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The 4K reaction

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ABSTRACT

The classical Koenigs-Knorr glycosidation of bromides or chlorides promoted with Ag_2O or Ag_2CO_3 works only with reactive substrates (ideally both donor and acceptor). This reaction was found to be practically ineffective with unreactive donors such as per-*O*-benzoylated mannosyl bromide. Recently, it was discovered that the addition of catalytic (Lewis) acids to a silver salt-promoted reaction has a dramatic effect on the reaction rate and yield. A tentative mechanism for this cooperatively-catalyzed glycosylation reaction has been proposed, and the improved understanding of the reaction led to more efficient protocols and broader applications to a variety of glycosidic linkages. Since Ag_2O-mediated activation was introduced by German chemists Koenigs and Knorr, and "cooperatively catalyzed" is *Kooperativ Katalysiert* in German, we refer to this new reaction as "the 4K reaction."

1. Introduction

Oligosaccharides or glycans, in which multiple monosaccharides are connected via glycosidic bonds, are common synthetic targets for chemists. Despite of the plethora of methodologies that have been developed for the synthesis of glycosidic bonds, a universal glycosylation method that proceeds with complete chemo-, regio-, and stereoselectivity and high yields for a wide range of substrates is still lacking [1,2]. The early investigations on chemical glycosylations performed by Michael [3], Fischer [4,5], and Koenigs/Knorr [6] at the turn of the 20th century, led to excellent methods, some of which are still used for the synthesis of simple alkyl/aryl glycosides [7]. Although many other methodologies have been developed along the years [8], limitations of practically all glycosylation methods persuaded researchers to reinvestigate the original glycosyl donors. Recent work with hemiacetals [9–11] and glycosyl halides [12–14] has dramatically expanded the scope of these classical glycosyl donors. This review is dedicated to the 4K reaction, which dramatically enhanced the scope and application of the Koenigs-Knorr approach. The authors guide the reader through the main milestones of reaction development and provide an outlook for further innovations in the area.

2. Classical Koenigs-Knorr glycosylation reaction and related early studies by Fischer

The first glycosylation reaction can be traced back to 1879 when Michael reported the reaction between glucosyl chloride and potassium phenoxide to give unprotected phenyl glucoside as the product. Only few years later (1901) Koenigs and Knorr demonstrated that glycosyl bromides can react with neutral alcohols rather than alkoxides used by Michael to produce the corresponding glycosides [6]. As shown in Scheme 1A, the first reactions involved glycosidation of acetylated glucosyl bromide **1** (described as β-anomer in the original literature) with simple alcohols (methanol or ethanol). It should be noted that current understanding implies that the formation of pure β-anomer of acetobromoglucose is unlikely. These reactions could be conducted in the presence of excess alcohol without any activators or additives. However, reactions in the presence of silver carbonate (Ag_2CO_3) or silver nitrate ($AgNO_3$) provided the most promising results, and it was believed that the main role of silver salts was to scavenge the acid (HBr) formed during the reaction. The synthesis of methyl glucoside **2** was also achieved by the treatment of glycosyl bromide **1** in the presence of either barium carbonate ($BaCO_3$) or pyridine.

An alternative synthesis of methyl glucoside **2** from α-acetochloroglucose in the presence of silver carbonate was introduced by Fischer and co-workers [5]. The extension of this work led to the application of silver oxide (Ag_2O) as an alternative acid scavenger [15]. This methodology was also applied to per-*O*-benzoylated glucosyl bromide **3** (described as β-anomer in the original literature) by glycosylation with MeOH in the presence of Ag_2O to obtain the corresponding methyl glycoside **4** (Scheme 1B).

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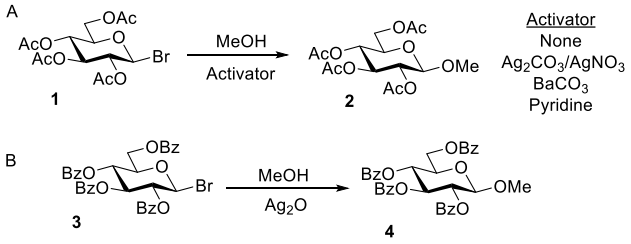


