β,β-Disilylated Sulfones as Versatile Building Blocks in Organic Chemistry – A New Sulfonyl Carbanion Transmetalation

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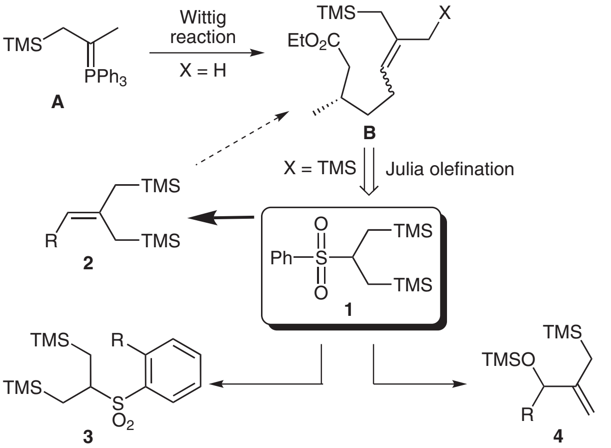
Abstract: 1,3-Bis(trimethylsilyl)propyl phenyl sulfone undergoes, in contrast to all reported sulfones bearing α-hydrogen atoms, an initial *ortho* metalation to an aryllithium at low temperature, which transmetalates quantitatively to the corresponding α-sulfonyl organolithium intermediate. Both organolithiums react selectively with aldehydes to give the corresponding products in good to excellent yields with high selectivity.

Key words: carbanions, transmetalation, silanes, sulfones, Julia olefination

The formation of carbon–carbon double bonds is one of the most important reactions in organic synthesis, since olefins are prevalent in many naturally occurring and biologically active molecules, polymer precursors, and organic materials. Numerous methods ranging from Wittig and related reactions, through Peterson- or Tebbe-type olefinations to cross-metathesis were developed over the years. Among those, the Julia olefination and its variants[1] represents one of the most powerful tools of organic chemistry, since it is known to be *E*-selective, well controlled, and easy to perform.

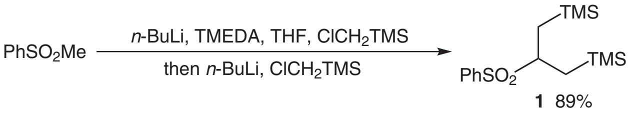
In a recent total synthesis of dihydronepetalactone,[2] a Wittig reaction using phosphorane **A** was applied to construct the pivotal trisubstituted allylsilane cyclization precursor **B** (Scheme 1, X = H). This reaction was plagued by low yield and the formation of side products. Thus, an alternative selective approach to allylsilanes of type **B** (X = H) or **2** (X = TMS) was highly needed. Since known methods[3] to access compounds of type **2** were not applicable with respect to functional-group tolerance and ease of precursor synthesis, we aimed for the development of a Julia olefination using unknown silylated sulfones **1**.

We present herein, initial results of a reactivity study of the so far unknown bissilylated sulfone **1** (Scheme 1). This sulfone proves to be a true synthetic chameleon because of its distinct behavior under defined metalation conditions, but also since the resulting anions can be recognized easily visually by their colors. Not less than three classes of so far more or less explored compound classes, compounds **2**–**4** can be synthesized with a good substrate scope in good to excellent yield applying defined metalation conditions. This reactivity diversity is based on a new sulfonyl carbanion transmetalation.



Scheme 1

Bis(trimethylsilylmethyl)methyl phenyl sulfone (**1**) was prepared by successive alkylation of methyl phenyl sulfone with (chloromethyl)trimethylsilane in the presence of TMEDA in excellent yield in a one-pot process (Scheme 2). It is worth underlining that a single addition of two equivalents of *n*-BuLi and (chloromethyl)trimethylsilane does not lead to compound **1**, but gives only the monoalkylated product even after long reaction time at elevated temperature.



