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, and have been marked increase in their use. Sulfoximine containing compounds in particular have entered clinical trials including roniciclib (Bayer) and ceralasertib (AstraZeneca). 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. 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, including facile methods for NH transfer, and new reagents containing the SON motif. Pre-formed methyl sulfoximine reagents have recently been demonstrated to undergo S_NAr reactions with heteroarenes. 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 1,3-butyl-sulfinamide as a chiral framework.

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 and Johnson, but reaction with organometallic reagents resulted in attack at chlorine and reduction to the sulfinamide (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). More recently, Sharpless demonstrated the reaction of phenyl-sulfonimidoyl fluorides with organolithium reagents. 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 sulfinimides bearing a chiral auxiliary on nitrogen. Building on the work of Reggelin, Stockman recently developed cyclic sulfinimides

Fig. 1 Clinical candidates containing stereochemically pure sulfoximines and electrophilic reagents for sulfoximine synthesis.
as separable diastereomers at sulfur, which reacted with Grignard reagents (Fig. 1d).17b Stereospecific conversion was achieved for phenyl sulfinimides whereas methyl derivatives gave lower stereoselectivity, leading to mixtures of S-stereoisomers, likely via an initial elimination. The auxiliary was removed using O2 and base.17b

Here we report the generation of highly enantoienriched aryl and alkyl sulfinimido-1-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 was successful to generate highly enantoienriched sulfoximines. Notably, an enantiopure methyl sulfinimido-1-fluoride reactant reacted without loss of ee.

The first reports of enantoienriched sulfinimido-1-fluorides were in 2020 from ourselves18 and Zuilhof19 for reaction with amines and phenolates respectively. Enantoienriched sulfinimido-1-fluorides present interesting potential as synthetic intermediates, and in chemical biology20 and polymer science.21 Fluoride ions were found to cause racemisation of the sulfinimido-1-fluorides through a degenerate exchange,22 which could be avoided by their sequestration.18,21 Aiming to prepare sulfoximines, we investigated the reaction of sulfinimido-1-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 counter-ion could scavenge fluoride and prevent fluoride-mediated racemisation of the sulfinimido-1-fluoride.

Initially we investigated NBoc-tolylsulfinimido-1-fluoride 1, prepared at high ee by our previously reported electrophilic fluorination of sulfinamide salts.18 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 nucleophiles18 saw a small increase in yield (1a, 2a-Piv 1.2 1.2 Et2O (0.3 M) 58 77 99 81 90 Isolated yield. 9 Reaction time 3 h at rt.)

Table 1. Optimisation of the reaction of sulfinimido-1-fluoride 1 with Grignard reagents

| Entry | M        | R-[M] equiv. | Solvent (conc.) | Yielda | ee (%)b |
|-------|----------|-------------|-----------------|--------|---------|
| 1     | MgBr     | 1.5         | THF (0.3 M)     | 31     | 58      |
| 2     | MgBr     | 1.5         | THF (0.3 M)     | 62     | 23 > 99 |
| 3     | MgBr     | 1.5         | 1,4-Dioxane (0.3 M) | 50 | 39 98 |
| 4     | MgBr     | 1.5         | Et2O (0.3 M)    | —      | 70      |
| 5     | MgBr     | 1.5         | Et2O (0.3 M)    | —      | 77      |
| 6     | MgBr     | 1.5         | Et2O (0.3 M)    | —      | 99      |
| 7     | MgBr     | 1.5         | Et2O (0.3 M)    | —      | 90      |
| 8     | MgBr     | 1.2         | Et2O (0.3 M)    | 81     | 90      |
| 9     | MgBr     | 1.2         | Et2O (0.3 M)    | 91     | > 99    |
| 10    | Li       | 1.2         | THF (0.3 M)     | 37     | > 99    |
| 11    | [CuAr]   | 1.2         | Et2O (0.3 M)    | 87     | 98      |
| 12    | ZnCl     | 1.2         | Et2O (0.3 M)    | 90     | 0 n/a   |

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

The choice of N-group proved to be critical to the success of the sequence. While the NBoc derivative gave excellent enantioselectivity, 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-tolysulfinimido-1-fluoride 1 was then explored with a wide variety of Grignard reagents to rapidly prepare a collection of highly enantoienriched sulfoximines (Scheme 2).24 Grignard reagents were used as supplied or prepared by halogen exchange with iPrMgCl-LiCl, which gave comparable results.23 Aryl Grignard reagents gave sulfoximines 2b–2h in excellent yields and enantioselectivity for electron-rich and electron-poor reagents. Notably, these enantoienriched sulfoximines could not be accessed using oxidation/imidation
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. This indicated the substitution reaction proceeded with inversion, consistent with an SN2 process. Lithium z-anions of sulfones and sulfoximines were also successfully reacted with $2b$ with retention of ee.\(^\text{23}\)

Next, the sulfonimidoyl fluoride was varied (Scheme 3). The 4-bromophenyl sulfonimidoyl fluoride, which was prepared in high ee,\(^\text{18}\) gave sulfoximine 4 enantiospecifically on reaction with PMPMgBr. Notably, Br–Mg exchange was not observed, 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 sulfinimidoyl fluorides, including pyridine derivatives gave good yields (5–9). Pleasingly, the NBoc-methylsulfinimidoyl fluoride gave a high yield using 1.2 equiv. of the Grignard reagent (10). The reaction also worked well with the iPr derivative (11), however, tBu derivative 12 did not form. The unreactive nature of the tBu-sulfinimidoyl fluoride is consistent with the required nucleophile approach trajectory for $S_N2$. 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-sulfinimidoyl fluoride.\(^\text{18}\) 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.\(^\text{13,25}\) Applying Maruoka's conditions for arylation and alkylation generated enantioenriched sulfoximines 17–19 and sulfinamides 20–22 in a process demonstrated to retain ee.\(^\text{13}\) 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 sulfinimidoyl 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
flourination and substitution process (29,30), demonstrating that racemisation is prevented, and substitution occurs without deprotonation/elimination from the allyl sulfonimidoxy fluorides. Interestingly, deprotonation of the sulfoxime product was detected with the methyl derivative under these conditions, resulting in intermolecular attack at the Piv group.23 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 sulfoximes using enantioenriched sulfonimidoxy fluorides. It is notable that N-Boz sulfonimidoxy fluorides react with Grignard reagents exclusively at sulfur without reduction and react stereospecifically with inversion. We report the first example of enantioenriched methyl sulfonimidoxy 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 sulfonimidoxy fluorides. While the NBoz 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 sulfonimidoxy fluorides and sulfoximes, particularly alkylic and methyl derivatives.

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Conflicts of interest

There are no conflicts to declare.

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