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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.5b07895 • Publication Date (Web): 11 Sep 2015

Just Accepted

ACS Publications

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

An Alternative Reaction Course in *O*-Glycosidation with *O*-Glycosyl Trichloroacetimidates as Glycosyl Donors and Lewis Acidic Metal Salts as Catalyst: Acid-Base Catalysis with Gold Chloride-Glycosyl Acceptor Adducts

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ABSTRACT: Gold(III) chloride as catalyst for *O*-glycosyl trichloroacetimidate activation revealed low affinity to the glycosyl donor but high affinity to the hydroxy group of the acceptor alcohol moiety, thus leading to catalyst-acceptor adduct formation. Charge separation in this adduct, increasing the proton acidity and the oxygen nucleophilicity, permits donor activation and concomitant acceptor transfer in a hydrogen-bond mediated S_N2-type transition state. Hence, the sequential binding between acceptor and catalyst and then with the glycosyl donor enables self-organization of an ordered transition-state. This way, with various acceptors even at temperatures below -60 °C fast and high yielding glycosidations in high anomeric selectivities were recorded, showing the power of this gold(III) chloride acid-base catalysis. Alternative reaction courses via hydrogen chloride or $HAuCl_4$ activation or intermediate generation of glycosyl chloride as the real donor could be excluded. With partially *O*-protected acceptors, prone to bidentate ligation to gold(III) chloride, particularly high reactivities and anomeric selectivities were observed. Gold(I) chloride follows the same catalyst-acceptor adduct driven acid-base catalysis reaction course.

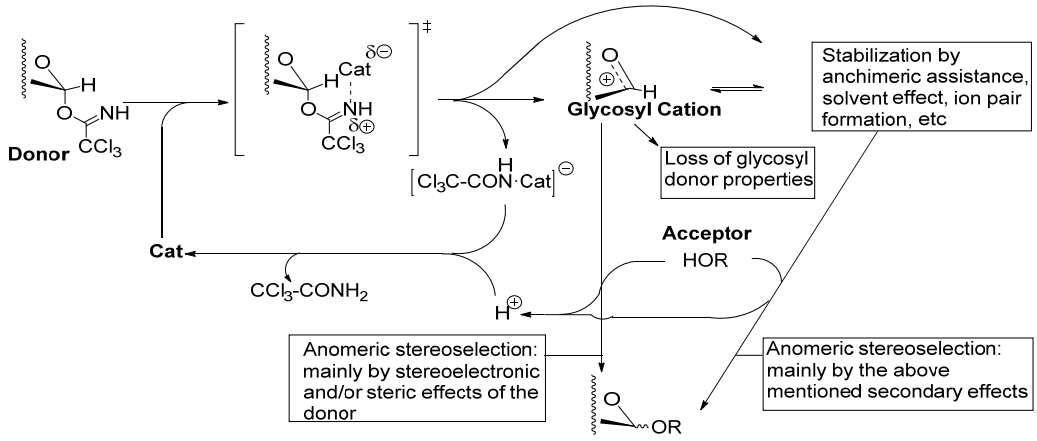
Introduction

For the activation of *O*-glycosyl trichloroacetimidate glycosyl donors in the presence of glycosyl acceptors (for instance, hydroxy compounds) mainly catalytic amounts of trimethylsilyl trifluromethanesulfonate (TMSOTf) or borontrifluoride etherate ($BF_3{\cdot}Et_2O$), respectively, are employed.[1-5] There is good evidence that the activation of *O*-glycosyl trichloroacetimidates is effected by direct attack of the Lewis acid or the Brønsted acid catalyst (Cat) at the imidate nitrogen (Scheme 1). Thus, via an *O*-glycosyl trichloroacetimidate-catalyst transition state a glycosyl oxocarbenium ion (short: glycosyl cation) intermediate and trichloroacetamide (TCAA) as leaving group are generated. The glycosyl cation reacts directly with the acceptor to the glycoside, thus the anomeric selectivity is essentially determined by steric and/or stereoelectronic effects of the glycosyl donor. Alternatively, the evolving glycosyl cation is stabilized by anchimeric assistance, the solvent or by other nucleophiles present in the reaction mixture; this way these effectors influence the yield and particularly the anomeric selectivity in the glycosidation step.

