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# Gold(I)-Catalyzed Glycosylation with Glycosyl Ynenoates as Donors

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Supporting Information


**ABSTRACT:** A simple and versatile glycosylation method with both armed and disarmed glycosyl ynenoates as donors is developed. Employing a gold(I) complex as catalyst with or without the assistance of TfOH, the scope of the present glycosylation protocol is very wide. The utility of the present ynenoate donors is demonstrated in the efficient synthesis of oligosaccharides via the latent-active strategy and the multiple orthogonal one-pot strategy. Finally, this approach enables the formal synthesis of the tetrasaccharide hapten of *Streptococcus pneumoniae* serotype 3 and the highly convergent synthesis of the 32mer polymannoside.



Carbohydrates, one of the four major classes of biomolecules, are widely distributed in nature and mediate a broad spectrum of biological processes including energy storage, cell adhesion, cell signaling and differentiation, pathogen recognition, bacterial and viral infections, as well as tumor progression and metastasis.[1−3] To decipher the sugar code for the development of drugs, vaccines, and diagnostic tools, well-defined carbohydrates are required to evaluate the role of glycans in vivo.[4,5] Because it is very difficult to isolate pure and sufficient carbohydrates from natural sources in most cases due to the micro-heterogeneity of saccharides, chemical synthesis serves as a major approach for the preparation and modification of naturally occurring carbohydrates.[6] Along this line, the key glycosylation reaction has been studied for over a century, leading to numerous *O*-glycosylation methods mostly by replacing the leaving group at the anomeric position of the glycosyl donor with an alcohol.[7] However, a glycosylation method that can meet the stereoselective construction of all types of glycosidic linkages is still missing due to the inherent structural complexity of carbohydrates.

In the search of popular glycosylation methods, gold-catalyzed glycosylation with alkyne-containing glycosides as donors was widely investigated due to the unique catalytic mechanism.[8] In 2008, Yu et al. reported the gold(I)-catalyzed glycosylation with glycosyl *ortho*-alkynylbenzoates as donors.[9] Although great success with Yu glycosylation was achieved in the precedent reports,[8a,b] the pursuit of a simpler and more versatile glycosylation method never ceases. In 2018, Zhang et al. reported the silver-catalyzed glycosylation using glycosyl ynenoates as donors, which are absent of the fused benzene ring compared to the glycosyl *ortho*-alkynylbenzoate donors.[10] However, the silver-catalyzed glycosylation did not work with the disarmed glycosyl ynenoate donors, thus severely limiting its application to the synthesis of complex carbohydrates.

In continuation of our efforts toward the discovery of new glycosylation methods, we recently described a gold(I)-catalyzed intermolecular rearrangement reaction of glycosyl alkynoic $\beta$-ketoesters for the synthesis of 4-*O*-glycosylated 2-pyrones.[11] Here, we report a simple and versatile gold(I)-catalyzed glycosylation with both armed and disarmed glycosyl ynenoates as donors for the synthesis of complex glycans and glycoconjugates.

In the beginning, we tried to prepare D-glucosyl (*Z*)-ynenoate **3a** by condensation of perbenzoylated D-glucosyl lactol **1a** with ynenoic acid[12] **2a** under the promotion of EDCI (1.5 equiv) and DMAP (1 equiv) at 0 °C (Table 1). However, this reaction produced a mixture of D-glucosyl (*Z*)-ynenoate **3a** (55%) and (*E*)-ynenoate **4a** (42%) that might arise from the isomerization of the conjugated ynenoates (entry 1). Under the similar conditions, condensation of perbenzoylated D-mannosyl lactol **1b** with **2a** also gave a mixture of D-mannosyl (*Z*)-ynenoate **3b** (58%) and (*E*)-ynenoate **4b** (35%) (entry 2). By decreasing the amount of DMAP to 0.1 equiv and using DCC (1.2 equiv) as the promoter, reaction of **1a** with **2a** led to D-glucosyl ynenoate **3a** as the only product in 91% yield (entry 3). Similarly, 3,4,6-tri-*O*-acetyl-2-deoxy-D-glucosyl lactol **1e** was effectively condensed with **2a** to give ynenoate **3e** in 89% yield (entry 4). Alternatively, **1a** could also be condensed with (*Z*)-3-iodoacrylic acid[13] **2b** in the presence of DCC and DMAP to afford the glycosyl (*Z*)-3-iodoacrylate, which was subjected to Sonogashira coupling with 1-hexyne to provide **3a** in 80% yield over two steps (entry 5). This approach was then applied to the preparation of D-mannosyl ynenoate **3b**, L-rhamnosyl ynenoate **3c**, and perbenzylated D-glucosyl ynenoate **3d** in 71−82% yields over two steps (entries 6−8). Lactols **1a**−**1d** could also be converted into the corresponding trichloroacetimidate[14] or *N*-phenyl trifluoroacetimidate[15] donors, which were reacted with **2a** under the promotion of TMSOTf to give glycosyl ynenoates **3a**−**3d** in excellent yields (80−91%) over two steps (entries 9−

