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Synthesis of allyl sulfoxides from allylsilanes via silyl sulfinates

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ABSTRACT

Allylsilanes underwent sila-ene reaction with sulfur dioxide in the presence of Lewis acid catalysts. The obtained Vogel's silyl sulfinates were found to act as sulfinyl transfer agents in reactions with aryl, heteroaryl, alkyl, and allyl Grignard reagents proceeding with the expulsion of the trialkylsilyloxy group to give allyl sulfoxides in up to 83% yield. The nucleophilic attack of Grignard reagents was accelerated in toluene and in the presence of LiCl or ZnCl₂ as Lewis acidic additives. The developed method allows the transformation of allylsilanes into allyl sulfoxides.

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Sulfoxides are versatile compounds for three major reasons: (1) their structural motif is present in many naturally occurring¹ and biologically active² compounds, and marketed pharmaceuticals;³ (2) they are well-recognized synthetic intermediates;⁴ (3) the sulfoxide moiety is known for forming complexes with transition-metals and as such is effectively used in catalysis.⁵ Synthetic applications of sulfoxides include methodologies based on Mislow-Evans⁶ and Pummerer rearrangements.⁷ Enantiomerically enriched sulfoxides are also used as chiral auxiliaries⁴ in natural product syntheses⁸ which includes polyols⁹ and polypropionates.¹⁰

Habitually, sulfoxides are prepared either by oxidation of the corresponding sulfides^{3a,11} or by nucleophilic attack on a sulfinyl center bearing a suitable leaving group.¹² In the latter case the traditional S-electrophiles are alkyl or aryl sulfinates esters,¹³ their corresponding thio-counterparts,¹⁴ sulfites, mixed anhydrides of sulfinic and boric acids,¹⁵ and sulfinamides (Scheme 1).¹⁶ Interestingly, aryl,¹⁷ vinyl,¹⁸ and benzyl¹⁹ groups also can be replaced when the appropriate sulfoxides are reacted with I- and II-group organometallic reagents. Similarly, methylphosphonates²⁰ and other specific C-nucleofuges²¹ act as good carbon leaving groups.

The search for novel methodologies for the synthesis of sulfoxides is an ongoing area of research²² and in many cases involves transition metal catalyzed transformations.²³ To the best of our knowledge, trialkylsilyl sulfinates have not been applied to the

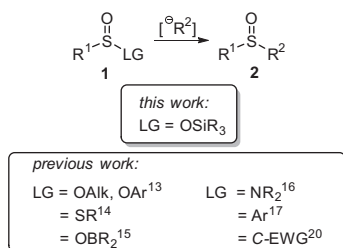
synthesis of sulfoxides thus far. On the other hand sila-ene reactions between allylsilanes and sulfur dioxide offer an easy entry to trialkylsilyl allylsulfinates (Vogel's silyl sulfinates) (**3**→**4**, Scheme 2).²⁴ The latter have been used in the synthesis of sulfones, sulfonamides, and sulfonic esters.^{24,25} Vogel's silyl sulfinates were also shown to silylate alcohols, phenols, and carboxylic acids.²⁶ This property has recently found application in the user-friendly derivatization and GC-analysis of non-volatile polyhydroxylated organic compounds.²⁷

Herein, we report the application of Vogel's silyl sulfinates, obtained from the sila-ene reaction between allylsilanes and sulfur dioxide (**3**+SO₂→**4**), in the synthesis of allyl sulfoxides (**4**→**5**, Scheme 2). This is a logical continuation of our previously reported method involving mixed anhydrides of sulfinic and boric acids,¹⁵ which suffered from eventual attack of the organometallic reagent onto the electrophilic boron center (attack A ≧ attack B). It was expected that in trialkylsilyl allylsulfinates the selectivity between the S- and Si-reactive centers would favor nucleophilic attack on the sulfur center (attack A ≫ attack C).

