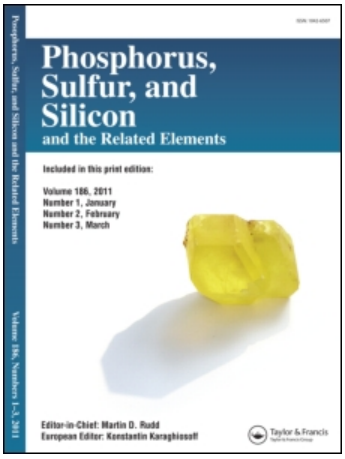

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Carbohydrate Chemistry of the Anomeric Carbon-Sulfur Bond

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CARBOHYDRATE CHEMISTRY OF THE ANOMERIC CARBON-SULFUR BOND

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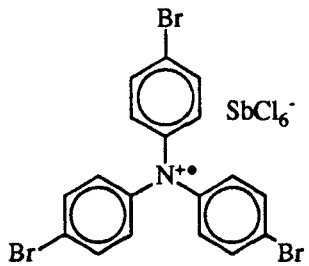
Abstract: Aryl and alkyl *S*-glycosides and sulfones are ideal precursors of three classes of reactive intermediates : anomeric carbenium, anion, and radical, and thus play a remarkable role in carbohydrate chemistry of the anomeric carbon atom. Reported reactions will include :
- A conceptually novel glycosylation reaction based on the activation of thioglycosides by a one electron -transfer reagent
- Uses of a novel class of glycosyl donors : anomeric *S*-xanthates of 2-azido sugars.
- Selective synthesis of α and β *C*-glycosides using anomeric reductive lithiation or reductive samariation of phenyl *S*-glycosides or sulfones.
- Convenient synthesis of substituted pyranoid glycals
- Expeditious synthesis of *C*-disaccharides by SmI_2 induced intramolecular coupling reaction of tethered glycosyl phenyl sulfone and exomethylene sugar.

Key words : Aryl and alkyl *S*-glycosides, phenyl glycosyl sulfones, one electron oxidation, electrolysis, anomeric *S*-xanthates, *C*-glycosides, pyranoid glycals, *C*-disaccharides, samarium (II) diiodide

The main stream of carbohydrate chemistry is devoted to the use of sugars as chiral pool for the synthesis of optically active natural products and to selective preparation of oligosaccharides[1] which are compounds of growing importance in biology. The simple and efficient construction of α or β *O*- and *C* -glycosides is indeed a central problem in the field. The aim of this lecture is to present results obtained in the author's laboratory which demonstrate the usefulness of the anomeric carbon sulfur bond within the context of glycosylation.

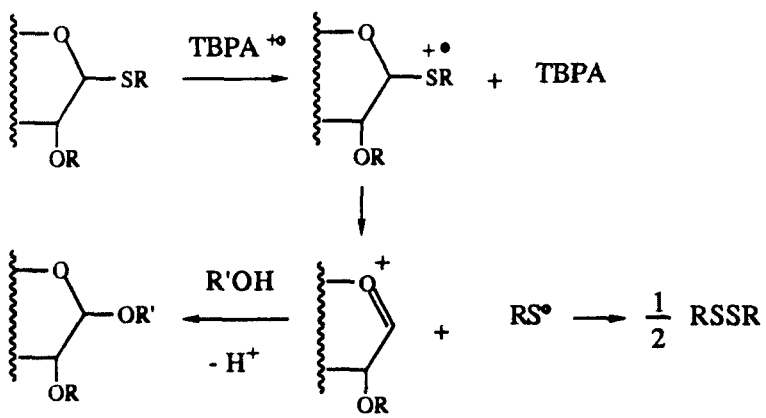
THE ONE-ELECTRON CHEMICAL OR ELECTROCHEMICAL TRANSFER APPROACH TO GLYCOSIDES

Thioglycosides[1] are currently attracting considerable attention as glycosylating agents, mainly due to their stability during various chemical transformations. The activation of 1-thioglycosides usually involves the formation of a reactive sulfonium intermediate through a two-electron process, taking advantage of the well-know affinity of the sulfide group for soft electrophiles[2], or the use of heavy metal salts[3]. It is interesting to note that $NOBF_4$ [4] and $Cu(CH_3CN)_4(BF_4)_2$ have been shown by Musker[5] to be typical one-electron oxidizing agents of peculiar thioethers in acetonitrile. We thus decided to use the property of sulfur to easily undergo a one-electron oxidation, resulting in a reactive sulfur-centered radical cation, to achieve novel types of *O*-glycosylation. We anticipated that tris (4-bromophenyl) ammoniumyl hexachloroantimonate ($TBPA^{+\bullet}$), a stable commercial radical cation known as a one-electron transfer reagent, might be a suitable promoter for homogeneous one-electron oxidation of sulfur in acetonitrile.



