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Fascione, Martin Anthony orcid.org/0000-0002-0066-4419, Brabham, Robin and Turnbull, W. Bruce (2016) Mechanistic Investigations into the Application of Sulfoxides in Carbohydrate Synthesis. Chemistry - a European Journal. ISSN 1521-3765

https://doi.org/10.1002/chem.201503504

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Mechanistic Investigations into the Application of Sulfoxides in Carbohydrate Synthesis
Martin A. Fascione*,[a] Robin Brabham,[a] and W. Bruce Turnbull*[b]
Abstract: The utility of sulfoxides in a diverse range of transformations in the field of carbohydrate chemistry has seen rapid growth since the first introduction of a sulfoxide as a glycosyl donor in 1989. Sulfoxides have since developed into more than just anionic leaving groups, and today have multiple roles in glycosylation reactions. These include as activators for thioglycosides, hemiacetals, and glycal, and as precursors to glycosyl triflates, which are essential for stereoselective β-mannoside synthesis, and bicyclic sulfonium ions that facilitate the stereoselective synthesis of α-glycosides. In this review we highlight the mechanistic investigations undertaken in this area, often outlining strategies employed to differentiate between multiple proposed reaction pathways, and how the conclusions of these investigations have and continue to inform upon the development of more efficient transformations in sulfoxide based carbohydrate synthesis.

1. Introduction

The widespread use of sulfoxides in organic chemistry is a result of their rich and varied reactivity\textsuperscript{[1]} showcased by an enviable plethora of reactions. Well-studied examples include the use of dimethyl sulfoxide in the oxidation of alcohols\textsuperscript{[2]}, the activation of sulfoxides in Pummerer-type reactions\textsuperscript{[3]} and pericyclic reactions of sulfoxides, such as the Mislow-Evans rearrangement.\textsuperscript{[4]} However, few fields have benefited more from the diverse chemical capabilities of sulfoxides than modern synthetic carbohydrate chemistry.\textsuperscript{[5]} where they often play integral roles as leaving groups, or as activating agents in high yielding glycosylation reactions. An all-encompassing review of the use of sulfoxides in carbohydrate chemistry has been forsaken here in favour of an in-depth analysis of the elegant mechanistic investigations performed in this area, which have begun to underpin many of the contemporary theories regarding stereoselectivity and efficiency in challenging sulfoxide based carbohydrate synthesis. Included will be a discussion on the use of glycosyl sulfoxides as glycosyl donors, as well as the application of sulfoxide reagents in dehydrative glycosylations, glycal activation and thioglycoside donor activation.

2. Glycosyl sulfoxides

The use of thioglycoside donors has been widespread since their introduction by Ferrier.\textsuperscript{[6]} The next substantial step forward in the use of thioglycoside derivatives came from Kahne and co-workers\textsuperscript{[7]} who originally developed the concept of using a sulfoxide glycosyl donor after unsuccessful attempts to glycosylate deoxycholic ester derivative 1 (Scheme 1), where the target axial alcohol is very unreactive due to 1,3-diaxial steric hindrance. Sulfoxide glycosylation reactions with benzylated donor 2 and deoxycholic ester 1 afforded glycoside 3 in excellent yield, in a number of different solvents (Scheme 1).

\begin{align*}
\text{Scheme 1.} \quad &\text{The challenging glycosylation of a deoxycholic ester is feasible using sulfoxide based glycosyl donors.} \\
&\text{Activation of the sulfoxide was achieved with triflic anhydride at } -78 \degree \text{C, and proceeded } \text{via} \putative \text{ sulfonium triflate species 4. Further examples with benzyl and pivaloyl-protected donors were also high yielding, and included the first example of glycosylation of an amide nitrogen, using trimethylsilylacetamide - an early demonstration of the potential utility of glycosyl sulfoxides as novel glycosyl donors. Kahne and co-workers noted the glycosylation of less reactive trimethylsilylacetamide stalled at } -78 \degree \text{C, but re-initiated between 0 } \degree \text{C and ambient temperature over 12 hours.\textsuperscript{[7]}} \text{Having previously demonstrated the reactivity of glycosyl sulfoxides at low temperatures, the authors postulated any reactive intermediates present at } -78 \degree \text{C would decompose at higher temperatures.} \text{This implied that glycosylation at the higher temperatures occurred via an unidentified more stable intermediate. After further investigation, this unknown intermediate was subsequently assigned as a glycosyl sulfenate as the sulfenate 5 and disaccharide 6 were isolated in a 2:1 ratio (Scheme 2) following activation of fucose donor 7 at } -60 \degree \text{C.\textsuperscript{[8]}} \text{Application of glycosyl sulfenates as donors had previously been performed at } 0 \degree \text{C,\textsuperscript{[9]}} \text{therefore the isolated glycosyl sulfenate 5 seemed a likely candidate as a reactive intermediate in the sulfoxide reactions at higher temperatures.}
\end{align*}
Martin Fascione received his Ph.D. from the University of Leeds in 2009, working under the tutelage of W. Bruce Turnbull on the stereoselective synthesis of 1,2-cis-glycosides. Following a postdoctoral period in Leeds, he was then awarded a Marie Curie International Outgoing Fellowship to study the mechanisms of carbohydrate-processing enzymes with Professor Steve Withers, FRS, at the University of British Columbia in Vancouver, Canada (2012-2013) and Professor Gideon Davies, FRS, FMedSci, at the University of York, UK (2013-2014). In August 2014 he took up a lectureship in the York Structural Biology Laboratory, within the Department of Chemistry. His research interests include chemical glycobiology, synthetic carbohydrate chemistry and the chemical/ enzymatic modification of proteins.

