Stereoselective Synthesis of γ,δ-Unsaturated β-Amino Sulfones from Ellman's *N-tert*-Butylsulfinyl Ketimines and Methyl Phenyl Sulfone

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Abstract: A practical and straightforward approach for the highly stereoselective synthesis of γ,δ-unsaturated β-amino sulfones by nucleophilic (phenylsulfonyl)methylation of *N-tert*-butylsulfinyl ketimines with methyl phenyl sulfone was achieved. With lithium bis(trimethylsilyl)amide as the base, the corresponding sulfone-stabilized carbanion derived from methyl phenyl sulfone can be transferred to (*S*)-α,β-unsaturated *N-tert*-butylsulfinyl ketimines in very good yields and with high diastereoselectivities. Electron-withdrawing or electron-donating substituents on the aryl rings of (*S*)-α,β-unsaturated *N-tert*-butylsulfinyl ketimines did not exert a significant effect on the outcome of the diastereoselective nucleophilic (phenylsulfonyl) methylation.

Key words: amines, ketimines, nucleophilic addition, β-amino sulfones

Chiral β-amino sulfones are prevalent as a common motif in natural and unnatural products,[1] and have been extensively used as important building blocks in the design of many enzyme inhibitors such as novel HIV protease inhibitors[2] and matrix metalloproteinase inhibitors.[3] Besides, β-amino sulfones are useful synthetic intermediates as exemplified by their utility in the synthesis of allylic amines, nonproteinogenic α-amino acids,[4] amino alcohols,[5] carbohydrate derivatives,[6] and nitrogen heterocycles,[7] taking advantage of the varying chemical reactivities of sulfones (so-called 'chemical chameleon') such as electrophilic substitution in the α-position and reductive cleavage of the sulfone group.[8]

Not surprisingly, the synthesis of β-amino sulfones have attracted a lot of synthetic endeavors. The classic method developed for their asymmetric synthesis involves a synthetic sequence starting from natural amino acids.[9] The other straightforward approach was achieved via aza-Michael addition of chiral amines to α,β-unsaturated sulfones.[10] Also, the same process employing achiral amines and optically active α,β-unsaturated sulfones as reactive partners has also been described. However, in many cases these reactions proceeded with low stereoselectivity, and separation of the corresponding diastereomeric products was laborious. Recently, we developed a practical approach for the highly stereoselective synthesis of β-amino sulfones, based on nuleophilic (phenylsulfonyl) alkylation of Ellman's *N-tert*-butylsulfinyl aldimines with alkyl phenyl sulfones.[11] A remarkable feature of this reaction is that it can be applied to nonenolizable, enolizable, aromatic, and heterocyclic imines alike with very high yields and excellent diastereoselectivities. However, although significant progress has been made in the area of synthesis of chiral β-amino sulfones, the asymmetric synthesis of structure diverse β-amino sulfones, especially those with the amino group adjacent to a chiral tertiary carbon center, is yet to be developed.

Ideally, we can envision that a straightforward (arylsulfonyl)alkylation of chiral ketimines with alkylaryl sulfone would provide a highly attractive route to the target structures. It should be mentioned that Shiau, Jain, and coworkers recently developed a method to prepare racemic β-amino sulfonate esters from *N-tert*-butanesulfinyl ketimines and ethoxysulfonylmethide in strong basic conditions, and only low to moderate yields (15–42%) were

Table 1 Optimization of Reaction Conditions[a]

Entry[a]	Base	Molar ratio (**2a**/**1**/base)	Solvent	Yield (%)[b]	dr (%)[c]
1	LiHMDS	1:1.2:1.3	CH_2Cl_2	83	95:5
2	NaHMDS	1:1.2:1.3	CH_2Cl_2	32	94:6
3	KHMDS	1:1.2:1.3	CH_2Cl_2	25	92:8
4	LDA	1:1.2:1.3	CH_2Cl_2	trace	–
5	*n*-Buli	1:1.2:1.3	CH_2Cl_2	trace	–
6	LiHMDS	1:1.2:1.3	THF	20	95:5
7	KHMDS	1:1.2:1.3	THF	45	10:1

[a] In all cases, base was added to a mixture of **1** and **2a** at –65 °C, and the reactions were usually complete within 4 h.
[b] Yield of isolated analytically pure material.
[c] Diastereomeric ratios were determined by ^{1}H NMR of the crude reaction mixture.