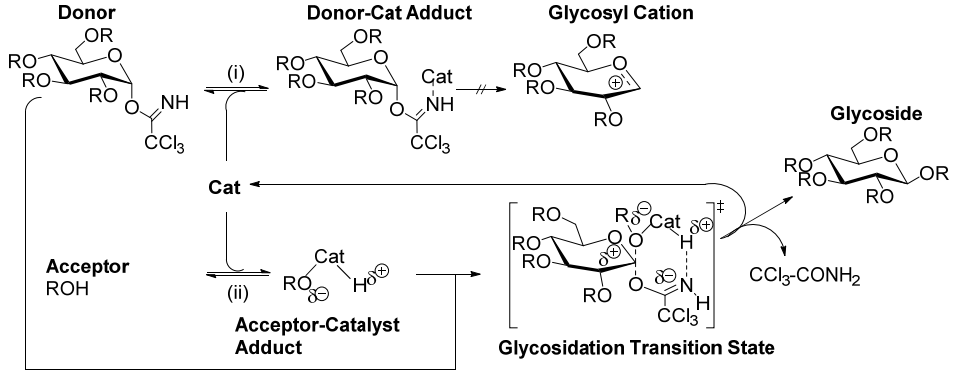
For the *O*-glycosyl trichloroacetimidate activation also quite a few Lewis acidic metal salts were investigated and the same reaction course was envisaged. Worth mentioning are Ni(II)[6-11] and Pd(II) salts[12-14], $ZnBr_2$,[15] $MgBr_2{\cdot}Et_2O$ in the presence and absence of a Brønsted acid,[16] AuCl,[17] $InCl_3$,[18] $InBr_3$,[18] $In(OTf)_3$,[18] $Sm(OTf)_3$,[19] $Yb(OTf)_3$,[20] $Sn(OTf)_2$,[21] AgOTf.[22,23]

In accordance with this general reaction scheme, catalysts with high affinity to the glycosyl donor leaving group (as for instance TMSOTf or $BF_3{\cdot}Et_2O$, respectively) exhibit also disadvantages: As these catalysts generate the highly reactive glycosyl cation intermediate irrespective of the presence or absence of an acceptor, they permit competing reactions that may lead to loss of the glycosyl donor properties. To overcome this problem, recently a variation of this reaction scheme was designed by choosing Lewis acid catalysts (i) with low affinity to the glycosyl donor leaving group, thus not directly generating glycosyl cations, however (ii) with high affinity to the glycosyl acceptor, generating in a rapid and reversible reaction an acceptor-catalyst adduct RO-Cat-H (Scheme 2).[24] The ensuing (iii) increase in proton acidity and (iv) increase of acceptor nucleophilicity in this adduct should provide the glycosyl donor activation via proton transfer of the acidified acceptor proton to the glycosyl donor and concomitantly to acceptor transfer from the negatively charged $[RO\text{-}Cat]^-$ moiety to the incipient glycosyl cation in an S_N2-type transition state. Thus, in an hydrogen-bond mediated self-organizing intramolecular acid-base catalyzed reaction the glycoside should be generated in high yield and generally high anomeric selectivity.[24,25] This reaction design could be verified by us, for instance, for $PhBF_2$, Ph_2BF or $PhSiF_3$, respectively, as catalysts.[24,26-28]

As some of the metal salts employed for *O*-glycosyl trichloroacetimidate activation are relatively weak Lewis acids, the generally claimed direct activation of the



Scheme 1. Glycosyl cation generation and eventual concomitant intra-/intermolecular stabilization and final transformation into glycoside.



Scheme 2. Acceptor-Catalyst adduct formation leads to acid-base catalyzed glycosidation with a catalyst having (i) low affinity to the donor but (ii) high affinity to the acceptor.

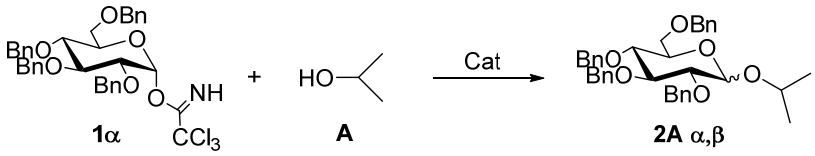
glycosyl donor by these catalysts is questionable. Rather a high affinity to the acceptor hydroxy group is expected, that favors the pathway outlined in Scheme 2. In order to study this question, that has a major impact on product formation, gold(III) chloride, with its strong tendency to form dimers (2 $AuCl_3 \rightleftharpoons Au_2Cl_6$) and in addition to position four ligands in a square-planar orientation,[29] seemed to be an ideal catalyst candidate: De-dimerization of Au_2Cl_6 by alcohols (HOR) should lead to an $RO^{\delta-}$-$AuCl_3$-$H^{\delta+}$ adduct with strong charge separation for proton-induced *O*-glycosyl trichloroacetimidate activation and sufficient propensity to concomitant alkoxide transfer to the incipient glycosyl cation (Scheme 2). Binding of the acceptor in a square-planar orientation will lead to a less hindered transition state than in a tetrahedral orientation of the four ligands around the central atom (as for instance in the PhF_2B·HOR or the Ph_2FB·HOR adducts).

