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COMMUNICATION

Gold-catalysed glycosylation reaction using an easily accessible leaving group

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Gold(III)-catalysed glycosylation reaction has been developed by employing a new and easily accessible leaving group synthesized from ethyl cyanoacetate. Several nucleophiles like alcohols, thiols, allyltrimethylsilane, trimethylsilyl azide and triethylsilane have been reacted to make the corresponding glycosides in good yields and with marginal to excellent α-selectivity.

Chemical glycosylation reaction involves formation of glycosidic bond between glycosyl donor and glycosyl acceptor.[1] Numerous glycosyl donors such as glycosyl halides,[2] glycosyl trichloroacetimidates,[3] *n*-pentenyl glycosides,[4] thio glycosides,[5] phosphates[6] and propargyl glycosides[7] have been reported for the glycosylation reaction. Among them, glycosyl trichloroacetimidates and thio glycosides are routinely employed in oligosaccharide synthesis. Still, there is a quest for finding new glycosyl donors which favour smooth glycosylation.

Transition metal catalysis has taken centre stage in organic synthesis in the recent time because of their versatility and wider applicability in organic synthesis. Several transition metals such as Pd, Au, Ni, Re, Rh, Cu and Ti have been known to activate glycosyl donors like glycosyl trichloroacetimidate, glycals and glycal epoxides.[8] There is considerable interest in finding novel leaving groups to employ transition metal based catalyst systems for synthesising glycosides. Gold catalysis has already marked its uniqueness in catalysing organic transformations very efficiently under ambient conditions.[9] Till now, few reports are there for the application of gold catalysis in carbohydrate chemistry. Hotha and co-workers utilised the leaving group ability of propargyloxy group under gold(III)-catalysed conditions.[7] Further, 1,2-ortho esters[10a] and methyl glycosides[10b] have also been activated using gold catalysts to make glycosides and oligosaccharides in good yields. Glycosyl halides and trichloroacetimidates have been activated under Au(I) catalysis for glycosylation reaction.[11] Gold catalysis has been applied in the activation of epoxides in glycalepoxides for glycosylation reaction to make 2-hydroxy free sugars.[12a] Glycosyl *ortho*-alkynylbenzoates have been reported as efficient glycosyl donors in the synthesis of cyclic triterpene saponin and Lupane type saponin under gold(I) catalysis.[12b] This glycosylation strategy has been applied for making nucleosides[12c] and kaemferol[12d] derivatives as well. Even the proposed isochromen-4-yl gold(I) intermediate has been isolated and structurally characterised.[12e] Because of synthetic simplicity and chemical stability, glycosyl esters have emerged as glycosyl

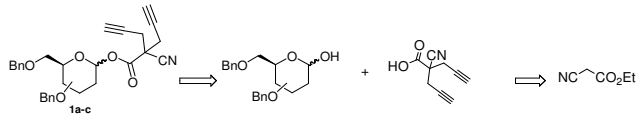
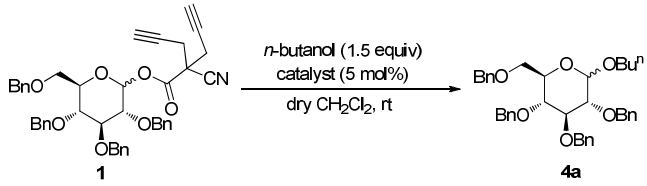


Fig. 1 Strategy for making glycosyl donor

donors for the construction of glycosidic bond. Glycosyl acetates,[13a] 2-pyridyl esters,[13b] glycosyl *p*-bromophenyl phthalates[14] and 4-pentenyl glycosyl esters[15] have been used as donors until now. Very recently, Vankar and co-workers have utilized glycosyl acetates as glycosyl donors in the gold-catalysed glycosylations.[16]

Table 1. Results of catalyst optimisation for the glycosylation

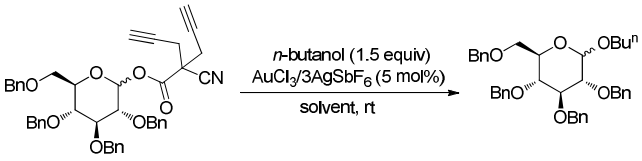


Entry[a]	Catalyst (5 mol%)	Time (h)	Yield[b] (%)	α/β[c]
1	$AuCl_3$	48	28	0.6:1
2	$AgSbF_6$[d]	48	50	1:1
3	$Cu(OTf)_2$	24	5	1.4:1
4	**$AuCl_3$/3AgSbF$_6$**	**12**	**78**	**1.2:1**
5	$AuCl_3$/3AgOTf	24	66	1.1:1
6	$AuCl_3$/3$AgBF_4$	24	22	1.1:1
7	$Au(PPh_3)Cl$	48	NR	-
8	$Au(PPh_3)Cl/AgSbF_6$	24	69	1.8:1
9	$Au(PPh_3)Cl$/AgOTf	24	44	1.3:1
10	$Au(PPh_3)Cl/AgBF_4$	24	12	1.3:1
11	$PtCl_4$/4$AgSbF_6$	24	30	1.4:1