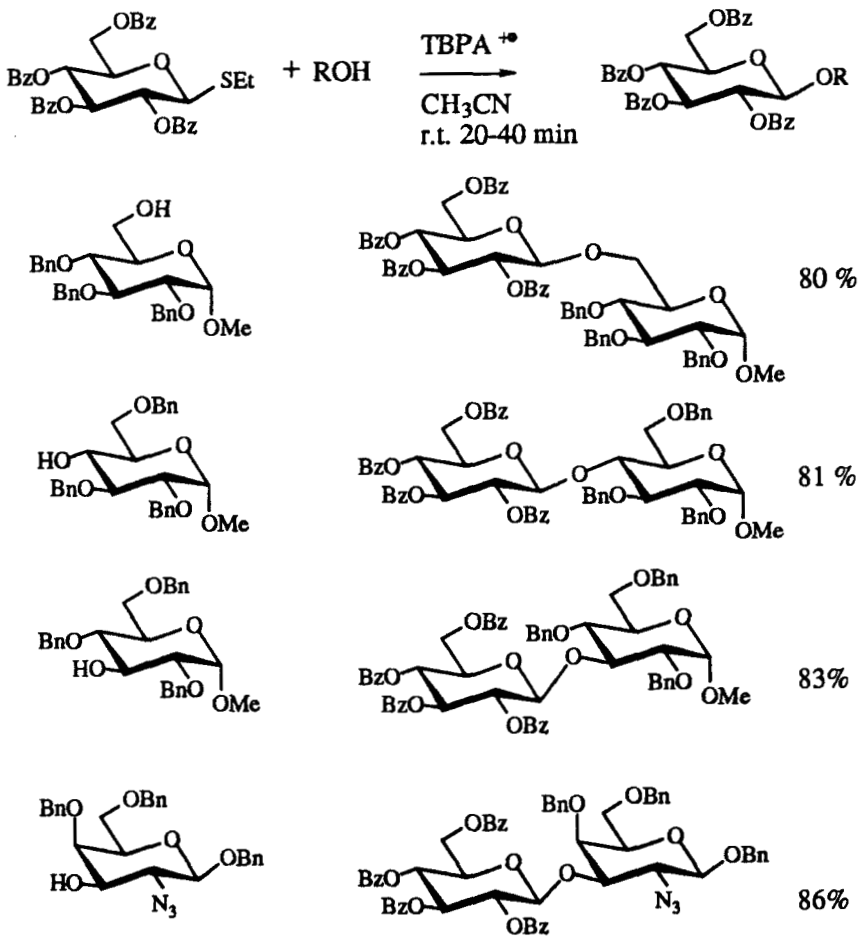
$TBPA^{+\bullet}$

The principle of this conceptually novel glycosylation would be as follows :

