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Versatile gold catalyzed transglycosidation at ambient temperature†

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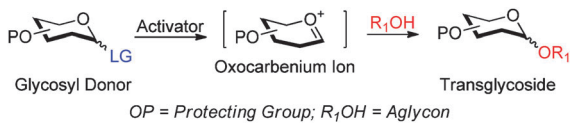
Glycosidation with stable alkyl glycosyl donors using a catalytic amount of gold salts is promising. Herein, 1-ethynylcyclohexanyl glycosides are identified as novel donors at room temperature and mechanistic investigation showed that the leaving group simply extrudes out.

Glycoconjugates and oligosaccharides belong to a class of biomolecules that play pivotal roles in various cellular events.[1] Information transfer across cells, antigen-antibody interactions, transport of toxins through the cell membrane and a host of other molecular recognition events are found to occur through glycoconjugates.[2] Glycoconjugates contain an oligosaccharide unit or glycan attached to a lipid, peptide and/or steroid in a stereodefined fashion and thus access to oligosaccharides is required.[3] Hence, development of a robust and reliable glycan-specific platform for the synthesis of oligosaccharides is highly welcomed by the entire glycobiology community.[3b]

Construction of glycans relies upon two important building blocks which are called glycosyl donors and glycosyl acceptors (or aglycons).[3a] A glycosyl donor is defined as any substance that can donate its glycon to the acceptor through an inter-glycosidic bond. Activators promote the formation of an intermediate called the oxocarbenium ion which is attacked by a nucleophile present in the form of an aglycon to form glycosides (Scheme 1). Over the last century, several glycosyl donors have been developed, explored and exploited by various groups.[3] From our laboratory, stable propargyl/methyl glycosides were discovered as glycosyl donors when activated in the presence of catalytic amounts of gold(III) halides.[4a,b] Subsequently, Yu, Mamidyala and Kunz have independently studied utility of gold salts in glycosidation reaction (Scheme 1).[5]

A gold-catalyzed transglycosidation strategy was found to be superior for glycopolymers[4c–i] though a high reaction



Scheme 1 General glycosidation reaction.

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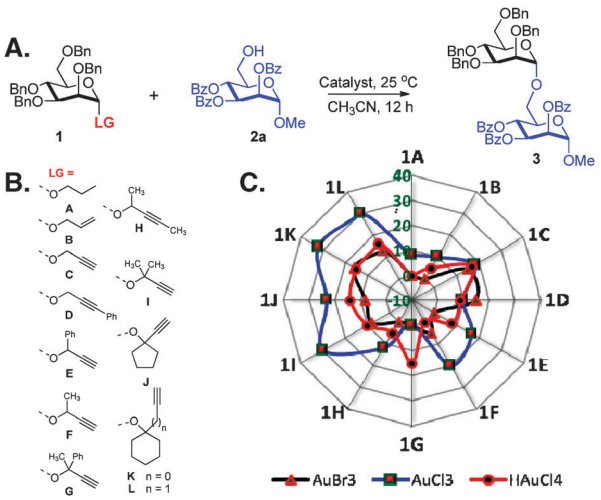


Fig. 1 Screening of leaving groups for gold-catalyzed transglycosidation at room temperature. Reaction Scheme (A), Leaving groups studied (B) and the % yield *versus* leaving group with $AuBr_3$, $AuCl_3$, $HAuCl_4$(C).

temperature (60 °C) was found to be limiting in some cases.[4j] Thus, systematic investigation of various alkyne bearing appendages at the anomeric position was carried out to find a leaving group that would facilitate transglycosidation at ambient temperatures. To begin with, synthesis of mannopyranosyl disaccharide (**3**) was considered as a model reaction (Fig. 1A) in view of earlier observations.[4a–b,4j] Alkyl substituted mannopyranosyl donors (**1A–1L**) were prepared in parallel by three simple steps; first, per-*O*-acetyl mannopyranose was reacted with alcohols **A–L** using $BF_3{\cdot}Et_2O$ and then deacetylated under Zemplén conditions and per-*O*-benzylated using NaH, BnBr in DMF (Fig. 1B).[6] Aglycon **2a** was allowed to react with potential mannosyl donors (**1A–1L**) in the presence of three gold catalysts $AuBr_3$, $AuCl_3$ and $HAuCl_4$ at room temperature for 12 h in CH_3CN.