Robin Brabham was born in Southampton (UK) in 1993, and was awarded a MChem degree from the Department of Chemistry at the University of York, UK (July 2015). In October 2015 he commences Ph.D. studies in the Fascione group. Robin’s Masters research focussed upon developing new routes to stereoselective glycosyl donors to be deployed in the synthesis of chemical probes with potential use as therapeutic agents.

Bruce Tumbull completed his Ph.D. with Prof Rob Field at University of St Andrews in 1998 before taking up a Wellcome Trust International Prize Travelling Research Fellowship at University of California Los Angeles with Prof Sir Fraser Stoddart FRS. He returned to the UK for further postdoctoral studies with Prof Steve Homans at University of Leeds, where he subsequently held a Royal Society University Research Fellowship in the School of Chemistry. He was awarded the Royal Society of Chemistry Carbohydrate Chemistry Award in 2013 for his studies of glycoside synthesis and carbohydrate-binding proteins. He chairs EU COST Action CM1102 on multivalent glycosystems for nanoscience and has research interests in synthetic glycochemistry.

3. Stereoselective synthesis of β- mannopyranosides and α-glucopyranosides

While pursuing a radical-based solution to the ubiquitous problem of stereoselective β-mannopyranoside synthesis, Crich and co-workers serendipitously uncovered an unappreciated level of complexity in Kahne’s sulfoxide glycosylation method. When using benzylidene acetal protected donor 8, Crich observed that the stereoselectivity of the reaction was dependent on the order of addition of the acceptor and activating agent (Scheme 4). If donor 8 and acceptor 9 were premixed in diethyl ether and then activated with triflic anhydride, α-mannopyranoside 10a was formed stereoselectively (in-situ activation protocol, Scheme 4a). However, when the donor 8 was activated with triflic anhydride in diethyl ether prior to the addition of the acceptor 9, a complete reversal in selectivity was observed and β-mannopyranoside 10b was formed stereoselectively (pre-activation protocol, Scheme 4b).

Subsequently, formation of glycosyl sulfenates from glycosyl sulfoxides was achieved using catalytic triflic anhydride. Based upon this observation a mechanism to account for formation of both glycosides and glycosyl sulfenates in sulfoxide glycosylations was proposed (Scheme 3). Following these mechanistic insights, Kahne and co-workers developed a strategy to scavenge by-products in the sulfoxide glycosylation reaction using 4-allyl-1,2-dimethoxybenzene, an improvement which aided their program of challenging synthetic endeavours including the synthesis of the blood group antigens, the calicheamicin oligosaccharide, and the ciclamycin trisaccharide.

Scheme 2: At sufficiently low temperatures, glycosyl sulfenate 5 can be isolated from glycosylations involving glycosyl sulfoxides.

Scheme 3: Proposed mechanism for triflic anhydride-activated glycosylation of sulfoxide donors, accounting for the glycosyl sulfenate by-product.

Scheme 4: Proposed mechanism for triflic anhydride-activated glycosylation of sulfoxide donors, accounting for the glycosyl sulfenate by-product.
This observation was initially substantiated by increased β-selectivities (α:β 1:13→1:32) when less bulky O-2-benzyl donor 15 was used in a less-ionizing dichloromethane solvent. It should also be noted that other groups have established that pre-activation of Crich’s benzylidene acetal donors is not necessarily a prerequisite for β-mannoside selectivity when glycosylations are performed in dichloromethane as opposed to diethyl ether.[18]

Subsequent evidence for the existence of α-triflate species came from low temperature NMR studies of the glycosylation reaction.[19] Using simplified donor 16 the mechanism was probed by activation at −78 °C with triflic anhydride (Scheme 6). Within acquisition of the 1H-NMR spectrum a new intermediate had formed with a characteristic H1 shift of 6.20 ppm, and 13C-NMR C1 shift of 104.6 ppm.[17] The intermediate was assigned as glycosyl triflate 17, and subsequently afforded β-mannopyranoside 18 on addition of methanol.

