Synthesis of aza-S(VI) motifs

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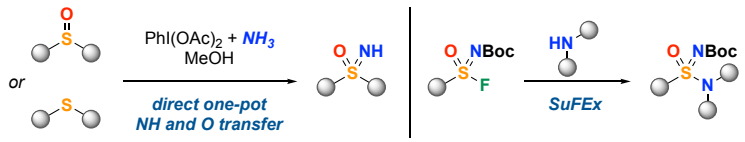
Abstract Sulfoximines and sulfonimidamides are of interest as design options for medicinal chemists. This article describes the development of methods for the synthesis of sulfoximines by metal-free NH-transfer to sulfoxides, and NH/O transfer to sulfides, using convenient sources of ammonia and hypervalent iodine reagents. Similarly, sulfonimidamides are prepared from sulfenamides. Methods for the preparation of enantioenriched sulfonimidoyl fluorides are also described, as is their stereospecific reactions with amines and Grignard reagents. This work was presented at the 29th International Symposium on the Organic Chemistry of Sulfur (Guelph, July 2022).

Graphical abstract



Introduction

Aza-Sulfur(VI) motifs offer extremely valuable design options in medicinal chemistry.[1] Sulfoximines and sulfonimidamides are the aza-analogues of sulfones and sulfonamides and much less commonly considered in drug design (Figure 1).[2,3] The additional nitrogen atom in these chemically and configurationally stable motifs can form a chiral sulfur center, introduces a hydrogen-bond donor, offers tunable physical properties, and provides an additional vector through which to functionalise. Sulfoximines have now become relatively established as valuable motifs in medicinal chemistry.[4] Sulfonimidamides remain underexplored and offer significant potential in drug design.

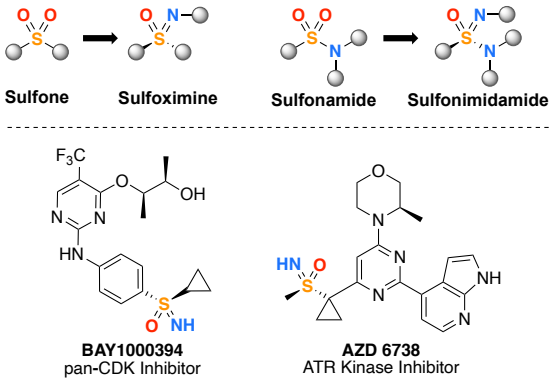


Figure 1: Aza-sulfur (VI) motifs and examples of sulfoximine containing clinical candidates

Sulfoximines emerged to prominence as sulfonamide alternatives. Bayer led the way in the development of BAY10000394 (Roniciclib),[5] a pan-CDK inhibitor, which was the first sulfoximine containing compound to enter clinical trials. Roniciclib is a single enantiomer, with *R*-stereochemistry at the sulfur center itself. An earlier lead-compound contained a sulfonamide; replacement with the sulfoximine gave improved solubility, reduced carbonic anhydrase activity and overall improved toxicology profile vs the sulfonamide series. AstraZeneca's AZD6738 (Ceralasertib), an ATR kinase inhibitor, incorporated a methyl sulfoximine in place of an earlier sulfone moiety.[6] The sulfoximine

gave improved activity and improved solubility vs the sulfone, again as single diastereoisomer and single enantiomer compound (*R*-stereochemistry at sulfur).

We first entered the field in 2014 at which time the state-of-the-art in sulfoximine synthesis was arguably a method from Bolm, using Rh catalysis for trifluoroacetamide transfer to sulfoxides.[7,8] Condensation of trifluoroacetamide with a hypervalent iodine reagent forms an iminoiodinane which in turn forms an electrophilic rhodium nitrene to be is attacked by the sulfoxide. In collaboration with Prof Luisi (University of Bari), we developed related conditions that employed carbamates such as Boc and Cbz as well as alkyl (Me, Et) carbamates, to form sulfoximines bearing these common protecting group motifs.[9] There was less known about NH transfer, though surprisingly the hazardous combination of sodium azide with sulfuric acid was still used to transfer NH to sulfoximines.[10] More recent developments used continuous flow chemistry to generate the HN_3 reagent, though it was notable that the strongly acid conditions led to the racemisation of enantioenriched sulfoxide starting materials.[11] Richards reported a rhodium catalysed process, that required the use of DPH.[12,13] This article represents a personal account of the work of my group and collaborators as presented at the 29th International Symposium on the Organic Chemistry of Sulfur (Guelph, July 2022), rather than a comprehensive review of the field.

