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Communication

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Aryne 1,2,3-Trifunctionalization with Aryl Allyl Sulfoxides

Yuanyuan Li,† Dachuan Qiu,† Rongrong Gu, Junli Wang, Jiarong Shi, Yang Li*

School of Chemistry and Chemical Engineering, Chongqing University, 174 Shazheng Street, Chongqing, P. R. China, 400030

Supporting Information Placeholder

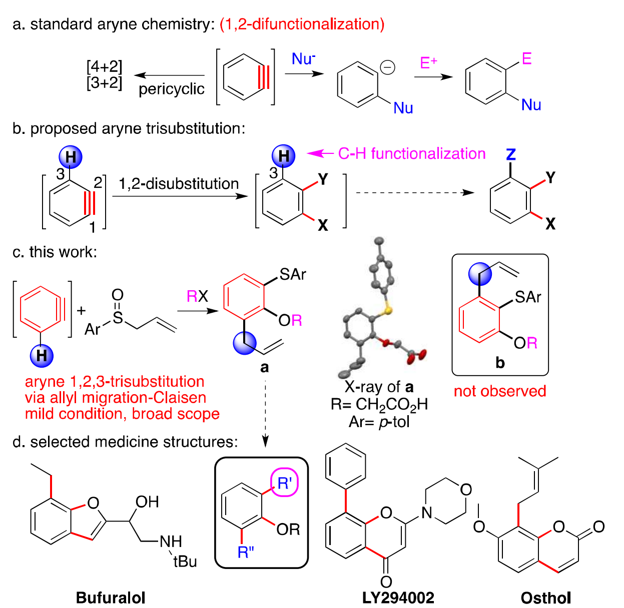
ABSTRACT: An aryne 1,2,3-trisubstitution with aryl allyl sulfoxides is accomplished, featuring an incorporation of C-S, C-O, and C-C bonds on the consecutive positions of a benzene ring. The reaction condition is mild with broad substrate scope. Preliminary mechanistic study suggests a cascade formal [2+2] reaction of aryne with S=O bond, an allyl S→O migration, and a Claisen rearrangement.

Arynes are ubiquitous active intermediates with numerous synthetic applications, primarily attributed to their versatility in the concomitant incorporation of various functional groups on the vicinal positions of an arene ring.[1] Along with the development of mild aryne generation conditions by Kobayashi[1f,1g,2] and Hoye,[3] aryne chemistry has commenced a renaissance in recent years. Certain limitations, however, remain to be solved in aryne chemistry. For instance, the existence of a formal triple bond of a standard aryne intermediate could only allow functionalization on the 1,2-positions of an arene ring (Scheme 1a). Whereas, three or more substituted arenes are widespread in natural products and medicines. Breaking this two-site bonding restriction of an aryne intermediate could provide synthetic chemists a broader spectrum of means in terms of constructing multi-substituted arenes for the purpose of quick synthesis of drug molecules as well as other high-value compounds.

Our research focuses on the efficient construction of multisubstituted arenes via aryne chemistry.[4] We wonder if we could manipulate the 3-position of a benzyne intermediate and convert this C-H bond to other types of bonds in an aryne process. As depicted in Scheme 1b, successfully merging a C-H functionalization with traditional aryne chemistry would provide us a chance to reach aryne trifunctionalization. To the best of our knowledge, there is no previous report to accomplish this hypothesis from a benzyne intermediate yet. We conceived that aryne insertion into a σ-bond[5] or a multiple bond[6] might act as the predecessor for this purpose. Because sulfonium-involved Claisen rearrangement, generated from aryl sulfoxides via various activation methods, has recently been extensively studied,[7] in addition with the potential *in situ* generation of sulfonium intermediate via aryne insertion into the S=O bond of sulfoxide,[6f,6g] we decided to investigate the reaction behavior of aryl allyl sulfoxide with arynes (Scheme 1c).