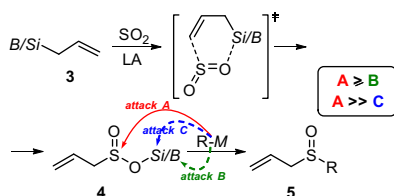
Although some of Vogel's silyl sulfinates are commercially available, we developed and optimized a synthesis of the key starting material **7** on a multi-gram scale. We found that depending on the solvent, temperature, and Lewis acid catalyst, the sila-ene reaction of methallyltrimethylsilane (**6**) competed with H-ene reactions as shown by the trace amounts of the corresponding sulfinates **10** and **11** that were observed in the mixture reaction (Scheme 3). Reaction at H^a and H^b would produce, respectively, sulfinic acids **8** and **9**, which can both accept a trimethylsilyl group from the

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Scheme 1. Sulfoxide synthesis using different sulfinyl transfer agents.



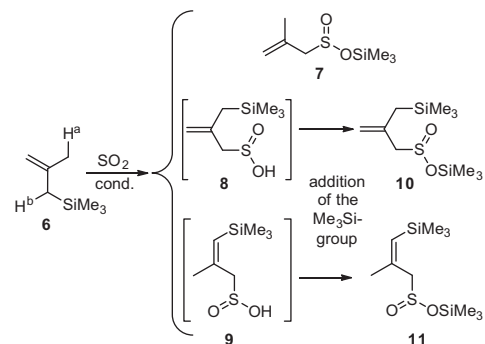
Scheme 2. General approach for the synthesis of allyl sulfoxides **5** from allylsilanes and allylboron derivatives.

reaction mixture to give products **10** and **11**, respectively. The structures of both **10** and **11** were elucidated from their NMR data and from analysis of the corresponding sulfoxides (see **Scheme 6** and **ESI**). It was found, that simply bubbling SO_2 gas through a toluene solution of **6** in the presence of Ghosez Lewis acid²⁸ (trimethylsilyl bis(trifluoromethanesulfonyl)imide, Tf_2NTMS) resulted in the clean transformation to **7** in 71% isolated yield.²⁷

Next, we turned our attention to the development of experimental conditions for sulfoxide synthesis (**Scheme 4**, **Table 1**).

Initially we used silyl sulfinatate **7** and phenylmagnesium bromide as the nucleophile to examine the role of solvent, temperature and additive on the yield of methallyl sulfoxide **12a** ($\text{R} = \text{Ph}$) (**Table 1**). Simple addition of PhMgBr to a solution of **7** in anhydrous THF at -78°C gave methallyl sulfoxide **12a** in a moderate 43% yield (**Table 1**, entry 1). Addition of silicon-based Lewis acids increased the isolated yields to $\sim 60\%$ (**Table 1**, entries 2–5). Encouraged by Knochel's reports²⁹ on the generation of functionalized organometallic reagents in the presence of LiCl as an activator, we tested this in several experiments (**Table 1**, entries 6–8). The addition of LiCl did not give any reasonable improvement when the reaction was performed in THF. However, when the solvent system was switched to toluene/THF 15:1–20:1, the isolated yields of sulfoxide **12a** reached 70% and 72% with 10 mol % and 100 mol % of LiCl , respectively, (**Table 1**, entry 6 vs entries 7 and 8). Finally, the addition of 1.0 equiv of PhMgBr/LiCl in toluene/THF at -100°C increased the isolated yield of **12a** to 79% (**Table 1**, entry 8). Experiments using various other organometallic reagents including copper and cerium derivatives showed low reactivity. Competitive results were obtained when a premixed mixture of PhMgBr/ZnCl_2 was added to sulfinatate **7** in toluene/THF at -78°C (**Table 1**, entry 15). We propose that the coordination of lithium and zinc centers to the Lewis basic sulfinatate is more profound in toluene as a non-coordinating solvent. On the other hand, a recent study has shown that a metathesis reaction between ZnCl_2 and Grignard reagents leads to the formation of mixed Mg-Zn hybrids and thus modulates the reactivity of the organometallic species.³⁰

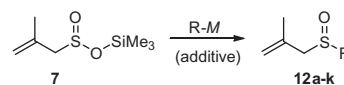
Application of the optimized reaction conditions to other Grignard reagents gave better yields of sulfoxides **12b-h** (**Table 2**) in comparison with experiments performed without the additive. In the cases of 2,4,6-trimethylphenyl-, 4-methylphenyl-, 2-thienyl-, and 1-decylmagnesium substituents the isolated yields of sulfoxides **12c,d,f,g** were over 70%.