Gold(III) chloride mediated activation of glycosyl donors having alkyne moiety containing leaving groups has been reported.[30-35] Very recently, Vankar *et al*. also reported on the activation of *O*-glycosyl trichloroacetimidates by gold(III) chloride in the presence of phenylacetylene.[36] Some annotations on their results will be discussed below.

Results and Discussion

Reaction course of gold(III) chloride catalysis. In order to cope with this task, first the interaction of gold(III) chloride with glycosyl donor **1α** (Scheme 3) in $CDCl_3$ as solvent was studied by NMR spectroscopy: Interaction of **1α** with 0.1 equivalents of gold(III) chloride at -50 °C was, if at all, only very weak, as indicated by NMR shift differences (Figure 1); **1α** was also not decomposed (Table 1, entry 1). Only by raising the temperature (entry 2) or by adding 1.0 equivalent of gold(III) chloride (entry 3) slow decomposition of **1α** took place. However, interaction of gold(III) chloride with an acceptor, as for instance isopropanol (**A**), was very strong (Figure 2), thus demonstrating the formation of the RO-$AuCl_3$-H adduct (entry 4). Addition of **1α** to this mixture at -60 °C, (hence, employing the inverse procedure[37] for glycosidation) led practically to exclusive formation of the *β*-glucoside **2Aβ** (Table 1, entry 5). Essentially the same result was obtained with the standard glycosidation procedure, where the donor **1α** and the acceptor **A** were dissolved first in dichloromethane (DCM) and then 0.1 equivalents of gold(III) chloride were added to the reaction mixture at -70 °C (entry 6). However, addition of the catalyst to the donor **1α** at -70 °C and thereafter adding the acceptor **A** led only to a very sluggish reaction (entry 7) that could be accelerated by raising the temperature; yet, this resulted

Table 1. Interaction and reactions between glycosyl donor 1α, acceptor A and gold(III) chloride as catalyst[a].



entry	reaction procedure	temp (°C)	time	result
1	**1**α (1 equiv) + $AuCl_3$ (0.1 equiv)	-50	30 min	no reaction, no decomp.
2	**1**α (1 equiv) + $AuCl_3$ (0.1 equiv)	rt	30 min	decomp.
3	**1**α (1 equiv) + $AuCl_3$ (1 equiv)	-50	30 min	decomp.
4	**A** (1 equiv) + $AuCl_3$ (1 equiv)	rt	30 min	adduct formation
5	**A** (1.5 equiv) + $AuCl_3$ (0.1 equiv), then **1**α (1 eq)	-70	10 min	**2A**β (90%, β)
6	**1**α (1 eq) + **A** (1.5 equiv), then $AuCl_3$ (0.1 equiv)	-70	10 min	**2A**β (87%, β)
7	**1**α (1 eq) + $AuCl_3$ (0.1 equiv), then **A** (1.5 equiv)	-70 to rt	overnight	**2A**α/β (40%, 1:2)
8	**A** (1.5 equiv) + HCl (0.1 equiv) in Et_2O, then **1**α (1 eq)	-70 to rt	overnight	trace
9	**A** (1.5 equiv) + HCl (1 equiv) in Et_2O, then **1**α (1 eq)	-70	10 min	**2A**α/β (20%, 1:3), **3**α (15%)
10	**A** (1.5 equiv) + $HAuCl_4$ (0.1 equiv), then **1**α (1 equiv)	-70	10 min	**2A**β (85%) **3**α (3%)
11	**A** (1.5 equiv) + $AuCl_3$ (0.1 equiv), then **3**α (1 equiv)	-70	3h	no reaction
12	**D** (1.5 equiv) + $AuCl_3$ (0.1 equiv) in MeCN (0.2 mL), then **1**α (1 equiv)	-60	30 min	**2D**β (85%, β)
13	PhCCH (0.1) + $AuCl_3$ (0.1 equiv) + **D** (1 equiv) then **1**α (1 equiv)	-70 to rt	overnight	no reaction
14	PhCCH (0.5 equiv) + $AuCl_3$ (0.1 equiv) + **D** (1 equiv) then **1**α (1 equiv)	rt	10 min	no reaction
15	**1**α (1 equiv) + **D** (1 equiv), then PhCCH (0.5 equiv) + $AuCl_3$ (0.1 equiv)	rt	10 min	**2D**α/β (70%, 1:1)

[a]Entries 1-4 were carried out in $CDCl_3$ (in the NMR spectrometer), entries 5-15 were carried out in DCM.

