loading, indicating a thermodynamically controlled process for the anomerization.

Surprisingly, when replacing $Ph_3PAuOTf$ with $Ph_3PAuNTf_2$ as the catalyst, the anomerization of **1β** (under otherwise identical conditions) was found to be much slower, with the ratio of **1α**/**1β** reaching only 1:4.9 after 10 h (Figure 4A, line f). Additionally, the elimination product (**4**) was not detected. The dramatic difference in the catalytic property of $Ph_3PAuOTf$ and $Ph_3PAuNTf_2$ in a few of other reactions has been disclosed.[32a] This might be attributed to the fact that $^-NTf_2$ is a much stronger coordinating anion than ^-OTf so that dissociation of $Ph_3PAuNTf_2$ is more difficult than that of $Ph_3PAuOTf$ to provide the catalytic species $[Ph_3PAu]^+$.[25,32b] The conjugated acids of ^-OTf and $^-NTf_2$ generated in situ might also play a role in the reaction[33,34] and cause the disparate rates of the present anomerization (HOTf is a much stronger acid than $HNTf_2$).[35] In fact, in the presence of 2,6-di-*tert*-butylpyridine (0.15 equiv) as a H^+ scavenger, the anomerization (of **1β**) under $Ph_3PAuOTf$ (0.03 equiv) still proceeded much faster than under $Ph_3PAuNTf_2$, nevertheless, both came to an early stop with all the Au(I) rested at isochromen-4-yl gold(I) **2** (Figure S3). Recharging a second portion of $Ph_3PAuOTf$ brought up a second round of anomerization. The stop of anomerization is because of depletion of the oxocarbenium **E1** (which undergoes decomposition to give glycal **4**) and the Au(I) catalyst (which rests as vinyl complex **2**). Without the base, the H^+ generated from the decomposition of **E1** would release the LAu^+ catalyst from vinyl complex **2** and thus ensure anomerization of the remaining **1β** to completion.

Another reason accounting for the disparate rate of anomerization catalyzed by $Ph_3PAuOTf$ and $Ph_3PAuNTf_2$ could be a disparate involvement of ^-OTf and $^-NTf_2$ in association with the oxocarbenium **E1** and a reactivity disparity of the resultant complexes (i.e., contact ion pairs, solvent-separated ion pairs, and covalent species) for anomerization.[36,37] It should also be noted that a sugar dioxolenium intermediate (not shown) developed from **E1** (via participation of the 2-*O*-benzoyl group) was believed to prevail over **E1** in the glycosylation reaction.[38] The involvement of the dioxolenium intermediate in the present anomerization (to afford the *β* anomer) seemed minimal in the presence of ^-OTf. However, this pathway could be competitive in the presence of $^-NTf_2$, leading to the apparent slow rate of anomerization. Thus, glycosyl *ortho*-alkynylbenzoates devoid of a 2-*O*-participating group were examined next.

Comparison on the Anomerization of 'Armed' and 'Disarmed' Glycosyl *ortho*-Alkynylbenzoates Catalyzed by $Ph_3PAuOTf/Ph_3PAuNTf_2$. Protecting groups on the glycosyl donors have a big impact on their reactivity in glycosidation. Thus, a donor, 'armed' with electron-donating protecting groups, could be activated for glycosidation selectively in the presence of another donor bearing the same leaving group but 'disarmed' with electron-withdrawing protecting groups.[39] Such a disparity of donor reactivity was

examined in the present gold(I)-catalyzed anomerization, employing 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl *ortho*-hexynylbenzoate (**6**) as a 'armed' donor and 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-glucopyranosyl *ortho*-hexynylbenzoate (**7**) as a 'disarmed' counterpart, which are devoid of the possibility of neighboring group participation (cf., **1**). The anomerization processes starting from **6*β*** or **7*β*** were monitored by HPLC (as previously described for donor **1*β***) comparatively under identical conditions (0.10 mmol donor in 0.55 mL CH_2Cl_2, 0.03 equiv $Ph_3PAuOTf/Ph_3PAuNTf_2$, 0 °C) (Figure 5). The 'armed' donor **6*β*** underwent anomerization extremely fast, reaching the equilibrium at only ~3.5 min with **6*α***/**6*β*** = 11.8:1. The 'disarmed' donor **7*β*** (so as the 'disarmed' donor **1*β***) underwent anomerization in a much slower rate, with the equilibrium being reached at ~3 h (**7*α***/**7*β*** = 8.1:1). The yields of **7*α*** increased gradually before the equilibrium and remained unchanged afterward. This indicates that donor **7** is resistant to elimination under catalytic amount of $Ph_3PAuOTf$.