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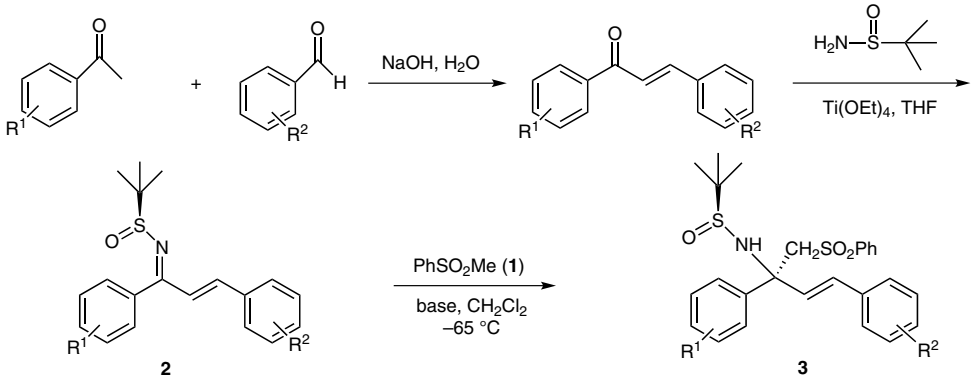
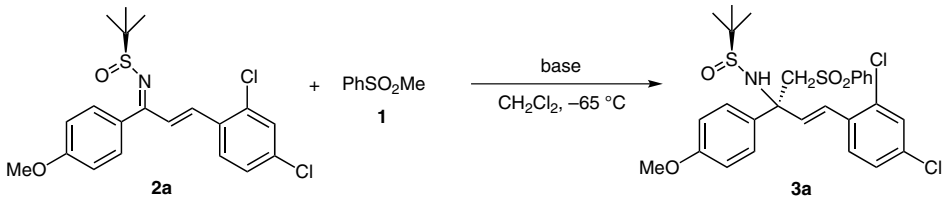
obtained with the optimized reaction conditions (*n*-BuLi, THF, HMPA, –78 °C).[12] In this paper, as part of our continuing effort to develop structure-diverse β-amino sulfones, we wish to disclose the highly diastereoselective (phenylsulfonyl) methylation of α,β-unsaturated *N*-*tert*-butylsulfinyl ketimines, which has enabled us for the first time to efficiently synthesize γ,δ-unsaturated β-amino sulfones containing chiral tertiary carbon centers through a simple and reliable protocol. It is also worthy to point out that another significant structural feature of this kind of β-amino sulfones is the existence of allylic amine subunit, as it is well-known that allyllic amines are widely applied in medicinal chemistry and drug discovery since a variety of synthetically and biologically important organic compounds can be obtained through the functionalization of their double bond.