[a] α/β of starting glycosyl ester is 1.3:1. [b] Isolated yields. [c] Ratio is based on the ^{1}H NMR integration. [d] 15 mol% of the catalyst was used.

Imagava *et al.* reported the $Hg(OTf)_2$-catalysed glycosylation reaction with glycosyl 5-hexynoates as the glycosyl donors.[17] Kunz and Zimmer have reported N-allyl carbamates as leaving group for glycosylation *via* electrophilic cyclization.[18] In our continuing efforts to synthesise glycosides under gold catalysis,[19] we have found out a simple and easily accessible leaving group for the glycosylation reaction. The design of leaving group presented in this manuscript is based on the work by Genet and co-workers. They reported a gold-catalysed cyclisation of 4-alkynyl carboxylic acids to make γ-methylene lactones.[20] In this regard, glycosyl donors **1-3** were obtained from easily accessible anomeric unprotected sugars and dipropargylcyanoacetic acid. This leaving group was designed for two reasons. First, it is easy to propargylate ethyl cyanoacetate. Additionally, there is a chance for the cyano group to participate in the stereochemical outcome of glycosylation reaction by coordinating to the oxacarbenium ion intermediate. Moreover, the cyano group cannot cyclise on the propargyl group under gold catalysis. Our initial glycosylation studies were carried out on 2,3,4,6-tetra-*O*-benzylglucopyranosyl ester **1** which was made by coupling 2,3,4,6-tetra-*O*-benzyl-D-glucose and dipropargylcyanoacetic acid. The acid fragment was made by base hydrolysis of the dipropargylated ethyl cyanoacetate.[21] We were unable to carry out monopropargylation on ethyl cyanoacetate as it always resulted in dipropargylated product preferentially.[22] Therefore the study was conducted using the leaving group having dipropargyl group. Sugar fragment and acid fragment were coupled using $DIAD/PPh_3$ system in THF solvent to form glycosyl esters **1-3** in very good yields.

Table 2. Results of solvent optimisation for the glycosylation

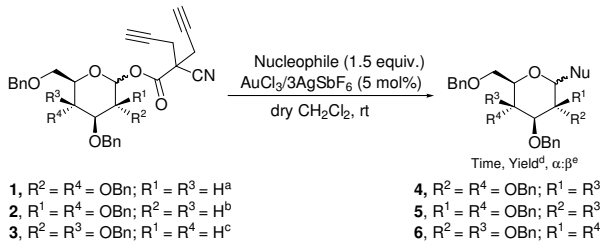


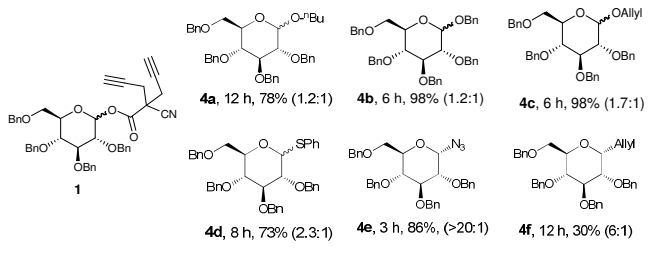
S.No[a]	Solvent	Time (h)	Yield (%)[b]	α:β[c]
1	THF	48	23	0.8:1
2	**CH_2Cl_2**	**12**	**78**	**1.2:1**
3	$ClCH_2CH_2Cl$	48	66	1.1:1
4	CH_3CN	36	67	0.6:1
5	Dioxane	48	trace	-
6	DMF	48	NR	-
7	Acetone	48	19	0.6:1

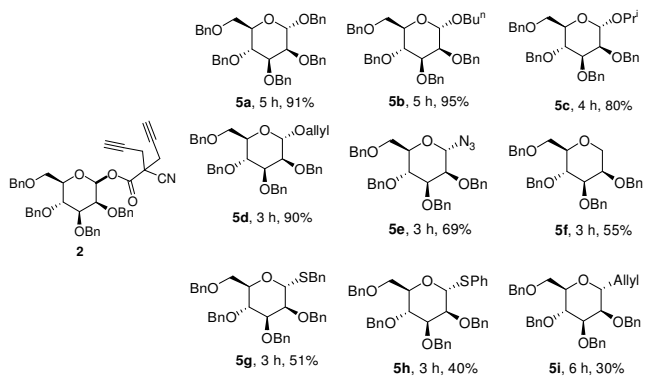
[a] Starting glycosyl ester α /β is 1.3:1, [b] Isolated yields, [c] Ratio is based on the ^1H NMR integration

