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Synthetic approaches and applications of sulfonimidates

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This review article explores the synthesis of the organosulfur(VI) species named sulfonimidates, focusing on their synthesis from sulfur(II), sulfur(IV) and sulfur(VI) reagents, and investigates their recent resurgeance in interest as intermediates to access other important organosulfur compounds. Sulfonimidates have been utilized as precursors for polymers, sulfoximine and sulfonimidamide drug candidates and as alkyl transfer reagents.

1. Introduction

The discovery of sulfonimidate synthesis over 50 years ago[1] has arguably allowed the development of this class of organosulfur compounds to be intensively studied and flourish over time.[2] In this review article, we describe specifically the synthesis of these important sulfur-containing compounds, and their subsequent transformations to other sulfur(VI) derivatives including sulfonimidamides[3] and sulfoximines,[4] the latter of which has increased prominence due to their medicinal chemistry properties (Fig. 1).[5]

Sulfonimidates are a sulfur(VI) species bearing a tetrahedral sulfur centre, with four different groups attached (this review consistently represents them as S–O, S–C, S=N and S=O as shown in Fig. 2). The stereogenic sulfur centre of sulfonimidates can act as viable chiral templates that can be employed in asymmetric syntheses – an important application that is discussed in detail in the latter part of this review. One of the main advantages of such compounds is the possibility to modify up to three points of diversity; the O–R^1 bond, the S–C (R^2) bond and finally the nitrogen R^3 substituent. The foregoing R^1 and R^2 substituents bear carbon containing alkyl or aryl moieties, whilst the broadest variation is found at the R^3 substituent.[6–16] Furthermore, sulfonimidates can be divided into two categories, acyclic and cyclic sulfonimidates. Cyclic variations of sulfonimidates arise when R^1 and R^3 are linked, usually through a short carbon chain that has been derived from chiral amino alcohols.

Aside from their most prominent application as building blocks to access alternative sulfur(VI) compounds, sulfonimidates have found uses as alkyl transfer reagents to acids, alcohols and phenols,[17] playing on the lability of sulfonimidates under acidic conditions (also noted by Levchenko in 1967).[1] In addition to their acid sensitivity, they are also susceptible to elevated temperatures, being converted into sulfonamides over extended periods of time.[18] The use of elevated temperatures can therefore limit applications of sulfonimidates – but, in the case of polymer synthesis, sulfonimidate decomposition at raised temperatures proved a novel way to access poly(oxothiazene) polymers[8c] and thionylphosphazene monomers and polymers.[8d]

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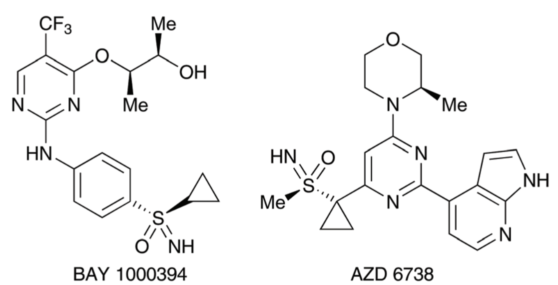


Fig. 1 Drug candidates found with a sulfur(VI) centre.

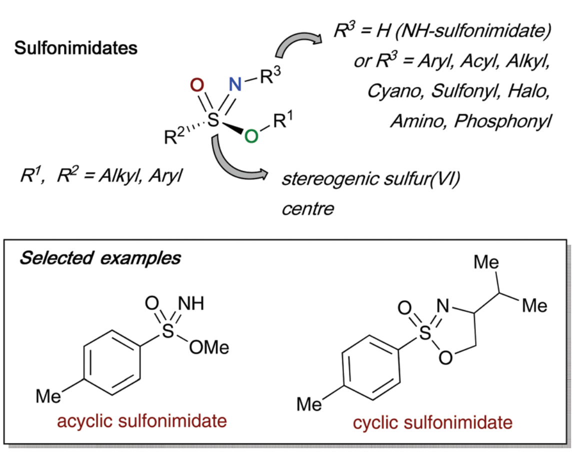


Fig. 2 General overview of the sulfonimidate structure.

The review is organised into two main sections – acyclic and cyclic sulfonimidates. The topics reported have focused on both seminal works as well as recent advancements on important organic chemistry features including syntheses and stereochemistry details where appropriate. Additionally, we wish to highlight to the readership that a complete overview focusing on a broad range of chiral sulfinyl compounds other than sulfonimidates has just been published this year.[2b]

2. Synthesis of acyclic sulfonimidates and their applications

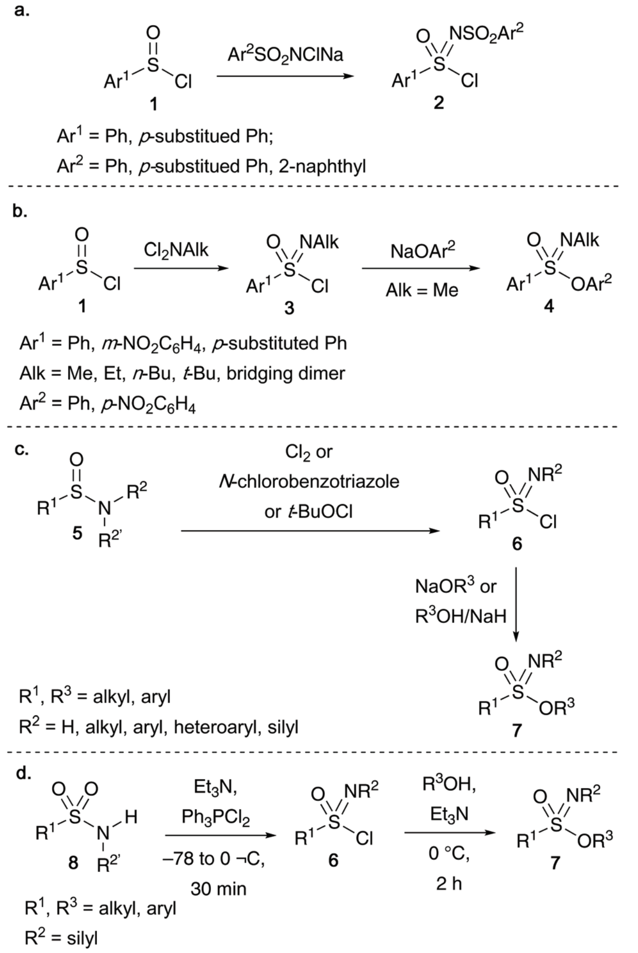
2.1 Synthesis of acyclic sulfonimidates *via* sulfonimidoyl halides

Most of the important early contributions towards the synthesis of acyclic sulfonimidates were developed from the esterification of alcohols or phenols with racemic sulfonimidoyl chlorides. Levchenko and co-workers discovered that oxidation of arylsulfinyl chlorides **1** with sodium salts of *N*-chloroarylsulfonamides afforded sulfonimidoyl chloride **2** (Scheme 1a).[19] Alternatively, sulfonimidoyl chlorides **3** bearing an *N*-alkyl moiety could also be accessed by the reaction of *N*,*N*-dichloroalkylamines on arene sulfinyl chlorides **1**. Subsequent substitution of **3** with sodium phenoxides gave the desired sulfonimidates **4** (Scheme 1b).[1]

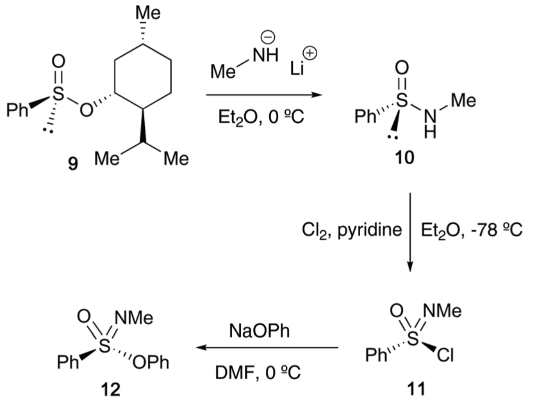
In the 1970s, Johnson and co-workers identified an alternative route to access sulfonimidoyl chlorides **6** through the oxidation of sulfinamides **5** using either chlorine/*N*-chlorobenzotriazole,[20a,b] or *tert*-butyl hypochlorite[20c] as the oxidant (Scheme 1c). Reacting sulfonimidoyl chlorides **6** with either sodium alkoxides or sodium hydride-alcohol afforded sulfonimidates **7**, furthermore, *O*-alkyoxy reagents gave slightly higher yields than the corresponding *O*-aryloxy derived reagents.[20c] This methodology was later utilized by Okuma and co-workers to access sulfonimidates (and subsequent transformation into amino (aryloxy)-oxosulfonium salts by reaction with Et_3OBF_4).[21]

Roy and co-workers disclosed that sulfonamides **8** react with bulky halophosphoranes to undergo a rearrangement reaction to access the key sulfonimidoyl chlorides **6** (Scheme 1d).[8a] The same group also disclosed that the bromo-derivative of **6**, sulfonimidoyl bromide, could be isolated when Ph_3PBr_2 was used. The desired sulfonimidates **7** could be isolated in yields of up to 78% after reacting sulfonimidoyl chloride **6** with alcohol and triethylamine at 0 °C for 2 hours.[8a] Roy's *N*-silylsulfonimidates synthesized *via* this method were subsequently utilized in polymerization studies,[8b,c] investigating the reactivity of the Si–N bond under thermal polycondensation conditions (Turner and co-workers also utilized *N*-silylsulfonimidates to react with *N*-silylphosphoranimines, giving access to thionylphosphazene monomers and polymers).[8d]

