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Diastereoselective Synthesis of C-Vinyl Glycosides via Gold(I)-Catalyzed Tandem 1,3-Acyloxy Migration/Ferrier Rearrangement

Nianyu Huang,^{§,‡} Hongze Liao,^{§,†} Hui Yao,[†] Tianpeng Xie,[‡] Shasha Zhang,[†] Kun Zou,^{*,‡} and Xue-Wei Liu^{*,†,‡}

[†]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371

[‡]Hubei Key Laboratory of Natural Products Research and Development, College of Biological and Pharmaceutical Sciences, China Three Gorges University, Yichang 443002, P. R. China

Supporting Information

ABSTRACT: A novel gold-catalyzed C-glycosylation has been developed to gain access to α ,(*Z*)-selective C-vinyl glycosides, starting from readily available glycals and propargylic carboxylate. This reaction involves a tandem intermolecular gold-catalyzed 1,3-acyloxy migration/Ferrier rearrangement with the involvement of allenic ester as the glycosyl acceptor. A wide range of substrate scope with good to excellent yields was achieved with complete diastereoselectivity.

In recent years, glycosylation with gold catalysis has received considerable attention owing to the high alkynophilicity and carbophilic Lewis acidity of gold salts.¹ The glycosyl donors such as propargyl-*O*-glycosides,² glycosyl *ortho*-alkynylbenzoates,³ thioglycosides,⁴ and glycosyl trichloroacetimidates⁵ were exploited to construct the glycosidic bonds. AuCl₃ was also reported to catalyze the Ferrier rearrangement of substituted glycals⁶ or to work with phenylacetylene as the catalyst system.^{5b,7} However, most cases focused on *O*- or *N*-glycosylation, and only a few examples about gold-catalyzed C-glycosylation were reported.

Propargylic carboxylate is a versatile molecular motif and is often used for studies on transition-metal catalyzed reactions.⁸ It can undergo two distinct transformations in the presence of gold catalysts, namely, 1,2-acyloxy migration and 1,3-acyloxy migration, to form gold vinyl carbenoid species 2' or carboxyallene 3', respectively.⁹ The two intermediates could initiate other transformations, depending on the reaction conditions or properties of substrates.¹⁰ For allenic intermediate, most studies covered the electrophilic character of the intermediate.¹¹ The studies about the nucleophilic character were limited to reactions through intramolecular fashion.¹² There were only two cases about the allenic intermediate that underwent an intermolecular addition to soft electrophiles such as NIS¹³ or oxocarbenium ion,¹⁴ respectively.

We were interested in developing highly efficient and stereoselective gold-catalyzed C-glycosylation. Inspired by the reports of gold-catalyzed reactions between glycals and propargylic carboxylates, we envisioned that there were two possible pathways for the reaction between glycal and propargylic carboxylate in the presence of gold catalysts (Scheme 1). In path A, after activation by the gold catalyst, the propargylic carboxylate underwent 1,2-acyloxy migration to generate the

Scheme 1. Two Proposed Pathways for Reaction between Glycal and Propargylic Ester

carbenoid intermediate 2', which subsequently took a cyclopropanation process to furnish the cyclopropane product.¹⁵ In path B, the allylic carbocation intermediate 5'¹⁶ would be generated first from the glycal via a Ferrier-type rearrangement and subsequently underwent electrophilic attack to allenic intermediate 3', which was transferred from the propargylic carboxylate via 1,3-acyloxy migration. Then after hydrolysis the C-vinyl-glycoside product was afforded. Our method holds great potential for the synthesis of various pyran-embedded natural products such as okadaic acid, forskolin, and aspergillide C.¹⁷

To validate our hypothesis, a gold-catalyzed tandem reaction of propargylic carboxylate **2d** and tri-*O*-acetyl-D-glucal **1** was carried out in the presence of catalytic AuCl₃. To our delight, the vinyl-C-glycoside product **3d** proposed in path A was furnished in 44% yield with complete α -selectivity in the anomeric position and *Z*-selectivity in the olefin position (Table 1, entry 1). It was

