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The stereochemistry of substitution at S(VI)

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Since the re-birth of sulfur-fluoride exchange (SuFEx) chemistry, coined by Sharpless in 2014 as a 'click' reaction, the prevalence of sulfur(VI) moieties in medicinal, polymer and materials chemistry has increased significantly. SuFEx and analogous substitution reactions at electrophilic S(VI) reagents are often performed on symmetrical, achiral S(VI) centres. However, when these substitution reactions are applied to chiral S(VI) substrates, often enantioenriched chiral-at-sulfur aza-S(VI) analogues, the stereochemical outcome of the reaction must be considered to obtain the appropriate 3D configuration. In this review, we aim to draw together the stereochemical outcomes and mechanistic understanding of substitution reactions occurring at electrophilic chiral S(VI) reagents to provide support, and potential word of caution, to the growing field. In addition, we review the significant developments in stereocontrolled reactions at S(VI) centres.

Introduction

Sulfur(VI) motifs are important and common across medicinal,[1–6] polymer,[7] and materials chemistry.[8,9] S(VI) moieties such as sulfones, sulfonamides, and sulfonates alongside their corresponding, often chiral, aza-analogues sulfoximines, sulfonimidamides, and sulfonimidates (Fig. 1a) can be prepared through a broad range of transformations,[10–20] including substitution reactions at S(VI) precursors.[21,22] Chiral S(VI) centres present in sulfoximines have been shown to instil beneficial properties to drug-like compounds, including high solubility and polarity, and hydrogen-bond acceptor and donor capability in NH-derivatives.[3,23–25] The asymmetry at sulfur offers potential directional interactions to better fit within protein binding sites. As a result, the prevalence of chiral S(VI)-containing biologically active compounds has increased across the pharmaceutical industry, with anti-inflammatory (DFV890) and anti-cancer (VIP152 and ceralasertib) drugs entering Phase II and Phase III clinical trials (Fig. 1b).[26–28]

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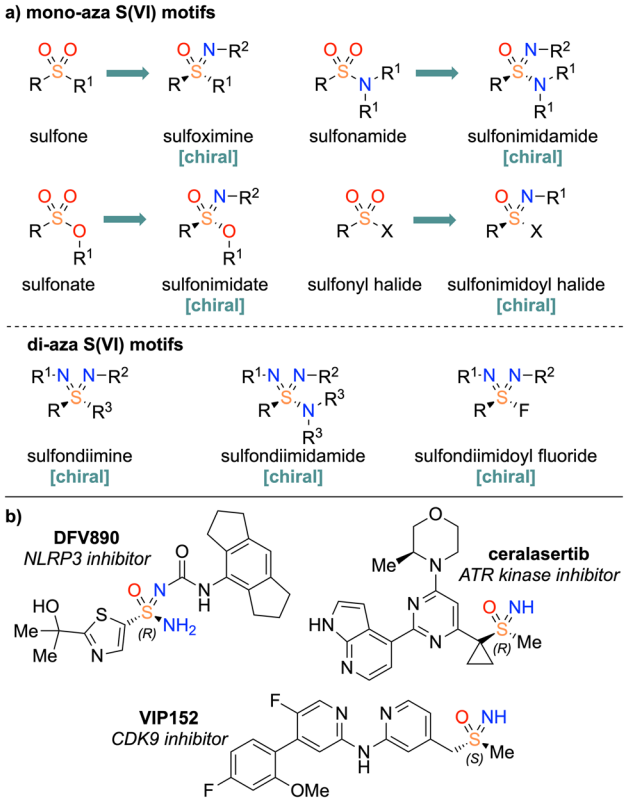

Fig. 1 (a) Common and emergent S(VI) motifs; (b) drug candidates containing S(VI) centres.

Sulfondiimine, and sulfondiimidamide motifs contain a two imine nitrogen groups bonded at sulfur, also creating the potential for a chiral S(VI) centre (Fig. 1a). Research into these scaffolds is a rapidly growing field, with notable recent advancements by Willis[29,30] and Lin and Ye[31] in their reactivity and synthesis. However, there are no reports on their enantioselective synthesis and therefore little is known about the stereochemical outcome of substitution reactions at sulfondiimidoyl centres.

Typical achiral S(VI) electrophilic precursors include sulfonyl halides (RSO_2X) and sulfonates (RSO_2OR) – reagents primed for substitution of the halide or alkoxy/phenolic leaving groups at the sulfur centre. While sulfonyl chlorides are historically established and widely adopted reagents, sulfonyl fluorides did not gain popularity following their discovery in 1927 by Steinkopf[32,33] and others.[34,35] Sulfonyl fluoride reagents remained largely forgotten until their recent resurgence following the establishment of sulfur-fluoride exchange (SuFEx) click chemistry by Sharpless in 2014.[36] Interest in SuFEx chemistry has since soared, with over 400 publications featuring SuFEx chemistry to date[37] and the field also expanding to incorporate the use of alternate leaving groups, such as triazole (termed SuTEx)[38] and imidazolium salts.[39] SuFEx and adjacent substitution reactions at S(VI) reagents are becoming increasingly prevalent transformations across medicinal[40–43] and polymer chemistry.[44–46]

When performing nucleophilic substitution reactions at chiral S(VI) electrophiles, such as sulfonimidoyl halides and sulfonimidates, the stereochemical outcome of the substitution must be considered to determine the 3D configuration at sulfur. With the growing application of chiral S(VI) motifs in medicinal chemistry,[24,25] and the need to control molecular geometry when designing ligands to interact with a biological target,[47–51] it is essential to understand the stereochemical consequences of substitution at chiral, electrophilic S(VI) reagents. This topic has been sporadically studied since the late 1960s, with a surge of interest in the last five years. Moreover, examining the stereochemical outcome for a transformation provides insight to the reaction mechanism. In aza-S(VI) systems, four plausible mechanisms can be considered for a nucleophilic substitution reaction: (1) S_N1; (2) S_N2; (3) addition–elimination *via* a 5-coordinate sulfurane intermediate or (4) elimination and subsequent addition to a sulfene-type intermediate (Fig. 2).

As discussed through this review, nucleophilic substitution reactions at chiral S(VI) centres are widely proposed to occur with inversion of the sulfur stereocentre *via* an S_N2-like process. However, some studies instead suggest an addition–elimination model is responsible, and may account for otherwise unexpected stereochemical outcomes. S_N1 processes and/or sulfene formation may account for observed racemisation. The formation of sulfene intermediates has been suggested in reactions with alkyl derivatives where significant racemisation has been observed. S_N1 processes are less commonly evoked, but in principle could be stabilised by the imine nitrogen lone pair or through the formation of an S≡N species. These processes may plausibly operate in tandem with other dominant mechanistic pathways.

This review examines substitution reactions of enantioenriched, chiral S(VI) electrophiles with nucleophiles and their experimentally determined stereochemical outcomes. Seminal works in the field are presented, highlighting key advancements and assessing the outcomes in the modern context. In this review, the examined works are organised by the class of chiral S(VI) electrophile utilised in the study: (1) sulfonimidoyl

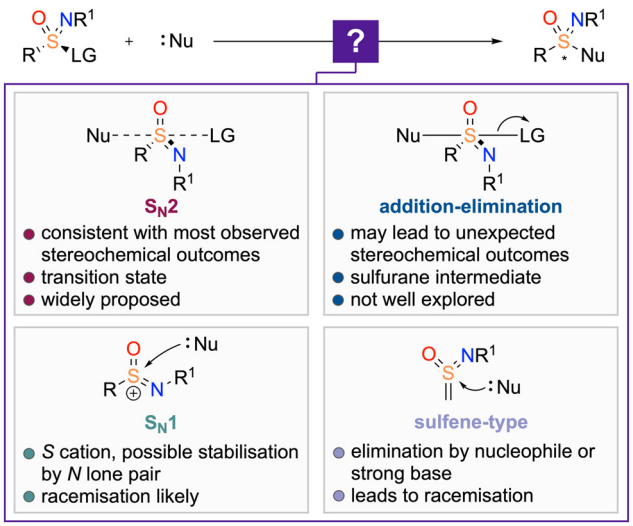

Fig. 2 Plausible mechanisms of displacement reactions at chiral S(VI) centres. Nu = nucleophile; LG = leaving group.

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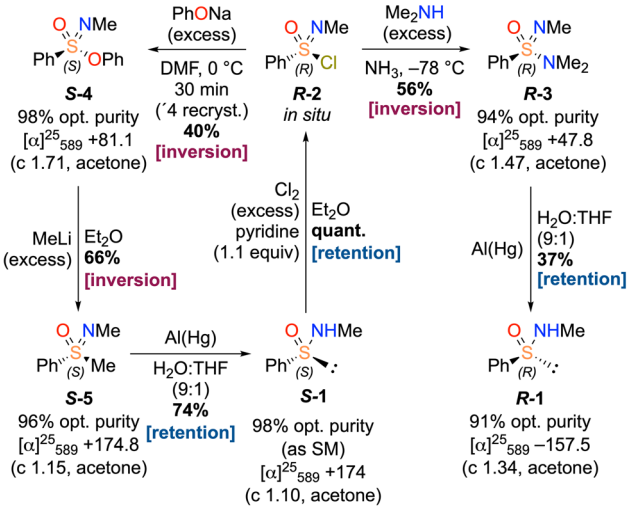
chlorides (LG≡Cl), (2) sulfonimidates (LG = OR), and (3) sulfonimidoyl fluorides (LG = F). Investigations are discussed chronologically within each section. For every reaction occurring at a chiral sulfur centre with a measured or deduced stereochemical outcome, [retention], [inversion], or [racemisation] will feature alongside the reaction arrow. Typical methodologies for elucidating the stereochemistry have evolved with the rise of more exact technologies. As such, older studies presented here often relied on measured optical rotation, while contemporary investigations provide more ironclad evidence such as chiral HPLC and X-ray crystallographic data to support their findings. In any case, the rationale behind every reaction reported to occur with retention or inversion will be presented. Examples and proposed mechanisms for sulfur centre racemisation will be examined, including fluoride ion or imidazole-mediated racemisation processes.