in partial decomposition of **1α**. Presumably, addition of the catalyst to the donor leads to formation of clusters $[AuCl_3 \cdot (\mathbf{1\alpha})_n$, n = 1, 2, 3...] that can only slowly be penetrated by the acceptor molecules, this way slowing down the reaction rate. Cluster formation between catalyst and acceptor has been previously observed in the "inverse procedure", [37] however in this case donor decomposition is obviously no problem and the mobility of the cluster constituents seems to be high, therefore there is only a small effect on the reaction rate.[38]

Besides the proposed gold(III) chloride mediated acid-base catalysis of this reaction (Scheme 2), alternative routes for product formation are available that had to be investigated (Scheme 3). (a) Reaction of **1α** and **A** under gold(III) chloride catalysis leads only to minor if any glycosyl chloride **3α, β** formation (Table 1, entries 5-7). Yet, as an alternative to gold(III) catalysis, acid catalysis of this reaction by hydrogen chloride (HCl), eventually generated from the reaction of gold(III) chloride with the acceptor,[39] had to be investigated. Therefore, 0.1 equivalents

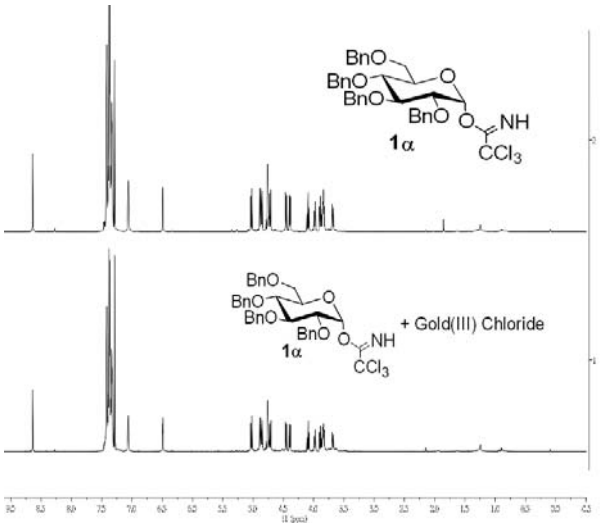


Figure 1. ^{1}H NMR of donor **1α** and a mixture of donor **1α** and gold(III) chloride (0.1 equivalents) in $CDCl_3$ at -50 °C.

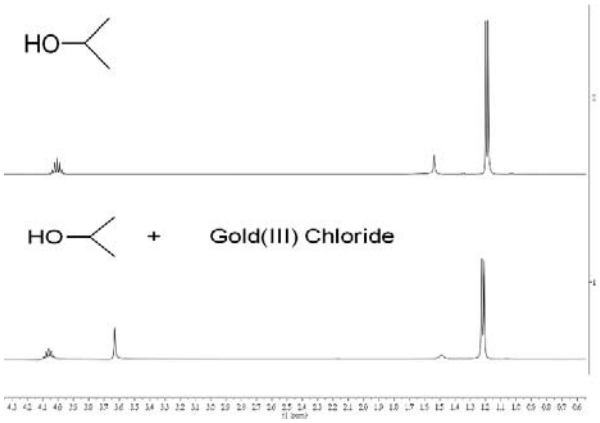
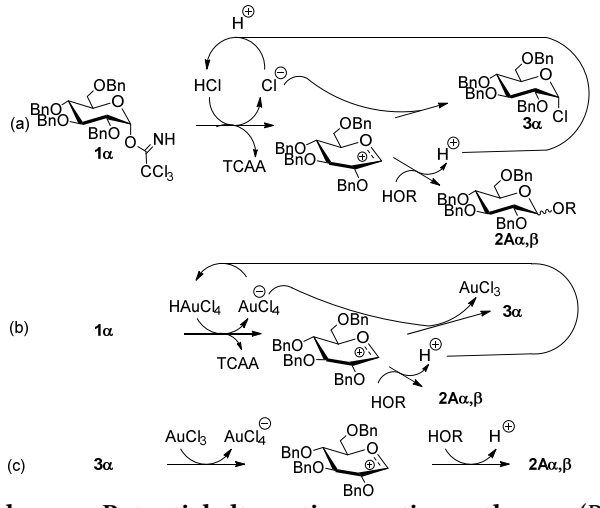


Figure 2. ^{1}H NMR of Isopropanol and a mixture of isopropanol and gold(III) chloride in $CDCl_3$ at room temperature.



