Glycosylation

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Characterization of the Isochromen-4-yl-gold(I) Intermediate in the Gold(I)-Catalyzed Glycosidation of Glycosyl *ortho*-Alkynylbenzoates and Enhancement of the Catalytic Efficiency Thereof**

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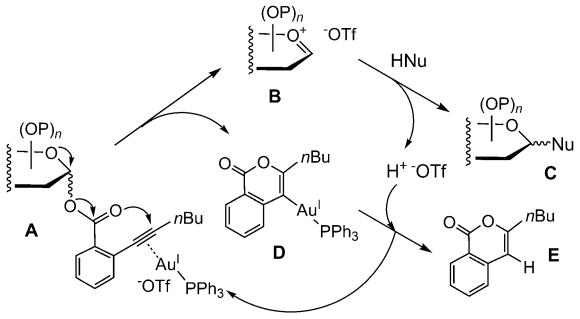
We have recently developed a new glycosylation protocol with glycosyl *ortho*-alkynylbenzoates as donors and a gold(I) complex (e.g., [$Ph_3PAuOTf$], $OTf = O_3SCF_3$) as catalyst.[1] The power and versatility of this gold(I)-catalyzed glycosylation method have been demonstrated in the effective construction of a wide variety of glycosidic linkages and the total synthesis of complex oligosaccharides and glycoconjugates.[1–6] Moreover, the unprecedented activation mechanism has endowed this protocol with unique merits, including 1) the absence of competitive nucleophilic species (which usually occur in the leaving entity or promoter in classical glycosylation reactions), which enables glycosylation-initiated polymerization of tetrahydrofuran to proceed smoothly;[3] 2) the lack of deteriorative electrophilic species (such as the soft Lewis acidic species used as promoters in classical glycosylation reactions), which enables flavonol 3-OH derivatives vulnerable toward electrophiles to be glycosylated efficiently;[4] and 3) the mild and nearly neutral conditions, which allow the extremely acid-labile aglycones, such as the *N*-Boc-protected purine derivatives (Boc = *tert*-butoxycarbonyl) and dammarane derivatives, to be glycosylated effectively.[5,6]

This glycosylation protocol has been developed on the basis of mechanistic rational as depicted in Scheme 1.[1b] Activation of the C–C triple bond positioned in the *o*-alkynylbenzoate moiety in donor **A** with a gold(I) complex (e.g., [$Ph_3PAuOTf$]) led to isochromen-4-yl-gold(I) complex **D** and sugar oxocarbenium ion **B**. Capture of the putative sugar oxocarbenium species **B** or related intermediates[7] by the nucleophilic acceptor HNu provided glycoside **C**. The H^+ released from HNu then protodeaurated the vinyl gold(I) complex **D** to give isocoumarin **E** with regeneration of the active Au^I species to complete the catalytic cycle. Activation of a C–C triple bond with gold(I) species toward nucleophilic attack has been reported for numerous gold(I)-catalyzed transformations.[8] Recently, a few of the proposed vinyl gold(I) intermediates in these transformations were characterized.[9] Herein we report the isolation and characterization of the isochromen-4-yl-gold(I) intermediate **D**, which has enabled us to gain insight into the detailed catalytic cycle so as to provide a solution to enhance the catalytic efficiency of the gold(I)-catalyzed glycosylation reaction.



Scheme 1. The proposed mechanism for the gold(I)-catalyzed glycosidation of glycosyl *o*-alkynylbenzoates.

