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# Stereospecific reaction of sulfonimidoyl fluorides with Grignard reagents for the synthesis of enantioenriched sulfoximines†

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Sulfonimidoyl halides have previously shown poor stability and selectivity in reaction with organometallic reagents. Here we report the preparation of enantioenriched sulfonimidoyl fluorides and their stereospecific reaction at sulfur with Grignard reagents. Notably the first enantioenriched alkyl sulfonimidoyl fluorides are prepared, including methyl. The nature of the N-group is important to the success of the stereocontrolled sequence to sulfoximines.

Aza-sulfur (VI) derivatives are increasingly validated in drug discovery,<sup>1,2</sup> and have seen a marked increase in their use. Sulfoximine containing compounds in particular have entered clinical trials including roniciclib (Bayer)<sup>3</sup> and ceralasertib (AstraZeneca).<sup>4,5</sup> It is notable that these sulfoximine derivatives, which are chiral at sulfur, are single stereoisomers. In comparison to sulfones, the additional N-vector in sulfoximines provides potential as a H-bond donor, for functionalization or to tune properties.<sup>6</sup> Methods for their enantiocontrolled synthesis are of particular value, to exploit the directional nature of potential interactions.

Methods to prepare sulfoximines have seen significant developments in recent years,<sup>6,7</sup> including facile methods for NH transfer,<sup>8,9</sup> and new reagents containing the SON motif.<sup>10,11</sup> Pre-formed methyl sulfoximine reagents have recently been demonstrated to undergo  $S_NAr$  reactions with heteroarenes.<sup>12</sup> However, there remain very few methods for the stereocontrolled construction of sulfoximine derivatives through S-C bond formation. Maruoka has recently reported powerful nucleophilic reagents for sulfoximine synthesis utilising *t*-butyl-sulfonamide as a chiral framework.<sup>13</sup>

Electrophilic reagents to form sulfoximines have been historically challenging, and there are few examples that can provide an enantioenriched product. Early examples of non-racemic sulfonimidoyl chlorides were reported by Cram<sup>14a</sup> and Johnson,<sup>14b</sup> but reaction with organometallic reagents resulted in attack at chlorine and reduction to the sulfonamide (*e.g.* with Grignard reagents, Fig. 1b). Johnson later found that racemic sulfonimidoyl fluorides could be reacted with a limited range of organolithium reagents to form sulfoximines (Fig. 1c).<sup>15,16</sup> More recently, Sharpless demonstrated the reaction of phenyl-sulfonimidoyl fluorides with organolithium reagents.<sup>11</sup> Notably, all examples to date were *N*-alkyl or aryl derivatives that were not readily removable to unveil the NH-sulfoximine.

To date, the most effective electrophilic reagents to form non-racemic sulfoximines have been cyclic sulfonimides bearing a chiral auxiliary on nitrogen.<sup>17</sup> Building on the work of Reggelin,<sup>17a</sup> Stockman recently developed cyclic sulfonimides

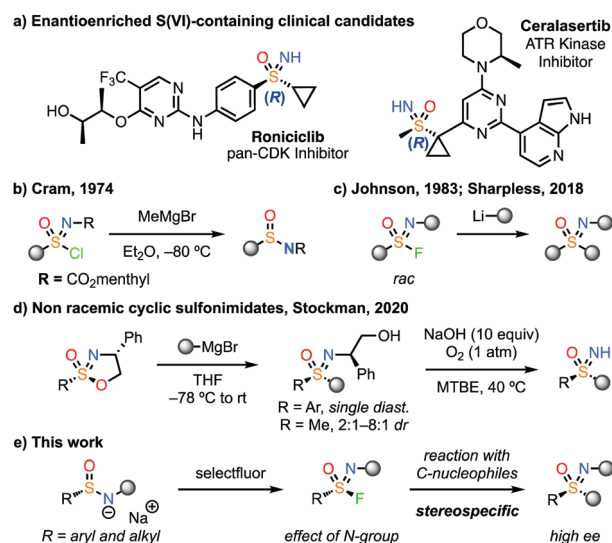


Fig. 1 Clinical candidates containing stereochemically pure sulfoximines and electrophilic reagents for sulfoximine synthesis.

