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Practical and stereoselective synthesis of β-amino sulfones from alkyl phenyl sulfones and *N*-(*tert*-butylsulfinyl) aldimines†

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A practical and straightforward approach for the highly stereoselective synthesis of β-amino sulfones was developed. With lithium bis(trimethylsilyl)amide as the base, the corresponding sulfone-stabilized carbanion derived from alkylphenyl sulfone can be transferred to *N*-(*tert*-butylsulfinyl) aldimines in excellent yields and with high diastereoselectivity.

The β-amino sulfone motif is a predominant substructure of many bioactive compounds,[1] and it was found to play important roles in a variety of enzyme inhibitors such as novel HIV protease inhibitors[2] and matrix metalloproteinase inhibitors,[3] among others. Additionally, β-amino sulfones are valuable intermediates in the preparation of cyclic and acyclic nonproteinogenic α-amino acids,[4] amino alcohols,[5] alkaloids,[6] carbohydrate derivatives,[7] and nitrogen heterocycles,[8] taking advantage of the basis that sulfones can be involved in versatile synthetic transformations,[9] such as electrophilic substitution in the α-position, replacement of the sulfone group with other functional groups, and reductive cleavage of the sulfone group.

Despite its importance for applications related to the life sciences, the synthesis of chiral β-amino sulfones has not been well explored. Currently, the commonly used method involves a synthetic sequence starting from natural amino acids,[10] which represents a viable approach to construct enantiopure β-amino sulfones. However, tedious multi-step transformations did not allow for a rapid and green synthesis of this kind of compounds. The other synthetic strategy involves asymmetric aza-Michael addition to alkenyl sulfones.[11] For example, Enders reported the conjugate addition of an enantiopure ammonia equivalent (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP) or (*R*,*R*,*R*)-2-amino-3-methoxymethyl-azabicyclo-[3.3.1]octane (RAMBO) to alkenyl sulfones to provide a novel access to enantiopure β-amino sulfones.[12] Despite the prominence of this reaction, the relatively expensive chiral auxiliary SAMP or RAMBO limits its practical uses in organic synthesis. Also, this reaction suffers from low yield and diastereoselectivity. Ideally, we can envision that a more straightforward (arylsulfonyl)alkylation of chiral imines with alkylaryl sulfone would provide a highly attractive route to the target structures. However, this approach appears to be underutilized: only scattered examples of direct (arylsulfonyl)alkylation of imines as synthetic steps towards constructing nitrogen heterocycles have been described with most of the reports dating back to ten years ago.[13] Furthermore, the sulfone-containing nucleophile was limited to allylphenyl sulfone (or its derivatives), which is a relatively easy case due to the aryl and allyl groups' dual stabilizing effects on the corresponding carbanion. To the best of our knowledge, there is no general and solid study available for the highly stereoselective synthesis of β-amino sulfones using a direct (arylsulfonyl)alkylation strategy, and the practical and direct asymmetric synthesis of β-amino sulfones remains challenging. As part of our continuing efforts in the development of efficient methodologies for synthesis of diverse chiral amines,[14] herein we report the practical synthesis of β-amino sulfones using readily accessible alkylphenyl sulfone and *N*-(*tert*-butylsulfinyl) aldimines.[15]

First, we choose methylphenyl sulfone **1**, the simplest alkylphenyl sulfone, as the nucleophile. It is worthwhile to note that while the addition reaction of compound **1** to carbonyl compounds has been well documented,[16] commonly carried out with n-BuLi as the base to pre-generate the corresponding carbanion $PhSO_2CH_2^-$, its direct (phenylsulfonyl)methylation to imines has not been disclosed. By using imine **2a** as the model compound, we examined the (phenylsulfonyl) alkylation reaction between **1** and **2** in different reaction conditions.‡ After screening several parameters (*e.g.*, solvent, base, and temperature), a reaction system comprising lithium bis(trimethylsilyl)amide (LiHMDS) as base, and THF as solvent proved to be efficient. Further study demonstrated that the base solution added slowly to the reaction mixture of compound **1** and imine **2a** in THF can give better results than that with pre-generated carbanion $PhSO_2CH_2^-$.