Scheme 2

Initial experiments of **1** with benzaldehyde using standard Julia olefination conditions (*n*-BuLi, –78 °C) furnished *ortho*-substituted **3a** instead of the expected olefination product (Scheme 3). Addition of TMEDA leads to the same result. This was surprising, since directed *ortho* metalation was never observed before as the initial event for sulfones bearing α-hydrogens.[4,5] On the other hand, allylic silyl ether **4a** was obtained as the only product using HMPA as an additive.

These results indicated that the *ortho*- or the α-carbanions **1a**-Li or **1b**-Li were either selectively generated or that a

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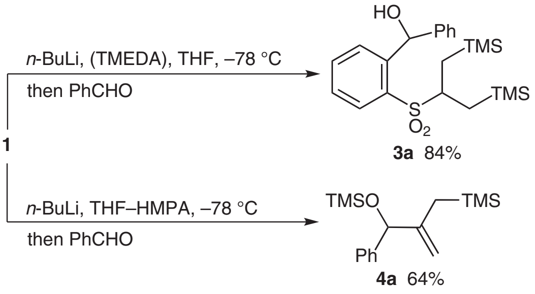
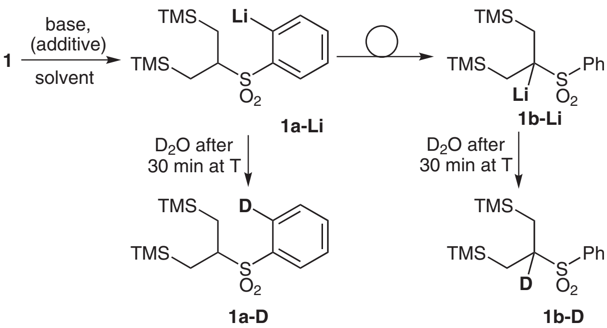


Scheme 3

rearrangement between them took place (Scheme 4). To distinguish these options, the deprotonation of **1** using different bases and additives was monitored by keeping the reaction mixtures for 30 minutes at the given temperatures, taking aliquots, quenching them by D_2O, and analyzing the products by ^1H NMR (Scheme 4, Table 1). Using *n*-BuLi as a base in THF at –78 °C, **1a**-D and **1b**-D were formed in a 2.3:1 ratio (entry 1). Warming successively to –40 °C, 0 °C, and 20 °C leads to a reversed ratio of **1a**-D/**1b**-D of 1:24. The course of the transmetalation of the *ortho*- to the α-carbanion can be monitored even visually, since **1a**-Li is pale yellow while **1b**-Li appears red in solution. The initial **1a**-Li/**1b**-Li selectivity is better with TMEDA (entry 2) and especially in DME (entry 3). Immediate α-deprotonation to **1b**-Li was predominant with HMPA even at –78 °C (entry 4). LDA deprotonated **1** less selectively to **1a**-Li at –78 °C, but rearrangement to **1b**-Li took place smoothly (entry 5). The conversion was quantitative for all entries. In contrast, widely used KHMDS was completely ineffective as a base (entry 6).

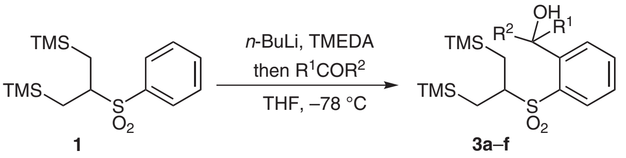


Scheme 4

With reliable conditions in hand to generate anions **1a**-Li and **1b**-Li selectively, the scope of their reactivity toward aldehydes was explored. Deprotonation of **1** with *n*-BuLi/TMEDA in THF at –78 °C for 30 minutes, followed by addition of aldehydes gave *ortho*-(hydroxyalkyl)phenyl sulfones **3a–d** in excellent yield (Scheme 5, Table 2, entries 1–4). This method is also applicable to ketones such as cyclohexanone or benzophenone to provide alcohols **3e–f** (entries 5 and 6).

