Gold mediated glycosylations: selective activation of propargyl 1,2-orthoesters in the presence of aglycones containing a propargyl moiety†

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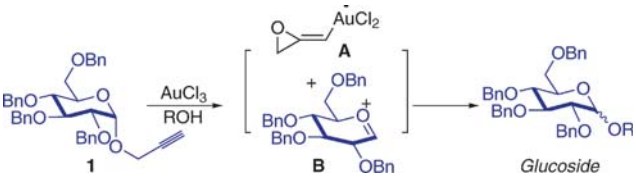
Selective activation of propargyl 1,2-orthoesters in the presence of propargyl glycosides and propargyl ethers was studied; a catalytic amount of $AuBr_3$ activated the propargyloxy group of the 1,2-orthoester thereby giving access to disaccharides with the propargyl group at the reducing end; furthermore, propargyl ethers were unaffected under the reaction conditions.

Synthesis of molecular scaffolds *via* alkyne activation exploiting alkynophilic gold catalysts has gained a lot of attention in the recent times.[1] Frequently, one of the intermediates (vinyl–Au) in the catalytic cycle is trapped by the carbon electrophiles,[2] a proton,[2] sulfonyl,[3] benzyl[4] and silyl groups[5] giving access to interesting chemical architectures.[6] However, we postulated that the expulsion of the vinyl–Au intermediate (**A**) from the pyranosyl ring occurs when a propargyl glucopyranoside (**1**) was treated with a gold(III) catalyst resulting in the formation of an oxocarbenium ion (**B**) which when attacked by an aglycone yielded a mixture of α,β-glucopyranosides (Scheme 1).[7]

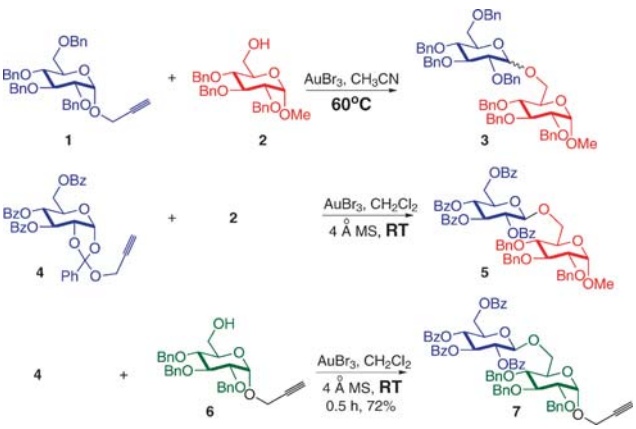


Scheme 1

Later on, propargyl 1,2-orthoesters were utilized for the 1,2-*trans* stereoselective synthesis of glycosides and disaccharides upon treatment with $AuBr_3$ in the presence of 4 Å molecular sieves powder at room temperature.[8] In this communication, we report our recent results which imply that $AuBr_3$ selectively activates the propargyloxy group of 1,2-orthoesters in the presence of competing propargyl glycosides or ethers.

To begin our investigation, propargyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranoside (**1**) and aglycone **2** were treated with 10 mol% of $AuBr_3$ in acetonitrile to obtain an α,β-mixture of disaccharides **3** in 68% yield at 60 °C while no reaction occurred at room temperature.[7a] The propargyl 1,2-orthoester of glucose (**4**) reacted with the same aglycone **2** at room temperature affording 1,2-*trans* disaccharide (**5**) in 65% yield (Scheme 2). In this premise, we envisioned that the preferential activation of propargyloxy group of the 1,2-orthoester can be achieved in the presence of propargyl glycoside if the reaction was performed at the room temperature in the presence of a catalytic amount of $AuBr_3$ and 4 Å molecular sieves powder. If successful, we should be able to synthesize disaccharides with the propargyl group at the reducing end which in turn can be exploited to synthesize glycoconjugates.[9] Many benefits envisaged by orthogonal activation[10] of *n*-pentenyl orthoesters in the presence of *n*-pentenyl glycosides were recently illustrated by Fraser-Reid *et al.*[10a] Thus we studied the effect of $AuBr_3$ in a reaction containing both propargyl 1,2-orthoester as well as the propargyl glycoside. Accordingly, we designed an aglycone **6** in such a way that it possesses both propargyl glycoside and hydroxyl functionality.