Although α,β-unsaturated ketimines have been widely used as important intermediates in organic synthesis, instances of nucleophilic 1,2-addition of α,β-unsaturated ketimines are scarce. Recently, Hu and coworkers reported nucleophilic 1,2-addition of the (phenylsulfonyl)difluoromethyl anion, generated in situ from $PhSO_2CF_2H$ and a base, to α,β-unsaturated ketones and *N*-*tert*-butylsulfinyl ketimines.[13] It was believed that, due to the existence of the high electronegativity of the fluorine atom(s), (phenylsulfonyl)difluoromethyl anion ($PhSO_2CF_2^-$) was regarded as a relatively 'hard' nucleophile, and thus undergo 1,2-addition reactions with α,β-enones or α,β-unsaturated ketimines. However, to the best our knowledge, the addition reaction between methyl phenyl sulfone and α,β-enones or α,β-unsaturated ketimines have not been disclosed. With these in mind, we initially prepared a variety of (*S*)-α,β-unsaturated *N*-*tert*-butylsulfinyl ketimines **2** by $Ti(OEt)_4$-mediated condensation of (*S*)-*N*-*tert*-butylsulfinamide and the requisite α,β-unsaturated ketones, according to the reported protocol.[14] With these α,β-unsaturated ketimines **2** in hand, we next chose (*S*)-α,β-unsaturated *N*-*tert*-butylsulfinyl ketimine **2a** as a model compound to test the nucleophilic (phenylsulfonyl) methylation with $PhSO_2Me$ (Scheme 1).

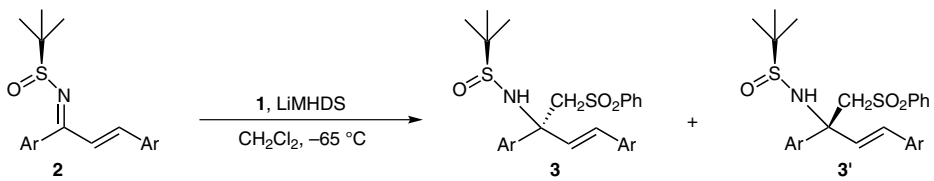
Following initial deprotonation with lithium hexamethyldisilazide (LiHMDS), $PhSO_2Me$ reacted with **2a** to afford the 1,2-addition product **3a** (not 1,4-addition product) with very good yield (83%) and diastereoselectivity (dr = 95:5). Several bases were then screened, and the results are summarized in Table 1 (Scheme 2). As shown, a significant drop in yield was observed when sodium hexamethyldisilazide (NaHMDS) or potassium hexa-



Scheme 1 Synthesis of γ,δ-unsaturated β-amino sulfones



Scheme 2 Stereoselective synthesis of **3a**



Scheme 3 Stereoselective synthesis of γ,δ-unsaturated β-amino sulfones

methyldisilazide (KHMDS) was used as base. Also, *n*-BuLi was not suitable for this reaction, probably due to its high nucleophilicity toward ketimine **2a**. Reactant molar ratios were also carefully examined to improve the product yield using LiHMDS as the base, and the best yield of product **3a** was obtained with a reactant molar ratio of **2a**/**1**/LiHMDS = 1:1.2:1.3. Having identified the optimal reaction conditions, the scope of this nucleophilic 1,2-addition reaction was investigated with various (*S*)-α,β-unsaturated ketimines (Table 2, Scheme 3).

The absolute configuration of product **3a** was determined to be S_S,*S* by its single-crystal X-ray structure (Figure 1), and the configurations of others were assigned by analogy.[22] The stereocontrol mode of the present diastereoselective (phenylsulfonyl)methylation of ketimines can be predicted by envisaging a cyclic six-membered transition state (Figure 2) in which the bulky *tert*-butyl group preferentially adopts an equatorial position, and the (phenylsulfonyl)methyl anion ($PhSO_2CH_2^-$) attack the *Re* face of the ketimine.[15]