It is notable that the synthesis and reactivity of chiral S(VI) derivatives more generally and also chiral S(IV) reagents have experienced significant interest in recent years. However, this work will not be covered explicitly here. Readers are also directed to excellent recent reviews on sulfur stereochemistry by Wojaczyńska,[52] Zhang and Tan,[53] and Shi.[54]

Sulfonimidoyl chlorides

The earliest investigations into the reactivity of sulfonimidoyl chlorides, and the first examples of enantioenriched aza-S(VI) derivatives, were from C. Johnson in 1971. Using electrophilic chlorination of enantiopure sulfinamide ***S*-1**, Johnson generated, but did not isolate, sulfonimidoyl chloride ***R*-2** (Scheme 1).†[55]

Johnson then subjected sulfonimidoyl chloride ***R*-2** to two distinct series of transformations to determine the stereochemical outcomes of the substitution reactions and assign the arrangement at sulfur for sulfonimidoyl chloride ***R*-2**.[56] One route involved first reacting sulfonimidoyl chloride ***R*-2** with dimethylamine to generate sulfonimidamide ***R*-3**, followed by treatment with aluminium amalgam to provide sulfinamide ***R*-1**. The transformation of ***S*-1** to ***R*-1** sulfinamide must proceed by either: (A) all three steps go with inversion or (B) one step gives inversion of configuration and two proceed with retention. Johnson had previously shown the aluminium amalgam reduction of sulfoximine ***S*-5** to sulfinamide ***S*-1** occurred with retention of stereochemistry (determined by the observed optical rotations and comparison with previous reports),[57] and proposed that the reduction of sulfonimidamide ***R*-3** to sulfinamide ***R*-1** should proceed similarly. Johnson also assumed that the chlorination of sulfinamide ***S*-1** proceeded with retention since it was an "electrophilic substitution occurring on sulfur without perturbation of the tetrahedral structure".[56] Consequently, Johnson concluded the S(VI) substitution reaction between sulfonimidoyl chloride ***R*-2** and dimethylamine must proceed with inversion of stereochemistry, thus following the single inversion sequence (B).[56]



Scheme 1 Routes to synthesize sulfonimidamide ***R*-3**, sulfonimidate ***S*-4**, sulfoximine ***S*-5**, and sulfinamides ***S*-1** and ***R*-1** from enantioenriched sulfonimidoyl chloride ***R*-2**. ***S*-1** prepared by methylation of free NH sulfinamide, $[\alpha]_{589}^{25}$ +36.5 (*c*. 1.20, acetone). opt. purity = optical purity as quoted by the authors; SM = starting material.

The second cyclic route involved reacting sulfonimidoyl chloride ***R*-2** with excess sodium phenolate to provide sulfonimidate ***S*-4** (Scheme 1).[56] This substitution was accompanied with a "loss of optical purity", likely caused by racemisation of the reactive sulfonimidoyl chloride ***R*-2** and required recrystallisation to regain enantiopurity. Enantioenriched sulfonimidate ***S*-4** was reacted with excess methyllithium to generate sulfoximine ***S*-5**. Treatment with aluminium amalgam reduced sulfoximine ***S*-5** to sulfinamide ***S*-1** starting material. Drawing again on the assumption that the chlorination from ***S*-1** to ***R*-2** and reduction from ***S*-5** to ***S*-1** occurred with retention of stereochemistry, Johnson deduced that both S(VI) substitution reactions, between sulfonimidoyl chloride ***R*-2** and sodium phenolate as well as between sulfonimidate ***S*-4** with methyllithium, must proceed *via* inversion of stereochemistry at the sulfur centre. There is no comment on mechanism of substitution.[56]

In 1974, Cram prepared and isolated diastereomerically pure sulfonimidoyl chloride ***S*-6** from oxidative chlorination of *N*-carbomenthoxy-*p*-toluenesulfinamide, followed by rapid chromatography and recrystallisation (Scheme 2a).[58] Sulfonimidoyl chloride ***S*-6** was then reacted with dimethylamine and sodium amide to provide sulfonimidamides ***S*-7** and ***R*-8**, respectively. Sulfonimidoyl chloride ***S*-6** was also treated with potassium 4-methylphenolate to afford sulfonimidate ***R*-9**, which itself was further reacted with methylmagnesium bromide to generate sulfoximine ***R*-10**.[58]

Considering the deduced stereochemical outcomes established by Johnson in prior work,[56] Cram assigned all nucleophilic substitution reactions with sulfonimidoyl chloride ***S*-6**, as well as that between sulfonimidate ***R*-9** and methyl-

† All *R* and *S* configurational assignments at sulfur are reported according to the following Cahn–Ingold–Prelog (CIP) priority rules: –Cl > –F > –OR > =O > =NSO_2R > –NR_2 > –NHR > =NR > –NH_2 > =NH > C (aryl) > C (alkene) > C (alkyne) > C (alkane).

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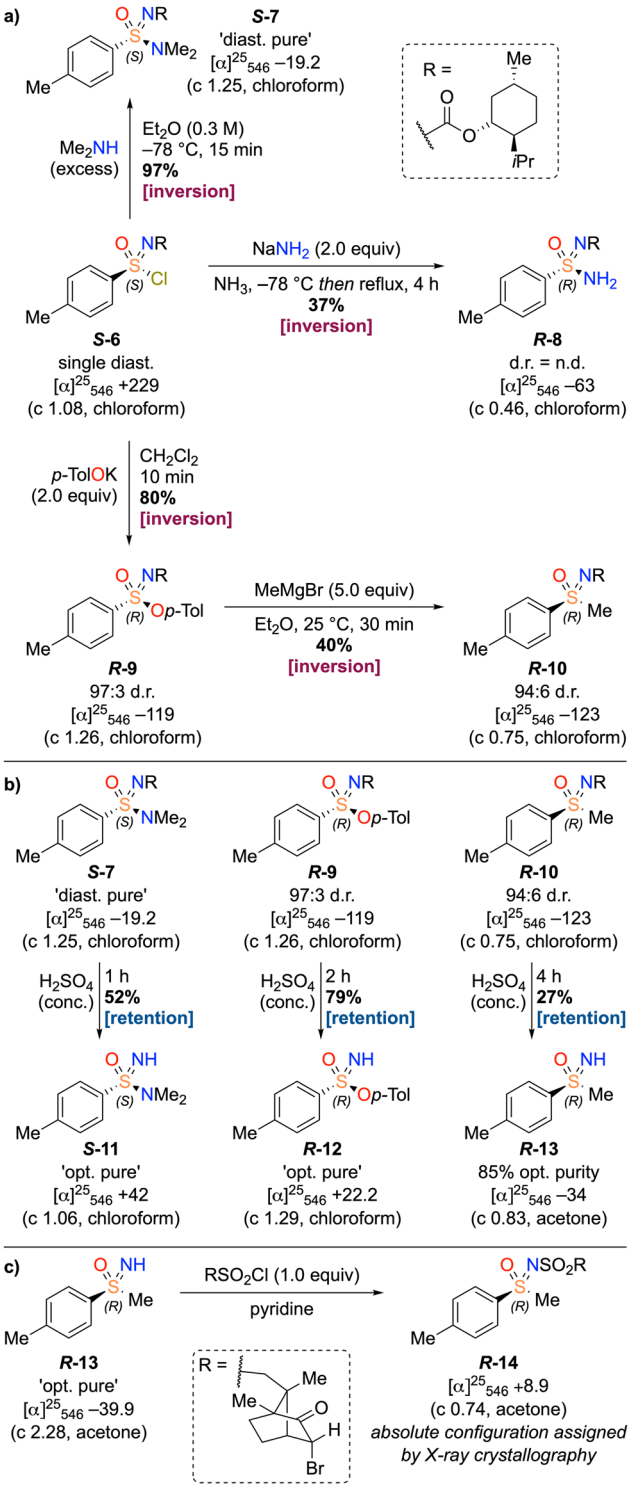

Scheme 2 (a) Synthesis of sulfonimidamides ***S*-7** and ***R*-8**, sulfonimidate ***R*-9** and sulfoximine ***R*-10** from diastereomerically pure sulfonimidoyl chloride ***S*-6**; (b) removal of carbomenthoxy chiral auxiliary to afford free NH products; (c) synthesis and configurational assignment of sulfoximine ***R*-14**. n.d. = not determined; 'diast. pure' = compound claimed as diastereomerically pure, no values quoted; 'opt. pure' = compound claimed as optically pure, no values quoted.

magnesium bromide, as proceeding with an inversion of stereochemistry. Enantiomeric optical purity of the deprotected chiral S(VI) products (***S*-11**, ***R*-12** and ***R*-13**) were also determined by optical rotation (Scheme 2b). Because the removal of the carbomenthoxy auxiliary does not involve the sulfur stereocentre, Cram assumed the deprotection must proceed with retention of configuration at sulfur. It is through this assumption that Cram assigned the configuration of diastereomeric products ***S*-7**, ***R*-9** and ***R*-10**. In prior work, Cram functionalised the nitrogen of free NH sulfoximine ***R*-13** with a camphor sulfonyl chloride to afford sulfoximine ***R*-14** (Scheme 2c).[59] An X-ray crystal structure of sulfoximine ***R*-14** confirmed the stereochemical configuration at sulfur.