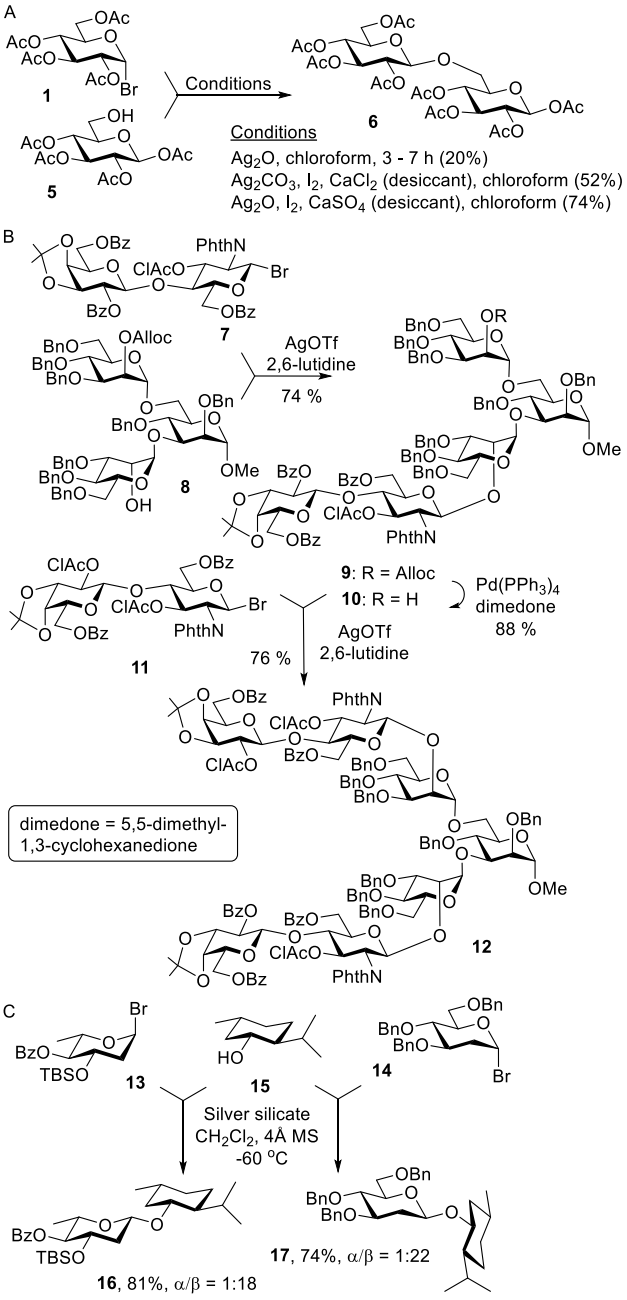
Scheme 1. First silver-promoted glycosylation reactions reported by Koenigs and Knorr (A) and Fischer (B).

3. Introduction of desiccants and other silver salts

Initially, Koenigs-Knorr glycosylation reactions were only applied to glycosylation of simple alcohols. The first synthesis of a disaccharide by coupling two monosaccharides building blocks was described by Helferich. As shown in Scheme 2A, glucosyl bromide **1** was coupled with acetylated acceptor **5** in the presence of silver oxide to afford gentiobiose **6** in 20% yield [16]. The modest yield was attributed to the presence of water that led to hydrolyzed by-products. In fact, when finely powdered calcium chloride was added as a desiccant, along with molecular iodine, gentiobiose **6** was obtained in a significantly improved yield of 52% [17]. Reynolds and Evans further improved the outcome by stirring the acceptor with silver oxide and Drierite ($CaSO_4$) followed by the addition of iodine and glycosyl bromide [18]. As a result of this improvement, an improved yield for the synthesis of gentiobiose **6** was obtained in 74% yield (Scheme 2A).

Slow reaction rates, even in the presence of a large excess of reagents and, in some cases, excess of reactants and poor yields of products led to the application of several partially soluble silver salts such as perchlorate [19,20], tetrafluoroborate [19,21], hexafluorophosphate [21], and trifluoromethanesulfonate (triflate) [21] instead of insoluble Ag_2O or Ag_2CO_3. Although being more efficient activators, these soluble silver salts were effective only upon addition of multiple equivalents. Among these, silver(I) triflate was found to be the most effective promoter for the activation of glycosyl halides [22,23]. For example, a convergent assembly of a biantennary heptasaccharide motif **12** of a human glycoprotein was accomplished as depicted in Scheme 2B [24]. Lactosamine bromide donor **7** was coupled with trimannosyl acceptor **8** using AgOTf in the presence of lutidine. As a result, pentasaccharide **9** was obtained in 71% yield. The allyloxycarbonyl (Alloc) group in compound **9** was then removed with $Pd(PPh_3)_4$ to provide glycosyl acceptor **10** in 88% yield. The latter was then glycosylated with glycosyl bromide donor **11**. Again, AgOTf and lutidine were used, and the target heptasaccharide **12** was obtained in 76% yield. Analogously, the synthesis of serotype 14 pneumococcal oligosaccharides (up to dodecasaccharide) was performed in the presence of AgOTf as reported by Oscarson [25]. Also in this application, all glycosylations were performed with glycosyl bromide donors. However, in several examples, particularly wherein underactive glycosyl donors were used, AgOTf-promoted reactions were somewhat ineffective [23,26].

