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A Facile and Efficient Approach to *N*-Protected-β-Sulfinylenamines *via C*-Sulfinylation of Enamides and Enecarbamates

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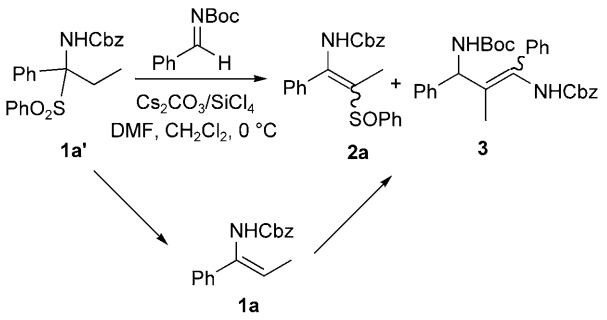
Abstract: A practical method has been developed for the *C*-sulfinylation of enamides and enecarbamates using sodium phenylsulfinate/methyltrichlorosilane ($PhSO_2Na/MeSiCl_3$) as the sulfinylating reagent and *N*,*N*-dimethylacetamide (DMAc) as the Lewis base promoter, which allows for the preparation of a variety of *N*-protected-β-sulfinylenamines in high yields and good stereoselectivities. The Lewis base is found to be important for both the *in situ* generation of the active sulfinylating species (PhSOCl) and the sulfinylation step.

Keywords: enamides; enecarbamates; Lewis base; sodium phenylsulfinate/methyltrichlorosilane ($PhSO_2Na/MeSiCl_3$); *C*-sulfinylation

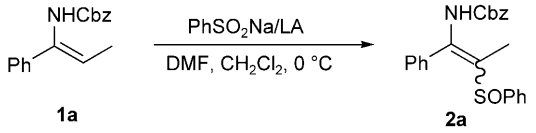
Organic sulfoxides are an important class of compounds that have found broad applications.[1] They serve as key structural components in some drug molecules.[2] Chiral sulfoxides are well known chiral auxiliaries and ligands for asymmetric synthesis.[3] Besides the oxidation of sulfides,[4] the sulfinylation of organometallic nucleophiles (Li,[5] Cu,[6] Zn,[7] and Mg[8] reagents) with sulfinates represents the most important method for the preparation of sulfoxides, which, however, suffers from limited practicality due to the use of relatively expensive organometallics that typically require low temperature and moisture-free conditions. Sulfinylation of organometallics-free carbon nucelophiles with sulfinyl chloride is in principle a more practical and cost-efficient method. Although the *O*-sulfinylation[9] of alcohols and the *N*-sulfinylation[10] of amines with sulfinyl chloride are well-known and efficient approaches to sulfinates and sulfinamides, respectively, so far there have been no effective methods available for the *C*-sulfinylation of organic carbon nucleophiles to synthesize sulfoxides. Glaros[11] and Lavilla[12] have reported that ketones and dihydropyridines can be directly sulfinylated with sulfinyl chloride to produce sulfoxide derivatives which, however, only give low yields. Herein, we present the first highly effective method for *C*-sulfinylation of enamides and enecarbamates with *in situ* generated phenyl sulfinyl chloride (PhSOCl), which allows for the preparation of *N*-protected-β-sulfinylenamines in high yields (up to 99%) and good stereoselectivities.

Recently, in an attempt to use *in situ* generated enecarbamate **1a** from **1a′** as the nucleophile for chlorosilane-promoted Mannich-type reactions,[13] a new compound **2a** was obtained as a by-product (Scheme 1). We speculated that this side reaction should be due to the nucleophilic attack of the enecarbamate **1a** to an active sulfinyl species. To explore if such a side reaction could be developed into a useful new method for the preparation of functionalized vinyl sulfoxides, we directly treated isolated **1a** with sodium phenylsufinate ($PhSO_2Na$) and $SiCl_4$ in the presence of DMF in dry CH_2Cl_2. To our delight, the desired product **2a** was achieved in 92% yield in 1.5 h (entry 1, Table 1).