Scheme 3. Potential alternative reaction pathways. (R = $CHMe_2$)

of HCl (Et_2O adduct) were added to a mixture of donor **1α** and acceptor **A**; however, only a trace of a **2Aα,β**-mixture and some glycosyl chloride **3α** were formed (Table 1, entry 8). Thus, it could be concluded that HCl is not a decisive catalyst for the observed fast *β*-glycoside formation. This was also supported by the fact that higher amounts of HCl led to formation of a product mixture of **2Aα,β** and **3α** (entry 9). (b) Alternatively, the HCl-addition product of gold(III) chloride i.e. 0.1 equivalents of $HAuCl_4$, was investigated as catalyst (entry 10). As expected, beside glycoside **2Aβ** some glycosyl chloride **3α** was now obtained. Hence, after consumption of some HCl from $HAuCl_4$ subsequently the above discussed intramolecular gold(III) chloride–mediated acid-base catalysis is effective in this reaction. Yet, these studies also exhibit that any compound in the reaction mixture with affinity to gold(III) chloride will inhibit the glycosidation, as found for substrates and/or reagents containing impurities. (c) Finally, the question remains is glycosyl chloride **3α,β**, generated as intermediate and then attacked by gold(III) chloride providing the glycosyl cation and stable tetrachloroaurate ($AuCl_4^-$), the real glycosyl donor? To this end, glycosyl chloride **3α** was activated by 0.1 equivalents of gold(III) chloride in the presence of acceptor **A**; however, no reaction was observed (entry 11). This result further supports the proposed acid-base catalysis of the glycosidation reaction between **1α** and **A** by gold(III) chloride.

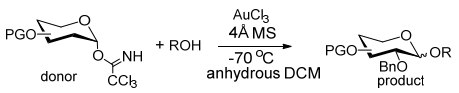
As the gold(III) chloride catalyzed reaction is sensitive to the presence of impurities that are capable of binding competitively to gold(III), it was of interest to study the influence of solvents with ligand properties. To this end, the influence of acetonitrile was studied. As expected, this molecule lowered the glycosidation rate, however not the final glycosidation result (entry 12).

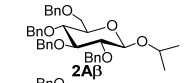
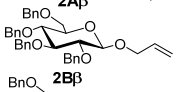
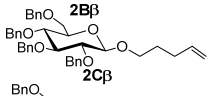
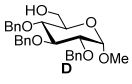
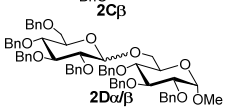
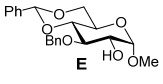
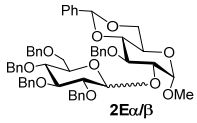
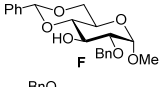
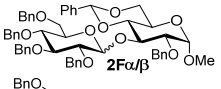
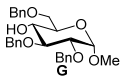
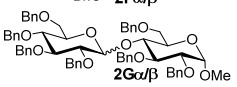
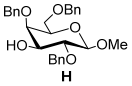
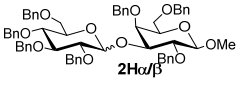
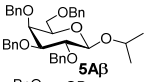
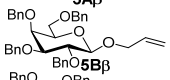
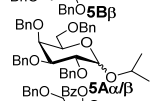
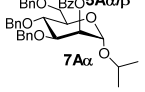
In this context also the influence of phenylacetylene was studied[36] because of the high alkynophilicity of gold(III). Application of the inverse glycosidation procedure at -70°C in the presence of phenylacetylene led to total inhibition of the glycosidation reaction; this was even so at room temperature (entries 13, 14; **D** was selected as acceptor). However, the reaction proceeded nicely with the standard glycosidation procedure,[36] i.e. first the donor, acceptor and phenylacetylene were dissolved at room temperature and then gold(III) chloride was added (entry 15). Therefore, NMR studies were performed at room temperature, that showed between gold(III) chloride and phenylacetylene complex formation. Following the inverse procedure, addition of isopropanol to this mixture leads to a new complex that can also be obtained by adding first isopropanol and then phenylacetylene to gold(III) chloride (see S.I.) However, this new complex is unable to activate *O*-glycosyl trichloroacetimidate glycosyl donor **1α** (Table 1, entries 13, 14). Hence, it seems that under the standard glycosidation procedure, formation of this inactive catalyst-phenylacetylene-acceptor complex is slower than the direct activation of glycosyl donor **1α** by the catalyst. (Table 1, entry 15).

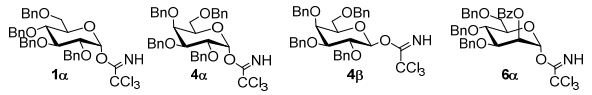
Applications to glycoside synthesis. The application of this gold(III) chloride acid-base catalysis to various acceptors (Table 2, **A-H**) having one unprotected hydroxy group and **1α** as donor led to excellent glycosidation yields and generally to high β-selectivities, particularly with reactive acceptors (Table 2, **2A-H**). Worth mentioning are the glycosidation results obtained with 2-*O*- and 4-*O*-unprotected acceptors **E** and **G**, respectively, exhibiting the high reactivity of these hydroxy groups that for steric reasons were found less reactive (particularly the 4-hydroxy group) in the $PhBF_2$ or Ph_2BF catalyzed reactions[24] (Scheme 2).

