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Reaction of Arynes with Vinyl Sulfoxides: Highly Stereospecific Synthesis of *ortho*-Sulfinylaryl Vinyl Ethers

Yuanming Li and Armido Studer*

Organisch-Chemisches Institut, Westfälische Wilhelms-Universität, Corrensstra*ß*e 40, 48149 Münster, Germany

Supporting Information

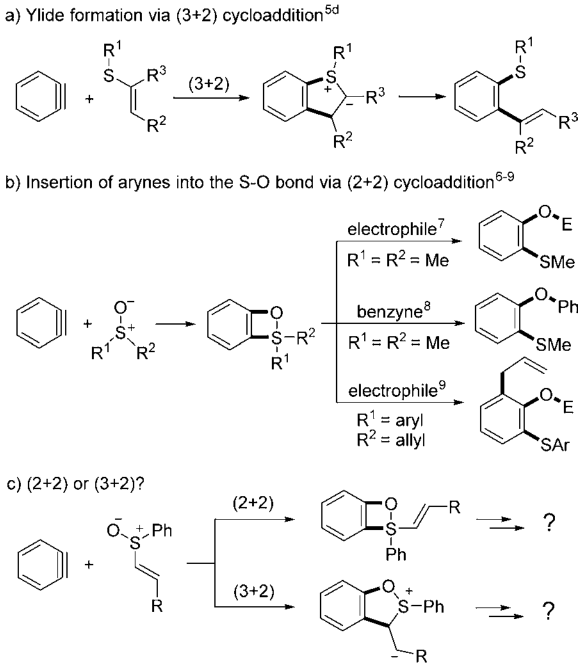
ABSTRACT: The reaction of in situ generated arynes with aryl vinyl sulfoxides provides *ortho*-arylsulfinylaryl vinyl ethers via aryne *σ*-bond insertion into the S−O-bond and concomitant stereospecific S−O-vinyl migration. The cascade allows preparing di- or trisubstituted vinyl ethers with excellent stereospecificity. The reactions proceed under mild conditions, the substrate scope is broad, and the products obtained are valuable.

Arynes have received considerable attention, as readily generated reactive intermediates over the past few years and many valuable transformations comprising arynes have been reported.[1−3] Notably, meanwhile over 75 natural products have been successfully synthesized by using arynes as key intermediates.[4]

As part of our ongoing research program on aryne chemistry,[5] we recently disclosed that vinyl thioethers lacking *α*-CH protons react with benzyne through direct (3 + 2) cycloaddition to give cyclic sulfonium ylides. Proton transfer and *β*-elimination eventually afford the corresponding trisubstituted alkenes with high stereoselectivity (Scheme 1a).[5d] It is known that dimethyl sulfoxide, used as a solvent, can react with benzyne to give the (2 + 2) cycloaddition intermediate,[6] which upon cleavage of the S−O bond leads to the corresponding zwitterionic sulfonium salt. Subsequent intermolecular trapping of the phenolate by either an electrophile[7] or benzyne[8] with concomitant S-CH_3 cleavage of the sulfonium salt moiety affords *ortho*-alkoxylated arylmethyl thioethers (Scheme 1b). Recently, Li et al. found that aryl allyl sulfoxides react with benzyne to provide 1,2,3-trisubstituted arenes via (2 + 2) cycloaddition, S−O-allyl migration, and subsequent Claisen rearrangement (Scheme 1b).[9] Based on this precedence and our own contribution, we decided to investigate the reaction of aryl vinyl sulfoxides with arynes and assumed that such a transformation can proceed via either initial (2 + 2) or (3 + 2) cycloaddition (Scheme 1c). Another point of interest was the follow-up chemistry of the initially generated cycloadduct. We herein report first results along those lines and will show that such reactions proceed via the (2 + 2) pathway to provide *ortho*-arylsulfinylaryl vinyl ethers as products.