The glycosylation reaction between propargyl 1,2-orthoester (**4**) and propargyl glucoside (**6**) at room temperature revealed that $AuBr_3$ activated the propargyloxy group of orthoester to work as a glycosyl donor resulting in the formation of a disaccharide **7** with the propargyl group at the reducing end.[11,12] In the ^{1}H NMR spectrum of compound **7**, the presence of the propargyl moiety was evident since the resonances due to the alkyne group were noticed at δ 2.38 ppm (1 H, t, J 2.3 Hz) and the ^{13}C NMR spectrum showed resonances due to two anomeric carbons at δ 95.0 and 101.3 ppm indicating the presence of two sugar residues.[11]



Scheme 2 Synthesis of disaccharides by gold catalysis.

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† Electronic supplementary information (ESI) available: General experimental procedures and ^{1}H, ^{13}C, DEPT NMR spectral charts. See DOI: 10.1039/b806707d

Table 1 Synthesis of disaccharides as propargyl glycosides

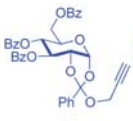
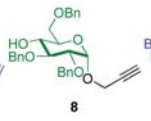
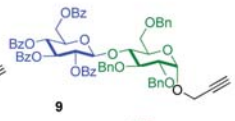
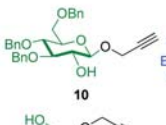
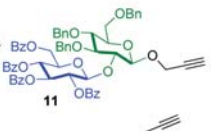
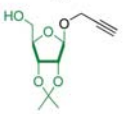
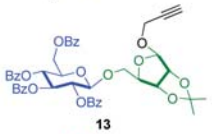
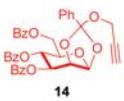
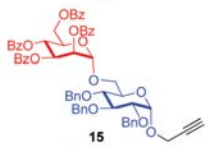
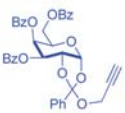
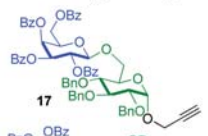
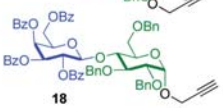
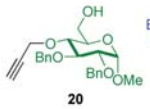
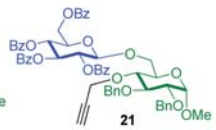
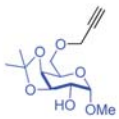
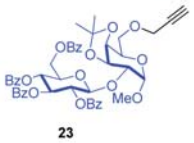
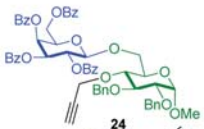
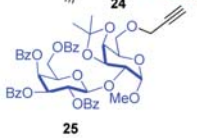
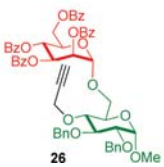
Glycosyl Donor	Glycosyl Acceptor	Product	Time	%Yield
 **4**	 **8**	 **9**	2h	68
4	 **10**	 **11**	1h	62
4	 **12**	 **13**	0.5h	63
 **14**	**6**	 **15**	2h	72
 **16**	**6**	 **17**	5h	65
16	**8**	 **18**	10h	55
16	**12**	 **19**	0.5h	60

Table 2 Synthesis of propargyl ether containing disaccharides

Glycosyl Donor	Glycosyl Acceptor	Product	Time	%Yield
4	 **20**	 **21**	0.5h	74
4	 **22**	 **23**	1h	71
16	**20**	 **24**	1h	63
16	**22**	 **25**	1h	62
14	**20**	 **26**	2h	66