Similar results were obtained with 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl trichloroacetimidate **4α** as glycosyl donor. With acceptor **A** and **B** the *β*-glycosides **5Aβ** and **5Bβ**, respectively, were generated (Table 2, entries 9, 10). In accordance with the general reaction scheme the corresponding *β*-D-galactopyranosyl trichloroacetimidate **4β** afforded with acceptor **A** mainly the **α**-glycoside **5Aα** (entry 11). However, neighboring group participation, as in 2-*O*-benzoyl protected *α*-D-mannopyranosyl trichloroacetimidate **6α** as glycosyl donor, overrides the formation of the S_N2-type arrangement between donor and catalyst-acceptor adduct and leads to exclusive formation of the 1,2-*trans* product, i.e. the **α**-glycoside **7Aα** (entry 12).

Table 2. Gold (III) chloride catalyzed glycosidations with Trichloroacetimidates donors and various mono-*O*-unprotected acceptors.



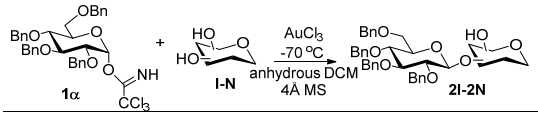
entry	donor	acceptor	product	yield β/α ratio[e]
1[a,b]	**1α**	 **A**	 **2Aβ**	90% β
2[a]	**1α**	 **B**	 **2Bβ**	88% β
3[a]	**1α**	 **C**	 **2Cβ**	91% β
4[c]	**1α**	 **D**	 **2Dα/β**	84% β:α= 12:1
5[c,d]	**1α**	 **E**	 **2Eα/β**	87% β:α= 7:1
6[c,d]	**1α**	 **F**	 **2Fα/β**	93% β:α=4:1
7[c,d]	**1α**	 **G**	 **2Gα/β**	80% β:α=6:1
8[c,d]	**1α**	 **H**	 **2Hα/β**	82% β:α=11:1
9[a]	**4α**	**A**	 **5Aβ**	87% β
10[a]	**4α**	**B**	 **5Bβ**	90% β
11[a]	**4β**	**A**	 **5Aα/β**	82% β:α=1:15
12[a]	**6α**	**A**	 **7Aα**	81% α

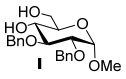
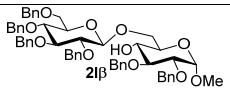
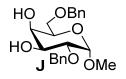
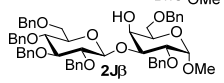
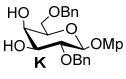
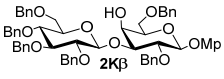
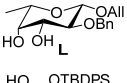
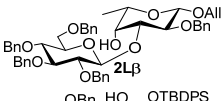
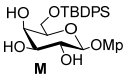
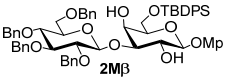
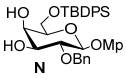
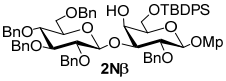


[a]Donor : acceptor ratio 1 : 1.5; [b]Under strictly anhydrous conditions the same result was obtained without addition of molecular sieves. [c]Donor : acceptor ratio 1.5 : 1; [d]The reactions were performed at – 60 °C. [e]β/α ratio was obtained from the ^{1}H-NMR spectra.

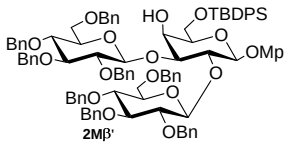
In total agreement with the proposed reaction scheme, partly protected acceptors, that act as bidentate ligands were more reactive and led to higher yields, and even higher *β*-selectivities than mono-*O*-unprotected acceptors in these gold(III) chloride catalyzed glycosidation reactions (Table 3, reactions with acceptors **I**-**N**). Obviously, this is due to binding of the acceptor via two oxygens to gold(III) under release of one molecule of HCl. However, as only 0.1 equivalents of gold(III) chloride were added, the amount of released HCl had practically no effect on the reaction result (see Table 1, entry 8). Thus, from 4,6-*O*-unprotected glucopyranoside **I** the *β*-(1-6)-linked disaccharide **2Iβ** and from 3,4-*O*-unprotected *α*-D-galactopyranoside **J** the *β*-(1-3)-linked disaccharide **2Jβ** were practically exclusively obtained (entries 1, 2).