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as separable diastereomers at sulfur, which reacted with Grignard reagents (Fig. 1d).<sup>17b</sup> Stereospecific conversion was achieved for phenyl sulfonimides whereas methyl derivatives gave low stereo-control, leading to mixtures of *S*-stereoisomers, likely *via* an initial elimination. The auxiliary was removed using O<sub>2</sub> and base.<sup>17b</sup>

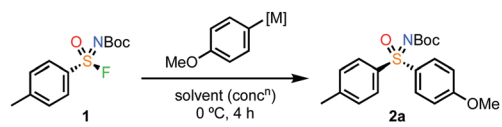
Here we report the generation of highly enantioenriched aryl and alkyl sulfonimidoyl fluorides and their stereospecific reaction to generate sulfoximines by S–C bond formation (Fig. 1e). A broad range of Grignard reagents and other organometallic species were successful to generate highly enantioenriched sulfoximines. Notably, an enantiopure methyl sulfonimidoyl fluoride reagent reacted without loss of ee.

The first reports of enantioenriched sulfonimidoyl fluorides were in 2020 from ourselves<sup>18</sup> and Zuillhof<sup>19</sup> for reaction with amines and phenolates respectively. Enantioenriched sulfonimidoyl fluorides present interesting potential as synthetic intermediates, and in chemical biology<sup>20</sup> and polymer science.<sup>21</sup> Fluoride ions were found to cause racemisation of the sulfonimidoyl fluorides through a degenerate exchange,<sup>22</sup> which could be avoided by their sequestration.<sup>18,21</sup> Aiming to prepare sulfoximines, we investigated the reaction of sulfonimidoyl fluorides with carbon nucleophiles. Despite little encouragement from the literature, we prioritised Grignard reagents as they are widely available and less basic than organolithium reagents. We anticipated that the magnesium halide counterion could scavenge fluoride and prevent fluoride-mediated racemisation of the sulfonimidoyl fluoride.

Initially we investigated NBoc-tolylsulfonimidoyl fluoride **1**, prepared at high ee by our previously reported electrophilic fluorination of sulfonamide salts.<sup>18</sup> On reaction with 4-methoxyphenylmagnesium bromide (PMPMgBr) we were delighted to observe that substitution occurred successfully, to give sulfoximine **2a** in 58% yield with only a small loss of ee (Table 1, entry 1). The addition of lithium salts (LiCl or LiBr) as had been useful previously with amine nucleophiles<sup>18</sup> saw a small increase in *es* but was detrimental to conversion (Entry 2). Changing the solvent to Et<sub>2</sub>O was beneficial to both yield and ee (entries 3 and 4) and varying the concentration did not have a significant effect (entries 4–7). Decreasing the equivalents of Grignard reagent and reducing the reaction time to 1 h resulted in a 91% yield (by <sup>1</sup>H NMR) and complete retention of ee (entry 9). By comparison, the use of the organolithium reagent (PMPLi) in THF was also successful in retaining the ee, but with significantly reduced yield (entry 10). Using the potentially more functional group tolerant organocuprate reagent, formed from the Grignard reagents as PMP<sub>2</sub>Cu(MgBr), gave both high ee and 81% isolated yield of **2a** in an extended reaction time at rt (entry 11).<sup>23</sup> Organozinc reagents were not sufficiently reactive, and returned the sulfonimidoyl fluoride.<sup>23</sup>

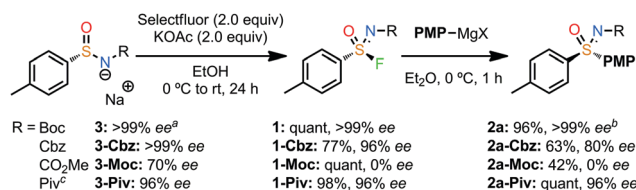
Using these optimised conditions (Table 1, entry 9) gave excellent isolated yields for both the fluorination (**1**)<sup>18</sup> and Grignard reaction (**2a** obtained in 96% isolated yield and 99% ee on 0.25 mmol scale; Scheme 1). Furthermore, performing the reaction in cyclopentyl methyl ether (CPME) in place of Et<sub>2</sub>O gave the same result, providing quantitative yield and complete enantiospecificity for **2a** in an industrially preferred solvent.