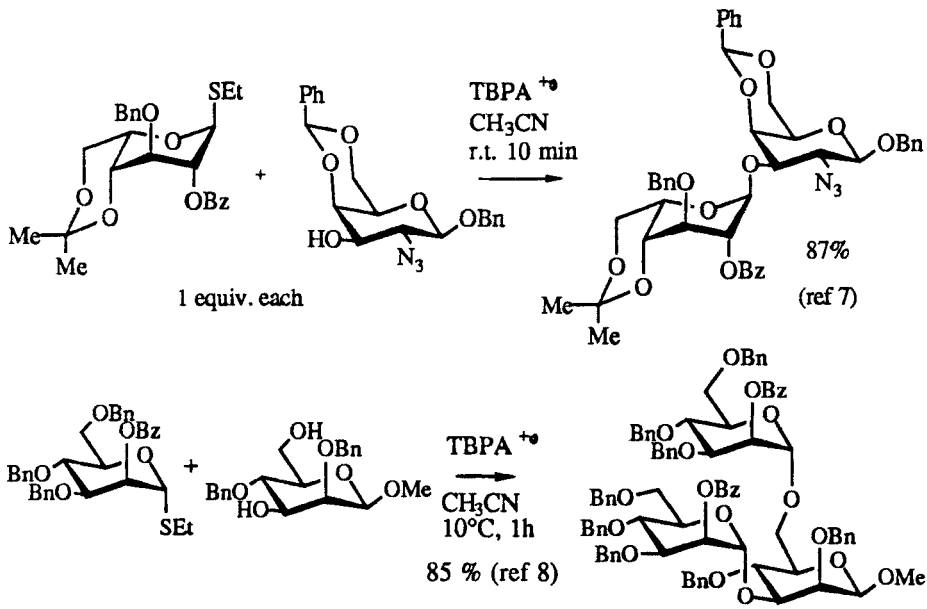


We found indeed that this idea worked extremely well, especially when thioethyl glycosides were used, rather than thiophenyl glycosides. The

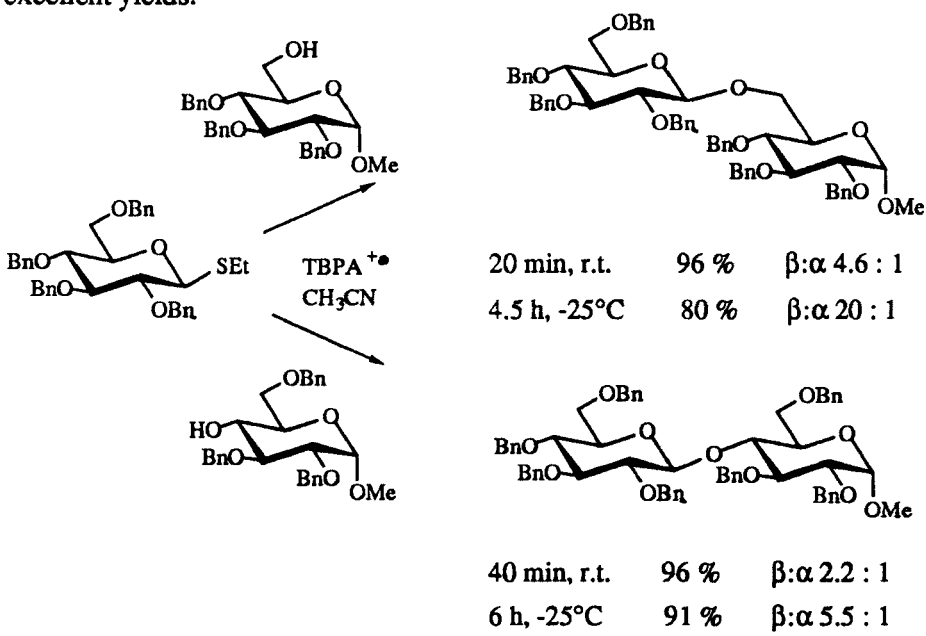
reaction probably operates through an inner-sphere mechanism, which is favoured for steric reasons in the case of thioethyl derivatives.
We first explored glycosyl donors having participating substituents of C-2. Ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside reacted smoothly with various sugar alcohols in acetonitrile at room temperature to give β-linked disaccharides in good yield.



TBPA$^{+\bullet}$ exhibits in acetonitrile a typical dark blue color which disappears when the reaction is completed, making easy the control of the reaction. The TBPA which is formed can be separated and re-used after one-electron oxidation to TBPA$^{+\bullet}$[6]. We have used this one-electron chemoselective oxidation of the anomeric sulfur atom of thioethyl glycosides to prepare protected di- and oligo-saccharides which are interesting intermediates for the synthesis of compounds of biological relevance.

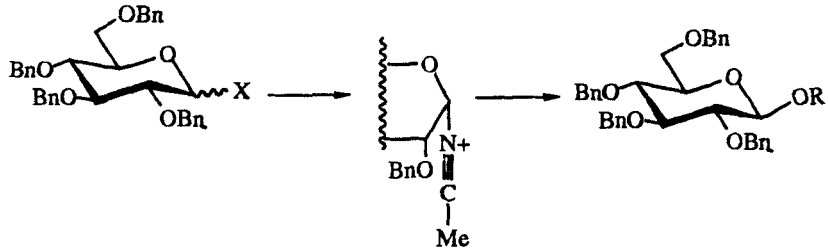


Glycosylation with non-participating substituents at C-2 was also successful in acetonitrile at room temperature, to selectively give β-*O*-glycosides in excellent yields.



The β-selectivity obtained in acetonitrile, with a non-participating benzyl protecting group at C-2 is consistently observed in the field and is explained

by the stereoselective kinetic formation[9] of a reactive α-nitrilium intermediate[10] acting as the glycosylating species[11].