Working under the assumption that the functionalisation of sulfoximine ***R*-13** did not impact the stereochemistry at sulfur, Cram extended the X-ray assigned configuration of ***R*-14** assignment to NH sulfoximine ***R*-13**. Moreover, the observed optical rotation of NH sulfoximine ***R*-13** ($[\alpha]^{25}_{546}$ −39.9, Scheme 2c) correlates well with the same product obtained from acid hydrolysis ($[\alpha]^{25}_{546}$ −34, Scheme 2b), providing greater support to the assumption that the deprotection reaction proceeded with retention of the sulfur stereocentre. It is important to note the empirical data used to support these deductions. Aside from the single X-ray crystal structure, conclusions here were largely derived from observed optical rotation values of the starting materials and products, and therefore "the stereochemical courses of these reactions can be assigned with a high, if not complete, degree of confidence".[58] By virtue of observing products with inverted stereochemistry, Cram suggests each nucleophilic substitution reaction proceeds through an S_N2-like mechanism.[58]

It was almost 25 years before any further investigation into enantioenriched sulfonimidoyl chlorides was reported, when Kluge re-performed and extended the work outlined by Cram. In this work, sulfonimidoyl chlorides ***S*-6** and ***R*-6** were reacted with imidazole and potassium 4-methylphenolate to generate both enantiomers of sulfonimidoyl imidazole **15** and sulfonimidate **9**, respectively. Sulfonimidoyl imidazoles ***R*-15** and ***S*-15** were also treated with potassium 4-methylphenolate to synthesize sulfonimidates ***S*-9** and ***R*-9** (Scheme 3).[60] Determined by chiral HPLC analysis, sulfonimidoyl imidazoles ***R*-15** and ***S*-15** were both generated with d.r. >97.5 : 2.5. Observed optical rotation of sulfonimidate ***R*-9** generated from sulfonimidoyl chloride ***S*-6** and sulfonimidoyl imidazole ***S*-15** was in agreement with that previously reported by Cram ($[\alpha]^{25}_{546}$ −119, Scheme 2a).[58] In later work, Kluge analysed sulfonimidoyl chlorides ***R*-6** and ***S*-6** with chiral HPLC and definitively determined their diastereomeric and optical purity (d.r. >99.5 : 0.5, >99% ee).[61] The same sulfonimidoyl chlorides (***R*-6** and ***S*-6**, Scheme 3) were also found to be in good agreement with specific rotation measurements previously reported by Cram, retrospectively confirming the stereochemical purity of Cram's sulfonimidoyl chlorides.[58]

Given sulfonimidate ***R*-9** was generated from sulfonimidoyl chloride ***S*-6** and sulfonimidoyl imidazole ***R*-15** following treatment with potassium 4-methylphenolate, Kluge assigned the

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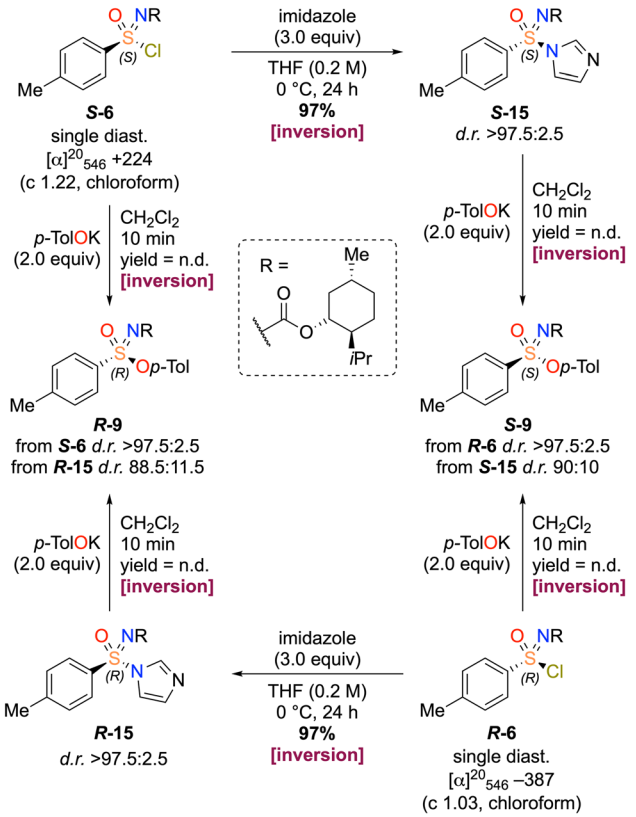
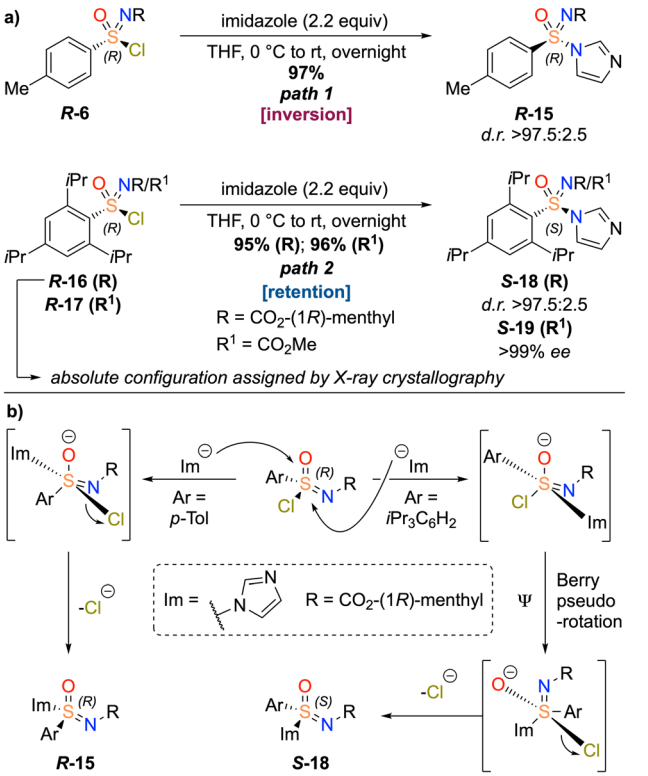


Scheme 3 Route to synthesise sulfonimidates ***R*-9** and ***S*-9** from sulfonimidoyl chlorides ***S*-6** and ***R*-6** and sulfonimidoyl imidazoles ***R*-15** and ***S*-15**, with all steps proceeding with inversion of stereochemistry. n.d. = not determined.



Scheme 4 (a) Synthesis of enantioenriched sulfonimidoyl imidazoles ***R*-15**, ***S*-18**, and ***S*-19** *via* inversion or retention of the sulfur stereocentre; (b) proposed substitution mechanism to account for observed retention of stereochemistry.

substitution of imidazole with 4-methylphenolate as an inversion of stereochemistry.[61] Kluge obtained an X-ray crystal structure of another sulfonimidoyl chloride (***R*-16**), unequivocally confirming the configuration at the sulfur centre. Kluge compared the circular dichroism (CD) spectra of ***R*-16** with those of the enantiopure diastereomers of sulfonimidoyl chloride ***R*-6**, arguing this provided independent proof and validation of their configurations,[61] previously only assigned according to optical rotation and chemical conversions.[58]

Kluge expanded this work by investigating the effect of the aryl substituent of the sulfonimidoyl chloride on the stereochemical course of substitution reaction with imidazole. Interestingly, the stereochemical outcome of the substitution reaction was shown to be highly dependent on the aryl substituent bonded directly to the sulfur centre (Scheme 4). Reacting *p*-tolyl sulfonimidoyl chloride ***R*-6** with imidazole provided sulfonimidoyl imidazole ***R*-15** in high yield. After measuring the absolute configurations of the sulfonimidoyl chloride and imidazole product by CD spectroscopy (***R*-6**: CD (*i*PrOH, *c.* 1.076×10^{-4} mol L^{-1}) $\Delta\varepsilon_{261.1nm}$ −10.68; ***R*-15**: CD (*i*PrOH, *c.* 1.62×10^{-5} mol L^{-1}) $\Delta\varepsilon_{207.4nm}$: −10.53, $\Delta\varepsilon_{270nm}$: +0.25), the sulfur centre was found to have undergone inversion.[61] However, when reacting the bulkier triisopropylphenyl sulfonimidoyl chloride ***R*-16** with imidazole, complete retention of the sulfur stereocentre was observed, providing sulfonimidoyl imidazole ***S*-18** (Scheme 4a). The absolute configuration of sulfonimidoyl chloride ***R*-16** was assigned by X-ray analysis as *R* at sulfur, while the absolute configuration of sulfonimidoyl imidazole ***S*-18** was determined by CD spectroscopy (***S*-18**: CD (*i*PrOH, *c.* 2.935×10^{-5} mol L^{-1}) $\Delta\varepsilon_{214.2nm}$: −17.22, $\Delta\varepsilon_{283.8nm}$: +0.98) and d.r. determined by ^{1}H NMR analysis.

This observed difference in stereochemical outcome must be related to the bulkier triisopropylphenyl group, as the same retention of the sulfur centre (determined by CD spectroscopy, ***R*-17**: CD (*i*PrOH, *c.* 7.87×10^{-5} mol L^{-1}) $\Delta\varepsilon_{247.2nm}$: −19.68, ***S*-19**: CD (*i*PrOH, *c.* 2.25×10^{-5} mol L^{-1}) $\Delta\varepsilon_{214.8nm}$: −27.2, $\Delta\varepsilon_{284.2nm}$: +1.51) was observed when the nitrogen protecting group was CO_2Me rather than the larger menthyl group (Scheme 4a).[61] Kluge reasons that the very bulky triisopropylphenyl group hinders the *anti*-attack (relative to chlorine) of the imidazole, instead promoting *anti*-attack relative to the triisopropylphenyl group. To allow elimination of the chlorine group, which should leave from the axial position,[59] the proposed 5-coordinate sulfurane intermediate undergoes a Berry-pseudorotation. Following this configurational perturbation, chlorine is removed to provide sulfonimidoyl imidazole ***S*-18** with retention of stereochemistry (Scheme 4b).[61] If the determination of stereochemical configuration by CD spectroscopy can be relied upon, this exists as one of the first examples in

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the literature of a substitution reaction at a chiral S(VI) centre occurring with retention of stereochemistry. This idea of a configurationally fluid sulfurane intermediate was originally suggested as a mechanism for nucleophilic substitution at tetravalent S(VI) by Mikołajczyk and Drabowicz.[62] Both Mikołajczyk and Kluge reason that, while sulfuranes were not observed as intermediates in these studies, they have been independently synthesised and isolated in prior work.[63,64]

A 2023 report by Tang greatly expanded the field, demonstrating the versatility of sulfonimidoyl chlorides as chiral S(VI) reagents.[65] Using an (*R*)- or (*S*)-TRIP chiral phosphoric acid catalyst, Tang and co-workers generated a range of enantioenriched (*R*)- and (*S*)-sulfonimidoyl chlorides, which was proposed to occur through an enantioselective hydrolysis process (Scheme 5a).