We commenced the studies using methyl (*Z*)-3-(phenylsulfinyl) acrylate **2a** and *ortho*-silylaryl triflate **1a** as reaction components (Table 1). Transformations were conducted in acetonitrile, and various fluoride sources to mediate aryne generation were tested. Water[5d] was applied as an additive. Using **1a** (1.2 equiv) with CsF (2.4 equiv) and H_2O (2 equiv) in the presence of **2a** (1 equiv) in CH_3CN at 80 °C for 3 h provided the *Z*-product **3a** in 50% yield with complete stereospecificity (Table 1, entry 1). As a side product, vinyl sulfide **4a** derived from deoxygenation of **2a** was observed in 17% yield as an *E*/*Z*-mixture of isomers. Other fluoride sources such as tetrabutylammonium fluoride (TBAF) or potassium fluoride in combination with 18-crown-6 provided significantly lower yields with similar conversions, and side product **4a** was formed in larger quantities (Table 1, entries 2, 3). Notably, increasing or decreasing the amount of water led to a lower yield of target **3a** (Table 1, entries 4−6). Other additives such

Scheme 1. Reaction of Benzyne with Vinyl Thioethers or Vinyl Sulfoxides


a) Ylide formation via (3+2) cycloaddition[5d]

b) Insertion of arynes into the S-O bond via (2+2) cycloaddition[6-9]

c) (2+2) or (3+2)?

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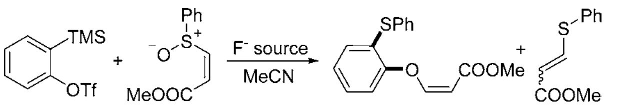
Table 1. Reaction of 1a with 2a under Different Conditions[a,b]



1a **2a** **3a** **4a**

entry	additive (equiv)	F$^-$ source	time (h)	temp (°C)	3a (%)	2a (%)	4a (%)
1	H_2O (2)	CsF	3	80	50	0	17
2	H_2O (2)	TBAF	3	80	10	0	47
3	H_2O (2)	KF/18-C-6	3	80	32	0	28
4	H_2O (1)	CsF	3	80	30	0	23
5	H_2O (3)	CsF	3	80	22	68	3
6	H_2O (5)	CsF	2	80	<5	87	0
7	MeOH (2)	CsF	3	80	27	0	28
8	AcOH (2)	CsF	3	80	0	0	28
9	**H_2O (3)**	**CsF**	**24**	**55**	**65**	**8**	**8**
10	–	CsF	24	55	10	0	36

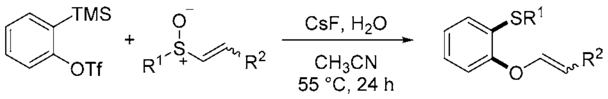
[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.2 mmol), and F$^-$source (0.48 mmol) in acetonitrile (2 mL). [b]Yield was determined by ^{1}H NMR spectroscopy.

as methanol and acetic acid turned out to be less efficient to mediate the cascade (Table 1, entries 7, 8). The yield of **3a** was improved to 65% upon running the reaction at 55 °C in the presence of 3 equiv of water (Table 1, entry 9). In the absence of water under otherwise identical conditions the yield of **3a** significantly decreased (10%) and **4a** was formed as the major product (Table 1, entry 10).[10] Water is necessary to suppress formation of the deoxygenation side product **4a** (see discussion below).

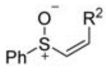
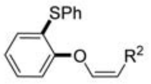
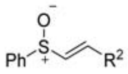
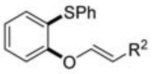
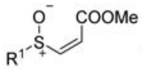
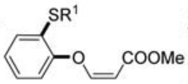
To demonstrate functional group compatibility of the sulfoxide component, vinyl sulfoxides **2b–o** were reacted with *in situ* generated benzyne under the optimized conditions, and the results are illustrated in Table 2. Exchanging the ester functionality in the acrylate moiety by an amide group does not alter the reaction outcome, and the target product **3b** was isolated in 63% yield. However, with the ketone functionalized sulfoxide desired compound **3c** was not formed. In this reaction we isolated the corresponding deoxygenated phenyl vinyl sulfide as the major product.[11] To test the stereospecificity of the cascade, (*E*)-3-(phenylsulfinyl) acrylate **2d** was reacted with **1a** and the *trans*-vinyl ether was obtained with complete stereoselectivity showing that this process is highly stereospecific. We noted that reaction with the *trans*-vinyl sulfoxide **2d** is far slower as compared to the transformation with its *cis*-congener **2a**, and therefore the reaction time had to be extended to 48 h. Product **3d** was isolated in 46% yield. A similar yield and complete stereospecificity were also obtained with the corresponding ethyl ester. This reaction was conducted at a larger scale (1.0 mmol) to provide **3e** in 48% yield. The trifluoromethylated vinyl sulfoxide **2f** provided the desired product **3f** in 52% yield. Target products (**3g–i**) were not formed with the phenylvinyl, methoxyvinyl, and vinyl sulfoxide **2g–i** showing that the activating substituent at the *β*-position of the vinyl group in the sulfoxide is of key importance for a successful reaction outcome.