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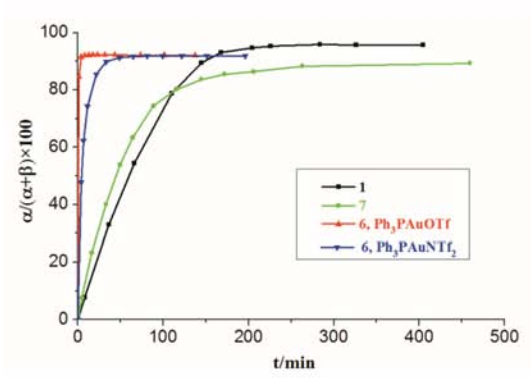

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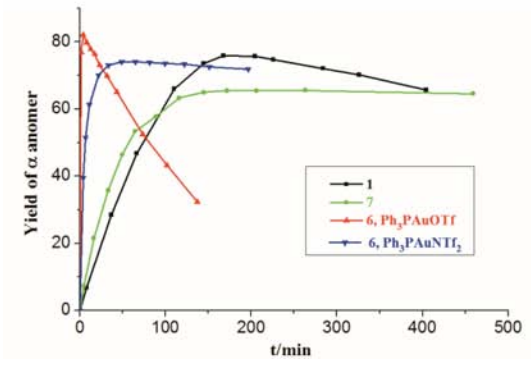

Figure 5. Anomerization of glycosyl *ortho*-alkynylbenzoates **6** and **7** (as well as **1**) catalyzed by $Ph_3PAuOTf/Ph_3PAuNTf_2$. (A) The percentage of the α-anomers; (B) the yield of the α-anomers, shown as a function of time.

Compared to the reaction with $Ph_3PAuOTf$ as catalyst, the anomerization of the 'armed' donor **6*β*** in the presence of $Ph_3PAuNTf_2$ under otherwise identical conditions was found to proceed at a much slower rate, reaching equilibrium after ~30 min, nevertheless, the position of the equilibrium remained essentially unchanged (**6*α***/**6*β*** = 11.3:1; Figure 5). In this case, the possibility of neighboring participation (as in the previous anomerization of **1*β***) is ruled out, therefore, we could conclude confidently that $Ph_3PAuOTf$ is indeed a stronger catalyst than $Ph_3PAuNTf_2$ for the present anomerization reaction. In addition, in the presence of $Ph_3PAuOTf$ the yields of **6*α*** decreased sharply after the equilibrium due to formation of the elimination product, in contrast, **6*α*** stayed nearly intact in the presence of $Ph_3PAuNTf_2$.

Anomerization Involves a Reversible C–Au Bond Formation/Cleavage. The mechanism of the present gold(I)-catalyzed anomerization was puzzling. If it proceeded (and most likely it did) via an exocleavage pathway (Figure 2), a nucleophilic addition of the isochromen-4-yl gold(I) complex **B1**[24,40] onto sugar oxocarbenium **E** as well as an elimination of the LAu^+ from vinyl gold(I) intermediate **D** (to give back alkyne **A1**) should take place. To prove this process, anomerization in the presence of an exogenous isochromen-4-yl gold(I) complex was examined (Figure 6). The corresponding scrambling glycosyl *ortho*-alkynylbenzoates were constantly isolated, confirming therefore unambiguously this mechanistic proposal.

Unexpectedly, the anomerization in the presence of an exogenous isochromen-4-yl gold(I) complex (so that the concentration of one reactant is greatly increased) was found to be not faster but much slower compared to the previous reaction without the additional isochromen-4-yl gold(I) complex. Some comparable results are depicted in Figure 6, in that all the reactions were carried out under similar conditions (30 mg donor in 0.8 mL CH_2Cl_2, 4 Å MS, 0 °C), and the yields and α/β ratio were determined accurately by HPLC analysis.[31] A 0.1 equiv of $Ph_3PAuOTf/Ph_3PAuNTf_2$ was used instead of the 0.03 equiv in the previous anomerization reactions to enable the present anomerization (in the presence of an equal equivalent of the isochromen-4-yl-gold(I) derivative **2**)[24] proceed in an appreciable rate.

