DOI: 10.1002/ejoc.201100134

Gold-Catalyzed Reactions of 2-*C*-Branched Carbohydrates: Mild Glycosidations and Selective Anomerizations

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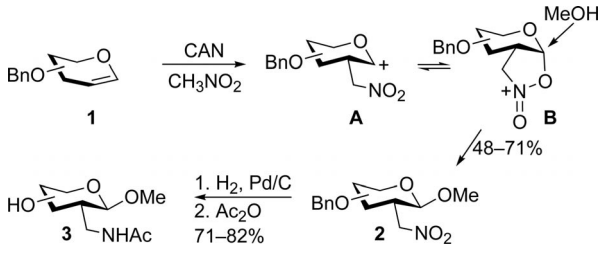
Keywords: Anomerization / Carbohydrates / Glycosidation / Gold / Synthetic methods

2-*C*-branched methyl glycosides react with various alcohols under gold catalysis to transglycosylated products. The method is applicable for the convenient synthesis of disaccharides. Without nucleophile a selective anomerization occurs, giving first access to α-configured 2-*C*-nitromethyl glycosides. The results are interesting for the mechanism of gold-catalyzed glycosidations.

Introduction

Glycosamine-containing glycopeptides and glycolipids play pivotal roles in a variety of cellular processes such as cell–cell adhesion, cell growth, fertilization and infection.[1] Glycosamine-lacking glycopeptides are found to be ineffective as anti-freeze agents or other biological applications thereby emphasizing the overall significance of glycosamines.[2] Artificial and unnatural *N*-functionalized glucosamines were studied as substrates for the inhibition of *N*-acetylglucosaminyl transferases.[3] Additionally, glycosamine homologs (e.g. **3**) are interesting, because they modulate the cellular molecular recognition events.[4] During our studies on transition-metal-mediated radical reactions in carbohydrate chemistry,[5] we developed a convenient entry to glycosamine homologs **3** (Scheme 1).[6]

Radical addition of nitromethane to protected glycals **1** proceeds smoothly in the presence of cerium ammonium nitrate (CAN) via glycosyl carbenium ions **A**. Cyclization with the adjacent nitro group to the intermediate **B** stabilizes reversibly the whole system. This explains the highly stereoselective attack of methanol from the opposite face to afford exclusively 1,2-*trans*-configured 2-*C*-branched chain carbohydrates **2**. Finally, glycosamine homologs **3** are obtained by catalytic hydrogenation and acetylation in good yields in analytically pure form (Scheme 1). Although our method is applicable to unsaturated hexoses, pentoses and disaccharides, the predetermined configuration at the anomeric center is disadvantageous. Thus, due to the selective opening of intermediate **B**, methyl α-glucosides are not available, which would represent interesting structures common in nature. Furthermore, the formation of more complex glycosidic bonds, especially attractive disaccharides, during the radical addition of nitromethane is not possible, since methanol is the superior solvent for such reactions. Thus, activation of the anomeric position of the methyl glycosides was the only way to afford either lactol or transglycosylated products. However, conventional procedures like heating in acidic medium failed, due to the lability of the branched chain carbohydrates. Herein, we describe a mild and convenient method for the transglycosidation, which gives access to disaccharides and to α-configured glycosides by a simple anomerization.



Scheme 1. Syntheses of 2-*C*-branched chain carbohydrates **2** and **3**.

Results and Discussion

During the course of our studies on gold-catalyzed glycosidations, we employed propargyl glycosides as stable glycosyl donors.[7] More recently, a serendipitous observation

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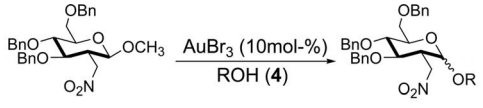
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100134.