It is known that alkyl phenyl sulfides (Ph-S-R) are easily anodically oxidized[12], so that one-electron electro-oxidative generation of oxycarbenium species from phenyl 1-thioglycosides (Gly-SPh) should result in electroglycosylation, which is an economical process.

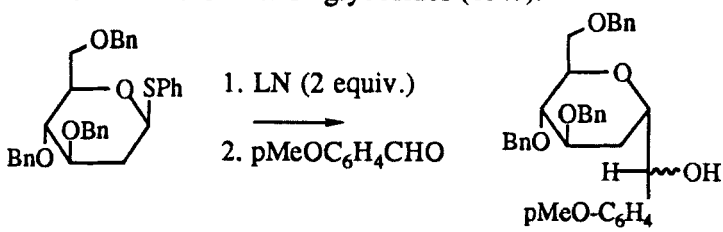
Gly-SPh			⟶	$[Gly\text{-}SPh]^{+\bullet}$	+	e^-
$[Gly\text{-}SPh]^{+\bullet}$			⟶	Gly^+	+	$PhS^\bullet$
Gly^+	+	ROH	⟶	Gly-OR	+	H^+
$PhS^\bullet$			⟶	$0.5\ (PhS)_2$		
Gly-SPh	+	ROH	⟶	Gly-OR + $0.5\ (PhS)_2$ + H^+ + e^-		

In this process, one electron is abstracted from the sulfur atom by an outer-sphere mechanism, thus phenyl 1- thioglycosides are advantageously used due to their ease of preparation. They have lower oxidation potentials than aryl glycosides which have already been used for the same purpose[13].

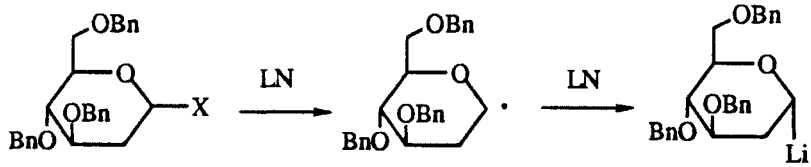
Most of the chemistry of the anomeric center of carbohydrates relies on its electrophilic character, the reactive intermediate being the oxocarbenium ion. We have just seen how sulfur can undergo a one-electron oxidation resulting in a reactive sulfur-centered radical cation, offering then a novel way to elicit this inherent electrophilic character. Sulfur may also undergo a one-electron reduction, with an appropriate reagent, to generate a radical anion which is cleaved to an anomeric radical. This radical can be trapped to give a *C*-glycoside. Under normal circumstances it is further reduced to give a reactive anomeric anion which can be used either to selectively synthesize *C*-glycosides when no leaving group is present at C-2, or to prepare glycals through a E1cb elimination. These aspects will now be examined.

THE "UMPOLUNG" OF THE ANOMERIC CENTER OF CARBOHYDRATES : A NOVEL ROUTE TO *C*-GLYCOSIDES

The reductive lithiation of 2-deoxy-D-glycopyranosyl phenyl sulfides[14] and phenyl sulfones[15] has been achieved by treatment with a solution of lithium naphthalenide (LN) in THF. This simple generation of an "umpoled" reactive lithium derivative reverses the characteristic electrophilicity of the anomeric center. In a typical example, reductive lithiation of phenyl 3,4,6-tri-*O*-benzyl-2-deoxy-1-thio-β-D-*arabino*-hexopyranoside (LN, 2eq., THF, -78°C, 45 min) and reaction with electrophilic p-anisaldehyde gave a 3 : 1 diastereoisomeric mixture of α-*C*- glycosides (65%).

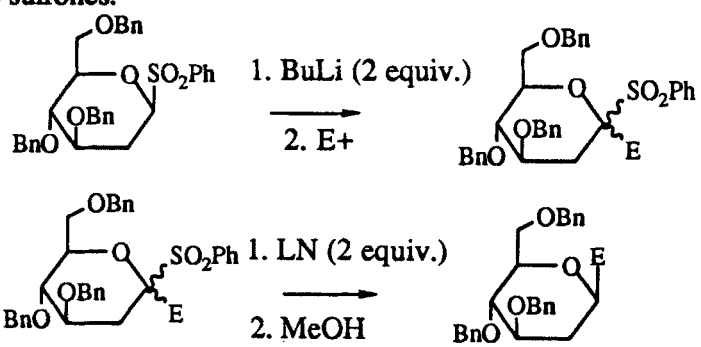


The reaction is explained by the initial one-electron transfer from LN to anomeric group X (thiophenyl or phenylsulfone) to give an anomeric radical, which is selectively reduced to afford a kinetic α-glycosyl lithium species. This species is configurationally stable at -78°C and provides a novel entry into α-*C*-glycosides.