Thus, treatment of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranosyl *ortho*-cyclopropylethynylbenzoate (**8*β***) and gold(I) complex **2** with 0.1 equiv $Ph_3PAuOTf$ for 2 h led to the scrambling product **7** in 10% yield (α/β = 1:1.8), with **8*β*** remaining largely intact (80%, α/β = 1:110). Replacing $Ph_3PAuOTf$ with $Ph_3PAuNTf_2$, **7** was also indentified, although in only 2% yield (α/β = 2.5:1); the yield of **7** could be increased to 15% (α/β = 4.7:1) when the reaction was carried out at 26 °C for 4 h.[31] The scrambling product **7** was not detected when the gold(I) complex **2** was replaced with isocoumarin **5**. In the absence of $Ph_3PAuOTf$ or $Ph_3PAuNTf_2$, no reaction took place. These results support strongly the proposed exocleavage pathway. It was noted that the anomerization was greatly inhibited by the additional vinyl gold(I) complex **2**, leading to the large recovery of the starting β-anomer. In comparison, in the absence of **2**, the anomerization of **8*β*** reached at α/β = 2.0:1 (cf., α/β = 1:110 in the presence of **2**) with $Ph_3PAuOTf$ and at α/β = 1:54.6 (cf.,

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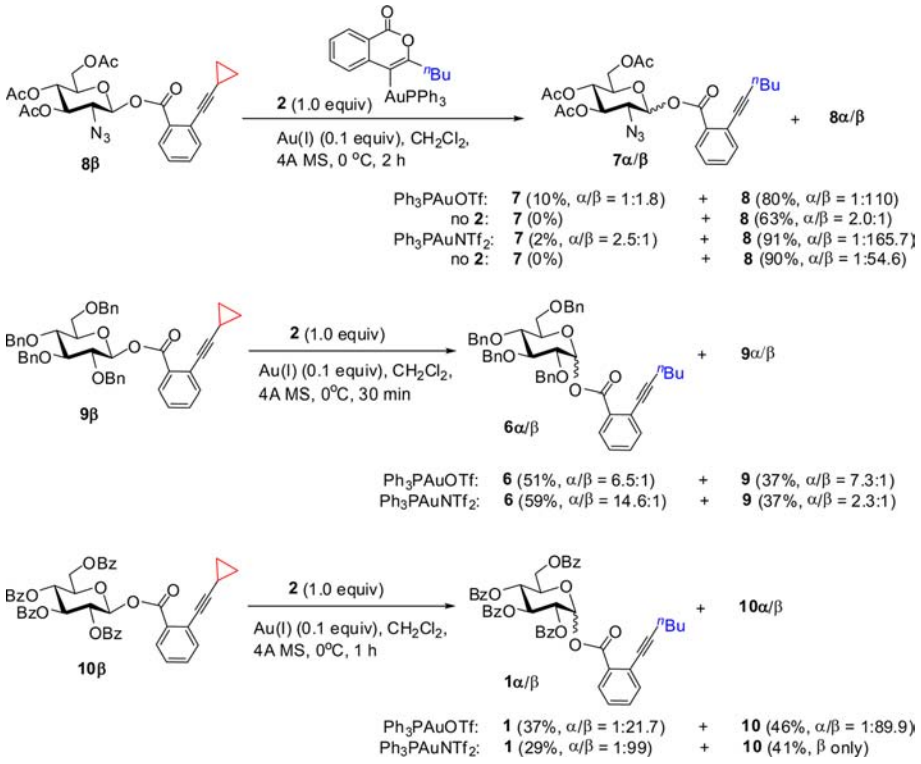

Figure 6. The gold(I)-catalyzed anomerization of glycosyl *ortho*-cyclopropylethynylbenzoates (**8*β*-10*β***) in the presence of an exogenous isochromen-4-yl gold(I) complex **2**. The hydrolysis product turned out to be the major byproduct in those cases where the recovery yield was low.

α/β = 1:165.7 in the presence of **2**) with $Ph_3PAuNTf_2$ as the catalyst.

The anomerization reaction of the 'armed' **9*β*** proceeded rather smoothly in the presence of 1.0 equiv isochromen-4-yl-gold(I) complex **2** catalyzed by either $Ph_3PAuOTf$ or $Ph_3PAuNTf_2$. The scrambling product **6** was formed in high yield in 0.5 h and predominantly in its α anomer (51%, α/β = 6.5:1 with $Ph_3PAuOTf$ and 60%, α/β = 14.6:1 with $Ph_3PAuNTf_2$), with the recovery **9** also existed predominantly in its α anomer (α/β = 7.3:1 with $Ph_3PAuOTf$ and α/β = 2.3:1 with $Ph_3PAuNTf_2$).