Additional silver-based reagents have been investigated as promoters for the activation of glycosyl bromides such as silver imidazole-$ZnCl_2$ [27], silver silicate [28], silver silicate-alumina [28], silver zeolite [29], silver silica-alumina [30]. In particular, Paulsen and co-workers reported the use of silver silicate as a superior promoter for the synthesis of β-linked glycosides [28]. This method was applied to the stereoselective synthesis of 2-deoxy and 2,6-dideoxy *β*-glycosides by Herzon and co-worker [31]. As depicted in Scheme 2C, glycosyl bromides **13** and **14** yielded glycosides **16** and **17** in good yields (74–81%) and with high stereoselectivity (α/β = 1:18–22) when reacted with (−)-menthol acceptor **15** in the presence of silver silicate. This high stereoselectivity achieved in this application is quite impressive because 2-deoxyglycosides remain among the notable challenges in carbohydrate synthesis

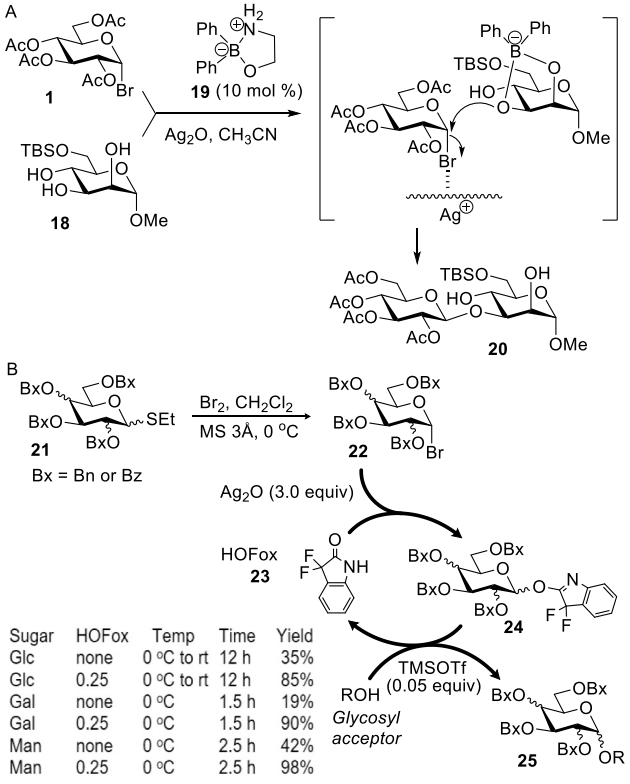


Scheme 2. Introduction of desiccants (A) and investigation of other silver salts (B–C).

[32].

4. Recent studies on enhancing silver(I)-promoted glycosylations

Borinic acid-catalyzed regioselective glycosidation of glycosyl halides was developed by Taylor and co-workers [33]. Complexation of partially protected glycosyl acceptor **18** with borinic acid **19** resulted in the formation of a borinate complex, which reacted with glycosyl bromide **1** to afford disaccharide **20** (Scheme 3A) [34]. In accordance with the Fukui index calculation [35], when bound to boron, oxygen is more nucleophilic than that of the free hydroxyl group. This allows to obtain the 1→3-linked disaccharide in a regio- and stereoselective manner. A similar approach was later taken by the authors to synthesize 2-deoxy and 2,6-dideoxy *β*-glycosides from glycosyl chlorides as donors [36].



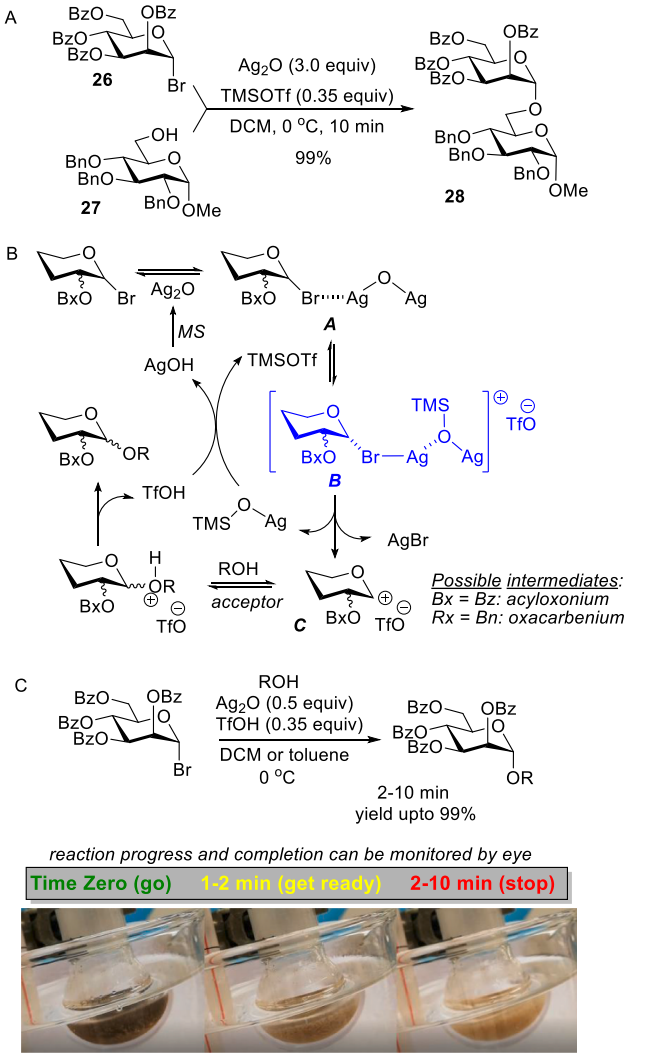
Scheme 3. Borinic acid-catalyzed reaction (A) and regenerative glycosylation (B) of glycosyl bromides.