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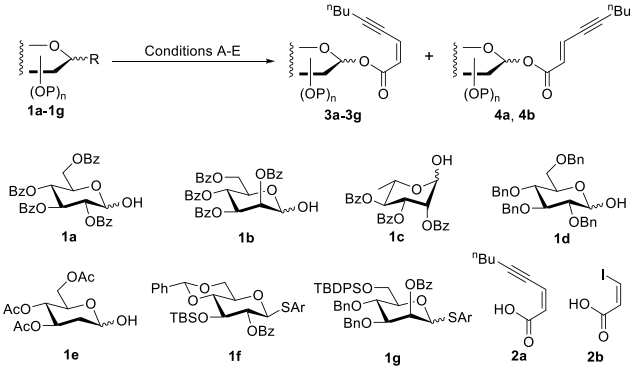
**Table 1. Preparation of a Series of Glycosyl Ynenoates 3a−3g as Donors**



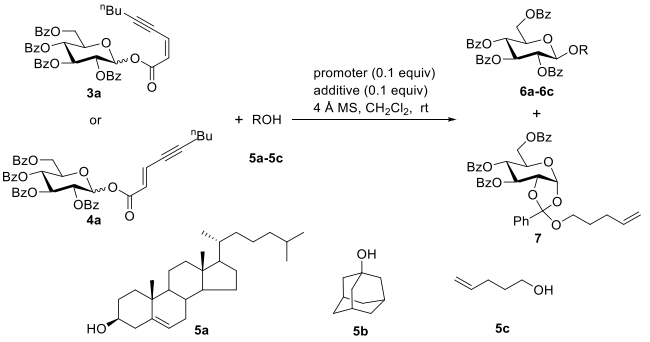

| entry | precursor | conditions[a] | product (yield, %)[b] |
|---|---|---|---|
| 1 | **1a** | A | **3a** (55), **4a** (42) |
| 2 | **1b** | A | **3b** (58), **4b** (35) |
| 3 | **1a** | B | **3a** (91) |
| 4 | **1e** | B | **3e** (89) |
| 5 | **1a** | C | **3a** (80) |
| 6 | **1b** | C | **3b** (76) |
| 7 | **1c** | C | **3c** (71) |
| 8 | **1d** | C | **3d** (82) |
| 9 | **1a** | D | **3a** (90) |
| 10 | **1b** | D | **3b** (80) |
| 11 | **1c** | D | **3c** (91) |
| 12 | **1d** | D | **3d** (88) |
| 13 | **1f** | E | **3f** (75) |
| 14 | **1g** | E | **3g** (86) |

[a]Conditions A: **2a**, EDCI (1.5 equiv), DMAP (1 equiv), $CH_2Cl_2$, 0 °C. Conditions B: **2a**, DCC (1.2 equiv), DMAP (0.1 equiv), $CH_2Cl_2$, rt. Conditions C: (i) **2b**, DCC (1.2 equiv), DMAP (0.2 equiv), $CH_2Cl_2$, rt; (ii) 1-hexyne, $Pd(PPh_3)_2Cl_2$, CuI, $Et_3N$, $CH_3CN$, THF, rt. Conditions D: (i) $CCl_3CN$, DBU (0.2 equiv), $CH_2Cl_2$, 0 °C, or $CF_3C(NPh)Cl$, $K_2CO_3$ (3 equiv), acetone, 0 °C to rt; (ii) **2a**, TMSOTf, $CH_2Cl_2$, −20 °C. Conditions E: (i) **2b**, NIS (1.2 equiv), TfOH (0.15 equiv), 4 Å MS, $CH_2Cl_2$, rt; (ii) 1-hexyne, $Pd(PPh_3)_2Cl_2$, CuI, $Et_3N$, $CH_3CN$, THF, rt. [b]Isolated yield.