Conditions:

- a) MeCN, Tf_2NTMS , -25°C :
7 (35%), **10** (11%), **11** (4%).
 b) MeCN, TMSOTf, $+23^\circ\text{C}$ (bubbling SO_2):
7 (46%), **10** (3%), **11** (3%).
 c) Toluene, Tf_2NTMS , $+23^\circ\text{C}$ (bubbling SO_2):
7 (71%), **10** (0%), **11** (0%).

Scheme 3. Sila-ene and H-ene reactions of **6** with sulfur dioxide.



Scheme 4. Synthesis of sulfoxides **12a-k** from trimethylsilyl methallylsulfinate (**7**) according to **Tables 1** and **2**.

Table 1

Optimization of the reaction conditions for sulfoxide synthesis using trimethylsilyl methallylsulfinate **7** according to **Scheme 4**^a

Entry	RM (equiv)	Solvent	Additive (equiv)	Yield of 12a ($\text{R} = \text{Ph}$) (%)
1	PhMgBr (1.0)	THF	—	43
2	PhMgBr (1.1)	THF	TMSOTf (0.1)	57
3	PhMgBr (1.3)	THF	TMSOTf (0.3)	63
4	PhMgBr (1.1)	Tol ^b	TMSOTf (0.1)	59
5	PhMgBr (1.1)	Tol ^b	TBSOTf (0.1)	54
6	PhMgBr (1.0)	THF	LiCl (0.1)	59
7	PhMgBr (1.0)	Tol^b	LiCl (0.1)	70
8	PhMgBr (1.0)	Tol^b	LiCl (1.0)	72 (79^c)
9	PhMgBr (1.0)	Tol ^b	$\text{BF}_3 \cdot \text{OEt}_2$ (0.1)	60
10	Ph_2CuLi (1.0)	Tol	—	37
11	Ph_2CuLi (1.1)	Tol	TMSOTf (0.1)	27
12	$\text{PhMgBr} \cdot \text{CeCl}_3$ (1.0)	Tol ^b	—	20
13	$\text{PhCeCl}_2 \cdot \text{LiCl}$ (1.0)	Tol	—	28
14	PhMgBr (1.0)	Tol ^b	ZnCl_2 (1.0) ^d	17
15	PhMgBr-ZnCl₂ (1.0)	Tol^b	—	69

^a Reactions were carried out at -78°C unless otherwise stated.

^b Toluene/THF 15:1–20:1 (see **ESI**).

^c The reaction was carried out at -100°C .

^d Sulfinatate **7** was added to a suspension of ZnCl_2 in toluene followed by the addition of PhMgBr .

The addition of LiCl turned out to be quite ineffective when isopropyl-, ethyl-, and allylmagnesium halides were used. In most cases the yields of sulfoxides **12i-k** were higher in experiments without the LiCl additive.

Gratifyingly use of ZnCl_2 as the additive gave good yields of sulfoxides **12i-k** (61–77%). Disappointingly experiments with other organometallic reagents (e.g., BuLi/CeCl_3 , BuLi/ZnCl_2) did not provide the expected products.

We also tested the ability of commercially available *t*-butyldimethylsilyl methallylsulfinate **13** to form sulfoxides **12a,j,k** (**Scheme 5**, **Table 3**). When the reaction was performed without additives, the more sterically bulky starting material **13** gave slightly higher yields of sulfoxides **12a,j,k** than its

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