Scheme 1. Observed *C*-sulfinylation of enecarbamate **1a**. Cbz = benzyloxycarbonyl, Boc = *tert*-butoxycarbonyl.

Table 1. Effects of Lewis acids on *C*-sulfinylation.[a]



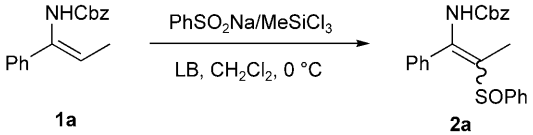
1a 2a

Entry	Lewis acid (LA)	Yield [%][b]
1	$SiCl_4$	92
2	$MeSiCl_3$	96
3	Me_2SiCl_2	84
4	Me_3SiCl	–
5	Ph_3SiCl	–
6	$HSiCl_3$	–
7	$AlCl_3$	–
8	$FeCl_3$	–
9	$CuCl_2$	–

[a] Unless stated otherwise, reactions were performed on a 0.1 mmol scale with **1a**/$PhSO_2Na$ in a 1:2 ratio in 4.0 equiv. Lewis acid and 5 equiv. DMF in 1.0 mL of CH_2Cl_2 at 0 °C for 1.5 h.

[b] Isolated yield of **2a** as *E/Z* mixture based on **1a**.

Table 2. Effects of Lewis bases on *C*-sulfinylation.[a]



1a 2a

Entry	Lewis base (LB)	Yield [%][b]
1	DMF	92
2	DMAc	>99
3	pyridine	74
4	HMAp	67
5	DMAP	61
6	TEA	trace
7	–	nr[c]

[a] Unless stated otherwise, reactions were performed on a 0.1 mmol scale with **1a**/$PhSO_2Na$ in a 1:2 ratio in 4.0 equiv. $MeSiCl_3$ and 5 equiv. base in 1.0 mL of CH_2Cl_2 at 0 °C for 1.5 h.

[b] Isolated yield of **2a** as *E/Z* mixture based on **1a**.

[c] No reaction.

Some other Lewis acids were also tested for this reaction. Methyltrichlorosilane ($MeSiCl_3$) was found to be as highly effective as $SiCl_4$, affording 96% yield in 1.5 h (entry 2), and dimethyldichlorosilane (Me_2SiCl_2) to be slightly less effective (84% yield, entry 3), whereas other chlorosilanes such as Me_3SiCl, Ph_3SiCl and $HSiCl_3$ were all shown to be totally inactive (entries 4–6), as were transition metal Lewis acids such as aluminium chloride, iron chloride, and copper chloride also (entries 7–9). Thus, we selected $MeSiCl_3$ as the Lewis acid promoter for further studies.

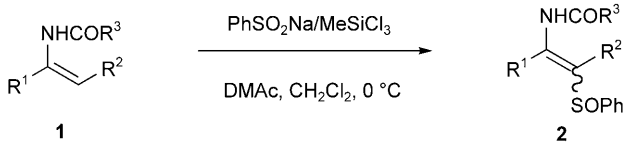
Next, we examined the effects of different Lewis bases other than DMF on the sulfinylation of **1a** with $PhSO_2Na/MeSiCl_3$ in CH_2Cl_2 at 0 °C. As shown in Table 2, the sulfinylation reaction went even more efficiently with *N*,*N*-dimethylacetamide (DMAc) than DMF, affording the product in quantitative yield (entry 2). Other Lewis bases such as pyridine, HMAP and DMAP could also promote the reaction, but with lower efficiency, affording 74%, 67% and 61% yields, respectively (entries 3–5). In contrast, triethylamine (TEA) proved to be completely ineffective (entry 6). Notably, no reaction occurred in the absence of Lewis base (entry 7), suggesting an indispensable role of Lewis base for activation.

After having demonstrated that the sulfinylation of **1a** with $PhSO_2Na/MeSiCl_3$ could be furnished in high efficiency and excellent yield with the assistance of DMAc, we next explored the scope and limitation of this reaction for various enamides and enecarbamates **1a–u**.[14] As shown in Table 3, the acyclic aromatic and aliphatic enecarbamates and enamides **1a–p**, all underwent smooth sulfinylation to produce the desired product *N*-protected-β-sulfinylenamines **2a–p** in good to excellent yields (entries 1–16). Moderate to good stereoselectivities with ratios of *Z/E* ranging from 1.5:1 to 15:1 were also observed. The stereochemistries of both isomers were unambiguously determined by 2D ^1H-^1H NOESY.