12). Treatment of 5-*tert*-butyl-2-methyl phenyl thioglycosides[16] **1f** and **1g** with **2b** under the assistance of NIS and TfOH followed by Sonogashira coupling with 1-hexyne afforded glycosyl ynenoates **3f** and **3g** in 75 and 86% yield, respectively (entries 13 and 14). These results revealed that glycosyl ynenoates could be prepared in a flexible manner, not only from the common lactols but also from the transformation of thioglycosides and imidates.

The glycosylation with glucosyl ynenoates as donors using gold(I) complex as catalyst was then explored. When common gold(I) catalysts ($Ph_3PAuOTf$, $Ph_3PAuNTf_2$, and SPhosAuNTf$_2$) were employed, glycosylation of (*Z*)-ynenoate **3a** (1.5 equiv) with cholesterol **5a** (1 equiv) catalyzed by SPhosAuNTf$_2$ (0.1 equiv) in dichloromethane at room temperature afforded *β*-linked glucoside **6a** in a higher 83% yield, probably due to less hydrolysis of the donor (Table 2, entries 1−3). However, (*E*)-ynenoate **4a** did not react with cholesterol **5a** under the same conditions (entry 4), revealing that the *Z*-configuration of the double bond is critical for the gold(I)-catalyzed activation and cyclization of the ynenoate leaving group. SPhosAuNTf$_2$ (0.1 equiv)-catalyzed coupling of ynenoate **3a** (1.5 equiv) with 1-adamantanol **5b** (1 equiv) proceeded smoothly to give *β*-glucoside **6b** in an excellent 95%

**Table 2. Optimization of Conditions for Glycosylation of Glucosyl Ynenoate 3a with Alcohols 5a−5c**




| entry | donor | acceptor | promoter | additive | product (yield, %)[a] |
|---|---|---|---|---|---|
| 1 | **3a** | **5a** | $Ph_3PAuOTf$ | | **6a** (53) |
| 2 | **3a** | **5a** | $Ph_3PAuNTf_2$ | | **6a** (50) |
| 3 | **3a** | **5a** | SPhosAuNTf$_2$ | | **6a** (83) |
| 4 | **4a** | **5a** | SPhosAuNTf$_2$ | | NR[b] |
| 5 | **3a** | **5b** | SPhosAuNTf$_2$ | | **6b** (95) |
| 6 | **3a** | **5c** | SPhosAuNTf$_2$ | | **7** (94) |
| 7 | **3a** | **5c** | SPhosAuNTf$_2$ | TfOH | **6c** (93) |
| 8 | **3a** | **5c** | SPhosAuOTf | TfOH | **6c** (91) |
| 9 | **3a** | **5c** | $Ph_3PAuOTf$ | TfOH | **6c** (90) |
| 10 | **3a** | **5c** | $Ph_3PAuOTf$ | TfOH, DTBP | **7** (17) |
| 11 | **3a** | **5c** | $Ph_3PAuOTf$ | DTBP | **7** (7) |
| 12 | **3a** | **5c** | | TfOH | NR[b] |

[a]Isolated yield. [b]No reaction.

