

Stereoselective Synthesis of β -Substituted β -Amino Sulfones and Sulfonamides via Addition of Sulfonyl Anions to Chiral *N*-Sulfinyl Imines

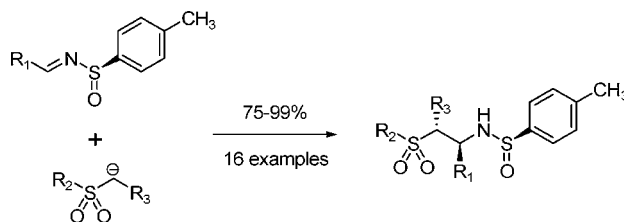
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ABSTRACT



A highly stereoselective synthesis of β -amino sulfones and sulfonamides via addition of sulfonyl anions to chiral *N*-sulfinyl imines is described. The addition reaction proceeds in good yield (75–99%) and stereoselectivity.

Optically active β -amino sulfones and β -amino sulfonamides have been identified as valuable molecules which display interesting biological properties. β -Amino sulfones in particular have been identified as HIV protease inhibitors,¹ MMP-13 inhibitors for treatment of rheumatoid arthritis,² and DNA alkylating agents for cancer treatment.³ Additionally, β -amino sulfones are useful synthetic intermediates as exemplified by their utility in the synthesis of allylic amines.⁴ Likewise, β -amino sulfonamides are important structural motifs found in biologically active molecules.⁵ Synthetic

methodologies for the preparation of racemic β -amino sulfones and sulfonamides have previously been reported.⁶ Their asymmetric synthesis has also been achieved via aza-Michael addition of chiral amines to α,β -unsaturated sulfones and sulfoxides.⁷ The same process employing achiral amines and optically active α,β -unsaturated sulfones and sulfoxides as reactive partners has also been described.⁸ However, in many cases these reactions proceeded with low stereoselectivity and separation of the corresponding diastereomeric products was laborious.

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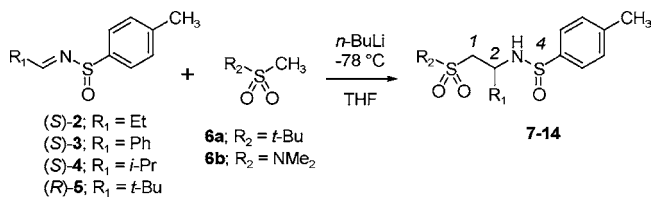
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Herein, we describe an efficient method for the synthesis of optically active substituted β -amino sulfones and sulfonamides via addition of lithiated sulfones/sulfonamides (sulfonyl anions) to chiral *N*-sulfinyl imines. This methodology represents a new application for chiral *N*-sulfinyl imines.⁹ The addition of sulfonyl anions to *N*-sulfinyl imines for rapid access to optically active β -amino sulfones and sulfonamides has not been extensively explored.¹⁰ However, addition of chiral sulfonyl anions to chiral *N*-sulfinyl imines has been reported.¹¹ Recently, the addition of lithiated difluoromethyl phenyl sulfone to *N*-sulfinyl imines for the synthesis of α -difluoromethylamines was reported.¹²

N-sulfinyl imines were synthesized for this study from commercially available (*S*)-*p*-tolyl sulfinamide (for imines **2–4**) and (*R*)-*p*-tolyl sulfinamide (for imine **5**) following reported procedures.¹³ *N*-Sulfinyl imines bearing different R_1 groups (Et, Ph, *i*-Pr, *t*-Bu) were chosen for this study to investigate the influence of substitution on the stereochemical outcome of the addition reactions. First, we investigated the synthesis of β -substituted β -amino sulfones/sulfonamides. Addition of sulfonyl anions to the chiral *N*-sulfinyl imines was expected to occur with good facial selectivity to form a new stereogenic center with an adequate level of stereocontrol. Initially, addition to imines was explored by reacting the sulfonyl anion (1.0 equiv) derived from *tert*-butyl methyl sulfone (**6a**) and *n*-butyllithium with *N*-sulfinyl imine **R-5** at low temperature (-78 °C).¹⁴ We observed clean addition of the lithiated sulfone to give β -aminosulfone **13**. However, unreacted *N*-sulfinyl imine was observed even after warming the reaction mixture (0 °C). After some experimentation, we found that complete and rapid (20 min) addition to the imine could be achieved by using excess sulfonyl anion to give **13** in excellent (99%) yield as a 10:1 mixture of diastereomers (entry 7, Table 1). The stereochemistry of the newly created stereogenic center was determined to be *R* based on single-crystal X-ray analysis.¹⁵ Furthermore, no difference in yield and selectivity was observed when using other bases such as NaHMDS. We then investigated the addition of lithiated *N,N*-dimethyl sulfonamide **6b** to imine **R-5** under the same conditions. In this reaction, addition occurred cleanly to afford β -amino sulfonamide **14** in 80% yield albeit with lower selectivity (entry 8). With the optimized conditions,