The anomerization reaction of the 'disarmed' **10*β*** in the presence of 1.0 equiv gold(I) complex **2** led to 37% yield of the scrambling product **1** (α/β = 1:21.7) under the action of $Ph_3PAuOTf$ and to 28% yield of **1** (α/β = 1:99) under $Ph_3PAuNTf_2$ in 1 h. Interestingly, both the scrambling product **1** and the recovery **10** were predominantly in their β anomers; in fact, with $Ph_3PAuNTf_2$ as the catalyst, **10*α*** was not detected at all. These results imply that the isochromen-4-yl gold(I) complexes add onto the sugar dioxolenium intermediate predominantly rather than onto the sugar oxocarbenium **E**. Because of the overwhelming presence of the exogenous isochromen-4-yl gold(I) complex **2**, the anomerization of the starting β-anomer (requiring addition with the transient endogenous isochromen-4-yl gold(I) complex) becomes even more negligible. Additionally, the reaction pathway via the dioxolenium intermediate is even more favorable under the catalysis of $Ph_3PAuNTf_2$ than under $Ph_3PAuOTf$.

Characterization of a *gem*-Diaurated Species (11). The inhibitory effect of the additional isochromen-4-yl gold(I) complex (i.e., **2**) on the gold(I)-catalyzed anomerization reaction was unexpected. This promoted us to investigate the additional role of this key intermediate in the present gold(I)-catalyzed process. Thus, a solution of the 2-azido-glucosyl *ortho*-hexynylbenzoate **7*α***, which proceeded anomerization at a slow rate without formation of glycal in the previous experiments, was monitored by NMR measurement in the presence of 1.1 equiv of $Ph_3PAuNTf_2$ in $CDCl_3$ at rt. ^{31}P NMR revealed formation of a new gold(I) species with a small singlet at 37.1 ppm, which disappeared after consumption of the substrate (Figure S6).[41,42] This new species corresponded to the appearance of a triplet at 3.05 ppm in the ^1H NMR spectra. The same species was also detected during the anomerization of **7*β*** under similar conditions (Figure S5). MALDI/TOF MS analysis of the reaction mixture revealed a weak peak at m/z = 1119.2057, in accordance to the *gem*-diaurated complex **11**.

The putative *gem*-diaurated complex **11** was then synthesized and fully characterized (Figure 7). Thus, dissolving an equal molar mixture of complex **2** and $Ph_3PAuNTf_2$ in $CDCl_3$ resulted in a nearly quantitative formation of the *gem*-diaurated complex **11**, as shown by ^1H NMR measurement. After many attempts, single crystals of complex **11** suitable for X-ray diffraction analysis were obtained by slow diffusion of *n*-hexane into a CH_2Cl_2-toluene solution of **11** at 0 °C.[43]

The distance between the two gold centers in complex **11** [2.7315(9) Å] shows a strong aurophilic interaction, with the Au1−C1−Au2 angle of 78.6(5)°, consistent with those of the previously reported *gem*-diaurated complexes.[42] A comparison between the crystal structures of *gem*-diaurated complex **11** and its monoaurated precursor **2**[24] provides additional structural information. The Au−C distances of 2.181(15) and 2.131(15) Å in complex **11** are slightly longer than that found in the monoaurated precursor **2**, at 2.068(7) Å. Remarkably, the C−Au−P angles in complex **11** are not equal, with C1−Au1−P1 170.7(4)° and C1−Au2−P2 177.5(4)°, smaller than in the linear structure (180°), whereas in complex **2**, the angle is

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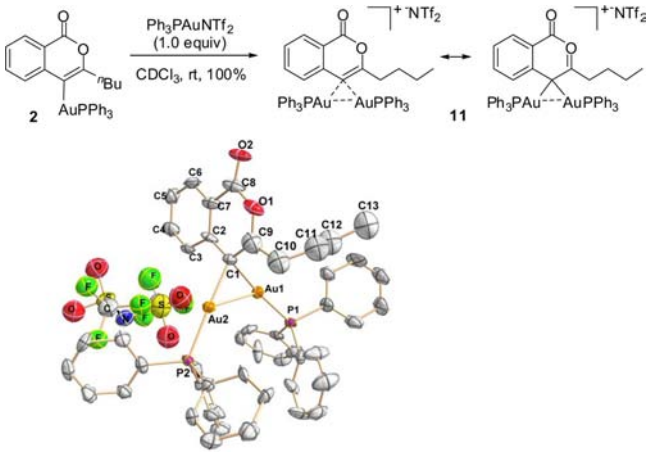
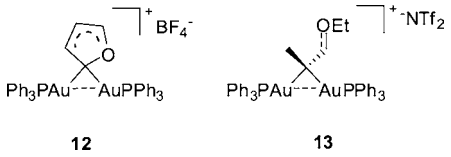


Figure 7. Preparation of *gem*-diaurated complex **11** and its ORTEP diagram with 50% probability ellipsoids (hydrogen atoms are omitted for clarity). Key bond lengths (Å) and angles (°): Au1−Au2 2.7315(9), Au1−C1 2.181(15), Au2−C1 2.131(15), Au1−P1 2.264(4), Au2−P2 2.277(4), C1−C9 1.37(3), C9−C10 1.51(4), O1−C9 1.36(3), O1−C8 1.41(3), O2−C8 1.19(2), C1−Au1−P1 170.7(4), C1−Au2−P2 177.5(4), Au2−C1−Au1 78.6(5), C9−C1−C2 114.5(17).