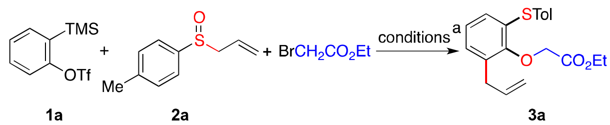
Initially, we postulated that a thio-Claisen rearrangement would produce compound **b** with the allyl group located on the *ortho*-position of the sulfur (Scheme 1c). Surprisingly, this transformation afforded a single product **a** instead, in which the allyl group migrated to the *ortho*-position of the oxygen. X-ray crystallographic analysis on the derivative of **a** confirmed the structural arrangement of **a** (see Fig S1). This result suggests that the allyl group experiences an "S→O migration" and a consequent Claisen rearrangement process. It is worth mentioning that product **a** could be readily converted to a variety of structures, such as 1,2,3-trisubstituted arenes with consecutive C-, O-, and C-substituents, the framework of which belongs to many natural products or medicines, such as bufuralol (*β*-adrenoceptor antagonist), LY294002 (phosphoinositide 3-kinase, PI3K, inhibitor), and Osthol (Scheme 1d). Herein, we report our study on a tandem assembly of 1,2,3-trisubstituted arenes from aryne and aryl allyl sulfoxide, and our mechanistic study suggested an unprecedented reaction pathway.

Scheme 1. Background and Our Work



Encouraged by our preliminary result, we started to optimize the reaction condition. As shown in Table 1, in the presence of 2.0 equiv of ethyl bromoacetate, the reaction of *p*-tolyl allyl sulfoxide (**2a**) with Kobayashi benzyne precursor **1a** in MeCN afforded **3a** as the only product (entries 1-3, Table 1). The highest yield is 87% at 50 °C (entry 2). Using KF/18-c-6 as the fluoride source, **3a** could be obtained in 74% yield (entry 4). There is no **3a** formation, however, when TBAF was employed (entry 5). Various solvents were screened as well, and it was found that MeCN was the best solvent (entries 6-9).

Table 1. Condition optimization

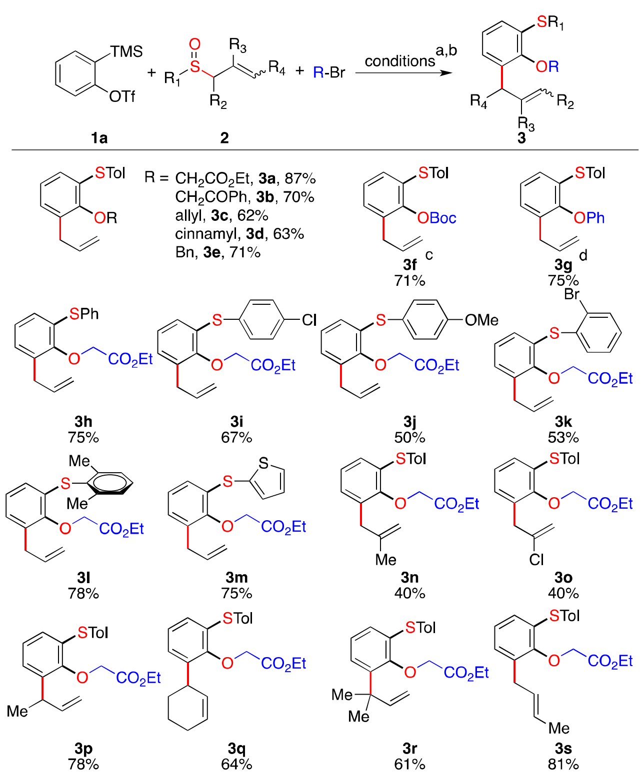


entry	"F" (equiv)	solvent	temp (°C)	yield^b (%)
1	CsF (4.0)	MeCN	rt	70
2	**CsF (4.0)**	**MeCN**	**50**	**87**
3	CsF (4.0)	MeCN	80	79
4	KF(4.0)/18-c-6	MeCN	50	74
5	TBAF (4.0)	MeCN	50	0
6	CsF (4.0)	dioxane	80	nr
7	CsF (4.0)	THF	50	80
8	CsF (4.0)	DME	80	71
9	CsF (4.0)	DCM	rt	nr

[a] Conditions: **1a** (0.6 mmol), **2a** (0.3 mmol), CsF (1.2 mmol), and $BrCH_2CO_2Et$ (0.6 mmol) in solvent (20 mL). [b] Isolated yield.