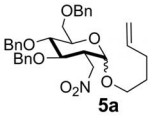
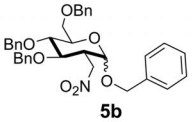
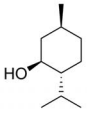
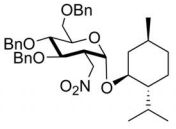
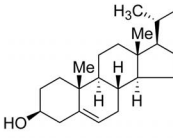
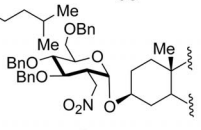
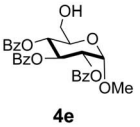
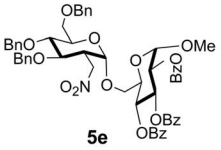
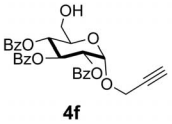
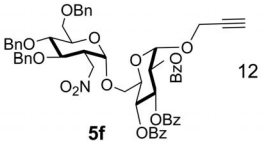
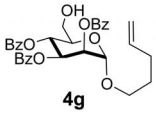
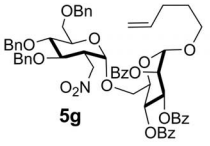
from our laboratory indicated that methyl glycosides react under similar conditions as well.[8] This is very attractive for the nitromethyl carbohydrates **2**, which might directly serve as precursors for transglycosidations. We started our initial studies with the *gluco* isomer **2a**, which is easily available and has the most common configuration in nature. Indeed, reaction with 1 equiv. of 4-penten-1-ol (**4a**) proceeded smoothly in the presence of 10 mol-% of $AuBr_3$ in acetonitrile at 70 °C, and an α/β (4:1) mixture of transglycosylated *n*-pentenyl glucoside **5a** was isolated in 65% yield after 2 h. Surprisingly, methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-nitromethyl α-D-glucopyranoside (**6a**) was obtained as by-product in 20% yield. This anomerization was hypothesized to follow an interesting mechanism, giving evidence in favour of an endocyclic C–O bond cleavage, which was observed to be completely diminished with 3 equiv. of the aglycon, and the overall yield increased to 80% (Table 1, Entry 1). Thus, gold(III) bromide is an ideal catalyst for the transglycosidation of 2-*C*-nitromethyl carbohydrates.

To further extend this method and to prove its generality we investigated other nucleophiles **4** (Table 1). Thus, benzyl glucoside **5b** was synthesized from another primary alcohol (BnOH, **4b**) in good yield as an anomeric mixture (Entry 2). Surprisingly, sterically demanding secondary alcohols such as menthol (**4c**) and cholesterol (**4d**) afforded the corresponding glycosides **5c** and **5d** as sole α-anomers after pro-

Table 1. Gold-catalyzed reaction of nitromethyl carbohydrate **2a** with various alcohols ROH (**4**).



2a **5**

Entry	ROH (**4**)	Product **5**	Time [h][a]	Ratio α/β[b]	Yield [%][c]
1	 **4a**	 **5a**	2	4:1	80
2	 **4b**	 **5b**	2	2:1	76
3	 **4c**	 **5c**	6	α only	72
4	 **4d**	 **5d**	24	α only	45
5	 **4e**	 **5e**	6	α only	56
6	 **4f**	 **5f**	12	α only	55
7	 **4g**	 **5g**	12	α only	52

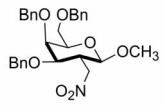
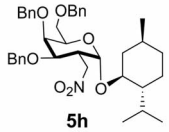
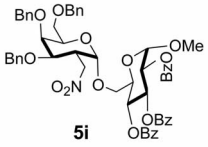
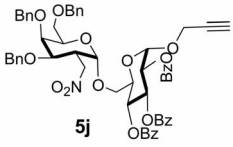
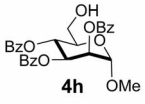
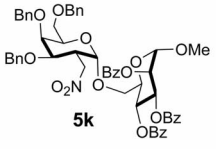
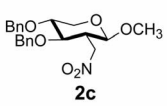
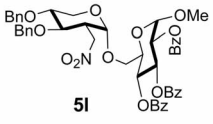
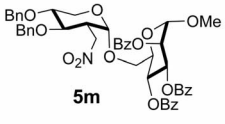
[a] Reaction of nitromethyl carbohydrate **2a** (0.2 mmol) and alcohol ROH (3 equiv.) in the presence of 10 mol-% $AuBr_3$ in CH_3CN. [b] Determined by NMR spectroscopy of the crude products. [c] Yield of analytically pure product, isolated by column chromatography.

longed reaction times (Entries 3 and 4). The moderate yield of cholesteryl α-glucopyranoside **5d** is due to the bad solubility of cholesterol (**4d**) in acetonitrile. Finally, synthetically interesting disaccharides **5e**–**g** are available according to the same procedure from sugar aglycones (**4e**–**g**). Again, only α-anomers were isolated in moderate yields (Entries 5–7). Thus, we developed a general strategy for the introduction of the nitromethyl group in the non-reducing sugar moiety of disaccharides, whereas in our previous studies only the terminal or reducing sugar could be *C*-functionalized.[6]