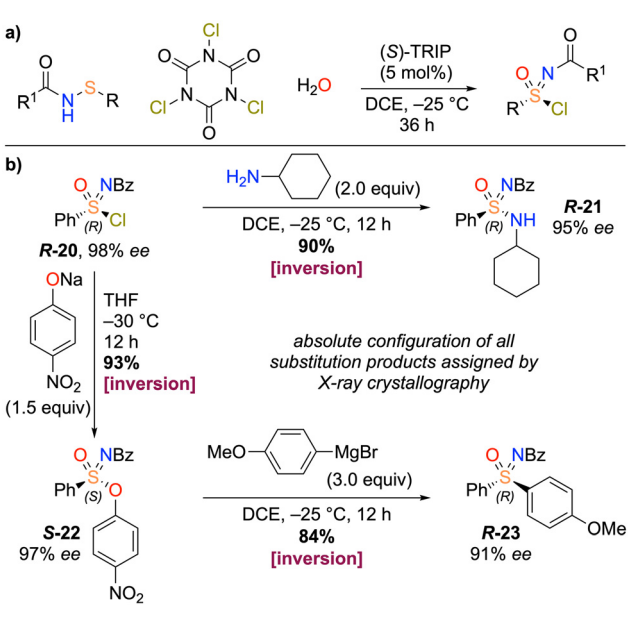
Remarkably stable to column chromatography purification, these enantioenriched sulfonimidoyl chlorides were treated with amines and sodium phenolate reagents to afford the corresponding sulfonimidamides and sulfonimidates, respectively. X-ray crystal structures were not obtained for any of the enantioenriched sulfonimidoyl chlorides, with the authors calculating ee by chiral HPLC. Configurational confirmation of sulfonimidamide ***R*-21** and sulfonimidate ***S*-22** by X-ray crystallography led the authors to assume these reactions proceeded with an inversion of stereochemistry in an S_N2 process, therefore assigning the absolute stereochemistry of sulfonimidoyl chloride ***R*-20** (Scheme 5b). Sulfonimidate ***S*-22** was treated with 4-methoxyphenylmagnesium bromide to afford corresponding sulfoximine ***R*-23**, with the inversion of stereochemistry proven with X-ray crystal structures of the starting material and product (Scheme 5b).[65] The same group have since expanded this methodology to enable the enantioselective synthesis of sulfonimidoyl fluorides.[66]

This year, Zuilhof and co-workers developed conditions for the solvent-free, mechanochemical enantiospecific synthesis of sulfonimidates and sulfonimidamides through SuFEx and SuPhenEx S(VI) exchange reactions.[67] In this work, X-ray crystal structures of enantiopure sulfonimidoyl chloride ***R*-24** and resulting sulfonimidate ***S*-25** were measured, providing proof of the sulfur stereocentre inversion (Scheme 6).[67]

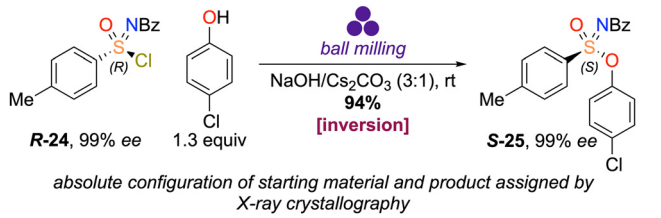
Sulfonimidates

In 1969, Sabol and Andersen established the first example of inversion at a tetracoordinate hexavalent sulfur centre.[68] Enantiopure ^{18}O-labelled chiral sulfonate ***R*-27** was reacted with *p*-tolylmagnesium bromide to provide known ^{18}O-labelled chiral sulfone ***S*-28**, synthesized previously by Stirling *via* oxidation of an enantiopure sulfoxide with ^{18}O-labelled peracetic acid (Scheme 7).[69]

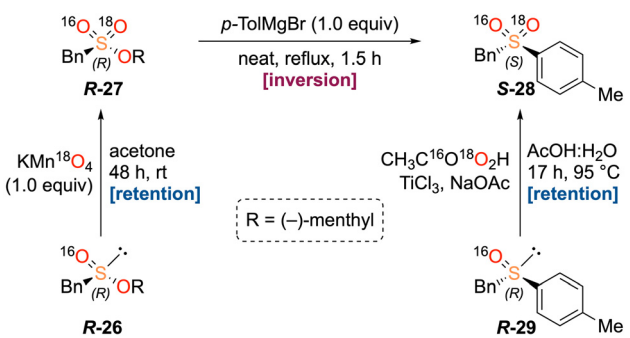
The optical activity of molecules in this study was measured using optical rotation dispersion (ORD) analysis – a variation of specific rotation analysis with respect to the wavelength of light.[70] It was observed that chiral sulfone ***S*-28** generated from the reaction between chiral sulfonate ***R*-27** with *p*-tolylmagnesium bromide produced a negative plain curve from 350 to 280 nm in the ORD analysis, which was similar in shape to the curve observed for chiral sulfone ***S*-28** obtained *via* oxidation of sulfoxide ***R*-29**. Following the assumption that oxidations of



Scheme 5 (a) Enantioselective hydrolysis to access enantioenriched sulfonimidoyl chlorides; (b) S(VI) substitution reactions with sulfonimidoyl chloride ***R*-20** to generate enantioenriched sulfonimidamide ***R*-21**, sulfonimidate ***S*-22**, and sulfoximine ***R*-23**.



Scheme 6 Mechanochemical synthesis of sulfonimidate ***S*-25** from sulfonimidoyl chloride ***R*-24**, with confirmation of sulfur stereocentre inversion by X-ray crystallography.



Scheme 7 Route to ^{18}O-labelled chiral sulfone ***S*-28** from sulfonate ***R*-27** and sulfoxide ***R*-29**.

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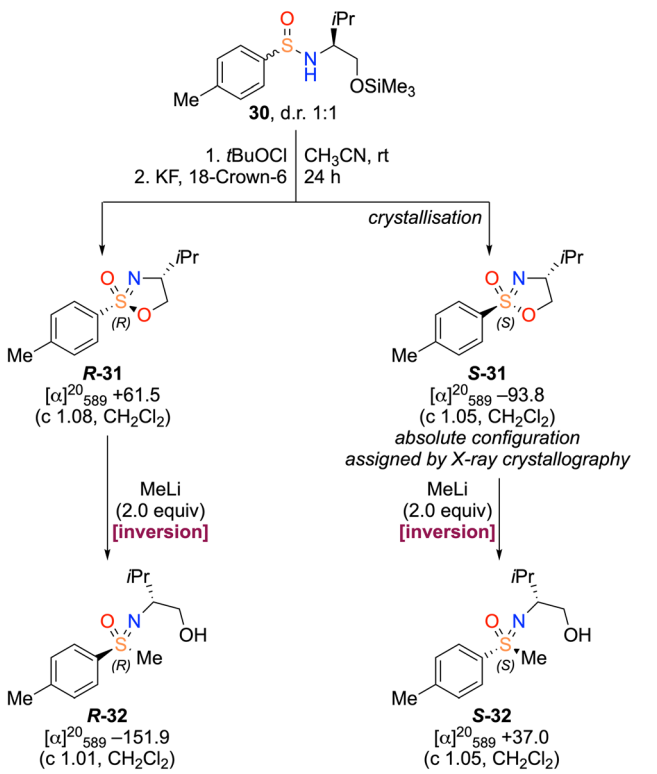
***R*-26** and ***R*-29** with ^{18}O-labelled oxidants proceeded with retention of stereochemistry, it was deduced that the nucleophilic substitution to generate chiral sulfone ***S*-28** from chiral sulfonate ***R*-27** must have occurred with inversion of the sulfur stereocentre. However, sulfone ***S*-28** displayed an exceptionally low optical rotation, with the authors unable to entirely rule out the possibility of highly optically active impurities, thereby introducing doubt to the reliability of the conclusion at this time.

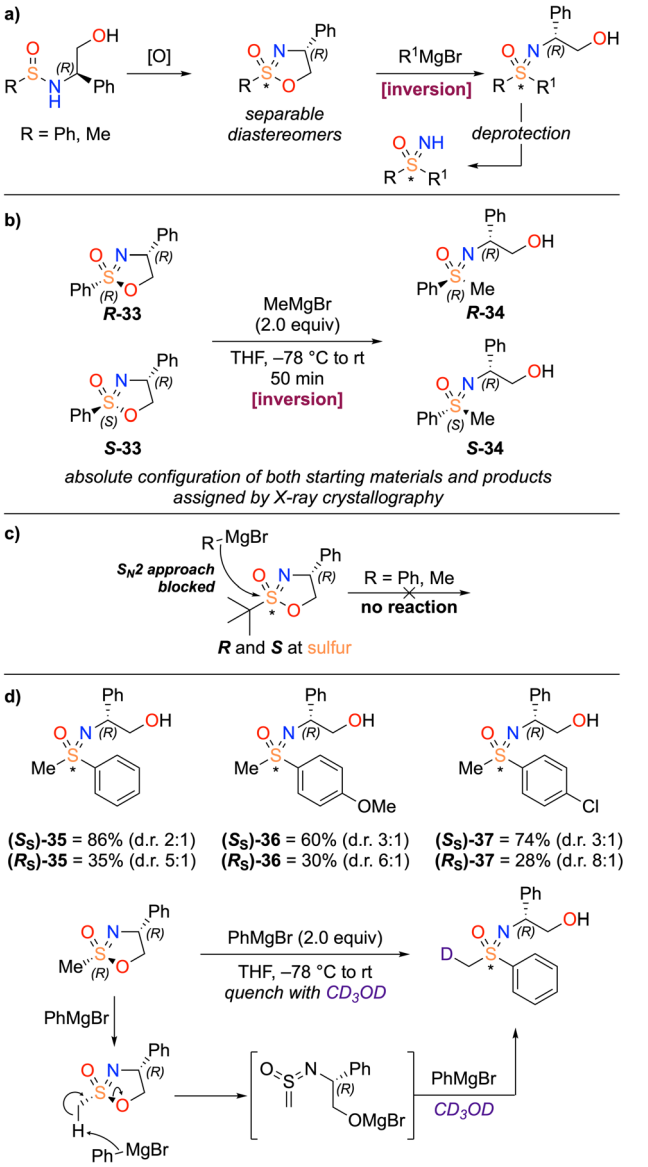
In the aza-S(VI) series, sulfonimidates are chiral, isolable S(VI) electrophiles, with an oxygen leaving group, historically generated from less stable sulfonimidoyl chlorides. In 1992, Reggelin and Weinberger pioneered the use of diastereomerically pure cyclic sulfonimidates as stable and chiral S(VI) electrophiles.[71] The cyclic sulfonimidates acted as stereochemical templates to provide starting materials with fixed and defined stereochemistry at the sulfur centre. Reacting cyclic sulfonimidates ***R*-31** and ***S*-31** with organometallic reagents afforded the corresponding enantioenriched sulfoximines through an inversion of the sulfur stereocentre (Scheme 8).

