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Convenient Route to Secondary Sulfinates: Application to the Stereospecific Synthesis of α-C-Chiral Sulfonamides

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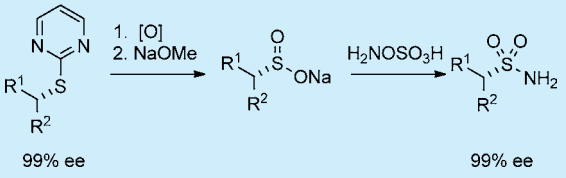
Supporting Information

ABSTRACT: A convenient synthesis of α-chiral sulfinates from readily available precursors has been accomplished via the corresponding heterocyclic thioethers and sulfones. Treatment of the sulfinates with hydroxylamine sulfonate in aqueous solution provides α-C-chiral primary sulfonamides in good yield (14 examples) with retention of stereochemical purity.



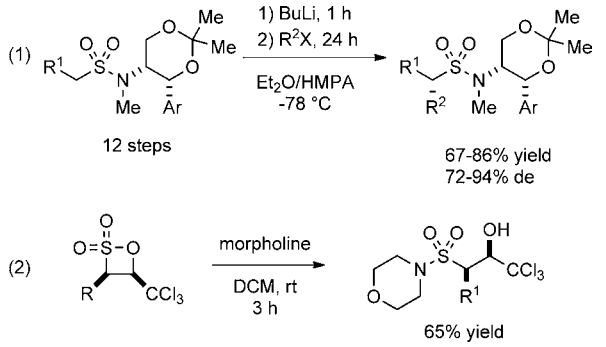
Sulfonamides have been a mainstay of pharmaceuticals since the discovery of the first synthetic antibacterial, sulfamidochrysoidine, in 1932.[1,2] By comparison, synthetic homochirality arrived to the field only lately, but over the last four decades single enantiomer drugs increasingly dominate the landscape of new molecular entities.[3,4] Despite the frequency with which medicinal chemists now employ both stereogenicity and sulfonamides in the design of therapeutics, to the best of our knowledge no example of a carbon stereocenter bearing the sulfur atom of a sulfonamide can be found in the entire pharmacopeia.[5]

Optically active sulfonamides have been known at least since the 1938 description of a Reychler's acid derivative.[6] Oppolzer's use of that molecule to influence the stereochemical course of reactions inaugurated a productive 30 years of sulfonamide use in asymmetric synthesis as auxiliaries,[7] ligands for reagents,[8] or catalysts[9−17] and, most recently, as organocatalysts.[18−21] Notably, most of these useful molecules can be described as sulfonylated chiral amines. It can further be said that none of them feature a secondary carbon stereocenter bound to sulfur.

It would seem that the three-dimensional display of oxygens and nitrogen in a sulfonamide might be usefully complemented by chirality on the immediately adjacent carbon. We suggest that the dearth of such compounds might be linked to the lack of robust and practical methods for the synthesis of a single enantiomer at the sulfur-bearing carbon, the first of which was published during the preparation of this manuscript.[22] This report describes a facile and functional group tolerant approach to this neglected class of molecules starting from readily accessible optically active thioethers.

In the course of our research on multiple drug discovery programs, we required a variety of enantiopure α-C-chiral primary sulfonamides. Chromatographic separation of racemates provided initial materials, but on larger scale this method became increasingly impractical. An examination of the literature at that time suggested only two known approaches for asymmetric synthesis (Scheme 1): (1) an auxiliary mediated alkylation as exemplified by the method of Enders[23] (eq 1) or (2) the opening of β-sultones and sultams as described by Peters[24,25] (eq 2).

Scheme 1. Methods To Synthesize α-C-Chiral Sulfonamides



Enders' method represents the most diastereoselective alkylation procedure described to date.[23−26] Unfortunately, the auxiliary itself requires a 10-step synthesis and must ultimately be cleaved by harsh acidic conditions. Even after such vigorous treatment, a methyl substituent remains on the sulfonamide nitrogen, limiting the scope of accessible products and making it unsuitable to our needs. Alternatively, β-sultams or β-sultones available from chiral base-catalyzed cyclocondensation of sulfonyl chlorides and sulfonyl imines or aldehydes can be opened by nucleophiles in stereoretentive fashion.[24,25] In this case, the sulfonamide *N*-substituent might be more easily modified, but products are otherwise limited to β-heterosulfonamides in one diastereomeric series in which the α-substituent is an electron-deficient functionality lacking protons.