In the 1970s, Johnson reported that access to optically active sulfonimidates **12** could be achieved when starting the synthesis from Andersen-type reagent (−)-menthyl (*S*)-benzenesulfinate **9** (Scheme 2). The starting reactant **9** has a known absolute configuration, and previous studies from Johnson's group showed that reaction of **9** with nucleophiles such as the lithium salt of methylamine or methyl magnesium bromide proceed with inversion of configuration.[22] Moreover, studies by Montanari[23] and Nudelman and Cram[24] had previously highlighted that displacement of sulfinates by lithium amine salts occurs with inversion of configuration at sulfur, a similar feature that was found in Johnson's transformation of **9** to **10**. Subsequent oxidation of **10** to **11** (retention of configuration), followed by reaction of sodium phenoxide with sulfonimidoyl chloride **11** (inversion of configuration) afforded sulfonimidate **12**. The transformation of **10** to **12** was carried out without isolation of sulfonimidoyl chloride **11**, which was found to racemise at high temperatures – maintaining **11** in an ethereal solution at −78 °C and transferring it to a solution of phenoxide in DMF at 0 °C proved fruitful, affording sulfonimidate **12** in 69% optical purity (97% on recrystallisation). Furthermore,



Scheme 1 Important historical routes towards sulfonimidoyl chlorides and sulfonimidates. (a) Levchenko's synthesis of aryl-substituted sulfonimidoyl chlorides **2**; (b) Levchenko's route to *N*-alkyl derived sulfonimidoyl chlorides **3** and conversion to sulfonimidates **4**; (c) Johnson's oxidative chlorination of sulfinamides **5** to access sulfonimidoyl chlorides **6**, and subsequent transformation into sulfonimidates **7**; (d) Roy's synthesis of sulfonimidoyl halides **6** and sulfonimidates **7** from *N*-silylated sulfonamides **8** and dihalophosphoranes.



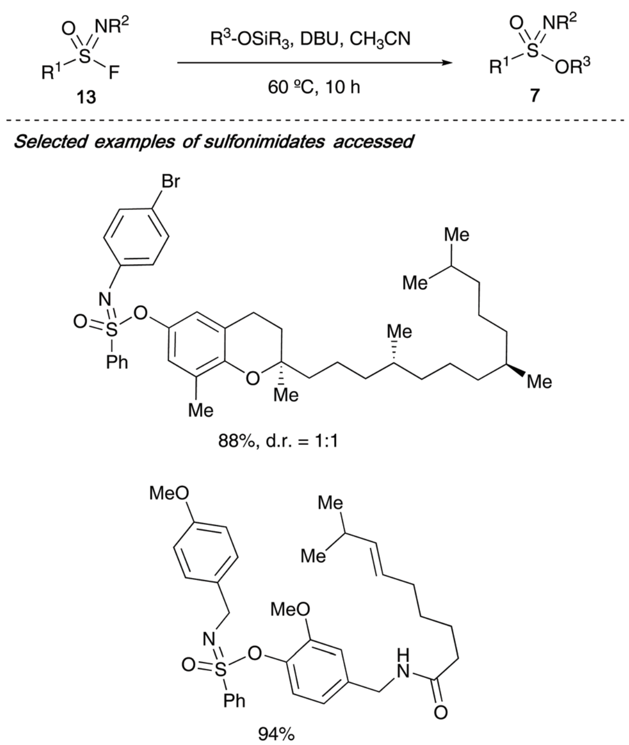
Scheme 2 Johnson's synthesis of optically active sulfonimidates **12**.

during the oxidation step, pyridine was added as a hydrogen chloride scavenger to avoid racemisation.[25]

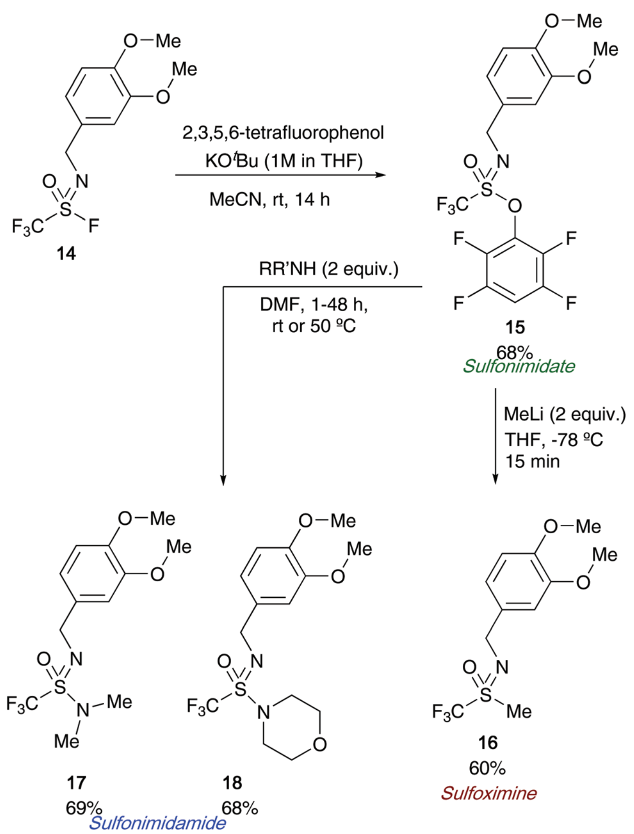
The synthesis of sulfonimidates from sulfonimidoyl halides has received a resurgence in attention – this may be due to the fact that sulfonimidates are being identified as a useful intermediate towards the synthesis of other sulfur(VI) containing molecules found in drug discovery programmes, such as sulfoximines and sulfonimidamides.

Nobel prize winner Barry Sharpless has recently expanded his click-chemistry concept towards sulfur-fluoride exchange chemistry or 'SuFEx' chemistry, and in 2018, reported the synthesis of sulfonimidates **7** from sulfonimidoyl fluorides **13** (Scheme 3). The authors advocate the use of sulfonimidoyl fluorides over the analogous chlorides due to the latter's lability to hydrolysis. Sharpless showed that through DBU-promoted formation of the S–O bond in the sulfonimidate product, complex natural products containing a phenol motif including (+)-δ-tocopherol and capsaicin could successfully be incorporated in excellent yields.[26]

Following on from Sharpless's use of sulfonimidoyl fluorides to access sulfonimidates, a joint research article from Wright, Oehlrich and co-workers also in 2018 led to the development of a bench stable sulfonimidate **15** that can be easily scaled for medicinal chemistry programmes looking to access CF_3-derived sulfonimidamides **17**/**18** (Scheme 4).[27a] The synthesis of sulfonimidates was realised by reacting tetrafluorophenol and sulfonimidoyl fluoride **14** – a precursor that the same group previously reacted with amines directly to access sulfonimidamides.[27b] The authors show that their sulfonimidate **15** had a few key advantages over its predecessor (sulfonimidoyl fluorides) for the synthesis of sulfonimidamides; firstly, the sulfonimidate reagent was found to be more reactive towards amines than sulfonimidoyl fluorides. Secondly, during the sulfonimidamide formation reactions, the authors report less unwanted sulfonamide by-product was observed when the bench stable sulfonimidate was utilised. The authors have shown a single example in which two equivalents of methyl lithium were reacted with the sulfonimidate, affording the desired sulfoximine **16** in 60% yield (Scheme 4).



Scheme 3 Sharpless's synthesis of sulfonimidates from sulfonimidoyl fluorides.

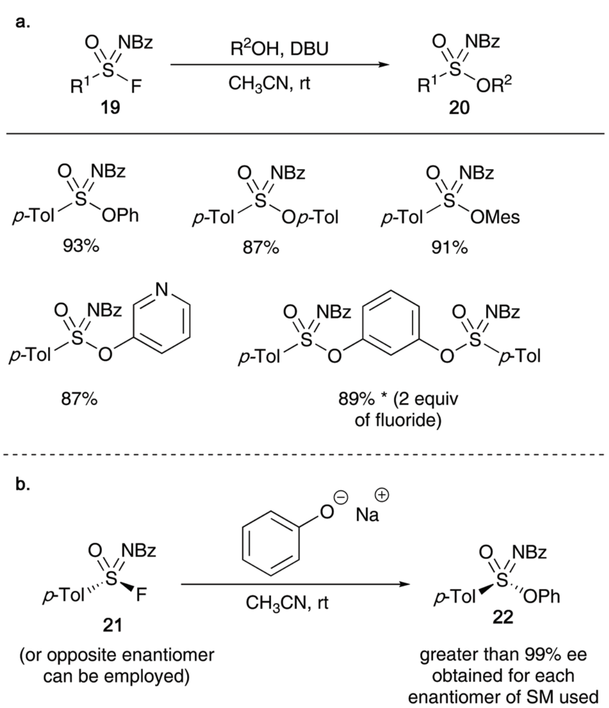


Scheme 4 Wright and Oehlrich's bench stable sulfonimidate from sulfonimidoyl fluorides, and further applications of sulfonimidates.

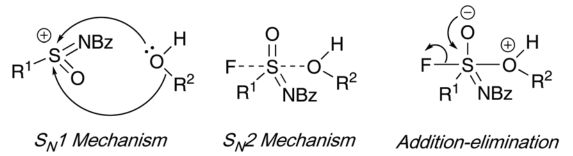
Building on the work of Sharpless's SuFEx chemistry, this year Zuilhof and co-workers reported the synthesis of sulfonimidates **20** from sulfonimidoyl fluorides **19** and phenols (a silicon-free SuFEx approach).[28] The authors show that utilizing a stoichiometric amount of base (DBU), the formation of the target products can be achieved in excellent yields in short reaction times (as little as 2 minutes, see Scheme 5). Moreover, submitting an enantioenriched sulfonimidoyl fluoride **21** afforded sulfonimidates **22** in enantiomeric excesses up to 99% ee.