Results and Discussion

In 2016, in collaboration with Prof Luisi, we reported the reaction of sulfoxides in the presence of ammonium carbamate and hypervalent iodine reagents. We were delighted to find the direct NH transfer under metal free conditions to form NH-sulfoximines (Figure 2a).[14] The reaction was operationally very simple and relatively non-hazardous, using convenient solid sources of ammonia and mediated by $PhI(OAc)_2$ as oxidant. The reaction is run at rt (usually in a room temperature water bath), in methanol and provides complete conversion in 30 min. The reaction is also successful in MeCN or toluene as solvent, though with increased reaction time due to limited solubility of the ammonium carbamate. We reported a broad reaction scope, with the reaction being notably tolerant of protic functionality, and pyridine-like N-heterocycles. Electron rich heterocycles are less well tolerated, as was indicated using the robustness screen described by Glorius.[15,16] For enantioenriched substrates, the *ee* of the sulfoximine was perfectly retained in the sulfoximine product, providing a route to highly enantioenriched sulfoximines.

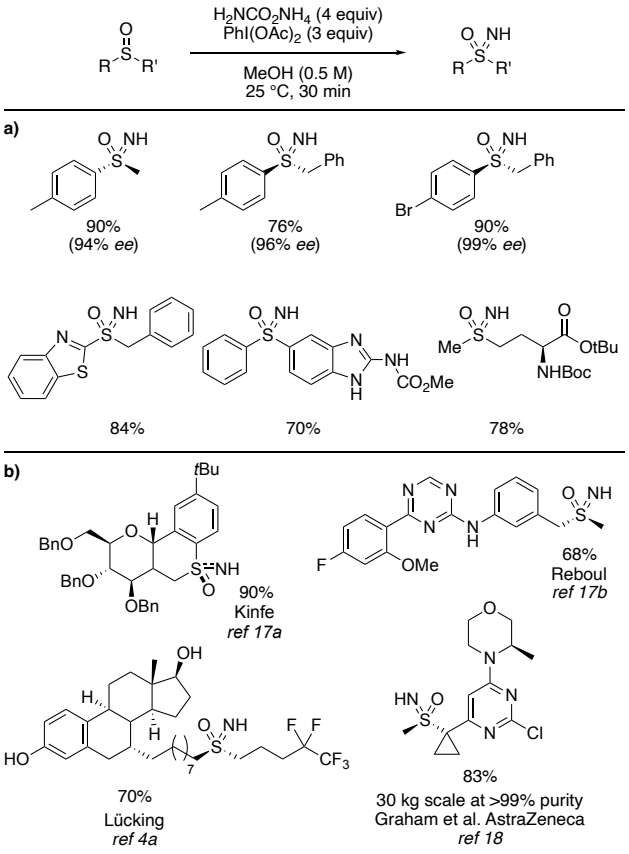


Figure 2: NH transfer to sulfoxides.

This method has provided an extremely convenient way to access sulfoximines from sulfoxides, and has seen broad application by other groups in the preparation of sulfoximine containing compounds (For examples, Figure 2b).[17] Perhaps most notably, AstraZeneca used the method in their preparation of an intermediate in AZD6738 on process scale, reporting a 30kg scale, using these reagents in a mixed MeOH/toluene solvent system.[18]

Mechanistically, we understand that the ammonium carbamate simply provides a convenient source of ammonia in methanolic solution. Condensation of ammonia with $PhI(OAc)_2$ forms an iminoiodinane, however, the ultimately reactive species as indicated by mass spectrometry analysis and reactivity observations is a short lived iodonitrene species $PhIN^+$.[14,19,20] The iodonitrene reacts directly with the sulfoxide to form an iodonium salt, that can be isolated,[8b] or converts to the sulfoximine by N–I cleavage. This occurs over time in solution, or very rapidly either on aqueous work up, or simply on evaporation of the methanol solvent prior to purification.[14]

