

Nucleophilic *ortho*-Propargylation of Aryl Sulfoxides: An Interrupted Pummerer/Allenyl Thio-Claisen Rearrangement Sequence**

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Selective C–C bond formation to aromatic systems is one of the most important synthetic objectives as the resulting motifs form the core of many pharmaceuticals, agrochemicals, and functional materials. In this regard, products of propargylation^[1] are valuable synthetic intermediates as they are established precursors to other functional groups, and to carbo- and heterocycles.^[1] Unfortunately, direct propargylation of aromatics is often difficult and can lead to mixtures of propargyl and allenyl products. Although metal-catalyzed couplings are possible,^[2] many methods rely on Friedel–Crafts-type processes that can require stoichiometric metal reagents.^[3] Using activating substituents to facilitate nucleophilic substitution in aromatic systems is a relatively under-exploited approach. In recent years, activation by sulfoxide substituents has been exploited in nucleophilic alkylations of electron-rich heteroaromatics^[4] that proceed through Pummerer-type reactions.^[5] Furthermore, Yorimitsu and Oshima^[6a–d] and Maulide^[6e] recently employed interrupted Pummerer reactions in approaches to targets such as benzofurans and α -aryl- β -ketoesters, while we have described an interrupted Pummerer approach for the allylation of aromatic and heteroaromatic rings.^[7]

Herein we report a nucleophilic *ortho*-propargylation of aryl sulfoxides that proceeds by a new interrupted Pummerer–allenyl thio-Claisen rearrangement^[8] sequence involving allenyl sulfonium salts **4** (Scheme 1).^[9] The operationally simple, metal-free procedure is general, regiospecific with

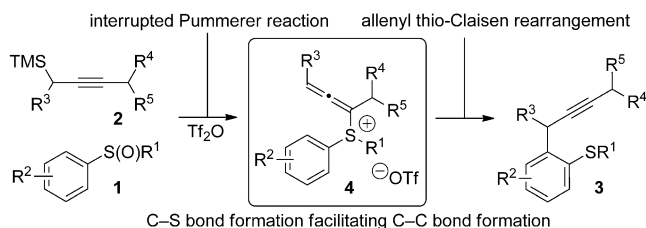
regard to the propargyl nucleophile, and shows complete selectivity for products of propargylation over allenylation.

Realizing the value of a process that would allow propargyl groups to be selectively introduced to aryl rings under metal-free conditions, we sought to develop a reaction in which intermolecular delivery of a nucleophile to sulfur is followed by an intramolecular relay to carbon (Scheme 1). We began by investigating the reaction of diphenyl sulfoxide **1a** with propargyl silane **2a** (Table 1). Using Tf₂O as an

Table 1: Optimization of the *ortho*-propargylation.^[a]

Entry	Solvent	<i>t</i> [h]	<i>T</i> [°C]	Base	Yield 3 [%]
1	CH ₂ Cl ₂	18	50	–	35
2	CHCl ₃	18	50	–	28
3	toluene	18	50	–	27
4	MeCN	18	50	–	63
5	MeCN	36	RT	–	72
6	MeCN	1	60	–	73
7	MeCN	18	60	pyridine	16
8	MeCN	18	60	2,6-lutidine	99 ^[b]
9	MeCN	18	60	2,6-DTBP	99

[a] Yields determined by ¹H NMR spectroscopy. Conditions: entries 7–9: base (2.5 equiv). [b] Yield of isolated product; 2,6-DTBP = 2,6-di-*tert*-butylpyridine.