Three mechanistic routes were debated by the authors. Their investigations on the asymmetric synthesis of sulfonimidates ruled out an S_N1 type intermediate, favoring a S_N2 or addition–elimination mechanism – enantiomeric excesses were maintained when using an excess (10 equiv.) of good nucleophilic phenols, and, ee was lost when a poor, electron-deficient phenol was utilized. Furthermore, quantum chemical calculations conducted show a preference for the addition–elimination mechanism (potential energy surface analysis) when sodium phenolate was used as a nucleophile – interestingly, the calculations showed that DBU was not necessary to aid fluoride loss when sodium phenolate was used as a nucleophile source (Scheme 6).

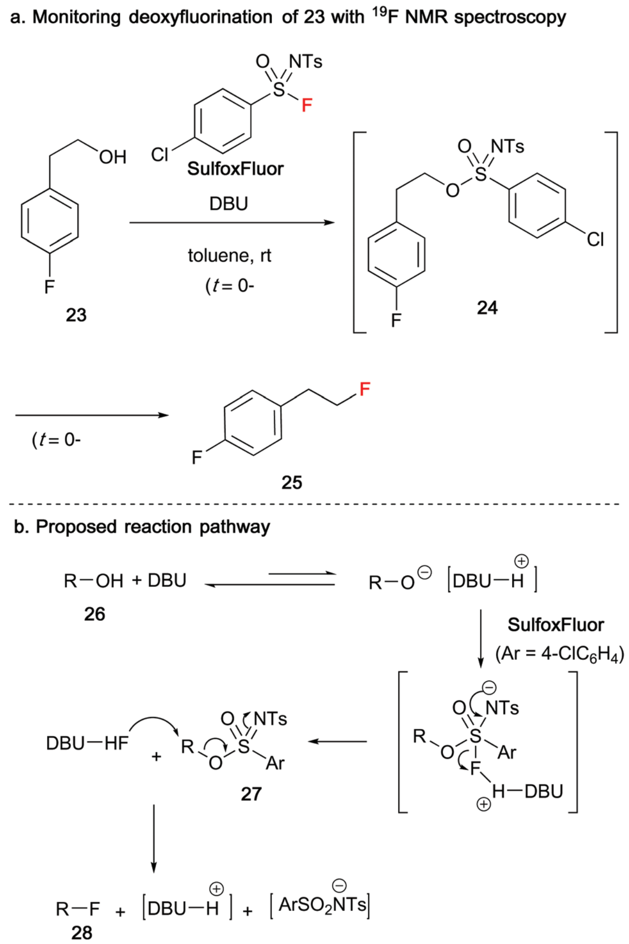
In 2019, Ni and Hu reported the use of sulfonimidoyl fluorides as reagents to affect the conversion of alcohols **23**/**26** into alkyl fluorides **25**/**28** (Scheme 7).[29] When 4-fluorophenethyl derived alcohol **23** was reacted with SulfoxFluor in the presence of DBU, ^{19}F NMR spectroscopy indicated that a sulfonimidate species **24** had formed after 3 minutes. After a further 10 minutes, slow consumption of sulfonimidate **24** provided the desired alkyl fluoride product **25**. The absence of DBU



Scheme 5 (a) Zuilhof's synthesis of sulfonimidates using a silicon free approach; (b) synthesis of optically active sulfonimidates.



Scheme 6 Zuilhof's proposed mechanistic routes to access sulfonimidates **20** and **22**.

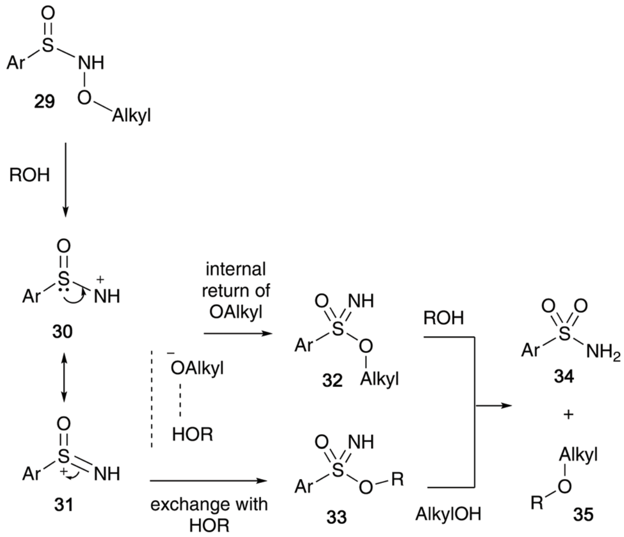


Scheme 7 Ni and Hu's deoxyfluorination of alcohols.

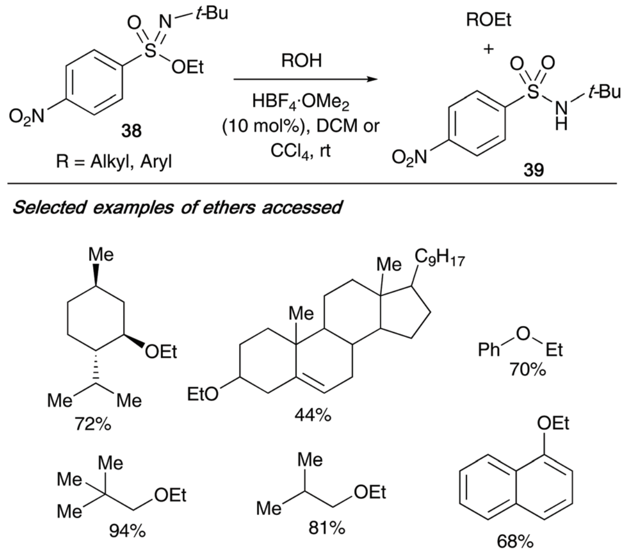
resulted in no reaction. In their proposed mechanism, DBU deprotonates the alcohol species **26** giving the alcoholate anion, that undergoes nucleophilic addition to SulfoxFluor to furnish a pentacoordinate intermediate. Protonated DBU promotes the loss of fluorine to yield sulfonimidate **27**, that subsequently undergoes nucleophilic displacement by DBU-HF to produce the alkyl fluoride **28**, along with a sulfonamide salt.

2.2 Synthesis of acyclic sulfonimidates from sulfinyl hydroxylamines and applications as alkyl transfer reagents

In 1973, Maricich *et al.* showed that sulfinyl hydroxylamines **29** undergo a rapid rearrangement to sulfonimidates **32**/**33**, in which an alkoxy group migrates from the nitrogen to the



Scheme 8 Maricich's proposed mechanism of alkyl transfer to alcohols.

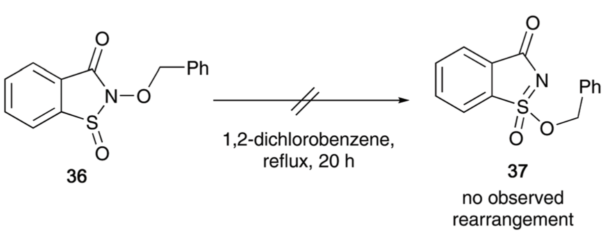


Scheme 10 Maricich's sulfonimidate **38**, and its application as an alkylation transfer reagent.

sulfur atom.[30] The sulfonimidates formed were unstable and were found to transfer their alkyl group to a range of alcohols when heated at 50 °C forming ethers **35** along with the corresponding sulfonamide **34** (Scheme 8).

The reaction proceeds *via* a mechanism involving sulfonimidate species **32** or **33**, that may have been formed through a dissociation process of the migrating alkoxy group and the solvent (ROH). Two possible sulfonimidates were postulated that could transfer the alkyl substituent to the alcohol. They also believe that a delocalised nitrenium species **30**/**31**, stabilised by the sulfinyl electron pair is possible, and this was supported when cyclic *N*-acyl derivative **36** failed to rearrange after refluxing in *ortho*-dichlorobenzene for 20 hours, since the nitrenium ion from **36** would be destabilised by the *N*-acyl group (Scheme 9).

In 2013, the same author exploited the application of their sulfonimidate rearrangements, utilizing them as alkyl transfer reagents to a range of acids, alcohols and phenols.[17] Utilizing nitro-containing sulfonimidate **38**, the ethylation of acids to esters was achieved without a catalyst – however, the reaction required catalytic amounts of fluoroboric acid-dimethyl ether complex (10 mol%) for the conversion of alcohols and phenols to ethers (yields up to 94%, Scheme 10). For each reaction conducted, the side product isolated was the resulting sulfonamide **39** from the sulfonimidate reagent.

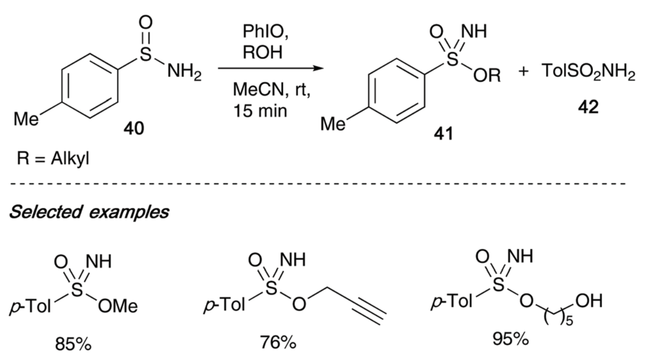


Scheme 9 Maricich's attempted rearrangement of *N*-acyl derived *N*-alkoxybenzenesulfinamides **36**.

2.3 Synthesis of acyclic sulfonimidates from sulfinamides utilising hypervalent iodine species & applications towards sulfoximine synthesis

Malacria and co-workers reported that sulfonimidates **41** could be formed from sulfinamides **40**, iodosobenzene and alcohols in a one-pot procedure, utilising mild conditions, allowing access to a broad range of sulfonimidates in yields up to 95% (Scheme 11).[6] The reaction tolerated a variety of primary alcohols (except benzyl alcohol), and further limitations were found on increasing the steric hindrance on the alcohol – isopropyl alcohol required a longer reaction time, whilst reaction failure was observed when using *tert*-butanol. Furthermore, phenol only resulted in degradation, with no *O*-aryl sulfonimidate formed.