Sulfide imination and oxidation presented an alternative approach to the rapid preparation of sulfoximines. In a remarkable observation in Prof Luisi's lab, the treatment of sulfide with related conditions, gave directly the sulfoximine, and not the sulfilimine. The reaction conditions used 2.5 equiv $PhI(OAc)_2$ and 2 equiv ammonium carbamate which were successful for broad range of sulfides, well tolerant of heterocycles and oxidatively sensitive positions (Figure 3a).[21] Ammonium carbamate could be replaced with ammonium acetate, and as such using ^{15}N labelled reagents ($AcO^{15}NH_4$) could generate the ^{15}N-sulfoximine products, which was demonstrated with methionine derivatives and biotin (Figure 3b). These substrates gave low *dr* in the sulfoximine formation, however, using thioglycosides, high levels of *dr* were obtained in the synthesis of glycosyl sulfoximines (Figure 3c).[22]

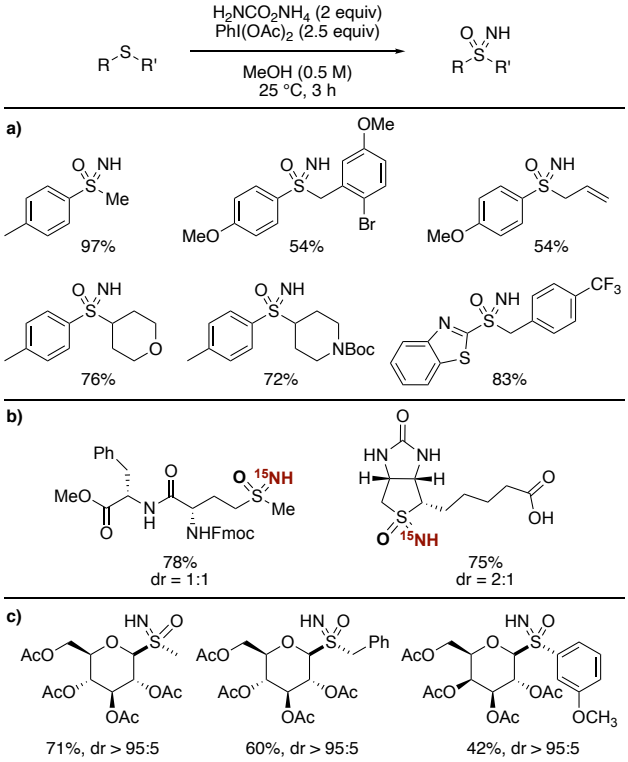


Figure 3: NH and O transfer to sulfides

We used this methodology to prepare a series of vinyl sulfoximines of potential interest as chiral covalent warheads.[23] A 2-step sequence of alkyne hydrothiolation, using conditions reported by Love,[24] followed by the NH/O transfer conditions,[21] gave these derivatives in high yield and selectivity, with exclusive reaction on sulfur (Figure 4).

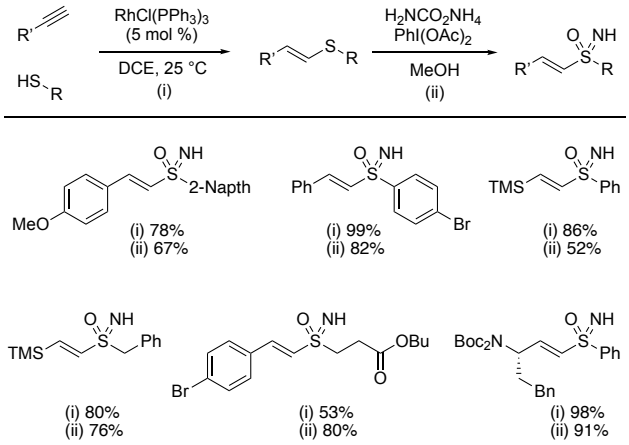


Figure 4: NH and O transfer to vinyl sulfides to form vinyl sulfoximines.