A key point established by Crich is the necessity of the benzylidene acetal protecting group for β-selective mannosylations.[16, 19] This is attributed to the increased conformational constraint imposed on the sugar ring by the benzylidene acetal, which disfavors the formation of the half-chair oxacarbenium ion[20], thus promoting the formation of a trans-decalin-like glycosyl intermediate.

An unexpected reversal of stereoselectivity was observed when glycosylation of glucosyl sulfoxide donors was performed. The authors isolated only α-glycosides selectively (Scheme 7b), compared to mannosyl sulfoxide donors, which afforded β-glycosides selectively (Scheme 7a).[21] The benzylidene acetal protecting group was again a prerequisite for stereoselectivity (although glycosylations with glucosyl sulfoxide 19 and triflic anhydride afford α-glucosides, better yields and selectivities were achieved by activation of thioglucosides with PhSOTf[22]).
The reaction proceeds through the less stable, and thus more reactive glycosyl triflates. However, until recently there remained a degree of ambivalence over whether the stereoselective attack on glycosyl triflates truly proceeded through an $S_N$ mechanism. To jettison any ambiguity, Crich retooled two classical approaches for elucidating chemical reaction kinetics—employing a cation-clock experiment, and a natural abundance kinetic isotope study to unequivocally prove the $S_N$ mechanism. Crich's cation-clock was developed to distinguish between different mechanisms by measuring the relative kinetics between $S_N$-1-like and $S_N$-2-like mechanisms. The cation-clock experiment demonstrated firstly that the ratio of formation of $\beta$-isopropyl mannoside $27\beta$ to cyclised products $23$ and $24$ increases as isopropanol concentration increases; therefore the formation of both products is rationalised by intramolecular attack from either the $\alpha$- or $\beta$-face of the $B_2,3$ twist boat mannosyl oxacarbenium ion $25$, which exists in equilibrium with a glycosyl triflate $26$. The authors then repeated triflic anhydride activation experiments, but rapidly followed with the addition of isopropanol as a glycosyl acceptor. This reaction manifold allowed the quantification of individual mannosyl anomers $27\beta$ and $27\alpha$ formation with respect to the intramolecular cyclisation products $23$ and $24$, as a function of isopropanol acceptor concentration. This methodology was also repeated with trimethyl methallylsilane as an external competing $C$-nucleophile, to report on the kinetics of $C$-glycoside formation.

**Scheme 7.** Differing selectivities in the glycosylation of mannosyl sulfoxide $16$ and glucosyl sulfoxide $19$.

The authors postulated selectivity arises from reaction of the acceptor with transient glycosyl triflates $20$ (Scheme 8). The mechanistic rationale used for the gluco series differs from that of the manno series, in that the reactive intermediate is $\beta$-glucosyl triflate $20\beta$ rather than $\alpha$-glucosyl triflate $20\alpha$. A Curtin-Hammet kinetic scheme was invoked to explain selectivity, where the reaction proceeds through the less stable, and thus more reactive $\beta$-glucosyl triflate $20\beta$.

**Scheme 8.** Stereoselective formation of $\alpha$-glucopyranoside $21\alpha$ by virtue of a Curtin-Hammet kinetic scenario.

These initial explorations were followed up with a number of mechanistic studies on the chemistry of glycosyl sulfoxides and glycosyl triflates. However, until recently there remained a degree of ambivalence over whether the stereoselective attack on glycosyl triflates truly proceeded through an $S_N$-2-like or an $S_N$-1-like mechanism. To jettison any ambiguity, Crich retooled two classical approaches for elucidating chemical reaction kinetics—employing a cation-clock experiment, and a natural abundance kinetic isotope study to unequivocally prove the reaction proceeds through an $S_N$-2-like mechanism. Crich’s cation-clock was developed to distinguish between different mechanisms by measuring the relative kinetics between $\alpha$- and $\beta$-O and $\beta$-C-mannopyranosylations and a competing intramolecular cyclisation (Scheme 9). Following triflic anhydride activation of the mannosyl sulfoxide $22$, which bears a prospective internal Sakurai nucleophile, a major $23$ (face attack affords $^1S_2$ twist boat conformer) and minor product $24$ (face attack affords $^1S_1$ chair conformer) were formed. The formation of both products was rationalised by intramolecular attack from either the $\alpha$- or $\beta$-face of the $B_2,3$ twist boat mannosyl oxacarbenium ion $25$, which exists in equilibrium with a glycosyl triflate $26$. The authors then repeated triflic anhydride activation experiments, but rapidly followed with the addition of isopropanol as a glycosyl acceptor. This reaction manifold allowed the quantification of individual mannosyl anomers $27\beta$ and $27\alpha$ formation with respect to the intramolecular cyclisation products $23$ and $24$, as a function of isopropanol acceptor concentration. This methodology was also repeated with trimethyl methallylsilane as an external competing $C$-nucleophile, to report on the kinetics of $C$-glycoside formation.