Malacria's procedure built upon the initial report of Maricich's *N*-alkoxybenzenesulfinamides,[30] in which they devised a way of oxidising the sulfinamide to form the key N–O bond,



Scheme 11 Malacria's synthesis of sulfonimidates from sulfinamides and iodosobenzene.

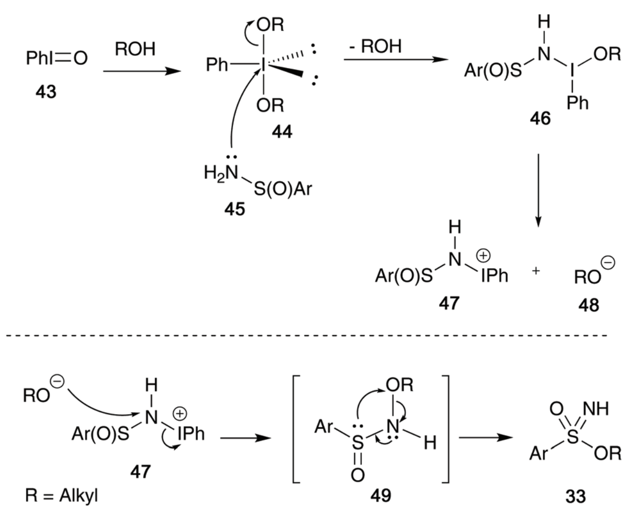
and minimised the amounts of unwanted sulfonamide **42** that was known to occur when oxidants such as *m*-CPBA were employed.[31] The use of a mild oxidising agent derived from iodine(III)[32] allowed the necessary N–O bond formation to proceed smoothly (Scheme 11).

Their initial mechanistic proposal is highlighted in Scheme 12 – solvation of iodosylbenzene **43** in the desired alcohol, followed by attack on **44** by sulfinamide species **45** initiates the synthesis.[6,33] This species can form a dissociated intermediate **47**, that in the presence of the remaining alkoxide anion **48** can re-attack the nitrogen centre and expel the iodobenzene moiety to give the key *N*-alkoxybenzenesulfinamides intermediate **49**, first identified by Maricich (Scheme 8). This can then rapidly rearrange to yield the key sulfonimidate product **33**.

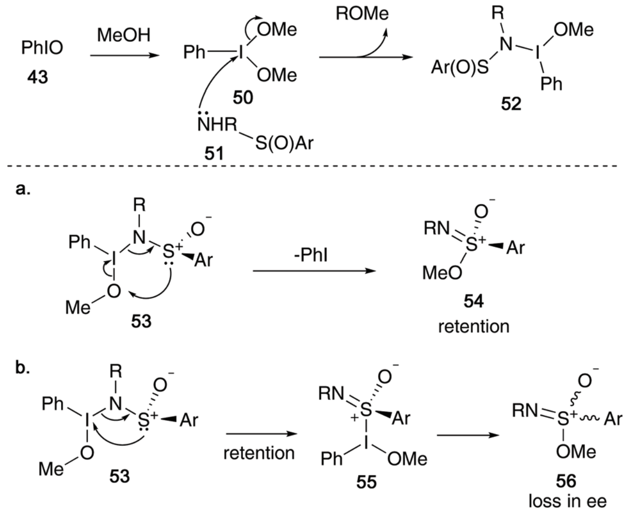
During the course of conducting an asymmetric version of the above transformation, the authors found that the reaction proceeded with retention of configuration at the sulfur centre in the product. As a result of these findings, Malacria proposed an alternative, more reasonable model (Scheme 13) – initial sulfinamide **51** attack on solvated iodosylbenzene **50** yields intermediate **52**. A rearrangement of **53** *via* a 6-electron transition state allowed access to sulfonimidates **54** with retention of configuration (Scheme 13a). However, from intermediate **53**, an alternative route *via* an three-atom rearrangement (first reported by Reggelin and co-workers)[34] would afford a sulfonimidoyl iodonium **55** – a species that could be responsible for loss in enantiomeric excess during the transformation, yielding sulfonimidate **56** (Scheme 13b).

In 2006, Malacria showed that *N*-aryl sulfinamides **57** could also be utilised in the formation of sulfonimidates **58** with their one-pot procedure utilising diacetoxyiodobenzene. With these examples, aryl derived sulfinamides required diacetoxyiodobenzene (DIB) and a mild base such as magnesium oxide to achieve high yields (Scheme 14).[7]

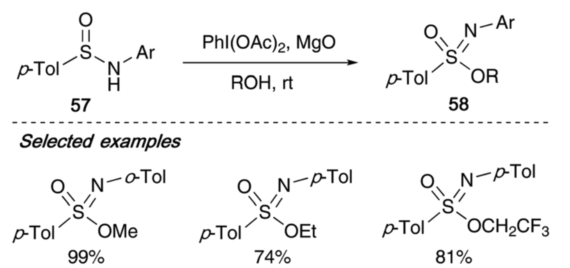
In 2018, Bull, Luisi and co-workers have most recently reported the conversion of aryl thiols **59** into sulfonimidates



Scheme 12 Malacria's initial mechanistic proposal for the formation of sulfonimidates **33**.



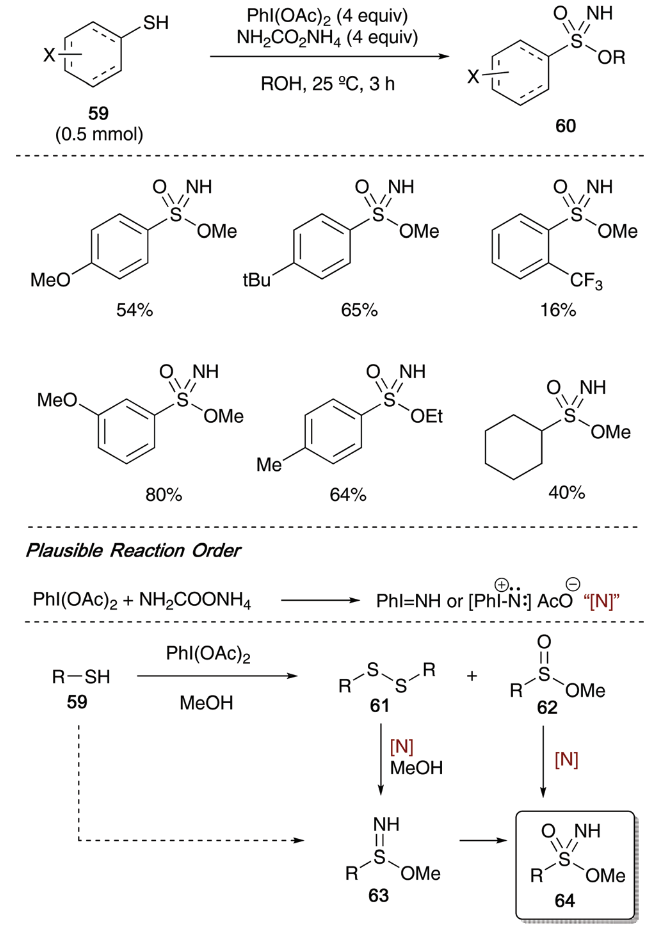
Scheme 13 Malacria's revised mechanism for the preparation of sulfonimidates.



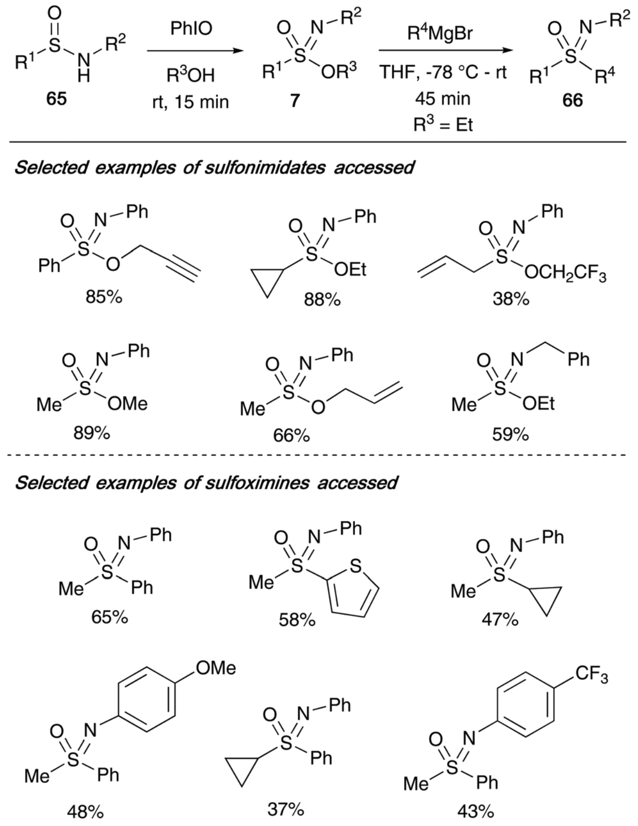
Scheme 14 Malacria's synthesis of arylsulfonimidates.

60 utilising hypervalent iodine reagents and ammonium carbamate as nitrogen source (Scheme 15).[16] Using a 4-equivalent loading of ammonium carbamate forced the reaction to produce exclusively sulfonimidate (at 1 equivalent of nitrogen source, sulfonamide was formed as the major reaction product). The reaction scope allowed a range of aryl thiols to participate in the reaction – substitution on the aromatic ring at *ortho*, *meta* and *para* with both electron withdrawing and donating substituents were well tolerated affording sulfonimidates in good yields. In one case, a cycloalkylthiol was submitted to the optimised conditions, and the desired sulfonimidate was isolated in moderate yield. Whilst the exact sequence of events to form the sulfonimidate **60**/**64** from thiol **59** is unclear, the mechanism of Bull and Luisi's method was based on a range of control experiments that allowed the identification of disulfides **61** and sulfinate esters **62** during the reaction (Scheme 15).