This interesting observation was then investigated for the generality by means of aglycones containing secondary alcohols (**8** and **10**) and a ribofuranoside (**12**). In all the cases the reaction proceeded smoothly giving the respective disaccharides (**9**, **11** and **13**) in good yields (Table 1).[11] In continuation, the general applicability of the current study has been extended to the propargyl 1,2-orthoesters of mannose (**14**) and galactose (**16**).[11] Gratifyingly, mannosyl orthoester **14** reacted with the aglycone **6** affording disaccharide **15** in good yield and concurrently galactosyl 1,2-orthoester **16** also reacted with aglycones **6**, **8** and **12** resulting in the formation of disaccharides **17–19** with the propargyl group at the reducing end.[11] It is pertinent to mention that the formation of 10–15% of propargyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glycopyranoside was observed along with the required disaccharides.

Furthermore, the selectivity of $AuBr_3$ towards the propargyl 1,2-orthoester in the presence of propargyl ether of monosaccharides was also explored (Table 2). Accordingly, the propargyl 1,2-orthoester of glucose (**4**) was allowed to react with aglycone having 4-*O*-propargyl ether (**20**) under $AuBr_3/CH_2Cl_2$/4 Å molecular sieves powder conditions at room temperature to obtain a disaccharide (**21**) with the 4-*O*-propargyl group intact.[11] In the ^{1}H NMR spectrum of compound **21** the alkyne –CH was noticed at δ 2.38 ppm (1 H, t, J 2.3 Hz) and the ^{13}C NMR spectrum confirmed the presence of two sugar residues by showing resonances due to anomeric carbons at δ 97.6 and 101.3 ppm. Also, we synthesized a disaccharide (**23**) from the glucosyl donor **4** and the galactosyl aglycone (**22**) in 71% yield.[11] In addition to this, we have also noticed that the aglycones **20** and **22** reacted well with propargyl 1,2-orthoesters of galactose (**16**) and mannose (**14**) to give disaccharides (**24–26**) containing the propargyl ether unaffected.[11]

In summary, we have investigated the selective activation of propargyl 1,2-orthoesters in the presence of propargyl glycosides and ethers using a catalytic amount of $AuBr_3$. It is interesting to note that the $AuBr_3$ activated the propargyloxy group of 1,2-orthoesters though there is a competing propargyl moiety present in the reaction system. The utility of these propargylated disaccharides is currently underway to synthesize pseudo-oligosaccharides, neoglycoconjugates and higher saccharides.[13] Results from such studies will be reported in future.

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Notes and references

1 (*a*) A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2005, **44**, 6990–6993; (*b*) S. Ma, S. Yu and Z. Gu, *Angew. Chem., Int. Ed.*, 2006, **45**, 200–203; (*c*) R. A. Widenhoefer and S. Han, *Eur. J. Org. Chem.*, 2006, 4555–4563; (*d*) N. Asao, *Synlett*, 2006, 1645–1656; (*e*) L. Zhang, J. Sun and S. A. Kozmin, *Adv. Synth. Catal.*, 2006, **348**, 2271–2296; (*f*) A. S. K. Hasmi and G. J. Hutchings, *Angew. Chem., Int. Ed.*, 2006, **45**, 7896–7936; (*g*) D. J. Gorin and F. D. Toste, *Nature*, 2007, **446**, 395–403; (*h*) A. Fürstner and P. W. Davies, *Angew. Chem., Int. Ed.*, 2007, **46**, 3410–3449; (*i*) A. S. K. Hashmi, *Chem. Rev.*, 2007, **107**, 3180–3211.