Table 1 Rearrangement of Carbanions **1**-Li

Entry	Base	Additive	Solvent	**1a/1b**			
				–78 °C	–40 °C	0 °C	20 °C
1	*n*-BuLi	–	THF	2.3:1	2.1:1	1:5.6	1:24
2	*n*-BuLi	TMEDA	THF	9.6:1	2.8:1	1:4.9	1:20
3	*n*-BuLi	TMEDA	DME	13.2:1	5.6:1	1:20	1:49
4	*n*-BuLi	HMPA	THF	1:5.6	1:49	1:99	1:99
5	LDA	–	THF	3.6:1	1.5:1	1:9	1:11.5
6	KHMDS	–	THF	–	–	–	–

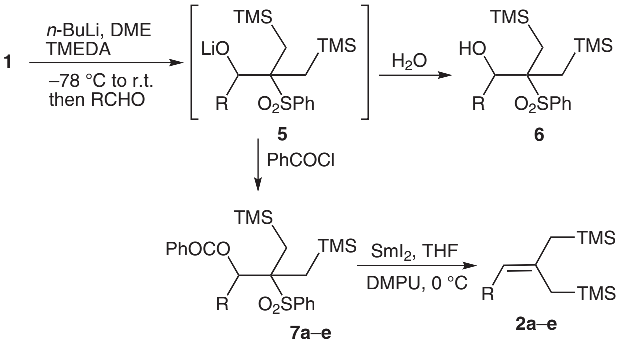


Scheme 5

Table 2 Scope of Aryllithium Addition to Aldehydes and Ketones

Entry	Product	R^1	R^2	Yield (%)
1	**3a**	Ph	H	91
2	**3b**	*i*-Pr	H	92
3	**3c**	EtCH=CH	H	88
4	**3d**	$PhCH_2CH_2$	H	88
5	**3e**	$-(CH_2)_5-$		85
6	**3f**	Ph	Ph	83

When the reaction mixture of **1**, *n*-BuLi, and TMEDA was allowed to warm to room temperature followed by addition of structurally different aldehydes, very unstable alcohols **6** resulted (Scheme 6). To circumvent isolation of **6**, benzoyl chloride[6] was added immediately after consumption of the aldehyde providing the more stable β-benzoyloxy sulfones **7a–e** in good yields (Table 3). The reagent used for the subsequent conversion of **7a–e** to allylic bissilanes **2a–e** in high yields was SmI_2 (0.1 M in THF; entries 1–5). Some isomerization was observed during reduction of **7b** (*E*/*Z* ratio = 4:1, entry 2). Even brominated compound **2e** was obtained in excellent yield (entry 5).



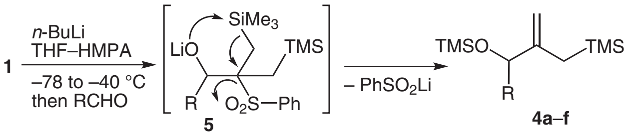
Scheme 6

Table 3 Scope of the Julia Olefination to **2**

Entry	R	Product	Yield (%)	Product	Yield (%)
1	Ph	**7a**	79	**2a**	89
2	EtCH=CH	**7b**	82	**2b**	84[a]
3	PhCH=CH	**7c**	76	**2c**	90
4	*n*-C_5H_{11}	**7d**	80	**2d**	64[b]
5	4-BrC_6H_4	**7e**	85	**2e**	91

[a] Product is a 4:1 *E*/*Z* diastereomeric mixture.
[b] Product is volatile.