In the same year, Stockman and co-workers utilized sulfonimidates **7** as versatile intermediates to access a broad library of sulfoximines **66**.[35] Building on the methodology developed by Malacria and co-workers, Stockman utilized iodosylbenzene to oxidise a range of sulfinamides **65** in an excess of alcohol as solvent to access a range of sulfonimidates that differ at three key positions (Scheme 16). During the oxidation reaction, mod-



Scheme 15 Bull and Luisi's sulfonimidate **60**/**64** synthesis from aryl thiols **59**.



Scheme 16 (a) Stockman's synthesis of sulfonimidates **7** and, (b) application of sulfonimidates to access a diverse library of sulfoximines **66**.

ifying the R[1] substituent to include allyl, cyclopropyl, methyl and phenyl moieties were all well tolerated – inclusion of a *tert*-butyl group however proved unsuccessful. Furthermore, a range of primary alcohols could be incorporated, as well as varying the *N*-moiety of the sulfinamide **65** (cycloalkyl, *tert*-butyl, substituted aryls) without loss of reactivity in the transformation. A broad library of sulfonimidates **7** (where OR[3] was OEt) were then converted to sulfoximines **66** by Grignard displacement of the OR[3] group.

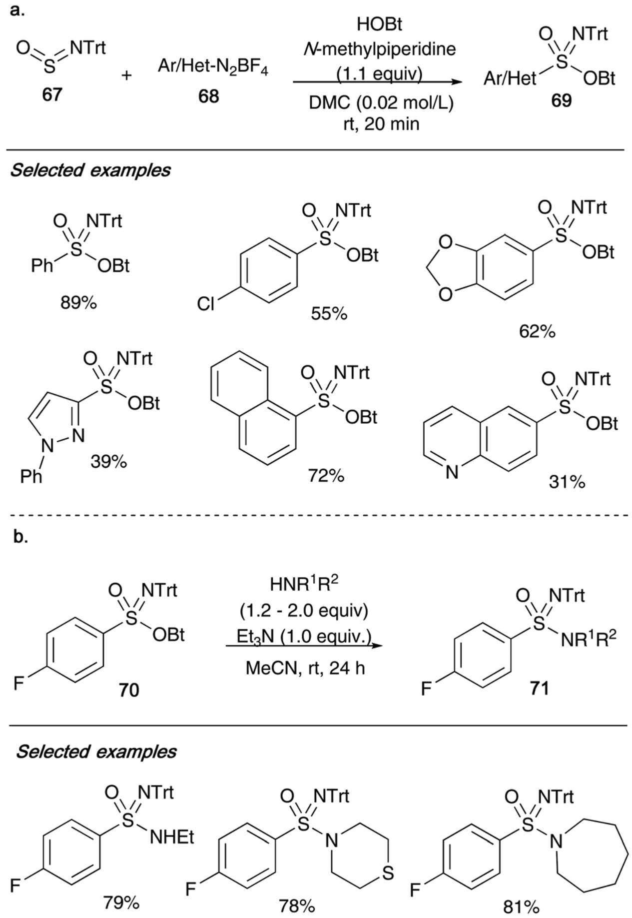
In 2019, Bolm and co-workers used *O*-benzotriazolyl sulfonimidates **69**/**70** as active intermediates in order to access sulfonimidamides **71** (Scheme 17).[36] Their group reported that aromatic or heteroaromatic diazonium salts **68** could be reacted with *N*-tritylsulfinylamine **67**[37] and 1-hydroxybenzotriazole hydrate with 1.1 equiv. of *N*-methyl-piperidine gives the desired sulfonimidates **69**. The method utilizes dimethyl carbonate, a green solvent for synthesis, and benefits from fast reaction times. As shown in Scheme 17, a range of functional groups from the diazo-aryl/heteroaryl moiety were well tolerated under the reaction conditions, providing structural diversity. Control experiments with TEMPO as radical scavenger showed complete suppression of sulfonimidate formation, indicating a potential radical mechanism involving pre-organized aggregates of the reactants. Bolm also showed that sulfonimidates **70** could be converted into sulfonimidamides **71** through reaction with either primary or secondary amines (2.0 or 1.2 equiv., respectively) under basic conditions (Scheme 17b). To highlight just a few of the examples, aliphatic amines such as ethylamine, thiomorpholine and azepane reacted smoothly affording the target sulfonimidamides **71** in good yields.

3. Synthesis of cyclic sulfonimidates

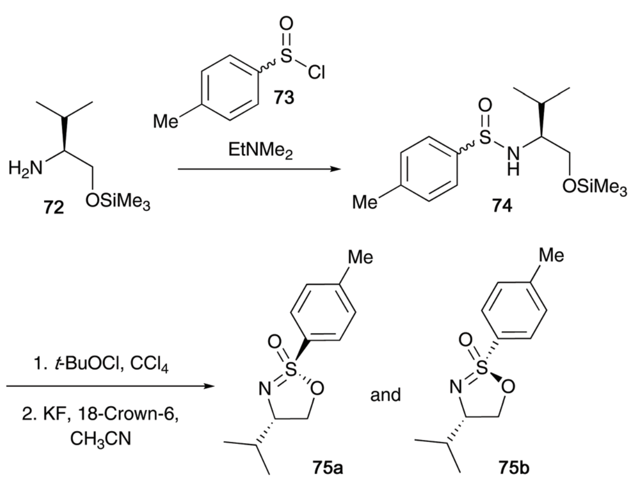
3.1 Synthesis of cyclic sulfonimidates *via* sulfonimidoyl chlorides

The research reported by the group of Reggelin has dominated this particular field of sulfur(VI) chemistry over the last three decades. In Reggelin's seminal work on the synthesis of cyclic sulfonimidates in 1992, a one pot procedure in which (*S*)-*O*-trimethylsilyl valinol **72** and *p*-toluenesulfinyl chloride **73** were reacted accessing sulfinamide **74**, followed by an oxidation affording the desired sulfonimidate products **75a** and **75b** without need of isolating reaction intermediates (Scheme 18).[38] Reggelin utilised potassium fluoride to conduct the desilylation of the primary alcohol, thus allowing the cyclisation to occur. Furthermore, sulfonimidates **75a** and **75b** were reacted with various organometallic reagents affording sulfoximines in up to quantitative yields.

In 1995, Reggelin followed up his seminal work by reporting an alternative route to access cyclic sulfonimidates **78**

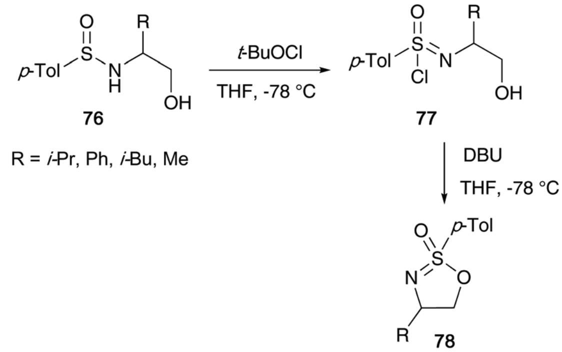


Scheme 17 (a) Bolm's synthesis of sulfonimidates **69** from *N*-tritylsulfinylamine **67**, heteroaromatic diazonium salts **68** and 1-hydroxybenzotriazole; (b) application to access sulfonimidamides **71** from sulfonimidates **70**.



Scheme 18 Reggelin's one-pot synthesis of cyclic sulfonimidates **75**.

(Scheme 19).[39] Sulfinamides **76** bearing chiral amino alcohols were identified as suitable starting materials that would be subjected to oxidative chlorination conditions to afford sulfo-

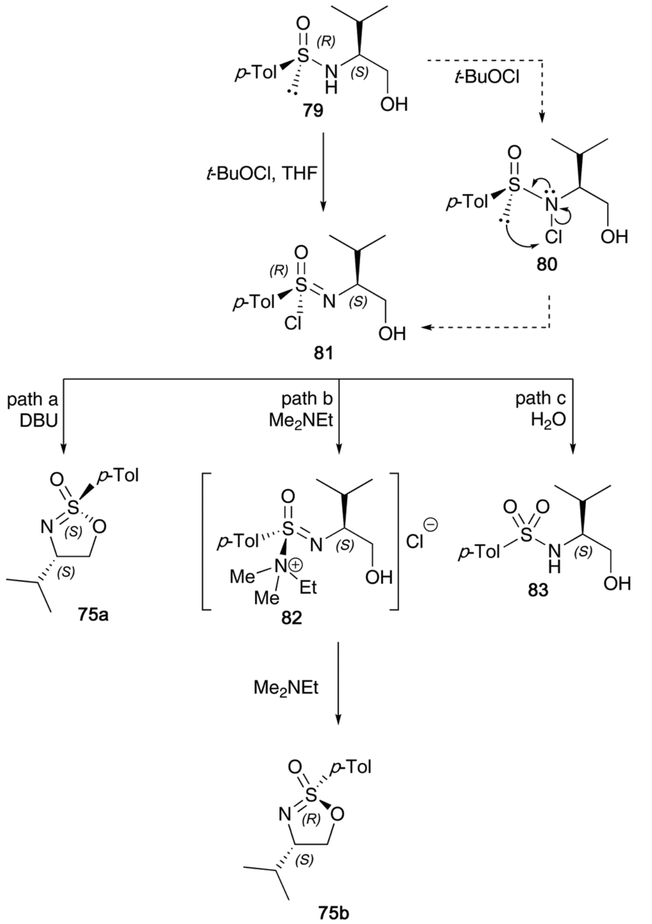


Scheme 19 Reggelin's synthesis of cyclic sulfonimidates **78**.