Table 1. Optimization of Gold-Catalyzed Glycosylation^a

entry	catalyst	solvent	time (h)	yield (%) ^d
1	AuCl ₃	CH ₂ Cl ₂	4	44
2	AuCl	CH ₂ Cl ₂	4	35
3	XPhosAuCl/AgOTf	CH ₂ Cl ₂	4	24
4	((<i>t</i> Bu) ₂ (<i>o</i> -biphenyl)P)-AuCl/AgOTf	CH ₂ Cl ₂	24	31
5	Ph ₃ PAuNTf ₂	CH ₂ Cl ₂	4	52
6	Ph ₃ PAuCl/AgSbF ₆	CH ₂ Cl ₂	4	57
7	Ph ₃ PAuCl/AgClO ₄	CH ₂ Cl ₂	4	64
8	Ph ₃ PAuCl/AgOTf	CH ₂ Cl ₂	4	72
9	Ph ₃ PAuCl	CH ₂ Cl ₂	24	n.r.
10	AgOTf	CH ₂ Cl ₂	24	n.r.
11	Ph ₃ PAuCl/AgOTf	DCE	4	66
12	Ph ₃ PAuCl/AgOTf	Toluene	4	43
13	Ph ₃ PAuCl/AgOTf	CH ₃ NO ₂	4	66
14	Ph ₃ PAuCl/AgOTf	CH ₃ CN	24	Trace
15 ^b	Ph ₃ PAuCl/AgOTf	CH ₂ Cl ₂	4	68
16 ^c	Ph ₃ PAuCl/AgOTf	CH ₂ Cl ₂	4	58

^aReaction conditions: tri-*O*-acetyl-D-glucal **1** (0.2 M in CH₂Cl₂), propargylic ester **2d** (0.2 M in CH₂Cl₂). ^bReaction was carried out on scale of 1 M **1** and **2d**. ^cCatalyst (10 mol %). ^dIsolated yield.

noted that the cyclopropanation product was not observed in the reaction. To improve the yields and investigate the stereo-selectivity, various gold catalysts and solvents were screened, and the results are summarized in Table 1. It was found that PPh₃AuOTf generated *in situ* from PPh₃AuCl/AgOTf afforded the best result for this reaction (Table 1, entry 8). Other commercially available gold catalysts such as AuCl, XPhosAuCl/AgOTf, and ((*t*Bu)₂(*o*-biphenyl)P)AuCl/AgOTf could also catalyze this reaction but gave lower yields (Table 1, entry 2–4). It is worth noting that Ph₃PAuCl or AgOTf was inactive when employed individually (Table 1, entries 9 and 10). The counterion effect was also investigated, and the OTf-ion presented the best performance (Table 1, entries 5–8). Solvent screen was also conducted, and CH₂Cl₂ was found to be most suitable for this reaction (Table 1, entries 11–14). Reaction on larger scale (1 M) also proceeded smoothly and afforded **3d** in 68% yield (Table 1, entry 15). Notably, lower yield was observed when the catalyst loading was increased (Table 1, entry 16).

With the optimized condition in hand, the scope of this gold-catalyzed tandem intermolecular 1,3-acyloxy migration/Ferrier rearrangement was investigated with a variety of propargylic carboxylates **2** and tri-*O*-acetyl-D-glucal **1** (Scheme 2). In general, the desired products were obtained in good to excellent yields. The aliphatic substituents of R¹ such as methyl, ethyl, *n*-propyl, isopropyl, and benzyl substituents provided good yields (Scheme 2, entries 3a–3f). For substrates with aromatic substituents R²,

Scheme 2. Substrate Scope with D-Glucal^{a,b}

^aReaction conditions: tri-*O*-acetyl-D-glucal **1** (0.2 M in CH₂Cl₂), propargylic carboxylate **2** (0.2 M in CH₂Cl₂), 5 mol % gold catalyst, 5 mol % silver catalyst. ^bIsolated yield. ^cTri-*O*-pivaloyl-D-glucal substrate. ^dTri-*O*-benzyl-D-glucal substrate.