Demchenko and co-workers developed a regenerative strategy to enhance the silver oxide promoted activation of glycosyl bromides via highly reactive *O*-imidate intermediates [37,38]. In this approach, the imidate intermediate is first generated *in situ* and then undergoes glycosidation reaction to yield the desired product and regenerate the initial aglycone. An example of this concept is depicted in Scheme 3B. Conversion of elthythio glycoside **21** gave glycosyl bromide **22** by the treatment with bromine, which was then used without purification for the regenerative glycosylation cycle. Reaction of glycosyl bromide **22** with a catalytic amount of HOFox aglycone **23** (0.25 equiv) in the presence of silver oxide yielded glycosyl OFox imidate **24** [39]. The formation of intermediate **24** was confirmed by spectroscopic techniques. Imidate **24** will then react with a glycosyl acceptor (ROH) in the presence of a Lewis acid (TMSOTf, 5–10 mol %) to afford the corresponding glycoside **25**. The leaving group from the OFox intermediate **24** departs as HOFox aglycone **23**, which can be reused to generate the next batch of OFox imidate **24**. The authors saw consistently increased yields for glycosyl donors of the gluco, galacto, and manno series (Scheme 3B). Also noticed were faster reaction rates with the increased amounts of HOFox. This methodology was applied to the synthesis of several oligosaccharides [38]. An additional improvement of this protocol was recently reported [40]. It was possible to bypass the intermediacy of glycosyl bromides by replacing Ag_2O with NIS, and the reaction could be conducted in the absence of added acidic catalyst.

5. Discovery of the 4K reaction

Recently, the Demchenko lab discovered the cooperatively-catalyzed silver-salt promoted glycosyl halide activation (internally referred to as the 4K reaction). A dramatic increase of reaction rates and yields was observed upon addition of catalytic amounts of TMSOTf to silver oxide-promoted glycosylations [41]. For example, in classical Koenigs-Knorr reaction conditions, glycosylation between per-*O*-benzoylated mannosyl bromide **26** and acceptor **27** in the presence of Ag_2O (3.0 equiv) in DCM gave only traces of disaccharide **28** (5%) after 30 h. In contrast, when essentially the same reaction was performed in the presence of 20 mol % of TMSOTf, disaccharide **28** was obtained practically instantaneously (<5 min) and nearly quantitatively (99% yield, Scheme 4A). After preliminary screening of the reaction conditions, the amount of Ag_2O could be reduced to 2.0 equiv. Since no reaction took place in the presence of TMSOTf only, this is an example of a cooperative catalysis. Ag_2O-mediated activation was introduced by German chemists Koenigs and Knorr, and "cooperatively catalyzed" is *Kooperativ Katalysiert* in German, we refer to this new reaction as "the 4K reaction." The 4K reaction was applied to the synthesis of a variety of glycosides of different series.

To gain a better understanding of these findings, we proposed a tentative reaction mechanism (Scheme 4B). Following the expected coordination step between silver oxide and the anomeric bromide (**A**), silylation of the oxide oxygen creates intermediate (**B**), characterized by a weaker Ag–O bond and a stronger Ag–Br bond, therefore shifting the equilibrium towards the departure of the anomeric bromide that results in precipitation of AgBr making this step irreversible. The nature of the protecting group at C-2 influences the nature of intermediate **C**, either as an oxacarbenium or acyloxonium ion, which then reacts with the glycosyl acceptor. Modest stereoselectivity observed when non-participating groups are present at C-2 is indicative of the presence of the oxacarbenium ion intermediate. Deprotonation followed by TMS



Scheme 4. The 4K reaction: cooperatively-catalyzed (*Kooperativ Katalysiert*) Koenigs-Knorr glycosylation.