Scheme 1. Nucleophilic *ortho*-propargylation of aryl sulfoxides. TMS = trimethyl silyl, Tf = 1,1,1-trifluoromethylsulfonyl.

electrophilic activating agent, propargylation product **3a** was obtained in low yield (entry 1). We next compared the reaction in various solvents and obtained the best result using MeCN (entry 4).^[10a] The reaction proceeded readily at room temperature in 36 h (entry 5) and the reaction time could be shortened to 1 h at 60 °C (entry 6). Addition of base significantly enhanced the reaction to give **3a** in an isolated yield of 99 % (entry 8).^[10b]

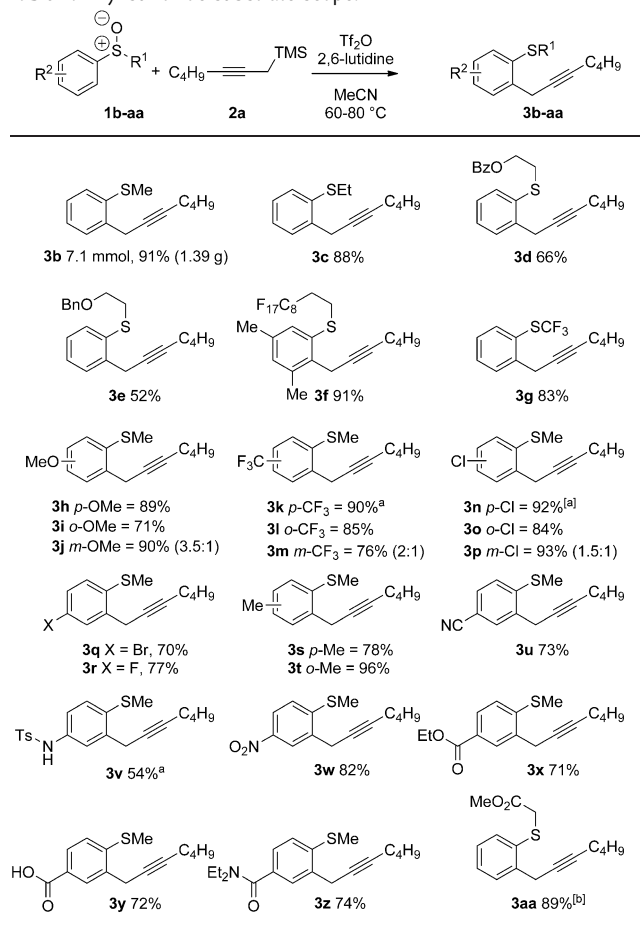
Having identified optimized reaction conditions we next investigated the substrate scope. Pleasingly the *ortho*-propargylation reaction is not restricted to diaryl sulfoxides, but works well with readily available, simple alkyl aryl sulfoxides **1b–aa** to give the corresponding products **3b–aa**, containing alkylsulfanyl groups that are of pharmaceutical relevance (Table 2). Methyl phenyl sulfoxide was easily converted to **3b** in excellent yield on a 1 gram scale. Surprisingly, the formation of classical Pummerer products (e.g. phenylthio-methyl trifluoromethanesulfonate from **1b**) was not observed, even in substrates containing electron-withdrawing

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Table 2: Aryl sulfoxide substrate scope.

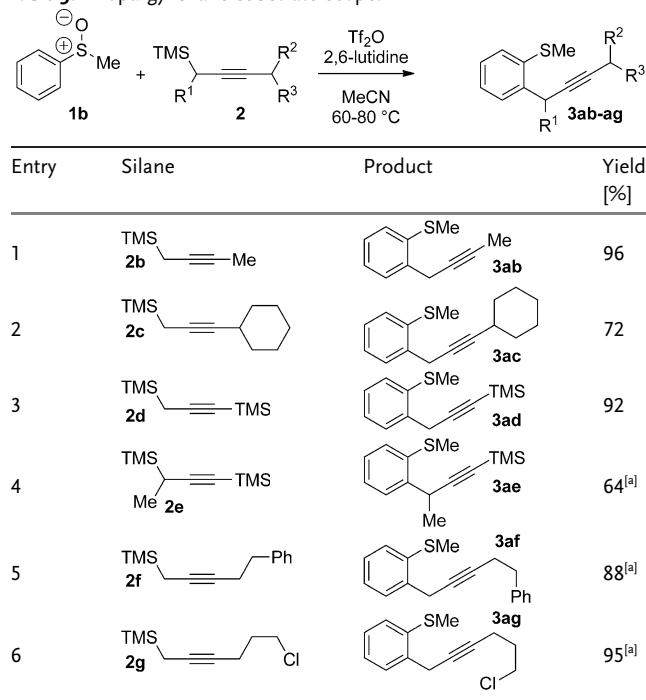


[a] 2,6-DTBP was used as the base. [b] No base.