In their reports, both Enders and Peters echo an earlier observation by Cram:[27] the most commonly utilized method for synthesis of sulfonamides, the reaction of an amine with a sulfonyl chloride, proceeds with epimerization of an adjacent secondary carbon stereocenter dependent on the nature of the amine and sulfonylating agent (Figure 1). We hypothesized that by directly engaging the sulfur in an electrophilic amidation,[28] the implicated achiral sulfene intermediate in the *N*-nucleophilic

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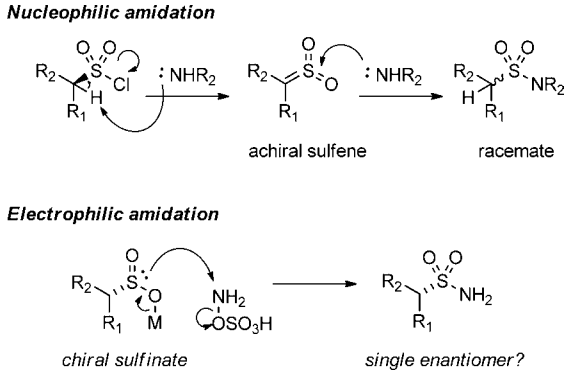
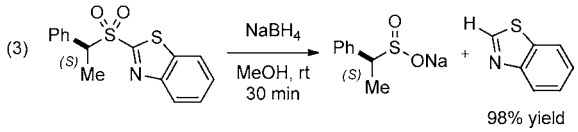


Figure 1. Nucleophilic amidation via sulfene intermediate vs direct electrophilic amidation.

process might be avoided and the adjacent carbon stereocenter survive unperturbed (Figure 1). A robust synthesis of α-*C*-chiral sulfonamides would then depend on availability of the corresponding sulfinates.

In developing a convenient route to chiral sulfinates, we were inspired by a report of the synthesis of optically enriched sodium (*S*)-1-phenylethanesulfinate by the action of sodium borohydride on the corresponding benzothiazole sulfone (eq 3).[29] While effective, Ueno's process affords sulfinates along with boron byproducts, requiring additional isolation or purification steps to obtain pure sulfinates.[30] As we aimed to examine further reactions with nitrogenous oxidants, we desired a protocol that would allow isolation of sulfinates without such contaminants.

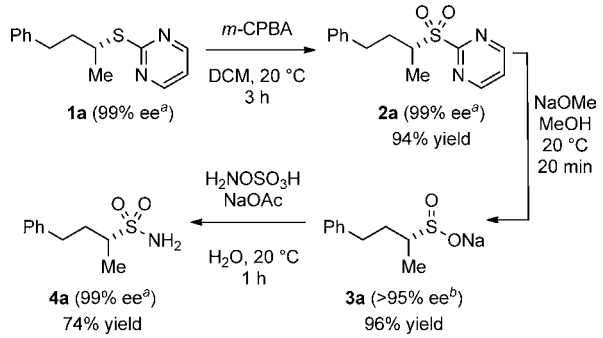


Ultimately, we would employ thioethers of a different heterocycle as starting materials. 2-Mercaptopyrimidine bears several practical advantages as a sulfur source and blocking group. The material itself is a commercially available, nonodiferous solid. Numerous methods for the generation of optically enriched pyrimidinyl thioethers from halides,[31,32] alcohols,[33,34] epoxides,[35,36] enones,[37] and allylic alcohols[38] can be found in the literature. The smallest possible resultant thioethers are suitably nonvolatile to be handled without special precaution and contain a chromophore for UV visualization. In our experience, pyrimidinyl sulfones have proven adequately stable for isolation, purification and storage, but can be readily cleaved by a variety of nucleophiles to liberate corresponding sulfinate salts free of other contaminants.[39,40]

We tested our synthetic plan on optically pure thioether **1a** (Scheme 2). Peracid oxidation cleanly afforded pyrimidinyl sulfone **2a** of similarly high enantiomeric excess. The pyrimidine blocking group was cleaved quickly by sodium methoxide in methanol to afford pure sodium sulfinate **3a** after trituration in Et_2O. Treatment of **3a** with hydroxylamine sulfonic acid (HOSA) in aqueous solution generated (*R*)-4-phenylbutane-2-sulfonamide (**4a**), which crystallized directly from the aqueous reaction mixture in 74% yield. Most importantly, the integrity of the lone stereocenter was maintained throughout the process.

Having validated our approach to enantiopure α-*C*-chiral primary sulfonamides, we next set out to define the scope of the sequence. Standard peracid oxidation afforded excellent yields of pyrimidinyl sulfones regardless of steric congestion at the adjacent carbon (Scheme 3, **2a**−**e**,**l**). Benzylic thioethers also

Scheme 2. Stereospecific Synthesis of (*R*)-4-Phenylbutane-2-sulfonamide



[a]Determined by chiral HPLC analysis. [b]Determined by chiral HPLC analysis after treatment with iodomethane.

perform well under these conditions (**2f**,**g** and **2m**,**n**). While affording slightly lower yields in general (**2a**,**f**,**n** method A vs method B), Noyori's tungsten-catalyzed oxidation[41] proved effective in selectively converting thioethers without competing alkene epoxidation (**2j**,**k**). Sulfones with vicinal oxidation were readily accessed (**2h**,**i**,**n**) with the caveat that the oxygen must be protected to avoid elimination via Smiles rearrangement.[42] It was noted that the aqueous solubility of small oxygenated sulfone **2h** complicated extractive isolation according to our standard procedures.