**Scheme 9.** Crich’s cation-clock. (a) Intramolecular Sakurai reaction of mannosyl sulfoxide $23$, and (b) competing $O$-glycosylation with isopropanol, or $C$-glycosylation $\text{CH}_2\equiv\text{C(CH}_3\text{)}\text{CH}_3\text{TMS}$.

The cation-clock experiment demonstrated firstly that the ratio of formation of $\beta$-isopropyl mannoside $27\beta$ to cyclised products increases as isopropanol concentration increases; therefore the formation of both products is first order with respect to nucleophile concentration. Conversely, the ratios of formation of $\alpha$-isopropyl mannoside $27\alpha$ and $\beta$-C-mannoside $28$ to cyclised products did not change with increasing nucleophile concentration, and was thus deemed zeroth order overall with respect to nucleophile concentration.
These results are consistent with Sn2-like isopropanol attack on an α-mannosyl triflate, or an α-contact ion pair, in accordance with Crich’s earlier postulate; the formations of the α-isopropyl mannoside 27α, and β-C-mannoside 28 were consistent with an Sn1-like isopropanol attack on an oxacarbenium ion or a solvent-separated ion pair. These results were then compared to the same ratio in the glycosyl sulfoxide starting material. The calculated KIEs for the formation of the β-mannopyranosides 29β, α- and β-glucosides 30β and 30α were all in the lower range expected for a unimolecular reaction (1.00-1.01), while the KIE measured for the formation of α-mannopyranoside 29α (1.005 ± 0.002) was in the range for a unimolecular reaction (1.00-1.01). These results again provided further confirmation for the formation of β-mannopyranosides through an exploded Sn2-like transition state, and α-mannopyranosides through Sn1-like attack on an oxacarbenium ion or a solvent separated ion pair such as 31. While formation of α- and β-glucopyranosides in the analogous glycosylation reaction are also a result of bimolecular Sn2-like attack on glycosyl triflates, e.g. 32α and 32β, once again the preference for the α-product can be explained by inference of a Curtin-Hammett kinetic scenario, where the less stable minor β-triflate reacts more quickly to afford the α-anomer preferentially.

Our own mechanistic studies in this field of stereoselective glycosylation of glycosyl sulfoxides have been focussed upon the activation and reactivity of oxathiane-S-oxide donors 33 and 34 (Scheme 11).28 The trans-decalin motif present in these oxathianes conferred unanticipated stability on aryl sulfonium ions 35 and 36, to the extent that their formation could be monitored with NMR at ambient temperature, following triflic anhydride activation in the presence of electron-rich arenes.28 All protected derivatives of the oxathiane ketal-S-oxide displayed complete α-anomeric stereoselectivity, even at 50 °C, suggestive of an Sn2-like attack on the aryl sulfonium ion from the α-face. While still highly α-stereoselective, the oxathiane-ether-S-oxide also afforded β-glycosides, indicative of at least partial Sn1-like attack on an

**Scheme 10.** Natural abundance 13C-NMR KIE study, on formation of (a) mannopyranosides 29α and 29β, and (b) glucopyranosides 30α and 30β.

**Scheme 11.** Activation of oxathiane ketal-S-oxide 33 and oxathiane ether-S-oxide 34 via umpolung S-arylation. Reproduced from Ref. 28b.
oxacarbenium ion, and raised the question of whether the exchange of an axial methoxy group for a hydrogen atom could effect a change in mechanism from stereospecific S$_2$2-like attack to a highly stereoselective S$_2$1-like attack. However, DFT calculations using model structures indicated that both the oxathiane ketal and ether were equally likely to act as stereospecific S$_2$-like mechanism, discounting this tantalising proposition. Instead calculations of the relative stability of the relevant oxacarbenium ion conformers: $^3$H$_4$ 38 (S$_2$1-like attack upon which affords a-glycosides) and $^4$H$_4$ 37 (attack upon which affords β-glycosides) indicate it is more likely the erosion in α-stereoselectivity results from an increase in the population of $^4$H$_4$ conformers upon removal of the axial methoxy group (Scheme 12).

Scheme 12. The equilibrium between the $^3$H$_4$ and $^4$H$_4$ oxacarbenium conformers 37 and 38 can govern the overall stereoselectivity of glycosylation

4. Dehydrative glycosylation

Sulfoxides have also been used as activating agents in glycosylation reactions to facilitate in situ formation of reactive glycosylating species. Gin and co-workers identified sulfoxides as the ideal reagents for dehydrative glycosylation of hemiacetal donors.$^{[29]}$ In a representative example, a combination of Ph$_3$SO and triflic anhydride was used to pre-activate hemiacetal donor 39 prior to the addition of a glycosyl acceptor (Scheme 13).

Scheme 13. Dehydrative glycosylation using Ph$_3$SO and triflic anhydride.