Eventually, the above conditions were applied to a wide array of structurally diverse imines as summarized in Table 1. A remarkable feature of this reaction is that it can be applied to non-enolizable, enolizable, aromatic, and heterocyclic imines alike. Also, this

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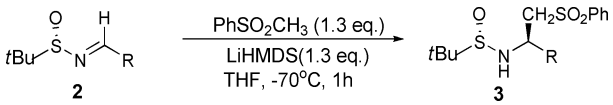
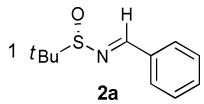
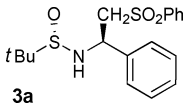
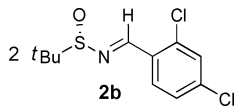
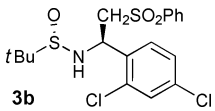
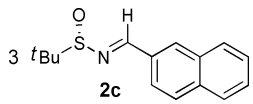
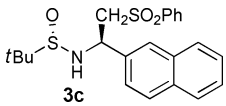
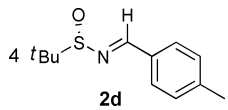
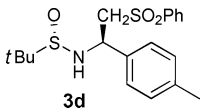
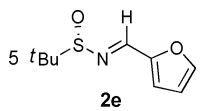
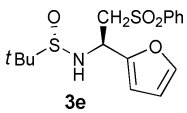
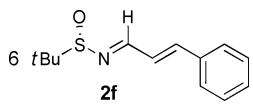
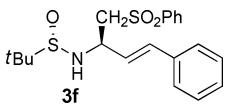
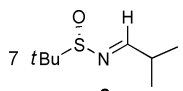
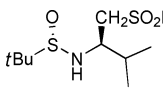
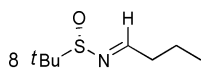
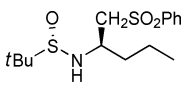
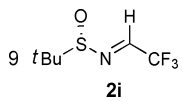
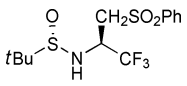
† Electronic supplementary information (ESI) available: Experimental details, characterization data, and copies of the ^1H and ^{13}C NMR spectra of the new compounds. CCDC reference number 830371. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05992k

Table 1 (Phenylsulfonyl)methylation of *N*-(*tert*-butylsulfinyl) aldimines **2**



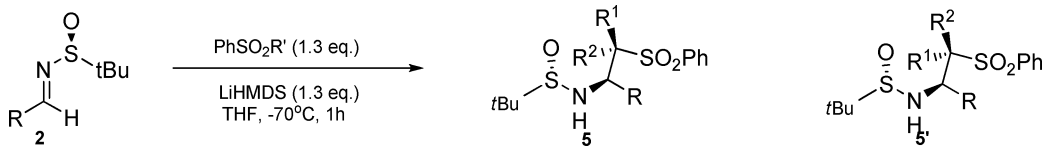
2 **3**

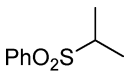
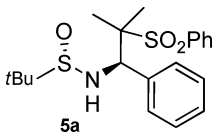
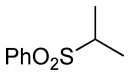
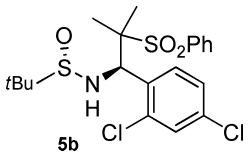
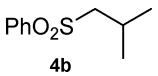
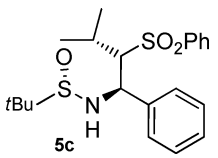
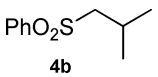
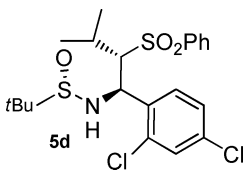
Entry	Sulfinylimine **2**	Product **3**	Yield (%)[a]	dr[b]
1	 **2a**	 **3a**	93	99 : 1
2	 **2b**	 **3b**	92	36 : 1
3	 **2c**	 **3c**	95	30 : 1
4	 **2d**	 **3d**	91	99 : 1
5	 **2e**	 **3e**	85	99 : 1
6	 **2f**	 **3f**	90	35 : 1
7	 **2g**	 **3g**	93	35 : 1
8	 **2h**	 **3h**	92	18 : 1
9	 **2i**	 **3i**	75	7 : 1