The effect of the R^1-substituent in the sulfoxide component was examined by replacing the phenyl group in **2a** with different aryl groups or by the *tert*-butyl group (**2j–o**). Reaction of the naphthyl and the *p*-methoxyphenyl sulfoxide with **1a** provided **3j** and **3k** in 50% yield each. A slightly lower yield was achieved using the sterically hindered electron-poorer *ortho*-bromophenyl sulfoxide (see **3l**). With the vinyl sulfoxide **2m** bearing the pentafluorophenyl group, the desired product **3m** was obtained in only 11% yield. The significantly lower yield is likely due to the reduced O-nucleophilicity of **2m** as compared to its nonfluorinated congener **2a**. The sterically hindered but electron-rich 2,6-dimethylphenyl-substituted sulfoxide **2n** provided vinyl ether **3n** in 87% yield. Using the *tert*-butyl vinyl sulfoxide **2o**, the target product **3o** was not formed.

Table 2. Reaction of 1a with Various Vinyl Sulfoxides[a]



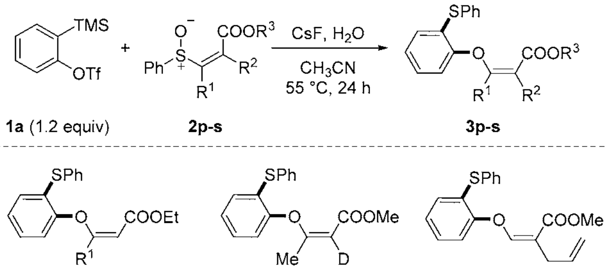
1a (1.2 equiv) **2a-o** **3a-o**

2a-o	3a-o	yield[b]
		**3a** (65%, R^2 = CO_2Me) **3b** (63%, R^2 = $CONEt_2$) **3c** (not formed, R^2 = COMe)
		**3d** (46%, R^2 = CO_2Me)[c] **3e** (48%, R^2 = CO_2Et)[c,d] **3f** (52%, R^2 = CF_3)[c] **3g** (not formed, R^2 = Ph) **3h** (not formed, R^2 = OMe) **3i** (not formed, R^2 = H)
		**3j** (50%, R^1 = 2-naphthyl) **3k** (50%, R^1 = 4-MeOC$_6$H$_4$) **3l** (44%, R^1 = 2-BrC$_6$H$_4$) **3m** (11%, R^1 = C$_6$F$_5$)[e] **3n** (87%, R^1 = 2,4-Me$_2$C$_6$H$_3$) **3o** (not formed, R^1 = *t*-Bu)

[a]Reaction conditions: **1a** (0.24 mmol), **2** (0.2 mmol), H_2O (0.6 mmol), and CsF (0.48 mmol) in acetonitrile (2 mL) at 55 °C for 24 h under an argon atmosphere. [b]Isolated yield. [c]The reaction was conducted for 48 h. [d]Larger-scale synthesis **2a** (1.0 mmol). [e]The reaction was conducted with H_2O (1.8 mmol).