The first step of the mechanism is assumed to be activation of Ph$_3$SO by triflic anhydride to give trifloxy sulfoxonium ion 40. This species could then react with hemiacetal 41 through its S(IV) centre to afford an oxosulfoxonium intermediate 42 (Scheme 14a), or through its S(VI) centre to afford glycosyl triflate 43 (Scheme 14b). The near quantitative incorporation of the label into recovered Ph$_3$SO (47±5 $^{18}$O incorporation, as two equiv. of Ph$_3$SO was used) ruled out the pathway involving glycosyl triflate 43 (Scheme 14b). $^1$H-NMR spectroscopy was used to identify the presence of an oxosulfoxonium triflate species and a glycosyl pyridinium species as reaction intermediates. The analogous glycosyl triflate previously synthesised by Chirch and co-workers$^{[18]}$ was not observed in the reaction mixture. The authors noted the observed formation of glycosyl pyridinium species does not necessarily imply it is a reactive intermediate involved in glycoside formation.

Following the initial studies by Gin and co-workers$^{[29-30]}$ into the use of sulfoxides in dehydrative glycosylations, the method was utilised in various other examples$^{[31]}$ including in the efficient synthesis of sialosides.$^{[32]}$

4.1. Sulfoxide covalent catalysis

Mechanistic studies into the dehydrative glycosylation (vide supra) suggested the possibility of using catalytic amounts of Ph$_3$SO in the reaction; however, attempts to reduce the amount of Ph$_3$SO were plagued by self-condensation of the sugar.$^{[29a]}$ To circumvent this problem Gin and co-workers developed a catalytic protocol using a nucleophilic sulfonate counteranion 44 that reacted to form an anomic sulfonate 45 as a “resting state” for the activated hemiacetal (catalytic cycle, Scheme 15).$^{[33]}$
For the protocol to work catalytically the sulfonate counteranion needed to be nucleophilic enough to displace/regenerate the sulfoxide, while the anomic sulfonate had to be reactive enough to afford glycosides, but also stable enough to prevent self-condensation with the hemiacetal.

Screening identified dibutyl sulfoxide and diphenyl sulfonic anhydride as the ideal combination for glycosyl sulfoxide-based covalent catalysis (Scheme 16).

The mechanism of the glycosylation reaction was again elegantly dissected using labelling studies. Transfer of the $^{18}$O label from Ph$_2$SO to C(2)-OH was observed (Scheme 18).

In addition to $^{18}$O transfer from the sulfoxide, the authors observed formation of diphenyl sulfide (0.7 equivalents) and the formation of 1,2-anhydropyranose 53 as an intermediate following methanol addition (by $^1$H-NMR). Therefore, two possible mechanistic pathways were proposed (Scheme 19, a and b).

5. Sulfoxide-based activation of glycal donors

Glycal donors 49 had previously been activated in a two-step procedure using oxidising agent dimethyldioxirane (DMDO) to afford C(2)-hydroxy pyranosides 50. Gin and co-workers extended their use of sulfoxides as activating agents to achieve the same goal in a one-pot process. The combination of Ph$_2$SO and triflic anhydride (2:1 ratio) facilitated the formation of 2-hydroxy pyranosides 50 from glycal donors 49, by a complex oxidative mechanism that was thought to proceed via a 1,2-anhydropyranose intermediate 51 (Scheme 17).
exploited in order to determine which mechanistic pathway was traversed. The oxosulfonium species is either connected to C-1 (Scheme 19) or C-2 (Scheme 19b). This difference in connectivity was exploited in order to determine which mechanistic pathway was traversed. When using $^{13}$C-1 labelled glucal donor 63 in a $^{13}$C-NMR tracking experiment, small perturbations in signals were measured when the $^{13}$C label was directly connected to an $^{18}$O label (Scheme 20). A comparison of the C-1 signals using unlabelled Ph$_2$SO and labelled Ph$_2$SO (60% $^{18}$O incorporation) made it possible to distinguish whether the disulfonium species 64 and C-1 α-sulfurane intermediate 65 postulated in mechanism a (Scheme 19a) truly existed. Using labelled Ph$_2$SO (60% $^{18}$O incorporation) perturbation in the C-1 signal of the first observed glycosyl intermediate established connectivity between $^{13}$C and $^{18}$O, consistent with glycosyl oxosulfonium species 64. After the addition of methanol, perturbation in the C-1 signal was also observed, consistent with putative C-1 α-sulfurane intermediate 65 which then fragmented to form 1,2-anhydropanoside 53 at −20 °C (Scheme 20), a small variance in δC-1 ($^{18}$O) shift for 65 was noted when using unlabelled or partially labelled $^{18}$O diphenyl sulfide, however two signals, for both the $^{18}$O and $^{16}$O isotopes, are unequivocally observed in the latter case.

The data from this labelling experiment therefore inferred that the reaction proceeded via mechanism a (Scheme 19a). Identical experiments using the analogous $^{13}$C-2 labelled glucal also confirmed a lack of connectivity between $^{13}$C-2 and $^{18}$O, therefore discounting mechanism b (Scheme 19b) as a possibility.