The absolute configuration at sulfur of cyclic sulfonimidate ***S*-31** was confirmed by X-ray crystallography, and the two cyclic sulfonimidates were reacted with excess methyllithium to provide the corresponding sulfoximines ***R*-32** and ***S*-32.** Reggelin and Weinberger claimed the reaction proceeded with inversion of the sulfur stereocentre, providing the observed difference in optical rotation between the two sulfoximine products as empirical evidence.

In 2020, Stockman and co-workers built on this work by developing a set of cyclic sulfonimidates with an easier-to-remove chiral auxiliary (Scheme 9a).[72] The cyclic sulfonimidate diastereomers were readily separable by column chromatography, allowing for the reaction of each diastereomer with organometallic reagents. In two examples, the absolute configuration of the cyclic sulfonimidate starting materials (***R*-33** and ***S*-33**, Scheme 9b) and sulfoximine products (***R*-34** and ***S*-**



Scheme 8 Use of cyclic sulfonimidates to generate enantioenriched sulfoximines ***R*-32** and ***S*-32**.



Scheme 9 (a) Route to access enantioenriched sulfoximines *via* cyclic sulfonimidates; (b) reaction between cyclic sulfonimidates and methyl magnesium bromide, unequivocally proving inversion at the sulfur centre by X-ray crystallography; (c) steric bulk of *tert*-butyl cyclic sulfonimidates potentially blocking the S_N2 trajectory of Grignard nucleophiles; (d) erosion of enantiopurity at the sulfur stereocentre *via* proposed sulfene intermediate.

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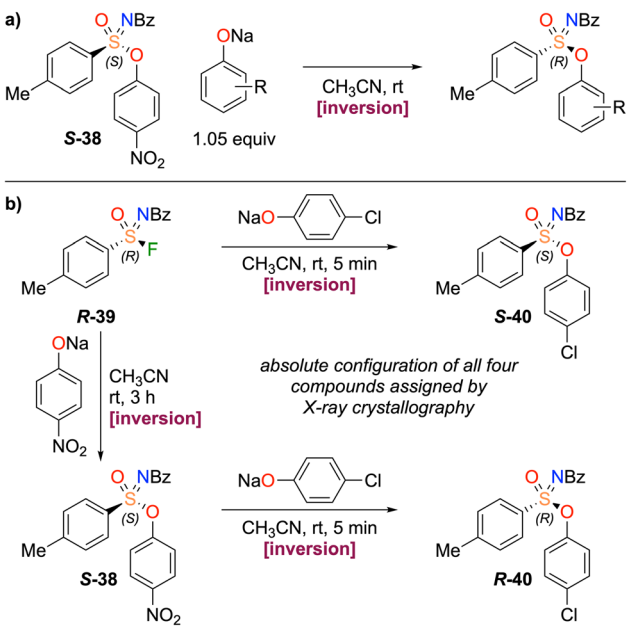
34, Scheme 9b) were assigned by X-ray crystallography, providing unequivocal evidence that this substitution reaction at the sulfur stereocentre proceeded with inversion.

Although no specific substitution mechanism was proposed, *tert*-butyl cyclic sulfonimidates were found to be unreactive towards phenyl and methylmagnesium bromide reagents, suggesting this bulky substituent blocks the S_N2 approach trajectory to the sulfur centre – a mechanism which would correlate well with the observed inversion of stereochemistry in this work (Scheme 9c). Erosion of enantiopurity at the sulfur stereocentre was observed with the methyl cyclic sulfonimidates, providing mixtures of diastereomers (Scheme 9d). The stereochemical degradation was proposed to be caused by a competitive base-mediated ring opening to generate a sulfene intermediate, which undergoes further nucleophilic addition at sulfur from another equivalent of Grignard reagent and subsequent carbanion quenching. This hypothesis was supported by deuterium incorporation from quenching with CD_3OD (Scheme 9d).[72]

In 2022, Zuilhof and co-workers developed a reaction between phenolates and a chiral sulfonimidate, replacing fluorides with *p*-nitro phenol as the leaving group (termed SuPhenEx, Scheme 10a).[73] Starting with the enantioenriched sulfonimidoyl fluoride ***R*-39**, Zuilhof and co-workers were able to access both enantiomers of sulfonimidate **40**. Reacting sulfonimidoyl fluoride ***R*-39** with the desired phenolate provided access to sulfonimidate ***S*-40**, while the opposite enantiomer (***R*-40**) could be synthesized through a double substitution *via* *p*-nitro sulfonimidate ***S*-38** (Scheme 10b).

Small molecule crystal structures of the sulfonimidoyl fluoride ***R*-39** and sulfonimidates ***S*-38**, ***S*-40**, and ***R*-40** were resolved, enabling assignment of absolute configuration and providing definitive proof that each nucleophilic substitution at the sulfur centre occurred with inversion of stereochemistry. Lower enantiospecificity of the SuPhenEx reaction was observed when using electron-poor (*o*-CHO and *p*-CN) phenolates, with the authors suggesting a phenolate-induced racemisation process is responsible. Temperature-dependent kinetic experiments unveiled the SuPhenEx activation enthalpy ($\Delta H^{\ddagger}$) between ***S*-38** and sodium *p*-Cl phenolate as 14 ± 1 kcal mol^{-1}, with the computationally calculated enthalpic barrier in good agreement (13.1 kcal mol^{-1}). Further computational calculations revealed the difference between SuPhenEx and racemisation ($\Delta\Delta H^{\ddagger}$) is related to the electronics of the phenolate – for phenolates bearing electron-donating groups (*e.g.* *p*-OMe) SuPhenEx is favoured over racemisation by ~7.5–10 kcal mol^{-1}. On the other hand, SuPhenEx is only slightly favoured in phenolates with electron-withdrawing groups (*p*-CN $\Delta\Delta H^{\ddagger}$ = 1.6 kcal mol^{-1}). These results align with the observed loss of enantiospecificity when using electron-poor phenolate nucleophiles. The authors conclude that this experimental and computational evidence presents their SuPhenEx process as a concerted S_N2-like reaction.

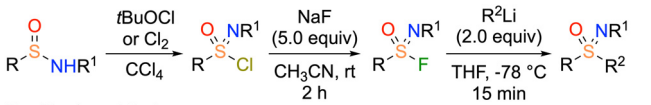


Scheme 10 (a) Generic SuPhenEx reaction; (b) access to both sulfonimidate enantiomers ***S*-40** and ***R*-40** from sulfonimidoyl fluoride ***R*-39** and sulfonimidate ***S*-38**, respectively.

Sulfonimidoyl fluorides

Sulfonimidoyl fluorides are the chiral, mono-aza analogues of the now widespread achiral sulfonyl fluorides. First synthesized by Johnson in 1983 through the fluorination of sulfonimidoyl chlorides with KF (Scheme 11),[74] their synthesis and application has been re-popularized by Sharpless in recent years.[75] Their enhanced stability over sulfonimidoyl chlorides makes them preferred reactive precursors, especially in studies regarding mechanism and stereochemical outcome of their reactions.

By reacting a racemic sulfonimidoyl chloride with KF and separating the enantiomers by chiral HPLC, Zuilhof isolated the first examples of enantioenriched sulfonimidoyl fluorides in 2020.[76] Phenols reacted with sulfonimidoyl fluorides without requiring silylation when in the presence of DBU. However, racemisation was observed, an issue that was remedied by switching to phenolates, thus providing enantioenriched sulfonimidates (Scheme 12a). In this study, the authors determined the ee of the sulfonimidate products by chiral HPLC and assumed the substitution occurred with inversion of the stereochemistry. The same authors (see



R = Ph, 1-naphthyl
R^1 = Me, Ph, $CH_3CH(Ph)$, (1-naphthyl)ethyl, 4-ClC_6H_4, 4-$MeOC_6H_4$, 2-pyridyl
R^2 = Me, *n*Bu, Ph

Scheme 11 Johnson's route to a range of sulfonimidoyl fluorides and sulfoximines from sulfonimidoyl chloride precursors.

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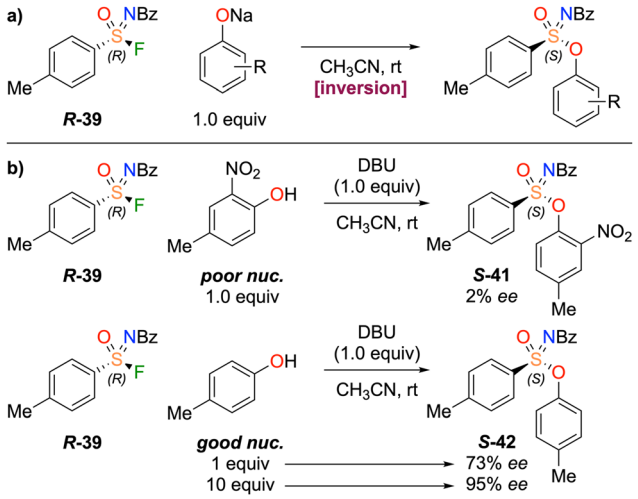
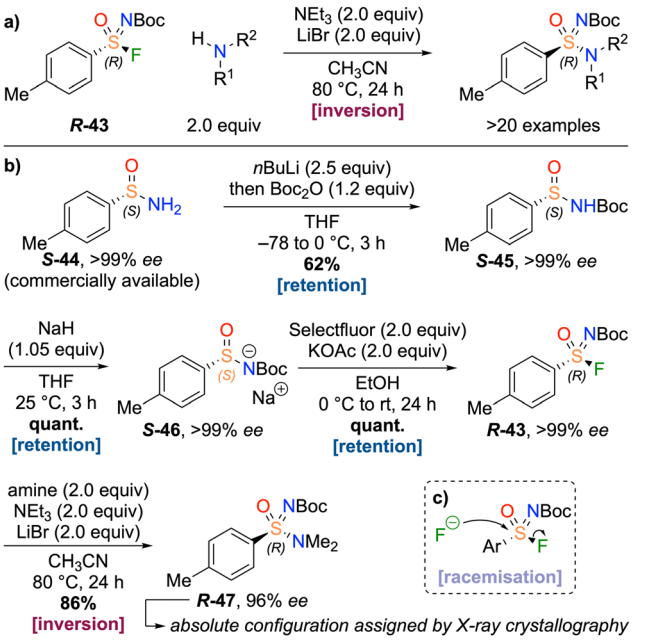


Scheme 12 (a) Accessing enantioenriched sulfonimidates from enantiopure sulfonimidoyl fluoride ***R*-39** and phenolate nucleophiles; (b) reacting enantiopure sulfonimidoyl fluoride ***R*-39** with phenols of high and low nucleophilicity at the OH oxygen, providing sulfonimidate ***S*-42** in different enantiopurities. nuc. = nucleophile.