**Table 1** Optimisation of the reaction of sulfonimidoyl fluoride **1** with Grignard reagents



Entry	[M]	R-[M] equiv.	Solvent (conc.)	Yield <sup>a</sup>	<i>es</i> (%) <sup>b</sup>
				<b>1</b>	<b>2a</b>
1	MgBr	1.5	THF (0.3 M)	31	58
2 <sup>c</sup>	MgBr	1.5	THF (0.3 M)	62	23
3	MgBr	1.5	1,4-Dioxane (0.3 M)	50	39
4	MgBr	1.5	Et <sub>2</sub> O (0.3 M)	5	77
5	MgBr	1.5	Et <sub>2</sub> O (0.1 M)	—	70
6	MgBr	1.5	Et <sub>2</sub> O (0.2 M)	—	69
7	MgBr	1.5	Et <sub>2</sub> O (0.5 M)	—	70
8	MgBr	1.2	Et <sub>2</sub> O (0.3 M)	—	81
9 <sup>d</sup>	MgBr	1.2	Et <sub>2</sub> O (0.3 M)	—	91
10 <sup>e</sup>	Li	1.2	THF (0.3 M)	—	37
11 <sup>f</sup>	[CuAr]	1.2	Et <sub>2</sub> O (0.3 M)	—	87 (81) <sup>g</sup>
12 <sup>h</sup>	ZnCl	1.2	Et <sub>2</sub> O (0.3 M)	90	0

Reactions performed on 0.10 mmol scale. <sup>a</sup> Calculated by <sup>1</sup>H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. <sup>b</sup> *es* determined by HPLC analysis of crude reaction product. <sup>c</sup> Lithium bromide (1.5 equiv.) added. <sup>d</sup> Reaction time 1 h. <sup>e</sup> Addition of organolithium at –78 °C followed by warming to 0 °C. <sup>f</sup> Reaction time 5 h at rt; 0.25 mmol scale. <sup>g</sup> Isolated yield. <sup>h</sup> Reaction time 3 h at rt.

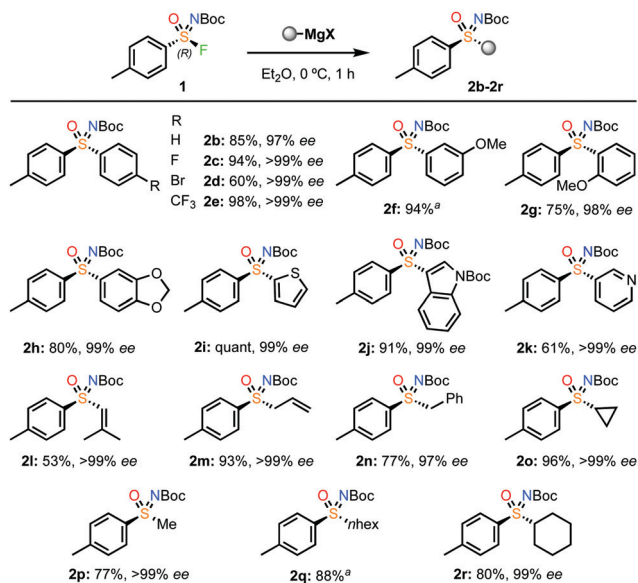


**Scheme 1** Effect of nitrogen protecting group on the enantiospecificity of the fluorination/Grignard reaction sequence. Fluorination reactions carried out on 0.50 mmol scale. Grignard reaction carried out on 0.25 mmol scale. All yields and %ee values are of isolated product. <sup>a</sup> ee of the salts recorded after reprotonation. <sup>b</sup> Comparable result obtained using CPME as solvent (See SI for further details). <sup>c</sup> Sequence also performed with the opposite enantiomer with comparable results.

The choice of N-group proved to be critical to the success of the sequence. While the NBoc derivative gave excellent enantiospecificity, the same sequence with NCbz gave reduced yields for each step, and a noticeable loss of ee in the Grignard reaction (**2a-Cbz**). The methyl carbamate was highly susceptible to racemisation, presumably due to reduced steric protection. The NPiv group performed similarly to the Boc group across the sequence retaining very high ee (**2a-Piv**).