In studying this sulfoximine forming reaction we made several observations that both demonstrated the excellent chemoselectivity of the reaction and were consistent with imination occurring before oxidation.[21] Under the reaction conditions, both diphenylsulfoxide and diphenylsulfilimine gave conversion exclusively to the sulfoximine. Diphenylsulfilimine was oxidised by $PhI(OAc)_2$ in the absence of a nitrogen source to the sulfoximine. Importantly, oxidation of diphenylsulfoxide by $PhI(OAc)_2$ does not occur even in absence of the ammonium carbamate, so unwanted oxidation to the sulfone was not observed. It was also apparent that a more reactive intermediate was formed: using only 1 equiv of oxidant gave 50% conversion to the sulfoximine, and 50% recovered sulfide. At a similar time, Reboul made observations of these reactive intermediates and proposed the formation of sulfane nitriles (see below).[25] Applying related conditions to thiols formed sulfonimidates, which on extended reaction times could be converted to primary sulfonamides.[26]

Next we examined a related NH/O transfer, aiming to form sulfonimidamides from sulfenamides.[27,28] Sulfenamides are readily formed from disulfides and amines according to a procedure by Davis using silver nitrate,[29] which can benefit from the addition of Et_3N to reduce the acidity.[23] Modified conditions were required for the NH/O transfer to the sulfonimidamides to achieve high yields (Figure 5). Iodosobenzene (PhIO) was used to avoid excess acidity with the addition of 1 equiv of AcOH, in *i*PrOH solvent. Aryl and cyclohexyl sulfenamides formed with secondary amines were successful.[27] This was exemplified in the formation of the aza-analogue of probenecid, a treatment for hyperuricemia (gout). A short sequence from a known disulfide gave the sulfenamide, which was converted to the sulfonimidamide. Hydrolysis of the ester was achieved using acidic conditions to form the drug analogue. To demonstrate the potential to exploit the additional vector, the sulfonimidamides were functionalised through arylation, propargylation and formation of a chloroacetamide.