Scheme 13 (a) Accessing enantioenriched sulfonimidamides from enantiopure sulfonimidoyl fluoride ***R*-43** and amines; (b) synthetic route to enantioenriched sulfonimidoyl fluorides from commercially available sulfinamide ***S*-44**; (c) proposed mechanism of fluoride ion induced racemisation of enantioenriched sulfonimidoyl fluorides.

Sulfonimidate section) have since proven this SuFEx reaction occurs with inversion of the stereocentre with X-ray crystal structures of the starting material and product.[73]

Zuilhof and co-workers used computation and experimental data to better understand the mechanism and stereochemical outcome of this reaction. The authors suspected that the presence of DBU was leading to racemisation of sulfonimidoyl fluoride ***R*-39** and thus providing sulfonimidates of low enantiopurity. They found that when a poorly nucleophilic phenol was used (4-methyl-2-nitrophenol), the resulting sulfonimidate (***S*-41**) was almost entirely racemic, while using a phenol with higher nucleophilicity (*p*-cresol) afforded desired sulfonimidate ***S*-42** in 73% ee (Scheme 12b).

Initially, the authors hypothesised the DBU-promoted racemisation pathway was competitive with the SuFEx pathway and found that increasing the equivalents of the *p*-cresol significantly reduced racemisation. However, DFT studies did not find an energetically feasible transition state for DBU addition. Sulfonimidoyl fluoride ***R*-39** was found to be stereochemically stable in polar aprotic (CH_3CN) and polar protic (IPA) solvents at room temperature, while rapid racemisation was observed in the presence of DBU, even at −30 °C. Moreover, the recovered, unreacted sulfonimidoyl fluoride ***R*-39** in the SuFEx reaction using 4-methyl-2-nitrophenol and DBU was found to have racemised. When this reaction was repeated with just sodium 4-methyl-2-nitrophenolate (no DBU), recovered sulfonimidoyl fluoride ***R*-39** after the 19 hours reaction time remained enantiopure.

In 2020, Bull and co-workers developed a stereocontrolled route to access enantioenriched sulfonimidoyl fluorides and sulfonimidamides by suppressing racemisation (Scheme 13). Enantioenriched aryl sulfonimidoyl fluorides were reacted with amines to afford the corresponding sulfonimidamides in high enantiopurities through the addition of LiBr. The reaction proceeded with inversion of the sulfur stereocentre and maintained high ee (Scheme 13a).[77] The route to enantioenriched sulfonimidoyl fluorides started with commercially available sulfinamide ***S*-44** (Scheme 13b). Boc protection and subsequent deprotonation to sulfinamide salt ***S*-46** were assumed to proceed with retention of configuration, with the high enantiopurity of both intermediates measured by chiral HPLC. Supported by early studies into sulfinamide chlorination from Johnson[56] and Cram,[58] Bull proposed the fluorination of sulfinamide salt ***S*-46** to sulfonimidoyl fluoride ***R*-43** occurred with retention of the sulfur stereocentre. Sulfonimidamide ***R*-47**, obtained by reacting sulfonimidoyl fluoride ***R*-43** with dimethylamine, was assigned definitively as the *R*-configuration at sulfur using X-ray crystallography (Scheme 13b), indicating this SuFEx reaction occurred with inversion of the sulfur stereocentre.

The first SuFEx conditions developed provided sulfonimidamide products in poor enantiopurities due to rapid racemisation of the sulfonimidoyl fluoride under the reaction conditions. Bull and co-workers hypothesized that liberated fluoride anions would attack the sulfur centre as a nucleophile, racemising the sulfonimidoyl fluoride substrate and liberating more fluoride ions in the process (Scheme 13c).[77] The racemisation process occurred at a rate that outcompeted the SuFEx process, leaving mostly racemic sulfonimidoyl fluoride to react with the amine. The LiBr was employed as a fluoride trap additive, which was sufficient to prevent the previously observed racemisation. Bull also proposed that fluoride caused the race-

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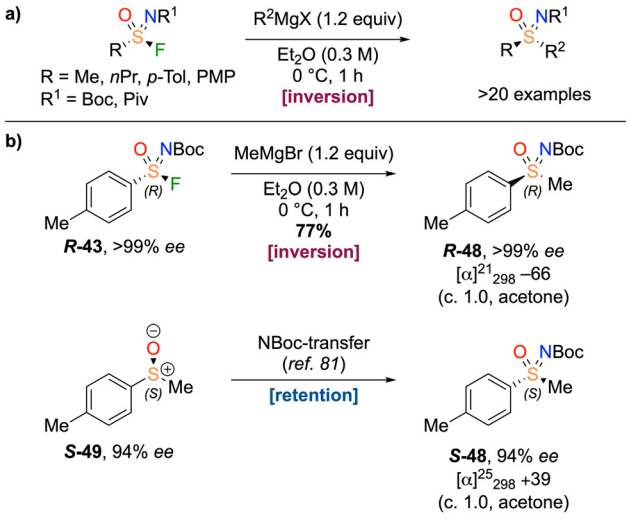
misation in Zuilhof's study (Scheme 12) and that the sodium counterion of the phenolate nucleophiles would trap the released fluoride anions as NaF, thus preventing fluoride anion-induced racemisation. Fluoride exchange has since been reported by Sharpless and others for the introduction of ^{18}F for PET imaging on fluorosulfates and sulfamoyl fluorides.[78,79] In more recent studies, Zuilhof and co-workers found computationally that the presence of the sodium cation lowers the energy barrier to their SuPhenEx reaction between enantioenriched sulfonimidates and the anionic phenolates.[76]

In 2022, Bull and co-workers found that treating enantioenriched aryl and alkyl sulfonimidoyl fluorides with Grignard reagents resulted in a stereospecific SuFEx reaction to provide enantioenriched sulfoximines (Scheme 14a).[80]

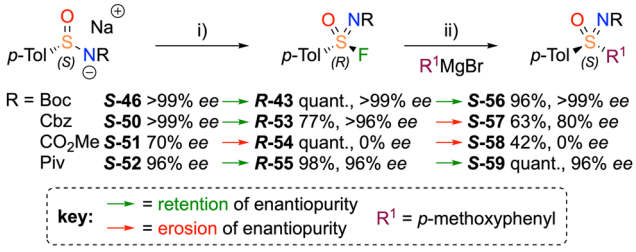
Enantiopure sulfoximine ***R*-48** generated from this methodology was found to have an opposing optical rotation value (and distinct HPLC R_f) to known enantiomer ***S*-48**,[81] confirming that the SuFEx reaction had occurred with inversion of the sulfur stereocentre (Scheme 14b). Enantioenriched *tert*-butyl sulfonimidoyl fluoride was found to be unreactive towards 4-methoxyphenylmagnesium bromide reagent under the standard conditions. This is consistent with the unreactive nature of *tert*-butyl sulfonimidates towards Grignard reagents observed by Stockman.[72] Together, these two observations support the idea that nucleophiles in S(VI) substitution reactions approach through an S_N2 trajectory.

Investigations into the effect of the nitrogen group on the electrophilic fluorination and Grignard SuFEx processes revealed varying results with regards to protecting the sulfur stereocentre (Scheme 15).[80]

Although Boc-, Cbz-, and Piv-protected sulfinamide salts were generated in high enantiopurities (≥96% ee), the CO_2Me-protected variant could only be accessed in 70% ee. Moreover,



Scheme 14 (a) Accessing enantioenriched sulfoximines from enantiopure sulfonimidoyl fluorides and organometallic reagents; (b) confirmation of stereochemical inversion at sulfur by comparison to the known enantiomer. PMP = *p*-methoxyphenyl.



Scheme 15 Effect of nitrogen protecting group on the enantiospecificity of the electrophilic fluorination and Grignard SuFEx reactions. (i) Selectfluor (2.0 equiv.), KOAc (2.0 equiv.), EtOH (0.2 M), 0 °C to rt, 24 h; (ii) 4-methoxyphenylmagnesium bromide (1.2 equiv.), Et_2O (0.3 M), 0 °C, 1 h.

while the Boc-, Cbz-, and Piv-protected sulfinamide salts (***S*-46**, ***S*-50**, and ***S*-52**) underwent electrophilic fluorination smoothly to deliver the corresponding sulfonimidoyl fluorides ***R*-43**, ***R*-53**, and ***R*-55** in high yields and enantiopurities (77%–quant., ≥96% ee), CO_2Me-protected salt ***S*-51** afforded sulfonimidoyl fluoride ***R*-54** as a racemate (Scheme 15). This could be attributed to the smaller size of the CO_2Me protecting group reducing the steric hinderance around the sulfur centre, therefore increasing susceptibility to fluoride anion-induced racemisation processes.[77] The subsequent Grignard SuFEx reaction with Boc- and Piv-protected sulfonimidoyl fluorides (***R*-43** and ***R*-55**) proceeded in high yields and enantiospecificities. Erosion of enantiopurity (96% to 80% ee) was observed in the Grignard SuFEx reaction with Cbz-protected sulfonimidoyl fluoride ***R*-53**, presumably due to organometallic attack at the carbonyl of the Cbz protecting group.

In 2023, Zuilhof and co-workers developed conditions for the enantiospecific synthesis of sulfonimidamides from enantiopure sulfonimidoyl fluoride ***R*-39** through a $Ca(NTf_2)_2$-mediated SuFEx reaction with aniline nucleophiles (Scheme 16a).[82] X-Ray crystal structures of sulfonimidamides ***R*-60** and ***R*-61**,[82] in combination with the previously measured crystal structure for sulfonimidoyl fluoride ***R*-39** (see Sulfonimidate section),[73] confirmed the SuFEx reaction proceeds with inversion of the sulfur stereocentre (Scheme 16b).