the aryl substituents with an electron withdrawing group increased the yields compared to the phenyl substrate. Interestingly, when the acetyl group was changed to pivaloyl or benzyl group, the reaction also worked but with lower yields (Scheme 2, entries 3j–3l). To our surprise, when the 3,4,6-tri-*O*-acetyl-D-galactal **4** was tested for this reaction, the desired vinyl-C-glycoside product **5** was obtained as expected, and the yields were much higher than the product from glucal (72%–85%), which could be ascribed to less steric hindrance between the substituted group on C4 of glycal and the propargylic carboxylate during the glycosidation process. It should be noted that all the substrates were detected as complete α ,(*Z*)-diastereoselective isomers, and the stereochemistry of this vinyl-C-glycoside product was further confirmed by X-ray analysis of compound **5i** (Scheme 3).¹⁸

Based on the experimental results, the following mechanistic pathways were proposed. The gold catalyst should serve two purposes in this reaction. First, it served as a Lewis acid to promote the formation of allylic oxocarbenium ion **A** from tri-*O*-acetyl-D-glucal **1** via a Ferrier rearrangement. Second, it promoted the transformation of the propargylic carboxylate **1a** into the nucleophilic allenic intermediate **B** through a gold-catalyzed 1,3-acyloxy migration, which subsequently took nucleophilic attack to intermediate **A**. Finally, hydrolysis of oxocarbenium ion **C** delivered the product **3** (Scheme 4). To confirm this mechanism, an isotopic labeling experiment was conducted. The tri-*O*-acetyl-D-glucal **1** and propargylic carboxylate **2d**-¹⁸O with an ¹⁸O-enriched carbonyl oxygen atom were subjected to the optimized conditions, and the ¹⁸O label was still present in the product **3d**-¹⁸O (Scheme 6). This result fully

Scheme 3. Substrate Scope with D-Galactal^{a,b}

^aReaction conditions: tri-O-acetyl-D-galactal **4** (0.2 M in CH₂Cl₂), propargylic carboxylate **2** (0.2 M in CH₂Cl₂), 5 mol % gold catalyst, 5 mol % silver catalyst. ^bIsolated yield.

Scheme 4. Proposed Mechanism

supported the proposed mechanism about the allene intermediate generated through the 1,3-acyloxy migration.

The stereochemistry of the anomeric position was mainly controlled by the conformation of oxocarbenium and the pathways of nucleophilic attack. Due to the lower energy transition state, the oxocarbenium intermediate favored conformation **I** more than **II**. The allene intermediate could attack from the bottom face to afford the α -anomer via half-chair conformation **A** or from the top face to afford the β -anomer via boat conformation **B**. Transition structures in this glycosylation were studied using the DFT method at the 6-311G(d,p) level, and the calculated results show that barrier energies for α -selectivity were much lower than β -selectivity, which is in agreement with the experimental result, which showed that only α -anomer was isolated. The complete (*Z*)-selectivity of the olefin could be ascribed to repulsion between the oxocarbenium and the allene intermediate during the nucleophilic attack process. It was geometrically favorable that the allene intermediate took the

nucleophilic attack to the oxocarbenium intermediate from the π face of the enol ether motif, which is *anti* to the substituent R¹ (Scheme 5).¹⁹ This was also fully supported by the DFT computation.¹⁹

Scheme 5. Proposed Transition State Accounting for α ,(*Z*)-Selectivity

Scheme 6. Isotope Labeling Experiments

In conclusion, an unprecedented homogeneous gold(I)-catalyzed C-glycosylation has been developed, and the mechanistic investigation suggests that this C-glycosylation proceeds through a tandem intermolecular 1,3-acyloxy migration/Ferrier rearrangement. This reaction can be utilized to access diastereomerically pure α ,(*Z*)-selective C-vinyl glycosides, which are very important structural motifs in pharmaceutical and natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03062.

Experimental procedures, characterization data, crystallographic data, and calculation details (PDF)

Accession Codes

CCDC 1573304 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: kzou@ctgu.edu.cn.

*E-mail: xuewei@ntu.edu.sg.

ORCID

Xue-Wei Liu: 0000-0002-8327-6664

Author Contributions

[§]N.H. and H.L. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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(18) See section E, Table 1 (Si, CCDC 1573304) in the [Supporting Information](#) for the crystal structure.

(19) See the [Supporting Information](#) for computation details.