Unexpected but easily understandable results were obtained when we attempted to glycosylate with 3,4,6-tri-*O*-acetyl-2-deoxy-2-*p*-methoxybenzylideneamino-β-D-glucopyranosyl-*o*-hexynylbenzoate (**1**) as donor (Scheme 2).[10] Under the normal conditions (0.1 equiv [$Ph_3PAuOTf$], toluene, 4 Å molecular sieves (M.S.), RT),[1] the coupling reaction of donor **1** with *n*-pentenol (**2**) was hardly observable; upon raising the loading of the gold(I) catalyst to 0.5 equiv, the reaction proceeded smoothly, albeit leading to the β-glycoside **3** and α-glycoside **4** in 37 and 47% yield, respectively (within 4 h). The α-glycoside **4** was assumed to be derived from the corresponding 2-*p*-methoxybenzylideneamino-α-glucoside by hydrolysis of the *N*-*p*-methoxybenzylidene group. It has been shown that the 2-*N*-substituent in α-D-glucosamine derivatives is much more labile than the corresponding 2-*N*-substituent in the β-counterpart.[11] Hydrolysis of the imine consumed H^+ generated in situ; thus, protodeauration of the isochromen-4-yl-gold(I) complex **5** (i.e., intermediate **D** in Scheme 1) to regenerate the active $[Ph_3PAu]^+$ would be hampered, leading to a stop of the activation of the donor and accumulation of the gold(I) complex **5**. Indeed, we managed after many attempts to isolate the desired gold(I) complex **5** in a high 91% yield (based on the amount of starting [$Ph_3PAuOTf$]) by flash chromatography on silica gel. Complex **5** was unambiguously characterized by spectroscopic (^1H, ^{13}C, and ^{31}P NMR and MS) and X-ray diffraction analysis (Figure 1).[12]

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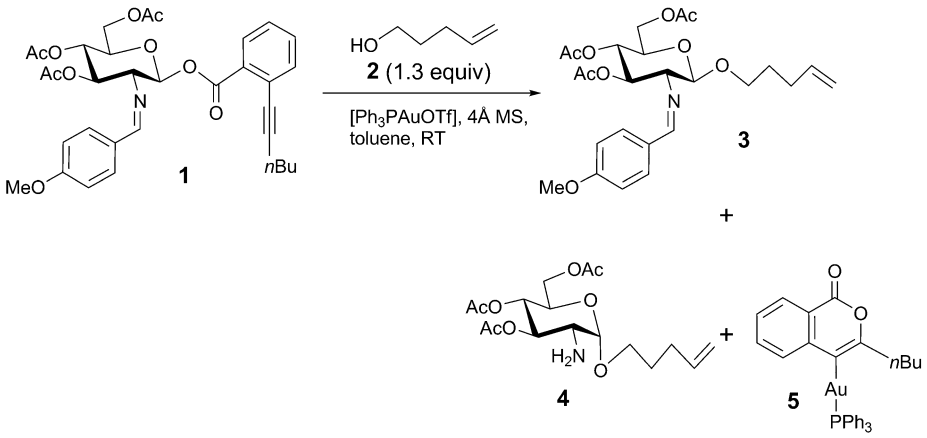


Scheme 2. Glycosylation with 2-*p*-methoxybenzylideneamino-β-D-glucopyranosyl-*o*-hexynylbenzoate **1** as donor and [$Ph_3PAuOTf$] as catalyst.

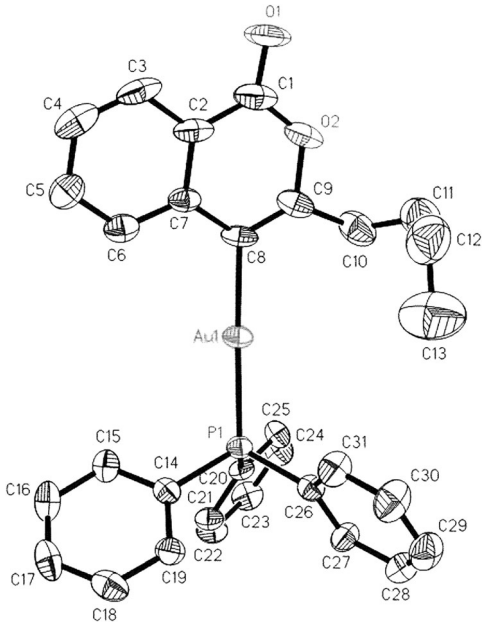
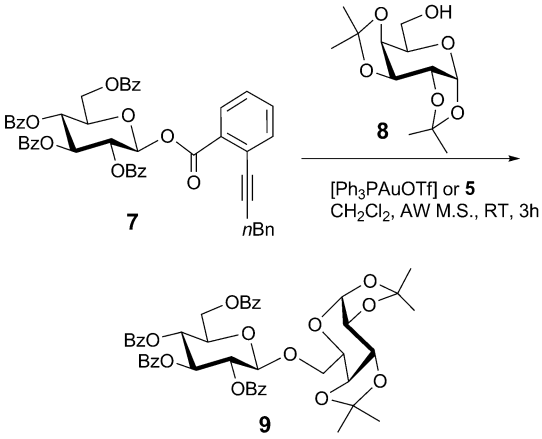