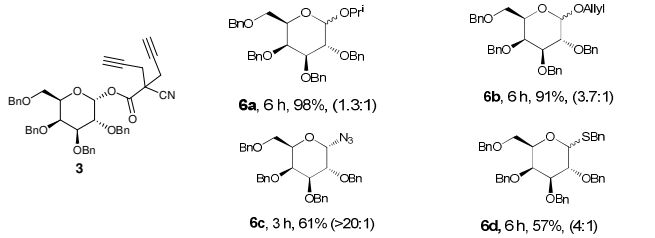
Screening of appropriate conditions for gold-catalysed glycosylation reactions was carried out on substrate **1** in dichloromethane using *n*-BuOH as the acceptor. The results are summarised in Table 1.With $AuCl_3$ alone as the catalyst, the glycosylation proceeded and gave the desired product in 23% yield as a mixture of anomers with α/β ratio 0.6:1 (Table 1, entry 1). Although the yield increased when $AgSbF_6$ was used as the catalyst, the catalyst was required in 15 mol% (Table 1, entry 2). With $AuPPh_3Cl$, the glycosylation reaction did not proceed (Table 1, entry 7). Among the catalysts screened $AuCl_3/3AgSbF_6$ was found to give good yield of *n*-butyl 2,3,4,6-tetra-*O*-benzylglucopyranoside (Table 1, entry 4). $AuPPh_3Cl/AgSbF_6$ and $AuPPh_3Cl/AgOTf$ catalytic systems also worked, but were less effective than $AuCl_3/3AgSbF_6$ in terms of yield of the product (Table 1, entries 8 and 9).

Table 3 Results of gold-catalysed glycosylation reaction to make 2,3,4,6-tetra-*O*-benzyl-D-glycopyranosides









[a] α/β ratio of **1** is 1.3:1, [b] α/β ratio of **2** is 25:1 (in the reactions resulting **5a**, **5b** and **5h**) and is 2:1 for other reactions, [c] Pure α-galactosyl ester **3** was used, [d] Isolated yields, [e] α/β ratio is based on the integration of anomeric protons in the ^1H NMR spectrum of the mixture of anomers.

After identifying $AuCl_3/3AgSbF_6$ as the suitable catalyst system, the reactions were carried out in different solvents to find the best