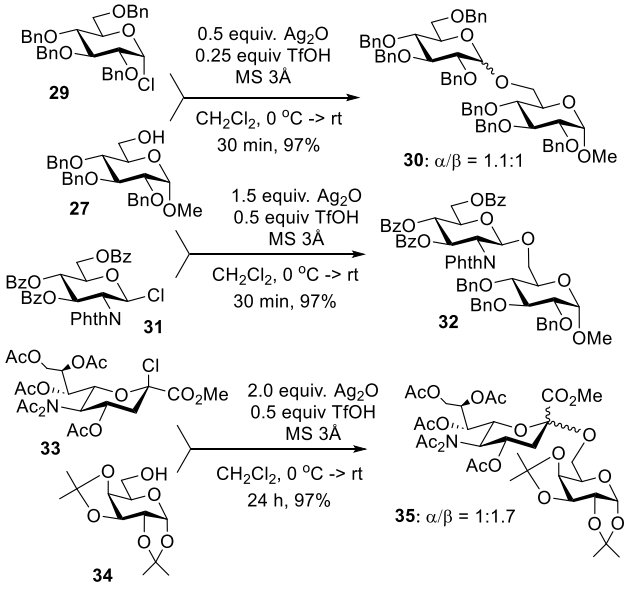
exchange regenerate TMSOTf that is recycled back into the reaction. Decomposition of silver hydroxide that loses a water molecule to the desiccant (molecular sieves) generates silver oxide. The formation of silver triflate *in situ* was excluded by the lack of activation of STaz [42] and SBox [43,44] glycosyl donors under these reaction conditions, because these thioimidate donors are readily activated with AgOTf.

By a detailed investigation of the optimal reaction conditions, and, by analyzing the proposed mechanism, it was concluded that a complete activation of glycosyl bromide donors can be accomplished with as little as 0.50 equiv of silver oxide (stoichiometric silver). Additional studies on the roles of different silver salts, Lewis/Brønsted acid additives, and solvents revealed further particulars of this cooperatively catalyzed reaction [45]. Finally the 'optimal' reaction conditions proved to be of 0.50 equiv of silver oxide and 0.35 equiv of TfOH in toluene (Scheme 4C). Interestingly, it is possible to perform a qualitative visual monitoring of the progress of the reaction, as the glycosidation proceeds from dark brown-black appearance due the presence of Ag_2O in the reaction mixture to decolorization when 0.50 equiv of Ag_2O has been entirely consumed. The proposed mechanism of the TfOH-catalyzed reaction will be discussed in the next subsection (refer to Scheme 6C).

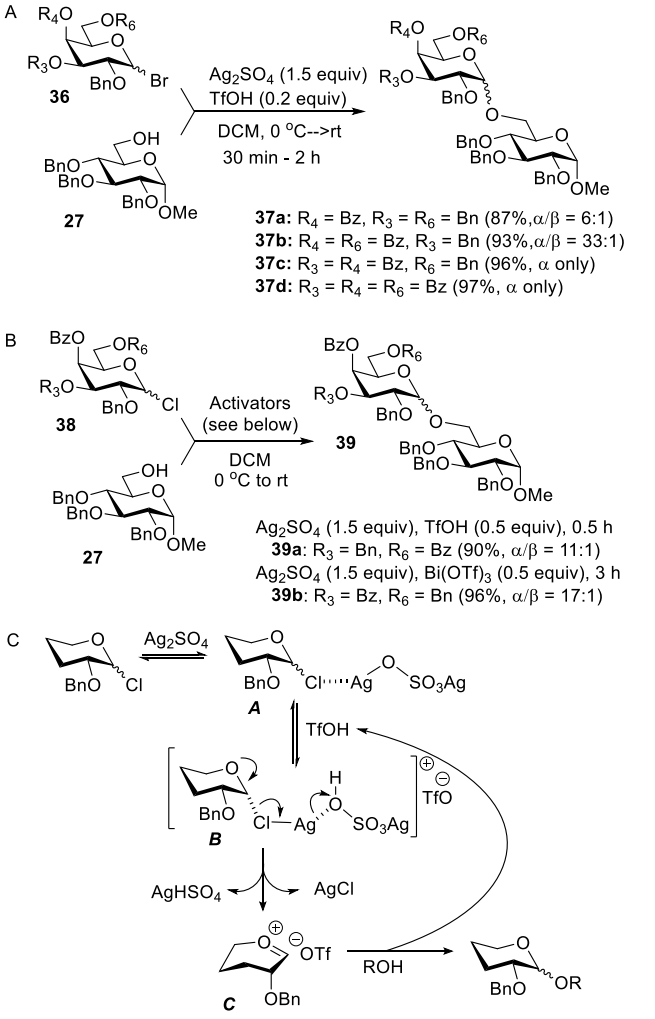
6. Expanding the scope of the 4K reaction