[a] Yields of isolated pure material. [b] Diastereomeric ratios were determined by HPLC–MS and ^{1}H NMR spectroscopy on the crude reaction mixture. For more details, see the ESI.†

addition reaction is compatible with a variety of functional groups. High diastereoselectivity was observed in each case, excellent yields were obtained with both non-enolizable (Table 1, entries 1–7) and enolizable imines that have one or two α-hydrogen atom(s) (entries 8 and 9). Note that the position and electronic withdrawing/donating nature of the substitution group(s) on the aromatic rings had no detectable effect on both the yield and diastereoselectivity. We also tried the same reaction conditions to *N*-(*tert*-butylsulfinyl)trifluroethanimine **2i**. Gratifying, the corresponding fluorinated β-aminosulfones **3i** can be obtained in very good yield. It should be pointed out that previous preparation of this compound starts from fluorinated imidoyl chlorides, which involves fluorinated *N*-aryl β-imido sulfone as a key intermediate.[17] Reduction of the latter compound usually required a very long reaction time (two to several days) and gave the corresponding β-aminosulfones in only moderate diastereoselectivity which required chromatographic separation to get the predominant diastereoisomer. Our highly stereoselective one-step procedure to prepare β-aminosulfones in conjunction with commercially available *tert*-butanesulfinamide, presented herein, represents an advantage over the previous reported methods, making it highly practical for organic synthesis.

Table 2 (Phenylsulfonyl)alkylation of *N*-(*tert*-butylsulfinyl) aldimines **2**



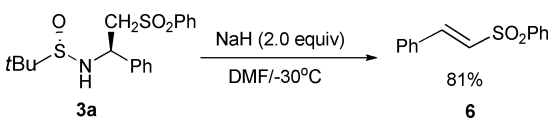
Entry	Imine **2**	$PhSO_2R$	Product **3**	Facial selectivity[a]	Isomer ratio[a] 5 : 5′	Yield[b] 5
1	**2a**	 **4a**	 **5a**	16 : 1	N/A	82
2	**2b**	 **4a**	 **5b**	27 : 1	N/A	80
3	**2a**	 **4b**	 **5c**	60 : 1	3 : 1	60
4	**2b**	 **4b**	 **5d**	75 : 1	5 : 1	61

[a] Facial selectivity and isomer ratio were determined by HPLC–MS and ^{1}H NMR spectroscopy on the crude products. For more details, see the ESI.† [b] Isolated yield of **5**.

Next, we turned our attention to the scope of other alkylphenyl sulfones. As shown in Table 2, sterically hindered *iso*-propylphenyl sulfone **4a** can react with imines smoothly and these transformations provided the expected products **5** in good yield with excellent diastereoselectivity. When *iso*-butylphenyl sulfone **4b** was applied to this reaction, the facial selectivities, *i.e.*, the diastereoselectivity during the nucleophilic addition of *in situ* generated anion into imine functionality of **2**, were excellent (99 : 1). Interestingly, moderate to good stereoselectivity was observed during the formation of another neighboring stereogenic center (the carbon adjacent to the phenylsulfonyl group) and the major diasteromers **5c** and **5d** can be separated in good yield (56% and 63% respectively). Compared to that widely used reaction of (phenylsulfonyl)methylation to aldehydes and ketones, this reaction showed some interesting chemical properties: when carbonyl compounds such as benzaldehyde **6** was subject to the above optimized reaction conditions, no product was obtained and the starting materials can be recovered completely, which indicates that the electrophilicity and hard-/softness of aldehyde/imine electrophiles can substantially affect the overall chemical outcome.

To further demonstrate the practical use of this direct (phenylsulfonyl)alkylation reaction, the experiment was conducted with compound **1** and imine **2a** at 0.5 mol scale under the above conditions. This reaction proceeded smoothly and completed in normal time. After the usual work-up, the crude product can be obtained, and NMR and HPLC–MS analysis indicated that the diastereoselectivity was comparable to that at the small scale (1.0 mmol). Pure product **3a** can be obtained in 85% yield after simple recrystallization from ethyl acetate/hexane.