yield (entry 5). Notably, glycosylation of the more reactive 4-penten-1-ol **5c** (1 equiv) with **3a** (1.5 equiv) under the almost neutral conditions (0.1 equiv of SPhosAuNTf$_2$ as catalyst) resulted in the formation of orthoester **7** in 94% yield (entry 6). By changing SPhosAuNTf$_2$ (0.1 equiv) into $Ph_3PAuOTf$ (0.1 equiv), this reaction still resulted in the formation of orthoester **7** in around 90% yield. Usually, addition of Lewis acids could avoid the formation of the orthoester intermediates and obtain the normal *β*-glucoside **6c**.[17] As expected, when 0.1 equiv of TfOH was added to the above glycosylation, we obtained the desired *β*-glucoside **6c** in 93% yield (entry 7). By replacing SPhosAuNTf$_2$ with SPhosAuOTf (0.1 equiv) or $Ph_3PAuOTf$ (0.1 equiv), the glycosylation of **3a** with **5c** in the presence of TfOH (0.1 equiv) still provided *β*-glucoside **6c** in 91 and 90% yields, respectively (entries 8 and 9). Addition of 2,6-di-*tert*-butylpyridine (DTBP; 0.2 equiv) into the above system led to orthoester **7** in very low yield (17%) without the formation of *β*-glucoside **6c** (entry 10). A similar result was also observed when $Ph_3PAuOTf$ (0.1 equiv) and DTBP (0.2 equiv) were employed for the above glycosylation (entry 11). It is noteworthy that no reaction took place when only TfOH (0.1 equiv) was added to the above glycosylation (entry 12). Based on the above results, the glycosylation reactions were activated by the gold(I) complex to give the desired glycosides or the orthoesters that could be converted into the normal glycosides with the assistance of catalytic TfOH.

Considering the effective formation of the orthoester in the glycosylation of ynenoate **3a** with **5d** under the catalysis of SPhosAuNTf$_2$ (0.1 equiv) in our initial experiment, the glycosylation of glycosyl ynenoates **3a−3c** (1.5 equiv) with sugar alcohols **5d−5g** (1 equiv) was investigated with the commonly used $Ph_3PAuOTf$ (0.1−0.2 equiv) and TfOH (0.1−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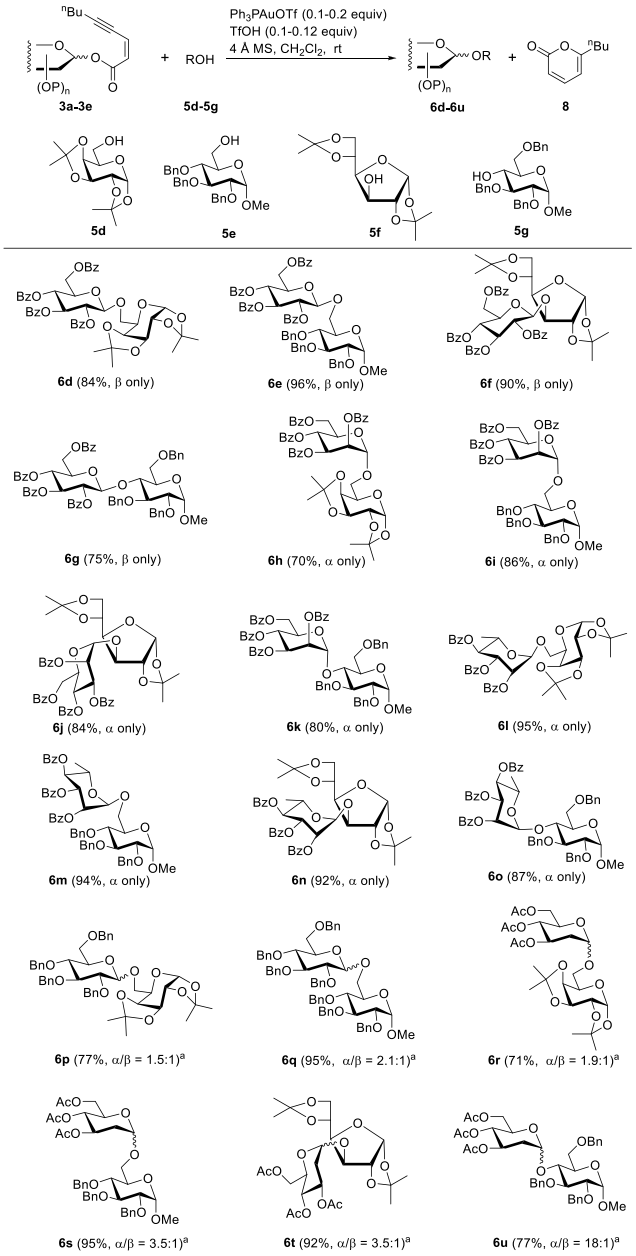
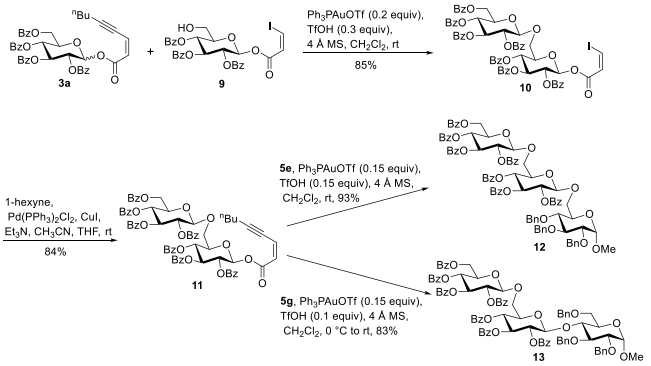
**Scheme 1. Glycosylation of Glycosyl Ynenoates 3a−3e with Sugar Alcohols 5d−5g under the Catalysis of $Ph_3PAuOTf$ with or without the Assistance of TfOH**