Table 3. Gold(III) chloride catalyzed glycosidation with partly *O*-protected acceptors.



entry[a]	acceptor	product	yield β/α ratio
1[b]	 **I**	 **2Iβ**	89% β:α> 20:1
2[b]	 **J**	 **2Jβ**	93% β:α> 20:1
3[b]	 **K**	 **2Kβ**	80% β:α> 20:1
4[b]	 **L**	 **2Lβ**	75% β:α> 20:1
5[c]	 **M**	 **2Mβ**	60% β:α> 20:1
6[b]	 **N**	 **2Nβ**	82% β:α> 20:1

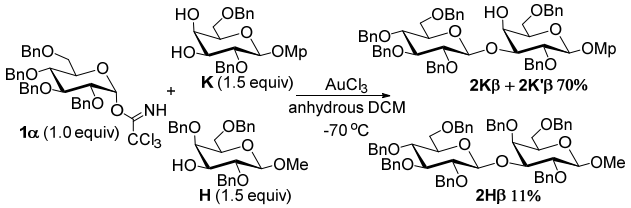
[a]Entries 1-6 were carried out with 1.0 equivalent of donor, 1.5 equivalents of acceptor and 0.15 equivalents of $AuCl_3$; [b]Small amounts (<8 %) of *β*-(1-4) linked disaccharide **2Iβ'**, **2Jβ'**, **2Kβ'**, **2Lβ'** and **2Nβ'** were also detected; [c]Trisaccharide **2Mβ'** was obtained in 16% yield.



Surprisingly, with the closely related *β*-D-galactopyranoside **K** as acceptor besides the *β*-(1-3)-linked disaccharide **2Kβ** as main product also the *β*-(1-4)-linked disaccharide **2Kβ'** was found as minor product (entry 3). Though acceptors **K** and **L** are pseudo-enantiomeric, similar regio- and stereoselectivity was observed for acceptor **L** leading to **2Lβ** and **2Lβ'** (entry 4). Hence, there is, if at all, only a minor effect of the acceptor stereochemistry on the glycosidation result. The 2,3,4-*O*-unprotected acceptor **M** afforded, as expected, the *β*-(1-3)-linked disaccharide **2Mβ** as main product. However, as minor product *β*-(1-2)-/*β*-(1-3)-linked trisaccharide **2Mβ'** was also obtained (entry 5). Linkage to the 4-position was not reported, as it is disfavored due to the presence of the bulky *tert*-butyldiphenylsilyl (TBDPS) 6-*O* protecting group, thus exhibiting how to control the regioselectivity in these reactions. This was also found for the reaction of acceptor **N** where mainly **2Nβ** was obtained (entry 6).

The glycosidation rate difference between one *O*-unprotected and di-*O*-unprotected bidentate ligands was established through a competition experiment between structurally closely related acceptors **H** and **K** under the general glycosidation conditions (see Table 2, 3). As expected, with excess **H** and **K** (1.5 equiv each) from the total disaccharide yield of 81% a 1:6 ratio of **2Hβ** vs **2Kβ** + **2Kβ'** was obtained. Hence, the initial glycosidation rate difference is about 1:10 in favor of diol **K** (Scheme 4). Contrary to the results with gold(III) chloride, use of $PhBF_2$, Ph_2BF and $PhSiF_3$ as acid-base catalysts led to a decrease in reaction rate and yield with di-*O*-unprotected bidentate ligands.[24] Thus, further support is provided that gold(III) chloride is available to bidentate ligation and to lower steric constraints in the glycosidation transition state in a square-planar ligand orientation compared with a tetrahedral ligand orientation of the acceptor oxygen(s).

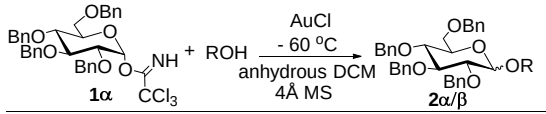
Borinic acid derivatives, accessible to bidentate ligation with the acceptors, have been studied with glycosyl halides as glycosyl donors and their activation by equivalent amounts of silver oxide.[40,41] However, as the glycosidation procedure is non catalytic, the high yielding anomeric selectivities are essentially based on neighboring group participation and high regioselectivities are only obtained with the help of bulky protecting groups, the results are not really comparable with the present work, that employs powerful gold(III) chloride acid-base catalysis for the concomitant activation of glycosyl donor and acceptor without resorting to archimeric assistance for anomeric selectivity control.



Scheme 4. Competitive reaction of 1α between acceptor K and H catalyzed by gold(III) chloride.