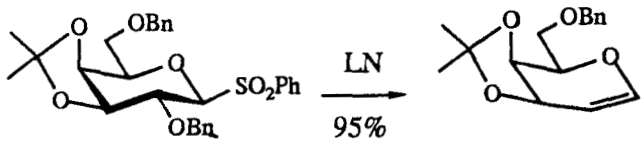
The detailed structure of the lithium species has not been investigated, but it reacted with electrophiles with retention of configuration.

The selective syntheses of β-*C*-glycosides has also been achieved from anomeric sulfones.



CONVENIENT SYNTHESES OF SUBSTITUTED PYRANOID GLYCALS

When a leaving group is present at C-2, the anomeric anion generated from LN undergoes elimination to give a cyclic enol ether (glycal). This novel approach allows an easy preparation of a variety of pyranoid glycal derivatives from phenyl thioglycosides[16], or sulfones.



We recently found[17] that a reductive samariation can be achieved on anomeric glycosyl phenyl sulfones. An almost quantitative reduction elimination occured when sulfones acetylated at C-2 were treated with a solution of samarium (II) iodide in THF, in the presence of HMPA. A transient unstable anomeric organosamarium species is formed, which undergoes a β-elimination of the acetate.

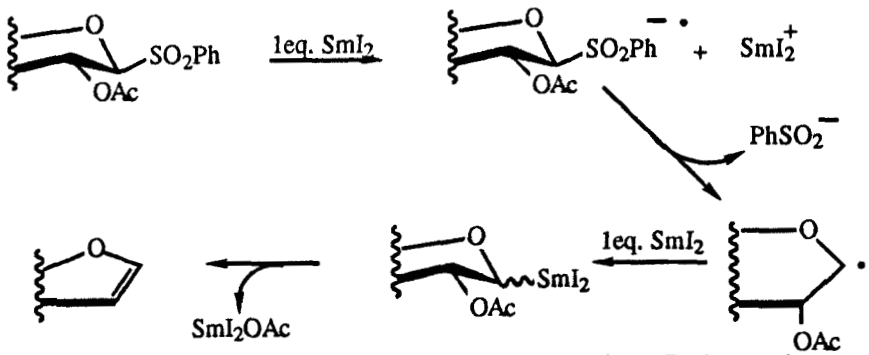
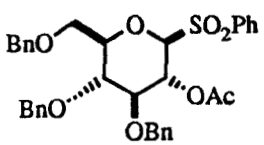
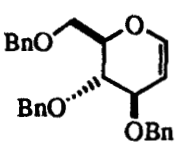
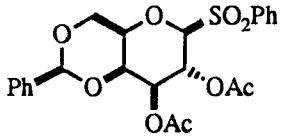
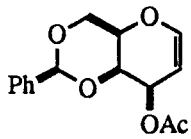


Table 1 demonstrates the efficiency of this procedure. It shows that acetates, acetals, cetals, and benzyl ethers are stable under these conditions.

Table 1. Conversion of glycosyl phenyl sulfones into glycals (SmI_2, THF/ HMPA)

Substrate	Product (yield %)
	 (96)





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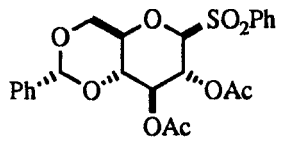

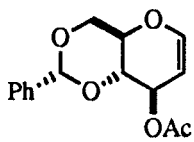

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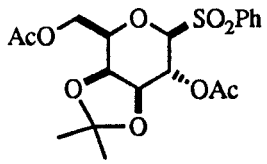

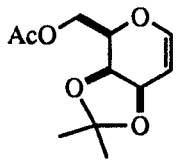

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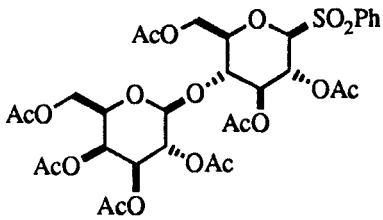