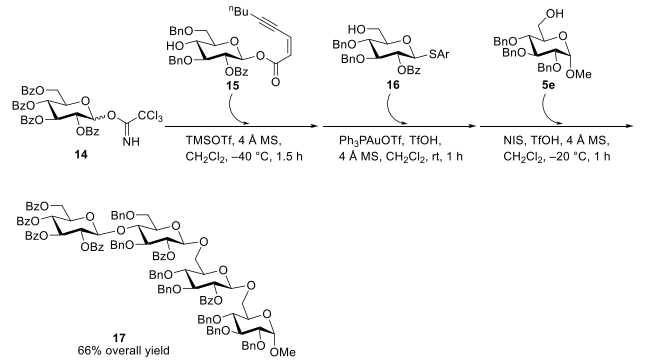



[a]TfOH was not used as additive.

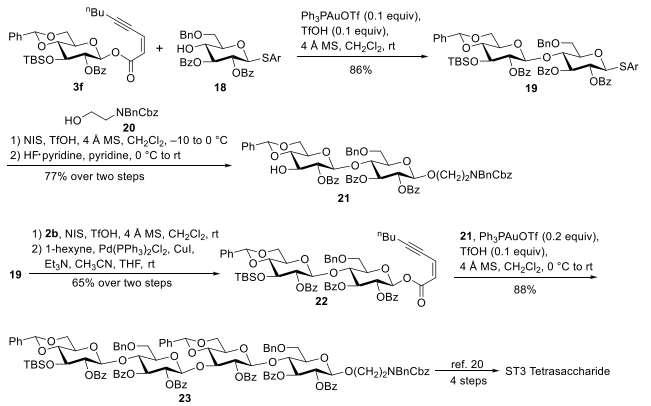
**Scheme 2. Latent-Active Synthesis of Trisaccharides 12 and 13 Based on the Glycosyl Ynenoates**