Next, the trisubstituted vinyl sulfoxides **2p–s** were investigated (Scheme 2). The cinnamic acid ester **2p** afforded in the reaction with benzyne the vinyl ether **3p** in 50% yield with complete stereospecificity. However, an *α*-CF$_3$-substituent at the vinyl group of the sulfoxide (see **2q**) is not tolerated and the corresponding product **3q** was not formed. *α*-Methyl-*β*-

Scheme 2. Reaction of Benzyne with Trisubstituted Vinyl Sulfoxides 2p–s

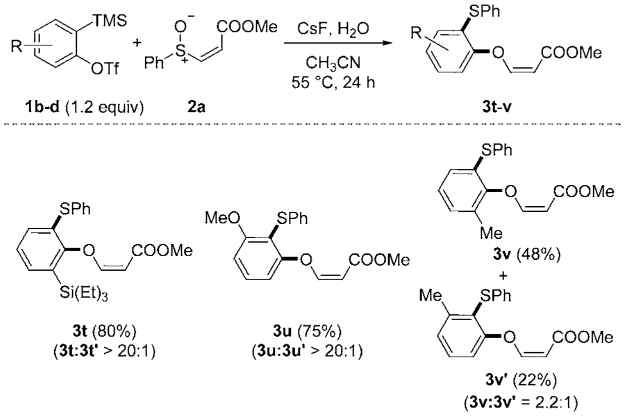


3p (50%, R^1 = Ph) **3r** (45%, H:D = 4:96) **3s** (44%)
3q (not formed, R^1 = CF_3)

deutero-substituted vinyl sulfoxide **2r** afforded the desired product **3r** in 45% yield keeping 96% deuterium incorporated. Importantly, β-alkyl-substituents at the vinyl moiety are tolerated as documented by the successful transformation of the β-allylvinyl sulfoxide **2s** to give **3s** in 44% yield with complete stereospecificity.

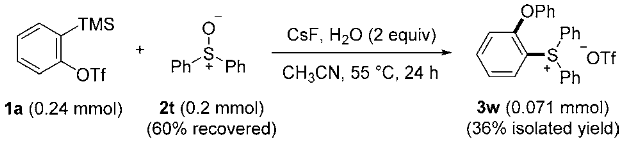
We continued the studies by investigating substituted aryne precursors to address the regiochemistry of the cascade with respect to the intermediate aryne (Scheme 3). Reaction with the unsymmetrical arynes, 3-triethylsilyl benzyne and 3-methoxybenzyne, occurred with complete regioselectivity to provide the corresponding products **3t** and **3u** in 80% and 75% isolated yield, respectively. The other regioisomers **3t′** and **3u′** were not identified in the mixture. The selectivity can be understood considering the aryne distortion model which shows that regioselectivity in the initial cycloaddition is dominated by inherent distortion present in these two unsymmetrical arynes.[12] Decreasing the size of the 3-substituent in the intermediate aryne led to a significantly reduced (2.2:1) regioselectivity (**3v**/**3v′**, 70% combined yield).

Scheme 3. Reaction of 2a with Various *in Situ* Generated Arynes



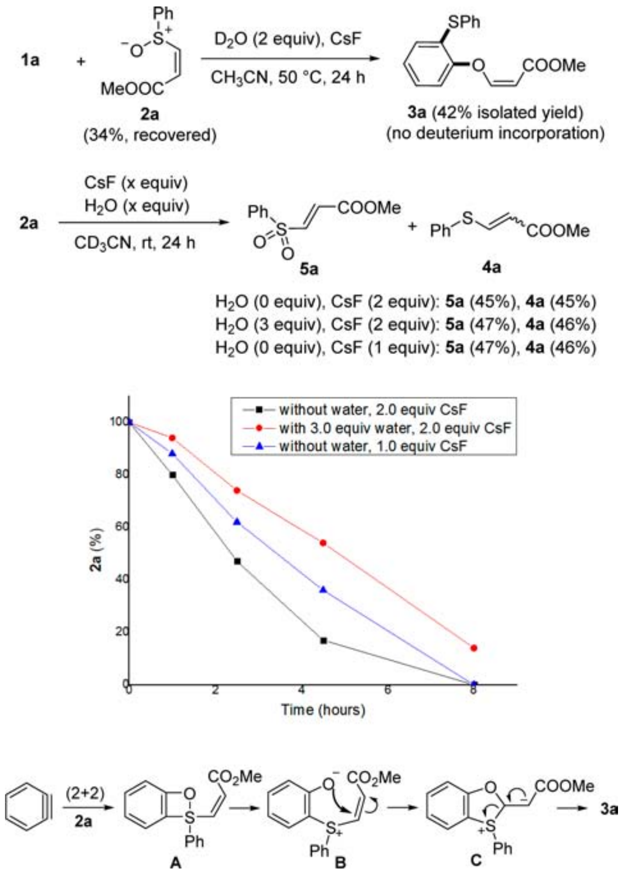
We also explored whether the vinyl substituent in **2a** could be replaced by a phenyl group and tested the reaction of **1a** with diphenyl sulfoxide (**2t**) to provide the triarylsulfonium salt **3w** in 36% yield (Scheme 4). Notably, such salts have been successfully employed in industry as acid generators in photolithography and also as photoinitiators in cationic polymerization.[13] In contrast to the efficient S−O-vinyl migration, obviously S−O-phenyl migration cannot compete with trapping of the phenolate by benzyne.