Figure 1. ORTEP diagram of complex **5** with 30% probability ellipsoids; hydrogen atoms are omitted for clarity. Key bond lengths [Å] and angles [°]: Au1–C8 2.068(7), Au1–P1 2.2843(18), C7–C8 1.444(12), C8–C9 1.351(13); C7-C8-Au1 122.2(6), C9-C8-Au1 118.3(7), C8-Au1-P1 176.0(2).

The isochromen-4-yl-gold(I) complex **5** was quite stable, and it remained intact in the solid state under ambient conditions for at least 30 days or in $CDCl_3$ at ambient temperature for at least five days. Protodeauration of **5** (in $CDCl_3$) took place instantly and quantitatively upon addition of a strong protic acid such as TfOH or CF_3COOH; however, the protodeauration did not proceed at all in the presence of common alcohols such as MeOH or EtOH. The kinetics of the protodeauration of **5** with acidic alcohols $(CF_3)_2CHOH$ ($pK_a = 9.39$), *m*-$O_2NC_6H_4OH$ ($pK_a = 8.38$), and *p*-$O_2NC_6H_4OH$ ($pK_a = 7.16$) were measured to be first-order for both alcohol and the complex **5**, with rate constants of $k = 0.022$, 0.485, and 1.4 $mL\,min^{-1}\,mmol^{-1}$, respectively, at 25 °C (see the Supporting Information).

These results prompted us to examine the gold(I)-catalyzed glycosylation with a focus on the effect of acidity on the reaction. The coupling of perbenzoyl-β-D-glucopyranosyl-*o*-hexynylbenzoate **7** and sugar primary alcohol **8**, which could proceed smoothly under the normal conditions (0.1 equiv [$Ph_3PAuOTf$], CH_2Cl_2, 4 Å M.S., RT) to give the coupled disaccharide **9** in excellent yield,[1a,b] were selected as the model reaction (Table 1, entry 1). Lowering the gold(I) catalyst loading to 0.01 equiv resulted in a sluggish reaction (Table 1, entry 2); addition of 0.1 equiv HOTf rescued the reaction (Table 1, entry 3). In the presence of 0.1 equiv HOTf, the

Table 1: Gold(I)-catalyzed coupling of glycosyl *o*-hexynylbenzoate **7** and alcohol **8** with or without HOTf as a co-catalyst.



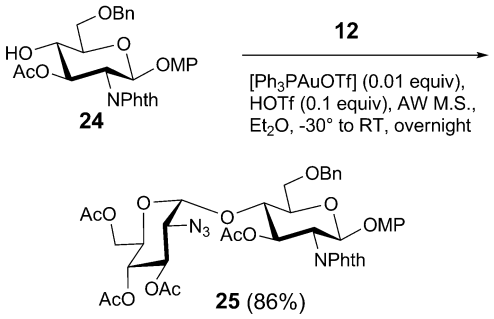
Entry	Gold(I) catalyst[a]	HOTf [equiv][b]	Yield [%][c]
1	[$Ph_3PAuOTf$] (0.1 equiv)	–	95
2	[$Ph_3PAuOTf$] (0.01 equiv)	–	23
3	[$Ph_3PAuOTf$] (0.01 equiv)	0.1	92
4	[$Ph_3PAuOTf$] (0.005 equiv)	0.1	86
5	[$Ph_3PAuOTf$] (0.001 equiv)	0.1	82
6	[$Ph_3PAuOTf$] (0.0001 equiv)	0.1	trace
7	**5** (0.1 equiv)	–	0
8	**5** (0.01 equiv)	0.1	92
9	**5** (0.001 equiv)	0.1	82
10	**5** (0.0001 equiv)	0.1	trace