**Scheme 3. One-Pot Synthesis of Tetrasaccharide 17 Based on the Glycosyl Ynenoate**




**Scheme 4. Formal Synthesis of the Tetrasaccharide Hapten of *Streptococcus pneumoniae* Serotype 3**




0.12 equiv) in dichloromethane at room temperature as the optimal condition (Scheme 1). To our delight, glucosyl ynenoate **3a** reacted with sugar alcohols **5d−5g** to provide the $\beta$-(1→6)-, $\beta$-(1→3)-, and $\beta$-(1→4)-disaccharides **6d−6g** in 75−96% yields. Meanwhile, the 2*H*-pyran-2-one derivative **8** (>90%) was isolated via the departure of the ynenoate leaving group from the sugar moieties. With D-mannosyl ynenoate **3b** and L-rhamnosyl ynenoate **3c** as donors, the glycosylation with **5d−5g** afforded the $\alpha$-(1→6)-, $\alpha$-(1→3)-, and $\alpha$-(1→4)-disaccharides **6h−6o** in 70−95% yields. As expected, glycosylation of perbenzylated D-glucosyl ynenoate **3d** (1.5 equiv) with **5d** (1 equiv) and **5e** (1 equiv) under the catalysis of $Ph_3PAuOTf$ provided the coupled disaccharides **6p** and **6q** in satisfactory yields as an anomeric mixture due to the absence of the neighboring-group participation effect (**6p**: 77%, $\alpha/\beta$ = 1.5:1; **6q**: 95%, $\alpha/\beta$ = 2.1:1). Notably, there was almost no change in glycosylation selectivity for the synthesis of **6p** based on the anomeric configuration of donor **3d** ($\alpha/\beta$ = 1.7:1 for **3d**-$\alpha$; $\alpha/\beta$ = 1.2:1 for **3d**-$\beta$). Similarly, 3,4,6-tri-*O*-acetyl-2-deoxy-$\alpha$-D-glucosyl ynenoate **3e** (1.5 equiv) was coupled with **5d−5g** (1 equiv) under the catalysis of $Ph_3PAuOTf$ to afford the thermodynamically stable (1→6)-, (1→3)-, and (1→4)-linked disaccharides **6r−6u** in 71−96% yields with the $\alpha$-anomers as the major products, particularly for the sterically hindered (1→4)-linked disaccharide **6u** ($\alpha/\beta$ = 18:1). When **3e**-$\beta$ was used as donor, the $\alpha$-selectivity for the synthesis of **6r** was slightly improved ($\alpha/\beta$ = 3.3:1).



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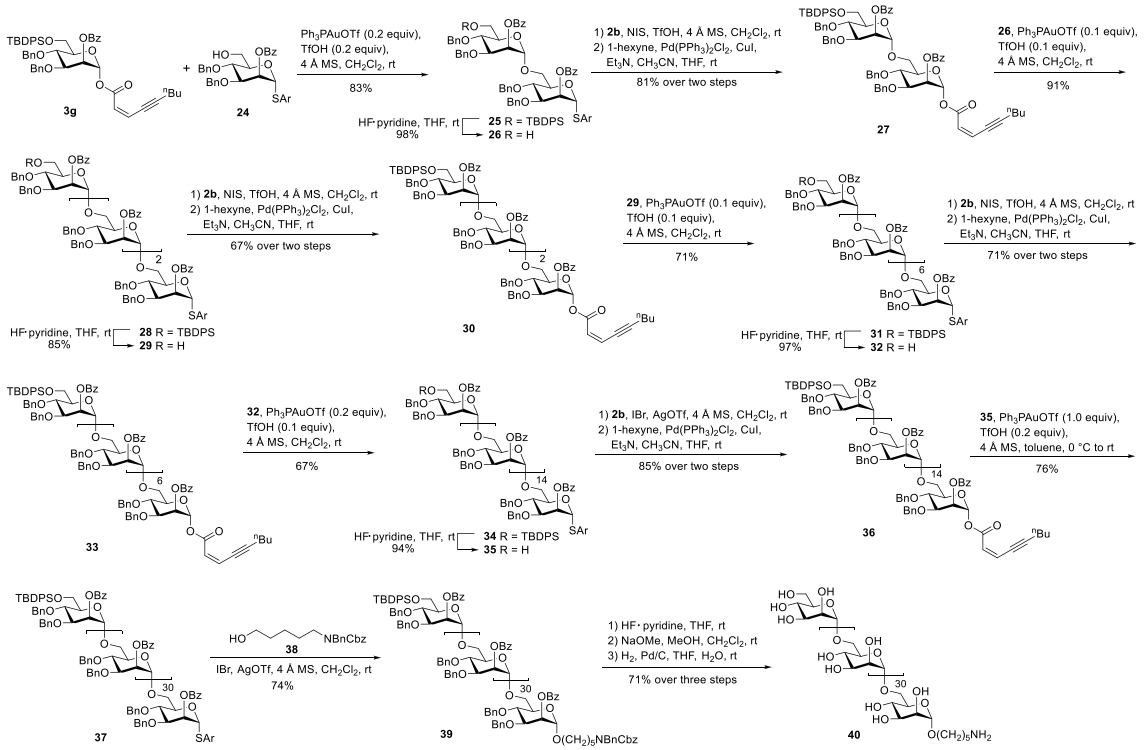
**Scheme 5. Synthesis of the 32mer Polymannoside 40**