Scheme 4. Reaction of Benzyne with Diphenyl Sulfoxide



To study the effect of water on the reaction outcome, we repeated the experiment of **1a** with **2a** using D$_2$O (2 equiv) as an additive and obtained vinyl ether **3a** without any deuterium incorporation (Scheme 5, top). This transformation revealed that water is likely not involved in any protonation/deprotonation steps in this cascade. To gain further understanding of the beneficial water effect, the reaction of **2a** in the absence of **1a** was followed by ^{1}H NMR spectroscopy at room temperature (Scheme 5, middle). When **2a** was reacted in CD$_3$CN with CsF, **2a** was consumed within 8 h and the sulfone **5a** along with the sulfide **4a** resulting from a sulfoxide disproportionation were formed in equal amounts. Sulfoxide disproportionation is a known reaction at high temperature;[14] however, the fluoride-mediated disproportionation at room temperature has not been reported. Disproportionation is slower in the presence of water and also if the amount of CsF is decreased (see Scheme 5). These results indicate that addition of water simply suppresses disproportionation of **2a** to **5a** and **4a**. We also found that the sulfone **5a** does not undergo a clean reaction under optimized conditions with *in situ* generated benzyne. Based on these studies and previous reports[6−9,15] we suggest the following mechanism (Scheme 5, bottom). Sulfoxide **2a** reacts with benzyne in a concerted (2 + 2) cycloaddition to intermediate **A**.[7,8] Cleavage of the S−O bond then leads to zwitterion **B**. Stereospecific S−O vinyl migration by intramolecular ionic addition elimination (least motion) via **C** eventually affords **3a**.[16]

Scheme 5. Mechanistic Experiments and Suggested Mechanism



In summary, we showed that *in situ* generated arynes react with aryl vinyl sulfoxides via (2 + 2) cycloaddition, S−O bond cleavage in the four-membered benzanellated cycloadduct, and subsequent ionic vinyl migration to *ortho*-arylsulfinylaryl vinyl ethers. These cascades proceed with complete stereospecificity in moderate to good yields. It was found that water as an additive is important to suppress fluoride-mediated disproportionation of the sulfoxide to the corresponding sulfide and sulfone. Reaction of the vinyl sulfone with the aryne leads to unidentified side products thereby consuming the aryne component. The chemistry presented is valuable for the stereoselective preparation of highly substituted vinyl ethers. In contrast to the vinyl migration, the analogous sequence comprising a phenyl migration starting with diphenyl sulfoxide was not observed and reaction of diphenyl sulfoxide with benzyne provided the corresponding triarylsulfonium salt as a result of initial (2 + 2) cycloaddition, S−O bond cleavage, and trapping of the zwitterionic phenolate with benzyne.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03827.

Experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: studer@uni-muenster.de.

ORCID

Armido Studer: 0000-0002-1706-513X

Notes

The authors declare no competing financial interest.

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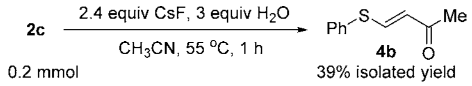
(11) A 39% yield of **4b** was obtained by using CsF (2.4 equiv) and H_2O (3 equiv) in the presence of **2c** (1 equiv) in CH_3CN at 55 °C for 1 h.



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