Subsequently, the Demchenko group investigated the 4K reaction with glycosyl chlorides [45]. High yields were obtained in the reaction between glucosyl chloride **29** and acceptor **27** in the presence of 0.50 equiv of Ag_2O and 0.25 equiv of TfOH. As a result, disaccharide **30** was obtained in 30 min in 97% yield (Scheme 5) [46]. Similar results were also achieved with secondary glycosyl acceptors. For chloride donors of the manno- and galacto-series, higher amounts of TfOH (0.50 equiv) were needed to maintain high yields (98%+) and fast reaction rates. Similar reaction conditions were needed for glycosidation of glucosamine and sialic acid building blocks. Thus, coupling between glycosyl acceptor **27** and phthalimide-protected glycosyl chloride **31** in the presence of 1.5 equiv of Ag_2O and 0.5 equiv of TfOH gave disaccharide **32** in 97% yield. Similarly, coupling between sialyl chloride **33** and primary glycosyl acceptor **34** gave disaccharide **35** in an excellent yield of 97% yield, albeit with poor stereoselectivity ($\alpha/\beta = 1{:}1.7$, Scheme 5).

Since glycosyl bromide donors bearing a non-participating (benzyl) group at C-2 provided no stereoselectivity, Demchenko and co-workers investigated galactosylations with glycosyl donors equipped with



Scheme 5. The 4K reaction with glycosyl chlorides.



Scheme 6. Application of the 4K reaction to the stereoselective synthesis of α-galactosides.

remote benzoyl groups, which are known to favor 1,2-*cis* glycosides. Earlier studies by Boons showed that the 4-*O*-acyl group is helpful to ensure high stereoselectivity in galactosylations [47]. However, under the 4K reaction conditions, the single acyl group was insufficient. Thus, when galactosyl bromide **36**, equipped with 4-*O*-benzoyl group, was glycosylated with acceptor **27** disaccharide **37a** was obtained in 87% yield with predominant albeit unimpressive α-selectivity ($\alpha/\beta = 6.0{:}1$, Scheme 6A) [48]. Cooperative catalysis of choice for this application consisted of Ag_2SO_4 (1.5 equiv) and TfOH (0.20 equiv) in DCM. A much higher 1,2-*cis* α-galacto selectivity was achieved from galactosyl bromide **36** equipped with 4- and 6-OBz groups. This reaction produced the respective disaccharide **37b** in 93% yield ($\alpha/\beta = 33.0{:}1$). Similarly, chloride having 3- and 4-OBz groups or 3-, 4-, and 6-OBz groups produced the respective disaccharides **37c** and **37d** in excellent yields and with exclusive α-selectivity.

Subsequently, this study was extended to glycosyl chloride donors **38** (Scheme 6B). In this application, the optimal reactions conditions comprised cooperative Ag_2SO_4/TfOH or Ag_2SO_4/$Bi(OTf)_3$ promoter system [49]. It is known that $Bi(OTf)_3$ alone can activate chlorides and bromides [50], but the 4K reactions with silver(I) are typically much faster, give higher yields and stereoselectivities. It is believed that the activation of chlorides follows a similar 4K activation pathway as that proposed for bromides (*vide supra*). Interaction of the glycosyl chloride donor with Ag_2SO_4 yields intermediate **A** which is then activated by the action of TfOH to produce highly polarized intermediate **B** (Scheme 6C).

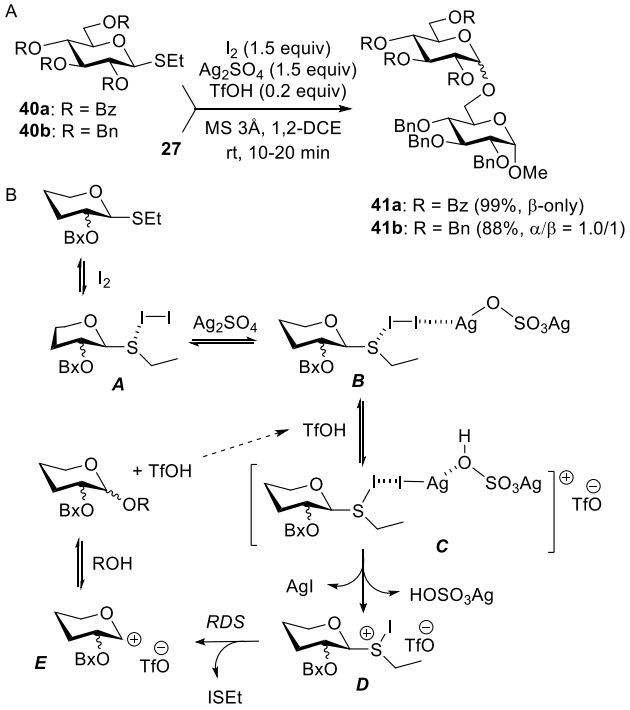
This step can therefore be accomplished when different protic or Lewis acids are added, such as $Bi(OTf)_3$. The departure of the leaving group leads the formation of insoluble AgCl, $AgHSO_4$, and generates intermediate oxacarbenium ion **C**. The latter undergoes a poorly stereoselective nucleophilic attack by the acceptor, unless other stereocontrolling factors are employed. At this step, regeneration of TfOH used in catalytic cycle takes place.

