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

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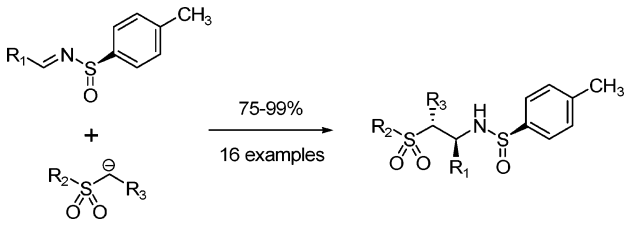
ABSTRACT



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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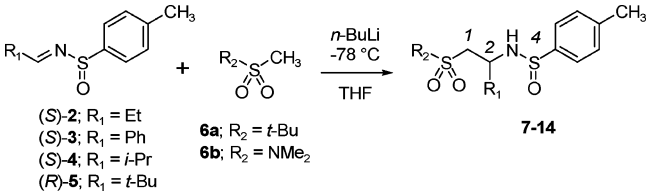
Herein, we describe an efficient method for the synthesis of optically active substituted β-amino sulfones and sulfonamides via addition of lithiated sulfones/sulfonamides (sulfonyl anions) to chiral *N*-sulfinyl imines. This methodology represents a new application for chiral *N*-sulfinyl imines.[9] 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 sulfinyl 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	(*S*)-**2**	**6a**	(2*R*,4*S*)-**7**	76	3:1[c]
2	(*S*)-**2**	**6b**	(2*R*,4*S*)-**8**	75	3:1[c]
3	(*S*)-**3**	**6a**	(2*R*,4*S*)-**9**	84	3:1[c]
4	(*S*)-**3**	**6b**	(2*R*,4*S*)-**10**	82	8:1[c]
5	(*S*)-**4**	**6a**	(2*R*,4*S*)-**11**	81	3:1[c]
6	(*S*)-**4**	**6b**	(2*R*,4*S*)-**12**	91	3:1[c]
7	(*R*)-**5**	**6a**	(2*S*,4*R*)-**13**	99	10:1[d]
8	(*R*)-**5**	**6b**	(2*S*,4*R*)-**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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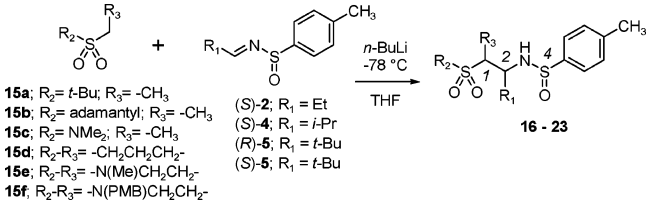
(14) See the Supporting Information for detailed experimental procedures for addition reactions and synthesis of imines and sulfones.

(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.

(16) A number of addition products were *N*-deprotected under acidic conditions. The *N*-sulfinyl group was readily cleaved by treatment of methanolic solutions of addition products with 4 M HCl in dioxanes to give the corresponding amine hydrochloride salts.

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	(*R*)-**5**	**15a**	(1*R*,2*S*,4*R*)-**16**	90	>99:1[c]
2	(*R*)-**5**	**15b**	(1*R*,2*S*,4*R*)-**17**	92	>99:1[c]
3	(*R*)-**5**	**15c**	(1*R*,2*S*,4*R*)-**18**	85	>99:1[c]
4	(*R*)-**5**	**15d**	(1*R*,2*S*,4*R*)-**19**	92	>99:1[c]
5	(*S*)-**2**	**15d**	(1*S*,2*R*,4*S*)-**20**	76	10:1[d]
6	(*S*)-**4**	**15d**	(1*S*,2*R*,4*S*)-**21**	86	7:1[d]
7	(*R*)-**5**	**15e**	(1*R*,2*S*,4*R*)-**22**	90	>99:1[c]
8[e]	(*S*)-**5**	**15f**	(1*S*,2*R*,4*S*)-**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

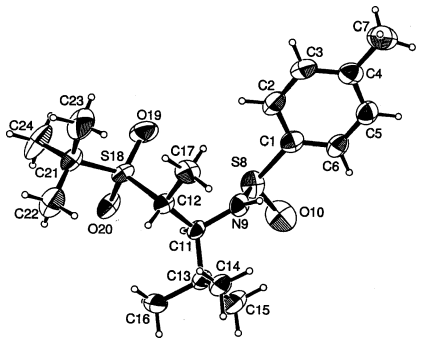


Figure 1. ORTEP diagram for *β*-amino sulfone **16**.

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*-

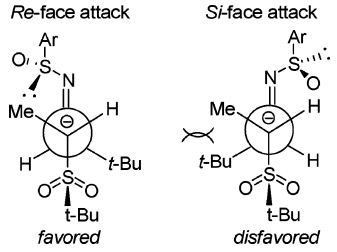


Figure 2. Proposed transition state for addition of lithiated sulfone **15a** to *N*-sulfinyl imine *R*-**5**.

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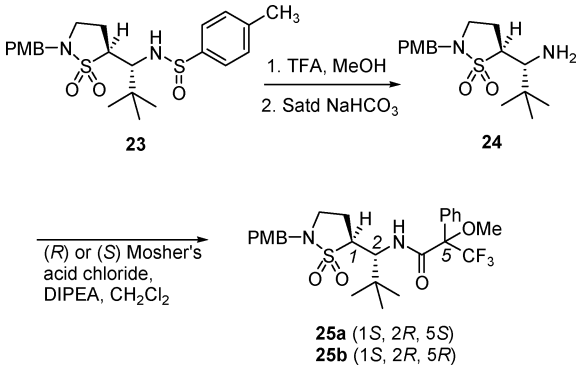
Scheme 1. Synthesis of Mosher's Amide from Sultam **23**



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

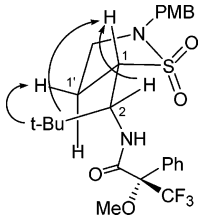


Figure 3. Observed nOe effects in Mosher's amide **25a**.

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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