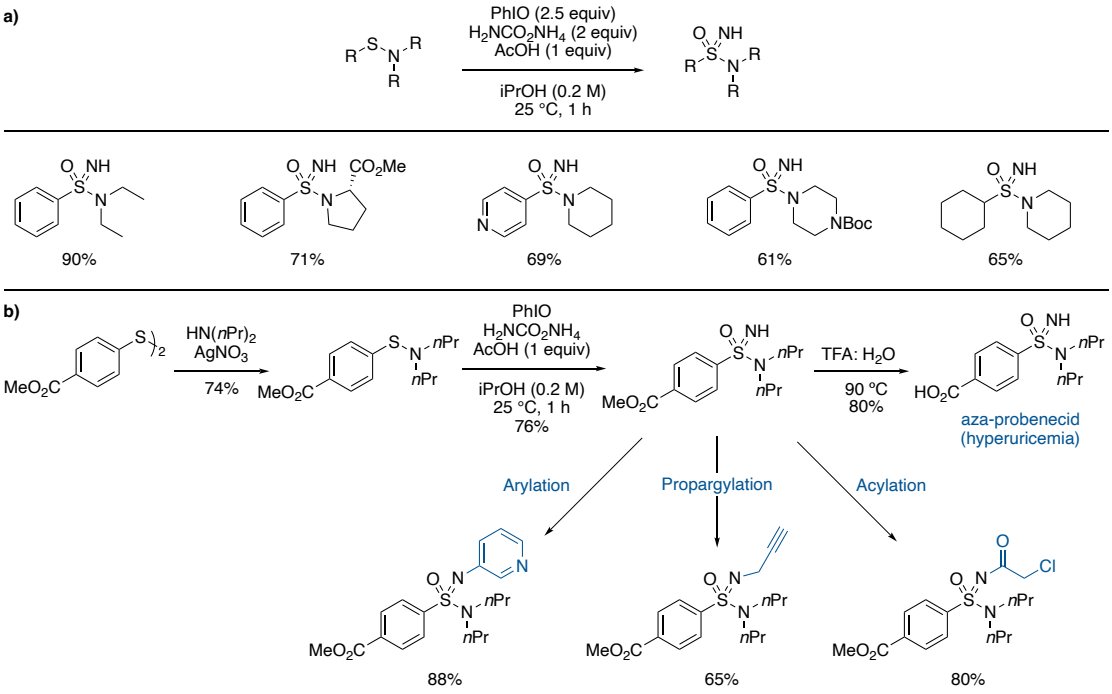


Figure 5: a) Sulfonimidamide synthesis from sulfenamides by NH/O transfer. b) Preparation of aza-probenecid and N-functionalisation.

Importantly, in the absence of the acetic acid additive a new class of sulfane nitrile was formed, amino-alkoxy-sulfane nitriles (Figure 6a).[27] Sulfane nitriles have been previously observed by Yoshimura, demonstrated to provide powerful alkylating agents.[30] Furthermore, Reboul detected related compounds in NMR and mass spectrometry investigations in sulfoximine synthesis from sulfides.[25] We demonstrated that these new derivatives were relatively stable and could be isolated using various solvents, along with varying quantities of the sulfonimidamide.[27] The sulfane nitriles reacted directly with mildly acidic reagents as alkylating agents to transfer the alcohol R group to AcOH, thiols and phenols for example, though were stable in alcohols. This initial observation suggested that the solvent was the source of the oxygen atom. However, additional observations with labelled water addition gave some ^{18}O incorporation, and furthermore, we demonstrated that the acetate itself was also a viable source of oxygen. Each of these is likely to be a complementary oxygen source in the full reaction condition, and each leads to the same sulfonimidamide product, again providing high levels of chemoselectivity (Figure 6b).

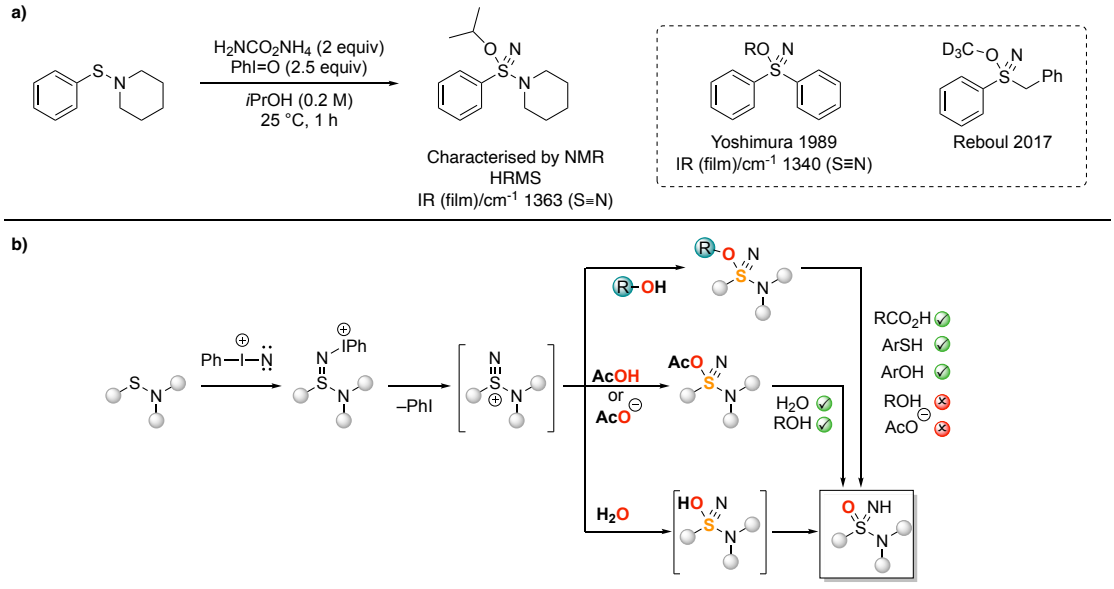


Figure 6: Sulfane nitriles as intermediates in the formation of sulfonimidamides (and sulfoximines).