Considering that the glycosyl ynenoate donors can be prepared from the stable glycosyl (*Z*)-3-iodoacrylate intermediates, the latent-active synthesis of trisaccharides **12** and **13** based on the glycosyl ynenoates was envisaged (Scheme 2).[18] Indeed, glycosylation of the active glucosyl ynenoate **3a** (1.3 equiv) with the latent glucosyl (*Z*)-3-iodoacrylate **9** (1 equiv) under the promotion of $Ph_3PAuOTf$ and TfOH proceeded cleanly to provide the $\beta$-(1→6)-disaccharide **10** in 85% yield, thus demonstrating the inertness of the (*Z*)-3-iodoacrylate group toward the present glycosylation condition. Compound **10** was then converted into the disaccharide ynenoate **11** in 84% yield by Sonogashira coupling with 1-hexyne. Glycosylation of donor **11** (1.2−1.26 equiv) with the glucose-6-OH derivative **5e** (1 equiv) and the glucose-4-OH derivative **5g** (1 equiv) under similar conditions furnished trisaccharides **12** and **13** in 93 and 83% yields, respectively.

Compared to the linear stepwise synthetic procedure, a one-pot synthetic strategy holds the advantages of accelerating the assembly of oligosaccharides and avoiding the intermediates' workups and purifications.[19] With the glycosyl trichloroacetimidate **14**, the glycosyl ynenoate **15**, the thioglycoside **16**, and the sugar alcohol **5e** in hand, the multistep orthogonal one-pot synthesis of tetrasaccharide **17** was carried out (Scheme 3). Orthogonal glycosylation of trichloroacetimidate **14** (1.2 equiv) with ynenoate acceptor **15** (1.0 equiv) under the catalysis of TMSOTf (0.2 equiv) at −40 °C for 1.5 h afforded the disaccharide intermediate, which was coupled with thioglycoside acceptor **16** (0.9 equiv) under the activation of $Ph_3PAuOTf$ (0.2 equiv) and TfOH (0.1 equiv) at room temperature for another 1 h to provide the trisaccharide intermediate. Coupling of the above trisaccharide intermediate with acceptor **5e** (0.9 equiv) promoted by NIS (1.5 equiv) and TfOH (0.2 equiv) at −20 °C for another 1 h furnished tetrasaccharide **17** in 66% overall yield. As shown in the efficient synthesis of tetrasaccharide **17**, this multistep orthogonal one-pot synthesis required only 3.5 h for completion of the multistep reactions and only one purification step for accessing the target tetrasaccharide **17**, which is very appealing for the assembly of oligosaccharides.

To demonstrate the synthetic efficiency of the present glycosylation protocol with glycosyl ynenoates as donors, the formal synthesis of the highly immunological tetrasaccharide hapten from the capsular polysaccharide of *Streptococcus pneumoniae* serotype 3 (ST3) was completed (Scheme 4).[20] Glycosylation of glucosyl ynenoate **3f** (1.5 equiv) with the glucose-4-OH derivative **18** (1 equiv) under the catalysis of $Ph_3PAuOTf$ (0.1 equiv) and TfOH (0.1 equiv) at room temperature generated the $\beta$-linked disaccharide **19** in 86% yield. Union of thioglycoside **19** (1 equiv) with the ethanolamine linker **20** (6 equiv) using NIS and TfOH as activator followed by removal of the TBS group with HF·pyridine gave disaccharide acceptor **21** in 77% yield over two steps. Compound **19** was then converted into disaccharide ynenoate **22** via a two-step sequence involving coupling with **2b** using NIS and TfOH and subsequent Sonogashira coupling with 1-hexyne. The [2 + 2] coupling of ynenoate **22** (1.5 equiv) with acceptor **21** (1 equiv) promoted by $Ph_3PAuOTf$ (0.2 equiv) and TfOH (0.1 equiv) furnished fully protected tetrasaccharide **23** in an excellent 88% yield. Following the literature procedures,[20] tetrasaccharide **23** was transformed into ST3 tetrasaccharide in four steps. In the formal synthesis of this tetrasaccharide hapten, glycosyl ynenoate donors proved to be very efficient for construction of the glycosidic bonds especially in the [2 + 2] coupling (88%) that is far superior to the previous [2 + 2] coupling using ethyl thioglycoside as the donor (54%).[20]