Table 2 Stereoselective Synthesis of γ,δ-Unsaturated β-Amino Sulfones

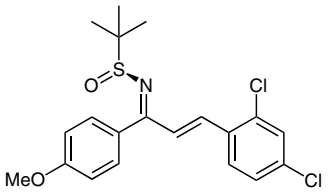
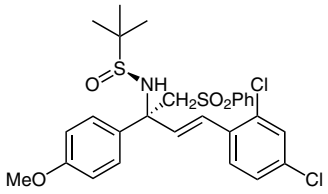
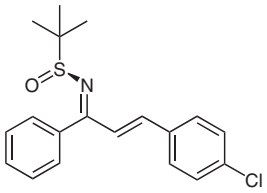
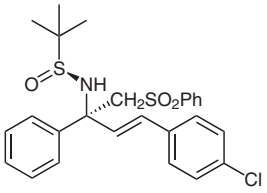
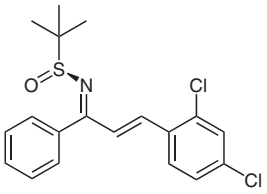
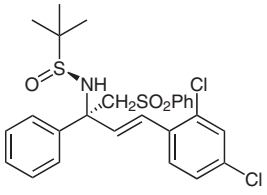
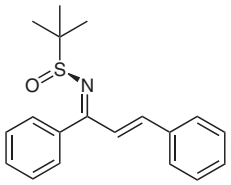
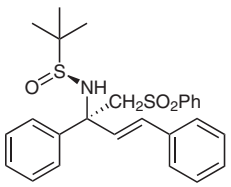
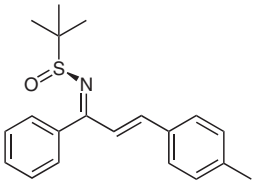
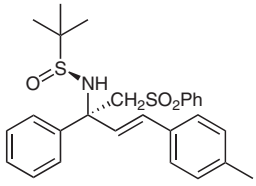
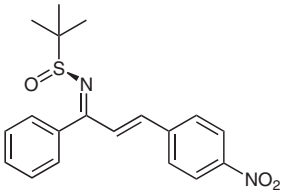
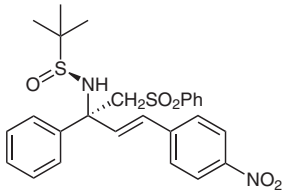
Entry	Ketimines **2**	Products **3**	Yield (%)[a]	dr (%)[b]
1			83	95:5
	2a	**3a**		
2			87	92:8
	2b	**3b**		
3			82	95:5
	2c	**3c**		
4			85	93:7
	2d	**3d**		
5			86	92:8
	2e	**3e**		
6			81	92:8
	2f	**3f**		

Table 2 Stereoselective Synthesis of γ,δ-Unsaturated β-Amino Sulfones (continued)