As an approach to enantioenriched sulfonimidamides, we envisaged applying chiral sulfonimidoyl electrophiles to form S–N bonds with amine nucleophiles, to allow stereocontrolled late-stage diversification of amines. Various powerful electrophilic reagents have been developed, most involving the sulfonimidoyl chloride, which is susceptible to hydrolysis and decomposition.[31] Recent developments have seen alternative leaving groups, that offer more stable derivatives.[32] Willis has developed new reagents for one-pot sulfoximine synthesis with different carbon nucleophiles.[33] However, none of these approaches were amenable to stereocontrolled synthesis of building blocks that would be suitable for construction of enantiopure libraries. We were drawn to work by Sharpless and others looking at sulfonyl fluorides due to their improved stability in comparison to chlorides.[34,35,36,37] Sharpless had also demonstrated the reaction of N-aryl sulfonimidoyl fluorides with amine anions.[38] We targeted N-Boc sulfonimidoyl fluorides, whereby the Boc group would activate the reagent to substitution and provide a readily removable N-protecting group.

We first demonstrated that sulfinamide salts could be converted cleanly to the corresponding sulfonimidoyl fluoride, and then were able to show substitution of fluoride to form the sulfonimidamide.[39] On the racemic series this was achieved with the neutral amine on warming in THF. However, when using enantioenriched materials, these conditions led to rapid loss of *ee* in the substitution step (Figure 7a). The cause of this was demonstrated to be due to the fluoride ions liberated in solution causing racemisation by degenerate exchange.[39] This phenomenon has since been used to introduce ^{18}F into sulfonyl fluorides as possible imaging agents.[40] We investigated various reagents to scavenge the inorganic fluoride. Loss of *ee* in the initial step was reduced using selectfluor in ethanol with the addition of potassium acetate. Crucially, for arylsulfonimidoyl fluorides, the addition of LiBr to a reaction in MeCN as solvent successfully retained the *ee* of the substrate (Figure 7b). The reaction was successful for a wide range of primary and secondary amines generating sulfonimidamides with excellent yield and *ee*.[39] The substitution was shown to proceed with inversion by X-ray crystallography. The Boc group was readily removed to form enantioenriched NH-sulfonimidamides. 4-Bromophenylsulfonimidoyl fluoride was also prepared (involving enantioselective oxidation) and demonstrated in the SuFEx reaction with retention of *ee*.