While these results for glycosidation of bromides and chlorides were quite impressive, all halides, except per-*O*-benzoylated bromides, were obtained from thioglycoside precursors. Therefore, on practice this is a two-step conversion from thioglycosides to *O*-glycosides, which appealed to us as one of the conceptual limitations of the 4K reaction. Therefore, we began a quest for identifying reaction conditions which would ensure direct conversion of thioglycosides into O-glycosides and glycans. For this purpose, we have explored molecular iodine, which was originally investigated by Field as a mild promoter for the activation of methyl thioglycosides [51]. Our own study with this promoter was very instrumental for creating the basis for differentiating the reactivity levels of the armed and superarmed thioglycosides [52]. Indeed, iodine is able to activate reactive thioglycosides. However, no reaction took place with less reactive per-*O*-benzoylated donor such as donor **40a**, even after 24 h. When the same reaction was performed with I_2 (1.5 equiv), under the 4K reaction conditions in the presence of Ag_2SO_4 (1.5 equiv) and TfOH (0.2 equiv), disaccharide **41** was rapidly produced (20 min) in 99% yield (Scheme 7A) [53]. We then applied the 4K reaction conditions to glycosidation of benzylated thioglycoside donor **40b**. This reaction was very swift, and the disaccharide was produced in 10 min in 88% yield. This reaction was non-stereoselective due to the lack of stereodirecting handles such as a participating group at C-2.

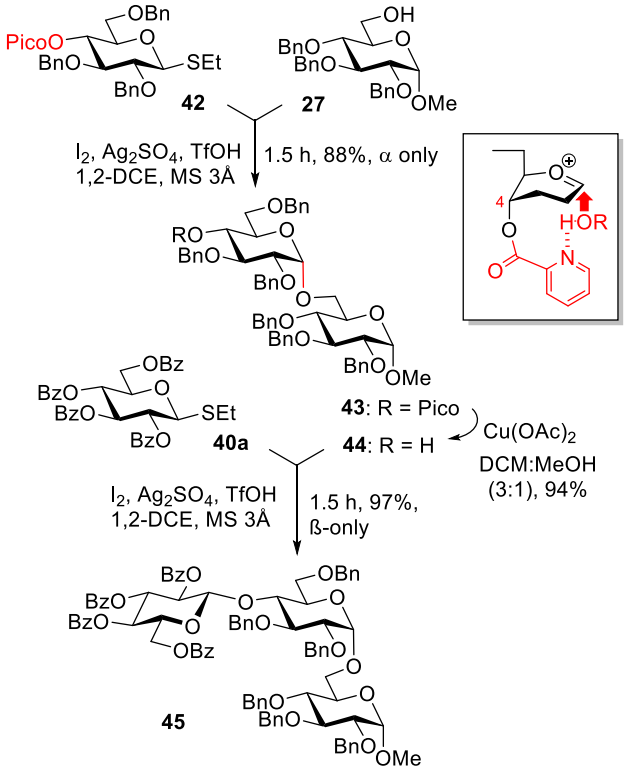
Mechanistically, the reaction with thioglycosides differs from those reactions when glycosyl halides are used. In this case, interaction of the thioglycoside starting material with thiophilic iodine will result in intermediate **A** (Scheme 7B). It should be noted that neither Ag_2SO_4 nor TfOH, individually or in cooperation, prompt the leaving group departure in thioglycosides. Intermediate **A** will dissociate only in the case of reactive (armed) glycosyl donors. However, with unreactive thioglycosides it will remain intact, and will eventually equilibrate back to the starting material. That is unless the halophilic silver salt is added, which will advance the reaction to complex **B**. Even complex **B** would not yet prompt the leaving group departure with the unreactive substrates. Only upon addition of catalytic TfOH, a strongly ionized species **C** is formed. The latter will readily dissociate producing the reactive intermediate **D** along with AgI and $AgHSO_4$. The formation of insoluble AgI implies that there is no clear path by which glycosyl iodide can be formed in this reaction because iodide anion is removed from the reaction medium. Intermediate **D** will then dissociate to form glycosyl cation **E**. Depending on the nature of the protecting group at C-2, intermediate **E** will be stabilized either via acyloxonium or oxacarbenium intermediate. The latter will react with the glycosyl acceptor (ROH) to form a protonated glycoside, which, upon deprotonation, will lead to the desired glycoside product. Also produced at this stage is TfOH that can be used in the next catalytic cycle.