Different additives were then studied (Scheme 2). It was found that a broad spectrum of alkyl bromides, i. e. 2-bromoacetophenone, allyl bromide, cinnamyl bromide, and benzyl bromide, could all afford the corresponding products **3b**-**3e** in good yields. Interestingly, when Boc anhydride was used instead of alkyl bromide, **3f** was obtained in 71% yield. In the absence of bromoalkane, the reaction still proceeded smoothly with diaryl ether **3g** formation in 75% isolated yield, where the excess benzyne acted as the protecting group for phenol oxygen. The optimal condition is 2.5 equiv of **1a** at 110 °C using mixed solvents (MeCN-toluene, 1:2).

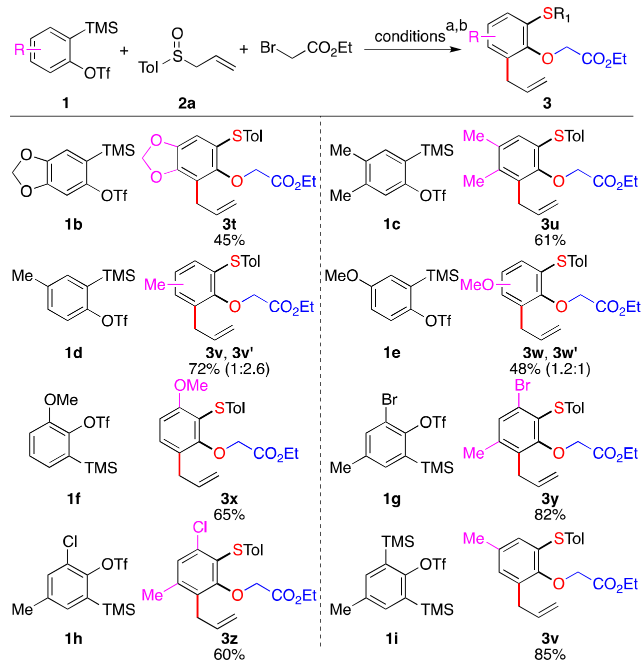
Scheme 2. Reaction with Different Sulfoxides



[a] Conditions: **1a** (0.6 mmol), **2** (0.3 mmol), CsF (1.2 mmol), and RBr (0.6 mmol) in MeCN (20 mL) at 50 °C or 80 °C. [b] Isolated yield. [c] Boc2O (0.6 mmol) was used. [d] **1a** (0.75 mmol) and CsF (1.5 mmol) were used in the absence of RBr in MeCN-tol (1:2).

Sulfoxide substrates were then explored. The sulfoxides with different substituents on the aryl ring could afford the products in good to high yields (Scheme 2, **3h**-**3l**). Steric repulsion on **2k** and **2l** did not affect the reaction efficiency. When 2-(allylsulfinyl)thiophene (**2m**) with a heteroaryl group was used, **3m** could be obtained in 75% yield. Unfortunately, alkyl allyl sulfoxides did not give any desired products. The substrate scope was further expanded to the allyl groups with various substituents. Both sulfoxides with 2-methylallyl and 2-chloroallyl groups gave the corresponding products **3n** and **3o** in 40% yields. Furthermore, in the presence of crotyl and cyclohex-2-en-1-yl groups, **3p** and **3q** were obtained in 78% and 64% yields, respectively. Sterically more hindered aryl prenyl sulfoxide **2r** could also give product **3r** in 61% yield. These results suggest that this transformation can tolerate the steric repulsion on the allyl group site as well. When aryl but-3-en-2-yl sulfoxide **2s** was employed, **3s** was obtained in 81% yield as the sole product. The structures of **3p**, **3r**, and **3s** indicate that the overall allylic shift is the same as an *ortho*-Claisen rearrangement.

Scheme 3. Reaction with Various Aryne Precursors

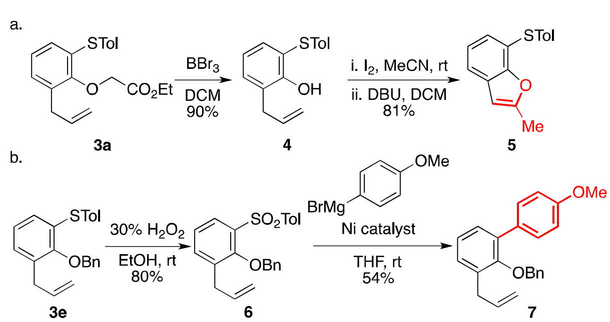


[a] Conditions: **1a** (0.6 mmol), **2** (0.3 mmol), CsF (1.2 mmol), and $BrCH_2CO_2Et$ (0.6 mmol) in MeCN (20 mL) at 50 °C or 80 °C. [b] Isolated yield.