Deprotonation of **1** in the presence of HMPA as an additive and subsequent reaction with aldehydes at low temperature furnished the allylic silyl ethers **4a**–**f** in good yield (Scheme 7, Table 4). These compounds are very valuable as substituted allylic silane nucleophiles[7] or trimethylene methane precursors after conversion of the silyl ether unit to a triflate.[8]

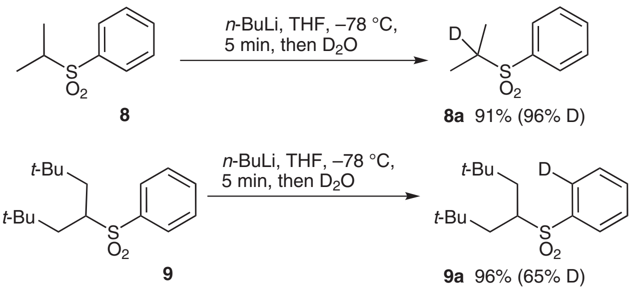


Scheme 7

Table 4 Scope of the Synthesis of Allylic Silyl Ethers **4**

Entry	R	Product	Yield (%)
1	Ph	**4a**	74
2	*n*-C_5H_{11}	**4b**	71
3	*c*-C_6H_{11}	**4c**	68
4	EtCH=CH	**4d**	72
5	PhCH=CH	**4e**	72
6	$PhCH_2CH_2$	**4f**	70

This divergent reactivity can be rationalized as follows at the current stage: Initial *ortho* deprotonation of **1** with *n*-BuLi is strongly kinetically favored at low temperature. The resulting anion **1a**-Li is stable at low temperature and reacts selectively with electrophiles to benzylic alcohols **3**. On warming, the aryllithium transmetalates to thermodynamically favored α-sulfonyllithium **1b**-Li and provides Julia olefination products **2**. Immediate α-deprotonation to **1b**-Li seems to prevail in the presence of HMPA, suggesting that good ligands for the lithium ion prevent precoordination of BuLi to the sulfone necessary for the formation of **1a**-Li more effectively. This fact together with the synergistic facilitation of the Brook rearrangement[9] leads to silyl ethers **4** and contributes favorably to the diversity of the reactivity of **1**.



Scheme 8

How general is the sulfonyl anion transmetalation? It is known that deprotonation of isopropyl phenyl sulfone **8** occurs exclusively in α-position at room temperature (Scheme 8).[10] To shed more light on a potentially similar initial metalation selectivity, orienting deprotonation/deuteration experiments were performed with **8** and phenyl (2,2,6,6-tetramethylhept-4-yl)phenyl sulfone (**9**), the carbon analogue of **1**. For **8**, exclusive but common α-deprotonation was found at –78 °C even after short deprotonation times. Compound **9**, which was obtained by twofold alkylation of methyl phenyl sulfone with neopentyl iodide (see the Supporting Information), gave *ortho*-deuterated product **9a** exclusively after five minutes deprotonation time. The lower D incorporation of 65% into **9** may be due to incomplete deprotonation of this even more hindered sulfone after the short metalation time. This result demonstrates that the initial *ortho* deprotonation and the subsequent rearrangement may be a more general process even when more acidic α-protons are available. The results of **8** and **9** vs. **1** point to steric reasons being responsible for the divergent deprotonation behavior. A potential kinetically destabilizing β-silyl carbanion effect[11] can be excluded based on the common reactivity of **1** and **9**. Future studies must determine how far the steric hindrance of the sulfones can be reduced to still allow initial *ortho* deprotonation. Other factors such as whether the transmetalation is inter- or intramolecular must be studied in detail.

In summary, a new sulfonyl carbanion transmetalation was discovered. It seems to be based on the limited accessibility of the α-proton in sulfones such as **1** or **9**. A selective rich reactivity of bissilylated sulfone **1** based on its carbanion chemistry was uncovered. Directed *ortho* metalation/nucleophilic additions, Julia olefinations and Brook rearrangements can be selectively addressed. All products **2**–**4** are synthetically interesting in their own right. Especially the bis(allylic) silanes **2** will be interesting functional dinucleophiles and radical acceptors for future applications. Compounds **4** represent nucleophiles, which are applicable in Sakurai reactions or as substituted trimethylenemethane synthons after conversion of the silyl ether to a triflate. The synthetic potential and structural prerequisites of the new transmetalation must be explored in future studies. On this basis, many applications of **1** and other similar compound classes can be foreseen. Research along these lines is under way in this laboratory.

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

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