Table 1. Addition of Lithiated Sulfones/Sulfonamides to Chiral *N*-Sulfinyl Imines **2–5**



entry	imine	sulfone/ sulfonamide	major product	yield (%) ^a	dr ^b
1	(<i>S</i>)- 2	6a	(2 <i>R</i> ,4 <i>S</i>)- 7	76	3:1 ^c
2	(<i>S</i>)- 2	6b	(2 <i>R</i> ,4 <i>S</i>)- 8	75	3:1 ^c
3	(<i>S</i>)- 3	6a	(2 <i>R</i> ,4 <i>S</i>)- 9	84	3:1 ^c
4	(<i>S</i>)- 3	6b	(2 <i>R</i> ,4 <i>S</i>)- 10	82	8:1 ^c
5	(<i>S</i>)- 4	6a	(2 <i>R</i> ,4 <i>S</i>)- 11	81	3:1 ^c
6	(<i>S</i>)- 4	6b	(2 <i>R</i> ,4 <i>S</i>)- 12	91	3:1 ^c
7	(<i>R</i>)- 5	6a	(2 <i>S</i> ,4 <i>R</i>)- 13	99	10:1 ^d
8	(<i>R</i>)- 5	6b	(2 <i>S</i> ,4 <i>R</i>)- 14	80	6:1 ^d

^a Isolated yield. ^b Determined by HPLC analysis of crude mixtures. ^c Diastereomeric ratio for (2*R*,4*S*):(2*S*,4*S*) isomers. ^d Diastereomeric ratio for (2*S*,4*R*):(2*R*,4*R*) isomers.

we explored addition of sulfonyl anions derived from **6a** and **6b** to other *N*-sulfinyl imines. The results are shown in Table 1.¹⁶

Addition of lithiated sulfone **6a** to imine *S*-**2** cleanly delivered β -amino sulfone **7** in moderate yield without detecting enamine byproducts arising from α -deprotonation of the imine (entry 1). Likewise, lithiated sulfonamide **6b** added to imine *S*-**2** to give compound **8** with similar yield and selectivity (entry 2). Then, addition of lithiated sulfone **6a** to imine *S*-**3** gave the β -amino sulfone **9** as a 3:1 mixture of diastereomers (entry 3). In contrast, when lithiated sulfonamide **6b** was reacted with imine *S*-**3** the reaction proceeded with slightly better selectivity to give an 8:1 mixture of diastereomers (entry 4). Addition of lithiated sulfone **6a** or sulfonamide **6b** to imine *S*-**4** gave the corresponding products **11** and **12** in good yields but poor diastereoselectivities were observed (entries 5 and 6). The poor diastereoselectivity observed in the addition of lithiated sulfone **6a** to *N*-sulfinyl imines *S*-**2**, *S*-**3**, and *S*-**4** (entries 1, 3, and 5) suggests that similar levels of stereoinduction are obtained from Et, Ph, or *i*-Pr groups in the imine.

We then turned our attention to the synthesis of α,β -substituted β -amino sulfones/sulfonamides. Our interest was to investigate the stereochemical outcome of addition reactions when using prochiral sulfonyl anions to create two new stereogenic centers. As mentioned earlier, the stereochemistry of the β -stereocenter in the product arises from facial selectivity on the *N*-sulfinyl imine moiety. However, it was important to determine the level of stereoinduction that could be achieved for the α -stereocenter of the addition products.