Glycosyl donors **1A** and **1B** which do not possess alkyne groups did not proceed satisfactorily and simple propargyl substitution (**1C**) was found to give about 18% yield after 12 h at room temperature in the presence of $AuCl_3$ (Fig. 1). Single aromatic substitution on the propargyl moiety (**1D** and **1E**) also failed to give good yields where methyl substitutions (**1F**, **1H**) showed good conversion with $AuCl_3$ but not with $AuBr_3$ and $HAuCl_4$. Between *gem*-disubstituted donors **1G** and **1I**, the dimethyl donor **1I** was found to be superior. However, placing the cyclic substitution (**1J–1L**) in place of *gem*-dimethyl was found to be highly beneficial. Nevertheless, best results in the screening process were observed with donors **1I**, **1K** and **1L** (Fig. 1C).[6,7]

Increased reactivity of *gem*-disubstituted donors can be attributed to the earlier reported Thorpe–Ingold like effect.[8] Mannosyl donors **1I** and **1J** were not considered further either due to the observed instability or ease in preparation. Donor **1K** was found be better than **1L** purely because of the easy availability and low cost of **1K** though both **1K** and **1L** fared equally (Fig. 1).

To understand the mechanism, tetrahydropyran (THP) protected 1-ethynylcyclohexanol **4** (Ech–OH) was chosen as the model glycosyl donor for gas chromatography (GC) studies since glycosyl donor **1K** and THP-Ech ether (**4**) are both acetals and hence, the later should be sufficient to act as a glycosyl donor for the transglycosidation with 4-methylbenzyl alcohol (**5**).[6] Initially, the individual components THP-Ech ether (**4**), aglycon (**5**), the desired transglycosylated product (**6**), leaving group (**7**) and 4-methylbenzyl bromide (**8**) were injected into the gas chromatograph and obtained well separated retention times (Rt) (Fig. 2).

The donor **4** at Rt 36.5 min disappeared completely in 4 h and a newly formed transglycosylated product **6** (Rt 38.0 min) coincided with that of the standard and to our surprise, we observed simple 1-ethynylcyclohexanol **7** at retention time of 25.3 min and 4-methylbenzyl bromide **8** at Rt 33.2 min. Independently, 4-methylbenzyl alcohol was found to give bromide **8** in the presence of $AuBr_3$. Formation of intermediate **7** is surprising since it contradicts earlier studies which postulated that the propargyloxy group is converted to cyclopropanone through a series of unidentified intermediates.[4a]

Therefore the gold-catalyzed transglycosidation mechanism can be envisaged as alkynophilic AuX_3 co-ordinates with exocyclic oxygen and the alkyne (**9**) which can collapse to give a cyclopropenyl gold halide intermediate **10** (Fig. 3). Subsequently, exocyclic oxygen can get protonated to give intermediate **11** that could further get converted to the oxocarbenium ion **12** which is available for the attack of ROH to result in the transglycosylated product. Prototropic demetallation would result in the regeneration of AuX_3 for further catalytic action and 1-ethynylcyclohexanol (Ech-OH) **7** (Fig. 3). Important to mention that the leaving group can be removed easily under high vacuum from the reaction mixture thereby making the leaving group traceless after the reaction. Addition of a drop of Et_3N to the reaction mixture quenched the reaction suggesting the formation of HX.

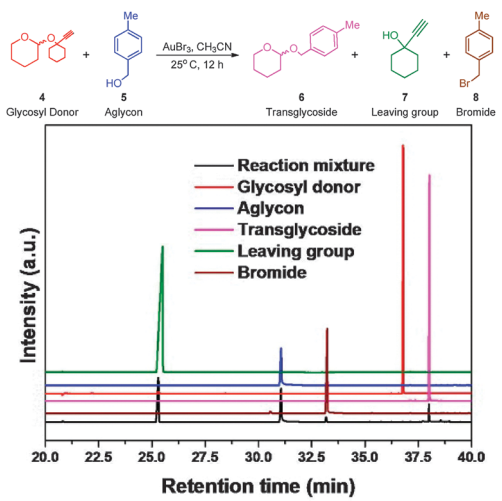


Fig. 2 Gas Chromatography studies.