176.0(2)°. The diauration also results in a change of bond lengths in the isocoumarin ring, with a lengthening of C1−C9 and O1−C8 distances from 1.351(13) to 1.37(3) Å and 1.366(15) to 1.41(3) Å, and a shortening of O1−C9 and O2−C8 distances from 1.409(11) to 1.36(3) Å and 1.222(11) to 1.19(2) Å on going from monoaurated complex **2** to *gem*-diaurated complex **11**. This observation indicates clearly a partial charge delocalization over the isocoumarin ring in *gem*-diaurated complex **11**, which contains an oxygen atom at the adjacent position, analogous to the complexes reported by Schmidbaur and Fürstner et al.[11,19,42d] The extent of charge delocalization in complex **11**, however, is intermediate between Schmidbaur complex **12** and Fürstner complex **13**, with the former shows bond length change of about ∼2 pm, while the latter shows ∼10 pm in bond length change.



12 **13**

In solution ($CDCl_3$), the ^{31}P NMR spectra of complex **11** showed a broad singlet at 37.1 ppm, indicating the occurrence of a dynamic equilibrium (vide infra). The ^{1}H NMR signals of the isocoumarin ring in **11** shifted downfield compared to those in complex **2**. The allylic H10 showed a characteristic triplet at 3.05 ppm, which is downfielded by 0.23 ppm from its position in vinyl gold(I) precursor **2** (2.82 ppm), whereas the methyl protons H13 shifted upfield from 0.89 ppm (in complex **2**) to 0.76 ppm. Similar trends were observed in the ^{13}C NMR spectra, where the allylic carbon C10 shifted downfield from 38.17 ppm (in complex **2**) to 41.21 ppm, whereas the carbonyl carbon C8 and the methyl carbon C13 shifted upfield from 165.13 and 14.10 ppm (in complex **2**) to 160.77 and 13.75 ppm, respectively.

The dynamics of complex **11** in solution was then investigated by NMR spectroscopy. Experimentally, portions of $Ph_3PAuNTf_2$ were added gradually to a $CDCl_3$ solution of complex **2**, and the ^{1}H and ^{31}P NMR spectra were recorded after each addition. The ^{31}P NMR signal of **2** at 45.1 ppm decayed, while that of **11** at 37.1 ppm enhanced along with each addition of $Ph_3PAuNTf_2$. The signal of **2** disappeared after more than 1 equiv of $Ph_3PAuNTf_2$ was added, while the signal of $Ph_3PAuNTf_2$ at 30.7 ppm started to appear. Coalesced signals were observed in the ^{1}H NMR spectra before <1 equiv of $Ph_3PAuNTf_2$ was added, in that the allylic H10 exhibited a broad singlet between the H10 signal in complex **2** (2.82 ppm) and in complex **11** (3.05 ppm, Figure S9A). In the ^{13}C NMR spectra, each carbon of the *n*-butyl group showed only one signal in the presence of substoichiometric amount of $Ph_3PAuNTf_2$, especially the allylic C10 and the adjacent C11 showed board yet weak signals. These results prove again the existence of a dynamic equilibrium of the *gem*-diaurated complex and its monoaurated precursor in solution (Figure S9B), that has been described by Nesmeyanov et al.,[44] Schmidbaur et al.,[45] and recently Gagné et al.[10] Interestingly, addition of more than 1 equiv of $Ph_3PAuNTf_2$ into complex **2** led to a further slightly downfield shift of the H10 signal from 3.050 ppm (at 1.0 equiv) to 3.063 ppm (at 1.91 equiv). This result suggests a partial dissociation of complex **11** in solution (Figure S8).[46]

Trapping of a Glycosyloxypyrylium Intermediate. The key intermediate, which is the glycosyloxypyrylium gold(I) complex **D** (Figure 2), in the present anomerization reaction was left undetected in the NMR measurement, owing conceivably to its short lifetime and low concentration in the