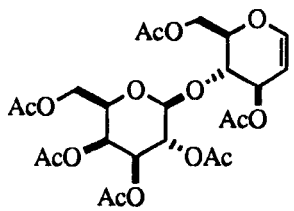

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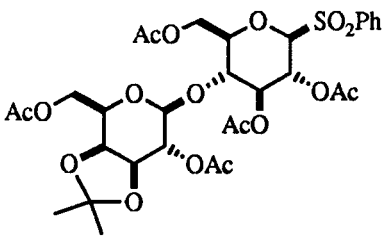
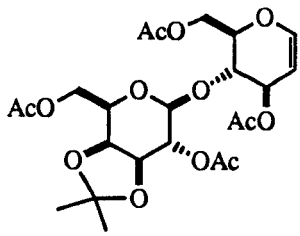


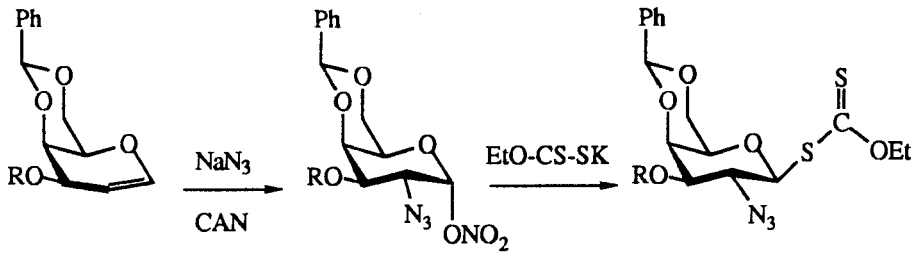


(93)

THE USE OF ANOMERIC *S*-XANTHATES OF 2-AZIDO-2-DEOXY SUGARS AS EFFICIENT GLYCOSYL DONORS

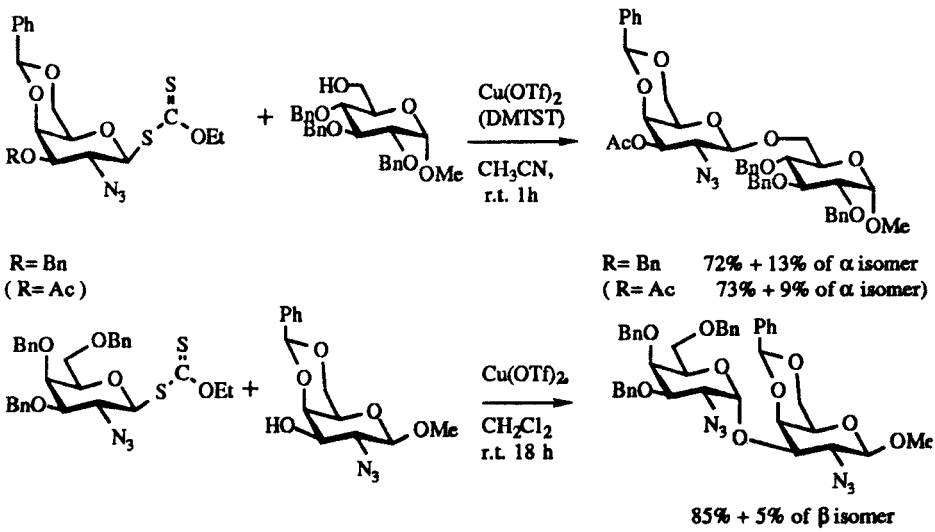
The "umpolung" of the anomeric center, made possible by initial one-electron reduction of sulfides or sulfones, by LN or by SmI_2, may result in the formation of glycals when a leaving group is present at C-2. We decided to reintroduce sulfur at the anomeric position, using the classical azidonitration reaction of glycals[18]. Anomeric denitration was observed[19]