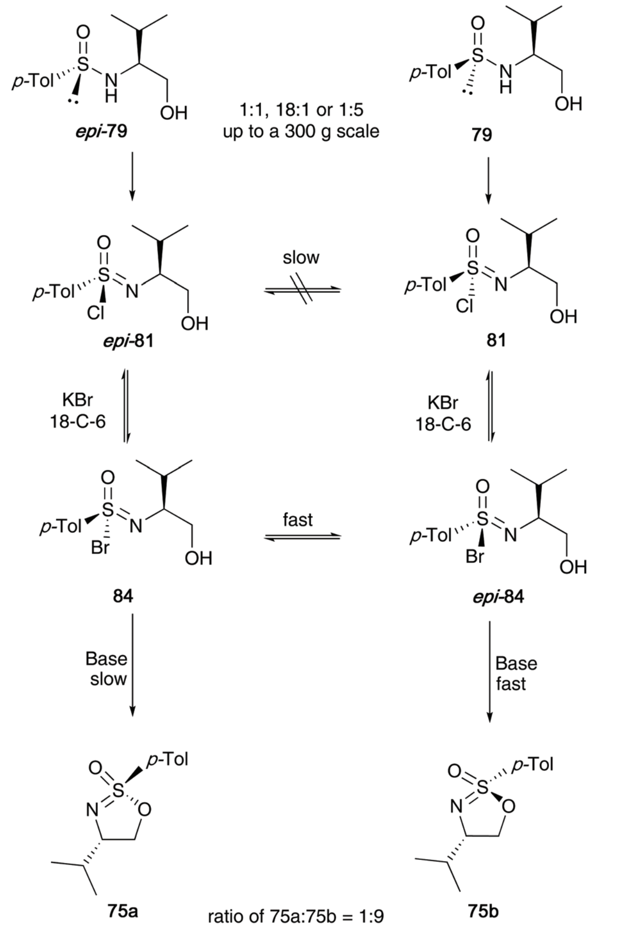
nimidoyl chlorides **77**. Previous reports by Johnson and Cram independently showed that sulfinamides are oxidised using *tert*-butyl hypochlorite at low temperatures to give sulfonimidoyl chlorides, proceeding with retention of configuration.[25,40] However, sulfonimidoyl chlorides are not configurational stable at raised temperatures used in ensuing nucleophilic reactions.[25] Reggelin showed that intramolecular attack of the internal alcohol at the sulfur centre, in the presence of DBU, was expeditious at −78 °C, and that the desired isomeric purity of the starting material is retained in the isolated product.

Nearly two decades ago, Reggelin shed light on the mechanism believed to be in operation during the synthesis of cyclic sulfonimidates.[34] He found through optimisation reactions that two particular pathways were in operation, depending on the base used in the reaction (Scheme 20). Oxidative cyclisation of an enantiomer of sulfinamide involved two key stereoselective steps; the first process is an oxidative chlorination reaction to afford sulfonimidoyl chloride intermediate **81**, that proceeds with retention of configuration at sulfur. The mechanism of this chlorination was proposed to firstly involve chlorination of the nitrogen, followed by rearrangement to give the sulfonimidoyl chloride, which was supported through NMR control experiments (integration of *meta*-aromatic signals to NH signal changed from 2 : 1 to 3.58 : 1 during the course of the chlorination reaction). The second step is a base-induced cyclisation. If the base used is bulky, for example, DBU, and the reaction conducted at low temperatures, the chloride is displaced directly by the tethered alcohol in a S_N2-like fashion, giving the product with inversion of configuration at sulfur (path a, Scheme 20). However, when dimethylethylamine was used as a smaller, more nucleophilic base (path b), sulfonimide ammonium salt **82** would be generated as an intermediate, which in turn could undergo base-catalysed cyclisation to form sulfonimidate **75b** with retention of configuration due to a double displacement. A third pathway was identified (path c), which shows that if the base used is not strong enough, such as pyridine or 2,6-lutidine, then hydrolysis of the intermediate sulfonimidoyl chloride was found.

This intricate procedure comes with a few drawbacks; firstly, the separation of diastereomeric sulfinamide starting materials is necessary (crystallisation and recrystallisation is required to purify the cyclic sulfonimidate products). During



Scheme 20 Oxidative chlorination of sulfinamides and cyclisation of the generated sulfonimidoyl chlorides to the target sulfonimidates **75a** and **75b**.



Scheme 21 Formation of sulfonimidoyl bromides **84** and their epimerisation and interconversion.

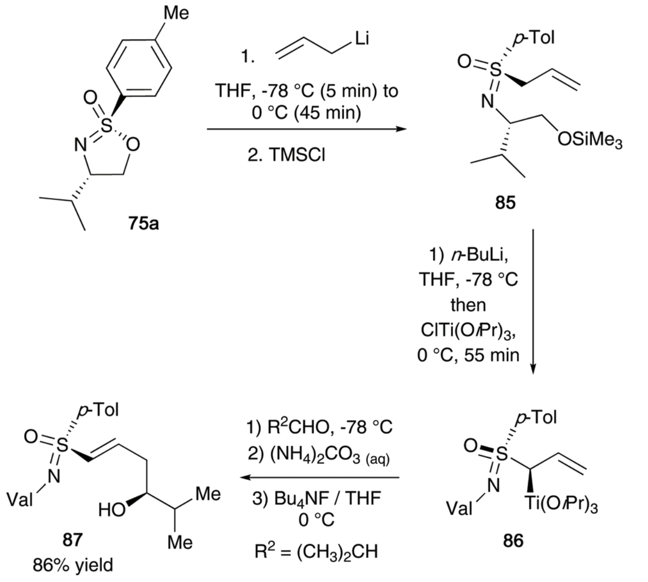
these recrystallizations, the authors disclose that for each sulfonimidate shown in Scheme 20, a maximum yield of around 35% was achieved for each epimer.

In the same article, Reggelin later described the conversion of the sulfonimidoyl chlorides **81** into sulfonimidoyl bromides **84** using 1.2 equivalents of KBr and 5 mol% 18-crown-6 (Scheme 21). These species were initially thought to be labile, albeit undetectable intermediates, yet NMR studies conducted at −20 °C showed <5% of a species that was not the chloride **81**, but potentially the bromide **84**. Through further NMR experiments at low temperatures, they observed that starting from either a 1 : 1, 18 : 1 or 1 : 5 diastereomeric mixture of sulfinamides **79**/***epi*-79**, an enriched ratio of 9 : 1 was observed in favour of the final sulfonimidate product **75b**. The catalyst loading was found to be crucial in maintaining the stereoselectivity and found that at catalyst loadings of 0.5 mol%, the selectivity halved to 4.6 : 1 in favour of the target sulfonimidate **75b**. The reaction was impressively shown to be reproducible on a large scale (checked up to a 300 g scale). The authors reported that the bromides react faster than chlorides. Furthermore, fast interconversion between the epimers is observed (dynamic epimer differentiation, in which *epi*-**84** reacts 9–10 times faster than **84**).

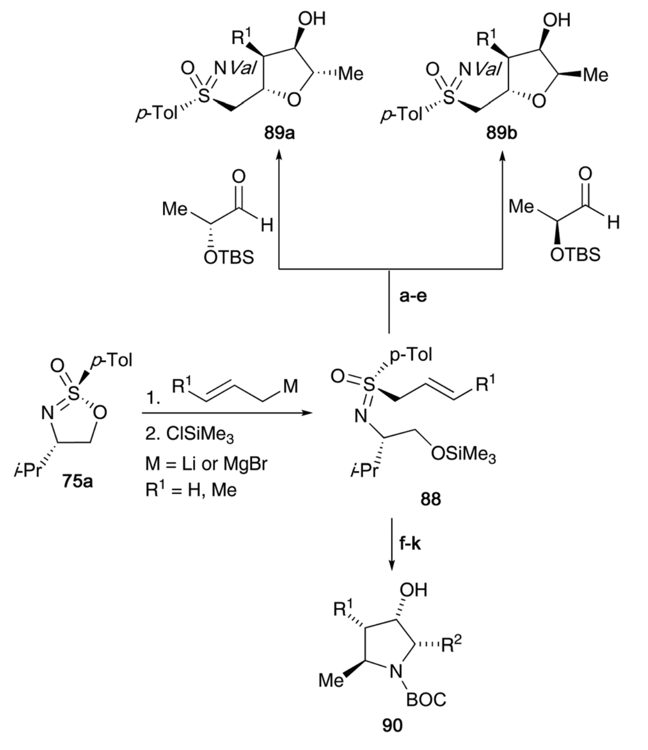
3.2 Cyclic sulfonimidates as chiral templates to access sulfoximines

In 1994, Reggelin and co-workers utilized their chiral sulfonimidate template **75a** to access enantiomerically pure allyl-derived sulfoximines.[41] After reaction of the sulfonimidate core with allyl lithium,[38] the desired sulfoximines **85** were accessed (Scheme 22). Subsequently, the authors utilized a deprotonation and transmetallation step to obtain optically active titanated 2-alkenylsulfoximines **86** – such compounds could be reacted with aldehydes (2-methylpropanal shown below) under γ-hydroxyalkylation conditions to access chiral allyl alcohol substrates (product **87** was obtained in 86% yield starting from **85**).