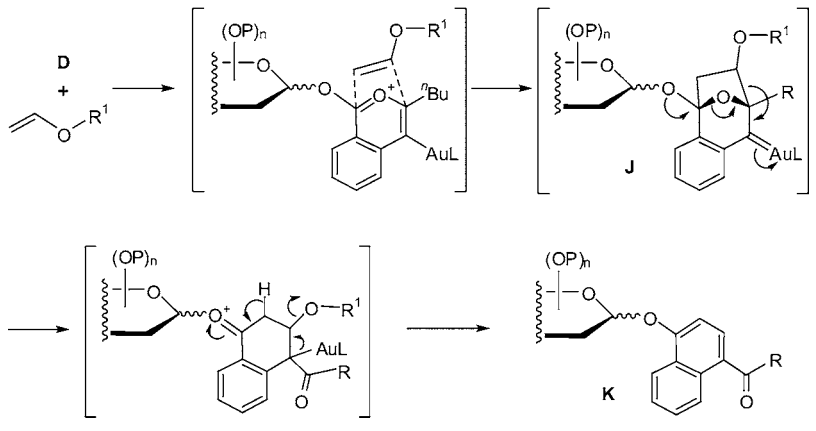


Figure 8. A proposed transformation of the glycosyloxypyrylium intermediate **D** with a vinyl ether.

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reaction mixture. To prove the occurrence of this transient species, we sought to trap it via a chemical transformation. Iwasawa et al. have reported a Pt(II)-catalyzed condensation of *ortho*-alkynylbenzoates with vinyl ethers to provide 1-acyl-4-alkyoxynaphthalenes (**K**), in that a [3 + 2]-cycloaddition of the alkyloxypyrylium salts (analogous to **D**) with vinyl ethers (followed by 1,2-alkyl-migration and subsequent eliminations) was involved (Figure 8).[47,48] However, a similar reaction of a glycosyl *ortho*-alkynylbenzoate with a vinyl ether would be complicated by easy degradation of the glycosyloxypyrylium intermediate **D** (Figures 2 and 3), including the elimination and hydrolysis reactions (to give the corresponding glycal and lactol, respectively).

Thus, the 2-azido-glucopyranosyl *ortho*-hexynylbenzoate **7**, which was previously found to be resistant to elimination, was selected as the substrate and 4 Å MS (300% w/w) was added in the reaction to prevent hydrolysis by exclusion of moisture (Figure 9). Experimentally, a toluene solution of the pure

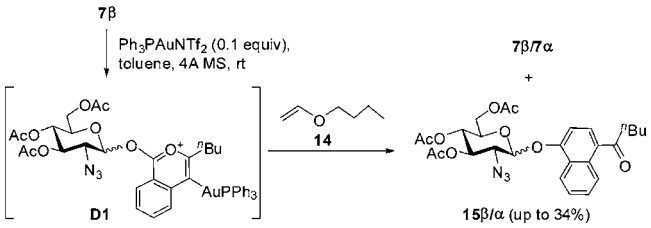
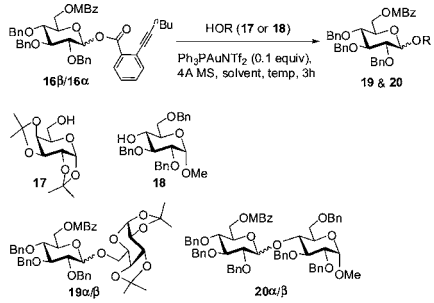


Figure 9. Trapping of the glycosyloxypyrylium intermediate **D1** via cycloaddition with vinyl ether **14** and cascade transformations.

anomer **7*β*** and vinyl ether **14** (2 equiv) was dried by 4 Å MS (300% w/w) for 1 h, and then $Ph_3PAuNTf_2$ (0.1 equiv) was added. As shown on TLC, the anomerization proceeded as under the previous conditions, however, the desired naphthalene glycoside **15** was not detected within 4 h. A second portion of vinyl ether (8 equiv) was then added, gratifyingly, the desired product **15** was then detected and finally isolated in 12% yield (α/β = 5.6:1, with **7** being recovered in 42% yield with α/β = 9.3:1). Further experiments showed that the yield of **15** was dependent on the level of anomerization at the time of the addition of vinyl ether **14**. Thus, addition of vinyl ether after 0.6 h at the time the **7*α*/7*β*** ratio reached 2.7:1 led to only 2% of **15** (α/β = 5:1) with 40% recovery of **7** (α/β = 5.3:1). In comparison, addition of the vinyl ether after 4 h when the anomerization reached equilibrium resulted in 20% of **15** (α/β = 10:1) with 27% recovery of **7** (α/β = 11.4:1). By addition of vinyl ether **14** (40 equiv) into an equilibrated anomerization mixture of **7** in four equal portions at intervals of 1 h, we managed to isolate **15** in 34% yield (α/β = 13:1). These results confirm the occurrence of the glycosyloxypyrylium intermediate (i.e., **D**) in the anomerization process and indicate that the α-glycosyloxypyrylium intermediate occur (and react with vinyl ether) favorably compared to its β-counterpart.