2 (*a*) L. Zhang, *J. Am. Chem. Soc*., 2005, **127**, 16804–16805; (*b*) I. Nakamura, T. Sato and Y. Yamamoto, *Angew. Chem., Int. Ed*., 2006, **45**, 4473–4475.
3 I. Nakamura, U. Yamagishi, D. Song, S. Knota and Y. Yamamoto, *Angew. Chem., Int. Ed*., 2007, **46**, 2284–2287.
4 P. Dube and F. D. Toste, *J. Am. Chem. Soc*., 2006, **128**, 12062–12063.
5 I. Nakamura, T. Sato, M. Terada and Y. Yamamoto, *Org. Lett*., 2007, **9**, 4081–4083.
6 (*a*) A. Hoffmann-Röder and N. Krause, *Org. Biol. Chem*., 2005, **3**, 387–391; (*b*) A. S. K. Hashmi and G. J. Hutchings, *Angew. Chem., Int. Ed*., 2006, **45**, 7896–7936; (*c*) A. S. K. Hashmi, *Chem. Rev*., 2007, **107**, 3180–3211; (*d*) R. Skouta and C.-J. Li, *Tetrahedron*, 2008, **64**, 4917–4938; (*e*) J. Muzart, *Tetrahedron*, 2008, **64**, 5815–5849.
7 (*a*) S. Hotha and S. Kashyap, *J. Am. Chem. Soc*., 2006, **128**, 9620–9621; (*b*) S. Kashyap and S. Hotha, *Tetrahedron Lett*., 2006, **47**, 2021–2023; (*c*) S. Kashyap, S. R. Vidadala and S. Hotha, *Tetrahedron Lett*., 2007, **48**, 8960–8962.
8 G. Sureshkumar and S. Hotha, *Tetrahedron Lett*., 2007, **48**, 6564–6568.
9 (*a*) R. R. Schmidt, *Angew. Chem., Int. Ed. Engl*., 1986, **25**, 212–235; (*b*) K. Toshima and K. Tatsuta, *Chem. Rev*., 1993, **93**, 1503–1531; (*c*) R. R. Schmidt and W. Kinzy, *Adv. Carbohydr. Chem. Biochem*., 1994, **50**, 21–123; (*d*) K. M. Koeller and C.-H. Wong, *Chem. Rev*., 2000, **100**, 4465–4494; (*e*) H. M. Nguyen, Y. Chen, S. G. Duron and D. Y. Gin, *J. Am. Chem. Soc*., 2001, **123**, 8766–8772; (*f*) O. J. Plante, E. R. Palmacci and P. H. Seeberger, *Adv. Carbohydr. Chem. Biochem*., 2003, **58**, 35–54; (*g*) G. Ragupathi, F. Koide, P. O. Livingston, Y. S. Cho, A. Endo, Q. Wan, M. K. Spassova, S. J. Keding, J. Allen, O. Ouerfelli, R. M. Wilson and S. J. Danishefsky, *J. Am. Chem. Soc*., 2006, **128**, 2715–2725; (*h*) D. P. Galonić and D. Y. Gin, *Nature*, 2007, **446**, 1000–1007.
10 (*a*) B. Fraser-Reid, J. Ku, K. N. Jayaprakash and J. C. Lopez, *Tetrahedron: Asymmetry*, 2006, **17**, 2449–2463; For orthogonal activation studies see: ; (*b*) R. Geurtsen, D. S. Holmes and G.-J. Boons, *J. Org. Chem*., 1997, **62**, 8145–8154; (*c*) P. Pornsuriyasak and A. V. Demchenko, *Tetrahedron: Asymmetry*, 2005, **16**, 433–439; (*d*) P. Pornsuriyasak and A. V. Demchenko, *Chem. Eur. J*., 2006, **12**, 6630–6646; (*e*) A. V. Demchenko and C. D. Meo, *Tetrahedron Lett*., 2002, **43**, 8819–8822.
11 See ESI†.
12 *General experimental procedure for $AuBr_3$ mediated glycosylation*: To a solution of glycosyl donor (0.1 mmol), glycosyl acceptor (0.11 mmol) and 4 Å powdered molecular sieves in anhydrous CH_2Cl_2 (5 mL) was added $AuBr_3$ (10 mol%) under argon at room temperature. The reaction mixture was stirred at room temperature for the specified time and then filtered and the filtrate concentrated *in vacuo*. The resulting residue was purified by silica gel column chromatography using ethyl acetate–petroleum ether as the mobile phase.
13 S. Hotha and S. Kashyap, *J. Org. Chem*., 2006, **71**, 364–367.