To explore the scope of this reaction, we investigated other series of glycosyl donors and comparable results were obtained with *S*-phenyl and *S*-tolyl glycosides. Our subsequent studies with glycosyl donors of the galacto- and manno-series demonstrated that I_2/Ag_2SO_4/TfOH-catalyzed reactions are swift and high yielding [53]. However, it also became evident that these 4K reactions entirely lack stereocontrol in case of 2-*O*-benzylated glycosyl donors.

To gain a stereocontrolling mode we moved on to investigating whether these new reaction conditions would be compatible with the H-bond-mediated Aglycone Delivery (HAD) pathway [54]. The HAD reaction is based on the discovery that glycosyl donors equipped with 3-, 4-, or 6-*O*-picoloyl (Pico) protecting group provide high *syn*-selectivities in respect to the Pico group [54]. In the HAD reactions, the glycosyl acceptor forms a H-bond with the Pico nitrogen of the donor. Upon activation of the leaving group, the acceptor (aglycone) is delivered to form the glycosidic bond with high *syn*-selectivity in respect to the remote Pic/Pico group (illustrated for 1,4-*syn* in Scheme 8) [54]. Using the 4K reaction conditions comprising I_2/Ag_2SO_4/TfOH, glycosidation of 4-*O*-picoloylated glucosyl donor **42** with 6-OH acceptor **27** produced



Scheme 7. The 4K reaction for the direct activation of thioglycosides.



Scheme 8. Application of the 4K reaction to HAD-assisted α-glucosylation and iterative glycan synthesis.

the corresponding disaccharide **43** in 88% with complete α-selectivity. We then turned our attention to investigating multi-step glycan syntheses. For this purpose, we subjected disaccharide **43** to chemoselective removal of the Pico group in the presence of $Cu(OAc)_2$-H_2O in a mixture of DCM/MeOH (3/1, v/v) [55] that was achieved in 94% yield. The resulting 4′-OH disaccharide acceptor **44** was glycosylated with donor **40a** to afford trisaccharide **45** in 97% yield with complete β-selectivity (Scheme 8).

7. Conclusions and outlook

To address the need for accessible glycans in the expanding areas of glycoscience, it is imperative to keep on investigating new synthetic strategies and/or improvement of past methodologies. Towards this goal, many scientists have turned their attention to reinvestigating glycosyl halides. Initial studies of the cooperatively catalyzed Koenings-Knorr (4K) reaction showed that the activation of glycosyl bromides and chlorides can be swift and efficient. Excellent yields have been achieved with many substrates. As demonstrated by several substrates and targets, this method offers new synthetic capabilities and helps to revisit cases where glycosylations previously showed slow rates, gave low yields, or did not work at all. This reaction evolved into the 4K reaction in the presence of iodine for the direct activation of conventional thioglycosides using cooperative catalysis. Interestingly, this reaction does not proceed via intermediacy of glycosyl halides. The stereoselectivity of the 4K reaction can be enhanced by remote groups. The fact that the 4K reaction is compatible with the HAD method offers a promising avenue for further exploration.

Along the optimization studies, an unusual reactivity trend has been noticed in these cooperatively catalyzed glycosylation conditions, where benzoylated α-bromides were much more reactive compared to their benzylated counterparts [45]. The higher reactivity of benzoylated α-bromides compared to their benzylated counterparts strikingly contradicts the armed-disarmed theory proposed by Fraser-Reid [56]. This was found to be consistent irrespective of silver salts, acids, and sugar series employed. Subsequent studies are needed to uncover the nature of this phenomenon.

Monosaccharide building blocks are a popular choice for synthetic chemists because they provide a green source of chirally pure materials. Many methods for connecting two monosaccharides via a glycosidic bond have been developed, but many current approaches rely on toxic reagents for the activation of the leaving group. The enhanced knowledge of reaction intermediates and pathways of the 4K reaction with thioglycosides have a potential to lead to future breakthroughs. The availability of dependable and general methods is essential for producing synthetic glycans to boost innovations and applications in glycosciences. As future development, we envisage focus on greener metal salts that have affinity to iodine rather than sulfur. This emphasis sets the 4K reaction in the presence of iodine apart from all previous studies involving thioglycosides.

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CRediT authorship contribution statement

Alexei V. Demchenko: Writing – original draft, Supervision, Funding acquisition, Conceptualization. **Cristina De Meo:** Writing – review & editing, Resources, Formal analysis.

Declaration of competing interest

The authors declare no competing financial interests.

Data availability

No data was used for the research described in the article.

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