Curiously, the reactions between sulfonimidoyl fluoride ***R*-39** and 3-aminopyridine or imidazole resulted in complete loss of enantiopurity in the respective sulfonimidamide products, **62** and **63** (Scheme 16c).[82] The authors suggest the racemisation process is due to degenerate nucleophilic substitution of the initially formed sulfonimidamide, whereby imidazole or 3-aminopyridine is additionally activated by the $Ca(NTf_2)_2$ Lewis acid or through protonation by the $ArNH_3^+$ species generated in the reaction, akin to how Grygorenko and co-workers developed imidazolium salts as leaving groups at S(VI) centres.[39]

Recently, Zuilhof and co-workers reported the mechanochemical, enantiospecific synthesis of sulfonimidamides from enantiopure sulfonimidoyl fluorides and sulfonimidoyl chlorides (Scheme 17a).[67]

Similar to the solvent-based version of this transformation,[82] the reactions between sulfonimidoyl fluoride ***R*-39** (or

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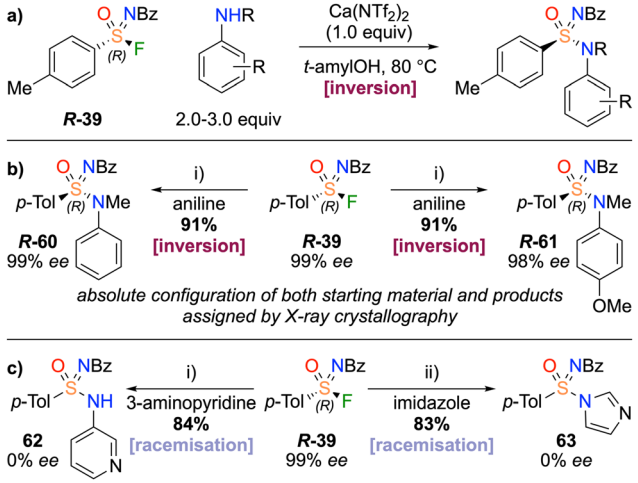
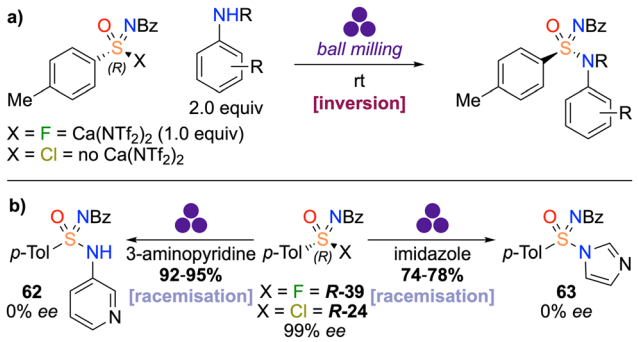


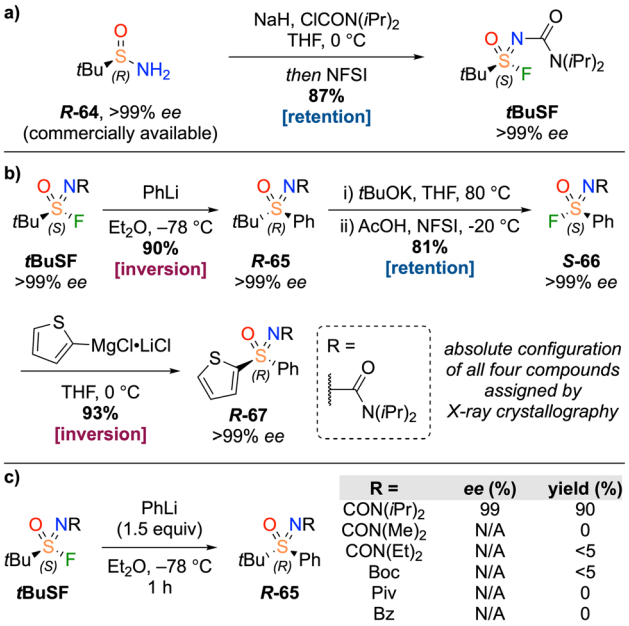
Scheme 16 (a) Accessing enantioenriched sulfonimidamides from enantiopure sulfonimidoyl fluoride ***R*-39** and anilines; (b) confirmation of sulfur stereocentre inversion by X-ray crystallography; (c) observed racemisation in reactions between ***R*-39** and 3-aminopyridine or imidazole. (i) ***R*-39** (1.0 equiv.), 3-aminopyridine (2.0 equiv.), $Ca(NTf_2)_2$ (1.0 equiv.) in *t*-amyl alcohol (0.2 M) at 80 °C; (ii) ***R*-39** (1.0 equiv.), imidazole (3.0 equiv.), $Ca(NTf_2)_2$ (1.0 equiv.) in *t*-amyl alcohol (0.2 M) at 80 °C.



Scheme 17 (a) Mechanochemical, enantiospecific synthesis of sulfonimidamides from sulfonimidoyl fluorides and sulfonimidoyl chlorides; (b) observed racemisation in reactions between ***R*-39** (or ***R*-24**), 3-aminopyridine, and imidazole.

sulfonimidoyl chloride (***R*-24**) and 3-aminopyridine and imidazole resulted in complete loss of enantiopurity in the corresponding sulfonimidamide products, **62** and **63** (Scheme 17b). In agreement with their previous rationale,[82] the authors suggest this racemisation process is due to protonation of the initially formed sulfonimidamide, which is then susceptible to subsequent substitution reactions by the same nucleophile, ultimately resulting in a racemised final product.[67]

In 2024, Lopchuk reported the development of a *tert*-butyl sulfonimidoyl fluoride (*t*BuSF) as a chiral, S(VI) transfer reagent to access enantiopure sulfonimidamides and sulfoximines (Scheme 18).[83,84] *t*BuSF was generated from *tert*-butyl sulfinamide ***R*-64** (also known as Ellman's sulfinamide) in a one-pot *N*-functionalisation and fluorination sequence, maintaining enantiopurity throughout (Scheme 18a). As a crystalline solid,



R =	ee (%)	yield (%)
$CON(iPr)_2$	99	90
$CON(Me)_2$	N/A	0
$CON(Et)_2$	N/A	<5
Boc	N/A	<5
Piv	N/A	0
Bz	N/A	0

Scheme 18 (a) Generating *t*BuSF from *tert*-butyl sulfinamide ***R*-64**; (b) synthetic sequence from *t*BuSF to sulfoximine ***R*-67**, with each compound structure confirmed by X-ray crystallography; (c) effect of different N-protecting groups on the SuFEx between *t*BuSF and phenyllithium.

the X-ray crystal structure of *t*BuSF was obtained, confirming the *N*-functionalisation and fluorination sequence proceeded with retention of the sulfur stereocentre. *t*BuSF was reactive directly with organolithium reagents to provide enantiopure sulfoximines. The *t*Bu group was cleaved, and the sulfur centre fluorinated to generate a second electrophilic sulfonimidoyl fluoride reagent, which was then treated with organometallic reagents or amines/Turbo-amides to afford enantioenriched sulfoximines and sulfonimidamides. This sequence was exemplified with the synthesis of sulfoximine ***R*-67** (Scheme 18b).

The X-ray crystal structures for all compounds in this sequence were obtained, unequivocally confirming the stereochemistry of two steps: (1) the fluorination of sulfinamide salts proceeds with retention of the sulfur stereocentre; and (2) the SuFEx reactions of sulfonimidoyl fluorides proceeds with inversion of the sulfur stereocentre. Curiously, the success of the initial SuFEx between *t*BuSF and organolithium reagents was highly reliant on the $CON(iPr)_2$ N-protecting group. The analogous methyl and ethyl urea protecting groups provide very low yields, as did more commonly utilised protecting groups such as Boc, Piv, and Bz (Scheme 18c). Unlike the acyl, carbamate, or less bulky urea protecting groups, the authors suggest the $CON(iPr)_2$ group provided sufficient electron density and steric bulk to prevent reactivity at the carbonyl centre of the protecting group while allowing SuFEx. Organolithium reagents were therefore suitable nucleophiles, enabling successful nucleophilic attack at the congested, *t*Bu-substituted sulfur centre – a substrate class found to unreactive by Stockman[72] and Bull[80] in previous studies. More

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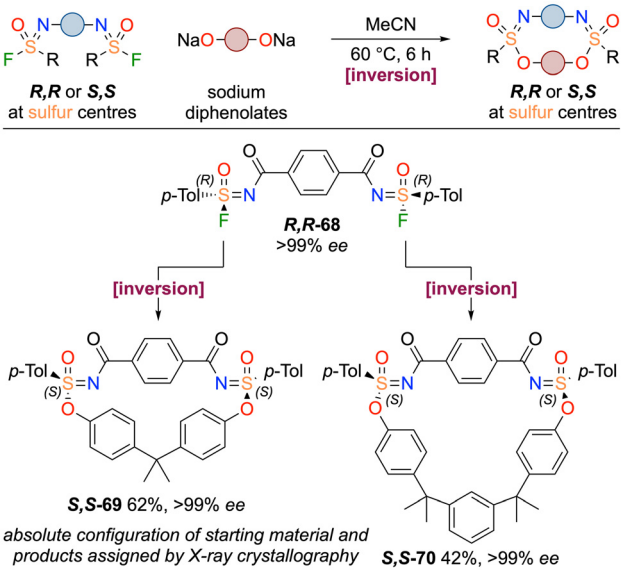
recently, Lopchuk and co-workers demonstrated how the torsion strain-release of the N–CO bond of CON(iPr)$_2$ can be leveraged to modify the protecting group with a variety of amines.[85]

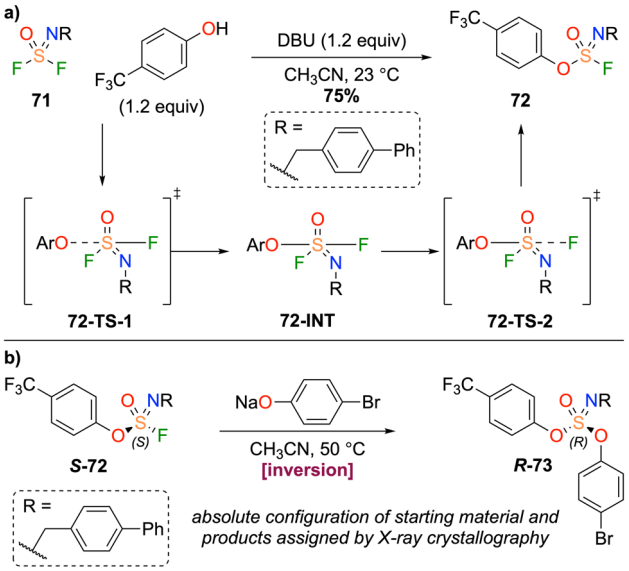
In 2023, Zuilhof and coworkers generated macrocycles with defined sulfur stereocentres through a stereospecific SuFEx reaction between diastereomerically pure di-sulfonimidoyl fluorides and diphenolates (Scheme 19).[86]