β-amino sulfone **3** showed some interesting chemical properties: when compound **3a** was treated with 2.0 equivalent NaH, alkenyl sulfone **6** can be obtained in exclusively *E* form. The *tert*-butyl sulfinamide group acted as a leaving group in this reaction, which was not observed in previous related studies.[13,15]



Scheme 1 Conversion of **3a** to compound **6**.

The absolute configuration of sulfinamide **5c** was determined by single-crystal X-ray analysis (see Fig. 1a), and the facial selectivity was consistent with our prediction based on a commonly used non-chelation-controlled transition-state mode to give the Cram products (Fig. 1b), in which *tert*-butyl group adopts the

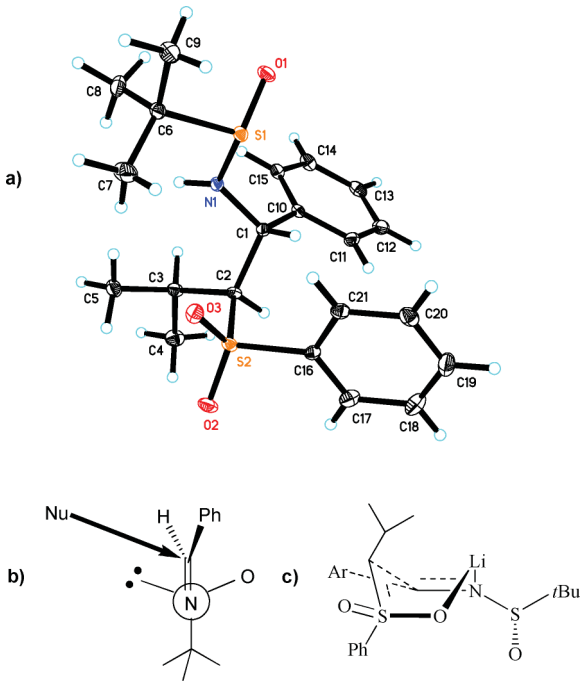


Fig. 1 The X-ray crystal structure of **5c** (a) and depiction of its stereoselective formation (b) and (c).

antiperiplanar arrangement with respect to the C═N bond.[14] Based on computational studies (see the ESI† for details), the observed diastereoselectivity can also be rationalized by involving a six membered cyclic boat-like transition state (Fig. 1c), wherein Li^+ chelates with one of the sulfonyl oxygens and the sulfinylimine nitrogen atom, which directs the aryl group to the equatorial position thus allowing the sulfonyl carbanion to attack exclusively from the *si* face on the C═N bond. We tentatively assume that one or both transition-state modes are involved in this addition reaction. The configurations of **3a–3i** and **5a–5d** were assigned by analogy.

In summary, we have successfully developed a highly stereoselective and practical approach to β-amino sulfones. Not only methylphenyl sulfone, but also sterically hindered alkylphenyl sulfone can react with structurally diverse *N*-(*tert*-butylsulfinyl) aldimines, delivering the corresponding β-amino sulfones in good to excellent yields with high diastereoselectivities. Starting from cheap and commercially available starting materials, our described one-step procedure allows for large scale synthesis of this kind of compounds, thus making it highly practical for organic synthesis.

Acknowledgements

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Notes and references

‡ General procedure for (phenylsulfonyl)methylation of *N*-(*tert*-butylsulfinyl) aldimines **2**: LiHMDS (1.3 equiv, 1.3 ML, 1.0 mol L^{-1}) was added to a mixture of the imine **2a** (1 mmol) and methylphenyl sulfone **1** (1.3 equiv, 1.3 mmol) in THF (5 mL) at −70 °C. Reaction mixtures were stirred over 1 h. Then half-saturated NH_4Cl-H_2O solution (2 mL) was added at lower temperature and the quenched reaction mixture was extracted three times with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the crude product, which was subject to flash chromatography to give the corresponding sulfonamide **3a**.

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