The reactions of allyl sulfoxide **2a** with various Kobayashi aryne precursors were then examined, which could all afford the desired products (Scheme 3). Symmetrical arynes generated from **1b** and **1c** afforded single isomers **3t** and **3u** in 45% and 61% yields, respectively. Whereas, when aryne precursors **1d** and **1e** were used, mixtures of regioisomers were obtained in low ratios, indicating a weak-biasing effect of the distal methyl and methoxy groups on these aryne precursors. Aryne precursors **1f**-**1h** with additional vicinal electron-withdrawing groups (EWGs) could all produce the desired products in good to high yields. The EW conductive effect by oxygen on **1f** and halogens on **1g** and **1h** manipulates the formal [2+2] step, allowing sulfoxide oxygen to attack these arynes preferentially from the *meta*-position of the EWG.[1c,8]

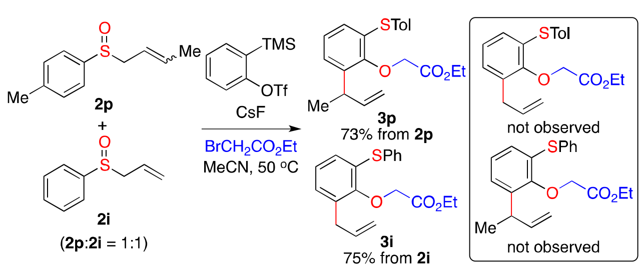
In contrast to EW effect, this transformation also obeys the electron-donating effect rule discovered by Akai.[9] When **1i** with an additional TMS group was used, this TMS group could alter the addition selectivity with the formation of an *ortho* C-O bond and a *meta* C-S bond. Uncommonly, in the consequent steps, the allyl group replaced this TMS directing group, affording **3v** as the sole product in 85% yield. This result can be explained by the fact that the TMS group can act as an equivalent of proton and departs after the allyl group migrates to its side.

Scheme 4. Elaboration of the Products



The products in this transformation were tested for further elaboration. As an exhibition, the dealkylated product **4** from **3a** could cyclize in the presence of I_2/DBU, affording benzofuran **5** in 81% yield (Scheme 4a). Moreover, product **3e** was oxidized to sulfone **6**, which could undergo Ni-catalyzed cross coupling reaction with Grignard reagent[10] to afford biphenyl **7** in 54% yield (Scheme 4b). These convenient conversions of the products show their diversified potential on structural modification, which might be applied in the synthesis of useful molecules, such as those shown in Scheme 1d.

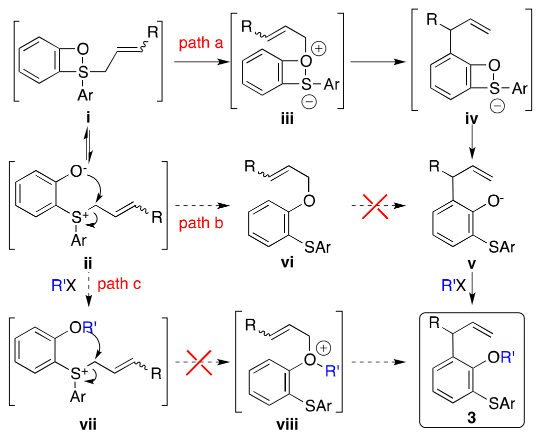
Scheme 5. Crossover Experiment



To understand whether the allyl migration step is intramolecular or intermolecular, crossover experiment was conducted (Scheme 5). It was found that, when a 1:1 mixture of **2p** and **2i** was treated with benzyne, only two products, namely **3p** and **3i**, were isolated. The absence of both crossover products suggests that this transformation is intramolecular.