The sulfinylation of aromatic six-membered cyclic substrates **1q–t** could also proceed smoothly to afford the corresponding products in high yield (entries 17–20). Substrate **1u** with a five-membered ring could also undergo the sulfinylation, albeit with moderate yield (entry 21).

The mechanistic pathway of the Lewis base-promoted sulfinylation of **1** is proposed as follows (Scheme 2): $PhSO_2Na$ first reacts with $MeSiCl_3$ to give sulfinate **A1**, which, with the assistance of Lewis base, gives rise to PhSOCl as the active sulfinylating species. PhSOCl then encounters the nucleophilic attack of the C=C bond of **1** to give intermediate **A2**, which subsequently undergoes elimination and tautomerization to furnish product **2** as an *E*/*Z* mixture. The involvement of PhSOCl as the actual sulfinylating species was confirmed by the smooth sulfinylation of **1a** using the freshly prepared and distilled PhSOCl (Scheme 3). Notably, when PhSOCl was directly used, the sulfinylation could proceed in the absence of a Lewis base, but only afforded moderate yield, whereas in the presence of either *N*,*N*-diisopropylethylamine (DIEA) or DMAc, high yields were again obtained. This clearly indicates that besides assisting the generation of PhSOCl, the Lewis base also plays a role in promoting the sulfinylation, possibly through the activation of the sulfinyl group by forming a positively charged active species ($PhSOLB^{\oplus}$). We thus envisioned that an asymmetric version of this reaction

Table 3. *C*-Sulfinylation of various enamides/enecarbamates **1**.[a]



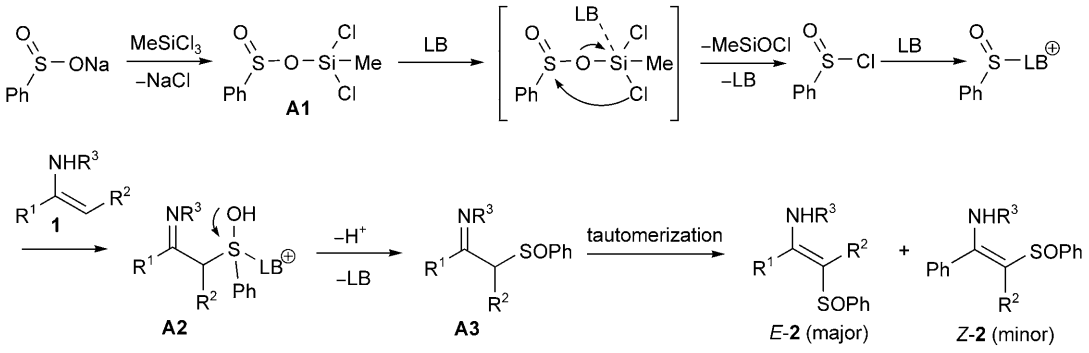
Entry		Substrate		Product	Yield [%][b]	*E*/*Z*[c]
1	**1a**		$R^3 = OCH_2Ph$		99	7.8/1
2	**1b**		$R^3 = Me$		90	15/1
3	**1c**		$R^3 = t$-Bu		99	6.7/1
4	**1d**		$R^3 = Ph$		94	6.6/1
5	**1e**		OEt		99	4.5/1
6	**1f**				99	5.6/1
7	**1g**		$R^1 = Ph$		99	7.8/1
8	**1h**		$R^1 = 4\text{-F-}C_6H_4$		63	3.2/1
9	**1i**		$R^1 = 2\text{-Cl-}C_6H_4$		86	1.5/1
10	**1j**		$R^1 = 4\text{-OAc-}C_6H_4$		66	4.6/1
11	**1k**		$R^1 = 4\text{-Me-}C_6H_4$		53	1.6/1
12	**1l**		$R^1 = 2$-naphthyl		79	2.2/1
13	**1m**		$R^2 = n\text{-}C_3H_7$		77	11.2/1
14	**1n**		$R^2 = Me$		75	nd[d]
15	**1o**		$R^2 = Bn$		99	2.8/1
16	**1p**				87	10.3/1
17	**1q**		$R^3 = OEt$		99	
18	**1r**		$R^3 = Me$		86	
19	**1s**		$R^3 = t$-Bu		89	
20	**1t**		$R^3 = Ph$		90	
21	**1u**				51	