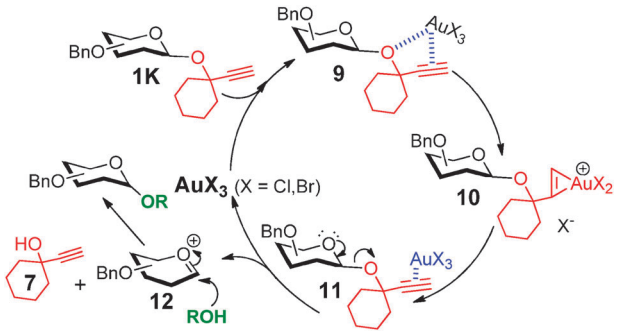


Fig. 3 Plausible mechanism for the transglycosidation.

Furthermore, the reaction of **1K** and **2a** failed to proceed in the presence of $Et_2O{\cdot}HCl$ or $AgSbF_6$/*tert*-BuCl ruling out any hidden simple Brønsted acid catalysis.[8e] In addition, reaction with Au_2O_3 which has Au(III) but not a Lewis acid showed no reaction suggesting a role for both Lewis and Brønsted acidity in the transglycosidation. Identification of a good leaving group and a plausible mechanism for the gold-catalyzed transglycosidation reaction prompted us to optimize the reaction for the right catalytic conditions (Table 1).

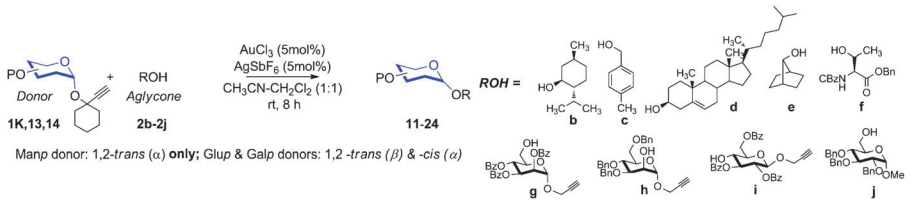
Heating the donor **1K** and aglycon **2a** to 45 °C in the presence of $AuCl_3$ or $AuBr_3$ increased the yield of the reaction substantially (Table 1, entry 1,2); further increase to 70 °C showed further improvement of yield (>80%) (Table 1, entry 3,4). Inspired by several recent literature reports on the enhancement of performance in gold catalyzed reactions by the addition of Ag-salts, addition of Ag-based co-catalysts was then studied.[9] Accordingly, optimization of glycosidation with 5 mol% each of $AuCl_3$ and AgOTf showed that the reaction can be carried out at room temperature without compromising yields (entry 5). Nevertheless, transglycosidation between **1K** and **2a** in the presence of AuX_3-$AgSbF_6$ was found to be highly efficient (91% in 4 h) at desired room temperature (entry 6,7). The best result (96% in 4 h) of disaccharide **3** was obtained when the transglycosidation reaction between **1K** and **2a** was conducted in acetonitrile–dichloromethane (1 : 1) at room temperature for 4 h in the presence of 1 : 1 quantity of 5 mol% of $AuCl_3$ and $AgSbF_6$ (entry 8) and thus all further studies were conducted with these optimized reaction conditions only.

The generality of the newly identified gold-catalyzed transglycosidation at room temperature was evaluated with a panel of aglycons (**2b–2j**) and glycosyl donors **1K**, **13** and **14**.