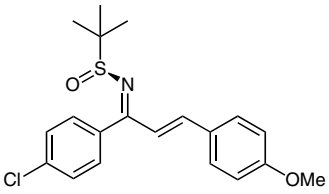
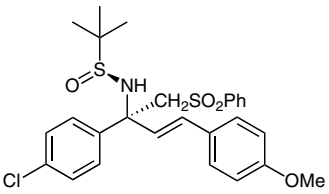
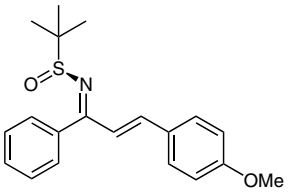
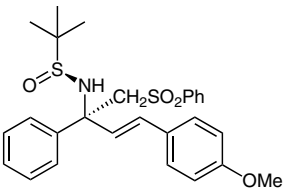
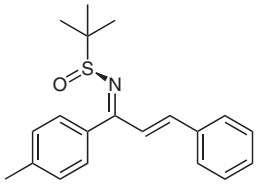
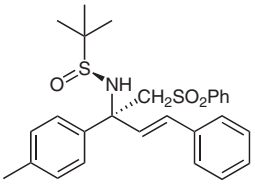
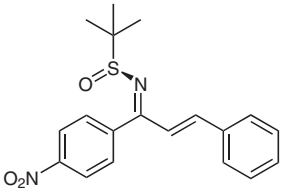
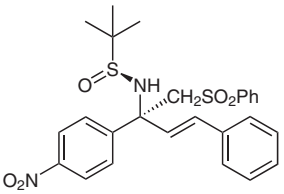
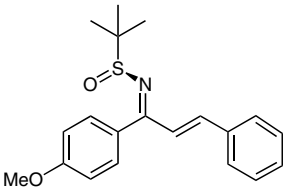
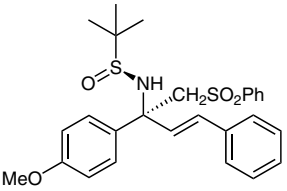
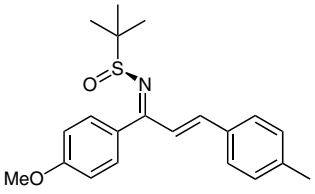
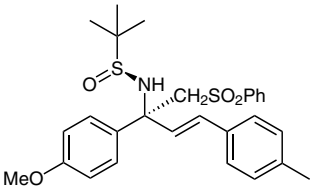
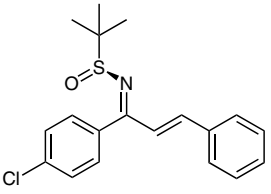
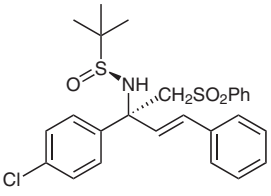
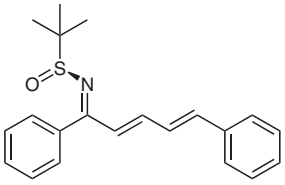
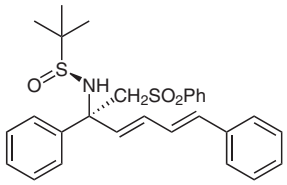
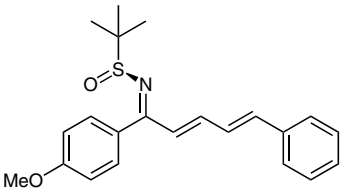
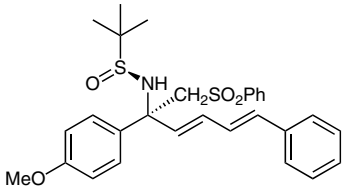
7			85	93:7
	2g	**3g**		
8			83	98:2
	2h	**3h**		
9			87	95:5
	2i	**3i**		
10			81	96:4
	2j	**3j**		
11			87	94:6
	2k	**3k**		
12			82	94:6
	2l	**3l**		
13			85	92:8
	2m	**3m**		

Table 2 Stereoselective Synthesis of γ,δ-Unsaturated β-Amino Sulfones (continued)

14	 **2n**	 **3n**	82	97:3
15	 **2o**	 **3o**	85	98:2

[a] Isolated yield.
[b] Diastereomeric ratios were determined by ^{1}H NMR of the crude reaction mixture