alkyl chains (e.g. formation of **3d**, **3e**, **3f**, and **3aa**). Interestingly, the procedure also tolerates the synthetically important perfluorinated alkyl chain^[11] in **3f** and the medically relevant trifluoromethyl sulfide group in **3g**.^[12] The reaction is also general with respect to ring substituents: neutral, electron-rich and electron-deficient benzene rings are propargylated in high yields (**3h–z**) with no significant changes in overall reaction efficiency when substitution position was varied (**3h–p**, 71–93%). Even sterically hindered *ortho*-substituted substrates underwent propargylation to give **3l** and **3t** in 85% and 96% yield. The reaction tolerates a wide range of functional groups: Substrates containing halogens (**3n–r**), nitriles (**3u**), nitro (**3w**), and protected amines (**3v**)^[13] were all readily propargylated in good to excellent yields. Furthermore, substrates bearing ester, amide and acid groups underwent successful propargylation to give **3x–z**. Importantly, a substrate known to undergo classical Pummerer chemistry,^[14] gave **3aa** in 89% yield when exposed to Tf₂O in the presence of **2a**.

Methyl phenyl sulfoxide **1b** was exposed to propargyl silanes **2b–g** under the described conditions (Table 3). In all cases the expected products of propargylation were obtained in good to excellent yields. For example, commonly used silane **2b** (entry 1) and the protected propargyl silane **2d** (entry 3) produced products of selective propargylation in

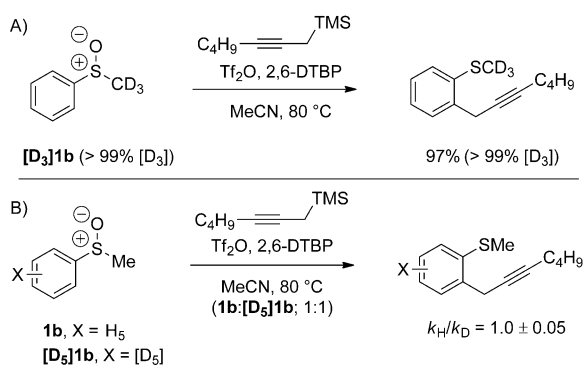
Table 3: Propargyl silane substrate scope.



[a] 2,6-DTBP was used as the base.

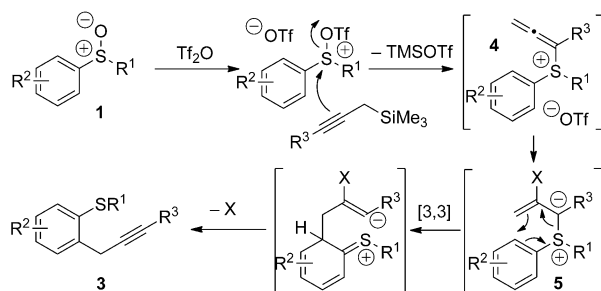
high yields. Sterically more demanding silanes (entries 2, 4), including those with substitution at both propargylic positions, and functionalized silanes (entries 5, 6) were also effective.