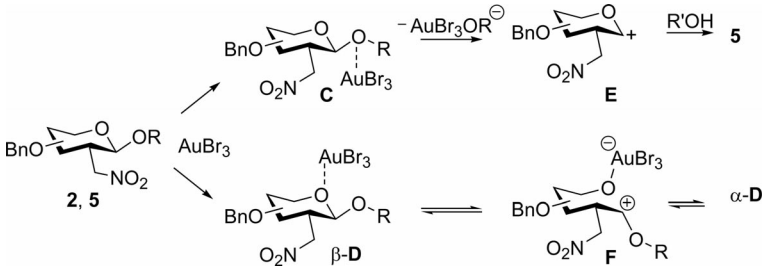
Our successful method of gold-catalyzed transglycosidations under mild conditions could be applied for other 2-deoxy-*C*-nitromethyl pyranosides **2** (Table 2). Thus, the *galacto* isomer **2b** afforded various 2-*C*-branched carbohydrates **5h**–**k** in moderate to good yields. Again, longer reaction times were necessary, resulting in the selective formation of α-anomers. Even pentose derivative **2c** reacted smoothly to the disaccharides **5l** and **5m**, demonstrating the general applicability of 2-*C*-branched methyl glycosides as glycosyl donors in the presence of $AuBr_3$.

The selective formation of α-anomers is interesting from the mechanistic point of view. During our studies on radical additions of nitromethane to glycals,[6] we established a stabilization of anomeric cations by the adjacent nitro group (Scheme 1). Thus, nucleophiles can only attack from the opposite face, resulting in β-glucosides with high selectivity. The difference in our herein described gold-catalyzed reactions might be a complexation of the nitro group by the transition-metal atom, inhibiting its propensity for neighboring-group participation. On the other hand, we see a remarkable time dependence on the α/β ratio when the transglycosylation was conducted between **2a** and **4a** to give **5a** (Tables 1 and 2),[9] which speaks for a gold-catalyzed anomerization with formation of the thermodynamically more stable α-glycoside after longer reaction times.[10] In the first step, the Lewis-acidic $AuBr_3$ might activate the anomeric center by coordination to the adjacent exocyclic oxygen

Table 2. Synthesis of various 2-*C*-nitromethyl branched glycosides **5h**–**m**.

Glycosyl donor **2**	ROH[a]	Product **5**	Time [h]	Yield [%][b]
 **2b**	**4c**	 **5h**	6	71
	4e	 **5i**	12	54
	4f	 **5j**	12	54
 **4h**	OMe	 **5k**	12	58
 **2c**	**4e**	 **5l**	12	48
	4h	 **5m**	12	50

[a] Reaction of glycosyl donor (0.2 mmol) with 3 equiv. of ROH. [b] Yield of analytically pure product, isolated by column chromatography.



Scheme 2. Proposed mechanism of glycoside activation with $AuBr_3$.

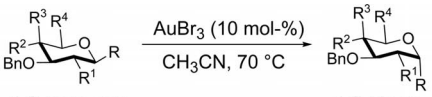
atom (intermediate **C**), as postulated very recently for Au^I-catalyzed glycosidations.[7h] However, our studies reveal that the ring oxygen atom (intermediate **D**) might be attacked as well. The issue of exo- or endocyclic oxygen activation during anomerization has been discussed for many years[11] and was kinetically examined very recently.[12] Both pathways afford different oxocarbenium ions **E** and **F**, leading to transglycosylated products **5** or α/β-anomerization (Scheme 2).

This mechanistic rationale is in accordance to our observed α/β selectivities (Tables 1 and 2). Thus, intermediate **C** is only formed if R is small (e.g. Me), which explains why only methyl glycosides serve as donors in gold-catalyzed reactions. For other simple primary alcohols **4a** and **4b** the transglycosidation is still possible to some extent, and α/β mixtures result (Table 1, Entries 1 and 2). On the other hand, secondary alcohols and disaccharides are sterically too demanding, and only intermediate **D** can be formed. Therefore, the exocyclic C–O bond cannot be cleaved anymore, but the anomerization takes place. Additionally, a coordination of Au to the nitro group has to be taken into account, resulting in a faster anomerization as discussed by Murphy for other Lewis acids and ester groups very recently.[12] Finally, α-configured products are isolated with high selectivities after longer reaction times.