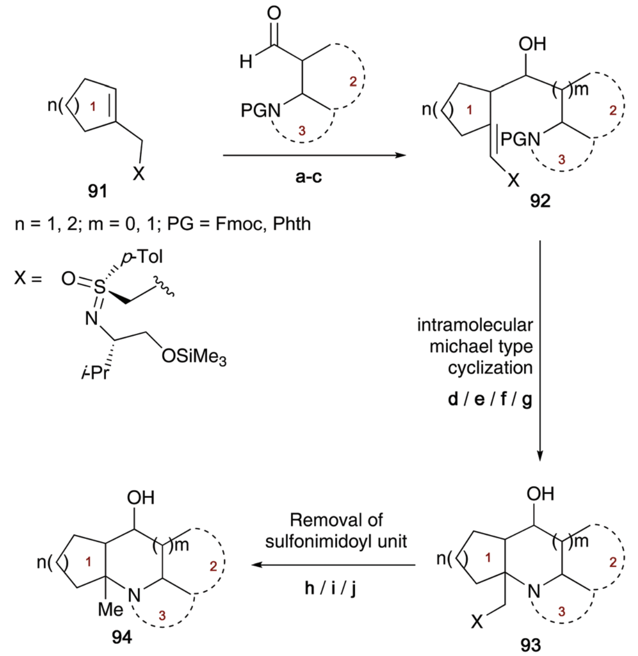
The synthesis of important oxygen and nitrogen containing heterocyclic compounds[42] was realized using the common intermediate derived from alkenyl organometallic addition to optically active cyclic sulfonimidate **75**. The diastereoselective γ-hydroxyalkylation of 2-alkenylsulfoximines **88** with enantiomeric lactaldehydes afforded tri- and tetrasubstituted tetrahydrofuran derivatives **89a/b** (shown in Scheme 23).[42a] They were also able to access pyrrolidine derivatives **90** from the addition of α-aminoaldehydes to titanated 2-alkenylsulfoximines as the key synthetic step.[42b] Moreover, the oxabicyclic



Scheme 22 Reggelin's synthesis of alkenyl sulfoximines **85** and further modifications to **86** and **87**.

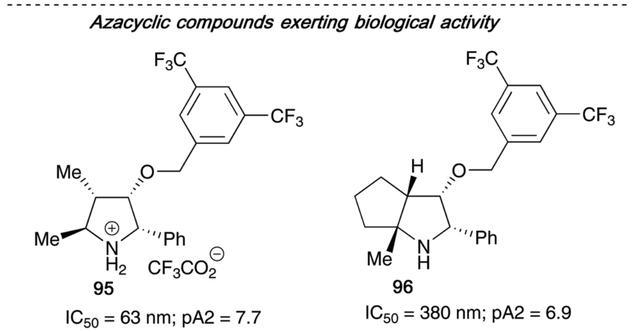


Scheme 23 Application of 2-alkenylsulfoximines **88** towards the construction of important organic heterocycles **89** and **90**. Reaction conditions: (a) *n*BuLi, THF, −78 °C; (b) ClTi(OiPr)$_3$, 0 °C; (c) aldehyde, −78 °C; (d) $(NH_4)_2CO_3$; (e) Bu_4NF; (f) *n*-BuLi, toluene, −78 °C; (g) ClTi(OiPr)$_3$, 0 °C; (h) FMOC-protected α-aminoaldehydes, −78 °C; (i) piperidine, 20 °C, $(NH_4)_2CO_3$, NH_4Cl; (j) K_2CO_3, MeOH; BOC_2O, $NaHCO_3$; (k) SmI_2.



Reaction conditions: (a) *n*-BuLi, -78 ºC; (b) ClTi(O*i*Pr)$_3$, 0 ºC; (c) aldehyde, -78 ºC; (d) piperidine, $(NH_4)_2CO_3$ or (e) hydrazine, -78 ºC, then either EtOH (heat), followed by 5% HCl in EtOH or (f) hydrazine (80% in H_2O), EtOH then K_2CO_3, MeOH or (g) hydrazine, -78 ºC to rt; (h) SmI_2 or (i) lithium naphthalenide or (j) Raney-nickel.

**template X can also be alternative 2-alkenyl sulfoximines containing cyclic or acyclic alkenes*



Scheme 24 General overview of route to accessing (poly)heterocyclic ring systems **94**, and some of the key compounds explored in biological assays.

systems could be accessed from (2-cyclohexenylmethyl) sulfoximines.[42c]

Following on from their studies on using metalated 2-alkenylsulfoximines to access (poly)heterocyclic ring systems, Reggelin showed that reacting α- and β-aminoaldehydes with a range of titanated 2-alkenylsulfoximines allowed access to highly substituted aza(poly)cyclic compounds **94** (Scheme 24).[42d] Moreover, the authors employed 2-alkenylsulfoximines **91** bearing a range of chiral units (derived from cyclic sulfonimidates **75a**/**75b**, allowing variation of the configuration at the sulfur atom and also at the amino alcohol carbon chiral centre) to control the stereochemical outcome in the final heterocycles obtained. Depending on the ring size of the heterocycle required, a range of preformed α- and β-aminoaldehydes could be reacted with titanated 2-alkenylsulfoximines, followed by nitrogen driven nucleophilic attack intramolecularly on the acceptor-substituted olefin bond in the vinyl sulfoximines to generate the desired heterocyclic core structures. Access to this key intramolecular nucleophilic attack is a result of piperidine driven cleavage of the nitrogen Fmoc group (the authors also use hydrazine when the nitrogen atom is protected with phthalic anhydride, a method that benefits from an easily separable phthalhydrazide byproduct). A final samarium iodide/lithium naphthalenide/RANEY®-nickel cleavage of the sulfonimidoyl moiety affords the nitrogen heterocycles.

During the allyl transfer step, chirality at the carbon atoms in the newly formed bond was controlled by both the prochirality of the double bond, and sense of chirality in the sulfur auxiliary. Examples of nitrogen heterocycles accessed using this approach include pyrrolidines, piperidines, pyrrolizidine, benzopiperidines, 2-azabicycloalkanes and azapolycycles. A number of the molecules synthesized using this protocol were aiming to be type III peptidomimetics – an important group of pharmaceuticals targeting enzyme inhibition. Two heterocyclic ring systems were tested for bioactivity in NK1-functional assays; both pyrrolidine derivative **95** and azabicycle **96** showed high activities.

This work was further extended by exploring the synthesis of endocyclic 2-alkenyl sulfoximines (derived from sulfonimidate template **75b**) bearing an additional heteroatom (nitrogen) or group (acetal, that could later be converted into the ketone), thereby installing an extra point of diversity into ring system 1 (see Scheme 24 for numbering of rings) on the bicycles generated. Some examples of the endocyclic 2-alkenyl sulfoximines **97–100** employed by Reggelin in this subsequent work are shown below in Fig. 3.[42e]

One issue that was further addressed utilizing this type of methodology was the cleavage of the sulfonimidoyl auxiliary in tandem with C–C bond formation to give the desired azaheterocyclic systems.[42f] Whilst RANEY® Nickel, lithium naphthalenide and samarium iodide all facilitate the transformation, they result in a methyl group in the desired product which is unable to undergo further modifcations (see Scheme 24, **93** → **94**). Utilizing a technique employed by Julia and co-workers for

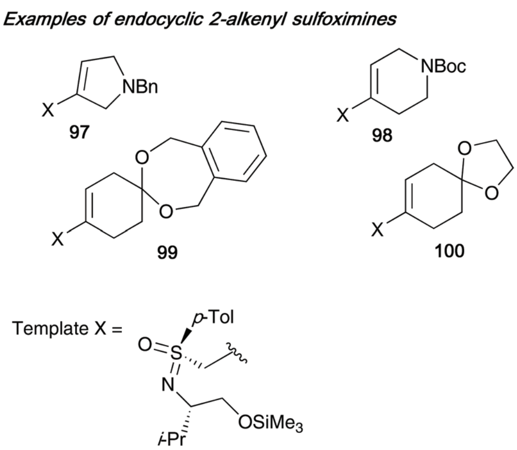
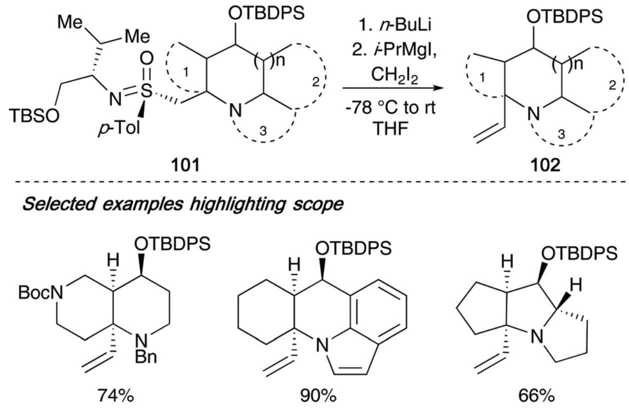


Fig. 3 Endocyclic 2-alkenyl sulfoximines **97–100** employed to add a further point of diversity to bicyclic ring systems.



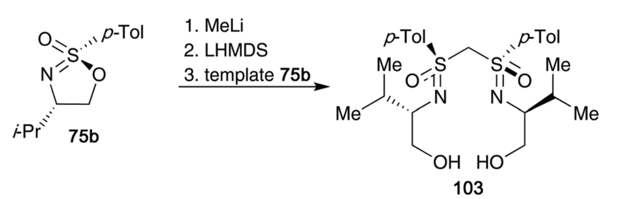
Scheme 25 Reggelin's C–C bond-forming desulfurizations of sulfoximines.

the olefinating desulfurization of sulfones using haloalkylmagnesium/lithium derived carbenoids,[43] Reggelin was able to remove the sulfonimidoyl moiety in compound **101** employing the carbenoid iodomethylmagnesium iodide. The resulting olefin products **102** from β-elimination could be isolated in good to excellent yields (selected examples shown below, Scheme 25).

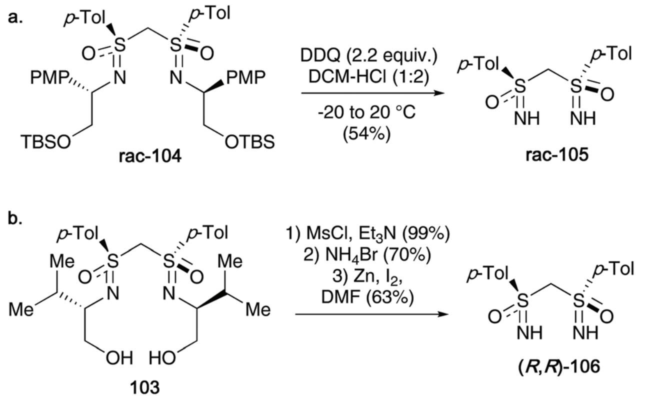
These metalated sulfoximines proved integral towards the synthesis of important natural products, for example, euglobals G1 and G2 and arenaran A.[42g] 2-Oxabicyclo[*n*.3.0]alkane core structures were accessed using 2-cyclohexenylmethyl- and 2-cyclopentenylmethyl sulfoximines in an overall one-pot approach.