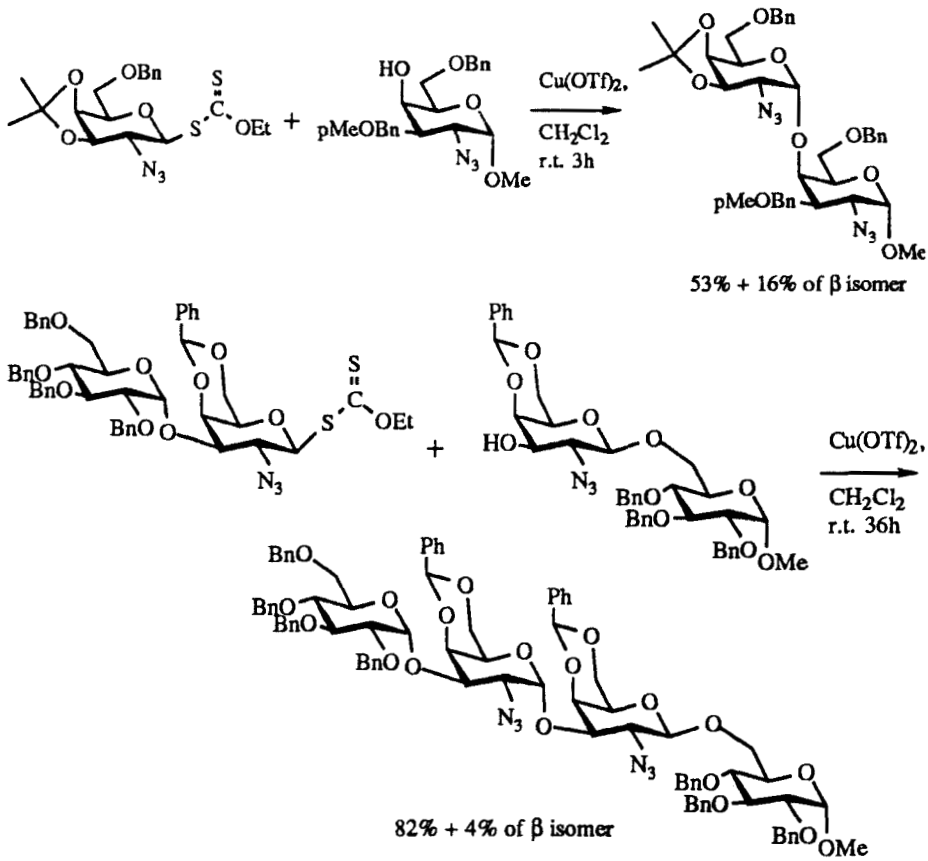
upon treatment with thiophenol at room temperature from 10 minutes, in the presence of diisopropyl ethylamine. SN_2 type direct anomeric displacement of nitrate was cleanly achieved upon treatment with *O*-ethyl-*S*-potassium dithiocarbonate.



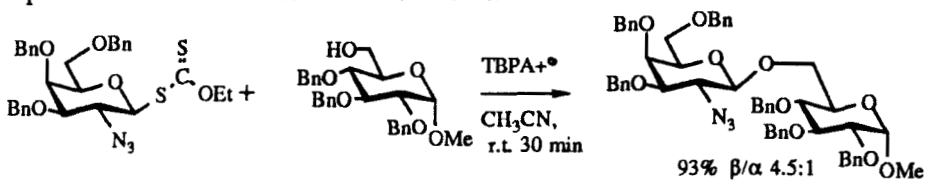
R= Ac	R= Ac	44%	R= Ac	97%
R= Bn	R= Bn	40%	R= Bn	91%

We have thus achieved a two-step azido xanthation of glycals, which are themselves derived from thiophenyl glycosides (or sulfones) through reductive metalation (lithiation or samariation). We are thus in a position to evaluate their glycosylating properties in order to extend the carbohydrate chemistry of the anomeric carbon-sulfur bond. As shown from the selected example presented here, anomeric *S*-xanthates of 2-azido-2-deoxy-D-galatopyranosyl derivatives are efficient glycosyl donors[20]. Goods yields were obtained using either dimethyl(methylthio) sulfonium triflate[21] (DMTST) or copper (II) triflate as promoters and operating at room temperature. The reaction time was about 2h, except in the case of the combination dichloromethane / $Cu(OTf)_2$ (3-36h).



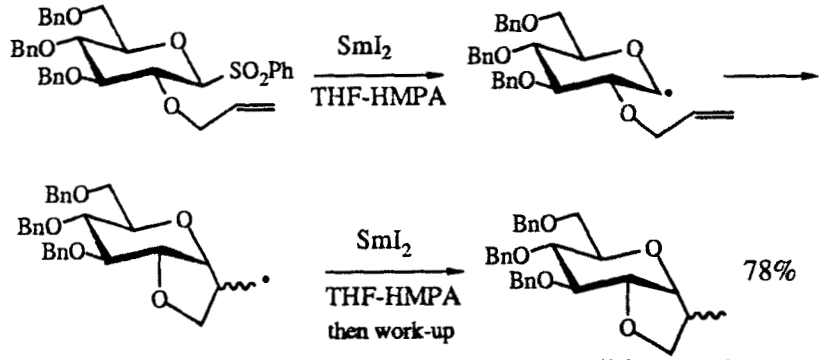


We also found that the one-electron transfer reagent $TBPA^{+\bullet}$ previously reported activated *S*-xanthates in acetonitrile.