After activation of the sulfoxide with Tf₂O,^[15] two mechanisms are possible: A nucleophile could directly attack the aromatic ring with concomitant triflate expulsion followed by rearomatization,^[4a,b] or the nucleophile could react at sulfur in an interrupted Pummerer-type reaction,^[7] followed by rearrangement. The former pathway would be expected to deliver, *ortho* and *para* regioisomeric products of allenylation. In contrast, our process provides products of propargylation, with no allenylation and with complete *ortho*-selectivity. This suggests that the interrupted Pummerer pathway is operational. Indeed, allenyl sulfonium salt **4** (Scheme 1) formed by reaction at sulfur can be observed when reactions are monitored by ¹H and ¹³C NMR spectroscopy.^[16,17] The formation of **4** is fast^[18] and outcompetes classical thionium ion formation and Pummerer reaction. This conclusion is supported by the observation that **3aa** undergoes smooth propargylation despite the presence of acidic α-protons. In an additional experiment, labeled sulfoxide **[D₃]**1b**** (Scheme 2A) was propargylated with no ¹H incorporation, further highlighting the rapid formation of allenyl sulfonium salts **4** rather than loss of a proton α to sulfur. The nature of substituents on the aryl ring, as well as their positions,^[19] affect the rate of the rearrangement of **4** to products **3** as shown by preliminary rate and Hammett studies.^[20] Furthermore, a competition experiment involving a 1:1 mixture of **1b** and its aryl-deuterium labeled analog **[D₅]**1b**** (Scheme 2B) showed no isotope effect, suggesting that rearomatization is not the rate-determining step.



Scheme 2. Labeling experiments (yields and conversions measured by ¹H NMR spectroscopy).

A proposed mechanism for the selective *ortho*-propargylation is shown in Scheme 3. Interrupted Pummerer reactions, in which sulfoxides **1** activated by Tf₂O undergo nucleophilic attack by the propargyl silanes at sulfur give allenylsulfonium salts **4** (Scheme 3). These intermediates may then convert to

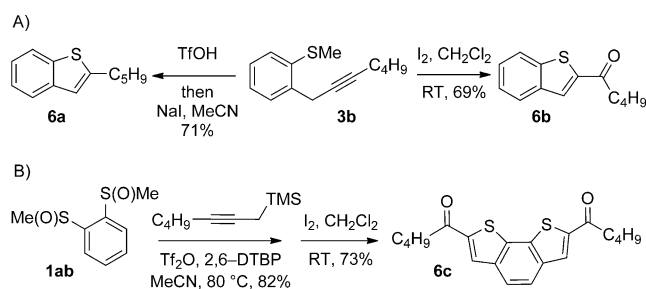


Scheme 3. Proposed mechanism for *ortho*-propargylation.

ylides **5** prior to [3,3]-sigmatropic rearrangement^[8,21,22] and rearomatization to yield **3**.^[23]

The products of *ortho*-propargylation are rich in synthetic potential as the combination of the propargyl^[1] and organosulfanyl groups opens up a wide range of bond-forming possibilities. In particular, recent developments have shown that the C–S bond can be readily utilized in transition-metal-catalyzed cross-couplings to form C–C bonds.^[6d,7,24] Preliminary studies show the potential of the dual functionality in the adducts. For example, **3b** was converted to benzothiophenes **6a** and **6b** by treatment with TfOH/NaI and I₂,^[25] respectively. Furthermore, double cyclization of the adduct formed by the two-directional propargylation of bis-sulfoxide **1ab**, completed an efficient metal-free approach to **6c**, a motif found in organic semiconductors (Scheme 4).^[26]

In summary, readily available aryl sulfoxides undergo *ortho*-selective propargylation by a new interrupted Pummerer/allenyl thio-Claisen rearrangement sequence. The operationally simple, metal-free procedure allows propargylic carbon nucleophiles to be added *ortho* to sulfur on a benzene ring, regioselectively with regard to the propargyl nucleophile, and with complete selectivity for products of propargylation over allenylation. The organosulfanyl group and



Scheme 4. Manipulation of *ortho*-propargylation products.

the propargyl motif in the products are versatile handles for further manipulation.

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