6. Sulfoxide-based activation of thioglycosides

The combination of sulfoxide reagents and triflic anhydride has also been applied to the activation of thioglycoside donors. In the pursuit of an expedient route to the aforementioned reactive glycosyl triflate intermediate 17 (Scheme 6), Crich and co-workers identified electrophilic benzene sulfonyl triflate (PhSO-Tf) as an effective reagent for the activation of armed and disarmed
thioglycosides.\textsuperscript{21} In situ generation of PhSOTf (from benzene sulfenyl chloride (PhSCl) and silver triflate) and subsequent thioglycoside 66 activation provided access to glycosyl triflates 67 quantitatively at low temperatures. The advantage of this method over the glycosyl sulfoxide approach to glycosyl triflates 67 is the exclusion of the sulfide oxidation step prior to the final glycosylation reaction (Scheme 21).

\[
\begin{array}{cccc}
\text{S} & \text{Cl} & \text{AgOTf} & \text{RS} \text{S} \\
\text{O} & \text{O} & \text{Cl} & \text{OR} \\
\end{array}
\]

\text{Scheme 21. Synthetic routes to a glycosyl triflate 67 species.}

The necessary in situ synthesis of PhSOTf, as a result of its marked reactivity and inherent instability, made the process arduous however. To navigate this problem shelf stable S-(4-methoxyphenyl) benzenethiosulfinate (MPBT) 68 (Scheme 22) was developed and showed reactivity in the activation of armed thioglycosides,\textsuperscript{40} but lacked potency in combination with disarmed donors. An alternative shelf stable sulfinamide (BSP) 69 showed much more promise with a range of thioglycoside donors and acceptors, examples included glycosylations with primary, secondary and tertiary alcohols, affording glycosides in excellent yields.\textsuperscript{41}

\[
\begin{array}{cccc}
\text{O} & \text{S} & \text{Tf} & \text{O} \\
\text{O} & \text{O} & \text{O} & \text{OMe} \\
\end{array}
\]

\text{Scheme 22. Triflic anhydride activation of MPBT 68 and BSP 69.}

A testament to the efficacy of the BSP/triflic anhydride activation of thioglycosides is the wealth of examples in the literature.\textsuperscript{21c-42} These notably include use in a one-pot “reactivity-based” synthesis of a Fuc-GM\textsubscript{1} oligosaccharide,\textsuperscript{43} use with 2,3-oxazolidinone N-acetyl glucosamine donors\textsuperscript{44} and the activation of 2-dialkyl phosphate thioglycoside donors.\textsuperscript{45}

Despite the obvious utility of the activation strategy, attempts to glycosylate unreactive 2,3-carbonate protected rhamnopyranoside donors were unsuccessful using either MPBT or BSP/triflic anhydride. To solve this problem van der Marel and co-workers intuitively\textsuperscript{29, 37} opted to use a combination of Ph\textsubscript{2}SO/triflic anhydride as a promoter, and discovered an even more potent reagent system for the activation of thioglycoside donors.\textsuperscript{46} The replacement of the electron donating piperidine ring in BSP with a conventional phenyl group presumably destabilises the adjacent charge on sulfur, and thus increases the reactivity of the sulfonium species. Glycosylation of disarmed donors proceeded in excellent yields (Scheme 23), and selectivities were in line with the proposed formation of glycosyl triflates as intermediate species in the glycosylation reaction.

\[
\begin{array}{cccc}
\text{O} & \text{S} & \text{Tf} & \text{O} \\
\text{O} & \text{O} & \text{O} & \text{OMe} \\
\end{array}
\]

\text{Scheme 23. Ph\textsubscript{2}SO/triflic anhydride activation of thioglycosides 66.}

Attempts to activate thioglycoside 70 with Ph\textsubscript{2}SO/triflic anhydride or BSP/triflic anhydride in the presence of glycosyl acceptors were unsuccessful as the reactive alcohol sequestered the activating sulfonium species to afford proposed by-product 71 (Scheme 24),\textsuperscript{47} reiterating the necessity of pre-activation of the donor. Similarly, chemoselective glycosylations were initially plagued by putative transient species 72, formed on activation of a thiophenyl donor.\textsuperscript{46a} Yields were low as the disaccharide products formed were activated by sulfonium triflate species 72 and subsequently hydrolysed on work-up. Yields could be increased however, by the addition of triethyl phosphite (TEP) as a reagent to quench the sulfonium triflate species \textsuperscript{46} at low temperature before decomposition could take place. A range of other glycosidic transformations have also been effected using thioglycosides in combination with Ph\textsubscript{2}SO/triflic anhydride.\textsuperscript{48} An impressive example illustrated the advantage of Ph\textsubscript{2}SO over the less reactive BSP in conjunction with triflic anhydride. The former was the only reagent successful in the glycosylations of 5-N-7-O-oxazinanone protected sialoside donors,\textsuperscript{49} and more conventional peracetylated thiosialoside donors were also efficiently activated with Ph\textsubscript{2}SO/triflic anhydride to afford sialosides in excellent yields and \(\alpha\)-selectivities,\textsuperscript{50} with excess Ph\textsubscript{2}SO essential to suppress problematic glycal formation.\textsuperscript{51} In this example the authors observe formation of oxosulfonium salts at low temperature and propose glycal formation \textit{via} elimination of the C-2-oxosulfonium leaving group is reduced in these intermediates.
7. Stereochemical preferences of glycosyl sulfoxides