Gold(I) chloride as catalyst. The results obtained with gold(III) chloride raise the question, do other Lewis acidic metal salts employed for *O*-glycosyl trichloroacetimidate activation follow the same reaction course? Due to the close relationship with gold(III) chloride we looked briefly into the behavior of gold(I) chloride, for which good glycosidation results with varying anomeric selectivities were obtained at room temperature.[17] We noticed that even 1.0 equivalent of gold(I) chloride is unable to directly activate and this way decompose *O*-glycosyl trichloroacetimidate **1α**. However, with acceptor **A** complex formation was observed; following addition of donor **1α**, furnished glycoside **2Aβ** even at -60°C in very good yield (Table 4, entry 1). 3-*O*-Unprotected acceptor **F** afforded under these conditions disaccharide **2Fα, β** in 78% yield in a 1:3 ratio (entry 2); this way, the reaction rate difference became obvious, with gold(III) chloride being the more active catalyst. Yet, gold (I) chloride acts also as diol accepting entity, as it led with acceptor **K** practically to the same result, as obtained with gold(III) chloride (Tables 3 and 4, compare entries 3). This result is either due to expansion of the linear two-coordinate gold(I) complexation to a three-coordinate, trigonal-planar complexation[42] or alternatively, due to disproportionation of gold(I) chloride to gold(0) and gold(III) chloride.[43]

Table 4. Gold(I) chloride catalyzed glycosidations.



entry	acceptor	product	yield β/α ratio[c]
1[a]	**A**	**2Aβ**	84% β
2[b]	**F**	**2Fβ**	78% β:α=3:1
3[a]	**K**	**2Kβ**	81% β

[a]Donor : Acceptor ratio 1:1.5; [b]Donor : Acceptor ratio 1.5:1; [c]β/α ratio was obtained from the ^{1}H-NMR spectra.

Conclusion

Lewis acids with low affinity to the glycosyl donor leaving group but with high affinity to the glycosyl acceptor are expected to form catalyst-acceptor adducts that - appropriately selected - permit glycosyl donor activation and concomitant acceptor transfer to the incipient glycosyl cation in an S_N2-type intramolecular fashion. This novel conceptual approach to glycosidations that is facilitated by glycosyl donors accessible to activation by catalysis, as the highly reactive *O*-glycosyl trichloroacetimidate donors,[1,3] works particularly well with gold(III) chloride as catalyst. This Lewis acid turned out to be a powerful catalyst by binding firstly to the alcohol generating an adduct that reacts with the donor to the glycoside via acid-base catalysis, i.e. via intramolecular dual catalysis. The superior reactivity of this system even at low temperatures exhibits the power of this approach and permits the use of a broad acceptor range, resulting in high glycoside yields and anomeric selectivities. The access of gold(III) chloride to bidentate ligation of diols and the square-planar arrangement of the ligands turns out to be a further advantage of this catalyst system that seems to hold many more surprises, as the studies with competing ligands for gold(III) and the extension of this catalysis to gold(I) chloride display.

Experimental Section

General procedure for gold(III) catalyzed glycosidation To a solution of gold (III) chloride (4.4 μmol) and 4 Å molecular sieves (200 mg)* in 2 mL of anhydrous DCM was added acceptor **A** (66 μmol) at room temperature. After cooling down the reaction mixture to – 70 °C, highly pure donor **1α** (44 μmol), dissolved in 1 mL of anhydrous

DCM, was slowly added into the reaction. The reaction was further stirred for 30 min at this temperature. After the TLC analysis showed the completion of the reaction, the reaction was quenched by addition of triethylamine and diluted with 50 mL of DCM. Then the precipitate was filtered off through a pad of Celite. The organic layer was washed with $NaHCO_3$ (aq.) (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (hexane/acetone or hexane/ethyl acetate) on silica gel.

*When substrates, reagents and solvents are particularly carefully dried, molecular sieves are not required in order to obtain the same results. (see Table 2, entry 1).

ASSOCIATED CONTENT

Supporting Information

Full experimental details and ^1H and ^{13}C NMR spectra for all new compounds.The Supporting Information is available free of charge on the ACS Publication website.http://pubs.acs.org."

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We are grateful to the University of Konstanz for support of this work.

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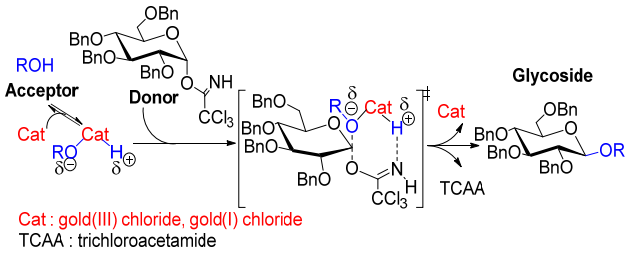
SYNOPSIS TOC



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