[a] A CH_2Cl_2 solution of [PPh_3AuOTf] (5.8×10^{-3} M) was freshly prepared[1b] and the corresponding amount of catalyst was transferred by syringe. [b] The reaction proceeded better in the presence of acid-washed molecular sieves (AW M.S.; AW300 from Alfa Aesar) than in the presence of normal molecular sieves; however, HOTf was required as the co-catalyst to promote the reaction. [c] Yield of isolated product. Bz = benzoyl.

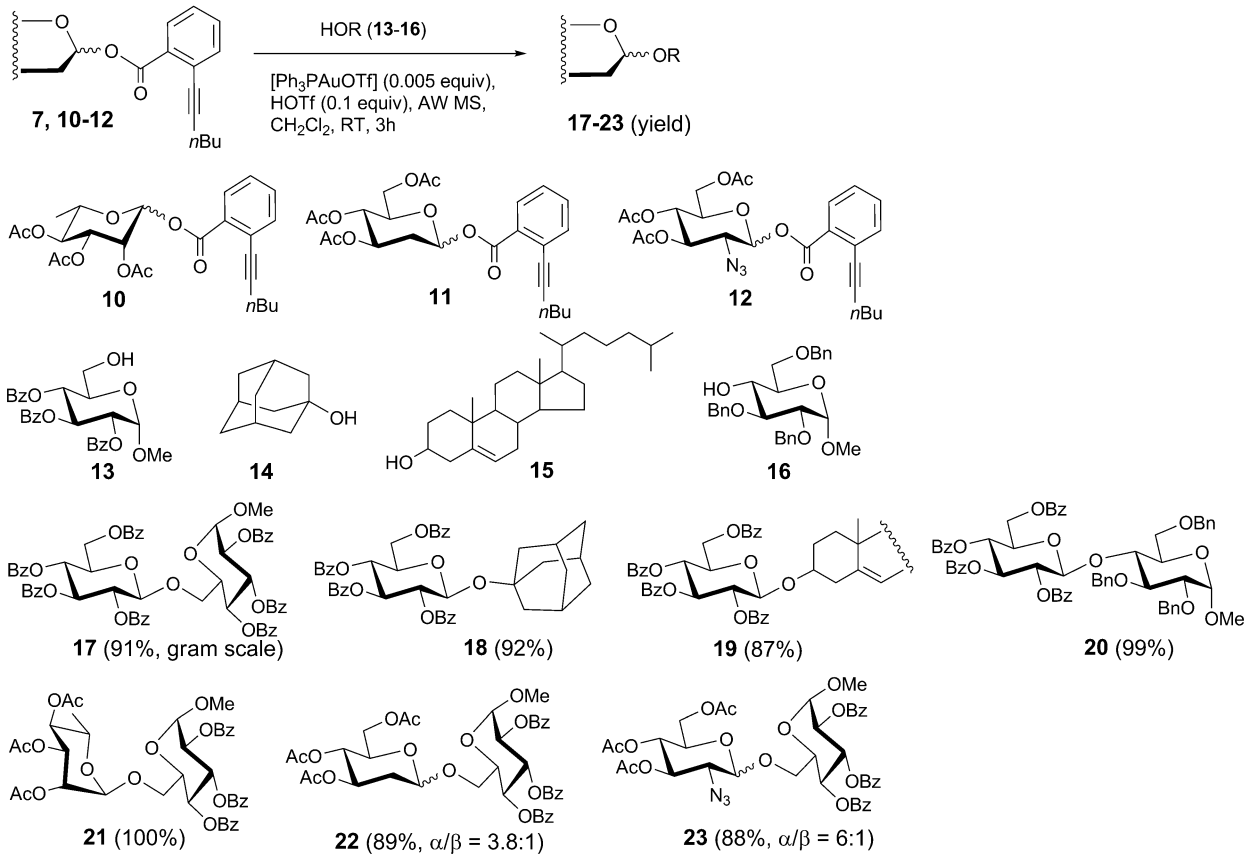
reaction could proceed satisfactorily with only 0.005 or 0.001 equiv gold(I) catalyst (Table 1, entries 4 and 5). However, 0.0001 equiv gold(I) catalyst was not sufficient to promote the reaction, even in the presence of 0.1 equiv HOTf (Table 1, entry 6). Expectedly, isochromen-4-yl-gold(I) complex **5** itself could not promote the glycosylation reaction (Table 1, entry 7); together with 0.1 equiv HOTf, the reaction proceeded as well as with [$Ph_3PAuOTf$] as the catalyst (Table 1, entries 8–10).