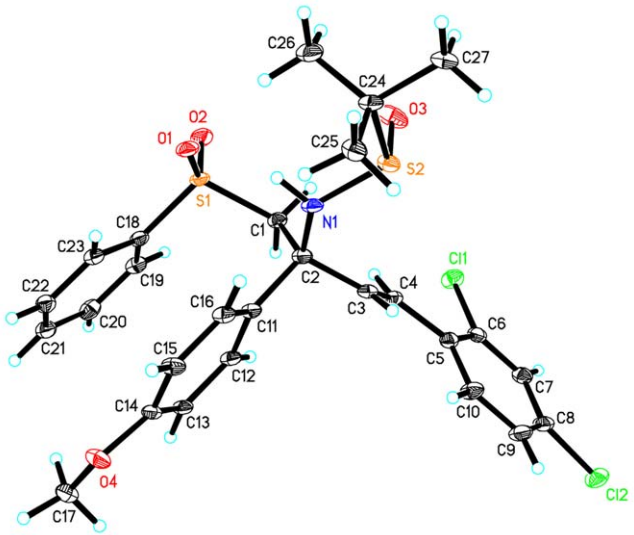


Figure 1 Single-crystal X-ray structure of compound **3a**

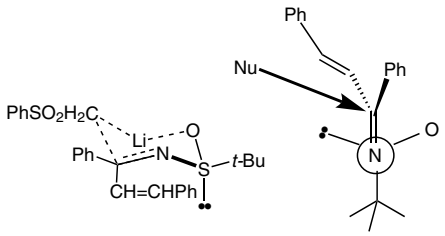


Figure 2 Cyclic six-membered transition state

It has been rationalized that 'hard' nucleophiles usually undergo 1,2-addition reaction with α,β-unsaturated ketimines, whereas 'soft' nucleophiles prefer attacking the β-carbon atom of α,β-unsaturated ketimines. Our herein-reported (phenylsulfonyl)methylation of α,β-unsaturated ketimines afforded 1,2-addition products, indicating that the (phenylsulfonyl)methyl anion is still a relatively hard nucleophile. Our further attempts to (phenylsulfonyl)methylate (*S*)-2-methyl-*N*-(1-phenylethylidene)propane-2-sulfin amide with predeprotonated or in situ generated (phenylsulfonyl)methyl anion failed, and we assume that unwanted aza-enolization of the ketimines occurred.[16–20]

In summary, we have developed the highly efficient synthesis of γ,δ-unsaturated β-amino sulfones through diastereoselective nucleophilic of (*S*)-α,β-unsaturated *N*-*tert*-butylsulfinyl ketimines, with in situ generated $PhSO_2CH_2^-$ anion and an appropriate base (LiHMDS). The reaction afford the 1,2-addition products with good diastereoselectivities and very good yields.[21] Electron-withdrawing or electron-donating substituents on the aryl rings of (*S*)-α,β-unsaturated *N*-*tert*-butylsulfinyl ketimines did not exert a significant effect on the outcome of the diastereoselective nucleophilic (phenylsulfonyl)methylation. Our further attempts to (phenylsulfonyl)methylation of (*S*)-2-methyl-*N*-(1,5-diphenylpenta-2,4-dienylidene)propane-2-sulfinamide with predeprotonated or in situ generated (phenylsulfonyl)methyl anion **3n** succeeded.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(21) **General Procedure for the Synthesis of Compounds 3** LiHMDS (1.3 equiv, 1.3 mL, 1.0 mol/L) was added to a mixture of the (*S*)-α,β-unsaturated *N*-*tert*-butylsulfinyl ketimines **2** (1 mmol) and methyl phenyl sulfone (**1**, 1.2 equiv, 1.2 mmol) in CH_2Cl_2 (5 mL) at –65 °C. Reaction mixtures were stirred over 4 h. Then a half-saturated NH_4Cl/H_2O solution (2 mL) was added at lower temperature, and the quenched reaction mixture was extracted three times with EtOAc. The combined organic layers were dried over anhyd $MgSO_4$. Evaporation of the solvent afforded the crude product, which was subject to flash chromatography to give the corresponding γ,δ-unsaturated β-amino sulfones **3**. **Spectral Data of the Product 3a** White solid; mp 157.5–158.1 °C; $[\alpha]^{25}$ 128.4 (*c* 0.61, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77–7.76 (d, *J* = 8 Hz, 2 H), 7.75–6.80 (m, 10 H), 6.82–6.80 (d, *J* = 8 Hz, 1 H), 6.29–6.27 (d, *J* = 8 Hz, 1 H), 6.23 (s, 1 H), 4.39–4.35 (d, *J* = 14 Hz, 1 H), 4.13–4.09 (d, *J* = 14 Hz, 1 H), 3.80 (s, 3 H), 1.41 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 140.7, 134.8, 134.2, 134.0, 133.3, 133.0, 131.4, 129.4, 129.1, 128.1, 128.0, 127.7, 127.2, 126.5, 113.7, 64.6, 63.3, 56.6, 55.2, 23.1. ESI-HRMS: *m/z* calcd for $C_{27}H_{29}Cl_2NO_4S_2Na$ $[M + Na]^+$: 588.08073; found: 588.07789. Other spectral data can be found in the Supporting Information.

(22) The crystal structure of **3d** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 884490.