In general, all pyrimidinyl sulfones were cleaved with sodium methoxide in methanol. The resulting sulfinate salts were subsequently amidated by the action of HOSA in aqueous reaction media (Scheme 3). It was observed that beginning the deprotection reaction at 0 °C afforded the highest yields.[43] Three variations of the general procedure were adopted to facilitate isolation and maximize yield of the products. Aliphatic sulfinates **3a**−**d**,**l** were precipitated from ethereal solvents after removal of methanol. The isolated salts reacted rapidly with amidating reagent in water to afford homochiral sulfonamides which could be isolated in uniformly high yields and purity by extraction (**4b**,**c**) or crystallization from the reaction mixture (**4a**,**l**). Solutions of less crystalline (**3e**,**j**,**k**) or highly hygroscopic (**3h**,**i**) sulfinates were concentrated *in vacuo* and then treated with HOSA in water without intervening isolation. The 2-methoxypyrimidine byproduct of the deprotection did not negatively impact the efficiency of the amination as evidenced by the similarly high overall yields of the corresponding sulfonamides (**4e**,**h**−**k**).[44] In the case of terminal alkenes, maintenance of reaction temperature below 40 °C and ensuring pH <10 in the amidation step was found to suppress trace reduction caused by the formation of diimide from HOSA in situ.[45]

Finally, we observed that the highest yields of benzylic sulfonamides (**4f**,**g**,**m**,**n**) were obtained when the methanolysis was performed entirely at 0 °C and the sulfinates treated with aqueous amidating reagents in the same pot. This last variation does require the longest reaction times (1−2 h for deprotection versus minutes and 6−12 h for amidation in methanol/water as compared to <1 h), but this treatment was found to prevent formation of styrene byproducts arising from elimination of sulfur species and was found to be generally applicable to all substrates.

Conducting these reactions on preparative scale proved tractable (Scheme 4). Thioether **1a** was converted to sulfonamide **4a**

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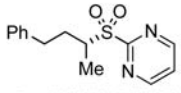
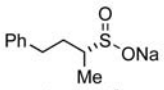
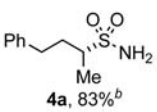
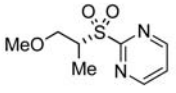
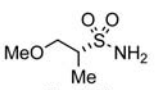
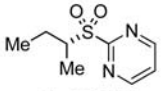
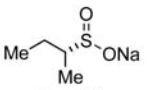
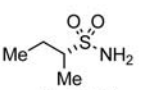
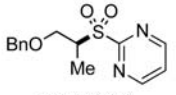
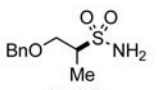
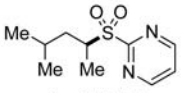
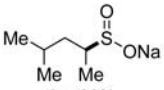
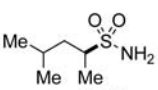
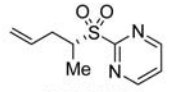
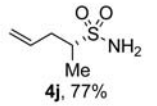
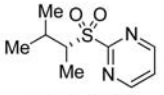
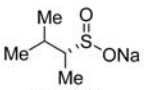
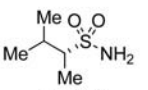
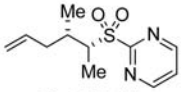
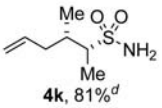
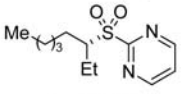
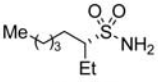
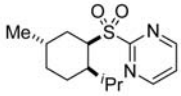
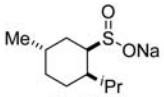
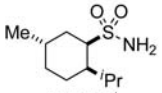
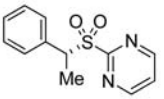
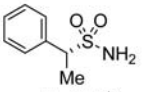
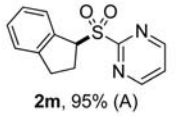
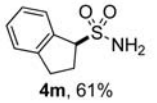
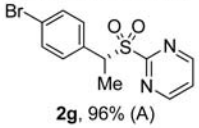
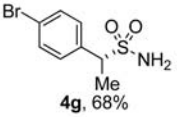
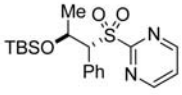
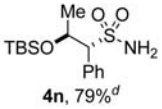
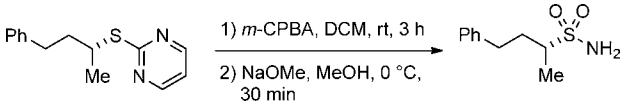
Scheme 3. Three-Step Conversion of 2-Pyrimidinyl Thioethers to Primary α-C-Chiral Sulfonamides