Our previous puzzles, that the gold(I)-catalyzed glycosylation reaction could not proceed in the present of a base[1c] and that addition of TfOH could accelerate greatly the reaction rate,[6] have thus been solved. Moreover, a solution to lower the catalyst loading in the gold(I)-catalyzed glycosylation has emerged. The scope of this alternative was then examined briefly (Scheme 3). Thus, catalyzed by 0.005 equiv [$Ph_3PAuOTf$] and 0.1 equiv HOTf (CH_2Cl_2, acid-washed M.S., RT, 3 h), glycosylation of the sugar primary alcohol **13**, admantanol **14**, cholesterol **15**, and the hindered sugar 4-OH derivative **16** with perbenzoyl glucopyranosyl *o*-hexynylbenzoate **7** gave the coupled β-glycosides (**17**–**20**) in excellent yields (87–99%). With rhamnopyranosyl, 2-deoxy-glucopyranosyl, and 2-deoxy-2-azido-glucopyranosyl *o*-hexynylbenzoate **10**–**12** as donors and sugar alcohol **13** as acceptor, the glycosylation also proceeded smoothly to provide the corresponding disaccharides **21**–**23** in high yields (88–100%).

We then revisited a difficult glycosylation reaction with the present new conditions (Scheme 4). Previous coupling of the glucosamine 4-OH derivative **24** with 2-azido-glucopyranosyl *o*-hexynylbenzoate **12** (toward the total synthesis of TMG-chitotriomycin (TMG = *N*,*N*,*N*-trimethyl-D-glucosamine) required 0.5 equiv of [$Ph_3PAuOTf$] to promote the reaction to completion.[2] In this case, with the assistance of 0.1 equiv HOTf, 0.01 equiv [$Ph_3PAuOTf$] could promote the coupling to provide the α-disaccharide **25** in a satisfactory 86% yield.



Scheme 4. A challenging glycosidic coupling with low loading of [$Ph_3PAuOTf$] catalyst. Phth = phalimido, MP = *p*-methoxyphenyl.



Scheme 3. Glycosylation with glycosyl *o*-hexynylbenzoates in the presence of [$Ph_3PAuOTf$] (0.005 equiv) and HOTf (0.1 equiv). Bn = benzyl.

In conclusion, we have unambiguously characterized the isochromen-4-yl-gold(I) complex **5** as an important intermediate in the gold(I)-catalyzed glycosylation reaction with glycosyl *o*-alkynylbenzoates as donors. Effective protodeauration of this vinyl gold(I) complex has been shown to require strong protic acid, and this acid is found to be critical for regeneration of the active gold(I) species for the catalytic cycle. This finding has enabled reduction of the loading of the gold(I) catalyst in the reaction significantly (from the previous ca. 10 mol% to the present ca. 0.5 mol%) with the assistance of an externally added strong protic acid (e.g., ca. 10 mol% HOTf). The present protocol will be valuable to the large-scale preparation of carbohydrates. Moreover, the present finding has added a solid piece of evidence to highlight the importance of the protodeauration step in the numerous gold(I)-catalyzed transformations.[8,13] In fact, the benefit of addition of acid to some of those gold(I)-catalyzed reactions has already been appreciated during experimentation.[9a,14]

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