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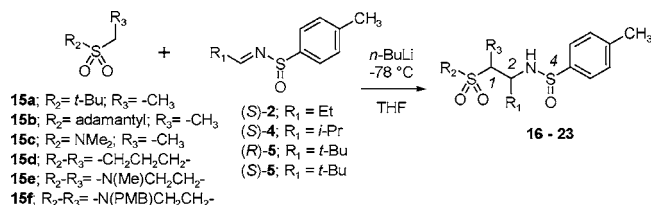
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(15) Single-crystal X-ray analysis was performed for β -amino sulfone **16** and the configuration of the rest of the addition products was assigned by analogy based on the proposed transition state.

Toward this end, we explored the addition of lithiated *tert*-butyl ethyl sulfone **15a** to imine *R*-5. We were delighted to see that addition occurred with excellent stereocontrol for both α - and β -stereocenters to afford disubstituted β -amino sulfone **16** as a single diastereomeric product in 90% yield (entry 1, Table 2). The absolute stereochemistry for this

Table 2. Synthesis of α,β -Substituted β -Amino Sulfones/Sulfonamides via Addition of Sulfonyl Anions to Chiral *N*-Sulfinyl Imines



entry	imine	sulfone/ sulfonamide	major product	yield (%) ^a	dr ^b
1	(<i>R</i>)-5	15a	(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)- 16	90	>99:1 ^c
2	(<i>R</i>)-5	15b	(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)- 17	92	>99:1 ^c
3	(<i>R</i>)-5	15c	(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)- 18	85	>99:1 ^c
4	(<i>R</i>)-5	15d	(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)- 19	92	>99:1 ^c
5	(<i>S</i>)-2	15d	(1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)- 20	76	10:1 ^d
6	(<i>S</i>)-4	15d	(1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)- 21	86	7:1 ^d
7	(<i>R</i>)-5	15e	(1 <i>R</i> ,2 <i>S</i> ,4 <i>R</i>)- 22	90	>99:1 ^c
8 ^e	(<i>S</i>)-5	15f	(1 <i>S</i> ,2 <i>R</i> ,4 <i>S</i>)- 23	91	>99:1 ^d

^a Isolated yield. ^b Determined by HPLC analysis of crude mixtures. ^c Diastereomeric ratio for (1*R*,2*S*,4*R*):(1*R*,2*R*,4*R*) isomers. ^d Diastereomeric ratio for (1*S*,2*R*,4*S*):(1*S*,2*S*,4*S*) isomers. ^e NaHMDS was used for deprotonation.

compound was assigned as (1*R*,2*S*,4*R*)-**16** by single-crystal X-ray analysis, Figure 1. The stereochemical outcome of the

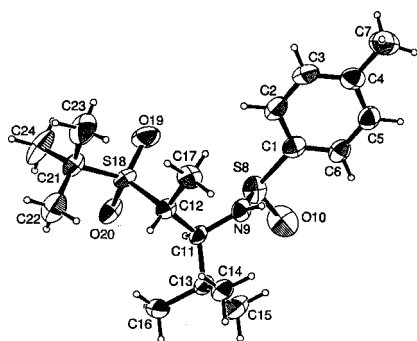


Figure 1. ORTEP diagram for β -amino sulfone **16**.

reaction can be explained on the basis of an open transition state in which the sulfonyl anion attacked the *Re*-face of the imine resulting in stereoselective formation of the β -stereocenter. The α -stereocenter was controlled by the approach of the sulfonyl anion in such a manner that the methyl group maintained antiperiplanar orientation with respect to the *tert*-

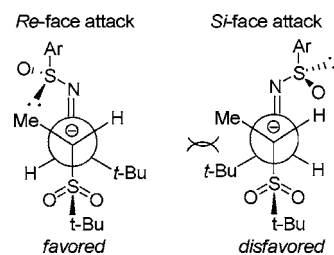


Figure 2. Proposed transition state for addition of lithiated sulfone **15a** to *N*-sulfinyl imine *R*-5.