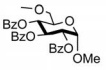
To demonstrate the generality of this anomerization, we investigated various carbohydrates under gold catalysis without addition of a nucleophile (Table 3). Thus, 2-deoxy-*C*-nitromethyl pyranosides β-**2a**–**c** reacted smoothly with 10 mol-% of $AuBr_3$ in acetonitrile at 70 °C. Complete conversion was achieved within 1–2 h, and the α-methyl glycosides α-**6a**–**c** were isolated in good to high yields (Entries 1–3). Interestingly, this anomerization proceeds faster than the transglycosidations, which explains why compound α-**6a** was formed as by-product in our initial experiments (Table 1).

Furthermore, simple methyl per-*O*-benzyl-β-glycosides **7a** and **7b** reacted selectively to the corresponding α-anomers **8a** and **8b** (Table 3, Entries 3 and 4). This important finding demonstrates that the complexation of Au^{III} by the nitro group is not a prerequisite for the anomerizations. Finally, propargyl glucoside β-**7c** and even disaccharide β-**9** can be converted into their α-anomers **8c** and **10** in slightly lower yields (Entries 5 and 6). Although anomerizations in

Table 3. Gold-catalyzed anomerizations of various β-glycosides.



1,2-*trans* or β → 1,2-*cis* or α

Entry	Substrate	R^1	R^2	R^3	R^4	R	Product	Time [h] Yield [%][a]
1	**2a**	$-CH_2NO_2$	-OBn	-H	$-CH_2OBn$	$-OCH_3$	**6a**	2 86
2	**2b**	$-CH_2NO_2$	-H	-OBn	$-CH_2OBn$	$-OCH_3$	**6b**	1 80
3	**2c**	$-CH_2NO_2$	-OBn	-H	-H	$-OCH_3$	**6c**	2 71
4	**7a**	-OBn	-OBn	-H	$-CH_2OBn$	$-OCH_3$	**8a**	12 55
5	**7b**	-OBn	-H	-OBn	$-CH_2OBn$	$-OCH_3$	**8b**	8 70
6	**7c**	-OBn	-OBn	-H	$-CH_2OBn$		**8c**	12 51
7	**9**	-OBn	-OBn	-H	$-CH_2OBn$		**10**	12 41

[a] Yield of analytically pure product, isolated by column chromatography.

the presence of $SnCl_4$ or other Lewis acids are known for many years,[11] our gold-catalyzed reactions proceed under mild conditions and give very high α-selectivities.

Conclusions

Gold-catalyzed transglycosidations can be applied for 2-*C*-branched carbohydrates. Methyl glycosides are suitable donors, which react with various alcohols at the anomeric center. Thus, 2-*C*-nitromethyl-containing glycosides are available for the first time. The reactions proceed with moderate to good yields and with high selectivity for the α-anomers. Our method is applicable for simple benzyl glycosides, the introduction of menthyl or steroidal substituents, and even the synthesis of disaccharides. All products contain nitro groups, which might be reduced and offer an easy entry to analogs of glycosamines. During the gold catalysis we observed an interesting anomerization, which was hypothesized to undergo the cleavage of the endocyclic C–O bond, and the reaction was applied to various other carbohydrates. Thus, gold(III) bromide is an efficient catalyst for transglycosidations of 2-*C*-branched carbohydrates and can be employed for β- to α-anomerizations as well. Studies for further chemical transformations, especially into analogs of glycosamines are currently in progress.

Experimental Section

General Procedure for $AuBr_3$-Mediated Transglycosylations: To a solution of glycosyl donor (0.2 mmol) and aglycon (0.6 mmol) in anhydrous acetonitrile (5 mL) was added $AuBr_3$ (10 mol-%) under argon at room temperature. The resulting mixture was heated to 70 °C and stirred until TLC showed complete conversion. The reaction mixture was concentrated in vacuo to obtain a crude residue, which was purified by silica gel column chromatography using ethyl acetate/petroleum ether as mobile phase.

Supporting Information (see footnote on the first page of this article): Spectral charts of all compounds.

Acknowledgments

S. H. thanks the Department of Science & Technology, New Delhi for a SwarnaJayanti Fellowship. T. L. acknowledges the generous supports by the Deutsche Forschungsgemeinschaft (Li 556/7-3) and the University of Potsdam. S. R. V. acknowledges a fellowship from the Council of Scientific & Industrial Research, New Delhi.

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Received: January 28, 2011
Published Online: March 4, 2011