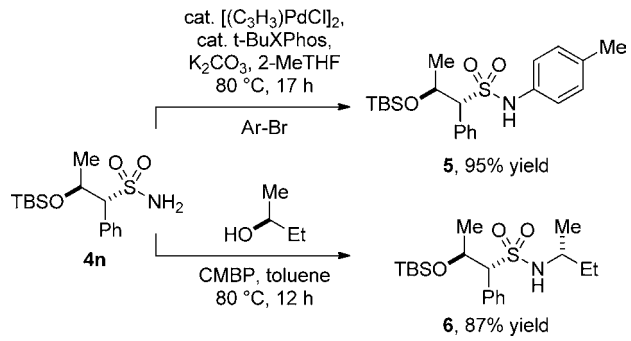
sulfone **2** yield % (method)	sulfinate **3** yield %	sulfonamide **4** yield % from sulfone	sulfone **2** yield % (method)	sulfinate **3** yield %	sulfonamide **4** yield % from sulfone
 **2a**, 94%(A); 70%(B)	 **3a**, 99%[a]	 **4a**, 83%[b]	 **2h**, 49% (A)	—	 **4h**, 83%
 **2b**, 88% (A)	 **3b**, 95%	 **4b**, 84%[c]	 **2i**, 77% (A)	—	 **4i**, 90%
 **2c**, 95% (A)	 **3c**, 80%	 **4c**, 78%[c]	 **2j**, 77% (B)	—	 **4j**, 77%
 **2d**, 96% (A)	 **3d**, 96%	 **4d**, 91%	 **2k**, 78% (B)	—	 **4k**, 81%[d]
 **2e**, 97% (A)	—	 **4e**, 94%	 **2l**, 94% (A)	 **3l**, 89%[d]	 **4l**, 78%[d]
 **2f**, 95% (A); 72%(B)	—	 **4f**, 82%[b]	 **2m**, 95% (A)	—	 **4m**, 61%
 **2g**, 96% (A)	—	 **4g**, 68%	 **2n**, 96% (A); 77%(B)	—	 **4n**, 79%[d]

[a]>95% ee determined by chiral HPLC analysis of methyl sulfone derivative. [b]>99% ee determined by chiral HPLC analysis. [c]>99% ee determined by chiral HPLC analysis of benzoyl sulfonamide. [d]>95:5 dr determined by ^{1}H NMR analysis.

Scheme 4. Preparative-Scale Synthesis of (*R*)-4-Phenylbutane-2-sulfonamide



Scheme 5. *N*-Arylation and Alkylation of an α-C-Chiral Sulfonamide



in 76% yield over three operations and 74% overall yield from commercial, optically pure alcohol.[46] The efficiency of each step coupled with the physical properties of the intermediates obviated the need for any purification beyond phase separation.

The primary sulfonamide products (**4**) and the chiral sulfinates (**3**) generated in this fashion can be further functionalized without effect on the adjacent carbon stereocenter. Palladium coupling[47] of **4n** provides aryl sulfonamide derivative **5** and monoalkylation of **4n** can be accomplished via Mukaiyama's method[48] to afford the unusual stereoarray of **6**, both reactions proceeding without compromise of the original stereocenter

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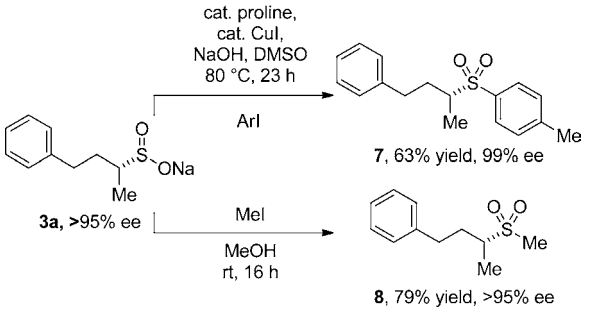
Scheme 6. *S*-Arylation and Alkylation of Chiral Sulfinates



(Scheme 5). Alkylation and copper-catalyzed arylation of sulfinate salt **3a** proceed smoothly to provide divergent one-step access to chiral sulfones (Scheme 6).

In summary, we have demonstrated a novel, stereospecific route to α-*C*-chiral sulfonamides. This functionality is prepared via mild, stepwise increases in sulfur oxidation state which are compatible with a range of functionality and largely independent of the substitution at the carbon stereocenter. Efforts to further define the scope of this process and the utility of the sulfinate intermediates are currently ongoing in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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