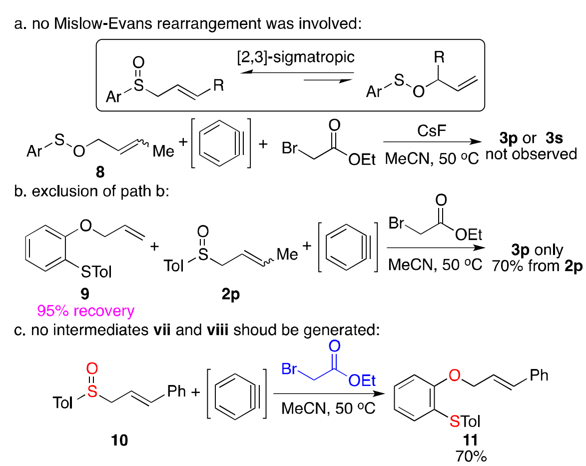
An emerging need is to elucidate why this transformation gives the product with a structural arrangement of **a**, instead of **b** (Scheme 1c). As shown in Scheme 6, to answer this question, three plausible mechanistic pathways are proposed. A formal [2+2] cycloaddition of benzyne with S=O bond gives adduct **i** first. In path a, direct allyl S→O migration generates intermediate **iii**, which undergoes an oxonium Claisen rearrangement to produce **iv**. After ring opening and O-protection, product **3** could be afforded. Alternatively, both paths b and c involve a common intermediate **ii**, a ring-opening resonance structure of **i**. The difference between path b and path c resides on allyl migration to either phenoxy anion (path b) or ether oxygen (path c) prior to Claisen rearrangement.

Scheme 6. Proposed Mechanism



In order to gain further insights on feasible reaction route, preliminary mechanistic studies were performed. Since the interconversion between allyl sulfoxide and allyl sulfenate is well-known as Mislow-Evans rearrangement (Scheme 7a),[11] we decided to first examine this possibility. When compound **8** was used, there was no observation of either **3p** or **3s**, suggesting that Mislow-Evans rearrangement did not involve in the reaction. Moreover, when independently prepared **9** was added to the reaction of aryl crotyl sulfoxide **2p** with benzyne, the only product was **3p** in 70% yield from **2p** (Scheme 7b). The 95% recovery of **9** from this reaction indicates that compound **vi** was not involved in the reaction. Therefore, path b could be ruled out (Scheme 6). Meanwhile, when aryl cinnamyl sulfoxide **10** was treated with benzyne and ethyl bromoacetate, the only product was **11** in 70% yield, where the cinnamyl group stays on oxygen and the Claisen rearrangement did not happen under the reaction condition (Scheme 7c). This observation suggests that O-alkylation should not take place earlier than allyl S→O migration. Hence, both intermediates **vii** and **viii** might not be formed during the reaction, which reduces the odds for path c.

Scheme 7. Mechanistic Investigation



As for path a, a competition exists for intermediate **i** between allyl "S→O migration" to give **iii** and ring-opening to produce **ii**. Indeed, previous study on the reaction of benzyne with DMSO observed a methyl S→O migration as a minor pathway after [2+2] cycloaddition.[6g] Therefore, we postulated that allyl group migration on intermediate **i** occurs readily so as to promote a consequent oxonium Claisen rearrangement prior to ring opening step. Surprisingly, there is no observation of any thio-Claisen rearrangement product in this transformation, supporting the hypothesis that intermediates **ii** and **vii** might not be generated in the reaction. Moreover, as shown by the structures of **3p**, **3r**, and **3s**, the overall process has a net allylic shift as a standard *ortho*-Claisen rearrangement. Because the concerted nature of *ortho*-Claisen rearrangement requires the same allyl group conversion, the allyl S→O migration step in this transformation has to be a direct 1,2-shift. Although uncommon, an ion-pair migration mechanism was previously observed in the Mislow-Evans rearrangement with cinnamyl group.[12]

In summary, a tandem aryne S=O bond insertion/C-H functionalization process was successfully developed, featuring arene 1,2,3-trisubstitution from relatively simple aryl allyl sulfoxide. This transformation proceeded through an unprecedented formation of C-S, C-O, and C-C bonds on three consecutive positions of an arene ring. The reaction condition is mild and efficient with a broad substrate scope. Preliminary mechanistic investigation suggests that the reaction might occur through an allyl S→O migration on a four-membered intermediate with a consequent Claisen rearrangement. Future work of our study involves the in-depth mechanistic study of this transformation as well as the development of other aryne cascade processes.

ASSOCIATED CONTENT

Supporting Information. Experimental details for all chemical reactions and measurements and X-ray single crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

y.li@cqu.edu.cn

Author Contributions

†Li, Y. and Qiu, D. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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