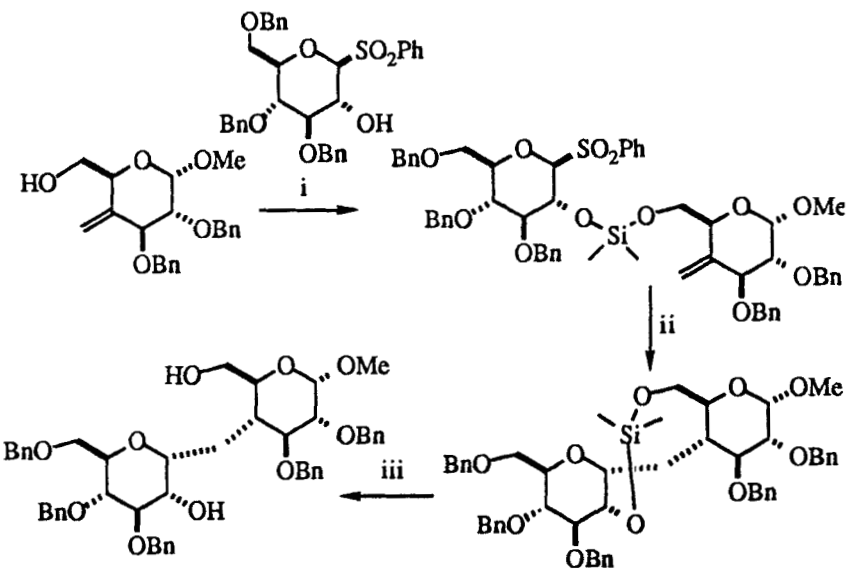


SYNTHESIS OF *C*-DISACCHARIDES BY A SAMARIUM DIIODIDE INDUCED INTRAMOLECULAR COUPLING REACTION OF TETHERED SUGARS

We have previously demonstrated that a glycosyl phenyl sulfone is converted into a transient anomeric radical upon reaction with a solution of SmI_2 in THF containing HMPA. This radical may undergo a fast exo-trig radical cyclisation with appropriate substrates[17c].



We decided to extend this strategy to open an expeditious and potentially general approach to *C*-disaccharides[22]. They are close mimics of disaccharides, in which the interglycosidic oxygen atom has been replaced by a methylene group[23]. Because of their potential utility in glycobiology, they are currently attracting a great deal of attention.
As shown in the following scheme, two appropriate sugar alcohols were connected together through a temporary silaketal bridge.



i) nBuLi (1.2 eq.), Me_2SiCl_2 (5 eq.), imidazole (1.5 eq.), THF (82%);
ii) SmI_2 / PhH / HMPA 9/1, PhMe
iii) aq.HF, r.t. (50% two steps)

One-electron reduction of the sulfone by a benzene-HMPA solution of SmI_2[24] generated an anomeric radical which undergoes a most welcome 9-endo-trig cyclisation to selectively give a *C*-maltose derivative. Since the 9-endo-trig cyclisation is a rather slow process, it is essential to have recourse

to a slow addition (17h) of the SmI_2 solution. Benzene was selected as a solvent to avoid hydrogen atom transfer onto the anomeric radical, which significantly occured when THF was used.

This approach based on sulfur chemistry complements a similar methodology based on selenium chemistry[25]. The use of the system samarium diiodide in HMPA-benzene indeed affords a mild way to synthesize *C*-disaccharides from easily available anomeric sulfones.

This lecture has demonstrated the versatility of the chemical manipulation of the anomeric carbon-sulfur bond. Depending upon reaction conditions, three classical intermediates - oxycarbenium, anion, or radical - can be generated and transformed into derivatives of current interest in the field of carbohydrates.

ACKNOWLEDGEMENTS

The author wishes to express his acknowledgements to J.-M. Mallet for his invaluable contribution to this programme. I am also grateful to my co-workers whose names appeared on quoted publications from my research group. The excellent technical assistance of J. Esnault is appreciated. The electrochemical glycosylation reaction was developed in collaboration with the group of Dr. C. Amatore (A. Jutand, G. Meyer) at Ecole Normale Supérieure. This research was supported by Ecole Normale Supérieure and Centre National de la Recherche Scientifique (URA 1110 and 1686).

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