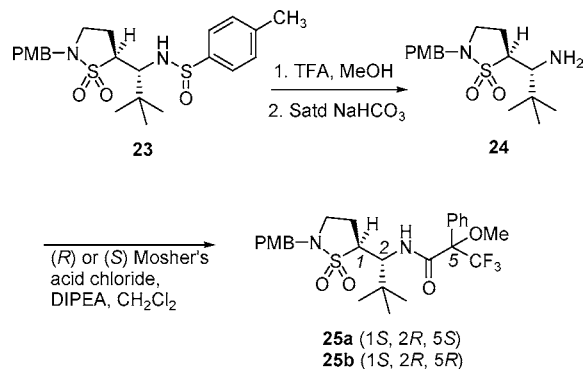
butyl group in the imine (Figure 2). Similarly, addition of lithiated adamantyl ethyl sulfone **15b** to imine *R*-5 gave disubstituted β -amino sulfone **17** as a single diastereomer in excellent yield (entry 2).

The synthesis of α,β -substituted β -amino sulfonamides was also investigated. The stereoinduction for the reaction of lithiated *N,N*-dimethyl sulfonamide **15c** with imine *R*-5 was also remarkable giving sulfonamide product **18** as a single diastereomer in good yield (entry 3). Likewise, addition of lithiated sulfolane (**15d**) to imine *R*-5 cleanly delivered cyclic sulfone **19** in excellent yield (92%) as a single diastereomer (entry 4). However, when we investigated the addition of lithiated sulfolane (**15d**) to imines *S*-2 and *S*-4, a decrease in yield and selectivity was observed (entries 5 and 6). These results are in agreement with the proposed open transition state whereby smaller R_1 substituents in the imine moiety led to diminished facial selectivity on the imine. Addition of lithiated *N*-methyl sultam **15e** to imine *R*-5 gave a single diastereomeric product **22** in excellent yield (entry 7). Deprotonation of *N*-PMB sultam **15f** with NaHMDS, followed by treatment with imine *S*-5 gave addition product **23** as a single diastereomer in nearly quantitative yield (entry 8).

The stereochemical outcome of the sultam addition product **23** was established via proton NMR analysis of the resultant Mosher's amide.¹⁷ Thus, as shown in Scheme 1, removal of the *N*-sulfinyl group of **23** followed by basic workup resulted in amine **24**. Treatment of the amine **24** with commercially available *R*- or *S*-Mosher's acid chloride in the presence of DIPEA afforded the Mosher's amide **25a** or **25b**, respectively. Stereochemical assignment of the α -center (C2) was determined to be *R* by comparison of the proton chemical shift of amides **25a** and **25b**.¹⁷

Further NMR studies (nOe and coupling constant) were carried out to establish the configuration of the β -center (C1). Thus, fixing the stereogenic center at C2 (for each of the amides, **25a** and **25b**) there were two possible diastereomers, based on the chirality at C1. For each diastereomer, there were three possible major conformers around the C1–C2 bond, one conformation in which H1 and H2 were anti and two in which H1 and H2 were gauche with respect to one

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Scheme 1. Synthesis of Mosher's Amide from Sultam **23**

another. The observed H1/H2 coupling constant of 4.7 Hz for **25a** was consistent with H1 and H2 in a gauche relationship. Furthermore, nOe was observed between H1 and H2 confirming the gauche conformation (Figure 3). Additionally, protons of the *tert*-butyl group (attached to C2) exhibited nOe with H1 and H1'. These detailed NMR studies clearly demonstrated that the configuration at the β -center (C1) for compound **25a** was *S*.

In summary, we have successfully developed a simple and effective approach for the stereocontrolled synthesis of β -amino sulfones and sulfonamides utilizing chiral *N*-sulfinyl imines. The presented method involves addition of lithiated

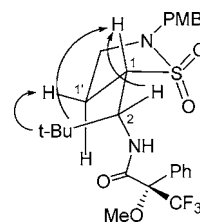


Figure 3. Observed nOe effects in Mosher's amide **25a**.

sulfones and sulfonamides to chiral *N*-sulfinyl imines and delivers mono- and disubstituted β -amino sulfones/sulfonamides in excellent yields. The reaction proceeded with good selectivity in the synthesis of β -substituted β -amino sulfones/sulfonamides and gave remarkable stereoselectivity in the synthesis of α,β -disubstituted β -amino sulfones/sulfonamides. The described methodology is an important tool that should find wide application in the synthesis of biologically important molecules.

Supporting Information Available: Experimental procedures, spectral data, crystallographic data, and copies of spectra for selected compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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