[a] Unless specified otherwise, all reactions were performed on a 0.1 mmol scale with **1**/$PhSO_2Na$ in a 1:2 ratio and 4.0 equiv. $MeSiCl_3$ and 5.0 equiv. DMAc in 1.0 mL of CH_2Cl_2 at 0 °C for 0.5–9 h.

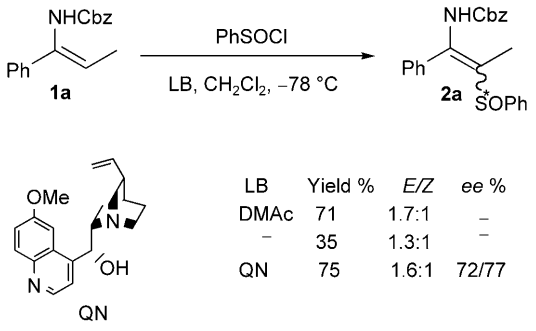
[b] Isolated yield of **2** as *E*/*Z* mixture based on **1**.

[c] The *E*/*Z* ratio of **2** was analyzed by HPLC, the *E* and *Z* configuration were determined by 2D ^1H-^1H NOESY, details are given in the Supporting Information.

[d] The *E* and *Z* isomers were not distinguishable.



Scheme 2. Proposed mechanism of the Lewis base-promoted *C*-sulfinylation.



LB	Yield %	*E/Z*	*ee* %
DMAc	71	1.7:1	–
–	35	1.3:1	–
QN	75	1.6:1	72/77

Scheme 3. Asymmetric *C*-sulfinylation of **1a**.

could be implemented if a chiral Lewis base promoter was used.

We briefly screened several chiral Lewis bases and found that quinine promoted the reaction of **1a** with PhSOCl in CH_2Cl_2 at −78 °C to afford **2a** in 75% yield with 72% and 77% *ee* values for the *E* and *Z* isomers, respectively (Scheme 3).

In conclusion, we have developed a practical method for the preparation of *N*-protected-β-sulfinylenamines *via* Lewis base-promoted *C*-sulfinylation of enamides and enecarbamates with $PhSO_2Na$/$MeSiCl_3$. Good to high yields and stereoselectivities were achieved for a broad range of enamides and enecarbamates. The Lewis base plays important roles in promoting both the generation of the active sulfinylating species PhSOCl and the subsequent sulfinylation. Using chiral Lewis bases to implement highly enantioselective version of this transformation is under active investigation in this laboratory.

Experimental Section

All starting materials were of the highest commercially available grade and used without further purification. All solvents used in the reactions were distilled from appropriate drying agents prior to use.

General Procedure for the *C*-Sulfinylation of Enamides/Enecarbamates 1a–u

Under an argon atmosphere, methyltrichlorosilane (50 μL, 0.4 mmol) was added dropwise to a stirred solution of enamide/enecarbamate **1** (0.10 mmol), sodium phenylsulfinate (32.8 mg, 0.20 mmol) and DMAc (47 μL, 0.50 mmol) in anhydrous CH_2Cl_2 at 0 °C. The mixture was allowed to stir at the same temperature for 0.5–9 h. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with ethyl acetate. The combined extracts were washed with brine and dried over anhydrous $MgSO_4$ and the solvents were evaporated under vacuum. Purification by column chromatography (silica gel, PE/EtOAc) afforded pure *N*-protected-β-sulfinylenamines **2**. The *E/Z* ratio values were determined by using established HPLC techniques.

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