Cyclic sulfonimidates also proved to be important building blocks to access bis(sulfoximines).[44] Subjecting one equivalent of the cyclic template **75b** to MeLi gave the monosulfoximine product, but deprotonation with LHMDS and reaction with a further equivalent of template **75b** gave the desired bis(sulfoximine) product **103** in 62% yield (one-pot) (Scheme 26). The designed bis(sulfoximines) were trialled as ligands in copper catalysed 1,4-additions to 2-cyclohexenone. Enantiomeric excesses for the isolated addition products reached up to 36% ee.

In 2012, Reggelin discussed methods to cleave the template from bis-sulfoximines (two main examples highlighted), affording free NH-bis sulfoximines. Firstly, a racemic *para*-methoxyphenyl derived template **104** was subjected to DDQ oxidation conditions – the desired racemic bis-NH sulfoximine **105** was obtained in up to 54% yield (Scheme 27a). For their aforementioned optically active valinol derived template **103**, these conditions could not be employed. Instead a three-step protocol, including a mesylation, bromination and a final



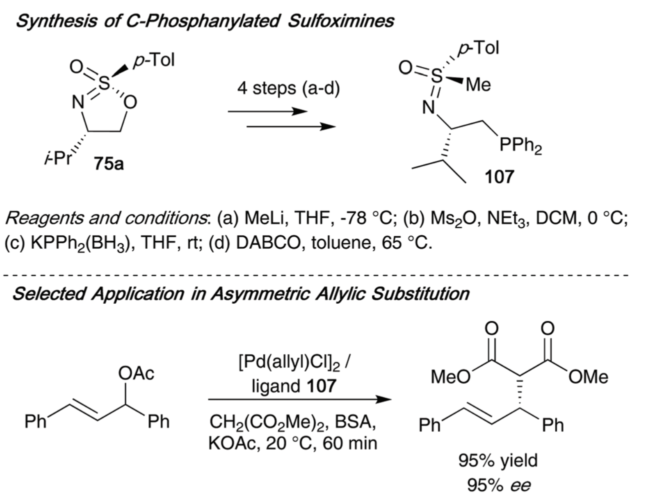
Scheme 26 Utilization of template **75b** to access bis(sulfoximines) **103**.



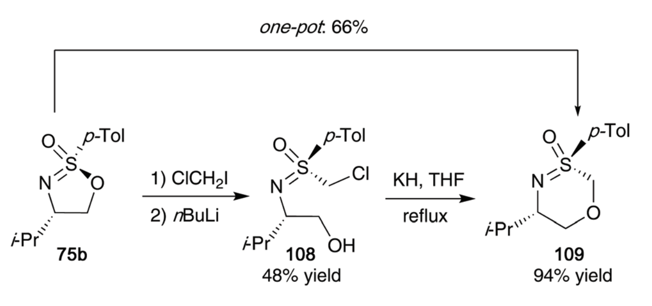
Scheme 27 (a) DDQ promoted cleavage of the PMP group towards racemic bis-NH sulfoximines **105**; (b) three-step procedure to access optically active bis-NH sulfoximines **106**.

zinc induced β-elimination, afforded the enantiomerically pure NH-bis-sulfoximine **106** (see Scheme 27b).[45]

The same group later applied these cyclic sulfonimidates to access optically active phosphanylated sulfoximines **107** – these compounds were subsequently employed as ligands in palladium-catalyzed allylic substitution reactions (Scheme 28).[46] The ligands can be accessed through a short synthetic route over 4 steps, and ligand **107** was found to be highly enantioselective when applied in the palladium-catalyzed asymmetric allylic substitution of 1,3-diphenylallyl acetate and dimethylmalonate.

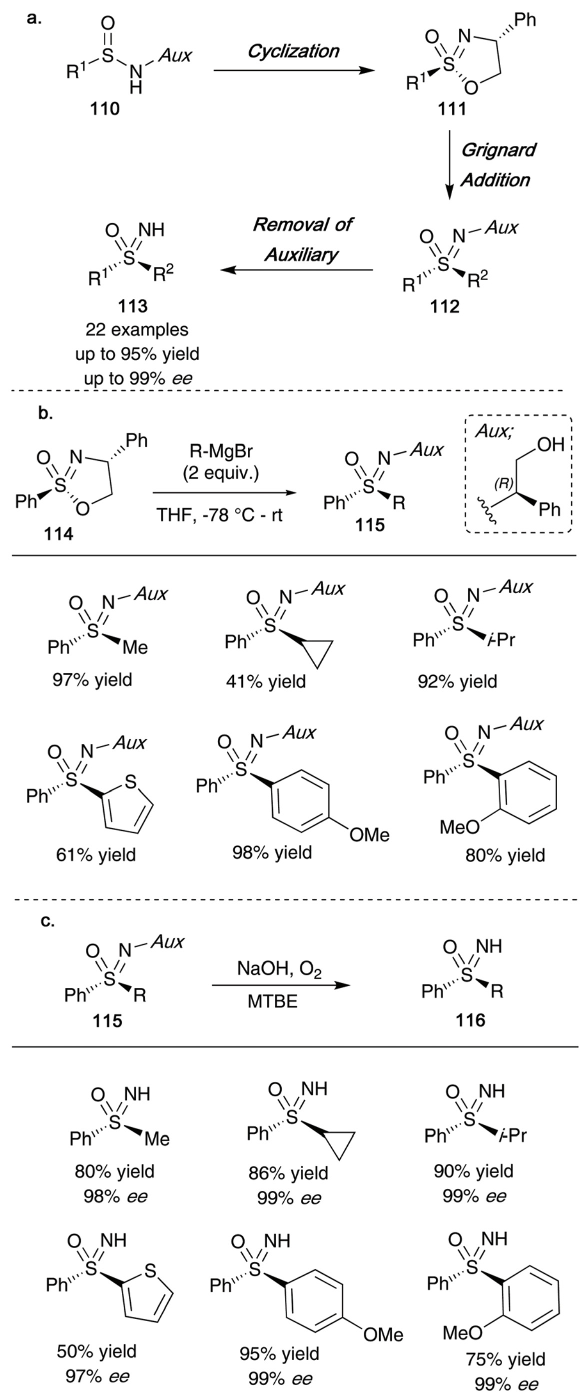


Scheme 28 (a) Synthesis of ligand **107** from sulfonimidate **75a**; (b) utilization of ligand **107** in allylic substitution reactions.



Scheme 29 Reggelin's route to access oxathiazines **109** from cyclic sulfonimidates **75b**.

Sulfonimidates such as **75b** were also shown to participate as electrophiles in Barbier-type reactions with dihalomethanes and *n*-BuLi (Scheme 29). Reggelin showed that *S*-(chloro-



Scheme 30 (a) Stockman's general route to enantioenriched NH-sulfoximines **113**; (b) Grignard additions to sulfonimidate derived template **114**; (c) oxidative debenzylation of sulfoximines **115** to give NH-sulfoximines **116**.

methyl)sulfoximines **108** from this reaction could then be reacted with potassium hydride in THF to access their desired oxathiazines **109**.[47] The protocol could also be conducted in a one-pot synthesis, providing a good yield of 66% for the desired oxathiazines **109**.

In 2020, the Stockman group reported that optically active cyclic sulfonimidate templates **111** could be employed to access enantioenriched NH-sulfoximines **113** (overall route shown in Scheme 30a).[48] Building on the work reported by Reggelin and co-workers, amino acid derived phenyl glycinol provided a suitable auxiliary that could be carried through the oxidation of sulfinamides **110** using *t*-BuOCl/DBU to give cyclic sulfonimidates **111**, followed by a Grignard addition step to yield sulfoximine products **112**. Importantly, the auxiliary could be easily removed using molecular oxygen under basic conditions in MTBE to obtain the final NH-sulfoximines **113** whilst maintaining optical purity. For clarity, one epimer is shown in Scheme 30, however, the reaction proceeds smoothly for the other epimer as well under the reaction sequence, resulting in isolation of the opposite enantiomers of **113** shown (in similarly high enantiomeric excesses). Such optically active compounds synthesized mimic structures of chiral sulfoximines currently involved in drug discovery programmes, and as such may provide a useful tool to accessing necessary enantiomers for future drug molecule syntheses.

4. Conclusions

This review article has summarised the synthetic approaches to access sulfonimidates, and their various utilities and applications towards accessing high value compounds over the last half century. Since their discovery, a plethora of methods have been discovered to access these molecules. With the presence of a stereogenic tetrahedral sulfur centre, sulfonimidates have found applications as chiral templates to access enantioenriched sulfoximines – these in turn can subsequently be converted into other chiral molecules including highly substituted saturated heterocycles. In other cases, exploiting weaknesses of sulfonimidates, including acid sensitivity and heat lability, have led to important discoveries, such as acting as alkyl transfer agents or the synthesis of sulfur containing polymers. Due to the rising interest in other sulfur(VI) compounds including sulfonimidamides and sulfoximines as pharmaceutical leads in the medicinal chemistry sector, the need to develop fast, efficient routes using sulfonimidates as reactive (and potential optically active) intermediates is ever present. To address the growing need for routes to access these sought-after molecules, we envisage this field to continue to expand over the coming years. Sulfonimidate chemistry still offers many undiscovered leads and applications, which we anticipate to see in the near future.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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