Although a lack of detailed studies have been reported on the activation of thioglycosides by sulfonium triflate species, the observations discussed vide supra implied that glycosyl sulfides attack the S(IV) centre of sulfonium triflate species, or similar reactive intermediates. We provided further strong evidence that this is the case and also gained insight into the stereochemical preferences governing glycosyl sulfoxide formation in a novel transfer sulfoxidation reaction, by once again using the glycosyl oxathiane as a scaffold for serendipitous mechanistic explorations.\[52\] When \(\text{Ph}_2\text{SO}^\text{OTf}\) activation of the ring sulfur in the oxathiane 73/74 was attempted, hopeful of stereoselective glycosylation, we were instead surprised to observe stereoselective oxidation to the oxathiane-oxide 75/76 (Scheme 25). DFT calculations indicated that the most stable stereoisomer was formed preferentially when starting from both oxathiane ketal 73 and oxathiane ether 74, while low temperature \(^1\text{H}-\text{NMR}\) also demonstrated that the product was formed within minutes at \(-60^\circ\text{C}\) in the absence of adventitious water or alcohol. We hypothesised that the reaction must proceed through a novel sulfoxide transfer mechanism after isotopic labelling studies using \(\text{Ph}_2\text{S}^{18}\text{O}\) (87% labelled) unequivocally proved the oxygen in the sulfoxide product originated from \(\text{Ph}_2\text{SO}\) (Scheme 25).

Further detailed \(^18\text{O}\) isotopic labelling studies provided evidence for a number of steps that must occur during the sulfoxidation reaction, including that the first committed step in the mechanism must be the reaction of the oxathiane sulfur atom with an activated \(\text{Ph}_2\text{SO}\) species and a \(\text{Ph}_2\text{SO}\) oxygen atom must become covalently bound to the oxathiane sulfur atom. Although we were never able to observe or isolate diphenyl sulfide from the sulfoxidation reaction, the quantitative formation of triaryl sulfonium salt \(\text{Ph}_3\text{S}^\text{OTf}\) (Scheme 26) was confirmed by HPLC-mass spectrometric comparison of the crude product mixture with authentic samples of sulfonium salt 82 of known concentration, thus proving diphenyl sulfide also must be produced during the reaction and then react with some activated \(\text{Ph}_2\text{SO}\) species to produce the triarylsulfonium salt by-product. Several mechanistic pathways could be proposed and were consistent with these observations (Scheme 26).\[52\] In the first (a), oxathiane 77 initially attacks an electrophilic oxygen atom in triflyoxy sulfonium ion 55 to produce activated oxathiane 78 and diphenyl sulfide. Activated oxathiane 78 could then react with the excess \(\text{Ph}_2\text{SO}\) to provide oxodisulfonium ion 79. Similarly 79 could also be formed via an alternative pathway (b) which also involves reaction at an electrophilic oxygen atom, but on this occasion dication 59. However, based on literature precedent, vide supra, we deemed routes (a) and (b) to be less likely than attack at the softer electrophilic sulfur atoms in intermediates 55 and 59 (Scheme 26 c-d). If oxathiane 77 were to react at the sulfonium centres of cation 55 (route c) or dication 59 (route d), a dithiadiadication intermediate 80 would be produced (although seemingly unlikely, intermediate dithiadiacations have been synthesised previously by reaction between a sulfide and an activated sulfoxide).\[52\] Subsequent \(\text{Ph}_2\text{SO}\) attack at the oxathiane sulfur atom of the dithiadication would then afford oxodisulfonium ion 79. Thus, regardless of the early steps in the reaction, all pathways converge on oxodisulfonium ion 79. The final step in the reaction is then a quench of the oxodisulfonium
ion by diphenyl sulfide to afford the oxathiane-S-oxide $^{81}$ and triaryl sulfonium ion $^{82}$. We favoured route (d) as the pathway for the formation of the dication $^{59}$ - first postulated by Gin and co-workers (Scheme 19) as the reactive intermediate in a 2:1 $\text{Ph}_2\text{SO}/\text{OTf}_2\text{O}$ activation mix, and then confirmed by our own experiments in this study using $^{19}$F-NMR and $^{18}$O labelling studies. Extension of the labelling studies to a simple non-glycosyl oxathiane, demonstrated that the stereoselective sulfoxidation was not limited to substrates containing a sugar ring which have the ability to interconvert between axial and equatorial orientated intermediates through anomic bond breaking and generation of an oxacarbenium ion, followed by bond rotation and then intramolecular ring closing. It must therefore also be possible for the axial and equatorial activated sulfoxide intermediates to also interconvert through an intermolecular attack of $\text{Ph}_2\text{SO}$ on the activated oxodisulfonium ion $^{79}$, where the lowest energy stereoisomer is quenched to afford the lowest energy sulfoxide (Scheme 26).