S_N2-Like Glycosylation under Forced Conditions. Now that the activation of a glycosyl *ortho*-alkynylbenzoate with LAu^+ does lead to the glycosyloxypyrylium intermediate (i.e., **D**), a stereoselective glycosidation via S_N2-like substitution of this intermediate should be possible.[22,49] Nevertheless, it is required that the glycosidation takes place on the glycosyloxypyrylium intermediate or a contact ion pair before it falls apart to the solvent-separated oxocarbenium species (i.e., **E**).[22,36,49] With a pair of the easily available glycosyl *ortho*-hexynylbenzoate anomers **16*β*** and **16*α*** as donors and two sugar alcohols **17** and **18** representing good and poor nucleophiles, respectively, we examined the stereochemistry outcomes of their glycosylation reactions (Figure 10).



entry	donor	acceptor (equiv)	solvent	temp.	product (yield)[a]	α/β[b]
1	**16β**	**17** (1.0)	CH_2Cl_2	0°C	**19** (89%)	3.7:1
2		**17** (10.0)	CH_2Cl_2	0°C	**19** (99%)	18:1
3		**17** (10.0)	CH_2Cl_2	-20°C	**19** (99%)	24:1
4		**17** (10.0)	CH_2Cl_2	27°C	**19** (99%)	13:1
5		**17** (10.0)	Et_2O	0°C	**19** (55%)[d]	7.9:1
6		**18** (1.0)	CH_2Cl_2	0°C	**20** (91%)	3.7:1
7		**18** (10.0)	CH_2Cl_2	0°C	**20** (99%)	7.0:1
8	**16α**	**17** (1.0)	CH_2Cl_2	0°C	**19** (89%)	1.3:1
9		**17** (10.0)	CH_2Cl_2	0°C	**19** (97%)	1:3.7
10[c]		**17** (10.0)	CH_2Cl_2/*n*-hexane	-20°C	**19** (90%)	1:14
11[c]		**18** (1.0)	CH_2Cl_2/*n*-hexane	-20°C	**20** (86%)	1:0
12[c]		**18** (10.0)	CH_2Cl_2/*n*-hexane	-20°C	**20** (94%)	3.8:1

Figure 10. S_N2-like glycosidation of *ortho*-alkynylbenzoate donor **16*α*/*β*** driven by a large excess (10 equiv) of the acceptors. (a) Isolated yield. (b) The α/β ratio was determined by ^1H NMR measurement. (c) 0.2 equiv of $Ph_3PAuNTf_2$ was used. (d) 44% **16** was recovered.

The glycosidation of **16*β*** with **17** (1.0 equiv) under usual conditions (0.1 equiv $Ph_3PAuNTf_2$, 4 Å MS, CH_2Cl_2, 0 °C) led to the coupled disaccharide **19** in good yield and poor stereoselectivity (α/β = 3.7:1; entry 1). This α/β ratio is indicative of a S_N1 glycosidation (and the present anomerization as well via oxocarbenium **E**) which favors formation of the α anomer due to the anomeric effect.[50] Simply increasing the amount of acceptor **17** to 10.0 equiv resulted in a remarkable increase of the α/β ratio of the disaccharide (α/β = 18:1; entry 2).[51] It is known that a S_N2 reaction is favored at lower reaction temperature and less polar solvent. Indeed, the condensation of **16*β*** and **17** at −20 °C led to further increase of the α-selectivity (α/β = 24:1; entry 3), while at 27 °C led to decrease of the α-selectivity (α/β = 13:1; entry 4); and the reaction with Et_2O as solvent led to a considerable decrease of the α-selectivity (α/β = 7.9:1; entry 5). Under the fixed reaction conditions (0.1 equiv $Ph_3PAuNTf_2$, 4 Å MS, CH_2Cl_2, 0 °C), the glycosidation of **16*β*** with the poorly nucleophilic glucose-4-OH derivative **18** led to similar results as with **17** as the acceptor. Thus, in the presence of 1 equiv of **18**, the coupled disaccharide **20** was obtained in a α/β ratio of 3.7:1 (entry 6); and the α/β ratio of **20** was increased remarkably to a high 7.0:1 when 10.0 equiv of **18** was charged (entry 7).