The glycosylation properties with glycosyl ynenoates as donors were further evaluated in the highly convergent synthesis of the 32mer polymannoside **40** based on the orthogonal and consecutive activation of glycosyl ynenoates and thioglycosides (Scheme 5).[21] Orthogonal glycosylation of mannosyl ynenoate **3g** (1.08 equiv) with thioglycoside acceptor **24** (1 equiv) using



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$Ph_3PAuOTf$ (0.2 equiv) and TfOH (0.2 equiv) as promoter afforded the $\alpha$-(1→6)-dimannoside **25** in 83% yield, which was subjected to the removal of the TBDPS group using HF·pyridine to provide disaccharide acceptor **26** in 98% yield. On the other hand, thioglycoside **25** was converted into glycosyl ynenoate **27** in 81% yield over two steps via the activation of **25** with **2b** using NIS and TfOH and subsequent Sonogashira coupling with 1-hexyne. With ynenoate **27** (1.3 equiv) and acceptor **26** (1 equiv) as the coupling partners, repetition of the similar reaction sequence for three times provided the 16mer polymannosyl ynenoate **36** and the 16mer polymannoside acceptor **35** in a highly efficient and convergent manner (glycosylation yields 91% for tetrasaccharide **28**, 71% for octasaccharide **31**, 67% for hexadecasaccharide **34**). The [16 + 16] coupling of ynenoate **36** (2 equiv) with acceptor **35** (1 equiv) promoted by $Ph_3PAuOTf$ (1.0 equiv) and TfOH (0.2 equiv) in toluene furnished the $\alpha$-(1→6)-linked 32mer polymannoside **37** in 76% yield. Given that a linker could be installed at the reducing end of **37** for further conjugation to carrier proteins and array surfaces, compound **37** (1 equiv) was coupled with *N*-benzyl-*N*-benzyloxycarbonyl pentyl linker **38** (1.5 equiv) under the activation of IBr and AgOTf to provide the 32mer polymannoside **39** in 74% yield. Global deprotection of **39** involving removal of the TBDPS group with HF·pyridine, saponification of the 32 benzoyl groups with sodium methoxide in methanol and dichloromethane, and hydrogenolysis of the 65 benzyl and one benzyloxycarbonyl groups over Pd/C in THF and water furnished the target 32mer polymannoside **40** in 71% yield over three steps.

In conclusion, we have developed a simple and versatile gold(I)-catalyzed glycosylation with glycosyl ynenoates as donors for the synthesis of a variety of oligo- and polysaccharides. Structurally, the glycosyl ynenoate donors described here are relatively simple and atom-economical due to the absence of the fused benzene ring. Moreover, the stable glycosyl ynenoate donors can be easily prepared from various precursors such as sugar lactols and thioglycosides. The present glycosylation protocol with glycosyl ynenoates as donors under the catalysis of gold(I) complex with or without the aid of TfOH was found to possess a very wide substrate scope as exemplified in the efficient synthesis of ST3 tetrasaccharide and the 32mer polymannoside. In combination with the glycosyl trichloroimidate and the thioglycoside, the glycosyl ynenoate proved to be an effective donor in the multiple orthogonal one-pot synthesis of the tetrasaccharide. Additionally, the glycosyl ynenoates have found application in the latent-active synthesis of oligosaccharides. With the simplicity and versatility as promising properties, we believe this new glycosylation method shall find wide application in the synthesis of a diverse class of glycans and glycoconjugates.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03851.

Experimental procedures, characterization data, and spectra (PDF)

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### Notes

The authors declare no competing financial interest.

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