X-Ray crystallographic structures of di-sulfonimidoyl fluoride ***R,R*-68** and macrocycles ***S,S*-69** and ***S,S*-70** (among others not shown here) confirmed the SuFEx reactions occurred with inversion of the sulfur stereocentre. Very recently, this approach has been leveraged by the same group to assemble oligomers through sequential stereospecific SuFEx and SuPhenEx reactions.[87]

Very recently, Zuilhof and coworkers interrogated the kinetics and stereochemical outcome of SuFEx and SuPhenEx reactions at prochiral and chiral S(VI) electrophiles.[88] Sulfur centres with electronegative fluorine atoms directly attached experienced a faster rate of substitution compared to those substituted with electron-poor phenols (*e.g.* *p*-NO_2 and *p*-CF_3). Computational studies suggested that the SuFEx reaction between iminosulfur oxydifluoride **71** and *p*-trifluoromethylphenol proceeds *via* an addition–elimination pathway (Scheme 20a). As the phenol approaches (**72-TS-1**) a 5-coordinate sulfurane intermediate forms (**72-INT**), which rapidly releases a fluoride ion (**72-TS-2**) to afford sulfurofluoridoimidate **72** (Scheme 20a). All calculated energy barriers for this sequence were found to be so low that the reaction would appear experimentally as an S_N2 process.[88] This study supports the notion that multiple mechanisms of substitution may be operating in any given reaction, and reactions perceived as an S_N2 process may involve rapid addition–elimination sequence



Scheme 19 Accessing macrocycles with defined sulfur stereocentres *via* stereospecific SuFEx reactions.



Scheme 20 (a) Kinetically and computationally studied SuFEx reaction between iminosulfur oxydifluoride **71** and *p*-CF_3-phenol, with proposed 5-coordinate transition states and intermediate; (b) stereospecific SuFEx between sulfurofluoridoimidate **72** and *p*-Br phenolate, confirmed to proceed with inversion by X-ray crystallography.

via a sulfurane intermediate. The authors were also able to confirm the SuFEx reaction between sulfurofluoridoimidate **72** and *p*-Br phenolate occurred with inversion of the sulfur stereocentre through comparison on starting material and product X-ray crystal structures (Scheme 20b).[88]

In 2024, in a conceptually different but nonetheless stereoselective process at sulfur, Gao, Dong and co-workers reported a stereoselective SuFEx reaction to form sulfonimidoyl fluorides (Scheme 21a).[89] Using prochiral iminosulfur oxydifluorides, enantioselective addition of organolithium reagents was achieved with a bisoxazoline (BOX) ligand at low temperature. In the proposed mechanism, the aryllithium reagent first forms a complex with the BOX ligand, followed by coordination of the iminosulfur oxydifluoride and successive SuFEx to furnish enantioenriched sulfonimidoyl fluorides. Density functional theory (DFT) studies revealed that, upon coordination with the iminosulfur oxydifluoride, two 5-coordinate, trigonal–bipyramidal sulfurane transition states were possible (Scheme 21b).[89]

While both transition states place the entering (phenyl) and leaving (fluoride) groups in the axial position and all others equatorial, the difference in energy is driven by steric repulsion between the imino substituent and *tert*-butyl group observed in **TS-*S*** (Scheme 21b), inducing enantioselectivity towards the *R* over the *S* stereoisomer. Furthermore, the potential isomerisation of trigonal bi-pyramidal intermediate **INT-*R*** was deemed unlikely due to the high associated energy barrier ($\Delta G^{\ddagger}$ = 7.5 kcal mol^{-1}).[89] The generated enantioenriched sulfonimidoyl fluorides underwent stereospecific SuFEx with amines, phenols, and organometallic reagents, proceeding

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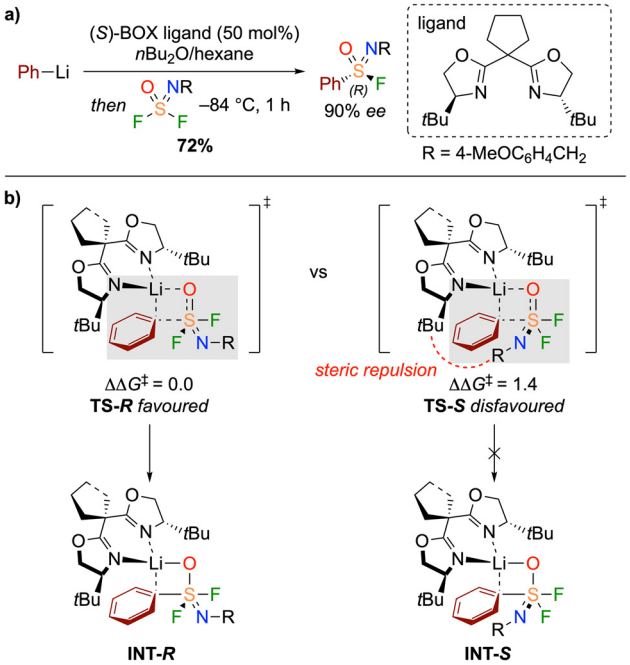

Scheme 21 (a) Ligand-induced enantioselective SuFEx reaction of iminosulfur oxydifluorides with aryllithiums; (b) proposed 5-coordinate transition states and intermediates.

with inversion of the sulfur stereocentre (confirmed by X-ray crystallography).[89]

Very recently, Jiang and Wang reported the use of a chiral organocatalyst and $NaHF_2$ to generate enantioenriched sulfonimidoyl fluorides from racemic sulfonimidoyl chlorides.[90] Mechanistic studies revealed that $NaHF_2$ and the organocatalyst form a hydrogen-bonding network to promote stereoinversion of sulfonimidoyl chlorides through dynamic kinetic fluorination.

Summary

We have examined the historical and current data pertaining to the stereochemical outcome of nucleophilic substitution reactions occurring at chiral S(VI) electrophiles. Seminal works have been discussed and dissected, aiming to place their findings and into a broader context. The earliest and most contemporary studies on each chiral S(VI) electrophile class have been explored, presenting a clear timeline of evolution on the synthesis and known reactivity of each reagent type.

Sulfonimidoyl chlorides

The pioneering work by Johnson and Cram provided early understanding of substitution reactions at hexavalent S(VI) electrophiles and their stereochemical outcomes. It was generally believed these substitutions occurred with inversion of the S(VI) stereocentre through an S_N2-like mechanism of exchange. To rationalise an observed retention in stereochemistry, Kluge suggests an alternative addition–elimination mechanism *via* a 5-coordinate sulfurane intermediate, the path of which is influenced by the size of the carbon substitution at the sulfur (VI) centre. However, it is important to consider that most conclusions drawn in these early studies are based on optical rotation and circular dichroism measurements – techniques which are susceptible to influence from highly optically active impurities. Regardless, the recent work by Tang supports the early observations, with X-ray crystallographic data from Zuilhof providing compelling evidence that substitution at S(VI) of sulfonimidoyl chlorides proceeds with inversion of stereochemistry, through an S_N2 process.

Sulfonimidates

Reggelin and Weinberger's early investigations into cyclic sulfonimidates provided key evidence of inversion at sulfur upon nucleophilic substitution, and sparked further interest into this class of S(VI) electrophile. Stockman expanded this work and established concrete evidence of stereochemical inversion with X-ray crystallographic data. The lack of reactivity observed in the *t*Bu cyclic sulfonimidates by Stockman and additional investigations by Zuilhof point towards an S_N2-like process for aryl derivatives. Less substituted alkyl sulfonimidates are also prone to initial elimination and sulfene formation, with loss of stereochemical information.

Sulfonimidoyl fluorides

The enhanced chemical and configurational stability of sulfonimidoyl fluorides, alongside the more contemporary period of the research, has enabled rigorous recent investigations in the stereochemical outcomes of substitution reactions at these chiral S(VI) electrophiles. Reports of enantioenriched sulfonimidoyl fluorides from Zuilhof and Bull in 2020 provided evidence of inversion of the sulfur stereocentre when treated with phenolates, amines, and Grignard reagents. Several recent works have unequivocally confirmed the S(VI) stereocentre undergoes inversion when reacted with organometallic reagents, each suggesting an S_N2 mechanism.

Conclusions

A growing consensus suggests substitution reactions at chiral S(VI) reagents, irrespective of leaving group (–Cl, –OR, –F), proceed with inversion of stereochemistry at the sulfur centre. The one exception to this trend can be considered an outlier and perhaps not definitively proven, using only optical rotation, but remains distinct in the steric demands of the reaction. The currently available data and the generally observed inversion at sulfur indicates the substitution of chiral S(VI) reagents occurs through an S_N2 mechanism. An addition–elimination mechanism, through a 5-coordinative sulfurane intermediate, is also plausible and potentially consistent with the observed stereochemical outcomes, but there is little empirical evidence to support this mechanism.

As such, chemists may predictably expect to achieve inversion in reactions under appropriate conditions. However, we would

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add some important notes of caution to the understanding in the field, as well as the stereochemical outcome, to avoid incorrect assignments or loss of stereochemical information.

1. It is possible that the operative mechanism(s) cannot be defined just as S_N2 or addition–elimination but instead a combination of possible mechanisms, the proportion of which may be affected by subtle structural features, such as steric bulk. These could lead to different stereochemical outcomes.

2. Different nucleophiles have been demonstrated to cause racemisation (fluoride, imidazole), and products can react again (phenolates). It is likely other nucleophilic species will enable such facile racemisation processes.

3. Examples of stereocontrolled substitution at *S*-alkyl derivatives remain limited, with sulfene formation through elimination a concern, causing loss of stereochemical information.

4. Questions remain: for example, what is the effect of the electron-donating or electron-withdrawing nature of the nitrogen group of these S(VI) mono-aza analogues? How does the size and nature of the carbon group on sulfur or nitrogen impact the trajectory of incoming nucleophiles or leaving groups? The examples detailed here begin to expand the range of data, but there remains significant scope for systematic investigation of such factors. However, individual examples will continue to require careful investigation to prove and understand the stereochemical outcome, supplementing the overall body of evidence.

Author contributions

O. L. S initiated the review and prepared first draft. O. L. S. and J. A. B. reviewed, edited and revised the manuscript. Both authors have read and approved the final version.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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