The reaction of the NBoc-tolylsulfonimidoyl fluoride **1** was then explored with a wide variety of Grignard reagents to rapidly prepare a collection of highly enantioenriched sulfoximines (Scheme 2).<sup>24</sup> Grignard reagents were used as supplied or prepared by halogen exchange with iPrMgCl–LiCl, which gave comparable results.<sup>23</sup> Aryl Grignard reagents gave sulfoximines **2b–2h** in excellent yields and enantiospecificity for electron-rich and electron-poor reagents. Notably, these enantioenriched sulfoximines could not be accessed using oxidation/imidation

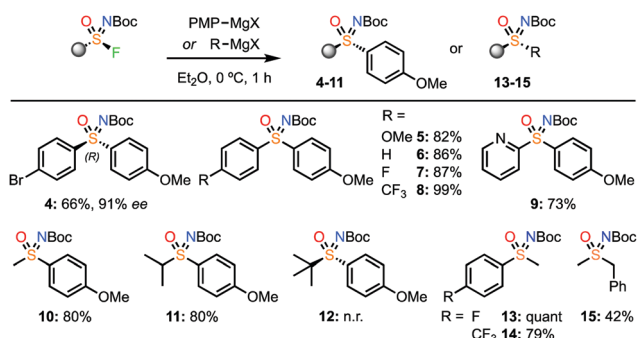




**Scheme 2** Reaction scope varying the Grignard reagents with sulfonimidoyl fluoride **1**. <sup>a</sup> ee not recorded as separation of enantiomers by HPLC not achieved.

approaches where chiral catalysts would be required to distinguish between electronically and sterically similar substituents on either side of the sulfur atom. Heteroaromatic Grignard reagents derived from thiophene, NBoc-indole and pyridine gave an excellent yield and ee (**2i-2k**). 2-Methyl-1-propenylmagnesium bromide gave enantiopure vinyl sulfoximine **2l**. Allyl and benzyl Grignard reagents were also successful (**2m** and **2n**). Finally, alkyl Grignard reagents, including methyl and cyclopropyl derivatives, gave aryl-alkyl sulfoximines in high yields and with excellent ee (**2o-2r**). The tolyl methyl sulfoximine derivative **2p** allowed confirmation of the stereochemical outcome, by comparison with a known compound.<sup>9b,23</sup> This indicated the substitution reaction proceeded with inversion, consistent with an  $\text{S}_{\text{N}}2$  process. Lithium  $\alpha$ -anions of sulfones and sulfoximines were also successfully reacted with **2b** with retention of ee.<sup>23</sup>

Next, the sulfonimidoyl fluoride was varied (Scheme 3). The 4-bromophenyl sulfonimidoyl fluoride, which was prepared in high ee,<sup>18</sup> gave sulfoximine **4** enantiospecifically on reaction with PMPMgBr. Notably, Br-Mg exchange was not observed,

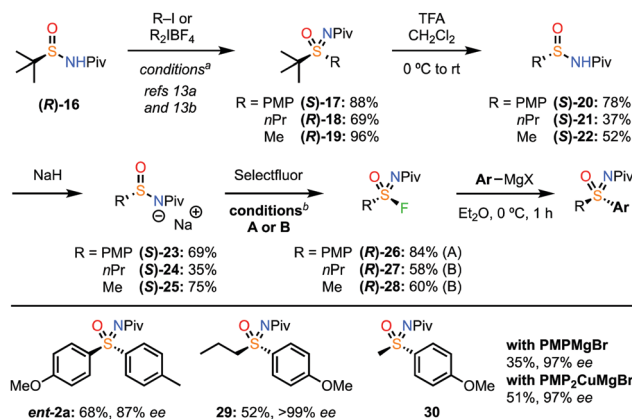


**Scheme 3** Variation of sulfonimidoyl fluoride.

retaining a handle for further functionalisation, and providing another advantage of the Grignard reagents over organolithium reagents. Varying the aryl group in a racemic series of sulfonimidoyl fluorides, including pyridine derivatives gave good yields (**5-9**). Pleasingly, the NBoc-methylsulfonyl fluoride gave a high yield using 1.2 equiv. of the Grignard reagent (**10**). The reaction also worked well with the *i*Pr derivative (**11**), however, *t*Bu derivative **12** did not form. The unreactive nature of the *t*Bu-sulfonimidoyl fluoride is consistent with the required nucleophile approach trajectory for  $\text{S}_{\text{N}}2$ . Additional methyl and benzyl derivatives were also demonstrated (**13-15**).