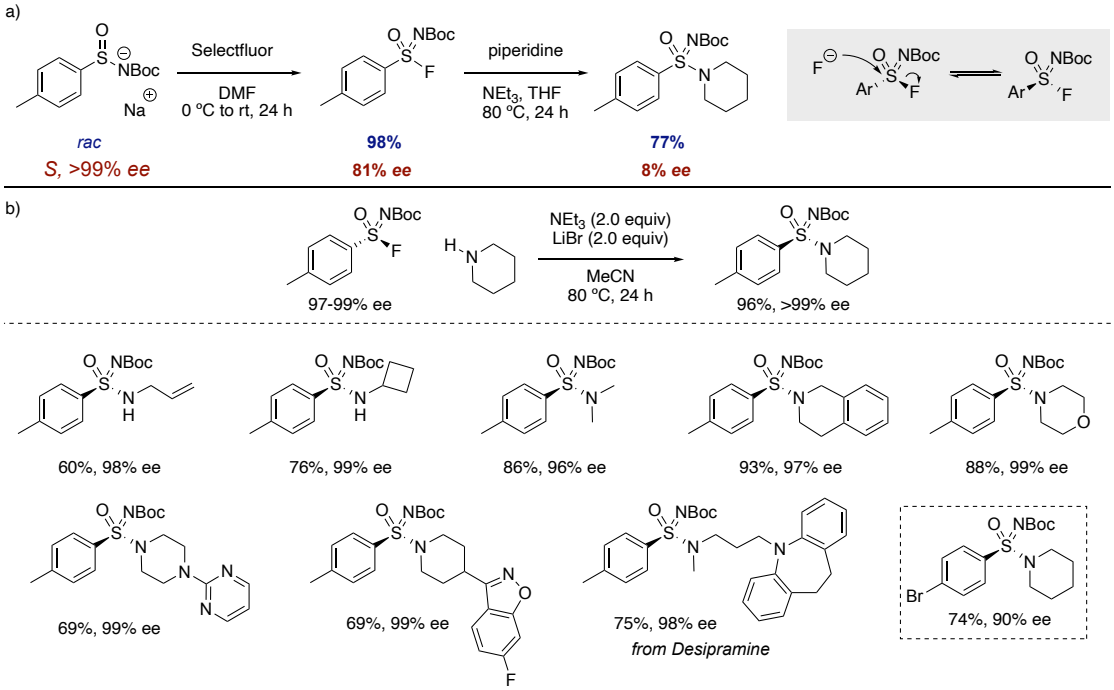


Figure 7: a) Racemisation of enantiopure sulfonimidoyl fluorides under initial conditions. b) Enantiospecific amine SuFEx to generate sulfonimidamides with high *ee*.

Very recently, we demonstrated that the N-Boc sulfonimidoyl fluorides were also suitable electrophiles to react with Grignard reagents, to form enantioenriched sulfoximines, including highly symmetrical versions.[41] A wide range of Grignard reagents were successful, including heteroaromatics, and vinyl, alkyl and cyclopropyl derivatives, to form medicinally relevant substructures (Figure 8). It is notable that these sulfonimidoyl fluoride reagents react smoothly with Grignard reagents, whereas the corresponding chlorides would be expected to undergo reduction

by attack at the chlorine atom.[42] In addition to the N-Boc derivatives, Maruoka's methods for sulfinamide preparation[43] were exploited to form enantioenriched alkyl and aryl N-Piv sulfonimidoyl fluorides in high *ee*, which also reacted stereospecifically.[41] Grigand reagent were also successful using an enantioenriched methylsulfonimidoyl fluoride with retention of *ee*, though an improved yield was obtained with the cuprate reagent.

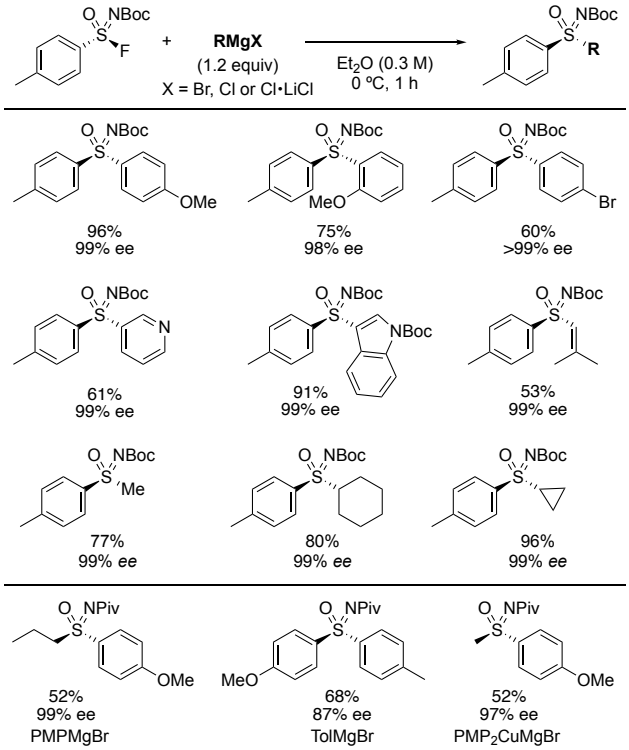


Figure 8: Stereospecific reaction of enantioenriched N-Boc or N-Piv sulfonimidoyl fluorides with Grignard reagents.

Conclusions

Overall, these methods have afforded practical and scalable methods for the preparation of sulfoximines and sulfonimidamides. Both the N-transfer methods and the substitution methods have provided improved access to these aza-S(VI) derivatives. We hope these methods help to provide new options for the medicinal chemist and may lead to the further exploitation of these motifs in a drug discovery setting.

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