Table 1 Identification of the right catalytic conditions for the room temperature activation

Entry	Catalyst	Solvent	Time/h	*T*/°C	Yield (%)
1	$AuCl_3$	CH_3CN	8	45	71
2	$AuBr_3$	CH_3CN	8	45	74
3	**$AuCl_3$**	**CH_3CN**	**8**	**70**	**86**
4	$AuBr_3$	CH_3CN	8	70	82
5	$AuCl_3$ + AgOTf	CH_3CN	3	25	83
6	**$AuCl_3$ + $AgSbF_6$**	**CH_3CN**	**4**	**25**	**91**
7	$AuBr_3$ + $AgSbF_6$	CH_3CN	12	25	90
8	**$AuCl_3$ + $AgSbF_6$**	**CH_3CN + CH_2Cl_2**	**4**	**25**	**96**

Table 2 Transglycosidation at room temperature



Donor	Aglycone	Product	Yield (%)	Donor	Aglycone	Product	α : β	Yield (%)
	2b	15	93		2d	24	1 : 8.9	92
	2c	16	95		2f	25	1 : 1.3	73
	2d	17	90		2g	26	1 : 3.1	95
	2e	18	68		2i	27	1 : 3.2	73
	2f	19	74		2j	28	1 : 2.8	95
1K	2g	20	91	13	2d	29	1 : 2.7	94
	2h	21	78		2f	30	1 : 8.1	71
	2i	22	71		2g	31	1 : 8.2	94
	2j	23	96	14	2j	32	1 : 7.9	95

Transglycosidation reaction using mannopyranosyl donor **1K** and aglycons **2b**,**2c** and **2d** resulted in the formation of the corresponding glycosides **15–17** in excellent yields. Interestingly, newly identified gold-catalyzed transglycosidation conditions on monosaccharide-based primary alcohols (**2g**, **2j**) resulted in quantitative yield to give disaccharides **20**,**23** where as secondary alcohols (**2h**, **2i**) gave greater than 70% yield of disaccharides **21**, **22**. Gratifyingly, secondary alcohols **2e** and **2f** also underwent transmannopyranosylation resulting in the formation of corresponding mannopyranosides **18** and **19** (Table 2).

Furthermore, room-temperature transglycosidation using Ech-glycosides was successfully extended to glucosyl and galactosyl donors **13** and **14**. For example, aglycons which are alicyclic or carbohydrate derived primary alcohols resulted in transglycosylated products in quantitative yields where the secondary alcohols gave very high yields of tranglycosylated products (Table 2). Transglycosylated products resulting from glucosyl donor **13** and galactosyl donor **14** are found to be an α,β mixture of anomers (**24–32**) with the β-anomer being the major anomer due to the participating nature of CH_3CN which is in complete agreement with earlier observations.[5]

In summary, we identified a new gold-catalyzed transglycosidation that can be conducted at room temperature. We have studied the reaction with a panel of diverse leaving groups and found that 1-ethynylcyclohexanyl (Ech) glycosyl donors give excellent transglycosidations. Furthermore, Ech- glycosyl donors were found to be superior to simple propargyl glycosyl donors. Primary alcohols, alicyclic, steroidal alcohols were observed to give quantitative yields of transglycosylated products whereas carbohydrate-derived secondary alcohols and others result in high yields. In addition, we have also performed gas chromatography studies that gave mechanistic insights and showed that the leaving group is just coming out as 1-ethynylcyclohexanol.

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6 See Supporting Information†.

7 *General transglycosidation procedure for room temperature activation of1-ethynylcyclohexanol glycosides:* To a 3 mL 1 : 1 CH_3CN–CH_2Cl_2 solution of mannopyranosyl donor **1K** (100 mg, 0.155 mmol) and aglycon **2a** (86 mg, 0.170 mmol) was added a solution of $AuCl_3$ (2.3 mg, 7.7 μmol) and $AgSbF_6$ (2.7 mg, 7.7 μmol) in 3 mL of 1 : 1 CH_3CN–CH_2Cl_2 and stirred at 25 °C. After 4 h, dark brown reaction mixture was concentrated *in vacuo* and purified through silica gel column chromatography using 1 : 5 ethyl acetate–petroleum ether to obtain disaccharide **3** (153 mg, 96%) as a pale yellow solid.

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