The preparation of enantioenriched sulfinamide derivatives remains challenging and there is very limited commercial availability. Previously we reported an enantioselective oxidation-imination-elimination sequence for 4-bromophenyl-sulfonimidoyl fluoride.<sup>18</sup> However, this is much less viable for alkyl derivatives. As such, we turned to the powerful recent reports from Maruoka for the preparation of sulfinamides and sulfoximines, starting from *t*-butylsulfinamide which is readily available in both enantiomers (Scheme 4).

Starting from sulfinamide (**R**)-**16**, we employed the NPiv group as described by Maruoka, which was shown to be suitable for retaining ee (**2a-Piv**, Scheme 1) and can also be readily removed to generate the NH sulfoximine.<sup>13,25</sup> Applying Maruoka's conditions for arylation and alkylation generated enantioenriched sulfoximines **17-19** and sulfinamides **20-22** in a process demonstrated to retain ee.<sup>13</sup> Deprotonation gave salts **23-25**. Applying the fluorination and Grignard sequence with PMP derivative (**S**)-**23** gave high ee for sulfoximine **ent-2a**. On the other hand, for the alkyl derivatives an alternative set of conditions were required to ensure high conversion in the formation of the sulfonimidoyl fluorides. A mixture of DMF and EtOH was necessary to ensure both reactivity and retention of ee. We were delighted to find that the propyl and even methyl derivatives gave complete retention of ee through this



**Scheme 4** Generation and reaction of enantioenriched sulfonimidoyl fluorides. <sup>a</sup> For alkylation: R-I, NaH, 15-crown-5, dioxane,  $70^\circ\text{C}$ , 24 h. For arylation:  $\text{R}_2\text{IBF}_4$ ,  $\text{Cu}(\text{OTf})_2$  (10 mol%), *i*Pr<sub>2</sub>EtN, DMSO,  $60^\circ\text{C}$ , 24 h. <sup>b</sup> Conditions A for **23**: selectfluor (2.0 equiv.), KOAc (2.0 equiv.), EtOH,  $0^\circ\text{C}$  to rt, 24 h. Conditions B for **24** and **25**: selectfluor (2.0 equiv.), DMF/EtOH (1:2),  $0^\circ\text{C}$  to rt, 24 h.



fluorination and substitution process (29,30), demonstrating that racemisation is prevented, and substitution occurs without deprotonation/elimination from the alkyl sulfonimidoyl fluorides. Interestingly, deprotonation of the sulfoximine product was detected with the methyl derivative under these conditions, resulting in intermolecular attack at the Piv group.<sup>23</sup> Instead, the use of the cuprate reagent prevented this, improved the yield of **30** and gave very high ee.

In summary, we report the preparation of enantioenriched sulfoximines using enantioenriched sulfonimidoyl fluorides. It is notable that N-Boc sulfonimidoyl fluorides react with Grignard reagents exclusively at sulfur without reduction and react stereospecifically with inversion. We report the first example of enantioenriched methyl sulfonimidoyl fluorides, and the stereospecific reaction of these motifs, avoiding elimination or racemisation. New conditions for enantiospecific fluorination of alkyl sulfonamides are presented to maximise conversion and retain ee in the sulfonimidoyl fluorides. While the NBoc and NPiv derivatives react stereospecifically, other N-groups such as Cbz and methyl carbamate are susceptible to racemisation. We expect the methods disclosed will provide further opportunities to exploit enantioenriched sulfonimidoyl fluorides and sulfoximines, particularly alkyl and methyl derivatives.

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## Conflicts of interest

There are no conflicts to declare.

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- See ESI† for further details.
- Grignard reagents were used as supplied or prepared by halogen exchange using *i*PrMgCl–LiCl, with comparable results.
- Alkylation of NBoc sulfonamides were successful, but cleavage of the NBoc group occurred preferentially to cleavage of the S–tBu bond on treatment with TFA.