one which favours high yield of the product. Among the solvents screened, CH_2Cl_2, DCE and CH_3CN were found to be good for glycosylation reaction (Table 2, entries 2, 3 and 4). The selectivity observed was different in different solvents. More β-selectivity was observed in CH_3CN, THF and acetone due to possible coordination of solvents to the oxocarbenium ion from α-face making the nucleophile to attack from the β-face (Table 2, entries 1, 4 and 7). Based on these experiments, $AuCl_3/3AgSbF_6$ system in CH_2Cl_2 was chosen for investigation of substrate scope. 2,3,4,6-Tetra-*O*-benzylglucosyl ester **1** was treated with various acceptors to get the corresponding glucosides **4a-4f** as mixture of anomers. Acceptors such as *n*-butyl, benzyl and allyl alcohols reacted smoothly to give the corresponding *n*-butyl, benzyl and allyl glycosides **4a-4c** respectively in very good yields with marginal α-selectivity. Thiophenol also reacted with glucosyl donor **1** to give thioglucoside **4d** in 73% yield. Because of growing number of applications of azides in click chemistry,[23] we attempted the glycosylation with $TMSN_3$. To our delight we were successful in getting the 1-azido-2,3,4,6-tetra-*O*-benzylglucose **4e** in good yield with excellent α-selectivity. The yield was poor when allyltrimethylsilane was used as nucleophile. The reactions using monosaccharide acceptors such as methyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside and methyl-2,3,6-tri-*O*-benzyl-α-D-glucopyranoside were unsuccessful as the desired disaccharides were not obtained. Reaction of corresponding peracetyl glycosyl donor analogue of **1** with *n*-butanol under the present reaction condition did not result in any product even after 24 h. The starting material was recovered. It was the same case when $AuPPh_3Cl/AgSbF_6$ was used in the place of $AuCl_3/3AgSbF_6$. Then the glycosylation studies were carried out on 2,3,4,6-tetra-*O*-benzylmannopyranosyl ester **2** with several nucleophiles under gold-catalysed conditions. Mannosyl donor **2** reacted faster than the glucosyl donor **1** under the present reaction conditions. Nucleophiles like benzyl alcohol, *n*-butanol, isopropanol and allyl alcohol reacted smoothly to give the respective mannosides **5a-5d** in excellent yields with exclusive α-selectivity. With $TMSN_3$, α-1-azidomannoside **5e** was obtained in good yield. Interestingly, with hydride donors like Et_3SiH the donor **2** furnished the 1,5-anhydromannitol **5f** in moderate yield. Benzyl mercaptan and thiophenol were also reacted with mannosyl ester **2** to get thioglycosides **5g** and **5h** in moderate yields. As in the case of glucosyl donor **1**, mannosyl donor **2** also resulted in poor yield of C-glycoside with allyltrimethylsilane. In all the cases, mannosides were obtained as pure α-anomer. Glycosylation reactions on galactosyl donor **3** were performed with *n*-propanol and allyl alcohol to get the corresponding galactosides **6a** and **6b** in excellent yields and slight α-selectivity. Then, using $TMSN_3$ and benzyl mercaptan, 1-azidogalactoside, thiogalactoside **6c** and **6d** were synthesised in 61% and 57% yields respectively with good α-selectivity. From the mechanistic perspective,[24] we hypothesise that gold(III) first coordinates to the triple bond of the leaving group. Intramolecular attack of the carboxyl oxygen on the alkyne in 5-*exo-dig* fashion give γ-methylene lactone **A** and the oxacarbenium ion intermediate **B**. Then, sugar oxocarbenium ion **B** reacts with nucleophiles to form anomeric glycosides. To understand the mechanism of the reaction, ethyl dipropargylcyanoacetate was treated with catalytic Au(III)/$3AgSbF_6$ under the optimised conditions (Table 1, entry 4). To our surprise, we didn't observe the formation of γ-methylene lactone derivative **A**. Whereas the corresponding acid gave the methylene lactone derivative under identical reaction conditions. These observations reveal that the ring oxygen of the sugar unit facilitates the gold-catalysed cycloisomerisation to form oxocarbenium ion required for glycosylation as shown in Figure 2.

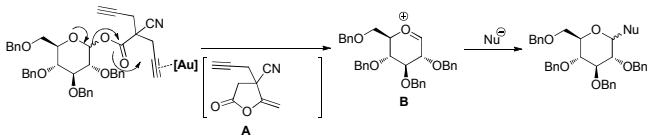


Figure 2. Plausible mechanism for gold-catalysed glycosylation

In summary, we have developed a leaving group for glycosylation reaction under gold catalysis. By employing this leaving group, gluco, manno and galactopyranosides could be prepared using a variety of nucleophiles.

Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedure, analytical data of the compounds and the spectra of glycosylated products. See DOI: 10.1039/b000000x/

1 X. Zhu and R. R. Schmidt, *Angew. Chem., Int. Ed*., 2009, **48**, 1900.

2 W. Koenigs and E. Knorr, *Berichte der deutschen chemischen Gesellschaft*, 1901, **34**, 957.

3 R. R. Schmidt and J. Michel, *Angew. Chem. Int. Ed. Engl*., 1980, **19**, 731.

4 B. Fraser-Reid, J. R. Merritt, A. L. Handlon and C. W. Andrews, *Pure & Appl. Chem.*, 1993, **65**, 779.

5 L. J. van den Bos H. S. Overkleeft G. A. van der Marel, *Chem. Soc. Rev*., 2005, **34**, *769*.

6 O. J. Plante, R. B. Andrade and P. H. Seeberger, *Org. Lett.*, 1999, **1**, 211.

7 S. Hotha and S. Kashyap, *J. Am. Chem. Soc*., 2006*,* **128***,* 9620.

8 (a) M. J. Mckay and H. M. Nguyen, *ACS Catal.*, 2012, **2**, 1563; (b) X. Li and J. Zhu, *J. Carbohydr. Chem.*, 2012, **31**, 284.