A number of other detailed mechanistic studies have also been used to dissect some of the more nuanced stereocchemical preferences observed in glycosyl sulfoxide formation $^{[53]}$. Including Crich and co-workers $^{[54]}$ who established inherent stereocchemical trends in the oxidation of thioglycosides. The authors concluded that (R)$_\alpha$ sulfoxides are strongly favoured when axial-(a)-thioglycosides are oxidised, as the exo-anomeric effect leads to shielding of the pro-S sulfur lone pair under the ring and exposes the pro-R lone pair to the solvent, while equatorial-(b)-thioglycosides afford sulfoxide diastereomers with reduced inherent substrate stereoccontrol, only weakly favouring the (S)$_\beta$ sulfoxide. An example of the dominance of this stereocchemical preference observed for axial-(a)-thioglycoside oxidation was noted in the preferential formation of an $\alpha$-xylopyranosyl sulfoxide in a seemingly unlikely inverted $^1\text{C}_4$ chair conformation. To investigate this preference Crich deployed a glycosyl allyl sulfoxide-sulfenate rearrangement to probe the kinetic and thermodynamic preferences of sulfoxide formation from thioxylosides. As expected oxidation of $\beta$-thioxyloside $^{83\beta}$ preferentially afforded the (S)$_\beta$ sulfoxide $^{84\beta}$ (S)$_\beta$ as the major (kinetic) product (Scheme 27a), while the $\alpha$-thioxyloside $^{83\alpha}$ afforded the inverted $^1\text{C}_4$ conformer of (R)$_\alpha$ sulfoxide $^{84\alpha}$ (R)$_\alpha$ as the major (kinetic) product (Scheme 27b). In the former $\beta$-series, following thermal allyl sulfoxide $^{84\alpha}$-sulfenate $^{85}$ rearrangement in deuteriobenzene, the thermodynamic product proved to be the same as the kinetic product. However, following thermal equilibration of the latter $^1\text{C}_4$ conformer of the sulfoxide $^{84\alpha}$ (R)$_\alpha$ conversely thermodynamic reversion to the minor kinetic product $^{84\alpha}$ (S)$_\alpha$ occurred.

![Scheme 26 (a-d). Possible reaction pathways for the oxidation of generic oxathiane 77. Mechanisms are depicted as $\text{S}_\beta\text{2}$ processes for simplicity, although it is likely that some mechanisms may proceed via sulfurane intermediates. Reproduced from Ref. 52](image-url)
The observation that the kinetic sulfoxide $\text{84a}$ 4R exists in the tri-axial inverted $^{13}$C$_2$ conformation is explained by the authors as a preference for minimising repulsions between the sulfoxide S-O and C2-O2 dipoles, which are unfavourably aligned in the minor $^{13}$C$_2$ conformation of the (R)$_2$ diastereomer, but following thermodynamic equilibration to the $\text{84a}$ (S)$_2$ diastereomer, the preference to ring flip is obviated by a lack of dipole repulsion, meaning $\text{84a}$ (S)$_2$ exists in the expected $^{13}$C$_2$ conformation.

Since their first deployment as an anomic leaving group over 25 years ago, sulfoxides have become increasingly attractive to synthetic carbohydrate chemists because of their penchant for facilitating interesting and unexpected transformations. As examples of such transformations in the literature have multiplied, so has the ability of chemists to harness and direct this complex reactivity. This has led to the emergence of significant roles for sulfoxides as mediators in a range of innovative mechanistic strategies for probing glycosylation and other cognate reactions, including the development of cation clocks, mass spectrometry and $^{13}$C-NMR isotopic labelling studies, and DFT molecular modelling studies. Feedback from these mechanistic studies has in-turn led to improvements in the reactivity, and anomic stereoselectivity of sulfoxide glycosyl donors for the synthesis of challenging and complex oligosaccharides, as well as a panel of increasingly potent thioglycoside activators for the synthesis of biologically important deoxy sugars, among others. These pioneering studies have also begun to influence the manner in which carbohydrate chemists approach and rationalise glycosylations using other classes of glycosyl donor.

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Acknowledgements

The authors thank The University of York, The Royal Society, and the European Commission for the award of a Marie Curie Fellowship to MAF (FP7-PEOPLE-2011-IOF-302246). The work was supported by the Engineering and Physical Sciences Research Council (EP/G043302/1).