The S_N2-like glycosidation of **16*α*** to give the corresponding β-glycoside would be much more difficult, because the corresponding α-glycosyloxypyrylium is more stable than its

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β-counterpart and thus reluctant to undergo substitution. The condensation of **16α** with **17** (1.0 equiv) under usual conditions led to **19** in poor stereoselectivity (α/β = 1.3:1; entry 8). This outcome implies that a certain extent of S_N2 glycosidation does occur, if compared to the higher α selectivity (α/β = 3.7:1) resulted from the reaction of **16β** under identical conditions (entry 1). Increasing the amount of acceptor **17** to 10 equiv, the β-selective glycosidation was achieved (α/β = 1:3.7; entry 9). Under more favorable conditions for a S_N2 reaction (with 0.2 equiv of the precatalyst $Ph_3PAuNTf_2$ in a less polar solvent CH_2Cl_2/*n*-hexane (1:4) and at a lower temperature of −20 °C), the condensation of **16β** and **17** furnished disaccharide **19** in an excellent β-selectivity (α/β = 1:14; entry 10). Under this optimized set of conditions, the glycosidation of **16α** with the poorly nucleophilic sugar alcohol **18**, however, led to the α-product predominantly even in the presence of 10 equiv of the acceptor. Nevertheless, the increase of the amount of acceptor **18** (from 1.0 to 10.0 equiv) did led to a remarkable increase of the β-product (from α only to α/β = 3.8:1; entries 11 and 12).

CONCLUSION

The gold(I)-catalyzed glycosylation reaction with *ortho*-alkynylbenzoates as donors has recently been proven to be a versatile method for the synthesis of various glycosidic linkages, including remarkably those vulnerable to acidic conditions. Herein we studied in details the gold(I)-catalyzed transformation of *ortho*-alkynylbenzoates in the absence of acceptor, that is disclosed to be mainly the anomerization. An exocleavage mechanism, as shown in Figure 2, has been proved for the anomerization. Thus, LAu^+ coordinated to the C−C triple bond installed in the glycosyl *ortho*-alkynylbenzoate (**A1**, either α or β anomer); the activated triple bond induced an intramolecular nucleophilic addition of the benzoyl oxygen, leading to the 1-glycosyloxy-isochromenylium-4-gold(I) complex **D** (which was proven by tripping via a cycloaddition with a vinyl ether); the resulting glycosyloxypyrylium fall apart quickly to give sugar oxocarbenium **E** and isochromen-4-gold(I) complex **B1** (which has been characterized previously and prepared readily); significantly, **E** and **B1** underwent S_N1-type nucleophilic addition to provide the glycosyloxypyrylium **D** as a mixture of the α and β anomers (that was proven by crossover experiments with an exogenous **B1** congener); and the vinyl gold(I) complex **D** then underwent elimination to give the alkyne derivative **A1**. Through these reversible steps (glycosyl *ortho*-alkynylbenzoate + LAu^+ ↔ **A1** ↔ **D** ↔ **E** + **B1**), anomerization reached finally to an equilibrium. In addition, the isochromen-4-yl *gem*-gold(I) complex **C1** was characterized and found to be in equilibrium with the vinyl gold(I) complex **B1** (**B1** + LAu^+ ↔ **C1**). These two gold(I) complexes were proved to be inactive species in the catalysis; the *gem*-gold(I) complex **C1** could release readily the catalytic LAu^+ and monogold(I) **B1**, while **B1** required H^+ to release LAu^+ and isocoumarin **G**.

Additionally, $Ph_3PAuOTf$ has been disclosed to be a stronger precatalyst than $Ph_3PAuNTf_2$ in the present anomerization reaction, and the weaker $Ph_3PAuNTf_2$ facilitates the addition of isochromen-4-yl gold(I) complex **B1** onto the sugar dioxolenium intermediate (if a neighboring participating acyl group was equipped at the sugar moiety) instead of the sugar oxocarbenium **E**, leading to an apparent slow rate of the anomerization.

It should be noted that all these intermediates and reversible steps would be involved in the glycosylation reaction when an acceptor is added. Therefore, understanding this anomerization process shall help to find solutions to address the problems in glycosylation reactions. As a preliminary effort, we attempted at S_N2-like glycosylation via intercepting the initially formed glycosyloxypyrylium intermediate (**D**). With a good nucleophile and in an excess amount (10 equiv), high α-selective glycosylation from the β-glycosyl *ortho*-alkynylbenzoate or high β-selective glycosylation from its α-counterpart has been showcased, although the scope awaits as a subject of future research.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data, and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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