9 (a) A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem., Int. Ed.*, 2006, **45**, 7896; (b) L. Zhang, J. Sun and S. A. Kozmin, *Adv. Synth. Catal.*, 2006, **348**, 2271; (c) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410; (d) E. Jiménez-Núñez and A. M. Echavarren, *Chem. Commun.*, 2007, 333; (e) A. S. K. Hashmi, *Chem. Rev*., 2007, **107**, 3180; (f) N. Marion and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2007, **46**, 2750; (g) Z. Li, C. Brouwer and C. He, *Chem. Rev.*, 2008, **108**, 3239; (h) H. C. Shen, *Tetrahedron*, 2008, **64**, 3885. (i) H. C. Shen, *Tetrahedron*, 2008, **64**, 7847; (j) A. S. K. Hashmi, M. Rudolph, *Chem. Soc. Rev*., 2008, **37**, 1766; (k) N. Marion and S. P. Nolan, *Chem. Soc. Rev.*, 2008, **37**, 1776; (l) D. J. Gorin, B. D. Sherry and F. D. Toste, *Chem. Rev*., 2008, **108**, 3351; (m) N. Bongers and N. Krause, *Angew. Chem., Int. Ed*., 2008, **47**, 2178; (n) R. A. Widenhoefer, *Chem. -Eur. J*., 2008, **14**, 5382; (o) A. Corma, A. Leyva-Pérez and M. J. Sabater, *Chem. Rev*., 2011, **111**, 1657; (p) M. Rudolph and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2012, **41**, 2448; (q) B.-L. Lu, L. Dai and M. Shi, *Chem. Soc. Rev.*, 2012, **41**, 3318; (r) Y. Zhang, T. Luo and Z. Yang, *Nat. Prod. Rep*., 2014, **31**, 489.

10 (a) G. Suresh Kumar and S. Hotha, *Tetrahedron Lett*., 2007, **48**, 6564; (b) S. R .Vidadala and S. Hotha, *Chem. Commun*., 2009, 2505.

11 (a) S. Gotze, R. Fitzner and H. Kunz, *Synlett*, 2009, **20**, 3346; (b) For hydroamination of trichloroacetimidate derivatives of propargyl

alcohols under gold catalysis, see: A. S. K. Hashmi, M. Rudolph, S. Schymura, J. Visus and W. Frey, *E. J. Org. Chem.,* 2006, 4905.
12 (a) Y. Li, P. Tang, Y. Chen and B. Yu, *J. Org. Chem.*, 2008, **73**, 4323; (b) Y. Li, X. Yang, Y. Liu, C. S. Zhu, Y. Yang and B. Yu, *Chem. Eur. J*., 2010, **16**, 1871; (c) Q. Zhang, J. Sun, Y. Zhu, F. Zhang and B. Yu, *Angew. Chem. Int. Ed.*, 2011, **50**, 4933; d) Y. Li, W. Yang, Y. Ma, J. Sun, L. Shan, W.-D. Zhang and B. Yu, *Synlett*, 2011, 915; e) Y. Zhu and B. Yu, *Angew. Chem. Int. Ed.*, 2011, **50**, 8329.
13 (a) I. Cepanec and M. Litvić, *Arkivoc*, 2008 (ii) 19; (b) K. Koide, M. Ohno and S. Kobayashi, *Tetrahedron Lett.*, 1991, **48**, 7065.
14 S. Y. Kwon, B. -Y. Lee, H. B. Jeon and K. S. Kim, *Bull. Korean Chem. Soc.*, 2005, **26**, 815.
15 J. C. López, A. M. Gómez, S. Valverde and B. Fraser-Reid, *J. Org. Chem.*, 1995, **60**, 3851.
16 R. Roy, P. Rajasekaran, A. Mallick and Y. D. Vankar, *Eur. J. Org. Chem.*, 2014, 5564.
17 H. Imagava, A. Kinoshita, T. Fukuyama, H. Yamamoto and M. Nishizawa, *Tetrahedron Lett.*, 2006, **47**, 4729.
18 H. Kunz and J. Zimmer, *Tetrahedron Lett.,* 1993, **34**, 2907.
19 R. Balamurugan and S. R**.** Koppolu, *Tetrahedron*, 2009, **65,** 8139.
20 E. Genin, P. Y. Toullec, S. Antoniotti, C. Brancour, J.-P. Genêt and V. Michelet, *J. Am. Chem. Soc*., 2006, **128**, 3112.
21 S. Mattsson, M. Dahlström and S. Karlsson, *Tetrahedron Lett.*, 2007, **48**, 2497-2499.
22 A. S. Demir, M. Emrullahoglu and K. Buran, *Chem. Commun.*, 2010, **46**, 8032.
23 H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004.
24 (a) A. S. K. Hashmi, *Angew. Chem., Int. Ed.* 2010, **49**, 5232; (b) Y. Tang, J. Li, Y. Zhu, Y. Li and B. Yu, *J. Am. Chem. Soc*., 2013, **135**, 18396.